An Olefin Metathesis/Double Bond Isomerization Sequence Catalyzed by an In Situ Generated Ruthenium Hydride Species

Bernd Schmidt[a]

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The direct conversion of allyl ethers to cyclic enol ethers using an olefin metathesis/double bond migration sequence is described. Ruthenium carbene complexes were activated to catalyze the double bond migration step by addition of hydride sources, such as NaH or $NaBH_4$.

The combination of transition metal-catalyzed reactions into a sequence is an attractive concept in organic synthesis.[1] In the field of olefin metathesis[2] several sequences of ring closing (RCM), ring opening (ROM) and cross metathesis (CM) reactions have been developed and applied to the synthesis of target molecules over the past few years.[3] In contrast, comparatively little work has been published on the sequential catalysis of an olefin metathesis reaction and a non-metathesis reaction. Recently, Grubbs et al. discovered that ruthenium carbene complexes, after mediating an olefin metathesis reaction, catalyze the hydrogenation of the C-C double bond formed in the metathesis step if the reaction vessel is pressured with hydrogen.[4a] Fogg et al. have obtained unusual polyolefins via a ruthenium-catalyzed ring opening metathesis polymerization (ROMP)/hydrogenation sequence.[4b] The reactivity of ruthenium carbene complexes such as **I**[5a] or **II**[5b] (Figure 1) in hydrogenation reactions originates from a hydrogenolysis of the carbene complex to a ruthenium hydride species, a process that has been investigated mechanistically.[6]

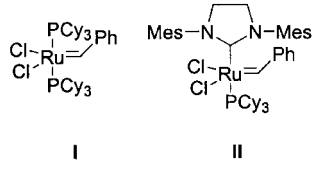
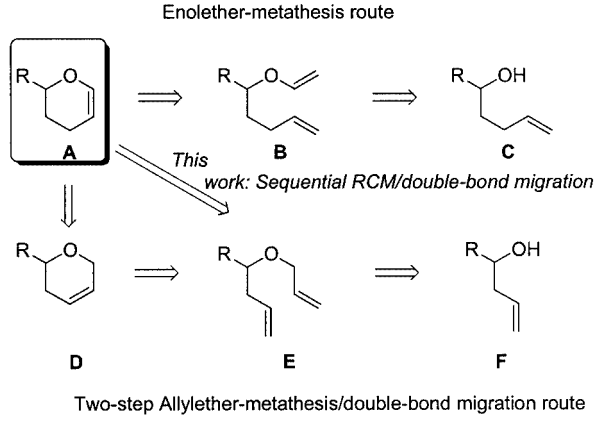


Figure 1. First (**I**) and second (**II**) generation Grubbs' catalyst

In the course of our studies directed towards the stereoselective synthesis of 2,6-difunctionalized di- and tetrahydropyrans[7] we required a short and efficient synthesis of six-membered cyclic enol ethers. Cyclic enol ethers are versatile substrates in organic synthesis, and several syntheses of complex target molecules rely on the selective functionalization of these substrates.[8] In Scheme 1 two routes to cyclic enol ethers based on ring closing metathesis are illustrated for dihydropyrans: The enolether metathesis pathway (**A** → **B** → **C**)[9] and the allyl ether metathesis/double-bond migration pathway (**A** → **D** → **E** → **F**).[10] The former route is a single-step procedure that requires only one catalyst, but the reactivity of enol ethers **B** is significantly lower than allyl ethers **E**. The latter route has the advantages of using a smooth allyl ether metathesis[11] and homoallylic alcohols **F** as starting materials, which are, in contrast to pentenols **C**, available in enantiomerically pure form by numerous methods, for example well-established allylboration strategies.[12] The disadvantage is obviously the additional double-bond migration step (**A** → **D**), which can be mediated by stoichiometric amounts of strong bases or catalytic amounts of various transition metal complexes of rhodium,[13a] iridium,[13b] nickel[13c] and ruthenium.[13d−13f] In most reports describing the isomerization of allyl ethers to enol ethers this transformation is used to remove the allyl protecting group.[14] Frauenrath et



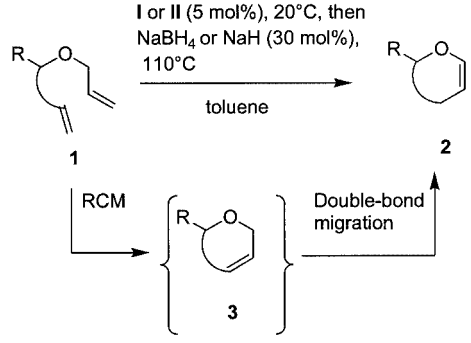
Scheme 1

[a] Universität Dortmund, FB Chemie − Organische Chemie
Otto-Hahn-Straße 6, 44227 Dortmund, Germany

al. have demonstrated that the regio- and stereoselective double-bond migration in 1,3-dioxepines gives useful building blocks for polyether synthesis.[15] In-situ-generated ruthenium-hydride species are particularly active catalysts for the conversion of these substrates.[16]

