Chapter 1

General Introduction
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1.1. Introduction

The year 1951 was marked by the discovery of ferrocene molecule whose unique sandwich structure attract many chemists to the point that today it is one of the most widely studied molecule in organometallic chemistry. In addition to its unique structural feature other properties such as low price, thermal stability and insensitivity to moisture as well as oxygen also fuels to its popularity as most sought after organometallic compound. Ferrocene and its derivatives found wide applications in chemistry including nano science, bioactivity, sensor activity and as catalyst. Out of these, the last two found especial attention from the chemists. Till date various literature are available where ferrocene derivatives are applied for the catalysis of various reactions as well as sensor activity.

1.2. Recent Advances of Ferrocene Based Ligands in the Catalysis of Various Reactions

In recent times, a great number of both chiral as well as achiral ferrocene based ligands have been discovered for the application in various reactions including asymmetric synthesis. Ferrocene acts as electron rich aromatic compound in electrophilic aromatic substitution and it can stabilize carbocations at benzylic like position. Moreover it can be easily undergo lithiation and dilithiation at 1,1'-position. These are the chemical property of ferrocene that allow easy synthesis of functionalized and substituted ferrocene.

In the synthesis of ferrocene based catalytic system various substitution pattern have been applied. These include 1-substituted, 1,1'-disubstituted, 1,2-disubstituted, 1,1',2-trisubstituted, 1,1',2,2'-tetrasubstituted as well as
polysubstituted ferrocenes. Similarly from the point of view of the atom, through which the ligand binds to the metal, the most common ferrocene based ligand systems have phosphorous and/or nitrogen. Some alternative atom combinations are phosphorous-sulfur and phosphorous-oxygen. Some of the common ferrocene based ligand systems are given in the Fig. 1.1.

Fig 1.1. Representative Structure of (A) 1-substituted ferrocene ligands, (B) 1,1'-disubstituted ferrocene ligands, (C) 1,2-disubstituted P-ligand, (D) 1,2-disubstituted P,P ligand, (E) 1,2-disubstituted P,N ligand, (F) 1,2-disubstituted P,S; P,O and N,O ligand, (G) 1,1',2-trisubstituted ferrocene ligands, (H) 1,1',2,2'-tetrasubstituted and poly substituted ferrocene ligands, (I) Bis-ferroeene ligand and (J) Symmetrical achiral ferrocene ligands.
The important reaction where ferrocene based ligands were employed extensively are hydrogenation, coupling reaction, addition reaction and cycloaddition reactions.

1.2.1. Ferrocene Based Ligands in the Hydrogenation of Alkenes, Ketones and Imines

Homogeneous asymmetric hydrogenation of C=C and C=O as well as C=N bond are one of the most frequently studied reaction for the application of ferrocene based ligands. Rh is the most common metal applied for the hydrogenation reaction.

Boaz et al. have applied for the first time a bidantate P,P type ferrocene based ligand for the asymmetric hydrogenation of (Z)-dehydroamino acid derivative (Scheme 1.1).² The process is highly enantioselective and highly efficient for various protecting group for the nitrogen atom.

Chan and coworkers have carried out extensive study on the stereoselective hydrogenation of dehydro-α-amino acid using many ferrocenylethyl scaffolds.³ This approach resulted in the desired product with enantiomeric excess upto 99.6%.
Zheng et al. have developed a new family of chiral ferrocene, based on phosphine-phosphoramidite ligands. The ligand gives excellent enantioselectivity in the Rh-catalyzed hydrogenation of enamides and methyl (Z)-acetamidocinnamate even at low catalyst loadings (Scheme 1.3). However it was observed that effective enantioselective hydrogenation of enamides and dehydro-α-amino acid is possible without the presence of phosphine moiety in the above mentioned ligand. Zheng et al. have synthesized another ferrocene based monophosphoramidite ligand for the enantioselective synthesis of chiral alkylphosphonates bearing a β-stereogenic center, using Rh-catalyzed asymmetric hydrogenation of corresponding β-substituted β,γ-unsaturated phosphonates.

![Scheme 1.3](image1.png)

**Scheme 1.3**

Kim et al. have synthesized a novel chiral (iminophosphoranyl)ferrocenes by the reaction of 1,1'-bis(diphenylphosphino)-2-[(dimethylamino)ethyl]ferrocene with aryl azides. The ligand have been effectively employed in the Rh catalyzed asymmetric hydrogenation of (Z)-2-Acetamidocinnamate, Methyl (Z)-2-Acetamidoacrylate and (E)-2-Methylcinnamic Acid.

Chen and co-workers have synthesized a new class of ferrocene based C₂-symmetric diphosphine ligand and applied to the hydrogenation of α-substituted cinnamic acids with ee upto 99.6% (Scheme 1.4).

![Scheme 1.4](image2.png)

**Scheme 1.4**
Recently, Zhang et al. have applied Iridium/S,S-f-binaphane (a ferrocene based ligand) based catalyst for the asymmetric hydrogenation of a wide range of 3,4-dihydroisoquinolines with high enantioselectivity as well as high turnover number. It was observed that the use of I$_2$ as additive increase the performance of the catalyst. Earlier Reetz et al. have synthesized a ferrocene based diphosphonite ligand from ferrocene and (R)- or (S)-BINOL. Asymmetric hydrogenation of itaconate and 2-acetamido methyl acrylate with this ligand in presence of Rh catalyst results in the enantioselectivity as high as 99.5%. Kim and coworkers have demonstrated that Ir and Rh complexes of chiral (iminophosphoranyl) ferrocenes are highly effective catalyst for the hydrogenation of di and tetrasubstituted olefins. However in some cases Rh catalyst is better than its Ir counterpart. Zhang et al. have synthesized chiral diphosphine ligand from D-mannitol. Complex of this ligand with Rh give high enantioselectivity and reactivity in the asymmetric hydrogenation of dehydroamino acid derivatives (Scheme 1.5).

\[
\text{R} \quad \text{COOR} \quad \text{NHAc}
\]

\[
\text{Rh(COD)} \quad \text{PF}_6 (1 \text{ mol%}) / \text{Ligand (1 mol%)} \quad \text{H}_2
\]

\[
\text{NHAc} \quad \text{COOR}
\]

Scheme 1.5

Enantioselective hydrogenation of various $N$-(3,5-dimethyl-4-methoxy)phenylimines was performed by Konchel et al. in the presence of new P,N-ferrocenyl complexes with iridium forming (R)-$N$-(3,5-dimethyl-4-methoxy)phenylamines in high yields with high enantioselectivity. These amines can be easily deprotected using CAN to get primery amines.

\[
\text{Ph} \quad \text{OMe} \quad \text{Ph}
\]

\[
\text{NH} \quad \text{CO}_2 \text{Me}
\]

Scheme 1.6

\[
\text{Tol} \quad \text{MeOH (4 l), } \text{rt} \quad \text{H}_2, 10 \text{ bar, 6h}
\]

\[
\text{Ph} \quad \text{OMe} \quad \text{Ph}
\]

\[
\text{NH} \quad \text{CO}_2 \text{Me}
\]

5
Chen and co-workers have prepared a series of ferrocene based aminophosphine ligands for the enantioselective hydrogenation of ketones. The enantioselectivity is mainly dependent on the carbon centered chirality of the ligand. Some other ferrocene based ligands which have been employed in the hydrogenation of ketones include BoPhoz\textsuperscript{2b} and Fc-Phox\textsuperscript{14} (Fig. 1.2).

