Synthesis of novel chiral P-Phos derivative for asymmetric catalysis and development of air-stable and recyclable chiral catalyst systems

A Thesis Submitted to

Department of Applied Biology and Chemical Technology

In Partial Fulfilment of the Requirements

For

The Degree of Doctor of Philosophy

At

The Hong Kong Polytechnic University

By

Lam Kim Hung

July, 2004

Declaration

I hereby declare that this thesis summarize my own research work carried out since my registration at The Hong Kong Polytechnic University for the degree of Doctor of Philosophy in 1998, and that, to the best of my knowledge and belief, it produces no material previously published or written nor material which has been accepted for the award of any other degree or diploma, except where due acknowledgement has been made in the text.

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Abstract of thesis entitled "Synthesis of a *o*-phenyl-P-Phos for asymmetric catalysis and development of air-stable and recyclable chiral catalyst systems"

Submitted by Lam Kim Hung
for the degree of Doctor of Philosophy
at The Hong Kong Polytechnic University in June 2004

The air-stable Ir/(*R*)-**P-Phos**/THF system for asymmetric hydrogenation of a variety of quinolines has been investigated and 2-methyl quinoline shows the highest ee value of 91%. This catalyst system can give the same results without using glovebox and degased THF. The Ir/(*R*)-**P-Phos** and Ir/(*R*)-**MeO-BIPHEP** catalysts can also be immobilized in polyethylene glycol dimethyl ether (MW = 500) for the effective asymmetric hydrogenation of 2-methyl quinoline over 5 cycles with ee up to 86% and 84%, respectively, and the operation can be carried out with non-degased hexane and without the use of glovebox.

The air sensitive Ir/(*R*)-**BINAPO**/THF and Ir/(*S*)-**H*8*-BINAPO**/THF systems can also be applied for asymmetric hydrogenation of quinolines with high ee value. In addition, Ir/(*R*)-**BINAPO** and Ir/(*S*)-**H*8*-BINAPO** catalyst systems can be immobilized in polyethylene glycol dimethyl ether (MW = 500) for effective asymmetric hydrogenation of 2-methyl quinoline with similar enantioselectivities. However, the results on recycling are not satisfactory.

We have also extended the application of Ru(*R*-**P-Phos**)$Cl_2(DMF)_n$ catalyst in room temperature ionic liquids ($BMImBF_4$ and $BMImPF_6$) with methanol as co-solvent

for asymmetric hydrogenation of alpha keto-esters with enantioselectivities up to 93% while for beta keto-esters with enantioselectivities up to 99%.

Finally, a new chiral ortho phenyl substituted **P-Phos** (2,2',6,6'-tetramethoxy-5,5'-diphenyl-4,4'-bis(diphenylphosphino)-3,3'-bipyridine, ***o*-Ph-P-Phos**) has been synthesized and its application in asymmetric catalysis has been investigated in comparison with **P-Phos**. The results show that the phenyl ring at the ortho position have significant effect on the enantioselectivity of the asymmetric catalysis. The catalytic reactions included (1) iridium catalyzed asymmetric hydrogenation of 2-methyl quinoline with 37% ee (91% ee for **P-Phos**); (2) palladium catalyzed asymmetric allylic substitution of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate with 16% ee (78% for **P-Phos**); (3) rhodium catalyzed asymmetric hydrogenation of enamides with **o-Ph-P-Phos** performs better than **P-Phos** with ee up to 65%; and, (4) asymmetric hydrogenation of beta enamidophosphonate with 15% ee while no expected conversion was detected by using **P-Phos**. The result of MM2 calculation shows that the torsion angle for the new ligand is 85° while for **P-Phos** is 75°.

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Chapter 1

Introduction

The discovery of molecular chirality (handedness) in nature has greatly influenced the development of science and technology.[1] Many fundamental phenomena and laws of nature result from the dissymmetry of enantiomeric pairs. The enantiomers of chiral compounds, similar to our pair of hands, are mirror images of each other which cannot be superimposed. This molecular discrimination explains why many enantiomeric biologically active agents within a chiral surrounding often behave selectively. However, many chiral compounds cannot be easily obtained in the optically pure form; and the development of truly efficient methods for enantio-pure compounds is a crucial challenge for chemists.

Asymmetric catalysis presents an attractive route to synthesize optically pure compounds as a large quantity of naturally and non-naturally occurring chiral materials can be produced by employing small amount of man-made catalyst. Knowles, Noyori and Sharpless were awarded the Nobel prizes in 2001 for their significant contribution and brilliant achievement in the transition-metal catalyzed enantioselective hydrogenation of prochiral olefins and ketones as well as enantioselective epoxidation of olefins.[2-4] Today asymmetric catalysis has become an important subject of research, and the number of industrial applications has increased significantly.[5]

However, truly industrially applicable chiral catalysts are still very limited.[5] Besides enantioselectivity, there are still many problems to be resolved, such as the catalytic efficiency, the application range, reliability, accessibility of the catalyst and the

functional group tolerance. In this respect, the quest for improvement in present methods and new approaches is attracting more and more attention.

On the contrary, asymmetric catalysis suffers from the difficulty in separation and recycling of the expensive chiral catalysts as well as the toxicity of trace amount of metal contaminants in the products.[6] As much attention is drawn to the protection of environment, the development of environmentally friendly process is becoming especially important nowadays and in the future.

1.1 Transition-metal Catalyzed Homogeneous Asymmetric Hydrogenation with Phosphorous Ligands

Asymmetric hydrogenation is an efficient and versatile method for the preparation of a wide spectrum of optically pure precursors and building blocks for biologically active compounds (such as pharmaceuticals, agrochemicals, flavors, and fragrances) synthesis.[7] In general the reaction involves the addition of hydrogen to a double bond (C=C, C=O, or C=N) in the presence of a transition metal catalysts with chiral ligands. If applicable, asymmetric hydrogenation is economical and clean in producing the desired products, and the process is easy for scaling up. Asymmetric hydrogenation is attracting more and more attention in both industry and academia. Recently, it has been estimated that 11 out of 22 enantioselective chemocatalytic processes operated and produced on an industrial scale are asymmetric hydrogenation.[8] More significantly, 27 out of 30 pilot-stage processes as well as 20 out of 27 bench scale enantioselective chemocatalytic processes are being operated with asymmetric hydrogenation technology.[8]

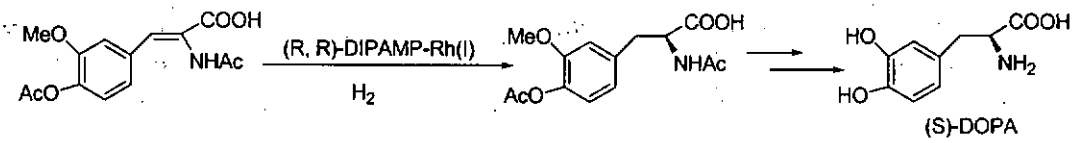
1.1.1 The Background of Homogeneous Asymmetric Catalytic Hydrogenation

Before the 1960s, heterogeneous catalysis was undeniably the most important area in catalysis research. Many attempts to perform asymmetric hydrogenation of prochiral olefins with chiral heterogeneous catalyst only lead to products with very low enantioselectivities. However, a new approach to asymmetric hydrogenation of prochiral olefins emerged in late 1960s. Encouraged by the discovery of the pioneer Wilkinson's homogeneous hydrogenation catalyst $[RhCl(PPh_3)_3]$,[9] Knowles[10] and Horner[11] replaced triphenylphosphine of the Wilkinson's catalyst with a chiral triaryl phosphine, such as $P(C_6H_5)(n\text{-}C_3H_7)(CH_3)$, and reported their earliest asymmetric hydrogenation results of hydrocarbon olefins with 3-15% enantioselectivites. Although the enantioselectivities of the hydrogenated products were not satisfactory, their preliminary findings established a new field of research: homogeneous asymmetric hydrogenation.

A breakthrough in homogenous asymmetric hydrogenation came when Dang and Kagan prepared the C_2 chiral bidentate phosphine ligands, **DIOP**, from optically pure tartaric acid (see Figure 1-1).[12] The enantioselective hydrogenation of α-(acrylamino)acrylic acids and esters with **DIOP**-Rh(I) produced the corresponding chiral products with enantioselectivities up to 80%. The success of **DIOP** revealed several significant directions for the ligand design in asymmetric hydrogenation: (1) the chelating bisphosphine ligands led to higher enantioselectivity compared with monodenate phosphine ligands; (2) the P-chiral phosphorous ligands were not necessary for achieving high enantioselectivity, and the ligands with backbone chirality can also efficiently induce high enantioselectivity; (3) C_2 symmetry was an important structural feature for

developing new efficient chiral ligands. Kagan's pioneering work triggered the rapid development of chiral bisphosphorous ligands.

Later, another important breakthrough was made by Knowles and his coworkers with their C_2-symmetric P-chiral diphosphine **DIPAMP** (see Figure 1-1).[13] **DIPAMP** exhibited very high catalytic efficiency in Rh-catalyzed asymmetric hydrogenation of dehydroamino acids, especially the famous commercial process for the production of anti-Parkinsonian amino acid, **L-DOPA** (Scheme 1-1). This is the first successful industrial application of asymmetric hydrogenation with great potential for manufacturing chiral compounds.



Scheme 1-1 The Monsanto process for the synthesis of ***L-DOPA***

The exploration of numerous efficient chiral phosphorus ligands with different structures for asymmetric hydrogenation in the area of academic studies and industrial production has been a continuous process since the late 1960s.[14,15] At present, there are three ways to design a chiral phosphorous ligand. (1) The chirality can be located on the P atom; (2) the chirality can be located on a side chain, where the ligand chirality depends on the backbone with central chirality, axial chirality or planar chirality; and, (3) the chirality can be located on both the P atom and the side chain. Currently the chirality of most chiral P-ligands used in asymmetric hydrogenation derives from the chiral side chains. Take Kagan's **DIOP** as a model example, a large number of chiral bidentate

phosphine ligands with excellent selectivities were designed. Among those successful ligands, we have some typical C_2-symmetric examples (Figure 1-1), such as the above mentioned **DIPAMP** and **CHIRAPHOS**. Figure 1-2 illustrates some frequently used bidentate ligands, such as **BINAP**, **BICEP**, **MeO-BIPHEP**, **DUPHOS**, **TRAP**, **PHANEPHOS**, **BICP**, **PennPhos**, **P-Phos**, **BDPMI**, **Ph-o-NAPHOS** and **TangPhos** while **BPPFA**, **BCPM**, **Meo-NAPhePHOS**, **Josiphos**, **TaniaPhos**, and **Walphos** are other classical examples, which have been found to be very effective in asymmetric hydrogenation. Compared to the rapid development of chiral bisphosphine ligands, bisphosphinites, bisphosphonites and bidentate aminophosphines, amidophosphines and phosphoramides are relatively less investigated. Recently several efficient bidentate ligands with P-O or P-N bonds have been synthesized, which exhibited excellent reactivities and enantioselectivities (Figure 1-3). Despite the successful use of monophosphines as ligands in the pioneering studies on asymmetric hydrogenation of dehydroamino acid derivatives, however, bidentate chiral ligands have still been dominated for three decades based on our common assumption that bidentate ligands were essential for achieving high enantioselectivites in asymmetric hydrogeantion. Recently, a number of highly enantioselective asymmetric hydrogenation have been achieved with chiral monodentate phosphorous ligands, which in turn contradicted our common belief that the high enantioselectivities should be achieved by chiral bidendate ligands. These chiral monodentate phosphorous ligands include monophosphines, monophosphonites, monophonites, monophosphoramidites and monophosphites (Figure 1-4). Chiral P, N-ligands have been found to mediate the asymmetric hydrogenation of unfunctionalized olefins, and some selected examples are listed in Figure 1-5. Most of these above-mentioned P-ligands are modular, with tunable steric and electronic

properties. It is also notable that rhodium or ruthenium based catalytic systems are the most commonly used transition metal catalysts for asymmetric hydrogenation, and iridium based systems are relatively less explored.

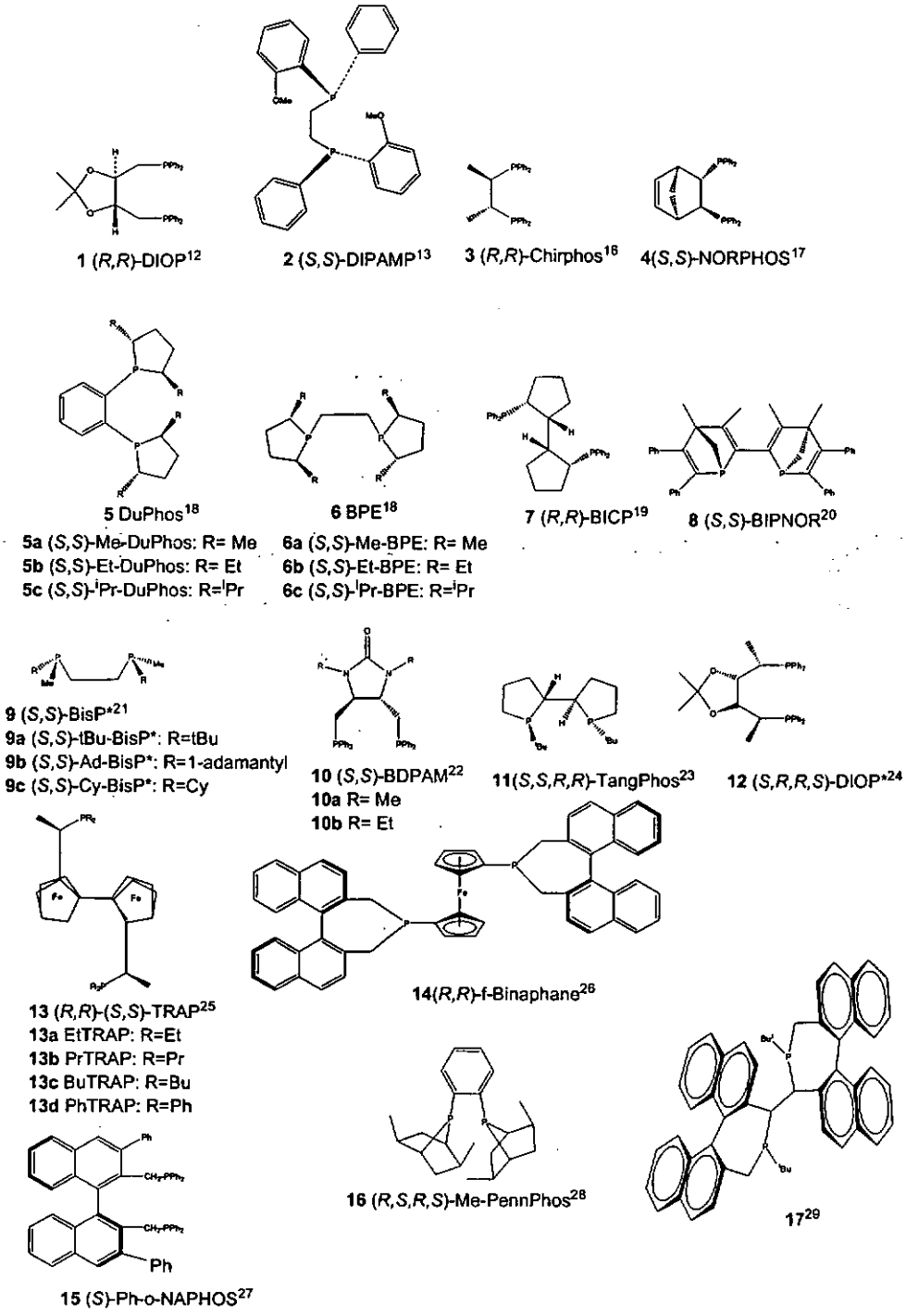
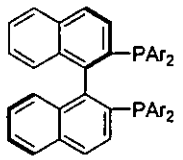
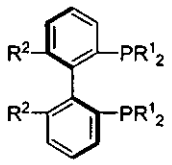


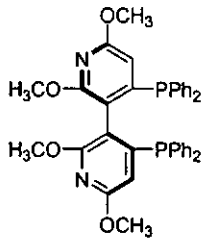
Figure 1-1 Some C_2-symmetry bidentate phsophine ligands.



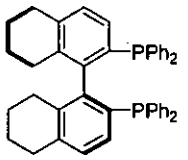
18a (*R*)-BINAP[30a] R=Ph
18b (*R*)-TolBINAP[30b] R=4-MePh
18c (*R*)-XylBINAP[30b] R=3,5-$(Me)_2$Ph



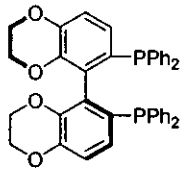
19a (*S*)-BICHEP[31a,b] R^1=Cy; R^2= CH_3
19b (*S*)-BIPHEMP[31c] R^1=Ph; R^2= CH_3
19c (*S*)-MeO-BIPHEP[31d] R^1= Ph; R^2= OCH_3



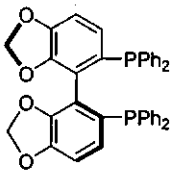
20a (*S*)-P-Phos [32a] R=Ph
20b (*S*)-Tol-P-Phos[32b] R=4-MePh
20c (*S*)-Xyl-P-Phos[32c] R=3,5-$(Me)_2$Ph



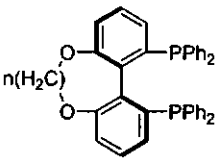
21 (*S*)-H8-BINAP[33]



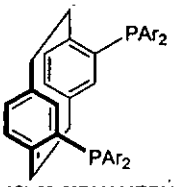
22 (*S*)-BisbenzodioxanPhos[34]



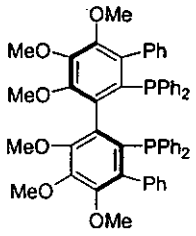
23 (*S*)-SEGPHOS[35]



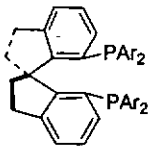
24 (*S*)-Cn-TunaPhos[36]



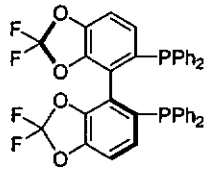
(*S*)-[2,2]PHANEPHOS[37]
25a[37a] Ar=Ph
25b[37b] Ar= 3, 5-Me_2Ph



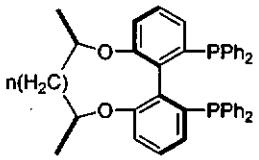
26 (*S*)-o-Ph-HexaMeO-BIPHEP[38]



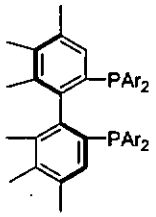
SDP[39]
27a (*S*)-SDP: Ar=Ph
27b (*S*)-Tol-SDP: Ar=4-MePh
27c (*S*)-An-SDP: Ar=4-MeOPh
27d (*S*)-Xyl-SDP: Ar=3,5-Me_2Ph



28 (*S*)-DIFLUORPHOS[40]

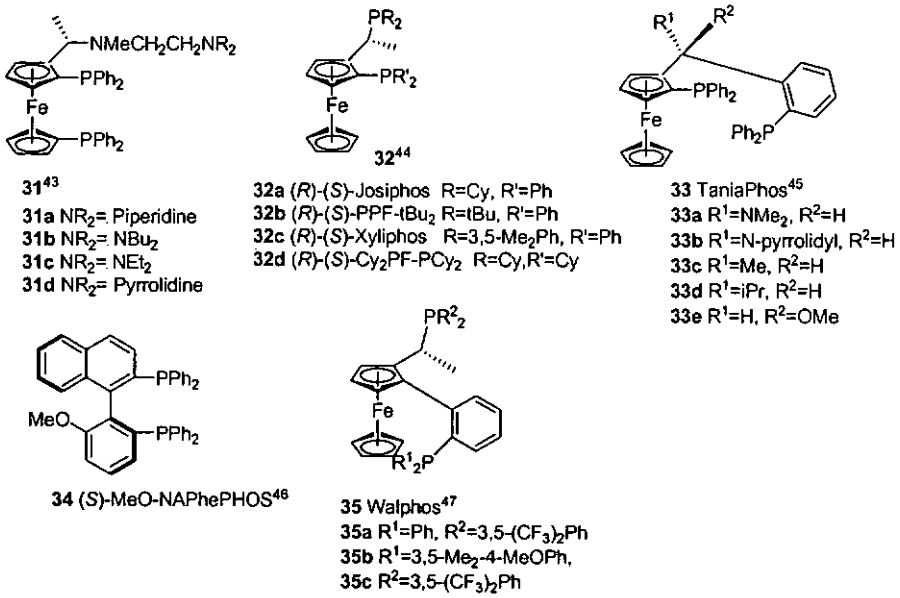


29a[41a] n=0
29b[41b] n=1



30a (*S*)-HexaPHEMP [42] Ar=Ph
30b (*S*)-Xyl-HexaPHEMP[42] Ar=3,5-Me_2Ph

Figure 1-1 Some C_2-symmetry bidentate phsophine ligands (continued).



31[43]
31a NR_2= Piperidine
31b NR_2= NBu_2
31c NR_2= NEt_2
31d NR_2= Pyrrolidine

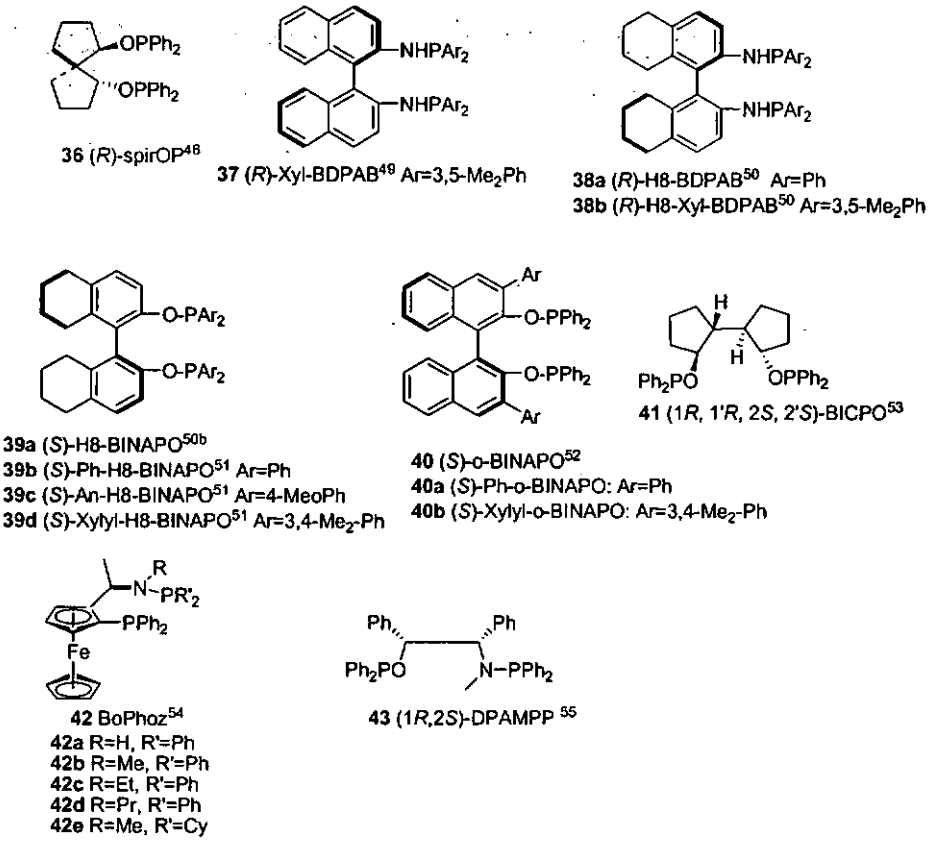
32[44]
32a (*R*)-(*S*)-Josiphos R=Cy, R'=Ph
32b (*R*)-(*S*)-PPF-tBu_2 R=tBu, R'=Ph
32c (*R*)-(*S*)-Xyliphos R=3,5-Me_2Ph, R'=Ph
32d (*R*)-(*S*)-Cy_2PF-PCy_2 R=Cy,R'=Cy

33 TaniaPhos[45]
33a R^1=NMe_2, R^2=H
33b R^1=N-pyrrolidyl, R^2=H
33c R^1=Me, R^2=H
33d R^1=iPr, R^2=H
33e R^1=H, R^2=OMe

34 (*S*)-MeO-NAPhePHOS[46]

35 Walphos[47]
35a R^1=Ph, R^2=3,5-$(CF_3)_2$Ph
35b R^1=3,5-Me_2-4-MeOPh,
35c R^2=3,5-$(CF_3)_2$Ph

Figure 1-2 Some unsymmetric bidentate phsophine ligands.



36 (*R*)-spirOP[48]

37 (*R*)-Xyl-BDPAB[49] Ar=3,5-Me_2Ph

38a (*R*)-H8-BDPAB[50] Ar=Ph
38b (*R*)-H8-Xyl-BDPAB[50] Ar=3,5-Me_2Ph

39a (*S*)-H8-BINAPO[50b]
39b (*S*)-Ph-H8-BINAPO[51] Ar=Ph
39c (*S*)-An-H8-BINAPO[51] Ar=4-MeoPh
39d (*S*)-Xylyl-H8-BINAPO[51] Ar=3,4-Me_2-Ph

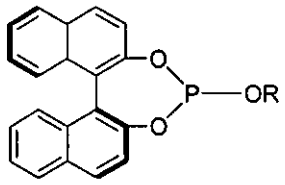
40 (*S*)-o-BINAPO[52]
40a (*S*)-Ph-o-BINAPO: Ar=Ph
40b (*S*)-Xylyl-o-BINAPO: Ar=3,4-Me_2-Ph

41 (1*R*, 1'*R*, 2*S*, 2'*S*)-BICPO[53]

42 BoPhoz[54]
42a R=H, R'=Ph
42b R=Me, R'=Ph
42c R=Et, R'=Ph
42d R=Pr, R'=Ph
42e R=Me, R'=Cy

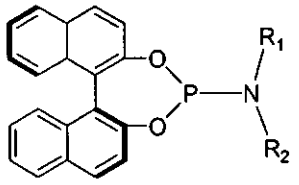
43 (1*R*,2*S*)-DPAMPP [55]

Figure 1-3 Some bidentate P-O and P-N ligands.



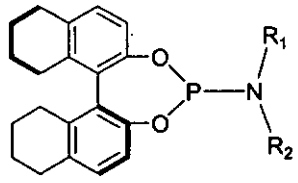
44[56]**a-c**

R= iPr, Ph, (*R*)-CH(Me)Ph

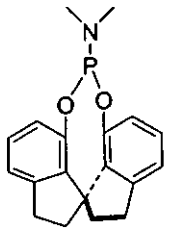


45[57]

45a[57a] (*S*)-MonoPhos: R^1=R^2= Me
45b[57c] R^1=R^2= Et
45c [57b] R^1=Bn, R^2=Me
45d[57b] R^1= (*R*)-MeCHPh, R^2= H



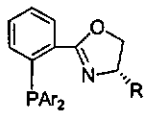
46[58]



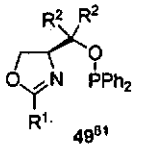
46a: (*S*)-H8-MonoPhos: R^1=R^2= Me
46b: (*S*)-Et-H8-MonoPhos; R^1=R^2= Et

47 (*S*)-SIPHOS[59]

Figure 1-4 Some monodentate P-O and P-N ligands.

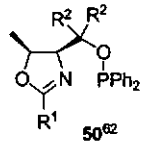


48 (*S*)-^{t}Bu-phox[60] Ar=o-Tol, R=^{t}Bu



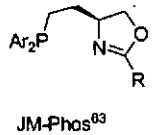
49[61]

49a R^1= Ferrocenyl R^2=iPr
49b R^1=ferrocenyl R^2=Bn
49c R^1=3,5-tBu_2Ph, R^2=Bn

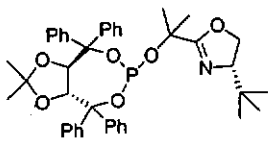


50[62]

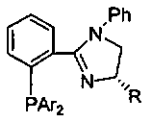
50a R^1=Ph, R^2=Bn
50b R^1=3, 5-Me_2Ph, R^2=Bn



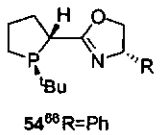
JM-Phos[63]
51 R=Ph_2CH, Ar=o-Tol



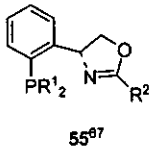
52[64]



53 (*S*)-^{t}Bu-PHIM[65]. Ar=o-Tol, R=^{t}Bu

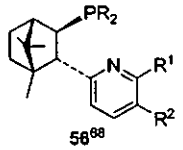


54[66] R=Ph



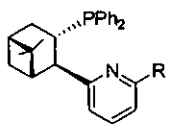
55[67]

55a R^1=Ph, R^2=*t*Butyl
55b R^1=Ph, R^2=CHPh2
55c R^1=Ph, R^2=3,5-di-*t*-butyl-Ph
55d R^1=Ph, R^2=Adamantyl
55e R^1=Cy, R^2=*t*Butyl



56[68]

56a R=Ph, R^1=R^2=H
56b R=Ph, R^1=Ph, R^2=H
56c R=Cy, R^1=R^2=H
56d R=Ph, R^1-R^2=CH-CH=CH-CH



57[68] R=H, Ph

Figure 1-5 Some bidentate P, N ligands.

1.1.2 Applications of Chiral Phosphorous Liagnds in Asymmetric Hydrogenation

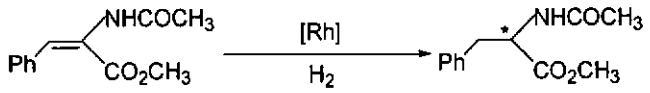
1.1.2.1 Asymmetric Hydrogenation of α-Dehydroamino Acid Derivatives

Asymmetric hydrogenation of α-dehydroamino acid derivatives has provided an effective and practical route to synthesize optically active amino acids. Today, this reaction has become a model reaction to test the efficiency of newly synthesized chiral phosphorous ligands. High enantioselectivities have been obtained with many chiral phosphorous ligands including both bidentate and monodentate ligands. In general, cationic rhodium complexes and low hydrogenation pressure are applied for the hydrogenation reactions. Some promising results with different ligands are listed in Table 1-1.

1.1.2.2 Asymmetric Hydrogenation of β-Dehydroamino Acid Derivatives

Optically pure β-amino acid derivatives are important building blocks and intermediates for the synthesis of β-peptides, β-lactams, antibiotics and many chiral drugs. Simple asymmetric hydrogenation of β-dehydroamino acids provides an attractive and convenient way to get these chiral compounds. The starting β-dehydroamino acids are generally produced simultaneously in a mixture of (*Z*)- and (*E*)-isomers, and most of the rhodium and ruthenium catalysts with chiral phosphorous ligands are effective for the hydrogenation of the (*E*)-isomers while only a few candidates can efficiently hydrogenate the (*Z*)-isomers. Some representative results are summarized in Table 1-2.

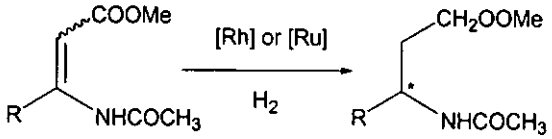
Table 1-1 Typical results of asymmetric hydrogenation of α-methyl acetamidocinnamate



Ligand	S/C ratio	Reaction Conditions	% ee	Ref
(*R,R*)-DIPAMP	900	MeOH, 50°C, 3 atm H_2	96 (*S*)	13a
(*S*)-BINAP[a]	100	EtOH, rt, 3 atm H_2	100 (*S*)	30a
(*R*)-BICHEP[b]	1000	EtOH, rt, 1 atm H_2	95 (*S*)	31b
(*R*)-(*S*)-JosiPhos	100	MeOH, 35°C, 1 atm H_2	96 (*S*)	44
TaniaPhos **33d**	100	MeOH/Toluene, rt, 1 atm H_2	96.6 (*R*)	45a
TaniaPhos **33e**	100	MeOH/Toluene, rt, 1 atm H_2	99 (*S*)	45c
(*S,S*)-^{t}Bu-BisP*	500	MeOH, rt, 2 atm H_2	99.9 (*R*)	21
(*S,S,R,R*)-TangPhos	10000	MeOH, rt, 1.3 atm H_2	99.8 (*S*)	23
(1*R*,2*S*)-DPAMPP	10000	MeOH, rt, 50 atm H_2	97 (*R*)	55
(*S*)-Ph-*o*-NaPHOS	100	Toluene, rt, 3 atm	97.8 (*S*)	52
(*S*)-Xyl-BDPAB	500	MeOH, rt, 3.3 atm H_2	98 (*S*)	49
BoPhoz (R=Me, R'=ph)	10000	THF rt, 0.7atm H_2	99.4 (*S*)	54
(*S*)-Xyl-H8-BINAPO	500	CH_2Cl_2, rt, 3.3 atm H_2	94 (*S*)	51b
(*S*)-SIPHOS	200	CH_2Cl_2, rt, 1 atm H_2	96.4 (*S*)	59a
(*R*)-H8-MonoPhos	500	Acetone, rt, 1.5 atm H_2	96.4 (*R*)	58a

[a]Benzoyl derivative. [b] Ethyl ester.

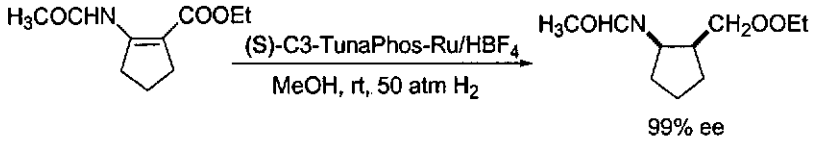
Table 1-2 Asymmetric hydrogenation of β-dehydroamino acids



Catalyst	R	Geometry	Reaction Conditions	% ee	Ref
(*R*)-BINAP-Ru	Me	*E*	MeOH, 25°C, 1 atm H_2	96 (*S*)	69
(*R*)-Xyl-P-Phos-Ru	Me	*E*	MeOH, 0°C, 8 atm H_2	98.1(*S*)	32e
(*S,S*)-Me-DuPhos-Rh	Me	*E*	MeOH, 25°C, 1 atm H_2	98.2 (*S*)	70
(*R,R*)-BICP-Rh	Me	*E*	Toluene, rt, 2.7 atm H_2	96.1 (*R*)	19b
10a-Rh	Me[a]	*E*	DCM, rt, 1 atm H_2	94.6 (*R*)	22b
(*S,S*)-^{t}Bu-BisP*-Rh	Me	*E*	THF, rt, 3 atm H_2	98.7 (*R*)	71
(*S,S,R,R*)-TangPhos-Rh	Me	*E*	THF, rt, 1.3 atm H_2	99.6 (*R*)	23
(*S*)-**45c**-Rh	Me	*E*	DCM, rt, 10 atm H_2	99 (*R*)	57b
(*S,S*)-Me-DuPhos-Rh	Me	*Z*	MeOH, 25°C, 1 atm H_2	87.8 (*S*)	70
10a-Rh	Me[a]	*Z*	DCM, rt, 6.7 atm H_2	95 (*R*)	22b
(*S,S,R,R*)-TangPhos-Rh	Me	*Z*	THF, rt, 1.3 atm H_2	98.5 (*R*)	23
(*S*)-**45d**-Rh	Me	*Z*	^{i}PrOH, rt, 10 atm H_2	95 (*R*)	57b
(*S,S,R,R*)-TangPhos-Rh	Me	*E/Z*[b]	THF, rt, 1.3 atm H_2	99.5 (*R*)	23
(*S*)-**45d**-Rh	Ph	*Z*	^{i}PrOH, rt, 10 atm H_2	92 (*S*)	57b
(*S*)-Xylyl-o-BINAPO-Ru	Ph	*Z*	EtOH, 50°C, 5 atm H_2	99 (*S*)	52
(*S,S,R,R*)-TangPhos-Rh	Ph	*Z*	THF, rt, 1.3 atm H_2	93.8 (*S*)	23

[a] Ethyl ester. [b] *E/Z*=1:1.

Most recently, Zhang and his coworkers reported the asymmetric hydrogenation of cyclo-β-dehydroamino acid derivatives with enantioselectivities attained up to 99% (Scheme 1-2).[72]

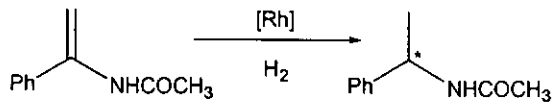


Scheme 1-2

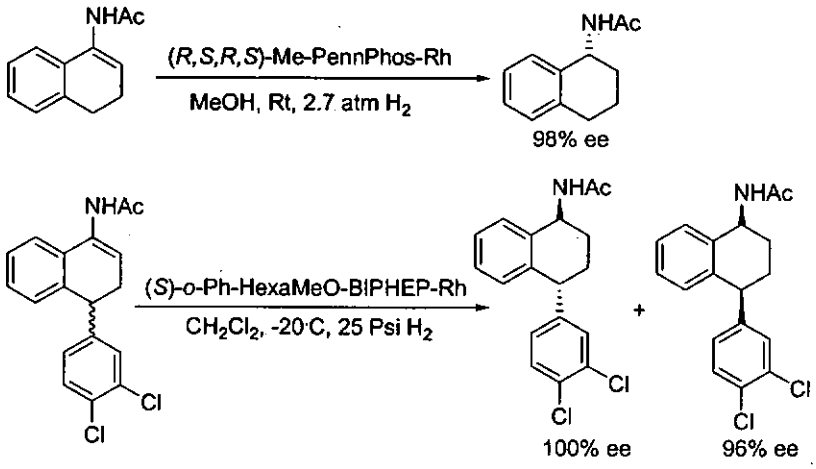
1.1.2.3 Asymmetric Hydrogenation of Enamides

Optically pure amines have been widely used as resolving agents, chiral auxiliaries, and chiral building blocks for asymmetric synthesis and medicinal chemistry. Direct asymmetric hydrogenation of enamides is one of the most attractive routes for the preparation of chiral amines. Recently rhodium catalyzed asymmetric hydrogenation of simple enamides has attracted much attention, and very high enantioselectivities have been obtained with some newly designed phosphorous ligands. Among these ligands, the best results have been obtained by *P*-Chiral ligand, TangPhos, which can achieve excellent enantioselectivities of 99.3% and turnover numbers up to 10000. Some typical examples are listed in Table 1-3. Some cycloenamides have also been asymmetrically hydrogenated with high enantioselectivities with the rhodium catalysts of PennPhos[76] and *o*-Ph-HexaMeO-BIPHEP[38] (Scheme 1-3).

Table 1-3 Asymmetric hydrogenation of enamide



Ligand	S/C	Reaction Conditions	% ee	Ref
(*R,R*)-Me-BPE	500	MeOH, 22 °C, 0.4 atm H_2	95.2 (*R*)	73
(*R,S,S,R*)-DIOP*	50	MeOH, rt, 10 atm H_2	98.8 (*R*)	24a
10a	100	CH_2Cl_2, rt, 1 atm H_2	98.5 (*R*)	22a
33e	100	MeOH/Toluene rt, 1 atm H_2	96 (*S*)	45c
(*S,S*)-^{t}Bu-BisP*	100	MeOH, rt, 3 atm H_2	98 (*R*)	74
(*S,S,R,R*)-TangPhos	10000	MeOH, rt, 1.3 atm H_2	99.3 (*R*)	23
(*R*)-H8-BDPAB	200	THF, 5 °C, 1 atm H_2	96.8 (*R*)	50
(*S*)-MonoPhos	100	CH_2Cl_2, -20 °C, 20 atm H_2	95 (*S*)	75
(*S*)-SIPHOS	200	Toluene, 5 °C, 10 atm H_2	98.7 (*S*)	59b
45b	200	THF, 5 °C, 20 atm H_2	97 (*S*)	57c

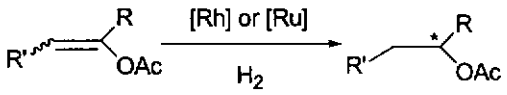


Scheme 1-3

1.1.2.4 Asymmetric Hydrogenation of Enol Esters

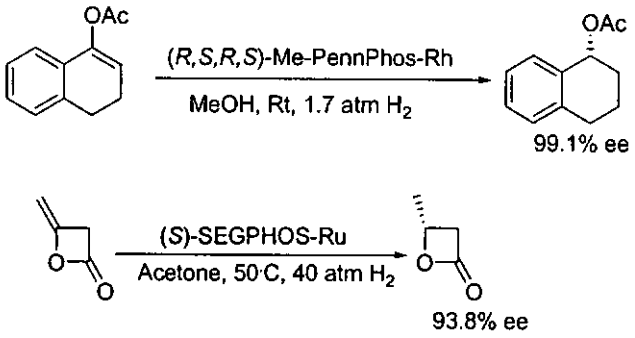
Asymmetric hydrogenation of enol esters provides a convenient approach to prepare chiral alcohols. Enol esters have similar structures to enamides, but only limited numbers of successful asymmetric hydrogenation of enol esters have been reported due to the weak coordinating ability of acyl group to the metal. In the presence of rhodium or ruthenium complexes of chiral bidentate phosphine ligands, moderate to high enantioselectivities have been achieved. Some leading results are listed in Table 1-4.

Table 1-4 Asymmetric hydrogenation of enol esters



Catalyst	R	R'	Geometry	Reaction Conditions	% ee	Ref
(*R, R*)-Et-DuPhos-Rh	COOEt	H	N/A	MeOH, rt, 2 atm H_2	>99(*R*)	77
(*R, R*)-Et-DuPhos-Rh	COOEt	^{i}Pr	E/Z	MeOH, rt, 6 atm H_2	96.1(*R*)	78
(*R*)-BINAP-Ru	COOEt	^{i}Pr	E/Z	MeOH, 50°C, 6 atm H_2	96.1(*R*)	79
(*R, R*)-Et-DuPhos-Rh	COOEt	Ph	E/Z	MeOH, rt, 3 atm H_2	95.6(*R*)	78
(*S, S*)-Me-DuPhos-Rh	Ph	H	N/A	MeOH, rt, 3 atm H_2	89 (*S*)	77
(*S, S, R, R*)-TangPhos-Rh	Ph	H	N/A	EtOAc, rt, 1.3 atm H_2	96 (*R*)	23
(*S, S*)-Me-DuPhos-Rh	1-Np	H	N/A	MeOH, rt, 3 atm H_2	93 (*R*)	77
(*S, S, R, R*)-TangPhos-Rh	1-Np	H	N/A	EtOAc, rt, 1.3 atm H_2	97 (*R*)	23
(*S*)-C_2-TunaPhos-Ru	1-Np	H	N/A	EtOH/DCM, rt, 3 atmH_2	97.7(*S*)	80
29b-Ru	Ph	H	N/A	EtOH/DCM, rt, 3 atmH_2	94.9(*R*)	41b
29b-Ru	1-Np	H	N/A	EtOH/DCM, rt, 3 atmH_2	96.7(*R*)	41b

In asymmetric hydrogenation of cyclo-enol esters, PennPhos and SEGPHOS have shown high catalytic efficiencies (Scheme 1-4).[76b, 81]



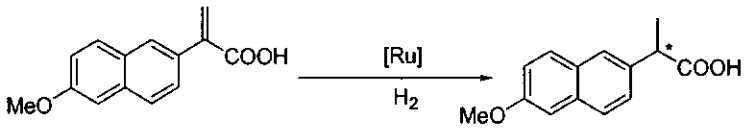
Scheme 1-4

1.1.2.5 Asymmetric Hydrogenation of Acrylic Acids & Derivatives

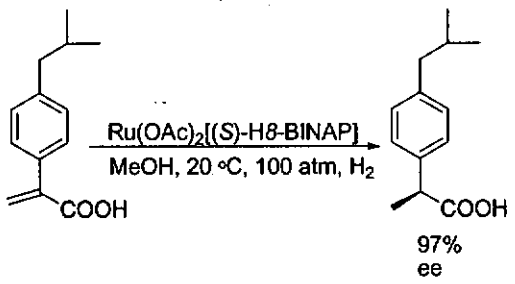
Optically pure carboxylic acids are important building blocks for pharmaceuticals, flavors, fragrances, and agrochemicals. Asymmetric hydrogenation of α,β-unsaturated carboxylic acids serves as a convenient way to synthesize these chiral compounds. Since Morrison and coworkers reported the first asymmetric hydrogenation of (*E*)-3-phenyl-2-butenoic acid with rhodium catalyst in 1971,[82] significant progress has been achieved in this area herein. Ruthenium complexes of chiral bidentate phosphine ligands are highly effective catalysts for this transformation. The highly enantiopure anti-inflammatory drug (*S*)-naproxen can be readily prepared via asymmetric hydrogenation (Table 1-5). Similarly ruthenium complex of H8-BINAP provided (*S*)-ibuprofen in high ee (Scheme 1-5).[83] (*R*)-BIPHEMP-Ru catalyzed asymmetric hydrogenation allowed the synthesis of (*S*)-2-(4-fluorophenyl)-3-methylbutanoic acid (94% ee), which is a key intermediate for the preparation of calcium antagonist Mibefradil (Scheme 1-6).[84] The saturated acid, an important intermediate for the synthesis of the renin inhibitor SPP100, can be efficiently

synthesized via asymmetric hydrogenation with WalPhos-Rh up to 95% ee at a S/C ratio of 5700 achieved (Scheme 1-7).[47]

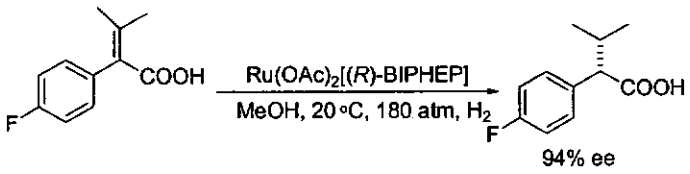
Table 1-5 Asymmetric hydrogenation of 2-(6'-methoxy-2'-naphthyl) acrylic acid



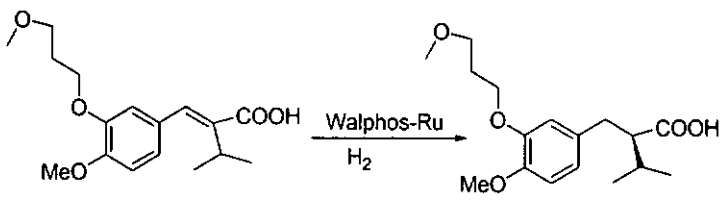
Ligand	Reaction Conditions	% ee	Ref
(*S*)-BINAP	MeOH, rt, 13 atm H_2	97 (*S*)	85
(*R*)-P-Phos	MeOH, 0 °C, 1000 psi H_2	95 (*R*)	48
(*R*)-BisbenzodioxanPhos	MeOH, rt, 1700 psi H_2	92 (*R*)	34
29a	MeOH, rt, 1500 psi H_2	96 (*R*)	31a



Scheme 1-5



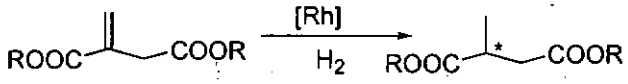
Scheme 1-6



Scheme 1-7

There were many successful examples for asymmetric hydrogenation of itaconic acid and its dimethyl ester. High catalytic efficiency has been observed with electron-rich phosphine ligands as well as electron-deficient phosphonite or phosphite ligands. Some good examples are shown in Table 1-6.

Table 1-6 Asymmetric hydrogenation of itaconic acid and its dimethyl ester

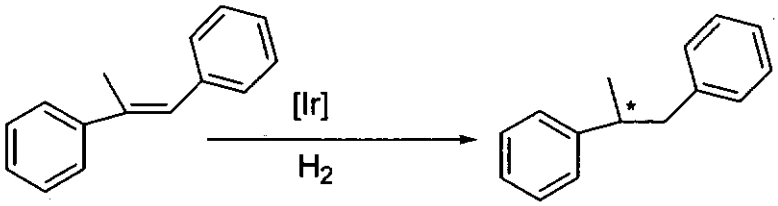


Ligand	R	S/C	Reaction Conditions	% ee	Ref
(*R*)-BICHEP	H	1000	EtOH, 25°C, 1 atm H_2	96 (*R*)	31b
(*R,R*)-Et-DuPhos	Me	10000	MeOH, 25°C, 5 atm H_2	98 (*R*)	86
(*R,R*)-(*S,S*)-Et-TRAP	Me	200	CH_2Cl_2, reflux, 1 atm H_2	96 (*S*)	25c
(*R*)-(*S*)-Josiphos	Me	100	MeOH, rt, 1 atm H_2	99 (*S*)	44
(*S, S*)-Ad-BisP*	Me	500	MeOH, rt, 1.6 atm H_2	99 (*S*)	21b
(*S, S, R, R*)-TangPhos	Me	5000	THF, rt, 1.3 atm H_2	>99.5(*S*)	23
(*S*)-MonoPhos	H	20	CH_2Cl_2, 25°C, 1 atm H_2	96.6(*S*)	75
45c	Me	5000	CH_2Cl_2, 20°C, 1.3 atm H_2	97.4(*S*)	56a

1.1.2.6 Asymmetric Hydrogenation of Unfunctionalized Olefins

The rhodium or ruthenium catalysts of chiral phosphorous ligands have been found to be efficient for asymmetric hydrogenation of a number of olefins bearing polar groups that can coordinate with the metal, but they failed to catalyze the asymmetric hydrogenation of unfunctionalized olefins efficiently. To date only limited numbers of successful examples have been reported. Encouraged by Crabtree's catalyst,[87] $[Ir(COD)(PY)PCy_3]^+PF6^-$, several iridium complexes of chiral P, N ligands have been developed and high enantioselectivities have been achieved in the asymmetric hydrogenation of unfunctionalized olefins. Table 1-7 summarizes some of the best results achieved with some newly synthesized P, N-ligands.

Table 1-7 Asymmetric hydrogenation of α-methylstilbene



Ligand	S/C	Reaction Conditions	% ee	Ref
48	1000	CH_2Cl_2, 23 °C, 50 atm H_2	97(*R*)	60
52	100	CH_2Cl_2, rt, 50 atm H_2	99 (*R*)	64
53	100	CH_2Cl_2, 25 °C, 50 atm H_2	94 (*R*)	65
49	250	CH_2Cl_2, 25 °C, 50 atm H_2	98 (*R*)	61
50	5000	CH_2Cl_2, rt, 50 atm H_2	99 (*R*)	62
51	500	CH_2Cl_2, 25 °C, 50 atm H_2	95(*R*)	63
54	100	CH_2Cl_2, rt, 50 atm H_2	95(*R*)	66

55b	100	CH_2Cl_2, rt, 50 atm H_2	99	67
56a	100	Toluene, rt, 50 atm H_2	95	68

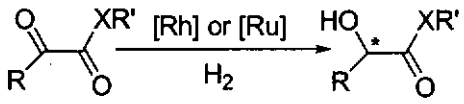
1.1.3 Applications of Chiral Phosphorous Ligands in Asymmetric Hydrogenation of Ketones

Asymmetric hydrogenation of ketones with transition-metal catalysts is the most versatile and efficient method for the preparation of a large variety of chiral secondary alcohols. A wide range of ketones have been successfully hydrogenated with rhodium or ruthenium catalysts of chiral phosphorous ligands.

1.1.3.1 Asymmetric Hydrogenation of Functionalized Ketones

The rhodium or ruthenium catalysts of chiral phosphorous ligands have shown high enantioselectivities in the asymmetric hydrogenation of α-keto esters. For example, the Ru catalysts of bidentate phosphine ligands, such as **BINAP**, **BICHEP**, **MeO-BIPHEP**, worked efficiently to give the products with high ee values (Table 1-8).

Table 1-8 Asymmetric hydrogenation of α-ketoesters



Catalyst	R	XR'	S/C	Reaction Conditions	% ee	Ref
BoPhoz-Rh	$Ph(CH_2)_2$	OEt	100	THF, rt, 20 atm H_2	92.4(*R*)	54
(*R*)-SEGPHOS-Ru	^{t}Bu	OEt	1000	EtOH, 70°C,50atm H_2	98.5(*R*)	35
(*R*)-BICHEP-Ru	Ph	OMe	100	EtOH, rt, 5atm H_2	>99(*S*)	88
(*S*)-BINAP-Ru	4-MePh	OMe	150	MeOH, 30°C,	93(*S*)	89

				100atm H_2 HBF_4		
(*R*)-BICHEP-Ru	Ph	NHBn	100	MeOH, rt, 40atm H_2	96(*R*)	88
29b-Ru	Ph	OMe	600	MeOH, rt,40 atm H_2	97 (*R*)	41b

Asymmetric hydrogenation of β-keto esters has been widely investigated, and high enantioselectivites have been achieved using ruthenium catalysts of chiral atropisomeric biaryl phosphine ligands. The Ru/**BINAP** catalyst has been proved to be highly active and enantioselective. In addition to **BINAP**, other biaryl ligands, such as **P-Phos**, C4-**TunaPhos**, **MeO-BIPHEP** and **JosiPhos** also work impressively for this transformation. Some good results are listed in Table 1-9.

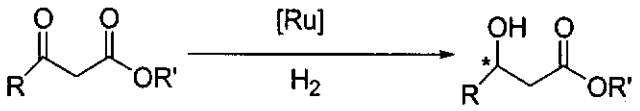
1.1.3.2 Asymmetric Hydrogenation of Simple Ketones

In contrast to the many successful examples for asymmetric hydrogenation of functionalized ketones, enantioselective hydrogenation of simple ketones remains a challenging area for a long time. Some ruthenium and rhodium catalysts of chiral bisphosphorous ligands have been tried with few successful results due to the lack of heteroatoms that enable the substrate to anchor strongly to the metal.

A breakthrough in this area was made by Noyori and coworkers.[95a] They found that when the Ru-BINAP complex was further complexed with a chiral 1,2-diamine ligand, combining with the use of a strong base, the enantioselectivity of asymmetric hydrogenation of simple ketones was enhanced significantly. With this novel catalyst, a wide variety of simple aryl ketones could be hydrogenated quantitatively with excellent ee values.[95] Recently similar good results have been obtained with Ru catalysts associated with other bidentate bisphosphine ligands, such as **PhanePhos**,[37b] **P-Phos**,[32d,g] **SDP**[39].

Meanwhile, rhodium catalyst was also found to catalyze this transformation. Zhang and coworkers reported that Rh/PennPhos/lutidine catalyst could efficiently mediate asymmetric hydrogenation of aryl ketones. Representative examples are shown in Table 1-10.

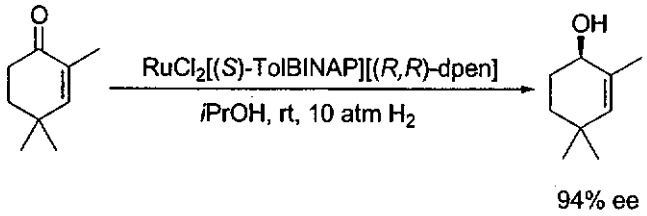
Table 1-9 Asymmeyric hydrogenation of β-keto esters



Ligand	R	R'	S/C	Reaction Conditions	% ee	Ref
(*R*)-BINAP	Me	Me	2000	MeOH, 23 °C,100 atm H_2	>99(*R*)	90
(*R*)-BisbenzodioxanPhos	Me	Me	1000	MeOH, 80 °C, 3.3 atm H_2	98.1(*R*)	34
(*S*)-P-Phos	Me	Me	400	MeOH/CH_2Cl_2, 70 °C, 3.3 atm H_2	98.5(*S*)	32a
(*R*)-C4-TunaPhos	Me	Me	100	MeOH, 60 °C, 50 atm H_2	99.1(*R*)	36
(*R*)-MeO-BIPHEP	Me	Me	100	MeOH, 50 °C, 20 atm H_2	>99(*R*)	91
(*S*)-BIPHEMP	Me	Me	100	MeOH, 80 °C,10 atm H_2	>99(*S*)	91
(*R,R*)-^{i}Pr-BPE	Me	Me	500	MeOH/H_2O, 35 °C, 4 atm H_2	99.3(*S*)	92
(*S,S*)-^{t}Bu-BisP*	Me	Me	200	MeOH/H_2O, 70 °C, 6 atm H_2	98	93
(*R*)-(*S*)-Josiphos	Me	Et	100	MeOH, rt, 20 atm H_2	97(*S*)	44
(*R*)-BINAP	Ph	Et	760	MeOH, 23-30 °C, 91 atm H_2	85(*S*)	90
(*R*)-MeO-BIPHEP	Ph	Et	50	EtOH, 50 °C, 1 atm H_2	96(*S*)	94
(*R*)-SEGPHOS	Ph	Me	10000	MeOH, 80 °C, 30 atm H_2	97.6(*S*)	35
(*R*)-Xyl-P-Phos	Ph	Et	800	EtOH/CH_2Cl_2, 90 °C, 20 atm H_2	96.2(*S*)	32b
(*S*)-Xylyl-o-BINAPO	Ph	Et	100	EtOH/CH_2Cl_2, 50 °C, 5.3 atm H_2	99(*R*)	52

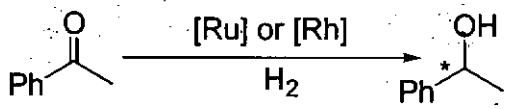
However, the asymmetric hydrogenation of simple aliphatic ketones remains problematic. It is difficult for the chiral catalyst to differentiate between two alkyl groups or between methyl and other alkyl groups. Some promising results have been obtained by PennPhos-Rh and Ru/BINAP/diamine systems.[28, 95a, 95d, 96]

Excellent chemoselectivity and enantioselectivity have been achieved in the asymmetric hydrogeantion of α,β-unsaturated ketones by using the combination of Ru-diphosphine complexes and (*R,R*)-diamine as catalyst[37b, 95a, 95d, 97]. For example, cyclic enone can be hydrogenationed in high enantioselectivity with the double bond intact (Scheme 1-8).[97]



Scheme 1-8

Table 1- 10 Asymmetric hydrogenation of acetophenone

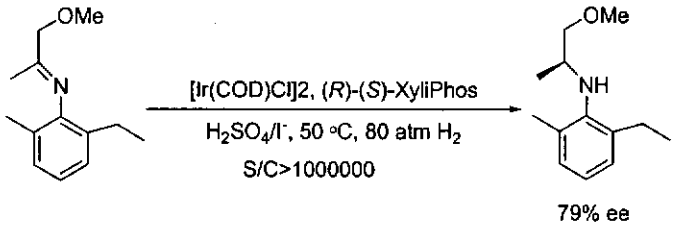


Catalyst	S/C	Reaction Conditions	% ee	Ref
Ru-(*S*)-Xyl-BINAP	10000	*i*PrOH, 28-30 °C, 8 atm H_2	99 (*R*)	95a
Ru-(*S*)-Xyl-BINAP	2400000	*i*PrOH, 24-30 °C, 45 atm H_2	99 (*R*)	95b
Ru-(*R*)-**25b**	20000	*i*PrOH, 18-20 °C, 8 atm H_2	99 (*R*)	37b
Ru-(*R*)-Xyl-P-Phos	100000	*i*PrOH, 25-28 °C, 33 atm H_2	99.1 (*S*)	32
Ru-(*R*)-Xyl-HexaPHEMP	15000	*i*PrOH, 30 °C, 10 bar H_2	98 (*S*)	42
Ru-(*S*)-Xyl-SDP	100000	*i*PrOH, 40 °C, 50 atm H_2	98 (*S*)	39
Rh-PennPhos	100	MeOH, rt, 30 atm H_2	95(*S*)	28

1.1.4 Applications of Chiral Phosphorous Liagnds in Asymmetric Hydrogenation of Imines

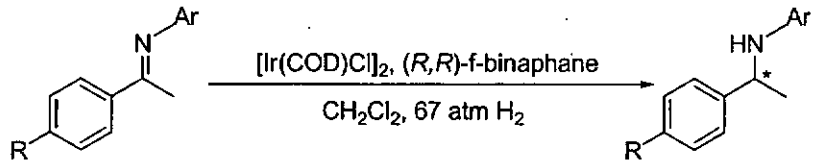
Despite the fact that much advance has been achieved in the highly enantioselective hydrogenation of prochiral olefins and ketones in the last few decades, limited progress has been made in the asymmetric hydrogenation of imines. Since chiral amines play an important role in many biologically active molecules, the development of practical methods to obtain these chiral compounds is extremely important in organic synthesis. The asymmetric hydrogenation of imines with phosphorous ligand and transition-metal complexes offers a convenient route for the preparation of chiral amines. Several types of imines can be asymmetrically hydrogenated in excellent ee values with a few chiral Ir-catalysts.[26, 99-100] A famous example is the very active and productive Ir-XyliPhos catalyst used in the metolachor process carried out by Syngenta with a production volume of over 10000 ton per year. It is the largest known production process with TONs up to 2000000 and TOFs over 400000 h^{-1} with 79% ee (Scheme 1-9).[99] More recently, Zhang and coworkers reported that up to 99% enantioselectivities have been obtained in the asymmetric hydrogenation of *N*-aryl imine with a neutral Ir-f-binaphane as catalyst (Table 1-11).[26]

High enantioselectivities have also been obtained with iridium complexes of chiral P-N ligands. Pfaltz and coworkers have found that Ir-PHOX complex could catalyze the hydrogenation of imines with up to 89% ee. Besides the chiral iridium catalyst, some Rh, Ru and Pd complexes of chiral phosphorous ligands are also effective for the asymmetric hydrogenation of imines.[101-106]



Scheme 1-9

Table 1-11 Asymmetric hydrogenation of N-aryl imines



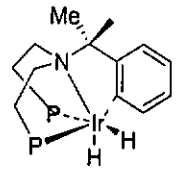
R	Ar	S/C	Reaction Conditions	%ee
H	Ph	100	I_2, -5°C, 40 h	94
MeO	Ph	100	I_2, -5°C, 24 h	95
H	2,6-Me_2Ph	100	Rt, 44 h	>99
MeO	2,6-Me_2Ph	100	Rt, 44 h	98
CF_3	2,6-Me_2Ph	100	Rt, 44 h	99

1.1.5 Applications of Chiral Phosphorous Liagnds in Asymmetric Hydrogenation of Heteroaromatic Compounds

Since many optically pure heterocycloalkanes and their derivatives are very valuable building blocks and intermediates for the synthesis of structurally interesting and biologically active compounds, the development of highly effective systems for the preparation of these heterocycles is not only of arising interest to the academic world, but also to the industrial scientists.[108] From both scientific and commercial points of view, a one-step enantioselective catalytic hydrogenation of the corresponding heteroaromatic

compounds would be a very attractive approach. A variety of chiral Rh, Ru and Ir complexes have been demonstrated to be highly efficient and enantioselective in the hydrogenation of a number of prochiral functional groups, such as functionalized and unfunctionalized olefins, ketones, and imines. However, these catalysts often failed to give good results with heteroaromatic compounds. The resonance stability of heteroaromatic rings might impede the enantioselective hydrogenation.[109] So far only limited examples have been reported for the homogeneous asymmetric hydrogenation of heteroaromatic compounds. Studer and his co-workers used chiral rhodium complexes of bidentate phosphines to hydrogenate monosubstituted pyridines and furans, but low enantioselectivites with only 24-27% ees were attained.[110] Murata *et al.* investigated the asymmetric hydrogenation of 2-methylquinoxaline with [(+)-(**DIOP**)RhH] complex as a catalyst, but only 3% ee was obtained.[111a] Enhanced enantioselectivities up to 90% have been achieved by Bianchini and his co-workers in the asymmetric hydrogenation of 2-methylquinoxaline with an orthometalated dihydride iridium complex, **58** (Figure 1-6), but the use of Ru catalysts with bidentate phosphine as ligands only led to lower ee values.[111b, 42b] Recently, Ito and his co-workers reported their attempts on the asymmetric hydrogenation of *N*-Ac or BOC-substituted indoles.[25g] They discovered that the Rh/**Ph-TRAP**/Cs_2CO_3 catalyst system exhibited high efficiency and good enantioselectivity (Scheme 1-10). More recently, Zhou and co-workers found that the iridium complex generated in situ from $[Ir(COD)Cl]_2$ and (*R*)-**MeO-Biphep** is a good catalyst for the enantioselective hydrogenation of quinolines. The 2- or 2,6-substituted quinolines have been smoothly hydrogenated at room temperature without reduction of the fused aromatic ring, leading to very high yields as well as enantioselectivites with up to 96% ee (Table 1-

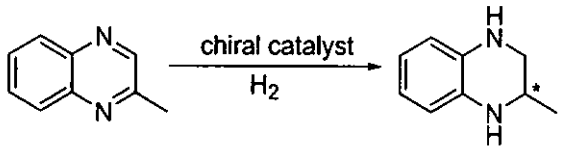
13). Other bidentate phosphine ligands, such as **BINAP**, **DIOP** and **DuPhos**, did not give active complexes with high enantioselectivities. [112]



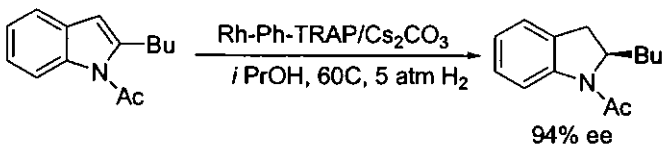
58

Figure 1-6

Table 1-12 Asymmetric hydrogenation of 2-methylquinoxaline

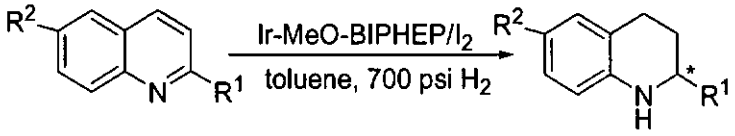


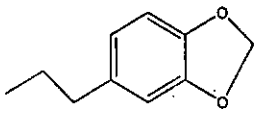
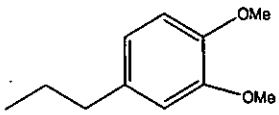
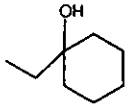
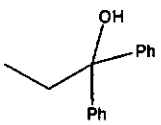
Catalyst	S/C	Reaction Contidions	%Conv	% ee	Ref
58	50	MeOH, 100 °C, 5 bar H_2	53.7	90	111b
(*R, R*)-Et-DuPhos-Ru	1000	t-BuOH, rt, 430 psi H_2, (*R,R*)-DACH	98	40 (*S*)	42b
(*R*)-BINAP-Ru	1000	t-BuOH, rt, 430 psi H_2, (*R,R*)-DAIPEN	94	62 (*S*)	42b
(*R*)-BINAP-Ru	1000	t-BuOH, rt, 430 psi H_2, (*R,R*)-DPEN	99	66 (*S*)	42b
(*S*)-HexaPHEMP-Ru	1000	t-BuOH, rt, 430 psi H_2, (*R,R*)-DPEN	>99	69 (*R*)	42b
(*S*)-Xyl-HexaPHEMP-Ru	1000	t-BuOH, rt, 430 psi H_2, (*R,R*)-DPEN	>99	72 (*R*)	42b
(*S*)-BINAP-Ru	1000	t-BuOH, rt, 430 psi H_2, (*R,R*)-DACH	>99	61 (*S*)	42b
(*S*)-HexaPHEMP-Ru	1000	t-BuOH, rt, 430 psi H_2, (*R,R*)-DACH	>99	65 (*R*)	42b
(*S*)-Xyl-HexaPHEMP-Ru	1000	t-BuOH, rt, 430 psi H_2, (*R,R*)-DACH	99	73 (*R*)	42b



Scheme 1-10

Table 1-13 Asymmetric hydrogenation of quinolines



R^1	R^2	% Yield	% ee
H	Me	94	94 (*R*)
H	Et	88	96 (*R*)
H	n-Pr	92	93 (*R*)
H	n-bu	86	92 (*R*)
H	3-Butenyl	91	92 (*R*)
H	n-Pentyl	92	92 (*R*)
H	Phenethyl	94	94 (*R*)
H		88	93 (*R*)
H		86	96 (*R*)
F	Me	88	96 (*R*)
Me	Me	91	91 (*R*)
MeO	Me	89	84 (*R*)
H	Ph	95	72 (*S*)
H		87	94 (*S*)
H		89	92 (*S*)
H		94	91 (*S*)
H	CH_2OH	83	75 (*S*)

H	i-Pr	92	94 (*S*)
H	CH_2OCOCH_3	90	87(*S*)

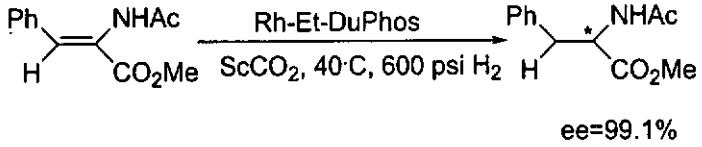
1.2 Transition-metal Catalyzed Homogeneous Asymmetric Hydrogenation in Novel Reaction Media

Despite the laboratory success of transition-metal catalyzed homogenous asymmetric hydrogenation reactions, the industrial applications of such processes have been limited due to the difficulty in separating and recycling of the expensive chiral catalysts as well as the toxicity of trace metal contaminants in organic products. Methods that can immobilize these chiral organometallic catalysts have attracted a great deal of interest.[113-115] The use of two-phase systems presents a practical and convenient solution to these obstacles. The principle of this separation approach lies in the fact that the phase of preference of the catalyst differs from that of the substrate, thus allowing the recovery of the catalyst from products by phase-separation. In this context, the use of novel reaction media is very appealing. Recently many asymmetric catalytic reactions have been carried out in this novel reaction medium, and the results have shown great potential for the immobilization of chiral catalysts.

