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Non-heme iron catalysts for the benzylic oxidation: a parallel ligand screening approach

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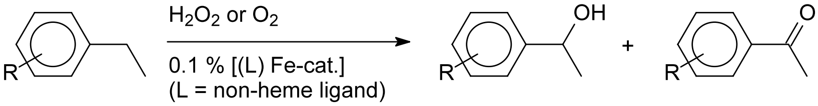
Abstract—Ethylbenzene and 4-ethylanisole were used as model substrates for benzylic oxidation with H_2O_2 or O_2 using a range of non-heme iron catalysts following a parallel ligand screening approach. Effective oxidation was found for Fe complexes based on tetra- and pentadentate nitrogen ligands affording the corresponding benzylic alcohol and ketone. © 2003 Published by Elsevier Science Ltd.

Benzylic oxidation allows the conversion of methylene and methyl groups flanking an aromatic ring to alcohols or ketones.[1] Recently catalysts based on Ce and Mn complexes have been reported to effect benzylic oxidation.[2] Also oxygenases and oxygenase mimics have been used for benzylic oxidation reactions, e.g. cytochrome P450 and heme iron complexes were found to be capable of catalyzing the oxidation of ethylbenzene with H_2O_2 to afford α-phenylethanol and acetophenone.[3] Also the non-heme iron enzyme, methane monooxygenase, was used employing oxygen as the terminal oxidant.[4] So far little effort has been devoted to the use of non-heme iron complexes in the oxidation of ethylbenzene.[5] The development of benign, non-toxic and catalytic alkane oxidations, based on iron, with H_2O_2 and O_2 is a major challenge. In this article we describe novel non-heme iron complexes as effective catalysts for benzylic oxidation.

A series of non-heme iron complexes was tested for the oxidation of ethylbenzene and 4-ethylanisole with both H_2O_2 and O_2 as terminal oxidant (Eq. (1)). The structures of the ligands employed are shown in Figure 1. Most of these complexes are already known and well-characterized.[5–10] Complexes with pentadentate (**1**–**7**, **9**),[6,7] hexadentate (**8**),[8] tetradentate (**10**–**17**),[6,9] and tridentate (**18**–**20**)[10] ligands were tested for these oxidations.[11] The pentadentate ligands coordinate to the iron leaving one of the six coordination sites on iron open for binding of O_2 or H_2O_2.[6] With tetradentate ligands an additional coordination site is open for binding of the oxidant, which is known to have a significant influence on the activity and selectivity of the catalyst.[12] With one hexadentate or two tridentate ligands on one iron-core all coordination sites on the iron will be occupied. For catalytic oxidation by these complexes one of the iron–ligand bonds should be dissociated before oxidation can occur.

For a fast screening of the different catalysts a parallel approach using a Chemspeed ASW 2000 robot was used. The reactions with hydrogen peroxide were carried out under a nitrogen atmosphere. Each reaction vessel was charged with 0.9 mL of a stock solution containing 1.75 mmol of the substrate in acetonitrile. Next, a solution of 1.75 μmol of the catalyst in 0.6 mL of acetonitrile was added. The reaction was started by addition of 87.5 μmol of 30% hydrogen peroxide dissolved in 0.5 mL of acetonitrile. The solution was stirred under vortex (500 rpm) at 30°C for 3.5 h and then quenched with 115 mg of triphenylphosphine in 2



(1)