![Figure 1.2. Structures of BoPhoz and Fc-Phox](image)

Rh catalyzed transfer hydrogenation of ketone catalyzed by ferrocene based planner chiral $N$-heterocyclic carbene ligand promoted transfer hydrogenation of ketone was put forwarded by Kuang \textit{et al.}\textsuperscript{15} Earlier, Cadierno and co-workers have prepared dimeric $\{\text{RuX(\mu-X)(CO)(PP)}\}_2$ (X=Cl, Br; PP= 1,1'-bis(diphenylphosphino)ferrocene, 1,1'-bis(diisopropylphosphino)ferrocene). These catalysts are found to be extremely active towards transfer hydrogenation of ketones.\textsuperscript{16} Zhang \textit{et al.} have synthesized a new chiral Schiff base ligand and employed in ruthenium catalyzed asymmetric transfer hydrogenation of simple ketones. Upto 94% ee with 90% conversion was obtained through this methodology.\textsuperscript{17} Nishibayashi \textit{et al.} have reported a one pot $\alpha$-alkylation of ketone followed by hydrogen transfer reaction of the elongated ketone using Ir and Ru based catalyst (Scheme 1.7).\textsuperscript{18} This methodology is a good example of sequential transition metal catalyzed reaction involving two compatible metal complexes.

![Scheme 1.7](image)
1.2.2. Coupling reactions

1.2.2.1. Heck Reaction

Both inter as well as intramolecular Heck reaction have been carried out using ferrocene based ligands. In 1991, Cabri and co-workers have provided for the first time a ferrocene based ligand, DPPF(1,1'-bis(diphenylphosphino)ferrocene) with palladium as catalyst (Scheme 1.8).\textsuperscript{19} Latter Hallberg \textit{et al.} have carried out further study on the Heck reaction between allyltrimethylsilane with aryl triflates using the same catalyst system.\textsuperscript{20} Skrydstrup and Hansen extended the use of DPPE in the heck reaction of α, β-unsaturated tosylate/mesylates and electron rich olefins.\textsuperscript{21} In 2000, Hou \textit{et al.} have shown that both regio as well as stereoselective intermolecular Heck reaction can be carried out using chiral ferrocene based ligands.\textsuperscript{22} It has been observed that absolute configuration of the reaction product can be controlled just by changing the configuration and/or size of the planar chiral group of these ligands.

![Scheme 1.8](image)

A combination of ferrocenyli\textit{tetraphosphate} 1,1',2,2'-tetakis(diphenylphosphino)-4,4'-\textit{di-tert}-butylferrocene and [PdCl(η3-C3H5)]\textsubscript{2} results in a catalyst which can effectively catalyzed the reaction between aryl halides with various alkenes.\textsuperscript{23} Very low catalyst loading was necessary with this catalyst and very high TON was observed. Guiry and co-workers has demonstrated the efficiency of Fc-Phox as ligand in the Pd catalyzed Heck reaction. It has been shown
that the ligand can be successfully used in both intramolecular\textsuperscript{24} as well as intermolecular\textsuperscript{25} Heck reaction.

\textbf{1.2.2.2. Suzuki Coupling}

The Suzuki coupling provides a general method for the C-C bond formation between aryl halides and aryl boronic acid or ester. The first example of the application of ferroocene based ligand in the Suzuki reaction was put forwarded by Thompson \textit{et al.} in 1988.\textsuperscript{26} They applied \textit{l,r-}bis(diphenylphosphino)ferrocene (dpff) bonded palladium to couple substituted bromo- and chloropyrazinoate esters with aryl and heteroaryl boronic acids (\textbf{Scheme 1.9}).

\begin{equation}
\begin{array}{c}
\text{R} \quad \text{X} \quad \text{N'} \quad \text{NH}_2 \\
\text{N} \quad \text{C} \quad \text{O}_2\text{CH}_3
\end{array}
\begin{array}{c}
+ \text{ArB(OH)$_2$} \\
\text{3 mol\% [Pd(OAc)$_2$/dpff}$ \\
\text{NEt$_3$, DMF, 90 $^\circ$C, 12h}$ \\
\text{R} \quad \text{N} \quad \text{C} \quad \text{O}_2\text{CH}_3
\end{array}
\end{equation}

\textbf{Scheme 1.9}

Latter, Suzuki and co-workers have demonstrated that the complex PdCl$_2$(dpff) is also a good catalyst for the coupling of 1-alkenyl- and aryl triflates with 9-alkyl-9-borabicyclo[3.3.1]nonane (9-R-9-BBN) derivatives.\textsuperscript{27} After their successful study, many research groups have utilized this catalytic system to carry out Suzuki reaction on wide range of substrate.\textsuperscript{28}

In 2004, Kwong \textit{et al.} have synthesized an air stable ferrocenyl triarylphosphine ligand from ferrocene. The ligand is highly active in the Pd catalyzed Suzuki reaction.\textsuperscript{29} Even highly hindered aryl bromides undergo Suzuki coupling at room temperature to give the expected product in high yield. Latter, Sheloumov and co-workers have synthesized a series of ferrocene based pincer complexes (\textbf{Fig. 1.3}) of palladium to carry out Suzuki coupling between aryl halides and boronic acid.\textsuperscript{30} These catalysts are not only efficient for Suzuki reaction but it shows moderate activity under conditions of phase transfer catalysis also.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure13.png}
\caption{Ferrocene based pincer complexes}
\end{figure}
An effective 1,1'-bis(oxazolinyl)ferrocene-based palladium catalysts have been synthesized by Lee which can promote Suzuki reaction between aryl bromide and boronic acid.\(^{31}\) In addition, the catalyst shows promising result in the heck reaction in presence of K\(_2\)CO\(_3\) as base. Colacot and co-workers have synthesized Cp\(_2\)Fe(PR\(_2\))\(_2\)PdCl\(_2\) (R = i-Pr, t-Bu). These complexes were stable in air. It has been observed that the t-Bu version of the two catalysts is more active for unreactive and sterically hindered aryl chlorides. Comparison with the other commercial catalysts such as dpptPdCl\(_2\), (Ph\(_3\)P)\(_2\)PdCl\(_2\), (Cy\(_3\)P)\(_2\)PdCl\(_2\), DPEPhosPdCl\(_2\), dppbPdCl\(_2\), dppePdCl\(_2\), Pd(t-Bu\(_3\)P)\(_2\), and [Pd-(t-Br)(t-Bu\(_3\)P)]\(_2\) shows superior activity of the catalyst.\(^{32}\) More recently Zheng have synthesized a series of ferrocene based phosphine-triazine ligands for efficient Suzuki reaction catalyzed by Palladium.\(^{33}\)

Other ferrocene based ligands which have been employed in the Suzuki reaction include (2,2,2-triferrocenylethyl)diphenylphosphane,\(^{34}\) 1,1'-P/O-Ferrocenyl Ligands,\(^{35}\) \([\gamma-C_5H_4(CH_2)_2N(CH_3)_2]_2\)Fe,\(^{36}\) and some ferrocene-based phosphinimine-phosphine ligand.\(^{37}\)

**1.2.2.3. Allylic Substitutions**

Various types of ferrocene ligands have been applied in the asymmetric allylation using palladium as metal source. These ferrocene ligands have PP, PN, PS, NS, SS, and PPNN coordinating sites. Moyano and co-workers have applied a PN type of ligand in the allylic alkylation of 1,3-diphenyl-2-propenyl acetate and report a ee upto 99.6% (Scheme 1.10).\(^{38}\)
Latter, they have shown that an analogous ligand to the above PN type ligand but with a geminal dimethyl group at the C5 position of the oxazoline ring leads to significant enantioselectivity in the asymmetric allylic alkylation reaction of dimethyl malonate with 2-cyclohexenyl acetate (Scheme 1.11).  

