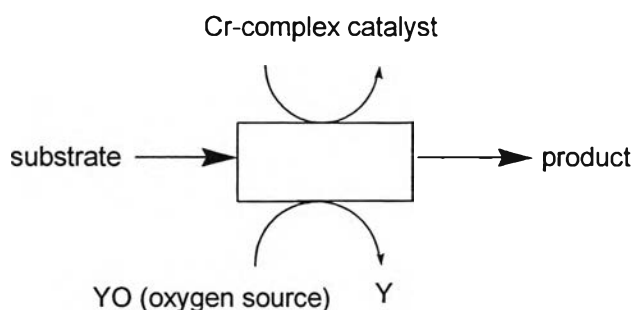


CHAPTER I

INTRODUCTION

Chromium-Catalyzed Oxidations in Organic Synthesis

Chromium oxidations have been widely explored since the very beginning of organic chemistry and the topic remains of current interest as exemplified by the extensive number of papers in which at least one step involves the use of an oxochromium(VI) reagent [1]. This is primarily due to the wide variety of oxidizable functions by the proper choice of reagent. A plethora of chromium reagents and procedures have been proposed in wide variety of reviews and books [2]. However, these methods imply either the use of stoichiometric quantities of poisonous chromium reagents or toxic metallic byproduct residues. Considering cost and environmental factors, it would be advantageous to use catalytic methods which is illustrated in Scheme 1.1 [3].

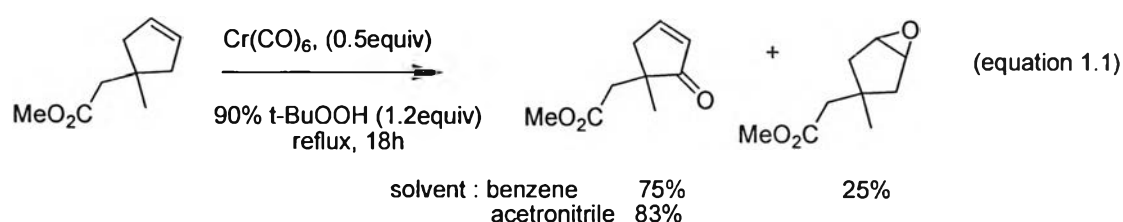


Scheme 1.1 model of catalytic reaction

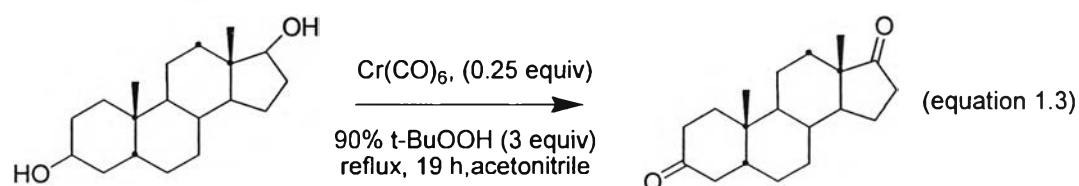
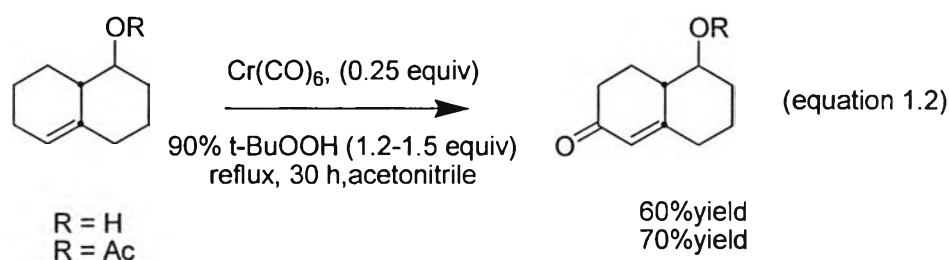
The chromium-catalyzed oxidations of organic compounds led to the formation of new C-O and C=O bond as products. These process has to employ an inexpensive YO as an oxygen source such as O₂, hydroperoxide while by product Y has to be easily disposable or recyclable.

1.1 Chromium(0) as catalyst

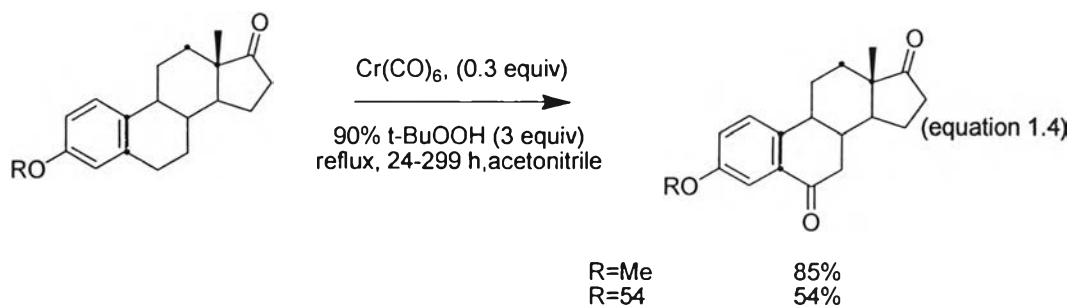
Chromium carbonyl complex only have been used as chromium(0) to achieve the oxidation. $\text{Cr}(\text{CO})_6$ was used as the catalyst complex for cyclohexane oxidation afforded cyclohexanone and cyclohexanol, respectively. A fair selectivity was obtained at low conversion for the cyclohexane oxidation to cyclohexanone (87% conversion) by O_3 [4]. Otherwise, epoxidation and allylic oxidation of an alkene were achieved with $\text{Cr}(\text{CO})_6$ and either O_2 or a benzenic solution of 90% t-BuOOH (equation 1.1) [5]. In contrast, when using acetonitrile as a solvent the oxidation produces only allylic oxidation product.



