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Investigation Of Stoichiometric And Catalytic Palladium Mediated Reactions

Purna Chandra Rao Vasireddy

INVESTIGATION OF STOICHIOMETRIC AND CATALYTIC PALLADIUM MEDIATED REACTIONS

By

Purna Chandra Rao Vasireddy

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Name: Purna Chandra Rao Vasireddy

Degree: Doctor of Philosophy

This document, submitted in partial fulfillment of the requirements for the degree from the University of North Dakota, has been read by the Faculty Advisory Committee under whom the work has been done and is hereby approved.

DocuSigned by:
Dr. Irina Smoliakova
Dr. Irina. P. Smoliakova

DocuSigned by:
Dr. Qianli (Rick) Chu
Dr. Qianli (Rick) Chu

DocuSigned by:
Guodong Du
Dr. Guodong Du

DocuSigned by:
David Pierce
Dr. David Pierce

DocuSigned by:
Frank Bowman
Dr. Frank Bowman

This document is being submitted by the appointed advisory committee as having met all the requirements of the School of Graduate Studies at the University of North Dakota and is hereby approved.

DocuSigned by:
Chris Nelson
Chris Nelson
Dean of the School of Graduate Studies

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TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF CHARTS

LIST OF SCHEMES

LIST OF ABBRIVIATIONNS

Ac	Acyl group
Ar	Aryl
Bu	Butyl
CPC	Cyclopalladated complex
de	Diastereomeric excess
DMF	*N*,*N*-Dimethylformamide
Et	Ethyl group
Hal	Halogen
HRMS	High resolution mass spectra
IR	Infrared
Me	Methyl group
M.p.	Melting point
NMP	*N*-Methylpyrrolidone
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser effect
ORTEP	Oak Ridge thermal ellipsoid plot
Tf	Triflyl (trifluoromethyl) group
Ph	Phenyl
ppm	Parts per million

rt	Room temperature
TBAF	Tetra-*n*-butyammonium fluoride
TEMPO	2,2,6,6-Tetramethylpiperidinyloxyl
TFA	Trifluoroacetic acid
TLC	Thin layer chromatography
p-TSA	*p*-Toluenesulfonic acid

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ABSTRACT

This dissertation describes the investigation of stoichiometric and catalytic transformations involving Pd(II) compounds. The first two parts of the dissertation are focused on the preparation, characterization and application of the well-known group of Pd(II) derivatives called cyclopalladated complexes (CPCs). Specifically, *N*,*N*-dimethylhydrazone of D-camphor (**I.1)** was obtained as the single *E* isomer in 80% yield by treating the enantiopure ketone with *N*,*N*-dimethylhydrazine in the presence of an equimolar amount of *p*-TSA·H_2O in ethanol. Direct cyclopalladation of hydrazone **I.1** was accomplished at the C(3)H_2 group using Pd(MeCN)$_2$Cl$_2$ and NaOAc in MeCN at the reflux temperature. The product of the reaction, dinuclear cyclopalladated complex (**I.2**), was isolated in 89% yield as a mixture of diastereoisomers, which differ by the absolute configuration of the chiral carbon bound to the metal. Compound **I.2** was converted to the mononuclear complex **I.3** by treating the dimer with PPh_3. Compound **I.3** was a mixture of two diastereomers with the Pd atom either in the endo or exo position of the bornane scaffold. Isomers of complex **I.3** were partly separated by column chromatography to obtain samples of endo-**I.3** and exo-**I.3** with 96% and 86% de, respectively. The structures of two diastereomers, endo-**I.3** and exo-**I.3,** were supported by ^{1}H, ^{13}C{^{1}H}, ^{31}P{^{1}H} and 1D NOE NMR spectra and X-ray crystallographic data.

The dimeric complex **I.2** (named as **II.12** in Chapter II) and five known (*sp*^{2})*C*,*N* and (*sp*^{3})*C*,*N* cyclopalladated complexes (**II.1**, **II.4**, **II.6**, **II.8**, and **II.10**) derived from *N*,*N*-dimethylbenzylamine, 4,4-dimethyl-2-phenyl-2-oxazoline, 2-*tert*-butyl-2,2-dimethyl-2-

oxazoline, *O*-methyloxime of D-camphor, and 8-methylquinoline were used in C–C bond formation reactions with aryl, benzyl and allylboronic acids or esters. Two protocols for a C–C coupling were developed; both involve the use of a base and the conversion of dimeric cyclopalladated complexes to the mononuclear derivatives with PPh_3 as an auxiliary ligand. The (sp^2)C–(sp^2)C bond formation was successfully achieved by reacting complexes PPh_3-**II.1** and PPh_3-**II.4** with $ArB(OH)_2$ in acetone at 60 °C in the presence of Cs_2CO_3, and the corresponding products **II.3** and **III.5** were isolated in 73–90%. Reactions of (i) (sp^3)*C,N* complexes PPh_3-**II.6**, PPh_3-**II.8,** and PPh_3-**II.10** with $ArB(OH)_2$ (Ar = Ph, *p*-$NO_2C_6H_4$, *p*-$MeOC_6H_4$, 8-quinolyl and 2-pyridyl) and (ii) (sp^2)*C,N* palladacycle PPh_3-**II.4** with pinacol esters of allyl- and benzylboronic acids occurred in a refluxing 4:1 mixture of dioxane-water in the presence of K_3PO_4 and afforded (sp^2)C–(sp^3)C coupling products **II.7**, **II.9**, **II.11** and **II.15** in 46–89% yield. Compounds **II.16b**–**II.18b** with an (sp^3)C–(sp^3)C bond were isolated in 67, 38, and 17% in the reactions of pinacol ester of benzylboronic acid with (sp^3)*C,N* palladacycles PPh_3-**II.6**, PPh_3-**II.8,** and PPh_3-**II.10**, respectively. The stereoselectivity of the transformation was investigated using reactions of *p*-$NO_2C_6H_4B(OH)_2$ with two diastereomeric complexes having different absolute configurations of the chiral center attached to the metal, (1*R*,2*S*,4*R*,*Z*)-**II.12** and (1*R*,2*R*,4*R*,*Z*)-**II.12**. Both reactions yielded the same isomer, (1*R*,3*R*,4*R*,*Z*)-**II.13b**. The X-ray crystallographic data of (1*R*,3*R*,4*R*,*Z*)-**II.13b** were obtained.

In the third part of the dissertation, the Pd-catalyzed arylation of arylboronic acids with triarylphosphines was investigated. Various parameters of this transformation, such as the oxygen presence, choice of solvent, temperature, palladium source, bases and oxidants, were tested and the optimal conditions of the aryl transfer were determined. The

effect of electron-withdrawing and electron-donating substituents on the aryl groups of both reactants was also studied. The unusual transfer of the acetate group from $Pd(OAc)_2$ to *p*-nitrophenylboronic acid in the presence of PAr_3 was observed. A plausible mechanism of the Pd-catalyzed aryl group transfer from PAr_3 to the arylboronic acid was proposed.

INTRODUCTION AND GOALS OF THE STUDY

Palladium-mediated and palladium-catalyzed reactions are well known for their wide application and extraordinary results in organic and organometallic synthesis. There are many reasons why transformations of organopalladium compounds have been one of the primary foci in synthetic chemistry. Many Pd-containing reagents are compatible with a variety of functional groups. Also, the metal can form a stable sigma bond with many carbon-containing groups, such as alkyl, aryl, vinyl and alkynyl. Compared to other metals, Pd-containing compounds have low toxicity and, therefore, are often used in industry to produce fine organic chemicals.

One of the research directions pursued by our group has been the preparation, characterization and application of the specific group of Pd(II) derivatives called cyclopalladated complexes (CPCs). In contrast with other organometallic compounds, CPCs are moisture- and air-stable. Many of them, especially those with an (sp^2)C–Pd bond, can be readily synthesized from compounds with donor atoms such as N, P and S. CPCs can be obtained as pure enantiomers with C, P and N-stereocenters.

This dissertation has three Chapters. They all focus on preparing and using Pd(II) compounds as reactants or catalysts. Chapter I describes the preparation and characterization of the unique camphor-derived chiral CPCs with the stereogenic center directly bonded to palladium. Chapter II reports reactions of the camphor-derived palladacycle and related Pd(II) complexes with boronic acids. These reactions represent a new approach for the creation of (sp^2)C–(sp^2)C, (sp^2)C–(sp^3)C, and (sp^3)C–(sp^3)C bonds. While studying transformations of boronic acids, we observed their arylation by PPh_3 in

the presence of Pd(II) species. The scope, limitations, and possible mechanism of this reaction are described in Chapter III.

Specific goals of the study presented in this dissertation are as follows:

1. To obtain a diastereomerically pure cyclopalladated complex based on *N*,*N*-dimethylhydrazone of D-camphor, ascertain the absolute configuration of the formed chiral center bonded to the metal in the complex, and determine palladacycle's stability in solutions and solid form.
2. To determine the scope and limitations of the reactions between boronic acids and *C*,*N*-cyclopalladated complexes with an (sp^2)C–Pd or (sp^3)C–Pd bond.
3. To develop the general procedure for the formation of (sp^2)C–(sp^2)C, (sp^2)C–(sp^3)C, and (sp^3)C–(sp^3)C bonds using the reaction of cyclopalladated complexes with boronic acids or esters.
4. To investigate the stereoselectivity of the C–C bond formation in the reactions of boronic acids with the cyclopalladated complex having a Pd-bound chiral center with a specific absolute configuration.
5. To determine the factors promoting the Pd(II)-catalyzed arylation of boronic acids using triarylphosphines.

CHAPTER I. NEW OPTICALLY ACTIVE CAMPHOR-DERIVED CYCLOPALLADATED COMPLEXES WITH AN ASYMMETRIC CARBON BONDED METAL

I.1. Background

Direct cyclopalladation via (sp^3)C–H bond activation using Pd(II) salts remains challenging in spite of a number of studies focused on this topic. As a rule, cyclopalladation at a primary (1°) (sp^3)C is the most straightforward task,[1–29] while the formation of a tertiary (3°) (sp^3)C–Pd bond requires special conditions.[30,31] Cyclopalladation of alkyl groups is likely to be successful when (sp^3)C–H bond activation takes place (i) at the benzylic position,[1–4,6–12,29,32–35] (ii) at the *tert*-butyl[4,17,18,23–25] or a structurally similar[13,26–28] fragment, (iii) next to a heteroatom or an electron-withdrawing group[14–21,36,39–41] or (iv) when a pincer complex can be produced.[13,31,32,42–46] Palladacycles formed via secondary (sp^3)C–H bond activation are relatively rare,[2,13,32–37,39] and all known examples were formed from the preligands with the features mentioned above. Metalation at the CH_2 group of non-symmetrical preligands deserves special attention because it results in the formation of a stereogenic center. The presence of a chiral center near the metal is likely to increase chirality induction in asymmetric reactions catalyzed by such complexes. Also, optically active palladacycles with a chiral center bonded to the metal are excellent models for studying mechanisms, including stereochemistry, of various known transformations at an (sp^3)C–Pd bond. Such reactions, in their turn, may be used to predict stereoselectivity of Pd-catalyzed reactions occurring with the formation of palladacycles as intermediates. So far, only a limited number of chiral non-racemic cyclopalladated complexes (CPCs) with an asymmetric carbon bonded the metal have been reported (Chart I.1).[2,13,32,33,36,38,39,42,47] All of them were formed by direct cyclopalladation of an (sp^3)C

atom. There are also racemic CPCs with an asymmetric carbon attached to the metal, which were obtained either through C–H bond activation[33,37,39–41,48,49] or transmetallation.[50,51]

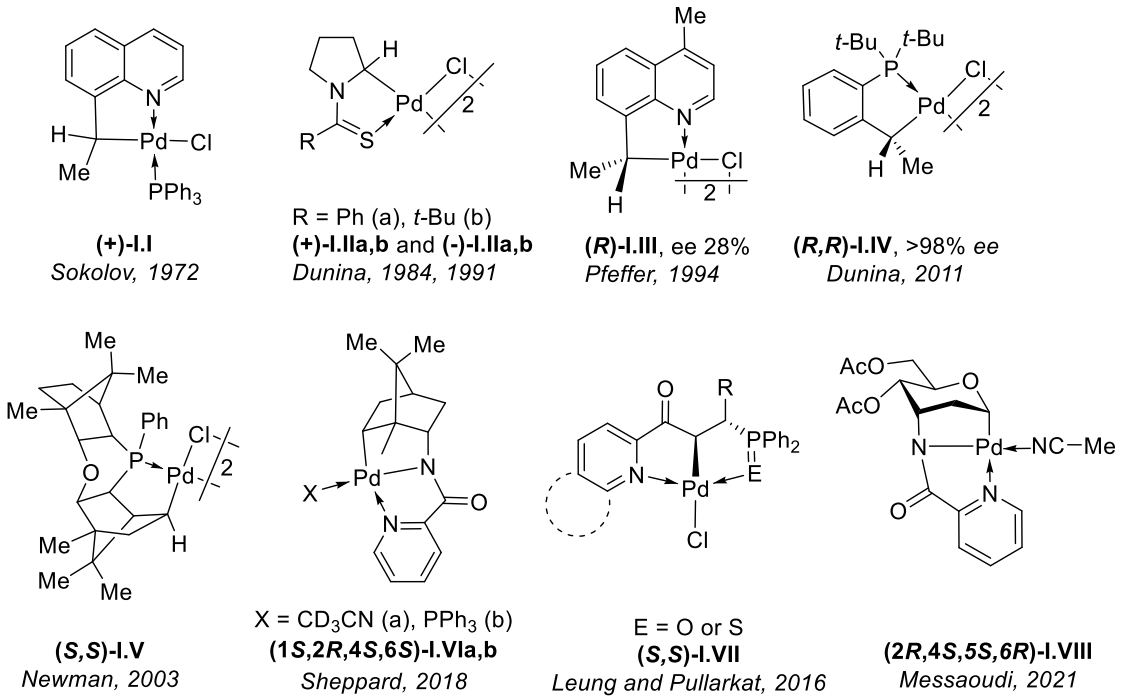


Chart I.1. Reported optically active cyclopalladated complexes with the metal bonded to a chiral center and obtained by 2° (sp^3)C–H bond activation using Pd(II) salts.[2,13,32,33,36,38,39,42,47]

Considering the applications of enantiopure CPC's in organic synthesis, natural products from the chiral pool with rigid structures such as bicyclic monoterpenoids are advantageous for the synthesis of CPC's and studying their structure using spectroscopic analysis. Having the above structural features, readily available D-camphor has been chosen as the starting material for this study of interest.

Previously, the Kuchin group and we reported direct cyclopalladation of *N*-benzylimine and oximes of D-camphor[27,52] and closely related L-fenchone[28] (Chart I.2, structures **I.IXa,b** and **I.Xa,b**). In all the cases, metalation occurred at the CH_3 group attached to one of the two bridgehead 4° carbons of the norbornane framework. In this

Chapter of the dissertation, we describe our detailed study of the regioselective cyclopalladation of D-camphor *N*,*N*-dimethylhydrazone at a CH_2 group resulting in metallacycle **I.X** (Chart I.2) with a new chiral center bonded to a metal. Preliminary results were obtained by the former member of our group Dr. Gerard C. Dickmu.[53]

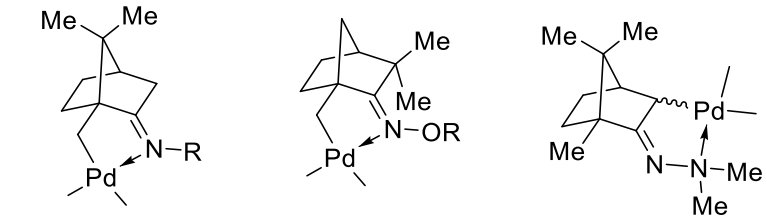
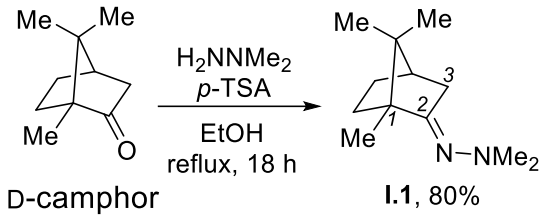


Chart I.2. Reported (**I.IXa,b**[28] and **I.Xa,b**[29]) and possible (**I.IXc** and **I.XI**) palladacycles derived from *N*-benzylimine, *O*-methyloxime and *N*,*N*-dimethylhydrazone of D-camphor and L-fenchone.

I.2 Results and Discussion

I.2.1 Cyclopalladation of *N*,*N*-Dimethylhydrazone of D-Camphor

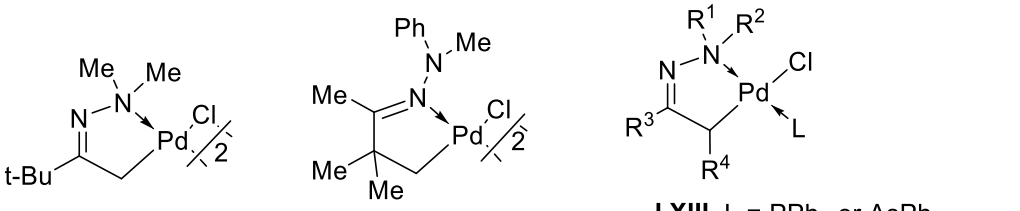
N,*N*-Dimethylhydrazone of D-camphor (**I.1**, Scheme I.1) was synthesized from the ketone and *N*,*N*-dimethylhydrazine in the presence of *p*-toluenesulfonic acid (*p*-TSA) using a modified procedure reported by Chelucci *et al.*[54,55] We used an equimolar quantity of *p*-TSA instead of the catalytic amount recommended by Chelicci *et al.* This modification allowed us to reduce the reaction time from 8 days to 18 hours. NMR spectral data of compound **I.1** matched those reported for this compound previously by Dr. Dickmu and others.[53–55]



D-camphor **I.1**, 80%

Scheme I.*1*. Synthesis of D-camphor *N*,*N*-dimethylhydrazone **I.1**.

The hydrazone moiety is a well-known directing group in cyclometalation.[16–21] Reported hydrazone-based palladacycles with (sp^3)C–Pd bonds are five-membered and have either the (sp^2)N or (sp^3)N atom forming the dative bond with the metal (Chart I.3). In the synthesis of the dinuclear derivative **I.XII**, either Na_2PdCl_4[18,19] or the coordination complex $Pd(HL)_2Cl_2$ (HL = pinacolone)[17] in MeOH in the presence of NaOAc were used.[16,21] Compound **I.XIV** was obtained by reacting pinacolone with $Pd(PhCN)_2Cl_2$ in benzene for seven days.[17] Mononuclear complexes of type **I.X** were prepared by treating the corresponding hydrazones with $Pd(PPh_3)_2Cl_2$ and NaOAc in MeCN at 65–75 °C for 24–48 h.[16,21] It is noteworthy that the reported attempt to form a cyclopalladated complex by reacting *N*,*N*-dimethylhydrazone of D-camphor with $Pd(PPh_3)_2Cl_2$ was unsuccessful.[16]



I.XI
McDonald & Shaw, 1980

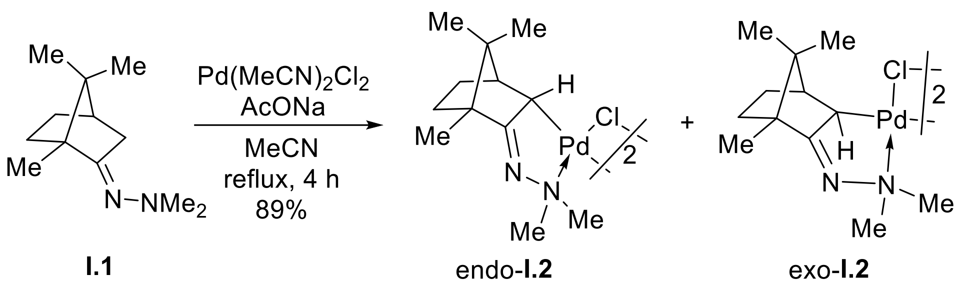
I.XII
Natile, 1983

I.XIII, L = PPh_3 or $AsPh_3$
$R^1 = R^2$ = Me, R^3 = Ph, Me, *i*-Pr, R^4 = H
$R^1 = R^2$ = Me, R^3 = *i*-Pr, R^4 = Me
R^1-R^2 = Cy, R^3 = Me, R^4 = H
$R^1 = R^2$ = Me, R^3-R^4 = Cy
Echavarren, 1994 and 1995

Chart I.3. Known hydrazone-derived palladacycles with an (sp^3)C–Pd bond.

Assuming the formation of a five-membered metallacycle, direct cyclopalladation of *N*,*N*-dimethylhydrazone of D-camphor (**I.1**) may give two types of palladacycle, **I.IXc**

and **I.XI** (Chart I.2), with an (sp^2)N–Pd bond and an (sp^3)N–Pd bond, respectively. According to the preliminary data obtained by Dr. Dickmu, the four-hour reaction of hydrazone **I.1** with $Pd(MeCN)_2Cl_2$ in the presence of NaOAc in MeCN at reflux provided 92% of the desired CPC, **I.2**.[52] In our hands, the continuous reaction monitoring revealed that the cyclometallation is completed within 30 min at reflux (82 °C). After workup and purification, the yield of the pure complex was 89%, which is closed to Dr. Dickmu's result. The necessity of the high temperature, >80 °C, to achieve the cyclopalladation was confirmed by monitoring the reaction progress by thin-layer chromatography at room temperature and 55 °C. In both cases, only coordination complex $Pd(HL)_2Cl_2$ (HL = **I.1**) was observed.



Scheme I.2. Cyclopalladation of D-camphor *N,N*-dimethylhydrazone **I.1**.

In our hands, all successful cyclopalladation reactions of **I.1** resulted in the formation of only one palladacycle, **I.XI**. This conclusion was made based on the ^{1}H and $^{13}C\{^1H\}$ NMR spectra of the isolated product **I.2**, which showed signals of the three methyl groups on the camphor moiety in addition to the nonequivalent methyl groups on the (sp^3)N atom. Overall, the ^{1}H and $^{13}C\{^1H\}$ NMR spectra of **I.2** were somewhat challenging to interpret. The spectra complexity appears to be due to the presence of endo and exo palladacycles in dimer **I.2** as well as cis and trans forms of both dimeric isomers (Chart I.4).[53]

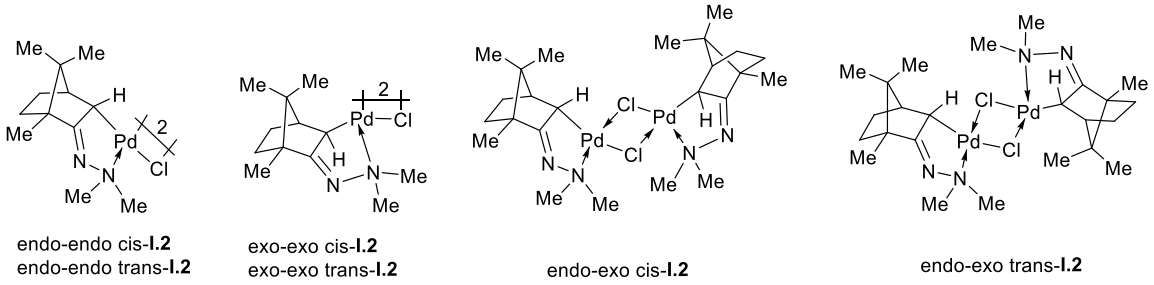
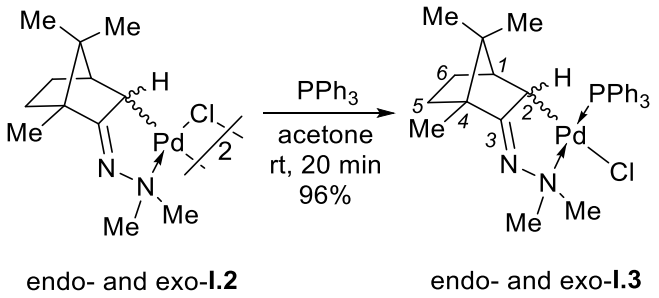


Chart I.4. Possible isomers of complex **I.2**.

To simplify ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra and attempt to separate endo and exo palladacycles, complex **I.2** was reacted with 2 equiv. of PPh_3 in acetone at rt to give the mononuclear adduct **I.3** (Scheme I.3). The ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra of complex **I.3** confirmed the presence of two stereoisomers in a 1:1 ratio, one with an endo C−Pd bond (endo-**I.3**) and the other with an exo C−Pd bond (exo-**I.3**, Scheme 1.3). The isomers were partly separated by column chromatography on silica gel using a 1:4 mixture of ethyl acetate and hexanes. According to the ^{1}H NMR spectra, the isomeric purity of the isolated samples of endo-**I.3** and exo-**I.3** were 96 and 86% de, respectively. The solutions of endo- (96% de) and exo-**I.3** (86% de) in $CDCl_3$ and C_6D_6 slowly epimerized at rt and became the 1:1 mixtures in two weeks. After the third week, the ^{1}H NMR spectra contained several new signals suggesting decomposition of the isomers. Some of the new signals were identified as those belonging to triphenylphosphine oxide and dimer **I.2**. Neither epimerization nor degradation was observed for isomerically enriched samples of endo- and exo-**I.3** kept in C_6D_6 solutions for five months at +3 ^{o}C.



Scheme I.3. Reaction of complex **I.2** with PPh_3.

The absolute configurations of the chiral center attached to the metal are different for endo-**I.3** and exo-**I.3**. 1D NOE experiments were conducted for each isomer by irradiating the protons at C(1) and C(2). The spectral data confirmed the endo and exo positions of hydrogens at C(2) in complexes exo-**I.3** and endo-**I.3**, respectively. It is noteworthy that the chemical shift values of the $^{31}P\{^{1}H\}$ NMR signals of endo- and exo-**I.3** were very similar, 32.8 and 33.4 ppm, respectively. The structures of these two diastereomers were further confirmed by X-ray crystallographic data (Section I.2.2).

I.2.2 X-Ray Crystallographic Studies of endo-**I.3** and exo-**I.3**

We were able to obtain the crystals of endo-**I.3** and exo-**I.3** suitable for single-crystal X-ray crystallographic study. The crystals were grown in ethyl acetate. The X-ray study was performed by Dr. Ugrinov from NDSU. The X-ray single-crystal data of complexes endo-**I.3** and exo-**I.3** unambiguously proved their cyclopalladated structure and the palladation at the CH_2 group next to the hydrazone functionality. The molecular structures of endo-**I.3** and exo-**I.3** and the numbering schemes are presented in Figures I.1 and I.2, respectively.

Dr. Dickmu described the X-ray crystallographic study of the dimeric complex **I.2**.[53] To the best of our knowledge, there are no other reported crystal structures for *C,N*-

CPCs with a 2° (sp^3)C–Pd bond; however, there are X-ray data for the related *C*,*N*,*N*-pincer complex (1*S*,2*R*,4*S*,6*S*)-**I.VI** with PPh_3 as the auxiliary ligand (see Chart I.1).

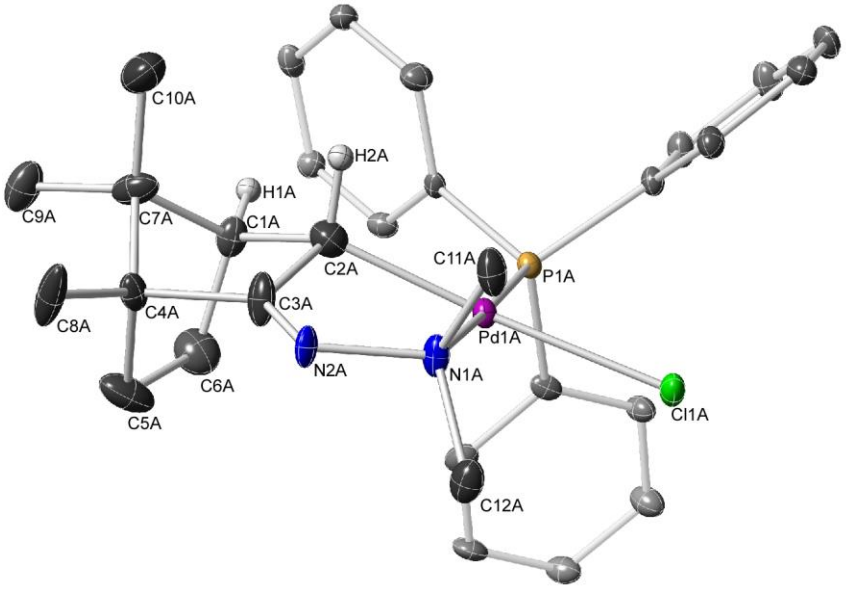


Figure I.1. ORTEP drawing of the molecular structure of CPC endo-**I.3**. Thermal ellipsoids are shown at the 50% probability level.

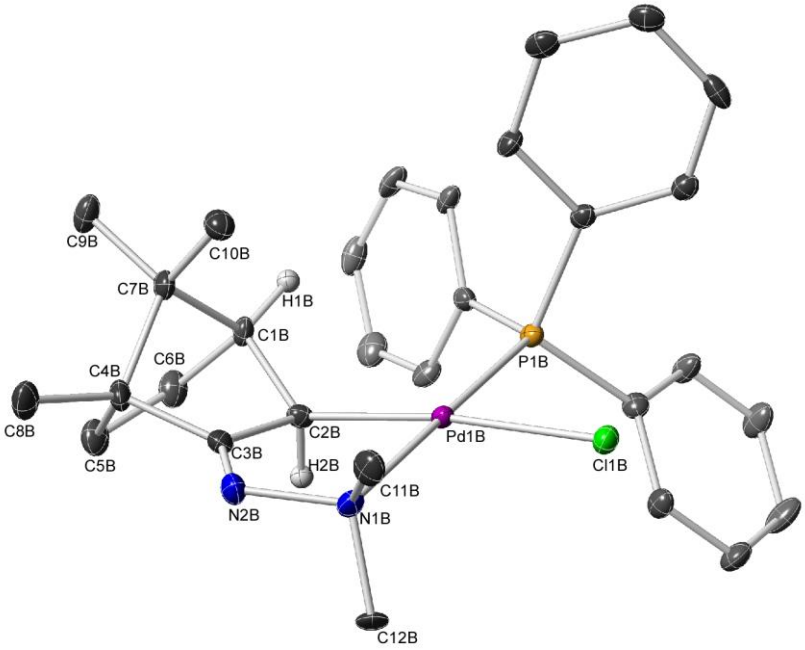


Figure I.2. ORTEP drawing of the molecular structure of CPC exo-**I.3**. Thermal ellipsoids are shown at the 50% probability level.

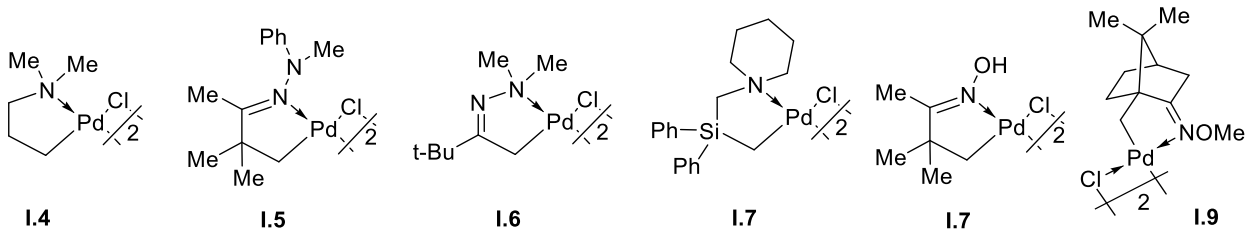


Chart I.5. Examples of chloro-bridged dimeric *C,N*-CPCs with an (sp^3)C–Pd bond and a known molecular structure.[17,27,28,60,61]

A mixture of two diastereomers, exo-**I.3** and endo-**I.3**, crystallized from ethyl acetate at rt in the space group *P*1. Two isomers, endo-**I.3** and exo-**I.3**, were found in a crystallographic unit cell. Both structures have the *N,P*-trans geometry typical for mononuclear *C,N*-complexes with PPh_3 as the auxiliary ligand.

We compared bond lengths and angles determined for endo-**I.3** and exo-**I.3** with the data reported previously for dimer **I.2**[53] and related complexes **I.4**–**I.6**. The (sp^3)C–Pd bond length in complexes endo-**I.3,** and exo-**I.3** varied noticeably. First, these lengths were shorter in the dimer regardless of the metallacycle type. Secondly, the C–Pd distances in the endo palladacycles of complexes **I.2** and endo-**I.3** were 1.982 and 2.031 Å, while in the corresponding exo metallacycles those lengths were longer, 2.006 and 2.072 Å, respectively. The last value was higher than those reported for complexes **I.4**–**I.9** and **I.VI** (1.959–2.034 Å).

The (sp^3)N–Pd bonds in **I.2**,[53] exo-**I.3** and endo-**I.3** were a little bit longer than the (sp^3)C–Pd bonds in the corresponding metallacycles that is typical for chloro-bridged dimeric *C,N*-CPCs with the (sp^2)N and (sp^3)C or (sp^3)N and (sp^3)C donor atoms and trans geometry of cyclopalladated ligands.[27,56–59] In dimer **I.2**, both N–Pd distances were practically the same: 2.077 Å in the endo palladacycle and 2.078 Å in the exo analog. As

in the case of the C–Pd bond, the Pd–N distances in the mononuclear complexes endo- **I.3** and exo-**I.3** were longer than those in the dimer, 2.144 and 2.157 Å, respectively. For comparison, the (sp^3)N–Pd bond length in the closest analog **I.6** is 2.063(1) Å.[17]

The C-Pd-N torsion angles in mononuclear exo- and endo-**I.3** were slightly different from each other: 80.42 and 81.16°, respectively. For comparison, the C-Pd-N bite angles in both palladacycles of dimer **I.2** were practically the same: 80.81° for the endo palladacycle and 80.80° for the exo analog.[52] These four values fall in the range reported for compounds **I.4**–**I.6** and **I.9**: 84.5(1), 80.7(7), 82.9(6), and 82.14(10), respectively.[17,28,60] In complex **I.7** with a silicon atom in the metallacycle, the angle reached 86.81(9)°.[61] For comparison, the C-Pd-N angle for chloro-bridged CPCs with the (sp^2)N and (sp^2)C donor atoms varied from 80.3 to 81.2°.[56–58] For the corresponding complexes with (sp^3)N and (sp^2)C, the C-Pd-N bite angle was slightly larger, 80.6−82.8°.[59,60]

The palladium atoms in complexes endo-**I.3,** and exo-**I.3** were nearly in square-planar coordination with a slight tetrahedral distortion. The same coordination was reported for complex **I.2**.[53] The angles between the planes {N-Pd-C} and {Cl-Pd-Cl} for the endo palladacycles in dimer **I.2** and endo-**I.3** are only 6.02 and 6.00°. The angles between the corresponding planes determined for two exo palladacycles in complexes **I.2** and exo-**I.3** were even smaller, 3.61 and 3.30°, respectively. Such almost ideal square-planar geometry has been reported for many aliphatic palladacycles.[63]

The endo and exo metallacycles of dimer **I.2** was described as slightly twisted envelopes with C(2) and Pd(1A) serving as the envelope flaps.[53] The distortion of each metallacycle from planarity was estimated using the sum of absolute values of intrachelate torsion angles.[64] The sums were equal to 89.68 and 72.32° for the endo and exo

palladacycles in the dimer. These values were similar to those calculated for the palladacycles in endo-**I.3** and exo-**I.3**, 88.26 and 71.60°. A similar distortion of the *C,N*-palladacycle was reported for the oxime camphor-derived complex **I.9**. Interestingly, the palladacycle's distortion in camphor-derived complexes **I.2**,[53] endo-**I.3**, exo-**I.3**, and **I.9**[27] was significantly less than that reported for the amine-derived dimer **I.4**, 158°.[60]

I.3. Experimental

I.3.1 General Methods and Materials

Materials. The laboratory grade D-camphor (Alfa Aesar), $PdCl_2(MeCN)_2$ (Strem Chemicals), *N*,*N*-dimethylhydrazine (Acros Organics), and anhydrous NaOAc (Sigma-Aldrich, 99%) were used as purchased. PPh_3 (Sigma Aldrich) was recrystallized from ethanol-water. $Pd(OAc)_2$ (Strem Chemicals) was dissolved in hot benzene, and the resulting solution was filtered. After filtration, benzene was removed using a rotavapor, and $Pd(OAc)_2$ was dried in vacuum. All solvents were purified using standard methods.[65] Deuterated solvents were purchased from Cambridge Isotope Laboratories, Inc. and kept over molecular sieves 4Å.

General Methods and Instrumentation. Reactions were monitored using Merck TLC aluminum sheets precoated with silica gel 60 F_{254}. Column purifications were carried out by using 100–200 mesh silica gel from Natland International Corporation. ^1H, $^{13}C\{^1H\}$, $^{31}P\{^1H\}$, DEPT, COSY, HMQC, and 1D NOE NMR spectra were recorded on a Bruker AVANCE 500 NMR spectrometer. Chemical shifts are reported in ppm relative to $SiMe_4$ as an internal standard for ^1H and $^{13}C\{^1H\}$ NMR spectra and $P(OEt)_3$ as an external standard for $^{31}P\{^1H\}$ NMR spectra. Coupling constants, *J*, are given in Hz. IR spectra were recorded using a Thermo Scientific Nicolet iS5 IR spectrometer. Optical rotations were measured using a Jasco P-2000 polarimeter. Melting points were determined using a Melt-Temp II apparatus. CHN elemental analyses were carried out by Atlantic Microlabs, Inc., Norcross, GA.

1.3.2 Preparation of Complexes and Their Spectra

(*E*)-1,1-Dimethyl-2-[(1*S*,4*R*)-bicyclo[2.2.1]heptan-2-ylidene]hydrazine (D-Camphor *N*,*N*-Dimethylhydrazone) (**I.1**). Monohydrate of *p*-toluenesulfonic acid (6.24 g, 32.8 mmol) and *N*,*N*-dimethylhydrazine (5.74 mL, 75.4 mmol) were added to a solution of D-camphor (4.99 g, 32.8 mmol) in ethanol (40 mL) at rt. The reaction mixture was refluxed for 18 h and then cooled to rt. The solvent was removed on a rotavapor, then water (50 mL) was added to the residue. The mixture was extracted with ethyl acetate (3 × 20 mL). Organic layers were combined and washed with saturated aq. $NaHCO_3$ solution (2 × 25 mL) followed by water (30 mL) and saturated brine solution (30 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to yield 5.2 g (80%) of compound **1** as a colorless liquid. R_f 0.52 (1:4, EtOAc–hexanes); $[\alpha]_D^{22}$ = + 30.5 (*c* 25.6, acetone). IR (neat, *v*, cm^{-1}): 1665 (C=N). ^{1}H NMR (δ, ppm, C_6D_6): 0.72 (s, 3H, C(9)H_3), 0.73 (s, 3H, C(10)H_3), 0.99–1.06 (m, 1H, exo-C(6)H), 1.16 (s, 3H, C(8)H_3), 1.39 (ddd, $^2J_{endo\text{-}5,exo\text{-}5}$ = 12.5, $^3J_{exo\text{-}5,exo\text{-}6}$ = 9.5, $^4J_{exo\text{-}5,exo\text{-}3}$ = 4, 1H, exo-C(5)H), 1.53 (td, $^2J_{endo\text{-}5,exo\text{-}5}$ = $^3J_{endo\text{-}5,endo\text{-}6}$ = 12.5, $^3J_{endo\text{-}5,exo\text{-}6}$ = 3.4, 1H, endo-C(5)H), 1.58–1.65 (m, 2H, C(4)H and endo-C(6)H), 1.99 (d, $^2J_{endo\text{-}3,exo\text{-}3}$ = 18, 1H, endo-C(3)H), 2.48 (s, 6H, N(CH_3)$_2$), 2.53 (dt, $^2J_{endo\text{-}3,exo\text{-}3}$ = 18, $^3J_{exo\text{-}3,4}$ = $^4J_{exo\text{-}3,exo\text{-}5}$ = 4, 1H, exo-C(3)H). ^{13}C{^{1}H} NMR (δ, ppm, C_6D_6): 12.3 (C(8)), 19.2 (C(9)), 19.9 (C(10)), 28.1 (C(6)), 33.3 (C(5)), 36.1 (C(3)), 44.7 (C(4), 47.7 (N(CH_3)$_2$), 52.8 (C(1) and C(7)), 177.0 (C(2)=N).

Di-μ-chlorobis[(1*R*,2R,4*R*)- and (1*R*,2S,4*R*)-3-(2,2-dimethylhydrazono)-4,7,7-trimethylbicyclo[2.2.1]heptan-2-yl-*C*,*N*]dipalladium(II) (**endo- and exo-I.2**). Anhydrous NaOAc (0.063 g, 0.77 mmol) and $PdCl_2(MeCN)_2$ (0.20 g, 0.77 mmol) were added to a solution of hydrazone **I.1** (0.15 g, 0.77 mmol) in MeCN (15 mL). The mixture

was refluxed for 30 min, cooled to rt, and then passed through a plug of celite. The filtrate was concentrated under a reduced pressure. Ice cold water (15 mL) was added to the residue, and the resulting mixture was stirred for 10 min. The solid formed was filtered and dried. Then ice cold ethyl acetate (5 mL) was added to the crude product, and the mixture was stirred for 5 min at 0–5 ^{o}C. The yellow solid was collected and dried to yield 0.23 g (89%) of compound **2**. According to ^{13}C NMR data, the product existed in solution as a mixture of at least 4 isomers. The following data are given for the mixture as separation of these isomers was unsuccessful. M.p. 209–210 °C; R_f 0.4 (1:3 EtOAc–hexanes); $[\alpha]_D^{21}$ = +0.0795 (*c* 5.12, chloroform). R (thin film in mineral oil, *v*, cm^{-1}): 1667 (C=N). ^{1}H NMR (δ, ppm, C_6D_6, integration values are tentative): 0.62–0.71 (m, 9H), 0.93–0.95 (m, 3H), 1.00 (m, 3H), 1.04–1.41 (m, 4H), 1.41–1.60 (m, 5H), 1.72–1.86 (m, 1H), 1.95–2.23 (m, 2H), 2.22–2.40 (m, 7H), 2.93–3.06 (m, 6H), 4.42–4.29 (m, 1H), 5.07–5.23 (m, 1H). ^{13}C{^{1}H} NMR (δ, ppm, C_6D_6): 11.23, 11.28, 12.39, 19.77, 19.80, 20.27, 20.30, 20.34, 20.37, 21.12, 21.15, 21.42, 21.45, 21.53, 26.35, 26.38, 26.41, 29.00, 29.07, 30.72, 30.79, 37.01, 37.07, 47.87, 48.96, 49.29, 49.35, 50.56, 50.67, 50.75, 50.95, 51.15, 51.32, 51.38, 51.48, 51.53, 51.57, 51.60, 52.07, 52.15, 52.52, 52.64, 53.35, 53.44, 53.82, 53.89, 53.99, 54.24, 54.46, 54.81, 54.85, 195.91, 196.13, 196.85, 196.99. Anal. Calcd for $C_{24}H_{42}Cl_2N_4Pd_2$: C 43.00, H 6.32, N 8.36. Found: C 43.18, H 6.18, N 8.38.

