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A hexafluorobenzene promoted ring-closing metathesis to form tetrasubstituted olefins

Daniel Rost, Marta Porta, Simon Gessler, Siegfried Blechert *

TU Berlin—Berlin University of Technology, Institute of Chemistry, Strasse des 17. Juni 115, Sekr. C3, 10623 Berlin, Germany

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ABSTRACT

Highly efficient formation of tetrasubstituted olefins is described by ring-closing metathesis (RCM) using catalyst **2** in presence of hexafluorobenzene. This combination with hexafluorobenzene shows an unexpected promoting effect, which requires low catalysts loadings and allows the conversion of deficient olefins in high yields and very short reaction times.

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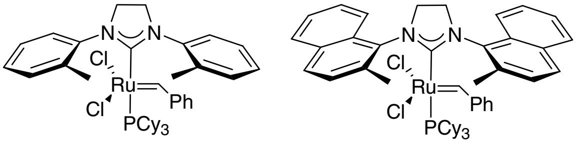
With the advent of stable Ru-based catalyst that combines high catalytic activity and excellent functional group tolerance olefin metathesis reactions have emerged as one of the most attractive and powerful tools for the formation of new carbon–carbon double bonds.[1] In particular ring-closing metathesis (RCM) to generate functionalized cyclic olefins, which are very common synthetic intermediates in organic synthesis, has received much attention.[2] Nevertheless, sterically demanding substrates leading to tetrasubstituted cyclic olefins are still challenging and typically require high loadings of second-generation catalysts.[3] Recently, Grubbs et al. have investigated the catalytic properties of novel ruthenium-based catalysts in this particular RCM.[4] They could demonstrate the superior performance of complex **1** over the standard Grubbs' 'second-generation' catalyst. This finding has been attributed to a less crowded steric environment of **1** at the ruthenium center.[4b] Despite its high initiation rates complex **1** decomposes readily under the reaction conditions, and the use of the corresponding more stable phosphine-free isopropoxybenzylidene-based catalyst is mandatory. Still transformations with these ruthenium complexes require high catalyst loadings, and attempts to form electron-deficient tetrasubstituted olefins have not shown satisfactory results. In our search for stable catalysts for the formation of tetrasubstituted olefins, we focused our interest on the use of catalyst **2**, which was synthesized by our group a few years ago.[5] We anticipated that an enlargement of the π-system in the *N*-aryl substituent of the NHC ligand would provide an increased stability of the corresponding active catalytic complex. An *ortho*-substituted *N*-naphthyl group would also offer a less bulky environment around the metal center than the mesityl moiety in the second generation Grubbs catalyst. In addition, any potential deactivation through intramolecular carbene–arene bond formation, reported by our group, would also be prevented.[6] Recently, Dorta et al. have reported a different synthetic route for catalyst **2** and found moderate conversion of a standard substrate in the RCM to tetrasubstituted olefins with this catalyst.[7]

Herein we report systematic studies of the employment of **2** in the highly efficient generation of tetrasubstituted olefins in hexafluorobenzene as the solvent, which shows an unexpected promoting effect on the RCM reaction. In accordance with previous observations we obtained higher yields in RCM reactions upon changing the solvent from dichloromethane at 40 °C to toluene at 80 °C.[8] Several other solvents with similar boiling points were also tested, including perfluorinated benzene derivatives, which had already been successfully employed in metathesis reactions in our group.[9] During these studies we discovered a pronounced effect of fluorinated benzene on the performance of **1** and **2** in the RCM reactions. We then conducted several comparative studies with catalyst **2** and the commercially available complex **1** to evaluate their synthetic potential under these reaction conditions (Fig. 1).[10]



1 **2**

Figure 1. Ru-catalysts for RCM to form tetrasubstituted olefins.

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* Corresponding author. Tel.: +49 030 314 22255; fax: +49 030 314 23619.
E-mail address: blechert@chem.tu-berlin.de (S. Blechert).

