The Hong Kong Polytechnic University

Department of Applied Biology and Chemical Technology

An Efficient Approach to Chiral Ferrocenyl Ligands *via* Asymmetric Hydrogenation of Ferrocenyl Ketones

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A thesis submitted in partial fulfillment of the

requirements for the Degree of Master of Philosophy

October 2005

Declaration

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Name of Student: LAM WING SZE

October, 2005

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Lam Wing Sze

October, 2005

Abstract of thesis entitled “An Efficient Approach to Chiral Ferrocenyl Ligands *via* Asymmetric Hydrogenation of Ferrocenyl Ketones”

Submitted by Lam Wing Sze
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Asymmetric hydrogenation is one of the most advanced industrial technologies to access chiral alcohols in consideration of its high S/C ratio, clean in process and slim in the cost of multi-steps of synthesis. In this project, a simple, efficient and highly enantioselective method for the synthesis of enantiomerically pure ferrocenyl alcohols has been developed. We found that (*R*)-Xylyl-P-PhosRuCl$_2$(*R*,*R*)-DPEN was the most efficient precatalyst for the hydrogenation of ferrocenyl ketones to the corresponding ferrocenyl alcohols. The best result of 99.3% ee with full conversion was obtained in the hydrogenation of acetylferrocene. The reaction can be easily upgraded to industrial entry level with S/C ratio of 100,000 and the conversion completed in 48 hours without deterioration of enantioselectivity.

Starting from optically pure ferrocenyl alcohols, new ferrocenyl ligands were easily synthesized *via* three steps and used for screening different asymmetric catalysis. Ru-Complexes of these ferrocenyl ligands and diamine or diphosphine ligands were firstly selected for catalyzing hydrogenation of acetophenone. The diamine-Ru-complexes have better enantioselectivity in comparison with diphosphine-Ru-complexes. The catalysts prepared from ferrocenyl ligands with DPEN gave hydrogenation product with up to 68.7% ee and complete conversion. Matching and mismatching effect were observed. The BINAP-Ru-complexes exhibited high activity regardless of the presence of *N*-methyl substituent on

hydrogenation of acetophenone although preliminary results in enantioselectivity were poor. Presence of non-substituted amine on ferrocenyl ligand significantly reduced the activity in P-Phos-Ru-complexes. Our results showed that *N*-methyl substituent on the ligand is crucial for the control of product's configuration in the diphosphine Ru-complexes.

In addition, our ferrocenyl ligands were also active in asymmetric allylic alkylation and gave products with up to 88.7% ee. The product's configuration and enantioselectivity were controlled by structure of the *N*-alkyl group and alkyl group on central chirality of ferrocenyl ligand as they determined the conformational structure of the π-allylpalladium intermediate. The ferrocenyl ligand in the presence of *t*-butyl amine and phenyl group α-stereogenic center provided the highest enantioselectivity in catalyzed allylic alkylation under optimized reaction condition.

Abbreviation

AAA	Asymmetric allylic alkylation
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthalene
CBS	Corey Bakshi Shibata
Cp	Cyclopentadienyl
DAIB	(Diacetoxy)iodobenzene
DAIPEN	1,1-Bis(4-methoxyphenyl)-3-methyl-1,2-butanediamine
DPEN	Diphenylethylenediamine
ee	Enantiomeric excess
Fc	Ferrocene
Nu	Nucleophile
$Pd(dba)_2$	Bis(dibenzylideneacetone)palladium(0)
$Pd(OAc)_2$	Palladium(II) acetate
$Pd_2(dba)_3$	Tris(dibenzylideneacetone)dipalladium(0)
$[Pd(allyl)Cl]_2$	Allylpalladium(II) chloride dimmer
P-Phos	2,2’,6,6’-Tetramethoxy-4,4’-bis(diphenylphosphino)-3,3’-bipyridine
S/C	Substrate to Catalyst ratio
S/B	Substrate to Base ratio
TOF	Turn over frequency
Tol-P-Phos	2,2’,6,6’-Tetramethoxy-4,4’-bis[di(*p*-methylphenyl)phosphino)-3,3’-bipyridine
Xylyl-P-Phos	2,2’,6,6’-Tetramethoxy-4,4’-bis[di(3,5-dimethylphenyl)-phosphino)-3,3’-bipyridine

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Chapter 1

Introduction

1.1 Significance of Catalytic Asymmetric Reactions

The demand for enantiomerically pure compounds is increasing in the field of pharmaceuticals, agrochemicals, and flavors. This is due to dramatic difference(s) in the activities of the enantiomers. Their smell, taste and biologically activity are different. The structural difference between enantiomers can be serious with respect to the actions of synthetic drugs.[1] Chiral receptor sites in the human body interact only with drug molecules having the proper absolute configuration, and this results in marked differences in the pharmacological activities of enantiomers. The unwanted enantiomer may cause adverse effect to human.[2]

The U.S. Food and Drug Administration encouraged companies to synthesize and market clinical drugs consisting of single enantiomers since 1992.[3] Efficient methods have been developed to obtain pure enantiomers. These methods include the classical resolution of racemate and asymmetric synthesis. Resolution can be affected through formation of diastereomers where the functional group of the racemic compound can interact or react with another chiral agent to produce diastereomers which can be physically separated. Asymmetric synthesis is another powerful method to produce a single enantiomer. Asymmetric synthesis was described as changing a

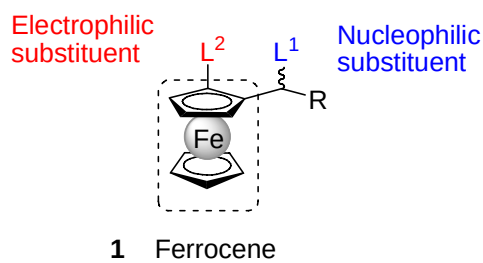
reactant into a chiral unit that formed stereoisomeric products in unequal amount. This definition was expanded by Morrison and Mosher in 1971[2] to include reactions accomplished by the use of chiral reagent or auxiliaries. Asymmetric catalysis has obvious advantages over the reagent and auxiliary approach since a small amount of enantiomerically pure material can produce large quantities of enantiomerically enriched or enantiopure material. This research area includes the use of enzymes, non-metal-base catalysts and metal catalysts.[2]

Metal catalysts for homogeneous catalysis allow for the flexible synthesis of a wide array of enantiopure organic substances from achiral precursors. The asymmetry of metal-catalyzed process is almost always induced by the organic ligands attached to that metal.[4] These organic ancillaries control the binding of reactants and their subsequent reaction paths through steric and electronic interactions. The chiral ligands modify intrinsically achiral metal atoms to provide suitable three-dimensional structures and functionality which affect the reactivity and stereoselectivity of catalysts.

A vast number of mono-, bi- and polydentate ligands have been successfully applied in asymmetric catalysis. Phosphorus[4], nitrogen[5], oxygen[6] and sulfur[7] are commonly used donor atoms for the chiral ligands and they allowed for electronically tuning. The ligands also contain central, planar and axial chirality

and/or combinations of these on the scaffold. After novel ligands have been developed, their metal complexes are tested for their catalytic activity and enantiodifferentiating ability in standard transformations. These reactions include hydrogenation of olefins and carbonyl groups, allylic substitution and the addition of diethylzinces to aldehydes and other.[8]

1.2 Development of Ferrocenyl Ligands



1 Ferrocene

Figure 1.2.1

Ferrocene-containing compounds, first discovered over 50 years ago, were extensively applied to catalysis and material science.[9] Ferrocene is thermally stable and tolerant of oxygen and moisture. It is commercially available and inexpensive. Ferrocene **1** is suitable for use as a scaffold for chiral ligands, because the cyclopentadienyl ring (Cp ring) has adequate rigidity and bulky shield to give an appropriate chiral environment. Cp ring carries a partial negative charge and is susceptible to substitution reactions with various electrophiles. Ferrocene easily

introduces additional planar chirality when two functional groups substitute on the same Cp ring. In coordination chemistry, the ferrocene moiety has played a significant role as a backbone or a substituent in ancillary ligands because ferrocene has an unique sandwich structure. Among a vast number of applications in various areas, the use of chiral ferrocenyl compounds as ligands in asymmetric synthesis is most prominent.[9] Some of them have played a key role in the development of important catalytic system in industrial processes.[10]

Many chiral ferrocene ligands are 1,2-disubstituted ferrocenes with two ligating fragments L^1 and L^2 attach to the central and planar chirality (Figure 1.2.1). It gives opportunity to expeditiously tune both the steric and electronic properties of the ligands for application to different catalytic reactions. Most 1,2-disubstituted ferrocenyl ligands precursor is Ugi's amine **2** (*N*,*N*-dimethyl-1-ferrocenylethyl-amine)[11] which gives high distereoselectivity in lithation to introduce electrophile, such as chlorodiphenylphosphine. The dimethylamino unit could be replaced by a large array of derivatives in nucleophilic substitution with retention of configuration.[12] The demand for high optically pure Ugi's amine increased because of widely development and application of 1,2-disubstituted ferrocenyl ligands. The pure enantiomer may be obtained by resolution using tartaric acid but this method is not efficient in a large scale production. Therefore a number of new methods for the

asymmetric synthesis of stereogenic center α to ferrocene were developed.[13]

Ugi's amine is an important intermediate for some of the most efficient chiral ferrocene ligands, such as PPFA[14], Joisphos[15], TaniaPhos[16], BoPhoz[17], Walphos[18], Pigiphos[19], Ferriphos[20], Trap[21] (Figure 1.2.2). These ferrocenyl ligands are successfully applied to asymmetric catalysis that includes hydrogenation, allylic substitution, hydrosilylation, hydroformylation and hydroamination reactions.[22]

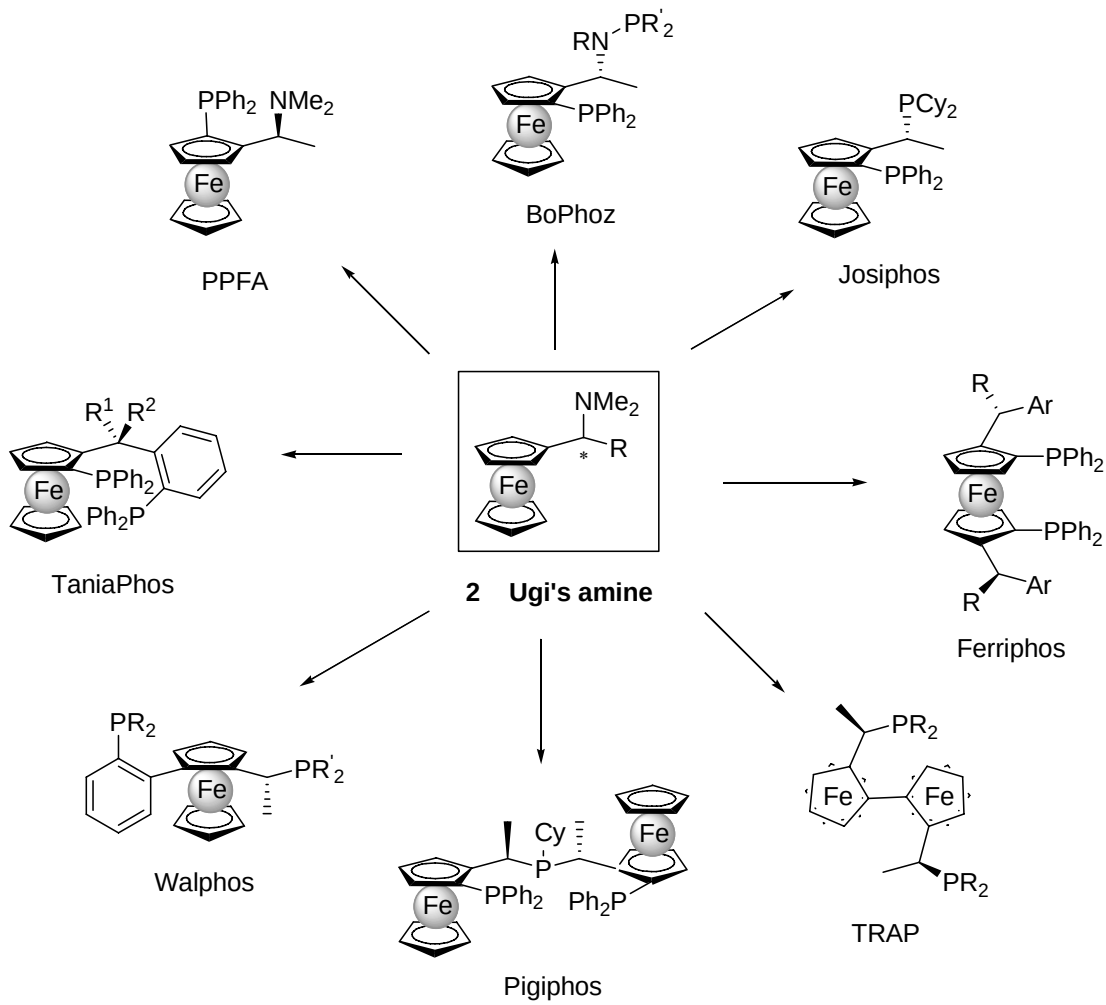
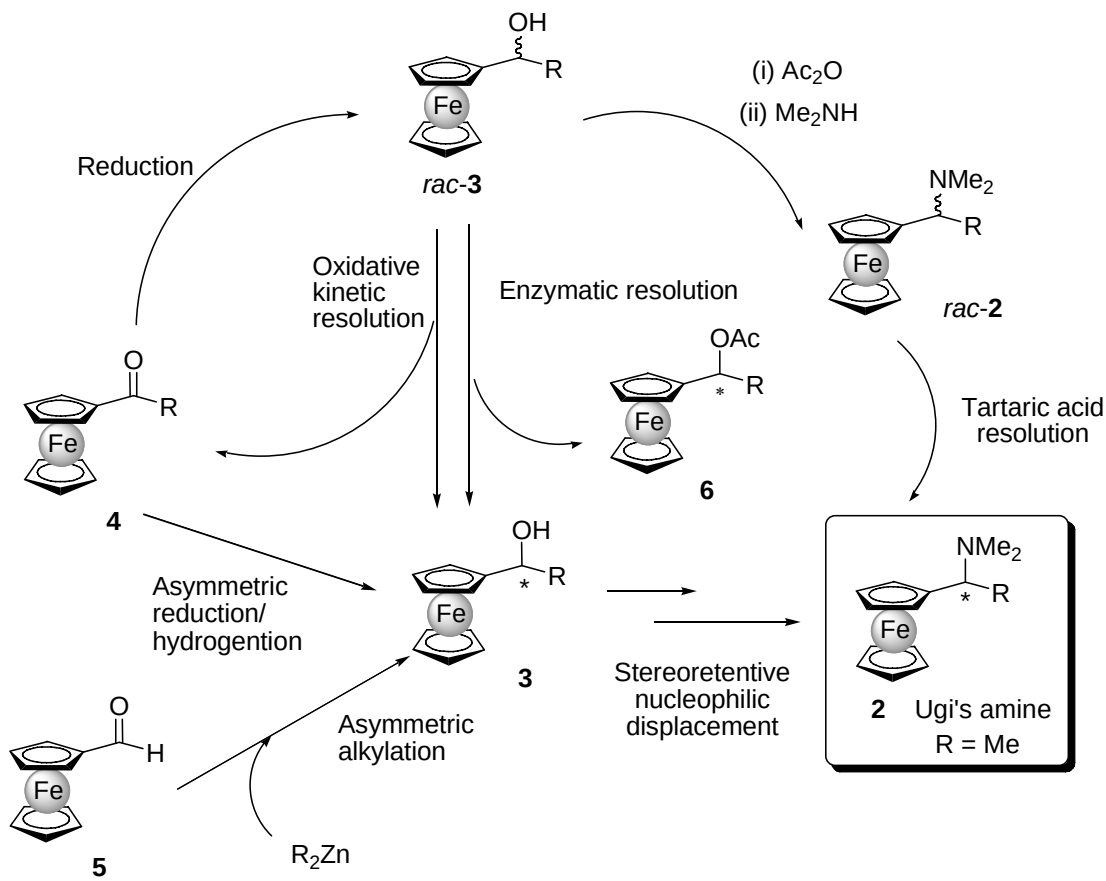


Figure 1.2.2

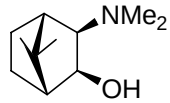
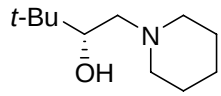
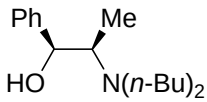
1.2.1 Methods in the Preparation of Chiral Ferrocenyl Alcohols

Chiral Ugi's amine was first prepared in 1970.[11] Its original synthesis started from racemic 1-ferrocenylethanol which was sequentially reacted with acetic anhydride and dimethylamine. Pure enantiomer was obtained by the resolution using tartaric acid in methanol. This process required approximately a week of laboratory work for repeated crystallization of the diastereomeric salts (Scheme 1.2.1).



Scheme 1.2.1

Table 1.2.1 Asymmetric addition of dialkylzincs to ferrocenyl aldehyde

Dialkyl zinc	Catalyst	**3** (R = alkyl)	Yield %	Ee %
Me_2Zn	 (-)-DAIB	Me	60	81 (*S*)
Et_2Zn		Et	No data	96 (*S*)
(*i*-Pr)$_2$Zn		*i*-Pr	96.6	97.7 (*S*)

In contrast, direct synthesis of chiral ferrocenyl alcohols could reduce the effort of resolution because nucleophilc substitution on α-stereogenic centre of ferrocenyl alcohols can lead to the enantiomeic pure amine with complete retention of configuration.[11-13] Noyori used (−)-DAIB to catalyze enantioselective addition of dimethylzinc to ferrocenyl aldehyde with 81% ee (Table 1.2.1; entry 1).[23] Chiral amino alcohols are more efficient and give the products with more than 96% ee (entries 2 and 3).[24-26]

Another approach is construction from chiral cyclopentadienylides which was first reported by Müller utilising fulvalene and MeLi (Figure 1.2.3). The diastereoisomeric product was generated in a 93.5:6.5 ratio and the corresponding dimethylamine product is having 75% ee.[27] Similar approach was introduced by Hayashi using (−)-sparteine to catalyze the addition of an aryllithium to

6-(dimethylamino)fulvene forming chiral lithium cyclopentadienide (Figure 1.2.4).[28] Oxidative kinetic resolution[29,30] and enzymatic resolution[31,32] are alternative methods to synthesize optically pure alcohol. However, acquisition of both enantiomers are often difficult using these methods due to the unavailability of the antipodic catalyst. Consequently, asymmetric reduction of ferrocenyl ketones is an attractive route for the synthesis of chiral ferrocenyl alcohol.[33] High yield and enantioselectivity were obtained by using chiral oxazaborolidine (CBS reduction). This method works well with mono-[34] and diacylferrocenes (Figure 1.2.5)[35,36]. However, it requires high catalyst loading in order to maintain a good enantioselectivity. It is therefore an expensive way to obtain a large quantity of the Ugi's-type amine.

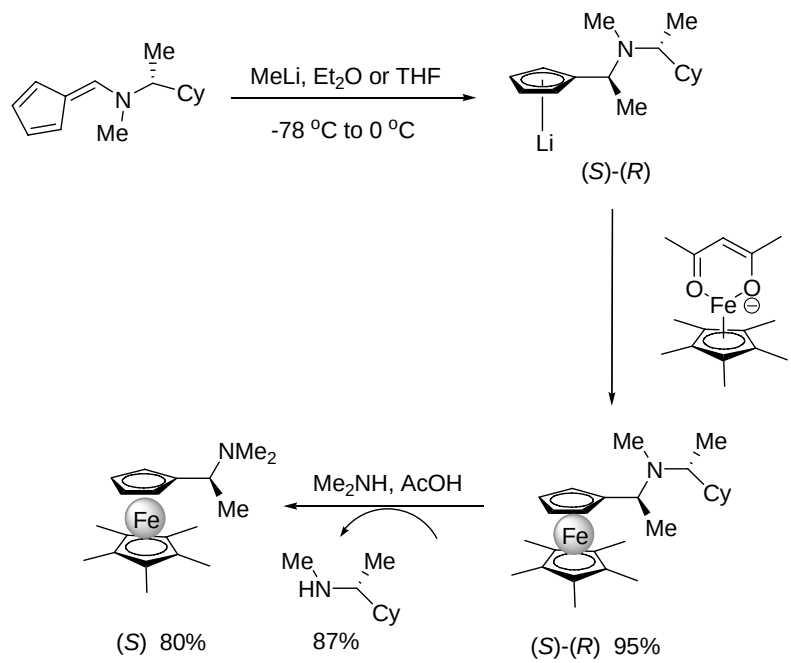


Figure 1.2.3

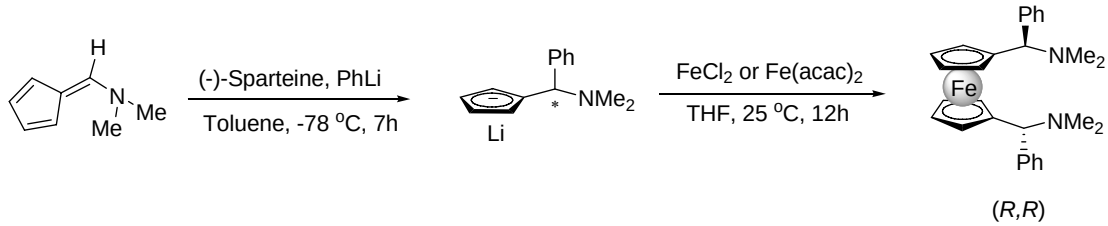


Figure 1.2.4

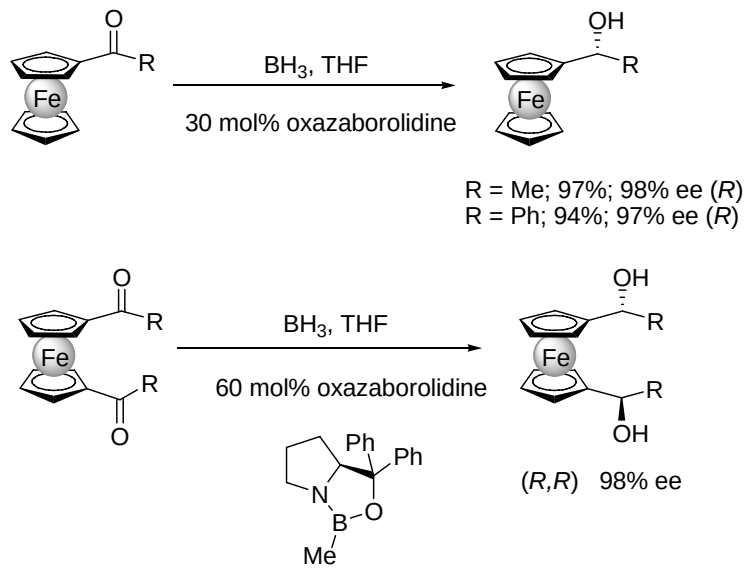
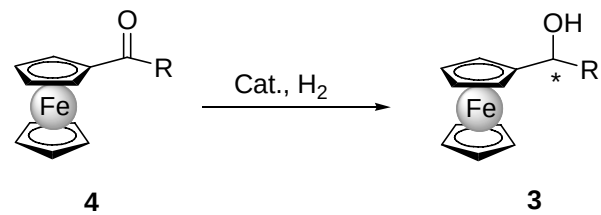


Figure 1.2.5

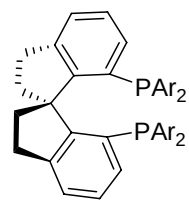
Since the discovery by Noyori and co-workers,[37] the asymmetric catalytic hydrogenation of prochiral ketones with [(diphosphine)$RuCl_2$(diamine)] has quickly become a method of choice for the synthesis of simple chiral secondary alcohols. The best result was reported for catalytic hydrogenation of ferrocenyl ketones using (*S*)-SDP as the disphosphine and (*R*,*R*)-DPEN as the diamine (Table 1.2.2) with 98% ee and TOF 1000 h^{-1}. The enantiomeic pure amine could be easily prepared from chical ferrocenyl alcohols by retention of configuration. The planar chirality of

1,2-disubstituted ferrocenyl ligands is introduced by the asymmetric *ortho*-lithation of Ugi's amine in excellent diastereoselectivity.

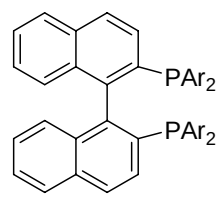
Table 1.2.2 Enantioselective catalytic hydrogenation of ferrocenyl ketones.[a]



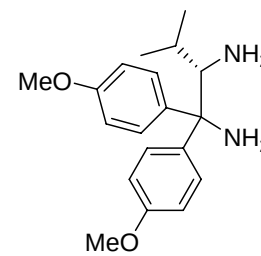
4 **3**



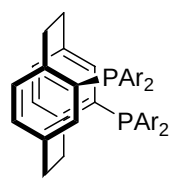
(*S*)-Xylyl-SDP Ar = 3,5-$Me_2C_6H_3$



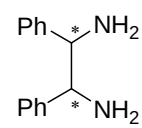
Tol-BINAP Ar = 4-MeC_6H_4
Xylyl-BINAP Ar = 3,5-$Me_2C_6H_3$



(*S*)-DAIPEN



(*R*)-Xylyl-PhanePhos Ar = 3,5-$Me_2C_6H_3$



DPEN

entry	**4**	Catalyst	S/C	ee (%)	Conv. (%)	Config.
1	R = Me	[((*S*)-Xylyl-SDP)$RuCl_2$ ((*R,R*)-DPEN)][38]	5000	98	100	*S*
2	R = Me	([((*R*)-Xylyl-PhanePhos)$RuCl_2$ ((*S,S*)-DPEN)][39]	1000	92	>99	*R*
3	R = Me	[((*R*)-Tol-BINAP)$RuCl_2$ ((*S*)-DAIPEN)][40]	*b*	87	*b*	*S*
4	R = Ph	[((*S*)-Tol-BINAP)$RuCl_2$ ((*S*)-DAIPEN)][41]	2000	95	100	*S*
5	R = Ph	[((*S*)-Xylyl-BINAP)$RuCl_2$ ((*S*)-DAIPEN)][41]	*b*	45	*b*	*S*

[a]General operation temperatures ranged from 18-24 ˚C. [b] Data unavailable.

1.2.2 1,2-Disubstituted Ferrocenyl Ligands

1,2-disubstituted ferrocene constitutes one of the most successful class of auxiliaries used in asymmetric catalysis. Centre and/or planar chirality was found to be the dominant enantiocontrolling elements in different catalytic reactions. The first 1,2-disubstituted ferrocenyl ligands is PPFA (**7)** synthesisd by Kumada and Hayashi and it was applied to nickel- and palladium-catalyzed asymmetric cross-coupling of alkyl Grignard reagents with vinyl halides with up to 68% ee.[14] PPFA was also used in the Pd catalyzed preparation of optically-active allyl silanes using asymmetric Grignard cross-coupling with very high enantiomeric excess (93-95% ee).[42]

Some of the diphosphine ferrocenyl ligands were derived from PPFA *via* nitrogen-phosphorous exchange (Figure 1.2.2). The most important example is Josiphos which was firstly synthesised by Togni.[15] It was active in asymmetric rhodium-catalyzed hydrogenation and hydroboration, palladium-catalyzed allylic alkylation reactions, and carbonylation of chloroarenes.[15] Other important diphosphine ferrocenyl ligands, such as TaniaPhos[16], BoPhoz[17], Walphos[18], Pigiphos[19], Ferriphos[20], were found to give high activities and enantioselectivities in catalysis.

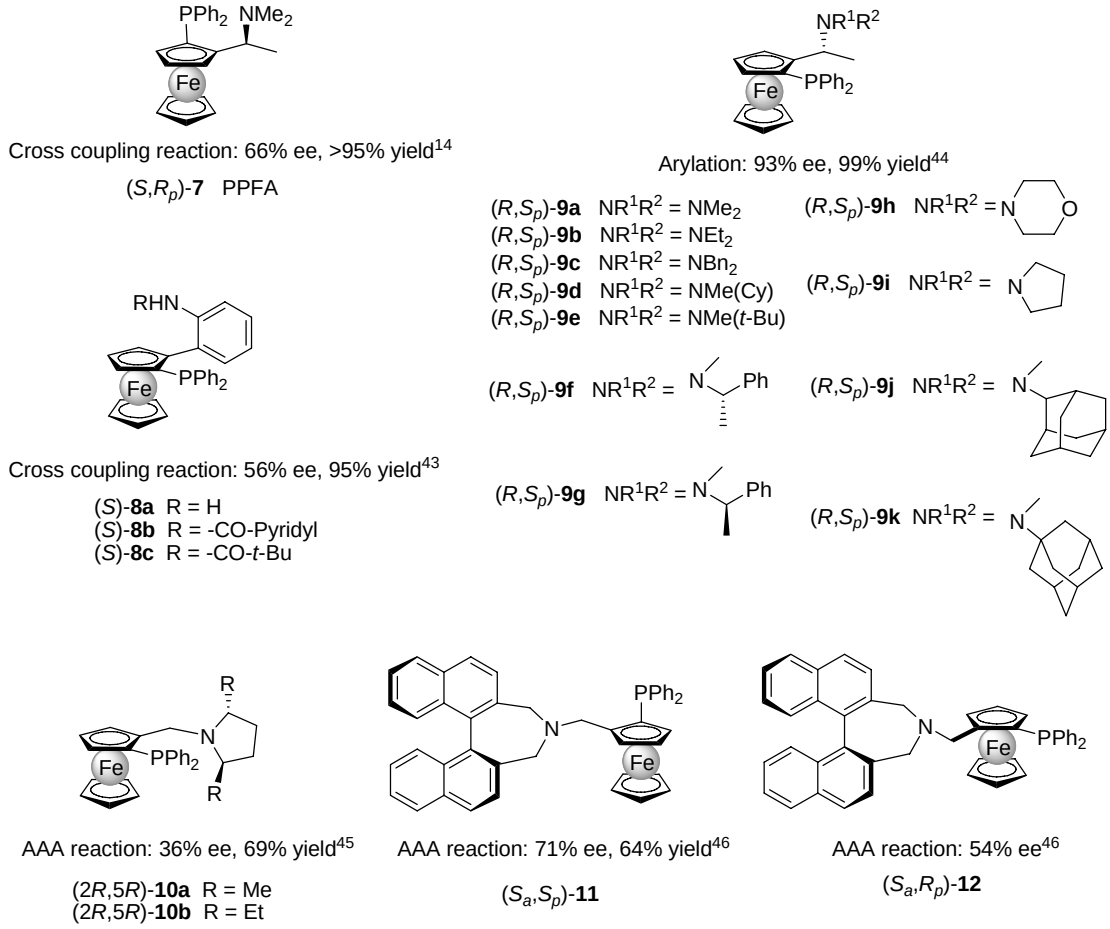
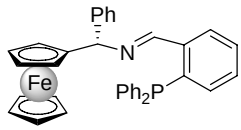


Figure 1.2.6 1,2-Disubstituted ferrocenyl amino phosphine ligands

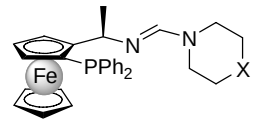
Other successful ferrocenyl ligands use nitrogen and phosphorus as their donor atoms (Figures 1.2.6 to 8). These heterodentate ligands generate electronic and steric asymmetry on the metal centre inducing enantioselectivity and regioselectivity. The π-acceptor character of phosphorus can stabilize a metal centre in its lower oxidation state, while the nitrogen σ-donor ability makes the metal more susceptible to oxidation addition reactions. This combination can help to stabilize intermediate oxidation states or geometries which form during a catalytic cycle. Figures 1.2.6 to 8

give the examples of bidentate P,N-ligands in the presence of amino, imino or pyridine as N donor. Their metal complexes have been applied to different asymmetric transformations.[47] The first example of using amino N donor on ferrocene is PPFA. Uemura and co-workers employed the ligand family (*R*,S_p)-**9** in palladium-catalyzed asymmetric arylation, vinylation and allenylation of *tert*-cyclobutanols *via* C-C bond cleavage with high enantioselectivity.[44] This is the first example of enantioselective C-C bond cleavage. Ligands (*S*)-**8** were applied to copper-catalyzed ditheylzinc additons with high conversion and moderate enantioselection.[43] The cyclic amino group of (2*R*,5*R*)-**10** gave poor enantioselection in palladium-catalyzed allyic alkylation.[45] Widhalm et al. prepared ligands (S_a,S_p)-**11** and **12** which incorporate both axial and planar chiral elements. The enantioselectivities obtained in allylic alkylation of 2-cyclopenten-1-yl acetate was 71% ee with (S_a,S_p)-**11**.[46]



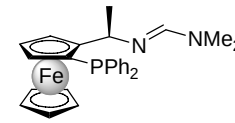
AAA reaction: 97% ee, 98% yield[48]

(*S*)-**13**



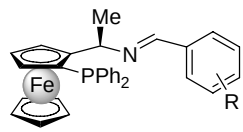
AAA reaction: 81% ee, 91% yield[49]

(*R*,S_p)-**14a** X = O
(*R*,S_p)-**14b** X = CH_2



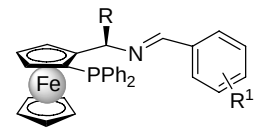
AAA reaction: 92% ee, 96% yield[50]

(*R*,S_p)-**15**



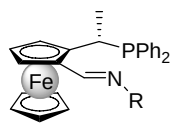
AAA reaction:93% ee, 99% yield[51,52]
Hydrosilylation: 90% ee, 90% yield[53]

(*R*,S_p)-**16a** R = H
(*R*,S_p)-**16b** R = *m*-Cl
(*R*,S_p)-**16c** R = *m*-NO_2
(*R*,S_p)-**16d** R = *m*-CF_3
(*R*,S_p)-**16f** R = *m*-OMe
(*R*,S_p)-**16g** R = *p*-Cl
(*R*,S_p)-**16h** R = *p*-NO_2
(*R*,S_p)-**16i** R = *p*-OMe
(*R*,S_p)-**16j** R = *p*-NMe_2
(*R*,S_p)-**16k** R = *p*-CF_3



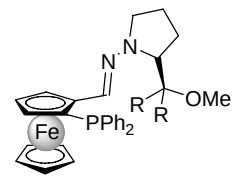
AAA reaction: >98% ee, 95% yield[51]

(*R*,S_p)-**17a** R = Et; R^1 = *p*-NO_2
(*R*,S_p)-**17b** R = Ph; R^1 = *p*-NO_2



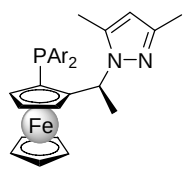
AAA reaction: 75.5% ee, 99% yield[54]

(*S*,R_p)-**18a** R = Ph
(*S*,R_p)-**18b** R = 2,6-$(Me)_2$-C_6H_3
(*S*,R_p)-**18c** R = Cy
(*S*,R_p)-**18d** R = Et
(*S*,R_p)-**18f** R = Me



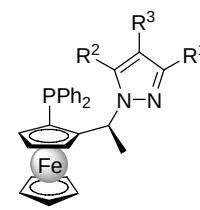
AAA reaction: 96% ee, 93% yield[55]

(*S*,S_p)-**19a** R = H
(*S*,S_p)-**19b** R = Me
(*S*,S_p)-**19c** R = Et



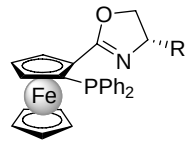
Hydroboration: 98% ee, 68% yield[56]

(*S*,R_p)-**20a** Ar = 4-CF_3-C_6H_4
(*S*,R_p)-**20b** Ar = 4-MeO-C_6H_4



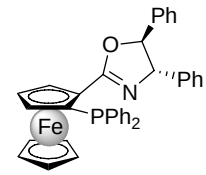
Silylation: >99.5% ee, 59% yield[57]
Hyboration: 90% ee, 96% yield[56]
AA Aminaiton: 99.5% ee, 99% yield[58]

(*S*,R_p)-**21a** R^1 = Me, R^2 = H, R^3 = Me
(*S*,R_p)-**21b** R^1 = Me, R^2 = Me, R^3 = Me
(*S*,R_p)-**21c** R^1 = Me, R^2 = Br, R^3 = Me
(*S*,R_p)-**21d** R^1 = Ph, R^2 = H, R^3 = Me



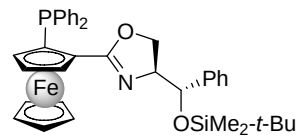
Reduction of ketone: 95% ee, 82% yield[59]
AAA reaction: 99% ee, 99% yield[60]
Heck reaction: 87% ee, 73% yield[61]
Transfer hydrogenation of ketone: 94% ee, 93% yield[62]
Hydrogenation of quinoline: 90% ee, >95% yield[63]

(S,S_p)-**22a** R = Me
(S,S_p)-**22b** R = *i*-Pr
(S,S_p)-**22c** R = *t*-Bu
(S,S_p)-**22d** R = Ph
(S,S_p)-**22e** R = Bn
(S,S_p)-**22f** R = *s*-Bu



Reduction of ketone: 91% ee, 100% yield[64]

(S,S,S_p)-**23**



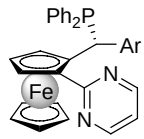
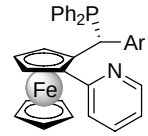
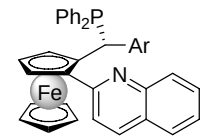
AAA reaction: 95% ee, 98% yield[65]

(S,S,S_p)-**24**

Figure 1.2.7 1,2-Disubstituted ferrocenyl imino phosphine ligands

Most of the imino ligands (Figure 1.2.7) and pyridine ligands (Figure 1.2.8) gave a moderate to excellent enantioselectivity and high conversion under optimal conditions in palladium-catalyzed allylic alkylation. Some of them have been employed in other metal-catalyzed transformations giving good results in selectivity. These reactions include hydrosilylation of acetophenone catalyzed by (R,S_p)-**16** and (S,S_p)-**22** or hydrosilylation of norbornene catalyzed by (S,R_p)-**20** and (S,R_p)-**21**, hydroboration of styrene catalyzed by (S,R_p)-**20**-**21** and (R,R_p)-**25**-**27**. Ligands (S,S_p)-**22** were active in asymmetric Heck reaction, transfer hydrogenation, reduction of ketone and imine. Results have demonstrated that bidenate P,N-ferrocenyl ligands are current success in catalysis. Tuning electronic and steric properties of donor atoms

could provide higher reactivity and selectivity across a wide range of substrates and industrial applications.

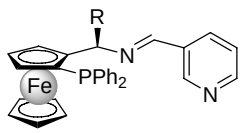




Hydroboration: 92% ee, >99% yield; AAA reaction: 92% ee, 94% yield[66]

(*R*,R_p)-**25a** Ar = Ph
(*R*,R_p)-**25b** Ar = 2-Me-C_6H_3
(*R*,R_p)-**25c** Ar = 3,5-$(Me)_2$-C_6H_3

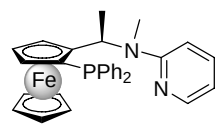
(*R*,R_p)-**26a** Ar = Ph
(*R*,R_p)-**26b** Ar = 2-Me-C_6H_3
(*R*,R_p)-**26c** Ar = 3,5-$(Me)_2$-C_6H_3

(*R*,R_p)-**27a** Ar = Ph
(*R*,R_p)-**27b** Ar = 2-Me-C_6H_3
(*R*,R_p)-**27c** Ar = 3,5-$(Me)_2$-C_6H_3



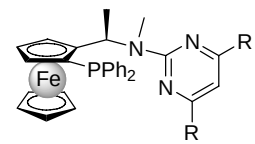
AAA reaction: 98% ee, 95% yield[67]

(*R*,S_p)-**28a** R = Me
(*R*,S_p)-**28b** R = Et
(*R*,S_p)-**28c** R = Ph



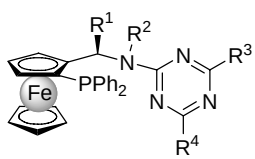
AAA reaction: 81% ee, 53% yield[68]

(*R*,S_p)-**29**



AAA reaction: 98% ee, 99% yield[68]

(*R*,S_p)-**30a** R = H
(*R*,S_p)-**30b** R = OMe



AAA reaction: 97% ee, 93% yield[68]

(*R*,S_p)-**31a** R^1 = Me, R^2 = H, R^3 = OMe
(*R*,S_p)-**31b** R^1 = Me, R^2 = Me, R^3 = OMe
(*R*,S_p)-**31c** R^1 = Me, R^2 = Et, R^3 = OMe
(*R*,S_p)-**31d** R^1 = Me, R^2 = Bz, R^3 = OMe
(*R*,S_p)-**31f** R^1 = Me, R^2 = CH_2CH_2OH, R^3 = OMe
(*R*,S_p)-**31g** R^1 = Me, R^2 = Me, R^3 = OPh
(*R*,S_p)-**31h** R^1 = Me, R^2 = Me, R^3 = 4-morpholinyl
(*R*,S_p)-**31i** R^1 = Et, R^2 = Me, R^3 = OPh

Figure 1.2.8 1,2-Disubstituted ferrocenyl pyridine phosphine ligands

An example of the industrial importance of these ligands was demonstrated by Lonza, who used the Josiphos type ligand **34** in the industrial synthesis of (+)-biotin (vitamine H) (Figure 1.2.9). **34** catalyzed hydrogenation of **32** to give **33** in high distereoselectivity. Josiphos's derivative, **38**, is highly active in Ir(I)-catalyzed asymmetric hydrogenation of imine **35** to give **36** which is an intermediate in the

synthesis of (*S*)-Metolachlor, a commercially important herbicide. Although the enantiomeric excess is only 80%, this is tolerable for an agrochemical. More important though is the activity of the catalyst, as the ratio of the substrate to Ir(I) is more than 1,000,000:1.[9]

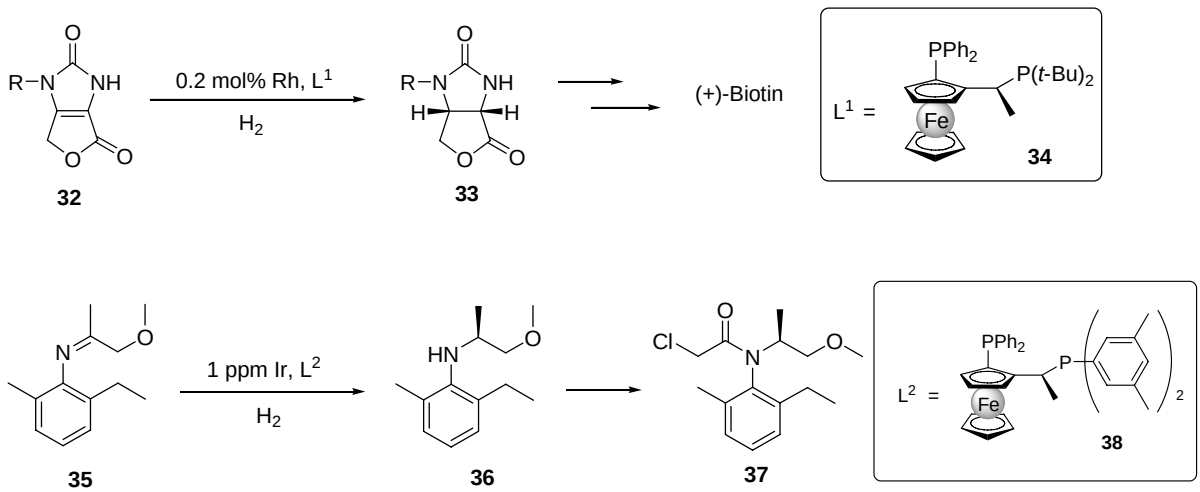


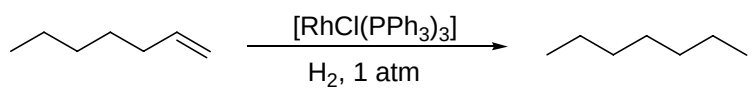
Figure 1.2.9 Industrial application of ferrocenyl ligands

1.3 Catalytic Asymmetric Hydrogenation of Ketones

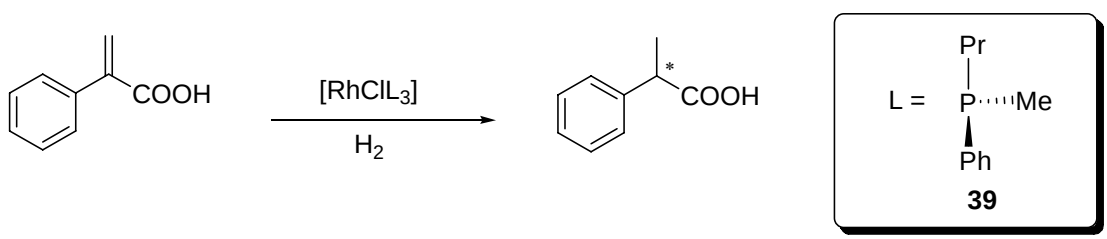
1.3.1 Asymmetric Hydrogenation

A great number of optically active compounds contain a hydrogen atom at the stereogenic center. Asymmetric hydrogenation is a core technology by which a small amount of catalyst repeatedly delivers hydrogen atoms to one of the enantiofaces of the substrates and a large number of optically active saturated compounds are produced. Hydrogen is the simplest molecule and its properties are fully understood. It can be used in excess because unreacted hydrogen is very easily removed at the end

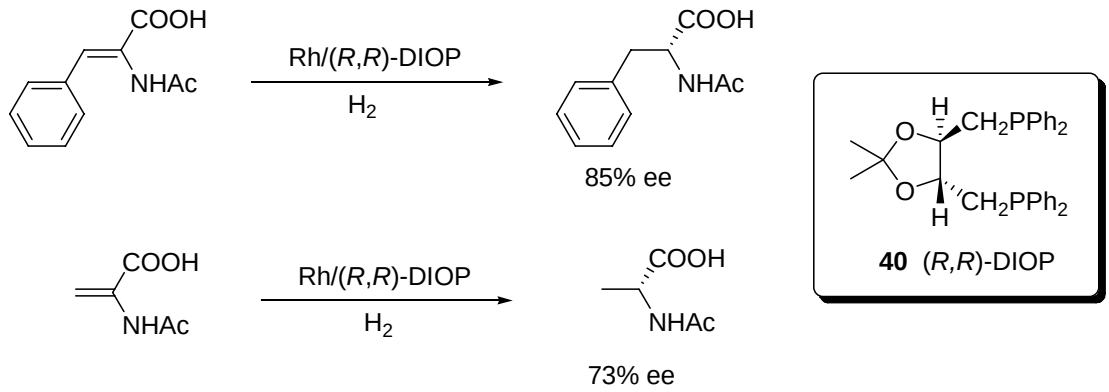
of the reaction. It is economical and environment friendly giving no hazardous by-products. This process has become increasingly important in the synthesis of a wide variety of chiral compounds such as pharmaceuticals, agrochemicals, flavors, fragrances and other industrial chemicals.[3] Procedures in the synthesis of morphine, naproxen (an anti-inflammatory drug)[69], morphinans (an antitussive dextomethorphan)[3], L-DOPA (a drug for treating Parkinson's disease)[70] could be simplified by incorporation of asymmetric hydrogenation.



Scheme 1.3.1

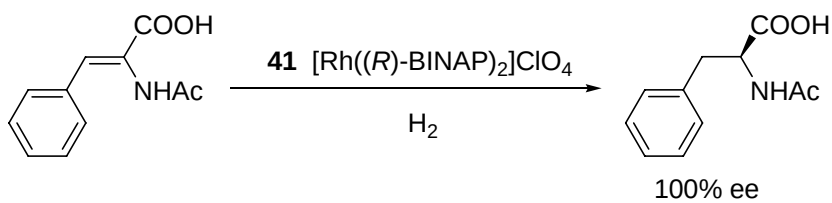


Scheme 1.3.2

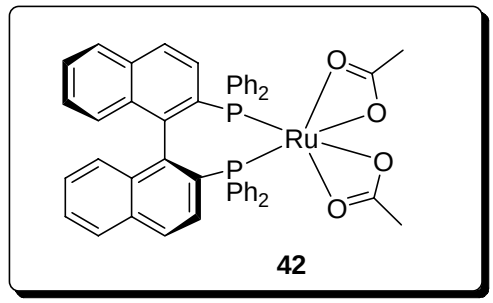


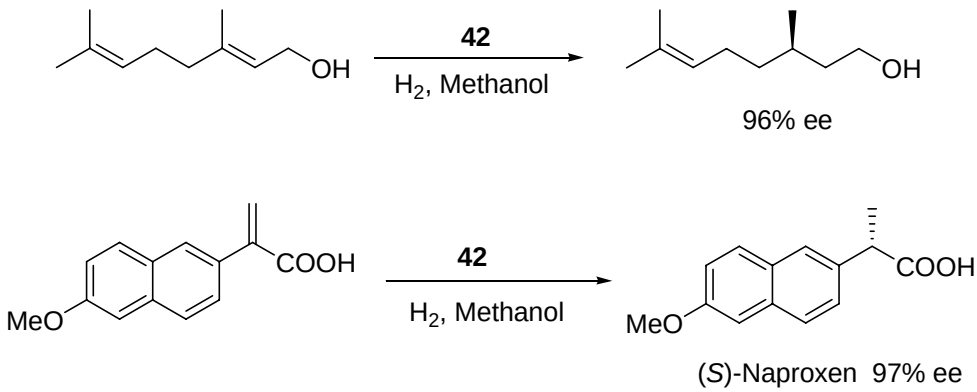
Scheme 1.3.3

Hydrogenation was initiated at the end of the 19th century by Sabatier P. who used fine metal particles as heterogenenous catalysts. In 1965, Wikinson G. used [$RhCl(PPh_3)_3$] catalyst in the hydrogenation of olefinic compounds (Scheme 1.3.1).[71] Knowles[72] and Horner[73] replaced PPh_3 by the chiral phosphine **39** which has the phosphorus atom as a stereogenic center (Scheme 1.3.2). Kagan introduced the important idea of using a chiral bidenate ligand, such as the C_2-symmetric diphosphine ligand DIOP **40** without a chiral phosphorus atom. The chirality located within the carbon skeleton (Scheme 1.3.3). He used its Rh complex for asymmetric hydrogenation of dehydroamino acids leading to phenylalanine with more than 70% ee.[74]

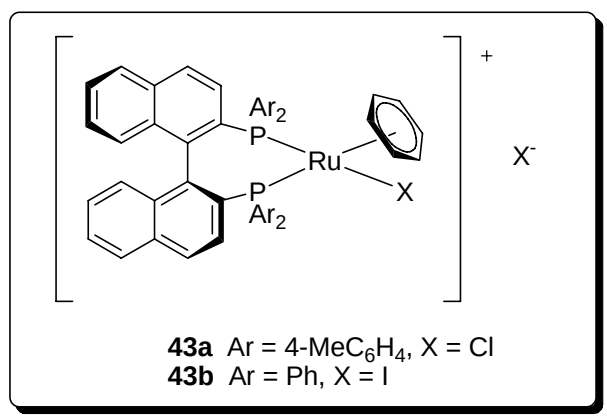


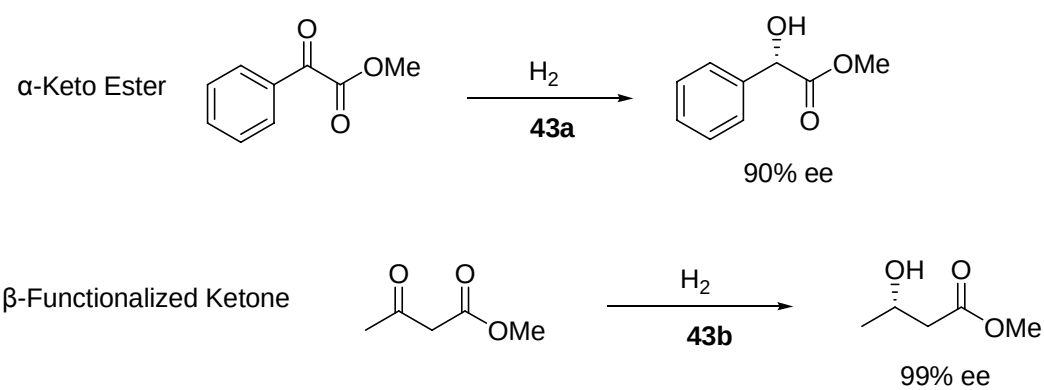
Scheme 1.3.4





Scheme 1.3.5





Scheme 1.3.6

Noyori invented the bidenate ligand BINAP and the cationic BINAP-Rh complexes catalyzed hydrogenation of dehydroamino acid or ester to give the corresponding amino acid derivaties in high ee values (Scheme 1.3.4).[75] The BINAP-Ru(II) dicarboxylate complex **42** was an excellent catalyst for asymmetric hydrogenation of various functionalized olefins (Scheme 1.3.5).[76] The halogen-containing BINAP-Ru(II) complexes **43** are efficient catalysts for the asymmetric hydrogenation of α- and β-functionalized ketones (Scheme 1.3.6). A wide variety of prochiral ketones are hydrogenated enantioselectivity to the corresponding chiral alcohol with 90-100% ee.[77]

In 1995, Noyori discovered the Ru(diphosphine)(1,2-diamine)Cl_2 complexes in 2-propanol with *t*-BuOK system, which is the most efficient method for the hydrogenation of various simple ketones.[37] This catalytic hydrogenation proceeds with an exceptionally high turnover number (TON), high turnover frequency (TOF), and excellent enantioselectivity.

1.3.2 Asymmetric Hydrogenation of Ketones by Diphosphine/Diamine-Ruthenium Complexes

More than half a century ago, selective reduction of simple ketones relied on the metal-hydride chemistry. Chemoselective reduction of a C=O function in the presence of a C=C group is the best effected by stoichiometric $NaBH_4$ reagent.

Enantioselective reduction of prochiral ketones are effected by stoichiometric chiral reagents including BINAL-H[78], chiral amino alcohol with BH_3[79], alpine-borane[80], or chiral oxazaborolidine catalyst with BH_3 (CBS method)[33].

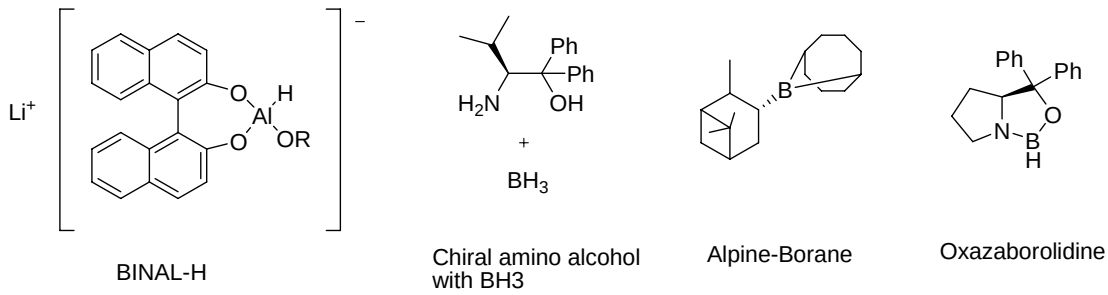
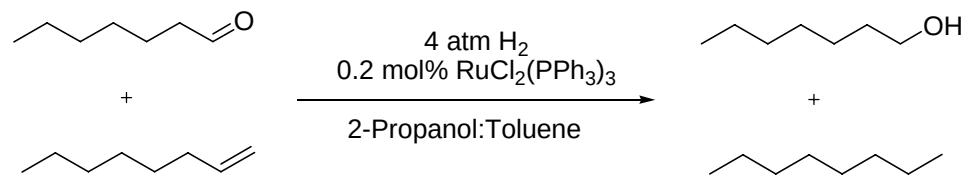
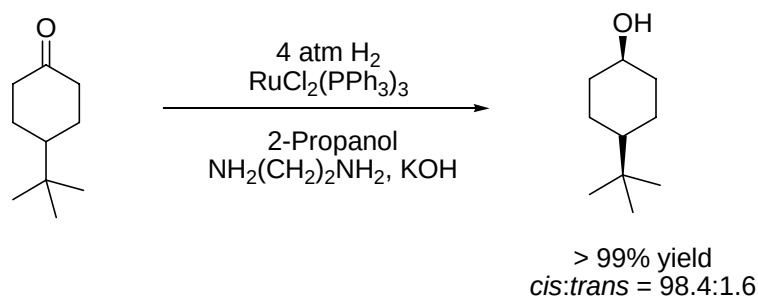


Figure 1.3.1



Additive	Time, min	1-heptanol:octane
No base and amine	150	1:250
$NH_2(CH_2)_2NH_2$ and KOH	10	1500:1

Figure 1.3.2

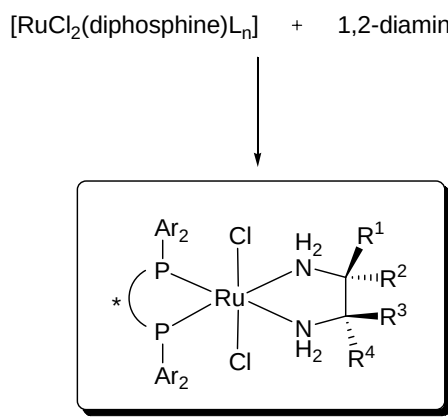


Scheme 1.3.7

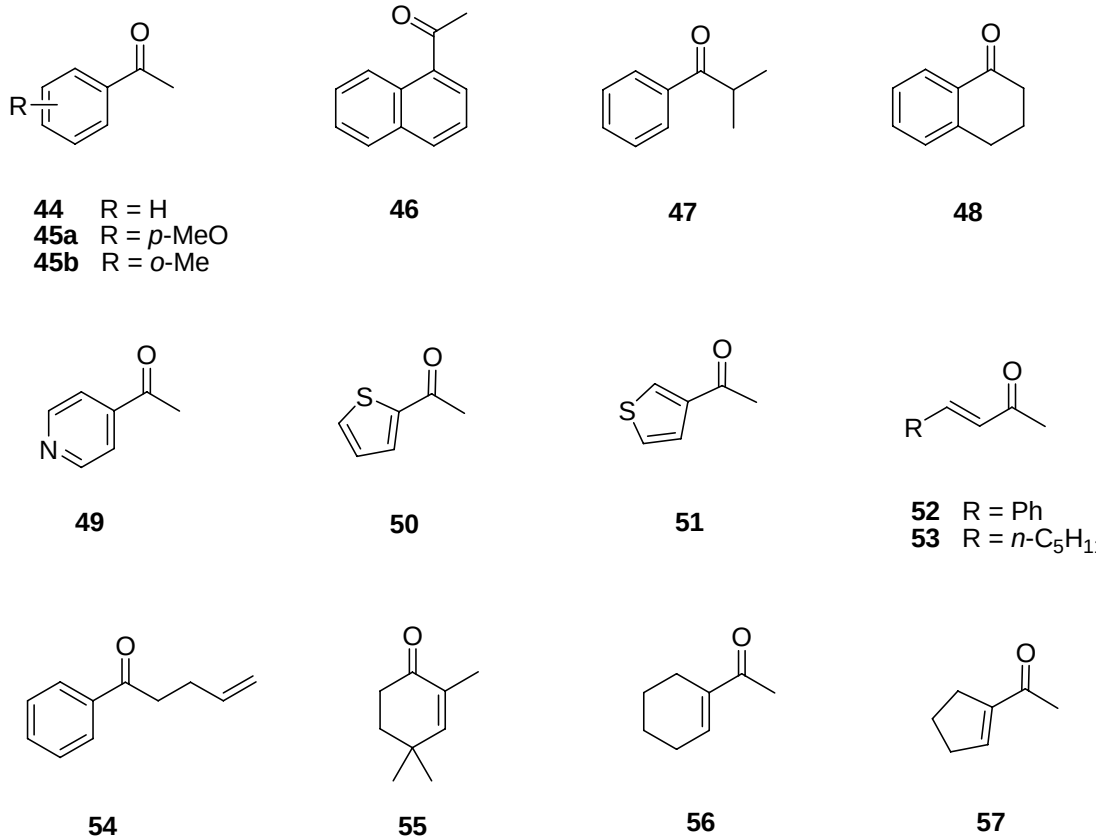
In 1995, Noyori introduced the $RuCl_2(PPh_3)_3/NH_2(CH_2)_2NH_2$/KOH catalyst system which provided a general solution with excellent carbonyl selectivity for hydrogenation.[81] The combined effects of $NH_2(CH_2)_2NH_2$ and KOH decelerate olefin hydrogenation catalyzed by $RuCl_2(PPh_3)_3$ and in turn accelerate carbonyl hydrogenation. This selective hydrogenation is applicable to a range of carbonyl compounds having an unsaturated carbon-carbon bond (Figure 1.3.2). Aliphatic and aromatic ketones with unconjugated terminal olefinic bond were hydrogenated preferentially at the carbonyl site and the products were 98-100% pure. Besides, the Ru complexes were useful for diastereoselective hydrogenation of ketones. For example, hydrogenation of 4-*t*-butylcyclohexanone with $RuCl_2(PPh_3)_3/NH_2(CH_2)_2NH_2$/KOH system took place preferentially from the less crowded equatorial direction to give a 98.4:1.6 mixture of *cis*-4-*t*-butylcyclohexanol and its *trans* isomer (Scheme 1.3.7).[82] However, these Ru catalysts are unable to hydrogenate simple ketones because they lack of heteroatoms (nitrogen, oxygen and halogen atoms) near the carbonyl group for anchoring of the Ru metal.