Chloro[(1*R*,2*R*,4*R*)- and (1*R*,2*S*,4*R*)-3-(2,2-dimethylhydrazono)-4,7,7-trimethylbicyclo[2.2.1]heptan-2-yl-*C*,*N*](triphenylphosphine-*P*)palladium(II) (endo-I.3 and exo-I.3). Triphenylphosphine (0.0401 g, 0.153 mmol) was added to a yellow suspension of complex **I.2** (0.0492 g, 0.0733 mmol) in acetone (5 mL). The mixture was stirred at rt for 20 min. During that time, the bright yellow reaction mixture turned a clear

and pale-yellow solution. The crude product was isolated in the amount of 0.0891 g (96%) after solvent removal in vacuum. According to ^{1}H NMR data, the crude product was a mixture of (1*S*,2*S*,4*S*) (endo-**I**.**3**) and (1*S*,2*R*,4*S*) (exo-**I.3**) diastereomers in a ratio of 1:1. The isomers were partly separated by silica gel column chromatography using a 1:4 mixture of ethyl acetate and hexanes. The yield was 0.030 g (32%, 96% de) of endo-**I.3** (a pale-yellow solid) and 0.025 g (28%, 86% de) of exo-**1.3** (a pale-yellow solid). Anal. Calcd. for $C_{30}H_{36}ClN_2PPd$: C 60.31, H 6.07, N 4.69. Found: C 60.04, H 6.01, N 4.66. Data for (1*R*,2*S*,4*R*) isomer (*endo*-**I.3**): m.p. 190–194 °C (decomp.). R_f 0.72 (3:5 EtOAc–hexanes), $[\alpha]^{22}_D$ = +253 (*c* 0.450, acetone), IR (thin film in mineral oil, *v*, cm^{-1}): 1660 (C=N). ^{1}H NMR (δ, ppm, C_6D_6): -0.10 (t, $J_{exo\text{-}2,exo\text{-}6}$ = 4, 1H, C(1)H), 0.49 (s, 3H, C(9)H_3), 0.68 (s, 3H, C(10)H_3), 1.14 (s, 3H, C(8)H_3), 1.17–1.26 (m, 2H, exo-C(5)H and exo-C(6)H), 1.33–1.43 (m, 2H, endo-C(5)H, endo-C(5)H), 2.87 (d, $^{4}J_{HP}$ = 2.9, 3H, NCH_3^A), 3.35 (d, $^{4}J_{HP}$ = 2.0, 3H, NCH_3^B), 4.56 (t, $^{3}J_{1,2}$ = $^{4}J_{exo\text{-}2,exo\text{-}6}$ = 4, 1H, PdC(2)H), 6.99–7.05 (m, 9H, *m*,*p*-PPh_3), 7.91–7.95 (m, 6H, *o*-PPh_3). ^{13}C{^{1}H} NMR (δ, ppm, C_6D_6): 11.2 (C(8)), 19.7 (C(9)), 20.8 (C(10)), 27.9 and 36.3 (C(5), C(6)), 47.6 (C(7)), 48.7 (C(1)), 50.1 and 51.7 ($N(CH_3)_2$), 52.9 (C(4)), 57.8 (d, $^{2}J_{CP}$ = 2.6, C(2)), 128.0 (d overlapped with C_6D_6, *m*-PPh), 130.0 (d, $^{1}J_{CP}$ = 2.8, *p*-PPh), 133.2 (d, $^{1}J_{CP}$ = 49, PC), 135.1 (d, $^{2}J_{CP}$ = 11, *o*-PPh), 194.5 (C(3)). ^{31}P{^{1}H} NMR (δ, ppm, C_6D_6): 32.8. Data for (1*R*,2*R*,4*R*) isomer (exo-**I.3**): m.p. 172–176 °C (decomp.); R_f 0.67 (3:5 EtOAc–hexanes); $[\alpha]^{22}_D$ = -181 (*c* 0.515, acetone), IR (thin film in mineral oil, *v*, cm^{-1}): 1665 cm^{-1} (C=N). ^{1}H NMR (δ , ppm, C_6D_6): 0.47 (s, 3H, C(10)H_3), 0.56 (ddd, $^{3}J_{exo\text{-}5,exo\text{-}6}$ = 13, $^{2}J_{endo\text{-}6,exo\text{-}6}$ = 10, $^{3}J_{1,exo\text{-}6}$ = 4, 1H, exo-C(6)H), 0.63 (t, *J* = 4, 1H, C(1)H), 1.01 (s, 3H, C(9)H_3,), 1.04 (s, 3H, C(10)H_3), 1.36–1.32 (m, 2H, endo-C(5)H and endo-C(6)H), 1.48 (ddd, $^{3}J_{exo\text{-}5,exo\text{-}6}$ = 13, $^{2}J_{exo\text{-}5,exo\text{-}6}$ = 8, $^{3}J_{exo\text{-}5,endo\text{-}6}$ = 4, 1H,

exo-C(5)H), 2.86 (d, $^4J_{HP}$ = 2.8, 3H, NCH_3^A), 3.71 (d, $^4J_{HP}$ = 1.9, 3H, NCH_3^B), 3.73 (s, 1H, PdC(2)H), 7.05–7.00 (m, 9H, *m*- and *p*-PPh_3), 7.86–7.82 (m, 6H, *o*-PPh_3). $^{13}C\{^1H\}$ NMR (δ, ppm, C_6D_6): 12.8 (C(8)), 20.1 (C(9)), 20.5 (C(10)), 30.5 (C(5)), 30.9 (d, J_{CP} = 3, C(6)), 49.47 (d, J_{CP} = 6, C(1)), 50.5 (d, J_{CP} = 2.5, C(7)), 51.1 and 52.8 ($N(CH_3)_2$), 55.6 (d, $^2J_{CP}$ = 4, C(2)), 128.0 (d overlapped with C_6D_6, *m*-PPh), 130.7 (d, $^3J_{CP}$ =3, *p*-PPh), 132.9 (d, $^1J_{CP}$ = 48, PPh), 134.9(d, $^2J_{CP}$ =11, *o*-PPh), 193.6 (C(3)). $^{31}P\{^1H\}$ NMR (δ, ppm, C_6D_6): 33.4.

I.3.3 Crystallographic Study of a Mixture of endo-**I.3** and exo-**I.3**

Complexes endo-I.3 and exo-I.3 (CCDC 1942704). Data collection and structure solution were conducted at the X-Ray Crystallographic Facility, Department of Chemistry and Biochemistry, NDSU, Fargo, ND. A crystal (approximate dimensions 0.220 × 0.180 × 0.120 mm^3) was placed onto the tip of a 0.1-mm diameter glass capillary and mounted on a Bruker APEX-II CCD diffractometer for a data collection at 110(2) K. A preliminary set of cell constants was calculated from reflections harvested from four sets of 30 frames. These initial sets of frames were oriented such that orthogonal wedges of reciprocal space were surveyed. This produced initial orientation matrices determined from 259 reflections. The data collection was carried out using IμS Cu radiation with a frame time of 10 seconds and a detector distance of 4.0 cm. A randomly oriented region of reciprocal space was surveyed to the extent of one sphere and to a resolution of 0.84 Å. Forty-three major sections of frames (39 ω and 4 ϕ scans) were collected with 2.0º steps at different 2θ detector positions in order to achieve the desired completeness. The intensity data were corrected for absorption and decay (SADABS).[64] Final cell constants were calculated from

the xyz centroids of 9757 strong reflections from the actual data collection after integration (SAINT).[67] Please refer to Table I.1 for additional crystal and refinement information.

The structure was solved and refined using SHELX (Sheldrick, 2014)[67] set of programs with Olex 2 software package. SHELXT solution was calculated which provided most non-hydrogen atoms and full-matrix least squares/difference Fourier cycles were performed which located the remaining non-hydrogen atoms. All non-hydrogen atoms were refined with anisotropic displacement parameters. All hydrogen atoms were placed in ideal positions and refined as riding atoms with relative isotropic displacement parameters. The final full matrix least squares refinement converged to $R1$ = 4.65% and $wR2$ = 12.15% (F^2, all data).

I.4 Conclusions

The known procedure for the synthesis of D-camphor *N*,*N*-dimethylhydrazone, **I.1**, was modified to allow one to obtain the single *E* isomer in 18 hours instead of eight days in 80% yield using equimolar amounts of *p*-toluenesulfonic acid. Direct cyclopalladation of hydrazone **I.1** with either $Pd(MeCN)_2Cl_2$, $Pd(OAc)_2$ or Na_2PdCl_4 took place at a secondary carbon affording a new optically active aliphatic cyclopalladated complex **I.2** with an asymmetric carbon directly bonded to the metal. Complex **I.2** appeared to be a mixture of cis/trans isomers having palladacycles with the exo and endo positions of the C–Pd bond. Diastereomeric mixtures of mononuclear complexes endo- and exo-**I.3** with PPh_3 as the auxiliary ligand were partially separated. It appears that epimerization of endo-**I.3** and exo-**I.3** occurred in $CDCl_3$ and benzene at rt, while the isomers were stable in solid form and C_6D_6 solutions at +3 ^oC. X-ray single-crystal structures for compounds endo-**I.3**

and exo-**I.3** represent the first crystallographic data for mononuclear *C,N*-cyclopalladated complexes with the metal directly connected to a chiral center.

Appendix I. NMR Spectral and X-Ray Crystallographic Data

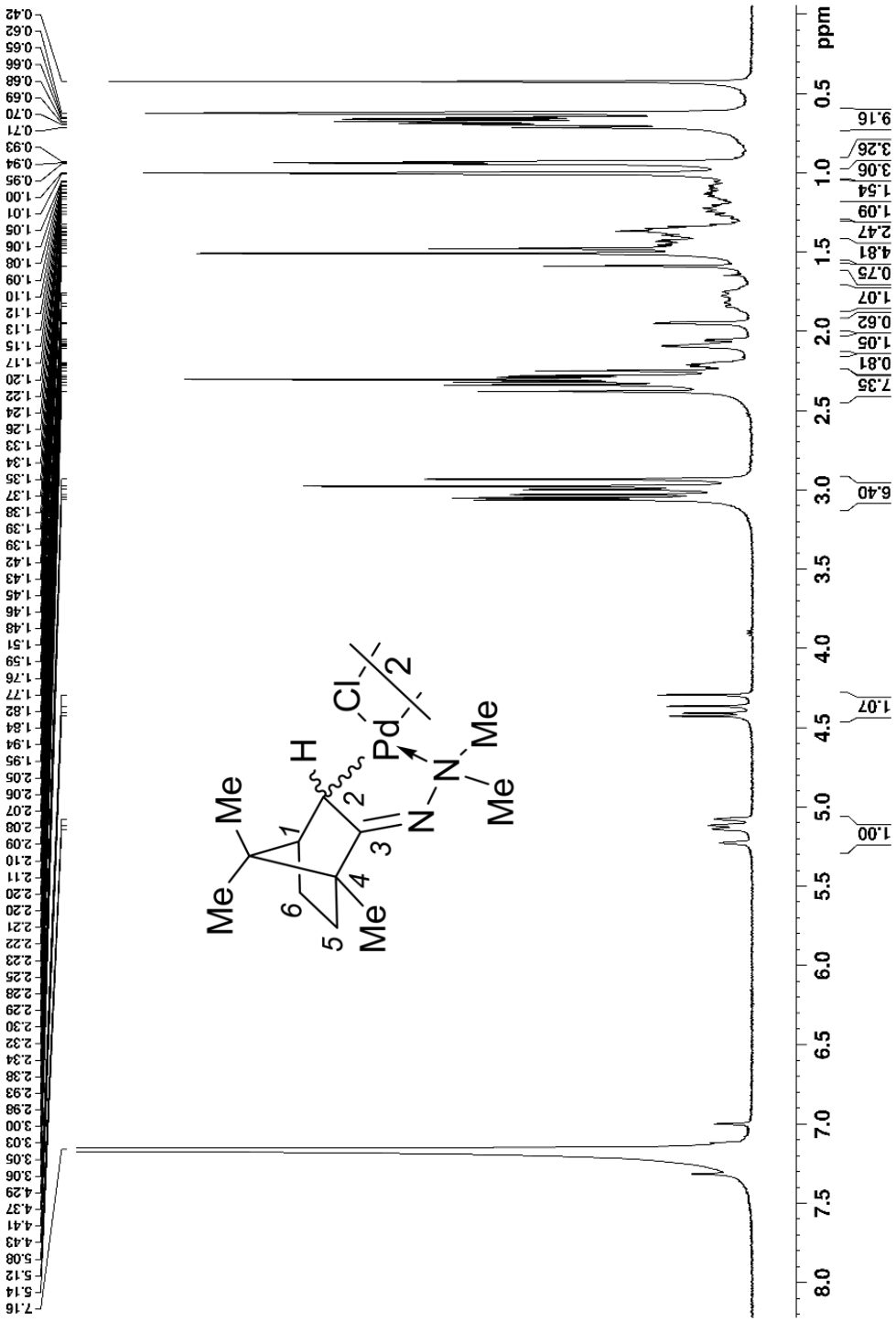


Figure I.3. ^{1}H NMR spectrum of dimer **I.2.**

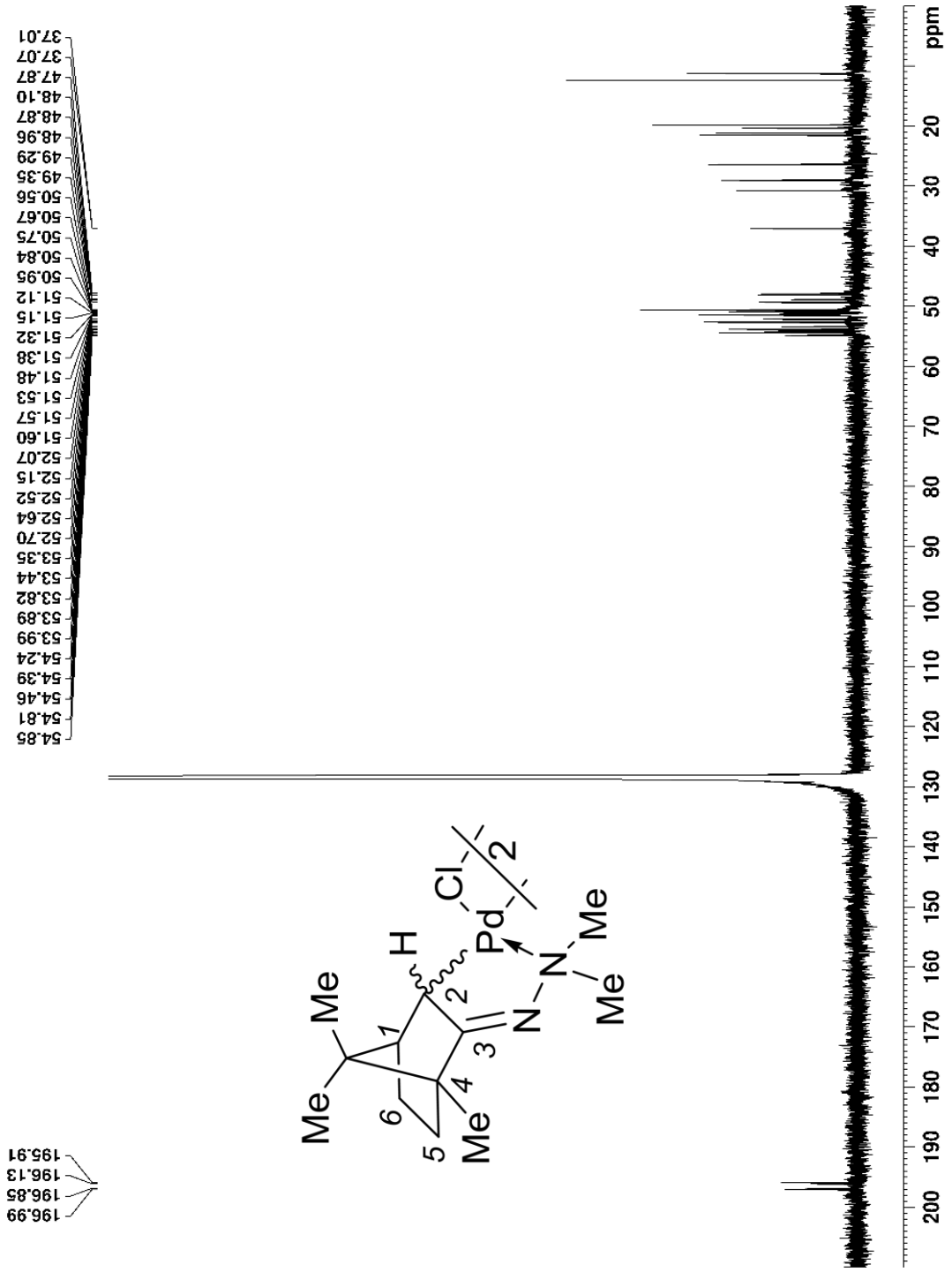


Figure I.4. $^{13}C\{^{1}H\}$ NMR spectrum of dimer **I.2**.

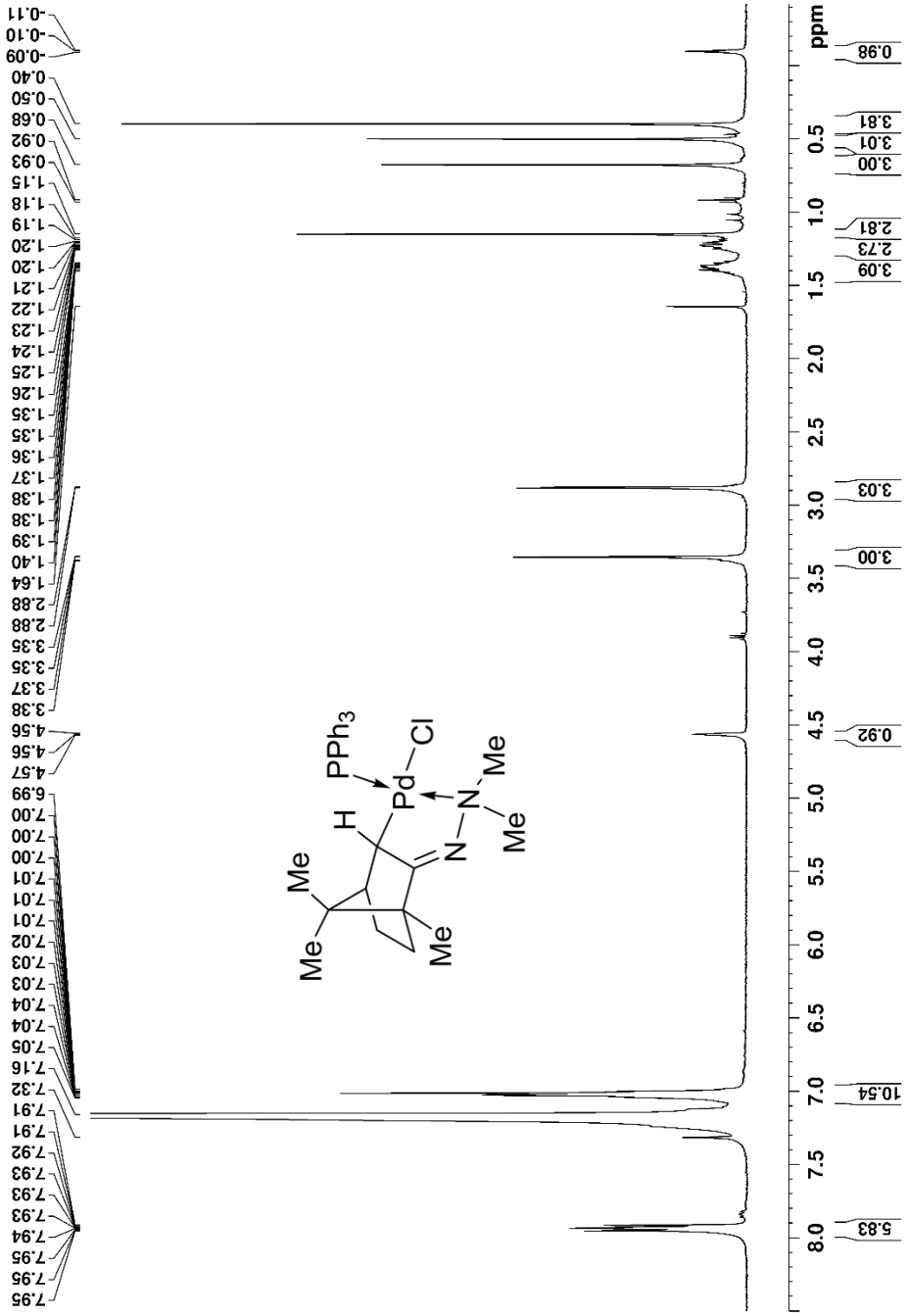


Figure I.5. ^{1}H NMR spectrum of endo-**I.3**.

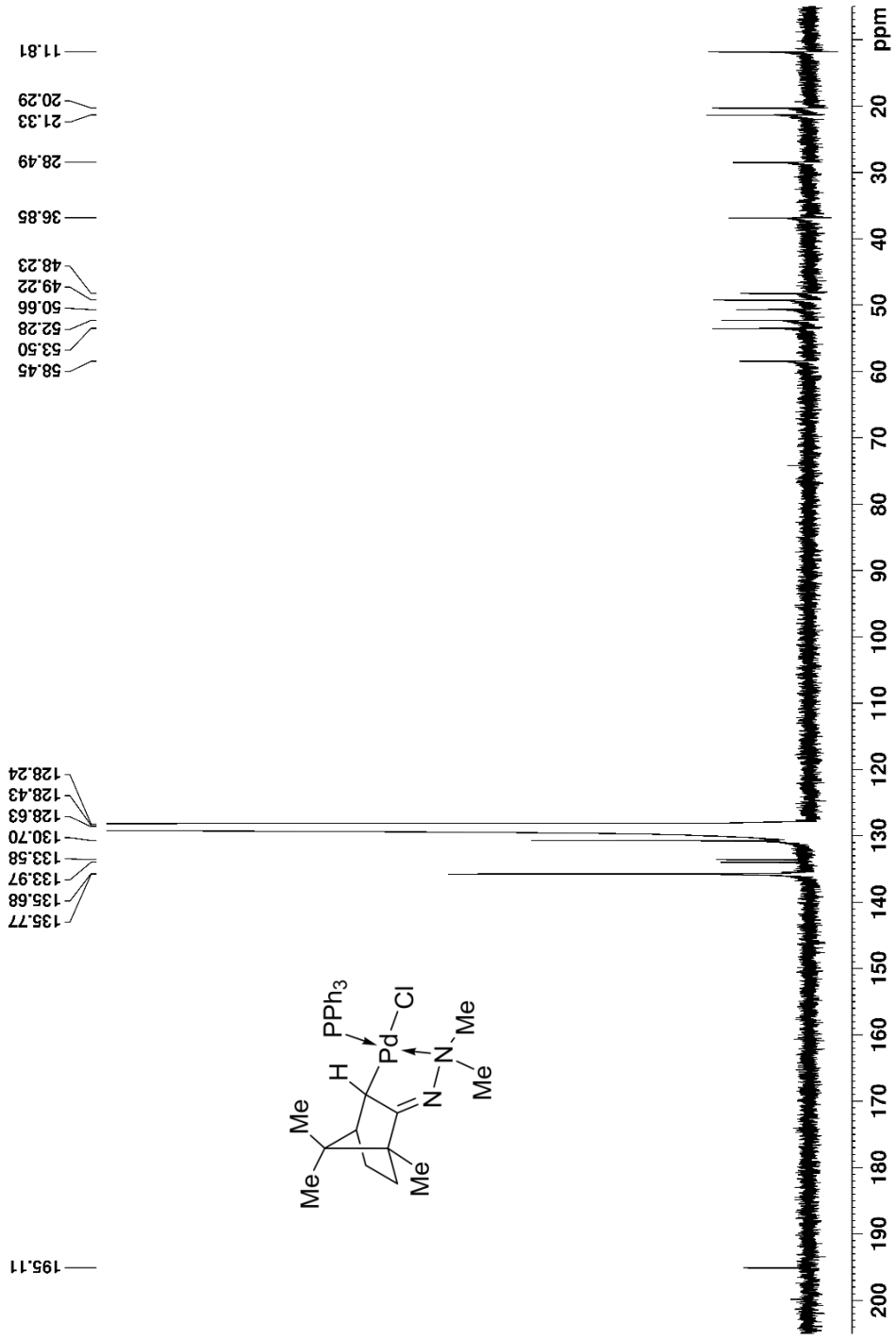


Figure I.6. $^{13}C\{^{1}H\}$ NMR spectrum of endo-**I.3**.

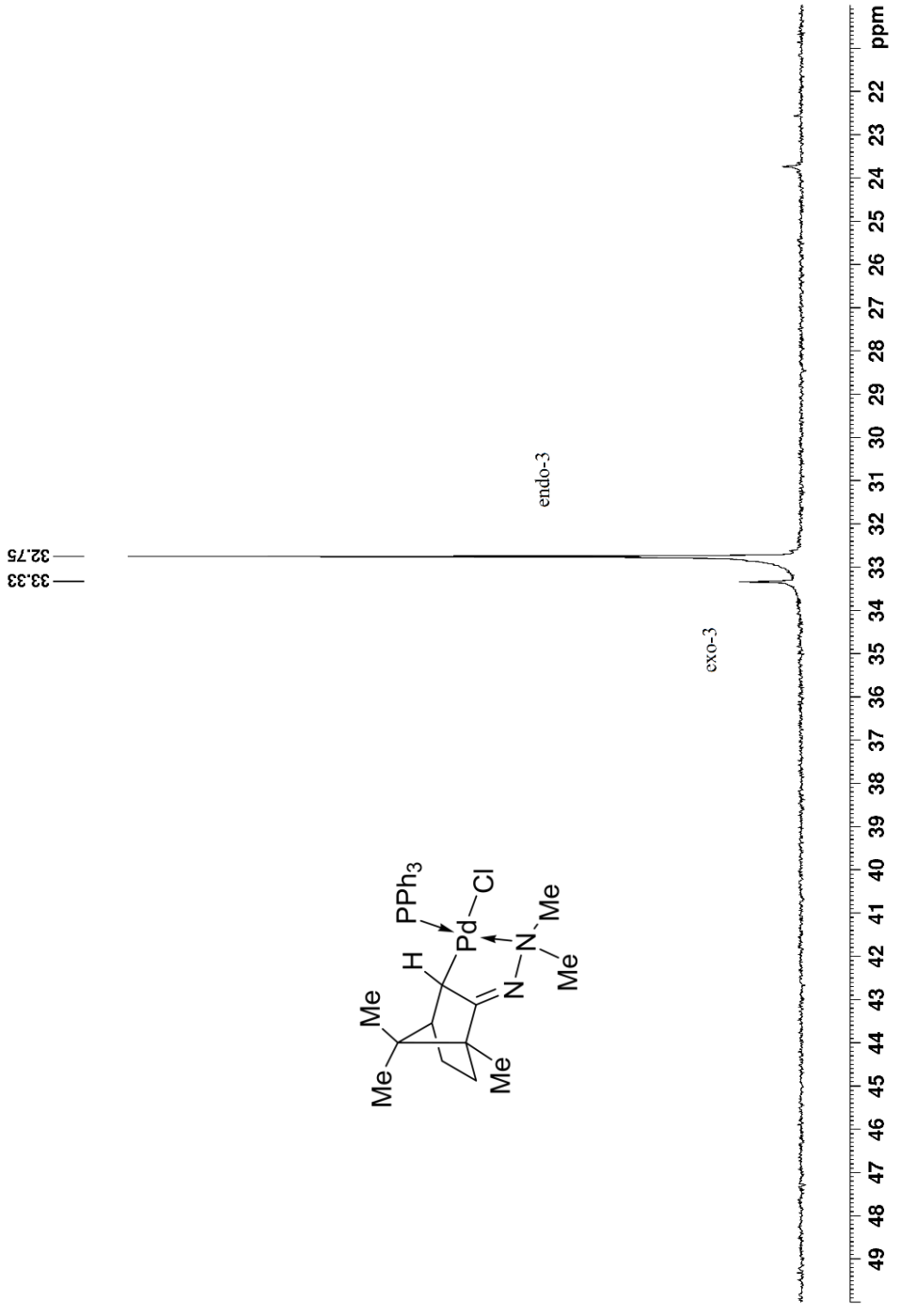


Figure I.7. $^{31}P\{^{1}H\}$ NMR spectrum of endo-**I.3**.

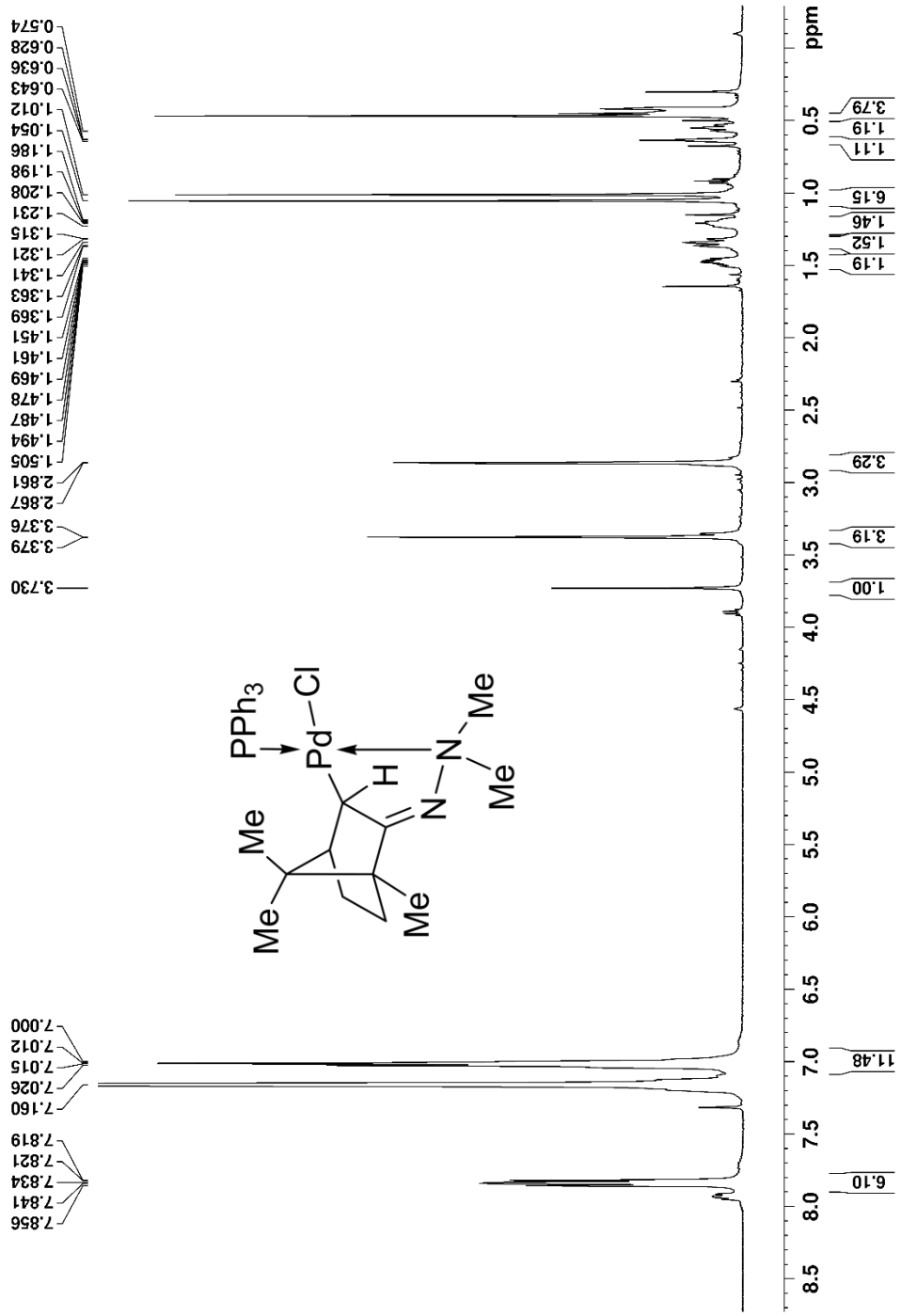


Figure I.8. ^{1}H NMR spectrum of exo-**I.3**.

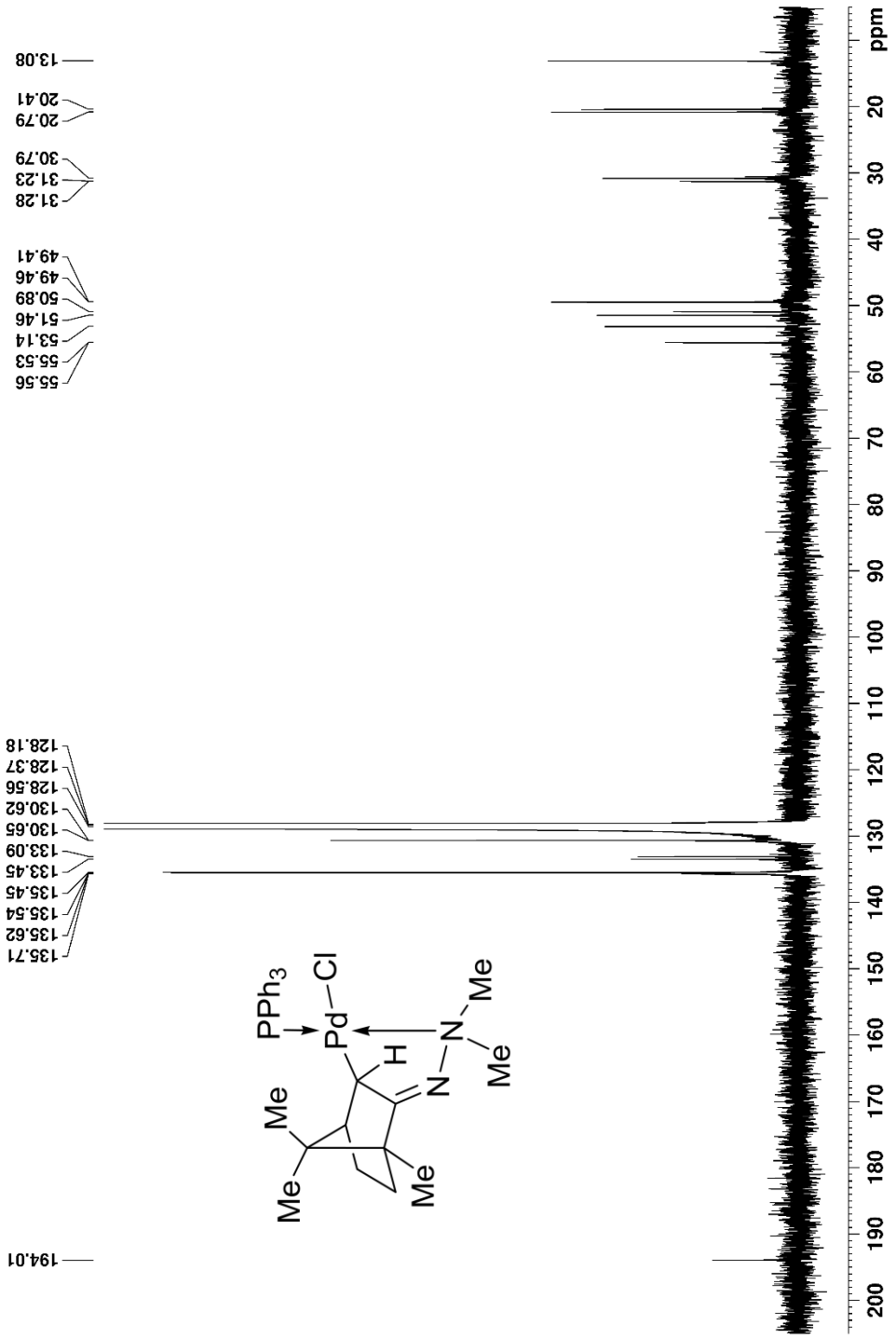


Figure I.9. $^{13}C\{^{1}H\}$ NMR spectrum of exo-**I.3**.

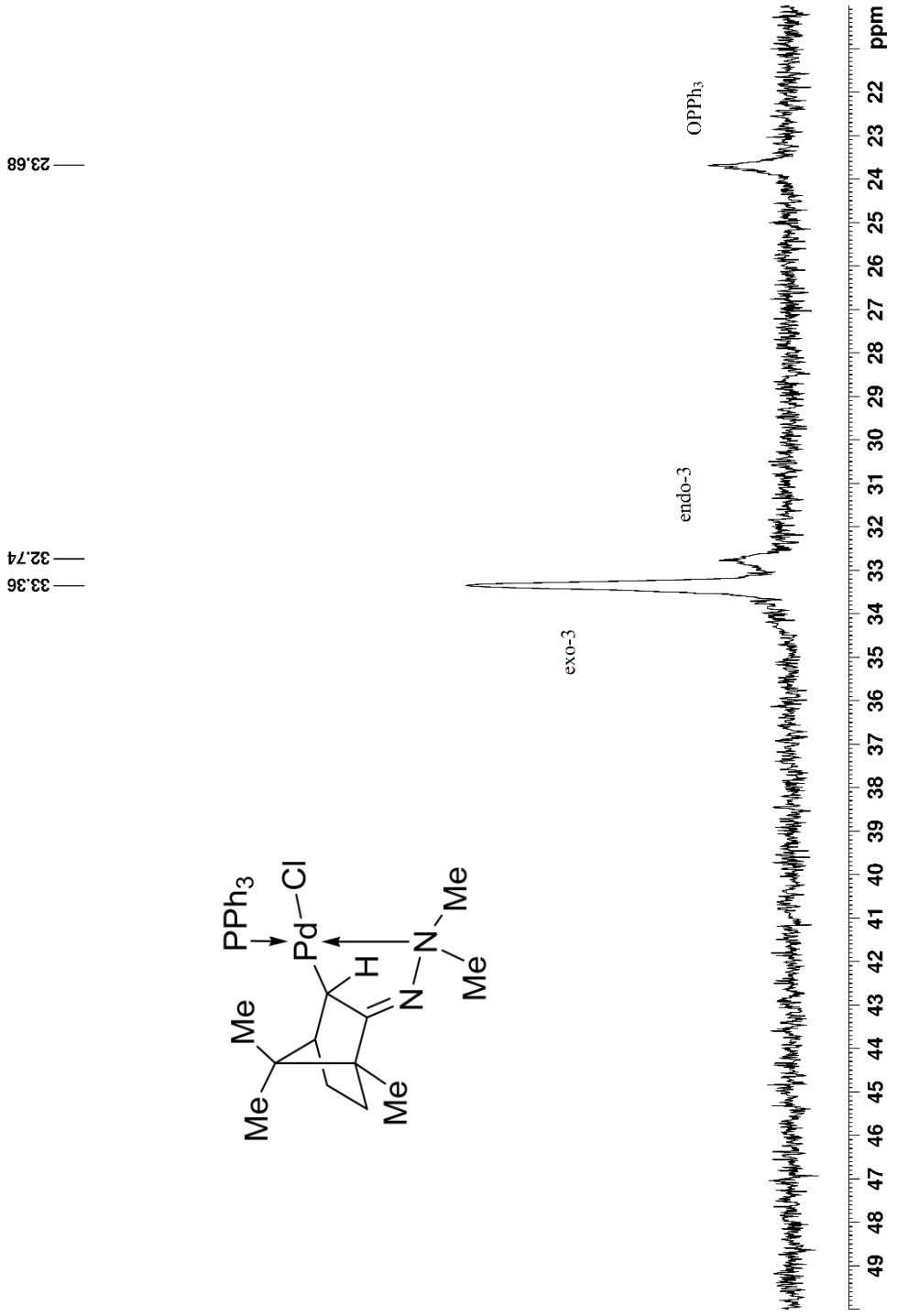


Figure I.10. $^{31}P\{^{1}H\}$ NMR spectrum of exo-**I.3**.

Table I.1. Crystal data and structure refinement for complexes endo-**I.3** and exo-**I.3**.

Identification code	CCDC 1942704	
Empirical formula	$C_{30}H_{36}ClN_2PPd$	
Formula weight	597.43	
Temperature	110(2) K	
Wavelength	1.54178 Å	
Crystal system	Triclinic	
Space group	P1	
Unit cell dimensions	a = 9.8077(4) Å	α = 103.557(2)
	b = 10.8804(4) Å	β= 106.270(2)°
	c = 13.9097(6) Å	γ= 90.907(2)
Volume	1379.9(1) $Å^3$	
Z	2	
Density (calculated)	1.438 mg/m^3	
Absorption coefficient	7.013 mm^{-1}	
F(000)	616	
Crystal color, morphology	Yellow, Block	
Crystal size	0.220 × 0.120 × 0.120 mm^3	
Theta range for data collection	3.417 to 66.696°	
Index ranges	$-11 \leq h \leq 11$, $-12 \leq k \leq 12$, $-16 \leq l \leq 16$	
Reflections collected	32602	
Independent reflections	9199 [R(int) = 0.0391]	
Observed reflections	9512	
Completeness to theta = 66.7°	97.0%	
Absorption correction	Multi-scan	
Max. and min. transmission	0.7528 and 0.5804	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	9512 / 3 / 636	
Goodness-of-fit on F^2	1.071	
Final R indices [I>2sigma(I)]	R1 = 0.0455, wR2 = 0.1205	
R indices (all data)	R1 = 0.0465, wR2 = 0.1215	
Absolute structure parameter	0.015(10)	
Extinction coefficient	n/a	
Largest diff. peak and hole	1.2 and -1.0 e.$Å^{-3}$	

Table I.2. Bond lengths for compound endo-**I.3**.

Bond	d/ Å	Bond	d/ Å
Pd(1A)-P(1A)	2.258(3)	C(11A)-H(11A)	0.98
Pd(1A)-Cl(1A)	2.391(3)	C(11A)-H(11B)	0.98
Pd(1A)-C(2A)	2.03(2)	C(11A)-H(11C)	0.98
Pd(1A)-N(1A)	2.14(1)	C(18A)-H(18A)	0.95
P(1A)-C(25A)	1.84(1)	C(18A)-C(17A)	1.41(2)
P(1A)-C(19A)	1.833(8)	C(4A)-C(7A)	1.56(2)
P(1A)-C(13A)	1.83(1)	C(4A)-C(5A)	1.56(1)
C(22A)-H(22A)	0.95	C(4A)-C(8A)	1.49(2)
C(22A)-C(21A)	1.38(2)	C(20A)-H(20A)	0.95
C(22A)-C(23A)	1.38(2)	C(27A)-H(27A)	0.95
C(25A)-C(26A)	1.41(2)	C(7A)-C(10A)	1.50(1)
C(25A)-C(30A)	1.38(2)	C(7A)-C(9A)	1.59(2)
C(26A)-H(26A)	0.95	C(23A)-H(23A)	0.95
C(26A)-C(27A)	1.40(2)	C(23A)-C(24A)	1.42(1)
C(28A)-H(28A)	0.95	C(24A)-H(24A)	0.95
C(28A)-C(27A)	1.37(2)	C(5A)-H(5A)A)	0.99
C(28A)-C(29A)	1.36(2)	C(5A)-H(5A)B	0.99
C(15A)-H(15A)	0.95	C(5A)-C(6A)	1.55(2)
C(15A)-C(16A)	1.39(2)	C(29A)-H(29A)	0.95
C(15A)-C(14A)	1.38(2)	C(29A)-C(30A)	1.41(1)
C(16A)-H(16A)	0.95	C(14A)-H(14A)	0.95
C(16A)-C(17A)	1.39(1)	C(8A)-H(8AA)	0.98
C(19A)-C(20A)	1.37(1)	C(8A)-H(8AB)	0.98
C(19A)-C(24A)	1.39(1)	C(8A)-H(8AC)	0.98
C(21A)-H(21A)	0.95	C(6A)-H(6AA)	0.99
C(21A)-C(20A)	1.39(1)	C(6A)-H(6AB)	0.99
C(2A)-H(2A)	1	C(10A)-H(10A)	0.98
C(2A)-C(1A)	1.54(2)	C(10A)-H(10B)	0.98

C(2A)-C(3A)	1.56(2)	C(10A)- (10C)	0.98
C(1A)-H(1A)	1	C(30A)-H(30A)	0.95
C(1A)-C(7A)	1.54(1)	C(9A)-H(9AA)	0.98
C(1A)-C(6A)	1.49(1)	C(9A)-H(9AB)	0.98
N(1A)-C(12A)	1.50(2)	C(9A)-H(9AC)	0.98
N(1A)-C(11A)	1.45(2)	C(17A)-H(17A)	0.95
N(1A)-N(2A)	1.49(1)	C(13A)-C(14A)	1.41(1)
C(3A)-C(4A)	1.51(2)	C(11A)-H(11A)	0.98
C(3A)-N(2A)	1.28(2)	C(11A)-H(11B)	0.98
C(12A)-H(12A)	0.98	C(11A)-H(11C)	0.98
C(12A)-H(12B)	0.98	C(18A)-H(18A)	0.95
C(12A)-H(12C)	0.98	C(18A)-C(17A)	1.41(2)
C(13A)-C(18A)	1.36(2)	C(4A)-C(7A)	1.56(2)
C(13A)-C(14A)	1.41(1)		

Table I. 3. Bond lengths for compound exo-**I.3**.