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We first assessed the activity and stability of both catalysts in the RCM of sulfonamide **3** in hexafluorobenzene (Fig. 2).

The conversion over time to the desired reaction product **4** with 0.25 mol % catalyst in 0.1 M C_6F_6 at 80 °C was measured by ^1H NMR analysis. Figure 2 clearly shows the superior catalytic activity of catalyst **2** in the conversion of substrate **3**. Catalyst **1** is less stable, and fails to efficiently promote this reaction. After 5 min the activity of both catalysts breaks down, accounting for the short lifetimes of the respective catalytic active species. In summary, complex **2** due to its rapid initiation and its higher stability catalyzes the conversion of **3** more efficiently than catalyst **1**. To compare the overall performance of catalysts, studies of conversion versus catalyst loading and the determination of the amount of product yielded by a given amount of catalyst have to be carried out.[11] We therefore investigated the lower catalyst loading limit for the RCM to a tetrasubstituted olefin and determined the reactivity profile for **1** and **2** under the novel reaction conditions.

First, we focused on the transformation of **5** to the six-membered lactone **6**. The presence of such lactones as structural subunits in numerous natural products makes electron-deficient alkenes, such as α,β-unsaturated esters, very attractive substrates for metathesis reactions.[12] Catalyst **1** was reported to fail to promote this reaction in benzene at 60 °C.[4] We found a conversion of diene **5** to lactone **6** of 23% with 5 mol % of catalyst **1** in hexafluorobenzene clearly demonstrating the strong promoting effect of this solvent.

The use of **2** under the same reaction conditions gave 83% of conversion of substrate **5**. Figure 3 again shows the superiority of catalyst **2**. Only 0.25 mol % of **2** is needed to obtain the same conversion as found for 5 mol % of catalyst **1**. Substrate **7** was then chosen as a model for a RCM reaction for seven membered rings. Once more, **2** was remarkably more efficient than catalyst **1**. Quantitative conversion was found for 3 mol % of catalyst **2**. Using complex **1**, only 72% of conversion was found with the same catalyst loading. In fact, for full conversion more than 5 mol % of catalyst **1** were needed in this reaction.

These findings demonstrated the superior efficiency of catalyst **2** in hexafluorobenzene, and we decided to evaluate catalyst **2** in a variety of RCM reactions with sterically challenging substrates (Table 1). In all cases catalyst **2** in hexafluorobenzene showed faster reactions and superior yields with lower catalyst loadings than catalyst **1** in benzene.[4b]

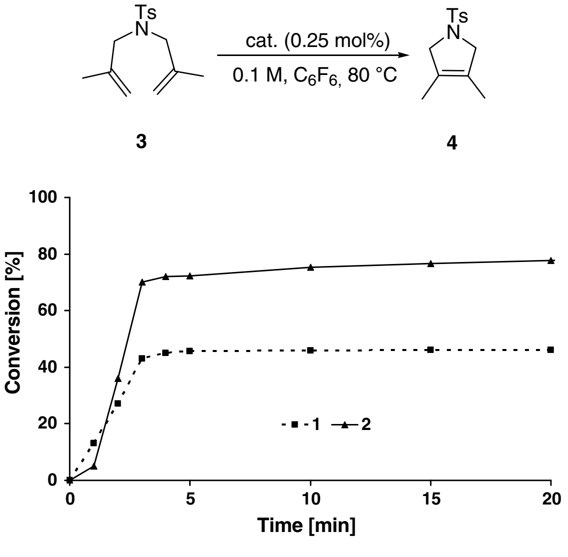


Figure 2. RCM to form tetrasubstituted olefin **4**.

