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**A study of new planar chiral monophosphine
ligands based on [2.2]paracyclophane and their
use in catalysis**

Jingjing Wang

**Chemistry – Institute of Fundamental Sciences,
Massey University**

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J. Rowlands**

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Abstract

The Suzuki-Miyaura coupling reaction is one of the most powerful methods for the construction of biaryls. The biaryl motif has great importance in pharmaceutical, agrichemical and material science industries, and is often axially chiral. The outcome of a Suzuki-Miyaura coupling reaction can be influenced by many factors, but the ligand plays the most vital role. A large number of ligands have been developed, including many chiral ligands for asymmetric reactions. While ligand design has focused on molecules containing either central or axial chirality, little has been focused on planar chiral ligands.

In this project, three new ligands based on the [2.2]paracyclophane backbone have been designed, *pseudo-ortho* substituted monophosphines (**L1** and **L2**), secondary phosphine oxide and arylindolyl phosphine ligands (**L3** and **L4**). Unfortunately, similar analogues of **L1** and **L2** were reported before our results, and a synthesis route to the secondary phosphine oxide ligands was not achieved. The use of **L1** in gold mediated cyclisation was investigated, which concluded that **L1** was not suitable for this kind of reaction. However, arylindolyl phosphine ligands were prepared successfully, and produced promising preliminary results in achiral Suzuki-Miyaura coupling reactions.

Interesting X-ray crystallography structure of brominated indole is discussed.

Acknowledgements

I would like to thank everyone who contributed to this project, and give a special thanks to my supervisor Gareth J. Rowlands, for the knowledge he passed on and his patience. I also wish to acknowledge that David Martin and Geoff B. Jameson collected and processed all the X-ray crystallography data for my molecules.

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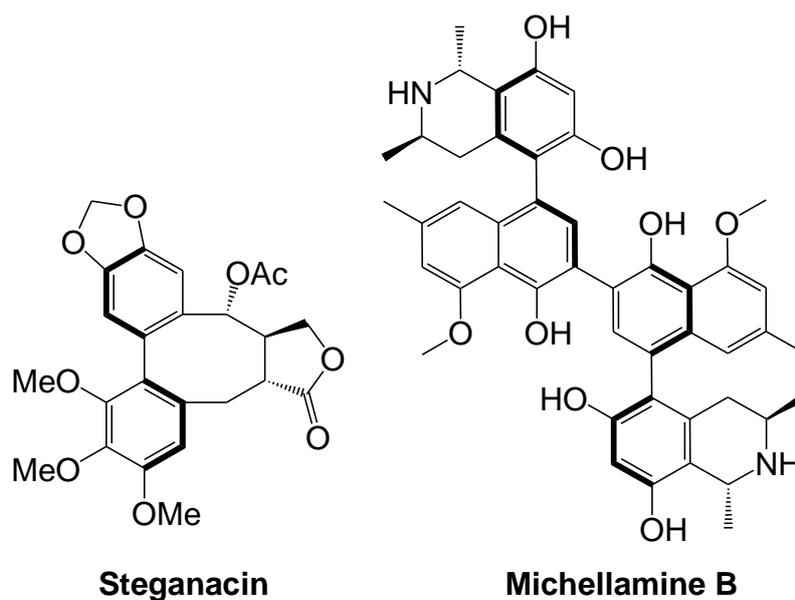
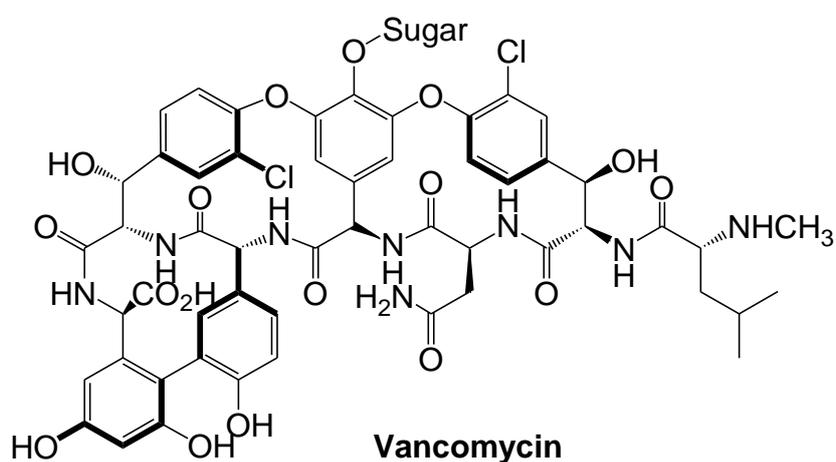
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Abbreviations

(<i>S</i>)-PEA	(<i>S</i>)-phenethylamine
AAA	Asymmetric Allylic Alkylation
Ac	Acetate
aryl-MOPFs	aryl-monophosphinoferrocene
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-Bi-2,2-naphthol
Bz	Benzyl
Cbz	Carbobenzyloxy
Cy	Cyclohexyl
DCM	Dichloromethane
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
dppf	1,1'-bis(diphenylphosphino)ferrocene
ee	enantiomeric excess
HIV	Human immunodeficiency virus
NBS	N-bromosuccinimide
<i>n</i> -Bu	<i>n</i> -Butyl
Ph	Phenyl
r.t.	room temperature
SPO	Secondary phosphine oxide
<i>t</i> -Bu	<i>t</i> -Butyl
TDMPP	tri(2,6-dimethoxyphenyl)phosphine
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TON	Turnover number
TTMPP	tri(2,4,6-trimethoxyphenyl)phosphine

1. Introduction

Natural products played an important part in modern drug development. Since the 20th century, the pharmaceutical industry has advanced from isolating and identifying biologically important compounds, to synthesising compounds with improved biological properties, as well as being able to produce these compounds in greater quantities.^{1,2} In a wide range of natural products, including the antibiotic vancomycin, tubulin binding lignan steganacin and anti-HIV alkaloid michellamine B, axially chiral biaryl motifs had been found to be important substructures. It is also an important constituent of many pharmaceutical and agrichemicals, and has found considerable use in chiral ligands and reagents, such as BINOL and BINAP (Figure 1).²



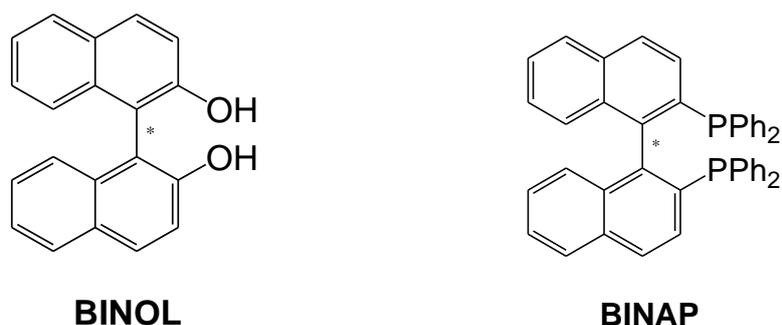
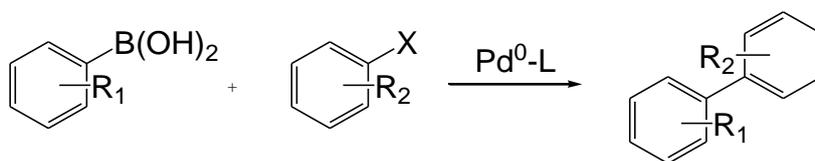


Figure 1.1: Biaryl compounds vanomycin, steganacin, michellamine B, BINOL and BINAP

1.1 Suzuki-Miyaura coupling reaction

Great effort has been invested in finding the best way to synthesise biaryl compounds, and the Suzuki-Miyaura coupling reaction is one of the most powerful methods. This palladium-mediated coupling reaction of an aryl halide and an aryl boronic acid has a number of advantages over other methods, it is very versatile, can tolerate a wide range of functional groups, and it can also be performed under mild reaction conditions. High yields can be achieved, even in aqueous media with water-soluble catalysts and substrates.^{3,4} Furthermore, most boronic acids and aryl halides are air-stable compounds that are easy to handle, and many of them are commercially available.⁵ However, this reaction does have limitations, both electron-deficient and heterocyclic boronic acids are problematic, with proto-deboronation becoming a competitive side reaction, which reduces the yield.⁶



Scheme 1.1: Suzuki-Miyaura coupling reaction.

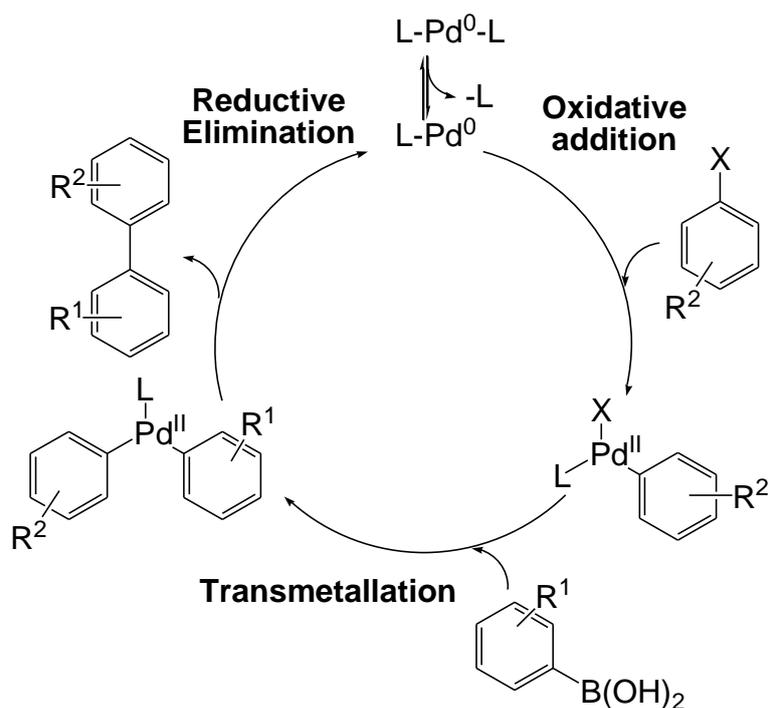
Multiple substituents are possible on both the aryl boronic acid and the aryl halide, but if these substituents are in the *ortho* position, steric hindrance becomes an issue. Of more relevance is the fact that *ortho* substituents can lead to restricted rotation around the central biaryl carbon-carbon bond, and the formation of chiral molecules. The stereoisomers that exist due to restricted rotation of a single bond are called

atropisomers, and are said to display axial chirality.⁷ A Suzuki-Miyaura coupling reaction that preferentially produces one atropisomer is an asymmetric Suzuki-Miyaura coupling reaction. This is quite significant, due to the large number of axially chiral natural products, pharmaceutical and agricultural products.

The Suzuki-Miyaura coupling reaction is thought to proceed by three steps: oxidative addition, transmetallation and reductive elimination (Scheme 2). The reaction normally involves a low valent palladium species that is stabilised by a suitable ligand. These ligands can have a profound effect on the activity of the system. Oxidative addition is facilitated by electron-rich ligands, because the electron-donation from the ligand to the Pd(0) centre makes the centre more nucleophilic. Good σ -donor ligands can accelerate the coupling, because they donate electrons to fill the low-lying orbitals in palladium, which increase the electron density of the metal. On the other hand, π -acceptor ligands remove electrons from palladium. It decreases the electron density of palladium, thus makes it harder for the coordinatively unsaturated species L-Pd(0) to form. Therefore, these ligands would suppress the catalysis.

The coordinatively unsaturated species L-Pd(0) is the active catalytic species, which can accommodate the incorporation of the aryl halide substrates. Its formation is promoted by electron-donating and bulky ligands. The electronic effect of the ligands was stated before, and the bulkiness provides the steric hindrance that facilitates the departure of one of the ligands, consequently forming the L-Pd(0) species.

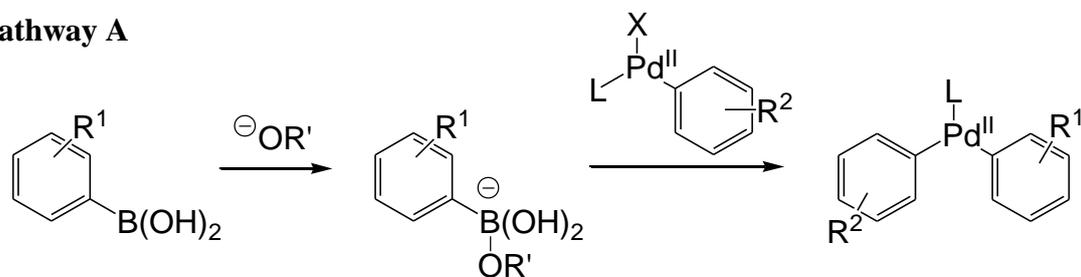
During oxidative addition, the palladium inserts into the aryl halogen bond. Two new bonds are formed, and the palladium is oxidised from Pd(0) to Pd(II). Insertion is usually the rate-determining step, due to the high thermal stability and strength of the aryl halogen bond. This step is particularly slow for aryl chlorides, as the bond strength of carbon-chlorine bond is 327 kJ/mol, which is only slightly lower than carbon-carbon bond (346 kJ/mol).⁸ However, aryl chlorides are more stable, readily available and less expensive than aryl bromides or iodides, thus there is a demand for ligands that are sufficiently active to catalyse the coupling of aryl boronic acids with aryl chlorides.^{6,7,9}



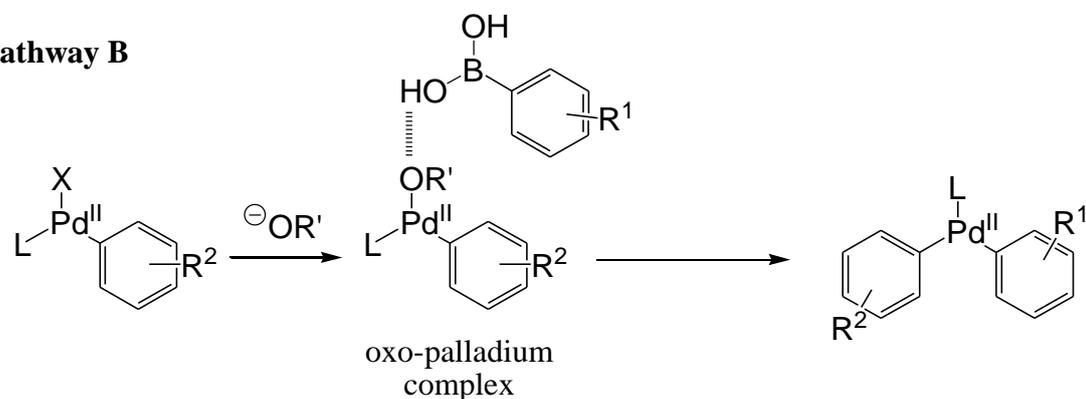
Scheme 1.2: Mechanism of Suzuki-Miyaura coupling reaction.

Transmetalation is the least understood step. Literatures agree that organoboronic acid is normally inert to halogen-palladium complex, unless base is added, but the role of base in the mechanism is debatable. The two pathways below are the most supported ones (Scheme 1.3).¹⁰

Pathway A



Pathway B



Scheme 1.3: Two mechanisms proposed for transmetalation.

Pathway A suggests that the base transforms the boronic acid to a nucleophilic boronate, which then attacks the palladium halide complex. The fast equilibration of boronic acid to boronate in alkaline solution was discovered in the middle of 19th century. It was confirmed by ^{11}B NMR study, that the equilibrium largely favours the production of boronate.¹¹ On the other hand, pathway B suggests that the base substitutes the halide first, forming an oxo-palladium complex, and it then reacts with the boronic acid. Although the previous kinetics study concluded that the substitution of halide by a base is too slow to compete with pathway A,¹¹ the most recent kinetic study showed that the reaction between pre-synthesised palladium hydroxo complex and boronic acid occurs much faster than between palladium halide complex and boronate, thus pathway B could be favoured.¹² There is also computational thermodynamics and a structural study, that believes that the interaction between the palladium complex resulted from oxidative addition and the boron species is stabilised by hydrogen bonding, thus the oxo-palladium complex and boronic acid is much more stable.^{13,14} However, the data also show that pathway B requires higher activation energy.¹³

The actual mechanism could be even more complicated, knowing that the reaction can proceed through both pathways simultaneously, and the relative contribution of both is dependent on the relative reaction rate of each step, concentration of reagents and intermediates, types of base and the counter cation of the base.^{10,12}

The result of the transmetallation is that the two aryl moieties are bound to the palladium centre, ready for the final step, reductive elimination. Reductive elimination can be accelerated by bulky ligands, which can provide a steric effect to promote the formation and the dissociation of the product. Upon the departure of the biaryl product, Pd(II) is reduced to Pd(0). The L-Pd(0) species can then enter another cycle of catalysis.⁶

The outcome of the reaction can be influenced by solvent, base, temperature, ligand, palladium source, and ligand:palladium ratio. The ligand plays the most vital role. An appropriately designed ligand can facilitate better reaction efficiency, milder reaction conditions and lower catalyst loadings.⁷ The features of a good ligand for Suzuki-Miyaura coupling reaction not only cover those mentioned previously, but also practical

features, such as stability, toxicity, ease of synthesis, and be compatibility with a wide range of reaction conditions.^{7,9,15}

1.2 Ligands of Suzuki-Miyaura coupling reaction

Ligand design for Suzuki-Miyaura coupling reaction is a very active field of study. Out of all types of ligands, monophosphine ligands have attracted particular interest, because they have several advantages over other ligands. One of the advantages is that the palladium/phosphine system normally has a large turnover number (TON), due to the high affinity of phosphine to palladium that prolongs the life-time of the catalytically active species.¹⁶ Another one is the ease of appending the phosphine motif to the main structure, which can be achieved by Grignard or organolithium reagents in just one step, and many of the reagents are commercially available.⁵ Furthermore, many of the monophosphine ligands developed are thermally stable and resistant to air and moisture.⁵ Apart from Suzuki-Miyaura coupling reaction, the monophosphine ligands had success in catalysing other common reactions, such as Stille cross-coupling,¹⁷ and Buchwald-Hartwig amination.¹⁸ Hence, the monophosphine ligands are the focus of this project.

Triphenylphosphine is one of the most widely used tertiary phosphine ligands. It can effectively promote the generation of the Pd(0) catalytic species. Tetrakis(triphenylphosphine)palladium(0), Pd(PPh₃)₄, is commercially available and can catalyse reactions without further modification. It can catalyse simple examples of the Suzuki-Miyaura coupling reaction effectively, but is unstable, sensitive towards light and air, which makes it hard to handle. The overligated palladium is less active as well, thus elevated temperature and more active substrates are usually required. Bulkier and more electron donating ligands, such as tri-*tert*-butylphosphine, tri(2,4,6-trimethoxyphenyl)phosphine (TTMPP) and tri(2,6-dimethoxyphenyl)phosphine (TDMPP) have been shown to improve the reactivity, but they are still of limited use, due to being even less stable, and still require high temperature to function.⁹

Buchwald's ligands are amongst the most successful monophosphine ligands used in catalysis. To date, there are 21 ligands that have been commercialised. The basic structure of Buchwald's ligands is shown below (Figure 1.3). There are multiple points

of substitution on the biaryl scaffold, which allows the steric and electronic properties of the ligand to be tuned readily to each reaction.¹⁹

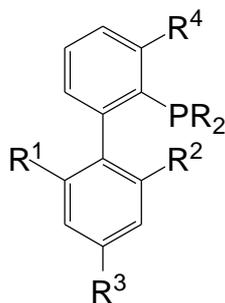


Figure 1.3: General structure of Buchwald's ligands.

The phosphine is attached to the upper aryl ring. Like other monophosphine ligands, bulkier and more electron donating alkyl substituents are normally more reactive than aryl substituents. Additional modification on the upper ring can also affect the electronics, and substituent at R⁴ is particularly useful, as it can help to confine the conformation of the phosphine motif.

The lower ring not only increases the size of the ligand, but also adds extra stability to the catalyst, because it can slow down the oxidation of the phosphine by the oxygen, and the substituents R¹ and/or R² can protect the ligand from forming an unwanted palladacycle. Furthermore, the lower ring can stabilise the LPd(0) species through palladium-arene interaction, and also palladium-oxygen interaction if R¹ and R² are methoxy groups. The substituent R³ is not relevant to the activity of the ligand, its existence is usually for the ease of synthesis, or altering the physical properties of the ligand, such as water solubility.

All the features above make the Buchwald ligands very versatile. These ligands have succeeded in catalysing a wide range of coupling reactions, even some that were always considered problematic. For example, even the simplest, JohnPhos, has achieved excellent activities in the coupling of aryl chloride and aryl boronic acid at room temperature. Even the coupling of heterocyclic aryl chlorides has succeeded, catalysed by SPhos at elevated temperature. Moreover, DavePhos is particularly effective in constructing carbon-nitrogen bonds (Figure 1.4).⁵

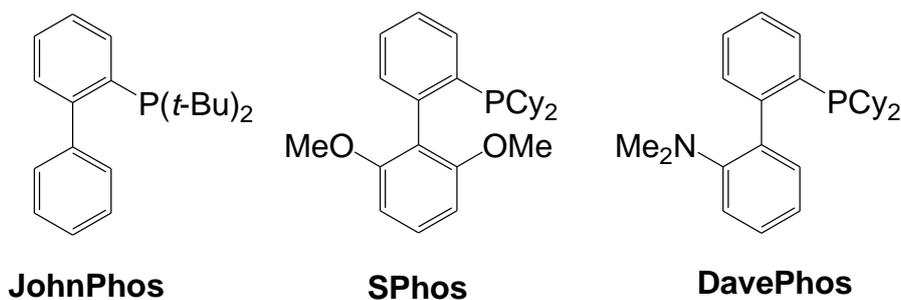


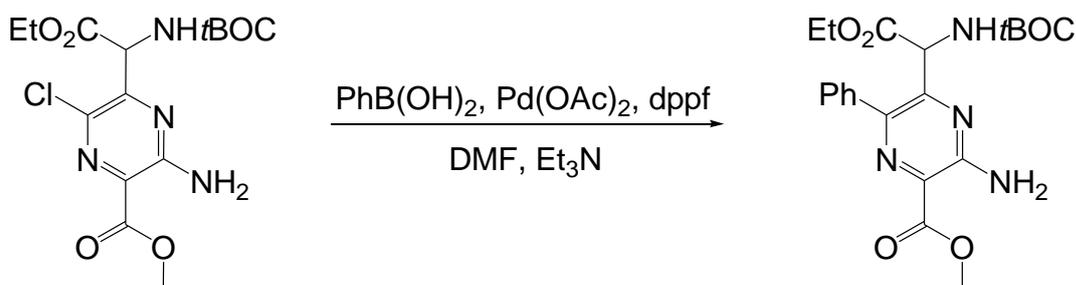
Figure 1.4: Structures of JohnPhos, SPhos and DavePhos.

The development of more Buchwald's ligand is still very active, and they continue to produce more ligands optimised to different reactions and substrates.

The ligands mentioned above are achiral, thus they cannot be used in asymmetric reactions. The synthesis of axially chiral biaryls is difficult and often requires enantiopure ligands. The use of ferrocenyl-based phosphine ligands were amongst the earliest exploited in this area.²⁰

Ferrocenylphosphine ligands cover a huge range of structural motifs. It is possible to modify the rings of the ferrocene backbone, add extra phosphine motifs, and alter the phosphine itself. Through these modifications, central, axial, or planar chirality can be introduced individually, or in combination.^{21,22}

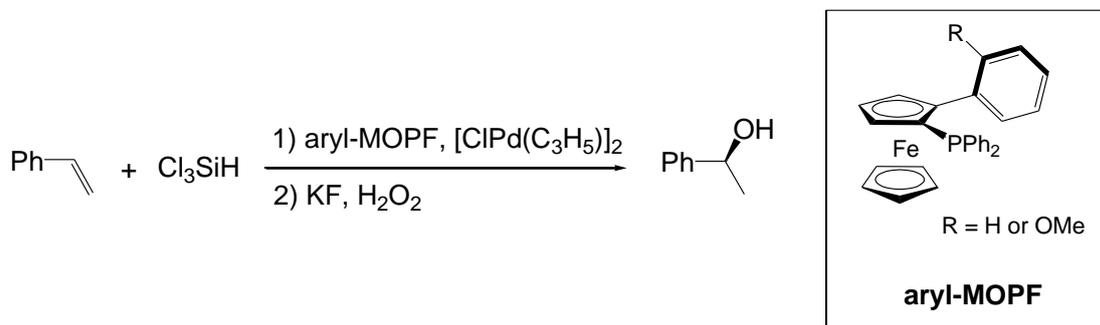
A ferrocenylphosphine ligand was first used to catalyse a Suzuki-Miyaura coupling reaction in 1988.²³ Thies' group reported that the palladium acetate ($\text{Pd}(\text{OAc})_2$) and 1,1'-bis(diphenylphosphino)ferrocene (dppf) together can form the catalytic species $\text{Pd}(\text{dppf})(\text{OAc})_2$ in situ, which successfully catalysed the coupling of a 6-chloropyrazine with phenylboronic acid (Scheme 1.4). However, this reaction took 5 days at room temperature to reach 64 % of yield.²³



Scheme 1.4: $\text{Pd}(\text{dppf})(\text{OAc})_2$ catalysed coupling reaction.

The ligand, dppf, was not only the first ferrocenylphosphine ligand used in Suzuki-Miyaura coupling reactions, but remains one of the best. It is a very versatile ligand, can coordinate with various transition metals, and tolerates a range of different substrates. So far, it has been reported in the coupling of aryl triflates and aryltrialkyltin reagents (Stille reaction), aryl halides and amines (Buchwald-Hartwig amination), aryl halides with Grignard reagents (Kumada-Corriu reaction), as well as the Suzuki-Miyaura coupling reaction.²⁰

Use of dppf in coupling reactions opened the door to the study of monophosphine ferrocene ligands (MOPFs). The first successful use of a chiral aryl-MOPF in enantioselective catalysis was the hydrosilylation of alkenes by Pedersen and Johanssen (Scheme 1.5).²⁴ Having the two adjacent substituents on one cyclopentadienyl ring breaks the symmetry of ferrocene, and introduces planar chirality to the ligands. The test reactions were carried out at room temperature, and the enantiomeric excess (ee) obtained was up to 70%.



Scheme 1.5: Pedersen and Johanssen's aryl-MOPF in enantioselective hydrosilylation.

A number of ligands similar to aryl-MOPF have been developed, and proved to be successful. A few of the commercialised examples are shown below (Figure 1.5). They are commonly used in asymmetric hydrogenations, allylic alkylations, aldol, Diels-Alder and addition reactions, and quantitative yields and excellent enantioselectivities were often achieved.²¹

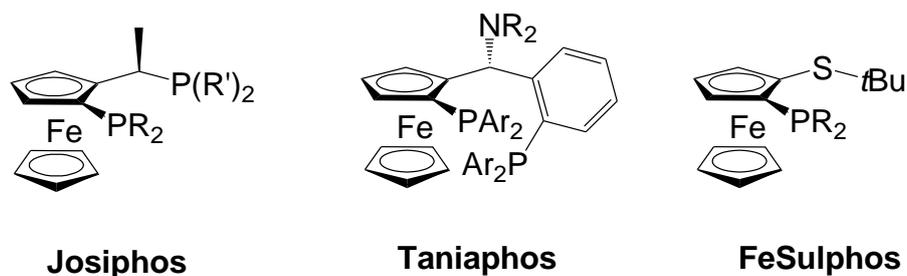
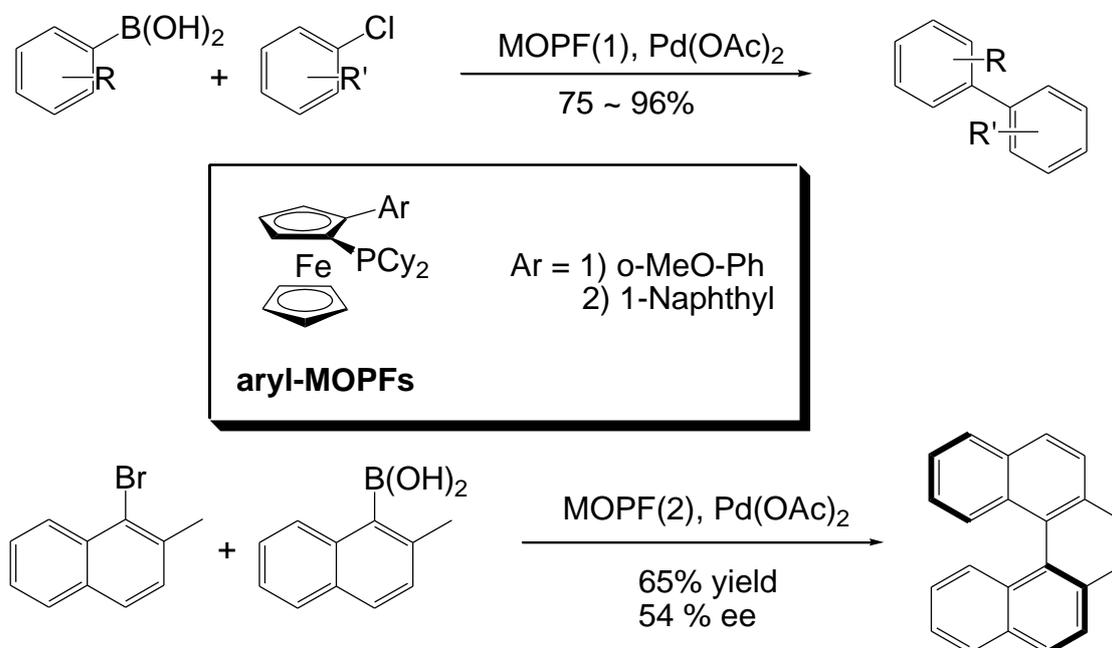


Figure 1.5: The structure of Josiphos, Taniaphos and FeSulphos.

The use of aryl-MOPFs in the catalysis of asymmetric Suzuki-Miyaura coupling reactions was reported by Jensen and Johannsen in 2003.²⁵ It generated good to excellent yields in forming biaryl compounds with various substituents, and 43 - 54% enantioselectivities in producing the axially chiral binaphthalene (Scheme 1.6).



Scheme 1.6: Aryl-MOPFs in SMCs.

1.3 [2.2]Paracyclophane-based ligands and this project

The focus of this project is to prepare planar chiral ligands based on [2.2]paracyclophane. [2.2]Paracyclophane was discovered only a few years later than ferrocene, but its importance was over shadowed by ferrocene. Its use in catalysis was not studied extensively until the late 20th century. The structure of [2.2]paracyclophane consists of two benzene rings connected by two ethylene bridges at the *para*-position. This brings those two rings into close proximity, that the π -orbitals are directly interacting to form an extended system (Figure 1.6).²⁶

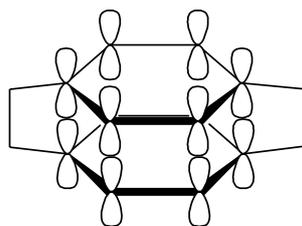


Figure 1.6: The extended π -system of [2.2]paracyclophane.

The interaction between the two aromatic rings creates an interesting phenomenon, the “transannular effect.”²⁷ It was observed that when a substituent was attached to one of the rings, the electronic properties of both rings are affected. This has been proven by both the spectroscopic studies such as IR and NMR, and the outcomes of reactions such as the bromination of mono-substituted acetyl[2.2]paracyclophane.²⁷

Depending on the position of substitution, different types of chirality can be introduced to the [2.2]paracyclophane skeleton. If the substituent is added to the ethyl bridge (**1**, Figure 1.7), then the resulting molecule possesses central chirality. The introduction of substitution on the aromatic ring can lead to planar chirality. The mono-substituted [2.2]paracyclophane is always chiral (**2**, Figure 1.7), while the chirality of di-substituted [2.2]paracyclophanes depends on the position and the nature of the substituents. The *pseudo-ortho* substitution always produces planar chirality (**3**, Figure 1.7). However, in the case of *ortho* and *pseudo-gem* substitution (**4** & **5**, Figure 1.7), two different substituents are required to break the plane of symmetry in those compounds. Other planar chiral derivatives are also possible, but rarely synthesised.²⁸

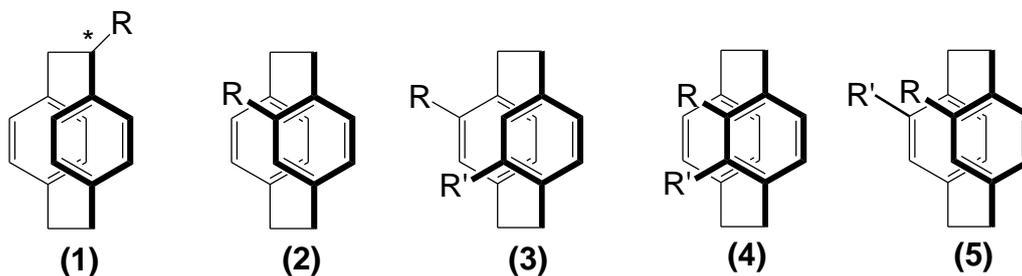


Figure 1.7: Examples of chiral [2.2]paracyclophane structures.

The planar chiral compounds do not have a chiral centre or axis. Their chirality arises from a chiral plane.²⁹ In the case of [2.2]paracyclophane, the most substituted aromatic ring is the chiral plane. The introduction of the substituent(s) breaks the symmetry of the two planes, producing two nonsuperposable compounds.

Furthermore, if the substituent on the aromatic ring displays restricted rotation, there could also be the possibility of axial chirality. The compounds produced in Part III of this project are good examples of this latter phenomenon.

The numbering of atoms for [2.2]paracyclophane is shown below (Figure 1.8). Carbon-1 is called the “pilot atom”, which is assigned to the furthest carbon in the ethyl linker that is adjacent to the highest priority substituent, according to Cahn-Ingold-Prelog system of stereochemical assignment.³⁰ Viewing from pilot atom, if carbon-2, 3, 4 are in clockwise arrangement, this molecule is assigned as R_p , and if counterclockwise, it is S_p .

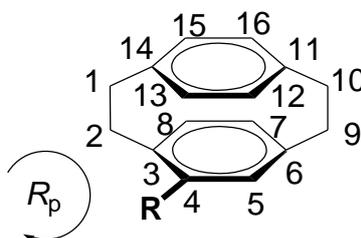
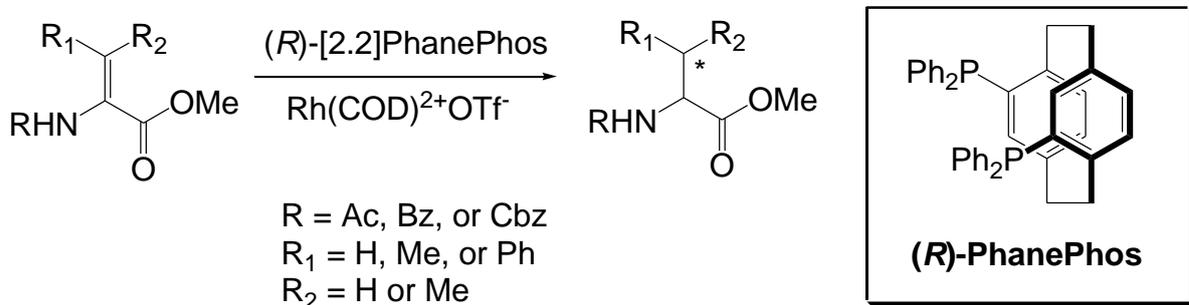


Figure 1.8: The numbering of atoms and R_p , S_p assignment for [2.2]paracyclophane.

The most successful planar chiral [2.2]paracyclophane-derivative is PhanePhos, which was reported in 1997 by Pye and Rossen (Scheme 1.7).^{30,31} The enantiopure ligand is effective for the rhodium-catalysed hydrogenation of dehydroamino acids, and gives over 90 % enantioselectivities.³¹ Soon, this group also used PhanePhos to resolve the racemic *pseudo-ortho*-dibromo[2.2]paracyclophane.³² Since then, PhanePhos has catalysed the hydrogenation of β -ketoesters efficiently,³³ as well as the hydroboration of cyclopropenes with 94% yield and 97% ee.³⁴



Scheme 1.7: The (R)-PhanePhos in the rhodium-catalysed hydrogenation.

Following the publication of PhanePhos, this area of research became more active, and many ligands have been developed. The most recent achievements in this area include the mono-substituted imidazole-based phosphine ligands, which a former colleague was involved in the development (Figure 1.8).³⁵ This ligand produced promising results for the palladium-mediated Suzuki-Miyaura coupling reaction, but further resolution and investigation in asymmetric catalysis is required. Another example is the tri-substituted imine-based ligands, which were tested in the copper-catalysed Henry reaction (Figure 1.9).³⁶ The best ligand gave 85 % yield and 94 % ee.