In this contribution we report a novel sequential reaction that combines an olefin metathesis-based formation of cyclic allyl ethers with a subsequent isomerization to the corresponding cyclic enol ether (route **A** → **E** in Scheme 1). It has previously been noted that olefin isomerization reactions may interfere with olefin metathesis reactions, normally as an undesired side-reaction.[17] During preparation of this manuscript a paper by Snapper et al. was published that describes an olefin metathesis-double bond migration sequence, presumably proceeding via ruthenium hydride intermediates. The metathesis catalyst was activated to promote the isomerization step by treatment with molecular hydrogen diluted with nitrogen.[18]

Ruthenium carbene complexes were activated to catalyze the double-bond migration by addition of a hydride donor, such as $NaBH_4$ or NaH, after complete consumption of the starting materials **1** (monitored by TLC). Ring-closing metathesis of these substrates is a very smooth process; complete consumption of **1** is observed in the presence of five mol % of ruthenium catalysts **I** or **II** (Figure 1) within one hour at ambient temperature. Formation of the cyclic enol ethers **2** requires elevated temperatures and is complete within two to five hours (Scheme 2).

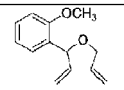
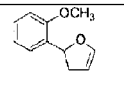
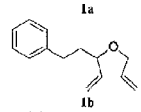
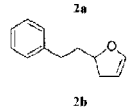
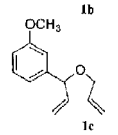
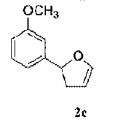
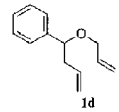
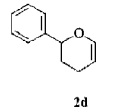
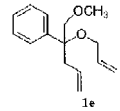
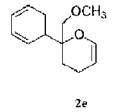
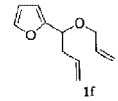
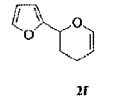
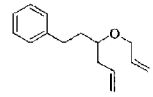
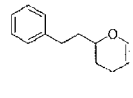
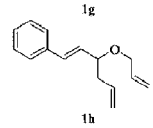
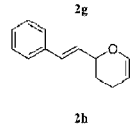
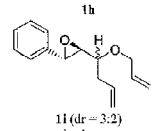
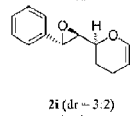
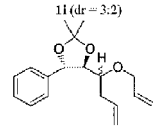
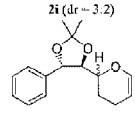
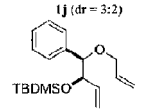
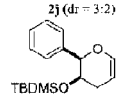
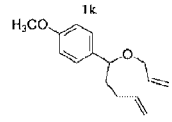
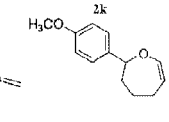
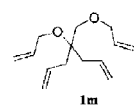
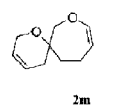
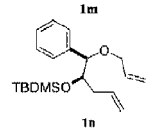
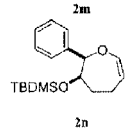


Scheme 2

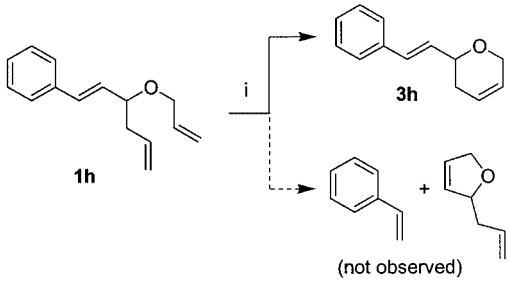
As shown in Table 1, the five-, six- and seven-membered oxacycles **2** were obtained in good to excellent yields and selectivities following this sequence. Only in the case of dihydrofurans **2a**−**c** (entries 1−3) were significant amounts of the alternative regioisomer with a triply substituted double bond observed. These products were easily removed by column chromatography, thus the yield given in these cases refers to a single isomer of **2**. Dihydropyrans **2d**−**k** (entries 4−11) are generally formed in excellent yields and regioselectivities (better than 10:1), with the exception of **2h** (entry 8). Ring-closing metathesis of **1h** is a fast and clean process, giving **3h** in 90% isolated yield. The alternative cyclization mode, leading to a dihydrofuran and styrene, was not observed (Scheme 3).

