Stony Brook University

Applications of Biphenol-Based Phosphine Ligands in Asymmetric Reactions

A Thesis Presented

by

Winnie Situ

to

The Graduate School

in fulfillment of the

Requirements

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Abstract of the Thesis

Applications of Biphenol-Based Phosphine Ligands in Asymmetric Reactions

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Catalytic asymmetric synthesis plays a crucial role in organic synthesis as it provides a means in which one or more chiral centers can be produced in complex compounds. Within the last 5 decades, significant new developments in asymmetric catalysis have been reported. Chiral ligands, such as chiral phosphines, are useful for their abilities to produce complex compounds bearing chiral centers. Bidentate ligands have been frequently employed in asymmetric synthesis, however the synthesis of these ligands is difficult. As such, focus has been given to the preparation of monodentate phosphorous ligands and their application in asymmetric synthesis.

In 2003, the Ojima group has developed a series of chiral biphenol-based monophosphoramidite (MPN) ligands which have performed nicely in various asymmetric reactions. Futhermore, in 2010, a series of chiral biphenol-based diphosphonite (BOP) ligands was developed that showed to be successful in the asymmetric allylic amination reaction. To further demonstrate the applicability of the ligands, they were employed in the asymmetric rhodium-catalyzed 1,4-conjugate addition and palladium-catalyzed intermolecular Heck reaction.

The BOP ligand was employed for the synthesis of a versatile key intermediate of the indoline derivative which can be used towards the total synthesis of *Strychnos* indole alkaloids. The synthesis of this key intermediate entails an intermolecular asymmetric allylic amination catalyzed by BOP-Pd complex and an intramolecular Heck reaction of the resulting allylic amination product. The intramolecular Heck reaction and subsequent reactions is demonstrated.

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List of Abbreviations

Ac	acetyl
acac	acetylacetonate
atm	atmosphere
BINAP	2,2-bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-bis(2-naphthol)
BOP	Diphosphonite
Bz	Benzyl
Celite ®	diatomaceous earth filter agent, ®Celite Corp,
COD(cod)	1,5-cyclooctadiene
d	doublet
dd	doublet of doublet
DCM	dichloromethane
DMAP	4-(*N*,*N*-dimethylamino)pyridine
DME	dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
dppb	1,4-bis(diphenylphosphino)butane
dppp	1,3-bis(diphenylphosphino)propane
ee	enantiomeric excess
Eq,	equivalent
Et	ethyl
GC-MS	gas chromatography-mass spectrometry
h	hour
HMPT	hexamethylphosphorous triamide

HPLC	high performance liquid chromatography
Hz	hertz
i	iso
J	coupling constant
m	multiplet
Me	methyl
min	minute
mp	melting point
MPN	monophosphoramidite
Ms	mesylate
NMR	nuclear magnetic resonance
Ph	phenyl
ppm	parts per million
i-Pr	isopropyl
psi	pounds per square inch
pyr.	Pyridine
q	quartet
Red-Al®	sodium bis(2-methoxyethoxy)aluminum hydride
Rt	room temperature
S	singlet
T	triplet
TADDOL	α,α,α',α'-tetraphenyl-2,2'-dimethyl-1,3-dioxolane-4,5-dimethanol
TBAF	tetrabutylammonium fluoride
Tert	tertiary
Tf	trifluoromethanesulfonyl

THF	tetrahydrofuran
TIPS	triisopropylsilyl
Ts	*p*-toluenesulfonyl
δ	chemical shift

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With utmost sincerity, I would like to thank my advisor the Distinguished Professor Iwao Ojima for giving me the opportunity to do research in his laboratory. He has shown profound patience and utter devotion to his craft: teaching me organic chemistry. This was done through persistent inquiry and his unwavering desire to share a plethora of knowledge. All of this combined has made my work, my research and my time here much more meaningful. Next, I would like to thank my mentor Chih-Wei Chien, who much like Professor Ojima, has shown an insurmountable amount of patience and guidance. This has been crucial for my development and growth not only as a chemist but as a person. A huge part of the lab, I would like to thank Patricia Marinaccio, who, as the entire lab knows, is the mother of the lab. Simply put, she is awesome. Then I would like to thank the Ojima Group Members who have made my stay here much more delicious and colorful. Without all of their constant jibber-jabber, life in the lab would have been bland and grey.

All of my work in the lab could not have been done without the help and guidance from Professors Goroff and Koch. Not only are they a part of my committee, they were also my professor during my undergraduate and master's coursework. Professor Goroff has shown a genuine devotion to her students. I would like to thank Professor Koch for his openness. I would also like to thank Dr. James Marecek and Francis Picart for their help with NMR techniques and general advice.

Furthermore, I would like to thank Chih-Wei Chien and Edison S. Zuniga for proofreading this thesis. Their help and work were unfaltering. Lastly, I would like to thank my family and friends for all of their support.

Chapter 1

§ 1.1 Introduction

Catalytic asymmetric synthesis is of great importance due to its usefulness in producing one or more chiral centers. Asymmetric catalysis is the process by which a chiral catalyst aids the conversion of an archiral substance into a chiral product that has preference for formation of one enantiomer. Three different kinds of chiral catalysts are usually employed for asymmetric catalysis: metal ligand complexes derived from chiral ligands, chiral organocatalysts and biocatalyst. The first example of asymmetric synthesis was reported in 1904 by Marckwald, which was the enantioselective decarboxylation of malonic acid in the presence brucine.[1] In 1956, Akabori *et al.* reported a silk-palladium catalyst that was capable of asymmetric reduction of certain unsaturated compounds.[2]

Since the 1960s, new developments in asymmetric catalysis have been reported. In 1961, Natta *et al.* obtained an optically active polymer through the polymerization of benzofuran using $AlCl_3$ and phenylalanine as the catalyst.[3] In 1966, the first organometallic asymmetric catalysis was reported by Noyori *et al.* where a chiral salen-copper complex catalyst was employed in the cyclopropanation of alkenes.[4] In the same year, Wilkinson reported the homogenous hydrogenation of alkenes catalyzed by rhodium complex $[RhCl(PPh_3)_3]$.[5-7] By modifying Wilkinson's catalyst through a simple ligand exchange, in 1968 Knowles and Horner introduced the chiral monodentate phosphine (**Figure 1.1**).[8,9]

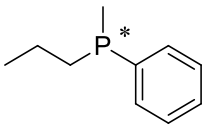


Figure 1.1 Chiral Monodentate Phosphine

In 1980, significant developments in asymmetric catalysis were published by Sharpless and Noyori. Sharpless published the asymmetric epoxidation of allylic alcohols using a diethyl titrate-titanium complex and Noyori reported the asymmetric hydrogenation induced by BINAP-rhodium complex.[10,11] These two catalytic reactions described by Sharpless and Noyori are very

useful in organic synthesis due to their extensive applications and high enantioselectivitities. As pioneers of the asymmetric catalysis, Knowles, Noyori and Sharpless were awarded the 2001 Nobel Prize in Chemistry for their work on chirally catalyzed hydrogenation (Knowles and Noyori) and oxidation (Sharpless) reactions.[10, 11]

§ 1.1.1 Development of Biphenol-based phosphorous ligands

Chiral catalysts, such as chiral phosphines, are useful ligands in asymmetric catalysis since the use of these ligands in reactions can produce valuable chiral compounds. These chiral phosphines are prepared from naturally occurring compounds, synthesized in laboratories or separated by resolution. Phosphorous ligands have been highly studied and among these, bidentate ligands have long dominated the area of research. Various examples of chiral bidentate ligands, including DIOP[12], BINAP[11] and DuPHOS[13] (**Figure 1.2**), were used for asymmetric synthesis. DIOP was prepared from naturally occurring tartaric acid by Kagan.[12] Noyori separated enantiomers of BINAP by resolution with chiral Pd complex.[10]

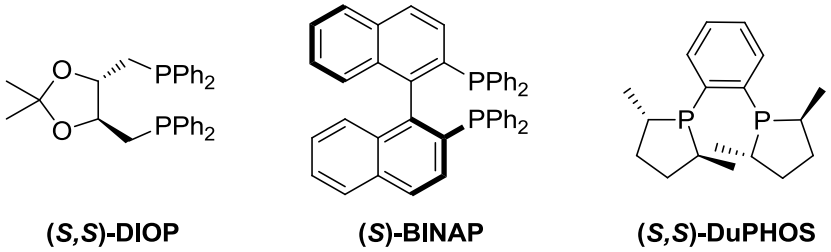


Figure 1.2 Examples of Bidentate Ligands

Though several bidentate ligands have been prepared, they are difficult to synthesize, thus monodentate phosphorous ligands have become the new focus in current research. In 1998, Alexakis *et al.*[14] synthesized a series of monodentate phosphorous ligands derived from TADDOL (**Figure 1.3**). The ligands were used for the asymmetric conjugate addition of diethyl zinc to enones with copper (II) triflate that gave products with up to 96% enantiomeric excess (*ee*).

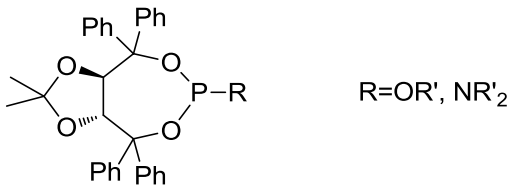


Figure 1.3 Monodentate Phosphorous Ligands based on (-)-TADDOL

In 2000, Reetz[15] and Feringa[16] separately published the discovery of the highly enantioselective hydrogenation of methyl-2-acetamido acrylate catalyzed by rhodium (I) complex accompanied with BINOL-based ligand family (**Figure 1.4**).

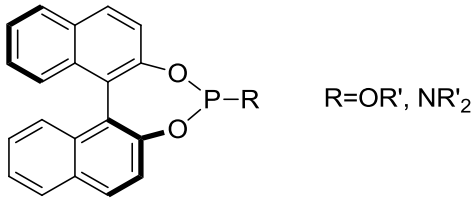
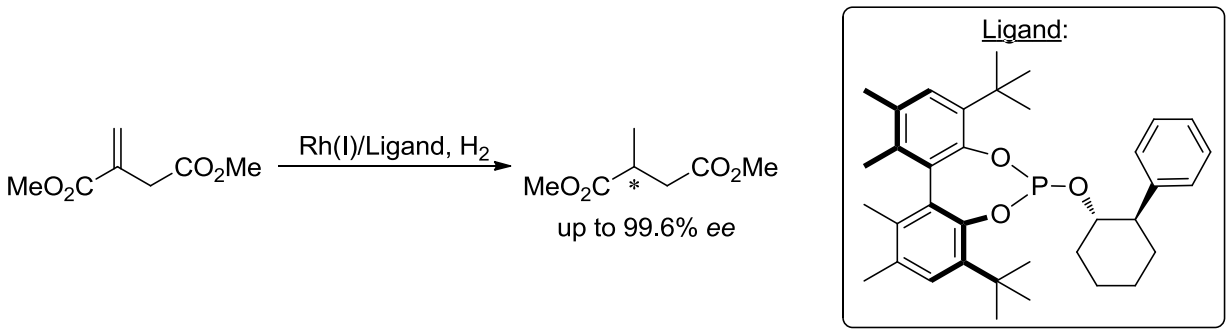


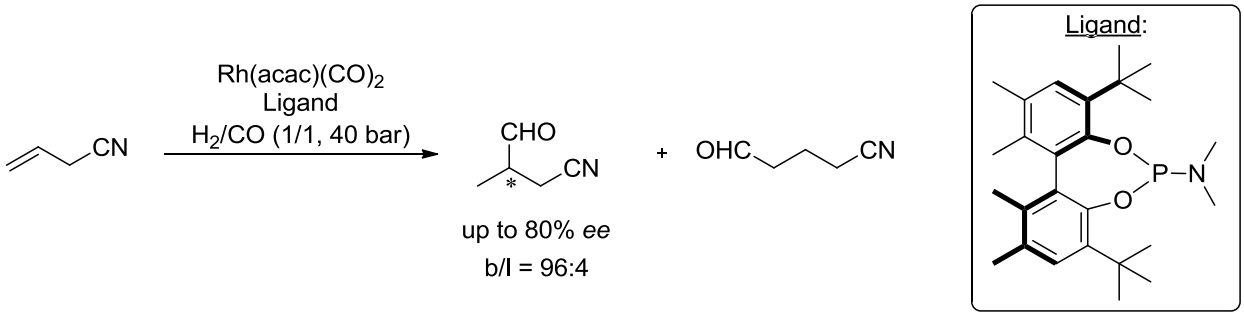
Figure 1.4 Monodentate Phosphorous Ligands based on (*S*)-BINOL

In 2003, Ojima *et al.*[17] developed a new class of chiral monodentate phosphorous ligands that were derived from accessible enantiopure chiral biphenol backbone. Using these biphenol-based ligands in Rh-(I)-catalyzed hydrogenation of dimethyl itaconate gave products with up to 99.6% *ee* (**Scheme 1.1**).

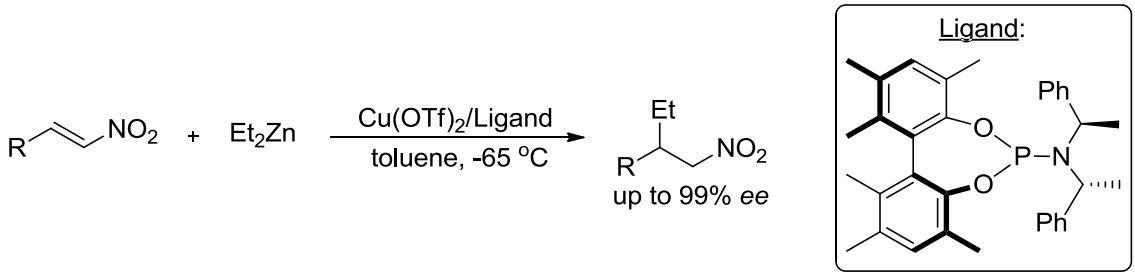


Scheme 1.1 Rh-Catalyzed Hydrogenation using Biphenol-Based Ligand

In 2004, the Ojima group demonstrated that phosphoramidite ligands can be applied to Rh-catalyzed hydroformylation of allyl cyanides (**Scheme 1.2**)[18] and Cu-catalyzed conjugate addition of diethylzinc to alkenes (**Scheme 1.3**).[19]

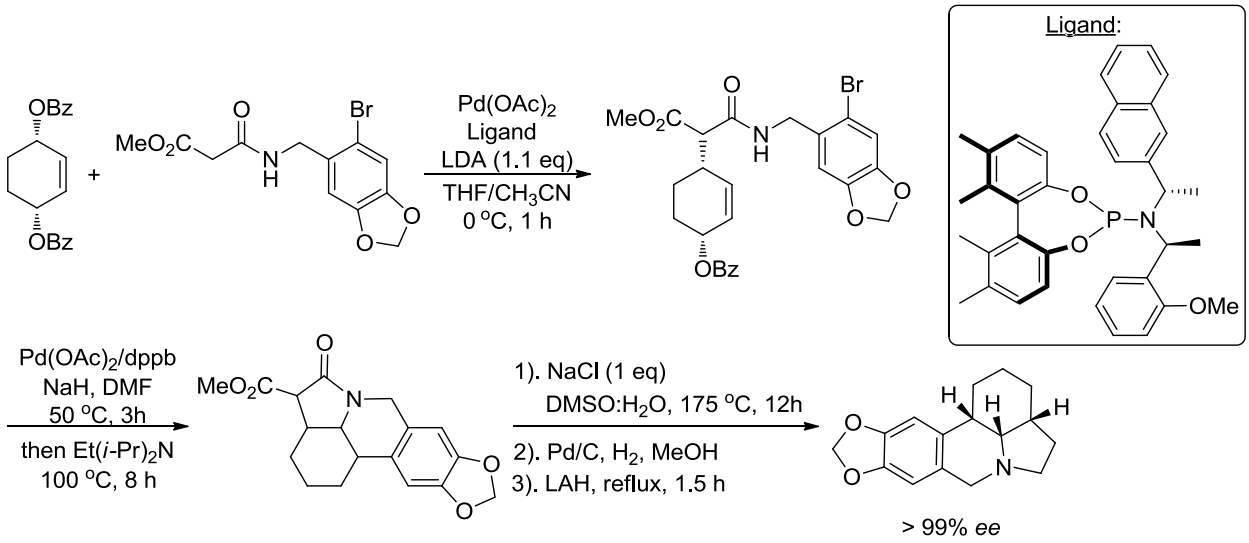


Scheme 1.2 Rh-Catalyzed Hydroformylation using Phosphoramidite Ligand

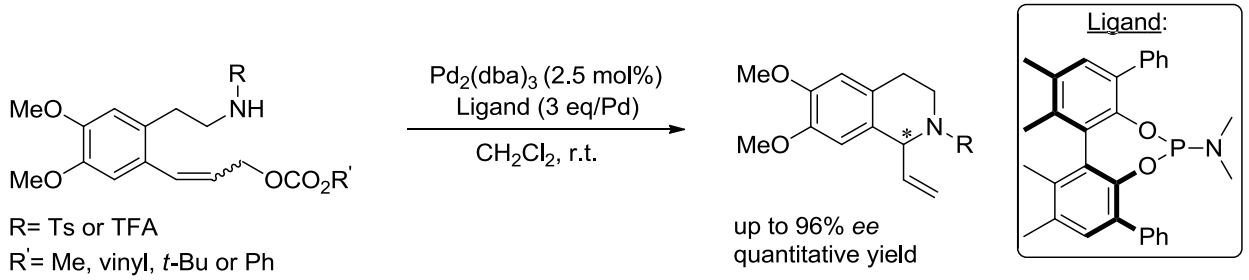


Scheme 1.3 Cu-Catalyzed Conjugate Addition using Phosphoramidite Ligand

In 2006 and 2007, Ojima *et al.* further expanded the biphenol-based ligand library. Through a short synthesis that used Pd-catalyzed asymmetric allylic alkylation as a crucial step, (+)-γ-lycorane was obtained with more than 99% *ee* by using chiral phosphoramidite ligands (**Scheme 1.4**).[20] 1-Vinyltetrahydroisoquinoline was obtained with 96% *ee* via Pd-catalyzed intramolecular allylic amination when using the chiral phosphoramidite ligands (**Scheme 1.5**).[21]

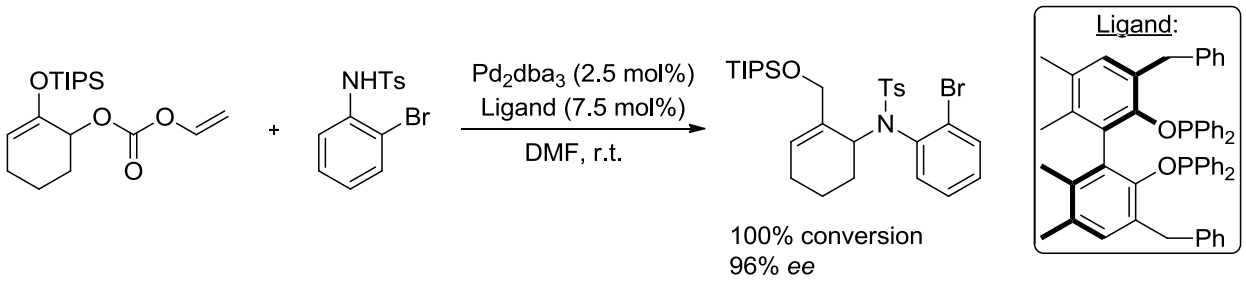


Scheme 1.4 Pd-Catalyzed Allylic Alkylation using Biphenol-Based Ligand



Scheme 1.5 Pd-Catalyzed Allylic Amination using Phosphoramidite Ligand

In 2010, Ojima *et al.* synthesized a series of new chiral biphenol-based diphosphonite (BOP) ligands based on the enantiopure biphenol backbone. Application of the chiral BOP ligands to the palladium-catalyzed intermolecular allylic amination, which results in a key intermediate for the total synthesis of *Strychnos* indole alkaloids, afforded the product with up to 96% *ee* (**Scheme 1.6**).[22]

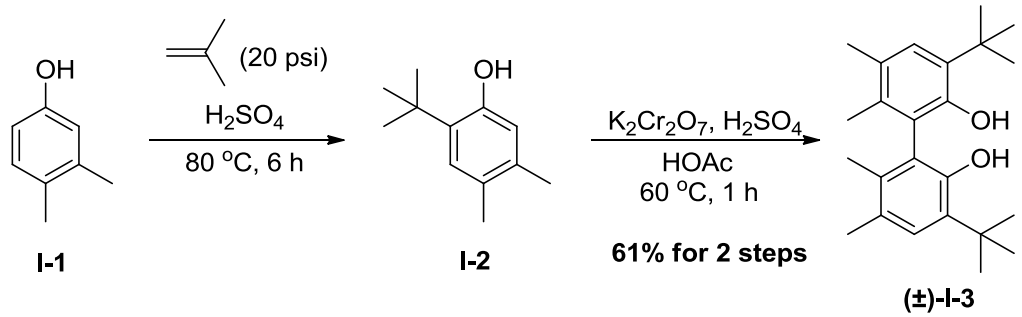


Scheme 1.6 Pd-Catalyzed Allylic Amination using Diphosphonite Ligand

§ 1.2 Results and Discussion

§ 1.2.1 Synthesis of Enantiopure 3,3'-di-tert-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol

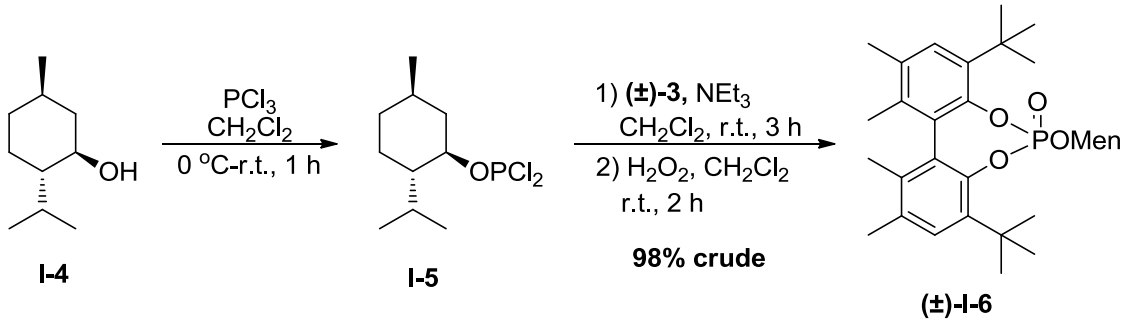
The synthesis of racemic 3,3'-di-*tert*-butyl-5,5',6,6'-tetramethyl-2,2'-biphenol [**(±)-I-3**] was done with slight alterations made from the literature reported procedure[24]. A Friedal-Crafts alkylation was achieved by treating 3,4-dimethylphenol (**I-1**) with 20 psi of 2-methylpropene at 80 °C in the presence of excess sulfuric acid to produce crude 2-*tert*-butyl-4,5-dimethylphenol (**I-2**). The crude **I-2** was converted to the racemic biphenol **(±)-I-3** by oxidative coupling using potassium dichromate that resulted in 61% yield for the two steps (**Scheme 1.7**).



Scheme 1.7 Synthesis of racemic biphenol (±)-I-3[24]

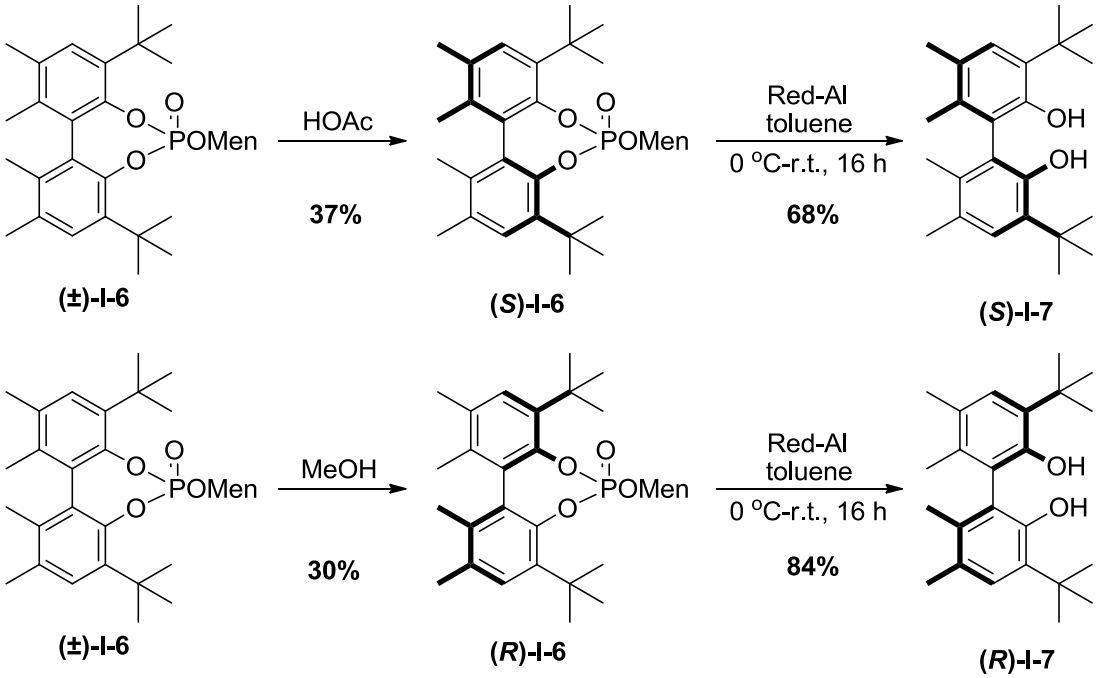
Separation of the racemic biphenol **(±)-I-3** was achieved by optical resolution of readily prepared menthyl phosphates. Addition of (-)-menthol, **I-4**, to a dichloromethane solution with

excess phosphorous trichloride yielded (-)-menthyl dichlorophosphite (**I-5**). Adding a mixture of **(±)-I-3** and triethylamine to the dichloromethane solution of **I-5**, and followed by treatment with hydrogen peroxide gave a diastereomeric mixture of phosphate **(±)-I-6** (**Scheme 1.8**).



Scheme 1.8 Synthesis of diastereomeric phosphate (±)-I-6[24]

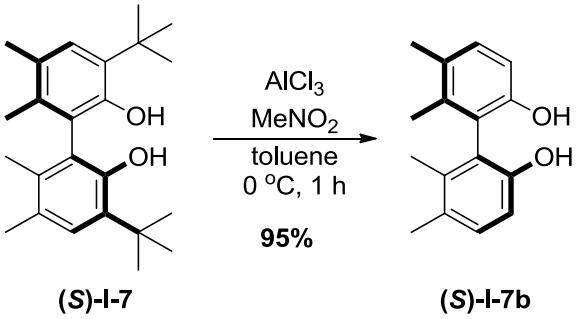
(*S*)-I-6 was separated from **(±)-I-6** by crystallization from acetic acid. The mother liquor was evaporated to give crude **(*R*)-I-6**, which was then recrystallized from methanol to obtain pure **(*R*)-I-6**. The purity of both **I-6** isomers was checked using ^{31}P NMR. For each diastereomer, only one peak was seen in each spectrum, δ -3.99 ppm for **(*S*)-I-6** and δ -4.43 ppm for **(*R*)-I-6)**. Compound **(*S*)-I-6** was isolated with a yield of 37% whereas **(*R*)-I-6** was isolated with a yield of 30%. Both diastereomers were reduced with Red-Al® to give **(*S*)-I-7** in 68% yield and **(*R*)-I-7** in 84% yield (**Scheme 1.9**).



Scheme 1.9 Separation of (*S*)-I-6 and (*R*)-I-6 and synthesis of (*S*)-I-7 and (*R*)-I-7[24]

§ 1.2.2 Synthesis of Enantiopure 5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol

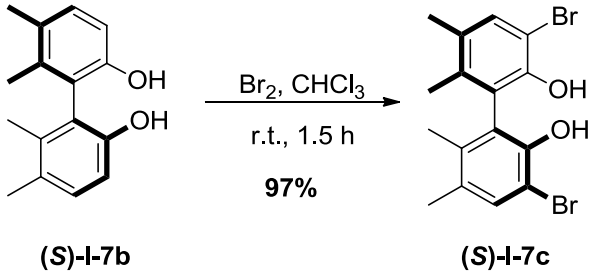
The *tert*-butyl groups at the 3 and 3' positions were removed by treating **(*S*)-I-7** with aluminum trichloride in nitromethane-toluene at 0 °C giving **(*S*)-I-7b** in 95% yield (**Scheme 1.10**). The resulting product can be used as an intermediate to prepare various biphenols with different substituents at the 3 and 3' positions. **(*R*)-I-7b** was prepared the same way from **(*R*)-I-7** using the same protocols, resulting in 84% yield (not shown).



Scheme 1.10 Synthesis of biphenol (*S*)-I-7b[17]

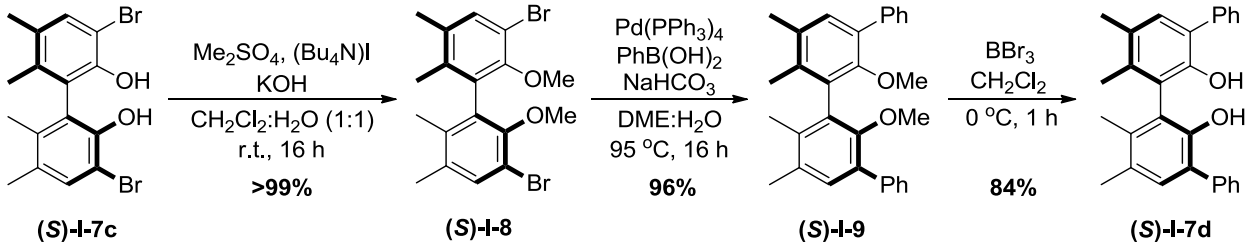
§ 1.2.3 Synthesis of (S)-3,3'diphenyl-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol

Treating **(*S*)-I-7b** with excess bromine in chloroform gave compound **(*S*)-I-7c** in 97% yield (**Scheme 1.11**).



Scheme 1.11 Synthesis of biphenol (*S*)-I-7c[17]

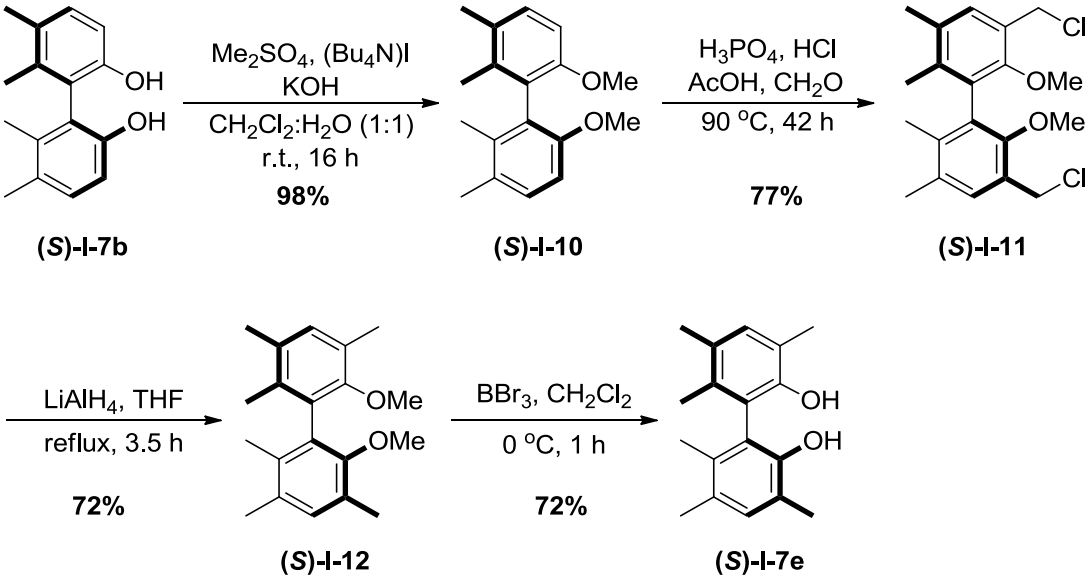
Biphenol **(*S*)-I-7c** was used to produce the desired phenyl–substituted biphenol **(*S*)-I-7d** by a series of steps. Biphenol **(*S*)-I-7c** was protected by methylation with dimethyl sulfate to give **(*S*)-I-8** in quantitative yield. **(*S*)-I-8** was then subjected to $Pd(PPh_3)_4$ catalyzed Suzuki coupling with phenylboronic acid to give **(*S*)-I-9** in 96% yield. Removal of the methyl group from **(*S*)-I-9** with boron tribromide gave the desired **(*S*)-I-7d** in 84% yield (**Scheme 1.12**).



Scheme 1.12 Synthesis of biphenol (*S*)-I-7d[17]

§ 1.2.4 Synthesis of (S)-3,3'-dimethyl-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol

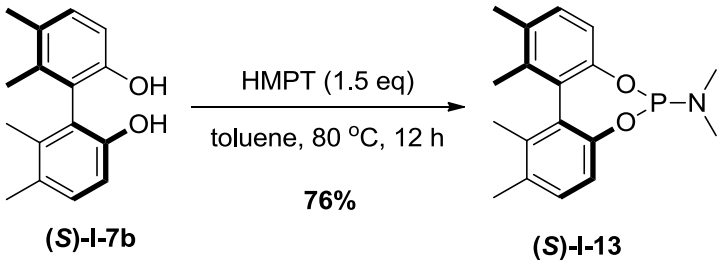
Biphenol **(*S*)-I-7b** can be used to synthesize the desired methyl-substituted biphenol **(*S*)-I-7e** through a series of steps as shown in **Scheme 1.13**. Biphenol **(*S*)-I-7b** was first subjected to methylation with dimethyl sulfate in the presence of potassium hydroxide and tetrabutylammonium iodide to give **(*S*)-I-10** in 98% yield. **(*S*)-I-10** was then subjected to chloromethylation to give biphenol **(*S*)-I-11** in 77% yield, which was reduced by $LiAlH_4$ to give **(*S*)-I-12** in 72% yield. Finally, deprotection of **(*S*)-I-12** using boron tribromide gave the desired biphenol **(*S*)-I-7e** in 72% yield.



Scheme 1.13 Synthesis of (*S*)-I-7e[17]

§ 1.2.5 Synthesis of chiral Biphenol-based phosphoramidite (MPN) ligands

Biphenol **(S)-I-7b** was used to synthesize the chiral biphenol-based phosphoramidite (MPN) ligand [**(*S*)-I-13**]. Using an excess amount of hexamethylphosphorous triamide (HMPT), the reaction was heated to 80 °C to give the ligand in 76% yield.



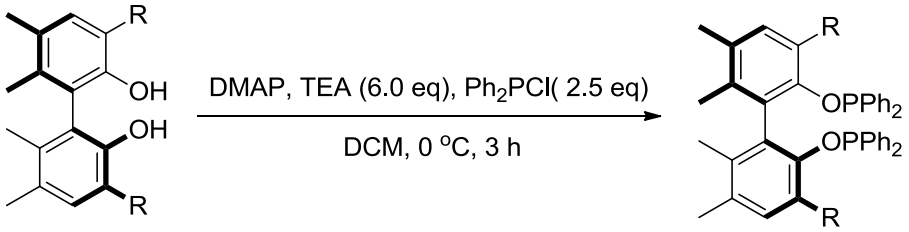
(*S*)-I-7b (*S*)-I-13

Scheme 1.14 Synthesis of MPN ligand (*S*)-I-13[18]

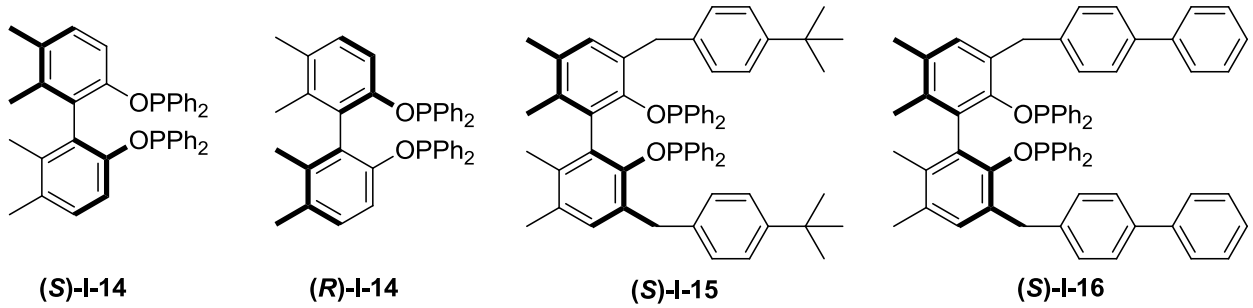
§ 1.2.6 Synthesis of chiral Biphenol-based diphosphonite (BOP) ligands

Biphenol **(*S*)-I-7b** was used to synthesize the chiral biphenol-based diphosphonite (BOP) ligand by treating with an excess amount of chlorodiphenyl phosphine and a catalytic amount of DMAP in the presence of TEA at 0 °C. **(*S*)-I-14** was obtained in a 66% yield (entry 1). Biphenol **(*R*)-I-7b** can also be used to synthesize the **(*R*)-I-14** in the same manner (entry 2). Biphenol **(*S*)-I-11** can be subjected to substitution reactions to obtain different functional groups in the 3 and 3' positions. The substituted biphenols can be treated in the same way as biphenol **(*S*)-I-7b** to obtain the 3 and 3' susbtituted BOP ligands **(*S*)-I-15** and **(*S*)-I-16** (entry 3 and 4).

Table 1.1 Synthesis of Chiral BOP Ligands



Entry	Ligand	Yield (%)
1	(*S*)-I-14	66
2	(*R*)-I-14	43
3	(*S*)-I-15	70
4	(*S*)-I-16	36



(*S*)-I-14 (*R*)-I-14 (*S*)-I-15 (*S*)-I-16

Figure 1.5 Various BOP Ligands synthesized

§ 1.3 Conclusion

Asymmetric catalysis is an essential process due to its ability to introduce elements of chirality. Significant progress in asymmetric catalysis was made in the 1960s and again in the 1980s. Chiral phosphorous ligands have been extensively studied. Bidentate phosphines originally dominated the phosphorous ligand arena, however their difficult synthesis has given way to monodentate phosphorous ligands.

The Ojima group developed a new class of monodentate chiral biphenol-based ligands in 2003. The monophosphoramidite ligands' effectiveness was demonstrated in their ability to give good yield and high enantioselectivity for various asymmetric reactions. In 2010, using the chiral biphenol-backbone, a series of diphosphonite ligands was developed. They proved to be quite successful for allylic amination.

A variety of biphenols have been synthesized that can be used as intermediates for the synthesis of various monophosphoramidite and diphosphonite ligands. The MPN and BOP ligands have been synthesized that can be applied to various asymmetric catalytic reactions.

§ 1.4 Experimental

General Information:

All chemical were obtained from Sigma-Aldrich, Fisher Scientific or VWR International, and used as is unless otherwise noted. All reactions were performed under Schlenk conditions with oven dried glassware unless otherwise noted. Dry solvents were degassed under nitrogen

and were dried using the PURESOLV system (Inovatative Technologies, Newport, MA). Tetrahydrofuran was freshly distilled from sodium metal and benzophenone. Dichloromethane was also distilled immediately prior to use under nitrogen from calcium hydride. Toluene was also distilled immediately prior to use under nitrogen from calcium hydride. ^{1}H, ^{13}C and ^{31}P data were obtained using either 300 MHz Varian Gemni 2300 (75 MHz ^{13}C, 121 MHz ^{31}P) spectrometer or the 400 MHz Varian INOVA 400 (100 MHz ^{13}C, 162 MHz ^{31}P) spectrometer in $CDCl_3$ as solvent unless otherwise stated. Chemical shifts (δ) are reported in ppm and standardized with solvent as internal standard based on literature reported values.[14] Melting points were measured on Thomas Hoover Capillary melting point apparatus and are uncorrected. Optical rotations were measured on Perkin-Elmer Model 241 polarimeter. GC/MS was performed on Agilent 6890GC/5973 Mass Selective Detector.

Preparation of 2-*tert*-butyl-4,5-dimethylphenol (I-2)[17, 23, 24]

3,4-Dimethylphenol (**I-1**) (80.76 g, 661 mmol) and concentrated sulfuric acid (0.8 mL) were added to a 300 mL autoclave with a glass liner and stirring bar. The autoclave was then pressurized with 2-methylpropene (20 psi) and heated to 80 °C while stirring. After 6 hours of heating, the autoclave was opened and the mixture was analyzed by TLC and GC-MS. The crude product, 2-*tert*-butyl-4,5-dimethyl phenol (**I-2**), was used directly in the next step without further purification.

Preparation of 3,3'-di-*tert*-butyl-5,5'-6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol ((±)-I-3)[17, 23, 24]

Potassium dichromate (60.85 g, 44 mmol) in sulfuric acid (120 mL) and water (320 mL) was added to crude **I-2** dissolved in acetic acid (520 mL). The mixture was cooled to room temperature after stirring for 1 hour at 60 °C. The precipitate was obtained by filtration and washed by water (2x200 mL) and methanol (3x160 mL). The precipitate was added to methanol and stirred for an additional 15 minutes and filtered again. The solid diol **(±)-I-3** was dried *in vacuo* to give pure diol **(±)-I-3** (71.3 g, 61% yield for 2 steps), as a white solid: m.p. 162-164 °C. All data were consistent with literature results.[17]

Preparation and Resolution of (*R*)-I-6 and (*S*)-I-6[17, 23, 24]

(1*R*, 2*S*, 5*R*)-(-)-Menthol (**I-4**) (32.72 g, 209 mmol) dissolved in CH_2Cl_2 (65 mL) was added to phosphorous trichloride (1.5 eq, 23.6 mL, 270 mmol) in CH_2Cl_2 (130 mL) at 0 °C, over a period of 30 minutes. After the addition, the reaction mixture was removed from the ice bath and kept at room temperature for 1 hour. The solvent and other volatile liquids were removed *in vacuo* to obtain an oil **I-5**. **(±)-I-3** (64.17g, 180 mmol) dissolved in CH_2Cl_2 (200 mL) and triethylamine (3eq, 540 mmol) was added to **I-5** dissolved in CH_2Cl_2 (100 mL), over a period of 30 minutes. After allowing the solution to stand for 2 hours, it was filtered. Then, 35% H_2O_2 (111 mL) was added slowly while stirring. The resulting mixture was stirred rapidly for 2 hours. The organic layer was separated, washed with water (2x125 mL) and brine (125 mL) and then dried over anhydrous $MgSO_4$. The $MgSO_4$ was removed by filtration and the solution was concentrated by rotary evaporation to obtain a solid. The resulting solid was dried *in vacuo* to afford **(±)-I-6** (97.9 g, 98% yield), as a white solid.

