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Ruthenium Complex Bearing a Hydroxy Group Functionalised N-Heterocyclic Carbene Ligand – A Universal Platform for Synthesis of Tagged and Immobilised Catalysts for Olefin Metathesis

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In memory of Klaus Hafner

Six olefin metathesis catalysts, based on a common ruthenium precursor featuring a hydroxy-substituted N-heterocyclic carbene ligand, were successfully prepared and fully characterised. As proof-of-concept, two of them ($[Ru]_{isonico}$ and $[Ru]_{dmab}$) were directly immobilised on a solid support. These non-covalently heterogenised catalysts are efficient in different metathesis reactions and sufficiently stable to be used for repeated runs under batch and continuous flow conditions. In nonpolar media such as *n*-hexane, the catalytic character of the metathesis reactions is truly heterogeneous, and the contamination of the products with ruthenium is very low.

Introduction

One of the greatest challenges of modern organic chemistry is the development of sustainable processes that have the least possible impact on the environment. The theoretical foundations of this approach have been summarised in 12 principles of green chemistry.[1] Among other methods, catalytic reactions can form the backbone for such processes and provide products with the highest possible atomic economy and safety. The first two of the twelve postulates can be realised, among others, with the help of olefin metathesis reactions[2] for obtaining a wide range of simple and advanced organic compounds, including active pharmaceutical ingredients (APIs),[3] natural products,[4] polymers[5] or musk-scented macrocycles.[6] The third principle is closely related to the "enabling technology",[7] flow chemistry, which allows improved control of reaction parameters and reproducibility compared to batch chemistry. It also enables rapid (online) analysis, optimization, and scale-up with increased process safety.[8] It was also shown that metathesis chemistry can be advantageously combined with the flow-through technique.[9]

The rise of olefin metathesis was strongly coupled with the discovery of well-defined catalysts, in particular the second-generation air- and moisture-stable ruthenium complexes in which one of the neutral ligands is an N-heterocyclic carbene (NHC, Figure 1a).[2] The introduction of these ligands into the ruthenium coordination sphere resulted in increased stability of the complexes to oxygen and moisture, as well as in broadening the chemoselectivity of the metathesis reaction, thereby facilitating the application of this process in the final stages of the synthesis of complex APIs and natural products.

However, the products generated with the aid of these homogeneous complexes can only be obtained free of metal traces with a great deal of effort, which can also affect the yield.[3c,10] The source of contamination can be associated with two mechanisms. First, the still-active catalyst, which is present during the workup of the reaction mixture, can cause a series of undesirable metathesis reactions leading to the formation of isomers, oligomers, and polymers. Indeed, this proved to be a problem in early manufacturing campaigns of the anti-hepatitis C virus agent BILN-2061.[11] Secondly, the active catalyst during workup can be relatively easily converted to Ru hydrides,[12] dimeric Ru-complexes,[13] or even nanoparticles.[14] These have

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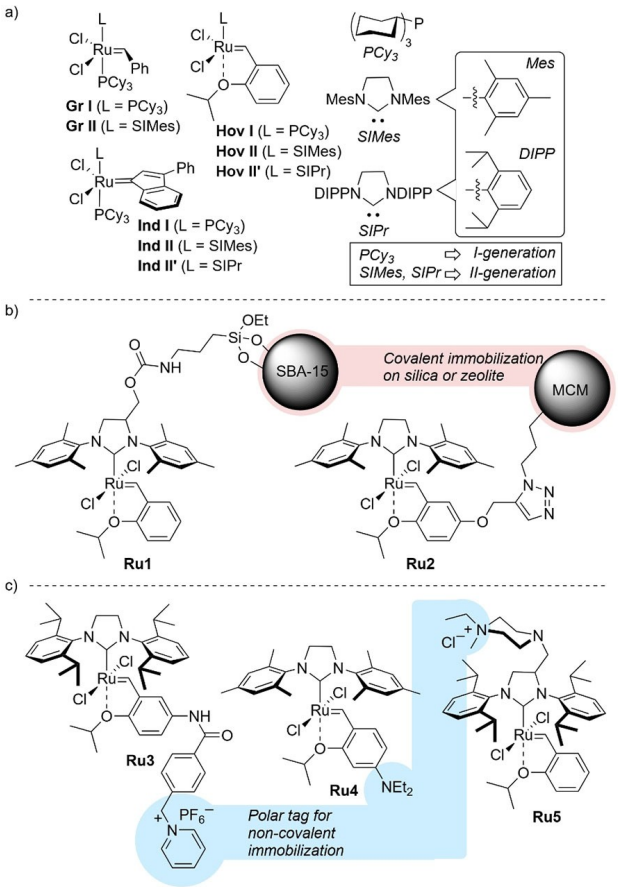


Figure 1. Selected ruthenium olefin metathesis catalysts: a) Grubbs (**Gr**), Hoveyda-Grubbs (**Hov**), and indenylidene (**Ind**) type general use complexes. b) Examples of complexes covalently bound to the support. c) Examples of complexes non-covalently bound to the support. SBA-15 = Santa Barbara Amorphous-15, highly stable mesoporous silica sieve, MCM = class of micro- and mesoporous zeolites.

been shown to catalyse the migration/isomerisation of the double bond present in the product. These parasitic side reactions not only reduce the yield of the expected product, but also lead to complex mixtures of by-products with similar polarity or boiling points, which significantly complicates purification.[15] There are several solutions to circumvent this problem, and one of them is based on immobilising the catalyst on a solid support,[16] allowing its facile separation e.g. by filtration. Not only can this reduce the ruthenium content in the final product, but also the products of possible catalyst degradation should thus remain on the support and can also be easily separated. Heterogenisation of Ru catalysts can be achieved in two chemically controlled forms of interactions with the solid phase, covalent[17] as well as two non-covalent immobilisation modes.[18] Covalent immobilisation typically requires the lengthy and expensive preparation of specially designed complexes and modified carriers (selected examples are shown in Figure 1b). However, once the complex is cleaved from the support, it is irretrievably lost.[11] In addition, most systems of this type display lower catalytic reactivity, and after reuse, a further reduction in its activity is observed.[19] Non-covalent immobilisation can be electrostatic, coordinative or based on π-π interactions).[18a,b,20] Their preparation is less cumbersome from a synthetic point of view (selected examples are shown in Figure 1c), and non-covalent attachment appears to be more efficient than covalent bonding to the solid phase in terms of catalytic activity and, above all, recyclability. The latter property is of key importance for metathesis catalysts when used heterogenised under flow conditions.

The combination of heterogenised catalysts in flow devices can be considered as an ideal technology platform for the development of processes for industrial applications.[21] Several factors must be taken into account when designing such flow devices. The catalyst must be robust both in chemical terms and with respect to the attachment to the solid support. The latter point is closely related to the issue of leaching and thus contamination of the product with ruthenium in the case of metathesis catalysts. Ideally, recycling of flow reactors with the active catalyst must be straightforward.

