DOI: 10.1002/adsc.200600442

Mesocellular Foam-Supported Catalysts: Enhanced Activity and Recyclability for Ring-Closing Metathesis

Jaehong Lim,[a] Su Seong Lee,[a] Siti Nurhanna Riduan,[a] and Jackie Y. Ying[a,*]

[a] Institute of Bioengineering and Nanotechnology, 31 Biopolis Way, The Nanos, Singapore 138669
Fax: (+65)-6478-9020; e-mail: jyying@ibn.a-star.edu.sg

Received: August 28, 2006

Supporting information for this article is available on the WWW under http://asc.wiley-vch.de/home/.

Abstract: Although ring-closing metathesis (RCM) has been one of the most powerful methodologies for creating cyclic compounds, the pharmaceutical industry has not yet widely adopted this process commercially due to the high costs and leaching problems of homogeneous ruthenium catalysts. To circumvent these problems, we have immobilized the second-generation Hoveyda–Grubbs catalyst effectively onto siliceous mesocellular foam (MCF). The open and interconnected pores of MCF facilitated ligand immobilization and substrate diffusion. We have observed that the ligand and metal loadings significantly affected the catalytic activity and recyclability. Enhanced recyclability by suppression of ruthenium leaching was achieved by using excess immobilized ligands. The resulting novel heterogenized catalysts demonstrated excellent activity and reusability for the RCM of various types of substrates.

Keywords: heterogenized catalysts; immobilization; recyclability; ring-closing metathesis; siliceous mesocellular foam

Introduction

Ring-closing metathesis (RCM)[1] has played a key role in the generation of cyclic motifs since Grubbs and co-workers reported the seminal discovery of well-defined and highly active ruthenium catalysts.[2] Many academic research groups have utilized the versatile process for the synthesis of various heterocyclic and macrocyclic compounds as well as biologically active natural products.[3] A great deal of industrial interest has been placed on the production of polymers by ring-opening metathesis polymerization (ROMP).[4] Nevertheless, the pharmaceutical industry[5] has not yet widely adopted RCM in large-scale manufacturing,[6] due largely to the high costs of the ruthenium-containing catalysts, and the significant metal leaching problem.[7] Although the first- and second-generation[8] Grubbs' catalysts **1** (Figure 1) were modified to improve their stability and reusability,[9] Hoveyda and co-workers observed significant activity loss in repeated runs.[9b] In addition, the process was complicated by the need for purification by column chromatography.[9b]

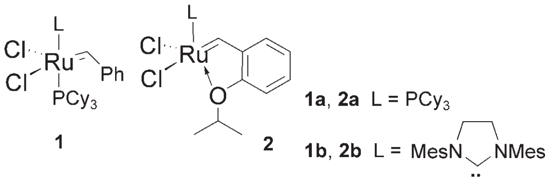


Figure 1. Structures of the ruthenium catalysts.

In an attempt to overcome these drawbacks, several research groups reported immobilization methods using soluble[10] and insoluble[11] polymers, monolithic gels,[12] ionic liquids,[13] fluorous materials,[14] supercritical fluids,[15] and silica.[16] Despite their improved reusability, these supported catalysts suffered from shortcomings such as low reactivity due to diffusion-related issues, reduced activity upon reuse, and the requirement for further purification, etc.[12] Among the previous reports, the commercially available glass-type[12] and one-pot functionalized monolith[17] by ROMP appeared to be complicated to fabricate, despite the advantage of high-throughput synthesis for use in combinatorial chemistry.[17c] A recent report on a silica gel-supported metathesis catalyst was noted for its facile synthesis, mild reaction conditions, high turnover number and ease of purification.[18] Unfortunately, the catalyst suffered from low recyclability even for a reaction involving a simple substrate. Only 68% yield was achieved in three runs, which could result from the inefficient loading and instability of the immobilized Grubbs' catalyst. The bis-silylated Hoveyda-type ligands were recently reported to allow for ease of preparation, and good activity towards diene and enyne substrates.[19] Elias and co-workers compared the performance of the supported catalysts generated by co-polymerization and by grafting methods, in conjunction with the issue of postcapping by trimethylsilyl (TMS) groups. However, these heterogenized catalysts fell short of achieving good recyclability in up to five runs.[19] Another study by Bannwarth and co-workers also illustrated the effect of support materials.[15b] From these previous studies, it is obvious that the activity and recyclability of the heterogenized Hoveyda–Grubbs catalysts depend considerably upon the physical and chemical properties of the support material. Other important factors may include the type of linker group and the reaction conditions, such as temperature and substrate concentration.

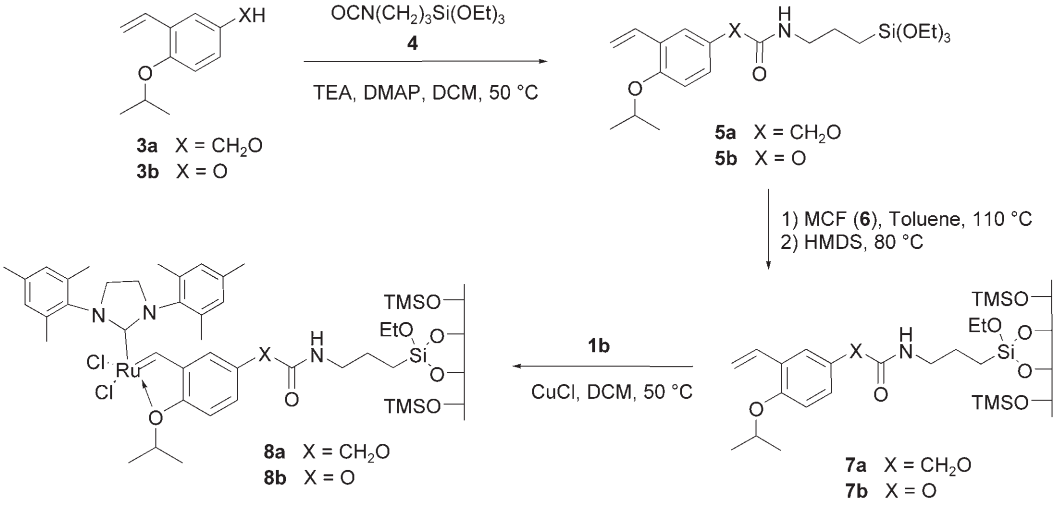
In this article, we present the synthesis and application of immobilized second-generation Hoveyda–Grubbs catalysts using siliceous mesocellular foam (MCF) as the solid support. The physical and chemical robustness of MCF allowed this catalyst to be easily handled at the laboratory scale, and to be scaled up potentially for manufacturing. Moreover, the three-dimensional pore structure of MCF with ultralarge cell-like pores (24–42 nm) interconnected by windows (9–22 nm) should be suitable for reactions involving large substrates.[20] The resulting heterogenized catalysts were easily recycled for reuse, which would be of great benefit both economically and environmentally.