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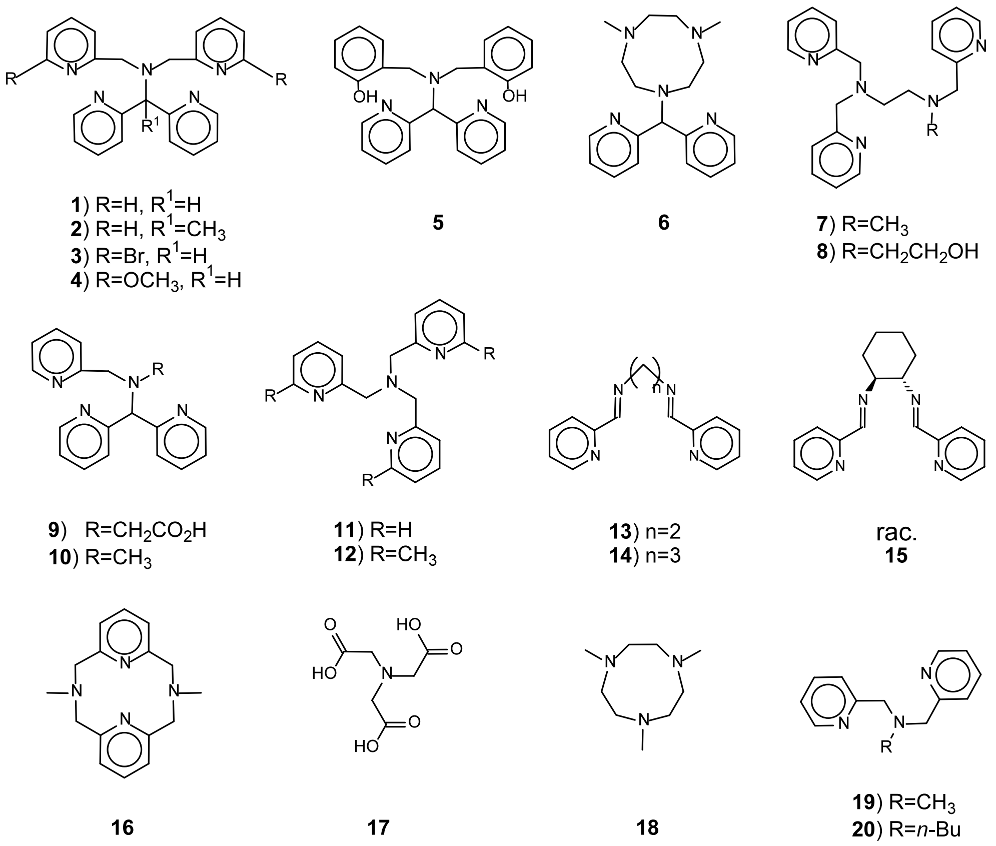

Figure 1. Non-heme ligands used for the iron complexes.

mL of acetonitrile. Aliquots were taken from the reaction mixture and analyzed by GC. For the reactions with oxygen as the oxidant, the reaction vessels were put under an oxygen atmosphere before addition of the reagents. In this case the peroxide solution was substituted for 0.5 mL of acetonitrile. The reactions were stirred under vortex (1000 rpm) at 30°C overnight and subsequently quenched with triphenylphosphine. The results of the oxidations with H_2O_2 and O_2 are summarized in Table 1.

In most cases catalytic activity in the benzylic oxidation of ethylbenzene was observed, affording both the alcohol and ketone. However, some of the catalysts gave significant higher turnover numbers. For the oxidation of ethylbenzene with hydrogen peroxide the alcohol was normally obtained as the major product with an alcohol/ketone (A/K) ratio of 1.1–3.2. The highest yields were obtained with the complexes of the pentadentate ligands **1**, **3**, **6**, and **7**. The most active complexes with tetradentate ligands were derived from the imines **13** and **15**. In the case of ethylanisole as a substrate, with an electron-donating methoxy group at the *para*-position, yields were generally higher. The highest yields were found for the complexes of the pentadentate ligands **1**, **6**, **9**, and the tetradentate ligands **13**, **14**, and **15**. For ethylanisole the complexes of the imines also showed a high A/K ratio of 5.6–6.1. The complexes of the tridentate ligands showed low or complete lack of activity for both substrates. On using O_2 as the oxidant for the benzylic oxidation of ethylbenzene a lower activity was found in all cases. The major product was found to be the ketone instead of the alcohol. To enhance the conversion the reaction temperature was increased from 30 to 80°C. The results are shown in Table 2. The catalytic activity was increased drastically in almost all cases. The best results were found for the Fe complexes of the tetradentate ligands **10** and **11**. For the complex of **10**, up to 54 μmol of the alcohol and up to 107 μmol of the ketone were obtained. Also the complexes of the tetradentate ligand **12** and the pentadentate ligands **1**, **2** and **6** showed enhanced turnover numbers. Only with the imine **15** was a lower activity found at 80°C. This probably arises from degradation of the catalyst at this temperature. Again, in all cases the ketone was found to be the major product with an A/K ratio of 0.5 to 1.0. Also benzaldehyde was found to be an oxidation product with up to 56 μmol, whereas at 30°C only traces of benzaldehyde were observed. The formation of benzaldehyde can be explained by degradation of 1-phenylethyl hydroperoxide, which might be formed during the reaction (vide supra).[3]