Supercritical CO_2 is one of the environmentally benign and alternative reaction media for chemical synthesis.[116] The miscibility of $ScCO_2$ with many gases and the absence of a liquid/gas-phase boundary in the supercritical state lead to the maximum availability of gaseous reactants, avoiding potential problems of mass-transfer limitations. Beneficial effects can also arise from the high compressibility of $ScCO_2$, allowing selectivity changes by variation of density with comparably small changes in the reaction

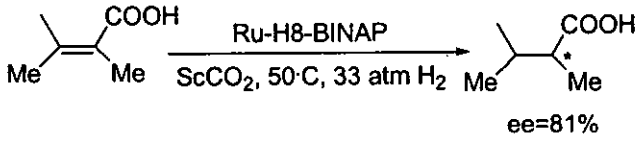
conditions. The chemical interaction of CO_2 with functional groups of the substrates can result in better compatibility with the employed catalysts. Moreover, the attractive properties of $ScCO_2$ may allow remarkable efficient and simple separation of catalysts and products.

The first application of $ScCO_2$ as reaction medium for asymmetric hydrogenation was reported by Burk and coworkers (Scheme 1-11).[117a] The results obtained were comparable to those in normal organic solvents.



Scheme 1-11

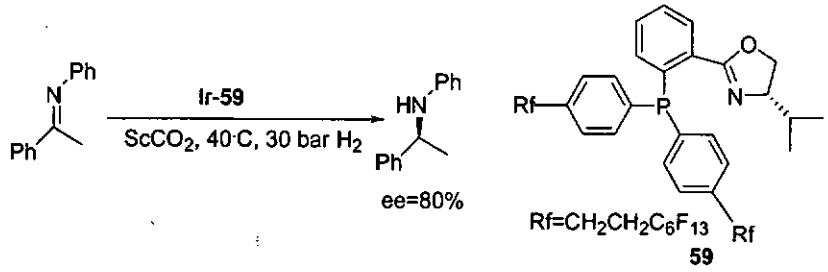
Xiao *et al.* reported Ru-catalyzed asymmetric hydrogenation of α,β-unsaturated carboxylic acids with **H8-BINAP** as ligand, and up to 81% ee was obtained (Scheme 1-12).[117b]



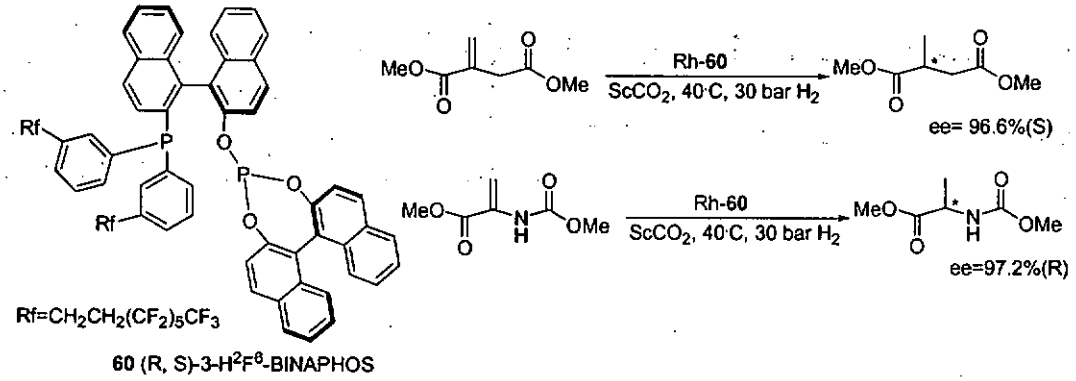
Scheme 1-12

With perfluoroalkylated chiral phosphinodihydrooxazole **59** as ligand, Leitner and coworkers described the Ir-catalyzed asymmetric hydrogenation of imines in $ScCO_2$ that give the hydrogenated products in high yields and up to 81% ee.[101b] Moreover, the catalyst could be readily recovered and recycled several times without significant loss of activity and enantioselectivity (Scheme 1-13). Leitner's group also prepared a

perfluoroalkylated chiral bidentate ligand, (*R,S*)-3-H^2F^6-BINAPHOS, **60**, and they found that it could efficiently mediate the asymmetric hydrogenation of dehydroamino acid and dimethyl itaconate in $ScCO_2$ (Scheme 1-14).[117c] The ee values were comparable to those obtained in organic solvents.

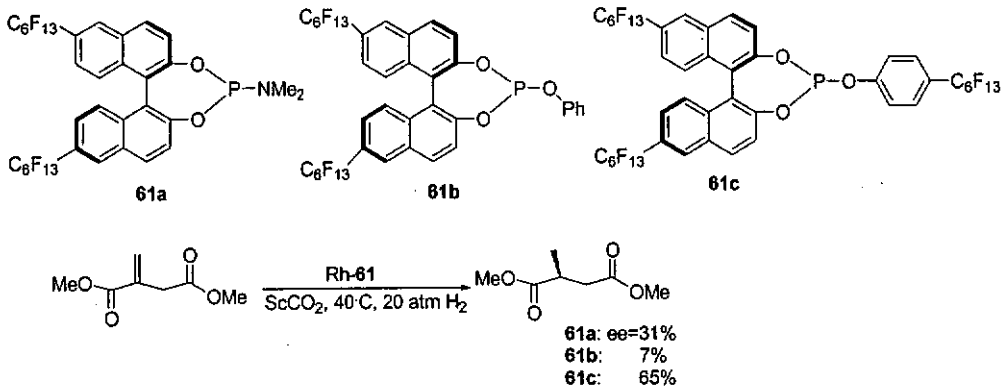


Scheme 1-13



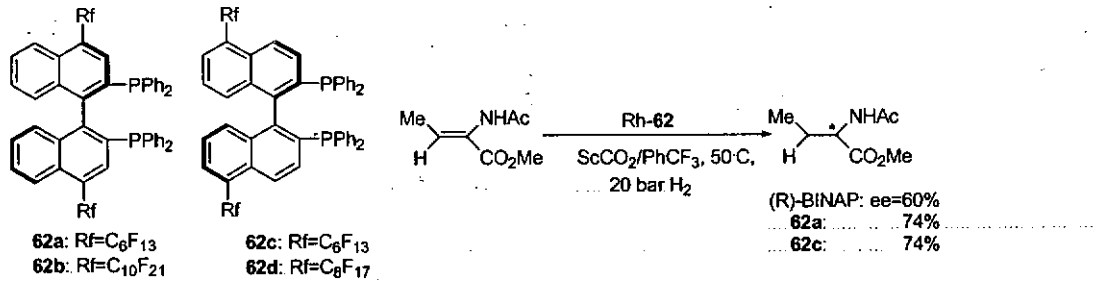
Scheme 1-14

Hope and coworkers reported the synthesis of perfluoroalkylated chiral monodentate ligands, **61a-c**, and their application in asymmetric hydrogenation of dimethyl itaconate in $ScCO_2$ (Scheme 1-15).[117d] However, the enantioselectivities were much lower than those in convenient solvents.



Scheme 1-15

More recently, Lemaire and coworkers reported the synthesis of perfluoroalkylated BINAP ligands, **62a-c**, and their application in asymmetric hydrogenation of methyl-2-acetamidoacrylate in $ScCO_2$.[117e] However, no conversion was observed. With the addition of co-solvent, trifluorotoluene, good conversion and enantioselectivity were obtained (Scheme 1-16).

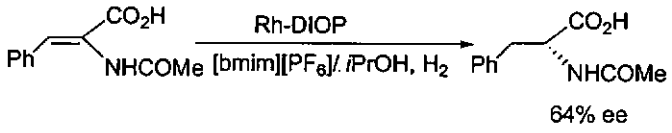


Scheme 1-16

However, the use of $ScCO_2$ as a reaction medium has its limitations. The solubility of reagents / or catalysts in the fluid may be relatively low. Furthermore, in some cases, the CO_2 itself may be inserted into metal-hydride bonds of catalyst resulting in the formation of formate complexes. Although some perfluoroalkylated ligands have been synthesized to increase the solubility of catalysts in $ScCO_2$, the synthesis is very tedious and requires much synthetic effort. Moreover, the safety of the reaction in this fluid and the catalyst recycling remains a problem.

Recently, room temperature ionic liquids have been highlighted as one of the most promising candidates to hazardous organic solvents for clean chemical reactions.[118] The high polarity of ionic liquids ensures that the transition-metal catalysts bearing polar or ionic character can be easily immobilized, separated and recycled. Numerous studies of asymmetric catalysis in ionic liquids have been reported.

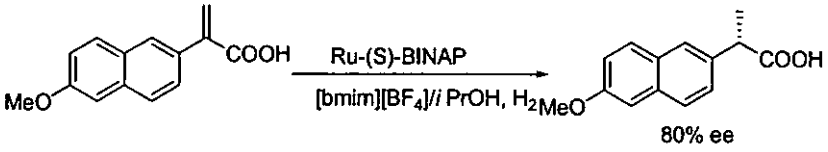
The first asymmetric hydrogenation in ionic liquid was reported in 1995 by Chauvin and coworkers (Scheme 1-17).[119] In a biphasic [bmim][PF_6]/iPrOH mixture, a [Rh(COD)((-)-DIOP)]PF_6 provided 64% ee in the asymmetric hydrogenation of α-acetamidocinnamic acid. The product retained in the alcohol phase could be separated quantitatively by simple decantation while the catalyst contained in ionic liquid phase proved reusable.



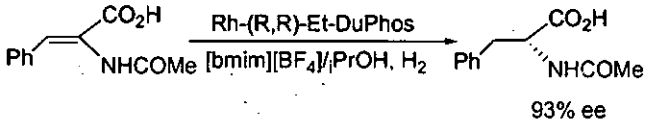
Scheme 1-17

In 1997, Dupont and coworkers investigated the Ru-catalyzed asymmetric hydrogenation of 2-arylacrylic acids with BINAP as ligand in [bmim][BF_4]/iPrOH medium (Scheme 1-18).[120a] The results obtained were comparable to those achieved in

homogeneous organic solvents. The Ru-catalyst could be readily immobilized in ionic liquid and recycled for several times without significant loss of activity and enantioselectivity. The same group also studied the asymmetric hydrogenation of α-acetamidocinnamic acid with Rh(I)-Et-DuPhos as catalyst in ionic liquid/*i*PrOH mixture, and the best result attained was 93% ee in [bmim][BF_4]/*i*PrOH medium (Scheme 1-19).[120b] The catalyst immobilized in ionic liquid could be reused 4 times.

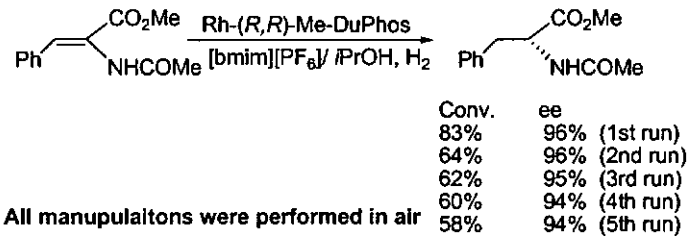


Scheme 1-18



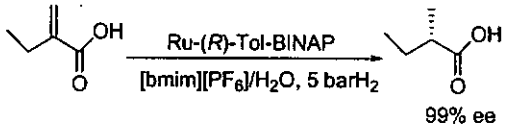
Scheme 1-19

Geresh and coworkers found that asymmetric hydrogenation of enamides with Rh-Me-DuPhos as catalyst in the biphasic [bmim][PF_6]/*i*PrOH system could lead to high yields and enantioselectivity which were comparable to those obtained in iPrOH.[121] Moreover, it was found that the ionic liquid could provide additional stability to the air-sensitive catalyst, enabling all experiments including catalyst recycling to be conducted in air without significant loss of enantioselectivity (Scheme 1-20).



Scheme 1-20

Jessop and coworkers described the asymmetric hydrogenation of tiglic acid with Ru-Tol-BINAP as catalyst in wet [bmim][PF_6] followed by the extraction of the product with $ScCO_2$ (Scheme 1-21).[122] Due to the high insolubility of catalyst in $ScCO_2$, the extremely pure product could be obtained while the catalyst was retained in ionic liquid phase. The recovered catalyst was reused five times with retained activity and even enhanced enantioselectivity. Clearly this procedure offers a good solution to the leaching of the catalyst during the extraction.



Scheme 1-21

In order to suppress the leaching of catalyst, the use of modified phosphine ligands with polar groups is a good choice. Recently Lin and coworkers reported the synthesis of modified BINAP ligands, **62** and **63** (Figure 1-7), which possess polar phosphonic acid groups as appendages and their application in the asymmetric hydrogenation of β-ketoesters in biphasic ionic liquid/MeOH system.[123a] Higher *ee* values were attained than those obtained in MeOH. The products can be separated by easy extraction and the immobilized catalyst could be recycled for 4 times without any significant loss of activity and enantioselectivity (Table 1-14).

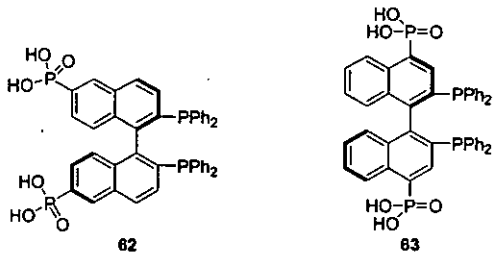
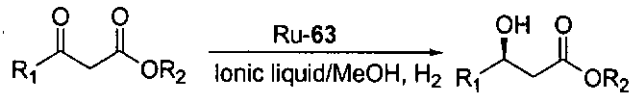


Figure1-7

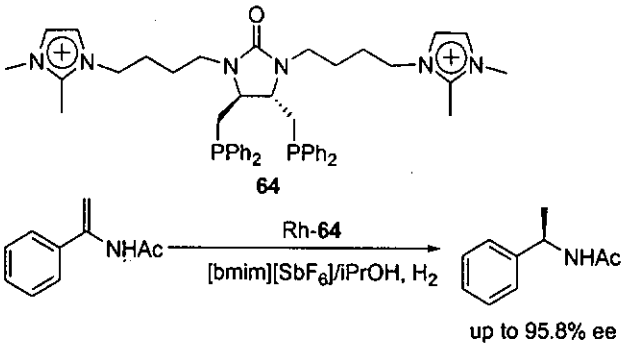
Table 1-14 Asymmetric hydrogenation of β-ketoesters in ionic liquids



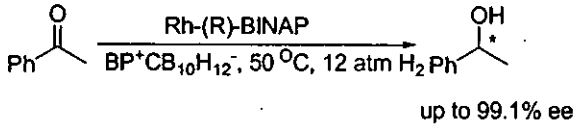
R1	R2	MeOH	[dmpim][NTf_2]	[bmim][BF_4]	[bmim][PF_6]
Me	Me	98.3	99.0	98.9	99.3
nPr	Et	98.6	99.3	99.1	99.1
Me	iPr	94.2	98.1	98.9	98.9
Me	tBu	96.7	97.5	98.5	97.5

Similar strategy to reduce the catalyst leaching has been adopted by Lee and coworkers.[123b] They prepared the new polar bidentate chiral ligand **64** bearing two imidazolium salt tags on the framework and found that the Rh-complex of **64** was efficiently immobilized in ionic liquid, and could be reused several times without significant loss of catalytic efficiency (Scheme 1-22).

More recently, the asymmetric hydrogenation of simple ketones has also been realized in ionic liquid.[124] Zhu and coworkers found that the Rh-catalyst derived from rhodacarborane [close-1, 3-{μ-(η^2-3-CH_2=$CHCH_2CH_2$)}-3-H-3-PPh_3-3,1,2-$RhC_2B_9H_{10}$] and (*R*)-BINAP was very effective for the asymmetric hydrogenation of simple ketones and functionalized ketones in ionic liquids (Scheme 1-23). The results obtained in ionic liquids were better than those in THF. The best result was achieved in new ionic liquid, $BP^+CB_{10}H_{12}^-$. The catalyst could be readily recovered and reused for 6 times without degration of catalytic activity and selectivity.



Scheme 1-22



Scheme 1-23

Although the catalyst immobilized in ionic liquid phase could be recycled and reused for several times without significant loss of activity and enantioselectivity, the lower activities of the catalysts and the leaching of the metals are still problems for industrial applications. Another difficulty is that the recent development of asymmetric hydrogenation in ionic liquids is only limited to rhodium or ruthenium catalyst systems, which often require a polar and ionic reaction medium. In addition, we should carefully consider the high prices of the ionic liquids and the uncertainties in their toxicity as well as their impact on the environment before the real industrial applications. Hence, in the future, there clearly exists a need to find a cheaper and reusable reaction medium that can entrap the catalyst and meet the environmental requirements.

1.3 Aims and Objectives

Chan *et al.* have developed a new class of highly effective chiral pyridylphosphine ligand, 2,2',6,6'-tetramethoxy-4,4'-bis(diphenylphosphino)-3,3'-bipyridine (**P-Phos**) and its analogs,[32] 2,2',6,6'-tetramethoxy-4,4'-bis[di(p-methylphenyl)phosphino]-3,3'-bipyridine (**Tol-P-Phos**), 2,2',6,6'-tetramethoxy-4,4'-bis[di(3,5-dimethylphenyl)phosphino]-3,3'-bipyridine (**Xyl-P-Phos**) and 2,2',6,6'-tetramethoxy-4,4'-bis(dicyclohexylphosphino)-3,3'-bipyridine (**Cy-P-Phos**). The electronic and steric properties on the phosphorus of these ligands can be tunable by substitution of different groups on the phosphorus atoms. All these dipyridylphosphine ligands show high activity and enantioselectivity in ruthenium and rhodium catalyzed asymmetric hydrogenation of beta keto esters, simple ketones, 2-(6'-methoxy-2'-naphyl)propenoic acid and dehydroamino acids.[32] **P-Phos** and its derivatives were shown to be air-stable even in ruthenium catalyzed asymmetric hydrogenation. Zhou and his co-workers reported their successful work in iridium catalyzed asymmetric hydrogenation of quinolines with **MeO-BIPHEP**.[112a] Following their impressive work, our first objective was to develop an air-stable and recyclable catalyst system with our **P-Phos** systems and other types of ligands for industrial application of asymmetric hydrogenation of quinolines.

In recent years, room temperature ionic liquids (ILs) have attracted much attention for scientists working in the field of green chemistry. ILs are non-volatile and they possess hydrophilicity, lipophilicity and hydrogen-bond donor and acceptor ability, which can easily be controlled by suitable changes in either the cationic or anionic

components. Lin *et al.* [123a] reported their excellent findings in asymmetric hydrogenation of beta keto esters in room temperature ionic liquids (RTILs) with their BINAP derivatives. Their catalysts can be recycled in RTILs over 5 cycles with enantioselectivities over 95%. Hence, our second objective focused on exploring the application of **P-Phos** in RTILs for asymmetric hydrogenation of a variety of substrates.

Ortho-substituted biaryl ligands in asymmetric catalysis are relatively less explored. Zhang and his co-workers[38] reported their ortho-substituted **BIPHEP** ligand and its effectiveness in rhodium catalyzed asymmetric hydrogenation of cyclic enamide with enantioselectivities up to 98%. This result is significantly better than its unsubstituted counterpart (65% ee) and other classical ligands such as **BINAP** (55% ee), **Me-DuPhos** (N/A) and **DIOP** (13% ee).

Inspired by the success of this ortho-substituted ligand and to extend our patented work, we tried another approach to study the steric and electronic effect on **P-Phos** by substitution at the ortho positions. In this thesis, we report our preliminary work on the first ortho-substituted analog of **P-Phos**, ***o*-Ph-P-Phos**, and its effect in the same asymmetric catalytic reactions.

Chapter 2

Development of air stable and recyclable catalyst system for enantioselective hydrogenation of quinolines

2.1 Introduction

Optically pure tetrahydroquinoline derivatives are important organic synthetic intermediates and building blocks for the preparation of biologically active compounds. However, methods for the enantioselective formation of these chiral compounds are scarce. Asymmetric hydrogenation of quinoline derivatives offers an attractive and convenient approach. Recently, Wang and his co-workers reported the first example of highly enantioselective iridium-catalyzed hydrogenation of quinoline derivatives in toluene at room temperature under 700 psi of hydrogen for 18 h using $[Ir(COD)Cl]_2$/(*R*)-**MeO-BIPHEP**/I_2 system with ee up to 96%.[112a] Using their reported methodology, a series of optically active tetrahedroquinoline alkaloids, such as angustrureine and flumequine, could be successfully synthesized through asymmetric hydrogenation.

Our colleagues have recently prepared a new family of chiral dipyridylphosphane ligands **P-Phos** and its derivatives, and have established their effectiveness in the catalytic asymmetric hydrogenation of many substrates, including unsaturated carboxylic acids, dehydroamino acid derivatives and ketones. They were also effective in asymmetric carbonylations of olefins and asymmetric conjugate additions of arylboronic acids to enones. These results suggested that the rigidity of the bipyridyl backbone allowed good transfer of chiral information. It is notable that the ruthenium complexes, $[Ru(C_6H_6)$(**P-Phos**)$Cl_2]$ and $[RuCl_2$(**P-Phos**)(DPEN)], displayed very strong air-stability even in solution, indicating the high potential for

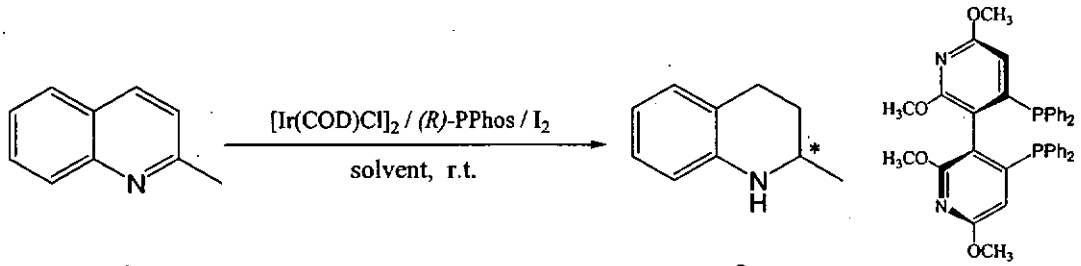
industrial application. Herein we report that the highly air-stable and very effective iridum catalyst precursor which was generated in situ from chiral **P-Phos** and $[Ir(COD)Cl]_2$ for enantioselective hydrogenation of a series of 2,6-di-substitited quinolines, and the whole process was carried out in air without the use of dry box. Following our former studies on the immobilizaion and recycle of the chiral catalysts in asymmetric hydrogenation, we found that it is possible to replace the organic solvent with cheap and environmentally benign liquid polymer, PEG-dimethyl ether, as a reaction medium. In the study, no loss of the activity and enantioselectivity was detected. The products were easily isolated and the catalyst could efficiently recovered and recycled. To the best of our knowledge, the described catalytic system represents the only known protocol with which the asymmetric hydrogenation of quinolines can be achieved in highly efficient and environmentally-appealing fashion.

2.2 Results and Discussion

2.2.1 Asymmetric hydrogenation of quinoline derivatives with Ir-**P-Phos**

To determine if **P-Phos** was active in the asymmetric hydrogenation of quinolines, we employed quinaldine **1a** as the test substrate under the conditions previously optimized by Zhou and coworkers, in which the active catalyst was derived in situ from $[Ir(COD)Cl]_2$ and **P-Phos** in combination with I_2 as an additive (Scheme 2-1). After stirring for 20 h at room temperature, the reaction went to completion to give the product with 84% yield and 84% ee (Table 2-1, entry 1). Although the results were not as good as those obtained with **MeO-BIPHEP**, they were very promising and indicated that our dipyridyl ligand could also mediate this asymmetric transformation. Considering the strong solvent-dependence of the reaction in the presence of **MeO-BIPHEP** as a ligand, we envisioned that in our case

the choice of the solvent should be similarly important. Therefore a screening of the solvent is necessary. Several organic solvents were examined, and the results are summarized in Table 2-1. As can be seen from the table, the solvent had a significant effect on both the enantioselectivity and yield. When benzene was chosen as the reaction medium, a better enantioselectivity but poor yield was obtained as compared with those in toluene (entry 2). In both CH_2Cl_2 and $ClCH_2CH_2Cl$, good ee values were obtained, but the reaction became very sluggish, and the yields decreased substantially (entries 3-4). The use of protic solvents led to poor yields and enantioselectivites (entries 5-7). The best results were obtained when THF was used as the reaction solvent with 91% enantioselectivity and 97% yield (entry 8). Under this condition, (*S*)-BINAP showed only 77% ee with >99% conversion while only 35% ee with 97% conversion for (*R*)-**MeO-BIPHEP**. With **PM-Phos (65)**[126] as a ligand, only 43% ee and 63% conversion were attained. In comparison with those **MeO-BIPHEP** mediated system, our **P-Phos**–based asymmetric catalytic process seems more sensitive to the choice of solvent, which may be ascribed to its bipyridyl structure.



1a 2a (*R*)-**P-Phos**

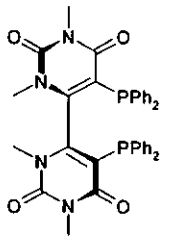
Scheme 2-1

Table 2-1 Catalytic asymmetric hydrogenation of **1a**[a]

Entry	Solvent	ee[b] (%)	Yield (%)	Absolute configuration[c]
1	Toluene	88	84	*R*
2	Benzene	91	55	*R*
3	CH_2Cl_2	88	47	*R*
4	$ClCH_2CH_2Cl$	89	76	*R*

5	iPrOH	84	60	*R*
6	MeOH	48	33	*S*
7	EtOH	18	83	*R*
8	THF	91	97	*R*

[a]Reaction conditions: 1 mmol quinoline, $[Ir(COD)Cl]_2$ (0.5 mol%), (*R*)-P-Phos (1.1 mol%), I_2 (10 mol%), 5 mL solvent, 700 psi H_2 pressure and 25 °C. [b]The enantioselectivities of product was determined by HPLC analysis with Chiralpak OJ-H column. [c]The absolute configuration is assigned by comparing the HPLC retention time with those reported in the literature data.



***(S)*-PM-Phos 65**[126]

With THF as the reaction medium, the effect of pressure and temperature on the hydrogenation was investigated. Table 2-2 shows that the enantioselectivity was relatively insensitive to changes in hydrogen pressure, but the isolated yield was decreased slightly at lower pressure (entries 1-3). The reaction favoured low temperature (entries 4-5), and at higher temperature, the enantioselectivity deteriorated (entry 6).

Table 2-2. Effect of pressure and temperature on catalytic asymmetric hydrogenation of **1a**[a]

Entry	H_2 (psi)	*T* (°C)	Yield (%)	ee[b] (%)	Absolute configuration[c]
1	1500	25	97	91	*R*
2	700	25	97	91	*R*
3	100	25	90	91	*R*
4	700	-35	82	91	*R*
5	700	0	92	92	*R*
6	700	55	85	38	*R*

[a]Reaction conditions: 1 mmol quinoline, $[Ir(COD)Cl]_2$ (0.5 mol%), (*R*)-P-Phos (1.1 mol%), I_2 (10 mol%), 5 mL THF. [b]The enantioselectivities of product was determined by HPLC analysis with Chiralpak OJ-H column. [c]The absolute configuration is assigned by comparing the HPLC retention time with those reported in the literature data.

The effect of substrate-to-catalyst (S/C) ratio on the hydrogenation was also examined and the results are listed in Table 2-3. From the table, it can bee seen that a change in S/C ratio had no effect on enantioselectivity (entries 1-4). Remarkably, this reaction could even be performed at a substrate-to-catalyst ratio of 2000:1 without loss in enantioselectivity, and the highest yield was obtained at a S/C ratio of 200:1 in this reaction.

Table 2-3 Effect of substrate-to-catalyst ratio on catalytic asymmetric hydrogenation of **1a**[a]

Entry	S/C ratio	Isolated Yield (%)	ee[b] (%)	Absolute Configuration[c]
1	200:1	97	91	*R*
2	500:1	92	91	*R*
3	1000:1	86	91	*R*
4	2000:1	51	91	*R*

[a]Reaction conditions: $[Ir(COD)Cl]_2$/(*R*)-P-Phos (1:2.2), 1 mmol quinoline, I_2 (0.05 mmol), 5 mL THF, 700 psi H_2 pressure and 25 °C. [b]The enantioselectivities of product was determined by HPLC analysis with Chiralpak OJ-H column. [c]The absolute configuration was assigned by comparing the HPLC retention time with those reported in the literature data.

Considering the remarkable impact of additives on catalytic performance in asymmetric catalysis,[8,10] a number of additives were screened in our Ir-P-Phos-catalyzed hydrogenation. Without any additive, the reaction was very sluggish, and only 38% ee was obtained (entry 1). Table 2-4 shows that iodine, potassium iodide and bismuth (III) iodide are effective additives for this reaction while other additives are unable to provide high enantioselectivities. From these results, it appears that iodine or iodide is important for this catalysis. Iodine or iodide may play a very important role for the Ir-catalyzed mechanism. From Table 2-4, further experimental studies show that the change of Ir precursor to a cationic $[Ir(COD)]BF_4$ or $[Ir(COD)]PF_6$ resulted in the decrease of yield and enantioselectivity with the inversion of product configuration from *R* to *S* (entries 9-10). Thus the optimized

conditions for our catalyst system $[Ir(COD)Cl]_2$/**P-Phos**/I_2 are 700 psi H_2 and room temperature with THF as a solvent.

Table 2-4 Effect of additives on catalytic asymmetric hydrogenation of **1a**[a]

Entry	Additives	Yield (%)	ee[b] (%)	Absolute Configuration[c]
1	NIL	15	58	*R*
2	I_2	97	91	*R*
3	KI	78	89	*R*
4	NaI	2	8	*R*
5	BiI_3	90	88	*R*
6	tetrabutylammonium iodide	67	67	*R*
7	LiCl	20	60	*R*
8	Phthalimide	64	60	*R*
9[d]	I_2	37	47	*S*
10[e]	I_2	83	14	*S*

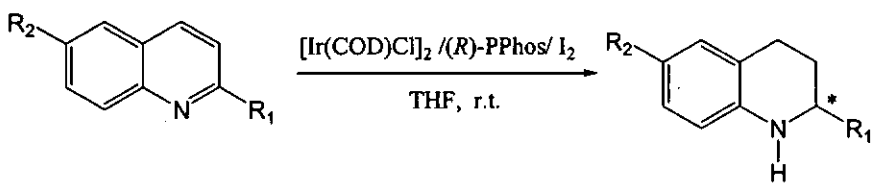
[a]Reaction conditions: 1 mmol quinoline, $[Ir(COD)Cl]_2$ (0.005 mmol), (*R*)-P-Phos (0.011 mmol), additive (10-20 mmol%), 5 mL THF, 700 psi H_2 pressure and 25 °C. [b]The enantioselectivities of product was determined by HPLC analysis with Chiralpak OJ-H column. [c]The absolute configuration was assigned by comparing the HPLC retention time with those reported in the literature data. [d]$[Ir(COD)]BF_4$ is used. [e]$[Ir(COD)]PF_6$ is used.

The air stability of our catalyst system has also been tested. The $[Ir(COD)Cl]_2$ and (*R*)-P-Phos were first dissolved and stirred in normal AR grade THF (i.e, without degasing and pre-drying) in air for 1 day. The catalyst solution was then mixed with a solution of 2-methyl-quinoline **1a** and iodine in THF in air and stirred for one day. Finally, the reaction mixture was transferred into the autoclave and charged with H_2 at 700 psi and the reaction was allowed to proceed at room temperature for 20 hours. To our surprise, the enantioselectivity (91%) and the isolated yield (97%) of 2-methyl-1,2,3,4-tetrahydroquinoline **2a** were still retained, indicating the strong air-stability of our Ir-P-Phos complex. The following ^{31}P-NMR studies showed that there was no change of the spectrum even after two weeks. However, when the same experiment performed with **MeO-BIPHEP** as ligand under the same conditions, the

enantioselectivity and the conversion of 2-methyl-1, 2, 3, 4-tetrahydroquinoline obtained were only 21% and 28%, respectively, and this can be explained by the strong air-sensitivity of **MeO-BIPHEP**. Encouraged by the strong air-stability of our Ir-**P-Phos** catalytic system, the subsequent hydrogenation reactions were all performed in untreated THF without the use of glove box.

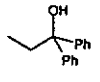
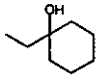
A series of substituted quinoline derivatives were hydrogenated using Ir/**P-Phos**/I_2/THF catalyst system, and the results are listed in Table 2-5. In general, our Ir-**P-Phos** catalytic system provided very good yields and moderate to high enantioselectivities (over 80%) except entries 9 and 10. This reaction was relatively insensitive to the length of side chain of 2-alkylated substituted quinolines, and good yields and enantioselectivities have been obtained (entries 1-5). The presence of substituted group on position 6 had no effect on both yield and enantioselectivity (entries 7-8, 12). Good results were also achieved with 2-arenethyl-substituted quinoline (entry 11). Lower enantioselectivity was attained with 2-phenyl or 2-CH_2OCOCH_3-substituted quinoline (entries 9-10). The tolerance of hydroxyl group was well demonstrated by the successful hydrogenation of substrates **1l-n** with excellent yields and high enantioselectivities (entries 14-16).

Table 2-5 Catalytic asymmetric hydrogenation of other quinolines[a]



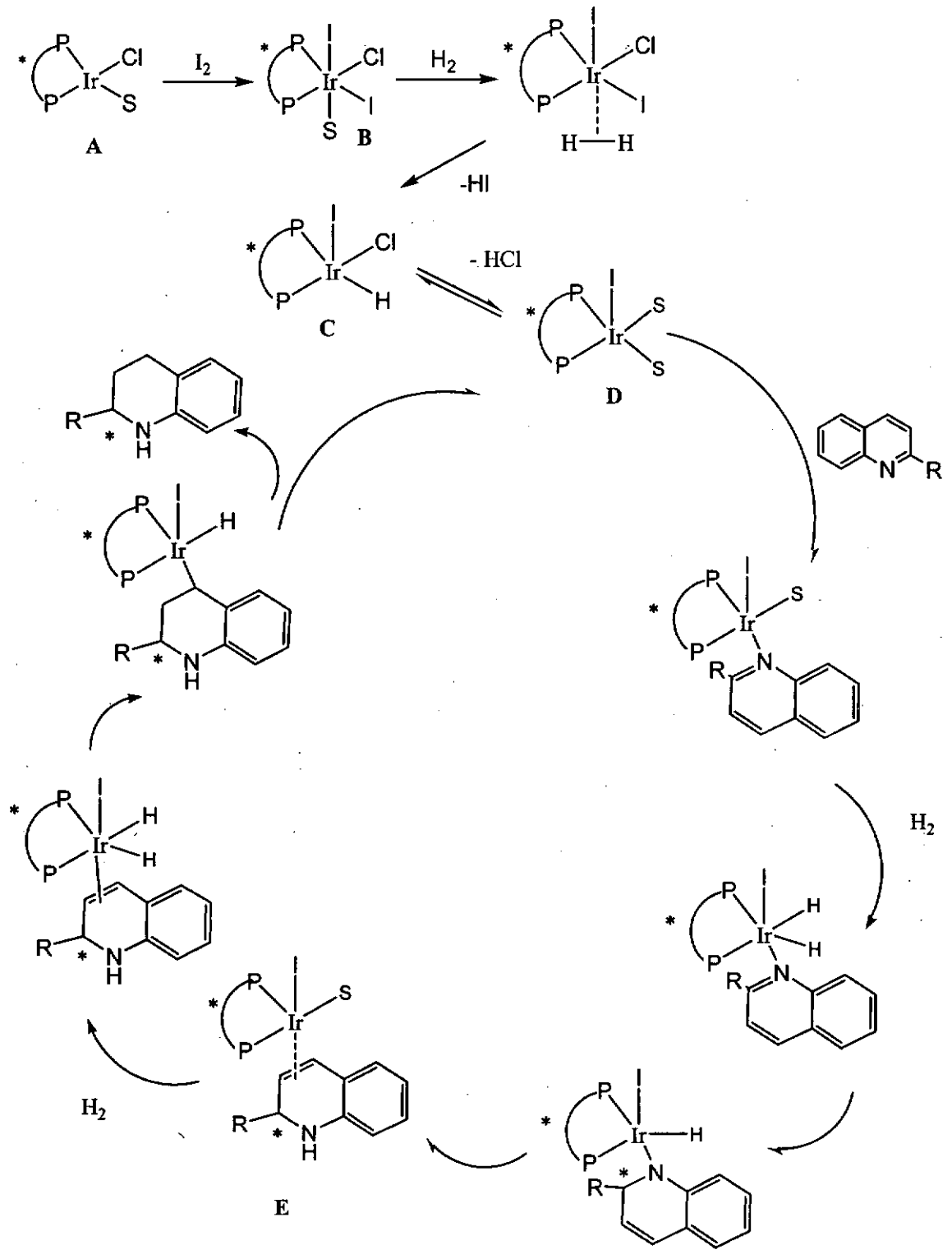
1 **2**

Entry	R_1 / R_2	Yield (%)	ee[b] (%)	Absolute configuration[c]
1	Me / H (**1a**)	97 (**2a**)	91	*R*
2	Et / H (**1b**)	99 (**2b**)	91	*R*
3	*n*-Pr / H (**1c**)	98 (98)[†](**2c**)	88 (90)[†]	*R*

4	*n*-Bu / H (**1d**)	99 (99)†(**2d**)	88 (88)†	*R*
5	3-Butenyl / H (**1d'**)	99 (**2d**)	86	*R*
6	*n*-Pentyl / H (**1e**)	97 (**2e**)	91	*R*
7	Me / Me (**1f**)	97 (97)†(**2f**)	87 (88)†	*R*
8	Me / MeO (**1g**)	97(**2g**)	87	*R*
9	$CH_2OC(O)CH_3$ / H (**1h**)	99 (**2h**)	65	*S*
10	Ph / H (**1i**)	99 (**2i**)	57	*R*
11	Phenethyl / H (**1j**)	99 (**2j**)	90	*R*
12	Me / F (**1k**)	90 (**2k**)	90	*S*
14	 / H (**1l**)	99 (**2l**)	91	*S*
15	 / H (**1m**)	98 (**2m**)	90	*S*
16	 / H (**1n**)	99 (**2n**)	85	*S*

[a]Reaction conditions: 1 mmol quinoline, $[Ir(COD)Cl]_2$ (0.005 mmol), (*R*)-P-Phos (0.011 mmol), I_2 (0.5 mmol), 5 n THF, 700 psi H_2 pressure and 25 °C. [b]The enantioselectivities of products were determined by HPLC analysis w Chiralpak OJ-H (**2a-h**), AS-H (**2i-j**), OD-H (**2k-m**) and OJ (**2n**) column. [c]The absolute configuration was assigned comparing the HPLC retention time with those reported in the literature data. [†]The catalytic reactions were perform at 0 °C.

Based on the studies of Osborn[112c] about the mechanism of Ir-catalyzed asymmetric hydrogenation of imines as well as our own observation, the following mechanism about Ir-catalyzed asymmetric hydrogenation of quinolines is proposed (Scheme 2-2). We think that the oxidative addition of I_2 to Ir^{I} precursor **A** is necessary for generating Ir^{III} complex **B**, where cleavage of HI would lead to Ir^{III}-H specie **C**.[112d] The complex will transform to intermediate **D** which goes through the catalytic cycle. The quinoline substrate can coordinate with **D** followed by migratory insertion of the quinoline into the Ir^{I}-H bond to generate an Ir-amide complex. The heterolytic cleavage of H_2 gives rise to the η^2olefin complex **E**. After migratory insertion of the η^2-olefin into the Ir^{I}-H bond, cleavage of H_2 gives an amine product and regenerates the Ir-H species **D**.



Scheme 2-2 Proposed mechanism for the Ir-**P-Phos**-catalyzed hydrogenation of quinolines

2.2.2 Development of Recyclable Asymmetric Hydrogenation Reaction in PEGDME

Encouraged by the strong air-stability of our Ir-P-Phos catalytic system, we decided to explore the recyclability of this catalyst in hydrogenation reaction. Considering that recently many transition-metal-catalyzed asymmetric hydrogenation reactions have been carried out in room temperature ionic liquids with the successful immobilization and reuse of catalysts, we became interested in the use of these novel reaction media to immobilize our catalyst. As shown in Table 2-6, the catalytic asymmetric hydrogenation of **1a** in homogeneous 1-butyl-3-methyl-imidazolium tetrafluoroborate [BMIM.BF_4]/CH_2Cl_2 or 1-butyl-3-methyl-imidazolium hexafluorophosphate [BMIM.PF_6]/CH_2Cl_2 only resulted in very low conversions and poor enantioselectivities (entries 1-2). Since our Ir-**P-Phos** catalytic system only favoured in less polar reaction medium, the retardation of this reaction in the highly polar ionic liquids fell within anticipation. Similar observation has been reported by Burgess and coworkers in their Ir-catalyzed asymmetric hydrogenation of unfucntionalized arylalkenes.[63]

It is well known that liquid polyethylene glycol (PEG) and its derivatives possess many interesting properties, such as low price, nonvolatility, high stability, recoverability, nontoxicity and environmental safety.[19] Because these solvents are immiscible with many non-polar solvents, it is very attractive to use PEG as a solvent for biphasic catalysis. Recovery of the PEG layer containing the catalyst can be achieved after a simple extraction of the product. Recent research has demonstrated the use of PEG as solvent for some catalytic asymmetric transformations and the catalysts could be simply recovered and reused several times with retention of catalytic efficiency. Thus, we attempted the hydrogenation with PEG as solvent. For

PEG with average molecular weight 200, only 43% ee was obtained (entry 3). However, when PEG with the average weight 400 was employed, the enantioselectivity increased to 77% (entry 4). Since we have confirmed that alcoholic solvents would lead to poor enantioselectivity, the low ee values obtained in PEG should be related to the OH groups at the terminal ends.

In order to avoid the effect of terminal OH groups, the application of less polar polyethylene glycol dimethyl ether (PEGDME) containing OCH_3 groups at the terminal ends (Table 2-7) was explored. Two types of PEGDME were examined, namely, high and medium molecular weight PEGDME. A simple test showed that the chiral Ir complex was totally soluble in PEGDMEs of both type. However, the PEGDME with an average molecular weight of 500 is immiscible with hexane whereas the PEGDME with an average molecular weight of 250 does not form a biphasic system with hexane. Thus, in order to develop a recyclable system, a high molecular weight PEGDME (MW=500) should be used. We next attempted the hydrogenation of **1a** in pure PEGDME (MW=500). To our delight, our Ir-**P-Phos** was highly effective in the homogeneous solution with nearly complete conversion and 85% ee (Table 2-7, entry 1). The product could be easily separated by simple extraction with hexane while the catalyst could be readily immobilized in PEGDME phase. Figure 2-1 shows that the catalyst immobilized PEGDME layer (bottom layer) was immiscible with the hexane layer (upper layer). Similar to the asymmetric hydrogenation in ionic liquids, the use of a co-solvent in PEGDME is also very important to improve the enantioselectivity. When the hydrogenation was carried out in pure PEGDME (MW=500) with equal volume of CH_2Cl_2, a higher enantioselectivity of 88% was obtained, but the reaction was relatively slow with 89% conversion after 20 h (Table 2-7, entry 2). However, when hexane was chosen as the

co-solvent, similarly high ee (88%) and nearly complete conversion (>99%) were achieved (Table 2-7, entry 3). It is obvious that the enantioselectivity obtained by the Ir/*(R)*-**P-Phos**/PEGDME/hexane system is comparable to the result performed in normal solvent such as ether, THF or DCM. We also examined the catalytic performance of Ir/*(R)*-**MeO-BIPHEP** in PEGDME (MW=500) as well as its combination with different co-solvents (Table 2-7, entry 4-6). The best enantioselectivity of 86% ee was obtained in PEGDME/hexane. However, only 61% ee was obtained for Ir/*(S)*-**BINAP**/PEGDME system. It is notable that this PEGDME was not only a good host for the chiral catalyst, but it also protected the complex from attack by atmosphere oxygen and facilitated easy recycling.

We also demonstrated that both the PEGDME and chiral Ir catalysts can be easily recovered and reused 10 times for asymmetric hydrogenation of **1a**. At the end of each hydrogenation run, the product was easily separated via simple decantation and the PEGDMG phase was washed two times with undegassed hexane in air. After being dried in vacuum, the PEGDMG phase was simply recharged with **1a** and hexane, and then subjected to the hydrogenation conditions. It was found that both Ir/*(R)*-**P-Phos** and Ir/*(R)*-**MeO-BIPHEP** could be reused for 10 times without any loss in enantioselectivity (Figure 2-2). Figure 2-3 shows that high conversion for Ir/*(R)*-**P-Phos**/PEGDME/hexane system could be maintained for over 8 cycles, while only 5 more cycles with enough conversion could be maintained for the Ir/*(R)*-**MeO-BIPHEP**/PEGDME/hexane system. These encouraging findings may help us to develop the air stable and recyclable catalyst systems for the asymmetric hydrogenation of quinolines.

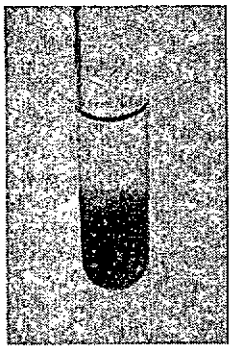
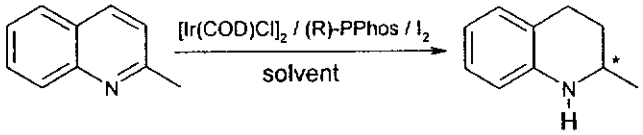


Figure 2-1 The catalyst immobilized PEGDME layer and the hexane layer

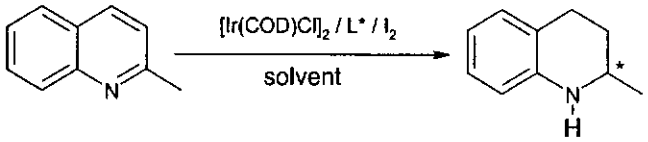
Table 2-6 Asymmetric hydrogenation of 2-methylquinolines[a] in common recyclable liquid media



Entry	Solvent*	Co-solvent*	ee[b] (%)	Conversion[c] (%)	Absolute Configuration
1	BMIM. BF_4	CH_2Cl_2	48	4	*S*
2	BMIM. PF_6	CH_2Cl_2	52	10	*S*
3	Polyethylene glycol (average M.W. ca 200)	THF	43	>99	*R*
4	Polyethylene glycol (average M.W. ca 400)	THF	77	>99	*R*

[a]Reaction conditions: 0.5 mmol quinoline, $[Ir(COD)Cl]_2$ (0.25 mol%), (*R*)-P-Phos (0.55 mol%), I_2 (5 mol%), 2 mL solvent, 700 psi H_2 pressure and 25 °C. [b]The enantioselectivities of product was determined by HPLC analysis with Chiralpak OJ-H column and the absolute configuration was assigned by comparing the HPLC retention time with those reported in the literature data. [c]The conversion was determined by ^{1}HNMR spectroscopy. *1mL solvent and 1mL co-solvent were used here.

Table 2-7 Asymmetric hydrogenation of 2-methylquinolines[a] in polyethylene glycol dimethyl (PEGDME, average M.W. ca 500)



Entry	Catalyst system	Solvent*	Co-solvent*	ee[b] (%)	Conversion[c] (%)
1	Ir/(*R*)-P-Phos	PEGDME	NIL	85 (*R*)	98
2	Ir/(*R*)-P-Phos	PEGDME	CH_2Cl_2	88 (*R*)	89
3	Ir/(*R*)-P-Phos	PEGDME	Hexane	88 (*R*)	>99
4	Ir/(*R*)-MeO-BIPHEP	PEGDME	Toluene	84 (*R*)	96
5	Ir/(*R*)-MeO-BIPHEP	PEGDME	Hexane	85 (*R*)	>99
6	Ir/(*R*)-MeO-BIPHEP	PEGDME	NIL	81 (*R*)	>98
7	Ir/(*S*)-BINAP	PEGDME	NIL	61 (*S*)	>98

[a]Reaction conditions: 0.5 mmol quinoline, $[Ir(COD)Cl]_2$ (0.25 mol%), (*R*)-P-Phos (0.55 mol%), I_2 (5 mol%), 2 m solvent, 700 psi H_2 pressure and 25 °C. [b]The enantioselectivities of product was determined by HPLC analysis wit Chiralpak OJ-H column and the absolute configuration was assigned by comparing the HPLC retention time wit those reported in the literature data. [c]The conversion was determined by ^{1}HNMR spectroscopy. *2mL solvent an 2mL co-solvent were used here.

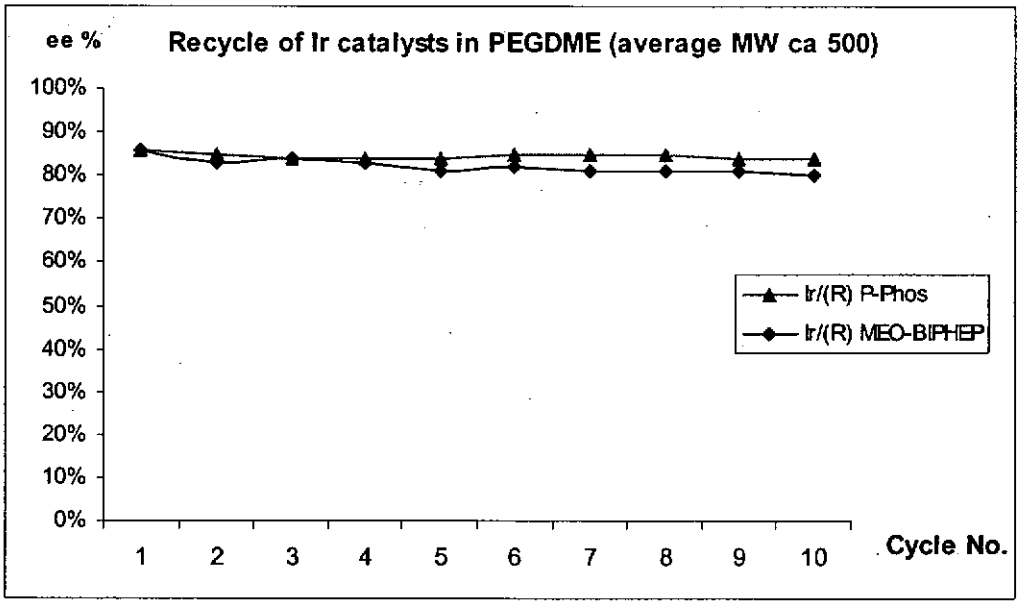


Figure 2-2 The enantioselectivity obtained for the reusable Ir/(*R*)-**P-Phos**/PEGDME/hexane and Ir/(*R*)-**MeO-BIPHEP**/hexane systems in 10 cycles

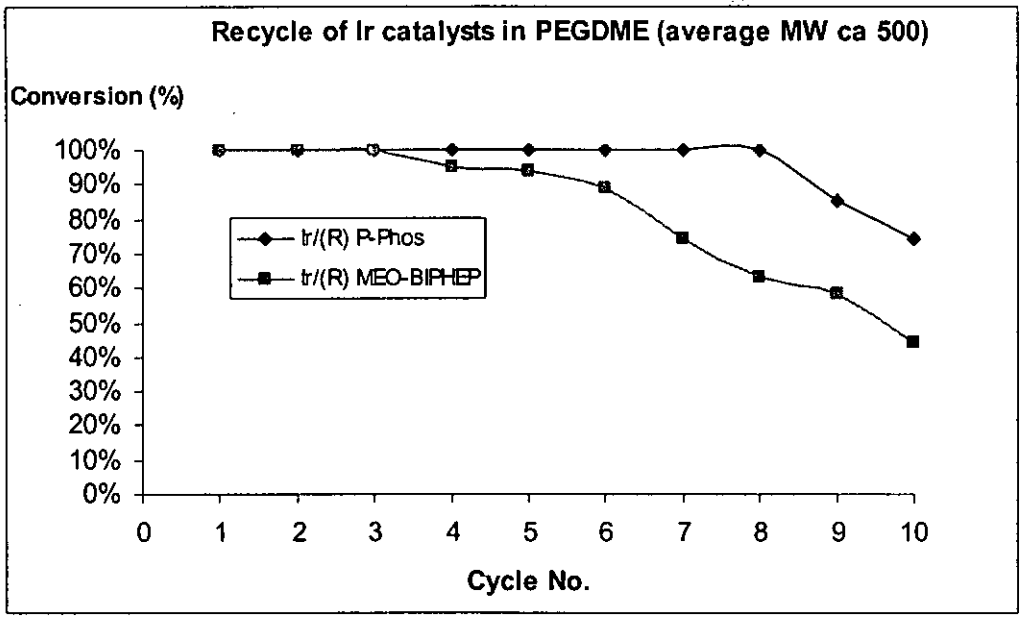


Figure 2-3 The conversion obtained for the reusable Ir/(*R*)-**P-Phos**/PEGDME/hexane and Ir/(*R*)-**MeO-BIPHEP**/hexane systems in 10 cycles

Chapter 3

Development of a highly effective and recyclable chiral Ir-Phosphinite catalyst system for asymmetric hydrogenation of quinolines

3.1. Introduction

Transition-metal catalyzed homogeneous asymmetric hydrogenation is one of the most powerful methods for the synthesis of optically active compounds, and high enantioselectcivites have been obtained in the preparation of chiral amino acid derivatives, chiral alcohols, chiral carboxylic acids and chiral amines. However, the asymmetric hydrogenation of heteroaromatic compounds has proved to be problematic in terms of overcoming their strong resonance stability. So far there have been only limited examples of asymmetric hydrogenation of heteroaromatic compounds. Today, these hydrogenation approaches all rely on bidentate phosphine complexes with rhodium, ruthenium or iridium, and no chiral phosphinite ligand has been found to induce high enantioselectivity.

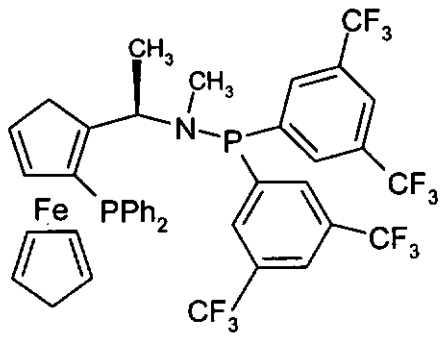
Chiral phopshinite ligands offer advantages over the corresponding phosphine ligands by their facile preparation and easy derivatization. In general, the phosphinites can be conveniently synthesized in good yields by reacting the corresponding alcohols with chlorophosphines in the presence of an organic base. From a practical standpoint, it is very attractive and economical to develop highly effective chial phosphinite ligands for asymmetric catalysis.

Noyori and coworkers suggested that the highly skewed position of the naphthyl rings in **BINAP** was responsible for the high efficiency of the ligand in asymmetric catalysis. The structure comparison between **BINAP** and the less effective **BINAPO** reveals two possible reasons for the difference in their effectiveness as chiral ligands in asymmetric catalysis: (1) The oxygen atoms in **BINAPO** increase the distance between the chiral binaphthyl moiety and the PPh_2 groups and therefore decrease the influence of the binaphthyl functionality on the stereopositions of the phenyl rings of the PPh_2 group. Consequently there is less control of stereoselectivity in the catalyst-substrate interaction. (2) The presence of the C-O-P bond in **BINAPO** substantially increases the flexibility of the backbone and consequently decreases the enantioselectivity of the catalyst. To develop highly effective **BINAPO** ligands, Zhang and coworkers found that the introduction of bulky groups to 3,3'-positions of the binaphthyl ring can lead to effective ligands for the asymmetric hydrogenation of β-dehydroamino acids derivatives.[52] In our pursuit of the novel and effective chiral ligands for asymmetric hydrogenation, we have demonstrated that the easily accessible **H*8*-BINAPO** ligand provided greater enantioselectivities in the Rh-catalyzed asymmetric hydrogenation of enamides and α-dehydroamino acid derivatives than their unmodified **BINAPO** ligand. Compared with **BINAPO** ligand, **H*8*-BINAPO** ligand could perform better result because the electron-rich H*8*-binaphthyl structure is a more rigid structure which could compensate for the conformational flexibility caused by the introduction of C-O-P bond.[127, 128]

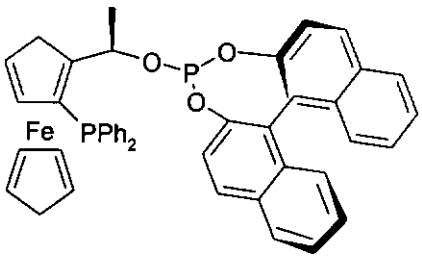
In this chapter, we reported that the iridium complex of **H*8*-BINAPO** was capable of catalyzing the asymmetric hydrogenation of quinoline derivatives to give tetrahydroquinoline derivatives with high enantioselectivity (up to 97%).

3.2. Results and Discussion

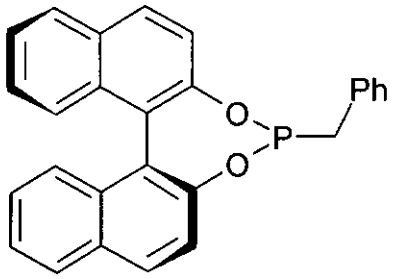
We first examined the catalytic performance of **BINAPO** and **H8-BINAPO** ligands in Ir-catalyzed hydrogenation with quinaldine as model substrate. The catalysts were prepared *in situ* from the phosphinites and $[Ir(COD)Cl]_2$, and I_2 was chosen as the additive. Under the conditions previously optimized by Zhou and coworkers,[112a] **H8-BINAPO** gave a promising enantioselectivity (Table 3-1, entry 2, 89% ee) but the enantioselectivity given by **BINAPO** was comparatively lower (entry 1, 79% ee) under otherwise identical conditions. In order to increase the enantioselectivity of the product, a series of the solvents were screened and the results are listed in Table 3-1. As can be seen from this table, the conversion was not sensitive to reaction solvents, but the enantioselectivity of the reaction was sensitive to the solvents used. Obviously higher ee values of **2a** were achieved in aprotic solvents whereas in alcoholic solvents the enantioselectivity was lower. The ethereal solvents gave more desirable results than other aprotic solvents, and the highest enantioselectivity (95%) was obtained in THF. It should be pointed out that in all cases only the tetrahydroquinoline product was obtained and the fused aromatic ring remained perfectly intact.



66[129]



67[129]

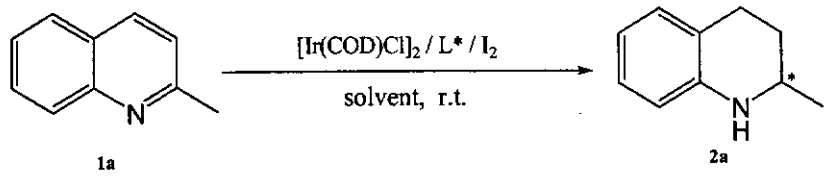


68[129]

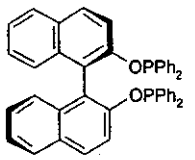
We also tested the catalytic performance of other P-O or P-N ligands. However, the results were very disappointing. With **66**[129] as a ligand, only 27% ee and 76% conversion were obtained. The enantioselectivty given by **67**[129] was also very low (10% ee). The iridium complex of **68**[129] only generated racemic product, although conversion was nearly completed.

From Table 3-2, it can be found that the conversion was insensitive to changes in H_2 pressure and temperature when Ir/**H8-BINAPO** was used. Enantioselectivity, however, was relatively dependent on H_2 pressure, and lower pressure (entries 1-5) had deleterious effect on the enantioselectivity. It is clear that the H_2 pressure of 700 psi gave the best ee, and was thus chosen for subsequent study.

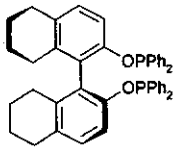
Table 3-1 Asymmetric hydrogenation of quinoline **1a** with different Ir-Phosphinite catalysts[a]



L* =



(*R*)-**BINAPO 1**



(*S*)-**H8-BINAPO 2**

Entry	Ligand	Solvents	ee (%)[b]	Conversion[c] (%)
1	(*R*)-**1**	Toluene	79	92
2	(*S*)-**2**	Toluene	89	>99
3	(*R*)-**1**	CH_2Cl_2	75	91
4	(*S*)-**2**	CH_2Cl_2	79	93
5	(*R*)-**1**	MeOH	68	81
6	(*S*)-**2**	MeOH	68	13
7	(*R*)-**1**	EtOH	67	80
8	(*S*)-**2**	EtOH	41	11
9	(*R*)-**1**	Et_2O	80	>99
10	(*S*)-**2**	Et_2O	**95**	>99
11	(*R*)-**1**	THF	81	>99
12	(*S*)-**2**	THF	**95**	>99

[a]Reaction conditions: 1 mmol quinoline, $[Ir(COD)Cl]_2$ (0.5 mol%), L* (1.1 mol%), I_2 (10 mol%), 2 mL solvent, 700 psi H_2 pressure and 25 °C. [b]The enantioselectivities of product was determined by HPLC analysis with Chiralpak OJ-H column and the absolute configuration was assigned by comparing the HPLC retention time with those reported in the literature data. [c]The conversion was determined by ^1H NMR spectroscopy.

Table 3-2 Effect of pressure and temperature on catalytic asymmetric hydrogenation of **1a**[a]

Entry	H_2 (psi)	T (°C)	ee[b] (%)	Conversion[c] (%)	Absolute Configuration
1	1200	r.t.	94	>99	*R*
2	700	r.t.	95	>99	*R*
3	700	0	96	>99	*R*
4	700	-30	96	>99	*R*
5	200	r.t.	78	99	*R*

[a]Reaction conditions: 1 mmol quinoline, $[Ir(COD)Cl]_2$ (0.5 mol%), (*S*)-H8BINAPO (1.1 mol%), I_2 (10 mol%), 2 mL THF. [b]The enantioselectivities of product was determined by HPLC analysis with Chiralpak OJ-H column and the absolute configuration was assigned by comparing the HPLC retention time with those reported in the literature data. [c]The conversion was determined by ^{1}HNMR spectroscopy.

The effect of substrate-to-catalyst (S/C) ratio on enantioselectivity was also studied, and the results are listed in Table 3-3. It can be seen from the table that with an increase in thee S/C ratio, the conversion decreased very quickly; and when the ratio was increased to 5000, there was nearly no conversion. In comparison, the enantioselectivty diminished less dramatically with an increase in S/C ratio. The best result was attained with a low S/C ratio of 200 to afford 95% ee and nearly complete conversion.

Table 3-3 Effect of substrate-to-catalyst ratio on catalytic asymmetric hydrogenation of **1a**[a]

Entry	S/C ratio	ee[b] (%)	Conversion[c] (%)	Absolute Configuration
1	200:1	95	>99	*R*
2	500:1	76	48	*R*
3	1000:1	65	26	*R*
4	2000:1	61	16	*R*
5	5000:1	67	7	*R*

[a]Reaction conditions: $[Ir(COD)Cl]_2$/(*R*)-PPhos (1:2.2), 1 mmol quinoline, I_2 (0.05 mmol), 5 mL THF, 700 psi H_2 pressure and 25 °C. [b]The enantioselectivities of product was determined by HPLC analysis with Chiralpak OJ-H column and the absolute configuration was assigned by comparing the HPLC retention time with those reported in the literature data. [c]The conversion was determined by ^{1}H NMR spectroscopy.

Additives had been reported to have remarkable impact on catalytic turnover and enantioselectivity.[8,10]. Therefore we surveyed a series of additives, which were often used in many Ir-catalyzed asymmetric reactions, and the results are shown in Table 3-4. We first attempted the hydrogenation without any additive, and it turned out that the reaction became very sluggish with only 55% ee obtained after 20 h reaction time (entry 1, Table 3-4). Table 3-4 shows that iodine was the only effective additive for this reaction while other additives were ineffective for producing high enantioselectivities. Similar results have been obtained in Ir-**MeO-BIPHEP** and Ir-**P-Phos** catalyzed asymmetric hydrogenation of quinolines. With I_2 as an additive, the change of Ir precursor from neutral $[Ir(COD)Cl]_2$ to ionic $[Ir(COD)]BF_4$ or $[Ir(COD)]PF_6$ led to the decrease of both conversion and enantioselectivty, but no inversion of configuration was observed which is in sharp contrast with the results reported in previous chapter.

Table 3-4 Effect of additives on catalytic asymmetric hydrogenation of **1a**[a]

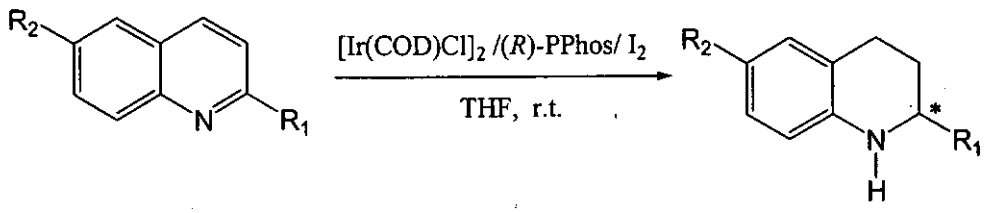
Entry	Additives	ee[b] (%)	Conversion[c] (%)	Absolute configuration
1	NIL	55	24	*R*
2	I_2	**95**	>99	*R*
3	KI	66	34	*R*
4	NaI	78	51	*R*
5	BiI_3	6	85	*R*
6	tetrabutylammonium iodide	80	9	*R*
7	LiCl	77	44	*R*
8	phthalimide	57	20	*R*
9	I_2[d]	78	9	*R*
10	I_2[e]	90	74	*R*

[a]Reaction conditions: 1 mmol quinoline, $[Ir(COD)Cl]_2$ (0.005 mmol), (*R*)-PPhos (0.011 mmol), additive (10-20 mmol%), 5 mL THF, 700 psi H_2 pressure and 25 °C. [b]The enantioselectivities of product was determined by HPLC analysis with Chiralpak OJ-H column and the absolute configuration was assigned by comparing the HPLC retention time with those reported in the literature data. [c]The conversion was determined by ^{1}HNMR spectroscopy. [d]$[Ir(COD)]BF_4$ was used. [e] $[Ir(COD)]PF_6$ was used.