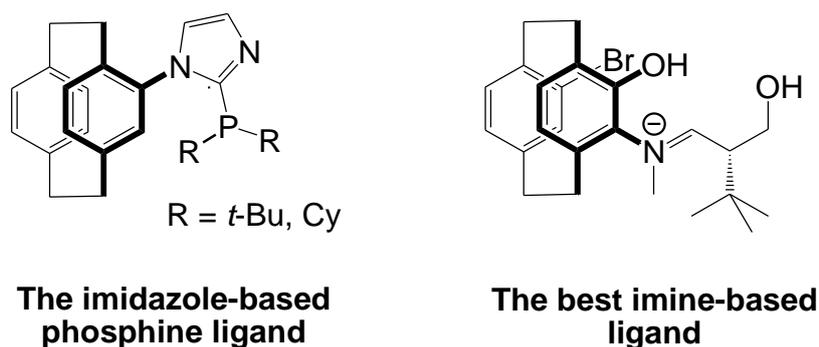


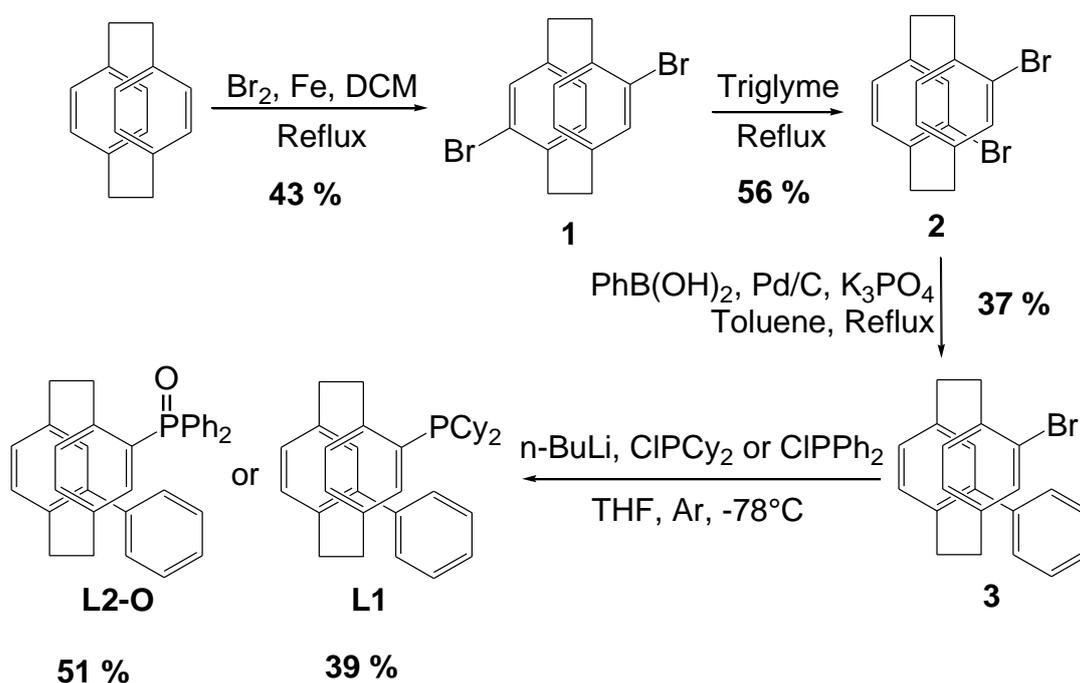
Figure 1.9: Two recent examples of [2.2]paracyclophane-based ligands.

Three types of the [2.2]paracyclophane-based ligands were designed for this project, the *pseudo-ortho*-substituted monophosphine ligand, the mono-substituted secondary phosphine oxide ligand and the aryl indolyl phosphine ligand.

2. Results and Discussion

2.1 *Pseudo-ortho* substituted [2.2]paracyclophane based monophosphine ligands

During the first year of the study, two monophosphine ligands, based on *pseudo-ortho* substituted [2.2]paracyclophane, were synthesized by a four-step procedure, using [2.2]paracyclophane as the starting material (Scheme 2.1).



Scheme 2.1: Synthetic procedure of ligand 1 (L1) and 2 (L2).

The literature procedure for the dibromination of [2.2]paracyclophane used carbon tetrachloride as solvent and no iron filings, but we found that the use of dichloromethane as the solvent and the addition of iron filing greatly improved the reaction. Dichloromethane simplifies the purification of *pseudo-para*-dibromo[2.2]paracyclophane (1), as it allows 1 to crystallise out of the solution upon cooling.³⁷ The filtered product could be recrystallized from dichloromethane, but it was later found that this was unnecessary. The only impurity was [2.2]paracyclophane, which does not interfere with the subsequent steps, and can be removed at a later stage. The iron filings react with bromine to form a small amount of ferric bromide, which catalyses the bromination.³⁸ It not only increased the yield by four-fold, but also improved the regioselectivity by eliminating the *pseudo-meta* substituted by-product,

which was accounting for a third of the overall production in the method without iron filings.

The next step was an isomerization. Heating **1** to approximately 230 °C, the boiling point of triglyme, results in scission of one of the ethylene bridges and thus allows rotation of the aromatic rings. Cooling results in restoration of [2.2]paracyclophane structure, but as a 1:1 mixture of *pseudo-para*- (**1**) and the desired *pseudo-ortho*-dibromo[2.2]paracyclophane (**2**). While **2** stays in the triglyme solution, starting material **1** can be filtered off and subjected to a second isomerisation. Usually, three isomerisations were performed, before the triglyme solution of **2** are combined, and distilled under vacuum to yield **2**. The new compound **2** is planar chiral (Figure 2.1), and a racemic mixture was produced.

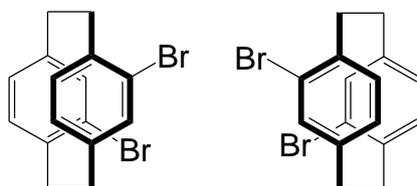


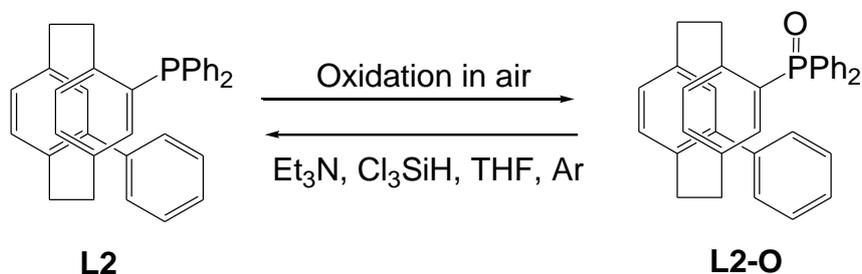
Figure 2.1: Planar chiral 4,12-dibromo[2.2]paracyclophane.

The third step was a Suzuki-Miyaura coupling reaction, coupling **2** with phenylboronic acid to produce 4-bromo-12-phenyl[2.2]paracyclophane (**3**). Pd(PPh₃)₄ was initially used in this coupling. At first, these reaction conditions successfully furnished the desired product, producing **3** with 76 % yield, along with some unreacted starting material and 4-phenyl[2.2]paracyclophane by-product. The catalyst Pd(PPh₃)₄ is air-sensitive, and readily undergoes oxidation to give an inactive species. Therefore, the reaction was found to be capricious with yield varying from good to trace amount, so a new method was required. The coupling of **2** with 2-methoxyphenylboronic acid was also tested, but the yield was not satisfactory, and the separation of the product and the starting material was too hard to achieve.

Using a mixture of palladium (II) acetate and 1,1'-bis(diphenylphosphino)ferrocene (dppf) reportedly gives a very active catalyst for the Suzuki-Miyaura coupling reaction.³⁹ This method was also tested, but the starting material was returned untouched. A microwave method in aqueous media later attracted our attention, as it uses cheap and stable palladium on carbon (Pd/C) as the catalyst.⁴⁰ Because the starting

material has a low solubility in water, a mixture of water:toluene (1:9) spiked with ethanol was used. The ethanol serves as an emulsifier to allow mixing of water and toluene. This reaction was not air sensitive, and the reaction time was shortened from overnight to 15 minutes. It was believed that the high pressure of the microwave method promotes the coupling of molecules. Although the yield was not as high as using fresh $\text{Pd}(\text{PPh}_3)_4$, the results were more consistent, and the unreacted **2** could easily be recycled. It was thought that higher catalytic loading would improve the yield, but 0.01 mol% of Pd/C gave the highest conversion, while both 0.02 mol% and 0.04 mol% gave reduced yields, with most of the starting material unreacted. In the case of 0.04 mol% Pd/C, the yield was only about 10.5 %. Therefore, 0.01 mol% was the optimum catalytic loading. This method successfully produced several batches of **3**, but when a new batch of Pd/C was purchased, the yield markedly fell. Activation by keeping this Pd/C under vacuum did not improve its reactivity. Currently, it is unclear why different batches of Pd/C gave such different results. One theory is that the quality of the commercial Pd/C was low, and it could be contaminated by other metals, which were actually catalysing the reaction. Unfortunately, we did not keep any of the original Pd/C to allow further analysis.

The final step was the *n*-butyllithium-mediated coupling of **3** with diarylchlorophosphine. Two ligands were produced for further testing, the air-stable 4-dicyclohexylphosphino-12-phenyl[2.2]paracyclophane (**L1**) and 4-diphenylphosphino-12-phenyl[2.2]paracyclophane (**L2**), which oxidises to phosphine oxide rapidly in air. Although the phosphine oxide can be reduced back to **L2** by trichlorosilane, **L2** is still hard to handle in practise, which is a limiting factor of this ligand (Scheme 2.2).



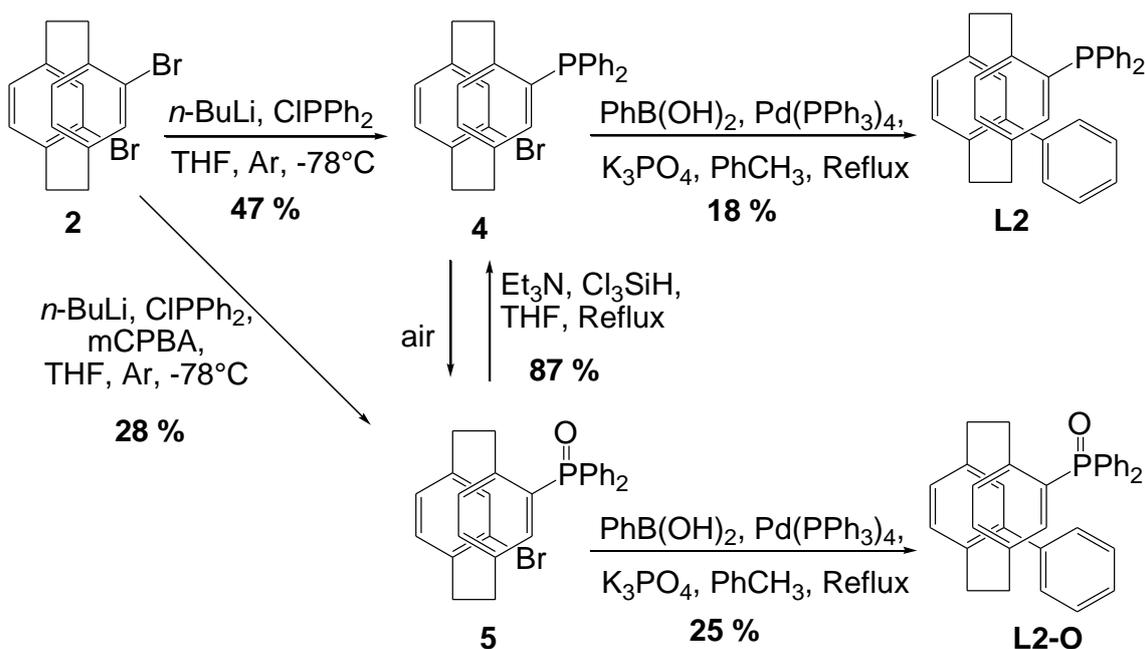
Scheme 2.2: The phosphine and phosphine oxide conversion.

Attempts to prepare the di-*tert*-butylphosphine analogue were unsuccessful. Although lithium-bromide exchange occurred to generate the requisite anion, this failed to react

with bis-(*tert*-butyl)chlorophosphine. Thus, only the debrominated molecule was isolated. It may be due to that the *tert*-butyl groups are too bulky, and the steric hindrance blocks the access of the bulky 4-lithio[2.2]paracyclophane.

Phosphorus splittings were observed in ^1H NMR spectra of **L1** and **L2**. The effect of phosphorus-proton heteronuclear J coupling is magnified by the high level of conjugation within the molecules. It resulted in large numbers of multiplets, which made the assignment of the ^1H NMR difficult. This splitting also caused problem in ^{13}C NMR, as more peaks were observed with lower intensity.

The overall yield of the four steps was extremely low with the best results being 4.04% for **L1** and 2.5% for **L2**. Thus, the third and the fourth steps were reversed to see whether the yield would be improved (Scheme 2.3). This was first trialed with the synthesis of **L2**.



Scheme 2.3: The alternative route to synthesise **L2**.

The first step in the new route involved selective monometallation and addition of the phosphine. The mono-bromine-lithium exchange of the dibromonated **2** with one equivalent of *n*-butyllithium produces 4-lithio-12-bromo[2.2]paracyclophane, which can react with the diphenylchlorophosphine. Unfortunately, this reaction always gave a mixture of the desired phosphine (**4**) and the phosphine oxide (**5**), due to the

spontaneously oxidation of **4** to **5** in air. To simplify the purification, 1.2 equivalent of *m*-chloroperoxybenzoic acid (mCPBA) was added to the reaction to ensure that all the phosphine was oxidised to phosphine oxide. However, the addition of mCPBA reduced the yield greatly to only 28 %, while most of the starting material, **2** remains unreacted. A lower yield was also observed for the Suzuki-Miyaura coupling reaction between **5** and boronic acid. Although **5** was reduced back to **4** efficiently (87 %), **4** was oxidised again during the work-up of the reaction, and the yield of the Suzuki-Miyaura coupling reaction of **4** was reduced still further. Therefore, reversing these two steps offered no benefit.

The original plan was to use the ligands in palladium-mediated reactions. Unfortunately, an analogous ligand was reported before our results.³⁹ Xiao's group reported that JPhos (Figure 2.2) shows good to excellent yields (84-96%) in catalysis of Suzuki-Miyaura coupling reaction of aryl chlorides with arylboronic acids, as well as Buchwald-Hartwig amination. Thus, we changed our focus to gold-mediated cyclisation.

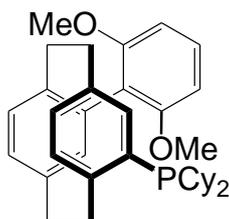


Figure 2.2: The structure of JPhos.

L1 successfully ligated with dichloroaurate(I) anion, and crystals of excellent quality were produced by slow diffusion of *n*-pentane into a solution of **L1** in toluene. The X-ray crystallography structure was obtained (Figure 2.3). On the other hand, **L2** formed a dark purple solid during the ligation with dichloroaurate (I) anion. The solid does not dissolve in any common organic solvents. The purple solid was thought to be gold nanoparticles, but further investigation is needed to confirm this. Consequently, further testing was only performed with **L1**. Attempts to grow crystals of unligated **L2** suitable for X-ray also met with failure.

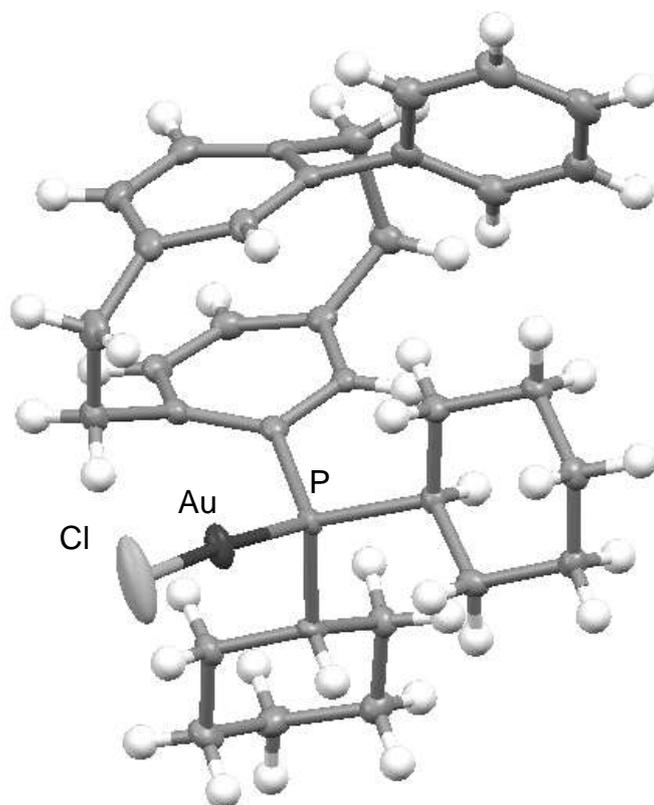


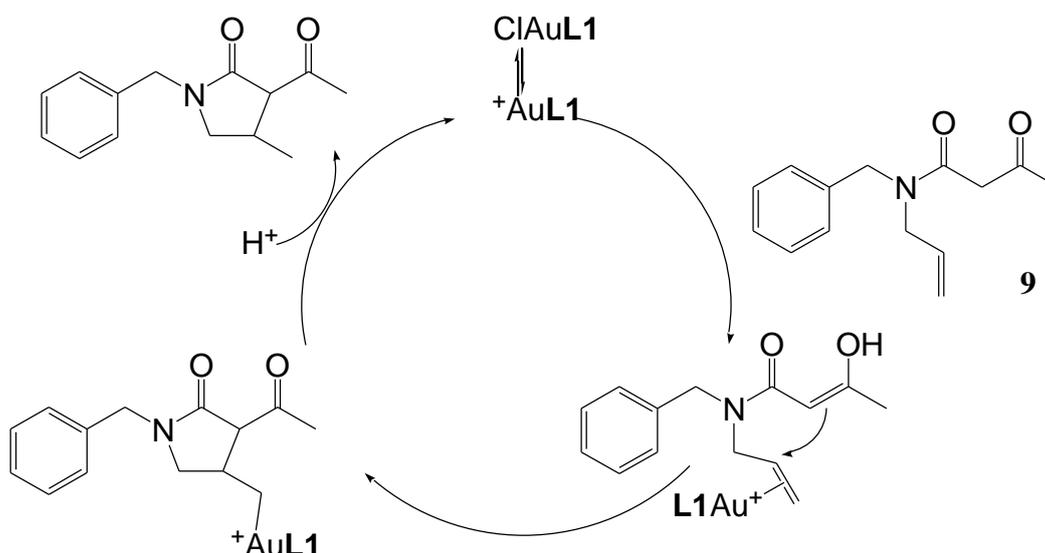
Figure 2.3: The X-ray crystal structure of **L1**-AuCl.

The X-ray crystal structure of **L1**-AuCl shows that the gold atom adopts a linear geometry, and the phosphorus is tetrahedral. The bond distance between gold and phosphorus is 2.24Å. Both the geometry and the bond distance agree with similar complexes published, such as the complexes of Buchwald ligands.^{41,42} The bond distance roughly corresponds to the sum of covalent radius of tetrahedral phosphorus (1.10Å) and the ionic radius of Au⁺ (1.37Å),⁸ which suggests that this bonding is somewhere between a covalent and an ionic bond. Another distinctive feature of the structure is that the two *pseudo-ortho* positioned substituents on the [2.2]paracyclophane distorted the [2.2]paracyclophane structure significantly. The two aromatic rings have been bent backwards 17.8° and 14.3° respectively, and slightly twisted within the plane of the aromatic rings. This distortion is expected, due to the high steric hindrance of the two *pseudo-ortho* positioned substituents.

This structure is constructed to accommodate a substrate upon the departure of the chloride. The gold atom is oriented away from the [2.2]paracyclophane, this provides easy access for the substrate to bind. The binding site of the substrate is where the

chloride was located, and the other sides are blocked by the two cyclohexyl rings and the [2,2]paracyclophane. The plane of the phenyl substituent is twisted 63.9° out of the plane of the [2,2]paracyclophane, this brings the phenyl ring 3.5 \AA to one of the cyclohexyl ring. As a result, the plane of phenyl would face the substrate, consequently hold the substrate in position through head-on π - π interactions with the aromatic part of the substrate.

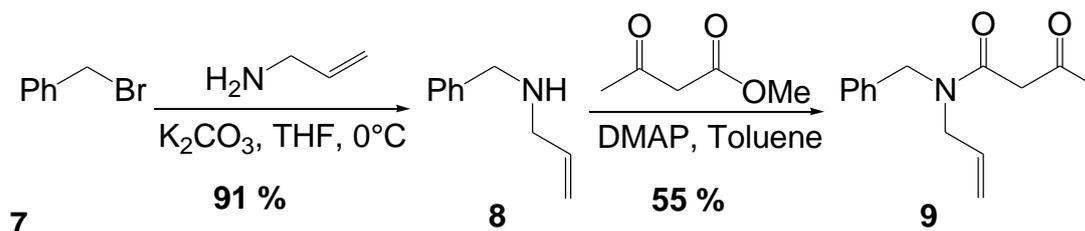
The activity of the **L1**-AuCl complex was tested against the intramolecular addition of *N*-allyl-*N*-benzyl-3-oxobutanamide (**9**) to produce 3-acetyl-*N*-benzyl-4-methyl-2-pyrrolidinone. The mechanism reported suggests that the coordination of gold to the alkene can activate the alkene to nucleophilic attack from a carbon nucleophile (Scheme 2.4). In this case, the nucleophile was the enol tautomer of the β -ketoamide starting material (**9**).⁴³



Scheme 2.4: Mechanism of gold-mediated cyclisation of *N*-allyl- β -ketoamide

β -Ketoamide **9** was synthesised easily in two steps, with total yield of 52 % (Scheme 2.5). Mukherjee⁴⁴ suggested that quantitative yield can be achieved for the first step with a solvent-free system, but our experimental result shows that the compound produced was the disubstituted *N,N*-diallyl-benzylamine. This could be the result of the high reaction rate. Therefore, this reaction was carried out in THF to reduce the concentration, consequently reduce the reaction rate, and near quantitative yield was obtained. The second step was catalysed by 4-dimethylaminepyridine (DMAP), which

replaces the methoxy group in the methyl acetylacetonate to provide a better leaving group for the substitution reaction.



Scheme 2.5: The synthesis route of N-allyl-N-benzyl-3-oxobutanamide (**9**).

The ^1H NMR spectrum of **9** shows that the product is a mixture of **9** and a closely related compound. This is the result of keto-enol tautomerisation. **9A** is stabilised by hydrogen bonding, therefore, quite stable. However, the disruption of the amide structure is not favoured, so the formation of **9B** is usually not observed (Figure 2.3). A weak signal at 14.7 ppm was observed in the ^1H NMR spectrum, which could be the hydrogen that was involved in the hydrogen bonding.

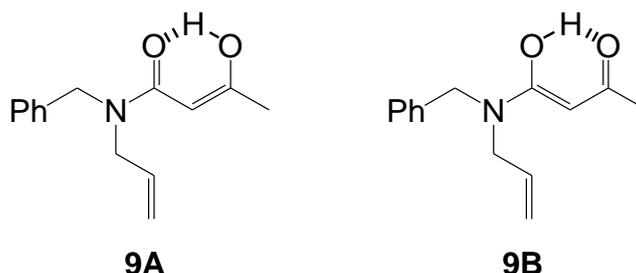
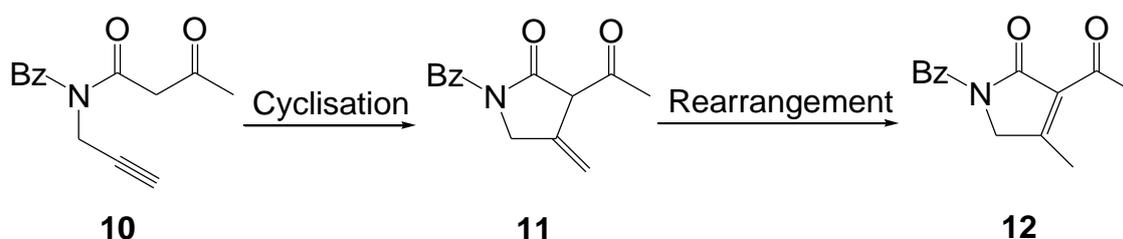


Figure 2.3: Two possible enol structures of **9**.

Gagosz's group published a paper that suggested that phosphine gold bis(trifluoromethanesulfonyl)imide complexes (LAuNTf_2) are more stable and easy to handle than phosphine gold chloride complexes, and yet still catalyse cycloisomerisations efficiently.⁴⁵ Therefore, we formed **L1**- AuNTf_2 , by stirring a suspension of **L1**- AuCl and silver bis(trifluoromethanesulfonyl)imide, AgNTf_2 , for 15 minutes at room temperature. A change of chemical shift was observed in ^{31}P NMR. However, this complex did not show any catalytic activity towards the cyclisation of **9** with several solvent and temperature variations. It was thought that the bis(trifluoromethanesulfonyl)imide may compete with the substrate to bind to the gold catalytic site, and the alkene may have low affinity to the gold-phosphine complex. Hence, the **L1**- AuCl complex was used with silver triflate as the cocatalyst. This system

only managed about 33% yield in toluene at elevated temperature, and it proved impossible to purify the cyclised product from the starting material **9**, even after reducing the ketone on both molecules to alcohol by sodium borohydride. The yield might be improved by optimising the reaction conditions, but the long duration of the process, due to the large number of parameters that can vary, makes it unsuitable for this project.

The gold-mediated cycloisomerisation of enynes is meant to be a facile process, so the reaction of *N*-propargyl-*N*-benzyl-3-oxobutanamide (**10**) to give **11** was proposed. However, it was recognised soon that the cyclisation product of **10** was likely to undergo rearrangement to form the achiral **12** (Scheme 2.6), because **12** has the alkenyl in conjugation with the two carbonyls. Therefore, the test reaction of **10** was never attempted.

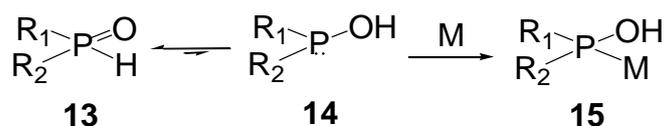


Scheme 2.6: The possible cyclisation product of **10**.

The result suggests that **L1** is not suitable for the cyclisation of *N*-allyl- β -ketoamine, but it may be suitable for other gold-mediated reactions. However, it is impractical to screen **L1** against a variety of precursors, and there is no guarantee of success in any of them. With the poor yield of the ligand being a constant problem, we decided to turn our attention to simpler ligands.

2.2 Secondary phosphine oxide ligand with [2.2]paracyclophane backbone

Secondary phosphine oxides have only recently garnered attention as ligands in cross-coupling reactions, even though the catalytic potential of trivalent phosphinous acid has been known for sometime. The unstable nature of the secondary phosphine oxides make them hard to handle. Therefore, their use in catalysis was not explored. This all changed with the discovery of the tautomerisation of pentavalent phosphine oxide (**13**) and the trivalent phosphinous acid (**14**), (Scheme 2.7).⁴⁶



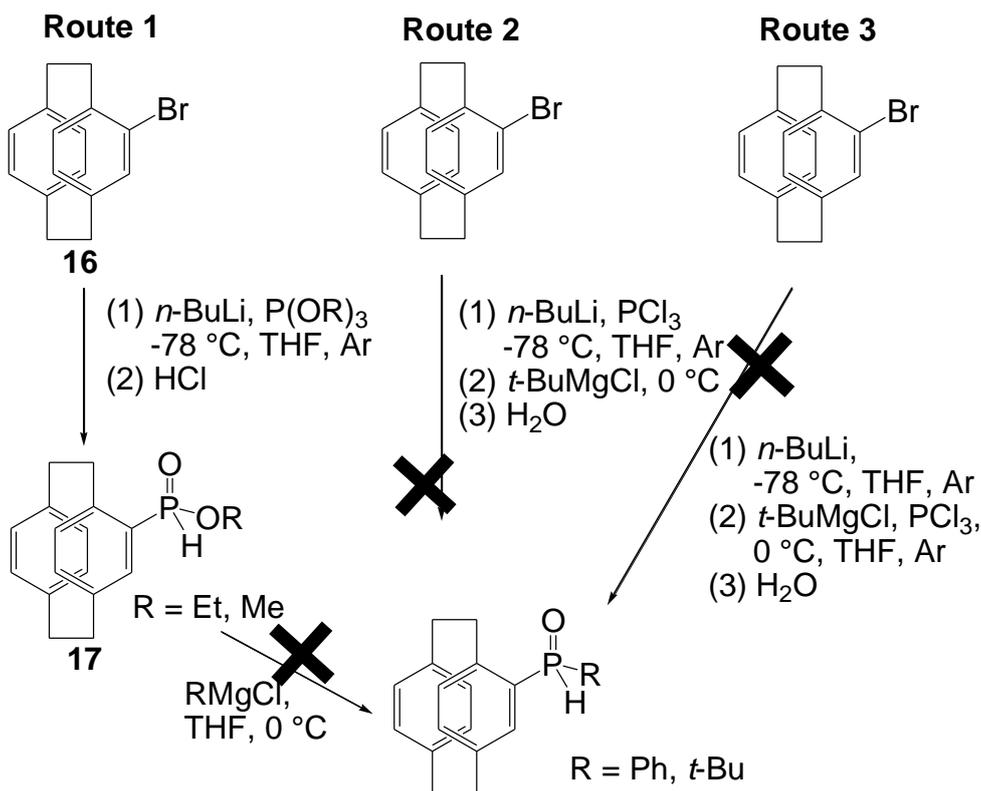
Scheme 2.7: The tautomerisation equilibrium of H-phosphinate (**13**).

This tautomerisation equilibrium largely favours initial phosphorus (III) species **13**, which is relatively stable. This allows this compound to be stored and handled with reasonable ease. In the presence of a suitable metal, **13** rapidly equilibrates to the requisite metal coordinated **15**. Therefore, the unstable trivalent phosphane **14** is only produced when required, and does not need to be isolated. The metal-ligand complex is quite stable, because its conformation is stabilised by intramolecular hydrogen bonding.⁴⁷ Furthermore, the tetravalent complex **15** would have tetrahedral geometry. In the case of $\text{R}^1 \neq \text{R}^2$, it would be chiral with the phosphorus atom being the stereocentre. This can be quite useful for asymmetric catalysis.

Han's study shows that the phosphine oxide can be prepared in two or three steps.⁴⁸ Following their procedure, a number of routes were proposed for the synthesis of the target ligands (Scheme 2.8). The starting material, 4-bromo[2.2]paracyclophane (**16**) was synthesized by the mono-bromination of [2.2]paracyclophane with bromine. Unfortunately, none of the subsequent chemistry was successful.

Route 1 involved a two-step synthesis. *P*-Alkoxy-*P*-[2.2]paracyclophanylphosphinic acid (**17**) was prepared from the bromide by halogen-metal exchange, and the addition of a trialkoxyphosphine, followed by acid hydrolysis. The ethoxy derivative was attempted first, and the yield was reproducible, with the best yield of 48 %. The product obtained exhibited ¹H NMR signals for two similar, but distinctive molecules. As **17**

possesses both planar and centre chirality, those two molecules could be the diastereoisomers. This was confirmed by the observation of two sets of doublets with huge J coupling constant of 552 and 548 Hz respectively, which corresponded to the hydrogen bonded to the phosphorus. This unusually powerful splitting of proton signal by the phosphorus is the signature signal of H-phosphinate, and commonly observed in practice.^{49,50}



Scheme 2.8: Proposed synthesis routes to secondary phosphine oxide ligand.

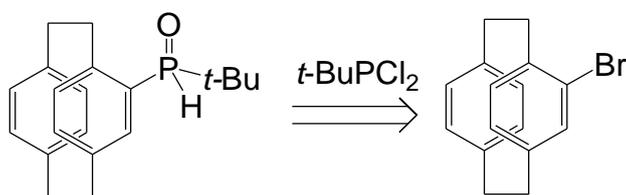
The literature suggested that displacement of the ethoxy group would be facile, but in our hands, two Grignard reagents, phenyl magnesium chloride and t -butyl magnesium chloride, failed to react. Mixtures of compounds were produced in all cases, and the ^{31}P NMR indicates that each of the mixture has four to five phosphorus containing compounds, but the desired ligands did not appear to be amongst them. To understand the outcome of the reaction better, this mixture was purified with a column chromatography, but only to find that the separated portions are still mixtures. According to the spectra obtained, the signals for ethoxy protons are present in the ^1H NMR spectra of the product mixture, although the peak for starting material has disappeared in ^{31}P NMR. This observation raised the question of what has caused the change of the shift in ^{31}P NMR, if the substitution of the ethoxy did not occur. One

possibility is the deprotonation of the phosphorus, followed by the attack of the Grignard reagent, but this is hard to confirm with all the spectra of the mixtures.

It was thought that maybe the ethoxy group was not a sufficiently good leaving group in this reaction. Thus, the methoxy version of **17** was synthesised, and similar yield was produced. However, it did not alter the result of step 2. The by-products remain unidentified.

Route 2 and 3 were one-pot reactions. Route 2 is similar to the two-step method in route 1, but proceed by the reactive [2.2]paracyclophosphanyldichlorophosphine species without isolation. Unfortunately, a mixture of unidentifiable molecules that did not resemble the target was achieved. Route 3 employs a different strategy, by producing the lithium salt of [2.2]paracyclophane and *t*-butyldichlorophosphine in separate flasks first, and then replacing one chloride on the phosphine by [2.2]paracyclophane. All it produced was [2.2]paracyclophane. That indicates that **16** did react with *n*-BuLi, but the second stage of the reaction did not occur at all.

The cause of the failure is hard to analyse, as the problem could be at each step of the multi-step reactions. It is impossible to take sample during the reactions for analysis, because both are sensitive to air and moisture. However, the outcome of route 3 suggested that the synthesis of *t*-butyldichlorophosphine *in situ* is the most likely problem of this method. Therefore, *t*-butyldichlorophosphine was purchased, and it might lead us to success (Scheme 2.9). While waiting for the reagent, another type of ligands was explored.



Scheme 2.9: Newly proposed route to secondary phosphine oxide.

2.3 [2.2]Paracyclophanyl indolyl phosphine ligands

Biarylphosphine ligands have shown great potential in palladium-mediated coupling reactions, such as the Suzuki-Miyaura coupling reaction; they are readily prepared, allow easy modifications and have a number of useful characteristic that have been described earlier. So far, it has proven impossible to make [2.2]paracyclophane analogues of the benchmark Buchwald ligands, but those with heteroaromatic groups are accessible. Fortunately, a number of achiral varieties, such as Kwong's ligands, have been reported and show good potential. Kwong has developed a series of indole-based ligands that show promising activity (Figure 2.4). The ligand developed in 2007 (Kwong 2007) showed great catalytic activity towards the coupling reactions of aryl chlorides.⁵¹ The structure was designed to be easily tuned to suit a number of substrates, as a result, quantitative yields were obtained even with the couplings of heterocyclic aryl chlorides. Another ligand was produced in 2008 (Kwong 2008), which effectively catalysed the formation of C_(sp²)-N bond, using the relatively inert aryl mesylates as the starting materials.⁵² The most recent achievement was published in 2010 (Kwong 2010).⁵³ This group of ligands were designed to catalyse the coupling of unactivated aryl chlorides, and the yields ranges from 80 % to 97 % for substrates of various electronic and steric properties.

