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Ring-Closure Metathesis in Supercritical Carbon Dioxide as Sole Solvent with Use of Covalently Immobilized Ruthenium Catalysts

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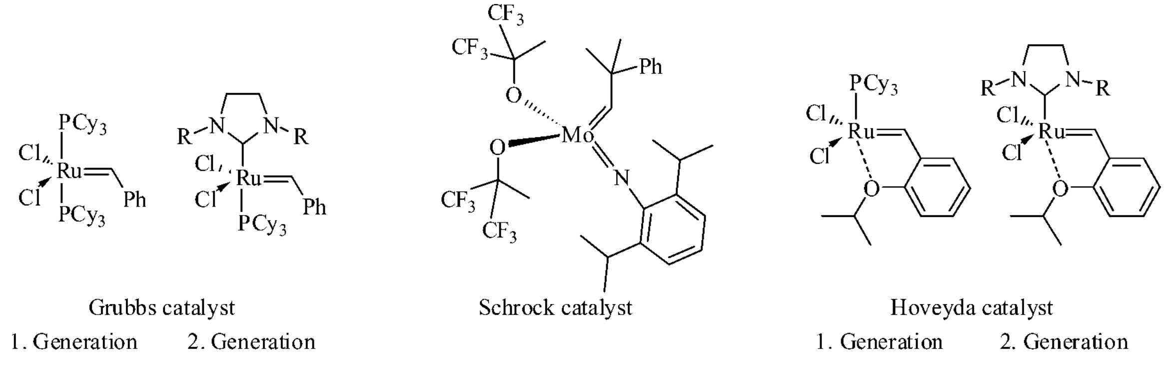
We describe RCM reactions in the presence of a Hoveyda-type catalyst covalently immobilized on different support materials. The performance of the catalyst was highly dependent on the nature of the support, and in some cases high levels of conversion were obtained, allowing for repetitive cycles. In addition, remarkably low levels of leaching of ruthenium into the product (20 ppm) were observed. This environmentally benign process has potential for continuous applications.

Introduction

In only one decade, metathesis with the well defined complexes **1a**, **1b**, and **2** (Figure 1) developed by Grubbs and Schrock has become a very powerful method for the synthesis of cyclic compounds, functionalized alkenes, natural products, and new materials.[1,2] With the arrival of the Hoveyda catalysts **3a** and **3b** (Figure 1) olefin metathesis has reached the next level, thanks to the high stabilities of these complexes towards moisture and air and the possibility of purifying and recycling them by column chromatography.[3] The only disadvantages are the necessity for relatively large amounts of the catalyst (generally 2–5 mol-%) and the high degree of leaching of Ru into the products.

Supercritical carbon dioxide ($scCO_2$) has emerged as a benign and environmentally friendly reaction medium for organic synthesis and in this respect also for catalytic reactions. Its non-flammability and non-toxicity, together with its easy availability in high purity, make it especially attractive as an alternative to common organic and often hazardous solvents. Furthermore, high diffusion rates are obtained in $scCO_2$ and can give higher reaction rates, especially in reactions in which gases are involved, due to their complete miscibility. Variation of the pressure and/or the temperature can be used to tune the solubility in $scCO_2$, which may also have an influence on the outcome of the reaction.[4]



1a **1b** **2** **3a** **3b**

Figure 1. Olefin metathesis catalysts.

Homogeneous catalysis in $scCO_2$ is often hampered by low solubility of catalysts in the nonpolar medium and requires special methods to make them soluble.[5] At present, the most popular technique is modification of the ligand sphere with perfluoro tags to increase solubility.[6] Promi-

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nent examples are transition metal perfluoro phosphane complexes.[7] In this context we have applied perfluoro-tagged Pd complexes for Stille couplings in $scCO_2$.[8]

Akgerman et al. recently reported the application of poly(perfluoroalkyl acrylate) for the immobilization of a Wilkinson-type catalyst in $scCO_2$.[9]

On the one hand, the perfluoro tags afford enhanced solubility of the catalysts in $scCO_2$, but on the other hand, introduction of these tags opens up the possibility of leaching of the catalyst into the product.

