

PDF hosted at the Radboud Repository of the Radboud University Nijmegen

The following full text is a postprint version which may differ from the publisher's version.

For additional information about this publication click this link.

<http://hdl.handle.net/2066/57280>

Please be advised that this information was generated on 2017-12-06 and may be subject to change.

Mechanistic studies on the Mukaiyama epoxidation

Bastienne B. Wentzel,^a Paul L. Alsters,^b Martinus C. Feiters,^{a,*} Roeland J. M. Nolte^{a,*}

^a*Department of Organic Chemistry, University of Nijmegen, Toernooiveld 1, 6525 ED Nijmegen, The Netherlands.*

^b*DSM Research, LS-CC, P.O. Box 18, 6160 MD Geleen, The Netherlands.*

Abstract

A detailed mechanistic study on the Mukaiyama epoxidation of limonene with dioxygen as oxidant, bis(acetylacetonato)nickel(II) as catalyst, and an aldehyde as co-reagent is reported. All major products of the reaction have been quantitatively identified, both with *i*-butyraldehyde and 2-methylundecanal as co-reacting aldehydes. Limonene epoxide is formed in good yield. The main products evolving from the aldehyde are carboxylic acid, CO₂, CO, and lower molecular weight ketone and alcohol (K+A). A mechanism is proposed in which an acylperoxy radical formed by the autoxidation of the aldehyde is the epoxidizing species. The observation of carbon dioxide and (K+A) in a 1:1 molar ratio supports this mechanism. CO₂ and (K+A) are formed in molar amounts of 50-60% with respect to the amount of epoxide produced, indicating that epoxidation not only takes place via acylperoxy radicals, but also via a peracid route.

Cyclohexene epoxidation was also investigated with a number of different metal complexes as catalysts. Cyclohexene is very sensitive for allylic oxidation, which provides information about the action of the catalyst, *e.g.* metals which form strongly oxidizing stable high valence complexes are more likely to induce allylic oxidation. Color changes in the reaction mixture indicate the presence of such high valence species. In the case of nickel, it was found that high valence complexes are absent during the reaction which is in line with the fact that this metal displays the highest selectivity for epoxide. A mechanism which accounts for the observations is presented.

Introduction

The aerobic epoxidation of alkenes with an aldehyde as a co-reagent is an efficient and useful method for the production of fine chemicals. In general, there is a distinction between methods that do not use transition metal catalysts (see for example Kaneda¹ and Lassila²) and the more widely explored systems which make use of such a catalyst. The latter method was investigated in detail by Mukaiyama *et al.*,³⁻¹⁸ and is therefore often referred to as the Mukaiyama epoxidation. The method is very mild: usually the reactions are performed at room temperature and they often display epoxide selectivities up to 100% at full conversion of the alkene. Furthermore, the product formation is complete in a few hours, whereas the uncatalyzed reaction takes a day or more to reach the maximum conversion. These characteristics make the Mukaiyama method attractive for industrial applications, despite the fact that more than stoichiometric amounts of the co-reacting aldehyde are needed.

The uncatalyzed epoxidation of alkenes using molecular oxygen with co-oxidation of an aldehyde appears to proceed via a mechanism related to aldehyde autoxidation (Scheme 1, eq. 1, 2). The acylperoxy radical formed in eq. (2) has been shown by Lassila² to be the epoxidizing species (eq. 3, 4a). It was suggested that the carbon dioxide which is found as a side product originates from the unstable carboxyl radical generated during the epoxidation. This radical is so unstable that it decarboxylates before it can abstract a hydrogen atom, forming CO₂ and an alkyl radical (eq. 4b). The latter radical is subsequently oxidized by O₂ to give an alkyl peroxy radical which abstracts a hydrogen atom and forms an alkylhydroperoxide (Scheme 2, eqs. 6, 7). Alternatively, two alkylperoxy radicals may combine to form a tetroxide. This compound rearranges via a so-called Russell termination¹⁹ to generate a ketone and an alcohol (K + A), provided that α -hydrogens are present (Scheme 2, eqs. 8, 9). If no α -hydrogens are available, the alkylperoxy radical abstracts a hydrogen and forms an alkylhydroperoxide. Lassila found *t*-butylhydroperoxide and CO₂ in a 1:1 ratio as the products of the epoxidation of diisobutylene with pivaldehyde (R = *t*-butyl) as co-reagent, supporting eqs. 4-7. The epoxidation-decarboxylation reaction is likely to proceed concertedly (eq. 5) as Lassila has shown.²

- - - SCHEME 1, SCHEME 2 - - -

In addition to epoxidation, the acylperoxy radical which is formed in eq. 2 may abstract a hydrogen atom from another aldehyde molecule to give a peroxy acid and an acyl radical, thus propagating the autoxidation chain (Scheme 3, eq. 10). Peroxy acid (or peracid for short) is a competing epoxidizing agent (eq. 11), generating carboxylic acid in a non-radical epoxidation pathway. Peracid may also react with aldehyde yielding two molecules of carboxylic acid which terminates the radical chain (eq. 12). Furthermore, the acyl radical generated during the autoxidation steps (eqs. 1 and 10) may decarbonylate in an endothermic reaction to form an alkyl radical and carbon monoxide (eq. 13). All these reactions consume aldehyde without generating epoxide via the radical epoxidation pathway, and therefore do not generate ketone and alcohol (K + A) and CO₂.

- - - SCHEME 3 - - -

The transition-metal catalyzed epoxidation of alkenes using molecular oxygen and *i*-butyraldehyde as a co-reagent (the Mukaiyama epoxidation) was studied in detail by Nam *et al.*²⁰ As substrates, limonene, stilbene, styrene, and cyclohexene were used, and as catalysts several cyclam and porphyrin complexes of *e.g.* nickel(II), cobalt(II), manganese(III), and iron(III) were tested. It was proposed that autoxidation of aldehyde plays an important role in this metal catalyzed reaction, just as it does in the uncatalyzed oxidation of alkene and aldehyde with molecular oxygen. On the basis of the results of *cis*-stilbene epoxidation it was concluded that the oxidizing species is an acylperoxy radical, and not a peroxy acid. A mixture of *cis*- and *trans*-stilbene was obtained indicating that a freely rotating radical (as in eq. 3) is the main intermediate. Acylperoxy radicals are known to preferentially react with the double bonds of alkenes yielding epoxides (Scheme 4, eq. 14), whereas hydroxy and alkylperoxy radicals tend to abstract allylic hydrogens giving allylic oxidation products (Scheme 4, eq. 15). A good substrate to investigate whether the oxidizing species has a preference for allylic oxidation or epoxidation is cyclohexene. This molecule has four allylic hydrogen atoms and is therefore very sensitive to allylic oxidation. Using cyclohexene as a substrate, Nam *et al.* found epoxide as the predominant product. The product distributions appeared not to depend on the type of metal complex that was used as the catalyst.²⁰ It was concluded that the only role of the metal complex was the stabilization the acylperoxy radical. Unfortunately, the products evolving from the aldehyde were not isolated as was done for the uncatalyzed co-oxidation of the alkene and aldehyde by Lassila *et al.*² It was assumed that

carboxylic acid, formed through hydrogen abstraction by the carboxyl radical from either the substrate or the aldehyde was the exclusive product.

- - - SCHEME 4 - - -

In an earlier study,²¹ we investigated the scope and mechanism of the Mukaiyama epoxidation. We provided new evidence for the radical nature of the reaction, and we proposed a tentative mechanism in which the nickel catalyst may serve to stabilize the epoxidizing species, *i.e.* the acylperoxy radical.

Mizuno *et al.*²² also investigated the Mukaiyama epoxidation using three different polyoxometalates as catalysts, *i*-butyraldehyde as co-reagent, and cyclohexene as substrate. In contrast to Nam *et al.*,²⁰ they noted the formation of allylic oxidation products *i.e.* cyclohexanol and cyclohexanone, and observed that the uncatalyzed co-oxidation of cyclohexene and *i*-butyraldehyde gave a very high selectivity ratio (SR) of epoxide to allylic oxidation product, albeit in a very slow reaction. On the other hand, the catalyzed reaction gave lower selectivity ratios, but was much faster. The SR was found not to vary between the three different catalysts.

Despite the interesting results of the study of Lassila *et al.* on the uncatalyzed reaction,² no comparable studies have been published for the metal catalyzed epoxidation of alkenes using molecular oxygen as oxidant and an aldehyde as co-reagent. With this paper, we intend to fill this gap by presenting a quantitative study of all the products evolving from the Mukaiyama epoxidation. We were particularly interested in the aerobic epoxidation of *S*-limonene (Scheme 5, *S-1*), under Mukaiyama's conditions using nickel(II) β -diketonate complexes (**3**) as catalysts. Limonene epoxidation is of interest as the first step in a new industrial route for the manufacture of carvone [2-methyl-5-(1-methylethenyl)-2-cyclohexen-1-one], an important spearmint flavor compound, and was therefore investigated as the main substrate in this study. As a co-reacting aldehyde in the Mukaiyama epoxidation, *i*-butyraldehyde **4** is widely applied. However, since it was expected that low molecular weight ketone and alcohol (*i*-propanol and acetone in this case, Scheme 2, eq. 9) which are volatile and not easily analyzed quantitatively, will evolve from the reaction, we chose to use a higher molecular weight aldehyde as well for our studies. The results obtained with this aldehyde will be compared to those obtained with *i*-butyraldehyde.

- - - SCHEME 5, CHART 1 - - -

Furthermore, we felt that in addition to Mizuno's studies²² much can be learned from a detailed study of the use of various transition metal catalysts in the Mukaiyama epoxidation. Preliminary results from our group had indicated that there is indeed a difference in selectivity ratio (SR) between different metal catalysts in the Mukaiyama epoxidation of cyclohexene in contrast to Mizuno's conclusions.²² This would suggest that the metal catalyst has a more complex role than just stabilizing the oxidizing species in the reaction as Nam *et al.* concluded.²⁰ For these studies cyclohexene instead of limonene was used as the substrate, since the former compound in contrast to the latter is more sensitive to allylic oxidation (*vide infra*).