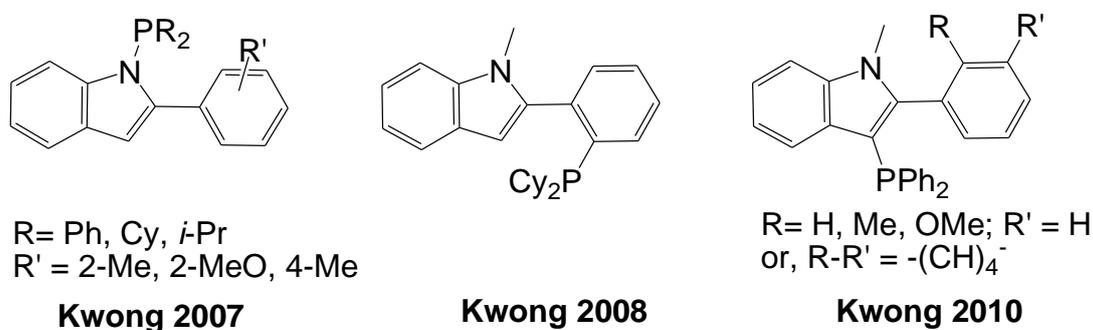
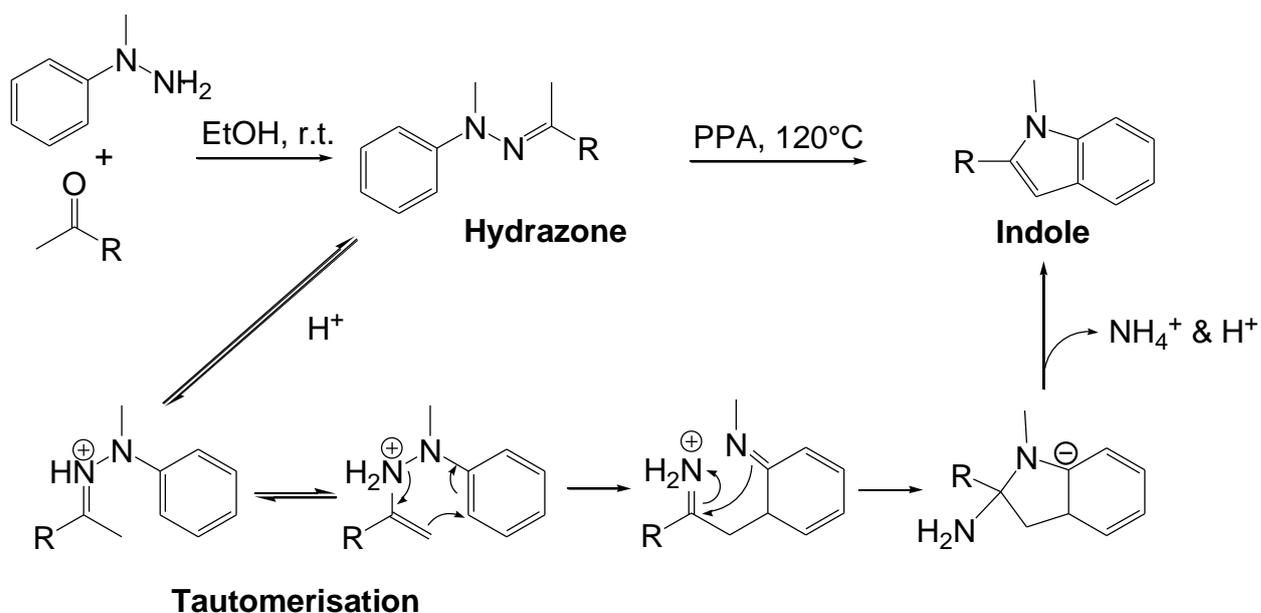


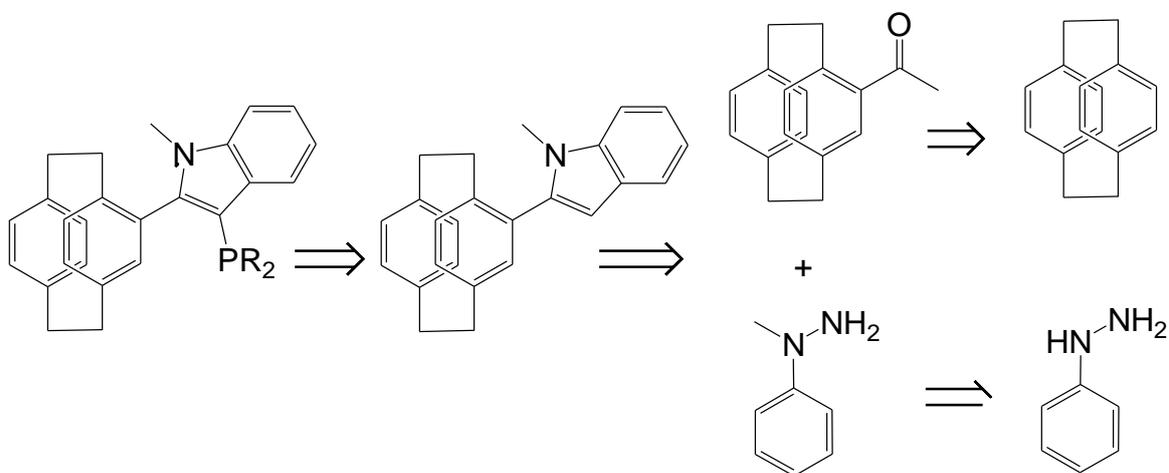
Figure 2.4: The ligands developed by Kwong's group.

All the ligands above were synthesised by the straightforward Fischer indole synthesis, and they are reported to be stable as solid and in solution. The one-pot Fischer indole synthesis actually takes two steps. It produces the hydrazone as an intermediate, which tautomerises to ene-hydrazine with acid-catalysis, which then undergoes [3,3]sigmatropic rearrangement, followed by the 5-exo-trig cyclisation to produce the bicyclic structure (Scheme 2.10).^{54,55}



Scheme 2.10: The mechanism of Fischer indole synthesis.

With the inspiration of Kwong's ligands, the third part of this project focuses on producing two ligands similar to **Kwong 2010**, through Fischer indole synthesis (Scheme 2.11). The starting material, ketone and hydrazine have to be synthesised prior to the cyclisation.

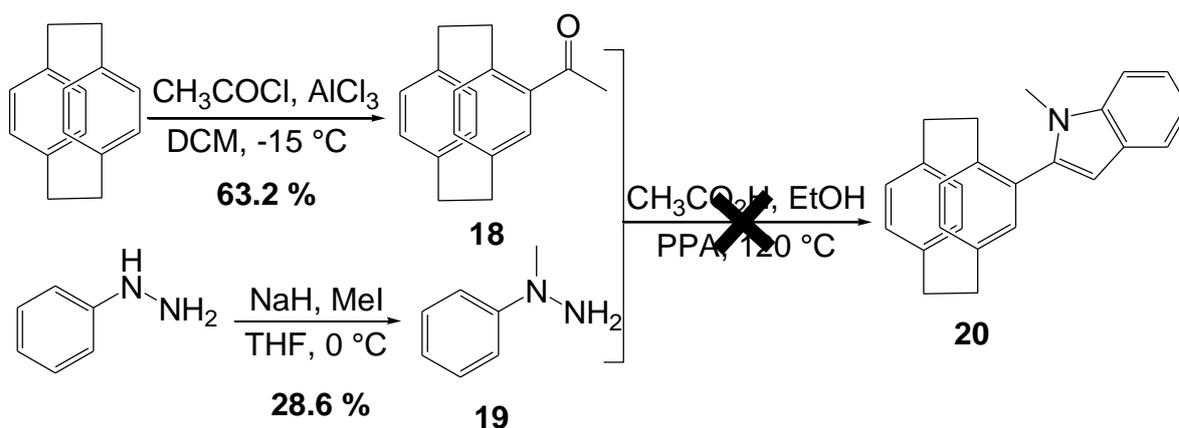


Scheme 2.11: Proposed Fischer indole synthesis.

The first step in the reaction sequence was acetylation of [2.2]paracyclophane by Friedel-Crafts acylation (Scheme 2.12). This allows simple elaboration of the [2.2]paracyclophane backbone. The acetyl group also serves as an excellent group for the resolution of planar chirality, it has previously been resolved by Schiff's base condensation with (*S*)-phenethylamine.⁵⁶⁻⁵⁸ The 4-acetyl[2.2]paracyclophane (**18**) was

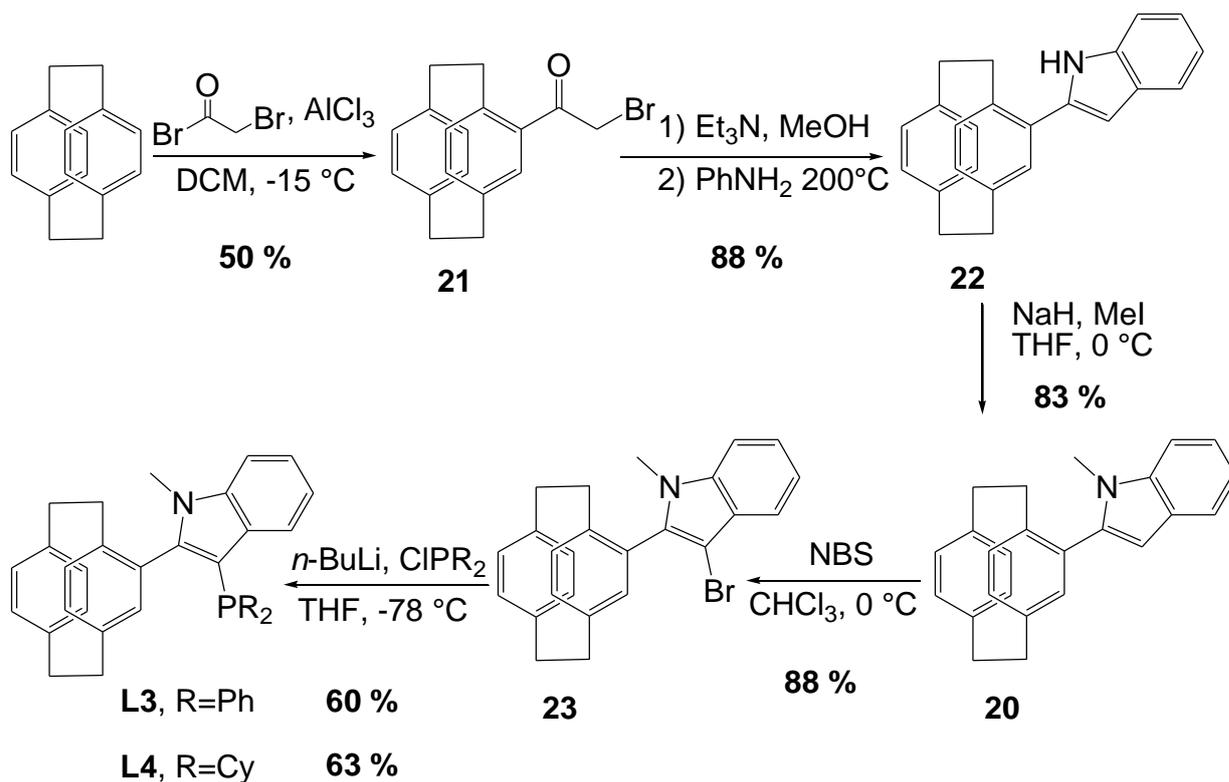
then subjected to Fischer indole synthesis with 1-methyl-1-phenylhydrazine (**19**). Unfortunately, this reaction yielded a mixture of the hydrazone intermediate and the indole product, which failed to separate.

[2.2]Paracyclophane has the unique structural and electronic properties, that are quite different from other aromatic moieties. It might interfere with the tautomerisation, thus disrupt the process from occurring. However, systematic study is required to give a conclusive explanation.



Scheme 2.12: The Fischer indole synthesis route.

A second route to the desired indole, which involves cyclocondensation, was also investigated (Scheme 2.13). The starting material of the cyclocondensation, 4-bromoacetyl[2.2]paracyclophane (**21**) was made by the classic Friedel-Crafts acylation. The low yield of **21** is thought to arise due to the high reactivity of bromoacetyl bromide, which readily decomposes under the reaction conditions. However, with care, it was possible to isolate **21** in 50 % yield.



Scheme 2.13: Synthesis procedure of ligands **L3** and **L4**.

The cyclocondensation is a one-pot, two-step process (Scheme 2.14).⁵⁹ First, the moisture sensitive (2-[2.2]paracyclophanyl-2-oxoethyl)trimethylammonium bromide is generated, and then reacted with aniline to give **22** in 88 % yield. Although it was a one-pot reaction, the solvent of the first step had to be removed before the subsequent step. This reaction is believed to proceed by formation of an imine, followed by cyclisation, in which the electron rich aromatic ring displaces the ammonium. The aromaticity is restored by proton rearrangement at the end.

2.5). The [2,2]paracyclophane structure in both compounds is not distorted significantly, and the two aromatic rings only bend outwards about 1° . To our surprise, the bromine atom was facing the [2,2]paracyclophane in both case. It was always thought to be the opposite, in which the bromine should be away from [2,2]paracyclophane, due to electronic repulsion and steric hindrance.

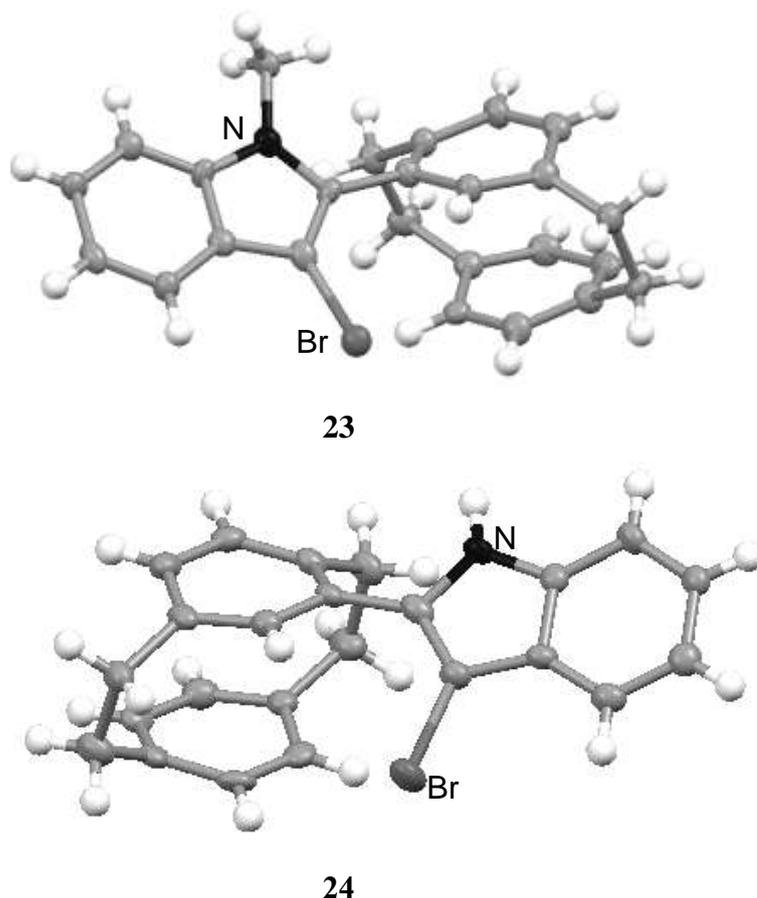


Figure 2.5: X-ray crystallography structure of **23** and **24**.

Initially, it was thought that the proton on the nitrogen was capable of forming hydrogen bonding, therefore, having that hydrogen at the exo-position could maximise the chance of intermolecular hydrogen bonding. After analysing the packed molecules in a unit cell, it was concluded that the tertiary structure of **24** was mainly stabilised by π - π interactions, and no hydrogen bonding was observed (Figure 2.6). It is clear that the two molecules at the centre of the unit cell are stabilised by π - π staggering of the two indole motifs, and two more molecules were packed around the central two through head-on π - π interactions. This conclusion is supported by both the distance and the geometry, and the distance of the interacting aromatic motifs are between 3.5 to 3.8 Å.

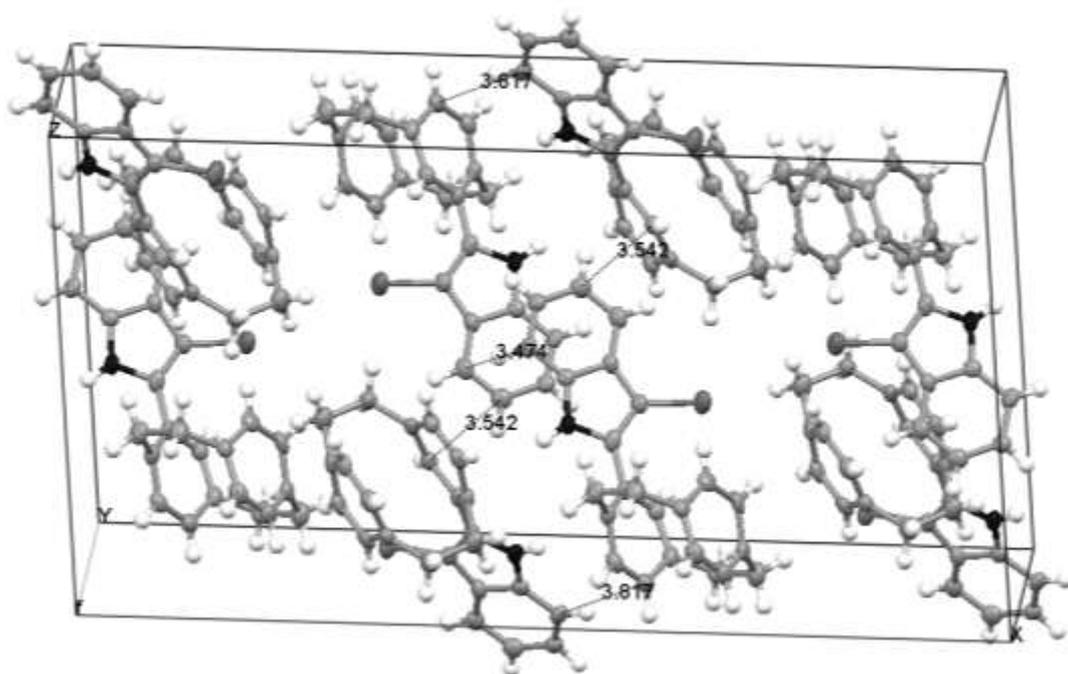


Figure 2.6: The packed molecules of **24** in a unit cell.

Similar tertiary structure was also observed for **23**, but the insertion of the methyl group weakened the structure, which resulted in longer distance of head-on π - π interactions and the sliding of the two central indole rings against each other (Figure 2.7). The interaction between the [2.2]paracyclophane on one of the central molecules and the near-by indole ring was disrupted greatly by methyl group, lengthening from 3.8 Å to 5.3 Å.

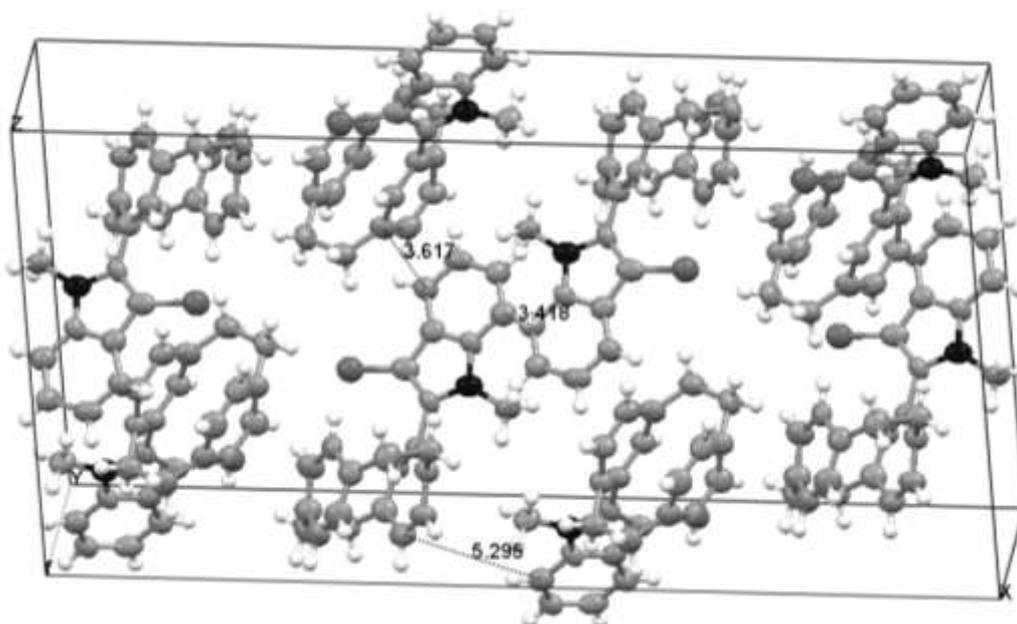


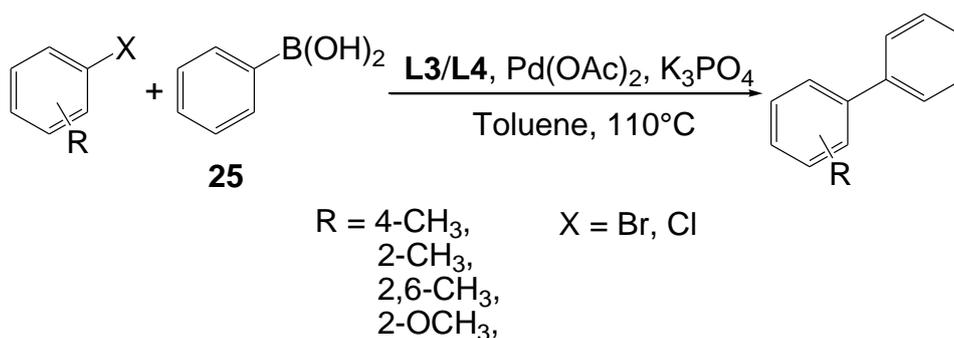
Figure 2.7: The packed molecules of **23** in a unit cell.

The last step is the addition of the appropriate phosphine through halogen-metal exchange and phosphination. This reaction is analogous with the final step in Part I. Fortunately, the new derivatives did not undergo oxidation, even when we prepared the diphenylphosphine ligand (**L3**). Therefore, this reaction proceeded with relatively high yields of 60 % and 63 % for **L3** and **L4**, respectively on their best run. Unfortunately, the formation of **L3** is capricious, occasionally, a mixture of the target ligand and a new by-product, that was inseparable with **L3** by column chromatography, was produced. The by-product has not yet been fully identified, but it is believed to be a compound closely related to the target ligand. Apart from the similar rate of flow in column chromatography, the by-product also produces signals with chemical shifts similar to the target, in both ^1H and ^{31}P NMR. The cause of this problem is not yet known. However, it is speculated that atropiomerism around the biaryl bond might be the problem. More studies are required to investigate this.

Both of the ligands produced had gel-like texture, which turned into solid foams under high vacuum. The texture was believed to be problematic for growing crystals, but attempts were still performed. All of the attempts to grow crystals of **L3** and **L4** had failed, including slow evaporation and slow diffusion with different combinations of solvents. Ligation of the two ligands to palladium might give us a better chance to obtain crystals.

Ligation of **L3** with palladium chloride failed, due to the low solubility of palladium (II) chloride in d-chloroform. Shift of signal in ^{31}P NMR spectra was observed for the attempts to ligate both **L3** and **L4** with palladium bis(acetonitrile)dichloropalladium (II). However, there was not sufficient data to support the success of the ligation, and the attempt to grow crystals of the resulted complexes did not succeed.

These two ligands were tested in the palladium-catalysed Suzuki-Miyaura coupling reactions, following a procedure developed in our laboratory by D. J. Martin (Scheme 2.16). The phenylboronic acid (**25**) was prepared in the lab.



Scheme 2.16: The palladium-catalysed SMC test reaction.

The yields reported are the gas chromatography (GC) yields, and not that of isolated biaryl compounds. Two alterations to the method were made to suit the ligands synthesised in this project. One of them was the temperature. Initially, the temperature of the reactions was set to 60 °C, but the reaction did not proceed with satisfactory yields (Table 2.1). Using toluene at reflux gave better results. Another one is the method of adding ligands and palladium source to the reaction. As discussed in the introduction, Suzuki-Miyaura coupling reaction is very sensitive to the amount of the ligand and palladium, which both were used in microgram scale in the test reactions. Due to the limitations of the laboratory equipment, those quantities cannot be measured accurately. Therefore, the ligands and palladium acetate stock solutions were used, instead of adding the solid reagents directly into the reaction vessels.

Table 2.1: The results of Suzuki-Miyaura coupling test reactions at 60 °C for **L4**.

	Aryl halide	Yield (%)			
		1h	2h*	3h	24h
1	4-bromotoluene	44.3	23.9	52.3	50.3
2	2-bromotoluene	40.5	17.4	39.1	41.8
3	2-bromo-m-xylene	38.9	33.3	48.3	46.8
4	2-bromoanisole	32.1	11.1	39.1	50.4
5	2-chlorotoluene	1.42	1.23	1.95	4.18
6	2-chloroanisole	0.634	0.013	2.07	12.3

*The yields at 2h are not reliable, that could be due to experimental errors.

Only one set of test was able to proceed for **L3**, due to the small quantity of the ligand (Table 2.2). While four sets of test were carried out for **L4** at 110 °C, which provided enough results to reach some conclusion (Table 2.3). The fact that the yield of any test reaction at 24h does not differ much from that at the 1h suggests that the **L4** has a fast turnover time, and most of the conversions were done within the first two hours. The

decreasing trend of the yield from the less hindered aryl halide to the more hindered and less electrophilic ones also fits the expectation.

Table 2.2: The results of Suzuki-Miyaura coupling test reactions at 110 °C for **L3**.

	Aryl halide	Yield (%) [*]			
		1h	2h	3h	24h
1	4-bromotoluene	64.5	78.3	84.9	74.2
2	2-bromotoluene	55.8	72.0	65.0	67.5
3	2-bromo-m-xylene	70.8	84.1	84.3	86.9
4	2-bromoanisole	73.8	63.8	59.7	89.7
5	2-chlorotoluene	9.3	12.3	12.1	18.4
6	2-chloroanisole	9.5	12.3	15.0	31.1

Table 2.3: The results of Suzuki-Miyaura coupling test reactions at 110 °C for **L4**.

	Aryl halide	Yield (%) [*]			
		1h	2h	3h	24h
1	4-bromotoluene	79.4	86.3	87.8	88.5
2	2-bromotoluene	47.1	49.8	52.1	58.3
3	2-bromo-m-xylene	57.8	64.2	58.4	60.1
4	2-bromoanisole	58.1	67.3	60.5	71.8
5	2-chlorotoluene	23.7	28.1	25.7	28.7
6	2-chloroanisole	5.8	6.3	7.0	9.5

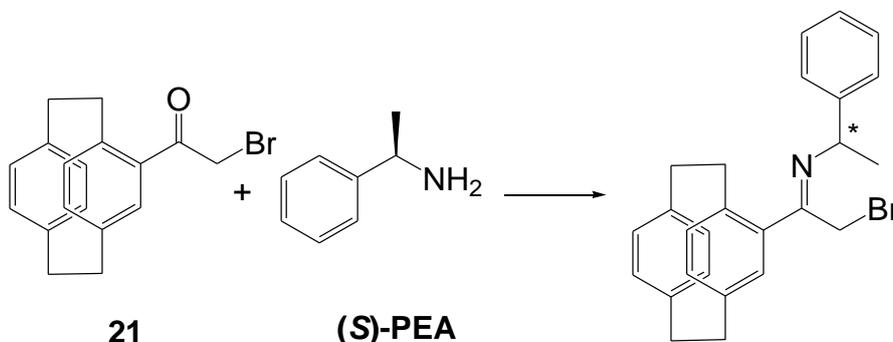
^{*}The yields reported are the average of four runs.

Although the results produced by **L4** for aryl bromides are promising, the ones for aryl chlorides are not as good. However, the reaction conditions were not optimised, thus there is still room for improvement. Test 3 and 5 were also performed with higher palladium acetate loading, which was increased from 1.0 mol% to 2.0 mol%, but no improvement of the yield was observed.

Further investigation is required for these two compounds. Other factors, including the type of palladium source, base and solvent, palladium : ligand ratio and temperature, can all affect the outcome of the Suzuki-Miyaura coupling reactions. Additionally, these two nitrogen-containing ligands, **L3** and **L4**, could potentially be useful for the coupling of nitrogen-containing compounds.

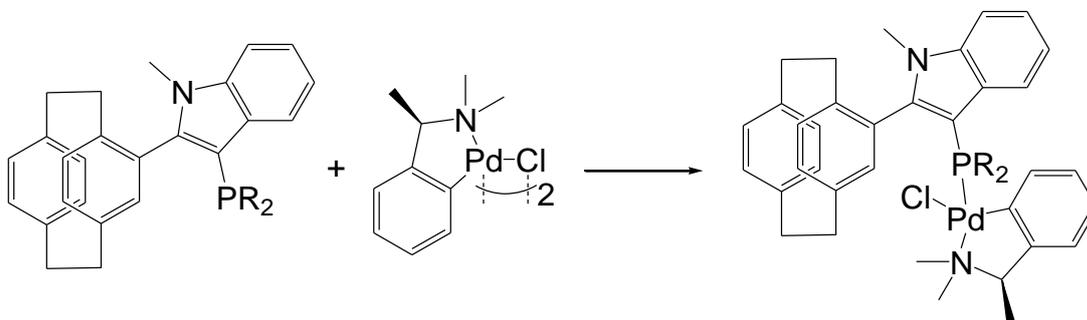
The planar chiral ligands, **L4** and **L3**, were designed for asymmetric reactions, therefore, enantiopure ligand need to be produced. Two methods have been proposed for future work. One is the asymmetric preparation of these ligands, by resolving the starting

material, 4-bromoacetyl[2.2]paracyclophane (**21**) before the synthesis (Scheme 2.17). As mentioned before, the resolution of [2.2]paracyclophane based ketones is normally achieved by Schiff's base condensation using (*S*)-phenethylamine ((*S*)-PEA).^{56,58} It involves the formation of a racemic mixture of imines, which can be purified easily by silica chromatography, or selective recrystallisation.



Scheme 2.17: Resolution of **21** by Schiff's base condensation.

Another proposal to produce enantiopure ligands is to resolve the racemic ligand by incorporating an enantiopure palladacycle (Scheme 2.18), and the diastereoisomeric palladacycle-phosphine complexes can be resolved by silica chromatography.⁶⁰



Scheme 2.18: Resolution of the ligands by palladacycle.

Once a route to enantiopure ligands is established, the ligands will be tested in asymmetric Suzuki-Miyaura coupling reactions. It was also proposed to synthesise a group of derivatives by varying the substituents on the indole motif and [2.2]paracyclophane systematically, which will allow us to influence the electronic properties through the conformation. By comparing the activities of the derivatives, and the spectroscopic data, it was expected to gain insight knowledge of the structure in relationship to the activities of the ligands. Moreover, the ligands will be screened against a range of reactions, such as arylation of enolates and amide arylation, to study its capacity of producing valuable compounds.

3. Conclusion

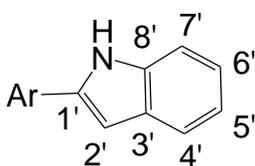
In this project, four planar chiral monophosphine ligands, that were based on [2.2]paracyclophane backbone were synthesised successfully, whereas the attempt to produce the secondary phosphine oxide ligands has not been successful. A *pseudo-ortho* substituted monophosphine ligand showed low catalytic activity in the gold-mediated cyclisation of N-allyl- β -ketoamide, but no conclusive result was achieved. Fortunately, one of the monophosphine ligands displayed reasonably good catalytic activity towards the Suzuki-Miyaura coupling reactions with aryl bromide substrates. This could lead us to a new family of planar chiral ligands in asymmetric catalysis. Further study to optimise the test reactions, gain more knowledge on the structure and explore more potentials of this ligand is required.

4. Experimental Section

Dry toluene, tetrahydrofuran and dichloromethane used in reactions were obtained from 600mm columns of dry activated alumina under positive pressure of argon, and were thoroughly degassed prior to passage through the alumina column. Tetrahydrofuran and toluene were stored over sodium, and dichloromethane was over 4 Å molecular sieves.

^1H , ^{13}C and ^{31}P NMR spectra were collected either on Bruker AVANCE 400 MHz or 500 MHz NMR spectrometer, operating at frequencies of 400/500, 100/125 and 162/202.5 MHz respectively. The samples were dissolved in deuterated-chloroform, and the chemical shifts were in ppm and referenced to the NMR solvent. The multiplicities were abbreviated as follows: s = singlet, d = doublet, t = triplet, dd = doublet of doublets, ddd = doublet of doublets of doublets, m = multiplet, br = broad. Where ^1H assignments refer to *a* or *b* protons, *a* implies *endo* and *b* implies *exo*. The probe in 400 MHz NMR spectrometer was contaminated by a pectin containing sample for a while, which gives a broad signal between 3.79 and 6.12 ppm, and multiple peaks below 1.6 ppm.

The indoles were labelled as following:



Mass spectrometry data were collected on Waters micromass ZMD mass spectrometer with standard electrospray ionisation probe.

Infra-red spectra were recorded on Perkin Elmer FT-IR spectrometer, Paragon 1000. The frequencies were reported in cm^{-1} , and the intensity was abbreviated as follows: w = weak, m = medium, s = strong.

X-ray diffraction was performed on a Rigaku spider X-ray diffractometer, equipped with a graphite monochromator and CCD area detector using Cu $K\alpha$ radiation at 1.54178Å from a rotating anode generator.

pseudo-para-dibromol[2.2]paracyclophane (**1**)

A stock solution of bromine (8.13 mL, 158 mmol) in dichloromethane (40.7 mL) was prepared. 5.0 mL of the bromine solution was added dropwise to a suspension of iron filing (0.197 g, 3.53 mmol) in dichloromethane (80.6 mL). The resulting solution was stirred for 1 h at room temperature, and then heated up to nearly reflux. A suspension of [2.2]paracyclophane (15.0 g, 72.0 mmol) in dichloromethane (360 mL) was added via a cannula. The remaining bromine solution was added dropwise in an hour. This reaction was refluxed overnight. The solution was cooled to room temperature, and filtered. The filtrate was dried, and washed with dimethylformamide (30 mL). The solid was combined to yield a slightly pink powder (11.4 g, 43.1 %). ¹H NMR (400 MHz): δ = 7.16 (2H, dd, J = 7.9, 1.6 Hz, H7, H13), 6.53 (2H, d, J = 1.5 Hz, H5, H15), 6.46 (2H, d, J = 7.9 Hz, H8, H12), 3.51 (2H, ddd, J = 13.1, 10.7, 2.3 Hz, H2a, H10a), 3.17 (2H, ddd, J = 10.4, 12.9, 5.0 Hz, H2b, H10b), 3.00 – 2.82 (4H, m, H1 \times 2, H9 \times 2). The data is in agreement with literature values.³⁷

(\pm)-*pseudo-ortho*-dibromol[2.2]paracyclophane (**2**)

A suspension of **1** (2.49 g, 6.80 mmol) in triglyme (9.7 mL) was refluxed at 230 °C for 3 h. After cooling to room temperature, the solution was filtered. The liquor was retained, and solid was returned to the reaction flask with triglyme (5 mL). This process was repeated twice more. All the filtrate was combined, concentrated by vacuum distillation at 120°C, and further purified by passing through a short silica gel plug (5 % ethyl acetate in *n*-hexane). The collected solvent was dried under reduced pressure to yield a white powder (1.05 g, 56.0 %). ¹H NMR (400 MHz): δ = 7.20 (2H, d, J = 7.8 Hz, H5, H13), 6.57-6.49 (4H, m, H7, H8, H15, H16), 3.44 (2H, ddd, J = 13.2, 9.4, 2.4 Hz, H2a, H11a), 3.14-2.98 (4H, m, H1, H9), 2.81 (2H, ddd, J = 13.4, 7.3, 10.0 Hz, H2b, H11b). The data is in agreement with literature values.³⁷

(\pm)-4-bromo-12-phenyl[2.2]paracyclophane (**3**), bench-top method

A solution of **2** (1.00 g, 2.73 mmol), phenylboronic acid (0.500 g, 4.10 mmol), tripotassium phosphate monohydrate (1.26 g, 5.48 mmol) and Pd(PPh₃)₄ (63.2 mg, 5.47 \times 10⁻³ mmol) in toluene (39.1 mL) were refluxed overnight at 115 °C, under argon atmosphere. The reaction was cooled. Ethyl acetate (40 mL) and 10 % sodium hydroxide aqueous solution (40 mL) were added. The organic layer was separated, and

the aqueous layer was extracted with 1:1 toluene:tetrahydrofuran (20 mL × 2). The combined organics was dried (magnesium sulfate), then concentrated under reduced pressure to yield a brown oil, which was purified by column chromatography on silica gel (*n*-hexane) to give **3** as a clear oil (0.754 g, 75.9 %). ¹H NMR (400 MHz): δ = 7.70 (2H, d, *J* = 7.7 Hz, H7, H16), 7.52 (2H, t, *J* = 7.4 Hz, H8, H15), 7.40 (1H, t, *J* = 7.4 Hz, H13), 7.14 (1H, s, H5), 6.70-6.75 (2H, m, -(CHCH)₂CH), 6.60-6.67 (2H, m, -(CHCH)₂CH), 6.55 (1H, dd, *J* = 7.6, 1.6 Hz, -(CHCH)₂CH), 3.53-3.68 (2H, m, H2), 3.15-3.26 (2H, m, H1), 2.81-2.95 (3H, m, H9, H10b), 2.32-2.44 (1H, m, H10a). ¹³C NMR (400 MHz): δ = 141.8, 141.5, 141.0, 139.5, 138.9, 136.7, 136.0, 135.0, 133.4, 132.0, 131.6, 129.5, 128.9, 128.7, 126.9, 125.9, 36.2, 34.8, 33.6, 32.5. IR: 3047.5 (w, aromatic C-H), 2933.8-2856.2 (m, alkane C-H), 1587.4-1541.9 (w, aromatic C-C), 1478.0-1389.8 (m, alkane C-H), 730.9 (s, aromatic C-H), 650.4 (s, C-Br). *m/z* (*M*⁺) = 365.6.

(±)-4-bromo-12-phenyl[2.2]paracyclophane (**3**), microwave method

A solution of **2** (1.45 g, 3.97 mmol), phenylboronic acid (0.520 g, 3.97 mmol), sodium carbonate (1.56 g, 106 mmol) and 10 % Pd/C (42.0 mg, 39.7 × 10⁻³ Pd mmol) in 1:9 water:toluene (7.90 mL) were sealed in a microwave tube. After 30 seconds stirring, 300 W irradiation was used to ramp the temperature up to 120 °C, under the pressure of 200 psi. This reaction was kept at 120 °C and 200 psi for 15 minutes. The work-up was same as the bench-top method, and clear oil was yielded (0.538 g, 37.4 %). The unreacted starting material, **2**, was also recovered (0.819g, 56.4 %).