The diastereomeric mixture **(±)-I-6** was separated into two isomers by crystallization. The solid **(±)-I-6** was dissolved in a minimum amount of hot acetic acid (~200 mL), which formed white crystals after 24 hours at room temperature. The crystals were collected by filtration and washed with cold acetic acid (2x35 mL). Recrystallization with hot acetic acid was done to further purify the crystals, to afford pure **(*S*)-I-6** (35.8 g, 73%), as a white solid. The crude **(*R*)-I-6** was obtained by concentrating the liquid of the first crystallization *in vacuo*. The remaining solid was dissolved in hot MeOH (~175 mL) and then cooled to 0 °C to form **(*R*)-I-6** crystals. These crystals were then recrystallized with hot MeOH to obtain pure **(*R*)-I-6** (29.3 g, 60% yield), as a white solid: ^{31}P NMR (121.5 MHz, $CDCl_3$) δ -3.99 ppm for **(*S*)-I-6**, and -4.43 ppm for **(*R*)-I-6**. All data were consistent with literature results.[17]

Preparation of Enantiopure 3,3'-di-*tert*-butyl-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol ((*S*)-I-7) and ((*R*)-I-7) [17, 23, 24]

(S)-I-6 (35.81 g, 65.0 mmol) was dissolved in toluene (305 mL) in a round-bottomed flask equipped with an addition funnel. Red-Al® (49 mL, 70% wt. in toluene) was added

dropwise to the **(*S*)-I-6** solution with continuous gas evolution at 0°C. The mixture was stirred at room temperature for 16 hours and then quenched with water (72 mL) and bleach (72 mL). The slurry was the filtered through Celite® pad and washed with toluene (224 mL). The filtrate was extracted to obtain the organic layer. The organic layer was further washed with 5% bleach (180 mL) and brine (180 mL) and then dried with anhydrous $MgSO_4$. The $MgSO_4$ was removed by filtration and the toluene was removed by vacuum distillation to obtain a white solid. The side product, menthol, was expelled by washing the solid with cold MeOH several times until no minty odor remained. **(*S*)-I-7** was obtained by filtration and dried *in vacuo* (15.6g, 68% yield), as a white solid: m.p. 139-141 ^oC; ^1H NMR (300MHz, $CDCl_3$) δ 1.40 (s, 18H), 1.82 (s, 6H), 2.26 (s, 6H), 4.80 (s, 2H), 7.13 (s, 2H). All data were in agreement with the reported values.[17]

The reduction of **(*R*)-I-6** to **(*R*)-I-7** followed the same procedure. **(*R*)-I-7** was obtained as white solid (15.6 g, 84% yield): ^1H NMR (300 MHz, $CDCl_3$) δ 1.40 (s, 18H), 1.82 (s, 6H), 2.25 (s, 6H), 4.80 (s, 2H), 7.13 (s, 2H). All data were in agreement with the reported values.[17]

Preparation of Enantiopure 5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol ((*S*)-I-7b) and ((*R*)-I-7b) [17]

Toluene (59 mL) consisting of $AlCl_3$ (9.80 g, 73.5 mmol) and nitromethane was added dropwise to **(*S*)-I-7** (15.63 g, 44.1 mmol) dissolved in benzene (176 mL) at 0 °C, over a period of 30 minutes. The mixture was stirred for an additional 30 minutes, quenched with 75 mL of water and extracted with Et_2O (3x40 mL). The combined organic layers were washed with 75 mL brine, dried over Na_2SO_4 and then concentrated *in vacuo* to afford crude **(*S*)-I-7b.** The resulting crude was purified by recrystallization with hexanes-CH_2Cl_2 solvent pair to afford **(*S*)-I-7b** (10.2 g, 95% yield), as a cotton-like white solid: ^1H NMR (300, $CDCl_3$) δ 1.89 (s, 6H), 2.26 (s, 6H), 4.49 (s, 2H), 6.82 (d, J = 8.1 Hz, 2H), 7.14 (d, J = 8.4 Hz, 2H). All data were in agreement with the reported values.[15]

The reduction of **(*R*)-I-7** to **(*R*)-I-7b** followed the same procedure. **(*R*)-I-7b** was obtained as a white solid (9.0g, 84%). ^1H NMR (300 MHz, $CDCl_3$): δ 1.90 (s, 6H), 2.26 (s, 6H), 4.49 (s, 2H), 6.81 (d, J = 8.1 Hz, 2H), 7.13 (d, J = 8.4 Hz, 2H). All data were in agreement with the reported values.[17]

Preparation of (*S*)-3,3'-ddibromo-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol ((*S*)-I-7c) [17]

Br_2 (0.6 mL, 11.4 mmol) dissolved in $CHCl_3$ (6 mL) was added to **(*S*)-I-7b** (1.00 g, 4.1 mmol) dissolved in $CHCl_3$ (26 mL), over a period of 30 minutes. The mixture was stirred for 1 hour at room temperature. The reaction mixture was then quenched with 6 mL saturated Na_2SO_3 aqueous solution and extracted with Et_2O (3x20 mL). The organic layers were washed with water (2x10 mL) and brine (20 mL), dried with Na_2SO_4 and then concentrated *in vacuo* to afford **(*S*)-I-7c** (1.60 g, 97% yield) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.86 (s, 6H), 2.25 (s, 6H), 5.12 (s, 2H), 7.34 (s, 2H). All data were in agreement with the reported values.[17]

Preparation of (*S*)-3,3'-diphenyl-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol ((*S*)-I-7d) [17]

Dimethyl sulfate (1.15 mL, 12.0 mmol) was added to a mixture containing **(*S*)-I-7c** (1.60 g, 4.0 mmol), $(Bu_4N)I$ (0.15 g, 0.401 mmol) and KOH (0.70 g, 12.2 mmol) in CH_2Cl_2:H_2O (1:1 ratio) (27 mL). The mixture was stirred overnight at room temperature. The organic and aqueous layers were than separated by extraction. The aqueous layer was further extracted with CH_2Cl_2 (3x25 mL) and the combined organic layers are washed with brine (20 mL), dried with Na_2SO_4 and then concentrated *in vacuo* to afford **(*S*)-I-8** (1.8 g, quantative) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.83 (s, 6H), 2.26 (s, 6H), 3.50 (s, 6H), 7.39 (s, 2H). All data were in agreement with the reported values.[17]

A suspension of **(*S*)-I-8** (1.01 g, 2.3 mmol) and Pd $(PPh_3)_4$ (138.5 mg, 0.12 mmol) in DME (25 mL) was stirred for 30 minutes at room temperature. A slight change of color was observed. To the suspension was added a solution of $PhB(OH)_2$ (634.7 mg, 5.2 mmol) and $NaHCO_3$ (1.19 g, 14.1 mmol) in water (15 mL). The mixture was stirred under reflux conditions for 16 hours. After the reaction was cooled to room temperature, Et_2O (40 mL) was added to the mixture. The organic layer was washed with brine (30 mL), dried over Na_2SO_4 and then concentrated *in vacuo*. The residue was purified by column chromatography on silica gel in hexanes/ethyl acetate (30:1) to afford **(*S*)-I-9** (957 mg, 96% yield) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.98 (s, 6H), 2.33 (s, 6H), 3.19 (s, 6H), 7.18 (s, 2H), 7.30-7.33 (m, 2H), 7.37-7.42 (m, 4H), 7.60-7.63 (m, 4H). All data were in agreement with the reported values.[17]

BBr_3 (5.1 mL, 1 M in CH_2Cl_2) was added dropwise to a stirring solution of **(*S*)-I-9** (957 mg, 2.3 mmol) dissolved in CH_2Cl_2 (17 mL) at 0°C. The reaction was stirred for 1 hour, quenched with water (45 mL) and extracted with CH_2Cl_2 (2x40 mL). The collected organic layer was washed with brine (35 mL), dried with Na_2SO_4, and then concentrated *in vacuo* to obtain the crude **(*S*)-I-7d**. The resulting crude was purified by column chromatography on silica gel in hexanes/ethyl acetate (15:1) to afford **(*S*)-I-7d** (746 mg, 84% yield), as a solid: m.p. 151-152 ^oC; ^1H NMR (300 MHz, $CDCl_3$) δ 1.99 (s, 6H), 2.32 (s, 6H), 4.88 (s, 2H), 7.22-7.61 (m, 12H). All data were in agreement with the reported values.[17]

Preparation of (*S*)-3,3'-dimethyl-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol ((*S*)-I-7e) [17]

Dimethyl sulfate (9.1 mL, 97.2 mmol) was added to a mixture containing **(*S*)-I-7b** (7.85 g, 32.4 mmol), $(Bu_4N)I$ (1.20 g, 2.6 mmol) and KOH (5.57 g, 97.2 mmol) in 263 mL CH_2Cl_2-H_2O (1:1). The mixture was stirred for 16 hours, and then the aqueous and organic layers were separated by extraction. The aqueous layer was further extracted with CH_2Cl_2 (3x90 mL) and the combined organic layers are washed with 105 mL water, 105 mL NH_4OH and 105 mL brine. They were then dried with Na_2SO_4 and concentrated *in vacuo* to afford crude **(*S*)-I-10**. Purification of **(*S*)-I-10** was not necessary since TLC showed only one spot, thus **(*S*)-I-10** (8.67 g, 98% yield) was used as is for next step. ^1H NMR (300 MHz, $CDCl_3$) δ 1.83 (s, 6H), 2.63 (s, 6H), 3.66 (s, 6H), 6.73 (d, *J*=8.4 Hz, 2H), 7.10 (d, *J*=7.8 Hz, 2H). m.p. 111-113°C (lit. mp 110-112°C). All data were in agreement with the reported values.[17]

(*S*)-I-10 (8.67 g, 31.7 mmol) was dissolved in 85% H_3PO_4 (87 mL). To this solution was added concentrated HCl (87 mL), AcOH (87mL) and paraformaldehyde (24.56 g). The mixture was stirred for 42 hours at 90 °C and then cooled to room temperature. The reaction mixture was extracted with benzene (3x100 mL). The collected organic layers were washed with water (100 mL), saturated Na_2CO_3 solution (100 mL) and brine (100 mL). The organic layers were dried with $MgSO_4$ and then concentrated *in vacuo* to afford crude **(*S*)-I-11.** Crude **(*S*)-I-11** was purified by column chromatography on silica gel in hexanes/ethyl acetate (15:1) to afford **(*S*)-I-11** (9.02 g, 77%), as an off-white solid: ^1H NMR (300 MHz, $CDCl_3$) δ1.94 (s, 6H), 2.29 (s, 6H), 3.37 (s, 6H), 4.55 (d, *J* = 10.8 Hz, 2H), 4.79 (d, *J* = 11.1 Hz, 2H), 7.25 (s, 2H). All data were in agreement with the reported values.[17]

(*S*)-I-11 (1.00 g, 2.7 mmol) dissolved in THF (8 mL) was added dropwise to a suspension of $LiAlH_4$ (0.32 g, 8.4 mmol) in THF (4 mL). The reaction mixture was stirred under reflux conditions for 3.5 hours. The reaction mixture was slowly quenched with 3 mL THF/water (3:1) at 0 °C and then extracted with Et_2O (3x10 mL). The organic layers were dried with $MgSO_4$ and then concentrated *in vacuo*. The residue was purified using column chromatography on silica get in hexanes/ethyl acetate (10:1) to obtain **(*S*)-I-12** (583.5 mg, 72% yield) a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.87 (s, 6H), 2.25 (s, 6H), 2.28 (2s, 6H), 3.33 (s, 6H), 7.00 (s, 2H). All data were in agreement with the reported values.[17]

BBr_3 (4.9 mL, 1 M in CH_2Cl_2) was added dropwise to **(*S*)-I-12** (583.5 mg, 1.9 mmol) dissolved in CH_2Cl_2 (8 mL) at 0 °C. The mixture was stirred for another hour at 0 °C. The reaction was then quenched with 40 mL water and extracted with CH_2Cl (2x15 mL). The collected organic layer was washed with water (25 mL) and brine (25 mL), dried with $MgSO_4$ and then concentrated *in vacuo* to obtain the crude **(*S*)-I-7e**. The crude was purified by column chromatography on silica gel in hexanes/ethyl acetate (9:1) to obtain pure **(*S*)-I-7e** (383.7 mg, 72% yield), as a white solid: m.p. 166-168 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.85 (s, 6H), 2.23 (s, 12H), 4.53 (s, 2H), 7.00 (s, 2H). All data were in agreement with the reported values.[17]

Synthesis of Biphenol-Based Monophosphoramidite Ligands (MPN)[18]

(*S*)-(5,5',6,6'-tetramethylbiphenyl-2,2'-diyl)oxy(*N*,*N*-dimethylphosphinamine) ((*S*)-I-13)

Biphenol **(*S*)-I-7b** (100 mg, 0.42 mmol) was dissolved in toluene (2.5 mL). To this solution was added hexamethylphosphorous triamide (0.11 mL, 0.63 mmol) under N_2 gas. The resulting mixture was stirred at 80 ^{o}C for 12 hours. The solvent was evaporated under reduced pressure to obtain the crude MPN ligand. The crude was purified by column chromatography (silica gel neutralized by 3% TEA using 19:1 ratio of hexanes/ethyl acetate) to afford **(*S*)-I-13** (100 mg, 76% yield), as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.01 (d, J = 14.4 Hz, 6H), 2.29 (s, 6H), 2.50 (d, J = 8.7 Hz, 6H), 6.82 (d, J = 8.1 Hz, 1H), 7.00 (d, J = 8.1 Hz,, 1H), 7.07 (d, J = 8.1 Hz, 1H), 7.13 (d, J = 8.1 Hz, 1H). All data were in agreement with the reported values.[18]

Synthesis of Biphenol-Based Diphosphonite Ligands[25]

(R)-((5,5',6,6'-tetramethyl-[1,1'-biphenyl]-2,2'-diyl)bis(oxy))bis(diphenylphosphine) ((*R*)-I-14):

A mixture of biphenol **(*R*)-I-7b** (267 mg, 0.5 mmol) and DMAP (61 mg, 0.05 mmol) were dissolved in CH_2Cl_2 (7 mL). The solution was cooled to 0 ^oC. To this solution was added triethylamine (0.42 mL, 3 mmol), followed by the dropwise addition of chlorodiphenylphosphine (0.23 mL, 1.25 mmol) in CH_2Cl_2 (3 mL). The solution was stirred for 3 hours at 0 ^oC. The solvent was then concentrated *in vacuo* to obtain the crude BOP ligand. The crude was purified by column chromatography on silica gel (neutralized by 3% TEA) in hexanes/ethyl acetate (20:1) to obtain **(*R*)-I-14** (265 mg, 43% yield), as a white solid. ^1H NMR (300 MHz, $CDCl_3$): δ 1.81 (s, 6H), 2.15 (s, 6H), 6.87 (d, *J* = 7.8 Hz, 2H), 7.03 (d, *J* = 8.1 Hz, 2H), 7.13-7.24 (m, 20H); ^{31}P NMR (300 MHz, $CDCl_3$) δ 109.55; $[\alpha]_D^{21}$= +41.1 (CH_2Cl_2, *c* 1.1) All data were in agreement with the reported values.[26]

(S)-((3,3'-bis(4-(tert-butyl)benzyl)-5,5',6,6'-tetramethyl-[1,1'-biphenyl]-2,2'-diyl)bis(oxy))bis(diphenylphosphine) ((*S*)-I-15):

(*S*)-I-15 (316 mg, 70% yield) was obtained as a white foam: m.p. 71-73 ^oC; ^1H NMR (300 MHz, $CDCl_3$): δ 1.25-1.31 (m, 18H), 1.74 (s, 6H), 1.84 (s, 6H), 3.46 (d, *J* = 15.6 Hz, 2H), 3.61 (d, *J* = 15.6 Hz, 2H), 6.39 (s, 2H), 6.91 (d, *J* = 8.1 Hz, 4H), 7.02-7.38 (m, 24H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 22.5, 34.1, 36.9, 38.4, 109.9, 127.5, 130.3, 130.5, 131.3, 131.5, 132.2, 132.4, 132.6, 133.2, 133.7, 134.1, 137.3, 140.7, 150.9; ^{31}P NMR (300 MHz, $CDCl_3$) δ 110.47; $[\alpha]_D^{21}$= +93.9 (CH_2Cl_2, *c* 1.0); $C_{62}H_{64}O_2P_2$ (M= 903.12) FIA *m/z* 903.5 (M)

(S)-((3,3'-bis([1,1'-biphenyl]-4-ylmethyl)-5,5',6,6'-tetramethyl-[1,1'-biphenyl]-2,2'-zzdiyl)bis(oxy))bis(diphenylphosphine) ((*S*)-I-16):

(*S*)-I-16 (129 mg, 36% yield) was obtained as a white foam: m.p. 70-72 ^oC; ^1H NMR (300 MHz, $CDCl_3$): δ 1.78 (s, 6H), 1.88 (s, 6H), 3.52 (d, *J* = 16.2 Hz, 2H), 3.69 (d, *J* = 16.2 Hz, 2H), 6.44 (s, 2H), 7.00 (d, *J* = 8.1 Hz, 4H), 7.07-7.45 (m, 30H), 7.56 (d, *J* = 7.5 Hz, 4H); ^{13}C NMR (400 MHz,

$CDCl_3$) δ 19.7, 22.6, 38.7, 129.4, 129.6, 130.4, 130.5, 131.3, 131.5, 131.6, 132.2, 132.4, 132.5, 132.6, 133.3, 133.8, 134.2, 137.6, 141.0, 142.9, 143.9; ^{31}P NMR (300 MHz, $CDCl_3$) δ 110.62; $[\alpha]_D^{21}$= +111.2 (CH_2Cl_2, *c* 1.0); $C_{66}H_{56}O_2P_2$ (M= 943.10) FIA *m/z* 943.5 (M)

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Chapter 2

§ 2.1 Introduction

§ 2.1.1 Rhodium-Catalyzed 1,4-Conjugate Addition

Carbon-carbon bond forming reactions are useful in synthesis, yet they generally do not perform too well in terms of catalytic activity and enantioselectivity. Among the carbon-carbon bond forming reactions, the asymmetric 1,4-conjugate addition shows potential since the non-asymmetric version is generally used in synthesis for forming carbon-carbon bonds.[1] Considerable effort has been made to develop the asymmetric 1,4-conjugate addition and good enantioselectivity has been reported for organozinc reagents using copper catalysts with chiral phosphine ligands.[2] For example, the addition of diethylzinc to 2-cyclohexenone in the presence of a phosphoramidite ligand gave the coupled product with high enantioselectivity. Despite relatively good results, the copper-catalyzed 1,4-conjugate additions are limited to primary alkyl groups and the reactions must be carried out at very low temperatures, usually below 0 ^{o}C. Thus, chemists have looked to other transition-metal catalyzed 1,4-conjugate additions to widen the scope of the substrates and to achieve higher enantioselectivity.

Miyaura reported the first non-asymmetric 1,4-conjugate addition of aryl- and alkenyl-boronic acids to α,β-unsaturated ketones using a rhodium catalyst and phosphine ligand in 1997.[3] This 1,4-conjugate addition piqued the interest of chemists who were interested asymmetric catalysis to modify the reaction conditions to achieve high enantioselectivity.

§ 2.1.2 Mechanism

The mechanism for the Rh-catalyzed 1,4-conjugate addition follows a three step catalytic cycle.[4] The catalytic cycle is shown for the reaction of phenylboronic acid with 2-cyclohexenone (**Figure 2.1**). The cycle starts with the phenyl-rhodium-ligand-complex **A**. The carbon-carbon double bond of 2-cyclohexenone inserts into phenyl-rhodium-ligand complex **A**, which then isomerizes to form the more thermodynamically stable complex **B**. The rhodium-complex **B** is converted to the hydroxorhodium complex **D** by addition of water, which results in the formation of the product **C**. Phenylboronic acid in the presence of the ligand results in transmetallation of

the phenyl group from the boron to rhodium, regenerating the phenyl-rhodium-ligand complex **A**.

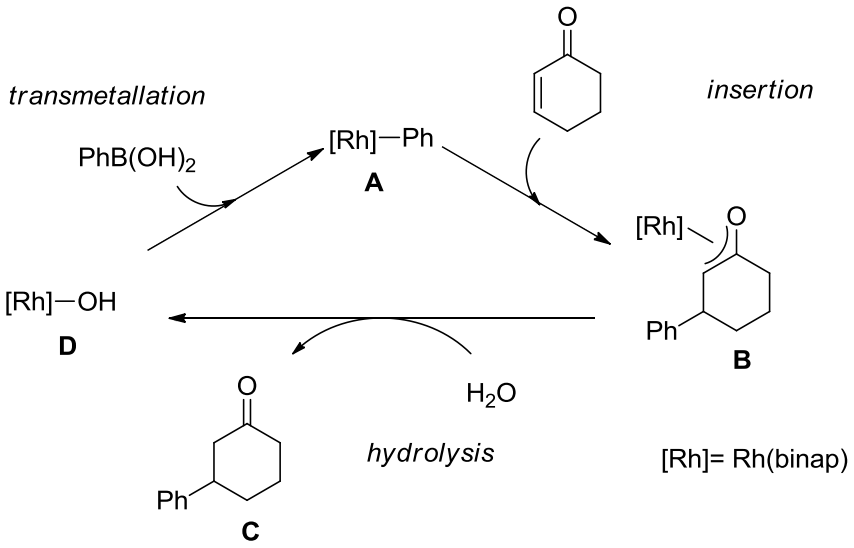


Figure 2.1 Rh-Catalyzed 1,4-Conjugate Addition Mechanism

The enantioselectivity arises from how the cyclohexenone inserts into the carbon-carbon double bond. Using (*S*)-BINAP as the ligand, the structure for the rhodium-BINAP complex is severely skewed (**D**), therefore the complex has an open space at the lower part of the coordination site, whereas the upper part is blocked by one of the phenyl rings of the BINAP ligand. The carbon-carbon double bond of the cyclohexenone coordinates to the rhodium with its α*si* face forming **E,** rather than with its α*re* face, which undergoes migratory insertion to form a stereogenic carbon center in **F**, with *S* configuration. The absolute configurations of all products from the 1,4-conjugate addition can be predicted based on this model, which uses the α*si* face to insert into the rhodium-ligand complex (**Figure 2.2**).[5]

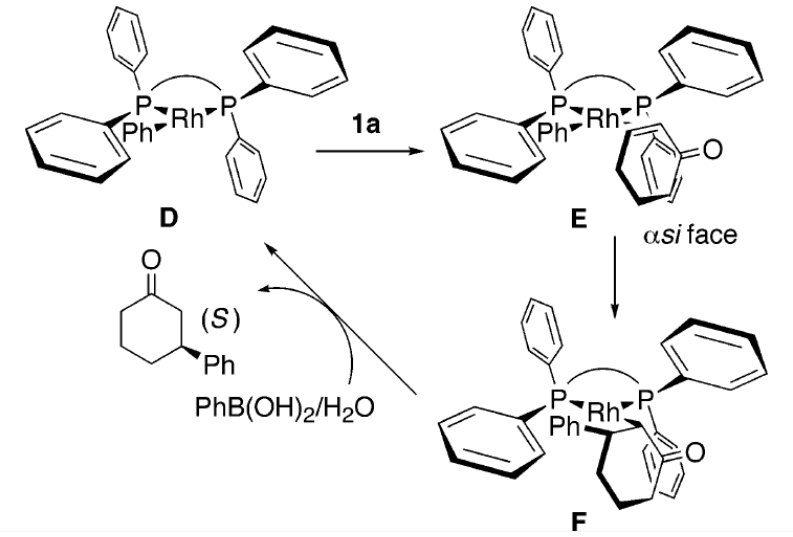
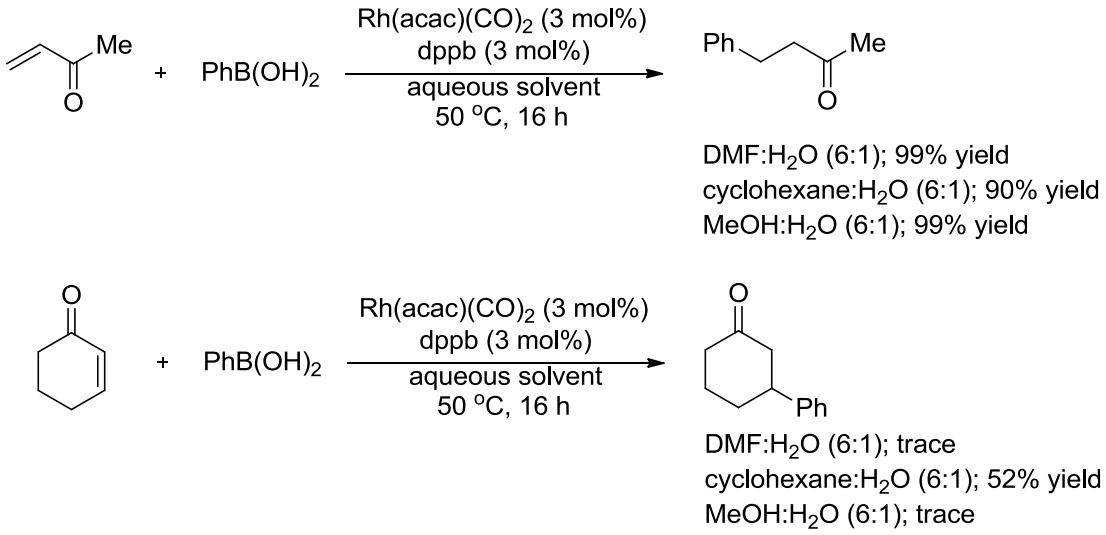


Figure 2.2 Determination of Enantioselectivity

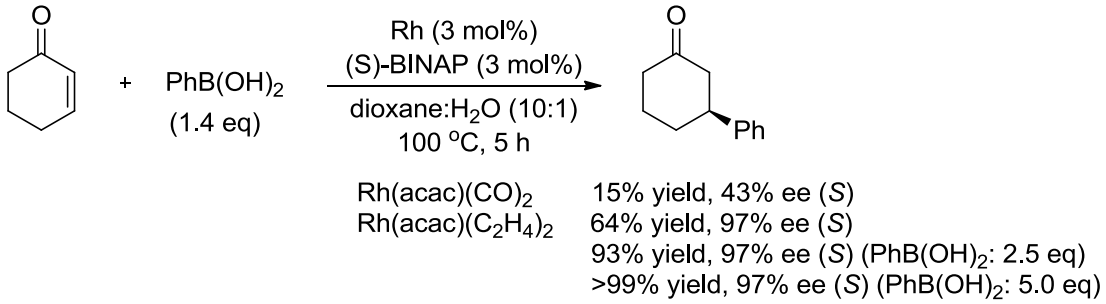
§ 2.2 Asymmetric Rhodium-Catalyzed 1,4-Conjugate Addition

When Miyaura first reported the non-asymmetric version of the 1,4-conjugate addition, the results were generally good for β-unsaturated enones, however yields were only moderate for β-substituted enones (**Scheme 2.1**) [3], thus the reaction conditions needed to be improved before the asymmetric version could be attempted. Despite this, the rhodium-catalyzed 1,4-conjugate addition has several advantages over other 1,4-conjugate additions. First, the organoboronic acids used in this reaction are relatively stable to oxygen and moisture, thus the reaction can be run in protic solvents or even aqueous solutions. Second, the organoboronic acids are less reactive toward the enones in the absence of the rhodium catalyst and the 1,2-addition to enones does not take place. Third, aryl and alkenyl groups can be introduced at the β-postion. Finally, the reaction is mainly catalyzed by transition metal complexes coordinated with phosphine ligands.[6]



Scheme 2.1 Non-asymmetric 1,4-Conjugate Addition

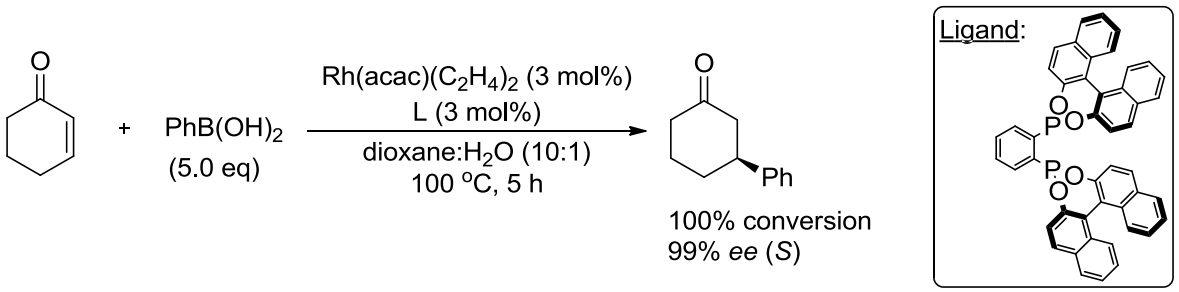
In 1998, Hayashi and Miyaura reported the first asymmetric rhodium-catalyzed 1,4-conjugate addition by modifying the original conditions reported by Miyaura in 1997, resulting in catalytic activity and high enantioselectivity.[5] These modifications include, changing the rhodium catalyst, using BINAP as the ligand, increasing the reaction temperature and using a mixture of dioxane and water in a ratio of 10 to 1 as the solvent. By using 1.4 equivalents of the phenylboronic acid, the reaction gave the desired product in 64% yield. The moderate yield was due to the consumption of phenylboronic aicd in a side reaction, where phenylboronic acid is hydrolyzed giving benzene. By increasing the equivalents of the phenylboronic acid used, the yield can be increased (**Scheme 2.2**). Use of $Rh(acac)(CO)_2$ as a catalyst resulted in a lower enantioselectivity. The use of $Rh(acac)(C_2H_4)_2$ may have resulted in a higher enantioselectivity, as there is weaker coordination of the ethylene moiety compared to the carbon monoxide.[5] The reaction conditions reported by Hayashi and Miyaura have been used as standards for the rhodium catalyzed asymmetric 1,4-conjugate addition.



Scheme 2.2 Optimization of the Asymmetric 1,4-Conjugate Addition

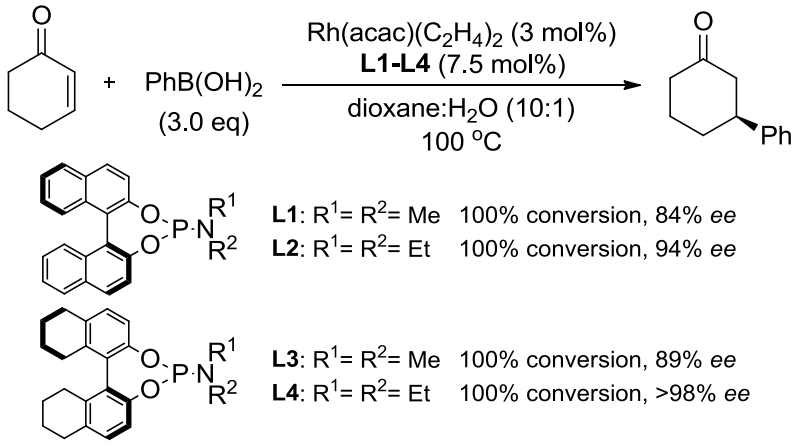
§ 2.2.1 Other Phosphine Ligands for Asymmetric 1,4-Conjugate Addition

For the rhodium-catalyzed 1,4-conjugate addition, BINAP is one of the best ligands, with over 90% *ee* for various types of enones and organoboronic acids. Although BINAP gives very good *ee*, other bidentate and monodentate phosphine ligands were employed that give as good, if not better, enantioselectivity. One example was reported by Reetz in 2001, using 1,1'-binapthol-based diphosphonites that resulted in very high enantioselectivity for several combinations of enones and arylboronic acids (**Scheme 2.3)**.[7]

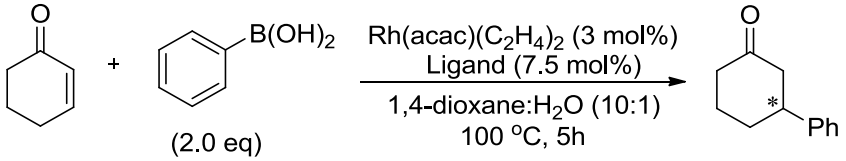


Scheme 2.3 1,4-Conjugate Addition using 1,1'-Binapthol-Based Diphosphonite

In 2003, Feringa reported the use of simple monodentate phosphoramidites.[8] Good conversions and relatively high enantioselectivities were obtained when using the monodentate phosphine ligands (**Scheme 2.4)**.

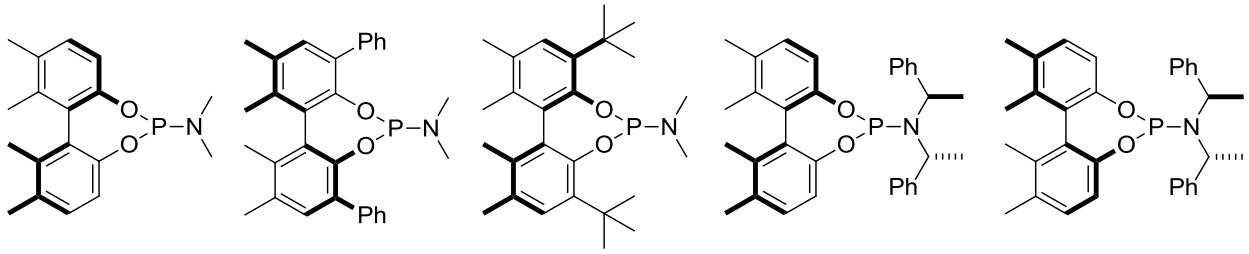


Scheme 2.4 1,4-Conjugate Addition using Monodentate Phosphine Ligands



Entry	Ligand	Conversion[1]	*ee*[2]
1	(*R*)-MPN-H	100	86.1(*R*)
2	(*S*)-MPN-Ph	100	61.5 (*S*)
3	(*R*)-MPN-*t*-Bu	100	54.9 (*R*)
4	(*R,R,R*)-MPN-H	76	5.1 (*R*)
5	(*S,R,R*)-MPN-H	80	85.5 (*S*)

[1]Determined by ^{1}H NMR; [2] Determined by GC on Supelco β DEX-225 Column and comparison with authentic samples



(*R*)-MPN-H **(*S*)-MPN-Ph** **(*R*)-MPN-*t*-Bu** **(*R,R,R*)-MPN-H** **(*S,R,R*)-MPN-H**

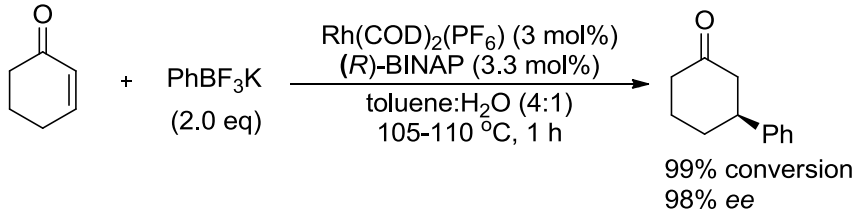
Scheme 2.5 1,4 Conjugate Addition Using Biphenol-Based Monophosphoramidite

In 2004, good conversion and enantioselectivity was demonstrated using the biphenol-based monophosphoramidite ligands developed by the Ojima group[9]. Using the hydrogen

substituted MPN ligand, the Ojima group was able to obtain results similar to those obtained by Feringa (entry 1). Using bulkier substituents at the 3 and 3' positions didn't enhance the enantioselectivity, in fact the *ee* was lowered (entry 2 and 3). Use of bulkier substituents on the amine moiety did not give as good results as entry 1 in addition to incomplete conversion to the product (entry 4 and 5).

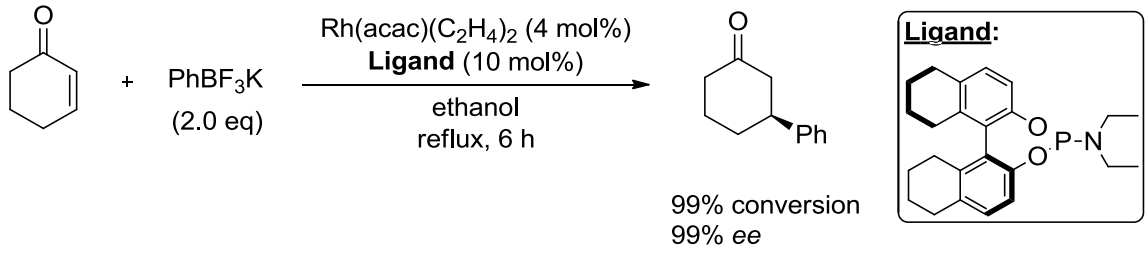
§ 2.2.2 Other Borane Sources for Asymmetric 1,4-Conjugate Addition

Other borane sources can also be used in the asymmetric 1,4-conjugate addition. Potassium organotrifluoroborates, which are generally more stable than the organoboronic acids, were used for the synthesis of 3-phenylcyclohexanone.[9] The reaction of organotrifluoroborates are quite different than that of organoboronic acids. First, the reaction is not catalyzed well by $Rh(acac)(C_2H_4)_2$, although it does work in some cases, as shown by Feringa. Thus, a different rhodium source is used, $Rh(COD)_2(PF_6)$. Second, the enantioselectivity is highly dependent on the solvent used. High enantioselectivity requires excess amounts of water that would render the corresponding organoboronic acid to be unstable in such reaction conditions. Despite the differences, 1,4-conjugate additions of organotrifluoroborates yield good conversions and high enantioselectivities when BINAP is used as a ligand (**Scheme 2.5**).[10]



Scheme 2.6 1,4-Conjugate Addition Using Potassium Organotrifluoroborate

In addition, in 2004 Feringa *et al.* reported that the use of monodentate phosphine ligands also resulted in high enantioselectivity when organotrifluoroborates were used as a substrate (**Scheme 2.6**).[11]



Scheme 2.7 1,4-Addition of $PhBF_3K$ using Monodentate Phosphine Ligand

§ 2.3 Results and Discussion

§ 2.3.1 Asymmetric 1,4-Addition with Phenylboronic Acid

The application of the biphenol-based monophosphoramidite (MPN) and diphosphonite (BOP) ligands to the 1,4-conjugate addition is shown in **Table 2.1**. Furthormore the ligands used for the 1,4 conjugate addition are shown in Figure 2.3.

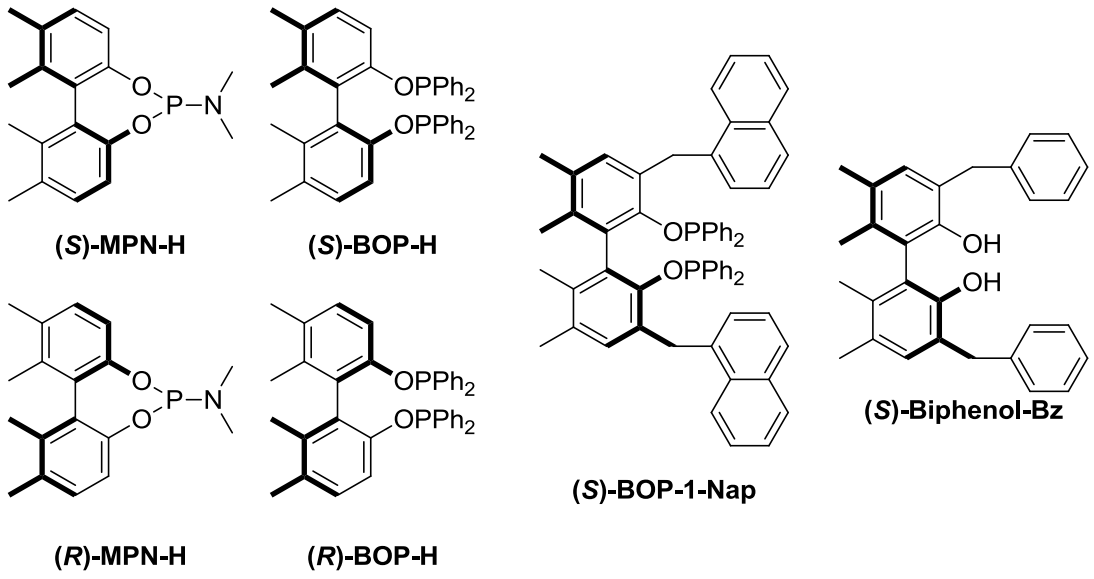
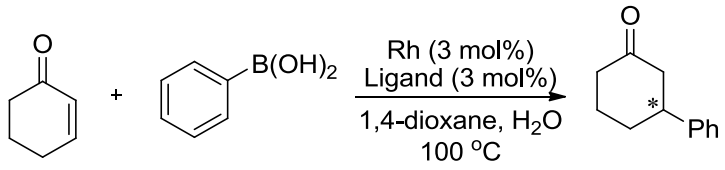


Figure 2.3 Ligands used for Rh-catalyzed 1,4-Addition

Table 2.1 Application of Biphenol-Based Ligands to Asymmetric 1,4-Conjugate Addition



II-1 II-2 II-3

Entry	$PhB(OH)_2$	Rh	Ligand	Time (h)	Conversion (SM:Prod)[3]	*er*[4]
1	5.0	$Rh(acac)(C_2H_4)_2$	(*R*)-MPN-H	71	90:10	-
2	5.0	$Rh(acac)(C_2H_4)_2$	(*R*)-BOP-H	71	79:21	-
3[1]	2.5	$[Rh(COD)Cl]_2$	(*S*)-MPN-H	75	83:17	49:51
4	2.5	$[Rh(COD)Cl]_2$	(*S*)-BOP-H	4	2:98	48:52
5	2.5	$[Rh(COD)Cl]_2$	(*S*)-BOP-1-Nap	2	3:97	49:52
6	2.5	$[Rh(COD)Cl]_2$	(*S*)-Biphenol-Bz	72	90:10	-
7[1,2]	2.5	$[Rh(COD)Cl]_2$	(*R*)-MPN-H	2	>99	50:50
8[2]	2.5	$[Rh(COD)Cl]_2$	(*S*)-BOP-1-Nap	2	>99	51:49

[1]6 mol% of ligand; [2]Reaction done in the presence of $NaHCO_3$ in toluene at 30 °C; [3]Determined by GC-MS; [4]HPLC Condition: Chiralpack AD, Hexanes/IPA (98:2), 1.0mL/min

Using the conditions[5] reported by Hayashi and Miyaura, reactions were carried out using the hydrogen substituted MPN and BOP ligands. When monophosphoramidite was used as the ligand, there was a 10% conversion to the product after 71 hours (entry 1). Previous Ojima group members were able to obtain good conversion and enantioselectivity using the same MPN ligand[9]. A plausible reason for the difference is that the ligand may have degraded over time. The BOP gave a slightly better conversion after 71 hours (21%, entry 2). The % *ee* was not determined as excess amounts of phenylboronic acid made purification difficult. Thus, the amount of phenylboronic acid (still in excess) used for subsequent reactions was modified to make the purification easier. In addition, the $Rh(acac)(C_2H_4)$ and biphenol-based combination did not appear to have catalyzed the reaction, thus a different rhodium source was used for later reactions.

Using $[Rh(COD)Cl]_2$ and 2.5 equivalents of phenylboronic acid, the 1,4-conjugate addition was first carried out using the hydrogen substituted MPN and BOP ligands. The overall conversions were actually higher, which indicates that lowering the equivalents of phenylboronic acid does not affect the conversion. However, it showed that $Rh(acac)(C_2H_4)_2$ was not a good rhodium source when used with the biphenol-based ligands for the 1,4-conjugate addition.

When monophosphoramidite was used with $[Rh(COD)Cl]_2$, the conversion to the product was slightly higher after 75 hours (17%, entry 3). After purification and HPLC analysis, the product was found to be racemic. Surprisingly, the hydrogen substituted BOP afforded 98% conversion to the product after 4 hours (entry 4). However, the product was racemic. In other asymmetric reactions, the hydrogen substituted biphenol-based ligand was also found to yield racemic products. This may be due to hydrogen being a rather small substituent, therefore it cannot guide the substrate to access the metal in a certain orientation to give a high enantiomeric excess. Thus, the reaction was carried out using a bulkier substituted ligand, 1-naphthyl at the 3 and 3' positions. The reaction proceeded with a 97% conversion to product, which was racemic (entry 5).

Since the BOP ligand gave good conversion, but poor enantioselectivity, it was hypothesized that the ligand was altered with the addition of water. In aqueous conditions, the BOP ligand may be unstable, as water could hydrolyze the ligand, generating biphenol. Thus, a benzyl substituted biphenol was used as the ligand for the reaction. After 72 hours, the reaction only gave a 10% conversion (entry 6). This indicates that it was not the biphenol-rhodium complex that catalyzed the reaction, as the reaction took longer and resulted in a lower conversion.

Hayashi *et al.* reported that the enantioselectivity is higher when the reaction is carried out at a lower temperature (35 ^{o}C)[12]. The high reaction temperature of 100 ^{o}C is necessary as the transmetallation is very slow at lower temperatures due to the high stability of the rhodium-acac moiety. Miyaura reported that at temperatures over 90 ^{o}C, there was decomposition of the $[Rh(COD)Cl]_2$ due to the dissociation of the COD ligand from the rhodium source[13]. It was found that using more $[Rh(COD)Cl]_2$ could push the reaction to completion, although decompostition of the metal catalyst could reduce the enantioselectitivity of the reaction product. Furthermore, the use of a base accelerates the transmetallation step at lower temperatures. Hence the 1,4-conjugate addition reactions were carried out at lower temperatures with a base to give high yields and enantioselectivities.

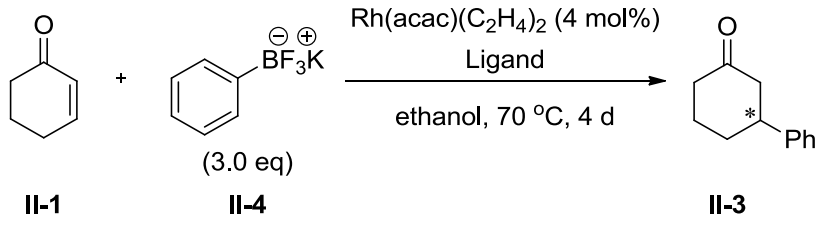
Using the optimized conditions for the 1,4-conjugate addition in the presence of a base[14], the reaction was carried out using the biphenol-based ligands. The addition of a base catalyzed the reaction as shown in entries 7 and 8. Both reactions reached completion in 2 hours with over

99% conversion to the product. However, the products obtained were racemic with both MPN and BOP ligands.

§ 2.3.2 Asymmetric 1,4-Conjguate Addition with Potassium Organotrifluoroborates

The biphenol-based ligands were applied to the reaction conditions reported by Feringa for the asymmetric 1,4-conjugate addition of 2-cyclohexenone with potassium organotrifluoroates. The results are shown in **Table 2.2**.

Table 2.2 Application of Biphenol-Based Ligands to 1,4-Conjugate Addition of Potassium Organotrifluoroborates to 2-Cyclohexenone



II-1 II-4 II-3

Entry	Ligand	Mol %	Conversion[1]
1	(*S*)-MPN-H	10.0	<5%
2	(*S*)-BOP-H	5.0	<5%

[1]Determined by GC-MS

Using the biphenol-based ligands and $Rh(acac)(C_2H_4)_2$ as catalyst, the reaction was allowed to react at 70 °C. Use of the monophosphoramidite ligand resulted in less than 5% conversion to the product after 4 days (entry 1). The BOP ligand also afforded less than 5% conversion after 4 days (entry 2).

§ 2.4 Conclusion

The 1,4-conjugate addition reaction is an important carbon-carbon bond forming reaction. Although asymmetric 1,4-conjugate additions with organozinc reagents were possible, the reactions were limited to specific substrates and harsh reaction conditions. Reaction conditions for the non-asymmetric version have been modified by Hayashi and Miyaura to afford high yields for the asymmetric 1,4-conjugate addition. Since their report, Hayashi and Miyaura's

reaction conditions have been used as a standard for the 1,4-conjugate addition. When BINAP is used as the ligand, high enantioselectivities are achieved. Various other ligands, such as diphosphonites and monodentate phosphines, have been applied to the asymmetric 1,4-conjugate addition and resulted in high yields and high *ee*.

The biphenol-based monophosphoramidite and diphosphonite ligands have been applied to the asymmetric 1,4-conjugate addition. Use of the monophosphoramidite resulted in low conversions and enantioselectivities. However, Feringa *et al.* reported high yields and enantioselectivities when they used their monodentate phosphines, which are quite similar to the monophosphoramidites were used. The BOP ligand afforded high conversions, however the products obtained were racemic. The high temperature at which the reaction was carried out may have caused the low enantioselectitvities. The high temperature is needed as the transmetallation step is slow; therefore to overcome the problem, a base was used to allow the reaction temperature to be lowered. The use of a base did not increase the enantiomeric excess when the biphenol-based ligands were applied; it did however catalyze the reactions to over 99% conversion in 2 hours.

In addition to phenylboronic acid, potassium organotrifluoroborates have been used for the 1,4-conjugate addition. The biphenol-based ligands have been applied to the 1,4-conjugate addition of 2-cyclohexenone with potassium organotrifluoroborates, however they gave low conversions. The low conversion may be due to the coordination between the ligands and the rhodium source. The rhodium source, $Rh(acac)(C_2H_4)_4$, when coordinated with either of the biphenol-based ligands afforded low conversions regardless of the substrate used.

§ 2.5 Experimental

General Information:

All chemical were obtained from either Sigma-Aldrich, Fisher Scientific or VWR International, and used as is unless otherwise noted. All reactions were performed under Schlenk conditions with oven dried glassware unless otherwise noted. Dry solvents were degassed under

nitrogen and were dried using the PURESOLV system (Inovatative Technologies, Newport, MA). Tetrahydrofuran was freshly distilled from sodium metal and benzophenone. Dichloromethane was also distilled immediately prior to use under nitrogen from calcium hydride. Toluene was also distilled immediately prior to use under nitrogen from calcium hydride. ^{1}H, ^{13}C and ^{31}P data were obtained using either 300 MHz Varian Gemni 2300 (75 MHz ^{13}C, 121 MHz ^{31}P) spectrometer or the 400 MHz Varian INOVA 400 (100 MHz ^{13}C, 162 MHz ^{31}P) spectrometer in $CDCl_3$ as solvent unless otherwise stated. Chemical shifts (δ) are reported in ppm and standardized with solvent as internal standard based on literature reported values.[15] Melting points were measured on Thomas Hoover Capillary melting point apparatus and are uncorrected. Optical rotations were measured on Perkin-Elmer Model 241 polarimeter. GC/MS was performed on Agilent 6890GC/5973 Mass Selective Detector.

