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Ruthenium-catalyzed tandem ring closing metathesis (RCM) – atom transfer radical cyclization (ATRC) sequences

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Abstract

α-ω-Dienes bearing a pendant trichloroacetoxy group undergo a tandem RCM – radical cycloisomerization sequence leading to bicyclic γ-butyrolactones, with both steps of the sequence being catalyzed by ruthenium.

Keywords: Ruthenium; Metathesis; Radical cyclization; Tandem sequence

The enormous progress achieved on the field of ruthenium-catalyzed olefin metathesis [1] over the past few years has been accompanied by the discovery of novel and unexpected non-metathesis reactivity patterns of ruthenium carbene complexes [2]. These include hydrogenation [3], isomerization [4], hydrosilylation [5], atom transfer radical addition [6], and, as recently demonstrated by Quayle et al. [7], the radical cycloisomerization of polyhalogenated compounds, which had previously been catalyzed by other metal complexes [8]. The novel reactivity patterns of ruthenium carbene complexes hold a number of opportunities for organic synthesis. For instance, they open up perspectives towards diversity oriented synthesis [9], "catalyst economy" [10b], and novel catalyzed tandem reactions [11–13]. However, reaction conditions have to be found that allow for the strict separation of metathesis and non-metathesis reactivity in order to obtain high selectivities. For radical reactions this has recently been achieved by us [10a] and by Quayle et al. [10b] In this contribution, we report our preliminary results on a tandem ring closing metathesis – radical cyclization reaction as a tool for the stereoselective synthesis of bicyclic lactones.[1] We started our investigation with diene **1a**. The RCM product of **1a** is trichloroacetoxy-substituted cyclohexene **2a**, which is one of the substrates investigated by Quayle and co-workers in their investigation of radical cycloisomerization reactions catalyzed by first generation

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[1] Representative procedure and analytical data: (3a*R**, 4*R**, 6*R**, 7a*R**)-6-Benzyloxy-3,3,4-trichloro-hexahydro-benzofuran-2-one (**8a**). To a solution of **7a** (300 mg, 0.8 mmol) in toluene was added precatalyst **C** (33 mg, 4.9 mol%). The mixture was stirred at ambient temperature until the starting material was fully consumed (TLC hexanes–MTBE (5:1), approximately 1 h), and then heated to reflux until the intermediate RCM product was fully consumed (TLC hexanes–MTBE (5:1), approximately 4 h). The solvent was evaporated, and the residue was purified by chromatography on silica to give **8a** (170 mg, 62%) as a colourless solid, mp 110 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36–7.28 (5H, Ph), 5.10 (ddd, 1H, $J = 4.4, 4.0, 4.0$ Hz, H-7a), 4.57 (d, 1H, $J = 11.7$ Hz, –OCH_2Ph), 4.52 (d, 1H, $J = 11.7$ Hz, –OCH_2Ph), 3.82 (ddd, 1H, $J = 12.1, 9.2, 4.8$ Hz, H-4), 3.58 (dddd, 1H, $J = 10.6, 10.6, 4.0$ Hz, 4.0, H-6), 3.12 (dd, 1H, $J = 9.2, 4.5$ Hz, H-3a), 2.66-2.58 (2H, H-5$_{eq}$, H-7$_{eq}$), 1.82 (ddd, 1H, $J = 12.1, 10.6, 10.6$ Hz, H-5$_{ax}$), 1.78 (ddd, 1H, $J = 14.7, 10.3, 4.0$ Hz, H-7$_{ax}$). ^{13}C NMR (150 MHz, $CDCl_3$)δ 166.8 (0, C=O), 137.5 (0, ipso-C, Ph), 128.6 (1, Ph), 128.0 (1, Ph), 127.6 (1, Ph), 80.8 (0, CCl_2), 77.2 (1, C-7a), 71.0 (2, –OCH_2Ph), 69.8 (1, C-6), 58.5 (1, C-3a), 52.8 (1, C-4), 40.7 (2, C-5), 33.1 (2, C-7). IR (neat, NaCl) ν [cm^{-1}] 2921 (m), 1802 (s), 1095 (s), 956 (s).