\[
\text{MeO} \text{C}^+ \text{CO;Me}
\]

\[
\text{[Pd(h}_3\text{C}_5\text{H}_5)\text{C}_1\text{]}_2 (5-2 \text{ mol%})
\]

\[
\text{XOoMe Ligand (1 1-5 mol%)}
\]

\[
\text{BSA (3 0 equiv), LiOAc (cat)}
\]

\[\text{Scheme 1.11}\]

Jin et al. have shown that same enantioselectivity as in Scheme 1.10 can be obtained by using phosphinoimidazolidine based ligand (Fig. 1.4a) and slight change of solvent. 40 They have applied benzene instead of CH\(_2\)Cl\(_2\) in that reaction. Zheng and coworkers have successfully applied ferrocene based phosphine-triazine (Fig. 1.4b) ligand in the asymmetric allylic alkylation reaction with dimethyl malonate.41 Same group have applied ferrocene based meta-nitrophenyl imine (Fig: 1.4c) asymmetric allylic alkylation reaction of 2-cycloalkenyl esters with dimethyl malonate.42

\[\text{Figure 1.4}\]

Hou and coworkers have developed many new methodologies for the application of ferrocene based ligands in the asymmetric allylic alkylation. They have first synthesized chiral P,N-1,1'-disubstituted ferrocene based ligand and
demonstrated its applicability in the asymmetric allylic alkylation of monosubstituted allylic acetates.\textsuperscript{43} Latter, they have designed some more ferrocene based ligands to promote the allylic alkylation and amination of dienyl esters.\textsuperscript{44} Some of the ligands were shown in the Fig. 1.5.

![Figure 1.5](image)

**Figure 1.5**

Chan and coworkers have synthesized air-stable ferroceny1 PS ligands with heterocyclic moieties. Their application in the palladium catalyzed allylic alkylation of indoles shows that high enantioselectivity can be achieved irrespective of the steric or electronic nature of indoles.\textsuperscript{45} Latter, Fukuzawa \textit{et al.} have synthesized a series of ferrocene based PS ligands based on a triazoleferroceny1 ethyl backbone. These PS ligands were applied in allylic alkylations, etherifications, and aminations of 1,3-diphenylprop-2-enyl acetate catalyzed by Pd complexes. It has been observed that the novel ligand is highly effective for the reactions, especially for asymmetric allylic etherifications with enantioselectivity as high as 90\%.\textsuperscript{46}

Although in most of the cases palladium based catalyst have been utilized in the allylic alkylation, some examples are available in which other metals such as nickel and copper have been applied. Alexakis and co-workers have attained great success in the Cu–phosphoramidite-catalyzed asymmetric allylic alkylation with Grignard reagents.\textsuperscript{47} Latter, Feringa \textit{et al.} demonstrated that Taniaphos is a highly effective ligand in the Cu-catalyzed asymmetric allylic alkylation of primary allyl bromides with Grignard reagents.\textsuperscript{48} Maiti \textit{et al.} developed a procedure for Ni\textsuperscript{0}-catalyzed enantioselective intramolecular asymmetric-allylic amination to prepare vinylglycinol derivatives with the help of ferrocene ligands.\textsuperscript{49}
1.2.3. Addition Reactions

Most common organometallic reagent for the nucleophilic 1,2-addition to aromatic aldehyde is diethylzinc. Various ferrocene based ligands have been applied in the enantioselective addition to aromatic aldehydes. For example, ferrocenyl aziridino alcohols can provide very high ee in the reaction between aldehyde and diethylzinc (Scheme 1.12).50

![Scheme 1.12](image)

It has been demonstrated that enantioselective addition of phenylacetylene to aldehydes using the combination phenylacetylene/diethylzinc, catalyzed by the 1,1'-disubstituted oxazoline–hydroxyalkyl ferrocene produces propargyl alcohols up to 99% ee (Scheme 1.13).51

![Scheme 1.13](image)

In 2002, Bolm et al. have synthesized diarylmethanols by diethylzinc promoted addition of aryl boronic acids to aldehydes in the presence of the ferrocenyl–oxazoline carbinol ligand.52 During their study it was observed that, even small amount of dimethoxy poly(ethylene glycol) increase the yield as well as enantiomeric excess. In some of the cases diphenylzinc in combination with
diethylzinc has been used as a phenyl source in the reduction of aldehyde to alcohols. In this case also presence of dimethoxy poly(ethylene glycol) is highly beneficial. It not only increases the yield and ee but also decrease the amount of catalyst needed by a factor of about ten.\textsuperscript{53}

Although diphenylzinc is highly efficient as phenyl source, high price associated with it makes it undesirable for such type of reactions. Letter triphenyl borane is found to be low cost and easily handable alternative phenyl source for the synthesis of arylphenylmethanols. Bolm and co-workers have developed chiral ferrocene based catalyst for asymmetric phenyl transfer to aldehydes using boron-based aryl sources (Scheme 1.14).\textsuperscript{54}

![Scheme 1.14](image)

Recently, coupling of alkynes with aldehydes, in both its reductive and alkylative state, has emerged as an efficient method for the synthesis of useful allylic alcohols. Jamison and co-workers first put forward catalytic enantioselective coupling reaction between alkyne and aldehyde employing $[\text{Ni(cod)}_2]/\text{PBu}_3$ as catalyst and $\text{Et}_3\text{B}$ as reducing agent through the use of monodentate phosphines.\textsuperscript{55} Latter, Jamison and coworkers have developed $\text{FcPPh}_2$, a novel class of P-chirogenic monodentate ferrocenyl phosphines. This ligand is found to promote the Ni-catalyzed reductive couplings between aliphatic internal alkynes and aldehydes to give the allylic alcohols with complete E selectivity in all cases (Scheme 1.15).\textsuperscript{56}

![Scheme 1.15](image)
Millar et al. have extended this procedure for the coupling of conjugated enynes with aldehydes\textsuperscript{57} and ketones\textsuperscript{58} using desymmetrized FcPPh\textsubscript{2} replacing a phenyl group by a 2-isopropylphenyl or a o-tolyl group (Fig. 1.6).

![Figure 1.6](image)

**Figure 1.6**

In 2003, Jamison and Patel have developed intermolecular coupling of alkynes and imines.\textsuperscript{59} Latter, they have developed the enantioselective variant of this reaction using P-chirogenic ligand (Scheme 1.16).\textsuperscript{60} It was observed that as long as the group attached to the nitrogen atom is aliphatic in nature, high regioselectivity, complete E selectivity and high enantioselectivities are obtained.

![Scheme 1.16](image)

**Scheme 1.16**

Another most important and widely used synthetic tool for C-C bond formation is the conjugate addition to $\alpha,\beta$-unsaturated carbonyl compounds. Earlier, zink base reagents have been used as Michal acceptors for effective 1,4-addition reactions. However in 2004, Feringa and coworkers have demonstrated that Grignard reagent can be used as nucleophiles for the copper-catalyzed asymmetric conjugate addition to a variety of activated cyclic (Scheme 1.17)\textsuperscript{61} and acyclic\textsuperscript{62} alkenes using ferrocenyl diphosphine Taniaphos or Josiphos-type ligands.