Representative Procedure for 3-phenylcyclohexanone[14]:

(*R*)-MPN-H (7.6 mg, 0.024 mmol), $PhB(OH)_2$ (122.4 mg, 1.00 mmol) and $NaHCO_3$ (13.4 mg, 0.16 mmol) were added to $[Rh(COD)Cl]_2$ (5.9 mg, 0.012 mmol) in a single-use test tube that was equipped with a stir bar. Air was replaced with N_2 by means of five evacuation/refill cycles. Degassed toluene (0.7 mL) was added to the mixture and the solution was stirred for 30 minutes. Cyclohexenone (39.2 mg, 0.40 mmol) diluted with toluene (0.3 mL) was added to the solution. Degassed water (0.1 mL) was added. The solution was stirred for 2 hours at 30 ^{o}C. GC-MS showed greater than 99% conversion to 3-phenyl-cyclohexanone. The reaction was quenched with ether and $NaHCO_3$. The aqueous layer was extracted with ether 3 times, and the combined organic layers were dried with Mg_2SO_4 and concentrated *in vacuo* to obtain a yellow oil. The oil was purified using column chromatography on silica gel using hexanes/ethyl acetate (1-10% ethyl acetate) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.71-1.88 (m, 2H), 2.06-2.20 (m, 2H), 2.38-2.60 (m, 4H), 3.01 (tt, J_1 = 11.7 Hz, J_2 = 3.6 Hz, 1H), 7.20-7.24 (m, 3H), 7.31-7.37 (m, 1H); HPLC Condition (Chiralpack AD, Hexanes/IPA (98:2), 1.0mL/min), t_r= 8.4, 10.2 min. All data were in agreement with the reported values.[7]

§ 2.6 References

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Chapter 3

§ 3.1 Introduction

§ 3.1.1 Heck Reaction

The reaction of triflates, aryl halides or alkenyl halides with alkenes in the presence of a base and a palladium catalyst to form substituted alkenes was first discovered independently in the 1970s by Mizoroki *et al.*[1] and Heck *et al.*[2], resulting in what is currently known as the Mizoroki-Heck reaction (Heck reaction). The substrate for the Heck reaction can be activated alkenes or simple olefins. In addition, the Heck reaction is tolerant of water and several functional groups, such as ketones, esters, amides, ethers and heterocyclic rings. Thus, the Heck reaction is an important carbon-carbon bond-forming reaction that can be applied to a variety of product syntheses, usually resulting in high enantioselectivity. Interest in the Heck reaction increased dramatically, but asymmetrization using the phosphine-mediated Heck reaction was not attempted until the late 1980s, although successful asymmetrization through the use of chiral phosphine ligands for various other reactions were reported as early as the 1970s.[3]

The first successful asymmetric Heck reaction was reported independently by Shibasaki *et al.*[4] and Overman *et al.*[5] in 1989. The reaction has since been developed successfully where both tertiary and quaternary carbons can be synthesized. The asymmetric intramolecular Heck reaction has demonstrated to be highly successful with a large variety of less reactive alkene substrates, whereas the asymmetric intermolecular Heck reaction has generally been limited to reactive substrates; such as *O*- and *N*-heterocycles.

§ 3.1.2 Mechanism

The mechanism of the Heck reaction is thought to follow a four step catalytic cycle (**Figure 3.1**). Starting with the palladium-ligand complex **1**, oxidative addition of the aryl or alkenyl halide (or triflate) to the palladium-ligand complex generates palladium species **2**, then coordination and insertion of the alkene substrate gives **3**, β-hydride elimination from **3** gives the desired product¸ **5a**, which can isomerize to **5b**. Finally, reductive elimination of **4** regenerates the palladium-ligand complex.[6]

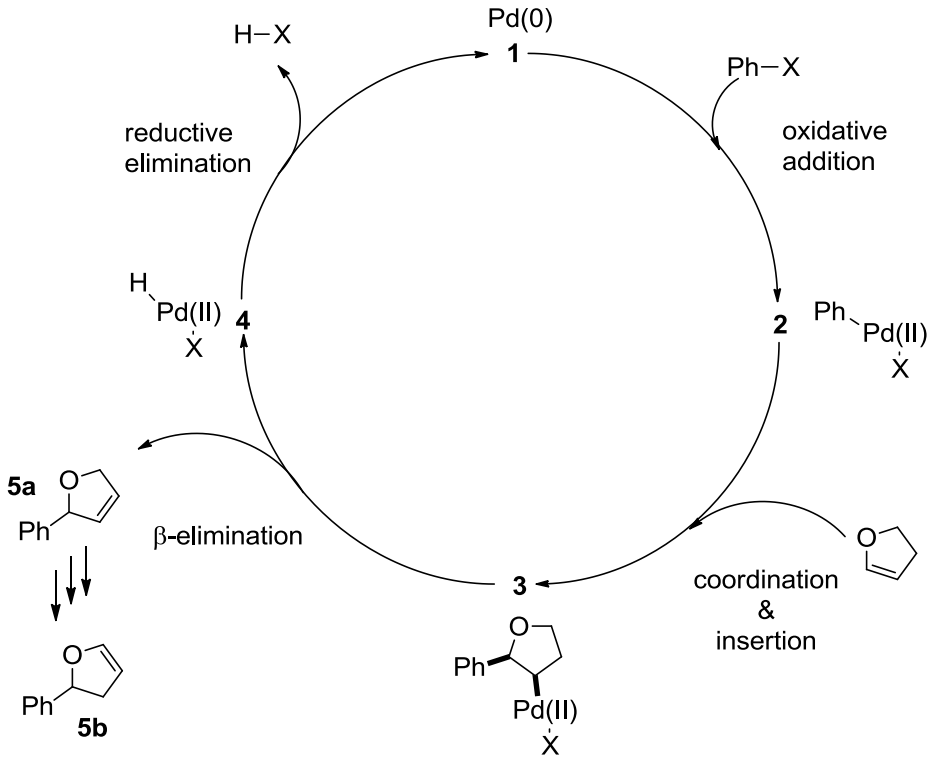


Figure 3.1 Mechanism for the Heck Reaction

Enantioselectivity is determined at the coordination and insertion steps of the substituted alkene to the palladium-ligand complex. The mechanism for this process is thought to follow either a cationic pathway or neutral pathway. The cationic pathway starts with the dissociation of the halide or triflate from palladium-ligand complex, whereas the neutral pathway begins with the dissociation of one of the phosphorous atoms. The pathway taken is still debated, however rationalizations independently proposed by Hayashi *et al*,[7] and Cabri *et al.*[8], favor the cationic pathway (**Figure 3.2**).

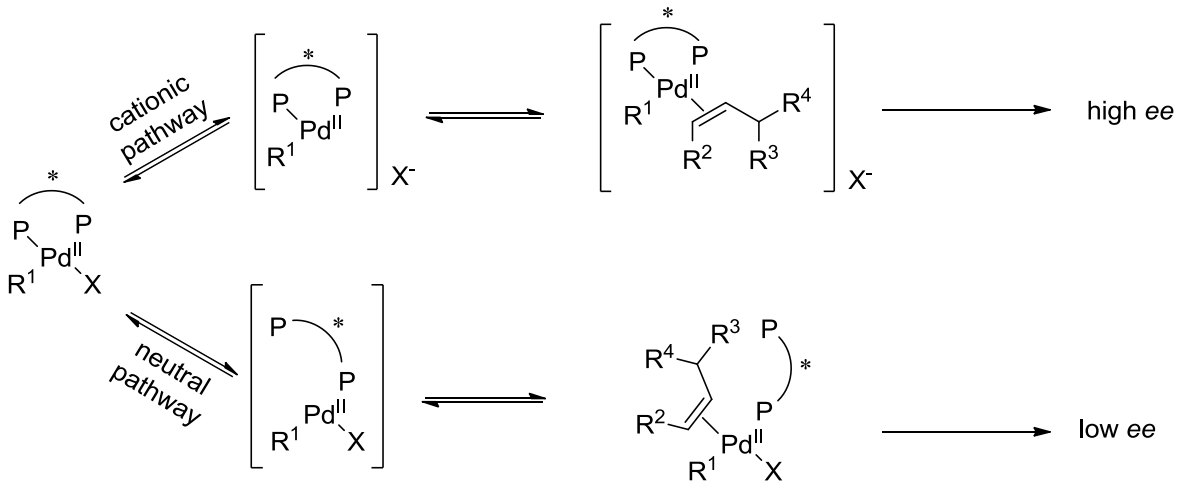
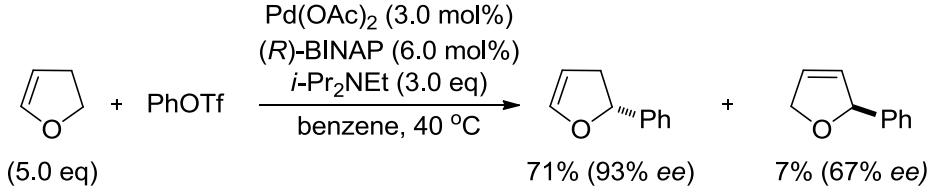


Figure 3.2 Cationic vs. Neutral Pathway

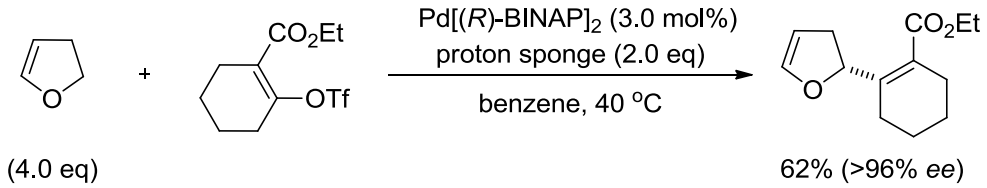
§ 3.1.3 Asymmetric Intermolecular Heck Reaction

The first successful intermolecular asymmetric Heck reaction was reported by Hayashi *et al.* in 1991, which involved the arylation of 2,3-dihydrofuran with phenyl triflate (**Scheme 3.1**)[7]. Although little to no enantioselectivity was obtained when an aryl iodide and silver salt combination was used, the combination of phenyl triflate and *N*,*N*-diisopropylethylamine (*i*-Pr_2NEt) gave 2-phenyl-2,3-dihydrofuran as the major product with minor amounts of the 2,5-dihydrofuran isomer.



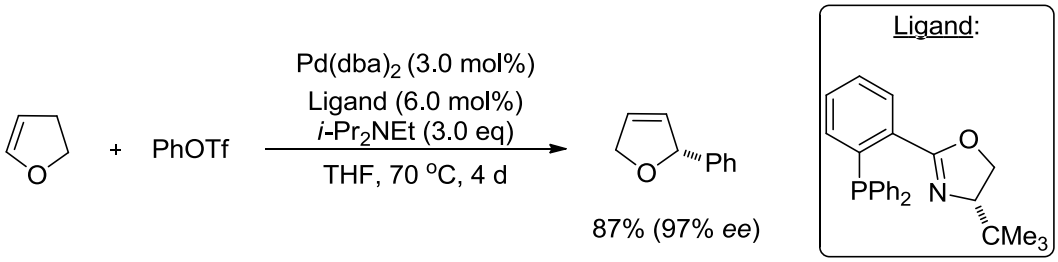
Scheme 3.1 First Example of Intermolecular Heck Reaction

Since the introduction of this intermolecular Heck reaction, reaction conditions have been optimized to obtain greater enantiomeric excess (*ee*) or regioselectivity of the product. The use of alkenyl triflates has yielded even better results (**Scheme 3.2**).[9]



Scheme 3.2 Intermolecular Heck Reaction of Alkenyl Triflate

The majority of intermolecular Heck reactions use the BINAP ligand system, which has been relatively effective for most cases. Recently, developments in chiral phosphine ligands have been reported where different types of ligands give products with improved *ee* compared to previously reported asymmetric Heck reactions. One such example, is the use of the oxazoline-based *P,N*-ligand developed by Pfaltz *et al.*[10] for the intermolecular Heck reaction of dihydrofurans with aryl triflates. Employing this ligand system greatly improved the reaction yield and *ee* for the obtained product compared to the results obtained with BINAP. For example, when the *P,N*-ligand was used in the arylation of 2,3-dihydrofuran with phenyl triflate, the major product obtained was the 2,5-dihydrofuran isomer with high enantioselectivity, as opposed to the 2,3-dihyrdofuran isomer (**Scheme 3.3**).



Scheme 3.3 Intermolecular asymmetric Heck reaction using P,N-ligand

§ 3.1.4 Heck-type reaction

The asymmetric palladium-catalyzed Heck reaction is a powerful method for the construction of tertiary and quaternary chiral centers. Both the intramolecular and intermolecular Heck reactions are useful in syntheses, however, the reaction is generally limited to substrates such as aryl or vinyl triflates and iodides. Therefore, the nucleophile-mediated palladium(II)-

catalyzed Heck, or Heck-type reaction, is a good alternative to the asymmetric Heck, allowing for a wider scope of substrates. The key differences in the mechanism for the Heck-type reaction include a transmetallation as the initial step and a reoxidation of the palladium catalyst as the final step (**Figure 3.3**).

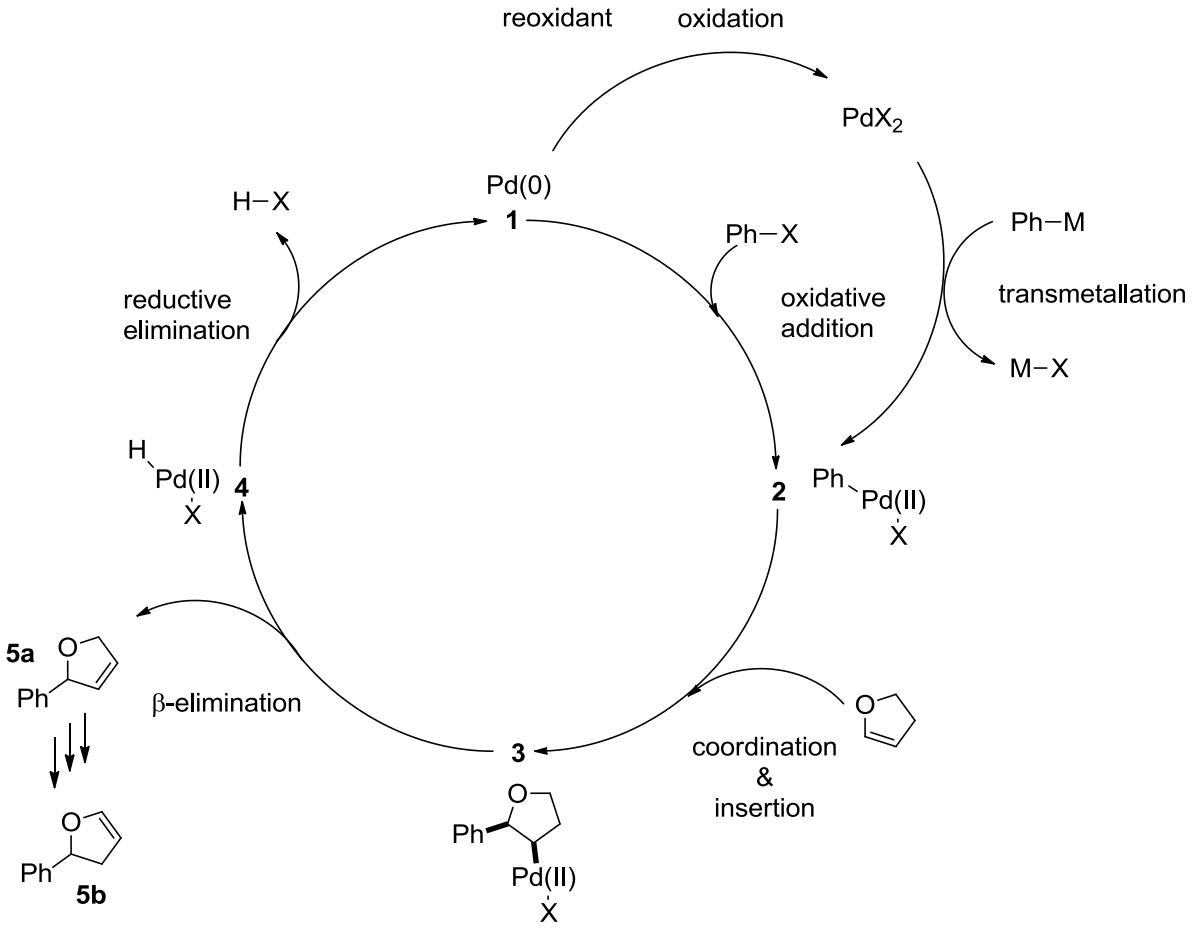
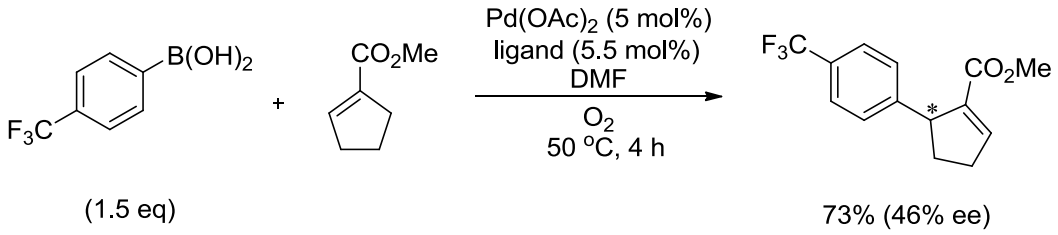


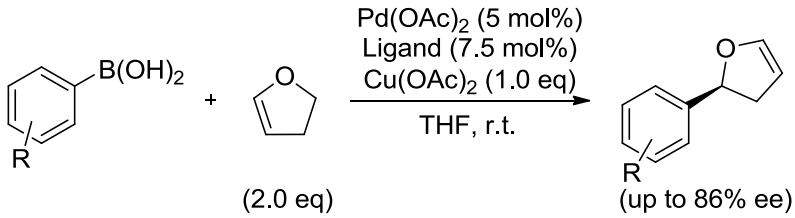
Figure 3.3 Mechanism for the Heck and Heck-type

The Heck-type reaction was first reported by Mikami and co-workers[11], where it was demonstrated that an enantioselective Pd(II)/Chiraphos-catalyzed organoboron-mediated Heck-type reaction is possible. Mikami *et al.* reported the use of only 4-trifluoromethylphenylboronic acid and alkyl 1-cyclopentene-1-carboxylates for the Heck-type reaction (**Scheme 3.4**).



Scheme 3.4 Heck-type using 4-Trifluoromethylphenylboronic Acid and Alkyl 1-Cylopentene-1-Carboxylate

The Heck-type reaction using various arylboronic acids and 2,3-dihydrofurans was reported by Gelman and co-workers.[12] They found that the arylboronic acid had to be the limiting reagent under the above conditions. Using BINAP as the ligand achieved 57% *ee*. Using their optimized conditions, Gelman *et al.* examined other chiral ligands and found that (*R)*-MeOBiphep gave the highest *ee* of 86% (**Scheme 3.5**).

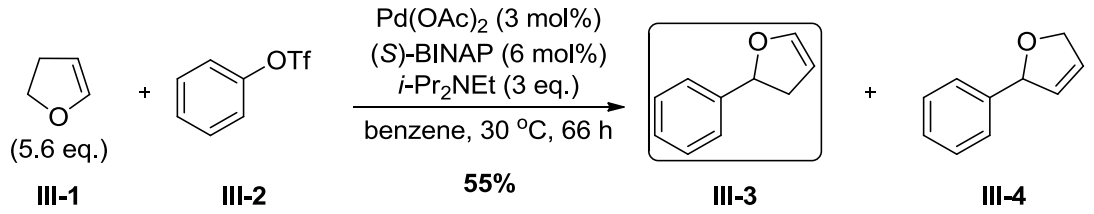


Scheme 3.5 Heck-type Reaction Arylboronic Acids with 2,3-Dihydrofuran

§ 3.2 Results and Discussion

§ 3.2.1 Nucleophilic-Mediated Heck Reaction

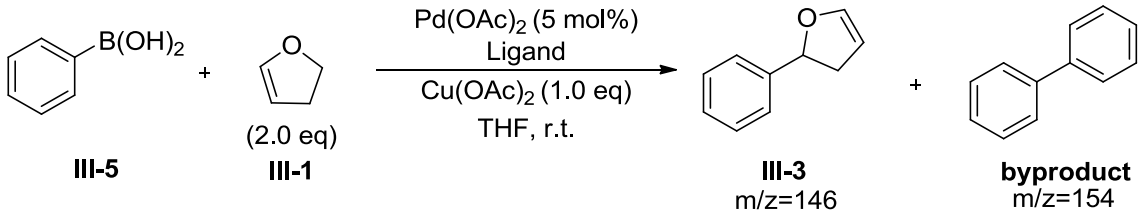
2-Phenyl-2,3-dihydrofuran was prepared using the classic Heck reaction. This compound was used as a standard for the Heck-type reaction as both result in the same product. Using the conditions reported by Hayashi *et al.*, the arylation of 2,3-dihydrofuran with phenyl triflate was catalyzed by $Pd(OAc)_2$ and (*S*)-BINAP in the presence of *i*-Pr_2NEt in benzene at 30 °C. After 66 hours, the reaction gave both the 2,3- and 2,5-dihydrofuran isomers. The isolated yield was only quantified for the 2,3-dihydrofuran isomer as it was the desired isomer. The reaction gave the desired product in 55% yield (**Scheme 3.6).**



Scheme 3.6 Arylation of 2,3-Dihydrofuran and Phenyl Triflate

Attempted the Heck-type reactions are shown in **Table 3.1**.

Table 3.1 Application of Ligands to Heck-Type Reaction



Entry	Ligand	Time	Mol% of ligand	m/z observed[1]
1	(*rac*)-BINAP	40	7.5	146
2	(*S*)-MPN-H	44	15	146, 154
3	(*S*)-BOP-H	44	7.5	146,154

[1]based on GC-MS

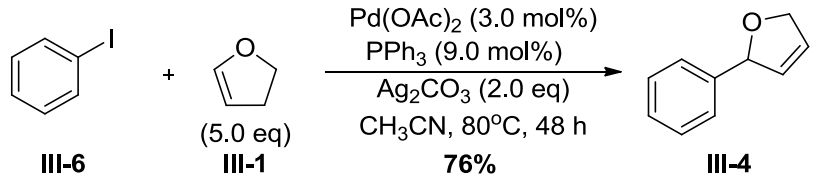
With 2-phenyl-2,3-dihydrofuran in hand, the Heck-type reaction was attempted using the conditions reported by Gelman *et al.* The arylation of 2,3-dihydrofuran with phenylboronic acid was catalyzed by $Pd(OAc)_2$ and (*rac*)-BINAP in the presence of $Cu(OAc)_2$ in THF at room temperature. The reaction was finished after 40 hours, 28 hours after the literature reported time (entry 1). GC-MS and ^1H NMR were used to monitor the reaction. GC-MS analysis showed the m/z for the product (146). The crude ^1H NMR was messy, thus column chromatography was attempted for product purification. However, after this purification attempt, ^1H NMR showed that no 2-phenyl-2,3-dihydrofuran was obtained.

Nevertheless, our ligand library was applied to examine the effectiveness of our ligands in generating the desired product. The hydrogen substituted MPN (entry 2) and BOP ligands (entry 3) were used for the Heck-type reaction. After 44 hours, both reactions were completed.

When the GC-MS was taken, both showed a minor peak with *m/z* 146 and a larger peak with *m/z* 154. However, after purification attempts, no desired product was isolated based on ^{1}H NMR. The *m/z* 154 peak is biphenyl byproduct that is formed due to the reaction conditions used.

§ 3.2.2 Asymmetric Intermolecular Heck Reaction

Hayashi's reaction conditions produce both the 2,3- and 2,5-dihydrofuran isomers. Neither was generated in high yields, therefore different reaction conditions were considered for the application of the biphenol-based ligands to the asymmetric Heck reaction. Reaction conditions reported by Larock gave the 2-phenyl-2,5-dihydrofuran in 98% yield, thus Larock's conditions were used. The arylation of 2,3-dihydrofuran with phenyl iodide was catalyzed by $Pd(OAc)_2$ and PPh_3 in the presence of silver carbonate (Ag_2CO_3) in acetonitrile at 80 ^oC. After 48 hours, the desired 2,5-dihyrofuran isomer was obtained in 76% yield (**Scheme 3.7**).



Scheme 3.7 Arylation of Phenyl Iodide with 2,3-Dihydrofuran

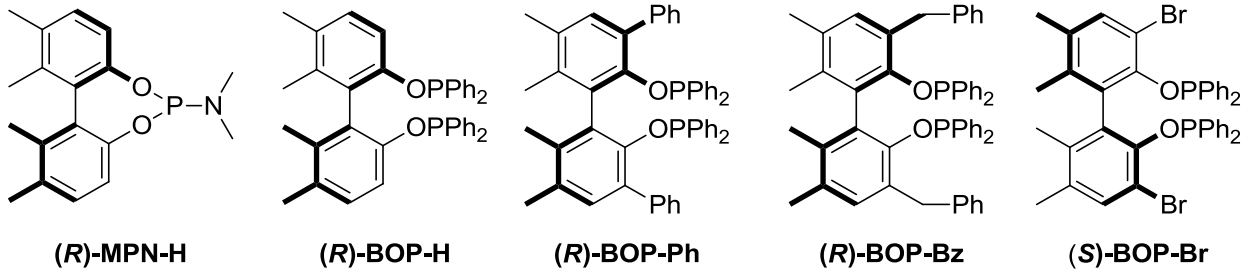
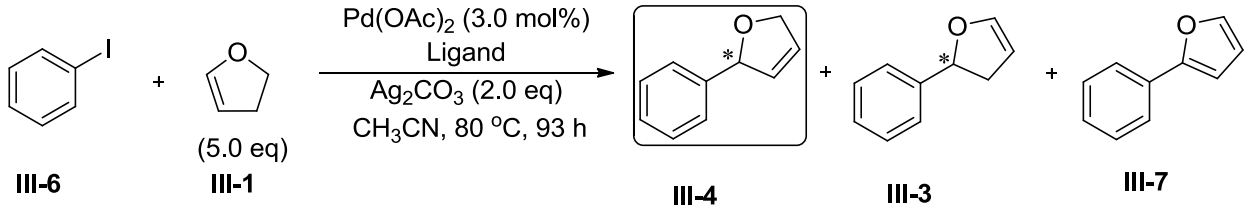


Figure 3.4 Ligands applied to the Intermolecular Heck Reaction

The biphenol-based ligands that were applied to the asymmetric intermolecular Heck reaction are depicted in **Figure 3.4**. The results are shown in the **Table 3.2**.

Table 3.2 Application of Biphenol-Based Ligands to Heck Reaction Using Phenyl Iodide



Entry	Ligand	Conversion at 44h [III-6:(III-4+III-7)]	Conversion at 93 h (III-6:III-4:III-3:III-7)	*er*[3] (III-4)
1[1]	(*R*)-BOP-H	-	-	-
2	(*R*)-MPN-H	-	50:28:12:10	50:50
3[2]	(*R*)-BOP-Ph	52:48	53:36:0:11	50:50
4[2]	(*S*)-BOP-Br	89:11	84:13:0:3	51:49
5[2]	(*R*)-BOP-Bz	90:10	78:18:0:4	51:49

[1]Conversion was not taken, 31% yield; [2]At 44 hours, 5.0 equivalents 2,3-dihyrofuran was added to try to push reaction to completion; [3]HPLC Condition: Chiralcel OD-H, Hexanes/IPA (99:1), 1.0mL/min

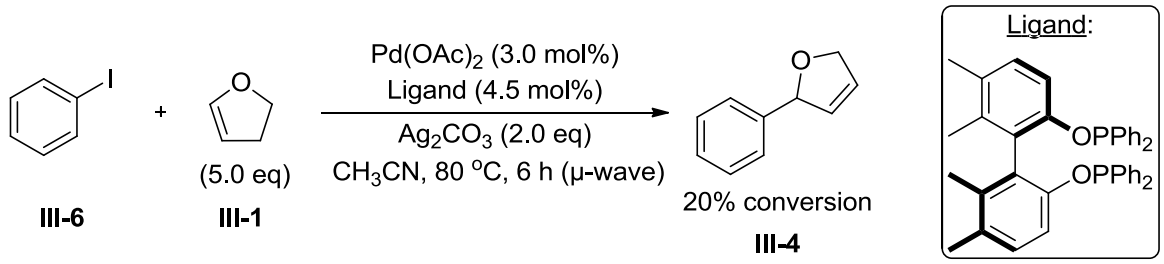
Using Larock's reaction conditions and the hydrogen substituted BOP ligand, the reaction did not complete after 93 hours. The compound was purified by column chromatography, using hexanes/ethyl acetate to obtain the product in 31% yield (entry 1) and a side product, 2-phenylfuran that was not quantified. 2-Phenyl-2,5-dihydrofuran has a boiling point of 104 ^{o}C, thus the product is easily lost when using reduced pressure to evaporate the solvents after purification. Hence, for subsequent reactions, the conversion to the desired product will be reported as conversions instead of percent yield.

When the hydrogen substituted MPN ligand was used, the reaction did not complete after 93 hours. Based on GC-MS, there was 50% conversion of the starting material and of the 50% converted material, 28% was converted to the desired 2,5-dihydrofuran product. Other compounds made included the 2,3-dihydrofuran isomer and 2-phenylfuran. The desired product was subjected to HPLC and the product was found to be racemic (entry 2).

As the use of the BOP ligand generated only the desired product and a side product, other BOP ligands with different substituents at the 3 and 3' positions were examined to see if the reaction would go to completion and give high enantiomeric excess. The reaction conditions were the same except for one change, the addition of more phenylboronic acid. After 44 hours, the reactions were monitored by GC-MS to reveal that they were not complete. Thus, to push the

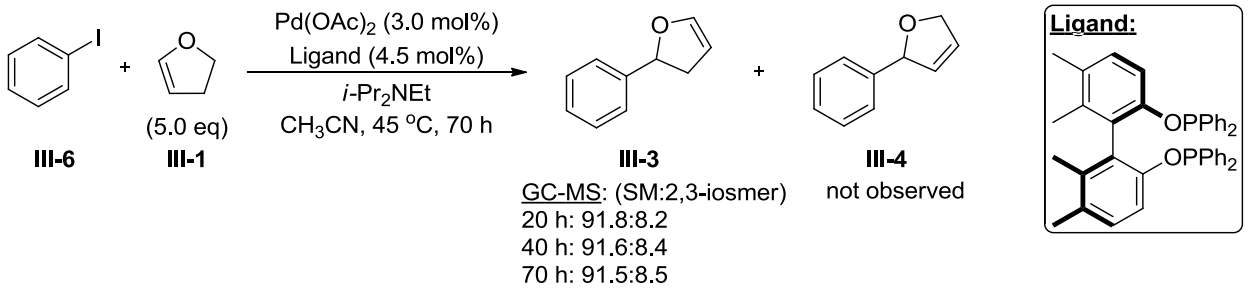
reaction to completion, 5 more equivalents of $PhB(OH)_2$ were added. The phenyl-substituted BOP afforded the best conversion to the desired product (36%, entry 3). However, the product was racemic. Substituting a bromine at the 3 and 3' positions resulted in the worst conversion to the product, only 13% (entry 4). The product was also racemic. When a benzyl substituted BOP was used, the conversion to the product was 18%. Nevertheless, the product was racemic (entry 5). Since the reaction neither finished nor achieved high *ee*, it was hypothesized that the reaction conditions were not sufficient; therefore changes were made to the reaction conditions.

One change was the use of microwave heating instead of conventional heating. Using the same reaction conditions and the BOP ligand, the reaction was subjected to microwave heating for 2 hour intervals, for a total of 6 hours, and then monitored. After 4 hours, the reaction was revealed to have a 20% conversion to the desired product. However, not much progress was made in the next 2 hours, hence the reaction was stopped. The overall conversion to the product was 20% in 6 hours (**Scheme 3.8**).



Scheme 3.8 Use of Microwave Heating for the Heck Reaction

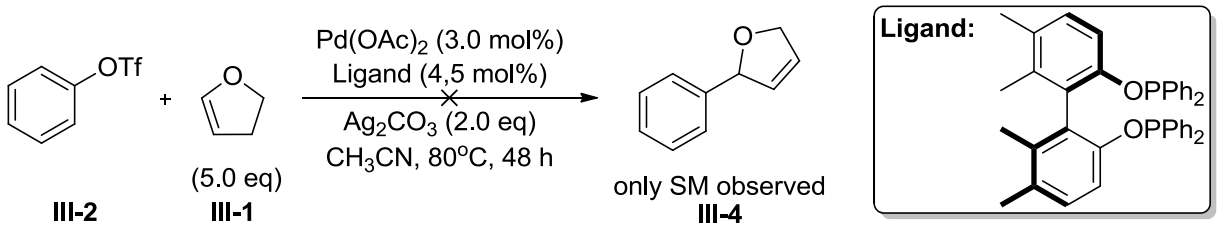
Changing to microwave heating did not facilitate reaction completion, thus conventional heating was used with a different base. Using $Pd(OAc)_2$ and the hydrogen substituted BOP as the catalyst and *i*-Pr_2NEt as the base in acetonitrile, the reaction was heated to 45 ^oC for 70 hours. The reaction was monitored by GC-MS after 20 hours to reveal an 8% conversion. Subsequent monitoring did not show much progress. The overall conversion of the starting material was 8%. Based on GC-MS, the retention time for the compound was different than that of the 2,5-dihydrofuran isomer. The compound obtained was the 2,3-dihydrofuran isomer as opposed to the 2,5-dihydrofuran isomer, and there was no other side product formation (**Scheme 3.9**).



Scheme 3.9 Change of Base for the Heck Reaction

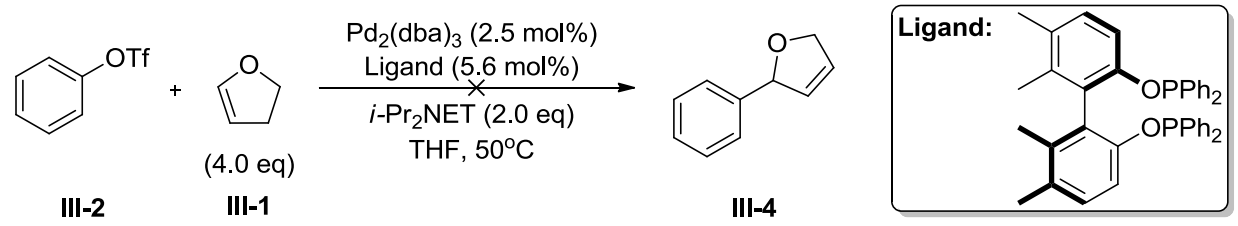
Failing to increase the reaction rate and having the reaction not reach completion led us to realize that the problem lay with the phenyl iodide. Similar to Hayashi's initial attempts, which involved the use of phenyl iodide and a silver salt, the products obtained had little to no enantioselectivity. Hayashi *et al.* rationalized that the low enantioselectivity was caused by the partial dissociation of the BINAP ligand during the coordination and insertion steps when using phenyl iodide. This rationalization can also be applied to the biphenol-based ligands when using phenyl iodide. The mechanism for the coordination and insertion step, which determines the enantioselectivity, shows that the neutral pathway would result in low *ee*, whereas if the process followed the cationic pathway, the resultant product would have high *ee*. Hayashi *et al.* overcame the low enantioselectivity by changing the substrate to phenyl triflate. Since triflate is a good leaving group, the palladium-ligand complex is more likely to form the cationic species during the coordination and insertion step. Using phenyl triflate, Hayahsi *et al.* achieved significantly higher *ee*, 97% for the 2,3-dihydrofuran isomer and 67% for the 2,5-dihydrofuran isomer.[7]

The same reaction conditions were used with the hydrogen substitute BOP and the substrate was changed to phenyl triflate. The reaction was heated at 80 ^{o}C for 48 hours. The reaction however did not proceed, as only starting material and no other product was observed on TLC (**Scheme 3.10**).



Scheme 3.10 Use of Phenyl Triflate in Heck Reaction

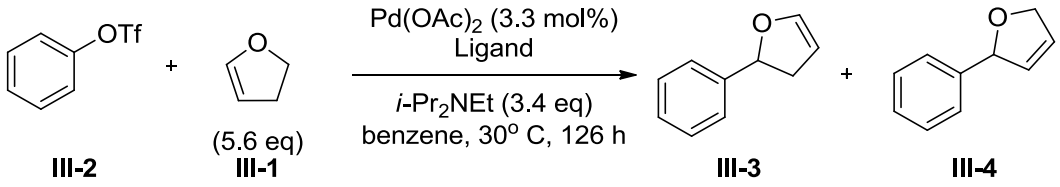
As changing the substrate from the original conditions did not produce the product or any other compound, a different reaction condition was attempted. The arylation of 2,3-dihydrofuran with phenyl triflate was attempted using $Pd_2(dba)_3$ and the hydrogen substitute BOP in the presence of *i*-Pr_2NEt in THF at 50 ^oC. After 24 hours, the reaction was completed and a crude ^1H NMR was taken. The NMR showed that the compound obtained was neither the 2,3-dihydrofuran isomer nor the 2,5-dihydrofuran isomer (**Scheme 3.11**).



Scheme 3.11 Use of $Pd_2(dba)_3$ for Heck Reaction

Hayashi's reported conditions for the intermolecular Heck reaction gave moderate yields, and good enantioselectivity, thus the reaction conditions were attempted with the biphenol-based ligands. The results are depicted in **Table 3.3**.

Table 3.2 Application of Biphenol-Based Ligands to Heck Reaction Using Phenyl Triflate



Entry	Ligand	Mol%	Conversion (SM:Product)
1	(*R*)-BOP-H	6.6	99:1 (III-4)
2	(*R*)-MPN-H	13	Mostly SM

Using the reaction conditions stated and the hydrogen substituted BOP ligand, the reaction resulted in a 1% conversion to 2-phenyl-2,5-dihydrofuran after 126 hours (entry 1). When the hydrogen substituted monophosphoramidite ligand was used, the reaction did not complete after 126 hours. Only starting material was observed when the GC-MS was taken (entry 2).

§ 3.3 Conclusion

Mizoroki and Heck independently reported the Heck reaction in the 1970s. The Heck reaction is an important carbon-carbon bond forming reaction due to the wide range of substrates and the tolerance it has for water and other functional groups. The first successful Heck reaction reported was for the intramolecular Heck reaction, which is much more tolerant of less reactive alkene substrates. Hence, the asymmetric intramolecular Heck has been successfully developed. The intermolecular Heck reaction, until recently, has been limited to reactive substrates, such as *O*- and *N*- heterocycles.

Hayashi reported the first asymmetric intermolecular Heck reaction. Since then, reaction conditions have been optimized to give good yields and high enantioselectivity. The majority of Heck reactions use BINAP as the ligand, however various other ligands have been used that show improved enantioselectivity with previously reported Heck reactions.

As mentioned, the Heck reaction is generally limited to substrates such as triflates or aryl halides, hence an alternative Heck-type reaction is used. The nucleophile-mediated Heck or

Heck-type allows for a wider range of substrates. The main difference between the Heck and Heck-type is the initial transmetallation and final reoxidation steps.

The biphenol-based ligands have been applied to both the Heck-type and the classic Heck reactions. The application of the biphenol-based ligands to the Heck-type failed to generate the desired product. When the ligands were applied to the classic Heck reaction, the reactions proceeded at a slow rate with no enantioselectivity. Initially, it was hypothesized that the cause was due to the phenyl iodide substrate. However, when the substrate was changed, and the reaction conditions modified, the reactions still failed to complete within a given time period.

§ 3.4 Experimental

General Information:

All chemical were obtained from either Sigma-Aldrich, Fisher Scientific or VWR International, and used as is unless otherwise noted. All reactions were performed under Schlenk conditions with oven dried glassware unless otherwise noted. Dry solvents were degassed under nitrogen and were dried using the PURESOLV system (Inovatative Technologies, Newport, MA). Tetrahydrofuran was freshly distilled from sodium metal and benzophenone. Dichloromethane was also distilled immediately prior to use under nitrogen from calcium hydride. Toluene was also distilled immediately prior to use under nitrogen from calcium hydride. ^{1}H, ^{13}C and ^{31}P data were obtained using either 300 MHz Varian Gemni 2300 (75 MHz ^{13}C, 121 MHz ^{31}P) spectrometer or the 400 MHz Varian INOVA 400 (100 MHz ^{13}C, 162 MHz ^{31}P) spectrometer in $CDCl_3$ as solvent unless otherwise stated. Chemical shifts (δ) are reported in ppm and standardized with solvent as internal standard based on literature reported values.[14] Melting points were measured on Thomas Hoover Capillary melting point apparatus and are uncorrected. GC/MS was performed on Agilent 6890GC/5973 Mass Selective Detector.

Representative Procedure for Intermolecular Heck Reaction:

$Pd(OAc)_2$ (3.4 mg, 0.015 mmol) and Ag_2CO_3 (276 mg, 1.00 mmol) were added to (*R*)-MPN-H (14.2 mg, 0.045 mmol) in a single-use test tube that was equipped with a stir bar. Air was replaced by N_2 by means of five evacuation/refill cycles. Acetonitrile (3 mL) was added to

the mixture and the solution was allowed to stir for 30 minutes at room temperature. To this solution was added phenyl iodide (102 mg, 0.50 mmol) in acteonitrile (1.5 mL), followed by the addition of 2,3-dihydrofuran (175 mg, 2.5 mmol in 1.5 mL CH_3CN). The solution was stirred at 80 ^oC for 93 hours. GC-MS of the black solution showed 50% conversion of the phenyl iodide and the formation of 2-phenyl-2,3-dihydrofuran (12% yield), 2-phenyl-2,5-dihydrofuran (28% yield), and 2-phenylfuran (10% yield). The reaction mixture was diluted with pentane, then filtered through Celite. The filtrate was concentrated to dryness, and purified by column chromatography on silica gel using hexanes/ethyl acetate (1-5%, ethyl acetate).

2-Phenyl-2,3-dihydrofuran: 12% conversion based on GC-MS, yellow oil
HPLC (Chiralcel OD-H, hexanes: *i*-PrOH 99:1, 1.0 mL/min): t_R= 9.7 min, 12.4 min
^{1}H NMR: (300 MHz, $CDCl_3$) δ 2.63 (ddt, J_1 = 15.0 Hz, J_2 = 8.4 Hz, J_3 = 2.1 Hz, 1H), 3.09 (ddt, J_1 = 15.3 Hz, J_2 = 10.8 Hz, J_3 = 2.4 Hz, 1H), 4.98 (q, J= 2.7 Hz, 1 H), 5.54 (dd, J_1 = 10.5 Hz, J_2 = 8.5 Hz, 1 H), 6.47 (q, J_1 = 2.1 Hz, 1 H), 7.27-2.39 (m, 5H). All data were in agreement with the reported values.[7]

2-Phenyl-2,5-dihydrofuran: 28% conversion based on GC-MS, yellow oil
HPLC (Chiralcel OD-H, hexanes: *i*-PrOH 99.2:0.8, 1.0 mL/min): t_R= 7.8 min, 8.6 min
^{1}H NMR: (300 MHz, $CDCl_3$) δ 4.74-4.92 (m, 2H), 5.77-5.82 (m, 1 H), 5.87-5.91 (m, 1 H), 6.02-6.06 (m, 1 H), 7.28-7.34 (m, 5 H). All data were in agreement with the reported values.[7]

2-Phenylfuran: 10% conversion based on GC-MS, colorless oil
^{1}H NMR: (300 MHz, $CDCl_3$) δ 6.48 (s, 1H), 6.65 (s, 1H), 7.11 (m, 1H), 7.36-7.47 (m, 1H), 7.59-7.69 (m, 1H). All data were in agreement with the reported values.[1]

§ 3.5 References

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Chapter 4

§ 4.1 Introduction

§ 4.1.1 Indole Alkaloids

Alkaloids are naturally-occurring, nitrogen-containing bases, usually containing complex fused-ring systems. Although many alkaloids are toxic to other organisms, they are often used as medications and recreational drugs due to their pharmacological effects. Alkaloids are significantly diverse in structure, thus they are grouped by their core structure. Alkaloids with an indole moiety form the core skeleton of numerous natural products and compounds with biological activity. The highly toxic, complex fused polycyclic compound, strychnine, was the first indole alkaloid identified and isolated from plants of the genus *Strychnos*. Containing six chiral quaternary carbon centers, the total synthesis of strychnine, in addition to a number of other complex indole alkaloids, has posed a huge challenge to organic chemists. Recent developments in the use of organometallic complexes have provided an answer to this synthetic challenge.

In 2003, Mori *et al.* reported a new synthetic pathway for the total synthesis of chiral strychnos indole alkaloids using palladium-catalyzed asymmetric allylic substitution.[1] Using this method, chiral indole alkaloids, such as tubifoline, aspidospermine and strychnine can be synthesized from a chiral indoline derivative (**Figure 4.1**).

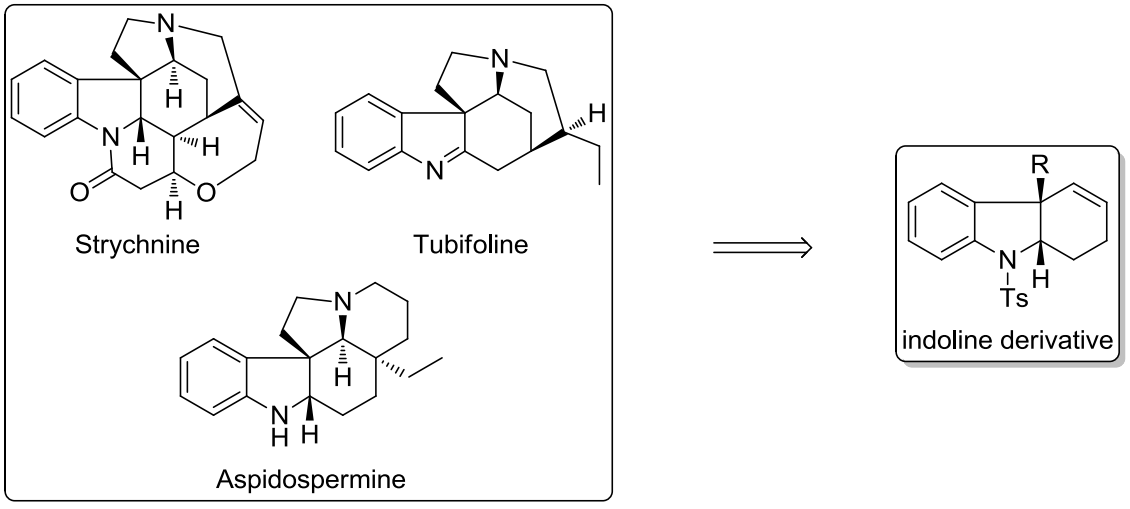
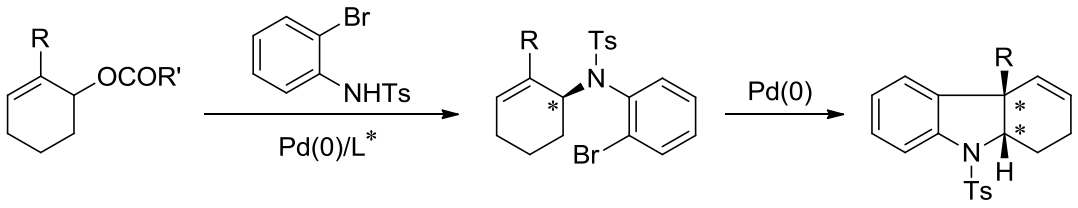


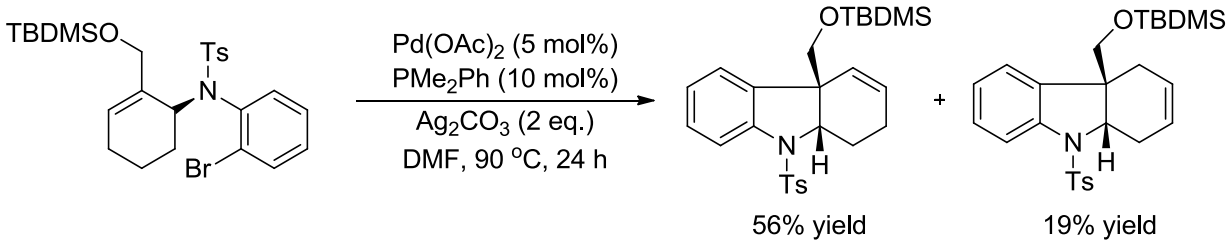
Figure 4.1 Total synthesis of alkaloids based on indoline derivative

The chiral indoline derivative could be constructed using a palladium-catalyzed allylic substitution followed by a palladium-catalyzed Heck reaction (**Scheme 4.1**).



