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High temperature microwave-accelerated ruthenium-catalysed domino RCM reactions

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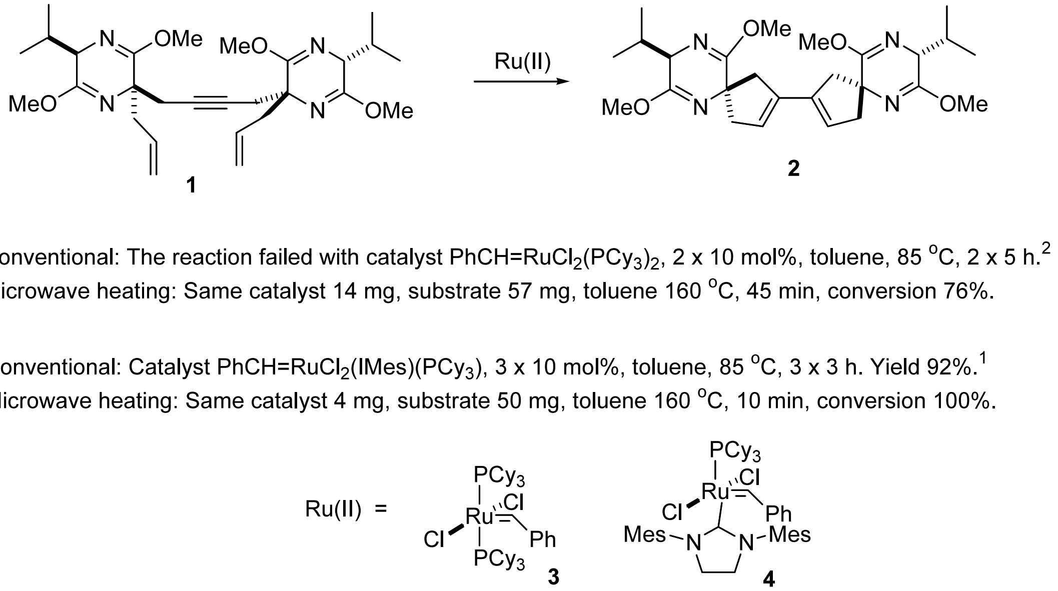
Abstract—The thermal instability of ruthenium(II)-catalyst systems under prolonged heating at 88°C in RCM reactions of dienyne and triyne substrates has been circumvented by a microwave temperature increase to 160°C when the reaction times were reduced to minutes. © 2003 Elsevier Science Ltd. All rights reserved.

In previous reports we have described the use of Grubbs' catalyst in the construction of cyclic and rigid bis(α-amino acids) where the key step was a domino ring-closing metathesis (RCM) reaction of dienynes to the corresponding bicyclic products (Scheme 1).[1,2] No significant conversion to products was observed below 80°C and the RCM reactions were conducted by heating at 88°C for several hours. The high temperature caused a gradual decomposition of the catalyst, and additional catalyst was therefore added to drive the reaction to completion.

An attempt has been made to overcome thermal instability as a limiting factor of the catalyst in RCM reactions by exposure of the catalyst to microwave heating at a high temperature for a short time. Microwave energy leads to extremely rapid heating by direct transfer of heat into the reaction medium in



A

Conventional: The reaction failed with catalyst $PhCH{=}RuCl_2(PCy_3)_2$, 2 x 10 mol%, toluene, 85 °C, 2 x 5 h.[2]

Microwave heating: Same catalyst 14 mg, substrate 57 mg, toluene 160 °C, 45 min, conversion 76%.

B

Conventional: Catalyst $PhCH{=}RuCl_2(IMes)(PCy_3)$, 3 x 10 mol%, toluene, 85 °C, 3 x 3 h. Yield 92%.[1]

Microwave heating: Same catalyst 4 mg, substrate 50 mg, toluene 160 °C, 10 min, conversion 100%.

Scheme 1.

Keywords: microwave; accelerated RCM-reactions; dienyne and triyne substrates; Ru(II)-catalysis.

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contrast to conventional heating where the energy is transferred via the vessel wall. In microwave-transparent vessels, the walls are not thermally affected. A thermally unstable catalyst may be expected to deteriorate more rapidly at the hot vessel walls under conventional reaction conditions than in the uniformly heated interior of the microwave heated solution.[3,4] It has been amply confirmed that the use of controlled microwave heating, also expedites metal-catalysed organic synthesis.[5] Most studies have been on palladium-catalysed transformations,[5–7] but also include molybdenum,[8,9] and very recently ruthenium.[10] The report on microwave-accelerated ruthenium-catalysed olefin metathesis appeared in the midst of our own studies of the influence of elevated temperature. In the published microwave work, emphasis was on simple RCM reactions using Grubbs' catalysts in dichloromethane below 34°C with short heating times. A monocyclic ring system was formed.[10] In contrast, our studies have been directed towards high temperature cascade reactions leading to the formation of a bicyclic and a tricyclic annulated ring system.

