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Role of Cyclopropanes as Activating Groups during Oxidation Reactions with RuO_4 Generated *in situ*

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Abstract. Ruthenium tetroxide generated *in situ* under the Sharpless conditions was applied to different hydrocarbons containing cyclopropane groups either spiroanellated or ring-fused. In all cases oxidation occurred exclusively at the positions α to the cyclopropyl group to give ketones. Ring cleavage was observed when such positions were tertiary. Copyright © 1996 Published by Elsevier Science Ltd

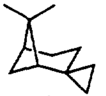
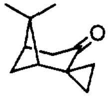
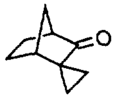
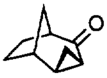
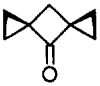
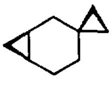
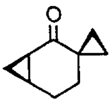
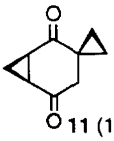
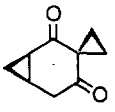
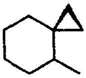
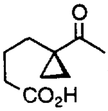
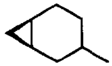
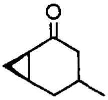
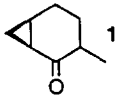
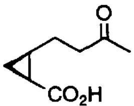
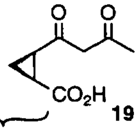
It is now well known that ruthenium tetroxide generated *in situ* under the Sharpless conditions[1] is able to oxidize unactivated saturated hydrocarbons[2] as initially illustrated by the pioneering work of Carlsen.[3] The reactivity of the carbon-hydrogen bonds decreases in the order tertiary > secondary > primary. Accordingly, highly stereoselective tertiary hydroxylation[2b,e] is the reaction most commonly and preferentially observed. Bridgehead hydroxylation has been reported in the case of adamantane[2a] and pinane.[4] Oxidation of methylene groups to the corresponding ketones can occur[2c] and may compete with tertiary hydroxylation, as has been reported earlier.[3,4b] The oxidation of methyl groups, although much more seldom, is nevertheless possible.[4] In some peculiar cases[2a,c,4,5] the cleavage of carbon-carbon bonds has been observed. Therefore it would have been expected that strained carbon-carbon bonds[4] such as those of cyclopropane rings would undergo oxidative cleavage. But this is not the case as illustrated by the behaviour[6,7] of compounds **1** and **7** which undergo oxidation of the methylene group α to the cyclopropane ring to yield the corresponding ketone.

We report further examples showing that this kind of oxidation appears to be quite general. Several cyclopropane derivatives have been chosen in such a way that the eventual competition between a tertiary C–H, a non-activated CH_2, a bridgehead C–H and a CH_2 group adjacent to a cyclopropane ring could be uncovered. As can be seen from the results (Table 1, Entries 1–4), the cyclopropane ring behaves like an activating group for the α position, no matter whether it is spiroanellated or ring-fused, as emphasized by the formation of the ketones **2**, **4**, **6**, and **8**, respectively, from **1**, **3**,[8] **5**,[9] and **7**.[10] The fact that the cyclopropane ring remains unchanged, definitely allows to reject an oxidation mechanism involving a radical type intermediate which had been considered. If such a radical would have been formed as an intermediate it would have rearranged before being attacked by any reagent.[11] In view of this activating role of a cyclopropane ring, it is noteworthy that the tricyclo[4.2.1.0^{2,4}]nonane **5** was not hydroxylated at the bridgehead adjacent to the cyclopropyl group (Entry 3). In view of the probable mechanism of this RuO_4 oxidation of C–H bonds (see below) it is not surprising that no bridgehead hydroxylation was observed for the spiroanellated hydrocarbons **1** and **3**.[12]

The oxidation of **7**[10] to **8** (Entry 4) proceeds with a rather good yield, but requires the addition of a phosphate buffer.[7]

In the case of the spiro[cyclopropane-1,3'-bicyclo[4.1.0]heptane] **9**[9] (Entry 5), the oxidation yields ketone **10** as the major product; this indicates a cumulative activation of the 2-methylene group in **9** by both adjacent cyclopropane groups. The fused cyclopropane ring appears to be more activating than the spiroanellated one as the amount of diketone **11** is slightly higher than that of the isomeric diketone **12**.

Table 1. Products resulting from the oxidation of various cyclopropyl hydrocarbons with RuO_4 generated *in situ*.

Entry	Starting material	Conditions[a]	Product[b] (Yield)
1	 **1**	25 °C / 20 h[c]	 **2** (57%)
2	 **3**	60 °C / 6 h	 **4** (65%)
3	 **5**	60 °C / 8 h	 **6** (72%)
4	 **7**	25 °C / 24 h[d]	 **8** (86%)
5	 **9**	60 °C / 8 h	 **10** (49%)  **11** (10%)  **12** (8%)
6	 **13**	60 °C / 8 h	 **14** (44%)
7	 **15**	60 °C / 8 h	 **16** (33%)  **17** (12%)  **18**  **19** (19%)
8	 **20**	20 °C / 10 min	Polymers

