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Ene-yne-ene and ene-yne-yne metathesis of norbornene derivatives

Donatella Banti and Michael North*

Department of Chemistry, King's College London, Strand, London WC2R 2LS, UK

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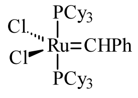
Abstract—Norbornene derivatives **4** and **5** containing sidechains bearing an internal alkyne and either a terminal alkene or a terminal alkyne were found to undergo a cascade of metathesis reactions when treated with ruthenium based metathesis catalysts to form highly functionalised pentacyclic products. The reactions illustrate an interesting difference in reactivity between Grubbs' catalyst and the second generation catalyst, with the former being more reactive for the early steps of the cascade.

The discovery by Grubbs of the air stable ruthenium complex **1** has sparked an enormous increase in interest in alkene and ene-yne metathesis.[1] Recently, we have shown that readily available substrates **2** and **3** undergo a cascade of alkene and ene-yne metathesis reactions when treated with catalyst **1**, leading to stereochemically controlled tricyclic products. The combination of these reactions with Diels–Alder reactions provides a one-pot conversion of compounds **2** and **3** into (up to) heptacyclic products.[2] In this communication, we report the extension of this metathesis cascade to the more complex substrates **4** and **5**.



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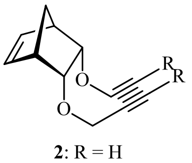
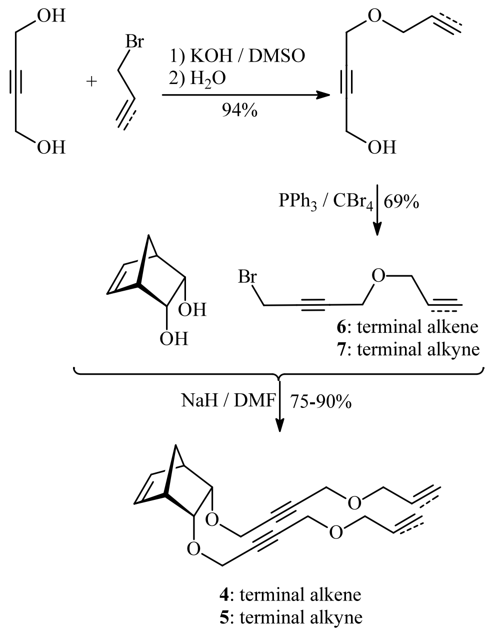


2: R = H
3: R = Me

Ene-yne **6** and diyne **7** were prepared by the same route starting from butyne-1,4-diol as shown in Scheme 1. Thus, treatment of allyl or propargyl bromide with an excess of the diol resulted in formation of the corresponding mono-ethers[3,4] which could be brominated to give the desired bromides **6**[4,5] and **7**. Reaction of compounds **6** or **7** with *endo*-*cis*-5,6-dihydroxynorborn-2-ene[6] gave the desired metathesis precursors **4** and **5** respectively.[7]

The metathesis of compound **4** was investigated using catalyst **1** and the second generation ruthenium metathesis initiator **8**.[8] Initial reactions carried out under an inert atmosphere failed to give any identifiable products. However, when the atmosphere was changed to ethene,[9] a mixture of three products (**9**–**11**) was obtained as shown in Scheme 2. In each case, the starting material had undergone ring-opening metathe-



Scheme 1.

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* Corresponding author. Tel.: +44-207-848-1164; fax: +44-870-131-3783; e-mail: michael.north@kcl.ac.uk