Bond	d/ Å	Bond	d/ Å
Pd(1B)-Cl(1B)	2.411(3)	C(21B)-C(22B)	1.41(2)
Pd(1B)-P(1B)	2.248(3)	C(29B)-H(29B)	0.95
Pd(1B)-N(1B)	2.16(1)	C(29B)-C(28B)	1.38(2)
Pd(1B)-C(2B)	2.07(1)	C(12B)-H(12D)	0.98
P(1B)-C(13B)	1.83(1)	C(12B)-H(12E)	0.98
P(1B)-C(25B)	1.799(9)	C(12B)-H(12F)	0.98
P(1B)-C(19B)	1.82(1)	C(1B)-H(1B)	1
N(2B)-N(1B)	1.49(1)	C(1B)-C(6B)	1.55(1)
N(2B)-C(3B)	1.28(2)	C(1B)-C(2B)	1.56(2)
C(24B)-H(24B)	0.95	C(1B)-C(7B)	1.56(1)
C(24B)-C(23B)	1.39(2)	C(10B)-H(10D)	0.979
C(24B)-C(19B)	1.40(2)	C(10B)-H(10E))	0.98
C(26B)-H(26B)	0.95	C(10B)-H(10F)	0.981
C(26B)-C(27B)	1.37(1)	C(10B)-C(7B)	1.55(1)
C(26B)-C(25B)	1.38(1)	C(11B)-H(11D)	0.98
C(14B)-H(14B)	0.95	C(11B)-H(11E)	0.98
C(14B)-C(13B)	1.39(1)	C(11B)-H(11F)	0.98
C(14B)-C(15B)	1.40(2)	C(3B)-C(2B)	1.50(2)
C(23B)-H(23B)	0.95	C(6B)-(6BA)	0.99
C(23B)-C(22B)	1.38(2)	C(6B)-H(6BB)	0.99
N(1B)-C(12B)	1.49(1)	C(6B)-C(5B)	1.53(1)
N(1B)-C(11B)	1.47(2)	C(2B)-H(2B)	1
C(27B)-H(27B)	0.95	C(19B)-C(20B)	1.38(2)
C(27B)-C(28B)	1.38(2)	C(15B)-H(15B)	0.95
C(8B)-H(8BA)	0.98	C(15B)-C(16B)	1.37(2)
C(8B)-H(8BB)	0.98	C(16B)-H(16B)	0.95
C(8B)-H(8BC)	0.98	C(7B)-C(9B)	1.51(1)
C(8B)-C(4B)	1.53(2)	C(20B)-H(20B)	0.95

C(17B)-H(17B)	0.95	C(9B)-H(9BA)	0.98
C(17B)-C(18B)	1.38(2)	C(9B)-H(9BB)	0.98
C(17B)-C(16B)	1.38(1)	C(9B)-H(9BC)	0.98
C(13B)-C(18B)	1.43(2)	C(5B)-H(5BA)	0.99
C(18B)-H(18B)	0.95	C(5B)-H(5BB)	0.99
C(30B)-H(30B)	0.95	C(22B)-H(22B)	0.95
C(30B)-C(29B)	1.39(1)	C(28B)-H(28B)	0.95
C(30B)-C(25B)	1.43(1)	C(21B)-C(20B)	1.38(2)
C(4B)-C(3B)	1.48(2)	C(21B)-C(22B)	1.41(2)
C(4B)-C(7B)	1.58(1)	C(29B)-H(29B)	0.95
C(4B)-C(5B)	1.57(1)	C(29B)-C(28B)	1.38(2)
C(21B)-H(21B)	0.95	C(12B)-H(12D)	0.98
C(21B)-C(20B)	1.38(2)		

Table I.4. Bond angles for compound endo-**I.3**.

Bond	Angle/°	Bond	Angle/°
P(1A)-Pd1A)-Cl(1A)	89.8(1)	C(13A)-C(18A)-H(18A)	119
P(1A)-Pd(1A)-C(2A)	97.3(4)	C(13A)-C(18A)-C(17A)	121(1)
P(1A)-Pd(1A)-N((1A)	177.8(3)	H(18A)-C(18A)-C(17A)	119
Cl(1A)-Pd(1A)-C(2A)	170.7(4)	C(3A)-C(4A)-C(7A)	99.7(9)
Cl(1A)-Pd(1A)-N((1A)	91.6(3)	C(3A)-C(4A)-C(5A)	98.5(9)
C(2A)-Pd(1A)-N((1A)	81.2(5)	C(3A)-C(4A)-C(8A)	116(1)
Pd(1A)-P(1A)-C(25A)	114.2(3)	C(7A)-C(4A)-C(5A)	100.4(9)
Pd(1A)-P(1A)-C(19A)	109.8(3)	C(7A)-C(4A)-C(8A)	121(1)
Pd(1A)-P(1A)-C(13A)	119.7(3)	C(5A)-C(4A)-C(8A)	117(1)
C(25A)-P(1A)-C(19A)	108.9(5)	C(19A)-C(20A)-C(21A)	121(1)
C(25A)-P(1A)-C(13A)	100.3(5)	C(19A)-C(20A)-H(20A)	120
C(19A)-P(1A)-C(13A)	103.0(5)	C(21A)-C(20A)-H(20A)	120
H(22A)-C(22A)-C(21A)	120	C(26A)-C(27A)-C(28A)	120(1)
H(22A)-C(22A)-C(23A)	120	C(26A)-C(27A)-H(27A)	120
C(21A)-C(22A)-C(23A)	121(1)	C(28A)-C(27A)-H(27A)	120
P(1A)-C(25A)-C(26A)	118.0(8)	C(1A)-C(7A)-C(4A)	94.7(8)
P(1A)-C(25A)-C(30A)	120.7(8)	C(1A)-C(7A)-C(10A)	121.3(9)
C(26A)-C(25A)-C(30A)	121.0(9)	C(1A)-C(7A)-C(9A)	109.9(9)
C(25A)-C(26A)-H(26A)	121	C(4A)-C(7A)-C(10A)	114.2(9)
C(25A)-C(26A)-C(27A)	118(1)	C(4A)-C(7A)-C(9A)	111.0(8)
H(26A)-C(26A)-C(27A)	121	C(10A)-C(7A)-C(9A)	105.4(9)
H(28A)-C(28A)-C(27A)	119	C(22A)-C(23A)-H(23A)	120
H(28A)-C(28A)-C(29A)	119	C(22A)-C(23A)-C(24A)	119(1)
C(27A)-C(28A)-C(29A)	121(1)	H(23A)-C(23A)-C(24A)	120
H(15A)-C(15A)-C(16A)	119	N(1A)-N(2A)-C(3A)	110(1)
H(15A)-C(15A)-C(14A)	120	C(19A)-C(24A)-C(23A)	119(1)
C(16A)-C(15A)-C(14A)	121(1)	C(19A)-C(24A)-H(24A)	120
C(15A)-C(16A)-H(16A)	121	C(23A)-C(24A)-H(24A)	120

C(15A)-C(16A)-C(17A)	119(1)	C(4A)-C(5A)-H(5AA)	111
H(16A)-C(16A)-C(17A)	120	C(4A)-C(5A)-H(5AB)	111
P(1A)-C(19A)-C(20A)	117.4(8)	C(4A)-C(5A)-C(6A)	104.4(9)
P(1A)-C(19A)-C(24A)	122.0(8)	H(5AA)-C(5A)-H(5AB)	109
C(20A)-C(19A)-C(24A)	121(1)	H(5A)-A)-C(5A)-C(6A)	111
C(22A)-C(21A)-H(21A)	120	H(5AB)-C(5A)-C(6A)	111
C(22A)-C(21A)-C(20A)	119(1)	C(28A)-C(29A)-H(29A)	120
H(21A)-C(21A)-C(20A)	120	C(28A)-C(29A)-C(30A)	120(1)
Pd(1A)-C(2A)-H(2A)	106	H(29A)-C(29A)-C(30A)	120
Pd(1A)-C(2A)-C(1A)	135(1)	C(15A)-C(14A)-C(13A)	120(1)
Pd(1A)-C(2A)-C(3A)	104.1(9)	C(15A)-C(14A)-H(14A)	120
H(2A)-C(2A)-C(1A)	106	C(13A)-C(14A)-H(14A)	120
H(2A)-C(2A)-C(3A)	106	C(4A)-C(8A)-H(8AA)	109
C(1A)-C(2A)-C(3A)	97(1)	C(4A)-C(8A)-H(8AB)	109
C(2A)-C(1A)-H(1A)	113	C(4A)-C(8A)-H(8AC)	109
C(2A)-C(1A)-C(7A)	100(1)	H(8AA)-C(8A)-H(8AB)	109
C(2A)-C(1A)-C(6A)	111(1)	H(8AA)-C(8A)-H(8AC)	110
H(1A)-C(1A)-C(7A)	113	H(8AB)-C(8A)-H(8AC)	110
H(1A)-C(1A)-C(6A)	113	C(1A)-C(6A)-C(5A)	103(1)
C(7A)-C(1A)-C(6A)	105.5(9)	C(1A)-C(6A)-H(6AA)	111
Pd(1A)-N(1A)-C(12A)	114.4(7)	C(1A)-C(6A)-H(6AB)	111
Pd(1A)-N(1A)-C(11A)	109.6(8)	C(5A)-C(6A)-H(6AA)	111
Pd(1A)-N(1A)-N(2A)	112.3(7)	C(5A)-C(6A)-H(6AB)	111
C(12A)-N(1A)-C(11A)	109(1)	H(6AA)-C(6A)-H(6AB)	109
C(12A)-N(1A)-N(2A)	104.6(9)	C(7A)-C(10A)-H(10A)	109
C(11A)-N(1A)-N(2A)	106.7(9)	C(7A)-C(10A)-H(10B)	109
C(2A)-C(3A)-C(4A)	109(1)	C(7A)-C(10A)-H(10C)	109
C(2A)-C(3A)-N(2A)	126(1)	H(10A)-C(10A)-H(10B)	109
C(4A)-C(3A)-N(2A)	124(1)	H(10A)-C(10A)-H(10C)	109
N(1A)-C(12A)-H(12A)	109	H(10B)-C(10A)-H(10C)	109
N(1A)-C(12A)-H(12B)	109	C(25A)-C(30A)-C(29A)	119.0(9)

N(1A)-C(12A)-H(12C)	109	C(25A)-C(30A)-H(30A)	121
H(12A)-C(12A)-H(12B)	109	C(29A)-C(30A)-H(30A)	121
H(12A)-C(12A)-H(12C)	109	C(7A)-C(9A)-H(9AA)	109
H(12-C(12A)-H(12C)	110	C(7A)-C(9A)-H(9AB)	109
P(1A)-C(13A)-C(18A)	123.4(8)	C(7A)-C(9A)-H(9AC)	109
P(1A)-C(13A)-C(14A)	117.3(8)	H(9AA)-C(9A)-H(9AB)	109
C(18A)-C(13A)-C(14A)	119.3(9)	H(9AA)-C(9A)-H(9AC)	109
N(1A)-C(11A)-H(11A)	109	H(9AB)-C(9A)-H(9AC)	110
N(1A)-C(11A)-H(11B)	110	C(16A)-C(17A)-C(18A)	119(1)
N(1A)-C(11A)-H(11C)	110	C(16A)-C(17A)-H(17A)	120
H(11A)-C(11A)-H(11B)	109	C(18A)-C(17A)-H(17A)	120
H(11A)-C(11A)-H(11C)	109	C(13A)-C(18A)-H(18A)	119
H(11B)-C(11A)-H(11C)	109	C(13A)-C(18A)-C(17A)	121(1)

Table I.5. Bond angles for compound exo-**I.3**.

Bond	Angle/°	Bond	Angle/°
Cl1B-Pd1B-P1B	88.9(1)	H17B-C17B-C18B	120
Cl1B-Pd1B-N1B	91.8(3)	H17B-C17B-C16B	119
Cl1B-Pd1B-C2B	171.7(3)	C18B-C17B-C16B	121(1)
P1B-Pd1B-N1B	178.3(3)	P1B-C13B-C14B	117.9(8)
P1B-Pd1B-C2B	98.8(3)	P1B-C13B-C18B	123.4(8)
N1B-Pd1B-C2B	80.4(4)	C14B-C13B-C18B	119(1)
Pd1B-P1B-C13B	118.0(4)	C17B-C18B-C13B	119(1)
Pd1B-P1B-C25B	109.5(4)	C17B-C18B-H18B	120
Pd1B-P1B-C19B	116.1(4)	C13B-C18B-H18B	120
C13B-P1B-C25B	104.0(5)	H30B-C30B-C29B	120
C13B-P1B-C19B	100.6(5)	H30B-C30B-C25B	120
C25B-P1B-C19B	107.4(5)	C29B-C30B-C25B	120(1)
N1B-N2B-C3B	110.1(9)	C8B-C4B-C3B	117.0(9)
H24B-C24B-C23B	120	C8B-C4B-C7B	117.9(9)
H24B-C24B-C19B	119	C8B-C4B-C5B	113.3(9)
C23B-C24B-C19B	121(1)	C3B-C4B-C7B	97.3(8)
H26B-C26B-C27B	119	C3B-C4B-C5B	108.9(9)
H26B-C26B-C25B	119	C7B-C4B-C5B	100.1(8)
C27B-C26B-C25B	121(1)	H21B-C21B-C20B	120
H14B-C14B-C13B	120	H21B-C21B-C22B	120
H14B-C14B-C15B	120	C20B-C21B-C22B	119(1)
C13B-C14B-C15B	120(1)	C30B-C29B-H29B	120
C24B-C23B-H23B	120	C30B-C29B-C28B	120(1)
C24B-C23B-C22B	121(1)	H29B-C29B-C28B	120
H23B-C23B-C22B	120	N1B-C12B-H12D	109
Pd1B-N1B-N2B	111.6(7)	N1B-C12B-H12E	109
Pd1B-N1B-C12B	110.6(7)	N1B-C12B-H12F	110
Pd1B-N1B-C11B	113.0(8)	H12D-C12B-H12E	109
N2B-N1B-C12B	106.7(9)	H12D-C12B-H12F	109
N2B-N1B-C11B	105.2(9)	H12E-C12B-H12F	109
C12B-N1B-C11B	109.4(9)	H1B-C1B-C6B	115
C26B-C27B-H27B	119	H1B-C1B-C2B	115.1
C26B-C27B-C28B	121(1)	H1B-C1B-C7B	115
H27B-C27B-C28B	119	C6B-C1B-C2B	105.1(8)
H8BA-C8B-H8BB	110	C6B-C1B-C7B	101.1(7)
H8BA-C8B-H8BC	110	C2B-C1B-C7B	103.8(8)
H8BA-C8B-C4B	109	H10D-C10B-H10E	109.5
H8BB-C8B-H8BC	109	H10D-C10B-H10F	109.5
H8BB-C8B-C4B	109	H10D-C10B-C7B	109.5
H8BC-C8B-C4B	109	H10E-C10B-H10F	109.4

Bond	Angle/°	Bond	Angle/°
N1B-C11B-H11E	109	C7B-C9B-H9BB	109.5
N1B-C11B-H11F	109	C7B-C9B-H9BC	109.5
H11D-C11B-H11E	109	H9BA-C9B-H9BB	109.4
H11D-C11B-H11F	110	H9BA-C9B-H9BC	109.4
H11E-C11B-H11F	109	H9BB-C9B-H9BC	109.4
P1B-C25B-C26B	126.3(9)	C4B-C5B-C6B	105.4(8)
P1B-C25B-C30B	116.2(8)	C4B-C5B-H5BA	110.7
C26B-C25B-C30B	117(1)	C4B-C5B-H5BB	110.6
N2B-C3B-C4B	123(1)	C6B-C5B-H5BA	110.7
N2B-C3B-C2B	128(1)	C6B-C5B-H5BB	110.7
C4B-C3B-C2B	108.1(9)	H5BA-C5B-H5BB	108.8
C1B-C6B-H6BA	111.4	C23B-C22B-C21B	119(1)
C1B-C6B-H6BB	111.4	C23B-C22B-H22B	120
C1B-C6B-C5B	102.2(7)	C21B-C22B-H22B	120
H6BA-C6B-H6BB	109.2	C27B-C28B-C29B	120(1)
H6BA-C6B-C5B	111.3	C27B-C28B-H28B	120
H6BB-C6B-C5B	111.3	C29B-C28B-H28B	120
Pd1B-C2B-C1B	131.8(7)		
Pd1B-C2B-C3B	105.1(7)		
Pd1B-C2B-H2B	105.6		
C1B-C2B-C3B	100.7(9)		
C1B-C2B-H2B	105.6		
C3B-C2B-H2B	105.6		
P1B-C19B-C24B	120.7(8)		
P1B-C19B-C20B	121.8(9)		
C24B-C19B-C20B	117(1)		
C14B-C15B-H15B	120		
C14B-C15B-C16B	120(1)		
H15B-C15B-C16B	120		
C17B-C16B-C15B	121(1)		
C17B-C16B-H16B	120		
C15B-C16B-H16B	120		
C4B-C7B-C1B-	93.4(7)		
C4B-C7B-C10B	113.7(7)		
C4B-C7B-C9B	115.0(7)		
C1B-C7B-C10B	111.4(7)		
C1B-C7B-C9B	115.2(7)		
C10B-C7B-C9B	107.7(7)		
C21B-C20B-C19B	123(1)		
C21B-C20B-H20B	119		
C19B-C20B-H20B	119		
C7B-C9B-H9BA	109.5		

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CHAPTER II. REACTIONS OF CYCLOPALLADATED COMPLEXES WITH BORONIC ACIDS

II.1. Background

Cyclopalladated complexes (CPCs) are readily available, air- and moisture-stable compounds with well-defined structures and diverse applications in various fields of chemistry.[1–8] Their uses as catalysts and reactants are the most valuable and studied. Specifically, palladacycles have been employed as efficient catalysts in several C–C bond formation reactions,[9–18] including the Suzuki-Miyaura reaction of boronic acids with aryl halides.[19–24] CPCs have been successfully used as reactants for the modifications of cyclopalladated ligands by taking advantage of the C–Pd bond reactivity.[1,25–35] One of the known transformations of CPCs is the arylation and alkylation of cyclopalladated ligands using boronic acids or their derivatives (Chart II.1).[36–42] The most detailed data about this reaction are reported for the couplings of the acetate-bridged dimeric (*sp*^{2})*C,N*-CPC **II.D** with boronic acids[39] and the related dichloro-bridged complex **II.G** with potassium trifluoroborates.[42] At the same time, a few publications describe transition metal-catalyzed transformations of boronic acids leading to the formation of C–C bonds, which may proceed through metalacyclic intermediates.[41,43–45]

Inspired by these promising but limited published data and following our interest and expertise in the preparation and reactions of palladacycles, we undertook our study of the reactions between various boronic acids and structurally diverse CPCs. The goals of this study were to investigate the types of CPCs and boronic acids, which can be used in (*sp*^{2})C–(*sp*^{2})C, (*sp*^{2})C–(*sp*^{3})C, and (*sp*^{3})C–(*sp*^{3})C bond formations, and determine the best conditions and limitations of these transformations.

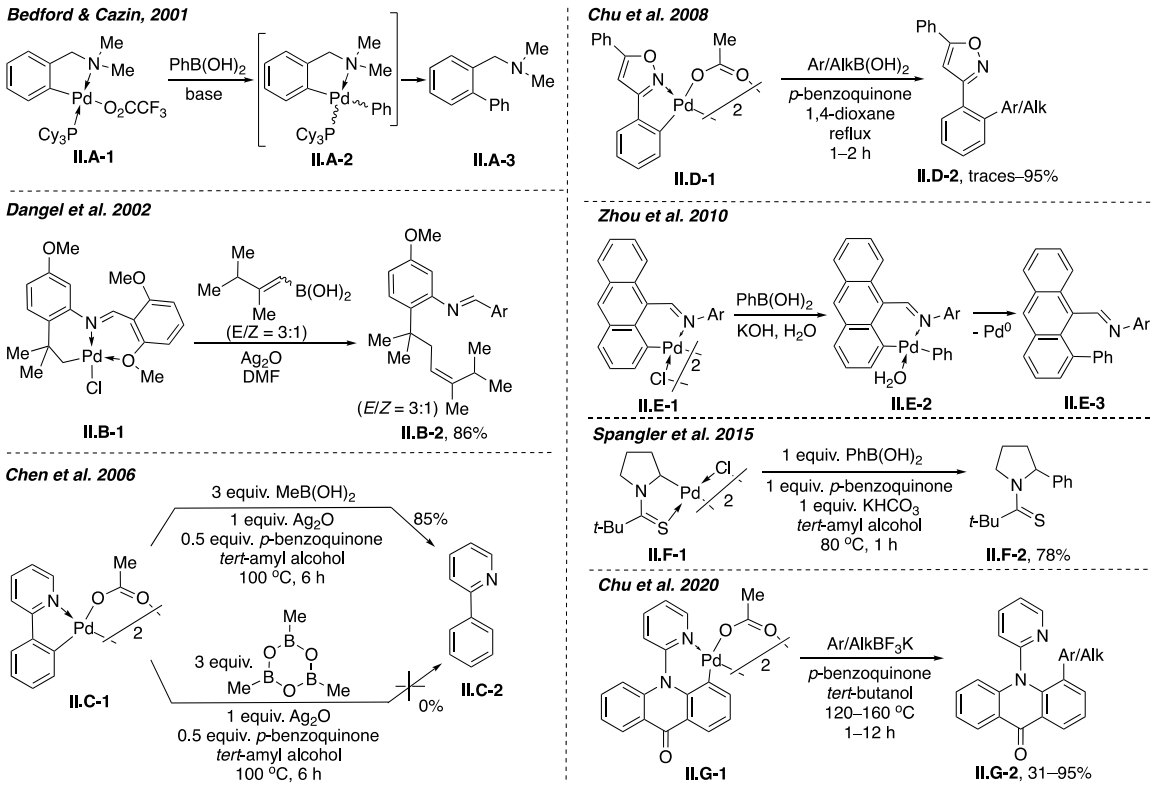


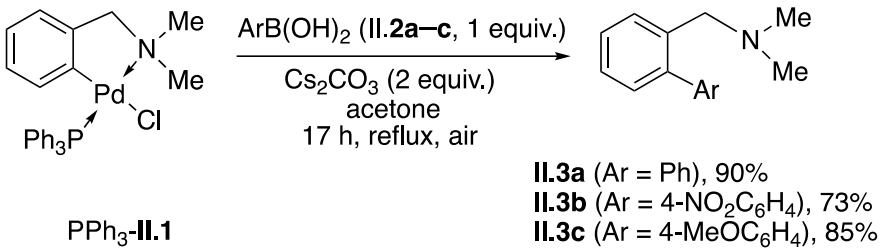
Chart II.1. Reported reactions of cyclopalladated complexes with boronic acids and their derivatives.[36–42]

II.2. Results and Discussion

II.2.1. Case A: (sp^2)C–(sp^2)C Bond Formation

First, we studied the transformations of dimeric chloro- and acetato-bridged *C,N*-CPCs obtained from *N,N*-dimethylbenzylamine (μ-Cl-**II.1** and μ-AcO-**II.1**). In our hands, both complexes did not react with $PhB(OH)_2$ under the conditions described by Chu et al.[39] for the arylation of 3,5-diphenylisoxazole-derived CPC **II.D** with $ArB(OH)_2$ (Chart II.1). This group[39,42] and others[38,44] used *p*-benzoquinone as an essential component in the reactions of CPCs with boronic acids or their derivatives. Chu et al. explained the role of *p*-benzoquinone as an oxidant.[39,41] However, the application of this chemical as an oxidant would be more relevant in Pd(II)-catalyzed reactions[43–45] than in stoichiometric

transformations of palladacycles. Sanford[46], Yu[47] and others[48] proposed several other roles of *p*-benzoquinone in Pd(II)-catalyzed reactions, including but not limited to (i) a promoter of C–C bond formation, i.e., the reductive elimination step, and (ii) a promoter of C–H activation due to the coordination of the quinone to the metal. The hypothesis of *p*-benzoquinone's role as a ligand prompted us to use mononuclear derivatives instead of dimeric CPCs. We selected palladacycle **II.1** in its mononuclear form with PPh_3 as an auxiliary ligand (PPh_3-**II.1**). Trial reactions of this complex with phenylboronic acid (**II.2a**) in the presence of Cs_2CO_3 at 60 °C in dioxane and the argon atmosphere led to the desirable product **II.3a** in 75% yield (Scheme II.1 and entry 1 in Table II.1). In some of the reported Pd-promoted reactions of boronic acids,[49] yields were improved in the presence of water. In our experiments with palladacycles bearing an (sp^2)C–Pd bond, the water addition to dioxane slowed the reaction (entry 2). When the reaction time was doubled, the yield of **II.3a** was about the same as in the experiment without water (entry 3).



Scheme II.1. Reactions of PPh_3-**II.1** with arylboronic acids **II.2a**–**c** using Method A.

Table II.1. Reactions of complex PPh_3-**II.1** with $PhB(OH)_2$ in the presence of a base.

Entry	Base	Solvent	Atmo-sphere	Temp. (°C)	Time (h)	Yield (%)	
						II.3a	**Ph_2**
1	Cs_2CO_3	1,4-dioxane	Ar	60	17	75	30
2	Cs_2CO_3	1,4-dioxane-H_2O (4:1)	Ar	60	17	32	22
3	Cs_2CO_3	1,4-dioxane-H_2O (4:1)	Ar	60	36	77	15
4	Cs_2CO_3	MeCN	Ar	60	17	50	34
5	Cs_2CO_3	$CHCl_3$	Ar	60	17	0	20
6	Cs_2CO_3	acetone	Ar	reflux (~56 °C)	17	79 (64)[a]	10 (25)[a]
7	Cs_2CO_3	acetone	Ar	rt	17	43	15
8	Cs_2CO_3	acetone	air	reflux	17	90 (71)[a]	5 (10)[a]
9	none	1,4-dioxane	Ar	60	17	0[b]	0
10	K_2CO_3	acetone	Ar	reflux	17	58	20
11	K_3PO_4	acetone	Ar	reflux	17	0[c]	60
12	NaOAc	acetone	Ar	reflux	17	0[d]	58

[a] Yields in parentheses are given for the corresponding pinacol ester.
[b] Complex PPh_3-**1** was recovered in 49% yield.
[c] Complex PPh_3-**1** was recovered in 61% yield.
[d] Complex PPh_3-**1** was recovered in 70% yield.

We also carried out the experiments in acetonitrile and chloroform at 60 °C and acetone at reflux (entries 4–6). The reaction in $CHCl_3$ did not provide compound **II.3a** at all, but the use of acetone resulted in a 79% yield of the desired product. The reactions of PPh_3-**II.1** with $PhB(OH)_2$ in acetone at rt afforded **II.3a** in a relatively low yield (entry 7). Finally, it was concluded that product **II.3a** could be formed in acetone not only in an inert atmosphere but also in the air (Method A, entry 8); moreover, the yield was better in the latter case.

In all experiments described above, we used Cs_2CO_3. The importance of this additive was confirmed when no product was detected in the reaction without any base in dioxane at 60 °C (entry 9). Replacing Cs_2CO_3 with K_2CO_3 yielded 58% of **II.3a** along with 20% of

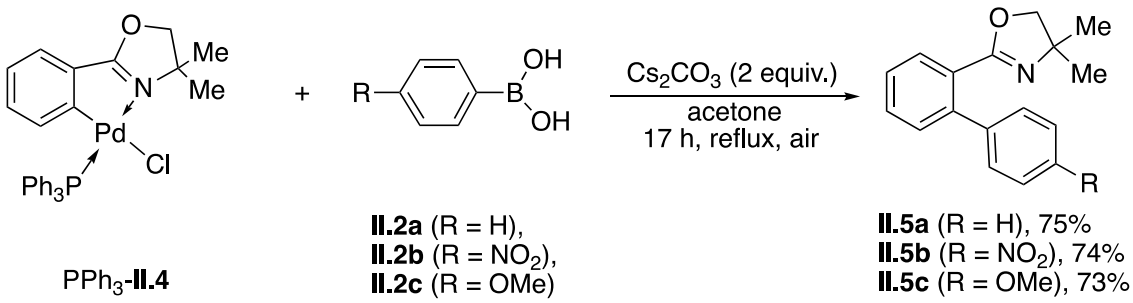
diphenyl (entry 10); however, the applications of K_3PO_4 and NaOAc were unsuccessful (entries 11 and 12).

The possibility of using boronic esters instead of the corresponding acids was proven by isolating product **II.3a** in the reactions of complex PPh_3-**II.1** with pinacol ester of phenylboronic acid (entries 6 and 8). However, the results were better for $PhB(OH)_2$ than for the ester.

Our attempts of using palladacycle **II.1** as the dimeric chloro-bridged complex μ-Cl-**II.1** under the conditions mentioned in Table II.1 were unsuccessful. The pyridine adduct of complex **II.1**, Py-**II.1**, did not react with $PhB(OH)_2$ in acetone at 60 ^oC in the presence of Cs_2CO_3 either. The latter experiment provided 68% of Ph_2, and 66% of the starting CPC was recovered. It is unclear why PPh_3-**II.1** reacted with $ArB(OH)_2$ while μ-Cl-**II.1** and Py-**II.1** did not. One of the possible explanations is that PPh_3, like benzoquinone,[47] promotes the reductive elimination step that yields Pd(0) complexes with PPh_3 or benzoquinone[47,50] as ligands. The recently published data by Bruns et al. indirectly suggest that Pd(II) complexes with pyridine are likely poor choices for reductive elimination reactions.[51]

To check whether para substituents in $ArB(OH)_2$ affect the reaction with complex PPh_3-**II.1**, *para*-nitro- and *para*-methoxyphenyl derivatives **II.2b** and **II.2c** were used under the best conditions determined for $PhB(OH)_2$ (Method A, i.e., Cs_2CO_3, acetone, reflux in the air for 17 h). Boronic acids **II.2b** and **II.2c** reacted with PPh_3-**II.1** to yield 73 and 85% of the desired products **II.3b** and **II.3c**, respectively. Therefore, the electronic effect of the aryl group substituents in $ArB(OH)_2$ was noticeable but insignificant in the reactions leading to the (sp^2)C–(sp^2)C bond formation.

One more cyclopalladated complex, PPh_3-**II.4**, was tested in the reactions with $ArB(OH)_2$ **II.2a**–**c** (Scheme II.2). The results obtained for this palladacycle were similar to those described above for PPh_3-**II.1**.

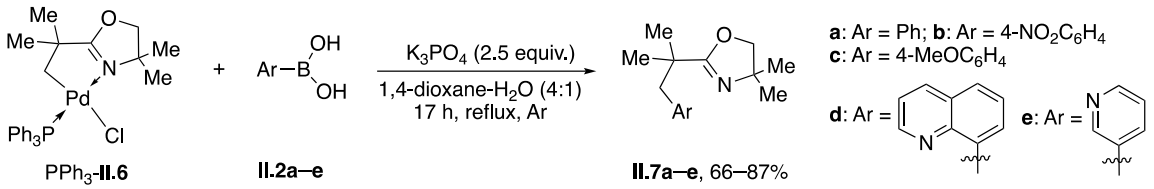


Scheme II.2. Arylation of PPh_3-**II.4** using $ArB(OH)_2$ **II.2a**–**c**.

II.2.2. Case B: (sp^3)C–(sp^2)C Bond Formation Using Cyclopalladated Complexes with an (sp^3)C–Pd Bond and Arylboronic Acids

In this part of our investigation, we studied reactions of four (sp^3)*C,N*-palladacycles with several arylboronic acids. Arylation of the known complex PPh_3-**II.6** using $PhB(OH)_2$ was chosen as a model reaction to determine optimal conditions for the desirable (sp^3)C–(sp^2)C bond formation. At first, we used the conditions found suitable for the (sp^2)C–(sp^2)C coupling described above, i.e., acetone, dioxane, or 1,4-dioxane-water (4:1) at 60 °C in the presence of Cs_2CO_3. However, in all cases, unreacted complex PPh_3-**II.6** was isolated in high amounts (51–72%), and no traces of the expected product were detected. Several other conditions were tested (e.g., *tert*-amyl alcohol and DMF at 100–110 °C with various bases), and at last, the desired product **II.7a** was obtained in 87% yield using K_3PO_4 at 110 °C in 1,4-dioxane-water (Scheme II.3 and entry 1 in Table II.2, Method B). The electronic effect of the para substituents in arylboronic acids was remarkable when *p*-$NO_2C_6H_4B(OH)_2$, **II.2b**, and *p*-$MeOC_6H_4B(OH)_2$, **II.2c**, were reacted with complex PPh_3-**II.6** under the same

conditions. The transformation of boronic acid **II.2b** with the electron-withdrawing nitro group afforded product **II.7b** in 85% yield, while the other reaction gave only 15% of **II.7c** (entries 2 and 3).



Scheme II.3. Synthesis of compounds **II.7a–e** using Method B.

Table II.2. Reactions of complex PPh_3-**II.6** with $ArB(OH)_2$ **II.2a**–**e** in argon at 110 °C.

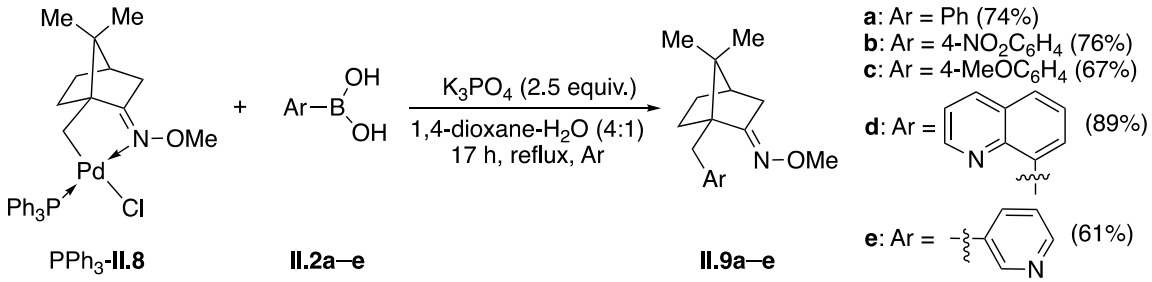
Entry	$ArB(OH)_2$	Base	Solvent	Product	Yield (%)
1	**II.2a**	K_3PO_4	1,4-dioxane-water (1:4)	**II.7a**	87
2	**II.2b**	K_3PO_4	1,4-dioxane-water (1:4)	**II.7b**	85
3	**II.2c**	K_3PO_4	1,4-dioxane-water (1:4)	**II.7c**	15
5	**II.2d**	K_3PO_4	1,4-dioxane-water (1:4)	**II.7d**	68 (44)[a]
6	**II.2d**	Cs_2CO_3	1,4-dioxane-water (1:4)	**II.7d**	30[b]
7	**II.2d**	K_3PO_4	1,4-dioxane	**II.7d**	22[c]
8	**II.2d**	K_3PO_4	*tert*-amyl alcohol	**II.7d**	15[d]
9	**II.2e**	K_3PO_4	1,4-dioxane-water (1:4)	**II.7e**	66

[a] The yield in parentheses is for the corresponding reaction in the air.
[b] Complex PPh_3-**II.6** was recovered in 52%.
[c] Complex PPh_3-**II.6** was recovered in 48%.
[d] Complex PPh_3-**II.6** was recovered in 30%.

The reaction of complex PPh_3-**II.6** with 8-quinolineboronic acid **II.2d** carried out using Method B gave desired product **II.7d** in 68% yield (entry 5). Further modifications in temperature, solvent, and base did not afford better yields (see, for example, entries 6–8). Notably, the experiment in pure dioxane gave a lower yield of **II.7d** than that in dioxane-water (entries 5 and 7). Complex PPh_3-**II.6** also successfully reacted with 3-pyridinylboronic acid (**II.2e**); see entry 9. It is important to note that all our attempts to isolate desirable products **II.3d,e** and **II.5d,e** in the reactions of these two heterocycle-

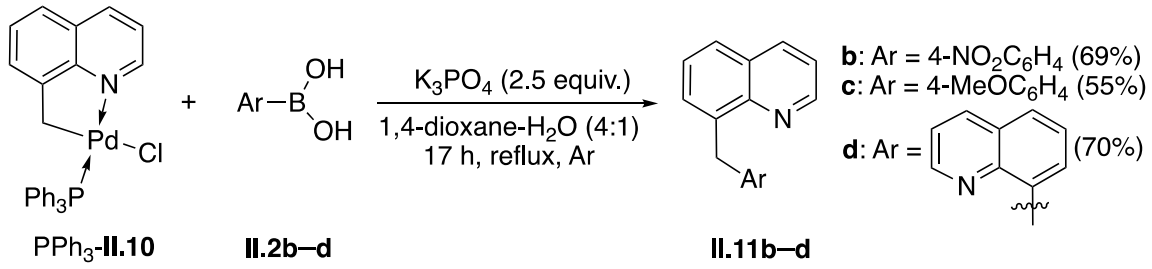
containing boronic acids, **II.2d,e**, with complexes PPh_3-**II.1** and PPh_3-**II.4** were unsuccessful.

One more complex with an (sp^3)C–Pd bond, PPh_3-**II.8**, was reacted with $ArB(OH)_2$ **II.2a–e** under the conditions found the best for PPh_3-**II.6**, i.e., using Method B. The formation of an (sp^3)C–(sp^2)C bond was observed in all cases, and the desired products, **II.9a–e**, were obtained in a 61–89% yield (Scheme II.4).



Scheme II.4. Preparation of compounds **II.9a–e** using Method B.

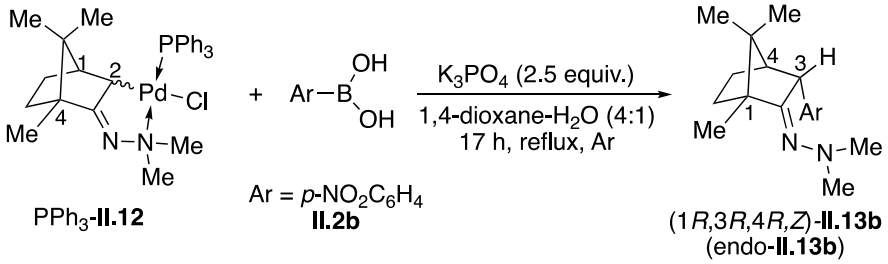
Next, we tested the complex with the metal bonded to a benzylic carbon, PPh_3-**II.10**. Reactions with three boronic acids, **II.2b**–**d**, afforded 8-arylquinoline derivatives **II.11b**–**d** in good yields (Scheme II.5).



Scheme II.5. Reactions of complex PPh_3-**II.10** with $ArB(OH)_2$ **II.2b–d**.

The recently reported complex PPh_3-**II.12**[52] differs from other palladacycles used in the study by the connection of the metal to a secondary carbon. In addition, this secondary carbon is a *C*-chiral center making the complex a unique model for determining

the stereochemistry of reactions at a C–Pd bond. In our initial experiments, we used PPh_2-**II.12** as a 1:1 mixture of two diastereomers. Only one boronic acid, **II.2b**, reacted with complex PPh_3-**II.12** to afford the desired product **II.13b** in good yield (Scheme II.6). Other tested boronic acids, **II.2c–e**, gave no products **II**.**13c–e** or only its traces (**II.13a**). Therefore, the presence of a strong electron-withdrawing substituent in $ArB(OH)_2$ is a substantial factor for the efficient formation (sp^3)C–(sp^2)C bond formation reactions of (sp^3)*C,N* palladacycles.



(1*R*,2*S*,4*R*,*Z*)-**II.12** : (1*R*,2*R*,4*R*,*Z*)-**II.12** = 1:1 ⇨ (1*R*,3*R*,4*R*,*Z*)-**II.13b** : (1*R*,3*S*,4*R*,*Z*)-**II.13b** = 30:1, 49%
(1*R*,2*S*,4*R*,*Z*)-**II.12** : (1*R*,2*R*,4*R*,*Z*)-**II.12** = 10:1 ⇨ (1*R*,3*R*,4*R*,*Z*)-**II.13b** : (1*R*,3*S*,4*R*,*Z*)-**II.13b** = 14:1, 66%
(1*R*,2*S*,4*R*,*Z*)-**II.12** : (1*R*,2*R*,4*R*,*Z*)-**II.12** = 1:13 ⇨ (1*R*,3*R*,4*R*,*Z*)-**II.13b** : (1*R*,3*S*,4*R*,*Z*)-**II.13b** = 5.4:1, 54%

Scheme II.6. Reaction of complex PPh_3-**II.12** with boronic acid **II.2b**.

To better understand the reason for high diastereoselectivity of the C–C bond formation in the reaction, we carried out two additional experiments using fairly pure (1*R*,2*S*,4*R*,*Z*)-**II**.**12** (endo-**II.12**, 82% *de*) and (1*R*,2*R*,4*R*,*Z*)-**II.12** (exo-**II.12**, 86% *de*). Both reactions afforded the same diastereomer, (1*R*,3*R*,4*R*,*Z*)-**II.13b** (endo-**II.13b)**, having the *p*-$NO_2C_6H_4$ substituent in the endo position, as the major product (Scheme II.6). The X-ray crystallographic study of this compound confirmed the endo position of the *p*-$NO_2C_6H_4$ group in the isolated product (Figure II.1). These results strongly suggest that the final step of both reactions involves the structurally identical intermediates. This is possible in two cases: (i) the intermediate participating in the reductive elimination step has no sigma bond between Pd and C(2) of the camphor moiety, e.g., this ligand has the

allyl-like structure, and (ii) epimerization of two isomers takes place during the reaction, and one of the two diastereomers reacts with $RB(OH)_2$ much faster. We refluxed pure diastereomers, endo-**II.12** and exo-**II.12**, in 1,4-dioxane-H_2O (4:1) and recorded ^1H NMR spectra of the complexes every two hours. The NMR data showed a substantial isomerization already in two hours. The careful signal integration suggested an approximate 1:0.4 ratio of the starting diastereomer to the alternative for both samples, indicating similar epimerization rates for both isomers. After six hours of heating, each complex became a 1:1 mixture of endo and exo isomers.

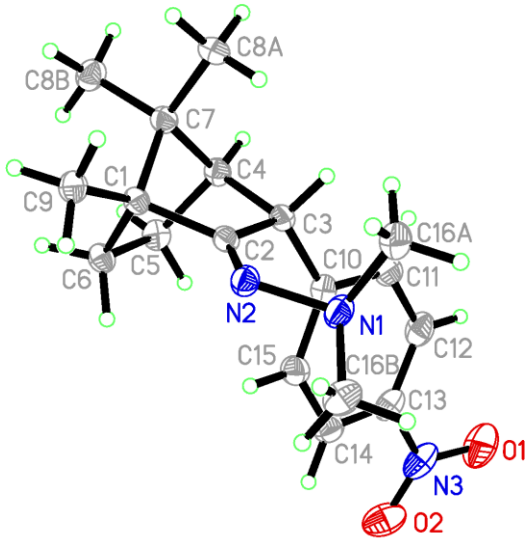


Figure II.1. ORTEP drawing of the molecular structure of compound (1*R*,3*R*,4*R*,Z)-**II.13b**.

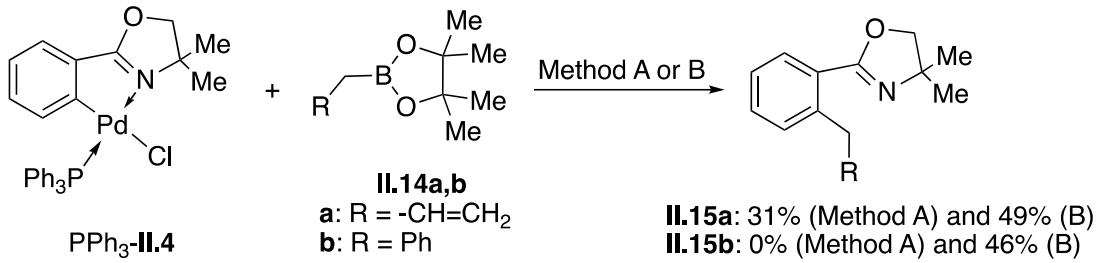
To the best of our knowledge, there is only one study describing the stereoselectivity of the (sp^3)C–(sp^2)C bond formation in the reactions of palladacycles having the metal attached to the chiral carbon with a known absolute configuration.[53] Ghouilem et al. postulated the formation of the (sp^3)*C,N,N*-palladacycle with a well-defined stereochemistry in the Pd(II)-catalyzed transformations involving ArI. The

researchers proposed the oxidative addition of ArI to the Pd(II) atom of the metallacycle followed by the reductive elimination step resulting in diastereoselective (sp^3)C–(sp^2)C bond formation. The transformation proceeded with the retention of the absolute configuration. The reactions described in our research involve different intermediates; however, the last step of the transformation is expected to be also reductive elimination, though from the Pd(II) complexes rather than Pd(IV). These Pd(II) intermediates undergoing reductive elimination are likely to have structures similar to **II.A-2** and **II.E-2** (Chart II.1) proposed by Bedford[37] and Zhou.[40] Since the (sp^3)C–(sp^2)C bond formation proceeded with retention of the absolute configuration in the only known related study of the reactions of (sp^3)*C,N,N*-palladacycles,[53] we hypothesize that CPC **II.12** and $ArB(OH)_2$ **II.2b** form the (sp^3)C–(sp^2)C bond with the retention of the absolute configuration too. Therefore, endo-**II.13** is formed from endo-**II.12,** and the later complex reacts with **II.2b** much faster than exo-**II.12**.