Results and Discussion

Preparation of Catalysts

The synthesis of the heterogenized catalysts **8** is illustrated in Scheme 1. Hydroxy groups were introduced to link the isopropoxystyrene ligand onto the surface of the MCF support. Starting with the commercially available 3-bromo-4-hydroxybenzaldehyde and 2,5-dihydroxybenzaldehyde, the alcohol **3a** and phenol **3b** were readily prepared, respectively, by known procedures.[10,12] These unstable intermediates were immediately reacted with the isocyanate **4** to generate the carbamates **5**, which were used without further purification.[21]

Monodisperse, spherical MCF microparticles were freshly prepared by a novel synthesis scheme.[22] They were used either directly or subjected to partial precapping by treatment with hexamethyldisilazane (HMDS) in toluene. The benefit of precapping with TMS groups has been well demonstrated in other catalytic systems,[22] presumably by facilitating the uniform immobilization and high dispersion of ligands. The hygroscopic nature of bare (uncapped) and partially TMS-precapped MCF **6** necessitated a thorough drying under vacuum at elevated temperatures prior to the immobilization process. Carbamate **5** was smoothly incorporated onto the surface of **6** in refluxing toluene for 24 h. The ligand loading was determined by controlling the ratio of **5** to **6**.[23] The remaining silanol groups were also capped with TMS groups by treatment with HMDS under vapor-phase conditions.[22] This postcapping might play an important role in minimizing undesired catalyst interactions with the hydrophilic surface of MCF. The overall yields from **3** were excellent (>88% in three steps), and the Fourier-transform infrared (FT-IR) and cross-



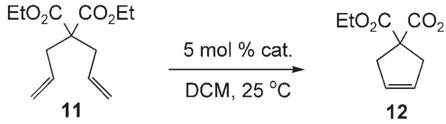
Scheme 1. Synthesis of the heterogenized ruthenium catalysts **8**.

Table 1. Loadings of TMS, ligands and ruthenium in **8**.

Entry	Catalyst	TMS in **6**[a] [mmol g^{-1}]	Ligand in **7**[b] [mmol g^{-1}]	Ru in **8**[c] [mmol g^{-1}]	Ru/ligand ratio
1	**8a1**	0.8	0.22	0.18[d]	0.91
2	**8a2**	0.6	0.36	0.21	0.64
3	**8a3**	-	0.74	0.14	0.20
4	**8b1**	0.4	0.44	0.17	0.42
5	**8b2**	0.6	0.24	0.13	0.57

[a] Determined by the initial amount of HMDS, and confirmed by elemental analysis.
[b] Determined by elemental analysis.
[c] Determined by the weight gain in the product, and confirmed by elemental analysis, except for entry 1.
[d] Determined by the weight gain in the product.

Table 2. The activity of **8** in the RCM of diene **11** in DCM.



Entry	Catalyst	Substrate concentration [M]	Conversion [%][a]			
			0.5 h	1 h	1.5 h	2 h
1	**8a1**	0.05	78	96	>99	-
2		0.10	89	>99	-	-
3	**8a2**	0.05	60	91	>99	-
4		0.10	89	>99	-	-
5	**8a3**	0.05	26	44	56	63
6		0.10	58	85	96	>99
7	**8b1**	0.05	81	97	>99	-
8		0.10	89	>99	-	-
9	**8b2**	0.05	79	97	99	>99
10		0.10	89	>99	-	-
11	**10**	0.05	95	>99	-	-
12	**2b**	0.05	98	>99	-	-

[a] Determined by gas chromatography (GC).

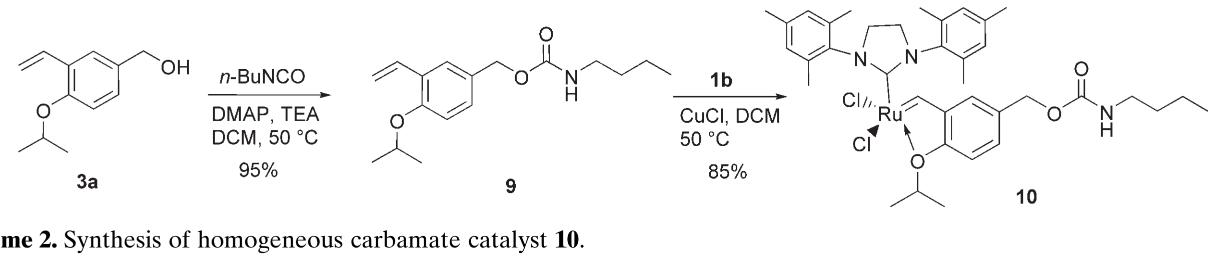
polarization magic angle spinning nuclear magnetic resonance (CP-MAS NMR) ^{13}C and ^{29}Si spectra of **7** indicated the formation of well-dispersed Hoveyda-type ligands on the surface of MCF. The heterogenized catalysts **8** were isolated in good yields by refluxing **1b** and **7** in dichloromethane (DCM) in the presence of copper(I) chloride,[24] followed by filtration, washing, and drying. The ligand was smoothly exchanged to achieve partial to full loading of ruthenium, which caused the material to turn green in color.

Table 1 shows the loadings of TMS, ligands and metal in **6**, **7**, and **8**, respectively. It appeared that the ruthenium loading was saturated at *ca.* 0.2 mmol g^{-1} with the increased steric encumbrance between neighboring ligands. To our knowledge, 0.21 mmol g^{-1} in **8a2** represents the highest density of ruthenium on silica reported thus far. The ultralarge pore size, high surface area and high porosity of the MCF might account for this efficient incorporation of ruthenium. The uniform and effective grafting of the ligand might also contribute to this high level of loading. Catalysts **8** were found to be highly stable, and could be stored for more than several months without any decrease in activity.[25]

To examine the effect of the use of carbamate group in the linker, homogeneous catalyst **10** was prepared in good yield from alcohol **3a** and *n*-butyl isocyanate in the same manner as **8a** *via* the ligand **9** (Scheme 2). The derivative of the Hoveyda–Grubbs catalyst (**10**) maintained good stability in a series of manipulations, such as column chromatography on silica gel and recrystallization in organic solvents.[9a]

Activity and Stability of Catalysts

Heterogenized catalysts **8** were tested for RCM by using diethyl diallylmalonate **11** as the benchmark substrate (Table 2). The diene **11** was smoothly transformed into the cyclized product **12** by using 5 mol% of **8** in DCM at ambient temperature. It was found that the reaction rates were influenced by the ruthenium/ligand ratio in **8a**, while the effect of ruthenium density was rather negligible. The conversion rates decreased when the ruthenium/ligand ratio was reduced. Most notably, **8a3**, which has excess ligand loading *vs.* ruthenium loading, showed significantly lower reaction rates (entries 5 and 6). The abundance of free ligands might have increased the probability of the reactive ruthenium carbene species to return to the solid phase for stabilization,[9a] which slowed down the progress of the reaction as a consequence. This tendency could be exploited to enhance the catalyst



Scheme 2. Synthesis of homogeneous carbamate catalyst **10**.

recyclability, which is discussed below. The reduced reaction rates could be overcome by employing a higher substrate concentration. The reaction was apparently accelerated at a substrate concentration of 0.10 M in all cases, without forming significant side-products, as indicated by NMR spectroscopy. The reaction was completed in 2 h even with the least efficient catalyst, **8a3** (entry 6). It is interesting that the initial reaction rates were higher with catalysts **8b** (entries 7 and 9), despite their lower ruthenium/ligand ratios compared to **8a1** and **8a2**. It is well known that the substituents of the benzylidene ligand have a strong impact on the reaction rates,[26] and the direct placement of the carbamate moiety seemed to enhance the reaction rate in this case. We note that a catalyst loading of less than 5 mol% was sufficient for the RCM reaction. One example showed the complete transformation of **11** to **12** in 2 h over 2.5 mol% of **8a2** at room temperature. When 1 mol% of **8b2** was used, full conversion was achieved in 7 h at 50 °C in DCM.

Homogeneous catalyst **10** appeared comparable to the commercially available **2b** in reaction rates (entries 11 and 12). This showed that the carbamate moiety in the linker did not significantly affect the catalytic activity.[27] Although the reaction rates were compromised when the catalysts were immobilized on a solid support, high catalytic activities were still observed in some of the heterogenized catalysts **8**, justifying further investigations.

Table 3. The activity of **8** in the RCM[a] of **11** in toluene.