A possible solution to deal with this problem would be the application of heterogeneous catalysis. For metathesis reactions in solution, it has been demonstrated in several examples that immobilization of the catalyst significantly reduces the leaching of Ru into the product in relation to the use of homogeneous catalysts.[10]

So far, heterogeneous catalytic reactions in $scCO_2$ are mainly restricted to reactions involving Pd and Pt on Al_2O_3, polysiloxane, or zeolite, with hydrogenation as the salient reaction.[11] We reasoned that ring-closing metathesis (RCM) in a heterogeneous fashion with the metathesis catalyst covalently bound to a solid support should also be possible in $scCO_2$, as long as the catalytic sites on the support are accessible to the substrate, which would be strongly influenced by the swelling properties of the polymer. Alternatively, it is also possible that a precatalyst immobilized on the support might release a catalytic carbene species that could be recaptured by the styrene ether ligand prior to decomposition, as impressively demonstrated in organic solvents.[12]

Results and Discussion

Here we report the synthesis and application of novel solid phase-bound Hoveyda-type catalysts and their successful application in RCM reactions in $scCO_2$. Since the accessibility of the catalytic sites is unquestionably dependent on the swelling properties of the polymer in $scCO_2$, we applied different support materials to which the catalyst was coupled covalently through an amide bond, designing a new hybrid support material with a rigid core structure covered by an ultra-thin layer (≈ 10 nm) of an acrylamide-styrene copolymer, the basic structure of which is shown in Figure 2.[13]

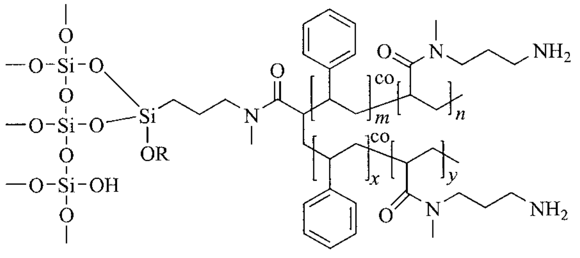


Figure 2. Novel hybrid support – silica gel with a thin layer of a copolymer (co) of styrene and acrylamide.

This new support material was evaluated in comparison with amino-modified HypoGel 400 [polystyrene bearing low molecular weight oligo(ethylene glycol) units], PEGA (polyacrylamide interspaced with ethylene glycol units), and Trisoperl (aminopropyl-modified silica gel) as alternative solid support materials, all of which are commercially available.

For the covalent attachment of Ru-metathesis catalysts to solid supports there are several options. Besides attachment through the benzylidene entity,[3b,10b,14] it is also possible through phosphane or the *N*-heterocyclic carbene.[10c,14c,15–17]

We have recently reported on the synthesis of the Hoveyda-type ligand **4**.[18] This ligand was coupled to the amino-modified supports to yield **5** as outlined in Scheme 1.

A capping step using acetic anhydride was carried out after the coupling to ensure masking of possible residual free amino groups. Starting from **5**, the immobilized catalysts **6**–**9** were prepared in the presence of **1a** or **1b**, with CuCl as activator. The removal of insoluble Cu phosphane residues was performed in two different ways. For catalysts bound to silica-based materials (**6** and **9**) the reaction mixture was filtered and washed until the filtrate was colorless. Then, neocuproine was added to remove Cu ions specifically, and their absence was subsequently confirmed by XPS measurements.[19]

Catalysts on HypoGel 400 and on PEGA (**7** and **8**) were purified by a method described by Blechert et al.[14d] The Ru loadings of all immobilized catalysts were determined by atom absorption in order to ensure equivalency during the reactions with **6**–**9**.