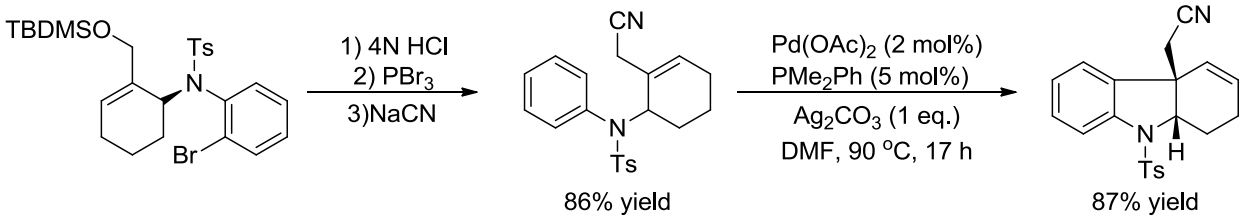
Scheme 4.1 Proposed pathway to indoline derivative

Mori *et al.* obtained moderate yields and relatively good enantiomeric excess (*ee*) for the palladium-allylic amination product, 64% yield and 84% *ee*, respectively. However, when the Heck reaction was employed on the amination product, the best yield obtained for the indoline derivative was 56% yield when PMe_2Ph was used as the ligand (**Scheme 4.2**).



Scheme 4.2 Intramolecular Heck Reaction using PMe_2Ph

This may have been a result of the steric hindrance generated by the silyl-protecting group. Thus, the OTBMDS group was replaced with a cyano group, introducing a smaller and more electron-withdrawing moiety. Deprotection of the silyl group with 4 N HCl, followed by bromination and cyanation using NaCN yielded the nitrile product in 86% yield. The intramolecular Heck reaction of the resulting nitrile product gave the desired indole derivative in 87% yield (**Scheme 4.3**).

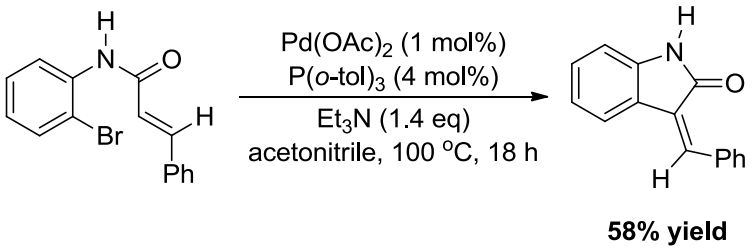


Scheme 4.3 Steps to cyanated product and subsequent Heck reaction

Following Mori's original idea, it would be ideal if the intramolecular Heck reaction can be done on the silyl-protected product obtained after the palladium-catalyzed allylic amination. Thus, we hypothesize that the intramolecular Heck reaction will provide the desired indole derivative in high yields if the TBDMS group were replaced by a different silyl moiety or if the alcohol were left unprotected.

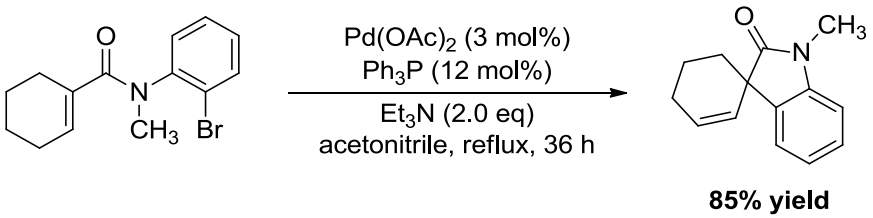
§ 4.1.2 Intramolecular Heck Reaction

The use of the Heck reaction as a carbon-carbon bond forming reaction of open chain products is well known.[2] However, the use of the reaction to form cyclic products were not attempted until the pioneering works of the Mori[3] and Heck[4] groups. They both demonstrated that tertiary carbons can be formed through the use of the intramolecular Heck reaction. Heck found that the cyclization of *N*-cinnamoyl-2-bromoaniline can be done using $Pd(OAc)_2$ and tri-*o*-tolylphosphine as the catalyst in the presence of triethylamine in acetonitrile at 100 °C. They obtained a 58% yield for the product and found that the results were consistent with the findings of Mori. (**Scheme 4.4**)



Scheme 4.4 Formation of tertiary carbon

In 1989, Overman *et al*.[5] demonstrated that quaternary carbons can also be prepared through the intramolecular Heck reaction. Using $Pd(OAc)_2$ and Ph_3P as the catalyst in the presence of triethylamine in acetronitrile under reflux conditions afforded the spirooxindole in 83% yield (**Scheme 4.5**).



Scheme 4.5 Formation of quaternary carbon

Furthermore, the reaction has been successfully developed to the point where chiral tertiary and quaternary carbon centers can be obtained with high enantioselectivity. Due to the success of the Heck reaction for carbon-carbon bond formation in organic synthesis, Richard Heck, Ei-ichi Negishi and Akira Suzuki were awarded the 2010 Nobel Prize in Chemistry for their work on palladium-cross couplings in organic synthesis.

§ 4.1.3 Palladium Catalyzed Allylic Amination

Palladium catalyzed allylic substitution reactions are useful methods for carbon-carbon and carbon-heteroatom bond formation. The allylation step involves nucleophiles, such as active methylenes, enolates, amines and phenols, with allylic compounds such as allyl acetates and allyl bromides. In 1965, Tsuji and co-workers reported the first example of a palladium-catalyzed allylic alkylation. [6] In 1973, Trost *et al.* reported the first asymmetric allylic alkylation by introducing phosphine ligands into the reaction conditions. [7]

The general mechanism for the allylic substitution reaction is shown in **Figure 4.2.** Starting with a palladium-ligand complex **1**, the allylic substrate coordinates to the palladium-ligand complex to form complex **2**. An oxidative addition, or ionization, occurs in which the leaving group is expelled to form complex **3**. Depending on the strength of the nuleophile, the reaction can occur in two different pathways. Soft nucleophiles add directly to the allyl moiety as

shown in the mechanism to give **4**. Then decomplexation occurs to give product **5**. Hard nucleophiles attack the metal center first, followed by reductive elimination to give the product (not shown).

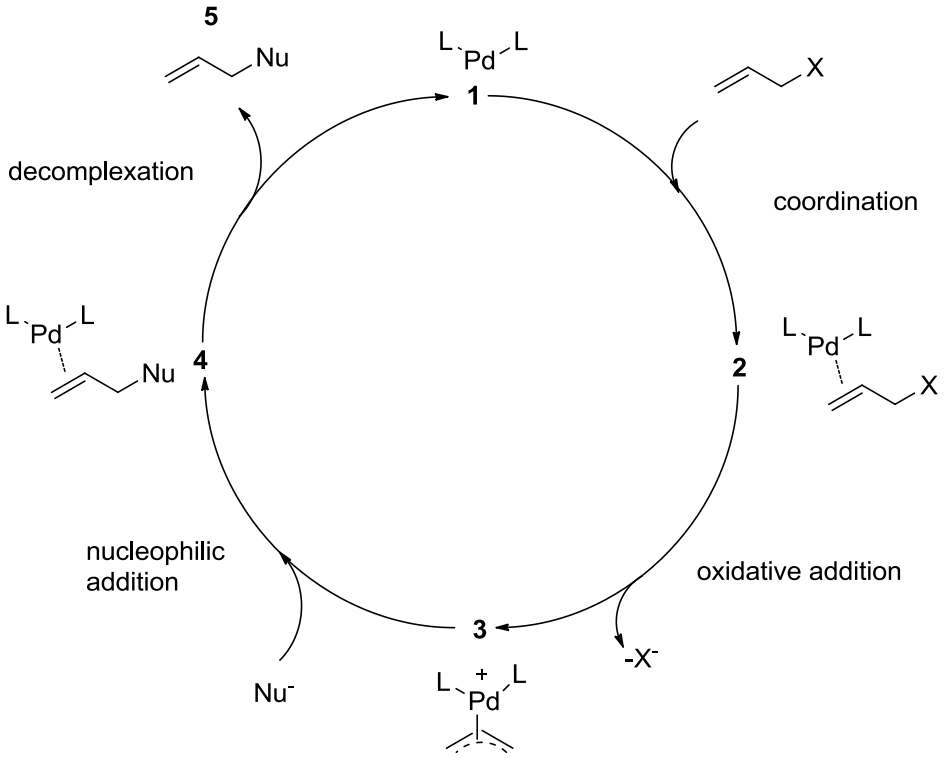
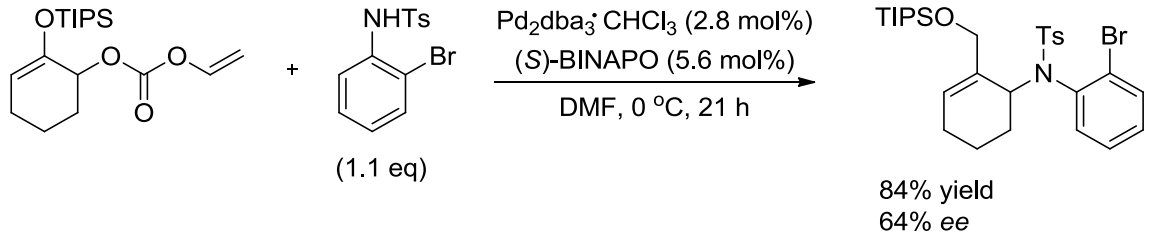


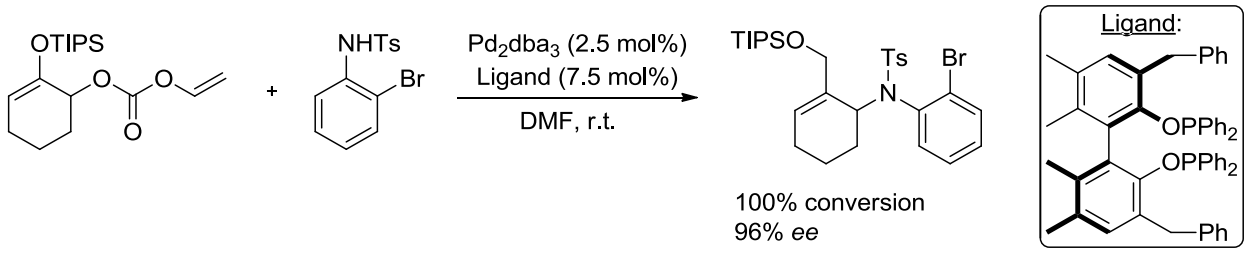
Figure 4.2 Mechanism for Allylic Substitution

The palladium-catalyzed allylic amination step is a key step for determining the chirality of the indoline derivative. Although, Mori *et al*. reported good yields and moderate enantioselectivity for the amination step, the results can be improved (**Scheme 4.6**).



Scheme 4.6 Asymmetric Allylic Amination using (*S*)-BINAPO

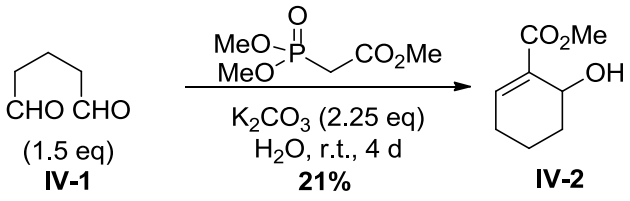
In 2010, the Ojima group demonstrated that enantioselectivity can be significantly improved through the use of chiral biphenol-based diphosphonite (BOP) ligands (**Scheme 4.7**). [8]



Scheme 4.7 Application of BOP ligand to Asymmetric Allylic Amination

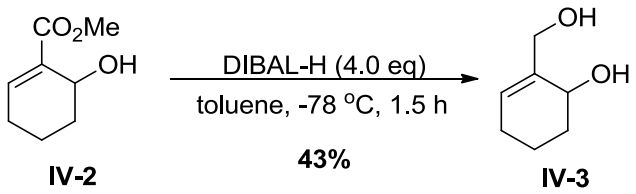
§ 4.2 Results and Discussion

Optimization of the intramolecular Heck reaction begins with the synthesis of the indoline substrate. This substrate is prepared via the coupling of a cyclic substrate to an aryl ring system through palladium-catalyzed allylic amination. The Horner-Wadsworth-Emmons reaction was used for the synthesis of methyl-6-hydroxy-1-cyclohexenecarboxylate. Methyl 2-dimethoxyphosphoryl-2-formamidoacetate was reacted with glutaraldehyde (**IV-1)** in the presence of potassium carbonate at room temperature to give the desired carboxylate (**IV-2**) in a 21% yield (**Scheme 4.8**).



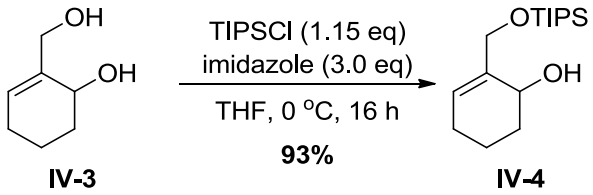
Scheme 4.8 Synthesis of IV-2

Carboxylate **IV-2** was reduced with DIBAL-H in toluene at -78 ^{o}C to give the corresponding diol (**IV-3**) in a 54% yield (**Scheme 4.9**).



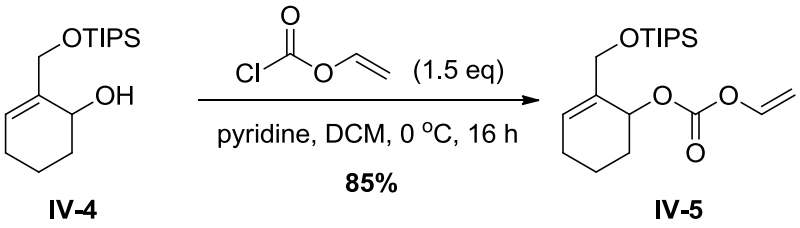
Scheme 4.9 Synthesis of IV-3

Diol **IV-3** was protected with TIPSCl in the presence of imidazole in THF at 0 °C to give the TIPS-protected alcohol (**IV-4**) in a 93% yield (**Scheme 4.9**).



Scheme 4.10 Synthesis of IV-4

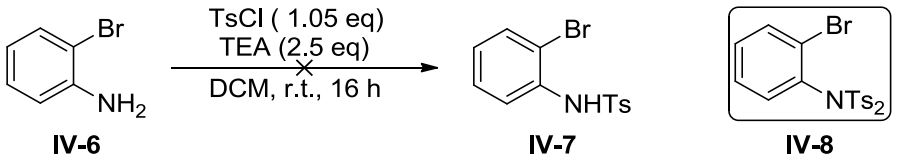
Alcohol **IV-4** is then reacted with vinyl chloroformate in the presence of pyridine in DCM at 0 °C to give the corresponding carbonate (**IV-5**) in an 85% yield (**Scheme 4.11**).



Scheme 4.11 Synthesis of IV-5

With the carbonate in hand, *N*-tosyl-2-bromoaniline was prepared for the palladium-catalyzed allylic amination step. Reacting 2-bromoaniline with tosyl chloride in the presence of TEA in DCM at room temperature gave the di-substituted amine (**Scheme 4.12**). Disubstitution may have been caused by the presence of the *ortho*-bromine, which may have increased the

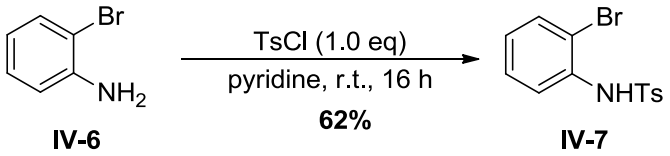
acidity of the amide after the first tosyl protection. Thus, the additional equivalents of base deprotonated the amide leading to disubstitution.



IV-6 **IV-7** **IV-8**

Scheme 4.12 Attempted Synthesis of IV-7

Using pyridine as solvent and base, the desired *N*-tosyl-amine was obtained in 62% yield (**Scheme 4.13**).

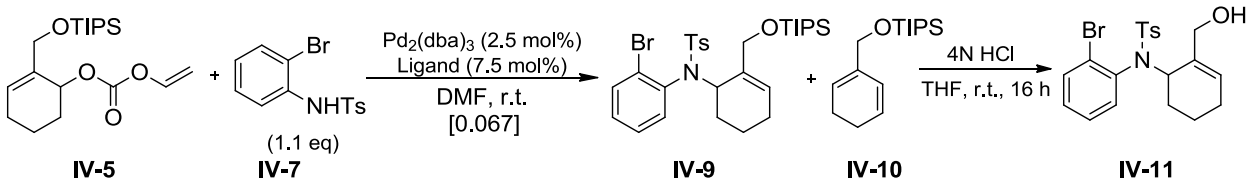


IV-6 **IV-7**

Scheme 4.13 Synthesis of IV-7

The *N*-tosyl-2-bromoaniline was then subjected to palladium-catalyzed allylic amination. **Table 4.1** shows the results for the various ligands applied to the palladium-catalyzed allylic amination and the subsequent desilylation.

Table 4.1 Application of Ligands to Asymmetric Allylic Amination



IV-5 **IV-7** **IV-9** **IV-10** **IV-11**

Entry	Ligand	Time (h)	Conversion to IV-9	IV-9:IV-10	*ee*[5] (IV-11)
1[1]	PPh_3	24	>95%	24:76	-
2[2]	$Pd(PPh_3)_4$	96	np	-	-
3[3]	Quasi-BOP	24	>95%	95:5	0
4	(*R*)-BOP-Ph	96	51%	71:29	91
5	(*R*)-BOP-1-Nap	24	>95%	81:19	93
6[4]	(*S*)-BOP-1-Nap	21	>95%	75:25	92

[1]PPh_3 (15 mol%) in THF, at 80 °C (19% yield); [2]reaction was done with $Pd(PPh_3)_4$ (10 mol%) and proton sponge (3.0 eq); [3]concentration [0.2] (75% yield); [4]reaction was done using carbonate in excess (1.5 eq) (>99% yield); [5]HPLC condition: Chiralcel OJ, Hexanes/IPA (80:20), 1mL/min

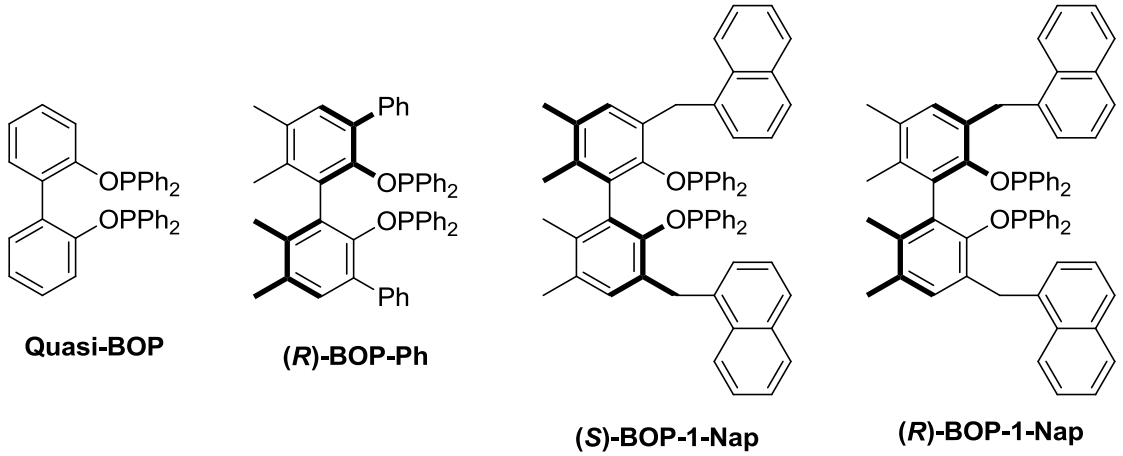


Figure 4.3 Various Biphenol-Based Ligands Used for Allylic Amination

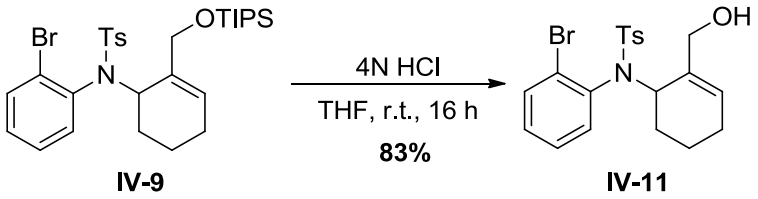
As seen from Table 1, a greater than 95% conversion with a 24 to 76 product (**IV-9**) to byproduct (**IV-10**) ratio was obtained when PPh_3 was used as the ligand (entry 1). The low yield formation of **IV-9** was the result of high reaction temperature, which led to an increased formation of **IV-10**. As such, the reaction was carried out using $Pd(PPh_3)_4$ and proton sponge (1,8-bis(dimethylamino)naphthalene) at room temperature. The proton sponge was used to help deprotonate the *N*-tosyl-amine so that the reaction would proceed at room temperature to give a

higher product to byproduct ratio. Unfortunately, the reaction did not produce any desired product after 96 hours (entry 2). A non-chiral BOP-type ligand was used for the allylic amination. After 24 hours, the reaction gave over 95% conversion with a 95 to 5 product to byproduct ratio (entry 3). The reaction gave an isolated product yield of 75%.

In addition, chiral ligands were used for the allylic amination to obtain a chiral product that could also be subjected to the Heck reaction. Previous Ojima group members optimized the reaction conditions for the palladium-catalyzed allylic amination using the BOP ligand. The optimized reaction conditions involved the use of a phenyl-substituted BOP ligand, which gave the best results with high yields and enantioselectively. When the phenyl-substituted BOP was used as the ligand for the allylic amination of compounds **IV-5** and **IV-7**, the reaction proceeded with a 51% conversion and a 71 to 29 product to byproduct ratio after 96 hours. The low conversion may be due to degradation of the ligand. **IV-9** was then desilylated using 4 N HCl in THF at room temperature to obtain the alcohol product (**IV-11**) to determine the enantiomeric excess (91%, entry 4).

The 1-naphthyl-substituted BOP ligand also gave good results for the amination. When the 1-naphthyl-substituted BOP ligand was used, the reaction reached completion in 24 hours with an 81 to 19 product to byproduct ratio. The product had a 93% *ee* (entry 5). A larger scale reaction was done using the carbonate in excess and the 1-naphthyl-subtituted BOP ligand. The reaction completed with greater than 95% conversion in 21 hours and a 75 to 25 product to byproduct ratio (entry 6). **IV-9** was obtained in quantitative yield with 92% *ee*.

With the amination step optimized, the intramolecular Heck reaction with the free alcohol (**IV-11**) was attempted. The silyl group was deprotected using 4 N HCl in THF at room temperature to give the alcohol in 83% yield (**Scheme 4.14**).

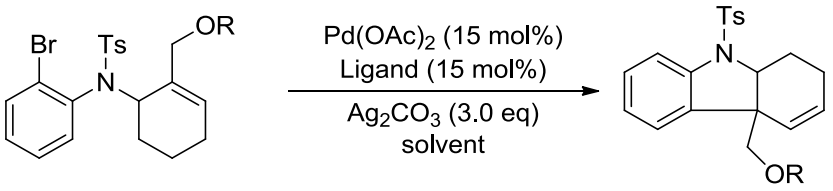


IV-9 **IV-11**

Scheme 4.14 Deprotection of IV-9

The results of the various conditions used for the intramoleuclar Heck reaction are depicted in **Table 4.2**.

Table 4.2 Intramolecular Heck Reaction



IV-9 R=TIPS
IV-11 R=H

IV-12 R=TIPS
IV-13 R=H

Entry	R	Ligand	Solvent	Temp (^{o}C)	Time (h)	Yield
1[1]	H	PMe_2Ph	DMSO	90	192	np
2[2]	TIPS	PMe_2Ph	DMSO	120	24	23
3	H	dppp	toluene	107	96	-
4[3]	TIPS	dppp	toluene	107	24	>99
5[3]	TIPS	dppp	toluene	100	48	90
6[4]	TIPS	dppp	toluene	100	5	-
7	TIPS	dppp	toluene	110	16	84
8[4]	TIPS	dppp	toluene	110	21	85

[1]$Pd(OAc)_2$ (2 mol%), PMe_2Ph (4 mol%), Ag_2CO_3 (1.0 eq); [2]$Pd(OAc)_2$ (5 mol%), PMe_2Ph (10 mol%), Ag_2CO_3 (1.0 eq); [3]small scale; [4]μ-wave at 100 ^{o}C; [5]HPLC condition: Chiralpack AD, Hexanes/IPA (98.5:1.5), 1mL/min (95% *ee*)

The intramolecular Heck reaction conditions reported by Mori for the cyano product were used to carry out the reaction for the deprotected amination product (**IV-11)**. Using $Pd(OAc)_2$ and PMe_2Ph as the catalysts in the presence of Ag_2CO_3 in DMSO, the reaction was heated at 90 ^{o}C. After 192 hours, the reaction did not give the desired product (**IV-13**) (entry 1). Using different reaction conditions reported by Mori, the Heck reaction was attempted on the TIPS-protected amination product (**IV-9**). After 24 hours at 120 ^{o}C, the reaction gave the desired product (**IV-12**) in 23% yield (entry 2).

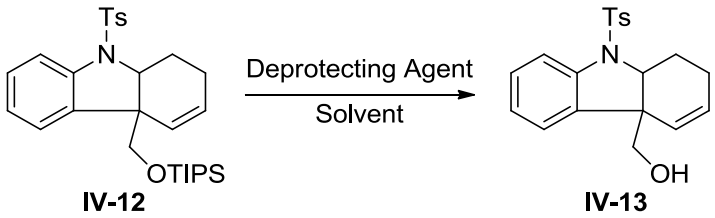
Using the reaction conditions reported by Trost[9], the intramolecular Heck reactions using **IV-11** and **IV-9** were attempted. Using $Pd(OAc)_2$ and dppp in the presence of Ag_2CO_3 in toluene, the reactions were heated at 107 ^{o}C. After 96 hours, the reaction using **IV-11** completed, however the reaction was very messy, thus the compound was not isolated (entry 3). The reaction using **IV-9** completed in 24 hours giving a quantitative isolated yield (entry 4).

As 107 ^{o}C is a peculiar reaction temperature, more traditional reaction temperatures were used. Initially, 100 ^{o}C was used as the reaction temperature as toluene has a boiling point of 110 ^{o}C. The reaction finished in 48 hours with 90% yield (entry 5). Microwave heating was also

employed to shorten the reaction time. After 5 hours of microwave heating at 100 ^{o}C, the reaction did not complete (entry 6). In addition, the reaction was messy using microwave heating, therefore it was decided that the reaction time could be shorten using conventional heating at higher temperature to give **IV-12** with a slightly lower 84% yield (entry 7). A larger scale reaction was performed using chiral **IV-9**. This reaction completed in 21 hours with 85% yield and 95% *ee* (entry 8).

The Heck reaction using the TIPS-protected amination product gave good yields and good enantioselectivity, thus the steps leading to the cyano-substituted product were attempted. Deprotection of the Heck product proved to be problematic. These results are depicted in **Table 4.3**.

Table 4.3 Deprotection of IV-12



IV-12 **IV-13**

Entry	Deprotecting Agent	Solvent	Temp (^{o}C)	Time (h)	Yield
1	6 N HCl	THF	r.t.	120	50
2	TBAF	THF	r.t.	3	65
3	HF-pyridine	CH_3CN-py	r.t.	96	60
4	TFA	THF, H_2O	50	144	n/c
5	CBr_4	MeOH	70	96	n/c
6[1]	TBAF	THF	50	3	-
7[1]	TBAF	THF	0	3	-
8	TBAF	THF	-78- -20	167	79
9	TBAF	THF	-30	69	70
10[2]	TBAF	THF	-20	17	74
11	TBAF	THF	-20	17	61

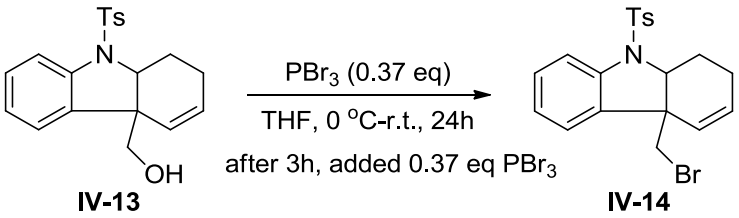
[1]yield not determined; [2]4 Å molecular sieves were used

Using standard conditions for deprotection, 6 N HCl in THF at room temperature gave the product in 50% yield after 120 hours (entry 1). Tetrabutylammonium fluoride (TBAF) in THF at room temperature gave the product at 65% yield after 3 hours (entry 2). After 96 hours, deprotecting with HF-pyridine in CH_3CN-pyridine gave the product in 60% yield (entry 3).

When TFA was used for the deprotection, the reaction did not complete in 144 hours (entry 4). In addition, the reaction was messy, thus the product was not isolated. Carbon tetrabromide (CBr_4) was also used for the deprotection, however after 96 hours, the reaction did not reach completion (entry 5).

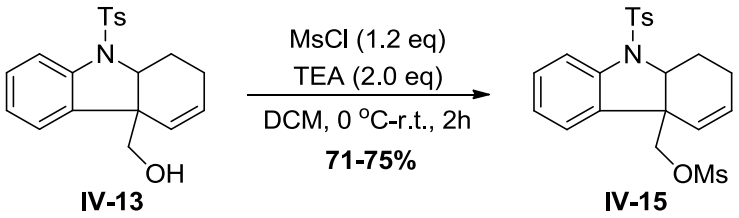
The use of TBAF resulted in a short reaction time, thus optimization of the deprotection reaction was attempted using TBAF and varying the reaction temperatures. When the reaction temperature was increased to 50 ^oC, the reaction completed in 3 hours, but there was more side product formation (entry 6). When the reaction temperature was lowered to 0 ^oC, the reaction also completed in 3 hours, and there was less side product formation (entry 7). Hence, lower reaction temperatures were used. At -78 ^oC, the reaction did not complete after 75 hours, thus the temperature was raised to -40 ^oC. After 70 hours at -40 ^oC, the starting material was still present. Hence, the temperature was increased to -20 ^oC. After 22 hours, the reaction reached completion and the overall isolated yield for the reaction was 79% (entry 8). Seeing that the reaction at -20 ^oC gave moderate yield, the reaction was attempted at -30 ^oC, hoping that the yield could be improved. The reaction finished in 69 hours with 70% isolated yield (entry 9). With no significant change in yield, -20 ^oC was chosen as optimal temperature for subsequent reactions. At -20 ^oC with 4 Å molecular sieves, to adsorb any trace of water in TBAF, the reaction completed in 17 hours and gave 74% yield (entry 10). The 4 Å molecular sieves did not improve the yield significantly (compared to entry 8), thus were not used for the large scale reaction. The large scale reaction using the chiral Heck product was carried out at -20 ^oC and the reaction completed in 17 hours giving the product in 61% yield (entry 11).

The next step toward the cyano-substituted product was to substitute the alcohol group with a good leaving group. Using the reaction conditions reported by Mori, bromination was done using PBr_3 in THF. After 24 hours, the reaction was done, but the TLC was messy. Although purification of the product was attempted, no product was obtained after column chromatography. Recrystallization was attempted; however the product was not obtained (**Scheme 4.15**).



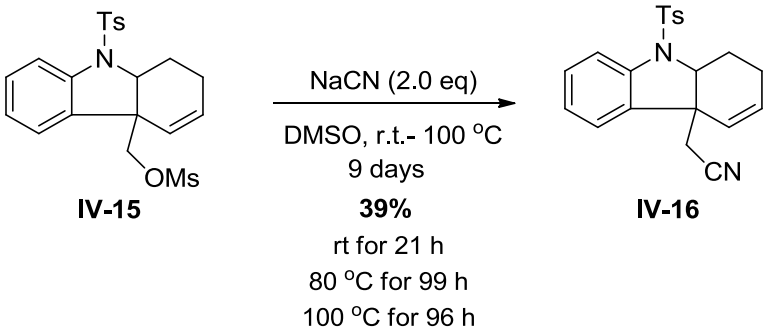
Scheme 4.15 Attempted Bromination of IV-13

As bromination of the alcohol was unsuccessful, mesylation was attempted. Mesyl chloride in the presence of TEA in dichloromethane was added to the alcohol. After 2 hours, the reaction was finished and after recrystallization, the product was obtained in 75% yield. In a slightly larger scale, the yield was slightly lower (71% yield), but within error (**Scheme 4.16**).



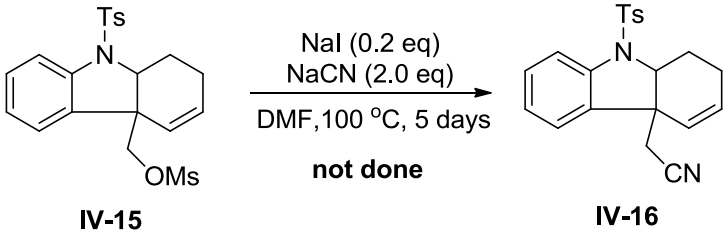
Scheme 4.16 Mesylation of IV-13

Cyanation of the mesyl product was attempted using the conditions reported by Mori. The reaction was stirred at room temperature for 21 hours. However, only the starting material was observed on the TLC. Thus, the temperature was increased to 80 °C. After 99 hours at 80 °C, the starting material was still present. To push the reaction to completion, the temperature was increased to 100 °C. After 96 hours at 100 °C, a small amount of the starting material was still present. Nevertheless, the reaction was worked up affording the product in 39% yield (**Scheme 4.17**).



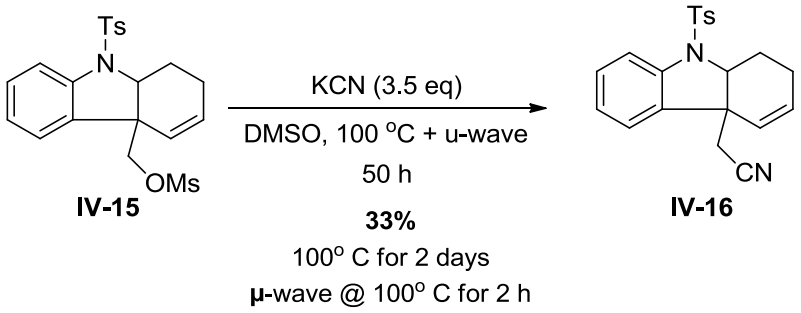
Scheme 4.17 Cyanation of IV-15 using NaCN

With low yields and slow reaction rates, additional reaction conditions were attempted. To assist the cyano substitution, NaI was used to convert the mesylate to iodide, which is a better leaving group. However, after 5 days at 100 ^{o}C, the reaction was not complete (**Scheme 4.18**).



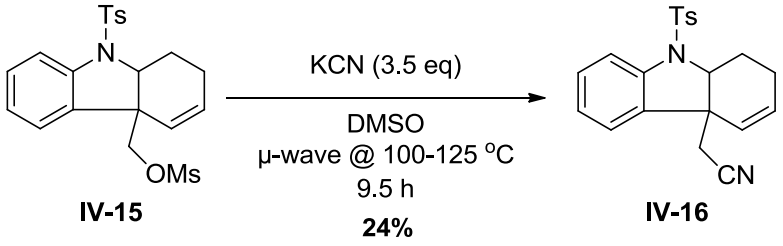
Scheme 4.18 Cyanation of IV-15 usig NaI and NaCN

To increase the nucleophilicity of the cyano group, KCN was used given the larger radius of the potassium ion. The larger radius allows KCN to dissociate more readily than NaCN, thereby the reaction may proceed faster and with a better yield. Using KCN in DMSO at 100 ^{o}C, the reaction mixture was stirred for 2 days. After 2 days, the reaction made some progress, but the reaction rate was still slow, therefore, the reaction was subjected to microwave heating at 100 ^{o}C for 2 hours. The reaction completed after 2 hours and the product was obtained in 33% yield (**Scheme 4.19**).



Scheme 4.19 Cyanation of IV-15 using KCN

Microwave heating increased the reaction rate, thus the microwave was used as the heating source. Using the same reaction conditions, the reaction mixture was heated in the microwave at 100 ^{o}C for 9 hours. Starting material was still present, thus to push the reaction to completion, the reaction was re-subjected to microwave heating at a higher temperature, 125 ^{o}C, for an additional 30 minutes. After the extended time, the starting material was consumed and the product was obtained in 24% yield (**Scheme 4.20**).



Scheme 4.20 Cyanation of IV-15 Using Microwave Irradiation

The low reaction rate is a result of steric hinderance generated from the tosyl group. Since the cyanation is an S_N2 reaction, the cyano group attacks from the back side. The tosyl group in the mesylated Heck product can take on either of the two orientations, A or B, as they are relatively close in energy (**Figure 4.4**). If the tosyl group orients as shown in Figure A, the tosyl group clearly blocks the position from which the cyano group can attack, hence the slow reaction and low yields. If the tosyl group orients as shown in Figure B, the two hydrogen atoms from the tosyl group are oriented in such a way that they still block the cyano group from attacking from the back side.

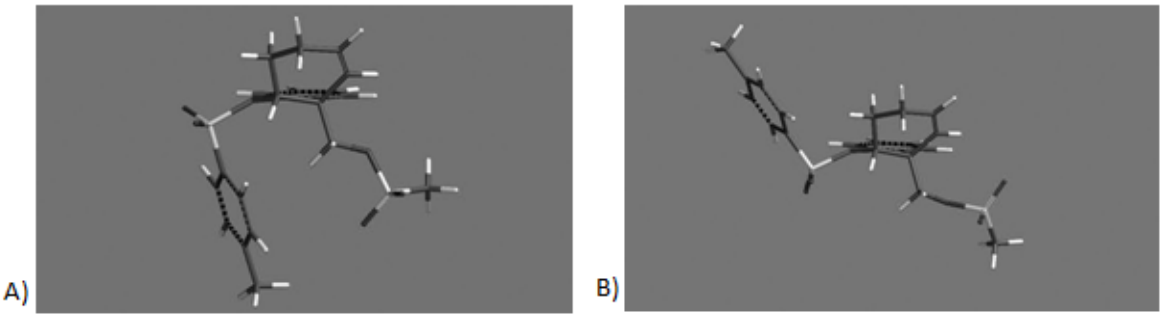
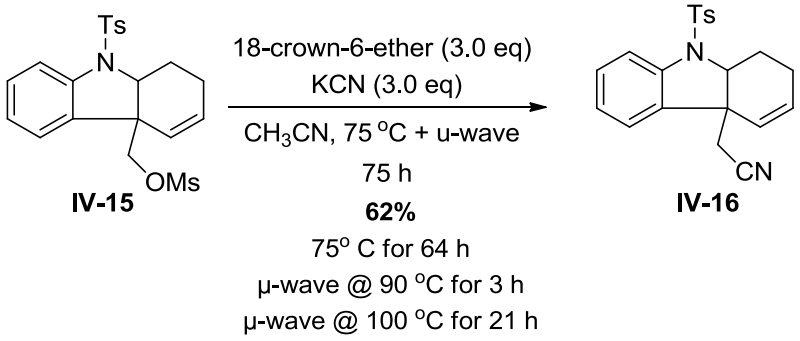


Figure 4.4 Possible Orientations of the Tosyl Group

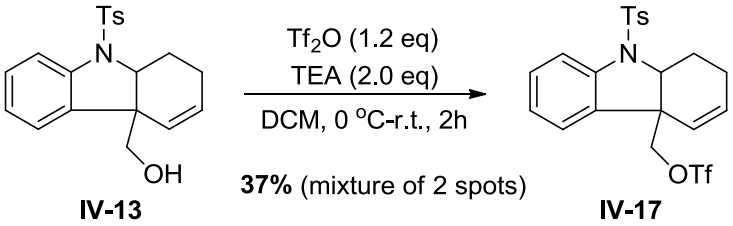
To overcome the low yields, crown ethers were used to trap the potassium. Another possibility was the use of triflate in place of the mesyl group, as it is a better leaving group. Furthermore, the removal of the tosyl group from the amine may facilitate a faster reaction, as it appears to be hindering the substitution.

Since the use of crown ethers is synthetically easier, the substitution in the presence of 18-crown-6-ether was attempted. The crown ether has a strong affinity for the potassium cation, therefore it will bind to the cation, which frees the smaller cyano anion to attack the leaving group. Using the KCN and 18-crown-6-ether in acetonitrile, the reaction mixture was heated at 75 ^{o}C for 64 hours. After 64 hours, the reaction proceeded, but it did not finish. To push the reaction, the reaction mixture was subjected to microwave heating at 90 ^{o}C for 3 hours. Still not complete, the reaction mixture was re-subjected to microwave heating at 100 ^{o}C for 21 hours. After the extended microwave heating periods, the product was obtained in 62% yield (**Scheme 4.21**).



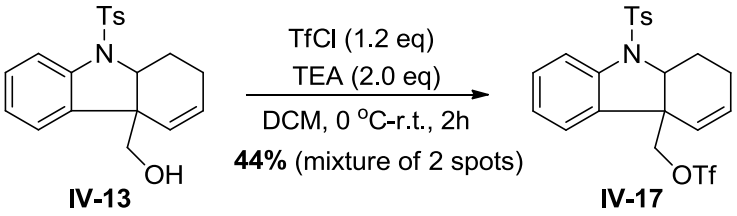
Scheme 4.21 Cyanation of IV-15 Usig KCN and 18-Crown-6-Ether

The use of crown ethers with the mesylated product gave moderate yields, therefore if the mesyl group was replaced with triflate, a better leaving group, then perhaps the yield can be higher. Trifluoromethanesulfonyl anhydride in the presence of TEA was added to the deprotected Heck product in DCM. After 2 hours at room temperature, the reaction was complete. After purification, the product on TLC appeared to be one spot, but ^{1}H NMR showed the product to be two compounds. Upon developing the TLC plate with a lower polarity solvent, it was revealed that there were indeed two spots that had very similar R_f values, thus they could not easily be separated by column chromatography (**Scheme 4.22**).



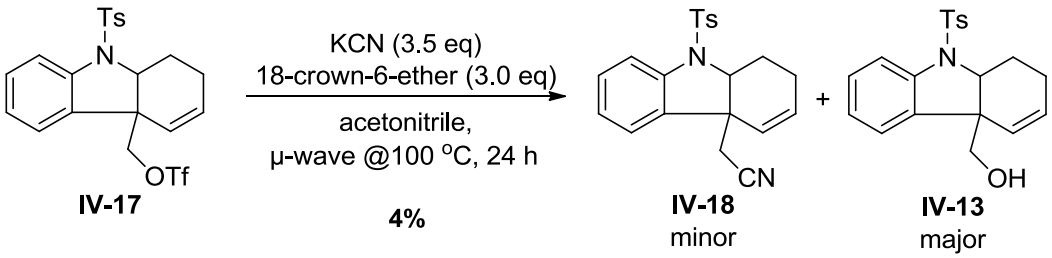
Scheme 4.22 Synthesis of IV-17 Using Trifluoromethanesulfonyl Anhydride

As the trifluoromethanesulfonyl anhydride did not give a clean product, trifluoromethanesulfonyl chloride was tried instead. Trifluoromethanesulfonyl chloride was added to the deprotected Heck product in the presence of TEA in DCM. The reaction finished in 2 hours at room temperature. However, the purified triflate product contained two compounds that also could not be separated (**Scheme 4.23**).



Scheme 4.23 Synthesis of IV-17 Using Trifluoromethanesulfonyl Chloride

Nevertheless, the cyanation was attempted using the impure product obtained from the trifluoromethanesulfonyl chloride. Using KCN and 18-crown-6-ether in acetonitrile, the reaction was subjected to microwave heating for 16 hours at 100 ^{o}C. The reaction did not reach completion, and it was heated in the microwave reactor for another 2 hours. The reaction still did not complete, so it was heated for another 6 hours. There was very little starting material present, thus the reaction was worked up. The reaction afforded only 4% yield of the desired product as the byproduct was the major product (**Scheme 4.24**). After ^{1}H NMR and ^{13}C NMR analysis, the byproduct was revealed to be **IV-13**, the hydrolyzed product of **IV-17**.



Scheme 4.24 Cyanation of IV-17 Using KCN and 18-Crown-6-Ether

§ 4.3 Conclusion

Indole alkaloids are naturally occurring compounds with pharmacological effects. However, the total syntheses for indole alkaloids have been difficult due to the complex fused rings containing chiral carbon centers. Developments in the use of organometallic complexes have made it easier for organic chemists to synthesize the indole alkaloids. Mori *et al.* proposed a pathway to the total synthesis of chiral strychnos indole alkaloids via palladium-catalyzed reactions. Using the palladium-catalyzed allylic amination, they were able to obtain the intermediate with good yields and moderate enantioselectivity. However, they struggled with the intramolecular Heck reaction. They performed the Heck in a subsequent step as opposed to directly following the allylic amination step.

The intramolecular Heck reaction has been shown to be successful following directly after the allylic amination when a larger protection group, TIPS, and a different ligand, dppp, is used. The Heck product was obtained in good yields with high enantioselectivity (85% yield,

95% *ee*). The use of the chiral biphenol-based BOP ligand afforded the amination product in higher enantioselectivity as compared to the results obtained by Mori.

Subsequent steps following the Heck reaction and to the cyanated Heck product proved to be more problematic. Deprotection of the Heck product resulted in only moderate yields. The cyanation step also proved to be difficult and as of now, yields for the cyanated product are only moderate.