![Scheme 1.17](image)

**Scheme 1.17**
It was observed that in the addition to cyclohexenone, Taniaphos was the most efficient while in the addition to acyclic (E)-enones, Josiphos was most efficient (Fig. 1.7).

![Figure 1.7](image)

Zheng and coworkers have synthesized a new family of chiral bis(1-ferrocenylethyl)amine-derived monodentate phosphoramidite ligands. The synthesized compounds have been successfully applied to Cu-catalyzed asymmetric 1,4-conjugate addition of diethylzinc to a variety of α,β-unsaturated compounds. It has been demonstrated that 99% ee was obtained for nitroalkenes at -78 °C and >98% ee for cyclohexenone at -30 °C.

Ohta and coworkers have synthesized ferrocene based ligand, (S,Rp)-[1-(2-bromoferrocenyl)ethyl]diphenylphosphine. The ligand is active in presence of Pd(dba)$_2$ for both 1,4-addition aryloboronic acids to α,β-unsaturated ketone as well as 1,2-addition to aldehyde. In both the cases high enentioselectivity as well as good yield was observed.

The Josiphos/Cul catalyst system was later extended to the conjugate addition of Grignard reagents to α,β-unsaturated esters and α,β-unsaturated thioesters. Other results for conjugate addition using ferrocene based ligands include Cu(OTf)$_2$-catalyzed addition of Et$_2$Zn to chalcones, enantioselective Rh-catalyzed conjugate addition of aryl boronic acids to α,β-unsaturated pyridyl sulfones and Cu-catalyzed conjugate addition of the organoaluminium reagents Et$_3$Al and [Me$_2$AlCH=C(Me)(Ph)] to cyclohexenone.
1.2.4. Cycloaddition and Pericyclic Reactions

One of most famous cycloaddition reaction is Diels Alder reaction and other [4+2] cycloaddition reaction. However, till now only a few ferrocene-based Lewis acids have been applied in this transformation. Carretero and coworkers have reported that the dichloride complex of the o-Tol-Fesulphos ligand ([ligand-PdCl2] (10 mol%) (Scheme 1.18, ligand a), in combination with AgBF4 (20 mol%), acts as an efficient chiral Lewis acid catalyst when N-acryloyloxazolidinone is used as the dienophile. In this case, the endo cycloadduct was obtained in 95% ee at -78 °C.

Fukuzawa and co-workers reported that the Yb(OTf)3 complex of the bisferrocenyl oxazoline ligand (Scheme 1.18 Ligand b), provides moderate levels of enantioselectivity (up to 80% ee) in the above reaction (Scheme 1.18).

It has been demonstrated that Copper (I) complexes of Fesulphos ligands can effectively catalyzed the asymmetric aza-Diels–Alder reaction of N-sulfonyl imines with Danishefsky-type dienes. The copper bromide complex of the ferrocene ligand in combination with AgClO4, provides good yields and enantioselectivities for a wide variety of substrates, including N-sulfonyl imines of aromatic, alkenyl, and enolizable aliphatic aldehydes. The reaction gives the Mannich-type addition product, which is easily transformed into the valuable optically active Diels–Alder cycloadduct upon addition of trifluoroacetic acid to the reaction mixture (Scheme 1.19).
In 2002, Tanaka et al. have described a rhodium(I) catalyzed [4+2] cycloaddition of 4-alkynals with alkynes to form 4-alkylidene cyclohexanones.\(^7\) Latter, Noguchi et al. have put forward the enentioselective version of this reaction.\(^7\) The proposed procedure is based on cationic rhodium(I) catalyst system [Rh-(cod)\(_2\)]BF\(_4\)/Ferrocene based ligand (Scheme 1.20). Very high enantioselectivity was obtained for a variety of 4-pentynals and 2-alkynylbenzaldehydes with aryl, alkenyl, and alkyl substituents at the alkyne.

Another important cycloaddition reaction is [3+2] cycloaddition. Still first example on the enentioselective [3+2] cycloaddition reaction was reported only in 2002 by Zhang and co-workers.\(^7\) They have found that AgI complex of the bisferrocenyl P,P ligand in the presence of the Hunig’s base led to complete endo selectivity as well as enantioselectivity in the cycloaddition of a variety of iminoesters with dimethyl maleate (Scheme 1.21).
Zhang and co-workers have demonstrated that copper(I) complexes of the Fc-Phox ligand promote the asymmetric 1,3-dipolar cycloaddition of iminoesters with acrylates in excellent \textit{exo} selectivity and enantioselectivity (Scheme 1.22, Ligand a).\textsuperscript{76} Latter, Hou and co-workers have carried out the reaction using same Cu source and similar type of ferrocene ligand.\textsuperscript{77} They have found that the nature of the aryl group on the phosphorus atom of the ligand have dramatic effect on the \textit{endo}/\textit{exo} selectivity of the product. It has been observed that electron-rich phosphines gave the \textit{exo} cycloadduct as the major or the only product with excellent enantioselectivities while ligand with two electron withdrawing substituents on each phenyl ring at phosphorus, afforded mainly the \textit{endo} isomer.

Zheng and coworkers have synthesized a series of chiral ferrocene-based phosphine–phosphoramidite ligands.\textsuperscript{78} Out of these, the ligand with a stereogenic P-center in the phosphino moiety displayed the best diastereo- and enantioselectivities in the Ag(I)-catalyzed asymmetric [3+2] cycloaddition of azomethine ylides with dimethyl maleate.
Another reaction where ferrocene based ligands have been applied is [3,3] rearrangement reactions. First catalytic asymmetric [3,3] rearrangement of allyl imidates to allylic amides, reported by Overman and coworkers in 1997.\(^{79}\) Thereafter, many palladium based catalyst system have been reported. Overman and coworkers have prepared ferrocenyl-oxazoline palladacyclic scaffold which can catalyzes the allylic rearrangement of both E and Z prochiral primary allylic \(N\)-(4-methoxyphenyl)benzimidates to give the corresponding protected benzamides in high yield and good enantioselectivity (Scheme 1.23).\(^{80}\)

Peters and co-workers have prepared structurally related complexes derived from pentamethylferrocenyl- and pentaphenylferrocenyl- 2-imidazolines (Fig. 1.8a) which provided excellent yields and enantioselectivities in the aza-Claisen reaction of several trifluoroacetimidates.\(^{81}\) They have later extended their work on aza-Claisen reaction using less electron-rich catalyst (Fig. 1.8b) which shows very good activity.\(^{82}\) In 2009, same group have developed a planar chiral pentaphenylferrocenyl oxazoline palladacycle complex.\(^{83}\) This complex is more reactive and has a broader substrate tolerance than the other two catalyst systems for asymmetric aza-Claisen rearrangements. Moyano and co-workers have reported a ferrocenyl oxazoline palladacycle complex (Fig. 1.8c) which provided moderate yields and up to 90% \(ee\) in the \(\text{Pd}^{II}\)-catalyzed aza-Claisen rearrangement of (\(E\))-3-phenylallyl-(\(N\)-phenyl)benzimdate.\(^{84}\)
Zheng and co-workers have applied their P,N,N phosphine–heteroaryl imine ligands in the ruthenium(II)-catalyzed asymmetric cyclopropanation of styrene with ethyl diazoacetate. Latter Kim et al. have put forwarded enantioselective and cis-diastereoselective cyclopropanation of olefins catalyzed by ruthenium complexes of (iminophosphoranyl)ferrocenes.