General method of producing aryl dialkylphosphine (**L1**, **L2-O**, **5**, **L3**, **L4**)

n-Butyl lithium (1.6 M or 2.5 M in *n*-pentane, 1.1 eqv.) was added dropwise to a solution of the aryl bromide (**3**, **23**) (1 eqv.) in tetrahydrofuran (0.15 M) at -78 °C, under argon atmosphere. The resulting red solution was stirred for 10 minutes at -78 °C. Dialkylphosphine chloride (1.2 eqv.) was added. This solution was slowly warmed up to room temperature, and stirred overnight. Water was added, and the organic phase as separated. The aqueous phase was extracted with dichloromethane three times. The organic phases were combined and dried (magnesium sulfate). The solvent was removed under reduced pressure. The crude product was purified by column chromatography to yield the product.

(±)-4-dicyclohexylphosphino-12-phenyl[2.2]paracyclophane (**L1**): White powder. Gradient column chromatography on silica (*n*-hexane to 10 % ethyl acetate in *n*-hexane). 39.3 % yield. ¹H NMR (500 MHz): δ = 7.39-7.48 (4H, m, H7, H8, H15, H16), 7.33 (1H, tt, *J* = 1.6, 7.0 Hz, H13), 6.69 (1H, d, *J* = 1.2 Hz, H5), 6.61-6.68 (4H, m, -(CHCH)₂CH), 6.54 (1H, dd, *J* = 1.5, 4.6 Hz, -(CHCH)₂CH), 3.96 (1H, ddt, *J* = 1.7, 11.6, 13.2 Hz, H2a), 3.54 (1H, ddd, *J* = 1.6, 9.9, 13.5 Hz, H2b), 3.17-3.30 (2H, m, H9), 3.13 (1H, t, H10b), 2.95-3.04 (1H, m, H10a), 2.85-2.94 (2H, m, H1), 0.86-1.96 (22H, m, -(C₆H₁₁)₂). ¹³C NMR (400 MHz): δ = 145.3, 145.1, 141.2, 140.1, 139.5, 137.8, 136.5, 135.4, 135.2, 134.0, 133.9, 132.8, 132.2, 131.7, 130.8, 129.0, 128.4, 128.3, 126.4, 36.3, 36.1, 35.4, 34.7, 34.6, 34.5, 34.4, 34.0, 32.4, 32.1, 31.9, 31.8, 31.6, 30.6, 30.5, 28.9, 28.4, 28.3, 27.9, 27.7, 27.5, 27.4, 27.3, 27.2, 26.9, 26.6, 26.4, 26.2, 25.3, 22.7. ³¹P NMR (500 MHz): δ = 0.77 ppm. IR: 3053.3 (w, aromatic C-H), 2927.9-2851.9 (m, alkane C-H), 1591.3 (w, aromatic C-C), 1479.7-1422.0 (w, alkane C-H), 739.9 (s, aromatic C-H). *m/z* (*M*⁺) = 481.8.

(±)-4-diphenylphosphinyl-12-phenyl[2.2]paracyclophane (**L2-O**): White powder. Column chromatography (10 % ethyl acetate in *n*-hexane). 50.5 % yield. ¹H NMR (400 MHz): δ = 7.92-7.81 (3H, m), 7.67-7.73 (2H, m), 7.63 (2H, d, *J* = 7.1 Hz), 7.44-7.56 (4H, m), 7.40 (2H, td, *J* = 2.9, 7.6 Hz), 7.32 (2H, t, *J* = 7.4 Hz), 7.24-7.28 (1H, m), 7.17 (1H, d, *J* = 1.6 Hz), 6.71-6.79 (3H, m), 6.61-6.67 (2H, m), 3.68 (1H, dd, *J* = 9.2, 13.8 Hz), 3.41-3.48 (1H, m), 3.34 (1H, t, *J* = 11.8), 3.09 (1H, t, *J* = 11.5), 2.81-2.94 (2H, m), 2.72-2.80 (1H, m), 2.08-2.16 (1H, m). ³¹P NMR (500 MHz): δ = 23.46, 31.12 ppm.

(±)-4-diphenylphosphinyl-12-bromo[2.2]paracyclophane (**5**): White powder. Silica column chromatography (8:1 *n*-hexane:ethyl acetate followed by 1:1 ethyl acetate:dichloromethane). 57.5 % yield. 28.0 % of (±)-4-diphenylphosphino-12-bromo[2.2]paracyclophane (**4**) was also produced. ¹H NMR (400 MHz): δ = 7.78 (2H, ddd, *J* = 1.4, 7.7, 11.7 Hz), 7.53-7.62 (3H, m), 7.44-7.52 (3H, m), 7.36-7.44 (2H, m), 7.29 (1H, d, *J* = 1.7 Hz), 6.84 (1H, dd, *J* = 1.8, 14.7 Hz), 6.59-6.70 (3H, m), 6.51 (1H, d, *J* = 7.7 Hz), 3.36-3.54 (3H, m), 2.91-3.10 (3H, m), 2.70-2.81 (1H, m), 2.81-2.91 (1H, m). ¹³C NMR (400 MHz): δ = 145.5, 145.4, 142.0, 139.0, 138.9, 138.5, 138.4, 137.2, 135.9, 135.6, 135.5, 134.8, 133.9, 133.3, 133.1, 132.8, 132.7, 132.3, 131.5, 131.4, 131.3, 130.9, 130.6, 129.5, 128.3, 128.2, 128.1, 128.0, 127.2, 35.8, 35.7, 34.6, 32.3.

(±)-4-dicyclohexylphosphino-12-phenyl[2.2]paracyclophane gold chloride complex
(**L1**-AuCl)

A suspension of tetra-*n*-butylammonium dichloroaurate (**I**) (71.5 mg, 0.14 mmol) and **L1** (67 mg, 0.14 mmol) in dimethylformamide (1.4 mL, 0.1 M) was made. It was stirred at 90 °C for 10 min, and the solid was filtered. A white powder was yielded (42 mg, 31.2 %). ¹H NMR (400 MHz): δ = 7.47 (2H, t, *J* = 7.6 Hz, H7, H15), 7.38 (2H, d, *J* = 7.5 Hz, H8, H16), 7.33 (1H, t, *J* = 7.2 Hz, H13), 6.79 (1H, d, *J* = 11.4 Hz, H5), 6.72-6.77 (2H, m, -(CHCH)₂CH), 6.66-6.72 (3H, m, -(CHCH)₂CH), 4.33 (1H, t, *J* = 11.7 Hz, H2a), 3.62 (1H, dd, *J* = 1.6, 9.5, 13.5 Hz, H2b), 3.47-3.57 (1H, m, H10b), 3.17-3.30 (2H, m, H9), 3.05-3.16 (1H, m, H10a), 2.93-3.04 (1H, m, H1a), 2.78-2.88 (1H, m, H1b), 0.89-2.25 (22H, m, -(C₆H₁₁)₂). ¹³C NMR (400 MHz): 144.9, 144.8, 140.6, 140.0, 139.3, 139.2, 139.1, 136.9, 136.5, 136.4, 135.1, 132.8, 132.6, 131.9, 128.9, 128.6, 126.9, 122.0, 121.5, 37.1, 36.7, 36.6, 36.5, 35.0, 34.9, 34.6, 32.6, 32.3, 31.2, 30.1, 28.8, 28.3, 28.2, 26.9, 26.8, 26.7, 26.6, 26.5, 26.4, 25.6. ³¹P NMR (500 MHz): δ = 39.48 ppm. *m/z* (M⁺) = 957.1.

(±)-4-diphenylphosphino-12-phenyl[2.2]paracyclophane (**L2**)

Triethylamine (0.94 mL, 6.79 mmol) and trichlorosilane (1.34 mL, 10.21 mmol) were added to a solution of **L2-O** (332 mg, 0.686 mmol) in tetrahydrofuran (9.1 mL) under argon atmosphere, and this solution was then refluxed for 22 hours. After a mixture of 5 mL of sodium hydroxide aqueous solution (2M) and 5 mL of dichloromethane were added, the aqueous layer was extracted with dichloromethane twice. The organic layers were combined and dried over magnesium sulfate and under reduced pressure. A white powder was obtained (157 mg, 48.9 %).

¹H NMR (400 MHz): δ = 7.63 (2H, t, *J* = 7.8 Hz, -P((CHCH)₂CH)₂), 7.36-7.48 (5H, m, -(CHCH)₂CH), 7.21-7.35 (8H, m, -P((CHCH)₂CH)₂), 7.05 (1H, s, H5), 6.73 (1H, d, *J* = 7.7 Hz, H8), 6.58-6.68 (3H, m, H7, 15, 16), 6.18 (1H, d, *J* = 8.2 Hz, H13), 3.50 (1H, dd, *J* = 9.4, 13.4 Hz, H2a), 3.26-3.43 (2H, m, H2b, H9a), 3.13 (1H, t, *J* = 10.3, H9b), 2.69-2.92 (3H, m, H1, H10b), 2.07—2.17 (1H, m, H10a). ¹³C NMR (400 MHz): δ = 143.6, 143.4, 140.9, 139.9, 139.8, 139.6, 139.4, 136.9, 136.8, 136.5, 136.3, 136.2, 135.7, 134.5, 133.0, 132.8, 132.7, 132.5, 131.7, 130.2, 129.8, 129.6, 129.4, 128.6, 128.5, 128.4, 128.3, 128.2, 126.6, 35.9, 35.8, 35.1, 34.7, 33.7, 33.4, 26.9, 14.2, 1.22. ³¹P NMR (500 MHz): δ = -1.66 ppm. IR: 3053.3 (w, aromatic C-H), 2927.9-2851.9 (m, alkane C-H), 1591.3 (w, aromatic C-C), 1479.7-1422.0 (w, alkane C-H), 739.9 (s, aromatic C-H).

N-(2-propenyl)-N-benzylamine (**8**)

A solution of benzyl bromide (5.0 mL, 42.1 mmol) in tetrahydrofuran (140 mL) was added drop-wise to a solution of potassium carbonate (11.6 g, 84.2 mmol) and allylamine (12.6 mL, 168 mmol) in tetrahydrofuran (842 mL), at 0 °C, and this reaction was stirred overnight at room temperature. This solution was then filtered on celite, and the filtrate was condensed under reduced pressure. A pale yellow liquid was yielded (5.65 g, 91.3 %). ¹H NMR (400 MHz): δ = 7.32-7.37 (4 H, m, $-(\text{CHCH})_2\text{CH}$), 7.24-7.30 (1 H, m, $-(\text{CHCH})_2\text{CH}$), 5.90-6.02 (1 H, m, $-\text{CH}=\text{CH}_2$), 5.22 (1H, d, $J = 17.2$ Hz, $-\text{NHCH}_a\text{H}_b\text{CH}-$), 5.14 (1H, d, $J = 10.1$ Hz, $-\text{NHCH}_a\text{H}_b\text{CH}-$), 3.82 (2H, s, PhCH_2-), 3.30 (2H, d, $J = 6.0$ Hz, $-\text{CH}=\text{CH}_2$), 1.71 (1H, br, $-\text{NH}-$). The data is in agreement with literature values.⁶¹

3-oxo-N-benzyl-N-(2-propenyl)butanamide (**9**) and the tautomerised enol (**9A**)

A solution of **8** (1.22 g, 8.16 mmol), 4-dimethylaminopyridine (0.415 g, 3.40 mmol) and acetoacetate (0.73 mL, 6.80 mmol) was refluxed for 6 hours. After cooling, the solvent was evaporated under reduced pressure. This residue was extracted with diethyl ether from aqueous solution, and the organic extract was washed successively with aqueous hydrochloric acid solution (2N) and water. The extract was then dried over magnesium sulfate, and under reduced pressure. A dark red liquid was yielded (0.870 g, 55.4%), a mixture of **9** and **9A**.

(**9**): ¹H NMR (400 MHz): δ = 7.13-7.42 (5H, m, Ph), 5.67-5.86 (1H, m, $-\text{CH}=\text{CH}_2$), 5.09-5.28 (2H, m, $-\text{CH}=\text{CH}_2$), 4.49 (2H, s, PhCH_2-), 4.03 (2H, d, $J = 5.7$ Hz, $-\text{NHCH}_2\text{CH}-$), 3.59 (2H, s, $-\text{COCH}_2\text{CO}-$), 2.27 (3H, s, $-\text{COCH}_3$). The data is in agreement with literature values.⁴³

(**9A**): ¹H NMR (400 MHz): δ = 14.72 (1H, d, $J = 11.9$ Hz, $-\text{OH}$), 7.13-7.42 (5H, m, Ph-H), 5.67-5.86 (1H, m, $-\text{CH}=\text{CH}_2$), 5.09-5.28 (2H, m, $-\text{CH}=\text{CH}_2$), 4.62 (2H, s, PhCH_2-), 3.80 (2H, d, $J = 4.9$ Hz, $-\text{NHCH}_2\text{CH}-$), 3.57 (1H, s, $-\text{COCH}_2\text{CO}-$), 2.31 (3H, s, $-\text{COCH}_3$).

(±)-4-bromo[2.2]paracyclophane (**16**)

A bromine (0.25 mL, 4.80 mmol) stock solution in dichloromethane (48.0 mL) was prepared. 10% of the bromine stock solution was added into a flask containing the iron

filing (77 mg, 1.37 mmol) under argon, and stirred for 1 hour. [2.2]Paracyclophane (1.00 g, 4.80 mmol) was suspended in dichloromethane (48.0 mL), which was added to the previous flask. The remaining bromine solution was then added drop-wise to the reaction. The progress of this reaction was monitored by thin layer chromatography (TLC). After stirring for 40 minutes, it reached completion. The reaction mixture was washed successively with saturated ammonium chloride (50 mL), sodium thiosulphate (50 mL) and brine (50 mL) twice. The dichloromethane layer was then dried over magnesium sulfate, and under reduced pressure. A creamy white powder was yielded (1.49 g, 101 %). ^1H NMR (400 MHz): δ = 7.18 (1H, dd, J = 1.8, 7.8 Hz, H5), 6.44-6.61 (5H, m, H7, 8, 12, 13, 15, 16), 3.48 (1H, ddd, J = 2.1, 10.2, 13.4 Hz, H2a), 3.17-3.26 (1H, m, H2b), 3.02-3.17 (4H, m, H1, 9), 2.79-2.99 (2H, m, H10). The data is in agreement with literature values.⁶²

(±)-[2.2]paracyclophanyl alkoxyphosphinic acid (**17**)

n-BuLi (1.6 M or 2.5 M in *n*-pentane, 1.1 eqv.) was added dropwise to a solution of **16** (1 eqv.) in tetrahydrofuran (0.067 M) at -78°C, under argon atmosphere. The resulting red solution was stirred for 30 minutes at -78°C. Trialkoxyphosphine (1.3 eqv.) was added. This solution was slowly warmed up to room temperature, and stirred overnight. The aqueous hydrochloric acid solution (2M) was added, and the organic phase as separated. The aqueous phase was extracted with dichloromethane three times. The organic phases were combined and dried (magnesium sulfate). The solvent was removed under reduced pressure. The crude product was purified by gradient silica column chromatography (40 % to 60 % of ethyl acetate in *n*-hexane) to yield the product.

(±)-[2.2]paracyclophanyl ethoxyphosphinic acid (**17-Et**): White powder obtained, 47.6 % yield.

Diastereoisomer 1: ^1H NMR (500 MHz): δ = 7.66 (1H, d, J = 552 Hz, -PH), 7.15 (1H, dd, J = 1.9, 15.3 Hz, H5), 6.64-6.74 (5H, m, H7, 8, 12, 15, 16), 6.51 (1H, dd, J = 1.7, 8.0 Hz, H13), 4.05-4.25 (5H, m, -OCH₂CH₃), 3.64 (1H, t, J = 11.4 Hz, H2a), 3.00-3.27 (7H, m, H1, 2b, 9, 10). ^{13}P NMR (500 MHz): δ = 24.58 ppm.

Diastereoisomer 2: ^1H NMR (500 MHz): δ = 7.52 (1H, d, J = 548 Hz, -PH), 7.15 (1H, dd, J = 1.8, 19.3 Hz, H5), 6.80-6.84 (1H, dd, J = 1.6, 8.0 Hz, H12), 6.54-6.64 (4H, m,

H7, 8, 15, 16), 6.42 (1H, dd, $J = 1.7, 8.0$ Hz, H13), 4.05-4.25 (5H, m, $-\text{OCH}_2\text{CH}_3$), 3.80 (1H, t, $J = 11.9$ Hz, H2a), 3.33 (1H, td, $J = 4.7, 11.9$ Hz, H2b), 3.00-3.27 (6H, m, H1, 9, 10). ^{13}P NMR (500 MHz): $\delta = 29.50$ ppm.

(±)-[2.2]paracyclophanyl methoxyphosphinic acid (**17-Me**): White powder obtained, 47.9 % yield.

Diastereoisomer 1: ^1H NMR (500 MHz): $\delta = 7.64$ (1H, d, $J = 554$ Hz, $-\text{PH}$), 7.15 (1H, dd, $J = 1.9, 15.3$ Hz, H5), 6.67-6.74 (5H, m, H7, 8, 12, 15, 16), 6.51 (1H, dd, $J = 1.7, 7.9$ Hz, H13), 3.77 (3H, d, $J = 11.8$ Hz, $-\text{OCH}_3$), 3.64 (1H, m, H2a), 3.02-3.28 (7H, m, H1, 2b, 9, 10). ^{13}P NMR (500 MHz): $\delta = 27.10$ ppm.

Diastereoisomer 2: ^1H NMR (500 MHz): $\delta = 7.48$ (1H, d, $J = 550$ Hz, $-\text{PH}$), 6.84 (1H, dd, $J = 1.7, 19.6$ Hz, H5), 6.78-6.82 (1H, dd, $J = 1.5, 8.0$ Hz, H12), 6.55-6.63 (4H, m, H7, 8, 15, 16), 6.42 (1H, dd, $J = 1.7, 8.0$ Hz, H13), 3.82 (3H, d, $J = 12.0$ Hz, $-\text{OCH}_3$), 3.64 (1H, m, H2a), 3.02-3.28 (7H, m, H1, 2b, 9, 10). ^{13}P NMR (500 MHz): $\delta = 32.73$ ppm.

(±)-4-acetyl[2.2]paracyclophane (**18**)

Acetyl chloride (0.90 mL, 12.7 mmol) was added dropwise to a flask of aluminium chloride (1.43 g, 10.7 mmol) suspending in dichloromethane (1.33 mL), under argon atmosphere. This solution was stirred for 5 minutes, and added dropwise to another flask of [2.2]paracyclophane (1.00 g, 4.80 mmol) suspending in dichloromethane (5.33 mL) at -70°C . This reaction was stirred for 30 minutes, while warmed up to -20°C slowly. It was then filtered through glass-wool into a flask, which contains ice in aqueous hydrochloric acid solution (6M, 10 mL). This mixture was stirred until clear. Ethyl acetate was added to the mixture, and the organic layer was washed successively with saturated aqueous sodium bicarbonate solution and brine twice. The organic layer was dried over magnesium sulfate, and under reduced pressure. The crude product was recrystallised from diethyl ether:*n*-hexane (1:1), and a white powder was yielded (758 mg, 63.2 %). ^1H NMR (400 MHz): $\delta = 7.01$ (1H, s, H5), 6.67 (1H, d, $J = 7.9$ Hz, H12), 6.46-6.59 (4H, m, H7, 8, 15, 16), 6.39 (1H, d, $J = 7.6$ Hz, H13), 3.93-4.03 (1H, m, H2a), 2.98-3.26 (6H, m, H1, 2b, 9b, 10), 2.80-2.90 (1H, m, H9a), 2.48 (3H, s, $-\text{COCH}_3$).

N-methyl-N-phenylhydrazine (**19**)

Phenylhydrazine was added dropwise to a flask of sodium hydride (60 % wt. in oil, 89 mg, 2.23 mmol) in tetrahydrofuran (10.0 mL) at 0°C. This reaction was removed from ice bath, and argon was bubbled through this reaction for 1 hour. It was then cooled back down to 0°C, and iodomethane (0.139 mL, 2.23 mmol) was added. This reaction was stirred for 1 ½ hours. After THF was removed under reduced pressure, water and dichloromethane was added to the reaction vessel, and it was extracted with dichloromethane. The organic layers were combined and dried over magnesium sulfate, and under reduced pressure. The crude product was purified by silica column chromatography (2.5 % ethyl acetate in *n*-hexane), a yellow oil was yielded (71 mg, 28.6 %). ¹H NMR (400 MHz): δ = 7.22 (2H, t, *J* = 7.7 Hz, -(CHCH₂)₂CH), 6.73 (1H, t, *J* = 7.4 Hz, -(CHCH₂)₂CH), 6.64 (2H, d, *J* = 8.2 Hz, -(CHCH₂)₂CH), 3.71 (2H, br, -NH₂), 2.86 (3H, s, -CH₃). The data agrees with AIST: Integrated Spectral Database System of Organic Compounds. (Data were obtained from the National Institute of Advanced Industrial Science and Technology (Japan)).

(±)-4-bromoacetyl[2.2]paracyclophane (**21**)

Bromoacetyl bromide (22.0 mL, 254 mmol) was added dropwise to a flask of aluminium chloride (28.4 g, 213 mmol) suspending in dichloromethane (26.6 mL), under argon atmosphere. This solution was stirred for 8 minutes, and transferred to another flask of [2.2]paracyclophane (20.0 g, 96.0 mmol) suspending in dichloromethane (96.0 mL) at -15°C, via a cannula. This reaction was then stirred for 1 hour at -15°C. The resulted mixture was then filtered through glass-wool into a flask, which contains ice in aqueous hydrochloric acid solution (6M, 100 mL). This mixture was stirred until clear. The organic layer was washed successively with saturated aqueous sodium bicarbonate solution and brine twice, and dried over magnesium sulfate and under reduced pressure. The crude product was purified by a silica column chromatography (10 % diethyl ether in *n*-hexane), and a white powder was yielded (15.7 g, 49.6 %). ¹H NMR (400 MHz): δ = 6.98 (1H, d, *J* = 1.7 Hz, H5), 6.73 (1H, dd, *J* = 7.8 Hz, H12), 6.51-6.61 (4H, m, H7, 8, 15, 16), 6.40 (1H, d, *J* = 1.6, 8.0 Hz, H13), 4.28 (2H, dd, *J* = 12.4, 86.0 Hz, -COCH₂Br), 3.89 (1H, td, *J* = 1.8, 11.2 Hz, H2a), 3.15-3.31 (4H, m, H1a, 2b, 10), 2.99-3.08 (2H, m, H1b, 9b), 2.84-2.93 (1H, m, H9a). The data agrees with the predicted NMR data calculated using Advanced Chemistry

Development, Inc. (ACD/Labs) Software V11.01. It was synthesised before, but the NMR data was not reported, due to the age of the paper.⁶³

(±)-2-[2.2]paracyclophan-4-ylindole (**22**)

20 (4.71 g, 14.3 mmol) was suspended in methanol (19.1 mL), and triethylamine (3.98 mL, 28.6 mmol) was added. This solution was stirred for 24 hours at room temperature, under argon atmosphere. The solvent was removed. After adding aniline (3.91 mL, 42.9 mmol), this reaction was refluxed for 8 hours at 200°C. The reaction was then cooled, and dissolved in ethyl acetate (50 mL). 10 % of hydrochloric acid solution (50 mL) was added, and this solution was stirred for 30 minutes. The organic layer was separated out, and washed with diluted hydrochloric acid solution. The organic layers were combined and dried over magnesium sulfate, and under reduced pressure. The crude product was purified by silica column chromatography (5 % ethyl acetate in *n*-hexane), a white powder was yielded (4.1 g, 88.4 %). ¹H NMR (400 MHz): δ = 8.08 (1H, br, NH), 7.73 (1H, d, J = 7.8 Hz, H4'), 7.44 (1H, d, J = 7.8 Hz, H7'), 7.15-7.27 (2H, m, H2', 6'), 6.64 (2H, m, H5, 12), 6.68 (1H, d, J = 1.7 Hz, H13), 6.63 (1H, d, J = 1.8, 7.8 Hz, H5'), 6.52-6.61 (4H, m, H7, 8, 15, 16), 3.64 (1H, t, J = 10.2 Hz, H2a), 2.92-3.24 (6H, m, H1, 2b, 9b 10), 2.73-2.86 (1H, m, H9a). The data is in agreement with literature values.⁵⁹

(±)-2-[2.2]paracyclophan-4-yl-N-methyl-indole (**20**)

Sodium hydride (60 % wt. in oil, 495 mg, 12.4 mmol) was added bits by bits to a solution of **21** (2.00 g, 6.18 mmol) in tetrahydrofuran (12.4 mL). Argon was bubbled through this reaction for 15 minutes. Iodomethane (0.77 mL, 12.4 mmol) was added. This reaction was stirred for 20 minutes at and then stirred at room temperature overnight. After tetrahydrofuran was removed under reduced pressure, the mixture was extracted with dichloromethane from water. The organic layers were combined and dried over magnesium sulfate, and under reduced pressure. The crude product was purified by silica column chromatography (5 % ethyl acetate in *n*-hexane), a white powder was yielded (1.74 g, 83.3 %). ¹H NMR (400 MHz): δ = 7.78 (1H, d, J = 7.8 Hz, H4'), 7.38 (1H, d, J = 8.1 Hz, H7'), 7.29 (1H, t, J = 7.2 Hz, H5'), 7.21 (1H, t, J = 7.3 Hz, H6'), 6.88 (1H, d, J = 1.8, 8.0 Hz, H5), 6.77 (1H, s, H2'), 6.66-6.72 (2H, m, H12, 13), 6.54-6.64 (4H, m, H7, 8, 15, 16), 3.55 (3H, s, -CH₃), 3.00-3.22 (5H, m, H1, 2, 10a), 2.80-2.98 (3H, m, H9, 10b). The data is in agreement with literature values.⁵⁹

(±)-2-[2.2]paracyclophan-4-yl-3-bromo-N-methyl-indole (**23**)

N-Bromosuccinimide (498 mg, 2.80 mmol) was added slowly to a solution of **22** (946 mg, 2.80 mmol) in chloroform (70.1 mL) at 0°C, and this reaction was stirred for 30 minutes at 0°C. The solvent was evaporated under reduced pressure, and purified by a column (5 % ethyl acetate in *n*-hexane), and a white powder was yielded (1.03 g, 88.0 %). ¹H NMR (400 MHz): δ = 7.73 (1H, d, *J* = 7.5 Hz, H4'), 7.28-7.37 (3H, m, H5', 6', 7'), 7.17 (1H, d, *J* = 1.8 Hz, H5), 6.85 (1H, d, *J* = 1.9, 7.8 Hz, H12), 6.71 (2H, m, H7, 8), 6.62 (1H, dd, *J* = 1.8, 7.9, H13), 6.54 (1H, d, *J* = 7.8 Hz, H7), 6.48 (1H, dd, *J* = 1.7, 7.7 Hz, H8), 3.50 (3H, s, -CH₃), 3.22-3.41 (2H, m, H2), 2.98-3.22 (4H, m, H1, 10), 2.76-2.94 (2H, m, H9). ¹³C NMR (400 MHz): δ = 139.7, 139.7, 139.3, 139.3, 137.4, 137.1, 135.4, 134.7, 134.3, 133.6, 132.5, 132.2, 131.7, 129.1, 128.0, 123.0, 120.7, 119.7, 109.9, 89.6, 35.6, 35.2, 35.2, 33.5, 31.5. IR: 3031.2-3012.4 (w, aromatic C-H), 2926.5-2852.1 (s, alkane C-H), 1590.0 (w, aromatic C-C), 1463.1 (m, alkane C-H), 732.8 (s, aromatic C-H), 612.6 (w, C-Br). *m/z* (M⁺) = 418.7.

(±)-2-[2.2]paracyclophan-4-yl-3-diphenylphosphino-N-methyl-indole (**L3**): White foam. 60.1 % yield. ¹H NMR (400 MHz): δ = 7.62 (2H, t, *J* = 7.4 Hz), 7.52 (2H, t, *J* = 7.3 Hz), 7.28-7.41 (5H, m), 7.21 (1H, t, *J* = 7.4 Hz), 7.09-7.16 (2H, m), 6.99 (1H, d, *J* = 8.0 Hz), 6.89 (1H, t, *J* = 7.5 Hz), 6.65-6.73 (3H, m), 6.51 (1H, d, *J* = 7.7 Hz), 6.36-6.46 (3H, m), 3.53 (3H, s, -CH₃), 3.15-3.40 (3H, m, H1a, 2), 2.91-3.06 (3H, m, H1b, 10), 2.76-2.91 (2H, m, H9). ¹³C NMR (400 MHz): δ = 149.8, 149.4, 139.7, 139.1, 139.0, 138.9, 138.5, 138.4, 134.7, 134.6, 134.5, 134.3, 133.7, 133.6, 132.6, 132.5, 132.4, 132.0, 131.8, 131.5, 130.3, 130.2, 129.8, 128.5, 128.4, 128.4, 128.3, 127.8, 127.4, 122.6, 121.9, 120.0, 109.9, 102.8, 100.0, 35.4, 35.2, 35.0, 33.5, 31.3. ³¹P NMR (400 MHz): δ = -28.78 ppm. IR: 3053.5-2928.3 (m, aromatic C-H), 2889.5-2852.1 (w, alkane C-H), 1584.0-1498.7 (w, aromatic C-C), 1474.0-1408.6 (m, alkane C-H), 740.9-703.8 (s, aromatic C-H). *m/z* (M⁺) = 522.6.

(±)-2-[2.2]paracyclophan-4-yl-3-dicyclohexylphosphino-N-methyl-indole (**L4**): Pale yellow foam. 62.7 % yield. ¹H NMR (400 MHz): δ = 7.96 (1H, d, *J* = 8.0 Hz, H4'), 7.37 (1H, d, *J* = 8.0 Hz, H7'), 7.30 (1H, d, *J* = 7.8 Hz, H5'), 7.21 (1H, t, *J* = 7.5 Hz, H6'), 7.16 (2H, m, H5, 12), 6.79-6.86 (1H, m, H13), 6.69-6.79 (2H, m, H7, 8), 6.44 (1H, d, *J* = 7.7, H15), 6.39 (1H, d, *J* = 7.8 Hz, H16), 3.42 (3H, s, -CH₃), 3.28-3.39 (1H, m, H2a), 2.98-3.22 (4H, m, H1, 2b, 10a), 2.81-2.92 (1H, m, H10b), 2.61-2.76 (2H, m, H9), 1.09-

2.55 (22, m, Cy-H). ^{13}C NMR (400 MHz): $\delta = 149.6, 149.2, 139.8, 139.0, 138.8, 138.5, 138.3, 135.0, 134.8, 134.4, 134.2, 134.1, 133.9, 133.7, 133.6, 131.6, 131.3, 131.0, 131.0, 130.3, 121.9, 121.6, 119.6, 109.9, 104.8, 104.6, 37.5, 37.4, 35.4, 35.1, 35.0, 34.7, 34.6, 34.4, 34.1, 33.2, 32.8, 32.6, 31.8, 31.7, 31.6, 31.2, 30.6, 30.5, 27.9, 27.8, 27.5, 27.4, 27.4, 27.3, 26.7, 26.6, 26.5, 25.3, 22.7, 20.8, 14.2$. ^{31}P NMR (400 MHz): $\delta = 20.87$ ppm. IR: 3044.4-3010.9 (m, aromatic C-H), 2924.2-2849.2 (s, alkane C-H), 1588.7-1570.3 (w, aromatic C-C), 1446.9-1407.9 (s, alkane C-H), 739.5 (s, aromatic C-H). m/z (M^+) = 524.0.

(\pm)-2-[2.2]paracyclophan-4-yl-3-bromo-indole (**24**): It was produced from bromination of **22**, following the same procedure as the production of **23**. White powder, 91.9 % yield. ^1H NMR (400 MHz): $\delta = 8.23$ (1H, br, -NH-), 7.69 (1H, d, $J = 7.2$ Hz, H4'), 7.47 (1H, $J = 7.7$ Hz, H7'), 7.32 (1H, m, H5'), 6.92 (1H, s, H5), 6.52-6.77 (7H, m, H5, 7, 8, 12, 13, 15, 16), 3.37-3.48 (1H, m, H2a), 3.02-3.31 (6H, m, H1, 2b, 10a), 2.76-3.02 (3H, m, H9, 10b).

Phenyl boronic acid (**25**)

n-Butyl lithium (2.5 M in *n*-pentane, 11.2 mL, 28.0 mmol) was added dropwise to a solution of bromobenzene (2.68 mL, 25.5 mmol) in tetrahydrofuran (380 mL) at -78°C , under argon atmosphere. The resulting red solution was stirred for 30 minutes at -78°C . Trimethoxyborane (2.55 mL, 22.9 mmol) was added. This solution was stirred for a further 30 minutes at -78°C , and then another 30 minutes at room temperature. The aqueous hydrochloric acid solution (10 %, 15.5 mL, 51.0 mmol) was added. After stirring for 30 minutes, the mixture was extracted with dichloromethane three times. The organic phases were combined and dried over magnesium sulfate, and under reduced pressure. The crude product was washed with *n*-hexane to yield the product (2.037 g, 65.5 %). ^1H NMR (400 MHz): $\delta = 8.28$ (1H, d, $J = 7.0$ Hz, -(CHCH) $_2$ CH), 7.12-7.67 (4H, m, -(CHCH) $_2$ CH).