§ 4.4 Experimental

General Information:

All chemical were obtained from either Sigma-Aldrich, Fisher Scientific or VWR International, and used as is unless otherwise noted. All reactions were performed under Schlenk conditions with oven dried glassware unless otherwise noted. Dry solvents were degassed under nitrogen and were dried using the PURESOLV system (Inovatative Technologies, Newport, MA). Tetrahydrofuran was freshly distilled from sodium metal and benzophenone. Dichloromethane was also distilled immediately prior to use under nitrogen from calcium hydride. Toluene was also distilled immediately prior to use under nitrogen from calcium hydride. ^{1}H, ^{13}C and ^{31}P data were obtained using either 300 MHz Varian Gemni 2300 (75 MHz ^{13}C, 121 MHz ^{31}P) spectrometer or the 400 MHz Varian INOVA 400 (100 MHz ^{13}C, 162 MHz ^{31}P) spectrometer in $CDCl_3$ as solvent unless otherwise stated. Chemical shifts (δ) are reported in ppm and standardized with solvent as internal standard based on literature reported values.[14] Melting points were measured on Thomas Hoover Capillary melting point apparatus and are uncorrected. Optical rotations were measured on Perkin-Elmer Model 241 polarimeter. GC/MS was performed on Agilent 6890GC/5973 Mass Selective Detector.

Methyl 6-hydroxycyclohex-1-enecarboxylate (IV-2)

Trimethyl phosphonoacetate (14.4 mL, 100 mmol) was added dropwise to a 50% aqueous solution of gluteraldehyde (**IV-1**) (60.1 g, 150 mmol) through an addition funnel over 2 hours. Simultaneously, 2.5 mL of an aqueous solution of potassium carbonate (31.0 g, 225 mmol in 38 mL H_2O) was added dropwise through a second addition funnel. After the addition of trimethyl

phosphonoacetate was complete, the remainder of the potassium carbonate solution was added over 2 hours. The resulting solution was stirred at room temperature for 4 days. 1 N HCl (250 mL) was then added to the solution and extracted with diethyl ether. The combined organic layers were dried with Mg_2SO_4 and concentrated *in vacuo*. The resulting compound was purified by column chromatography on silica gel, with hexanes/ethyl acetate (30-40% ethyl acetate) to afford the carboxylate (**IV-2**) in 21% yield (3.24 g, 20.7 mmol), as a colorless oil.

2-(Hydroxymethyl)cyclohex-2-enol (IV-3)[1]

To a solution of **IV-2** (3.07 g, 19.7 mmol) dissolved in toluene (100 mL) and cooled to -78 ^oC was added DIBAL-H (1.01 M, 65.6 mL, 78.8 mmol) over a period of 20 min. The reaction mixture was stirred for 1.5 hour at -78 ^oC. To this solution was added MeOH (1.0 mL) and saturated Rochelle's salt. Then ethyl acetate was added and the organic layer was washed with water, dried over Mg_2SO_4 and concentrated *in vacuo*. The crude was then purified by column chromatography on silica get using hexanes/ethyl acetate (30% ethyl acetate) to obtain the diol **IV-3** (1.09 g, 43% yield), as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 1.52-2.17 (m, 6H), 2.31 (s, 1H), 2.48 (s, 1H), 4.19 (dt, J_1 = 12.0 Hz, J_2 = 5.7 Hz, 2H), 4.31 (br s, 1H), 5.82 (t, $J_1 = J_2$ = 3.9 Hz, 1 H). All data were in agreement with the reported values.[1]

2-[Triisopropylsilyloxy)methyl]cyclohex-2-enol (IV-4)[1]

To a solution of **IV-3** (1.09 g, 8.5 mmol) and imidazole (1.74 g, 25.5 mmol) dissolved in THF (8 mL) and cooled to 0 ^oC was added TIPSCl (2.0 mL, 9.4 mmol) over a period of 20 min. The reaction was stirred for 16 h at 0 ^oC. The solution was quenched with NH_4Cl, extracted with diethyl ether, dried over Mg_2SO_4 and then concentrated *in vacuo*. The crude was purified by column chromatography on silica gel. Elution with hexanes/ethyl acetate (2-10% ethyl acetate) afforded the TIPS-protected alcohol **IV-4** (2.16 g, 89 % yield), as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ1.05-1.10 (m, 21 H), 1.59 (s, 3H), 1.68-1.87 (m, 3H), 3.16 (d, J = 2.4 Hz, 1H), 4.21-4.39 (m, 3H), 5.75 (t, $J_1 = J_2$ = 3.3 Hz, 1H). All data were in agreement with the reported values.[1]

2-[Triisopropylsilyloxy)methyl]cyclohex-2-en-1-yl vinyl carbonate (IV-5)[1]

To a solution of **IV-4** (2.13 g, 7.5 mmol) dissolved in DCM and pyridine (1 mL) cooled to 0 ^{o}C was added vinyl chloroformate (1.1 mL, 11.2 mmol). The reaction was stirred at 0 ^{o}C for 1 h. The solvent was removed and the residue was purified by column chromatography on silica gel. Elution with hexanes gave the carbonate **IV-5** (2.26 g, 85% yield), as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.02-1.09 (m, 21H), 1.64-1.84 (m, 3H), 1.98-2.13 (m, 3H), 4.14 (dd, J_1 = 12.9 Hz, J_2 = 1.5 Hz, 1H), 4.24 (dd, J_1 = 13.2 Hz, J_2 = 2.1 Hz, 1H), 4.55 (dd, J_1 = 6.0 Hz, J_2 = 2.1 Hz, 1H), 4.89 (dd, J_1= 14.1 Hz, J_2= 1.8 Hz, 1H), 5.29 (t, J_1 = J_2 = 3.6 Hz, 1H), 6.03 (q, J = 1.5 Hz, 1H), 6.09 (dd, J_1 =13.8 Hz, J_2 = 6.0 Hz, 1H). All data were in agreement with the reported values.[1]

***N*-Tosyl-2-bromoaniline (IV-7)[10]**

2-Bromoaniline (**IV-6**) (3.44 g, 20.0 mmol) and *p*-toluenesulfonyl chloride (3.82 g, 20 mmol) were cooled to 0 ^{o}C. Pyridine (30 mL) was added to the mixture under nitrogen. The reaction was stirred for 16 h at room temperature. The solvent was removed. The residue was extracted using DCM and water. The aqueous layer was washed 3 times using DCM. The combined organic layers were dried over Mg_2SO_4 and concentrated *in vacuo*. The crude was recrystallized using methanol to obtain **IV-7** (4.05 g, 62% yield), as a white solid: m.p. 93-95 ^{o}C ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.38 (s, 3H), 6.94-7.25 (m, 4H), 7.27-7.68 (m, 5H). All data were in agreement with the reported values.[10]

General procedure for Asymmetric Allylic Amination (IV-9)

(*S*)-BOP-1-Nap (174 mg, 0.20 mmol) and $Pd_2(dba)_3$ (60 mg, 0.065 mmol) were added to a single use test tube equipped with a stir bar. Air was replaced by N_2 by means of five evacuation/refill cycles. DMF (39 mL) was added to the mixture and the solution was stirred for 30 minutes. Carbonate **IV-5** and tosyl amine **IV-7** were combined together and diluted with DMF (10 mL). The reaction was stirred at room temperature for 21 hours. The solution was diluted with diethyl ether and extracted with water. The aqueous layer was extracted 3 times. The

organic layer was washed 3 times with brine. The combined organic layers were dried with Mg_2SO_4 and concentrated *in vacuo* to afford the crude. The crude was purified by column chromatography on silica gel using hexanes/ethyl acetate (5-10% ethyl acetate) to afford **IV-9** (1.55 g, quantitative yield), as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.99-1.14 (m, 21H), 1.55-1.81 (m, 4H), 2.42 (s, 3H), 3.68-3.80 (m, 2H), 4.54-4.61 (m , 1H), 5.99 (s, 1H), 6.91-6.94 (m, 1H), 7.15-7.26 (m, 6H), 7.58-7.67 (m, 3H); HPLC condition (Chiralcel OJ, Hexanes/IPA (80:20), 1mL/min), t_R= 11.2, 20.2 min. All data were in agreement with the reported values.[8]

Representative procedure for Intramolecular Heck Reaction (IV-12)

Silver carbonate (1.96 g, 7.1 mmol) was added to a mixture containing **IV-9** (1.41 g, 2.4 mmol), $Pd(OAc)_2$ (80 mg, 0.36 mmol) and dppp (147 mg, 0.36 mmol) in a single use test tube. Air was replaced by N_2 by means of five evacuation/refill cycles. Toluene (24 mL) was added to the mixture and the solution was stirred at 110 ^{o}C equipped with condenser for 16 hours. The solvent was concentrated *in vacuo*. The crude was purified by column chromatography on silica gel using hexanes/ethyl acetate (5% ethyl acetate) to afford **IV-12** in 85% yield (1.03 g, 2.0 mmol) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.79-0.93 (m, 18H), 1.56 (s, 3H), 1.75-1.89 (m, 1H), 2.01-2.08 (m, 2H), 2.21-2.26 (m, 1H), 2.34 (s, 3H), 2.92 (dd, J_1 = 29.4 Hz, J_2 = 9.0 Hz, 2H), 4.11 (dd, J_1 = 10.5 Hz, J_2 = 5.4 Hz, 1H), 5.92 (s, 2H), 6.95-7.09 (m, 2H), 7.17-7.24 (m, 3H), 7.68-7.72 (m, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 11.7, 17.8, 21.4, 21.9, 28.2, 50.6, 64.3, 70.0, 115.5, 123.5, 124.8, 126.7, 127.6, 128.2, 128.9, 129.6, 135.6, 135.7, 139.7, 143.6; HPLC condition (Chiralpack AD, Hexanes/IPA (98.5:1.5), 1mL/min), t_r= 5.2, 7.4 min; $C_{29}H_{41}NO_3SSi$ (M= 511.79) FIA *m/z* 512.2 (M+1)

(9-Tosyl-2,4a,9,9a-tetrahydro-1H-carbazol-4a-yl)methanol (IV-13)

To a solution of **IV-12** (523 mg, 1.0 mmol) dissolved in THF (21 mL) at -20 ^{o}C for 5 minutes was added tetrabutylammonium fluoride (TBAF) (2.05 mL, 2.0 mmol). The resulting solution was allowed to stir at -20 ^{o}C for 17 hours. The solvent was evaporated. The residue was extracted with ether and water. The combined organic layers were dried with Mg_2SO_4 and concentrated *in vacuo*. The crude was purified by column chromatography on silica gel using

hexanes/ethyl acetate (10-20% ethyl acetate) to afford **IV-13** (216 mg, 61% yield), as a yellow oil, which solidifies into a waxy solid over time: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26-1.30 (m, 1H), 1.73-1.83 (m, 1H), 2.04-2.10 (m, 2H), 2.22-2.29 (m, 1H), 2.36 (s, 3H), 2.38 (s, 1H), 5.71-5.74 (m, 1H), 6.10-6.14 (m, 1H), 6.89-7.03 (m, 2H), 7.20-7.26 (m, 3H), 7.69-7.72 (m, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 21.5, 22.0, 28.2, 51.2, 63.6, 68.4, 116.2, 123.6, 126.2, 126.9, 128.6, 129.6, 132.2, 134.8, 135.4, 140.0, 144.0; $C_{20}H_{21}NO_3S$ (M=355.45) FIA *m/z* 356.1 (M+1)

(9-Tosyl-2,4a,9,9a-tetrahydro-1H-carbazol-4a-yl)methyl methanesulfonate (IV-15)

To a solution of **IV-13** (145 mg, 0.41 mmol) dissolved in DCM (1.5 mL) cooled to 0 ^{o}C was added TEA (0.11 mL, 0.82 mmol) and MsCl (0.04 mL, 0.49 mmol). The resulting solution was stirred for 30 minutes at 0 ^{o}C. The ice bath was removed and the solution was stirred at room temperature for 1.5 hours. The solution was extracted with ethyl acetate. The organic layer was washed with water. The combined organic layers were dried with Mg_2SO_4 and concentrated *in vacuo*. The crude was recrystallized with hexanes and DCM to afford **IV-15** (125 mg, 71% yield), as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.82-1.83 (m, 1H), 2.07-2.11 (m, 2H), 2.20-2.26 (m, 1H), 2.37 (s, 3H), 2.67 (s, 3H), 3.06 (d, J = 9.9 Hz, 1H), 3.46 (d, J = 9.9 Hz, 1H), 4.26 (dd, J_1 = 10.8 Hz, J_2 = 5.4 Hz, 1H), 5.75 (dt, J_1 = 9.9 Hz, J_2 = 1.5 Hz, 1H), 6.03-6.09 (m, 1H), 7.04-7.07 (m, 2H), 7.24-7.25 (m, 1H), 7.26-7.31 (m, 2H), 7.68-7.74 (m, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 22.0, 28.0, 37.4, 48.8, 64.0, 73.1, 116.6, 124.5, 125.2, 126.9, 129.6, 130.2, 131.8, 133.4, 135.4, 140.3, 144.8; $C_{21}H_{23}NO_5S_2$ (M=433.54) FIA *m/z* 451.0 (M+18)

2-(9-tosyl-2,4a,9,9a-tetrahydro-1H-carbazol-4a-yl)acetonitrile (IV-16)

To a solution of **IV-15** (26 mg, 0.06 mmol) and 18-crown-6-ether (47 mg, 0.18 mmol) in acetonitrile (0.6 mL) was added potassium cyanide (13.5 mg, 2.1 mmol). The solution was stirred at 75 ^{o}C for 64 hours, and then subjected to microwave heating at 90 ^{o}C for 3 hours and at 100 ^{o}C for 21 hours. The solution was diluted with ethyl acetate and washed with brine (4x50 mL). The combined organic layers were dried with Mg_2SO_4 and concentrated *in vacuo*. The crude was purified by column chromatography on silica gel using hexanes/ethyl acetate (1-10% ethyl acetate) to afford **IV-16** (13.4 mg, 62% yield), as an off-white to brown solid: ^{1}H NMR

(400 MHz, $CDCl_3$) δ 1.35 (d, *J* = 16.4 Hz, 1H), 1.70-1.75 (m, 1H), 1.82 (d, *J* = 16.4 Hz, 1H), 2.13-2.17 (m, 2H), 2.25-2.29 (m, 1H), 2.38 (s, 3H), 4.16 (dd, J_1 = 11.2 Hz, J_2 = 5.2 Hz, 1H), 5.82 (d, *J* = 10.0 Hz, 1H), 6.07-6.11 (m, 1H), 7.05-7.12 (m, 2H), 7.26-7.32 (m, 2H), 7.71-7.74 (m, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 21.8, 22.1, 28.1, 30.9, 46.7, 66.5, 116.6, 117.1, 123.6, 124.9, 125.5, 126.8, 126.9, 129.6, 130.2, 130.3, 131.7. 135.5, 135.7, 139.2, 144.8. All data were in agreement with the reported values.[1] CAUTION: Potassium cyanide should be handled with care.

§ 4.5 References

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Appendix

^{1}H, ^{13}C, ^{31}P NMR Spectra, HPLC trace

PS2CH3 31P

Pulse Sequence s2pul
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Temp 25.0 C / 298.1 K
GEMINI-300BB "gem2300"

Relax delay 1.000 sec
Pulse 70.0 degrees
Acq. time 1.280 sec
Width 31004.9 Hz
40 repetitions
OBSERVE P31 121.4712147 MHz
DECOUPLE H1 300.0735793 MHz
Power 34 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
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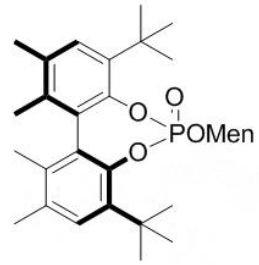
Total time 2 min 21 sec



(*S*)-I-6

PS2CH3 31P

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GEMINI-300BB "gem2300"

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Pulse 70 0 degrees
Acq time 1 280 sec
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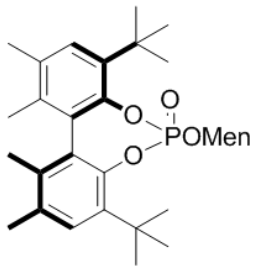

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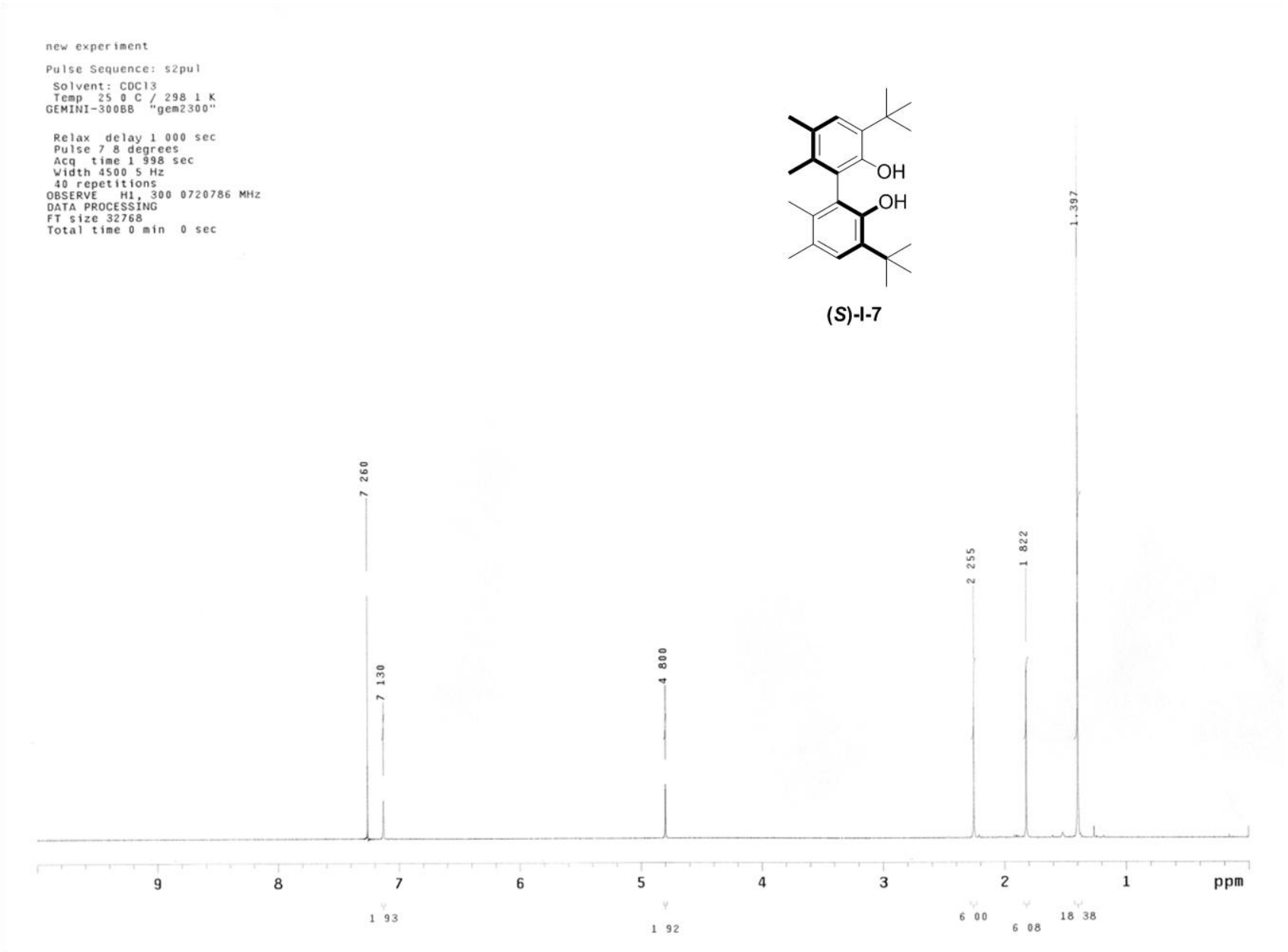
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Pulse 7 8 degrees
Acq time 1 998 sec
Width 4500 5 Hz
40 repetitions
OBSERVE H1, 300 0720786 MHz
DATA PROCESSING
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7 130
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2 255
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8
7
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2
1
ppm
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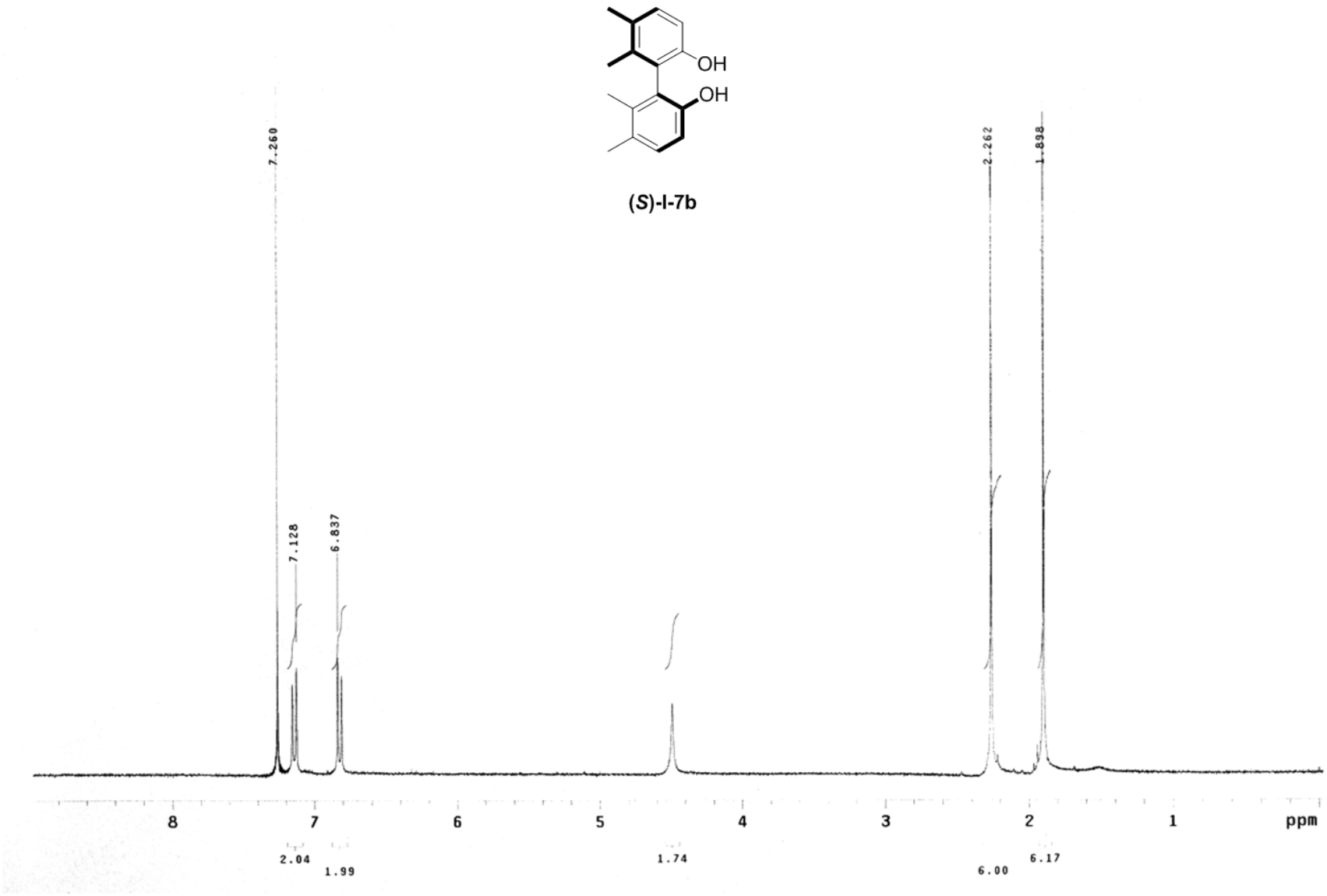
1 92
6 00
6 08
18 38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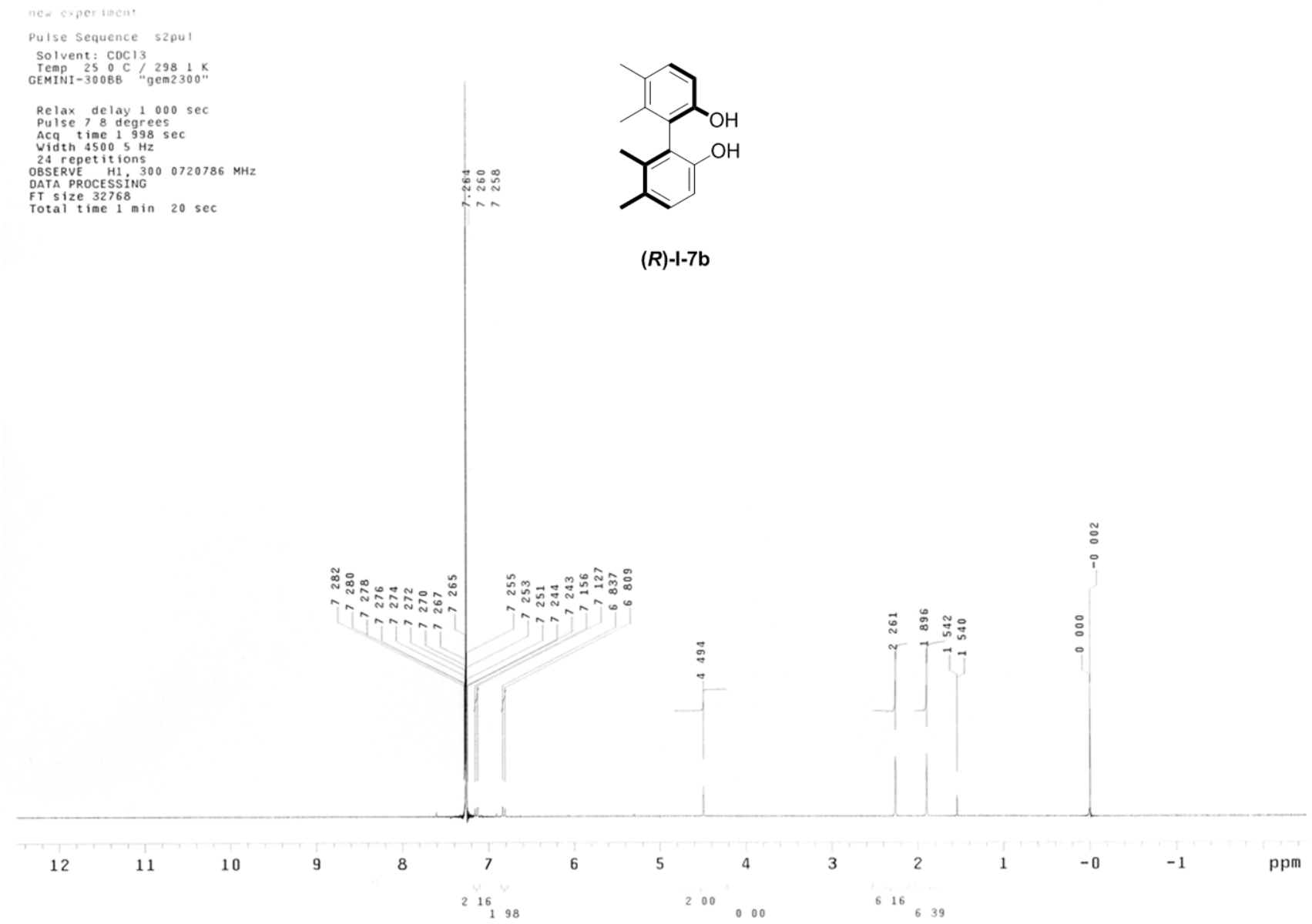
1.74
6.00
6.17


new experiment
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Pulse 7 8 degrees
Acq time 1 998 sec
Width 4500 5 Hz
24 repetitions
OBSERVE H1, 300 0720786 MHz
DATA PROCESSING
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Total time 1 min 20 sec
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7 258
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7 265
7 255
7 253
7 251
7 244
7 243
7 156
7 127
6 837
6 809
4 494
2 261
1 896
1 542
1 540
0 000
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12
11
10
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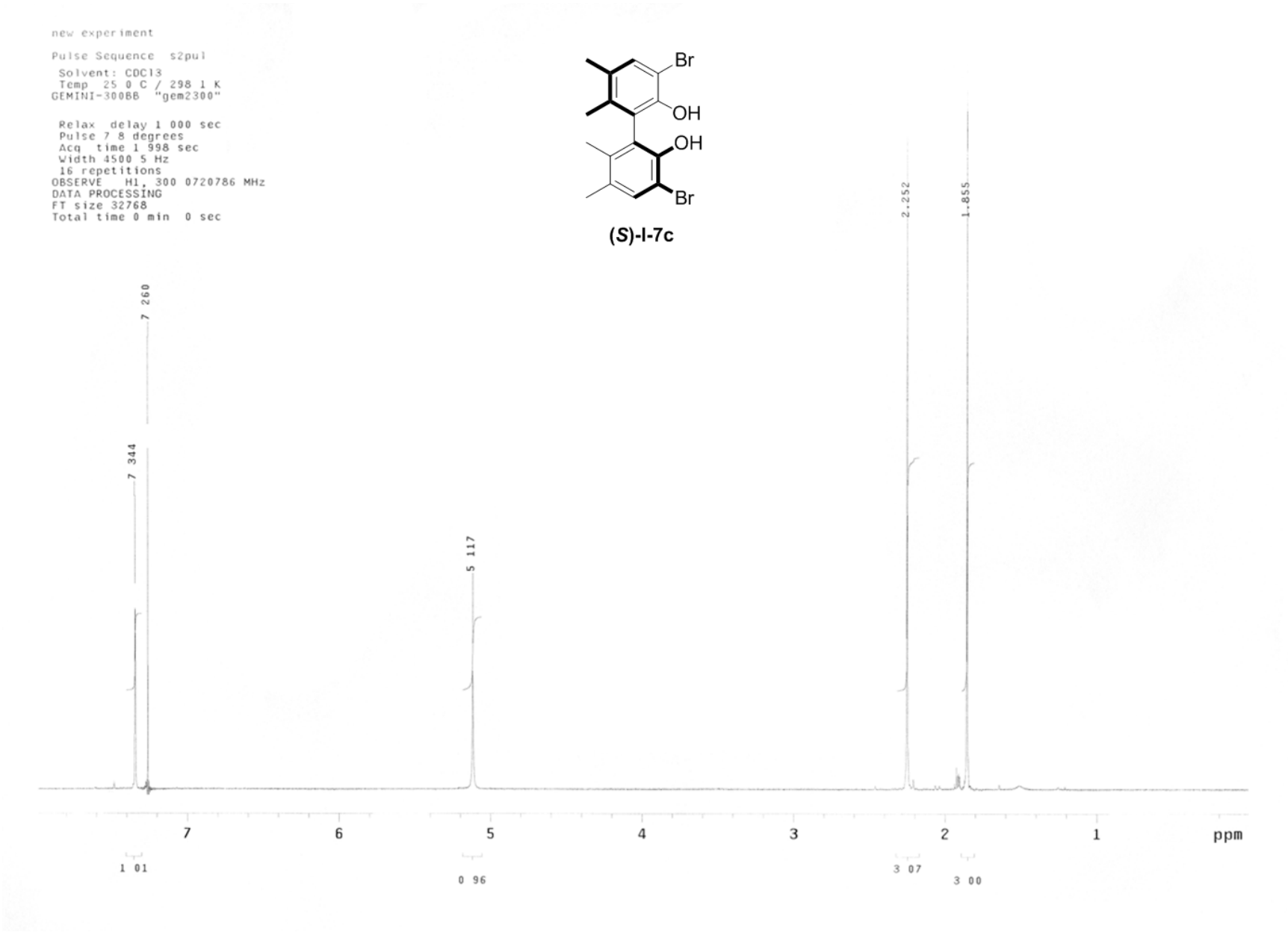
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Relax delay 1 000 sec
Pulse 7 8 degrees
Acq time 1 998 sec
Width 4500 5 Hz
16 repetitions
OBSERVE H1, 300 0720786 MHz
DATA PROCESSING
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Total time 0 min 0 sec
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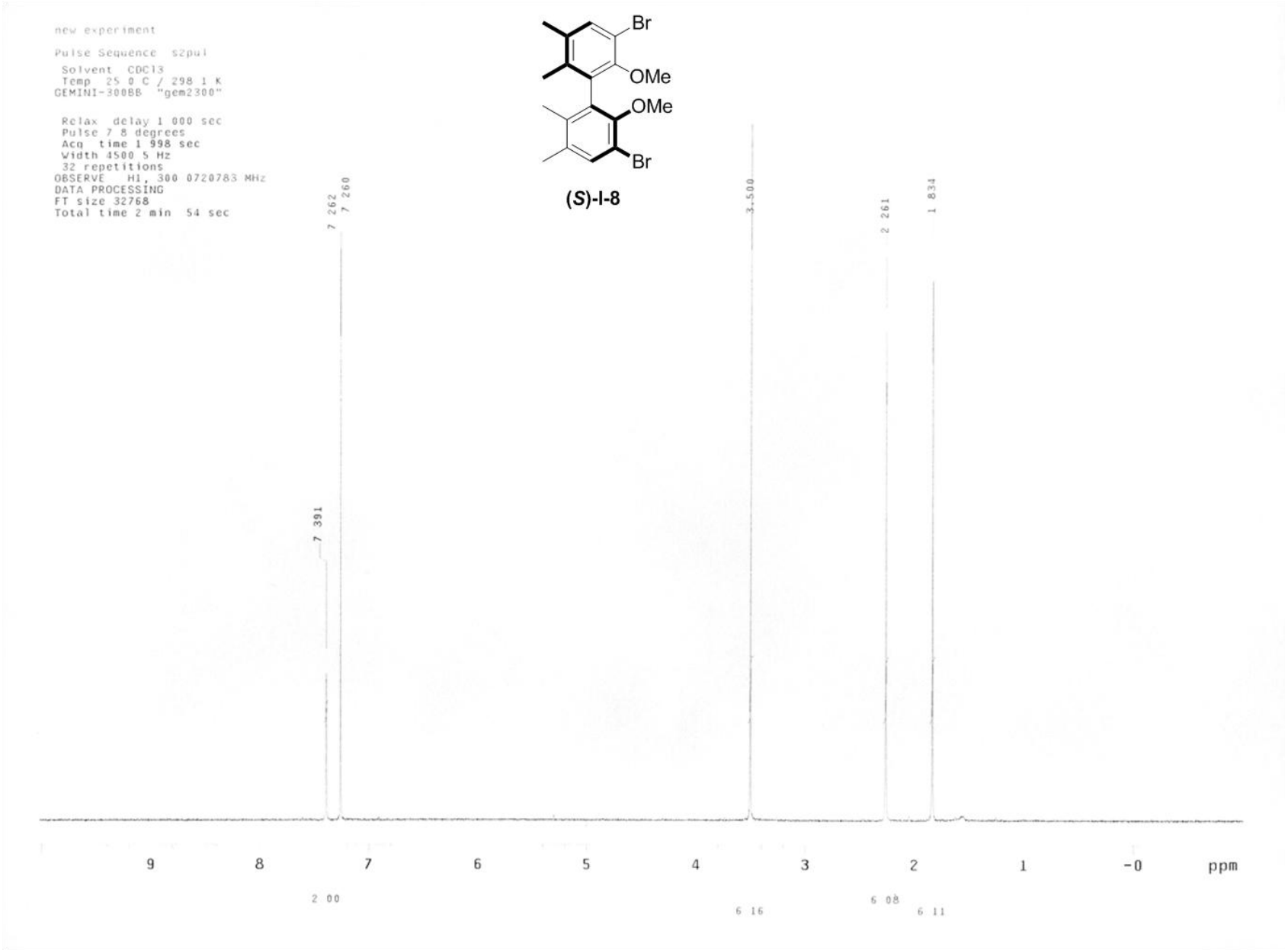
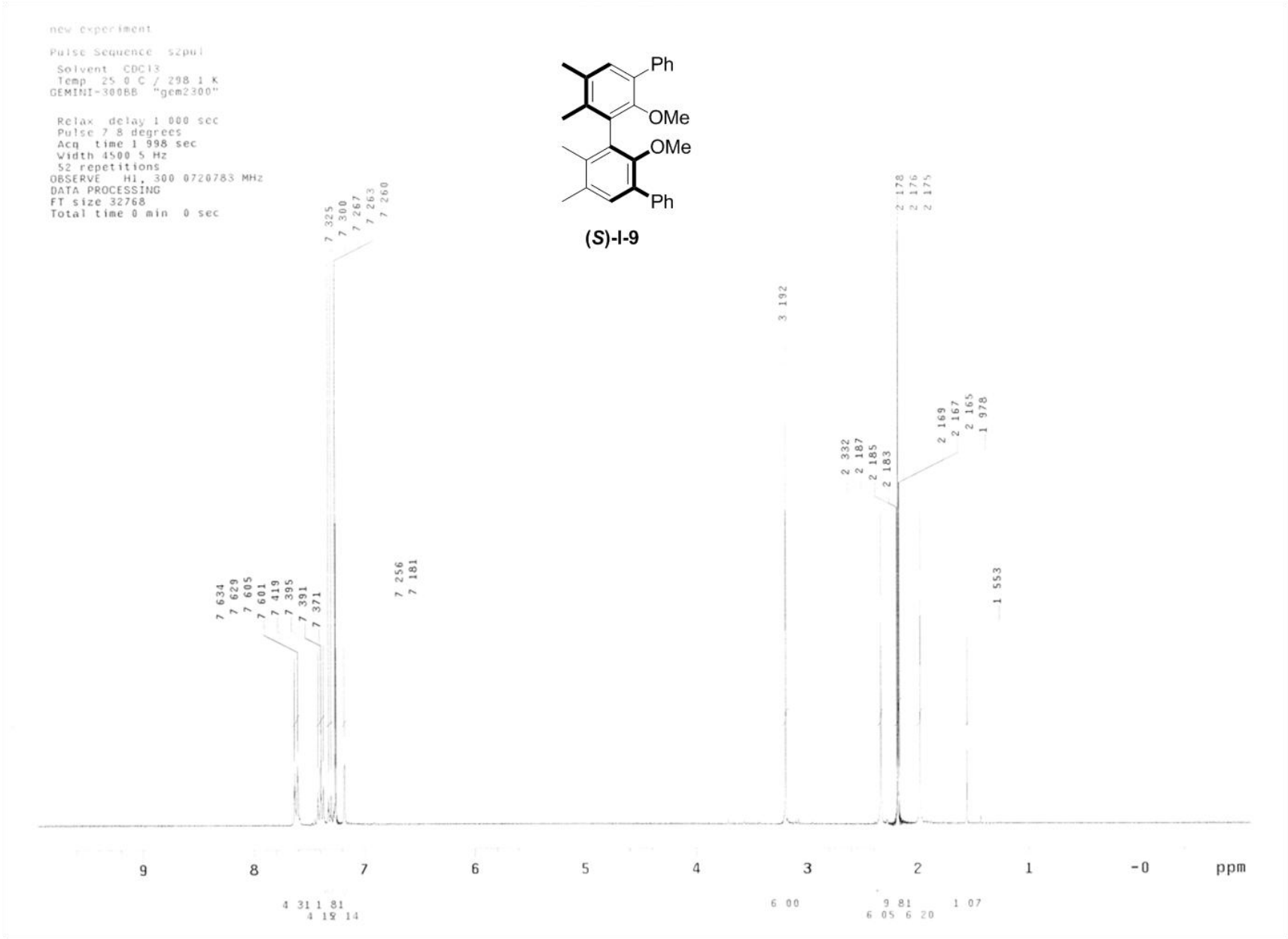
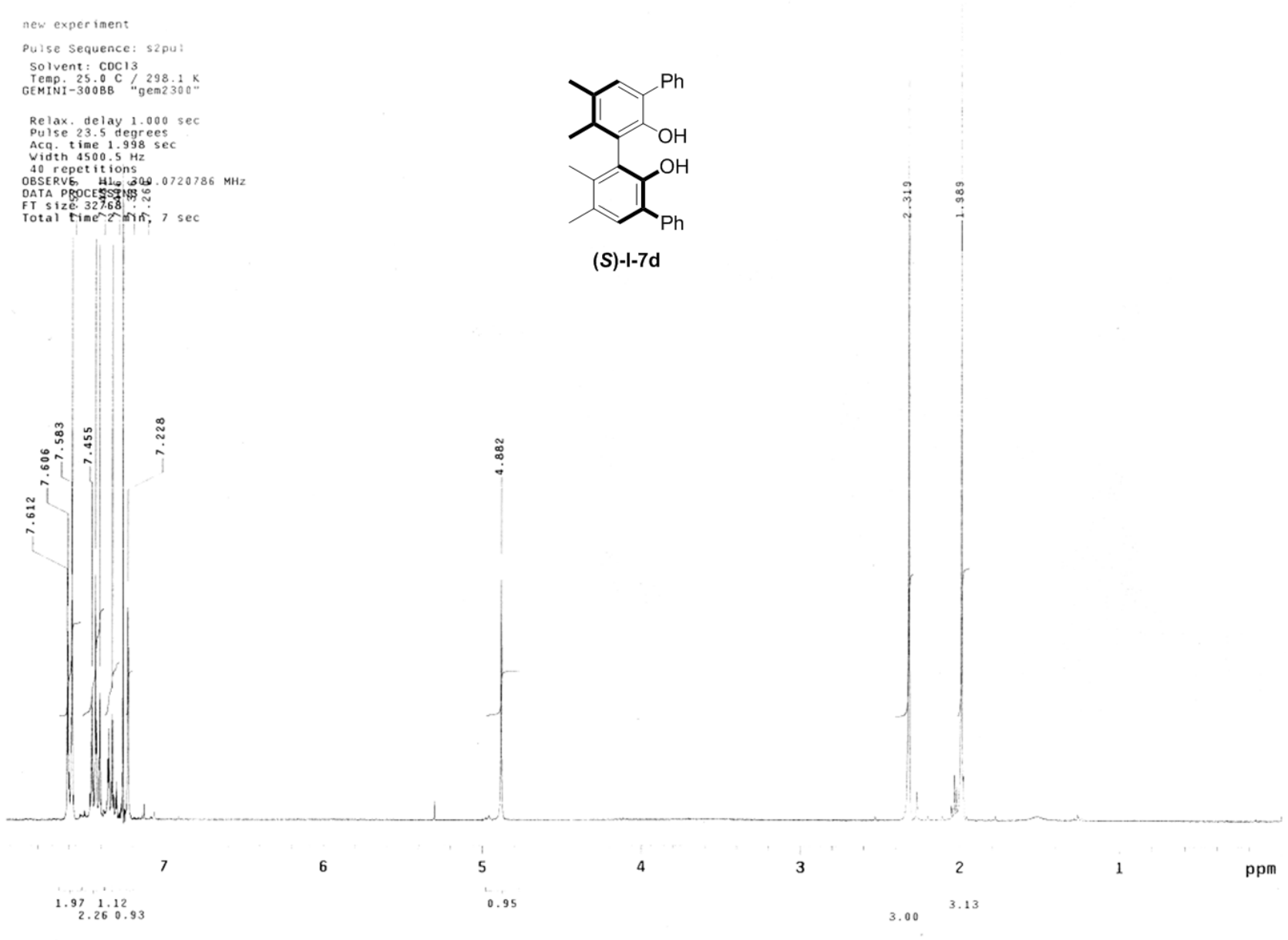
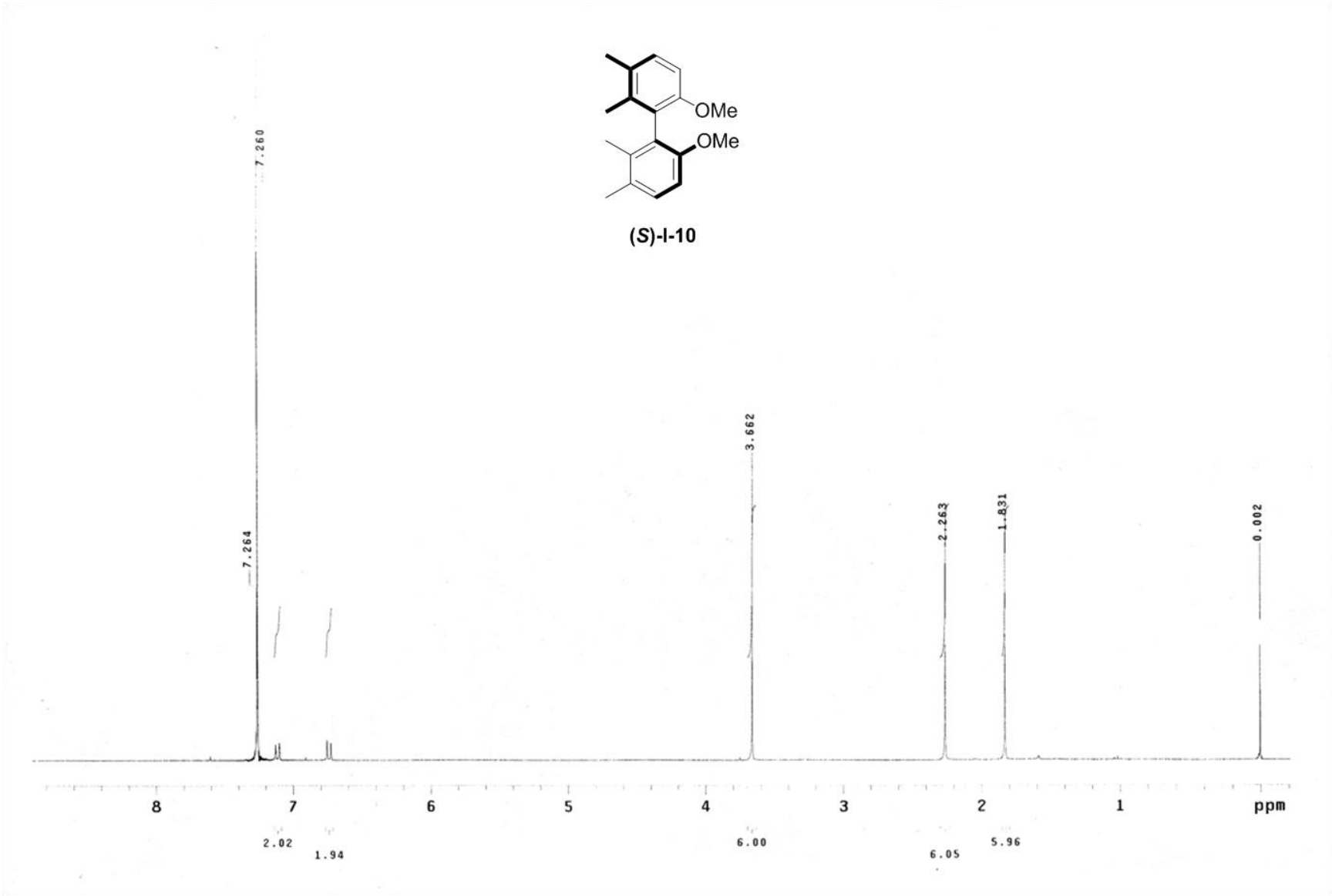
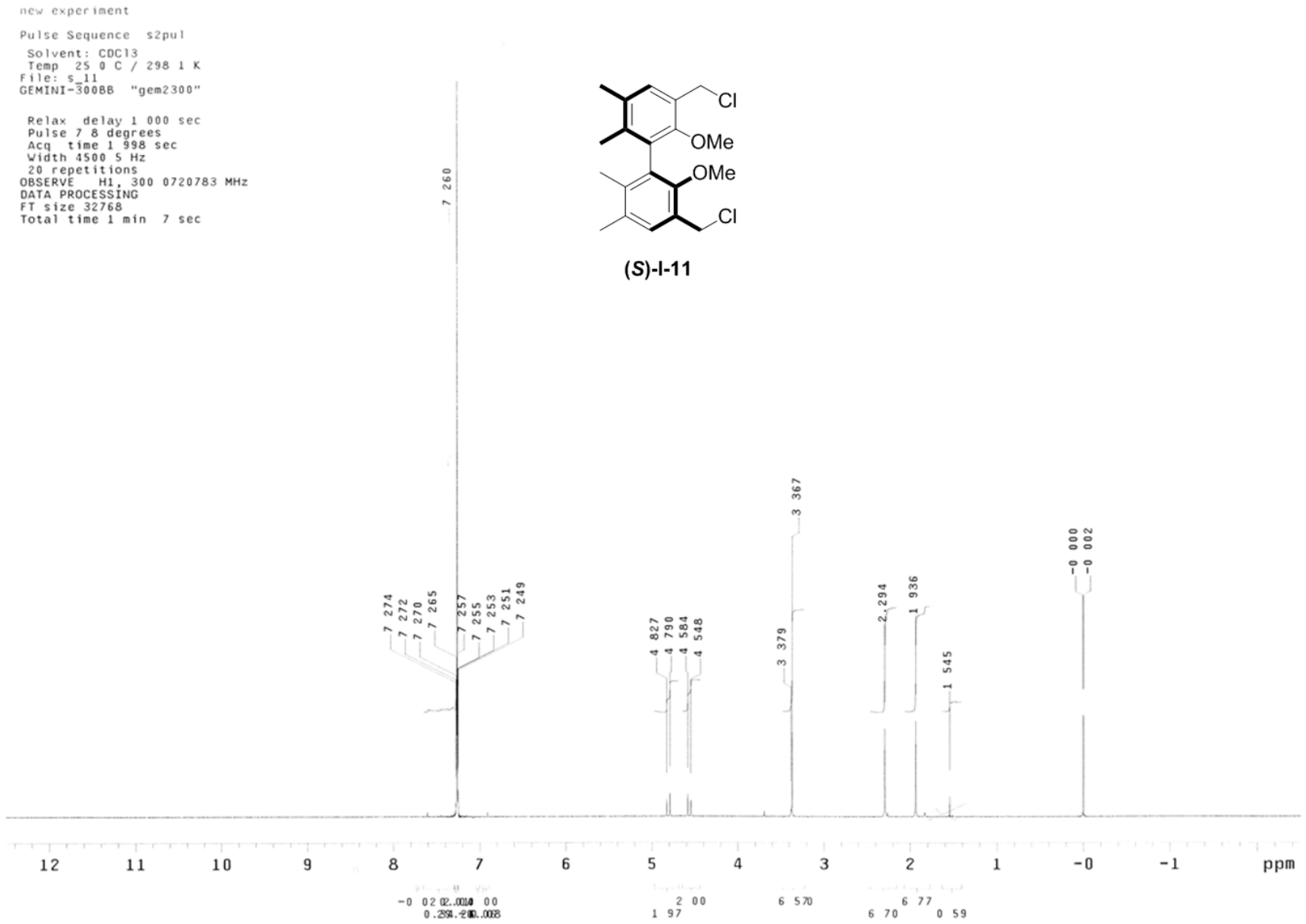
7
6
5
4
3
2
1
ppm
1 01
0 96
3 07
3 00

