

1,4-Cyclohexadienes as mechanistic probes for the Jacobsen epoxidation: evidence for radical pathways†

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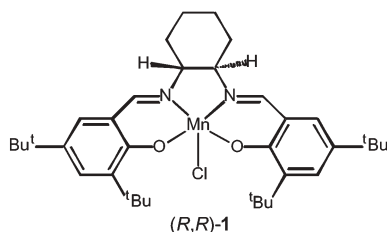
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1,4-Cyclohexadienes allow a direct comparison of epoxidation and C–H oxidation within the same molecule and give evidence for radical pathways during the Jacobsen epoxidation.

The enantioselective epoxidation of unfunctionalized olefins by optically active Mn(III) salen complexes (Jacobsen–Katsuki epoxidation) has become a very important and versatile tool for organic synthesis.¹ From the broad variety of salen ligands, the *tert*-butyl substituted catalyst **1** is most often used, since both enantiomers are commercially available and provide epoxides with excellent *ee*.



Besides the synthetic benefit of the Jacobsen epoxidation, the mechanism of the oxygen transfer to the double bond is still a matter of debate, and both radical and concerted pathways were discussed in the literature.² Recently, theoretical investigations have demonstrated the importance of different spin states during the reaction³ and Mn(V) and Mn(IV) species were detected by spectroscopy.⁴ However, no information on the nature of the organic intermediates was provided and radicals could not be trapped. Furthermore, the epoxidation of vinylcyclopropanes as “radical clocks” did not give a clear-cut picture, since the amount of ring-opening products strongly depends on the substitution pattern at the double bond and on the stoichiometric oxidant.^{2,5} Therefore, we became interested in the Jacobsen epoxidation of substrates, which provide a double bond and a sensitive radical probe within the same molecule. Thus, a direct comparison of epoxidation and radical reaction would be possible.

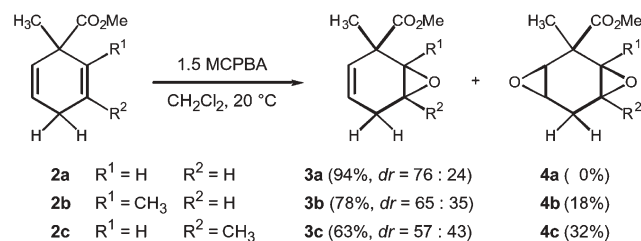
During the course of our studies on regio- and stereoselective photooxygenations,⁶ we investigated the oxidation of 1,4-cyclohexadienes **2**, which are synthesized conveniently by Birch reduction.⁷ Due to the bis-allylic hydrogen atoms, which can be easily abstracted by a radical pathway,⁸ such compounds should be ideal mechanistic probes for the Jacobsen epoxidation. Allylic and benzylic C–H oxidations by metal oxo complexes are known

in the literature,⁹ but no 1,4-cyclohexadienes were examined until now.

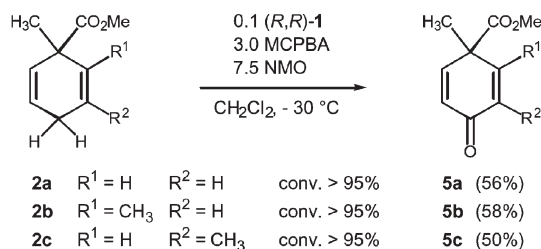
To establish the structure of the expected epoxides and to compare the Jacobsen reaction with conventional epoxidations, we first investigated the uncatalyzed epoxidation of various substituted 1,4-cyclohexadienes **2a–c** with *m*-chloroperoxy-benzoic acid (MCPBA) as oxidant (Scheme 1).

The reactions proceed smoothly at room temperature, and the epoxides **3** and **4** were isolated in almost quantitative yield. Interestingly, only one double bond is oxidized in the unsubstituted derivative **2a**, whereas the methyl substituted cyclohexadienes **2b** and **c** afford mixtures of mono-**3** and bis-epoxides **4**. This is contrary to known epoxidations of 1,4-cyclohexadienes in the literature,¹⁰ but is immaterial to the planned mechanistic studies. On the other hand, our observed diastereomeric ratios are in accordance with these publications.