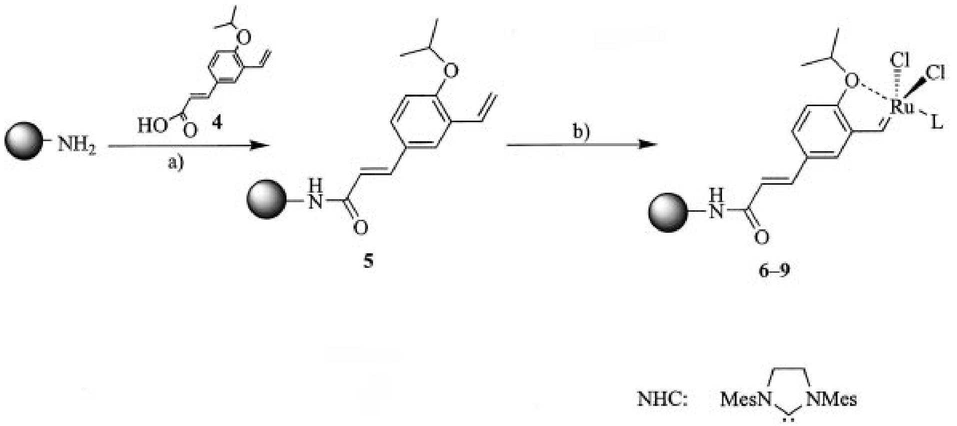
Olefin metathesis in $scCO_2$ with catalysts **1a**, **1b**, and **2** and their application for RCM and ROMP was reported for the first time in two seminal papers by Fürstner and Leitner in 1997 and 2001, respectively.[20]

Those results served as a benchmarks to test the performance of our solid phase-bound catalysts **6**–**9**, so we have included **1a** and **1b** in our present study. As a test reaction, we used the RCM of *N*,*N*-diallyl tosylamide **10** to afford **11** (Scheme 2).

The reaction conditions were very similar to those reported by Fürstner and Leitner (2.5% of catalyst, 40 °C, 150 bar, 24 h).[20b] The obtained results are summarized in Table 1.

Catalysts **1a** and **1b** gave quantitative conversions as reported in ref.[20b] Furthermore, we were able to perform five consecutive runs without any loss of activity.

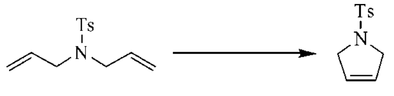
None of our solid phase-bound catalysts **6**–**9** reached quite the excellent performance of **1a** and **1b**. Nevertheless, we observed high levels of conversion in the application of catalysts **6a**, **6b**, **7a** and **7b**. In some cases the high conversion could also be obtained in subsequent runs. Relatively poor results were observed with catalysts **8a**, **8b**, **9a** and **9b**. Obviously, the performance of the catalyst was highly dependent on the support material: HypoGel 400 and our home-made hybrid support were superior to amino-modified silica gel (Trisoperl) and PEGA material. This might be explained by swelling properties and polarity effects influencing the accessibility of catalytic sites on the support.



Support	Ligand	Solid Phase-bound Catalyst	Loading [µmol/g]
Hybrid Silica Gel	PCy_3	**6a**	32[a]
	NHC	**6b**	56[a]
HypoGel 400	PCy_3	**7a**	67[b]
	NHC	**7b**	217[b]
PEGA	PCy_3	**8a**	53[b]
	NHC	**8b**	41[b]
Trisoperl	PCy_3	**9a**	16[b]
	NHC	**9b**	5[b]

[a] Determined by ICP-MS.[19] [b] Determined by AAS.[19]

Scheme 1. Synthesis of the supported olefin metathesis catalysts. a) 1) DCC, HOBt, Huenig's base, DMF, 24 h, room temp., 2) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 5 h, room temp. b) **1a** or **1b**, CuCl, CH_2Cl_2, 4 h, reflux.



10 **11**

Scheme 2. Benchmark RCM reaction for comparison of the supported olefin metathesis catalysts with **1a** and **1b**.

Table 1. RCM recycling experiments of **10** with different catalysts.

Entry	Catalyst	Conversion[a] (cycle 1, 2, 3, 4, 5) [%]
1	**1a**	≥ 98, ≥ 98, ≥ 98, ≥ 98, ≥ 98
2	**6a**	83, 75, 66, 66, 56
3	**7a**	95, 95, 90, 89, 84
4	**8a**	40, 13, 5, 4, 2
5	**9a**	46, 45, 45, 45, 14
6	**1b**	≥ 98, ≥ 98, ≥ 98, ≥ 98, 90
7	**6b**	93, 92, 77, 54, 57
8	**7b**	92, 95, 85, 34, 12
9	**8b**	69, 12, 5, 3, 1
10	**9b**	63, 57, 21, 12, 0

[a] Determined by ^1H NMR spectroscopy.