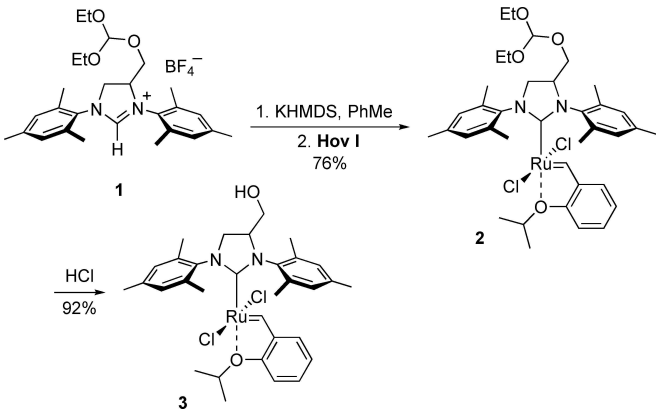
However, previous work has shown that the heterogenisation of homogeneous metathesis catalysts and their use under flow conditions poses the aforementioned major challenges. In addition, the lack of thermal stability and the relatively low catalytic activity of these complexes compared to heterogeneous industrial catalysts.[9d,22]

Here we present the modular synthesis of six ruthenium complexes based on the direct reaction between various acyl chlorides and a Hoveyda-Grubbs type catalyst. The catalyst is equipped with an NHC ligand with an additional primary OH group. Two of the chosen acyl chlorides, based on isonicotinic acid and 4-(dimethylamino)-benzoic acid, contained basic Brønsted tags which could be used for immobilisation of the corresponding ruthenium complexes to a solid phase by ion exchange. The functionalised carriers are suitable for use under batch as well as fixed bed materials for flow chemistry.

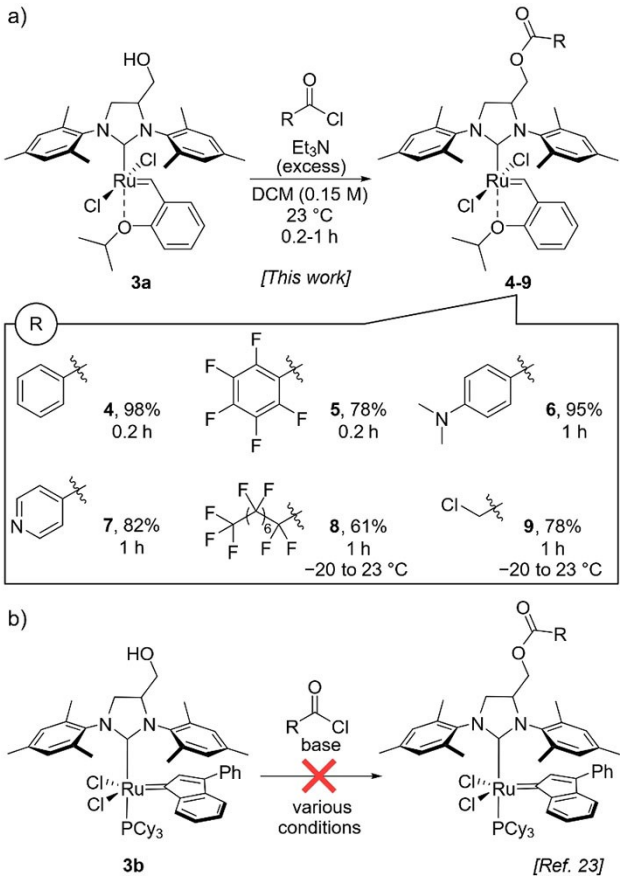
Results

Recently, we developed the practical high-yielding synthesis of racemic salt **1**.[23] We realised that it can be utilised in the synthesis of Hoveyda-Grubbs catalyst NHC ligand (Scheme 1). To do so, the free carbene was generated *in situ* by treatment of **1** with KHMDS and reacted with **Hov I** to provide "protected" complex **2** in a good yield of 76%. Two drops of concentrated hydrochloric acid were sufficient to obtain complex **3a** possessing a free OH group in good yield (70% after two steps). This complex was previously obtained by Koehler (from a TMS protected analogue)[24] as well as by Schwaneberg and Okuda (from a THP protected analogue),[25] but the overall yields of these literature preparations were only 34 and 47%, respectively.

Next, we tested the usefulness of complex **3a** as a universal platform for the preparation of catalysts with various aromatic and aliphatic substituents in the backbone of the imidazoline ligand (Scheme 2). In order to functionalise the free hydroxyl group of complex **3a**, we opted for a simple direct acylation reaction between **3a** and the corresponding acyl chloride in the



Scheme 1. Preparation of ruthenium complex **3a** possessing a free hydroxy group associated with the NHC ligand.



Scheme 2. a) Direct reaction between Hoveyda-Grubbs type catalyst **3a** and selected acid chlorides (this work). The complexes **4**–**9** were obtained as a racemic mixture. b) Failed direct esterification of **3b** tested previously (Ref. 23).

presence of an excess of triethylamine. To first test the feasibility of such a reaction, **3a** was treated with 3 equivalents of Et_3N in DCM (0.25 M), followed by the addition of a slight excess of benzoyl chloride (1.5 equiv.). These conditions resulted in the complete conversion of **3a** to the corresponding benzoyl-substituted complex **4** within just 0.2 h. Simple column chromatography of the crude reaction mixture afforded the pure product in an excellent 98% yield. This finding prompted us to consider various aromatic chlorides such as pentafluorobenzoyl chloride, 4-dimethylaminobenzoyl chloride, and isonicotinoyl chloride as partners for this reaction. Gratifyingly, under the above conditions (excess of Et_3N, 1.5 equivalents of acid chloride in DCM), the expected complexes **5** (R = C_6F_5), **6** (4-Me_2N-C_6H_4), and **7** (C_5H_4N) could be isolated in good to excellent yields ranging from 78 to 95%. Next, we turned our attention to more reactive functionalised alkanoyl chlorides such as perfluorononanoyl chloride[26] or chloroacetyl chloride. In these cases, the acylation reaction of the free hydroxyl residue of complex **3a** revealed pronounced exothermicity, which was consequently detrimental to the yield, as the corresponding complexes **8** and **9** decomposed rapidly. Nevertheless, lowering the temperature of the reaction mixture to −20 °C with simultaneous addition of the corresponding acyl chloride allowed the isolation of the desired products **8** and **9** in good yields of 61% and 78%, respectively.

Of interest, the same strategy applied not to the Hoveyda-type precursor **3a**, but to the related indenylidene complex **3b** failed completely in providing the corresponding acylated complexes (Scheme 2b).[23] Such differences of behaviour between **3a** and **3b** are assumed to rely on the greater stability of phosphine-free complex **3a** under basic conditions required for acylation reaction. Indeed, the decomposition of complex **3b** was systematically observed during all attempted reactions with acyl chloride and the excess of triethylamine in DCM, and even when the corresponding indenylidene complexes were formed, such derivatives degraded quickly during the workup involving column chromatography on silica gel.[23]

The new catalysts (**4**–**9**)[27] were fully characterised by ^1H and ^{13}C NMR spectroscopy as well as HRMS and/or elemental analysis and IR spectroscopy. The signals of the benzylidene protons in the NMR spectra ranged from 16.36 to 16.45 ppm, which is typical of Hoveyda-type complexes, and the IR spectra of all these complexes exhibited an intense band at about 1760 cm^{-1}, confirming the presence of ester units. Remarkably, all of these complexes were isolated as green microcrystalline solids, except for isonicotin derivative **7**, which was obtained as a dark orange solid. Nevertheless, this complex turned green in solution (in DCM or AcOEt).

