SYNOPSIS

The thesis entitled "**Studies on Catalytic Oxygen Transfer Reactions in Organic Synthesis**" is divided into two parts

Part A Catalytic Aerobic Oxidation of Olefins uisng a novel Ruthenium(II) complex

Part B Aerobic Oxygenation of Cycloalkanes with Nanostructured Amorphous Metals/Alloy as Catalysts

Part A is subdivided into three chapters

Part A: Chapter 1

In this chapter, a general methodology for the facile conversion of simple olefins to epoxides using a novel ruthenium(II) complex is described Ruthenium-bis(oxazoline) complex **1** was synthesized by refluxing trans-tetrakis(acetonitrile)dichloro ruthenium with 4,4',5,5'-tetrahydro-bis(oxazoline) in ethanol (Scheme-1)

When the oxidation of alkenes was carried out with ruthenium-bis(oxazoline) **1**
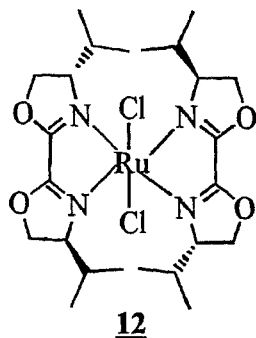
Scheme-1
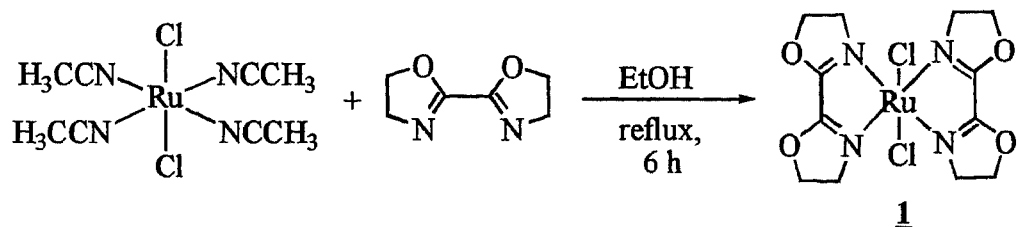
(2 5 mol%) in dichloromethane (25 °C) in the presence of molecular oxygen as the oxidant and isobutyraldehyde as the co-reductant and sodium bicarbonate as buffer excellent yields of epoxides were obtained This catalytic epoxidation with ruthenium-complex **1** is stereospecific E-Stilbene (**2**) and Z-stilbene (**4**) under the reaction conditions afford the corresponding epoxides stereospecifically in high yields Styrene epoxide (**6**) which is highly unstable under conditions of peracid epoxidation is quite stable under the present reaction conditons Another salient feature of the present methodology is the high regioselectivity Thus in the oxidation of 4-vinylcyclohexane (**8**) catalysed by **1**, the monoepoxide **9** was the exclusive product isolated in very good yield Under the conditions of epoxidation, 5-cholestene (**10**) afforded the 5β, 6β-epoxide (**10A**) in excess of 94% selectivity and in excellent yield (Scheme-2)

Scheme-2

Part A: Chapter 2

In chapter 1, it was demonstrated that oxidation of 5-cholestene (**10**) gave rise to 5β,6β-epoxide as the major product In Chapter 2, the potential of the ruthenium complex **1** towards epoxidation of Δ⁵-unsaturated steroid derivatives was explored and it was found to yield the corresponding 5β,6β-epoxides in very good yields and with >88% stereoselectivity (Scheme-3)

Scheme-3

The nature of 3β-ester has only a marginal effect on the rate of the reaction and has no effect on the stereoselectivity of the reaction The stereochemistry of the substituent at C-3 does not have any profound effect on the stereoselectivity of epoxidation The present catalytic epoxidation methodology using ruthenium catalyst **1** is compatible with functional groups like carbonyl and ether linkage in the steroid molecule