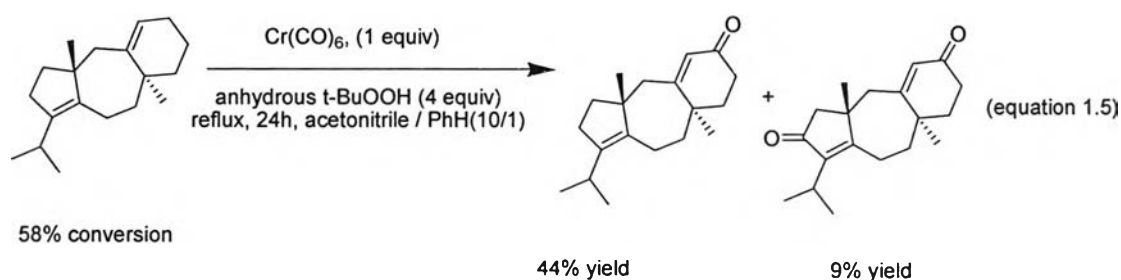
Moreover, this system oxidizes selectively to allylic methylene group which also bears a secondary hydroxyl function (equation 1.2) [6]. Alcohols can also be oxidized in the absence of double bonds (equation 1.3).



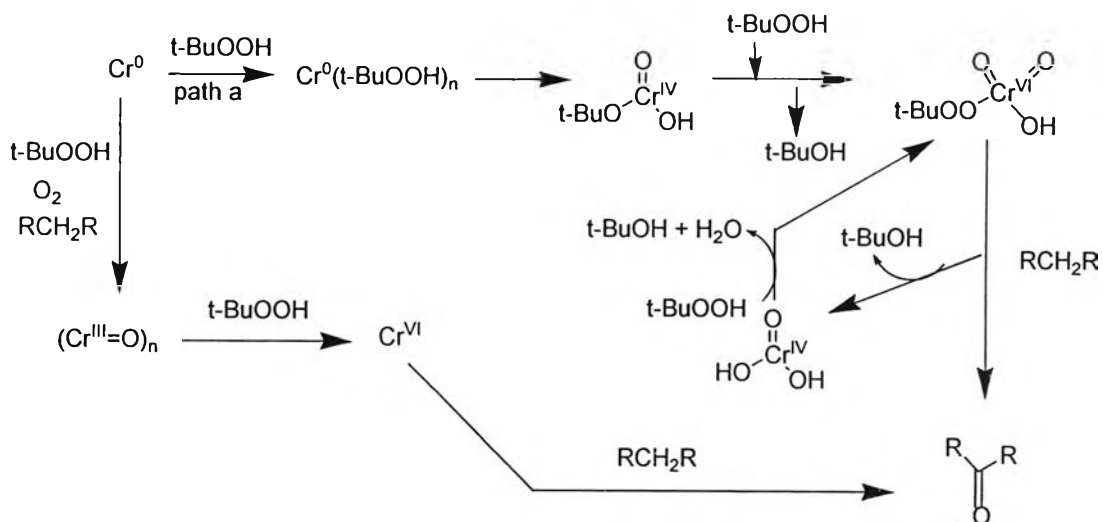
In addition, the regioselectivity for benzylic oxidation was easily achieved with this system in acetonitrile (equation 1.4) [7].



On the other hand when the amounts of catalyst were increased in order to excess of TBHP, the oxidation of allylic methylene group led only to 58% conversion after 1 day reaction time (equation 1.5) [8].



The $\text{Cr(CO)}_3(\text{MeCN})_3$ complex could be produced *in situ* in acetonitrile, and it was assumed that oxidation in this solvent involved catalysis only by Cr^0 species because the chromium-carbonyl bands in the IR spectra were unchanged throughout the reaction. After completion of the oxidation, the original catalyst could be recovered almost quantitatively. In contrast, the oxidation of alkanes by $\text{Cr}/(\text{CO})_6$ system could involve complexable between TBHP and Cr^0 followed by the oxidation of Cr^0 within the complex produced Cr^{VI} which was the active species (Scheme 1.2, path a) [5,6]. When the reaction mixture was exposed to air for a long periods, a polymeric Cr^{III} oxide was formed which presented catalytic activity far superior to Cr(CO)_6 (Scheme 1.2, path b).



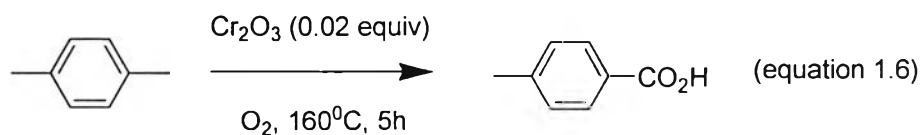
Scheme 1.2 Catalytic cycle for Cr⁰/ TBHP system