The crucial experiment was the oxidation of the 1,4-cyclohexadienes **2** in the presence of the Jacobsen catalyst **1**. To directly compare these reactions with the uncatalyzed epoxidations (Scheme 1), MCPBA was chosen as the stoichiometric oxidant. It was important that in a control experiment at $-30\text{ }^{\circ}\text{C}$ no conversion was obtained with sole MCPBA. The best conditions for the Jacobsen epoxidations were found with 0.1 equiv. of catalyst (*R,R*)-**1**, 3 equiv. of oxidant, and *N*-methylmorpholine-*N*-oxide (NMO) as co-ligand.† Indeed, all 1,4-cyclohexadienes **2** gave complete conversion under such conditions (Scheme 2).



Scheme 1



Scheme 2

† Electronic supplementary information (ESI) available: Experimental procedures. See <http://www.rsc.org/suppdata/cc/b4/b415723k/>
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Interestingly, no epoxides **3** or **4** could be detected, even in the crude reaction mixture, whereas 1,3-cyclohexadienes afford the corresponding epoxides.¹¹ This demonstrates the importance of the bis-allylic position. The cyclohexadienones **5** were the sole products, isolated after column chromatography. The moderate yields are due to the formation of oligomeric and polymeric material. This complete change in the product distribution of the catalyzed and direct oxidation can only be rationalized by a different reaction mechanism.

Obviously, a manganese(V)-oxo complex **6** is generated in the first step, by reaction of the catalyst **1** with MCPBA. This intermediate can transfer the oxygen to the double bonds to afford epoxides **3** and **4**. However, isolated alkyl-substituted alkenes are epoxidized slower than conjugated systems.^{1,2} Furthermore, due to the electron-withdrawing ester group, the 1,4-cyclohexadienes **2** should be less reactive. Thus, a hydrogen atom transfer⁸ from the bis-allylic position can compete with the epoxidation (Scheme 3). This result can only be rationalized by a radical character of the manganese(V)-oxo complex **6**, which is in accordance with the recent theoretical postulation of a quintet state,³ and gives experimental evidence for a radical pathway during the attack of the Jacobsen catalyst.

After the H-transfer the stabilized cyclohexadienyl radical **7** and the manganese(IV)-hydroxy complex **8** are formed. Indeed, such paramagnetic manganese(IV) intermediates were detected by EPR spectroscopy very recently.⁴ The lifetime of the intermediary bisallylic radical **7** must be very short, since no isomerization to 2,4-allylic radicals and no formation of regioisomeric cyclohexadienones was observed. Furthermore, a homolytic cleavage of the ester group, which was described in the literature for radicals like **7**,⁸ could not compete with the fast oxygen rebound from the manganese(IV)-hydroxy complex **8**. This is in accordance with the well-known picosecond kinetics for the hydroxylation with cytochrome P-450.¹² Thus, the allylic alcohol **9** is formed and the Jacobsen catalyst **1** is regenerated, closing the reaction cycle after re-oxidation with MCPBA (Scheme 3). That molecular oxygen is not involved in the allylic oxidation was proven by

experiments under careful exclusion of air under an argon atmosphere. Furthermore, control reactions with no manganese-(salen) complex, no additive (NMO), or no MCPBA gave no conversions. Therefore, the manganese(V)-oxo complex **6** is indeed the oxidizing species, which affords the allylic alcohols **9** by a radical pathway. In the last step of the reaction, the second allylic hydrogen is abstracted even faster by the same mechanism, due to the stabilizing effect of hydroxy groups to radicals. Thus, the hydrate **10** is formed as an intermediate, and after dehydration the ketones **5** were isolated as the final products, which is in accordance with the oxidations of allylic alcohols by chromium-(salen) complexes.¹³

Finally, a direct concerted insertion of the manganese(V)-oxo complex **6** into the allylic C-H-bond was excluded by the reaction of unsubstituted 1,4-cyclohexadiene under our reaction conditions, to afford benzene quantitatively by a second H-atom abstraction in the 4-position.

