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Domino metathesis of alkynyl substituted cycloolefins

Anke Rückert, Dirk Eisele and Siegfried Blechert*

Institut für Chemie, Technische Universität Berlin, Strasse des 17. Juni 135, D-10623 Berlin, Germany

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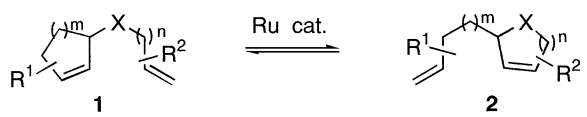
Abstract—Cycloolefins with *N*- and *O*-propargyl side chains were converted in good yields to disubstituted dihydropyrroles and dihydrofurans using Grubbs' catalyst in a sequence of enyne metathesis, RCM–ROM and CM. Olefins employed in the final CM step were ethylene and various monosubstituted alkenes.

In the last few years, olefin metathesis has emerged as a powerful tool for C–C–bond formation in organic synthesis.[1] In this field, especially ruthenium catalyzed ring-closing metathesis (RCM) has found widespread application. Cross metathesis (CM) and ring-opening metathesis (ROM) reactions can also be accomplished with catalysts of the Grubbs type. We are particularly interested in RCM–ROM rearrangements of unstrained olefinic carbocycles with alkenyl side chains (Scheme 1). The general applicability of this concept has been demonstrated in several stereocontrolled syntheses of highly substituted heterocycles and natural products.[2]

However, rearrangements of this type are equilibrium reactions. In contrast to olefin metathesis, ene-yne metathesis[3] is an irreversible process because 1,3-butadienes are formed, which do not undergo further reactions. Thus, employing enyne metathesis in a RCM–ROM sequence should yield the ring rearranged products irreversibly. Recently, such a strategy was also used by Mori et al.[4]

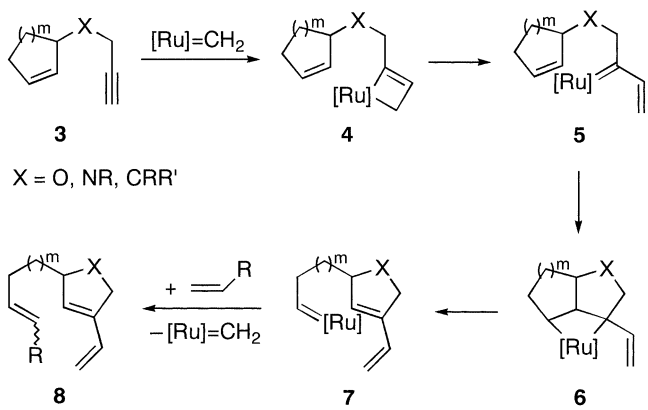
The reaction is initiated by a selective attack of the catalyst at the triple bond (Scheme 2). Cycloaddition and subsequent cycloreversion lead to vinylcarbene complex **5**, which reacts with the cycloalkene moiety via metallacyclobutane **6** yielding carbene complex **7**. In the presence of stoichiometric amounts of an olefin, complex **7** undergoes a CM reaction releasing the product **8** along with the catalytically active methylene–ruthenium species.



Scheme 1.

Preliminary experiments have been carried out with malonate **9** and 5 mol% of Grubbs' catalyst [Ru] in CH_2Cl_2 at 50°C in a sealed vessel. As expected, in the absence of an additional olefin no conversion was observed. Repetition of the experiment in the presence of an excess of ethylene gave the desired product **10** in 80% yield (Scheme 3).

We tried to extend this methodology to the synthesis of *N*- and *O*-heterocyclic systems in particular. The examples shown in Table 1 demonstrate that terminal olefins other than ethylene can also be successfully employed as CM partners.[5]



Scheme 2.

Keywords: metathesis; enynes; rearrangements; ruthenium.