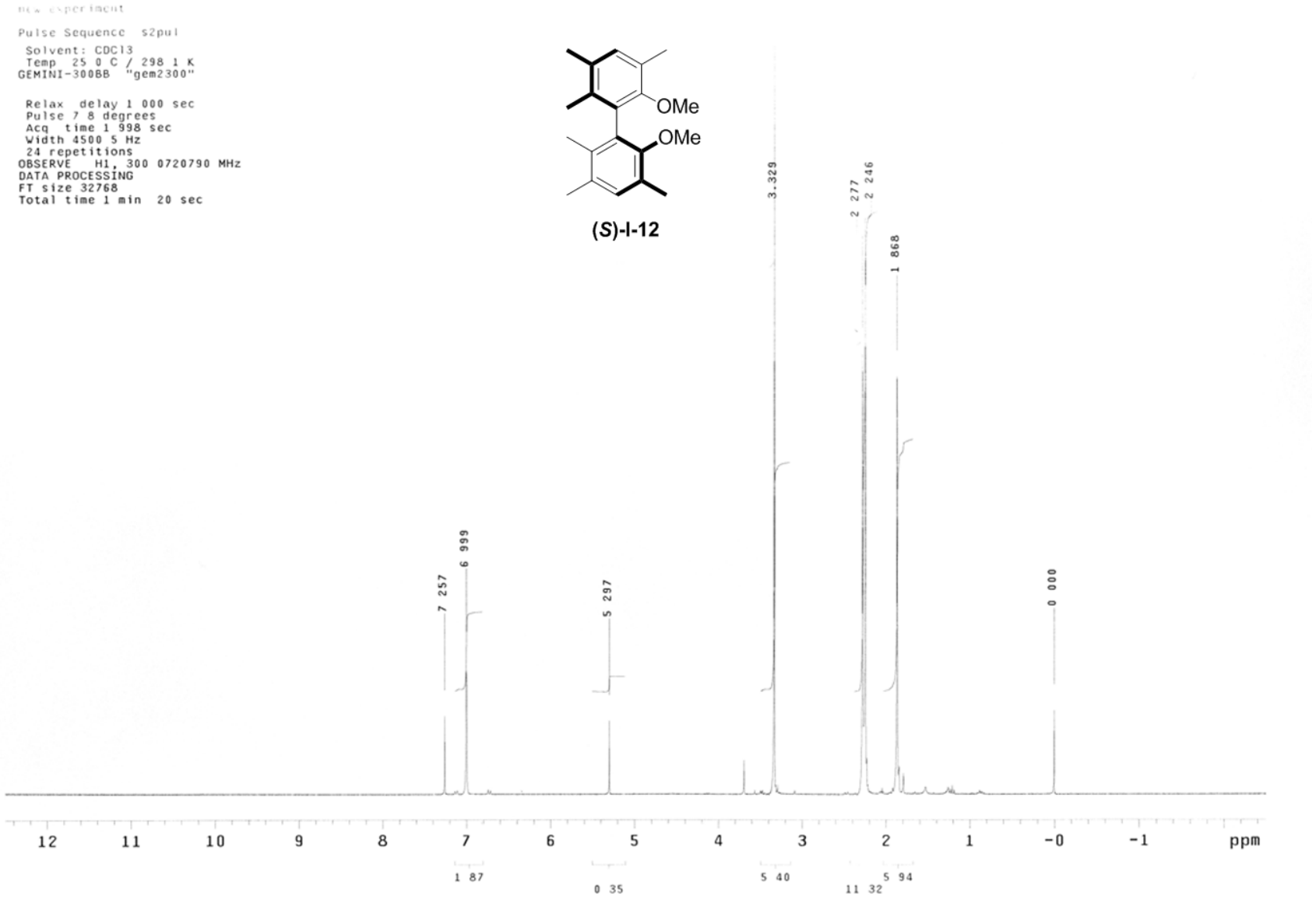

new experiment
Pulse Sequence s2pul
Solvent CDCl3
Temp 25 0 C / 298 1 K
GEMINI-300BB "gem2300"
Relax delay 1 000 sec
Pulse 7 8 degrees
Acq time 1 998 sec
Width 4500 5 Hz
32 repetitions
OBSERVE H1, 300 0720783 MHz
DATA PROCESSING
FT size 32768
Total time 2 min 54 sec
Br
OMe
OMe
Br
(S)-I-8
7 391
7 262
7 260
3.500
2 261
1 834
9
8
7
6
5
4
3
2
1
-0
ppm
2 00
6 16
6 08
6 11

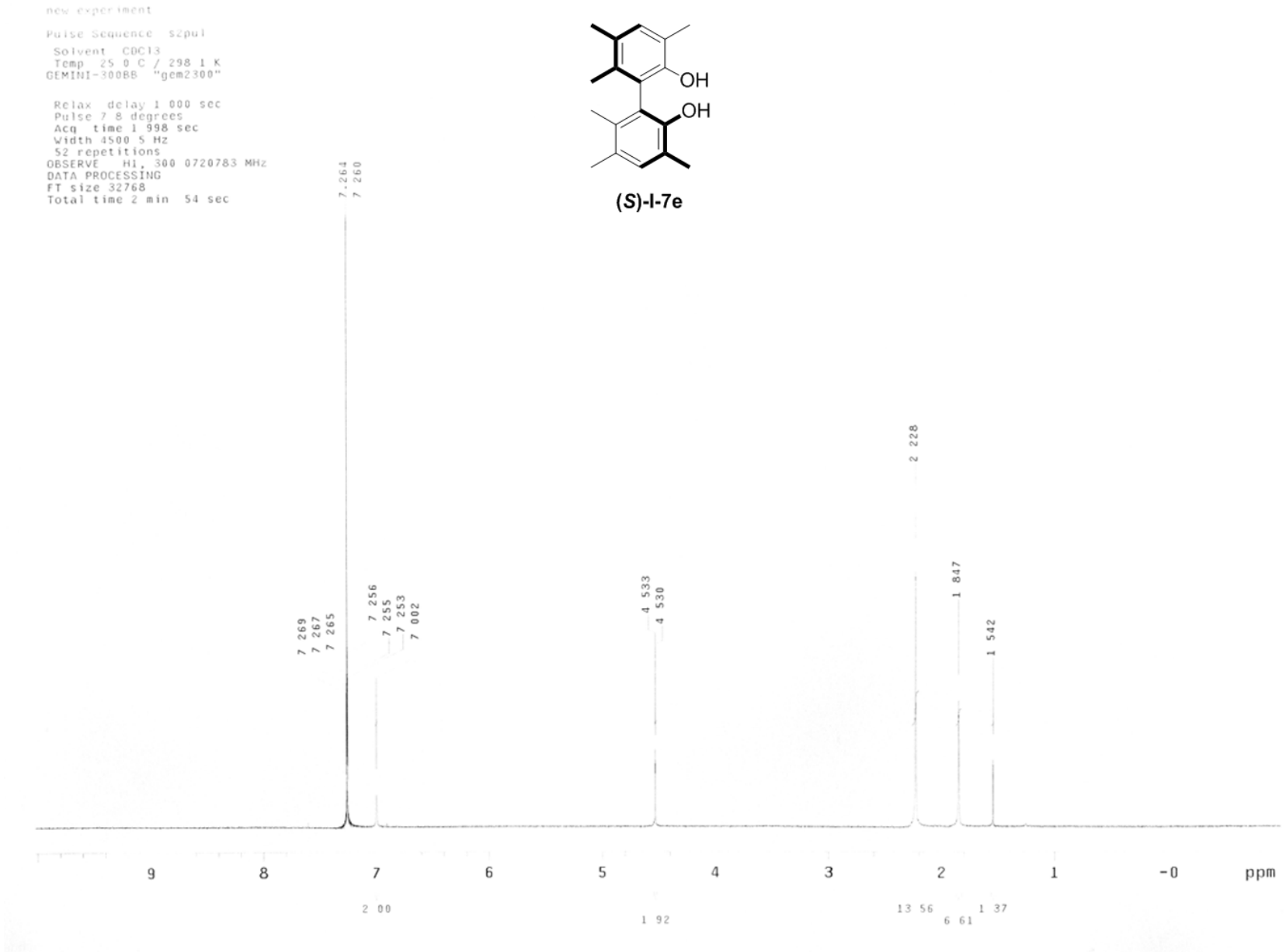

new experiment
Pulse Sequence s2pul
Solvent CDCl3
Temp 25.0 C / 298.1 K
GEMINI-300BB "gem2300"
Relax delay 1.000 sec
Pulse 7.8 degrees
Acq time 1.998 sec
Width 4500.5 Hz
52 repetitions
OBSERVE H1, 300.0720783 MHz
DATA PROCESSING
FT size 32768
Total time 0 min 0 sec
Ph
OMe
OMe
Ph
(S)-I-9
7.325
7.300
7.267
7.263
7.260
7.634
7.629
7.605
7.601
7.419
7.395
7.391
7.371
7.256
7.181
3.192
2.332
2.187
2.185
2.183
2.178
2.176
2.175
2.169
2.167
2.165
1.978
1.553
9
8
7
6
5
4
3
2
1
-0
ppm
4.31
1.81
4.19
2.14
6.00
9.81
6.05
6.20
1.07

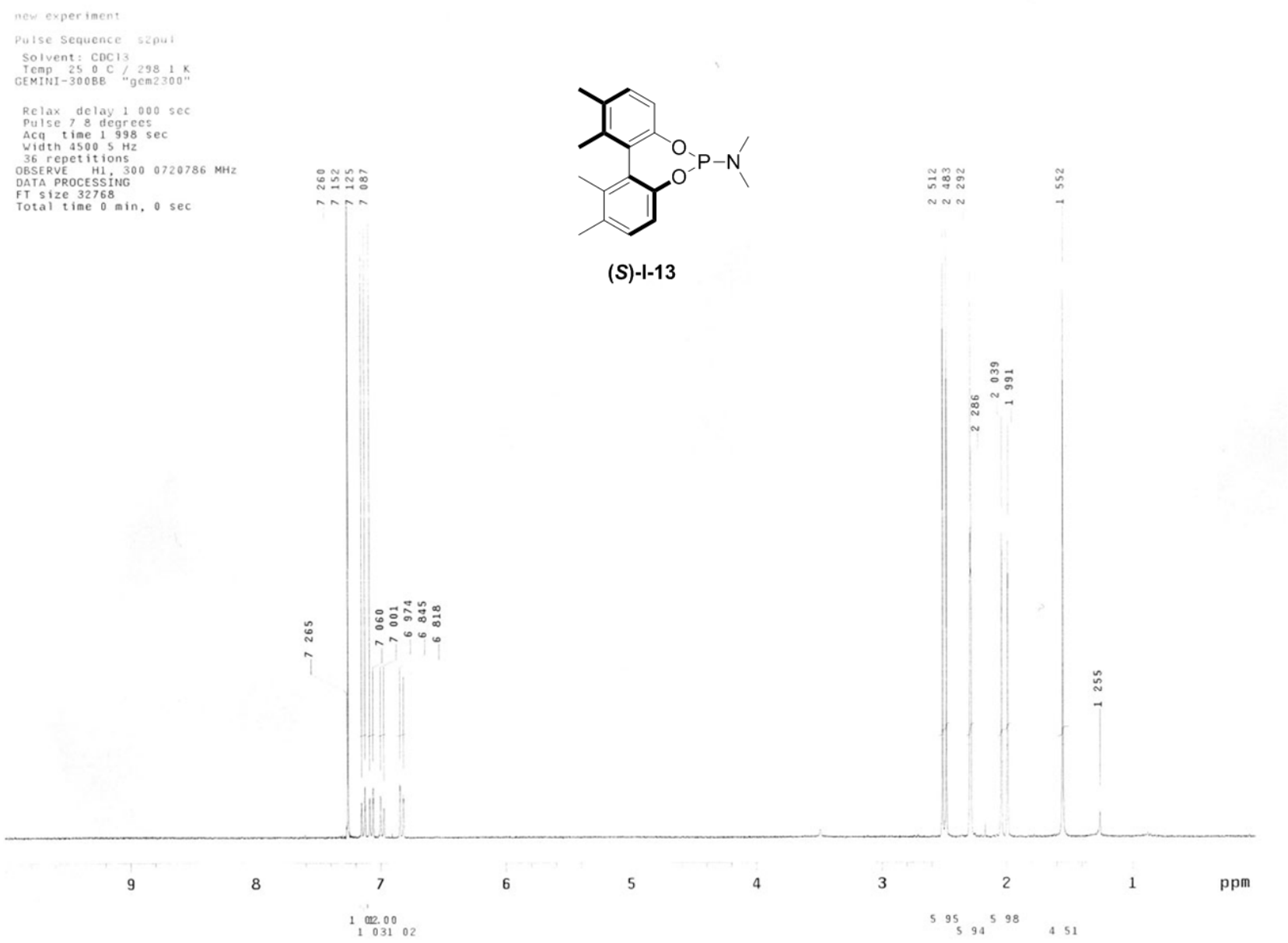

new experiment
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
GEMINI-300BB "gem2300"
Relax. delay 1.000 sec
Pulse 23.5 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
40 repetitions
OBSERVE H1, 300.0720786 MHz
DATA PROCESSING
FT size 32768
Total time 2 min, 7 sec
Ph
OH
OH
Ph
(S)-I-7d
7.612
7.606
7.583
7.455
7.228
4.882
2.319
1.989
7
6
5
4
3
2
1
ppm
1.97 1.12
2.26 0.93
0.95
3.00
3.13

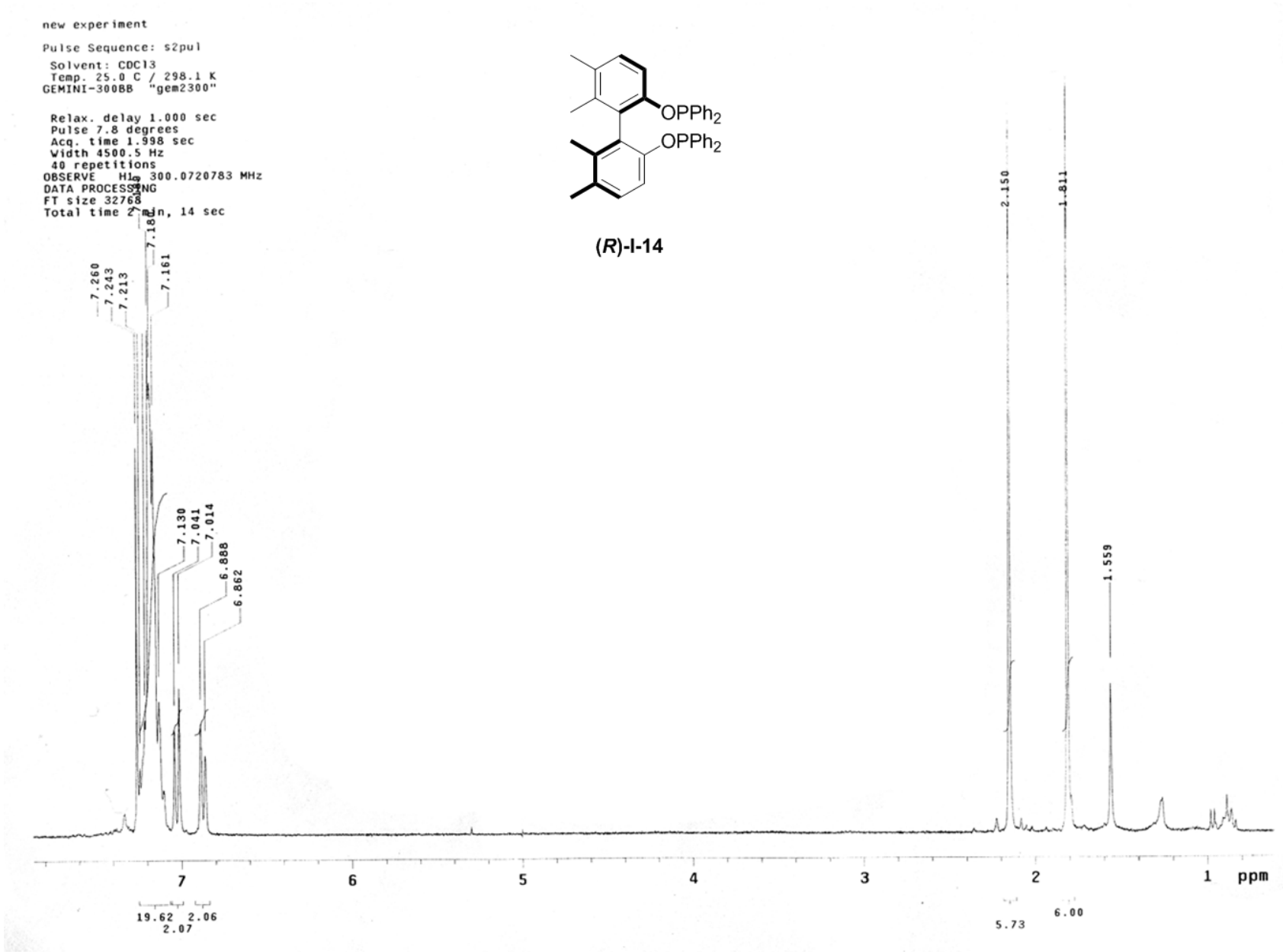

OMe
OMe
(S)-I-10
7.260
7.264
3.662
2.263
1.831
0.002
8
7
6
5
4
3
2
1
ppm
2.02
1.94
6.00
6.05
5.96


new experiment
Pulse Sequence s2pul
Solvent: CDCl3
Temp 25 0 C / 298 1 K
File: s_11
GEMINI-300BB "gem2300"
Relax delay 1 000 sec
Pulse 7 8 degrees
Acq time 1 998 sec
Width 4500 5 Hz
20 repetitions
OBSERVE H1, 300 0720783 MHz
DATA PROCESSING
FT size 32768
Total time 1 min 7 sec
Cl
OMe
OMe
Cl
(S)-I-11
7 260
7 274
7 272
7 270
7 265
7 257
7 255
7 253
7 251
7 249
4 827
4 790
4 584
4 548
3 379
3 367
2 294
1 936
1 545
0 000
0 002
12
11
10
9
8
7
6
5
4
3
2
1
-0
-1
ppm
2 00
1 97
6 570
6 77
6 70
0 59


new experiment
Pulse Sequence s2pul
Solvent: CDCl3
Temp 25.0 C / 298.1 K
GEMINI-300BB "gem2300"
Relax delay 1.000 sec
Pulse 7.8 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
24 repetitions
OBSERVE H1, 300.0720790 MHz
DATA PROCESSING
FT size 32768
Total time 1 min 20 sec
OMe
OMe
(S)-I-12
7.257
6.999
5.297
3.329
2.277
2.246
1.868
0.000
12
11
10
9
8
7
6
5
4
3
2
1
-0
-1
ppm
1.87
0.35
5.40
11.32
5.94


new experiment
Pulse Sequence s2pul
Solvent CDCl3
Temp 25.0 C / 298.1 K
GEMINI-300BB "gem2300"
Relax delay 1.000 sec
Pulse 7.8 degrees
Acq time 1.998 sec
Width 4500.5 Hz
52 repetitions
OBSERVE H1, 300.0720783 MHz
DATA PROCESSING
FT size 32768
Total time 2 min 54 sec
OH
OH
(S)-I-7e
7.264
7.260
7.269
7.267
7.265
7.256
7.255
7.253
7.002
4.533
4.530
2.228
1.847
1.542
9
8
7
6
5
4
3
2
1
-0
ppm
2.00
1.92
13.56
6.61
1.37

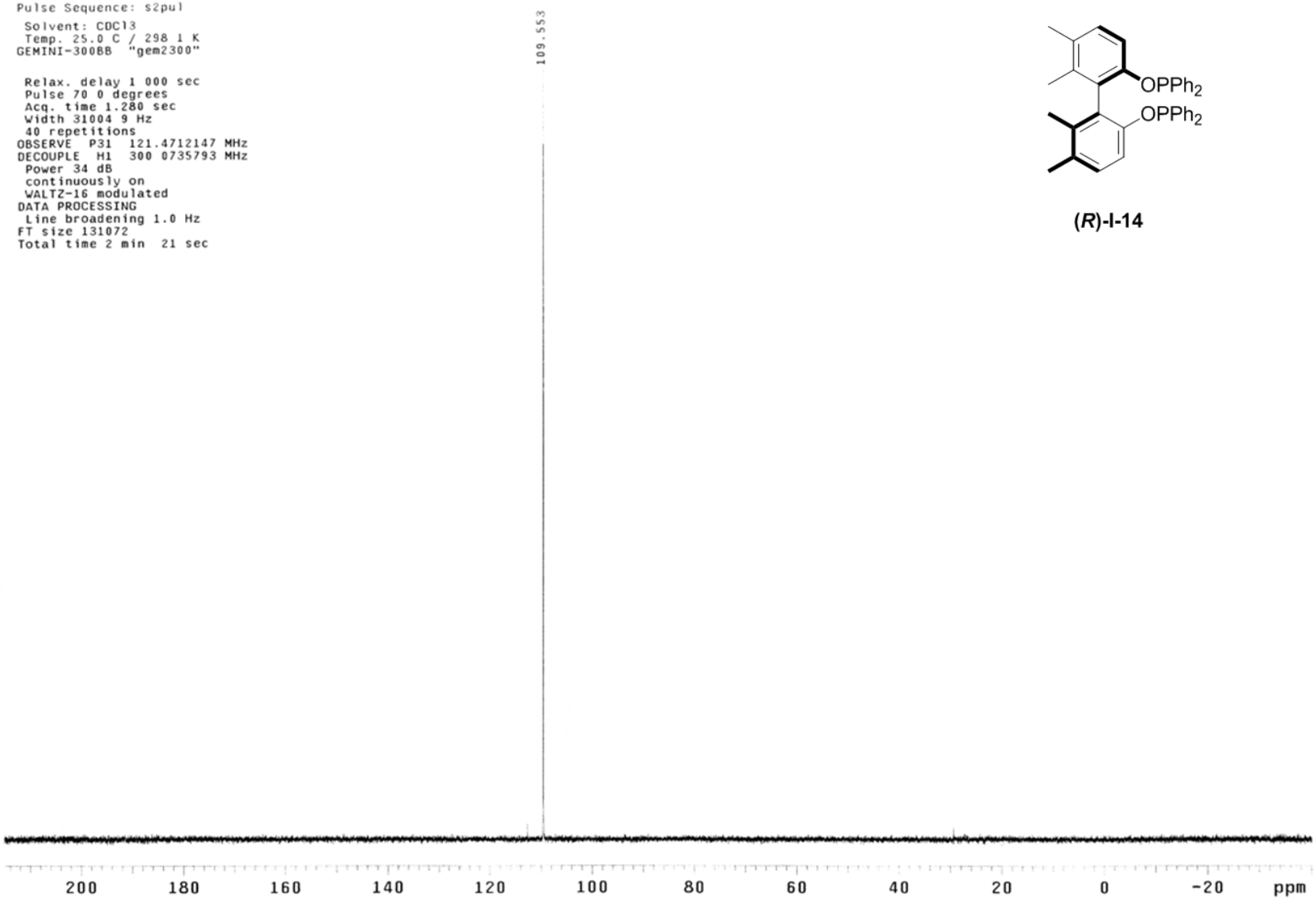

new experiment
Pulse Sequence s2pul
Solvent: CDCl3
Temp 25.0 C / 298.1 K
GEMINI-300BB "gem2300"
Relax delay 1.000 sec
Pulse 7.8 degrees
Acq time 1.998 sec
Width 4500.5 Hz
36 repetitions
OBSERVE H1, 300.0720786 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 0 sec
7.260
7.152
7.125
7.087
7.265
7.060
7.001
6.974
6.845
6.818
2.512
2.483
2.292
2.286
2.039
1.991
1.552
1.255
O
P
N
O
(S)-I-13
9
8
7
6
5
4
3
2
1
ppm
1.00
1.031
2.00
5.95
5.94
5.98
4.51


new experiment
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
GEMINI-300BB "gem2300"
Relax. delay 1.000 sec
Pulse 7.8 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
40 repetitions
OBSERVE H1, 300.0720783 MHz
DATA PROCESSING
FT size 32768
Total time 2 min, 14 sec
OPPh2
OPPh2
(R)-I-14
7.260
7.243
7.213
7.184
7.161
7.130
7.041
7.014
6.888
6.862
2.150
1.811
1.559
7
6
5
4
3
2
1
ppm
19.62
2.07
2.06
5.73
6.00

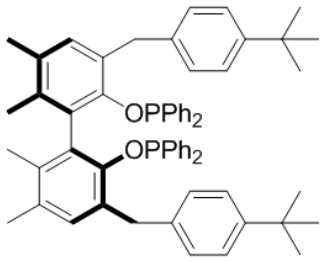
PS2CH3 31P

Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298 1 K
GEMINI-300BB "gem2300"

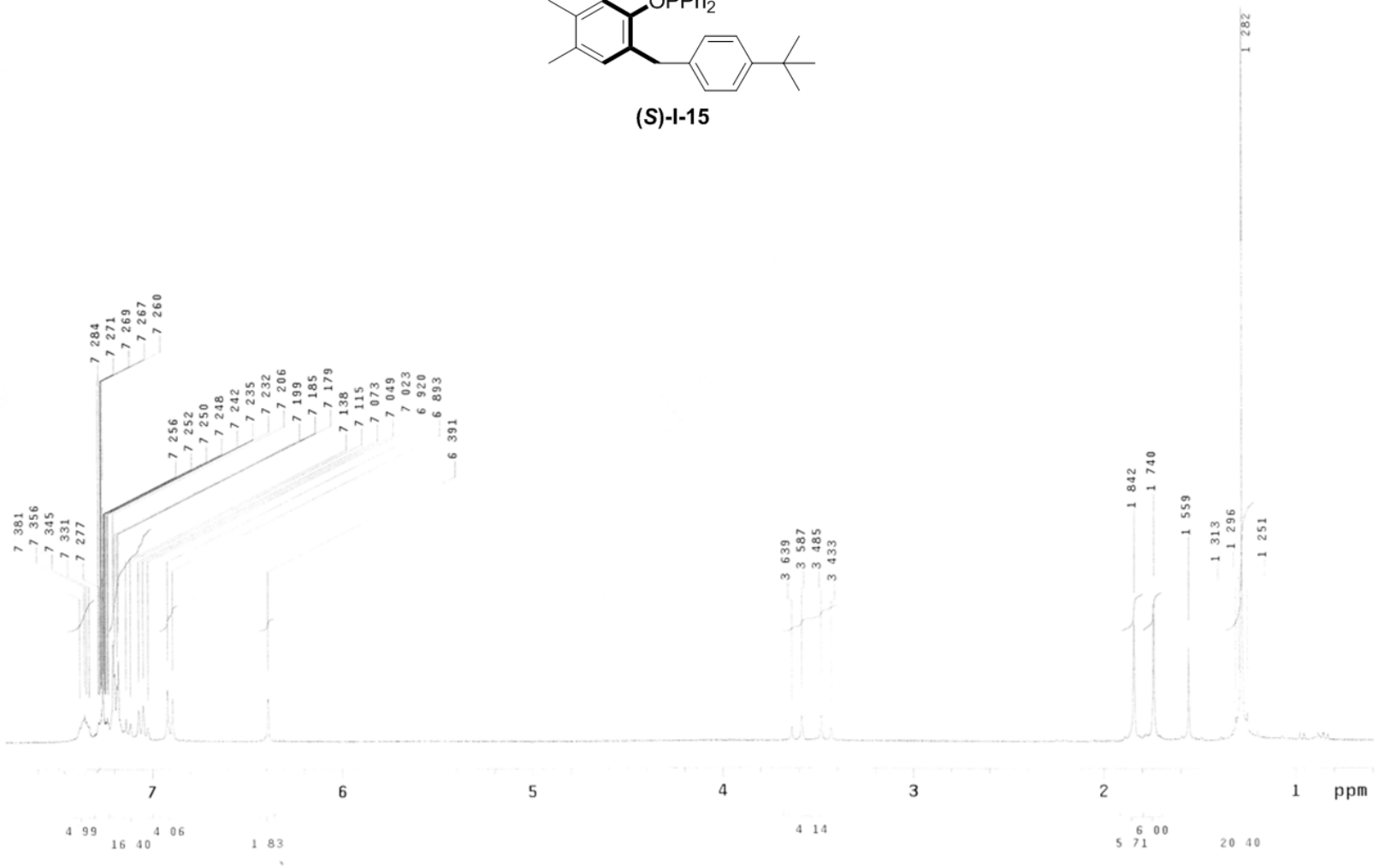
Relax. delay 1 000 sec
Pulse 70 0 degrees
Acq. time 1.280 sec
Width 31004 9 Hz
40 repetitions
OBSERVE P31 121.4712147 MHz
DECOUPLE H1 300 0735793 MHz
Power 34 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 2 min 21 sec

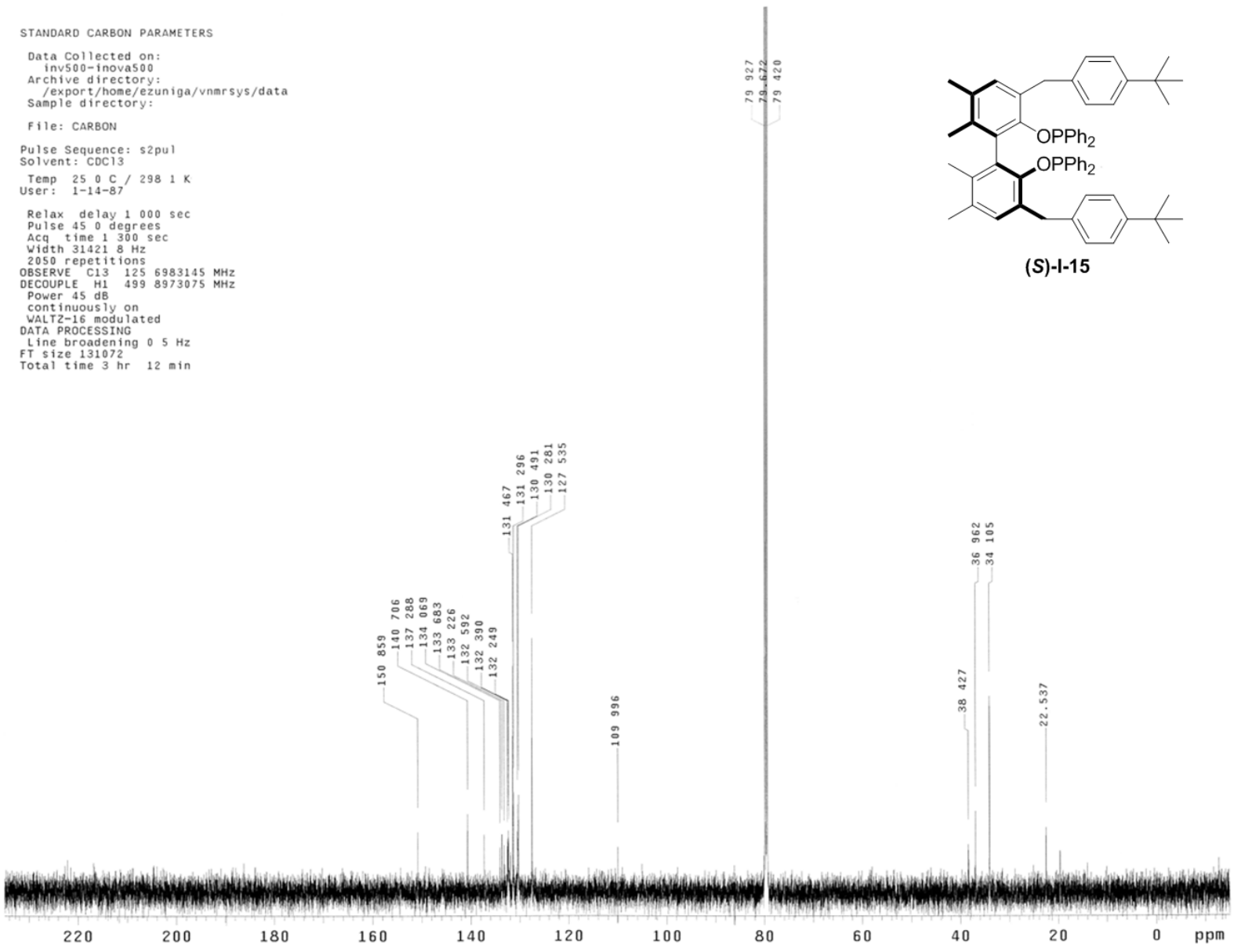


(*R*)-I-14


OPPh2
OPPh2

(*S*)-I-15


7.381
7.356
7.345
7.331
7.277
7.284
7.271
7.269
7.267
7.260
7.256
7.252
7.250
7.248
7.242
7.235
7.232
7.206
7.199
7.185
7.179
7.138
7.115
7.073
7.049
7.023
6.920
6.893
6.391
3.639
3.587
3.485
3.433
1.842
1.740
1.559
1.313
1.296
1.282
1.251
7
6
5
4
3
2
1
ppm
4.99
4.06
16.40
1.83
4.14
6.00
5.71
20.40


STANDARD CARBON PARAMETERS
Data Collected on:
inv500-inova500
Archive directory:
/export/home/ezuniga/vnmrsys/data
Sample directory:
File: CARBON
Pulse Sequence: s2pul
Solvent: CDCl3
Temp 25 0 C / 298 1 K
User: 1-14-87
Relax delay 1 000 sec
Pulse 45 0 degrees
Acq time 1 300 sec
Width 31421 8 Hz
2050 repetitions
OBSERVE C13 125 6983145 MHz
DECOUPLE H1 499 8973075 MHz
Power 45 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0 5 Hz
FT size 131072
Total time 3 hr 12 min
79 927
78 622
79 420
OPPh2
OPPh2
(S)-I-15
150 859
140 706
137 288
134 069
133 683
133 226
132 592
132 390
132 249
131 467
131 296
130 491
130 281
127 535
109 996
38 427
36 962
34 105
22.537
220
200
180
160
140
120
100
80
60
40
20
0
ppm

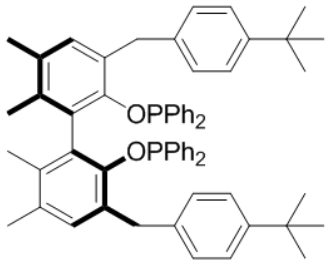
PS2CH3 31P

Pulse Sequence s2pul

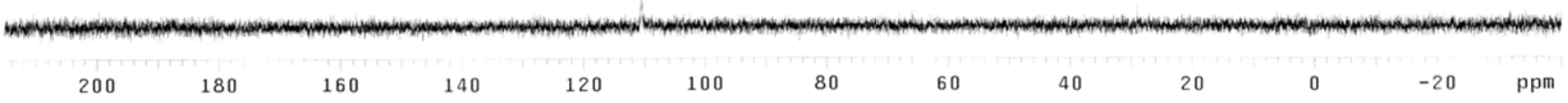
Solvent: CDCl3
Temp 25 0 C / 298 1 K
GEMINI-300BB "gem2300"

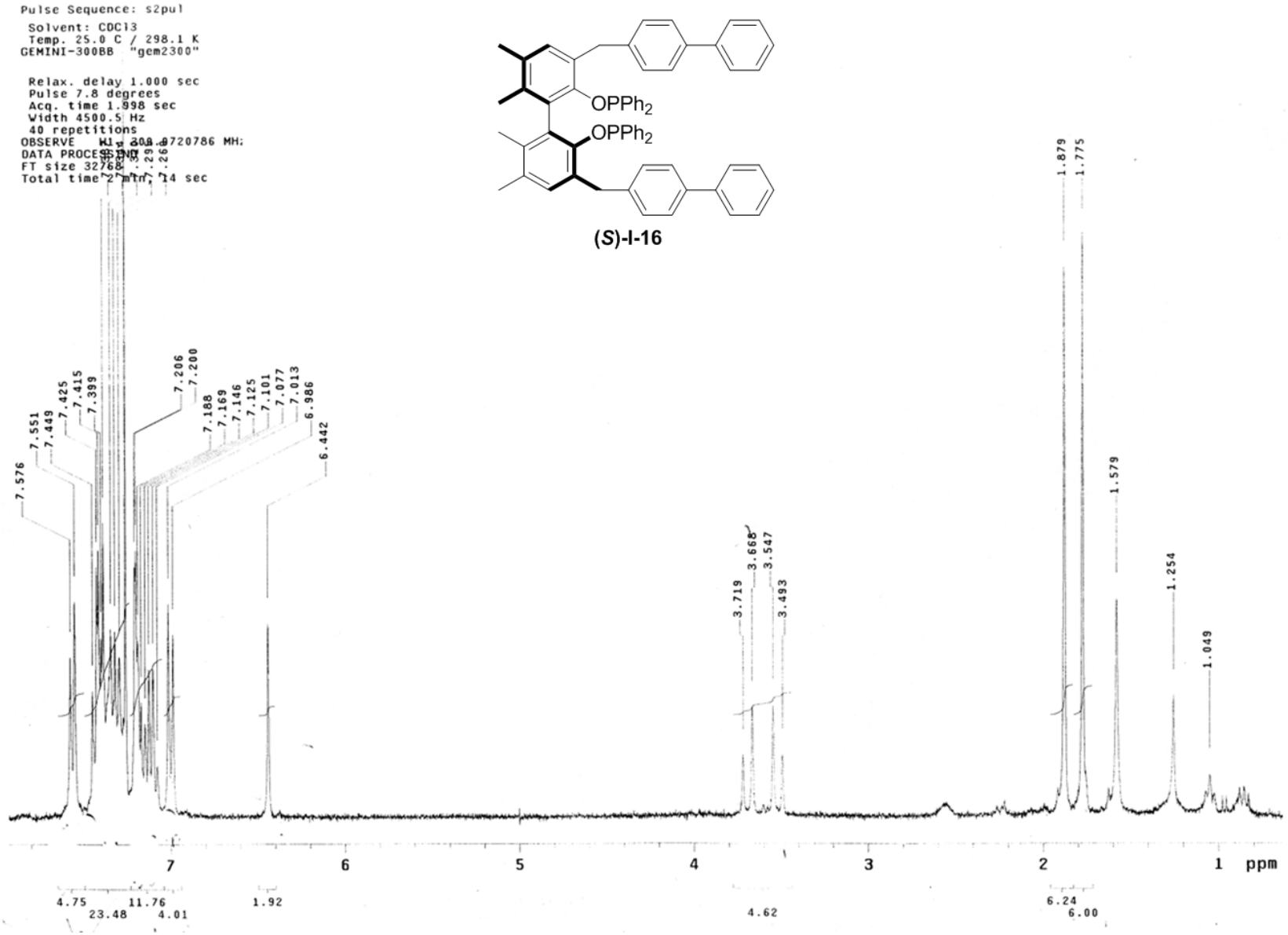
Relax delay 1 000 sec
Pulse 70 0 degrees
Acq time 1 280 sec
Width 31004 9 Hz
40 repetitions
OBSERVE P31 121 4712147 MHz
DECOUPLE H1 300 0735793 MHz
Power 34 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1 0 Hz
FT size 131072
Total time 2 min 21 sec

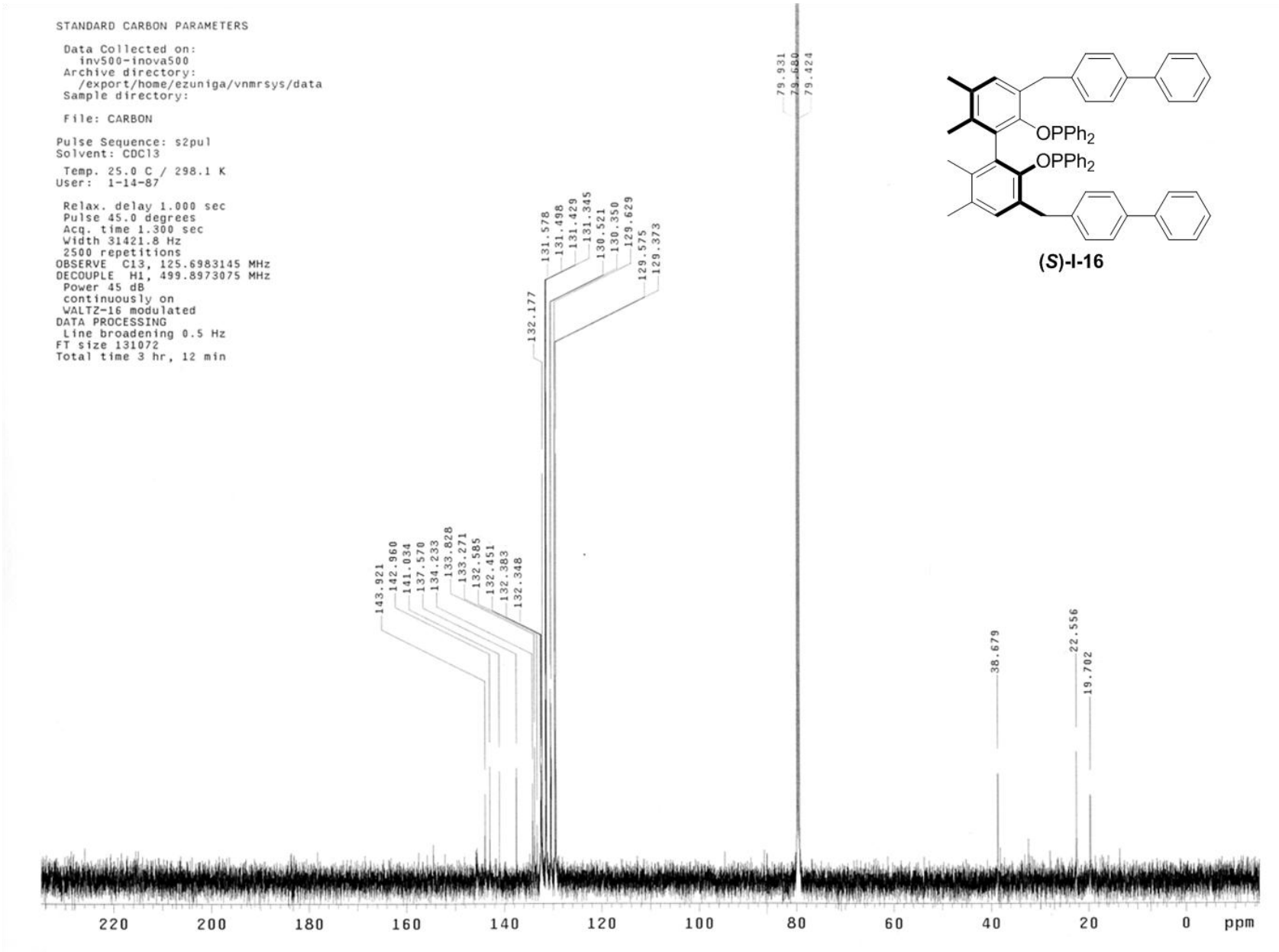
110 472



(*S*)-I-15




Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
GEMINI-300BB "gem2300"
Relax. delay 1.000 sec
Pulse 7.8 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
40 repetitions
OBSERVE H1, 300.0720786 MHz
DATA PROCESSING
FT size 32768
Total time 2 min, 14 sec
OPPh2
OPPh2
(S)-I-16
7.576
7.551
7.449
7.425
7.415
7.399
7.206
7.200
7.188
7.169
7.146
7.125
7.101
7.077
7.013
6.986
6.442
3.719
3.668
3.547
3.493
1.879
1.775
1.579
1.254
1.049
7
6
5
4
3
2
1
ppm
4.75
23.48
11.76
4.01
1.92
4.62
6.24
6.00