Experimental

Materials

Dipentene (*RS*-limonene, [1-methyl-4-(1-methylethenyl)cyclohexene], Aldrich, tech.), toluene (Baker, analytical grade) and cyclohexene (Aldrich, 99% or Fluka, 99.5%) were used as received. Dichloromethane (Baker, analytical grade), *i*-butyraldehyde (Aldrich) and 2-methylundecanal (Aldrich, 95%) were distilled before use. Bis{pentane-2,4-dionato}cobalt(II) (Co(acac)₂), bis{pentane-2,4-dionato}nickel(II) (Ni(acac)₂, **3a**) and bis{3-(*p*-*tert*-butylbenzyl)pentane-2,4-dionato}nickel(II) (**3b**) were prepared as described earlier²³ and dried by azeotropic distillation with toluene. All other metal salts and complexes were commercial samples and were used as received. Oxygen and nitrogen gases were from Air Liquide and Hoek Loos and were used as received.

Instrumentation

The GC analyses were performed on a Varian 3800 instrument with a Supelco fused-silica capillary column (15 m length, 35 μm ID, d_f = 1.0) containing a FFAP stationary phase; data were analyzed with Varian Star 5.2 software. GC analyses of the cyclohexene oxidation products were performed with a Chrompack fused silica CP-Sil 5CB column (25 m length, 32 μm ID, d_f = 1.2 μm). GC-MS analyses were performed on a Varian Saturn II instrument with

a Chrompack WCOT fused silica capillary column (25 m length, 25 μm ID, $d_f = 0.2 \mu\text{m}$) containing a FFAP stationary phase (CP-Wax 58) using an ion-trap MS detector.

The epoxidation reactions were carried out in a Premex autoclave reactor with Hastelloy C276 wet parts, equipped with a HC276 Dean-Stark water separator, a 4-blade stirrer (max. 1500 rpm), a sintered HC276 gas-inlet (5 μm frit) and a sampling tube. The temperature was regulated with a Premex C-M2 control unit to $\pm 0.1^\circ\text{C}$. The nitrogen and oxygen gas inlet was regulated by mass-flow controllers (MFC's) and could be controlled to $\pm 0.1\%$ v/v O_2 in N_2 . The exhaust gas was cooled (-80°C at atmospheric pressure) to condense any vapor that was present. The gas was then analyzed for carbon dioxide and carbon monoxide with a Maihak Multor 610 CO_2/CO analyzer (IR detection) and for oxygen content with a Servomex 570A O_2 analyzer.

Epoxidation runs

A standard epoxidation run was performed as follows. Approx. 60 mmol of dipentene (a mixture of *R*- and *S*-limonene, **1**) was accurately weighed and dissolved in 75 or 150 ml of toluene. This solution was loaded into the autoclave and the Dean-Stark cooler was filled with toluene. This mixture was equilibrated for at least one hour at 25.0°C under an atmosphere of approx. 8% v/v O_2 in N_2 , total pressure 7 bar. No reaction was observed during this period. The autoclave was opened and $\text{Ni}(\text{acac})_2$ and aldehyde **4** or **5** (corresponding to 0.1 mol% and 3 mol equivalents with respect to alkene respectively) were added quickly and the autoclave was closed and pressurized again. This point was taken as $t = 0$. During the reaction the pressure was kept at 7.0 ± 0.1 bar, the temperature was $25.0 \pm 0.1^\circ\text{C}$, and the stirring rate was 1500 rpm. Samples were taken regularly and analyzed with GC using 1,2,4-trichlorobenzene as the external standard and 2-(*t*-butyl)-4-methylphenol as a stabilizer for the samples. The oxygen content of the exhaust gas was registered and the CO_2 and CO content were read on-line with a personal computer. The experimental error (deviations of the measuring apparatus) was much less than 1%.

The epoxidations of cyclohexene catalyzed by different metal complexes were performed in a glass vessel at room temperature. A 50 ml two-neck flask was loaded with 0.03 mmol of the appropriate metal complex, and subsequently equipped with a balloon, a septum, and a 1 cm magnetic stirring bar. The flask was thermostatted with a water bath at 25°C . The vessel was flushed with 100% O_2 at least three times. A solution containing cyclohexene (0.30 M), 1,3-dichlorobenzene (0.25 M, internal standard), and *i*-butyraldehyde

(0.84 M, Aldrich, redistilled quality) in dichloromethane was freshly prepared. Of this solution, 10 ml was injected in the vessel at $t = 0$. The reaction was stirred at 1200 rpm. Samples were taken regularly and analyzed with GC.

Results

Epoxidation of limonene using 2-methylundecanal as co-reagent

As a co-reagent in the Mukaiyama epoxidation an α -branched aliphatic aldehyde is most suitable. While *i*-butyraldehyde (**4**) is commonly employed in this reaction (*vide infra*), we used 2-methylundecanal (**5**) to study the product that evolve from the reaction. The choice for **5** was based on the high boiling point of this compound and of the potential oxidation products, which assures that these products do not evaporate during their analysis allowing a quantitative identification by GC and GC-MS. In the epoxidation run shown in Figure 1, limonene was reacted with 2.9 equivalents of 2-methylundecanal **5** ($R = C_9H_{19}$ in Scheme 5) in toluene in an autoclave. 0.1 Mol% of $Ni(acac)_2$ (**3a**) was used as the catalyst. In the upper panel of Figure 1, the consumptions of limonene **1** and aldehyde **5** are plotted, together with the formation of epoxide **2**. Furthermore, the *consumption* of O_2 is plotted (an increasing curve, not a decreasing one). In Figure 1 (lower panel) the formation of 2-methylundecanoic acid (**8**) as an oxidation product of aldehyde **5** is plotted. Moreover, 2-undecanol (**9**, alcohol, A) and 2-undecanone (**10**, ketone, K) were detected in the reaction mixture by GC-MS analysis ($M/z = 171$ and 170). These products were identified by comparison with authentic samples. Their formation is also plotted in Figure 1 (lines g and h). When the molar amounts of ketone and alcohol ($K + A$) are added, line f in Figure 1 is obtained. Small amounts of epoxides **6** and **7** were also found (not shown in this figure).[†]

--- FIGURE 1, CHART 2 ---

After the reaction had been allowed to run for 130 minutes, the conversion of limonene was 94% (30.9 mmol of the initial 32.8 mmol had reacted), the consumption of aldehyde being 56.9 mmol (note that this is approximately 2 equivalents with respect to limonene). The selectivity for epoxide **2** reached a maximum (74%) after 2 hours reaction

time. Thereafter, limonene epoxide was further oxidized into diepoxide **7** and other unidentified oxidation products. Formation of the diepoxide **7** started after nearly all limonene had been converted into the monoepoxide **2**, *i.e.* the maximum selectivity for monoepoxide was obtained at >95% conversion of limonene. 2-Methylundecanoic acid **8** was formed at approximately the same rate as epoxide during at least the first two hours of the reaction (Figure 1, bottom): after 130 minutes, 19.5 mmol of **8** and 22.8 mmol of **2** had formed. At this point, 54.6 mmol of O₂ had been consumed, *i.e.* approximately two times the amount of consumed alkene. An important observation was that in the first two hours of the reaction (up to 80% conversion), ketone and alcohol were formed in equimolar amounts and that the cumulative amount of alcohol **9** and ketone **10** (K + A) was approximately one half of the amount of epoxide in these first two hours.

CO₂ formation was measured with methylundecanal **5** present in slight excess with respect to limonene. A solution of limonene in toluene was treated with 1.2 equivalents of 2-methylundecanal **5** and 0.3 mol% of Ni(acac)₂ **3a** in the autoclave under otherwise standard conditions (see Experimental section and Figure 2). After an induction period which is usually observed at low aldehyde concentrations, limonene epoxide was formed at the same rate as CO₂. At 76% conversion, 68% of limonene epoxide had been formed as well as 62% of CO₂ (8.6 mmol). At this point, the cumulative amount of **9** and **10** was 59% (8.1 mmol, not shown), *i.e.* under these conditions employing a slight excess of aldehyde, approximately equimolar amounts of epoxide, CO₂, and K+A (combined amounts of alcohol plus ketone) are generated.

- - - FIGURE 2 - - -

Epoxidation using *i*-butyraldehyde as co-reagent

While 2-methylundecanal **5** is a good co-reagent for studying the progress of the reaction and the products of the Mukaiyama epoxidation of limonene, it is not a very practical additive for use in industrial processes, for which the inexpensive *i*-butyraldehyde **4** is preferred.

i-Butyraldehyde has been widely studied as a co-reagent in this epoxidation system, but only limited quantitative information is available concerning the fate of this aldehyde. We decided, therefore, to perform some quantitative studies using dipentene (a mixture of *R*- and *S*-

[†] In this particular experiment, CO₂ formation was not recorded although it is expected to be occur on the basis of Scheme 1 and Scheme 2.

limonene **1**) in toluene with 3 equivalents of *i*-butyraldehyde and 0.1 mol% of Ni(acac)₂ at 7 bar of 8% O₂ in N₂ (standard conditions, see Experimental section and Figure 3). As can be seen in Figure 3, the conversion of limonene reaches 88% after 24 hours with an epoxide selectivity of 54%. The latter is at maximum after 3 hours (90% at 78% conversion of alkene) after which the exocyclic double bond is oxidized to form **6** and further oxidation of limonene *mono*-epoxide is observed (*i.e.* **7** is formed).

- - - FIGURE 3 - - -

Since it was difficult to quantitatively determine the low molecular weight, volatile products formed from *i*-butyraldehyde during the oxidation, the amount of carbon dioxide and carbon monoxide present in the exhaust gas were measured instead to follow the course of the *i*-butyraldehyde conversion. From Scheme 1 and Scheme 2 and the data presented above it can be concluded that CO₂ and K+A are formed in equimolar amounts since they evolve from the same reaction step (eq. 4). CO is expected as a byproduct (Scheme 3), but at the standard reaction temperature of 25°C, no carbon monoxide was detected in the exhaust gas. As can be judged from Figure 3, the amount of CO₂ formed during the first 3 hours (up to 70% conversion of the reaction at 25°C) is approximately 60% of the amount of epoxide formed. CO₂ and CO formation was also determined at three other temperatures, *viz.* at 18.8°C, 35°C, and 45.0°C (Figure 4). The experiments were performed in duplicate and the deviation was found to be less than ±5%. CO formation was negligible at 18.8°C and 25.0°C, but at higher temperatures appreciable amounts of this gas were formed (solid lines in Figure 4) as expected for an endothermic decay of an intermediate acyl radical (see Introduction section). At 45°C, decarbonylation had increased to 4 mmol (about 10% of the amount of epoxide formed). The temperature dependence of the CO and CO₂ formation was found to be different. Whereas CO formation increased rapidly with temperature, CO₂ formation ceased to increase on raising the temperature from 35.0°C to 45.0°C, after an initial increase on going from 18.8°C to 35.0°C. We presume that the rate of the epoxidation reaction (eqs. 3-5) does increase with increasing temperature, but that the rate of formation of the oxidizing species, *viz.* the acylperoxy radical (eq. 2), is reduced at these temperatures due to premature decarbonylation of the acyl radical (eq. 13). We may conclude that 25°C is the optimum temperature for this reaction, because no side reactions leading to CO are taking place.