Noyori focused on the development of an efficient method to hydrogenate unfunctionalized simple ketones to optically active secondary alcohols. Among the catalysts studied, chiral (diphosphine)(1,2-diamine)Ru(II) in combination with 2-propanol as solvent is the best in carbonyl hydrogenation (Scheme 1.3.8). This

catalytic hydrogenation proceeds with an exceptionally high turnover number, high turnover frequency, and excellent enantioselectivity for various simple ketones (Table 1.3.1).[37, 40] Normally, C=C bonds are much more reactive than C=O in catalytic hydrogenation, but this system allows for the preferential saturation of a C=O function over a coexisting C=C linkage (ketone substrates **52**–**57**; figure 1.3.3). Olefinic ketones, either conjugated or nonconjugated, can be converted to olefinic alcohols selectively (entries 39 to 49 in table 1.3.1).[83] The hydrogenation tolerates various functionalities including F, Cl, Br, I, CF_3, OCH_3, $OCH_2C_6H_5$, $COOCH(CH_3)_2$, NO_2, NH_2 and NRCOR.[37,84] Both electronic rich (furan, thiophene, thiazole, etc.) and electronic deficient rings (pyridine and pyrimidine) are successfully hydrogenated to give up to > 99% ee with *trans*-$RuCl_2$[(*R*)-XylylBINAP(*R*)-DAIPEN] and *trans*-$RuCl_2$[(*R*)Xylyl-P-Phos(*R*,*R*)DPEN] catalysts (entries 33-38**)**.[85] Our group had previously developed the chial $RuCl_2$[(P-Phos)(DPEN)] precatalyst which had high activity and enantioselectivity in asymmetric hydrogenation of various ketones.



Scheme 1.3.8



44 R = H
45a R = *p*-MeO
45b R = *o*-Me

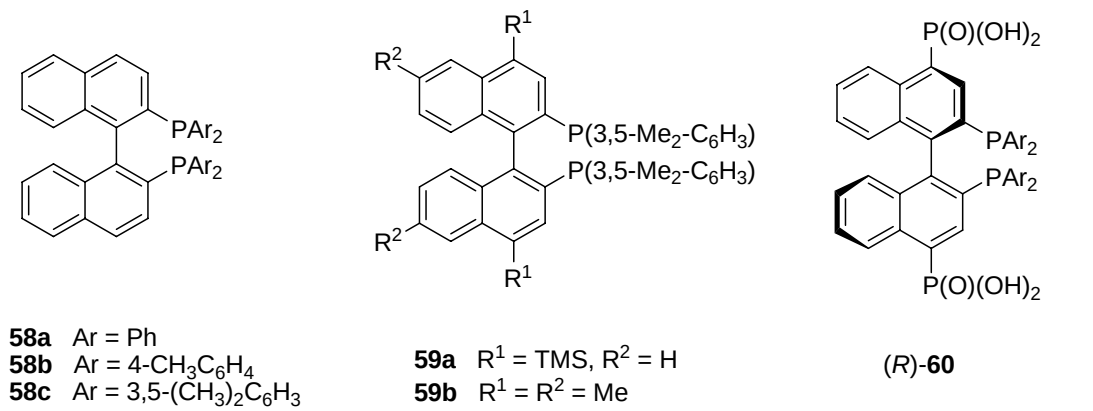
46 **47** **48**

49 **50** **51**

52 R = Ph
53 R = *n*-C_5H_{11}

54 **55** **56** **57**

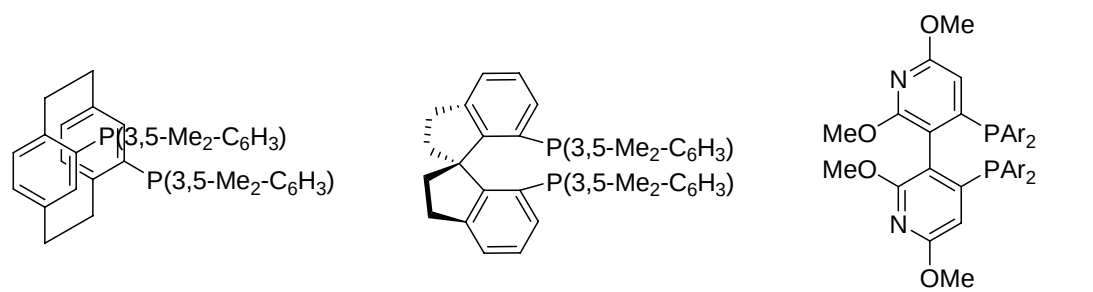
Figure 1.3.3 Various ketone substrates



58a Ar = Ph
58b Ar = 4-$CH_3C_6H_4$
58c Ar = 3,5-$(CH_3)_2C_6H_3$

59a R^1 = TMS, R^2 = H
59b R^1 = R^2 = Me

(*R*)-**60**



61

(*S*)-**62**

63a Ar = Ph
63b Ar = 3,5-$(CH_3)_2C_6H_3$

Figure 1.3.4 Diphosphine ligands

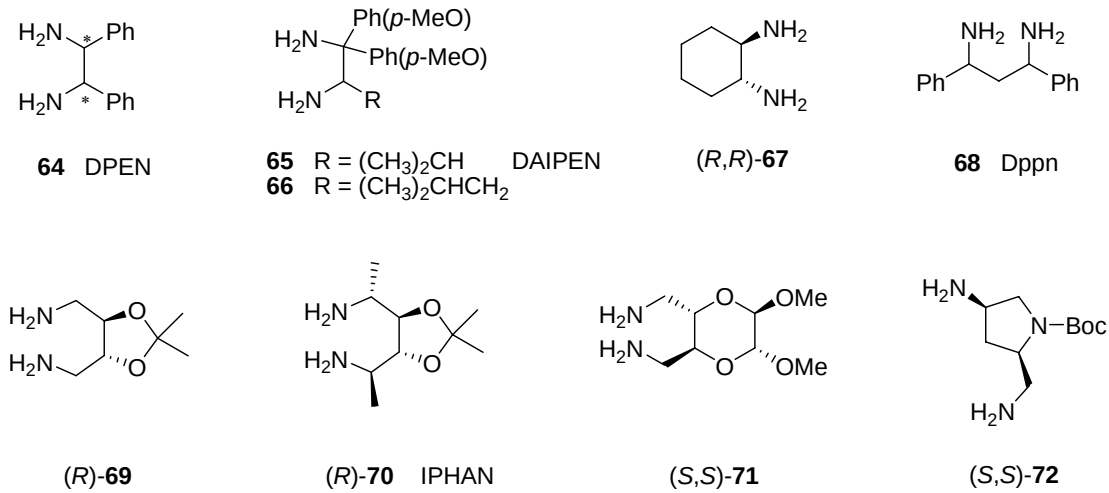


Figure 1.3.5 Diamine ligands

Table 1.3.1 Asymmetric Hydrogenation of Ketones Catalyzed by (diphosphine)(diamine)Ru(II) Complexes.

Entry	Sub.	Diphosphine	Diamine	H_2 (bar)	S/C	Yield %	Ee %	Config.	Ref.
1.	44	(*S*)-**58a**	(*S*)-**66**	4	500	> 99	87	*R*	37
2.	44	(*S*)-**58c**	(*S*)-**65**	8	100000	97	99	*R*	83
3.	44	(*S*)-**58c**	(*R*,*R*)-**64**	4	2000	98	99	*S*	83
4.	44	(*R*)-**59a**	(*R*)-**65**	48.3	1000	> 99	99.8	/	3
5.	44	(*R*)-**59b**	(*R*)-**65**	48.3	1000	> 99	99.6	/	3
6.	44	(*R*)-**60**	(*R*,*R*)-**64**	48.3	1000	> 99	97.1	*S*	86
7.	44	(*R*)-**60**	(*R*)-**65**	48.3	1000	> 99	98.5	*S*	86
8.	44	(*R*)-**61**	(*S*,*S*)-**64**	8	20000	> 99	99	*R*	87
9.	44	(*S*)-**62**	(*R*,*R*)-**64**	50	5000	100	99	*S*	88
10.	44	(*R*)-**63b**	(*R*,*R*)-**64**	34	100000	99.7	99.1	*S*	89
11.	44	(*S*)-**63b**	(*S*,*S*)-**68**	8.3	10000	100	95.3	/	90
12.	45a	(*S*)-**58b**	(*S*)-**65**	4	500	98	99	*R*	37
13.	45a	(*S*)-**58c**	(*S*)-**65**	10	2000	100	100	*R*	83
14.	45a	(*R*)-**59a**	(*R*)-**65**	48.3	1000	> 99	98.7	/	3
15.	45a	(*R*)-**59b**	(*R*)-**65**	48.3	1000	> 99	99.0	/	3
16.	45a	(*R*)-**60**	(*R*,*R*)-**64**	48.3	1000	> 99	95.4	*S*	86

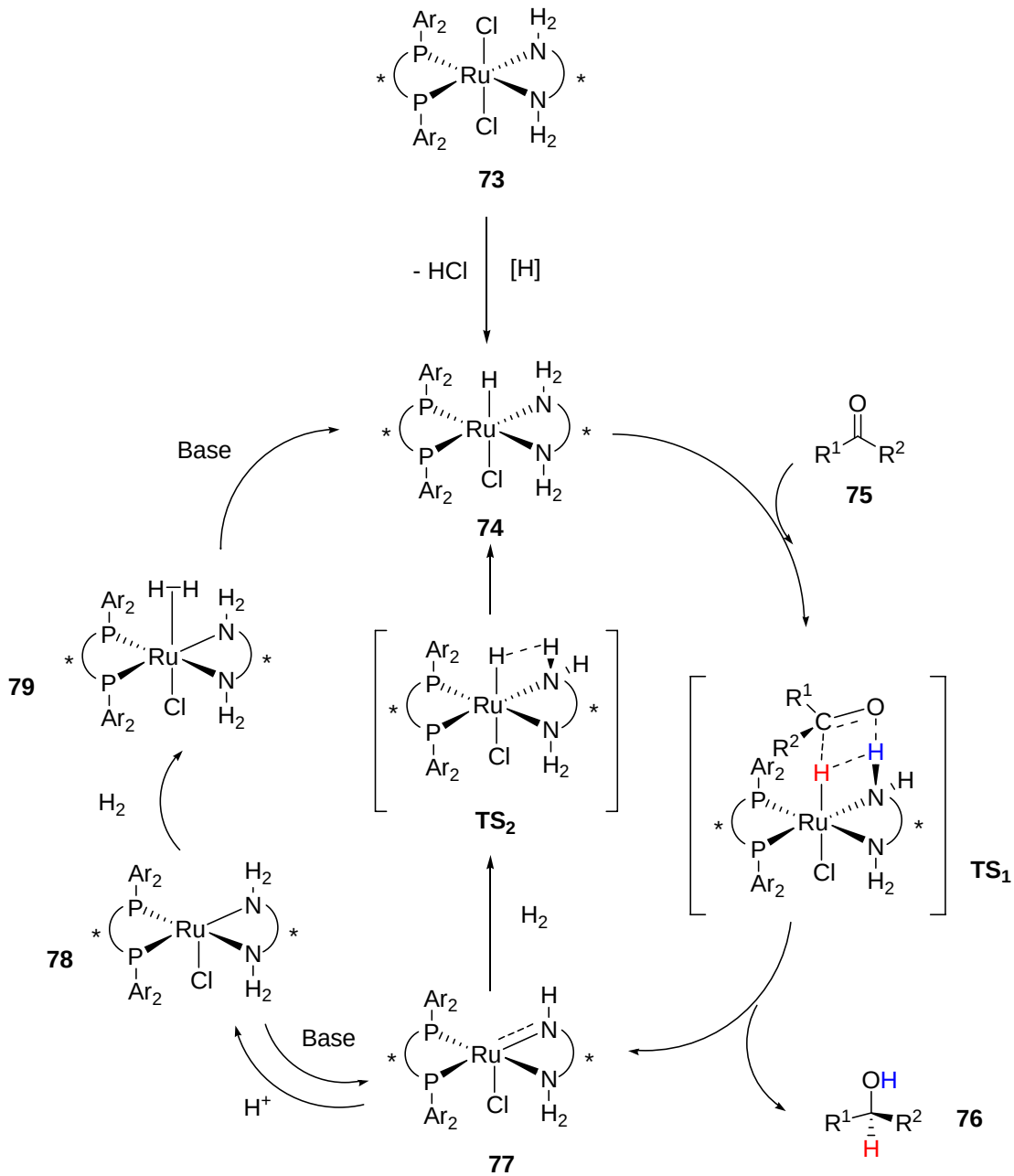
17.	45a	(*R*)-**60**	(*R*)-**65**	48.3	1000	> 99	98.6	*S*	86
18.	45a	(*S*)-**61**	(*R*,*R*)-**64**	5.5-8.0	3000	> 99	97	/	91
19.	45a	(*S*)-**62**	(*R*,*R*)-**64**	50	5000	100	98	*S*	88
20.	45a	(*R*)-**63b**	(*R*,*R*)-**64**	21	20000	99.6	98.7	*S*	89
21.	45a	(*S*)-**63b**	(*S*,*S*)-**68**	10	2500	> 99	97.3	/	90
22.	45b	(*S*)-**58b**	(*S*)-**65**	10	100000	94	99	*R*	84
23.	45b	(*R*)-**63b**	(*R*,*R*)-**64**	21	4000	100	97.7	*S*	89
24.	46	(*S*)-**58b**	(*S*,*S*)-**64**	10	100000	98	99.5	*R*	84
25.	47	(*S*)-**58b**	(*S*,*S*)-**64**	8.3	1000	50	73	*R*	92
26.	47	(*S*)-**58b**	(*R*)-**69**	10	1000	> 99	97	*S*	92
27.	47	(*S*)-**58b**	(*S*,*S*)-**72**	8.3	1000	> 98	80	/	90
28.	47	(*S*)-**63a**	(*R*)-**69**	10	1000	> 99	97	*S*	92
29.	48	(*S*)-**58b**	(*S*,*S*)-**64**	8.3	500	98	24	/	90
30.	48	(*S*)-**58b**	(*S*,*S*)-**71**	8.4	500	23.5	81	/	90
31.	48	(*S*)-**58c**	(*R*)-**70**	50	11000	99.8	98	*R*	93
32.	48	(*S*)-**63b**	(*R*)-**69**	10	250	99	96	*R*	92
33.	49	(*R*)-**58c**	(*R*)-**65**	8	5000	> 99	99.8	*S*	85
34.	49	(*R*)-**63b**	(*R*,*R*)-**64**	24	4000	> 99.9	97.9	*S*	94
35.	50	(*R*)-**58c**	(*R*)-**65**	8	5000	> 99	99	*S*	85
36.	50	(*R*)-**63b**	(*R*,*R*)-**64**	24	4000	> 99.3	98.3	*S*	94
37.	51	(*R*)-**58c**	(*R*)-**65**	8	5000	> 99	99.7	*S*	85
38.	51	(*R*)-**63b**	(*R*,*R*)-**64**	24	10000	> 99.9	99.0	*S*	94
39.	52	(*S*)-**58c**	(*S*)-**65**	80	100000	100	97	*R*	83
40.	52	(*R*)-**58c**	(*R*,*R*)-**67**	10	2000	100	91	*S*	83
41.	52	(*S*)-**62**	(*R*,*R*)-**64**	50	5000	100	96	*S*	88
42.	53	(*S*)-**58c**	(*S*)-**65**	8	2000	98	97	*R*	83
43.	54	(*S*)-**58a**	(*S*)-**65**	8	500	97	90	*R*	81
44.	55	(*S*)-**58b**	(*R*,*R*)-**64**	10	10000	100	94	*R*	84
45.	55	(*S*)-**58b**	(*R*)-**70**	50	10000	99.5	96	*R*	93
46.	56	(*S*)-**58a**	(*S*)-**65**	8	500	91	98	*R*	81
47.	56	(*S*)-**58c**	(*S*)-**65**	10	10000	99	100	*R*	83
48.	56	(*R*)-**61**	(*S*,*S*)-**64**	5.5-8.0	3000	> 99	94	*R*	91
49.	57	(*S*)-**58a**	(*S*)-**65**	4	500	98.7	91	*R*	81

The combination of diphosphine and diamine ligands is important for achieving a high ee. Different combinations of diphosphine and diamine ligands having similar conformation successfully catalyzed hydrogenation of ketones (Table 1.3.1). Diphosphine ligands, such as ligands **58**-**60** and **63**, form 7-membered chelate ring with the ruthenium center and 1,2-diamine ligands **64** and **65** form 5-membered chelate ring with the ruthenium center (Figure 1.3.4 and 1.3.5). This conformation could give high activity and enantioselectivity. Some research groups modified to use other diphosphine ligands such as **61** and **62** without the 7-membered ring in the Ru complexes but DPEN ligand remained to form 5-membered ring with metal center. These precatalysts were also efficient in hydrogenation of simple ketone (entries 8-9). Various diphosphine ligands, which improve their enantioselectivity, were employed. Some ketone substrates, such as isobutyrophenone and tetralone, remain unreactive or are hydrogenated with undesirablely low ee with the 1,2-diamine ruthenium catalysts. For a few cases, replacement of 1,2-diamine with 1,3-diamine **68** or 1,4-diamine **69**-**72** provides larger ring structures (6- or 7-membered) and give higher enantiomeric excesses (entries 25-32). [90,92,93]

1.3.3 Mechanism of Hydrogenation of Ketones Catalyzed by Ruthenium Complexes

Mechanisms of hydrogenation are divided into two types according to different proton sources. Hydrogen gas is the proton source in the mechanism of H_2-hydrogenation mechanism. The other type of mechanism is transfer hydrogenation, in which proton sources are usually secondary alcohols, such as 2-propanol, or formic acid with triethyl amine.[95] H_2-hydrogenation mechanism only is discussed here.

Noyori and co-workers have developed very active and selective ruthenium catalysts for asymmetric hydrogenation of ketones.[40] The ruthenium catalysts are usually generated in 2-propanol solution by mixing a ruthenium dichloride precursor complex with an excess of a strong base such as potassium *t*-butoxide under hydrogen gas in the presence of the ketone substrate. The ruthenium complex *trans*-$RuCl_2$-(diphosphine)(diamine) contains bidentate phosphine ligands, especially BINAP, and an achiral or chiral diamine ligand, such as DPEN and DAIPAN.



Scheme 1.3.9 Mechanism of hydrogenation of ketones

The H_2-hydrogenation mechanism involves a hydride on the ruthenium catalyst which is formed by base-aided heterolysis or *via* a metal hydride (MH). The metal hydride is generated by oxidative addition of molecule H_2 to the metal. Hydride transfer from the metal center to the carbonyl carbon atom is considered to occur by a

[2+2] reaction of the substrate-MH π complex forming a metal alkoxide (Scheme 1.3.9).[45,96,97] The presence of an NH_2 end in the diamine auxiliary is crucial for the catalytic activity. First, the Ru complex **73** is converted to the RuHX complex **74** with the aid of an alkaline base and hydrogen source, H_2. Hydridic Ru-H and protic N-H are simultaneously transferred to the C=O linkage from **75** *via* a six-membered pericyclic $\mathbf{TS_1}$. The hydrogenative reactivity of coordinatively saturated **74** originates from the charge alternating arrangement $H^{\delta-}$-$Ru^{\delta+}$-$N^{\delta-}$-$H^{\delta+}$, which fit well with the $C^{\delta+}$=$O^{\delta-}$ dipole. Thus, the hydride on Ru possesses sufficient nucleophilicity, while the NH moiety exhibits a hydrogen-bonding ability to activate the carbonyl function. The 16-electron complex **77** and alcoholic product **76** are formed directly. The Ru center and the ligand cooperate in the bond-breaking and bond-forming processes. Although several diastereomers are possible for the octahedral reducing species **74**, the hydride and the two nitrogen atoms must have a *fac* relationship. Morris had demonstrated that the axial NH is aligned with the ruthenium hydride by X-ray crystal structure study.[45] The 16-electron complex **77** resonates with the Ru=N bond bearing 18-electron amido complex through electron release from the nitrogen to the electron-deficient Ru atom. The unique $Ru^{\delta+}$-$N^{\delta-}$ dipolar bond caused **77** to split H_2 molecules *via* transition state $\mathbf{TS_2}$ thus restoring the ruthenium hydride **74**. Alternatively, **74** may be regenerated from **77** and H_2 by the way of **78** and **79** in

protic medium with base addition.

1.3.4 Reactive Catalyst System

Both diamine and metal alkoxide base are having important roles for the catalytic H_2 hydrogenation. The activity of catalysts is increased by the addition of diamine and base.[40] For example, in the hydrogenation of acetophenone, ethylenediamine enormously accelerated hydrogenation with hydrogen molecules in the presence of a base giving a TOF of 6700 h^{-1} at 3 atm whereas TOF of 70h^{-1} was obtained in the presence of KOH alone without the diamine. A TOF of less than 5 was obtained in the presence of diamine without KOH. In the absence of hydrogen gas, the addition of diamine and base retarded the transfer hydrogenation to TOF of 7 h^{-1}.[40]

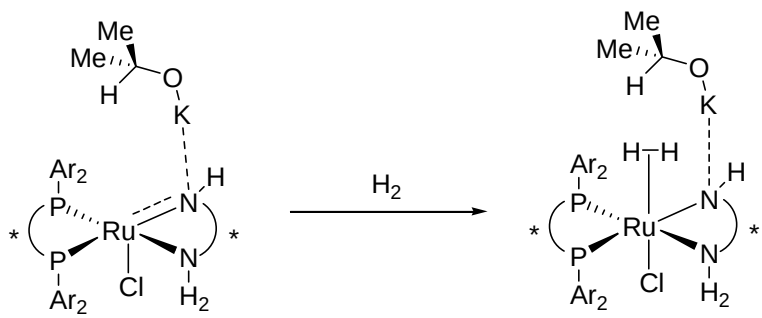


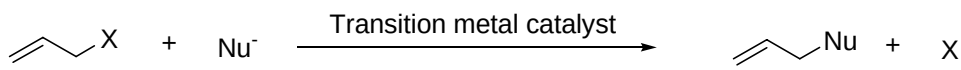
Figure 1.3.6

The chelating diamine ligands must contain at least one primary or secondary amine end. The axial proton on the diamine ligand is transfered from the catalyst to the carbonyl oxygen (**TS_1** in Scheme 1.3.9). *N*,*N*,*N*',*N*'- tetramethylethylenediamine (TMEDA) which is a tertiary amine is totally ineffective.[45,96] On the other hand, metal

alkoxide base is important in this system for ketone hydrogenation.[98] The ruthenium amido moiety (Ru=N) is not sufficiently basic to cleave hydrogen efficiently enough in the absence of alkali metal cations (Figure 1.3.6). The coordination of the alkali metal cation to the N atom of the ruthenium amide should withdraw electron density from the amide ligand, and hence from the ruthenium center. A hydrogen molecule coordinates to the more acidic ruthenium center and then deprotonates to restore the metal hydride complex in the catalytic cycle.

1.4 Catalytic Asymmetric Allylic Alkylation

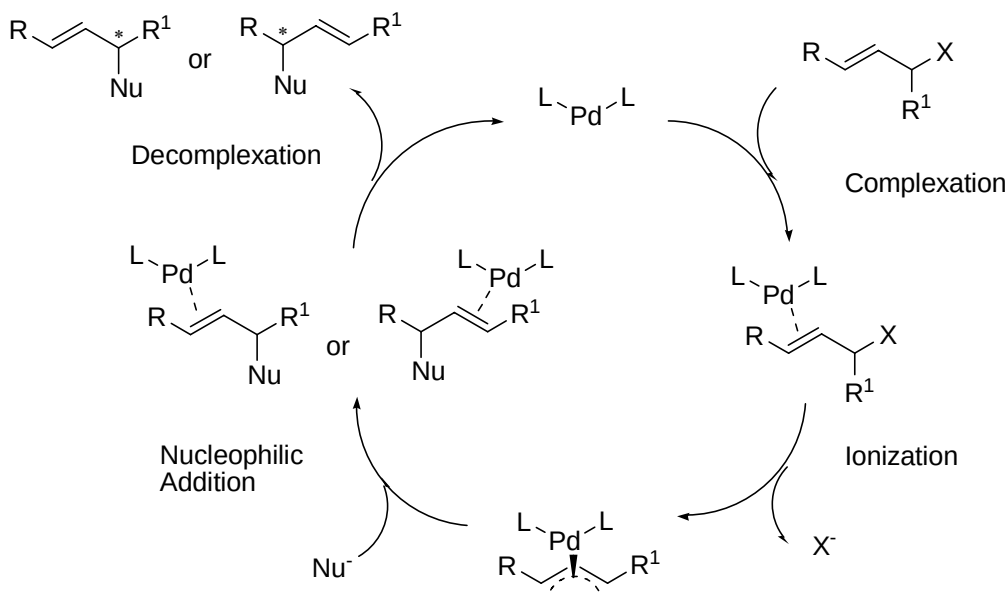
The first example of asymmetric allylic substitution with palladium catalyst was demonstrated in 1973 by Trost.[99] Since then, the asymmetric allylic alkylation reaction has undergone a revolutionary development in recent years to establish its synthetic viability. It has been shown to be a powerful method for the formation of carbon-carbon and carbon-heteroatom bonds.[100] In addition, this reaction has been demonstrated to be useful in the syntheses of valuable small molecules and complex natural products.[101,102]



Scheme 1.4.1

The allylic alkylation reaction is a nucleophilic substitution of allylic compound, and the process is catalyzed by transition metal catalyst (Scheme 1.4.1). The key intermediate of the catalytic cycle in metal-catalyzed allylic alkylation is the (π-allyl)metal complex which undergoes nucleophilic attack to yield a chrial alkylation product with high chemo-, regio- and stereoselevtivities. This process is catalyzed by a variety of transition-metal complexes derived from palladium[103], rhodium[104], iridium[48], ruthenium[105] and molybdenum[106]. Among the metals that are used for carbon-carbon bond forming, palladium is the most widely studied.

1.4.1 Fundamental of Enantioselective Allylic Alkylation[100,101]



Scheme 1.4.2 Catalytic cycle in palladium-catalyzed asymmetric allylic alkylations

Transition metal catalyzed asymmetric allylic alkylation (AAA reaction) has

been shown to be an effective method for the synthesis of quaternary substituted carbon centers. The catalytic cycle consists of four steps as illustrated in Scheme 1.4.2: coordination of the transition metal to the olefin (electrophile), ionization of the allylic leaving group to generate a (π-allyl)metal complex, alkylation by the nucleophile to generate a new transition metal olefin complex and finally decomplexation which gives the product and returns the transition metal. The general catalytic cycle of the AAA reaction offers at least five opportunities for enantiodiscrimination depending on structure of the substrates and transition metal complexes, as chiral induction can be derived in the bond-breaking and bond-making events which occur on the π-allyl face opposite the metal and its attendant ligand.

1.4.2 Mechanisms for Enantiodiscrimination[100,102]

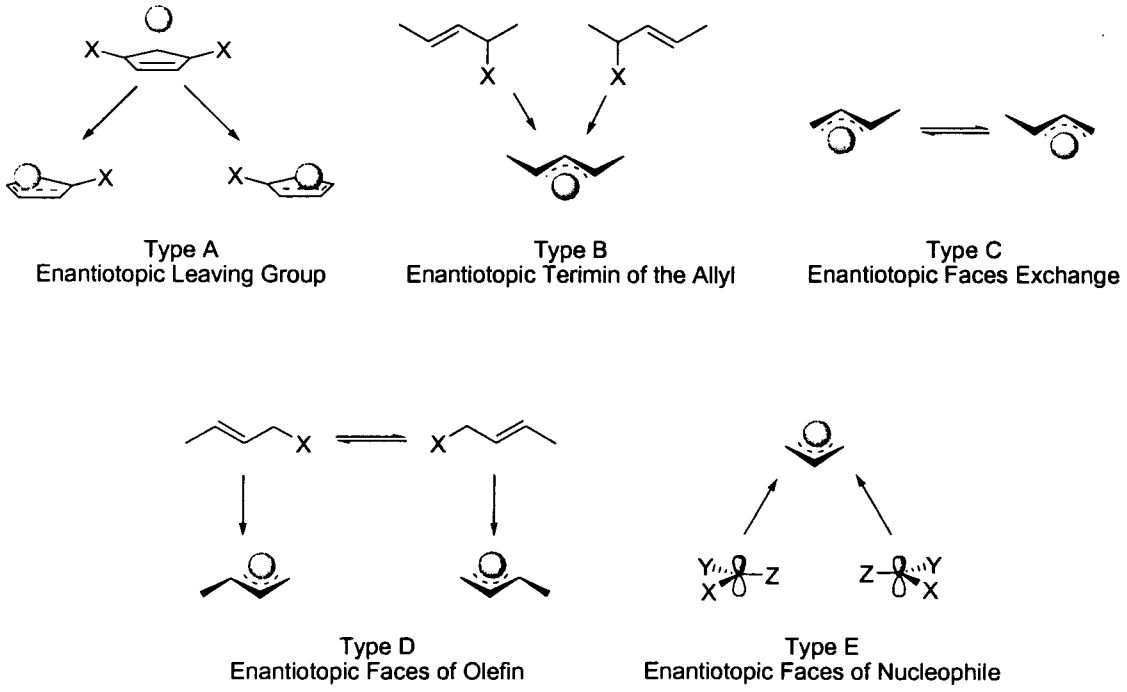


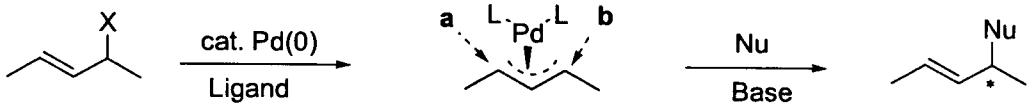
Figure 1.4.1 Various sources of enantiodiscrimination in asymmetric allylation.

The ionization step in the catalytic cycle has five opportunities for chiral inducing events that has be summarized in Figure 1.4.1.

Type A: Enantiotopic Leaving Group

Selective ionization of enantiotopic leaving groups induces specific stereochemistry during substitution.

Type B: Enantiotopic Termini of the Allyl

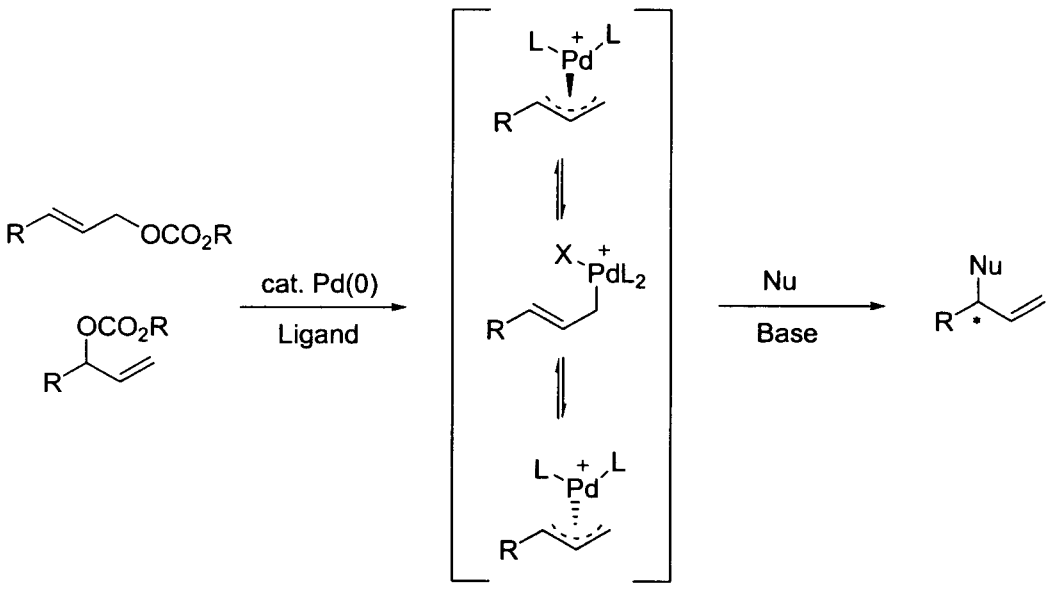


Scheme 1.4.3 Desymmetrization of π-allyl intermediate with nucleophile

A racemic substrate generates a *meso*-π-allyl complex intermediate after ionization. Two allylic termini of the complex are enantiotopic (Scheme 1.4.3).[102] This allows for the enantioselectivity with respect to product. It is determined by the regiochemistry of the nucleophilic addition to the allyl complex.

Type C: Enantiotopic Face Exchange

The two diastereomeric complexes that result from ionization can interconvert through π-σ-π equilibration on the terminal carbon of the allyl system (Scheme 1.4.4).[102] The rate of this interconversion is faster than nucleophilic addition.



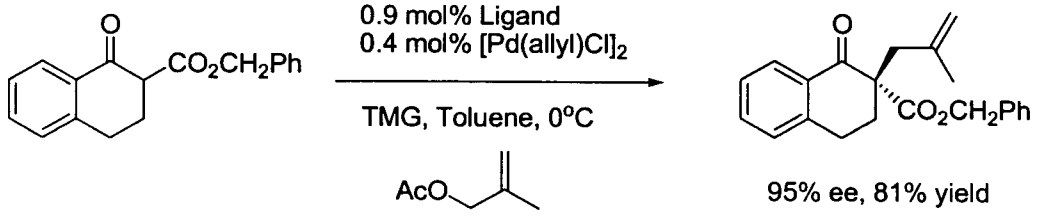
Scheme 1.4.4 Asymmetric allylic alkylaltion via enantioface exchange of allylpalladium Complex

Type D: Enantiotopic Faces of Olefin

When the olefin is not symmetrically substituted, the transition-metal-ligand complex must distinguish between the two prochiral faces of the olefin.

Type E: Enantiotopic Faces of Nucleophile

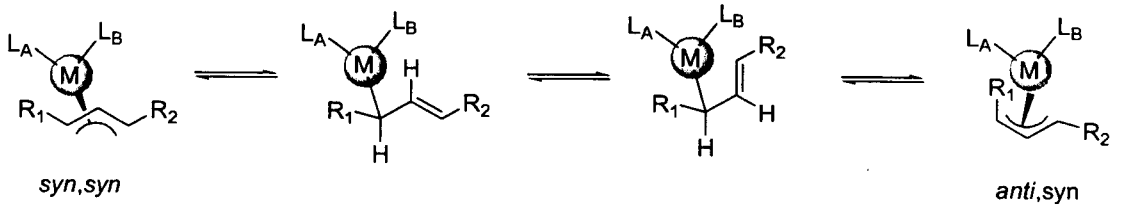
When the nucleophile is a prochiral compound or a rapidly equilibrating racemic mixture, asymmetric induction is also possible at the nucleophile (Scheme 1.4.5).[107]



Scheme 1.4.5

1.4.3 Stereodynamics of Allyl Transition Metal Complexes

The (π-allyl)metal complexes exist are dynamic equilibrium under typical alkylation reaction conditions during which their conformation and geometry may change by intramolecular processes as well as by reversible ligand-dissociation and reassociation processes. In general, the equilibration occurs at a faster rate when compared with the nucleophilic addition. Depending on the mechanism from which enantioselectivity derives, such behavior of (π-allyl)metal complexes can be detrimental or mandatory.

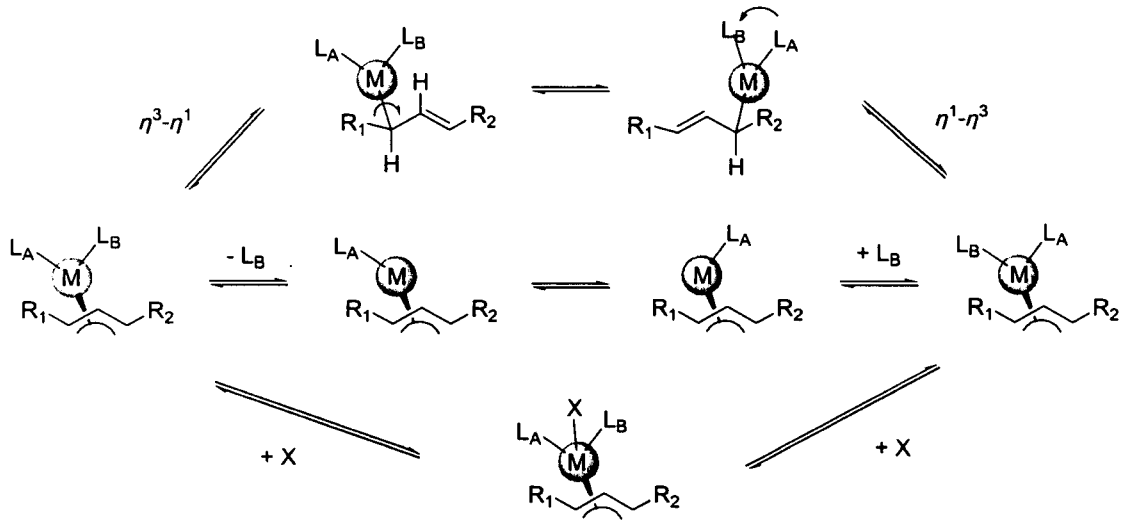


Scheme 1.4.6 *Syn/anti* isomerization by (η^3-η^1-η^3) mechanism

A metal-bound allyl ligand can undergo geometric interconversion by changing its conformation. The well know π-σ-π (η^3-η^1-η^3) isomerizaiton, which involves the rotation around the carbon-carbon bond in allyl unit, leads to the *syn/anti* interconversion as illustrated in Scheme 1.4.6. The R^1 group on carbon changes its configuration but it still remains *trans* to the ligand L_B. If the metal is bound to a non-C_2 symmetric ligand, the exchange process represents an important *endo/exo*

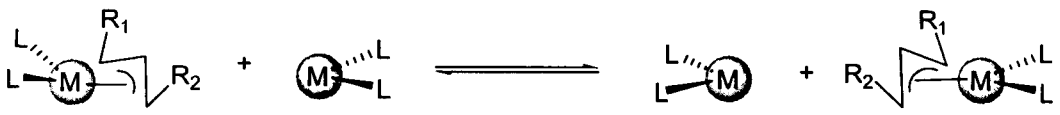
isomerization process: the "W" shaped ally unit becomes "M" shaped.

The reorganization of the relative orientation between the ligand and the allyl unit is more likely to follow the mechanisms depicted in Scheme 1.4.7. These mechanisms include rotation of metal-carbon bond, dissociation of one of the ligands and association of external ligands (halide ions and solvents).



Scheme 1.4.7 Mechanisms for apparent allyl rotation

Isomerization of a π-allyl species can arise from a bimolecular reaction as shown in Scheme 1.4.8. In the case of unsymmetrically substituted allyl systems, this process constitutes enantioface exchange; the stereochemistry of three allyl carbons is simultaneously inverted.



Scheme 1.4.8 Mechanism for racemization

1.4.4 Ligand Design

In order for chiral ligands to control enantiodiscrimination in this reaction, they must influence bond making and bond breaking events occurring outside the coordination sphere of the metal; thus, they must transmit their stereochemical information through space.[103] The distal design of ligands is important to transmit enantioselectivity in this reaction. Three concepts have been proposed and shown in Figure 1.4.2. The ligand is attaching to a substituent via a tether long enough to reach the other side of the π-allyl unit to interact with any incoming nucleophile (Type I). Electronic dissymmetrization on the donor atom of the ligand is imposed where different bond length **a** and **b** promote differential reactivity at each allylic terminus (Type II). The conformational bias for edge-face interactions of the phenyl groups of diarylphosphine moieties provides the substrate with chiral space (Type III). Increasing this angle will push the aryl groups creating the chiral space upward then it is better embracing the π-allyl moiety.

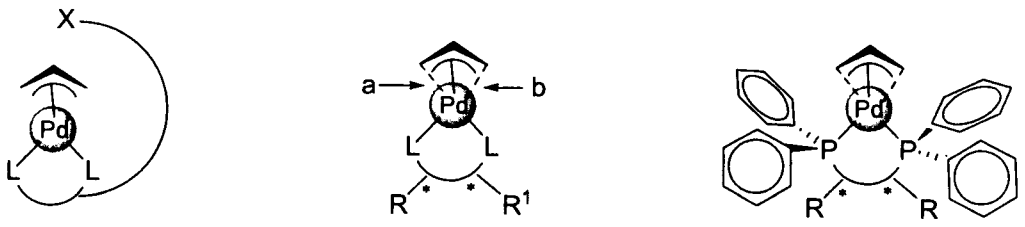


Figure 1.4.2 Concepts used in ligand design

The ligand design plays an important role in the development of the

asymmetric allylic alkylation. A variety of P,P-, P,N- and N,N-based ligands, with C_1 as well as C_2 symmetry, have proven to induce high selectivity in the process. Figures 1.4.4 to 1.4.6 show a selection of ligands that have been successfully used in palladium-catalyzed AAA reaction. Table 1.4.1 summarizes the ligands that give high enantioselectivities (>90% ee) in the alkylation of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate (Figure 1.4.3). This typical reaction could generate *meso* π-allyl intermediates where the two allylic termini of such intermediates would be enantiotopic. Enantioselectivity is derived from the regiochemistry of nucleophilic addition (**a** vs. **b**). Therefore the structure of the nucleophile greatly affects the enantioselectivity. Research workers employed dimethyl malonate with *N,O*-bis(trimethylsilyl)acetamide (BSA) and sodium dimethyl malonate to influence the enantioselectivity. In a number of cases, better enantioselectivities have been obtained when the nucleophile is generated by using BSA as base, often in the presence of acetate ion (KOAc or LiOAc).

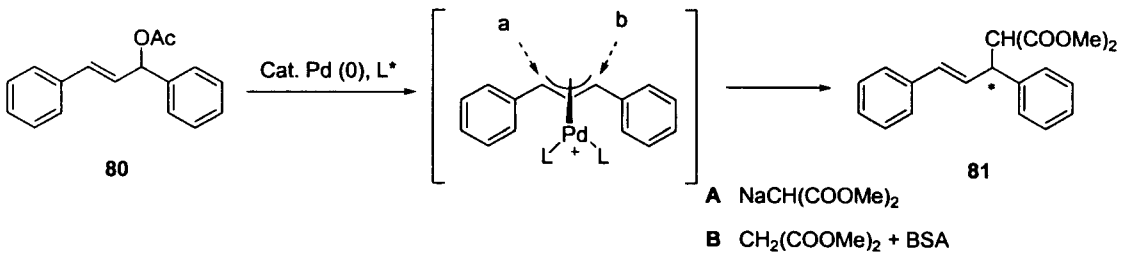


Figure 1.4.3 General equation of alkylation of 1,3-diphenyl-2-propenyl acetate.

Table 1.4.1 Alkylation of 1,3-diphenyl-2-propenyl acetate **80** with carbon nucleophiles

Entry	Ligand	Nu	% Yield	% ee	Ref.
		Chiral Phosphorous Ligands			
1	**82**	A	86	90	108
2	***ent*-58a**	B	85	90	109
3	**83b**	A	40	92	110
4	**83c**	A	85	96	111
5	**84**	B	nd	93	112
6	**85a**	B	95	92	113
7	**85b**	B	>90	91	111
8	**85c**	B	> 90	92	114
9	**86**	B	>90	91	114
10	**87**	B	99	97	115
11	**88**	B	56	92	116
12	**89**	A	90	91	114
13	**90**	B	> 99	94.2	117
14	**62b**	B, Et_2Zn	98	97	118
15	**62c**	B, Et_2Zn	95	97.3	119
16	**62d**	B, Et_2Zn	95	97.6	119
17	**62a**	B, Et_2Zn	97	98.8	119
18	**62e**	B, Et_2Zn	96	99.1	119
19	**91a**	B	99	96.8	120
20	**91b**	B	99	95.8	121
21	**91c**	B	99	98.0	121
22	**91d**	B	99	96.1	121
23	**91e**	B	99	97.3	121
24	**91f**	B	99	97.5	121
		Chiral Dinitrogen Ligands			
25	**92**	B	97	95	122
26	**93**	A	100	90	119
27	**93**	B	97	97	121
28	**94**	B	83	95	123
29	**95**	A	81	95	124
30	**96**	B	89	99	125
31	**97**	B	98	91	126
32	**98**	B	80	92	127
33	**99**	B	97	99	128

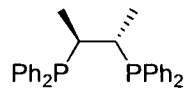
34	**100**	B	83	99	129
35	**101**	B	92	91	130
36	**102**	B	91	98	131
37	**103**	B	15	92	129
38	**104**	B	72	94	132
		Chiral P,N-chelate Ligands			
39	**105a**	B	98	98	133
40	**105b**	B	99	99	134
41	**106**	B, LiOAc	99	92	135
42	**107**	A	99	95	132
43	**109**	B	94	98	134
44	**109**	B, THAB	99	97	136
45	**110**	B	78	94	137
46	**111**	A	90	99	138
47	**112**	A	94	92	139
48	**113**	A, 15-c-5	nd	90	113
49	**114a**	B	96	96	123
50	**114a**	B	96	93	123
51	**114b**	A	95	96	140
52	**114c**	B	99	96	141
53	**115a**	A	99	91	142
54	**115b**	B	99	96	107
55	**116**	B	62	91	141
56	**117**	A	41	94	143
57	**118a**	A	82	91	144
58	**118b**	A	93	98	145
59	**119**	A	89	90	146
60	**120**	B	94	94	147
61	**121a**	B	94	92	147
62	**121b**	B	94	94	147
63	**122a**	B	81	91	145
64	**122b**	B	61	90	145
65	**122c**	B	89	90	145
66	**123**	B	97	98	145
67	**124a**	B	98	98	148
68	**124b**	B	94	97	149
69	**124c**	B	94	94	149
70	**125**	B	98	96	150

71	**126**	B	100	98	151
72	**127a**	B	84	95	149
73	**127b**	B	75	95	149
74	**128**	B	98	94	152
75	(*S*)-**13**	B	98	97	153
76	**129**	B	98	95	154
77	(S,S_p)-**19a**	B	90	96	154
78	(R,S_p)-**16a**	B	96	90	155
79	(R,S_p)-**16b**	B	99	93	155
80	(R,S_p)-**16a**	B	80	98	156
81	**130b**	B	95	98	156
82	**130c**	B	95	98	156
83	**131a**	B	> 95	96	157
84	**131b**	B	> 95	90	157
85	**132a**	B	96	93	158
86	**132b**	B	98	93	159
87	**132c**	B	96	99	159
88	**133**	B	99	98.6	160
89	(S,S,S_p)-**24**	B	98	95	161
90	**134**	B	> 90	94	162
91	**135**	A	94	95	163
92	**135**	B	80	99	163
93	(R,S_p)-**28a**	B	96	97	67
94	(R,S_p)-**31b**	B	93	97	68

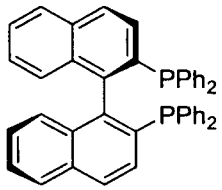
Chiral Phosphorus Ligands

Chiral phosphorus ligands are very useful and versatile for metal-catalyzed asymmetric reactions. Diphosphine ligands (such as DIOP[4], BINAP[1], BPPFA[164], Josiphos and Duphos) gave high enantioselectivities in asymmetric hydrogenation of olefins and ketones. Although not many chiral phosphorus ligands were employed in AAA reaction during the last two decades, some of them could form highly active and

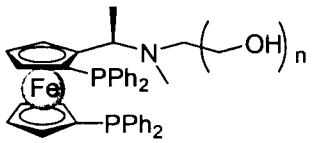
enantiodiscriminative complexes. Chiral C_2-symmetric ligands, such as **62** and **91**, had given good enantioselectivities (95.8% - 99.1%; entries 14-24, table 1.4.1). Non-chiral C_2-symmetric ligands (entry 3-5 and 10-12 in Table 1.4.1) also had given successful results.



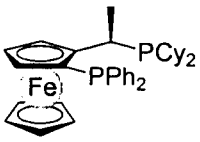
(*S*,*S*)-chiraphos **82**



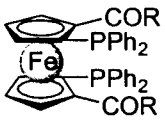
(*R*)-BINAP **58a**



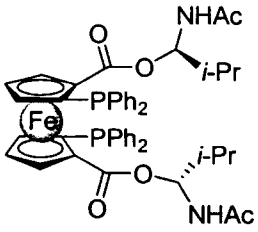
83a n = 1
83b n = 2
83c n = 3



Josiphos **84**



85a R = OMe
85b R = OEt
85c R = O*i*-Pr



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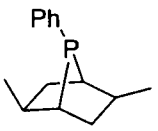

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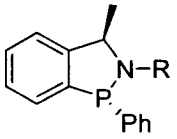

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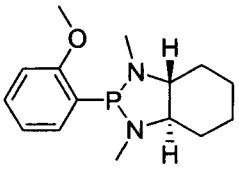

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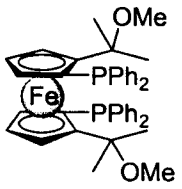

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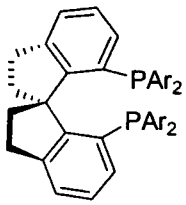
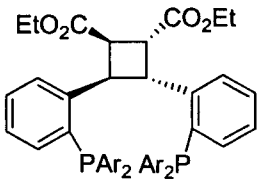


62a Ar = 3,5-$(Me)_2C_6H_3$
62b Ar = Ph
62c Ar = *p*-MeC_6H_4
62d Ar = *p*-$MeOC_6H_4$
62e Ar = 4-MeO-3,5-$(Me)_2C_6H_2$



91a Ar = Ph
91b Ar = *p*-MeC_6H_4
91c Ar = *p*-$MeOC_6H_4$
91e Ar = *m*-MeC_6H_4
91f Ar = 3,5-$(Me)_2C_6H_3$
91g Ar = 4-$(Me)_3CC_6H_4$

Figure 1.4.4 Chiral phosphorus ligands

Chiral Dinitrogen Ligands

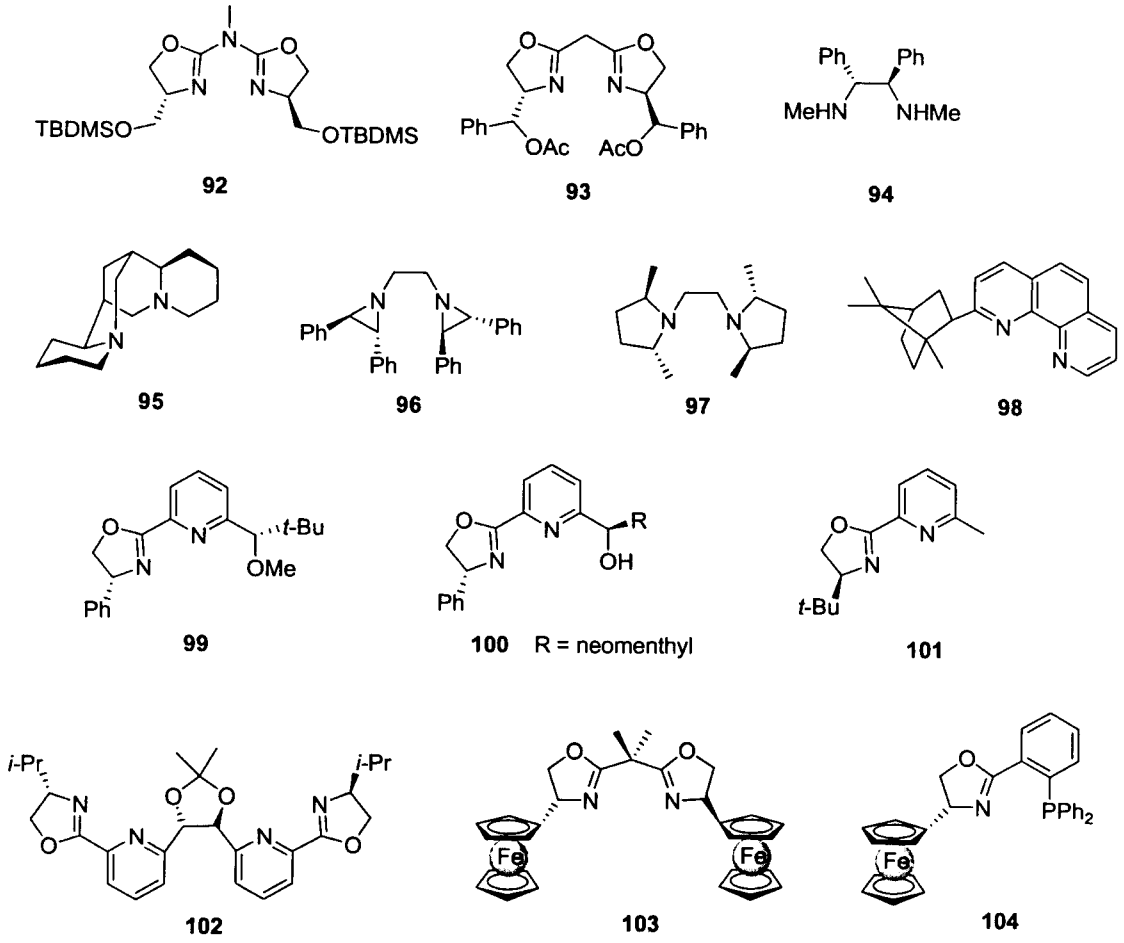
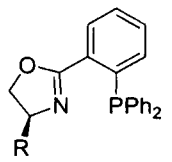


Figure 1.4.5 Chiral dinitrogen ligands

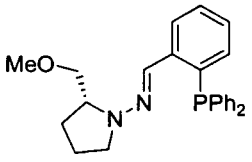
Both sp^2 (imine) and sp^3 (amine) hybridized nitrogens are effective donor atoms. Chiral oxazolinylpyridines has been prepared and tested by Chelucci. Ligand **104** bearing a bulky *t*-butyl group on the oxazoline ring gave up to 91% ee in AAA reaction. Ligands **99** and **100** gave high yield of the product and excellent enantioselectivity with >99% ee. These bidentate ligands have the same donor atom which has similar electronic properties. Therefore, steric factors of the ligands are

important to determine the regioselectivity and stereoselectivity of the nucleophilic attack. The bulky group that substituted the hydrogen on the 6-position of the pyridine ring or on the oxazoline ring (ligand **99-104)** could increase the stabilization of the sterically favoured diastereomeric transition state. In addition, it could vary the electronic properties of the two nitrogen donor atoms to influence the selectivity.

Chiral P,N-chelate ligands



105a R = *i*-Pr
105b R = Ph



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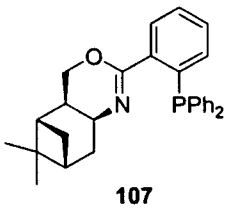

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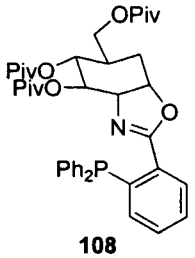

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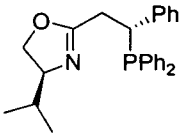

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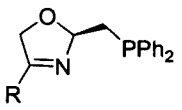
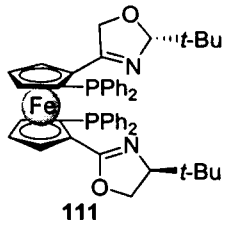


110 R = Adamantyl



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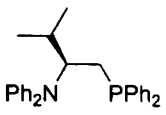

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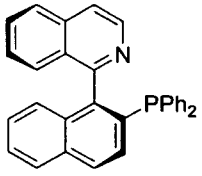

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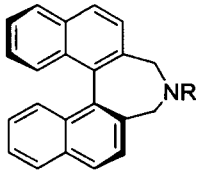
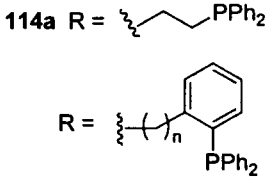
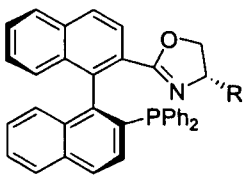
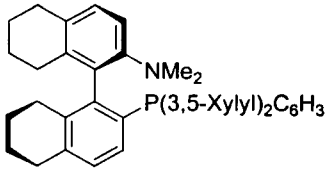




114b n = 0
114c n = 1



115a R = *i*-Pr
115b R = *t*-Bu



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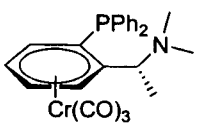

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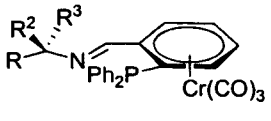
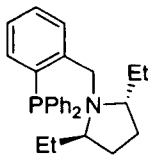


118a R^1 = Ph, R^2 = H, R^3 = H
118b R^1 = Ph, R^2 = Ph, R^3 = H



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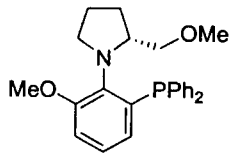

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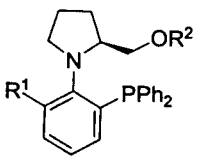
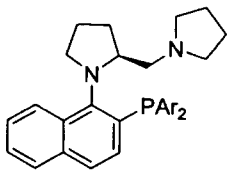
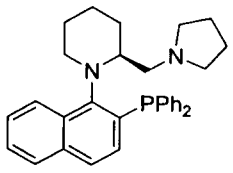


121a R^1 = Me, R^2 = H
121b R^1 = OMe, R^2 = H

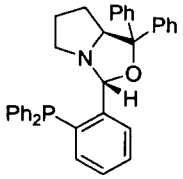


122a Ar = Ph
122b Ar = 4-Tolyl
122c Ar = 4-CF_3-C_6H_4



123

124a R^1 = Me, R^1 = *i*-Pr
124b R^1 = Bu, R^1 = *i*-Pr
124c R^1 = Me, R^1 = Ph



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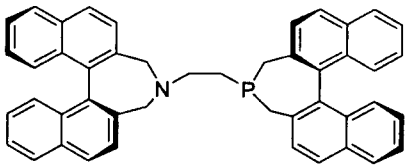

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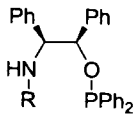
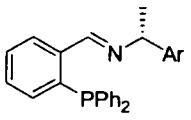
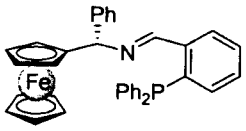


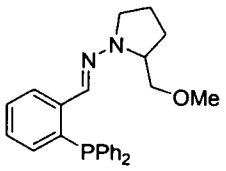
127a R = Bu
127b R = *i*-Pr



128 Ar = Mesityl



(*S*)-**13**



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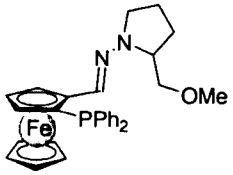
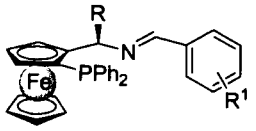
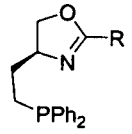


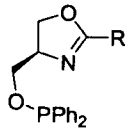
(S,S_p)-**19a**



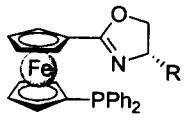
(R,S_p)-**16a** R = Me, R^1 = *m*-Cl
(R,S_p)-**16b** R = Me, R^1 = *m*-NO_2



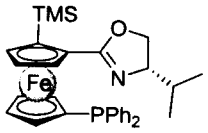
130a R = *t*-Bu
130b R = Adamnatyl
130c R = 3,5-di-*t*-Bu-C_6H_3



131a R = Ph
131b R = Ferrocenyl



132a R = Ph
132b R = *i*-Pr
132c R = *t*-Bua



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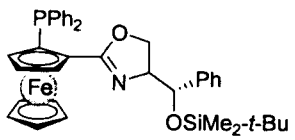
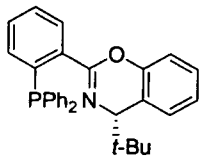


(S,S,S_p)-**24**



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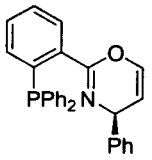
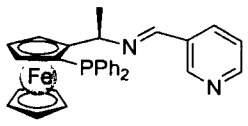
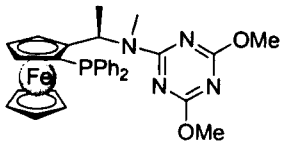


135



(R,S_p)-**28a**



(R,S_p)-**31b**

Figure 1.4.6 Chiral P,N-chelate ligands

Bidentate ligands of transition metal complexes with phosphorus and nitrogen donor have been used for a long time and have a great potential in a variety of catalytic asymmetric reactions. The π-acceptor character of phosphorus can stabilize the metal centre in a low oxidation state (Figure 1.4.6). The nitrogen σ-donor ability makes the metal more susceptible to oxidation addition reactions. This combination can help to stabilize intermediate oxidation states or geometries formed during a catalytic cycle. The nucleophile attack preferentially at the allylic carbon terminus *trans* to the the Pd-P bond in the metal complexes.[154,165] As a results, the enantioselectivity of P,N type ligands can lead to better results when compared with N,N and P,P bidentate ligands.