Under the optimized conditions, a variety of valuable 2-substituted quinoline derivatives were employed as substrates for the Ir-catalyzed asymmetric hydrogeantion reactions with **H*8*-BINAPO** or **BINAPO** as ligand (Table 3-5). It can be found that with Ir-(*S*)-**H*8*-BINAPO** as a catalyst, all the reactions went to completion in 20 h with more than 90% yields, indicative of the high activity of this Ir-phosphite catalytic system. High enantoselectivities were achieved in the hydrogenation of 2-alkyl substituted quinolines, and it seems that the length of alkyl chain did not adversely affect the ee values. The introduction of R_2 group on position 6 had no clear effect on enantiomeric excess, and good ee values have been obtained with these 2,6-substituted quinolines. The asymmetric hydrogenation proceeded smoothly with the quinolines bearing hydroxyl groups as substrates affording high enantioselectivites. However, only 30% enantioselectivity was achieved with the substrates containing C=C bond in side chain (entry 5). The presence of an ester substituent led to a drop in the enantioselectivty (entry 8). When the alkyl group at 2-position was replaced by a phenyl group, lower enantioselectivity was observed (entry 9). It is noted that most of these results are comparable to those obtained by Ir/**MeO-BIPHEP**, and in some cases, outperformed them. In general, **H*8*-BINAPO** performed better than **BINAPO** in this reaction, but in some cases the **BINAPO** also displayed good catalytic performance.

Encouraged by the successful development of an air stable and recyclable Ir/**P-Phos** and Ir/**MeO-BIPHEP** catalytic systems, we investigated the air-stability and recyclability of Ir/(*R*)-**BINAPO**/PEGDME/hexane and Ir/(*S*)-**H*8*-BINAPO**/PEGDME/hexane in the asymmetric hydrogenation of quinoline derivatives.

Table 3-5 Catalytic asymmetric hydrogenation of other quinolines[a]



1 **2**

Entry	R_1 / R_2	ee[b] (%)	Conversion[c] (%)	Absolute configuration
1	Me / H (**1a**)	95	>99 (**2a**)	*R*
2	Et / H (**1b**)	92 (90)[d]	>99 (97)[d] (**2b**)	*R (S)*[†]
3	n-Pr / H (**1c**)	88	>99 (**2c**)	*R*
4	n-Bu / H (**1d**)	90	>99 (**2d**)	*R*
5	3-Butenyl / H (**1d'**)	30	>99 (**2d**)	*R*
6	Me / Me (**1f**)	92 (83)[d]	>99 (>99)[d] (**2f**)	*R (S)*[†]
7	Me / MeO (**1g**)	94 (76)[d]	90 (77)[d] (**2g**)	*R (S)*[†]
8	$CH_2OC(O)CH_3$ / H (**1h**)	23	>99 (**2h**)	*R*
9	Ph / H (**1i**)	73 (30)[d]	>99 (>99)[d] (**2i**)	*R (S)*[†]
10	Phenethyl / H (**1j**)	57	>99 (**2j**)	*R*
11	Me / F (**1k**)	83 (64)[d]	99 (81)[d] (**2k**)	*S (R)*[†]
12	 / H (**1l**)	95 (89)[d]	>99 (>99)[d] (**2l**)	*S (R)*[†]
13	 / H (**1n**)	96 (89)[d]	>99 (>99)[d] (**2n**)	*S*

[a]Reaction conditions: 1 mmol quinoline, $[Ir(COD)Cl]_2$ (0.005 mmol), (*S*)-H8-BINAPO (0.011 mmol), I_2 (0.5 mmol), 5 mL THF, 700 psi H_2 pressure and 25 °C. [b]The enantioselectivities of products was determined by HPLC analysis with Chiralpak OJ-H(**2a-h**), AS-H(**2i-j**), OD-H(**2k-m**) and OJ (**2n**) column and the absolute configuration was assigned by comparing the HPLC retention time with those reported in the literature data. [c]The conversion was determined by 1HNMR spectroscopy. [d]The value in parenthesis was the result obtained with (*R*)-BINAPO.

We first tested the stability of the catalysts in the THF and PEGDME without the use of glovebox. The preliminary results (Table 3-6) showed that the Ir/phosphonites exhibited higher enantioselectivities and conversion in PEGDME than in degassed THF without the use of glove box. It is evident that the decrease in enantioselectivity may be attributed to the moisture or air-sensitivity of the Ir-phosphinite complex. However, the

high enantioselectivity in PEGDME indicated that PEGDME could protect the Ir/phosphinites against moisture and air to a certain extent. Similar phenomenon has been observed in Ir-**MeO-BIPHEP** catalyzed hydrogenation in PEGDME.

In order to keep the unstable Ir/phosphinites active for several cycles, our first approach was to perform the harvest step inside the glove box with degassed solvent. Our experimental processes were adopted as follows. Inside the glove box, 0.0025 mmol $[Ir(COD)Cl]_2$ and 0.005 mmol (*R*)-**BINAPO** or (*S*)-**H8-BINAPO** were first immobilized in 2 mL PEGDME. Next, 10 mol% I_2 and 0.5 mmol quinoline in 2 mL hexane (dried and degassed) were transferred into the autoclave. The resulting mixture inside the autoclave was then charged with 1000 psi H_2. After 20 hours, the pre-dried and degassed hexane was then used for extraction inside the glove box. After product extraction, 0.5 mmol substrate **1a** was then refilled into the system without any catalyst replenishment. Unfortunately, both the enantioselectivities and conversion of the product dropped continuously after each cycle of extraction (Table 3-7).

Table 3-6 Catalytic asymmetric hydrogenation of quinolines **1a** without using glovebox[a]

Entry	Ligand	Solvents	ee[b] (%)	Conversion[c] (%)
1	**Ir/(*R*)-BINAPO**	THF (degas)	63 (*S*)	95
2	**Ir/(*S*)-H8-BINAPO**	THF (degas)	90 (*R*)	95
3	**Ir/(*R*)-BINAPO**	PEGDME	73 (*S*)	>99
4	**Ir/(*S*)-H8-BINAPO**	PEGDME	94 (*R*)	>99

[a]Reaction conditions: 1 mmol quinoline **1a**, $[Ir(COD)Cl]_2$ (0.5 mol%), L* (1.1 mol%), I_2 (10 mol%), 2 mL solvent, 700 psi H_2 pressure and 25 °C. [b]The enantioselectivities of product was determined by HPLC analysis with Chiralpak OJ-H column and the absolute configuration is assigned by comparing the HPLC

retention time with those reported in the literature data. [c]The conversion was determined by ^{1}H NMR spectroscopy.

After the recycle experiments, the hexane layer separated was then analysed by ICP-AES method using Perkin Elmer Optima 3300DV for the determination of catalyst leaching if any. For both Ir/(*R*)-**BINAPO**/PEGDME/hexane and Ir/*(S)*-**H8-BINAPO**/PEGDME/hexane systems, only 0.1 ppm of Ir had been leached into the hexane extract from the PEGDME layer. This led us to believe that the drop in enantioselectivity and conversion was due to the instability of the phosphinites. Therefore, in order to improve the recycle efficiency, we further added 1 mol% (*S*)-**H8-BINAPO** in each cycle. Table 3-8 shows that the enantioselectivities dropped slowly as compared with the results obtained without extra ligand addition; however, the conversion still dropped drastically after each recycle. It is unclear as to why such results were observed at this stage.

Table 3-7 The enantioselectivities and the conversion obtained for the Ir/(*R*)-**BINAPO**/PEGDME/Hexane and Ir/(*S*)-**H8-BINAPO**/Hexane systems in 5 cycles

	Ir/(*R*)-BINAPO		Ir/(*S*)-H8-BINAPO	
Cycle	Ee[b] %	Conversion[c] %	Ee[b] %	Conversion[c] %
1	83 *(S)*	>99	97 *(R)*	>99
2	61 *(S)*	85	72 *(R)*	65
3	44 *(S)*	72	57 *(R)*	48
4	31 *(S)*	62	46 *(R)*	38
5	22 *(S)*	55	37 *(S)*	34

[a]Reaction conditions: 0.5 mmol quinoline, $[Ir(COD)Cl]_2$ (0.0025 mmol), (*S*)-H8-BINAPO or (*R*)-BINAPO (0.006 mmol), I_2 (10 mmol%), 2 mL PEGDME and 2 mL hexane, 1000 psi H_2 pressure and 25 °C. [b]The enantioselectivities of product was determined by HPLC analysis with Chiralpak OJ-H column and the absolute configuration was assigned by comparing the HPLC retention time with those reported in the literature data. [c]The conversion is based on ^1H NMR analysis of the crude products obtained.

Table 3-8 The enantioselectivities and the conversion obtained for the Ir/(*S*)-**H8-BINAPO**/Hexane systems (with the replenishment of 1 mol % ligand in each cycle) in 5 cycles

Cycle	Ir/(*S*)-H8-BINAPO	
	Ee[b] %	Conversion[c] %
1	96% ***(R)***	>99%
2	93% ***(R)***	42%
3	91% ***(R)***	20%
4	88% ***(R)***	11%
5	87% ***(R)***	5%

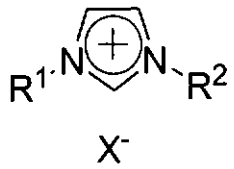
[a]Reaction conditions: 0.5 mmol quinoline, $[Ir(COD)Cl]_2$ (0.0025 mmol), (*S*)-H8-BINAPO (0.006 mmol), I_2 (10 mmol%), 2 mL PEGDME and 2 mL hexane, 1000 psi H_2 pressure and 25 °C. [b]The enantioselectivities of product was determined by HPLC analysis with Chiralpak OJ-H column. The absolute configuration was assigned by comparing the HPLC retention time with those reported in the literature data. [c]The conversion is based on ^1H NMR analysis of the crude products obtained.

Chapter 4

Ruthenium catalyzed asymmetric hydrogenation of *a*- and *β*-ketoesters in ionic liquids with chiral P-Phos ligand

4.1 Introduction

Room temperature ionic liquids (RTIL) such as those based on imidazolium salts have widely been recognized as one of the most promising alternatives to hazardous organic solvents for clean chemical reactions, due to their extremely low vapor pressure and their novel, tunable physicochemical properties. A great number of catalytic reactions have proved feasible in these ionic liquids, with many displaying enhanced reactivities and selectivities, and some of which have not been observed in common organic solvents. Studies have shown that ionic liquids could stabilize organometallic reagents and biocatalysts, and they also provided easy access for recovery of products and recycling of catalysts. In particular, room temperature ionic liquids represent viable alternative solvents for the synthesis of high-valued chiral organic compounds by catalytic process. A series of prochiral olefins and ketones have been successfully hydrogenated in ionic liquids, and the results were comparable to or even outperformed those obtained in normal reaction solvents. In most cases, the organic products could be easily separated by extraction with less polar solvents and the ionic liquid phase containing the active catalyst could be readily reused for several times without significant loss of catalytic activity.



BMIM=1-butyl-3-methylimidazolium

$X=BF_4, PF_6$

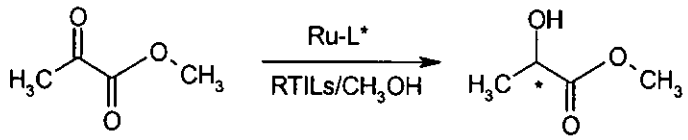
Recently dipyridyl-based diphosphine ligands, **P-Phos** and its derivatives, have been successfully developed in our laboratory, and have been used in transition-metal catalysed enantioselective hydrogenation of olefins and ketones with high *ee* values and yields.[32] Here we report that it is possible to replace the organic solvent with ionic liquids in Ru-**P-Phos** catalyzed asymmetric hydrogenation of ketoesters without loss of enantioselectivity and catalytic activity, and the use of ionic liquids allows easy isolation of the pure product and efficient recovery of the catalyst.

4.2 Asymmetric Hydrogenation of α-keto Esters

To determine if asymmetric hydrogenation of α-keto esters with Ru-**P-Phos** as catalyst could occur in ionic liquids, we examined the hydrogenation of methyl pyruvate in 1-butyl-3-methylimidazolium tetrafluoroborate ($BMIM.BF_4$) and 1-butyl-3-methylimidazolium hexafluorophosphate ($BMIM.PF_6$). For comparison, we also tested the catalytic performance of **BINAP** in ionic liquids. We first attempted the hydrogenation in pure ionic liquids, but the reaction became sluggish with very low conversions (5% and 10% in $BMIM.BF_4$ and $BMIM.PF_6$, respectively) after 20 h. Considering the significant co-solvent effect of alcohol in asymmetric hydrogenation in ionic liquids, we used MeOH as a co-solvent. The best result was obtained with equal volume of MeOH and ionic liquids. Similar observation has been made by Lin and co-

workers, who found that the use of equal volume of MeOH and ionic liquids was beneficial to the asymmetric hydrogenation of β-keto esters.[123a] Thus we attempted the subsequent hydrogenations in ionic liquids with equal volume of MeOH as co-solvent. As shown in Table 4-1, high enantioselectivities could be obtained with Ru-**P-Phos** in both BMIM.BF_4 and BMIM.PF_6, and the results are comparable to the *ee* values achieved in MeOH. It seems that the enantioselectivity is insensitive to the nature of ionic liquids. However, the reaction in BMIM.PF_6 was slow, and only 73% conversion was achieved after 20 h while nearly complete conversion was observed in BMIM.BF_4. In constrast, lower enantioselectivities were observed in Ru-**BINAP** catalyzed hydrogenation, though nearly complete conversions were attained in both ionic liquids. With **BINAP** as a ligand, the enatioselectivity is quite dependent on the nature of ionic liquids. As can be seen in Table 4-1, in BMIM.BF_4, 81% *ee* was produced while only 55% enantioselectivity could be obtained in BMIM.PF_6. It is notable that our **P-Phos** has a better catalytic performance in ionic liquids than **BINAP**, which may be attributed to the dipyridyl-backbone of **P-Phos**. Encouraged by these positive results, we decided to further explore the catalytic activity of **P-Phos** in the asymmetric hydrogenation of α-ketoesters in ionic liquids.

Table 4-1 Asymmetric hydrogenation of methyl pyruvate in ionic liquids



Ru-L* = Ru((*R*)-P-Phos)$Cl_2(DMF)_n$			Ru-L* = Ru((*S*)-BINAP)$Cl_2(DMF)_n$		
MeOH	$BMIMBF_4$	$BMIMPF_6$	MeOH	$BMIMBF_4$	$BMIMPF_6$
Ee% (Conv.%)	Ee%(Conv.%)	Ee% (Conv.%)	Ee% (Conv.%)	Ee% (Conv.%)	Ee% (Conv.%)
88 (97)	83 (95)	86 (73)	83 (90)	55 (98)	81 (98)

All the reactions were carried out with 1 mol % catalyst at a H_2 pressure of 1000 psi in a 50 : 50 mixture of RTIL and MeOH at rt for 20 h. The ee values (%) were determined by GC on a Cyclosil-B [J&W scientific] (30m) x 0.25mm x 0.25μm column. The conversions were determined by ^1H NMR spectroscopy.

Since co-solvent has a significant effect on enantioselectivty in asymmetric hydrogenation in ionic liquids, catalytic hydrogenation of methyl pyruvate by Ru((*R*)-**P-Phos**)$Cl_2(DMF)_n$ in different co-solvents were examined. The results are listed in Table 4-2. It was found that methanol was the best solvent for the catalysis (see Table 4-1) while other less polar and aprotic solvents were less efficient for this reaction (entries 1-4).

The effect of temperature, pressure and S/C ratio was also examined, and the results are summarized in Table 4-3. Pressure appeared to have an important effect on this reaction with complete conversion only attainable when the pressure was 1000 psi or higher (entry 2-3). The temperature and substrate to catalyst ratio were also very important to both the enantioselectivity and conversion in both ionic liquids. The catalysis in $BMIM.BF_4$ was more sensitive to change in temperature and S/C ratio

(entries 4-6). No conversion was detected in BMIM.BF_4 when the temperature was 0 °C (entry 6). When the S/C ratio was increased from 100:1 to 400:1, low to no conversions with decreased enantioselectivity were observed in BMIM.BF_4. Compared to the catalysis in BMIM.BF_4, it seems that enantioselectivity obtained in BMIM.PF_6 is relatively insensitive to change in temperature and S/C ratio.

Table 4-2 Asymmetric hydrogenation of methyl pyruvate in several co-solvents

Ru((*R*)-P-Phos)$Cl_2(DMF)_n$		Ionic Liquids			
		BMIM.BF_4		BMIM.PF_6	
Entry	Co-solvent	Ee%	Conversion%	Ee%	Conversion%
1	Ether	68	19	65	19
2	THF	62	15	65	34
3	DCM	61	22	66	19
4	Toluene	49	4	52	10

All the reactions were carried out with 0.25 mol % catalyst at a H_2 pressure of 1000 psi in a 50 : 50 mixture of RTIL and solvent at rt for 20 h. The ee values (%) were determined by GC on a Cyclosil-B [J&W scientific] (30m) x 0.25mm x 0.25μm column. The conversions were determined by ^1H NMR spectroscopy.

Table 4-3 Effect of temperature and pressure

	Ru-(*R*)-P-Phos		Ionic Liquids			
			BMIM.BF_4		BMIM.PF_6	
Entry	H_2, psi	Temp., °C	Ee%	Conversion%	Ee%	Conversion%
1	500	r.t.	83	81	86	>99
2	1000	r.t.	81	>99	79	>99

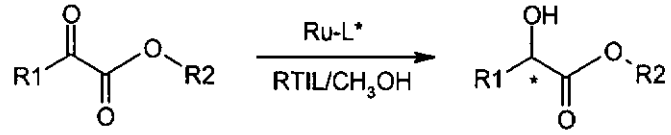
3	1500	r.t.	86	>99	86	>99
4*	500	r.t.	62	9	84	25
5*	1000	r.t.	48	2	82	39
6*	1000	0	0	0	83	1

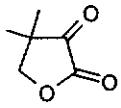
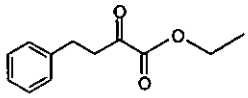
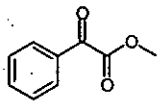
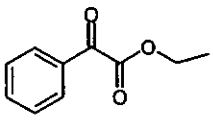
All the reactions were carried out with 1 mol% catalyst at a H_2 pressure of 1000 psi in a 50 : 50 mixture of RTIL and methanol at rt for 20 h. The ee values (%) were determined by GC on a Cyclosil-B [J&W scientific] (30m) x 0.25mm x 0.25μm column. The conversions were determined by ^{1}H NMR spectroscopy. *For entries 4-6, the reaction was performed at S/C ratio of 400:1.

Under the optimized conditions several α-ketoesters were tested, and the results are tabulated in Table 4-4. As can be seen form the table, low to high enantioselectivities were observed, but all of these reactions proceeded very slowly with less than 70% conversions after 20 h.

Ketopantolactone (entry 1) is a good substrate for testing the catalytic performance of chiral catalysts. The hydrogenated product, chiral pantoyl lactone, is a key intermediate for pantothenic acid synthesis, a constituent of coenzyme A.[1c] The catalyst Ru-**P-Phos** complex only provided low enantioselectivities (47% and 60% in BMIM.BF_4 and BMIM.PF_6, respectively) and low conversions. Moderate enantioselectivities and low conversions were also observed with ethyl 2-oxo-4-phenylbutyrate as a substrate in both ionic liquids (entry 2). It is notable that high ee values but low conversion were attained in both ionic liquids with methyl benzoylformate as a substrate (entry 3). The related ethyl benzoylformate was hydrogenated with low conversion and enantioselectivity in both ionic liquids (entry 4).

Table 4-4 Asymmetric hydrogenation of other substrates



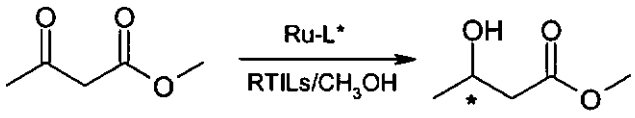
Ru-(*R*)-P-Phos		Ionic Liquids			
Entry	Substrate	$BMIM.BF_4$		$BMIM.PF_6$	
		Ee[a] %	Conv[b] %	Ee[a] %	Conv[b] %
1		47 (*R*)	34	60 (*R*)	46
2		74 (*R*)	37	76 (*R*)	63
3		90 (*R*)	18	93 (*R*)	65
5		55 (*R*)	26	38 (*R*)	20

All the reactions were carried out with 1 mol % catalyst at a H_2 pressure of 1000 psi in a 50 : 50 mixture of RTIL and methanol at r.t. for 20 h. [a]The *ee* values (%) were determined by GC on a Cyclosil-B [J&W scientific] (30m) x 0.25mm x 0.25μm column. [b]The conversions were determined by ^1H NMR spectroscopy. The absolute configuration was assigned by comparing the retention time with the commercial available products.

4.3 Asymmetric Hydrogenation of β-keto-esters

Both Ru((*R*)-**P-Phos**)$Cl_2(DMF)_n$ and Ru((*S*)-**BINAP**)$Cl_2(DMF)_n$ were applied in the asymmetric hydrogenation of methyl acetoacetate at room temperature and 1000 psi of hydrogen in a 50 : 50 mixture of ionic liquid (BMIM.BF_4 or BMIM.PF_6) and MeOH at rt for 20 h. The desired product, methyl-3-hydroxybutanoate was obtained with quantitative conversion and >99% ee. The effect of co-solvent was not investigated as methanol has been reported as the best solvent for the asymmetric hydrogenation of beta keto-esters with Ru-**BINAP**,[123c] Ru-**P-Phos** and its derivatives.[32] As can be seen from Table 4-5, the enantioselectivities obtained in ionic liquids with our Ru-**P-Phos** were slightly higher than in MeOH. In contrast, with **BINAP** as a ligand, excellent ee's and conversions were observed in both ionic liquids and MeOH.

Table 4-5 Asymmetric hydrogenation of methyl acetoacetate in ionic liquids



Ru-L* = Ru(*R*-P-Phos)$Cl_2(DMF)_n$			Ru-L* = Ru(*S-BINAP*)$Cl_2(DMF)_n$		
MeOH*	$BMILBF_4$	$BMILPF_6$	MeOH*	$BMILBF_4$	$BMILPF_6$
Ee% (Conv.%)	Ee%(Conv.%)	Ee% (Conv.%)	Ee% (Conv.%)	Ee% (Conv.%)	Ee% (Conv.%)
96 (>99)	96 (>99)	97 (>99)	>99 (>99)	>99 (>99)	>99 (>99)

All the reactions were carried out with 1 mol % catalyst at a H_2 pressure of 1000 psi in a 50 : 50 mixture of RTIL and MeOH at rt for 20 h. [a]The ee values (%) were determined by GC on a Supelco γ-Dex 225 column. [b]The conversions were determined by ^{1}HNMR spectroscopy. *The reactions were carried out with 1 mol % catalyst at a H_2 pressure of 100 psi in MeOH at 70 °C for 20 h.

The substrate to catalyst ratio is important for the asymmetric hydrogenation of methyl acetoacetate in ionic liquids. The results are listed in Table 4-6. The reaction can be applied at various S/C ratios up to 400:1 (entry 1-3) with high enantioselectivity and conversion. The best S/C ratio was 100:1. However, when the S/C ratio was increased to 1000: 1, the reaction became very slow, and only very low conversion and *ee* values were obtained in both ionic liquids (entry 4). The use of a rather high catalyst loading represents a general disadvantage accompanied with the use of ionic liquid in transition metal catalyzed reactions.

Table 4-6 Effect of S/C ratio on asymmetric hydrogenation of methyl acetoacetate in ionic liquids

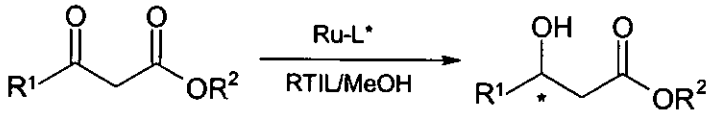
		$BMIM.BF_4$/MeOH 0.25:0.25 mL		$BMIM.PF_6$/MeOH 0.25:0.25 mL	
Entry	S/C ratio	Ee[a] %	Conv[b] %	Ee[a] %	Conv[b] %
1	100:1	>99%	>99%	97%	>99%
2	200:1	97.3%	>99%	97.4%	>99%
3	400:1	96.3%	>99%	97.1%	>99%
4	1000:1	67%	[c]	78%	[c]

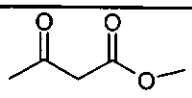
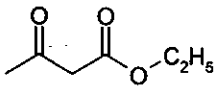
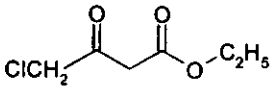
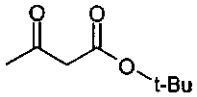
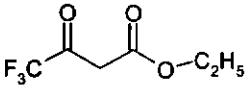
All the reactions were carried out with 1 mol % catalyst at a H_2 pressure of 1000 psi in a 50 : 50 mixture of RTIL and MeOH at rt for 20 h. [a]The ee values (%) were determined by GC on a Supelco γ-Dex 225 column. [b]The conversions were determined by ^{1}HNMR spectroscopy. [c]Only trace amount of product was determined.

The catalysis was applied for other *β*-ketoesters under the optimized conditions and the results are summarised in Table 4-7. High enantioselectivities (97% to 99%) and high conversion (92% to >99%) were obtained for methyl acetoacetate, ethyl acetoacetate

and *tert*-butyl acetoacetate where the alkyl group R^1 is methyl group (entries 1, 2 and 4). When R^1 was switched to other electronegative groups, both the enantioselectivity and the conversion declined (entries 3 and 5). The Ru-**P-Phos** catalyst showed a higher activity in $BMIM.PF_6$, but it gave a better enantioselectivity in $BMIM.BF_4$. It should be pointed out that these results in ionic liquids are comparable to those obtained in normal organic solvents.

Table 4-7 Asymmetric hydrogenation of β-ketoesters in ionic liquids



		Ru-L* = Ru((*R*)-P-Phos)$Cl_2(DMF)_n$			
		$BMIM.BF_4$		$BMIM.PF_6$	
Entry	Substrate	Ee%	Conversion%	Ee%	Conversion%
1		>99	>99	97	>99
2		>99	>99	97	>99
3		54	91	58	93
4		>99	86	>99	92
5		50	21	21	78

All the reactions were carried out with 1 mol % catalyst at a H_2 pressure of 1000 psi in a 50 : 50 mixture of RTIL and MeOH at rt for 20 h. [a]The ee values (%) were determined by GC on a Supelco γ-Dex 225 column. [b]The conversions were determined by ^1H NMR spectroscopy.

Chapter 5

Synthesis of novel chirl P-Phos derivative for asymmetric catalysis

5.1 Introduction

The design of highly effective chiral ligands, especially phosphine ligands, has received extensive attention both from academia and industry. Excellent results obtained from axially chiral C_2-symmetric diphosphine ligands, such as **BINAP (18)**, **BIPHEMP (19a)** and **MeO-BIPHEP (19c)**, have led to persistent interest in the development of chiral diphosphine ligands bearing biaryl backbones. Using these chiral bidentate phosphines as ligands, a series of prochiral olefins have been successfully hydrogenated to produce optically active amino acids, carboxylic acids, alcohols and amines. However, the use of these ligands in asymmetric hydrogenation of cyclic enamides has been relatively unsuccessful.

Asymmetric hydrogenation of cyclic enamides provides a convenient route to produce the important intermediates for the preparation of biologically active chiral aminotetralines and aminoindanes. Only a few catalytic systems have been developed in the metal-catalyzed asymmetric hydrogenation of cyclic enamides, such as the Rh-**PennPhos**[76a] and Rh-**BPE**[18d] systems. Recently, Zhang and coworkers found that an *ortho*-substituted BIPHEP ligand, ***o*-Ph-hexaMeo-BIPHEP**, showed high enantioselectivities in Rh-catalyzed hydrogenation of cyclic enamides.[38] Compared

with the ***o*-Ph-hexaMeO-BIPHEP** ligand, significantly lower *ee* values were observed with other chiral biaryl phosphines, such as **hexaMeO-BIPHEP**, **MeO-BIPHEP**, and **BINAP**[38]. These results clearly indicate that the introduction of phenyl groups at the 3,3'-positions could have a strong influence on the enantioselectivity in asymmetric hydrogenations.

Recently, metal complexes of bipyridyl-based diphosphine, **P-Phos**, and its derivatives have been developed in our lab and shown to be highly active and enantioselective catalysts in asymmetric hydrogenations and carbonylations, suggesting that the rigidity of the bipyridyl backbone allows good transfer of chiral information. Encouraged by the impressive catalytic performance of **P-Phos** and Zhang's research, we have designed and synthesized an *ortho*-substituted **P-Phos** ligand, ***o*-Ph-P-Phos**, and investigated the influence of the 3,3'-disubstitution on asymmetric hydrogenation of enamides and other substrates as well as palladium catalyzed allylic substitution.

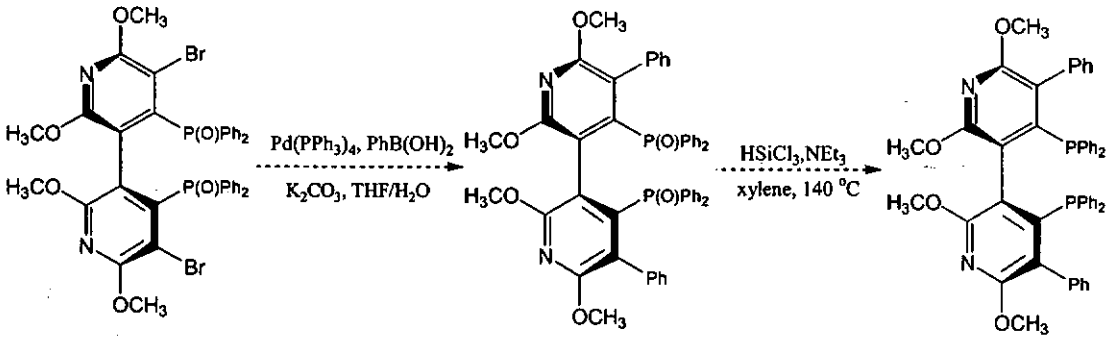
5.2 Synthesis of *ortho*-**Ph-P-Phos** Ligand

With the aim to avoid the difficulty in the optical resolution step to produce the chiral target ligand, 2,2',6,6'–tetramethoxy-5, 5'-diphenyl-4,4'-diphenyl-phosphino-3, 3'-bipyridine, we first started our synthesis from optically pure 3,3'-dibromo-4, 4'-diphenyl phosphinoyl-5,5'-bipyridine (**69**), which could be easily obtained in high

yield (Scheme 5-1). With $Pd(PPh_3)_4$ as catalyst, the Suzuki cross coupling of compound **69** with phenylboronic acid failed to give 71, and the main product was the debrominated compounds. It is believed that the bulkiness of the chiral dibromo phosphine oxide **69** may account for the failure of the palladium-catalyzed cross coupling reaction. This is in line with the fact that Pd-catalyzed C-C coupling reaction is very sensitive to steric effects. Thus, we turned to another approach (Scheme 5-2) to synthesize 71.

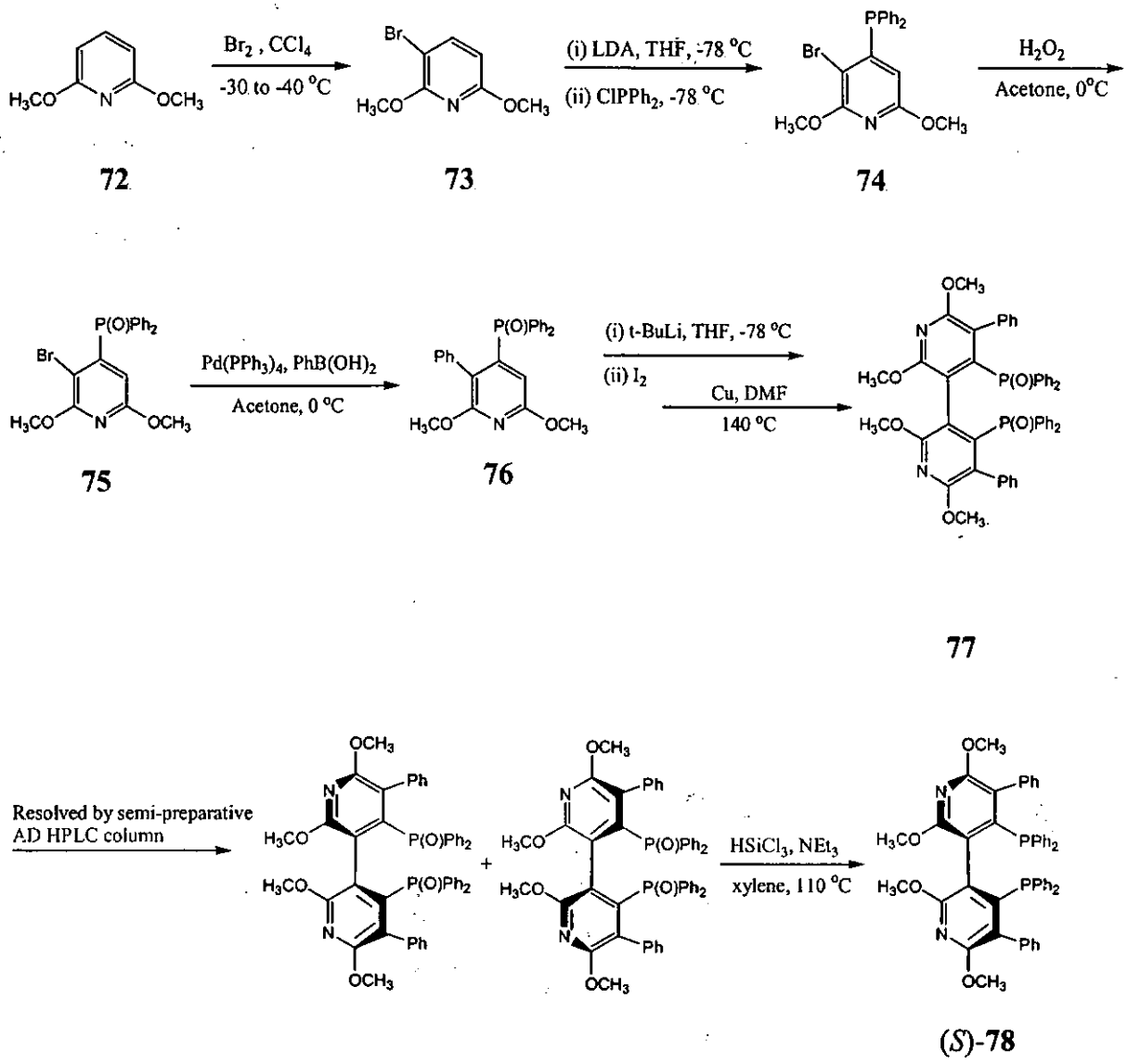
With the commercially available compound 2,6-dimethoxypyridine (**72**) as a starting material, 3-bromo-2,6-dimethoxypyridine (**73**) was synthesized by adding bromine in carbon tetrachloride slowly to **72** at temperature between -30 and -40 °C to give the product with 76% yield. To a solution of **73** in THF, lithium diisopropylamide (LDA) in THF at -78 °C was added, followed by the addition of chlorodiphenylphosphine to produce 3-bromo-2,6-dimethoxy-4-diphenylphosphino-pyridine (**74**) in 95% yield. Addition of hydrogen peroxide dropwise to a acetone-dichloromethane (1:1) solution of **74** at 0 °C gave 3-bromo-2,6-dimethoxy-4-diphenylphosphinoylpyridine (**75**) with 96% yield. 2,6-dimethoxy-3-phenyl-4-diphenylphosphinoylpyridine (**76**) was synthesized via a Suzuki coupling of **75** with phenyl boronic acid in 89% yield. *t*-BuLi was then added to deprotonate **76**, which was followed by quenching with I_2 to produce the

crude intermediate iodinated product, which was inseparable from **76.** Copper-mediated Ullmann coupling of the iodinated product led to the formation of the racemic dipyridylphosphine oxide (**77**) in 79% yield. The enantiomers of **77** were then obtained via resolution with a semi-preparative chiral AD HPLC column. The structure of (*S*)-**77** was determined by single crystal X-ray diffraction. Reduction of (*S*)-**77** with trichlorosilane in the presence of triethylamine led to the enantiomers of atropisomeric ***o*-Ph-P-Phos** ligand (**78**) with 80% yield, and the product was characterized by ^{1}H, ^{31}P, ^{13}C NMR and high-resolution mass spectrometry. All of the synthetic intermediates are air-stable, and the overall synthesis steps are easy to handle.



69 **70** **71**

Scheme 5-1. Possible synthesis approach of the *(S)-o*-**Ph-P-Phos** Ligand



Scheme 5-2 Synthesis of *(S)*-***o*-Ph-P-Phos** Ligand

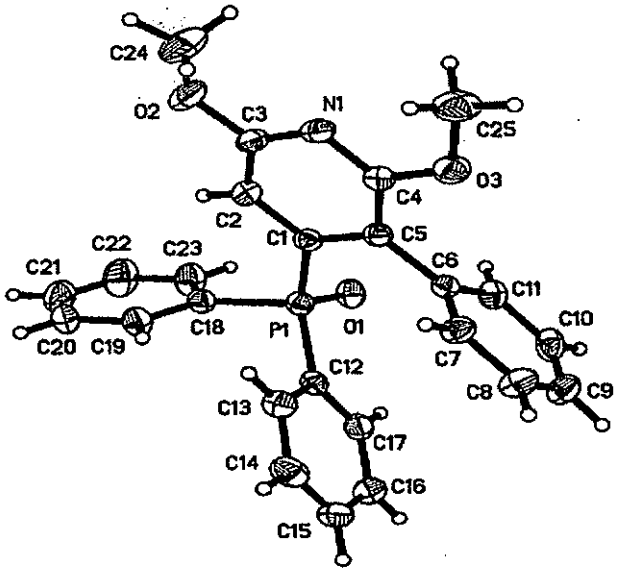


Figure 5-1 The ORTEP drawing of 2,6-dimethoxy-3-phenyl-4-diphenylphosphinoylpyridine

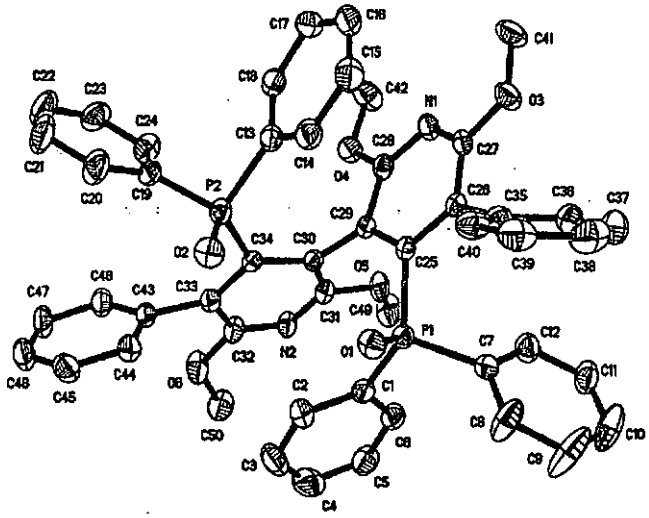


Figure 5-2 The ORTEP drawing of 2,2',6,6'-tetramethoxy-5,5'-diphenyl-4,4'-bis(diphenylphosphinoyl)-3,3'-bipyridine (**77**)

5.3 Asymmetric Catalysis

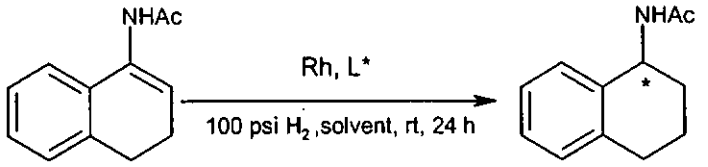
5.3.1 Asymmetric Hydrogenation of Cyclic Enamide

The catalytic activity of *(S)-o-***Ph-P-Phos** in hydrogenation of cyclic enamide was first tested with *N*-(3,4-dehydro-1-naphthyl)acetamide **79** as the model substrate. In order to investigate the influence of phenyl group on the ortho-positions, the

catalytic performance of the rhodium complexes of **P-Phos** and **BINAP** was also investigated. The results are listed in Table 5-1. As can be seen from Table 5-1, *(S)*-***o*-Ph-P-Phos** gave better enantioselectivities than **P-Phos** and **BINAP**. It is clear that there was a strong solvent effect. Both dichloromethane and THF were found to be good solvents in this reaction, and dichloromethane is the choice of solvent. The enantioselectivity is highly dependent on the Rh precursor.[38] $[Rh(NBD)_2]SbF_6$ was found to be a suitable choice. The best enantioselectivity (65%) was achieved when the hydrogenation was carried out with ***(S)*-o-Ph-P-Phos**/$[Rh(NBD)_2]SbF_6$ as catalyst precursor and dichloromethane as solvent. These results indicated that the presence of *o*-phenyl groups of ***(S)*-*o*-Ph-P-Phos** were important in controlling the enantioselectivity of the reaction. Although ***(S)*-*o*-Ph-P-Phos** performed better than its unsubstituted derivative, the result was less satisfactory as compared with Zhang's ligand.[38]

In order to explain the difference in the effectiveness between **P-Phos** and ***o*-Ph-P-Phos**, their torison angles were theoretically calculated (Figure 5-1). The calculated torison angles (based on MM2 of Chem3D Pro) for ***o*-Ph-P-Phos** and **P-Phos** are 85° and 75°, respectively. As the two dihedral angles have a significant difference, this may explain the difference in catalytic behaviour between the two ligands in the asymmetric hydrogenation. As the two phenyl groups on 3 and 3'

positions greatly increase the rigidity of the biheteroaryl system, the rotation of the two *P*-phenyl groups should also be significantly restricted. This may give rise to the better chiral differentiation observed for ***o*-Ph-P-Phos** in the asymmetric hydrogenation of 79.

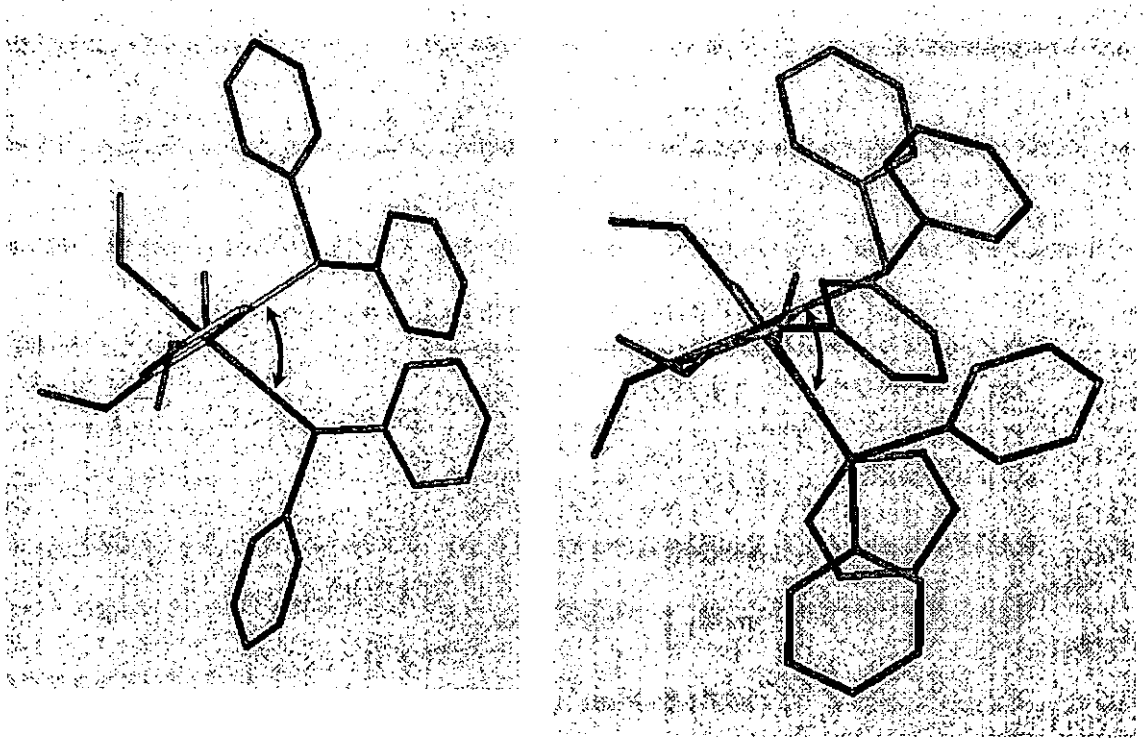


79 **80**

Table 5-1. Catalytic asymmetric hydrogenation of **79**

Entry	Rh precursor	Ligand	Solvent	ee[b] (%)	Conversion[c] (%)
1	$Rh(NBD)_2SbF_6$	*(R)*-**P-Phos**	DCM	11	95
2	$Rh(NBD)_2SbF_6$	*(S)*-**BINAP**	DCM	18.4	62
3	$Rh(NBD)_2SbF_6$	*(S)*-***o*-Ph-P-Phos**	DCM	65	>99
4	$Rh(NBD)_2SbF_6$	*(S)*-***o*-Ph-P-Phos**	THF	64	>99
5	$Rh(NBD)_2SbF_6$	*(S)*-***o*-Ph-P-Phos**	EtOH	59.1	90
6	$Rh(NBD)_2SbF_6$	*(S)*-***o*-Ph-P-Phos**	MeOH	52.5	90
7	$Rh(NBD)_2SbF_6$	*(S)*-***o*-Ph-P-Phos**	Toluene	56.2	68
8	$Rh(NBD)_2SbF_6$	*(S)*-***o*-Ph-P-Phos**	CH_3CN	/	No product detected
9	$Rh(NBD)_2Cl_2$	*(R)*-**P-Phos**	MeOH	17	98
10	$Rh(NBD)_2Cl_2$	*(S)*-***o*-Ph-P-Phos**	MeOH	26	96
11	$Rh(COD)_2Cl_2$	*(R)*-**P-Phos**	MeOH	6	92
12	$Rh(COD)_2Cl_2$	*(S)*-***o*-Ph-P-Phos**	MeOH	36	95
13	$Rh(COD)_2BF_4$	*(R)*-**P-Phos**	MeOH	2	93
14	$Rh(COD)_2BF_4$	*(S)*-***o*-Ph-P-Phos**	MeOH	35	94

[a]The catalyst was prepared in situ by stirring a solution of Rh precursor and phosphine ligand in the solvent for 30 minutes [substrate/Rh/L* = 100/1/1.1]. The catalysis was carried out at 100 psi H_2. [b]Enantiomeric excesses were determined by chirasil DEX CB column (25m x 0.25mm x 0.25μm film thickness). [c]The conversion was determined by ^1H NMR.

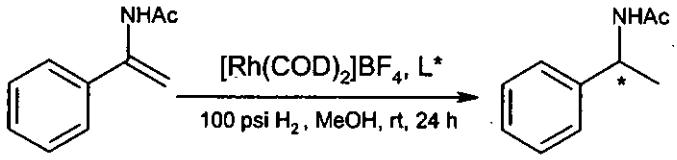


P-Phos $\theta = 75°$

***o*-Ph-P-Phos** $\theta = 85°$

Figure 5-3 Torison angle calculation based on MM2 of Chem3D Pro

5.3.2 Asymmetric Hydrogenation of Allylic Enamide



81 **82**

Table 5-2 Asymmetric hydrogenation of *N*-(1-Phenylethyl)acetamide **81**

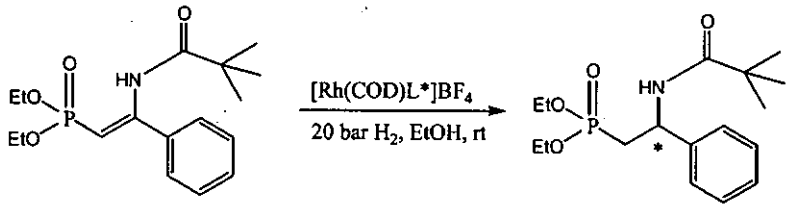
Entry	Rh precursor	Ligand	ee[b] (%)	Conversion[c] (%)
1	$Rh(COD)_2BF_4$	*(R)*-**P-Phos**	1.6	>99
2	$Rh(COD)_2BF_4$	*(S)*-***o*-Ph-P-Phos**	1.2	>99

[a]The catalyst was made in situ by stirring a solution of Rh precursor and phosphine ligand in methanol for 30 minutes [substrate/Rh/L* = 100/1/1.1]. The catalysis was carried out at 100 psi H_2. [b]Enantiomeric excesses were determined by chirasil DEX CB column (25 m x 0.25 mm x 0.25 μm film thickness). [c]The conversion was determined by ^1H NMR.

In order to explore the catalytic efficiency of our ligand, we also tested the asymmetric hydrogenation of acyclic enamides based on the rhodium complex derived from [Rh(NBD)$_2$]SbF6 and **P-Phos** or *(S)*-**o-Ph-P-Phos**. Again, excellent conversion were detected using either *(R)*-**P-Phos** or *(S)*-**o-Ph-P-Phos** for the asymmetric hydrogenation of *N*-(1-Phenylethyl)acetamide (**81**). Nevertheless, poor enantioselectivities were obtained for both ligands (Table 5-2).

5.3.3 Asymmetric Hydrogenation of *β*-enamidophosphonate

In the hydrogenation of beta *β*-enamidophosphonate, both **P-Phos** and *(S)*-**o-Ph-P-Phos** were unsuccessful (Table 5-3). The Rh/**P-Phos** gave no products at all while Rh/**o-Ph-P-Phos** provided only 18% conversion and 15% ee.



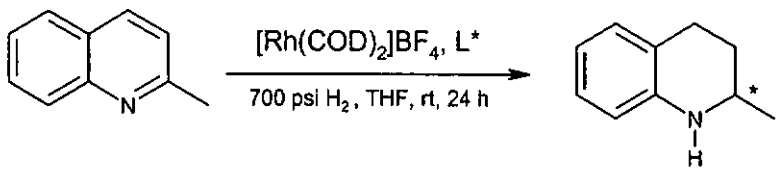
83 **84**

Table 5-3 Catalytic asymmetric hydrogenation of **83**

Entry	Ligand	H_2 (bar)	Conversion[a] (%)	ee[b] (%)
1	*(S)*-**P-Phos**	20	N/A	N/A
2	*(S)*-**o-Ph-P-Phos**	20	18	15

[a]Determined by HPLC analysis with Chiralpak OD-H column (5% iso-propanol in hexane, 1 mL/min). [b]The conversion was determined by ^{1}H NMR analysis of the crude product. *(The above results were contributed by Mr. Lam F. L. and Dr. Au-yeung T. L. of our research group.)

5.3.4 Hydrogentaion of Quinolines



85 **86**

Table 5-4 Catalytic asymmetric hydrogenation of **85**[a]

Entry	Ligand/L*	H_2 (psi)	T (°C)	ee[b] (%)	Conversion[c] (%)	Configura
1	*(R)*-**P-Phos**	700	r.t.	91	97	R
2	*(S)-o*-**Ph-P-Phos**	700	r.t.	34	96	R

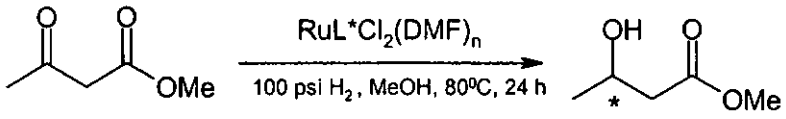
[a]Reaction conditions: 1 mmol quinoline, $[Ir(COD)Cl]_2$ (0.5%), chiral ligand (1.1%), 5 mL solvent. [b]The enantioselectivities were determined by HPLC analysis with Chiralpak OJ-H column, the absolute configuration of product was assigned by comparing the HPLC retention time with those reported literature data.[112a] [c]The conversion was determined by ^1H NMR analysis of the crude product.

$[Ir(COD)Cl]_2$/*(S)-o*-**Ph-P-Phos**/THF system was examined for the asymmetric hydrogenation of 2-methylquinoline (**85**). According to the preliminary results, we found that the stereoselectivity was very low. Although high conversion was obtained, the enantioselectivity was only 34% as compared with the non-substituted ***P-Phos*** (91% ee).

5.3.5 Asymmetric Hydrogenation of β-ketoester

When $Ru[(R\text{-}\mathbf{P\text{-}Phos})Cl_2(DMF)_n]$ was replaced with $[(S\text{-}o\text{-}\mathbf{Ph\text{-}P\text{-}Phos})Ru\ Cl_2(DMF)_n]$ in the asymmetric hydrogenation of methyl acetoacetate (**87**), the enantioselectivity dropped to 24% whilst the conversion obtained was only half of that obtained from *(R)*-**P-Phos**. From the preliminary results, we can conclude that the

presence of *ortho*-substituted phenyl groups greatly reduce the conversion and enantioselectivity for this reaction.



87 **88**

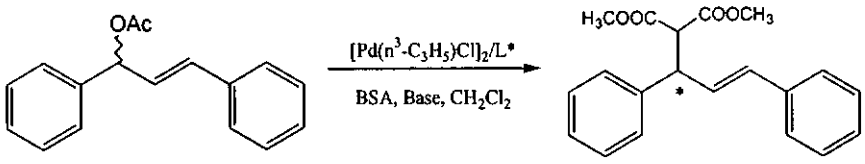
Table 5-5 Catalytic asymmetric hydrogenation of **87**[a]

Entry	Catalyst	[b]conv. (%)	[c]ee (%)
1	Ru(*R*-P-Phos)$Cl_2(DMF)_n$	>99	96.3
2	Ru(*S*-*o*-Ph-P-Phos)$Cl_2(DMF)_n$	57	24

[a]Reaction conditions: 100 psi H_2,; 230μm substrate [b]The conversion was determined by ^{1}H-NMR analysis of the crude product. [c]The ee values were determined by Supelco γ-Dex 225 (30 m x 0.25 mm x 0.25 μm).

5.3.6 Asymmetric Allylic Alkylations

In the asymmetric allylic alkylation of 1,3-diphenyl-2-propenyl acetate **(89)** with dimethyl malonate, ***(S)-o*-Ph-P-Phos** offered poor enantioselectivity (16%) as compared to the non-substituted counterpart ***(R)*-P-Phos** which exhibited 78% ee in this reaction (Table 5-6). It is evident that *ortho*-substituted phenyl group reduces the stereoselectivity of this catalyst.



89 **90**

Table 5-6 Asymmetric allylic alkylation of **89**[a]

Entry	Ligand/L*	Base	Pd/sub	T (°C)	T (h)	ee[b] (%)	Conv.[c] %
1	*(R)*-**P-Phos**	LiOAc	1/100	r.t	1.5	78 (*R*)	98
2	*(S)-o*-**Ph-P-Phos**	LiOAc	1/100	r.t.	1.5	16 (*S*)	99

[a]The reaction was carried out under inert atmosphere using 89 (1.0 mmol), dimethyl malonate (3.0 mmol), *N,O*-bis(trimethylsilyl)acetamide (BSA, 3.0 mmol), ligand (0.01 mmol), $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (0.005 mmol), base (0.05 mmol) and CH_2Cl_2 (10 ml). [b]Enantiomeric excess values were measured by HPLC on a Chiralcel-AD column. [c]Conversion was determined by ^1H NMR spectroscopy. *(The above results were contributed by Dr. Chen G. of our research group.)

Chapter 6

Experimental Section

6.1 General procedures

All reactions were performed under an inert atmosphere (e.g., dry nitrogen atmosphere) unless otherwise stated. The preparation of samples and the set-up of the high pressure reactor were either carried out in a nitrogen-filled continuous purge MBRAUN Model lab master 130 glovebox or using standard Schlenk-type techniques. All solvents used were dried with standard methods and were distilled before use. The hydrogenation reactions were performed in a 50 mL stainless-steel autoclave purchased from Parr Company.

Thin layer chromatography was carried out on Merck silica gel 60 F 254, unless otherwise stated, and visualized under ultra-violet light (254 nm), or through spraying with acidic ammonium molybdate (IV), basic potassium permanganate, 7% dodecaphosphomolybdic acid in ethanol, or by placing in iodine vapour.

Flash column chromatography was carried out on 230-400 (0.04-0.063 mm) silica gel (NA SILICA GEL).

Alpha and beta keto-ester substrates, which were purchased from Acros and Aldrich company, were used directly without further purification. Beta keto-ester

substrates were freshly distilled before use.

^{1}H NMR (500 MHz), ^{13}C NMR (125 MHz) and ^{31}P NMR (202 MHz) spectra were recorded on a Varian Oxford AS 500 spectrometer using $CDCl_3$ and $(CD_3)_2CO$ as a solvent unless otherwise specified. As internal reference for ^{1}H NMR, ^{13}C NMR and ^{31}P NMR spectra, tetramethylsilane (δ_H 0.00 ppm, s) and residual protic solvent in $CDCl_3$ (δ_C 77.7 ppm, t) were used respectively. Coupling constants were recorded in hertz (Hz). Multiplicities were recorded as the following abbreviations: s, singlet; bs, broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet.

Melting points were determined using a BUCHI Melting Point B-545 machine in capillaries sealed under atmosphere. Mass analyses were performed on a V. G. MICROMASS, Fisons VG platform or a Finnigan Model Mat 95 ST spectrometer. Optical rotations were measured on a Perkin-Elmer Model 341 polarimeter. Gas chromatographic analyses were conducted on a HP 5890 series II system. HPLC analysis was performed using a Hewlett-Packard Model HP 1050 LC.

6.2 Synthesis of 2,2'6,6'–tetramethoxy-5,5'–diphenyl-4,4'–diphenyl–phosphino- 3,3'-bipyridine (78)

Synthesis of 3-bromo-2,6-dimethoxypyridine (73)

2,6-dimethoxypyridine **72** (20 g, 0.145 mol) in carbon tetrachloride (200 mL) was placed into a round bottom flask with a mechanical stirring bar. A solution of bromine (24 g, 0.150 mol) in carbon tetrachloride (25 mL) was then slowly added to the solution containing **72** at -30 to -40 °C for 12 h. The solution was neutralized by sodium carbonate (250 mL) to pH = 7.5 at 0 °C. The organic product was extracted by dichloromethane (3 x 10 mL). The combined extracts were dried with anhydrous magnesium sulfate and concentrated *in vacuo* to give a crude product which was further purified by distillation under reduced pressure to give **73** in 76% yield (11.35 g).

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.90 (s, 3H, OCH_3), 3.99 (s, 3H, OCH_3), 6.23 (d, J = 8.5 Hz, PyH), 7.64 (d, J = 8.5 Hz, PyH); ^{13}C NMR (125MHz, $CDCl_3$): δ 53.9, 54.4, 95.5, 102.9, 143.8, 158.6, 162.3; Mass spectrum (ESI): 218.09 $[M(Br^{79})+H]^+$ and 220.09 $[M(Br^{81})+H]^+$

Synthesis of 3-bromo-2,6-dimethoxy-4-diphenylphosphinopyridine (74)

3-bromo-2,6-dimethoxypyridine **73** (2.16 g, 10 mmol) in dried THF (50 mL) was placed into a rounded bottom flask with a mechanical stirring bar. A solution of 40

mL (79.8 mmol) of ca. 2.0 M LDA was added slowly to the solution containing **73** at -78°C over the course of 2 h. A solution of chlorodiphenylphosphine (2.15 mL, 120 mmol) in 100 mL dried THF was added slowly to the resulting red-brown suspension at -78 °C and the mixture was maintained at -78 °C for 5 h. The reaction mixture was allowed to react at ambient temperature for a further 12 h before the removal of THF in vacuo. The reaction mixture was then poured into water (100 mL) and the organic product was extracted with CH_2Cl_2 (3 x 50 mL). The combined extracts were dried with anhydrous magnesium sulfate and concentrated *in vacuo* to give a solid residue which was recrystallized in methanol to give **74** in 95 % yield as a pale yellow solid (2.98 g).

Melting point: 143.2 – 144.1 °C. ^{1}H NMR (500MHz, $CDCl_3$): δ 3.83 (s, 3H, OCH_3), 4.00 (s, 3H, OCH_3), 5.71 (d, J_{PH} = 2.5 Hz, 1H, PyH), 7.40 ~ 7.27 (m, 10H, PhH); ^{13}C NMR (125MHz, $CDCl_3$): δ 53.9, 54.8, 101.9, 106.8, 128.99, 129.7, 134.4, 134.5, 134.6, 134.7, 154.3, 158.9, 161.7; ^{31}P NMR (200MHz, $CDCl_3$): δ 4.3; Mass spectrum (ESI): 403.9 $[M+H]^+$

Synthesis of 3-bromo-2,6-dimethoxy-4-diphenylphosphinoylpyridine (75)

3-bromo-2,6-dimethoxy-4-diphenylphosphinopyridine **74** (9.5 g, 24 mmol) in acetone (100 mL) was placed into a round bottom flask with a magnetic stirring bar. Ca. 35% hydrogen peroxide (5 x 5 mL) was slowly added to this solution at 0 °C. The

reaction was monitored by thin layer chromatography. The product was extracted with CH_2Cl_2 (3 x 20 mL). The combined extracts were dried with anhydrous magnesium sulfate and concentrated *in vacuo* to give a solid residue which was purified by column chromatography (silica gel, ethyl acetate : $CHCl_3$ = 1: 3, and then 1: 1) to give **75** with 99 % yield as a pale yellow solid (4.2 g).

Melting point: 157.3 – 158.7 °C; ^{1}H NMR (500MHz, $CDCl_3$): δ 3.85 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 6.34 (d, J = 15 Hz, 1H, PyH), 7.35 ~ 7.32 (m, 4H, PhH), 7.45 ~ 7.42 (m, 2H, PhH), 7.56 ~ 7.52 (m, 4H, PhH); ^{13}C NMR (125MHz, $CDCl_3$): δ 54.3, 55.1, 98.9, 108.4, 128.9, 130.4, 131.3, 132.1, 132.2, 146.0, 146.8, 160.0, 161.9; ^{31}P-NMR (200MHz, $CDCl_3$): δ 31.6; Mass spectrum (ESI): 441.8 $[M+Na]^+$

Synthesis of 2,6-dimethoxy-3-phenyl -4-diphenylphosphinoylpyridine (76)

3-bromo-2,6-dimethoxy-4-diphenylphosphinylpyridine **75** (4.19 g, 10 mmol), phenylboronic acid (1.83 g, 15 mmol), THF (130 mL), and a saturated aqueous K_2CO_3 solution were placed into a rounded bottom flask with a magnetic stirring bar. The mixture was degassed with nitrogen for 1 h. $Pd(PPh_3)_4$ (0.24 g, 0.4 mmol) was added into the mixture and the resulting solution was brought to reflux under nitrogen for 24 h. The THF was evaporated under reduced pressure. 200 mL of CH_2Cl_2 was added to the residue and the organic layer was washed with water (100 mL) and brine (100 mL). The extract was dried with Na_2SO_4 and concentrated *in vacuo* to give a

crude product which was recrystallized by EtOAc (50 mL) to give **76** as an off-white solid in 89% yield (3.6 g).

Melting point: 182.2 – 182.9 °C; ^{1}H NMR (500MHz, $CDCl_3$): δ 3.85 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 6.34 (d, J = 15 Hz, 1H, PyH), 7.08 ~ 6.95 (m, 6H, PhH) 7.35 ~ 7.32 (m, 4H, PhH), 7.45 ~ 7.42 (m, 2H, PhH), 7.56 ~ 7.52 (m, 4H, PhH); ^{13}C NMR (125MHz, $CDCl_3$): δ 54.0, 54.3, 105.5, 105.6, 105.7, 119.6, 119.7, 127.3, 128.4, 128.5, 128.6, 131.7, 131.8, 132.5, 133.8, 133.9, 145.7, 146.4, 161.4, 161.5, 161.8, 161.9; ^{31}P NMR (200MHz, $CDCl_3$): δ 27.6; Mass spectrum (ESI): 416.17 $[M+H]^+$; 438.15 $[M+Na]^+$

Synthesis of 2,2',6,6'-tetramethoxy-5,5'-diphenyl-4,4'-diphenylphosphinoyl-3,3'-bipyridine (77)

2,6-dimethoxy-3-phenyl-4-diphenylphosphinoylpyridine **76** (0.415 mg, 1 mmol) in dry THF was placed into a round bottom flask with a mechanical stirring bar. *t*-BuLi (0.73 mL, 1.5M) was added dropwise to the mixture at -100 °C for 30 minutes. The reaction temperature was warmed to -70 °C and the solution was stirred for additional 3 h. I_2 (0.381 g, 1.5 mmol) in THF (5 mL) was added to this solution slowly. The reaction temperature was then raised to 0 °C and was maintained for 2 h. The resulting dark solution was allowed to warm to room temperature and stirred overnight. A solution of $Na_2S_2O_3$ (0.4 g in 10 mL H_2O) was added and the resulting yellow solution was concentrated *in vacuo*. 3 x 20 mL of CH_2Cl_2 was added to the

residue and the organic layer was washed with water (10 mL) and brine (10 mL). The combined extracts were dried with Na_2SO_4 and concentrated *in vacuo* to give a crude product which was recrystallized in EtOAc (20 mL) to give a yellow solid. This yellow solid (1.6 g, 3 mmol), Cu powder (3.84 g, 60 mmol) and DMF (20 mL) were placed into a round bottom flask with mechanical stirring bar and were stirred at 140 ^{o}C for 24 h. The DMF was removed under vacuum and the residue was boiled for a few minutes with hot CH_2Cl_2 (30 mL), the insoluble solid was removed by filtration and was washed with CH_2Cl_2 (150 mL). The combined filtrate was dried with magnesium sulfate and the solvent was concentrated to give a crude product which was purified by flash column chromatography with ethyl acetate and chloroform mixture (1:1) to give a pure white powdery product **77** in 50% yield (1.24 g).

Melting-point: 160.3 – 162.1°C; ^{1}H NMR (500MHz, $CDCl_3$): δ 2.12 (s, 3H), 2.85 (d, 1H), 3.62-3.81 (m, 6H), 6.37 (d, 1H), 6.61-6.64 (t, 1H), 6.907-6.993 (t, 1H), 7.01-7.05 (s, 3H), 7.07-7.12 (m, 4H), 7.19-7.27 (m, 3H), 7.37 (d, 1H), 7.50-7.54 (t, 2H); ^{13}C NMR (125MHz, $CDCl_3$): δ 53.6, 53.8, 126.58, 126.6, 127.1, 127.6, 127.7, 127.8, 127.9, 130.5, 130.9, 131.0, 132.2, 132.9, 133.0, 133.3, 134.3, 159.5; ^{31}P-NMR (200MHz, $CDCl_3$): δ 27.2; Mass spectrum (ESI): 829.25 $[M+H]^+$

Separation of the enantiomers of 2,2'6,6' - tetramethoxy-5,5'-diphenyl- 4,4'-diphenyl- phosphinoyl - 3,3'- bipyridine (77) by semi-preparative HPLC

The enantiomers of 2,2'6,6'-tetramethoxy-5,5'-4,4'-diphenyl-phosphinoyl-3,3'-

bipyridine **77** were separated by HPLC with a semi-preparative DAICEL AD column (25 mm x 250 mm). The enantiomers were eluted with isopropanol : hexane = 10 : 90 with a flow rate of 6.0 mL per minute. The retention time of the (*S*)-enantiomer was at the 44th minute and that of (*R*)-enantiomer was at the 94th minute. For the determination of the enantiopurities of the enantiomers, analytical DAICEL AD column with the solvent system (isopropanol: hexane = 10 : 90) with a flow rate of 1.0 mL per minute was used. The retention time of (*S*)-enantiomer was 16.9 and that of (*R*)-enantiomer was 34.8 minute. $[\alpha]_D^{20} = -108$ (c = 0.95, $CHCl_3$).