1.2 Chromium(III) as catalyst

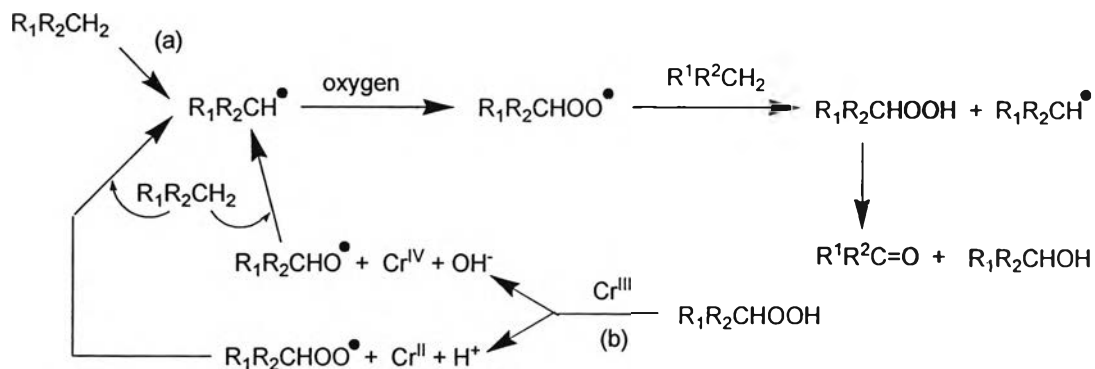
Chromium(III) oxide has been used since the beginning of chromium-catalyzed oxidations and has been associated almost exclusively with oxygen [9]. Many experiments thereafter have been carried out with chromium acetylacetonate or chromium esters in conjunction with oxygen or hydroperoxide. Recently, chromium porphyrins within a large variety of oxygen source have been subjected to intensive investigation [3].

1.2.1 Chromium(III)oxide, Cr₂O₃

It seems that the first uses of chromium(III)oxide as a catalyst occurred more than a half century ago during screening of heavy metal oxides to attempt to accelerate oxidations of benzylic methylene and methyl groups to the corresponding ketones and acids under a stream of oxygen (equation 1.6) [3].

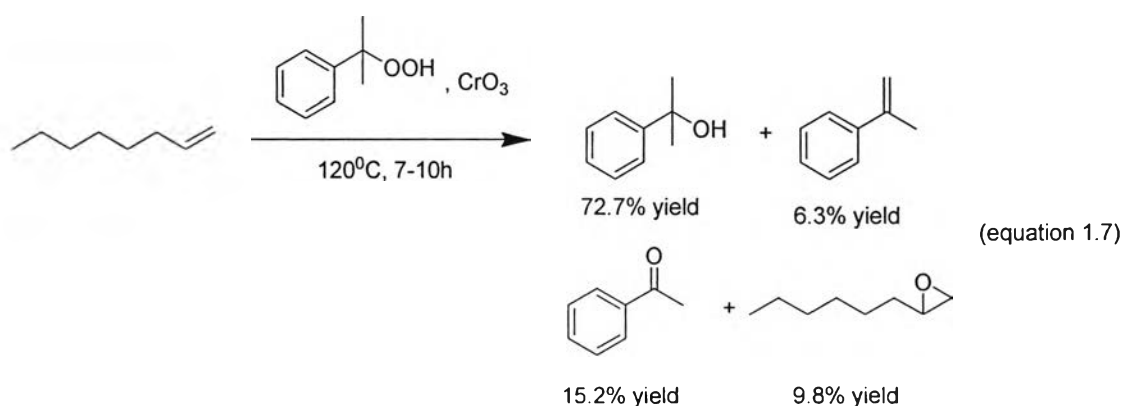


Hydroperoxidation of alkene and alkane by O₂ has been carried out in the presence of small amounts of Cr₂O₃, Cr₂O₃ + NiO, or MCr₂O₄ (M = Co, Cu, Ni) to decrease the period of reaction and to increase the conversion [3]. All of the preceding reactions were heterogeneous and involved peroxide derivatives of the substrate as intermediates (Scheme 1.3).



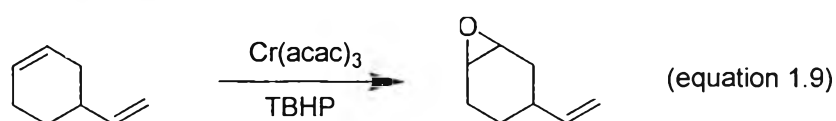
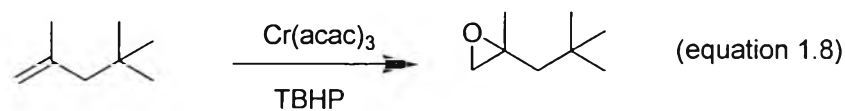
Scheme 1.3 The mechanism of the oxidation of alkane catalyzed by Cr(III)oxide

It was found that Cr_2O_3 acted as the initiator of a radical chain reaction rather than as a catalyst. The metal eliminated or decreased the induction period. It is very difficult to make correct mechanistic conclusions since alkyl hydroperoxides are ubiquitous in most starting hydrocarbon. Hence, there are considerable differences in opinion concerning the reaction pathways of these processes. Although the formation of $\text{R}_1\text{R}_2\text{CH}^\bullet$ by Cr_2O_3 directly from the hydrocarbon, $\text{R}_1\text{R}_2\text{CH}_2$ has been postulated (Scheme 1.3, path a), the first step has often been proposed to be an interaction between the metal and the hydroperoxide already present in the starting hydrocarbon mixture. This interaction will lead to produce the radicals or which can initiate a radical chain process (Scheme 1.3, path b). On the other hand, the oxidation of octenes within cumyl hydroperoxide, Cr_2O_3 induces the decomposition of hydroperoxide intermediate rather than epoxidation of octenes (equation 1.7) [3].