1.2.5. Miscellaneous Reactions

In addition to above mentioned reactions there are many reactions of ferrocene based ligands. Long and coworkers have applied ferrocene-substituted bis(imino)pyridine iron and cobalt complexes for the redox active polymerization of ethylene. Uemura and co-workers reported in 1999 a novel palladium(0)-catalyzed arylation of tert-cyclobutyl alcohol to give γ-arylated ketones. Subsequently, the enantioselective variant of this reaction was developed by using ppfa-type ligands by Uemura et al.

1.3. Recent Advances in Ferrocene Based Sensors

The selective recognition and sensing of various molecules by synthetic host molecules has become an important area of research activity. In addition to that, the design and synthesis of functional molecules that could serve as molecular devices for sensors, has emerged as a practical tool for this purpose. Recently, ferrocene based molecules found much attention in the field of sensor mainly due to its well defined electrochemical behaviors. Nevertheless other properties of ferrocene
molecules including fluorescence activity are also used as a tool for the molecule sensing.

The ferrocene based sensors can be mainly divided into two broad groups viz. Sensors for inorganic molecules and secondly sensors for organic molecules.

1.3.1. Ferrocene Based Sensors for Inorganic Molecules

1.3.1.1. Cation Sensors

There are many cation in nature which are important for human survival such as Ca, Mg, Na, K eth. However, cations such as lead, mercury and cadmium possesses serious threat for nature. So it is highly important to sense and recognizes various metal ion accurately and efficiently.

Among various metal ion mercury is a highly toxic metal ion which occurs in the environment through a variety of natural and manmade sources such as gold mining, solid waste incineration, and the combustion of fossil fuels. Many literatures are available in which ferrocene based molecules have been applied for selective recognition of mercury. Li and co-workers have developed a highly selective optical-electrochemical chemosensor for Hg$^{2+}$ based on a rhodamine dye bearing both a ferrocenyl group and an 8-hydroxyquinoline moiety.90 The proposed molecule can be used as a fluorescent probe for monitoring Hg$^{2+}$ in living cells using confocal laser scanning microscopy.

Scheme 1.24

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Duan et al. have designed and prepared a new chemosensor that combines a ferrocene unit and a rhodamine block via the linkage of a carbohydrazone binding unit. The compound shows selective mercury sensing in water using both electrochemical as well as optical methods. The chemosensor is highly active and signal response was obtained for Hg$^{2+}$ concentration as low as 1 ppm.

Molina and coworkers have designed and synthesized a series of ferrocene based sensors for cadmium ion detection (Fig. 1.9).

![Figure 1.9](image)

All the three dyes are highly selective for cadmium ion in solution. While compound (a) can be used in aqueous media mercury detection, compound (b) and (c) are active in acetonitrile solution. Moreover, in all the cases visual colour change is associated with addition of cadmium ion. Latter, they have synthesized a new chemosensor molecule based on a ferrocene-quinoxaline dyad which recognizes mercury (II) cations in acetonitrile solution through chromogenic as well as electrochemical procedure.

Kim and coworkers have developed a selective, sensitive, and importantly, re-usable electrochemical sensor for Hg$^{2+}$ ion detection. Their sensor is based upon ferrocene modified DNA molecule. The sensor has a very low detection limit (0.1 μM) and negligible response to other metal ions.

Recently, Ghosh and coworkers have designed two simple triazole-based multisignaling chemosensors that selectively bind with the Hg$^{2+}$ cation. These chemosensors not only exhibit the capability of highly selective detection of Hg$^{2+}$ cation through a fluorescent probe but also active in colorimetric sensing of Hg$^{2+}$ cation, thus allowing the potential for “naked-eye” detection over some other cations.
Lead is rank second in the list of toxic metals. Various health hazard associated with lead poisoning are memory loss, irritability, anemia, muscle paralysis, and mental retardation. Lead poisoning occurs mainly due to its application batteries, gasoline, and pigments. Molina et al. have synthesized a sensor molecule based on a deazapurine ring.\textsuperscript{96} This sensor distinguishes Pb\textsuperscript{2+} ion from other metal cation including strong competitor such as Hg\textsuperscript{2+} and Zn\textsuperscript{2+} with the help of redox as well as fluorescence properties. This molecule represents the first example of a Pb\textsuperscript{2+} chemosensor molecule, which combines redox detection, and the sensitivity of fluorescence with the ease of a colorimetric technique. Latter they have extended their work to some more ferrocene based sensors.\textsuperscript{97} All these molecules not only show strong interaction to Pb\textsuperscript{2+} but also distinguish it from other metal ions by electrochemical as well as spectroscopic techniques. The same group has reported a ferrocene-imidazophenazine heteroditopic receptors.\textsuperscript{98} Dyad (a) behaves as a highly selective redox/chromogenic/fluorescent chemosensor molecule for Pb\textsuperscript{2+} cations in CH\textsubscript{3}CN/H\textsubscript{2}O (9:1). On the other hand, dyad (b) bearing two fused pyridine rings, displays the same type of sensing properties but now toward Hg\textsuperscript{2+} cations.
Recently, Pandey and coworkers have synthesized a series of ferrocene derivatives viz 4-[2,5-diferrocenyl-4-(4-pyridyl)imidazolidin-1-ylmethyl]pyridine (1), ferrocenylmethylenepyridin-3-ylmethylamine (2), \( N,N'-\text{bis} \) (ferrocenylmethylene)-2,4,6-trimethylbenzene-1,3-diamine (3), and 6-ferrocenyl-5,6-dihydro[4,5]imidazo[1,2-c]-quinazoline (4). 1–3 are nonfluorescent, while 4 displays moderate fluorescence and chromogenic, fluorogenic, and electrochemical sensing selectively toward \( \text{Hg}^{2+} \) and \( \text{Pb}^{2+} \) ions. It represents the first example of a ferrocene/quinazolidine as a chemosensor for \( \text{Hg}^{2+}/\text{Pb}^{2+} \) through chromogenic, fluorogenic, and electrochemical responses.

Zinc, which is the second most abundant transition metal in natural biological system is essential nutrient required for cellular processes as well as in the DNA repair. Molina and coworkers have synthesized a new sensor, based on 1,1-disubstituted ferrocene for selective determination of \( \text{Zn}^{2+} \) (Fig. 1.12a). The chemosensor not only display the capability of electrochemical and fluorescent detection but also facile colorimetric sensing of \( \text{Zn}^{2+} \) metal cation thus allowing the potential for “naked-eye” highly selective detection over some other cations, including the strong competitor \( \text{Cd}^{2+} \). Latter they have extended their work on \( \text{Zn}^{2+} \) selective sensors by designing ferrocenophanes (Fig. 1.12b,c), in which the two ferrocene subunits are linked through two aldiminic or iminophosphorane moieties. In this structural motif, the aldimine groups act as a highly selective binding site for \( \text{Zn}^{2+} \) cations, whereas the iminophosphorane bridges display an unusually strong binding affinity towards \( \text{Li}^+ \) cations, which could be explained by an additional \( \text{Li}^+ \cdots \text{Fe} \) interaction.