Using these six complexes, their catalytic activity in the ring-closing metathesis reaction of the model substrate diethyl diallylmalonate (**10**) (Figure 2) was probed.[28] For this purpose, malonate **10** dissolved in DCM (0.1 M) was treated with 0.5 mol% of catalyst **4**–**9** at 23 °C. The reaction was monitored by ^1H NMR spectroscopy to determine the time-dependent conversion of **10**. While all complexes in this study were found to be less active than **Hov II**, complexes **4**–**6** and **8** were found to initiate rapidly (k_{rel} between 0.18 and 0.33 compared to **Hov II**)[29] and highly productive catalysts with final conversion after 120 min ranging from 94% for **4** (R=Ph in green; Figure 2) to 99% for **5** (R=C_6F_5 in orange). On the other hand, complexes **7** (R=C_5H_4N in brown) and **9** (R=CH_2Cl, in black; Figure 2) were found to be low-activity and low-productivity at the RCM of **10**, showing a low initiation rate (k_{rel} of 0.06 and 0.03 for **7** and **9**,

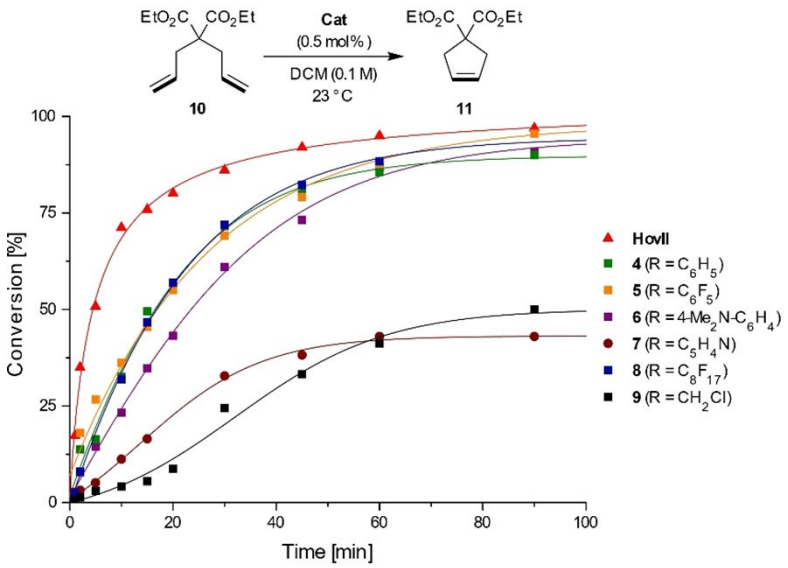


Figure 2. Plot of reaction conversion as a function of time for RCM of DEDAM (0.1 M) with complexes **4**–**9** and **Hov II** (0.5 mol%) in DCM at 23 °C: **Hov II** (red), **4** (green), **5** (orange), **6** (purple), **7** (brown), **8** (blue), and **9** (black). The transformation was determined by NMR spectroscopy. The lines serve as a visual aid.

respectively) and a low conversion of 43 and 50% after 120 minutes.

Interestingly, the severely reduced activity of catalyst **7** can be explained by a self-poisoning process of the Ru centre *via* coordination of the basic Lewis nitrogen atom of the pyridine unit an effect that has been demonstrated previously.[23] Such coordination of the pyridine with the Ru centre appears to disrupt the catalytic cycle and accelerate the decomposition of the catalytic species. To circumvent this limitation of complex **7**, the addition of a Brønsted acid was considered to quaternise the basic pyridine nitrogen atom. In our previous work, we added 1.1 equivalents of HCl in dioxane to a DCM solution of catalyst **7** and to our delight, this led to a dramatic improvement in the overall conversion of **10** up to 89% after 60 minutes.[23]

In the current study we decided to investigate the behaviour of complexes **6** and **7** (catalysts with Brønsted base moieties) in the RCM reaction of **10** in the presence of another Brønsted acid, *para*-toluenesulfonic acid monohydrate (*p*TsOH, 1.1 equiv.), which can be considered as a model of a solid support functionalised with sulfonic acid groups that we planned to use in the next part of the study. Surprisingly, a decrease in the relative initiation rate was observed for **6** (from 0.14 without acid to 0.06, orange and blue lines, respectively, in Figure 3) and for **7** (from 0.06 without acid to 0.02, green and purple lines, respectively, in Figure 3), and the conversion dropped from 99 to 55% for **6** and from 43 to 34% for **7**. In addition, a partial precipitation was observed in both cases, probably due to the formation of adducts between the complexes and the acid, which prevented the RCM reaction from proceeding efficiently under such conditions. However, these model studies have shown that an immobilisation strategy based on the catalyst protonation with a sulfonic acid-functionalised solids should be feasible.

It is known that silica itself can bind some unlabelled Ru-alkylidene complexes such as **Hov II** by physisorption, but only very low loadings of about 0.01 mmol/g can be achieved in this way.[30] Therefore, we assumed that the selective formation of salts should lead to a more stable heterogeneous catalyst and was carried out exemplarily for complexes **12** and **13**. For this purpose, a silica gel functionalised with *para*-toluenesulfonic acid groups (Si–TsOH, "Biotage," 0.64 mmol g^{-1}) was shaken in acetone at room temperature for one minute with an acetone solution of ruthenium catalyst **6** or **7**. Degassed water was then added, and shaking was continued for an additional 5 minutes. At this point, the solid phase had turned green and the supernatant had become colourless, indicating quantitative attachment to the solid phase. The supernatant was removed and the green solid was repeatedly washed with acetone and *n*-hexane and dried under vacuum at rt to give the heterogeneous catalysts **12** and **13** as dark green powders (Scheme 3).

Next, the catalytic activity of such obtained heterogeneous catalysts **12** and **13** was evaluated under batch conditions using ring-closing metathesis (RCM), cross-metathesis (CM), and enyne cycloisomerisation as standard test reactions (Scheme 4).