Subsequent isomerization of the intermediate **3h** to **2h** is extremely slow and stops at 70% conversion, even if 10

Table 1. Sequential RCM/Double-bond migration reaction

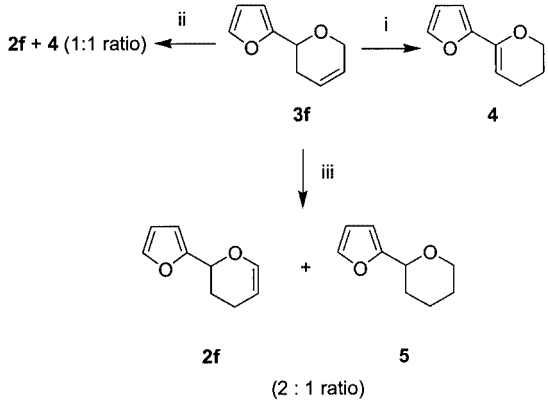
Entry	Substrates	Products	Conditions[a]	Yield[b]
1	 **1a**	 **2a**	1)	79% (8.0:1)
2	 **1b**	 **2b**	1)	70% (4.8:1)
3	 **1c**	 **2c**	1)	64% (3.6:1)
			2)	58% (3.0:1)
4	 **1d**	 **2d**	1)	87% (>12:1)
5	 **1e**	 **2e**	1)	80% (--)
6	 **1f**	 **2f**	1)	95% (11.5:1)
7	 **1g**	 **2g**	1)	89% (> 12:1)
8	 **1h**	 **2h**	3)	88%[c] (>12:1)
9	 **1i** (dr = 3:2)	 **2i** (dr = 3:2)	1)	91% (>12:1)
10	 **1j** (dr = 3:2)	 **2j** (dr = 3:2)	1)	73% (>12:1)
11	 **1k**	 **2k**	2)	87% (>12:1)
12	 **1l**	 **2l**	1)	44%
13	 **1m**	 **2m**	1)	36%
14	 **1n**	 **2n**	2)	82% (>12:1)

[a] Conditions: 1) Toluene, **I** (5 mol %), 20 °C, then NaH (30 mol %), 100 °C. 2) Toluene, **I** (5 mol %), 20 °C, then $NaBH_4$ (30 mol %), 100 °C. 3) Toluene, **II** (10 mol %), 20 °C, then NaH (50 mol %), 100 °C. [b] Ratio of regioisomers given in parentheses. [c] Reaction stops at 70% conversion. Yield refers to a 3.0:1 mixture of **2h** and **3h**.



Scheme 3. i, CH_2Cl_2, 20 °C, **I** (5 mol %) (90%)

mol % of catalyst **II** is used. One might speculate that the exocyclic C-C double bond coordinates intramolecularly to the ruthenium, leading to a significant retardation of the double-bond migration step. All structurally related examples without a double bond in this position (entries 7, 9 and 10) are smoothly converted under the conditions given in Scheme 2. The 2-furyl-substituted derivative **2f** (entry 6) is obtained in 90% yield, which is particularly remarkable as we have previously investigated various methods to synthesize **2f** from **3f** without success. While ring-closing metathesis of **1f** gives **3f** in good yield, several established methods for the double-bond migration failed (Scheme 4). Treatment with KO*t*Bu in DMSO at elevated temperatures gives exclusively the conjugated regioisomer **4**. With Wilkinson's catalyst and DBU a 1:1 mixture of regioisomers **2f** and **4** results, while the use of in situ generated ruthenium hydride species in methanol[16] yields a 2:1 mixture of the desired **2f** and tetrahydropyran **5**.



Scheme 4. i, KO*t*Bu, DMSO, 100 °C (75%); ii, $[RhCl(PPh_3)_3]$ (5 mol %), DBU (1.5 equiv.), EtOH, 78 °C (90% of **2f** and **4**); iii, $[RuCl_2(PPh_3)_3]$ (2.6 mol %), $NaBH_4$ (25 mol %), MeOH, 65 °C (40% of **2f** and 21% of **5**)