Entry	Catalyst	Concentration [M]	Conversion [%][b]			
			0.5 h	1 h	1.5 h	2 h
1	**8a1**	0.10	96	>99	-	-
2	**8a2**	0.10	94	97	>99	-
3	**8b1**	0.10	89	>99	-	-
4	**8b2**	0.10	88	>99	-	-
5	**10**	0.05	85	94	97	>99
6	**2b**	0.05	99	>99	-	-

[a] All reactions were performed over 5 mol% of catalyst at 25 °C.

[b] Determined by GC.

Initial reaction rates of catalysts **8a** were found to be higher when toluene was employed as a solvent (Table 3) instead of DCM. In contrast, homogeneous catalyst **10** was less reactive in toluene (Table 3, entry 5) than in DCM (Table 2, entry 11).

To assess the thermal stability of catalysts **8**, catalyst **8b2** was heated in toluene at a concentration of 2.5 mM at 80 °C for 24 h before testing for catalytic activity. Under the same reaction conditions as in Table 3, the conversion rate for **11** was decreased by only 5%, compared to a freshly prepared solution of **8b2** in toluene. These results were also consistent with the observation of Hoveyda and co-workers that the decomposition of **2b** was almost negligible upon exposure to 80 °C in toluene for 12 h.[25] Overall, catalysts **8** demonstrated good activity and stability for further reusability studies.

Recyclability

The recyclability of **8** in the RCM of diene **11** was evaluated in DCM and toluene at ambient temperature (Table 4). The reaction time was kept constant for all runs to monitor the variation in catalytic activity. Good conversions (≥90%) were obtained for up to 5 runs in DCM, while substantial loss in activity was noted after the first 2 runs in toluene. However, the subsequent loss of activity in toluene was minor so that *ca.* 80% conversion was still achieved in the 10th run. Compounds **8a1** and **8b1** exhibited similar recyclabilities at ambient temperature, suggesting that the substituent at the 4-position of the styrene ligand did not strongly impact the deactivation of catalytic species.

The gradual loss of activity might be attributed to the deactivation of the ruthenium-carbene complex in the solution phase. The stabilization of the reactive species by the ligands in the solid phase should be crucial towards retaining the catalytic activity.[28] The deactivated ruthenium complex could be leached out at the end of the reaction. Moreover, with the de-

Table 4. Recyclability of **8** in the RCM[a] of diene **11**.

Entry	Catalyst	Solvent	Conversion in each run [%][b]				
			Run 1	Run 3	Run 5	Run 7	Run 10
1	**8a1**	DCM	>99	97	94	85	79
2		Toluene	99	80	85	86	79
3	**8b1**	DCM	>99	98	90	85	77
4		Toluene	95	78	87	87	81

[a] All reactions were performed over 5 mol% of catalyst for 2 h at 0.05 M at 25 °C.

[b] Determined by GC.

creased ruthenium/ligand ratio due to metal leaching, conversion rates in RCM would be lowered in the subsequent runs. Despite the reduced activity, complete conversions were attained with prolonged reaction times (i.e., with an additional 1–2 h) in the 10th run in all cases. Catalysts **8** demonstrated superior recyclability under mild conditions, compared to previously reported systems under similar conditions[18,19] (e.g., silica-supported catalysts at ambient reaction temperature).

RCM of Various Dienes

The heterogenized catalysts were investigated for the RCM of various dienes (Table 5). For each reaction, the reaction time was determined in the first run for a near-complete conversion of the specific substrate, and was kept constant for the subsequent runs to monitor any decrease in catalytic activity. RCM of the nitrogen-containing diene **13** over 5 mol% of **8a1** produced the five-membered ring **14** in excellent yield for consecutive runs (entry 1), demonstrating a comparable reaction rate as in the case of **11**. Although the recyclability decreased over 7 runs, the full conversion could still be achieved by increasing the reaction time. Formation of the seven-membered ring **16** was also efficient, with excellent activity retained over 7 runs (entry 2).[29] As the results in entry 3 indicated, RCM involving the 1,1-disubstituted alkene of an α,β-unsaturated carbonyl substrate was especially effective with **8b1** as the catalyst. The reaction efficiency appeared similar in the case of an internal olefin **19** (entry 4), but the recyclability was lower than in the case of the corresponding terminal olefin, presumably because the product inhibition became greater due to the increased solubility of propene evolved in DCM. The reaction involving a 1,1-disubstituted olefin (**21**) proceeded more slowly for the synthesis of a trisubstituted cyclic alkene, and the activity was found to decrease over consecutive runs (entry 5). Formation of a tetrasubstituted cyclic alkene has been the most challenging target both in homogeneous and heterogeneous catalysis.[19] Surprisingly, our catalyst **8b2** was highly efficient, completing the RCM of **23** essentially in 20 h at 80 °C in toluene (entry 6). This catalyst also retained some activity in the second run.

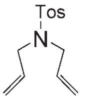
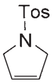
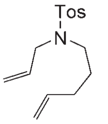
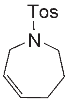
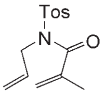
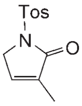
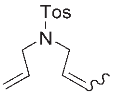
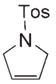
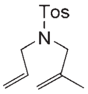
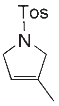
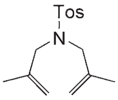
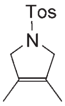
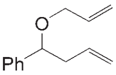
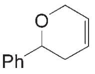
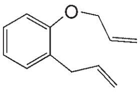
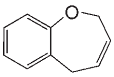
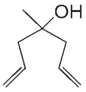
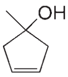
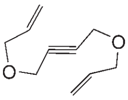
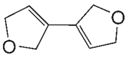
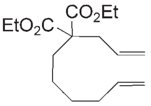
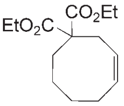
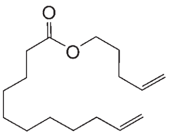
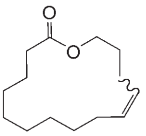
For oxygen-containing dienes, such as **25** and **27**, remarkably high conversions were achieved in 1 h for all 5 runs for the ether substrate **25** over catalyst **8b1** (entry 7), while a slightly lower recyclability was attained over catalyst **8a1** for the RCM of **27** (entry 8). Guillemin and co-workers observed the poor recyclability associated with catalyst decomposition and leaching due to the coordinating ability of oxygen to ruthenium.[13a] Catalyst **8a1** showed a significant loss in activity over consecutive runs for the RCM of a substrate containing free alcohol (**29**), and the activity was completely lost in 5 runs (entry 9). This could be attributed to the leaching problems associated with the strong affinity of hydroxy groups to the Grubbs' ruthenium catalysts,[30] despite the relatively high compatibility to polar protic moieties.[31] It is noteworthy that Grubbs and co-workers recently reported PEG-modified, water-soluble catalysts for metathesis reactions, which exhibited good compatibility and activity in water.[32]

The enyne substrate **31** produced a monocyclic compound, which was not further transformed to the desired bicyclic product **32** even with a prolonged reaction time (entry 10). This lack of selectivity was consistent with the finding of Grela and co-workers that the formation of the six-membered monocyclic compound was unavoidable over the second-generation Grubbs catalyst.[33] Thus, recyclability studies were not pursued for this particular reaction. With the growing importance of macrocyclic compounds in the pharmaceutical industry,[34] the formation of eight-membered ring **34** and macrocycle **36** was examined over heterogenized catalyst **8a2** at 50 °C (entries 11 and 12). The reactions proceeded successfully in both cases, although the conversions decreased over consecutive runs.