For non-covalently immobilised catalysts, the polarity of the solvent used for carrying out catalytic reactions plays a crucial role from the standpoint of the possible—and highly undesirable—desorption of the ruthenium complex from the support. It was demonstrated that in non-polar media, such as *n*-hexane where desorption is negligible, the catalysis is truly heterogeneous, and the contamination of the reaction products with ruthenium is very low; in more polar solvents such desorption can become more pronounced.[9c,d,30–31] Therefore, we investigated the performance of catalysts **12** and **13** in solvents with different polarity: *n*-hexane, toluene, and dichloromethane, using the ring-closing metathesis of diethyl diallylmalonate (**10**) as a test reaction. Alongside their time/conversion profiles, the

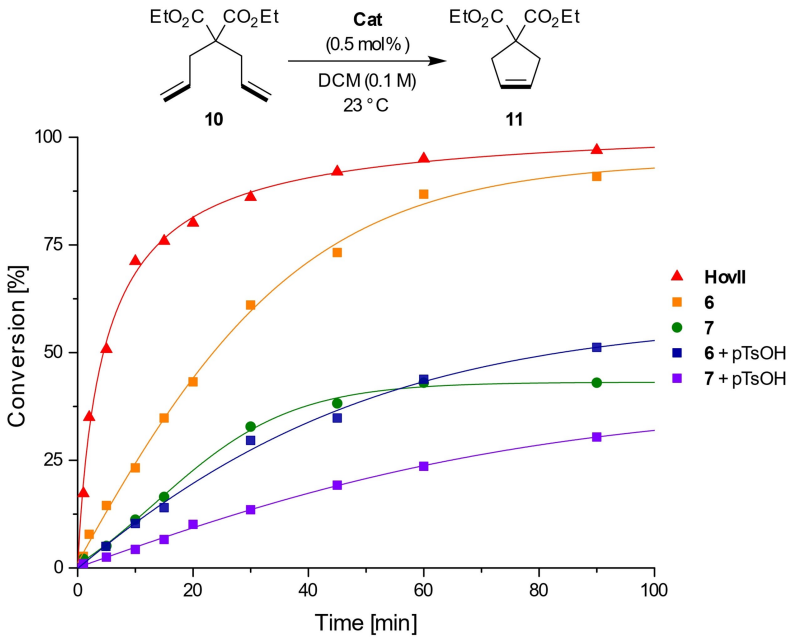
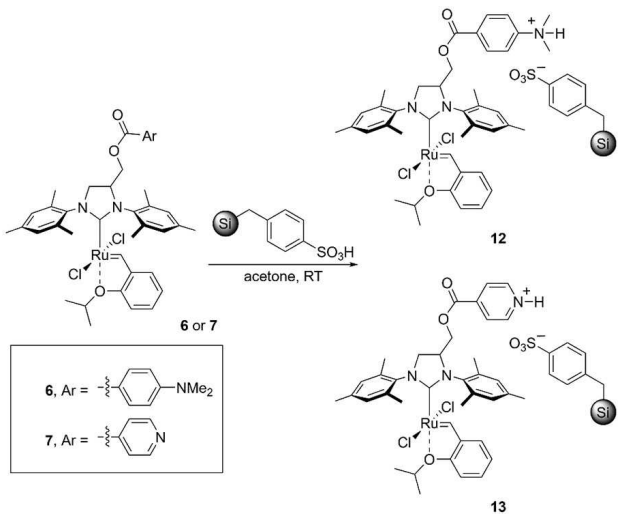
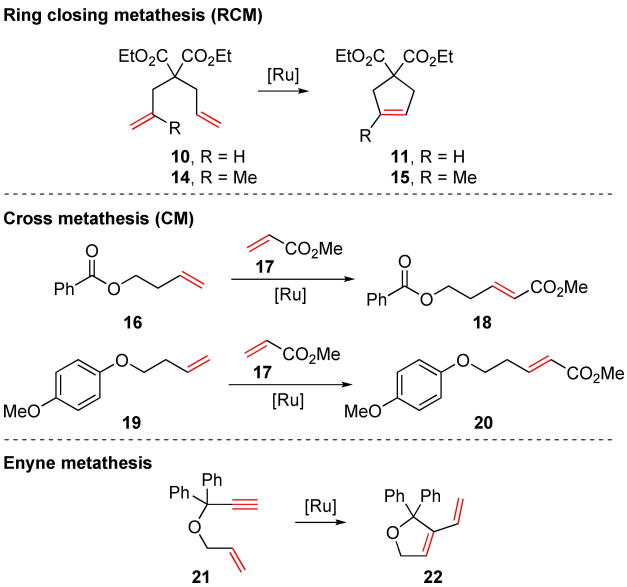


Figure 3. Plot of the reaction conversion in function of time for RCM of DEDAM (0.1 M) with complexes **6** and **7** (0.5 mol%) in the presence of acid (1.1 equiv.) in DCM at 23 °C: **Hov II** (red), **6** (orange), **6** + *p*-TsOH (blue), **7** (green), **7** + *p*-TsOH (purple). Conversion determined by NMR spectroscopy. Lines are visual aid only.



Scheme 3. Preparation of heterogenic Hoveyda-Grubbs type complexes **12** and **13**.



Scheme 4. Model metathesis reactions promoted by heterogeneous catalysts **12** and **13**.

contamination of the crude products with ruthenium was also determined by ICP-MS in order to quantify catalyst desorption. The results are shown in Figure 4 and Table 1.

Catalysts **12** and **13** showed similar behaviour in the RCM reaction tested and their catalytic activity was the highest in *n*-hexane. While the leaching of ruthenium complexes was very low in all solvents, it was especially low in *n*-hexane. From these data it is clear that *n*-hexane is the solvent of choice for performing metathesis reactions catalysed by complexes **12** and **13**, and, therefore, this solvent was used for carrying out the model reactions shown in Scheme 4. The results of these studies are presented in Table 2.

As seen from Table 2, heterogeneous catalysts **12** and **13** showed good activity in all tested metathesis reactions. High conversions over 90% were achieved after relatively short reaction times and at moderate thermal activation. The products of the metathesis transformations were isolated in good to very good yields after silica gel chromatography.

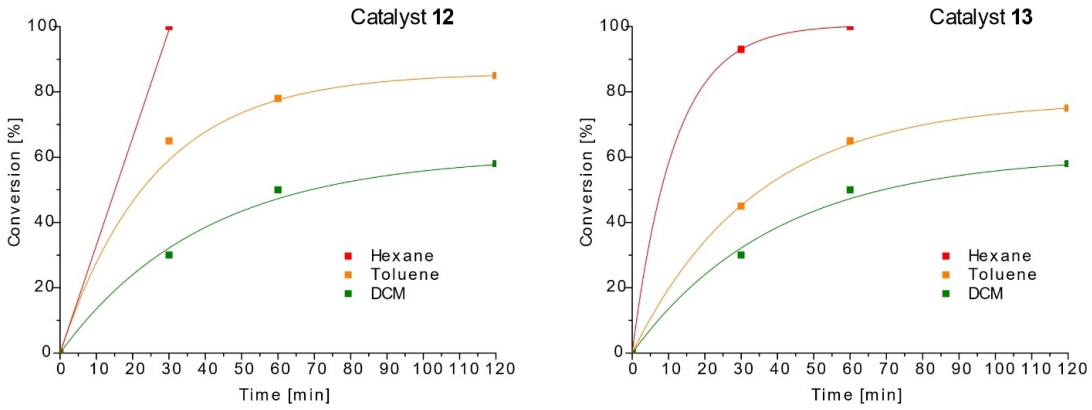


Figure 4. RCM of diethyl diallylmalonate (**10**) promoted by heterogeneous catalysts **12** and **13** in different solvents in a batch mode. Conditions: 0.2 mmol substrate in 2 mL solvent, 1 mol% catalyst **12** or **13**, 45 °C (*n*-hexane and toluene) or 40 °C (dichloromethane). The lines serve as a visual aid.