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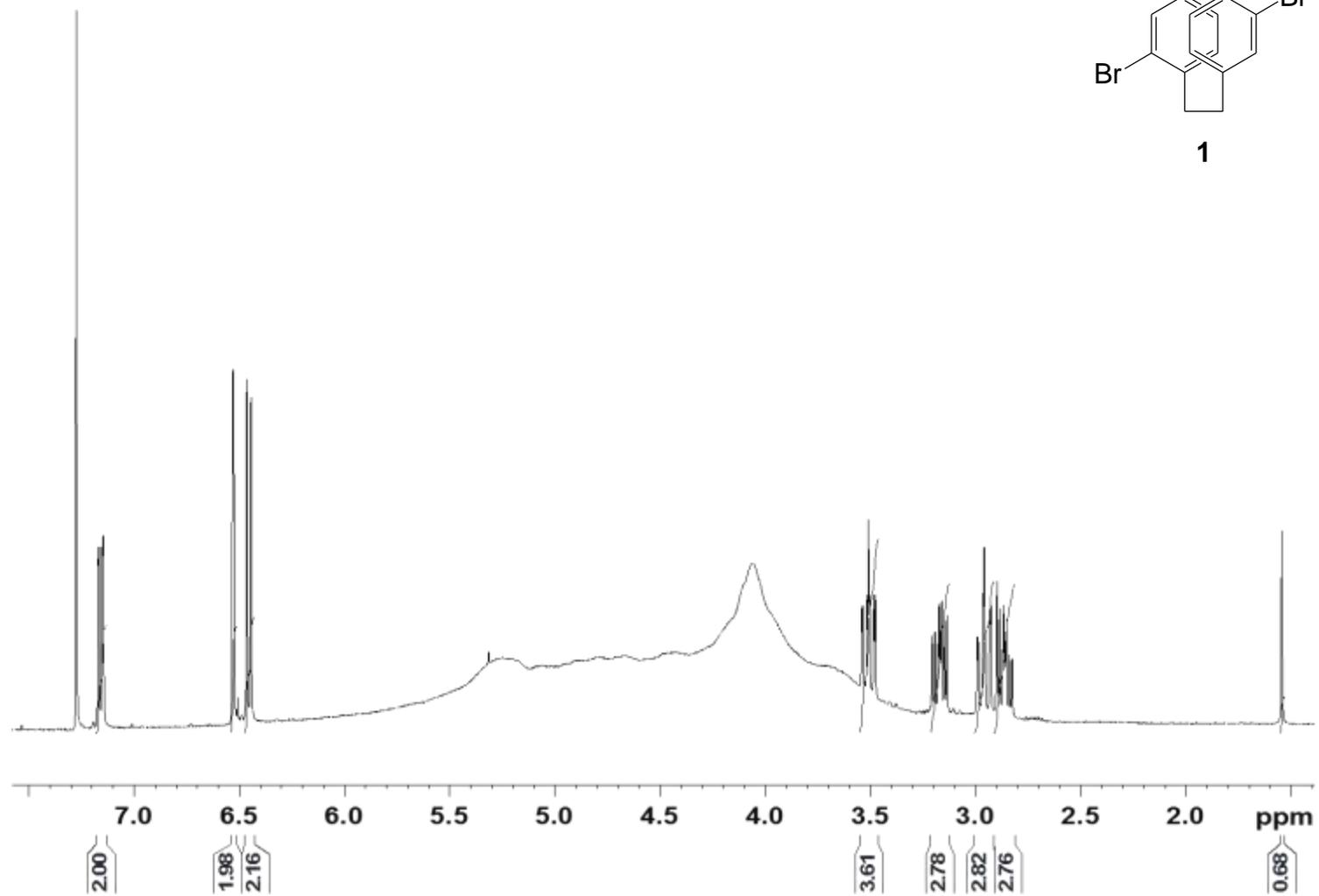
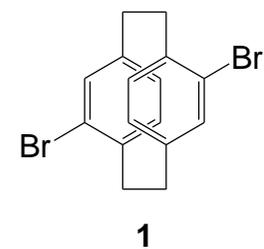
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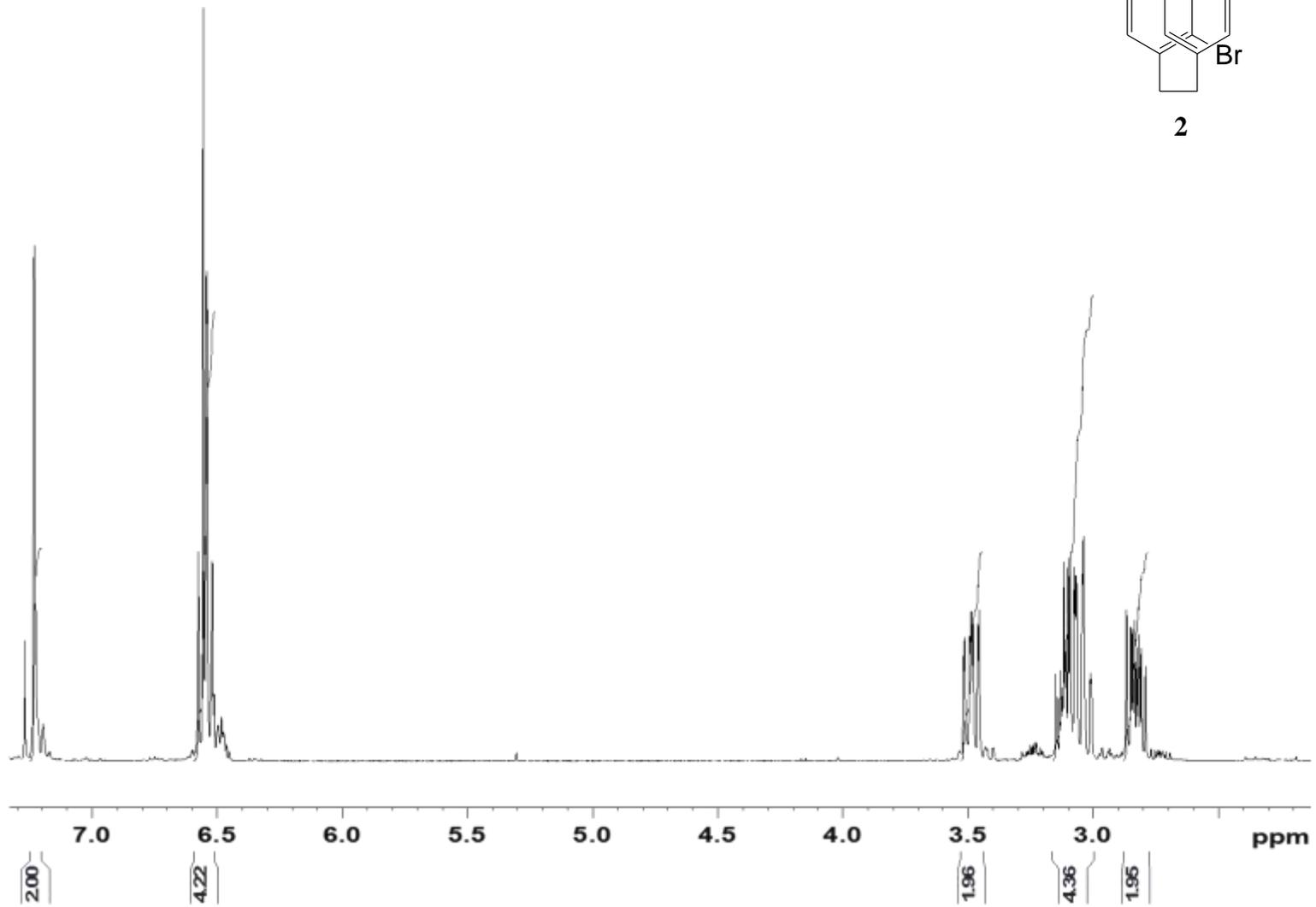
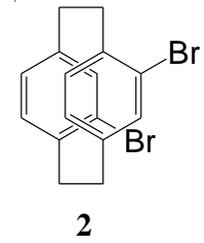
6. Additional information

This section includes the ^1H , ^{13}C , ^{31}P NMR spectroscopic information of the compounds synthesised, and the cif files of the X-ray crystallography.

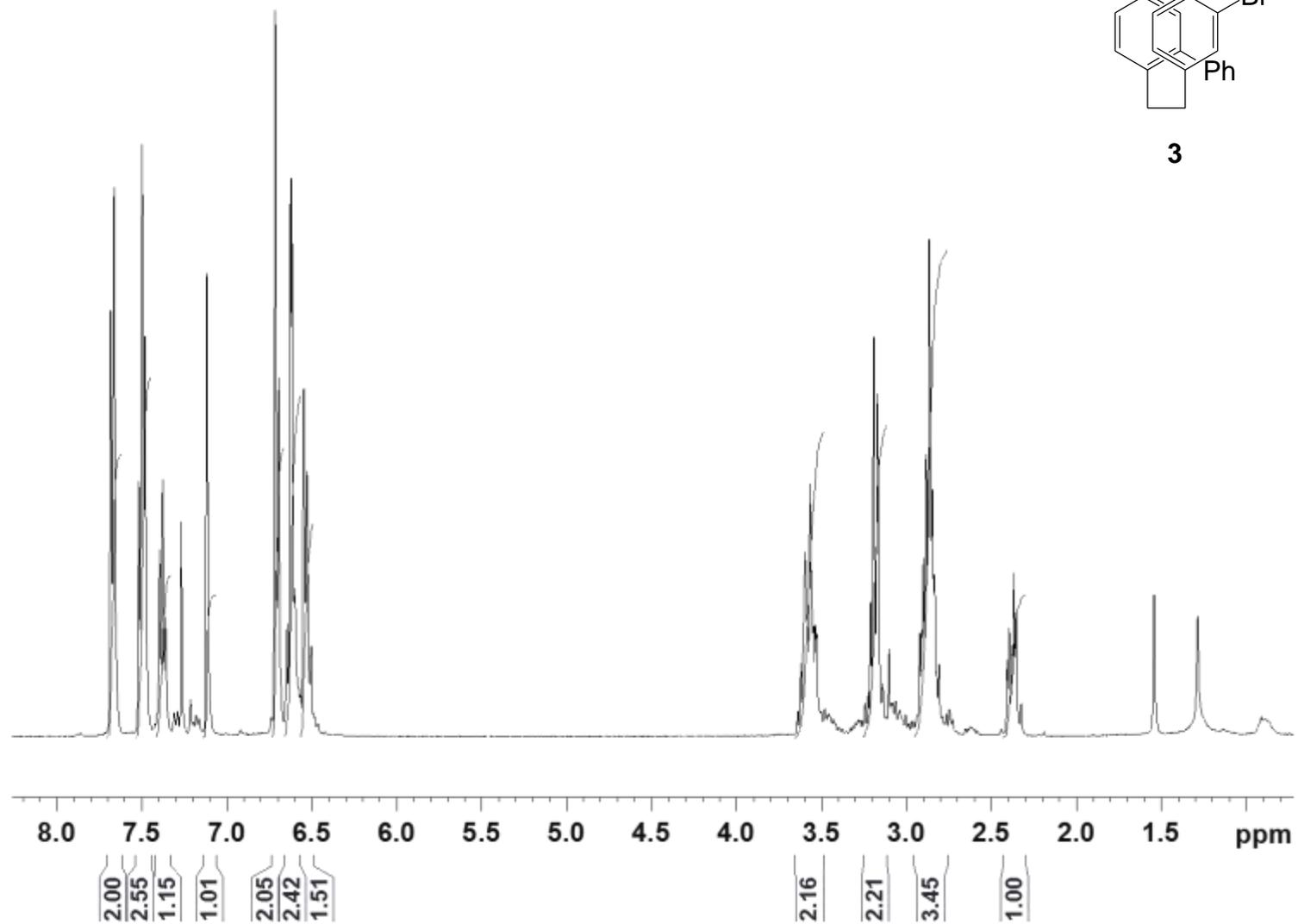
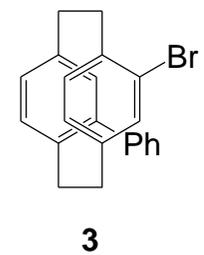
^1H NMR of *pseudo-para*-dibromol[2.2]paracyclophane (**1**)



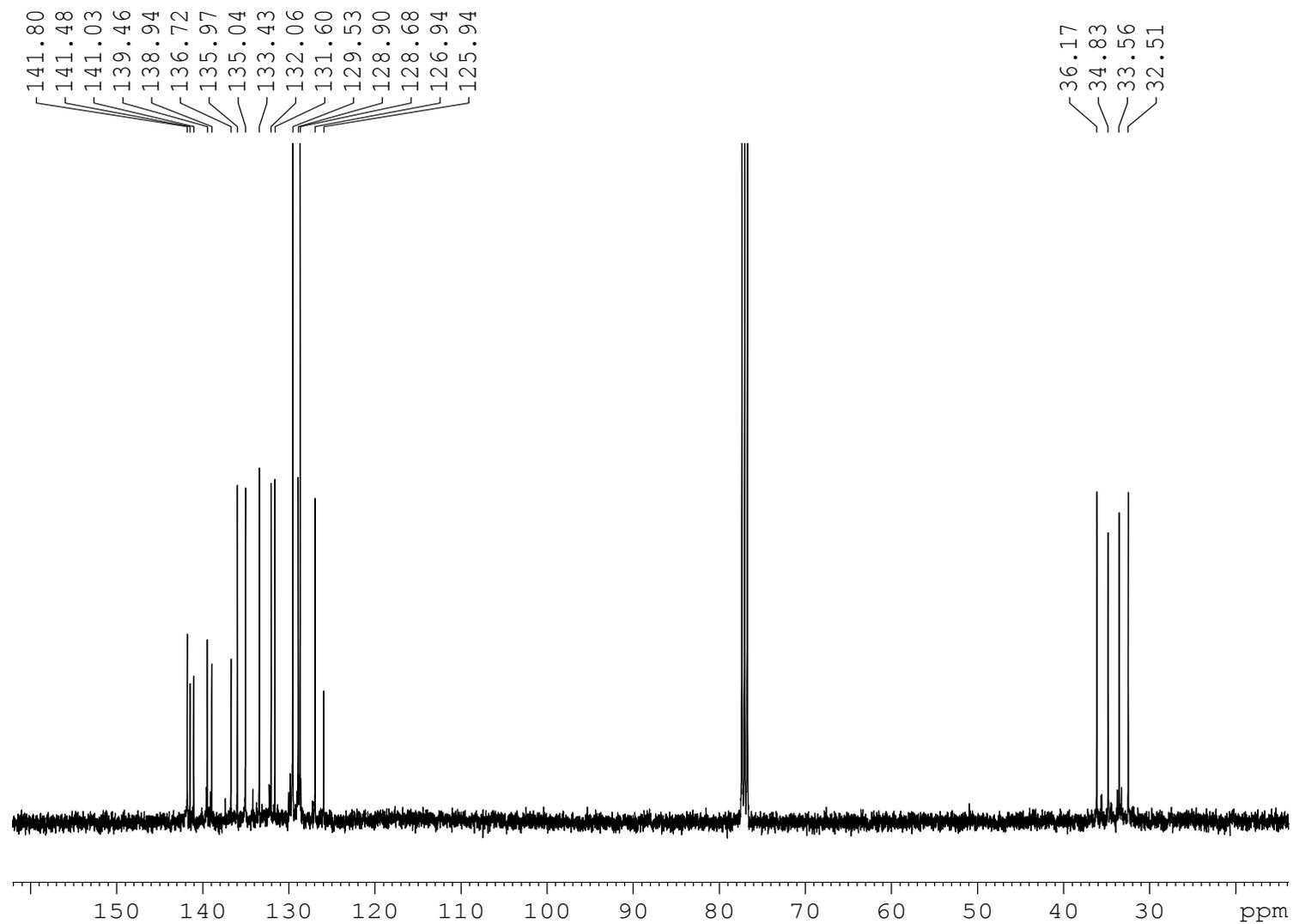
^1H NMR of (\pm)-*pseudo-ortho*-dibromol[2.2]paracyclophane (**2**)



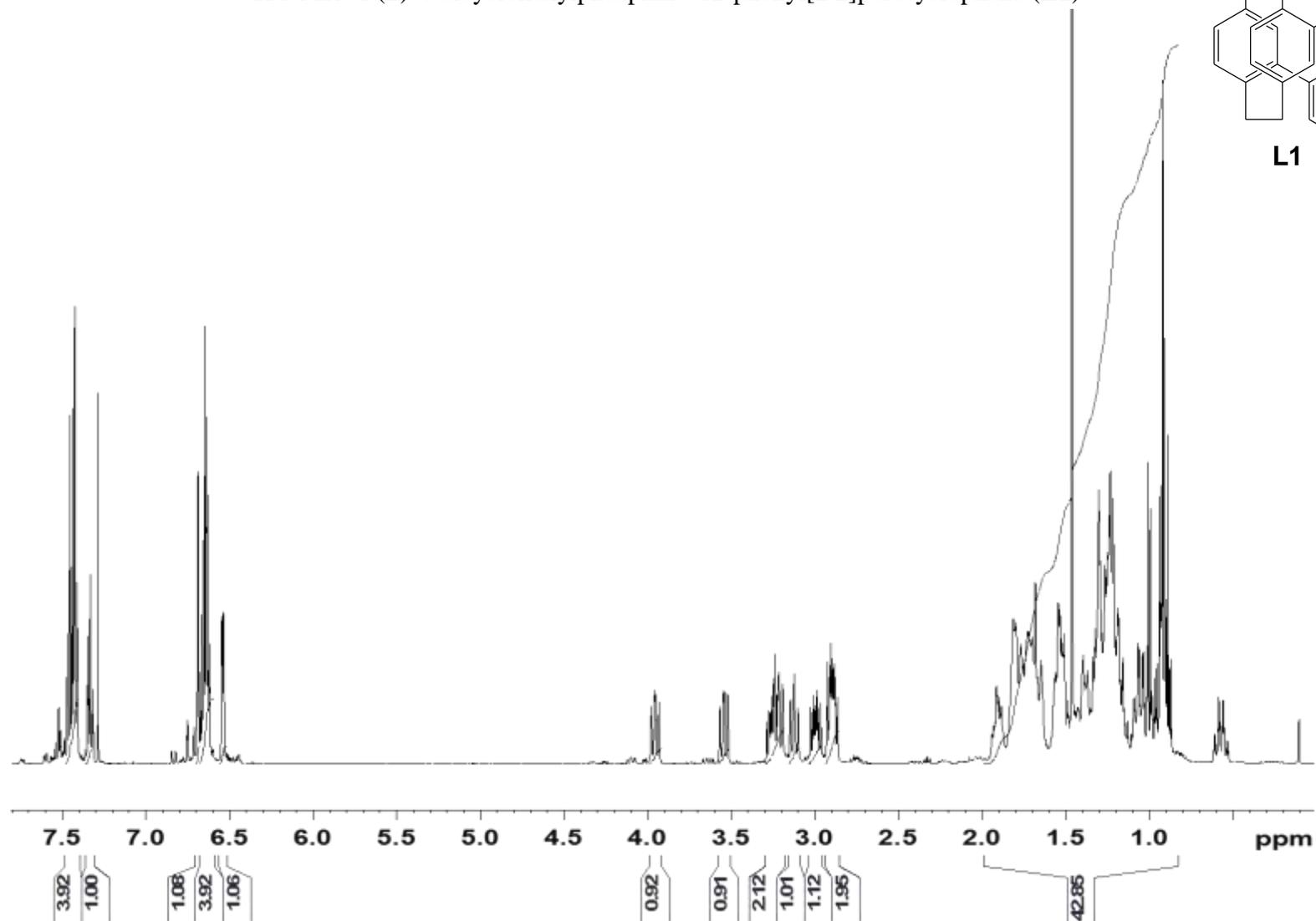
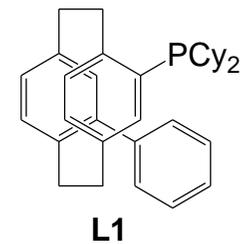
^1H NMR of (\pm)-4-bromo-12-phenyl[2.2]paracyclophane (**3**)



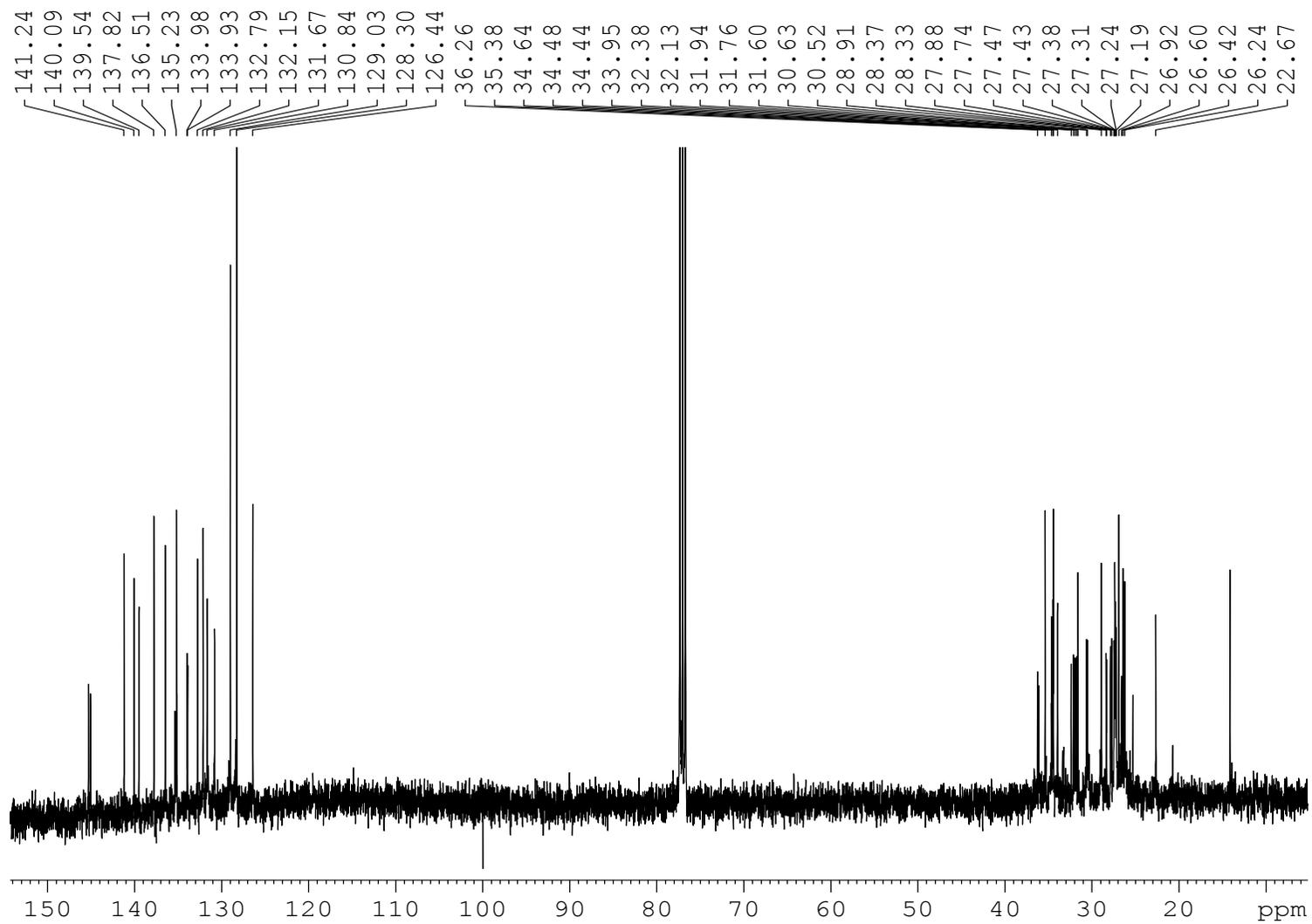
¹³C NMR of (±)-4-bromo-12-phenyl[2.2]paracyclophane (**3**)



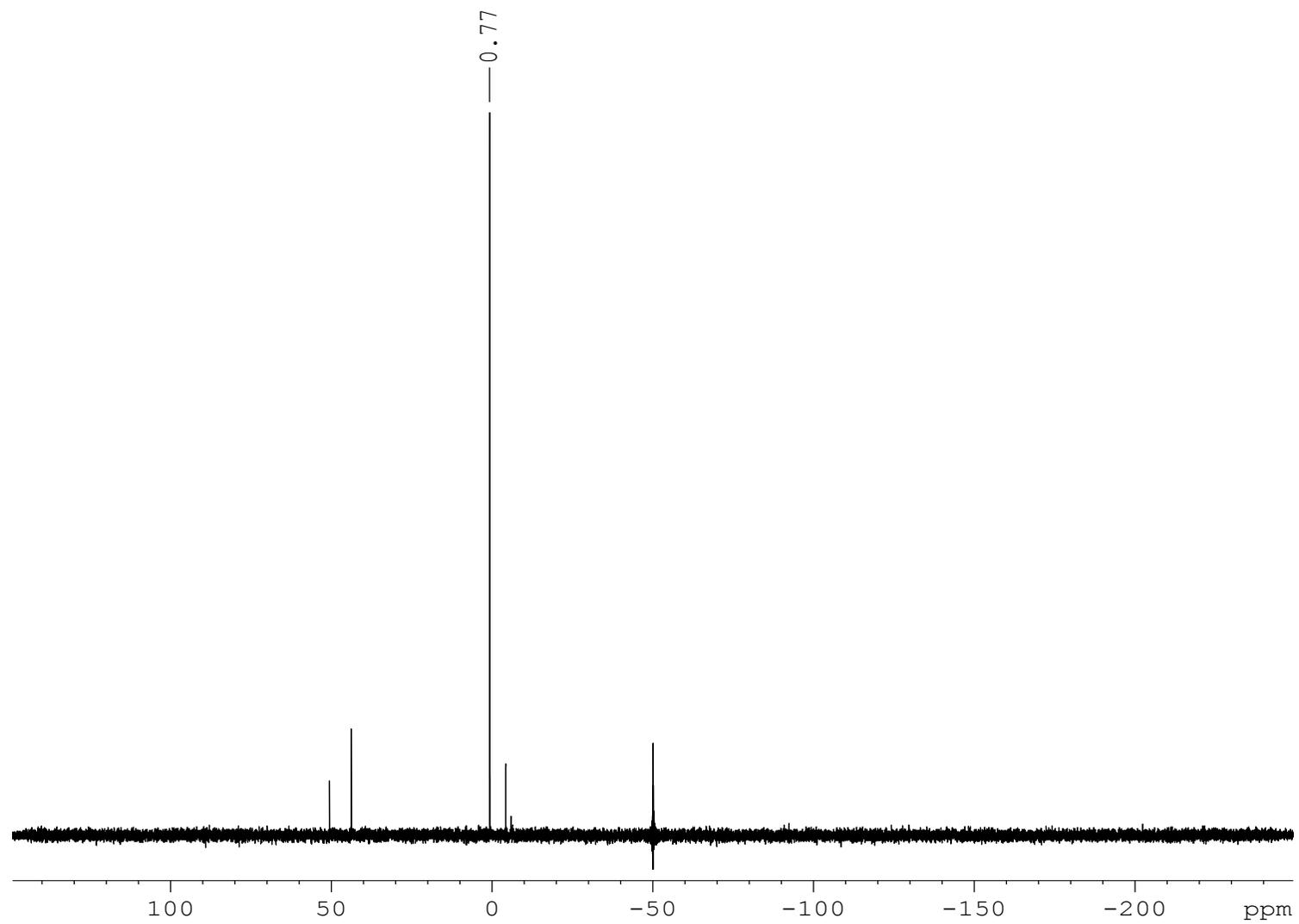
^1H NMR of (\pm)-4-dicyclohexylphosphino-12-phenyl[2.2]paracyclophane (**L1**)



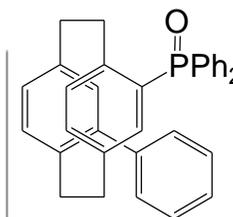
¹³C NMR of (±)-4-dicyclohexylphosphino-12-phenyl[2.2]paracyclophane (**L1**)



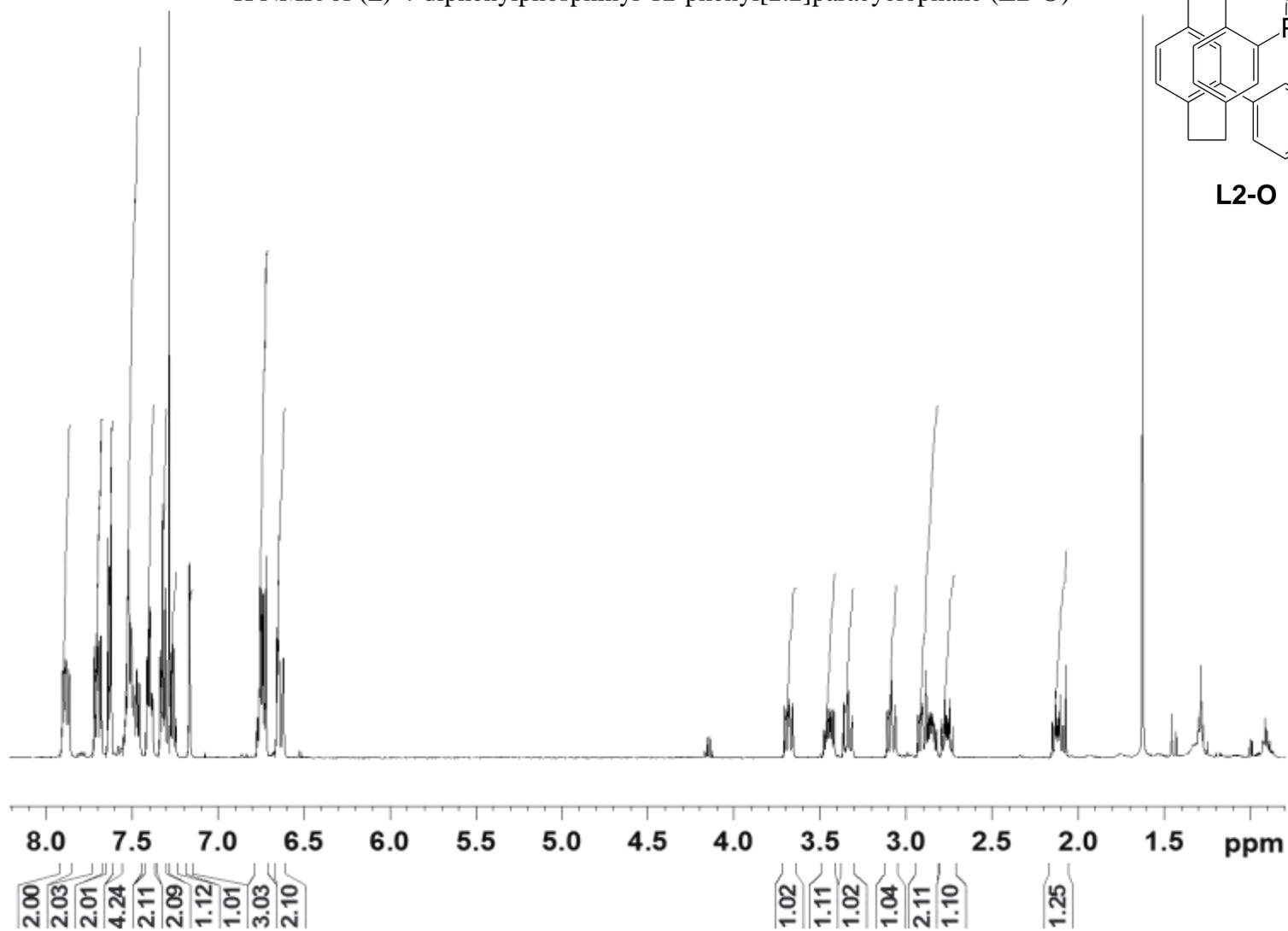
^{31}P NMR of (\pm)-4-dicyclohexylphosphino-12-phenyl[2.2]paracyclophane (**L1**)



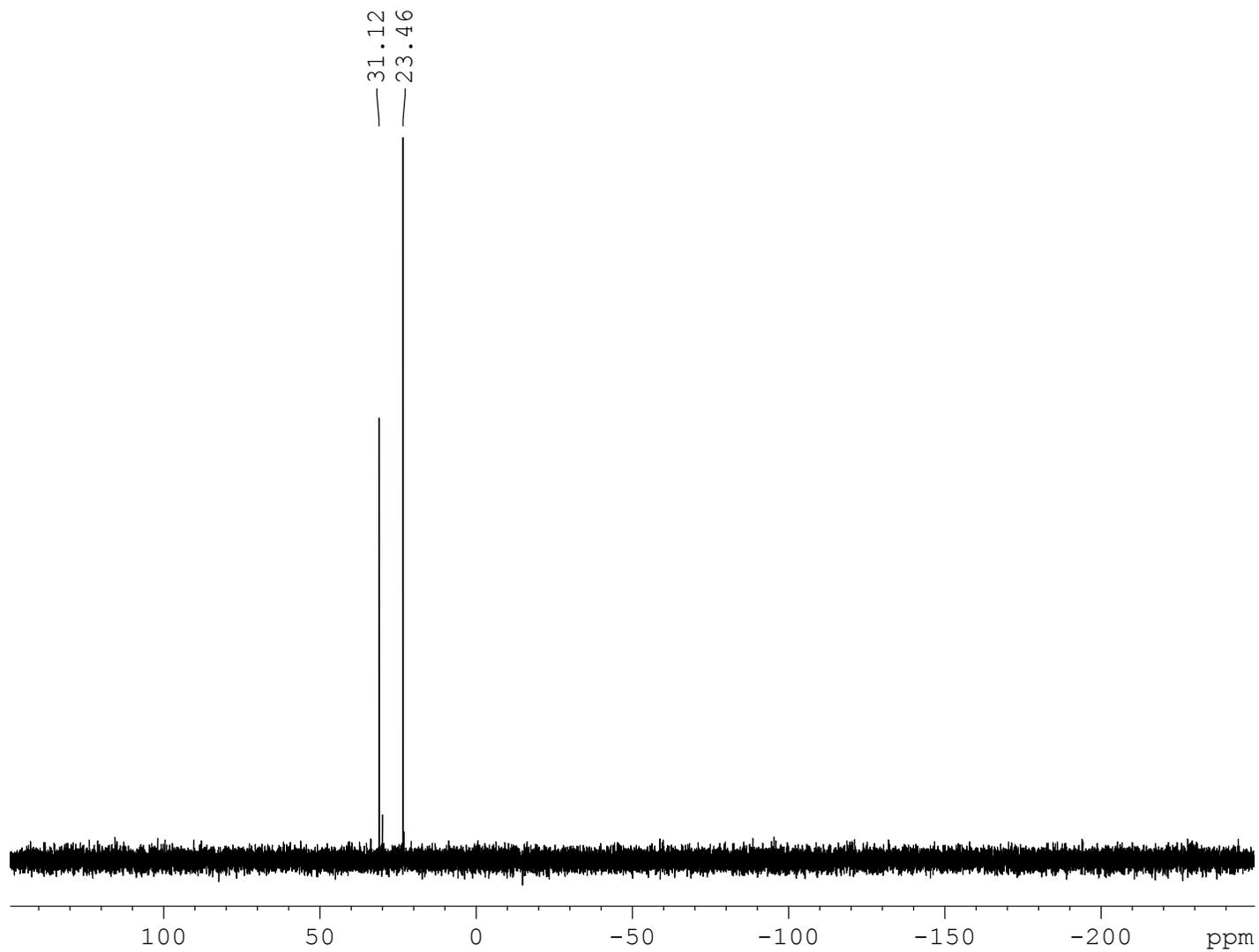
^1H NMR of (\pm)-4-diphenylphosphinyl-12-phenyl[2.2]paracyclophane (**L2-O**)



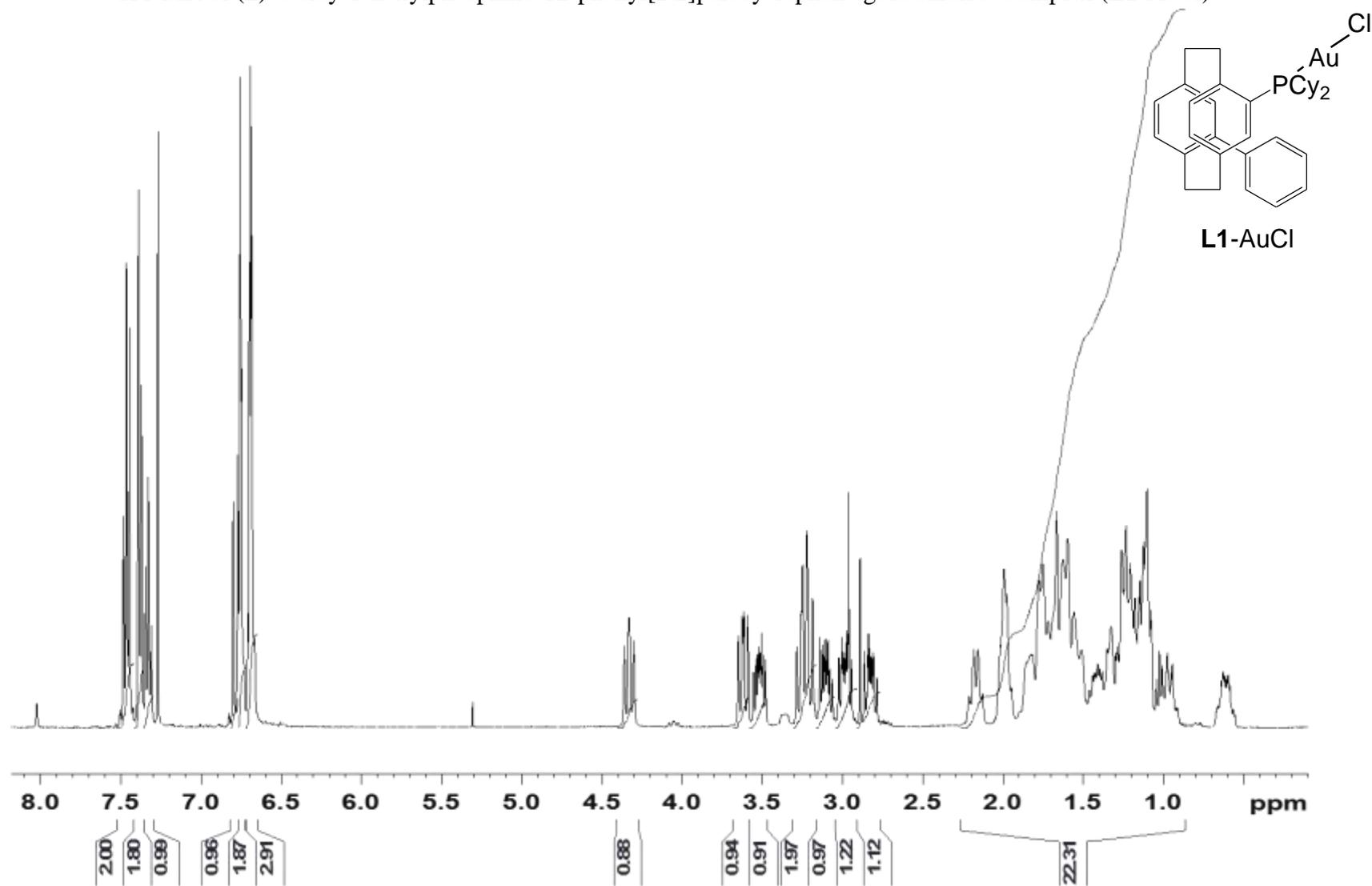
L2-O



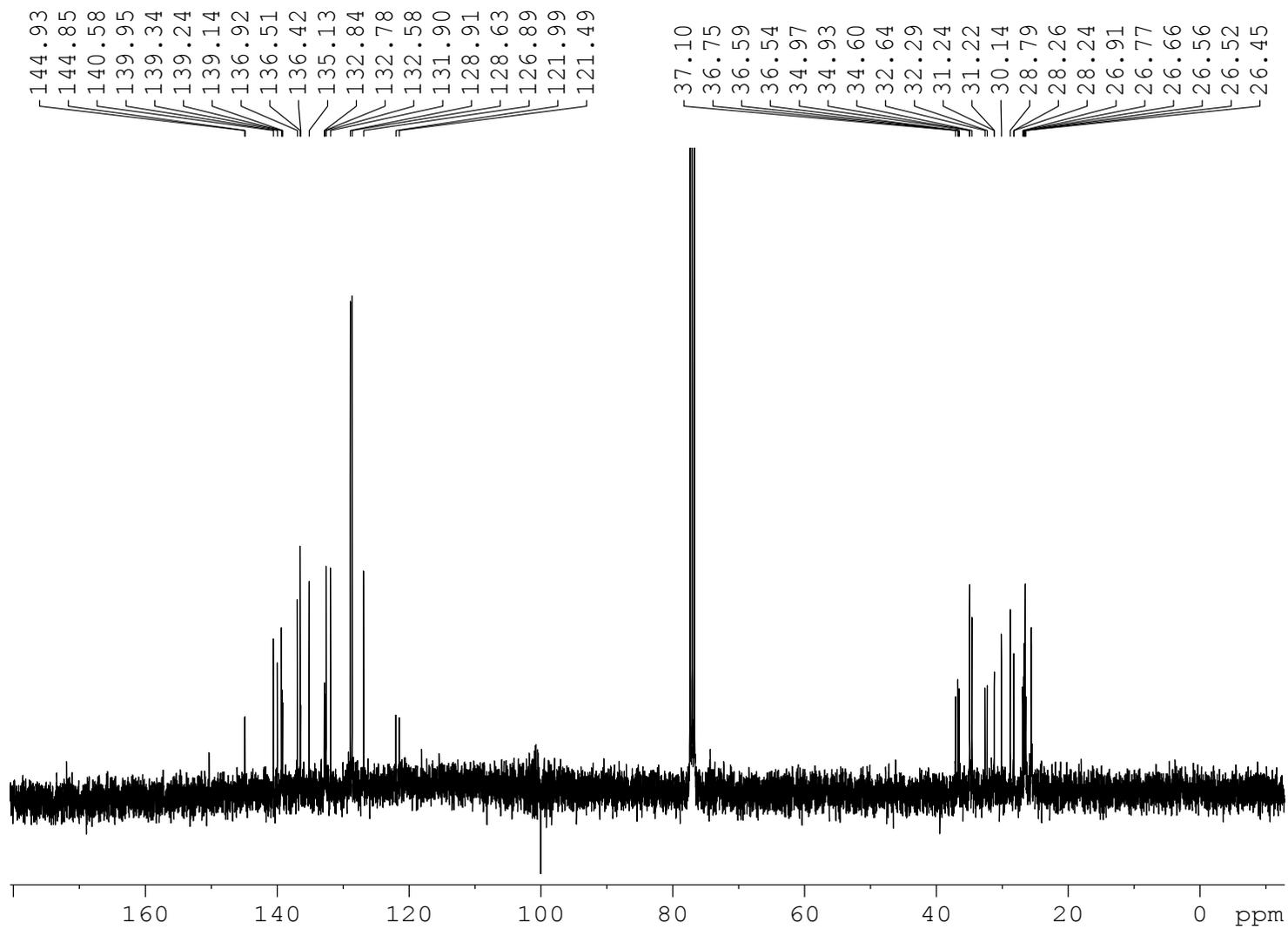
^{31}P NMR of (\pm)-4-diphenylphosphinyl-12-phenyl[2.2]paracyclophane (**L2-O**)