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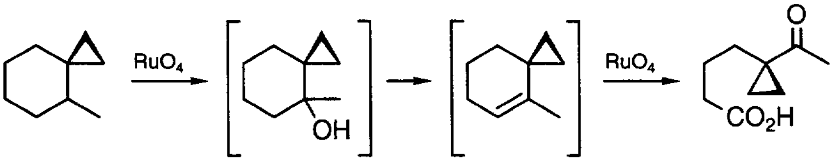
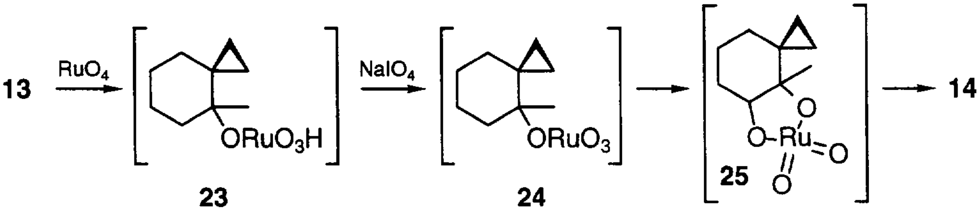
[a] Ref. 1 with $NaIO_4$ as reoxidising reagent. – [b] All compounds have been fully characterized (IR, ^1H, ^{13}C NMR as well as elemental analysis). Elemental analyses were not carried out on **18** and **19**, as they were only obtained as a mixture, and no attempt was made to separate them. – [c] Ref. 6. – [d] Addition of phosphate buffer.

Considering the formation of product **14** (Entry 6), it is reasonable to assume that the first step is the preferential hydroxylation of the tertiary C–H bond on C-4[2e] of **13**.[9] This step is probably followed by a dehydration, favoured by the formation of the double bond as in **22** conjugated with the cyclopropane ring.[13] Oxidative cleavage[14] of the latter leaves the cyclopropane ring untouched and yields ketoacid **14**.



13 **21** **22** **14**

According to previous work,[4a] it is also possible that alcohol **21** and alkene **22** are not formed, but rather that complexes **23** to **25** are successively involved, the latter of them giving **14**.



Action of RuO_4 on 3-methylbicyclo[4.1.0]heptane **15**[9] (Entry 7) yields several products. Their structures illustrate the different types of oxidations described above: Oxidation of the methylene group α to the cyclopropane ring giving compounds **16** and **17**, hydroxylation at the tertiary carbon bearing the methyl group which yields **18** following the same type of sequence as described above for the transformation of **13** into **14**. Compound **19** most likely results from further oxidation of **18**.

The oxidation product expected from bicyclo[2.1.0]heptane **20**[15] (Entry 8) was the corresponding bicyclo[2.1.0]pentan-2-one. But polymerisation was observed instead. This is certainly unusual, as these oxidation reactions generally proceed quite cleanly. Although we don't know the polymerisation mechanism, it might be possible that the cyclopropane bond which is common to the two rings and therefore highly strained might have been cleaved oxidatively as was observed upon dry ozonolysis.[16]

Several ideas can be put forward in trying to explain this peculiar role of a cyclopropane ring during the oxidation with ruthenium tetroxide generated *in situ*. We have previously emphasized[2e,4,5] the importance of the association step between the C–H bond of the hydrocarbon to be oxidized and ruthenium tetroxide. As suggested by Akermark,[17,4b] it might be possible that the cyclopropane ring enters the coordination sphere of ruthenium as a ligand thus facilitating further oxidation on an adjacent carbon-hydrogen bond. The overlap of the orbital describing such a bond with the cyclopropane orbital which depends on the dihedral angle, might also facilitate the association step. Finally, as the development of a partial positive charge on the carbon to be oxidized, is probably important in the reaction mechanism,[2d,4,12] the presence of an adjacent cyclopropane ring might play a decisive role in stabilizing such an intermediate.

Further work is in progress in our laboratories to study the general scope of the reaction and to elucidate the reaction mechanism involved in the oxidation of saturated hydrocarbons featuring a cyclopropane ring with RuO_4 generated *in situ*. The activating role of cyclopropane rings in these oxidation reactions also presents synthetic interest which deserves further investigation.

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8. Compound **3** has been prepared by cyclopropanation of 2-methylenenorbornane using the Simmons-Smith reagent, applying the general procedure described by: Denis, J. M.; Girard, C.; Conia, J. M. *Synthesis* **1972**, 549–551.
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12. In the rigid skeletons **1** and **3** the bridgehead C–H orbitals are perpendicular to the cyclopropyl Walsh orbitals, hence no stabilisation of a developing positive charge on the bridgehead would be possible. The situation is different in the case of compound **5** with an interorbital angle between the bridgehead C–H and the adjacent cyclopropyl group of about 60°. In such cases a significant stabilisation of bridgehead carbocations has been observed (*cf.* de Meijere, A.; Schallner, O.; Weitemeyer, C.; Spielmann, W. *Chem. Ber.* **1979**, *112*, 908) and hence such positions could be rapidly hydroxylated with ozone on silica gel (*cf.* Zarth, M.; de Meijere, A. *Chem. Ber.* **1985**, *115*, 2429).
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