Table 1. Ruthenium leaching during RCM of diethyl diallylmalonate (**10**) promoted by heterogeneous catalysts **12** and **13** in different solvents.[a]

Solvent	Ru content in the crude product[b] Catalyst **12**/Catalyst **13**	Ru leaching[c] Catalyst**12**/Catalyst **13**
n-hexane	0.3 ppm/0.3 ppm	< 0.01 %/< 0.01 %
toluene	2.5 ppm/18.6 ppm	0.05 %/0.37 %
DCM	7.4 ppm/30.5 ppm	0.13 %/0.66 %

[a] For conditions see Fig. 4. [b] Determined by ICP-MS performed on the crude products after filtration of the heterogeneous catalysts. [c] Calculated in % of starting Ru content in the catalyst used.

Table 2. Evaluation of heterogeneous catalysts **12** and **13** in the RCM, CM, and enyne metathesis under batch conditions.[a]

Entry	Substrate (s)[b]	Product	Catalyst [mol %]	Time	Conversion [%][c] (Yield [%])[d]
1	**10**	**11**	**12** (1.0)	0.5 h	> 99 (94)
2	**10**	**11**	**13** (1.0)	1 h	98 (96)
3	**14**	**15**	**12** (1.0)	1 h	99 (97)
4	**14**	**15**	**13** (1.0)	2 h	98 (93)
5	**16** + **17**	**18**[e] (*E*/*Z* = 93:7)	**12** (2.5)	2 h	95 (79)[f]
6	**16** + **17**	**18**[g] (*E*/*Z* = 93:7)	**13** (2.5)	2 h	96 (82)[f]
7	**19** + **17**	**20**[h] (*E*/*Z* = 93:7)	**12** (2.5)	3 h	91 (76)[f]
8	**19** + **17**	**20**[i] (*E*/*Z* = 93:7)	**13** (2.5)	2 h	97 (85)[f]
9	**21**	**22**	**12** (1.0)	2 h	98 (91)
10	**21**	**22**	**13** (1.0)	3 h	90 (81)

[a] All metathesis reactions were carried out in *n*-hexane at 45 °C. [b] 0.1 M solutions of **10**, **14**, **16**, **19**, and **21** were used; for CM, 4 equiv. **17** were employed. [c] Determined by GC and/or ^{1}H NMR spectroscopy. [d] Isolated yield after silica gel chromatography. [e] Homodimer derived from **16** (9 %) was also formed. [f]Isolated yield of pure (*E*) cross-product. [g] Homodimer derived from **16** (6 %) was also formed. [h]Homodimer derived from **19** (7 %) was also formed. [i] Homodimer derived from **19** (4 %) was also formed.

Catalyst **12** was more active than its pyridine analogue **13** in the RCM of dienes **10** and **14** and in enyne metathesis of compound **21** (Table 2, entries 1–4 and 9,10) whereas catalyst **13** was slightly superior in the cross-metathesis reactions giving higher yields of the cross-products and less homodimer by-products (Table 2, entries 5–8).

Next, the reusability of heterogeneous catalysts **12** and **13** under batch mode conditions was investigated using the RCM of diethyl diallylmalonate (**10**) as a model reaction. The RCM reactions were carried out in *n*-hexane at 45 °C. After each run, the heterogeneous catalysts were washed thoroughly with the solvent and then immediately used in the next run. Using catalyst **12**, nine consecutive runs of the RCM reaction were carried out with run durations of 30 min for runs 1 to 6, 90 min for run 7, and 120 min for runs 8 and 9. The results are summarised in Figure 5.

Catalyst **12** was found to be very active in the first six runs, giving conversions from more than 99 % (runs 1–4) to 90 % (run 6) within the reaction time of 30 min each. The activity was moderate in the seventh run and declined rapidly in runs eight and nine. However, increasing the duration of cycle 7 by 30 or 60 min allowed for an increase of yield of about 10 percentage points for each additional 30 min. A similar correlation was observed for cycles 8 and 9, although here extending the reaction time by 90 min was more beneficial. The heterogeneous character of catalyst **12** was confirmed by conducting a split test[32] during the first run. An aliquot of the supernatant was transferred into a second flask after 10 min (conversion of **10** was 92 %) and kept under identical reaction conditions. Product formation in both flasks was monitored by GC. While the RCM reaction went quickly to completion in the presence of catalyst **12**, no catalytic activity was observed in the supernatant (conversion of **10** stayed at 92 % after 80 minutes), thus indicating the truly heterogeneous character of the immobilised catalyst under the conditions employed here.

The second heterogeneous catalyst **13** turned out to be less efficient than **12**. Eight consecutive runs of the RCM reaction were performed using the same sample of catalyst **13**, with run durations of 30 min for runs 1 to 6 and 120 min for runs 7 and 8. The results are summarised in Figure 6.

Conversion over 90 % was achieved only in runs 1 through 3 and declined abruptly after the fifth run. Again, the split test carried out during the first run revealed no catalytic activity in the supernatant (Figure 6).

The split tests provide information only on catalytic activity in the supernatant but say nothing about the possible presence of catalytically inactive metal species in the solution, which

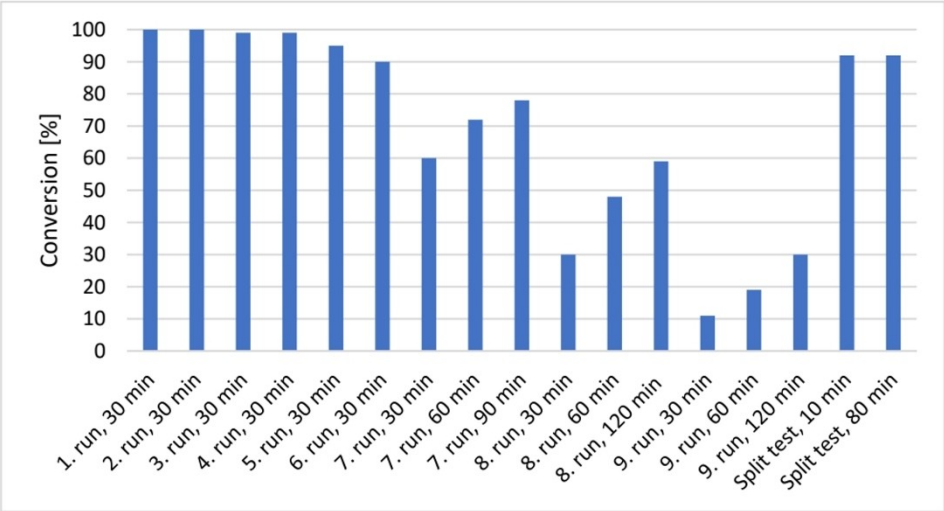


Figure 5. Consecutive RCM of diethyl diallylmalonate (**10**) promoted by catalyst **12**. Conditions: 0.2 mmol substrate in 2 mL *n*-hexane, 1 mol% catalyst, 45 °C. The split test was carried out during the first run.