To investigate the possibility of a kinetic resolution during the oxidations, which is still a challenge for Jacobsen epoxidations,¹⁴ we stopped the reaction of cyclohexadiene **2b** at 50% conversion. However, neither the reisolated starting material nor the product **5b** exhibit any enantiomeric excess. Thus, the stereogenic center is too far away from the reactive position, indicating again a hydrogen atom transfer by a radical mechanism.

In conclusion, we present experimental evidence for radical pathways during the oxidation with the Jacobsen catalyst. 1,4-Cyclohexadienes were used as mechanistic probes for the first time, to distinguish between two reaction routes within the same molecule. The Jacobsen catalyst attacked exclusively the homolytically labile hydrogen atoms, whereas MCPBA oxidized the double bond. This can be rationalized by a radical character of the manganese(V)-oxo complex, which is the reactive intermediate for both, epoxidations and allylic oxidations. Thus, double bonds with no sensitive radical probes should be attacked by a radical pathway as well, which is important for the mechanism of the Jacobsen epoxidation.

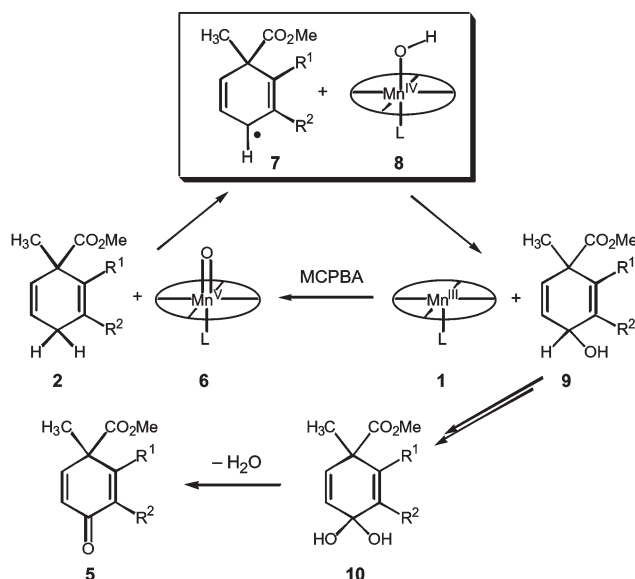
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Scheme 3

Notes and references

- Reviews: E. N. Jacobsen, *Acc. Chem. Res.*, 2000, **33**, 421–431; E. N. Jacobsen and M. H. Wu, in *Comprehensive Asymmetric Catalysis, Vol. 2*, ed. E. N. Jacobsen, A. Pfaltz and H. Yamamoto, Springer, Berlin, 1999, pp. 649–677; T. Katsuki, *J. Mol. Catal.*, 1996, **87**–107; L. Canali and D. C. Sherrington, *Chem. Soc. Rev.*, 1999, **28**, 85–93; T. Katsuki, *Synlett*, 2003, 281–297.
- T. Linker, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 2060–2062; Recent review and references cited therein: C. Limberg, *Angew. Chem., Int. Ed. Engl.*, 2003, **42**, 5932–5954.
- C. Linde, B. Åkermark, P.-O. Norrby and M. Svensson, *J. Am. Chem. Soc.*, 1999, **121**, 5083–5084; L. Cavallo and H. Jacobsen, *Angew. Chem., Int. Ed. Engl.*, 2000, **39**, 589–592; J. El-Bahraoui, O. Wiest, D. Feichtinger and D. A. Plattner, *Angew. Chem., Int. Ed. Engl.*, 2001, **40**, 2073–2076; Y. G. Abaskin, J. R. Collins and S. K. Burt, *Inorg. Chem.*, 2001, **40**, 4040–4048; P. Brandt, P.-O. Norrby, A. M. Daly and

