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The Functionalization of Saturated Hydrocarbons Part XXIX. Application of *tert*-Butyl Hydroperoxide and Dioxygen Using Soluble Fe(III) and Cu(II) Chelates.

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Abstract: New methodology for the selective transformation of saturated hydrocarbons into ketones/alcohols and alkenes is described. A crucial aspect of this new process is that no reaction solvent is required since the Fe(III) and Cu(II) complexes used are completely soluble in the hydrocarbon substrates. Thus, the large quantity of pyridine, acetic acid or acetonitrile required in previous systems is no longer a prerequisite.

The development of new procedures for the functionalization of saturated hydrocarbons has been the focus of intensive research in recent years.[1] The oxidation of cyclohexane to cyclohexanol/one is an important commercial reaction, providing one million tons of cyclohexanol/one per year for conversion into caprolactam and/or adipic acid and hence to nylon.[2] However, this commercial reaction is perhaps the least efficient major industrial chemical process. Typically, cyclohexane is oxidized at 160°C under a high pressure of oxygen using large quantities of a Cobalt (II) catalysts. The reaction is run to a 4% conversion and gives the desired oxidation product with a selectivity of around 85%. Thus, there is clearly a need for a milder and more efficient process for the oxidation of saturated hydrocarbons. The Gif-systems[3] developed by Barton and co-workers are attractive alternatives to the existing industrial process due to the mild conditions, relatively high efficiencies and high selectivities obtained. Unfortunately, their implementation on an industrial scale is undesirable due to the large quantities of pyridine required.

Our initial efforts to optimize an Fe^{III}–TBHP reaction[4] revealed that TBHP could be used catalytically without adversely affecting the overall yield of the reaction.[5] Clearly the catalytic TBHP was allowing us to initiate an autoxidation process under milder conditions than those traditionally employed.[2] In order to make a more cost effective process we decided to investigate systems in which the large quantities of pyridine and acetic acid were largely or totally replaced by the hydrocarbon substrate.

We now report that saturated hydrocarbons can be selectively converted into the corresponding ketones or olefins in the absence of solvent using a combination of *tert*-butyl hydroperoxide (TBHP) and catalytic amounts of soluble Fe(III) or Cu(II) chelates. The results collected in Table 1 are representative of the iron catalysts studied. Thus, the oxidations of hydrocarbon substrates using $Fe(tma)_3$[6] (Iron^{III} *tris*pivalate) the catalyst (entries 1-6) are very efficient and ultimately give a high yield of ketone and alcohol. However, the reactions are also rather slow and became heterogeneous after several days of reaction. In contrast, Fe(fod)$_3$[7] [Iron^{III} *tris* (2,2-dimethyl-6,6,7,7,8,8,8-heptafluoro-3,5-octanedionate)] and Fe(hfa)$_3$[8] [Iron^{III} *tris* (hexafluoroacetylacetonate)] promoted oxidations are superior to those catalysed by Fe(tma)$_3$. In addition, it is clear that reaction rates are enhanced by the presence of pyridine (entries 14 and 15), oxygen (entries 11 and 15) or a combination of both (entry 15).

Table 1: Oxidation of saturated Hydrocarbons Using Soluble Iron(III) Chelates.

Entry	Hydrocarbon (50 mmol)	Reaction Conditions^{a}	Time (hr)	Ketone (mmol)	Alcohol (mmol)	Total (mmol)	Effic.^{b} (%)
1	Cyclohexane	Fe(tma)$_3$^{c}, r.t., air	48	0.048	0.041	0.089	4
2	Cyclooctane	Fe(tma)$_3$, 50°C,air	24	0.679	0.152	0.831	∞
3	Cyclooctane	Fe(tma)$_3$, 50°C, air	96	2.396	0.590	2.986	∞
4	Cyclooctane	Fe(tma)$_3$, 50°C, air	264	7.466	1.290	8.756	1100
5	Cyclohexane	Fe(tma)$_3$, 70°C, air	18	0.354	0.318	0.672	480
6	Cyclohexane	Fe(tma)$_3$, 70°C, air	48	1.202	0.901	2.103	300
7	Cyclohexane	Fe(hfa)$_3$^{d}, 50°C, air	18	0.671	1.123	1.794	20
8	Cyclohexane	Fe(fod)$_3$^{e}, 50°C, air	24	0.068	0.057	0.125	∞
9	Cyclohexane	Fe(fod)$_3$, 70°C, air	18	0.625	0.637	1.262	49
10	Cyclohexane	Fe(fod)$_3$, 70°C, air	48	1.463	0.996	2.459	77
11^{f}	Cyclohexane	Fe(fod)$_3$, 70°C, O_2 3 atm (45 psi)	18	2.129	1.283	3.412	45
12	Cyclooctane	Fe(fod)$_3$, 70°C, air	18	1.727	1.016	2.743	∞
13	Cyclooctane	Fe(fod)$_3$, 70°C, air	48	2.187	0.934	3.121	51
14^{g}	Cyclooctane	Fe(fod)$_3$, 70°C, air	18	3.457	1.037	4.494	51
15^{g}	Cyclooctane	Fe(fod)$_3$, 70°C, O_2 (bubbled)	18	6.848	1.040	7.888	97