Enhanced Recyclability

As mentioned earlier in this article, the recyclability of the catalysts might be improved with the presence of excess free ligands. Assuming that the return of the reactive catalytic species to the MCF-supported isopropoxystyrene ligand would be crucial towards retaining the catalytic activity, additional free ligands were introduced into the system. This strategy was accomplished (i) by using catalyst **8a3** with a very high ligand loading and a partial ruthenium loading (see Table 1), or (ii) by adding MCF-supported free ligands **7a1** to catalyst **8a2**. In both cases the catalyst recyclability was dramatically enhanced over 10 runs, compared with the results over catalyst **8a2** (Table 6). The solid mixture of **8a2** and **7a1** microparticles also improved the catalyst recyclability over 10 runs (entry 3), giving a similar effect as **8a3** (entry 2) over consecutive runs by providing excess ligands for the return and stabilization of the reactive catalytic species. Although the reaction was retarded with the introduction of additional free ligands, this approach successfully increased the catalyst recyclability, and the reaction rate could be compensated by using a higher substrate concentration of 0.10 M. To the best of our knowledge, this is the first report of using excess free ligands to improve the recyclability of a heterogenized catalyst.

Table 5. Recyclability of **8** in the RCM[a] of various dienes.

Entry	Run no.	Substrate	Product	Time [h]	Conversion[b] (Yield[c]) [%]
1	1	**13** 	**14** 	1.5	>99 (97)
	3			1.5	97 (95)
	5			1.5	92 (91)
	7			1.5	84
				6	>99 (97)
2	1	**15** 	**16** 	1.5	94 (93)
	3			1.5	93 (91)
	5			1.5	91 (90)
	7			1.5	91 (90)
3[d]	1	**17** 	**18** 	2	96 (93)
	3			2	96 (94)
	5			2	98 (95)
	7			2	92 (90)
4	1	**19** 	**20** 	1.5	>99 (97)
	3			1.5	98 (96)
	5			1.5	86 (81)
	7			1.5	55
				3	95 (91)
5	1	**21** 	**22** 	4.5	96 (92)
	3			4.5	91 (88)
	5			4.5	76 (71)
	7			4.5	53
				24	98 (92)
6[e]	1	**23** 	**24** 	20	96 (95)
	2			20	31
7[d]	1	**25** 	**26** 	1	>99 (97)
	3			1	99 (97)
	5			1	98 (96)
	7			1	97 (94)
8	1	**27** 	**28** 	1.5	94
	3			1.5	91
	5			1.5	88
	7			1.5	86
9	1	**29** 	**30** 	1.5	84
	3			1.5	23
	5			1.5	2
10	1	**31** 	**32** 	24	67[f]
11[g]	1	**33** 	**34** 	2	84
	2			2	69
	3			2	61
12[g]	1	**35** 	**36** 	2.5	94[h]
	2			2.5	88[h]
	3			2.5	83[h]

---

[a] Unless otherwise noted, all reactions were performed over 5 mol% of **8a1** at 25°C at a substrate concentration of 0.05 M in DCM.

[b] Determined by gas chromatography (GC) or liquid chromatography (LC), unless otherwise specified.

[c] Isolated yield by column chromatography on silica gel.

[d] Performed over 5 mol% of **8b1**.

[e] Performed over 5 mol% of **8b2** at 80°C in toluene.

[f] Formation of the monocyclic compound was also observed (27% conversion in GC).

[g] Performed over 5 mol% of **8a2** at 50°C.

[h] Determined by ^{1}H NMR spectroscopy (400 MHz).

Table 6. Enhanced recyclability of **8** in the RCM[a] of diene **11** in DCM.

Entry	Catalyst	Time [h]	Conversion in each run [%][b]				
			Run 1	Run 3	Run 5	Run 7	Run 10
1	**8a2**	1	>99	98	90	84	77
2	**8a3**	2	99	99	98	94	91
3	**8a2+7a1**[c]	2	98	98	97	91	90
4	**8a2**[d]	0.5	>99	98	97	95	93

[a] Unless otherwise noted, all reactions were performed in DCM over 5 mol% of **8a** at 25 °C at a substrate concentration of 0.10 M in DCM.

[b] Determined by GC.

[c] Performed in the presence of 5 mol% of **7a1**.

[d] Performed at 50 °C at a substrate concentration of 0.05 M in DCM.

Table 7. Ruthenium leaching in the RCM[a] of diene **25** over **8a2**.[b]

Entry	**7a1** [mol%]	Temperature [°C]	Time [h]	Ru in each run [ppm][c]		
				Run 1	Run 3	Run 5
1	-	25	1	35	30	20
2	5	25	2	23	18	15
3	-	50	0.5	13	9	7
4	5	50	1	10	9	9

[a] All reactions were performed over 5 mol% of **8a2** at 0.05 M in DCM.

[b] Conversions (determined by GC) were above 98% in all runs.

[c] Determined by ICP-MS.

It is noteworthy that the recyclability was substantially improved at an elevated temperature (entry 4). The elevated temperature greatly shortened the reaction time and might have facilitated the removal of ethylene generated *in situ* to drive the reaction equilibrium forward, so that the reactive metal carbene species were less vulnerable to deactivation and leaching.

Ruthenium Leaching

Since metal contaminants significantly limit the application of RCM in industrial processes, several approaches have been reported on the removal of ruthenium residues from the final product of homogeneous catalysis.[35] Nevertheless, the application of solid-supported RCM has distinct advantages over the conventional homogeneous catalysis, as demonstrated in previous reports.[36] In this work, the effect of ruthenium leaching on the recyclability of the heterogenized catalyst was examined. In particular, the ether-containing diene **25** was investigated due to the coordinating ability of oxygen to ruthenium. The RCM of **25** over **8a2** was efficient enough to reach conversions above 98% in all runs (Table 7). In the presence of 5 mol% of MCF-supported free ligand **7a1**, the ruthenium concentration in the supernatant, as measured by inductively coupled plasma-mass spectroscopy (ICP-MS) at the end of each run, was substantially reduced despite the longer reaction time (entry 2). While the suppression of ruthenium leaching by additional free ligand was more apparent in reactions run at room temperature, leaching was also reduced at elevated temperature and for shorter reaction periods (entries 3 and 4). This observation agreed with our finding that the recyclability was higher under refluxing DCM (Table 6, entry 3). Table 7 confirmed that the catalyst recyclability could be enhanced by the use of additional MCF-supported free ligands and elevated reaction temperature, through suppressing ruthenium leaching during the course of reaction.

Ruthenium leaching from **8a2** was also measured in the RCM of **11** over 10 runs. On average only 4 ppm of ruthenium were leached in each run. This level of ruthenium leaching was considerably lower than that reported in previous studies.[37]

Conclusions

We have successfully developed MCF-supported Hoveyda–Grubbs catalysts for RCM. These novel heterogenized catalysts demonstrated excellent activity and recyclability under mild reaction conditions. The ultralarge pores and high surface area of MCF allowed the ligands and catalytic complexes to be immobilized without steric hindrance, and facilitated the diffusion of bulky substrates during reaction. Partial precapping of silanol groups with TMS groups promoted the uniform dispersion of ligands and catalytic complexes on the surface of the siliceous support. Postcapping of the residual silanol groups with TMS groups minimized any undesired interactions between the siliceous support and the catalytic species. The high efficiency of the heterogenized catalyst was attributed to the well-defined structure of **8** obtained *via* a facile synthetic pathway. Although the gradual loss of activity was unavoidable in multiple recycling runs over Hoveyda–Grubbs catalysts, the reusability of the heterogenized catalyst was significantly enhanced by introducing additional MCF-supported free ligands. The stable, versatile catalysts presented herein successfully catalyzed a wide variety of diene substrates. In conjunction with the remarkably low leaching of ruthenium to the reaction mixture, this cost-effective and environmentally benign catalytic process may be potentially employed in continuous reactor applications.[38]