Seven-membered cyclic enol ethers are formed in lower yields, although in these cases the RCM step seems to be a limitation due to competing acyclic diene metathesis (entries 12−14). Product **2m** is obtained by a double ring-closing metathesis/double-bond migration sequence. The double ring-closing metathesis reaction of **1m** yields the spirocycle **3m** in a moderate yield of 50%.[7c] It is likely that the selective double-bond migration in the seven-membered ring is due to steric effects. Fastest conversion into the cyclic enol ethers was observed in the five-membered series (between one and two hours), while six- and seven-membered rings appear to have similar reactivity (approximately five hours are required for full conversion). The geminally disubstituted compound **1e** requires significantly longer reaction times for full conversion (ca. seven hours). We have chosen one of the most reactive examples to check if addition of the hydride donor is necessary to activate ruthenium carbene complexes for double bond migration reactions. If **1a** is heated in refluxing toluene in the presence of 5 mol % of ruthenium complex **I**, only the olefin metathesis product **3a** and no rearrangement product **2a** is formed. If, however, a substoichiometric amount of $NaBH_4$ is added after this time, clean and rapid conversion into **2a** is observed. If NaH is used as an additive, a base-promoted rather than a ruthenium-catalysed rearrangement might be possible. To rule this out, the cyclic allyl ether **3a** was isolated and purified by flash chromatography and distillation, in order to remove all ruthenium species. Compound **3a** was then treated with an equimolar amount of NaH in refluxing toluene for four hours. After this time, no rearrangement product **2a** could be detected by TLC or NMR spectroscopy. These observations strongly suggest that a ruthenium hydride species is indeed formed upon addition of a hydride donor reagent to the reaction, and that this ruthenium hydride species catalyzes the double-bond migration step.

Experimental Section

The ruthenium complex **I** (82 mg, 5 mol %) or the ruthenium complex **II** (85 mg, 5 mol %) was added to a solution of the corresponding metathesis precursor **1** (2.0 mmol) in toluene (10 mL). After complete conversion of the starting material to the intermediate RCM product **3** (TLC, between 20 min and 1 hour), $NaBH_4$ (20 mg, 30 mol %) or NaH (25 mg of a 60% dispersion in mineral oil, 30 mol %) was added and the mixture heated to 110 °C. After complete conversion (TLC) the reaction mixture was cooled to ambient temperature and washed with water. The aqueous layer was extracted with ether, the combined organic extracts were dried with $MgSO_4$, filtered and the solvents were evaporated. The residue was purified by flash chromatography on silica.

2a: ^{1}H NMR (500 MHz, C_6D_6, 25 °C, TMS): δ = 2.43 (dddd, *J* = 15.2, 8.2, 2.3, 2.3 Hz, 1 H, -C*H*H-), 3.09 (dddd, *J* = 15.2, 10.7, 2.3, 2.3 Hz, 1 H, -C*H*H-), 3.25 (s, 3 H, -OCH_3), 4.73 (ddd, *J* = 2.5, 2.3, 2.3 Hz, 1 H, -OCH=C*H*-), 6.02 (dd, *J* = 10.7, 8.2 Hz, 1 H, -OC*H*CH_2-), 6.39 (ddd, *J* = 2.5, 2.3, 2.3 Hz, 1 H, -OC*H*=CH-), 6.53 (d, *J* = 8.2 Hz, 1 H, Ar), 6.95 (dd, *J* = 7.5, 7.5 Hz, 1 H, Ar), 7.10 (ddd, *J* = 8.2, 7.5, 1.7 Hz, 1 H, Ar), 7.68 (dd, *J* = 7.5, 1.2 Hz, 1 H, Ar) ppm. ^{13}C NMR (125 MHz, C_6D_6, 25 °C, TMS): δ = 156.1, 145.7, 132.4, 128.3, 125.9, 120.9, 110.4, 99.1, 78.0, 54.8, 37.7 ppm. IR (film, KBr plates): $\tilde{\nu}$ = 1621 cm^{-1}. $C_{11}H_{12}O_2$ (176.2): calcd. C 75.0, H 6.9; found C 74.9, H 6.6.

2g: ^{1}H NMR (400 MHz, C_6D_6, 25 °C, TMS): δ = 1.45−1.39 (2 H, -CH_2-), 1.58 (dddd, *J* = 13.8, 10.8, 7.0, 4.3 Hz, 1 H, -CH_2-), 1.92−1.68 (3 H, -CH_2-), 2.64 (ddd, *J* = 13.8, 9.5, 7.0 Hz, 1 H, -OCH=CHC*H*-), 2.78 (ddd, *J* = 13.8, 9.8, 5.3 Hz, 1 H, -OCH=CHC*H*-), 3.63 (m, 1 H, -OCH-), 4.59 (ddd, *J* = 6.3, 5.5, 2.5 Hz, 1 H, -OCH=C*H*-), 6.48 (d, *J* = 6.3 Hz, 1 H, -OC*H*=H-),

7.22−7.07 (5 H, Ph) ppm. ^{13}C NMR (125 MHz, C_6D_6, 25 °C, TMS): δ = 144.3, 142.4, 128.8, 128.6, 126.1, 100.2, 74.1, 37.5, 31.9, 28.2, 20.1 ppm. IR (film, KBr plates): $\tilde{\nu}$ = 1650 cm^{-1}. $C_{13}H_{16}O$ (188.3): calcd. C 82.9, H 8.6; found C 82.9, H 8.4.

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