Part A: Chapter 3

This chapter deals with the attempts towards asymmetric epoxidation of unfunctionalized olefins A novel ruthenium bis(oxazoline) **12** was prepared using a strategy similar to the one depicted in Scheme-1, by treating (-)-(4S, 4'S)-4,4'-diisopropyl-4,4',5,5'-tetrahydrobis(oxazoline) ligand with trans-RuCl₂(CH₃CN)₄ in ethanol Potential of the ruthenium complex **12** towards asymmetric oxygen transfer was explored Initially E-stilbene was chosen as substrate for study Under aerobic conditions, ruthenium catalyst **12** (2 5 mol%) in dichloromethane (25 °C, 9 h) in the presence of isobutyraldehyde as co-reductant and sodium bicarbonate as buffer resulted in very good yield of epoxide But, unfortunately the reaction was not enantioselective at room temperature However, at –10 °C, 8% ee was observed (Scheme-4)
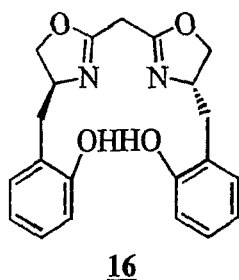
Scheme-4
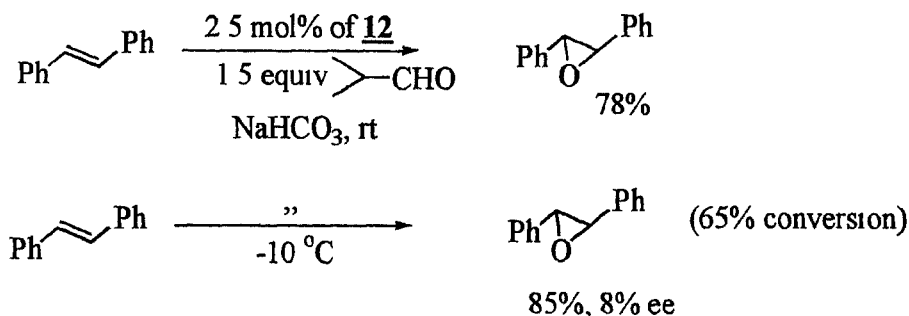
Epoxidation of 1,2-dihydronaphthalene was carried out under similar conditions as described earlier and the reaction led to the formation of corresponding epoxide (-10 °C, 4 days) in 65% yield Unfortunately, however, the epoxidation was not enantioselective. When sodium periodate was used as the oxidant, epoxidation of E-stilbene afforded 38% of E-stilbeneoxide after 48 h at –10 °C Under similar conditions 1,2-dihydronaphthalene yielded 34% of 1,2-dihydronaphthaleneoxide In both cases very poor enantioselectivity (<5%) was obtained

Another ligand (-)-(4S,4'S)-4,4'-diisopropyl-2,2'-methylene-4,4',5,5'-tetrahydro-bis(oxazoline) (**14**), which has a methylene spacer in between the oxazoline rings that might bring the substituents closer to ruthenium core, was prepared as depicted in scheme-5

<div align="center">Scheme-5</div>
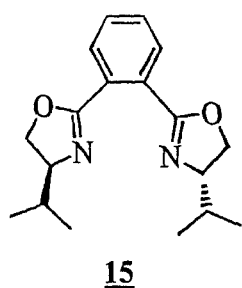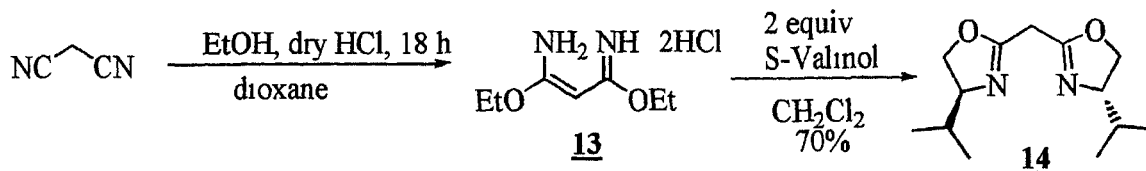
But unfortunately, ligand **14** did not form the complex like RuCl₂(biox)₂ Then the spacer between two oxazoline rings was changed to be part of a benzene ring Accordingly, ligand **15** was prepared, and was treated with RuCl₂(CH₃CN)₄ Again, it failed to form the complex Various inorganic precursors like RuCl₂(DMSO)₄, RuCl₂(Pyridine)₄, under various solvents (dichloroethane, toluene, benzene) were tried with these bis(oxazoline) ligands **14** and **15** Unfortunately, the corresponding RuCl₂(biox)₂ could not be obtained All the reactions and modifications led to a mixture of products