- D. G. Gilheany, *Chem. Eur. J.*, 2002, **8**, 4299–4307; L. Cavallo and H. Jacobsen, *J. Org. Chem.*, 2003, **68**, 6202–6207.
- 4 D. Feichtinger and D. A. Plattner, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 1718–1719; W. Adam, C. Mock-Knoblach, C. R. Saha-Möller and M. Herderich, *J. Am. Chem. Soc.*, 2000, **122**, 9685–9691; D. Feichtinger and D. A. Plattner, *Chem. Eur. J.*, 2001, **7**, 591–599; K. A. Campbell, M. R. Lashley, J. K. Wyatt, M. H. Nantz and R. D. Britt, *J. Am. Chem. Soc.*, 2001, **123**, 5710–5719.
- 5 H. Fu, G. C. Look, W. Zhang, E. N. Jacobsen and C.-H. Wong, *J. Org. Chem.*, 1991, **56**, 6497–6500; C. Linde, M. Arnold, P.-O. Norrby and B. Åkermark, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 1723–1725; Very recently, an elegant radical clock was employed to differentiate between cationic and radical intermediates: W. Adam, K. J. Roschmann, C. R. Saha-Möller and D. Seebach, *J. Am. Chem. Soc.*, 2002, **124**, 5068–5073.
- 6 T. Linker and L. Fröhlich, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 1971–1972; T. Linker and L. Fröhlich, *J. Am. Chem. Soc.*, 1995, **117**, 2694–2697; V. Nardello, J.-M. Aubry and T. Linker, *Photochem. Photobiol.*, 1999, **70**, 524–530.
- 7 H. van Bekkum, C. B. van den Bosch, G. van Minnen-Pathuis, J. C. de Mos and A. M. van Wijk, *Rec. Trav. Chim.*, 1971, **90**, 137–149; P. W. Rabideau and Z. Marzinow, *Org. React.*, 1992, **42**, 1–334.
- 8 G. Binmore, J. C. Walton and L. Cardellini, *J. Chem. Soc., Chem. Commun.*, 1995, 27–28; G. Binmore, L. Cardellini and J. C. Walton, *J. Chem. Soc., Perkin Trans. 2*, 1997, 757–762; P. A. Baguley and J. C. Walton, *Angew. Chem., Int. Ed. Engl.*, 1998, **37**, 3072–3082.
- 9 K. Srinivasan, P. Michaud and J. K. Kochi, *J. Am. Chem. Soc.*, 1986, **108**, 2309–2320; J. F. Larrow and E. N. Jacobsen, *J. Am. Chem. Soc.*, 1994, **116**, 12129–12130; K. Hamachi, R. Irie and T. Katsuki, *Tetrahedron Lett.*, 1996, **37**, 4979–4982; W. Adam, M. Herold, C. L. Hill and C. R. Saha-Möller, *Eur. J. Org. Chem.*, 2002, 941–946.
- 10 H. M. Sirat, E. J. Thomas and N. D. Tyrell, *Chem. Commun.*, 1979, 36–37; A. G. Schultz, R. E. Harrington and F. S. Tham, *Tetrahedron Lett.*, 1992, **33**, 6097–6100.
- 11 S. Chang, R. M. Heid and E. N. Jacobsen, *Tetrahedron Lett.*, 1994, **35**, 669–672.
- 12 J. T. Groves and G. A. McClusky, *J. Am. Chem. Soc.*, 1976, **98**, 859–861; J. T. Groves, *J. Chem. Educ.*, 1985, **62**, 928–931; M. Newcomb and P. H. Toy, *Acc. Chem. Res.*, 2000, **33**, 449–455.
- 13 W. Adam, G. G. Gelalcha, C. R. Saha-Möller and V. R. Stegmann, *J. Org. Chem.*, 2000, **65**, 1915–1918.
- 14 T. Linker, F. Rebien, G. Tóth, A. Simon, J. Kraus and G. Bringmann, *Chem. Eur. J.*, 1998, **4**, 1944–1951; Recent review: J. M. Keith, J. F. Larrow and E. N. Jacobsen, *Adv. Synth. Catal.*, 2001, **343**, 5–26.