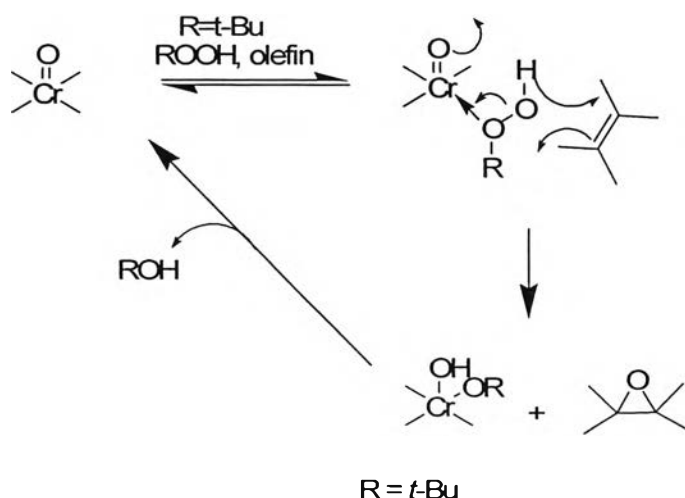


1.2.2 Chromium(III)acetyl acetonate, Cr(acac)₃

The first use of chromium(III)acetyl acetonate as an oxidation catalyst was probably encountered in the epoxidation of olefins by TBHP [10]. The epoxidation was regioselective and stereospecific and provided fair yields of the corresponding products at room temperature when oxygen was excluded from the medium (equations 1.8-1.10).

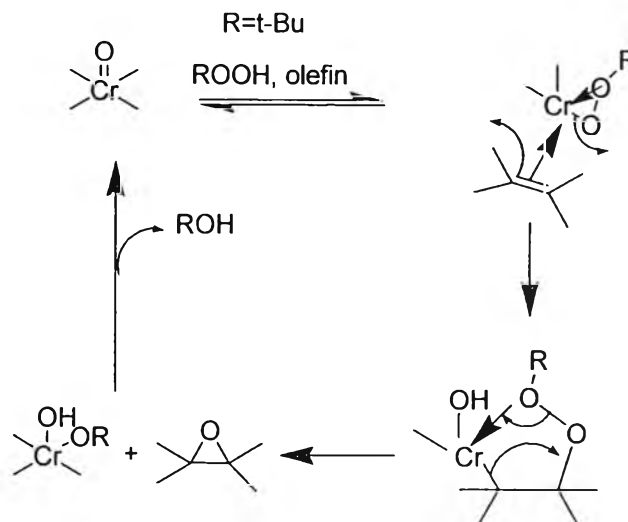


Moreover, stereospecific epoxidations achieved in high yields under appropriate conditions. The epoxidation process involves a complex between the catalyst and TBHP which leads to the metal in its higher oxidation state. Next, a transfer of oxygen from a TBHP molecule coordinated at the metal was postulated through a cyclic transition state where a Cr=O group functions in a manner similar to the carbonyl group in organic peracids (Scheme 1.4) [11].



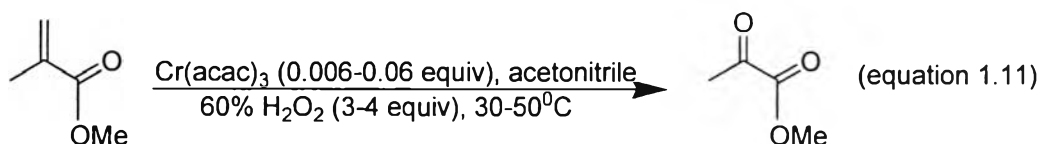
Scheme 1.4 The mechanism for epoxidation catalyzed by Cr(acac)₃

This attractive interpretation of the oxygen transfer is however doubtful: the coordination of the olefin to the metal followed by an insertion reaction leading to a pseudo peroxymetallacycle as an intermediate is more likely, as has been shown in more recent work (Scheme 1.5) [12].

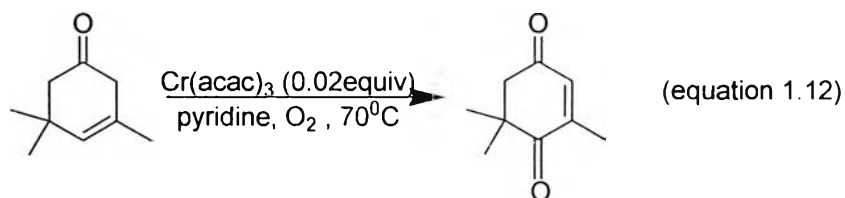


Scheme 1.5 the mechanism for epoxidation

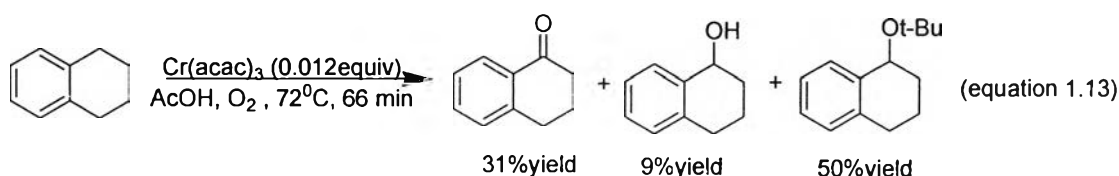
The decrease of the epoxide yield with the enhancement of either temperature or the amount of catalyst could be due to the decomposition of the epoxide and unproductive consumption of TBHP. Indeed, it is expected that an increase in temperature or of the amount of chromium which is a Lewis acid would increase the proportions of both side reactions. Recently, the efficient cleavage of the C=CH₂ group of methacrylic acid esters was carried out with hydrogen peroxide afforded high yield of the corresponding product (equation 1.11) [3].



Cr(III)acetylacetonate catalyzed oxidations with oxygen has also been investigated. Alkanes provided the corresponding ketones and alcohols with the ratio between ketones and alcohols more than 1 [3]. Although both epoxidation and allylic oxidation have been observed with alkenes, the selective oxidation of 8-isophorone to 3,5,5-trimethylcyclohex-2-ene-1,4-dione was achieved with the Cr(acac)₃/O₂ system in good yields when pyridine was used as solvent (equation 1.12) [3].