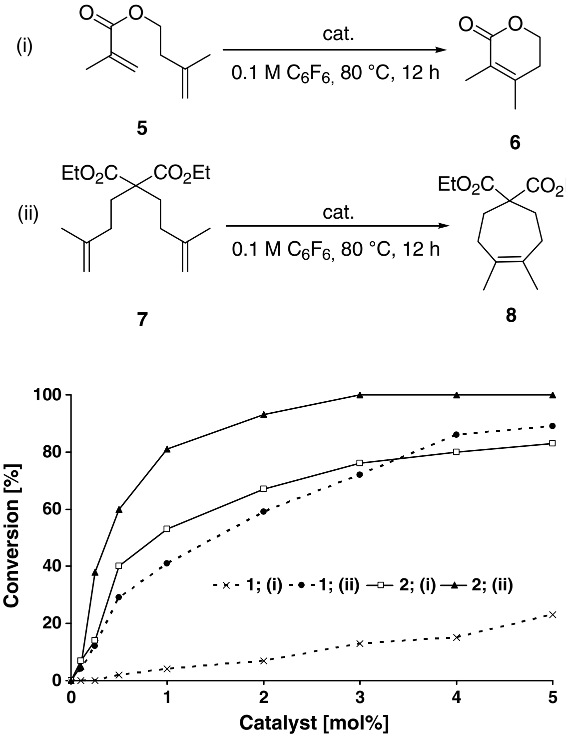
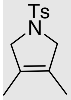
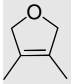
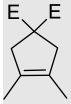
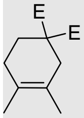
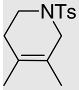
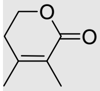
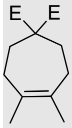


Figure 3. Conversion versus catalyst loading.

In view of these results we were interested in comparing the steric environment at the metal center of catalysts **1** and **2**. Since a crystal structure of the corresponding phosphine-free isopropoxybenzylidene complex of **1** has been published[4b] we decided to synthesize complex **9**,[13] assuming that the structural features of the phosphine-free complexes reflect the situation in complexes **1** and **2**. The X-ray crystal structure of **9** (Fig. 4) and the published structure show similar characteristics. Both complexes have the same open environment at the metal center.

Several factors may be responsible for the increased RCM efficiency in the formation of tetrasubstituted olefins in hexafluorobenzene. Grubbs et al. suggested that the initiation rate was roughly proportional to the dielectric constant of a given solvent.[14] The dielectric constant of hexafluorobenzene is, however, considerably lower than of benzene and of toluene at the same temperature.[15] Thus the effects seen in our investigations cannot be attributed to the dielectric constant of the solvent. Further, the known intermolecular π–π interaction between the *N*-aryl group of the NHC ligand and the aromatic solvent may be a factor explaining our findings.[16] This interaction was suggested as a reason for the increase in activity in metathesis reactions carried out in toluene at 80 °C, since the same transformations in dichloroethane at the same temperature led to lower yields. In addition, this π–π interaction would influence the intramolecular stabilizing interaction between the *N*-aryl group and the benzylidene carbene and consequently affect the initiation rate of the catalyst. In addition, a potential influence on the donating capacity of the NHC ligand through π–π intermolecular interaction with hexafluorobenzene can be discussed. Previous studies in different cyclophane-based rhodium dicarbonyl complexes showed (by measuring CO stretching frequencies) a decrease in the donor capacity when fluorinated cyclophanes were used.[17] Such a modification of the electron density around the ruthenium center could also influence the reactivity of the catalyst. Finally, a fluorine–ruthenium interaction could reduce the activation energy of the

Table 1
Formation of tetrasubstituted olefins with catalyst **2**

Product	Cat. (mol %)	Conversions (isolated yields) (%)
	1	>99 (99)
	1	>99[a]
	5	>99 (97)
	1	>99 (99)
	1	>99 (99)
	5	83 (80)
	3	>99 (98)

Conditions: 0.1 M C_6F_6, 80 °C, 1 h, E = CO_2Et.
[a] Isolated yield not determined due to product volatility.