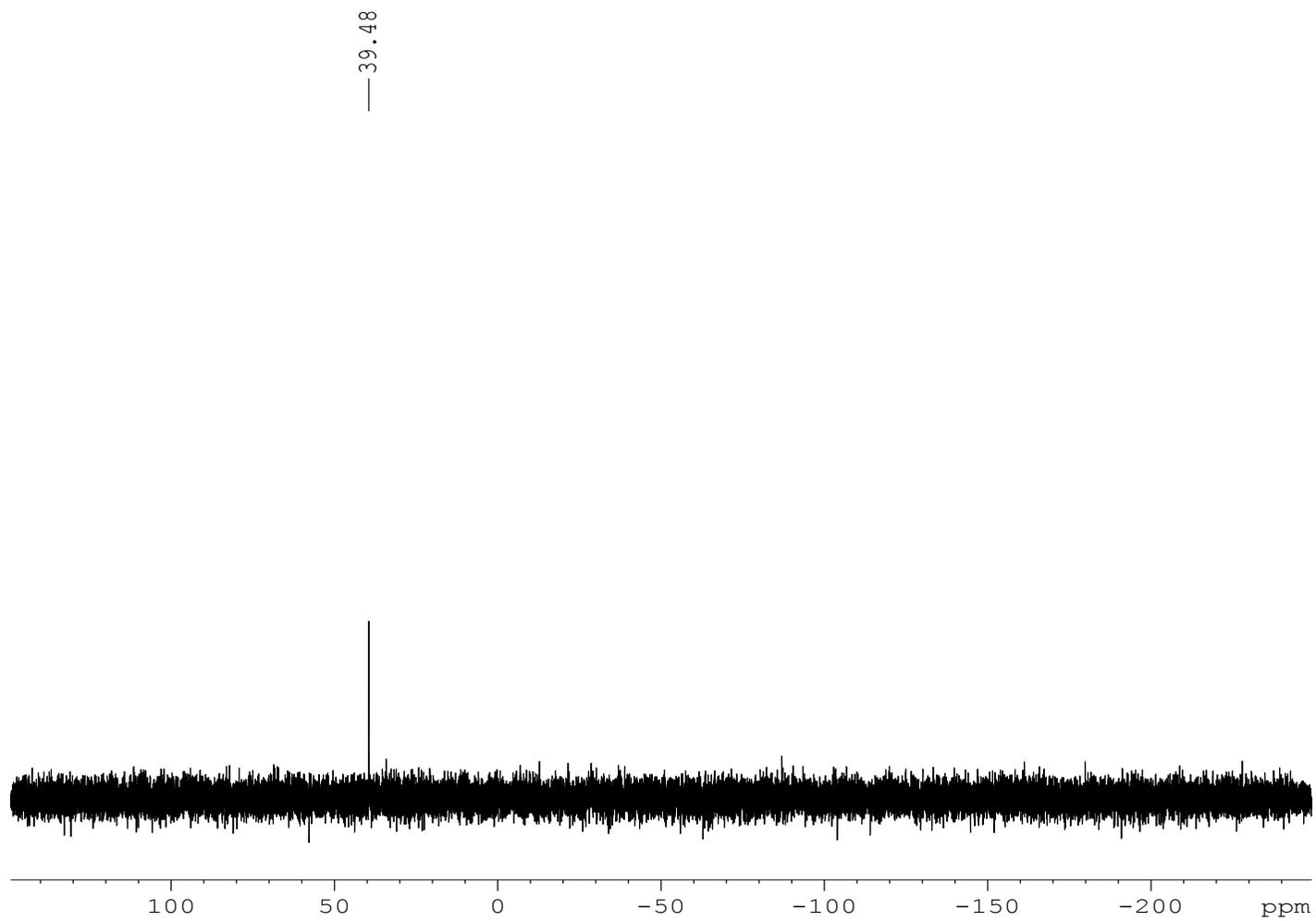
^1H NMR of (\pm)-4-dicyclohexylphosphino-12-phenyl[2.2]paracyclophane gold chloride complex (**L1**-AuCl)



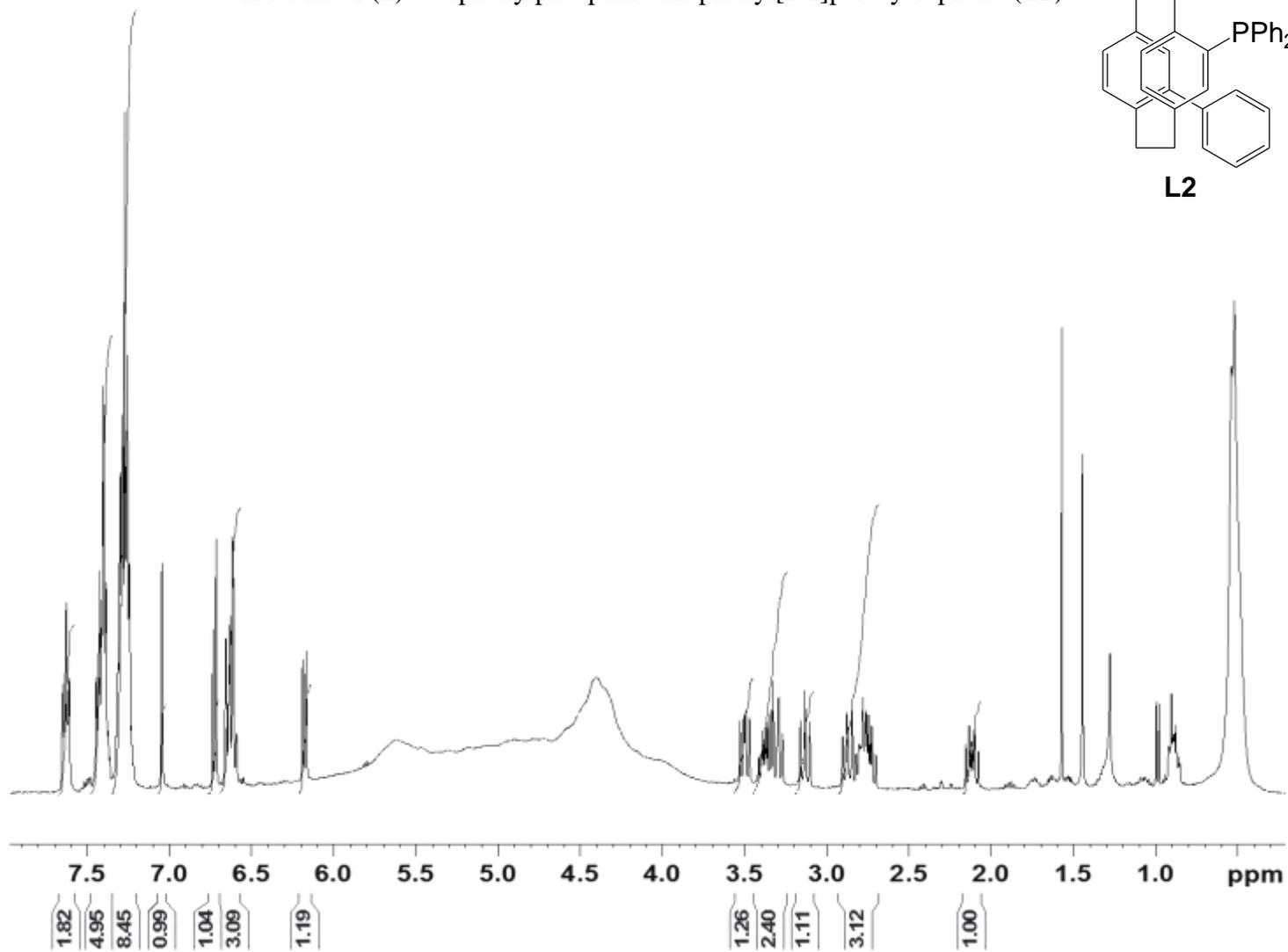
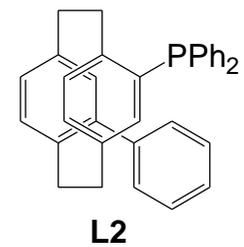
^{13}C NMR of (+)-4-dicyclohexylphosphino-12-phenyl[2.2]paracyclophane gold chloride complex (**L1**-AuCl)



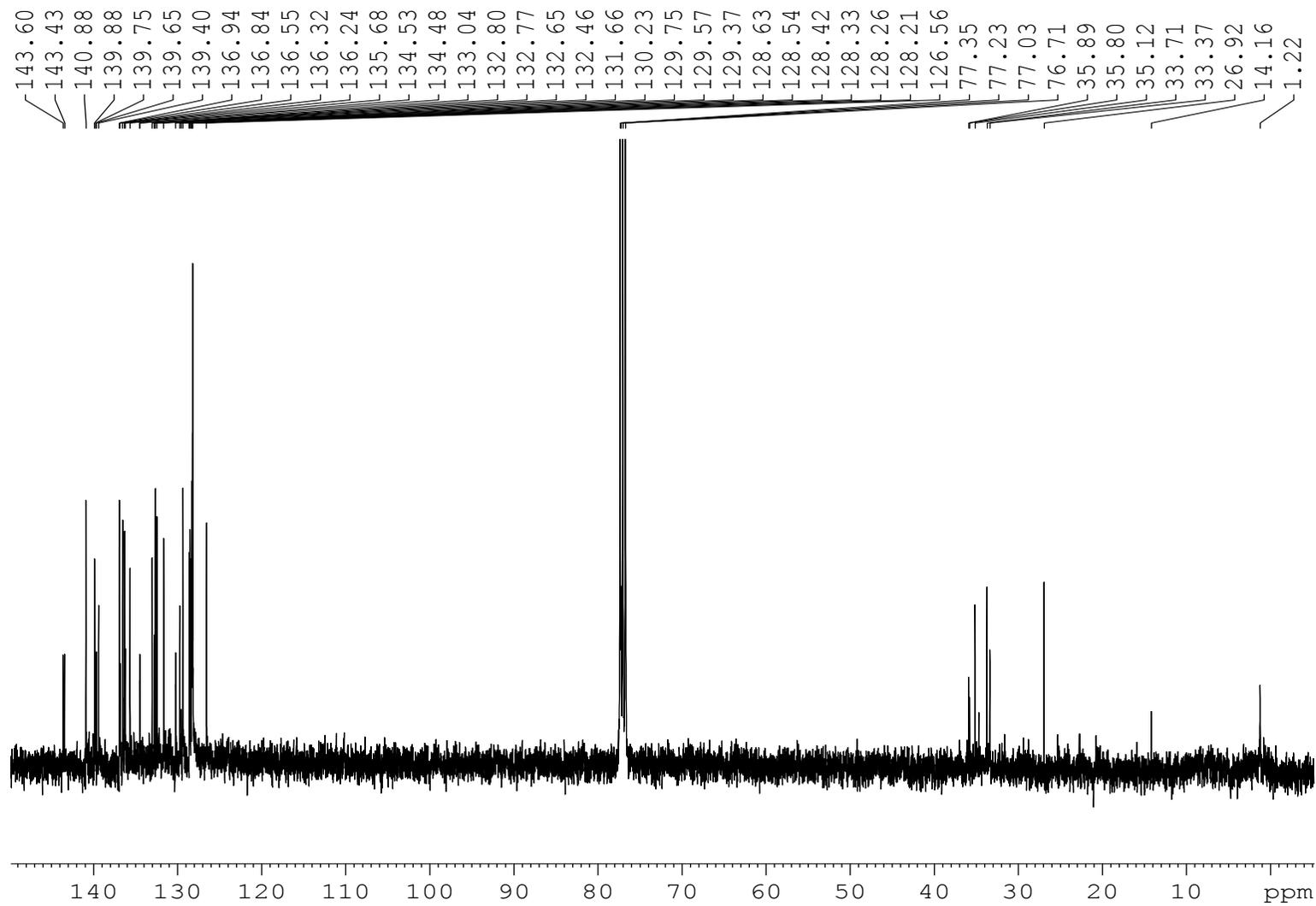
^{31}P NMR of (\pm)-4-dicyclohexylphosphino-12-phenyl[2.2]paracyclophane gold chloride complex (**L1**-AuCl)



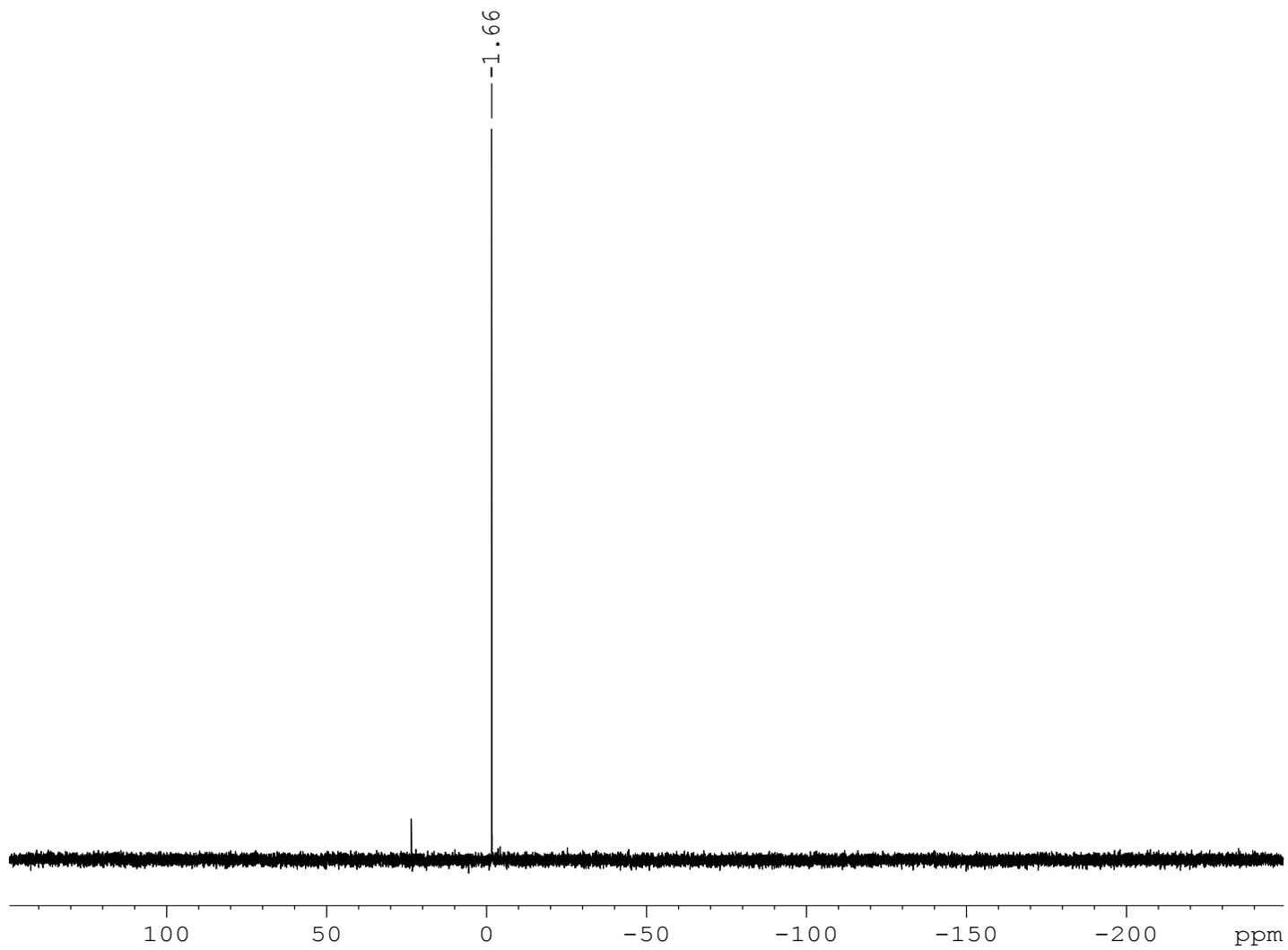
^1H NMR of (\pm)-4-diphenylphosphino-12-phenyl[2.2]paracyclophane (**L2**)



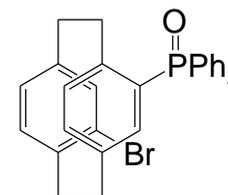
^{13}C NMR of (\pm)-4-diphenylphosphino-12-phenyl[2.2]paracyclophane (**L2**)



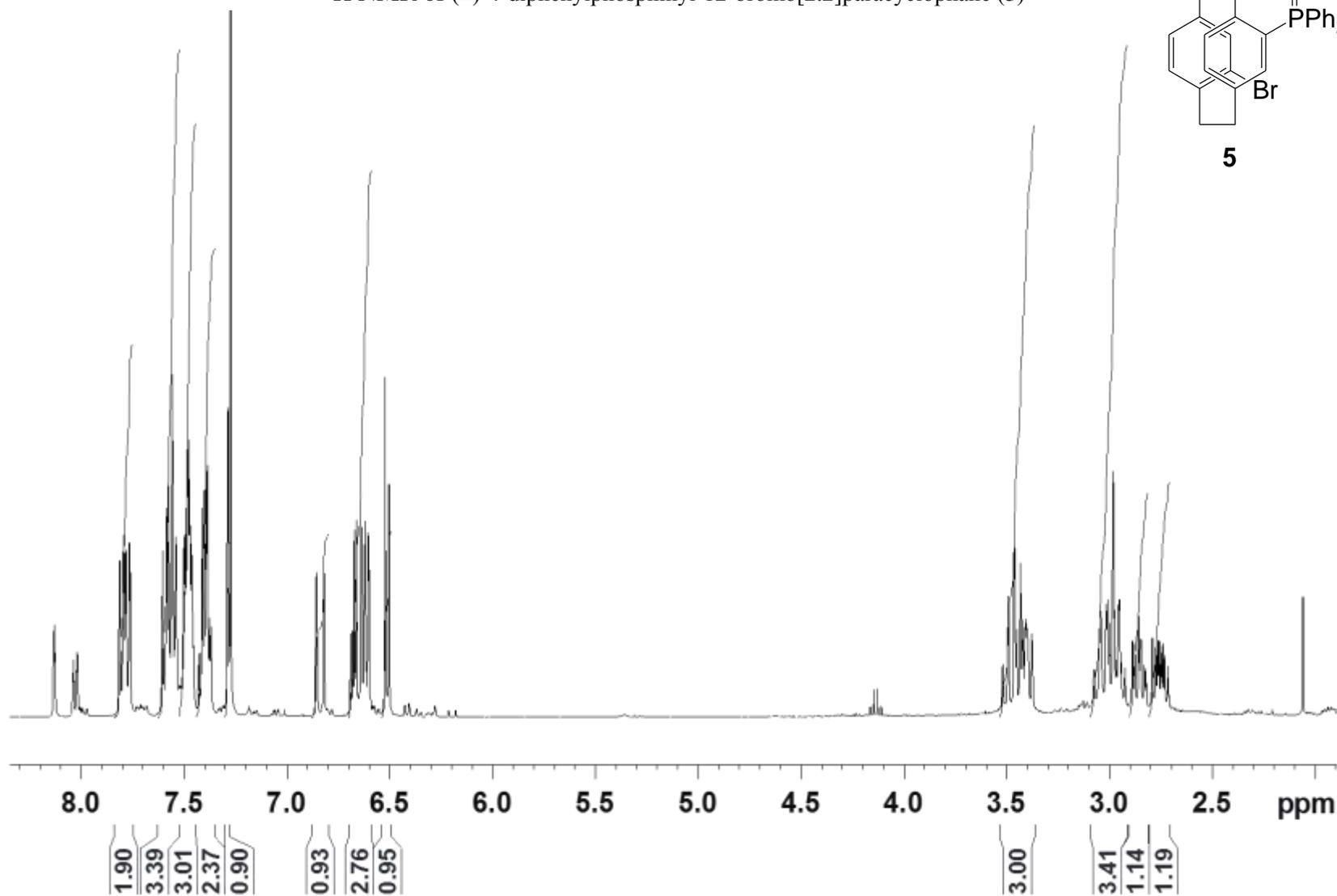
^{31}P NMR of (\pm)-4-diphenylphosphino-12-phenyl[2.2]paracyclophane (**L2**)



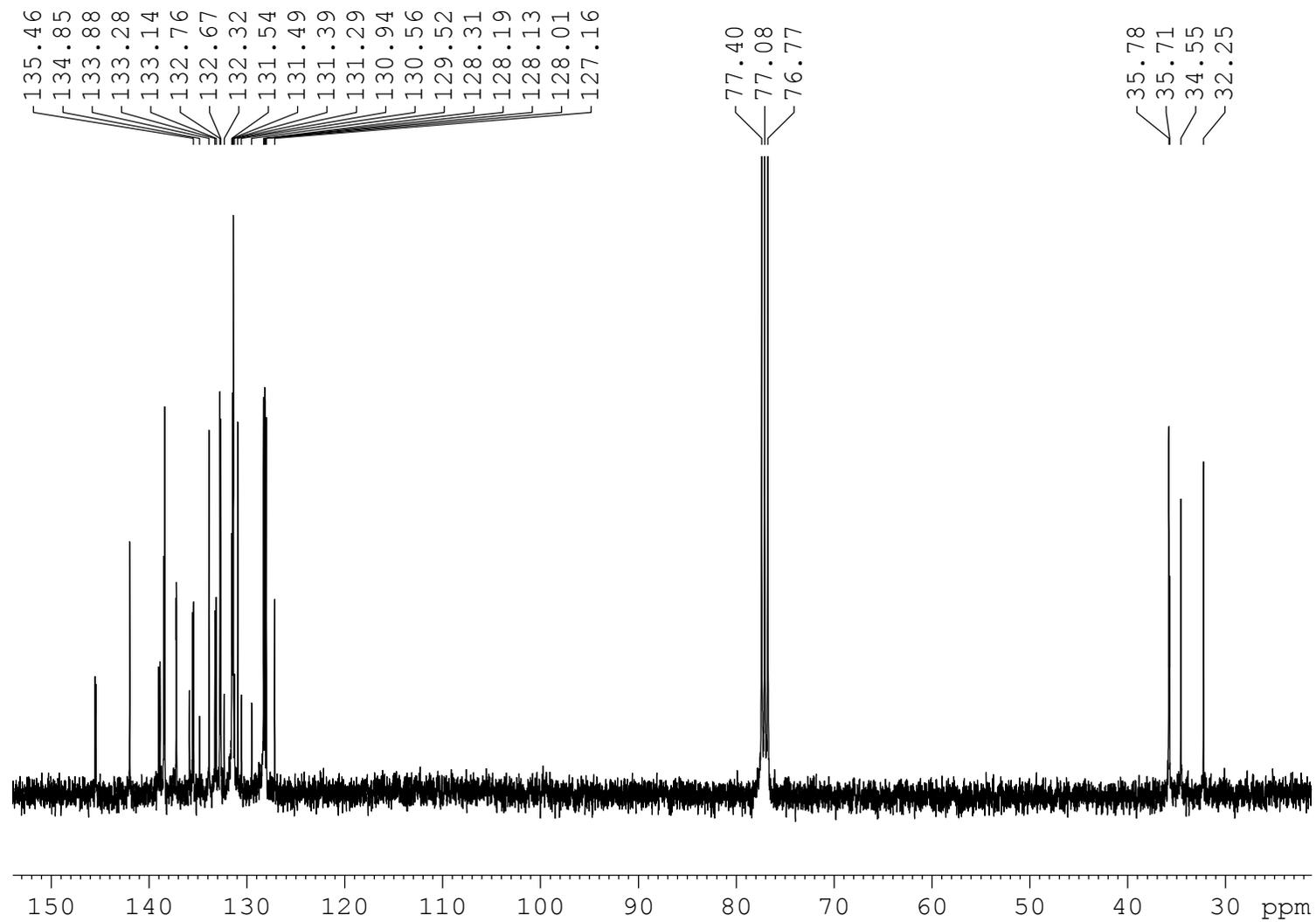
^1H NMR of (\pm)-4-diphenylphosphinyl-12-bromo[2.2]paracyclophane (**5**)



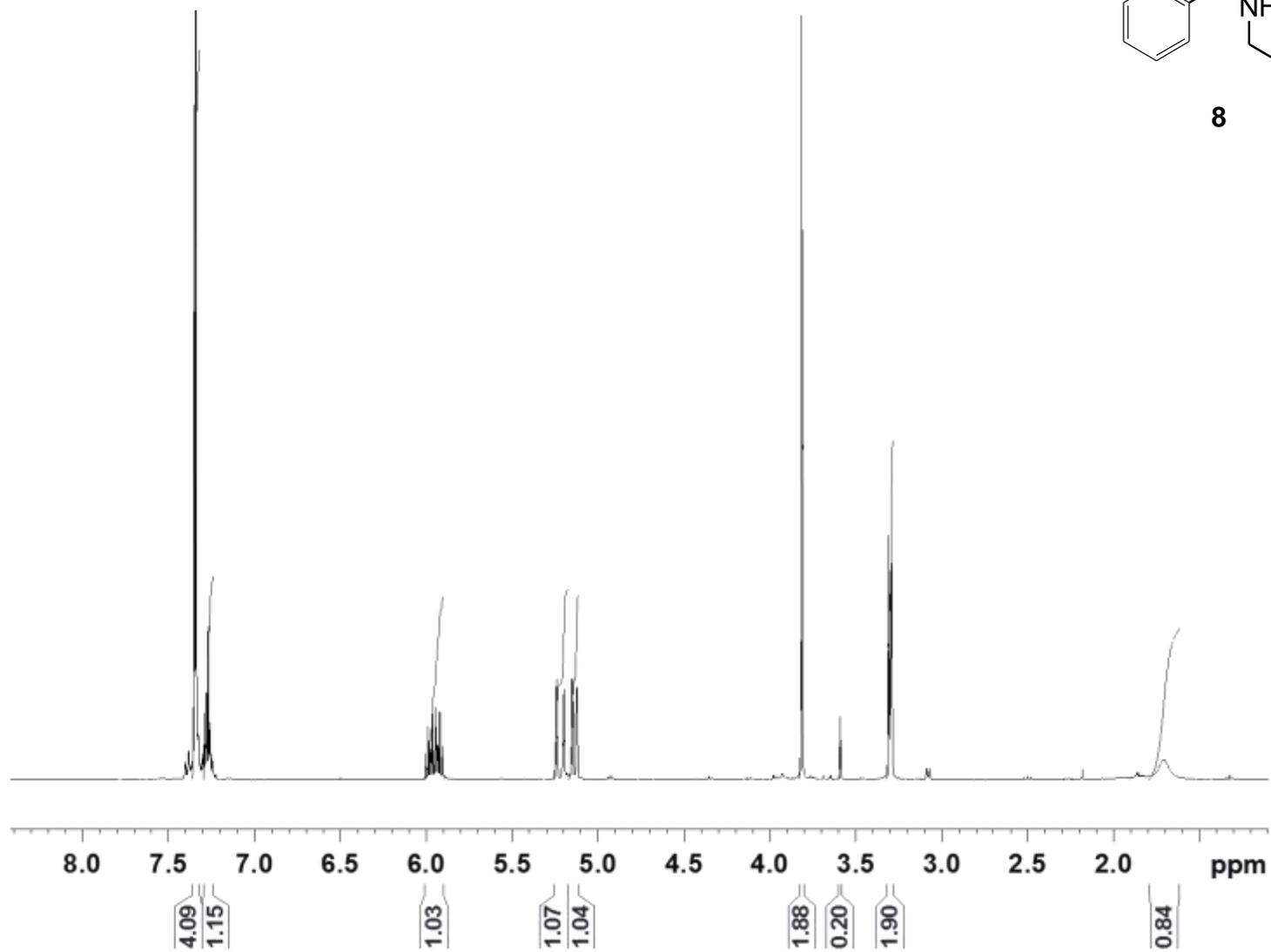
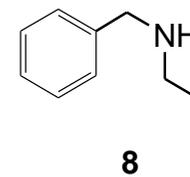
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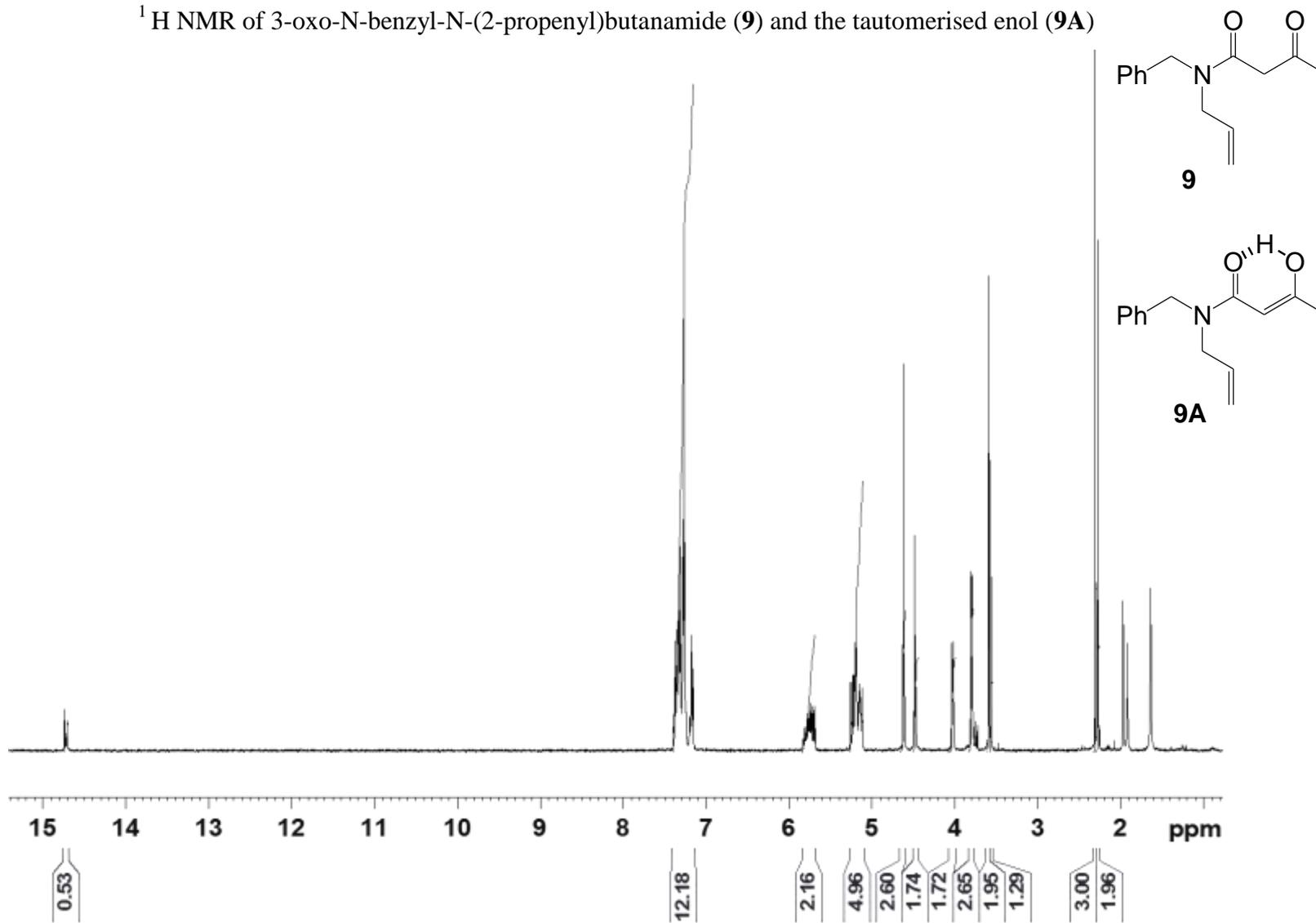
^{13}C NMR of (\pm)-4-diphenylphosphinyl-12-bromo[2.2]paracyclophane (**5**)



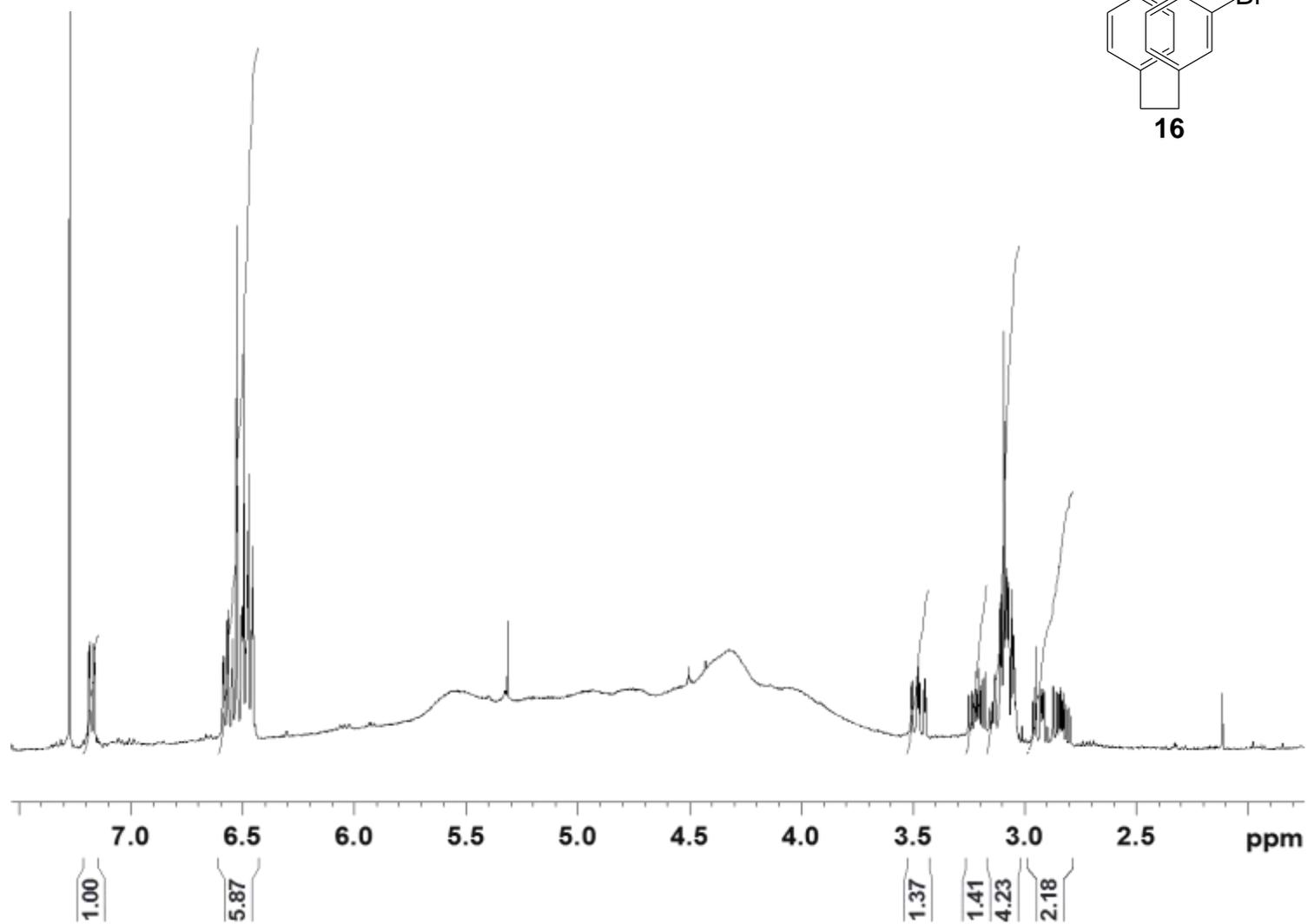
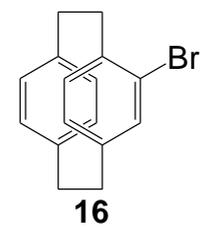
^1H NMR of N-(2-propenyl)-N-benzylamine (**8**)