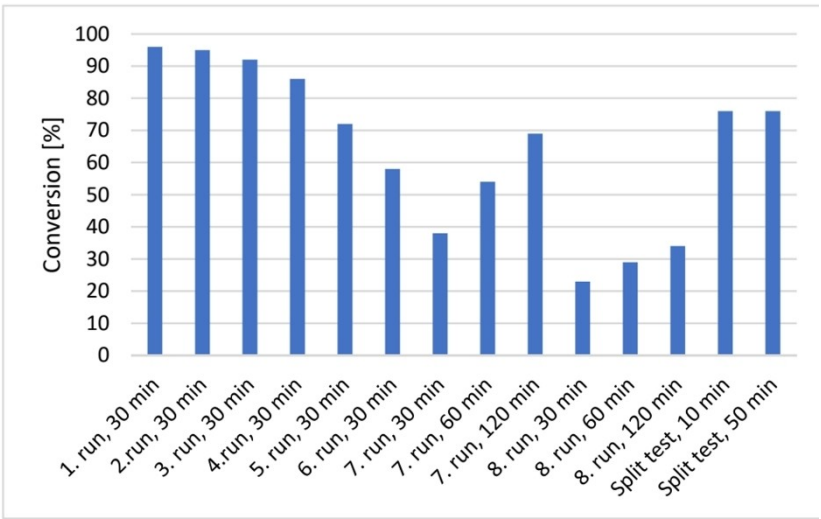


Figure 6. Consecutive RCM of diethyl diallylmalonate (**10**) promoted by catalyst **13**. Conditions: 0.2 mmol substrate in 2 mL *n*-hexane, 1 mol% catalyst, 45 °C. Split test was carried out during the first run.

could lead to undesired product contamination. Therefore, ruthenium leaching was quantitatively investigated by analysing the ruthenium content in the metathesis products. For this purpose, the crude products of the first five runs of RCM of diethyl diallylmalonate (**10**) catalysed by the heterogeneous catalysts **12** or **13** were analysed using ICP-MS. The results are listed in Table 3.

Table 3. Ruthenium leaching during consecutive RCM of diethyl diallylmalonate (**10**) promoted by catalysts **12** or **13** under batch conditions.

Run number	Catalyst **12**[a]	Catalyst **13**[b]
1	0.27 ppm[c]/0.005 %[d]	0.32 ppm[c]/0.005 %[d]
2	0.12 ppm[c]/0.002 %[d]	0.10 ppm[c]/0.002 %[d]
3	0.14 ppm[c]/0.003 %[d]	0.06 ppm[c]/0.001 %[d]
4	0.08 ppm[c]/0.002 %[d]	0.06 ppm[c]/0.001 %[d]
5	0.08 ppm[c]/0.002 %[d]	0.04 ppm[c]/0.001 %[d]

[a] For conditions see Figure 5; [b] For conditions see Figure 6; [c] Ruthenium content in the crude product in parts per million (ppm); [d] Calculated ruthenium leaching in % with respect to the starting content of Ru in the catalyst used.

The results obtained show that the leaching of ruthenium in *n*-hexane for the two immobilised catalysts **12** and **13** is neglectable low, which also confirms the heterogeneous character of the catalysis under the conditions used. Thus, in our view, the prerequisites for using **12** and **13** as fixed-bed catalysts in flow reactors were met (Figure 7).

First, flow experiments were performed in the loop set-up (Figure 7, left). The heterogeneous catalyst (100 mg of **12** or **13**, 2.5 mol%) was placed inside the flow-reactor (glass column, internal dimensions 100×2.5 mm) and a solution of diethyl

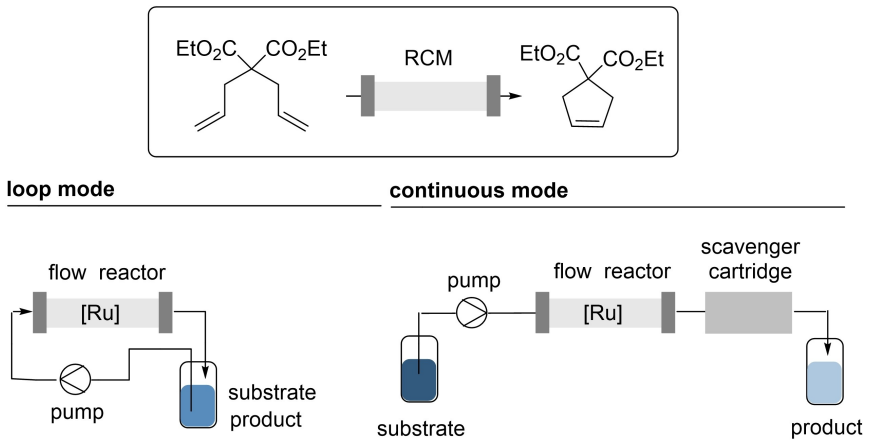


Figure 7. Alternative flow set-ups (circulating mode and continuous one-way mode).

diallylmalonate (**10**) in *n*-hexane was pumped through the reactor in a circulating mode at a flow rate of 2.5 mL/min, which was locally heated to 45 °C. The progress of the RCM reaction was monitored periodically. After completion of the experiment, the reactor was thoroughly washed with *n*-hexane and the next experiment could be performed with a new solution of starting material **10**.

The outcomes of these experiments using catalyst **12** are summarised in Figure 8. Eight consecutive runs were performed, each lasting 1 h, except for the 7th run (17 h) and the 8th run (2 h). Catalyst **12** showed good activity and stability and gave conversions ranging from 95–97% (runs 1–3) to 71% (run 6) within 1 h reaction time. In the 7th run, a moderate conversion of 57% was recorded after 1 h, but after circulating the reaction mixture overnight, a high conversion of 94% was achieved (not shown in Figure 8), illustrating the pronounced stability of this heterogeneous catalyst.

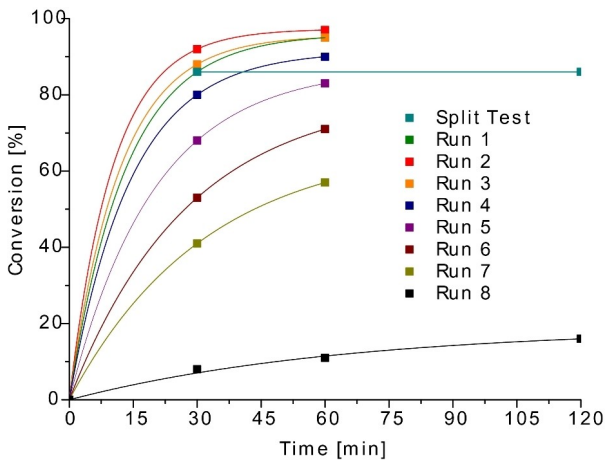


Figure 8. Consecutive RCM of diethyl diallylmalonate (**10**) promoted by catalyst **12** under circulating flow conditions: 2.5 mol% catalyst, 0.4 mmol substrate per run (0.05 M in *n*-hexane), flow rate 2.5 mL min^{-1}, 45 °C; runs 1–6: 1 h, run 7: 17 h, run 8: 2 h.