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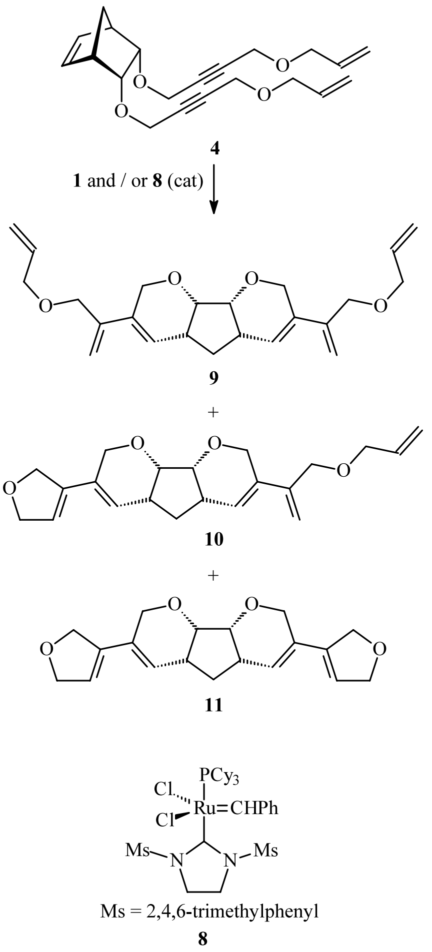


Scheme 2.

sis of the norbornene ring and subsequent ene-yne metathesis, but the products differed in the extent to which they had undergone a subsequent ring-closing metathesis with the terminal alkene. The results are summarised in Table 1.

At room temperature using 5 mol% of catalyst **1**, compounds **9**–**11** were obtained in 65% overall yield with the fully metathesized product **11** as the major product (Entry 1). No improvement in the ratio of the products, or the total yield was observed if the reaction time was extended (Entry 2), and increasing the reaction temperature was detrimental to both the yield and product ratio (Entries 3 and 4). The second generation catalyst **8** either at room temperature or in refluxing dichloromethane failed to induce any metathesis of substrate **4** (Entries 5 and 6), and the same result was obtained if the reaction was carried out under a nitrogen atmosphere. Catalyst **8** has previously been reported to be a poor initiator for the ROMP of norbornene due to a poor initiation to propagation ratio. This observation may have some relevance to the failure of catalyst **8** to initiate the metathesis of compound **4**.[10]

The overall conversion of substrate **4** to pentacyclic product **11** involves the elimination of one molecule of ethene and so will be retarded by the presence of an ethene atmosphere. However, the fact that no reaction occurs under a nitrogen atmosphere; and the isolation of compounds **9** and **10** indicate that the reaction actually occurs through a series of steps, some of which require ethene and some of which generate ethene. The conversion of substrate **4** into compound **9** requires one equivalent of ethene, and the subsequent conversions of **9** into **10** and **10** into **11** each release one equivalent of ethene. Hence, the early stages of the cascade leading to compound **11** are favoured by an ethene atmosphere, whilst the latter stages are inhibited by the presence of excess ethene. Therefore, a series of reactions were carried out in which after initial reaction with catalyst **1** under an ethene atmosphere, additional catalyst was

Table 1. Metathesis reactions on substrate **4**

Entry	Catalyst (mol%)	Temp (°C)	Time (h)	**9** (%)	**10** (%)	**11** (%)
1	**1** (5)	rt	20	18	14	33
2	**1** (5)	rt	69	16	22	28
3	**1** (5)	35	4	8	13	12
4	**1** (5)	35	20	13	6	16
5	**8** (5)	rt	20	0	0	0
6	**8** (5)	35	22	0	0	0
7	**1** (5)+**8** (5)	35	24	15	6	43

Table 2. Two stage metathesis of substrate **4**[a]

Entry	Second catalyst (mol%)	Atmosphere for second stage	Temp (°C)	**9** (%)	**10** (%)	**11** (%)
1	**1** (5)	ethene	rt	15	11	33
2	**1** (5)	nitrogen	rt	16	22	28
3	**8** (5)	nitrogen	rt	0	0	36
4	**8** (5)	ethene	35	0	0	37