(*S*)-2,2'6,6'–tetramethoxy-5,5'–diphenyl-4,4'–diphenylphosphino-3,3'-bipyridine (78)

(*S*)-2,2'6,6'–tetramethoxy-4,4'-diphenyl-phosphinoyl-3,3'-bipyridine **77** (0.166 g, 0.2 mmol), xylene (10 mL), triethylamine (0.34 mL, 2.44 mmol), and trichlorosilane (0.24 mL, 2.44 mmol) were placed into a round bottom flask at 0 °C. The mixture was then stirred under reflux for 2 days. After the solution was cooled to room temperature, a 10% aqueous sodium hydroxide solution (10 mL) was carefully added. The mixture was then stirred at 60 °C until the organic and aqueous layers became clear. The organic product was extracted with water (3 x 25 mL), dried with Na_2SO_4 and concentrated *in vacuo* to give a crude product. Under nitrogen, the residue was dissolved in dried CH_2Cl_2 (5 mL) and loaded onto a basic Al_2O_3 plug with extra 20 mL dried CH_2Cl_2 to wash through in order to elute the pure white powdery product **78**

(0.153 g, 77 % yield).

Melting point: 188.7 – 193.4 °C; ^{1}H NMR (500MHz, $CDCl_3$): δ 3.55 (s, 3H, OCH_3), 3.61 (s, 3H, OCH_3), 6.34 (d, J = 15 Hz, 1H, PyH), 7.35 ~ 7.32 (m, 4H, PhH), 7.45 ~ 7.42 (m, 2H, PhH), 7.56 ~ 7.52 (m, 4H, PhH); ^{13}C NMR (125MHz, $CDCl_3$): δ 53.2, 53.7, 119.8, 126.1, 127.1, 127.3, 127.5, 127.7, 127.8, 129.1, 131.2, 131.3, 133.6, 134.2, 134.3, 135.8, 136.9, 159.9; ^{31}P-NMR (200MHz, $CDCl_3$): δ -2.6; Mass spectrum (high resolution): 797.15 $[M+H]^+$

6.3 Synthesis of Ionic Liquids

Synthesis of butyl-3-methylimidazolium chloride (BMIM.Cl)

A vigorously stirred solution of 328 g (4 mol) 1-methylimidazole and 385 g (4.2 mol) 1-chlorobutane mixture was gentlely refluxed for 48 h. The crude product was then cooled to room temperature and recrystallized from toluene to obtain the desired product in quantitative yield. ^{1}H NMR (500MHz, $CDCl_3$): δ = 0.8 (t, 3H, J = 8.0 Hz), 1.2 (m, 2H), 1.8 (m, 2H), 4.0 (s, 3H), 4.2 (t, 2H, J = 7.5 Hz), 7.4 (s, 1H), 7.6 (s, 1H), 10.1(s, 1H); ^{13}C NMR (125MHz, $CDCl_3$): δ = 13.6, 19.6, 32.3, 36.7, 49.9, 122.2, 123.9, 137.7. Mass spectrum (ESI) m/z : 139 $(M-Cl)^+$

Synthesis of butyl-3-methylimidazolium tetrafluoroborate (BMIM.BF_4)

46.4 g (0.27 mol) butyl-3-methylimidazolium was dissolved in 100 mL deionized water. To this solution, 43.7 g (0.4 mol) potassium hexafluorophosphate in 300 mL

deionized water was added. After the addition, the resulting solution was allowed to react for 4 days. The resulting solution was then extracted ten times with 50 mL dichloromethane. The dichloromethane layer was then washed with saturated brine and dried with anhydrous magnesium sulfate. The dichloromethane was finally vacuum distilled off to obtain the desired product. ^{1}H NMR (500MHz, acetone-d_6): δ = 0.95 (t, 3H, J = 7.5Hz), 1.37 (m, 2H), 1.93 (m, 2H), 4.05 (s, 3H), 4.37 (t, 2H, J = 7.5Hz), 7.71 (s, 1H), 7.76 (s, 1H), 9.02 (s, 1H); ^{13}C NMR (125 MHz, acetone-d_6): δ = 13.0, 19.3, 32.1, 35.9, 49.5, 122.7, 124.0, 136.9. Mass spectrum (ESI) m/z : 139 $(M\text{-}BF_4)^+$.

Synthesis of butyl-3-methylimidazolium hexafluorophosphate ($BMImPF_6$)

65.6 g (0.37 mol) butyl-3-methylimidazolium chloride was dissolved in 70 mL deionized water, followed by the addition of a solution of 69.3 g (0.37 mol) potassium hexafluorophosphate in 70 mL deionized water. After the addition, the resulting solution was allowed to react for 4 days. The resulting solution was then extracted 5 times with 50 mL dichloromethane. The dichloromethane layer was then washed with saturated brine and dried with anhydrous magnesium sulfate. The dichloromethane was finally vacuum distilled off to obtain the desired product. ^{1}H NMR (500 MHz, acetone-d_6): δ = 0.94 (t, 3H, J = 7.5 Hz), 1.38 (m, 2H), 1.95 (m, 2H), 4.05 (s, 3H), 4.36 (t, 2H, J = 7.5 Hz), 7.71 (s, 1H), 7.76 (s, 1H), 9.01 (s, 1H); ^{13}C NMR (125 MHz,

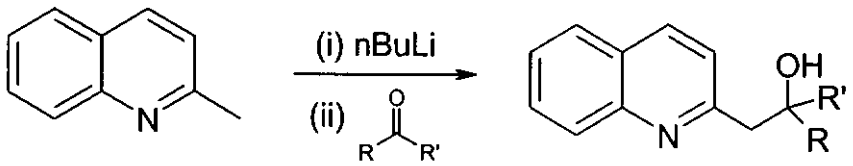
acetone-d_6): δ = 13.0, 19.3, 32.0, 36.0, 49.6, 122.7, 124.2, 136.7. Mass spectrum (ESI) m/z : 139 $(M\text{-}PF_6)^+$.

6.4 Synthesis of Quinolines for Iridium Catalyzed Asymmetric Hydrogenation

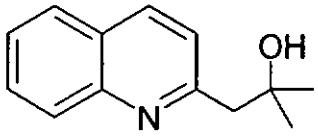
To a solution of quinaldine (5 mmol., 716 mg) in 15 mL ether was added a 1.6M solution of n-butyllithium in hexane (5.5 mmol., 3.5 mL) at 0 °C over 30 minutes. This solution was allowed to warm to room temperature and stirred for 1 h.

To the above mixture, a solution of either (i) ketone (5 mmol for synthesis of compounds **a** to **c**) or (ii) alkyl halide (RX, 5 mmol, where X = Br^- or I^- for synthesis of compounds **d** to **g**) in 15 mL ether was added dropwise over 15 minutes with vigorous stirring while the temperature cooled to 0 °C. The mixture was then stirred overnight and hydrolysed with a saturated aqueous ammonium chloride solution. The organic layer was separated and the aqueous layer was further extracted with ether (3 x 50 mL). The combined organic layers were washed with brine and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography to give the oil product.

(i) Synthesis of compound **a** to **c**

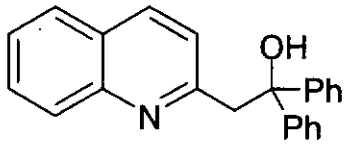


(a) 2-methyl-1-(quinolin-2-yl)-propanol



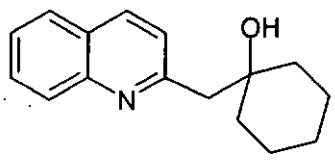
^{1}H-NMR (500MHz, $CDCl_3$): δ 1.20 (s, 6H), 3.04 (s, 2H), 6.09 (s, 1H), 7.19 (m, 1H), 7.46 (t, 1H, J = 8.0 Hz), 7.65 (t, 1H, J = 7.5 Hz), 7.74 (d, 1H, J = 8.5 Hz), 7.95 (d, 1H, J = 8.0 Hz), 8.04 (d, 1H, J = 8.5 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 29.87, 49.26, 71.21, 123.09, 126.42, 126.96, 127.79, 128.96, 130.06, 137.06, 147.09, 161.00. Mass spectrum (ESI): 202.15 $[M+H]^+$; Yield = 83%.

(b) 1,1-dipheyl-2-(quinolin-2-yl)-ethanol



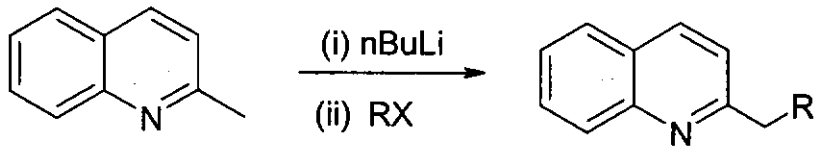
^{1}H-NMR (500MHz, $CDCl_3$): δ 3.88 (s, 2H), 7.13 (m, 2H), 7.22 (m, 4H), 7.5 (m, 5H), 7.66 (t, 1H, J = 8.0 Hz), 7.72 (d, 1H, J = 8.5 Hz), 7.97 (d, 1H, J = 8.0 Hz), 8.02 (d, 1H, J = 8.5 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 47.2, 78.9, 123.1, 126.4, 126.5, 126.7, 126.8, 127.8, 128.2, 128.7, 130.1, 137.2, 147.5, 160.3; Mass spectrum (ESI): 326.21 $[M+H]^+$; Yield = 79%.

(c) 1-(quinolin-2-ylmethyl)-cyclohexanol

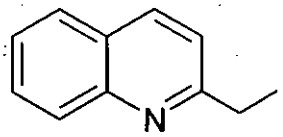


^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.56 (m, 10H), 3.09 (s, 2H), 6.0 (bs, 1H), 7.24 (d, 1H, J = 8.5 Hz), 7.52 (m, 1H), 7.67 (m, 1H), 7.70 (m, 1H), 7.80 (m, 1H), 8.00 (d, 1H, J = 8.0 Hz) , 8.10 (d, 1H, J = 8.0 Hz); ^{13}C-NMR (125MHz, $CDCl_3$): δ 22.6, 26.2, 38.3, 47.9, 72.1, 123.2, 126.3, 126.9, 127.8, 129.0, 130.0, 136.9, 147.2, 160.8; Mass spectrum (ESI): 242.19 $[M+H]^+$; Yield = 90%.

(ii) Synthesis of compound **d** to **i**

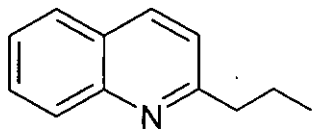


(d) 2-ethyl-quinoline



^{1}H-NMR ($CDCl_3$): δ 1.40 (t, 3H, J = 8.5 Hz), 3.02 (q, 2H, J = 8.0 Hz), 7.31 (d, 1H, J = 9.0 Hz), 7.48 (m, 1H), 7.68 (m, 1H), 7.76 (d, 1H, J = 8.0 Hz), 8.05 (d, 1H, J = 8.5 Hz), 8.08 (d, 1H, J = 8.0 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 14.26, 32.56, 121.08, 125.88, 126.96, 127.71, 129.04, 129.57, 136.58, 148.09, 164.26; Mass spectrum (ESI): 158 $[M+H]^+$; Yield = 90%.

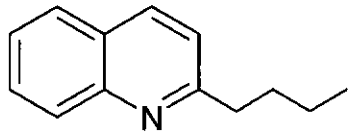
(e) 2-propyl-quinoline



^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.03 (t, 3H, J = 7.0 Hz), 1.84 (m, 2H), 2.96 (m, 2H), 7.30 (d, 1H, J = 8.5 Hz), 7.48 (m, 1H), 7.69 (m, 1H), 7.77 (m, 1H), 8.06 (t, 2H, J = 9.0

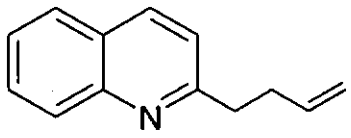
Hz); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 14.24, 23.52, 41.51, 121.63, 125.89, 126.96, 127.71, 129.04, 129.57, 136.44, 148.11, 163.14; Mass spectrum (ESI): 171 $[M+H]^+$; Yield = 89%.

(f) 2-butyl-quinoline



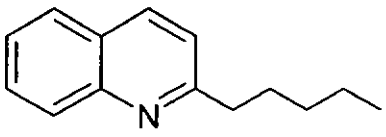
^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.97 (t, 3H, J = 6.5 Hz), 1.44 (m, 2H), 1.80 (m, 2H), 2.99 (t, 2H, J = 8.0 Hz), 7.32 (d, 1H, J = 8.5 Hz), 7.48 (t, 1H, J = 8.5 Hz), 7.70 (m, 1H), 7.79 (d, 1H, J = 8.5 Hz), 8.06 (t, 2H, J = 8.0 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 14.23, 22.91, 32.44, 39.29, 121.62, 125.90, 126.95, 127.71, 128.98, 129.59, 136.49, 148.05, 163.35; Mass spectrum (ESI): 186.14 $[M+H]^+$; Yield = 88%.

(g) 2-(3-butenyl)-quinoline



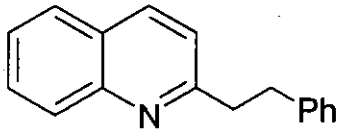
^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.60 (m, 2H), 3.09 (m, 2H), 5.0 (m, 1H), 5.10 (m, 1H), 5.94 (m, 1H), 7.30 (d, 1H, J = 9.0 Hz), 7.49 (t, 1H, J = 7.5 Hz), 7.69 (m, 1H) , 7.77 (d, 1H, J = 8.5 Hz), 8.07 (m, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 34.04, 38.71, 115.50, 121.66, 126.02, 127.00, 127.74, 129.01, 129.65, 136.53, 137.91, 148.08, 162.24; Mass spectrum (ESI): 184.11 $[M+H]^+$; Yield = 92%.

(h) 2-pentyl-quinoline



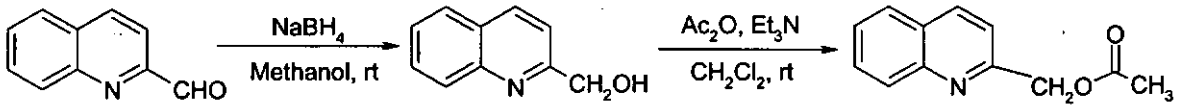
^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.90 (t, 3H, J = 7.5 Hz), 1.39 (m, 4H), 1.82 (m, 2H), 2.98 (t, 2H, J = 8.0 Hz), 7.30 (d, 1H, J = 8.5 Hz), 7.48 (t, 1H, J = 8.0 Hz), 7.69 (m, 1H), 7.77 (d, 1H, J = 8.0 Hz) , 8.07 (t, 2H, J = 8.5 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 14.26, 22.81, 30.02, 31.99, 39.53, 121.62, 125.91, 126.95, 127.72, 128.96, 129.61, 136.52, 148.01, 163.36; Mass spectrum (ESI): 200.16 $[M+H]^+$; Yield = 91%.

(i) 2-phenethyl-quinoline



^{1}H-NMR (500 MHz, $CDCl_3$): δ 3.20 (m, 2H), 3.30 (m, 2H), 7.30 (m, 6H), 7.52 (t, 1H, J = 7.5 Hz), 7.71 (t, 1H, J = 8.0 Hz), 7.78 (d, 1H, J = 8.0 Hz), 8.05 (dd, 2H, J = 8.0, 16.0 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 36.19, 41.19, 121.82, 126.08, 126.25, 127.05, 127.78, 128.65, 128.77, 129.04, 129.70, 136.55, 141.73, 148.14, 163.05; Mass spectrum (ESI): 234.13 $[M+H]^+$; Yield = 90%.

(j) acetic acid quinolin-2-ylmethyl ether



To a stirred solution of 2-quinolinecarboxaldehyde (5 mmol, 786 mg) in methanol (30 mL) was added in portion $NaBH_4$ (10 mmol, 378 mg) at room temperature. The reaction was monitored by TLC. After the reaction was complete, the solvent was removed under reduced pressure, and the residue was poured into 20 mL water, and extracted with dichloromethane (3 x 10 mL). The combined organic layers were

washed with brine, and dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure, and the crude product was purified by silica gel column chromatography to give the alcohol product as colorless oil in quantitative yield.

To a stirred solution of alcohol (2.0 mmol, 325 mg), acetic anhydride (4 mmol, 0.4 mL) and triethylamine (4 mmol, 0.6 mL) were added. The resulting mixture was stirred at room temperature for 24 hours. The reaction was quenched by adding 20 mL water, and the mixture was extracted with brine, and dried over anhydrous sodium sulphate. After removal of the solvent, the crude product was subject to silica gel chromatography to give the product in 96% yield.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.20 (s, 3H), 5.40 (s, 2H), 7.49 (d, 1H, J = 9.0 Hz), 7.55 (m, 1H), 7.73 (m, 1H), 7.83 (d, 1H, J = 8.5 Hz), 8.08 (d, 1H, J = 8.0 Hz), 8.18 (d, 1H, J = 9.0 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 21.18, 67.68, 119.74, 126.93, 127.77, 127.83, 129.41, 130.09, 137.23, 147.87, 156.37, 170.94, ; Mass spectrum (ESI): 202.09 $[M+H]^+$; Yield = 96%.

6.5 Asymmetric Catalysis

6.5.1 Asymmetric Hydrogenation of Enamide by in situ Made Catalyst

To a solution of $[Rh(NBD)_2]SbF_6$ (0.23 mg, 0.00045 mmol) or other complex

precursors in CH_2Cl_2 (0.2 mL) in a glovebox was added the ligand (0.0005 mmol). After the mixture was stirred for 10 min, the substrate (0.005 mmol) was added. The hydrogenation was performed at room temperature under 100 psi of H_2 for 24 h. The enantiomeric excesses of the crude products were measured by chiral GC directly without further purification.

GC Conditions:

Chirasil DEX CB column – 25 m x 0.25 mm – 0.25 m film thickness; temperature program – 170°C for 15 minutes; injector temperature at 250°C; detector temperature at 270°C; detection – FID at 200 °C; carrier gas – helium at 19 psi; sample solvent – ethanol; retention times: 13.9 min; 15.1 min

6.5.2 Asymmetric Hydrogenation of beta Enamidophosphonate 38

$[Rh(COD)_2]BF_4$ and ligands (**P-Phos** or *o*-**Ph-P-Phos**, 1.1 equiv. of Rh(I) complex) were weighted and dissolved in CH_2Cl_2 (500 μL). The solution was stirred for 1 h and CH_2Cl_2 was evaporated under vacuum. β–enamidophosphonate **38** was added and 500 μL EtOH was added. The system was purged with 20 bar H_2 and the reaction mixture was allowed to stir for 20 h at room temperature. Et_2O was added to precipitate the catalyst. The solvent was distilled off under vacuum. The crude product was passed through the flash chromatograph with ethylacetate/ hexane (60%

EA in hexane) and afforded the pure hydrogenated product.

6.5.3 Asymmetric Hydrogenation of Quinoline

A mixture of $[Ir(COD)Cl]_2$ (1.0 mg, 0.0015 mmol) and the ligand (0.003 mmol) in dried solvent (1.0 mL) was stirred at room temperature for 30 minutes in a glovebox. The mixture was then transferred by a syringe to stainless steel autoclave, in which I_2 (4 mg, 0.015 mmol) and substrate (0.3 mmol) in 0.5 mL dried solvent were placed beforehand. The hydrogenation was performed at room temperature under H_2 (700 psi) for 20 h. After carefully releasing the hydrogen, the reaction mixture was diluted with dichloromethane (5 mL), saturated sodium carbonate aqueous solution (2.0 mL) added and stirred for 15 minutes. The aqueous layer was extracted with CH_2Cl_2 (3 x 3 mL). The combined organic layer was dried with sodium sulfate and concentrated *in vacuo* to give the crude product. Purification by a silica gel column eluted with hexanes/ EtOAc gave the heterocyclic compound in pure state. The enantiomeric excesses were determined by HPLC equipped with chiral columns.

6.5.4 Asymmetric Hydrogenation of Quinoline in Green Solvent

A mixture of $[Ir(COD)Cl]_2$ (1.7 mg, 0.003 mmol) and ligand (0.006 mmol) in green solvent (2.0 mL) was stirred at room temperature for 30 minutes in a stainless steel autoclave which was placed inside a glovebox, then I_2 (7 mg, 0.03 mmol) and substrate (0.6 mmol) together with 2mL hexane were added and stirred for another 5

minutes. The hydrogenation was then performed at room temperature under H_2 (700 psi) for 24 h. After carefully releasing the hydrogen, the hexane layer was then removed and the products in the green solvent phase were then further extracted with hexane (2 mL x 5). The combined hexane layer was then concentrated *in vacuo* to give the crude product. Purification was performed by a silica gel column eluted with hexane/ EtOAc to give pure product. The enantiomeric excesses were determined by HPLC equipped with chiral columns (OJ, OJ-H, OD-H and AS-H). The conversion was determined by ^{1}H NMR.

6.5.5 Asymmetric Hydrogenation of β-ketoesters

Prepartion of RuL*$Cl_2(DMF)_n$

$[RuCl_2(benzene)]_2$ (2.0 mg, 4 x 10^{-3} mmol) and ligand (**P-Phos** or ***o*-Ph-P-Phos**, 8.4 x 10^{-3} mmol) in degassed DMF (2.0 mL) were added to a Schlenk tube with a magnetic stirring bar. The mixture was heated at 100 °C for 30 minutes and then concentrated *in vacuo* to give the catalyst a reddish brown color.

6.5.6 General Procedure for the Asymmetric Hydrogenation of β-ketoesters

Inside a glovebox, 230 μmol of β-ketoester and 23 μmol Ru[L*$Cl_2(DMF)_n$] (in 200 μL MeOH/CH_2Cl_2), and 1 mL methanol were added to a glass-lined stainless steel autoclave under nitrogen atmosphere. The mixture was stirred well with a magnetic

stirrer at 70 - 80°C under a pre-set pressure of H_2 (100 psi). The conversion and the enantiomeric excess were determined directly by chiral GC column and ^{1}H-NMR.

GC column Supelco γ-Dex 225 (30m x 0.25mm x 0.25μm) with conditions: Injector: 220°C, Column: 70°C (isothermal), Detector: 270°C.

6.5.6 Palladium-catlyzed Asymmetric Allylic Alkylation

The Pd/ ligand/ base/ substrate/ dimethly malonate/ BSA ratio was either in 1:1.2:5:100:300:300. The base solution (20 μl) was added into the Schlenk tube. The substrate solution (0.5 mL) together with 0.5 mL of the catalyst solution were added into the tube by using syringes. (The solvent dichloromethane would be removed off *in vacuo*, and then another solvent such as toluene, THF, diethyl ether could be added.) Dimethyl malonate (35 μl, 0.3 mmol) and N,O-bis(trimethylsilyl)acetamide (BSA) (75 μl, 0.3 mmol) were added and the resultant mixture was stirred at certain temperature. The reaction was monitored by TLC. After the reaction was completed, the mixture was diluted with hexane (1.5 mL) and quenched by the addition of saturated aqueous NH_4Cl solution. The organic layer was washed with brine and dried by addition of anhydrous sodium sulfate. The solution was flashed through a short silica gel column with 1:1 dichloromethane and hexane mixture as eluant. The solvent was distilled off to give a crude product which was further purified by preparative TLC (hexane: EA = 8:1) to

give a pure product. The enantiomeric excess was determined by HPLC (Chiralcel AD, 1.0 mL/min, hexane: 2-propanol = 95:5). The absolute configuration was determined by optical rotation.

Chapter 7

Conclusion

We have developed an air-stable Ir/(*R*)-**P-Phos**/THF/I_2 system for asymmetric hydrogenation of a series of quinolines, with 2-methyl quinoline achieving the highest ee value of 91%. To our astonishment, this catalyst system was very air-stable and could achieve the same results without using glovebox and degased THF. Encouraged by this findings, we tried to develop the catalyst in green recyclable media, such as ionic liquids and low molecular weight polyethylene glycol(s). However, the catalyst did not performed well in the above media. The high polarity of the ionic liquids and the presence of protons in polyethylene glycol(s) may account for the low enantioselectivities obtained. Then we immobilized Ir/(*R*)-**P-Phos** and Ir/(*R*)-**MeO-BIPHEP** catalysts in low molecular weight polyethylene glycol dimethyl ether (PEGDME, MW=500) in order to compare their performance in asymmetric hydrogenation of 2-methyl quinoline. Both Ir/(*R*)-**P-Phos** and Ir/(*R*)-**MeO-BIPHEP** catalysts could carry out the catalysis over 5 cycles with ee up to 86% and 84%, respectively, and the product tetrahydroquinoline can be harvested with non-degased hexane and without the use of glovebox. In organic solvent, **P-Phos** could not give better enantioselectivities than **MeO-BIPHEP** as reported by Zhou's group.[112a] However, the Ir/(*R*)-**P-Phos** complex was air stable in both organic solvent and PEGDME, and this system could be reused with 8 cycles without any loss in enantioselectivity and conversion while only 5 cycles could be achieved by Ir/(*R*)-**MeO-BIPHEP**.

The air sensitive Ir/(*R*)-**BINAPO**/THF and Ir/(*S*)-**H8-BINAPO**/THF systems could also be applied for asymmetric hydrogenation of 2-methyl quinoline with ee value of 80% and 94%, respectively. In addition, Ir/(*R*)-**BINAPO** and Ir/(*S*)-**H8-BINAPO** catalyst systems could also be immobilized in polyethylene glycol dimethyl ether (PEGDME, MW=500) for effective asymmetric hydrogenation of 2-methyl quinoline with similar enantioselectivities. The medium PEGDME could stabilize the unstable Ir-bisphosphinites to some extent. Although the catalysts showed high enantioselectivities in both organic solvent and green PEGDME, an air-stable and recyclable system with Ir-phosphinite catalysts could not be developed.

In this study, we can also extended the application of Ru(*R*-**P-Phos**)$Cl_2(DMF)_n$ catalyst in room temperature ionic liquids (BMImBF$_4$ and BMImPF$_6$) with co-solvent methanol for asymmetric hydrogenation of alpha keto-esters with enantioselectivities up to 93% while for beta keto-esters with enantioselectivities up to 99%. The best substrate-to-catalyst ratio was 100 to 1, and the ratio was not as high as those obtained in organic solvents.

At the final section of this study, 2,2',6,6'-tetramethoxy-5,5'-diphenyl-4,4'-bis(diphenylphosphino)-3,3'-bipyridine (***o*-Ph-P-Phos**) has been synthesized and its application in asymmetric catalysis has been studied and compared with **P-Phos**. The substituted phenyl ring at the ortho position was found to be important for rhodium catalyzed asymmetric hydrogenation of cyclic enamide; and ***o*-Ph-P-Phos** performed better than **P-Phos** with enantioselectivities up to 65%. However, ***o*-Ph-P-Phos** performed poorer than **P-Phos** in the following catalytic reactions: (i) iridium catalysed

asymmetric hydrogenation of 2-methyl quinoline with 37% ee (91% ee for **P-Phos**); (ii) palladium catalysed asymmetric allylic substitution of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate with 16% ee (78% for **P-Phos**); and (iii) asymmetric hydrogenation of beta enamidophosphonate with 15% ee (no conversion was detected with **P-Phos**). The MM2 calculation (Chem3D Pro) showed that the torsion angle for the newly synthesized ligand was 85° while for **P-Phos** was 75°. The large torsion angle and the steric effect may help to explain why poorer enantioselectivities were generally obtained by ***o*-Ph-P-Phos** compared with its unsubstituted counter-part, **P-Phos**.

Chapter 8

Recommendations

1. The air-stable and recyclable Ir/*(R)*-**P-Phos**/PEGDME system developed can be extended to the asymmetric hydrogenation of other substrates such as imines and functionalized olefins.

2. The application of PEGDME with other catalyst systems on asymmetric hydrogenation of quinolines should be further investigated.

3. The application of ionic liquids (BMIM.BF_4 and BMIM.PF_6) for ruthenium or rhodium catalyzed asymmetric hydrogenation of other substrates, such as acetophenone and dehydroamino acids, should be further studied.

4. The strong steric hinderance of phenyl rings at the ortho position of **P-Phos** would generally lead to poor results in asymmetric hydrogenation. In the future, in order to further understand the steric and electronic influence of the 3,3'-disubstitution pattern on **P-Phos**-based catalysis, we can change the substitution (R/R'), such as CH_3, OCH_3, F or Br, in the ortho-positions to determine its reactivity in asymmetric hydrogenation reaction and other catalytic reactions.

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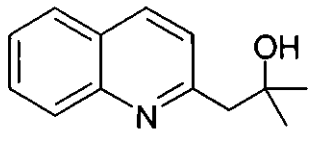
Appendix I

^{1}H, ^{13}C NMR, ^{31}P NMR and ESI-MS spectra



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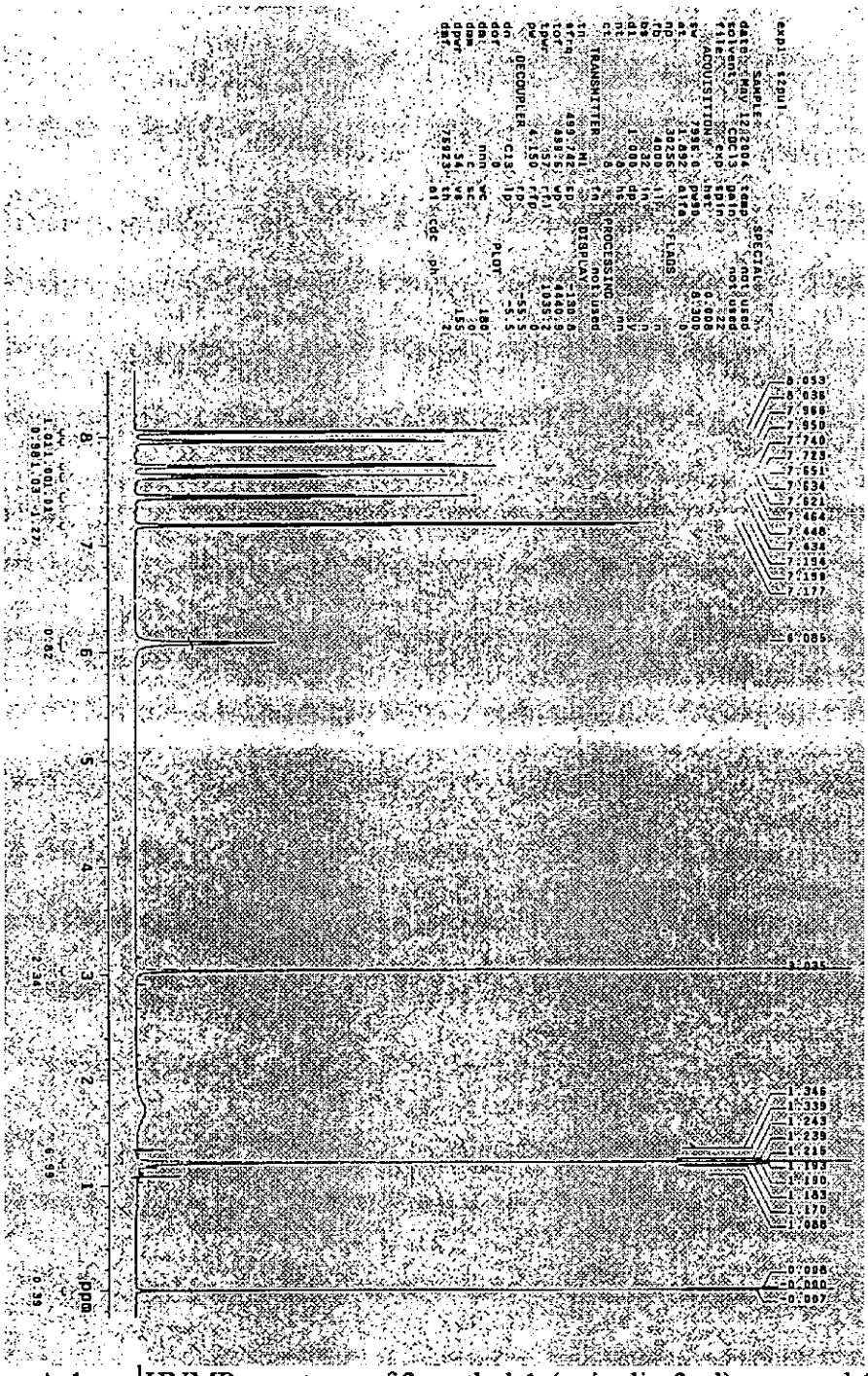
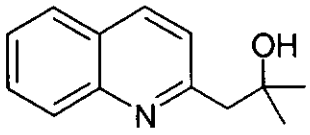


Figure A-1 ^{1}HNMR spectrum of 2-methyl-1-(quinolin-2-yl)-propanol **(91)**



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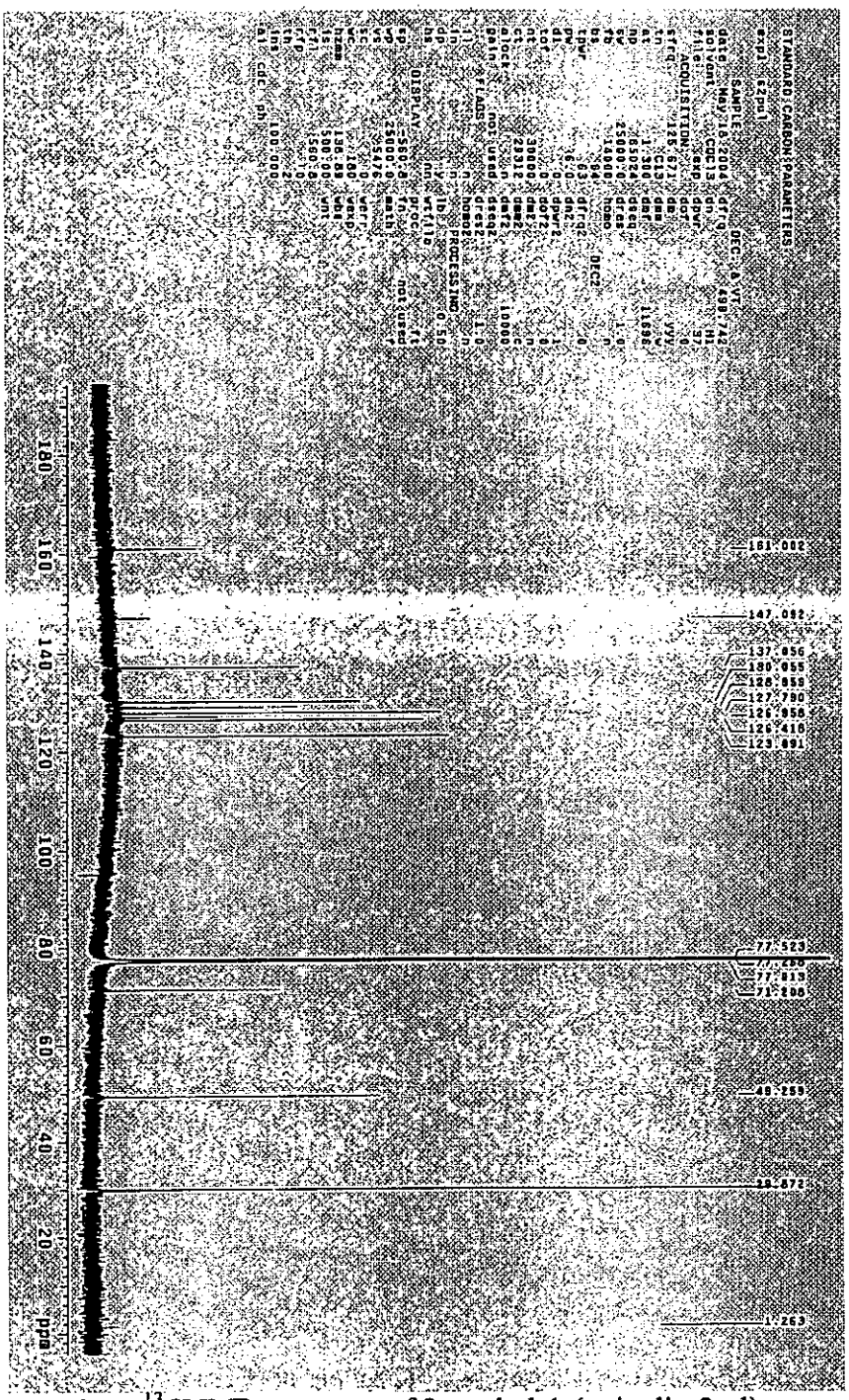
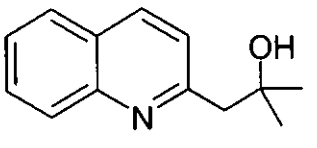


Figure A-2 ^{13}CNMR spectrum of 2-methyl-1-(quinolin-2-yl)-propanol **(91)**



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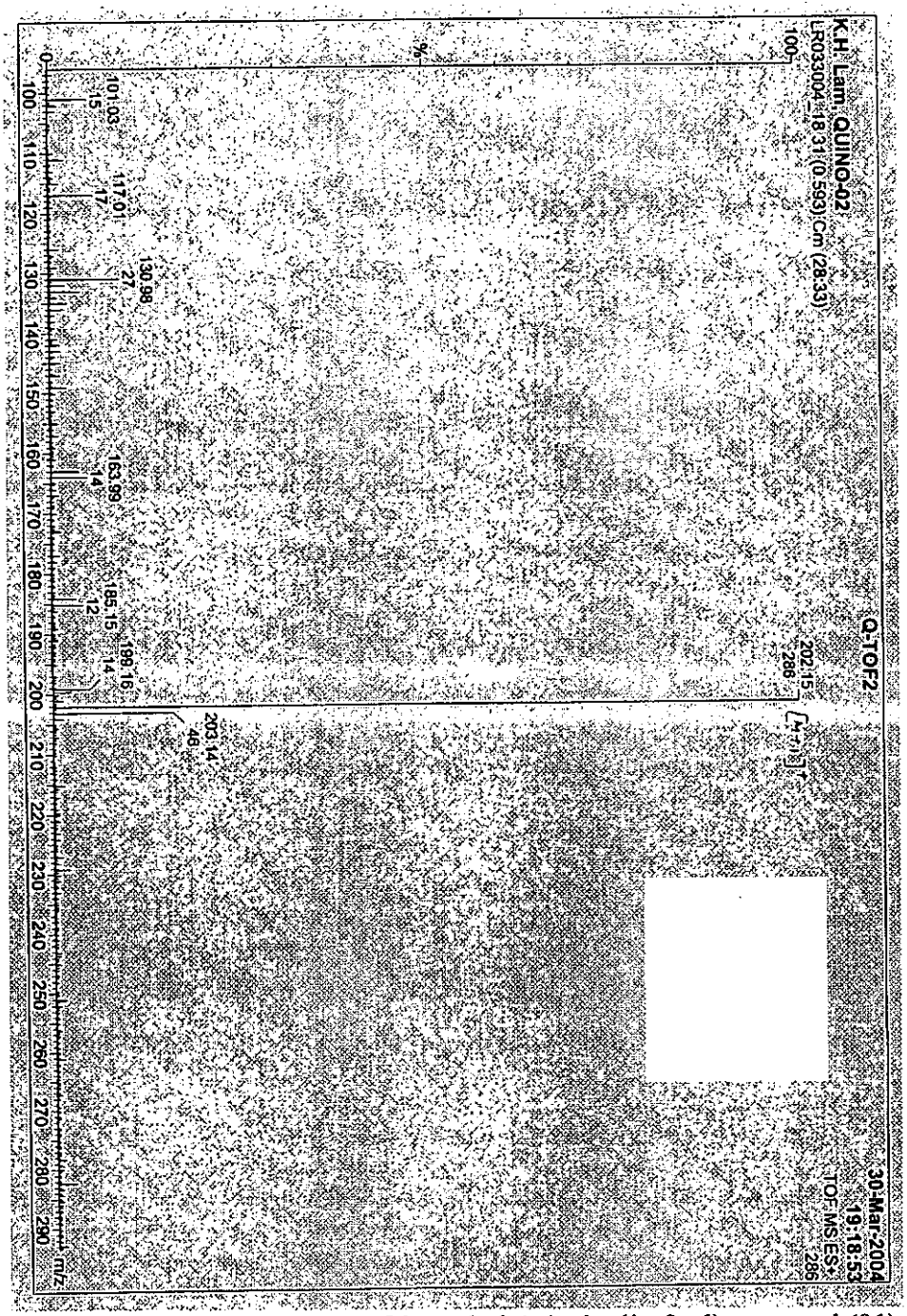
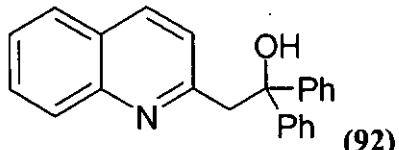


Figure A-3 ESI-MS spectrum of 2-methyl-1-(quinolin-2-yl)-propanol **(91)**



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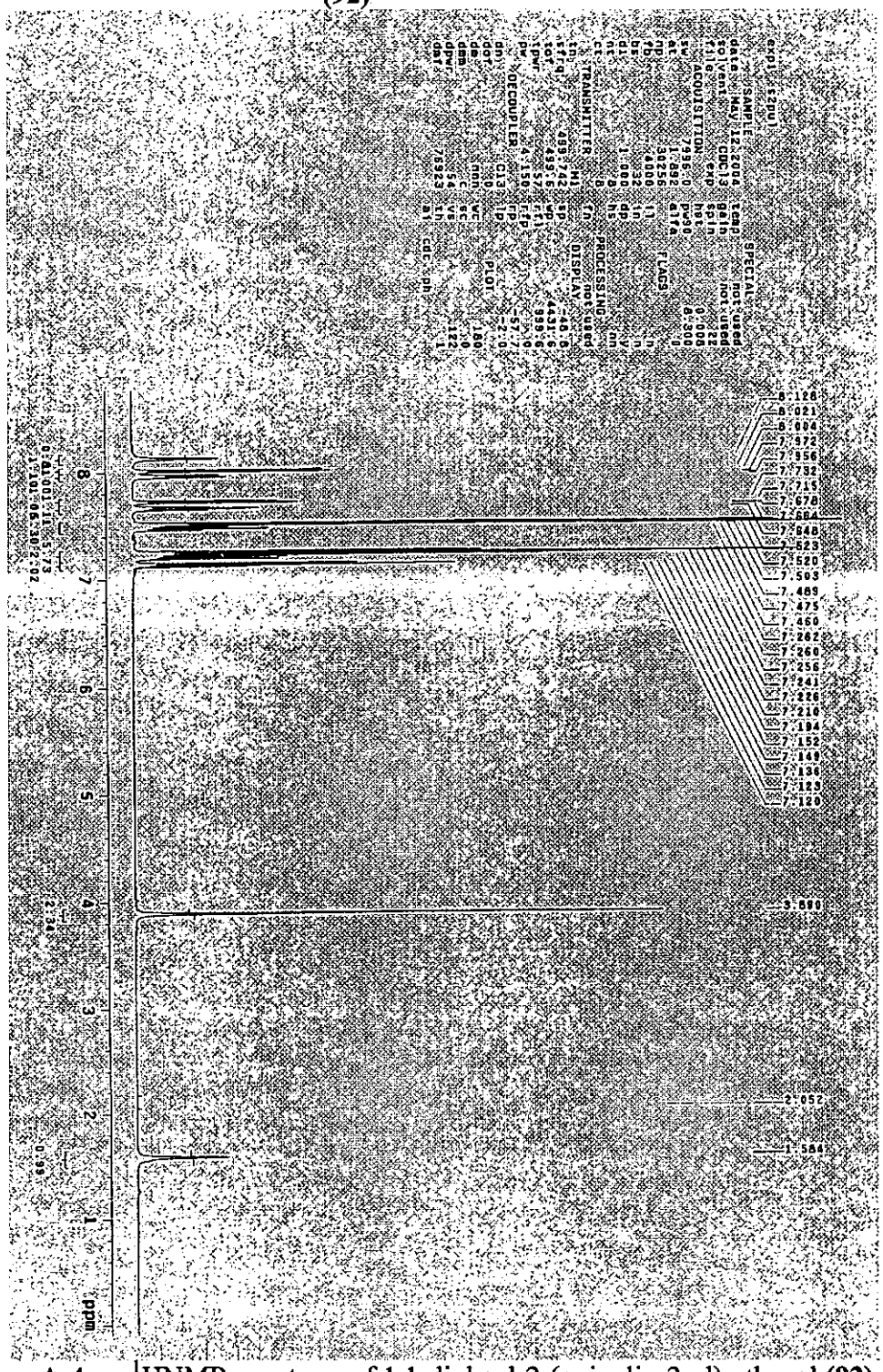


Figure A-4 ^{1}HNMR spectrum of 1,1-dipheyl-2-(quinolin-2-yl)-ethanol **(92)**

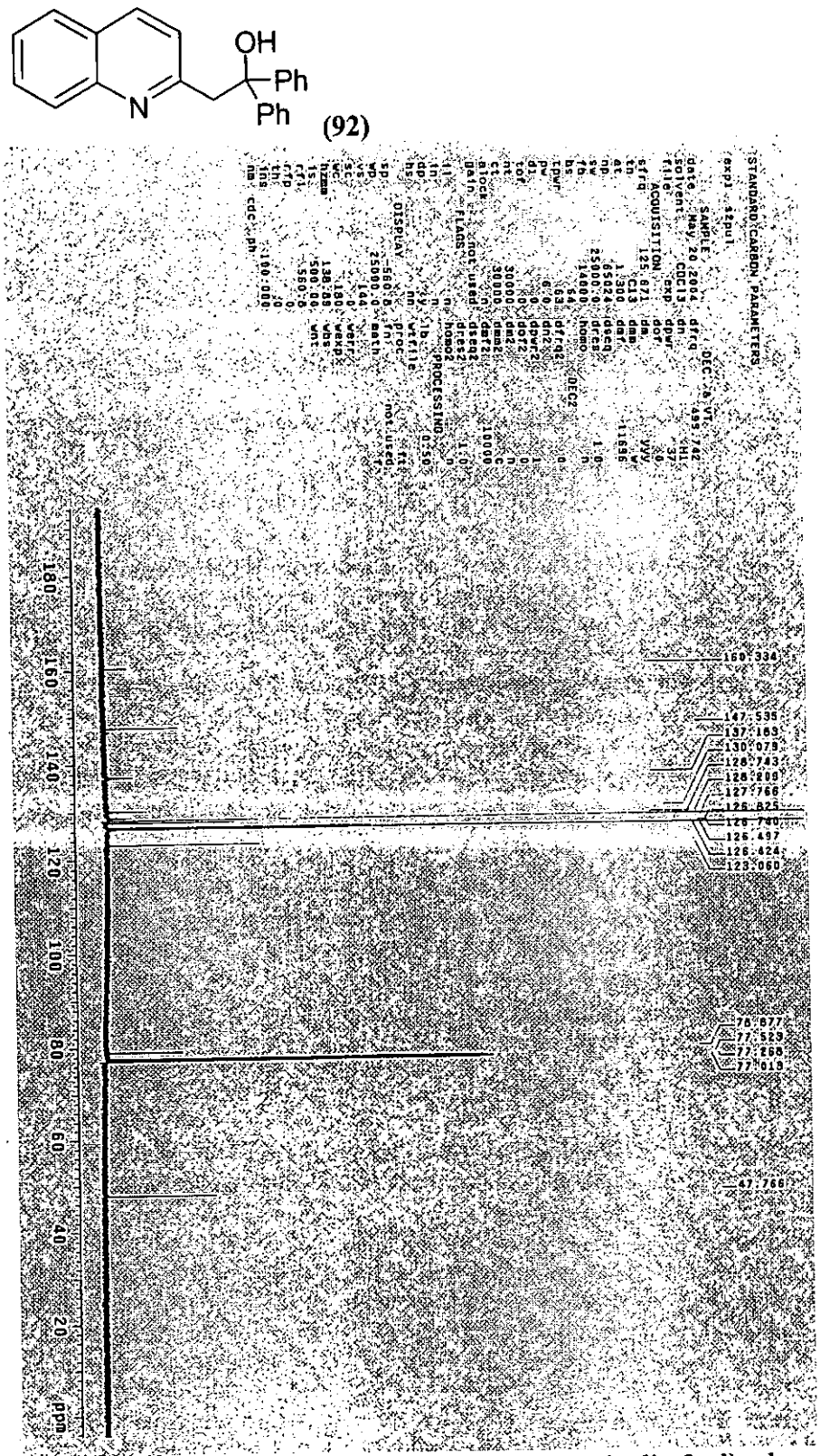
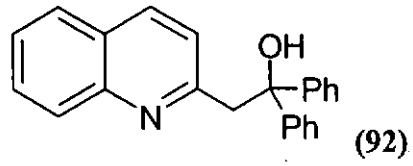


Figure A-5. ^{13}CNMR spectrum of 1,1-dipheyl-2-(quinolin-2-yl)-ethanol **(92)**



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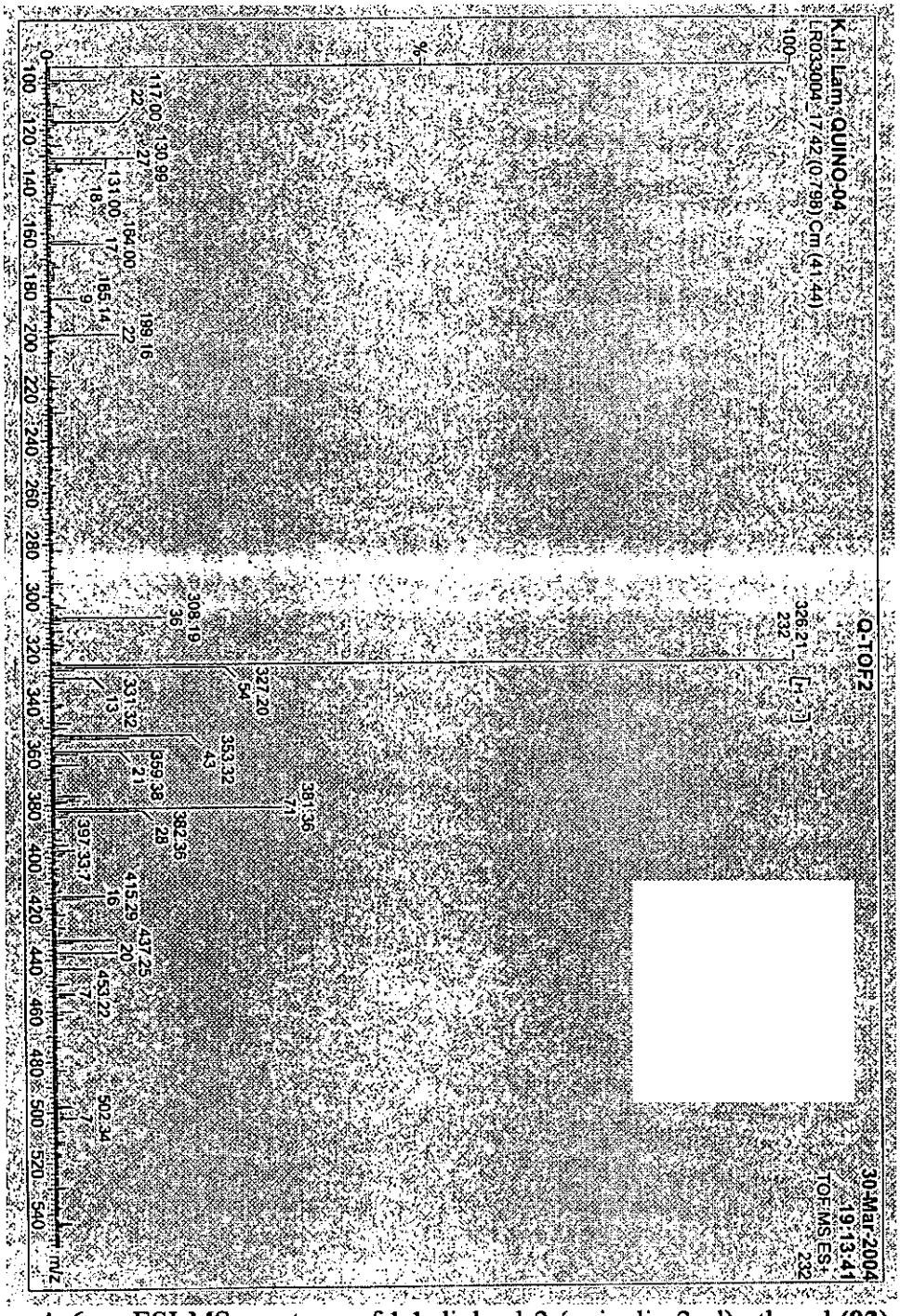
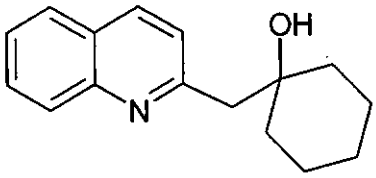


Figure A-6 ESI-MS spectrum of 1,1-dipheyl-2-(quinolin-2-yl)-ethanol **(92)**



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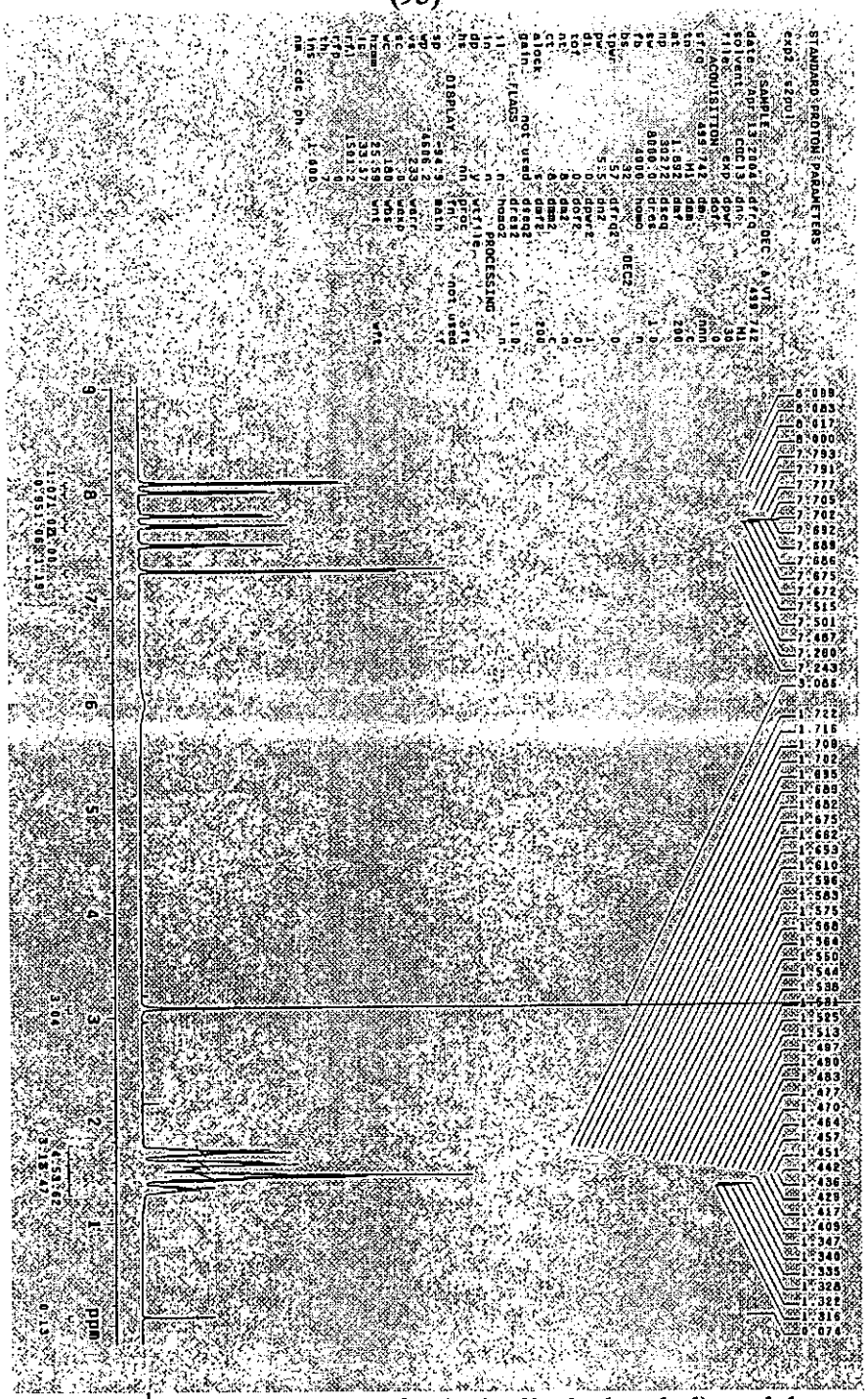
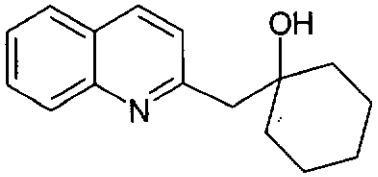


Figure A-7 ^{1}HNMR spectrum of 1-(quinolin-2-ylmethyl)-cyclohexanol **(93)**



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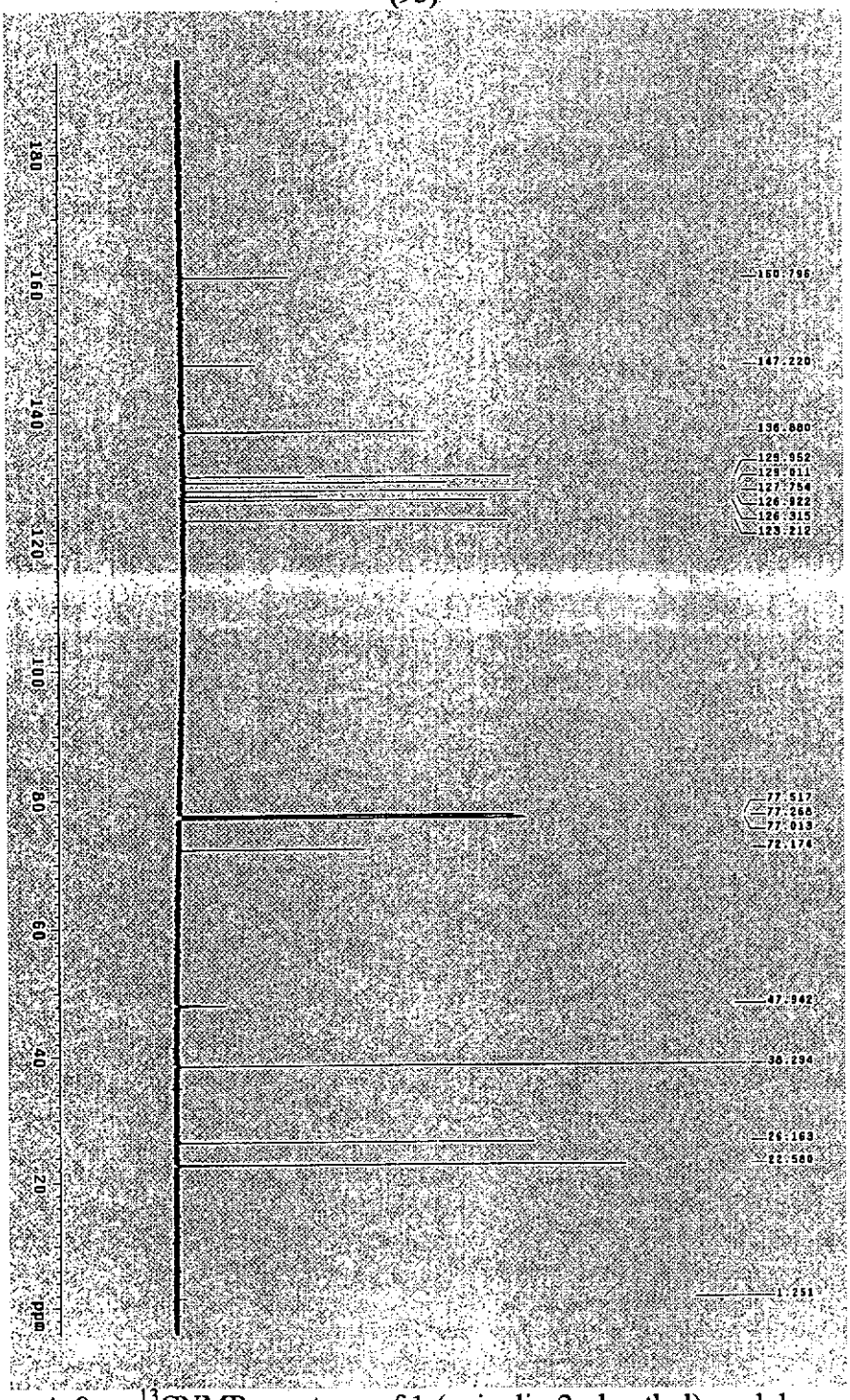
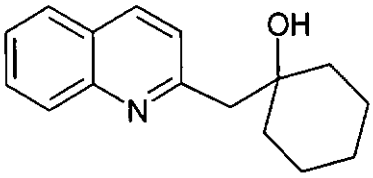


Figure A-8 ^{13}CNMR spectrum of 1-(quinolin-2-ylmethyl)-cyclohexanol **(93)**



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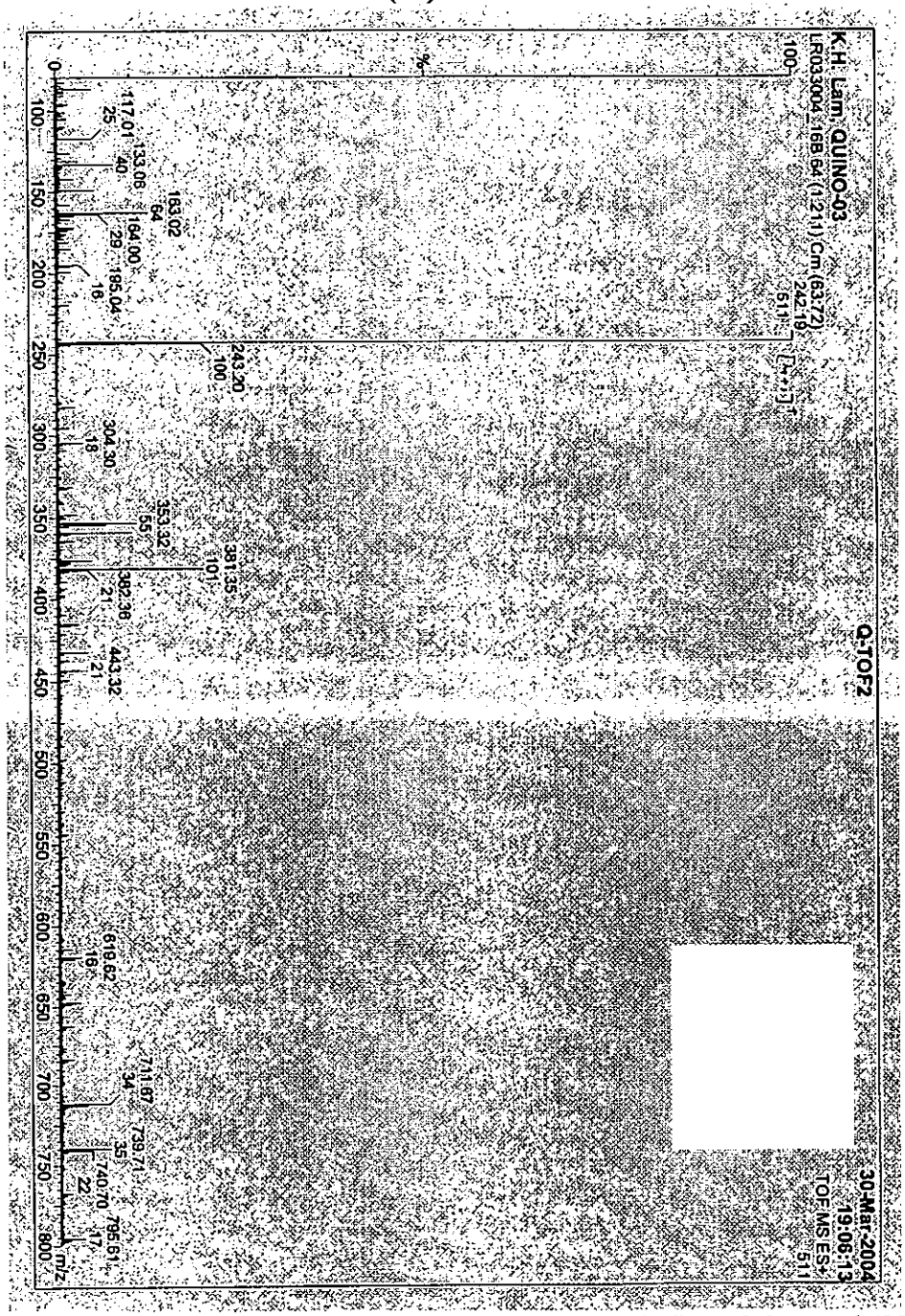
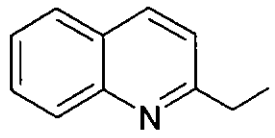


Figure A-9 ESI-MS spectrum of 1-(quinolin-2-ylmethyl)-cyclohexanol **(93)**



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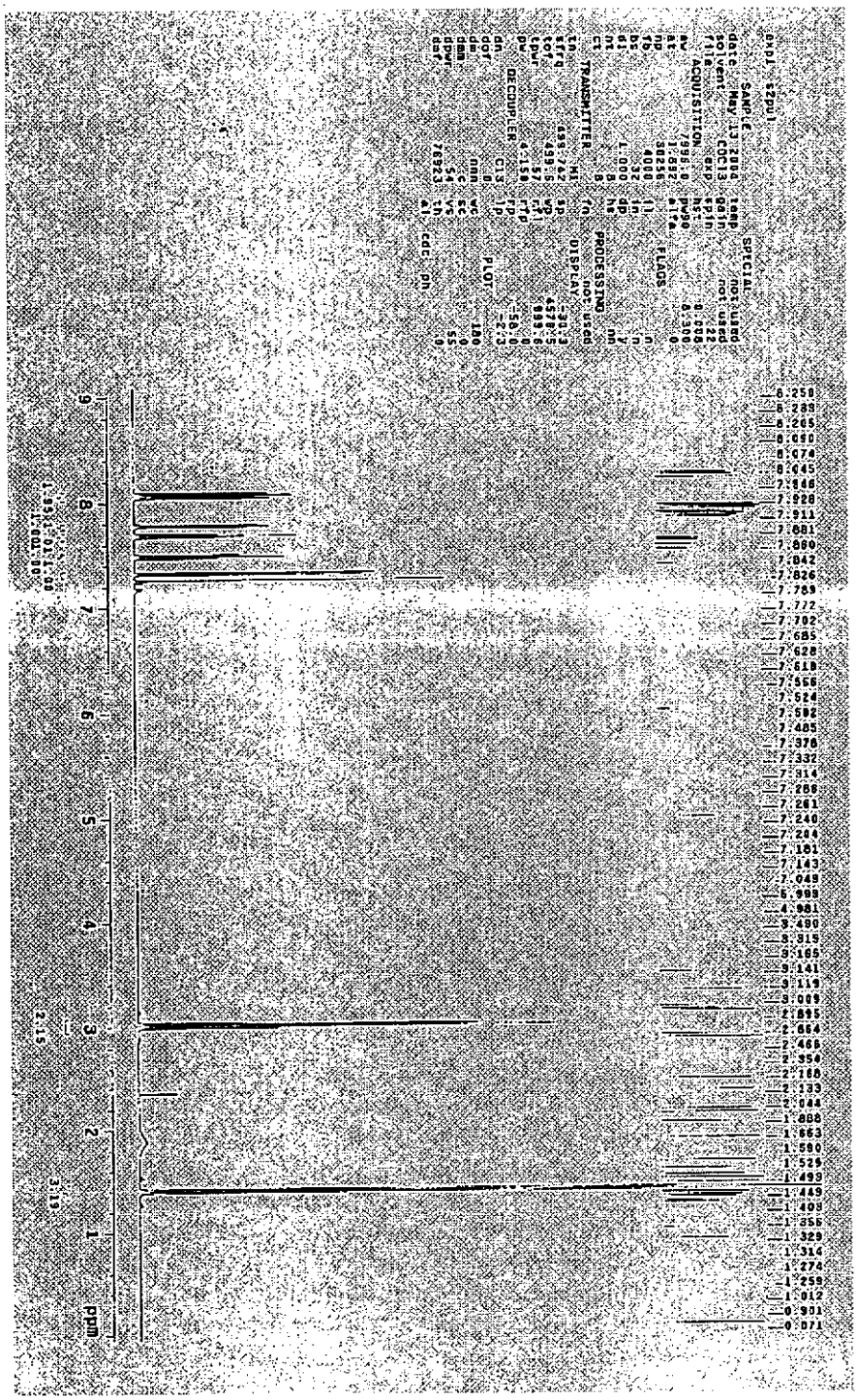
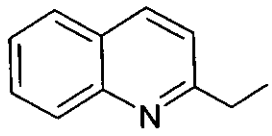