II.2.3. Case C: (sp^2)C–(sp^3)C Bond Formation Using Cyclopalladated Complexes with an (sp^2)C–Pd Bond and Boronic Acids having an (sp^3)C–B Bond

In this part of the study, we report our data on the reactions of cyclopalladated complexes PPh_3-**II.1** and PPh_3-**II.4** with two boronic esters, **II.14a,b**. The former complex did not react with both boronic esters under the conditions of Methods A and B. However, the use of Method A in the reaction of the oxazoline derivative PPh_3-**II.4** and allyllboronic acid pinacol ester **II.14a** provided 31% of the desired compound **II.15a** (Scheme II.7). When the reaction duration was doubled, the yield was improved only by a few percent; yet 43% of unreacted complex PPh_3-**II.4** was isolated. A similar result was obtained in the

experiments using excess (up to 2.5 molar equiv.) boronic ester **II.14a**. The best yield of **II.15a**, 49%, was achieved using Method B Interestingly, 4,4-dimethyl-2-phenyl-2-oxazoline was isolated in 29% in the same reaction. The preligand formation was also reported in other transformations of palladacycles due to β-hydride elimination.[22] The coupling of complex PPh_3-**II.4** with benzyl ester **II.14b** afforded the desired compound, **II.15b**, under the conditions of Method B (Scheme II.7). This product, **II.15b,** was not detected in the reaction of PPh_3-**II.4** with **II.14b** using Method A.



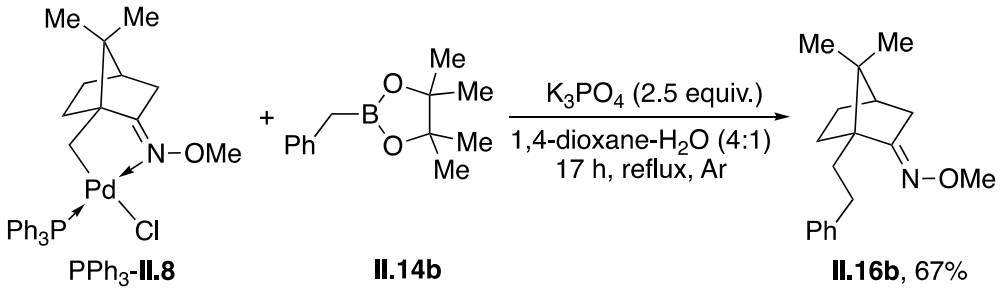
Scheme II.7. Formation of an (sp^2)C–(sp^3)C bond using boronic esters **II.14a,b**.

We also attempted reactions of PPh_3-**II.1** and PPh_3-**II.4** with $MeB(OH)_2$ and *i*-$BuB(OH)_2$ using Methods A and B. The experiments did not afford desired products. Starting complexes were recovered in all cases, 20–52%. In the experiments involving PPh_3-**II.4** and *i*-$BuB(OH)_2$, up to 21% of 4,4-dimethyl-2-phenyl-2-oxazoline was isolated as well.

II.2.4. Case D: (sp^3)C–(sp^3)C Bond Formation Using Cyclopalladated Complexes with an (sp^3)C–Pd Bond and Boronic Acids Having an (sp^3)C–B Bond

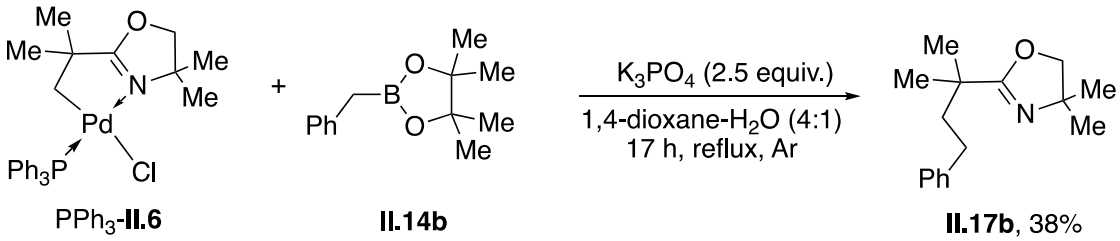
The reactions of two aliphatic, PPh_3-**II.6** and PPh_3-**II.8**, and one benzylic, PPh_3-**II.10**, palladacycles with the esters of allyl- and benzylboronic acids, **II.14a,b**, were expected to be the most challenging. In fact, our attempts to synthesize the desired product

II.16a from PPh_3-**II.8** and **II.14a** were unsuccessful using Methods A and B. However, the reaction of PPh_3-**II.8** with benzylboronic acid pinacol ester **II.14b** afforded compound **II.16b** in 67% yield when we used Method B (Scheme II.8).



Scheme II.8. The $(sp^3)C–(sp^3)C$ bond formation in the reactions of PPh_3-**II.8** with **II.14b**.

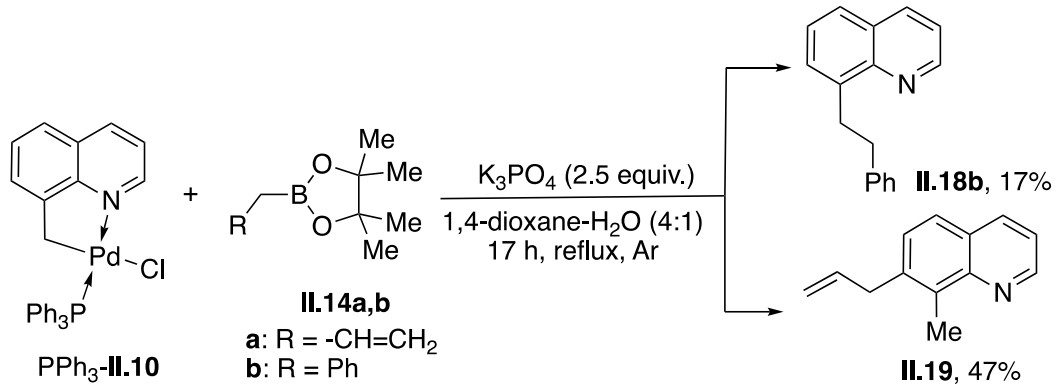
Similarly, the application of Method B was rewarding in the coupling of complex PPh_3-**II.6** with **II.14b** (Scheme II.9). The oxazoline derivative **II.17b** was isolated in 38%, and the unreacted CPC **PPh_3-II.6** was recovered in 22%.



Scheme II.9. Formation of oxazoline **II.17b** using Method B.

The experiment with 8-methylquinoline-derived complex PPh_3-**II.10** and boronic ester **II.14b** was also productive; however, the yield of the desired product (**II.18b**) was low, 17%. The unreacted CPC **PPh3-II.10** was recovered in 62%. An unexpected result was observed in the reaction of palladacycle PPh_3-**II.10** with boronic ester **II.14a**. Allylation took place at position 7 of the 8-methylquinoline core, and product **II.19** was isolated in 47% (Scheme II.10). It is noteworthy that the preparation of compounds **II.16b**–

II.18b are the first examples of the successful (sp^3)C–(sp^3)C bond formation reacting using palladacycles and boronic esters.



Scheme II.10. Reactions of PPh_3-**II.10** with esters **II.14a,b** under the conditions of Method B.

II.3. Conclusions

We developed two procedures, which can be used to form C–C bonds by reacting palladacycles with boronic acids or esters. The reactions do not require the application of benzoquinoline or Ag_2O. Cyclopalladated complexes have to be converted to the corresponding mononuclear derivatives with PPh_3 prior to the reaction. The use of a base is necessary for the successful transformation. For achieving the (sp^2)C–(sp^2)C bond formation, the best base was Cs_2CO_3, and the most advantageous solvent was acetone. For constructing an (sp^2)C–(sp^3)C bond, the best base was K_3PO_4, and the most beneficial solvent was a 4:1 mixture of dioxane and water. Reactions leading to the (sp^2)C–(sp^2)C bond formation proceed in higher yields and at lower temperatures compared to (sp^2)C–(sp^3)C bonds. The formation of an (sp^3)C–(sp^3)C bond was successful only using pinacol ester of allylboronic acid **II.14a**. Both boronic acids and esters can be used in the reactions with (sp^2)*C,N*-CPCs, but $RB(OH)_2$ seem to provide higher yields. The electronic effect of substituents in $ArB(OH)_2$ on the yield was negligible in the transformations leading to the

(sp^2)C–(sp^2)C bond formations. However, the presence of the electron-withdrawing nitro group in the para position of $ArB(OH)_2$ was critical in the reaction with the aliphatic palladacycle **II.12**. The coupling of pure (1*R*,2*S*,4*R*)-**12** and (1*R*,2*R*,4*R*)-**II.12** with *p*-$NO_2C_6H_4B(OH)_2$ afforded the same stereoisomer, (1*R*,3*R*,4*R*,*Z*)-**II.13**, suggesting (i) epimerization of two diastereomers, (ii) faster reaction of one of the two diastereomers, and (iii) high diastereoselectivity of the C–C bond formation.

II.4. Experimental

II.4.1. General Methods and Instrumentation

Routine ^{1}H (500 MHz) and $^{13}C\{^{1}H\}$ (126 MHz) as well as DEPT, COSY and HSQC spectra were recorded on a Bruker AVANCE 500 NMR spectrometer. Chemical shifts are reported in ppm with $SiMe_4$ as an internal standard. Spin-spin coupling constants, *J*, are given in Hz. Melting points were measured on a Laboratory Devices Mel-Temp apparatus and are uncorrected. Optical rotations were measured at room temperature on a JASCO P-2000 polarimeter.

High resolution mass spectra were recorded on a quadrupole time-of-flight mass spectrometer (Q-TOF, Synapt G2-S, Waters, Milford, MA) with electrospray ionization ion source. MassLynx V4.2 software (Waters) was used for instrument control, acquisition, and sample analysis. The source was operated in a positive ion mode with a cone voltage of 20V. The capillary voltage was 1.51 kV. The source temperature was 110 °C and the desolvation temperature was 100 °C. The analyzer was operated at 20,000 resolution (fwhm at m/z 554) and an acquisition time of 0.1 s. Data were acquired in MS^E mode where the transfer T-wave element was alternated between low energy (2V) and high energy states where the voltage applied to the transfer T-wave element was from 10–25V. The cone and desolvation gas flow rates were 10 L/h and 1000 L/h, respectively, with the nebulizer gas at 6 Bar. The lock spray for mass correction was leucine enkephalin (400 pg/μL, MeCN-water, 50:50) infused at a rate of 10 μL/min. Samples were dissolved in MeCN containing 0.1% formic acid and infused at a rate of 5 μL/min.

Boronic acids and esters (Combi-Blocks, 98%), Cs_2CO_3 (Sigma-Aldrich, ≥98%), K_3PO_4 (Sigma-Aldrich, ≥98%), acetone (HPLC grade), acetonitrile (HPLC grade), $CDCl_3$ (Alfa Aesar, 99.8%) were used as purchased. Other solvents were purified using standard methods.[23] Cyclopalladated complexes PPh_3-**II.1**[58], PPh_3-**II.4**[59], PPh_3-**II.6**[60], PPh_3-**II.8**[61], PPh_3-**II.10**[62], and PPh_3-**II.12**[52] were prepared using known literature procedures.

II.4.2. Synthesis of Compounds

II.4.2.1. General Procedures for the Reactions of PPh_3 Adducts of Cyclopalladated Complexes with Boronic Acids or Pinacol Esters

Method A: A solution of the PPh_3 adduct of the cyclopalladated complex (1.0 molar equiv.), arylboronic acid (1.0 molar equiv.), and Cs_2CO_3 (2.0 molar equiv.) in acetone (5.0 mL per 0.09 mmol of the complex) was heated and refluxed for 17 h under air. Reaction progress was monitored by thin-layer-chromatography. The reaction mixture was cooled to rt and filtered through a plug of celite. The celite was washed with excess acetone. Solvent in the filtrate was removed on a rotavapor. The residue was dissolved in CH_2Cl_2 and washed with water. The organic layer was dried over anhydrous Na_2SO_4, filtered through a plug of cotton, and evaporated on a rotavapor. The crude product was purified by column chromatography on silica gel.

Method B: A pressure tube was filled with argon. Then, a 4:1 mixture of 1,4-dioxane-water (5.0 mL per 0.09 mmol of the complex), cyclopalladated complex (1.0 molar equiv.), boronic acid or ester (1.0 molar equiv.), and K_3PO_4 (2.5 molar equiv.) were consecutively added to the tube under the flow of argon. The pressure tube with the reaction mixture was sealed and heated at 110 °C for 17 h. The reaction mixture was cooled to rt

and filtered through a plug of celite. The celite was washed with acetone. The filtrate was evaporated on a rotavapor. The residue was diluted with CH_2Cl_2 and washed with water. The organic layer was dried over anhydrous Na_2SO_4 and filtered through a plug of cotton. The solvent was removed on a rotavapor. The crude product was purified by column chromatography on SiO_2.

***N,N*-Dimethyl-(1,1´-biphenyl)-2-methanamine (II.3a).** The compound was obtained using Method A and isolated as a colorless liquid in 79% yield. R_f 0.49 (1:20 MeOH–CH_2Cl_2). ^1H and $^{13}C\{^1H\}$ NMR data were identical to those reported earlier for this compound.[63]

***N,N*-Dimethyl-4´-nitro-(1,1´-biphenyl)-2-methanamine (II.3b).** The compound was synthesized using Method A and isolated as a colorless liquid in 79% yield. R_f 0.51 (1:20 MeOH–CH_2Cl_2). ^1H and $^{13}C\{^1H\}$ NMR data were identical to those reported earlier for this compound.[63]

Methoxy-N,N-dimethyl-(1,1´-biphenyl)-2-methanamine (II.3c). The compound was obtained using Method A and isolated as a colorless liquid in 79% yield. R_f 0.62 (1:20 MeOH–CH_2Cl_2). ^1H and $^{13}C\{^1H\}$ NMR data were identical to those reported earlier for this compound.[63]

2-[1,1´-Biphenyl]-2-yl-4,5-dihydro-4,4-dimethyloxazole (II.5a). The compound was obtained using Method A and isolated as a colorless liquid in 75% yield. R_f 0.45 (3:7 EtOAc–hexanes). ^1H and $^{13}C\{^1H\}$ NMR data were identical to those reported earlier for this compound.[64]

4,5-Dihydro-4,4-dimethyl-2-(4´-nitro[1,1´-biphenyl]-2-yl)oxazole (II.5b). The compound was obtained using Method A and isolated as a yellow liquid in 74% yield. R_f

0.51 (3:7 EtOAc–hexanes). ^{1}H NMR (δ, ppm, $CDCl_3$): 1.28 (s, 6H, $CH_3 \times 2$), 3.83 (s, 2H, CH_2O), 7.36 (d, J = 7.6, 1H, CH arom.), 7.46 (m, 1H, CH arom.), 7.54 (m, 3H, CH arom.), 7.82 (d, J = 7.6, 1H, CH arom.), 8.25 (d, J = 8.6, 2H, CH arom.). ^{13}C{^{1}H} NMR (δ, ppm, $CDCl_3$): 28.0 ($CH_3 \times 2$), 67.8 ($(CH_3)_2\underline{C}N$), 79.5 (OCH_2), 123.2 (CH of $C_6H_4NO_2$), 127.7 (quart. C), 128.4 (CH of C_6H_4), 129.4 (CH of $C_6H_4NO_2$), 129.9, 130.4, 130.7 (CH × 3 of C_6H_4), 139.4, 147.0 and 148.0 (quart. C × 3), 162.7 (C=N). HRMS data: $[M + H]^+$ calcd for $C_{17}H_{17}N_2O_3$ 297.1239, found 297.1249.

4,5-Dihydro-2-(4´-methoxy[1,1´-biphenyl]-2-yl)-4,4-dimethyloxazole (II.5c). The compound was obtained using Method A and isolated as a colorless liquid in 73% yield. R_f 0.49 (3:7 EtOAc–hexanes). ^{1}H and ^{13}C{^{1}H} NMR data were identical to those reported earlier for this compound.[65]

2-(1,1-Dimethyl-2-phenylethyl)-4,5-dihydro-4,4-dimethyloxazole (II.7a). The compound was obtained using Method B and isolated as a colorless oil in 87% yield. R_f 0.72 (3:7 EtOAc–hexanes). ¹H NMR (δ, ppm, $CDCl_3$): 1.18 (s, 12 H, $CH_3 \times 4$), 2.83 (s, 2H, $C\underline{H}_2Ph$), 3.92 (s, 2H, CH_2O), 7.12 (m, 2H, CH arom.), 7.18–7.24 (m, 3H, CH arom.). ^{13}C{^{1}H} NMR (δ, ppm, $CDCl_3$): 25.7 and 28.4 ($CH_3 \times 4$), 37.6 ($\underline{C}(CH_3)_2$), 46.4 (CH_2), 66.9 ($(CH_3)_2\underline{C}N$), 78.9 (OCH_2), 126.3, 127.8, 130.3 (CH of Ph), 138.0 (quart. C), 170.6 (C=N). HRMS: $[M + H]^+$ calcd for $C_{15}H_{21}NO$ 232.1701, found 232.1703.

2-[1,1-Dimethyl-2-(4-nitrophenyl)ethyl]-4,5-dihydro-4,4-dimethyloxazole (II.7b). The compound was synthesized using Method B and isolated as a yellow solid in 85% yield. M. p. 92–94 °C. R_f 0.51 (3:7 EtOAc–hexanes). ¹H NMR (δ, ppm, $CDCl_3$): 1.20 and 1.22 (two s, 6H × 2, $CH_3 \times 4$), 2.94 (s, 2H, $C\underline{H}_2Ph$), 3.93 (s, 2H, CH_2O), 7.30 (m, 2H, CH arom.), 8.12 (m, 2H, CH arom.). ^{13}C {^{1}H} NMR (δ, ppm, $CDCl_3$): 25.8 and 28.4

(C($\underline{C}H_3$)$_2$ × 2), 37.6 (C$\underline{C}$(CH$_3$)$_2$C), 46.1 (CH$_2$), 67.0 (N$\underline{C}$(CH$_3$)$_2$), 79.0 (OCH$_2$), 123.1 and 131.0 (CH of Ar), 146.0 and 146.7 (quat. C of Ar), 169 (C=N). HRMS: $[M + H]^+$ calcd for $C_{15}H_{20}N_2O_3$ 277.1552, found 277.1555.

4,5-Dihydro-2-[1,1-dimethyl-2-(4-methoxyphenyl)ethyl]-4,4-dimethyloxazole (II.7c). The compound was prepared using Method B and isolated in 15% yield as a ca. 4:1 mixture with 4,4´-dimethoxybiphenyl. R_f 0.62 (3:7 EtOAc–hexanes). ^{1}H NMR (δ, ppm, $CDCl_3$): 1.18 and 1.20 (two s, 6H × 2, CH$_3$ × 4), 2.77 (s, 2H, C$\underline{H}_2$Ph), 3.77 (s, 3H, OCH$_3$), 3.91 (s, 2H, CH$_2$O), 6.80 (m, 2H, CH arom.), 7.05 (m, 2H, CH arom.). $^{13}C\{^1H\}$ NMR (δ, ppm, $CDCl_3$): 25.6 and 28.4 (C($\underline{C}H_3$)$_2$ × 2), 37.6 (C$\underline{C}$(CH$_3$)$_2$C), 45 (CH$_2$), 55 (OCH$_3$), 66.8 (N$\underline{C}$(CH$_3$)$_2$), 78.8 (OCH$_2$), 113.2 and 131.2 (CH of Ar), 130.1 (quart. C of Ar), 158.1 (arom. $\underline{C}$OCH$_3$), 170 (C=N). HRMS: $[M + H]^+$ calcd $C_{16}H_{24}NO_2$ 262.1807, found 262.1817.

4,5-Dihydro-4,4-dimethyl-2-[2-methyl-1-(quinoline-8-yl)propan-2-yl]oxazole (II.7d). The compound was obtained using Method B and isolated as a pale-yellow oil in 68% yield. R_f 0.39 (3:7 EtOAc-hexanes). ^{1}H NMR (δ, ppm, $CDCl_3$): 1.15 and 1.24 (two s, 2 × 6H, CH$_3$ × 4), 3.63 (s, 2H, C$\underline{H}_2$Ar), 3.90 (s, 2H, CH$_2$O), 7.34 (dd, J = 3.9, 7.9, 1H, NC(1)HC(2)$\underline{H}$ of quin.), 7.44 (m, 1H, C(6)H of quin.), 7.55 (d, J = 7.0 Hz, 1H, C(7)H of quin.), 7.67 (d, J = 7.9, 1H, C(5)H of quin.), 8.10 (d, J = 7.9, 1H, C(3)H of quin.), 8.91 (m, 1H, C(1)H). $^{13}C\{^1H\}$ NMR (δ, ppm, $CDCl_3$): 26.1, 28.3 (C($\underline{C}H_3$)$_2$ × 2), 38.4 ($\underline{C}$($\underline{C}H_3$)$_2$), 39.3 (Ar$\underline{C}$H$_2$), 66.7 (N$\underline{C}$($\underline{C}H_3$)$_2$), 78.8 (OCH$_2$), 120.6 (C(2)H of quin.), 125.7 (C(6)H of quin.), 126.5 (C(5)H), 128.3 (quart. C arom.), 130.6 (C(7)H), 136.2 (C(3)H), 137.4, 147.6 (2 quart. C arom.), 149.1 (NC1), 170.9 (C=N). HRMS $[M + H]^+$ calcd for $C_{18}H_{13}N_2O$ 283.1810, found 283.1812.

4,5-Dihydro-4,4-dimethyl-2-[2-methyl-1-(pyridin-3-yl)propan-2-yl]oxazole (II.7e). The compound was prepared using Method B as a dark yellow oil in 66% yield. R_f 0.61 (3:7 EtOAc-hexanes). ^{1}H NMR (δ, ppm, $CDCl_3$): 1.19, 1.22 (two s, 2 × 6H, CH_3 × 4), 2.8 (s, 2H, C$\underline{H}_2$Ar), 3.92 (s, 2H, CH_2O), 7.19 (dd, J = 4.8, 7.7, 1H, C(4)H), 7.47 (d, J = 7.7, 1H, C(3)H), 8.39 (s, 1H, C(1)H), 8.44 (d, J = 4.8, 1H, C(5)H). ^{13}C{^{1}H} NMR (δ, ppm, $CDCl_3$): 25.7, 28.4 (C($\underline{C}H_3)_2$), 37.4 ($\underline{C}(CH_3)_2$), 43.6 (Ar$\underline{C}H_2$), 67.0 (NC($\underline{C}H_3)_2$), 79.0 (OCH_2), 122.8 (NC(5)H$\underline{C}$(4)H), 133.5 (quart. C arom.), 137.4 ((NC(5)HC(4)H$\underline{C}$(3)H,), 147.8 (NC(5)H), 151.3 (NC(1)H), 169.8 (C=N). HRMS $[M + H]^+$ calcd for $C_{14}H_{20}N_2O$ 233.1654, found 233.1653.

(1*S*,4*R*,*E*)-1-Benzyl-7,7-dimethylbicyclo[2.2.1]heptan-2-one O-methyloxime (II.9a). The compound was obtained as a colorless oil in 74% yield using Method B. R_f 0.72 (1:20 EtOAc–hexanes). $[\alpha]_D^{22}$ = -190 (*c* 0.57, acetone). ^{1}H NMR (δ, ppm, $CDCl_3$): 0.82 and 0.84 (two s, 3H × 2, CH_3 × 2), 1.16 and 1.26 (two m, 1H × 2, C(6)H endo and C(5)H endo), 1.71–1.86 (m, 3H, C(4)H, C(5)H exo and C(6)H exo), 1.94 (d, $^2J_{3endo,3exo}$ = 17.8, 1H, C(3)H endo), 2.49 (dt, $^3J_{3exo,4}$ = $^4J_{3exo,5exo}$ 3.5, $^2J_{3exo,3endo}$ = 17.8, 1H, C(3)H exo), 2.67 and 3.09 (two d, ^2J = 14, 1H, PhC(9)H_2), 3.88 (s, 3H, OCH_3), 7.16 (m, 1H, CH arom.), 7.23 (m, 2H, CH arom.), 7.39 (m, 2H, CH arom.). ^{13}C{^{1}H} NMR (δ, ppm, $CDCl_3$): 19.4 and 19.9 (C($\underline{C}H_3)_2$), 27.0 (C(5)H_2), 29.9 (C(6)H_2), 33.2 (Ph$\underline{C}$(9)H_2), 33.3 (C(3)H_2), 44.3 (C(4)H), 48.9 and 55.1 (C(1) and C(7)), 61.4 (OCH_3), 125.7, 127.6, 131.0 (three CH arom.), 139.6 (quat. C arom.), 168.7 (C=N). HRMS: $[M + H]^+$ calcd $C_{17}H_{24}NO$ 258.1858, found 258.1857.

(*1S*,*4R*,*E*)-1-[(4-Nitrophenyl)methyl]-7,7-dimethylbicyclo[2.2.1]heptan-2-one O-methyloxime (II.9b). The compound was obtained in 76% yield as a colorless oil

following Method B. R_f 0.65 (1:20, EtOAc–hexanes). $[\alpha]_D^{22}$ = -229 (*c* 0.625, acetone). ^{1}H NMR (δ, ppm, $CDCl_3$): 0.84 and 0.92 (two s, 3H × 2, CH_3 × 2), 1.16–1.25 (m, 2H, C(5)H endo), C(6)H endo), 1.70–1.82 (m, 2H, C(6)H exo and C(5)H exo), 1.86 (t, $^3J_{4,3exo} = {}^3J_{4,5exo}$ = 3.5, 1H, C(4)H), 1.94 (d, $^2J_{3exo,3endo}$ = 17.5, 1H, C(3)H endo), 2.50 (dt, $^3J_{3exo,4} = {}^4J_{3exo,5exo}$ = 3.5, $^2J_{3exo,3endo}$ = 17.5, 1H, C(3)H exo), 2.72 and 3.16 (two d, ^2J = 14, 1H × 2, ArC(9)H_2), 3.87 (s, 3H, OCH_3), 7.60 (d, *J* = 9.0, 2H, CH arom.), 8.09 (d, *J* = 9.0, 2H, CH arom.). $^{13}C\{^1H\}$ NMR (δ, ppm, $CDCl_3$): 19.2 and 19.8 (C($\underline{C}H_3$)$_2$), 27.0 (C(5)H_2), 30.0 (C(6)H_2), 33.3 (overlap. C(3)H_2 and ArC(9)H_2), 44.0 (C(4)H), 49.1 and 54.9 (quart. C(1) and C(7)), 61.5 (OCH_3), 122.8 and 131.8 (two CH arom.), 146.3 (quart. C(10)), 148.0 (CNO_2), 167.9 (C=N). HRMS: $[M + H]^+$ calcd $C_{17}H_{23}N_2O_3$ 303.1709, found 303.1710.

(*1S,4R,E*)-1-[(4-Methoxyphenyl)methyl]-7,7-dimethylbicyclo[2.2.1]heptan-2-one O-methyloxime (II.9c). The compound was synthesized in 67% yield using Method B and isolated as a ca. 4:1 mixture with 4,4´-dimethoxybiphenyl. R_f 0.51 (1:20 EtOAc–hexanes). ^{1}H NMR (δ, ppm, $CDCl_3$): 0.830 and 0.835 (two s, 3H × 2, CH_3 × 2), 1.16–1.20 and 1.22–1.29 (two m, 1H × 2, C(5)H endo and C(6)H endo), 1.70–1.85 (m, 3H, C(4)H, C(5)H exo and C(6)H exo), 1.94 (d, $^2J_{3exo,3endo}$ = 17.7, 1H, C(3)H endo), 2.48 (dt, $^3J_{3exo,4} = {}^4J_{3exo,5exo}$ = 3.7, $^2J_{3exo,3endo}$ = 17.7, 1H, C(3)H exo), 2.64 and 3.01 (two d, ^2J = 14.2, 1H × 2, ArC(9)H_2), 3.78 and 3.88 (two s, 3H × 2, OCH_3 × 2), 6.78 (d, *J* = 8.5, 2H, CH arom.), 7.29 (d, *J* = 8.5, 2H, CH arom.). $^{13}C\{^1H\}$ NMR (δ, ppm, $CDCl_3$): 19.4 and 19.9 (C($\underline{C}H_3$)$_2$), 27.0 (C(5)H_2), 30.0 (C(6)H_2), 32.2 (ArC(9)H_2), 33.4 (C(3)H_2), 44.3 (C(4)H), 48.8 and 55.3 (quart. C(1) and C(7)), 55.2 and 61.4 (OCH_3 × 2), 112.9 and 131.9 (two CH arom.), 131.7 (quart. C arom.), 157.7 (quart. arom. $\underline{C}OCH_3$), 168.8 (C=N). HRMS: $[M + H]^+$ calcd $C_{18}H_{26}NO_2$ 288.1964, found 288.1964.

***(1S,4R,E)*-7,7-Dimethyl-1-(quinoline-8-ylmethyl)bicyclo[2.2.1]heptan-2-one O-methyloxime (II.9d).** The compound was prepared using Method B and isolated in 89% yield as a colorless oil. R_f 0.66 (1:20 EtOAc–hexanes). $[\alpha]_D^{22}$ = -389 (*c* 0.695, acetone). ^{1}H NMR (δ, ppm, $CDCl_3$): 0.83 and 0.94 (2s, 2 × 3H, $C(CH_3)_2$), 1.06–1.11 (m, 1H, C(5)H endo), 1.18–1.23 (m, 1H, C(6)H endo), 1.65–1.74 (m, 1H, C(6)H exo), 1.72–1.80 (m, 2H, C(5)H exo, C(4)H), 1.95 (d, $^2J_{3endo,3exo}$ = 17.7, 1H, C(3)H endo), 2.53 (dt, $^3J_{3exo,4} = {}^4J_{3exo,5exo}$ = 3.6, $^2J_{3exo,3endo}$ = 17.7, 1H, C(3)H exo), 3.42 (d, $^2J_{9a,9b}$ = 13.8, 1H, ArC(9)Ha), 3.92 (s, 3H, OCH_3), 3.96 (d, $^2J_{9b,9a}$ = 13.8, 1H, ArC(9)Hb), 7.34 (dd, *J* = 4.1, 8.2, 1H, quin. C(3)H), 7.46 (t, *J* = 8.2, 1H, quin. C(6)H), 7.65 (d, *J* = 8.2, 1H, quin. C(7)H), 8.09 (two overlapped d, 2H, quin. C(4)H, C(5)H), 8.91 (d, *J* = 4.1, quin. C(2)H). $^{13}C\{^1H\}$ NMR (δ, ppm, $CDCl_3$): 19.2 and 19.8 ($C(\underline{C}H_3)_2$), 25.7 ($Ar\underline{C}H_2$), 27.1 ($C(6)H_2$), 29.6 ($C(5)H_2$), 33.5 ($C(3)H_2$), 44.2 (C(4)H), 49.2 and 55.9 (C(1) and C(7)), 61.4 (OCH_3), 120.43 (quin. C(3)H), 125.8 and 125.9 (quin. C(6)H and C(7)H), (quin. quat. C), 132.3 and 136.2 (quin. C(4)H and C(5)H), 138.9 and 147.7 (two quin. quat. C), 148.9 (quin. C(2)H), 169.4 (C=NO). HRMS: $[M + H]^+$ calcd $C_{20}H_{25}N_2O$ 309.1967, found 309.1968.

(*1S,4R,E*)-1-[(3-Pyridinyl)methyl]-7,7-dimethylbicyclo[2.2.1]heptan-2-one O-methyloxime (II.9e). The compound was obtained following Method B in 61% yield as a colorless oil. R_f 0.35 (3:7 EtOAc–hexanes). $[\alpha]_D^{22}$ = -196 (*c* 0.350, acetone). ^{1}H NMR (δ, ppm, $CDCl_3$): 0.84 and 0.92 (two s, 3H × 2, CH_3 × 2), 1.16–1.26 (m, 2H, C(5)H endo, C(6)H endo), 1.75–1.80 (m, 2H, C(5)H exo, C(6)H exo), 1.85 (t, $^3J_{4,3exo} = {}^3J_{4,5exo}$ = 4.0, 1H, C(4)H), 1.95 (d, $^2J_{3exo,3endo}$ = 17.9, 1H, C(3)H endo), 2.49 (dt, $^3J_{3exo,4} = {}^3J_{3exo,5exo}$ = 4.0, $^2J_{3exo,3endo}$ = 17.6, 1H, C(3)H exo), 2.64 and 3.03 (two d, *J* = 14.7, 1H × 2, $C(9)H_2$), 3.87 (s, OCH_3), 7.16 (dd, *J* = 4.9, 7.6, 1H, C(5)H of Py), 7.82 (d, *J* = 7.1, 1H, C(4)H of Py), 8.41

(br. s, 1H, NC(6)H of Py), 8.60 (s, 1H, NC(2)H of Py). $^{13}C\{^{1}H\}$ NMR (δ, ppm, $CDCl_3$): 19.21 and 19.9 ($C(\underline{C}H_3)_2$), 27.0 ($Ar\underline{C}(9)H_2$), 30.0 and 30.5 ($C(5)H_2$ and $C(6)H_2$), 33.3 ($C(3)H_2$), 44.1 (C(4)H), 49.0 and 54.9 (two quat. C(1) and C(7)), 61.4 (OCH_3), 122.6 (C(5)H of Py), 135.1 (quart. C(3) of Py), 138.5 (C(4)H of Py), 147.2 (C(6)H of Py), 151.9 (NC(1)H of Py), 168.0 (C=N). HRMS: $[M + H]^+$ calcd $C_{16}H_{23}N_2O$ 259.1810, found 259.1808.

8-[(4-Nitrophenyl)methyl]quinoline (II.11b). The compound was synthesized using Method B and isolated as a yellow sold in 69% yield. M.p. 84–85 °C. R_f 0.66 (1:4 EtOAc–hexanes). ^{1}H and $^{13}C\{^{1}H\}$ NMR spectral data of the obtained compound matched those reported previously for **II.11b**.[66]

8-(4-Methoxybenzyl)quinoline (II.11c). The compound was obtained in 55% yield as a colorless liquid using Method B. R_f 0.67 (1:4 EtOAc–hexanes). ^{1}H and $^{13}C\{^{1}H\}$ NMR spectral data of the isolated compound matched those reported previously for **II.11c**.[66]

Di(quinoline-8-yl)methane (II.11d). The compound was synthesized using Method B and isolated in 70% yield as a pale-yellow oil. R_f 0.51 (3:7 EtOAc–hexanes). ^{1}H NMR (δ, ppm, $CDCl_3$): 5.38 (s, 2H, CH_2), 7.37–7.45 (m, 6H, C(3)H, C(6)H, and C(7)H), 7.69 (d, J = 7.9, 2H, C(5)H), 8.16 (dd, J = 1.7, 8.2, 2H, C(3)H), 8.98 (dd, J = 1.7, 4.2, 2H, C(1)H). $^{13}C\{^{1}H\}$ NMR (δ, ppm, $CDCl_3$): 31.9 (CH_2), 120.9, 126.1, 126.4, 129.9 and 136.3 (CH × 5), 128.4, 140.2 and 147.1 (quat. C × 3), 149.5 (NCH). HRMS: $[M + H]^+$ calcd for $C_{19}H_{14}N_2$ 271.1235, found 271.1235.

(*1R,3R,4R,Z*)-1,1-Dimethyl-2-[1,7,7-trimethyl-(4-nitrophenyl)bicyclo[2.2.1]heptan-2-ylidene]hydrazine ((*1R,3R,4R,Z*)-II.13b). The

compound was obtained as a major isomer [(1*R*,3*R*,4*R*,*Z*)-**II.13b** : (1*R*,3*S*,4*R*,*Z*)-**II.13b** = 30:1] from a 1:1 mixture of (1*R*,2*S*,4*R*,*Z*)-**II.12** and (1*R*,2*R*,4*R*,*Z*)-**II.12** using Method B and isolated as a pale-yellow solid in 49% yield. R_f 0.65 (1:9 EtOAc–hexanes). M.p 120–122 °C. $[\alpha]_D^{22}$ = +140 (*c* 1.03, acetone, 30:1 ratio of (1*R*,3*R*,4*R*,*Z*) and (1*R*,3*S*,4*R*,*Z*) diastereomers). ^{1}H NMR (δ, ppm, C_6D_6): 0.75 (m, 1H, C(6)H endo), 0.77, 0.81 and 1.15 (3 s, 3H × 3, CH_3 × 3), 1.22–1.25 (m, 1H, C(6)H endo), 1.35–1.41 (m, 1H, C(5)H exo), 1.52 (td, $^3J_{5exo,6endo}$ = 3.9, $^2J_{5exo,5endo}$ = $^3J_{5exo,6xo}$ = 12.7, 1H, C(5)H exo), 1.58 (t, $^3J_{4,3}$ = $^3J_{4,5exo}$ = 4.2, 1H, C(4)H), 2.19 (s, 6H, $N(CH_3)_2$), 3.76 (d, $^3J_{3,4}$ = 4.2, 1H, C(3)H), 6.72 (d, *J* = 8, 2H, CH arom.), 7.88 (d, *J* = 8, 2H, CH arom). ^{13}C{^{1}H} NMR (δ, ppm, C_6D_6): 12.7 (CH_3), 18.9 and 19.0 ($C(\underline{C}H_3)_2$), 21.2 ($C(6)H_2$), 32.1 ($C(5)H_2$), 45.9 ($N(CH_3)_2$), 47.2 (C(1)), 50.2 (C(3)H), 51.4 (C(4)), 53.7 (C(7)), 122.8 (CH arom.), 128.9 (CH arom.), 146.5 and 147.0 (two quart. C arom.), 171.2 (C=N). HRMS data: $[M + H]^+$ calcd for $C_{18}H_{26}N_3O_2$ 316.2025, found 316.2023.

4,5-Dihydro-4,4-dimethyl-2-[2-(2-propen-1-yl)phenyl]oxazole (II.15a). The compound was obtained as a colorless liquid from complex PPh_3-**II.4** and allylboronic acid pinacol ester **II.14a** using Method B in 49% yield. R_f 0.51 (1:4 EtOAc–hexanes). ^{1}H and ^{13}C{^{1}H} NMR data were identical to those reported earlier for this compound.[65]

4,5-Dihydro-4,4-dimethyl-2-[2-(phenylmethyl)phenyl]oxazole (II.15b). The compound was obtained as a colorless liquid from complex PPh_3-**II.4** and phenylboronic acid pinacol ester **II.14b** using Method B in 46% yield. R_f 0.62 (1:9 EtOAc–hexanes). ^{1}H and ^{13}C{^{1}H} NMR data were identical to those reported earlier for this compound.[67]

(*1R,4R,E*)-7,7-Dimethyl-1-phenethylbicyclo[2.2.1]heptan-2-one O-methyloxime (II.16b). The compound was obtained as a colorless liquid using Method B

in 67% yield. R_f 0.55 (1:9 EtOAc–hexanes). $[\alpha]_D^{22}$ = -23 (c 0.60, acetone). ^{1}H NMR (δ, ppm, $CDCl_3$): 0.82 and 0.92 (two s, 3H × 2, CH_3 × 2), 1.25 (m, 1H, C(5)H endo), 1.59 and 1.85 (two m, 2H and 4H, C(5)H exo, C(6)H_2, C(4)H and $PhCH_2C(9)\underline{H}_2$), 1.96 (d, $^2J_{3endo,3exo}$ = 18, 1H, C(3)H endo), 2.51 (m, 2H, C(3)H exo and $PhC(10)H_a$), 3.20 (td, $^2J_{10a,10b} = {}^3J_{10b,9a}$ = 13, $^3J_{10b,9b}$ = 4.2, 1H, $PhC(10)H_b$), 3.86 (s, 3H, OCH_3), 7.18 (m, 1H, CH arom.), 7.29 (m, 4H, CH arom.). $^{13}C\{^1H\}$ NMR (δ, ppm, $CDCl_3$): 19.1 and 19.8 ($C(\underline{C}H_3)_2$), 27.2 ($C(5)H_2$), 29.7 and 30.3 ($C(6)H_2$ and $PhCH_2\underline{C}H_2$), 31.8 ($Ph\underline{C}(10)H_2$), 33.4 ($C(3)H_2$), 43.9 (C(4)H), 48.8 and 54.4 (quat. C(1) and C(7)), 61.4 (OCH_3), 125.5, 128.3, 128.4 (three CH arom.), 144.0 (quat. C arom.), 168.3 (C=N). HRMS: $[M + H]^+$ calcd for $C_{18}H_{26}NO$ 272.2014, found 272.2020.

4,5-Dihydro-4,4-dimethyl-2-(1,1-dimethyl-3-phenylpropyl)oxazole (II.17b). The compound was prepared using Method B and isolated in 38% yield as a colorless liquid. R_f 0.35 (1:4 EtOAc–hexanes). ^{1}H NMR (δ, ppm, $CDCl_3$): 1.25, 1.27 (2 s, 2 × 6H, $C(CH_3)_2$ × 2), 1.81 and 2.54 (two m, 2 × 2H, CH_2CH_2), 3.89 (s, 2H, OCH_2), 7.17 (m, 3H, CH arom.), 7.25 (m, 2H, CH arom.). $^{13}C\{^1H\}$ NMR (δ, ppm, $CDCl_3$): 25.8, 28.4 ($C(\underline{C}H_3)_2$ × 2), 31.2 (CH_2), 36.3 (quart. C), 42.8 (CH_2), 66.8 (quart. C), 78.9 (OCH_2), 125.7, 128.32, 128.34 (three CH arom.), 142.5 (quat. C arom), 170.9 (C=N). HRMS data: $[M + H]^+$ calcd for $C_{16}H_{24}NO$ 246.1858, found 246.1860.

8-(2-Phenylethyl)quinoline (II.18b). The compound was obtained using Method B in 17% yield as a colorless liquid. R_f 0.42 (1:4 EtOAc–hexanes). ^{1}H and $^{13}C\{^1H\}$ NMR spectral data of the isolated product matched those reported previously for this compound.[68]

7-Allyl-8-methylquinoline (II.19). The compound was isolated in 47% yield as a pale-yellow oil from the reaction of boronic ester **II.14a** and complex PPh_3-**II.10** under the conditions described in Method B. R_f 0.57 (1:4 EtOAc–hexanes). ^{1}H NMR (δ, ppm, $CDCl_3$): 2.79 (s, 3H, C(10)H), 3.79 (d, J = 5.8, 2H, C(11)H), 5.04 (dd, J = 1.7, 7.0, 1H, C(13)H^a), 5.10 (dd, J = 1.3, 10.1, 1H, C(13)H^b), 6.07 (m, 1H, C(12)H), 7.30 (d, J = 7.2, 1H, C(6)H), 7.42 (dd, J = 4.2, 8.8, 1H, C(2)H), 7.51 (d, J = 7.2, 1H, C(5)H), 8.34 (dd, J = 1.7, 8.8, 1H, C(3)H), 8.95 (dd, J = 2.0, 4.3, 1H, C(1)H). ^{13}C{^{1}H} NMR (δ, ppm, $CDCl_3$): 18 (C10), 36 (C11), 116 (C13), 120 (C2), 126 (C6), 127 (C4), 129 (C5), 132 (C3), 134 (C7), 135 (C8), 136 (C12), 147 (C9), 148 (C1). HRMS data: $[M + H]^+$ calcd for $C_{13}H_{13}N$ 184.1126, found 184.1125.

