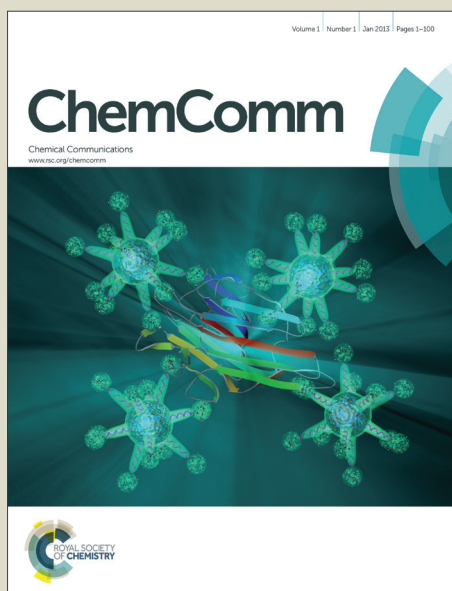


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COMMUNICATION

Role of Grafted Alkoxybenzylidene Ligand in Silica-Supported Hoveyda-Grubbs-Type Catalysts

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Using both circulating flow and batch reaction systems, we explored the role of immobilized alkoxybenzylidene ligands that is to capture and stabilize the active ruthenium species. The bidentate ligands considerably turned out affecting reaction rate, catalyst decomposition, leaching and recycling. It was also observed that the dynamic release-return catalytic pathway worked more efficiently in a batch system leading to less catalyst decomposition and leaching.

Since the seminal development of the metathesis catalyst by Hoveyda *et al.*,¹ the release-return mechanism has accounted for a proposed behaviour of its kinds.² Upon initiation the catalytically active 14-electron ruthenium carbene species are generated *in situ* to release the alkoxybenzylidene ligand, which in turn returns to revive the initial precatalyst. This mechanism is reversible and applicable to high catalytic dose conditions (>5 mol%), according to mechanism studies via labeling.^{2c} Envisaged on this mechanism, vigorous studies on immobilizing the versatile catalyst have involved in anchoring the bidentate ligand to the support material.^{3,4} There is, however, still a controversy in the reaction mechanism mainly due to difficulties in identifying the highly reactive and unstable intermediates.⁵ One study adopted a fluorophore tag to determine whether the tagged ligand was dissociated or not.⁶ Plenio *et al.* actually attributed the recovery of the initial precatalyst to the incomplete activation of the initial precatalyst. A computational study also revealed that the activation process requires to overcome relatively high energy barriers, which leads to incomplete catalyst initiation.⁷ However, their results do not provide direct evidence to support the hypothesis. Meanwhile, another recent study by employing ¹³C-labeling experiments indicated highly efficient catalyst initiation followed by rapid reuptake of the alkoxybenzylidene ligand.⁸ Foggs *et al.* clearly demonstrate that the release-return mechanism is operative and that facile shuttling from the recapture cycle into the metathesis cycle contributes to the performance of such catalysts. These previous studies cast a question over the efficiency of immobilization of Hoveyda-Grubbs-type catalysts by anchoring the alkoxybenzylidene ligand, particularly in terms of recycling.

Herein, we have investigated how the recycling efficiency is correlated to release-return pathway, incomplete catalyst initiation or both, in the case of anchoring the alkoxybenzylidene ligand to elaborate the corresponding heterogeneous catalysts. If the proposed release-return mechanism works in the heterogeneous reaction system, the decrease of the catalyst activity upon recyclings should stem, at least partially, from both the decomposition/leaching of ruthenium catalysts and the regeneration of free alkoxybenzylidene ligands. In addition, we have addressed the effect of catalyst loading density on the catalyst initiation through kinetic studies.

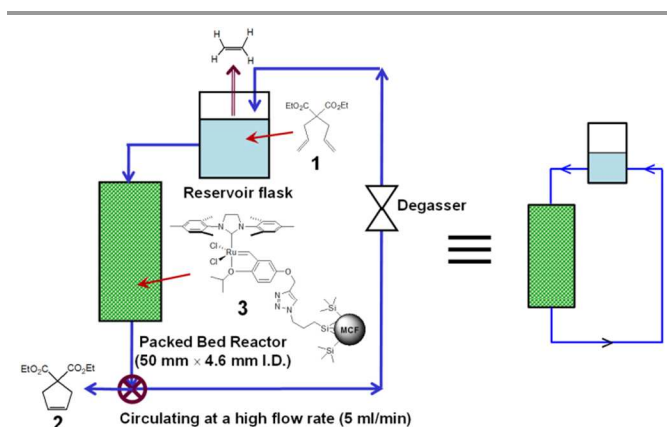


Fig. 1 A circulating flow reaction system.