![Figure 1.12](image-url)
Many ferrocene chemosensors for the effective detection of copper ion have been developed in the last decade. Delgado et al. have synthesized bis[1,1-N,N-(2-picoly]aminomethyl]ferrocene. This compound forms 1:1 complex with Cd$^{2+}$ and Pb$^{2+}$, 2:2 complex with Ni$^{2+}$ and 1:1 complex with Cu$^{2+}$. Electrochemical study of the compound clearly indicate that it is selective sensor for copper in environments containing transition and posttransition metal ions, such as nickel, zinc, cadmium and lead. Later Torroba and coworkers have designed ferrocene derivatives bearing two donor-acceptor systems. These molecules selectively sense Cu$^{2+}$ and benzoate, acetate, or cyanide anions by cooperative binding of the two $\alpha,\alpha'$-groups bonded to the ferrocene moiety. In the same year, Kandaswamy et al. have designed and synthesized ferrocene functionalized macrocyclic receptor, 1,8-bis(ferrocenylmethyl)-5,5,7,12,12,14-hexamethyl-1,4,8,11-tetraazacyclotetradecane. Electrochemical study of the synthesized receptor in dioxane–water system reveals that it can selectively sense Cu$^{2+}$ ion in presence of various metal cations on the basis of anodic shift of the ferrocene–ferrocenium half-wave potential. More recently, Kandaswamy et al. have reported a copper selective multi-channel signaling sensor molecule with two binding site containing nitrogen as Schiff’s base. A novel fullerene-ferrocene based sensor was developed by Menon et al. in 2009. A study on the complexation with different metal ion shows highly efficient and exclusive binding with Cu$^{2+}$ ion indicating a probable sensor for Cu$^{2+}$ ion.

Other metal ion which have been studied for selective sensor using ferrocene based molecules include Mg$^{2+}$, Ca$^{2+}$, Cr$^{3+}$, Li$^+$, and lanthanides.

1.3.1.2. Anion Sensor

Anions are frequently used in day to day life. They play crucial role in biology, medicine and environment. So it is highly desirable to design systems that can effectively detect various anions. Many report on the application of ferrocene based sensors for the selective detection of dihydrogen phosphate, a biologically important anion, have been reported. Fang et al. have synthesized a series of Ferrocene compounds bearing multiple amido groups that bind with the H$_2$PO$_4^-$ ion selectively over other anions (AcO$^-$, I$^-$, NO$_3^-$, ClO$_4^-$, and HSO$_4^-$). It has been
observed that the receptors with substitution in one ring of the ferrocene molecule form 1:1 complexes with the $\text{H}_2\text{PO}_4^-$ ion, whereas the two-arm receptors can accommodate two $\text{H}_2\text{PO}_4^-$ ions. Beer and coworkers have prepared calixarene based anion receptors featuring di- or tetraurea binding sites. It has been observed from NMR study that the prepared ferrocene based calixarene forms 1:1 complex with anions. All receptors show potential as electrochemical sensors for anions, with dihydrogen phosphate displaying markedly larger cathodic shifts than chloride and benzoate.\textsuperscript{113} Latter they have synthesized more ferrocene based calixarene receptors for selective detection of $\text{H}_2\text{PO}_4^-$.\textsuperscript{114} Moutet \textit{et al.} have observed that films synthesized by oxidative polymerization of pyrrole-containing (ferrocenylmethyl)trialkylammonium cations are able to electrochemically sense the dihydrogenphosphate anion in organic electrolytes.\textsuperscript{115} They have also shown that surface modified electrodes by (ferroacenyl)amidopropylpyrrole derivative can also selectively detect dihydrogen phosphate anion.\textsuperscript{116} Recently, Kenny and coworkers have synthesized $N$-(ferrocenyl)2 and $N$-(ferroacenyl)2 cystine dimethyl ester derivatives. These compounds were then successfully immobilized onto gold electrodes for the anion sensing in aqueous media. This immobilization of receptors onto gold electrode surfaces thus facilitates anion recognition particularly dihydrogen phosphate in an aqueous medium.\textsuperscript{117}

Among the biologically important anions, fluoride is of particular interest due to its various adverse effects in the human body. Lin and coworkers have synthesized 1,1'-di-(2"",4""-di-nitrophenylhydrazino-β-carbonyl)-ferrocene and investigated its property as fluoride sensor. It was demonstrated that it is highly selective fluoride ion sensor based on electrochemical as well as colorimetric study.\textsuperscript{118} Aldridge \textit{et al.} have synthesized a fluoride and cyanide ion sensor using ferrocene derivative of Lewis acid.\textsuperscript{119} In the same year Cheng \textit{et al.} have designed and synthesized redox anion receptors based on calix[4]pyrrole bearing ferrocene amide. \textsuperscript{1}H NMR titration study of the compound reveals that they were selective towards $\text{F}^-$ and $\text{AcO}^-$ ions.\textsuperscript{120} Other ferrocene based sensors for fluoride ion detection include polyborylated ferrocenes,\textsuperscript{121} 1,\textit{n}-diaza[\textit{n}]ferrocenophanes,\textsuperscript{122} and imidazolium and ferrocene-based macrocyclic receptors.\textsuperscript{123}
Shaabani and coworkers have shown that calix[4]arene derivatives containing ferrocene units at the upper rim can be used as sensor for various anions. They have synthesized two such type of compound and both the compounds are selectivity for chloride and bromide anions in comparison with hydrogen sulfate anion with Cl\(^-\) producing the largest shifts of the ferrocene/ferrocenium redox couple.\(^{124}\) Most of the study on the use of ferrocene based sensors for the selective detection of chloride ion was carried out by Beer et al.\(^{125}\)

In addition, there are some examples for the selective detection of sulfite ion using ferrocene based sensors. They include multiwalled carbon nanotubes/ferrocene-branched chitosan composites\(^ {126}\) and modified carbon nanotubes paste electrode\(^ {127}\).

### 1.3.1.3. Neutral Molecule Sensors

Of the neutral molecules H\(_2\)O\(_2\) is the most studied species in the sensor chemistry using ferrocene based sensors. In 2002, Armada et al. have described a H\(_2\)O\(_2\) sensor based on the modified electrode using ferrocene containing polymer. The redox polymer consists of a siloxane-based homopolymer, with pendant electronically communicated ferrocenyl moieties which can effectively sense H\(_2\)O\(_2\).\(^ {128}\) Latter, many research groups have applied modified electrode system for H\(_2\)O\(_2\) detection. Li and coworkers have used Fc-filled single-walled carbon nanotubes (Fc@SWNTs) modified electrode is very effective in the H\(_2\)O\(_2\) detection in solution.\(^ {129}\) Ju and coworkers have synthesized a novel biosensor for H\(_2\)O\(_2\) by trapping horseradish peroxidase (HRP) in a new ormosil composite doped with ferrocene monocarboxylic acid–bovine serum albumin conjugate and multiwall carbon nanotubes (MWNTs). The ormosil was prepared by polymerizing 3-(aminopropyl)triethoxysilane and 2-(3,4 epoxycyclohexyl)-ethyltrimethoxy silane.\(^ {130}\) Zhao et al. have immobilized ferrocene on room temperature ionic liquids (RTILs), 1-ethyl-3-methyl imidazolium tetrafluoroborate ([EMIM][BF\(_4\)]).\(^ {131}\) The system gives pair of stable, well-defined and quasi-reversible redox peak of ferrocene at pH 7.0 phosphate buffer. It has been observed that both anodic and cathodic peak currents of ferrocene vary linearly with the concentration of hydrogen.
peroxide (H$_2$O$_2$). Recently, Li and coworkers have synthesized Ferrocene functionalized graphene (Fc-GN). Electrochemical study in an aqueous solution of Fc–GNs modified glassy carbon electrodes (GCE) shows excellent mediators for the oxidation of H$_2$O$_2$ to O$_2$. Based on this strategy Fc-GN can be used as a sensor for H$_2$O$_2$ in solution.\textsuperscript{132}