The split test performed during the first circulation experiment did not reveal any catalytic activity outside the reactor (Figure 8). Quantification of the ruthenium content in the crude products by ICP-MS showed an extremely low leaching of metal species during this circulation process. The product of the 1st circulation experiment contained only 0.39 ppm ruthenium, corresponding to 0.003% of the initial content of Ru in the catalyst used. The ruthenium impurities in the products from runs 2–7 were even lower, ranging from 0.08 ppm to 0.17 ppm (i.e., $<$0.001% of the initial content of Ru in the catalyst). Heterogeneous catalyst **13** was less efficient under the same conditions and showed a greater decrease in activity than catalyst **12**. Five consecutive runs were performed with the same portion of catalyst **13**. After circulating the reaction mixture for one hour, 96% conversion was observed for runs 1 and 2, a good conversion of 82% in the 3rd run, and only a moderate conversion of 55% in the 4th run. Finally, the drop-in activity was very pronounced in run 5. Only an extension of the reaction time to 16.5 h increased the conversion to 79%.

Finally, we tested the performance of heterogeneous catalysts **12** and **13** under continuous (one-way) flow conditions (Figure 7, right). Again, the heterogeneous catalyst (360 mg of **12** or **13**, 0.036 mmol Ru catalyst) was loaded into the flow reactor (glass column, internal dimensions 100×2.5 mm) and a solution of diethyl diallylmalonate (**10**, 0.15 M in *n*-hexane) was pumped through a preheated (50 °C) reactor in one-pass mode at a flow rate of 0.25 mL/min. Aliquots were taken at the outlet of the reactor at regular intervals to determine the degree of conversion by GC. The results obtained are summarised in Figure 9.

Catalyst **12** proved to be superior to catalyst **13** in terms of catalytic activity and reusability under both batch and flow operation. With catalyst **12**, an almost quantitative conversion ($>$99%) to the metathesis product was still found after 3 h; after 5 h, this was 94%. For catalyst **13**, the corresponding values are 98% and 87%, respectively. No ruthenium traces could be detected in the solution by ICP-MS (Table 4); the leaching can thus also be evaluated as negligible for the flow processes, especially when *n*-hexane is used as solvent.

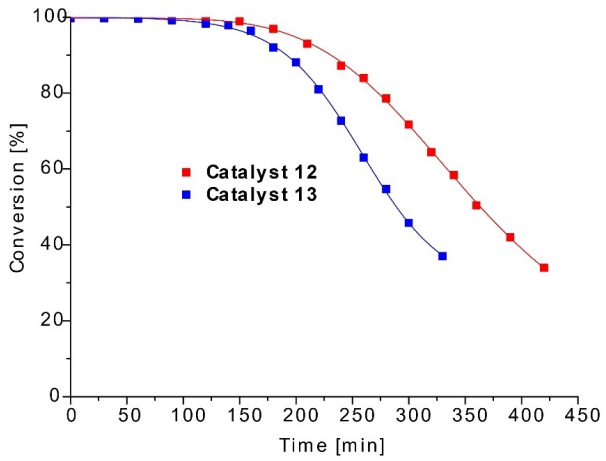


Figure 9. Ring-closing metathesis of diethyl diallylmalonate (**10**) promoted by catalysts **12** or **13** in a continuous flow reactor. Conditions: 36 μmol of catalyst **12** or **13**, 0.15 M substrate in *n*-hexane, 50 °C, flow rate 0.25 mL/min.

Table 4. Ruthenium leaching (determined by ICP-MS) during RCM of diethyl diallylmalonate (**10**) using catalysts **12** or **13** under continuous flow conditions (see Figure 5, right, for setup).[a]

Time interval of product collection	Catalyst **12**	Catalyst **13**
0–30 min	0.23 ppm[b]/0.001 %[c]	0.49 ppm[b]/0.004 %[c]
30–60 min	0.11 ppm[b]/ < 0.001 %[c]	0.16 ppm[b]/0.001 %[c]
60–80 min	0.10 ppm[b]/ < 0.001 %[c]	0.19 ppm[b]/0.001 %[c]
80–120 min	0.10 ppm[b]/ < 0.001 %[c]	0.17 ppm[b]/0.001 %[c]

[a] For conditions, see Figure 7; [b] Ruthenium content in the crude product in parts per million (ppm); [c] Calculated % of ruthenium leached with respect to the starting content of Ru in the catalyst used.

Conclusion

In summary, two new ruthenium catalysts **12** ($[Ru]_{isonico}$) and **13** ($[Ru]_{dmab}$), which bear neutral, Brønsted basic tags attached to the N-heterocyclic carbene ligand were successfully immobilised on silica gel functionalised with *p*-toluenesulfonic acid in a straightforward manner using the "*in situ* salt formation" strategy. The new, non-covalently heterogenised catalysts are efficient in various metathesis reactions and are stable enough (in terms of recyclability) to be used for repeated runs both under batch and flow—either circulating or continuous one-way—conditions. In non-polar media such as *n*-hexane, the catalytic character of the metathesis reactions is truly heterogeneous, and contamination of the products with ruthenium is very low.

Experimental Section

General Information

NMR spectra were recorded on a Bruker ARX 400 spectrometer at 400 MHz (^{1}H NMR) or 100 MHz (^{13}C NMR) in $CDCl_3$ using tetramethylsilane as internal standard. Gas chromatographic analyses were conducted using a Hewlett-Packard HP 6890 Series GS system equipped with a FID detector and an OPTIMA® 5 column (30 m × 0.32 mm ID, stationary phase thickness 0.25 μm, Macherey-Nagel). The determination of Ru impurities was carried out with an ICP-MS Thermo X2 ICP-QMS ('Thermo Fisher Scientific', Dreieich, Germany). Column flash chromatography was performed on silica gel 60 (Macherey-Nagel, 0.040–0.063 mm). All glassware was oven-dried and reactions were performed under an atmosphere of nitrogen using standard Schlenk techniques unless otherwise noted. All organic solvents were dried by passage through solvent purification columns containing activated alumina, except for *n*-hexane which was used as received ('Rotisolv for HPLC', Roth), and degassed. Acid chlorides as well as **10** and **17** are commercially available. All commercial chemicals were used as received unless otherwise noted. Compounds **14**,[33] **16**,[34] **19**,[35] and **21**[36] were prepared according to literature procedures. The following compounds have been previously described: **1**, **2**, and **3**. All compounds were fully characterised by ^{1}H and ^{13}C NMR, by mass spectrometry, and through comparison with the literature data after isolation by flash chromatography on silica gel.

Typical Procedure for immobilisation of the catalysts on functionalised silica (Si-TsOH, "Biotage")

Silica gel that was functionalised with *p*-toluenesulfonic acid groups (Si–TsOH, "Biotage", 0.64 mmol g^{-1} $-SO_3H$ groups as reported by the vendor) was washed thoroughly with water and MeOH, and dried under vacuum at 80 °C. This support (200 mg, 0.128 mmol) was shaken in a Schlenk tube under a nitrogen atmosphere at rt with a solution of ruthenium catalyst **6** (91.5 mg, 0.102 mmol, 0.8 eq.) and **7** (96.6 mg, 0.102 mmol, 0.8 eq.) respectively in acetone (4 mL) for 1 min, degassed water (4 mL) was added, and the shaking was continued for a further 5 min. At this point, the solid phase had turned green and the supernatant had become colourless. The supernatant was removed by a syringe and the solid was washed with acetone (5 × 5 mL) and *n*-hexane (3 × 5 mL) and dried under vacuum at rt to give heterogeneous catalysts **12** (277 mg) and **13** (278 mg) as dark-green powders. The established catalyst loading was 0.42 mmol g^{-1} for **12** and 0.40 mmol g^{-1} for **13** as determined by gravimetric analysis.