- - - FIGURE 4 - - -

Epoxidation using different nickel(II) complexes

Two different bis(acetylacetonato)nickel(II) catalysts, *viz.* **3a** and **3b**, were studied in the present Mukaiyama epoxidation system to investigate the role structure of the nickel complex on the reaction. These two nickel complexes were chosen because they have different structures in toluene solution. Ni(acac)₂ (**3a**) is known to be a trimer in non-coordinating solvents,²⁴⁻²⁷ with the nickel center being octahedrally coordinated. The complex has a green color and is paramagnetic with a magnetic moment of 3.27 B.M. at 27°C.²⁸ Nickel catalyst **3b** has more bulky and more electron withdrawing acetylacetonato ligands and is not able to rearrange into a trimer.²⁴⁻²⁹ This complex is square planar, diamagnetic and has a purple color.

The rate of epoxidation of limonene as a function of the *i*-butyraldehyde concentration catalyzed by the two Ni-complexes was monitored by measuring the rate of CO₂ formation. In the case of catalyst **3a**, this rate was also measured directly, *viz.* by determining the rate of epoxide formation. In the analysis, the reaction rate was taken as the slope of the linear part of the concentration-time plot, usually from circa 5% to 80% conversion. In Figure 5, the rate of the reaction is plotted against the concentration of *i*-butyraldehyde. The concentration of alkene and all other parameters were kept constant, so that the amount of aldehyde varied with respect to limonene from 1 molar equivalent (an aldehyde concentration of 0.4 M) to 10 molar equivalents (2.8 M). The lines (b) and (c) represent experiments with respectively catalyst **3a** and **3b**, respectively. Line (a) shows the rate of epoxide formation in the experiments with **3a** as a catalyst and should thus be compared to line (b).

- - - FIGURE 5 - - -

From Figure 5 it appears that for both catalysts the reaction is first order in aldehyde concentration between 1 and 4 molar equivalents of this co-reagent with respect to alkene. In this range, the linear fits afford a first order rate constant of $k_{1,3a} = (2.46 \pm 0.12) \times 10^{-5} \text{ s}^{-1}$ for **3a** (Figure 5, b) and $k_{1,3b} = (3.00 \pm 0.15) \times 10^{-5} \text{ s}^{-1}$ for **3b** (Figure 5, c). Thus, the reaction with catalyst **3b** is only slightly faster than that with **3a**. From the rate of epoxide formation the first order rate constant of the **3a**-catalyzed reaction was calculated to be

$k_{1,3a} = (2.8 \pm 0.2) \times 10^{-5} \text{ s}^{-1}$ (Figure 5, a), which is similar to that calculated from the CO_2 formation curve. We may conclude that the catalysts differ in reaction rate at a given aldehyde concentration, although the values of k_1 are similar.

The rate of the reaction was also measured at different catalyst concentrations varying from 0.01 to 0.5 mol% with respect to alkene at otherwise standard conditions (Experimental section). The results are shown in Figure 6. The rates of the reactions catalyzed by both **3a** and **3b** level off when the amount of nickel(II) becomes higher. The reaction catalyzed by **3b** is faster than that of **3a** at low catalyst concentrations, but the former catalyst seems to become more easily deactivated at high concentrations than the latter (see the Discussion section).

--- FIGURE 6 ---

Control experiments

Mizuno *et al.*²² have pointed out that it is extremely important in radical oxidations to assure that the reactions are not physically limited (*i.e.* by diffusion limitation) and that all compounds (substrates and products) are quantitatively identified. Furthermore, a blank reaction in the absence of a catalyst should be carried out in order to establish the presence or absence of an uncatalyzed oxidation process. These control experiments were performed in the present study and are described below.

By comparing the masses of all incoming reagents (including O_2) with the weight of the reaction mixture after reaction (including CO_2 and CO), the mass balance, as expressed in the formula (M , mass in g): $M(\text{limonene}) + M(\text{toluene}) + M(\text{aldehyde}) + M(\text{Ni}(\text{acac})_2) + M(\text{O}_2) = M(\text{reaction mixture}) + M(\text{CO}_2) + M(\text{CO})$, was determined. In all experiments reported here, more than 94% of the initial mass was recovered after the reaction had ended. This means that no large amounts of compounds had escaped from the reaction vessel by evaporation or otherwise. Typically, 85-90% of the products in the recovered reaction mixture could be identified. Among the unspecified products were several terpenes in amounts less than 0.5%.

In separate experiments the oxygen content of the incoming gas mixture was varied from 6% v/v to 15% v/v, corresponding to a partial oxygen pressure of 0.4 to 1.0 bar, under

otherwise standard conditions.[‡] This was found to have no influence on the formation of any of the products or the rates of their formation. In an earlier study²¹ we had found that, using a magnetically stirred (1000 rpm) glass vessel, the reaction rate did depend on the oxygen pressure between 0.2 and 1.0 bar. This implies a diffusion limited reaction. In the present setup we did not observe such a dependence. This discrepancy illustrates the importance of a good mixing of the phases when the kinetics of a gas-liquid reaction are studied.

The total pressure in the autoclave was varied between 2 to 15 bar, which again had no effect on the reaction at all. The stirring rate was changed from 500 to 1500 rpm and the rate of epoxide formation was measured. Going from 500 to 1000 rpm, the reaction rate increased, but from 1000 to 1500 rpm, the rate remained constant. We may conclude, therefore, that the epoxidation reaction was not physically limited under the conditions we applied to study the mechanism (1500 rpm; 7 bar of 8% O₂ in N₂; 25°C).

To establish the need for nickel(II) as an initiator in the Mukaiyama epoxidation, a blank reaction was run under standard conditions but in the absence of nickel catalyst.[‡] At ambient temperature this reaction did not start. Only after addition of a radical initiator (*m*-CPBA, 0.25 mol% with respect to alkene), a reaction could be detected. This reaction was much slower than the nickel-catalyzed reaction, reaching a maximum of 86% alkene conversion after 53 hours with a selectivity for epoxide of 81%. An uncatalyzed and uninitiated reaction could only be established at elevated temperature (45°C).[♦]

Epoxidation versus allylic oxidation

Mizuno *et al.* noted recently²² that the *uncatalyzed* epoxidation of the frequently studied substrate cyclohexene with *i*-butyraldehyde and oxygen is almost as efficient as the metal-catalyzed reaction (76-88% versus 88-94% yield of epoxide under their reaction conditions of 1 bar, 100% O₂, and 38°C). The selectivity ratio (SR) of the reaction, which is defined as the ratio of the desired product cyclohexene epoxide to the side products 2-cyclohexene-1-ol and

[‡] Conditions: limonene (60 mmol) and aldehyde (180 mmol) in 150 ml of toluene, 0.1 mol% **3a**, 8% O₂ in N₂, 7 bar, 25°C.

-1-one, was determined for both the catalyzed and the uncatalyzed reaction. Interestingly, this ratio is 10-15 for reactions catalyzed by an iridium polyoxoanion, and 28-37 for the uncatalyzed epoxidation initiated by alkylhydroperoxide. Mizuno concludes that the nature of the metal catalyst has only a relatively small effect on the selectivity, in agreement with the results of Nam *et al.*²⁰ This conclusion was, however, derived from experiments on only three different, structurally related polyoxometalates. In our previous work, we tested a number of transition metal β -diketonate complexes as catalysts in the Mukaiyama epoxidation of limonene,²¹ but no allylic oxidation products were found. Limonene is not a good substrate, however, to establish the occurrence of allylic oxidation (*vide infra*). Therefore, we decided to study the oxidation of the more sensitive substrate cyclohexene and to compare the selectivity ratios of a number of different transition metal salts and metal β -diketonate complexes (Table 1). These experiments were aimed at finding a catalyst that combines a reduced tendency for (unwanted) allylic oxidation with a high rate of epoxidation.

- - - TABLE 1 - - -

We found that the reaction in the absence of a catalyst gave a very high epoxide selectivity (entry 1) in agreement with Mizuno's results,²² but proceeded only very slowly at room temperature. * Highly interesting was the observation that at the catalyst concentration used in our experiments (1 mol%), the selectivity of epoxidation versus allylic oxidation was influenced by the type of metal catalyst (see Table 1, last column). Nickel(II) appeared to be the most efficient catalyst in these experiments, combining the highest selectivity for epoxide with the fastest reaction (full conversion was obtained after 5 hours, entries 2-4, except in the case of hydrated nickel(II) acetate, entry 5). The observed selectivity ratios of 10.6-12.5 are comparable to those published by Mizuno.²² Nickel was followed closely by Cu(acac)₂, which displayed an SR of 11.4 at 93% conversion (entry 10). The three metals that have been

* The reaction under standard conditions afforded 25 mmol (42%) of epoxide and 40 mmol of *i*-butyric acid after 4 hrs.. The induction period was ca. 50 min. When only *i*-butyraldehyde (180 mmol) and toluene (150 ml) were loaded into the autoclave and O₂ was added, no reaction took place: no oxygen was taken up and neither carboxylic acid nor CO₂ were formed. When Ni(acac)₂ was added to this mixture, CO₂ was formed in only very small amounts (ca. 4.5 mmol after 22 hrs.), and *i*-butyric acid was formed (117 mmol) as the exclusive product. It is concluded, therefore, that the uncatalyzed autoxidation of *i*-butyraldehyde is too slow to be observed at room temperature.

most frequently studied in oxidations, *viz.* cobalt(II), manganese(II), and iron(III). were somewhat less selective and less efficient (entries 6-9, 11). VO(acac)₂ (entry 12) gave epoxide and allylic oxidation products in an SR of 3, and Cr(acac)₃ gave almost no conversion (entry 13). Neither of these complexes are suitable as a catalyst for the Mukaiyama oxidation. Remarkably, in all experiments where a reaction took place, with the exception of the nickel and copper catalyzed reactions, clear color changes were observed (see Table 1). We found that the selectivity of the oxidation reaction was very sensitive to small changes in the reaction conditions. For example, the use of non-dehydrated or dehydrated nickel acetate as a catalyst resulted in a considerable SR difference (entries 4 and 5). Not all differences in SR, however, can be ascribed to the presence of water in the reaction mixture. The SR was already shown by Mizuno²² to be solvent dependent, a non-coordinating solvent such as dichloromethane giving a higher SR than a coordinating one such as acetonitrile.