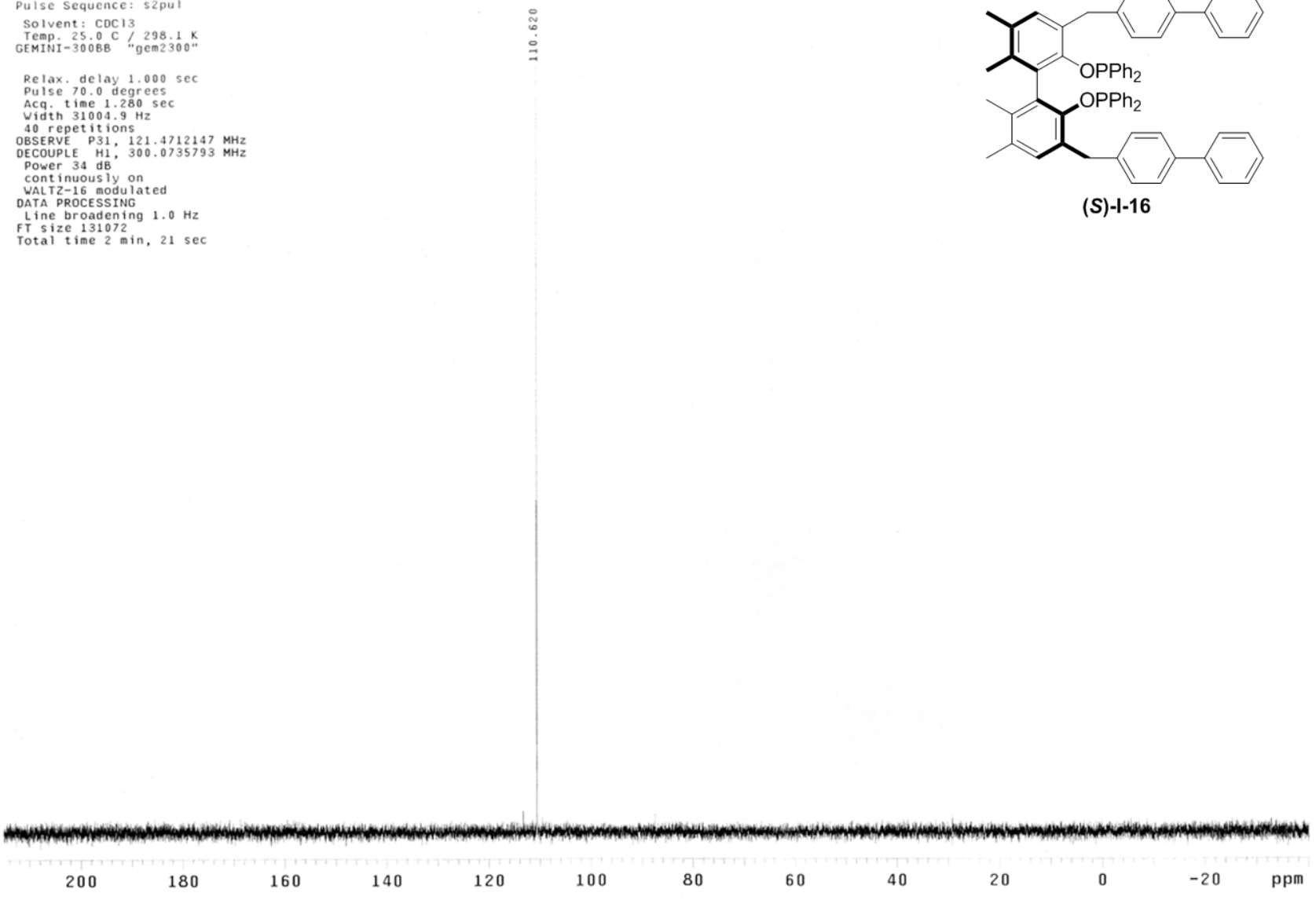

STANDARD CARBON PARAMETERS
Data Collected on:
inv500-inova500
Archive directory:
/export/home/ezuniga/vnmrsys/data
Sample directory:
File: CARBON
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
User: 1-14-87
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 31421.8 Hz
2500 repetitions
OBSERVE C13, 125.6983145 MHz
DECOUPLE H1, 499.8973075 MHz
Power 45 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 3 hr, 12 min
79.931
79.680
79.424
131.578
131.498
131.429
131.345
130.521
130.350
129.629
129.575
129.373
132.177
143.921
142.960
141.034
137.570
134.233
133.828
133.271
132.585
132.451
132.383
132.348
38.679
22.556
19.702
OPPh2
OPPh2
(S)-I-16
220
200
180
160
140
120
100
80
60
40
20
0
ppm

PS2CH3 31P

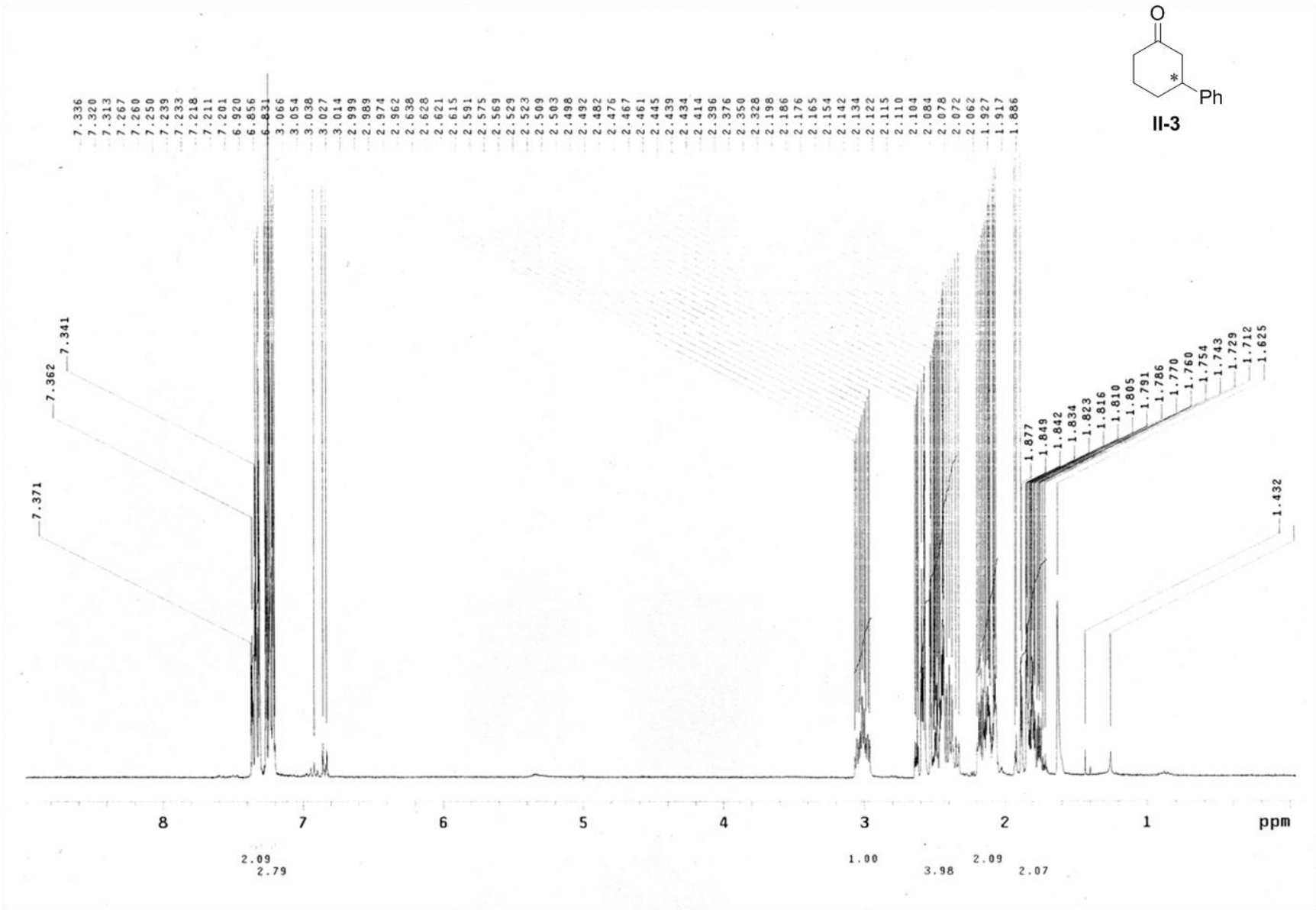
Pulse Sequence: s2pul

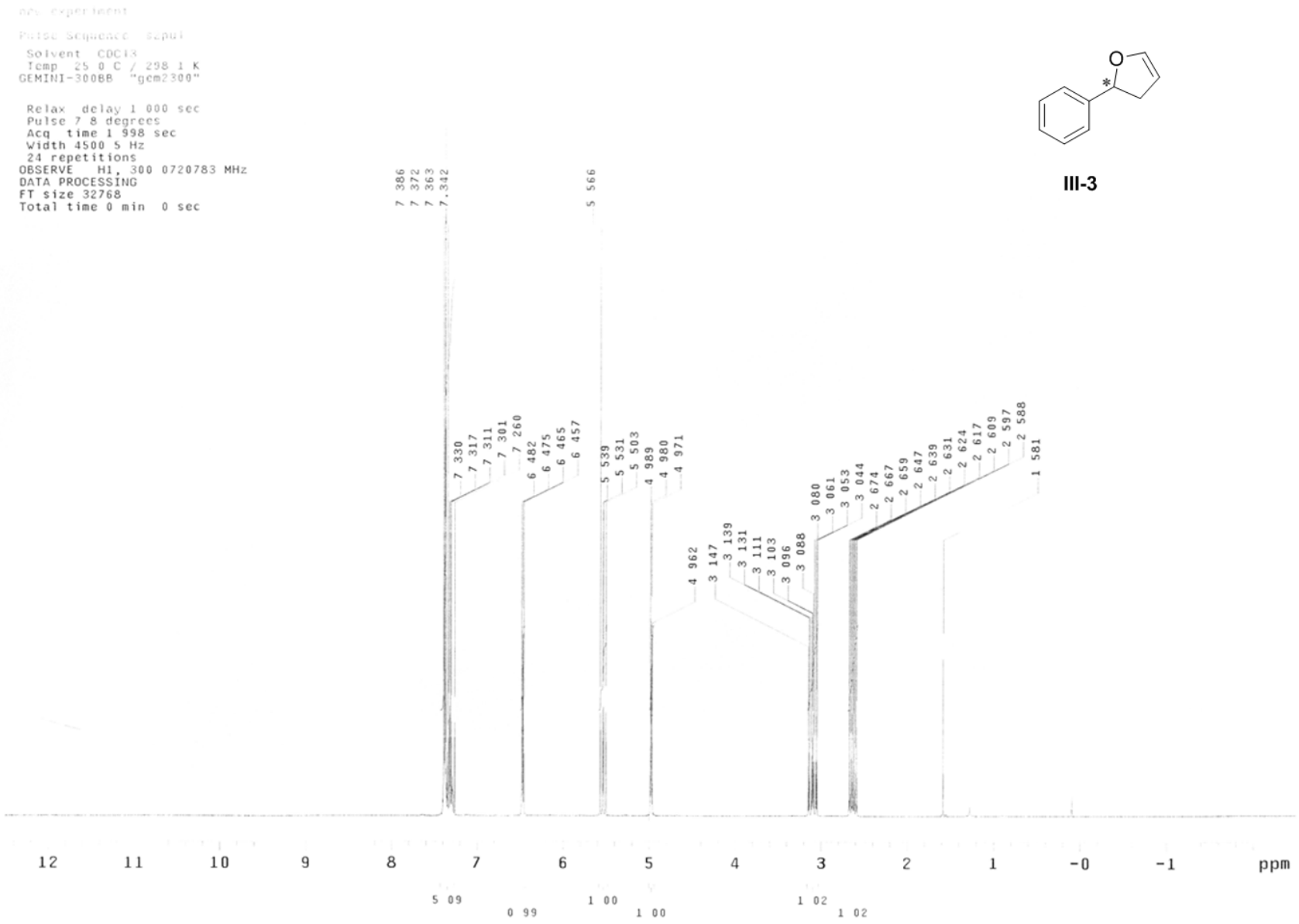
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
GEMINI-300BB "gem2300"

Relax. delay 1.000 sec
Pulse 70.0 degrees
Acq. time 1.280 sec
Width 31004.9 Hz
40 repetitions
OBSERVE P31, 121.4712147 MHz
DECOUPLE H1, 300.0735793 MHz
Power 34 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 2 min, 21 sec

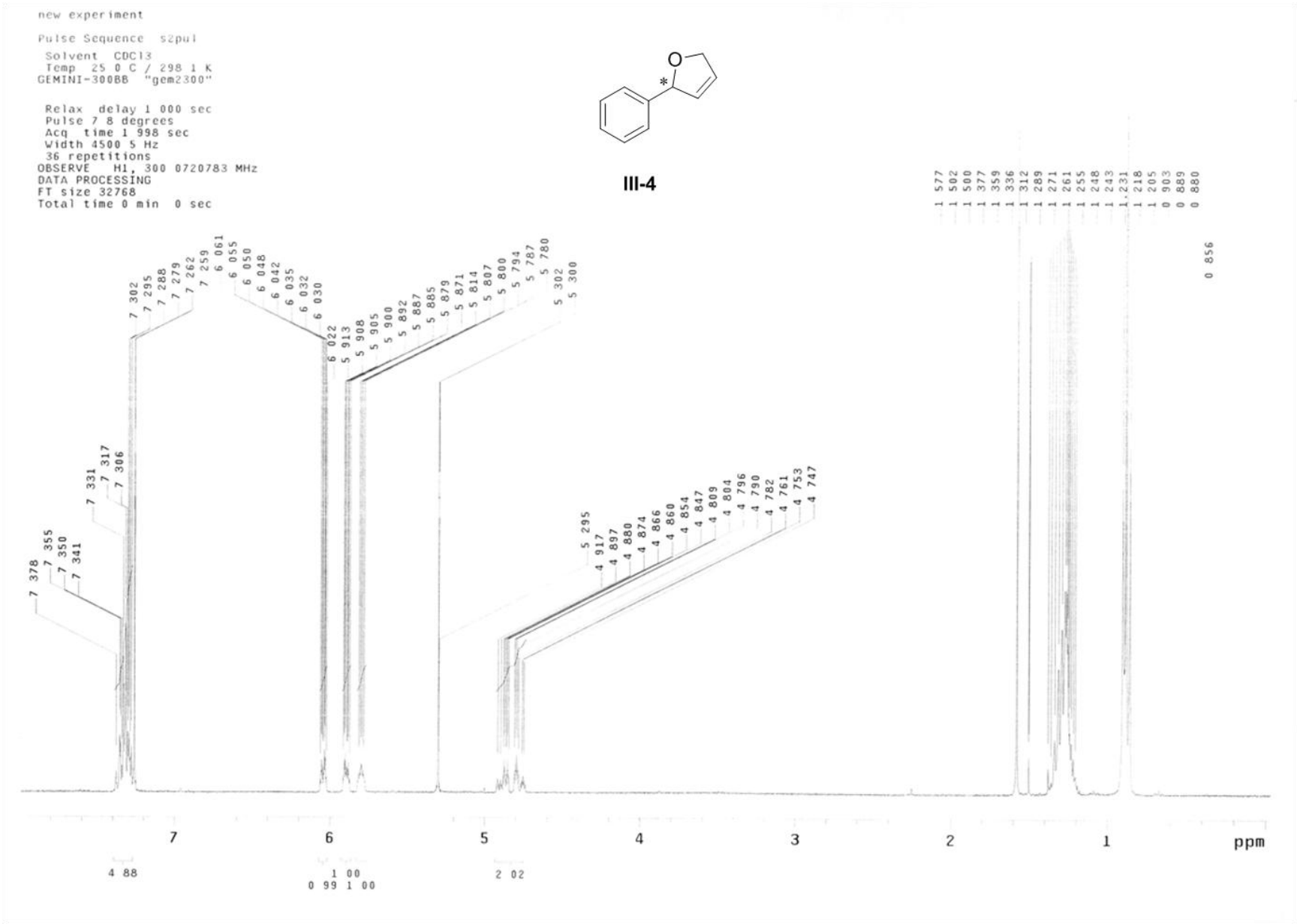


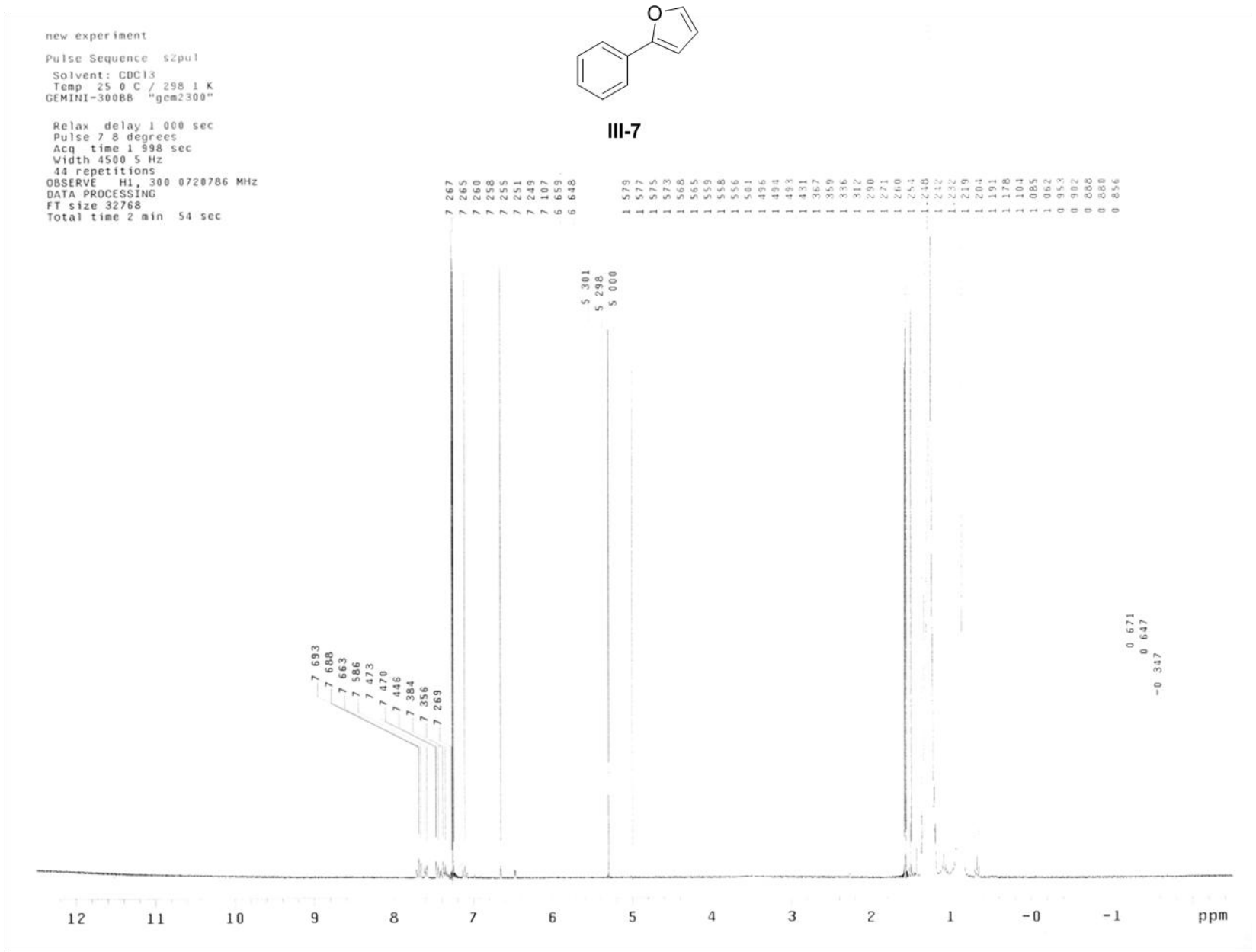
(*S*)-I-16

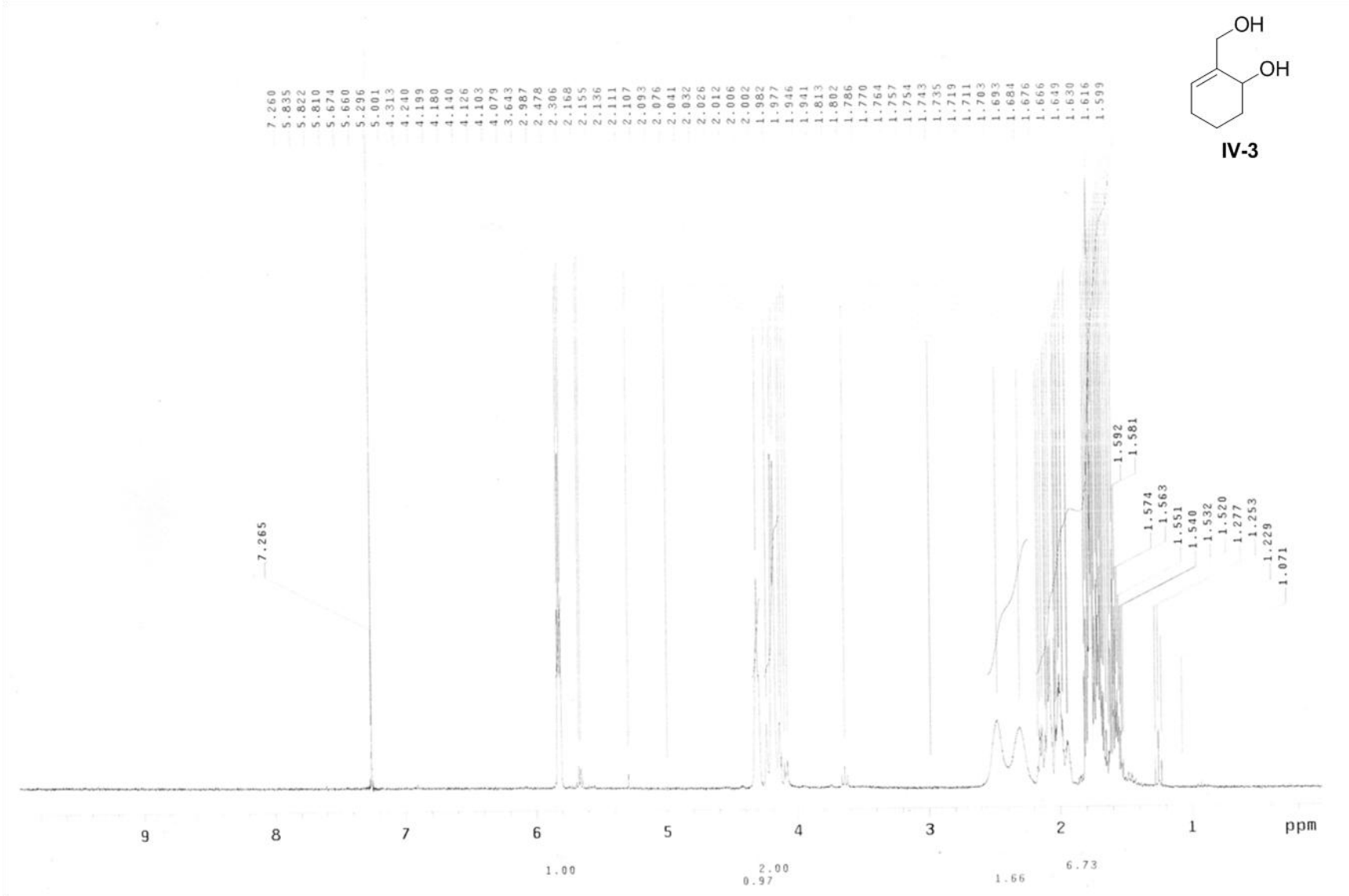

O
*
Ph
II-3
7.336
7.320
7.313
7.267
7.260
7.250
7.239
7.233
7.218
7.211
7.201
6.920
6.856
6.831
3.066
3.054
3.038
3.027
3.014
2.999
2.989
2.974
2.962
2.638
2.628
2.621
2.615
2.591
2.575
2.569
2.529
2.523
2.509
2.503
2.498
2.492
2.482
2.476
2.467
2.461
2.445
2.439
2.434
2.414
2.396
2.376
2.350
2.328
2.198
2.186
2.176
2.165
2.154
2.142
2.134
2.122
2.115
2.110
2.104
2.084
2.078
2.072
2.062
1.927
1.917
1.886
7.341
7.362
7.371
1.877
1.849
1.842
1.834
1.823
1.816
1.810
1.805
1.791
1.786
1.770
1.760
1.754
1.743
1.729
1.712
1.625
1.432
8
7
6
5
4
3
2
1
ppm
2.09
2.79
1.00
3.98
2.09
2.07

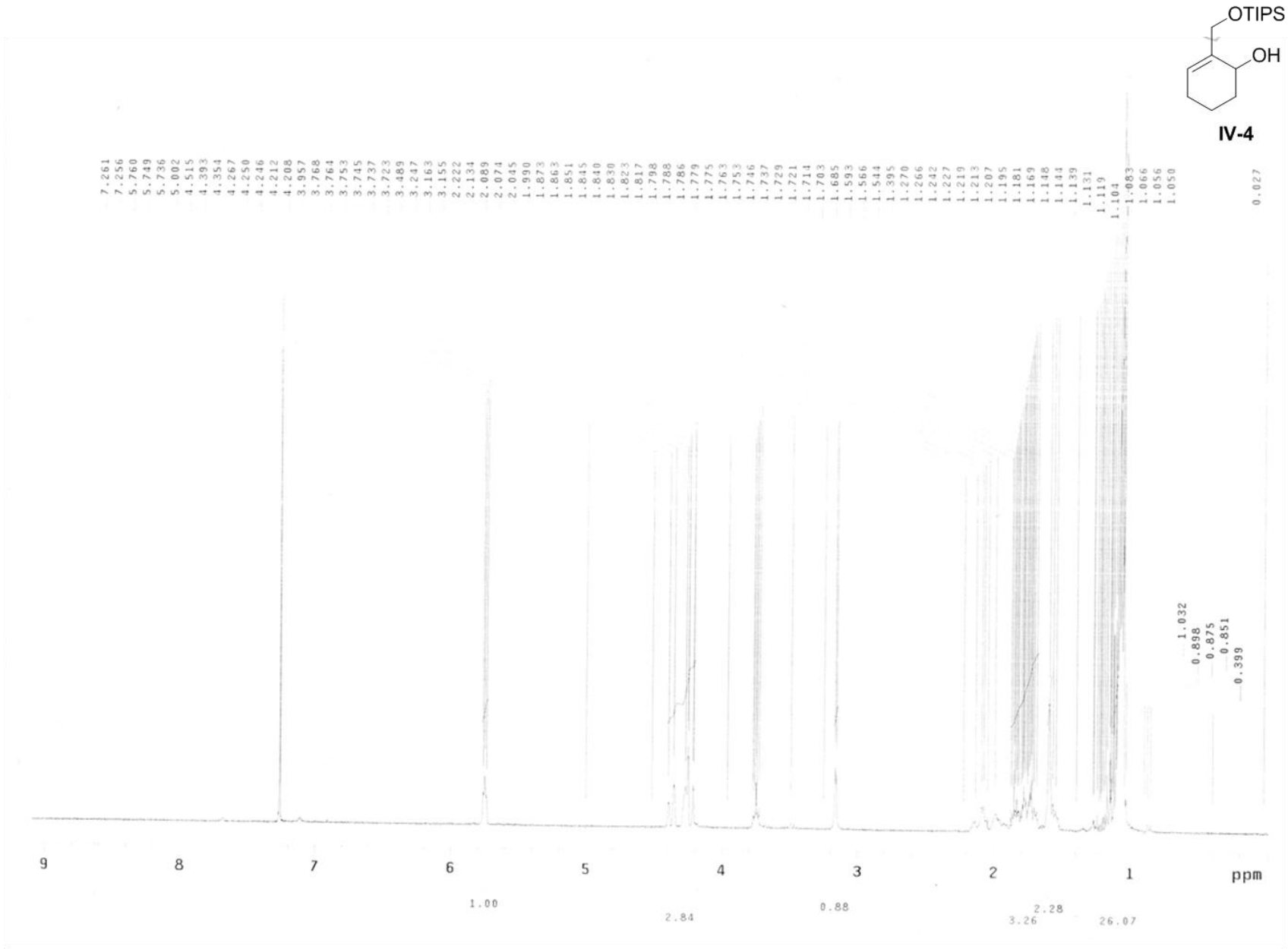

Solvent CDCl3
Temp 25 0 C / 298 1 K
GEMINI-300BB "gem2300"
Relax delay 1 000 sec
Pulse 7 8 degrees
Acq time 1 998 sec
Width 4500 5 Hz
24 repetitions
OBSERVE H1, 300 0720783 MHz
DATA PROCESSING
FT size 32768
Total time 0 min 0 sec
7 386
7 372
7 363
7 342
5 566
7 330
7 317
7 311
7 301
7 260
6 482
6 475
6 465
6 457
5 539
5 531
5 503
4 989
4 980
4 971
4 962
3 147
3 139
3 131
3 111
3 103
3 096
3 088
3 080
3 061
3 053
3 044
2 674
2 667
2 659
2 647
2 639
2 631
2 624
2 617
2 609
2 597
2 588
1 581
12
11
10
9
8
7
6
5
4
3
2
1
-0
-1
ppm
5 09
0 99
1 00
1 00
1 02
1 02

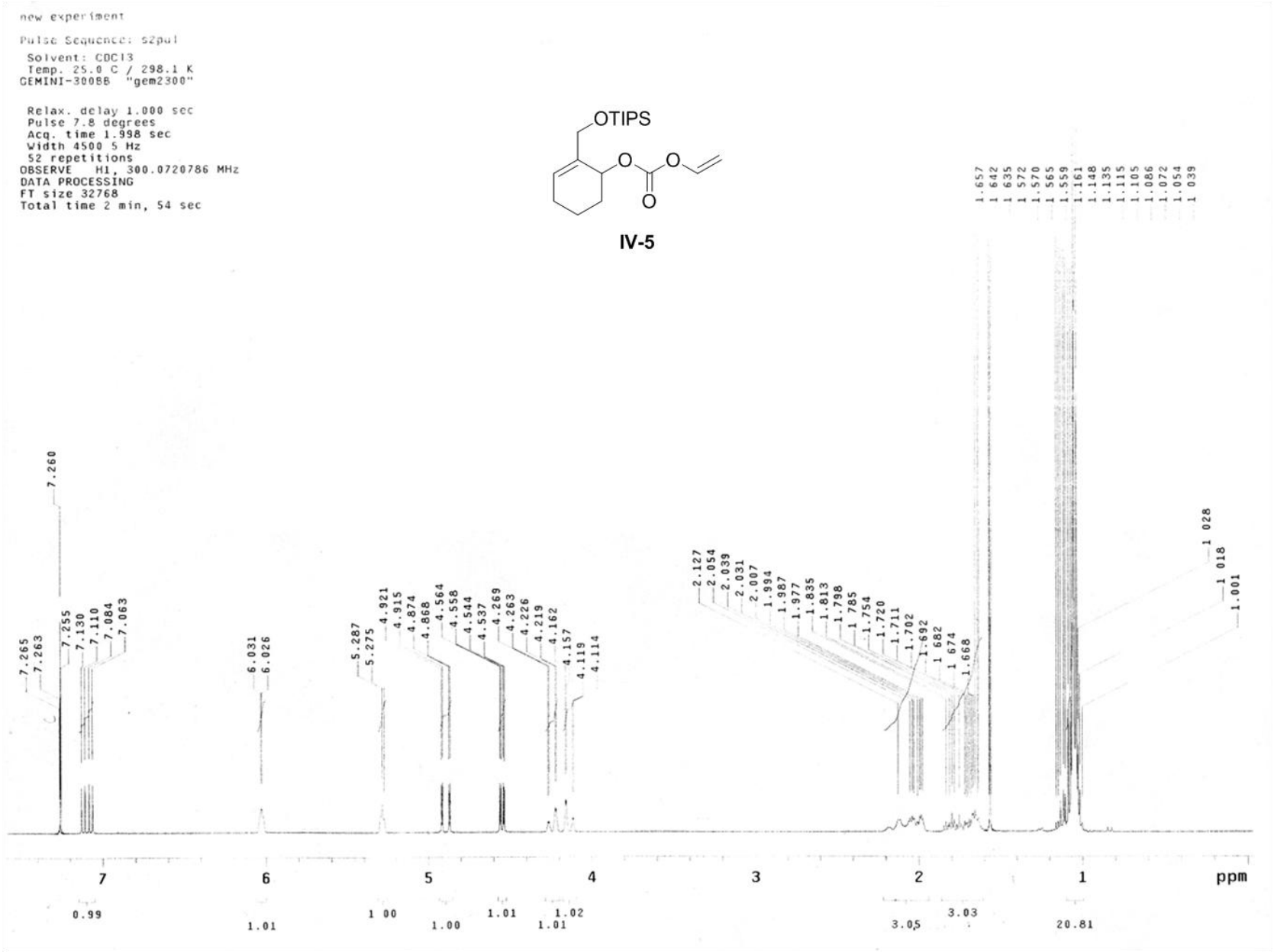
III-3

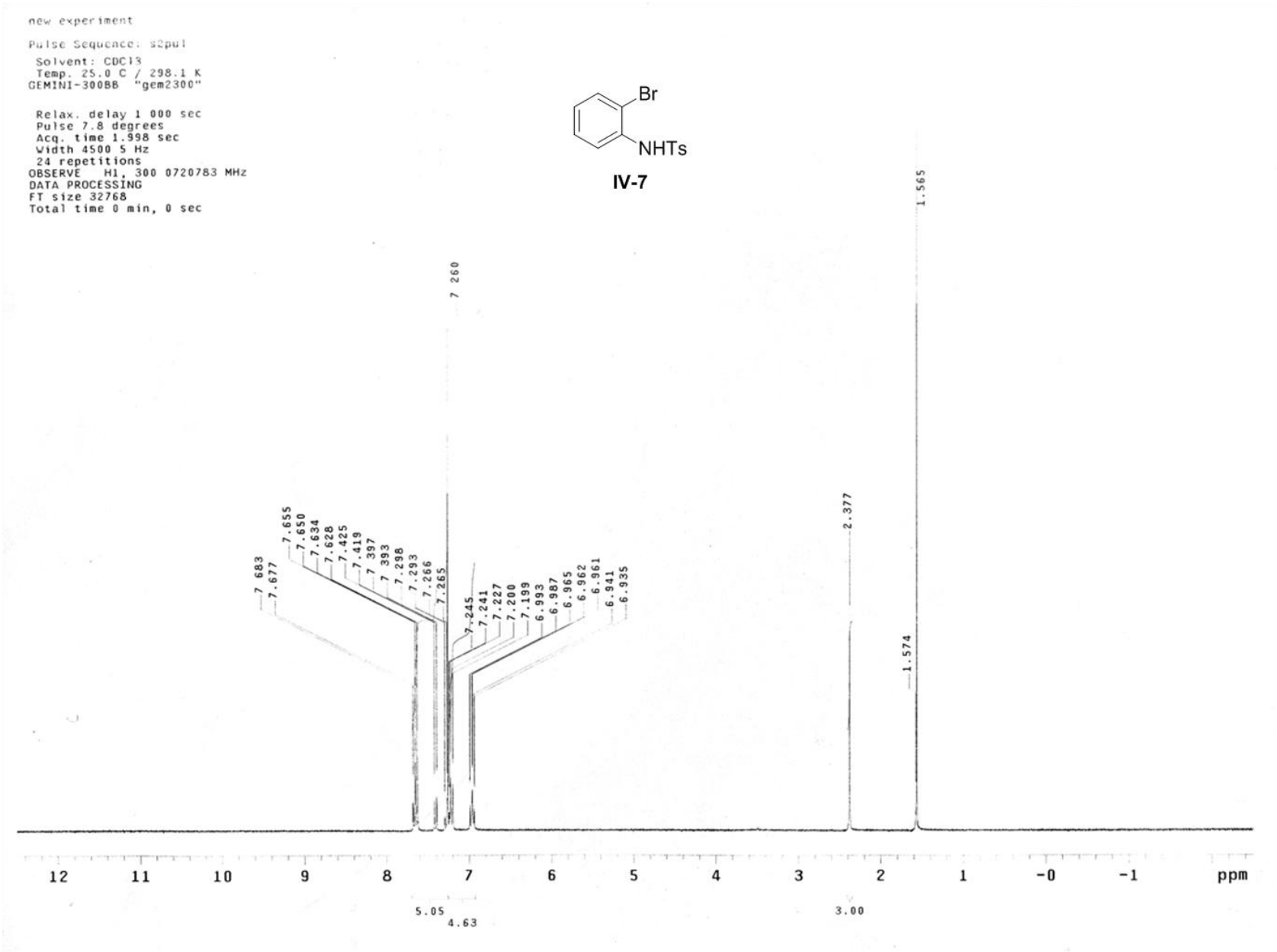

new experiment
Pulse Sequence s2pul
Solvent CDCl3
Temp 25 0 C / 298 1 K
GEMINI-300BB "gem2300"
Relax delay 1 000 sec
Pulse 7 8 degrees
Acq time 1 998 sec
Width 4500 5 Hz
36 repetitions
OBSERVE H1, 300 0720783 MHz
DATA PROCESSING
FT size 32768
Total time 0 min 0 sec
III-4
ppm
4 88
1 00
0 99 1 00
2 02

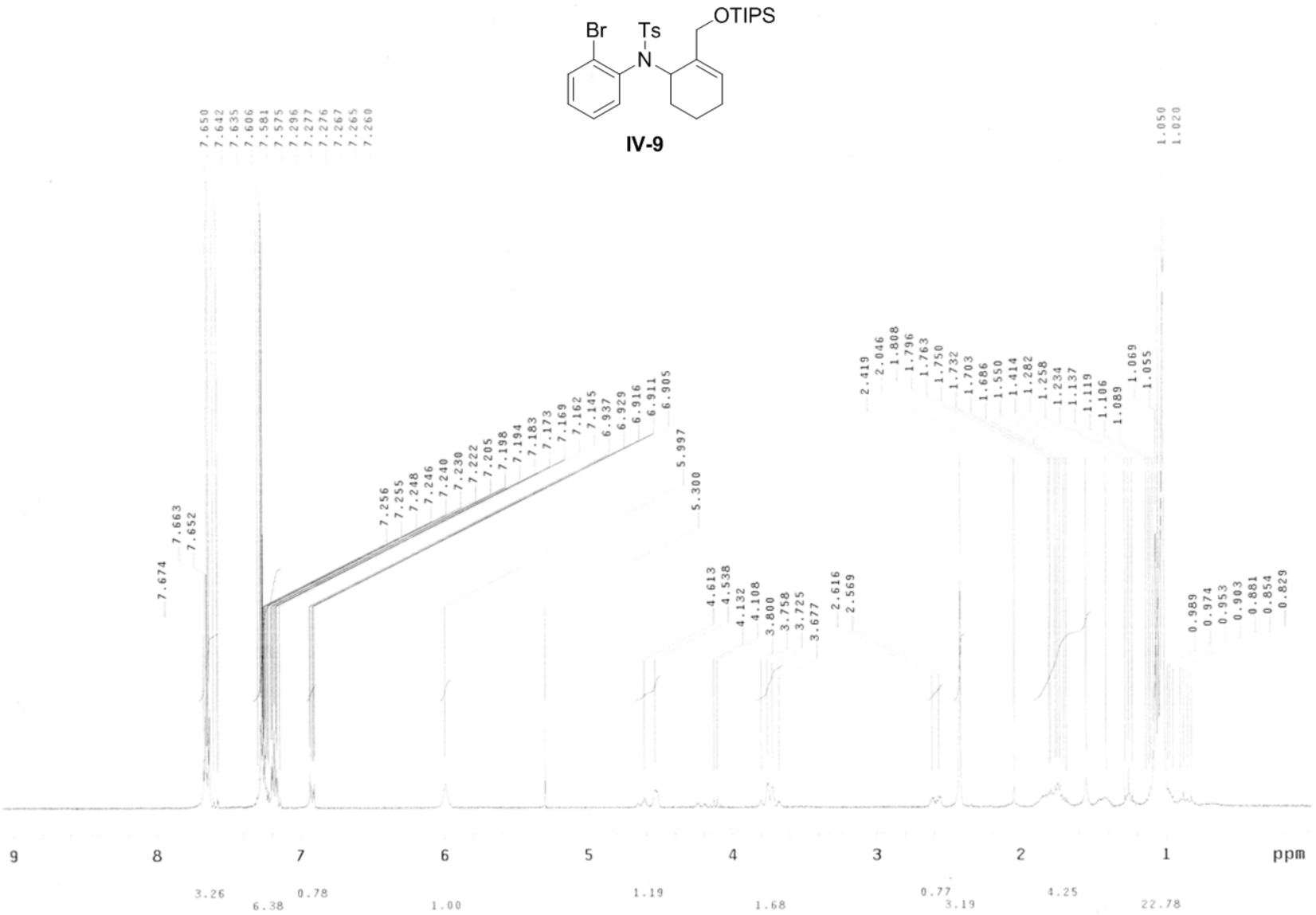

new experiment
Pulse Sequence s2pul
Solvent: CDCl3
Temp 25 0 C / 298 1 K
GEMINI-300BB "gem2300"
Relax delay 1 000 sec
Pulse 7 8 degrees
Acq time 1 998 sec
Width 4500 5 Hz
44 repetitions
OBSERVE H1, 300 0720786 MHz
DATA PROCESSING
FT size 32768
Total time 2 min 54 sec
O
III-7
7 693
7 688
7 663
7 586
7 473
7 470
7 446
7 384
7 356
7 269
7 267
7 265
7 260
7 258
7 255
7 251
7 249
7 107
6 659
6 648
5 301
5 298
5 000
1 579
1 577
1 575
1 573
1 568
1 565
1 559
1 558
1 556
1 501
1 496
1 494
1 493
1 431
1 367
1 359
1 336
1 312
1 290
1 271
1 260
1 254
1 248
1 219
1 204
1 191
1 178
1 104
1 085
1 062
0 671
0 647
-0 347
12
11
10
9
8
7
6
5
4
3
2
1
-0
-1
ppm

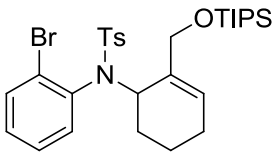

OH
OH
IV-3
7.260
5.835
5.822
5.810
5.674
5.660
5.296
5.001
4.313
4.240
4.199
4.180
4.140
4.126
4.103
4.079
3.643
2.987
2.478
2.306
2.168
2.155
2.136
2.111
2.107
2.093
2.076
2.041
2.032
2.026
2.012
2.006
2.002
1.982
1.977
1.946
1.941
1.813
1.802
1.786
1.770
1.764
1.757
1.754
1.743
1.735
1.719
1.711
1.703
1.693
1.684
1.676
1.666
1.649
1.630
1.616
1.599
1.592
1.581
1.574
1.563
1.551
1.540
1.532
1.520
1.277
1.253
1.229
1.071
7.265
9
8
7
6
5
4
3
2
1
ppm
1.00
2.00
0.97
1.66
6.73


OTIPS
OH
IV-4
7.261
7.256
5.760
5.749
5.736
5.002
4.515
4.393
4.354
4.267
4.250
4.246
4.212
4.208
3.957
3.768
3.764
3.753
3.745
3.737
3.723
3.489
3.247
3.163
3.155
2.222
2.134
2.089
2.074
2.045
1.990
1.873
1.863
1.851
1.845
1.840
1.830
1.823
1.817
1.798
1.788
1.786
1.779
1.775
1.763
1.753
1.746
1.737
1.729
1.721
1.714
1.703
1.685
1.593
1.566
1.544
1.395
1.270
1.266
1.242
1.227
1.219
1.213
1.207
1.195
1.181
1.169
1.148
1.144
1.139
1.131
1.119
1.104
1.083
1.066
1.056
1.050
0.027
1.032
0.898
0.875
0.851
0.399
9
8
7
6
5
4
3
2
1
ppm
1.00
2.84
0.88
3.26
2.28
26.07

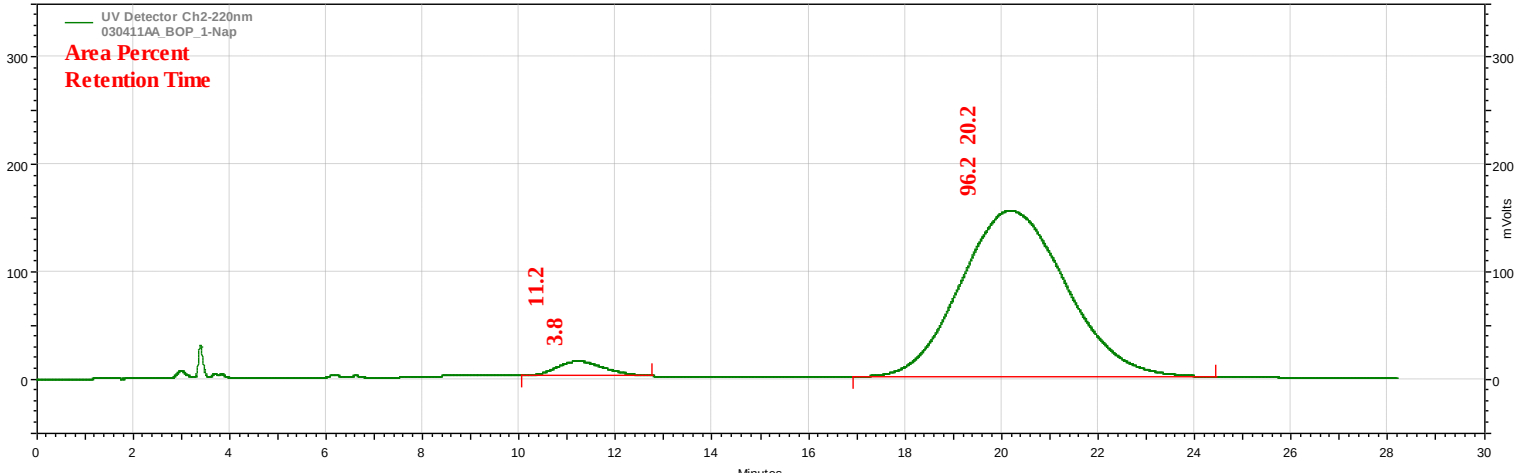

new experiment
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
GEMINI-300BB "gem2300"
Relax. delay 1.000 sec
Pulse 7.8 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
52 repetitions
OBSERVE H1, 300.0720786 MHz
DATA PROCESSING
FT size 32768
Total time 2 min, 54 sec
OTIPS
O
O
O
IV-5
7.260
7.265
7.263
7.255
7.130
7.110
7.084
7.063
6.031
6.026
5.287
5.275
4.921
4.915
4.874
4.868
4.564
4.558
4.544
4.537
4.269
4.263
4.226
4.219
4.162
4.157
4.119
4.114
2.127
2.054
2.039
2.031
2.007
1.994
1.987
1.977
1.835
1.813
1.798
1.785
1.754
1.720
1.711
1.702
1.692
1.682
1.674
1.668
1.657
1.642
1.635
1.572
1.570
1.565
1.559
1.161
1.148
1.135
1.115
1.105
1.086
1.072
1.054
1.039
1.028
1.018
1.001
7
6
5
4
3
2
1
ppm
0.99
1.01
1.00
1.00
1.01
1.01
1.02
3.05
3.03
20.81