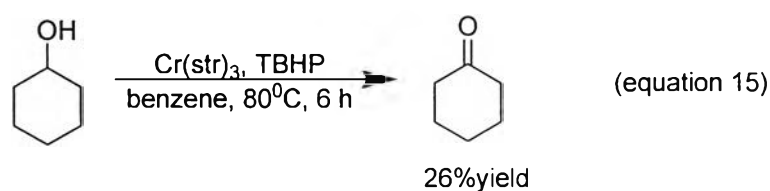
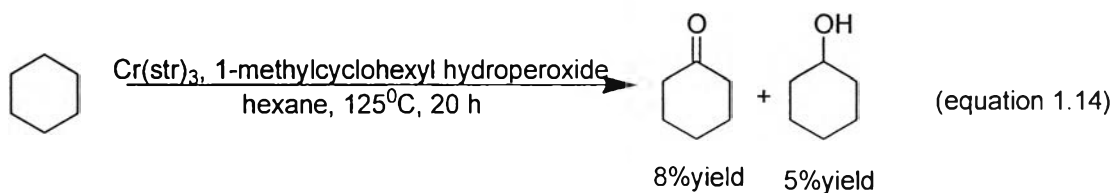


The benzylic oxidation of tetralin has been particularly studied and led to tetralone, tetralol and hydroperoxide (equation 1.13) [13]. In contrast, the oxidation of cumene was inefficient. Under alkaline conditions, the oxidation of nitro or chlorotoluenes and 4-nitro-*m*-xylene to the corresponding carboxylic acid salts [3].



1.2.3 Chromium(III)stearate, Cr(str)₃

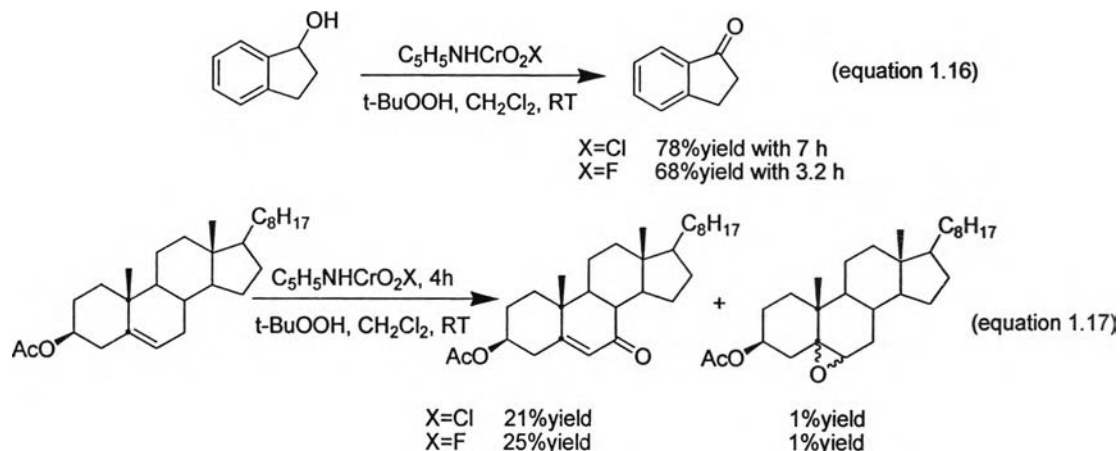
Chromium(III)stearate has been used to promote the autooxidation of alkanes, alkenes, primary or secondary benzylic carbons [22, 23, 24]. Chromium(III) stearate used in conjunction with alkyl hydroperoxides has been examined as a reagent for the oxidation of alkanes (low yields) and secondary alcohols at 80-125 °C (equations 1.14, 1.15) [14, 15].



1.3 Chromium(IV) as catalyst

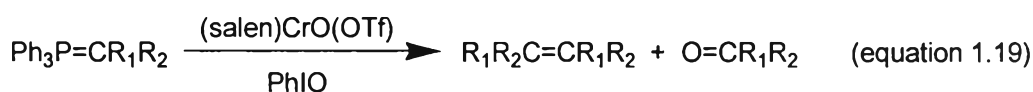
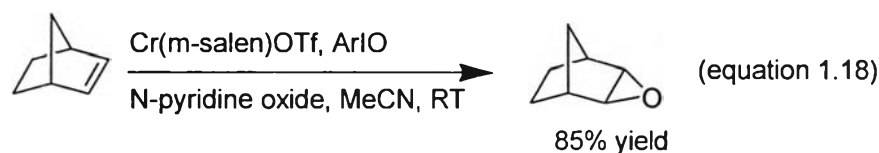
The Cr(IV) complex $C_5H_5NHCrO_2X$, easily obtained from pyridinium chlorochromate ($X = Cl$) or pyridinium fluorochromate ($X = F$), has been employed in conjunction with TBHP and presented similar activities. With these systems benzylic secondary alcohols were converted to ketones in fair yields (equation 1.16) [3]. Small amounts of alcohols or *tert*-butylperoxy derivatives were obtained from benzylic hydrocarbons. The oxidation of cyclic ethylenic substrate gave the α , β -

benzylic hydrocarbons. The oxidation of cyclic ethylenic substrate gave the α,β -unsaturated ketone as the main product while minute amounts of epoxides were isolated (equation 1.17) [3].



1.4 Chromium(V) as catalyst

It seems that the use of a Cr(V) as a catalyst has been only mentioned twice in the literature. PhIO was used as an oxygen source in both papers to achieve the epoxidation of norbornene catalyzed by (m-salen)Cr^VO(OTf) (equation 1.18) [16], and the cleavage of ylides (equation 1.19) [3].

