CHAPTER III

RESULTS AND DISCUSSION

During the last two decades, chromium–based catalysis reactions have been widely explored for the oxidation of various organic substrates **[1]**. Despite the readily commercial availability of several recent developed reagents for oxidation reactions, there still exists a desire to search for milder and more efficient method. This research focuses on the development of selective oxidation of model substrates (cyclohexanol, cyclohexene and 1-hexanol) catalyzed by chromium (III) complexes using 70% *tert*-butylhydroperoxide (TBHP) as oxidant for reaction conditions optimization, and afterwards applied for transformation of naturally occurring compounds. Many natural product substrates such as α-pinene, α-ionone, β-ionone, menthol, cholestanol, cinnamyl alcohol, α-terpinene, γ-terpinene and so on, can be oxidized into their corresponding oxygenated compounds which are the important precursors for a number of pharmaceutical, perfumery and food industries.

3.1 Characterization of chromium complexes

Four chromium (III) carboxylates, chromium (III) acetylacetonate and chromium (III) salen were synthesized using known procedure reported in chemical literatures **[27, 29]**. Their identities were confirmed by comparison the physical properties, elemental analysis (EA), X-ray diffraction (XRD) and IR spectroscopic data with those previously cited.

3.1.1 Elemental analysis (EA)

Percent composition of carbon and hydrogen in chromium (III) stearate was analyzed by elemental analysis technique (EA). The result is presented in Table 3.1.

Table 3.1 Elemental analysis of prepared Cr(III)stearate

Value	% C	% H
Theoretical	71.87	11.73
Experimental	70.58	16.28

Table 3.1 presents experimentally determined the composition of prepared Cr(III)stearate and the theoretical values. The result indicated that the complex contains 70.58% and 16.28% of carbon and hydrogen, respectively *versus* the theoretical value of 71.87% carbon and 11.73% hydrogen. The theoretical and experimental values for carbon were nearly but those for hydrogen were not good, possibly because of the moisture in sample.

3.1.2 X-ray diffraction (XRD)

The crystalline characteristic of the prepared Cr(III)stearate was investigated by XRD technique; the XRD pattern is shown in Figure 3.1.

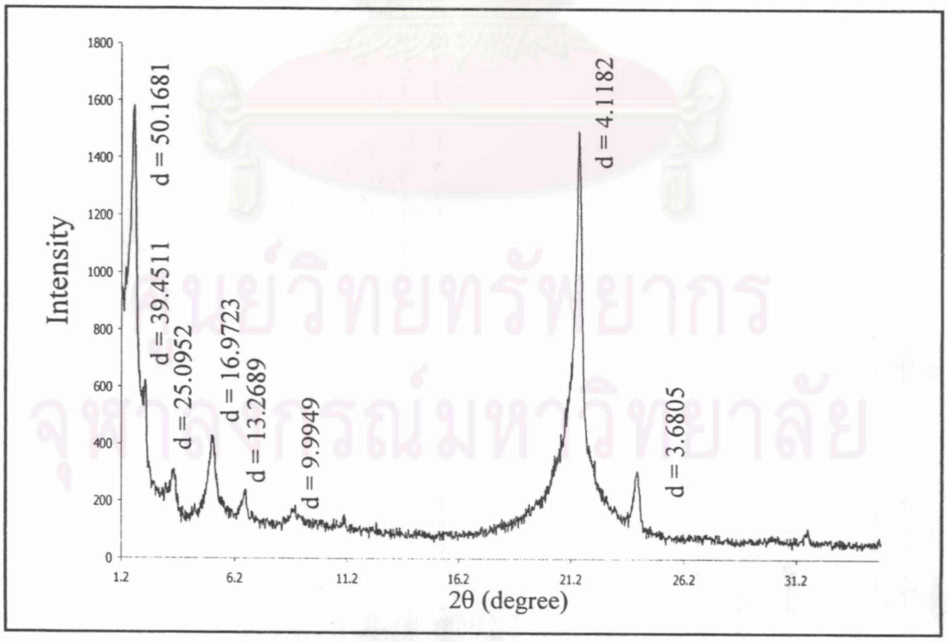


Figure 3.1 The XRD pattern of chromium (III) stearate

From the pattern depicted in Figure 3.1, It could be confirmed that this complex has the crystalline characteristic which showed the important characteristic peaks at 2θ 1.760 (d = 50.1681 A^{o}), 2.238 (d = 39.4511A^{o}), 3.518 (d = 25.0952A^{o}), 5.202 (d = 16.9723A^{o}), 6.656 (d = 13.2689A^{o}), 21.560 (d = 4.1182A^{o}) and 24.161(d = 3.6805A^{o}). The further characterization of the phase of crystal using X-ray crystallography was required.

3.1.3 Infrared spectroscopy (IR)

The instance of the IR spectrum of chromium (III) stearate is depicted as shown in Figure 3.2.

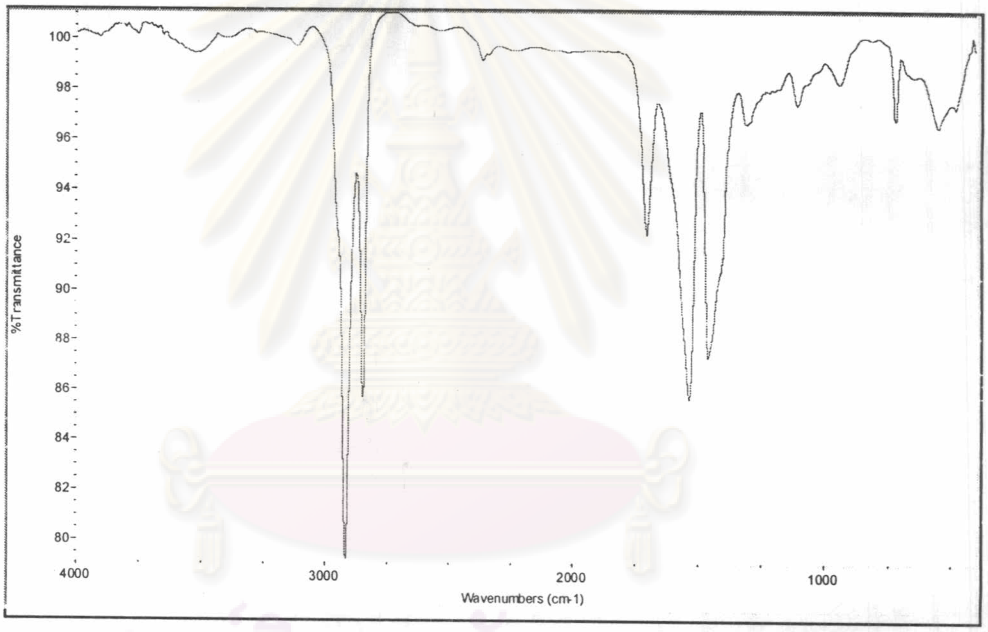


Figure 3.2 The IR spectrum of chromium (III) stearate

From IR spectrum, this chromium complex presents a significant absorption band of carbonyl C=O around 1710 cm^{-1}; in addition, the C-O band of carboxylate group was observed around 1400-1450 cm^{-1}. The C-H stretching vibration was detected around 2850-2900 cm^{-1}. Furthermore, the absorption peak around 3500 cm^{-1} corresponded to the –OH stretching was not observed. The C=O stretching vibration of chromium complex was found to absorb at higher frequency than that of free carboxylic acid (appeared at 1700 cm^{-1}), due to increasing of bond strength [**29**].

Part 1 Chromium-catalyzed oxidation of alcohols

3.2 Study on the optimum conditions for the oxidation of cyclohexanol

Various factors were required to evaluate prior to reach the optimal conditions for the oxidation of cyclohexanol, a representative of secondary alcohol. The parameters studied for this reaction included type of chromium complexes, temperature, the amount of oxidant and the amount of catalyst.

3.2.1 Effects of type of chromium complexes

The goal of this study was to screen for suitable catalysts that could mediate the transformation of cyclohexanol to the corresponding carbonyl function in high yield with good selectivity [**29**]. The results of the oxidation of cyclohexanol catalyzed by different chromium complexes are presented in Table 3.2.

Table 3.2 The oxidation of cyclohexanol catalyzed by chromium complexes

Entry	Catalysts	% cyclohexanol (recovery)	%yield cyclohexanone	MB
1	none	92	8	100
2	Cr(III)palmitate	20	82	102
3	Cr(III)stearate	14	91	105
4	Cr(III)behinate	25	81	106
5	Cr(III)acetylacetonate	31	74	105
6	Cr(III)SalenCl	18	76	94

reaction conditions: 5 mmol cyclohexanol, 0.20 mmol catalyst, 18 mmol TBHP, 5 mL isooctane, 70°C, 24 h

Five chromium complexes were screened to observe their potentially catalytic oxidation ability. It was disclosed that all chromium complexes afforded good yield for transformation of cyclohexanol to cyclohexanone without contamination of undesired products. Among those chromium complexes examined, chromium (III) stearate provided the highest yield of cyclohexanone. In the absence of chromium complex, the oxidation of cyclohexanol to cyclohexanone was not successful (entry 1). Therefore, in this work chromium (III) stearate was selected to further utilize as a catalyst for exploring the oxidation of secondary alcohols.

3.2.2 Effects of the amount of oxidant

With the suitable catalyst in hand, the amount of oxidant was the next parameter to examine. The amount of TBHP in the reaction was varied from 9-27 mmol. The results are summarized as shown in Table 3.3.

Table 3.3 Effect of the amount of TBHP in the oxidation of cyclohexanol catalyzed by Cr(III)stearate

Entry	TBHP (mmol)	% cyclohexanol (recovery)	%yield cyclohexanone	MB
1	9	29	73	102
2	12	30	76	106
3	18	14	91	105
4	20	16	88	104
5	27	13	86	99

reaction conditions: 5 mmol cyclohexanol, 0.20 mmol Cr(III)stearate, 5 mL isooctane, 70°C, 24 h

From Table 3.3, the large excess amount of oxidant is required in order to generate oxo-chromium species for cyclohexanol oxidation. When TBHP 18 mmol was used, the reaction gave the highest yield of desired product 91% (entry 3). In addition, when the amount of TBHP was decreased from 18 mmol, the yield was declined, possibly due to the less amount of active species present. On the other hand, when the amount of TBHP was increased (entries 4 and 5), the yield of cyclohexanone was similar to the use of 18 mmol of TBHP. This implied that the reaction was carried out with 20 and higher mmol of oxidant was not required.

3.2.3 Effects of temperature

Temperature is one of the important parameters for conditions optimization. The temperature examined was room temperature (30°C), 50°C, 70°C and at refluxing isooctane temperature (99°C). The results are pointed out in Table 3.4.

Table 3.4 Effect of temperature on the oxidation of cyclohexanol

Entry	Temp (°C)	time (h)	% cyclohexanol (recovery)	% yield cyclohexanone	MB
1	RT (30)	24	80	25	105
2	50	24	27	68	95
3	70	6	24	77	101
4	70	24	14	91	105
5	70	48	20	83	103
6	reflux isooctane (99)	6	28	75	103
7	reflux isooctane (99)	24	25	75	100

reaction condition: 5 mmol cyclohexanol, 0.20 mmol Cr(III)stearate, 18 mmol TBHP, 5 mL isooctane

From Table 3.4, it was observed that at 70°C for 24 h, the highest yield of cyclohexanone could be accomplished. This might be suggested that TBHP could be homolytically cleavaged forming a radical to initiate the oxidation reaction (entry 4). At 70 °C for 6 h (entry 3), it was found that the yield of desired product was formed only 77%. Likewise, when the reaction time was prolonged to 48 h, the yield of cyclohexanone was decreased. Whereas the reaction was carried out at lower temperature, the reaction was not successful. It might be explained that TBHP did not probably exposed well to form a radical to initiate the oxidation reaction (entries 1 and 2). At refluxing temperature of isooctane (99 °C), the conversion of cyclohexanol and the formation of cyclohexanone were slightly decreased due to the rapid decomposition of TBHP at high temperature (entries 6 and 7). According to the previous report on the first use of chromium(III) stearate for the oxidation of secondary alcohols into carbonyl using TBHP as an oxidant **[8,9]**, it was declared that the ratio of substrate/oxidant/ catalyst was 2/1/0.02 in benzene at 80°C for 6 h affording only lower yield (26% of cyclohexanone). For this work, cyclohexanol could be oxidized to cyclohexanone in high yield (91%) when the reaction was performed with the ratio 5/18/0.20 of substrate/oxidant/ catalyst in isooctane at 70°C for 24 h.

3.2.4 Effects of the amount of catalyst

Variable amounts of chromium complexes: 0.01 (0.2 % mol), 0.05 (1% mol), 0.10 (2% mol), 0.20 (4% mol), 0.25 (5% mol) and 0.50 mmol (10% mol) were used to search for the appropriate amount of catalyst in this oxidation reaction. The results are shown in Table 3.5.

Table 3.5 Effect of the amount of Cr(III)stearate on the oxidation of cyclohexanol

Entry	catalyst (mmol)	% cyclohexanol (recovery)	%yield cyclohexanone	MB	T.O.N.
1	0.01	64	35	99	153
2	0.05	26	74	100	73
3	0.10	16	80	106	39
4	0.20	14	91	105	23
5	0.25	20	87	107	18
6	0.50	20	77	97	8

reaction conditions: 5 mmol cyclohexanol, 18 mmol TBHP, 5 mL isooctane, 70°C, 24 h

From Table 3.5, it was disclosed that 0.20 mmol of chromium(III) stearate was the optimal amount of catalyst (entry 4). In addition, when the amount of catalyst was increased or decreased from 0.20 mmol, the lower yield was detected. When 0.50 mmol of catalyst was used, the yield of product was decreased. This might be explained by increasing agglomeration of catalyst when large amount of catalyst was loaded as well as the rapid decomposition of TBHP boosted by the overloaded catalyst [**32**]. The use of lower amounts of catalyst led to lower yields; on the other hand, turn over numbers was increased.