Experimental Section

General Remarks

FT-IR spectra were recorded on a Digilab FTS 7000 FTIR spectrometer equipped with an MTEC-300 photoacoustic detector. Solution NMR spectra were recorded on a Bruker spectrometer (400 MHz for ^{1}H and 100 MHz for ^{13}C) at ambient temperature in the solvents indicated, and referenced to the solvent peaks. ^{13}C and ^{29}Si CP-MAS NMR spectra of the immobilized catalysts were recorded on a 400 MHz Bruker spectrometer. Samples were packed into 4 mm ZrO_2 rotors and spun at 5 kHz. The spinning sideband suppression method was used for ^{13}C CP-MAS NMR. Elemental analyses were performed with a CE440 CHN Analyzer (Exeter Analytical). ICP-MS data were obtained by use of an Elan DRC II, Perkin Elmer SCIEX, USA. Mass spectra were obtained at the Elemental Analysis Laboratory, Department of Chemistry, National University of Singapore, Singapore. Conversions for RCM of dienes were determined by GC (Agilent 6890N) and LC (Agilent 1100 series), unless otherwise noted. ^{1}H NMR spectroscopy was used to monitor the conversion of **35**. Isolated yields were determined after purification by column chromatography on silica gel (Merck). Unless otherwise noted, reactions were carried out using standard Schlenk techniques. All chemicals were purchased from Aldrich, except for 3-isocyanatopropyltriethoxysilane (Gelest). Solvents were either purified by passage through a column of activated alumina or purchased in sealed bottles from Aldrich.

Carbamates 5

A Schlenk flask was charged with alcohol **3a** (1.60 g, 8.35 mmol), 3-isocyanatopropyltriethoxysilane (**4**) (1.98 mL, 8.09 mmol), 4-dimethylaminopyridine (12 mg, 0.10 mmol), triethylamine (2.79 mL, 20.0 mmol), and anhydrous DCM (10 mL) under argon. The reaction mixture was heated for 48 h under reflux. DCM and triethylamine were removed under reduced pressure. Hexane (10 mL) was added, and the precipitate was removed by filtration. The filtrate was concentrated under reduced pressure, and dried under vacuum to give the carbamate **5a** as a colorless oil, which was used without further purification; yield: 3.63 g (99%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=0.64$ (t, 2H, $J=8.0$ Hz), 1.24 (t, 9H, $J=7.2$ Hz), 1.35 (d, 6H, $J=6.0$ Hz), 1.62 (m, 2H), 3.19 (m, 2H), 3.82 (q, 6H, $J=7.2$ Hz), 4.54 (septet, 1H, $J=6.0$ Hz), 5.01 (bs, 1H), 5.03 (s, 2H), 5.25 (dd, 1H, $J=11.2$, 1.4 Hz), 5.75 (dd, 1H, $J=17.6$, 1.4 Hz), 6.86 (d, 1H, $J=8.4$ Hz), 7.04 (dd, 1H, $J=17.6$, 11.2 Hz), 7.22 (dd, 1H, $J=8.4$, 2.2 Hz), 7.48 (d, 1H, $J=2.2$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=7.6$, 18.3, 22.1, 23.3, 43.4, 58.4, 66.4, 70.9, 106.6, 114.0, 114.3, 126.9, 128.6, 129.0, 131.7, 155.1, 156.5; MS (FAB): *m/z* (%)=438 (38) $[M-H]^-$, 392 (20) $[(M-EtOH)-H]^-$, 364 (16), 297 (5), 264 (18), 220 (89), 174 (100); HR-MS (FAB): *m/z*=438.2328, calcd. for $C_{22}H_{36}NO_6Si$: 438.2331.

The general procedure using **3b** (752 mg, 4.22 mmol) gave carbamate **5b** as a colorless oil, which was used without further purification; yield: 1.77 g (99%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=0.68$ (t, 2H, $J=8.0$ Hz), 1.24 (t, 9H, $J=7.2$ Hz), 1.33 (d, 6H, $J=6.0$ Hz), 1.70 (quintet, 2H, $J=8.0$ Hz), 3.26 (q, 2H, $J=8.0$ Hz), 3.83 (q, 6H, $J=7.2$ Hz), 4.46 (septet, 1H, $J=6.0$ Hz), 5.24 (dd, 1H, $J=11.2$, 1.4 Hz), 5.42 (bs, 1H), 5.69 (dd, 1H, $J=17.6$, 1.4 Hz), 6.84 (d, 1H, $J=8.8$ Hz), 6.96 (dd, 1H, $J=8.8$, 2.2 Hz), 7.02 (dd, 1H, $J=17.6$, 11.2 Hz), 7.22 (d, 1H, $J=2.2$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=7.4$, 18.7, 22.0, 22.9, 43.3, 58.3, 71.3, 114.3, 114.9, 119.0, 121.4, 128.5, 131.1, 144.4, 152.2, 154.8; MS (FAB): *m/z* (%)=426 (37) $[M^++H]$, 380 (100) $[(M-EtOH)+H]^+$, 178 (69); HR-MS (FAB): *m/z*=426.2299, calcd. for $C_{21}H_{36}NO_6Si$: 426.2306.

Immobilized Ligands 7

A Schlenk flask was charged with MCF (2.05 g), and placed under vacuum for 24 h at 120 °C. The flask was purged with argon at room temperature, and charged with anhydrous toluene (20 mL) and the corresponding triethoxysilane **5** (0.85 mmol). The resulting mixture was heated at 110 °C for 24 h. Upon cooling to room temperature, the solid was thoroughly rinsed successively by toluene, DCM, methanol, and DCM (50 mL each). The white solid was transferred to a Schlenk flask, and dried under vacuum for 12 h at 80 °C. After cooling to room temperature, HMDS (1 mL) was added to the sealed flask. The flask was placed in a liquid nitrogen bath for 10 min under vacuum. It was sealed and then kept at 80 °C for 5 h. The resulting solid was cooled to room temperature, washed thoroughly with DCM (100 mL), and then dried under vacuum for 24 h to give the corresponding immobilized ligand as a white powder.

The general procedure using the derivative of **3a** (200 mg, 0.45 mmol) and MCF (1.95 g, precapped with 0.8 mmol of TMS/g) gave **7a1** (Table 1, entry 1); yield: 2.15 g. ^{29}Si CP-MAS NMR: $\delta=-109.0$, −65.0, −57.5, −46.6, 13.2; ^{13}C CP-MAS NMR: $\delta=1.7$, 11.1, 18.5, 23.3, 25.7, 46.0, 52.0, 61.4, 68.2, 72.5, 113.6, 115.7, 130.6, 134.5, 157.9; FT-IR: $\nu=759$, 810, 842, 1085, 1494, 1715, 2904, 2962, 3090 cm^{-1}; anal. found: C 8.16, H 1.66, N 0.31; loading of ligand: 0.22 mmol g^{-1}.

The general procedure using the derivative of **3a** (184 mg, 0.42 mmol) and MCF (1.00 g, precapped with 0.6 mmol of TMS/g) gave **7a2** (Table 1, entry 2); yield: 1.13 g. FT-IR: identical to that of **7a1**; anal. found: C 10.77, H 1.91, N, 0.51; loading of ligand: 0.36 mmol g^{-1}.

The general procedure using the derivative of **3a** (967 mg, 2.20 mmol) and MCF (2.00 g, not precapped with TMS) gave **7a3** (Table 1, entry 3); yield: 2.52 g. ^{29}Si CP-MAS NMR: $\delta=-108.6$, −64.0, −60.0, −46.4, 14.0; ^{13}C CP-MAS NMR: $\delta=1.8$, 10.8, 19.2, 22.6, 37.5, 44.7, 51.6, 61.2, 68.4, 71.9, 114.9, 130.0, 133.6, 158.0, 165.8; FT-IR: identical to that of **7a1**; anal. found: C 14.15, H 2.02, N 0.95; loading of ligand: 0.74 mmol.