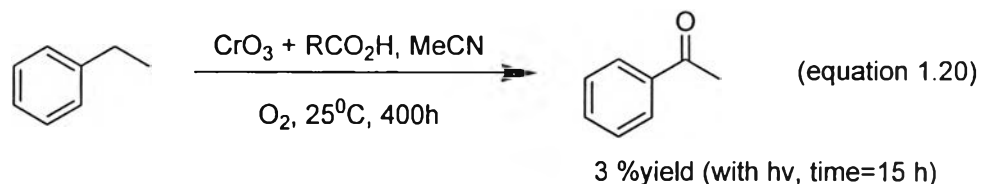


1.5 Chromium(VI) as catalyst

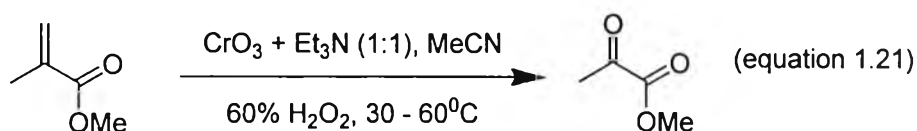
1.5.1 Chromium(VI)oxide, CrO₃

The autooxidation of benzylic carbons has been carried out in the presence of small amounts of chromium(VI)oxide. Tetraline led to tetralone with high selectivity when dimethylformamide or *N,N*-dimethylacetamide was used as solvent while the minute amounts of tetralol and tetralin hydroperoxide being formed. Ethylbenzene furnished acetophenone with a rate and yield only slightly modified in the presence of an organic acid (picolinic or trifluoroacetic acid) but both greatly increased under

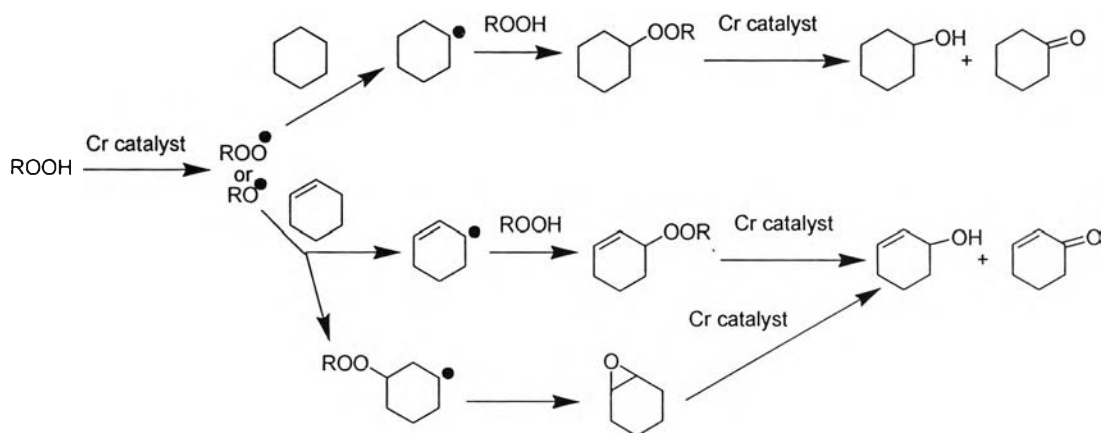
irradiation (equation 1.20) [3]. The radical character of these reactions precludes high conversion of starting substrates if good selectivities are desired.



Catalytic amounts of chromium(VI)oxide induced the oxidation of saturated and unsaturated compounds by H_2O_2 . Oxygenation of cyclohexane, monohydroxylation of the aromatic ring, dihydroxylation, epoxidation, and cleavages of double bonds, benzylic oxidation and oxidation of primary alcohols to aldehydes and carboxylic acids have been achieved, generally with low yields even in the presence of a phase-transfer catalyst. The oxidative cleavage seemed sometimes to be more efficient in the presence of triethylamine or when the double bond was substituted by an aromatic group (equation 1.21) [3].

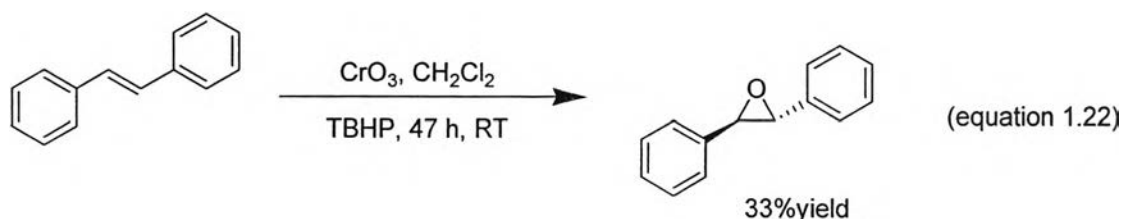


The use of acetone as solvent with hydrogen peroxide or urea adduct instead of H_2O_2 can improve the efficiency of benzylic oxidation. It was noticed early that the reaction stops at the formation of a bluish-green precipitate having the properties of chromium(III)oxide and cannot be reactivated by H_2O_2 . Hydroxyl radicals (scheme 1.6) and peroxochromium(VI) complexes have been successively proposed as the active species [3].

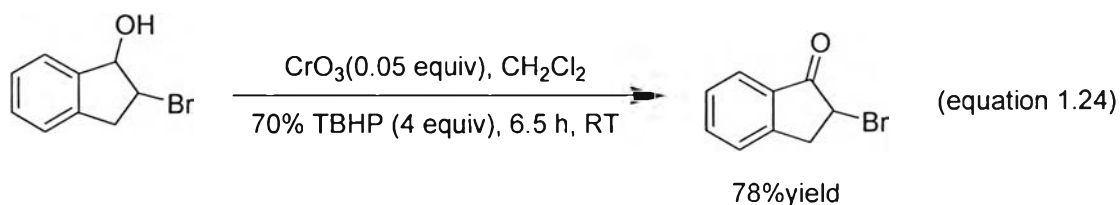
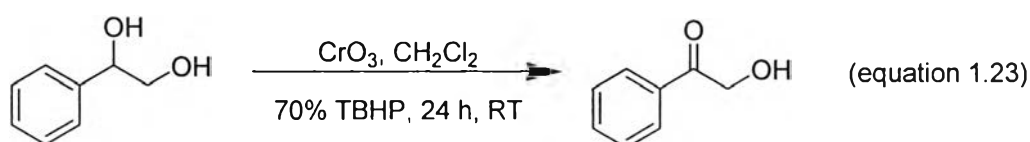


Scheme 1. 6 mechanism for generation of radical with TBHP catalyzed by Cr catalyst

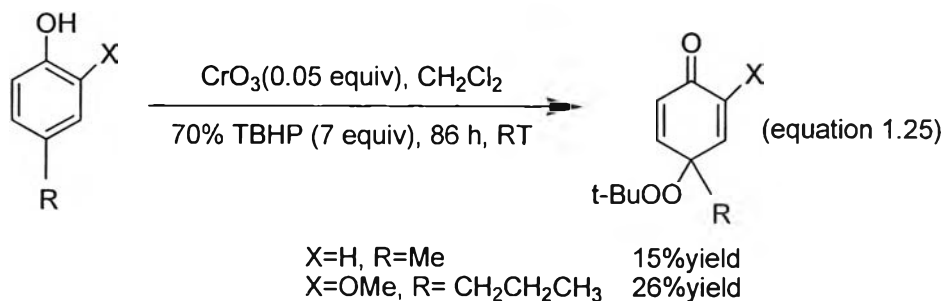
Chromium(III)oxide has been tested as catalyst for the epoxidation of octenes at 120°C by cumyl hydroperoxide but only low amounts of epoxides have been produced [3]. Catalytic amounts of CrO₃ with an excess of commercial aqueous 70% TBHP were used to oxidize benzylic, allylic carbons with fair yields at room temperature [17]. Dichloromethane was a good solvent used to achieve benzylic and allylic oxidations. The selectivity of the benzylic oxidations can be increased by decreasing the reaction temperature to 0°C while, as noted for stoichiometric chromium procedures, the allylic oxidation was efficient only for cyclic substrates [18]. In the presence of allylic hydrogens, the epoxidation of double bonds remained a minor reaction pathway which furthermore can be decreased by using benzene rather than dichloromethane as solvent. In contrast, the oxygenation of double bonds has been observed in the absence of available allylic hydrogen both (*E*) and (*Z*)-stilbenes afforded *trans*-stilbene oxide as the major compound with benzophenone, benzil, and benzoin as side products (equation 1.22) [3].



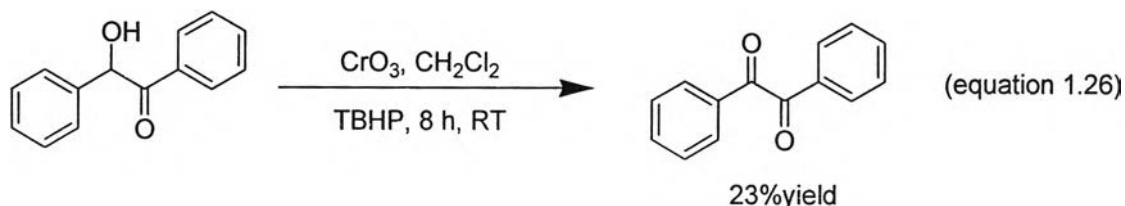
The CrO₃/ TBHP system also accomplished the oxidation of primary and secondary alcohols to carbonyl compounds. Particularly efficient for secondary benzylic alcohols and compatible with inactivated halogen groups, it brought about the selective oxidation of 1-phenyl-1,2-ethanediol to α -hydroxyacetophenone (equation 1.23) and 2-bromoindan-1-ol to 2-bromoindan-1-one, respectively (equation 1.24) [3].



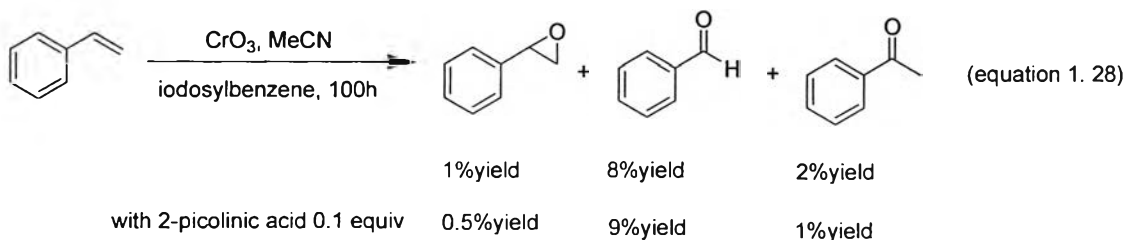
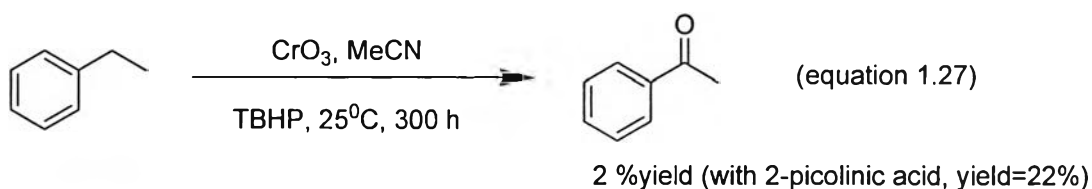
Moreover, the peroxidation of the *para* position of *para*-substituted phenols can be occurred with these systems but with yields no better than 30% (equation 1.25) [3].