Discussion

Mechanism of the aerobic limonene epoxidation with co-oxidation of an aldehyde

The mechanism of alkene epoxidation by aerobic co-oxidation with an aldehyde was thoroughly investigated in the early seventies (see for example Vreugdenhil and Reit³⁰ and Tsuchiya and Ikawa³¹) and has been reviewed by Sheldon and Kochi.¹⁹ For the uncatalyzed reaction, Lassila *et al.*² have envisaged both a radical and a non-radical pathway. Based on the results presented in the previous sections we propose that the mechanism of the Ni^{II}(acetylacetonate) catalyzed Mukaiyama epoxidation proceeds for the larger part via a radical pathway, *i.e.* autoxidation of the aldehyde (Scheme 1, eqs. 1-2) followed by epoxidation of the alkene by an acylperoxy radical. Support for this mechanism is the formation of CO₂ and the mixture of ketone and alcohol (K + A) (Scheme 2). A smaller part of the epoxidation follows the non-radical peracid epoxidation route (Scheme 3), resulting in the formation of carboxylic acid.

In the radical pathway, the active epoxidizing species are acylperoxy radicals formed by radical chain autoxidation of the aldehyde (Scheme 1).¹⁹ The ratio of the radical and non-radical pathways has an influence on the type of products derived from the aldehyde. Thus, in

* It should be noted that we did not deliberately initiate the oxidation reaction, which results in variable induction times, but not in different oxidation rates and reported conversions.

the non-radical peracid epoxidation pathway, the aldehyde is expected to be converted into the corresponding carboxylic acid, whereas in the radical epoxidation route lower molecular weight products are formed from the aldehyde (Scheme 2). Formation of these lower molecular weight compounds is accompanied by CO₂ formation as was shown by Lassila *et al.*² for pivaldehyde, which is degraded into *tert*-butylhydroperoxide and *tert*-butanol. These authors rationalized their findings by assuming a concerted decomposition of an acylperoxy-alkene adduct into epoxide, CO₂, and an alkyl radical (eq. 5) which is rapidly trapped by dioxygen (eq. 6). The fact that aromatic carboxyl radicals decarboxylate much slower (10⁶ s⁻¹)³² accounts for the observation²¹ that aromatic aldehydes such as benzaldehyde are not active as co-reagents in the Mukaiyama system. The alkyl radical that results from the decarboxylation may be stabilized by the nickel center and form a Ni-alkyl complex. This is known to occur in nature in the chemistry of the cofactor F₄₃₀, which converts thioethers to methane via a methyl-Ni complex.³³

A consequence of the concerted decomposition shown in Scheme 1, eq. (5), is that equimolar amounts of epoxide, CO₂, and lower molecular weight alkyl radical oxidation products are expected if epoxidation proceeds exclusively through the radical mechanism. In the case of 2-methylundecanal, we do not find alkylhydroperoxide besides CO₂, but instead 2-undecanol and 2-undecanone, which are formed in almost equal amounts during the first 2 hours of the reaction. Their equimolar formation is strong evidence for the intermediacy of unstable alkylperoxy radicals, which decompose into a 1:1 mixture of ketone and alcohol via a Russell termination,¹⁹ which is outlined in Scheme 2, eqs. (8) and (9). The fact that somewhat more ketone is formed is explained by the easy oxidation of the alcohol to the ketone under the autoxidation conditions. Howard³⁴ has provided a similar explanation of the formation of a slight excess of ketone in the Russell termination on the basis of a bicyclic tetroxide which decomposes to form ketone and hydrogen peroxide.

Since the combined amount of undecanone and 2-undecanol is only 50-60% of the total amount of epoxide observed during the first hours of the epoxidation (~90% conversion), we presume that circa 40-50% of the epoxide is formed through the non-radical peracid pathway. This pathway generates 2-methylundecanoic acid which was also detected as a major product derived from the aldehyde (Scheme 3). The combined occurrence of both peracid and radical epoxidation is also deduced from the amount of CO₂ formed during the aerobic epoxidation of limonene in the presence of *i*-butyraldehyde. Figure 3 shows that the amount of CO₂ is approximately 60% of the amount of epoxide formed during the first 2½ hours of the

reaction (at 70% conversion), whereas an equimolar amount is expected if radical epoxidation is the exclusive pathway. Thus, as with 2-methylundecanal, aerobic epoxidations with *i*-butyraldehyde are also likely to proceed via concomitant radical and peracid pathways.

In a study of the uncatalyzed co-oxidation of alkene and aldehyde Vreugdenhil and Reit³⁰ found that the percentage of radical epoxidation is around 45. This percentage was influenced by the ratio of olefin to aldehyde and by the reactivity of the alkene, but not by the type of aldehyde. This conclusion is supported by our results for the catalyzed reaction shown in Figure 2, which shows that the CO₂/epoxide ratio increases to a 1:1 level if the aldehyde/alkene ratio is lowered to 1.2:1, in contrast to the 3:1 ratio used in the other experiments.

Influence of the aldehyde/alkene ratio on the Mukaiyama epoxidation

The Mukaiyama epoxidation proceeds smoothly when an excess of aldehyde with respect to alkene is applied, as many researchers have noted.¹⁻¹⁸ This may be clarified by Scheme 3. In eq. (10), an acylperoxy radical abstracts a hydrogen atom from another aldehyde molecule, forming peroxy acid and an acyl radical, thus propagating the radical chain but not generating epoxide. Subsequently, two molecules of carboxylic acid may be formed from the reaction of a peroxy acid with an aldehyde (eq. 12). Aldehyde is consumed again without the formation of epoxide. The amount of acid formed and thus the amount of aldehyde consumed could depend on the catalyst, the substrate and the reaction conditions. In the system that we studied, only approximately half of the aldehyde is converted into carboxylic acid.

There are, however, more reasons why the ratio of aldehyde to alkene in the Mukaiyama epoxidation is larger than 1. For example, as can be seen in Figure 5, it is evident that epoxidation under our conditions only proceeds if the aldehyde/alkene ratio exceeds a certain value (~0.5 molar equivalents). In an interesting series of investigations by Wittig and co-workers,³⁵⁻⁴¹ it was shown that in the uncatalyzed co-oxidation of alkene and aldehyde some alkenes are capable of retarding the autoxidation of benzaldehyde. With an increasing ratio of alkene to benzaldehyde, the rate of autoxidation decreased. These results may bear upon the requirement of a minimum aldehyde/alkene ratio in our experiments: when this ratio is too low, *i.e.* when a large amount of alkene is present with respect to aldehyde, the alkene might inhibit the aldehyde autoxidation (eqs. 1-2) and hence no oxidizing acylperoxy radical is generated. Furthermore, at an aldehyde/alkene ratio where epoxidation does not proceed, the epoxidation cannot be induced by raising the concentration of Ni^{II} catalyst. Thus, the

aldehyde/alkene ratio seems to be more important than the ratio of aldehyde to Ni^{II} . A further rationalisation for the requirement of a minimum aldehyde/alkene ratio can be found in the work of Filippova and Blyumberg.⁴² They observed that the rate of the uncatalyzed alkene epoxidation with aldehyde co-oxidation ceases to depend on the alkene concentration above a certain threshold value of this concentration. They assume that the acylperoxy radical and the alkene form an adduct (Scheme 1, eq. 3) so that at a certain alkene concentration all acylperoxy radicals are trapped in this adduct. As a result, the concentration of free, unbound acylperoxy radicals, which can act as chain carriers during aldehyde autoxidation and as oxidizing agents, is too low to allow for efficient epoxidation.

At high aldehyde concentrations (more than four equivalents with respect to alkene, *i.e.* at an aldehyde concentration $>1.5\text{M}$), the epoxidation reactions show a sudden drop in rate (Figure 5). An explanation may be given based on the work by Mizuno²² who noted that the aerobic oxidation of aliphatic aldehydes becomes limited by mass-transfer at aldehyde concentrations higher than 2-5 mol%. The points where the curves in Figure 5 bend, correspond to 15 mol% of aldehyde (1.6 mol) in 150 ml of toluene and mass transfer might become a serious problem in that case. A solvent effect on the reaction rate may also play a role, since a 2.7M solution of aldehyde in toluene (10 equivalents of aldehyde with respect to alkene) consists for 30% v/v of aldehyde.

However, we favor a different explanation for the decreased reaction rate at high aldehyde concentration. It is important to note that the rate of reaction in Figure 5 was measured by the formation of epoxide or CO_2 , in other words: when no epoxide or CO_2 is formed in the oxidation process in the reaction vessel, no reaction is observed. One such a process is the reaction of the aldehyde with the acylperoxy radical yielding a peroxy acid and an acyl radical (Scheme 3, eq. 10), thus propagating the autoxidation chain (*i.e.* conversion of aldehyde) without generating epoxide or CO_2 . Competing with this reaction is the oxidation of alkene by the acylperoxy radical (Scheme 1, eqs. 3-5) which does yield CO_2 and epoxide that are measured and plotted in Figure 5. The relative rates of these two reactions, which depend on the alkene and aldehyde concentrations, determine the overall rate which is measured. When the aldehyde concentration is relatively high with respect to the alkene concentration, aldehyde oxidation is much faster than epoxidation (with CO_2 formation) and an epoxidation rate of zero is eventually measured.

Influence of the metal catalyst on the Mukaiyama epoxidation.