Lawrence and coworkers have designed a novel sensor system for electrochemical detection of oxygen. They have applied Anthraquinone–ferrocene film electrodes for pH sensor. The anthraquinone moiety was also found to respond to the presence of oxygen with no detrimental effect to its pH sensing capabilities.\textsuperscript{133} Ma et al. have also prepares a anthraquinone based fluorescent ferrocene molecule (Fig. 1.13). The (9-anthryl)ethenylferrocene have found to 100 fold fluorescent enhancement in presence of HOCl. Moreover the sensor is found to be highly selective for HOCl in presence of other oxygen species such as •OH, •O$_2$•$^\cdot$, O$_2$, and H$_2$O$_2$.\textsuperscript{134}

![Figure 1.13](image)

Berchmans et al. have put forwarded hydroxypropyl-β-cyclodextrin encapsulated soluble ferrocene for the estimation of NO in biological systems. The analytical procedure involves the modification of a glassy carbon electrode by an overlayer of Au nanocomposites prepared through galvanic reduction and the procedure is based upon the electrochemical reduction of NO.\textsuperscript{135}

1.3.2. Ferrocene Based Sensors for Organic Molecules

Amperometric biosensors for glucose have attracted much interest for decade. Zheng and coworkers have developed a novel glucose biosensor using
ferrocene-carbonyl-β-cyclodextrin (FcCD) inclusive complex as electron-transfer mediator and carbon nanotubes (CNTs) as electron-transfer promoter.\textsuperscript{136} Zaijun \textit{et al.} have developed a highly sensitive and stable glucose biosensor based on the synergetic contributions of C\textsubscript{60}, Ferrocene, Chitosan and Ionic liquid.\textsuperscript{137} The presence of C\textsubscript{60} and ferrocene remarkably improves the electron transfers for activation of oxidation of the glucose and accelerate electrochemical reaction. Tonelli and coworkers have prepared an amperometric biosensors based on glassy carbon electrodes modified with Mg/Al layered double hydroxides containing ferrocene-carboxylate or ferrocene-sulfonate, as interlayer anions. In this system Amperometric detection of glucose involves the electrochemical oxidation of H\textsubscript{2}O\textsubscript{2} mediated by the ferrocene derivative.\textsuperscript{138}

Heng and coworkers have developed a single-step fabrication method of a glucose biosensor by simultaneous immobilization of both ferrocene mediator and glucose oxidase in a photocurable methacrylic film consisting of poly(methyl methacrylate-co-2-hydroxylethyl methacrylate).\textsuperscript{139} The glucose biosensor fabricated by this photocuring method produced sensor reproducibility and repeatability with relative standard deviation of <10\% and long-term stability of up to 14 days. Şenel \textit{et al.} have prepared a polymer electrode in the form of a thin film by electrochemical copolymerization of thiophene, thiophene-3-acetic acid, and dicyclopentadienyl iron-1,4-dienylmethyl-2-(thiophen-3-yl)acetate to fabricate Glucose oxidase(GO\textsubscript{x})-immobilized electrodes for amperometric sensing of glucose. The copolymer transports electron between the active site of GO\textsubscript{x} and electrode.\textsuperscript{140} Other examples of the application of ferrocene and polymer material in the sensor preparation for glucose include ferrocene-modified linear poly(ethylenimine),\textsuperscript{141} ferrocene-containing poly(2-hydroxyl ethyl methacrylate) films,\textsuperscript{142} polyvinylferrocene immobilized on silica gel particles\textsuperscript{143} and polyethylene glycol modified enzyme.\textsuperscript{144}

Seong \textit{et al.} developed glucose biosensing electrodes using single-walled carbon nanotube (SWCNT) films on flexible, transparent poly(ethylene terephthalate).\textsuperscript{145} In this case when ferrocene monocarboxylic acid (FMCA) was introduced as diffusional electron mediator to the system, the current responses toward glucose were dramatically improved. Qiu \textit{et al.} have applied ferrocene-
modified multiwalled carbon nanotube nanocomposites as electron mediator for the determination of glucose.\textsuperscript{146} Other nano materials used in the detection of glucose include carbon nanotube electrodes functionalized with ferrocene by covalent coupling and π-stacking interactions,\textsuperscript{147} ferrocene modified polysiloxane/chitosan nanocomposite,\textsuperscript{148} single-walled carbon nanotubes incorporated ferrocene-modified linear polyethylenimine redox polymer films\textsuperscript{149} and mono-6-thio-β-cyclodextrin/ferrocene capped gold nanoparticles.\textsuperscript{150}

Detection of organic anions especially dicarboxylate anion is an important area of interest for recent times. Tuntulani \textit{et al.} have synthesized Calix[4]arene derivatives containing amide ferrocene units at the wide rim and ethyl ester groups at the narrow rim to investigate their anion binding property. It has been observed that all the ligands have selectivity towards dicarboxilate anions.\textsuperscript{151} Delgado and coworkers have synthesized tetraazamacrocycle containing ferrocene moieties (Fig 1.14a). The receptor strongly binds with phthalate (ph\textsuperscript{2-}), isophthalate (iph\textsuperscript{2-}) and dipicolinate (dipic\textsuperscript{2-}) and forms 1:2 adduct.\textsuperscript{152} The order of the β\textsubscript{2} binding constant is Ph\textsuperscript{2-} > dipic\textsuperscript{2-} > iph\textsuperscript{2-}. Miyaji \textit{et al.} have demonstrated that ferrocene-based bis(o-trifluoroacetylcarboxanilide) receptor (Fig. 1.14b) can selectively recognizes \textit{m}-phenylene diacetate through cooperative binding of 1:1 host-guest adduct.\textsuperscript{153}

Moody and coworkers have synthesized a series of chiral ureas containing the redox-active ferrocene group. Each of these ureas binds chiral carboxylates in organic solvents through hydrogen-bonding interactions, as evidenced by spectroscopic and cyclic voltammetry measurements.\textsuperscript{154}

Dopamine (DA) is an important neurotransmitter of the central nervous system. Variations in DA levels may result in brain disorders, such as Parkinson’s
disease. Kumar et al. have effectively detected catechol (CA) and dopamine (DA) without any interferences from cysteine, uric acid, hydrogen peroxide and ascorbic acid. For this they have utilized ferrocene bound nafion membrane modified glassy carbon electrode. Recently, Shi et al. have investigated the electrochemical behavior of dopamine at electrodes modified with ferrocene-filled double-walled carbon nanotubes.

The absence of ascorbic acid (AA) in our body causes several diseases. Routine and consistent determination of AA by is of great interest due to its medical importance. Song et al. have determined ascorbic acid using Gold nanoparticles functionalized selfassembled films of ferrocenylhexanethiol and mercaptoundecanoic acid (MUA). Under optimal conditions, response current of AA proportional in the concentration range from 8.0 µM to 6.0 mM, with a detection limit of 0.14 µM.

Levodopa (LD) is the most widely used drug in the treatment of Parkinson’s disease. LD is used to increase dopamine in the brain. However, high level of dopamine also causes adverse reactions such as nausea, vomiting and cardiac arrhythmias. Khalilzadeh et al. have used carbon paste electrode modified with ferrocene and carbon nanotubes for electrocatalytic determination of LD. The process is found to be reproducible, highly sensitivity, catalytically highly activity and have low detection limit.