II.5. Crystallographic Study of Compound (1*R*,3*R*,4*R*,*Z*)-II.13b

II.5.1. Data Collection

A crystal (approximate dimensions 0.260 × 0.190 × 0.120 mm^3) was placed onto the tip of a 200 μm diameter MiTeGen Dual-Thickness Microloop and mounted on a Bruker PHOTON-III CPAD diffractometer for a data collection at 150(2) K.[69] A preliminary set of cell constants was calculated from reflections harvested from three sets of frames. These initial sets of frames were oriented such that orthogonal wedges of reciprocal space were surveyed. This produced an initial orientation matrix determined from 511 reflections. The data collection was carried out using MoKα radiation (parabolic mirrors) with a frame time of 20 seconds and a detector distance of 4.0 cm. A strategy program was used to assure complete coverage of all unique data to a resolution of 0.70 Å. All major sections of frames were collected with 1.0^o steps in ω or φ at different detector

positions in 2θ. The intensity data were corrected for absorption and decay (SADABS).[70] Final cell constants were calculated from 2961 strong reflections from the actual data collection after integration (SAINT).[71] Please refer to Table SII.1 for additional crystal and refinement information.

II.5.2. Structure Solution and Refinement

The structure was solved using SHELXT 2018/2 (Sheldrick, 2018)[72,73] and refined using SHELXL-2018/3 (Sheldrick, 2018).[72,73] The space group $P2_12_12_1$ was determined based on systematic absences and intensity statistics. A direct-methods solution was calculated which provided most non-hydrogen atoms from the E-map. Full-matrix least squares / difference Fourier cycles were performed which located the remaining non-hydrogen atoms. All non-hydrogen atoms were refined with anisotropic displacement parameters. All hydrogen atoms were placed in ideal positions and refined as riding atoms with relative isotropic displacement parameters. The final full matrix least squares refinement converged to $R1 = 0.0370$ and $wR2 = 0.0926$ (F^2, obs. data).

Appendix II. NMR, IR Spectral and X-Ray Crystallographic Data

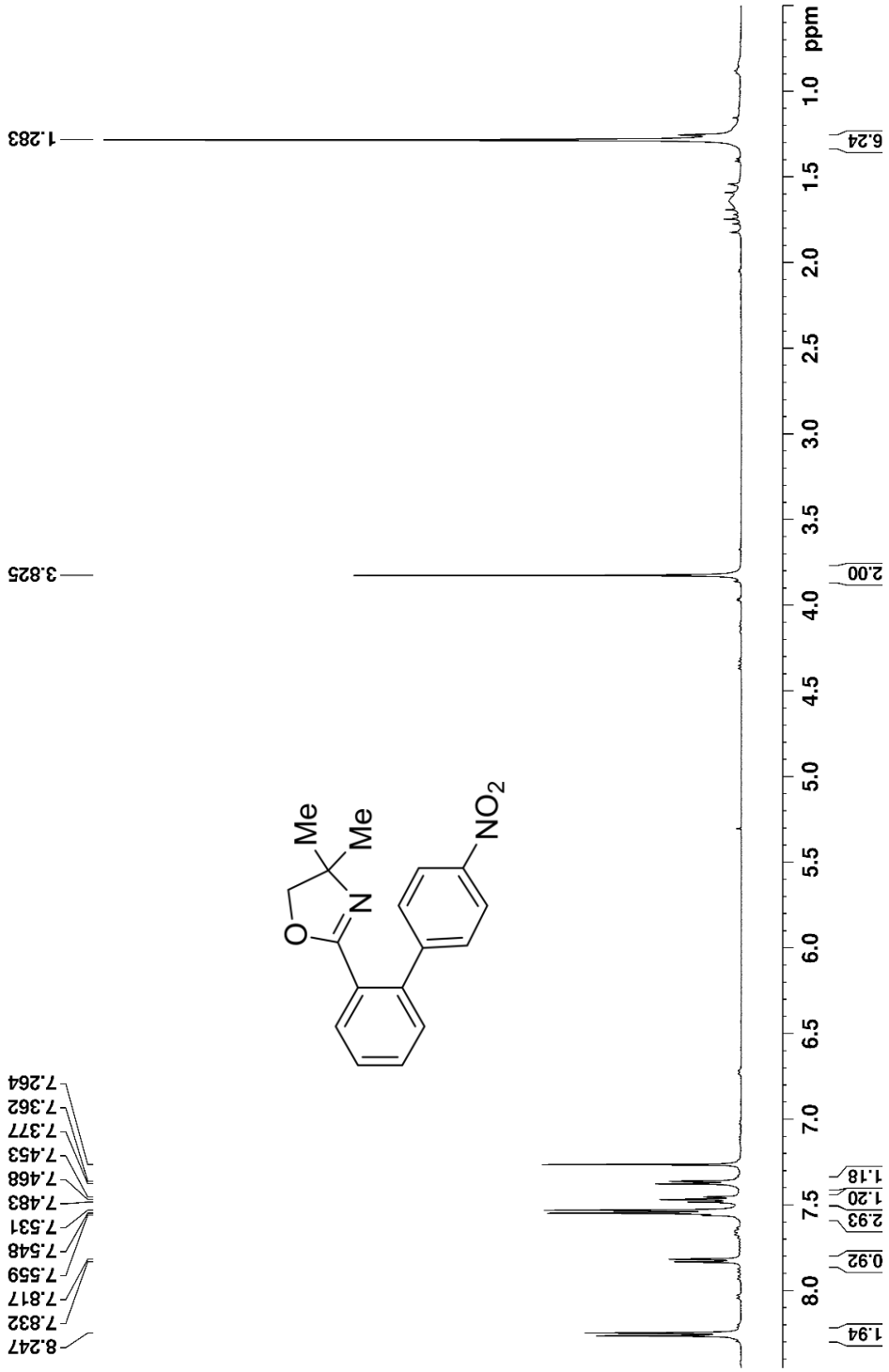


Figure II.2. ^{1}H NMR spectrum of compound **II.5b**.

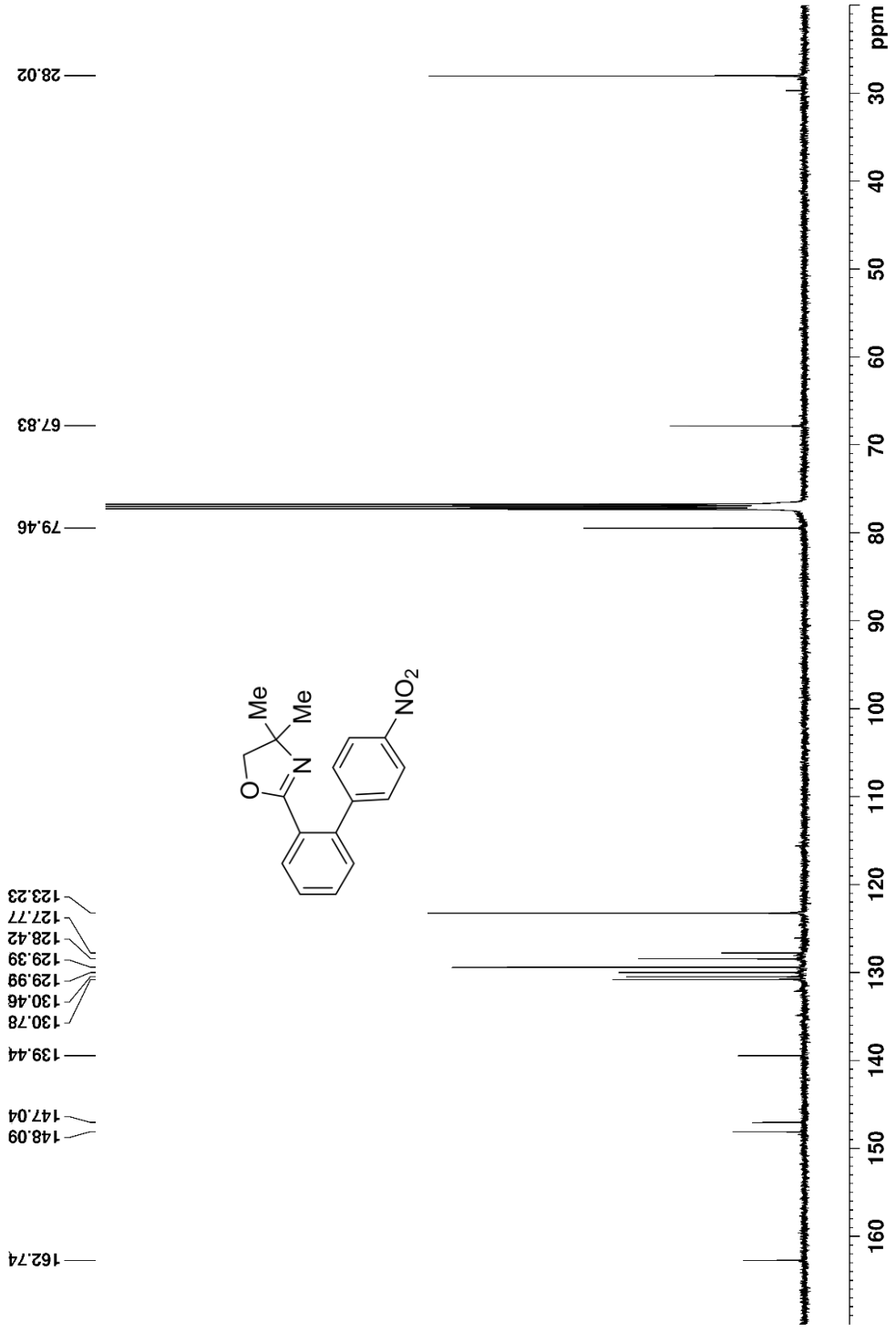


Figure II.3. $^{13}C\{^{1}H\}$ NMR spectrum of compound **II.5b**.

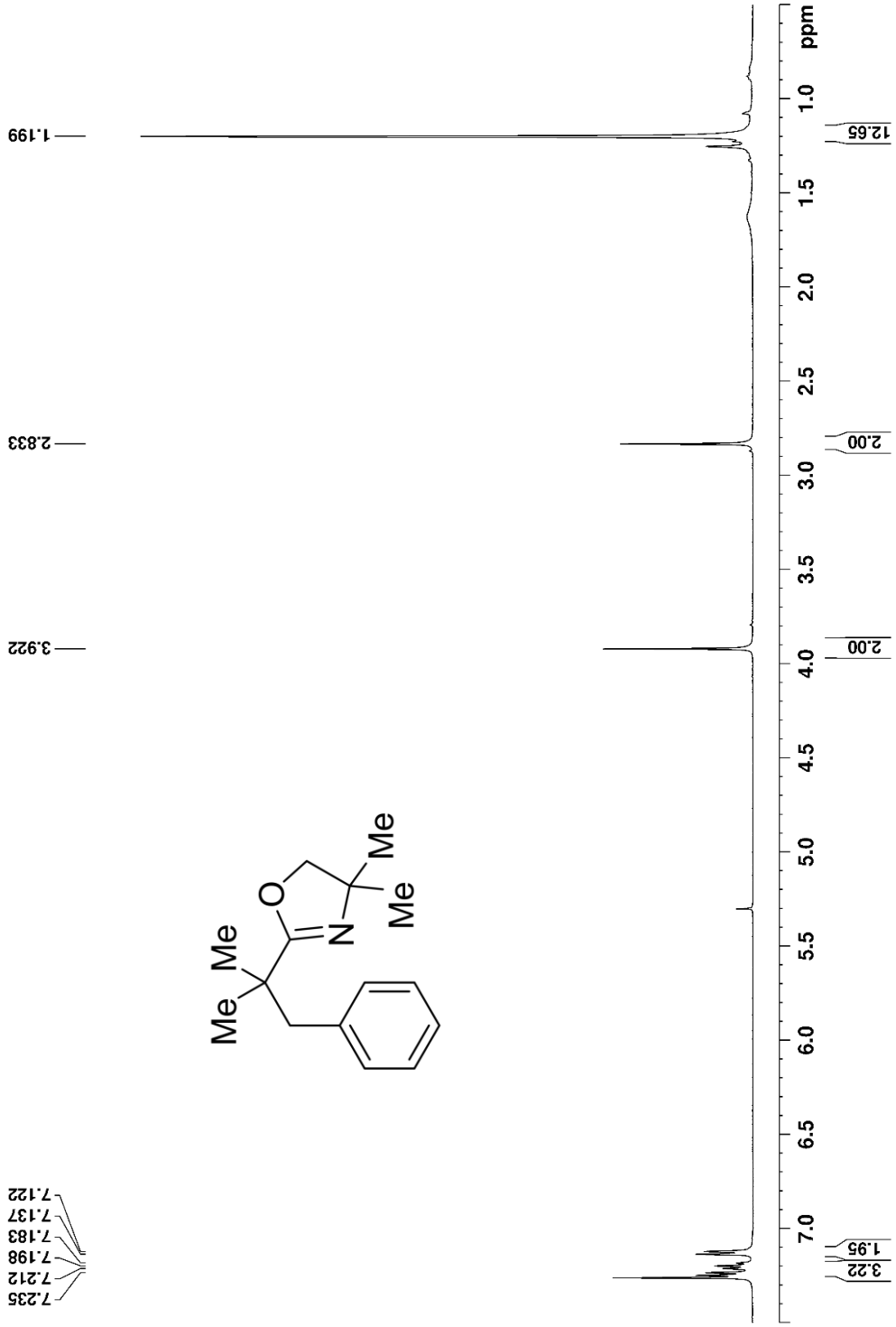


Figure II.4. ^{1}H NMR spectrum of compound **II.7a**.

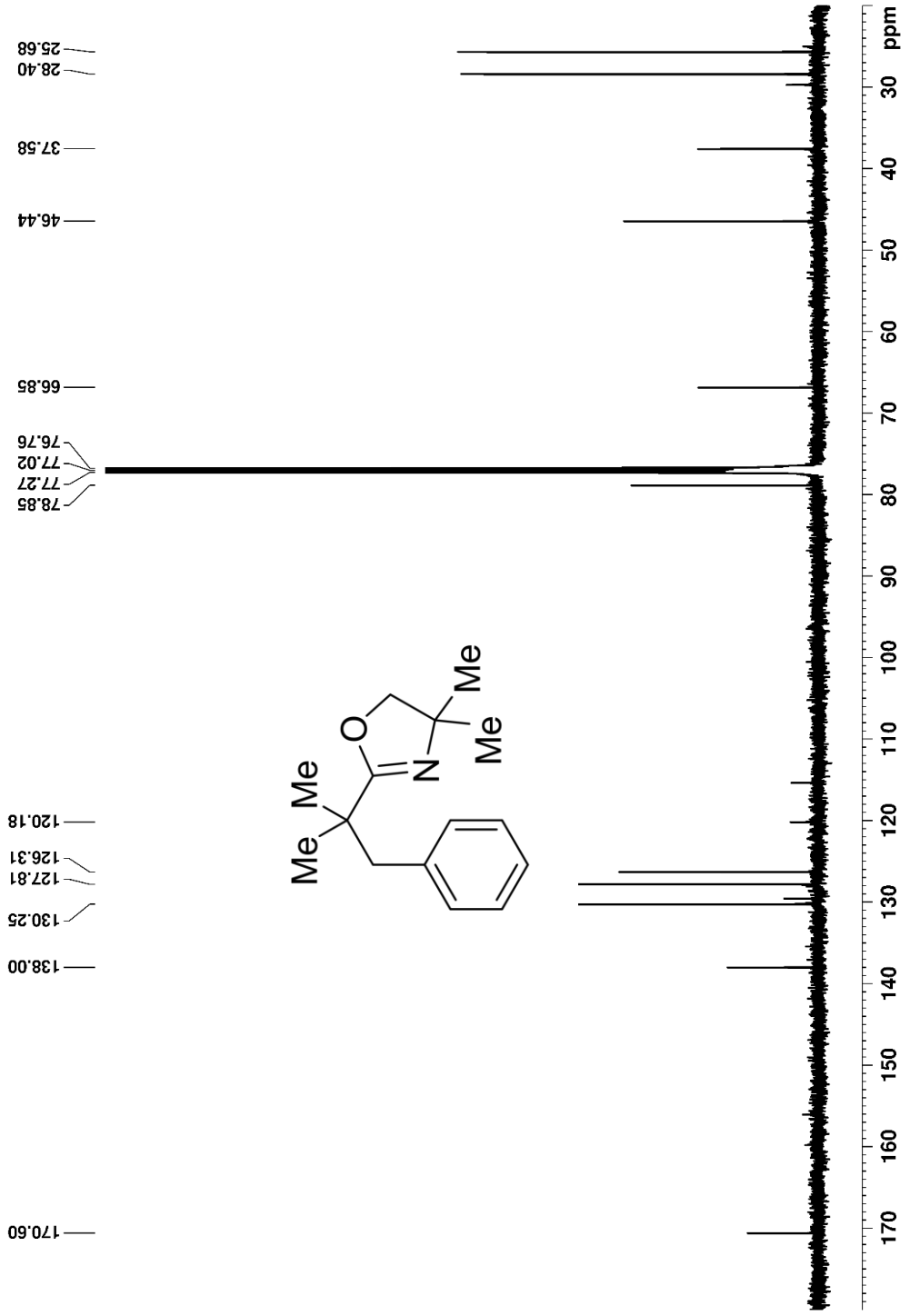


Figure II.5. $^{13}C\{^{1}H\}$ NMR spectrum of compound **II.7a**.

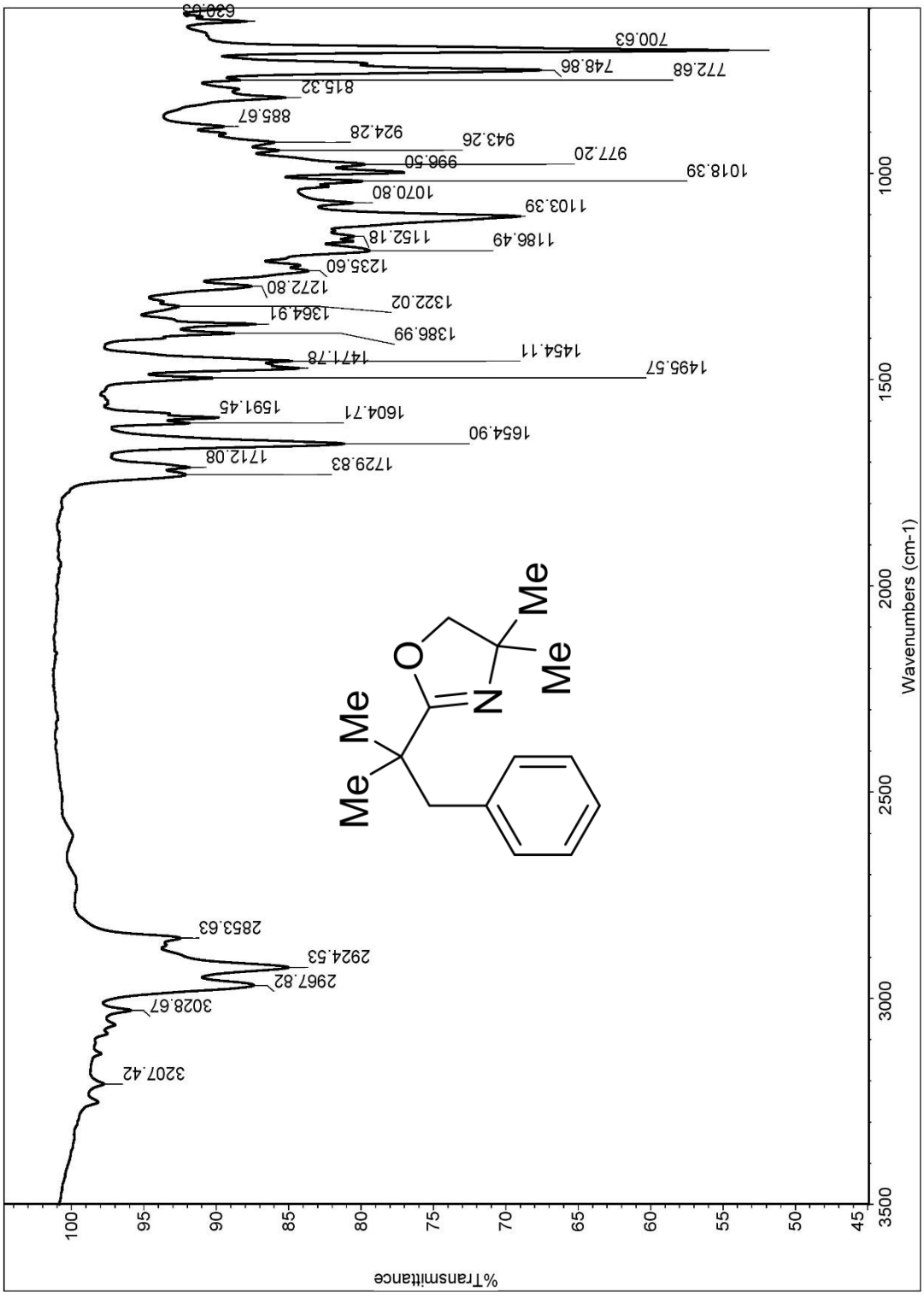


Figure II.6. IR spectrum of compound **II.7a**.

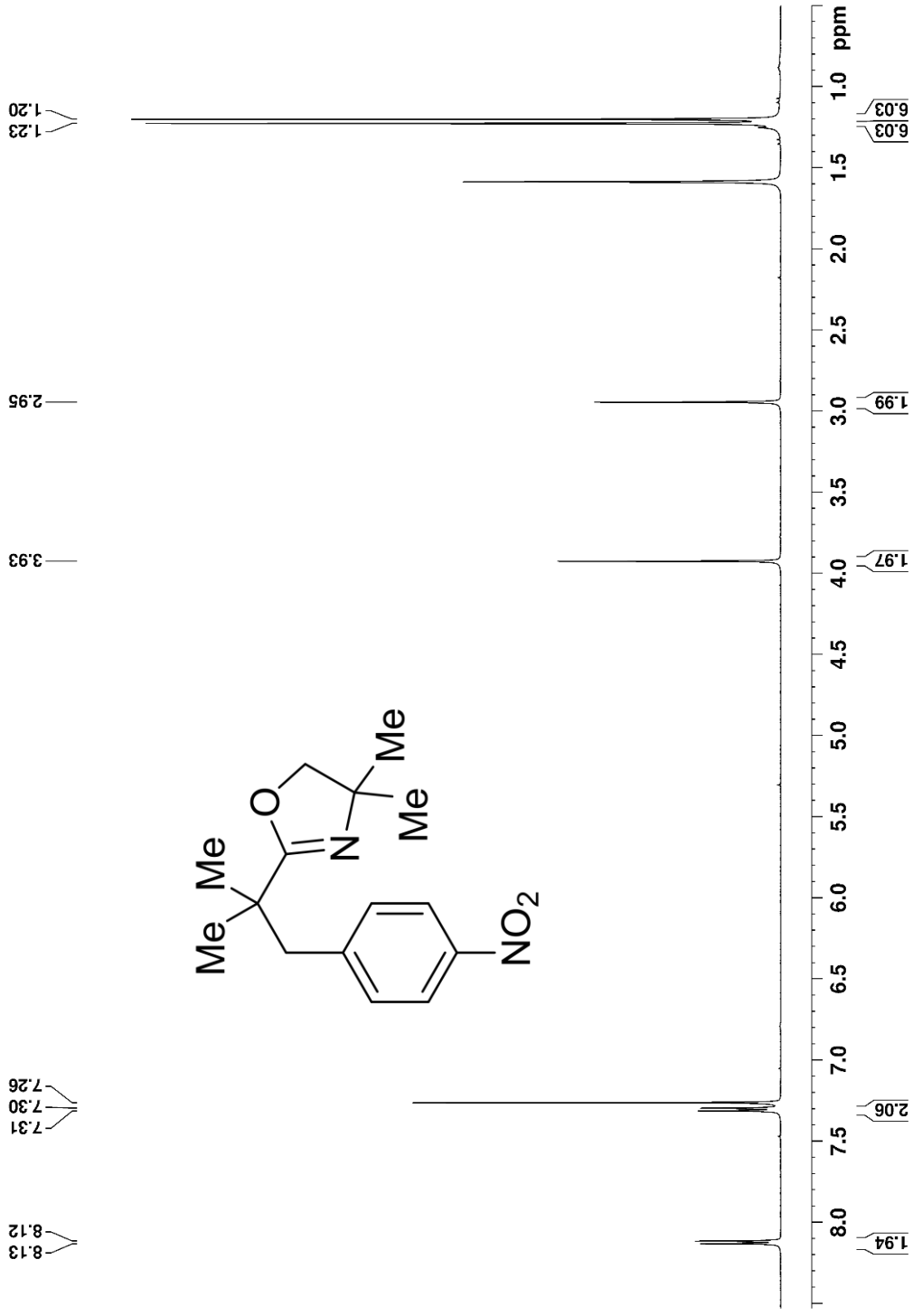


Figure II.7. ^{1}H NMR spectrum of compound **II.7b**.

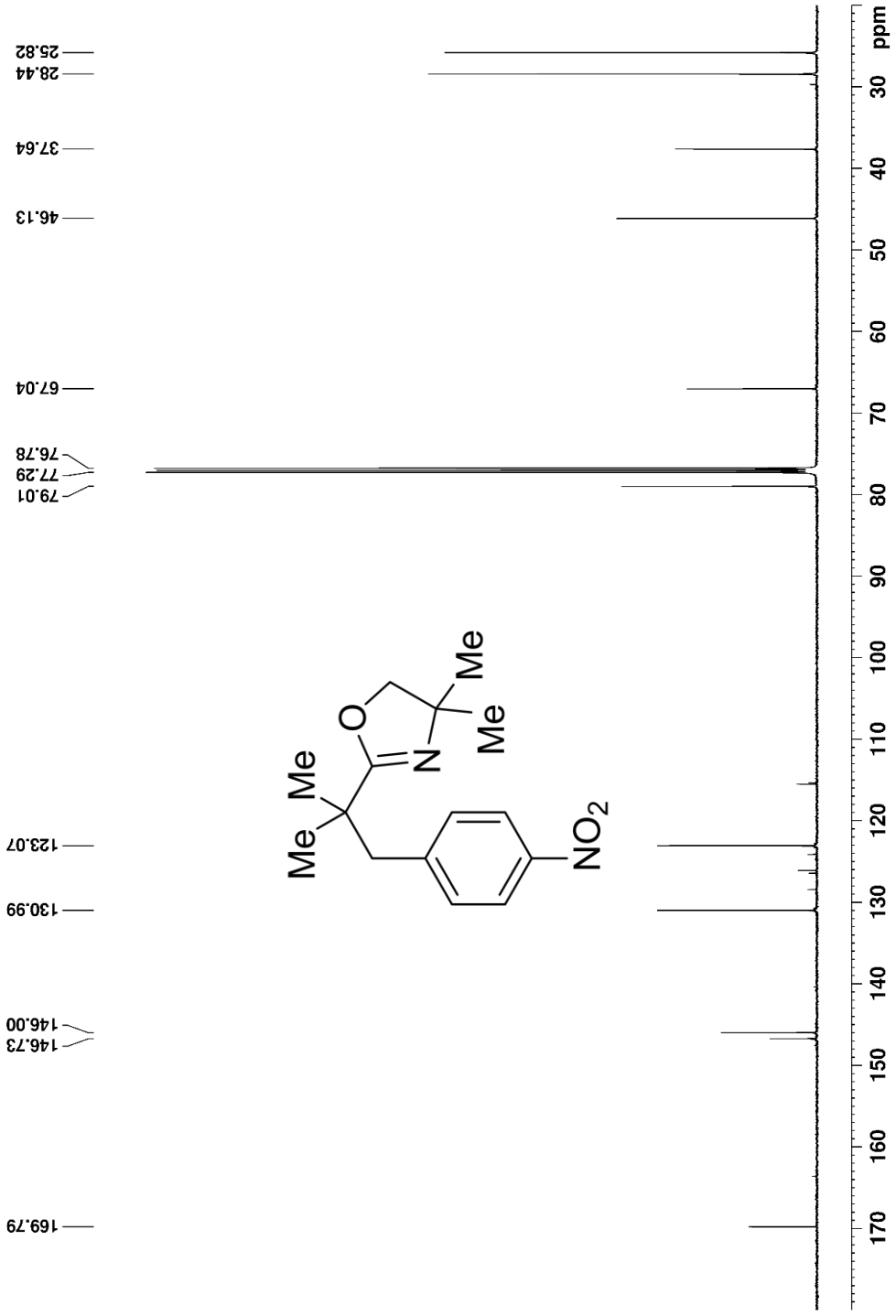


Figure II.8. $^{13}C\{^{1}H\}$ NMR spectrum of compound **II.7b**.

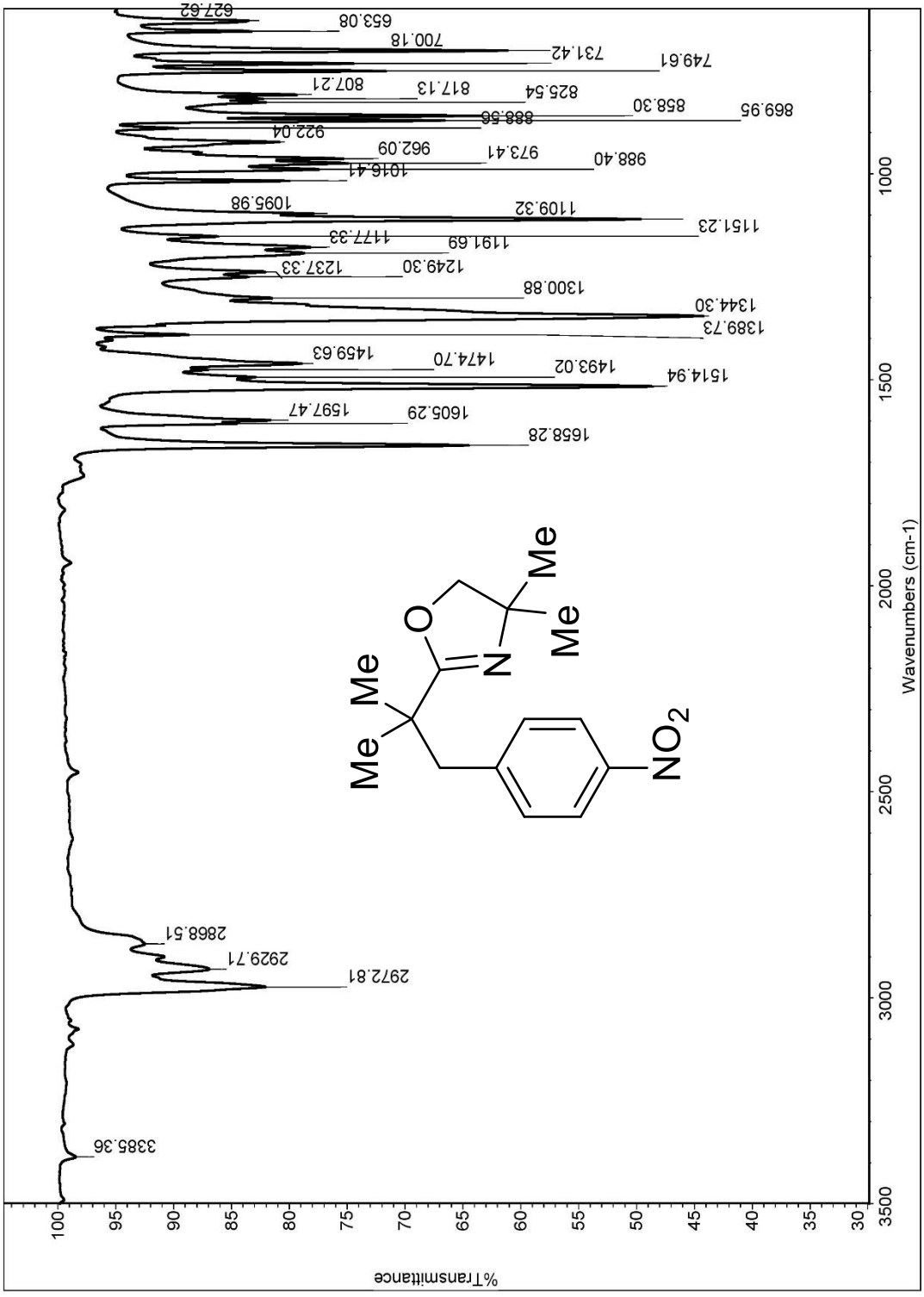


Figure II.9. IR spectrum of compound **II.7b**.

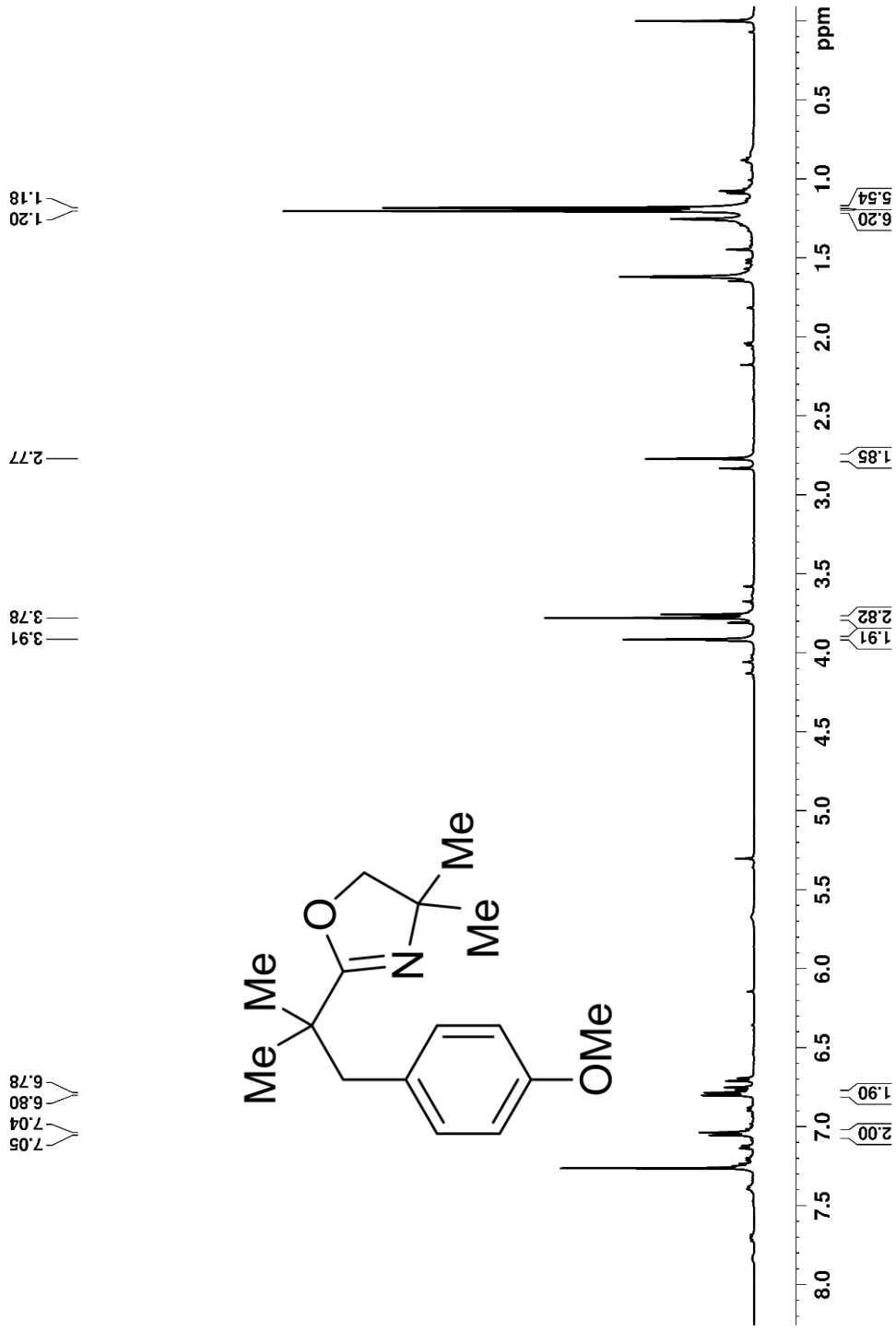


Figure II.10. ^{1}H NMR spectrum of compound **II.7c**.

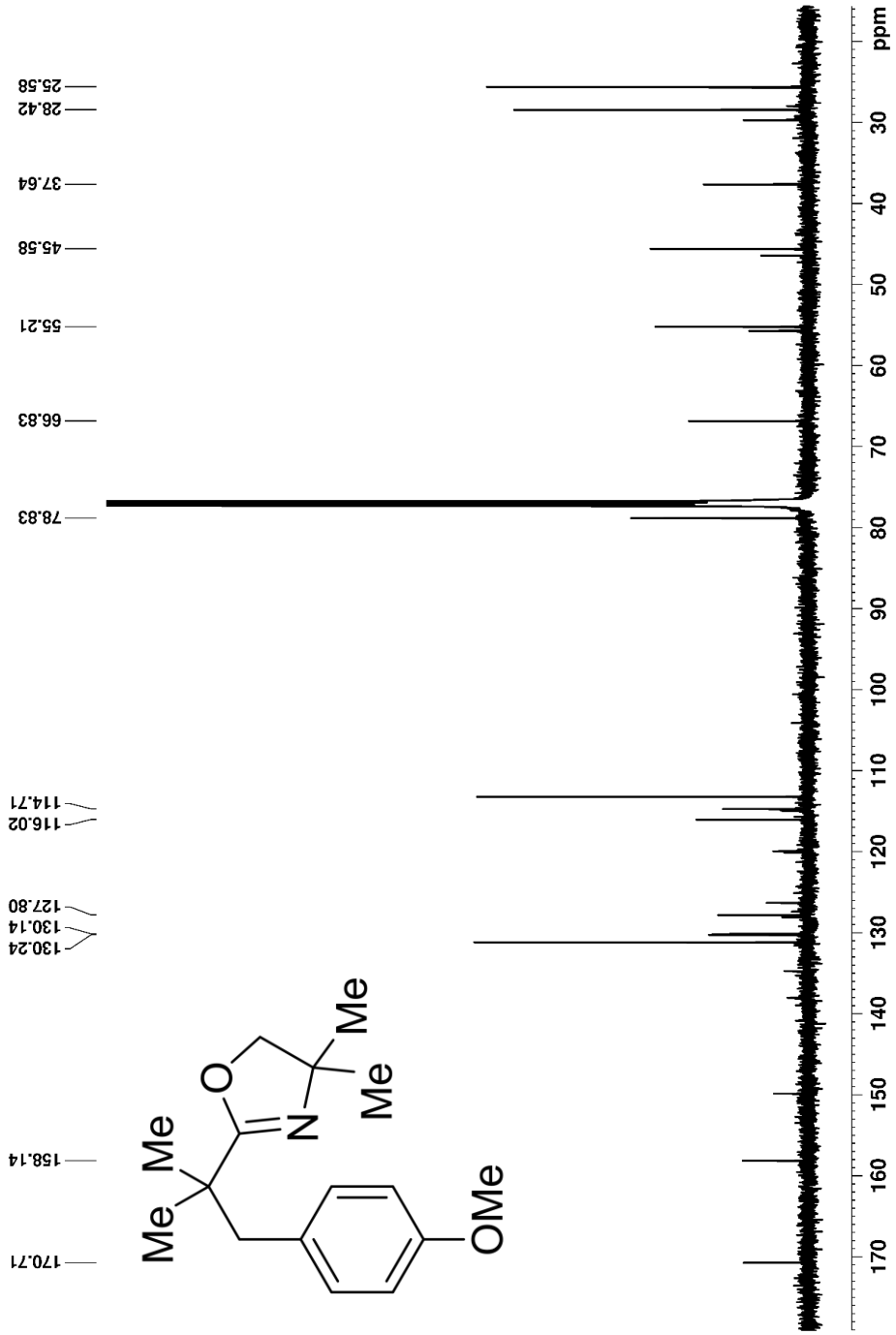


Figure II. 11. $^{13}C\{^{1}H\}$ NMR spectrum of compound **II.7c**.

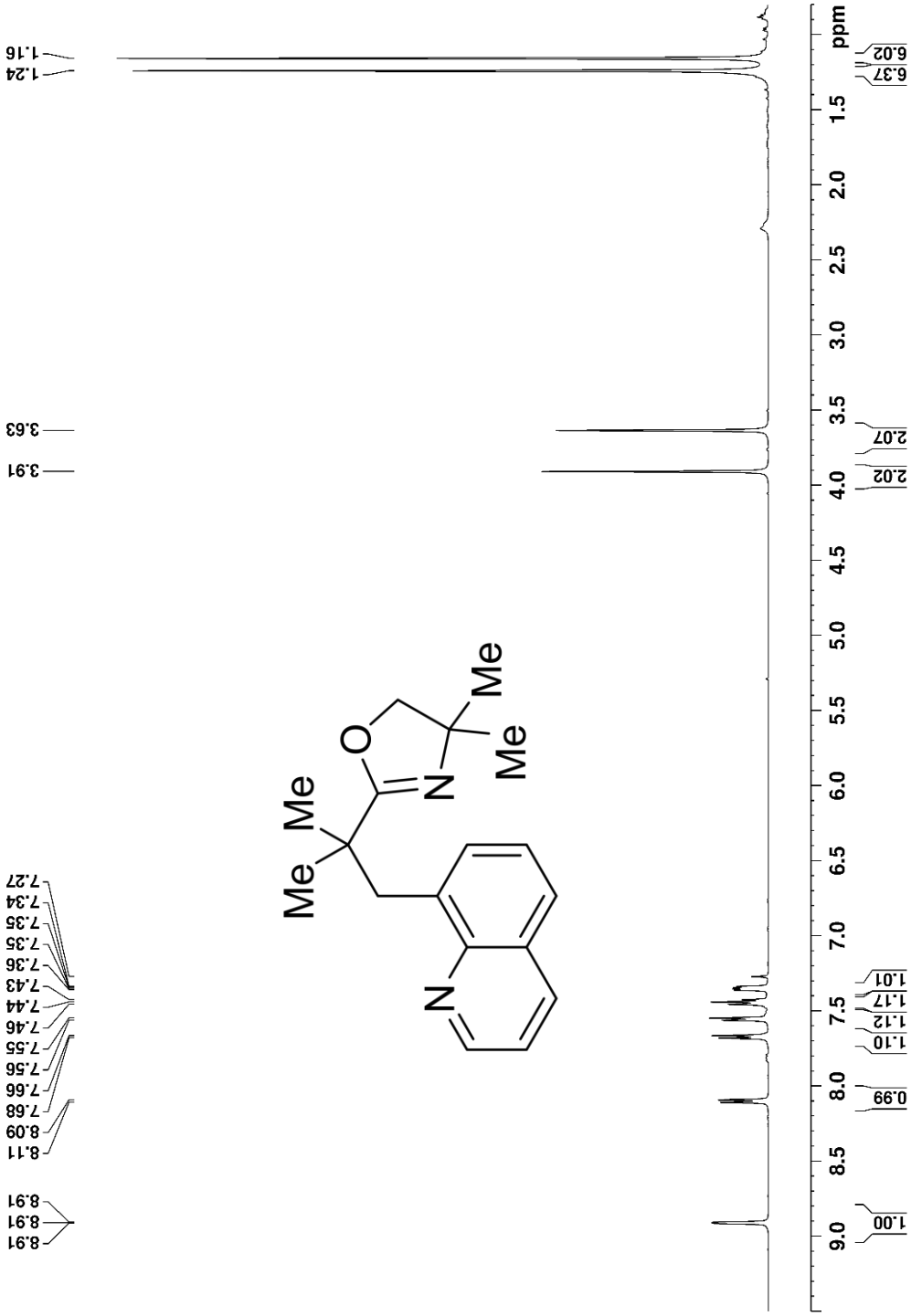


Figure II.12. ^{1}H NMR spectrum of compound **II.7d**.