Our previous report revealed an efficient flow reaction system optimized for ring-closing metathesis (RCM) (Fig. 1).⁴ With highly porous and spherical mesocellular siliceous foam (MCF) used as silica support in a packed bed reactor, this circulating flow system enables to reduce the decomposition of the active catalysts in conjunction with facilitated removal of *in situ* generated gaseous ethylene compared with a continuous flow reaction system. In addition, the isolation of the supported catalysts in the packed bed facilitates recovering the catalyst and allows the reaction medium to be easily sampled and monitored. If the release-return mechanism works in RCM by the supported catalyst, an aliquot of the medium isolated from the main reaction system would still show the conversion of the substrate because it contains the released active

ruthenium species. Likewise, the released reactive species should be able to return to the supported alkoxybenzylidene ligands by inserting additional packed bed to the circulating system.

Based upon these beneficial features, we designed three types of circulating systems to explore the reaction pathways of RCM by Hoveyda-Grubbs-type catalysts. The reservoir is an open vessel with a cooling condenser that releases the generated ethylene and holds the majority of reaction medium. The reservoir accommodates approximately 70 per cent of the total reaction medium. Whilst the system *a* represents a typical design, the system *b* comprise of additional packed bed **B** with the supported alkoxybenzylidene ligand (**4**) inserted after the packed bed **A** with the supported catalyst (**3**) and before the reservoir in the flow. In the system *c*, the packed ligand bed **B** is located after the reservoir and before the packed catalyst bed **A**.

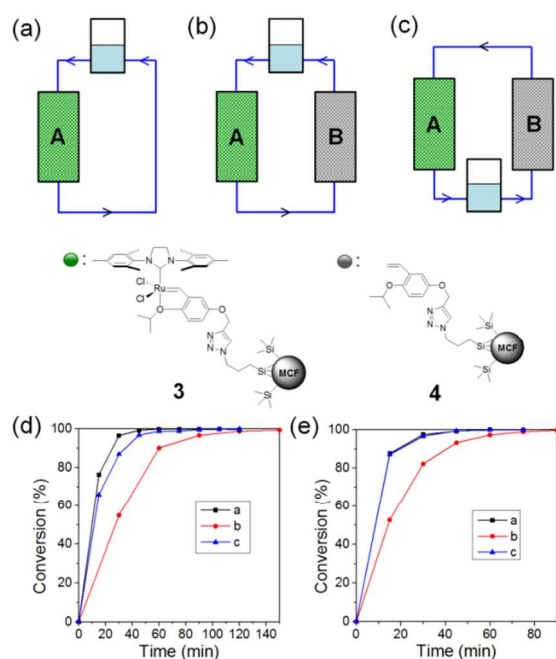


Fig. 2 Circulating flow reaction of (a) system *a*, (b) system *b*, and (c) system *c*; Conversion of substrate at (d) 25 °C, and (e) 50 °C. Reaction conditions: [diethyl diallylmalonate] = 0.15 M, 2 mol% catalyst. The loading amount of the catalyst **3** is 0.20 mmol/g and that of ligand **4** is 0.24 mmol/g.

If the release-return pathway accounts for the actual catalytic behaviour, the system *b* would show the slowest conversion because the active species released from the precatalysts in the first packed bed (**A**) are quickly inhibited via capturing by the supported ligands in the second bed (**B**). Indeed, the system *b* turned out significantly slower in RCM of a diene substrate. It is certain that some portions of the released active ruthenium species from the catalyst bed **A** were captured in the ligand bed **B** whilst the remaining portions flowed into the reservoir flask and participated in further conversion. In the system *c*, the released active catalysts from **A** would stay longer in the reservoir flask to result in a faster conversion. Some of the active species would be destined to decompose in the reservoir while some would be captured by the supported ligands **4** in **B**. To our expectation, the system *c* showed significantly faster reaction than the system *b*. It is noteworthy that the conversion rates in the systems *a* and *c* are comparable at 50 °C, which implies that the ruthenium species released from **A** are highly active and most of catalytic reactions occur in the reaction medium at higher

temperature prior to proceeding to decomposition in the reservoir or capture in **B**.