Mizuno *et al.* have observed that the metal catalyst influences the ratio of epoxidation versus allylic oxidation, but that the *nature* of the metal has no effect on this ratio.²² Our cyclohexene oxidation experiments with various metal catalysts confirm that there is an influence of the metal catalyst, but contrary to Mizuno we find a dependence of the selectivity ratio on the nature of the metal (see Table 1), *i.e.* metals with a tendency for high oxidation states (vanadium, manganese, cobalt) induce more allylic oxidation than metals which do not have such a tendency (nickel and copper). For nickel, the absence of a significant concentration of the Ni^{III} high oxidation state is evident from the absence of an EPR signal in the reaction mixture²¹ (Ni^{II} is silent in conventional EPR, whereas Ni^{III} complexes do exhibit EPR signals⁴⁸). In addition, both for nickel^{II} as well as for copper^{II} catalysts, no color changes are observed during the reaction, suggesting that no appreciable amounts of a highly colored Ni^{III} or Cu^{III} are present.⁴⁷ This contrasts with the marked color changes that result from the formation of higher oxidation state species derived from vanadium, manganese, and cobalt catalysts. Scheme 6 provides a reaction sequence for nickel catalyzed aldehyde oxidation that rationalizes the absence of measurable concentrations of high oxidation state Ni^{III}. This scheme is based on earlier work of Márta *et al.*, who studied the O₂ oxidation of benzaldehyde catalyzed by cobalt and nickel salts.⁴⁶ These two catalysts differ in that Co is mainly present in the form of Co^{III} whereas for Ni the lower, bivalent oxidation state prevails because oxidation of Ni^{II} to Ni^{III} by intermediate peracid (Eq 16) is slow compared to the rapid reduction of Ni^{III} by the aldehyde. The latter acyl radical producing reduction of Ni^{III} by the aldehyde is proposed to proceed via a Ni^{III}-acyl intermediate, whose formation is preceded by aldehyde coordination to the Ni^{III}(OH) species formed by oxidation of Ni^{II} by the peracid (Eqs 17; 18). In earlier work,²¹ we obtained evidence for aldehyde coordination to nickel by UV/Vis measurements, thus making equation (17) plausible. The formation of a metal acyl species from a group 10 metal compound and an aldehyde is supported by the work of Pregosin *et al.*, who have isolated stable metal acyl complexes from the reaction of Pd and Pt compounds with quinoline-8-carboxaldehyde.^{44,45} The initiation of the radical chain by peracid oxidation of Ni^{II} is similar to the initiation mechanism proposed by Kholdeeva *et al.* for Co^{II} catalyzed alkene oxidation by dioxygen in the presence of an aldehyde.⁴³ With EPR spectroscopy we were able to show²¹ that only oxygen centered radicals are trapped in the reaction mixture which means that all carbon centered radicals formed in Scheme 6 are quickly trapped by dioxygen (Scheme 1, eq. 2). The formation of acyl radicals (eq. 18) is supported by the

observation that at higher reaction temperatures CO is generated (see Scheme 3, eq. 13), since at these high temperatures acyl radical decarbonylation may be faster than their trapping by O₂.

The reaction sequence of Scheme 6, which explains the very low concentration of nickel in its high Ni^{III} oxidation state, rationalizes the low amount of allylic oxidation products (high SR value) observed for Ni catalyzed epoxidation with *i*-butryaldehyde and dioxygen, since it is known that transition metal complexes in a high oxidation state are capable of abstracting allylic hydrogens (in contrast to their more reduced counterparts),⁴⁹ thus initiating allylic oxidation. The observed SR's correlated with the Irving-Williams series of formation constants of complexes of divalent ions.⁵⁰⁻⁵² The Ni^{II} and Cu^{II} complexes have the highest formation constants and gave the highest SR's, whereas the Co^{II}, Fe^{II}, and Mn^{II} complexes, in order of decreasing formation constants, gave lower SR's. The vanadyl ion can not be placed in this series. This correlation indicates once more that the high valent complexes of Ni^{II} and Cu^{II} are much less stable than the high valent complexes of the other studied metals and will not be present in large amounts in the reaction mixture. The uncatalyzed reaction produces only acylperoxy and carboxyl radicals (Scheme 1 and Scheme 2) which are much more likely to add to a double bond than to abstract an allylic hydrogen atom, thus giving a very high selectivity ratio in favor of epoxidation.

In an earlier study we proposed that the epoxidizing acylperoxy radical is stabilized by a Ni^I species (a low oxidation state species).²¹ It was assumed that in the initiation step, proton abstraction is accompanied by the uptake of an electron from the aldehyde by Ni^{II}, thus generating an acyl radical and Ni^I. In our discussion we suggested that an intermediate Ni^{III} species would also be conceivable.²¹ From our present results, we may tentatively conclude that the latter possibility, *i.e.* Ni^{III}, is more likely, although only as an elusive intermediate species.

It may be expected that coordination of the aldehyde to the nickel center is hindered when the Ni is 6-coordinate (*i.e.* as in **3a**) which thus would slow down the reaction. Since the reaction with the square planar complex **3b** is faster at low catalyst concentrations (Figure 6), it may be concluded that aldehyde coordination is influenced by the catalyst structure in solution.* The same figure shows that at higher catalyst concentration, the rate of the reaction

* Note that in Figure 5 it appears as if there is only a slight difference in reaction rate between the two nickel catalysts. However, the nickel concentration at which these experiments were done correspond to the point in Figure 6 where the lines cross, *i.e.* the observation of equal rates in Figure 5 is a coincidence.

slows down. This feature has been observed earlier by our group²³ and also by Kholdeeva *et al.*,^{43,53} and is consistent with the radical autoxidation mechanism. Kholdeeva *et al.* concluded that the observed dependence may be interpreted as being the result of the participation of the catalyst (M^{n+}) in a chain termination reaction, for example, when acylperoxy radicals react to form $M^{(n+1)+}-RCO_3^-$, which is inactive. Nickel(II) cyclam complexes have also been shown to exhibit this behavior.⁵⁴ In our system, the monomeric complex **3b** apparently is more efficient in trapping radicals than the (partially) trimeric complex **3a** which becomes evident at higher catalyst concentrations. Interestingly, the concentration at which a negative effect of the nickel catalyst is observed is much higher than that of cobalt catalysts: 10^{-4} mol l^{-1} for cobalt^{43,53} versus more than 2×10^{-3} mol l^{-1} for nickel (Figure 6). Thus, nickel is fortunately under our conditions not an efficient chain terminating agent which allows us to use much higher concentrations of this catalyst to increase the reaction rate.

Conclusion

We have shown that the aerobic epoxidation of limonene with nickel(II) β -diketonate as a catalyst and an aldehyde as co-reagent shows some unexpected and interesting features when studied in detail. First of all, low molecular weight alcohol and ketone together (K + A) are formed in a less than 1:1 ratio (circa 50-60%) with respect to epoxide. Concomitant formation of carbon dioxide resulting from the decarboxylation of a carboxyl radical was detected quantitatively and also in a less than 1:1 ratio with respect to epoxide, as expected from Scheme 1 and Scheme 2. It is important to note that this ratio changes to a 1:1 ratio when the ratio of aldehyde to alkene is reduced from 3 to 1. The products (CO_2 , ketone and alcohol) are formed after radical epoxidation of alkene by an acylperoxy radical which is formed through autoxidation of aldehyde (Scheme 1). A non-radical epoxidation pathway via a peracid route (Scheme 3) plays an appreciable role when the ratio of aldehyde to alkene is 3:1. This produces carboxylic acid as the oxidation product from the aldehyde. Radical autoxidation becomes the exclusive pathway when the reaction conditions are altered to low aldehyde to alkene ratios, *e.g.* 1:1.

From the study of the oxidation of cyclohexene as substrate we conclude that the metal catalyst in the Mukaiyama epoxidation not only influences the initiation and the rate of the

reaction, but also the selectivity for epoxide versus allylic oxidation products. Nickel(II) appears to be the best epoxidation catalyst in a series of metal salts and metal complexes tested as catalysts. This metal enhances the rate of oxidation with respect to the blank reaction and also gives the highest epoxidation/allylic oxidation ratio. In other words, for a substrate that is sensitive to allylic epoxidation, a Ni^{II} catalyst is the best choice in the Mukaiyama epoxidation. The low degree of allylic oxidation with Ni catalysts is rationalized by the very low concentration of nickel in its Ni^{III} high oxidation state during the reaction. The very strong predominance of Ni^{II} species over Ni^{III} species is thought to result from the fast reduction of Ni^{III} by the aldehyde, compared to the slower oxidation of Ni^{II} to Ni^{III} by peracid. For metals that are less readily reduced by the aldehyde, such as vanadium, manganese, and cobalt, the high oxidation state of the catalyst prevails. Consequently, a significant degree of allylic oxidation is observed.

Acknowledgments

The authors thank Dr. P. J. M. van Kan for EPR measurements, and Dr. P. H. M. Budzelaar for valuable discussions. This research was financed by the Netherlands IOP Foundation for Innovative Research and the Netherlands Ministry of Economic Affairs (project no. IKA 94025).

References

- 1) Kaneda, K.; Haruna, S.; Imanaka, T.; Hamamoto, M.; Nishiyama, Y.; Ishii, Y. *Tetrahedron Lett.* **1992**, *33*, 6827-6830.
- 2) Lassila, K. R.; Waller, F. J.; Werkheiser, S. E.; Wressell, A. L. *Tetrahedron Lett.* **1994**, *35*, 8077-8080.
- 3) Mukaiyama, T. *Aldrichimica Acta* **1996**, *29*, 59-76.
- 4) Yamada, T.; Takai, T.; Rhode, O.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2109-2117.
- 5) Yamada, T.; Takahashi, K.; Kato, K.; Takai, T.; Inoki, S.; Mukaiyama, T. *Chem. Lett.* **1991**, 641-644.
- 6) Hata, E.; Takai, T.; Yamada, T.; Mukaiyama, T. *Chem. Lett.* **1994**, 535-538.
- 7) Yamada, T.; Takai, T.; Rhode, O.; Mukaiyama, T. *Chem. Lett.* **1991**, 1-4.
- 8) Takai, T.; Yamada, T.; Rhode, O.; Mukaiyama, T. *Chem. Lett.* **1991**, 281-284.
- 9) Takai, T.; Hata, E.; Yamada, T.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2513-2518.
- 10) Yamada, T.; Imagawa, K.; Nagata, T.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 2248-2256.
- 11) Yamada, T.; Imagawa, K.; Mukaiyama, T. *Chem. Lett.* **1992**, 2109-2112.
- 12) Yamada, T.; Imagawa, K.; Nagata, T.; Mukaiyama, T. *Chem. Lett.* **1992**, 2231-2234.
- 13) Nagata, T.; Imagawa, K.; Yamada, T.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1455-1465.
- 14) Nagata, T.; Imagawa, K.; Yamada, T.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 3241-3246.
- 15) Mukaiyama, T.; Yamada, T.; Nagata, T.; Imagawa, K. *Chem. Lett.* **1993**, 327-330.
- 16) Imagawa, K.; Nagata, T.; Yamada, T.; Mukaiyama, T. *Chem. Lett.* **1994**, 527-530.
- 17) Inoki, S.; Takai, T.; Yamada, T.; Mukaiyama, T. *Chem. Lett.* **1991**, 941-944.
- 18) Yanai, K.; Irie, R.; Ito, Y.; Katsuki, T. *Memoirs of the Faculty of Science, Kyushu Univ.* **1992**, *18*, 213-222.
- 19) Sheldon, R. A.; Kochi, J. K. *Metal-catalyzed oxidations of organic compounds*; Academic Press: New York, 1981.
- 20) Nam, W.; Kim, H. J.; Kim, S. H.; Ho, R. Y. N.; Valentine, J. S. *Inorg. Chem.* **1996**, *35*, 1045-1049.
- 21) Wentzel, B. B.; Gosling, P. A.; Feiters, M. C.; Nolte, R. J. M. *J. Chem. Soc. Dalton Trans.* **1998**, 2241-2246.
- 22) Mizuno, N.; Weiner, H.; Finke, R. G. *J. Mol. Catal. A: Chemical* **1996**, *114*, 15-28.

- 23) Gosling, P. A. *Catalyst systems for the epoxidation of alkenes by molecular oxygen*; University of Nijmegen: Nijmegen, 1996.
- 24) Addison, A. W.; Graddon, D. P. *Aust. J. Chem.* **1968**, *21*, 2003-2012.
- 25) Fackler Jr., J. P.; Cotton, F. A. *J. Am. Chem. Soc.* **1961**, *83*, 3775-3778.
- 26) Cotton, F. A.; Fackler, J. P. *J. Am. Chem. Soc.* **1961**, *83*, 2818-2825.
- 27) Bullen, G. J.; Mason, R.; Pauling, P. *Inorg. Chem.* **1965**, *4*, 456-462.
- 28) Cotton, F. A.; Fackler, J. P. *J. Am. Chem. Soc.* **1960**, *83*, 2818-2825.
- 29) Cotton, F. A.; Wise, J. J. *Inorg. Chem.* **1966**, *5*, 1200-1207.
- 30) Vreugdenhil, A. D.; Reit, H. *Rec. Trav. Chim. Pays-Bas* **1972**, *91*, 237-245.
- 31) Tsuchiya, F.; Ikawa, T. *Can. J. Chem.* **1969**, *47*, 3191-3197.
- 32) Bravo, A.; Bjorsvik, H.-R.; Fontana, F.; Minisci, F.; Serri, A. *J. Org. Chem.* **1996**, *61*, 9409-9416.
- 33) Wackett, L. P.; Honek, J. F.; Begley, T. P.; Shames, S. L.; Niederhoffer, E. C.; Hausinger, R. P.; Orme-Johnson, W. H.; Walsh, C. T. in: *The Bioinorganic Chemistry of Nickel*; Lancaster Jr., J. R., Ed.; VCH: Weinheim, 1988, pp 249-274.
- 34) Howard, J. A. *ACS Symposium Series* **1978**, *69*, 413-432.
- 35) Wittig, G.; Pieper, G. *Ann.* **1947**, *558*, 218-230.
- 36) Wittig, G.; Lange, W. *Ann.* **1938**, *536*, 266-284.
- 37) Wittig, G.; Henkel, K. *Ann.* **1939**, *542*, 130-144.
- 38) Wittig, G.; Pieper, G. *Ann.* **1940**, *546*, 142-171.
- 39) Wittig, G.; Pieper, G. *Ann.* **1940**, *546*, 172-179.
- 40) Wittig, G. *Ann.* **1947**, *558*, 201-206.
- 41) Wittig, G.; Pieper, G. *Ann.* **1947**, *558*, 207-218.
- 42) Filippova, T. V.; Blyumberg, E. A. *Russ. Chem. Rev.* **1982**, *51*, 582-591.
- 43) Kholdeeva, O. A.; Khavrutskii, I. V.; Romannikov, V. N.; Tkachev, A. V.; Zamaraev, K. I. *Selective alkene epoxidation by molecular oxygen in the presence of aldehyde and different type catalysts containing cobalt*; Grasselli, R. K., Oyama, S. T., Gaffney, A. M. and Lyons, J. E., Ed.; Elsevier Science, 1997, pp 947-955.
- 44) Anklin, C. G.; Pregosin, P. S. *J. Organometallic Chem.* **1983**, *243*, 101-109.
- 45) Anklin, C. G.; Pregosin, P. S.; Wombacher, F. J.; Rüegg, H. J. *Organometallics* **1990**, *9*, 1953-1958.
- 46) Márta, F.; Boga, E.; Matók, M. *Discuss. Faraday Soc.* **1968**, *46*, 173.
- 47) *Gmelins Handbuch der Anorganischen Chemie*; Meyer, R. J., Pietsch, E. H. E. and Kotowski, A., Ed.; Verlag Chemie: Weinheim, 1969; Vol. 57-C2.
- 48) Coyle, C. L.; Stiefel, E. I. in: *The Bioinorganic Chemistry of Nickel*; Lancaster Jr., J. R., Ed.; VCH: Weinheim, 1988, pp 1-28.
- 49) Shilov, A. E. *Activation of saturated hydrocarbons by transition metal complexes*; D. Reidel Publishing Company: Dordrecht, 1984.
- 50) Irving, H.; Williams, R. J. P. **1953**, 3192-3210.

- 51) Irving, H.; Williams, R. J. P. *Nature* **1948**, *162*, 746-747.
- 52) Shriver, D. F.; Atkins, P. W.; Langford, C. H. *Inorganic Chemistry*; 1st ed.; Oxford University Press: Oxford, 1990.
- 53) Kholdeeva, O. A.; Grigoriev, V. A.; Maksimov, G. M.; Fedotov, M. A.; Golovin, A. V.; Zamaraev, K. I. *J. Mol. Catal. A: Chemical* **1996**, *114*, 123-130.
- 54) Nam, W.; Baek, S. J.; Lee, K. A.; Ahn, B. T.; Muller, J. G.; Burrows, C. J.; Valentine, J. S. *Inorg. Chem.* **1996**, *35*, 6632-6633.

Captions

Table 1. Metal catalyzed aerobic oxidation of cyclohexene^a

Figure 1. Limonene epoxidation with oxygen and 2-methylundecanal catalyzed by Ni(acac)₂. Conditions: 32.8 mmol limonene **1**, 93.5 mmol aldehyde **5**, 0.1 mol% Ni^{II}(acac)₂ (**3b**) in 75 ml of toluene, 7 bar of 8% O₂ in N₂, 25°C. Analyses by GC.

Top: a: 2-methylundecanal (**5**), b: O₂ uptake, c: limonene epoxide (**2**), d: limonene (**1**).

Bottom: e: 2-methylundecanoic acid (**8**), f: (ketone **10** + alcohol **9**), g: 2-undecanone (**10**), h: 2-undecanol (**9**).

Figure 2. Formation of epoxide (squares) correlated with CO₂ formation (line) in the epoxidation of limonene with O₂ and 2-methylundecanal catalyzed by Ni(acac)₂. Conditions: 18 mmol limonene, 22 mmol aldehyde, 75 ml of toluene, 0.3 mol% Ni^{II}(acac)₂, 7 bar of 8% O₂ in N₂, 25°C.

Figure 3. Epoxidation of limonene with *i*-butyraldehyde and oxygen catalyzed by Ni(acac)₂. Conditions: limonene (**1**) (67 mmol), *i*-butyraldehyde (**4**) (184 mmol), 150 ml toluene, 0.1 mol% Ni(acac)₂ (0.4 mM), 25.0°C, 7 bar of 8% v/v O₂ in N₂. Analysis by GC. a: Oxygen uptake, b: *i*-butyric acid, c: CO₂, d: limonene epoxide, e: limonene.

Figure 4. Formation of CO₂ (symbols, left axis) and CO (drawn lines, right axis) as a function of time, at four different temperatures: a: 45.0°C, b: 35.0°C, c: 25.0°C, d: 18.8°C. For other conditions see Figure 3 and Experimental section.

Figure 5. Reaction rate as a function of aldehyde concentration in the epoxidation of limonene with O₂ and *i*-butyraldehyde catalyzed by Ni^{II} complexes. For conditions see Figure 3. a: Catalyst **3a**, rate of epoxide formation. b: Idem, rate of CO₂ formation, c: Catalyst **3b**, rate of CO₂ formation. Solid lines: linear fits of the data.

Figure 6. The rate of CO₂ formation as a function of the concentration of the nickel catalyst in the epoxidation of limonene with O₂ and *i*-butyraldehyde as co-reagent. For conditions see Figure 3. a: Catalyst 3a. b: Catalyst 3b.

Table 1. Metal catalyzed aerobic oxidation of cyclohexene^a

Entry	Catalyst	Color before reaction	Color after reaction	Conversion (%) ^b	Yield of epoxide (%) ^b	SR ^c
1	none	colorless	colorless	99 ^d	85	18
2	Ni(acac) ₂ 3a	pale green	pl. green	98	85	12.5
3	Ni(ptbbacac) ₂ 3b	pl. purple	pl. green	100	79	11.3
4	Ni(OAc) ₂	light green	l. green	99	83	12.7
5	Ni(OAc) ₂ ·4H ₂ O	l. green ^e	l. green	82	67	10.6
6	Co(acac) ₂	pl. pink	dark green	84	58	6.5
7	Co(OAc) ₂ ·4H ₂ O	pink	d. green	95	71	9.8
8	Mn(acac) ₂	l. brown	d. brown	49	33	6.0
9	Mn(OAc) ₂ ·4H ₂ O	n.d. ^f	n.d. ^f	97	71	6.9
10	Cu(acac) ₂	pl. blue ^e	bright blue	93	72	11.4
11	Fe(acac) ₃	d. red.	br. orange	78	59	9.8
12	VO(acac) ₂	d. green	br. yellow	70	30	2.9
13	Cr(acac) ₃	purple	purple	12 ^d	6	9.9

^aReaction conditions: 3.0 mmol of cyclohexene, 8.4 mmol of *i*-butyraldehyde, 0.03 mmol of catalyst (1 mol%), 1,3-dichlorobenzene as an internal standard, 10 ml of CH₂Cl₂ stirred glass vessel equipped with an O₂ reservoir, 25°C

^bGC analysis after 5 hrs.

^cSR = Selectivity ratio: mmol of epoxide / mmol of allylic oxidation products (2-cyclohexen-1-one + 2-cyclohexen-1-ol)

^dAfter 22 hrs.

^eCatalyst is only slightly soluble in the reaction mixture

^fNot determined.

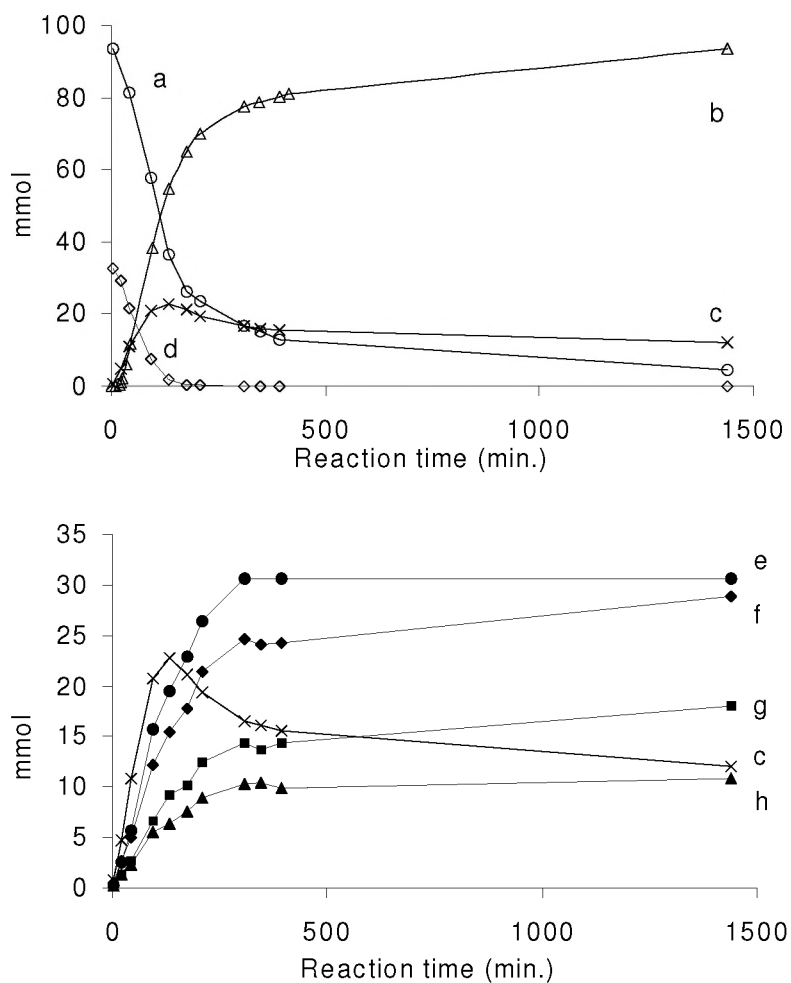


Figure 1. Limonene epoxidation with oxygen and 2-methylundecanal catalyzed by Ni(acac)₂. Conditions: 32.8 mmol limonene **1**, 93.5 mmol aldehyde **5**, 0.1 mol% Ni^{II}(acac)₂ (**3b**) in 75 ml of toluene, 7 bar of 8% O₂ in N₂, 25°C. Analyses by GC.

Top: a: 2-methylundecanal (**5**), b: O₂ uptake, c: limonene epoxide (**2**), d: limonene (**1**). Bottom: e: 2-methylundecanoic acid (**8**), f: (ketone **10** + alcohol **9**), g: 2-undecanone (**10**), h: 2-undecanol (**9**).

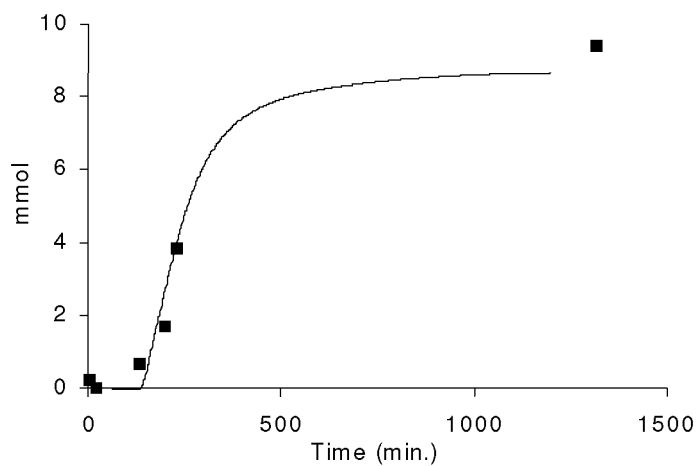


Figure 2. Formation of epoxide (squares) correlated with CO₂ formation (line) in the epoxidation of limonene with O₂ and 2-methylundecanal catalyzed by Ni(acac)₂. Conditions: 18 mmol limonene, 22 mmol aldehyde, 75 ml of toluene, 0.3 mol% Ni^{II}(acac)₂, 7 bar of 8% O₂ in N₂, 25°C.

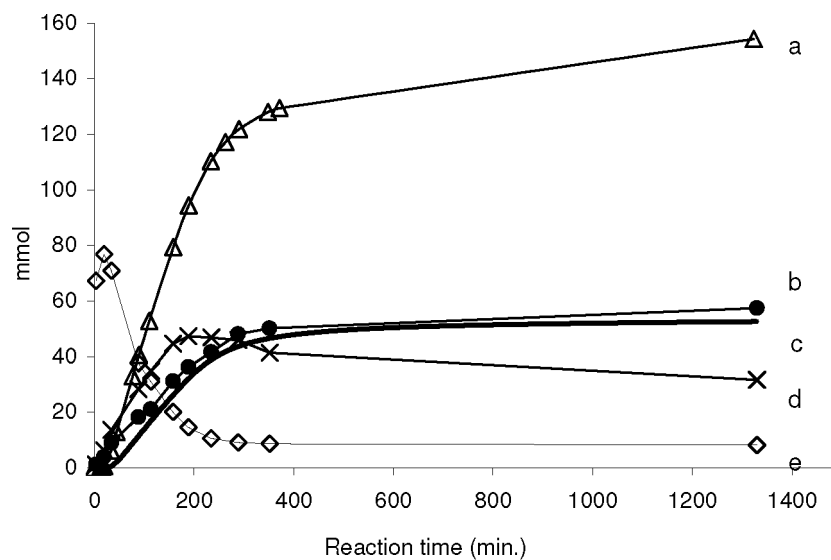


Figure 3. Epoxidation of limonene with *i*-butyraldehyde and oxygen catalyzed by Ni(acac)₂. Conditions: limonene (**1**) (67 mmol), *i*-butyraldehyde (**4**) (184 mmol), 150 ml toluene, 0.1 mol% Ni(acac)₂ (0.4 mM), 25.0°C, 7 bar of 8% v/v O₂ in N₂. Analysis by GC. a: Oxygen uptake, b: *i*-butyric acid, c: CO₂, d: limonene epoxide, e: limonene.

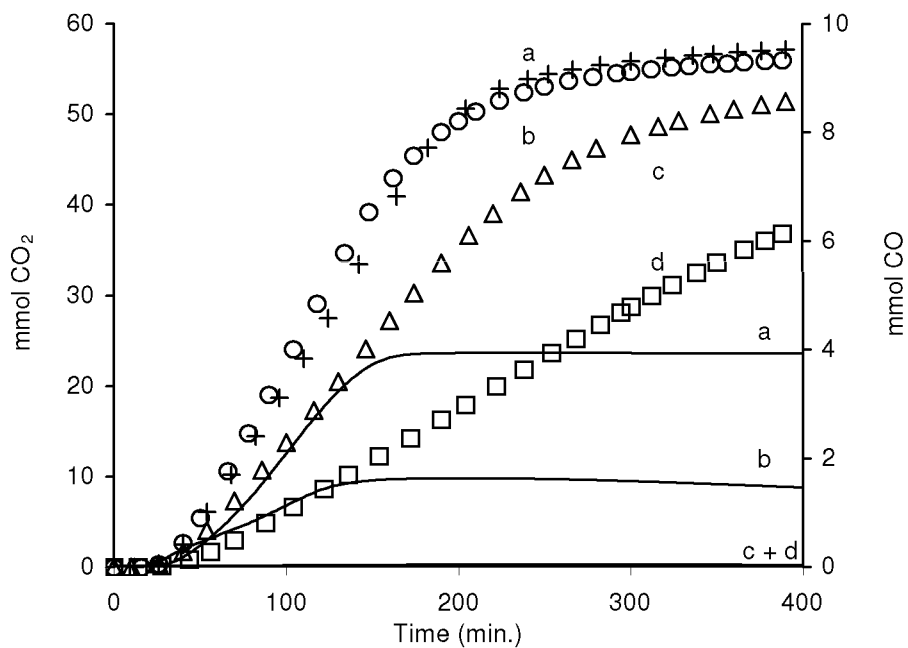


Figure 4. Formation of CO₂ (symbols, left axis) and CO (drawn lines, right axis) as a function of time, at four different temperatures: a: 45.0°C, b: 35.0°C, c: 25.0°C, d: 18.8°C. For other conditions see Figure 3 and Experimental section.

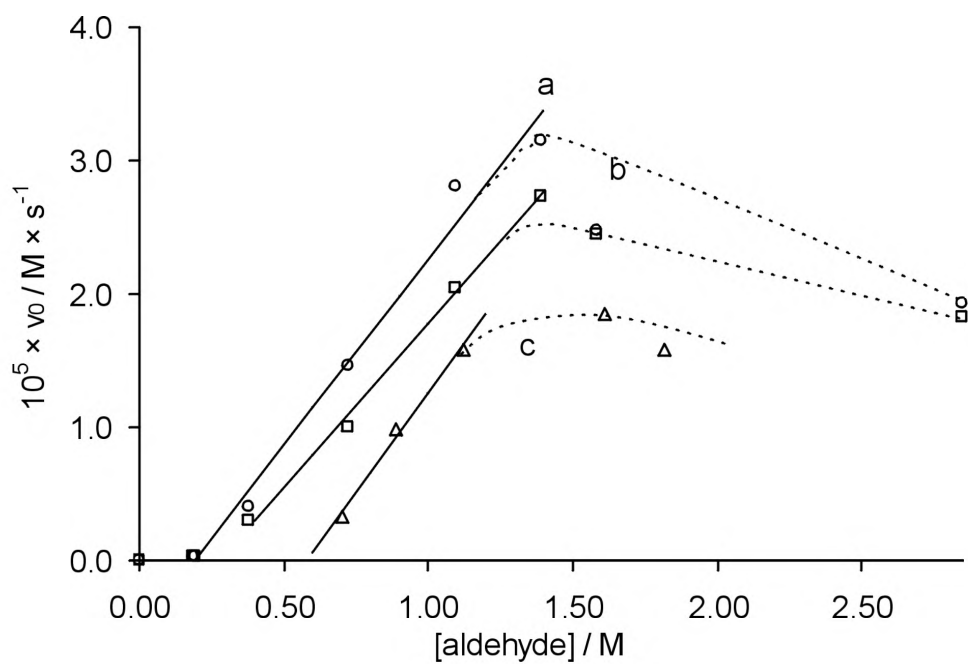


Figure 5. Reaction rate as a function of aldehyde concentration in the epoxidation of limonene with O₂ and *i*-butyraldehyde catalyzed by Ni^{II} complexes. For conditions see Figure 3. a: Catalyst **3a**, rate of epoxide formation. b: Idem, rate of CO₂ formation, c: Catalyst **3b**, rate of CO₂ formation. Solid lines: linear fits of the data.