1.5 Aim of this Project

The aim of this project is the development of efficient synthetic route for new chiral ferrocenyl ligands. Various phosphorous substituents on P-Phos are exploited for catalyzing asymmetric hydrogenation of ferrocenyl ketone and its derivatives. The catalyst loading will be optimised without decreasing enantioselectivity and reaction rate.

The method will easily provide an optically pure ferrocenyl alcohols for synthesis of new bidenate ferrocenyl amino-phosphine ligands. The backbone of these

ligands is ferrocene which introduces the planar and central chiralities. The two donor atoms, phosphorous and nitrogen, used together to provide electronic asymmetry for catalysis.

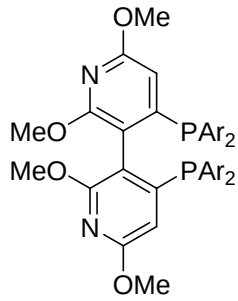
Activity and enantioselectivity of these 1,2-disubstituted ferrocenyl amino-phosphine ligands are examined in the next part of my project. They are applied to catalyzed allylic alkylation and hydrogenation of ketone. In the palladium-catalyzed allylic alkylation, different alkyl groups are introduced to the amine and are employed to investigate the steric effects. In the ruthenium-catalyzed asymmetric hydrogenation, new ferrocenyl-ruthenium precatalysts are prepared with diphosphine or dimaine ligands. This design is different to the (diphosphine)(diamine)Ru complex introduced by Noyori and has not been studied previously.

Chapter 2

Synthesis of Chiral Ferrocenyl Alcohols and Ferrocenyl Ligands

2.1 Introduction

An asymmetric catalyst is generally defined as an ensemble of metal ion and an optically active ligand whose combined action promotes the transfer of chiral information from the catalyst to product. The conformation of a chiral ligand is important for controlling the configuration of the product. Since 1970, numerous ligands derived from ferrocene have been successfully used in homogeneous catalysis. Unfortunately, their important intermediate, the optically pure Ugi's amine, is difficult to synthesis. The traditional method requires approximately a week of laboratory work and involves 4-6 times of fractional crystallizations of the diastereomeric salts. Enantiomerically pure ferrocenyl alcohol is a precursor of Ugi's amine, and therefore, development in hydrogenation of ferrocenyl ketones could reduce workload in resolution. This method is cost effective and gives a clean conversion without purification.



63a P-Phos; Ar = Ph
63b Xylyl-P-Phos; Ar = 3,5-$Me_2C_6H_3$
63c Tol-P-Phos; Ar = 4-MeC_6H_4

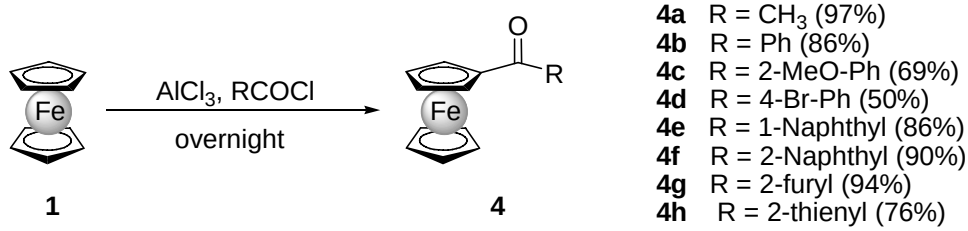
Figure 2.1.1 P-Phos and its derivatives

In 1995, Noyori discovered that Ru(diphosphine)(1,2-diamine)Cl_2 complexes in 2-propanol with *t*-BuOK was very efficient for the hydrogenation of various simple ketones.[45] Recently, our group developed the chiral ligand, P-Phos and its derivatives **63a-c** (Figure 2.1.1). They were applied to hydrogenation of various ketones and achieved high activities and enantioselectivities.

In this study, different phosphorus substituents on P-Phos were explored for their enantioselectivities in hydrogenation of ferrocenyl ketones catalyzed by [$RuCl_2$(P-Phos)(DPEN)] precatalysts. We found that (*R*)-Xylyl-P-Phos$RuCl_2$(*R*,*R*)-DPEN was the most efficient precatalyst for the hydrogenation of ferrocenyl ketones to the corresponding ferrocenyl alcohols. High enantioselectivity (99.3% ee) and >99% conversion has been obtained with this precatalyst for the hydrogenation of acetylferrocene. The reaction was scaled up to 150g scale with S/C ratio of 100,000 for 48 hours without deterioration of enantioselectivity.

2.2 Friedel-Crafts Acylation of Ferrocene

Ferrocenyl ketones derivatives were prepared using classical Friedel-Crafts conditions. They were widely used as precursors for the synthesis of ferrocenyl ligands derivatives. Attachment of different alkyl groups to their α-stereogenic centre is important for stereocontrol in the catalysis.

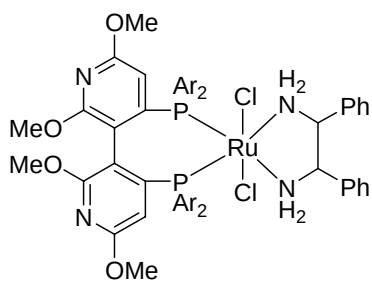


Scheme 2.2.1 Fridel-Crafts acylation of ferrocenyl ketones

Reaction of ferrocene with various acid chlorides under classical Friedel-Crafts conditions afforded ferrocenyl ketones (**4a-h**) in generally acceptable yields (Scheme 2.2.1).[166] Acetyl chloride reacted most readily with ferrocene to give an excellent yield of the corresponding ketone. Benzoyl, naphthoyl and heteroaroyl chlorides all gave good to excellent yields. It was noted that substituted benzoyl chlorides reacted relatively less efficiently with ferrocene.

2.3 Asymmetric Hydrogenation of Ferrocenyl Ketones catalyzed by P-Phos and its derivatives

Chiral C_2-symmetric dipyridylphosphine ligands, **63a**, **63b** and **63c**, were used to prepare [$RuCl_2$(diphosphine)(1,2-diamine)] complexes which are excellent precatalyst for homogeneous hydrogenation of simple ketones. To investigate the effects of various phosphorus substituents on the activity and the enantioselectivity in the hydrogenation of ferrocenyl ketones, different P-Phos ligands (Figure 2.3.1) were screened using **4a** as a model substrate. The reaction was carried out in 2-propanol with *t*-BuOK (S/B = 50).

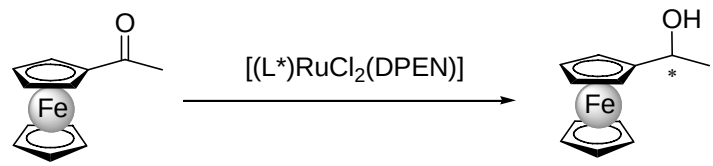


SSS-**136**: (*S*)-P-Phos, Ar = Ph; (*S*,*S*)-DPEN
SRR-**137**: (*S*)-P-Phos, Ar = Ph; (*R*,*R*)-DPEN
SRR-**138**: (*S*)-Xylyl-P-Phos, Ar = 3,5-$Me_2C_6H_3$; (*R*,*R*)-DPEN
RRR-**139**: (*R*)-Xylyl-P-Phos, Ar = 3,5-$Me_2C_6H_3$; (*R*,*R*)-DPEN
RSS-**140**: (*R*)-Tol-P-Phos, Ar = 4-MeC_6H_4; (*S*,*S*)-DPEN
RRR-**141**: (*R*)-Tol-P-Phos, Ar = 4-MeC_6H_4; (*R*,*R*)-DPEN

Figure 2.3.1

As shown in Table 2.3.1, the parent P-Phos (*SSS*-**136** and *SRR*-**137)**, irrespective of its configuration, gave poor conversion and selectivity whereas *RSS*-**140** provided full conversion but mediocre selectivity at a substrate-to-catalyst ratio (S/C) of 5000. The results improved dramatically with the use of *SRR*-**138** and *RRR*-**139** under identical conditions leading to 90.1% ee and 99.4% ee, respectively.

The latter value represents the best result so far attained for the synthesis of chiral **3a** catalytically without the need for further enrichment *via* recrystallization.



4a **3a**

Table 2.3.1 Initial catalyst screening using [(P-Phos)$RuCl_2$(DPEN)] system.[a]

Catalyst	Alcohol Product **3a**		
	Conv. (%)	% ee	Config.
SSS-**136**	18.5	76.5	*R*
SRR-**137**	19.5	35.7	*S*
SRR-**138**	100	90.1	*R*
RRR-**139**	100	99.4	*S*
RSS-**140**	100	38.1	*R*

[a]Standard conditions**:** sample size = 0.55-0.56 mmol; [sub] = 0.22-0.23 M; solvent = *i*PrOH; S/C = 5000; base = K^{t}OBu; substrate-to-base ratio = 50; pressure = 50 bar; temperature = rt; time = 15h. The enantioselectivity and conversion were determined by HPLC.

2.3.1 Determination of Optimal Catalyst Loading

Having found the most suitable P-Phos ligand, we then turned our attention to the determination of an optimal catalyst loading based on a balanced consideration between reaction rate and selectivity. This exercise was applied to both *SRR*-**138** (Table 2.3.2) and *RRR*-**139** (Table 2.3.3). The reaction time was fixed at 15 h and the

concentration at 0.55-0.60 M. Successive two-fold decreases of *SRR*-**138**'s loading brought about an abrupt diminution in conversion, but with no significant erosion of product ee. In the case of *RRR*-**139**, a similar trend was observed.

Table 2.3.2 S/C ratio tuning using *SRR*-**138**.[a]

S/C	Conv. (%)	%ee
5000	100	89.9
10000	100	88.0
25000	72.9	91.3
50000	50.3	91.6
100000	6.4	90.8
200000	0.9	89.0

[a]Standard conditions**:** substrate = **4a** sample size = 44-48 μmol; [sub] = 0.55-0.6M; solvent = *i*PrOH; base = KO^{t}Bu; S/B = 50; H_2 pressure = 50 bar; temperature = rt; time = 15 h. The configuration of product **3a** is *R*.

Table 2.3.3 S/C ratio tuning using *RRR*-**139**.[a]

S/C	Conv. (%)	%ee
5000	98.9	99.1
10000	82.1	99.2
15000	39.4	98.8
25000	18.7	98.7
30000	17.1	98.8
35000	7.7	97.7

[a]Standard conditions: substrate = **4a**; sample size = 0.22-0.23 mmol; [sub] = 0.55-0.56 M; solvent = *i*PrOH; base = KO^{t}Bu; S/B = 50; H_2 pressure = 50 bar; temperature = rt; time = 15 h. The configuration of product **3a** is *S*.

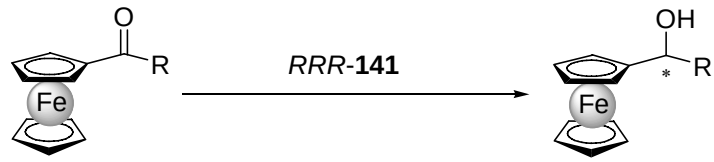
Conversion of the hydrogenation catalyzed by *RRR*-**139** was found to be complete even by changing the substrate concentration to 1.5 M and allowing the

reaction to take place at room temperature over 48 h at an S/C ratio of 40,000. Gratifyingly, this protocol was further up-scaled successfully to a 150-gram level using a Parr 4520 series stirred reactor with the resulting alcohol reaching the same level of ee (99.3%) even at S/C = 100,000, thereby setting the stage for potential industrial applications.

2.3.2 Asymmetric Hydrogenation of Ferrocenyl Ketone Derivatives

We attempted to extend the above methodology to different aryl and heteroaryl ferrocenyl ketones. Unfortunately, hydrogenation of these substrates in the presence of *RRR*-**139** led to both poor enantioselectivity and conversion under the same conditions as delineated for the foregoing experiments. In a similar connection, the analogous XylBINAP catalyst from the Noyori group also gave inferior results in the case of benzoylferrocene (Table 1.2.2, entry 5).[41] In a parallel experiment, the sterically less hindered *RRR*-**141** effected the reaction relatively more smoothly (Table 2.3.4**)**. As for the unsubstituted aryl and heteroaryl substrates (Table 2.3.4, entries 1, 6, 7), the conversions were generally excellent while the ee's were moderate to good (41-89%). Clearly, there were delicate and subtle matching and mismatching effects between the substituents on the phosphorus ligand and the structure of the ferrocenyl ketone substrate.

Table 2.3.4 Asymmetric hydrogenation of ferrocenyl aryl/heteroaryl ketones **4b-h** to ferrocenyl alcohols **3b-h** using *RRR*-**141**.[a]



4 **3**

Entry	Substrate (R =)		time (h)	ee (%)	yield (%)	config.
1[b]	**4b**	Ph	15	89	99	(*R*)/(−)
2[b]	**4c**	2-MeO-Ph	15	97	94	(−)
3	**4d**	4-Br-Ph	182	73	37	(−)
4	**4e**	1-Naphthyl	15	98	90	(−)
5[b]	**4f**	2-Naphthyl	15	83	94	(−)
6	**4g**	2-furyl	15	41	73	n.d.[c]
7[b]	**4h**	2-thienyl	15	68	93	n.d.[c]

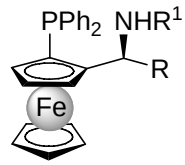
[a] Standard conditions: sample size = 28-37 μmol; [sub] = 0.23-0.31M; solvent = *i*PrOH; S/C = 1000; base = KO^{t}Bu; S/B = 50; pressure = 50 bar; temperature = rt. [b]Average of two experiments. [c]Not determined because samples were very susceptible to decomposition.

2.4 Preparation of Chiral Bidentate Ferrocenyl Amino-Phosphine Ligands

Chiral homobidentate ligands, especially diphosphines have been explored extensively to perform different asymmetric transformations.[22,167] Other type of chiral heterobidentate ligands, such as P,O[167] and P,S[168] mixed donor ligands were also studied for application towards asymmetric catalysis. Most common heterobidentate ligands are of P,N type which successfully catalyzed many transformations.[22,47]

We used enantiomeres pure ferrocenyl alcohols to synthesize a series of new

bidenate amino phosphine ligands (Figure 2.4.1). A phosphorus donor atom was introduced to the Cp ring creating planar chirality and a nitrogen donor atom was linked to the α-stereogenic center. These nonsymmetrical ligands with two electronically and sterically divergent coordinating units should permit more effective enantiocontrol.



(S,R_p)-**142**-**151**

(S,R_p)-**142**	R = Me; R^1 = H	(S,R_p)-**147**	R = Ph; R^1 = H
(S,R_p)-**143**	R = Me; R^1 = Me	(S,R_p)-**148**	R = Ph; R^1 = Me
(S,R_p)-**144**	R = Me; R^1 = *i*-Pr	(S,R_p)-**149**	R = Ph; R^1 = *i*-Pr
(S,R_p)-**145**	R = Me; R^1 = Cy	(S,R_p)-**150**	R = Ph; R^1 = Cy
(S,R_p)-**146**	R = Me; R^1 = *t*-Bu	(S,R_p)-**151**	R = Ph; R^1 = *t*-Bu

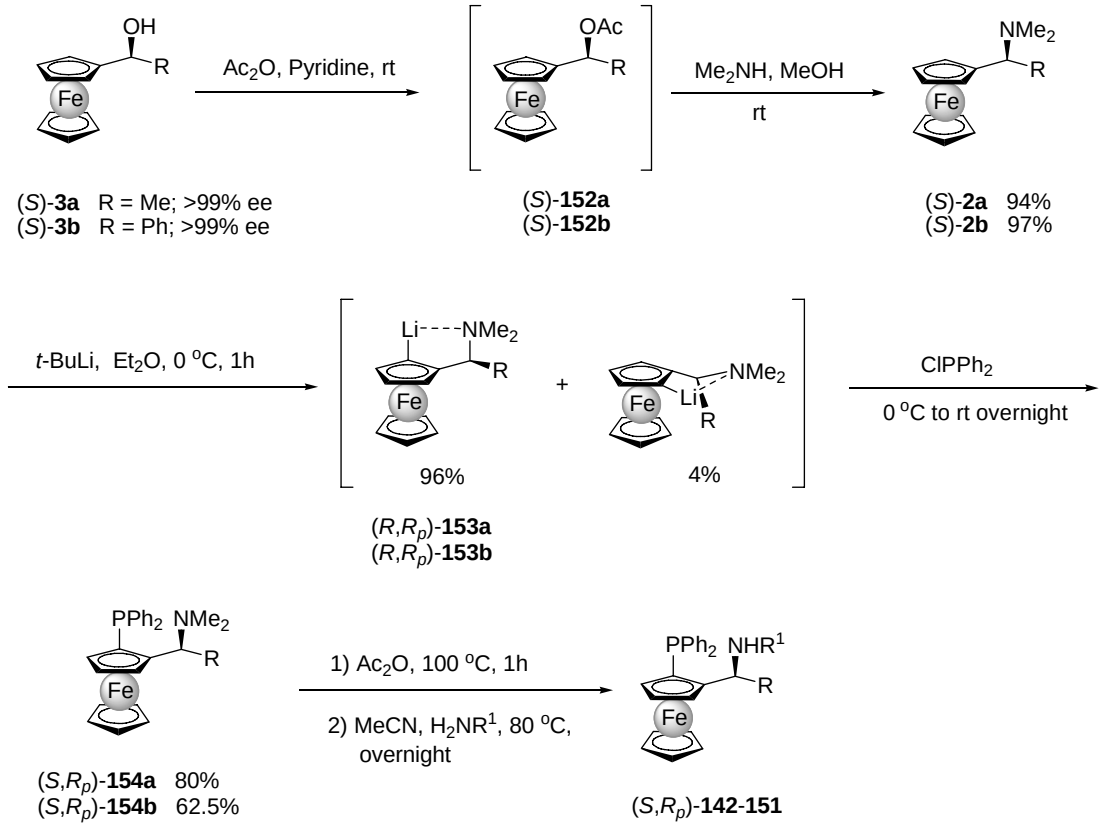
Figure 2.4.1 Chiral bidentate ferrocenyl amino-phosphine ligands

To investigate the steric effects, the α-stereogenic center was linked with a methyl or a phenyl group plus differently substituted alkyl amines. Literature studies showed that the amine group whether primary or secondary, is an important feature for catalyzed hydrogenation of ketone and allylic alkylation. Noyori pointed out that the N-H proton exhibits hydrogen bonding with the carbonyl of ketone followed by hydrogen transfer to oxygen atom.[45,96,97] For the Pd-catalyzed asymmetric allylic alkylation, the existence of proton could increase the selectivity of nucleophilic attack on the π-allylic compound.[103-106] Coordination of allyl with ferrocenyl palladium

complexes results in effective electronic discrimination of the allylic termini because of the different *trans* effect of the two electronically dissimilar donor atoms.

2.4.1 Synthesis of Ferrocenyl Amino-Phosphine Ligands

Acetylferrocene **4a** and benzoylferrocene **4b** were firstly hydrogenated to chiral ferrocenyl alcohol by P-Phos ruthenium catalyst as described in our previous work. The optically pure 1-ferrocenylethanol (*S*)-**3a** and ferrocenylphenylmethanol (*S*)-**3b** were quantitatively converted to the corresponding acetate (*S*)-**152** by treatment with acetic anhydride in pyridine. Removal of the volatiles by vacuum provided (*S*)-**152** as pure materials without the need for further purification. In the second step, nucleophilic substitution of the acetate was accomplished in methanol using an excess of dimethylamine.[14] Optically pure Ugi's amine (*S*)-**2a** and (*S*)-**2b** were easily obtained without any crystallization process due to retention of configuration in nucleophilic substitution.[12]



Scheme 2.4.1

Table 2.4.1 Yield of (S,R_p)-**142-151**

Entry	Ligand	R	R^1	Yield %
1.	(S,R_p)-**142**	Me	H	33.9
2.	(S,R_p)-**143**	Me	Me	98.9
3.	(S,R_p)-**144**	Me	*i*-Pr	99.4
4.	(S,R_p)-**145**	Me	Cy	77.0
5.	(S,R_p)-**146**	Me	*t*-Bu	81.7
6.	(S,R_p)-**147**	Ph	H	39.7
7.	(S,R_p)-**148**	Ph	Me	87.7
8.	(S,R_p)-**149**	Ph	*i*-Pr	73.5
9.	(S,R_p)-**150**	Ph	Cy	63.3
10.	(S,R_p)-**151**	Ph	*t*-Bu	83.2

The planar chirality was introduced by diastereoselective *ortho*-lithiation of ferrocenyl amine (*S*)-**2** using *sec*-BuLi. The high diastereoseleciton ratio of 96:4 is under kinetic control and is governed by the relative preference of the transition state leading to (S,R_p)-**153** (Scheme 2.4.1) which have their α-alkyl group in a position of less steric repulsion.[11] The diastereomerically pure (S,R_p)-**154** was obtained in moderate to good yield after electrophilic substitution. The dimethyl chine group of (S,R_p)-**154** underwent nucleophilic substitution with retention of configuration. A series of ferrocenyl amino-phosphine ligands (S,R_p)-**142**-**151** were obtained without any change in chirality (Table 2.4.1). If R^1 is a proton, the yields were low (<40%), no matter the α-alkyl group (R) is a methyl group ((S,R_p)-**142**) or a phenyl group ((S,R_p)-**147**). Other ligands could be obtained in moderate to good yield (63.3% to 99.4%).

Chapter 3

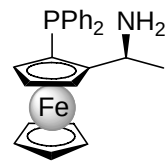
Application of Ferrocenyl Amino-phosphine Ligands in Ruthenium-catalyzed Asymmetric Hydrogenation of Ketones

3.1 Introduction

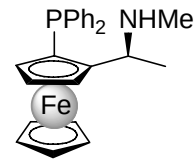
Hydrogenation is a core technology in chemical synthesis. High reaction rates and selectivities are attainable only by the coordination of structurally well-designed catalysts and suitable reaction conditions. The devised [$RuCl_2$(diphosphine)(1,2-diamine)] complexes are excellent precatalysts for homogeneous hydrogenation of ketones which lack functionality capable of interacting with the metal center.[37,84] This catalyst system allows for the preferential reduction of a C=O function over a co-existing C=C linkage in 2-propanol solution containing an alkaline base.[98] This catalytic hydrogenation proceeds with an exceptionally high turnover number, high turnover frequency, and excellent enantioselectivity for various simple ketones.

The hydrogenation of ketones is proposed to occur *via* a nonclassical metal-ligand bifunctional mechanism involving a chiral RuHX(diphosphine)(diamine) species. A hydride on Ru and a proton of the NH_2 ligand are simultaneously

transferred to the C=O function *via* a six-membered pericyclic transition state (Scheme 1.3.9). It has been shown that primary or secondary amine moiety in the diamine ligands (N-H effect) is crucial for high catalytic activity.

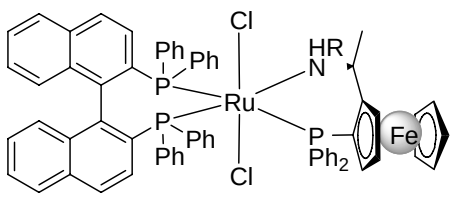


(S,R_p)-**142**

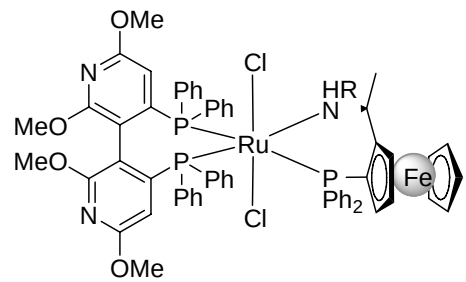


(S,R_p)-**143**

Figure 3.1.1 Ferrocenyl amino-phosphine ligands



(R,S,R_p)-**155** R = Me
(S,S,R_p)-**155** R = Me
(R,S,R_p)-**156** R = H
(S,S,R_p)-**156** R = H



(R,S,R_p)-**157** R = Me
(S,S,R_p)-**157** R = Me
(R,S,R_p)-**158** R = H
(S,S,R_p)-**158** R = H

Figure 3.1.2 [$RuCl_2$(diphosphine)(amino-Fc-phosphine)] complexes

Our ferrocenyl amino phosphine ligands (S,R_p)-**142** and (S,R_p)-**143** contain phosphine on the Cp ring and a primary or secondary amine on the stereogenic carbon center (Figure 3.1.1). As predicted by the N-H effect, ligands (S,R_p)-**142** and **143** bearing protic NH end should exhibit catalytic activity in the hydrogenation of ketones. These new ferrocenyl ligands formed [$RuCl_2$(diphosphine)-

(amino-Fc-phosphine)] complexes **155** to **158**, where BINAP **58a** or PPhos **63a** (pg. 24) was the diphosphine (Figure 3.1.2). These diphosphine ligands have been proven to be effective in hydrogenation of ketones. The ferrocenyl ligand with ruthenium center is expected to form a 6-membered ring.[32] The conformation of this complex is similar to that found in Song's studies of the modification of Noyori's efficient catalysts. They developed a *trans*-RuHCl[(*S*)-BINAP(*R*,*R*)-amino-phosphine] (Figure 3.1.3) catalyst in hydrogenation of acetophenone (ee up to 72%).[169] This catalyst also promoted a Michael addition reaction followed by a ketone hydrogenation.

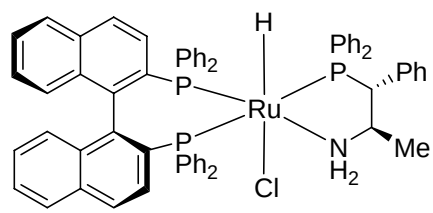
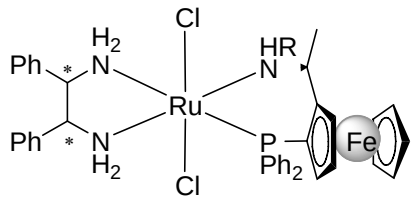
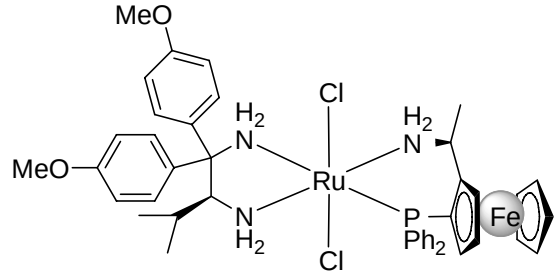


Figure 3.1.3

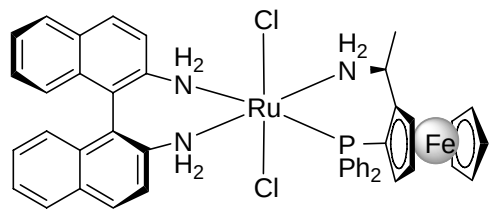
DPEN **64** and DAIPEN **65** (pg. 25) have been employed in ferrocenyl-ruthenium complexes **159** to **161** where the diamine forms a 5-membered chelate ring with Ru-metal center instead of a 7-membered diphosphine chelated ring (Figure 3.1.4). Complex **162** which uses binaphthylamine **163** as the diamine still forms a 7-membered chelated ring. Their catalytic activities are comparable to the complexes **159-161** with 5-membered ring.



(*R*,*R*,*S*,R_p)-**159** R = Me
(*S*,*S*,*S*,R_p)-**159** R = Me
(*R*,*R*,*S*,R_p)-**160** R = H
(*S*,*S*,*S*,R_p)-**160** R = H



(*S*,*S*,R_p)-**161**

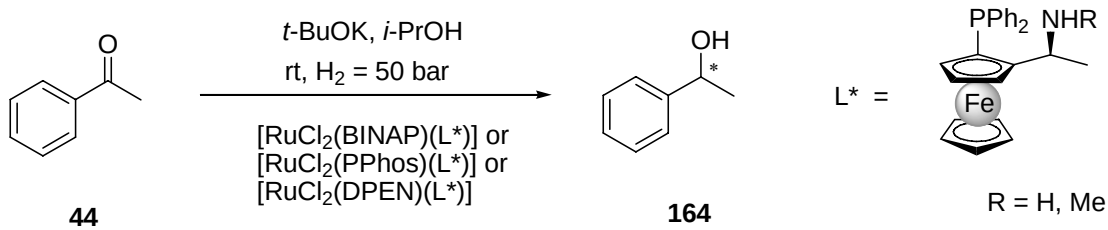


(S_a,*S*,R_p)-**162**

Figure 3.1.4 [$RuCl_2$(amino-Fc-phosphine)(diamine)] complexes

We had examined the activities and stereoselectivities in the hydrogenation of acetophenone of the following two new combinations of ferrocenyl-ruthenium precatalyst, [$RuCl_2$(diphosphine)(amino-Fc-phosphine)] and [$RuCl_2$(diamine)(amino-Fc-phosphine)]. Moderate ee values were obtained for the [$RuCl_2$(1,2-diamine)(amino-Fc-phosphine)] complexes catalyzed hydrogenation of acetophenone. Amongst them, (*R*,*R*,*S*,R_p)-**160** gave the highest ee of 68.7% (Table 3.2.2). The result proved that 1,2-diamine plays an important role for enantioselectivity.

3.2 Asymmetric Hydrogenation of Acetophenone Catalyzed by Ferrocenyl Amino-phosphine Ruthenium Complexes



Scheme 3.2.1 Asymmetric hydrogenation of acetophenone **44**

In this study, five ruthenium-catalysts were applied to the hydrogenation of acetophenone **44**. The reactions were carried out in 2-propanol with *t*-BuOK as base (S/B=50) in the presence of 1 mol% of **155-162** precatalysts (S/C=100). Hydrogen pressure was 50 bar at room temperature. After 40 h, the conversion and enantiomeric excess of product **164** were determined by HPLC.

3.2.1 Asymmetric Hydrogenation of Acetophenone Catalyzed by [$RuCl_2$(diphosphine)(amino-Fc-phosphine)] Complexes

Table 3.2.1 Asymmetric Hydrogenation of Acetophenone catalyzed by **161** to **164**[a]

Entry	Catalyst	Conv.(%)[b]	Ee (%)[b]	Config.[c]
1.	(*R*,*S*,R_p)-**155**	98.0	18.4	*S*
2.	(*R*,*S*,R_p)-**156**	96.9	17.7	*R*
3.	(*S*,*S*,R_p)-**155**	97.6	23.8	*S*
4.	(*S*,*S*,R_p)-**156**	94.7	16.7	*S*
5.	(*R*,*S*,R_p)-**157**	98.3	27.4	*S*
6.	(*R*,*S*,R_p)-**158**	8.0	13.2	*R*
7.	(*S*,*S*,R_p)-**157**	97.9	7.8	*S*
8.	(*S*,*S*,R_p)-**158**	4.9	25.6	*R*

[a]Reaction conditions: Sample size = 0.085-0.127 mmol; substrate concentration = 1.0M; Solvent = 2-propanol; S/C =100; S/B = 50; H_2 pressure = 50 bar; Room temperature; Time = 40 h. [b]Determined by HPLC analysis using a Chiralpak OD-H column. [c]Configuration was compared with literature data.

Studies on asymmetric hydrogenation of acetophenone catalyzed by the Ru complexes **155** and **156** prepared from BINAP revealed high reactivity regardless of the presence of *N*-methyl substituent; however, this catalyst system achieved poor enantioselectivity. The structure of ferrocenyl P-N ligand **155** in this Ru-catalyst system strongly affected the configuration of product. In the presence of *N*-methyl substituent (**155**), the product configuration remained unchanged. For the complexes **156** with a primary amine, the enantiomer of BINAP takes control of the product configuration. Thus, the presence of *N*-methyl substituent is crucial to determine the product configuration *via* this diphosphine catalyst system.

Similarly, ruthenium complexes **157** prepared from P-Phos and ferrocenyl P-N ligands (S,R_p)-**143** with *N*-methyl substituent showed a high activity for the hydrogenation of acetophenone. The product had a preference for the (*S*)-configuration. There was no effect on the variation of configuration for P-Phos. Complex (R,S,R_p)-**157** in the presence of (*R*)-P-Phos gave a higher ee value. In contrast to the primary amine analogue of Ru-complex **158**, the activity of reduction of acetophenone was dramatically reduced, whereas the configuration was unaffected by the change of P-Phos's configuration.

3.2.2 Asymmetric Hydrogenation of Acetophenone Catalyzed by [$RuCl_2$(diamine)(amino-Fc-phosphine)] Complexes

Table 3.2.2 Asymmetric Hydrogenation of Acetophenone Cataylzed by **165** to **168** [a]

Entry	Catalyst	Temp (℃)	Time (h)	Conv.(%)[b]	Ee (%)[b]	Config.[c]
1.	(R,R,S,R_p)-**159**	rt	40	>99	54.8	*S*
2.	(R,R,S,R_p)-**160**	rt	40	>99	68.7	*S*
3.	(S,S,S,R_p)-**159**	rt	40	>99	48.1	*R*
4.	(S,S,S,R_p)-**160**	rt	40	>99	28.9	*S*
5.	(S,S,R_p)-**161**	rt	40	97.8	9.1	*S*
6.	(S,S,R_p)-**162**	rt	40	96.9	12.1	*S*
7.	(R,R,S,R_p)-**159**	50	4	>99	50.3	*S*
8.	(R,R,S,R_p)-**160**	50	4	>99	31.4	*S*
9.	(S,S,S,R_p)-**159**	50	4	>99	16.0	*R*
10.	(S,S,S,R_p)-**160**	50	4	>99	13.0	*S*

[a]Reaction conditions: Sample size = 0.085-0.127 mmol; substrate concentration = 1.0M; Solvent = 2-propanol; S/C =100; S/B = 50; H_2 pressure = 50 bar. [b]Determined by HPLC analysis using a Chiralpak OD-H column. [c]Configuration was compared with literature data.

Asymmetric hydrogenation of acetophenone catalyzed by Ru-complexes **159**-**162** examined the effect of diamine in enantioselectivity. The Ru-complex (*R*,*R*,*S*,R_p)-**160** with no *N*-methyl substituent but with the presence of a chiral DPEN gave the highest enantioselectivity of 68.7% ee with complete conversion. In contrast to [$RuCl_2$(diphosphine)(amino-Fc-phosphine)] complex, the effect of *N*-methyl substituent on the product's configuration was opposite. In other word, the configuration of diamine was crucial for the determination the product configuration in the presence of *N*-methyl substituent on (*S*,R_p)-**143** (Table 3.2.2, entries 1 vs. 3 and 7 vs. 9). The configuration of product remained unchanged for different enantiomer DPEN of Ru-complex **160** (Table 3.2.2, entries 2 vs. 4 and 8 vs. 10). Although preliminary results for enantioselectivity was poor to moderate, a strong matching and mismatching effect was found in the (*S*,R_p)-**142** with diamine combination. The precatalyst formed with (*R*,*R*)-DPEN gave higher enantioselectivity than that formed with (*S*,*S*)-DPEN (entries 2 vs. 4). The reaction rates were increased by increasing reaction temperature but it decreased the enantioselectivities (entries 7-10).

The complexes (*S*,*S*,R_p)-**161** and (*S*,*S*,R_p)-**162** with DAIPEN and binaphthylamine were not effective in this reaction. They had high activities whereas the poor enantioselectivities obtained. The enantioselectivity could not be improved by replacing diphosphine with binaphthylamine which form a 7-member chelated ring

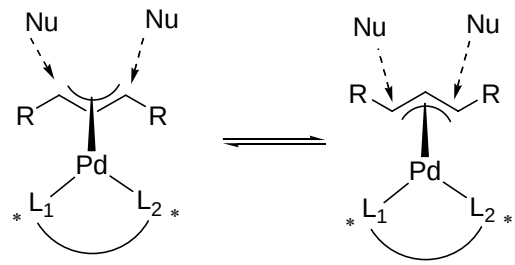
with ruthenium atom (Table 3.2.1 vs entry 6 in Table 3.2.2).

Chapter 4

Application of Ferrocenyl Amino-Phosphine Ligands in Palladium-catalyzed Asymmetric Allylic Alkylation

4.1 Introduction

The enantioselective palladium-catalyzed substitution of allylic acetates with soft nucleophiles is one of the important methods for C-C bond formation in asymmetric synthesis. C_1 and C_2 Symmetric ligands have different selectivity for nucleophile attack on symmetrical allylic substrates.[58]

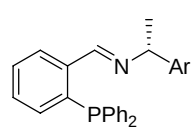


'M' Shape 'W' Shape

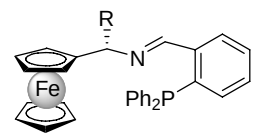
Figure 4.1.1 Configurational isomers of the (π-allyl)palladium complexes

For a C_2 symmetric ligand, the enantioselectivity is determined solely by the regioselectivity of attack on the π-allyl group. A C_1 symmetric ligand would form two different (π-allyl)metal complexes that are in dynamic equilibrium (Figure 4.1.1). They have different stability and reactivity but each one has the possibility to be attacked by the nucleophile at two different sites; therefore a large number of possible

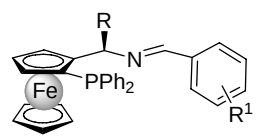
transition states occur. One of the diastereomic (π-allyl)metal complexes can be made more favorable by steric control of the ligand. The orientation and electronic properties of the donor atoms within the ligand significantly affect enantioselectivity in catalytic asymmetric allylic alkylation. The different *trans* influence of the ligand donor atoms induce the nucleophile to attack on the more electrophilic carbon atom. In the past two decades, a number of successful C_1 symmetric chiral ligands with phosphorous and nitrogen as donor atoms have been proven to be useful for this asymmetric allylic alkylation.



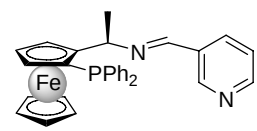
128 Ar = Mesityl
98% yield, 85% ee



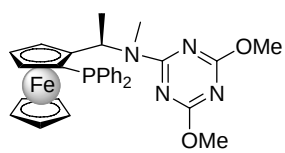
(*S*)-**13** R = Ph
97% yield, 94% ee (*S*)



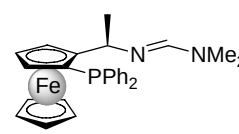
(R,S_p)-**16b** R = Me, R^1 = *m*-Cl; 96% yield, 90% ee (*S*)
(R,S_p)-**16c** R = Me, R^1 = *m*-NO_2; 99% yield, 93% ee (*S*)



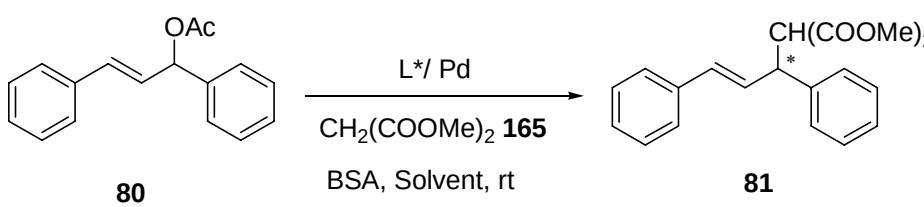
(R,S_p)-**28a** 96% yield, 97% ee (*S*)



(R,S_p)-**31b** 93% yield; 97% ee (*S*)



(R,S_p)-**15** 93% yield; 87% ee (*S*)



80 **81**

Figure 4.1.2 Ferrocenyl imine-phosphine ligands catalyzed allylic alkylaiton

Zheng et al. have developed several ferrocenyl imine-phosphine ligands (C_1 symmetry) to catalyze palladium allylic alkylation of 1,3-diphenyl-2-propenyl acetate **80** with dimethyl malonate **165** (Figure 4.1.2).[50,52,67,68] These ligands contain a sp^2-hybridized nitrogen atom which is more electron-rich than the sp^3-hydridized nitrogen of amino group. The ferrocenyl skeleton is responsible for the high reactivity and enantioselectivity in the reaction. Ligand (R,S_p)-**16** which has an electron withdrawing group on the phenyl ring gave enantioselectivity up to 93% ee.[52] Replacing the phenyl group with 3-pyridine in ligand (R,S_p)-**28a** further increased the reactivity and the enantioselectivity (97% ee).[67] Pyridine nitrogen donor at position 3 strongly affected the electronic properties of the chiral ligands. Ligand (R,S_p)-**31b** that contains a triazine unit in the ferrocenyl scaffold exhibited even higher enantioselectivity and reactivity. It gave the allyl product with 97% ee and 93% yield at room temperature in 12 hours (Figure 4.1.2).[68]

Hashimoto prepared an effective iminophosphine ligand, **128**, which carries the sterically bulky mesityl group, for allylic alkylation of 1,3-diphenyl-2-propenyl acetate.[152] This work provided the impetus for Iwao to develop the structurally similar ligand (*S*)-**13** which carries a very bulky ferrocenyl group. This ligand gave further improvements in enantioselectivity (97% ee).[153]

Our aminophosphine ligands are C_1 symmetric and contain two donor atoms

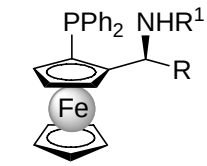
(nitrogen and phosphorous) of different electronic properties within the ferrocenyl scaffold. Different steric hindered alkyl groups were attached to the nitrogen donor atom of ferrocenyl ligands. The variation of enantioselectivity with steric structure of the ligands in palladium-catalyzed asymmetric allylic alkylation was studied. These ligands were then employed in palladium-catalyzed allylic alkylation under a variety of reaction conditions to examine their effects on enantioselection. Parameters, such as solvents, base additives, palladium precursors, ratio of palladium to ligand and nucleophiles, were varied to find out the optimal reaction condition.

Our data suggested that CH_3CN was the best solvent in the presence of base additive, Bu_4NCl. Ligand (S,R_p)-**151** which has a bulky *t*-butyl group on the amine function afforded high reactivity and enantioselectivity (88.8% ee) in the alkylation of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate under optimal condition.

The enantioselectivity of P,N-ferrocenyl ligands in allylic alkylation depends on the steric interaction between the substituent on the amine group and the alkyl group on the α-stereogenic carbon. Different interaction would lead to different reaction pathways and therefore different product configurations. The result showed that the product's configuration could be inverted by changing the nitrogen substituent of the ligands. The enantioselectivities were greatly enhanced by increasing the bulkiness around the nitrogen atom of the ligands. The *trans* effect of donor atoms

and the existence of proton on the nitrogen donor atom would initiate regioselectivity because nucleophile attacks *trans* to phosphorous donor atom and the proton of amine group interacts with the attacking nucleophile.

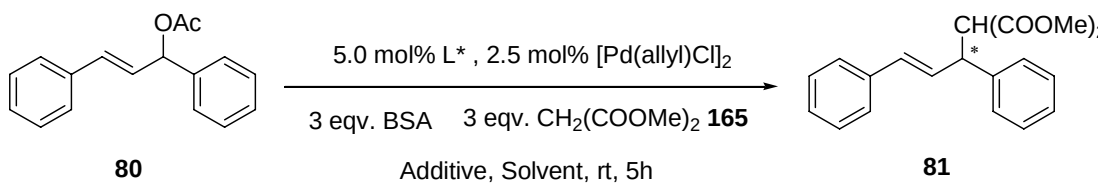
4.2 Palladium-catalyzed Asymmetric Allylic Alkylation Using Ferrocenyl Amino-Phosphine Ligands



(S,R_p)-**142**-**151**

(S,R_p)-**142**	R = Me; R^1 = H	(S,R_p)-**147**	R = Ph; R^1 = H
(S,R_p)-**143**	R = Me; R^1 = Me	(S,R_p)-**148**	R = Ph; R^1 = Me
(S,R_p)-**144**	R = Me; R^1 = *i*-Pr	(S,R_p)-**149**	R = Ph; R^1 = *i*-Pr
(S,R_p)-**145**	R = Me; R^1 = Cy	(S,R_p)-**150**	R = Ph; R^1 = Cy
(S,R_p)-**146**	R = Me; R^1 = *t*-Bu	(S,R_p)-**151**	R = Ph; R^1 = *t*-Bu

Figure 4.2.1 Ferrocenyl amino-phosphine ligands, L*



80 **81**

Scheme 4.2.1

Chiral ferrocenyl amino-phosphine ligands (Figure 4.2.1) were applied to the palladium-catalyzed asymmetric allylic alkylation of 1,3-diphenyl-2-propenyl acetate **80** with dimethyl malonate **165**. This reaction was carried out in different solvents in the presence of 2.5 mol% of allylpalladium(II) chloride dimmer, 5 mol% of chiral ligand, 3 equivalent of *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and a catalytic amount of a base additive at room temperature for 5 hours (Scheme 4.2.1).

4.2.1 Effect of Structures of the Ferrocenyl Amino-Phosphine Ligand

Effects of ligands on the catalytic activity and enantioselectivity were investigated and the results are summarized in Table 4.2.1 and Figure 4.2.2. The reaction (Scheme 4.2.1) was carried out in tetrahydrofuran with lithium acetate as a base additive. Complete conversion of the starting allylic acetate **80** to allylated product **81** occurred in 5 hours. Increasing the size of the *N*-alkyl group in ligands (S,R_p)-**147**-1**51**, which are having a phenyl group on the central chirality, improved the enantioselectivity (Figure 4.2.2 and Table 4.2.1, entries 6 to 10).

Table 4.2.1 Asymmetric allylic alkylation of **80** with **165** using ligands (S, R_p)-**142** to **151**[a]

Entry	L*	Conv. (%)[b]	Ee (%)[b]	Config.[c]
1	(S,R_p)-**142**	> 99	9.8	*R*
2	(S,R_p)-**143**	> 99	5.0	*S*
3	(S,R_p)-**144**	> 99	52.0	*R*
4	(S,R_p)-**145**	> 99	38.1	*R*
5	(S,R_p)-**146**	> 99	38.1	*R*
6	(S,R_p)-**147**	> 99	18.1	*S*
7	(S,R_p)-**148**	> 99	20.7	*S*
8	(S,R_p)-**149**	> 99	23.8	*R*
9	(S,R_p)-**150**	> 99	25.7	*R*
10	(S,R_p)-**151**	89.6	80.7	*R*

[a]Reaction Conditions: THF; 2.5 mol% $[Pd(allyl)Cl]_2$; 5.0 mol% of chiral ferrocenyl ligands; 3.0 equiv. of **165**; 3.0 equiv. of BSA and a catalytic amount of LiOAc at room temperature for 5 hours. [b]Determined by HPLC analysis using a Chiralpak AD column. [c]Configuration was compared with literature data.

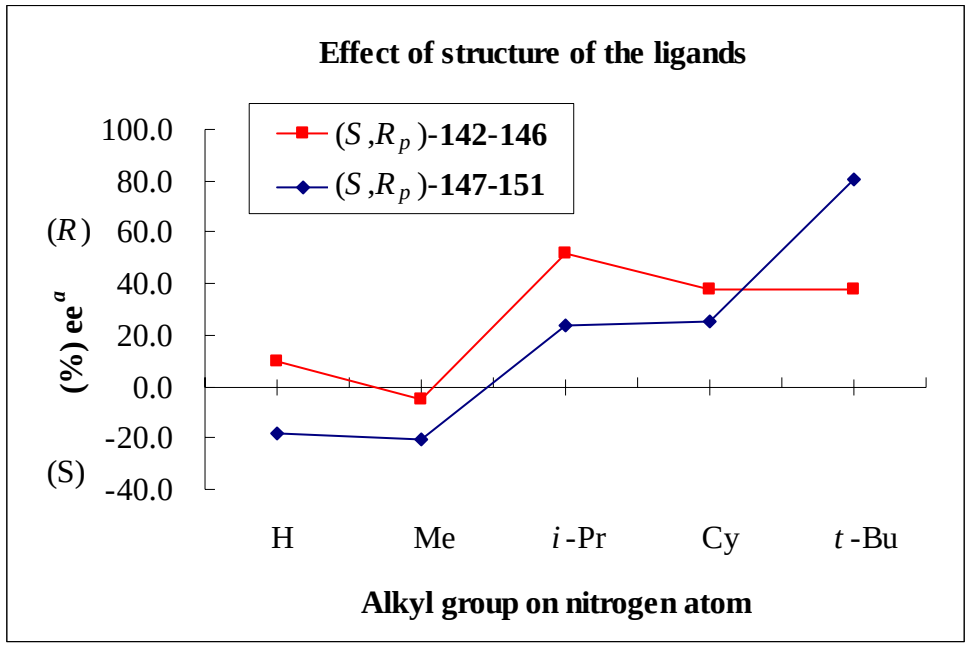


Figure 4.2.2 Effect of structure of ligands[a]

[a] A positive ee value means product with (*R*)-configuration and a negative ee value means product with (*S*)-configuration.

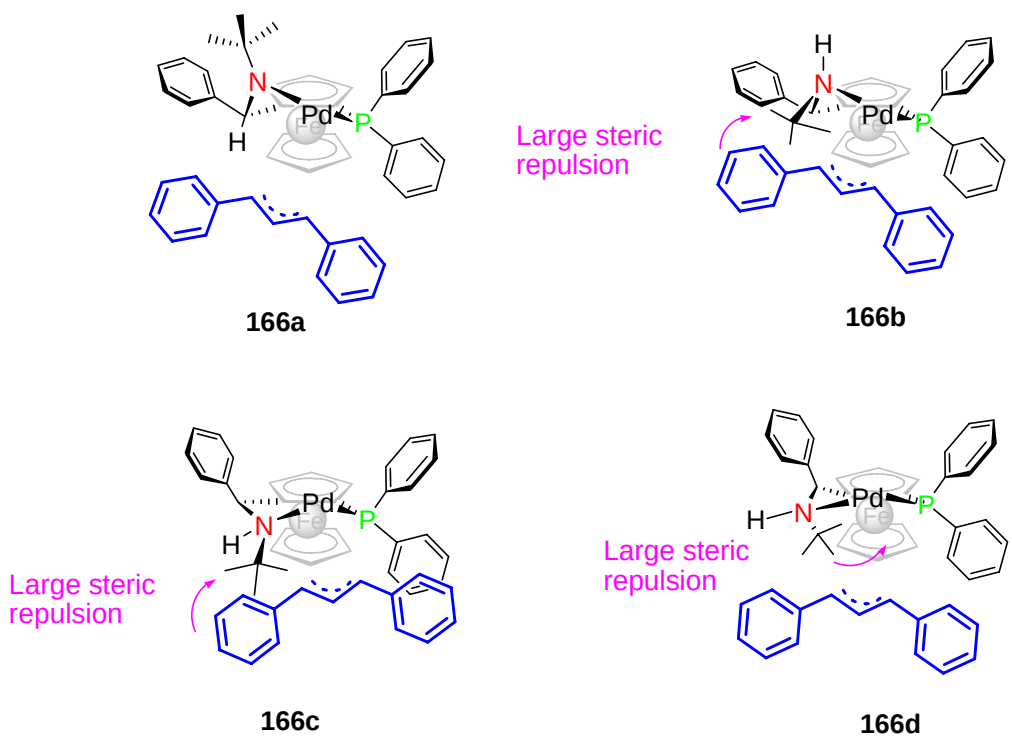
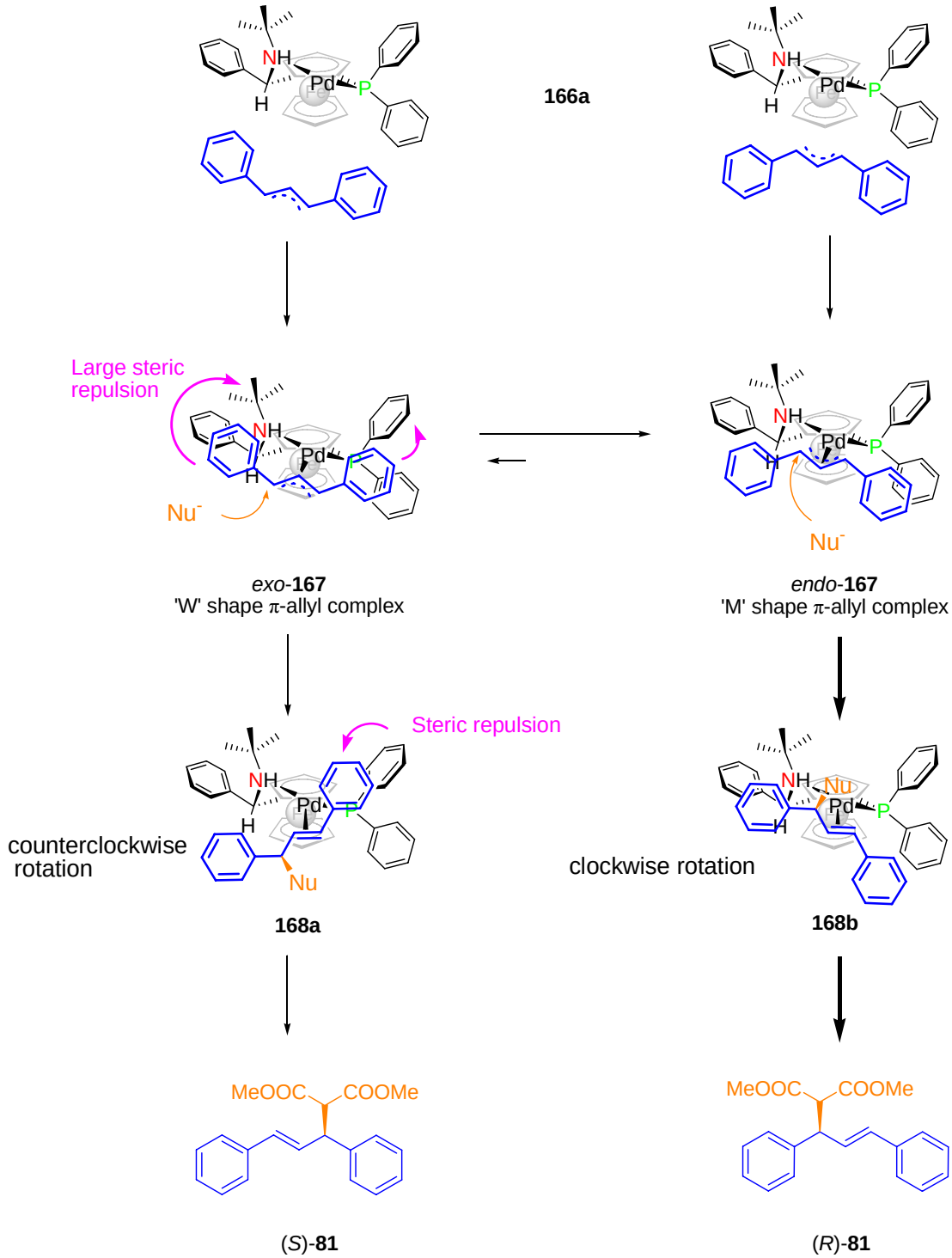


Figure 4.2.3 Four possible structures of palladium-complex
(Remark: The "M" configuration was selected as it is unreasonable for the "W" configuration to give the (*R*)-product in the experiment.)

Ligand (S,R_p)-**151** bearing a bulky *t*-butyl substituent on the nitrogen atom and a phenyl group on the α-stereogenic center gave the best result (80.7% ee) with a (*R*)-configuration product. In this case, different steric interactions may occur inside the intermediate complex or between the *N*-*t*-butyl group of the ligand and the phenyl group of the substrate (Figure 4.2.3). The possible conformational structures of palladium complexes are governed by the orientation of the amine group. The six-membered chelate ring of palladium complex **166a** bearing pseudoaxial *N*-*t*-butyl group represents the most preferable conformation. A poor coordination and strong steric repulsion may occur when the *N*-*t*-butyl group points face to face with the incoming substrate (i.e. complex **166b** and **166c**).

Structure **166d** is unlikely to occur owing to the severe steric repulsion generated by the *N*-*t*-butyl group when pointing towards the electron rich and bulky ferrocene. Based on this assumption, the most favorable structure, **166a**, is postulated as the major form with minimum steric repulsion within the coordination sphere and the *N*-*t*-butyl group orients anti to the iron of the backbone.



Scheme 4.2.2 Rationalization of the stereochemical outcome of the allylic alkylation reations mediated by ligand (S,R_p)-**151**

The enantioselectivity of asymmetric allylic alkylation is determined by the transition state structure during the attack of nucleophile to the intermediate

π-allylpalladium complex to generate palladium-olefin complex. Many research workers proposed similar intermediates and mechanisms for this reaction to explain their experimental results.[58,145,153] The proposed mechanism for asymmetric induction with ligand (S,R_p)-**151** is also rationalized on the basis of the stereochemical results obtained (Scheme 4.2.2). Configuration of the product is controlled by *trans* effect of donor atoms and the stability of π-allylpalladium complexes. For the P,N-ligand system, the nucleophilic attack takes place preferentially at the allyl terminus *trans* to phosphorus and this accounts for the regioselectivity. Guiry et al.[170] pointed out that two π-allylpalladium complexes, *exo*- and *endo*-, would be formed in conformational equilibrium. *Endo*-**167** would be the major isomer and more reactive than its diastereomer *exo*-**167**. For *endo*-**167**, the phenyl group attaching to the phosphorous atom of the ligand has to be face on with the phenyl group on the terminus carbon of allyl compound so as to minimize repulsion between each other. A nucleophile would attack the terminus carbon *trans* to the phosphorous of *endo*-**167** due to *trans* effect. The palladium-olefin complex **168b** would be formed after clockwise rotation of the olefin product. When the requirements of high enantioselectivity are according to the Curtin-Hammet principle[7,100,171], the interconversion of diastereomeric π-allylpalladium complexes is fast relative to the nucleophilic attack, and the asymmetric induction is determined by the reaction rate of the two diastereomeric

intermediates. The nucleophilic addition to *endo*-**167** is expected to be relatively fast because steric interaction is not present between the allylic unit and ligand after rotation of olefin product. The bottom-up nucleophilic addition pathway minimizes the repulsion between the *t*-butyl group of the ligand and the nucleophile. (*R*)-Configurational product would be obtained from this proposed mechanism and it is consistent with our experimental results and explains why ligand (S,R_p)-**151** gives high enantioselectivity.

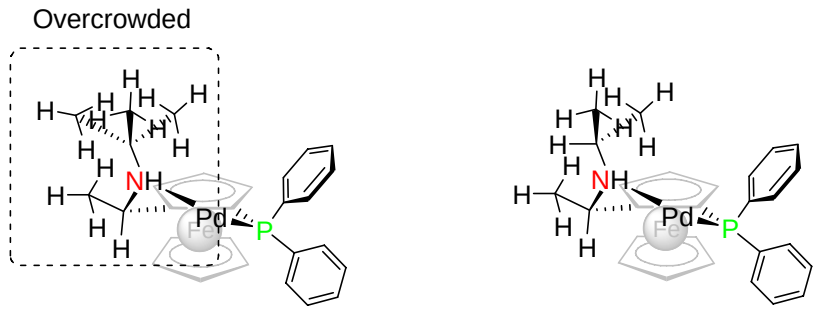
The other isomer, *exo*-**167** complex, is not favorable because the phenyl groups of the allylic substrate have large steric interactions with the phenyl group on the phosphorous atom and *t*-butyl group of the ligand. In addition, further steric repulsion could develop as a consequence of nucleophilic substitution. The substituted allyl moiety would induce counterclockwise rotation during the formation of the palladium-olefin complex **168a**; however, this process is restricted owing to the steric interaction between the phenyl group on the phosphorous atom and the phenyl group on the allylic unit. This pathway would be slow and give (*S*)-product as the major form. With the above mechanistic considerations, we presume that *endo*-**167** represents the predominant intermediate leading to (*R*)-product.