A novel optically active C_2-symmetric tetradentate bis(oxazoline) ligand **16**, having the similar topology as in 'salen' was designed and the synthesis of the ligand **16** was accomplished as shown in scheme-6 2-Benzyloxybenzyl alcohol (**17**) was prepared by alkylation of 2-hydroxybenzyl alcohol using benzyl bromide in dry DMF in the presence of potassium carbonate 2-Benzyloxybenzyl alcohol (**17**) was treated with phophorous tribromide in toluene to yield 2-benzyloxybenzyl bromide (**18**) Diethylacetamido malonate (**19**) was alkylated with 2-benzyloxybenzyl bromide (**18**) in the presence of sodium ethoxide to yield diethyl-1-acetamido-2-(2'-benzyloxyphenyl)-1,1-ethanedicarboxylate (**20**) N-Acetyl-2-benzyloxy-phenylalanine (**21**) was obtained by hydrolysis of diethyl-1-acetamido-2-(2'-benzyloxyphenyl)-1,1-ethanedicarboxylate (**20**) in 2 N aqueous sodium hydroxide solution (±)-R/S-N-Acetyl-2-hydroxyphenylalanine (**22**) was obtained by deprotection of (±)-dl-N-Acetyl-2-benzyloxyphenylalanine (**21**) using 10% Pd/C at room temperature and atmospheric pressure of H₂ (±)-R/S-N-Acetyl-2-hydroxyphenylalanine (**22**) was subjected

to resolution with *aspergillus* acylase at 40 °C for 24 h to give rise to optically pure (-)-S-2-hydroxyphenylalanine (<u>23</u>) (-)-S-2-Hydroxyphenylalanine (<u>23</u>) was subjected to reduction using NaBH$_4$/I$_2$ procedure The corresponding amino alcohol <u>24</u> which was isolated as hydroiodide salt, was condensed with imidate salt <u>13</u> in the presence of triethylamine to yield (-)-(4S,4'S)-4,4'-di(2-hydroxyphenyl)-2,2'-methylene-4,4',5,5'-tetrahydro-bis-(oxazoline) (<u>16</u>) in 72% yield