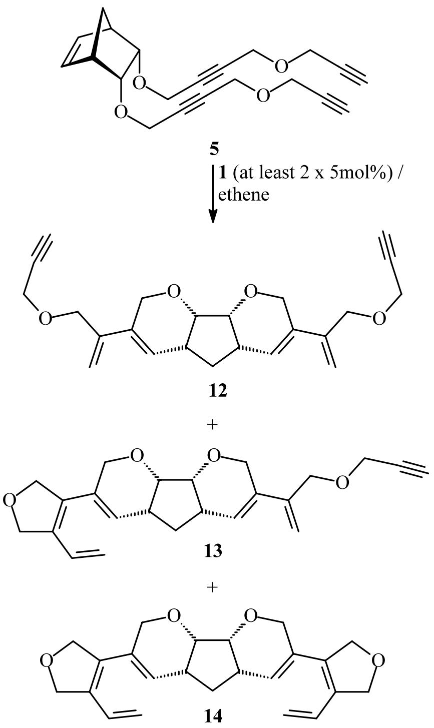
[a] In all cases the reaction was first treated with catalyst **1** (5 mol%, except entry 2 where 10 mol% was used) under an ethene atmosphere at the same temperature specified in the table for the second stage. The first stage of the reaction was left for 4–43 h until all starting material had been consumed, and the second stage was left overnight.

added and/or the atmosphere was changed. The results of these reactions are summarised in Table 2.

Simply adding a second batch of catalyst **1** did not improve the yield or ratio of products **9**–**11** (Entry 1). Simultaneously changing the atmosphere to nitrogen did double the amount of product **10** produced, but disappointingly did not increase the amount of product **11** or the overall yield (Entry 2). More encouraging results were obtained when the second batch of catalyst added was catalyst **8**, since under either an inert or ethene atmosphere, at room temperature or in refluxing dichloromethane, compound **11** was the only product isolated, though with no improvement in its yield (Entries 3 and 4). These results suggested that the replacement of the ethene atmosphere by nitrogen made no difference to the outcome of the reaction, but also suggested that catalyst **8** was beneficial to the later stages of the metathesis cascade although as shown by entries 5 and 6 of Table 1, it was unable to initiate the cascade. Therefore, an experiment was conducted in which catalysts **1** and **8** were simultaneously added to substrate **4** under an ethene atmosphere (Table 1: entry 7) and gratifyingly, this resulted in the highest isolated yield for compound **11**.[11]

Having optimised the metathesis of substrate **4**, the metathesis of the diyne analogue **5** was investigated. In this case however, all possible products resulting from metathesis of compound **5** involve the overall addition of one molecule of ethene to the substrate. Therefore, all reactions had to be carried out under an ethene atmosphere. The metathesis of substrate **5** by catalyst **1** was found to be relatively slow, and required two additions of 5 mol% of catalyst **1**, 48 hours apart and a total reaction time of 96 hours. Under these conditions, products **12**–**14** were obtained in 2:4:3 ratio and in 46% overall yield as shown in Scheme 3. By using six consecutive additions of 5 mol% of catalyst **1**, with a 24 hour reaction time between each addition, it was possible to avoid the formation of compound **12**, and compounds **13** and **14** were obtained in 1:2 ratio and in 55% overall yield. Raising the reaction temperature to 35°C did not improve the yield or ratio, and catalyst **8** was totally inactive with substrate **5**. Simultaneous or sequential addition of catalysts **1** and **8** was also not advantageous for this substrate.

Comparing substrates **4** and **5**, it is apparent that both substrates readily undergo ring-opening metathesis of the strained norbornene ring followed by ring-closing ene-yne metathesis and cross metathesis with ethene to give compounds **9** and **12** respectively. However, subsequent ring-closing diene-ene metathesis of compound **9** to give **10** and **11** is far more facile than the ring-closing diene-yne metathesis of compound **12** to give compounds **13** and **14**. These ring-closing metatheses can occur by two different mechanisms. The ruthenium catalyst can react with the diene component of compounds **9** and **12** to generate a conjugated ruthenium alkylidene complex which then cyclises onto the terminal alkene or alkyne. Alternatively, the ruthenium catalyst can react initially with the terminal alkene/alkyne and the resulting ruthenium alkylidene can then cyclise onto the diene unit of compound **9** or **12**. In the case of compound **9**, the latter mechanism seems far more likely for both steric and electronic reasons, but it is not clear which route would be more favourable for substrate **12**. However, it is well known that metathesis reactions involving alkynes or dienes are more difficult than those involving just unconjugated alkenes,[1] and this may explain the difference in reactivity between the two substrates whatever the actual mechanism.