For the intermediate complex formed by (S,R_p)-**151**, the *t*-butyl group on the amine of the ligand may have a dominant role in the course of reaction in the presence

of a phenyl group on the central chirality. When the *t*-Butyl group was replaced by a cyclohexyl, isopropyl or methyl group, their enantioselectivities obviously decreased. Smaller alkyl group provides less steric repulsion with the allylic substrate. We would expect a decrease in the rate of interconversion of diastereomeric π-allylpalladium complexes. This explains for the decrease of enantioselectivity according to Curtin-Hammet principle when using small *N*-alkyl groups in ligands (*S*,R_p)-**147** to **150** (Table 4.2.1, entries 6-9). When the reaction was catalyzed by (*S*,R_p)-**148**, the configuration of the major product changed to (*S*)-configuration. It is due to the higher reactivity of the *exo*- π-allylpalladium complex when compared to the *enod*- complex. The smaller steric hindrance of the *N*-methyl group would tolerate formation of the *exo*- π-allylpalladium complex and counterclockwise rotation of the olefin product after nucleophilic addition. Therefore, (*S*)-Product is preferred.

The effect of the *N*-alkyl group of ligands (*S*,R_p)-**142** to **146**, which has a methyl group on the central chirality, on enantioselectivity is different (Figure 4.2.2). Introduction of *N*-*t*-butyl group in ligand (*S*,R_p)-**146** induced an adverse effect on enantioselectivity. When it is compared to the phenyl analogue (i.e. (*S*,R_p)-**151**), steric-overloading may occur in **169** which has both methyl and *t*-butyl group within a local quadrant (Figure 4.2.4). To minimize the local steric congestion, a dramatic rearrangement of original model **169** may lead to different pathways in the reaction.

This may explain for the different experimental observations between phenyl and methyl analogues of the ferrocenyl ligand.



169 **170**

Figure 4.2.4

On the other hand, the *N*-isopropyl group present in (*S*,R_p)-**144** leads to small local steric congestion and allows for the favorable metal-chelate complex **170** (Figure 4.2.4). Consequently, this ligand gave higher ee value than (*S*,R_p)-**146** for the catalytic asymmetric allylic alkylation reaction (Table 4.2.1, entries 3 vs. 5).

The results provided evidence that the functionality of alkyl group on the central chirality may assist to influence the equilibrium of π-allylpalladium complex and the reaction rate. Comparing the results of ligands (*S*,R_p)-**144** to (*S*,R_p)-**149** (table 4.2.1, entries 3 vs. 8), the methyl group is more effective than the phenyl group in the presence of *N*-isopropyl group. The situation is reversed in the presence of *N*-*t*-butyl group (entries 5 vs. 10). The methyl group on the central chirality is likely to induce the M-conformation of the π-allylpalladium complex because ligand (*S*,R_p)-**142**

bearing the smallest primary amino group also gave the (*R*)-product (entry 1). It is important to recognize that both the *N*-alkyl group and the alkyl group on the central chirality perform a complementary effect to create a stable chiral coordination sphere. The combination of *N*-*t*-butyl group with phenyl group on the central chirality was found to be the best and resulted in high enantioselectivity.

According to literature, the presence of an amine proton (-NH group) in the ligand could significantly promote the enantioselectivity of Pd-catalyzed asymmetric allylic alkylation. This is probably due to interaction between amino proton in the ligand and the nucleophile.[149,172] The nucleophile interact with the amino proton in the proposed mechanism (Scheme 4.2.2). The nucleophilic addition occurred from the bottom in complex *endo*-**167**. This could increase selectivity and rate of nucleophile attack on the allylic terminus carbon to give (*R*)-**81**.

4.2.2 Effect of Solvents

Table 4.2.2 Solvents screening in palladium-catalyzed alkylation of **80** with using ligands (S,R_p)-**142-151**[a]

Entry	L*	Solvent	Conv. (%)[b]	Ee (%)[b]	Config.[c]
1	(S,R_p)-**142**	DCM	54.0	14.2	*R*
2	(S,R_p)-**143**	DCM	61.0	10.7	*R*
3	(S,R_p)-**144**	DCM	> 99	20.2	*R*
4	(S,R_p)-**145**	DCM	> 99	0.8	*R*
5	(S,R_p)-**146**	DCM	> 99	37.3	*R*
6	(S,R_p)-**147**	DCM	> 99	19.2	*S*
7	(S,R_p)-**148**	DCM	> 99	15.9	*S*
8	(S,R_p)-**149**	DCM	> 99	27.9	*R*
9	(S,R_p)-**150**	DCM	> 99	36.0	*R*
10	(S,R_p)-**151**	DCM	> 99	74.3	*R*
11	(S,R_p)-**142**	Toluene	97.8	11.5	*R*
12	(S,R_p)-**143**	Toluene	95.9	1.2	*S*
13	(S,R_p)-**144**	Toluene	> 99	41.3	*R*
14	(S,R_p)-**145**	Toluene	> 99	9.3	*R*
15	(S,R_p)-**146**	Toluene	> 99	18.7	*R*
16	(S,R_p)-**147**	Toluene	> 99	32.9	*S*
17	(S,R_p)-**148**	Toluene	> 99	30.2	*S*
18	(S,R_p)-**149**	Toluene	> 99	36.0	*R*
19	(S,R_p)-**150**	Toluene	> 99	34.0	*R*
20	(S,R_p)-**151**	Toluene	> 99	78.2	*R*
21	(S,R_p)-**142**	CH_3CN	26.4	5.5	*R*
22	(S,R_p)-**143**	CH_3CN	> 99	1.0	*R*
23	(S,R_p)-**144**	CH_3CN	71.6	68.2	*R*

24	(S,R_p)-**145**	CH_3CN	65.4	41.9	*R*
25	(S,R_p)-**146**	CH_3CN	> 99	55.5	*R*
26	(S,R_p)-**147**	CH_3CN	91.8	10.9	*S*
27	(S,R_p)-**148**	CH_3CN	55.8	13.9	*S*
28	(S,R_p)-**149**	CH_3CN	84.5	36.8	*R*
29	(S,R_p)-**150**	CH_3CN	50.6	33.8	*R*
30	(S,R_p)-**151**	CH_3CN	> 99	84.3	*R*
31	(S,R_p)-**142**	THF	> 99	9.8	*R*
32	(S,R_p)-**143**	THF	> 99	5.0	*S*
33	(S,R_p)-**144**	THF	> 99	52.0	*R*
34	(S,R_p)-**145**	THF	> 99	38.1	*R*
35	(S,R_p)-**146**	THF	> 99	38.1	*R*
36	(S,R_p)-**147**	THF	> 99	18.1	*S*
37	(S,R_p)-**148**	THF	> 99	20.7	*S*
38	(S,R_p)-**149**	THF	> 99	23.8	*R*
39	(S,R_p)-**150**	THF	> 99	25.7	*R*
40	(S,R_p)-**151**	THF	> 99	80.7	*R*

[a]Reaction Conditions: 2.5 mol% $[Pd(allyl)Cl]_2$; 5.0 mol% of chiral ferrocenyl ligands; 3.0 equiv. of **165**; 3.0 equiv. of BSA and a catalytic amount of LiOAc at room temperature for 5 hours. [b]Determined by HPLC analysis using a Chiralpak AD column. [c]Configuration was compared with literature data.

In order to improve the enantioselectivties, the effect of solvent was examined using ligands (S,R_p)-**142** to **151**. The allylic alkylation was carried out in tetrahydrofuran, dichloromethane, acetonitrile and toluene, all in presence of LiOAc. The results were summarized in Table 4.2.2, Figure 4.2.5 and 4.2.6. When different solvents were used with ligands (S,R_p)-**147** to **151** having a phenyl group on the chiral

center, ee values of the product had no obvious changes (Figure 4.2.6). The catalytic activities were lower in CH_3CN (entries 26-29). Ligands (S,R_p)-**147** and **148** with the smaller size amine group afforded the product in (S) form with higher ee in toluene (entries 16 and 17). Ferrocenyl ligands with large alkyl groups on the amine gave (R)-product as major isomer (Figure 4.2.6). The most effective ligand (S,R_p)-**151**, bearing the largest *t*-butyl group, afforded 84.3% ee in CH_3CN (entry 30).

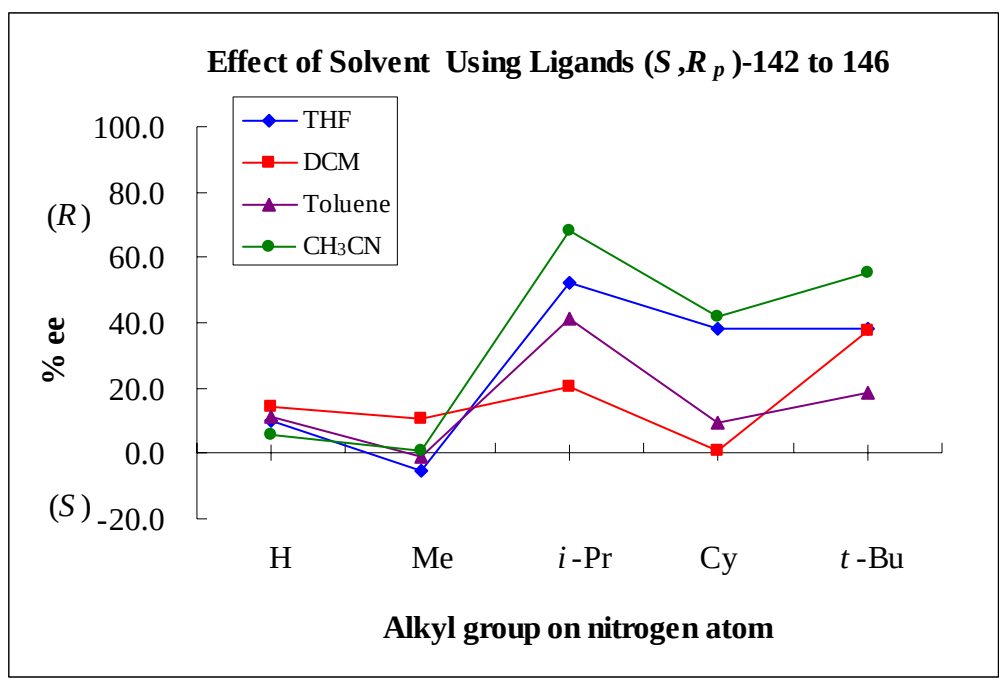


Figure 4.2.5 [a]

[a] The ee in positive value means product with (R)-configuration and in negative value means product with (S)-configuration.

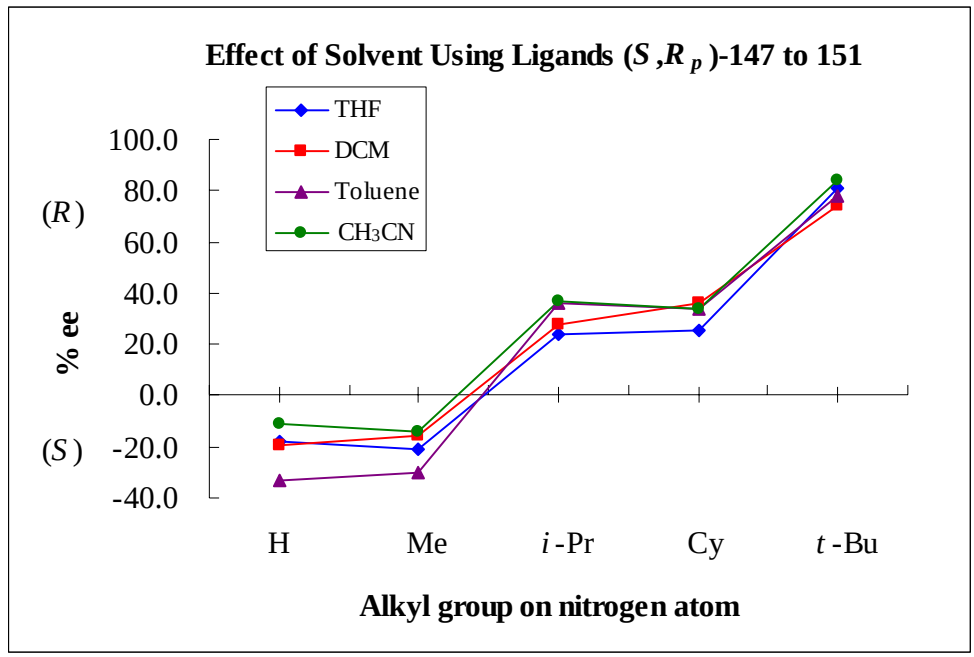


Figure 4.2.6 [a]

[a] The ee in positive value means product with (*R*)-configuration and in negative value means product with (*S*)-configuration.

The effect of solvent for ferrocenyl ligands having methyl groups at the chiral center (S,R_p)-**142** to **146** **(**Figure 4.2.5) was distinctly different when compared to their phenyl analogues **(**Figure 4.2.6). CH_3CN was found to be good for enantioselectivities when used with the bulky ligands (S,R_p)-**144-146** but their catalytic activities decreased (Table 4.2.2, entries 23 and 24). Selectivities of ligands (S,R_p)-**142** and **143** in DCM system were higher than in other solvents but the reaction proceeded at a low reaction rate (entries 1 and 2).

Ligands with large alkyl groups on the amine are similar to their phenyl analogues, giving the (*R*)-product in different solvents; but ligand (S,R_p)-**146** with the largest *N*-*t*-butyl group showed diminished enantioselectivity. The best result for the

methyl group analogues was 68.2% ee obtained with ligand (S,R_p)-**144** having the *N-iso*-propyl group (entry 23). CH_3CN remained the best choice of solvent for improving enantioselectivities.

Symmetrical π-allyl substrate in polar solvent is employed in allylic alkylation where the nucleophilic addition constitutes the enantioselective step under Curtin-Hammett conditions. Increasing the rate of interconversion or decreasing the rate of nucleophilic attack could enhance enantioselectivity. Polar solvents, such as DCM, CH_3CN and THF, may stabilize the π-allylpalladium complex and nucleophile better than nonpolar solvents (toluene). The stabilization by polar solvent would lead to an overall decrease in the rate of nucleophilic attack. Therefore, the nucleophilic addition process is slow relative to the rate of interconversion between diastereomeric π-allylpalladium complexes. [100,173,174]

4.2.3 Effect of Base Additives

Table 4.2.3 Additives screening in palladium-catalyzed alkylation of **80** with using ligands (S,R_p)-**151**[a]

Entry	Solvent	Additive	Conv. (%)[b]	Ee (%)[b]	Config.[c]
1	DCM	$Zn(OAc)_2$	> 99	76.9	*R*
2	DCM	KOAc	> 99	79.9	*R*
3	DCM	NaOAc	> 99	79.8	*R*
4	DCM	LiOAc	> 99	74.3	*R*
5	DCM	Bu_4NCl	> 99	79.4	*R*

6	CH_3CN	$Zn(OAc)_2$	> 99	86.3	*R*
7	CH_3CN	KOAc	> 99	86.7	*R*
8	CH_3CN	NaOAc	> 99	86.5	*R*
9	CH_3CN	LiOAc	> 99	84.3	*R*
10	CH_3CN	Bu_4NCl	> 99	88.8	*R*
11	THF	$Zn(OAc)_2$	> 99	62.7	*R*
12	THF	KOAc	> 99	82.4	*R*
13	THF	NaOAc	> 99	81.9	*R*
14	THF	LiOAc	89.6	80.7	*R*
15	THF	Bu_4NCl	98.2	77.6	*R*

[a]Reaction Conditions: 2.5 mol% $[Pd(allyl)Cl]_2$; 5.0 mol% of chiral ferrocenyl ligands; 3.0 equiv. of **165**; 3.0 equiv. of BSA and a catalytic amount of additives at room temperature for 5 hours. [b]Determined by HPLC analysis using a Chiralpak AD column. [c]Configuration was compared with literature data.

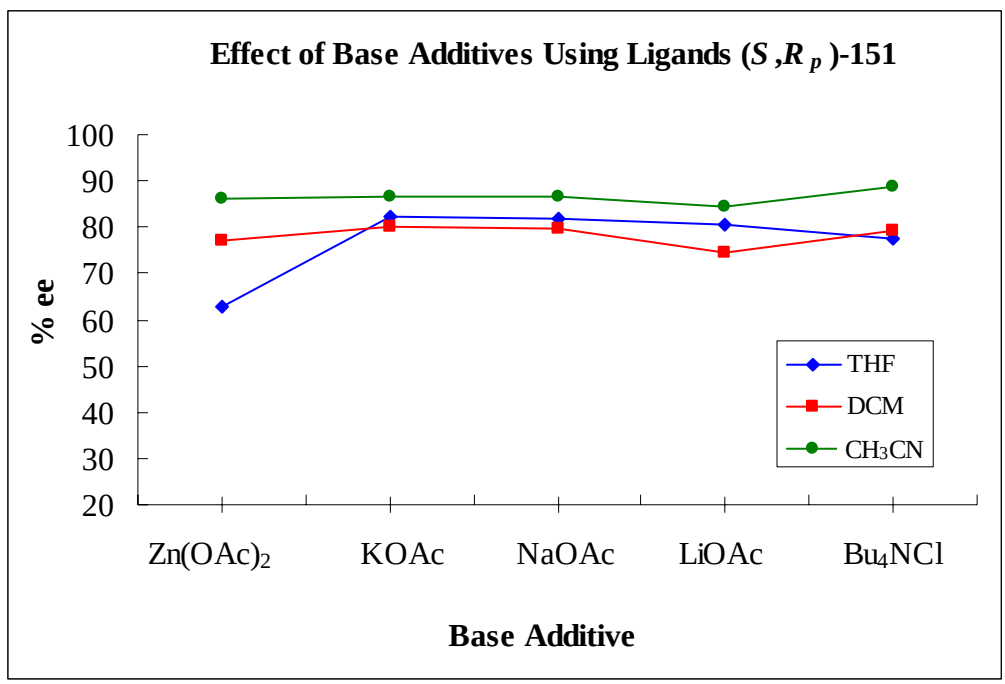


Figure 4.2.7

Since ligand (S,R_p)-**151** gave the best results in ferrocenyl ligands, this ligand was chosen for further study of the effect of base additives. Results were shown in table 4.2.3 and figure 4.2.7. Four alkali metal salts (LiOAc, KOAc, NaOAc and $Zn(OAc)_2$) and an ammonium salt (BuN_4Cl) were used to compare their effect on enantioselection in polar solvents. For metal ion, the order of size should be Zn^{2+} < Li^+ < Na^+ < K^+. In allylic alkylation, the nucleophilic attack is the enantioselective step. Therefore, the counterion of the nucleophile may influence the enantioselectivity of the catalytic reaction.

The change in enantioselectivity was not remarkable in acetonitrile and DCM but it appreciably decreased in the presence of LiOAc (entry 4 and 9). The ee value distinctly decreased to 62.7% in THF with $Zn(OAc)_2$ (entry 11). The effect of base additives on enantioselectivity was very distinct in THF (entries 10 to 11).

Reactions in DCM or CH_3CN were found to be insensitive to whether lithium, sodium, potassium or zinc was employed as the countercation. Good conversion and high enantioselectivity were always achieved (entries 1 to 10). In contrast, the base additive species turned out to play an important role upon the outcome of reactions in THF. Replacing $Zn(OAc)_2$ (entry 11) with KOAc, NaOAc or LiOAc (entries 12 to 15) increased the enantioselectivity to above 80% ee. It is because THF has a very limited ability to specifically solvate cations and almost no ability to solvate anions.[175] Then

the nucleophilic species might be viewed as simply the anion plus the cation in some minimal state of solvation. Higher ee was obtained in the presence of KOAc in THF solvent. The larger size of potassium ion is expected to slow down the rate of nucleophilic addition simply due to increased steric interactions with the (π-allyl)palladium intermediate.[175] The rate of nucleophilic addition is slower relative to the rate of interconversion between diastereomeric π-allylpalladium complexes which could enhance the enantioselectivity. The smallest cation, Zn^{2+}, would decrease the steric effect. The ee values dropped to 62.7% in THF with $Zn(OAc)_2$ (compare entries 11-15).

Moberg[173] and Fuji[176] had examined the effect of counter cation. The absolute configuration of product switched as the hardness of cation changed because of the variation in strength of coordination of nucleophile. This tendency was not observed in our results where all reactions gave (*R*)-configuration product.

Tetrabutylammonium chloride, which contains the large ammonium ion and chloride ion, gave 88.8% ee with complete conversion in CH_3CN. The alkylammonium ion might be large enough to increase the steric effect and slow down the nucleophilic attack. The chloride ion would bond strongly to palladium. Togni has examined the anion effect on allylic alkylation and found that the addition of hard anions had a beneficial effect on the enantioselectivity of allylic amination.[177] The

presence of halide ion enhances the rate of interconversion between diastereomeric π-allylpalladium complexes. It causes more rapid equilibrium of these two complexes relative to nucleophilic attack.[174,178] The effectiveness of tetrabutylammonium chloride was higher in polar solvent (CH_3CN, entry 10) than in other solvents (entries 5 and 15).

4.2.4 Effects of Palladium Precursors and the Ratio of Pd to Ligand

Table 4.2.4 Palladium precursors screening in palladium-catalyzed alkylation of **80** with using ligands (S,R_p)-**151**[a]

Entry	Additive	L*/Pd	Conv. (%)[b]	Ee (%)[b]	Config.[c]
1	$[Pd(allyl)Cl]_2$	1	> 99	86.7	*R*
2	$Pd(dba)_2$	1	> 99	85.9	*R*
3	$Pd_2(dba)_3$	1	> 99	86.1	*R*
4	$Pd(OAc)_2$	1	> 99	81.4	*R*
5	$[Pd(allyl)Cl]_2$	2	> 99	87.6	*R*
6	$[Pd(allyl)Cl]_2$	3	> 99	88.2	*R*

[a]Reaction Conditions: in CH_3CN; 2.5 mol% $[Pd(allyl)Cl]_2$, 5.0 mol% of chiral ferrocenyl ligand; 3.0 equiv. of **165**; 3.0 equiv. of BSA and a catalytic amount of KOAc at room temperature for 5 hours. [b]Determined by HPLC analysis using a Chiralpak AD column. [c]Configuration was compared with literature data.

For the reaction conditions screening experiments, we selected CH_3CN as the solvent and KOAc as the base for investigating the influence of palladium precursors on the catalytic activity and enaotioselectivity (Table 4.2.4). Using $Pd(dba)_2$, $Pd_2(dba)_3$, $Pd(OAc)_2$ as palladium precursors to replace $[Pd(allyl)Cl]_2$ also led to

appreciably decreased enantioselectivities (entries 1-4). When the ratio of palladium to ligands was increased, the ee values did not change. These results showed that the enantioselectivity of ferrocenyl amino-phosphine ligands was not influence by these two factors.

4.2.5 Effect of Nucleophiles

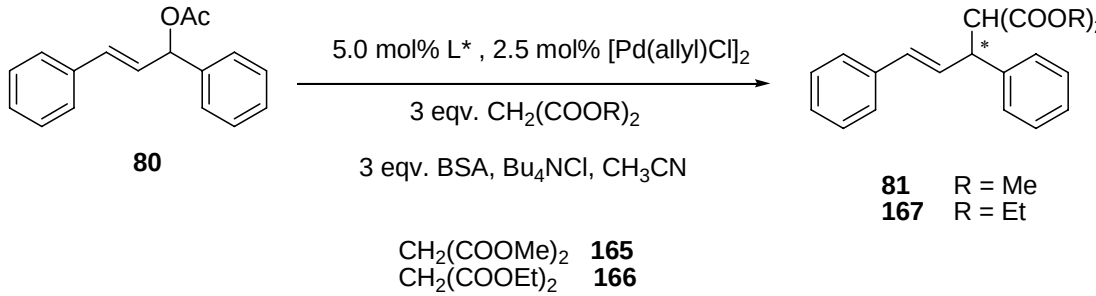


Figure 5.7-1 Asymmetric allylic alkylation with various nucleophiles

Table 4.2.5 Asymmetric allylic alkylation of **80** with **165** or **166** using ligands (*S*, R_p)-**142**-**151** [a]

Nucleophile		**165**		**166**		
Product		**81**		**167**		
L*	Entry	Conv. (%)[b]	Ee (%)[b]	Entry	Conv. (%)[b]	Ee (%)[b]
(*S*,R_p)-**142**	1	53.0	27.4	11	18.6	13.9
(*S*,R_p)-**143**	2	98.8	7.3	12	33.7	Rac.
(*S*,R_p)-**144**	3	> 99	68.5	13	85.8	69.4
(*S*,R_p)-**145**	4	> 99	62.5	14	84.2	61.1
(*S*,R_p)-**146**	5	> 99	65.5	15	> 99	60.3
(*S*,R_p)-**147**	6	21.6	18.8	16	11.4	1.9
(*S*,R_p)-**148**	7	98.6	14.8	17	88.2	16.5
(*S*,R_p)-**149**	8	> 99	68.0	18	> 99	70.7
(*S*,R_p)-**150**	9	77.9	75.7	19	> 99	67.1
(*S*,R_p)-**151**	10	> 99	88.8	20	> 99	82.5

[a]Reaction Conditions: in CH_3CN; 2.5 mol% $[Pd(allyl)Cl]_2$; 5.0 mol% of chiral ferrocenyl ligands; 3.0 equiv. of **165** or **166**; 3.0 equiv. of BSA and a catalytic amount of Bu_4NCl at room temperature for 5 hours. The configuration of product **81** and **167** are *R*. [b]Determined by HPLC analysis using a Chiralpak AD column.

After the optimization of the reaction conditions, dimethyl malonate **165** and diethyl malonate **166** were then employed as nucleophile to examine the influence of activity and enantioselectivity and the results were shown in Table 4.2.5. Increasing the size of the nucleophile is unfavorable to the activity and enantioselectivity of the reaction catalyzed by the ferrocenyl ligands with smaller alkyl groups on the amine (entries 11, 12, 16). However, it did not influence the enantioselectivities when the ferrocenyl ligands with the larger alkyl group (isopropyl, cyclohexyl and *t*-butyl) on the amine were employed. (entries 13 to 15 and 18 to 20). The reaction using diethyl malonate as nucleophile provided similar level of enantioselectivity. These results are not the same as the work of Fujita[179] who had used diethyl malonate to improve the enantioselectivity of chiral phosphine-oxazine ligands.

The effect of structure of ligands (*S*,R_p)-**142** to (*S*,R_p)-**151** had the same trend in allylic alkylation of the both nucleophiles. Ligands (*S*,R_p)-**142**, (*S*,R_p)-**143**, (*S*,R_p)-**147** and (*S*,R_p)-**148** having less sterically hindered nitrogen donor atom gave low enantioselectivities (entries 1, 2, 6, 7, 11, 12, 16, 17). Ligand (*S*,R_p)-**144** with *N*-isopropyl group in methyl analogue and ligand (*S*,R_p)-**151** with *N*-*t*-butyl group in phenyl analogue are the most effective ligands to catalyze the alkylation reaction.

Chapter 5

Experimental Section

5.1 General Procedure

Unless otherwise indicated, all reactions were carried out in an inert atmosphere glovebox or under nitrogen atmosphere. Melting points were measured using an electrothermal 9100 apparatus in capillaries and the data were uncorrected. NMR spectra were recorded on a Varian 500MHz Fourier transform spectrometer. ^{1}H and ^{13}C NMR spectra were recorded relative to residual protiated solvent; a positive value of the chemical shift denotes a resonance downfield from TMS. Mass analyses were performed on a Finnigan model Mat 95 ST mass spectrometer. High-performance liquid chromatography (HPLC) analyses were performed using a Hewlett-Packard model HP 1050/1100 LC interfaced to a HP 1050 series computer workstation using a variety of optically active column (Daicel Chiracel AS-H, Chiracel AS, Chiracel AD, or Chiracel AD-H). Optical rotations were measured on a Perkin-Elmer model 341 polarimeter at 20 ˚C. The solid prochiral ferrocenyl ketones were re-crystallized before use and all other chemicals were purchased from commercial suppliers and used without further purification. THF was freshly distilled from Na/benzophenone ketyl under nitrogen. Dichloromethane was freshly distilled from calcium hydride under nitrogen. All reactions were monitored by analytical thin-layer chromatography (TLC) on Merck aluminum-precoated plates of silica gel 60 F_{254} with detection by spraying with 5% (w/v) dodecamolybdophosphoric acid in ethanol or 5% (w/v) ninhydrin in ethanol and subsequent heating. E. Merck silica gel 60 (230–400 mesh) was used for flash chromatography. Hydrogenation reactions were carried out using a Parr 4714 bomb and a Parr 4520 series stirred reactor.

5.2 Friedel-Crafts Acylation of Ferrocene

General Procedure for Friedel-Crafts acylation of ferrocene

$AlCl_3$ was added portion-wise into a solution of ferrocene and acyl chloride (1.1 eqv.) in dichloromethane at 0 ˚C. The solution was allowed to warm up to rt and stirred overnight. The solution was then added slowly into a saturated $NaHCO_3$ solution cooled in ice-bath. The mixture was extracted with diethyl ether (30mL x 3). The combined organic solution was further washed with water (50mL × 3), and brine (50mL × 3), then dried over anhydrous $MgSO_4$, and filtered. Concentration of the filtrate followed by flash chromatography gave the corresponding ferrocenyl alcohol.

Acetylferrocene, 4a. Prepared according to the general procedure described above from ferrocene (2.0 g, 10.8 mmol), aluminum chloride (1.43 g, 10.8 mmol), and acetyl chloride (1.01 mL, 11.8 mmol) and isolated as a red solid (2.38 g, 10.4 mmol, 97%); mp 86.3℃; ^{1}H NMR ($CDCl_3$, 500MHz): δ 4.77 (s, 2H), 4.50 (s, 2H), 4.21 (s, 4H), 2.40 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 201.9, 79.0, 72.2, 69.7, 69.4, 27.2.

Benzoylferrocene, 4b. Prepared according to the general procedure described above from ferrocene (2.0 g, 10.8 mmol), aluminum chloride (1.43 g, 10.8 mmol), and benzoyl chloride (1.4 mL, 11.8 mmol) and isolated as a red solid (2.69 g, 9.27 mmol, 86.1%); mp 111.5℃; ^{1}H NMR ($CDCl_3$, 500MHz): δ 7.89 (d, *J* = 8 Hz, 2H), 7.56-7.53 (m, 1H), 7.48-7.45 (m, 2H), 4.90 (s, 2H), 4.58 (s, 2H), 4.20 (s, 5H); ^{13}C NMR ($CDCl_3$): δ 199.1, 139.7, 131.4, 128.2, 128.0, 78.1, 72.5, 71.5, 70.2; MS (ESI) *m/z* (%): 291 (M^++1, 27), 290 (M^+, 100), 288 (8), 187 (7), 186 (39), 184 (5).

(2-Methoxybenzoyl)ferrocene, 4c. Prepared according to the general procedure described above from ferrocene (2.0 g, 10.8 mmol), aluminum chloride (1.9 g, 14.2 mmol), and 2-methoxybenzoyl chloride (2.0 mL, 13.0 mmol) and isolated as a red solid (2.4 g, 7.57 mmol, 69.8%); mp 139.1℃; ^{1}H NMR ($CDCl_3$, 500MHz): δ 7.44-7.41 (m, 2H), 7.03-6.98 (m, 2H), 4.74 (s, 2H), 4.53 (s, 2H), 4.22 (s, 5H), 3.83 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 199.3, 156.4, 131.0, 130.2, 128.2, 119.9, 111.4, 79.2, 72.4, 70.9, 69.9, 55.4; MS (ESI) *m/z* (%): 321 (M^++1, 28), 320 (M^+, 100), 322 (5), 318 (7), 135 (8); HRMS (ESIMS) Calcd. for $C_{18}H_{17}O_2Fe$ ($C_{18}H_{16}O_2Fe$ + H), 321.0578; found 321.0526.

(4-Bromobenzoyl)ferrocene, 4d. Prepared according to the general procedure described above from ferrocene (2.0 g, 10.8 mmol), aluminum chloride (1.4 g, 10.8 mmol), and 4-bromobenzoyl chloride (2.6 g, 11.9 mmol) and isolated as a red solid (2.0 g, 5.44 mmol, 50.4%); mp 121.8℃ ^{1}H NMR ($CDCl_3$, 500MHz): δ 7.78 (d, *J* = 8.5 Hz, 2H), 7.61 (d, *J* = 8.5 Hz, 2H), 4.87 (s, 2H), 4.61 (s, 2H), 4.20 (s, 5H); ^{13}C NMR ($CDCl_3$): δ 197.9, 138.4, 131.5, 129.6, 126.2, 77.7, 72.8, 71.4, 70.3 ; MS (ESI) *m/z* (%): 369 (M^+, 100), 683 (4), 639 (4), 595 (11), 552 (7), 551 (13), 546 (8), 507 (15), 502 (4), 463 (10), 415 (7), 386 (24), 366 (7), 359 (4), 192 (6); ;HRMS (ESIMS) Calcd. for $C_{17}H_{14}BrOFe$ ($C_{17}H_{13}BrOFe$ + H), 368.9577; found 368.9503.

Ferrocenyl 1-naphthyl ketone, 4e. Prepared according to the general procedure described above from ferrocene (2.0 g, 10.8 mmol), aluminum chloride (1.72 g, 12.9 mmol), and 1-naphthoyl chloride (1.94 mL, 12.9 mmol) and isolated as a red solid (3.2 g, 9.29 mmol, 86.2%); mp 99.5℃; ^{1}H NMR ($CDCl_3$, 500MHz): δ 8.25 (brs, 1H), 7.97 (d, *J* = 8.5 Hz, 2H), 7.91 (d, *J* = 6.5 Hz, 1H), 7.76 (d, *J* = 7 Hz, 1H), 7.54-7.50 (m, 1H), 4.82 (s, 2H), 4.58 (s, 2H), 4.23 (s, 5H); ^{13}C NMR ($CDCl_3$): δ 137.9, 134.0, 130.9, 130.6, 128.6, 127.2, 126.6, 126.2, 125.8, 124.5, 95.0, 80.0, 73.1, 71.7, 70.2; MS (ESI) *m/z* (%): 340 (M^+, 100), 455 (4), 454 (19), 452 (5), 407 (11), 406 (11), 342 (5), 341 (29), , 338 (7), 155 (6); HRMS (ESIMS) Calcd. for $C_{21}H_{17}OFe$ ($C_{21}H_{16}OFe$ + H), 341.0629; found 341.0599.

Ferrocenyl 2-napthyl ketone, 4f. Prepared according to the general procedure described above from ferrocene (2.0 g, 10.8 mmol), aluminum chloride (1.72 g, 12.9 mmol), and 2-naphthoyl chloride (2.5 g, 12.9 mmol) and isolated as a red solid (3.3 g, 9.69 mmol, 90.1%); mp 89.0℃; ^{1}H NMR ($CDCl_3$, 500MHz): δ 8.46 (s, 1H), 7.99-7.91 (m, 4H), 7.60-7.57 (m, 2H), 5.00 (s, 2H), 4.63 (s, 2H), 4.25 (s, 5H); ^{13}C NMR ($CDCl_3$): δ 198.8, 135.9, 134.8, 132.3, 129.1, 128.7, 128.0, 127.7, 127.7, 126.6, 124.8, 78.3, 72.5, 71.6, 70.2; MS (ESI) *m/z* (%): 340 (M^+, 100), 454 (5), 417 (5), 415 (8), 414 (5), 359 (12), 342 (5), 341 (32), 338 (8), 192 (4), 155 (5); HRMS (ESIMS) Calcd. for $C_{21}H_{17}OFe$ ($C_{21}H_{16}OFe$ + H), 341.0629; found 341.0612.

Ferrocenyl 2-furyl ketone, 4g. Prepared according to the general procedure described above from ferrocene (2.0 g, 10.8 mmol), aluminum chloride (1.72 g, 12.9 mmol), and furan-2-carbonyl chloride (1.27 mL, 12.9 mmol) and isolated as a red solid (2.8 g, 10.1 mmol, 94.2%); mp 85.0℃; ^{1}H NMR ($CDCl_3$, 500MHz): δ 7.62 (brs, 1H), 7.32 (brs, 1H), 6.56 (brs, 1H), 5.16 (s, 2H), 4.59 (s, 2H), 4.17 (s, 5H); ^{13}C NMR ($CDCl_3$): δ 184.7, 153.6, 145.2, 116.6, 111.9, 77.7, 72.4, 70.7, 70.1; MS (ESI) *m/z* (%):

280 (M^+, 100), 478 (5), 391 (3), 359 (5), 358 (7), 282 (4), 281 (29), 278 (7), 192 (6); HRMS (ESIMS) Calcd. for $C_{15}H_{13}O_2Fe$ ($C_{15}H_{12}O_2Fe$ + H), 281.0265; found 281.0209.

Ferrocenyl 2-thienyl ketone, 4h. Prepared according to the general procedure described above from ferrocene (2.0 g, 10.8 mmol), aluminum chloride (1.72 g, 12.9 mmol), and 2-thiophenecarbonyl chloride (1.38 mL, 12.9 mmol) and isolated as a red solid (2.4 g, 8.2 mmol, 76.4%); mp 122.7℃; ^{1}H NMR ($CDCl_3$, 500MHz): δ 7.93 (d, *J* = 3 Hz, 1H), 7.62 (d, *J* = 4.5 Hz, 1H), 7.17-7.15 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 189.3, 144.0, 131.7, 131.5, 127.6, 78.7, 72.3, 70.9, 70.3; MS (ESI) *m/z* (%): 296 (M^+, 100), 298 (7), 297 (21), 294 (6); HRMS (ESIMS) Calcd for $C_{15}H_{13}OSFe$ ($C_{15}H_{12}OSFe$ + H), 297.0037; found 296.9987.

5.3 Asymmetric Hydrogenation of Ferrocenyl Ketones

5.3.1 General Preparation of [(P-Phos)RuCl$_2$(DPEN)] Pre-catalyst

[(P-Phos)RuCl$_2$(DPEN)] pre-catalyst[1]

$[RuCl_2(p\text{-cymeme})]_2$ (4.1 mg, 6.7μmol) and (*R*)-XylPPhos (10.6 mg, 14.5 μmol) in degassed DMF (0.5 mL) was stirred at 100 ˚C for 10 min to form a reddish brown solution. After cooling to room temperature, a solution of (*R*,*R*)-DPEN (4.3 mg, 13.7 μmol) in degassed DMF (0.5 mL) was added to the reaction mixture and was stirred for 3 h. The solvent was removed under reduced pressure and the crude residue was used directly without any further purification.[25]

5.3.2 Standard Procedure of Asymmetric Hydrogenation of Ferrocenyl Ketones

A stock solution of the ruthenium precatalyst in 2-propanol, ferrocenyl ketone, 2-propanol and $(CH_3)_3COK$ solution in 2-propanol were added to a stainless steel autoclave under a nitrogen atmosphere. The whole system was purged with hydrogen before being pressurized to 50 bar. The reaction mixture was stirred at room temperature for 15 h, after which the unreacted hydrogen was released slowly and carefully. The conversion and enantiomeric excess of ferrocenyl alcohol was

determined by HPLC immediately without further purification. Analytical samples were purified by flash column chromatography.

(*S*)-(+)-1-Ferrocenylethanol, 3a.[2] Yellow solid, 100% yield, 99.4% ee; mp 75.1℃; $[\alpha]_D^{20}$:= +26.9 (*c* = 1.15, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500MHz): δ 4.48 (s, 1H), 4.26 (s, 9H), 1.77 (s, 1H), 1.43 (d, *J* = 4.5 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 94.6, 68.2, 67.9, 67.8, 66.1, 66.0, 65.4, 23.8; MS (ESI) *m/z* (%): 230 (100), 304 (18), 301 (45), 231 (18), 213 (49), 130 (18); HRMS (ESIMS) Calcd. for $C_{12}H_{13}Fe$ ($C_{12}H_{14}OFe$ + H − H_2O), 213.0367; found 213.0376; Daical Chiralpack AS column, hexane/*i*-PrOH 90/10, 1.2 mL/min, 5.7 min (major), 10.5 min (minor).

(*R*)-(−)-Ferrocenylphenylmethanol, 3b.[3] Yellow solid, 99% yield, 89% ee; mp 89.1℃; $[\alpha]_D^{20}$:= −89.30 (*c* = 1.01, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500MHz): δ 7.47-7.43 (m, 4H), 7.39-7.37 (m, 1H), 5.05 (s, 1H), 4.24 (s, 1H), 4.10 (s, 1H), 4.06 (s, 1H), 4.03 (s, 1H), 3.97 (s, 1H), 3.92 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 143.2, 128.2, 127.4, 126.2, 94.2, 72.0, 68.4, 68.1, 68.0, 67.4, 66.0; MS (ESI) *m/z* (%): 275 ([M + H − H_2O]$^+$, 100), 341 (15), 315 (11), 301 (18), 292 (M, 64), 276 (25), 149 (8); HRMS (ESIMS) Calcd. for $C_{17}H_{15}Fe$ ($C_{17}H_{16}OFe$ + H − H_2O), 275.0523; found 275.0536; Daical Chiralpack AS-H column, hexane/*i*-PrOH 98/2, 1.2 mL/min, 22.0 min (major), 29.8 min (minor).

(−)-Ferrocenyl-2-methoxyphenylmethanol, 3c. 94% yield, 97% ee; mp 166.4℃; $[\alpha]_D^{20}$:= −40.57 (*c* = 0.44, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500MHz): δ 7.35 (d, *J* = 7.5 Hz, 1H), 7.24 (t, *J* = 8.5 Hz, 1H), 6.95 (t, *J* = 7.5 Hz, 1H), 6.87 (d, *J* = 8.5 Hz, 1H), 5.77 (d, *J* = 4.5 Hz, 1H), 4.29 (s, 1H), 4.23-4.16 (m, 8H), 3.85 (s, 1H), 2.87 (d, *J* = 2.3 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 156.4, 131.6, 128.4, 127.2, 120.6, 110.4, 68.6, 67.8, 67.8, 67.6, 66.6, 55.3; MS (ESI) *m/z* (%): 336 (100), 305 ([M + H − H_2O]$^+$, 22), 437 (3), 382 (5), 381 (21), 360 (8), 359 (29), 353 (13), 337 (21); HRMS (ESIMS) Calcd. for $C_{18}H_{17}OFe$ ($C_{18}H_{18}O_2Fe$ + H − H_2O), 305.0629; found 305.0622; Daical Chiralpack AS-H column, hexane/*i*-PrOH 90/10, 1.0 mL/min, 10.7 min (minor), 12.1 min (major).

(−)-α-Ferrocenyl-4-bromobenzyl alcohol, 3d. 37% yield, 73% ee; mp 184.2℃; $[\alpha]_D^{20}$:= −41.45 (*c* = 0.35, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500MHz): δ 7.45 (d, *J* = 8 Hz, 2H), 7.26 (d, *J* = 4 Hz, 2H), 5.38 (s, 1H), 4.25-4.20 (m, 9H), 2.49 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 142.5, 131.6, 128.2, 121.5, 94.6, 71.6, 69.1, 68.8, 68.0, 66.3; MS (ESI) *m/z* (%): 384 (100), 370 (M^+, 42), 372 (39), 386 (96), 387 (16), 381 (11), 356 (4), 353

(17); HRMS (ESIMS) Calcd for $C_{17}H_{15}OFeBr$, 369.9656; found 369.9656; Daical Chiralpack AD-H column, hexane/*i*-PrOH 95/5, 1.0 mL/min, 30.6 min (major), 43.0 min (minor).

(−)-Ferrocenyl-1-naphthylmethanol, 3e. 90% yield, 98% ee; mp 135.2℃; $[\alpha]_D^{20}$:= −92.69 (*c* = 1.02, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500MHz): δ 8.19 (d, *J* = 8 Hz, 1H), 7.89 (d, *J* = 7.5 Hz, 1H), 7.81 (d, *J* = 8 Hz, 1H), 7.62 (d, *J* = 7 Hz, 1H), 7.54-7.47 (m, 3H), 6.23 (s, 1H), 4.34-4.15 (m, 9H), 2.81 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 138.9, 133.6, 130.8, 128.6, 128.0, 125.8, 125.4, 125.2, 123.8, 123.7, 94.1, 68.4, 68.1, 67.8, 67.5, 67.4; MS (ESI) *m/z* (%): 356 (100), 325 ($[M + H - H_2O]^+$, 19), 382 (5), 381 (19), 379 (4), 357 (22), 353 (77), 326 (8),; HRMS (ESIMS) Calcd for $C_{21}H_{17}OFe$ ($C_{21}H_{18}OFe$ + H − H_2O), 325.0680; found 325.0691; Daical Chiralpack AS-H column, hexane/*i*-PrOH 98/2, 0.8 mL/min, 26.6 min (major), 29.2 min (minor).

(−)-Ferrocenyl-2-naphthylmethanol, 3f. 94% yield, 83% ee; mp 114.2℃; $[\alpha]_D^{20}$:= −48.76 (*c* = 1.027, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500MHz): δ 7.85-7.81 (m, 4H), 7.55-7.53 (m, 1H), 7.50-7.45 (m, 2H), 5.64 (s, 1H), 4.46 (s, 7H), 4.21 (s, 1H), 4.19 (s, 1H), 2.62 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 140.7, 132.9, 128.0, 127.9, 127.6, 126.0, 125.7, 124.7, 124.6, 94.3, 72.0, 68.5, 68.2, 68.1, 67.5, 66.0; MS (ESI) m/z (%): 342 (M^+, 100), 344 (7), 343 (27), 340 (9) 204 (3), 194 (3), 150 (4);HRMS (ESIMS) Calcd for $C_{21}H_{18}OFe$, 342.0707; found 342.0689; Daical Chiralpack AS-H column, hexane/*i*-PrOH 90/10, 0.5 mL/min, 26.9 min (minor), 29.3 min (major).

(−)-Ferrocenyl-1-furylmethanol, 3g. 73% yield, 41% ee ; ^{1}H NMR (C_6D_6, 500MHz): δ 7.09 (m, 1H), 6.12 (d, *J* = 3.5 Hz, 1H), 6.07-6.06 (m, 1H), 5.42 (s, 1H), 4.23-4.22 (m, 1H), 4.14-4.13 (m, 1H), 4.00 (s, 5H), 3.95-3.93 (m, 2H), 2.34 (brs, 1H); ^{13}C NMR (C_6D_6): δ 157.1, 141.8, 110.4, 106.5, 91.0, 69.1, 68.4, 68.3, 67.6, 67.4, 66.5; MS (ESI) *m/z* (%): 265 (M + H − H_2O, 100), 382 (9), 381 (37), 354 (5), 353 (19), 341 (3), 320 (10), 319 (46), 297 (19), 296 (99), 294 (6), 266 (23), 263 (6), 231 (3), 152 (7), 85 (5); HRMS (ESIMS) Calcd for $C_{15}H_{13}OFe$ ($C_{15}H_{14}O_2Fe$ + H − H_2O), 265.0316; found 265.0313; Daical Chiralpack AD-H column, hexane/*i*-PrOH 98/2, 1.2 mL/min, 49.6 min, 53.0 min.

(−)-Ferrocenyl-2-thienylmethanol, 3h. 93% yield, 68% ee ; ^{1}H NMR (C_6D_6, 500MHz): δ 6.84-6.83 (m, 1H), 6.78 (d, *J* = 3.5 Hz, 1H), 6.68-6.66 (m, 1H), 5.52 (s, 1H), 4.15 (m, 1H), 4.0 (m, 1H), 3.96 (s, 5H), 3.86 (m, 2H); ^{13}C NMR (C_6D_6): δ 148.7, 126.5, 124.8, 124.5, 93.9, 69.0, 68.6, 68.4, 68.3, 67.6, 66.6; MS (ESI) *m/z* (%):312 (100), 281 (M + H − H_2O, 42), 279 (3), 342 (3), 341 (12), 335 (8), 314 (7), 313 (19),

310 (6), 283 (3), 282 (14), 152 (6); HRMS (ESIMS) Calcd for $C_{15}H_{13}SFe$ ($C_{15}H_{14}OSFe$ + H − H_2O), 281.0087; found 281.0076; Daical Chiralpack AD-H column, hexane/*i*-PrOH 90/10, 1.0 mL/min, 15.4 min, 17.3 min.

5.4 Synthesis of Ferrocenyl Amino-Phosphine Ligands

5.4.1 General Procedure for Synthesis of Amines (*S*)-2a and (*S*)-2b

The ferrocenyl alcohol was dissolved in a mixture of pyridine and acetic anhydride (4.3 equiv), and stirred for 12 h at room temperature. Solvents were removed under vacuum. The acetate was treated with dimethylamine (1.8 equiv, 33% solution in water) in MeOH. After stirring for 12 h at room temperature, solvents were removed under reduced pressure and the crude product was extracted with acid and then base. The crude product was dissolved in Et_2O and washed with 10% H_3PO_4 (50mL × 3). After separation of organic phase, the acidic aqueous layer was neutralized by 10% NaOH (70 mL × 3) and extracted with Et_2O. The organic phase was washed with water and brine, and dried over $MgSO_4$. The crude product was purified by column chromatography to give the corresponding ferrocenyl amine.

(*S*)-1-Ferrocenyl-*N*,*N*-dimethylethylamine, (*S*)-2a Prepared according to the general procedure described above from (*S*)-**3a** (34 g, 0.148 mol), acetic acid (60 mL, 0.639 mol), pyridine (150 mL), dimethyl amine (41 mL, 0.263 mol), methanol (240 mL).[6] The crude product was purified by column chromatography in alumina (hexane/EA 10:1) and isolated as orange red oil (35.9 g, 0.140 mol, 94%). $[\alpha]_D^{20}$:= −1.88 (*c* = 1.68, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500MHz) : δ 4.15-4.09 (m, 6H), 3.60 (q, *J* = 7 Hz, 1H), 2.08 (s, 7H), 1.45 (d, *J* = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 87.0, 69.2, 68.4, 67.2, 67.1, 66.7, 58.5, 40.6, 16.0.

(*S*)-*N*,*N*-Dimethylaminophenylmethylferrocene, (*S*)-2b Prepared according to the general procedure described above from (*S*)-**3b** (10 g, 34.2 mmol), acetic acid (14 mL, 0.149 mol), pyridine (34 mL), dimethyl amine (9.4 mL, 61.2 mmol), methanol (55 mL).[6] The crude product was purified by column chromatography in silica gel (hexane/EA 3:1) and isolated as orange red solid (10.7 g, 0.140 mol, 97.9%). mp 76-77℃; $[\alpha]_D^{20}$:= −95.54 (*c* = 1.02, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500MHz) : δ 7.50 (d,

J = 7 Hz, 1H), 7.40 (t, *J* = 7.3 Hz, 1H), 7.31 (t, *J* = 7 Hz, 1H), 4.20 (d, *J* = 6 Hz, 1H), 4.15 (s, 1H), 4.10 (s, 1H), 3.79 (s, 1H), 3.72 (s, 1H), 2.08 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 143.4, 128.6, 128.1, 127.1, 72.4, 70.6, 68.8, 68.6, 67.3, 66.5, 44.5.

5.4.2 General Procedure for Diastereoselective Lithiation of the Amine (*S*)-2a and (*S*)-2b

The amine was dissolved in diethyl ether and cooled to 0℃. *t*-BuLi (1.2 equiv, 1.5M) was added, the mixture was stirred for 1 h at 0℃ and diphenylchlorophosphine (1.2 equiv) was added. After the reaction mixture warmed to rt and was stirred for overnight, water was added to hydrolyze the unreacted *t*-BuLi. The crude product was acid-base extracted, then dissolved in Et_2O and washed with 10% H_3PO_4 (50mL × 3). After separation of the organic phase, the acidic aqueous layer was neutralized by 10% NaOH (70 mL × 3) and extracted with Et_2O. The organic phase was washed with water and brine and dried over $MgSO_4$. The crude product was purified by column chromatography to give the corresponding ferrocenyl aminophosphine.

(*S*)-*N*,*N*-Dimethyl-1-[(*R*)-2-(diphenylphosphino)ferrocenyl]ethylamine, (S,R_p)-154a

Prepared according to the general procedure described above from (*S*)-**2a** (3.22 g, 12.5 mmol), *t*-BuLi (10 mL, 15.0 mmol), Et_2O (30 mL), diphenylchlorophosphine (2.70 mL, 15.0 mmol). The crude product was purified by column chromatography in silica gel (hexane/EA 2:1 pretreated with ammonia solution) and isolated as orange crystal (4.43 g, 10.0 mmol, 80.0%). mp 140.5-141.6℃; $[\alpha]_D^{20}$:= 341.64(*c* = 0.93, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500MHz) : δ 7.62-7.59 (m, 2H), 7.39-7.35 (m, 2H), 7.24-7.16 (m, 4H), 4.38 (q, *J* = 3 Hz, 1H), 4.26 (t, *J* = 2.5 Hz, 1H), 4.17 (q, *J* = 11.5 Hz, 1H), 3.95 (s, 3H), 3.87 (m, 1H), 1.78 (s, 6H), 1.27 (d, *J* = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 135.3, 135.1, 132.5, 132.3, 130.7, 130.6, 128.7, 128.0, 127.4, 72.1, 71.8, 70.3, 69.7, 69.4, 68.4, 57.8, 39.1; ^{31}P NMR ($CDCl_3$): δ -23.14

(*S*)-*N*,*N*-Dimethyl-1-[(*R*)-2-(diphenylphosphino)ferrocenyl]phenylmethylamine, (S,R_p)-154b

Prepared according to the general procedure described above from (*S*)-**2b** (1.54 g,

4.81 mmol), *t*-BuLi (3.8 mL, 5.77 mmol), Et_2O (15 mL), diphenylchlorophosphine (1.0 mL, 5.77 mmol). The crude product was purified by column chromatography in silica gel (hexane/EA 5:1 pretreated with ammonia solution) and isolated as orange solid (1.51 g, 3.01 mol, 62.5%). mp 104.7-110.1℃; $[\alpha]_D^{20}$:= 268.43 (*c* = 0.84, CH_2Cl_2);^{1}H NMR ($CDCl_3$, 500MHz) : δ 7.66-7.62 (m, 3H), 7.46-7.43 (t, *J* = 7.5 Hz, 2H), 7.40-7.36 (m, 4H), 7.32-7.25 (m, 3H), 4.63 (s, 1H), 4.47 (d, *J* = 4.5 Hz, 1H), 4.35 (t, *J* = 2.5 Hz, 1H), 4.00 (s, 1H), 3.39 (s, 3H), 1.79 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 135.3, 135.2, 133.1, 132.9, 129.0, 128.7, 128.2, 128.1, 128.0, 127.9, 127.8, 75.9, 75.8, 70.6, 70.6, 70.1, 69.8, 43.7; ^{31}P NMR ($CDCl_3$): δ -25.79

5.4.3 General Procedure for Synthesis of Ferrocenyl Amino-phosphine Ligands

The 1,2-disubstituted ferrocenyl amine was sealed in an air-free tube with acetic anhydride. After the reaction was heated to 100℃ for 1 h, the acetic anhydride was removed under reduced pressure. The residue was dissolved in CH_3CN and a primary amine (5 equiv) was added. The reaction was stirred at 80℃ for overnight. The reaction mixture was washed with water and extracted with Et_2O. The crude product was purified by column chromatography to give the corresponding ferrocenyl amino-phosphine.

(*S*)-1-[(*R*)-2-(Diphenylphosphino)ferrocenyl]ethylamine, (S,R_p)-142

Prepared according to the general procedure described above from (S,R_p)-**154a** (270 mg, 0.612 mmol), acetic anhydride (1 mL), 30% amine solution(195 μL, 3.06 mmol), CH_3CN (3 mL). The crude product was purified by column chromatography in silica gel (hexane/EA 2:1 pretreated with ammonia solution) and isolated as orange solid (98.9 mg, 0.239 mmol, 39.1%). mp 95.1-98.5℃; $[\alpha]_D^{20}$:= 239.63 (*c* = 0.70, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500MHz) : δ 7.56-7.52 (m, 2H), 7.38-7.37 (m, 1H), 7.26-7.24 (br, 4H), 4.44 (d, *J* = 1.5 Hz, 1H), 4.28 (t, *J* = 2.5 Hz, 1H), 4.22 (dq, J_1 = 2 Hz, J_2 = 6.75 Hz, 1H), 4.02 (s, 3H), 3.77 (s, 1H), 1.45 (d, *J* = 7 Hz, 3H), 1.38 (b, 2H); ^{13}C NMR ($CDCl_3$): δ139.8, 137.1, 135.0, 134.8, 132.9, 132.7, 129.2, 128.5, 128.4, 128.2, 74.8, 71.4, 70.8, 69.6, 69.2, 68.5, 45.5, 22.6; ^{31}P NMR ($CDCl_3$): δ -24.55; MS (ESI) *m/z* (%): 413 (M^+, 100), 395 (3), 397 (60), 440 (54), 452 (17), 453 (5), 495 (7); HRMS (ESI) Calcd for $C_{24}H_{24}NPFe$, 413.0996; found 413.0747.

(*S*)-*N*-Methyl-1-[(*R*)-2-(diphenylphosphino)ferrocenyl]ethylamine, (S,R_p)-143

Prepared according to the general procedure described above from (*S*,R_p)-**154a** (406 mg, 0.920 mmol), acetic anhydride (1 mL), 25% methylamine solution(618 μL, 4.60 mmol), CH_3CN (3 mL). The crude product was purified by column chromatography in silica gel (hexane/EA 2:1 pretreated with ammonia solution) and isolated as orange solid (389 mg, 0.910 mmol, 98.9%). mp 109.2-112.0℃; $[\alpha]_D^{20}$:= 317.43 (*c* = 0.59, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500MHz) : δ 7.57-7.54 (m, 2H), 7.38 (m, 2H), 7.27 (br, 4H), 4.50 (s, 1H), 4.31 (s, 1H), 4.03 (s, 3H), 4.00-4.97 (br, 1H), 3.81 (s, 1H), 1.84 (br, 4H), 1.48 (d, *J* = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 136.9, 136.8, 134.8, 134.6, 132.8, 132.6, 129.0, 128.4, 128.4, 128.3, 128.1, 75.3, 71.1, 70.5, 69.6, 69.4, 69.1, 52.4, 32.3, 18.7; ^{31}P NMR ($CDCl_3$): δ -25.12; MS (ESI) *m/z* (%): 427 (M^+, 100), 381 (7), 397 (36), 398 (10), 425 (7), 426 (22), 428 (43), 440 (24), 444 (20), 450 (9), 466 (3); HRMS (ESI) Calcd. for $C_{25}H_{26}NPFe$, 427.1152; found 427.1019.

(*S*)-*N*-Isopropyl-1-[(*R*)-2-(diphenylphosphino)ferrocenyl]ethylamine, (*S*,R_p)-144

Prepared according to the general procedure described above from (*S*,R_p)-**154a** (148 mg, 0.336 mmol), acetic anhydride (1 mL), isopropylamine (143 μL, 1.68 mmol), CH_3CN (3 mL). The crude product was purified by column chromatography in silica gel (hexane/EA 3:1 pretreated with ammonia solution) and isolated as yellow solid (152 mg, 0.334 mmol, 99.4%). mp 109.0-109.9℃; $[\alpha]_D^{20}$:= 278.49 (*c* = 0.69, CH_2Cl_2) ^{1}H NMR ($CDCl_3$, 500MHz) : δ 7.56-7.54 (m, 2H), 7.39 (b, 2H), 7.29-7.27 (m, 3H), 4.66 (b, 1H), 4.33 (s, 1H), 4.17 (s, 1H), 4.04 (s, 3H), 3.79 (s, 1H), 2.70 (q, *J* = 6.5 Hz, 1H), 1.59 (b, 3H), 0.68 (d, *J* = 5.5 Hz, 3H), 0.65 (d, *J* = 5.5 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 139.9, 136.8, 135.2, 135.0, 133.0, 132.9, 129.2, 128.6, 128.5, 128.2. 74.8, 71.3, 70.4, 69.7, 69.4, 48.6, 46.6, 23.5, 21.3, 20.2; ^{31}P NMR ($CDCl_3$): δ -25.43; MS (ESI) *m/z* (%): 455 (M^+, 100), 381 (11), 397 (56), 398 (16), 426 (5), 453 (5), 456 (34), 472 (9); HRMS (ESI) Calcd. for $C_{27}H_{30}NPFe$, 455.1465; found 455.1431.

