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Ring-opening–ring-closing metathesis of bicyclo[2.2.2]octenes: a novel synthesis of decalins and hydrindanes

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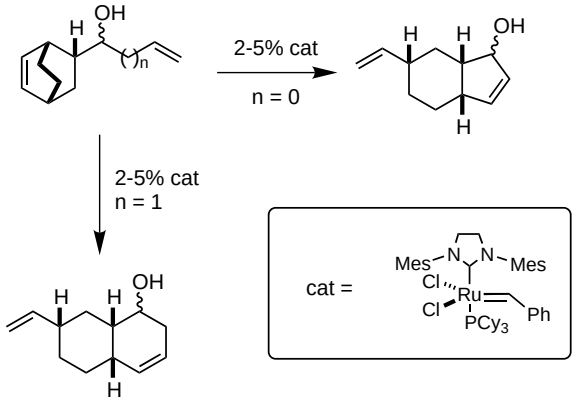
Abstract—Bicyclo[2.2.2]octenes containing an olefinic side-chain undergo ring-opening–ring-closing metathesis to give decalins and hydrindanes in reasonable yields.

In recent years, ring-closing metathesis (RCM) has garnered widespread interest as a powerful new synthetic method for the synthesis of cyclic olefins from acyclic diene precursors.[1] This attention has been underpinned in large part by the efforts of the Grubbs and Schrock research groups who have pioneered research into well-defined transition metal alkylidene complexes for metathesis reactions. These studies have led to functional group tolerant ruthenium and molybdenum alkylidene catalysts that can effect cyclization of a diverse range of substrates under mild reaction conditions.

One of the original applications for these catalysts was the ring-opening metathesis polymerization of strained cyclic olefins such as norbornene or cyclooctadiene.[2] Given the diverse (primarily cycloaddition) methods available for the synthesis of bridged bicyclic ring systems, surprisingly scant attention has been paid to the development of *tandem sequences* based around an initial ring-opening of a strained ring system.[3] Notable exceptions to this generalization include studies from the Snapper group on ring-opening reactions of cyclobutenes[4] and from Blechert[5] on ring-opening reactions of functionalized norbornenes. Hoveyda and Schrock have also developed asymmetric ring-opening metathesis reactions of norbornenes.[6] As part of synthetic studies on terpenoid natural products we have investigated the tandem ring-opening–ring-closing metathesis of bicyclo[2.2.2]octenes[7] as a novel entry to functionalized decalin and hydrindane ring systems (Scheme 1), and in this letter we report our preliminary studies.

Our initial studies focused on substrates readily prepared by a two step sequence involving $SnCl_4$-mediated Diels–Alder cycloaddition between 1,3-cyclohexadiene and acrolein to give **1** in 97% yield, followed by addition of vinylmagnesium bromide which provided a diastereomeric mixture of allylic alcohols **2** (66%, *dr* = 3:1, Scheme 2).[8] This mixture of alcohols was also readily oxidized by the Swern protocol to give enone **3**.

At this juncture we were able to examine the reactivity of substrates **2** and **3** towards Grubbs' ruthenium alkylidenes. Preliminary studies employing carbene **6**[9] failed to give any of the desired ring-opened–ring-closed products. Gratifyingly, we quickly discovered that the heterocyclic carbene-substituted ruthenium alkylidene **7**[10] mediated the desired transformation to give *cis*-hydrindane **4** in 69% yield (Scheme 2, **2**→**4**).



Scheme 1. A ring-opening–ring-closing metathesis approach to decalins and hydrindanes.

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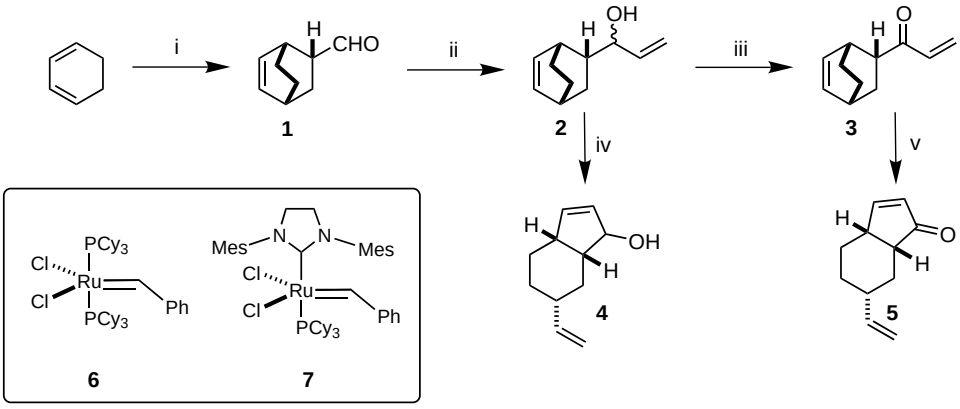