* Corresponding author. Fax: 30-31423619; e-mail: blechert@chem.tu-berlin.de

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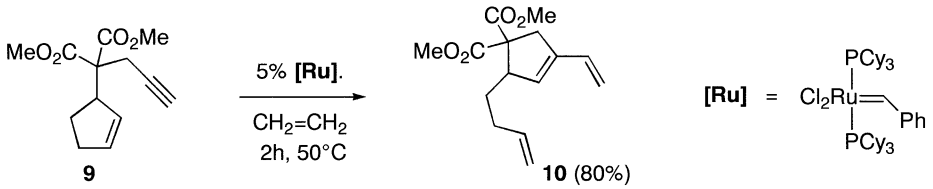
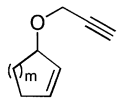
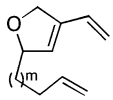
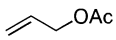
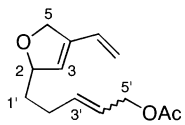
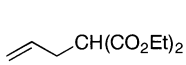
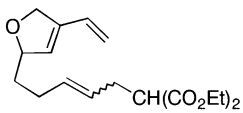
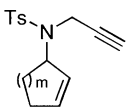
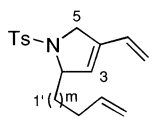


Scheme 3.

Table 1. Products of the RCM–ROM–CM sequence with [Ru]

Entry	Reactant	Olefin	Product (Yield)
1	 **11a** m = 1	$CH_2=CH_2$	 **12a** m = 1 (67%)
2	**11b** m = 2		**12b** m = 2 (5%)
3	**11a**	 **13**	 **14** (50%) (*E*/*Z* = 4:1)
4	**11a**	 **15**	 **16** (75%) (*E*/*Z* = 3:1)
5	 **17a** m = 1	$CH_2=CH_2$	 **18a** m = 1 (75%)
6	**17b** m = 2		**18b** m = 2 (60%)
7	**17c** m = 6		**18c** m = 6 (47%)

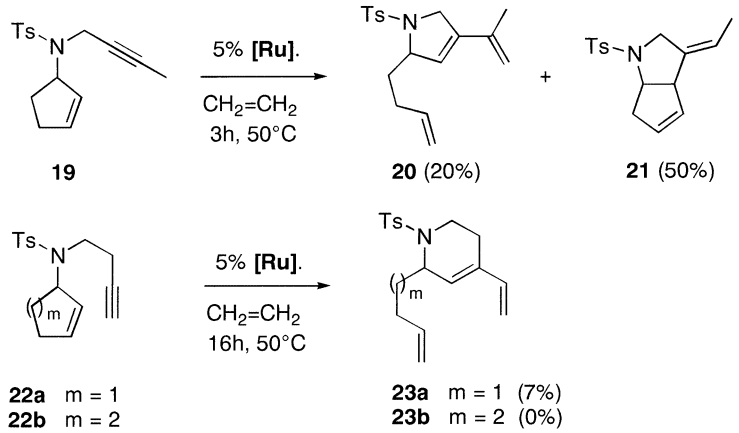
In the synthesis of the dihydrofuran systems **12a**,**b**, the extent of product formation is strongly dependent on the size of the carbocyclic ring. Whereas the cyclopentenyl ether **11a** gives **12a** in 67% yield, the corresponding cyclohexenyl derivative **11b** afforded only 5% of dihydrofuran **12b** along with 92% of starting material. At present, we cannot give an explanation of this observation especially because the analogous *N*-tosyl derivatives **17a** and **17b** give dihydropyrroles **18a**,**b** in good yields. Even the ten-membered **17c** can be rearranged to **18c** in 47% yield.

Examples **14** and **16** demonstrate that other terminal alkenes can be used successfully as CM partners. The *E*/*Z* stereoselectivity of the final CM reaction, however, is low with *E*/*Z* ratios varying from 2:1 to 4:1.[6] CM with the 1,3-butadiene moiety was not observed.

In a further study, the scope of application of this method was tested by varying the *N*-alkynyl side chain (Scheme 4). Therefore, we subjected a 2-butynyl cyclopentenylamine **19** to the same reaction conditions. However, the desired product **20** could be obtained in only 20% yield. The bicyclic compound **21** was isolated as the main product. This result was not observed by Mori et al.[4] on related examples. The formation of **21** can be explained by sequential hydrometallation of the triple bond, intramolecular carbometallation and β-hydride elimination. Similar processes have been reported in RCM reactions.[7]

Larger *N*-heterocyclic rings should be accessible using homologues of the *N*-propargyl side chain. Ring rearrangement of homopropargylamides **22a**,**b**, however, gave only a low yield or nothing of the desired tetrahydropyridine derivatives **23a**,**b**.