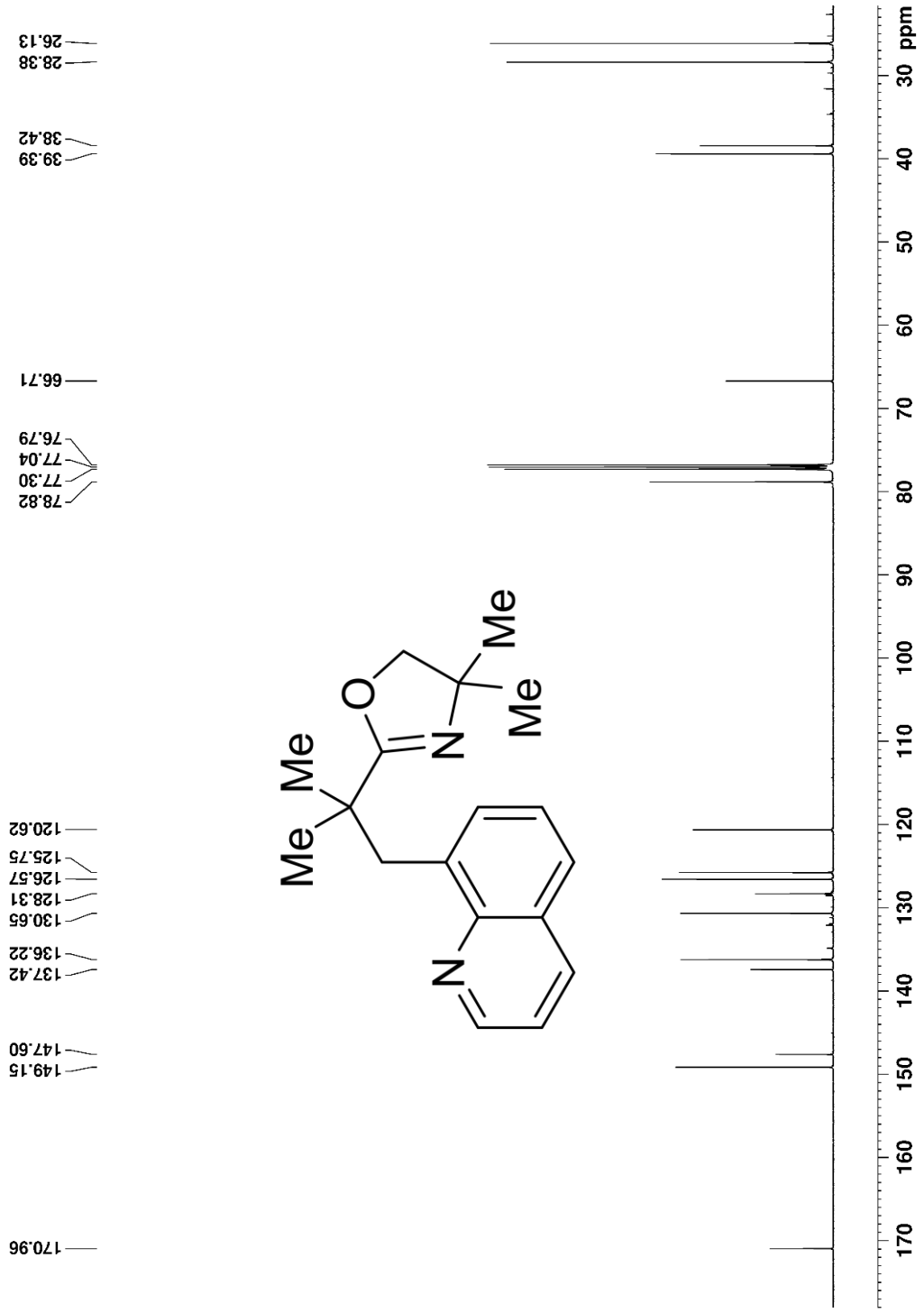


Figure II.13. $^{13}C\{^{1}H\}$ NMR spectrum of compound **II.7d**.

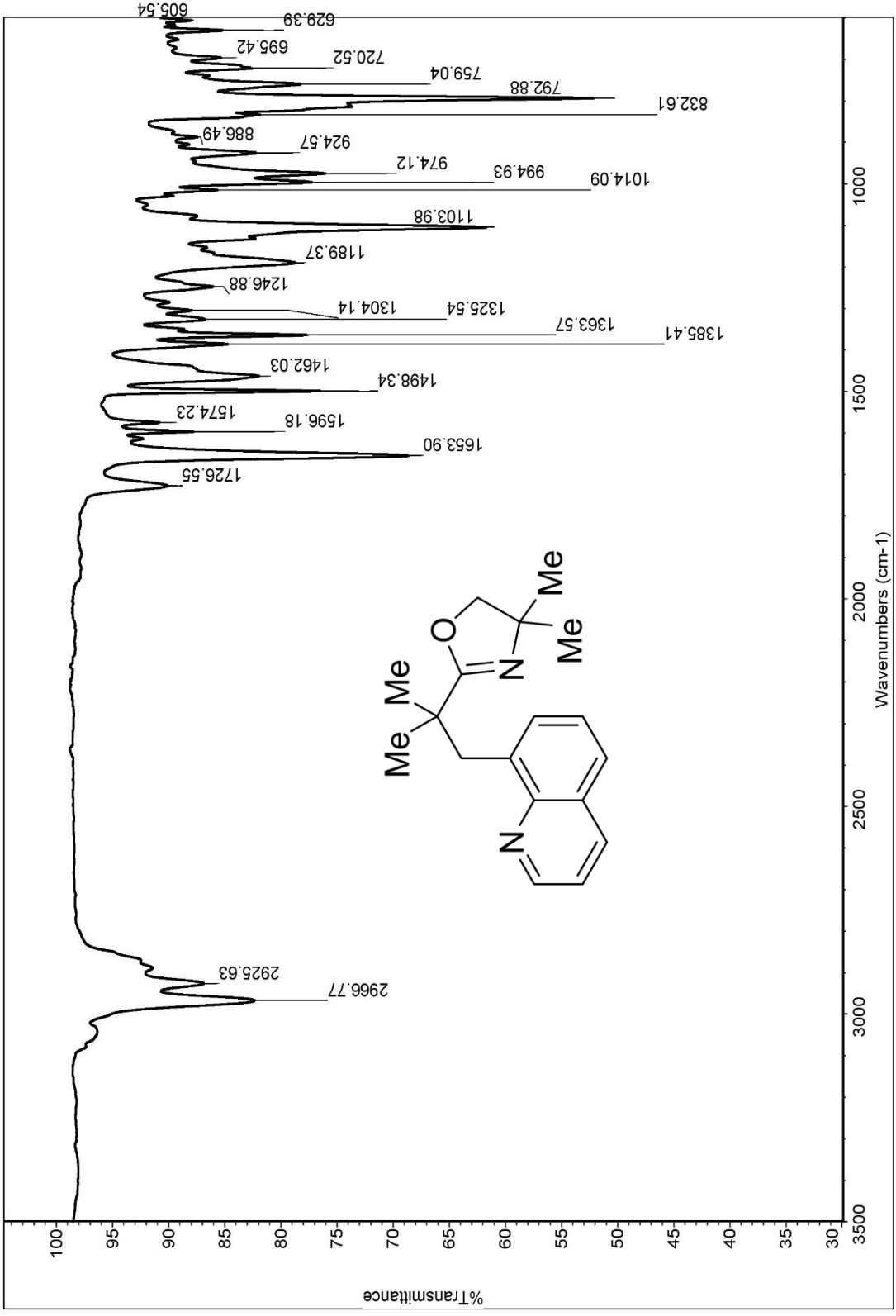


Figure II.14. IR spectrum of compound **II.7d**.

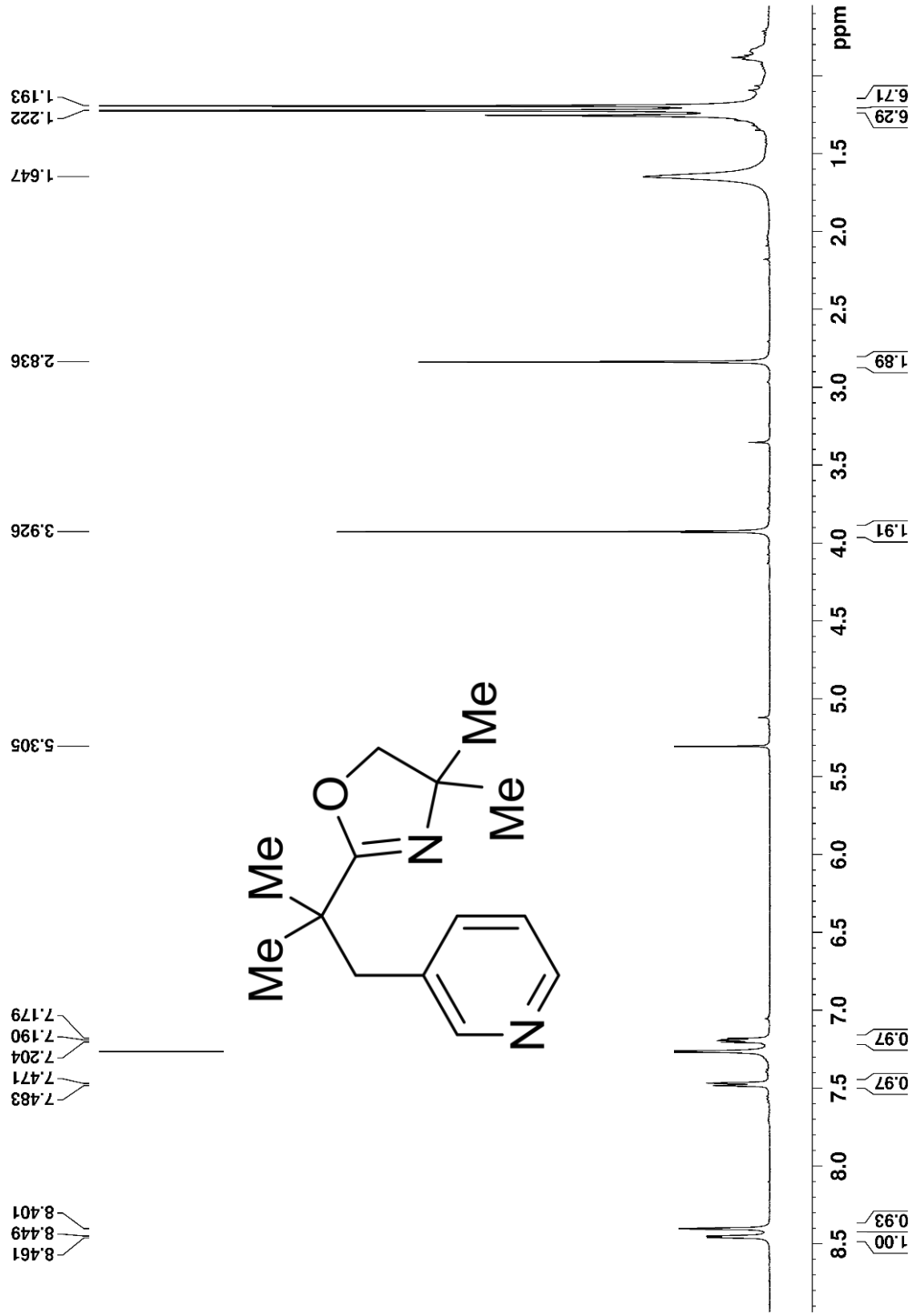


Figure II.15. ^{1}H NMR spectrum of compound **II.7e**.

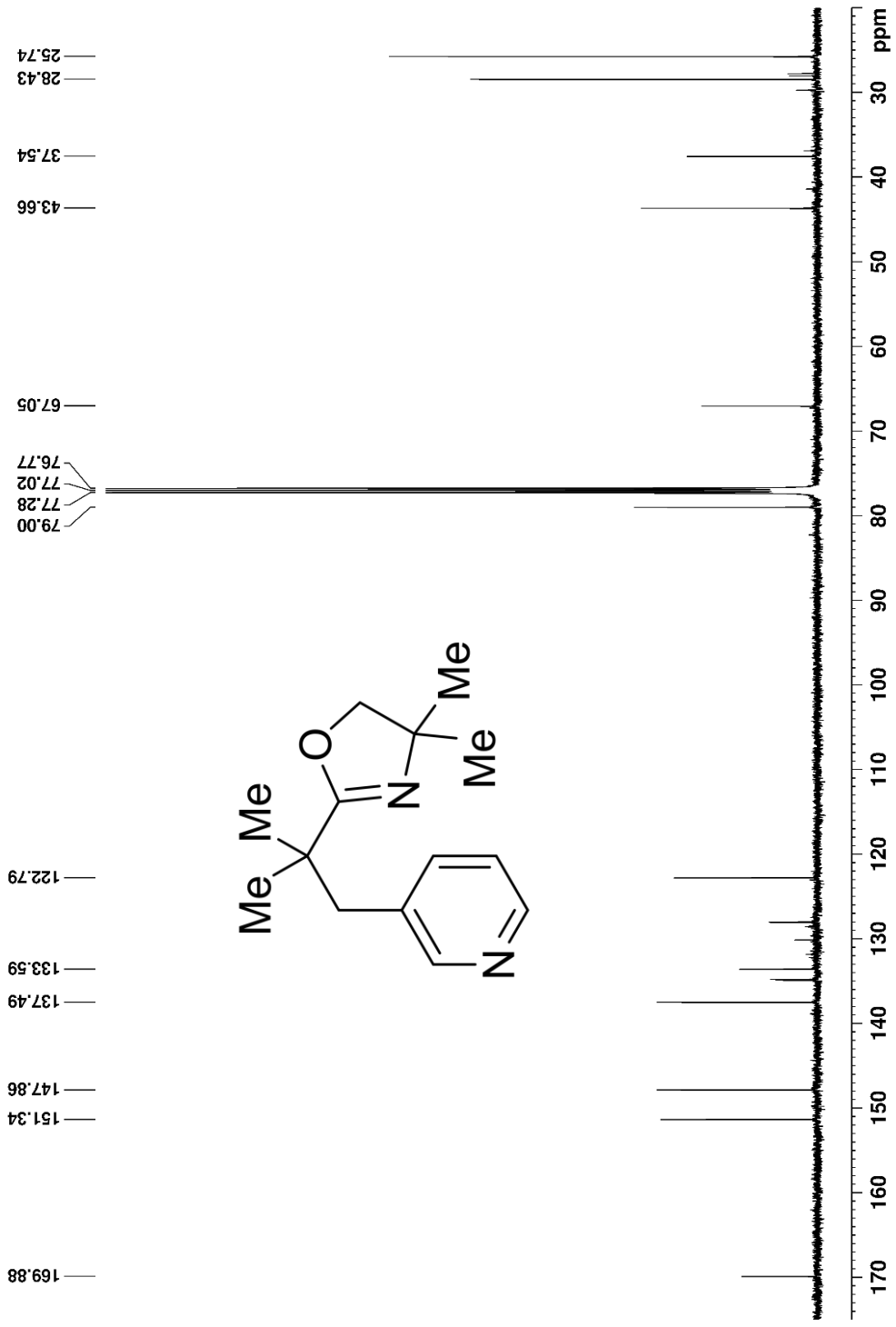


Figure II.16. $^{13}C\{^{1}H\}$ NMR spectrum of compound **II.7e**.

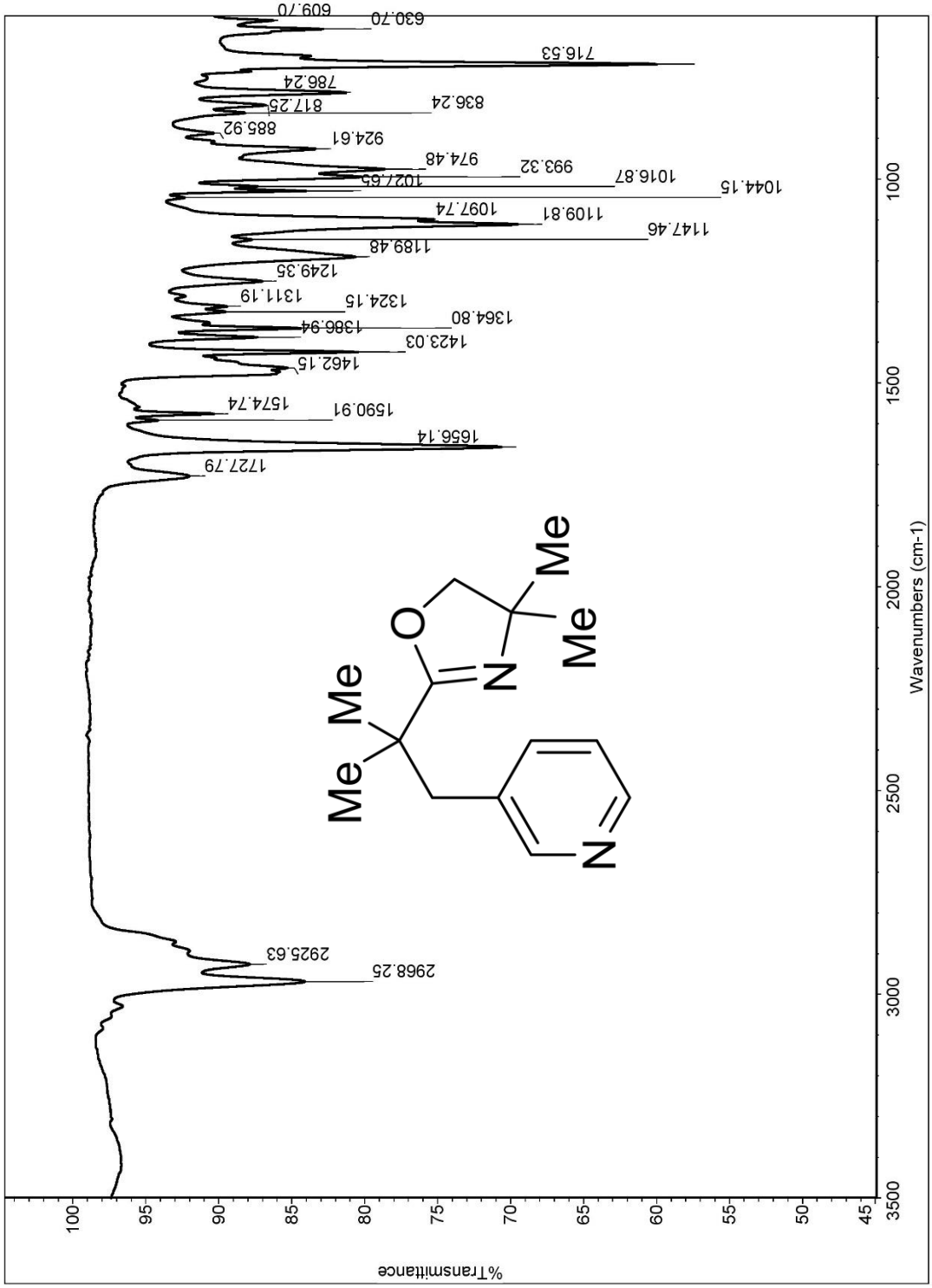


Figure II.17. IR spectrum of compound **II.7e**.

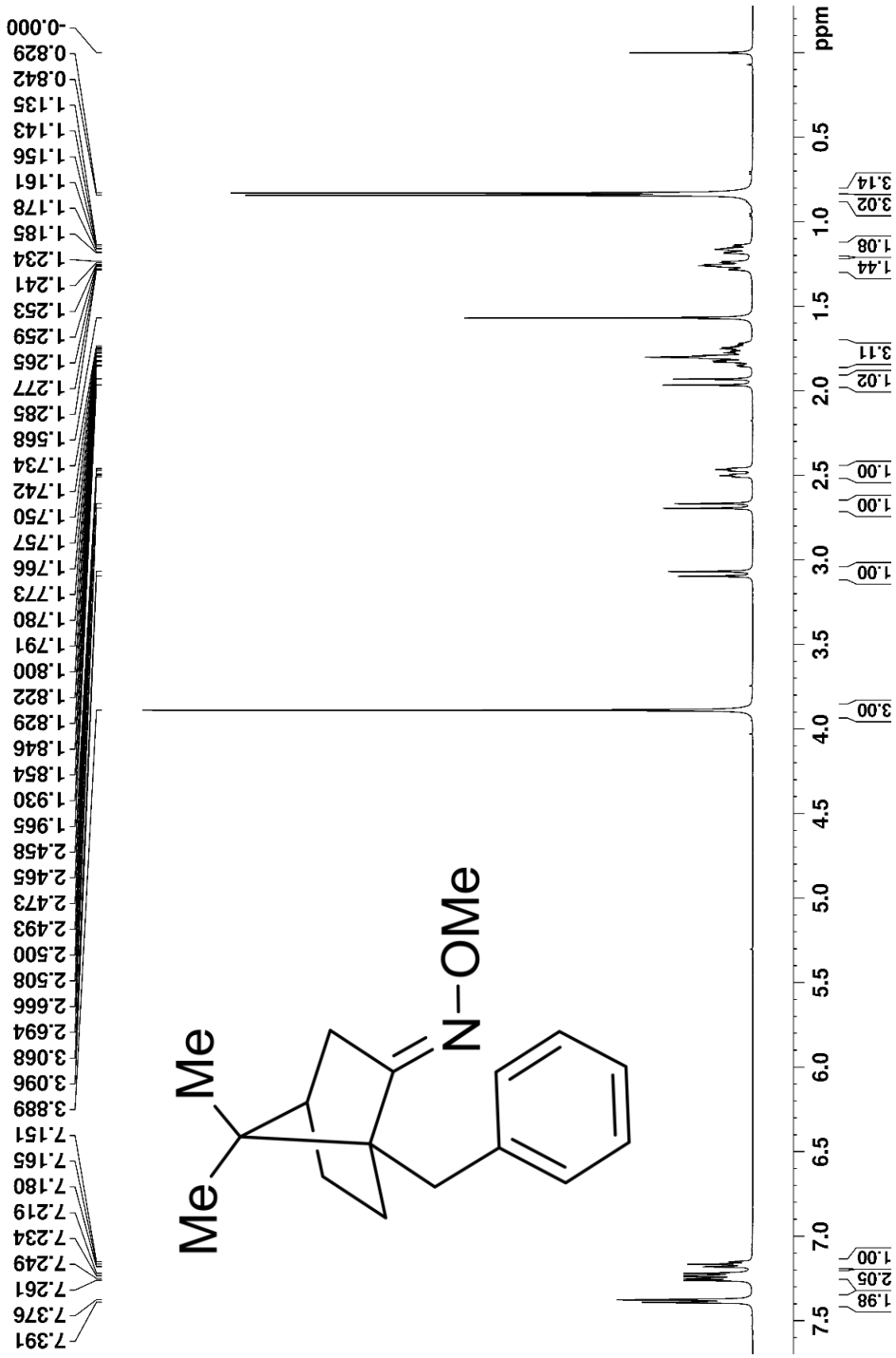


Figure II.18. ^{1}H NMR spectrum of compound **II.9a**.

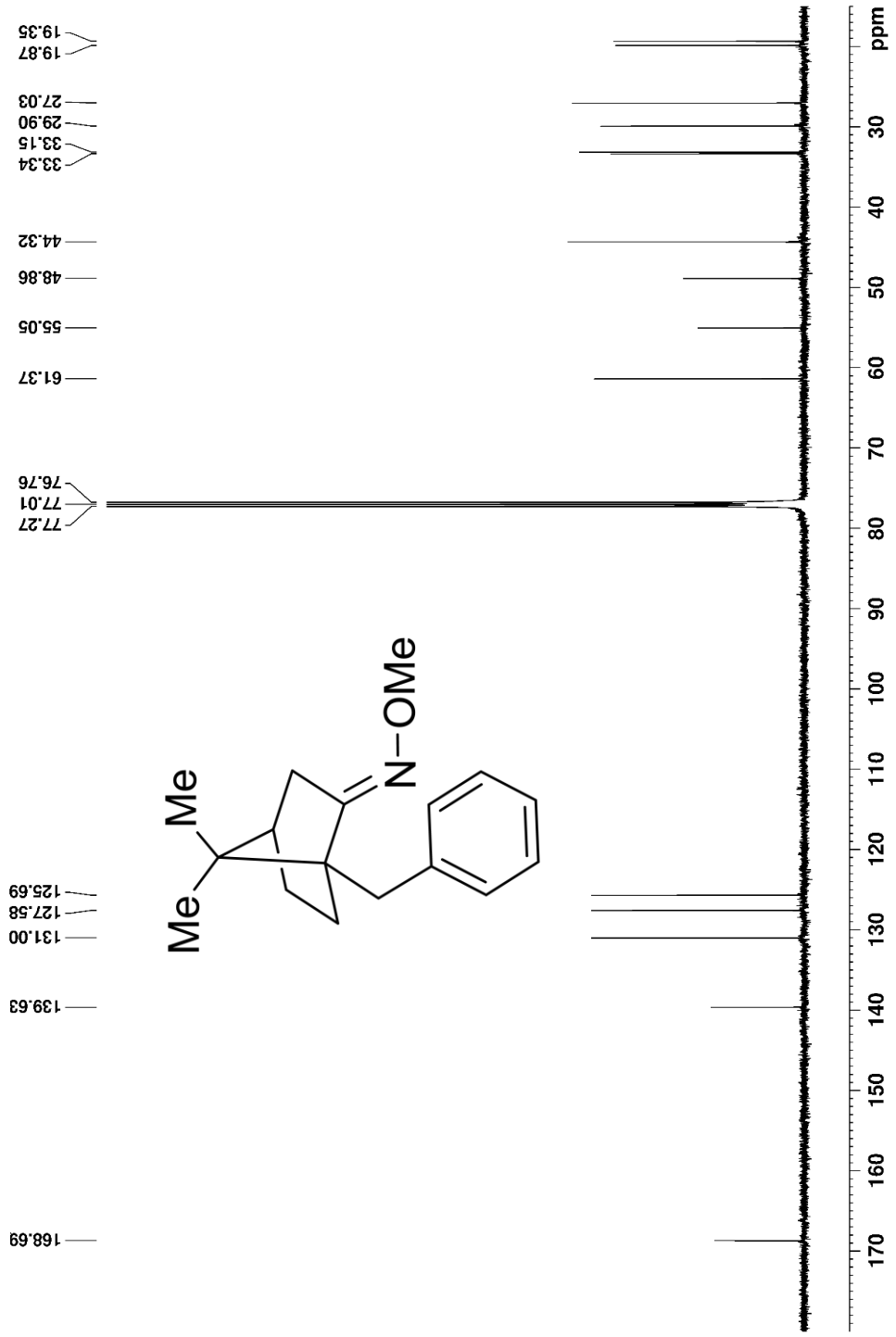


Figure II.19. $^{13}C\{^{1}H\}$ NMR spectrum of compound **II.9a**.

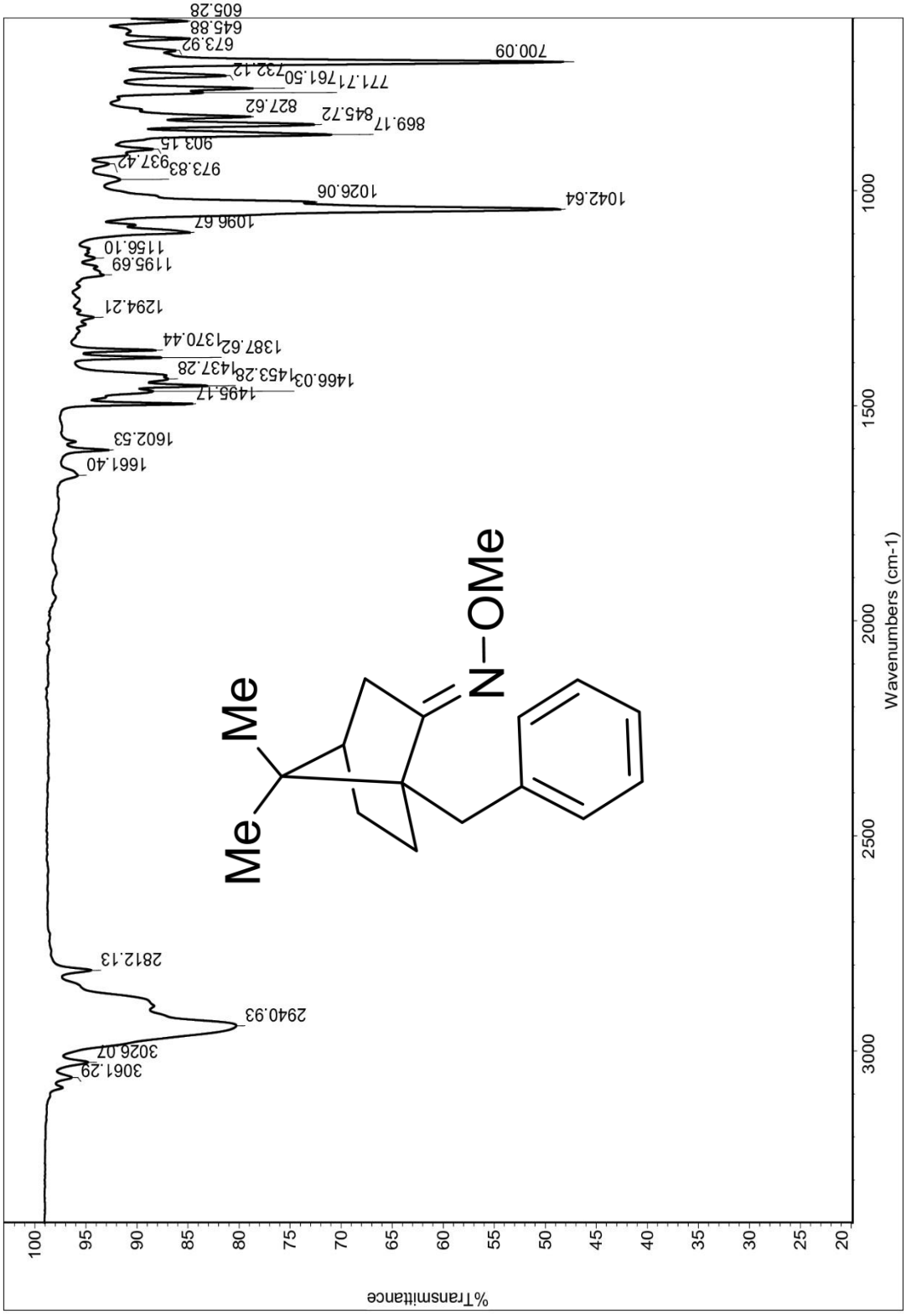


Figure II.20. IR spectrum of compound **II.9a**.

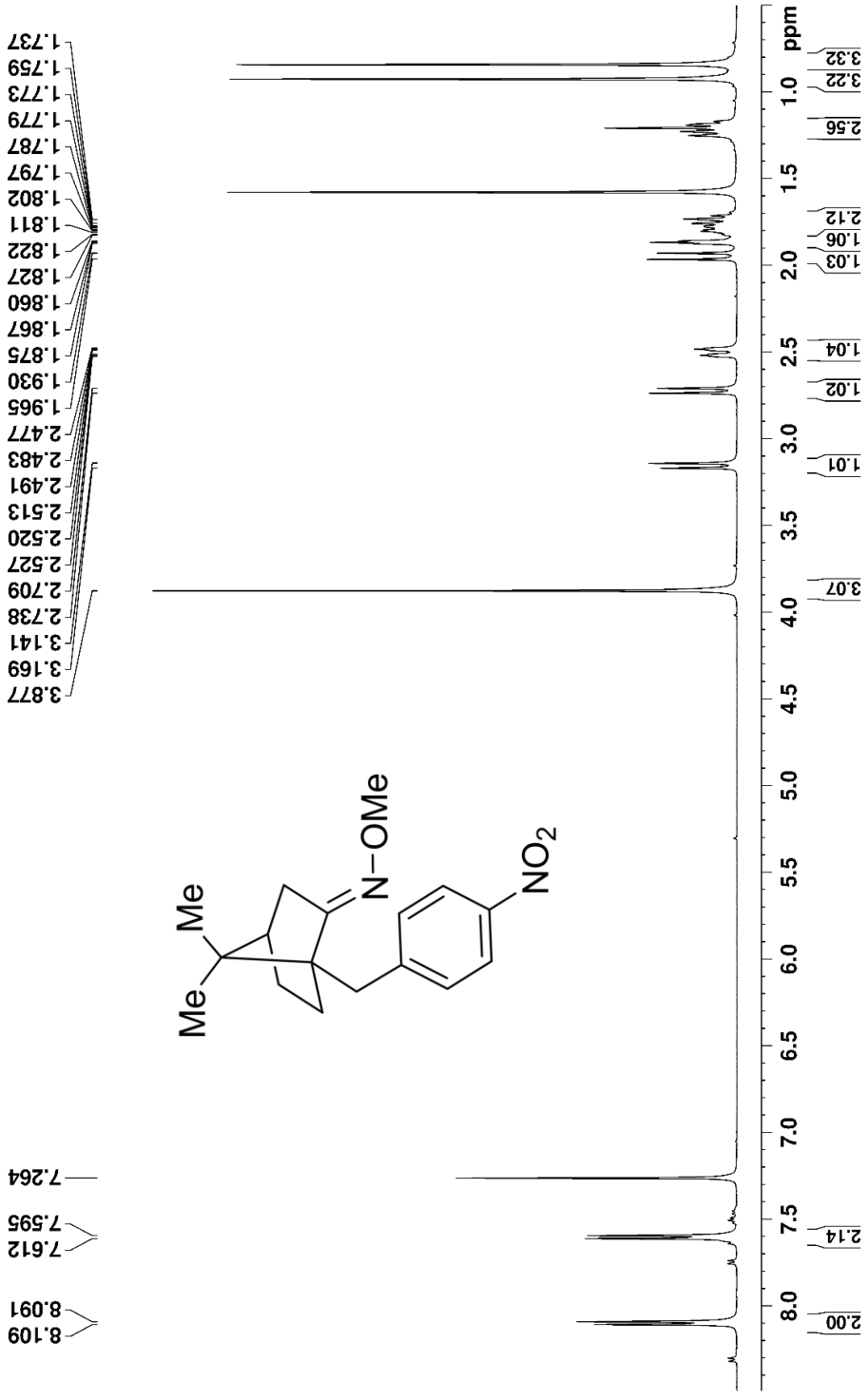


Figure II.21. ^{1}H NMR spectrum of compound **II.9b**.

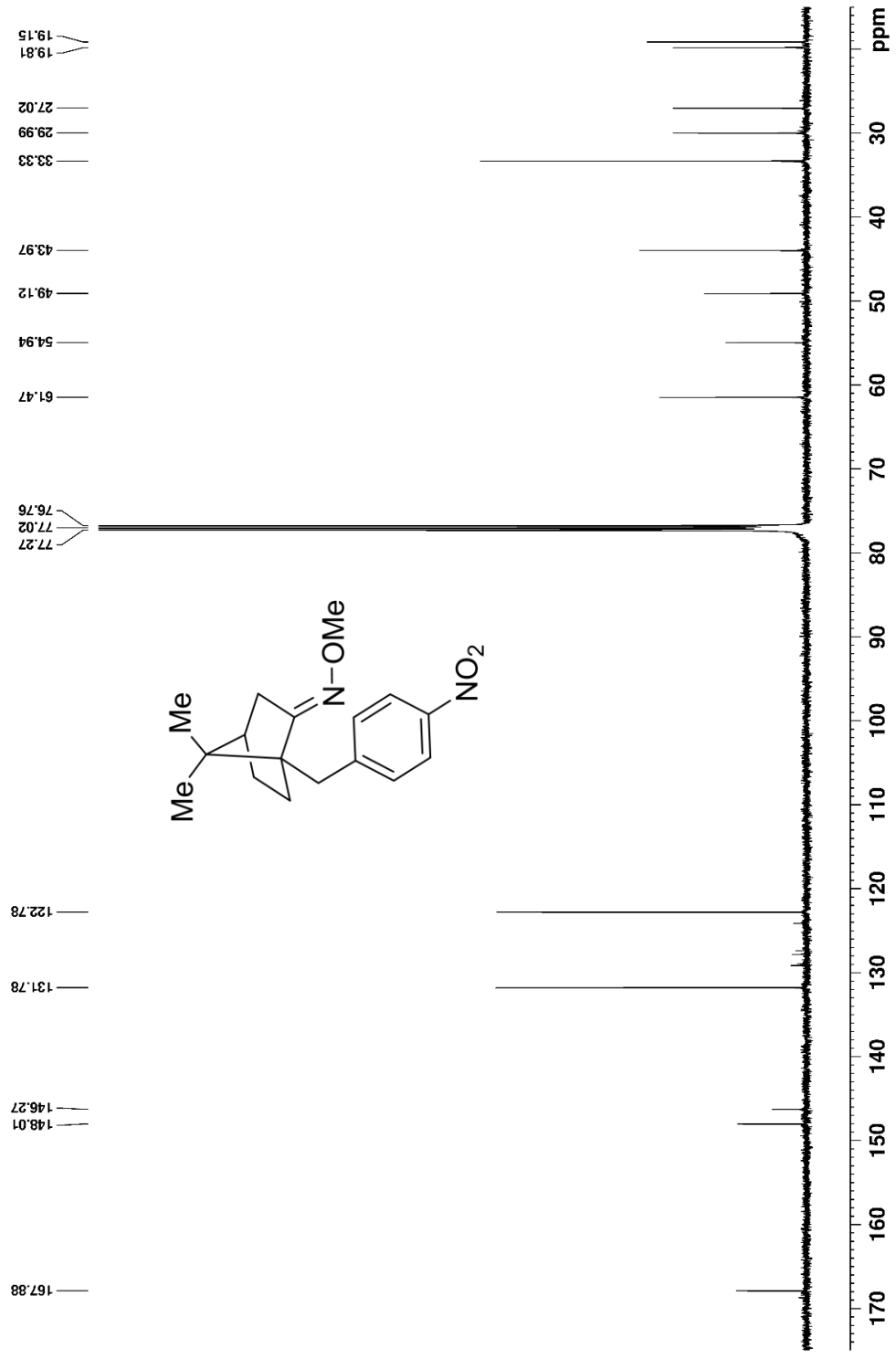


Figure II.22. $^{13}C\{^{1}H\}$ NMR spectrum of compound **II.9b**.

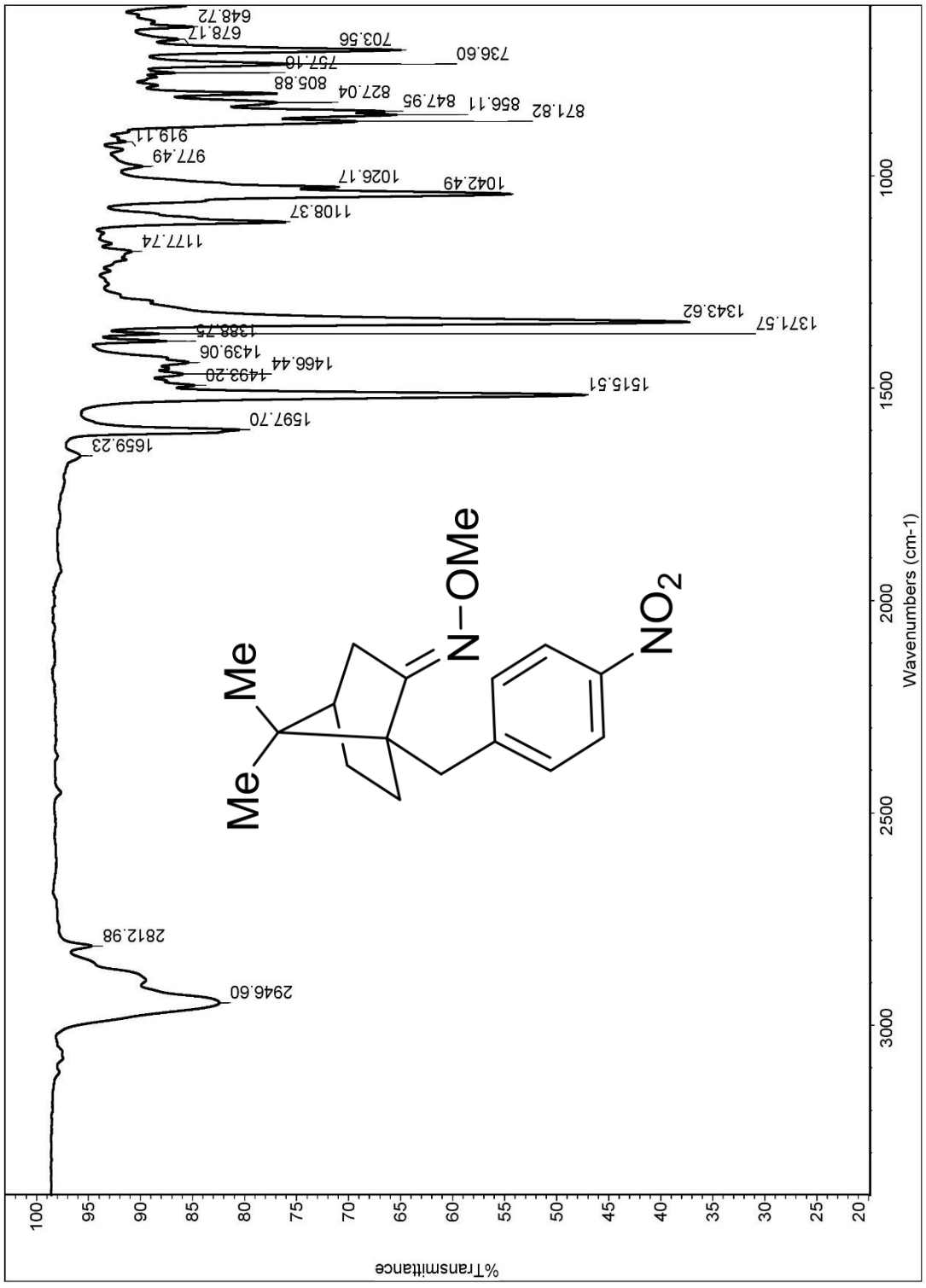


Figure II.23. IR spectra of compound **II.9d**.

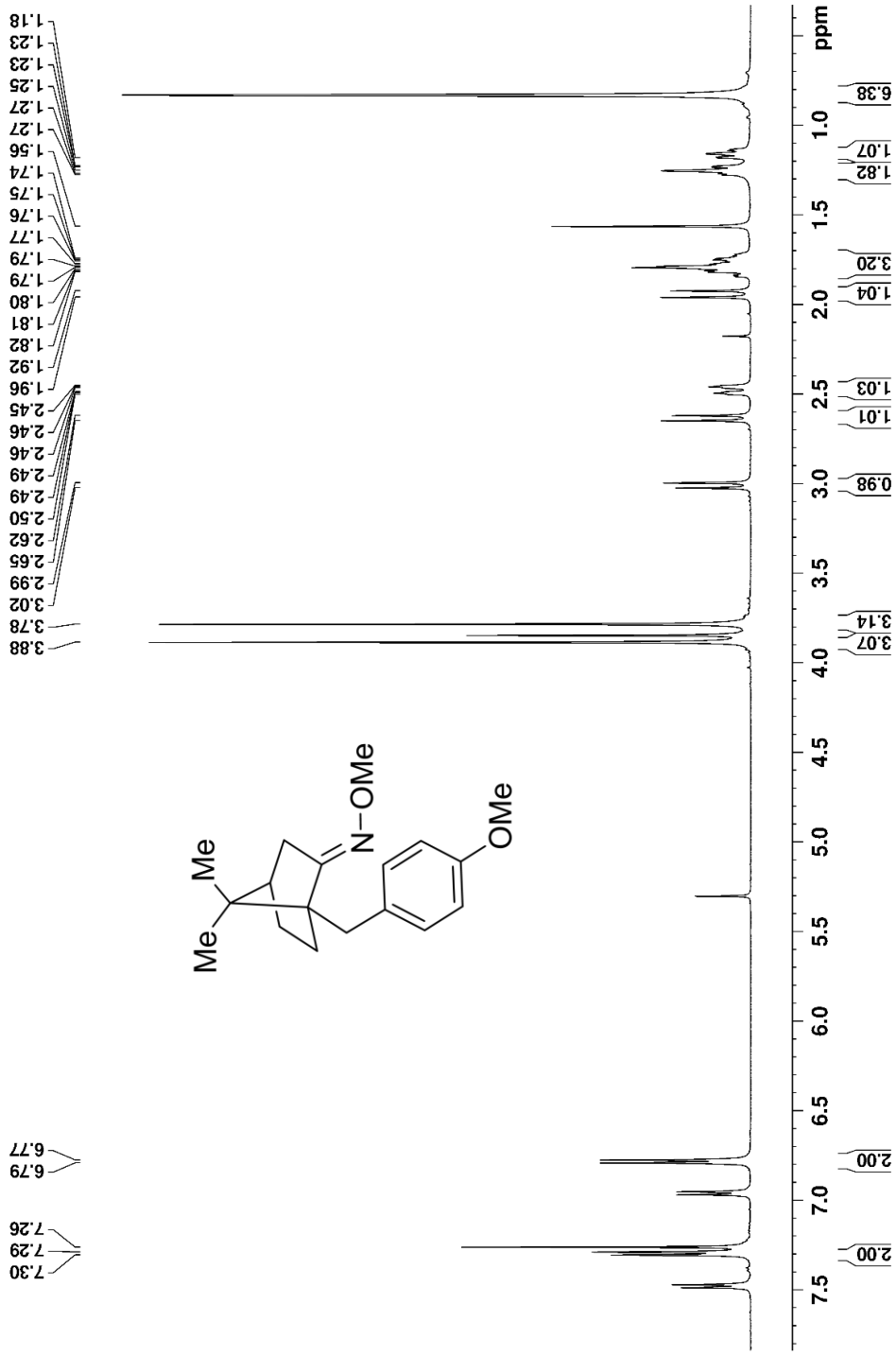


Figure II.24. ^{1}H NMR spectrum of compound **II.9c**.