a. Fe(III) catalyst (0.2 mmol) and TBHP (9.0 mmol) were employed in each case. *b.* Efficiency calculated based on oxidant consumed assuming that one mole of oxidant gives one mole of product. ∞ efficiency means that no TBHP (by titration) appears to be consumed. *c.* Fe(tma)$_3$ = Iron(III) *tris*(pivalate).*d.* Fe(hfa)$_3$ = Iron(III)*tris*(hexafluoroacetylacetonate). *e.*. Fe(fod)$_3$ = Iron(III) *tris*(2,2-dimethyl-6,6,7,7,8,8,8-heptafluoro-3,5-octanedionate).*f.* This reaction was carried out in a Parr Pressure Apparatus. *g.* This reaction was carried out in the presence of pyridine (5.0 mmol).

However, the addition of catalytic amounts of pyridine or other suitable ligands such as 1,10-phenanthroline or 2,2'-bipyridine was found to enhance the rate of the process and effect an augmented selectivity towards the formation of ketone

A more detailed study of the catalytic effect of pyridine has revealed a pronounced dependance on the amount of pyridine employed (Table 2).

Table 2: Catalytic Effect of Pyridine and other ligands[a]

Entry	Additive (mmol)	Ketone (mmol)	Alcohol (mmol)	Total (mmol)	one / ol ratio	O.P.[b] (mmol)	Effic.[c] (%)
1	——	0.068	0.057	0.125	1.19:1	9.5	—
2	Py[d], 0.6	1.095	0.704	1.799	1.56:1	1.42	24
3	Py, 1.2	1.393	0.877	2.270	1.58:1	0.52	27
4	Py, 3.0	1.822	1.043	2.865	1.75:1	0.13	32
5	Py, 5.0	2.029	0.926	2.955	2.19:1	0.19	34
6	Py, 10.0	2.779	0.921	3.700	3.02:1	0.10	42
7	Py, 20.0	3.072	0.751	3.823	4.09:1	0.16	43
8	Py, 30.0	3.518	0.784	4.302	4.49:1	0.11	48
9[e]	Bipy[f], 0.6	1.255	0.870	2.125	1.44:1	0.46	25
10[g]	Phen[h], 0.6	1.107	0.735	1.842	1.51:1	0.51	22

a. Experimental Conditions: Cyclohexane (50 mmol), TBHP (9 mmol), Fe(fod)$_3$ (0.2 mmol), Reaction temperature = 50°C, Reaction time = 24h, Atmosphere: Air. *b*. O.P. = Oxidizing power determined by iodometric titration. *c*. Efficiency calculated as in Table 1. *d*. Py = Pyridine; *e*. After 24h the reaction had become heterogeneous. *f*. Bipy = 2,2'-Bipyridine.*g*. After 24h the reaction had become heterogeneous. *h*. Phen = 1,10-Phenanthroline.

Thus, when the reaction is run in the absence of pyridine it is very efficient in terms of the oxidizing power remaining after 24h, however, the reaction is also slow at 50°C. In contrast, reactions performed with increasing quantities of pyridine gave a correspondingly large increase in the amount of ketone formed. Moreover, the quantity of alcohol produced in the above experiments initially increases, reaching a maximum when 3 mmol of pyridine was employed and then decreases leading to an observed ketone to alcohol selectivity of 4.5:1.

Mechanistic Studies

The addition of TEMPO (3 mmol) to a system comprising of cyclooctane (50 mmol), $Fe(fod)_3$ (0.2 mmol) and TBHP (9 mmol) at 70 °C for 24 hr. gave 1.88 mmol of cyclooctyl-TEMPO, together with cyclooctanone (0.464 mmol), cyclooctanol (0.162 mmol) and recovered TEMPO (0.832 mmol). In a second experiment, a mixture of cyclooctane (50 mmol), $Fe(fod)_3$ (0.2 mmol), pyridine (60 mmol) and TBHP (9 mmol) were reacted at 70°C for 24 hr. After work-up, the products isolated were cyclooctene (1.699 mmol), cyclooctanone (1.513 mmol), cyclooctanol (0.882 mmol) and *ortho*- and *para*-cyclooctyl pyridine coupled products (0.154 mmol and 0.039 mmol respectively). These results clearly indicate the participation of free alkyl radicals in these reactions.