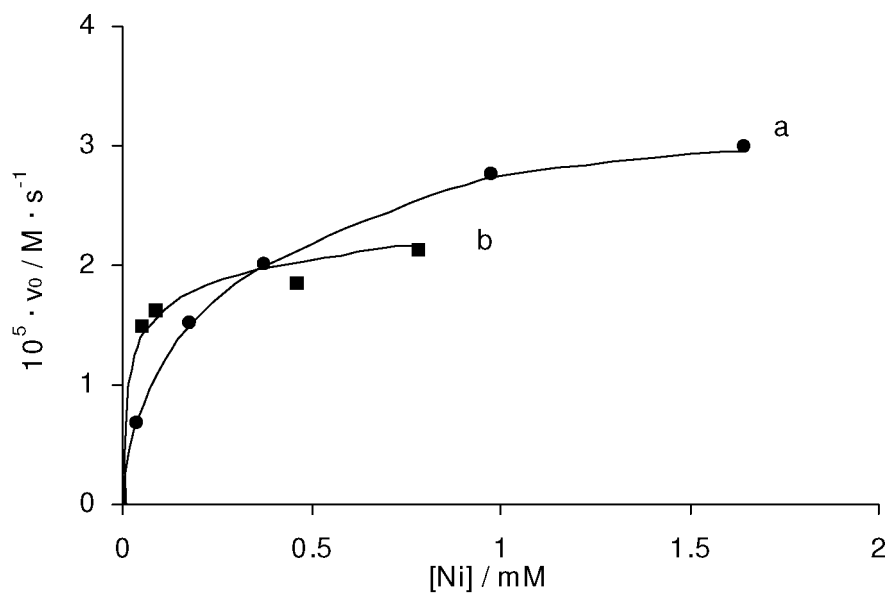
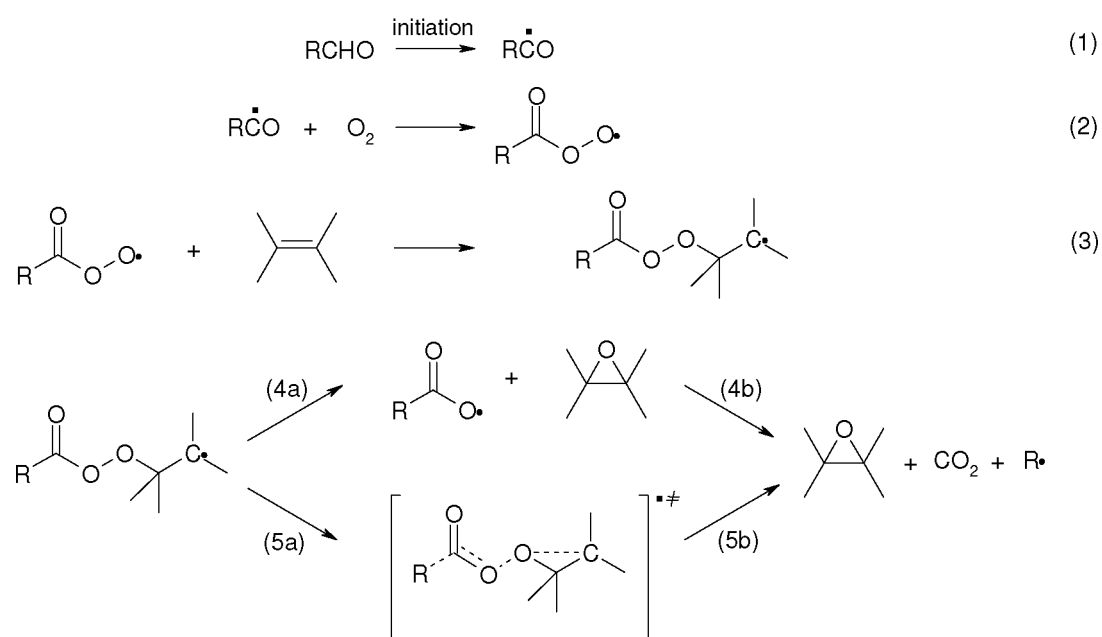
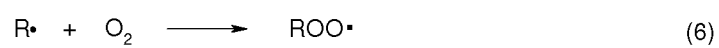


Figure 6. The rate of CO₂ formation as a function of the concentration of the nickel catalyst in the epoxidation of limonene with O₂ and *i*-butyraldehyde as co-reagent. For conditions see Figure 3. a: Catalyst **3a**. b: Catalyst **3b**.

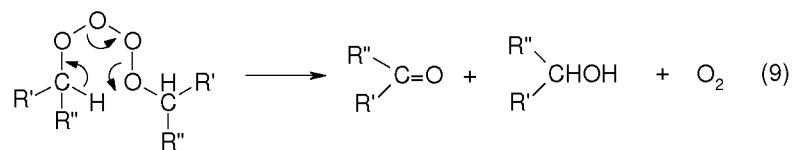
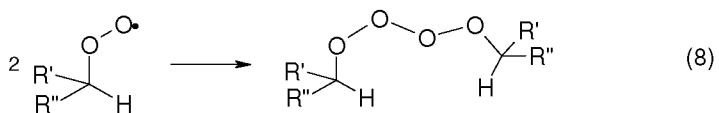
Scheme 1

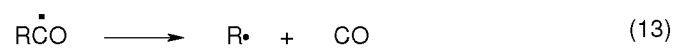
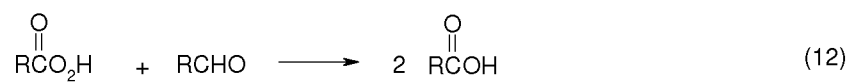
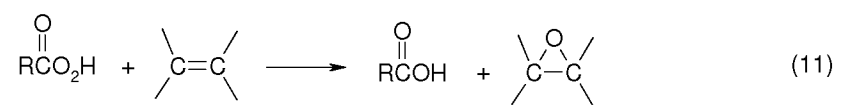
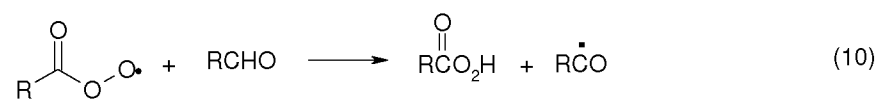


Scheme 2

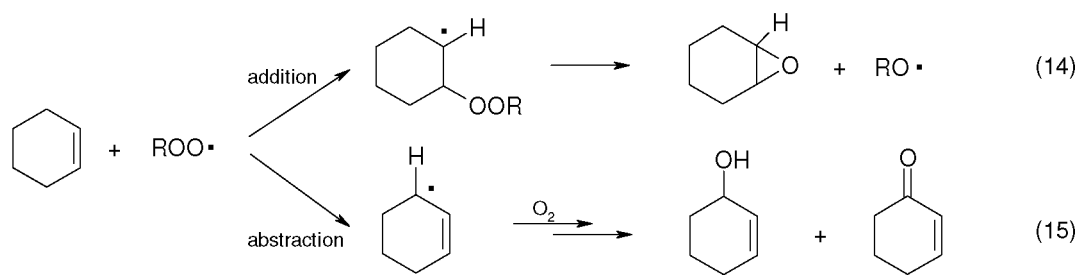


with $R = \begin{array}{l} R' \\ \diagdown \\ C \\ \diagup \\ R'' \end{array} H$:

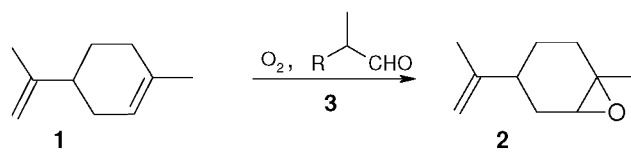


Scheme 3

Scheme 4



Scheme 5



Scheme 6

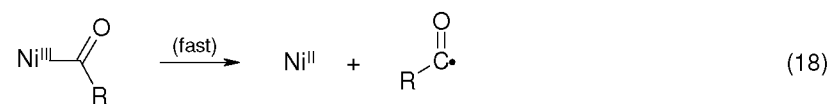
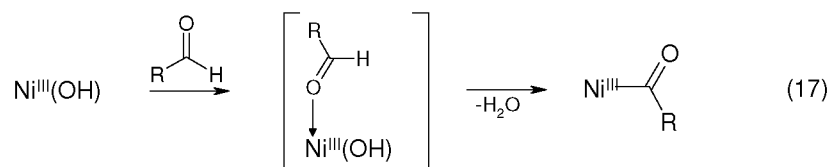
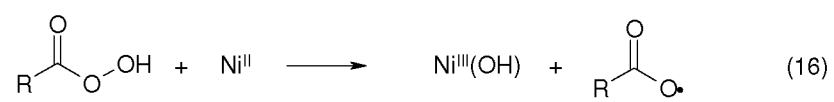


Chart 1

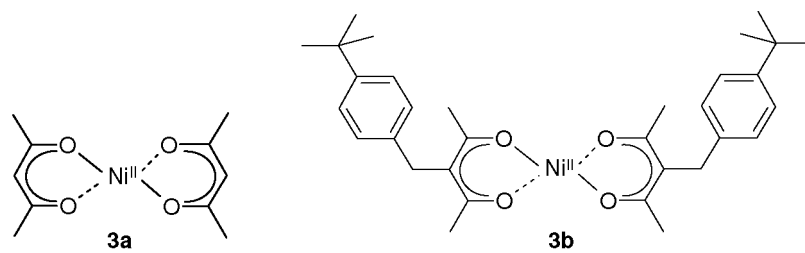


Chart 2