General procedure for ring closure and enyne metathesis in batch mode: A suspension consisting of the heterogenised ruthenium catalyst **12** or **13** (0.002 mmol, theoretical active catalyst) and degassed solvent (2 mL) in a Schlenk tube was preheated to the desired temperature. Diene or enyne (0.2 mmol) was added and the mixture was stirred under heating in a nitrogen atmosphere (a balloon was used to dampen the pressure rise during ethylene formation). Aliquots of the supernatant (10 μL) were taken at regular intervals and analysed by gas chromatography. After completion of the reaction, the supernatant was removed using a plastic syringe equipped with a 0.45 μm PTFE filter. The solid was stirred with a fresh portion of solvent (2 mL) for 1 min, and the supernatant was again removed using a syringe with a 0.45 μm PTFE filter attached. This procedure was repeated four more times. The combined organic phases were concentrated in vacuo, providing the crude product, which was then either analysed for Ru content or purified by flash chromatography on silica gel.

General procedure for the successive RCM runs in a batch mode. A suspension consisting of heterogeneous ruthenium catalyst **12** or **13** (0.002 mmol, theoretical active catalyst) and degassed solvent (2 mL) was preheated to the desired temperature in a Schlenk tube. The diene (0.2 mmol) was added and the mixture was gently shaken at the indicated temperature under a nitrogen atmosphere. Aliquots of the supernatant (10 μL) were taken at regular intervals and analysed by gas chromatography. After completion of the first run, the supernatant was decanted with a syringe and the catalyst

was shaken with a new portion of the solvent (2 mL) for 1 min, followed by removal of the supernatant. This washing procedure was repeated four more times. The solvent (2 mL) was then added to the catalyst, the mixture was preheated to the specified temperature, and the next run was started by adding the diene (0.2 mmol).

General procedure for the split test: Ring-closing and enyne metatheses were performed as described above. At a set time point, 0.1 mL of the supernatant was withdrawn using a plastic syringe equipped with a 0.45 μm PTFE filter (this procedure was performed at the appropriate reaction temperature to avoid possible retrapping of the homogeneous catalyst during cooling). The filtered supernatant was transferred to a second Schlenk tube previously purged and filled with nitrogen and containing a magnetic stir bar. GC analysis was performed immediately thereafter to determine the conversion at split time. Reactions in both Schlenk tubes were performed under identical conditions, with periodic GC analysis of aliquots of supernatant (10 μL) from both reactors to determine turnover.

General procedure for cross-metathesis: A mixture of heterogeneous ruthenium catalyst **12** or **13** (2.5 μmol, theoretical active catalyst) and the solvent (0.5 mL) in a Schlenk tube was pre-heated to the given temperature. Then, a solution of alkene (0.1 mmol) and methyl acrylate (0.4 mmol) in the same solvent (0.5 mL) was added and the mixture was stirred at the given temperature under a nitrogen atmosphere (balloon). After the required time, the mixture was filtered, the filtrate was concentrated in vacuum, and the residue was analysed by ^{1}H NMR spectroscopy and as well as by gas chromatography. Then, the cross-metathesis product was isolated by flash chromatography on silica gel.

General procedure for consecutive RCM runs in a circulating-flow mode: The reactor (glass column, 100 mm × 2.5 mm) loaded with the heterogeneous catalyst **12** (0.01 mmol, theoretical active catalyst) was connected to the pump and flushed with the solvent (15 mL) in one-way mode. Then, a three-neck reservoir containing the solvent (3 mL) filled with nitrogen gas was installed to create a setup suitable for a circulation flow process. The reactor was placed in the heating bath (45 °C) and the solvent was circulated at a flow rate of 2.5 mL min^{-1}. After preheating the reactor to the specified temperature, the diene (0.4 mmol) was added to the reservoir and the solution was circulated through the reactor at a flow rate of 2.5 mL min^{-1}. Aliquots of the supernatant (10 μL) were taken from the reservoir at regular intervals and analysed by gas chromatography. At the end of the run, the reservoir was disconnected, the reactor was washed with the solvent (20 mL) in one-way mode, and the next run was similarly performed after the three-neck reservoir containing diene (0.4 mmol) dissolved in the solvent (3 mL) was reinstalled.

Typical Procedure for the RCM Reaction under Continuous Flow Conditions (one-way): Heterogenised catalysts **12** or **13** (0.018 mmol g^{-1}) were added to the reactor (glass column, 120 × 8 mm). The reactor was connected to a solvent delivery system (syringe pump model 341 B, 'Sage Instrument', Orion Research Inc.) and preheated to 50 °C. Then, a 0.15 M solution of diethyl diallylmalonate (**10**) in *n*-hexane was pumped through the reactor at a flow rate of 0.25 mL min^{-1}. Periodically, 5 μL aliquots were taken from the outlet of the reactor and the degree of conversion was determined by GC, after which time the sampled fractions were concentrated in vacuo for analysis of ruthenium content by ICP-MS.

Split tests for continuous-flow reactions: For the split assay, the supernatant of the reservoir was taken at a specified time point (0.1 mL) and transferred to a vial filled with nitrogen gas. The vial was shaken at the specified temperature and the solution was analysed periodically by GC (10 μL aliquots) to determine the degree of conversion.

Analytical Determination of Ru Concentrations: All samples were digested in microbeakers in a microwave field with 0.5 mL HNO3 (~ 60 %) and 1 mL HCl (35 % p.a., Merck) followed by dilution with 2 % HCl. The microwave program was set to a maximum beaker temperature of 200 °C for 20 min after a warm-up period of 10 min. Digestion methods involving different combinations of acids were tested on a single sample. Ru determination was performed using an ICP-MS Thermo X2 ICP-QMS (Thermo Fisher Scientific, Dreieich, Germany, www.thermo.com). The instrument was set to 1400 W plasma power throughout the measurements. Gas flow rates were 0.98 L min^{-1} nebuliser, 0.8 L min^{-1} auxiliary gas, and 13 L min^{-1} plasma gas, all argon (purity 5.0; 99.999 %). Purge times were set to 40 s between samples and 40 s before measurement for purging with sample solution. Peak jump mode was used with 10 ms measurement time for each isotope measured in 100 cycles. For each solution, the measurement was repeated five times. Quantification was performed by averaging the concentrations obtained for ^{99}Ru, ^{102}Ru, and ^{104}Ru using at least five liquid ruthenium standards that matched the respective samples, with concentrations ranging from 90 ng L^{-1} to 10 μg L^{-1}. The standard solutions were prepared from 1000 mg L^{-1} ruthenium solution (Spex Certiprep, www.spex-certiprep.com) and diluted with 2 % HCl. Under the conditions used, the detection limit for ruthenium was 9 ng L^{-1}.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Flow chemistry · Immobilisation · N-Heterocyclic carbenes · Olefin metathesis · Ruthenium

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