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Grubbs' catalyst (**A**) [14a] (Fig. 1) [7]. Three prerequisites are required for the combination of ring closing metathesis and cycloisomerization to a tandem sequence: (1) the olefin metathesis step must proceed efficiently at temperatures where no radical reaction is initiated by the catalyst; (2) carbene complex **B**, which is formed from **A** after the first catalytic cycle, must be an equally efficient catalyst precursor for the actual [10b] radical cycloisomerization catalyst as **A**; (3) other non-metathesis side reactions, especially olefin isomerization [2b], must not interfere with either metathesis step or radical reaction.

We found that **1a** is cleanly converted to **2a** in the presence of 5 mol% **A** at ambient temperature within 3 h. Heating the reaction to reflux induces formation of the lactone **4a**, which could be isolated in 63% yield. This finding is in accord with Quayle's report [7], who also did not observe the primary radical cyclization product **3a** in this case. We wanted to extend the concept to other examples and were particularly interested in fivemembered bicyclic lactones, because this is an important structural pattern in prostacycline natural products. To this end, **1b** was subjected to the same reaction conditions as **1a**, however, even after 12 h at ambient temperature no significant conversion to the intermediate RCM product **2b** was observed. We hoped that upon heating ring closing metathesis would occur sufficiently faster than radical cyclization to allow clean conversion of **1b** to a bicyclic lactone. This is unfortunately not the case: although **4b** is the major product of the reaction, conversion is rather sluggish and several unidentified byproducts are formed, presumably resulting from radical reactions that occurred prior to the RCM step. An obvious way to solve reactivity problems in olefin metathesis reactions is to switch from first to second generation precatalysts, such as **C** [14b], which is well-known for its enhanced activity in metathesis reactions. It has, however, recently been stated by Snapper et al. [15] that it is "not nearly as active in Kharasch additions" compared to the first generation catalyst **A**. This statement is in accord with our observations that **A** catalyzes efficiently atom transfer radical cyclizations of certain α,ω-dienes, while **C** catalyzes selectively the olefin metathesis of the same substrates [10a]. Nevertheless, the attempted conversion of **1b** was repeated using 5 mol% of second generation catalyst **C** under otherwise identical conditions. Surprisingly, not only the RCM step proceeded smoothly at ambient temperature, but the subsequent radical cyclization step was also efficiently catalyzed upon heating. **4b**, presumably formed from **3b** via dehalogenation and double bond migration, was the sole product isolated from the reaction mixture (Scheme 1).

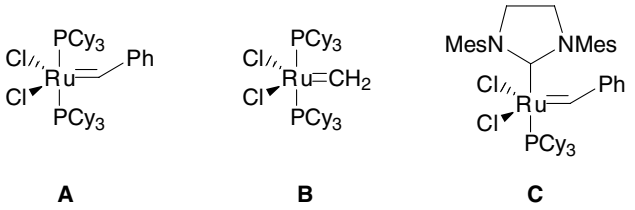
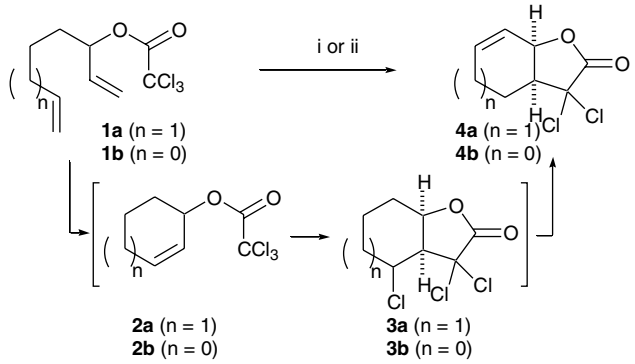


Fig. 1. Ruthenium carbene complexes.