3.3 The kinetic study on the oxidation of cyclohexanol catalyzed by Cr(III) stearate

This study was undertaken in order to assess the propagation of cyclohexanol oxidation. The results are reported in Table 3.6 and Figure 3.3.

Table 3.6 Kinetic study on cyclohexanol oxidation

Entry	Time (h)	% cyclohexanol (recovery)	% cyclohexanone	MB
1	0	100	0	100
2	1	80	26	106
3	2	73	30	103
4	3	68	34	98
5	4	33	69	102
6	5	32	71	103
7	6	24	77	105

reaction conditions: 5 mmol cyclohexanol, 0.20 mmol Cr(III) stearate, 18 mmol TBHP, 5 mL isooctane, 70°C, 24 h

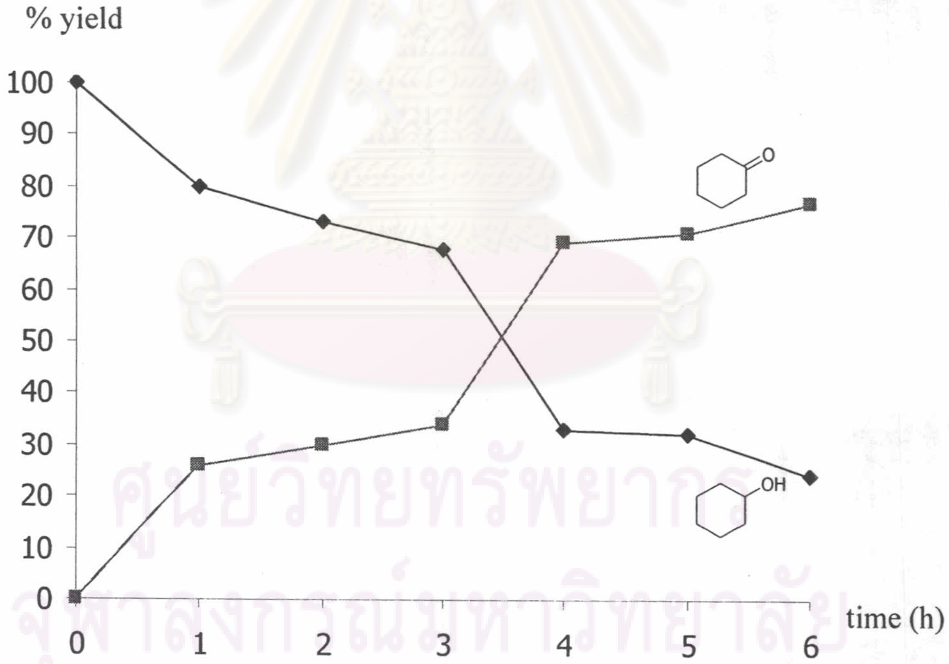


Figure 3.3 The kinetic study on the oxidation of cyclohexanol

Table 3.6 and Figure 3.3 exhibit that cyclohexanol was gradually converted to cyclohexanone. The half-life of cyclohexanone formation was around 3 h.

3.4 The oxidation of 1-hexanol

1-Hexanol was selected as a model substrate for primary alcohol under the oxidation conditions studied. The results of the oxidation of 1-hexanol catalyzed by different chromium complexes are presented in Table 3.7.

Table 3.7 The oxidation of 1-hexanol catalyzed by various chromium complexes

Entry	Catalysts	Percentage			MB
		1-hexanol (recovery)	hexanal	hexanoic acid	
1	Cr(III)palmitate	38	0	tr	38
2	Cr(III)stearate	48	0	9	57
3	Cr(III)behenate	32	0	tr	32
4	Cr(III)acetylacetonate	66	0	tr	66
5	Cr(III)SalenCl	58	0	tr	58

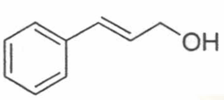
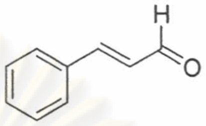
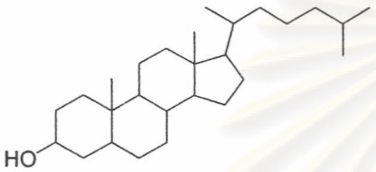
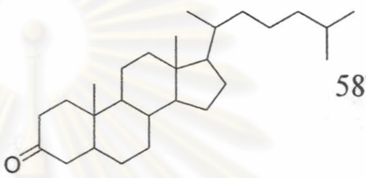
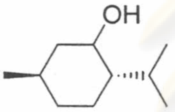
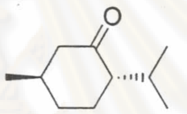
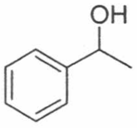
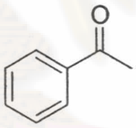
reaction conditions: 5 mmol 1-hexanol, 18 mmol TBHP, 0.20 mmol catalyst, isooctane 5 mL, 70°C, 24 h

From Table 3.7, it was observed that all chromium complexes failed to utilize for transformation of 1-hexanol into hexanal (capronaldehyde) and also gave poor yield of hexanoic acid (caproic acid). Chromium (III) stearate played the best reactivity for conversion of 1-hexanol to hexanoic acid with only 9% (assessed by TLC). The sum of 1-hexanol and all products were not taken as 100% because hexanoic acid may be adsorbed by celite. The attempt to separate hexanoic acid by basic extraction and then purify by column chromatograph gave the mixture of hexanoic acid and stearic acid.

3.5 Chromium (III) stearate – catalyzed oxidation of natural products containing hydroxyl group

Utilizing the optimized catalytic conditions for cyclohexanol oxidation, it can be possible apply to the conditions to oxidize naturally occurring compounds. Natural products bearing hydroxyl group are commonly found in nature [33]. Among those prominent examples include cinnamyl alcohol, cholestanol and menthol, these compounds were selected for evaluating the capability of this catalytic system. The outcomes are accumulated in Table 3.8.

Table. 3.8 The oxidation of natural products containing hydroxyl group catalyzed by chromium(III)stearate

Entry	Substrates	time (h)	Products	% yield	MB
1[a]		5		63	>96
2[b]		24		58[c]	-
3 [d]		24		45	98
4		24		51	96
5[e]		24		78	105
6[d]		24		98	98
7		24		82	82

reaction condition: 5 mmol substrate, 0.20 mmol chromium (III) stearate, 18 mmol TBHP, isooctane 5 mL, 70°C. [a] CH_3CN was used, [b] 0.5 mmol substrate was used, [c] isolated yield, [d] 9 mmol TBHP, [e] 27 mmol TBHP

From Table 3.8, the oxidation of activated primary alcohol (entry 1), cinnamyl alcohol provided a good yield of the corresponding cinnamaldehyde (63 %) and trace amount of cinnamic acid. The amount of the latter was increased when the reaction time was prolonged. In case of secondary alcohols, menthol was cleanly oxidized to menthone in moderate yields when 9 or 18 mmol of TBHP was used (entries 3 and 4). With the great extent, when the reaction was carried out with 27 mmol of TBHP, the yield of menthone was evidently increased up to 78% (entry 5). The significantly lower conversion and yield of the sterically hindered isopropyl-substituent in menthol compared to that of cyclohexanol implies that the oxidation catalyzed by Cr(III)stearate was sensitive to steric effect. The structure of attained product, menthone was fully verified by ^{1}H- and ^{13}C-NMR spectra. According to ^{13}C-NMR spectrum presented in Figure 3.5, an important peak of ketone functional group was clearly detected at δ 211.5 and the ^{1}H-NMR spectrum of menthone was depicted in Figure 3.4.

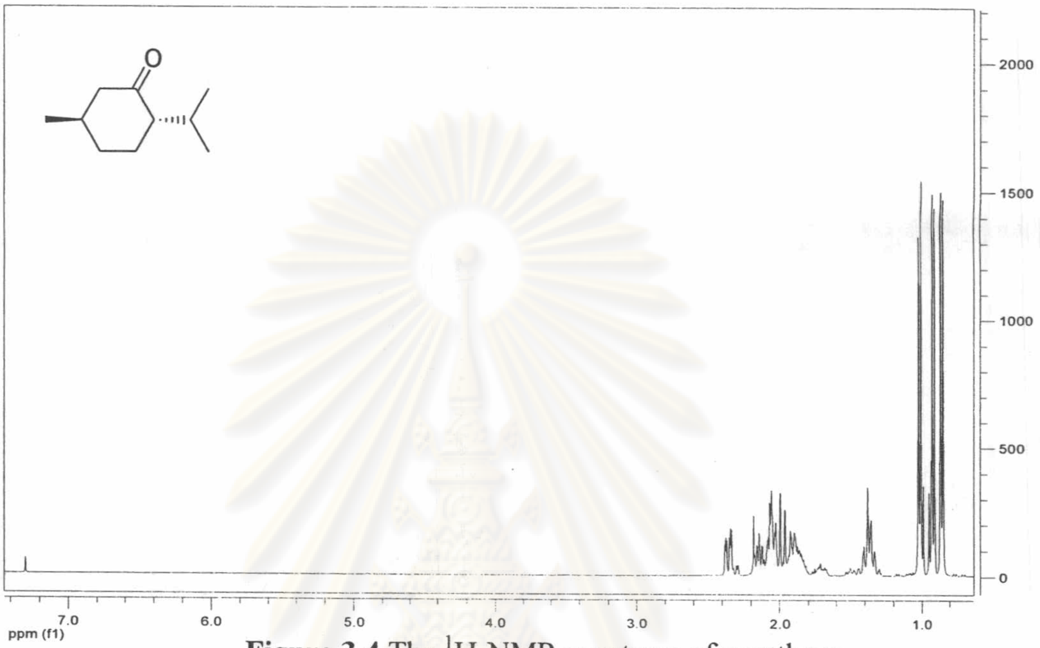


Figure 3.4 The ^{1}H-NMR spectrum of menthone

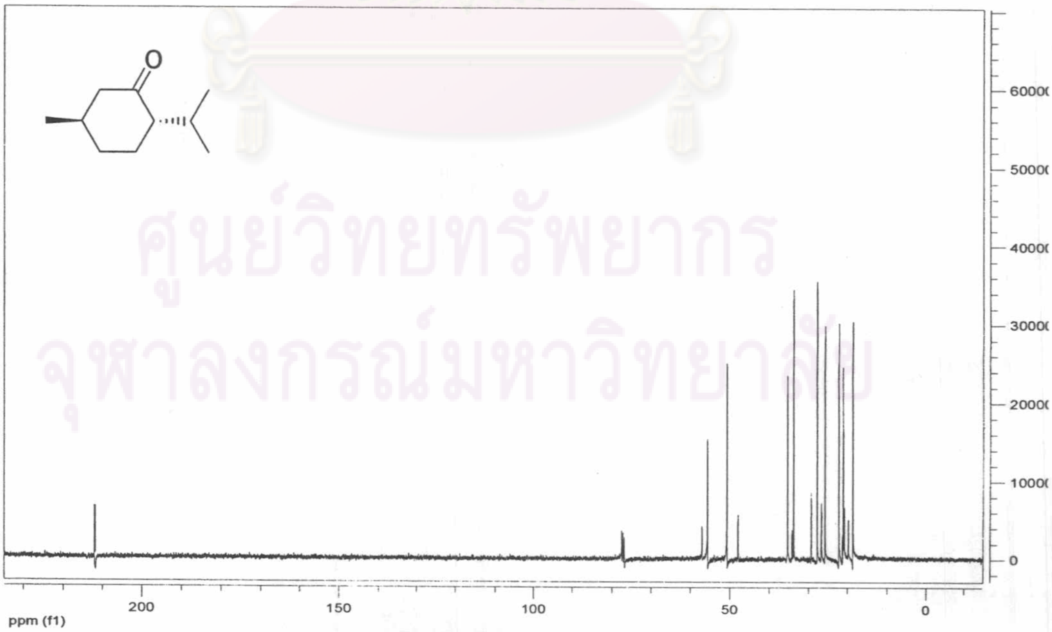


Figure 3.5 The ^{13}C-NMR spectrum of menthone

From the previous report, Adam and his colleagues carried on the oxidation of menthol mediated by (salen)chromium complex using iodozobenzene as oxidant to furnish low conversion of menthone [**25**].

In the case of a steroidal compound, cholestanol could be transformed into cholestanone in moderate yield. The identity of cholestanone was confirmed by IR spectroscopic data (Figure 3.6). From IR spectrum, the presence of the signal belonging to C=O stretching around 1700 cm^{-1} was visualized while O-H stretching of alcohol could not be observed.