Figure A-10 ^{1}HNMR spectrum of 2-ethyl-quinoline (**94**)



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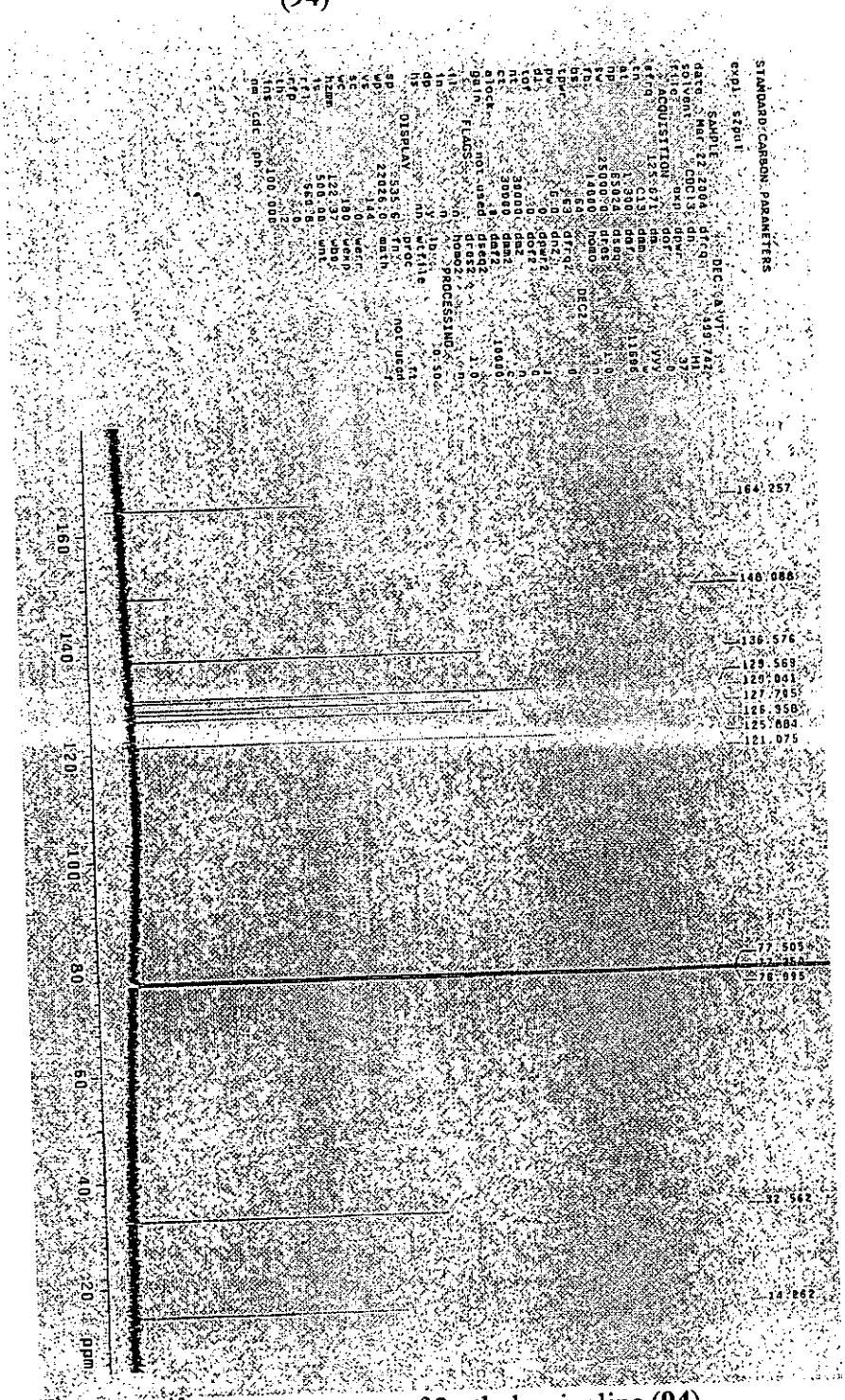
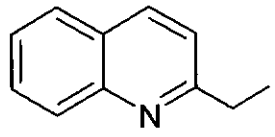


Figure A-11 ^{13}CNMR spectrum of 2-ethyl-quinoline **(94)**



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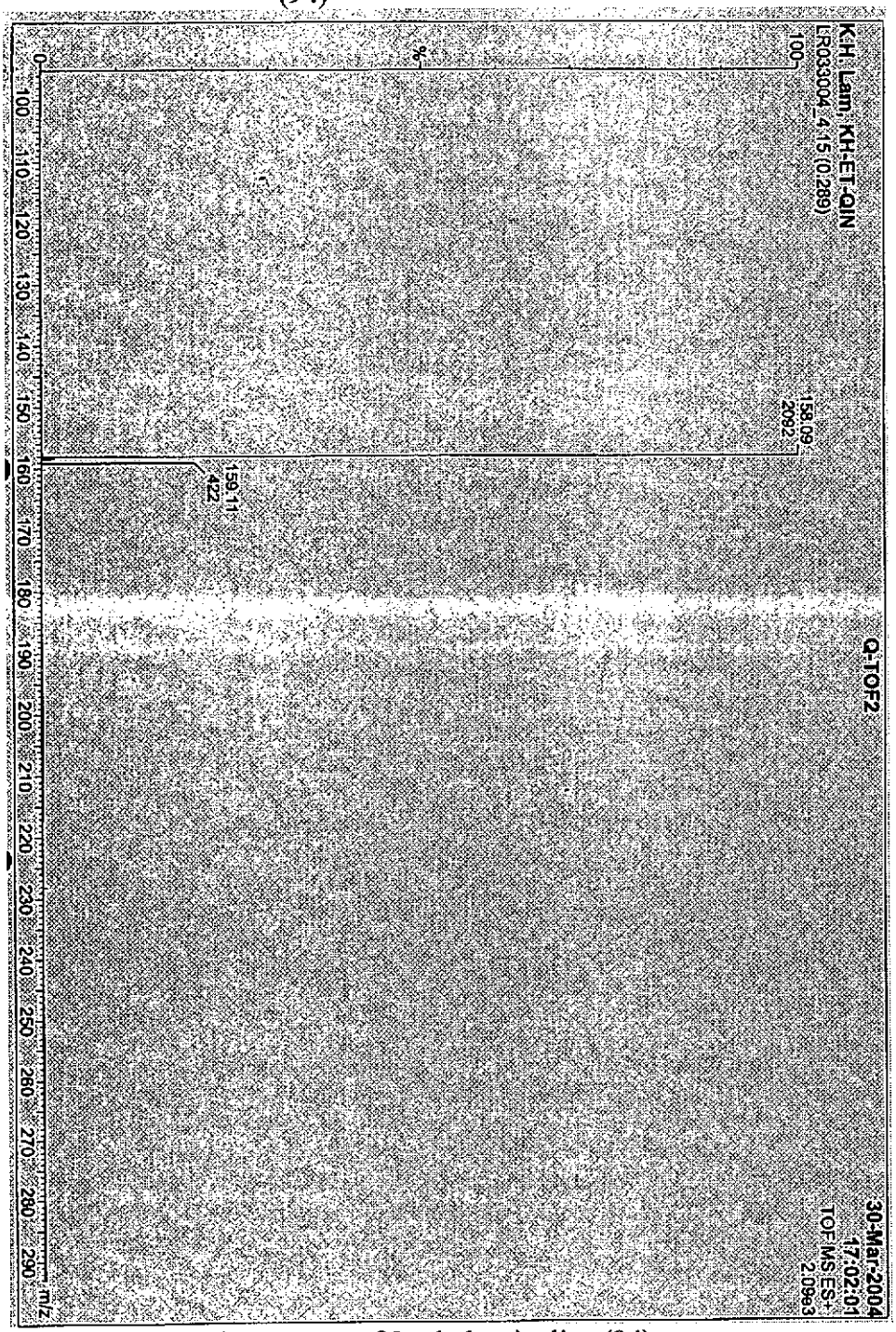
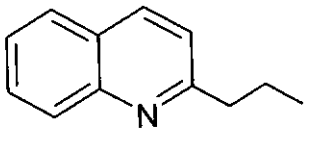


Figure A-12 ESI-MS spectrum of 2-ethyl-quinoline (**94**)



(95)

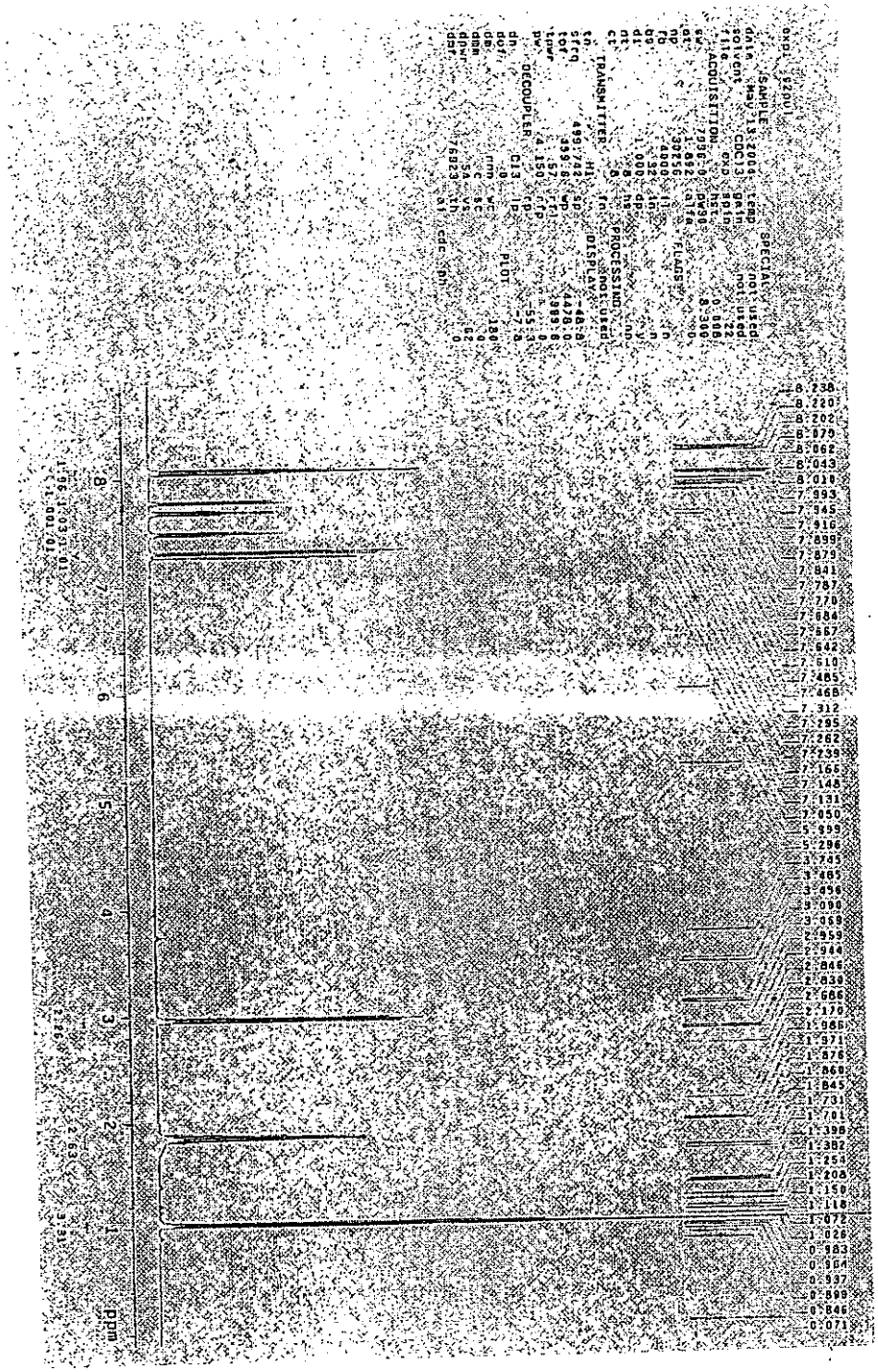
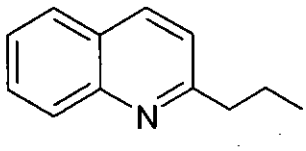


Figure A-13 ^{1}HNMR spectrum of 2-propyl-quinoline **(95)**



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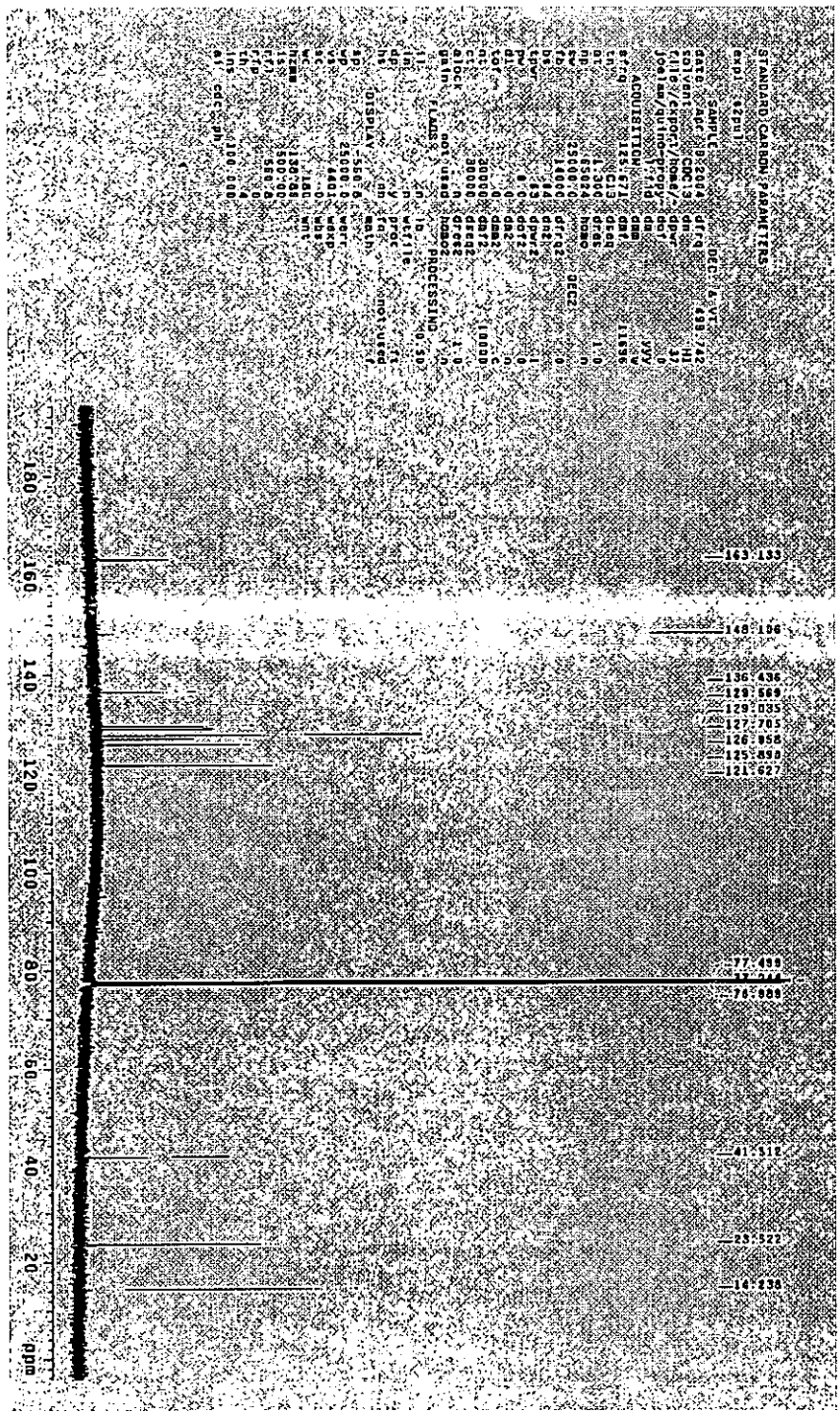
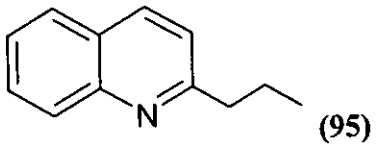


Figure A-14 ^{13}CNMR spectrum of 2-propyl-quinoline **(95)**



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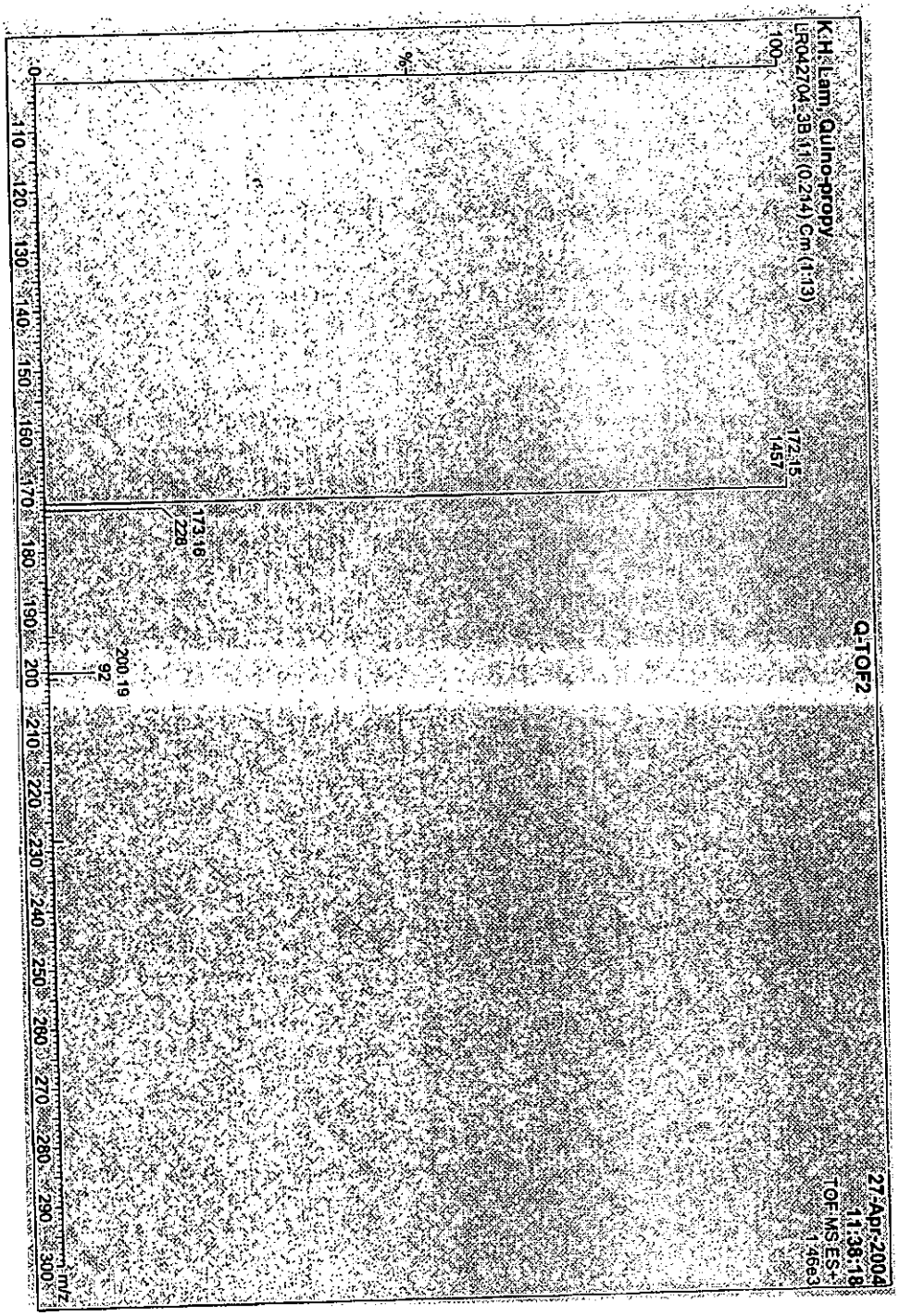
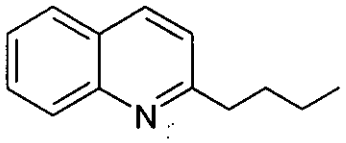


Figure A-15 ESI-MS spectrum of 2-propyl-quinoline **(95)**



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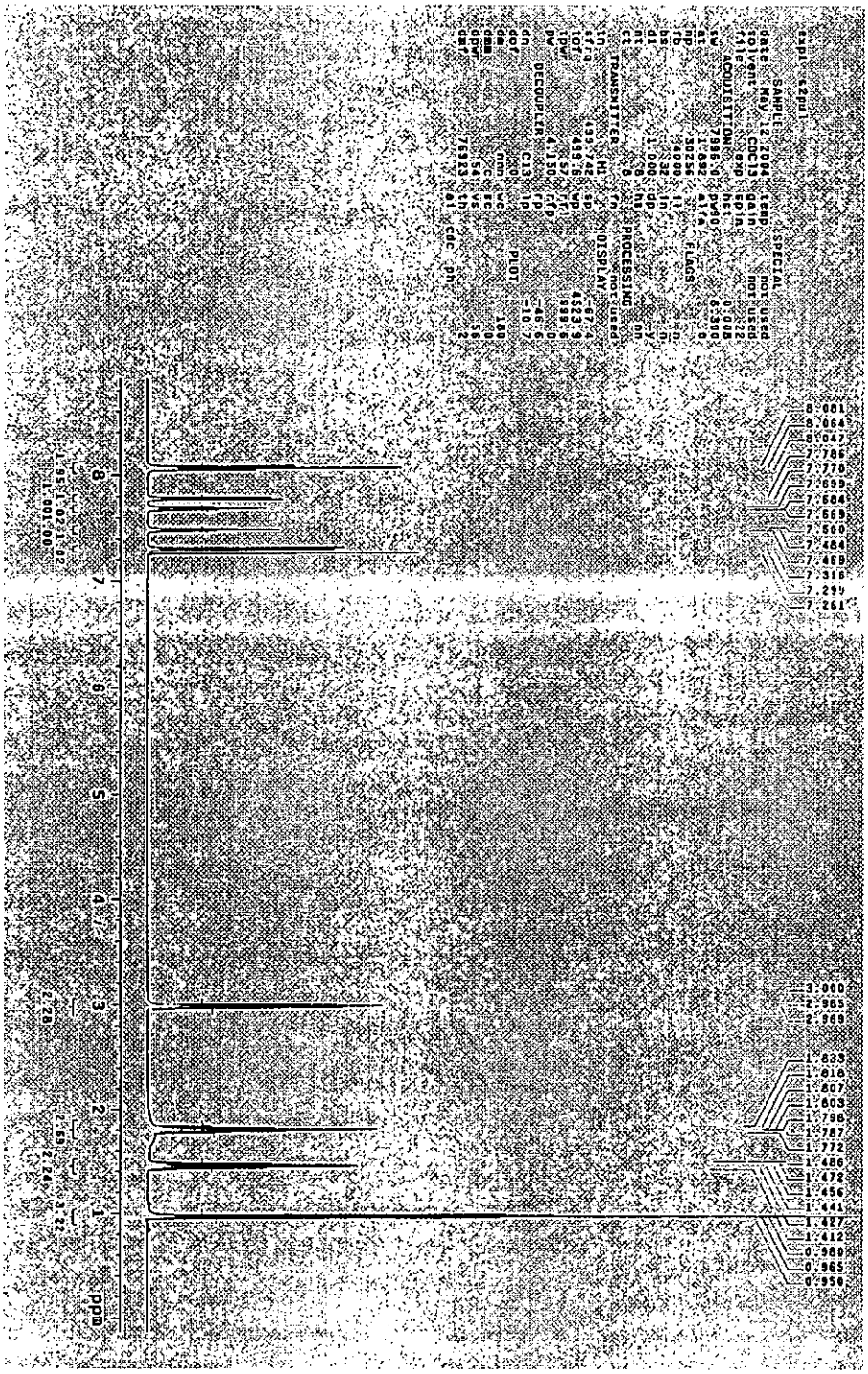
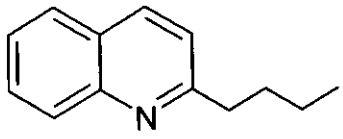


Figure A-16 ^{1}HNMR spectrum of 2-butyl-quinoline **(96)**



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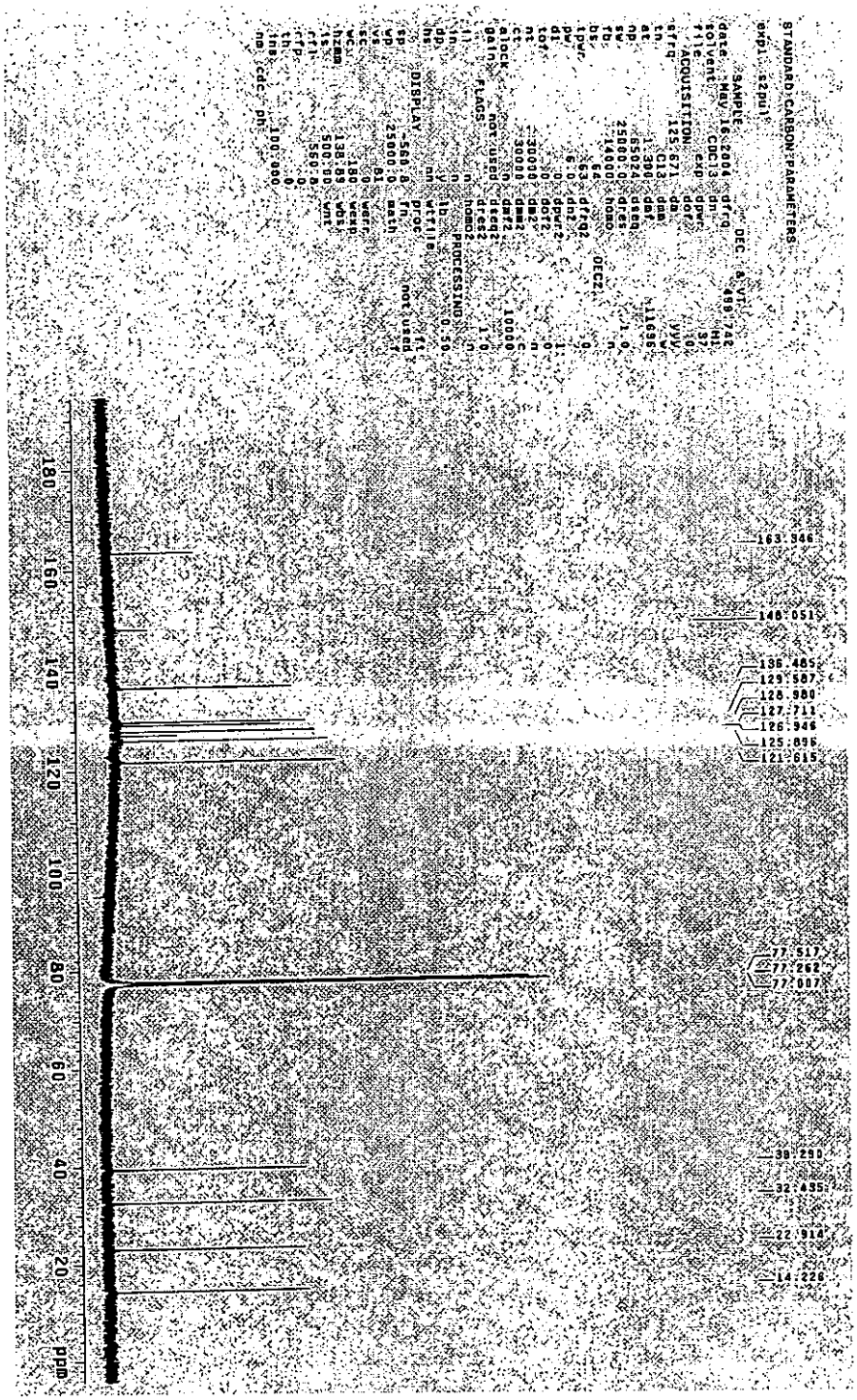
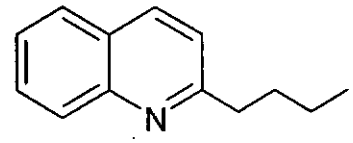


Figure A-17 ^{13}CNMR spectrum of 2-butyl-quinoline **(96)**



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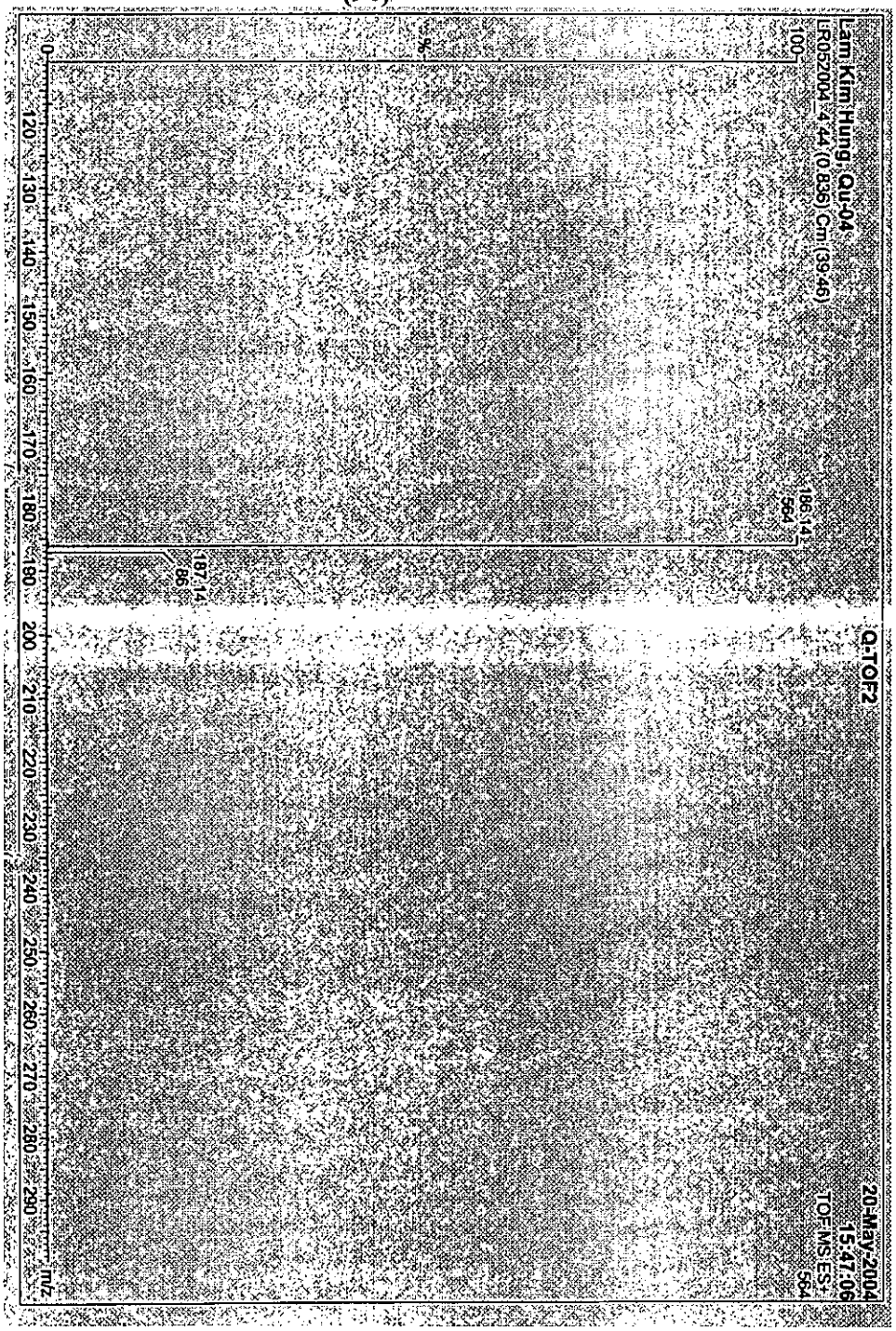
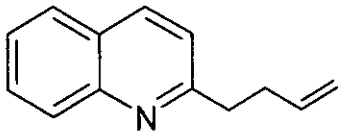


Figure A-18 ESI-MS spectrum of 2-butyl-quinoline **(96)**



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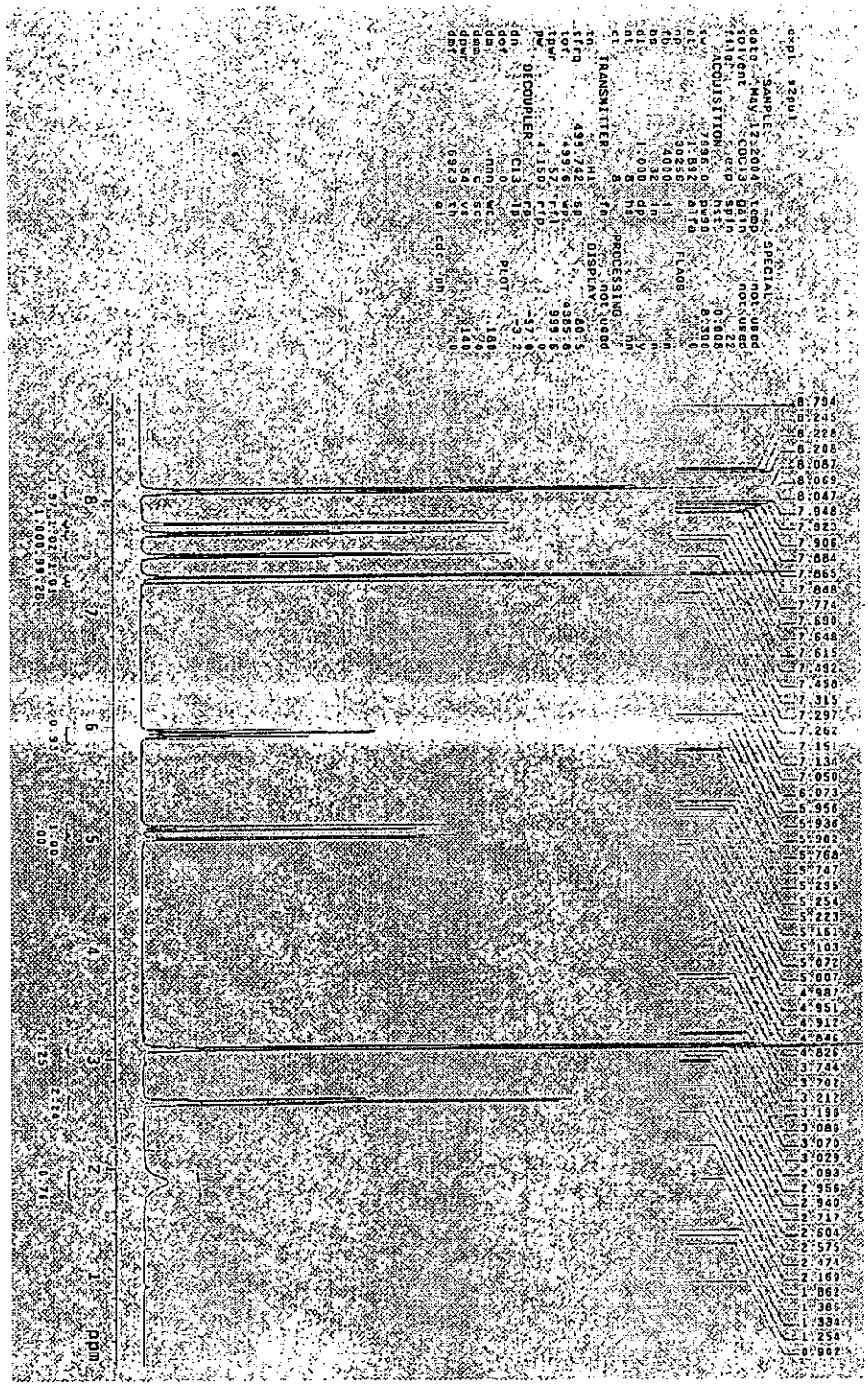
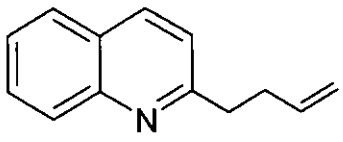


Figure A-19. ^{1}HNMR spectrum of 2-(3-butenyl)-quinoline (97)



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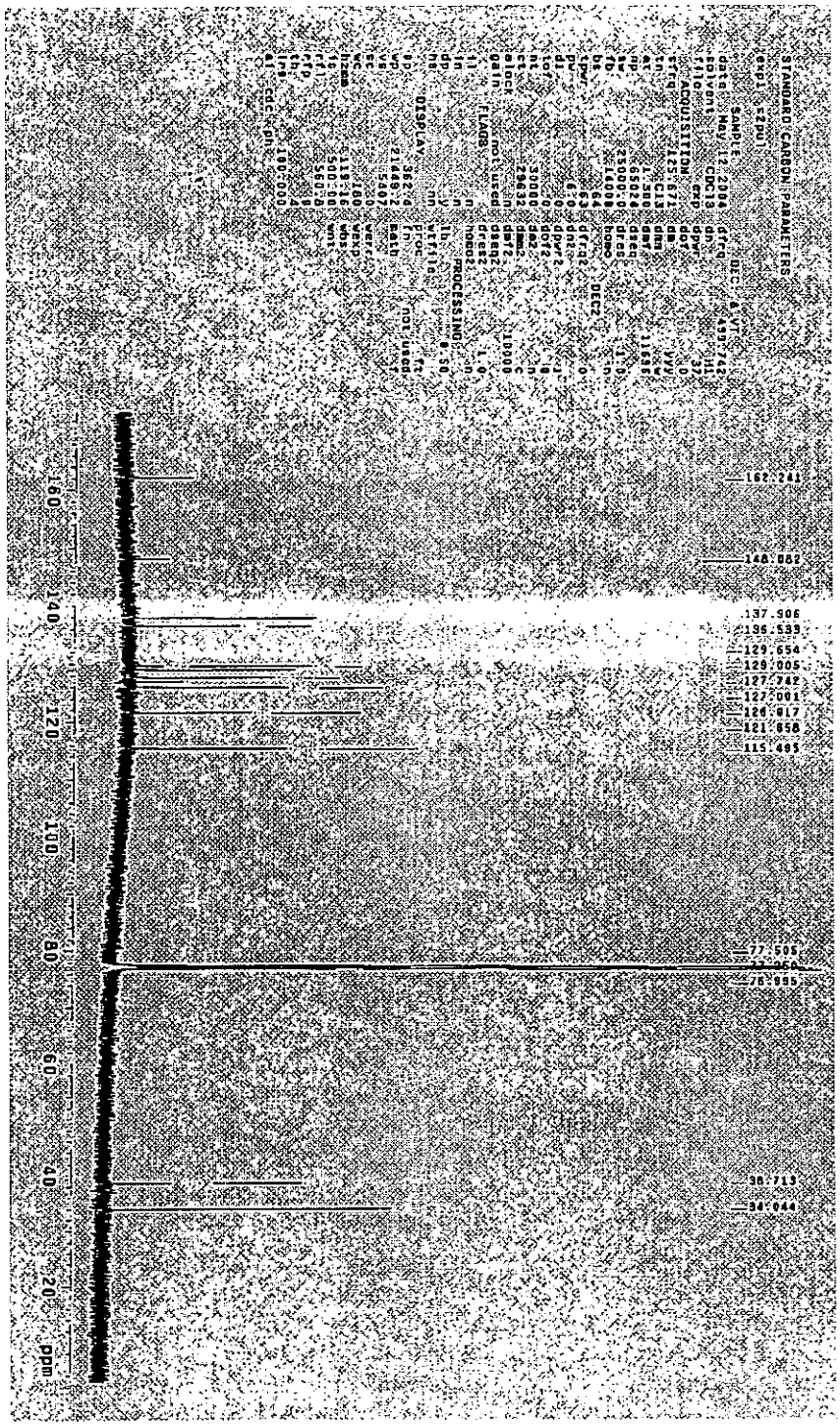
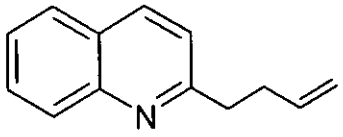


Figure A-20 ^{13}CNMR spectrum of 2-(3-butenyl)-quinoline **(97)**



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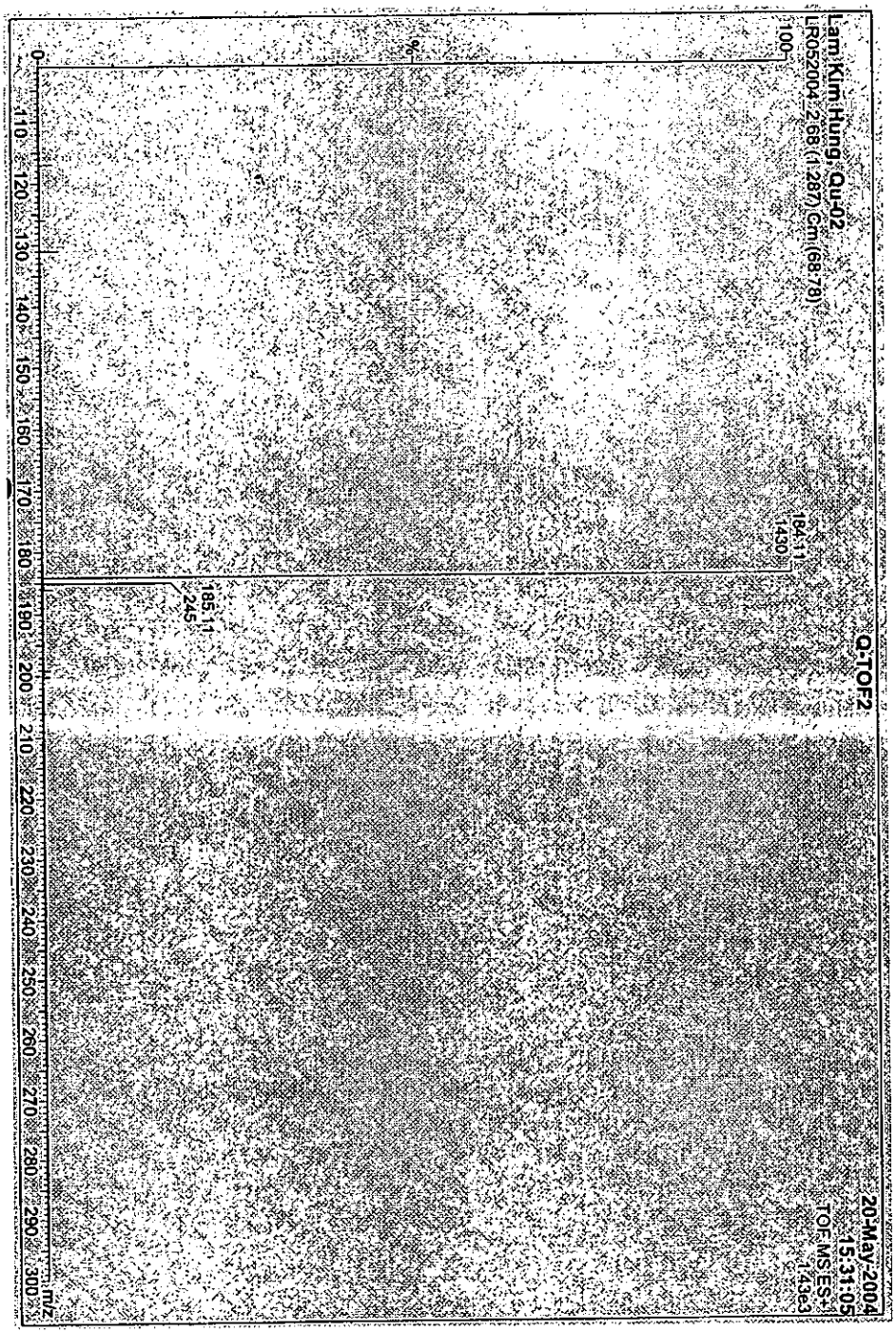
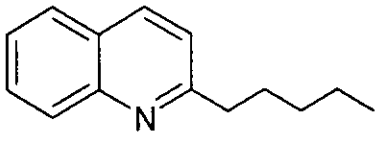


Figure A-21 ESI-MS spectrum of 2-(3-butenyl)-quinoline **(97)**



(98)

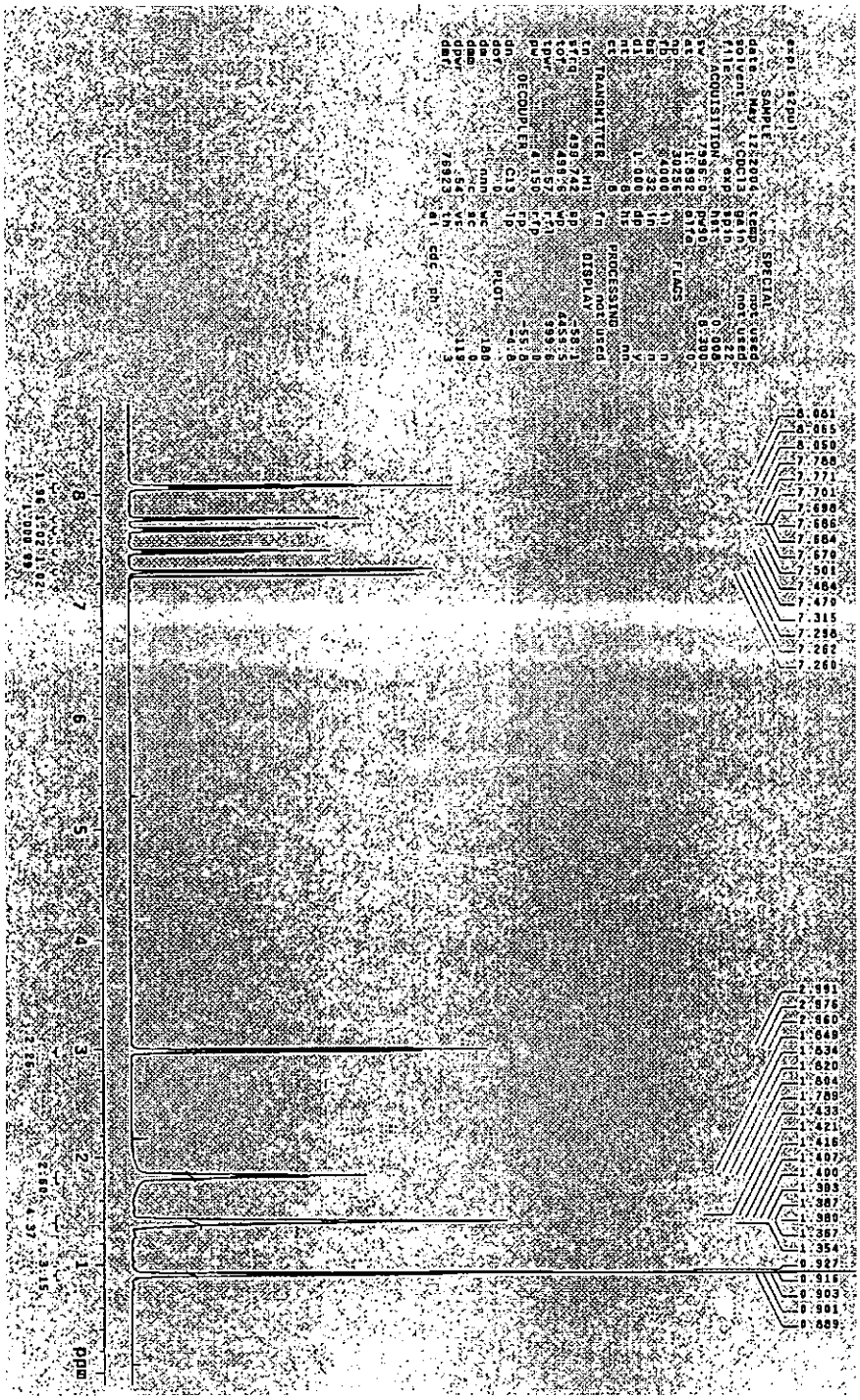
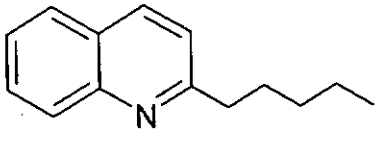


Figure A-22 ^{1}HNMR spectrum of 2-pentyl-quinoline **(98)**



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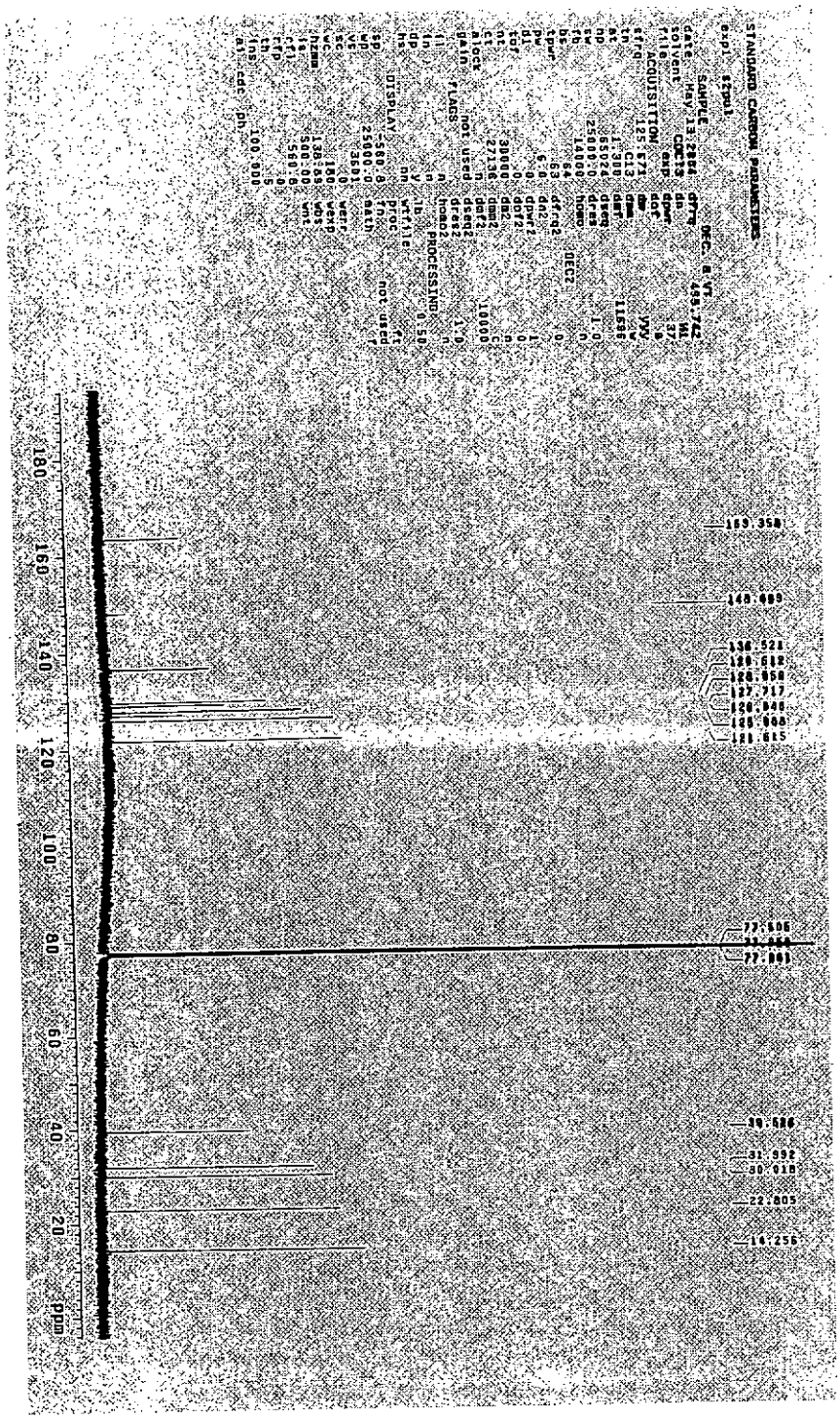
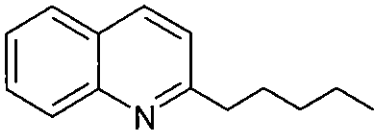


Figure A-23 ^{13}CNMR spectrum of 2-pentyl-quinoline **(98)**



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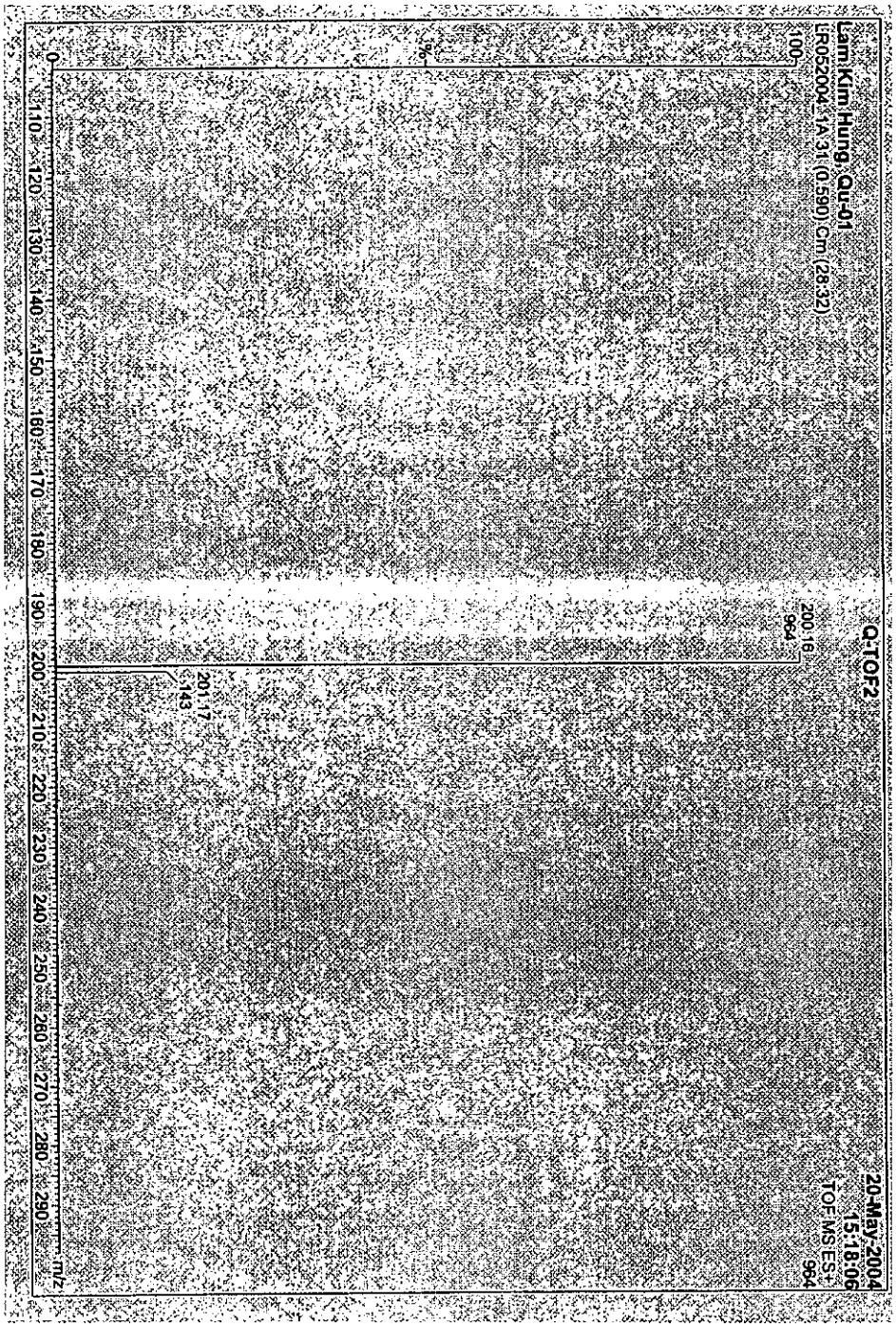
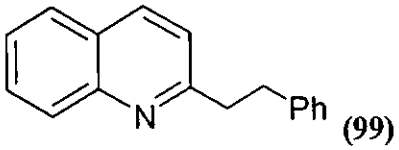


Figure A-24 ESI-MS spectrum of 2-pentyl-quinoline **(98)**



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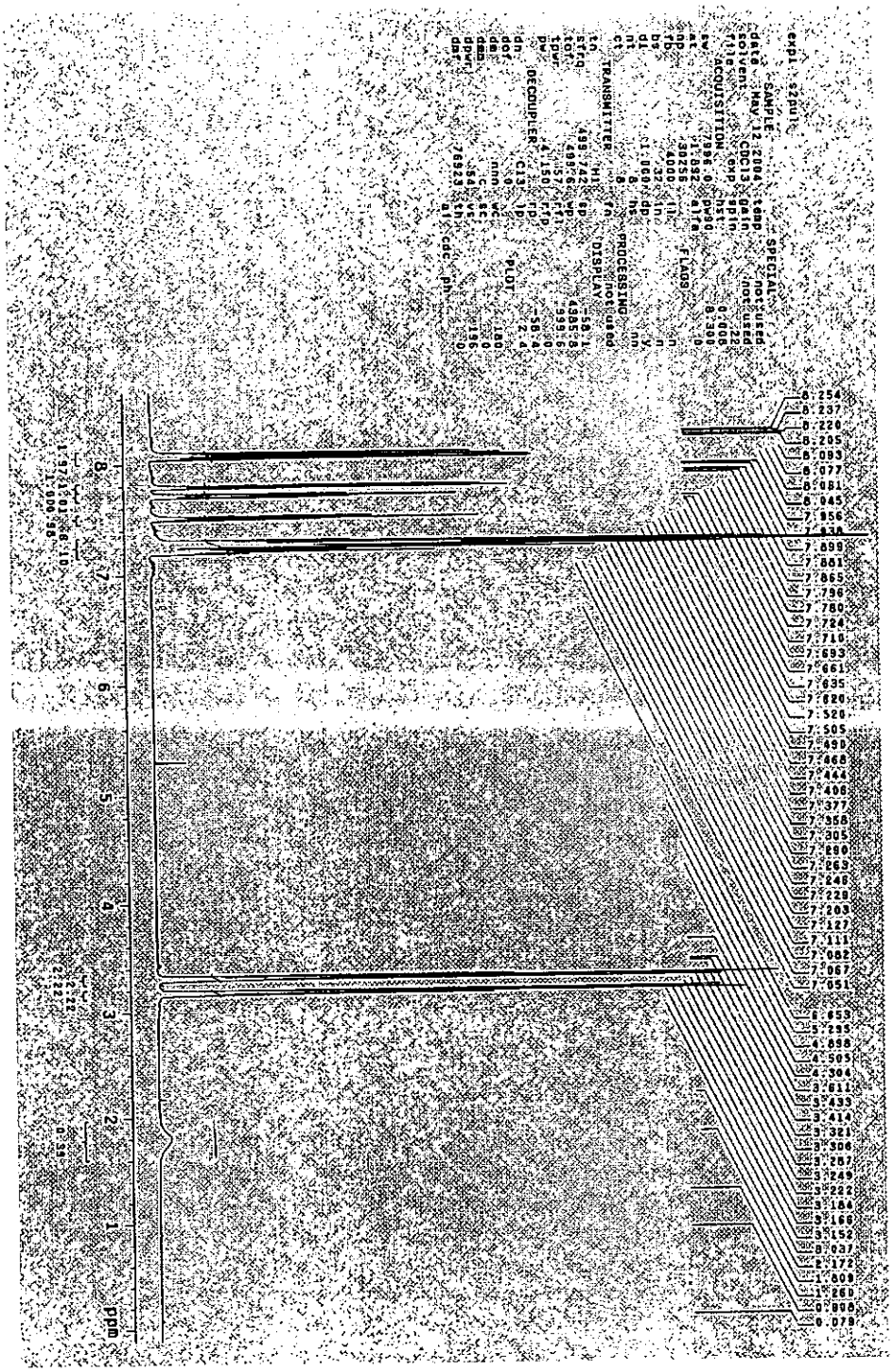
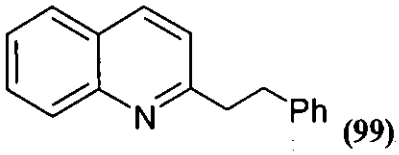


Figure A-25 ^{1}HNMR spectrum of 2-phenethyl-quinoline **(99)**



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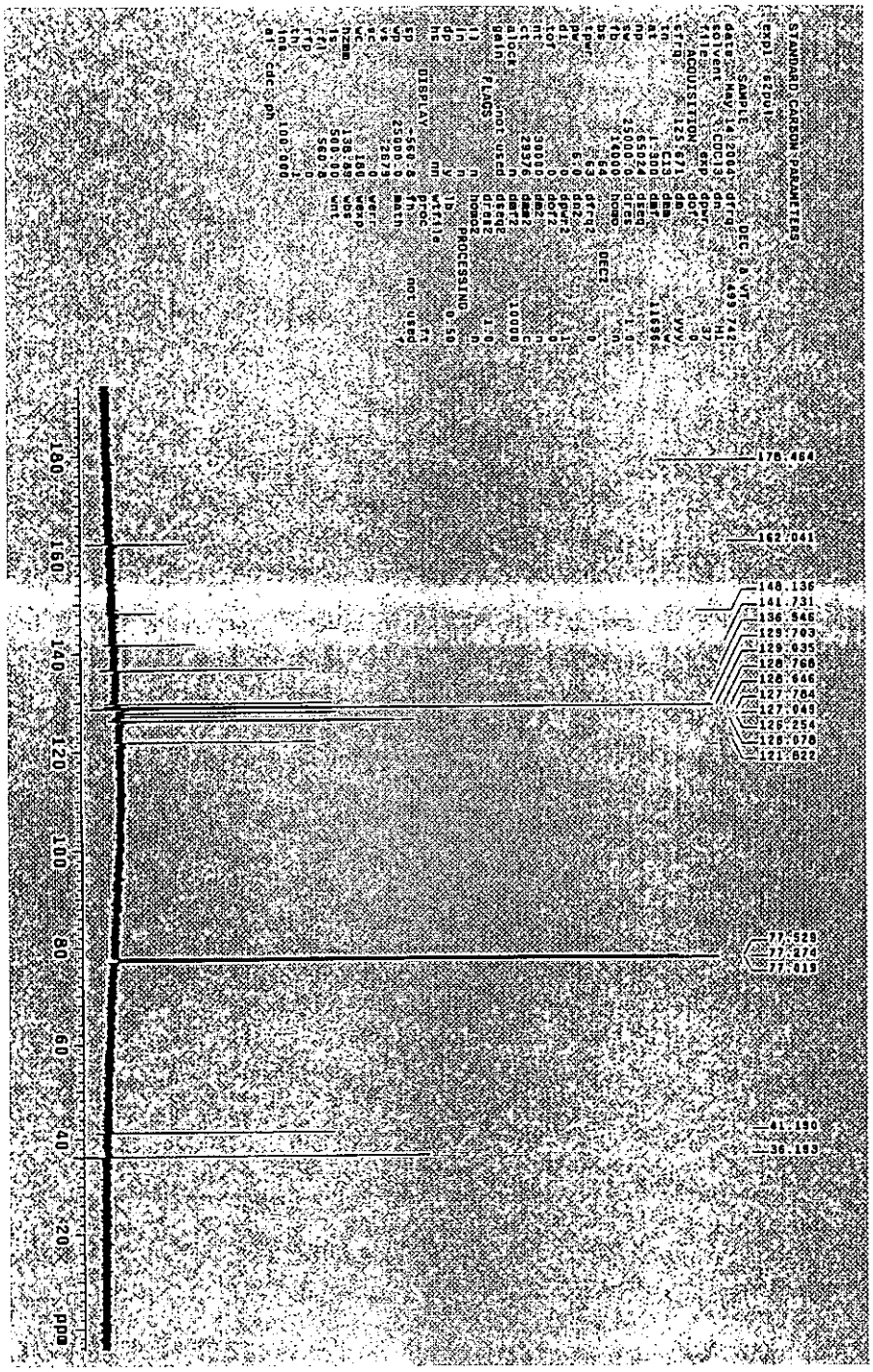


Figure A-26 ^{13}CNMR spectrum of 2-phenethyl-quinoline **(99)**

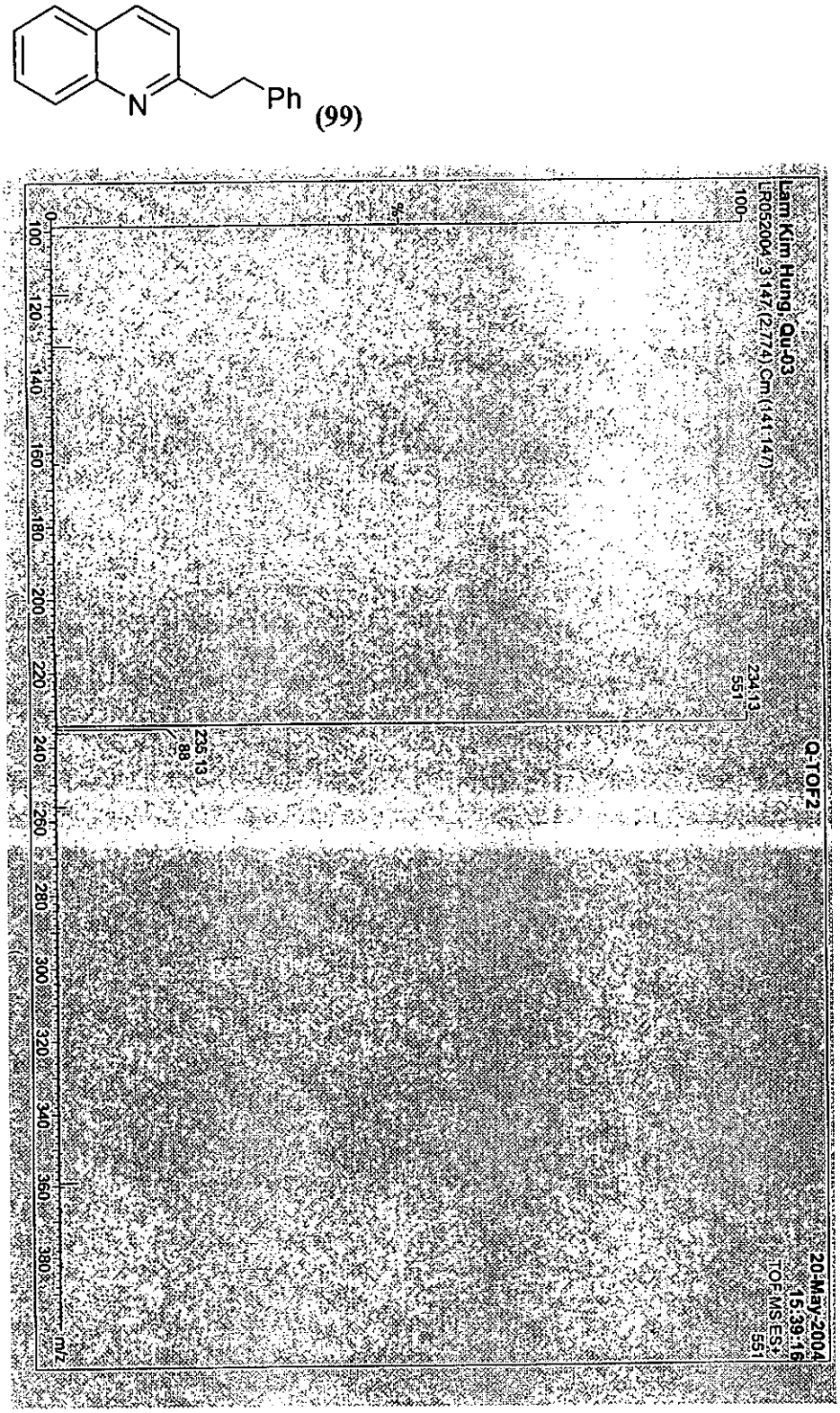
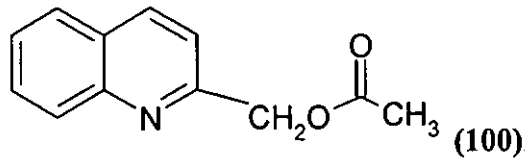