PEGA shows poor swelling properties in nonpolar solvents, so this can also be expected in $scCO_2$, hampering accessibility of active sites. Trisoperl, on the other hand, has a hydrophilic surface and the catalyst is bound close to the surface.

In contrast, HypoGel 400 consists of a nonpolar polystyrene core and is covered by a low molecular weight oligoethylene glycol spacer to which the catalyst is attached. We had chosen this specific spacer since, in contrast to its higher molecular weight analogues, it has a relatively high solubility in $scCO_2$,[21] so these units should facilitate accessibility in $scCO_2$. Our hybrid material was originally designed for applications in nonpolar solvents. On the one hand, the support is rigid (due to the SiO_2 core), while on the other, good accessibility is achieved in nonpolar solvents, due to the small organic co-polymer layer on the matrix, which does not require effective swelling.

In some of their RCM reactions carried out with macrocyclic dienes, Fürstner and Leitner observed an influence of the density of $scCO_2$ on the outcome of the reaction (RCM or oligomerization). When we investigated the pressure dependency with **6b** as catalyst, no pressure dependency of the reaction was observed between 80 and 160 bar and **11** was formed as the only product.

In a further set of experiments, we investigated the time dependence of the formation of **11** with solid phase-bound catalyst **6b** as well as with the Grubbs catalysts **1a** and **1b** (Figure 3).

With **1a** and **1b**, conversion was complete within 1 h, at which time the process with **6b** was about 50% complete. After 6 h, conversion of about 90% had been achieved, increasing only slightly when the reaction was continued for another 18 h.

In order to extend the scope of applicability of the highly active catalyst **6b**, further RCM reactions were carried out with various substrates (Table 2). The same reaction conditions as in the previous experiments were used. High levels of conversion were observed with almost all olefins: even the seven-membered ring **19** was formed quantitatively. Only for compound **13** was a somewhat lower result

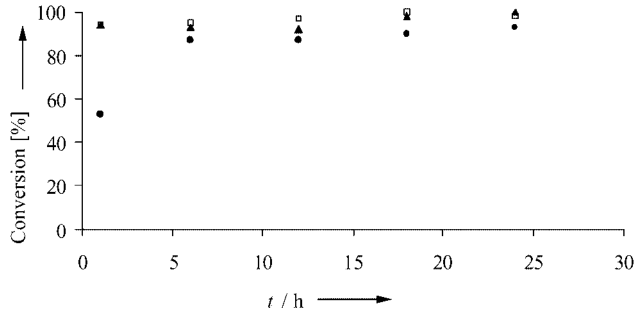
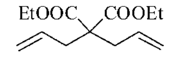
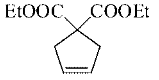
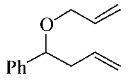
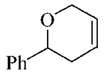
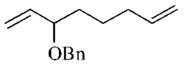
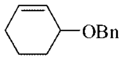
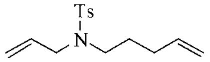
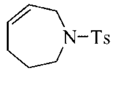
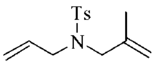
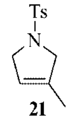
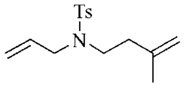
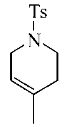


Figure 3. Time dependence of the RCM of **10** with catalyst **1a** (□), **1b** (▲), or **6b** (●), respectively.

achieved. Besides the cyclizations of the monosubstituted olefins, catalyst **6b** also showed high activities in the synthesis of trisubstituted cyclic alkenes, as exemplified with **21** and **23**.

Table 2. RCM reactions of various alkenes with catalyst **6b**.

Entry	Substrate	Product	Conversion[a] [%]
1	 **12**	 **13**	74
2	 **14**	 **15**	90
3	 **16**	 **17**	>98
4	 **18**	 **19**	>98
5	 **20**	 **21**	92
6	 **22**	 **23**	95

[a] Determined by ^1H NMR spectroscopy.