Scheme-6
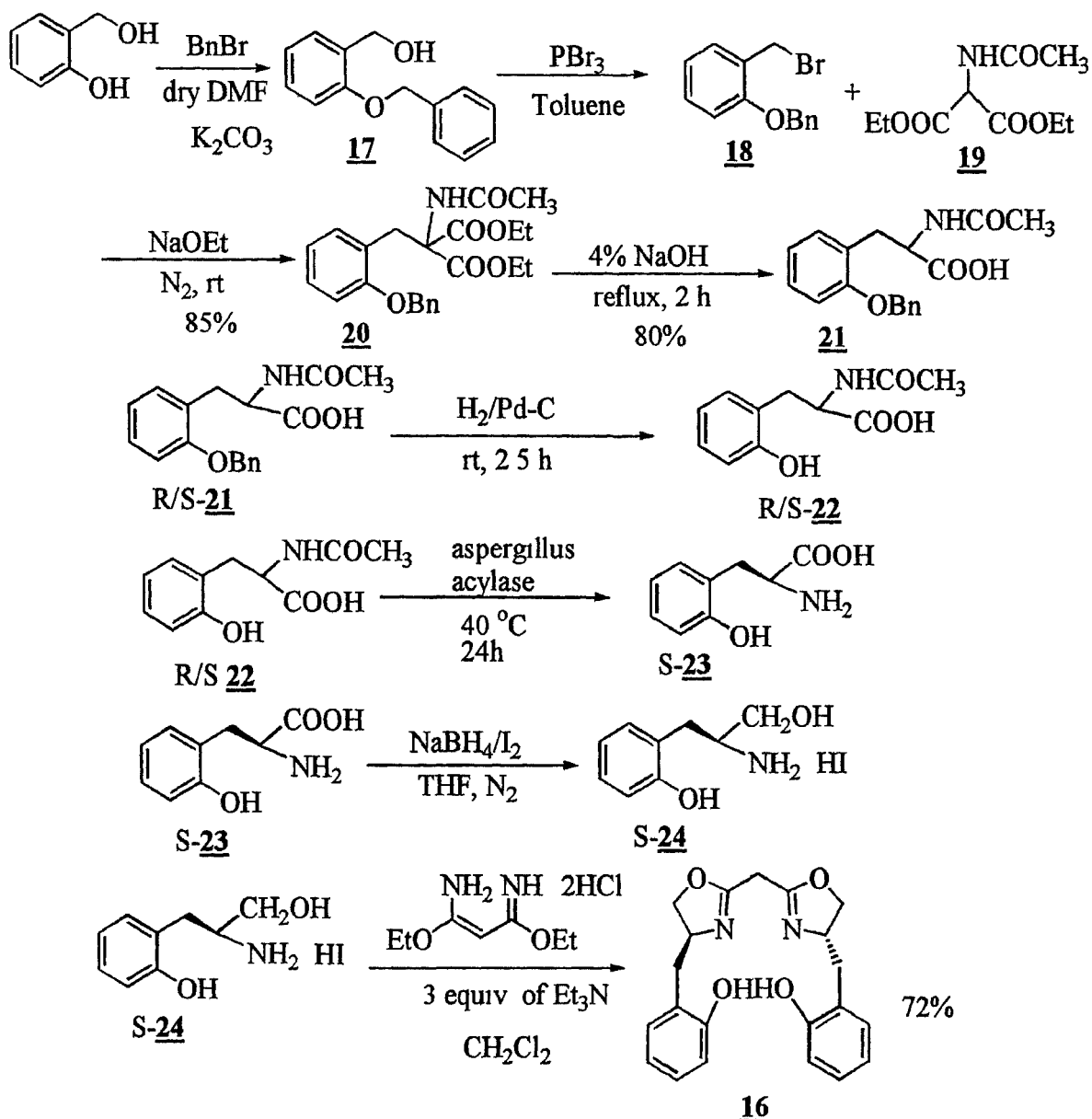
All attempts to form a manganese complex of the ligand <u>16</u> with Mn(OAc)$_2$ were unsuccessful The potential of this chiral tetradentate bis(oxazoline) ligand <u>16</u> for asymmetric synthesis remains to be explored

The oxidation of cyclohexane turns out to be the least efficient of all major industrial processes On the other hand it is an extremely important commercial process Typically, cyclohexane is air-oxidized at 160 °C and 15 atm in the presence of cobalt naphthenate as an oxidation initiator, giving, after 40 min of total reaction time, only 4% conversion of cyclohexane with 80% selectivity for cyclohexanone and cyclohexanol (one ol ratio 1 2) Suslick and co-workers demonstrated the first sonochemical use in the synthesis of metallic glass powders using microscopically extreme (yet macroscipically mild) conditions induced by high-intensity ultra-sound The sonolysis of iron pentacarbonyl, a volatile organometallic compuund, produces nearly pure amorphous iron particles (10-20 nm) and its utility as an efficient catalyst in Fischer-Tropsch hydrogenation of carbon monoxide and for hydrogenolysis and dehydrogenation of saturated hydrocarbons had been reported The amorphous powder was roughly ten times more reactive per gram than 5-μm-diameter crystalline powder At 250 °C, the overall activity for cyclohexane dehydrogenation to benzene and hydrogenolysis was >30 times greater for sonochemically produced amorphous iron relative to crystalline iron

We have been involved in the study of catalytic activity of nanostructured amorphous metal/alloys Amorphous Fe-Ni alloy was prepared by ultrasonic irradiation of the solution of $Fe(CO)_5$ and $Ni(CO)_4$ in the ratio of 1 4, in decalin at 273 K, under 100 to 150 kPa (1 to 1 5 atm) argon, with a high intensity ultrasonic probe After 3 h of irradiation, a black powder was obtained which was centrifuged and washed with dry pentane in a glove box Centrifuging and washings were repeated at least five times, and the product was dried in vacuum Similarly nanostructured amorphous iron and cobalt powders have been prepared The amorphous nature of the alloy particles was confirmed by techniques like, SEM and X-ray diffraction