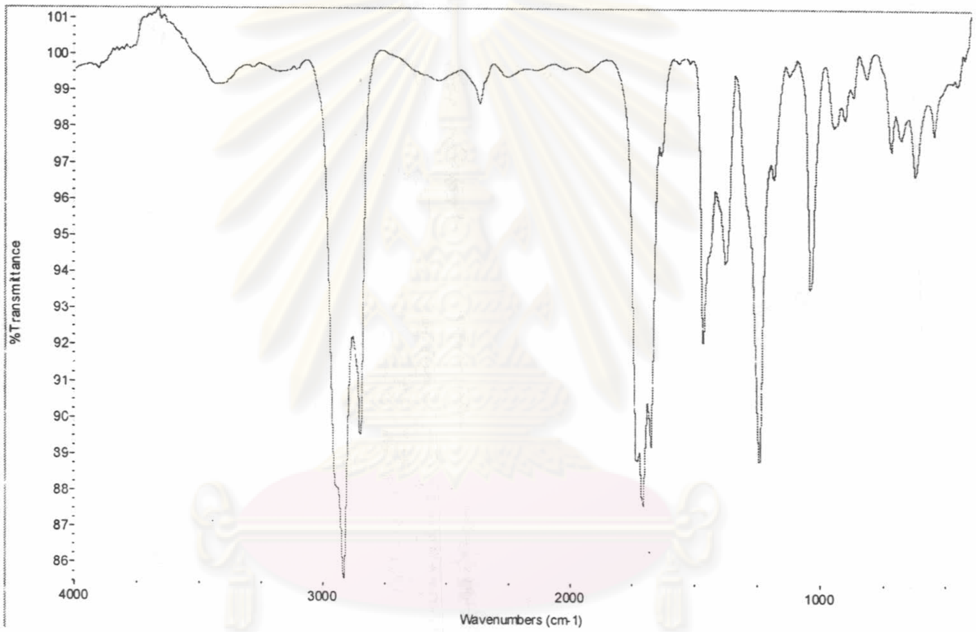


Figure 3.6 The IR spectrum of cholestanone

In addition, 1-phenylethanol was easily oxidized to acetophenone in excellent yield (entries 6 and 7). The isolated acetophenone from the reaction was further purified and analyzed by ^{1}H- and ^{13}C-NMR spectroscopy. The ^{1}H-NMR spectrum of acetophenone (Figure 3.7) shows a characteristic singlet peak with integrations of 3H due to the methyl group, at δ 2.62 and the aromatic proton signals around δ 7.40-8.00 The ^{13}C-NMR spectrum displays a singlet peak of new C=O at δ 198.2 as shown in Figure 3.8.

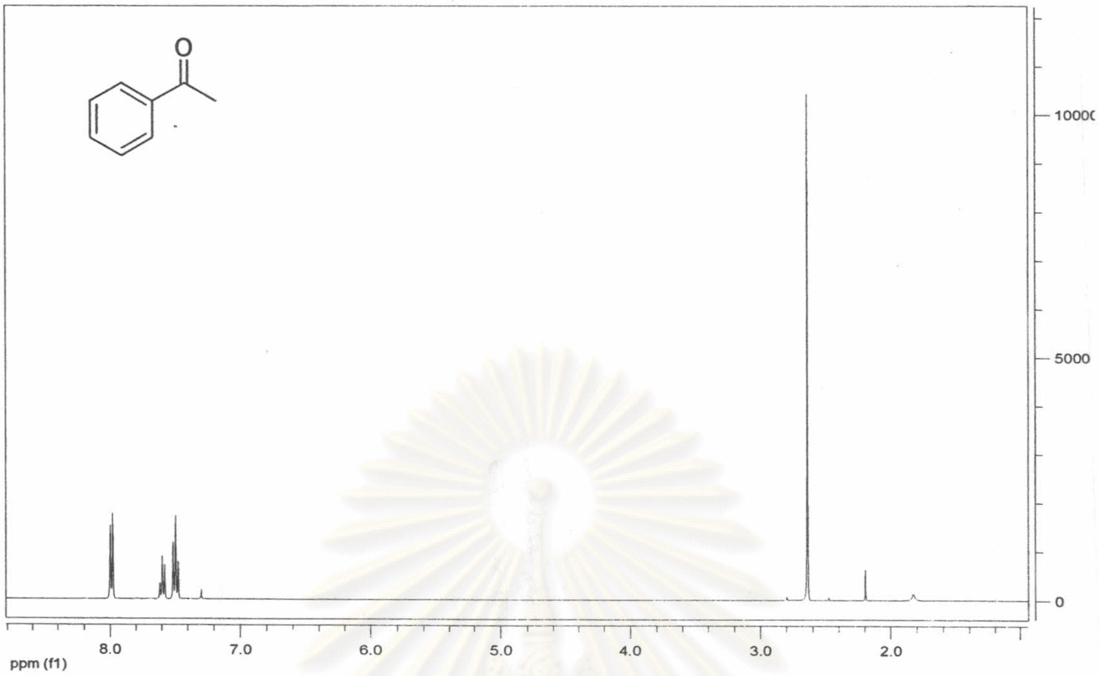


Figure 3.7 The ^{1}H-NMR spectrum of acetophenone

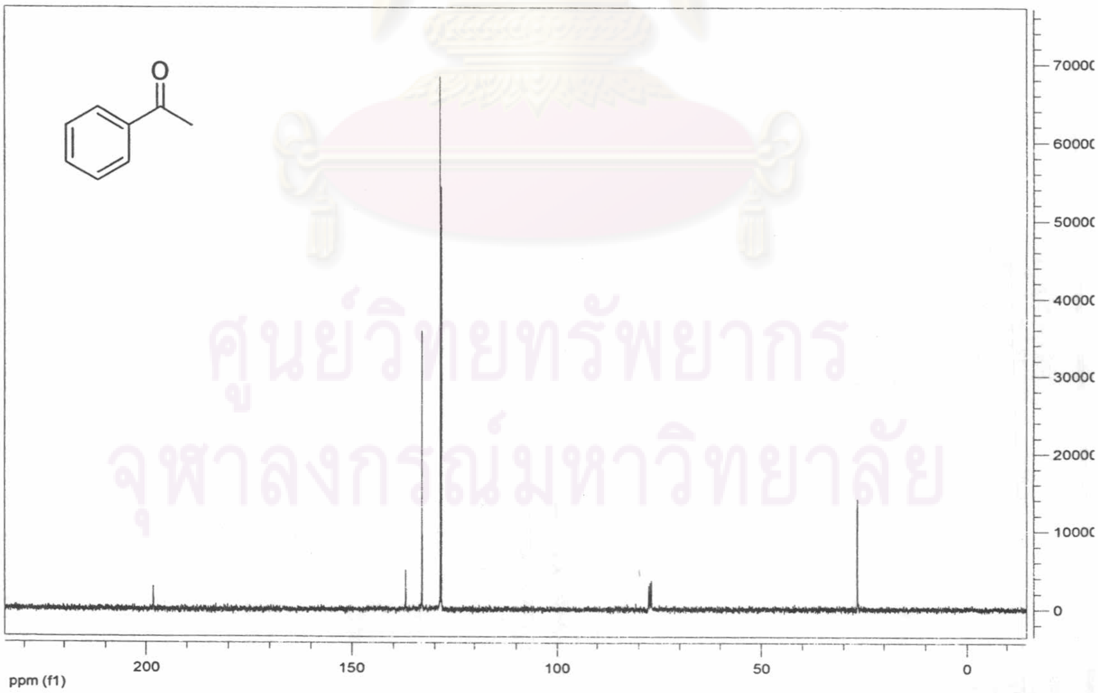


Figure 3.8 The ^{13}C-NMR spectrum of acetophenone

3.6 The kinetic study on the oxidation of cinnamyl alcohol catalyzed by chromium (III) stearate

This study examined the appropriate time for the oxidation of cinnamyl alcohol (allylic primary alcohol). The results are presented in Table 3.9 and Figure 3.4.

Table 3.9 The kinetic study on the oxidation of cinnamyl alcohol catalyzed by chromium (III)stearate

Time (h)	**% yield**			**MB**
	cinnamyl alcohol (recovery)	**cinnamaldehyde**	**cinnamic acid**	
0	100	0	0	100
2	56	30	0	86
3	55	50	0	105
4	39	60	0	99
5	33	63	tr	>96
6	23	62	tr	>85
7	18	59	tr	>77
8	14	59	tr	>69
9	9	53	tr	>59

reaction condition: 5 mmol cinnamyl alcohol, 0.20 mmol chromium (III) stearate, 5 mL of CH_3CN, 70°C

From the results depicted in Table 3.9, after 2 hours, cinnamyl alcohol was decreased dramatically while cinnamaldehyde was gradually occurred. The highest yield of cinnamaldehyde was attained after 5 hours (63%). During the first 4 hours, the formation of cinnamic acid was not detected hence imply that the further oxidation of cinnamaldehyde had not been initiated. After 5 hours, cinnamic acid was slightly produced. According to the sixth to the ninth hour of reaction time, mass balances were not good. This might be explained that the missing cinnamic acid was adsorbed by celite during filtration. The evolution of reaction could be depicted in Figure 3.9.

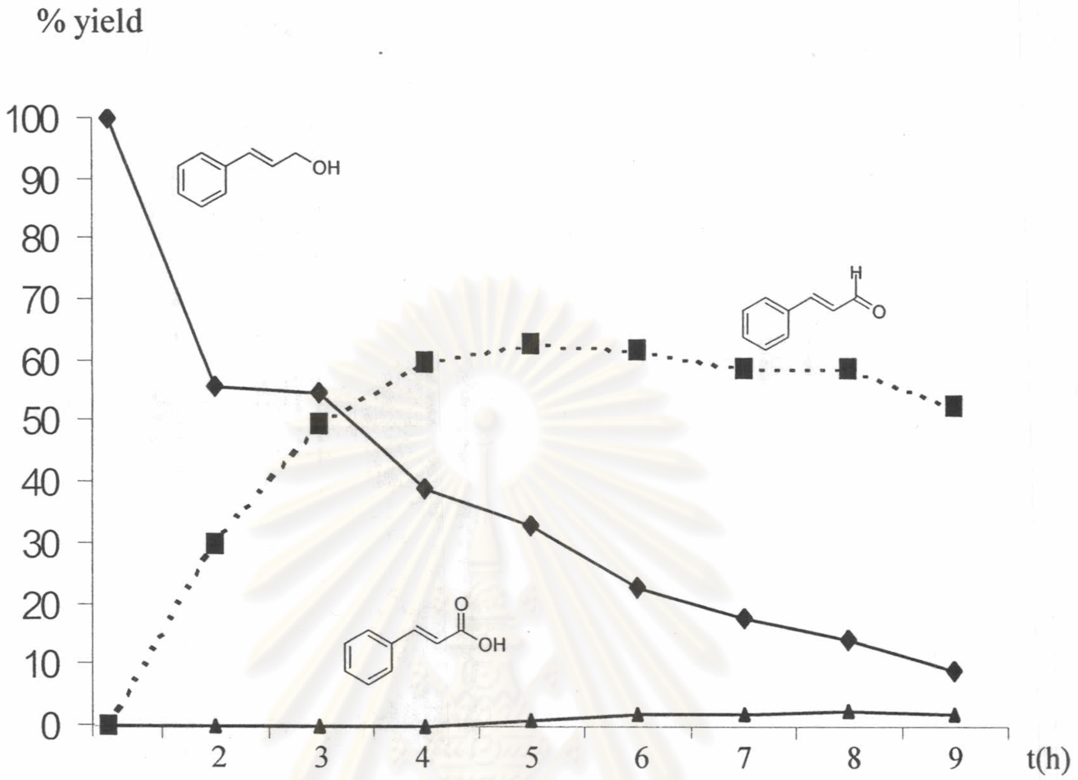
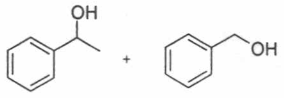
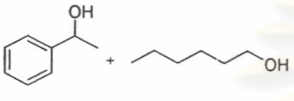
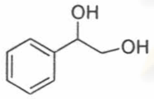


Figure 3.9 The kinetic study on the oxidation of cinnamyl alcohol

3.7 Comparative study on the selective oxidation of primary alcohols in the presence of secondary ones

The selectivity study would provide the significant characteristics of the reaction. For further study on the chemo- and regioselectivity, the reaction of a 1:1 mixture of primary and secondary alcohols was carried out under this developed condition. The results are shown in Table 3.10.

Table 3.10 The competitive study on the oxidation of primary and secondary alcohols

Entry	alcohols	TBHP (mmol)	time (h)	% products		
				ketone	aldehyde	acid
1		3	2	21	20	0
2		3	24	35	23	9
3		18	24	87	0	84
4		3	24	72	0	8
5		3	24	27	0	0
6[a]		3	24	23	0	0
7		9	24	52	0	0

reaction conditions: 5 mmol of each alcohol, 0.20 mmol Cr(III)stearate, isooctane 5 mL

[a] CH_3CN was used as solvent

This observation convinced a plausible use of these conditions as a chemo- and regioselective protocol for oxidizing secondary alcohols in the presence of primary ones. The reaction of a 1:1 mixture of alcohol substrates was carried out under this developed conditions. The mixture of benzyl alcohol with 1-phenylethanol after 2 hours preceeded a smooth conversion of benzyl alcohol into benzaldehyde and 1-phenylethanol into acetophenone (entry 1). When prolong the reaction time to 24 hours, small amounts of acetophenone and benzaldehyde were slightly enhanced; moreover, benzoic acid was produced in low yield (entry 2). When 18 mmol of TBHP was used, the reaction furnished only acetophenone and benzoic acid in which should stem from further oxidation of benzaldehyde in excellent yields (entry 3). The competitive oxidation of 1-phenylethanol *versus* 1-hexanol (entry 4) displayed that the oxidation of saturated primary alcohol to the corresponding carbonyl compound could not achieve whereas 1-phenylethanol could be converted to acetophenone in high yield. Even better results were obtained when primary and secondary alcohols were in competition on the same skeleton.