The association of CrO₃ with *bis*(trimethylsilyl)peroxide instead of TBHP has only been reported for the oxidation of 4-*tert*-butylcyclohexol to the corresponding ketone with 30% yield. The CrO₃/NaBO₃ mixture required a temperature of 60-80^o C in a biphasic system with a phase transfer catalyst to bring about the oxidation of alcohols but also to the cleavage of some C-C and C=C bonds (equation 1.26) [19].



Following studies with the (porphyrin)CrX/PhIO, this oxygen source was tested with CrO₃ in reactions with ethylbenzene and styrene (equations 1.27, 1.28) [20, 21].

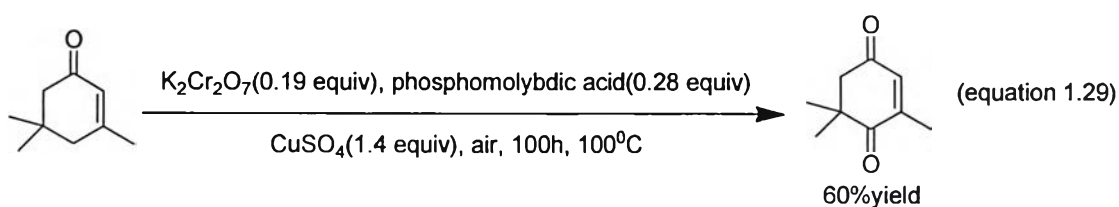


As with some stoichiometric oxidations by Cr(VI) the addition of α -picolinic acid accelerated the accumulation of the oxidation products, giving acetophenone (main product) and 1-phenylethan-1-ol from ethylbenzene. The opposite occurred

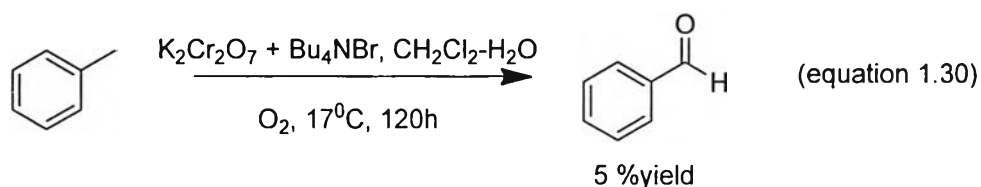
with styrene but larger amounts of α -picolinic acid were added, the rate of the formation of the oxidation products, benzaldehyde (main product), acetophenone, and styrene oxide, decreased and furthermore, the ratio of acetophenone/styrene oxide was reversed. It is interesting to note that with ethylbenzene as a substrate the regeneration of the active Cr species could be achieved at the end of the reaction by the addition of PhIO.

1.5.2 Potassium dichromate, $K_2Cr_2O_7$

Potassium dichromate has been mainly used as catalyst in association with oxygen. $K_2Cr_2O_7$ associated with $Cu(OAc)_2$ did not catalyze the oxidation of benzyl alcohol by oxygen, but a mixture containing an excess of $CuSO_4$, and catalytic amounts of both phosphomolybdic acid and $K_2Cr_2O_7$ successfully achieved the allylic oxidation of cyclohexenones at $100^\circ C$ under an air atmosphere (equation 1.29) [3].

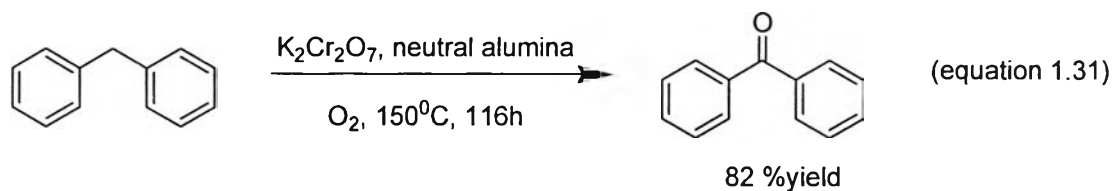


Light and catalytic amounts of $K_2Cr_2O_7$ and Bu_4NBr in a water/dichloromethane mixture induced the oxidation of toluene by air to benzaldehyde with selectivity to benzylic position (equation 1.30) [3].



$K_2Cr_2O_7$ supported on alumina catalyzed the oxidation of diphenylmethane to benzophenone by air at $150^\circ C$ (equation 1.31) [3]. Use of neutral alumina resulted in a more efficient catalyst than basic or acidic alumina, silica, charcoal, or montmorillonite. The rate of the reaction was enhanced by cosupporting very small amounts of $CoCl_2$. Several thousand turnovers with respects to chromium have been reached and the catalyst can be reused. The $K_2Cr_2O_7$ /alumina/ O_2 system has also been shown to catalytically oxidize benzyl alcohol to benzaldehyde and chlorodiphenylmethane to benzophenone. A mixture of $K_2Cr_2O_7$ and SiO_2 catalyzed

the formation of small amounts of phenol from benzene under an air atmosphere. In using H_2O_2 instead of O_2 , the yield was increased 100 times [22].



1.6 The goal of this research

The aims of this research can be summarized as follows:

1. To search for effective chromium complex catalysts for the oxidation of hydrocarbons, alcohols and sulfur containing compounds.
2. To study the optimum conditions for the oxidation of hydrocarbons, alcohols and sulfur containing compounds.
3. To apply the optimum conditions for the oxidation of selected hydrocarbons, alcohols and sulfur containing compounds.