The products obtained by RCM–ROM–CM domino sequence are of synthetic interest for further functionalization and as such may serve as useful building blocks



Scheme 4.

for natural product synthesis. Further systematic studies are currently in progress in our laboratories.

Acknowledgements

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4. Kitamura, T.; Mori, M. *Org. Lett.* **2001**, *3*, 1161–1163.
5. (a) General procedure for ring rearrangements with ethylene:
   Through a solution of 0.35 mmol of the propargylic compound (**11a**,**b**, **17a**–**c**) and 15 mg of Grubbs' catalyst in 10 ml dichloromethane were bubbled slowly 50 ml of ethylene at room temperature. The reaction vessel was sealed and heated to 50°C for 3 h. After evaporation of the solvent, the residue was purified by flash-chromatography on silica gel to yield **12a**,**b**, **18a**–**c**.
   Selected data (**18b**):
   ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.45 (tt, $J=7$; 7 Hz, 2′-H_2), 1.80 (dt, br, $J=7$; 7 Hz, 1′-H_2), 2.05 (dt, $J=$ 7; 7 Hz, 3′-H_2), 4.23, 4.25 (AB, br, $J=14$ Hz, 5-H_2), 4.52 (m_C, 2-H), 4.98 (d, br, $J=10$ Hz, 5′-H), 5.02 (d, br, $J=17$ Hz, 5′-H), 5.50 (d, br, $J=2$ Hz, 3-H), 5.80 (ddt, $J=17$; 10; 7 Hz, 4′-H); 4-CH=CH_2: 5.02 (d, $J=18$ Hz), 5.15 (d, $J=11$ Hz), 6.32 (dd, $J=18$; 11 Hz); Ts: 2.43 (s), 7.30, 7.72 (2 d, br, $J=8$ Hz). ^{13}C NMR ($CDCl_3$): δ 24.0 (t, C-2′), 33.8 (t, C-3′), 35.6 (t, C-1′), 54.4 (t, C-5), 67.4 (d, C-2), 114.7 (t, C-5′), 127.9 (d, C-3), 134.8 (s, C-4), 138.6 (d, C-4′); 4-CH=CH_2: 116.8 (t), 130.0 (d); Ts: 21.6 (q), 127.4, 129.8 (2 d), 136.7, 143.5 (2 s). $C_{18}H_{23}NO_2S$ calcd 317.1450. Found 317.1453 (HR-MS).
   (b) General procedure for ring rearrangements with monosubstituted olefins:
   1 mmol of the propargylic compound (**11a**, **17a**), 3 mmol of monosubstituted olefin (**13**, **15**) and 44 mg of Grubbs' catalyst in 15 ml dichloromethane were heated under reflux for 1–3 h (TLC control) in an Ar atmosphere. The products (**14**, **16**) were purified as described under (a).
   Selected data ((*E*)-**16**):
   ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.60 (dt, $J=7$; 7 Hz, 1′-H_2), 2.05 (dt, $J=7$; 7 Hz, 2′-H_2), 2.55 (dd, $J=7$; 7 Hz, 5′-H_2), 3.38 (t, $J=7$ Hz, 6′-H), 4.68 (ddd, $J=12$; 2; 2 Hz) and 4.74 (ddd, $J=12$; 6; 2 Hz, 5-H_2), 4.85 (tdd, $J=7$; 6; 2 Hz, 2-H), 5.73 (s, br, 3-H); 4-CH=CH_2: 4.96 (d, $J=18$ Hz), 5.15 (d, $J=11$ Hz), 6.50 (dd, $J=18$, 11 Hz); $(CO_2Et)_2$: 1.25 (t, $J=7$ Hz), 4.18 (q, $J=7$ Hz). ^{13}C NMR ($CDCl_3$): δ 28.2, 31.8, 35.4 (3 t, C-1′,-2′,-5′), 52.2 (d, C-6′), 73.6 (t, C-5), 85.9 (d, C-2), 125.7 (d, C-3′), 128.2 (d, C-3), 133.6 (d, C-4′); 4-CH=CH_2: 116.3 (t), 129.4 (d); $(CO_2Et)_2$: 14.1 (q), 61.2 (t), 169.0 (s). $C_{18}H_{26}O_5$ calcd 322.1780. Found 322.1786 (HR-MS).
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