(*S*)-*N*-Cyclohexyl-1-[(*R*)-2-(diphenylphosphino)ferrocenyl]ethylamine, (*S*,R_p)-145

Prepared according to the general procedure described above from (*S*,R_p)-**154a** (50 mg, 0.113 mmol), acetic anhydride (0.5 mL), cyclohexylamine (65.4 μL, 0.568 mmol), CH_3CN (2 mL). The crude product was purified by column chromatography in silica gel (hexane/EA 3:1 pretreated with ammonia solution) and isolated as orange oil (43.3 mg, 0.0874 mmol, 77.0%). $[\alpha]_D^{20}$:= 192.10 (*c* = 0.56, CH_2Cl_2); ^{1}H NMR (C_6D_6, 500MHz) : δ 7.66-7.62 (m, 2H), 7.36 (t, *J* = 6.5 Hz, 2H), 7.09-7.08 (m, 3H), 7.03-7.97 (m, 3H), 4.41 (b, 1H), 4.35 (dq, J_1 = 3 Hz, *J* = 6.25 Hz, 1H), 4.08 (t, *J* = 2.5 Hz, 1H), 3.95 (s, 4H), 3.81 (t, *J* = 1 Hz, 1H), 2.53 (m, 1H), 1.72 (m, 1H), 1.49 (m, 8H), 1.03 (m, 4H), 0.76 (m, 3H); ^{13}C NMR (C_6D_6): δ 140.0, 139.9, 136.9, 135.1, 135.0, 132.9, 132.8, 129.1, 128.5, 128.4, 128.4, 128.2, 128.1, 74.7, 74.6, 71.2, 70.3, 69.6,

69.5, 69.2, 59.0, 54.4, 47.9, 47.8, 34.3, 32.0, 26.0, 25.1, 25.0, 20.5; ^{31}P NMR (C_6D_6): δ –24.75; MS (ESI) *m/z* (%): 495 (M^+, 100), 381 (6), 397 (13), 398 (5), 494 (6), 496 (34), 512 (20), 513 (7); HRMS (ESI) Calcd. for $C_{30}H_{34}NPFe$, 495.1778; found 495.1766.

(*S*)-*N*-Tetrabutyl-1-[(*R*)-2-(diphenylphosphino)ferrocenyl]ethylamine, (*S*,R_p)-146

Prepared according to the general procedure described above from (*S*,R_p)-**154a** (373 mg, 0.846 mmol), acetic anhydride (1 mL), tetrabutylamine (448 μL, 4.28 mmol), CH_3CN (3 mL). The crude product was purified by column chromatography in silica gel (hexane/EA 5:1 pretreated with ammonia solution) and isolated as orange solid (324 mg, 0.691 mmol, 81.7%). mp 94.5-100.4℃; $[\alpha]_D^{20}$:= 297.00(*c* = 0.24, CH_2Cl_2) ^{1}H NMR ($CDCl_3$, 500MHz) : δ 7.52 (m, 2H), 7.36 (b, 2H), 7.25 (m, 4H), 4.56 (s, 1H), 4.29 (t, *J* = 2 Hz, 1H), 4.23 (dq, J_1 = 2.5 Hz, J_2 = 6 Hz, 1H), 4.02 (s, 3H), 3.72 (d, *J* = 1 Hz, 1H), 1.56 (d, *J* = 6.5 Hz, 3H), 0.78 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 140.1, 137.1, 135.3, 135.1, 132.8, 132.7, 129.2, 128.6, 128.4, 128.2, 128.1, 74.1, 71.1, 69.9, 69.7, 69.3, 51.1, 46.6, 30.0, 22.6; ^{31}P NMR ($CDCl_3$): δ -25.68; MS (ESI) *m/z* (%): 469 (M^+, 100), 381 (10), 397 (40), 412 (13), 426 (7), 467 (5), 470 (37), 486 (25), 487 (8); HRMS (ESI) Calcd. for $C_{28}H_{32}NPFe$, 469.1622; found 469.1479.

(*S*)-1-[(*R*)-2-(Diphenylphosphino)ferrocenyl]phenylmethylamine, (*S*,R_p)-147

Prepared according to the general procedure described above from (*S*,R_p)-**154b** (100 mg, 0.199 mmol), acetic anhydride (1 mL), 30% amine solution(100 μL, 1.57 mmol, 8 equiv), CH_3CN (5 mL). The crude product was purified by column chromatography in silica gel (hexane/EA 5:1 pretreated with ammonia solution) and isolated as orange red oil (37.5 mg, 0.0789 mmol, 39.7%). $[\alpha]_D^{20}$:= 251.46 (*c* = 1.05, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500MHz) : δ 7.62-7.59 (br, 2H), 7.56 (d, *J* = 7.5 Hz, 2H), 7.41 (br, 3H), 7.34 (t, *J* = 7.5 Hz, 2H), 7.26 (br, 6H), 5.26 (d, *J* = 2.5 Hz, 1H), 4.32 (s, 1H), 4.29 (d, *J* = 2 Hz, 1H), 3.85 (s, 1H), 3.82 (s, 4H), 2.31 (br, 2H); ^{13}C NMR ($CDCl_3$): δ 144.2, 139.9, 137.3, 135.2, 135.1, 132.6, 132.4, 132.4, 129.2, 128.3, 128.3, 128.2, 128.1, 128.1, 128.1, 127.6, 127.2, 99.0, 74.5, 71.4, 71.3, 70.4, 70.3, 69.7, 69.6, 54.9; ^{31}P NMR ($CDCl_3$): δ -25.65; MS (ESI) *m/z* (%): 475 (M^+, 100), 290 (8), 381 (4), 459 (9), 476 (23), 488 (13), 489 (4); HRMS (ESI) Calcd. for $C_{29}H_{26}NPFe$, 475.1152; found 475.1145.

(*S*)-*N*-Methyl-1-[(*R*)-2-(diphenylphosphino)ferrocenyl]phenylmethylamine, (*S*,R_p)-148

Prepared according to the general procedure described above from (*S*,R_p)-**154b** (200 mg, 0.397 mmol), acetic anhydride (1 mL), 25% methylamine solution(267 μL, 1.99

mmol), CH_3CN (2 mL). The crude product was purified by column chromatography in silica gel (hexane/EA 5:1 pretreated with ammonia solution) and isolated as orange red solid (170.4 mg, 0.348 mmol, 87.7%). mp 57.6-60.5℃; $[\alpha]_D^{20}$:= 191.60 (*c* = 0.95, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500MHz) : δ 7.62 (m, 4H), 7.39 (m, 6H), 7.32 (m, 4H), 4.73 (d, *J* = 3.5 Hz, 1H), 4.29 (s, 1H), 4.26 (b, 1H), 3.82 (s, 1H), 3.76 (s, 3H), 1.90 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 143.0, 139.9, 137.1, 135.0, 134.8, 132.9, 132.7, 129.1, 128.6, 128.5, 128.4, 128.2, 128.1, 128.0, 127.2, 97.2, 75.3, 70.9, 70.3, 69.7, 69.5, 63.9, 63.8, 35.1; ^{31}P NMR ($CDCl_3$): δ -24.74; MS (ESI) *m/z* (%): 489 (M^+, 100), 304 (6), 459 (27), 460 (11), 488 (18), 490 (27), 503 (5); HRMS (ESI) Calcd. for $C_{30}H_{28}NPFe$, 489.1309; found, 489.1291.

(*S*)-*N*-Isopropyl-1-[(*R*)-2-(diphenylphosphino)ferrocenyl]phenylmethylamine, (*S*,*R*$_p$)-149

Prepared according to the general procedure described above from (*S*,*R*$_p$)-**154b** (200 mg, 0.397 mmol), acetic anhydride (1 mL), isopropylamine (169 μL, 1.99 mmol), CH_3CN (3 mL). The crude product was purified by column chromatography in silica gel (hexane/EA 5:1 pretreated with ammonia solution) and isolated as orange solid (151 mg, 0.292 mmol, 73.5%). mp 104.5-110℃; $[\alpha]_D^{20}$:= 219.63 (*c* = 0.96, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500MHz) : δ 7.61 (m, 4H), 7.35 (m, 10H), 5.07 (d, *J* = 3.5 Hz, 1H), 4.24 (s, 2H), 3.76 (m, 4H), 2.35 (m, 1H), 0.55 (d, *J* = 6.5 Hz, 3H), 0.50 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 139.9, 135.2, 135.0, 133.0, 132.9, 131.5, 129.2, 128.8, 128.6, 128.5, 128.2, 128.0, 127.3, 74.7, 70.5, 69.7, 59.0, 47.0, 23.6, 20.8; ^{31}P NMR ($CDCl_3$): δ -26.71; MS (ESI) *m/z* (%): 517 (M^+, 100), 381 (14), 382 (4), 459 (34), 460 (15), 474 (8), 515 (6), 518 (29), 519 (5); HRMS (ESI) Calcd. for $C_{32}H_{32}NPFe$, 517.1622; found 517.1624.

(*S*)-*N*-Cyclohexyl-1-[(*R*)-2-(diphenylphosphino)ferrocenyl]phenylmethylamine, (*S*,*R*$_p$)-150

Prepared according to the general procedure described above from (*S*,*R*$_p$)-**154b** (100 mg, 0.199 mmol), acetic anhydride (1 mL), isopropylamine (115 μL, 0.994 mmol), CH_3CN (4 mL). The crude product was purified by column chromatography in silica gel (hexane/EA 5:1 pretreated with ammonia solution) and isolated as green yellow solid (70.1 mg, 0.126 mmol, 63.3%). mp 102.1-107.0℃; $[\alpha]_D^{20}$:= 202.54 (*c* = 0.44, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500MHz) : δ 7.75 (m, 4H), 7.47 (t, *J* = 7 Hz, 2H), 7.31 (t, *J* = 7.5 Hz, 2H), 7.20 (m, 3H), 7.14 (m, 3H), 7.07 (m, 4H), 5.44 (d, *J* = 4 Hz, 1H), 4.33 (s, 1H), 4.11 (t, *J* = 2.25 Hz, 1H), 3.90 (s, 1H), 3.84 (s, 4H), 2.36 (m, 1H), 1.79 (b, 1H), 1.65 (b, 1H), 1.52 (m, 1H), 1.36 (m, 3H), 0.94 (m, 5H), 0.72 (m, 3H); ^{13}C NMR ($CDCl_3$): δ 140.1, 135.5, 135.3, 133.2, 133.0, 129.4, 128.9, 128.8, 128.7, 128.6,

128.4, 128.3, 128.2, 127.4, 74.8, 71.3, 71.0, 70.6, 70.0, 69.9, 58.6, 54.8, 31.7, 26.1, 25.1, 24.9; ^{31}P NMR ($CDCl_3$): δ -23.65; MS (ESI) *m/z* (%): 557 (M^+, 75), 373 (9), 381 (42), 382 (12), 457 (8), 459 (100), 460 (30), 461 (6), 507 (5), 555 (6), 558 (31), 574 (21), 575 (8), 595 (4); HRMS (ESI) Calcd. for $C_{35}H_{36}NPFe$, 557.1935; found 557.1861.

(*S*)-*N*-Tetrabutyl-1-[(*R*)-2-(diphenylphosphino)ferrocenyl]phenylmethylamine, (*S*,R_p)-151

Prepared according to the general procedure described above from (*S*,R_p)-**154b** (170 mg, 0.338 mmol), acetic anhydride (1 mL), tetrabutylamine (177 μL, 1.69 mmol), CH_3CN (8 mL). The crude product was purified by column chromatography in silica gel (hexane/EA 5:1 pretreated with ammonia solution) and isolated as yellow solid (149 mg, 0.280 mmol, 83.2%). mp 109.5-111.5℃; $[\alpha]_D^{20}$:= 235.70 (*c* = 0.74, CH_2Cl_2) ^{1}H NMR ($CDCl_3$, 500MHz) : δ 7.72 (d, *J* = 7.5 Hz, 2H), 7.62 (m, 2H), 7.42 (m, 4H), 7.32 (m, 5H), 5.26 (d, *J* = 4 Hz, 1H), 4.37 (s, 1H), 4.29 (t, *J* = 2.5 Hz, 1H), 3.80 (s, 1H), 3.74 (s, 4H), 1.98 (s, 1H), 0.59 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 140.2, 140.1, 137.0, 135.4, 135.2, 132.7, 132.6, 129.1, 128.9, 128.5, 128.1,2, 128.1, 128.0, 127.6, 126.9, 74.0, 70.9, 70.8, 69.8, 69.5, 56.5, 56.4, 53.4, 51.7, 29.7; ^{31}P NMR ($CDCl_3$): δ -25.88; MS (ESI) *m/z* (%): 531 (M^+, 100), 353 (4), 381 (20), 382 (5), 457 (4), 459 (60), 460 (17), 474 (4), 529 (5), 532 (38), 564 (11), 565 (4); HRMS (ESI) Calcd. for $C_{33}H_{34}NPFe$, 531.1778; found 531.1799.

5.5 Asymmetric Hydrogenation of Acetophenone catalyzed by Ferrocenyl Amino-Phosphine Ruthenium Complexes

5.5.1 General Preparation of [$RuCl_2$(diphosphine)(amino-Fc-phosphine)] Pre-catalyst[84]

[$RuCl_2$(cymene)]$_2$ (0.5 equiv) and diphosphine (1.0 equiv) were placed in a 25 mL Schlenk flask. After the air in the flask was replaced with argon, DMF was added, the mixture was degassed and stirred under argon at 100 ℃ for 10 min to form an orange solution. After the solution was cooled to room temperature, ferrocenyl amino-phosphine (1.1 equiv) was added and the mixture was stirred for 3 h. The solvent was removed under reduced pressure. The crude residue was determined by ^{31}P NMR and was used directly without any further purification. It was dissolved in 2-propanol to prepare a stock solution.

[$RuCl_2$\{(*R*)-BINAP\}\{(*S*,R_p)-143\}] (*R*,*S*,R_p)-155 Prepared according to the general procedure described above from $[RuCl_2(cymene)]_2$ (3.2 mg, 5.3×10^{-3} mmol), (*R*)-BINAP (6.6 mg, 1.06×10^{-2} mmol), (*S*,R_p)-**143** (5 mg, 1.17×10^{-2} mmol) and DMF (2 mL). ^{31}P NMR: δ 40.6, 30.1, 26.1, 24.3, 22.1, 8.8, -25.9

[$RuCl_2$\{(*S*)-BINAP\}\{(*S*,R_p)-143\}] (*S*,*S*,R_p)-155 Prepared according to the general procedure described above from $[RuCl_2(cymene)]_2$ (3.2 mg, 5.3×10^{-3} mmol), (*S*)-BINAP (6.6 mg, 1.06×10^{-2} mmol), (*S*,R_p)-**143** (5 mg, 1.17×10^{-2} mmol) and DMF (2 mL). ^{31}P NMR: δ 40.2, 30.1, 26.9, 26.1, 24.7, 22.1, -15.1, -17.1

[$RuCl_2$\{(*R*)-BINAP\}\{(*S*,R_p)-142\}] (*R*,*S*,R_p)-156 Prepared according to the general procedure described above from $[RuCl_2(cymene)]_2$ (3.4 mg, 5.51×10^{-3} mmol), (*R*)-BINAP (6.8 mg, 1.10×10^{-2} mmol), (*S*,R_p)-**142** (5 mg, 1.21×10^{-2} mmol) and DMF (2 mL). ^{31}P NMR: δ 40.6, 40.2, 31.9, 24.8, 23.8

[$RuCl_2$\{(*S*)-BINAP\}\{(*S*,R_p)-142\}] (*S*,*S*,R_p)-156 Prepared according to the general procedure described above from $[RuCl_2(cymene)]_2$ (3.2 mg, 5.51×10^{-3} mmol), (*S*)-BINAP (6.8 mg, 1.10×10^{-2} mmol), (*S*,R_p)-**142** (5 mg, 1.21×10^{-2} mmol) and DMF (2 mL). ^{31}P NMR: δ 40.5, 40.2, 31.8, 24.7, 23.7, -15.1

[$RuCl_2$\{(*R*)-P-Phos\}\{(*S*,R_p)-143\}] (*R*,*S*,R_p)-157 Prepared according to the general procedure described above from $[RuCl_2(cymene)]_2$ (3.3 mg, 5.35×10^{-3} mmol), (*R*)-P-Phos (6.9 mg, 1.06×10^{-2} mmol), (*S*,R_p)-**143** (5 mg, 1.17×10^{-2} mmol) and DMF (2 mL). ^{31}P NMR: δ 30.1, 27.0, 26.1, 22.1, -12.5

[$RuCl_2$\{(*S*)-P-Phos\}\{(*S*,R_p)-143\}] (*S*,*S*,R_p)-157 Prepared according to the general procedure described above from $[RuCl_2(cymene)]_2$ (3.3 mg, 5.35×10^{-3} mmol), (*S*)-P-Phos (6.9 mg, 1.06×10^{-2} mmol), (*S*,R_p)-**143** (5 mg, 1.17×10^{-2} mmol) and DMF (2 mL). ^{31}P NMR: δ 30.1, 27.0, 26.1, 22.2

[$RuCl_2$\{(*R*)-P-Phos\}\{(*S*,R_p)-142\}] (*R*,*S*,R_p)-158 Prepared according to the general procedure described above from $[RuCl_2(cymene)]_2$ (3.4 mg, 5.51×10^{-3} mmol), (*R*)-P-Phos (7.1 mg, 1.10×10^{-2} mmol), (*S*,R_p)-**142** (5 mg, 1.21×10^{-2} mmol) and DMF (2 mL). ^{31}P NMR: δ 40.4, 40.2, 31.9, 26.6, 26.3, 23.8, 21.9, -12.5

[$RuCl_2$\{(*S*)-P-Phos\}\{(*S*,R_p)-142\}] (*S*,*S*,R_p)-158 Prepared according to the general procedure described above from $[RuCl_2(cymene)]_2$ (3.4 mg, 5.51×10^{-3} mmol),

(*S*)-P-Phos (7.1 mg, 1.10×10^{-2} mmol), (S,R_p)-**142** (5 mg, 1.21×10^{-2} mmol) and DMF (2 mL). ^{31}P NMR: δ 40.5, 40.2, 31.9, 26.6, 26.3, 23.8

5.5.2 General preparation of [$RuCl_2$(diamine)(amino-Fc-phosphine)] pre-catalyst

[$RuCl_2$(cymene)]$_2$ (0.5 equiv) and ferrocenyl amino-phosphine (1.0 equiv) were placed in a 25 mL Schlenk flask. After the air in the flask was replaced with argon, DMF was added, the mixture was degassed and stirred under argon at 100 ℃ for 10 min to form a yellow orange solution. After the solution was cooled to room temperature, diamine (1.1 equiv) was added and the mixture was stirred for 3 h. The solvent was removed under reduced pressure. The crude residue was determined by ^{31}P NMR and the crude residue was used directly without any further purification. It was dissolved in 2-propanol as stock solution.

[$RuCl_2${(*R,R*)-DPEN}{(S,R_p)-143}] **(R,R,S,R_p)-159** Prepared according to the general procedure described above from [$RuCl_2$(cymene)]$_2$ (3.7 mg, 6.09×10^{-3} mmol), (*R,R*)-DPEN (2.8 mg, 1.34×10^{-2} mmol), (S,R_p)-**143** (5.2 mg, 1.22×10^{-2} mmol) and DMF (2 mL). ^{31}P NMR: δ 29.7, 26.1, 23.8, 22.1, -25.6

[$RuCl_2${(*S,S*)-DPEN}{(S,R_p)-143}] **(S,S,S,R_p)-159** Prepared according to the general procedure described above from [$RuCl_2$(cymene)]$_2$ (3.8 mg, 6.20×10^{-3} mmol), (*S,S*)-DPEN (2.9 mg, 1.37×10^{-2} mmol), (S,R_p)-**143** (5.3 mg, 1.24×10^{-2} mmol) and DMF (2 mL). ^{31}P NMR: δ 33.1, 29.6, 26.1, 23.8, 22.1, -25.7

[$RuCl_2${(*R,R*)-DPEN}{(S,R_p)-142}] **(R,R,S,R_p)-160** Prepared according to the general procedure described above from [$RuCl_2$(cymene)]$_2$ (4.1 mg, 6.659×10^{-3} mmol), (*R,R*)-DPEN (3.1 mg, 1.46×10^{-2} mmol), (S,R_p)-**142** (5.5 mg, 1.33×10^{-2} mmol) and DMF (2 mL). ^{31}P NMR: δ 31.8, 23.9

[$RuCl_2${(*S,S*)-DPEN}{(S,R_p)-142}] **(S,S,S,R_p)-160** Prepared according to the general procedure described above from [$RuCl_2$(cymene)]$_2$ (3.7 mg, 6.05×10^{-3} mmol), (*S,S*)-DPEN (2.8 mg, 1.33×10^{-2} mmol), (S,R_p)-**142** (5.0 mg, 1.21×10^{-2} mmol) and DMF (2 mL). ^{31}P NMR: δ 31.6, 23.6, -25.2

[$RuCl_2${(*S*)-DAIPEN}{(S,R_p)-142}] **(S,S,R_p)-161** Prepared according to the general

procedure described above from $[RuCl_2(cymene)]_2$ (3.7 mg, 6.05×10^{-3} mmol), (*S*)-DAIPEN (4.2 mg, 1.34×10^{-2} mmol), (S,R_p)-**142** (5.0 mg, 1.21×10^{-2} mmol) and DMF (2 mL). ^{31}P NMR: δ 31.8, 23.8

[$RuCl_2${(*S*)-binaphthylamine}{(S,R_p)-142}] (S,S,R_p)-162 Prepared according to the general procedure described above from $[RuCl_2(cymene)]_2$ (3.7 mg, 6.05×10^{-3} mmol), (*S*)-2,2'-diamino-1,1-binaphthalene (3.8 mg, 1.33×10^{-2} mmol), (S,R_p)-**142** (5.0 mg, 1.21×10^{-2} mmol) and DMF (2 mL). ^{31}P NMR: δ 31.8, 23.7

5.5.3 General Procedure for the Ru(II)-catalyzed Asymmetric Hydrogenation of Acetophenone

A stock solution of ruthenium precatalyst in 2-propanol (0.01 equiv; S/C = 100), acetophenone (1 equiv), 2-propanol and a solution of $(CH_3)_3COK$ in 2-propanol (0.02 equiv; S/B = 50) were added to a stainless steel autoclave under a nitrogen atmosphere. The whole system was purged with hydrogen before being pressurized to 50 bar. The reaction mixture was stirred at room temperature for 40 h, after which the unreacted hydrogen was released slowly and carefully. The conversion and enantiomeric excess of 1-phenylethanol were determined by HPLC (Daical Chiralpack OD-H column; hexane/2-propanol = 98:2; flow rate: 1.0 mL/min) immediately without further purification. The retention time of the starting material was 5.8 min and that for the product was 11.8 min for (*R*) and 14.9 min for (*S*). The product configuration was compared with the reaction catalyzed by [Ru(*R*)-Tol-P-Phos(*R*,*R*)-DPEN]Cl_2.[89]

5.6 Palladium-catalyzed Asymmetric Allylic Alkylation Using Ferrocenyl Amino-Phosphine Ligands

5.6.1 Preparation of the Substrate (1,3-diphenyl-2-propenyl acetate) 80

Acetic anhydride (18 mL, 0.228 mol) was added dropwise to a solution of *trans*-1,3-diphenyl-2-propen-1-ol (4 g, 0.019 mol) in pyridine at 0℃. The reaction mixture was then warmed to room temperature and stirred for overnight. Pyridine and

acetic anhydride were removed by vacuum. The crude residue was washed with 10% hydrochloric acid and water and extracted by ethyl acetate. The crude product was purified by bulb to bulb distillation under vacuum (95% yield). ^{1}H NMR (C_6D_6, 500MHz) : δ 7.34 (d, *J* = 7.5 Hz, 2H), 7.11 (m, 4H), 7.01 (m, 4H), 6.59 (d, *J* = 6 Hz, 1H), 6.57 (s, 1H), 6.27 (q, *J* = 6 Hz, 1H), 1.66 (s, 3H)

5.6.2 A Typical Procedure for Asymmetric Allylation of 1,3-diphenyl-2-propenyl Acetate 80 with Dimethyl Malonate 165

A solution of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (0.54 mg, 0.001 mmol) and ferrocenyl amino-phosphine (*S*,R_p)-**142** (1.23 mg, 0.003 mmol) in THF (400 μL) was stirred at room temperature for 15 min in the glove box. To this Pd-catalyst was added allylic acetate **80** (15 mg, 0.059 mmol) in THF (200 μL), followed by dimethyl malonate **165** (20.4 μL, 0.178 mmol), *N*,*O*-bis(trimethylsilyl)-acetamide (BSA, 44.3 μL, 0.178 mmol), and a catalytic amount of KOAc sequentially. After stirring for 5 h, the reaction mixture was quenched with a saturated aqueous NH_4Cl solution and diluted with Et_2O. The organic layer was separated, dried over $MgSO_4$, and concentrated under reduced pressure. The conversion and enantiomeric excess was determined by HPLC (Daical Chiralpack AD, hexane/2-propanol = 95:5; flow rate: 1.0 mL/min) immediately without further purification. The retention time of the starting material was 6.7 min and the product was 13.0 min for (*R*) and 17.8 min for (*S*).

Chapter 6

Conclusion and Future Work

Ferrocenyl ligands had been successfully employed in asymmetric catalytic reactions. Important synthetic processes of many ferrocenyl ligands involved the classical resolution step which is the bottle-neck for the further development of ferrocenyl ligands.

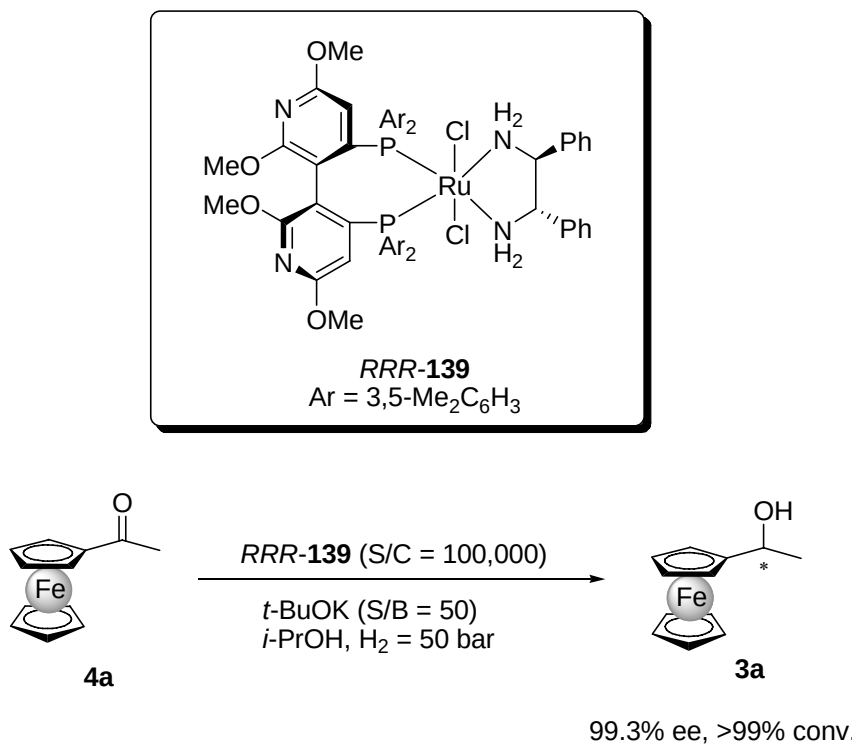
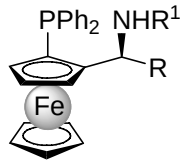


Figure 6.1 Asymmetric hydrogenation of ferrocenyl ketone

In this project, a simple, efficient and highly enantioselective method for the synthesis of enantiomerically pure **3a** and analogous chiral ferrocenyl alcohols has been developed. It was found that *RRR*-**139** ([Ru(*R*)-Xylyl-P-Phos(*R*,*R*)-DPEN]Cl_2)

was the best precatalyst for the hydrogenation of acetylferrocene **4a** with higher than >99% ee (Figure 6.1) whereas *RRR*-**141** ([Ru(*R*)-Tol-P-Phos(*R*,*R*)-DPEN]Cl_2) was more suitable for the hydrogenation of aryl/heteroaryl ferrocenyl ketones giving product with 98% ee.

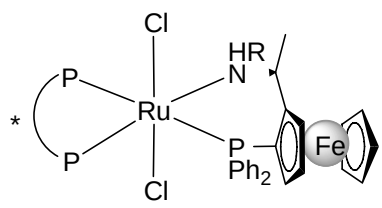


(S,R_p)-**142**-**151**

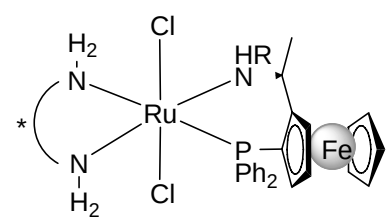
(S,R_p)-**142**	R = Me; R^1 = H	(S,R_p)-**147**	R = Ph; R^1 = H
(S,R_p)-**143**	R = Me; R^1 = Me	(S,R_p)-**148**	R = Ph; R^1 = Me
(S,R_p)-**144**	R = Me; R^1 = *i*-Pr	(S,R_p)-**149**	R = Ph; R^1 = *i*-Pr
(S,R_p)-**145**	R = Me; R^1 = Cy	(S,R_p)-**150**	R = Ph; R^1 = Cy
(S,R_p)-**146**	R = Me; R^1 = *t*-Bu	(S,R_p)-**151**	R = Ph; R^1 = *t*-Bu

Figure 6.2 1,2-Disubstituted ferrocenyl amino-phosphine ligands

1,2-Disubstituted ferrocenyl amino-phosphine ligands (S,R_p)-**142**-**151** (Figure 6.2) were easily prepared from enantiomeric pure ferrocenyl alcohol. Most of these ligands were synthesized with moderate to good yield (63.3% to 99.4%). In this synthetic scheme (Scheme 2.4.1), diastereoselective *ortho*-lithiation of ferrocenyl amine and retentive nucleophilic substitution led to enantiomeric pure products. These ligands were screened for their reactivity and enantioselectivity in catalytic reactions.



Ru(amino-Fc-phosphine)(diphosphine)Cl_2



Ru(amino-Fc-phosphine)(diamine)Cl_2

Figure 6.3

Ru-Complexes of these ferrocenyl amino-phosphine ligands and diphosphine

or diamine were used for catalytic asymmetric hydrogenation of acetophenone. The structure of ferrocenyl ligands (Figure 6.3) in Ru(amino-Fc-phosphine)(diamine)Cl_2 and Ru(amino-Fc-phosphine)(diphosphine)Cl_2 complexes showed different effects on the product's configuration. For the diphosphine-Ru-complexes, the chirality of the ferrocenyl ligands controlled the product's configuration if there was a *N*-methyl substituent. In the case of DPEN-Ru-complexes, a free amine on the ferrocenyl ligand was crucial for the product's configuration. In addition, the enantioselectivity and activity of the Ru(amino-Fc-phosphine)(diamine)Cl_2 precatalysts exceeded that effected by the Ru(amino-Fc-phosphine)(diphosphine)Cl_2 precatalysts.

Our initial enantioselectivity results for the asymmetric hydrogenation of acetophenone using Ru(amino-Fc-phosphine)(DPEN)Cl_2 complex were poor to moderate. Match and mismatch effect were also observed. The highest ee values of 68.7% was obtained with using the precatalyst generated from (*R*,*R*)-DPEN with a primary amine on the ferrocenyl ligands.

The Ru(amino-Fc-phosphine)(diamine)Cl_2 precatalysts were found to be more effective than the others; so I suggest to further investigate the effect of different diamine ligands, as well as the match and mismatching effect.

Attempts were also made in asymmetric allylic alkylation. The variation of steric demand with activities and eantioselectivities in ferrocenyl ligands were firstly

examined. We found that the ligand (S,R_p)-**151** bearing a bulky *t*-butyl substituent on nitrogen atom and phenyl group on α-stereogenic center was the most effective to give product with up to 88.8% ee in this reaction. Comparing all experimental results, it could be concluded that both *N*-alkyl group and the alkyl group on the central chirality performed a complementary effect on enantioselectivities and changed the product's configuration as the steric demand of alkyl groups might control the conformation of π-allylpalladium complex. Besides that, the presence of two different donor atoms promoted *trans* effect and leads to a general mode of selectivity in nucleophilic addition.

The optimal condition for asymmetric allylic alkylation was found. CH_3CN was the best solvent in the presence of Bu_4NCl as base additives. Experimental results showed that the effect of base additives on enantioselectivity depended on the solvent polarity. The ee values were influenced by different base additives in non-polar solvents but this effect was insignificant in polar solvents. Palladium precursor and the ratio of palladium to ligand were not decisive on the enantioselectivity of ferrocenyl amino-phosphine ligands.

In future work, the proton on *N*-alkyl of ferrocenyl ligands would be replaced with different alkyl groups. This can create different steric environment on ligand within the coordination sphere for investigation of their effects on enantioselectivity.

References

1. Genet, J. P. *Acc. Chem. Res.* **2003**, *36*, 908.
2. Ager, D. J.; East, M. B. *Asymmetric Synthetic Methodology*, CRC Press, Inc., Florida, **1996**
3. Noyori, R. *Angew. Chem. Int. Ed.* **2002**, *41*, 2008.
4. Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029.
5. Fache, F.; Schulz, E. Tommasino, M. L.; Lemaire, M. *Chem. Rev.* **2000**, *100*, 2159.
6. Knuhl, G.; Sennhenn, P.; Helmchen, G. *J. Chem. Soc., Chem. Commun.* **1995**, 1845
7. Mancheno, O. G.; Priego, J.; Cabrera, S.; Arrayas, R. G.; Llamas, T.; Carretero, J. C. *J. Org. Chem.* **2003**, *68*, 3679.
8. McCarthy, M.; Guiry, P. J. *Tetrahedron* **2001**, *57*, 3809.
9. Hayashi, T.; Togni, A. Eds. In *Ferrocenes* VCH, Weinheim, Germany, **1995**; Dai, L. X.; Tu, T.; You, S.; Deng, W.; Hou, X. *Acc. Chem. Res.* **2003**, *36*, 659.
10. Togni, A.; Dorta, R.; Köllner, C.; Pioda, G. *Pure Appl. Chem*, **1998**, *70*, 1477.
11. Marquarding, D.; Klusacek, H.; Gokel, G.; Hoffmann, P.; Ugi, I. *J. Am. Chem. Soc.* **1970**, *92*, 5389.
12. Gokel, G. W.; Marquarding, D.; Ugi, I. K. *J. Am. Chem. Soc.* **1972**, *37*, 3052.
13. Richards, C. J.; Locke, A. J. *Tetrahedron: Asymmetry* **1998**, *9*, 2377.
14. Hayashi, T.; Mise, T.; Fukushima, M.; Kagotani, M.; Nagashima, N.; Hamada, Y.; Matsumoto, A.; Kawakami, S.; Konishi, M.; Yamamoto, K.; Kumada, M. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1138; Hayashi, T.; Konishi, M.; fukushima, M.; Mise, T.; Kagotani, M.; Tajika, M.; Kumada, M. *J. Am. Chem. Soc.* **1982**, *104*, 180.
15. Togni, A.; Breutel, C.; Schnyder, A.; Spindler, F.; Landert, H.; Tijani, A. *J. Am. Chem. Soc.* **1994**, *116*, 4062; Zanetti, N. C.; Spindler, F.; Spencer, J.; Togni, A.; Rihs, G. *Organometallics* **1996**, *15*, 860; Leong, C. G.; Akotsi, O. M.; Ferguson, M. J.; Bergens, S. H. *Chem. Commun.* **2003**, 750; Mägerelein, W.; Indolese, A. F.; Beller, M. *Angew. Chem. Int. Ed.* **2001**, *40*, 2856.
16. Ireland, T.; Grossheimann, G.; Wieser-Jeunesse, C.; Knochel, P. *Angew. Chem. Int. Edu.* **1999**, *38*, 3212; Lotz, M.; Polborn, K.; Knochel, P. *Angew. Chem. Int. Edu.* **2002**, *41*, 4708; Feringa, B. L.; Badorrey, R.; Peña, D.; Harutyunyan, S. R.; Minnaard, A. J. *PNAS* **2004**, *101*, 5834; Ireland, T.; Tappe, K.; Grossheimann, G.; Knochel, P. *Chem. Eur. J.* **2002**, *8*, 843.
17. Boaz, N. W.; Debenham, S. D.; Mackenzie, E. B.; Large, S. E. *Org. Lett.* **2002**, *4*, 2421; Boaz, N. W. *Pat. Appl.* **2002**, WO226750.
18. Sturn, T.; Weissensteiner, W.; Spindler, F. *Adv. Synth. Catal.* **2003**, *345*, 160.

19. Fadini, L; Togni, A. *Chem. Commun.* **2003**, *1*, 30; Sadow, A. D.; Haller, I.; Fadini, L.; Togni, A. *J. Am. Chem. Soc.* **2004**, *126*, 14704.
20. Perea, J. J. A. ; Boroner Aa.; Knochel, P. *Tetrahedron Lett.* **1998**, *39*, 8073.
21. Sawamura, M.; Hamashima, H.; Sugawara, M. *Organometallics* **1995**, *14*, 4549.
22. Barbaro, P.; Bianchini, C.; Giambastiani, G.; Parisel, S. L. *Coord. Chem. Rev.* **2004**, *248*, 2131.
23. Noyori, R.; Suga, S.; Kawai, K.; Okada, S.; Kitamura, M. *J. Organomet. Chem.* **1990**, *382*, 19
24. Woltersdorf, M.; Kranich, R.; Schmalz, H. *Tetrahedron* **1997**, *53*, 7219
25. Matsumoto, Y.; Ohno, A.; Lu, S.; Hayashi, T. *Tetrahedron: Asymmetry* **1993**, *4*, 1763.
26. Soai, K.; Hayase, T.; Takai, K.; Sugiyama, T. *J. Org. Chem.* **1994**, *59*, 7908.
27. Abbenhuis, H. C. L.; Burckhardt, U.; Gramlich, V.; Togni, A.; Albinati, A.; Müller, B. *Organometallics* **1994**, *13*, 4481.
28. Suzuka, T.; Ogasawara, M.; Hayashi, T. *J. Org. Chem.* **2002**, *67*, 3355.
29. Nishibayashi, Y.; Yamauchi, A.; Onodera, G.; Uemura, S. *J. Org. Chem.* **2003**, *68*, 5875.
30. Jensen, D. R.; Pugsley, J. S.; Sigman, M. S. *J. Am. Chem. Soc.* **2001**, *123*, 7475.
31. Nicolosi, G.; Patti, A.; Piattelli, M. *J. Org. Chem.* **1994**, *59*, 251.
32. Lambusta, D.; Nicllosi, G.; Patti, A.; Piattelli, M. *Tetrahedron: Asymmetry* **1993**, *4*, 919.
33. Wright, J.; Frambes, L.; Reeves, P. *J. Organomet. Chem.* **1994**, *476*, 215; Corey, E. J.; Helal, C. J. *Angew. Chem. Int. Ed.* **1998**, *37*, 1986.
34. Schwink, L.; Knochel, P. *Tetrahedron Lett.* **1997**, *38*, 3711.
35. Schwink, L.; Knochel, P. *Tetrehedron Lett.* **1996**, *37*, 25.
36. Schwink, L.; Knochel, P. *Chem. Eur. J.* **1998**, *4*, 950
37. Ohkuma, T; Ooka, H.; Hashiguchi, s.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 2675.
38. Xie, J.; Wang, L.; Fu, Y.; Zhu, S.; Fan, B.; Duan, H.; Zhou, Q. *J. Am. Chem. Soc.* **2003**, *125*, 4404
39. Burk, M. J.; Hems, W.; Herzberg, D.; Malan, C.; Zanotti-Gerosa, A. *Org. Lett.* **2000**, *2*, 4173.
40. Noyori, R.; Ohkuma, T. *Angew. Chem. Int. Ed.* **2001**, *40*, 40.
41. Ohkuma, T.; Koizumi, M.; Ikehira, H.; Yokozawa, T.; Noyori, R. *Org. Lett.* **2000**, *2*, 659.
42. Hayashi, T. Konishi, M. Okamoto, Y., Kabeta, K. Kumada, M. *J. Org. Chem.* **1986**, *51*, 3772.
43. Jensen, J. F.; Sotofte, I.; Sorensen, H. O.; Johannsen, M. *J. Org. Chem.* **2003**, *68*,

1258.
44. Matsumura, S.; Maeda, Y.; Nishimura, T.; Uemura, S. *J. Am. Chem. Soc.* **2003**, *125*, 8862.
45. Abdur-Rashid, K.; Clapham, S. E.; Hadzovic, A.; Harvey, J. N.; Lough, A. J.; Morris, R. H. *J. Am. Chem. Soc.* **2002**, *124*, 15104.
46. Widhalm, M.; Mereiter, K.; Bourghida, M. *Tetrahedron: Asymmetry* **1998**, *9*, 2983.
47. Guiry, P. J.; Saunders, C. P. *Adv. Synth. Catal.* **2004**, *346*, 497.
48. Alexakis, A; Polet, D. *Org. Lett.* **2004**, *6*, 3529.
49. Hu, X.; Chen, H.; Hu, X.; Dai, H.; Bai, C.; Wang, J.; Zheng, Z. *Tetrahedron Lett.* **2002**, *43*, 9179.
50. Hu, X.; Chen, H.; Dai, H.; Hu, X.; Zheng, Z. *Tetrahedron: Asymmetry* **2003**, *14*, 2073.
51. Hu, X.; Chen, H.; Dai, H.; Zheng, Z. *Tetrahedron: Asymmetry* **2003**, *14*, 3415.
52. Hu, X.; Dai, H. Hu, X.; Chen, H.; Wang, J.; Bai, C. Zheng, Z. *Tetrahedron: Asymmetry* **2002**, *13*, 1687.
53. Hayashi, T.; Hayahsi, C.; Uozumi, Y.; *Tetrahedron: Asymmetry* **1995**, *6*, 2503.
54. Barbaro, P.; Bianchini, C.; Giambastiani, G.; Togni, A. *Tetrahedron Lett.* **2003**, *44*, 8279.
55. Mino, T.; Ogawa, T.; Yamashita, M. *J. Organomet. Chem.* **2003**, *665*, 122.
56. Schnyder, A.; Togni, A.; Wiesli, U. *Organometallics* **1997**, *16*, 255.
57. Pioda, G.; Togni, A. *Tetrahedron: Asymmetry* **1998**, *9*, 3903.
58. Togni, A.; Burckhardt, U.; Gramlich, V.; Pregosin, P. S.; Salzmann, R. *J. Am. Chem. Soc.* **1996**, *118*, 1031.
59. Nishibayashi, Y.; Takei, I.; Uemura, S.; Hidai, M. *Organometallics* **1999**, *18*, 2291.
60. Ahn, K. H.; Cho, C. W.; Park, J.; Lee, S. *Tetrahedron: Asymmetry* **1997**, *8*, 1179.
61. Hennessy, A. J.; Malone, Y. M.; Guiry, P. J. *Tetrahedron Lett.* **2000**, *41*, 2261.
62. Sammakia, T.; Stangeland E. L. *J. Org. Chem.* **1997**, *62*, 6104.
63. Lu, S. M.; Han, X. W.; Zhou, Y. G. *Adv. Synth. Catal.* **2004**, *346*, 909.
64. Nishibayashi, Y.; Segawa, K.; Ohe, K.; Uemura, S. *Organometallics* **1995**, *14*, 5486.
65. Manoury, E.; Fossey, J. S.; Aït-Haddou, H.; Daran, J. C.; Balavoine, G. G. A. *Organometallics* **2000**, *19*, 3736.
66. Kloetzing, R. J.; Lotz, M.; Knochel, P. *Tetrahedron: Asymmetry* **2003**, *14*, 255.
67. Hu, X.; Dai, H.; Bai, C.; Chen, H.; Zheng, Z. *Tetrahedron: Asymmetry* **2004**, *15*, 1065.
68. Hu, X.; Chen, H.; Zheng, Z. *Adv. Synth. Catal.* **2005**, *347*, 541.

69. Ohta, T.; Takaya, H.; Kitamura, M.; Nagai, K; Noyri, R. *J. Org. Chem.* **1987**, *53*, 3174.
70. Knowles, W. S. *Adv. Synth. Catal.* **2003** *345*, 3.
71. Young, J. F.; Osborn, J. A.; Jardine, F. H.; Wilkinson, G. *Chem. Comm.* **1965**, 131.
72. Knowles, W. S. *Angew. Cehm. Int. Ed.* **2002**, *41*, 1998.
73. Horner, L.; Siegel, H.; Büthe, H. *Angew. Chem. Int. Ed.* **1968**, *7*, 942.
74. Dang, T. P.; Kagan, H. B. *J. Chem. Soc. Chem. Commun.* **1971**, 481.
75. Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 7932.
76. Takaya, H.; Ohta, T.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Inoue, S.; Kasahara, I.; Noyori, R. *J. Am. Chem. Soc.* **1987**, *109*, 1596; Ohta, T.; Takaya, H. *J. Org. Chem.* **1987**, *52*, 3174.
77. Mashima, K.; Kusano, K.; Sato, N.; Matsumura, Y.; Nozaki, K.; Kumobayashi, H.; Sayo, N.; Hori, Y.; Ishizaki, T.; Akutagawa, S.; Takaya, H. *J. Org. Chem.* **1994**, *59*, 3064.
78. Noyori, R.; Tomino, I.; Tanimoto, Y.; Nishizawa, M. *J. Am Chem. Soc.* **1984**, *106*, 6709.
79. Itsuno, S.; Nakano, M.; Miyazaki, K.; Masuda, H.; Ito, K.; Hirao, A.; Nakahama, S. *J. Chem. Soc. Perkin Trans. 1* **1985**, 2039.
80. Midland, M. M.; McLoughlin, J. I.; Gabriel, J. *J. Org. Chem.* **1989**, *54*, 159.
81. Ohkuma, T.; Ooka, H.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 10417.
82. Noyori, R.; Ohkuma, T. *Pure Appl. Chem.* **1999**, *71*, 1493.
83. Ohkuma, T.; Koizumi, M.; Doucet, H.; Pham, T.; Kozawa, M.; Murata, K.; Katayama, E.; Yokozawa, T.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1998**, *120*, 13529.
84. Doucet, H.; Ohkuma, T.; Murata, K.; Yokozawa, T.; Kozawa, M.; Katayama, E.; England, A. F.; Ikariya, T.; Noyori, R. *Angew. Chem. Int. Ed.* **1998**, *37*, 1703.
85. Ohkuma, T.; Koizumi, M.; Yoshida, M.; Noyori, R. *Org. Lett.* **2000**, *2*, 1749.
86. Hu, A.; Ngo, H. L.; Lin, W. *Org. Lett.* **2004**, *6*, 2937.
87. Xu, Y.; Alcock, N. W.; Clarkson, G. J.; Docherty, G.; Woodward, G.; Wills, M. *Org. Lett.* **2004**, *6*, 4105.
88. Xie, J.; Wang, L.; Fu, Y.; Zhu, S.; Fan, B.; Duan, H.; Zhou, Q. *J. Am. Chem. Soc.* **2003**, *125*, 4404.
89. Wu, J.; Chen, H, Kwok, W. H.; Guo, R.; Zhou, Z.; Yeung, C. H.; Chan, A. S. C. **2002**, *67*, 7908.
90. Hems, W. P.; Grasa, G. A. *PCT Int. Appl.* **2005**, wo 2005/007662
91. Burk, M. J.; Hems, W.; Herzberg, D.; Malan, C.; Zanotti-Gerosa, A. *Org. Lett.*

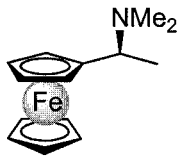
2000, *2*, 4173.
92. Grasa, G. A.; Zanotti-Gerosa, A.; Medlock, J. A.; Hems, W. P. *Org. Lett.* **2005**, *7*, 1449.
93. Ohkuma, T.; Hattori, T.; Ooka, H.; Inoue, T.; Noyori, R. *Org. Lett.* 2004**,** *6*, 2681.
94. Wu, J.; Ji, J.; Guo, R.; Yeung, C.; Chan, A. S. C. *Chem. Eur. J.* **2003**, *9*, 2963.
95. Clapham, S. E.; Hadzovic, A.; Morris, R. H. *Coor. Chem. Rev.* **2004**, *248*, 2201.
96. Sandoval, C. A.; Ohkuma, T.; Muñiz, K.; Noyori, R. *J. Am. Chem. Soc.* **2003**, *125*, 13490.
97. Noyori, R.; Koizumi, M.; Ishii, D.; Ohkuma, T. *Pure Appl. Chem.* **2001**, *73*, 227.
98. Hartmann, R.; Chen, P. *Angew. Chem. Int. Ed.* **2001**, *40*, 3581.
99. Torst, B. M.; Dietsche, T. J. *J. Am. Chem. Soc.* **1973**, *95*, 8200
100. Ojima, I. *Catalytic Asymmetric Synthesis*; VCH Publishers Inc.: New York, **2000**
101. Trost, B. M.; Shen, H. C.; Dong, L.; Surivet, J. P.; Sylvain, C. *J. Am. Chem. Soc.* **2004**, 126, 11966.
102. Trost, B. M.; Crawley, M.L. *Chem. Rev.* **2003**, *103*, 2921.
103. Trost. B. M.; Shcroeder, G. M. *J. Am. Chem. Soc.* **1999**, *121*, 6759
104. Fernandez, E.; Maeda, K.; Hooper, M. W.; Brown, J. M. *Chem. Eur. J.* **2000**, *6*, 1840.
105. Trost, B. M.; Fraisse, P. L.; Ball, Z. T. *Angew. Chem. Int. Ed.* **2002**, *41*, 1059.
106. Trost, B. M.; Hachyia, I. *J. Am. Chem. Soc.* **1998**, *120*, 1104.
107. Imai, Y.; Zhang, W. B.; Kida, T.; Nakatsuji, Y.; Ikeda, I. *Tetrahedron Lett.* **1998**, *39*, 4343.
108. Yamaguchi, M.; Shima, T.; Yamagishi, T.; Hida, M. *Tetrahedron: Asymmetry* **1991**, *2*, 663.
109. Brown, J. M.; Hulmes, D. I.; Guiry, P. J. *Tetrahedron* **1994**, *50*, 4493.
110. Hayashi, T.; Yamamoto, A.; Hagihara, T.; Ito, Y. *Tetrahedron Lett.* **1993**, *34*, 3149.
111. Zhang, W.; Shimanuki, T.; Kida, T.; Nakatsuji, Y.; Ikeda, I.; *J. Org. Chem.* **1999**, *64*, 6247.
112. Abbenhuis, H. C. L.; Burckhardt, U.; Gramlich, V.; Kollner, C.; Pregosin, P. S.; Salzmann, R.; Togni, A. *Organometallics* **1995**, *14*, 759.
113. Zhang, W. B.; Kida, T.; Nakatsuji, Y.; Ikeda, I. *Tetrahedron Lett.* **1996**, *37*, 7995.
114. Marinetti, A.; Kruger, V.; Ricard, L. *J. Organomet. Chem.* **1997**, *529*, 465.
115. Chen, Z. G.; Jiang, Q. Z.; Zhu, G. X.; Xiao, D. M.; Cao, P.; Guo, C.; Zhang, X. M. *J. Org. Chem.* **1997**, *62*, 4521.
116. Brenchley, G.; Merifield, E.; Wills, M.; Fedouloff, M. *Tetrahedron Lett.* **1994**, *35*, 2791.
117. Kang, J.; Lee, J. H.; Choi, J. S. *Tetrahedron: Asymmetry* **2001**, *12*, 33.
118. Xie, J. H.; Duan, H. F.; Fan, B. M.; Cheng, X.; Wang, L. X.; Zhou, Q. L. *Adv. Synth. Catal.* **2004,** *346*, 625.
119. Hoarau, O.; Aithaddou, H.; Castro, M.; Balavoine, G. G. A. *Tetrahedron: Asymmetry* **1997**, *8*, 3755.
120. Zhao, D.; Ding, K. *Org. Lett.* **2003**, *5*, 1349.
121. Pfaltz, A. *Acc. Chem. Res.* **1993**, *26*, 339.
122. Kubota, H.; Koga, K. *Tetrahedron Lett.* **1994**, *35*, 6689
123. Gamez, P.; Dunjic, B.; Fache, F.; Lemaire, M. *J. Chem. Soc., Chem. Comm.* **1994**, 1417.

124. Togni, A. *Tetrahedron: Asymmetry* **1991**, *2*, 683.
125. Andersson, P. G.; Harden, A. Tanner D.; Norrby, P. O. *Chem. Eur. J.* **1995**, *1*, 12.
126. Kubota, H.; Nakajima, M. Koga, K. *Tetrahedron Lett.* **1993**, *34*, 8135.
127. Pena-Cabrera, E.; Norrby, P. O.; Sjogren, M.; Vitagliano, A.; Defelice, V.; Oslob, J.; Ishii, S.; O'Neill, D.; Akermark, B.; Helquist, P. *J. Am. Chem. Soc.* **1996**, *118*, 4299.
128. Nordström, K.; Macedo, e.; Moberg, C. *J. Org. Chem.* **1997**, *62*, 1604.
129. Moreno, R. M.; Bueno, A.; Moyano, A. *J. Organomet. Chem.* **2002**, *660*, 62.
130. Chelucci, G.; Medici, S.; Saba, A. *Tetrahedron Asymmetry* **1997**, *8*, 3183.
131. Chelucci, G. *Tetrahedron: Asymmetry* **1997**, *8*, 2667.
132. Evans, P. A.; Brandt, T. A. *Tetrahedron Lett.* **1996**, *37*, 9143.
133. Dawson, G.. J.; Frost, C. G.; Williams, J. M. J. *Tetrahedron Lett.* **1993**, *34*, 3149.
134. Glaser, B.; Kunz, H. *Synlett* **1998**, 53.
135. Mino, T.; Imiya, W.; Yamashita, M. *Synlett* **1997**, 583.
136. Gilbertson, S. R.; Chang, C. W. T. *Chem. Commun.* **1997**, 975.
137. Porte, A. M.; Reibenspies, J.; Burgess, K. *J. Am. Chem. Soc.* **1998**, *120*, 9180
138. Zhang, W. B.; Hirao, T.; Ikeda, I. *Tetrahedron Lett.* **1996**, *37*, 4545.
139. Andreson, J. C.; Cubbon, R. J. ; Harling, J. D. *Tetrahedron: Asymmetry* **2001**, *12*, 923.
140. Bourghida, M.; Widhalm, M. *Tetrahedron: Asymmetry* **1998**, *9*, 1073.
141. Wang, Y.; Guo, H.; Ding, K.; *Tetrahedron: Asymmetry* **2000**, *11*, 4153.
142. Ogasawara, M.; Yoshida, K.; Kamei, H.; Kato, K.; Uozumi, Y.; Hayashi, *Tetrahedron: Asymmetry* **1998**, *9*, 1779.
143. Hayashi, Y.; Sakai, H.; Kaneta, N.; Uemura, M. *J. Organomet. Chem.* **1995,** *503*, 143.
144. Jang, H. Y.; Seo, H.; Han, J. W.; Chung, Y. K. *Tetrahedron Lett.* **2000**, *41*, 5083.
145. Kondo, K.; Kazuta, K.; Fujita, H.; Sakamoto, Y.; Murakami, Y. *Tetrahedron* **2002**, *58*, 5209.
146. Guiry, P. J. ; Cahill, J. P. *Tetrahedron: Asymmetry* **1998**, *9*, 4301.
147. Mino, T.; Tanaka, Y.; Sakamoto, M. Fujita, T. *Tetrahedron: Asymmetry* **2001**, *12*, 2435.
148. Jin, M. J.; Jung, J. A.; Kim. S. H. *Tetrahedron Lett.* **1999**, *40*, 5197.
149. Chen, G.; Li, X, Zhang, H.; Gong, L.; Mi, A.; Cui, X.; Jiang, Y.; Choi, M. C. K.; Chan, A. S. C. *Tetrahedron: Asymmetry*, **2002**, *13*, 809.
150. Okuyama, Y.; Nakano, H.; Hongo, H. *Tetrahedron: Asymmetry* **2000**, *11*, 1193.
151. Stranne, R.; Vasse, J. L.; Moberg, C. *Org. Lett.* **2001**, *3*, 2525.
152. Kohara, T.; hashimoto, Y.; Saigo, K. *Synlett* **2000**, *4*, 517
153. Fukuda, T.; Takehara, A.; Iwao, M.; *Tetrahedron: Asymmetry* **2001**, *12*, 2793.
154. Mino, T.; Ogawa, T.; Yamashita, M. *J. Organomet. Chem.* **2003**, *665*, 122.
155. Hu, X.; Dai, H.; Hu, X.; Chen, H.; Wang, J.; Bai, C.; Zheng, Z. *Tetrahedron: Asymmetry* **2002**, *13*, 1687
156. Hou, D. R.; Reibenspies, J.; Burgess, K. *J. Org. Chem.* **2001**, *66*, 206.
157. Jones, G.; Richards, C. J. *Tetrahedron Lett.* **2001**, *42*, 5553.
158. Park, J.; Quan, Z.; Lee, S.; Ahn, K. H.; Cho, C. W. *J. Organomet. Chem.* **1999**, *584*, 140.
159. Deng, W. P.; Hou, X. L.; Dai, L. X.; Yu, Y. H.; Xia, W. *Chem. Comm.* **2000**, 285.
160. You, S. L.; Hou, X. L.; Dai, L. X.; Yu, Y. H.; Xia, W. *J. Org. Chem.* **2002**, *67*, 4684.
161. Manoury, E.; Fossey, J. S.; Ait-haddou, H.; Daran, J. C. Balavoine, G. G. A.

Organometallic **2000**, *19*, 3736.
162. Kündig, E. P.; Meier, P. *Helv. Chim. Acta* **1999**, *82*, 1360.
163. Liu, S.; Muller, J. F. K.; Neuburger, M.; Schaffner, S.; Zehnder, M. *Helv. Chim. Acta.* **2000**, *83*, 1256.
164. Hayashi, T.; Ohno, A.; Lu, S. J.; Matsumoto, Y.; Fukuyo, E.; Yanagi, K. *J. Am. Chem. Soc.* **1994**, *116*, 4221.
165. Deng, W. P.; You, S. L.; Hou, X. L.; Dai, L. X.; Yu, Y. H.; Xia, W.; Sun, J. *J. Am. Chem. Soc.* **2001**, *123*, 6508.
166. Vukicevic, R. D.; Vukicevic, M.; Ratkovic, Z.; Konstantinovic, S. *Synlett.* **1998**, 1329.
167. Knuhl, G.; Sennhenn, P.; Helmchen, G. *J. Chem. Soc., Chem. Commun.* **1995**, 1845.
168. Mancheno, O. G.; Priego, J.; Cabrera, S.; Arrayas, R. G.; Llamas, T.; Carretero, J. C. *J. Org. Chem.* **2003**, *68*, 3679.
169. Guo, R.; Morris, R. H.; Song, D. *J. Am. Chem. Soc.* **2005**, *127*, 516.
170. Farrell, A.; Goddard, R.; Guiry, P. J. *J. Org. Chem.* **2002**, *67*, 4209.
171. Evans, D. A.; Campos, K. R.; Tedrow, J. S.; Michael, F. E.; Gagnè, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 7905.
172. Hayashi, T.; Yamamoto, A.; lto, Y.; Nishioka, E.; Miura, H.; Yanagi, K. *J. Am. Chem. Soc.* **1989**, *111*, 6301.
173. Vasse, J.; Stranne, R.; Zalubovskis, R.; Gayet, C.; Moberg, C. *J. Org. Chem.* **2003**, *68*, 3258.
174. Torst, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 4545.
175. Trost, B. M.; Bunt, R. C. *J. Am. Chem. Soc.* **1998**, *120*, 70.
176. Kinoshita, N.; Marx, K. H.; Tanaka, K.; Tsubaki, K.; Kawabata, T.; Yoshikai, N.; Nakamura, E.; Fuji, K. *J. Org. Chem.* **2004**, *69*, 7960.
177. Burckhardt, U.; Baumann, M.; Togni, A. *Tetrahedron: Asymmetry* **1997**, *8*, 155.
178. Boele, M. D. K.; Kamer, P. C. J.; Lutz, M.; Spek, A. L.; Vries, J. G. de; Leeuwen, P. W. N. M. van; Strijdonck, G. P. F. van *Chem. Eur. J.* **2004**, *10*, 6232.
179. Mino, T.; Hata, S.; Ohtaka, K.; Sakamoto, M.; Fujita, T. *Tetrahedron Lett.* **2001**, *42*, 4837.