Captopril, which is used in the treatment of renovascular toxic in high amount due to bone marrow suppression and proteinuria. Fouladgar reported electrocatalytic measurement of trace amount of Captopril using multiwall carbon nanotubes as a sensor and ferrocene as a mediator. They have applied differential pulse voltammetry for the determination of captopril in real samples such as drug and urine.

Another drug acetylcysteine or N-acetyl-L-cysteine (NAC) is used in the management of paracetamol (acetaminophen) overdose. Karimi-Maleh et al. have prepared ferrocene modified carbon nanotubes paste electrode for the detection of N-acetylcysteine (NAC) at trace level. The method is based on the fact that this sensor can catalyze the oxidation of NAC in phosphate buffer solution (PBS) and
produces a sharp oxidation peak current. By using cyclic voltammetry and double step chronoamperometry detections limit as low as 0.6 μmol L⁻¹ was obtained using this method.

Amino acids are one of the important substrates in biological as well as artificial processes. Tsukube et al. have designed a novel conjugate receptor based on ferrocenecarboxylic acid and crown ether to bind unprotected amino acids under acidic conditions and sense their chirality. Latter Zheng et al. have constructed a L-lysine sensor from ferrocene-labeled high molecular weight coenzyme derivative (PEI-Fc-NAD) and l-lysine 6-dehydrogenase. Both LysDH and PEI-Fc-NAD were immobilized on the surface of a gold electrode by consecutive layer-by-layer adsorption (LBL) technique.

In recent years, some electrochemical methods based on different mechanisms for detecting DNA have received particular attention due to their high sensitivity, high selectivity, simple instrumentation and low production cost. Maeda et al. have prepared redox-active DNA conjugate by ferrocene modification of oligonucleotide 12 mer as a DNA probe. Oligonucleotide (16 mer) complementary to the target (19 mer) was immobilized onto gold electrode through the specific chemisorption of successive phosphorothioates which were introduced into 5'-end of the oligonucleotide. So coupling of the oligonucleotide with the target DNA give electric currents based on the ferrocene oxidation. Chaix and coworkers have report the use of a four-ferrocene modified oligonucleotide as a probe for DNA detection with a gold electrode microsystem. The system's detection limit was estimated at 3.5 pM (0.07 fmol in 20 μL) with the 50-base length target and provided a dynamic detection range between 3.5 pM and 5 nM. Mao and coworkers described aptamer-based electrochemical sensor using a 15-mer thrombin-binding aptamer as the model oligonucleotide. The binding of the target (i.e. thrombin) towards the aptamer destroys the Watson–Crick helix structure of the ds-DNA oligonucleotide assembled onto the electrode and leads to the dissociation of the ferrocene-labeled short complementary DNA oligonucleotide from the electrode surface to the solution. This change results in a decrease in the current signal obtained at the electrode, which can be used for the determination of the target. Aoki and Tao report a strategy for gene detection based on the
hybridization-induced conformational flexibility change in probe structure. Probe structure was designed to place the ferrocene moiety at the flexible end of the linear probe chain. Upon hybridization with a complementary target DNA, the resultant rigid duplex restricts the interaction of ferrocene with the electrode surface, causing a decrease in the observed current. Some other examples of the application of ferrocene-based DNA conjugates for the detection of DNA are ferrocene/isoquinoline conjugate-connected DNA probes, cationic polythiophene incorporating both acridine and ferrocene units, DNA conjugates modified with ferrocene and β-cyclodextrin, Ferrocene-diamidopyridine conjugate, and ferrocene-functionalized polypyrrole.

A highly sensitive adenosine detection using reusable electrochemical sensing platform based on ferrocene labeled structure-switching signaling aptamers has been put forward by Shen et al. Latter Fang et al. also reported a ferrocene-labeled structure switching signaling aptamer (Fc-aptamer) for detection of small molecules using adenosine as a model analyte. Chen and coworkers developed an electrochemiluminescence (ECL) aptamer biosensor for detection of adenosine based on quenching ECL of Ru-SiNPs by Ferrocene. The biosensor offers several advantages such as good selectivity, high sensitivity, reproducibility and stability.

Spiccia et al. have synthesized ligand, [Fc(cyclen)₂] (Fc=ferrocene, cyclen=1,4,7,10-tetraazacyclododecane), and corresponding Zn'' complex receptor, [Fc{Zn (cyclen) (CH₃OH)}₂]ClO₄. It was observed that the Zn complex is highly selective electrochemical sensor of thymidilyl (3'-5')thymidine (TpT) relative to other nucleobases and nucleotides in Tris-HCl buffer solution (pH 7.4).

Zheng and coworkers have prepared a ferrocene-labeled high molecular weight cofactor derivative (PEI-Fc-NAD) by attaching both ferrocene and nicotinamide adenine dinucleotide (NAD⁺) to a water soluble polyelectrolyte, polyethylenimine (PEI). PEI-Fc-NAD provides a new way for immobilization of mediator and cofactor for reagentless NAD-dependent dehydrogenase biosensors.

Radhakrishnan and Paul have modified polypyrrole with ferrocene to increase its response to carbon monoxide. The Synthesis was carried out by chemical oxidative polymerization in the presence of ferrocene using ferric chloride.
It was observed that there is an optimum composition at which the maximum response is obtained even at low concentration (300 ppm) of the CO gas. Gooding et al. have synthesized an immuno-biosensing interface comprising a mixed layer of an oligo(ethylene glycol) (OEG) component, and an oligo(phenylethynylene) molecular wire (MW). They have efficiently utilized this system for the detection of small organic molecules (<1000 Da).\textsuperscript{178}

1.4. Aim and Scope of the Thesis

Literature search revealed that there are several ferrocene compounds have been utilized for various organic transformations and as sensors. In addition to easy functionalization, low price and stability of ferrocene based molecule is the main driving force for its application in various fields. Moreover, ferrocene based molecules shows well defined electrochemical behaviors. This property of ferrocenyl molecule is successfully utilized in the sensor application. Other properties of ferrocene molecules including fluorescence activity are also used as a tool for the molecule sensing.

In the work described in this thesis, we have synthesized and characterize some ferrocene based molecules. First part of the thesis deals with application of ferrocene based molecules in various organic transformations. Latter part of the thesis includes the application of ferrocene based sensors.

In chapter 2, we are discussing the use of ferrocene based bulky pyridine as reusable homogeneous catalyst. The reusability of the prepared catalyst was tested in case of synthesis of benzoyl fumarates and acetylation of alcohol.

In chapter 3, a methodology for allylation reaction of aldehydes using allyl bromide has been discussed. Here a comparative study was carried out to evaluate the efficiency of DMAP and a ferrocene based pyridine as ligand for the reaction.

Chapter 4 deals with Sonogashira coupling reaction using Cu based catalyst. Two ferrocene based ligand were synthesized and applied for this transformation.
As a continuation of our study on various ferrocene based compounds in various reactions, we have analyzed the scope of CuI as catalyst in presence of ferrocene based ligand for Henry reaction in chapter 5.

Chapter 6 is dedicated to application of ferrocene derivatives as sensor. Here we have synthesized simple ferrocenyl compounds which are applied as sensors for cadmium and dopamine.

In chapter 7, we have carried out structural and chemical characterization of few ferrocene derivatives. Section A deals with crystal structure analysis of few ferrocene substituted organic compounds while section B include amidation of ferrocene carboxaldehyde using $N,N$-dibromo-$p$-toluene sulfonamide without any catalyst.
1.5. References