Homogeneous olefin metathesis in organic solvents entails the risk of high Ru leaching into the products, which has limited the application of this very important reaction, especially in the synthesis of pharmaceuticals and fine chemicals. Several approaches to deal with this problem have been developed. With **1a**, the reported level of Ru in the product was between 12000 and 17000 ppm,[22] whilst after column chromatography this level could be reduced to about 2000 ppm. Grubbs devised a procedure using $P(CH_2OH)_3$ in order to make Ru soluble in water. After stirring with silica gel and extractive workup, the amount of Ru could be reduced to 200 ppm.[22a] Paquette applied $Pb(OAc)_4$ to oxidize the metal, which was followed by filtration through silica gel, after which the Ru level had dropped to 300 ppm.[22b] Georg used DMSO or PPh_3O followed by silica gel filtration or chromatography to suppress the content of Ru to 240–270 ppm.[22c] Kim used a combination of adsorption and filtration through silica gel, charcoal, and column chromatography on silica gel and, after this tedious procedure, observed a Ru level of 60 ppm.[22d] New pseudohalide Ru complexes more efficiently removable by silica gel chromatography have recently been described.[23]

As outlined in the Introduction, application of solid phase-bound metathesis also has advantages over homogeneous catalysis, as illustrated in several examples.[10] The best result was reported by Buchmeiser, for a catalyst immobilized through a heterocyclic carbene ligand, to be below 70 ppm but no details were given as far as the procedure was concerned.[10c] Blechert has also very recently presented a new supported olefin metathesis catalyst that showed an average leaching of 65 ppm.[24]

It was recently reported that RCM products could be separated from Ru contaminants by extraction with $scCO_2$,[25] which led us to assume that direct application of metathesis in $scCO_2$ should be especially favourable as far as leaching is concerned. Furthermore, the application of the solid phase-bound catalyst should also have advantages over the application of **1a** and **1b**. For this reason, we estimated and compared the Ru content of **11** after RCM in the presence of the Grubbs catalysts **1a** and **1b** or with the solid phase-bound catalysts **6a** and **6b** by ICP-AES.[19] For both Grubbs catalysts, the amount of Ru in the crude product was 100 ppm, whereas for **6a** and **6b** we observed 18 and 21 ppm, respectively.

Conclusions

In summary, we have presented, for the first time, RCM reactions employing covalently immobilized Hoveyda-type catalysts in $scCO_2$ as the sole reaction medium. The performance of the catalyst was highly dependent on the nature of the support material to which it was attached. This might be an indication of a heterogeneous catalytic process but since the catalysts are in reality precatalysts, which might release the active species into the medium, further investigations are necessary to provide more insight into this issue. Nevertheless, the obtained data concerning the different supports might be helpful in the design of further catalytic processes in $scCO_2$ with immobilized catalysts. High levels of conversion were obtained with some of our immobilized catalysts (**6a**, **6b 7a**, and **7b**), allowing for repetitive cycles. Furthermore, the RCM reactions could be demonstrated for an array of different starting materials. In addition, a remarkably low level of leaching of ruthenium into the crude product (20 ppm) was observed. This environmentally benign process has the potential for continuous applications.

Experimental Section

General: The reactions were carried out in a stainless steel autoclave (volume variable from 29–61 mL) fitted with a sapphire window and an internal stirrer from NWA GmbH, Lörrach (Germany). Carbon dioxide was added by use of a pressure module with a maximum outlet of 600 bar.

General Procedure for Catalysis under Supercritical Conditions: The catalyst (2.5 mol-%) was loaded into a specially designed small glass vessel in the autoclave. The reactor was carefully pressurized with CO_2 to 100 bar at 40 °C, the substrate was then delivered by a loop connected to the autoclave, and the pressure was raised to 140 bar. After 24 h, the reactor was vented at 40 °C. The organic compounds were collected in a flask filled with CH_2Cl_2 and ethyl vinyl ether, and the degree of conversion of the RCM was then determined by ^1H NMR spectroscopy.

All products were analyzed by ^1H NMR and mass spectrometry and compared with the literature data.

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