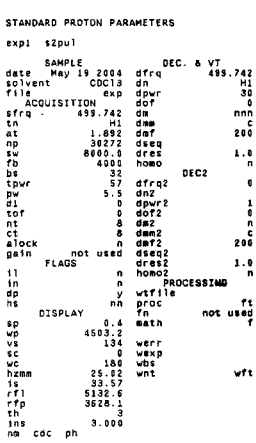
Appendix I

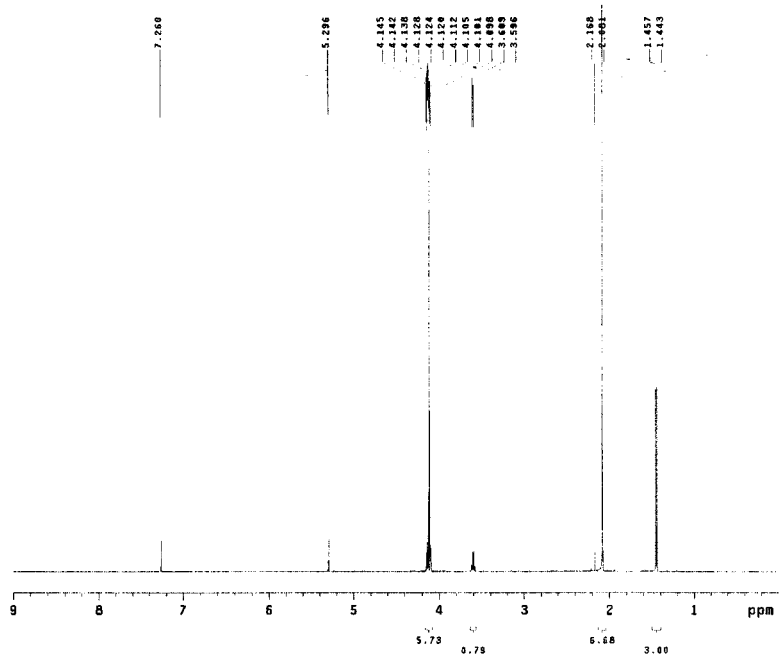
(^{1}H, ^{13}C, ^{31}P NMR spectra)



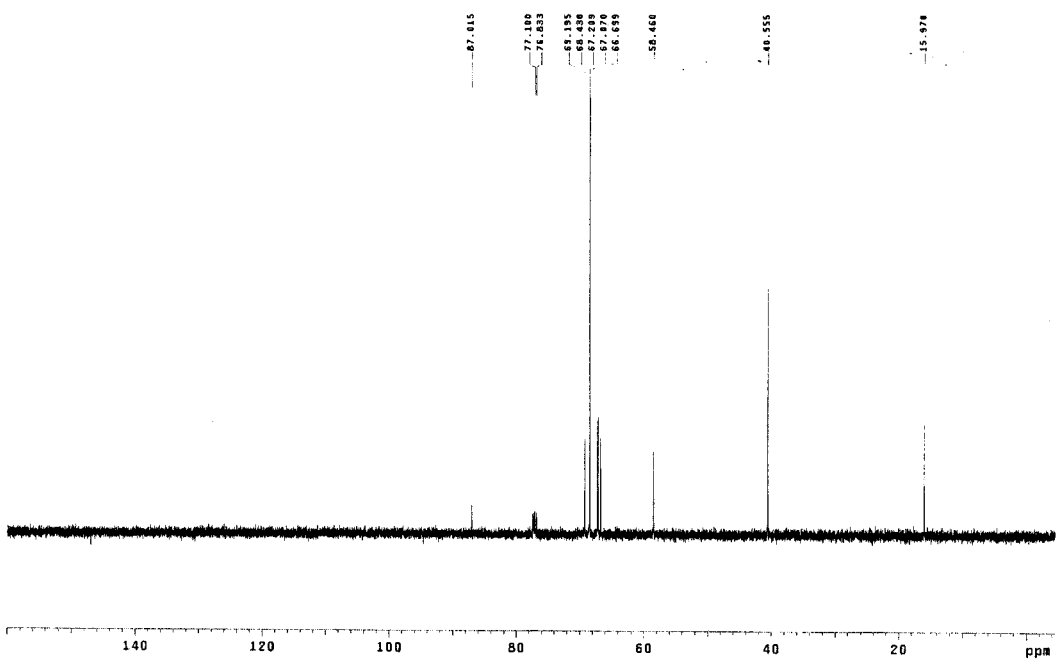
(*S*)-**2a**

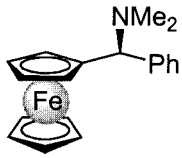
^{1}H NMR





^{13}C NMR





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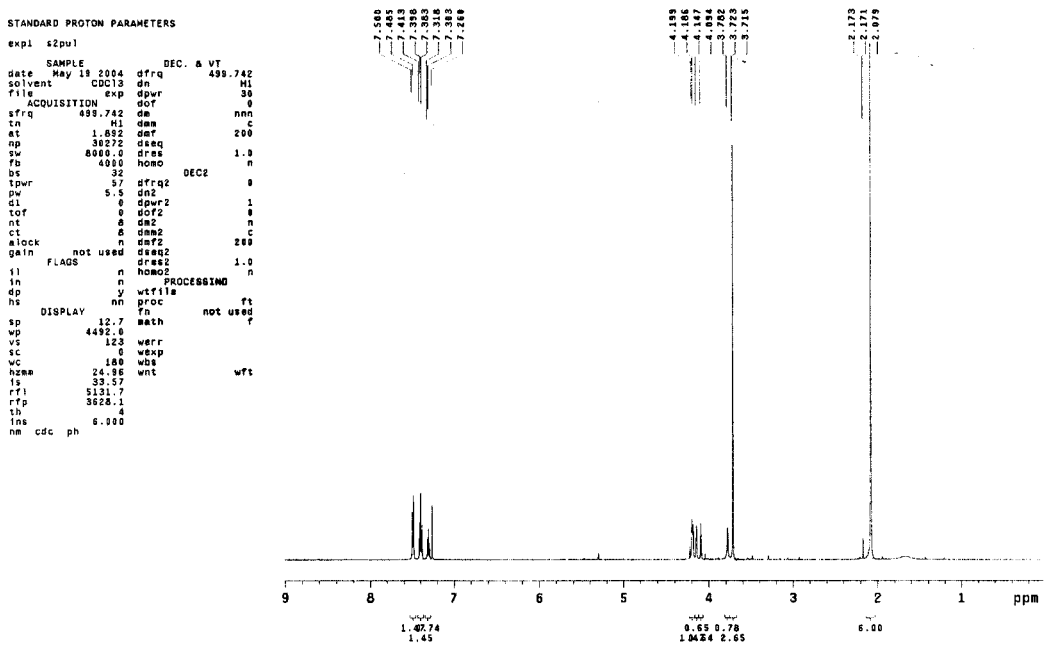

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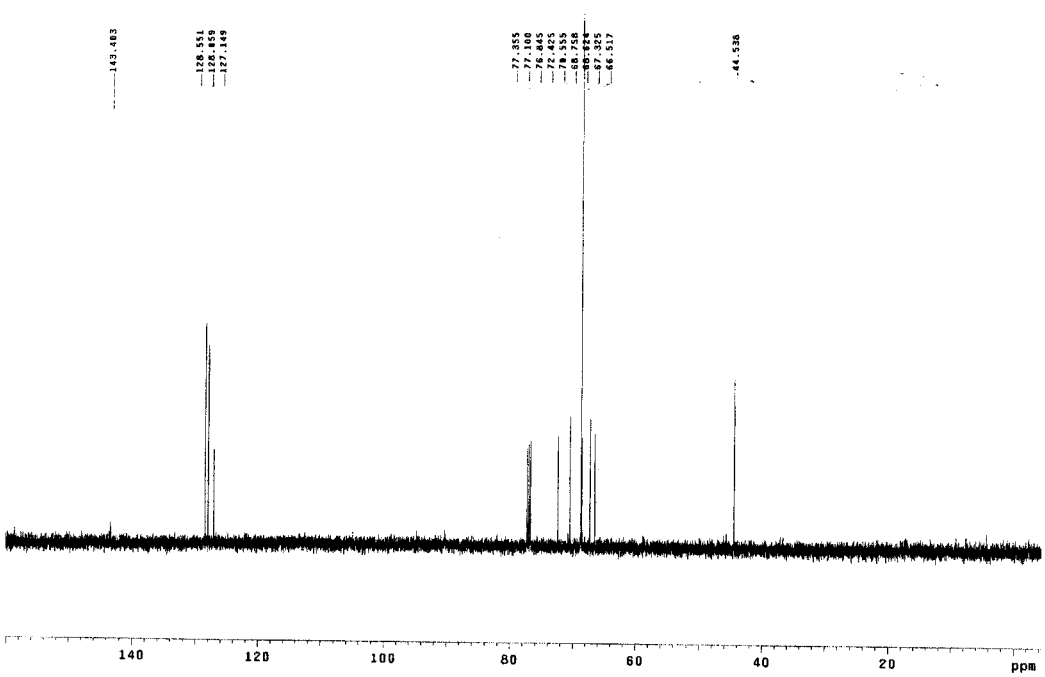
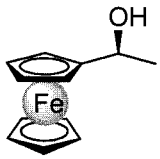
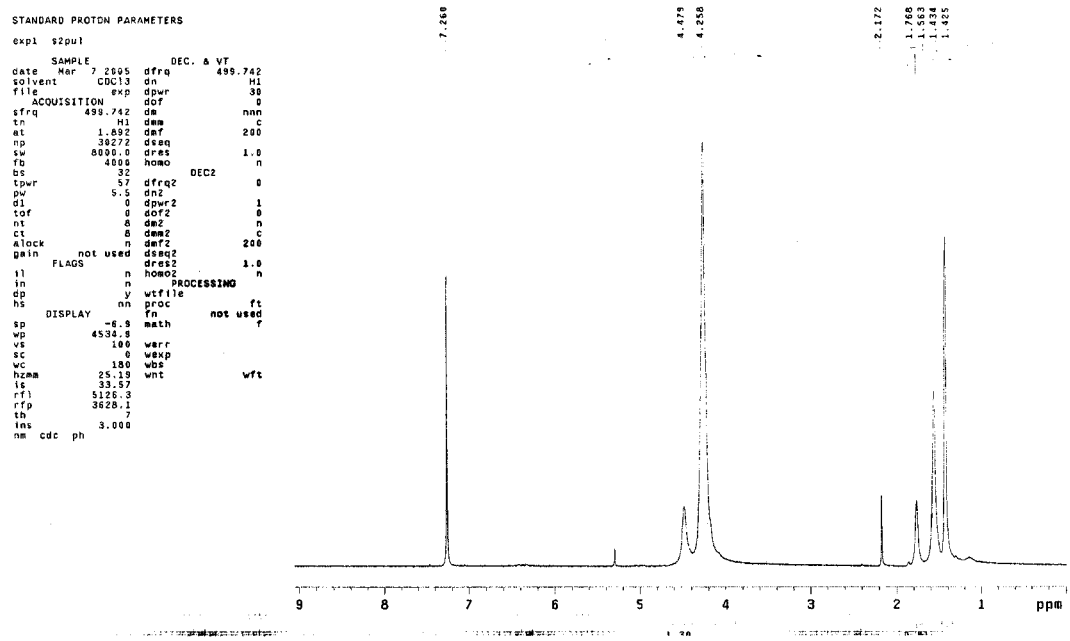




3a

^{1}H NMR



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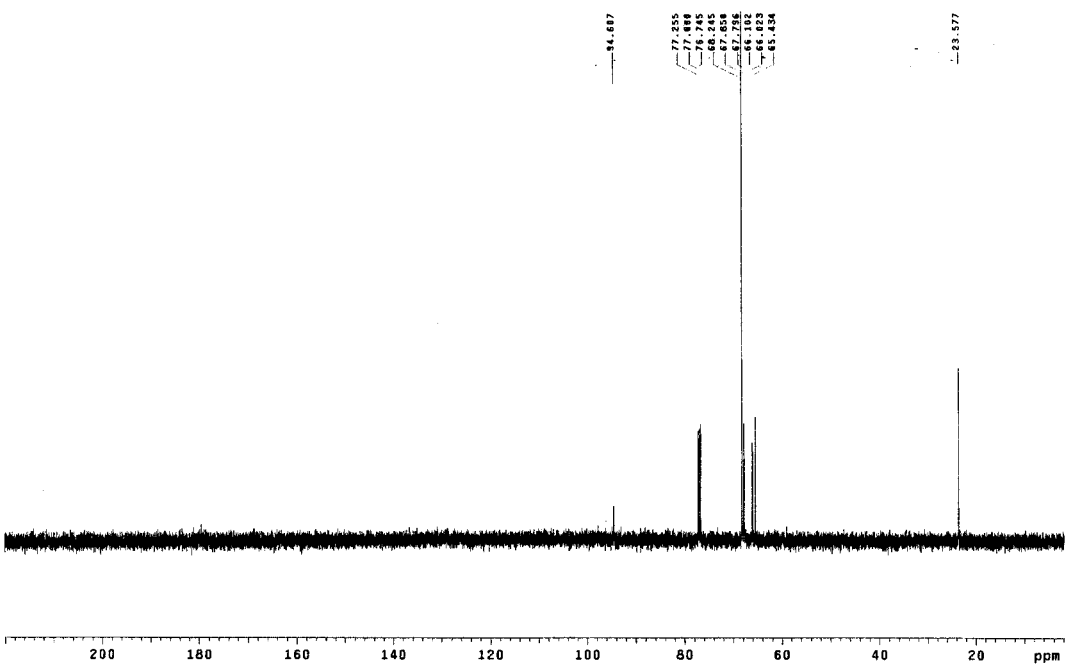

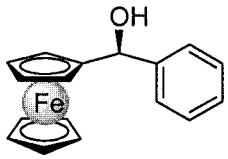

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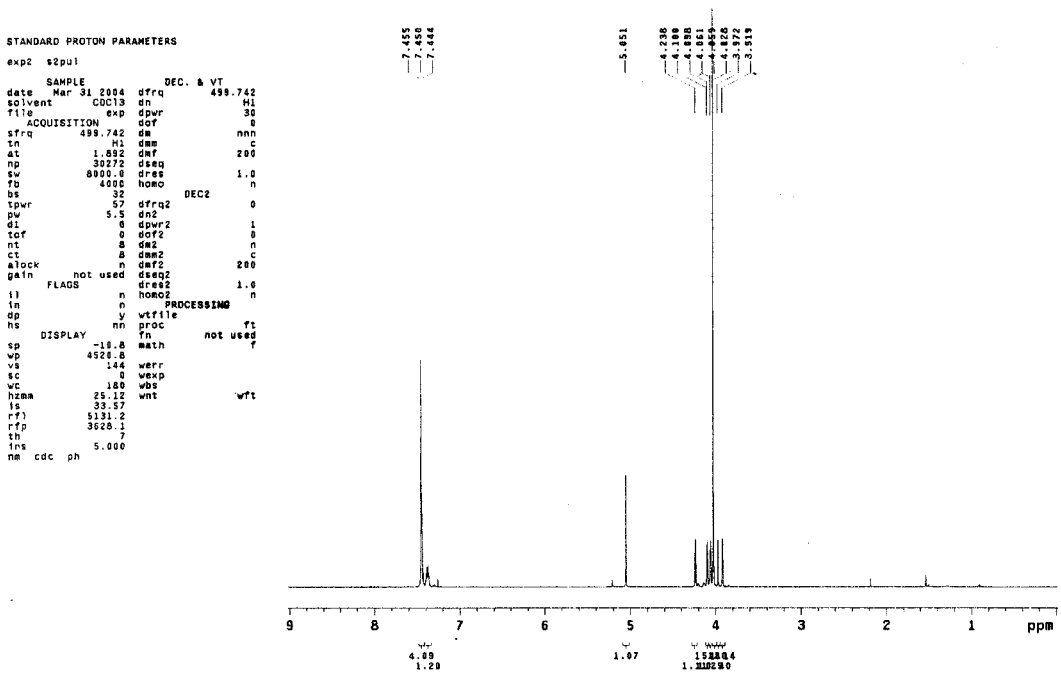
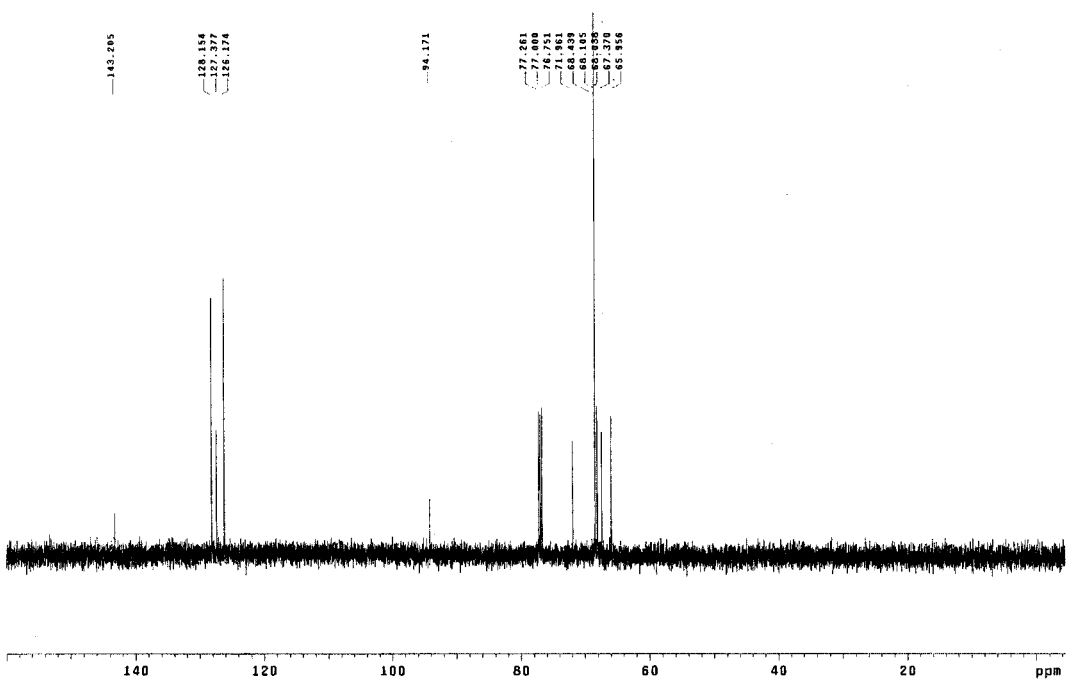
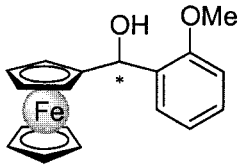


^{13}C NMR





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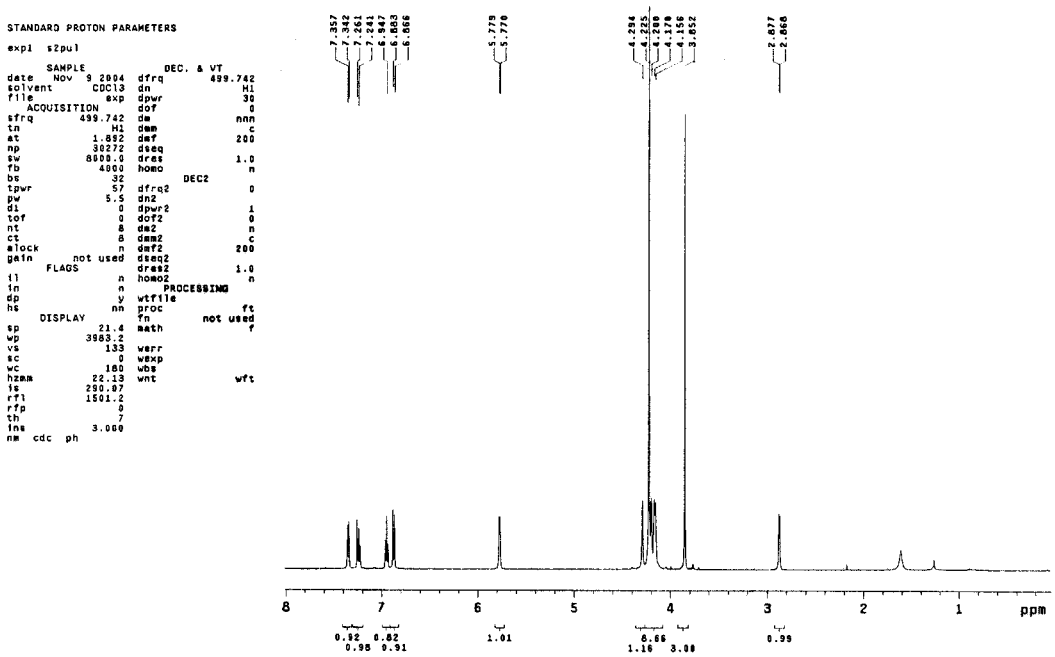
^{1}H NMR



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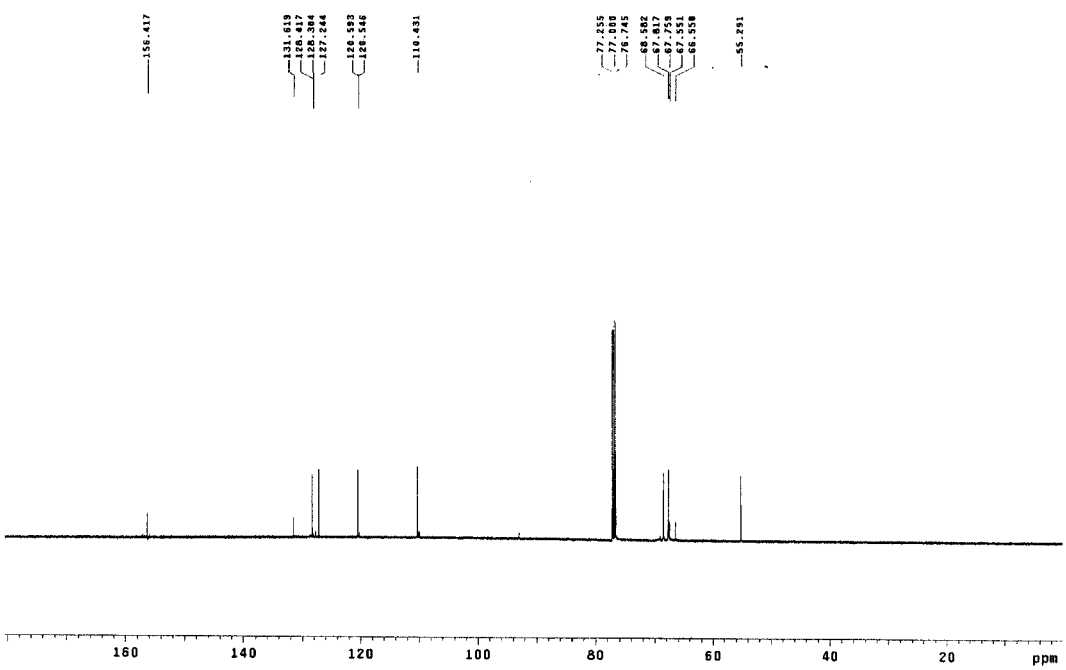
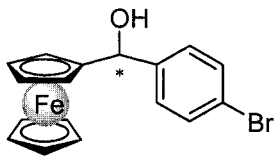
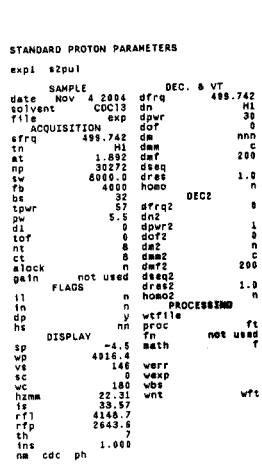
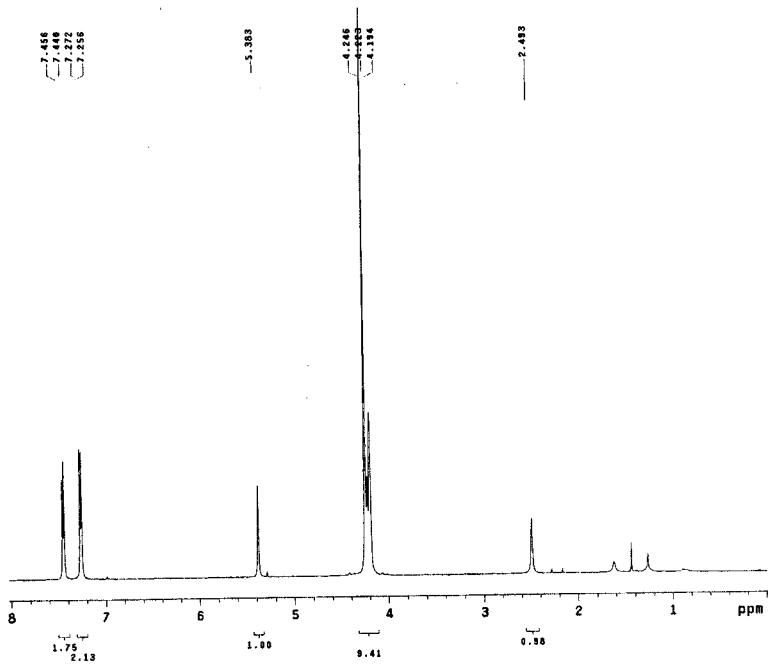




3d

^{1}H NMR





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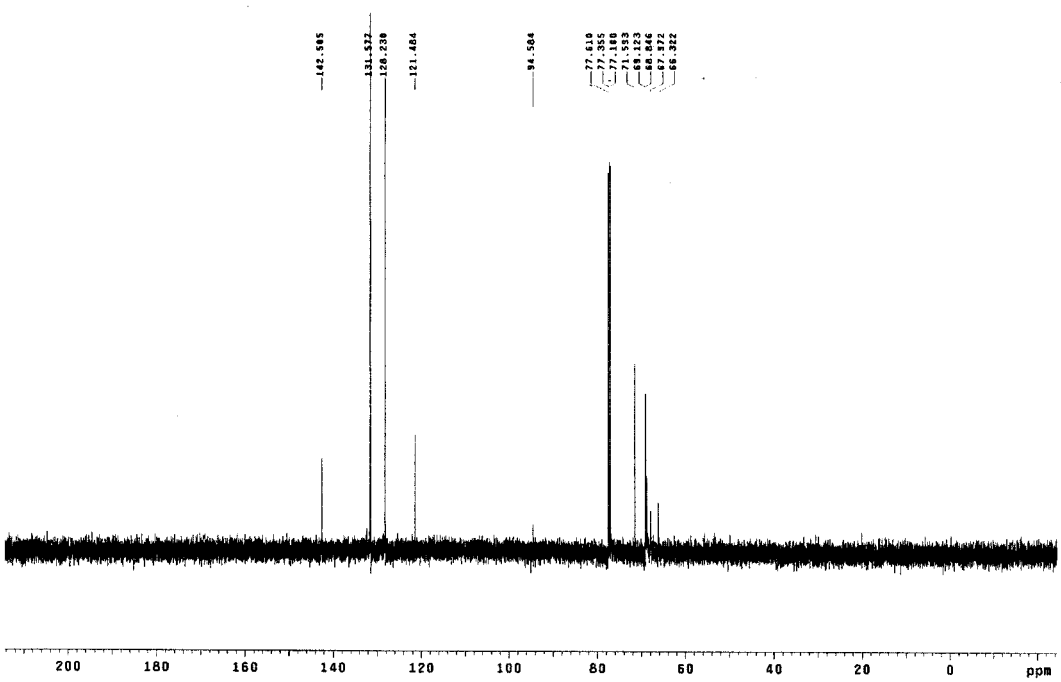

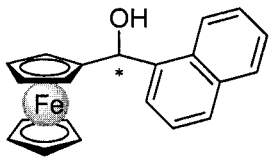

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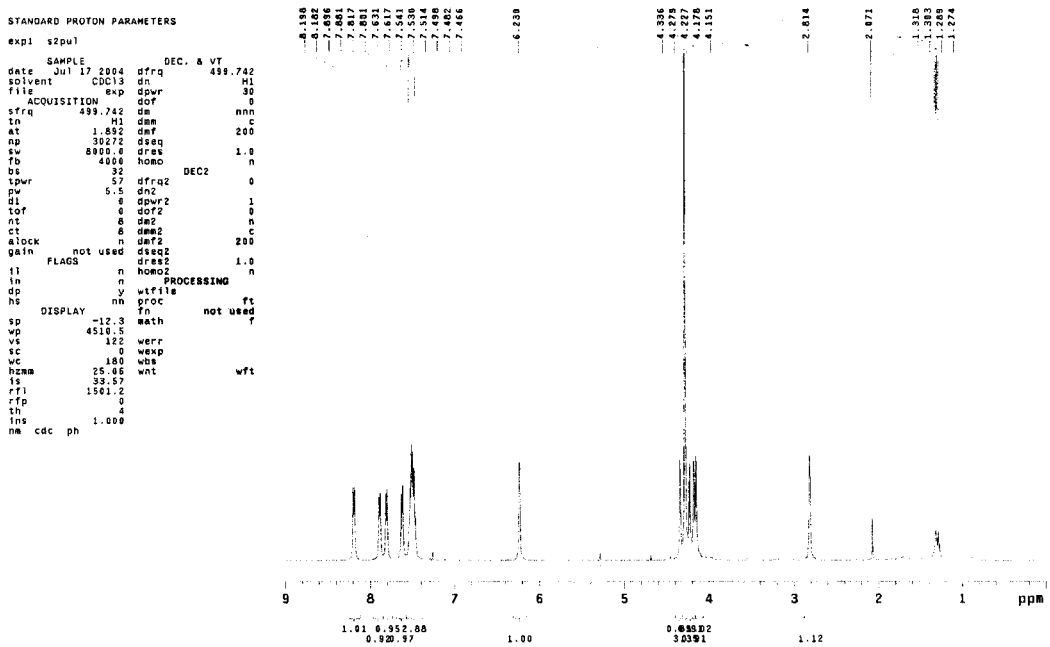

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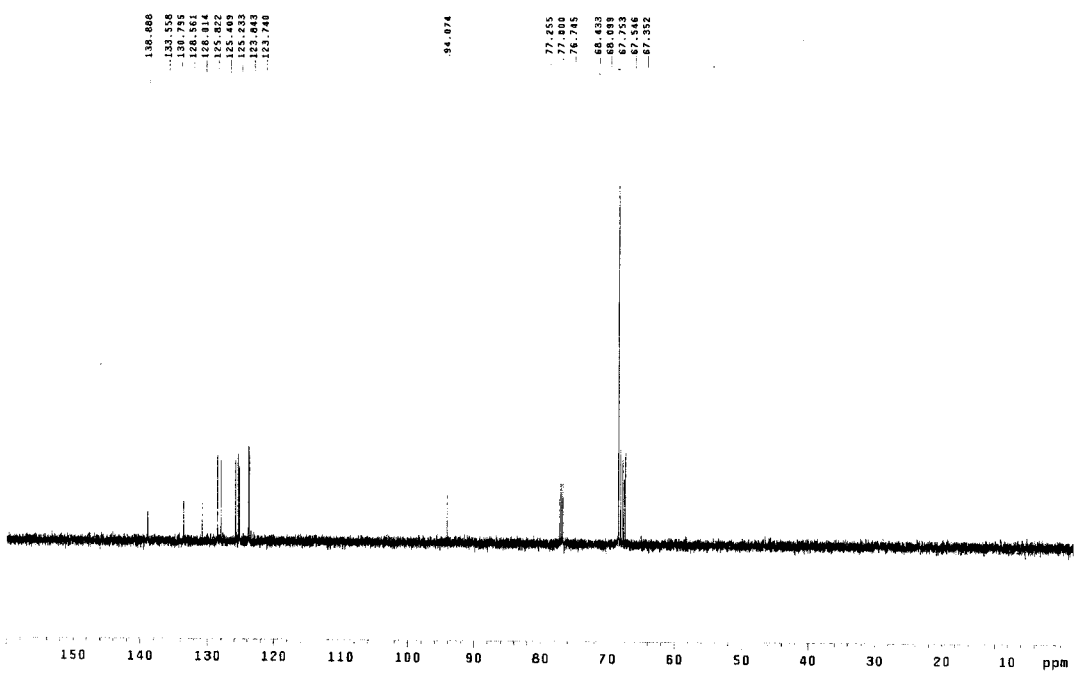
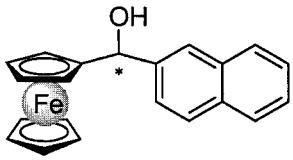
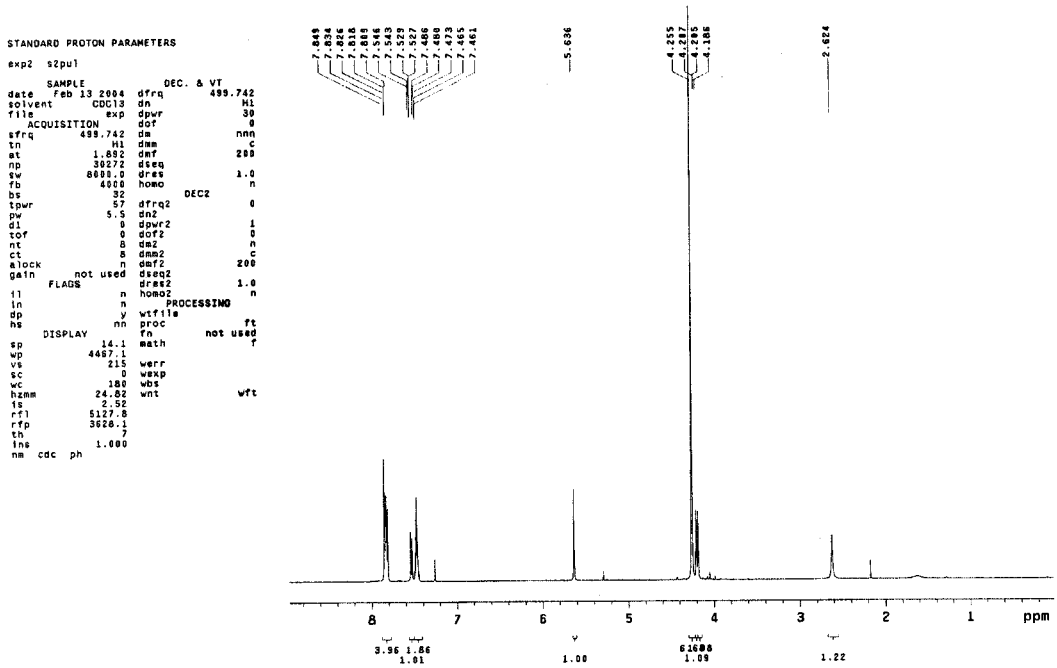




3f

^{1}H NMR



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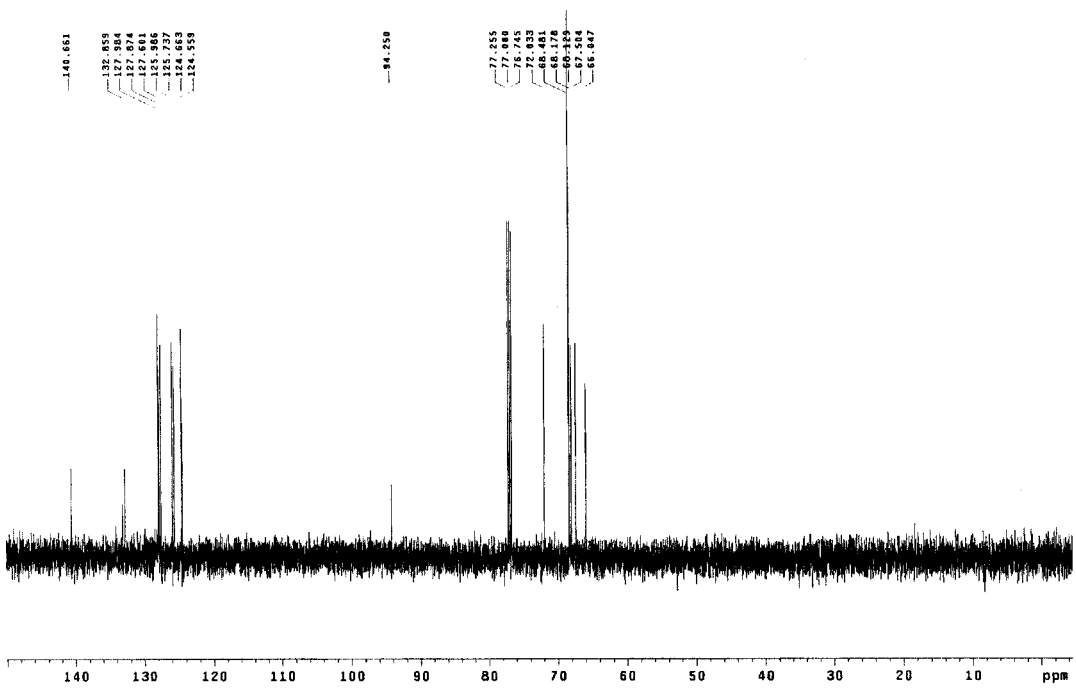

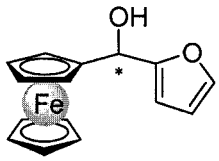

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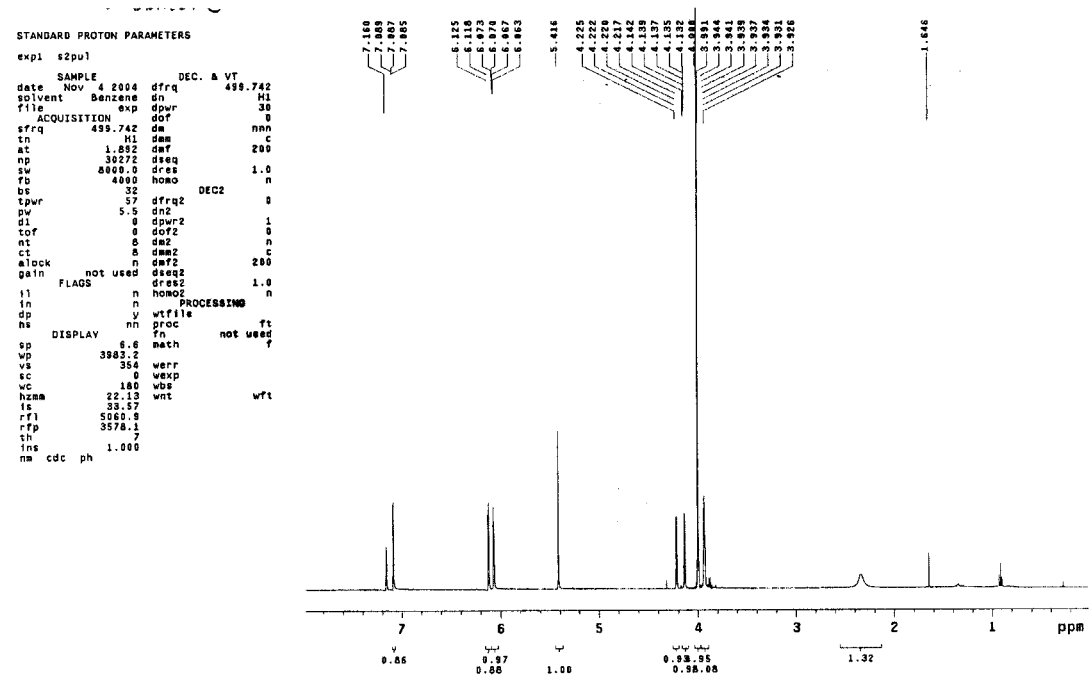

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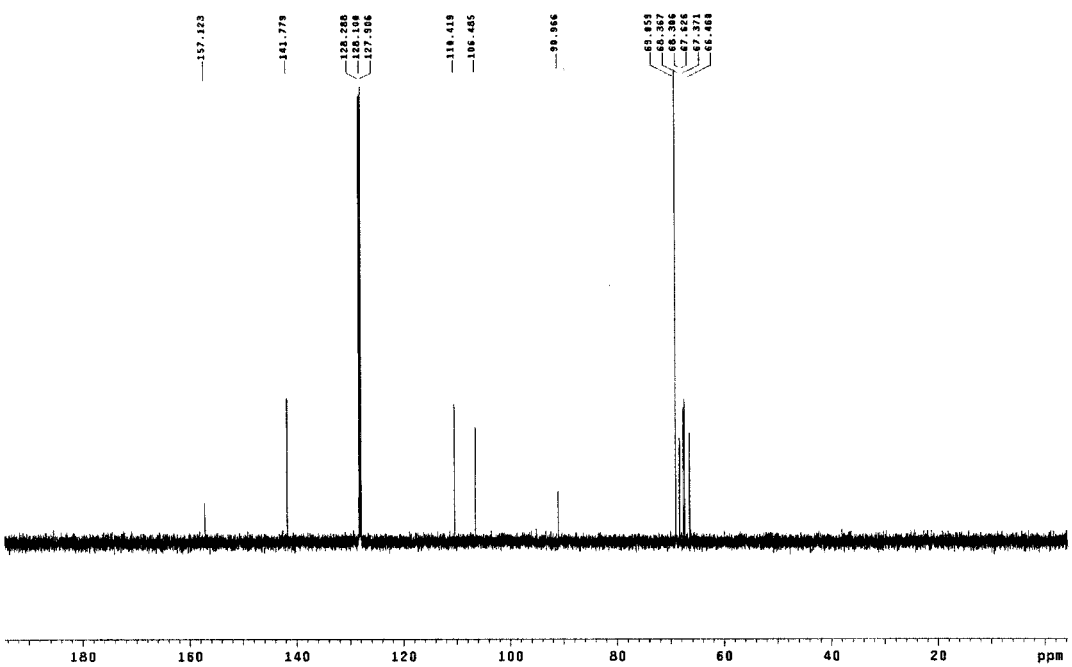

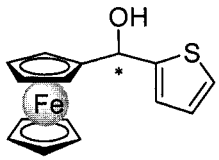

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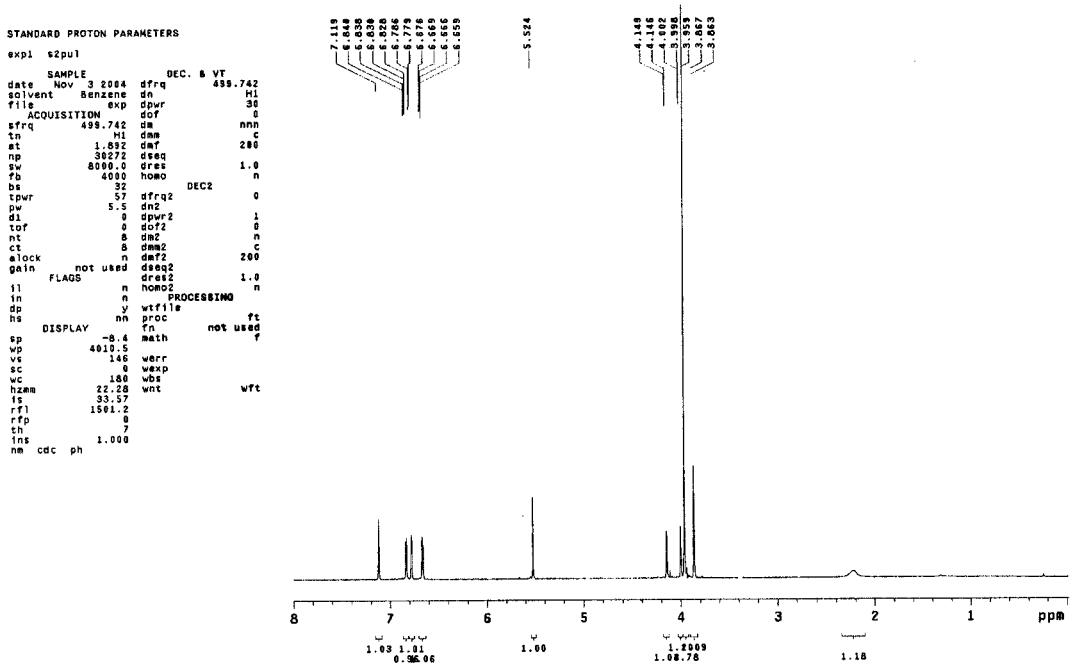

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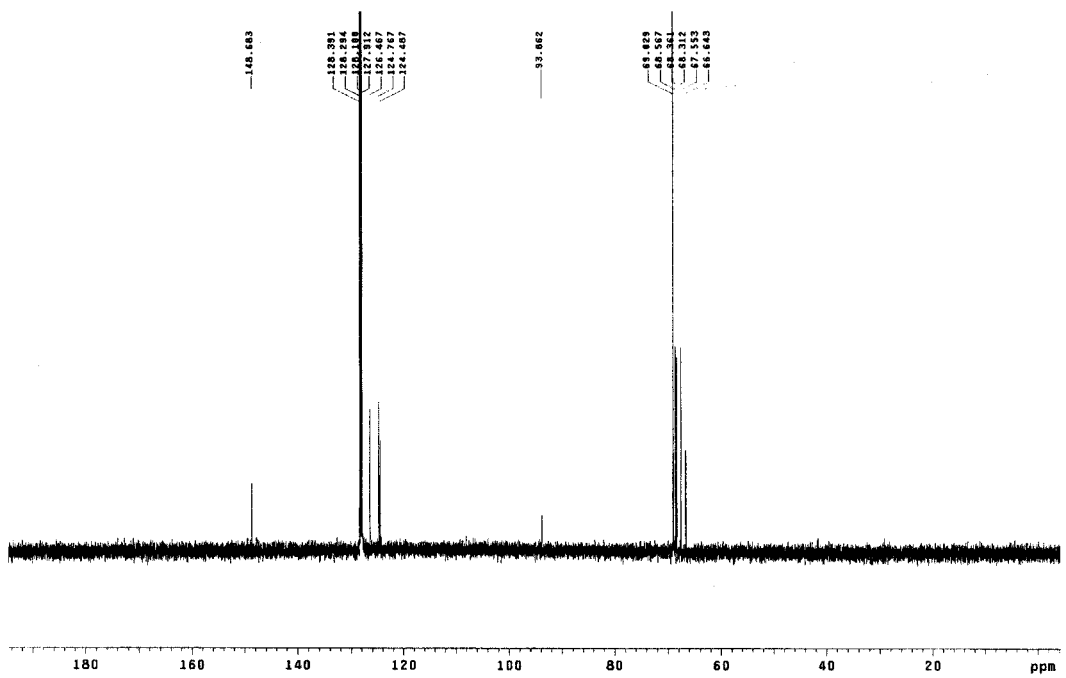

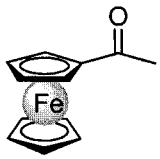

4a

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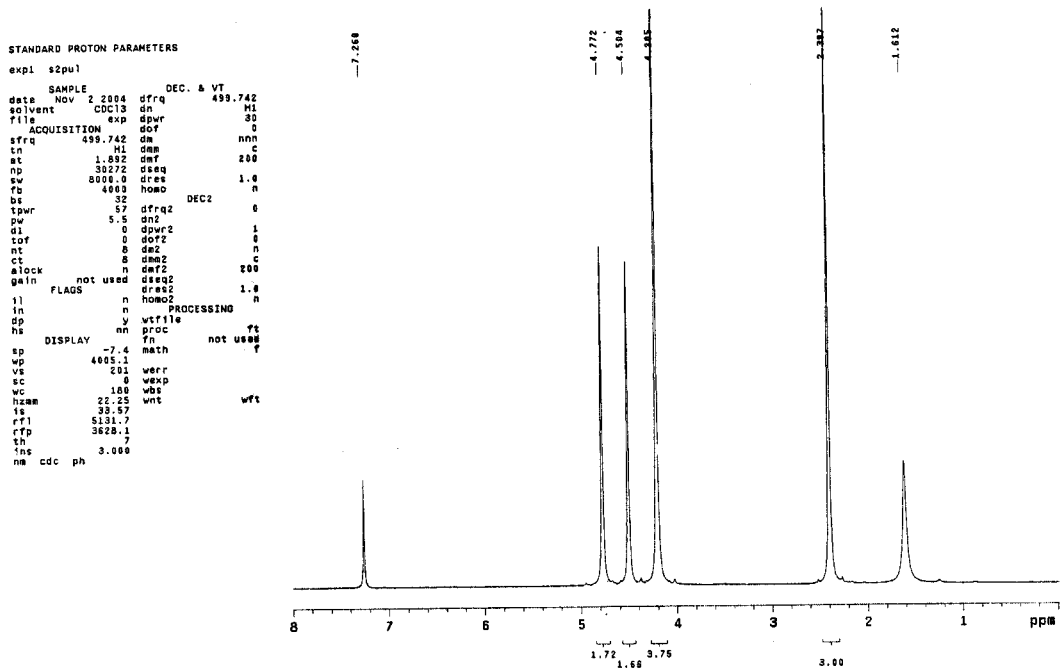

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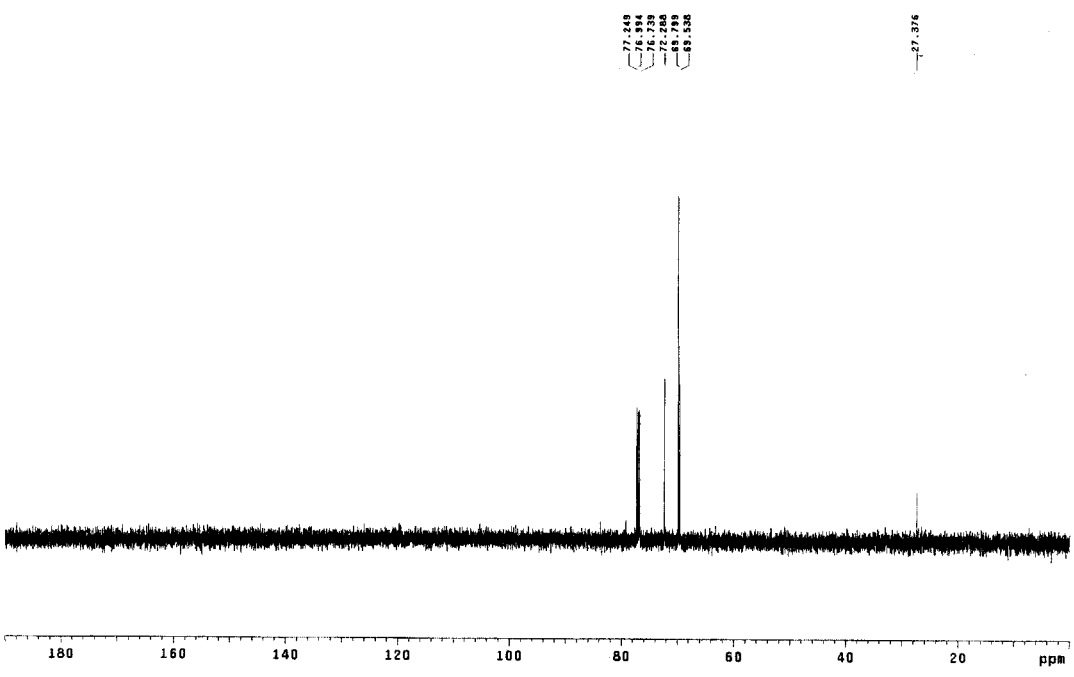
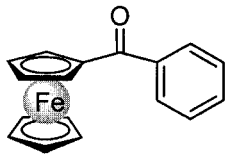
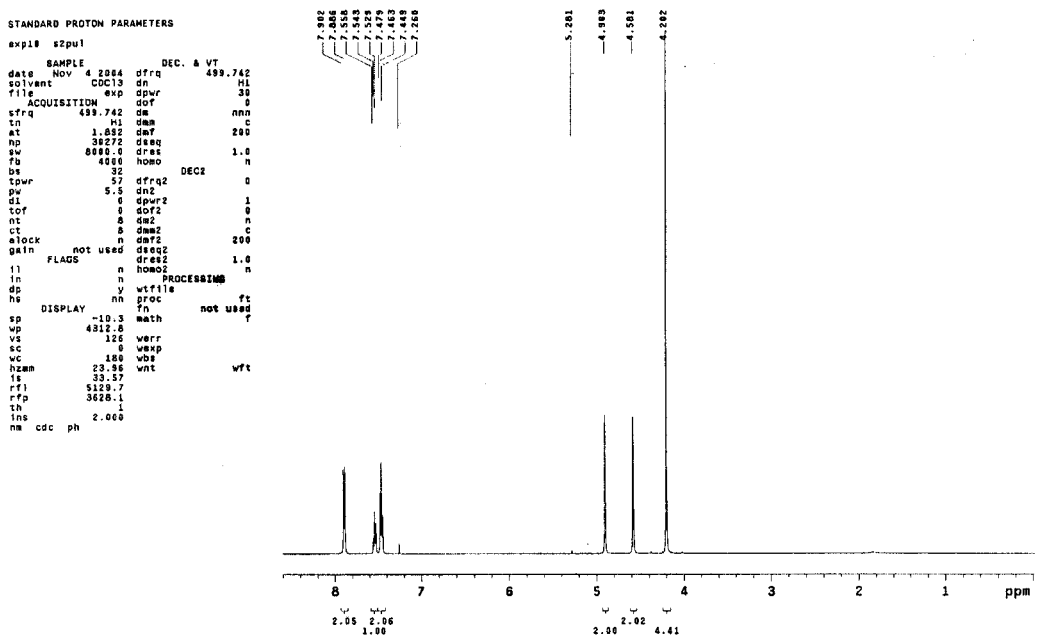