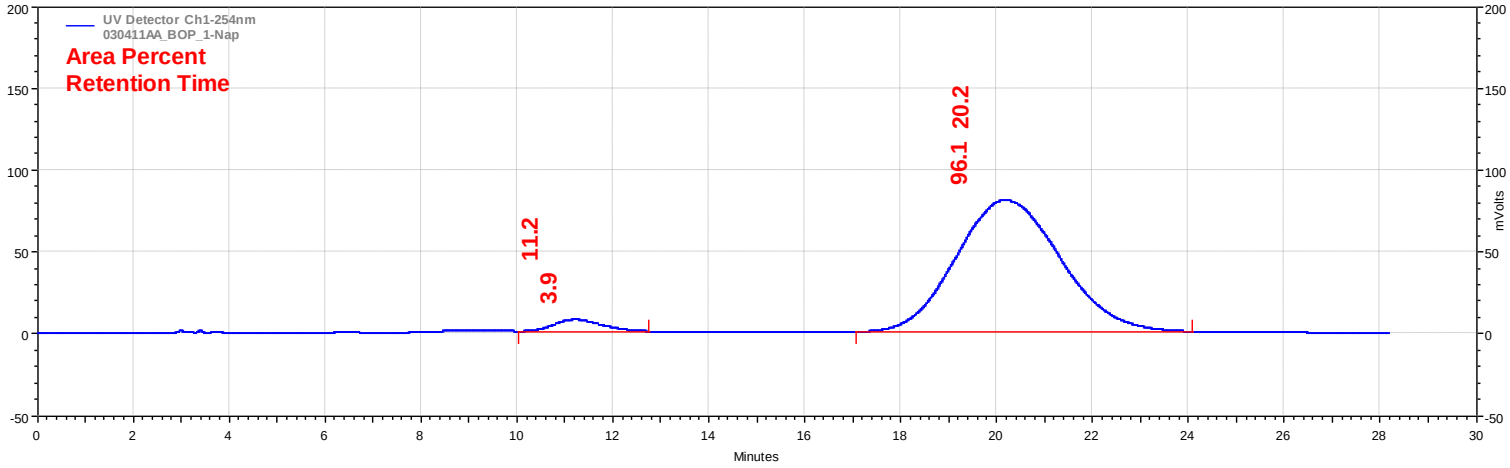

new experiment
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
GEMINI-300BB "gem2300"
Relax. delay 1.000 sec
Pulse 7.8 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
24 repetitions
OBSERVE H1, 300.0720783 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 0 sec
Br
NHTs
IV-7
7.683
7.677
7.655
7.650
7.634
7.628
7.425
7.419
7.397
7.393
7.298
7.293
7.266
7.265
7.260
7.245
7.241
7.227
7.200
7.199
6.993
6.987
6.965
6.962
6.961
6.941
6.935
2.377
1.574
1.565
12
11
10
9
8
7
6
5
4
3
2
1
-0
-1
ppm
5.05
4.63
3.00

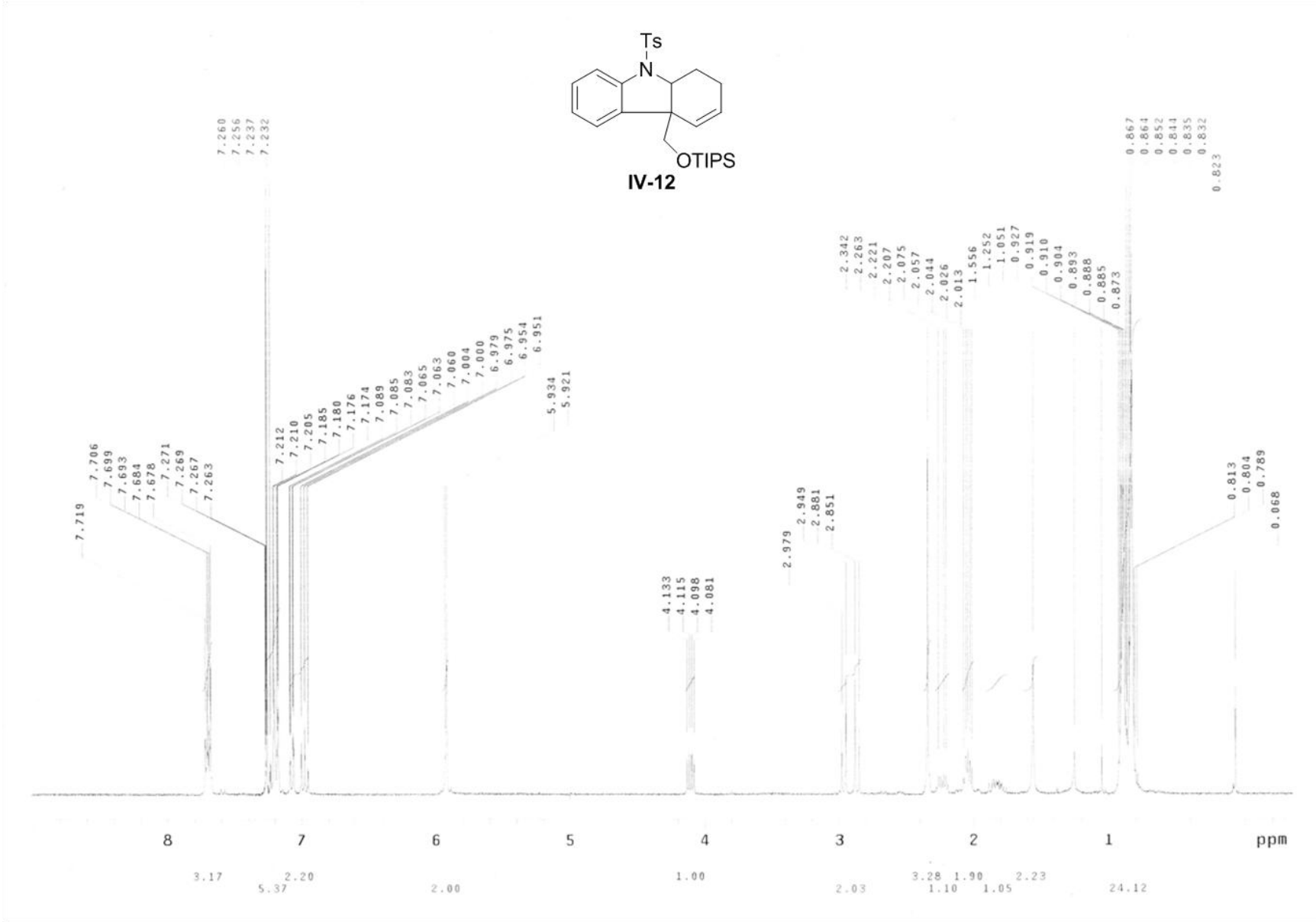

Br
Ts
N
OTIPS
IV-9
7.650
7.642
7.635
7.606
7.581
7.575
7.296
7.277
7.276
7.267
7.265
7.260
7.674
7.663
7.652
7.256
7.255
7.248
7.246
7.240
7.230
7.222
7.205
7.198
7.194
7.183
7.173
7.169
7.162
7.145
6.937
6.929
6.916
6.911
6.905
5.997
5.300
4.613
4.538
4.132
4.108
3.800
3.758
3.725
3.677
2.616
2.569
2.419
2.046
1.808
1.796
1.763
1.750
1.732
1.703
1.686
1.550
1.414
1.282
1.258
1.234
1.137
1.119
1.106
1.089
1.069
1.055
1.050
1.020
0.989
0.974
0.953
0.903
0.881
0.854
0.829
9
8
7
6
5
4
3
2
1
ppm
3.26
6.38
0.78
1.00
1.19
1.68
0.77
3.19
4.25
22.78

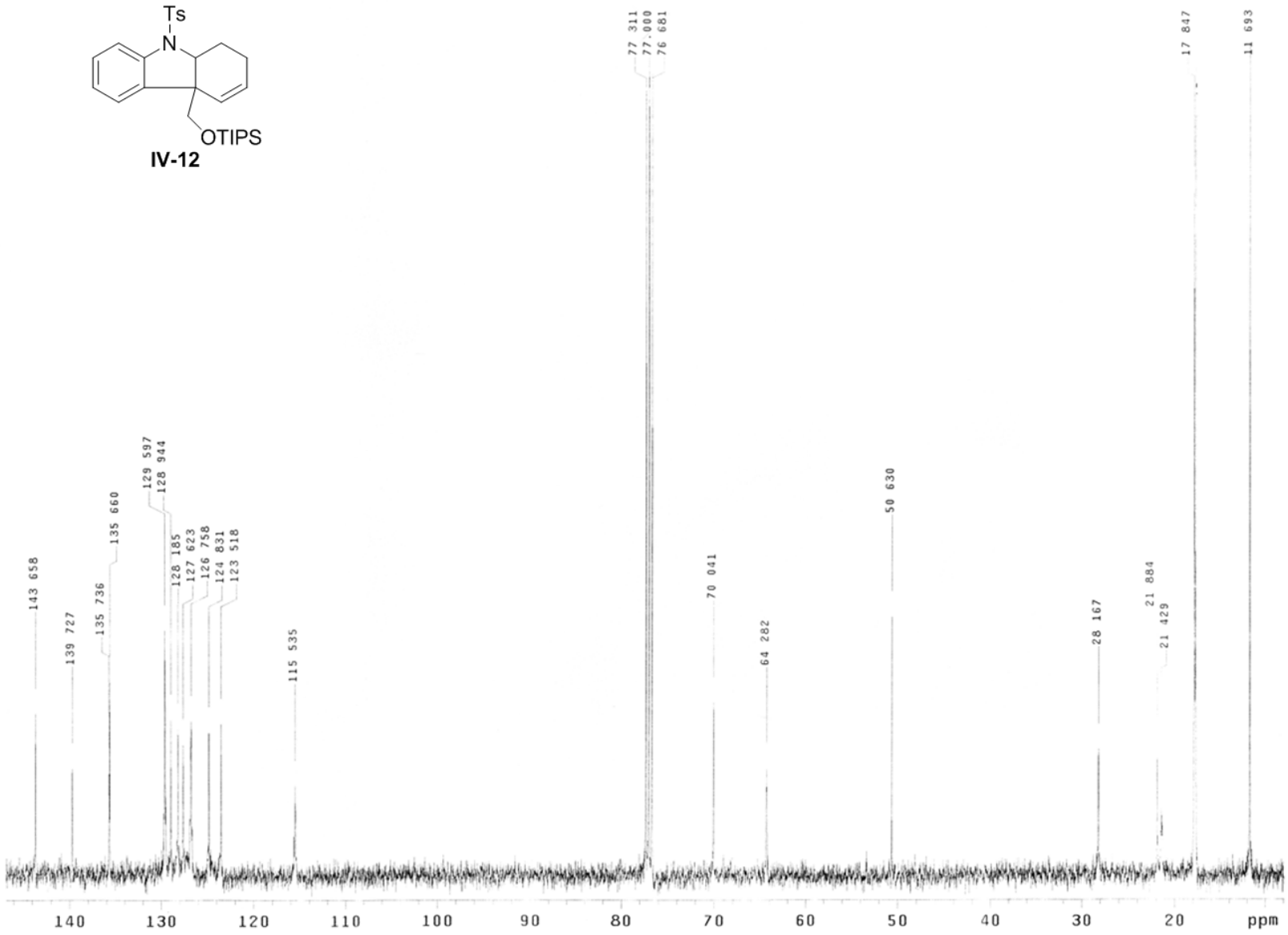

Br
Ts
N
OTIPS

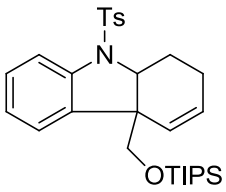
IV-9


UV Detector Ch2-220nm
030411AA_BOP_1-Nap
Area Percent
Retention Time
96.2 20.2
11.2
3.8
mVolts

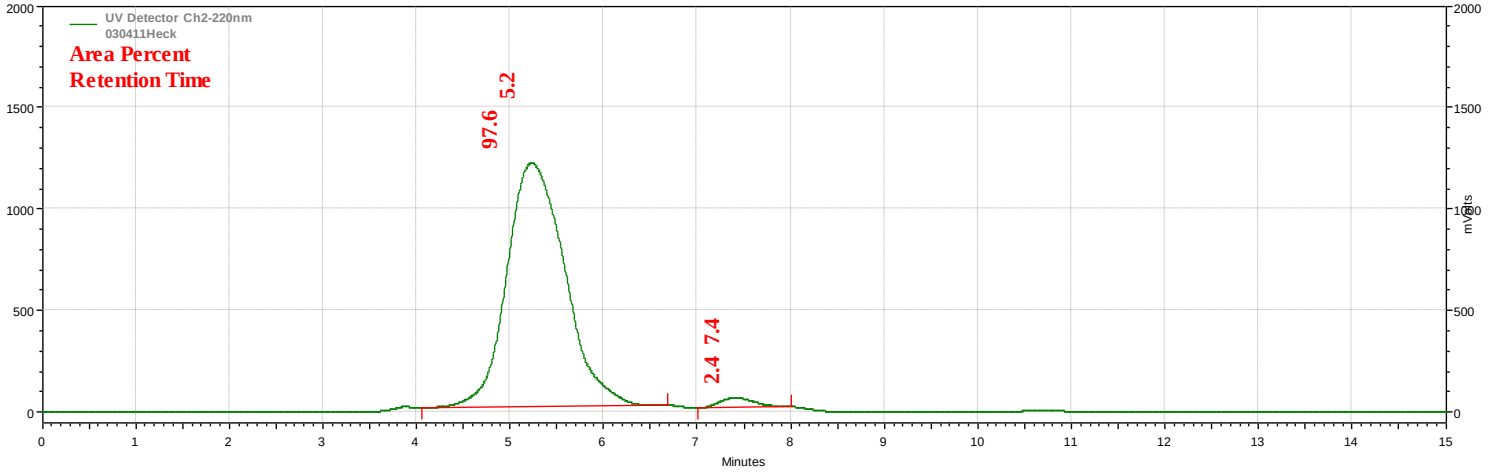

UV Detector Ch1-254nm
030411AA_BOP_1-Nap
Area Percent
Retention Time
96.1 20.2
11.2
3.9
mVolts
Minutes

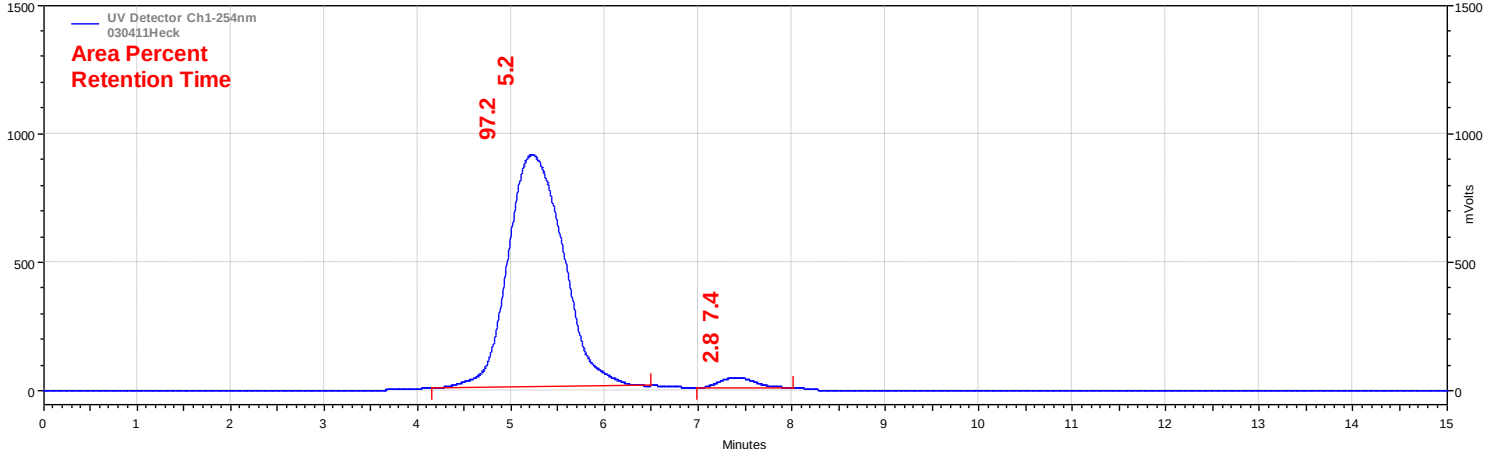

Ts
N
OTIPS
IV-12
7.719
7.706
7.699
7.693
7.684
7.678
7.271
7.269
7.267
7.263
7.260
7.256
7.237
7.232
7.212
7.210
7.205
7.185
7.180
7.176
7.174
7.089
7.085
7.083
7.065
7.063
7.060
7.004
7.000
6.979
6.975
6.954
6.951
5.934
5.921
4.133
4.115
4.098
4.081
2.979
2.949
2.881
2.851
2.342
2.263
2.221
2.207
2.075
2.057
2.044
2.026
2.013
1.556
1.252
1.051
0.927
0.919
0.910
0.904
0.893
0.888
0.885
0.873
0.867
0.861
0.852
0.841
0.835
0.832
0.823
0.813
0.804
0.789
0.068
8
7
6
5
4
3
2
1
ppm
3.17
2.20
5.37
2.00
1.00
2.03
3.28
1.90
2.23
1.10
1.05
24.12

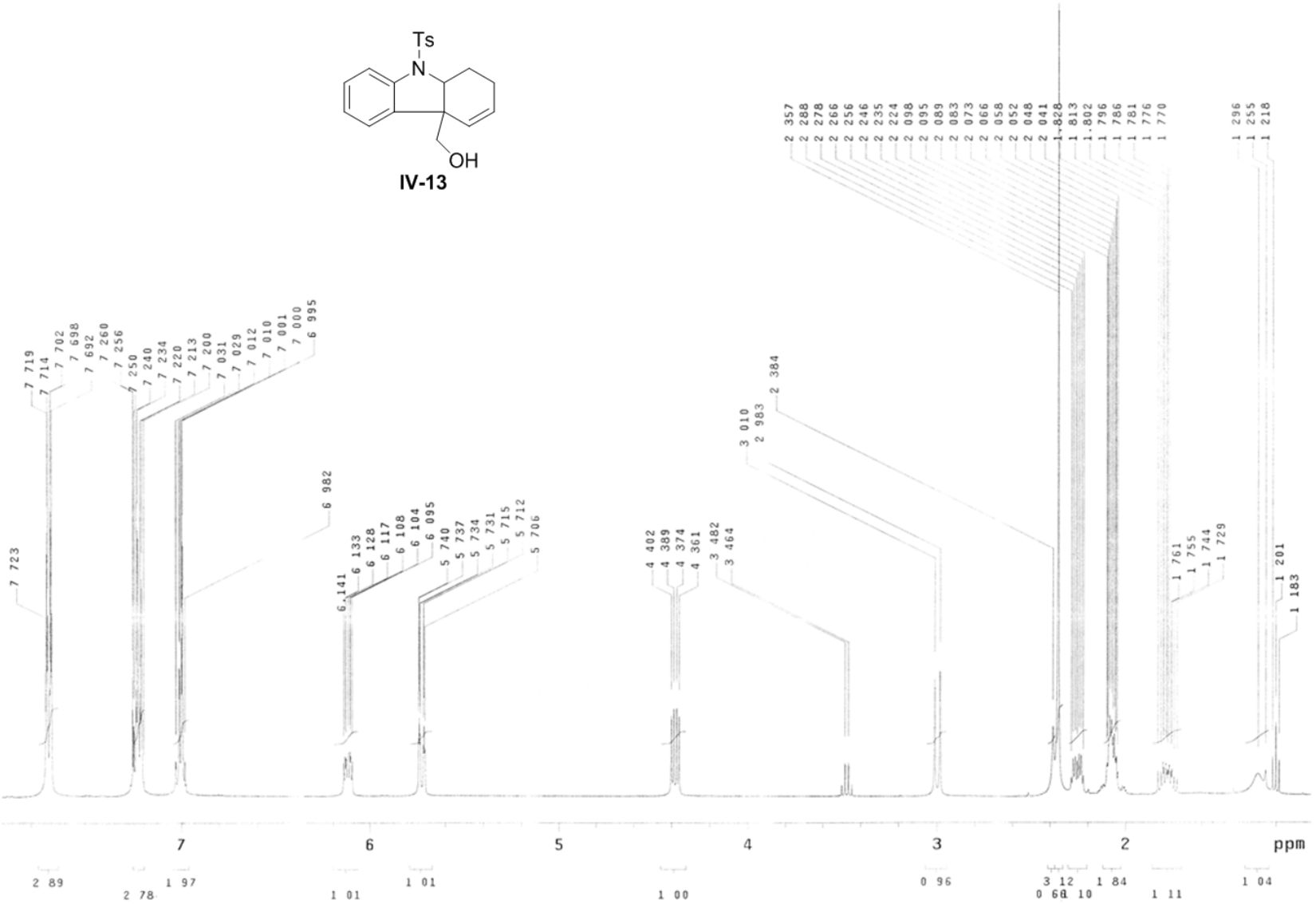

Ts
N
OTIPS
IV-12
143 658
139 727
135 736
135 660
129 597
128 944
128 185
127 623
126 758
124 831
123 518
115 535
77 311
77.000
76 681
70 041
64 282
50 630
28 167
21 884
21 429
17 847
11 693
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

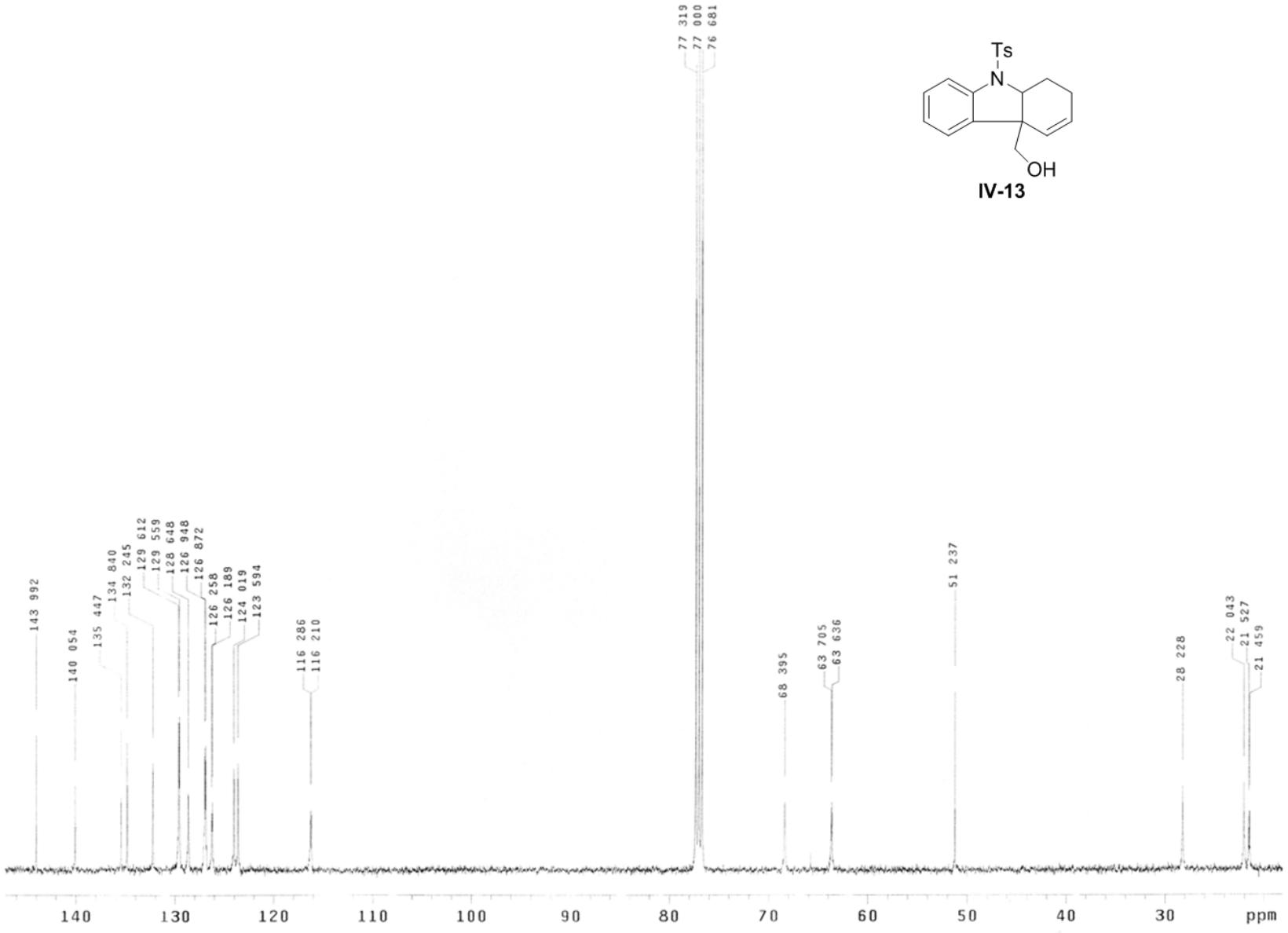

Ts
N
OTIPS

IV-12


UV Detector Ch2-220nm
030411Heck
Area Percent
Retention Time
97.6
5.2
2.4
7.4
mVolts
Minutes

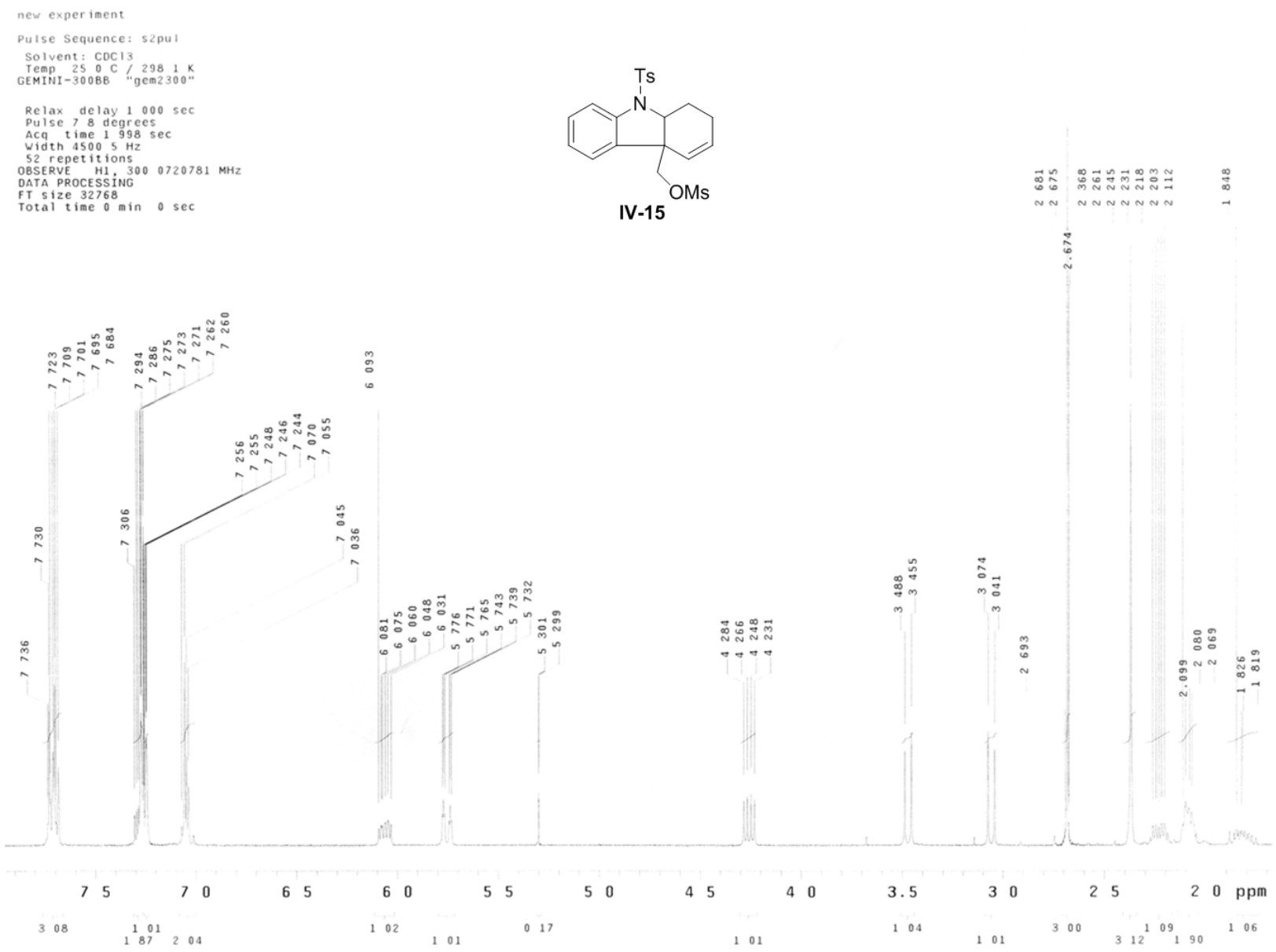

UV Detector Ch1-254nm
030411Heck
Area Percent
Retention Time
97.2
5.2
2.8
7.4
mVolts
Minutes

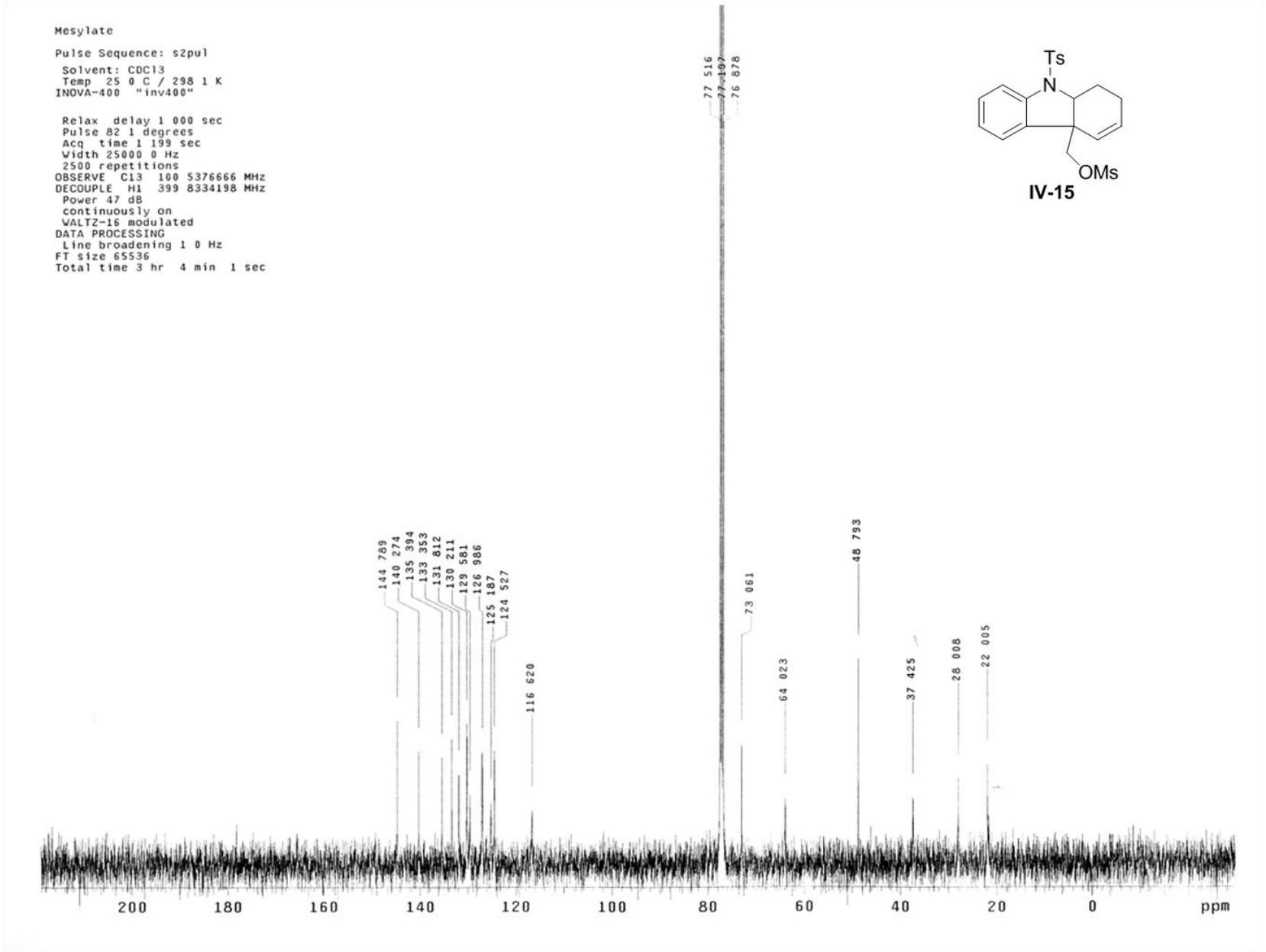

Ts
N
OH
IV-13
7.723
7.719
7.714
7.702
7.698
7.692
7.260
7.256
7.250
7.240
7.234
7.220
7.213
7.200
7.031
7.029
7.012
7.010
7.001
7.000
6.995
6.982
6.141
6.133
6.128
6.117
6.108
6.104
6.095
5.740
5.737
5.734
5.731
5.715
5.712
5.706
4.402
4.389
4.374
4.361
3.482
3.464
3.010
2.983
2.384
2.357
2.288
2.278
2.266
2.256
2.246
2.235
2.224
2.098
2.095
2.089
2.083
2.073
2.066
2.058
2.052
2.048
2.041
1.828
1.813
1.802
1.796
1.786
1.781
1.776
1.770
1.761
1.755
1.744
1.729
1.296
1.255
1.218
1.201
1.183
7
6
5
4
3
2
ppm
2.89
2.78
1.97
1.01
1.01
1.00
0.96
3.12
0.68
1.84
1.10
1.11
1.04

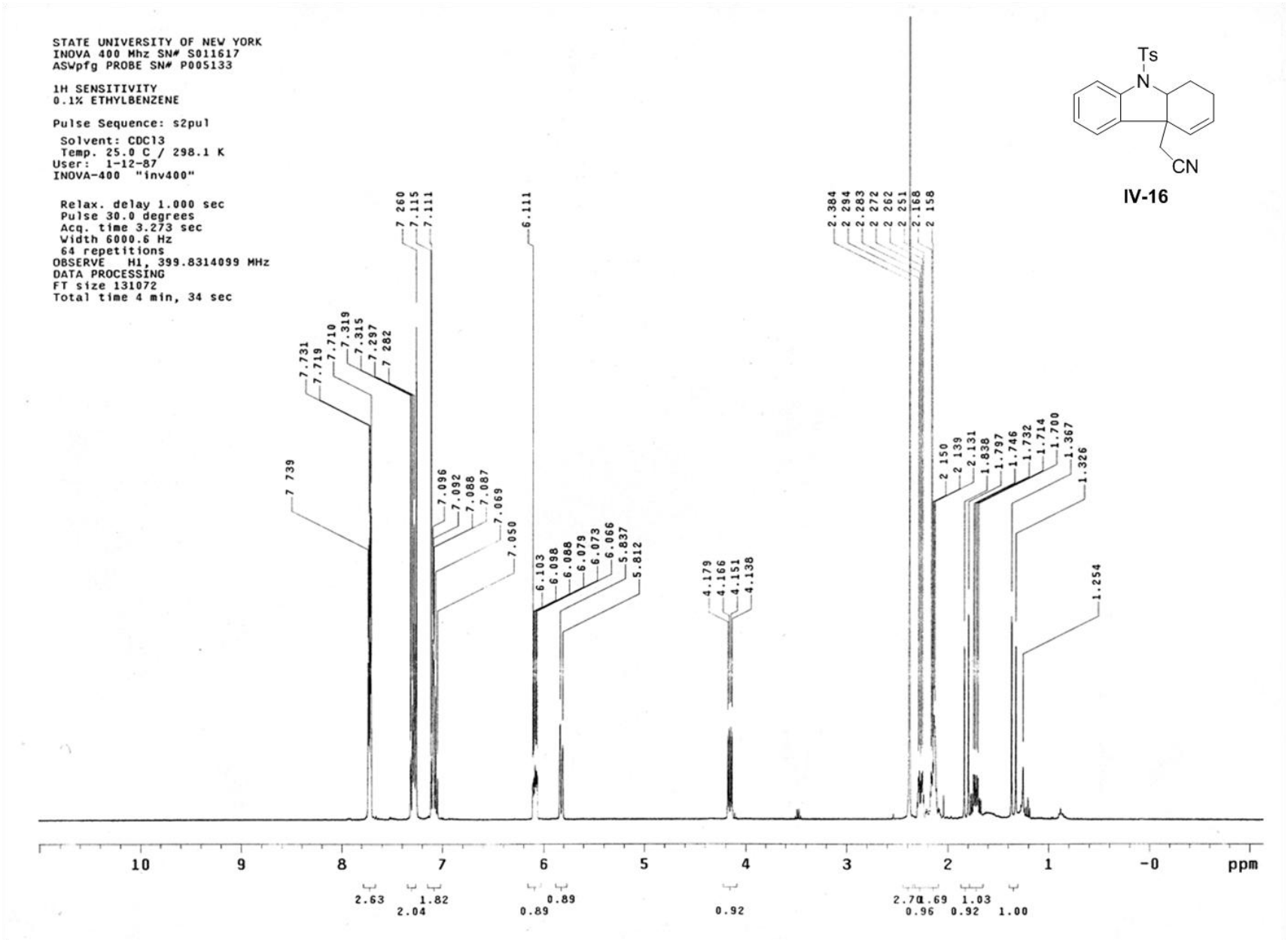

77 319
77 000
76 681
143 992
140 054
135 447
134 840
132 245
129 612
129 559
128 648
126 948
126 872
126 258
126 189
124 019
123 594
116 286
116 210
68 395
63 705
63 636
51 237
28 228
22 043
21 527
21 459
140
130
120
110
100
90
80
70
60
50
40
30
ppm

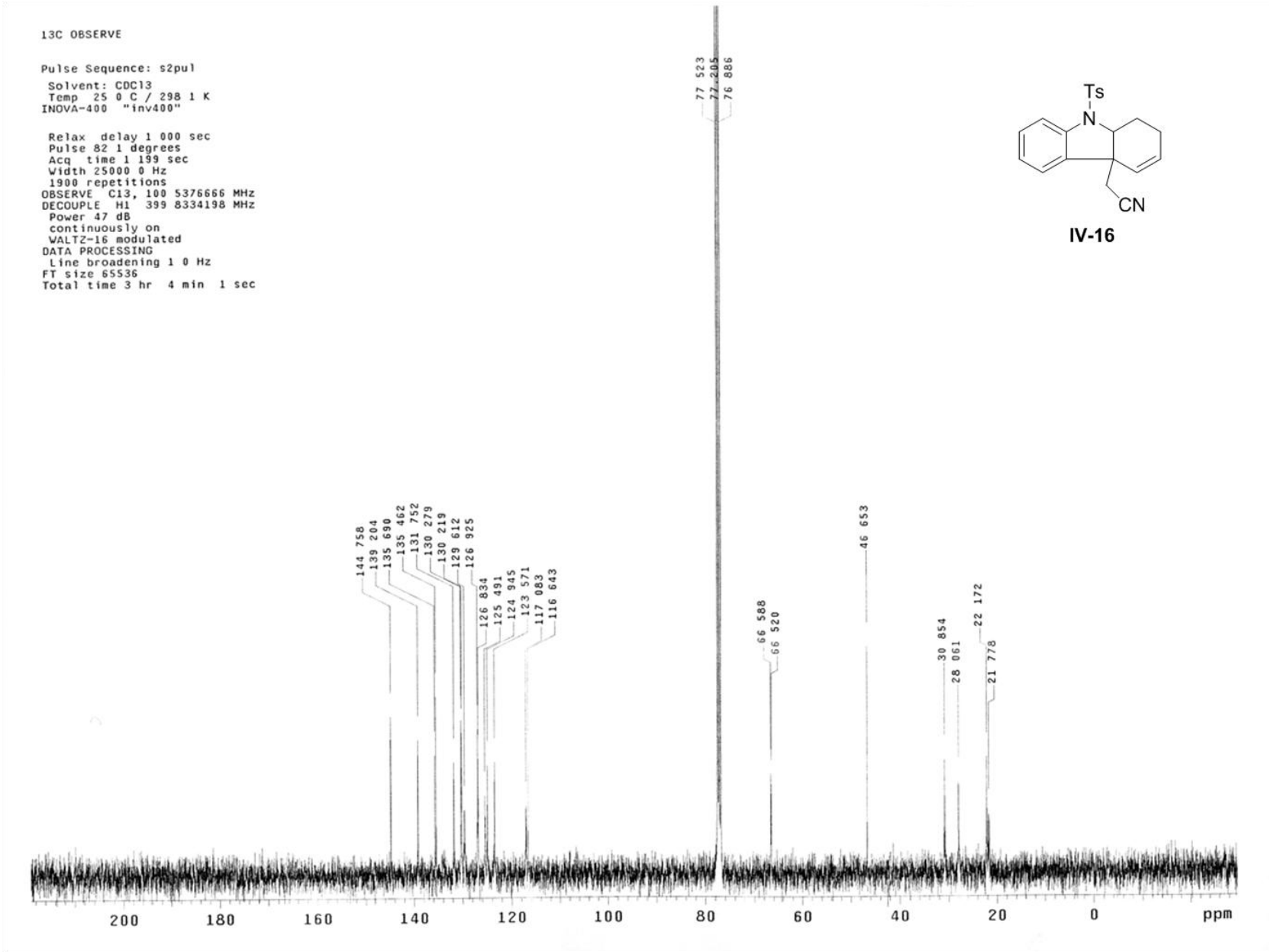
Ts
N
OH

IV-13


new experiment
Pulse Sequence: s2pul
Solvent: CDCl3
Temp 25 0 C / 298 1 K
GEMINI-300BB "gem2300"
Relax delay 1 000 sec
Pulse 7 8 degrees
Acq time 1 998 sec
Width 4500 5 Hz
52 repetitions
OBSERVE H1, 300 0720781 MHz
DATA PROCESSING
FT size 32768
Total time 0 min 0 sec
Ts
N
OMs
IV-15
7 736
7 730
7 723
7 709
7 701
7 695
7 684
7 306
7 294
7 286
7 275
7 273
7 271
7 262
7 260
7 256
7 255
7 248
7 246
7 244
7 070
7 055
7 045
7 036
6 093
6 081
6 075
6 060
6 048
6 031
5 776
5 771
5 765
5 743
5 739
5 732
5 301
5 299
4 284
4 266
4 248
4 231
3 488
3 455
3 074
3 041
2 693
2 681
2 675
2.674
2 368
2 261
2 245
2 231
2 218
2 203
2 112
2.099
2 080
2 069
1 848
1 826
1 819
7 5
7 0
6 5
6 0
5 5
5 0
4 5
4 0
3.5
3 0
2 5
2 0 ppm
3 08
1 01
1 87
2 04
1 02
1 01
0 17
1 01
1 04
1 01
3 00
3 12
1 09
1 90
1 06


Mesylate
Pulse Sequence: s2pul
Solvent: CDCl3
Temp 25 0 C / 298 1 K
INOVA-400 "inv400"
Relax delay 1 000 sec
Pulse 82 1 degrees
Acq time 1 199 sec
Width 25000 0 Hz
2500 repetitions
OBSERVE C13 100 5376666 MHz
DECOUPLE H1 399 8334198 MHz
Power 47 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1 0 Hz
FT size 65536
Total time 3 hr 4 min 1 sec
77 516
77 197
76 878
144 789
140 274
135 394
133 353
131 812
130 211
129 581
126 986
125 187
124 527
116 620
73 061
64 023
48 793
37 425
28 008
22 005
200
180
160
140
120
100
80
60
40
20
0
ppm
Ts
N
OMs
IV-15


STATE UNIVERSITY OF NEW YORK
INOVA 400 Mhz SN# S011617
ASWpfg PROBE SN# P005133
1H SENSITIVITY
0.1% ETHYLBENZENE
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
User: 1-12-87
INOVA-400 "inv400"
Relax. delay 1.000 sec
Pulse 30.0 degrees
Acq. time 3.273 sec
Width 6000.6 Hz
64 repetitions
OBSERVE H1, 399.8314099 MHz
DATA PROCESSING
FT size 131072
Total time 4 min, 34 sec
Ts
N
CN
IV-16
7.739
7.731
7.719
7.710
7.319
7.315
7.297
7.282
7.260
7.115
7.111
7.096
7.092
7.088
7.087
7.069
7.050
6.111
6.103
6.098
6.088
6.079
6.073
6.066
5.837
5.812
4.179
4.166
4.151
4.138
2.384
2.294
2.283
2.272
2.262
2.251
2.168
2.158
2.150
2.139
2.131
1.838
1.797
1.746
1.732
1.714
1.700
1.367
1.326
1.254
10
9
8
7
6
5
4
3
2
1
-0
ppm
2.63
2.04
1.82
0.89
0.89
0.92
2.70
0.96
1.69
0.92
1.03
1.00


13C OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Temp 25 0 C / 298 1 K
INOVA-400 "inv400"
Relax delay 1 000 sec
Pulse 82 1 degrees
Acq time 1 199 sec
Width 25000 0 Hz
1900 repetitions
OBSERVE C13, 100 5376666 MHz
DECOUPLE H1 399 8334198 MHz
Power 47 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1 0 Hz
FT size 65536
Total time 3 hr 4 min 1 sec
77 523
77 205
76 886
144 758
139 204
135 690
135 462
131 752
130 279
130 219
129 612
126 925
126 834
125 491
124 945
123 571
117 083
116 643
66 588
66 520
46 653
30 854
28 061
22 172
21 778
200
180
160
140
120
100
80
60
40
20
0
ppm
Ts
N
CN
IV-16