Figure A-27 ESI-MS spectrum of 2-phenethyl-quinoline **(99)**



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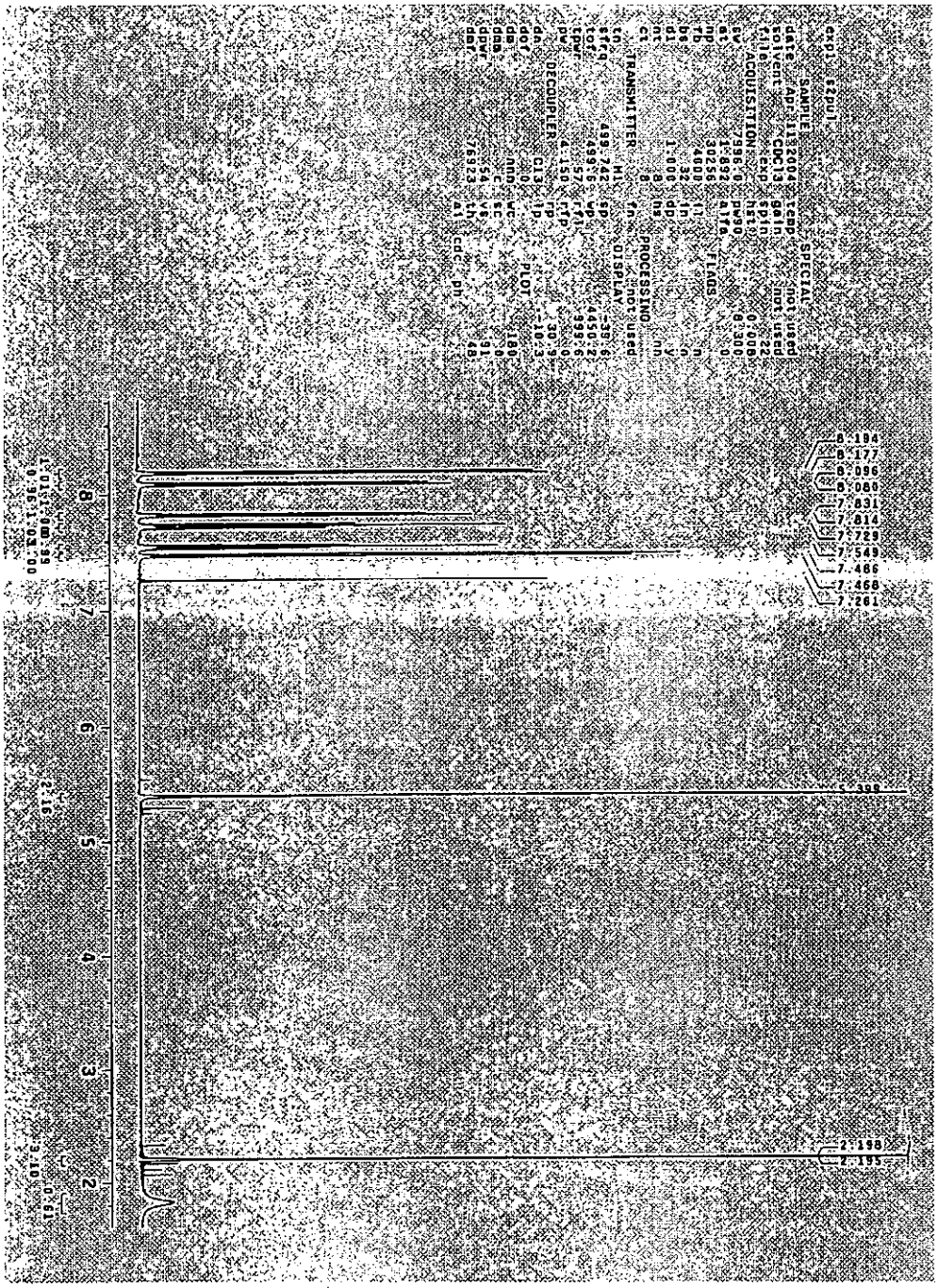


Figure A-28 ^{1}HNMR spectrum of acetic acid quinolin-2-ylmethyl ether **(100)**

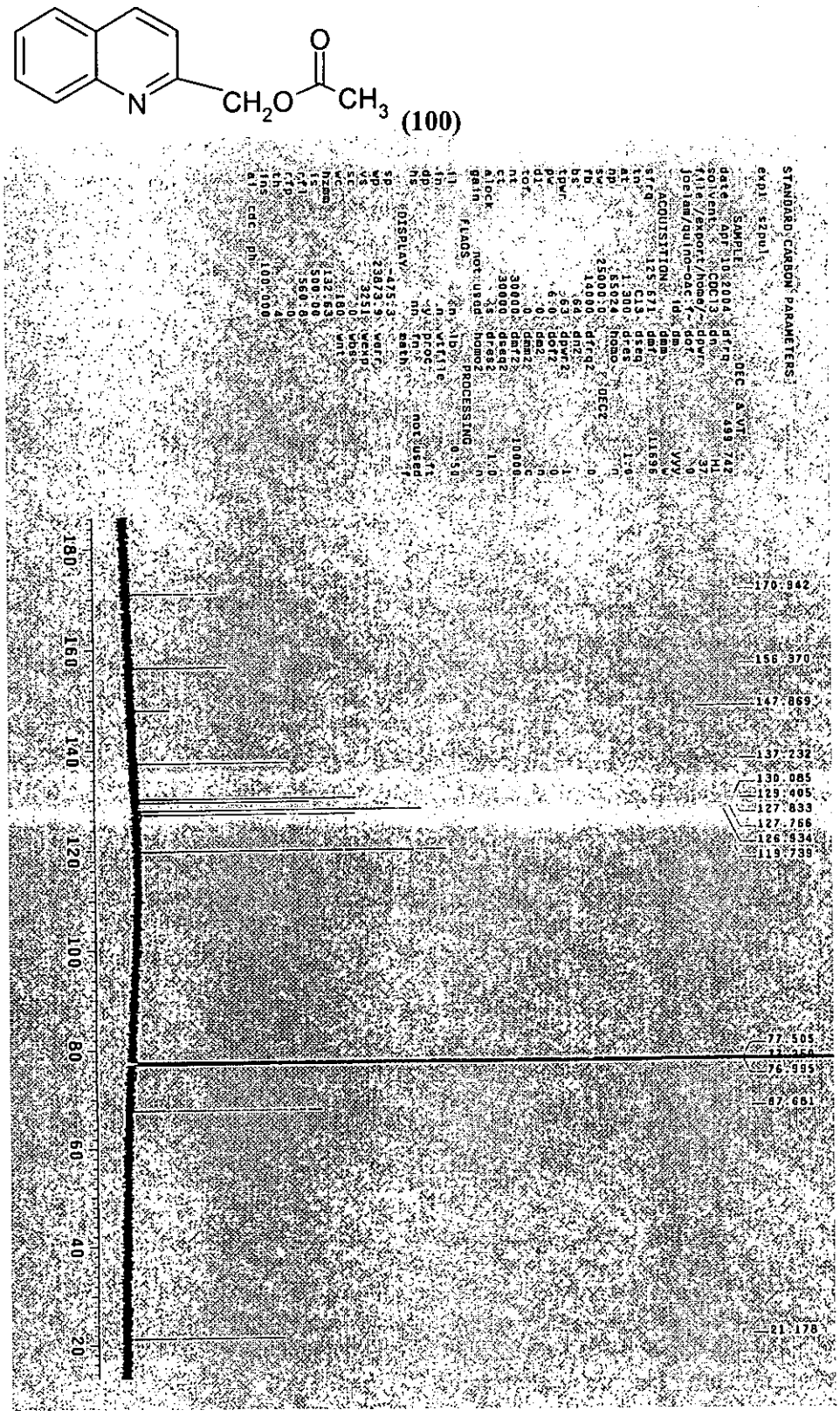
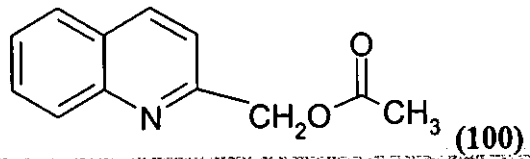


Figure A-29 ^{13}CNMR spectrum of acetic acid quinolin-2-ylmethyl ether **(100)**



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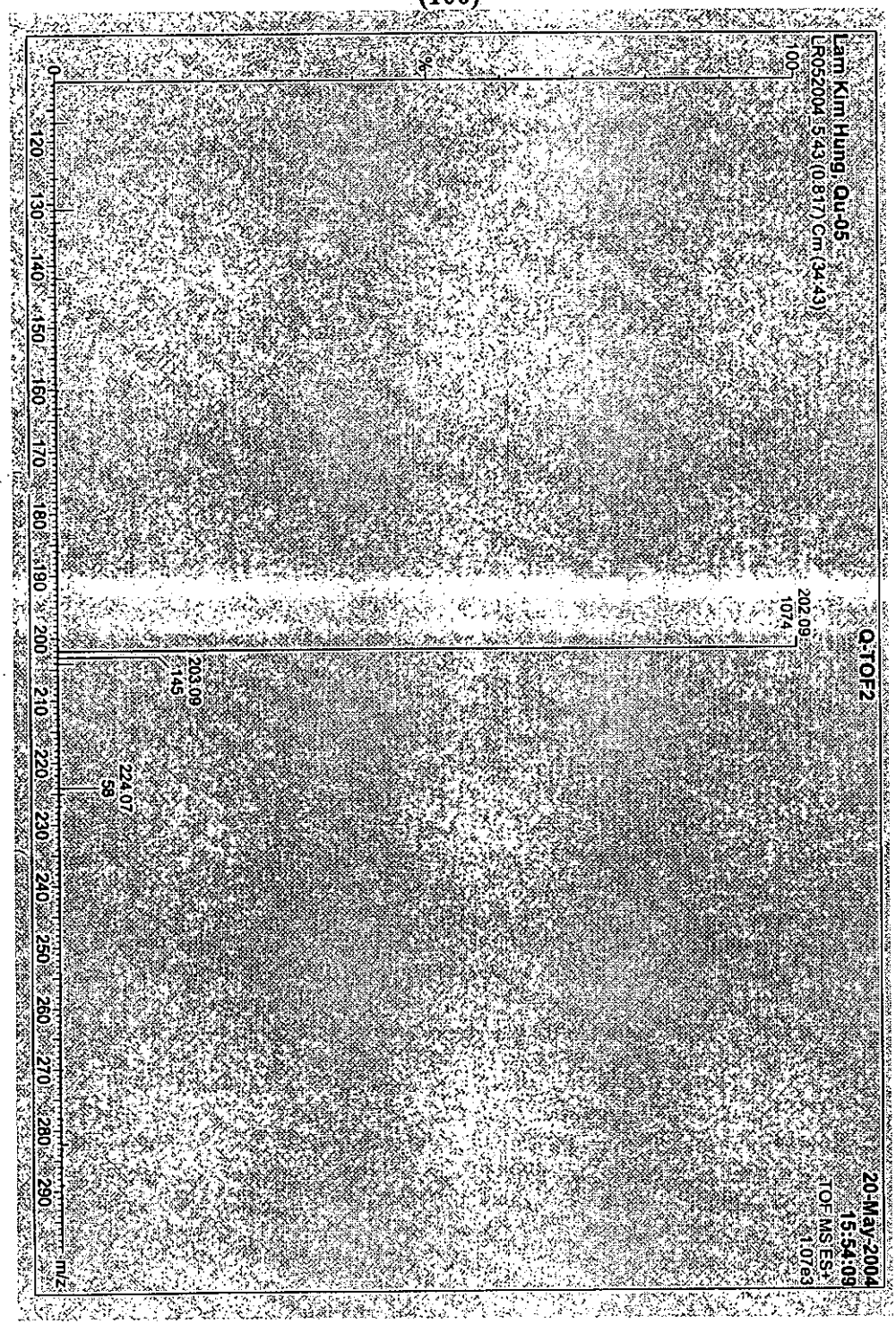


Figure A-30 ESI-MS spectrum of acetic acid quinolin-2-ylmethyl ether **(100)**

BMIM·Cl

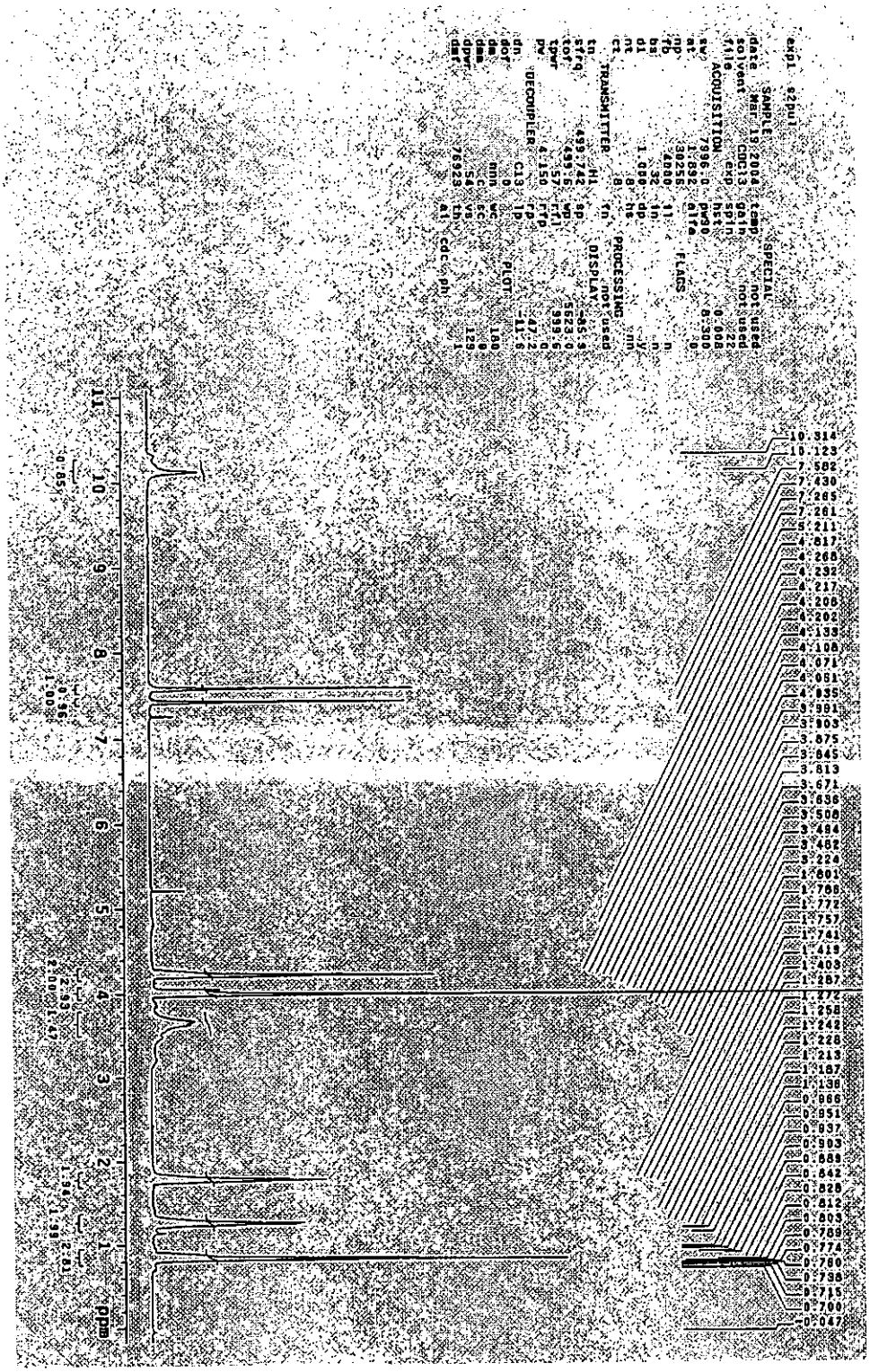


Figure A-31 ^{1}HNMR spectrum of BMIM·Cl

BMIM·Cl

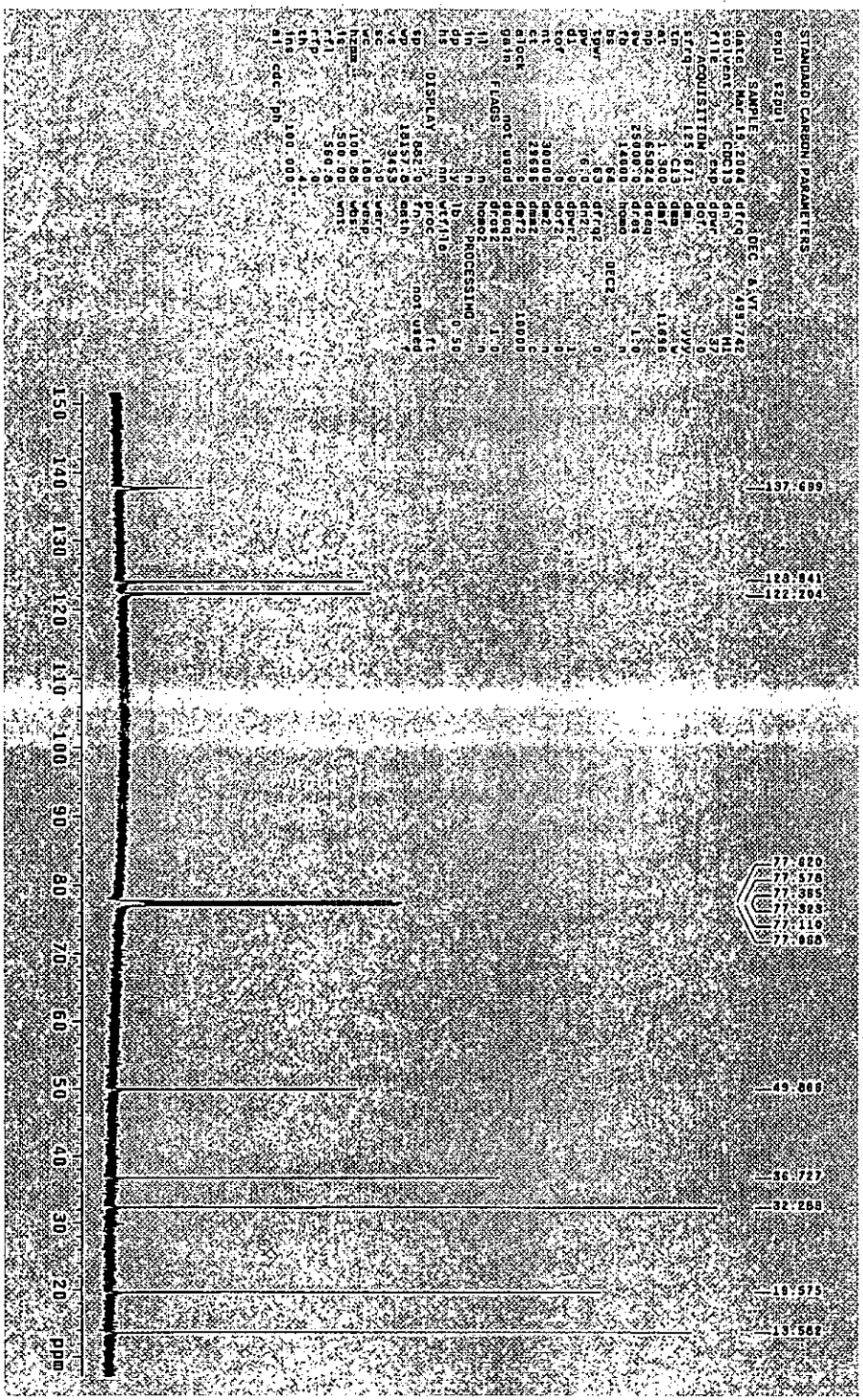


Figure A-32 ^{13}CNMR spectrum of BMIM·Cl

BMIM·Cl

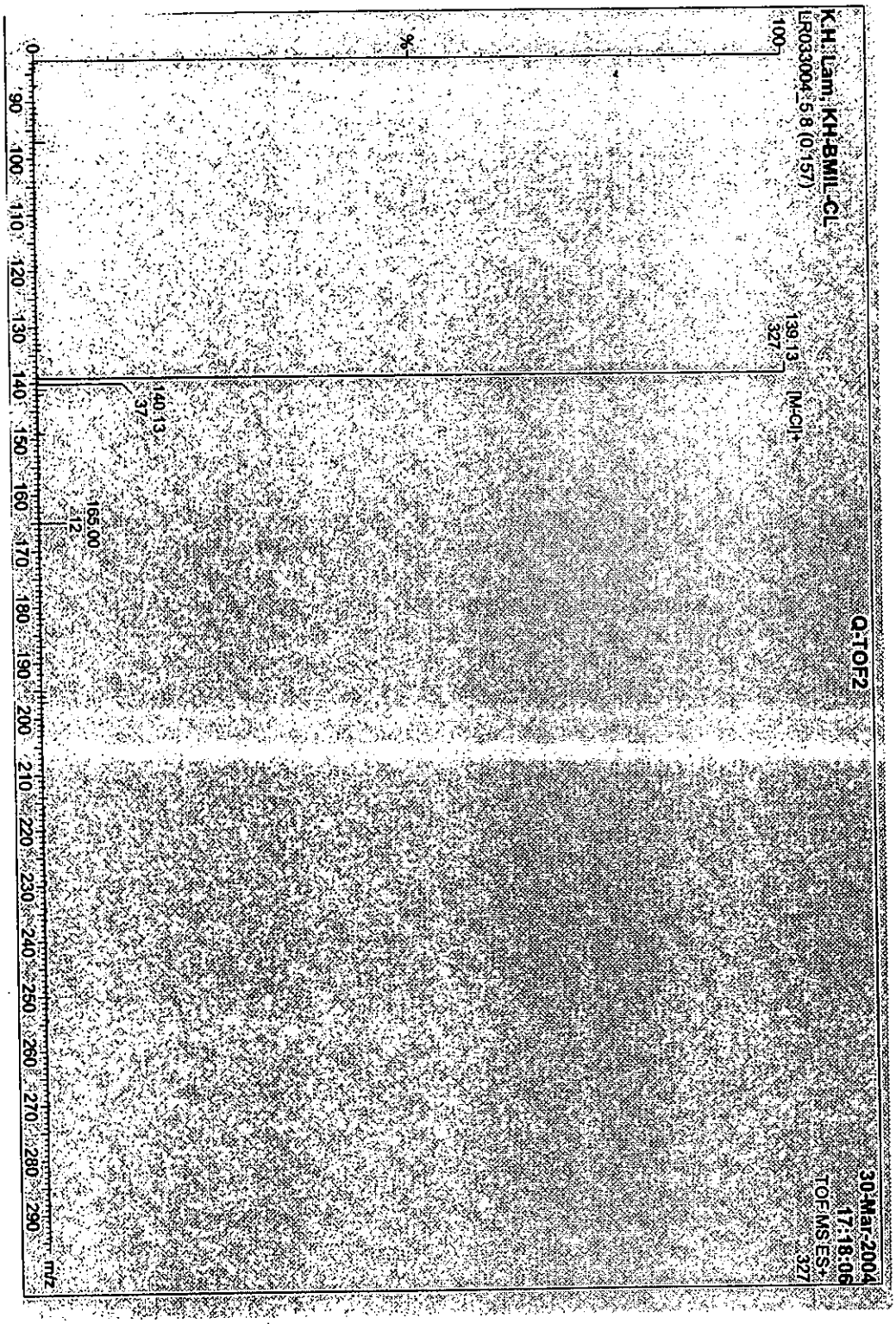


Figure A-33 ESI-MS spectrum of BMIM·Cl

BMIM·BF_4

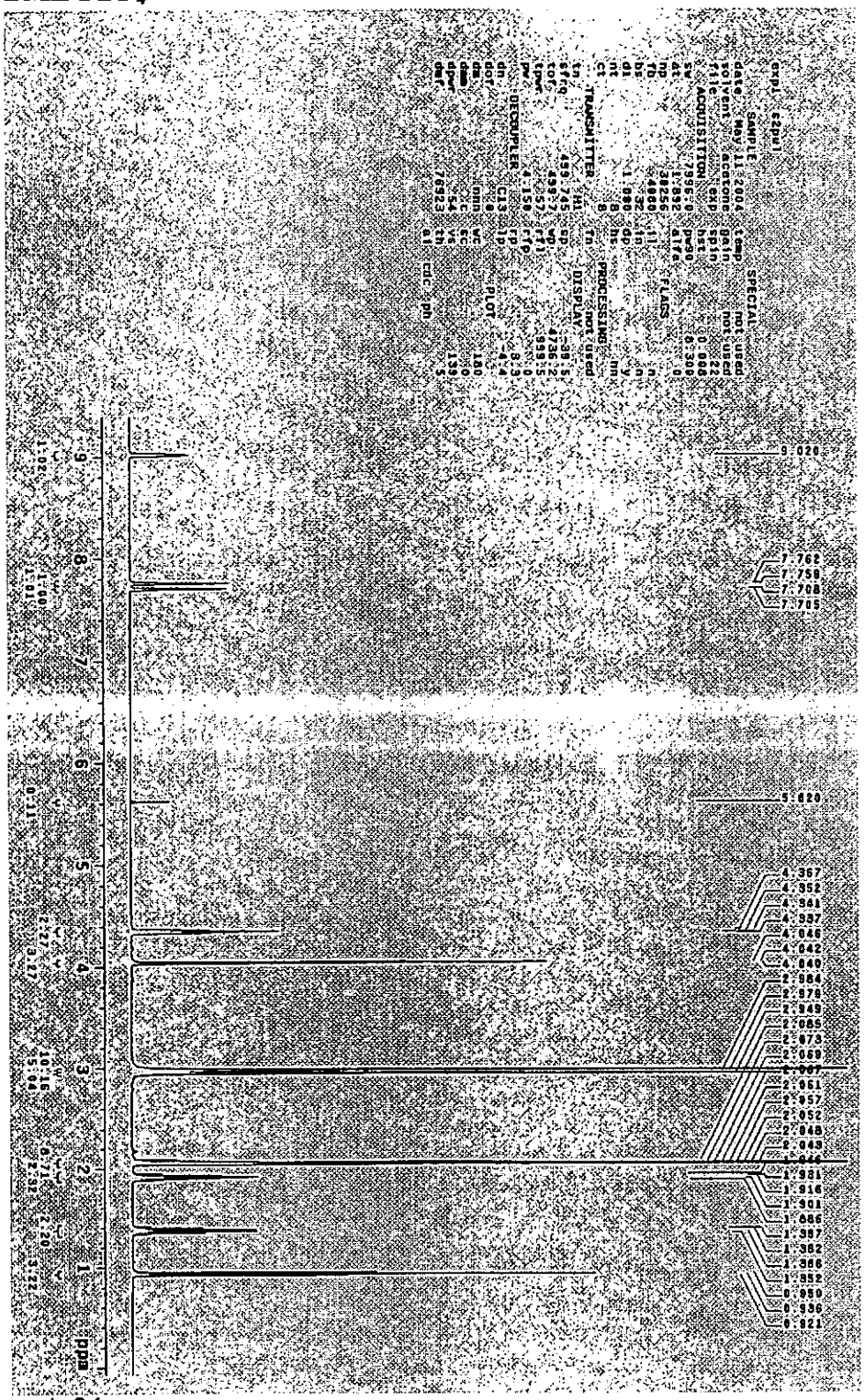


Figure A-34 ^{1}HNMR spectrum of BMIM·BF_4

BMIM·BF_4

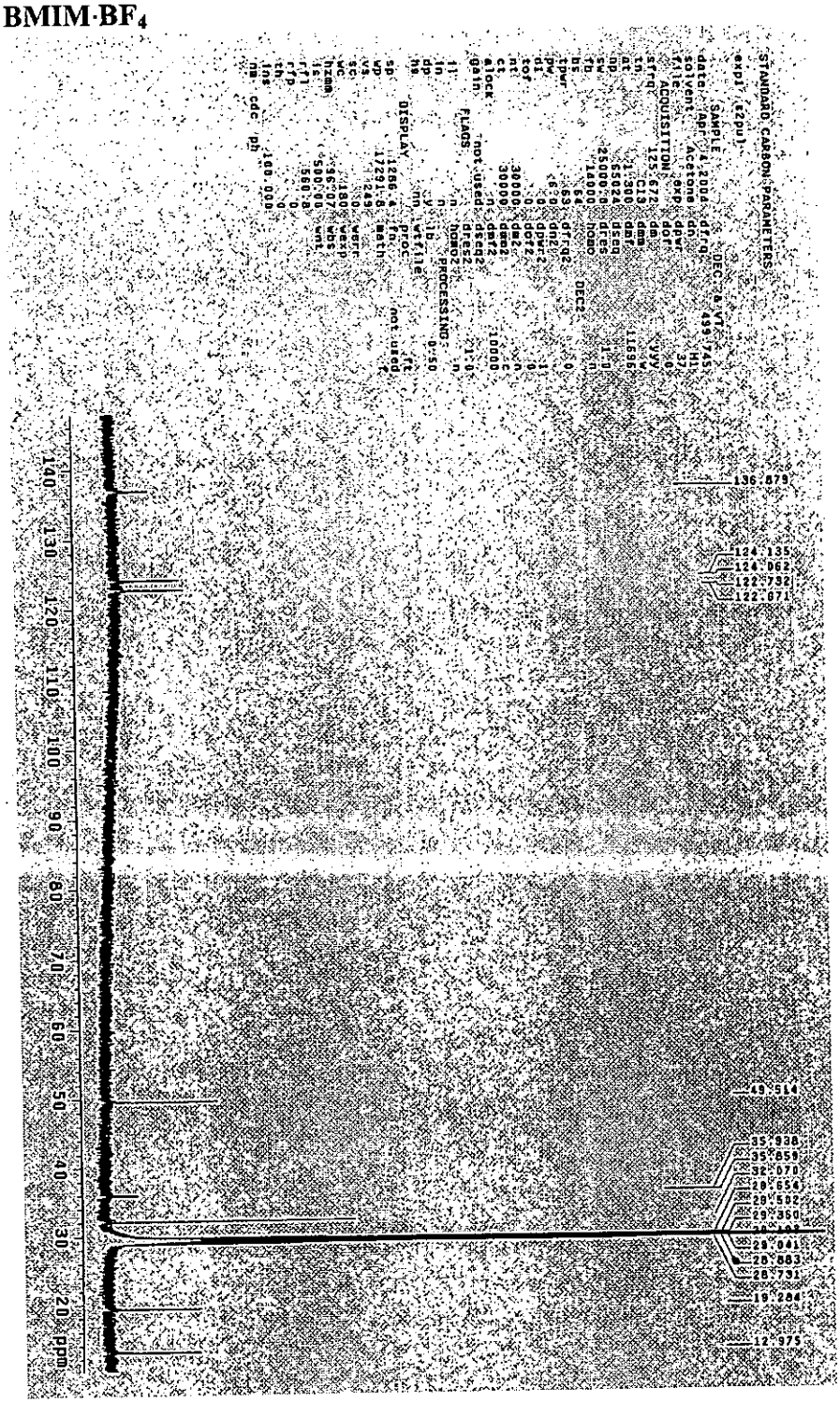


Figure A-35 ^{13}CNMR spectrum of BMIM·BF_4

BMIM·BF_4

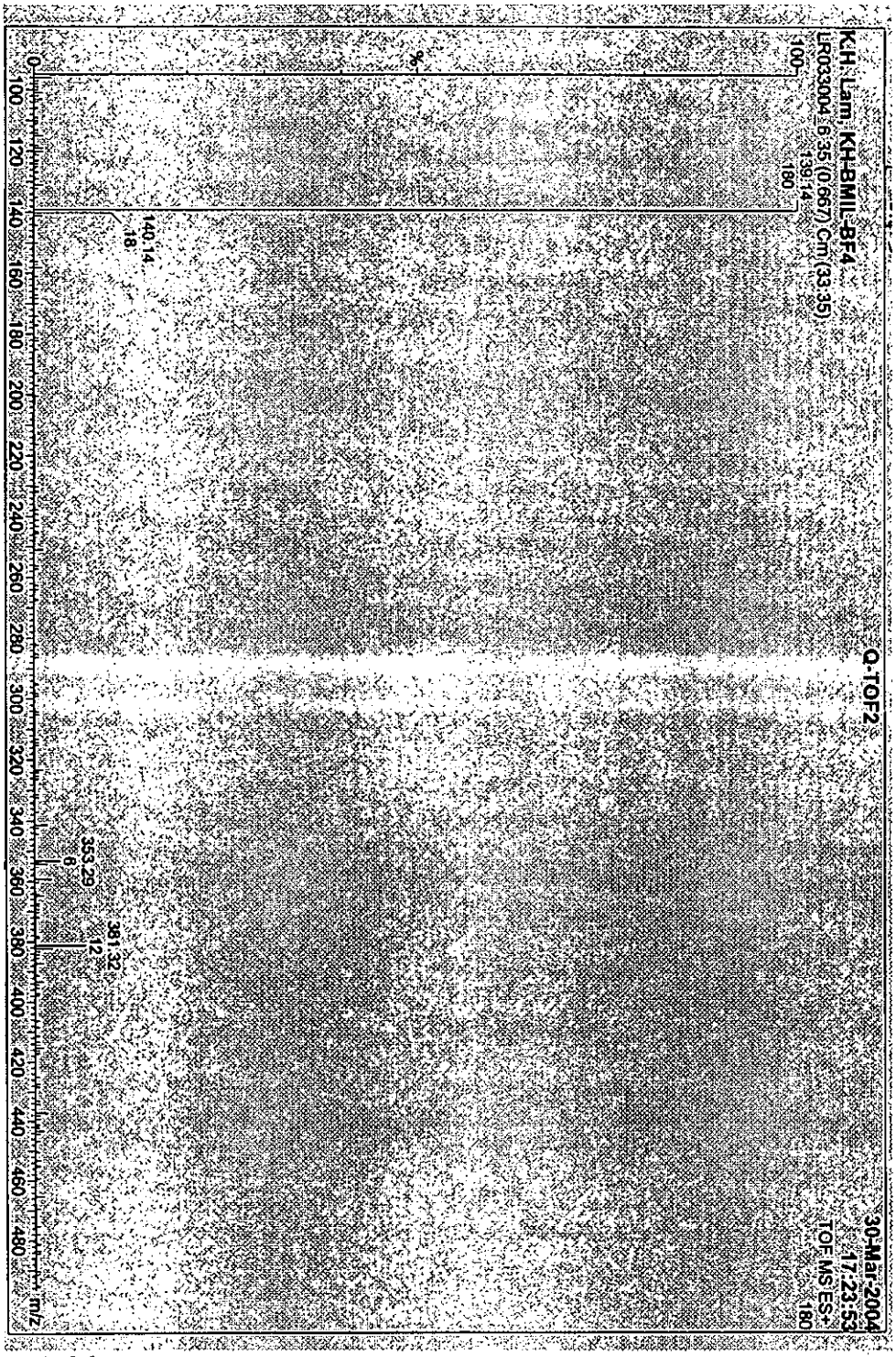


Figure A-36 ESI-MS spectrum of BMIM·BF_4

BMIM·PF_6

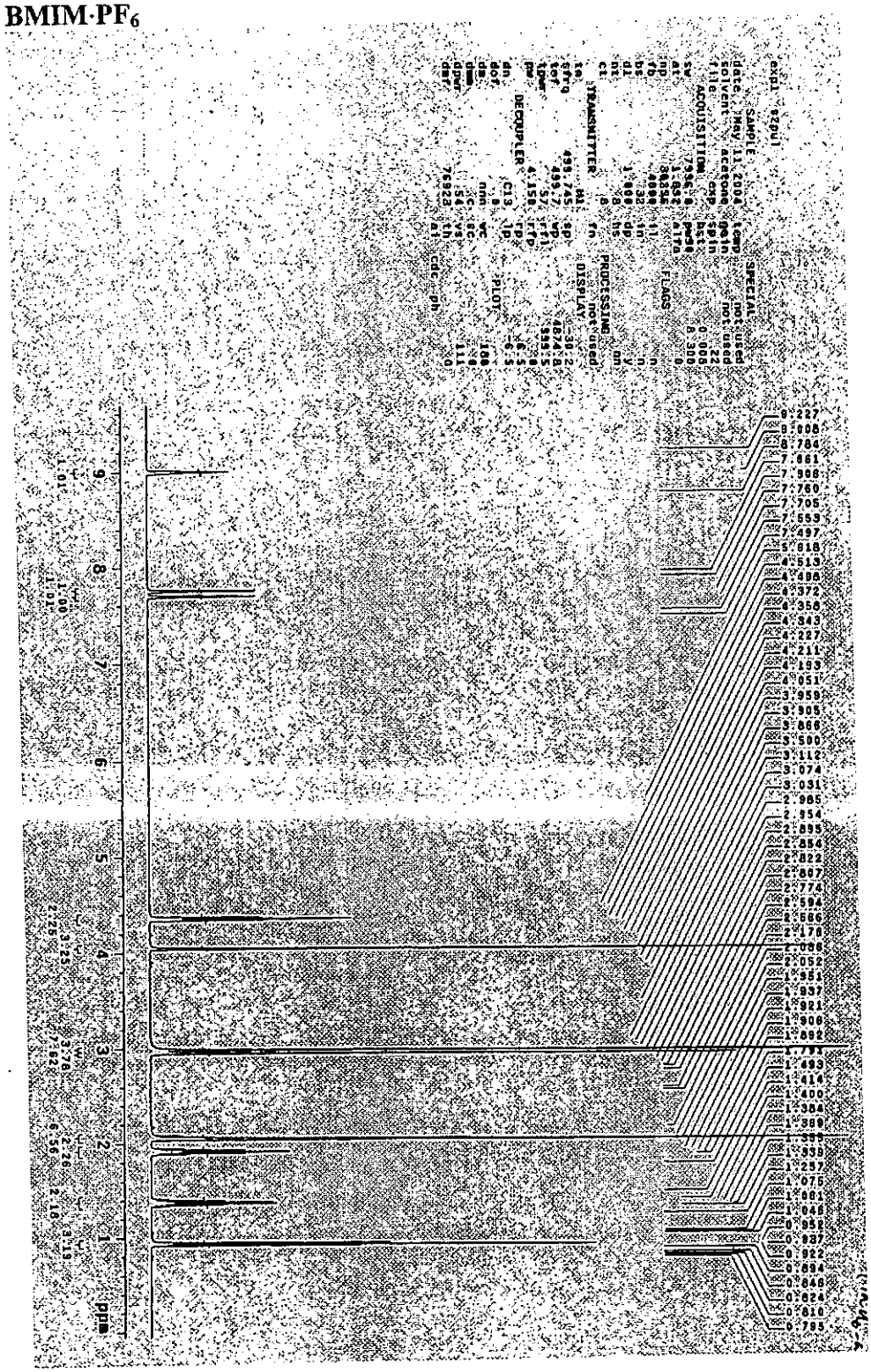


Figure A-37 ^{1}HNMR spectrum of BMIM·PF_6

BMIM·PF$_6$

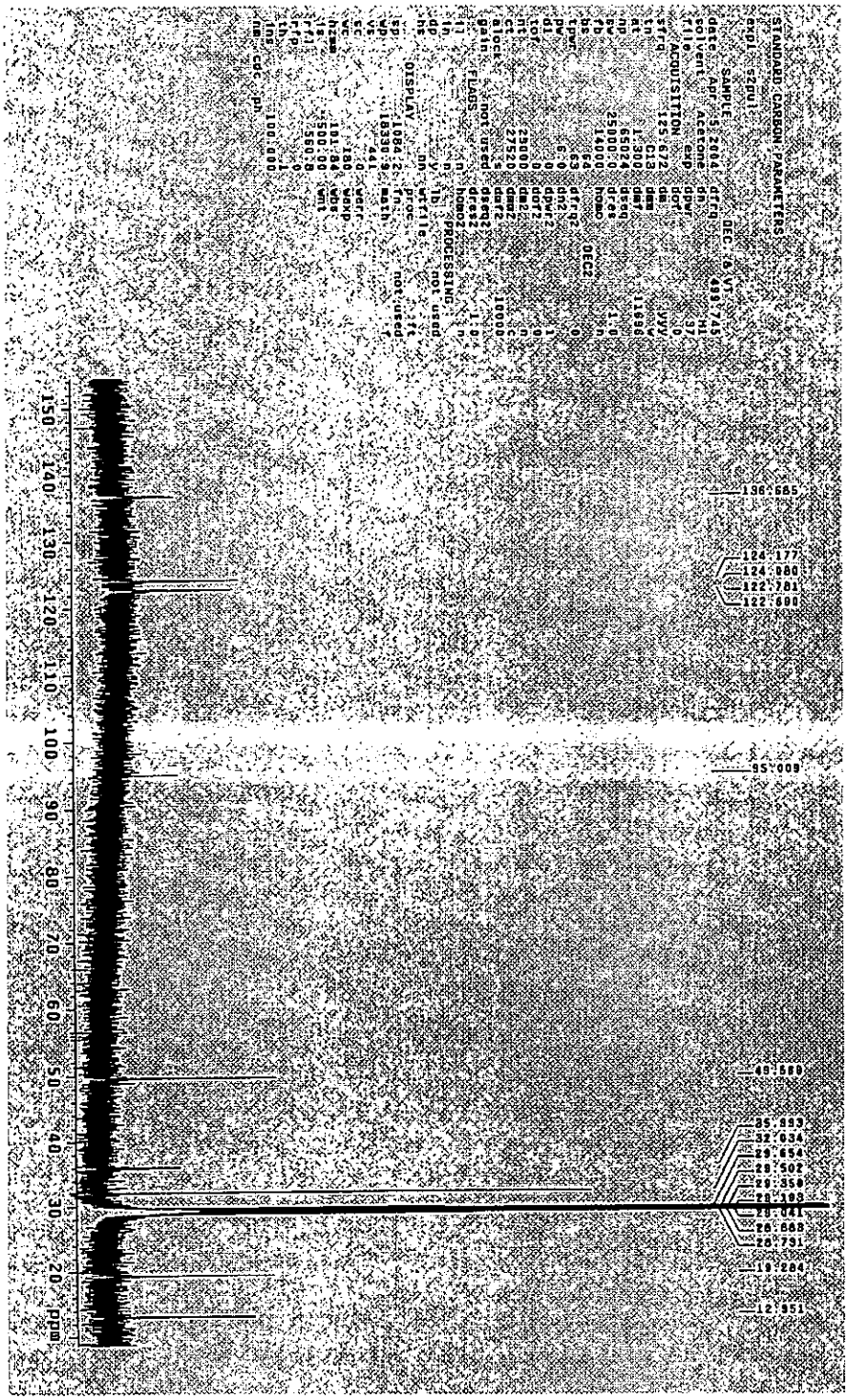


Figure A-38 ^{13}CNMR spectrum of BMIM·PF$_6$

BMIM·PF_6

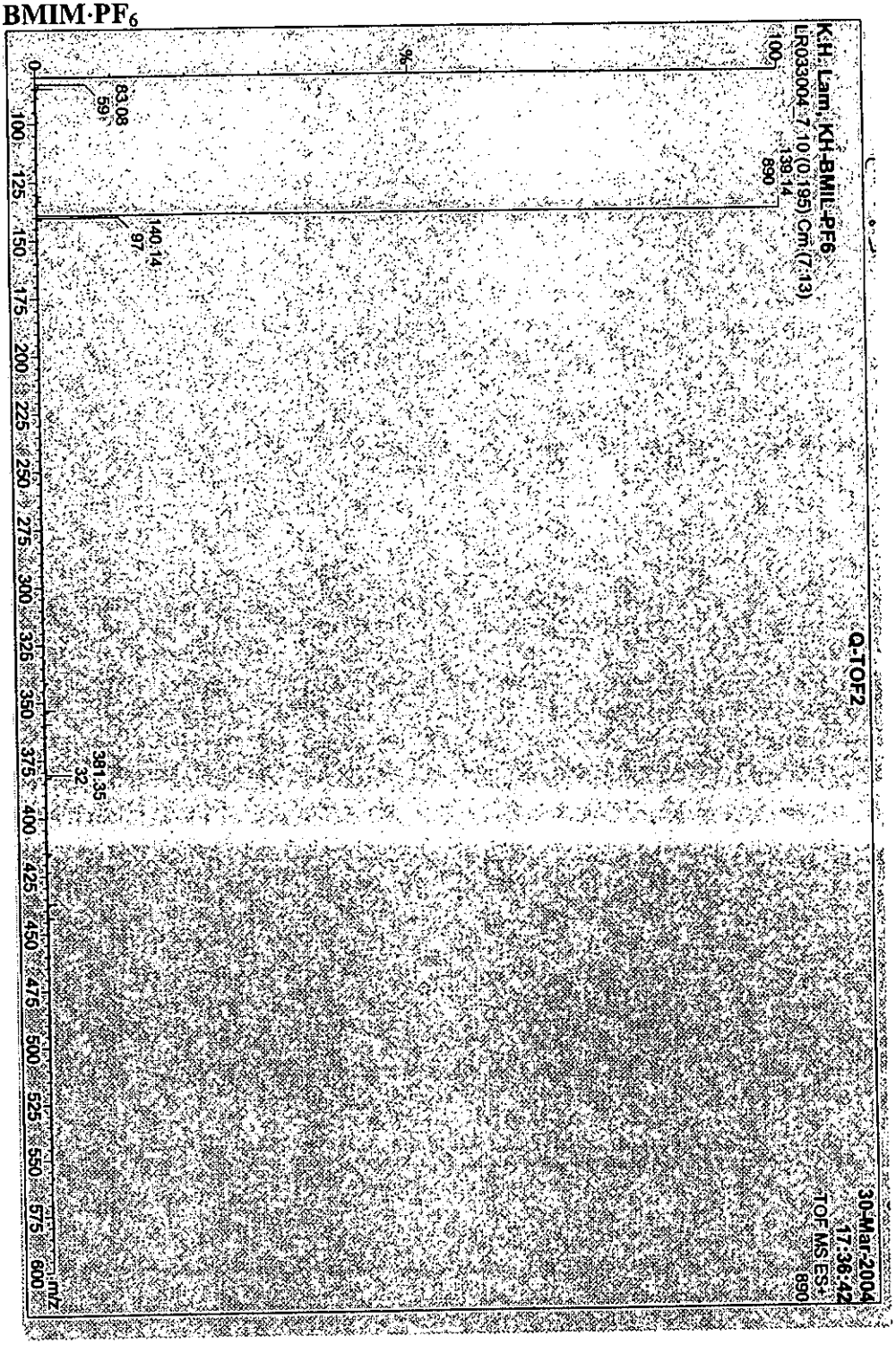
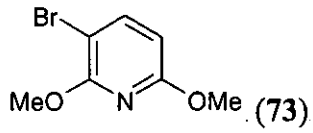


Figure A-39 ESI-MS spectrum of BMIM·PF_6



(73)

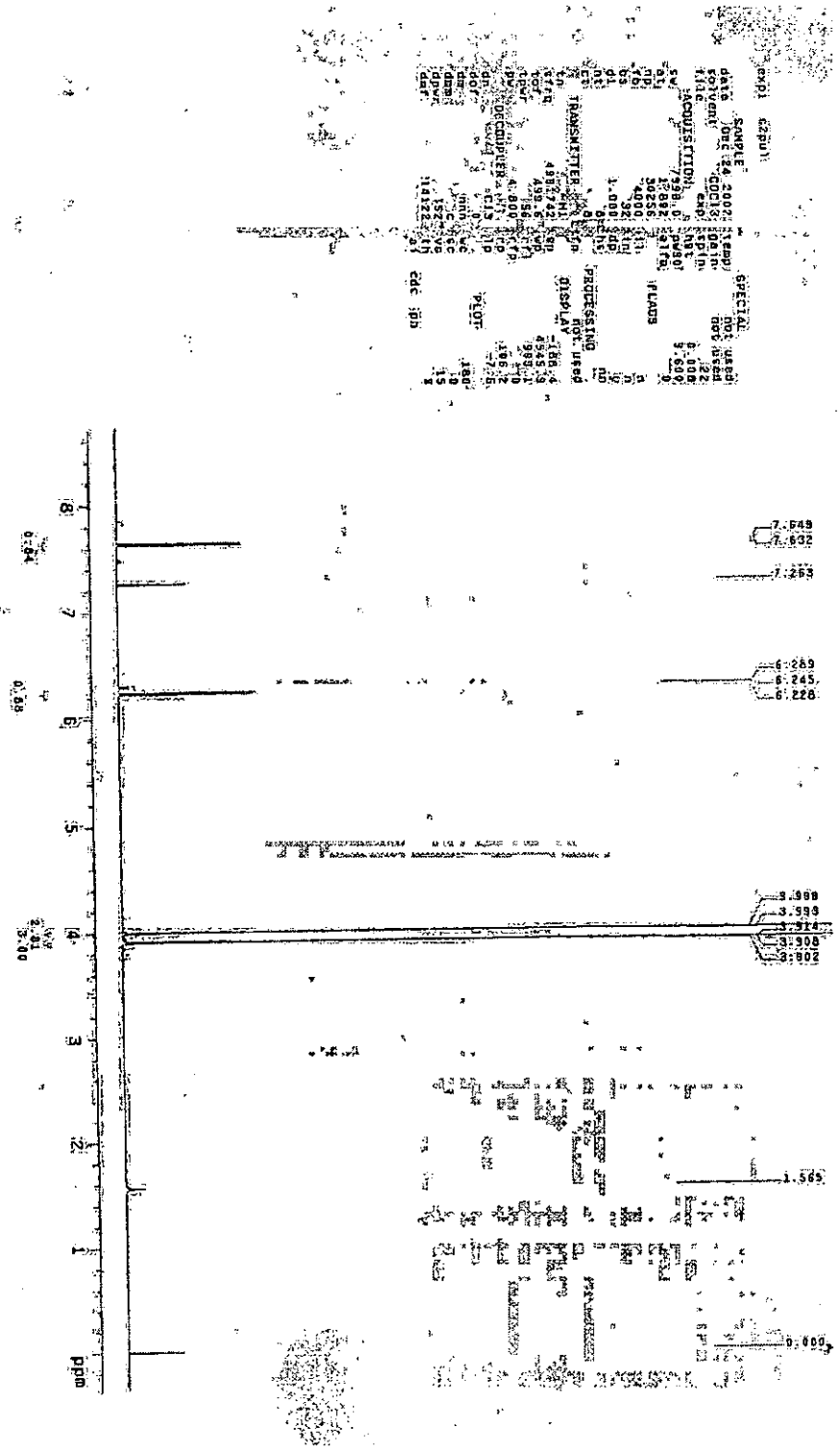
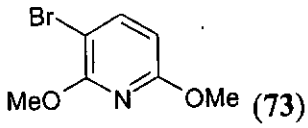


Figure A-40 ^{1}HNMR spectrum of 3-bromo-2, 6-dimethoxypyridine (**73**)



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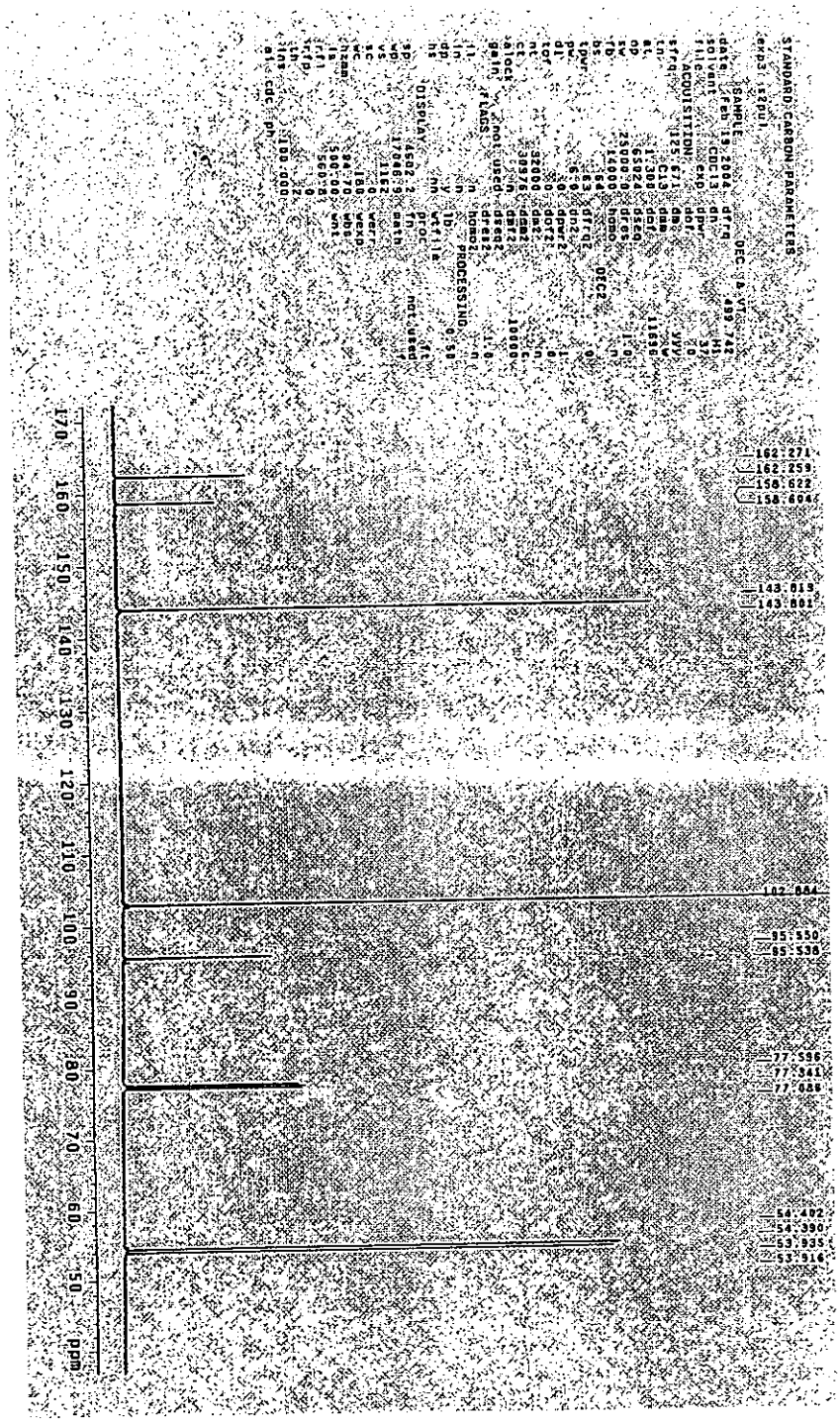


Figure A-41 ^{13}CNMR spectrum of 3-bromo-2, 6-dimethoxypyridine (73)

(73)

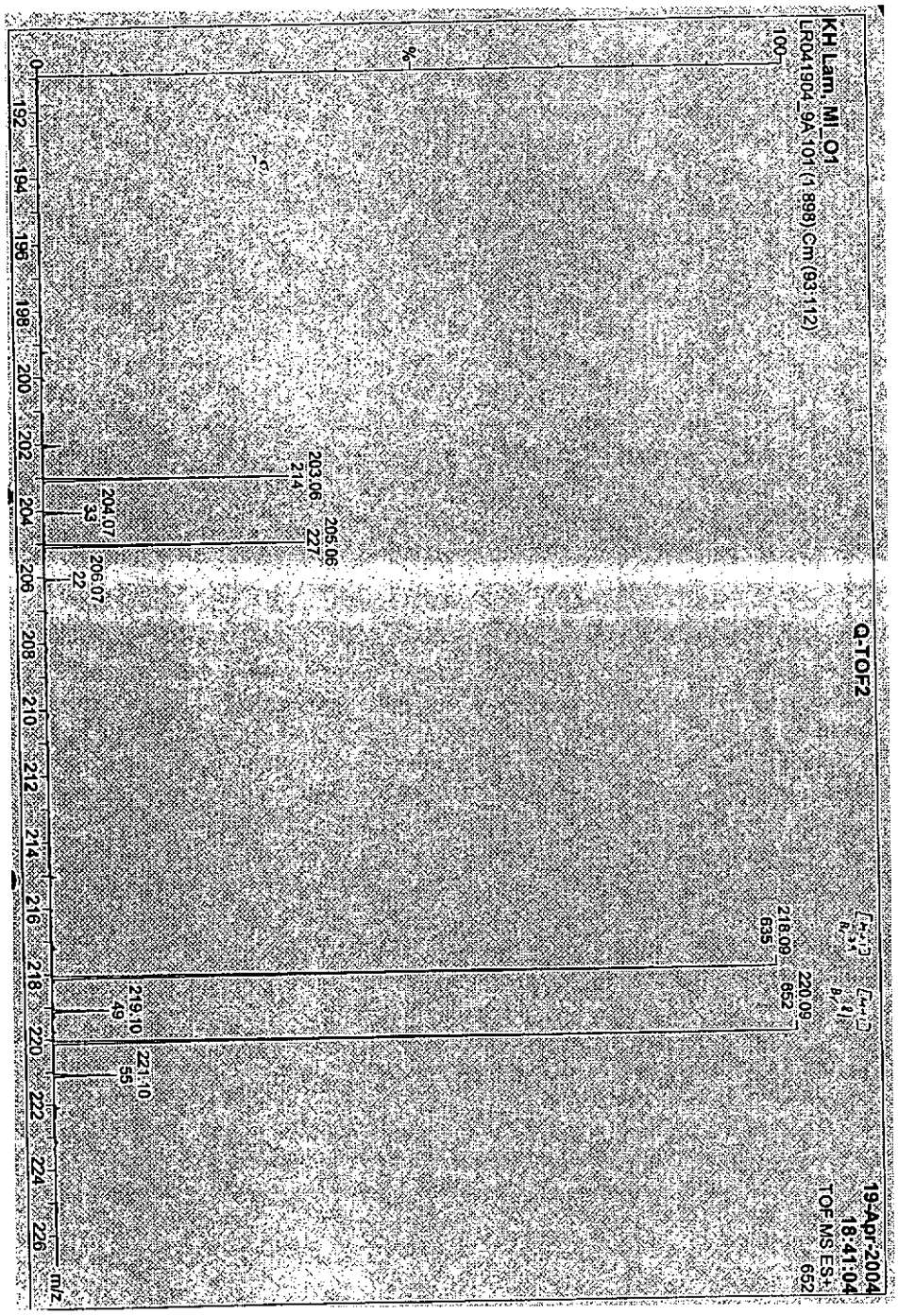
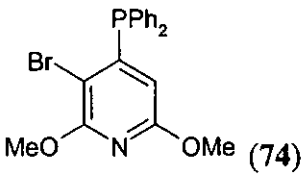


Figure A-42 ESI-MS spectrum of 3-bromo-2, 6-dimethoxypyridine (73)



(74)

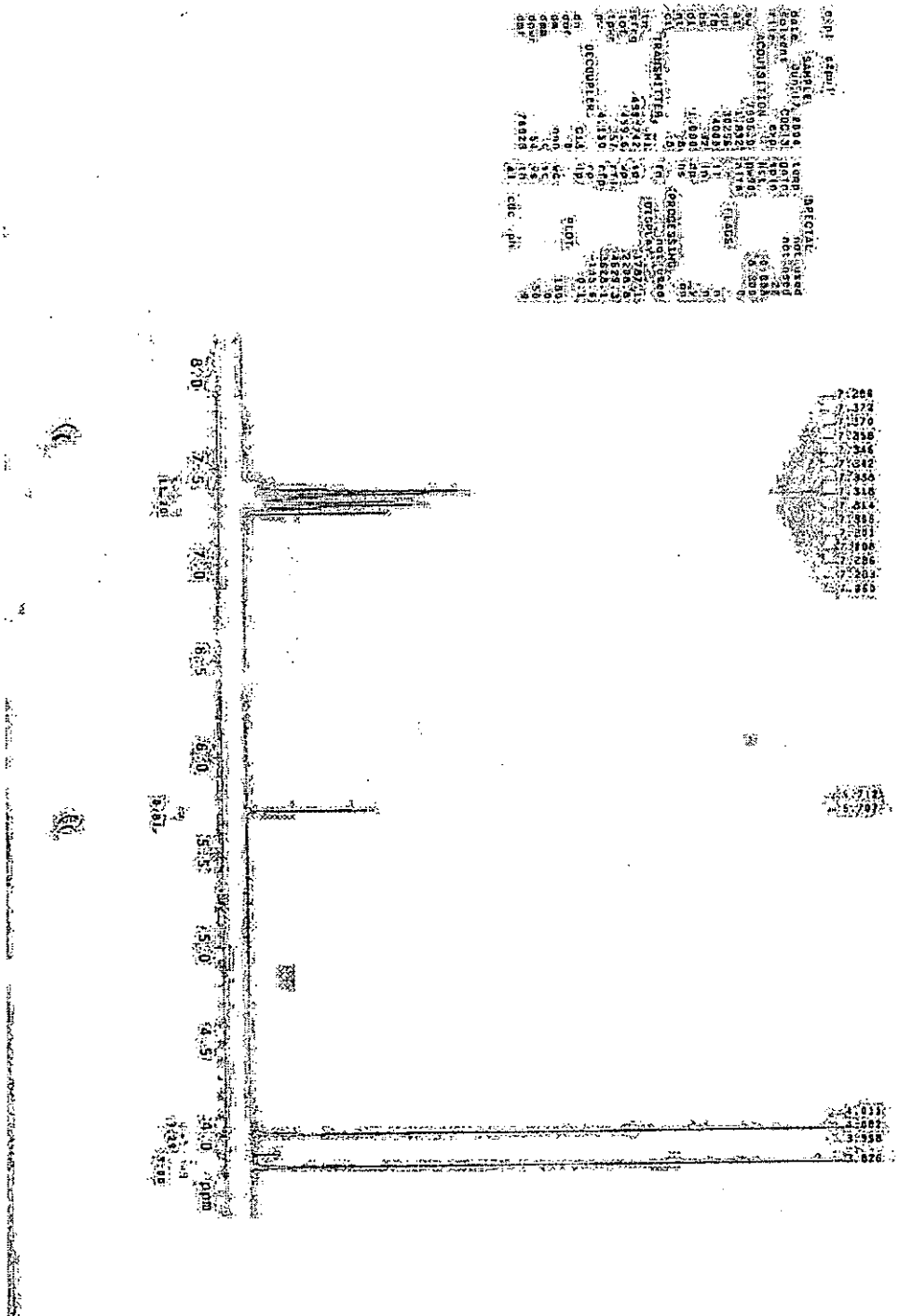
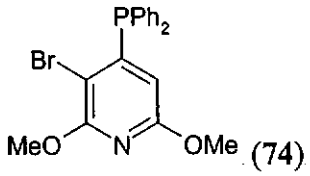


Figure A-43 ^{1}HNMR spectrum of 3-bromo-2, 6-dimethoxy-4-diphenylphosphino-pyridine (**74**)



(74)