The model compound used for this regard was 1-phenylethane-1,2-diol which could accomplishly prepare from the hydrolysis of styrene oxide [**34**]. The structure of obtained 1-phenylehtane-1,2-diol was elucidated by ^{1}H-NMR (Figure 3.10) which exhibited a characteristic doublet peak with integration of 1H due to a benzylic hydrogen at δ 4.81 and doublet of doublet signals around δ 3.63 and 3.73 (1H each). Moreover, the hydroxyl protons were visualized at δ 3.28. While the aromatic proton signals were detected around δ 7.35.

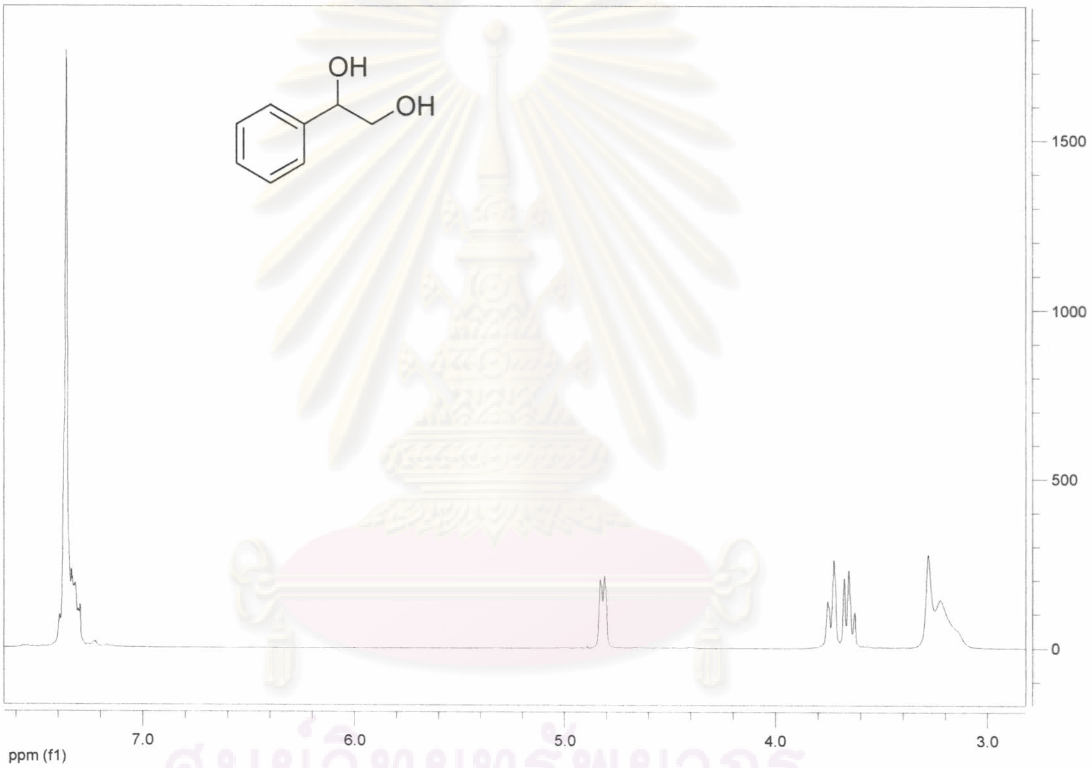


Figure 3.10 The ^{1}H-NMR spectrum of 1-phenylethane-1,2-diol

In the reaction carried out with 1-phenylethane-1,2-diol (entries 5 - 7), the major product observed from this reaction was a hydroxy ketone, (2-hydroxy-1-phenylethanone) without any contamination of either a dicarbonyl compound or ketone acid. The α-hydroxy ketone product was isolated by column chromatrograph and its structure was ascertained by ^{1}H- and ^{13}C-NMR spectroscopy as presented in Figures 3.11 and 3.12.

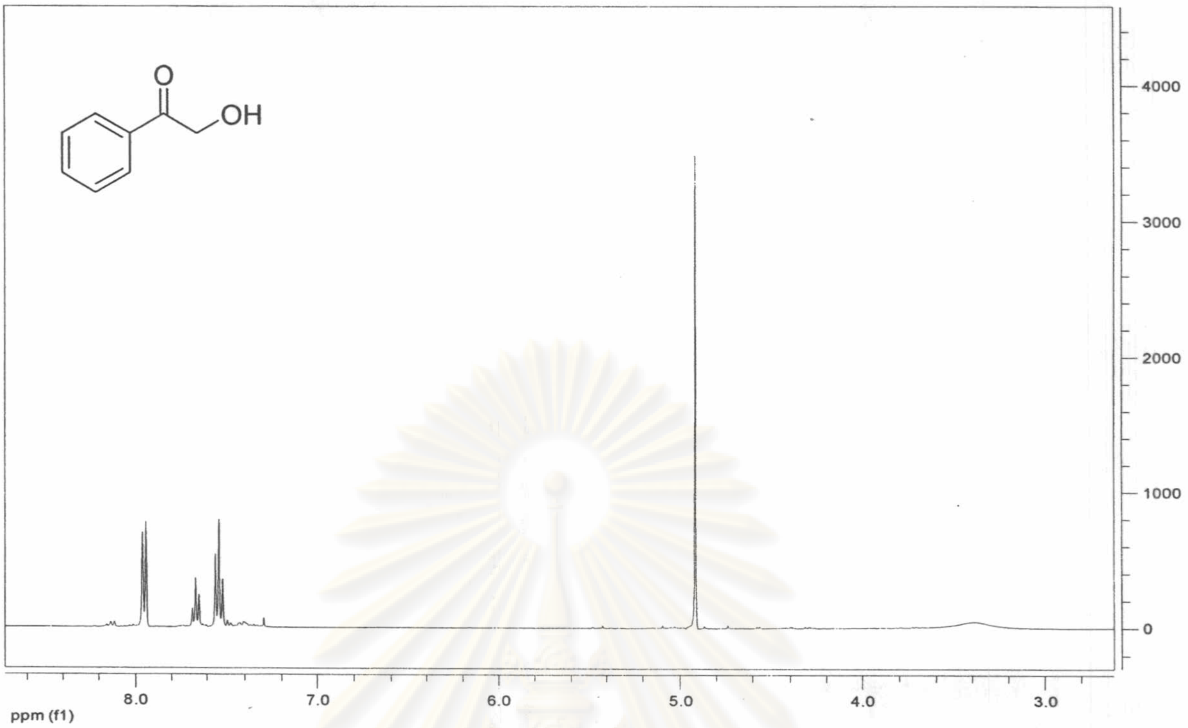


Figure 3.11 The ^{1}H-NMR spectrum of 2-hydroxy-1-phenylethanone

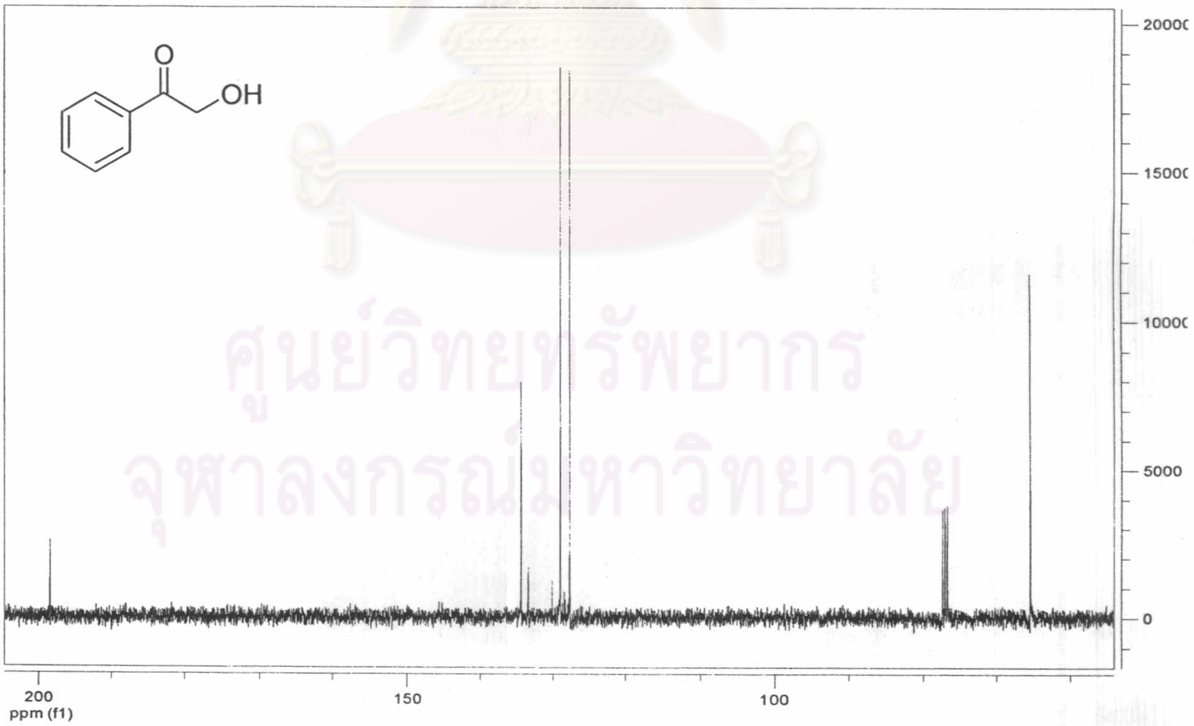


Figure 3.12 The ^{13}C-NMR spectrum of 2-hydroxy-1-phenylethanone

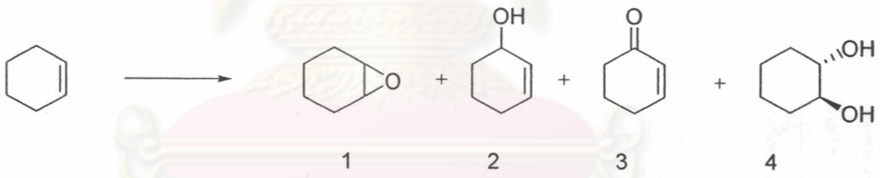
The depicted ^{1}H-NMR spectrum (Figure 3.11) of 2-hydroxy-1-phenylethanone revealed a characteristic singlet peak with integrations of 2H due to the $-CH_2$ at δ 4.95 and presented the important aromatic protons around δ 7.30 – 8.00. Moreover, the ^{13}C-NMR spectrum of 2-hydroxy-1-phenylethanone showed a singlet peak of new C=O at δ 198.4 along with δ 65.4 due to the carbon atom of $-CH_2-$ and the six signals belonging to aromatic carbons were detected around δ 130-140 as shown in Figure 3.12.

Part 2 Chromium-catalyzed oxidation of alkenes

3.8 Study on the optimum conditions for the oxidation of cyclohexene

Cyclohexene was chosen as a model substrate for studying the oxidation at allylic position. The results of cyclohexene oxidation catalyzed by various chromium complexes are presented in Table 3.11 and the selectivity of the reaction is depicted as shown in Figure 3.13.

Table 3.11 The oxidation of cyclohexene catalyzed by various chromium complexes



Entry	Catalysts	Products (mmol)				Total (mmol)
		1	2	3	4	
1	Cr(palmitate)$_3$	1.248	2.898	2.658	0.745	7.550
2	Cr(stearate)$_3$	0.380	2.003	5.053	2.670	10.107
3	Cr(behenate)$_3$	0.672	0.607	1.137	1.486	3.902
4	Cr(acac)$_3$	0.156	1.424	3.433	2.438	7.451
5	Cr(Salen)Cl	0	2.848	5.137	24.601	32.587

reaction conditions: 50 mmol cyclohexene, 0.20 mmol catalyst, 18 mmol TBHP, 70°C, 24 h