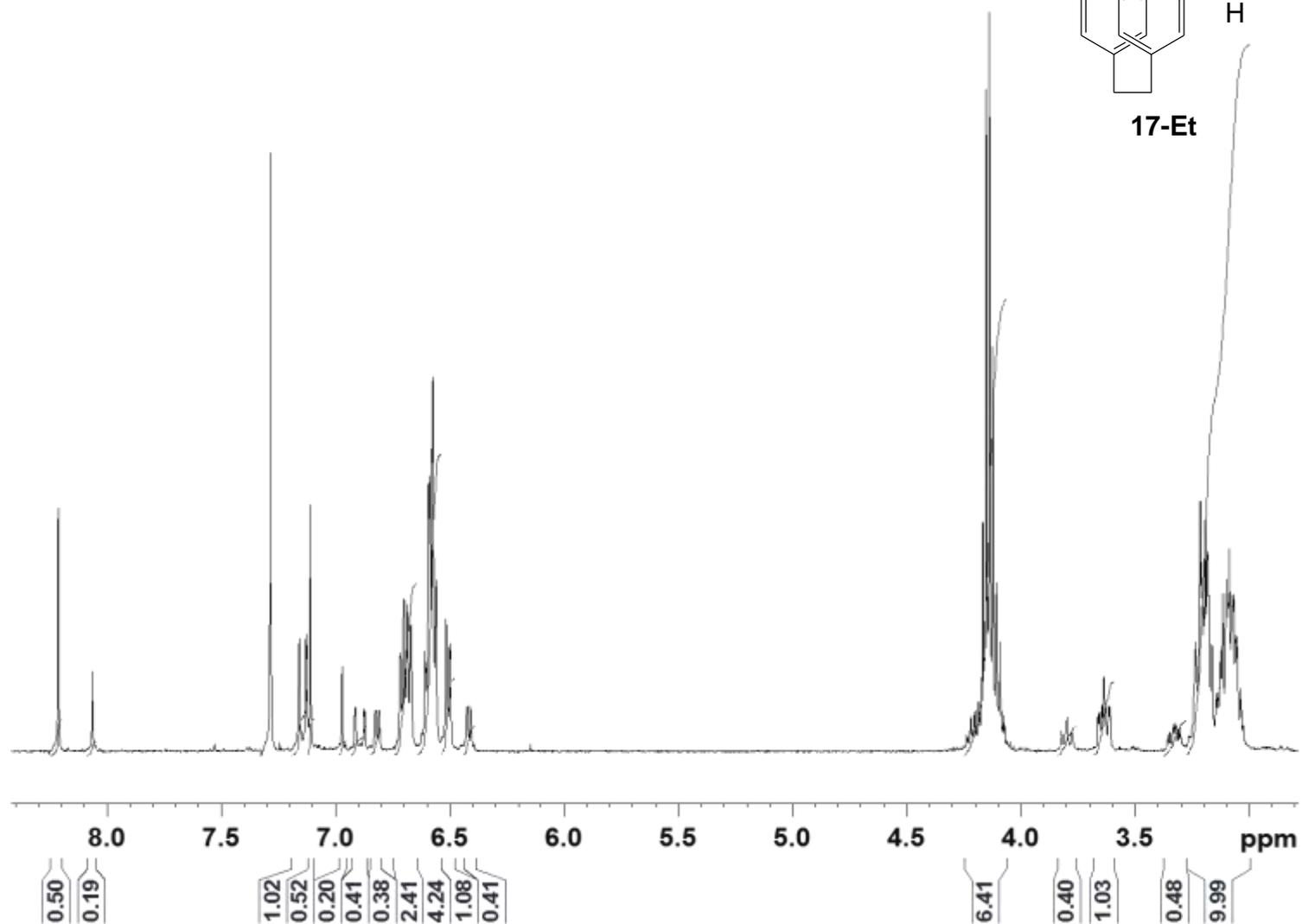
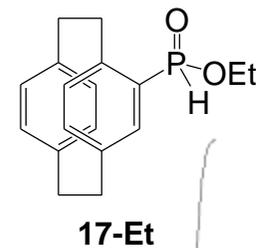
¹H NMR of 3-oxo-N-benzyl-N-(2-propenyl)butanamide (**9**) and the tautomerised enol (**9A**)



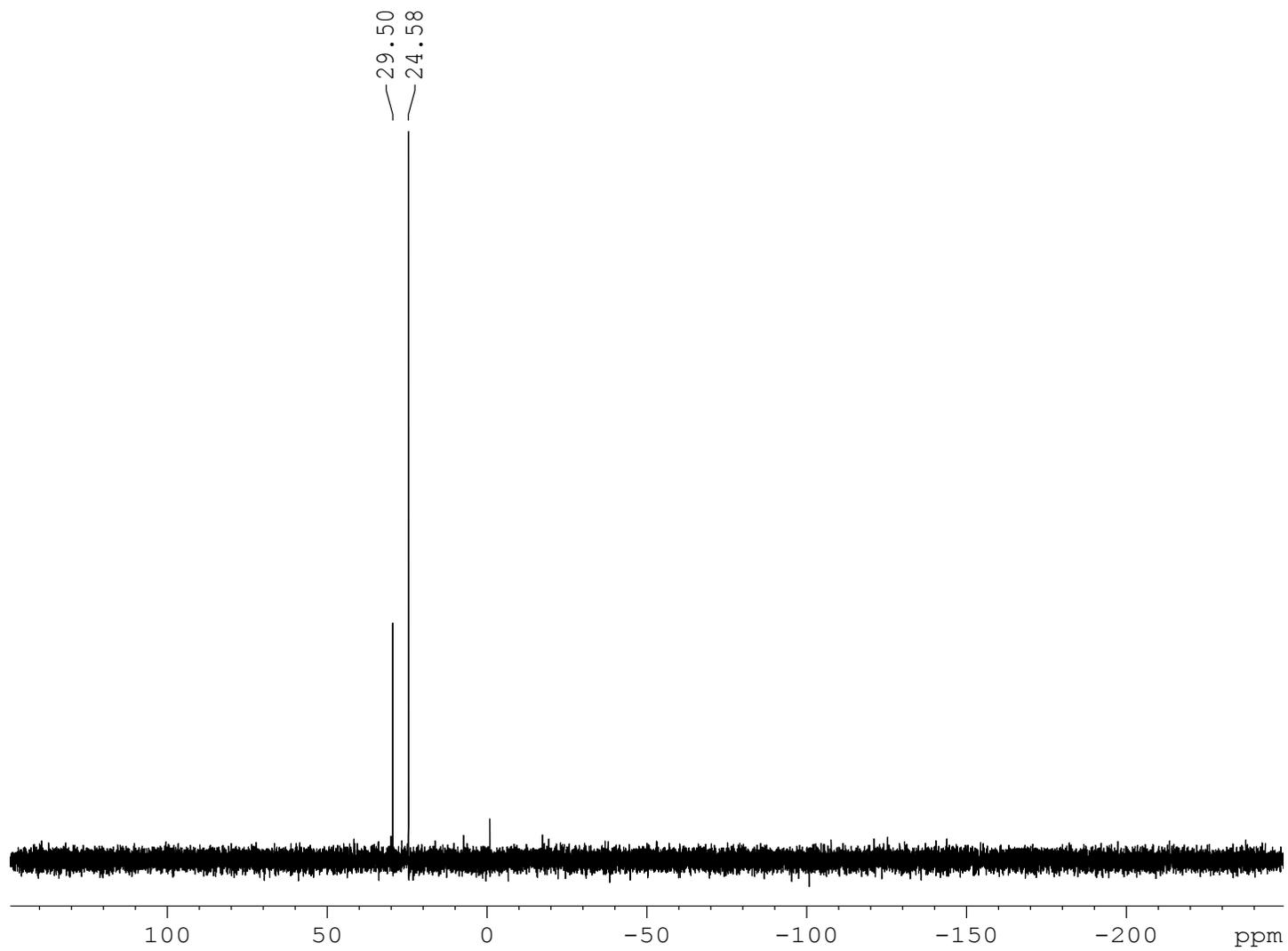
^1H NMR of (\pm)-4-bromo[2.2]paracyclophane (**16**)



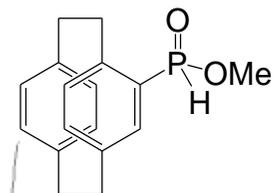
^1H NMR of (\pm)-[2.2]paracyclophanyl ethoxyphosphinic acid (17-Et)



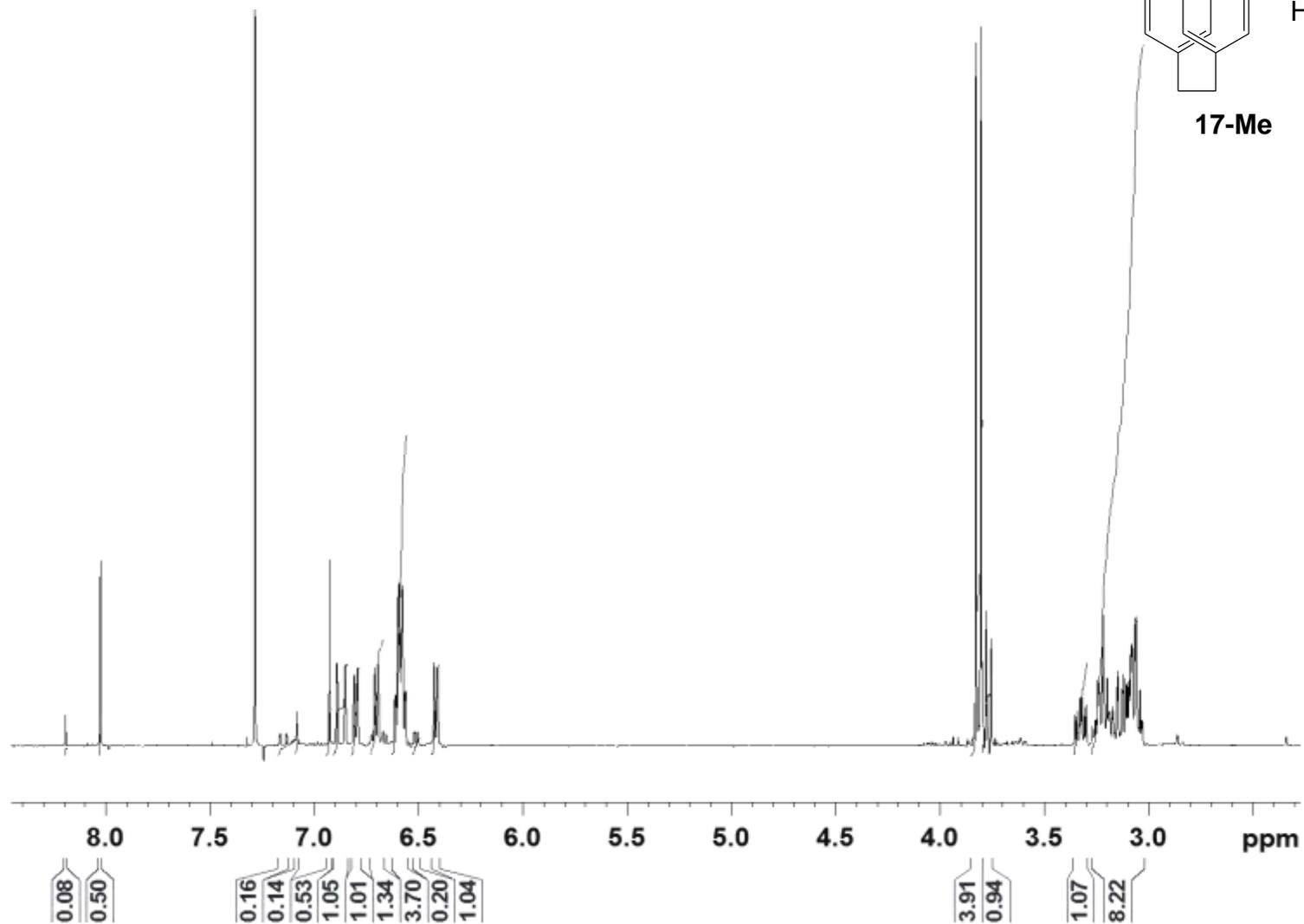
^{31}P NMR of (\pm)-[2.2]paracyclophanyl ethoxyphosphinic acid (17-Et)



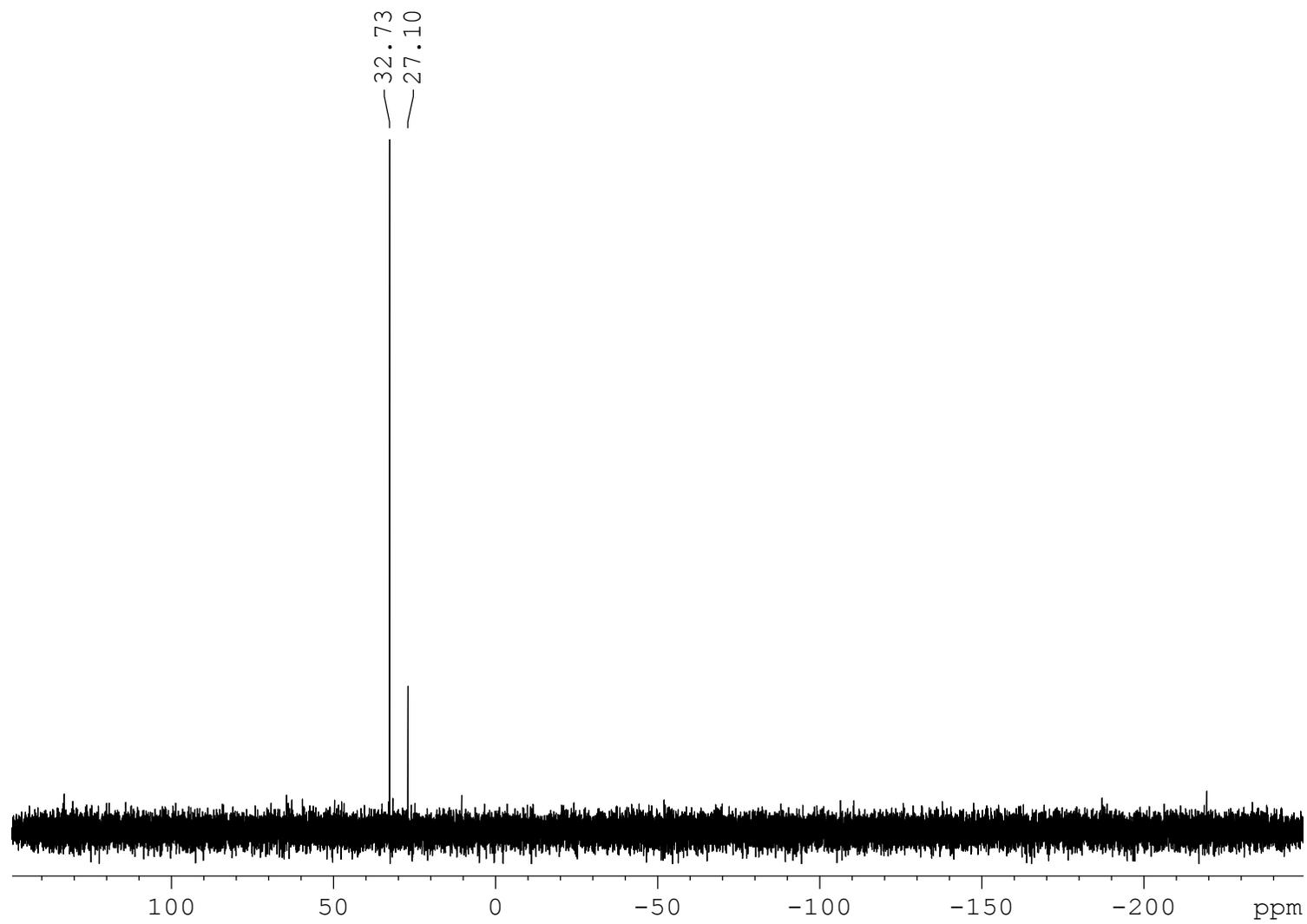
^1H NMR of (\pm)-[2.2]paracyclophanyl ethoxyphosphinic acid (17-Me)



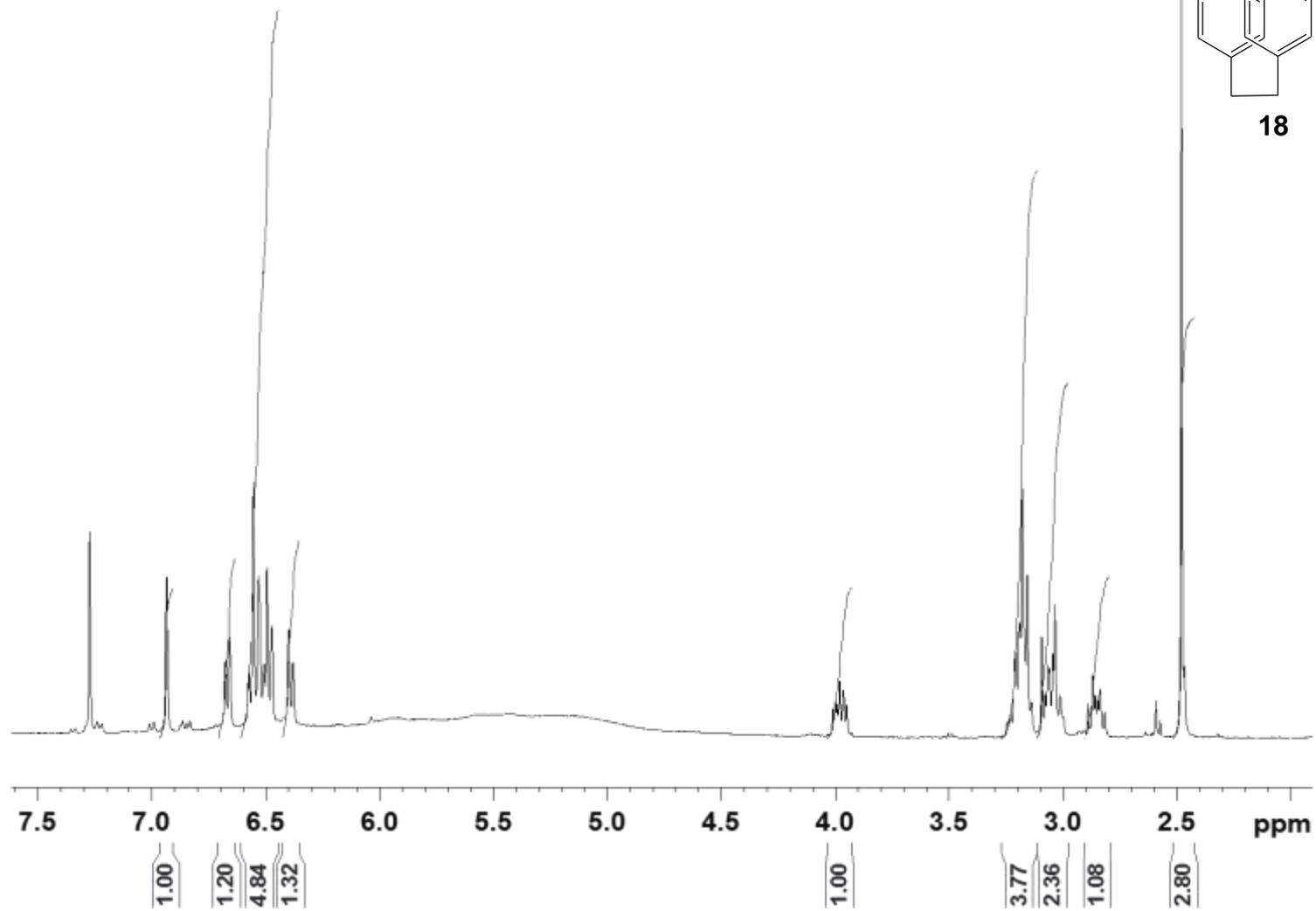
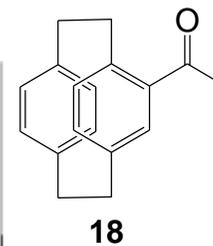
17-Me



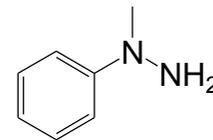
^{31}P NMR of (\pm)-[2.2]paracyclophanyl ethoxyphosphinic acid (**17-Me**)



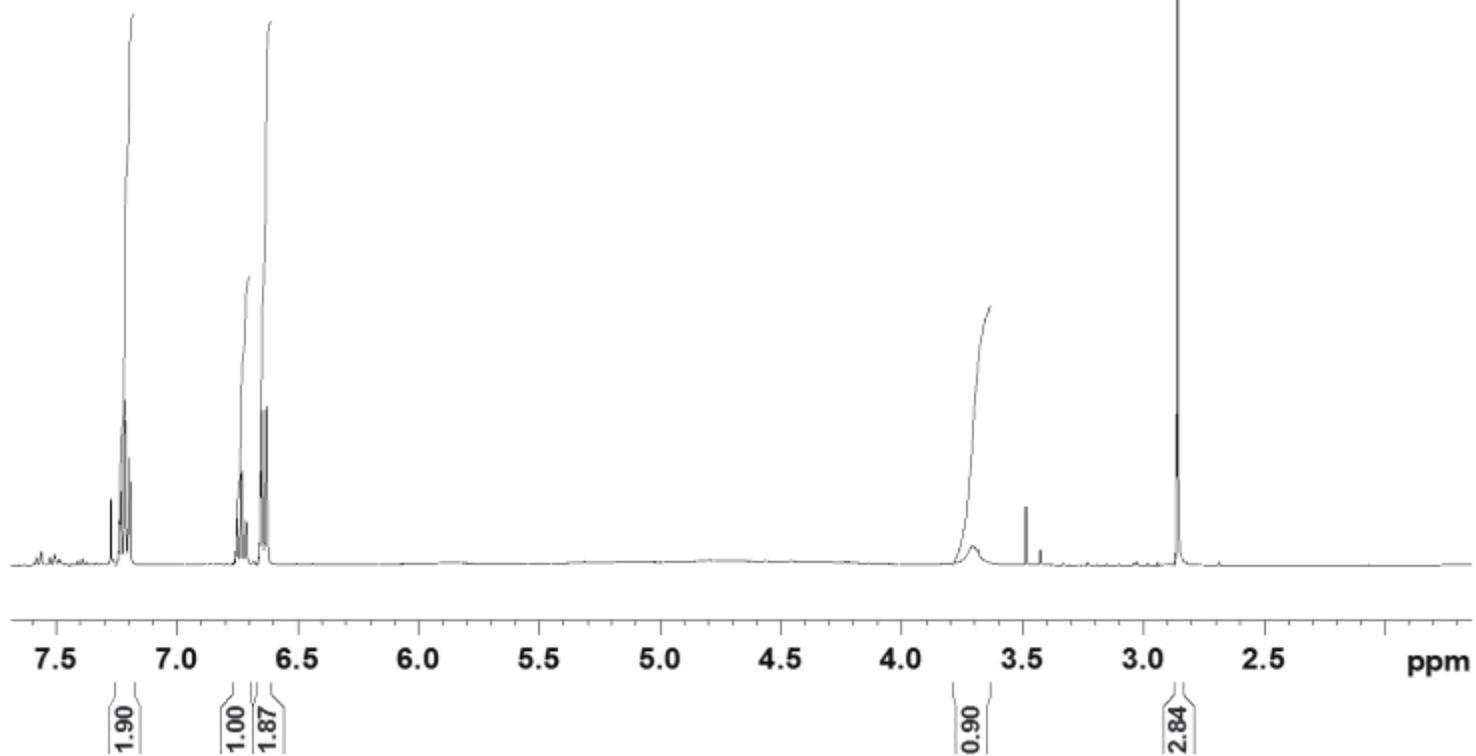
^1H NMR of (\pm)-4-acetyl[2.2]paracyclophane (**18**)



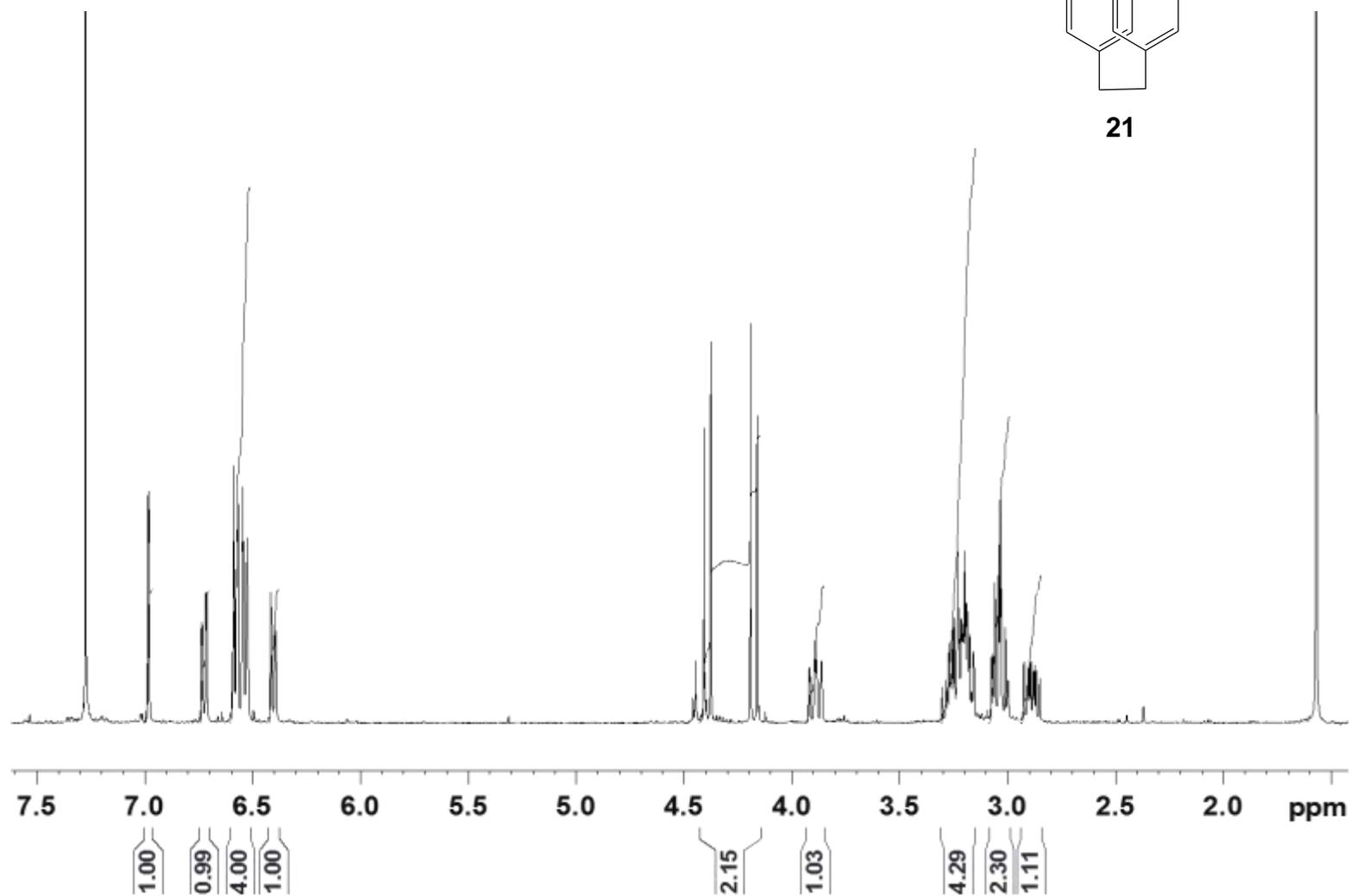
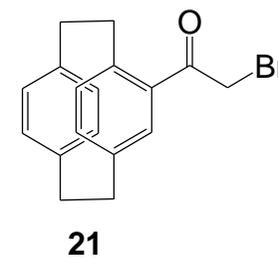
^1H NMR of N-methyl-N-phenylhydrazine (**19**)



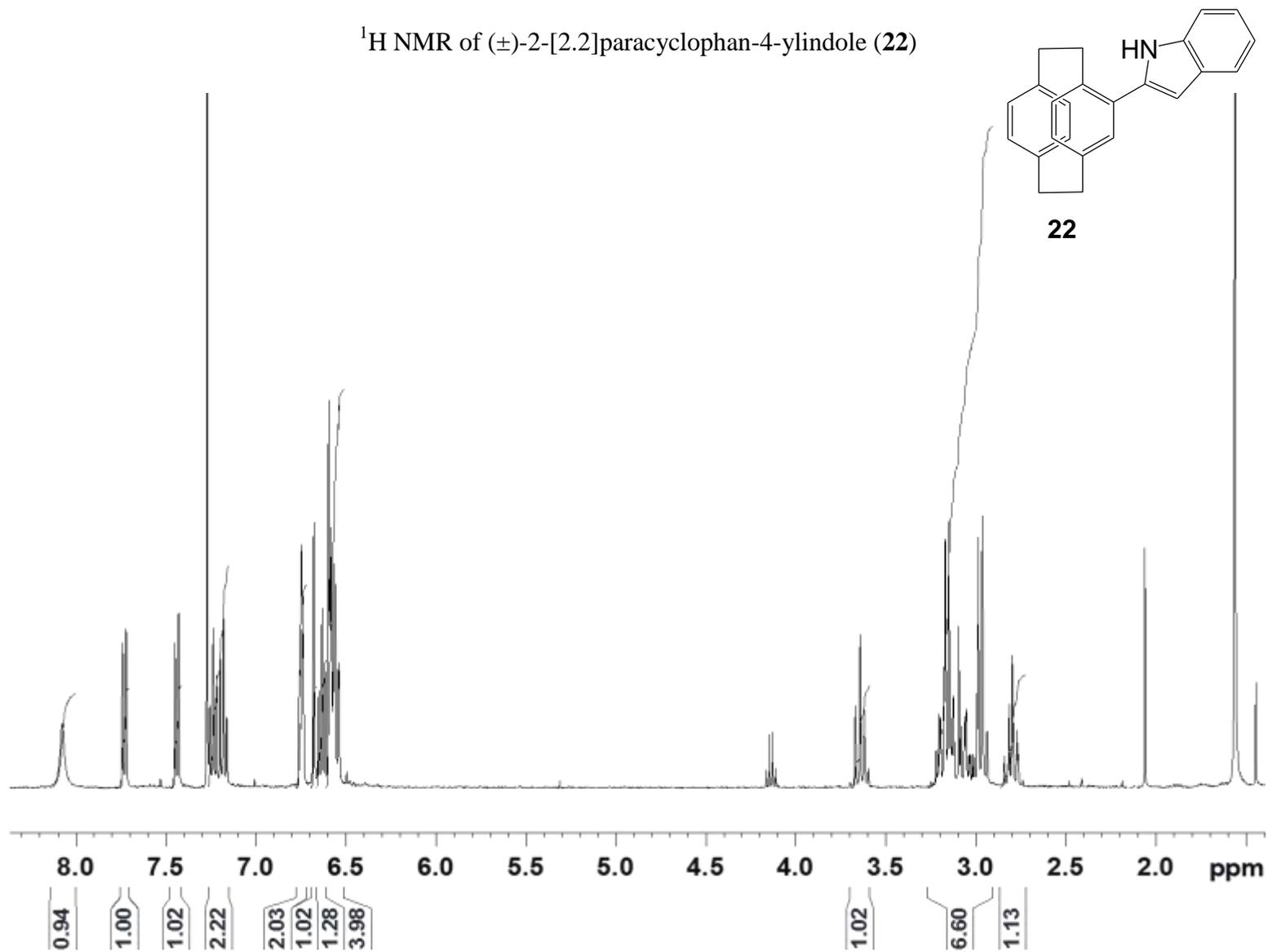
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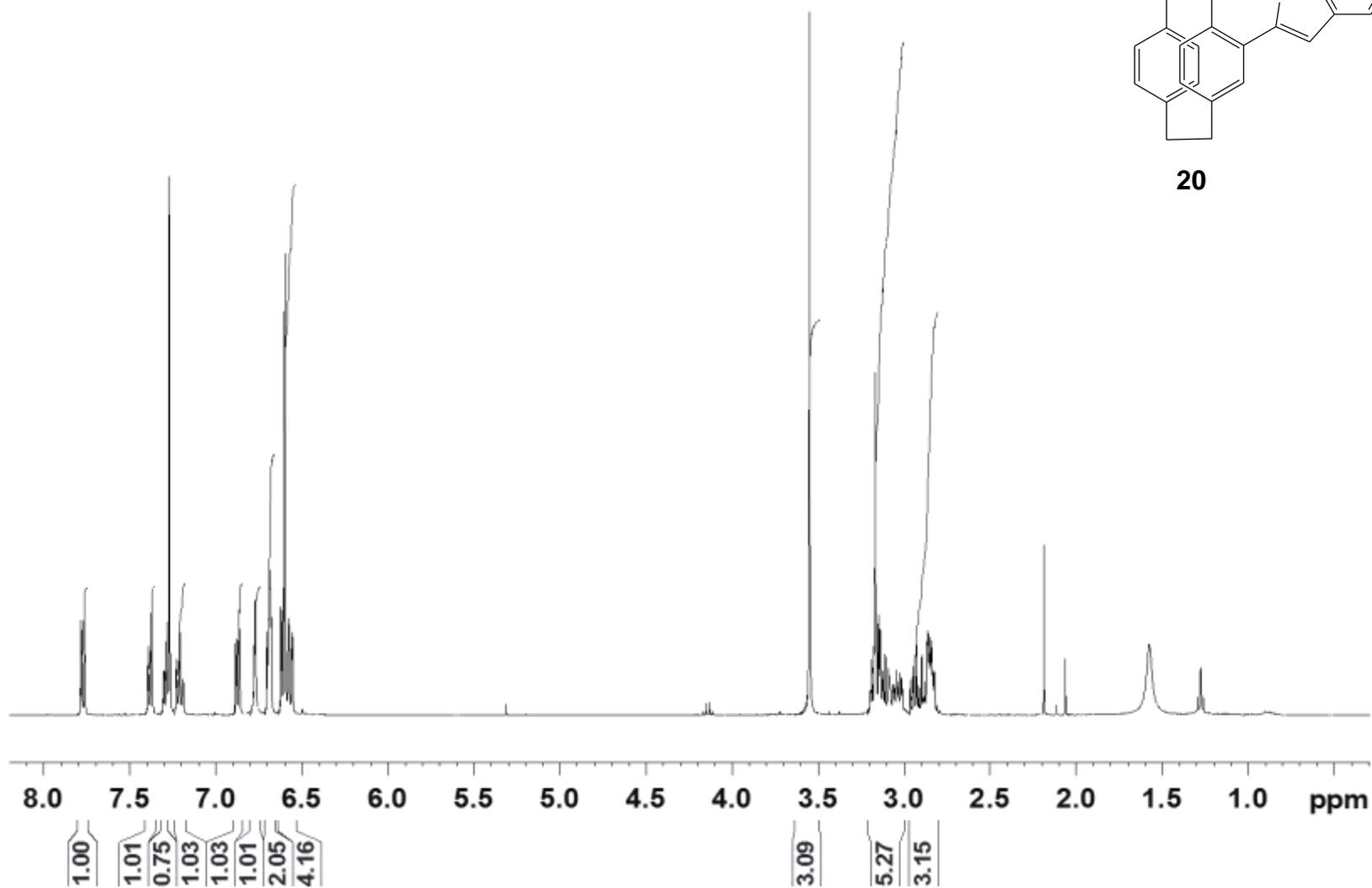
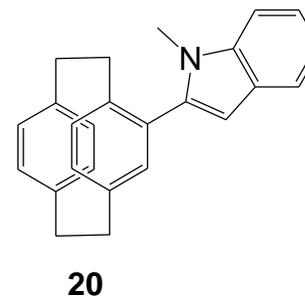
^1H NMR of (\pm)-4-bromoacetyl[2.2]paracyclophane (**21**)