We tried to observe the proposed intermediate **3b** by monitoring the reaction with NMR-spectroscopy. To this end, the reaction was repeated in d^6-benzene. After 1 h at room temperature, **1b** was completely consumed and **2b** was the only product observed by ^1H and ^{13}C NMR spectroscopy. The reaction mixture was then warmed to 40 °C for 1 h, but no change was observed in the NMR-spectra. Further heating to reflux (80 °C) induced consumption of **2b**, as monitored by TLC. In the H NMR-spectrum three additional signals appeared at low field from the aliphatic region, however, these were broad and shifted significantly compared to the spectra previously obtained from the reaction mixture. It was not possible to unambiguously assign any signal to either **2b**, **3b** or **4b**. We assume that these problems can be attributed to the formation of paramagnetic ruthenium species once the radical reaction is initiated. Unfortunately, it was also impossible to isolate the intermediate **3b** from the reaction mixture, because this compound could not be observed as a defined spot on TLC, indicating that decomposition occurs upon contact with silica. Structural assignment of compound **4b** is based on H,H- and H,C-correlation spectroscopy in combination with one-dimensional gradient-selected NOE-spectroscopy. All experiments reveal that the endocyclic double bond is located in the allylic position relative to the lactone oxygen. Quayle et al. [16] have recently addressed the issue of elimination and double bond isomerization in detail from a mechanistic point of view for the transformation of **2a** to **4a**.

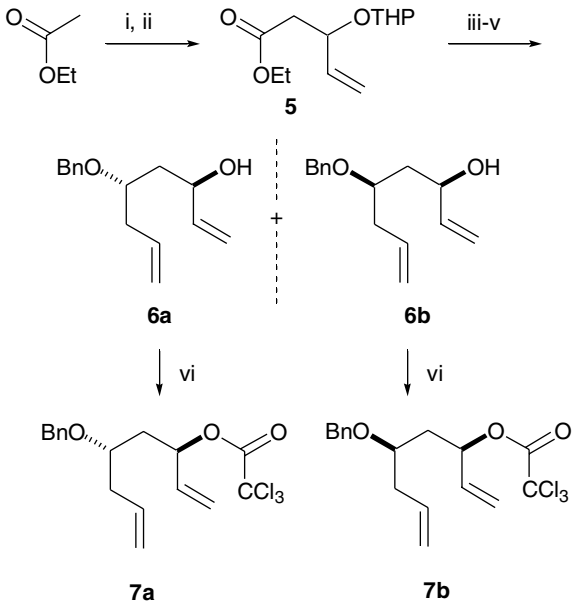
We assumed that the double bond migration observed during the conversion of **1a**,**b** to **4a**,**b** should be suppressed by introducing an additional substituent in



Scheme 1. *Reagents and conditions*: i, **A** (5 mol%), toluene, 20–110 °C, (63% of **4a**); ii, **C** (5 mol%), toluene, 20–110 °C, (61% of **4b**).

the metathesis precursor. As the relative configuration of these metathesis precursors might have influence on both cyclization steps, we wanted to have access to both diastereoisomers. To this end, **7a** and **7b** were synthesized starting from ethyl acetate, which was reacted with acroleine in an aldol reaction. The resulting aldol product was protected as a THP-ether to give ester **5**, which was converted to a 1:1 mixture of diastereomeric alcohols **6a** and **6b** via a one-pot DIBAL-H reduction of the ester function, trapping of the resulting aldehyde with allylmagnesium bromide, protection of the alcohol as a benzyl ether, and final cleavage of the THP–acetal. Diastereomers **6a** and **6b** could be separated by column chromatography on silica and were separately esterified using trichloroacetyl chloride to give the desired precursors **7a** and **7b** as single diastereoisomers (Scheme 2).