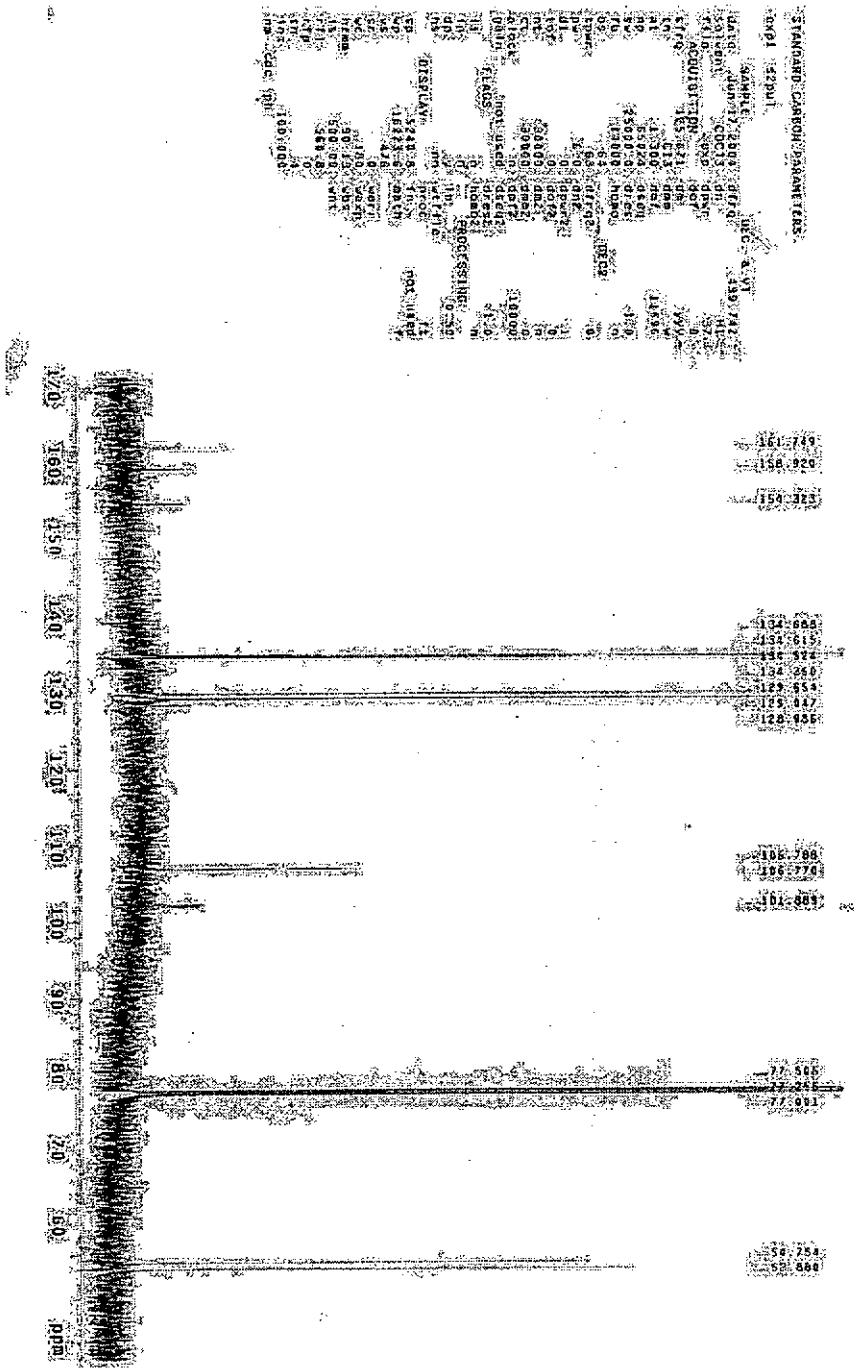
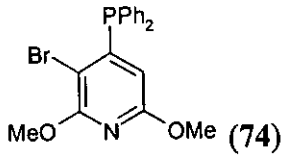
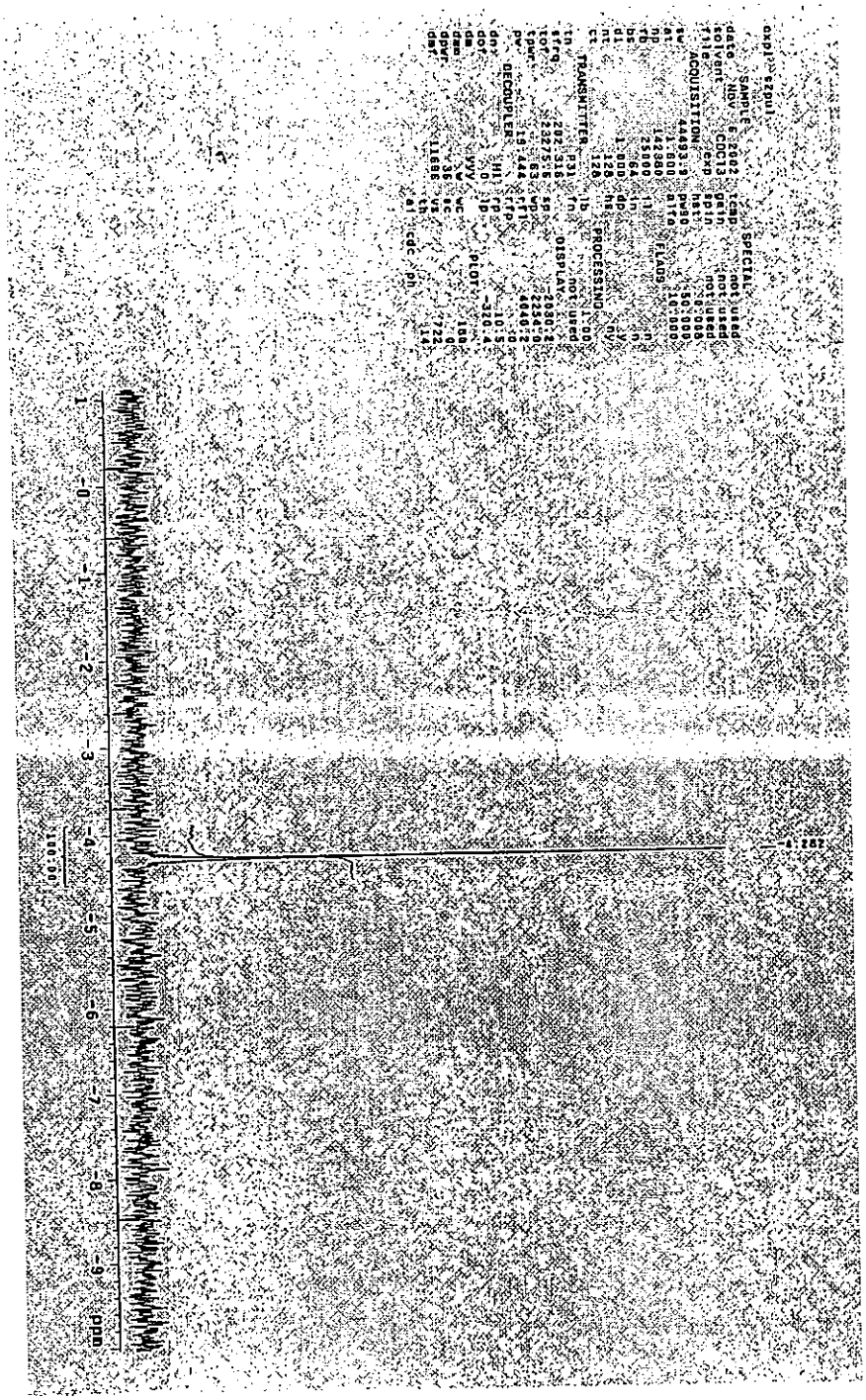


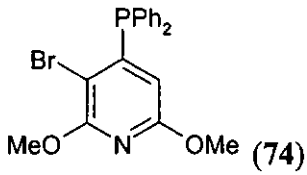
Figure A-44 ^{13}CNMR spectrum of 3-bromo-2, 6-dimethoxy-4-diphenylphosphino-pyridine (**74**)



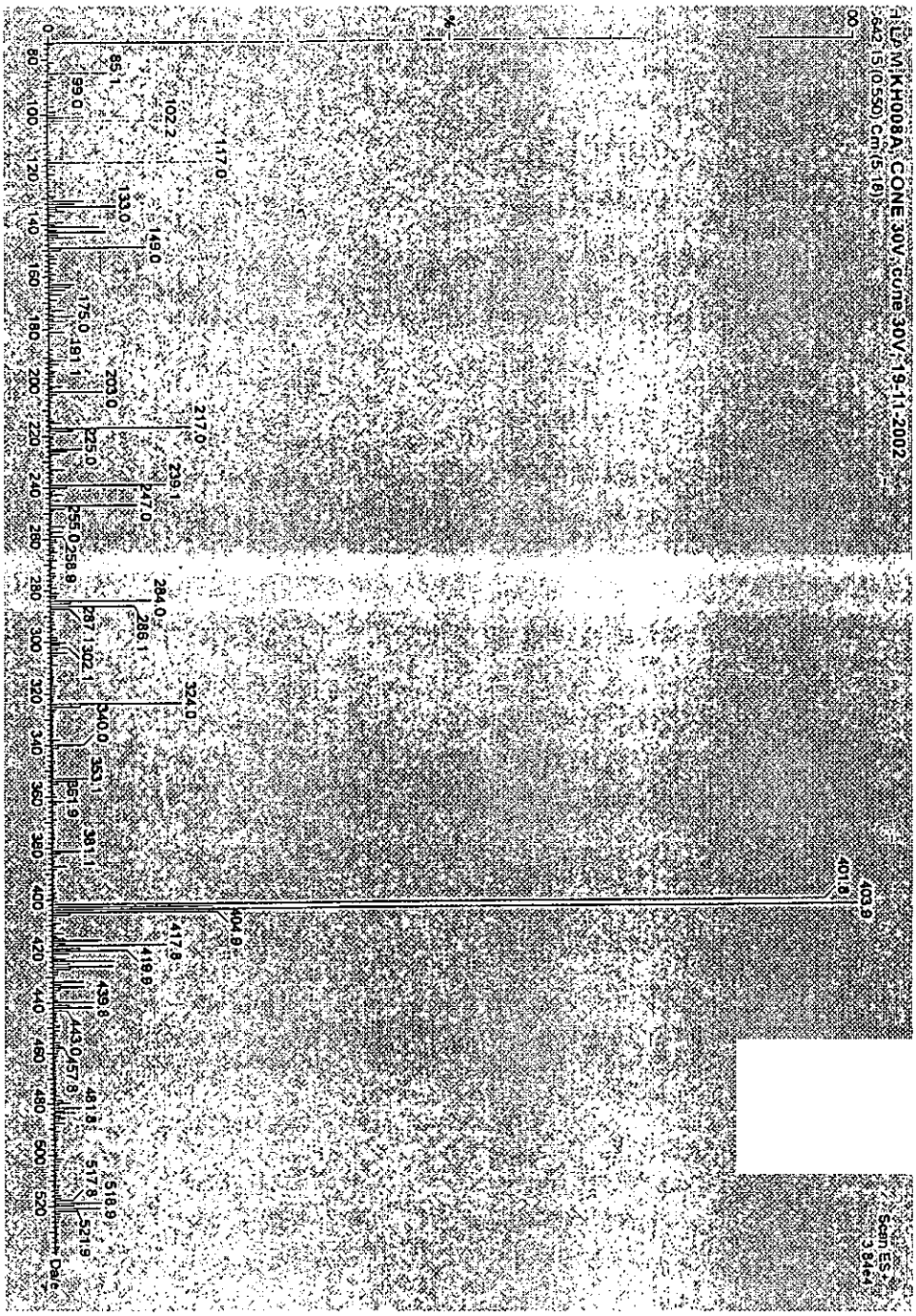
(74)



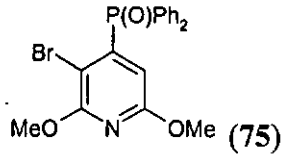
A-45 ^{31}PNMR spectrum of 3-bromo-2, 6-dimethoxy-4-diphenylphosphino-pyridine (74)



(74)



A-46 ESI-MS spectrum of 3-bromo-2, 6-dimethoxy-4-diphenylphosphino-pyridine (**74**)



(75)

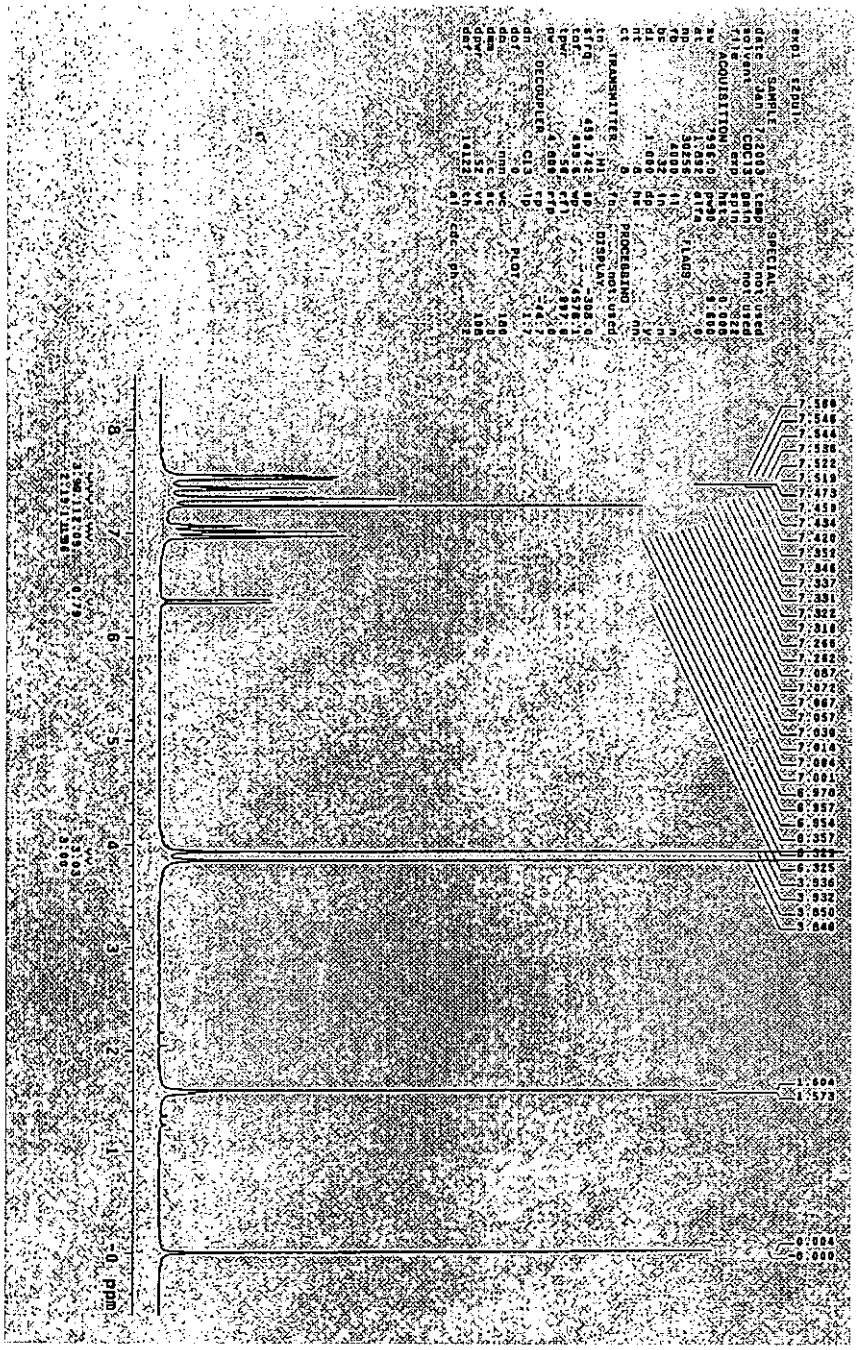
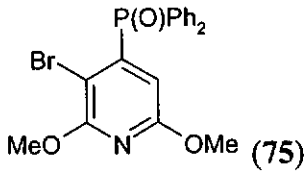


Figure A-47 ^{1}HNMR spectrum of 3-bromo-2, 6-dimethoxy-4-diphenylphosphinylpyridine (75)



(75)

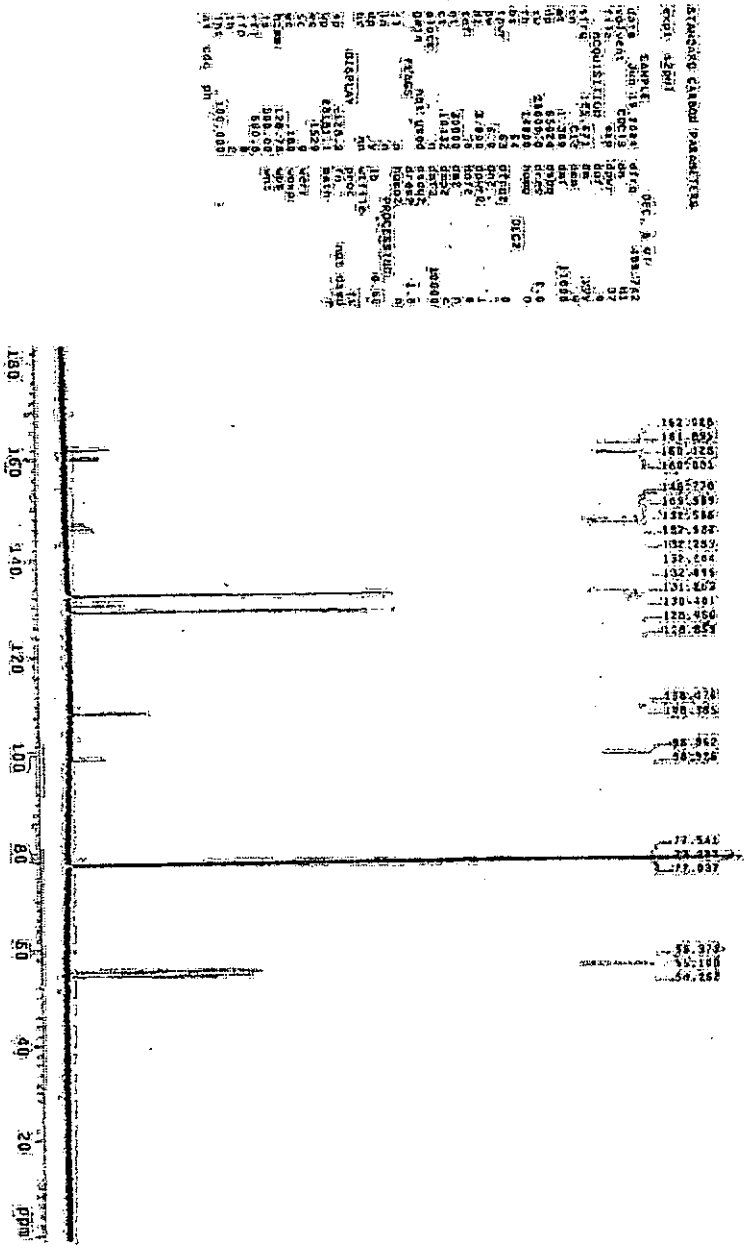
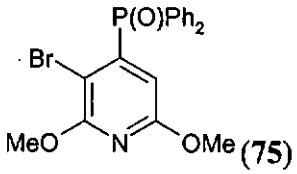


Figure A-48 ^{13}CNMR spectrum of 3-bromo-2, 6-dimethoxy-4-diphenylphosphinylpyridine (**75**)



(75)

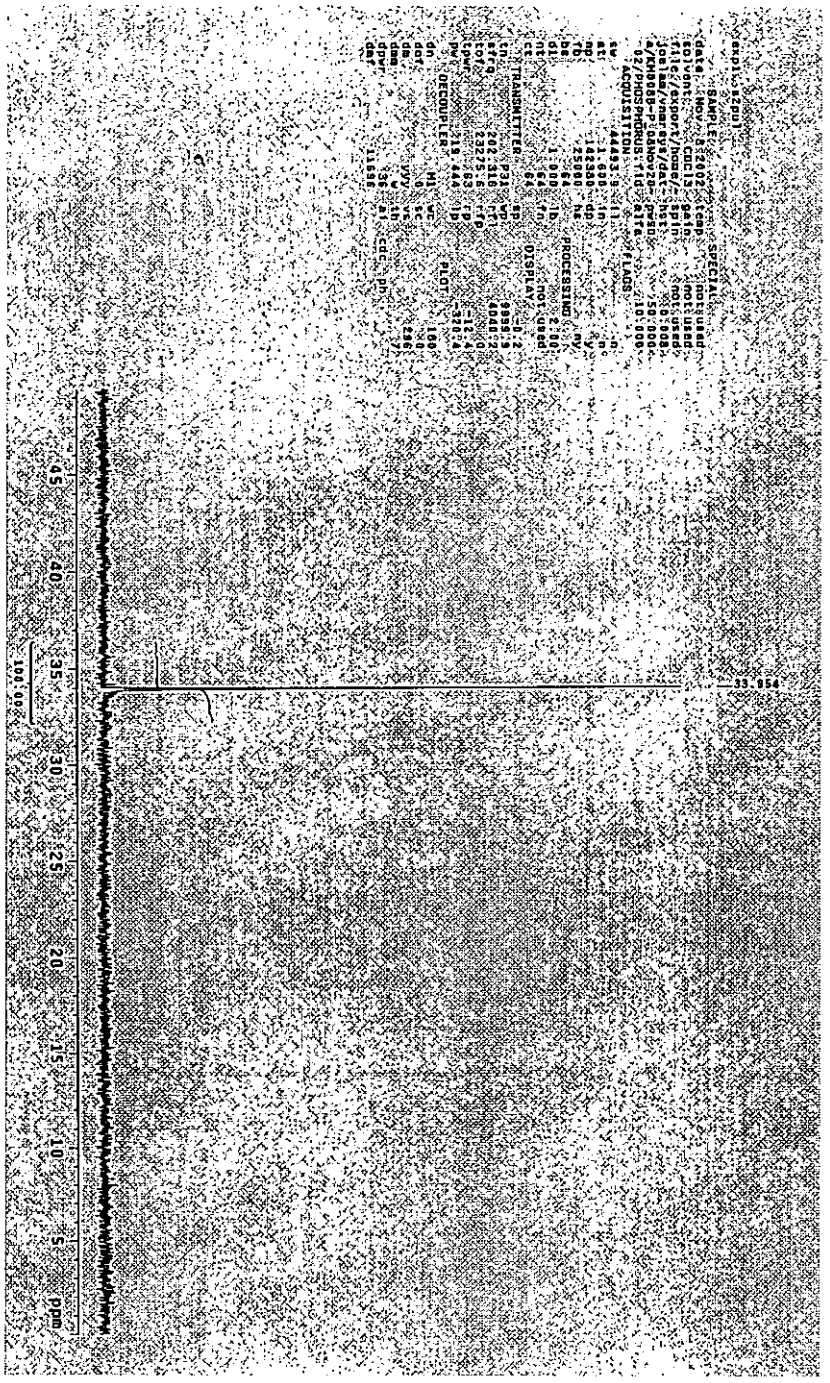
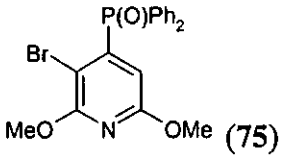


Figure A-49 ^{31}PNMR spectrum of 3-bromo-2, 6-dimethoxy-4-diphenylphosphinylpyridine (75)



(75)

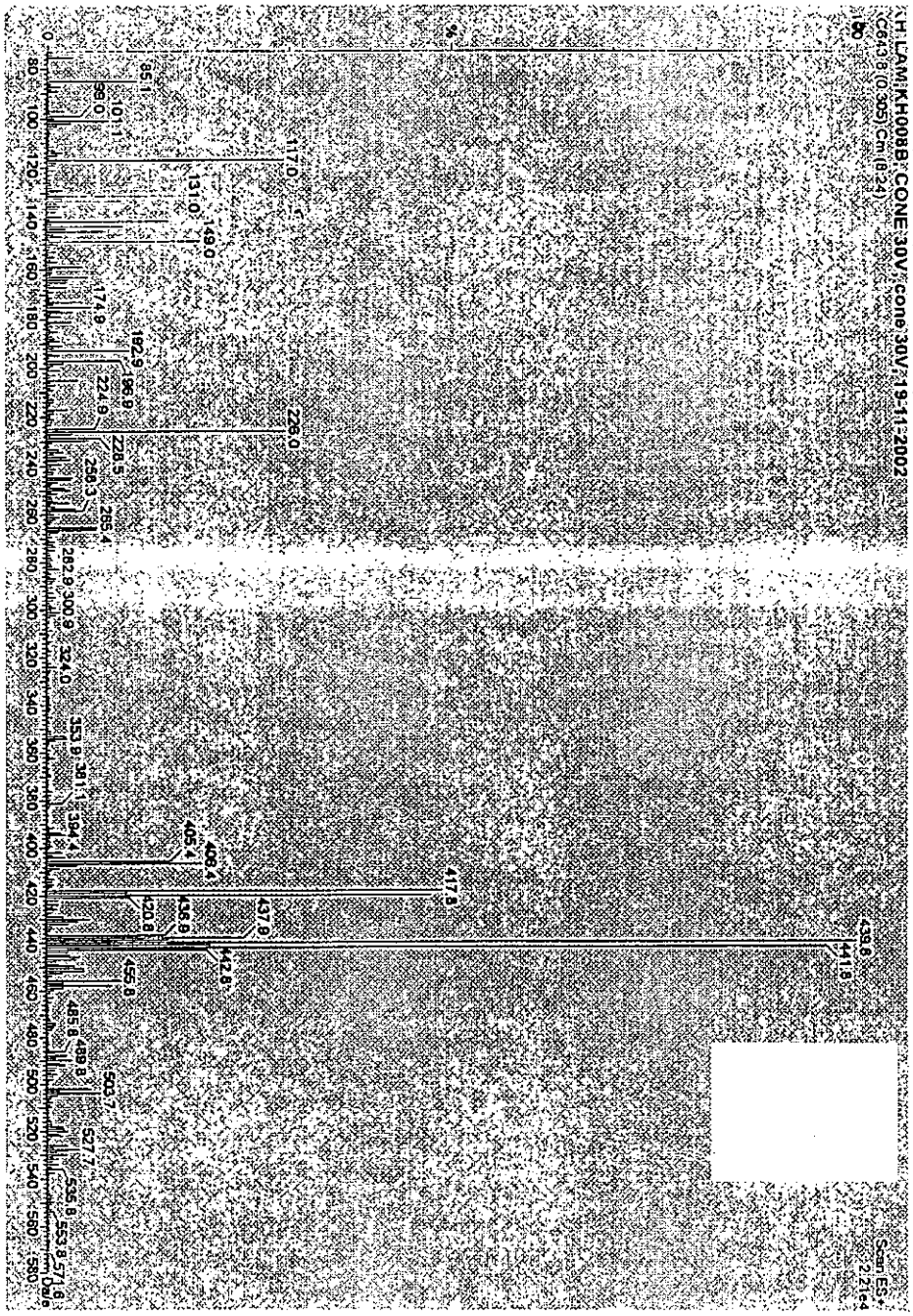
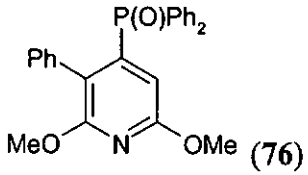


Figure A-50 ESI-MS spectrum of 3-bromo-2, 6-dimethoxy-4-diphenylphosphinylpyridine (75)



(76)

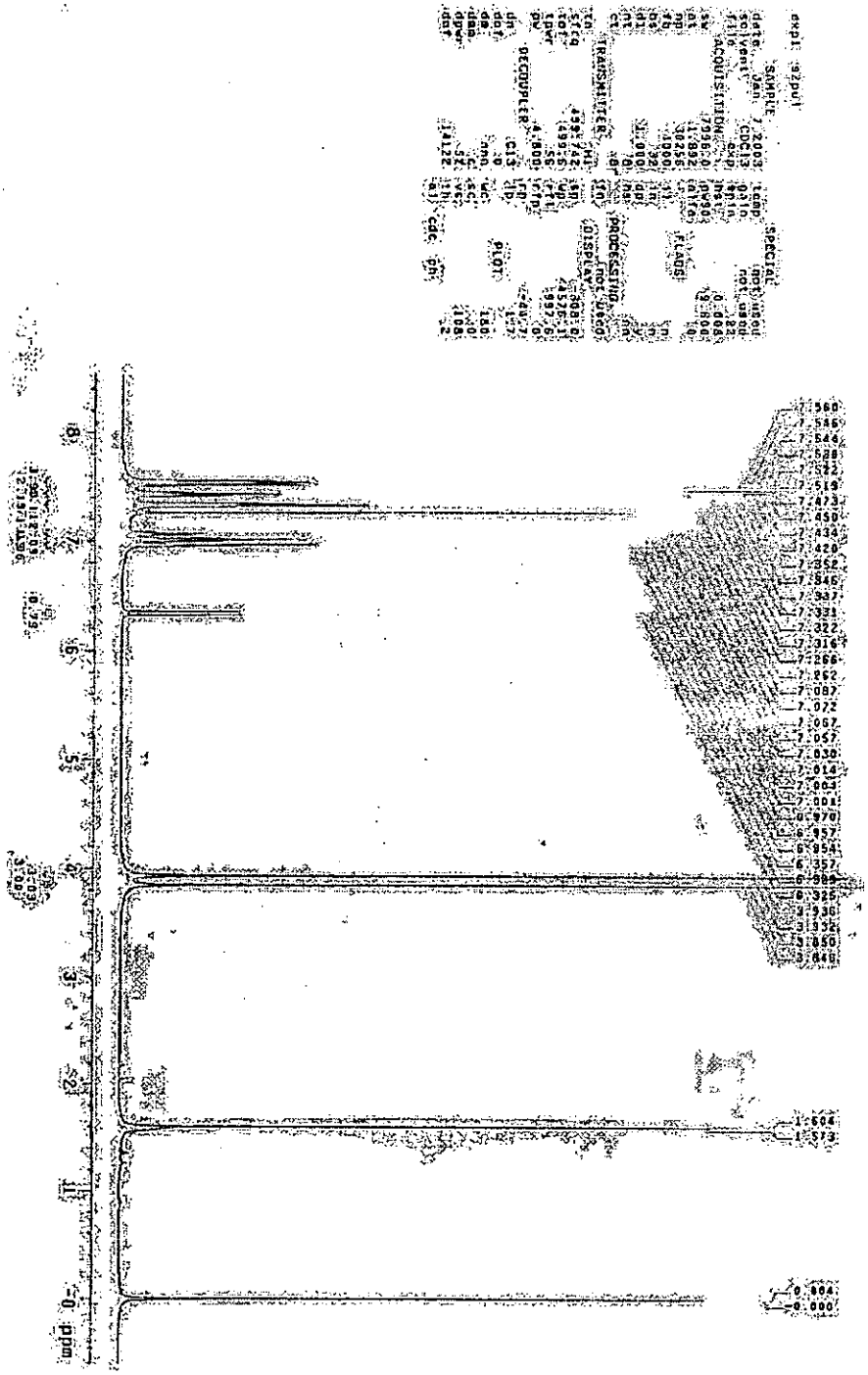
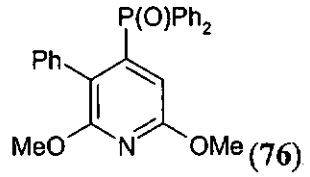


Figure A-51 ^{1}HNMR spectrum of 2, 6-dimethoxy-3-phenyl -4-diphenylphosphinylpyridine (76)



(76)

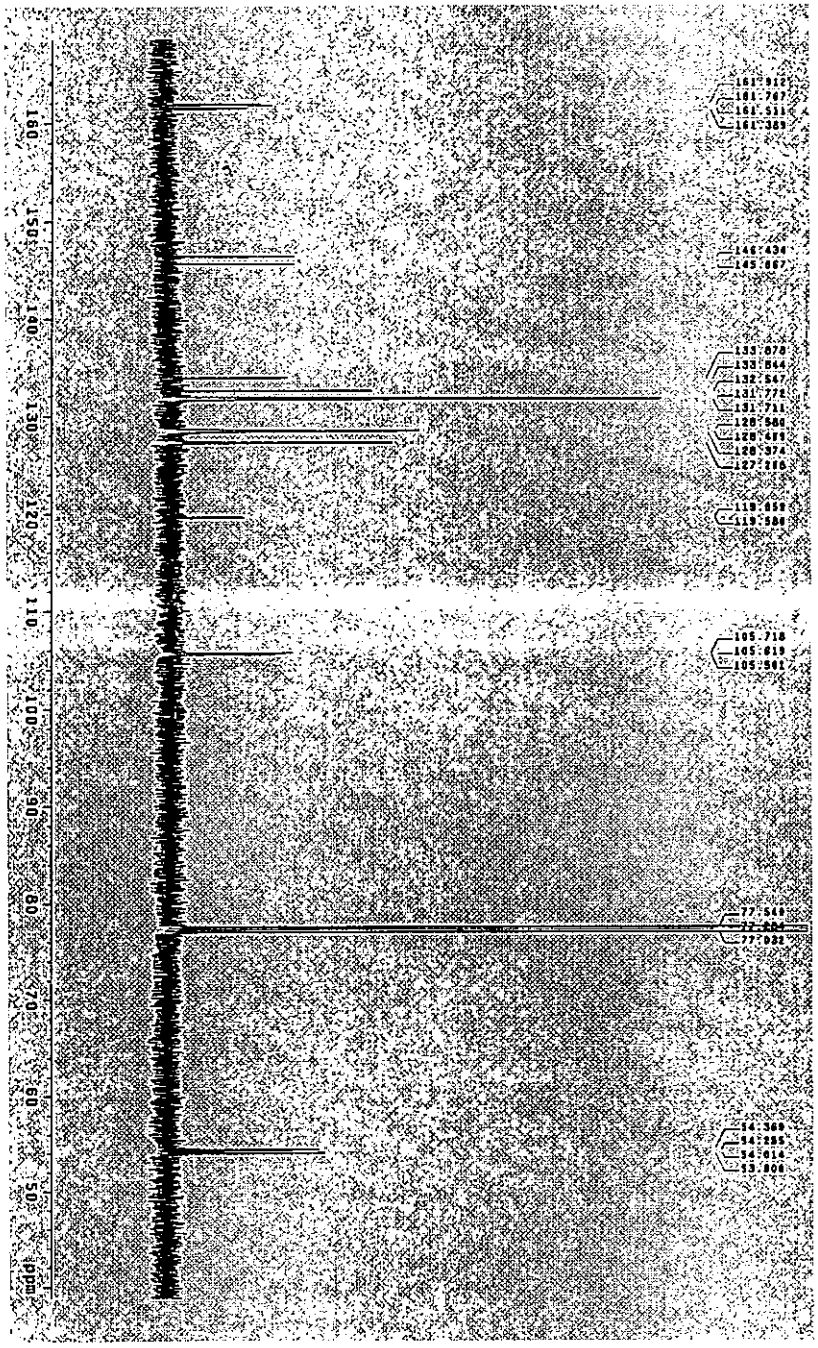
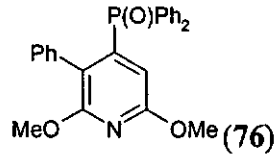


Figure A-52 ^{13}CNMR spectrum of 2, 6-dimethoxy-3-phenyl -4-diphenylphosphinylpyridine (**76**)



(76)

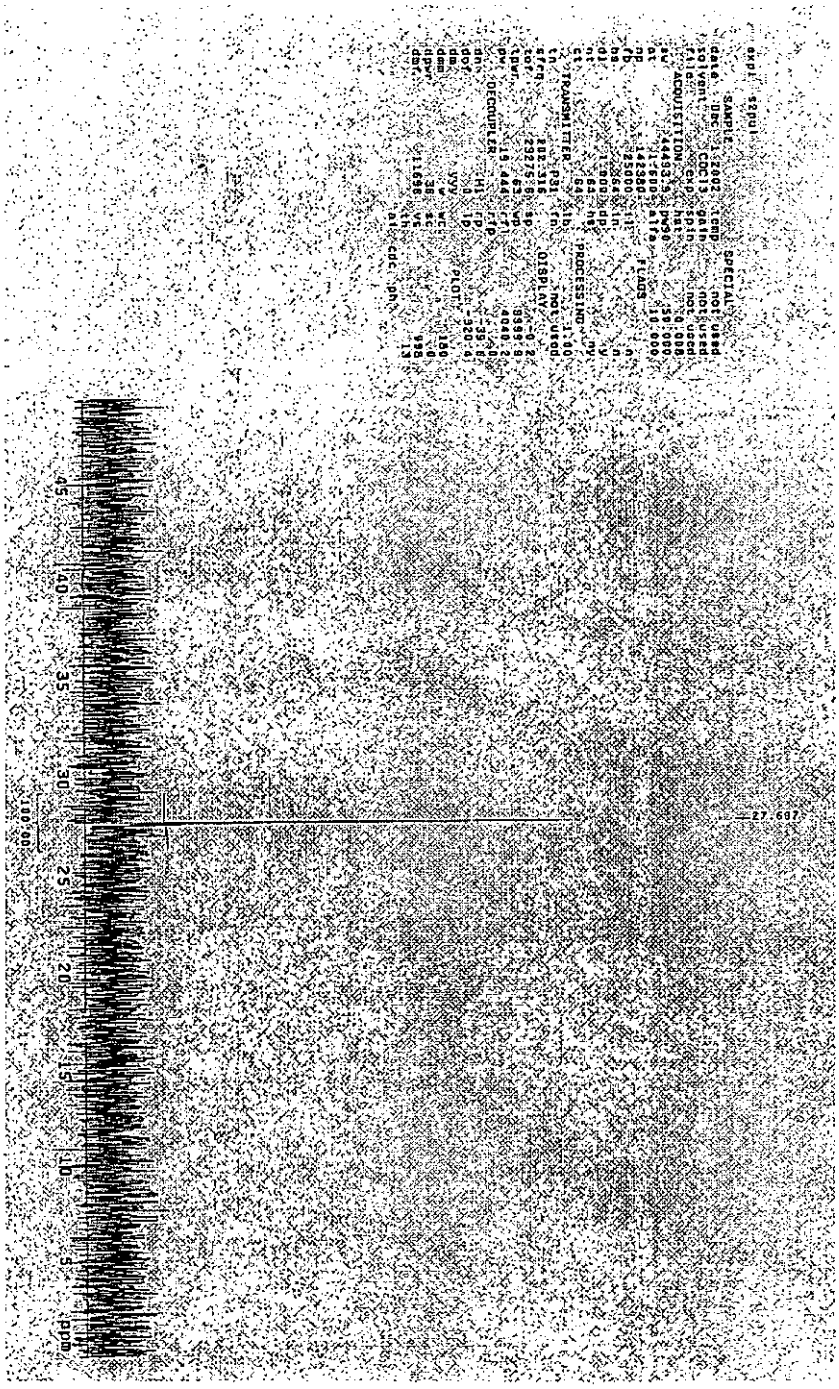
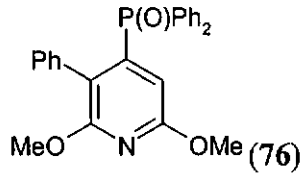


Figure A-53 ^{31}PNMR spectrum of 2, 6-dimethoxy-3-phenyl -4-diphenylphosphinylpyridine (76)



(76)

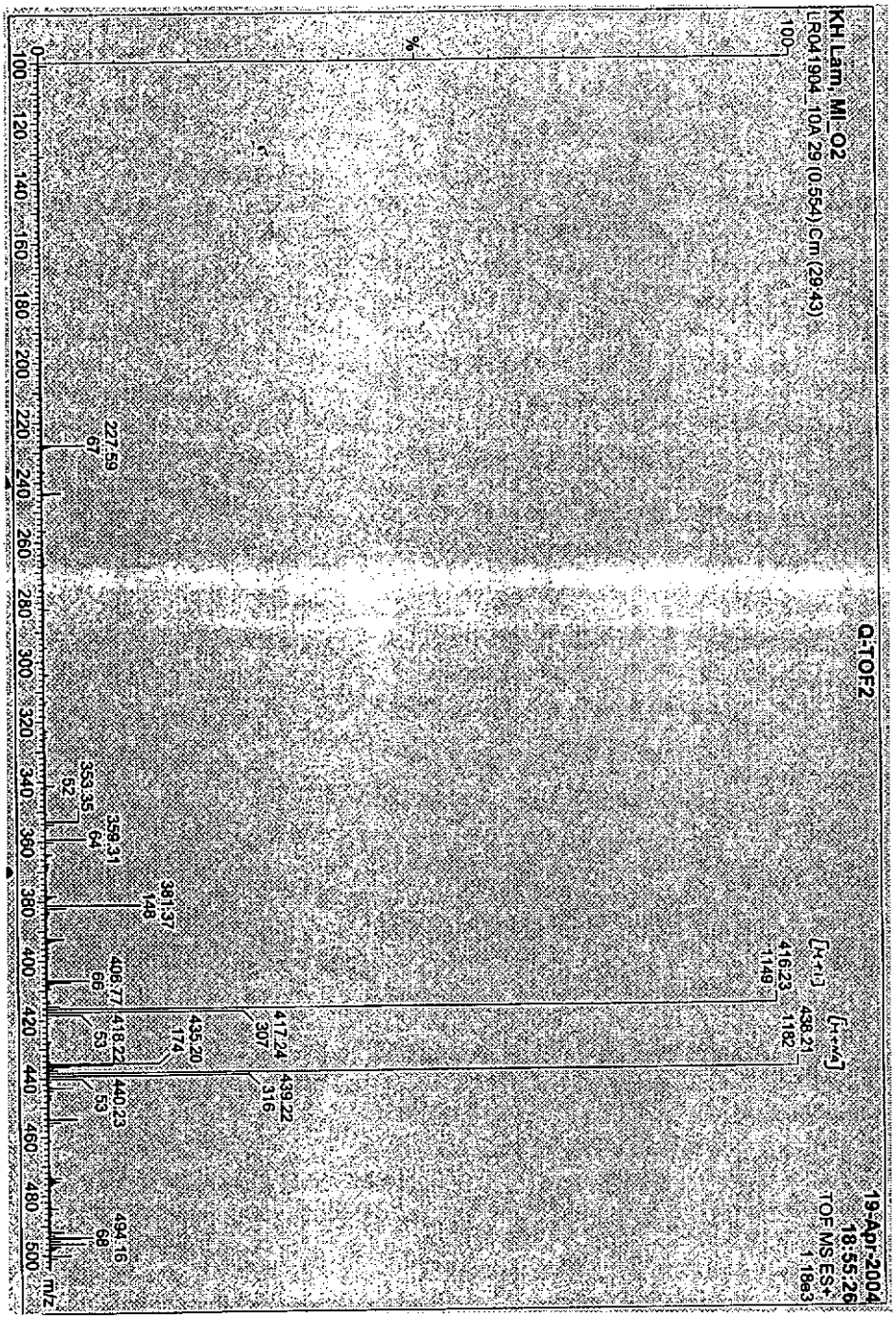
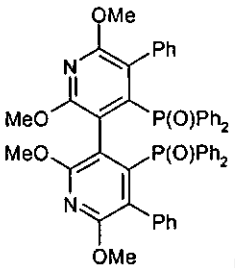


Figure A-54 . ESI-MS spectrum of 2, 6-dimethoxy-3-phenyl -4-diphenylphosphinylpyridine (**76**)



(rac-77)

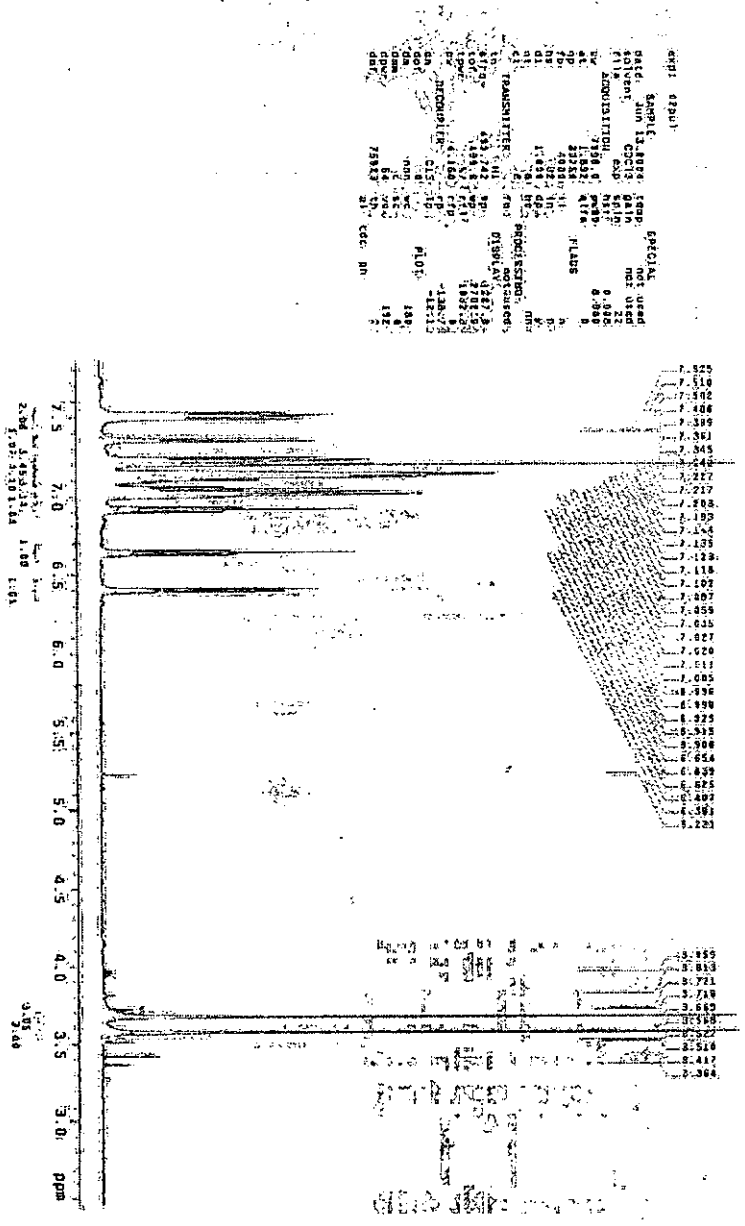
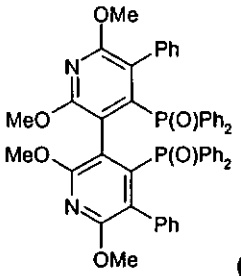


Figure A-55 ^{1}HNMR spectrum of 2,2',6,6'-tetramethoxy-5,5'-diphhenyl-4,4'-diphenylphosphinoyl- 3,3'-bipyridine (rac-77)



(rac-77)

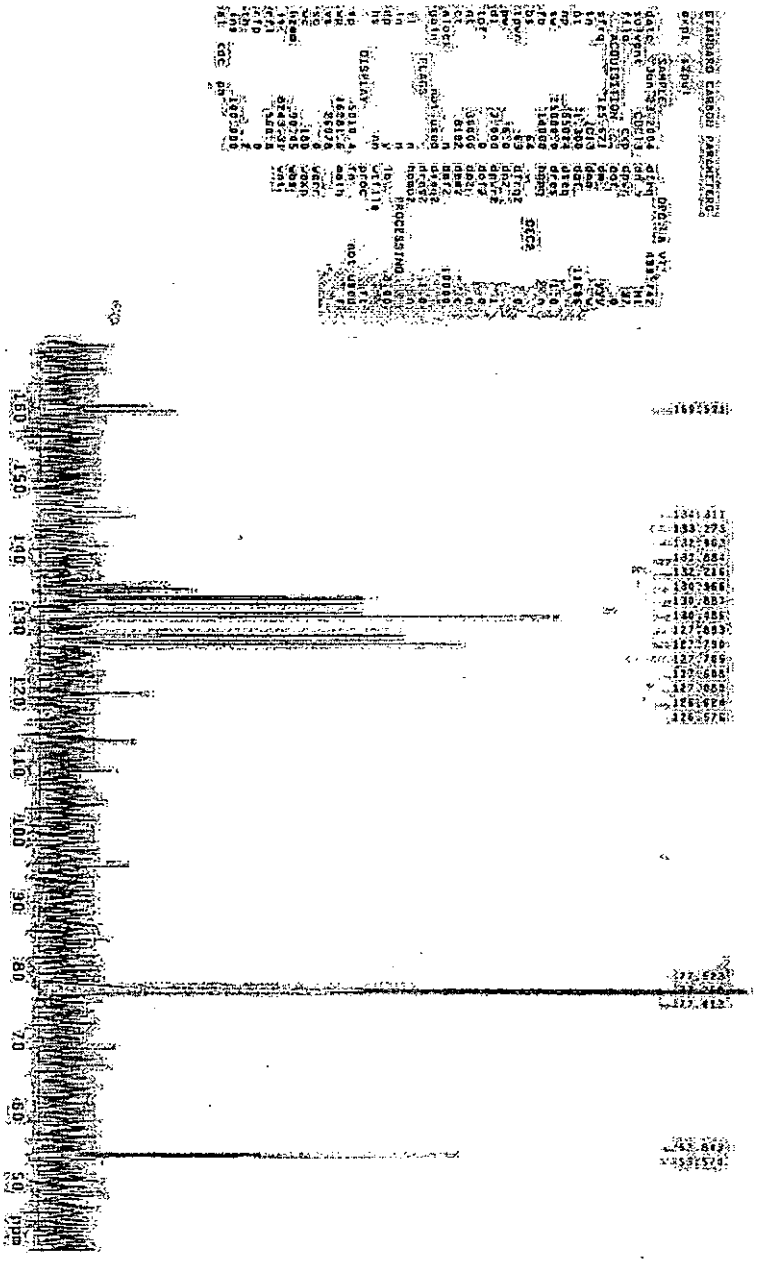
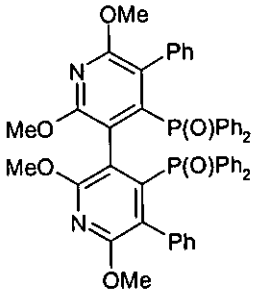


Figure A-56 ^{13}CNMR spectrum of 2,2',6,6'-tetramethoxy-5,5'-diphhenyl-4,4'-diphenylphosphinoyl- 3,3'-bipyridine (rac-77)



(rac-77)

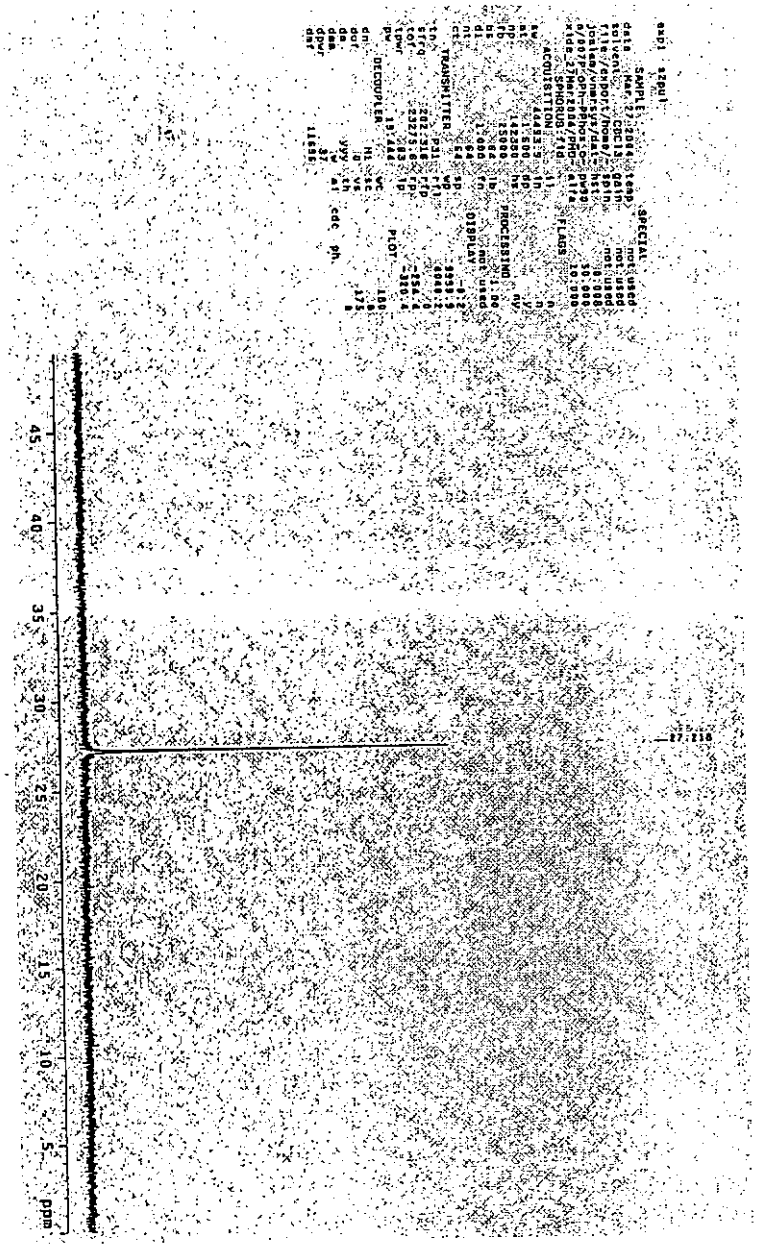
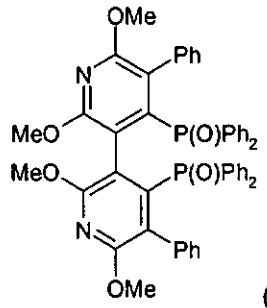


Figure A-57 ^{31}PNMR spectrum of 2,2',6,6'-tetramethoxy-5,5'-diphhenyl-4,4'-diphenylphosphinoyl- 3,3'-bipyridine (rac-77)



(rac-77)

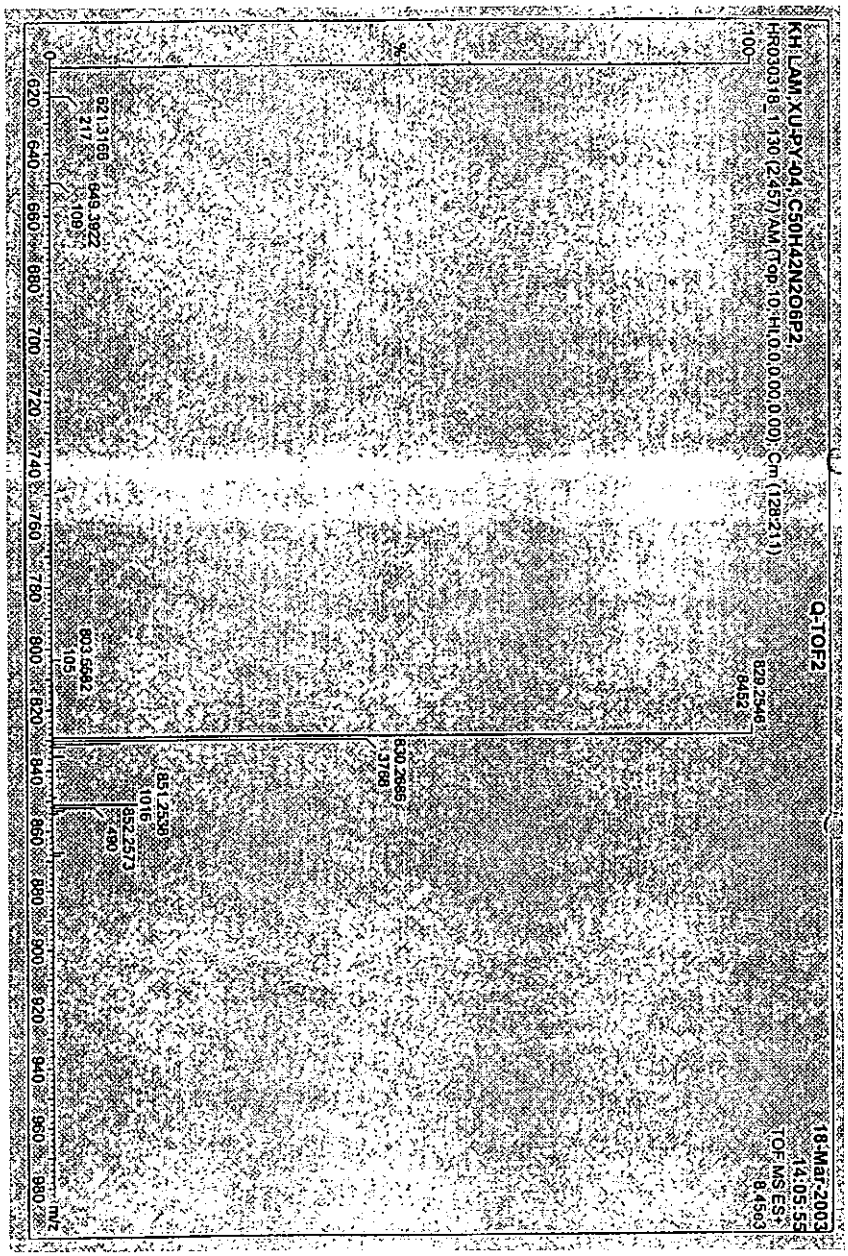
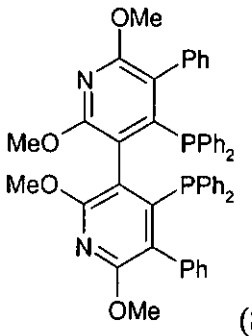


Figure A-58 ESI-MS spectrum of 2,2',6,6'-tetramethoxy-5,5'-diphhenyl-4,4'-diphenylphosphinoyl- 3,3'-bipyridine (rac-77)



(S-78)

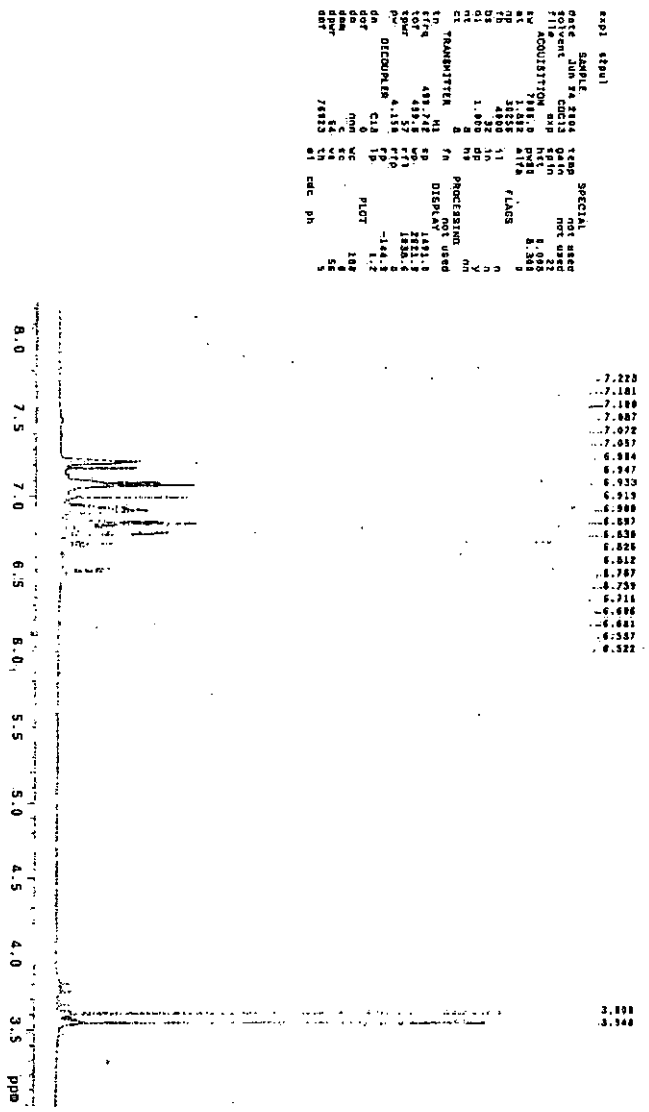
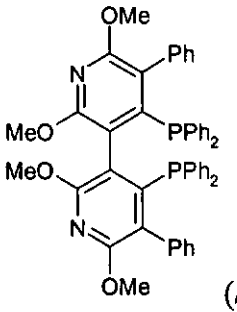


Figure A-59 ^{1}HNMR spectrum of (S) - 2,2'6,6' – tetramethoxy - 5,5' – diphenyl - 4,4' – diphenyl – phosphino - 3,3'- bipyridine (*S*-78)



(*S*-**78**)

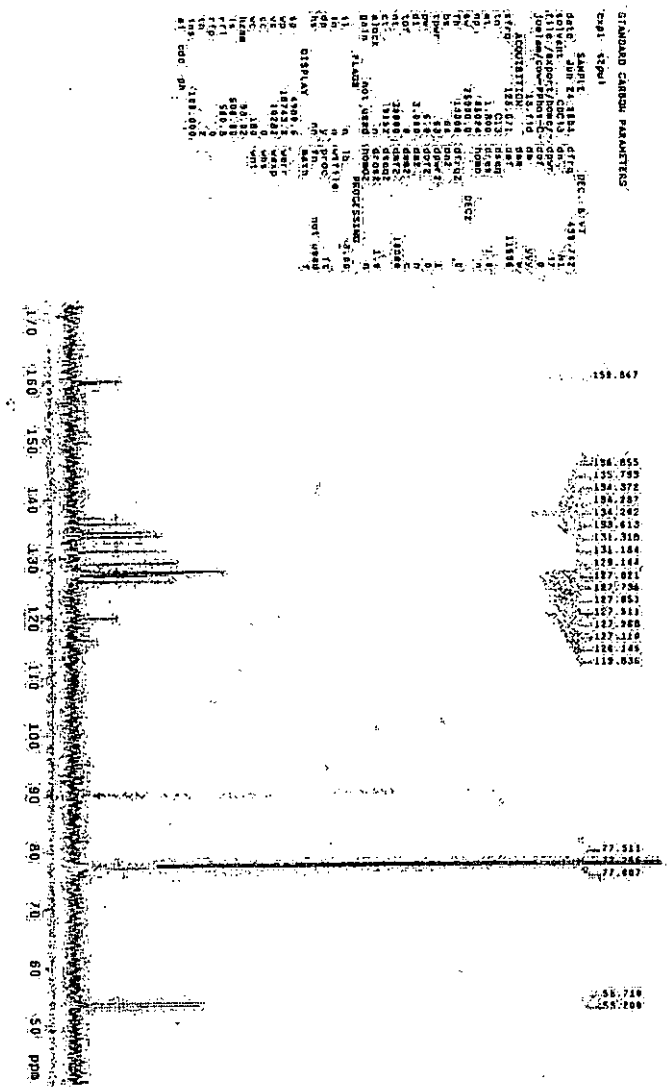
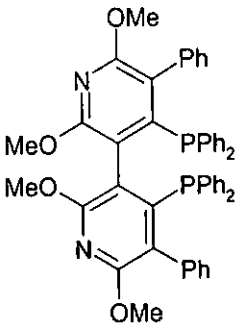


Figure A-60 ^{13}CNMR spectrum of (S) - 2,2'6,6' – tetramethoxy - 5,5' – diphenyl - 4,4' – diphenyl – phosphino - 3,3'- bipyridine (*S*-**78**)



(*S*-78)

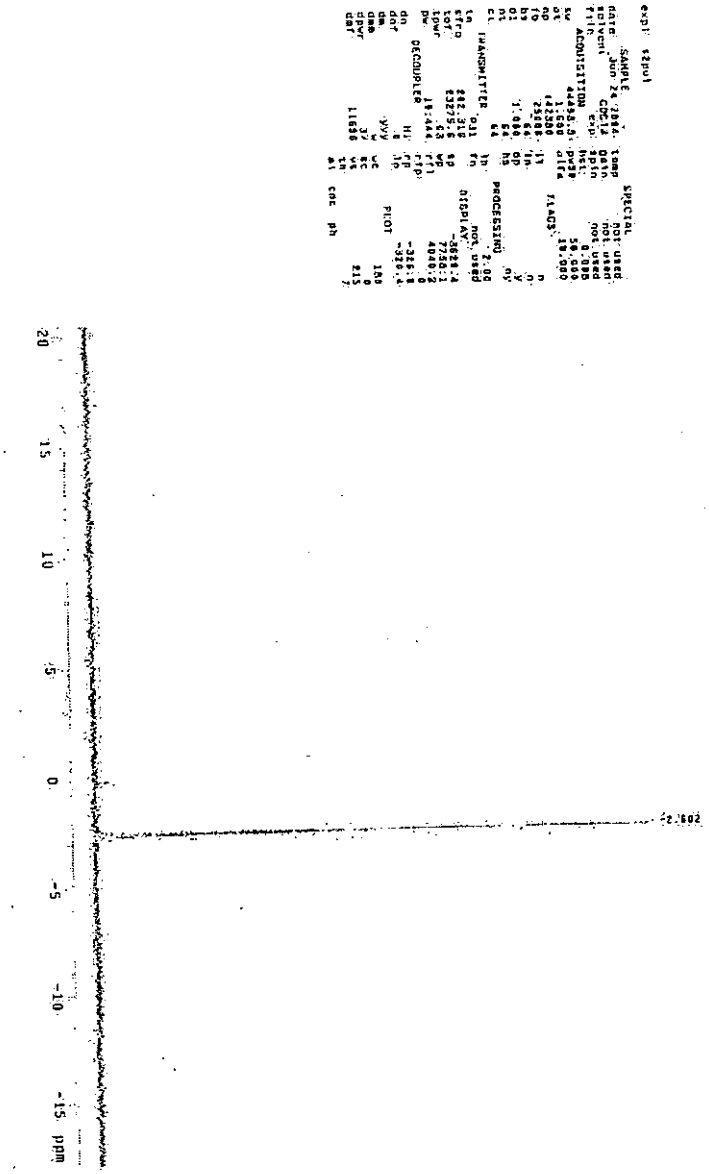
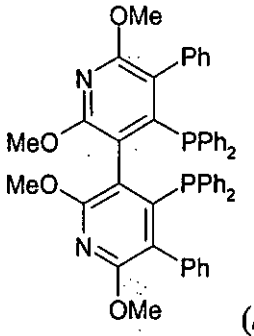


Figure A-61 ^{31}PNMR spectrum of (S) - 2,2'6,6' – tetramethoxy - 5,5' – diphenyl - 4,4' – diphenyl – phosphino - 3,3'- bipyridine (*S*-78)



(*S*-78)

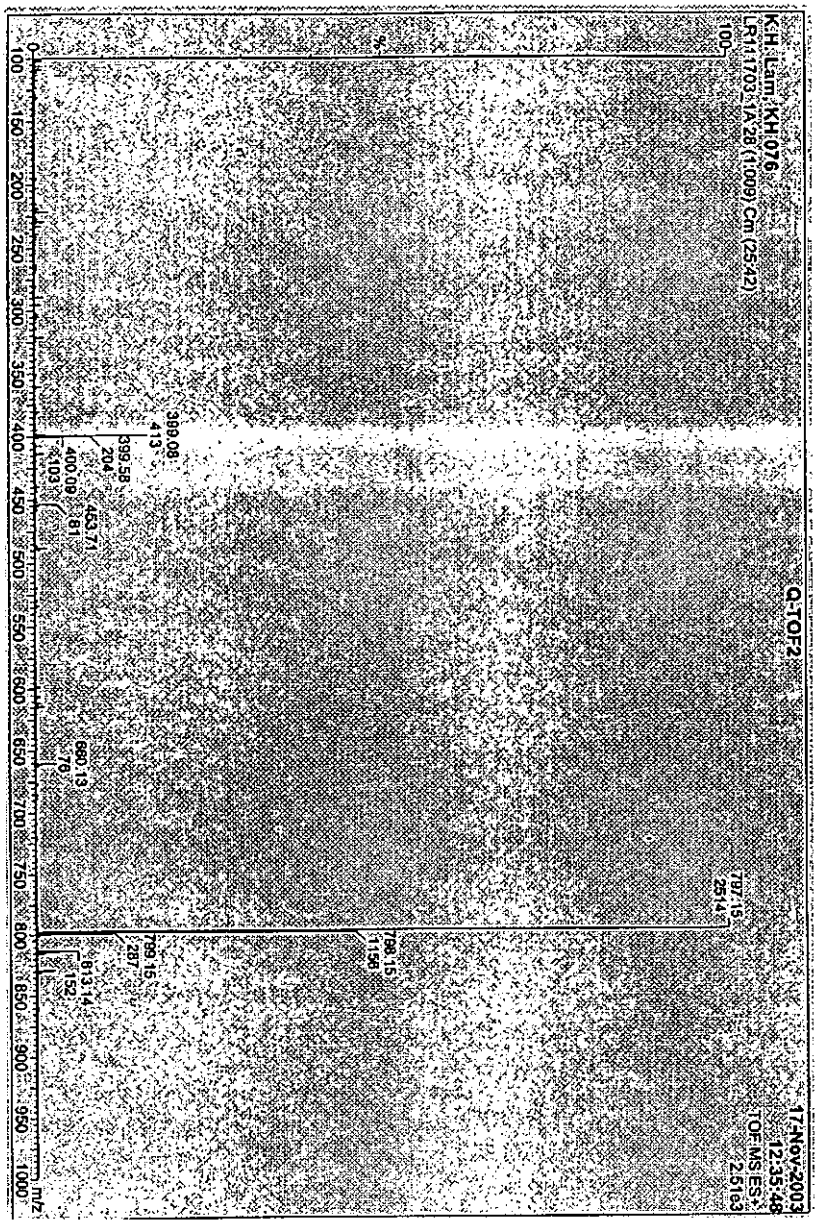
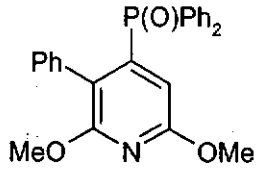


Figure A-62 ESI-MS spectrum of (S) - 2,2'6,6' – tetramethoxy - 5,5' – diphenyl - 4,4' – diphenyl – phosphino - 3,3'- bipyridine (*S*-78)

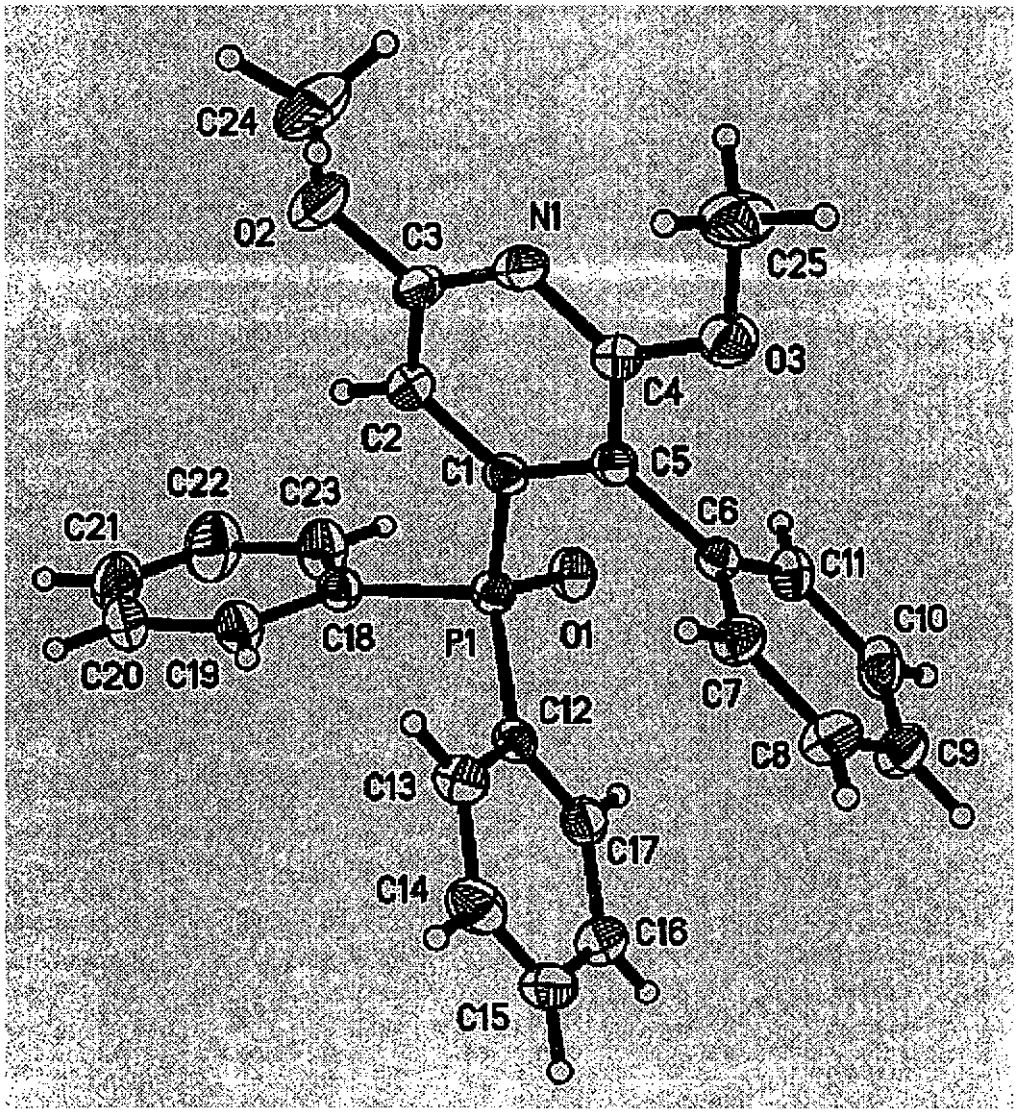
Appendix II

X-ray structures and data

a.) 2, 6-dimethoxy-3-phenyl -4-diphenylphosphinylpyridine (rac-76)



rac-76



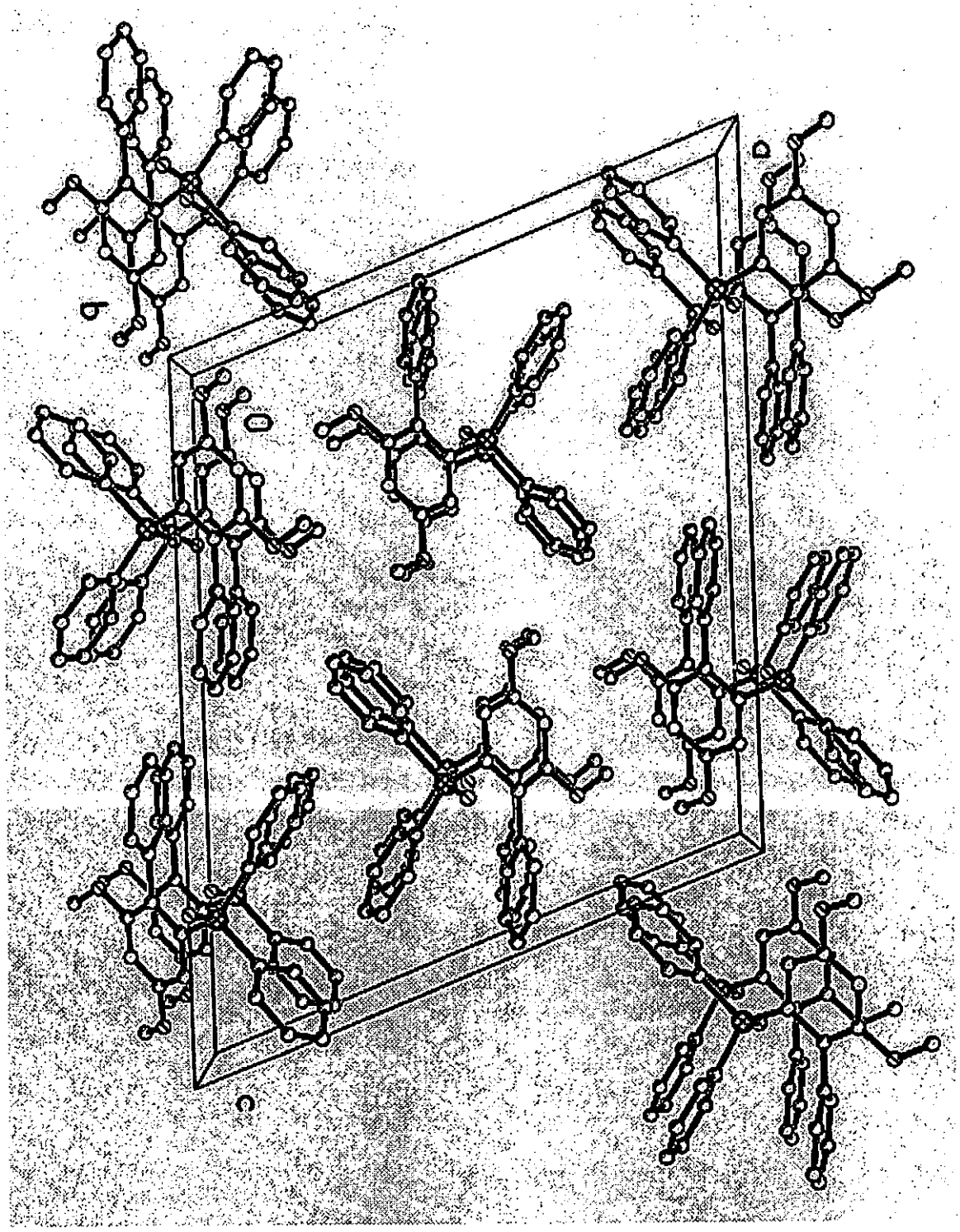

b
a
c

Table 1. Crystal data and structure refinement for ABClkh7. (4/7-2003)

Identification code	lkh7	
Empirical formula	C_{25} H_{22} N O_3 P	
Formula weight	415.41	
Temperature	294(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 17.972(4) Å	= 90°.
	b = 6.1067(12) Å	= 110.638(4)°.
	c = 20.962(4) Å	= 90°.
Volume	2152.9(7) $Å^3$	
Z	4	
Density (calculated)	1.282 Mg/m^3	
Absorption coefficient	0.154 mm^{-1}	
F(000)	872	
Crystal size	0.46 x 0.26 x 0.12 mm^3	
Theta range for data collection	1.29 to 27.53°.	
Index ranges	-21<=h<=23, -7<=k<=7, -27<=l<=23	
Reflections collected	13940	
Independent reflections	4923 [R(int) = 0.0423]	
Completeness to theta = 27.53°	99.4 %	
Absorption correction	Multi scans	
Max. and min. transmission	0.9818 and 0.9326	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4923 / 0 / 273	
Goodness-of-fit on F^2	1.032	
Final R indices [I>2sigma(I)]	R1 = 0.0464, wR2 = 0.1019	
R indices (all data)	R1 = 0.0934, wR2 = 0.1179	
Largest diff. peak and hole	0.302 and -0.374 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for lkh7. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
P(1)	9530(1)	174(1)	2190(1)	38(1)
O(1)	9905(1)	-1956(2)	2442(1)	49(1)
O(2)	10731(1)	5241(3)	865(1)	73(1)
O(3)	11835(1)	5651(3)	3202(1)	58(1)
N(1)	11293(1)	5459(3)	2038(1)	46(1)
C(1)	10232(1)	2273(3)	2145(1)	36(1)
C(2)	10234(1)	2951(3)	1511(1)	45(1)
C(3)	10763(1)	4568(4)	1491(1)	48(1)
C(4)	11290(1)	4775(3)	2636(1)	41(1)
C(5)	10776(1)	3205(3)	2737(1)	36(1)
C(6)	10778(1)	2751(3)	3436(1)	37(1)
C(7)	10542(1)	4396(4)	3776(1)	48(1)
C(8)	10486(1)	4021(4)	4405(1)	60(1)
C(9)	10665(1)	1992(4)	4706(1)	60(1)
C(10)	10919(1)	362(4)	4385(1)	56(1)
C(11)	10980(1)	724(3)	3748(1)	47(1)
C(12)	8983(1)	1267(3)	2696(1)	38(1)
C(13)	8682(1)	3387(3)	2634(1)	49(1)
C(14)	8225(1)	4026(4)	3011(1)	60(1)
C(15)	8081(1)	2600(5)	3461(1)	64(1)
C(16)	8390(1)	510(4)	3534(1)	63(1)
C(17)	8839(1)	-151(4)	3154(1)	48(1)
C(18)	8822(1)	-85(3)	1328(1)	42(1)
C(19)	8264(1)	1491(4)	998(1)	56(1)
C(20)	7739(1)	1164(5)	345(1)	67(1)
C(21)	7760(2)	-731(5)	12(1)	76(1)
C(22)	8301(2)	-2310(5)	324(1)	87(1)
C(23)	8831(2)	-1986(4)	984(1)	65(1)
C(24)	11165(2)	7178(5)	830(1)	95(1)
C(25)	12374(2)	7247(4)	3107(1)	77(1)

Table 3. Bond lengths [Å] and angles [°] for lkh7.