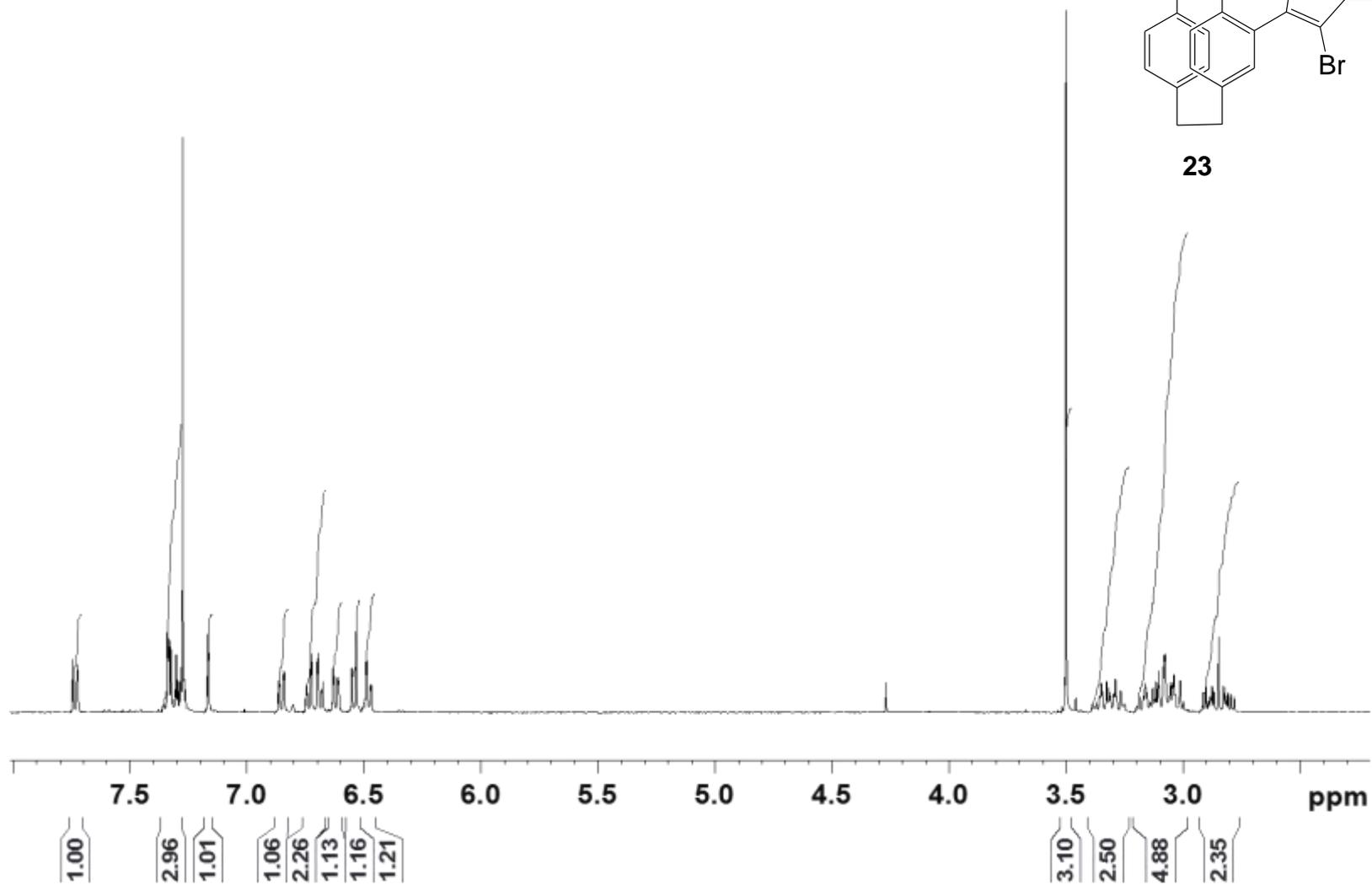
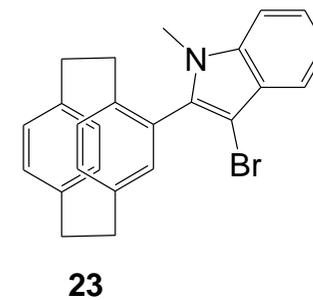
^1H NMR of (\pm)-2-[2.2]paracyclophan-4-ylindole (**22**)



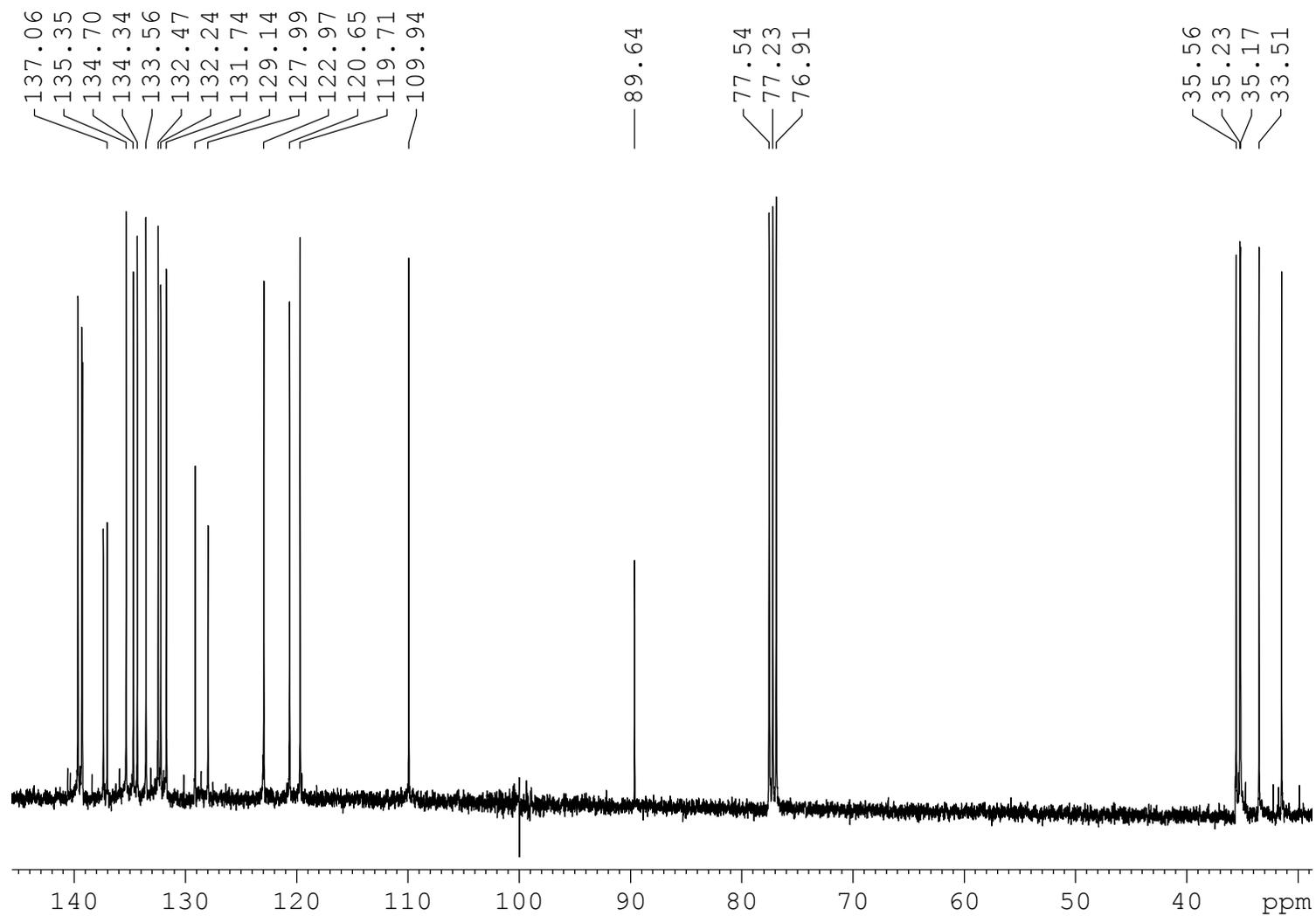
^1H NMR of (\pm)-2-[2.2]paracyclophan-4-yl-N-methyl-indole (**20**)



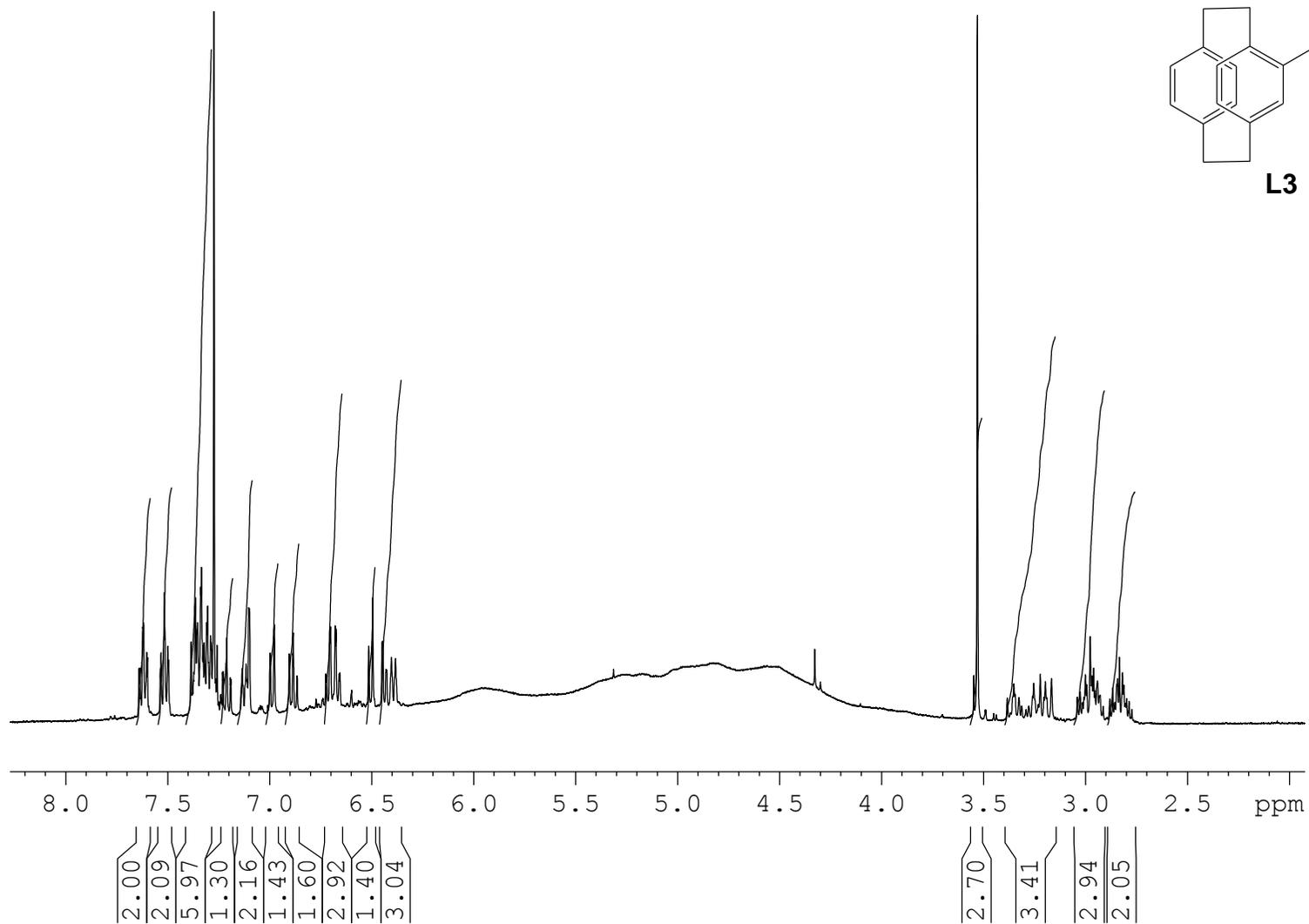
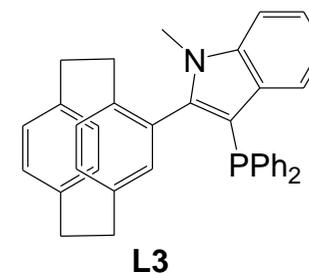
^1H NMR of (\pm)-2-[2.2]paracyclophan-4-yl-3-bromo-N-methyl-indole (**23**)



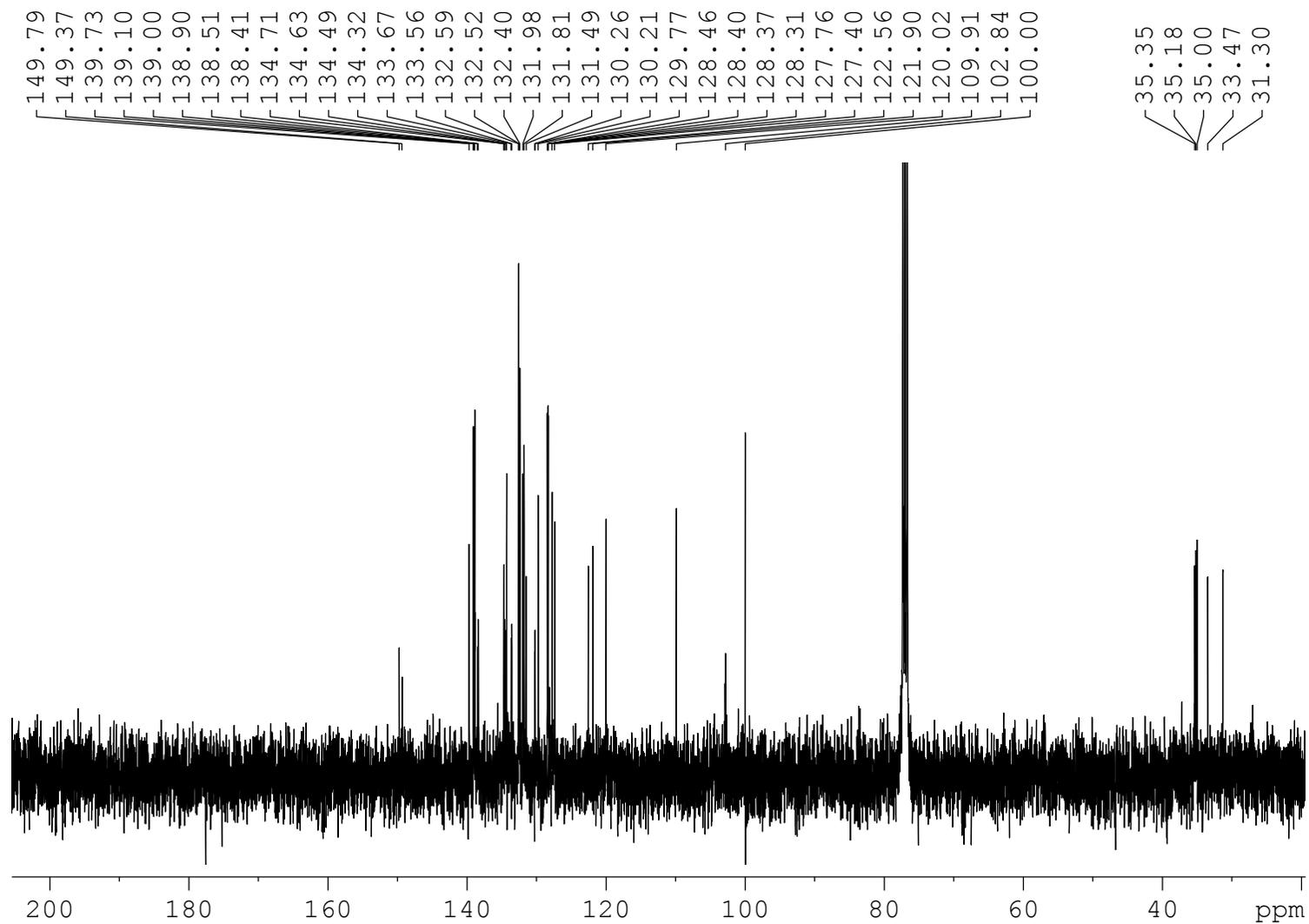
^{13}C NMR of (\pm)-2-[2.2]paracyclophan-4-yl-3-bromo-N-methyl-indole (**23**)



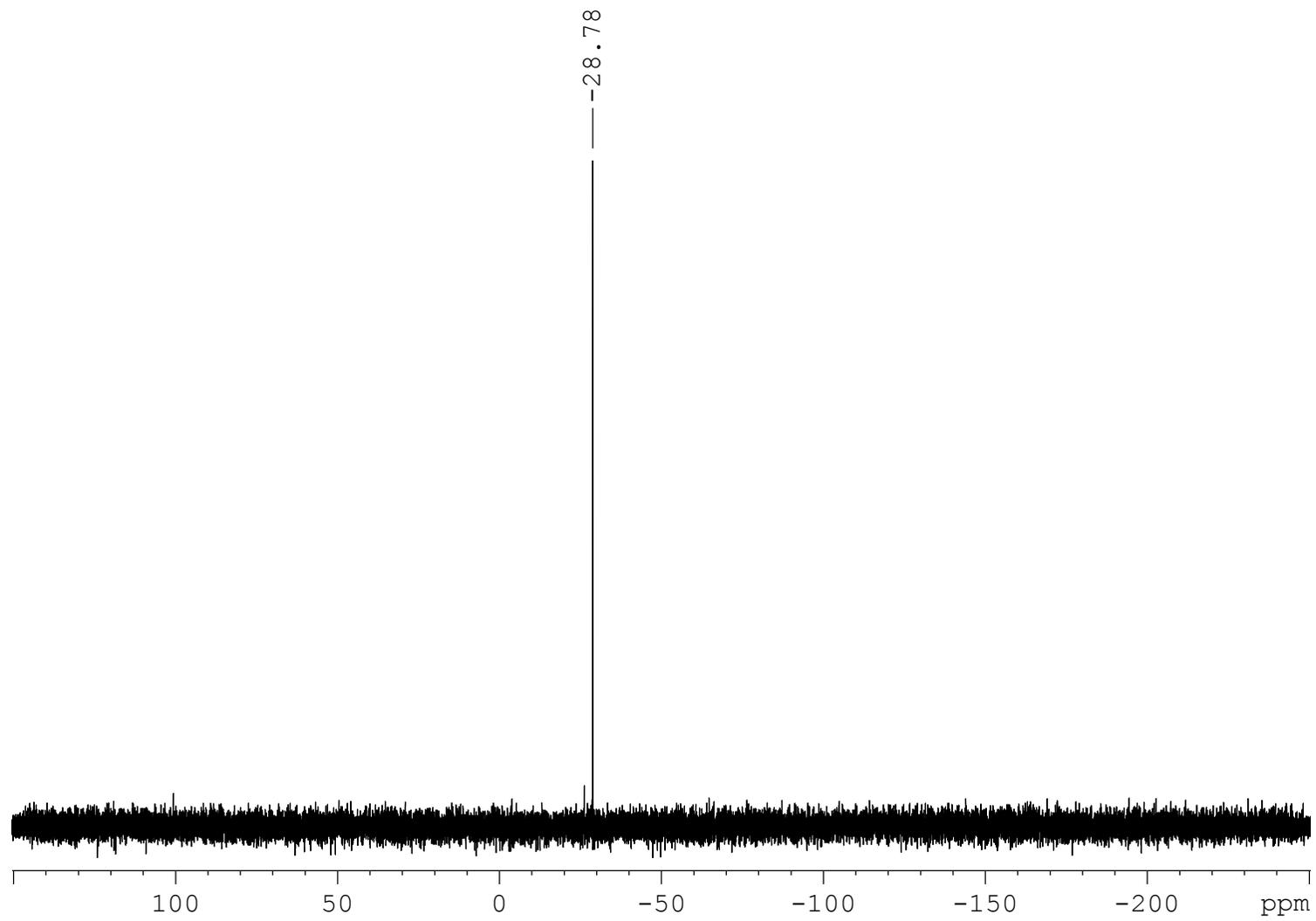
^1H NMR of (\pm)-2-[2.2]paracyclophan-4-yl-3-diphenylphosphino-N-methyl-indole (**L3**)



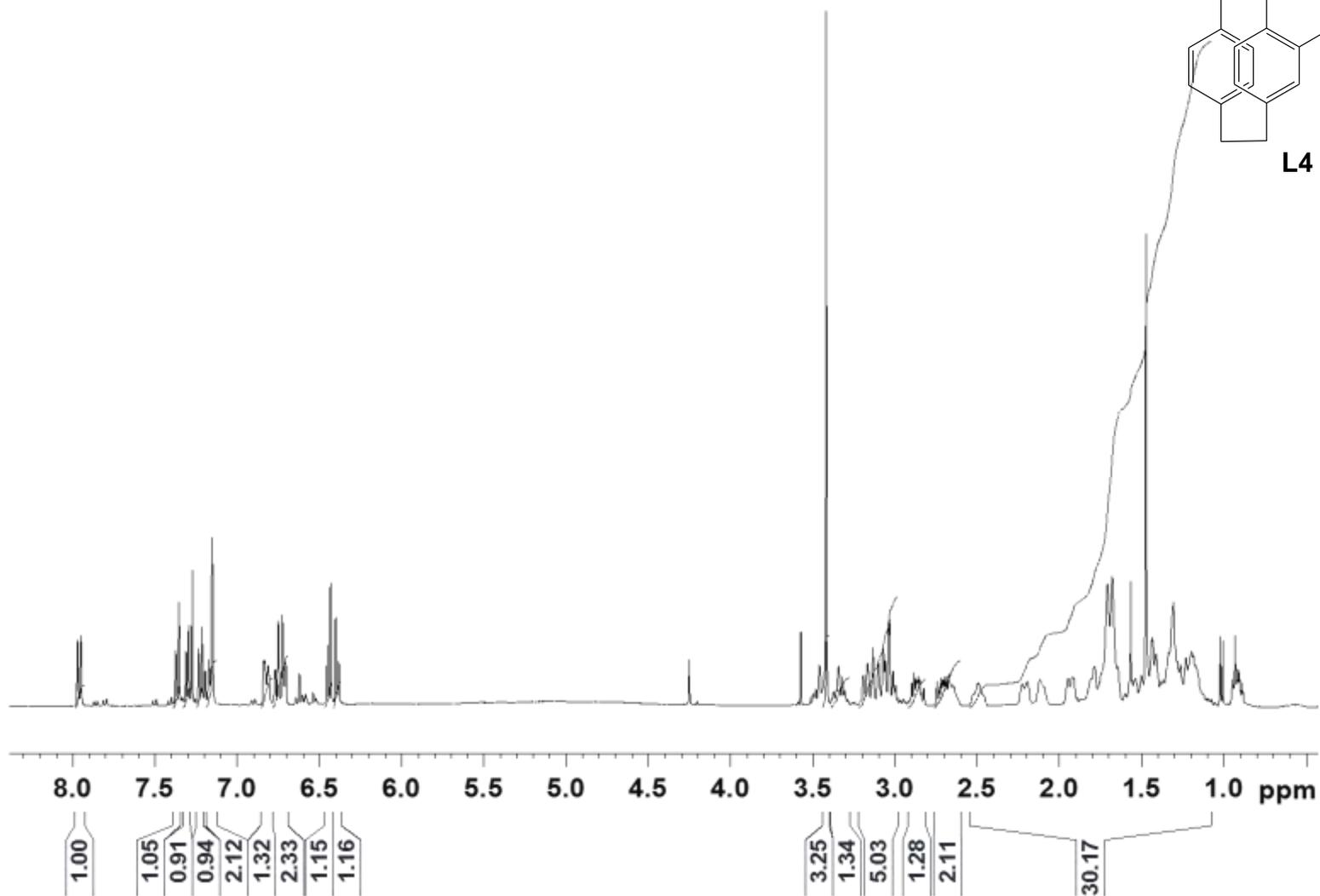
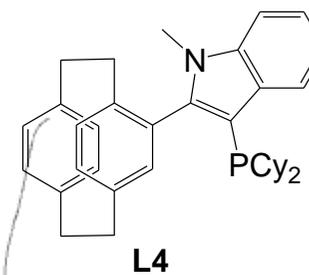
¹³C NMR of (±)-2-[2.2]paracyclophan-4-yl-3-diphenylphosphino-N-methyl-indole (**L3**)



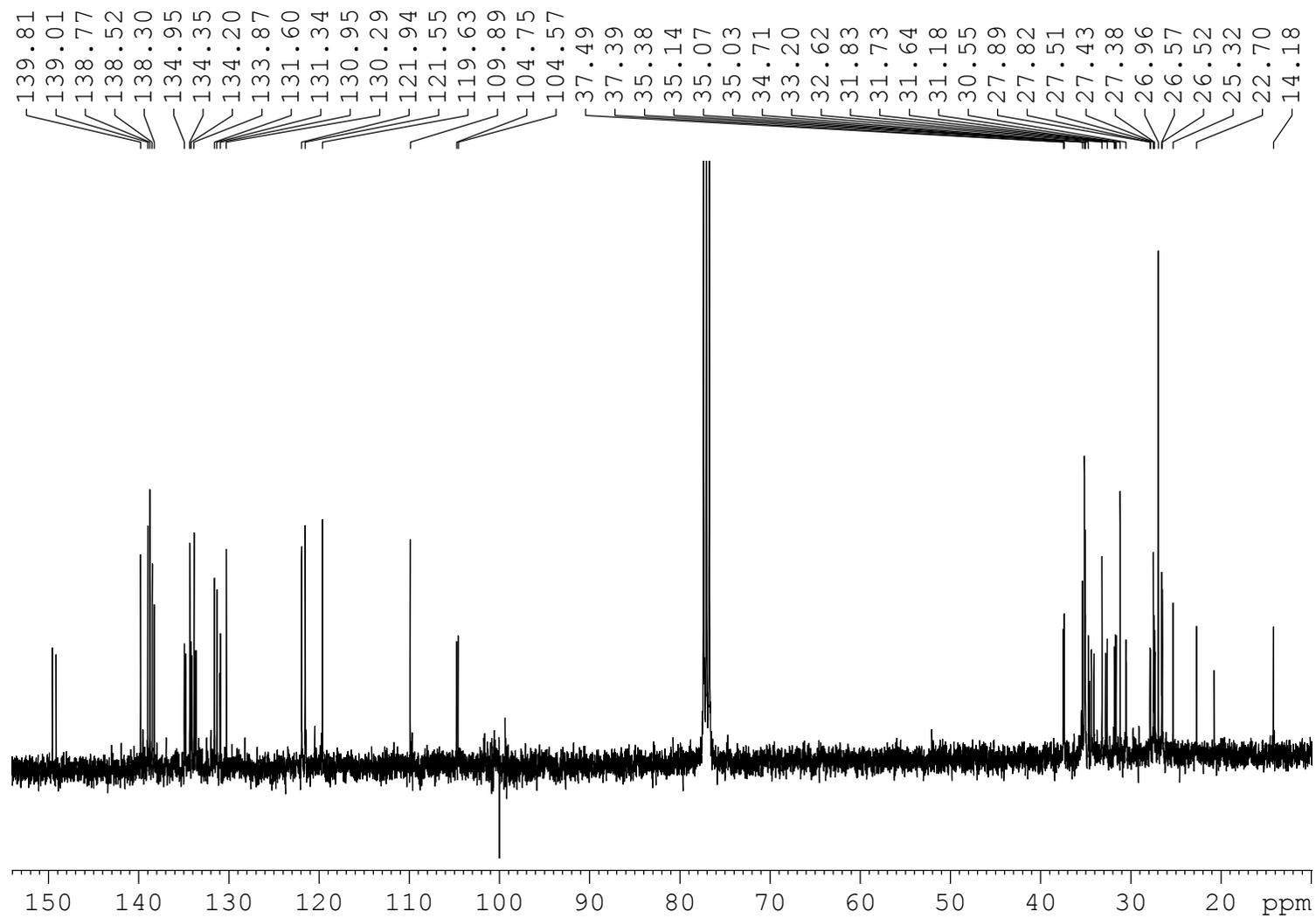
^{31}P NMR of (\pm)-2-[2.2]paracyclophan-4-yl-3-diphenylphosphino-N-methyl-indole (**L3**)



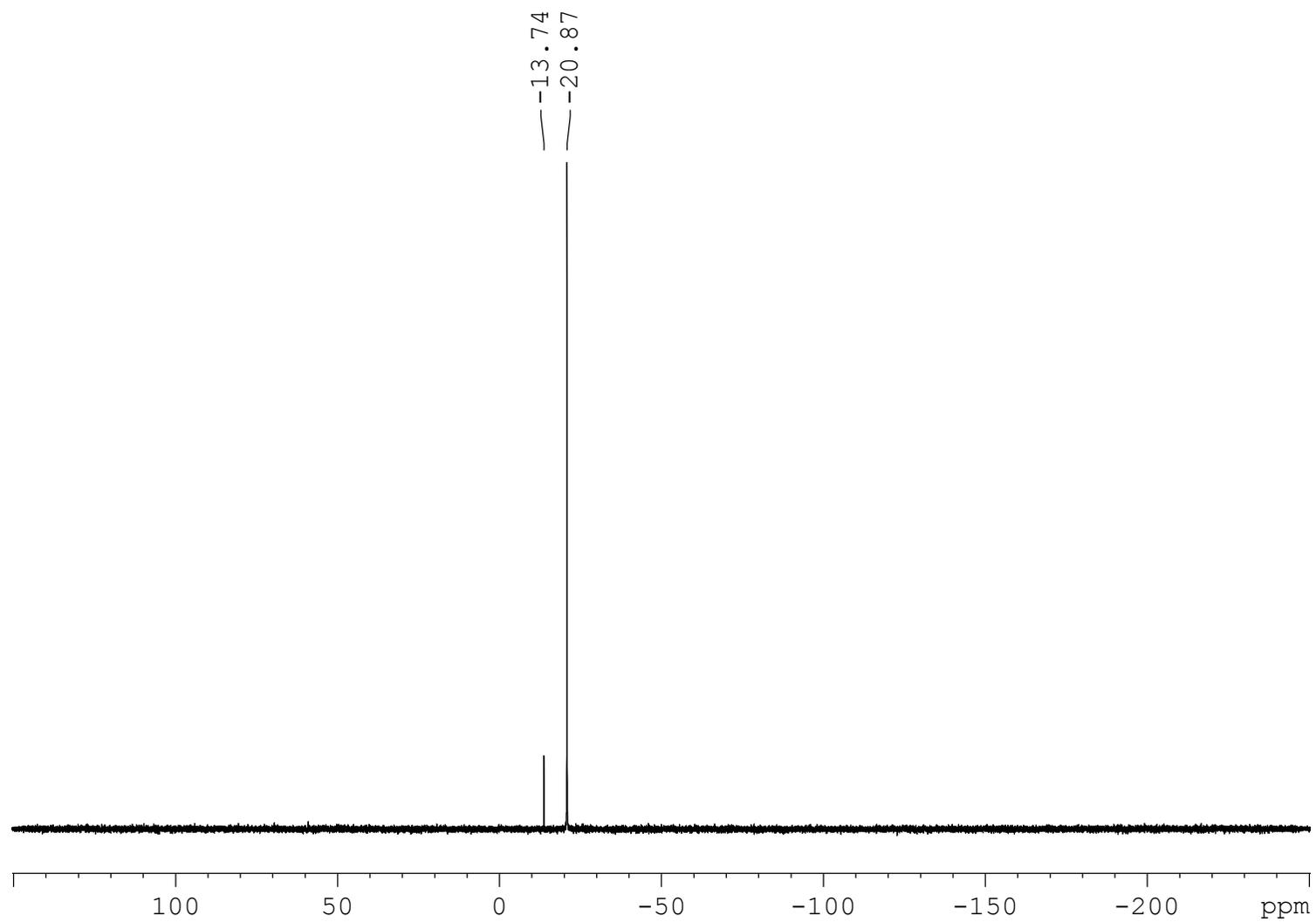
^1H NMR of (\pm)-2-[2.2]paracyclophan-4-yl-3-dicyclohexylphosphino-N-methyl-indole (**L4**)



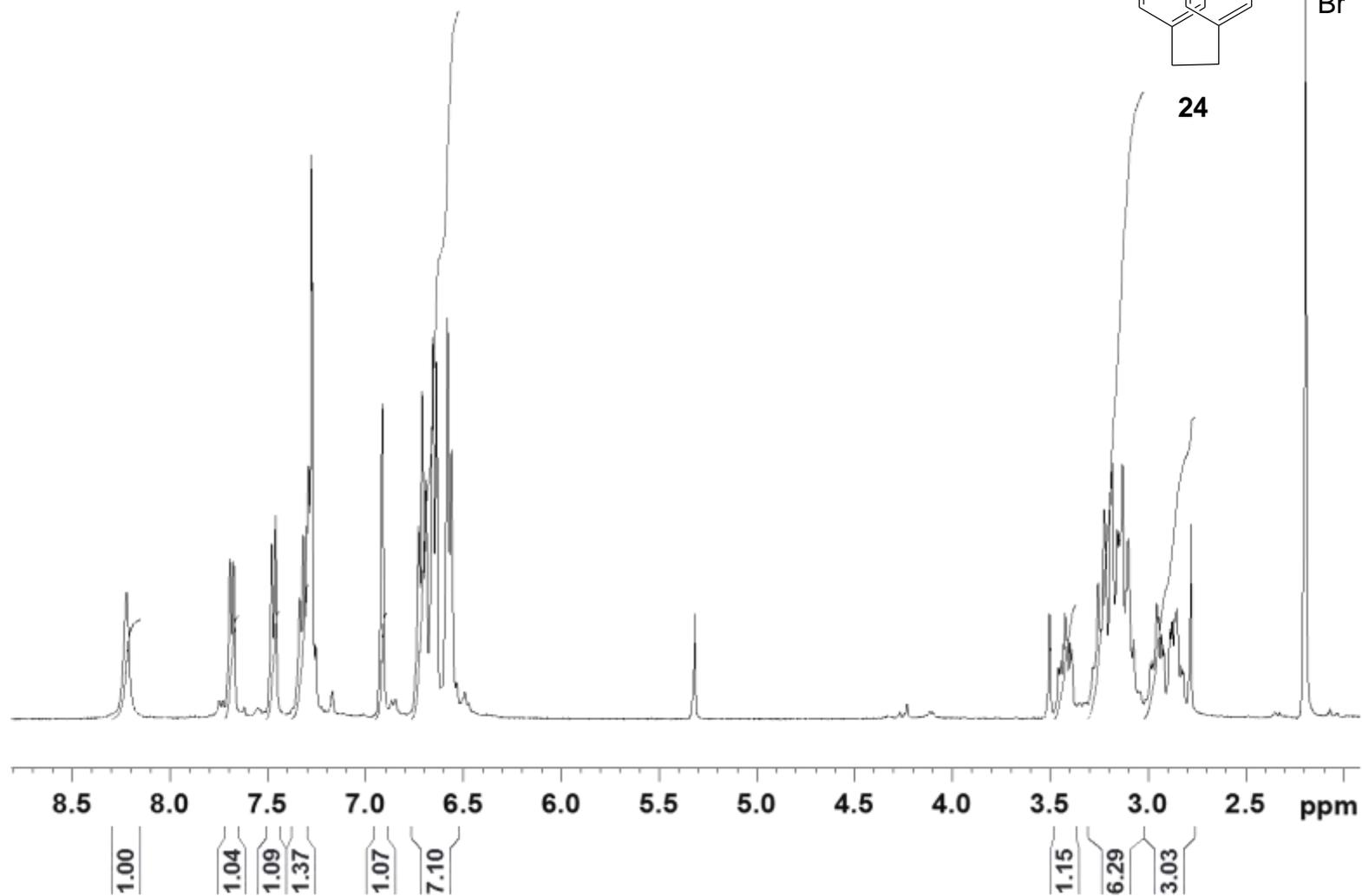
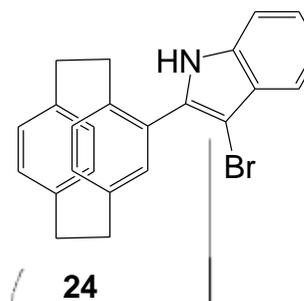
¹³C NMR of (±)-2-[2.2]paracyclophan-4-yl-3-dicyclohexylphosphino-N-methyl-indole (**L4**)



^{31}P NMR of (\pm)-2-[2.2]paracyclophan-4-yl-3-dicyclohexylphosphino-N-methyl-indole (**L4**)



^1H NMR of (\pm)-2-[2.2]paracyclophan-4-yl-3-bromo-indole (**24**)



^1H NMR of Phenyl boronic acid (25)