Scheme 3.

In summary, we have shown that the cascade metathesis of alkyne substituted norbornenes can be extended to substrates **4** and **5** leading to highly functionalised pentacyclic systems in a single step. The reactions also illustrate that the metathesis catalysts **1** and **8** have very different reactivities, and that the usual generalisation that compound **8** is more reactive than catalyst **1** is not always valid. Thus, compound **8** will not start the metathesis cascades of compounds **4** and **5**, but in the case of substrate **4**, it was found that simultaneous addition of catalysts **1** and **8** gave better results than either catalyst used separately. It may be that some steps of the cascade are catalysed by complex **8** more effectively than they are catalysed by complex **1**, but it is also possible that catalysts **1** and **8** react together in situ to form a new bimetallic metathesis initiator. Other bimetallic metathesis initiators have previously been reported.[12]

Acknowledgements

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11. Typical experimental procedure: A solution of diyne **5** (100 mg; 0.296 mmoles) in dry dichloromethane (22 ml) was cooled to −78°C and ethene was passed through the solution for 10 minutes. A solution of catalyst **1** (12.16 mg; 0.0148 mmoles) in dry dichloromethane (3 ml) was then added and after 15 minutes the mixture was warmed to room temperature and stirred for 48 hours. Additional catalyst **1** (12.16 mg; 0.0148 mmoles) in dry dichloromethane (3 ml) was then added and the solution stirred for a further 48 hours. The solvent was then removed in vacuo. The residue was subjected to flash chromatography (CH_2Cl_2/EtOAc 7:3) to give compounds **12** (oil, 12 mg, 11%), **13** (oil, 21 mg, 20%), and **14** (white solid, 16 mg, 15%). Selected analytical data: Compound **12**; δ_H 6.02 (d *J* 3.9 Hz, 2H), 5.10 (s, 2H), 4.98 (s, 2H), 4.50 (d *J* 15.0 Hz, 2H), 4.3–4.0 (m, 8H), 4.07 (d *J* 2.4 Hz, 4H), 2.38 (t *J* 2.3 Hz, 2H), 2.31 (m, 2H), 1.99 (dt *J* 12.1, 6.1 Hz, 1H), 1.52 (q *J* 12.3 Hz, 1H); Found (CI; M+NH_4^+): 384.2172; $C_{23}H_{30}NO_4$ requires: 384.2175. Compound **13**: δ_H 6.49 (dd *J* 17.6, 10.9 Hz, 1H), 6.1–6.0 (m, 1H), 5.7–5.8 (m, 1H), 5.12 (d *J* 10.1 Hz, 1H), 5.11 (s, 1H), 4.98 (s, 1H), 4.93 (d *J* 17.6 Hz, 1H), 4.8–4.7 (m, 4H), 4.49 (d, *J* 18.7 Hz, 1H), 4.45 (d *J* 18.7 Hz, 1H), 4.3–4.1 (m, 6H), 4.07 (d *J* 2.4 Hz, 2H), 2.38 (t *J* 2.3 Hz, 1H), 2.4–2.3 (m, 2H), 2.1–2.0 (m, 1H), 1.6–1.5 (m, 1H); Found (CI; M+NH_4^+): 384.2173; $C_{23}H_{30}NO_4$ requires: 384.2175. Compound **14**: δ_H 6.49 (dd *J* 17.5, 11.0 Hz, 2H). 5.71 (d *J* 3.7 Hz, 2H), 5.13 (d *J* 11.2 Hz), 4.94 (d *J* 17.6 Hz, 2H), 4.8–4.7 (m, 8H); 4.44 (d *J* 15.0 Hz, 2H), 4.24 (d *J* 15.0 Hz, 2H), 4.20 (d *J* 4.7 Hz, 2H), 2.4–2.3 (m, 2H), 2.02 (dt, *J* 12.2, 6.2 Hz, 1H), 1.53 (q *J* 12.1 Hz, 1H). *m*/*z* (CI; %): 384 (M+NH_4^+; 12), 351 (30), 319 (15), 297 (100).
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