The general procedure using the derivative of **3b** (255 mg, 0.60 mmol) and MCF (1.17 g, precapped with 0.4 mmol of TMS/g) gave **7b1** (Table 1, entry 4); yield: 1.34 g. ^{29}Si CP-MAS NMR: $\delta=-107.7$, −99.7, −64.3, −55.8, 14.5; ^{13}C CP-MAS NMR: $\delta=1.6$, 10.7, 21.5, 24.9, 44.8, 49.9, 51.9, 53.6, 60.4, 72.0, 112.8, 115.6, 119.9, 122.6, 126.2, 130.2, 132.9, 146.8, 150.9, 153.7, 156.9; FT-IR: ν=759, 806, 846, 1083, 1484, 1753, 2851, 2904, 2962, 3090 cm^{-1}; anal. found: C 9.77, H 1.72, N 0.62; loading of ligand: 0.44 mmol g^{-1}.

The general procedure using the derivative of **3b** (681 mg, 1.60 mmol) and MCF (3.19 g, precapped with 0.6 mmol of TMS/g) gave **7b2** (Table 1, entry 5); yield: 3.48 g. FT-IR: identical to that of **7b1**; anal. found: C 8.78, H 1.80, N 0.46; loading of ligand: 0.24 mmol g^{-1}.

Immobilized Catalysts 8

A two-necked flask equipped with a reflux condenser was charged with the ligand **7a1** (1.00 g, 0.22 mmol g^{-1} of loading), the second-generation Grubbs' catalyst **1b** (186 mg, 0.22 mmol), copper chloride (22 mg, 0.22 mmol), and anhydrous DCM (10 mL) under argon. The reaction mixture was heated overnight under reflux in a stream of argon. The reaction mixture gradually changed from dark brown to deep green. After cooling to room temperature, the fine powder was washed thoroughly with DCM (100 mL) under the open atmosphere, and dried under vacuum for 24 h to give the immobilized catalyst **8a1** as a green powder (Table 1, entry 1); yield: 1.09 g (91 %, based on **7a1**). FT-IR: ν=759, 808, 847, 1085, 1487, 1720, 2739, 2903, 2961 cm^{-1}; loading of ruthenium: 0.18 mmol g^{-1} (based upon the weight gain of **8a1**).

The general procedure using **1b** (170 mg, 0.20 mmol), copper chloride (20 mg, 0.20 mmol), and the ligand **7a2** (500 mg) gave **8a2** as a green powder (Table 1, entry 2); yield: 554 mg (65 %, based on **7a2**). FT-IR: similar to that of **8a1**; anal. found: C 15.28, H 2.23, N 1.06; loading of ruthenium: 0.21 mmol g^{-1}.

The general procedure using **1b** (93 mg, 0.11 mmol), copper chloride (11 mg, 0.11 mmol), and the ligand **7a3** (500 mg) gave **8a3** as a green powder (Table 1, entry 3); yield: 546 mg (27 %, based on **7a3**). FT-IR: similar to that of **8a1**; anal. found: C 17.26, H 2.31, N 1.30; loading of ruthenium: 0.14 mmol g^{-1}.

The general procedure using **1b** (188 mg, 0.22 mmol), copper chloride (22 mg, 0.22 mmol), and the ligand **7b1** (500 mg) gave **8b1** as a green powder (Table 1, entry 4); yield: 541 mg (40 %, based on **7b1**). FT-IR: similar to that of **8a1**; anal. found: C 12.81, H 2.02, N 1.06; loading of ruthenium: 0.17 mmol g^{-1}.

The general procedure using **1b** (280 mg, 0.24 mmol), copper chloride (24 mg, 0.24 mmol), and the ligand **7b2** (1.00 g) gave **8b2** as a green powder (Table 1, entry 5); yield: 1.07 g (52 %, based on **7b2**). FT-IR: similar to that of **8a1**; anal. found: C 11.85, H 2.08, N 0.81; loading of ruthenium: 0.13 mmol g^{-1}.

Homogeneous Catalyst 10

A Schlenk flask was charged with the alcohol **3a** (192 mg, 1.00 mmol), *n*-butyl isocyanate (109 mg, 1.10 mmol), 4-dimethylaminopyridine (1 mg, 0.01 mmol), triethylamine (0.28 mL, 2.00 mmol), and anhydrous DCM (5 mL) under argon. The reaction mixture was stirred overnight at room temperature. The resulting mixture was concentrated under reduced pressure, and purified by flash column chromatography (hexane:EtOAc=4:1) to give carbamate **9** as a colorless oil; yield: 270 mg (93 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.92 (t, 3H, *J*=7.2 Hz), 1.33 (m, 2H), 1.34 (d, 6H, *J*=6.0 Hz), 1.47 (m, 2H), 3.19 (m, 2H), 4.54 (septet, 1H, *J*=6.0 Hz), 4.70 (bs, 1H), 5.02 (s, 2H), 5.25 (dd, 1H, *J*=11.2, 1.4 Hz), 5.75 (dd, 1H, *J*=17.6, 1.4 Hz), 6.86 (d, 1H, *J*=8.4 Hz), 7.04 (dd, 1H, *J*=17.6, 11.2 Hz), 7.22 (dd, 1H, *J*=8.4, 2.2 Hz), 7.48 (d, 1H, *J*=2.2 Hz).

A two-necked flask equipped with a reflux condenser was charged with ligand **9** (260 mg, 0.89 mmol), second-generation Grubbs' catalyst (680 mg, 0.80 mmol), copper chloride (97 mg, 0.98 mmol), and anhydrous DCM (10 mL) under argon. The reaction mixture was stirred overnight at room temperature in a stream of argon. The reaction mixture gradually changed from dark brown to deep green. The resulting mixture was concentrated under reduced pressure, and purified by flash column chromatography (hexane:EtOAc:DCM=4:1:1), followed by recrystallization over hexane and diethyl ether to give catalyst **10** as a green powder; yield: 560 mg (85 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.93 (t, 3H, *J*=7.2 Hz), 1.26 (d, 6H, *J*=6.0 Hz), 1.35 (m, 2H), 1.48 (m, 2H), 2.41 (s, 9H), 2.47 (s, 9H), 3.19 (m, 2H), 4.18 (s, 4H), 4.64 (bs, 1H), 4.80 (septet, 1H, *J*=6.0 Hz), 5.04 (s, 2H), 6.76 (d, 1H, *J*=8.4 Hz), 6.91 (d, 1H, *J*=2.2 Hz), 7.07 (s, 4H), 7.53 (dd, 1H, *J*=8.4, 2.2 Hz), 16.53 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.7, 15.3, 19.9, 21.0, 21.1, 25.9, 32.0, 40.8, 51.5, 65.7, 65.9, 75.3, 112.9, 122.9, 129.4, 129.8, 130.6, 138.9, 145.2, 152.1, 211.1, 296.8; anal. calcd. for $C_{37}H_{49}ClNO_3Ru$: C 58.80, H 6.53, N 5.56; found: C 58.73, H 6.64, N 5.31.

Testing of Catalytic Activity

A sintered vial equipped with a septum and a stirring bar was charged with catalyst **8a1** (280 mg, 0.050 mmol) and anhydrous DCM (20 mL). The green suspension was stirred at 25 °C under argon. Substrate **11** (0.24 mL, 1.00 mmol) was injected *via* a syringe, and a small aliquot was taken from the reaction mixture every 15 min. The conversion to product **12** at each time point was monitored by GC, after filtering the aliquot through a short pad of silica gel by elution with DCM.

LC and NMR were used for monitoring the conversion of several substrates in Table 5, as specified in the footnotes.