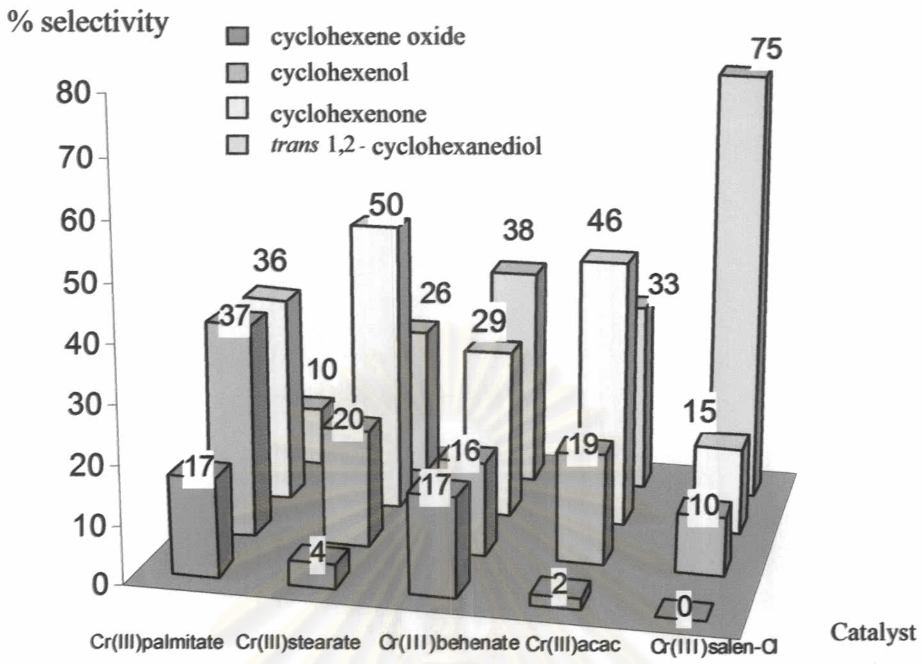
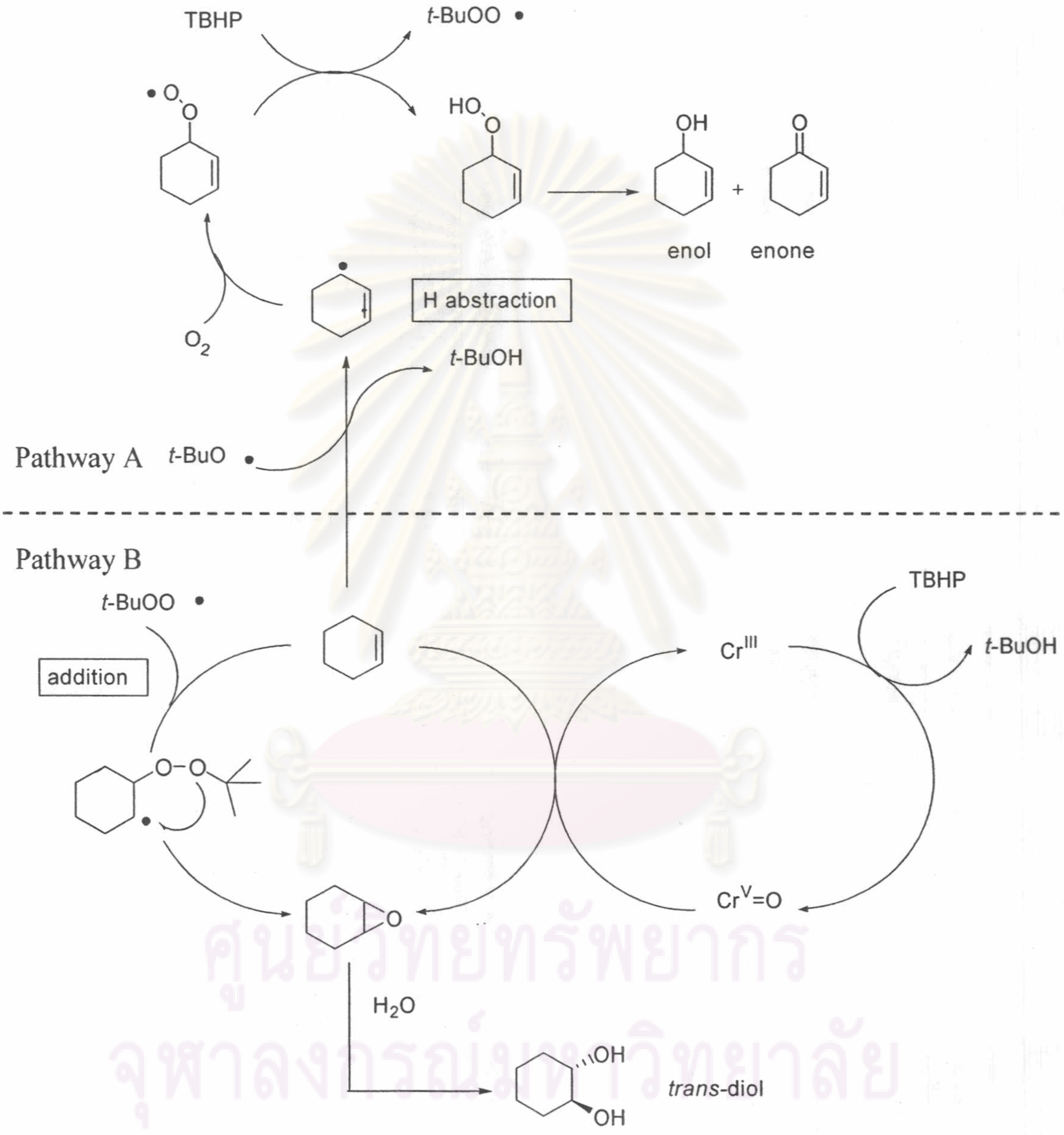


Figure 3.13 The selectivity of the oxidation of cyclohexene

From Table 3.11 and Figure 3.13, five chromium complexes were screened for potentially catalytic oxidation ability. It was observed that chromium (III) stearate and chromium (III) salen-Cl performed good reactivity as catalyst for oxidation at allylic position to the corresponding enone in moderate yield. It was noteworthy that chromium(III)stearate provided the highest yield of cyclohexenone and gave the best selectivity for the production of cyclohexenone over cyclohexenol (2.5:1) (entry 2) while others showed moderate catalytic activities and gave fair yield with poor selectivity. Among them, chromium(III) salen-Cl revealed excellent capability as a catalyst yielding *trans*-1,2-cyclohexane diol as an predominant product with low yield of allylic oxidation products (entry 5). *trans*-1,2-Cyclohexanediol was believed to form by ring opening of cyclohexene oxide with water containing in TBHP. Thus, in this work chromium (III) stearate would be employed as a catalyst for allylic oxidation of natural compounds.

Form the results mentioned above, it might be explained that there were two reactions were competitively taken place. The first route was allylic oxidation yielding enol and enone products (Scheme 3.1, pathway A) as well as the second reaction was epoxidation of alkene which eventually provided diol compound as prodominant product after ring opening of epoxide as presented in Scheme 3.1 (Pathway B).

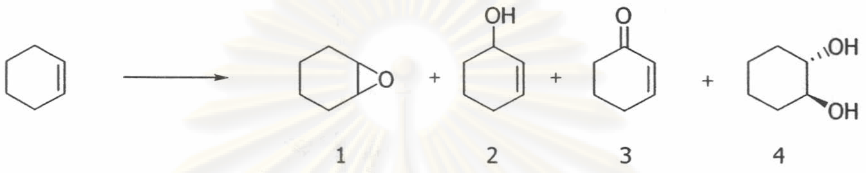


Scheme 3.1 Possible pathways of the oxidation of cyclohexane

3 .9 The study on the oxidation of cyclohexene catalyzed by Chromium (III) salen-Cl

In order to discover the appropriate efficient catalytic system towards the formation of diol, various reaction conditions are required to carefully evaluate the capability of Cr(III) salen-Cl catalyzed cyclohexene oxidation. The results are summarized in Table 3.12.

Table 3.12 The oxidation of cyclohexene catalyzed by Cr(III)salenCl under various conditions



Entry	Condition	Products (mmol)			
		1	2	3	4
1	50 mmol substrate,	0	2.848	5.137	24.601
2	10mmol substrate	0	Trace	2.022	5.365
3	50 mmol substrate, anhydrous TBHP	0.304	2.777	4.722	9.107
4	50 mmol substrate, N_2 atmosphere	0	2.062	2.566	15.600
5	50 mmol substrate, vacuum	0	1.841	2.800	17.228
6	50 mmol substrate, 12 h	0	1.411	1.757	14.820

reaction condition: 18 mmol TBHP, 0.2 mmol Cr(III)salen-Cl, 70°C, 24 h

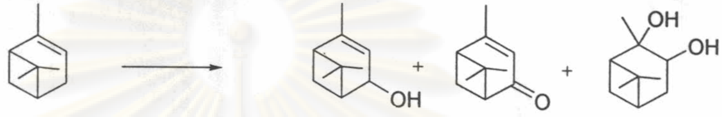
From Table 3.12, it was revealed that in the absence of air and under anhydrous TBHP (entries 3-6), as expected, the activity of transformation to cyclohexenol, cyclohexenone and *trans*–1,2–cyclohexanediol was decreased. This might be explained by the less formation of cyclohexenyl hydroperoxide, which gave enol and enone after decomposition was occurred. When the reaction was carried out under anhydrous condition, the small amount of cyclohexene oxide was also detected but the amount of *trans* - diol **(4)** was dramatically decreased whereas the amount of enol **(2)** and enone **(3)** remained constant (entry 3). This might be explained by the production of *trans*-1,2-cyclohexanediol *via* ring opening of cyclohexene oxide by water did not take place but the diol product was produced *via* ring opening of epoxide by radical species from exposed TBHP. Under nitrogen atmosphere and vacuum gave the nearly results (entries 4 and 5), which were inactive toward the formation of all products. At shorter reaction time (entry 6), low yields of enol **(2)** and enone **(3)** were occurred with a moderate amount of **(4)**. This could be explained that the formation of enol and enone products was slower than ring opening of epoxide. From the results mentioned above, the formation of enol and enone products of cyclohexene oxidation catalyzed by Cr(III)salen-Cl was believed to occur at an allylic position. Furthermore, the utilization of this catalyst provided the epoxide product. It was believed that the formation of epoxide was dealt with a high valent oxo-chromium which transferred oxygen atom into C=C giving the desired epoxide product. Moreover, it could form by ring closure of *tert*-butyl cyclohexyl peroxide. The production of *trans*-diol eventually took place by ring opening of epoxide [**35**].

3.10 Chromium (III) stearate–catalyzed oxidation of natural products containing C=C moiety

3.10.1 The oxidation of α–pinene catalyzed by various chromium complexes

An α–pinene, monoterpene containing allylic position, was used as a representative of a natural product substrate to observe the scope of this developed oxidation catalyzed by different chromium complexes. The results are presented in Table 3.13.

Table 3.13 The oxidation of α-pinene catalyzed by various chromium complexes



verbenol **1** verbenone **2** *trans* - diol **3**

Entry	Catalysts	% conversion	% yield 1	% yield 2	% yield 3	MB
1	Cr(III)palmitate	94	0	47	0	51
2	Cr(III) stearate	97	0	55	0	58
3[a]	Cr(III) stearate	91	0	64	19	92
4	Cr(III)behenate	97	0	34	0	37
5	Cr(III)acetylacetonate	98	0	46	0	48
6	Cr(Salen)-Cl	100	0	38	0	38

reaction condition: 5 mmol α - pinene, 18 mmol TBHP, 0.20 mmol Cr(III)stearate, isooctane 5 mL, 70°C, 24 h. [a]worked up by filtration through celite

From Table 3.13, it was displayed that all chromium complexes afforded moderate yield for transformation of α-pinene to verbenone **(2)**, whereas Cr(III)stearate provided the highest yield of the desired product (entry 2). The reaction which was generally worked up by acid extraction gave lower yield of all products and poor mass balance than that by filtration thought celite (entry 3); moreover, the low yield of diol **(3)** could be observed. This might be assumed that acidic work up was not suitable for products assessment. The formation of diol **(3)** was taken place *via* ring opening of α-pinene oxide. This was confirmed by the result of cylohexene oxidation. The role of Cr(III) complex was perhaps to accomplish the rapid decomposition of verbenyl hydroperoxide intermediate [**36**]. From the report suggested by Allal and his co-workers, the use of $CuCl_2$ catalyzed oxidation of α-pinene using TBHP afforded 71% yield of verbenone with high selectivity (78%) [**36**]. That system could provide similar yield of verbenone to this work.

3.10.1.1 The effects of the amount of oxidant

Based on preliminary studies, Cr(III)stearate appears to be the catalyst of choice for this catalytic process. Other chromium complexes were inferior as catalyst at the same loading amount. The amount of oxidant in the reaction was varied from 9-36 mmol to optimize the reaction conditions. The results are summarized in Table 3.14.

Table 3.14 The effect of the amount of TBHP on the oxidation of α-pinene catalyzed by Cr(III)stearate

Entry	oxidant (mmol)	time (h)	% conversion	% α-pinene (recovery)	% yield			MB
					1	2	3	
1[a]	9	12	<2	98	0	trace	0	>98
2	9	24	61	39	0	46	20	105
3	18	12	94	14	0	59	18	91
4	18	24	91	9	0	64	19	92
5	18	48	93	7	0	64	20	91
6	27	24	100	0	0	49	23	72
7	27	48	100	0	0	48	23	71
8	36	24	100	0	0	46	23	69
9	36	48	100	0	0	43	24	67

reaction conditions: 5 mmol α - pinene, 0.20 mmol Cr(III)stearate, 70°C, isooctane 5mL

[a] 50 mmol substrate was used

The results in Table 3.14 demonstrated that when 18 mmol of TBHP was employed together with 5 mmol of substrate for 24 h, the reaction afforded the highest yield of verbenone with good selectivity (entry 4). When the amount of TBHP was increased or decreased from 18 mmol, the yield and the selectivity of verbenone were declined. Using of 27 and 36 mmol of TBHP (entries 6-9), the significantly lower yield of product compared to the use of 18 mmol of TBHP was obtained, implied that the substrate and products could be further oxidized to undesired compounds. The suitable reaction time was 24 hours. The prolonged reaction time did not have any effect to increase the yield (entry 5). The mass balances were not summed as 100% because the unidentified and undesired products were produced.

3.10.1.2 Effects of the amount of catalyst

Variable amounts of chromium catalyst 0.10 (2% mol), 0.20 (4%mol) 0.25 (5%mol) and 0.50 mmol (10%mol) were used to search for the appropriate amount of catalyst in α-pinene oxidation. The results are presented in Table 3.15.

Table 3.15 The effect of the amount of catalyst on the oxidation of α-pinene

Entry	catalyst (mmol)	%α-pinene (recovery)	% yield		T.O.N.[a]	MB
			verbenone(2)	diol (3)		
1	0.10	12	63	12	31	87
2	0.20	9	64	19	15	92
3	0.25	8	64	28	13	100
4	0.50	8	61	37	6	106

reaction conditions: 5 mmol α-pinene, isooctane 5 mL, 70°C, 24 h. [a] based on verbenone

Table 3.15 shows the effect of varying the catalyst amount. It was found that 0.20 mmol of Cr(III)stearate was the optimum catalyst amount (entry 2). In addition, when the amount of catalyst was increased or decreased from 0.20 mmol, the yield of verbenone was decreased. On the other hand, the formation of diol **(3)** was slightly increased when the amount of catalyst was increased. It might be explained that the formation of epoxide and the rate of further ring open of epoxide were increased.

3.10.1.3 Effects of solvent

This study was to search for appropriate solvent that could mediate the formation of product in high yield with good selectivity. The results are summarized in Table 3.16.

Table 3.16 The effect of solvent on the oxidation of α-pinene

Entry	solvent	%α-pinene (recovery)	% yield		MB
			verbenone (2)	diol (3)	
1	isooctane	9	64	19	92
2	CH_3CN	14	58	9	81
3	CH_2Cl_2	13	57	7	77

reaction conditions: 5 mmol α-pinene, 0.20 mmol Cr(III)stearate, 5 mL solvent, 70°C, 24 h

Among the three solvents used as presented in Table 3.16, isooctane was the most suitable solvent for this reaction whereas; acetonitrile and dichloromethane were not appropriate solvent because a catalyst was insoluble in acetonitrile. This could affect to the selectivity of verbenone.

3.10.2 The kinetic study on the oxidation of α - pinene catalyzed by Cr(III)stearate

It is widely well-known that there are two possible mechanisms proposed for oxidation catalyzed by transition metal complexes. To begin with, the reaction involved a free radical pathway. The other was believed that not to take place *via* the radical partway. In order to gain a better insight on the oxidation of α–pinene, a kinetic study was considered. The results are shown in Figure 3.14.

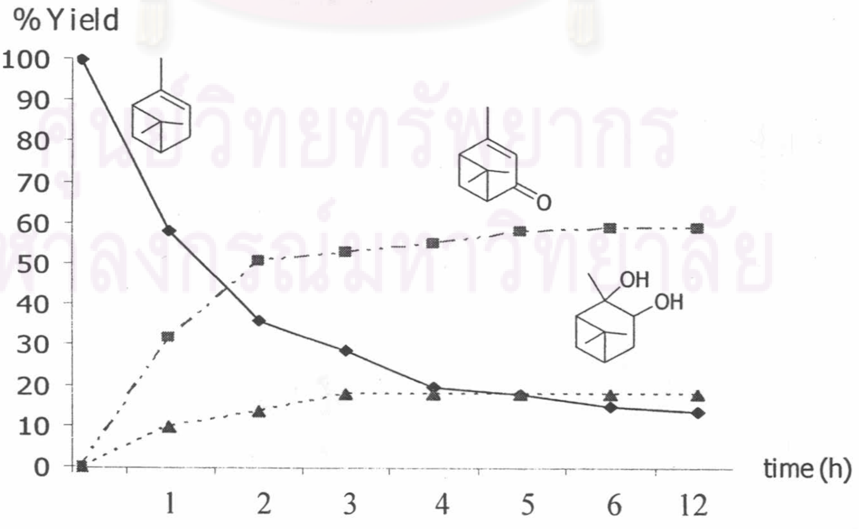


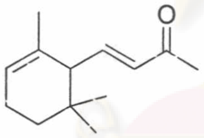
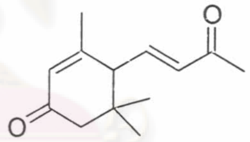
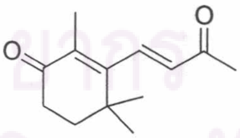
Figure 3.14 The kinetic study on the oxidation of α - pinene catalyzed by Cr(III)stearate

Figure 3.14, which clearly depicts the evolution of α - pinene, verbenone **(3)** and diol product **(4)** *versus* time, shows that α-pinene was slightly transformed to the desired allylic oxidation product **(3)** and the ring opening product **(4)**. When the time was prolonged, the yield of verbenone was increased together with a decrease of α-pinene while diol **(4)** remained constant. Moreover, α-pinene oxide **(1)** and verbenol **(2)** were not detected.

3.10.3 Chromium (III) stearate–catalyzed oxidation of α– and β–ionones

α–Ionone (α-jonone) and β–ionone (β–jonone), two naturally occurring monoterpenes widely distributed in nature, generally used in perfumery, flavoring, and vitamin A (retinol) production for cosmetics and toiletries were selected for evaluating the capability of this catalytic system. The results are presented in Table 3.17.

Table 3.17 Chromium(III)stearate catalyzed oxidation of α– and β–ionones

Entry	**substrate**	**TBHP (mmol)**	**Products**	**% yield** [a]
1		18		38
2^b		18		27
3	α-ionone	27	3-oxo-α-ionone	34
4		18		41
5^b		18		38
6	β-ionone	27	4-oxo-β-ionone	37

reaction condition: 5 mmol substrate, 0.2 mmol chromium(III) stearate,18 mmol TBHP, isooctane 5 mL, 70°C, 24 h. [a] isolated yield. [b] 2.5 mmol substrate was used

From Table 3.17, it was observed that α– and β–ionones (entries 1 and 4) were oxidized smoothly to the corresponding enone, (3-oxo-α-ionone) and (4-oxo-β-ionone) respectively in fair isolated yields. When the amount of TBHP was increased, the desired allylic oxidation product was slightly decreased. The identities of these products were ascertained by ^{1}H- and ^{13}C-NMR. The ^{1}H-NMR spectrum (Figure 3.4) of 3-oxo-α-ionone showed a characteristic of four singlet peaks with integrations of 3H due to the methyl protons and the important singlet of $O{=}C{-}HC{=}CCH_3$ at δ 6.00 along with alkenic protons around δ 6.15 to 6.70, $-CH_2-$ proton signal around δ 2 and one tertiary protons at δ 2.7. Moreover, the ^{13}C-NMR spectrum (Figure 3.16) revealed a singlet peak of a new carbonyl carbon at δ 198.3 and four signals of alkenic carbons around δ 120-160. Likewise the ^{13}C-NMR of 4-oxo-β-ionone (Figure 3.17) showed the peak of the carbonyl carbon at δ 198.7 and alkeneic carbons around δ 130-160 while the ^{1}H-NMR spectrum (Figure 3.18) depicted the important triplet signal at δ 2.54 with integration of 2H due to $CO{-}CH_2$. In addition, two alkenic protons presented the doublet of doublet signals at δ 7.2 and 6.1. The two triplet signals of $-CH_2-$ protons were detected around δ 2.5 and 1.9.

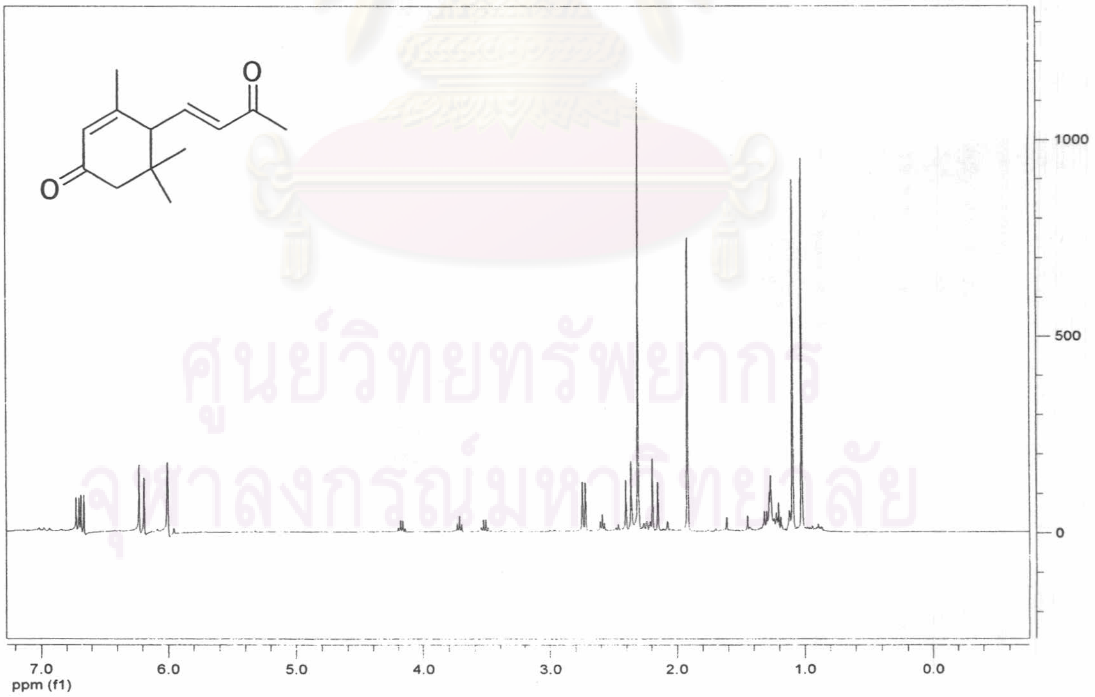


Figure 3.15 The ^{1}H-NMR spectrum of 3-oxo-α-ionone

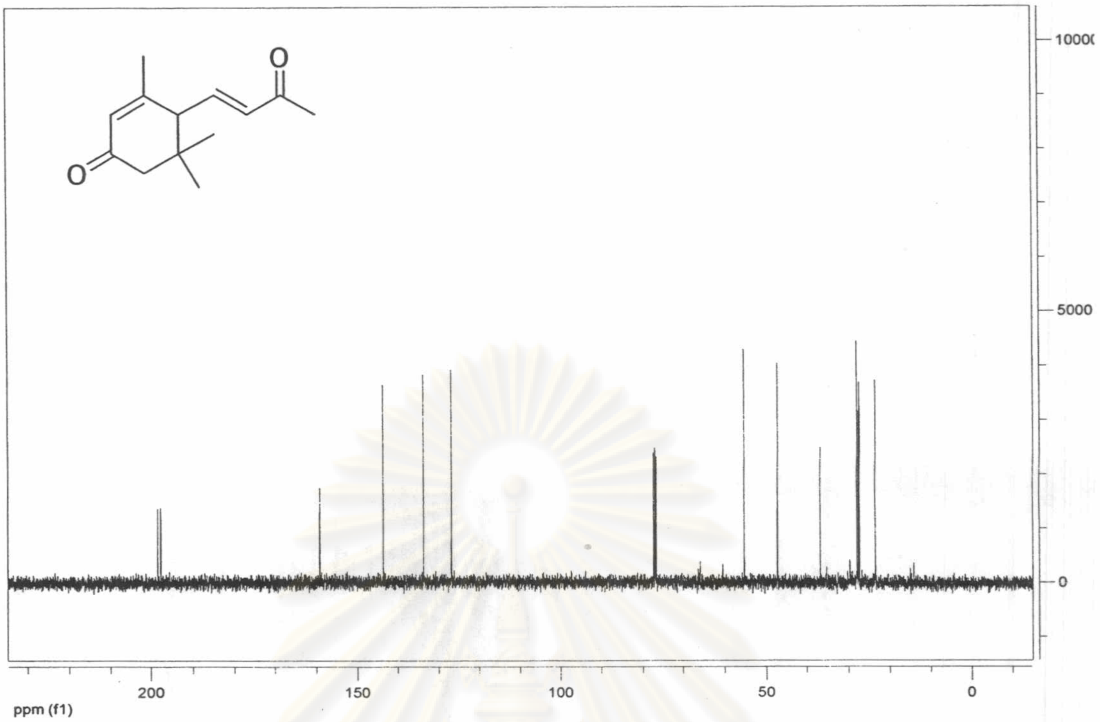


Figure 3.16 The ^{13}C-NMR spectrum of 3-oxo-α-ionone

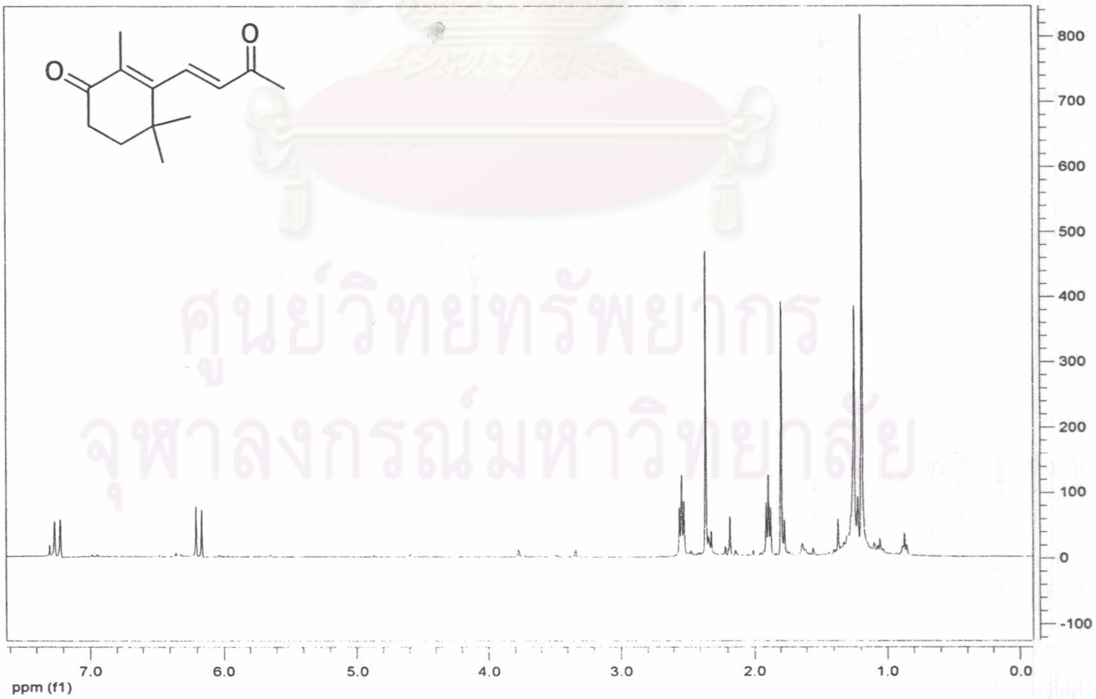


Figure 3.17 The ^{1}H-NMR spectrum of 4-oxo-β-ionone

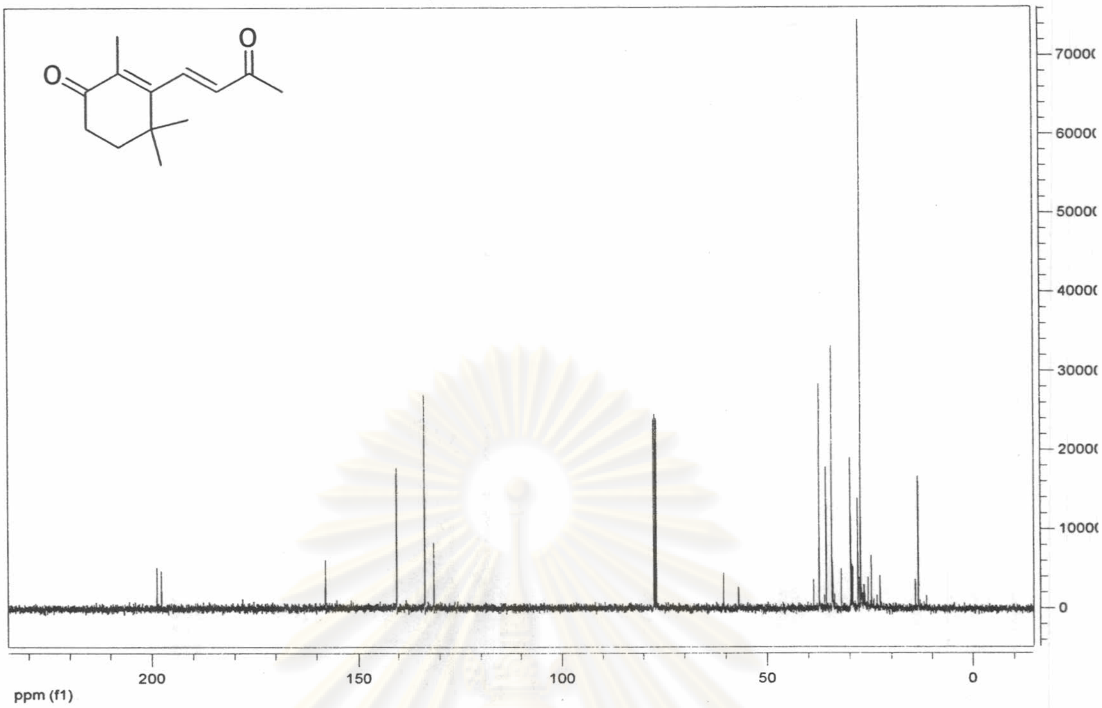
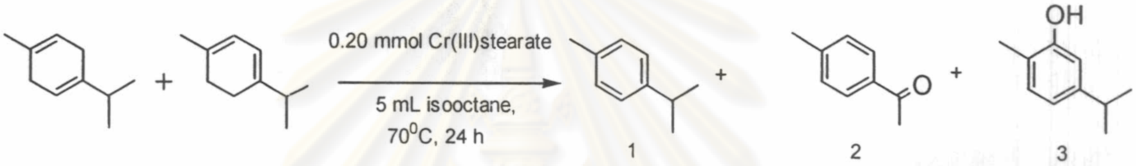


Figure 3.18 The ^{13}C-NMR spectrum of 4-oxo-β-ionone

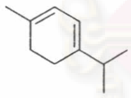
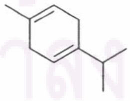
3.10.4 Oxidation of α- and γ-terpinenes catalyzed by chromium (III) stearate

Although the experiments mentioned above indicated some potential for the selective conversion of alkenes into enones, this oxidation system nonetheless does transform cyclic diene to aromatic compounds efficiently instead of formation of enones. To extend the scope of this oxidation system, α- and γ-terpinenes, two monoterpenes, were thus selected to examine. The obtained results are summarized and presented in Table 3.18 and the selectivity of the reaction is depicted in Figure 3.19.

Table 3.18 Chromium (III) stearate–catalyzed oxidation of α- and γ - terpinenes



1 *p*-cymene **2** 4-methylacetophenone **3** cavacrol

Entry	substrates	TBHP (mmol)	% yield 1	% yield 2	% yield 3	MB	% efficiency of TBHP
1		18	33	22	15	70	19
2		9	56	15	27	98	55
3	α-terpinene	3	77	0	14	103	153
4		18	52	48	7	107	30
5		9	67	32	0	99	55
6	γ-terpinene	3	83	0	0	103	139

reaction condition: 5 mmol substrate, 0.20 mmol chromium(III)stearate, isooctane 5 mL, 70°C, 24 h

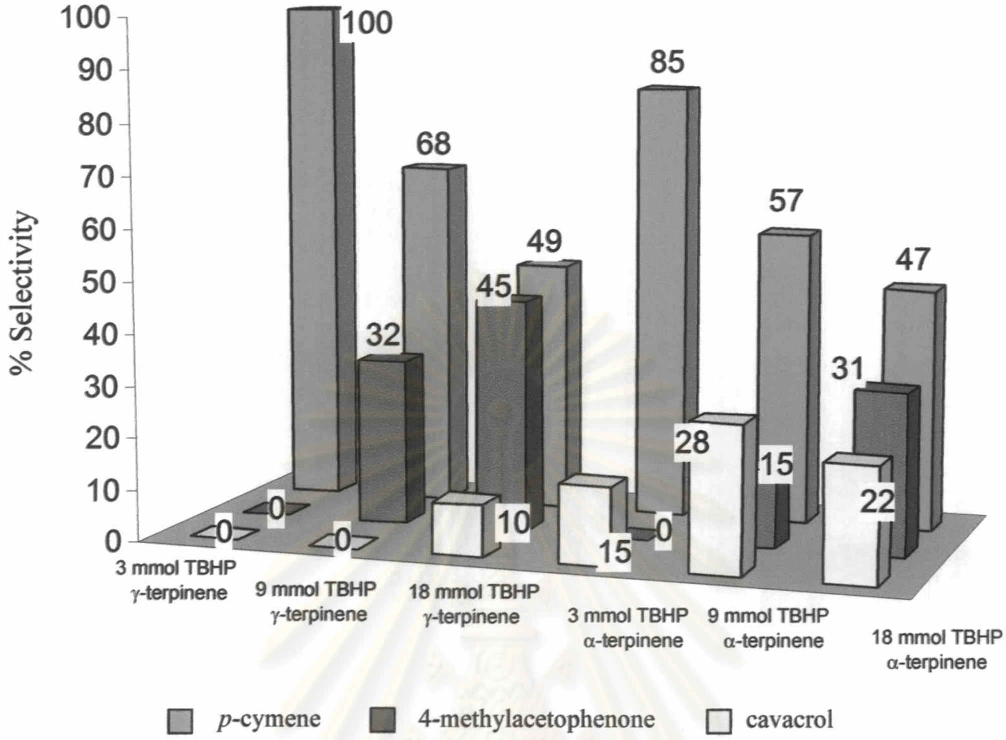
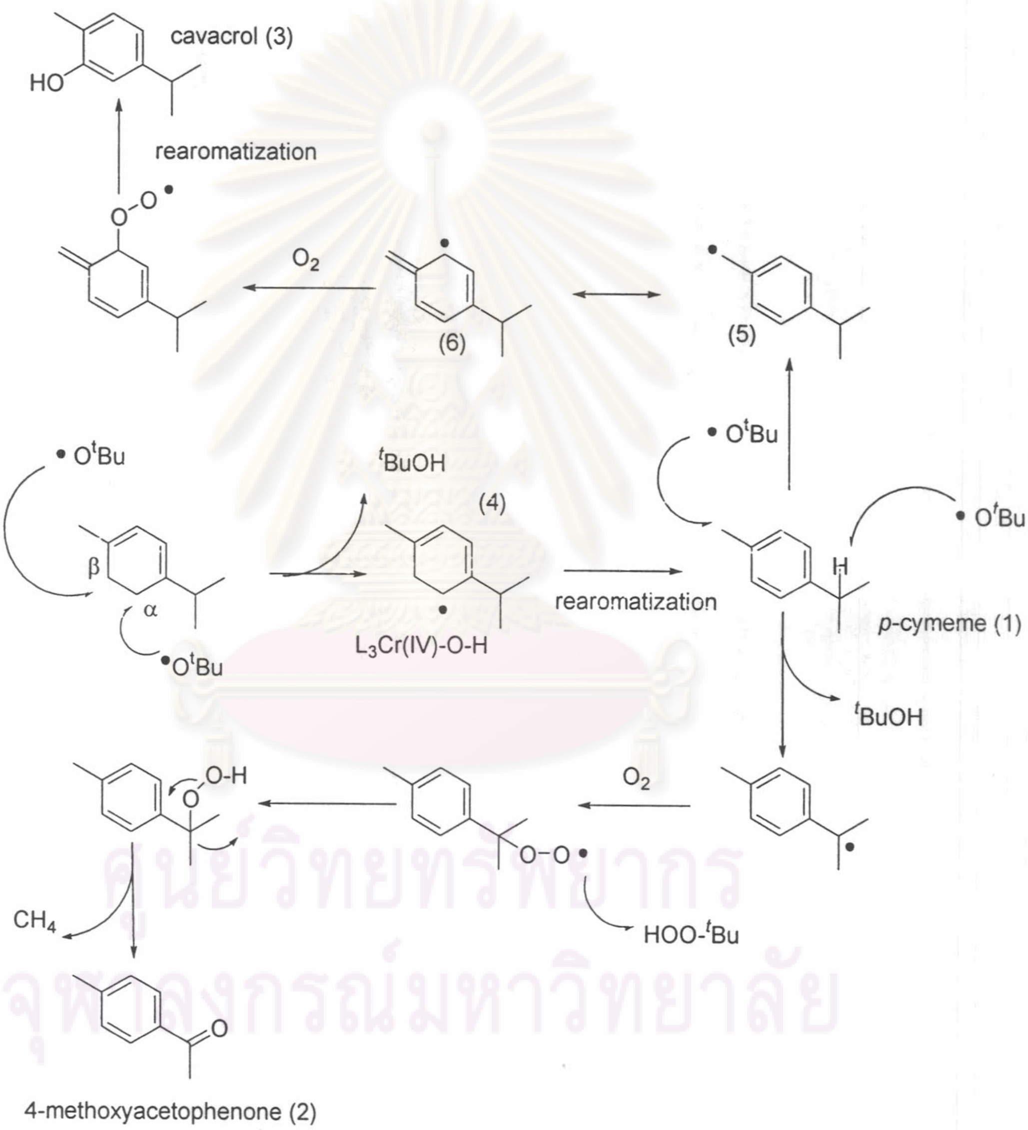


Figure 3.19 The selectivity of α- and γ-terpinene oxidation

According to Table.3.18 and Figure 3.19, the distribution of products and their selectivities were exhibited. A predominant product from the oxidation of α- and γ-terpinenes was *p*-cymene. Other two important detected products were 4-methylacetophenone and cavacrol. In addition, when the amount of oxidant was decreased, the production of the minor products was decreased as well while the yield of *p*-cymene was increased. The oxidation of α-terpinene catalyzed by chromium(III)stearate using 18 mmol of TBHP gave moderate yield of *p*-cymene **(1)**, 4-methylacetophenone **(2)** and carvacrol **(3)** in low yields (entry 1). Moreover, in the presence of 9 mmol of TBHP the higher yield of **(1)** was detected together with a decreased of compound **(2)** and with a slightly increased of **(3)** (entry 2). When the reaction was carried out with 3 mmol of TBHP, the predominant oxidized product was **(1)** in high yield with good selectivity while the small amount of **(2)** was obtained. In addition, the formation of **(3)** was not occurred (entry 3). The oxidation of γ-terpinene using 18 mmol of TBHP gave fair yields of **(1)** and **(2)** and low amount of **(3)** (entry 4).

In the presence of 9 mmol of TBHP, it was found that the yield of **(1)** was increased while **(2)** was decreased but **(3)** was not obtained (entry 5). The oxidation of γ-terpinene by using 3 mmol of TBHP gave only *p*-cymene in high yield with excellent selectivity (entry 6). The formation of *p*-cymene is believed to be formed by rearomatization of terpinyl radical and the production of other products were produced *via* further oxidation of *p*-cymene described by the possible mechanism in Scheme 3.2.