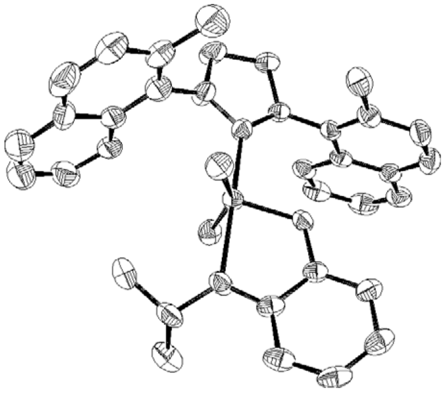


Figure 4. ORTEP diagram of complex **9**.

rate-limiting phosphine dissociation. Such an interaction has previously been described and discussed as a reason for the increased efficiency observed for the corresponding complex.[18]

To get more information about the role of hexafluorobenzene a suspension of **2** in hexafluorobenzene was heated up to 80 °C until dissolution of the catalyst. The solvent was then immediately removed under reduced pressure, yielding a solid of light pink color significantly differing from the color of complex **2**. This substance is stable at room temperature in solid form but unstable in solution. The substance was dissolved in $CDCl_3$, and after 10 min F NMR showed the presence of hexafluorobenzene, which can only be explained by the release of hexafluoro benzene from a ruthenium catalyst—hexafluorobenzene complex.

In conclusion, we have developed a new catalytic system for the efficient formation of tetrasubstituted olefins, which requires low catalyst loadings and even allows the conversion of electron deficient olefins in high yields and very short reaction times. Detailed studies on the influence of hexafluorobenzene in ruthenium complex catalyzed metathesis reactions are currently ongoing in our group.

Acknowledgment

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13. *Synthesis of catalyst* **9**: Two hundred and forty milligrams of the complex **2** (0.34 mmol) and 33 mg CuCl (0.33 mmol) were dissolved under nitrogen atmosphere in 20 ml dichloromethane followed by the addition of 160 mg 2-Isopropoxy styrene (0.68 mmol). The reaction mixture was stirred at 45 °C for 1 h. Catalyst **3** was purified by silica chromatography (100% hexane to 100% CH_2Cl_2), to afford the product as a bright green solid after removal of the solvent, which was recrystallized from hexane/CH_2Cl_2 (1:1). Yield: 155 mg (68%); mp > 230 °C, decomposition. ^{1}H NMR (500 MHz, $CDCl_3$): (isomers) δ (ppm) = 16.32, 16.16 (s, 1H), 8.48–6.48 (m, 16H), 4.68–4.34 (m, 4H), 2.83, 2.75 (s, 6H), 0.93, 0.88 (d, J^3 = 6.0 Hz 6H). ^{13}C NMR (125 MHz, $CDCl_3$): (isomers) δ (ppm) = 152.4, 144.8, 144.7, 133.3, 133.2, 131.7, 131.5 (C), 129.5, 129.3, 129.2, 129.1, 129.0, 127.8, 127.7, 127.6, 126.1, 126.0, 122.6, 122.6, 122.1, 112.7, 112.6, 74.9, 74.8 (CH), 53.0, 52.9 (CH_2), 20.8, 20.7 (CH_3). IR (ATR): ν (cm^{-1}) = 3470 (w), 3050 (w), 2973 (m), 2926 (m), 2852 (w), 1701 (m), 1589 (m), 1476 (s), 1414 (s), 1375 (m), 1272 (vs), 1255 (vs), 1218 (m), 1113 (s), 936 (m), 814 (m), 780 (s),

745 (s). MS (EI, 70 °C): m/z (%) = 670 (<1) [M$^+$], 488 (30), 97 (28), 81 (49), 69 (100). HR-MS ($C_{35}H_{34}N_2OCl_2Ru$, M$^+$): Calcd: 670.1085, found: 670.1093.

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