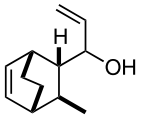
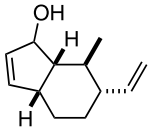
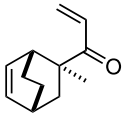
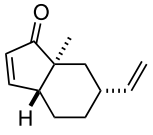
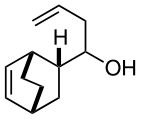
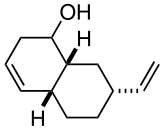
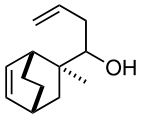
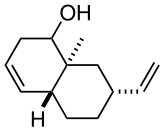
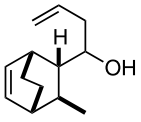
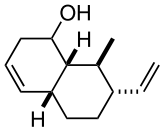
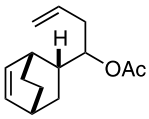
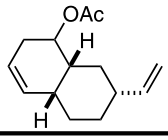
Scheme 2. *Reagents and conditions*: (i) H_2C=CHCHO, $SnCl_4$, CH_2Cl_2, −78→−30°C, 97%; (ii) H_2C=CHMgBr, THF, −78°C, 3 h, 65%; (iii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78°C, 41%; (iv) 2% cat. **7**, CH_2Cl_2, rt, 1.5 h, 93% [69% without initial sparging with H_2C=CH_2]; (v) 5% cat. **7**, CH_2Cl_2, rt, 3 h, 56%.

The major competitive reaction was simple dimerization of the starting material to produce material that was not reactive under the reaction conditions.

This side reaction could be readily suppressed by initially sparging the reaction with ethylene, followed by stirring under nitrogen. This simple modification raised the yield of **4** to 93%, and was also general in terms of its positive effect on yields for other substrates.[11]

A number of other compounds were also suitable substrates for the reaction (Table 1).[12] Cyclization proceeds readily in the presence of 2–5 mol% of catalyst **7** to give both *cis* and *trans* hydrindanes (**2**→**4**, **3**→**5** and entries 1–2) as well as *cis* and *trans* decalins (entries 3–6). Cyclization to give hydrindane ring systems proceeds readily at room temperature, whereas cyclization to give decalins required higher temperature—typically toluene at reflux.

Table 1. Ring-opening–ring-closing metathesis of bicycle[2.2.2]octenes to give hydrindanes and decalins. Catalyst in all cases is **7**

Entry	Substrate	Conditions	Product	Yield
1		4% cat, CH_2Cl_2, rt, 24h		53%
2		2% cat, CH_2Cl_2, rt, 2.5h		60%
3		4% cat, PhMe, ↯, 24h		58%
4		4% cat, PhMe, ↯, 18h		65%
5		4% cat, PhMe, ↯, 18h		52%
6		4% cat, PhMe, ↯, 24h		64%

In summary, we have demonstrated that ruthenium alkylidene **7** is a competent catalyst for ring-opening–ring-closing metathesis of bicyclo[2.2.2]octenes, and this provides a novel approach to the synthesis of functionalized decalins and hydrindane ring systems. Further studies on the generality of this transformation and applications to natural products synthesis are underway and will be reported in due course.

Acknowledgements

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7. Grubbs and co-workers have examined the ring-opening metathesis polymeriziation of bicyclo[2.2.2]octadienes, see: Conticello, V. P.; Gin, D. L.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 9708.
8. All new compounds were fully characterized by ^{1}H and ^{13}C NMR, HRMS and IR.
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10. Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.
11. **Representative experimental procedure**: Grubbs' catalyst **7** (4.8 mg, 2 mol%) was dissolved in CH_2Cl_2 (2 mL) and added by syringe to a solution of alcohol **2** (48 mg, 0.29 mmol) in CH_2Cl_2 (28 mL). Substrate concentration in the resulting solution was 0.01 M. This solution was then sparged with ethylene three times over a 30 min period for $\sim$60 s each time. At 30 min, the remaining ethylene was purged from the solution with nitrogen and the reaction was stirred at room temperature under a nitrogen atmosphere for 1 h [1.5 h total reaction time]. The solvent was then removed by rotary evaporation and the residue was purified by flash chromatography on SiO_2 with hexanes/ethyl acetate (4:1) to give **4** as a colorless oil (45 mg, 93%). ^{1}H NMR ($CDCl_3$, 500 MHz, major diastereoisomer of a 3:1 mixture of diastereoisomers): δ 0.98–1.10 (m, 2H), 1.50–1.63 (m, 2H), 1.81–1.90 (m, 2H), 2.46 (ddd, 1H, $J=5.5$, 11.5, 18.0 Hz), 2.63–2.65 (m, 1H), 4.80–4.85 (m, 1H), 4.86 (1H, ddd, $J=1.0$, 2.5, 10.5 Hz), 4.94 (1H, ddd, $J=1.5$, 3.0, 17.5), 5.64–5.67 (m, 2H), 5.73 (1H, ddd, $J=6.5$, 10.0, 17.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.7, 28.4, 32.2, 39.8, 41.2, 45.7, 83.4, 112.2, 132.3, 141.6, 144.4; MS/HRMS: calcd for $C_{11}H_{16}O$ (M^+) 164.1201, found 164.1195; IR (thin film): 991.17, 1015.63, 2854.36, 2923.67, 3331.37 cm^{-1}.
12. Substrates were prepared by sequences analogous to that shown in Scheme 2. The details will be reported in a full paper.