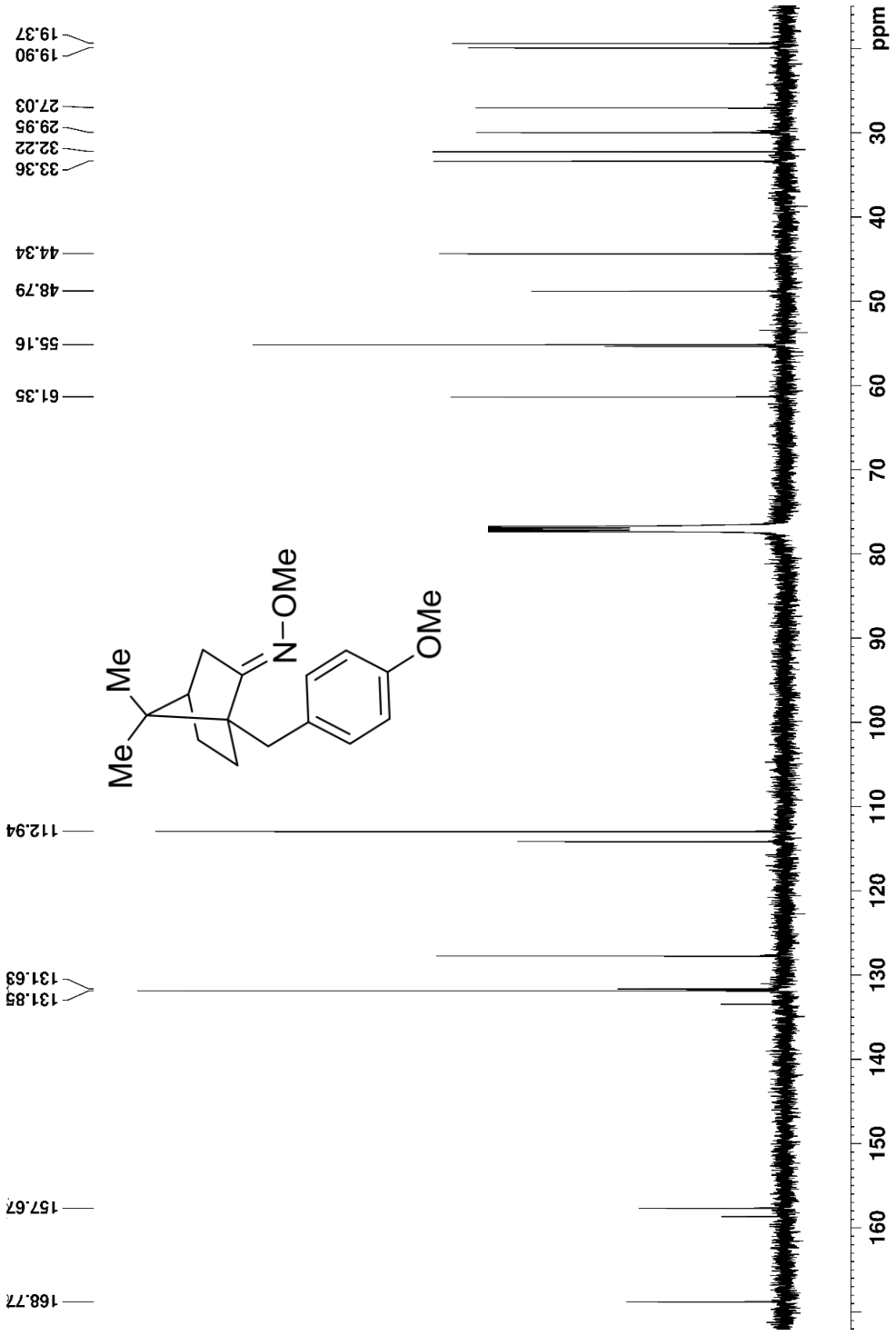


Figure II.25. $^{13}C\{^{1}H\}$ NMR spectrum of compound **II.9c**.

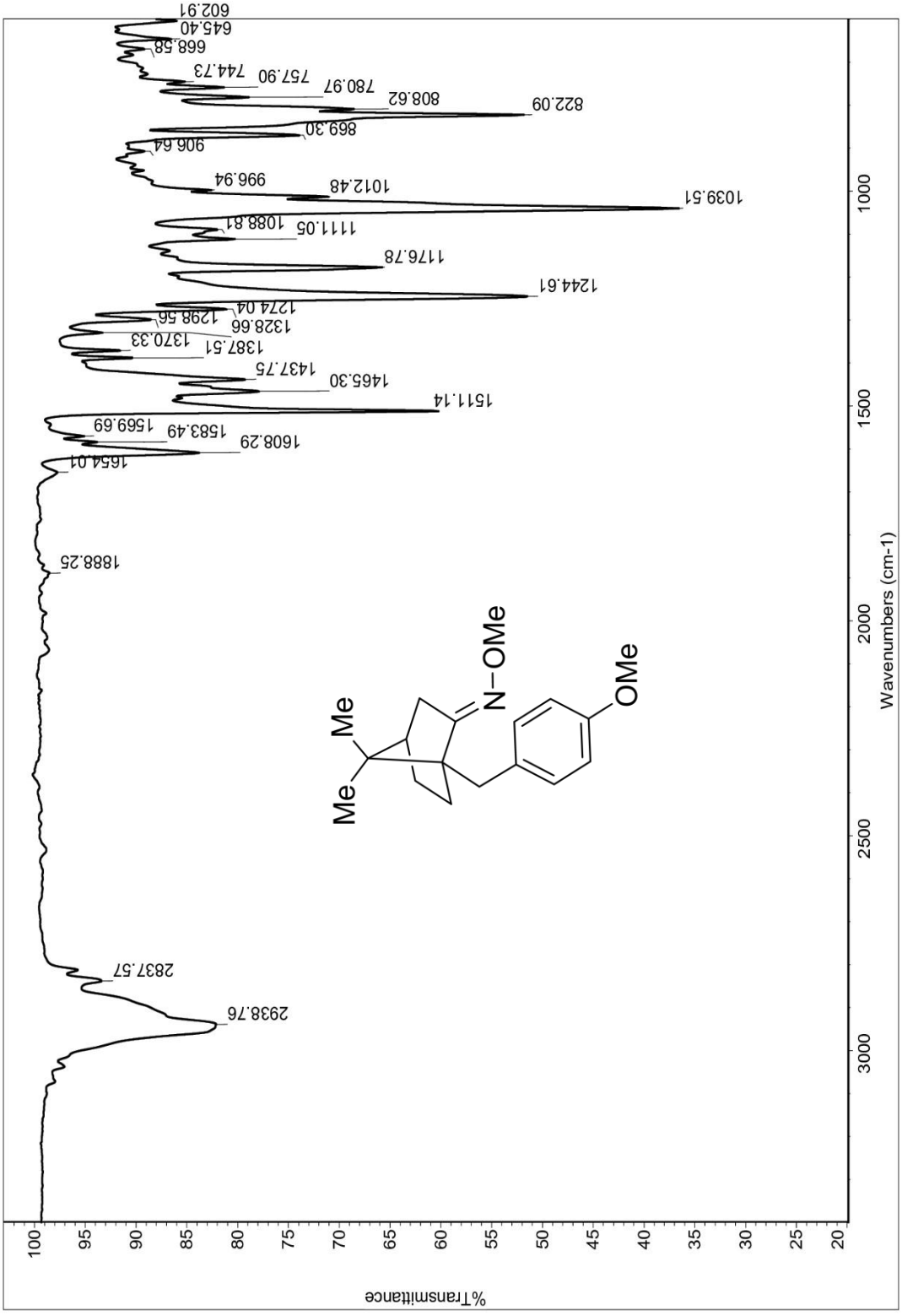


Figure II.26. IR spectrum of compound **II.9c**.

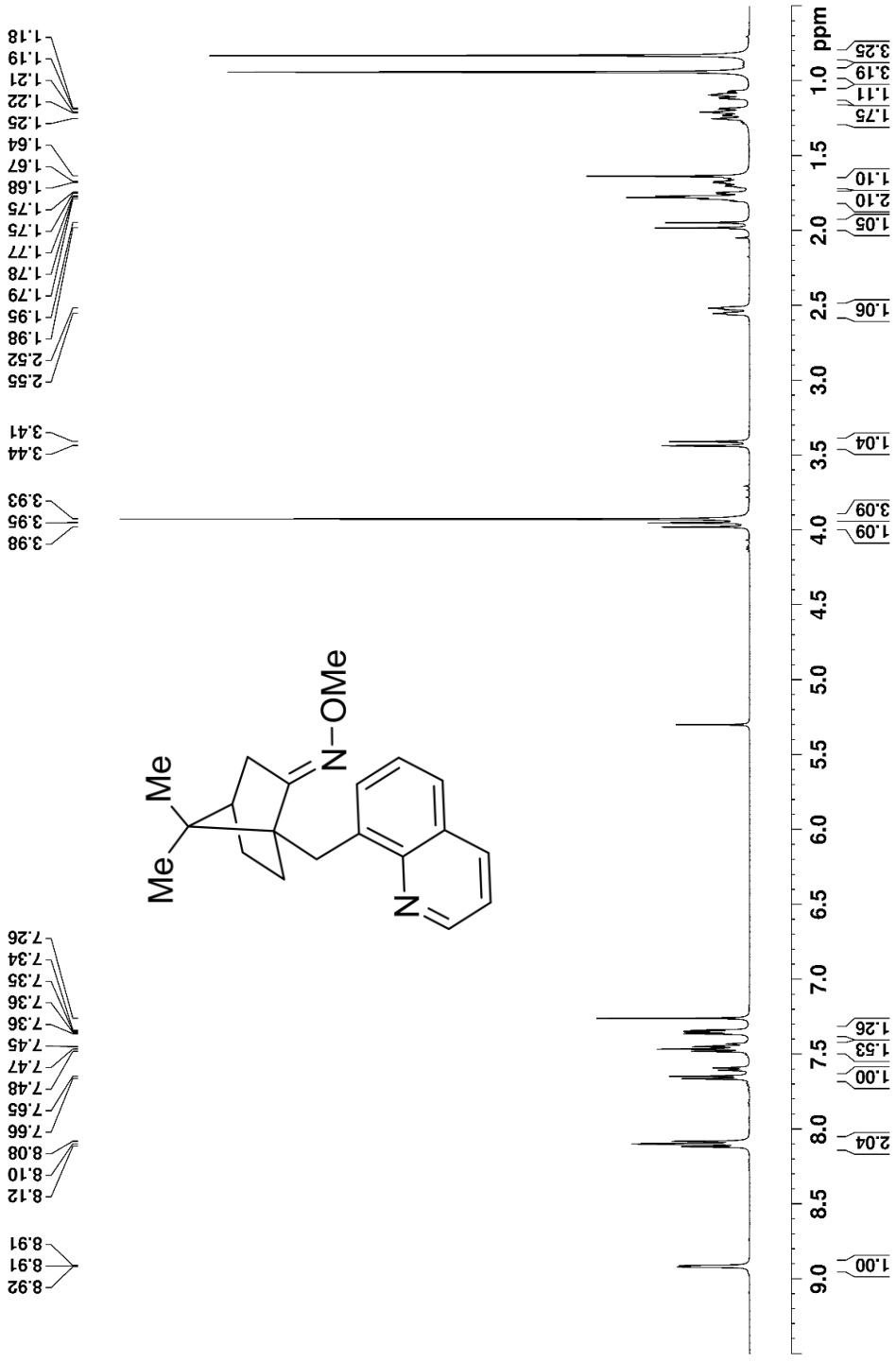


Figure II.27. ^{1}H NMR spectrum of compound **II.9d**.

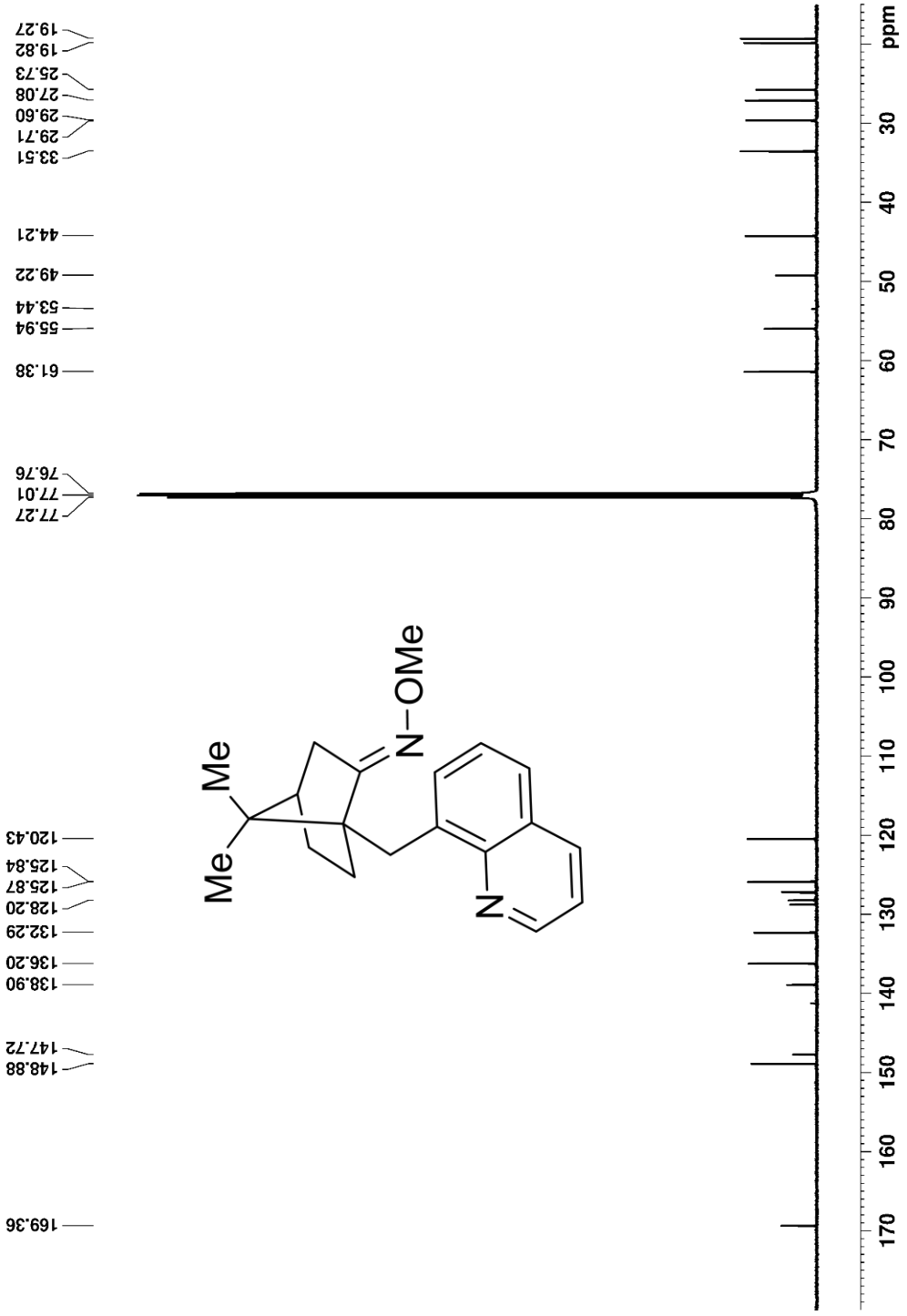


Figure II.28. $^{13}C\{^{1}H\}$ NMR spectrum of compound **II.9d**.

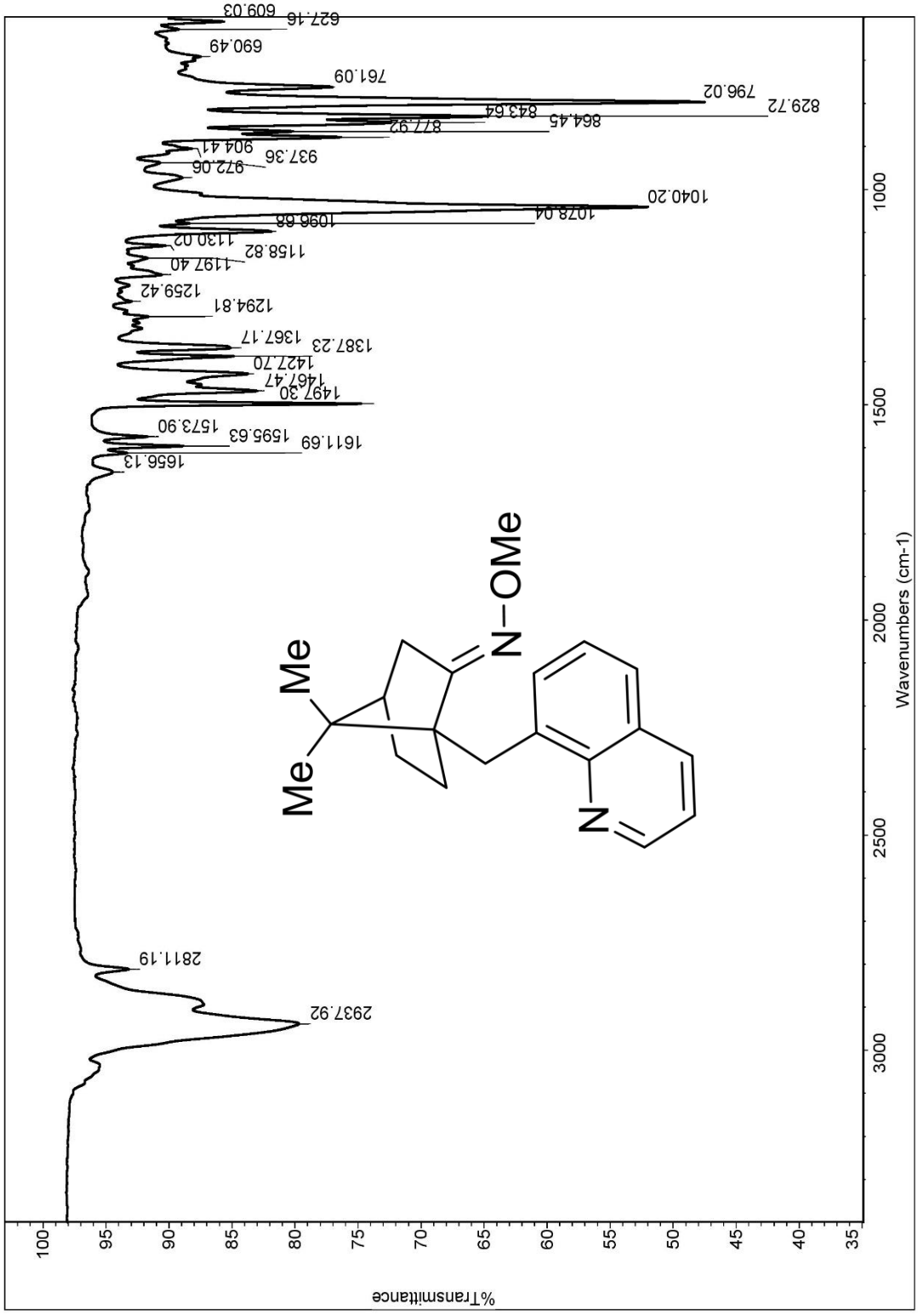


Figure II.29. IR spectra of compound **II.9d**.

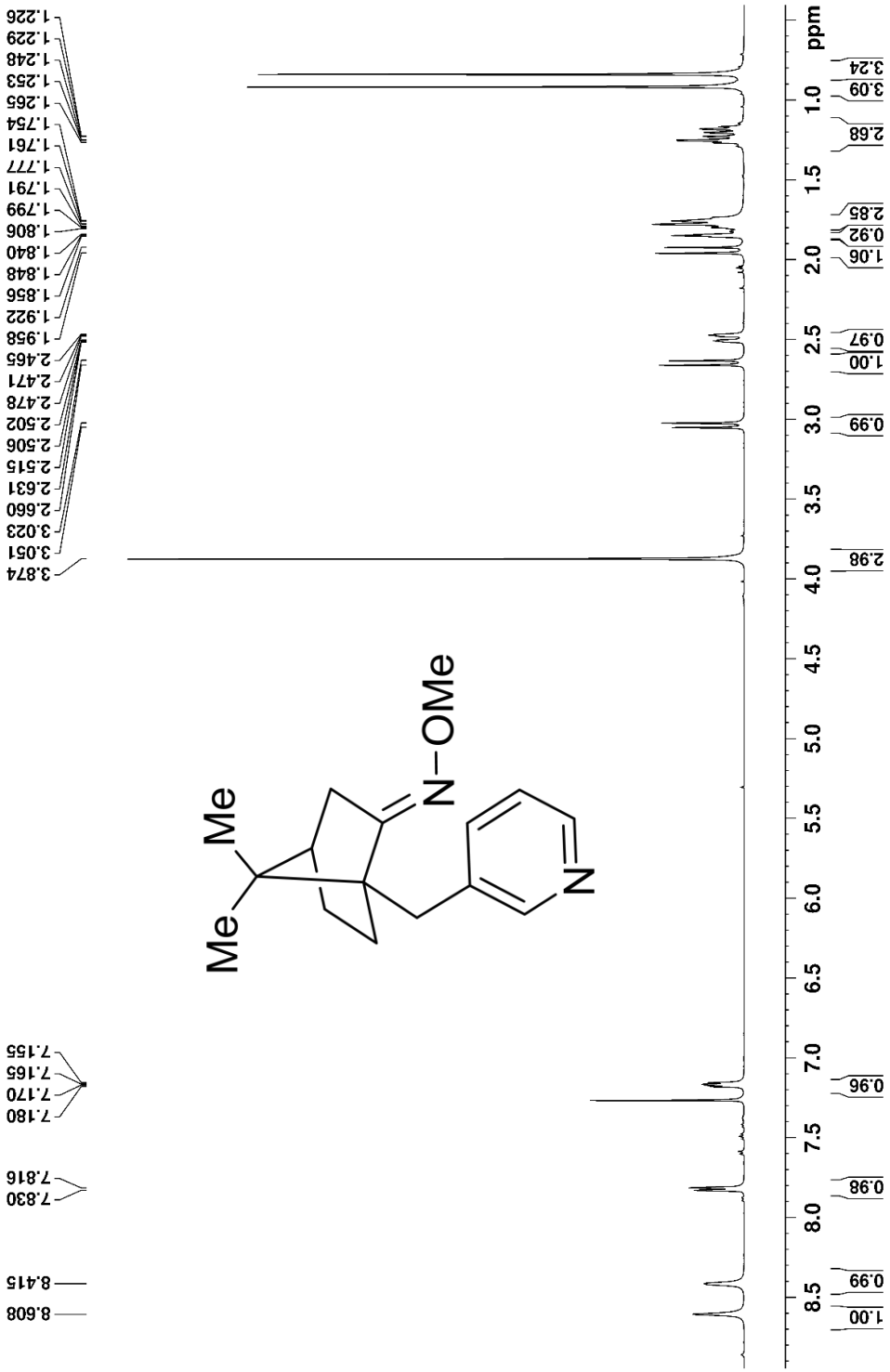


Figure II.30. ^{1}H NMR spectrum of compound **II.9e**.

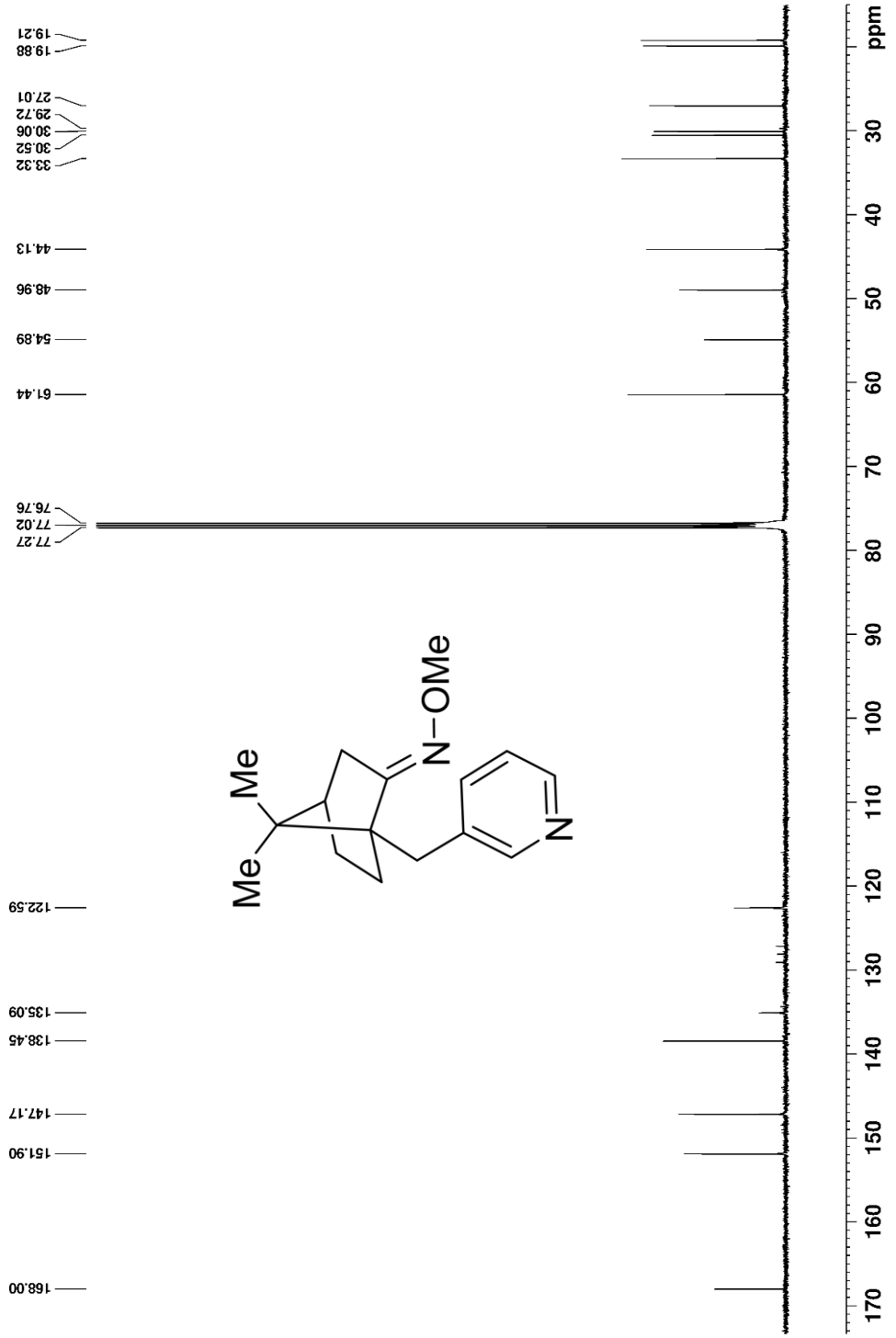


Figure II.31. $^{13}C\{^{1}H\}$ NMR spectrum of compound **II.9e**.

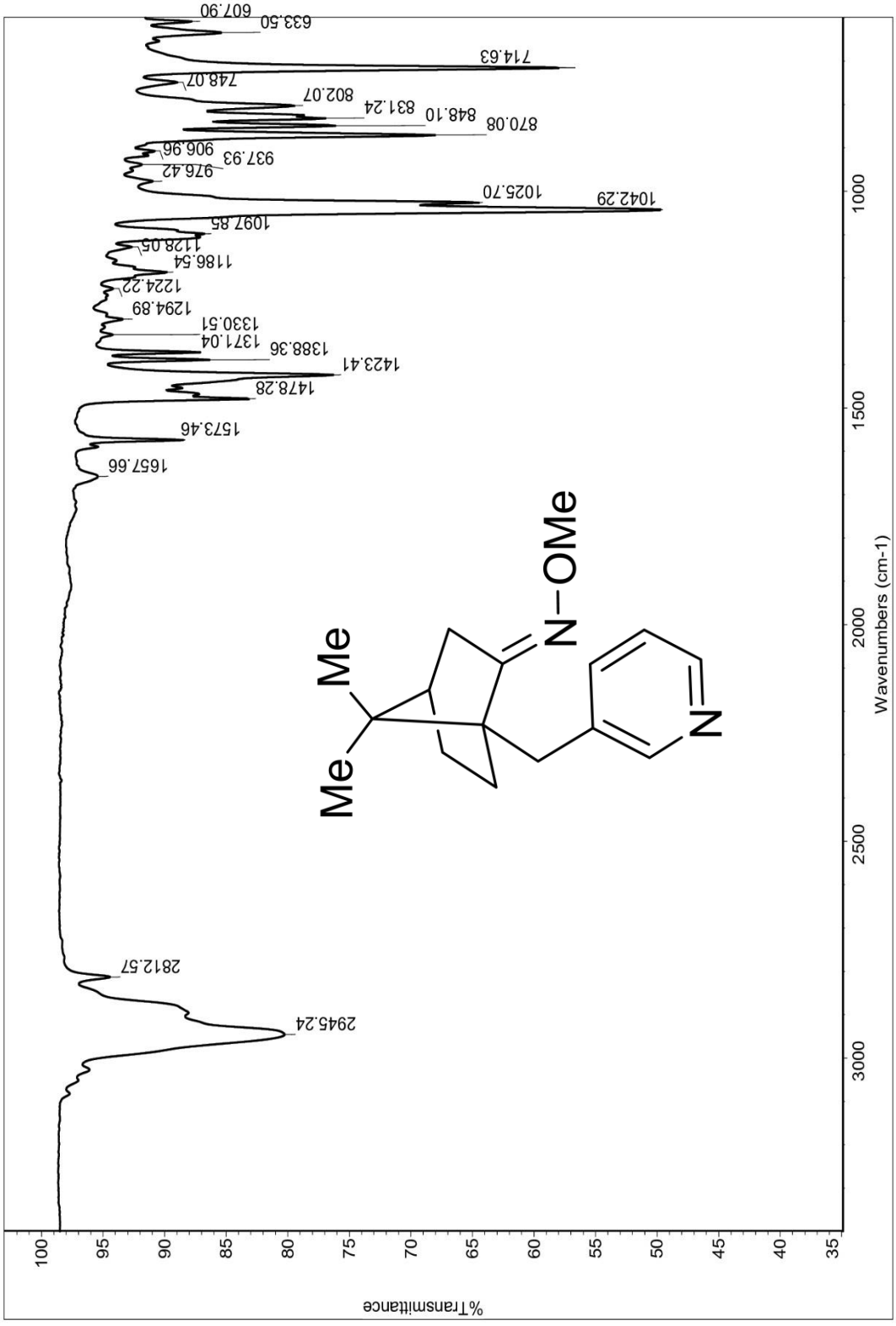


Figure II.32. IR spectrum of compound **II.9e**.

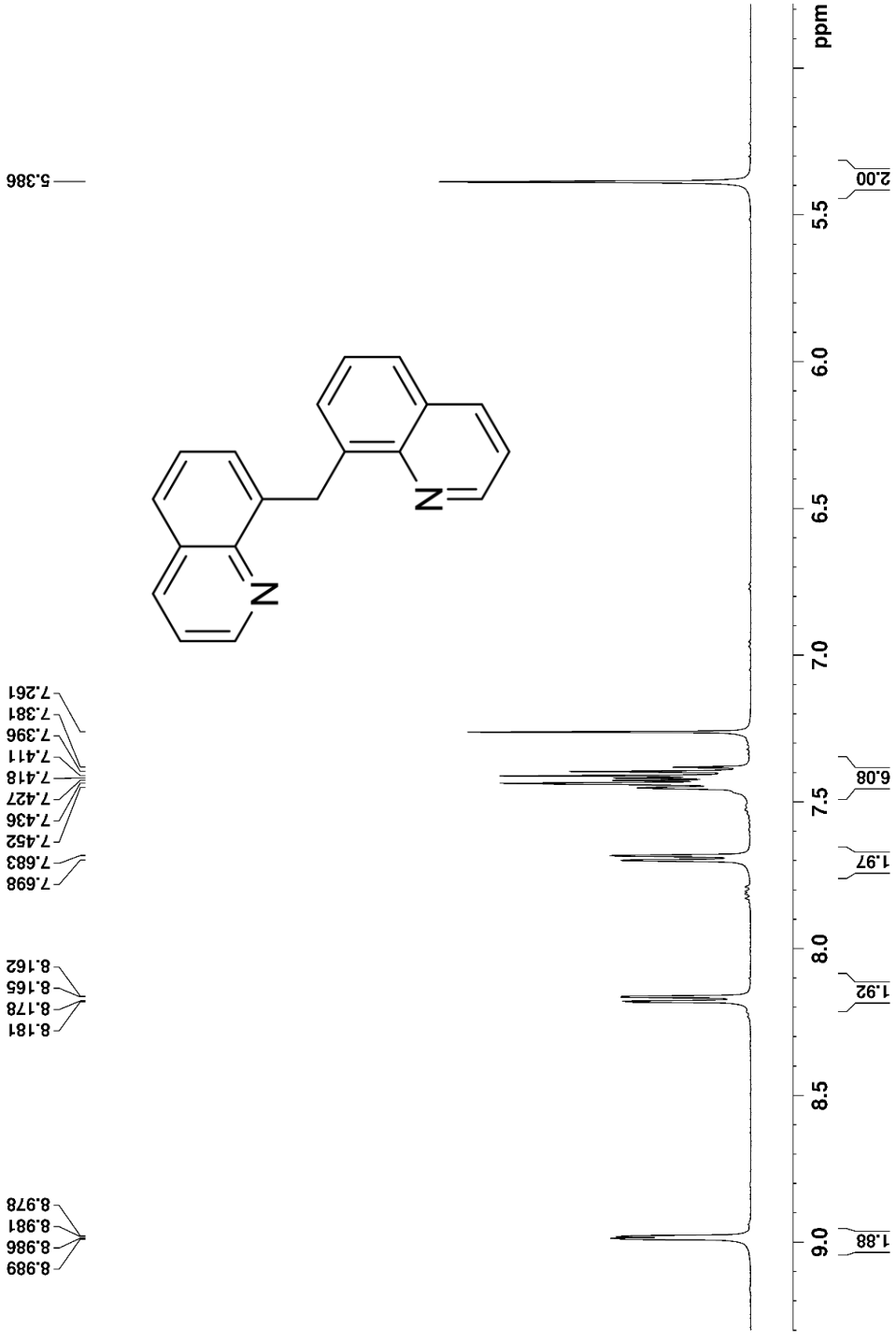


Figure II.33 ^{1}H NMR spectrum of compound **II.11d**.

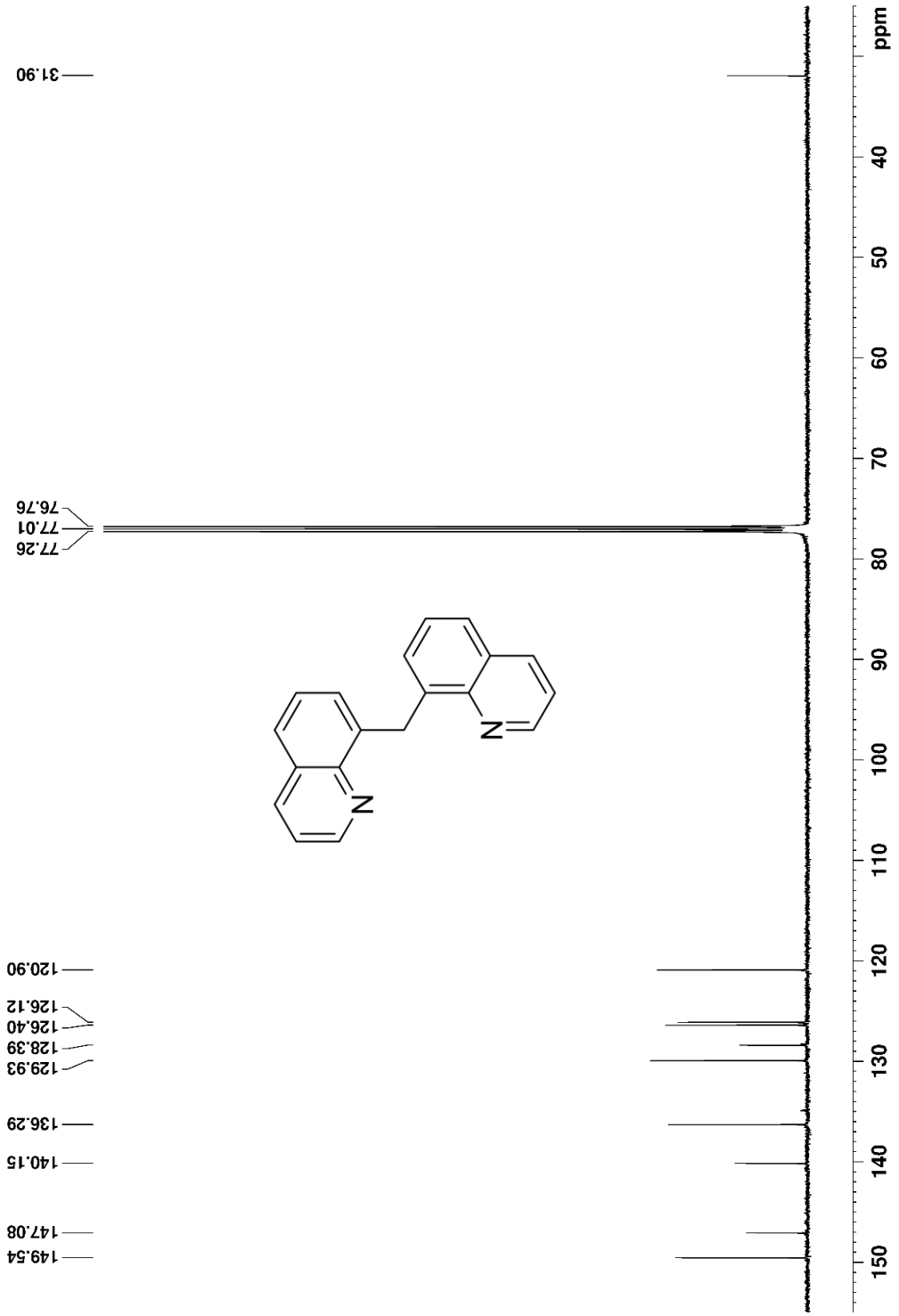


Figure II.34. $^{13}C\{^{1}H\}$ NMR spectrum of compound **II.11d**.

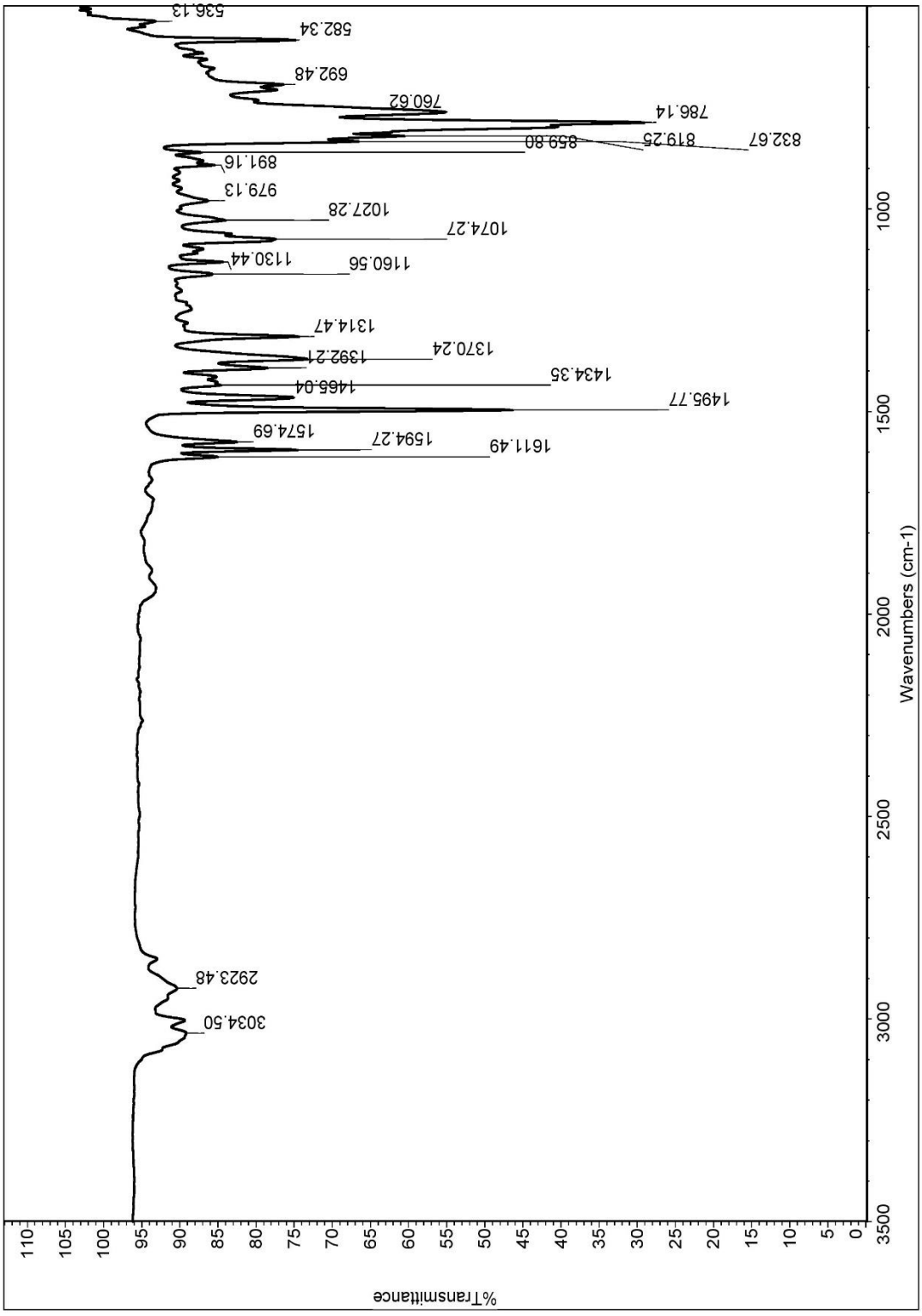


Figure II.35. IR spectrum of compound **II.11d**.