The MCF particles recovered from **B** of both the systems *b* and *c* after one round of the reaction appeared pale greenish in color, which accounted for the presence of the intact ruthenium precatalyst complex. The recovered particles from the system *b* were more greenish indicating that more active catalytic species were captured. It is apparent that a considerable portion of these reactive ruthenium carbene catalysts in the reservoir flask would end up decomposed during the catalytic cycles in the system *c*. The cross polarization magic angle spinning (CPMAS) ¹³C NMR spectra firmly revealed that some portions of the supported ligands captured the released active ruthenium species forming the intact second generation Hoveyda-Grubbs-type catalysts (Fig. S1). Interestingly, the overall NMR spectrum of the MCF particles recovered from **B** of the system *b* appeared nearly identical to that of a catalyst where ca. 30 per cent of the immobilized alkoxybenzylidene ligands were loaded with the ruthenium species. The recovered catalyst showed a comparable catalytic ability, as expected. In both systems *b* and *c*, the amount of the remaining ruthenium complexes in **A** was larger than that of the ruthenium complexes captured in **B**. These observations imply that all the ruthenium complexes on MCF are not released and activated in merely one round of catalytic reaction.

We also observed that these reactive species are highly vulnerable and easily decomposed to inactive species in the catalytic cycles even under inert conditions. According to the inductively coupled plasma (ICP)-MS analysis of the ruthenium species residing in the reaction medium after full conversion at 25 °C, the amount of leaching was the most in the system *a*, followed by the system *c* and then the system *b*. The amount of ruthenium species leached in the system *a* was 10.2 %, whilst the numbers were 6.6 and 3.8 % in the systems *c* and *b*, respectively. It is obvious that a higher population of the active species in the reaction medium leads to more decomposition of the catalysts in the systems *a* and *c*, in spite of higher reaction rates. We speculated that the ligand bed **B** in the system *c* would capture less amount of the ruthenium species than **B** in the system *b*, presumably due to the fast decomposition of the reactive species in the reservoir flask. The solid-state NMR spectra firmly support our hypothesis showing that the MCF particles recovered from **B** in the system *c* after one round of the reaction at 25 °C formed less ruthenium complex than the corresponding one in the system *b* (see SI, Fig. S4). These results are definitive enough to confirm that the alkoxybenzylidene ligand plays a role in capturing and stabilizing the active ruthenium species via the formation of the intact and stable precatalyst. It is also apparent to explain why a conventional continuous flow reaction system does not work with this sort of the supported catalyst.⁴

To further elucidate that the active species are released to the reaction medium in the system *a*, the reservoir flask was dislocated and placed under argon atmosphere after a short flash circulation of the substrate solution. The conversion in the isolated reservoir flask was monitored by GC. To our expectation, the diene substrate continued to undergo RCM upon time initially, and eventually ceased being converted at the complete deactivation of the catalysts (Fig. 3). Although the isolated solution was nearly colorless, and there was no change in color upon time, the substrate was rapidly converted. These findings imply that only a small portion of the immobilized catalysts participate in the RCM process by releasing the active ruthenium catalysts into the reaction medium. Therefore, the substrates continue to activate the immobilized catalysts in the packed bed, and some of the released species decompose during the catalytic runs, whilst other portions of them return to the alkoxybenzylidene ligand on the silica support. In this dynamic release-return process, the decomposition of the active species is still

unavoidable even with extra caution due to their nature of high reactivity and low stability.

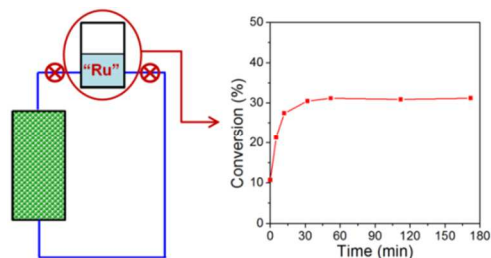


Fig. 3 Conversion of diethyl diallylmalonate in the reservoir flask at 25 °C, isolated from the main circulating flow reaction system at 3 min from the initiation. The conversion was 10.7% at the point of isolation.

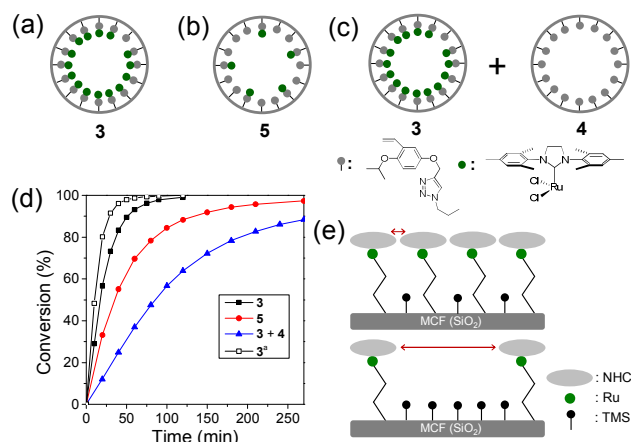


Fig. 4 Catalysts used for batch reactions by (a) Ru catalyst loading: 0.2 mmol/g, (b) Ru catalyst loading = 0.08 mmol/g, and (c) mixture of **3** and **4** (1:2); (d) Conversion of the substrate upon time ([diethyl diallylmalonate] = 0.05 M, 2 mol% catalyst, 25 °C), ⁰[diethyl diallylmalonate] = 0.15 M; (e) Schematic views of MCF-supported catalysts of two different loading densities.

Envisaged by the results from the circulating flow reaction systems, we investigated the effects of the immobilized alkoxybenzylidene ligands in a batch reaction system. Likewise the packed ligand bed in the circulating system, we provided additional free alkoxybenzylidene ligands in two different ways. As illustrated in Fig. 4, one is a partial complexation of N-heterocyclic carbene (NHC)-ruthenium species onto the immobilized ligands (**5**). The other way is additional use of free MCF-immobilized alkoxybenzylidene ligands (**3+4**). Each catalytic system was examined and compared for the conversion rate by using the identical dose of the ruthenium catalyst. Apparently, the amounts of free ligands are also equal in both reaction systems. Both **5** and **3+4** bearing additional free ligands retarded the catalytic reaction showing significantly slower conversion of the diene substrate than the catalyst **3** (Fig. 4d). It is interesting that the catalyst **5** showed much faster conversion than the catalyst **3+4** although free alkoxybenzylidene ligands in **5** are surrounding the ruthenium complexes in a more proximity. Given the situation that the relatively large pores of MCF would not restrict the diffusion of the substrates as well as the active ruthenium species, the initiation of the catalyst **5** is more efficient than the catalyst **3**, presumably due to less steric hindrance from more precatalyst population on the support surface because the bulky NHC ligands would prevent the substrate from accessing the ruthenium of the precatalyst (Fig. 4e). According

to our kinetic studies using the supported catalysts with different catalyst loading,⁹ a catalyst with lower loading (0.12 mmol/g) showed slightly faster conversion while another one with higher loading (0.32 mmol/g) resulted in much slower conversion than the one with a typical loading (0.20 mmol/g) (see SI, Fig. S2). In the same way, capturing the active species may be hindered to some extent by the existing precatalysts on the catalyst **5**. This may explain the reason why the conversion by the catalyst **5** is faster than the catalyst **3+4**. These results clearly demonstrate that the catalyst loading density is one of key factors to consider in catalyst immobilization on two dimensional silica surface. In addition, the conversion by **3** in the batch reaction system was slightly slower than that in the circulation flow reaction system (Fig. 2d and 4d).¹⁰ The longer residual time of the active species in the reaction medium might result in faster conversion in the circulating flow reaction system.

To investigate whether the additional alkoxybenzylidene ligands in a batch reaction can reduce the leaching of ruthenium, 1 mol% each of the catalysts **3** and **5** ([diene] = 0.15 M) was compared in a typical RCM reaction at 50 °C. Upon completion (30 min for **3**, 90 min for **5**), the amount of Ru leached into the resulting product solution measured by ICP-MS was 1.0 % by **3** and 0.8 % by **5**, respectively. It is noteworthy that the catalyst **3+4** resulted in the lowest amount of Ru leaching (0.6 %). When 2 mol% of the catalyst **3** were used for the RCM reaction ([diene] = 0.15 M) at 25 °C, the amount of Ru leaching was 2.0 %. This leaching amount is significantly smaller than that in the corresponding circulating flow reactor (10.2 %), which again proves that the alkoxybenzylidene ligand acts as inhibitor as well as stabilizer in the dynamic release-return reaction pathway. Although Hoveyda-Grubbs-type precatalysts are relatively stable, the released active ruthenium species are highly unstable and vulnerable to such decomposition and leaching. Under strictly inert atmosphere, a batch reaction resulted in much lower Ru leaching than a corresponding circulating flow reaction presumably due to the dominant dynamic release-return pathway along with a more efficient emission of ethylene in the batch system.

Plenio *et al.* observed an incomplete activation of the initial precatalyst complex during the metathesis reaction.⁵ Realizing that such an issue needs to be addressed with our MCF-supported catalysts, we quickly studied how the activation of the immobilized ruthenium catalysts is affected in the presence of a known ruthenium scavenger. Dimercaptotriazine (DMT) was selected¹¹ as such an agent and readily immobilized on MCF. Apparently, the strong heterogeneous scavenger quickly quenched the RCM reaction catalysed by the homogeneous metathesis catalyst. It was then provided in an excess amount to a reaction mixture catalysed by **3** and the conversion was monitored with diethyl diallylmalonate as substrate at 25 °C. As expected, the conversion of the substrate was sluggish and reached the maximum at 30 per cent in approximately 30 h (see SI, Fig. S3). With an obvious presumption that a majority of the immobilized DMT exists on the inner space of the porous MCF microparticles upon immobilization, the ruthenium species are segregated from the bulky reaction medium without any direct cross interactions between the immobilized catalysts and scavenger during the RCM process. Once the ruthenium species on MCF are activated and released to the reaction medium, the conversion rate is expected to become low because the released active species can now be quickly captured by DMT on the inner surface of MCF, which leads to loss of catalytic activity. Some of the activated species might be captured by the supported free ligands to revive the precatalysts. If the initiation of the supported ruthenium complex is considerably slow, the substrate would continue to be converted to the product for a longer period of time. These results imply that the initiation of the

second generation Hoveyda-Grubbs-type catalyst immobilized on MCF is slow by the substrate at 25 °C. That should be the main reason why many researches were focused on enhancing the catalyst activation by modifying the alkoxybenzylidene ligand. Such an enhancement can, however, lead to fast catalyst decomposition.

In conclusion, our experimental results present several interesting insights in RCM by a Hoveyda-Grubbs-type catalyst supported on silica through immobilization of the alkoxybenzylidene ligand. First, the reaction is governed mainly by the return and release of the active ruthenium species to and from the alkoxybenzylidene ligands. Second, the alkoxybenzylidene ligand acts as an inhibitor as well as a stabilizer. The circulating flow system causes more catalyst decomposition due to longer residual time of the active species in the reaction medium. This may explain the faster conversion by the circulating flow system than the batch system. Third, the catalyst activation proceeds in a slow fashion. One of the relevant factors can be the fast regeneration of the precatalysts via the release-return reaction pathway. Fourth, the presence of additional free alkoxybenzylidene ligands leads to slower reaction and less catalyst decomposition/leaching. Lastly, the loading level of the catalyst affects the initiation due to steric hindrance from the bulky NHC ligand. Our results clearly demonstrate that the catalyst recycling is affected by the dynamic release-return reaction pathway as well as incomplete catalyst initiation. The decrease of catalytic activity upon recyclings is caused by the catalyst decomposition/leaching as well as the subsequent regeneration of free alkoxybenzylidene ligands. The alkoxybenzylidene ligand plays the key role in reducing the catalyst decomposition by capturing and stabilizing the active ruthenium species. Therefore, linking the alkoxybenzylidene ligand covalently to a support material is a viable and efficient approach in terms of immobilization, regeneration, and recycles of these versatile catalysts. We suggest that the silica-supported metathesis catalysts can be further improved by controlling the loading density of catalysts and ligands with a precise balance between reactivity and recyclability in pursuit of the least decomposition. A certain level of catalyst decomposition is, however, still unavoidable in the use of these sort of heterogeneous catalysts. Decomposition via unstable reactive species is found also unavoidable in the case of covalent linkage of the NHC ligand for immobilization.¹²

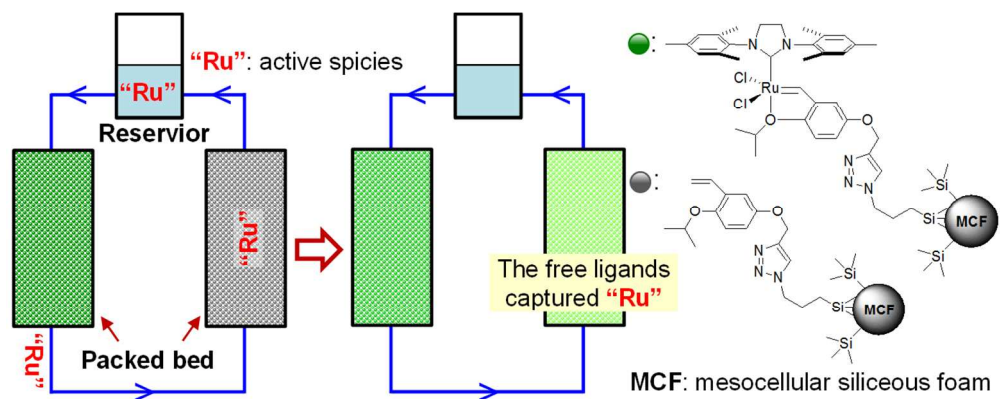
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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental procedures, additional kinetic data, CP-MAS NMR spectra. See DOI: 10.1039/c000000x/xxx

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