When the oxidation of cyclohexane was carried out in the presence 1 mol% of nanostructured amorphous Co catalyst, isobutyraldehyde, catalytic amount of acetic acid at 10 atm of oxygen in the absence of any solvent at 25 °C, it was observed that the conversion was 11% based on the cyclohexane equivalent to aldehyde used The efficiency of the reaction was >85% i e in the product the selectivity for cyclohexanone and cyclohexanol is >85% in the ratio of 1 6 respectively

The aerobic oxidation of cyclohexane was carried out with other nanostructured metals/alloy under various pressures of oxygen The best conversion was achieved at 40 atm of oxygen at room temperature (25 °C) without any solvent (Scheme-7)
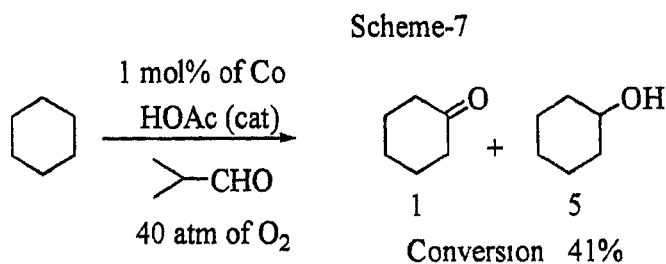
Scheme-7

1 mol% of Co
HOAc (cat)
$\succ$—CHO
40 atm of O_2

1   5
Conversion 41%

Table-1 Aerobic oxidation of cyclohexane using amorphous metals/alloy

Entry	Substrate	Nanometal/ Alloy used	Conversion (%)	One Ol
1		Fe	40	1 4 5
2	Cyclohexane	Co	41	1 5
3		$Fe_{20}Ni_{80}$	38	1 3 6

When nanostructured amorphous iron was used as catalyst the conversion was found to be 40% with 78% selectivity for cyclohexanol and cyclohexanone in the ratio of 4 5 1 respectively In the case of nanostructured amorphous cobalt, the conversion was 41% with 80% selectivity for cyclohexanol and cyclohexanone Whereas nanostructured amorphous alloy ($Fe_{20}Ni_{80}$) under similar conditions effected 38% conversion at 25 °C

Oxidation of adamantane with various nanostructured metal/alloys was carried out using 1 mol% of catalyst, 1 5 equivalent of isobutyraldehyde, catalytic amount of acetic acid, and O_2 (40 atm) at 25 °C and the results are summarised in scheme-8 and it was found that in general the conversion was in the range 52-57%

Scheme-8

Aerobic Oxidation of Adamantane using amorphous metals/alloy

H   OH
1 mol% Co

1   2   +   3   +   4
Conversion   88   8   4
57%
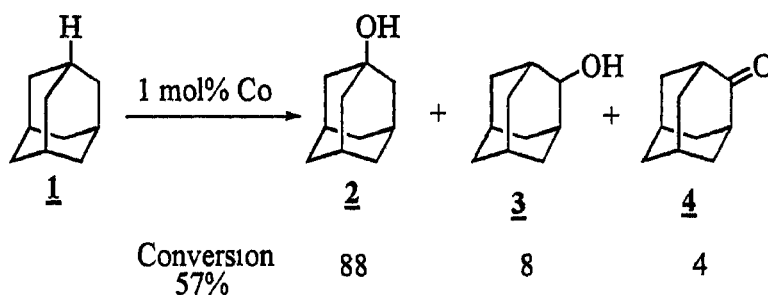
When methylcyclohexane was subjected to oxidation under the similar conditions with the above mentioned nanostructured amorphous metal/alloy as catalysts, the following results were obtained (Table-2)