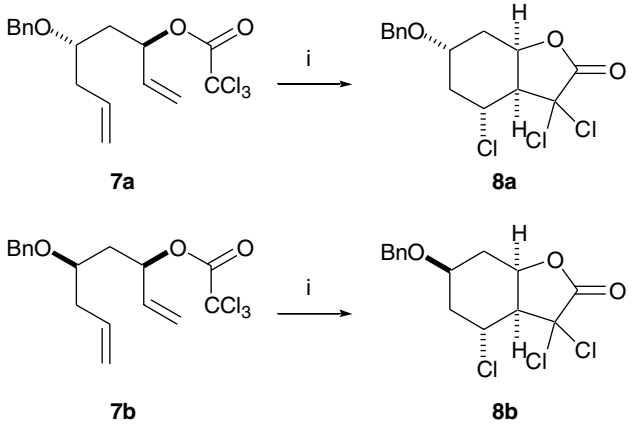
We first checked whether or not dienes **7** would undergo ring closing metathesis using the first generation catalyst **A** at ambient temperature. To this end, **7b** was treated with 5 mol% of first generation Grubbs' catalyst in toluene at ambient temperature. Unfortunately, under these conditions the reaction stops at approximately 30% conversion after 2 h. Even after 20 h at ambient temperature no improvement could be observed. We therefore repeated the experiment using 5 mol% of second generation catalyst **C**. This lead to a rapid consumption of the metathesis precursor within 30 min and clean formation of the primary metathesis product, as indicated by TLC. Gratifyingly, heating the mixture to reflux induces the formation of a bicyclic product via an atom transfer radical cyclization. Surprisingly, the trichlorinated compound **8b** was obtained as the sole product in high diastereoselectivity and no elimination products could be detected. Conversion of the diastereomeric precursor **7a** to the bicyclic product **8a** proceeds equally efficient, indicating that the different orientation of the additional benzyloxy group does not influence the efficiency of either cyclization step. In both cases complete conversion of the intermediate RCM product was observed within 4 h (Scheme 3).



Scheme 2. *Reagents and conditions*: i, LDA, THF, −78 °C, then add acroleine; ii, 2,3-dihydropyran, *p*-TSA (cat.) (58% from ethyl acetate); iii, DIBAL-H (1.3 equiv.), DCM, −90 °C, then add allylmagnesium bromide, −90 to 20 °C; iv, NaH, THF, 65 °C, then add benzyl bromide; v, dissolve in methanol, *p*-TSA (10 mol%), separate by chromatography (33% of **6a**, 31% of **6b** from **5**); vi, Cl_3COCl, NEt_3, DMAP (cat.), DCM (99% of **7a**, 99% of **7b**).

Elucidation of the relative configuration of **8a** and **8b** was achieved using one- and two-dimensional NMR-techniques. Especially NOE-experiments and analysis of vicinal coupling constants turned out to be very useful to prove the *cis*-junction of cyclohexane and lactone ring. The *trans*-orientation of the chloro-substituent relative to the lactone ring becomes obvious from the comparatively large *trans*-diaxial coupling constants observed for the proton –C*H*Cl–. These values are in the range of 8 to 10 Hz. It should be mentioned that the high diastereoselectivity observed for the ATRC step is not without precedence in the literature. Nagashima et al. [8d] demonstrated that the copper-catalyzed atom transfer radical cyclization of **2a** yields **3a** as a single diastereoisomer, with the chloro-substituent being in a *trans*-arrangement relative to the lactone ring.

In conclusion, we were able to demonstrate that tandem ring closing metathesis-atom transfer radical cyclization reaction sequences are in principle possible. The second generation Grubbs' catalyst, which had previously been reported by several groups to be less reactive in ATRA and ATRC reactions than the first generation catalyst, turned out to mediate *both* steps of these sequences in preparatively useful yields and rates of conversion. Further investigations into scope and



Scheme 3. *Reagents and conditions*: i, **C** (5 mol%), toluene, 20–110 °C, (61% of **8a**; 62% of **8b**).

limitations of this sequence are currently in progress in our laboratory.

Acknowledgements

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