Testing of Catalyst Recyclability

A sintered vial equipped with a septum and a stirring bar was charged with catalyst **8a1** (280 mg, 0.050 mmol) and anhydrous DCM (20 mL). The green suspension was stirred at 25 °C under argon, and substrate **11** (0.24 mL, 1.00 mmol) was injected *via* a syringe. After a given time period known from the activity test (2 h, in this case), the supernatant was taken after centrifugation to determine the conversion by GC and the isolatied yield by flash column chromatography. The catalyst **8a1** in the vial was thoroughly rinsed with DCM (10 mL) three times prior to the next run.

Reactions were run in a similar manner for the substrates in Table 5. LC and NMR were used for monitoring the conversion of several substrates in Table 5, as specified in the footnotes.

Acknowledgements

This work is supported by the Institute of Bioengineering and Nanotechnology (Biomedical Research Council, Agency for Science, Technology and Research, Singapore).

References

[1] For selected reviews, see: a) H.-G. Schmalz, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1833; b) R. H. Grubbs, S. J. Miller, G. C. Fu, *Acc. Chem. Res.* **1995**, *28*, 446; c) M. Schuster, S. Blechert, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2036; d) A. Fürstner, *Angew. Chem. Int. Ed.* **2000**, *39*, 3012; e) A. H. Hoveyda, R. R. Schrock, *Chem. Eur. J.* **2001**, *7*, 945; f) F.-X. Felpin, J. Lebreton, *Eur. J. Org. Chem.* **2003**, 3693; g) S. T. Diver, A. J. Giessert, *Chem. Rev.* **2004**, *104*, 1317; h) A. Deiters, S. F. Martin, *Chem. Rev.* **2004**, *104*, 2199; i) M. D. McReynolds, J. M. Dougherty, P. R. Hanson, *Chem. Rev.* **2004**, *104*, 2239; j) R. H. Grubbs, *Tetrahedron* **2004**, *60*, 7117.

[2] a) P. Schwab, M. B. France, J. W. Ziller, R. H. Grubbs, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2039; b) P. Schwab, R. H. Grubbs, J. W. Ziller, *J. Am. Chem. Soc.* **1996**, *118*, 100.

[3] Besides the reviews in ref.[1], see: a) A. Fürstner, K. Langemann, *J. Org. Chem.* **1996**, *61*, 3942; b) M. Scholl, R. H. Grubbs, *Tetrahedron Lett.* **1999**, *40*, 1425; c) A. Fürstner, N. Kindler, *Tetrahedron Lett.* **1996**, *37*, 7005; d) S. D. Burke, N. Müller, C. M. Beaudry, *Org. Lett.* **1999**, *1*, 1827; e) M. T. Crimmins, K. A. Emmitte, *Org. Lett.* **1999**, *1*, 2029; f) A. B. Smith, III; S. A. Kozmin, C. M. Adams, D. V. Paone, *J. Am. Chem. Soc.* **2000**, *122*, 4984; g) H. Mizutani, M. Watanabe, T. Honda, *Tetrahedron* **2002**, *58*, 8929; h) K. R. Buszek, N. Sato, Y. Jeong, *Tetrahedron Lett.* **2002**, *43*, 181; i) Y. Matsuya, T. Kawaguchi, H. Nemoto, *Org. Lett.* **2003**, *5*, 2939; j) E. J. Kang, E. J. Cho, Y. E. Lee, M. K. Ji, D. M. Shin, Y. K. Chung, E. Lee, *J. Am. Chem. Soc.* **2004**, *126*, 2680; k) J. Chen, C. J. Forsyth, *Angew. Chem. Int. Ed.* **2004**, *43*, 2148; l) C. O. Kangani, A. M. Brückner, D. P. Curran, *Org. Lett.* **2005**, *7*, 379; m) B. Nay, N. Gaboriaud-Kolar, B. Bodo, *Tetrahedron Lett.* **2005**, *46*, 3867; n) A. Fürstner, L. Turet, *Angew. Chem. Int. Ed.* **2005**, *44*, 3462; o) J. K. Cha, O. L. Epstein, *Tetrahedron* **2006**, *62*, 1329.

[4] For selected reviews, see: a) R. H. Grubbs, W. Tumas, *Science* **1989**, *243*, 907; b) R. R. Schrock, *Acc. Chem. Res.* **1990**, *23*, 158; c) M. R. Buchmeiser, *Chem. Rev.* **2000**, *100*, 1565.

[5] For articles related to RCM in the pharmaceutical industry, see: a) P. A. Evans, J. Cui, S. J. Gharpure, A. Polosukhin, H.-R. Zhang, *J. Am. Chem. Soc.* **2003**, *125*, 14702; b) S. Lebreton, X.-S. Xie, D. Ferguson, J. K. D. Brabander, *Tetrahedron* **2004**, *60*, 9635; c) A.-M. Faucher, M. D. Bailey, P. L. Beaulieu, C. Brochu, J.-S. Duceppe, J.-M. Ferland, E. Ghiro, V. Gorys, T. Halmos, S. H. Kawai, M. Poirier, B. Simoneau, Y. S. Tsantrizos, M. Llinàs-Brunet, *Org. Lett.* **2004**, *6*, 2901.

[6] T. Nicola, M. Brenner, K. Donsbach, P. Kreye, *Org. Process Res. Dev.* **2005**, *9*, 513.

[7] Ruthenium residue levels must be less than 5 ppm and 0.5 ppm for oral and parental drug products according to the guidelines of European Agency for the Evaluation of Medicinal Products. For details, see: A. Thayer, *Chem. Eng. News* **2005**, *83*, 55.

[8] M. Schroll, S. Ding, C. W. Lee, R. H. Grubbs, *Org. Lett.* **1999**, *1*, 953.

[9] a) J. S. Kingsbury, J. P. A. Harrity, P. J. Bonitatebus, Jr., A. H. Hoveyda, *J. Am. Chem. Soc.* **1999**, *121*, 791; b) S. B. Garber, J. S. Kingsbury, B. L. Gray, A. H. Hoveyda, *J. Am. Chem. Soc.* **2000**, *122,* 8168; c) S. Gessler, S. Randl, S. Blechert, *Tetrahedron Lett.* **2000**, *41*, 9973.

[10] a) Q. Yao, *Angew. Chem. Int. Ed.* **2000**, *39*, 3896; b) Q. Yao, A. R. Motta, *Tetrahedron Lett.* **2004**, *45*, 2447.

[11] a) A. G. M. Barrett, S. M. Cramp, R. S. Roberts, *Org. Lett.* **1999**, *1*, 1083; b) S. C. Schürer, S. Gessler, N. Buschmann, S. Blechert, *Angew. Chem. Int. Ed.* **2000**, *39*, 3898; c) P. Nieczypor, W. Buchowicz, W. J. N. Meester, F. P. J. T. Rutjes, J. C. Mol, *Tetrahedron Lett.* **2001**, *42*, 7103; d) R. Akiyama, S. Kobayashi, *Angew. Chem. Int. Ed.* **2002**, *41*, 2602; e) K. Grela, M. Tryznowski, M. Bieniek, *Tetrahedron Lett.* **2002**, *43*, 9055; f) T. S. Halbach, S. Mix, D. Fischer, S. Maechling, J. O. Krause, C. Sievers, S. Blechert, O. Nuyken, M. R. Buchmeiser, *J. Org. Chem.* **2005**, *70*, 4687; g) K. Grela, U. Kunz, A. Kirschning, *Synlett* **2005**, 2948.

[12] J. S. Kingsbury, S. B. Garber, J. M. Giftos, B. L. Gray, M. M. Okamoto, R. A. Farrer, J. T. Fourkas, A. H. Hoveyda, *Angew. Chem. Int. Ed.* **2001**, *40*, 4251.

[13] a) N. Audic, H. Clavier, M. Mauduit, J.-C. Guillemin, *J. Am. Chem. Soc.* **2003**, *125*, 9248; b) Q. Yao, Y. Zhang, *Angew. Chem. Int. Ed.* **2003**, *42*, 3395; c) Q. Yao, M. Sheets, *J. Organomet. Chem.* **2005**, *690*, 3577.

[14] a) Q. Yao, Y. Zhang, *J. Am. Chem. Soc.* **2004**, *126*, 74; b) M. Matsugi, D. P. Curran, *J. Org. Chem.* **2005**, *70*, 1636.

[15] a) A. Fürstner, L. Ackermann, K. Beck, H. Hori, D. Koch, K. Langemann, M. Liebl, C. Six, W. Leitner, *J. Am. Chem. Soc.* **2001**, *123*, 9000; b) F. Michalek, D. Mädge, J. Rühe, W. Bannwarth, *Eur. J. Org. Chem.* **2006**, 577.

[16] Besides ref.[15b] see: a) K. Melis, D. D. Vos, P. Jacobs, F. Verpoort, *J. Mol. Catal. A: Chem.* **2001**, *169*, 47; b) M. Mayr, M. R. Buchmeiser, K. Wurst, *Adv. Synth. Catal.* **2002**, *344*, 712; c) S. Prühs, C. W. Lehmann, A. Fürstner, *Organometallics* **2004**, *23*, 280; d) L. Li, J.-L. Shi, *Adv. Synth. Catal.* **2005**, *347*, 1745.

[17] a) F. Sinner, M. R. Buchmeiser, *Macromolecules* **2000**, *33*, 5777; b) L. Yang, M. Mayr, K. Wurst, M. R. Buchmeiser, *Chem. Eur. J.* **2004**, *10*, 5761; c) M. Mayr, D. Wang, R. Kröll, N. Schuler, S. Prühs, A. Fürstner, M. R. Buchmeiser, *Adv. Synth. Catal.* **2005**, *347*, 484.

[18] D. Fischer, S. Blechert, *Adv. Synth. Catal.* **2005**, *347*, 1329.

[19] X. Elias, R. Pleixats, M. W. C. Man, J. J. E. Moreau, *Adv. Synth. Catal.* **2006**, *348*, 751.

[20] a) P. Schmidt-Winkel, W. W. Lukens, Jr., D. Zhao, P. Yang, B. F. Chmelka, G. D. Stucky, *J. Am. Chem. Soc.* **1999**, *121*, 254; b) P. Schmidt-Winkel, W. W. Lukens, Jr., P. Yang, D. I. Margolese, J. S. Lettow, J. Y. Ying, G. D. Stucky, *Chem. Mater.* **2000**, *12*, 686; c) J. S. Lettow, Y. J. Han, P. Schmidt-Winkel, P. Yang, D. Zhao, G. D.

Stucky, J. Y. Ying, *Langmuir* **2000**, *16*, 8291; d) J. S. Lettow, T. M. Lancaster, C. J. Glinka, J. Y. Ying, *Langmuir* **2005**, *21*, 5738; e) Y. Han, J. Y. Ying, *Angew. Chem. Int. Ed.* **2005**, *44*, 288.

[21] Most impurities were unreacted starting materials, which could be easily removed after the immobilization step. For details, see Experimental Section.

[22] S. S. Lee, S. Hadinoto, J. Y. Ying, *Adv. Synth. Catal.* **2006**, *348*, 1248.

[23] The amount of **1b** varied from 30% to 110% of the loaded ligands. For details, see Experimental Section.

[24] For the rate-enhancing effect of CuCl by making phosphines marginally soluble in DCM, see ref.[9a] and references cited therein.

[25] For other studies on Ru catalyst decomposition and longevity, see ref.[9b] and references cited therein.

[26] a) K. Grela, S. Harutyunyan, A. Michrowska, *Angew. Chem. Int. Ed.* **2002**, *41*, 4038; b) H. Wakamatsu, S. Blechert, *Angew. Chem. Int. Ed.* **2002**, *41*, 794; c) H. Wakamatsu, S. Blechert, *Angew. Chem. Int. Ed.* **2002**, *41*, 2403; d) K. Grela, M. Kim, *Eur. J. Org. Chem.* **2003**, 963; e) M. Zaja, S. J. Connon, A. M. Dunne, M. Rivard, N. Buschmann, J. Jiricek, S. Blechert, *Tetrahedron* **2003**, *59*, 6545; f) S. Maechling, M. Zaja, S. Blechert, *Adv. Synth. Catal.* **2005**, *347*, 1413.

[27] We recently observed that the carbamate group accelerated the RCM of various dienes in the use of immobilized Hoveyda–Grubbs catalysts. A derivative of **8** bearing simple hydrocarbon linker exhibited reduced reaction rates and recyclability.

[28] For spectroscopic evidence for the return of the ruthenium carbene complex, see: J. S. Kingsbury, A. H. Hoveyda, *J. Am. Chem. Soc.* **2005**, *127*, 4510.

[29] For a representative synthesis of medium-sized rings, see: M. E. Maier, *Angew. Chem. Int. Ed.* **2000**, *39*, 2073.

[30] a) T. A. Kirkland, R. H. Grubbs, *J. Org. Chem.* **1997**, *62*, 7310; b) G. C. Fu, S. T. Nguyen, R. H. Grubbs, *J. Am. Chem. Soc.* **1993**, *115*, 9856.

[31] T. A. Kirkland, D. M. Lynn, R. H. Grubbs, *J. Org. Chem.* **1998**, *63*, 9904.

[32] S. H. Hong, R. H. Grubbs, *J. Am. Chem. Soc.* **2006**, *128*, 3508.

[33] A. Michrowska, R. Bujok, S. Harutyunyan, V. Sashuk, G. Dolgonos, K. Grela, *J. Am. Chem. Soc.* **2004**, *126*, 9318.

[34] a) A. Rivkin, Y. S. Cho, A. E. Gabarda, F. Yoshimura, S. J. Danishefsky, *J. Nat. Prod.* **2004**, *67*, 139; b) C. Gaul, J. T. Njardarson, D. Shan, D. C. Dorn, K.-D. Wu, W. P. Tong, X.-Y. Huang, M. A. S. Moore, S. J. Danishefsky, *J. Am. Chem. Soc.* **2004**, *126*, 11326; c) P. Blom, B. Ruttens, S. V. Hoof, I. Hubrecht, J. V. D. Eycken, *J. Org. Chem.* **2005**, *70*, 10109.

[35] a) H. Maynard, R. H. Grubbs, *Tetrahedron Lett.* **1999**, *40*, 4137; b) L. A. Paquette, J. D. Schloss, I. Efremov, F. Fabris, F. Gallou, J. Mèndez-Andino, J. Yang, *Org. Lett.* **2000**, *2*, 1259; c) Y. M. Ahn, K. Yang, G. I. Georg, *Org. Lett.* **2001**, *3*, 1411; d) J. H. Cho, B. M. Kim, *Org. Lett.* **2003**, *5*, 531; e) M. Westhus, E. Gonthier, D. Brohm, R. Breinbauer, *Tetrahedron. Lett.* **2004**, *45*, 3141; f) J. C. Conrad, H. H. Parnas, J. L. Snelgrove, D. E. Fogg, *J. Am. Chem. Soc.* **2005**, *127*, 11882.

[36] See ref.[15b] and references cited therein.

[37] Blechert and co-workers[18] and Bannwarth and co-workers[15b] showed 65 ppm and 20 ppm of ruthenium leaching in the RCM of **13**, respectively, using smaller quantities of catalysts.

[38] a) M. Mayr, B. Mayr, M. R. Buchmeiser, *Angew. Chem. Int. Ed.* **2001**, *40*, 3839; b) J. O. Krause, S. H. Lubbad, O. Nuyken, M. R. Buchmeiser, *Macromol. Rapid Commun.* **2003**, *24*, 875.