P(1)-O(1)	1.4743(14)
P(1)-C(12)	1.810(2)
P(1)-C(18)	1.813(2)
P(1)-C(1)	1.823(2)
O(2)-C(3)	1.358(2)
O(2)-C(24)	1.433(3)
O(3)-C(4)	1.355(2)
O(3)-C(25)	1.438(2)
N(1)-C(3)	1.321(3)
N(1)-C(4)	1.323(2)
C(1)-C(2)	1.392(3)
C(1)-C(5)	1.402(3)
C(2)-C(3)	1.382(3)
C(2)-H(2)	0.9300
C(4)-C(5)	1.398(3)
C(5)-C(6)	1.491(3)
C(6)-C(7)	1.382(3)
C(6)-C(11)	1.387(3)
C(7)-C(8)	1.377(3)
C(7)-H(7)	0.9300
C(8)-C(9)	1.376(3)
C(8)-H(8)	0.9300
C(9)-C(10)	1.368(3)
C(9)-H(9)	0.9300
C(10)-C(11)	1.393(3)
C(10)-H(10)	0.9300
C(11)-H(11)	0.9300
C(12)-C(17)	1.384(3)
C(12)-C(13)	1.392(3)
C(13)-C(14)	1.380(3)
C(13)-H(13)	0.9300
C(14)-C(15)	1.375(3)
C(14)-H(14)	0.9300
C(15)-C(16)	1.379(3)

C(15)-H(15)	0.9300
C(16)-C(17)	1.377(3)
C(16)-H(16)	0.9300
C(17)-H(17)	0.9300
C(18)-C(23)	1.371(3)
C(18)-C(19)	1.386(3)
C(19)-C(20)	1.377(3)
C(19)-H(19)	0.9300
C(20)-C(21)	1.359(4)
C(20)-H(20)	0.9300
C(21)-C(22)	1.361(4)
C(21)-H(21)	0.9300
C(22)-C(23)	1.390(3)
C(22)-H(22)	0.9300
C(23)-H(23)	0.9300
C(24)-H(24A)	0.9600
C(24)-H(24B)	0.9600
C(24)-H(24C)	0.9600
C(25)-H(25A)	0.9600
C(25)-H(25B)	0.9600
C(25)-H(25C)	0.9600

O(1)-P(1)-C(12)	112.86(9)
O(1)-P(1)-C(18)	110.58(9)
C(12)-P(1)-C(18)	106.29(9)
O(1)-P(1)-C(1)	113.73(9)
C(12)-P(1)-C(1)	107.42(9)
C(18)-P(1)-C(1)	105.42(9)
C(3)-O(2)-C(24)	117.5(2)
C(4)-O(3)-C(25)	117.39(17)
C(3)-N(1)-C(4)	116.70(18)
C(2)-C(1)-C(5)	119.16(18)
C(2)-C(1)-P(1)	119.49(15)
C(5)-C(1)-P(1)	121.34(14)
C(3)-C(2)-C(1)	118.36(19)
C(3)-C(2)-H(2)	120.8

C(1)-C(2)-H(2)	120.8
N(1)-C(3)-O(2)	119.1(2)
N(1)-C(3)-C(2)	124.14(19)
O(2)-C(3)-C(2)	116.8(2)
N(1)-C(4)-O(3)	117.62(18)
N(1)-C(4)-C(5)	125.66(18)
O(3)-C(4)-C(5)	116.72(17)
C(4)-C(5)-C(1)	115.94(17)
C(4)-C(5)-C(6)	120.26(17)
C(1)-C(5)-C(6)	123.56(17)
C(7)-C(6)-C(11)	118.80(18)
C(7)-C(6)-C(5)	118.51(17)
C(11)-C(6)-C(5)	122.65(18)
C(8)-C(7)-C(6)	120.8(2)
C(8)-C(7)-H(7)	119.6
C(6)-C(7)-H(7)	119.6
C(7)-C(8)-C(9)	120.3(2)
C(7)-C(8)-H(8)	119.8
C(9)-C(8)-H(8)	119.8
C(10)-C(9)-C(8)	119.6(2)
C(10)-C(9)-H(9)	120.2
C(8)-C(9)-H(9)	120.2
C(9)-C(10)-C(11)	120.5(2)
C(9)-C(10)-H(10)	119.7
C(11)-C(10)-H(10)	119.7
C(6)-C(11)-C(10)	119.9(2)
C(6)-C(11)-H(11)	120.1
C(10)-C(11)-H(11)	120.1
C(17)-C(12)-C(13)	119.01(19)
C(17)-C(12)-P(1)	116.75(16)
C(13)-C(12)-P(1)	124.21(16)
C(14)-C(13)-C(12)	120.0(2)
C(14)-C(13)-H(13)	120.0
C(12)-C(13)-H(13)	120.0
C(15)-C(14)-C(13)	120.5(2)
C(15)-C(14)-H(14)	119.7

C(13)-C(14)-H(14)	119.7
C(14)-C(15)-C(16)	119.7(2)
C(14)-C(15)-H(15)	120.1
C(16)-C(15)-H(15)	120.1
C(17)-C(16)-C(15)	120.2(2)
C(17)-C(16)-H(16)	119.9
C(15)-C(16)-H(16)	119.9
C(16)-C(17)-C(12)	120.5(2)
C(16)-C(17)-H(17)	119.7
C(12)-C(17)-H(17)	119.7
C(23)-C(18)-C(19)	117.8(2)
C(23)-C(18)-P(1)	117.66(17)
C(19)-C(18)-P(1)	124.53(17)
C(20)-C(19)-C(18)	121.2(2)
C(20)-C(19)-H(19)	119.4
C(18)-C(19)-H(19)	119.4
C(21)-C(20)-C(19)	120.0(2)
C(21)-C(20)-H(20)	120.0
C(19)-C(20)-H(20)	120.0
C(20)-C(21)-C(22)	120.1(2)
C(20)-C(21)-H(21)	120.0
C(22)-C(21)-H(21)	120.0
C(21)-C(22)-C(23)	120.0(3)
C(21)-C(22)-H(22)	120.0
C(23)-C(22)-H(22)	120.0
C(18)-C(23)-C(22)	120.9(2)
C(18)-C(23)-H(23)	119.6
C(22)-C(23)-H(23)	119.6
O(2)-C(24)-H(24A)	109.5
O(2)-C(24)-H(24B)	109.5
H(24A)-C(24)-H(24B)	109.5
O(2)-C(24)-H(24C)	109.5
H(24A)-C(24)-H(24C)	109.5
H(24B)-C(24)-H(24C)	109.5
O(3)-C(25)-H(25A)	109.5
O(3)-C(25)-H(25B)	109.5

H(25A)-C(25)-H(25B)	109.5
O(3)-C(25)-H(25C)	109.5
H(25A)-C(25)-H(25C)	109.5
H(25B)-C(25)-H(25C)	109.5

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for lkh7. The anisotropic displacement factor exponent takes the form: $-2\ ^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
P(1)	38(1)	34(1)	41(1)	4(1)	13(1)	4(1)
O(1)	54(1)	36(1)	52(1)	6(1)	13(1)	11(1)
O(2)	85(1)	91(1)	51(1)	18(1)	35(1)	-10(1)
O(3)	54(1)	68(1)	55(1)	-5(1)	23(1)	-24(1)
N(1)	46(1)	49(1)	52(1)	6(1)	28(1)	0(1)
C(1)	34(1)	37(1)	42(1)	5(1)	17(1)	6(1)
C(2)	44(1)	54(1)	40(1)	2(1)	17(1)	2(1)
C(3)	49(1)	59(2)	45(1)	12(1)	28(1)	7(1)
C(4)	39(1)	44(1)	44(1)	0(1)	19(1)	-1(1)
C(5)	36(1)	35(1)	41(1)	6(1)	16(1)	5(1)
C(6)	32(1)	41(1)	38(1)	3(1)	12(1)	-1(1)
C(7)	54(1)	45(1)	49(1)	7(1)	25(1)	3(1)
C(8)	72(2)	65(2)	55(2)	1(1)	35(1)	3(1)
C(9)	64(2)	76(2)	42(1)	10(1)	21(1)	-8(1)
C(10)	55(2)	52(2)	48(1)	17(1)	3(1)	-4(1)
C(11)	46(1)	44(1)	43(1)	4(1)	8(1)	3(1)
C(12)	33(1)	39(1)	41(1)	2(1)	10(1)	-2(1)
C(13)	49(1)	42(1)	59(1)	2(1)	22(1)	1(1)
C(14)	50(1)	58(2)	72(2)	-12(1)	20(1)	6(1)
C(15)	49(2)	91(2)	58(2)	-9(2)	26(1)	1(1)
C(16)	54(2)	86(2)	52(1)	13(1)	24(1)	-1(1)
C(17)	42(1)	52(1)	47(1)	7(1)	13(1)	0(1)
C(18)	39(1)	42(1)	44(1)	3(1)	15(1)	0(1)
C(19)	51(1)	57(2)	54(1)	3(1)	12(1)	8(1)
C(20)	47(2)	91(2)	55(2)	18(2)	7(1)	7(1)
C(21)	70(2)	101(2)	46(2)	-2(2)	9(1)	-15(2)
C(22)	105(2)	83(2)	59(2)	-23(2)	11(2)	1(2)
C(23)	74(2)	57(2)	55(2)	-8(1)	11(1)	8(1)
C(24)	124(3)	93(2)	84(2)	33(2)	58(2)	-13(2)
C(25)	75(2)	87(2)	82(2)	-21(2)	42(2)	-43(2)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for lkh7.

	x	y	z	U(eq)
H(2)	9888	2331	1112	54
H(7)	10420	5774	3578	57
H(8)	10326	5144	4628	72
H(9)	10613	1731	5126	72
H(10)	11053	-999	4593	67
H(11)	11154	-391	3534	56
H(13)	8788	4373	2339	59
H(14)	8014	5432	2959	72
H(15)	7776	3043	3716	77
H(16)	8295	-456	3839	75
H(17)	9047	-1562	3207	57
H(19)	8245	2793	1222	67
H(20)	7369	2241	131	81
H(21)	7406	-949	-430	91
H(22)	8314	-3607	95	105
H(23)	9198	-3074	1194	78
H(24A)	11014	8352	1063	142
H(24B)	11047	7575	361	142
H(24C)	11724	6904	1041	142
H(25A)	12681	6592	2864	116
H(25B)	12724	7753	3543	116
H(25C)	12078	8462	2850	116

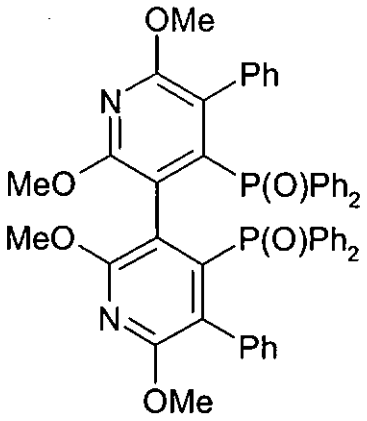
Table 6. Torsion angles [°] for lkh7.

O(1)-P(1)-C(1)-C(2)	108.42(16)
C(12)-P(1)-C(1)-C(2)	-125.94(16)
C(18)-P(1)-C(1)-C(2)	-12.89(18)
O(1)-P(1)-C(1)-C(5)	-70.83(17)
C(12)-P(1)-C(1)-C(5)	54.82(17)
C(18)-P(1)-C(1)-C(5)	167.87(15)
C(5)-C(1)-C(2)-C(3)	-1.7(3)
P(1)-C(1)-C(2)-C(3)	179.04(15)
C(4)-N(1)-C(3)-O(2)	178.81(18)
C(4)-N(1)-C(3)-C(2)	-1.9(3)
C(24)-O(2)-C(3)-N(1)	-12.1(3)
C(24)-O(2)-C(3)-C(2)	168.6(2)
C(1)-C(2)-C(3)-N(1)	2.9(3)
C(1)-C(2)-C(3)-O(2)	-177.85(18)
C(3)-N(1)-C(4)-O(3)	179.33(18)
C(3)-N(1)-C(4)-C(5)	-0.2(3)
C(25)-O(3)-C(4)-N(1)	-0.3(3)
C(25)-O(3)-C(4)-C(5)	179.20(19)
N(1)-C(4)-C(5)-C(1)	1.1(3)
O(3)-C(4)-C(5)-C(1)	-178.35(17)
N(1)-C(4)-C(5)-C(6)	-173.47(19)
O(3)-C(4)-C(5)-C(6)	7.0(3)
C(2)-C(1)-C(5)-C(4)	-0.1(3)
P(1)-C(1)-C(5)-C(4)	179.12(14)
C(2)-C(1)-C(5)-C(6)	174.28(18)
P(1)-C(1)-C(5)-C(6)	-6.5(3)
C(4)-C(5)-C(6)-C(7)	64.9(3)
C(1)-C(5)-C(6)-C(7)	-109.3(2)
C(4)-C(5)-C(6)-C(11)	-117.4(2)
C(1)-C(5)-C(6)-C(11)	68.4(3)
C(11)-C(6)-C(7)-C(8)	-1.8(3)
C(5)-C(6)-C(7)-C(8)	176.00(19)
C(6)-C(7)-C(8)-C(9)	0.0(3)
C(7)-C(8)-C(9)-C(10)	1.7(4)

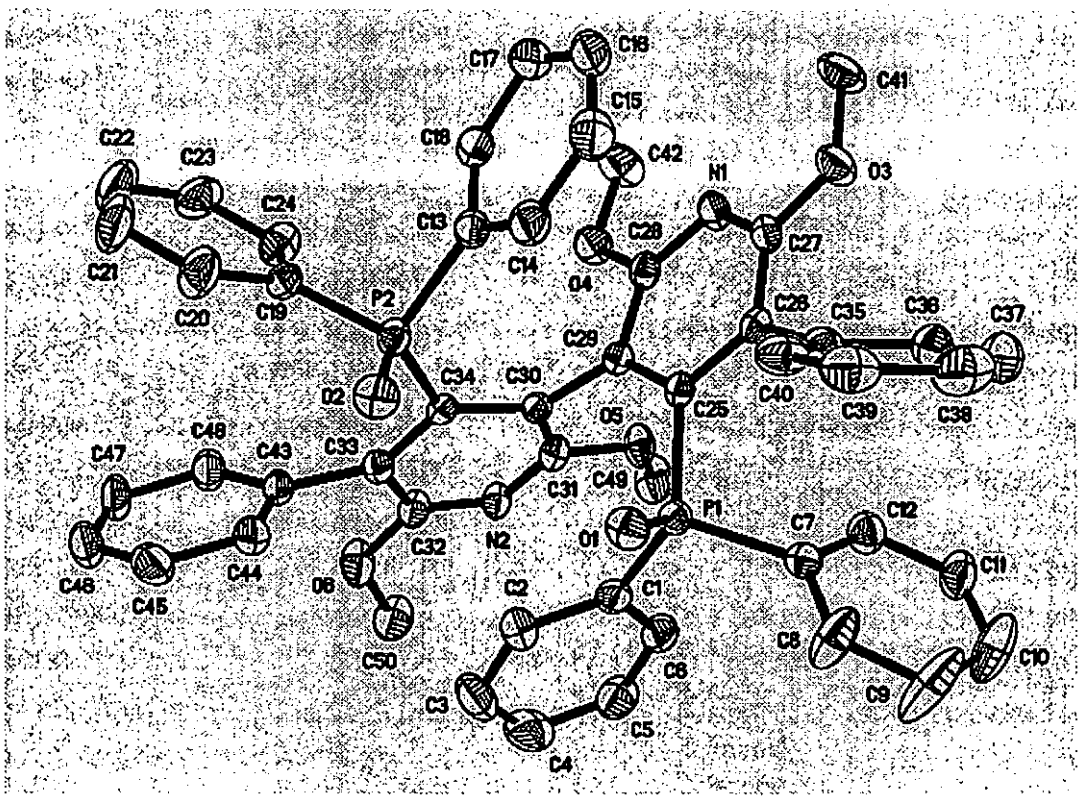
C(8)-C(9)-C(10)-C(11)	-1.6(3)
C(7)-C(6)-C(11)-C(10)	1.9(3)
C(5)-C(6)-C(11)-C(10)	-175.83(19)
C(9)-C(10)-C(11)-C(6)	-0.2(3)
O(1)-P(1)-C(12)-C(17)	-12.81(18)
C(18)-P(1)-C(12)-C(17)	108.57(16)
C(1)-P(1)-C(12)-C(17)	-138.97(15)
O(1)-P(1)-C(12)-C(13)	169.48(16)
C(18)-P(1)-C(12)-C(13)	-69.14(19)
C(1)-P(1)-C(12)-C(13)	43.31(19)
C(17)-C(12)-C(13)-C(14)	-2.1(3)
P(1)-C(12)-C(13)-C(14)	175.57(16)
C(12)-C(13)-C(14)-C(15)	1.7(3)
C(13)-C(14)-C(15)-C(16)	-0.5(4)
C(14)-C(15)-C(16)-C(17)	-0.3(4)
C(15)-C(16)-C(17)-C(12)	-0.2(3)
C(13)-C(12)-C(17)-C(16)	1.4(3)
P(1)-C(12)-C(17)-C(16)	-176.48(17)
O(1)-P(1)-C(18)-C(23)	-12.2(2)
C(12)-P(1)-C(18)-C(23)	-135.04(18)
C(1)-P(1)-C(18)-C(23)	111.12(18)
O(1)-P(1)-C(18)-C(19)	166.80(18)
C(12)-P(1)-C(18)-C(19)	44.0(2)
C(1)-P(1)-C(18)-C(19)	-69.9(2)
C(23)-C(18)-C(19)-C(20)	-0.2(3)
P(1)-C(18)-C(19)-C(20)	-179.23(18)
C(18)-C(19)-C(20)-C(21)	0.0(4)
C(19)-C(20)-C(21)-C(22)	0.1(4)
C(20)-C(21)-C(22)-C(23)	0.0(5)
C(19)-C(18)-C(23)-C(22)	0.3(4)
P(1)-C(18)-C(23)-C(22)	179.4(2)
C(21)-C(22)-C(23)-C(18)	-0.2(4)

Symmetry transformations used to generate equivalent atoms:

b.) **2,2',6,6'-tetramethoxy-5,5'-diphhenyl-4,4'-diphenylphosphinoyl- 3,3'-bipyridine (rac-77)**



rac-77



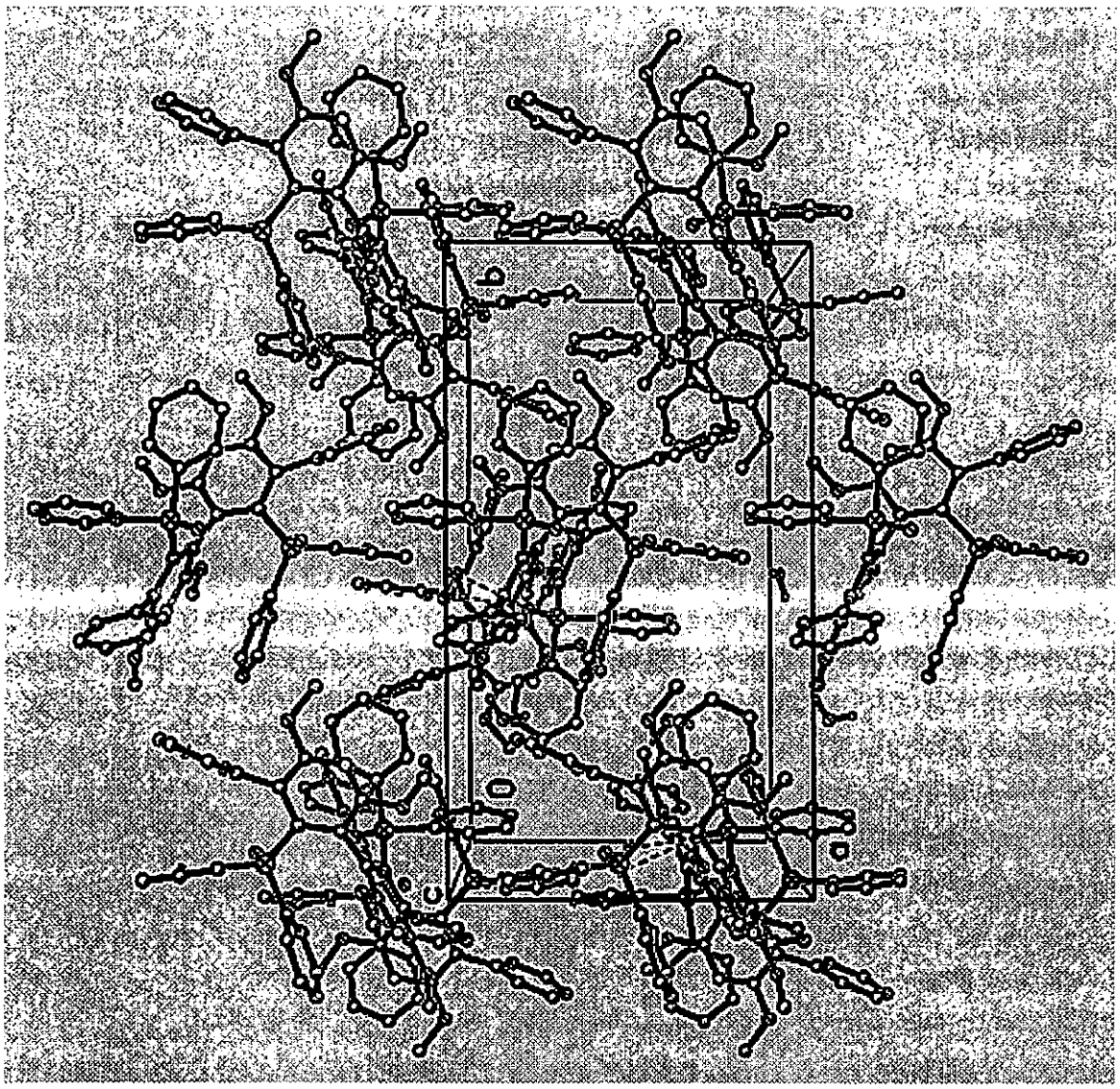

b
c

Table 1. Crystal data and structure refinement for abclkh5. (17/6-2003)

Identification code	lkh5	
Empirical formula	$C_{50} H_{42} N_2 O_6 P_2 \cdot 2H_2O$	
Formula weight	864.83	
Temperature	294(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 11.5524(16) Å	= 90°.
	b = 20.349(3) Å	= 90°.
	c = 20.474(3) Å	= 90°.
Volume	4813.0(11) $Å^3$	
Z	4	
Density (calculated)	1.194 Mg/m^3	
Absorption coefficient	0.143 mm^{-1}	
F(000)	1816	
Crystal size	0.48 x 0.30 x 0.20 mm^3	
Theta range for data collection	2.03 to 27.56°.	
Index ranges	-15<=h<=14, -26<=k<=23, -25<=l<=26	
Reflections collected	32648	
Independent reflections	11007 [R(int) = 0.0656]	
Completeness to theta = 27.56°	99.1 %	
Absorption correction	Multi scans	
Max. and min. transmission	0.9719 and 0.9344	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	11007 / 108 / 560	
Goodness-of-fit on F^2	1.042	
Final R indices [I>2sigma(I)]	R1 = 0.0765, wR2 = 0.2080	
R indices (all data)	R1 = 0.1399, wR2 = 0.2394	
Absolute structure parameter	0.11(14)	
Largest diff. peak and hole	0.980 and -0.698 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for lkh5. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
P(1)	2061(1)	5809(1)	7987(1)	36(1)
P(2)	5277(1)	5381(1)	6812(1)	39(1)
O(1)	2960(3)	5658(2)	8472(1)	48(1)
O(2)	5656(3)	5484(2)	7497(2)	54(1)
O(3)	774(3)	3600(2)	7022(2)	58(1)
O(4)	2404(3)	5045(2)	5580(1)	49(1)
O(5)	1317(2)	6330(2)	6070(2)	49(1)
O(6)	4453(3)	7694(2)	5923(2)	67(1)
C(1)	2239(3)	6644(2)	7685(2)	44(1)
C(2)	3321(4)	6932(2)	7767(2)	55(1)
C(3)	3488(5)	7594(2)	7642(3)	74(2)
C(4)	2554(4)	7960(3)	7439(3)	82(2)
C(5)	1483(5)	7683(2)	7333(3)	64(2)
C(6)	1334(4)	7028(2)	7469(2)	50(1)
C(7)	614(3)	5824(2)	8320(2)	42(1)
C(8)	524(4)	5976(4)	8978(2)	81(2)
C(9)	-564(4)	6070(5)	9249(3)	123(3)
C(10)	-1546(5)	5975(4)	8890(3)	94(2)
C(11)	-1458(4)	5838(3)	8237(2)	62(1)
C(12)	-384(3)	5765(2)	7955(2)	53(1)
C(13)	4657(4)	4580(2)	6713(2)	43(1)
C(14)	4338(4)	4234(2)	7268(2)	53(1)
C(15)	3905(5)	3602(2)	7238(3)	72(2)
C(16)	3819(5)	3294(3)	6641(3)	73(2)
C(17)	4158(4)	3609(2)	6069(3)	68(2)
C(18)	4550(4)	4261(2)	6114(2)	55(1)
C(19)	6476(3)	5368(2)	6246(2)	44(1)
C(20)	7569(3)	5288(3)	6482(3)	71(2)
C(21)	8511(4)	5225(4)	6079(3)	86(2)
C(22)	8381(4)	5255(3)	5419(3)	85(2)
C(23)	7303(4)	5352(3)	5175(3)	74(2)

C(24)	6346(4)	5420(2)	5574(2)	57(1)
C(25)	2001(3)	5212(2)	7316(2)	34(1)
C(26)	1447(3)	4607(2)	7451(2)	38(1)
C(27)	1244(3)	4194(2)	6902(2)	38(1)
N(1)	1510(3)	4347(2)	6294(2)	42(1)
C(28)	2075(4)	4902(2)	6192(2)	38(1)
C(29)	2409(3)	5357(2)	6683(2)	34(1)
C(30)	3077(3)	5929(2)	6470(2)	32(1)
C(31)	2461(3)	6438(2)	6156(2)	40(1)
N(2)	2891(3)	7000(2)	5960(2)	42(1)
C(32)	4003(3)	7094(2)	6062(2)	45(1)
C(33)	4772(4)	6631(2)	6337(2)	41(1)
C(34)	4283(3)	6022(2)	6518(2)	34(1)
C(35)	1129(3)	4360(2)	8114(2)	43(1)
C(36)	11(4)	4177(2)	8269(2)	60(1)
C(37)	-260(5)	3920(3)	8867(2)	81(2)
C(38)	587(5)	3832(3)	9324(3)	83(2)
C(39)	1694(5)	3997(3)	9181(2)	69(2)
C(40)	1970(5)	4258(2)	8578(2)	58(1)
C(41)	638(6)	3159(3)	6474(3)	71(2)
C(42)	2016(5)	4622(3)	5076(2)	69(2)
C(43)	5993(3)	6843(2)	6444(2)	42(1)
C(44)	6449(4)	6882(2)	7066(2)	52(1)
C(45)	7547(4)	7131(2)	7160(3)	64(2)
C(46)	8175(4)	7357(3)	6645(2)	71(2)
C(47)	7746(4)	7324(3)	6024(3)	68(2)
C(48)	6669(3)	7061(2)	5930(2)	54(1)
C(49)	677(4)	6805(3)	5681(3)	68(2)
C(50)	3679(5)	8223(3)	5772(3)	69(2)
O(1W)	5166(5)	5052(3)	8820(3)	134(2)
O(2W)	6249(8)	2511(5)	5616(3)	214

Table 3. Bond lengths [Å] and angles [°] for lkh5.

P(1)-O(1)	1.470(3)
P(1)-C(7)	1.806(4)
P(1)-C(1)	1.819(4)
P(1)-C(25)	1.835(4)
P(2)-O(2)	1.483(3)
P(2)-C(13)	1.792(4)
P(2)-C(19)	1.806(4)
P(2)-C(34)	1.840(4)
O(3)-C(27)	1.349(5)
O(3)-C(41)	1.444(6)
O(4)-C(28)	1.341(4)
O(4)-C(42)	1.417(5)
O(5)-C(31)	1.352(5)
O(5)-C(49)	1.455(6)
O(6)-C(32)	1.358(5)
O(6)-C(50)	1.433(6)
C(1)-C(6)	1.379(5)
C(1)-C(2)	1.392(5)
C(2)-C(3)	1.383(5)
C(2)-H(2)	0.9300
C(3)-C(4)	1.376(6)
C(3)-H(3)	0.9300
C(4)-C(5)	1.378(5)
C(4)-H(4)	0.9300
C(5)-C(6)	1.371(5)
C(5)-H(5)	0.9300
C(6)-H(6)	0.9300
C(7)-C(12)	1.378(5)
C(7)-C(8)	1.388(5)
C(8)-C(9)	1.386(5)
C(8)-H(8)	0.9300
C(9)-C(10)	1.366(6)
C(9)-H(9)	0.9300
C(10)-C(11)	1.369(5)

C(10)-H(10)	0.9300
C(11)-C(12)	1.377(5)
C(11)-H(11)	0.9300
C(12)-H(12)	0.9300
C(13)-C(14)	1.386(5)
C(13)-C(18)	1.393(5)
C(14)-C(15)	1.381(5)
C(14)-H(14)	0.9300
C(15)-C(16)	1.378(5)
C(15)-H(15)	0.9300
C(16)-C(17)	1.391(5)
C(16)-H(16)	0.9300
C(17)-C(18)	1.404(5)
C(17)-H(17)	0.9300
C(18)-H(18)	0.9300
C(19)-C(20)	1.363(5)
C(19)-C(24)	1.388(5)
C(20)-C(21)	1.372(5)
C(20)-H(20)	0.9300
C(21)-C(22)	1.360(6)
C(21)-H(21)	0.9300
C(22)-C(23)	1.356(6)
C(22)-H(22)	0.9300
C(23)-C(24)	1.381(5)
C(23)-H(23)	0.9300
C(24)-H(24)	0.9300
C(25)-C(29)	1.411(4)
C(25)-C(26)	1.416(4)
C(26)-C(27)	1.422(4)
C(26)-C(35)	1.494(5)
C(27)-N(1)	1.320(4)
N(1)-C(28)	1.319(4)
C(28)-C(29)	1.419(5)
C(29)-C(30)	1.463(5)
C(30)-C(34)	1.409(4)
C(30)-C(31)	1.413(4)

C(31)-N(2)	1.309(4)
N(2)-C(32)	1.316(4)
C(32)-C(33)	1.413(5)
C(33)-C(34)	1.411(4)
C(33)-C(43)	1.491(6)
C(35)-C(40)	1.375(5)
C(35)-C(36)	1.382(5)
C(36)-C(37)	1.368(5)
C(36)-H(36)	0.9300
C(37)-C(38)	1.366(6)
C(37)-H(37)	0.9300
C(38)-C(39)	1.355(6)
C(38)-H(38)	0.9300
C(39)-C(40)	1.380(5)
C(39)-H(39)	0.9300
C(40)-H(40)	0.9300
C(41)-H(41A)	0.9600
C(41)-H(41B)	0.9600
C(41)-H(41C)	0.9600
C(42)-H(42A)	0.9600
C(42)-H(42B)	0.9600
C(42)-H(42C)	0.9600
C(43)-C(44)	1.382(5)
C(43)-C(48)	1.383(5)
C(44)-C(45)	1.380(5)
C(44)-H(44)	0.9300
C(45)-C(46)	1.360(5)
C(45)-H(45)	0.9300
C(46)-C(47)	1.367(6)
C(46)-H(46)	0.9300
C(47)-C(48)	1.368(5)
C(47)-H(47)	0.9300
C(48)-H(48)	0.9300
C(49)-H(49A)	0.9600
C(49)-H(49B)	0.9600
C(49)-H(49C)	0.9600

C(50)-H(50A)	0.9600
C(50)-H(50B)	0.9600
C(50)-H(50C)	0.9600
O(1W)-H(1WA)	0.8501
O(1W)-H(1WB)	0.8501
O(2W)-H(2WA)	0.8500
O(2W)-H(2WB)	0.8501

O(1)-P(1)-C(7)	113.78(18)
O(1)-P(1)-C(1)	110.22(18)
C(7)-P(1)-C(1)	102.55(19)
O(1)-P(1)-C(25)	113.19(18)
C(7)-P(1)-C(25)	104.96(18)
C(1)-P(1)-C(25)	111.58(17)
O(2)-P(2)-C(13)	110.63(18)
O(2)-P(2)-C(19)	112.50(19)
C(13)-P(2)-C(19)	102.80(19)
O(2)-P(2)-C(34)	113.19(18)
C(13)-P(2)-C(34)	111.01(18)
C(19)-P(2)-C(34)	106.17(17)
C(27)-O(3)-C(41)	117.3(3)
C(28)-O(4)-C(42)	117.3(3)
C(31)-O(5)-C(49)	117.3(3)
C(32)-O(6)-C(50)	118.8(4)
C(6)-C(1)-C(2)	118.7(4)
C(6)-C(1)-P(1)	123.6(3)
C(2)-C(1)-P(1)	117.0(3)
C(3)-C(2)-C(1)	120.9(4)
C(3)-C(2)-H(2)	119.5
C(1)-C(2)-H(2)	119.5
C(4)-C(3)-C(2)	118.3(5)
C(4)-C(3)-H(3)	120.8
C(2)-C(3)-H(3)	120.8
C(3)-C(4)-C(5)	122.0(5)
C(3)-C(4)-H(4)	119.0
C(5)-C(4)-H(4)	119.0

C(6)-C(5)-C(4)	118.7(5)
C(6)-C(5)-H(5)	120.7
C(4)-C(5)-H(5)	120.7
C(5)-C(6)-C(1)	121.4(4)
C(5)-C(6)-H(6)	119.3
C(1)-C(6)-H(6)	119.3
C(12)-C(7)-C(8)	118.9(4)
C(12)-C(7)-P(1)	124.7(3)
C(8)-C(7)-P(1)	116.1(3)
C(9)-C(8)-C(7)	119.1(5)
C(9)-C(8)-H(8)	120.5
C(7)-C(8)-H(8)	120.5
C(10)-C(9)-C(8)	121.2(5)
C(10)-C(9)-H(9)	119.4
C(8)-C(9)-H(9)	119.4
C(9)-C(10)-C(11)	119.5(5)
C(9)-C(10)-H(10)	120.2
C(11)-C(10)-H(10)	120.2
C(10)-C(11)-C(12)	119.9(5)
C(10)-C(11)-H(11)	120.1
C(12)-C(11)-H(11)	120.1
C(11)-C(12)-C(7)	121.1(4)
C(11)-C(12)-H(12)	119.4
C(7)-C(12)-H(12)	119.4
C(14)-C(13)-C(18)	117.5(4)
C(14)-C(13)-P(2)	118.4(3)
C(18)-C(13)-P(2)	123.9(3)
C(15)-C(14)-C(13)	122.1(4)
C(15)-C(14)-H(14)	118.9
C(13)-C(14)-H(14)	118.9
C(16)-C(15)-C(14)	119.3(5)
C(16)-C(15)-H(15)	120.4
C(14)-C(15)-H(15)	120.4
C(15)-C(16)-C(17)	121.1(5)
C(15)-C(16)-H(16)	119.4
C(17)-C(16)-H(16)	119.4

C(16)-C(17)-C(18)	118.1(5)
C(16)-C(17)-H(17)	121.0
C(18)-C(17)-H(17)	121.0
C(13)-C(18)-C(17)	121.8(4)
C(13)-C(18)-H(18)	119.1
C(17)-C(18)-H(18)	119.1
C(20)-C(19)-C(24)	117.5(4)
C(20)-C(19)-P(2)	119.0(3)
C(24)-C(19)-P(2)	123.5(3)
C(19)-C(20)-C(21)	122.1(5)
C(19)-C(20)-H(20)	118.9
C(21)-C(20)-H(20)	118.9
C(22)-C(21)-C(20)	120.4(5)
C(22)-C(21)-H(21)	119.8
C(20)-C(21)-H(21)	119.8
C(23)-C(22)-C(21)	118.2(5)
C(23)-C(22)-H(22)	120.9
C(21)-C(22)-H(22)	120.9
C(22)-C(23)-C(24)	122.2(5)
C(22)-C(23)-H(23)	118.9
C(24)-C(23)-H(23)	118.9
C(23)-C(24)-C(19)	119.5(5)
C(23)-C(24)-H(24)	120.3
C(19)-C(24)-H(24)	120.3
C(29)-C(25)-C(26)	120.7(3)
C(29)-C(25)-P(1)	122.5(3)
C(26)-C(25)-P(1)	116.6(2)
C(25)-C(26)-C(27)	115.8(3)
C(25)-C(26)-C(35)	125.5(3)
C(27)-C(26)-C(35)	118.7(3)
N(1)-C(27)-O(3)	118.5(3)
N(1)-C(27)-C(26)	124.6(3)
O(3)-C(27)-C(26)	116.8(3)
C(28)-N(1)-C(27)	117.7(3)
N(1)-C(28)-O(4)	118.2(3)
N(1)-C(28)-C(29)	125.5(3)

O(4)-C(28)-C(29)	116.3(3)
C(25)-C(29)-C(28)	115.1(3)
C(25)-C(29)-C(30)	128.0(3)
C(28)-C(29)-C(30)	116.8(3)
C(34)-C(30)-C(31)	115.5(3)
C(34)-C(30)-C(29)	127.5(3)
C(31)-C(30)-C(29)	117.0(3)
N(2)-C(31)-O(5)	118.3(3)
N(2)-C(31)-C(30)	126.1(4)
O(5)-C(31)-C(30)	115.6(3)
C(31)-N(2)-C(32)	116.6(3)
N(2)-C(32)-O(6)	118.1(3)
N(2)-C(32)-C(33)	125.5(4)
O(6)-C(32)-C(33)	116.4(4)
C(34)-C(33)-C(32)	116.0(4)
C(34)-C(33)-C(43)	126.5(3)
C(32)-C(33)-C(43)	117.4(3)
C(30)-C(34)-C(33)	119.8(3)
C(30)-C(34)-P(2)	123.0(3)
C(33)-C(34)-P(2)	117.2(3)
C(40)-C(35)-C(36)	117.5(4)
C(40)-C(35)-C(26)	120.4(4)
C(36)-C(35)-C(26)	121.9(4)
C(37)-C(36)-C(35)	121.5(5)
C(37)-C(36)-H(36)	119.3
C(35)-C(36)-H(36)	119.3
C(38)-C(37)-C(36)	120.0(5)
C(38)-C(37)-H(37)	120.0
C(36)-C(37)-H(37)	120.0
C(39)-C(38)-C(37)	119.7(5)
C(39)-C(38)-H(38)	120.1
C(37)-C(38)-H(38)	120.1
C(38)-C(39)-C(40)	120.5(5)
C(38)-C(39)-H(39)	119.8
C(40)-C(39)-H(39)	119.8
C(35)-C(40)-C(39)	120.8(5)

C(35)-C(40)-H(40)	119.6
C(39)-C(40)-H(40)	119.6
O(3)-C(41)-H(41A)	109.5
O(3)-C(41)-H(41B)	109.5
H(41A)-C(41)-H(41B)	109.5
O(3)-C(41)-H(41C)	109.5
H(41A)-C(41)-H(41C)	109.5
H(41B)-C(41)-H(41C)	109.5
O(4)-C(42)-H(42A)	109.5
O(4)-C(42)-H(42B)	109.5
H(42A)-C(42)-H(42B)	109.5
O(4)-C(42)-H(42C)	109.5
H(42A)-C(42)-H(42C)	109.5
H(42B)-C(42)-H(42C)	109.5
C(44)-C(43)-C(48)	117.9(4)
C(44)-C(43)-C(33)	120.8(4)
C(48)-C(43)-C(33)	121.1(4)
C(45)-C(44)-C(43)	120.0(4)
C(45)-C(44)-H(44)	120.0
C(43)-C(44)-H(44)	120.0
C(46)-C(45)-C(44)	120.4(5)
C(46)-C(45)-H(45)	119.8
C(44)-C(45)-H(45)	119.8
C(45)-C(46)-C(47)	120.8(5)
C(45)-C(46)-H(46)	119.6
C(47)-C(46)-H(46)	119.6
C(46)-C(47)-C(48)	118.6(5)
C(46)-C(47)-H(47)	120.7
C(48)-C(47)-H(47)	120.7
C(47)-C(48)-C(43)	122.2(5)
C(47)-C(48)-H(48)	118.9
C(43)-C(48)-H(48)	118.9
O(5)-C(49)-H(49A)	109.5
O(5)-C(49)-H(49B)	109.5
H(49A)-C(49)-H(49B)	109.5
O(5)-C(49)-H(49C)	109.5

H(49A)-C(49)-H(49C)	109.5
H(49B)-C(49)-H(49C)	109.5
O(6)-C(50)-H(50A)	109.5
O(6)-C(50)-H(50B)	109.5
H(50A)-C(50)-H(50B)	109.5
O(6)-C(50)-H(50C)	109.5
H(50A)-C(50)-H(50C)	109.5
H(50B)-C(50)-H(50C)	109.5
H(1WA)-O(1W)-H(1WB)	109.0
H(2WA)-O(2W)-H(2WB)	108.1

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for lkh5. The anisotropic displacement factor exponent takes the form: $-2\ ^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
P(1)	33(1)	40(1)	34(1)	-3(1)	-1(1)	-1(1)
P(2)	33(1)	39(1)	44(1)	4(1)	1(1)	2(1)
O(1)	45(2)	51(2)	49(2)	0(1)	-13(1)	2(2)
O(2)	59(2)	58(2)	46(2)	4(1)	-9(2)	3(2)
O(3)	74(2)	54(2)	47(2)	-13(1)	10(2)	-26(2)
O(4)	61(2)	55(2)	30(2)	-5(1)	5(1)	-11(2)
O(5)	28(2)	57(2)	63(2)	14(2)	-9(1)	-1(1)
O(6)	45(2)	39(2)	118(3)	32(2)	10(2)	2(2)
C(1)	39(2)	53(3)	40(2)	-13(2)	-1(2)	-2(2)
C(2)	46(3)	54(3)	64(3)	-2(2)	2(2)	-10(2)
C(3)	73(4)	65(3)	83(4)	-4(3)	-2(3)	-32(3)
C(4)	112(5)	43(3)	91(4)	1(3)	24(4)	-18(3)
C(5)	67(3)	52(3)	72(3)	10(3)	17(3)	9(3)
C(6)	44(3)	43(2)	63(3)	1(2)	5(2)	6(2)
C(7)	45(2)	39(2)	41(2)	-4(2)	1(2)	-2(2)
C(8)	54(3)	148(6)	40(3)	-2(3)	9(2)	23(4)
C(9)	97(5)	214(9)	59(4)	7(4)	36(4)	69(6)
C(10)	43(3)	142(6)	95(5)	22(4)	21(3)	36(4)
C(11)	39(3)	69(3)	79(4)	5(3)	10(2)	2(2)
C(12)	45(3)	61(3)	52(3)	-2(2)	-1(2)	-5(2)
C(13)	38(2)	33(2)	58(3)	7(2)	5(2)	3(2)
C(14)	45(3)	50(3)	64(3)	5(2)	0(2)	4(2)
C(15)	58(3)	44(3)	114(5)	27(3)	9(3)	8(3)
C(16)	46(3)	45(3)	126(5)	5(3)	8(3)	-1(2)
C(17)	53(3)	52(3)	100(4)	-17(3)	-1(3)	1(3)
C(18)	46(3)	47(3)	72(3)	2(2)	13(2)	2(2)
C(19)	34(2)	39(2)	59(3)	0(2)	-2(2)	9(2)
C(20)	42(3)	99(4)	72(4)	-13(3)	-10(3)	14(3)
C(21)	35(3)	117(5)	106(5)	-12(4)	6(3)	11(3)
C(22)	54(3)	95(5)	106(5)	-3(4)	36(3)	13(3)
C(23)	86(4)	64(3)	73(3)	-6(3)	38(3)	4(3)

C(24)	57(3)	56(3)	58(3)	14(2)	12(2)	8(3)
C(25)	29(2)	41(2)	31(2)	2(2)	3(2)	-2(2)
C(26)	35(2)	44(2)	34(2)	-3(2)	10(2)	-2(2)
C(27)	35(2)	39(2)	41(2)	0(2)	4(2)	-7(2)
N(1)	41(2)	48(2)	36(2)	-2(2)	2(2)	-14(2)
C(28)	34(2)	48(2)	32(2)	2(2)	5(2)	-3(2)
C(29)	29(2)	36(2)	38(2)	-1(2)	4(2)	1(2)
C(30)	30(2)	35(2)	31(2)	-3(2)	1(2)	0(2)
C(31)	29(2)	50(3)	40(2)	2(2)	2(2)	2(2)
N(2)	30(2)	44(2)	51(2)	9(2)	2(2)	1(2)
C(32)	38(2)	41(2)	58(3)	14(2)	8(2)	5(2)
C(33)	37(2)	37(2)	48(2)	0(2)	5(2)	-1(2)
C(34)	32(2)	36(2)	34(2)	-3(2)	6(2)	2(2)
C(35)	57(3)	30(2)	41(2)	-1(2)	11(2)	-5(2)
C(36)	69(3)	49(3)	61(3)	-5(2)	31(3)	-7(2)
C(37)	99(4)	66(3)	77(4)	-4(3)	49(4)	-25(3)
C(38)	140(6)	62(3)	48(3)	11(3)	33(4)	8(4)
C(39)	107(5)	51(3)	49(3)	4(2)	5(3)	1(3)
C(40)	88(4)	42(3)	44(2)	1(2)	4(3)	3(3)
C(41)	98(4)	49(3)	67(3)	-19(2)	7(3)	-26(3)
C(42)	98(4)	71(3)	37(2)	-11(2)	2(3)	-27(3)
C(43)	32(2)	35(2)	58(3)	0(2)	5(2)	-2(2)
C(44)	40(3)	49(3)	66(3)	-5(2)	-1(2)	-1(2)
C(45)	52(3)	53(3)	88(4)	-13(3)	-17(3)	1(2)
C(46)	39(3)	58(3)	115(5)	-5(3)	0(3)	-11(2)
C(47)	36(3)	63(3)	107(5)	1(3)	14(3)	-14(2)
C(48)	39(3)	58(3)	66(3)	2(2)	5(2)	-4(2)
C(49)	39(3)	73(4)	92(4)	20(3)	-17(3)	12(3)
C(50)	64(3)	50(3)	92(4)	23(3)	13(3)	11(3)
O(1W)	112(4)	200(6)	92(4)	-1(4)	-25(3)	36(4)
O(2W)	210(5)	321(6)	113(5)	54(5)	-11(5)	114(6)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for lkh5.

	x	y	z	U(eq)
H(2)	3941	6677	7908	66
H(3)	4213	7785	7693	88
H(4)	2649	8409	7372	98
H(5)	874	7934	7172	76
H(6)	607	6840	7414	60
H(8)	1185	6014	9235	97
H(9)	-626	6201	9682	148
H(10)	-2269	6003	9087	113
H(11)	-2123	5795	7984	74
H(12)	-330	5674	7511	63
H(14)	4419	4434	7674	64
H(15)	3674	3387	7617	86
H(16)	3529	2868	6619	87
H(17)	4125	3395	5669	82
H(18)	4743	4486	5734	66
H(20)	7681	5274	6932	85
H(21)	9243	5163	6257	103
H(22)	9015	5209	5142	102
H(23)	7205	5375	4725	89
H(24)	5620	5499	5393	68
H(36)	-571	4229	7959	72
H(37)	-1021	3805	8962	97
H(38)	404	3659	9731	100
H(39)	2272	3935	9491	83
H(40)	2735	4365	8485	69
H(41A)	264	3387	6122	107
H(41B)	175	2790	6604	107
H(41C)	1385	3009	6334	107
H(42A)	2002	4177	5233	103
H(42B)	2532	4652	4710	103

H(42C)	1251	4749	4943	103
H(44)	6015	6740	7422	62
H(45)	7860	7145	7579	77
H(46)	8906	7535	6717	85
H(47)	8177	7479	5672	82
H(48)	6383	7027	5507	65
H(49A)	595	7207	5923	102
H(49B)	-76	6633	5581	102
H(49C)	1089	6891	5282	102
H(50A)	3444	8193	5323	103
H(50B)	4064	8635	5843	103
H(50C)	3009	8197	6049	103
H(1WA)	4957	5444	8735	161
H(1WB)	5360	5029	9220	161
H(2WA)	5857	2159	5582	257
H(2WB)	6924	2437	5468	257

Table 6. Torsion angles [°] for lkh5.

O(1)-P(1)-C(1)-C(6)	-150.5(4)
C(7)-P(1)-C(1)-C(6)	-29.1(4)
C(25)-P(1)-C(1)-C(6)	82.8(4)
O(1)-P(1)-C(1)-C(2)	20.1(4)
C(7)-P(1)-C(1)-C(2)	141.6(3)
C(25)-P(1)-C(1)-C(2)	-106.6(4)
C(6)-C(1)-C(2)-C(3)	0.7(7)
P(1)-C(1)-C(2)-C(3)	-170.4(4)
C(1)-C(2)-C(3)-C(4)	0.6(8)
C(2)-C(3)-C(4)-C(5)	-2.8(9)
C(3)-C(4)-C(5)-C(6)	3.7(9)
C(4)-C(5)-C(6)-C(1)	-2.4(8)
C(2)-C(1)-C(6)-C(5)	0.2(7)
P(1)-C(1)-C(6)-C(5)	170.7(4)
O(1)-P(1)-C(7)-C(12)	-160.5(4)
C(1)-P(1)-C(7)-C(12)	80.5(4)
C(25)-P(1)-C(7)-C(12)	-36.2(4)
O(1)-P(1)-C(7)-C(8)	26.7(5)
C(1)-P(1)-C(7)-C(8)	-92.3(4)
C(25)-P(1)-C(7)-C(8)	151.0(4)
C(12)-C(7)-C(8)-C(9)	-0.6(9)
P(1)-C(7)-C(8)-C(9)	172.6(6)
C(7)-C(8)-C(9)-C(10)	4.3(12)
C(8)-C(9)-C(10)-C(11)	-5.6(12)
C(9)-C(10)-C(11)-C(12)	3.3(10)
C(10)-C(11)-C(12)-C(7)	0.3(8)
C(8)-C(7)-C(12)-C(11)	-1.6(7)
P(1)-C(7)-C(12)-C(11)	-174.2(4)
O(2)-P(2)-C(13)-C(14)	15.7(4)
C(19)-P(2)-C(13)-C(14)	136.0(4)
C(34)-P(2)-C(13)-C(14)	-110.8(4)
O(2)-P(2)-C(13)-C(18)	-159.5(4)
C(19)-P(2)-C(13)-C(18)	-39.2(4)
C(34)-P(2)-C(13)-C(18)	74.0(4)

C(18)-C(13)-C(14)-C(15)	-1.4(7)
P(2)-C(13)-C(14)-C(15)	-176.9(4)
C(13)-C(14)-C(15)-C(16)	2.1(8)
C(14)-C(15)-C(16)-C(17)	-0.1(8)
C(15)-C(16)-C(17)-C(18)	-2.4(8)
C(14)-C(13)-C(18)-C(17)	-1.3(7)
P(2)-C(13)-C(18)-C(17)	174.0(4)
C(16)-C(17)-C(18)-C(13)	3.2(8)
O(2)-P(2)-C(19)-C(20)	15.9(5)
C(13)-P(2)-C(19)-C(20)	-103.1(4)
C(34)-P(2)-C(19)-C(20)	140.2(4)
O(2)-P(2)-C(19)-C(24)	-165.9(4)
C(13)-P(2)-C(19)-C(24)	75.1(4)
C(34)-P(2)-C(19)-C(24)	-41.5(4)
C(24)-C(19)-C(20)-C(21)	-3.2(8)
P(2)-C(19)-C(20)-C(21)	175.1(5)
C(19)-C(20)-C(21)-C(22)	1.2(10)
C(20)-C(21)-C(22)-C(23)	0.6(10)
C(21)-C(22)-C(23)-C(24)	-0.2(10)
C(22)-C(23)-C(24)-C(19)	-1.8(9)
C(20)-C(19)-C(24)-C(23)	3.5(7)
P(2)-C(19)-C(24)-C(23)	-174.8(4)
O(1)-P(1)-C(25)-C(29)	-106.3(3)
C(7)-P(1)-C(25)-C(29)	129.1(3)
C(1)-P(1)-C(25)-C(29)	18.7(4)
O(1)-P(1)-C(25)-C(26)	78.1(3)
C(7)-P(1)-C(25)-C(26)	-46.6(3)
C(1)-P(1)-C(25)-C(26)	-156.9(3)
C(29)-C(25)-C(26)-C(27)	-5.4(6)
P(1)-C(25)-C(26)-C(27)	170.3(3)
C(29)-C(25)-C(26)-C(35)	171.0(4)
P(1)-C(25)-C(26)-C(35)	-13.3(5)
C(41)-O(3)-C(27)-N(1)	2.5(6)
C(41)-O(3)-C(27)-C(26)	-175.8(4)
C(25)-C(26)-C(27)-N(1)	-1.7(6)
C(35)-C(26)-C(27)-N(1)	-178.3(4)

C(25)-C(26)-C(27)-O(3)	176.5(4)
C(35)-C(26)-C(27)-O(3)	-0.1(6)
O(3)-C(27)-N(1)-C(28)	-173.3(4)
C(26)-C(27)-N(1)-C(28)	4.9(6)
C(27)-N(1)-C(28)-O(4)	176.5(4)
C(27)-N(1)-C(28)-C(29)	-1.0(6)
C(42)-O(4)-C(28)-N(1)	6.4(6)
C(42)-O(4)-C(28)-C(29)	-175.9(4)
C(26)-C(25)-C(29)-C(28)	8.6(6)
P(1)-C(25)-C(29)-C(28)	-166.9(3)
C(26)-C(25)-C(29)-C(30)	-174.7(4)
P(1)-C(25)-C(29)-C(30)	9.8(6)
N(1)-C(28)-C(29)-C(25)	-5.6(6)
O(4)-C(28)-C(29)-C(25)	176.9(4)
N(1)-C(28)-C(29)-C(30)	177.3(4)
O(4)-C(28)-C(29)-C(30)	-0.2(5)
C(25)-C(29)-C(30)-C(34)	82.7(5)
C(28)-C(29)-C(30)-C(34)	-100.6(5)
C(25)-C(29)-C(30)-C(31)	-100.2(5)
C(28)-C(29)-C(30)-C(31)	76.5(5)
C(49)-O(5)-C(31)-N(2)	8.8(6)
C(49)-O(5)-C(31)-C(30)	-172.9(4)
C(34)-C(30)-C(31)-N(2)	-6.1(6)
C(29)-C(30)-C(31)-N(2)	176.4(4)
C(34)-C(30)-C(31)-O(5)	175.7(3)
C(29)-C(30)-C(31)-O(5)	-1.8(5)
O(5)-C(31)-N(2)-C(32)	178.8(4)
C(30)-C(31)-N(2)-C(32)	0.6(6)
C(31)-N(2)-C(32)-O(6)	-173.8(4)
C(31)-N(2)-C(32)-C(33)	2.9(7)
C(50)-O(6)-C(32)-N(2)	9.8(7)
C(50)-O(6)-C(32)-C(33)	-167.2(4)
N(2)-C(32)-C(33)-C(34)	-0.5(7)
O(6)-C(32)-C(33)-C(34)	176.3(4)
N(2)-C(32)-C(33)-C(43)	-177.1(4)
O(6)-C(32)-C(33)-C(43)	-0.3(6)

C(31)-C(30)-C(34)-C(33)	8.2(5)
C(29)-C(30)-C(34)-C(33)	-174.5(4)
C(31)-C(30)-C(34)-P(2)	-172.1(3)
C(29)-C(30)-C(34)-P(2)	5.2(5)
C(32)-C(33)-C(34)-C(30)	-5.4(6)
C(43)-C(33)-C(34)-C(30)	170.9(4)
C(32)-C(33)-C(34)-P(2)	174.9(3)
C(43)-C(33)-C(34)-P(2)	-8.9(6)
O(2)-P(2)-C(34)-C(30)	-102.1(3)
C(13)-P(2)-C(34)-C(30)	23.0(4)
C(19)-P(2)-C(34)-C(30)	134.0(3)
O(2)-P(2)-C(34)-C(33)	77.6(3)
C(13)-P(2)-C(34)-C(33)	-157.3(3)
C(19)-P(2)-C(34)-C(33)	-46.3(3)
C(25)-C(26)-C(35)-C(40)	-60.4(6)
C(27)-C(26)-C(35)-C(40)	115.9(5)
C(25)-C(26)-C(35)-C(36)	124.9(5)
C(27)-C(26)-C(35)-C(36)	-58.8(6)
C(40)-C(35)-C(36)-C(37)	1.8(7)
C(26)-C(35)-C(36)-C(37)	176.6(4)
C(35)-C(36)-C(37)-C(38)	-0.8(8)
C(36)-C(37)-C(38)-C(39)	-0.3(9)
C(37)-C(38)-C(39)-C(40)	0.3(9)
C(36)-C(35)-C(40)-C(39)	-1.7(7)
C(26)-C(35)-C(40)-C(39)	-176.6(4)
C(38)-C(39)-C(40)-C(35)	0.6(8)
C(34)-C(33)-C(43)-C(44)	-60.3(6)
C(32)-C(33)-C(43)-C(44)	115.9(5)
C(34)-C(33)-C(43)-C(48)	125.5(5)
C(32)-C(33)-C(43)-C(48)	-58.4(6)
C(48)-C(43)-C(44)-C(45)	-0.1(7)
C(33)-C(43)-C(44)-C(45)	-174.6(4)
C(43)-C(44)-C(45)-C(46)	1.9(7)
C(44)-C(45)-C(46)-C(47)	-1.9(8)
C(45)-C(46)-C(47)-C(48)	0.1(8)
C(46)-C(47)-C(48)-C(43)	1.7(8)

C(44)-C(43)-C(48)-C(47)	-1.7(7)
C(33)-C(43)-C(48)-C(47)	172.7(4)

Symmetry transformations used to generate equivalent atoms: