Chapter 1
Introduction and Literature Survey

This chapter presents a survey of the literature on multiphase catalytic reactions and its importance to chemical process industry and hence the mankind. For development of cleaner energy efficient and atom economical processes. The gradual build-up of the problems around certain issues of current economic and environmental concern for the present day technology of oxidation and hydroformylation reactions has been presented. Moreover, applications of multiphase catalytic reaction for the respective reactions from literature have been reviewed to identify & choose the most effective one for the studies. The thorough discussion of the different aspects of the existing state-of-the-art, and the understanding gained from this review has evolved into a well-defined objective to work with.
1.1. Introduction

Multiphase catalytic reactions have significant impact on the development of new synthetic routes and their scope has been expanding into diverse areas of applications for making value added products. Catalytic reactions in multiphase systems are prevalent in production of fuels, bulk and specialty chemicals, pharmaceuticals, food etc. The success of catalytic processing of multiphase systems has resulted from a synergetic approach to the problem by chemists and chemical engineers\textsuperscript{1,2}. Making useful products, at economical yields and selectivities, from the diverse chemistries in such a broad range of applications requires the ability to quantify the interplay of transport phenomena and kinetics\textsuperscript{3,4}.

The importance of catalysis to society is based on its great economic impact in the production of broad range of commodity products that improve our standards of living and quality of life. Most of the industrial reactions are catalytic and the number of chemical compounds produced world wide at the present time are roughly in the range of 20,000 to 30,000\textsuperscript{5}. Catalysis plays a key role not only in the production of a wide variety of products, which are having applications in food, clothing, drugs, plastics, agrochemicals, detergents, fuels etc\textsuperscript{6}, but also offers significant contribution in the balance of ecology and environment by providing cleaner alternative routes for stoichiometric technologies\textsuperscript{7,8} by conversion of polluting emissions to harmless streams.

Catalysis has been in broader terms classified in two different types as homogeneous and heterogeneous catalysis depending on the physical nature of the catalyst employed. In homogeneous catalysis, the catalyst is soluble in the reaction medium making a single phase whereas in heterogeneous catalysis the catalyst is present as a separate phase (a solid or an immiscible liquid phase). Though, both the types of catalysts have contributed significantly to the industry, homogeneous catalysts have distinct advantages like high activity at milder operating conditions, selectivity control, feasibility to understand detailed mechanistic aspects at microscopic level to tailor it further and negligible diffusion limitations. These advantages of homogeneous catalysts have been used in industry for several years for a number of processes involving carbonylation, hydroformylation, hydrogenation, oligomerization, isomerization, polymerization and
oxidation reactions\textsuperscript{9,10}. Industrial significance of homogeneous catalysis was realized several decades ago after the development of oxo process\textsuperscript{11} (hydroformylation technology), Wacker process (olefin oxidation),\textsuperscript{3} Acetic Acid manufacture by BASF\textsuperscript{12,13}, Monsanto\textsuperscript{14,15} and BP\textsuperscript{16,17} processes (methanol carbonylation technology), ethylene polymerization by Zeigler-Natta catalysts\textsuperscript{18} and p-xylene oxidation to terephthalic acid\textsuperscript{19,20}. Initially, the application of homogeneous catalysts was limited to Lewis and Brönsted acids, bases, simple metal salts and simple organic molecules. As the need for more specialized products increased, transition metals with tailored co-ordination environment were preferred as catalysts to achieve selectivity control at milder reaction conditions. Selectivity control is the main advantage of homogeneous catalysts, which is achieved by ligand design utilizing the knowledge of organometallic, coordination and theoretical chemistry. Chemistry of chiral synthesis via asymmetric catalysis is mainly based on homogeneous catalysis. Despite these advantages, about 80\% of the industrial catalytic processes employ heterogeneous catalysts for easier catalyst-product separation, which is often a tedious job in homogeneous catalysis. On the other hand, recent development in synthesis of new metal complex catalysts, novel ligands, new designs for tandem reactions and asymmetric catalysis indicates a strong potential of homogeneous catalysis for the synthesis of a wide variety of bulk, specialty and pharmaceutical products.

The multiphase reactions pose several challenges from a reaction-engineering viewpoint, such as complexities of process chemistry, kinetics, transport effects, energy management and mixing of fluid phases. Detailed analysis of reaction engineering aspects is therefore necessary in identification of critical design factors. Traditionally, the focus of the chemists has been on the catalyst, its preparation, active form, activity, active centers, turnover numbers, kinetics and poisons that might damage it. Engineers were mainly concerned with how to bring the reactants effectively in contact with the chosen catalyst form, and how to provide or remove the heat associated with the progress of reaction. They also concerned themselves with scale-up issues, as how to reproduce the selectivity and rates reached in the laboratory on large process scale. Catalytic reaction engineering (CRE) emerged as a powerful methodology that quantifies the interplay between transport phenomena and kinetics on a variety of scales and allows formulation
of quantitative models for various measures of reactor performance such as reaction rate, conversion and selectivity. The ability to establish such quantitative links between measures of reactor performance and input and operating variables is essential in optimizing the operating conditions in manufacturing, for proper reactor selection in design and scale-up, and in correct interpretation of data.

The aim of this thesis was to investigate in detail the catalysis, mechanism, kinetics and reaction engineering aspects of complex multiphase reactions like liquid phase oxidation and hydroformylation. Hence the focus of this chapter is a detailed survey of the relevant literature of multiphase catalytic reactions with reference to catalysis and kinetics of the reported homogeneous and heterogeneous catalysts for these two industrially important chemical reactions.

1.2. Multiphase Catalytic Reactions

Multiphase catalytic reactions have played an important role in the development of new processes for pharmaceuticals, fine chemicals and specialties. Multiphase catalytic processes have been expanding into diverse areas of applications and continue to make a significant impact on the development of new synthetic routes and high-value products. Conventional technologies for pharmaceuticals and fine chemicals were largely chemistry intensive with a focus on quality assurance and overall productivity. Due to the high cost of these products, the processes were commercially feasible even with lower yields so that issues related to reactor design and environmental needs were considered in low priority. However, the stoichiometric synthetic routes used in pharmaceuticals have several drawbacks, such as generation of waste products consisting of inorganic salts, and use of toxic and corrosive reagents or raw materials with significant safety issues. In recent years, increasingly stringent environmental regulations and societal awareness of safety aspects, coupled with increasing competition, have led to innovations in new processes that are largely based on multiphase catalysis. Therefore, analysis of reactor systems for fine chemicals and pharmaceuticals has gained considerable attention in the recent years. For example, catalytic reactions involving hydrogenation, oxidation, carbonylation, hydroformylation, epoxidation, and amination are extensively used in defining novel synthetic routes with significant economic advantages for pharmaceutical
products. Classification of multiphase reaction processes for pharmaceuticals, specialty and fine chemicals can generally be done using two methods: (1) classification based upon the mode of utility of the reactants and the type of phases involved, such as gas-liquid, gas-liquid-solid, liquid-solid, gas-liquid-liquid and gas-liquid-liquid-solid reactions and (2) classification depending on the process chemistry or type of catalysis involved. The first method is more convenient for analysis of reactor design issues, while the second method is more useful for describing the process routes, since each of the examples will belong to one of the categories in (1). In either case, the final applications of these multiphase processes occur in the manufacturing of products for agrochemicals, pharmaceuticals, detergents, dyestuffs, perfumery and fragrances, feed additives, flavors and food products, polymers, textiles and synthetic fibers. Hydroformylation, oxidation, epoxidation, hydrogenation, carbonylation, oxidative carbonylation and amination are some of the most important examples of multiphase catalytic reactions (Table 1.1).
**Table 1.1. Applications of multiphase catalytic reactions**

<table>
<thead>
<tr>
<th>Sr.</th>
<th>Reaction</th>
<th>Catalyst</th>
<th>Product</th>
<th>Type</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Oxidation of ( p-t )-butyl toluene</td>
<td>Co complex - Br promoted</td>
<td>( p-t )-Butylbenzaldehyde (fine chemicals and perfumery)</td>
<td>G-L</td>
<td>23</td>
</tr>
<tr>
<td>2</td>
<td>Hydrogenation of adiponitrile</td>
<td>Raney Ni</td>
<td>Hexamethylene diamine (HMDA) intermediate for Nylon 6,6(specialty chemicals)</td>
<td>G-L-S</td>
<td>24,25</td>
</tr>
<tr>
<td>3</td>
<td>Epoxidation of styrene followed by isomerization</td>
<td>Ti-silicate (TS-1)</td>
<td>Phenylacetaldehyde (fine chemicals)</td>
<td>L-S</td>
<td>26</td>
</tr>
<tr>
<td>4</td>
<td>Oxidation of glucose</td>
<td>Pd-Bi/C</td>
<td>Gluconic acid (food, detergents and pharmaceuticals)</td>
<td>G-L-S</td>
<td>27,28</td>
</tr>
<tr>
<td>5</td>
<td>Oxidation of indole to indigo</td>
<td>Cumyl hydroperoxide</td>
<td>Indigo - a dye stuff</td>
<td>G-L</td>
<td>29</td>
</tr>
<tr>
<td>6</td>
<td>Hydrogenation of 2,4-dinitrotoluene</td>
<td>Pd/alumina or Raney Ni</td>
<td>Toluenediamine - an intermediate for TDI (free chemicals)</td>
<td>G-L-S</td>
<td>30</td>
</tr>
<tr>
<td>7</td>
<td>Reductive amination of 4-chloroaerylcatechol</td>
<td>Pd/support</td>
<td>Adrenaline - a drug (pharmaceuticals)</td>
<td>G-L-S</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>Hydrogenation of glucose</td>
<td>Raney Ni</td>
<td>Sorbitol (pharmaceuticals)</td>
<td>G-L-S</td>
<td>32</td>
</tr>
<tr>
<td>---</td>
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<tr>
<td>9</td>
<td>Hydroformylation of higher olefins</td>
<td>HCo(CO)₃PB₃</td>
<td>Oxo alcohols</td>
<td>G-L</td>
<td>33</td>
</tr>
<tr>
<td>10</td>
<td>Acylation of substituted benzenes with carboxylic acids</td>
<td>Ce-Y or HZSM-5</td>
<td>Aromatic ketones (substituted) (fine chemicals)</td>
<td>L-S</td>
<td>34</td>
</tr>
<tr>
<td>11</td>
<td>Hydroformylation of Ethylene oxide</td>
<td>Co₂(CO)₈</td>
<td>2-hydroxy propanal</td>
<td></td>
<td>35</td>
</tr>
<tr>
<td>12</td>
<td>Condensation of isophytol with 2,3,5-trimethyl hydroquinone</td>
<td>Heteropolyacids PW/SiW</td>
<td>α-Tocopherol (vitamin E) (pharmaceuticals)</td>
<td>G-L-S</td>
<td>36</td>
</tr>
<tr>
<td>13</td>
<td>Hydrocyanation of bicyclo(2,2,1)-5-heptene-2-carboniwire followed by hydrogenation</td>
<td>Ni(OPPh₄)₄-ZnCl₁E-OPPh₃</td>
<td>Diaminomethylnorbornone (NBDA) - hardener for epoxy resin (fine chemicals)</td>
<td>G-L</td>
<td>37</td>
</tr>
<tr>
<td>14</td>
<td>Oxidation of ethylene</td>
<td>PdCl₂/CuCl₂</td>
<td>Acetaldehyde</td>
<td>G-L</td>
<td>38</td>
</tr>
<tr>
<td>15</td>
<td>Oxidation of p-xylene</td>
<td>Co/Mn-salts</td>
<td>Terephthalic acid/ester</td>
<td>G-L</td>
<td>39</td>
</tr>
<tr>
<td>16</td>
<td>Hydrodesulfurization of α-amino benzyl sulfides, 2-methyl (trimethyl-6-trifluromethylaniline)</td>
<td>Co-molybdate on Al₂O₃</td>
<td>2-Methyl-6-trifluoromethyl aniline (MTMA) - a pre-emergent herbicide intermediate (specialty agrochemicals)</td>
<td>G-L-S</td>
<td>40</td>
</tr>
</tbody>
</table>
Multiphase catalytic reactions would always involve reaction engineering issues, such as complexities of chemistry, kinetics, transport effects, energy management, mixing of fluid phases, and modes of operation. Although, it is not always feasible to develop a predictive reactor performance model in each case, a detailed analysis of reaction engineering aspects would certainly be useful in identification of critical design factors. The new design for gas-liquid-liquid reactors and the relevant mass transfer and hydrodynamic data is most essential to understand the design and scale-up of these emerging technologies in chemical process industries.

The need of catalytic technologies, for conversion of cheaper feedstock to industrially important products is the need of future. New routes for fine chemicals, pharmaceuticals and specialties, removal of pollutants, waste minimization and global supply and preservation of energy are the most important requirements. These objectives can be achieved by catalytic routes. Liquid Phase Oxidation (LPO) and hydroformylation are the most prominent examples of multiphase catalytic reactions in industry. These reactions have been employed for the synthesis of a variety of industrial products such as aldehydes, ketones, alcohols, carboxylic acids etc, few of which having industrial and academic importance are studied in detail for their catalytic and engineering aspects in this thesis.

1.3. Oxidation Reaction

Catalytic oxidation is the single most important technology for the conversion of hydrocarbon feedstocks (olefins, alkanes and aromatics) to industrially important oxygenated derivatives. The success of catalytic oxidation depends on metal catalysts to promote rates of reaction and selectivity to partial oxidation products. Liquid phase and gas phase oxidations, using homogeneous and heterogeneous catalyst are practiced in industry. Some of the well-known examples of liquid phase oxidation in industry are oxidation of \( p \)-xylene to terephthalic acid, cyclohexane to adipic acid, \( n \)-butane to acetic acid and higher homologues and ethylene to acetaldehyde, oxidation of butadiene to 2,4-diacetoxybutene, epoxidation of propylene to propylene oxide, and hydroxylation of phenol to hydroquinone and catechol using \( \text{H}_2\text{O}_2 \) as oxygen donor. Traditionally, in fine chemicals industry, the use of stoichiometric quantities of classical inorganic oxidants
such as potassium dichromate and potassium permanganate were more, which are not acceptable from environmental viewpoint. Because much smaller production volumes are involved, there was much less pressure in the past to replace such environmentally unacceptable technologies. Nevertheless, the amount of by-products (largely inorganic salts) per kilogram of product is generally much larger in fine chemicals and specialties. The substantial increase in waste generation is partly due to the fact that the production of fine chemicals and specialties generally involve multi-step synthesis and partly to the widespread use of stoichiometric rather than catalytic technologies. Consequently, the fine chemical industry is being subjected to increasing environmental pressure. One motivation in developing liquid phase catalytic oxidation processes is also due to increasingly stringent government regulations concerning emission of organic and inorganic wastes and related environmental problems. The older generation of oxidation processes was based on classical stoichiometric oxidants such as dichromate, permanganate, manganese dioxide and nitric acid, which are not accepted from environmental considerations as they produce large quantities of waste materials and employ toxic reagents. Catalytic liquid phase oxidation has played a vital role in providing alternative to these stoichiometric reagent based processes with minimal amount of undesired by-products.

In choosing suitable methodology for oxidation of particular organic substrate, there are various options as shown in the Figure 1.1. Each methodology has its advantages and disadvantages. In these, liquid phase oxidation expands the scope of catalytic oxidation to non volatile and thermally sensitive substrates and products. Higher heat capacity of the liquid phase facilitates temperature control of the exothermic reaction and avoids the formation of hot spots and temperature run away. Liquid phase oxidation requires less temperature and hence advantageous for energy saving and safe operations. Also, oxidants like H$_2$O$_2$ and hydroperoxide can be safely used in liquid phase oxidation. So depending on requirement, there is a choice of oxidants.
1.3.1. Hydrocarbon Oxidation

Liquid-phase air oxidation of hydrocarbons, notably oxidation of \( p \)-xylene to terephthalic acid and dimethyl terephthalate, cyclohexane to cyclohexyl hydroperoxide and cyclohexanol/cyclohexanone, cumene to cumene hydroperoxide, toluene to benzaldehyde, ethylbenzene to acetophenone, iso-butane to \( tert \)-butyl hydroperoxide and \( tert \)-butyl alcohol, is of great scientific, technological, and commercial importance. Oxidative transformations of functional groups are basic to organic chemistry and are used extensively in the laboratory and industrial synthesis of a variety of fine organic chemicals. Some of the major inefficiencies in the production of such chemicals can often be traced to the operation of the reactor. The study also lacks in the detailed understanding of the mechanism, kinetics and reaction engineering aspects of such important class of reaction. It is therefore not surprising that this class of reactions has spawned much study and research.

The major developments in hydrocarbon oxidations have most often been motivated by the need for appropriate feedstocks for the evergrowing polymer industry. From early days, the functionalization of naturally occurring petroleum components through reaction with air was naturally seen as the simplest way to derive useful...
chemicals. Industrial practice also developed alongside with vapour phase oxidation being the prime focus.

Liquid phase oxidation processes began from the 1950s. The Wacker process for the conversion of terminal olefins to carbonyl compounds and the Hock process for the production of phenol from cumene (via the hydroperoxide) were commercialized during this period. The cumene-phenol process was developed, by Distillers Co. in the U.K. and Hercules Powder Co. in the U.S., from a reaction discovered by Hock and Lang during the war\textsuperscript{46,47}. At that time, the free-radical chemistry of such reactions was establishing. Several major contributions to that field, such as the concept of activation of a tertiary C atom by a phenyl ring (which leads to the specificity of oxidation in this process) and an understanding of the role of impurities, came during the process development effort. Several developments of an engineering nature also played a part in the final commercialization, such as the improvement in rate and selectivity through staging of reactors and the imposition of a temperature profile (with the temperature decreasing as the hydroperoxide concentration increases) on the reactor cascade.

The discovery of the “Mid-Century” catalysts and the subsequent development of the Mid-Century (MC) process for the oxidation of \( p \)-xylene to terephthalic acid belong to this period. The impetus for the discovery of the Mid-Century catalyst was provided by the need for a cheap source of aromatic acids for the industrial production of aromatic polyesters, in particular, poly(ethylene terephthalate) (PET)\textsuperscript{48}. In searching for an alternative to esterification (Witten process of 1951) for overcoming the inhibiting effect of the first carboxyl group on further oxidation, Landau and co-workers at Scientific design discovered the promoting effect of the bromide anion\textsuperscript{13} and immediately obtained qualitative improvements in yield over the norm using cobalt catalyst alone and then further and proceeded to develop the oxidation technology\textsuperscript{49}. Landau has recently given a fascinating account of this development. In the subsequent decades, many aspects of the action of Mid-Century catalysts have been clarified, and the principle has been extended to over 200 other aromatic, alkylaromatic, and other systems. In particular, improvements in the technology for purification have today put Pure Terephthalic Acid (PTA) in a dominant position in the world market as the preferred raw material for PET fiber.
A broad survey of the commercially important processes employing liquid-phase hydrocarbon oxidation is presented in Table 1.2. The production volumes of the chemicals listed is high, and reflects the importance of liquid-phase oxidation in industry. It is interesting to note the different roles of the oxidation step in these processes. In some of the processes, such as the Amoco process for the manufacture of PTA, the oxidation step leads directly to the product of interest. There are others, such as the process for caprolactam, in which oxidation is the step that produces a key intermediate that is then further processed to the product of interest. In the oxirane process, hydrocarbon oxidation provides a convenient carrier of oxygen for the selective oxidation of propylene to propylene oxide. A choice of hydrocarbons is therefore available, and the market for the coproduct determines which hydrocarbon is chosen in a given context. Although treatises on hydrocarbon oxidations underline the similarities that exist in the mechanisms that govern various organic oxidations, from an engineering point of view, it is the differences that exist between hydrocarbons that are often of interest; these differences call for innovative technological developments. In the manufacturing of terephthalic acid, the product of interest forms fairly late in the reaction sequence, and, considering its resistance to oxidation, it may in fact be considered as the end product. In a majority of situations however, the desired product is an intermediate; susceptible to further oxidation, and selectivity considerations become extremely important like in toluenes oxidation, benzaldehydes overoxidizes to carboxylic acid. Synthesis of benzaldehyde selectively is the major challenge involved.

In many hydrocarbon oxidations, the desired intermediates have a tendency to undergo further reactions in the oxidizing medium. The limitation imposed by the chemistry on the selectivity to the desired intermediates that is achieved has often meant that conversions are kept low to minimize the formation of unwanted products. The need to achieve better selectivity at reasonable conversions has naturally been a major driving force for research. In reactions of complex molecules, the concepts of chemoselectivity (competing reactions at different functional groups), regioselectivity (e.g. ortho vs. para substitution in aromatics) and stereoselectivity (enantio- or diastereoselectivity) are commonly used. However, one category of selectivity is completely ignored by organic
chemists i.e. atom selectivity or atom utilization. The atom utilization concept is a useful tool for quickly evaluating the amount of waste produced by alternative processes.

Appropriate choice of reaction conditions for higher conversion and selectivity is a major problem area and a lot of scope exists for technology development. The reaction conditions are very harsh with respect to temperature, pressure etc which needs detailed experimentation and understanding. Some of the process parameters of the existing industrial process are given in Table 1.3. The thesis investigates some of the important aspects of this problem and validates the results on a laboratory scale reactor for few important oxidation reactions like liquid phase catalytic oxidation of toluene and ethylbenzene. Below, a detailed literature survey for these reactions is presented.
### Table 1.2. Major Chemical Processes Utilizing Hydrocarbon Oxidation\(^{52,49,53}\)

<table>
<thead>
<tr>
<th>Product</th>
<th>Capacity (10^6) tpy</th>
<th>Oxidation step</th>
<th>Important Processes</th>
<th>Main Application</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purified terephthalic Acid (PTA)</td>
<td>11.38</td>
<td>(p)-xylene to terephthalic acid</td>
<td>Amoco</td>
<td>PET (fiber, film, resin)</td>
<td>Applies also to other alkylaromatics such as (m)-xylene, pseudocumene, 2,6-dimethyl naphthalene</td>
</tr>
<tr>
<td>Dimethyl terephthalate (DMT)</td>
<td>4.06</td>
<td>(p)-xylene to (p)-toluic acid and monomethyl ester of pTA to DMT</td>
<td>Witten, BASF, DuPont</td>
<td>PET (fiber, film, resin)</td>
<td>Two-step process or one-step process</td>
</tr>
<tr>
<td>Benzoic acid</td>
<td>0.28</td>
<td>Toluene to benzoic acid</td>
<td>DSM, Dow</td>
<td>Phenol and salts, esters of benzoic acid</td>
<td>Coproduct: acetone also applies to cresols, resorcinol/hydroquinone from cymenes, diisopropylbenzenes</td>
</tr>
<tr>
<td>Caprolactam</td>
<td>3.7</td>
<td>cyclohexane to KA</td>
<td>BASF, Bayer, DuPont, DSM, Stamicarbon Scientific Des.</td>
<td>Nylon-6 (Perlon)</td>
<td>Also employed in the Snia-Viscosa route to caprolactam and Henkl route to TA</td>
</tr>
<tr>
<td></td>
<td>2.2</td>
<td>Cyclohexane to cyclohexanone/ cyclohexanol (KA) and KA to adipic acid</td>
<td>BASF, Bayer, Dupont, Stamicarbon Scientific Des.</td>
<td>nylon-6,6</td>
<td>K:A ratio depends on use of boric acid</td>
</tr>
<tr>
<td>----------------</td>
<td>-----</td>
<td>---------------------------------------------------------------------</td>
<td>-------------------------------------------------</td>
<td>-----------</td>
<td>---------------------------------------</td>
</tr>
<tr>
<td>Adipic acid</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propylene oxide</td>
<td>4</td>
<td>iso-butane to TBHP</td>
<td>Oxirane</td>
<td></td>
<td>Coproduct: tert-butyl alcohol</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>gasoline additive</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>phenyl methyl carbinol</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(dehydrated to styrene)</td>
</tr>
<tr>
<td>Acetic acid</td>
<td>6.0b</td>
<td>Ethylbenzene to hydroperoxide butane/naphtha</td>
<td>Celanese, BP, UCC</td>
<td></td>
<td>Main route is via carbonylation of methanol</td>
</tr>
</tbody>
</table>
Table 1.3. Some Important Process Parameters in the Commercially Important Oxidations

<table>
<thead>
<tr>
<th>Sr.</th>
<th>Hydrocarbon</th>
<th>Desired Product</th>
<th>Reaction Conditions</th>
<th>Process</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Temp., °C</td>
<td>Pressure bar</td>
</tr>
<tr>
<td>1</td>
<td>p-xylene</td>
<td>PTA</td>
<td>190-205</td>
<td>15-30</td>
</tr>
<tr>
<td>2</td>
<td>p-xylene</td>
<td>p-toluic acid p/TA</td>
<td>140-170</td>
<td>4-8</td>
</tr>
<tr>
<td>3</td>
<td>Monomethyl ester of p/TA</td>
<td>DMT</td>
<td>140-240</td>
<td>40</td>
</tr>
<tr>
<td>8</td>
<td>iso-butane</td>
<td>TBHP</td>
<td>120-140</td>
<td>35</td>
</tr>
<tr>
<td>9</td>
<td>Ethylbenzene</td>
<td>EBHP</td>
<td>120-140</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>110-120</td>
<td>2-3</td>
</tr>
<tr>
<td>10</td>
<td>Toluene</td>
<td>benzoic acid</td>
<td>165</td>
<td>9</td>
</tr>
</tbody>
</table>
1.3.1.1. Selective Liquid Phase Oxidation of Toluens to Benzaldehydes

In the modern chemical industry, the liquid-phase oxidation of aromatic hydrocarbons by molecular oxygen is a very attractive process from an economic and environmental point of view. A range of valuable oxygenated compounds can be produced by this process. For example, benzaldehyde and benzoic acid can be produced from toluene and p-toluic acid and terephthalic acid from p-xylene. Aromatic aldehydes like benzaldehyde, chlorobenzaldehyde, fluorobenzaldehyde etc. are FDA approved synthetic flavoring substances and have extensive applications in food, pharmaceutical, dye, agricultural and perfumery industries. Particularly, benzaldehyde is the most important aromatic aldehyde concerning industrial applications, and has a wide range of application from food and pharmaceuticals to perfumery industry. Conventionally benzaldehydes have been synthesized by chlorination of toluenes to give benzyl chloride, which after hydrolysis gives benzaldehydes. From an industrial viewpoint, chlorination method suffers from disadvantages like high production cost, large amount of polluting residues, formation of byproducts, and troublesome product purification; besides the use of toxic chlorine and associated corrosion problems. However, for the production of benzaldehydes, particularly for the grade conforming to perfumery and pharmaceutical applications that require chlorine free products, the vapour phase oxidation of toluenes is an obvious alternative route. However, in the vapour phase oxidation of toluenes, the lower value carboxylic acids are formed as major products and benzaldehyde is only a minor product. From the literature, it is also evident that, in vapour phase oxidation, the reaction conditions are too stringent; with temperatures in the range of >773K and pressures in the range of 0.5-2.5 MPa, to achieve an optimum selectivity (~25) to benzaldehyde. The major disadvantage is the recovery of the toluene from toluene-air mixture, owing to low concentration of toluene in the toluene-air feed. The major challenge is to avoid the formation of benzoic acid and the loss of carbon in the form of gaseous products such as CO and CO$_2$, which is highly undesirable and adversely affects atom economy. The liquid phase oxidation of toluene with homogeneous metal salt catalysts was industrially realized in the Rhodia, Dow and Snia-Viscosa processes using oxygen or peroxides as oxidants. For example, the Snia-Viscosa process operates at 165°C and under 10 atm of air in the presence of a homogeneous cobalt...
catalyst in acetic acid. At the optimal conditions, benzoic acid as the target product is produced with 90% selectivity, and benzaldehyde as a minor byproduct is obtained in 3% selectivity at 15% conversion of toluene. In these processes, however, halogen ions and acidic solvents are unavoidable, and they easily cause erosion. The formation of benzoic acid via toluene oxidation was also reported in supercritical CO₂ and ionic liquids as solvents\textsuperscript{70,71}. In the latter report, the maximum conversion of toluene was only 4.7% after 48 h. Hence, the recent interests are increasing in the development of an efficient and selective catalytic system for the liquid phase air oxidation of toluenes to benzaldehydes at milder reaction conditions.

The liquid phase catalytic oxidation of toluene to benzaldehyde has major advantages in avoiding the use of hazardous and toxic chlorine, mineral acids and improving the overall process economics as well as the product quality. In most of the reported literature,\textsuperscript{72,73,74} the catalyst systems used for this reaction contain mainly cobalt catalyst. Extensive work has been done on cobalt based catalyst system along with different co-catalyst and promoter. Recently Can-Cheng Guo et al\textsuperscript{75} have reported toluene oxidation by the use of cobalt tetraphenylporphyrin as catalyst has also reported but the reaction conditions are harsh (temperature \(\sim 170^\circ\text{C}\)) and also selectivity to benzaldehyde \(\sim 30\) for \(\sim 8\%\) conversion of toluene. Few other catalysts like Mo, Cu, Mn, Zn etc are also reported for the liquid phase oxidation of toluenes\textsuperscript{76,77}. Salts of cobalt along with bromide are highly active catalysts for oxidation of methyl benzenes in acetic acid media, which yield the corresponding carboxylic acids as the major product e.g. toluene to benzoic acid\textsuperscript{78,79}. Moreover, as the conversion increases, selectivity to aldehydes is further lowered. In MC-type catalyst systems with acidic solvents like acetic acid, benzoic acid and propionic acid, the aldehyde formed is usually over-oxidized to the aromatic acid, thus reducing the aldehyde selectivity\textsuperscript{80,81}. Formation of benzyl alcohol and a side reaction of equilibrium esterification of benzyl alcohol to benzyl acetate in presence of acetic acid solvent was observed, which reduces the selectivity to benzaldehyde. Thus, during liquid phase oxidation of toluene, benzyl acetate, and benzoic acid were formed as byproducts along with benzyl alcohol and benzaldehyde. Recent developments show significant improvement in benzaldehyde selectively with the incorporation of metal salts like Mn, Cr, Ni, Mo etc, which are weaker than cobalt.
As temperature of the reaction is a critical factor in oxidation reaction, at higher temperature the formation of byproducts increases due to over oxidation and the formation of CO and CO₂ is observed, thus reducing the selectivity and atom economy. Few attempts have been made for low temperature liquid phase oxidation of toluene using Zn, Cu, Al-layered double hydroxide with hydrogen peroxide as the oxidant using different radical generator, marginal increase in the selectivity of aldehyde was observed.

The use of promoters in the oxidation can increase the reaction rate and improve selectivity to the aldehyde product. Borgaonkar et al.⁵² have reported paraldehyde as a promoter which, however, results in higher benzoic acid formation⁷⁴. In conventional homogeneous oxidation cobalt, manganese, and bromine ions serve as promoters. Co/Mn/Br is highly active and selective catalyst system for liquid phase oxidation of toluene. Synergetic addition of salts of Mn to benzaldehyde selectivity and conversion of toluene has been reported by Kantam et al.⁸¹. Recently, MnCO₃ catalyzed liquid phase oxidation of toluene has been reported, however the conversion (6%) is poor with moderate selectivity (41.7%) to benzaldehyde.⁸³ Some of the important literature reports are tabulated in Table 1.4. Also, heterogeneous promoters containing Mn for the oxidation of aromatics have attracted increasing attention due to their practicability and relatively high activity. For example, amorphous, microporous Mn/Si mixed oxide, Mn (III) complexes of Salen, and Mn-layered double hydroxides (LDHs) have been used in the oxidation of aromatic hydrocarbons. However, these promoters were generally prepared in a multi-step process and combined with a particular oxidant, e.g. H₂O₂ or TBHP. Therefore, it is necessary to develop an active, reusable, and easily prepared active Mn promoter for the oxidation of aromatic hydrocarbons with molecular oxygen as oxidant, which is one of the motivation of investigating in the thesis.
Table 1.4. Liquid phase oxidation of toluenes

<table>
<thead>
<tr>
<th>Sr.</th>
<th>Catalyst</th>
<th>Temp., K</th>
<th>Activity</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Conv.,%</td>
<td>Ald. Sel.,%</td>
</tr>
<tr>
<td>1</td>
<td>Co-Mn-Br</td>
<td>100-140</td>
<td>12-16</td>
<td>25-35</td>
</tr>
<tr>
<td>2</td>
<td>Co-Br</td>
<td>100-140</td>
<td>13-20</td>
<td>35-42</td>
</tr>
<tr>
<td>3</td>
<td>MnCO₃</td>
<td>190</td>
<td>17-26</td>
<td>8-28.3</td>
</tr>
<tr>
<td>4</td>
<td>Fe,Cu,Mn zn, supported on Al₂O₃</td>
<td>190</td>
<td>5-26</td>
<td>12-74</td>
</tr>
<tr>
<td>5</td>
<td>Co(Oac)₂/NaBr/AIBN</td>
<td>110-150</td>
<td>30-36</td>
<td>5-10</td>
</tr>
<tr>
<td>6</td>
<td>cobalt tetraphenylporphyrin</td>
<td>150-180</td>
<td>6-15</td>
<td>28-35</td>
</tr>
<tr>
<td>7</td>
<td>Co/MTiO₂</td>
<td>90-110</td>
<td>20-45</td>
<td>78-99</td>
</tr>
<tr>
<td>8</td>
<td>Co(OAc)₂/MnSO</td>
<td>70-106</td>
<td>10-25</td>
<td>45-75</td>
</tr>
<tr>
<td>9</td>
<td>Cu/APO-5</td>
<td>60</td>
<td>10-27</td>
<td>25-30</td>
</tr>
<tr>
<td>10</td>
<td>Co-Br</td>
<td>100-130</td>
<td>12-30</td>
<td>70-90</td>
</tr>
<tr>
<td>11</td>
<td>Co-Mn-Br</td>
<td>80-160</td>
<td>10-30</td>
<td>25-40</td>
</tr>
<tr>
<td>12</td>
<td>bromide</td>
<td>110-130</td>
<td>10-36</td>
<td>10-27</td>
</tr>
<tr>
<td>13</td>
<td>vanadium(V) polyoxometalates</td>
<td>25</td>
<td>6-32</td>
<td>12-38</td>
</tr>
<tr>
<td>14</td>
<td>vanadium containing catalyst</td>
<td>70-150</td>
<td>13-45</td>
<td>60-80</td>
</tr>
<tr>
<td>15</td>
<td>Mn-Lewsi acid-Br</td>
<td>90-130</td>
<td>9-30</td>
<td>55-76</td>
</tr>
</tbody>
</table>
1.3.1.2. Selective Liquid Phase Oxidation of Side Chain Alkyl benzenes

Aromatic ketones are of significant importance in synthetic chemistry. For example, acetophenone (Acph) is an important intermediate in perfumery, drug and pharmaceutical industry. The industrial synthesis of aromatic ketones involves the Friedel-Craft's acylation of aromatic compounds by acid halide or acid anhydride, using stoichiometric amounts of anhydrous aluminium chloride or homogeneous acid catalysts, leading to formation of large volumes of highly toxic and corrosive wastes. In the past extensive work has been done to synthesize the aromatic ketones by oxidizing the methyl group attached to an aromatic ring using stoichiometric amount of oxidizing agents like KMnO₄. A few illustrations of this kind of oxidations are the oxidation of diphenylmethane to benzophenone by KMnO₄, SeO₂ or CrO₃-SiO₂ and the oxidation of alkylarenes by KMnO₄ supported on Mont-K. These reactions produce large amounts of salt waste, and also, the separation and isolation of the products and unconverted substrate from the reaction mixture is difficult. Recently, there has been an increased interest in developing cleaner, economical catalytic processes for synthesizing value-added products like ketones by benzylic oxidation of alkylaromatics.

Acetophenone can also be produced by liquid phase air oxidation of ethylbenzene using soluble salts of Co, Mn, Cu or Fe as catalysts and using acetic acid as solvent. Although the metal compounds used in these processes are in catalytic amounts, the reaction conditions are harsh; the ketone selectivity is poor, corrosive promoters like bromide ions are required along with the catalyst. Also the recovery and recycle of the catalyst is tedious and costly which becomes complicated due to formation of tarry compounds. In industrial processes, the cost centre is obviously the metal catalyst used, which implies that the reactions to be carried out in a manner that simplifies the separation, isolation and reuse of the catalyst. Due to this fact, extensive research has been done in heterogenization and recovery of the catalyst, catalyst poisoning etc.

There has been an increased interest in developing eco-friendly catalyst systems for the oxidation of alkylaromatics. The oxidation of many organic substrates using H₂O₂ as oxidant over Ti⁴⁺ analogues of ZSM-5 (TS-1) and ZSM-11 (TS-2) has been well-documented. Titanium substituted silicates have been thought to catalyze ring hydroxylation of arenes with H₂O₂, but vanadium, tin and chromium...
substitution into a variety of zeolites and aluminophosphate molecular sieves has led to favored oxidation at the side-chain. The presence of molecular oxygen or single oxygen atom donors such as tert-butyl hydroperoxide (TBHP) for the oxidation of alkanes to alcohols and ketones are shown to be important\textsuperscript{110,111,112}.

Oxidation using hydroperoxides is attracting great interest because of the fact that they yield the desired oxidation product with high selectivity under mild reaction conditions and generate easily separable co-products like water or aliphatic alcohols\textsuperscript{113}. Among the various transition metal catalyst systems reported for ethylbenzene oxidation, the most effective ones are the heterogenized cobalt catalysts like cobalt-containing hexagonal mesoporous materials (Co-HMS) and cobalt-substituted silicate xerogels. Chromium substituted aluminophosphate catalysts are found to yield ketones with high selectivity from alkyl arenes with TBHP as oxidant\textsuperscript{114}. Manganese analogues of these systems have also been shown to catalyze oxidation of alkanes using TBHP\textsuperscript{115}. Scanty literature is available on kinetics and mechanistic studies in liquid phase oxidation of ethylbenzene using TBHP as oxidant. Most of the work has been done on the homogeneous and supported Co, Cu, Ni, V, Sn etc as catalyst using TBHP as oxidant for liquid phase oxidation of ethylbenzene (Table 1.5).

Layered double hydroxides (hydrotalcites) have received much attention because of their potential as bulk catalysts, catalyst supports, and ion exchangers. This is due to their ability to accommodate a large variety of bivalent and trivalent cations, the homogeneous mixture of the cations on an atomic scale, and the formation of thermo stable mixed oxides with a high surface area\textsuperscript{116}. Transition metals, that are known to act as active catalysts can also be introduced in the brucite layer. Hydrotalcites containing metals like Ni, Cu, Co, Pd etc., have already been reported in the literature. Hydrotalcites with zirconium incorporated into the layers have been used for the selective oxidation of alcohols etc. The structural studies of hydrotalcites have shown that they are laminar structures consisting of positively charged brucite-type metal hydroxide layers with balancing anions and water molecules in the interlayer space, the most common and representative of this category being the Mg-Al hydrotalcite having the molecular formula \( \text{Mg}_3\text{Al(OH)}_8(\text{CO}_3)_{0.5}\cdot 2\text{H}_2\text{O} \). Cavani \textit{et al}\textsuperscript{116} have taken a detailed account of the catalytic activity of hydrotalcites (HT) and hydrotalcite like compounds (HTLcs) for
several chemical reactions. Hydrotalcites are effective catalysts for isomerization, Aldol, Knoevenegel and related condensations that are widely used in fine chemical synthesis. There few reports of oxidation of methylbenzenes using hydrotalcite like compounds using air as oxidant, where the rates of the reaction are very low. Literature lacks the detail study of oxidation of hydrotalcite using oxidants like TBHP, which is one of the motivations behind this study.

**Table 1.5. Liquid phase oxidation of ethylbenzene**

<table>
<thead>
<tr>
<th>Sr.</th>
<th>Catalyst</th>
<th>Temp., K</th>
<th>Activity</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mn-MCM-41</td>
<td>333</td>
<td>Conv.,% 29.1</td>
<td>117</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sel.,% PE =81.5, Acph=16.9,</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Bzald=1.1, Other= 0.5</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Co-MCM 41</td>
<td>353</td>
<td>36.1 Acph= 71, Bzald=18.2,</td>
<td>118</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Bzacid= 9.5</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Cu(tacn) (ClO₄)₂</td>
<td>333</td>
<td>49.6 Acph= 91, Other= 5.9</td>
<td>119</td>
</tr>
<tr>
<td>4</td>
<td>Mn/Co/Ni</td>
<td>343</td>
<td>29.4 PE =39.6, Acph=52.3,</td>
<td>120</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Other= 6</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Cr-MCM-41</td>
<td>353</td>
<td>88 Acph=85.3, Other= 13.5</td>
<td>121</td>
</tr>
<tr>
<td>6</td>
<td>Co-HMS</td>
<td>353</td>
<td>49.5 Acph= 60, Bzald=25,</td>
<td>122</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Bzacid= 15</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Mn complexes</td>
<td>313</td>
<td>13 Acph= 51, PE=25.7, others=</td>
<td>123</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Mn(tacn) (ClO₄)₂</td>
<td>313</td>
<td>27 Acph= 57, PE=15.7, others=</td>
<td>124</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Zeolite encapsulated Co(II), Ni(II), Cu(II)</td>
<td>323</td>
<td>24 Acph= 74, Others= 26</td>
<td>125</td>
</tr>
<tr>
<td>10</td>
<td>Iron complexes</td>
<td>303</td>
<td>16.8 Acph= 70, PE=10.7,</td>
<td>126</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Bzald=8, Bzacid= 9</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Cr exchanges ZSM-5</td>
<td>353</td>
<td>21 Acph= 85, PE=2.3,</td>
<td>127</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Bzald=4.6, Bzacid= 2</td>
<td></td>
</tr>
</tbody>
</table>
1.3.2. Selective Liquid Phase Oxidation of Aldehydes

The oxidation of aldehydes to their corresponding carboxylic acids is one of the most common organic reactions in organic chemistry\textsuperscript{128}. The oxidation products of aldehydes have wide range of applications in food, pharmaceuticals and fine chemical industries. Particularly oxidation of substituted aldehydes to carboxylic acid is of increasing interest due to its importance in pharmeculical industry. In addition to numerous versatile methods for the oxidation of aldehydes, more convenient methods such as Baeyer–Villiger oxidation\textsuperscript{129}, Cannizzaro reaction\textsuperscript{130}, and metal catalyzed oxidation have been reported. Aldehydes are prone to oxidation; they oxidize very easily with the oxidants like chromic acid, potassium dichromate, vanadium oxide etc. The conventional methods for the oxidation of aldehydes employ a) Chemical oxidation involving oxidants like chromic acid b) biochemical oxidation using enzymes. c) Electro chemical oxidation. d) Non-catalytic oxidation by using molecular oxygen e) Catalytic oxidation using homogeneous and heterogeneous catalyst\textsuperscript{131}.

Despite the growing awareness of the need for ‘green chemistry’, many chemists still use environmentally unacceptable reagents or unnecessarily sophisticated conditions for the oxidation of aldehydes\textsuperscript{132,133,134}. Several literature references quote oxidation of aldehydes to carboxylic acids using molecular oxygen as oxidant in acidic solvents like acetic acid, peracetic acid, butyric acid etc.\textsuperscript{135,136} Majority of the available literature on aldehyde oxidation is on reagent-assisted oxidation of aldehydes. From the literature it appears that non noble metal catalysts have been studied for the liquid phase oxidation of aldehydes. Oxidation of aromatic and aliphatic aldehydes to corresponding acids have been studied by Bhatia et al.\textsuperscript{1} by using cobalt chloride as a catalyst in presence of acetic anhydride and yields in the range of 41% to 80%. Choi et al.\textsuperscript{40} have reported benzeneseleninic acid catalyzed oxidation of aldehydes to corresponding acids with 80% to 98 % yield at room temperature, using hydrogen peroxide as an oxidant\textsuperscript{137}. Springer and Dinslaken have reported non-catalytic oxidation of aliphatic aldehydes with oxygen in pure or mixture forms with excellent yields of corresponding carboxylic acid. From the literature it is observed that transition metal catalysts like Mn, Co, Cu, Fe etc have been used for the oxidation of aldehydes to corresponding acids with conversions in the range of 85% to 95% and the selectivity more than 90% to corresponding carboxylic
Major work has been done on the homogeneous catalyst i.e. salts of transition metals, which are soluble in reaction phase and acidic solvents. Few authors have reported metal-based catalyst system and inorganic or organic promoters for the efficient oxidation of aldehydes using the more acceptable ‘green’ oxidants like H2O2, TBHP etc in acidic solvents\cite{140}. The use of such acidic solvents implies corrosion and safety hazards, besides the generation of salts, which usually have to be land filled. Some of the prominent literature report are given in Table 1.6.

The use of soluble catalysts, which leads to separation problems, and the corrosive acidic solvents, are major shortcomings of this process. Besides this, the isolation and purification of the products are the major issues, mainly because of the applications of the products are in food and pharmaceutical industry. While a number of catalytic systems need to investigate, a detailed study on the role of promoters, catalyst preparation methods, and supports has not been investigated. Similarly the information of kinetic modeling and reactor performance study has been very rare. So to understand the catalysis and reaction engineering aspects of aldehydes oxidation of 2-acetoxy propionaldehyde has been investigated in details using 2-acetoxypropanal, 3 acetoxy propanal and 2-MNP as substrate.
Table 1.6. Liquid phase oxidation of aldehydes

<table>
<thead>
<tr>
<th>Sr.</th>
<th>Catalyst</th>
<th>Temperature, °C</th>
<th>Other details (Solvent / Substrate)</th>
<th>Conversion/ Yield</th>
<th>Selectivity, %</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cobalt acetate</td>
<td>130</td>
<td>Acetic acid as solvent veratraldehyde</td>
<td>100</td>
<td>99</td>
<td>141</td>
</tr>
<tr>
<td>2</td>
<td>CeO₂-Ru</td>
<td>140-160</td>
<td>Toluene as solvent, Benaldehyde, octaldehyde</td>
<td>60-70</td>
<td>83 – 95</td>
<td>142</td>
</tr>
<tr>
<td>3</td>
<td>Cobalt H-form resin</td>
<td>20-22</td>
<td>Heptaldehyde in bubble column reactor</td>
<td>50-70</td>
<td>82-90</td>
<td>143</td>
</tr>
<tr>
<td>4</td>
<td>Cobalt (II) chloride</td>
<td>25</td>
<td>Acetic unhydride used, benzaldehyde, octaldehyde, propionaldehyde, butyaldehyde</td>
<td>40-60</td>
<td>80- 93</td>
<td>144</td>
</tr>
<tr>
<td>5</td>
<td>Au/C, Pt/C</td>
<td>90</td>
<td>Water as solvent, Propanal</td>
<td>85-93</td>
<td>86-92</td>
<td>145</td>
</tr>
<tr>
<td></td>
<td>Co(II) heteropolyacid</td>
<td>30</td>
<td>2-Phenyl acetalsaldehyde, isobutyaldehyde</td>
<td>54</td>
<td>76</td>
<td>146</td>
</tr>
<tr>
<td>6</td>
<td>CoTBCOPP</td>
<td>30</td>
<td>Acetic acid/ acetone as solvent p-chlorobenzaldehyde, benzaldehyde</td>
<td>85-93</td>
<td>92-95</td>
<td>147</td>
</tr>
<tr>
<td>7</td>
<td>NaClO2-HzOzn</td>
<td>60</td>
<td>furan-2-carboxaldehyde</td>
<td>93-96</td>
<td>-</td>
<td>148</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>15 thiophene- 2-carboxaldehyde</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>8</td>
<td>ebselen</td>
<td>75</td>
<td>H₂O₂, Aromatic aldehydes</td>
<td>95-100</td>
<td>95-98</td>
<td>149</td>
</tr>
<tr>
<td>9</td>
<td>[CH₃(CH₂)₃]H₂SO₄</td>
<td>75</td>
<td>H₂O₂, Aromatic aldehydes</td>
<td>80-90</td>
<td>95-98</td>
<td>150</td>
</tr>
<tr>
<td>10</td>
<td>Pd/C and NaBH₄, KOH</td>
<td>30</td>
<td>Methanol as solvent, Aromatic aldehyde</td>
<td>86-90</td>
<td>93-97</td>
<td>151</td>
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<tr>
<td>----</td>
<td>---------------------------</td>
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<td>---------------------------------------</td>
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<td>-------</td>
<td>-----</td>
</tr>
<tr>
<td>11</td>
<td>TBA₄HPW₁₁CoO₉</td>
<td>20</td>
<td>Acetonitrile as solvent, isobutyraldehyde</td>
<td>92</td>
<td>78-82</td>
<td>152</td>
</tr>
<tr>
<td>12</td>
<td>Cu, Ni and iPrCHO</td>
<td>25</td>
<td>Alcohol as solvent, methoxy aromatic aldehydes</td>
<td>92</td>
<td>85-94</td>
<td>153</td>
</tr>
</tbody>
</table>
1.3.3. Kinetics of Catalytic Reactions

The basic objective of the chemical reaction engineering is to model the reaction/process occurring in the chemical reactor as accurately as possible. It is generally divided into two subgroups i.e., reaction kinetics and heat and mass transport. Catalytic reactions are complex, involving reactions in series and parallel which, in most reaction engineering models are taken into account in complex rate equations.

Kinetic modeling of catalytic reactions is one of the key aspects investigated in order to understand the rate behavior of catalytic reactions as well as reaction mechanism. Knowledge of intrinsic reaction kinetics (a scale-independent property) and development of rate equations is most essential for reactor design. While the subject of kinetic modeling has been well investigated for heterogeneous catalysis, only limited information is available on this aspect in homogeneous catalysis especially for kinetics of hydrocarbon oxidation reactions.

1.3.3.1. Kinetics of Liquid Phase Oxidation

The determination of kinetics of liquid-phase organic oxidation presents a nontrivial problem. Over the years, reactor and process design aspects have received considerable attention. The models used in the early attempts were rather crude and did not pay adequate attention to the influence of mass transfer, and hence, process development usually involved extensive experimentation at different scales. The first attempt to explicitly acknowledge the role of mass transfer in organic oxidations was the work of Hobbs et al.\textsuperscript{154}, in which the possibility of the reaction become limiting mass transfer limited and the bulk becoming starved of oxygen was recognized. These authors made an attempt to explain certain experimental observations that could not be explained on the basis of considerations of chemistry alone by maintaining the role of mass transfer, even though in a qualitative manner.

Development of kinetic models for liquid phase oxidation systems using homogeneous catalyst has not received much attention from a reaction engineering perspective. However, reviews on the kinetics and mechanism from a chemical perspective are available in the literature\textsuperscript{155,156,157}. Oxidation reaction generally involves
several products in reaction system, the quantitative analysis of which is challenge. Considering the complex chemistry and mechanism of these reactions the detailed kinetic is usually not feasible. An engineering and industrial approach to kinetics involving lump is usually followed which postulates the series and parallel network depending on the nature and requirement of the reaction. The possible influence of mass transfer on the observed behavior considered carefully in the interpretation of the rate data because oxidation reactions are generally conducted using air or oxygen containing gas as oxidant. The theory of gas liquid reactions had made significant impact, starting with the work of Higbie in 1935, and hydrocarbon oxidations had been recognized as a major class of reactions of industrial significance falling within the scope of the theory applied to complex reactions with kinetics of the type encountered in organic oxidations. These attempts to bring hydrocarbon oxidations within the domain of the theories of mass transfer with chemical reaction, but could not get much success. In the last two or three decades, several studies have attempted to address these gaps, but much remains to be done.

The lack of data on the important mass transfer parameters in systems and under the conditions of temperature and pressure, were the industrial processes operates. Given the complexity of the chemistry involved in hydrocarbon oxidation, and the fact that one often must estimate the kinetics from rate data in heterogeneous (gas-liquid) systems, the planning and execution of laboratory studies to establish true kinetics is usually a demanding task. A growing appreciation for the interaction between physical transport phenomena and chemical kinetics in organic oxidations has led to an examination of the possibility of using oxygen-rich gases for oxidation. The issues of safe design and operation of oxidation reactors, always at upfront due to the use of oxygen and oxygen containing gases, which needs innovative reactor design.

A recent trend in kinetic modeling involves a molecular level approach to the development of rate models. Evidence suggests that there is a close analogy between reaction mechanisms based upon adsorption and those based on molecular species through organometallic intermediate species. This aspect can allow better understanding of the kinetic trends in complex reactions, which are otherwise modeled using empirical approaches. A recent review on this subject is by Waugh, though examples of the
molecular level approach for industrially important selective oxidation reactions are rare. This approach needs an independent study on the nature of catalytic sites and molecular species formed as intermediates. This might lead to a reaction scheme that can form the basis for deriving rate equations.

For many liquid-phase oxidation processes, detailed kinetic models that account for the formation of the various byproducts are still poorly understood. Moreover, the engineer must decide the level of detail at which he needs to investigate the kinetics of particular reaction to understand the particular phenomenon. Thus, the engineer is often forced to depend on the empirical approach to establish kinetics, with some basis from the known mechanisms.

1.3.4. The Mechanism of Oxidation Reactions

The chemistry of liquid-phase autoxidation of hydrocarbons, both catalyzed and uncatalyzed, has been the subject of several monographs and reviews\textsuperscript{160,161,162,163,164}. According to Sheldon et al\textsuperscript{165}, a detailed insight of the mechanism of oxidation reactions suggests that the mode of catalytic cycle depends on the 1) the metal catalyst employed, and 2) the oxidant used. MC type catalysts have been extensively investigated for their catalytic activity as well as mechanistic features in the oxidation of hydrocarbons in liquid phase. The mechanism of oxidation reaction, though complex, can be accounted in terms of two modes- one with molecular oxygen, as oxygen gas diluted with a neutral counterpart like nitrogen or as air; and the other with hydrogen peroxides or organic peroxides, both in aqueous or non-aqueous media.

1.3.4.1. One-electron Oxidations with Oxygen/ Air as Oxidant

One-electron oxidants, e.g. Co(III), Mn(III), Ce(IV), Fe(III), Cu(II), etc. catalyze free radical autoxidation processes by promoting the decomposition of alkyl hydroperoxides into chain initiating alkoxyl and alkyl peroxy radicals in one electron transfer processes (reactions 1 and 2). Strictly speaking the metal ion acts as an initiator of free radical autoxidation, which proceeds via reactions, rather than a catalyst.
As evident from the literature, catalysts used in hydrocarbon oxidations mostly involve transition metals. Cobalt has been the most prominent among the transition metals used. According to Partenheimer\textsuperscript{166}, cobalt performs at least three functions in the oxidation medium: (a) It quickly reacts with the primary peroxides via the Haber-Weiss cycle as in steps 1 and 2. (b) It acts as a radical initiating species when in the higher (+3) oxidation state (i.e., it generates \( R^- \) radicals from \( RH \)), thereby enhancing the rate by participating in the initiation step (see eq 11). (c) It reacts rapidly and selectively with peracids, which are formed in the oxidation of aldehydes, and thus facilitates intermediate product conversion at advanced stages of oxidation. The first two mechanisms can operate in all cobalt catalyzed reactions. The ease of reactions 1 and 2 depends on the redox potential of the Co(III)/Co(II) couple; the nature of the ligand (acetate or bromide, etc.) and the solvent also have some influence on this. The reason for the effectiveness of cobalt (and manganese) is the fact that the two-oxidation states in its case are of comparable stability, so that reactions 6 and 7 can occur concurrently, and a catalytic process results\textsuperscript{167}. With other metals (such as copper), alternative routes for reducing the metal, such as hydrogen transfer by the solvent, sometimes operate to close the catalytic cycle. The possibilities are discussed by Sheldon and Kochi\textsuperscript{167}.

**1.3.4.2. Oxidations with H\(_2\)O\(_2\)/ Organic Peroxides**

Metal ions which catalyze oxygen transfer reactions with H\(_2\)O\(_2\) or RO\(_2\)H can be divided into two types based on the active intermediate: a peroxometal or an oxometal complex\textsuperscript{168}. This is illustrated for alcohol oxidations in Figure 1.2\textsuperscript{169}. In the peroxometal
pathway the metal ion does not undergo any change in oxidation state during the catalytic cycle and no stoichiometric oxidation is observed in the absence of H$_2$O$_2$. In contrast, oxometal pathways involve a two electron change in oxidation state of the metal ion and a stoichiometric oxidation is observed, with the oxidized state of the catalyst, in the absence of H$_2$O$_2$. Indeed, this is a test for distinguishing between the two pathways. Peroxometal pathways are typically observed with early transition metal ions with a d(0) configuration, e.g., Mo(VI), W(VI), Ti(IV), Re(VII), that are relatively weak oxidants. Oxometal pathways are characteristic of late transition elements and first row transition elements, e.g., Cr(VI), Mn(V), Os(VIII), Ru(VI) and Ru(VIII), that are strong oxidants in their highest oxidation states. Some metals can operate via both pathways depending, inter alia, on the substrate, e.g., vanadium(V) operates via a peroxometal pathway in olefin epoxidations and via an oxometal pathway in alcohol oxidations.$^{161}$

Figure 1.2. Oxometal vs peroxometal pathway

In aerobic oxidations of alcohols a third pathway is possible with late transition metal ions, particularly those of Group VIII elements. The key step involves dehydrogenation of the alcohol, via β-hydride elimination from the metal alkoxide to form a metal hydride (Figure 1.3). This constitutes a commonly employed method for the synthesis of such metal hydrides. The reaction is often base-catalyzed which explains the use of bases as cocatalysts in these systems. In the catalytic cycle the hydridometal species is reoxidized by O$_2$, possibly via insertion into the M–H bond and formation of
H$_2$O$_2$. Alternatively, an alkoxy metal species can afford a proton and the reduced form of the catalyst, either directly or via the intermediacy of a hydridometal species (Figure 1.2). Examples of metal ions that operate via this pathway are Pd(II), Ru(II) and Rh(III). We note the close similarity of the β-hydride elimination step in this pathway to the analogous step in the oxometal pathway (Figure 1.2).

Some metals, e.g. ruthenium, can operate via both pathways and it is often difficult to distinguish between the two. A further variation on the hydridometal pathway is observed with supported noble metal catalysts, e.g., palladium or platinum on activated charcoal. In this case the zerovalent metal dehydrogenates the alcohol to form surface metal hydrides that subsequently react with O$_2$ to regenerate the metal. Some elements, e.g. vanadium, can employ oxometal or peroxometal pathways depending on the substrate. Reactions that typically involve peroxometal pathways are olefin epoxidation and heteroatom oxidations. Oxometal species, on the other hand, display a broader range of activities, including benzylic and allylic oxidations. An important difference is that peroxometal pathways do not involve any change in oxidation state of the metal, i.e. the metal acts as a Lewis acid and activity is not restricted to variable valence elements. An oxometal pathway, in contrast, involves two-electron redox reactions of the metal ion. Furthermore, most metals which catalyze oxygen transfer processes, via peroxometal or oxometal pathways, are also capable of catalyzing one-electron transfer processes with peroxides. Consequently, competition from free radical processes is often observed, to a greater or lesser extent, in oxygen transfer processes. When alkyl hydroperoxides are
used as oxidants homolytic versus heterolytic processes can be distinguished by the use of suitable probe molecules. We also note that immobilization of a redox-active element in a solid matrix will probably not influence the oxidation mechanism, e.g. one-electron oxidants such as Co(III) will still catalyze free radical processes when incorporated in the framework of a molecular sieve.

1.4. Literature Survey on Hydroformylation

Hydroformylation is one of the most flexible and important tools for the functionalisation of carbon-carbon double and triple bonds. The evolution of catalytic systems, especially ligands, has enabled control of the regio- and steroselectivity in the hydroformylation reaction. Hydroformylation is essentially the addition of H and the formyl group to an olefin or alkyne. It is a prototype of an efficient atom economic transformation as defined by B. Trost, since all the atoms of the starting materials are incorporated in the product. It also is one of the important and largest scale applications of homogeneous catalysis. It is used in the industry for the manufacture of aldehydes and alcohols from olefins. About 5.9 million TPA aldehydes [C_4 to C_{20+} range] are produced by this process all over the world. These are further hydrogenated to alcohols for different applications. The aldehydes act as intermediates for a variety of bulk and fine chemicals, whereas alcohols find applications as solvents, surfactants, detergents and plasticizers. Hydroformylation involves the reaction of alkenes with carbon monoxide and hydrogen in the presence of a catalyst to form linear and branched aldehydes. The stoichiometric reaction is as shown in scheme 1.1.

\[ \text{R-CH=CH}_2 + \text{CO/H}_2 \xrightarrow{\text{Catalyst}} \text{R-CH}_2\text{-CH}_2\text{-CHO} + \text{R-CH}_3\text{-CHO} \]

Scheme 1.1: General hydroformylation reaction

Discovered by Otto Roelen in 1938, the hydroformylation reaction was first named as “Oxo” reaction, with oxo being a short form of oxonation, i.e. addition of oxygen to double bond. Later on, the reaction was renamed as “Hydroformylation” since there is
The addition of hydrogen and formyl group across the double bond. Linear and branched aldehydes are the major products in the hydroformylation reaction along with some side products like alcohols and saturated hydrocarbons by hydrogenation of olefins and aldol derivatives by condensation of aldehydes. Selectivity to the $n$-isomer is an important consideration in the catalyst development, since the normal products are generally more useful in commercial practice.

Extensive work has been done on the hydroformylation reaction, which is very well documented in the literature. The role of different catalysts and promoters on product distribution and selectivity towards desired product and the kinetics and reaction mechanism has been studied in detail using cobalt and rhodium catalysts. These are incidentally the two metals around which the hydroformylation processes are built. Table 1.7 shows the comparison of various industrial oxo processes.

**Table 1.7.** Comparison of various industrial oxo processes

<table>
<thead>
<tr>
<th>Particulars</th>
<th>Cobalt</th>
<th>Rhodium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variant</td>
<td>Classical$^a$</td>
<td>Modified$^b$</td>
</tr>
<tr>
<td>Catalyst</td>
<td>HCo (CO)$_4$</td>
<td>[HCo (CO)$_3$ PBU$_3$]</td>
</tr>
<tr>
<td>T (°C)</td>
<td>110-180</td>
<td>160-200</td>
</tr>
<tr>
<td>P (bar)</td>
<td>200-350</td>
<td>50-100</td>
</tr>
<tr>
<td>Product</td>
<td>aldehyde</td>
<td>alcohol</td>
</tr>
<tr>
<td>n:iso ratio</td>
<td>80:20</td>
<td>88:12</td>
</tr>
<tr>
<td>By-product</td>
<td>alcohols, acetals and heavy ends.</td>
<td>paraffins</td>
</tr>
</tbody>
</table>

$^a$ BASF, Ruhrchemie; $^b$ Shell; $^c$ Ruhrchemie; $^d$ Union Carbide (LPO); $^e$ Ruhrchemie/Rhone-Poulenc, Hoechst.
The Table 1.7 reveals the immense potential of hydroformylation reaction in chemical industry, which has been realized in the past few decades. Hydroformylation therefore, has been one of the most studied catalytic reactions, the evolution of which can be explained into three phases or generations.

The first generation hydroformylation processes were exclusively based on cobalt catalyst\(^{176}\). The reaction conditions needed for this catalyst were relatively harsh (200-350 bar pressure and 150-180°C temperature). Later on, researchers\(^{177}\) at Shell discovered that phosphines (or arsines) were able to replace carbon monoxide as electron donating ligand to produce a modified cobalt catalyst, which shows improved regioselectivity towards the \(n\)-isomer, due to the electronic and steric properties of the phosphine ligand. The Shell process reduced the operating pressure to 50-100 bar and temperature to 80°C to 200°C. The major drawback of this process was the side reaction of hydrogenation of olefins to paraffins. The second generation processes combined the advantages of ligand modification with a changeover from cobalt to rhodium as the catalyst. The rhodium-phosphine catalysts achieved very high chemoselectivity and regioselectivity towards \(n\)-aldehydes, at milder reaction conditions (60-120°C and 1-50 bars) and hence this process is termed as the Low Pressure Oxo Process (LPO process)\(^{178}\). Owing to this advantage of LPO, most of the cobalt-based hydroformylation processes were shifted to LPO, especially for hydroformylation of propylene. The catalyst employed in LPO process is HRh(CO)(PPh\(_3\))\(_3\); also popularly known as Wilkinson's catalyst. The third generation process using aqueous biphasic catalysis was developed by Kuntz\(^{179}\) of Rhone-Poulenc in 1984, which addressed the catalyst product separation issue to some extent. The basic idea was to immobilize the catalyst in to an immiscible liquid. The necessity of this variation was to convert the organic soluble ligand to its water-soluble counterpart. Aqueous biphasic catalysis particularly gained importance because of the many advantages of water as the reaction solvent. The best example of the aqueous-biphasic catalysis is the hydroformylation of propylene using [Rh(COD)Cl]\(_2\)-TPPTS (triphenyl phosphine trisulfonate trisodium), which has been commercialized by Ruhrchemie-Rhone Poluenc at a 300 MTPA scale.

Apart from cobalt and rhodium catalysts, the hydroformylation reaction has also been explored with a few other transition metal complexes of Ni, Pd, Se, Cu, Fe, Ru, Ir,
Pt, Ag or Mn, though for academic interest\textsuperscript{20a}. Tin (II) chloride modified platinum catalysts have significantly gained importance in the field of asymmetric hydroformylation. The order of hydroformylation activity with regard to the central metal atom follows the trend Rh > Co > Ir, Ru > Os > Pt > Pd > Fe > Ni. The Rh catalyzed hydroformylation has been applied for a variety of olefins from linear \( \alpha \)-olefins to higher olefins as well as functionalized olefins, with numerous applications of the aldehyde products. A list of the rhodium catalyzed commercial hydroformylation processes is given in Table 1.8.

Similarly, a large variety of ligands have been screened for the cobalt and rhodium catalyst systems to improve activity/selectivity of hydroformylation. Phosphines are the most widely studied ligands in hydroformylation chemistry. Nitrogen containing ligands like amines, amides or isonitriles\textsuperscript{180} though active, show lower reaction rates in the oxo reaction due to their stronger co-ordination to the metal center. The order of reactivity of ligands according to the donor atom: Ph\textsubscript{3}P > Ph\textsubscript{3}N > Ph\textsubscript{3}As, Ph\textsubscript{3}Sb > Ph\textsubscript{3}Bi proves the superiority of phosphine ligands\textsuperscript{181}. Polydentate phosphines have also been used for hydroformylation reaction but their uses are limited, as they show much lower activities than their monodentate counterparts. In addition, the regioselectivities are not as high as expected for these bulky ligands\textsuperscript{182}. Due to the extensive use of phosphines in catalysis, their co-ordination chemistry has been studied in more detail\textsuperscript{183}. Carbene ligands obtained from imidazolium salts also show good activity and selectivity for hydroformylation of 1-hexene\textsuperscript{184}. 

36
<table>
<thead>
<tr>
<th>Sr.</th>
<th>Alkene</th>
<th>Products</th>
<th>Capacity KTPA</th>
<th>Ligand</th>
<th>Year</th>
<th>Developed by</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C_6-C_14</td>
<td>1-alkenes, higher alcohols</td>
<td>23</td>
<td>none</td>
<td>1970</td>
<td>Mitsubishi</td>
</tr>
<tr>
<td>2</td>
<td>ethene</td>
<td>propanol, butanol, isobutanol</td>
<td>400</td>
<td>TPP</td>
<td>1974</td>
<td>Celanese, Union Carbide</td>
</tr>
<tr>
<td>3</td>
<td>propene</td>
<td>2-EH, neopentyl glycol, 1,2-diacetox 3-butene</td>
<td>4000</td>
<td>TPP</td>
<td>1984</td>
<td>BASF, Celanese, RCH-RP</td>
</tr>
<tr>
<td>4</td>
<td>1,4-diacetox 2-butene</td>
<td>vitamin-A</td>
<td>3</td>
<td>TPP</td>
<td>1970</td>
<td>BASF</td>
</tr>
<tr>
<td>5</td>
<td>1-hexene, 1-octene</td>
<td>carboxylic acids</td>
<td>18</td>
<td>TPPTS</td>
<td>1980</td>
<td>Hoffmann-LaRoche</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>isononanol</td>
<td>30</td>
<td>TPPO</td>
<td>1987</td>
<td>Mitsubishi</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>branched internal octenes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>Starting Monomer</td>
<td>Epoxide/Alcohol</td>
<td>Company</td>
<td>Year</td>
<td>Initiator</td>
<td>Molar Mass (g/mol)</td>
</tr>
<tr>
<td>-----</td>
<td>------------------</td>
<td>-----------------</td>
<td>---------</td>
<td>------</td>
<td>-----------</td>
<td>------------------</td>
</tr>
<tr>
<td>8</td>
<td>3-methyl 3-butene1-ol</td>
<td>3-methyl-1,5-petanediol</td>
<td>Kuraray</td>
<td>1988</td>
<td>bulky mono-phosphite</td>
<td>3</td>
</tr>
<tr>
<td>9</td>
<td>allyl alcohol</td>
<td>1,4-butanediol</td>
<td>Kuraray</td>
<td>1990</td>
<td>TPP + dppb</td>
<td>180</td>
</tr>
<tr>
<td>10</td>
<td>7-octenal</td>
<td>1,9-nonanediol</td>
<td>Kuraray</td>
<td>1993</td>
<td>TPPMS</td>
<td>2-3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>bulky mono-phosphite</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>1-butene</td>
<td>2-propyl-1-heptanol</td>
<td>Hoechst</td>
<td>1995</td>
<td>TPPTS</td>
<td>40</td>
</tr>
<tr>
<td>12</td>
<td>1-butene/2-butenes</td>
<td>2-propyl-1-heptanol</td>
<td>Union Carbide</td>
<td>1995</td>
<td>diphosphites</td>
<td>80</td>
</tr>
<tr>
<td>13</td>
<td>higher 1-alkenes</td>
<td>detergent alcohols</td>
<td>Kvaerner, Union Carbide</td>
<td>2001</td>
<td>DPBS</td>
<td>120</td>
</tr>
</tbody>
</table>
Even though majority of the hydroformylation applications utilize linear hydrocarbon olefins (especially $\alpha$-olefins), there are many reports on hydroformylation of functionalized olefins e.g. acetates, alcohols, halides, ethers etc., and substrates other than olefins e.g. epoxides, alcohols, halides etc., as shown in Figure 1.2. Most of the lower olefins feedstock for hydroformylation is made available from the mineral oil processing units such as cracking processes, especially thermal cracking\textsuperscript{186} whereas higher olefins are mostly produced either by ethylene oligomerization, paraffins dehydrogenation, or SHOP process.\textsuperscript{186} In the past few decades, hydroformylation of diacetoxy butenes, allyl alcohol and ethylene oxide have found industrial applications. Thus, functionalized olefins, as substrates are useful, especially for the fine chemicals and pharmaceutical industries (Figure 1.4).

**Figure 1.4.** Classification of hydroformylation based on the substrates employed.
The work presented in this thesis, in part, deals with the application of hydroformylation reaction for the synthesis of (i) hydroxypropionic acids by the hydroformylation of vinyl acetate monomer (VAM), a functionalized lower olefin; and (ii) arylpropionic acids by the hydroformylation of 6-methoxy vinyl naphthalene (MVN), which is an aryl olefin. Hydroxypropionic acids are useful in dyeing wool and to make plasticizers for resin food industry as preservatives etc., while the arylpropionic acids are important non-steroidal anti-inflammatory agents (NSAIDs). Hence, a more detailed account of the literature on lower olefins and styrenes is taken in this chapter.

1.4.1. Hydroformylation of Functionalized Lower Olefins: VAM Hydroformylation

Functionalized olefins are important substrates for hydroformylation as they produce dual functional organic compounds, which are very useful fine chemicals for organic synthesis. The commercial utility of functionalized olefins category is very well demonstrated by various processes like, Ajinomoto process for acrylonitrile hydroformylation to L-glutamic acid (Na-salt)\textsuperscript{187}, Vit. A synthesis from diacetoxy butenes, Shell process for 1,3-propanediol from ethylene oxide etc. In spite of the importance, functionalized olefins are somewhat ignored by the hydroformylation researchers mainly because of the following limitations,

1. Because of two functional groups, chemoselectivities/ regioselectivities are often low.
2. Substrates sometimes are unstable under hydroformylation conditions.
3. Products formed, sometimes acts as a catalyst poison.
4. In general reaction rates are lower than those found for hydrocarbon olefins.

VAM is an important substrate for hydroformylation because of the possibility of obtaining propanediols through VAM hydroformylation followed by hydrogenation and hydrolysis (adjacent Scheme). Both 1,3- and 1,2-propanediols (1,3-PDO and 1,2-PDO) are commercially important products, 1,3-PDO has many applications in polymer industry and 1,2-PDO is mainly used as an antifreeze agent.

Prochiral nature is yet another reason for the continued interest of researchers in VAM hydroformylation. Most of the reports on VAM hydroformylation consist of
asymmetric synthesis to obtain optically pure 2-acetoxypropanal and 1,2-propanediol. Majority of the reports uses Rhodium complexes as catalysts and like α-esterification dominance in VAM carbonylation, in VAM hydroformylation α-formylation is predominant, thus always giving 2-acetoxy propanal (branched isomer) as a major product.

2-acetoxy propanal and also other 2-alkoxypropanals, are important intermediates for a novel one step synthesis of furan carboxylic acid derivatives, which are of great industrial importance in seed-disinfection\textsuperscript{188} and in wood preservation\textsuperscript{189}. Reaction of with acetoacetamides or acetoacetates leads to 2,5-dimethyl-3-furancarboxamides or the corresponding esters in high selectivity. Adkins \textit{et al}\textsuperscript{248} reported VAM hydroformylation for the first time in their survey of usefulness and limitations of the hydroformylation. The authors have studied dicobalt-octacarbonyl catalyzed hydroformylation of many olefinic substrates and in that they have reported one reaction with VAM. With 31.5 MPa syngas pressure, at 398 K they obtained 70 % conversion of VAM. The selectivity to 2-acetoxypropanal (branched isomer) was 65 % whereas 3-acetoxy propanal (normal isomer) selectivity was 35 %. The VAM hydroformylation was not explored further by Ajinomoto Co. Inc. have prepared 2-acetoxy propanal by VAM hydroformylation with rhodium tricarbonyl as a catalyst. With 16.4 MPa, 1:1 syngas pressure at 353 K, they obtained 96 % conversion with 72 % selectivity to 2-acetoxypropanal and < 2 % selectivity to 3-acetoxypropanal. Watanabe \textit{et al}\textsuperscript{186} studied hydrido cobalt carbonyl catalyzed hydroformylation of VAM in some detail with temperature and carbon monoxide and hydrogen partial pressure effects. They could obtain 100 % conversion of VAM in 1 h at 393 K and 12.3 MPa 1:1 syngas pressure. Watanabe \textit{et al}\textsuperscript{186}. observed that with 1:3 = CO:H\textsubscript{2} at 373 K, the VAM conversion stops at 18 %. Tinkar \textit{et al}\textsuperscript{190}. have studied VAM hydroformylation as a potential route for lactic acid production. In acetic acid solvent they have taken Rh-phosphine complexes and hydroformylation is carried out at 398 K with 3.7 MPa, 1:1 syngas pressure. The products were subjected to oxidation with 0.2 MPa air and 298 K temperature. After oxidation, hydrolysis was carried out with water at 423 K for 2 hours. 60 % yield of lactic acid yield (based on VAM reacted) was obtained along with 22 % propionic acid. No β-hydroxy propionic acid was observed indicating that 3-acetoxypropanal was not formed during VAM hydroformylation.
Different rhodium precursors and phosphine ligands for VAM hydroformylation were tested by the authors and observed that 3-acetoxypropanal doesn’t form during Rh catalyzed VAM hydroformylation.

Detailed study on rhodium catalyzed VAM hydroformylation was carried out and the effect of different phosphines at various temperatures on the decomposition of 3-acetoxypropanal and found that in presence of triphenyl phosphine or tri-n-butyl phosphine all the 3-acetoxypropanal is decomposed to acetic acid and acrolein at 333 K within an hour. Effect of different phosphines on the regioselectivity of rhodium catalyzed VAM hydroformylation is also studied but none of the phosphine ligand could improve the selectivity of 3-acetoxypropanal beyond 20 %. A side reaction of catalytic decomposition of vinyl acetate with HRh(CO)(PPh₃)₃ to yield ethylene and Rh(CO)(OCOCH₃)(PPh₃)₂ was observed and this rhodium complex was isolated and characterized by elemental analysis. Different vinyl carboxylates other than VAM were also hydroformylated but 3-acetoxypropanal formed was always < 10 %. Presence of acetic acid was found to retard the hydroformylation of vinyl acetate. The speculated formation of species responsible for higher selectivity to 2-acetoxypropanal (branched isomer) and lower selectivity to 3-acetoxypropanal (n-isomer). Two alkyl species formed after the hydride additions differ in their stability and five-member ring chelate predominates thus giving more branched aldehyde.

Two reports on kinetics of VAM hydroformylation catalyzed by HRh(CO)(PPh₃)₃ and [Rh(CO)Cl]₂ catalyst complexes are available in the literature (Deshpande et al¹²⁵). With HRh(CO)(PPh₃)₃ the kinetics of hydroformylation of vinyl acetate has been investigated in the temperature range 323 – 343 K. It was observed that certain minima of concentration of and H₂ partial pressure are necessary for the reaction to proceed. Beyond such critical concentrations, the rate was found to be first order with H₂ and catalyst. With increasing CO and vinyl acetate concentrations, the rates passed through maxima, indicating substrate inhibition at higher concentrations. The observed kinetics has been discussed on reaction mechanism. Several rate equations were examined and the activation energy was found to be 17.86 kcal / mol.
1.4.2. Hydroformylation of Vinylarenes: Synthesis of NSAIDs

Hydroformylation of styrene is a convenient model reaction to study the catalysis and kinetic modeling. Several different catalyst systems have been employed in the hydroformylation of styrene and a summary of literature on styrene hydroformylation are discussed in this section. The stoichiometry of the reaction is as shown below scheme 1.2.

\[
\text{Styrene} + \text{CO} + \text{H}_2 \xrightarrow{\text{HRhCO(PPh}_3\text{)}_3} \text{2-phenylpropanal} + \text{3-phenylpropanal}
\]

Scheme 1.2. Hydroformylation of styrene

The reaction has been attempted by using ruthenium\textsuperscript{191}, Cobalt\textsuperscript{192}, rhodium\textsuperscript{193}, Takeda and cowroker\textsuperscript{194}, Iridium\textsuperscript{195} and Pt catalysts\textsuperscript{196}, but high activities and selectivities to the branched aldehydes were achieved with rhodium-phosphine systems only. The rhodium-triphenylphosphine-catalyzed hydroformylation of styrene proceeds under mild conditions (298 K, 0.1 MPa) and selectivities to 2-phenyl propanal up to 94% can be achieved. Neibecker et al.\textsuperscript{197} have demonstrated that rhodium-phoshole and rhodium-phosphanorboranadiene systems show even better activity than triphenylphosphine systems (Four times more active than triphenylphosphine) with very high selectivity towards branched aldehyde and without any hydrogenation or other side reaction under mild reaction conditions. It was also found that 1,2,5- triphenylphosphine as a ligand is independent of 1,2,5- triphenylphosphine/Rh ratio above 2, unlike PPh\textsubscript{3}, where the activity decreases with increase in P/Rh ratio\textsuperscript{198}. Rhodium catalysts with bulky phosphate ligands are more active for sterically hindered less reactive alkenes. For example phosphate-modified rhodium catalysts with tris (o-t-butylphenyl) phosphate and tris(hexafluoroisopropyl) phosphate are thirty times higher active than that of triphenylphosphine towards unreactive olefins such as 2-methyl-1-hexene, limonene, cyclohexene and methylene cyclohexene. The high rates observed are attributed to the steric and electronic properties of these phosphate ligands and their ability to stabilize unsaturated rhodium species\textsuperscript{199}. 
Non-steroidal anti-inflammatory (NSAI) agents are one of the largest classes of drugs both due to their high number and to their therapeutic interest. All these compounds have a similar mode of action: by cyclooxygenase inhibition they stop the arachidonic acid cascade to prostaglandins and thromboxane A₂, which are responsible for the inflammation mechanism. Non-steroidal anti-inflammatory agents can be classified according to their chemical structure.

Figure 1.5. Anti-inflammatory compounds

Except for the latest class of oxicams with piroxicam and isoxicam, most of the more thoroughly studied NSAI agents can be categorized into three main classes.

1) Benzoic derivatives with salicylic group where aspirin is often the highlight and with the new diflunisal compound; anthranilic compounds with mefenamic and niflumic acids.
(2) Aryl acetic acid compounds among which the most representative ones are indomethacin, sulindac, ibufenac and diclofenac.

(3) α-Aryl propionic acids with ibuprofen as the first representative.

The structures of seven nonsteroidal anti-inflammatories are presented in Figure 1.5, of these seven, only naproxen is currently marketed exclusively in an optically pure form. The major manufacturers of the respective drug are given in the parentheses with each of the structure.

The synthesis of the optically active NSAIDs is possible through three general approaches (1) synthesis of the racemic mixture followed by separation of racemates (classical resolution, direct crystallization, kinetic resolution using an enzyme), (2) use of the chiral pool (R-amino acids, R-hydroxy acids, etc.), and (3) asymmetric synthesis (noncatalytic, catalytic, enzyme mediated). There is precedent for large-scale manufacturing of pharmaceutically important, optically active compounds using each of these approaches. The large list of examples of manufacturing using chiral pool technology includes nafarelin acetate, ampicillin, and three ACE inhibitors. The decapeptide nafarelin acetate, effective in the treatment of endometriosis, is manufactured at Syntex using D-naphthylalanine. D-Phenylglycine is a key component of the antibiotic ampicillin. The top-selling ACE inhibitors, enalapril, captopril, and lisinopril, are all derived from L-proline. There is an even longer list of manufacturing processes incorporating a resolution. D-Biotin is resolved using ephedrine. Technology for resolution of (S)-naproxen using an N-alkylglucamine was already in place in the 1980s. There is considerable interest in optically pure (S)-ibuprofen, which is accessible by resolution with R-ethylbenzylamine. The least preceded manufacturing processes to obtain optically active targets employ asymmetric synthetic methods. The list of examples is small but compelling.

Synthesis of NSAIDs has experienced continuous evolution. Ibuprofen is the most commonly used NSAID, and a survey of the literature on the synthesis processes for the same shows continuous improvements with regard to the number of steps involved, the atom economy, operating conditions for the synthesis and overall process cost. Boots process, which utilized isobutyl benzene as the starting material, was the first route
employed commercially for large-scale synthesis of ibuprofen. It is a multi-step, complex synthesis involving several reagents. This was later replaced by the BHC process, which involved lesser number of steps, and was more atom-economical\textsuperscript{200}.

The BHC process, a three step catalytic route for ibuprofen using catalytic acylation, hydrogenation and carbonylation represents one of the best examples of the use of catalysis for cleaner processes in pharmaceuticals. Similarly, naproxen- the second most important member of the NSAIDs is another important drug in this category, which is currently manufactured by multistep stoichiometric synthetic routes: (a) Syntex Process starting with β-naphthol and involving stoichiometric bromination, methylation and alkylmetal coupling reactions to yield naproxen, (b) Zambon Process involving acylation of nerolin (2-methoxynaphthalene), ketalization, bromination, hydrolysis and reductive cleavage as the key steps and (c) asymmetric hydrogenation of 6-methoxy naphthacrylic acid using Ru-(S) BINAP catalyst\textsuperscript{201}

The attempts towards direct synthesis of chiral naproxen via chiral pool using (S)-lactate, and asymmetric hydroformylation followed by oxidation were also made. These routes suffer from the drawbacks like use of hazardous reagents and generation of undesired waste consisting of inorganic salts. Therefore, it is most desirable to develop an environmentally benign catalytic route for the synthesis of naproxen. Hydroformylation of vinylarenes to 2-arylpropanals under mild conditions is of great significance, since these aldehydes can be easily oxidized to corresponding acids, which are used as the largest selling anti-inflammatory class of drugs\textsuperscript{202,203}. In the conventional process, 2-arylpropionic acids are synthesized using Friedel Crafts reaction, which generate large amount of waste and expensive raw materials such as 2-chloropropionic acid\textsuperscript{204}. The preparation of 2-arylpropionaldehydes by hydroformylation of easily available corresponding vinylarenes is a simple and environmentally attractive process. A typical example of this type is the synthesis of Ibuprofen from p-isobutyl styrene as shown in Figure 1.6.
Figure 1.6. Synthesis of ibuprofen from p-isobutyl styrene.

*p-isobutyl styrene* is hydroformylated in presence of Rh(CO)$_2$Cl$_2$ at 353 K and CO/H$_2$ pressure of 10 MPa in benzene for two hours to yield p-isobutyl-2-phenylpropionaldehyde, which upon subsequent oxidation with KMnO$_4$/H$_2$SO$_4$ mixture at 288 K for 2.5 hours yields Ibuprofen. [Arakawa (1977)]. Riley and co-workers (1987) have reported an efficient method for the oxidation 2-arylpropionaldehydes using manganese stearate as catalyst and m-chloro-peroxybenzoic acid as oxidizer.

Several approaches for industrial synthesis of naproxen have also been evaluated. There are several asymmetric technologies specifically designed for naproxen manufacture$^{205}$. The Zambon process is well known, which utilizes 2-Methoxy-6-propionyl-naphthalene (MPN) prepared by Friedel-Crafts acylation of nerolin, as the starting material. The synthesis involves several steps including ketalization, bromination, and ester hydrolysis to yield a 92:8 mixture of diastereoisomers. This mixture of diastereoisomers rearranges on heating to 90°C to produce an upgraded mixture of 1-bromonaproxen esters. Reductive cleavage of the 1-bromo substituent followed by ester hydrolysis affords (S)-naproxen (ee >98%). The yield from MPN is 70-75%$^{206}$. Apparently, the process is too complicated. There was also some concern about the mechanics of tartaric acid recycle. Finally, the problems associated with manufacture of MAN are also associated with manufacture of MPN: the regioisomer problem and generation of aluminum hydroxide wastes in the Friedel-Crafts acylation.

Catalytic asymmetric hydrogenation of a naphthacrylic acid using a ruthenium (S)-BINAP catalyst (135 atm) yields (S)-naproxen (ee >98%). A tol-BINAP based catalyst would mediate hydrogenation at a significantly lower pressure (30 atm)$^{207}$. Such high pressures would necessitate a significant capital investment for any manufacturing
facility. Perhaps of greater importance is the cost associated with the hydrogenation substrate, the naphthacrylic acid. Retrosynthetic analysis suggests the naphthylacetic acid or naphthylacetylene precursors, which in turn, might be derived from BMN or MAN208. In any event, manufacture of the naphthacrylic acid would involve at least two and more likely three-process steps.

Catalytic asymmetric hydroformylation (Figure 1.7), reported by Stille et al.\textsuperscript{209}, starting with 2-methoxy-6-vinylnaphthalene (MVN) and using a rhodium catalyst with BINAPHOS ligand can produce an optically active aldehyde, which on oxidation yields (S)-naproxen. Stille et al.\textsuperscript{209} have reported the asymmetric hydroformylation of several vinylarenes using platinum catalysts. The authors examined the activity of three complexes of Pt(II) containing the chiral ligands \(l\)-(tert-butoxycarbonyl)-(2S,4S)-2-[(diphenylphosphino)methyl]-4-(dibenzophospholyl)pyrrolidine, \(l\)-(tert-butoxycarbonyl)-(2S,4S)-2-[(dibenzophospholyl)methyl]-4-diphenylphosphino) pyrrolidine, and \(l\)-(tert-butoxycarbonyl)-(2S,4S)-4-(dibenzophospholyl)-2-[(dibenzophospholyl)methyl] pyrrolidine for the asymmetric hydroformylation of styrene.

![Scheme for the asymmetric hydroformylation of MVN for direct synthesis of (S)-naproxen](image)

\textbf{Figure 1.7.} Scheme for the asymmetric hydroformylation of MVN for direct synthesis of (S)-naproxen
Various branched/normal (b/n) ratios (0.5-3.2) and enantiomeric excess (ee) values (12-77%) were obtained. When the reactions were carried out in the presence of triethyl orthoformate, all catalysts gave virtually complete enantioselectivity (ee > 96%) and similar b/n ratios. The complex l-(tert-butoxycarbonyl)-(2S,4S)-4-(dibenzophospholyl)-2-[(dibenzophospholyl)methyl] pyrrolidine gave the highest b/n (3.3), and was also used for the asymmetric hydroformylation of diverse vinyl aromatic compounds that are the precursors to anti-inflammatory agents. With the platinum complex, however, the ee's were low because of in-situ racemization, and the n/iso ratios depended strongly on the structure of the aromatic substituent. However, when the reactions were carried out in the presence of triethyl orthoformate, enantiomerically pure acetals were obtained. Some of hydroformylation of vinyl aromatic compounds are tabulated in 1.9.
Table 1.9. Hydroformylation of vinyl aromatic compounds

<table>
<thead>
<tr>
<th>Sr.</th>
<th>Substrate</th>
<th>Time, h</th>
<th>Product</th>
<th>Conv., %</th>
<th>b/n</th>
<th>(S)ee %</th>
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</thead>
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<td>10</td>
<td>39</td>
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<td>2.</td>
<td>PhOC</td>
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<td><img src="image2.png" alt="image" /></td>
<td>100</td>
<td>3.3</td>
<td>27</td>
</tr>
<tr>
<td>3.</td>
<td>PhOC</td>
<td>38</td>
<td><img src="image3.png" alt="image" /></td>
<td>90</td>
<td>5.0</td>
<td>&gt;96</td>
</tr>
<tr>
<td>4.</td>
<td><img src="image4.png" alt="image" /></td>
<td>64</td>
<td><img src="image5.png" alt="image" /></td>
<td>65</td>
<td>4.0</td>
<td>9</td>
</tr>
<tr>
<td>5.</td>
<td>Ph</td>
<td>70</td>
<td><img src="image6.png" alt="image" /></td>
<td>95</td>
<td>3.8</td>
<td>19</td>
</tr>
<tr>
<td>6.</td>
<td><img src="image7.png" alt="image" /></td>
<td>37</td>
<td><img src="image8.png" alt="image" /></td>
<td>45</td>
<td>2.0</td>
<td>39</td>
</tr>
<tr>
<td>7.</td>
<td>MeO</td>
<td>48</td>
<td><img src="image9.png" alt="image" /></td>
<td>100</td>
<td>3.3</td>
<td>37</td>
</tr>
</tbody>
</table>

There are several potential problems with this technology. First, the ligand must provide not only good stereoselectivity but also the correct regioselectivity. A linear aldehyde is often the major product of an alkene hydroformylation. Second, the branched aldehydes can racemize under the hydroformylation conditions. The racemization can be avoided by converting the aldehyde to an acetal in situ (with an orthoformate), but this approach necessitates an acetal hydrolysis later in the sequence. Other related technologies for naproxen manufacture from MVN include: catalytic asymmetric
hydroesterification\textsuperscript{210}, hydrocarboxylation\textsuperscript{211}, or hydrocyanation\textsuperscript{212}. These approaches have not received as much attention even though they may be more efficient in some respects. All of the naproxen-specific technologies discussed thus far fall into the “asymmetric synthesis” category (noncatalytic or catalytic).

One example of (S)-naproxen manufacture using the chiral pool approach was developed at Syntex in 1982. Ethyl lactate is one of a very few chiral compounds which can be used in stoichiometric quantity in a cost effective synthesis of (S)-naproxen. (S)-Ethyl lactate is converted to a mesylate. Ester hydrolysis and conversion of the acid to the acid chloride provides a chiral acylating agent. Acylation of the BMN-derived Grignard reagent yields an optically pure ketone. Ketalization with 2,2-dimethyl-1,3-propanediol, followed by rearrangement and ester hydrolysis, yields (S)-naproxen. The overall yield from BMN to (S)-naproxen is 75%.

It becomes obvious from the literature available on the hydroformylation of vinylarenes and synthetic procedures for NSAIDs that, the former holds good potential for development of an atom-economical, convenient and more eco-friendly route for the synthesis of NSAIDs. The limitations of the asymmetric MVN hydroformylation with regard to the cost of the ligands, regioselectivity issues and overall yields also indicate that the racemic synthesis using the hydroformylation-oxidation approach followed by resolution of racemates holds good potential.

1.4.3. Hydroformylation in Tandem and Sequential Synthesis

Tandem as well as sequential syntheses using cheaper feedstocks as starting materials have gained a lot of interest in an attempt to avoid the old generation multi-step syntheses and development of cleaner and cheaper alternatives. Following a general trend in organic chemistry, hydroformylation can also be integrated in tandem or domino reaction sequences\textsuperscript{213,214,215}. In short, this implies that under hydroformylation conditions reduction, nucleophilic addition or aldol condensation can be achieved directly. The application of hydroformylation in this manner is quite extensive and for this reason only a few applications in the synthesis of important organic molecules are mentioned herein.
Hydroformylation followed by C-O, C-N and C-C bond forming steps offers a convenient and versatile method for the construction of new carbon skeletons that give access to a wide variety of natural products, pharmaceuticals and other modern synthetic materials. Hydroformylation of alkenes or alkenes or alkynes having another reactive functionality, or a reaction of simple alkenes or alkynes in the presence of other organic compounds can lead to formation of cyclic or linear derivatives, some of which are of considerable value in organic synthesis due to their applications in drug chemistry. For example, direct acetal formation under hydroformylation conditions have been reported in several hydroformylation reaction sequences\textsuperscript{216, 217}. This have been applied to various substrates e.g. a-olefins, allylic and homoallylic alcohols\textsuperscript{218}, cyano olefins\textsuperscript{219}, etc. More importantly, perhaps in organic synthesis, is intramolecular acetalation. The products obtained by this type of tandem hydroformylation process offer access to a wide variety of interesting compounds which can be used as subunits in the synthesis of natural occurring products with biological and pharmacological activities\textsuperscript{220, 221}. Borole \textit{et al.}\textsuperscript{222} have reported synthesis of 1,2-propanediol (1,2-PDO) and 1,3-propanedol (1,3-PDO) by hydroformylation of VAM followed by hydrogenation of aldehydes and hydrolysis of acetoxy propanols with high yields.

The important tandem or sequential hydroformylation reactions reported in the literature has been illustrated in the Table 1.10. The importance of the reactions basically lies in access to high value-added products starting with cheaper feedstock, in lesser number of steps. Synthesis of non-steroidal anti-inflammatories starting from hydroformylation of vinylarenes, followed by oxidation of the aldehyde is another example of these types of reactions.
<table>
<thead>
<tr>
<th>Sr.</th>
<th>Reaction sequence</th>
<th>Starting material</th>
<th>Final Product</th>
<th>Application of product</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Hydroformylation - acetalation</td>
<td>1,2-disubstituted alcohols</td>
<td>Prelog Djerassi lactone</td>
<td>Pharma-antibiotics</td>
<td>223,224,225</td>
</tr>
<tr>
<td>2</td>
<td>Hydroformylation - amination</td>
<td>D- serine</td>
<td>prosopine</td>
<td>Pharmaceutical</td>
<td>226,227,228</td>
</tr>
<tr>
<td>3</td>
<td>Hydroformylation - amination</td>
<td>α-alkenylamino benzyamines</td>
<td>quinazolines</td>
<td>Anti-cancer activity</td>
<td>229,230</td>
</tr>
<tr>
<td>4</td>
<td>Hydroformylation – amination</td>
<td>benzamides</td>
<td>quinazolinones</td>
<td>Antibacterial, analgesic</td>
<td>231,232</td>
</tr>
<tr>
<td>5</td>
<td>Hydroformylation - aldol</td>
<td>silyl enol ethers</td>
<td>β-silyloxy substituted cyclic ketones</td>
<td></td>
<td>233,234</td>
</tr>
<tr>
<td>6</td>
<td>Hydroformylation -aldol</td>
<td>1,3-butadiene</td>
<td>furnish formylcyclopentenes</td>
<td></td>
<td>235</td>
</tr>
<tr>
<td>7</td>
<td>Hydroformylation - aldol</td>
<td>1,1-bis(p-fluorophenyl)-2-propynol</td>
<td>4,4-bis(p-fluorophenyl) butylbromide</td>
<td>Neuroleptic agent</td>
<td>236,237,238</td>
</tr>
<tr>
<td>8</td>
<td>Hydroformylation –hydrogenation - hydrolysis</td>
<td>Vinyl acetate monomer</td>
<td>1,2-propanediol and 1,3-propanedol</td>
<td>Antifreeze agent in food and pharmaceuticals</td>
<td>222</td>
</tr>
<tr>
<td>9</td>
<td>Hydroformylation – oxidation - hydrolysis</td>
<td>Vinyl acetate monomer</td>
<td>2-hydroxy propionic acid</td>
<td>Preservative and stabilizer in food products</td>
<td>239</td>
</tr>
<tr>
<td>10</td>
<td>Hydroformylation – amination-hydrogenation (Hydroaminomethylation)</td>
<td>Olefins</td>
<td>Secondary and tert aliphatic amines</td>
<td>Bulk and fine chemicals, pharmaceuticals</td>
<td>240</td>
</tr>
</tbody>
</table>
1.4.4. Mechanism of Hydroformylation

Hydroformylation of olefins is one of the most well studied reaction in terms of mechanism. Among the industrial hydroformylation catalysts major differences are observed between modified and unmodified systems. The catalyst used in the conventional cobalt catalyzed hydroformylation process is the hydridocarbonyl complex, HCo(CO)₄. This catalyst is stable only at higher temperatures and CO/H₂ pressures, and therefore the reaction conditions are usually very severe (20-35 MPa and 383-453 K). The discovery of rhodium catalyst for hydroformylation of olefins was a significant development in the oxo process technology. Schiller (1956) was the first to report the use of Rh carbonyls HRh(CO)₄ as a catalyst in hydroformylation reaction. The generally accepted hydroformylation mechanism for the unmodified cobalt and rhodium catalysts are shown in Figure 1.9, which involves seven elementary steps such as, (1) reaction of the metal carbonyl Co₂(CO)₈ with hydrogen to form the hydridometal carbonyl species HCo(CO)₄; (2) dissociation of CO to generate the unsaturated 16e species HCo(CO)₃; (3) coordination of the olefin RCH=CH₂ (18e);

Figure 1.9. Catalytic cycle of hydroformylation with unmodified cobalt catalysts.
(4) formation of alkylmetal carbonyl species (16e); (5) coordination of CO (18e); (6) insertion of CO to form the acylmetal carbonyl RCH₂CH₂COCo(CO)₃ (16e); (7) cleavage of the acylmetal species by hydrogen to form the aldehyde and regeneration of the hydridometal carbonyl HCo(CO)₃. This mechanism was originally proposed by Heck and Breslow (1960, 1961) for unmodified cobalt catalysts, but the mechanism is valid for unmodified rhodium complexes as well.

Considerable improvements in terms of high chemo and regioselectivities, milder reaction conditions and reaction rates were achieved when rhodium catalysts were explored in detail. This improvement in activity and selectivity was achieved by use of triphenylphosphine as a ligand. It is used commercially for the hydroformylation of propylene in the LP oxo process and also in the Union oil process. This was followed with numerous studies on the role of ligands, solvents and substrates in Rh catalysed hydroformylation. According to Wilkinson et al., HRh(CO)₂(PPh₃)₂ is the key intermediate even though several species might exist in solution in equilibrium. It has been shown from NMR studies that out of HRh(CO)(PPh₃)₃ and HRh(CO)₂(PPh₃)₃, only the latter reacts with ethylene at 298K and 0.1 MPa. Two different pathways involving associative and dissociative mechanism as proposed by Evans et al. are shown in Figure 1.10. The dissociative pathway is initiated by dissociation of a phosphine ligand from HRh(CO)₂(PPh₃)₂ followed by the addition of olefin to give coordinately unsaturated square planar complex (step 9, Figure 1.10). The addition of olefin via π complex gives σ alkyl complex (species C₃, Figure 1.9). Alkyl migration or CO insertion leads to the formation of acyl complex, which on oxidative addition of hydrogen give rise to a dihydride complex (species G, Figure 1.10). This is reported to be the rate-controlling step in the mechanism. Finally, the dihydride complex reductively eliminates the products and the catalyst is regenerated. In the associative mechanism, the alkyl complex is formed, by the addition of olefin to the bisphosphine complex (species C, Figure 1.10).
The catalytic cycle again operates through the above

![Diagram of the catalytic cycle](image)

Figure 1.10. Mechanism for hydroformylation using modified rhodium catalysts ($L = PPh_3$)

steps giving the product and the regeneration of the catalyst. Brown and Wilkinson (1970) studied the kinetics of hydroformylation of 1-hexene using HRh(CO)(PPh$_3$)$_3$ complex catalyst at 298 K. They reported that rate was first order with respect to catalyst and hexene concentration and partial pressure of hydrogen and negative order with respect to partial pressure of carbon monoxide and the concentration of excess PPh$_3$. These results have been discussed in detail on the basis of the proposed mechanism.
1.4.5. Kinetics of Hydroformylation Reaction

Compared to the large volume of literature on catalysis of hydroformylation, there are only a few reports on kinetics of this important reaction. Study of kinetics of reaction is essential in understanding the catalyst and molecular process occurring around it. In the present section a brief survey of the kinetic studies on hydroformylation reactions is presented with emphasis on the unmodified and phosphine modified catalyzed reactions.

For the catalysts Co$_2$(CO)$_8$ and Rh$_4$(CO)$_{12}$ the rate of reaction is positively influenced by increase in the concentration of catalyst, olefin and hydrogen$^{241}$. While increasing the carbon monoxide partial pressure, the rate passes through a maximum. At lower partial pressures (1 MPa) an increasing concentration of carbon monoxide enhances the overall reaction rate, indicating the necessity of carbon monoxide to generate hydridocobalt carbonyls, namely the 16e$^-$ species HCo(CO)$_3$. At higher CO partial pressures the less reactive HCo(CO)$_4$ is formed and the reaction rate decreases. Unmodified rhodium catalyst also behaves in the same way. The equation derived by Natta and Ercoi is generally accepted

$$ R = k \times [\text{substrate}] \times [\text{catalyst}] \times \frac{[P_H]}{[P_{CO}]} $$

Gholap et al.$^{242}$ reported a detailed study on the kinetics of hydroformylation of propene under industrial hydroformylation conditions (temperature range 383-423K and syngas pressures of up to 10 MPa. A rate equation was derived, which was found to explain the observed kinetic data satisfactorily. The rate of reaction was found to be linearly dependent on the propene concentration and fractional order with respect to catalyst and hydrogen. With carbon monoxide partial pressure, the rate showed a positive dependence up to a CO partial pressure of 1 MPa and negative order beyond 1 MPa. The trends observed were almost similar to that observed by Natta although they were not obtained under industrial conditions.

Brown and Wilkinson$^{243}$ studied the kinetics of hydroformylation of 1-hexene using HRh(CO)(PPh$_3$)$_3$ complex catalyst at 298K. The rate of hydroformylation was first order with respect to catalyst, hexene concentration and hydrogen partial pressure and negative order with respect to partial pressure of carbon monoxide and concentration of excess PPh$_3$. The negative-order dependence of the reaction rate at higher carbon
monoxide pressures is mainly due to the formation of di- and tri-carbonyl rhodium complexes \( \text{RCORh(CO)}_2(\text{PPh}_3)_2 \) and \( \text{RCORh(CO)}_3(\text{PPh}_3)_3 \), which are unreactive toward oxidative addition of hydrogen. At lower carbon monoxide partial pressure, the formation of these species is expected to be negligible. A positive-order dependence of the rate is observed as the monocarbonyl species \( \text{RCORh(CO)(PPh}_3)_2 \) is stabilized.

Brown and Wilkinson\(^{244}\) studied the kinetics of hydroformylation of 1-hexene using \( \text{HRh(CO)(PPh}_3)_3 \) complex catalyst at 298K. The rate of hydroformylation was first order with respect to catalyst and hexene concentration and hydrogen partial pressure. The rate was negative order with respect to partial pressure of carbon monoxide and PPh\(_3\) concentration. The observed trends have been explained based on the mechanism shown in Scheme 1.2. The negative order dependence of the reaction rate at higher carbon monoxide pressures is mainly due to the formation of di- and tri-carbonyl rhodium complexes \( \text{(RCO)}\text{Rh(CO)}_2(\text{PPh}_3)_2 \) and \( \text{(RCO)}\text{Rh(CO)}_3(\text{PPh}_3)_3 \), which are unreactive towards oxidative addition of hydrogen. At lower carbon monoxide partial pressure, the formation of these species is expected to be negligible. A positive order dependence of the rate is observed for CO at low pressure as the mono carbonyl species \( \text{(RCO)}\text{Rh(CO)(PPh}_3)_2 \) is stabilized.

Deshpande et al\(^{245}\) have extensively studied kinetics and reaction engineering aspects of hydroformylation of a variety of olefinic substrates such as hexene\(^{245a}\), vinyl acetate\(^{66b}\), allyl alcohol\(^{66c}\), decene\(^{66d}\), dodecene\(^{66e}\), styrene\(^{66f}\) and 1,4 diacetoxy butene\(^{66g}\). The trends observed are generally first order with respect to catalyst, substrate (upto a certain concentration) and hydrogen, whereas inhibition was observed with partial pressure of CO. Kalck and co-workers\(^{246}\) have studied the hydroformylation of terminal olefins using a dimeric \([\text{Rh}(\mu-\text{S}^\dagger\text{Bu})(\text{CO})(\text{PPh}_3)]_2\) catalyst. Preliminary kinetic studies show that CO has an inhibiting effect but surprisingly the reaction is also inhibited by high pressure of hydrogen.

The kinetics of hydroformylation of propylene\(^{247a}\), allyl alcohol\(^{71b}\) and 1-butene\(^{71c}\) using supported liquid phase catalyst (SLPC) \( \text{HRh(CO)(PPh}_3)_3 \) has been investigated. The reaction order for propylene was found to be one, while for hydrogen the order was close to zero. The reaction order in CO pressure was found to 0.23 at lower CO pressure.
to 0.08 at higher CO pressure. The kinetics of hydroformylation of 1-octene, styrene and linalool was studied using Rh/TPPTS supported aqueous phase catalyst (SAPC). The trends were similar to those observed in the homogeneous medium except for the substrate inhibition observed at higher concentration. Similar observations were reported for the kinetics of hydroformylation of 1-hexene using Rh/TPPTS complex exchanged on anion exchange resin.

In general, the trends observed for kinetics of hydroformylation using phosphine-modified rhodium catalysts for different parameters can be summarized as follows.

1. First order in catalyst concentration
2. First order in hydrogen partial pressure
3. First order in olefin concentration and in some cases substrate inhibition at higher concentration.
4. At lower CO partial pressure ($P_{CO} < 1$ MPa), positive order and at high CO partial pressure, negative order

1.5. Scope and Objectives of the Thesis

Multiphase reactions in which reactants in different phases are converted into one or more selective products using homogeneous or heterogeneous catalyst provide the basis for a large number of chemical, petrochemical, biochemical and polymer processes. Liquid Phase Oxidation (LPO) and hydroformylation are two of the most prominent examples of multiphase catalytic reactions in industry. These reactions have been employed for synthesis of a variety of industrial products such as aldehydes, ketones, alcohols, and carboxylic acids etc, which proceed through a cleaner, cheaper and eco-friendly alternate route than the conventional pathways.

The state of the art on multiphase catalytic reactions shows that, the focus to analyze multi-step, complex multiphase reactions has been inadequate. Considering the increasing importance of catalysis in complex catalytic reactions for fine chemicals, pharmaceuticals and specialty products, there is a need to investigate case studies on catalysis and reaction engineering aspects. At the same time, it is also important to explore new types of catalysts and catalytic systems, which can provide better activity,
selectivity to the desired products. In the present era of green chemistry, the major emphasis is on alternative pathways for fine and specialty chemicals with the aim to enhance atom economy, and to reduce use or generation of wastes. The tremendous potential that the area of catalysis carries can further be strengthened and put to commercial use in a better way if the kinetics and reaction engineering aspects of catalytic transformations are thoroughly studied and implemented. Scale-up of new oxidation chemistries from invention to commercial operations can be facilitated and proceed with a higher probability of success if reaction engineering principles are incorporated and applied at various stages in process development program. For example, evaluation of new catalyst technology for activity, selectivity, and other measures of performance requires the use of modern laboratory reactor systems in which transport disguises are negligible so that the true kinetics can be studied as part of the catalyst screening methodology. Proper understanding of all of these may lead to further advancement of the catalysis and reaction engineering of the present age. Keeping these objectives in the background, the specific targets have been chosen for the present work as follows,

- Selective liquid phase oxidation of toluenes to benzaldehydes
- Selective oxidation of ethylbenzene using hydrotalcite like compounds as catalyst
- Hydroformylation of 6-methoxy-2-vinlnaphthalene as a potential route for the synthesis of naproxen
- Hydroformylation of vinyl acetate monomer as potential route for the synthesis of hydroxy propionic acids
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