The difference in A/K ratios between oxidation with H_2O_2 and O_2 is indicative of a different mechanism for the different oxidants. The formation of both alcohol and ketone with an A/K ratio of approximately 1 in the O_2 oxidation and the formation of benzaldehyde with O_2 are indicative of an autoxidation mechanism, in

Table 1. Catalytic activity of non-heme iron complexes in benzylic oxidation at 30°C expressed as μmol yield from 1.75 mmol of substrate

Catalyst	Ethylbenzene H_2O_2		Ethylbenzene O_2		Ethylanisole H_2O_2	
	Alcohol	Ketone	Alcohol	Ketone	Alcohol	Ketone
Blank	1.8	0	4.7	0.5	0	0
1	16.5	9.3	8.4	11.4	32.4	18.0
2	10.5	3.3	7.7	1.6	7.2	3.2
3	15.6	11.9	7.5	10.3	9.5	3.7
4	6.7	4.6	6.5	5.3	9.8	5.3
5	6.7	2.5	6.1	1.8	7.7	2.1
6	14.7	6.3	7.4	3.7	26.1	9.6
7	24.7	15.9	0.9	2.3	9.5	2.3
8	7.5	6.7	4.6	10.7	3.2	1.6
9	5.6	4.4	6.5	4.9	25.4	20.0
10	6.7	4.2	6.8	12.6	17.2	11.6
11	2.8	4.0	6.0	12.3	5.8	3.5
12	8.9	5.4	7.5	13.0	14.7	4.9
13	10.7	4.0	2.6	7.4	24.7	4.8
14	6.1	3.7	2.5	7.5	26.6	4.8
15	10.7	3.7	2.8	7.5	23.3	4.0
16	7.0	12.1	3.5	8.9	18.6	13.8
17	0.7	1.2	2.8	1.2	1.4	0
18	9.1	6.3	1.8	0.5	1.2	0
19	8.1	2.3	5.3	11.0	1.2	3.9
20	2.1	1.2	2.8	8.2	1.2	0

Table 2. Catalytic activity of non-heme iron complexes with O_2 in μmol at 80°C expressed as μmol yield from 1.75 mmol of ethylbenzene

Catalyst	Alcohol	Ketone	Benzaldehyde
Blank	3.5	0.4	0.2
1	65.1	83.5	59.3
2	54.8	53.2	48.0
6	39.4	26.4	7.4
10	53.6	107.1	56.0
11	43.4	90.5	54.3
12	40.8	39.4	32.6
15	0.7	1.8	0.4

which the Fe catalyst reacts with 1-phenylethyl hydroperoxide to afford the observed products.[3] However, in the oxidations with H_2O_2 this will not be the only source of product formation as indicated by considerably higher A/K ratios. Most of the catalysts are already known to form an active species with H_2O_2 that could participate in oxidation reactions.[7,9,12] To obtain further insight into the origin of ketone formation, 1-phenylethyl alcohol was used as a substrate with the complexes of **2**, **10**, **12**, and **15** at 30°C. With O_2 as the oxidant almost no ketone was formed, indicating that the ketone is directly formed from ethylbenzene and not from oxidation of the alcohol. This is in agreement with the expected autoxidation mechanism with O_2. With H_2O_2 some of the alcohol was converted into the ketone. In this case, at least part of the ketone formed during the oxidation of ethylbenzene will originate from the corresponding alcohol formed during the reaction. This can be due to an iron-oxo species formed from the iron complexes with H_2O_2.

In conclusion, we have discovered that a number of non-heme iron complexes are capable of benzylic oxidation both with H_2O_2 and O_2. In oxidations with O_2 the most active catalysts are the complexes derived from the pentadentate ligands **1** and **7** and the tetradentate ligands **10** and **11**, and with ethylbenzene at 80°C up to 107 μmol was obtained. With H_2O_2 the most active catalysts are the complexes of the pentadentate ligands **1** and **6** and of the imines **13**, **14**, and **15**. Up to 25 μmol alcohol formation was observed. Using the imine ligands the highest A/K ratios, up to 6 for ethylanisole, were reached. The alcohol was formed as the major product by the use of H_2O_2 and the ketone by O_2, the latter mainly resulting from a catalytic autoxidation mechanism.

Acknowledgements

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11. All complexes except that of **18** were isolated before being used in the catalytic oxidation reactions. For **7** the [Fe(**7**)Cl]PF_6 complex was used; for **18** the Fe complex was used as a solution in water; for **19** the Fe(**18**)Cl_3 complex was used; for the other ligands the Fe complexes with perchlorate as anion were used.
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