In this work both the standard Grubbs' catalyst $(PCy_3)_2Cl_2Ru{=}CHPh$ **3**,[11,12] as well as the more recent and more active $(PCy_3)(IMes)Cl_2Ru{=}CHPh$ catalyst system **4** were used.[13,14]

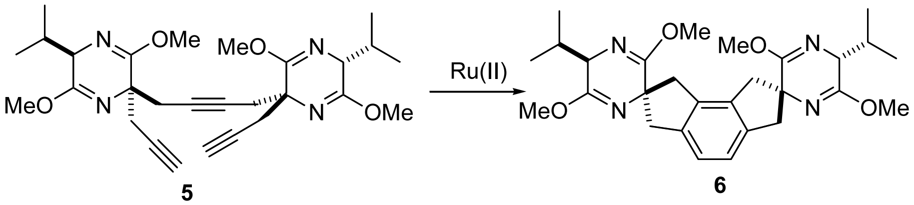
Microwave heating was performed in a Micro Well 10 single mode microwave cavity from Personal Chemistry AB, Sweden, producing continuous irradiation at 2.45 GHz. The reaction vessel was a round-bottom 100 mm Duran™ glass tube with a Schott GL18 screw cap, provided with a Teflon septa as a pressure relief device. The temperature was recorded using an IR pyrometer sensor. After irradiation was complete, the samples were left in the microwave cavity for 1 min to allow for thermal equilibration before cooling.

1,2-Dichloroethane and toluene were used as solvents in the exploratory phase to effect the reaction at high temperature for a short time. Both solvents are considered transparent in microwave irradiation studies. With toluene at 180°C the microwave oven was overheated, whereas dichloroethane could be used as solvent at this temperature. However, 1,2-dichloroethane did not seem to offer any advantage over toluene in the RCM reactions, neither mixed with toluene (1:4) nor neat. With toluene at 160°C the RCM reactions proceeded satisfactorily, and most exploratory reactions were run at this temperature.

The results presented in Scheme 1 were obtained by mixing the dienyne **1** with the ruthenium catalyst in a specially designed vial for use in a microwave oven, and the solvent added at room temperature before inserting the vial into the microwave oven. No reaction takes place at room temperature.[2] The RCM conversion with formation of product **2** was estimated by ^{1}H NMR. A number of reactions were run in toluene or in mixtures of toluene and 1,2-dichloroethane at elevated temperatures. Optimum conditions resulted with reactions at 160°C in which case 76% conversion was observed after 45 min. For comparison, in the conventional preparative work very little RCM product was obtained, even after prolonged reaction times. The RCM reactions should be run in an inert atmosphere as open exposure to air lowered the yield in contrast to what has been reported for some Pd-catalysed reactions.[6]

In the conventional chemistry, as shown in Scheme 1, series B, the modified catalyst **4** with one IMes ligand dramatically improved the RCM reaction from an almost zero yielding reaction with catalyst **3** to a high yielding process of ca. 92% when the catalyst **4** was added at intervals.[1] The change in reactivity was also seen during microwave heating. At ca. 5% catalyst loading, full conversion was observed in toluene at 160°C after only 10 min.

Having successfully explored the dienyne domino RCM reaction, the next substrate was to be a triyne, **5**, as shown in the Scheme 2. We have previously reported that under conventional conditions this reaction requires heating above 80°C and reloading with catalyst for reasons of thermal instability.[15] Five mol% catalyst gave 60% conversion to the product **6** after 5 h, and an



A

Conventional: Catalyst $PhCH{=}RuCl_2(PCy_3)_2$, 2 x 5 mol%, toluene, 85 °C, 14 h. Yield 90%.[15]

Microwave heating: Same catalyst 8 mg, substrate 40 mg, toluene 160 °C, 20 min, conversion 100%.

B

Conventional: Catalyst $PhCH{=}RuCl_2(IMes)(PCy_3)$. Not run

Microwave heating: Same catalyst 4 mg, substrate 50 mg, toluene 160 °C, 10 min, conversion 36%.

Scheme 2.

almost complete conversion when the same amount of catalyst was added a second time, and the heating continued for a total of 14 h. Under microwave conditions, series A in Scheme 2, 100% conversion to product **6** was observed after 20 min. RCM conditions using the second generation catalyst **4** was not run at the time of the conventional synthesis of the RCM product **6** because the first generation catalyst **3** had worked satisfactorily in this transformation as indicated in series A in Scheme 2. Surprisingly, the RCM reaction with the catalyst **4** under microwave heating was less satisfactory, 36% conversion after 10 min Series B (Scheme 2).

In conclusion, we have found that microwave heating greatly accelerates the ruthenium-catalysed domino-reaction of the dienyne substrate **1** in an inert atmosphere. In the dienyne reaction the IMes-ligated catalyst **4** was the better. For the triyne substrate **5** the RCM reaction with the IMes-ligated catalyst **4** was inferior to reactions with the standard catalyst **3**.

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