Table-2 Aerobic oxidation of methylcyclohexane using amorphous metals/alloys

Entry	Substrate	Nanometal/ alloy used	Conversion (%)	One Ol
1	Methylcyclo-	Fe	32	1 1
2	hexane	Co	38	1 3
3		$Fe_{20}Ni_{80}$	36	1 2

Scheme-9
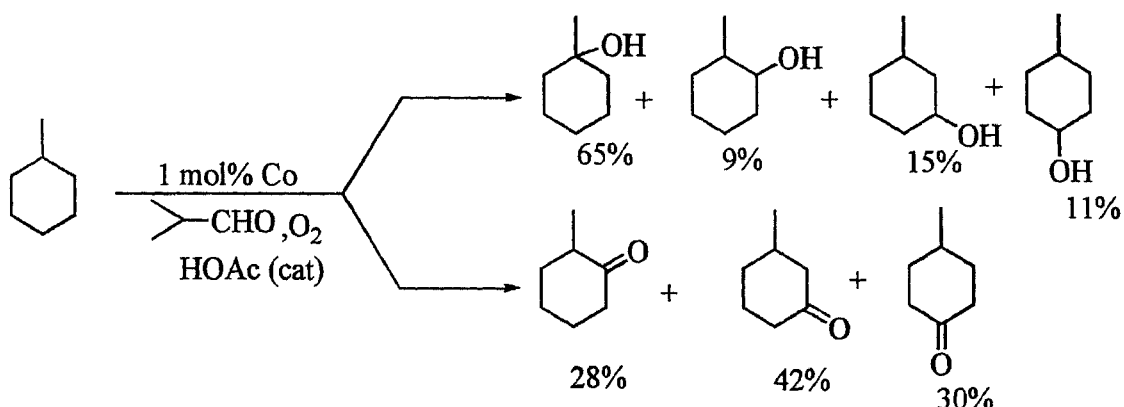
The oxidation of methylcyclohexane under similar conditions occurs only at secondary and tertiary carbon-hydrogen bonds and primary carbon-hydrogen bonds remain unaffected In the reaction catalyzed by amorphous cobalt the product was found to be a mixture of cyclohexanones and methylcyclohexanols as shown in scheme-9

When the oxidation was carried out in the presence of nanostructured amorphous metals and alloy ($Fe_{20}Ni_{80}$) (O_2, 40 atm) at 70 °C the conversion was found to be much higher (56-67% conversion) than what was observed at 25 °C (Table-3) It is interesting to note that there is not much change in the selectivity for cyclohexanone and cyclohexanol but change in the ratio of cyclohexanone and cyclohexanol is observed The selectivity for cyclohexanone and cyclohexanol in the case of nanostructured amorphous iron catalyst is 76% whereas in the case of amorphous alloy it was found to be 77% The ratios of cyclohexanone and cyclohexanol was found to be almost 1 1 5

Table-3 Aerobic oxidation of cyclohexane using amorphous metals/alloy at 70 °C

Entry	Substrate	Nanometal/ Alloy used	Conversion (%)	One Ol
1		Fe	62	1 1 5
2	Cyclohexane	Co	67	1 2
3		$Fe_{20}Ni_{80}$	56	1 2

It is noteworthy that there is no change in the efficiency of the reaction The change in the ratio might be due to the alcohol formed getting oxidized to the ketone under the reaction conditions

List of Publications

1 Stereospecific and Regioselective Catalytic Epoxidation of Alkenes by a Novel Ruthenium(II) Complex under Aerobic Conditions **Venkitasamy Kesavan** and Srinivasan Chandrasekaran *J Chem Soc Perkin Trans 1* **1997**, 3115

2 A Highly β-Stereoselective Catalytic Epoxidation of Δ^5-Unsaturated Steroids with a Novel Ruthenium(II) Complex under Aerobic Conditions **Venkitasamy Kesavan** and Srinivasan Chandrasekaran *J Org Chem* **1998**, 6999

3 Catalytic Aerobic Oxidation of Cycloalkanes with Nanostructured Amorphous Metals and Alloys **Venkitasamy Kesavan, P S Sivanand** and Srinivasan Chandrasekaran (Communicated)