Scheme 3.2 Possible mechanism of oxidation of α- and γ-terpinenes

From Scheme 3.2, the initial abstraction of an H-atom on the ring by *tert* –butyl hydroperoxyl radical species led to the formation of an intermediate radical **(4)**, and then the rearomatization was taken place to provide *p*-cymene **(1)**. This compound was induced by the H-atom transfer from the Cr(IV)-OH species and generated the new C=C bond. Moreover, the Cr(V)=O species initiated the reaction, boosting the abstraction of a hydrogen atom from tertiary-H atom of *p*-cymene **(1)**. The alkyl radical could react with oxygen to give the corresponding alkylperoxyl radical generating the 4-methyl acetophenone **(2)** after fragmentation of methane. In addition, the formation of cavacrol **(3)** took place *via* H-abtraction at methyl group on *p*-cymene gave radical intermediates **(5)** and **(6)**. The alkyl radical **(6)** could react with oxygen to give the corresponding alkylperoxide, and generated the cavacrol **(3)** after the rearomatization of intermediate **(6)**. The abstraction of proton on methyl group was preferred to tertiary proton on isopropyl group because of the less steric hindrance. The major product, *p*-cymene was ascertained by ^{1}H- and ^{13}C-NMR as shown in Figures 3.20 and 3.21. The ^{1}H-NMR depicted the signals of aromatic protons around δ 7.23 and multiplet peaks of 1H at δ 3.07; moreover, ^{13}C-NMR presented six signals of alkenic carbon around δ 130-150.

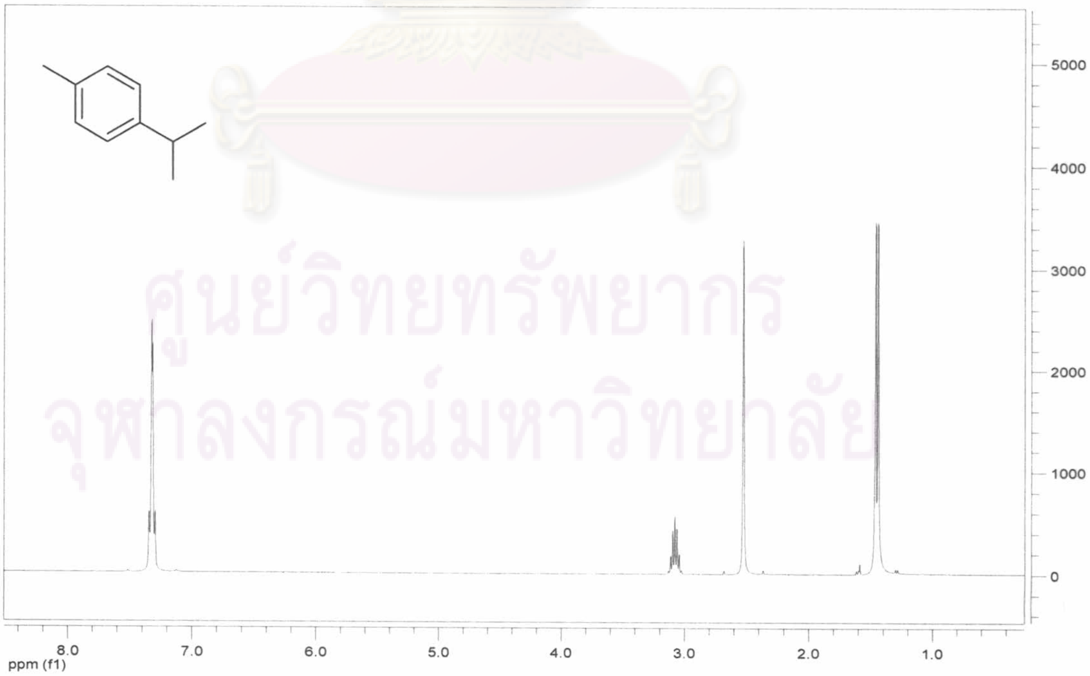


Figure 3.20 The ^{1}H-NMR spectrum of *p*-cymene

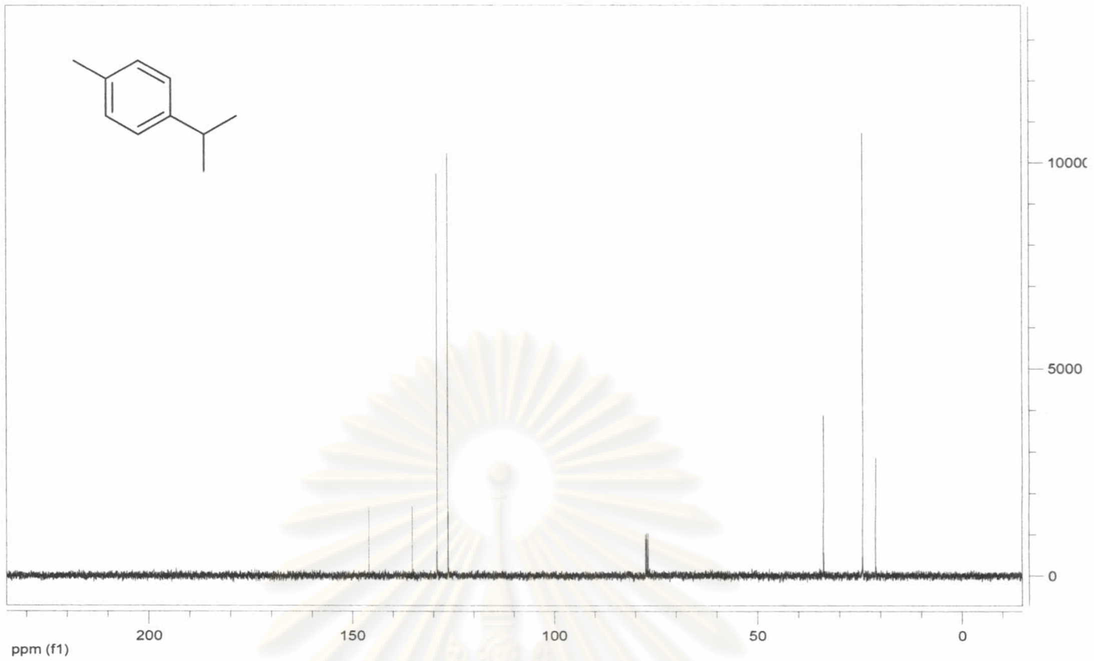


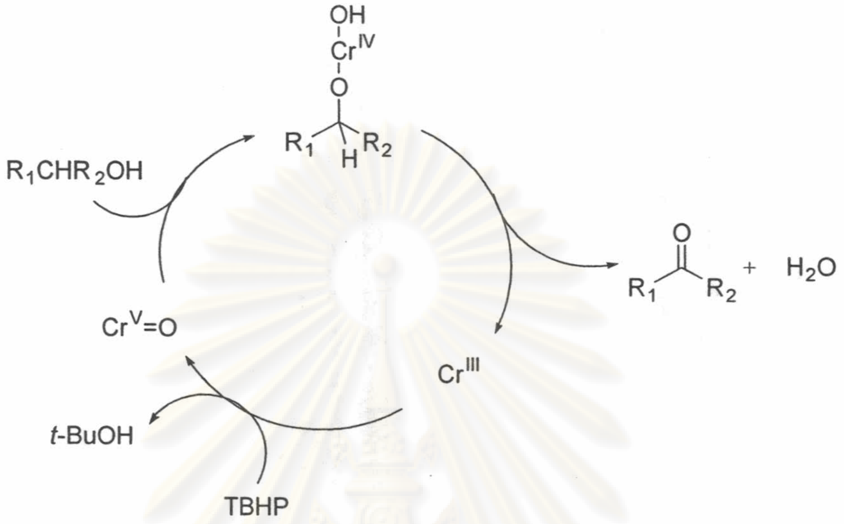
Figure 3.21 The ^{13}C-NMR spectrum of *p*-cymene

3.11 The proposed mechanistic pathway for chromium(III)stearate catalyzed oxidation by TBHP

Understanding the mode of the oxidation of alcohol catalyzed by chromium(III)complex using TBHP is important for predicting the formation of products. Besides the activity, the selectivity and the competitive study on the oxidation of various substrates mentioned above, the proposed mechanistic pathways were required. From the results also identified that the possible mechanism of oxidation of alcohols dealt with high valent oxo-metal species while the oxidation of alkene (allylic oxidation) was proceed *via* free radical pathway as depicted in Schemes 3.3 and 3.4.

3.11.1 The possible mechanistic pathway for the oxidation of alcohol catalyzed by chromium(III)stearate using TBHP

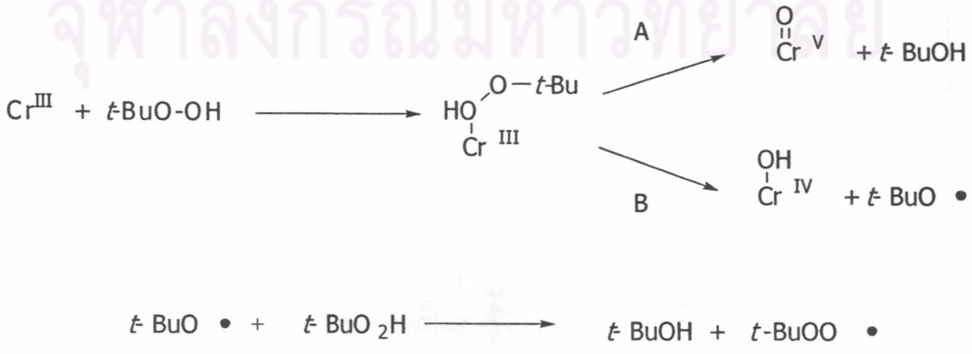
The oxidation of alcohols to the corresponding carbonyl compounds is well known to take place by high valent metal complexes [**37**]. The mechanistic pathway of the alcohol oxidation under Cr(III)/TBHP conditions was therefore conceived to take place *via* a high valent chromium species, (formally $^{V}Cr = O$) as shown in Scheme 3.3. This high-valent species subsequently reacted with the alcohol and then collapsed to the final carbonyl compounds with concurrent reduction of low valent chromium, generating Cr^{III}.

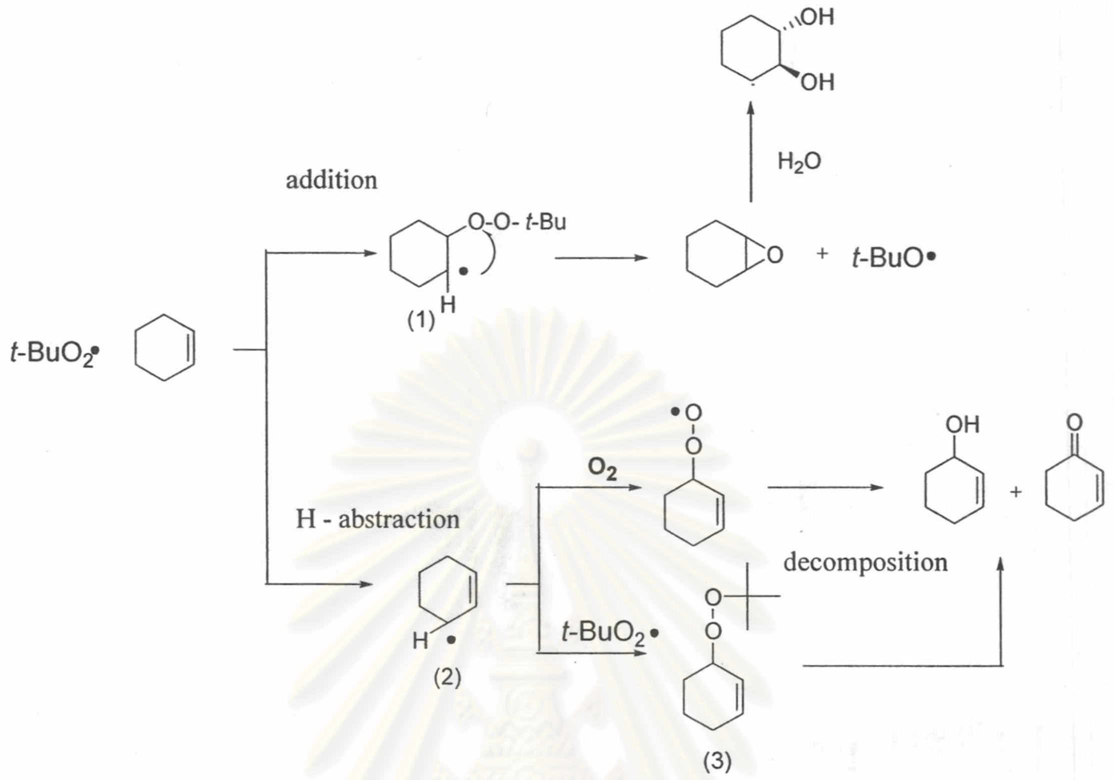


Scheme 3.3 The mechanism of oxidation of alcohol

3.11.2 The mechanistic pathway for the oxidation of alkene catalyzed by chromium(III)stearate using TBHP

The oxidation of alkene to the corresponding enol and enone compounds can take place *via* allylic proton abstraction by radical species generated from exposure of TBHP boosting by chromium(III). Moreover, the formation of diol can be observed. This product can react with water and/or other radicals. The mechanistic pathway for the oxidation of alkene is presented in Scheme 3.4.





Scheme 3.4 The proposed mechanism of allylic oxidation

Scheme 3.4, shows that cyclohexene was reacted *via* two pathways. The first route was carried out by addition of *tert*-butylhydroperoxyl radical provided intermediate **(1)**. Cyclohexene oxide was produced by ring closure and then this compound could be attacked by *tert*-buthyl hydroperoxyl radical, oxygen, water and so on to yield *trans*-diol. The other pathway dealt with allylic H-atom abstraction provided radical **(2)**. The alkyl radical **(2)** could react with oxygen to give the corresponding enol and enone, and/or *tert*-butyl hydroperoxyl radical to give peroxide **(3)** and generated enol and enone after the decomposition of intermediate **(3)**.