Preliminary optimisation studies dealing with the amount of Iron catalyst required have shown that around 1 mol percent (0.5 mmol) of catalyst (relative to the hydrocarbon) produced the most effective result as illustrated in Table 3.

Table 3: Optimization of the Amount of $Fe(fod)_3$.[a]

Entry	$Fe(fod)_3$ (mmol)	Ketone (mmol)	Alcohol (mmol)	Total (mmol)	Effic.[b] (%)
1	0.1	0.161	0.183	0.344	17
2	0.2	0.257	0.279	0.536	27
3	0.5	0.914	0.770	1.684	84
4	1.0	0.989	0.786	1.775	89

a. Experimental Conditions: Cyclohexane (50 mmol); TBHP (2.0 mmol); $Fe(fod)_3$ (X mmol); Reaction temperature = 70°C; Reaction time = 24h; Atmosphere: air. *b.* Efficiency calculated as in Table 1.

Recent studies have shown that oxidative functionalization of alkanes giving alkenes rather that ketones can be accomplished using Copper (II) salts.[9] The possibility of preparing alkenes using the hydrocarbon soluble copper catalyst $Cu(fod)_2$ was examined. Thus, $Cu(fod)_2$ was prepared in 81% yield according to the literature procedure.[10] The results obtained are collected in Table 4.

Table 4: Hydrocarbon Activation using Cu(fod)$_2$[a].

Reaction Atmosphere	Time (hr)	Additive (mmol)	Alkene (mmol)	Ketone (mmol)	Alcohol (mmol)	Total (mmol)	Effic.[b] (%)
Air	24	— —	1.466	1.139	0.422	3.027	195
Air	48	— —	2.273	2.588	0.791	5.652	174
Air	24	Py, 5.0	1.736	3.006	0.702	5.444	65
Argon	24	— —	5.481	0.096	0.049	5.626	77
Oxygen	24	— —	0.276	5.133	1.298	6.707	192

a. Experimental Conditions: Cyclooctane (50 mmol), TBHP (9 mmol), Cu(fod)$_2$ (0.5 mmol), Reaction temperature = 60°C. *b.* Efficiency calculated as in Table 1.

It is particularly noteworthy that under an atmosphere of air, approximately equal proportions of alkene and ketone were formed. The addition of pyridine (5 mmol) speeded up the reaction 2-fold and also altered the alkene to ketone ratio (1:2) in favor of the ketone. Moreover, under an atmosphere of oxygen, the amount of ketone formed increased substantially giving an alkene to ketone ratio of 1:19. In contrast, when the oxidation process was performed under an argon atmosphere, the alkene was by far the major product. Thus, in this case the alkene to ketone ratio was 57:1. The turnover number for this particular reaction was calculated to be 11.3 per catalyst molecule, with an efficiency of 77% and an overall conversion of 11.3%.

This reaction appears to be the most efficient, highest yielding and most selective procedure studied to date for the formation of cycloalkenes from the corresponding alkanes. The reactions proceed at relatively low temperatures and pressures with high conversions and yields. The efficiency ranges from 65-195% based on the oxidizing agent (TBHP). The unreacted substrate can be recovered and recycled thus, the reaction yields are high. Further studies in this area are in progress in these laboratories.

In recent publications[3b,11] Sawyer and his colleagues have obtained remarkable efficiencies of several times the theoretical value in hydrocarbon oxidation. At the same time coupling to pyridine is frequently observed. We consider that because of the use of Fe^{II} and TBHP as well as the formation of pyridine-coupling products these reactions, like the chemistry reported in the present article, represent a major contribution from radical chemistry. The fact that pyridine coupling occurs under conditions where radical reactivity is probable reinforces our conclusion that when no coupling to pyridine is seen a radical mechanism is not operative.[3a]

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5. In a typical experiment: a mixture of $Fe(NO_3)_3{\bullet}9H_2O$ (0.4 mmol), cyclooctane (10 ml; 75 mmol) and *tert*-butyl hydroperoxide (TBHP) (1.8 mmol) in pyridine (60 ml) and acetic acid (6 ml) was heated at 50°C for 96 hours giving, after the usual acidic work-up, cyclooctanone (2.71 mmol) and cyclooctanol (0.26 mmol) corresponding to a reaction efficiency based on TBHP consumed of 200%.
6. $Fe(tma)_3$ was prepared as follows: Trimethyl acetic acid (2.244g; 22 mmol) was dissolved in dilute sodium hydroxide solution (0.88g NaOH in 20 mL water). A solution of $FeCl_3{\bullet}6H_2O$ (1.98g; 7.3 mmol) in water (10 mL) was added in one portion causing the precipitation of a peach colored solid. After stirring for 30 min. the precipitate was collected and dried *in vacuo* giving the desired complex (2.44g; 93%).
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