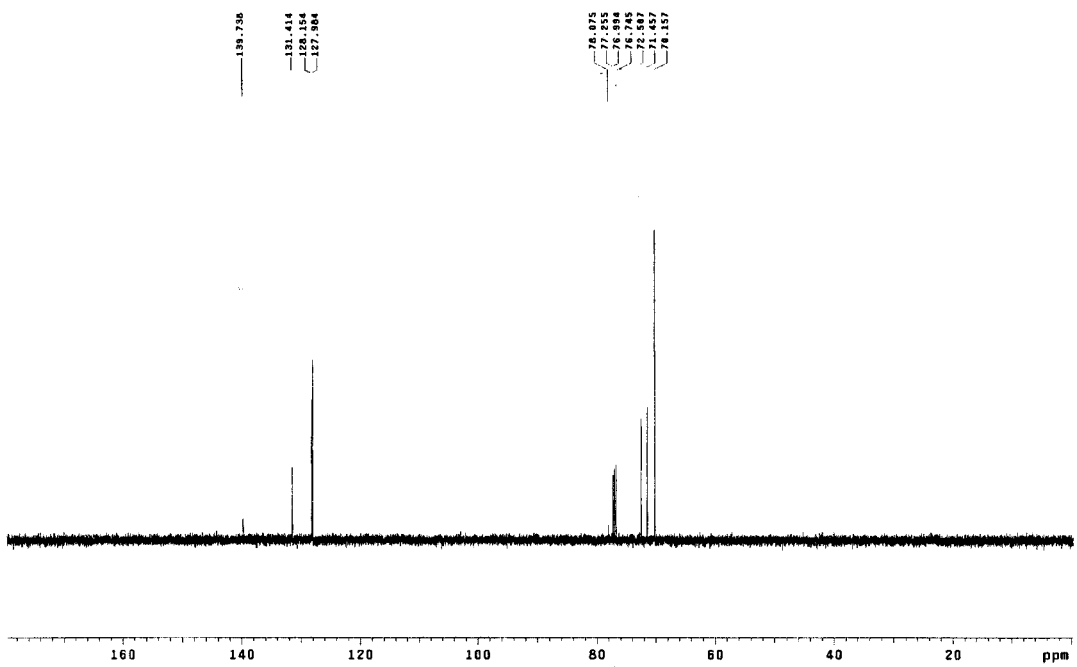


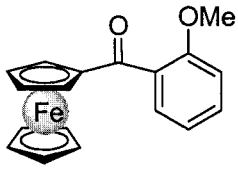
4b

^{1}H NMR



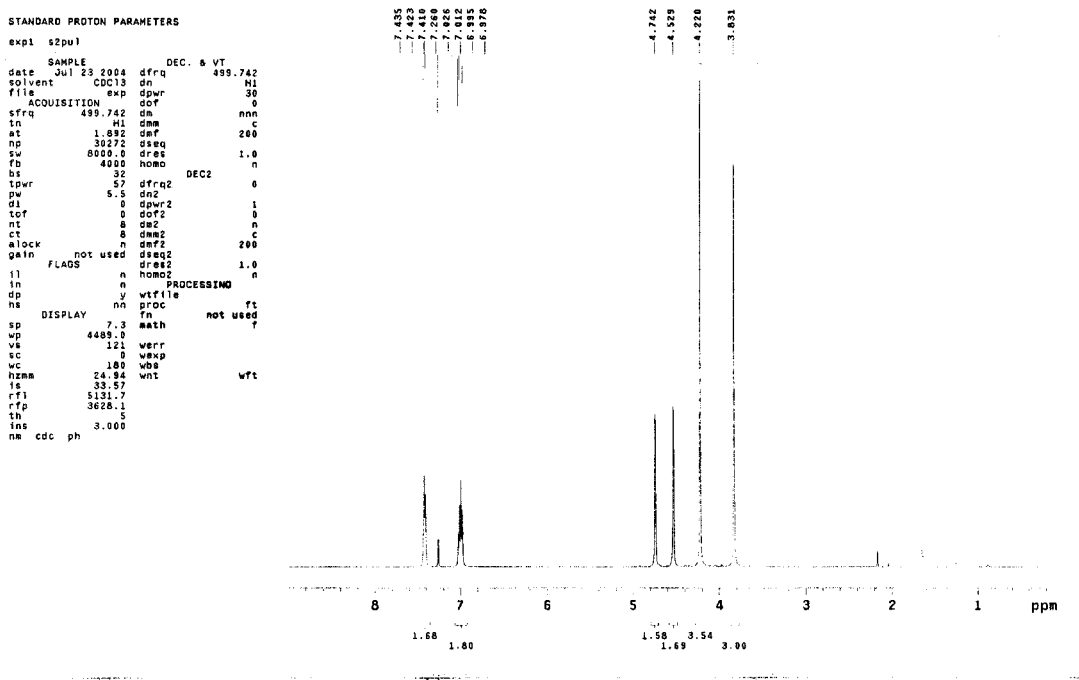
^{13}C NMR



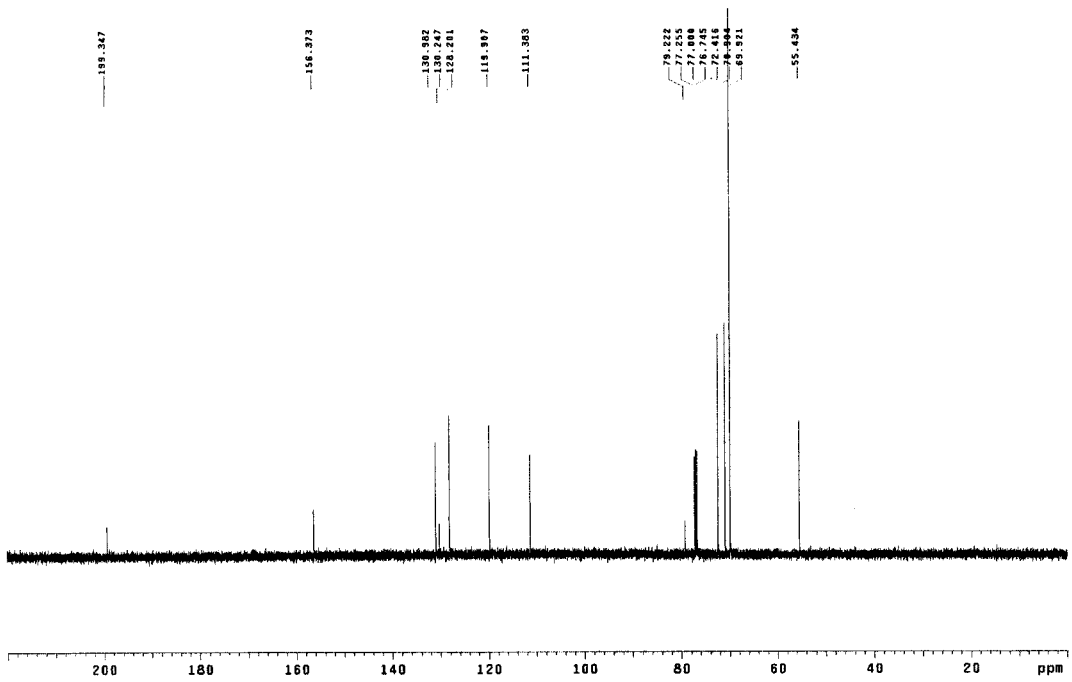


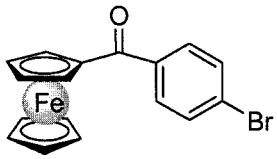
4c

^{1}H NMR



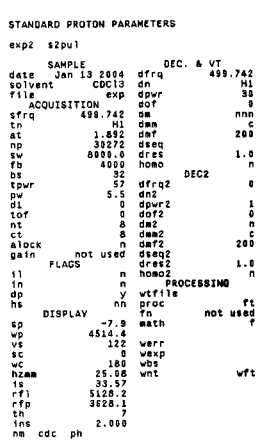
^{13}C NMR





4d

^{1}H NMR



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STANDARD PROTON PARAMETERS

exp2  szpul

        SAMPLE                    DEC. & VT
date    Jan 13 2004       dfrq        499.742
solvent       CDCl3       dn               H1
file           exp        dpwr             38
     ACQUISITION          dof               0
sfrq        499.742       dm              nnn
tn               H1       dmm               c
at            1.892       dmf             200
np            39272       dseq
sw           8000.0       dres            1.8
fb             4000       homo              n
bs               32                DEC2
tpwr             57       dfrq2             0
pw              5.5       dn2
d1                0       dpwr2             1
tof               0       dof2              0
nt                8       dm2               n
ct                8       dmm2              c
alock             n       dmf2            200
gain     not used         dseq2
                          dres2           1.8
     FLAGS                homo2             n
il                n                PROCESSING
in                n       wtfile
dp                y       proc             ft
hs               nn       fn          not used
     DISPLAY              math              f
sp             -7.9
wp           4514.4
vs              122       werr
sc                0       wexp
wc              180       wbs
hzmm          25.06       wnt              wft
is            33.57
rfl         5128.2
rfp         3828.1
th                7
ins           2.000
nm  cdc  ph
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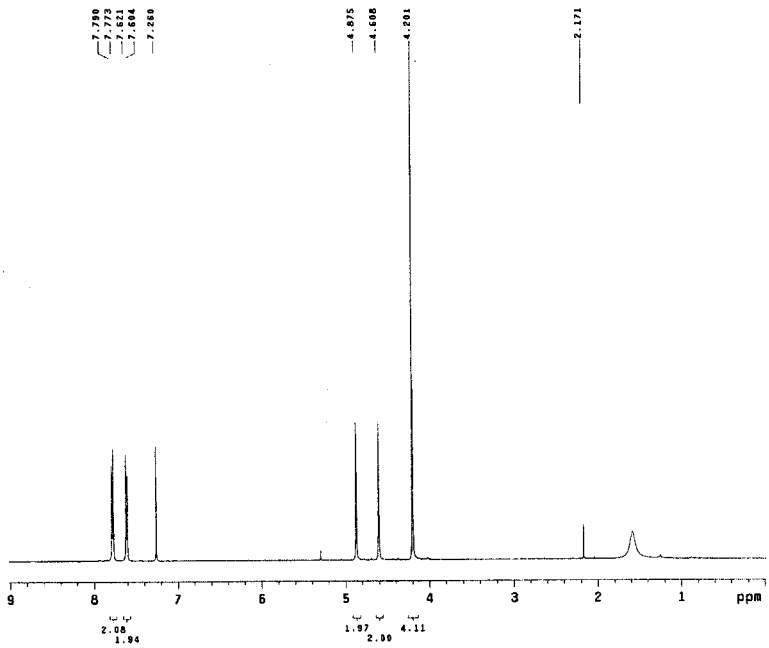
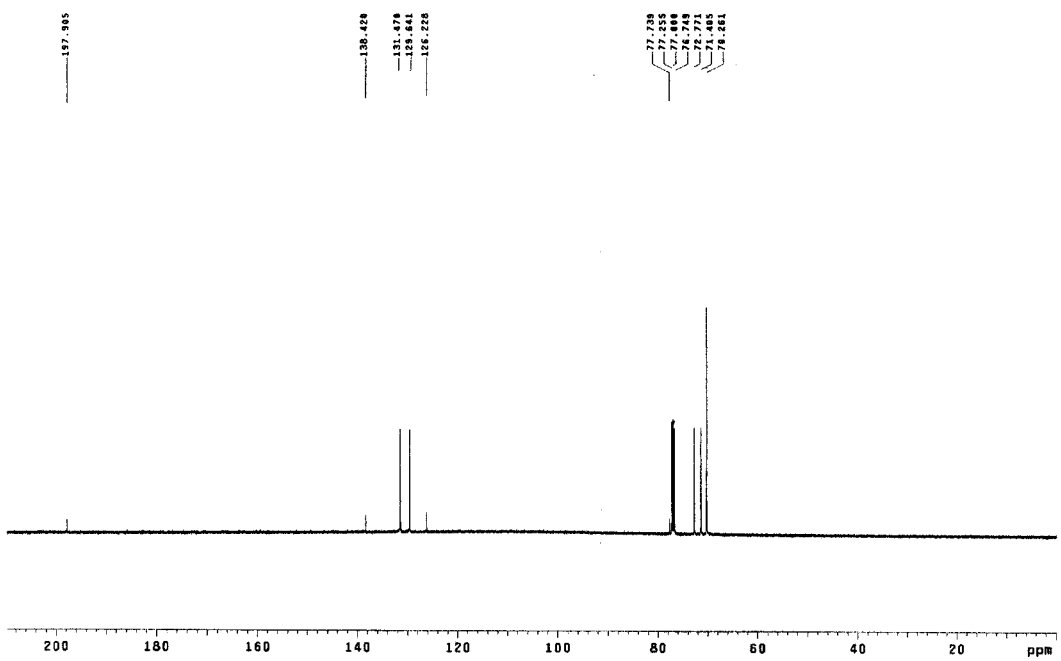
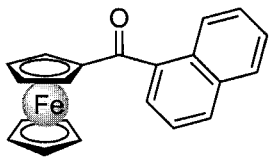


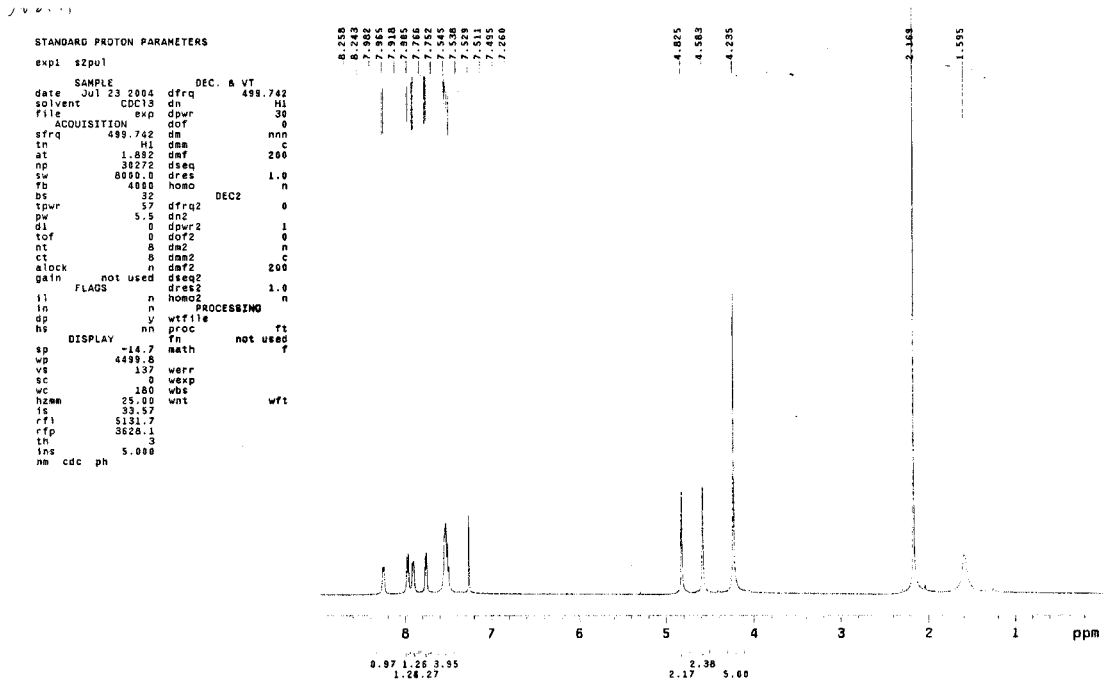
^{13}C NMR



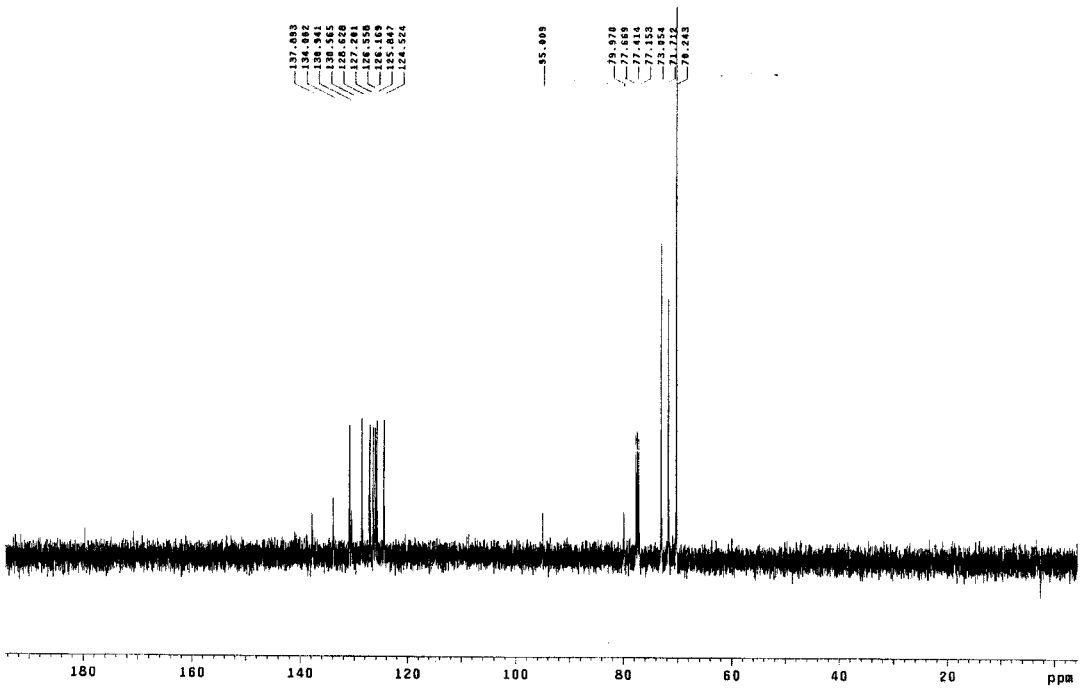


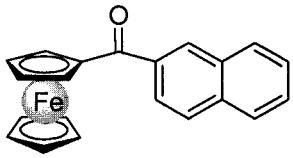
4e

^{1}H NMR



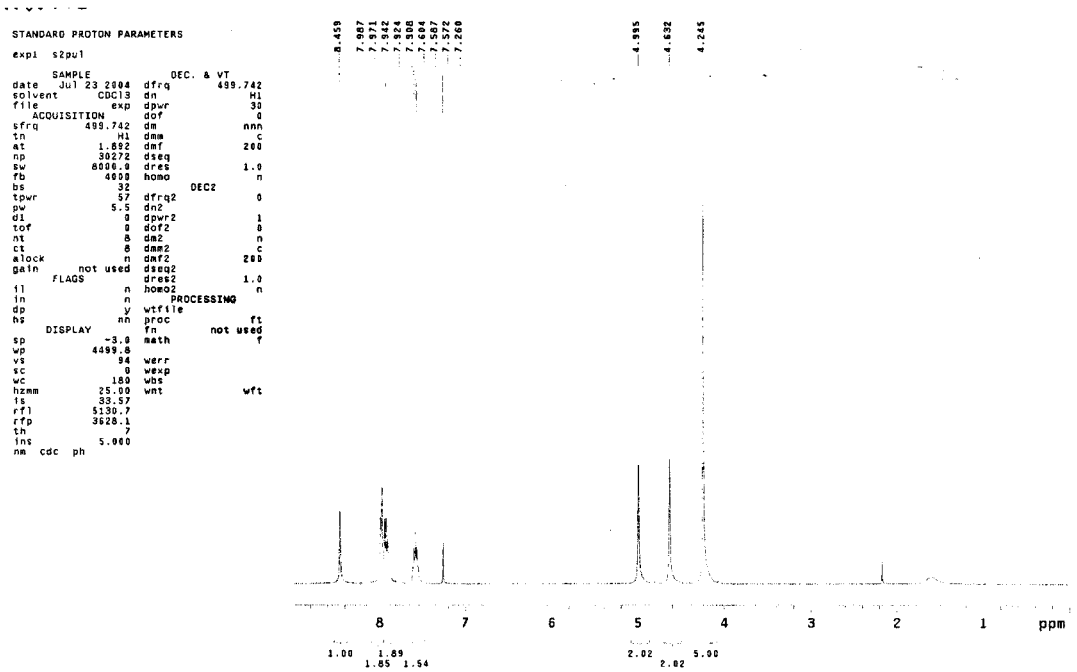
^{13}C NMR



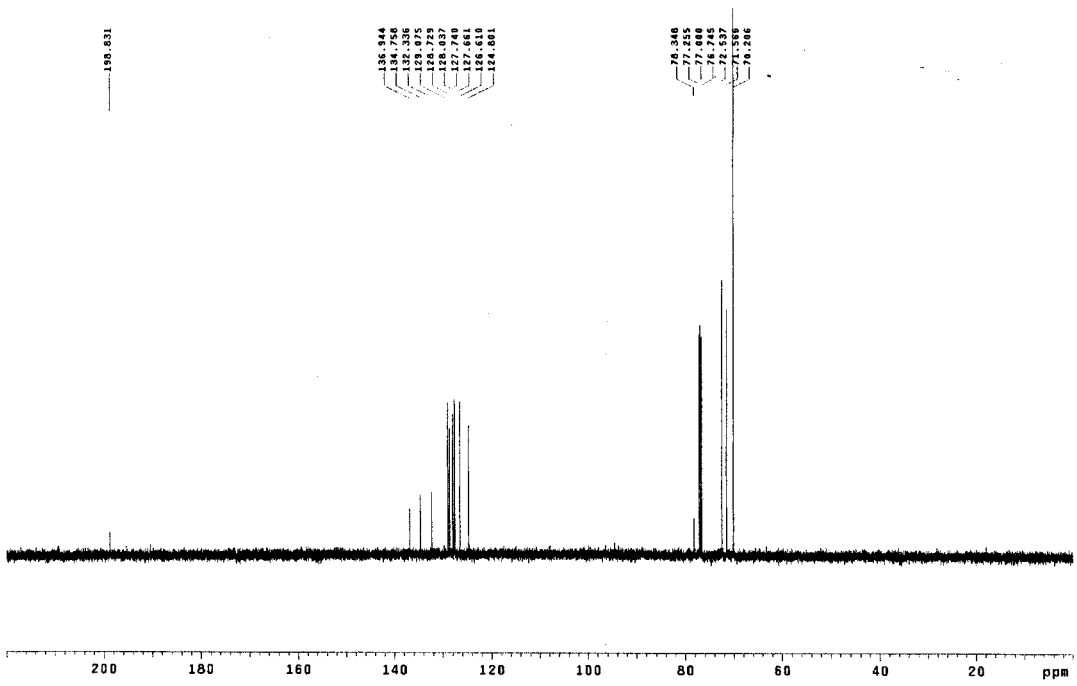


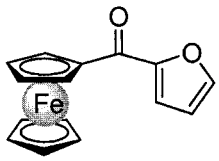
4f

^{1}H NMR



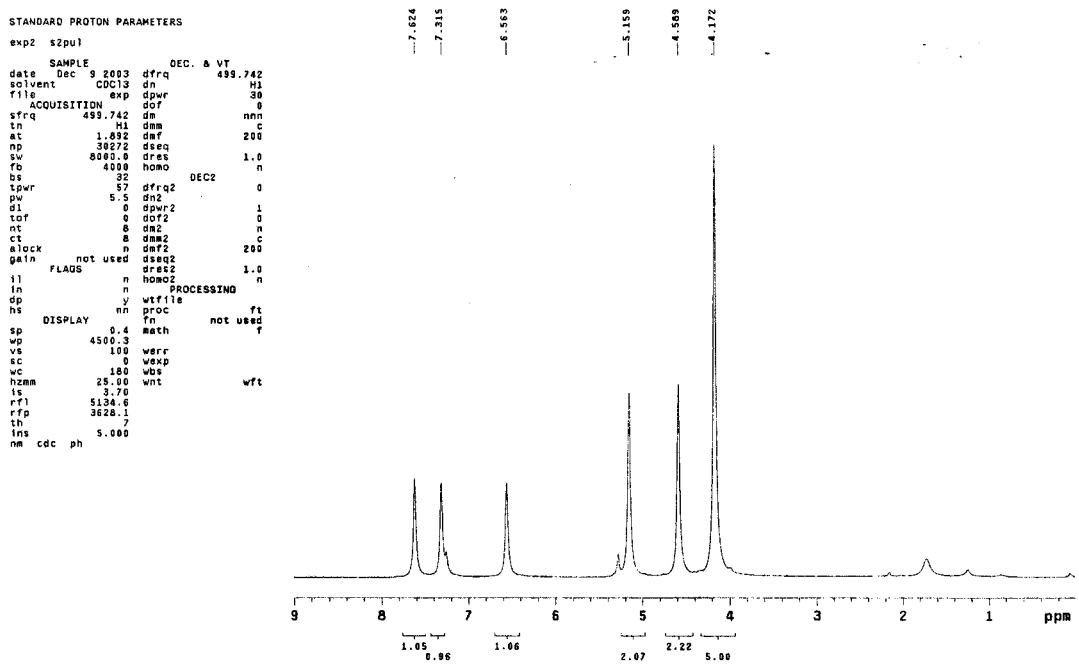
^{13}C NMR



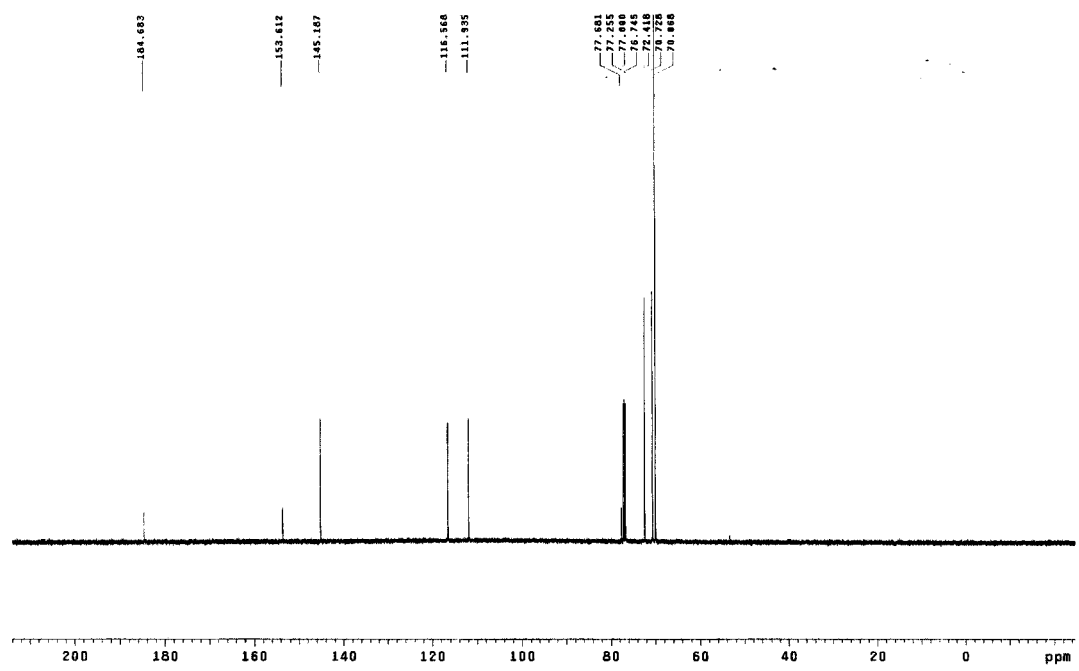


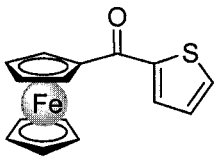
4g

^{1}H NMR



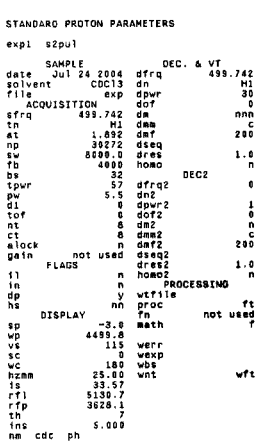
^{13}C NMR





4h

^{1}H NMR



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STANDARD PROTON PARAMETERS

expl  s2pul

      SAMPLE                DEC. & VT
date    Jul 24 2004   dfrq        499.742
solvent       CDCl3   dn              H1
file            exp   dpwr            30
   ACQUISITION        dof              0
sfrq        499.742   dm             nnn
tn              H1    dmm              c
at            1.892   dmf            200
np            39272   dseq
sw           8000.0   dres           1.0
fb             4000   homo             n
bs               32          DEC2
tpwr             57   dfrq2            0
pw              5.5   dn2
d1                0   dpwr2            1
tof               0   dof2             0
nt                8   dm2              n
ct                6   dmm2             c
alock             n   daf2           200
gain     not used     dseq2
      FLAGS           dres2          1.0
il                n   homo2            n
in                n        PROCESSING
dp                y   wtfile
hs               nn   proc            ft
      DISPLAY         fn       not used
sp             -3.8   math             f
wp           4499.8
vs              115   werr
sc                0   wexp
wc              180   wbs
hzmm          25.00   wnt            wft
is            33.57
rfl          5130.7
rfp          3628.1
th                7
ins           5.000
nm  cdc  ph
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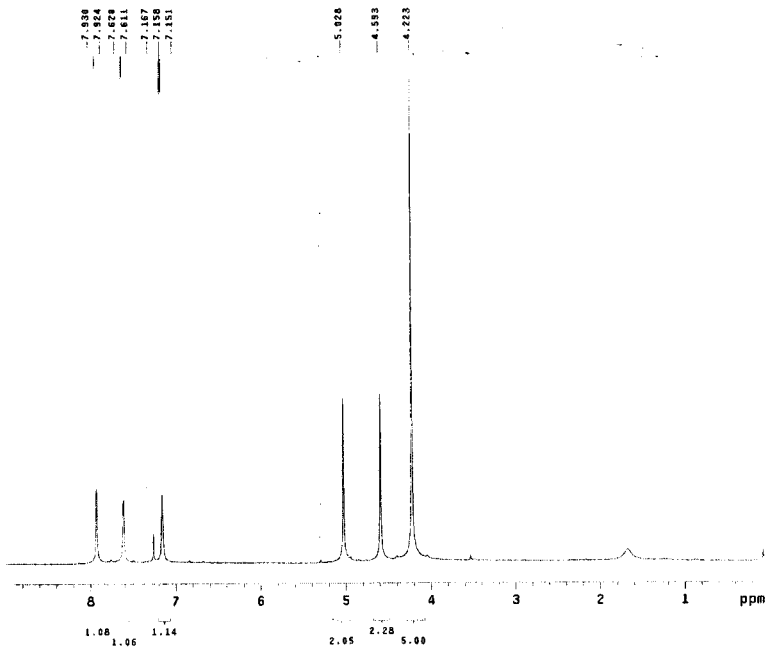
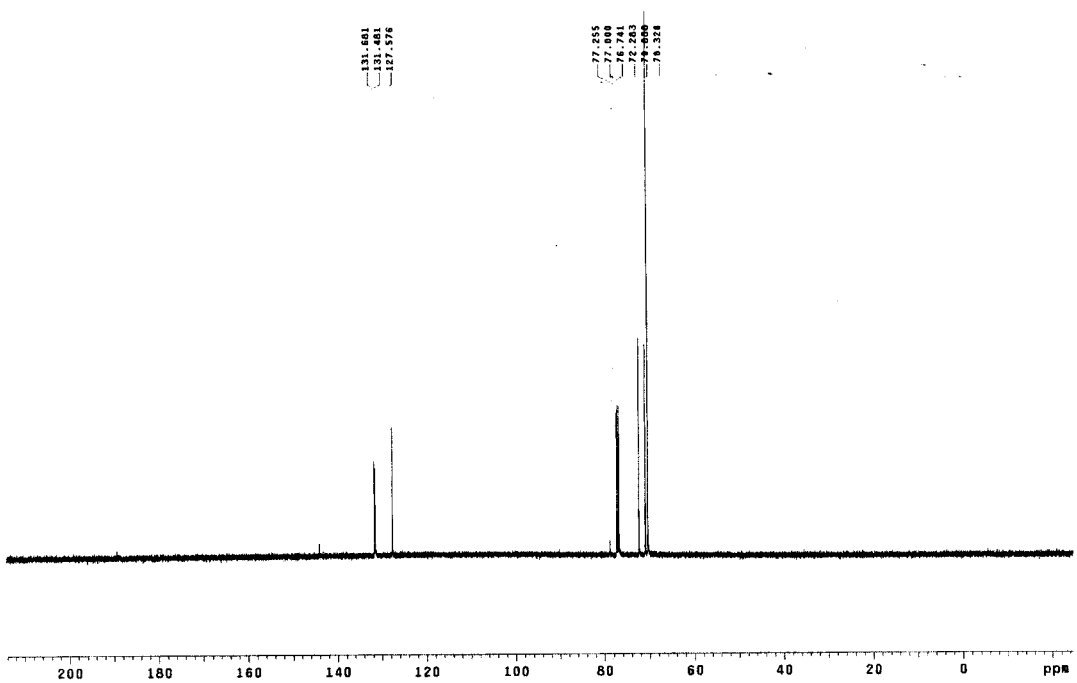
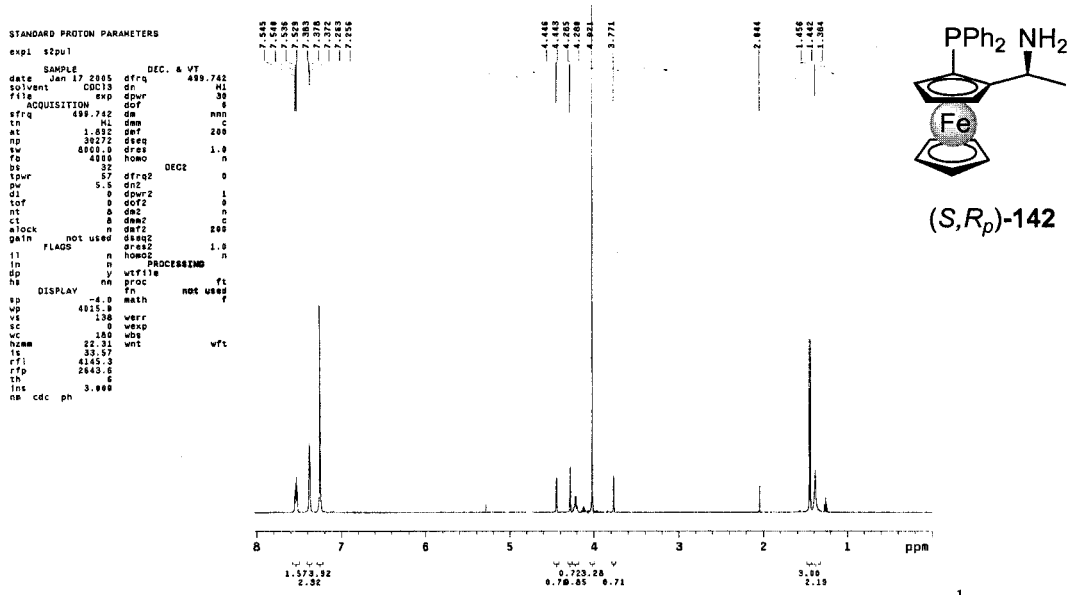


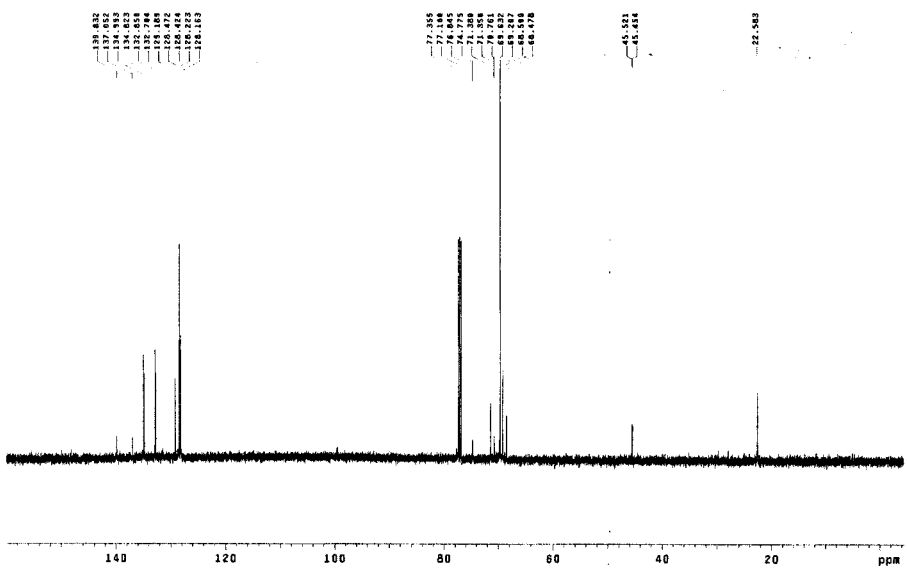
^{13}C NMR



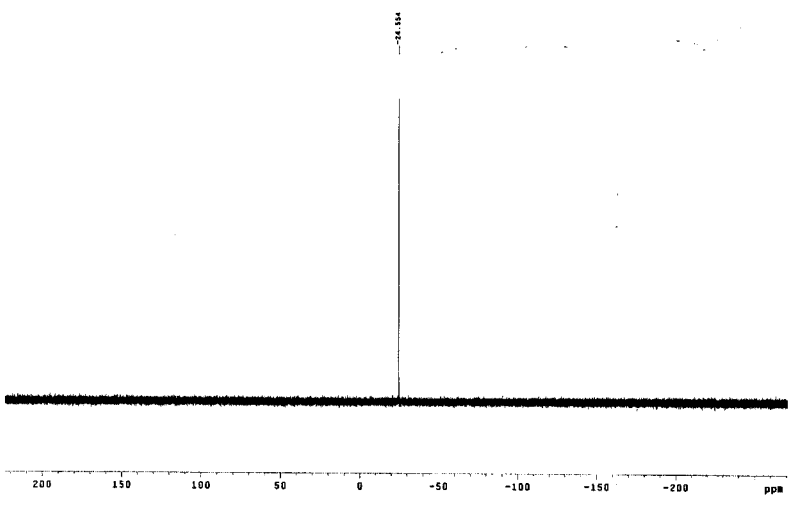


(*S*,*R*$_p$)-**142**

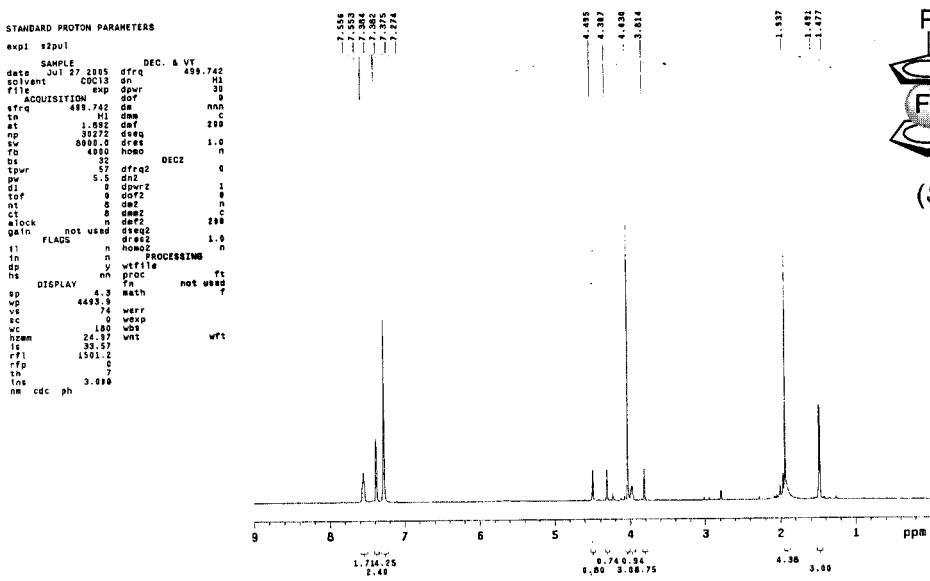
^{1}H NMR

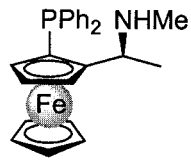


^{13}C NMR



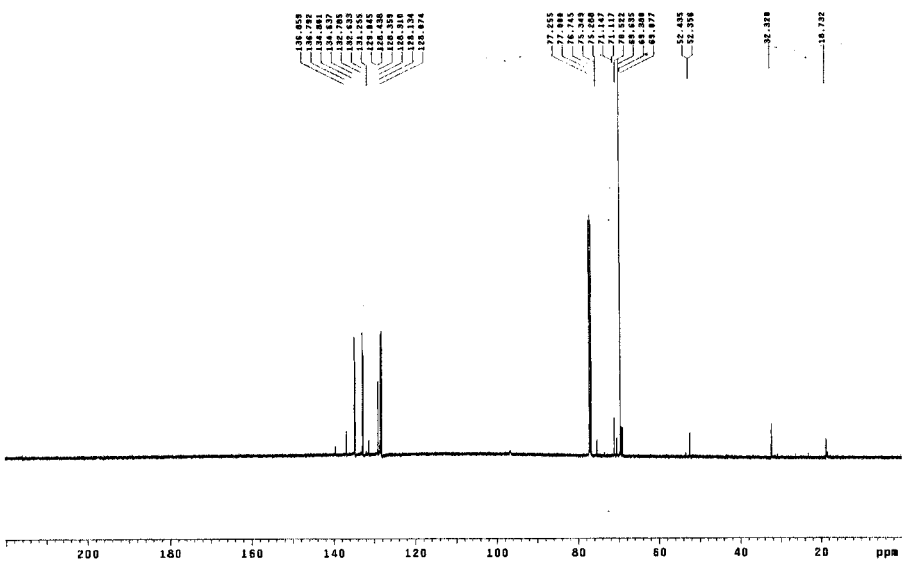
^{31}P NMR



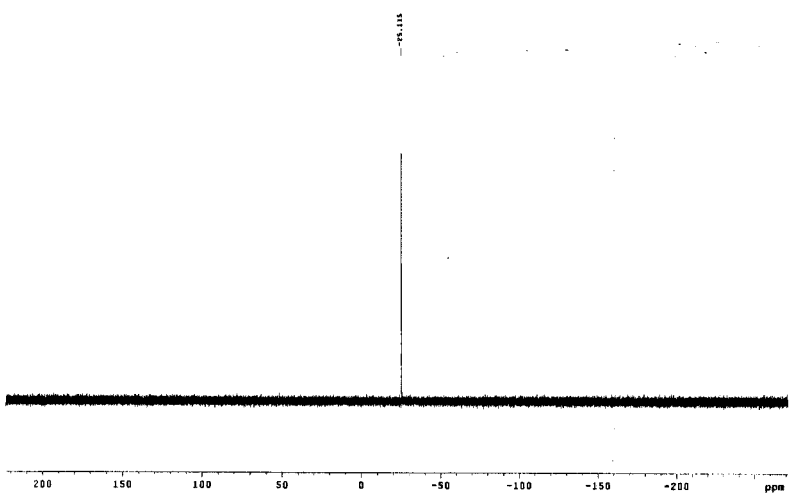


(S,R_p)-**143**

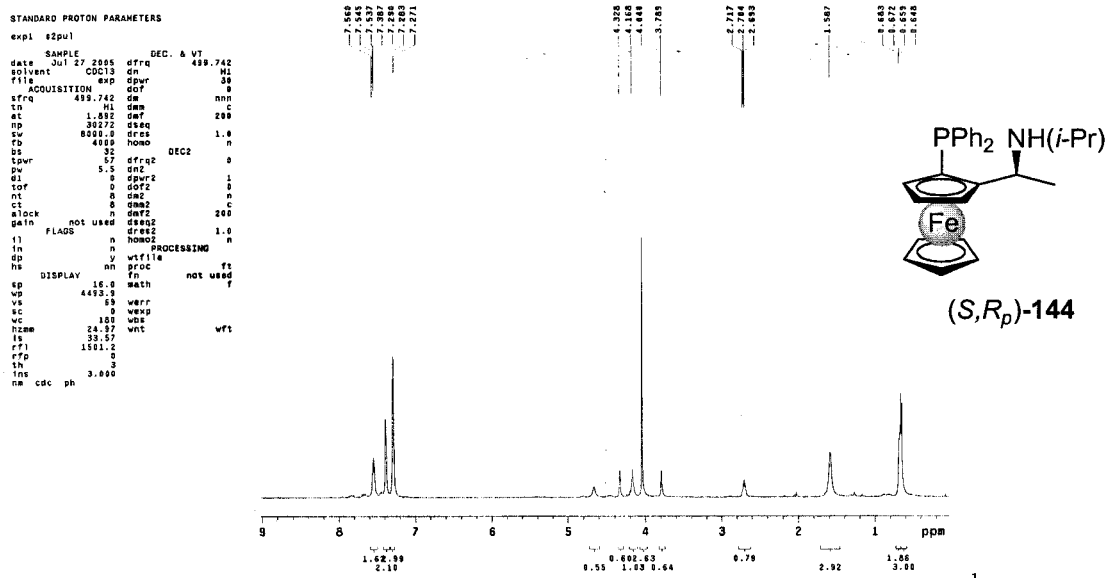
^{1}H NMR



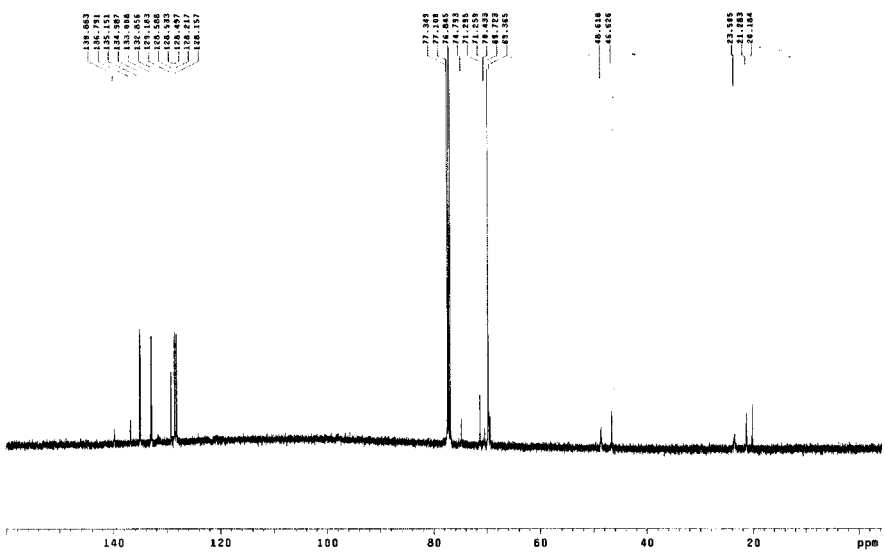
^{13}C NMR



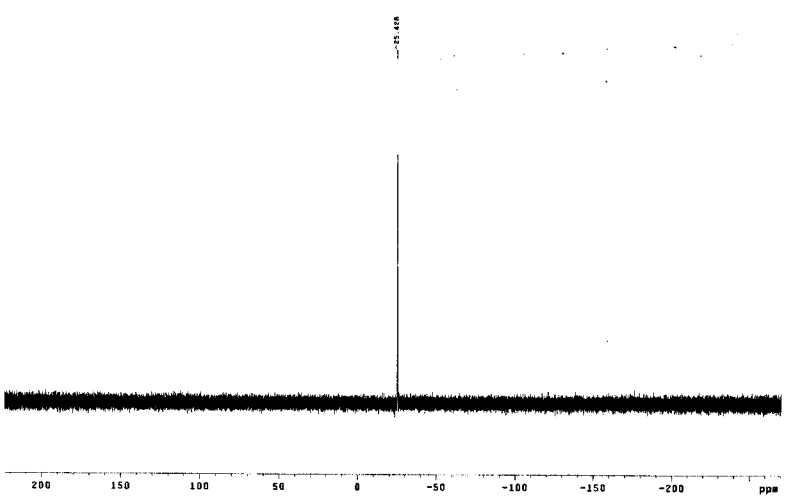
^{31}P NMR



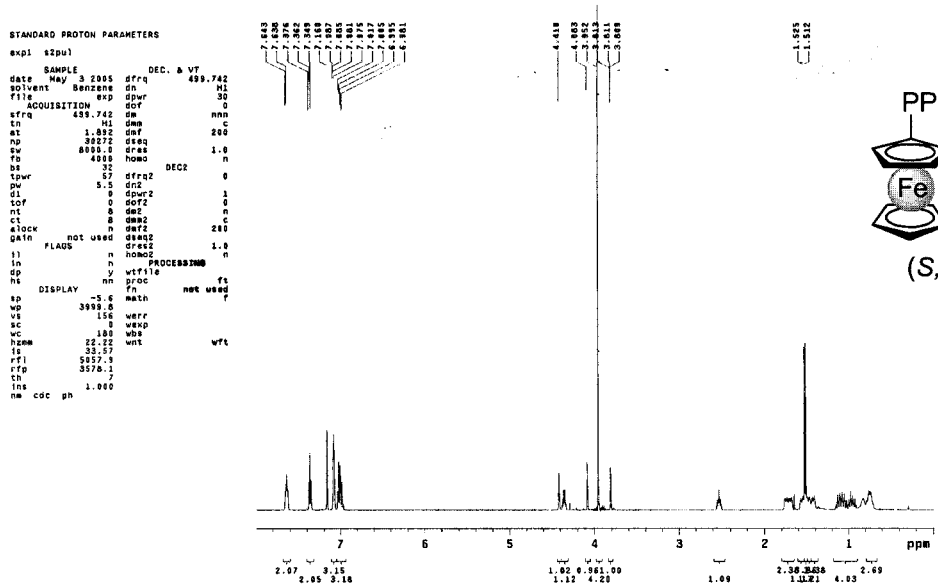
^{1}H NMR

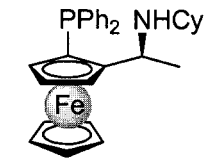


^{13}C NMR



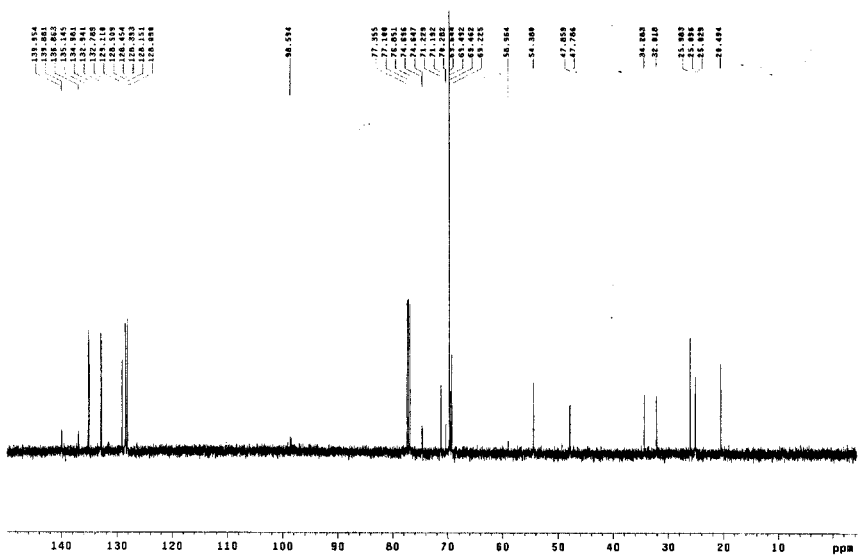
^{31}NMR



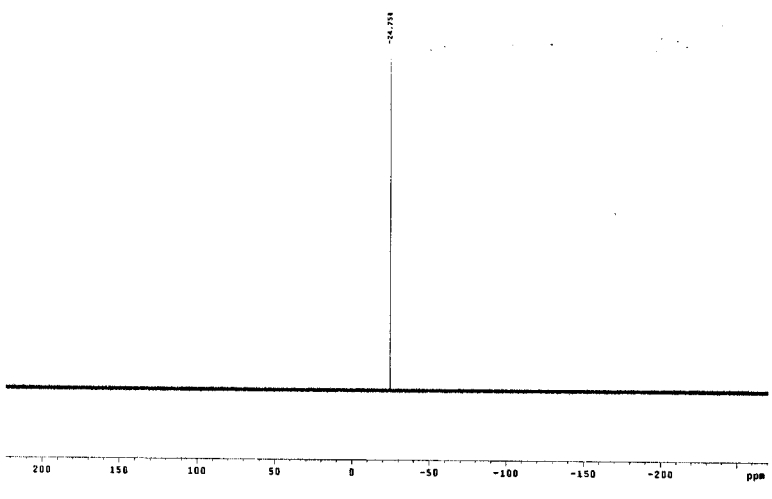


(S,R_p)-**145**

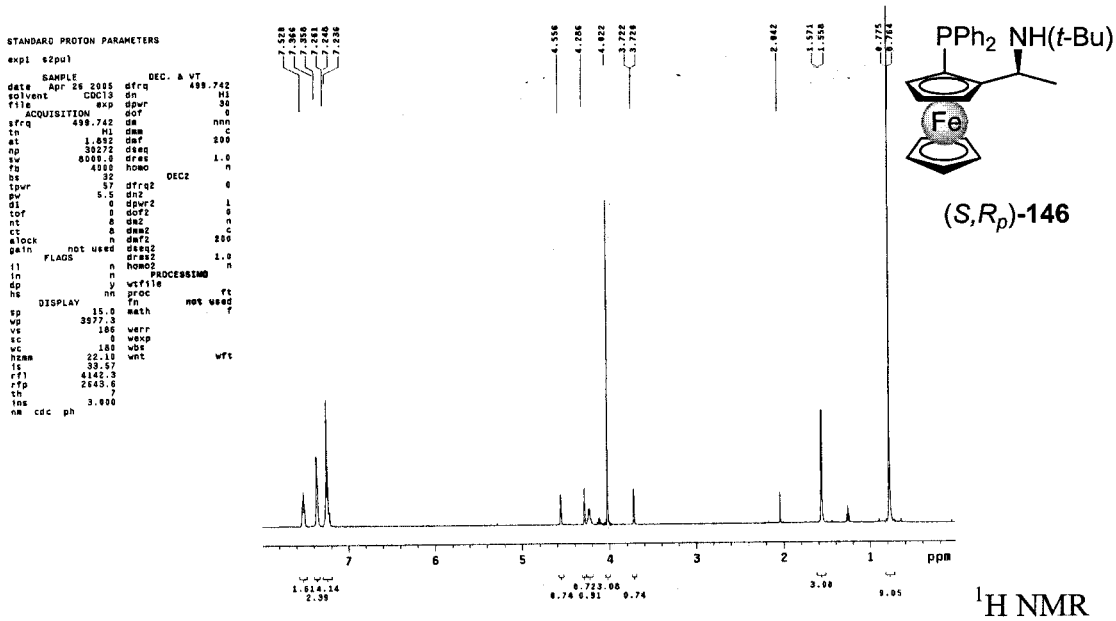
^{1}H NMR



^{13}C NMR

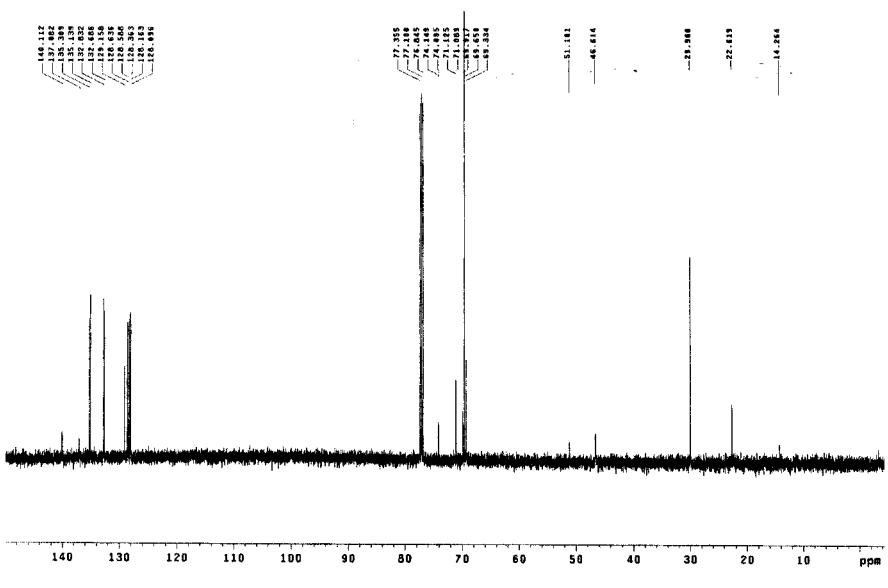


^{31}P NMR

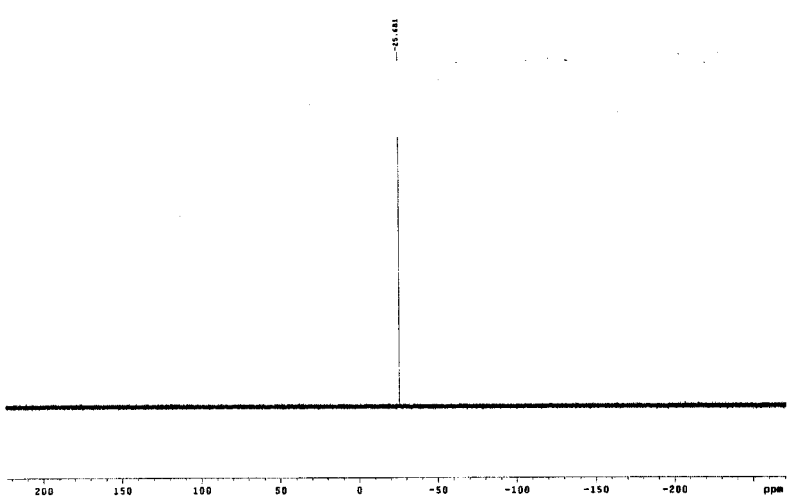


(S,R_p)-**146**

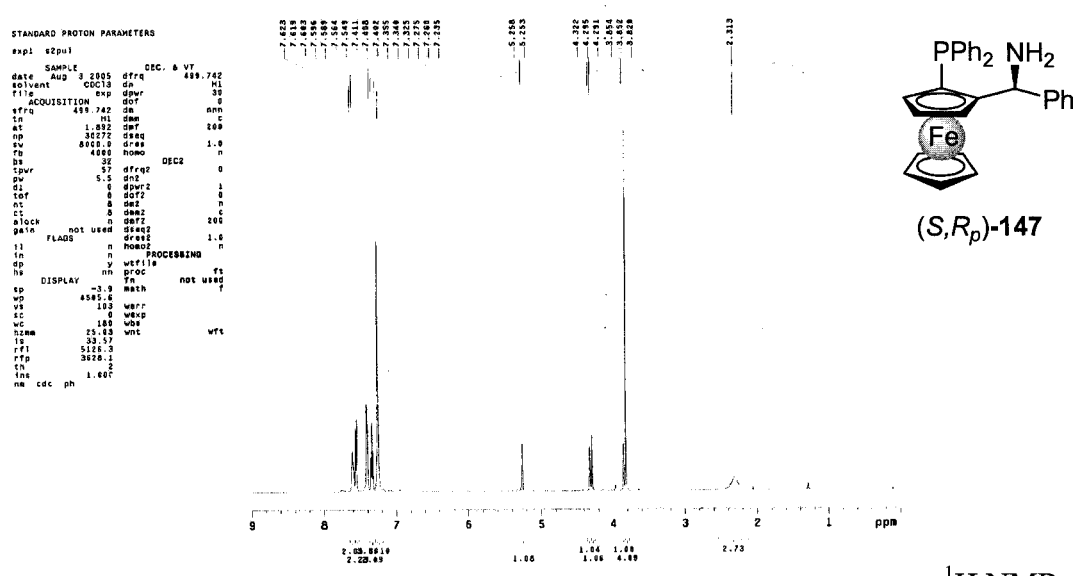
^{1}H NMR



^{13}C NMR

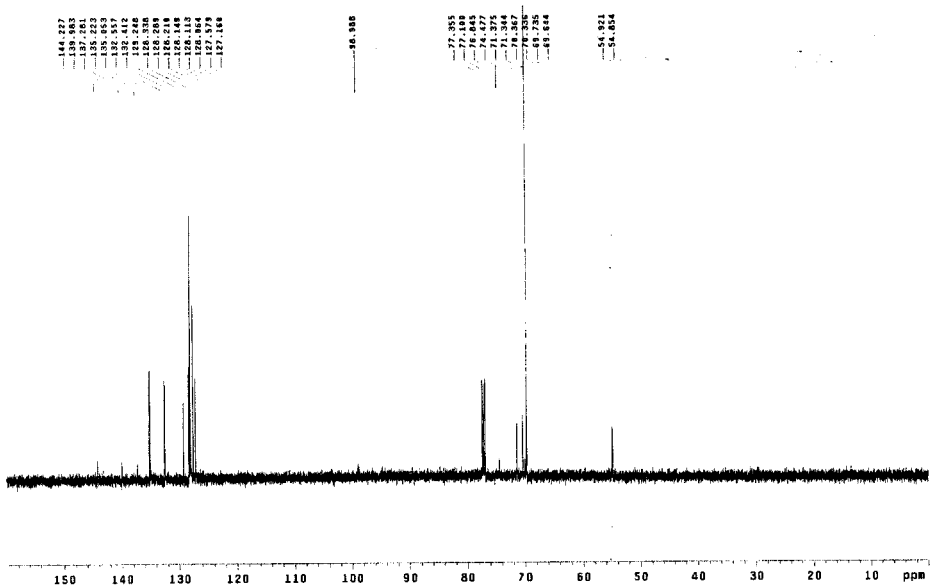


^{31}P NMR

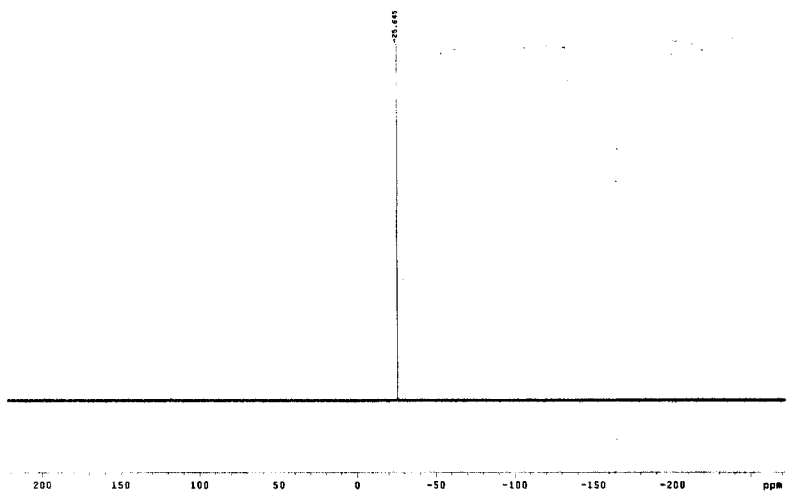


(*S*,R_p)-**147**

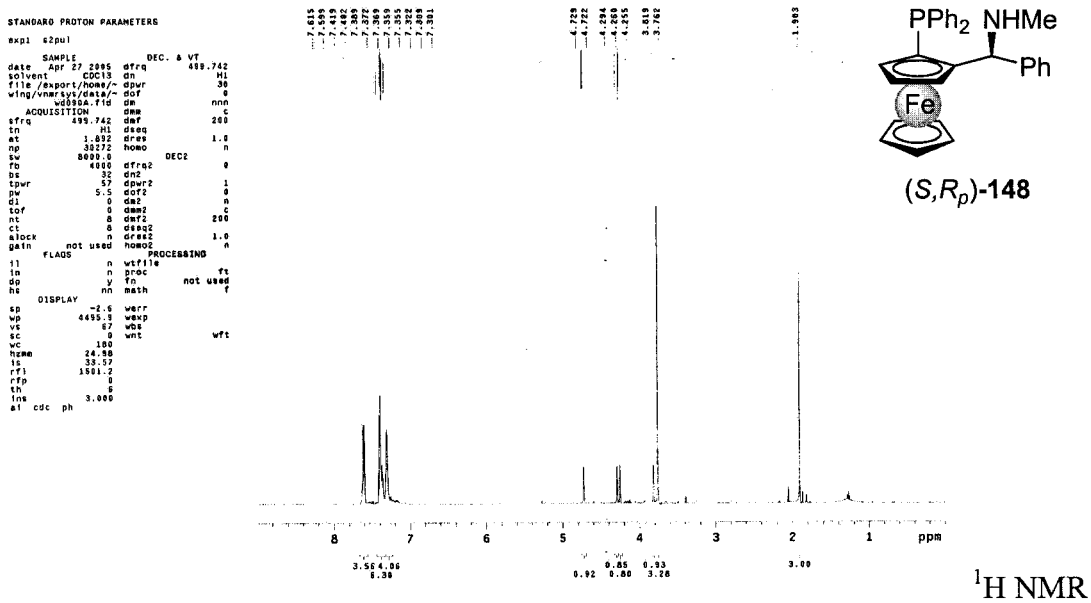
^{1}H NMR



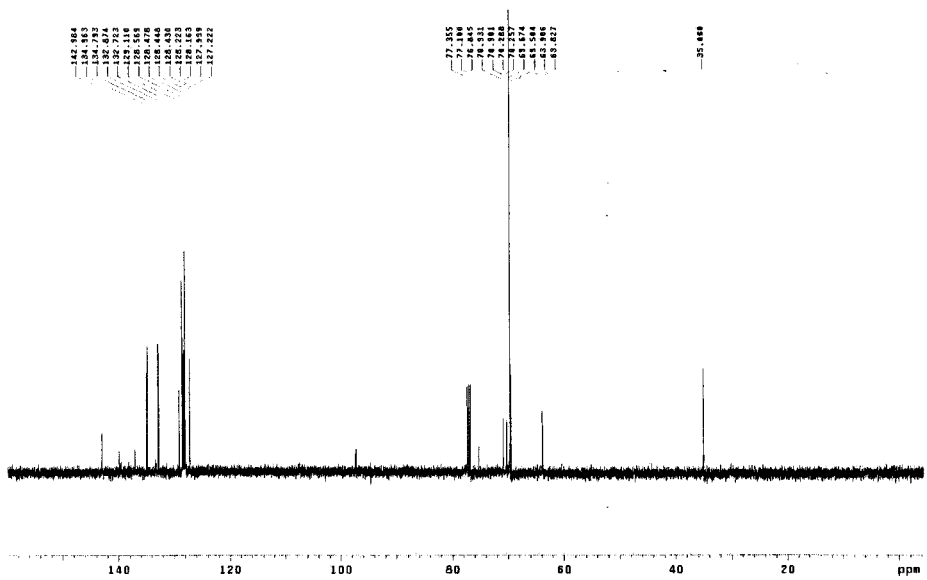
^{13}C NMR



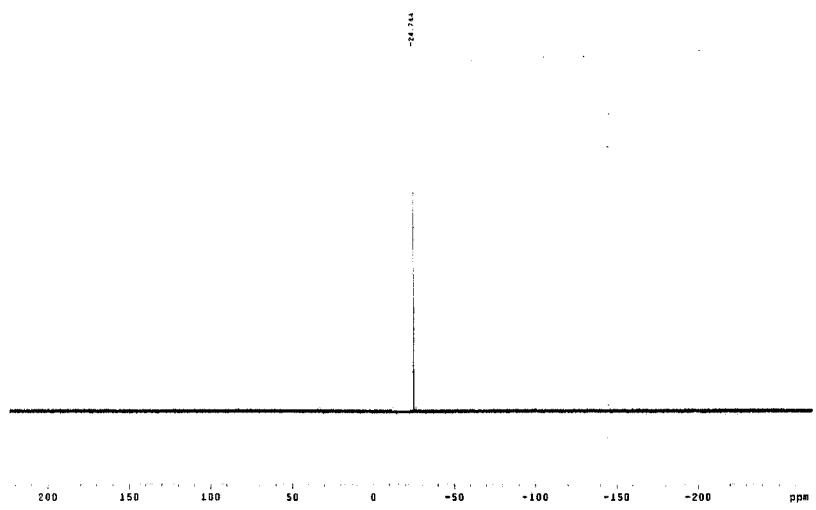
^{31}P NMR



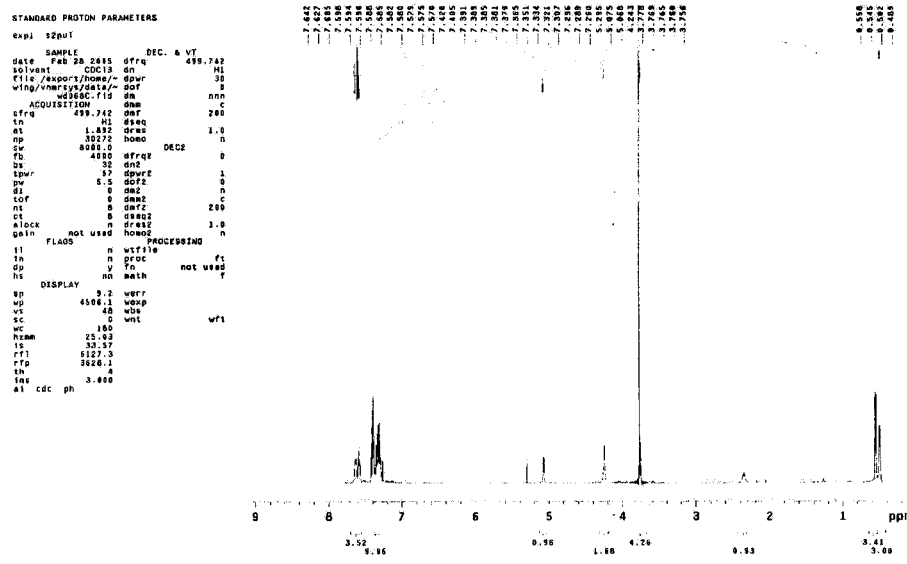
^{1}H NMR

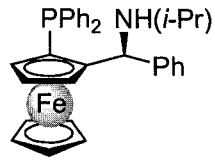


^{13}C NMR



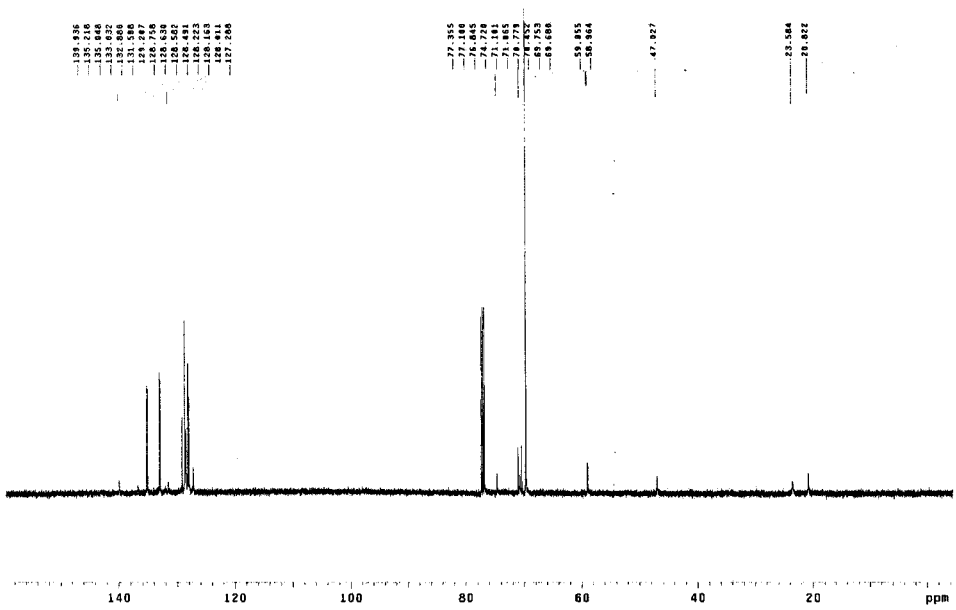
^{31}P NMR



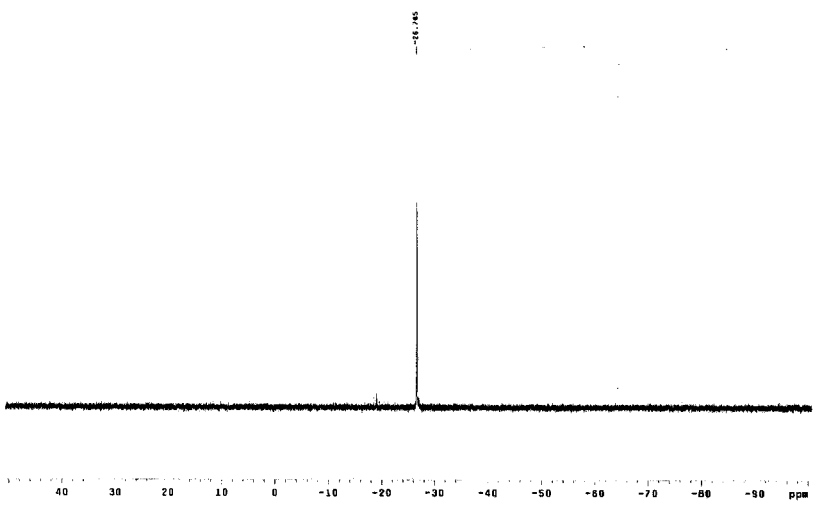


(S,R_p)-**149**

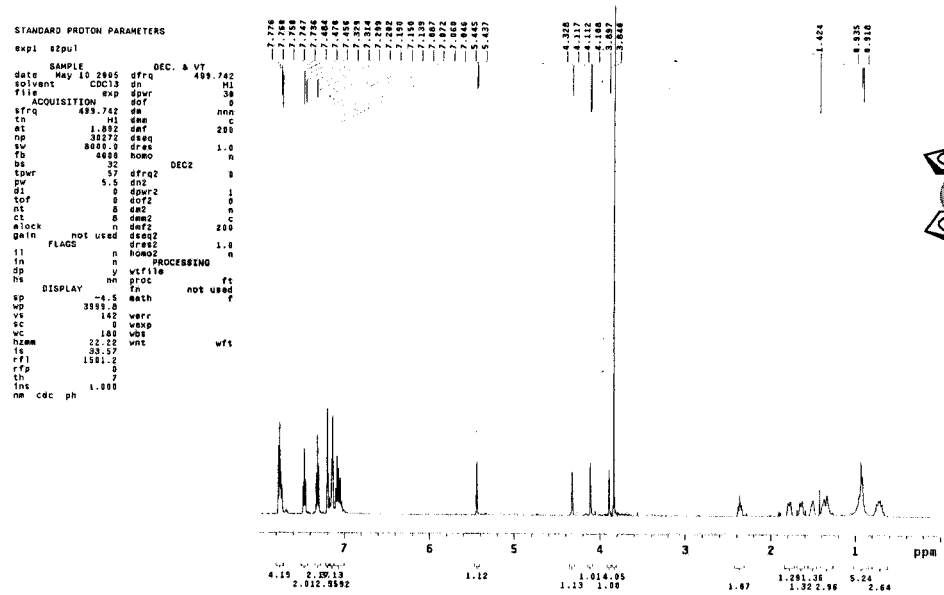
^{1}H NMR



^{13}C NMR

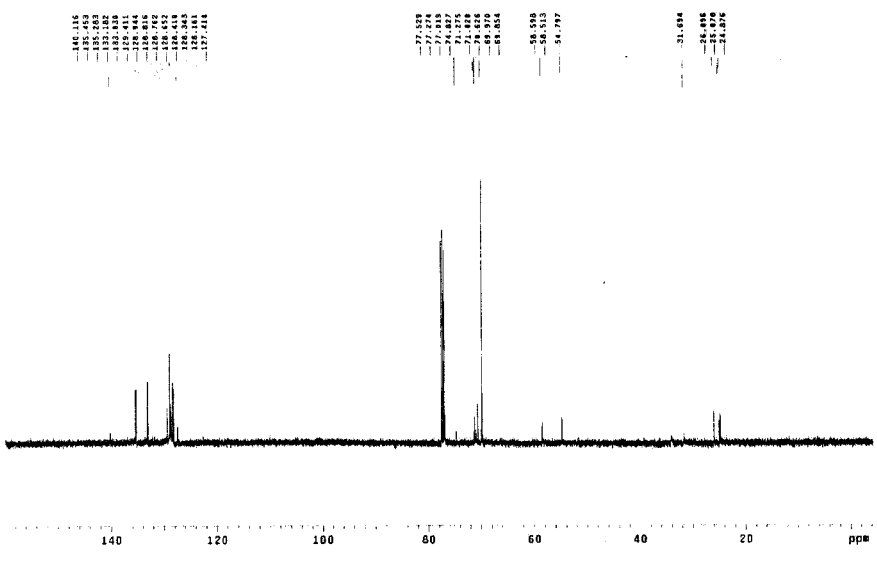


^{31}P NMR

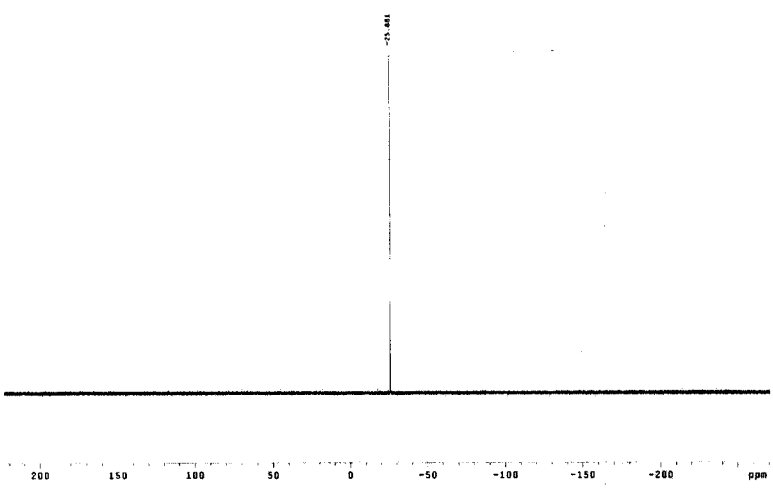


(S,R_p)-**150**

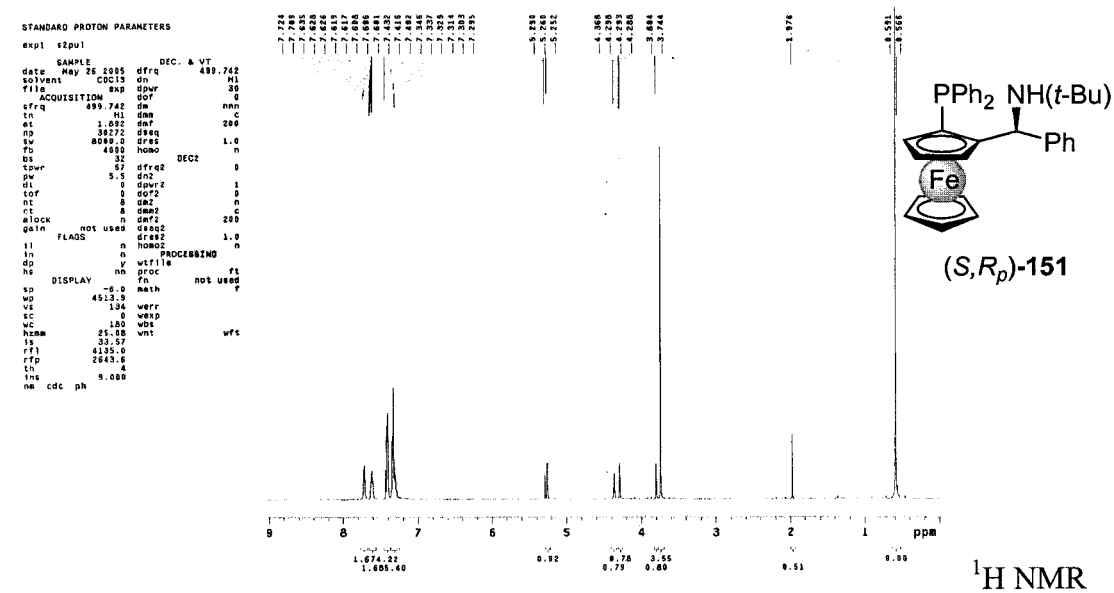
^{1}H NMR



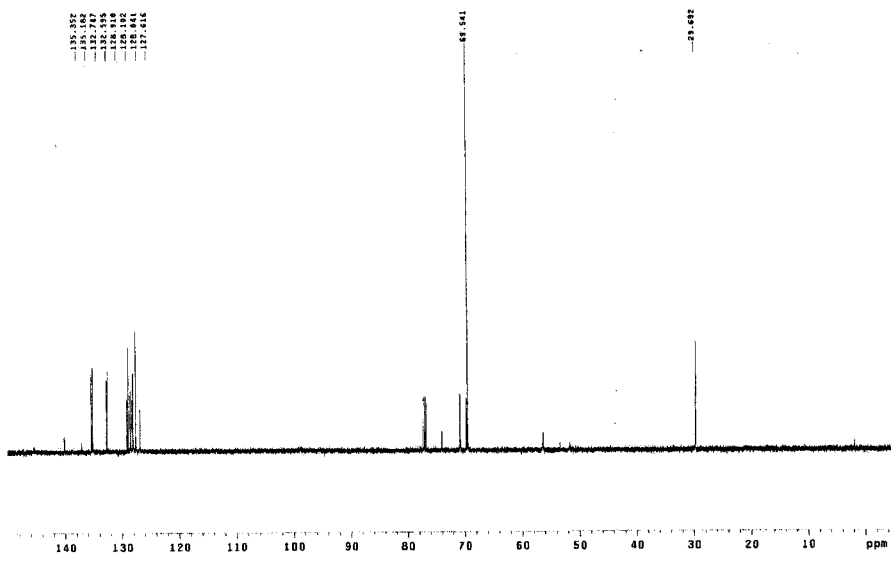
^{13}C NMR



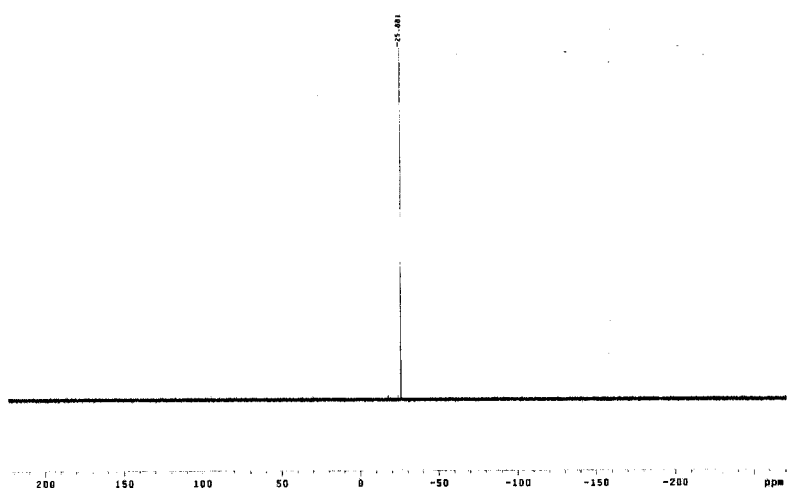
^{31}P NMR



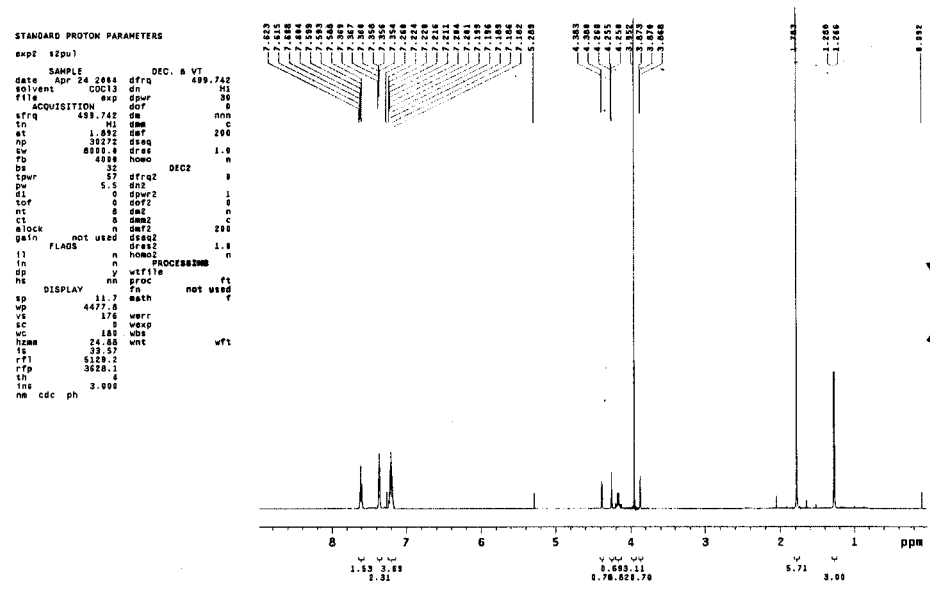
^{1}H NMR



^{13}C NMR



^{31}P NMR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d1 0
tof 0
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ct 8
alock n
gain not used
FLAGS
DISPLAY
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wp 4477.8
vs 176
sc 0
wc 188
hzmm 24.88
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drss 1.0
homo n
DEC2
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dmm2 c
dmf2 200
dseq2
drss2 1.0
homo2 n
PROCESSING
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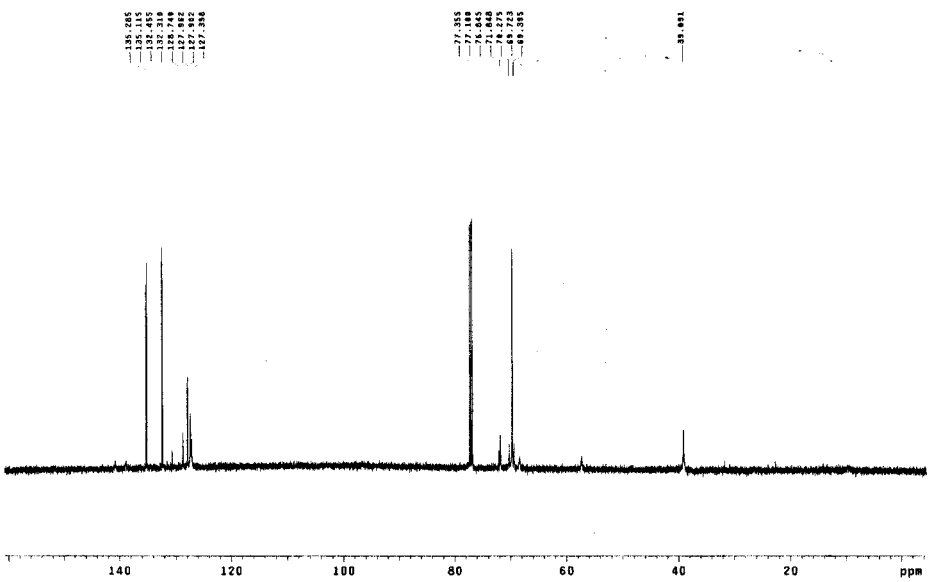
wnt wft
PPh2 NMe2
Fe
(S)-154a
ppm
1H NMR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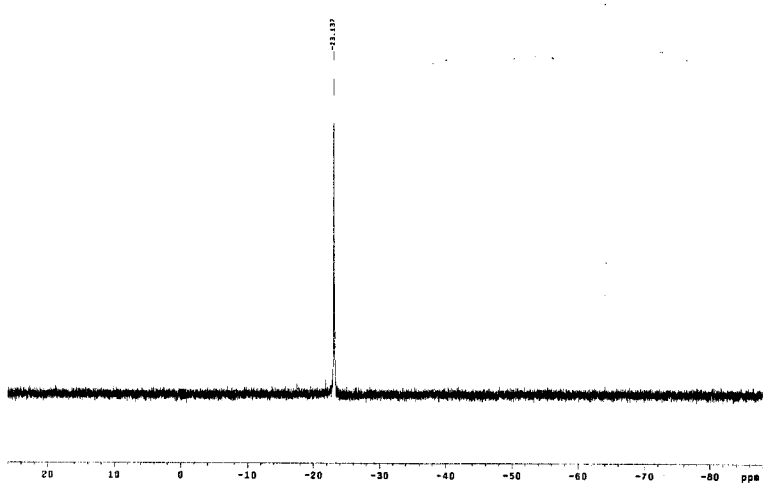
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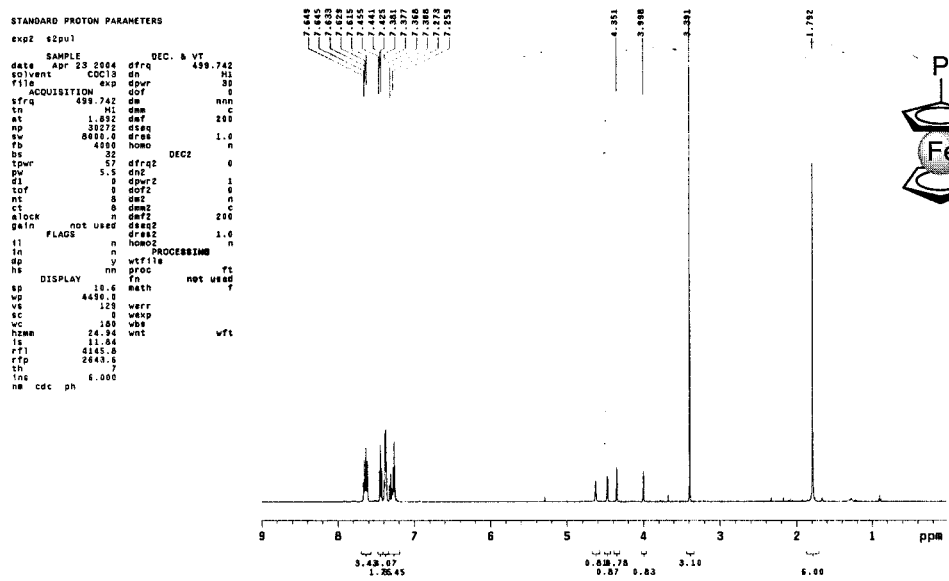
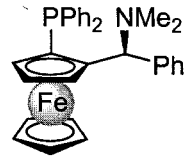
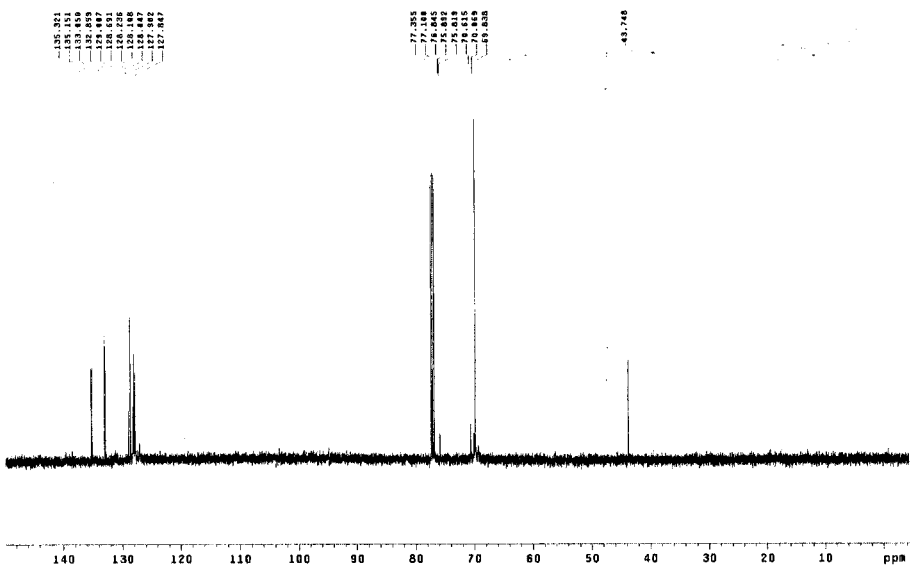


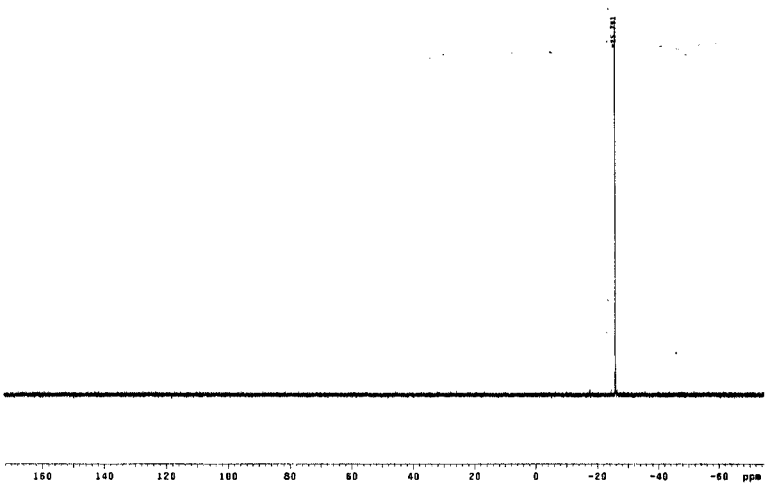


(*S*)-**154b**

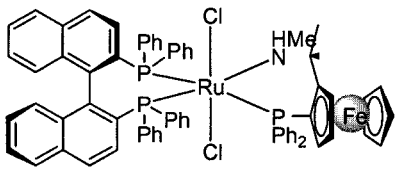
^{1}H NMR



^{13}C NMR

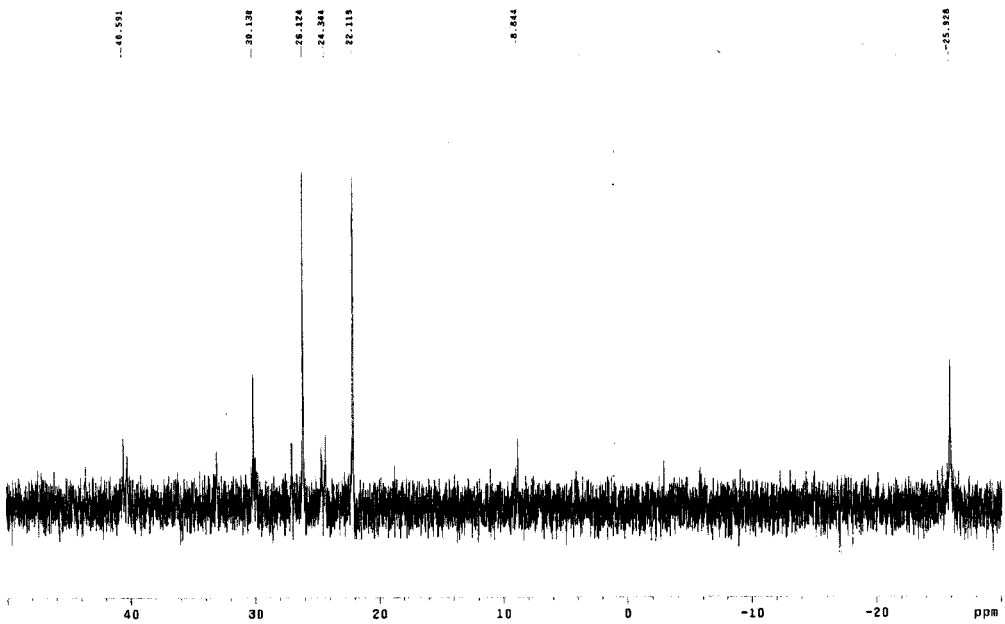


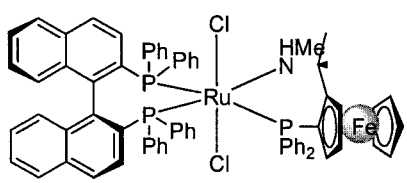
^{31}P NMR



(*R*,*S*,*R*$_p$)-**155**

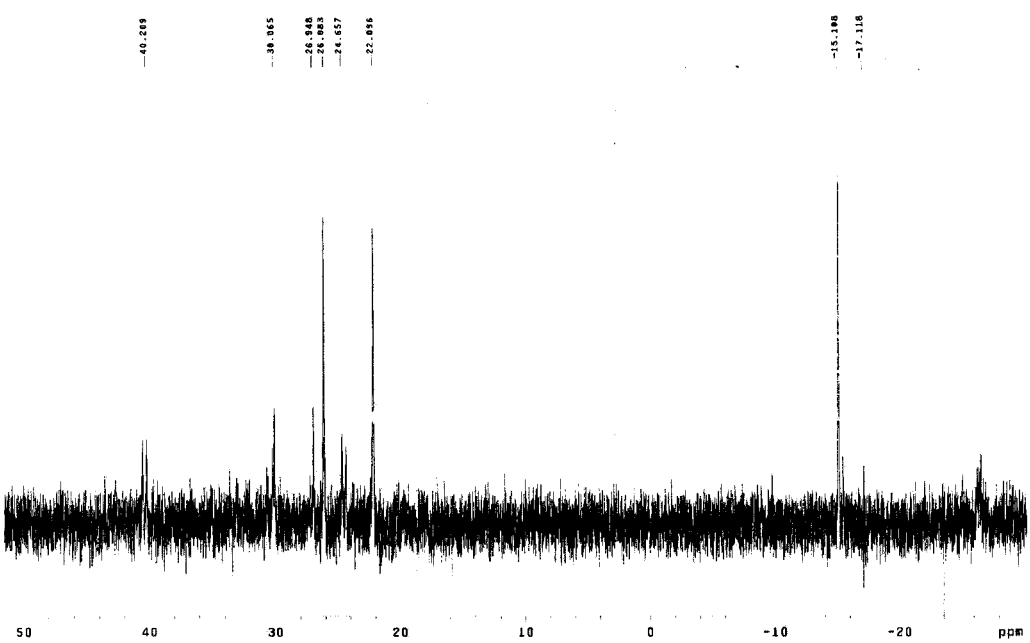
^{31}P NMR

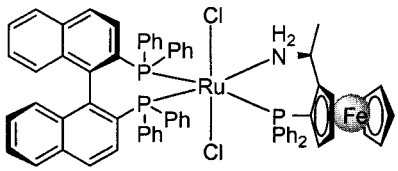




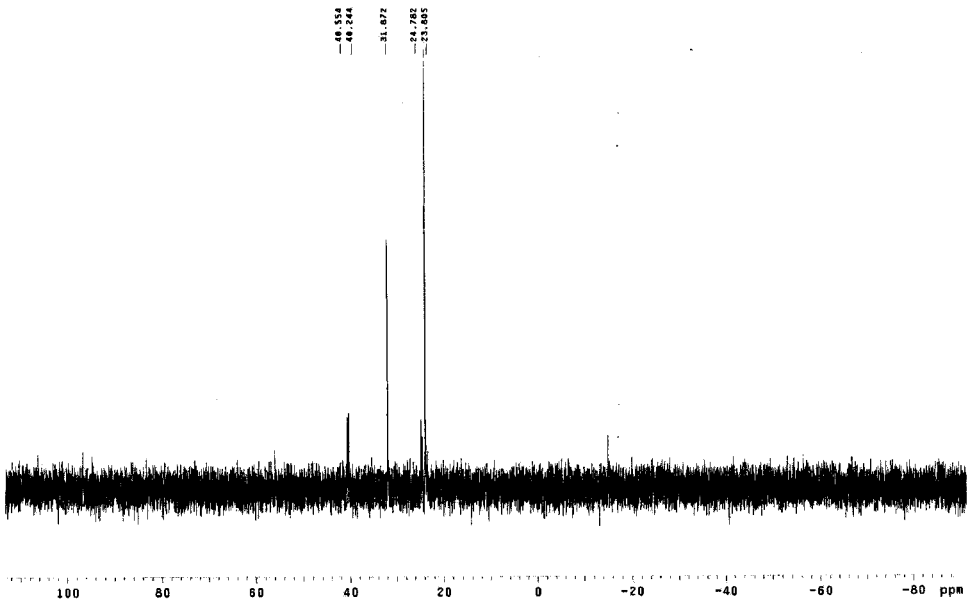
(*S*,*S*,*R*$_p$)-**155**

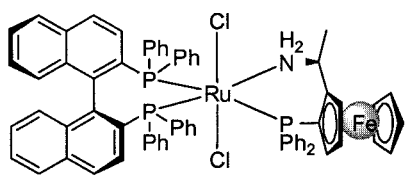
^{31}P NMR



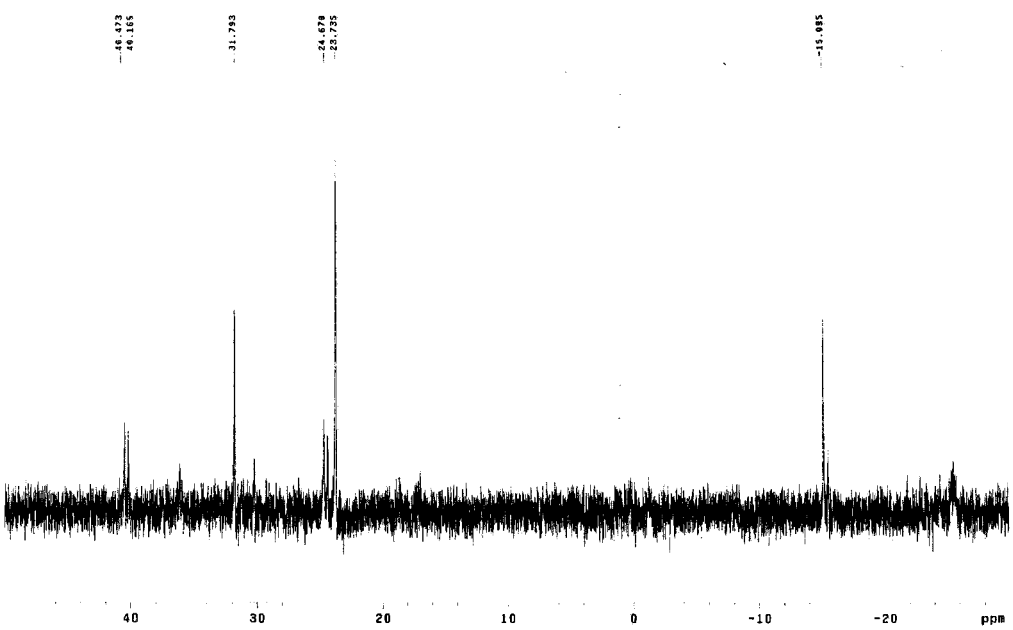


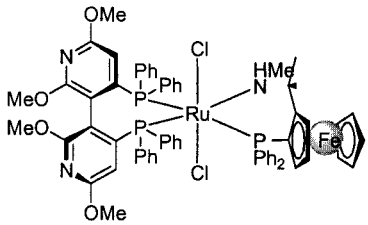
(*R*,*S*,*R*$_p$)-**156** ^{31}P NMR





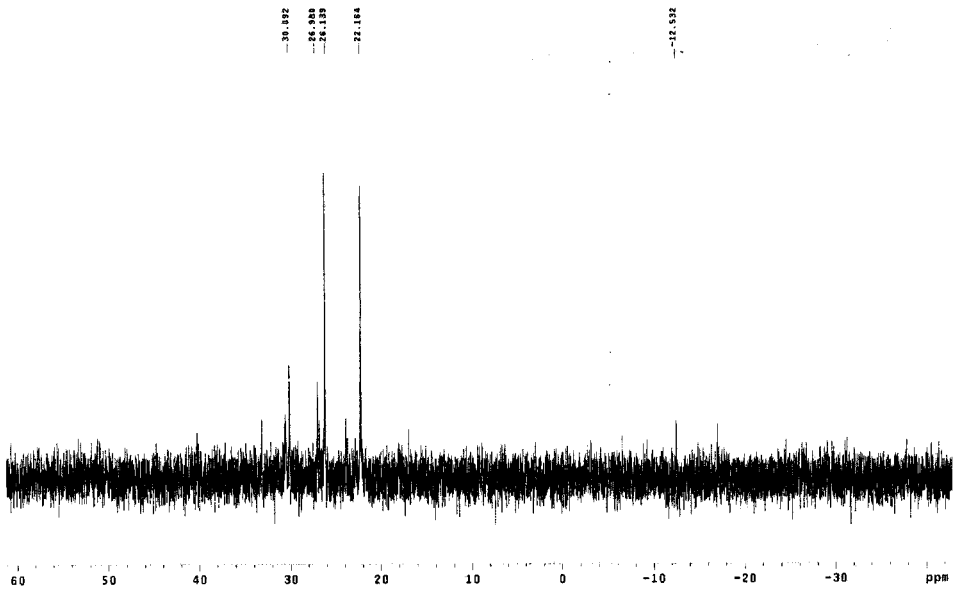
(*S*,*S*,*R*$_p$)-**156** ^{31}P NMR

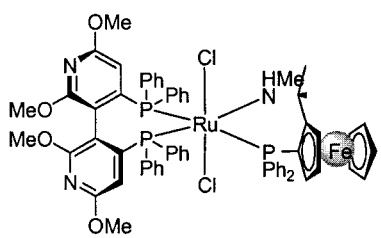




(R,S,R_p)-**157**

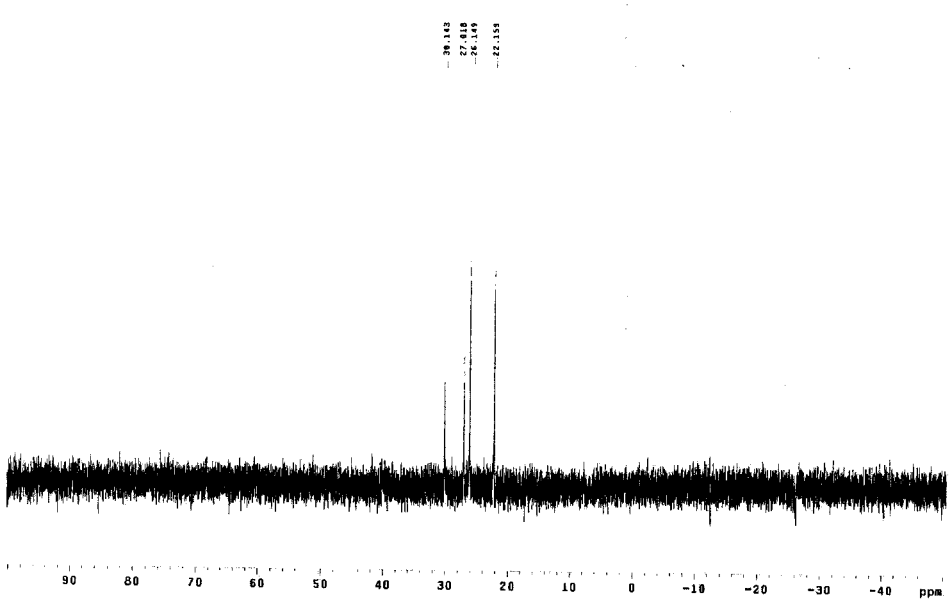
^{31}P NMR

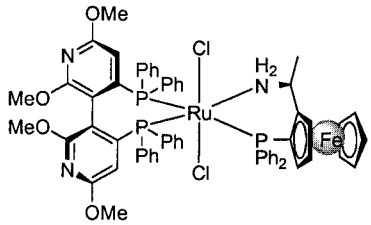




(S,S,R_p)-**157**

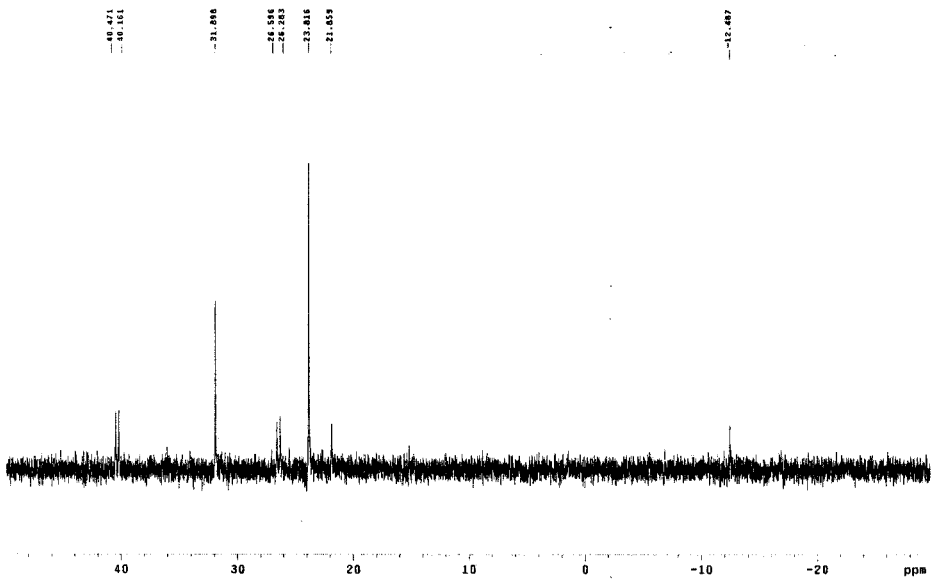
^{31}P NMR

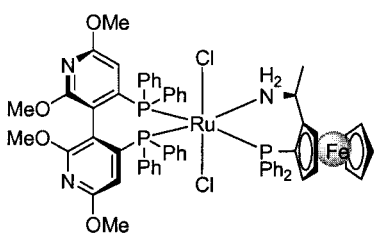




(*R*,*S*,*R*$_p$)-**158**

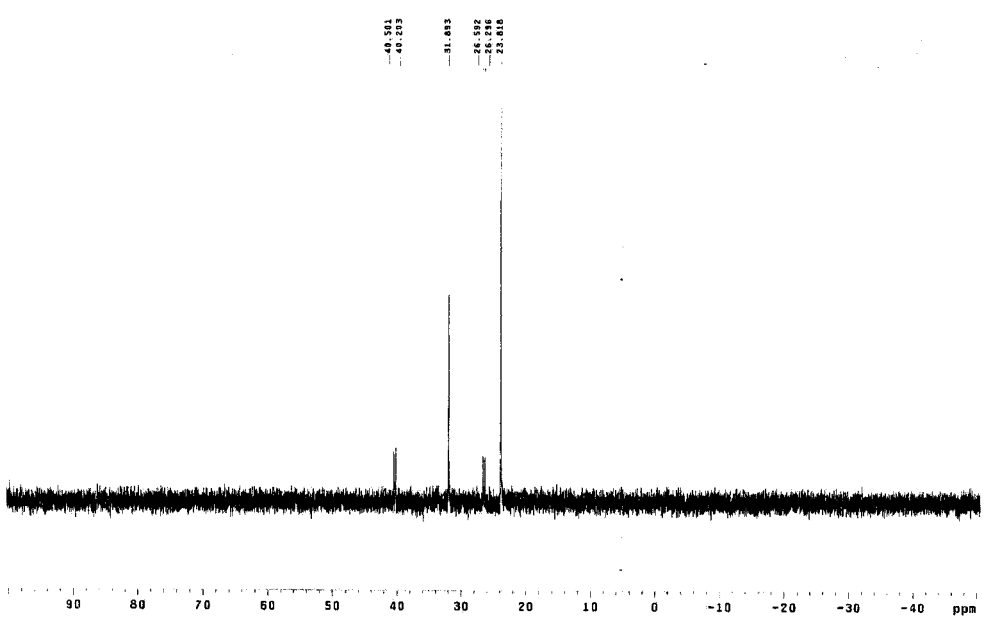
^{31}P NMR

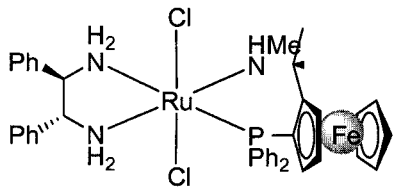




(*S*,*S*,*R*$_p$)-**158**

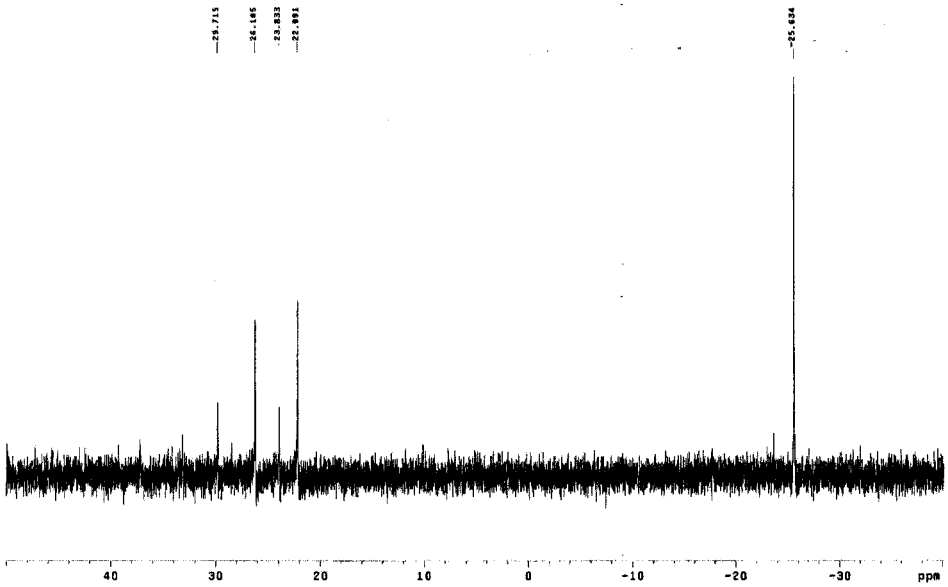
^{31}P NMR

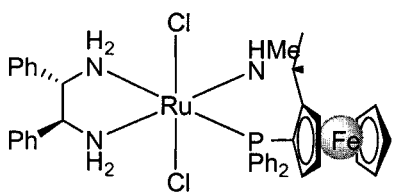




(*R*,*R*,*S*,R_p)-**159**

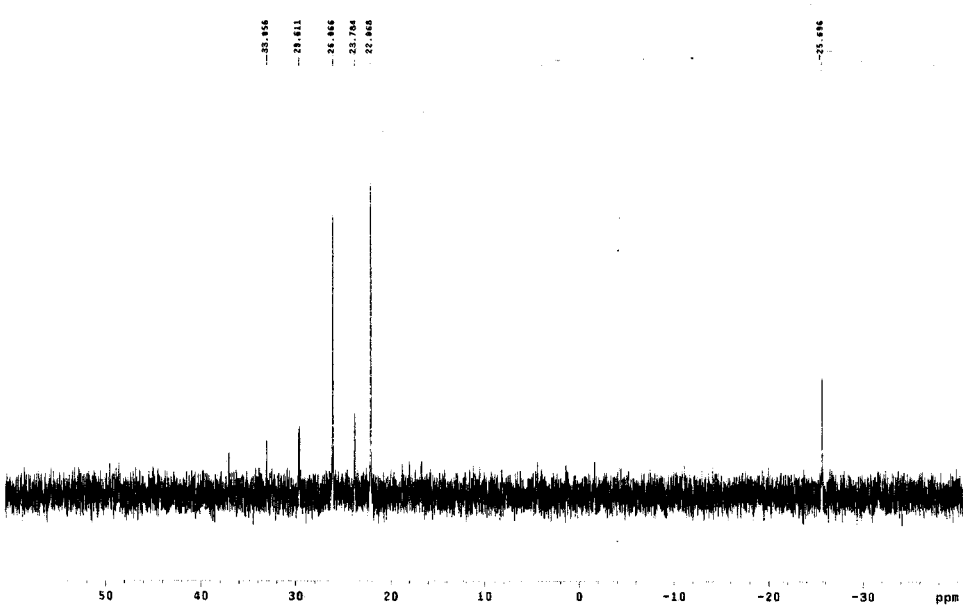
^{31}P NMR

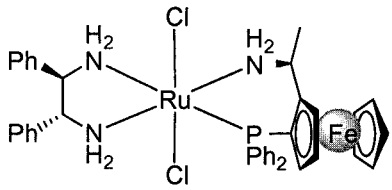




(*S*,*S*,*S*,R_p)-**159**

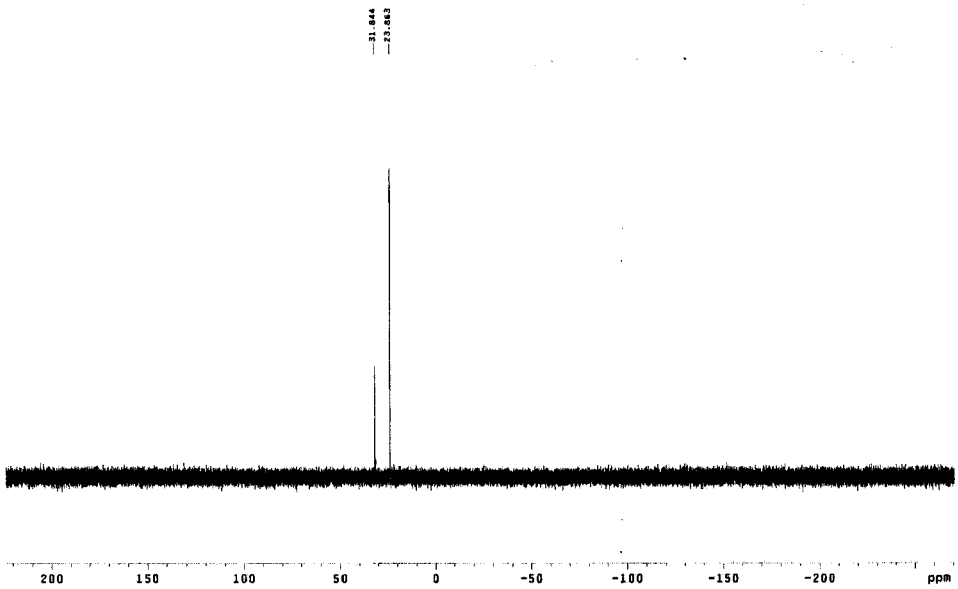
^{31}P NMR

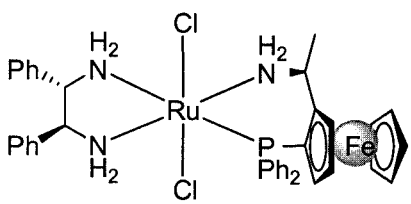




(*R*,*R*,*S*,*R*$_p$)-**160**

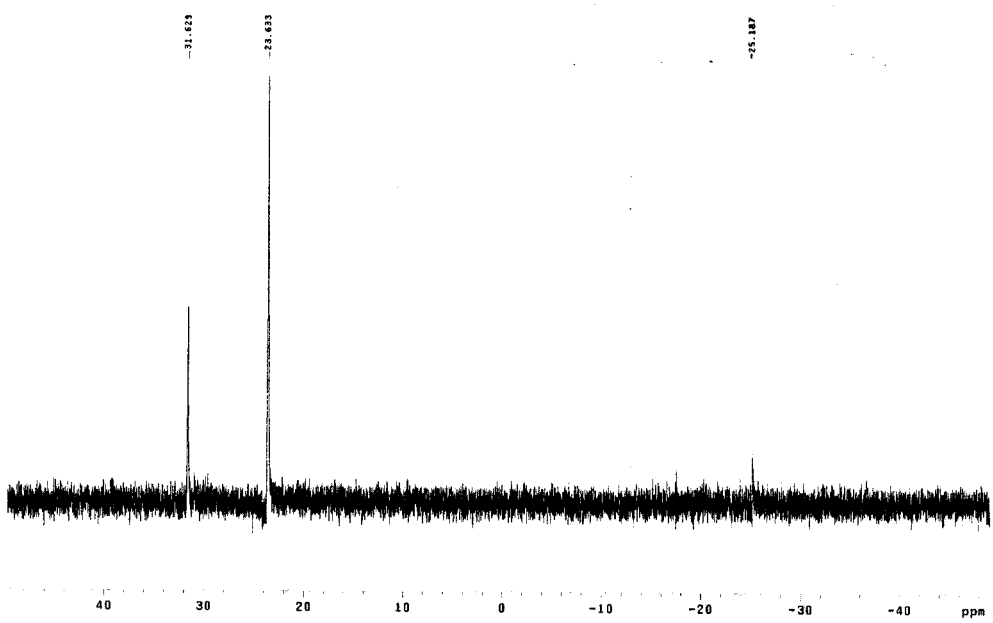
^{31}P NMR

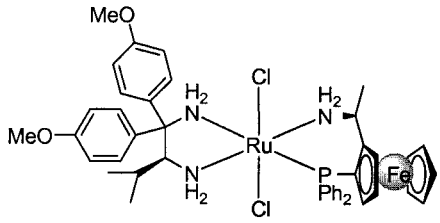




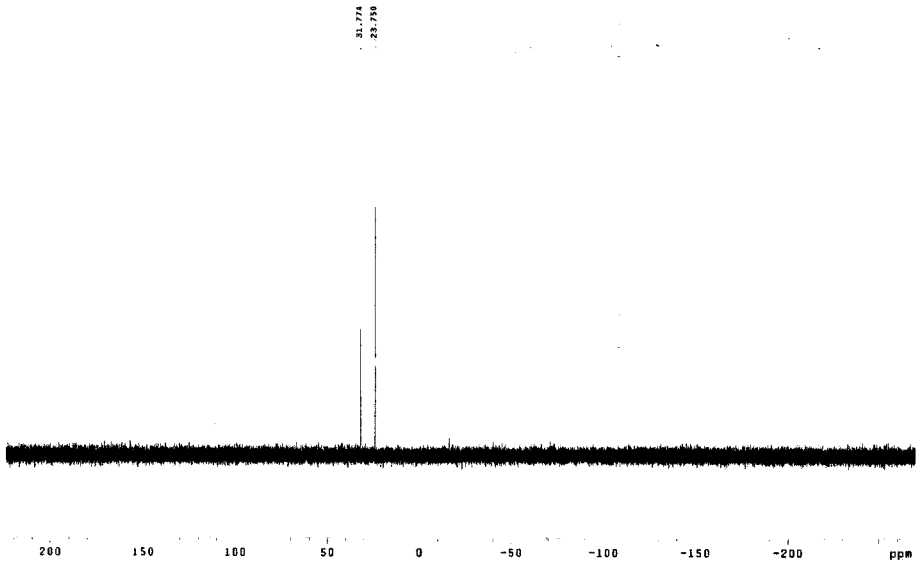
(*S*,*S*,*S*,*R*$_p$)-**160**

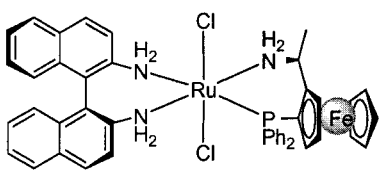
^{31}P NMR



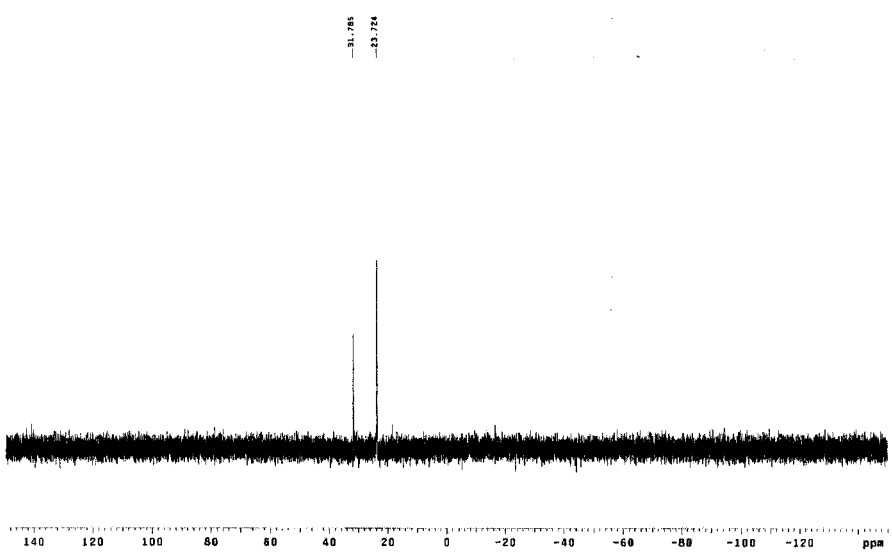


(*S*,*S*,*R*$_p$)-**161** ^{31}P NMR





(*S*$_a$,*S*,*R*$_p$)-**162** ^{31}P NMR



Appendix II

(Publications and conference papers)

1. Jia, X.; Li, X. S.; **Lam, W. S**.; Kok, S. H. L.; Xu, L. J.; Lu, G.; Yeung, C. H.; Chan, A. S. C. "The synthesis of new chiral phosphine-phosphinites, phosphine-phosphoramidite, and phosphine-phosphite ligands and their applications in asymmetric hydrogenation." *Tetrahedron: Asymmetry* **2004**, *15*, 2273-2278.

2. Chan, A. S. C.; **Lam W. S.**; Kok, S. H. L.; Lam F. L.; Cheung, H. Y.; Wu, J.; Au-Yeung, T. T. L.; Yeung, C. H. "Efficient approach to chiral ferrocenyl ligands via asymmetric hydrogenation of ferrocenyl ketone" *Abstracts of Papers, 229th ACS National Meeting, San Diego, United States, March 13-17*, **2005**.

3. **Lam, W. S**.; Kok, S. H. L.; Cheung, H. Y.; Lam, F. L.; Au-Yeung, T. T. L.; Yeung, C. H.; Chan, A. S. C. "Preparation of chiral bidentate N-P ferrocenyl ligands and their application in asymmetric hydrogenation of ketones." *the twelfth Symposium on Chemistry Postgraduate Research in Hong Kong*, **2005**, O-82.

4. **Lam, W. S.**; Kok, S. H. L.; Au-Yeung, T. T. L.; Wu, J.; Cheung, H. Y.; Lam, F. L.; Yeung, C. H.; Chan, A. S. C. "An efficient approach to chiral ferrocene-based secondary alcohols *via* asymmetric hydrogenation of ferrocenyl ketones." *Advanced Synthesis & Catalysis*, **2006**, *348*, 370-374.

5. Kok, S. H. L.; Chui C. H.; **Lam W. S**.; Chen, J.; Tang, J. C. O.; Lau, F. Y.; Cheng,

G. Y. M.; Wong, R. S. M.; Chan, A. S. C. “Induction of apoptosis on carcinoma cells by two synthetic cantharidin analogues.” *International Journal of Molecular Medicine* **2006**, *17*, 151-157.

6. Wang, H. J.; Wang L. L.; Lam W. S.; Yu, W. Y.; Chan, A. S. C. Pd-catalyzed asymmetric alternating co-polymerization of propene with carbon monoxide using ionic liquids. *Tetrahedron: Asymmetry* **2006**, *17*, 7-11.