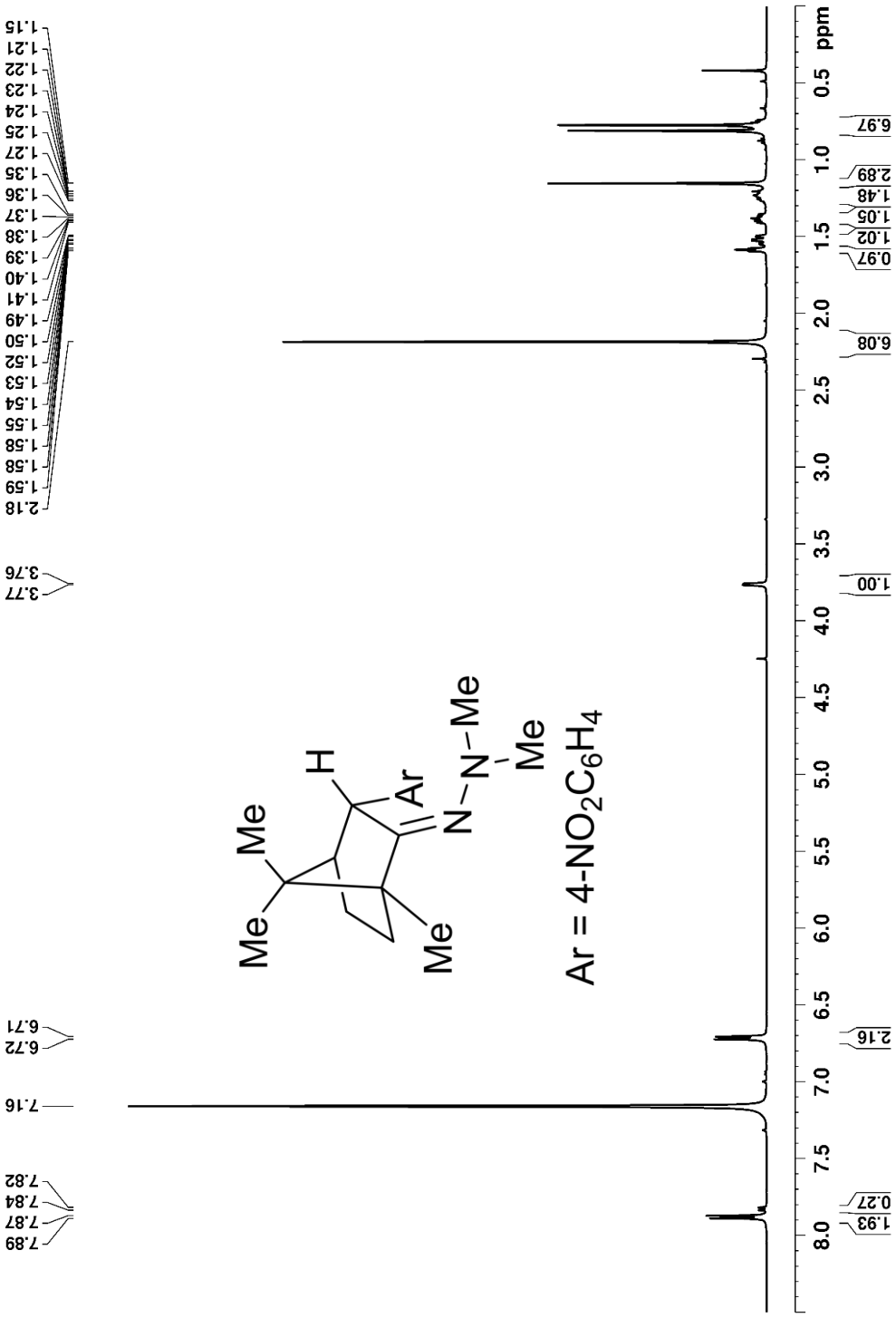


Figure II.36. ^{1}H NMR spectrum of compound **II.13b**.

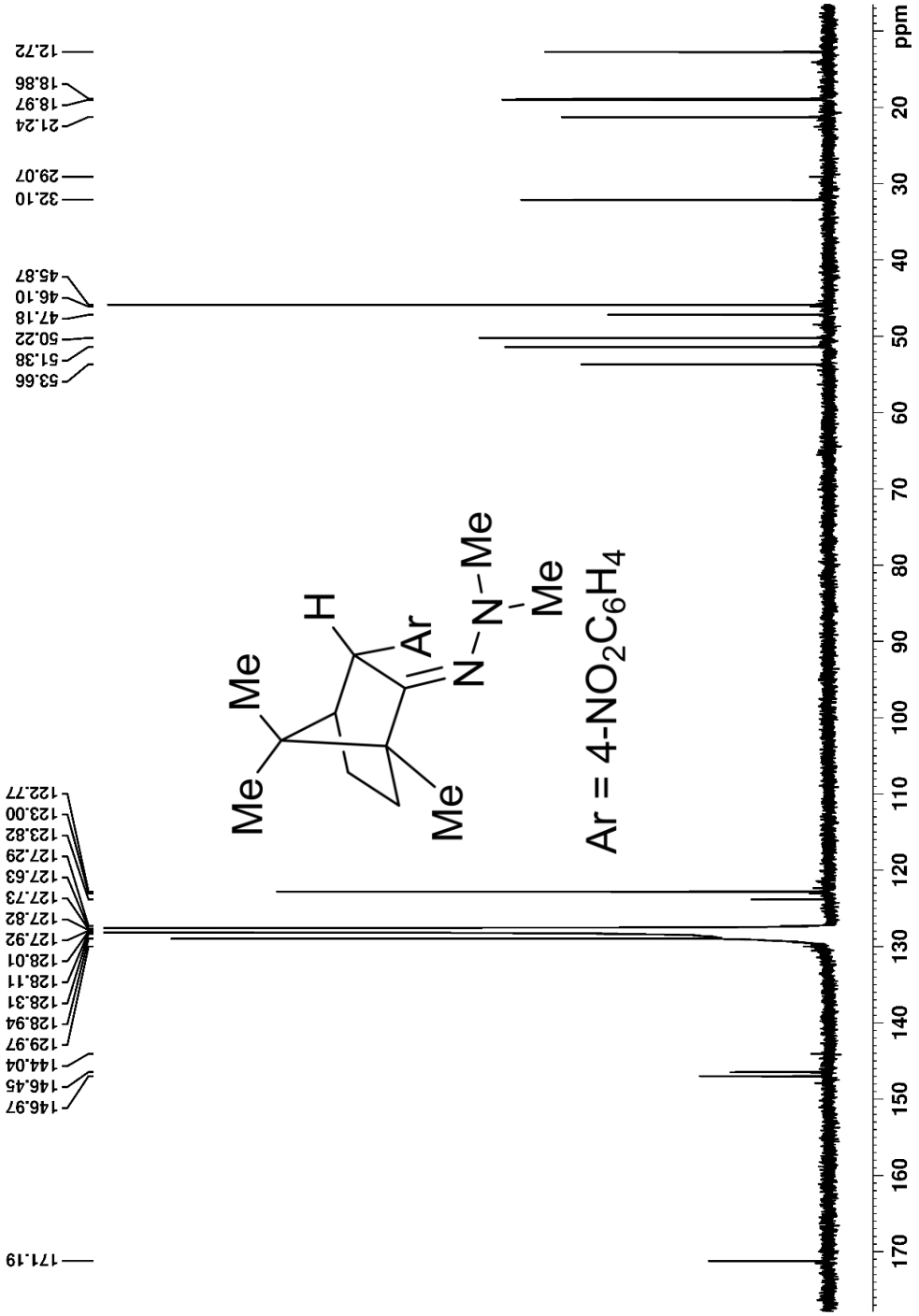


Figure II.37. $^{13}C\{^{1}H\}$ NMR spectrum of compound **II.13b**.

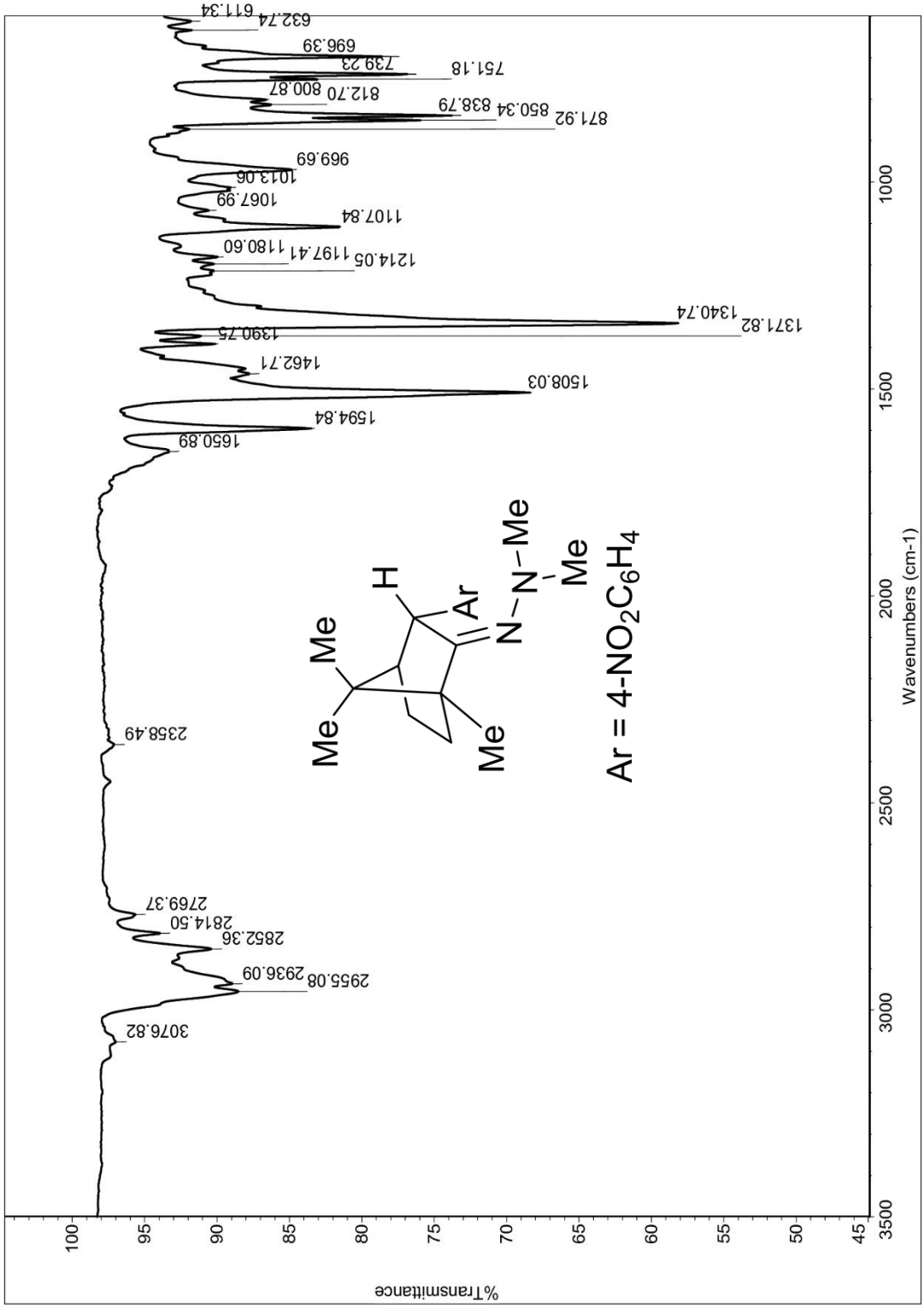


Figure II.38. IR spectrum of compound I**I.13b**.

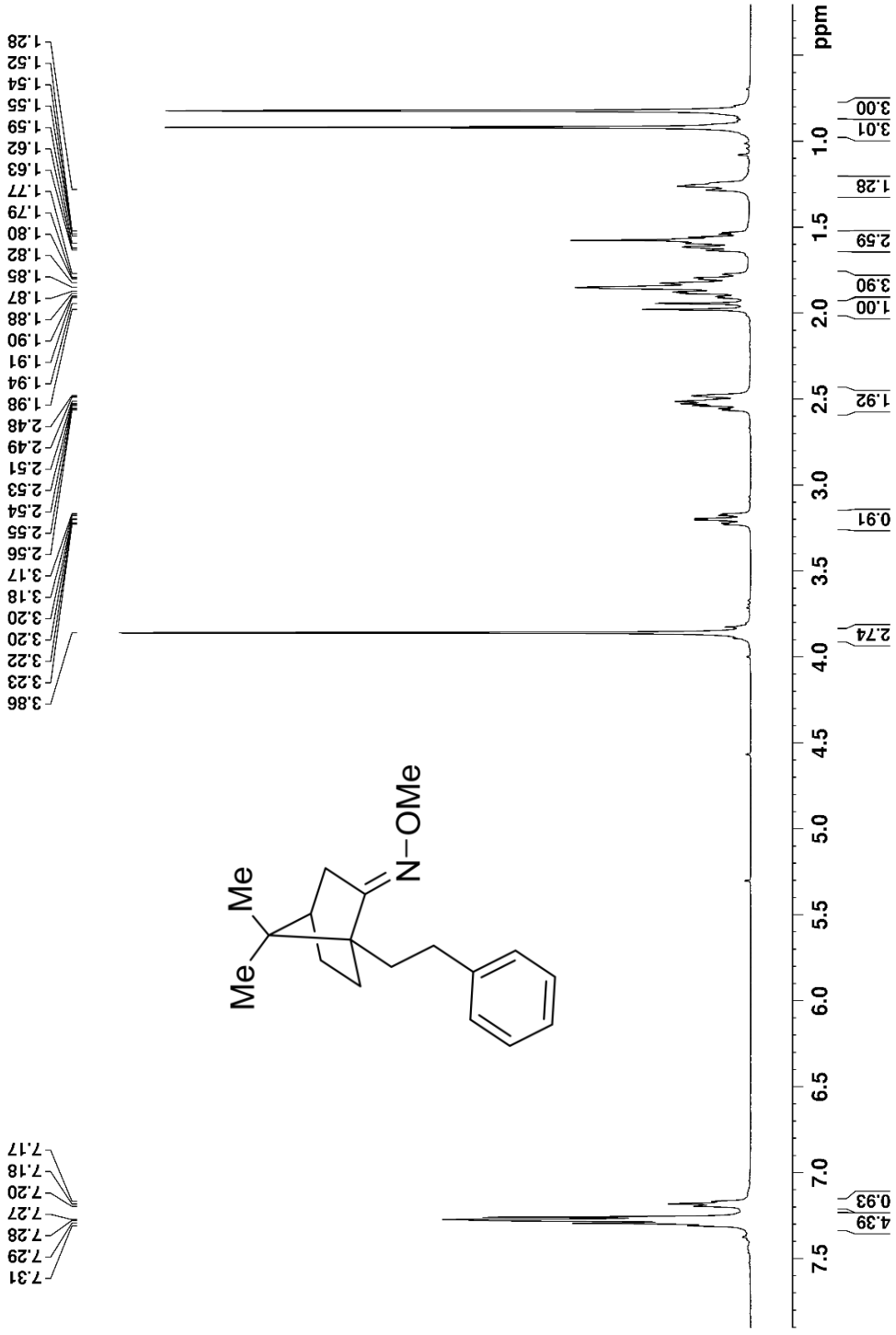


Figure II.39. ^{1}H NMR spectrum of compound **II.16b**.

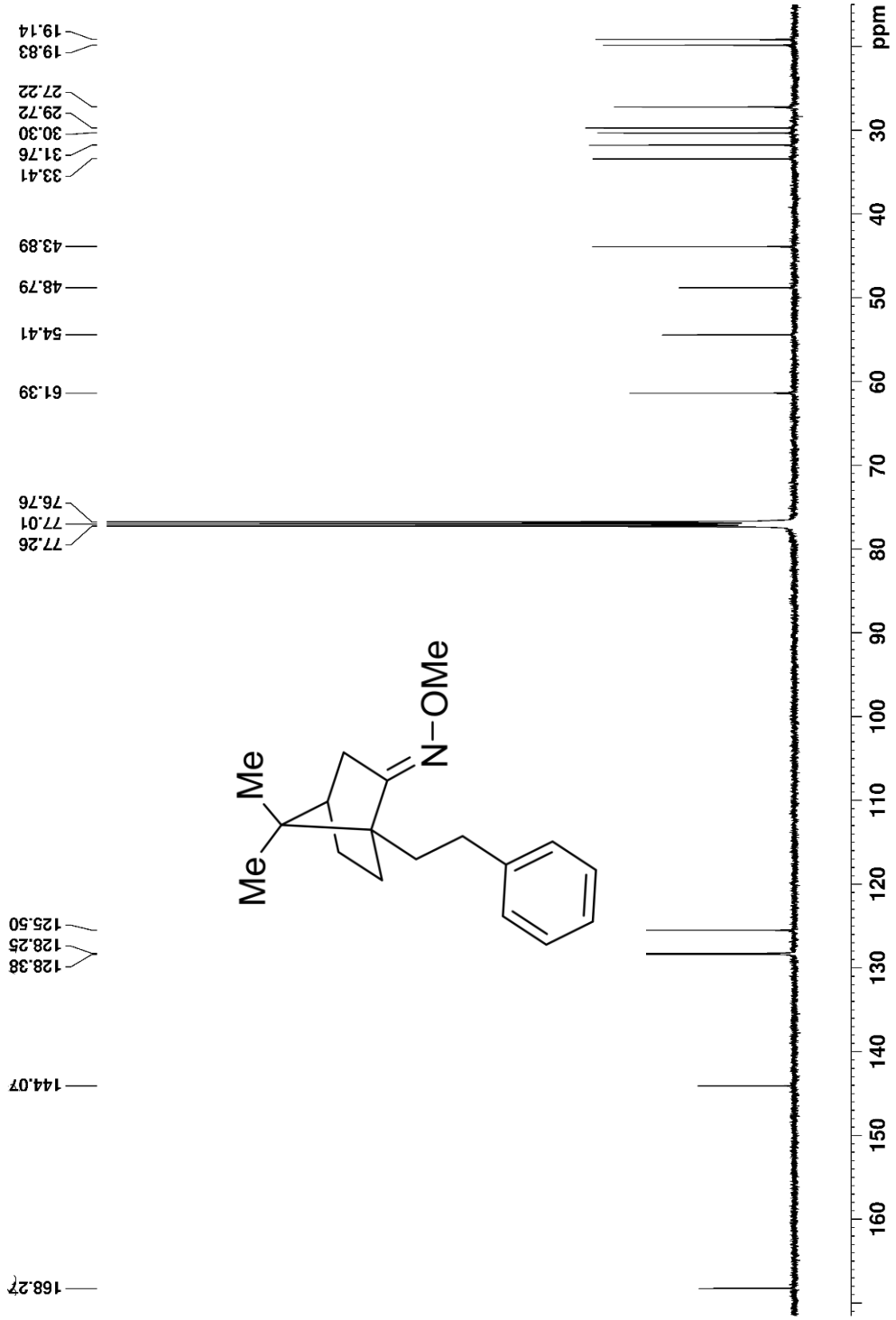


Figure II.40. $^{13}C\{^{1}H\}$ NMR spectrum of compound **II.16b**.

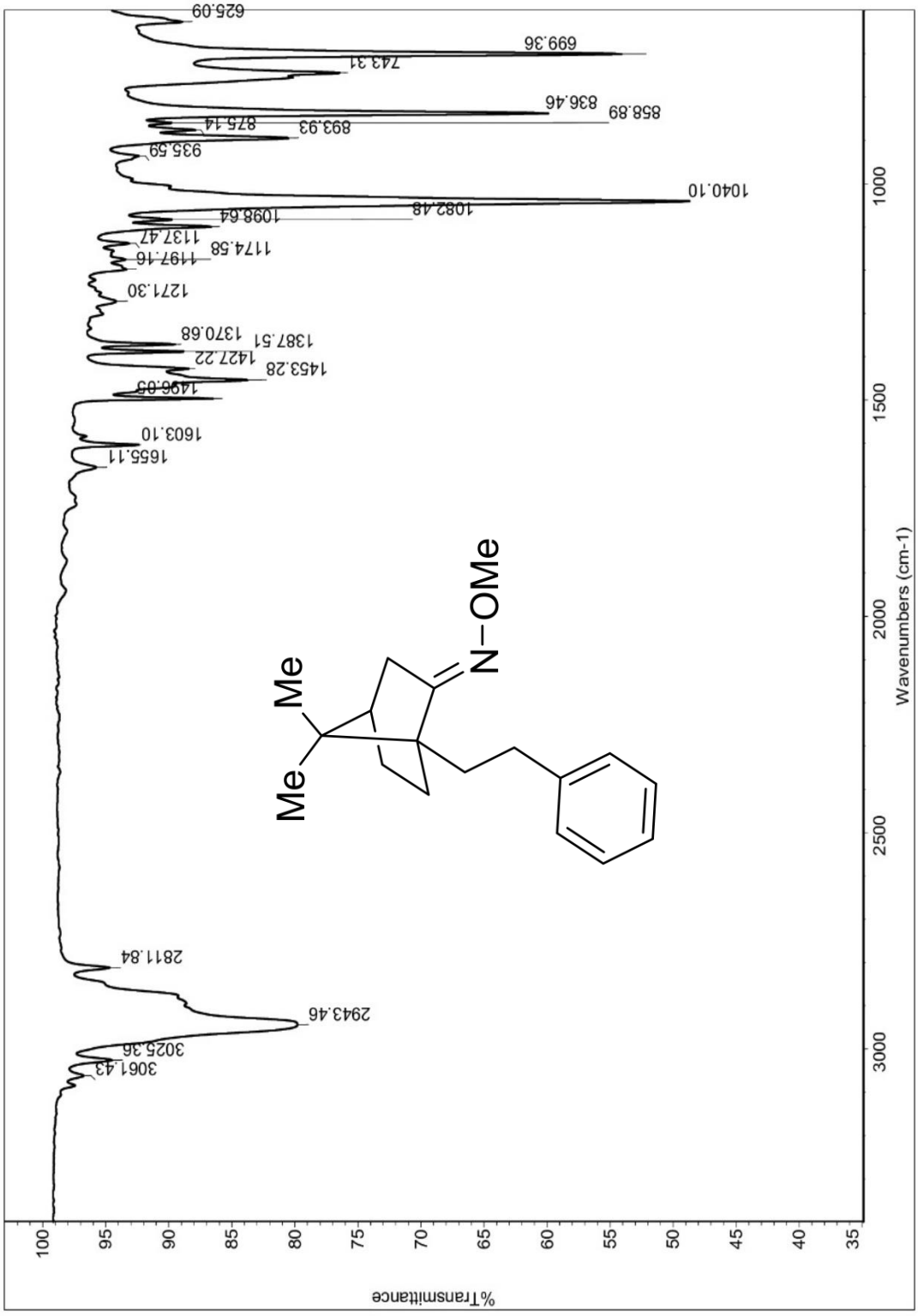


Figure II.41. IR spectrum of compound **II.16b**.

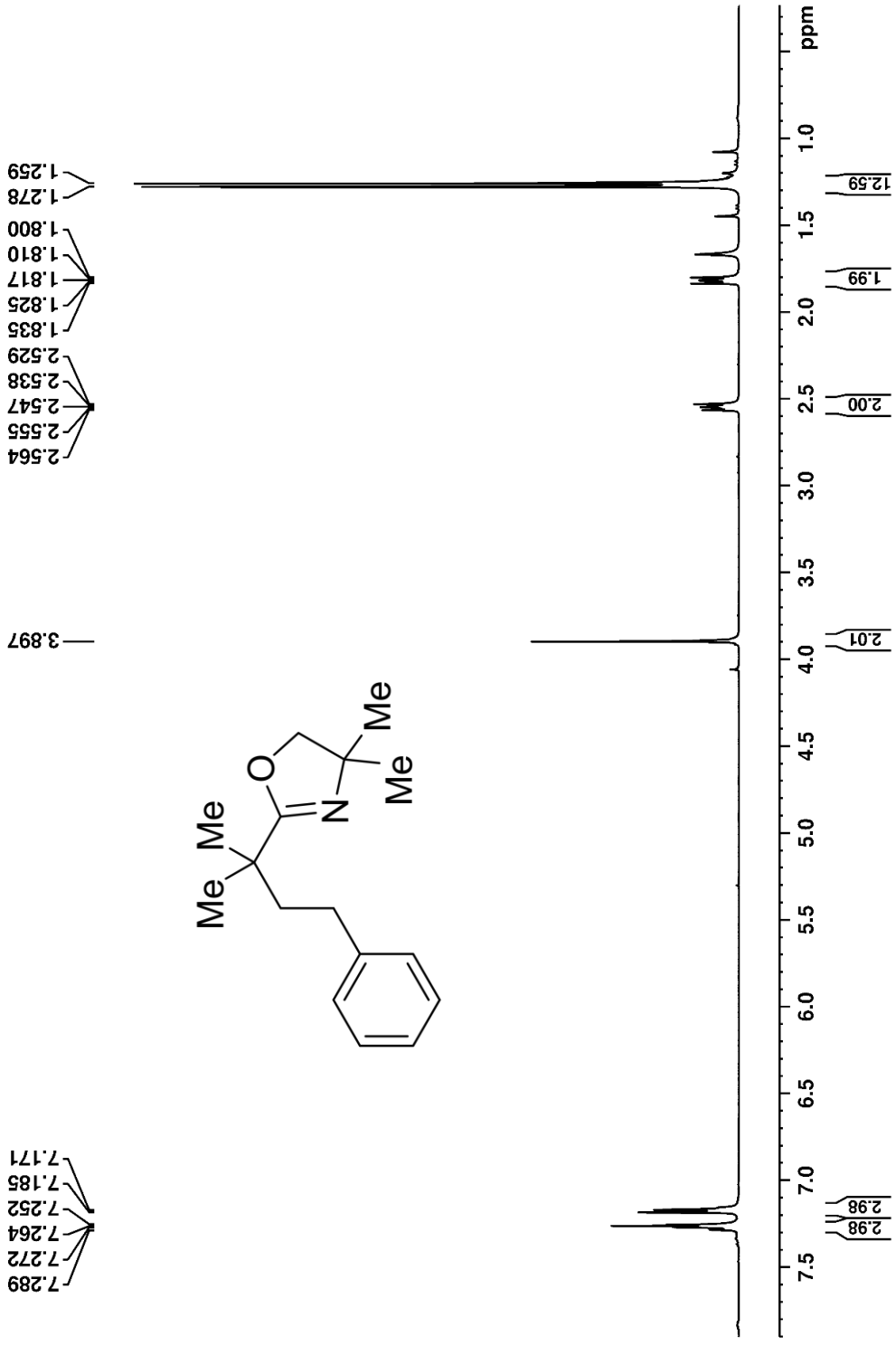


Figure II.42. ^{1}H NMR spectrum of compound **II.17b**.

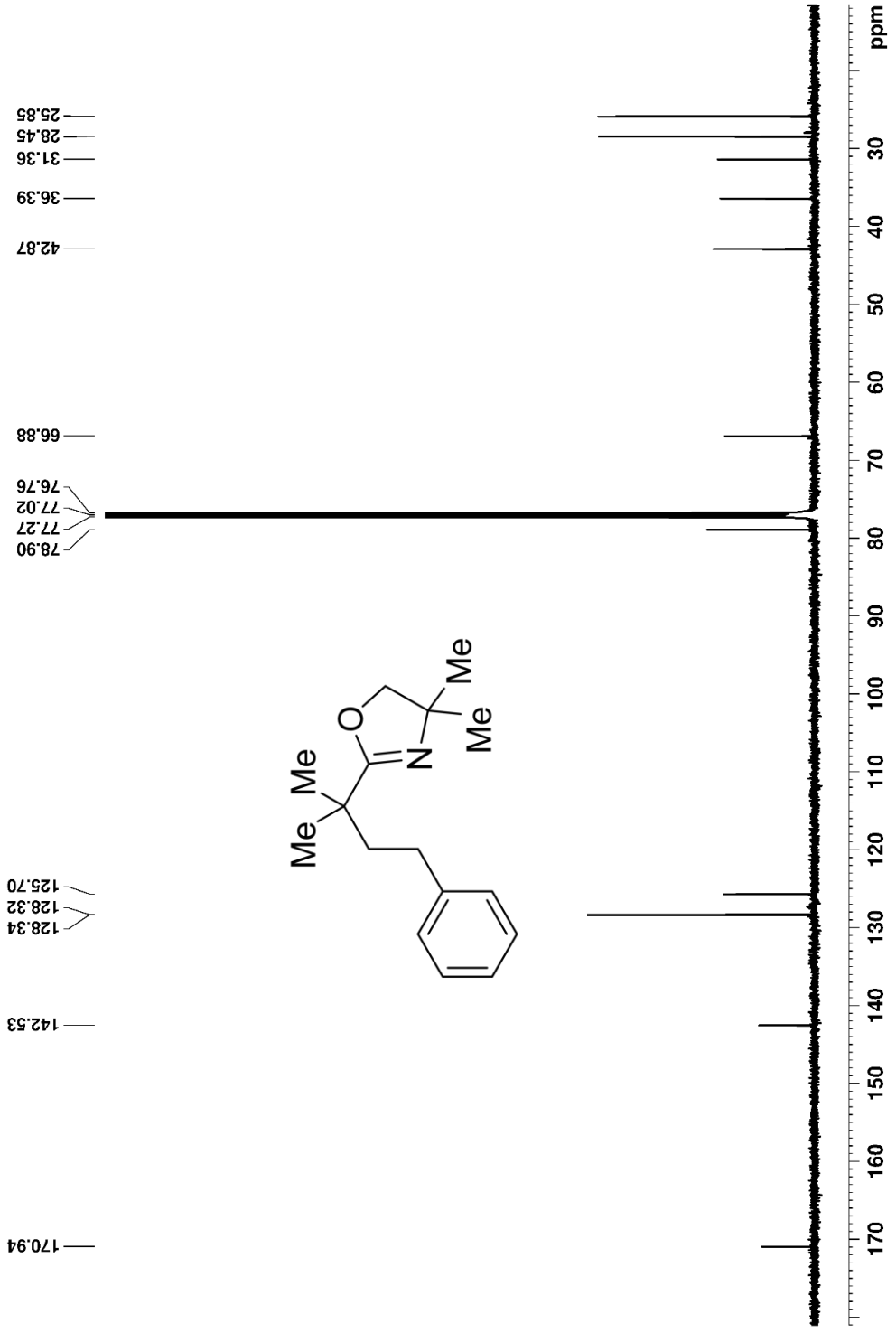


Figure II.43. $^{13}C\{^{1}H\}$ NMR spectrum of compound **II.17b**.

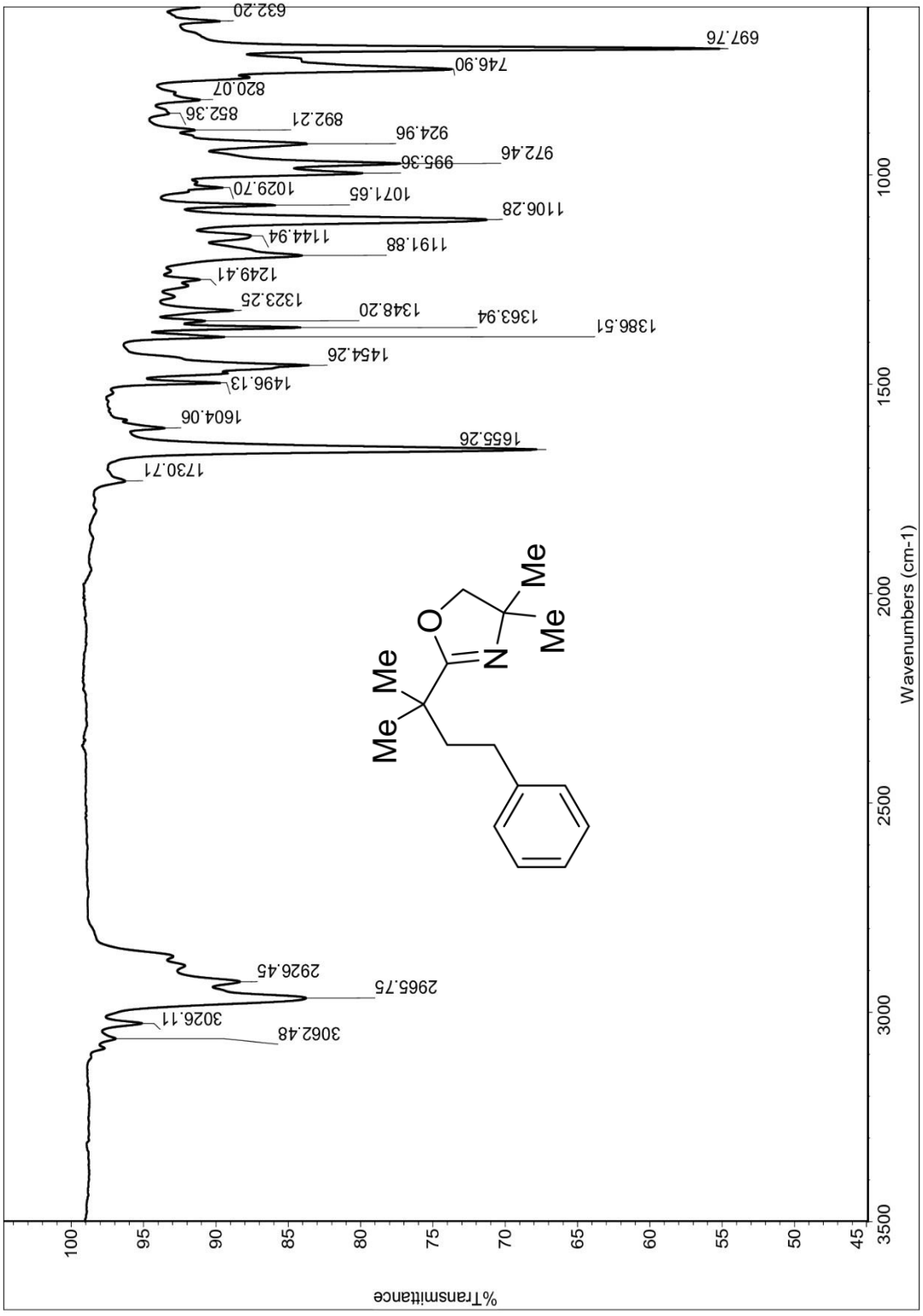


Figure II.44. IR spectrum of compound **II.17b**.

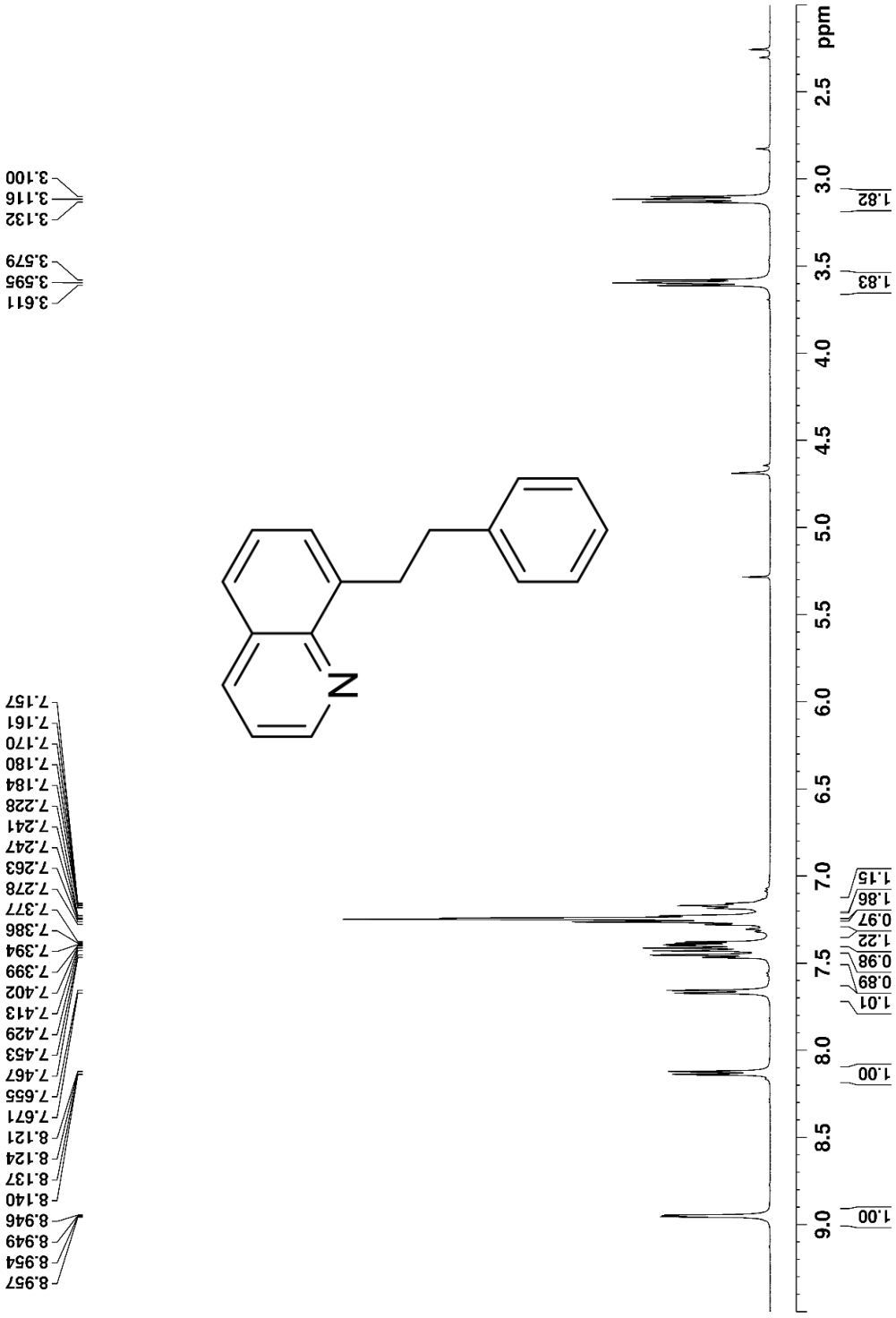


Figure II.45. ^{1}H NMR spectrum of compound **II.18b**.

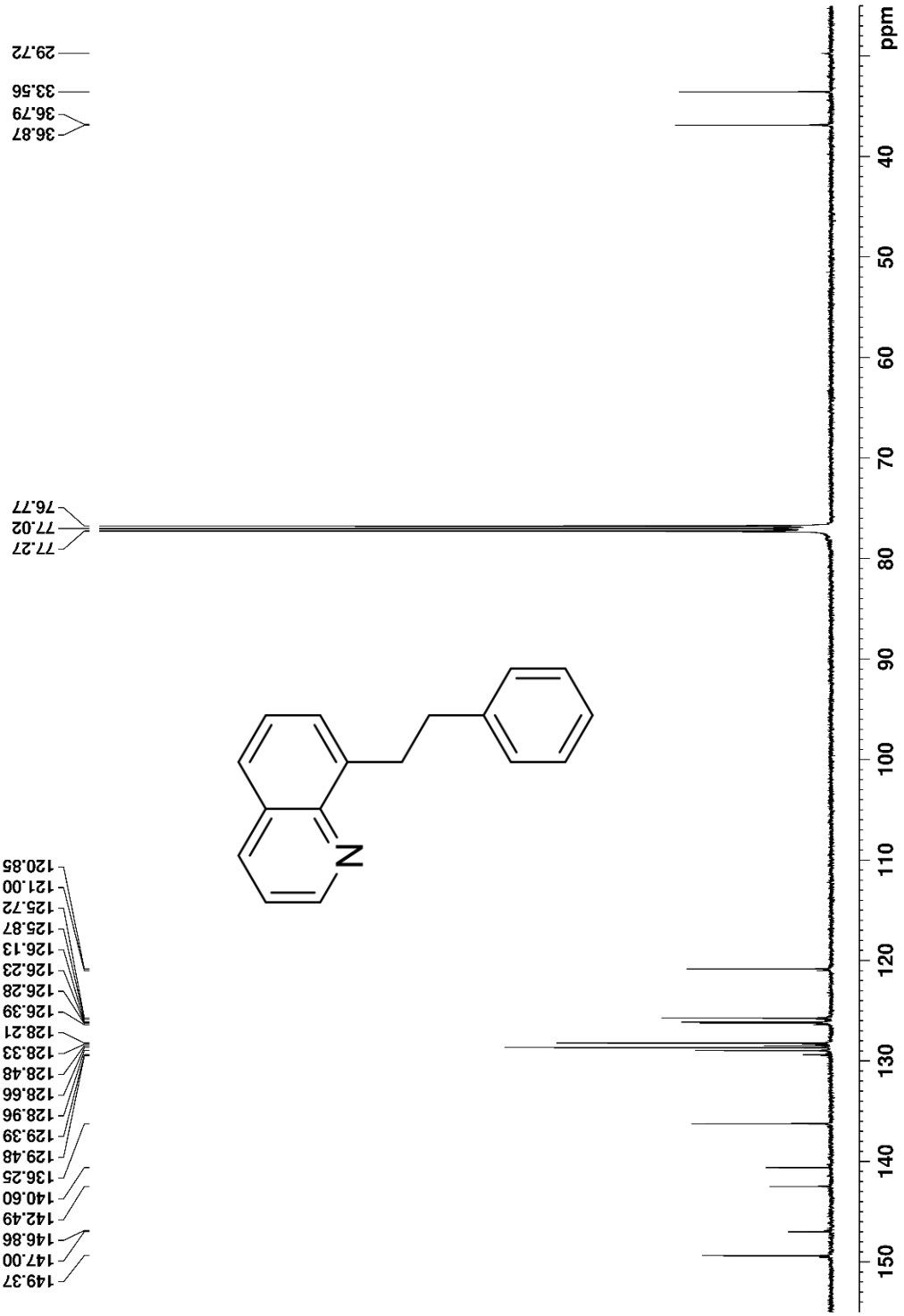


Figure II.46. $^{13}C\{^{1}H\}$ NMR spectrum of compound **II.18b**.

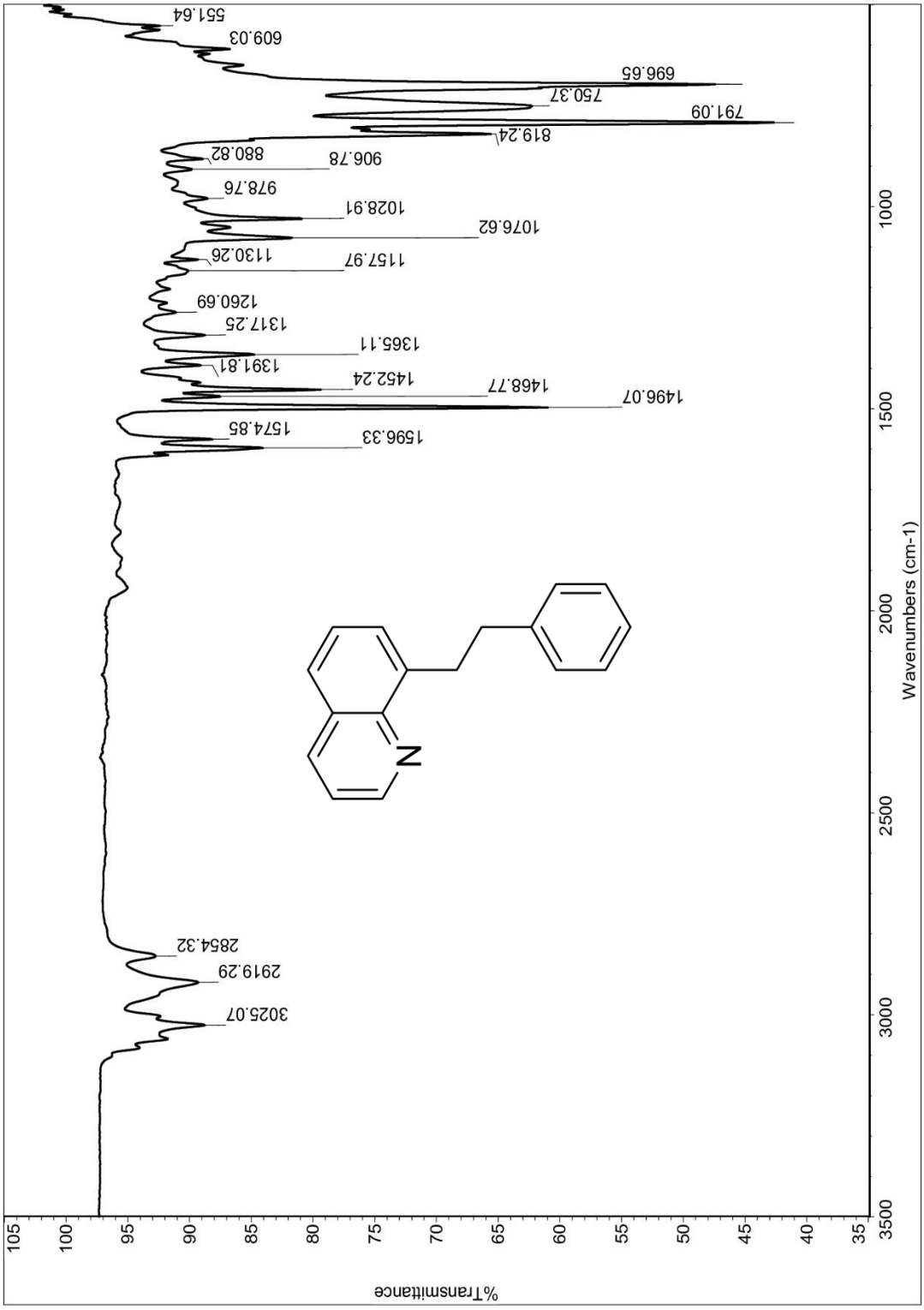


Figure II.47. IR spectrum of compound **II.18b**.

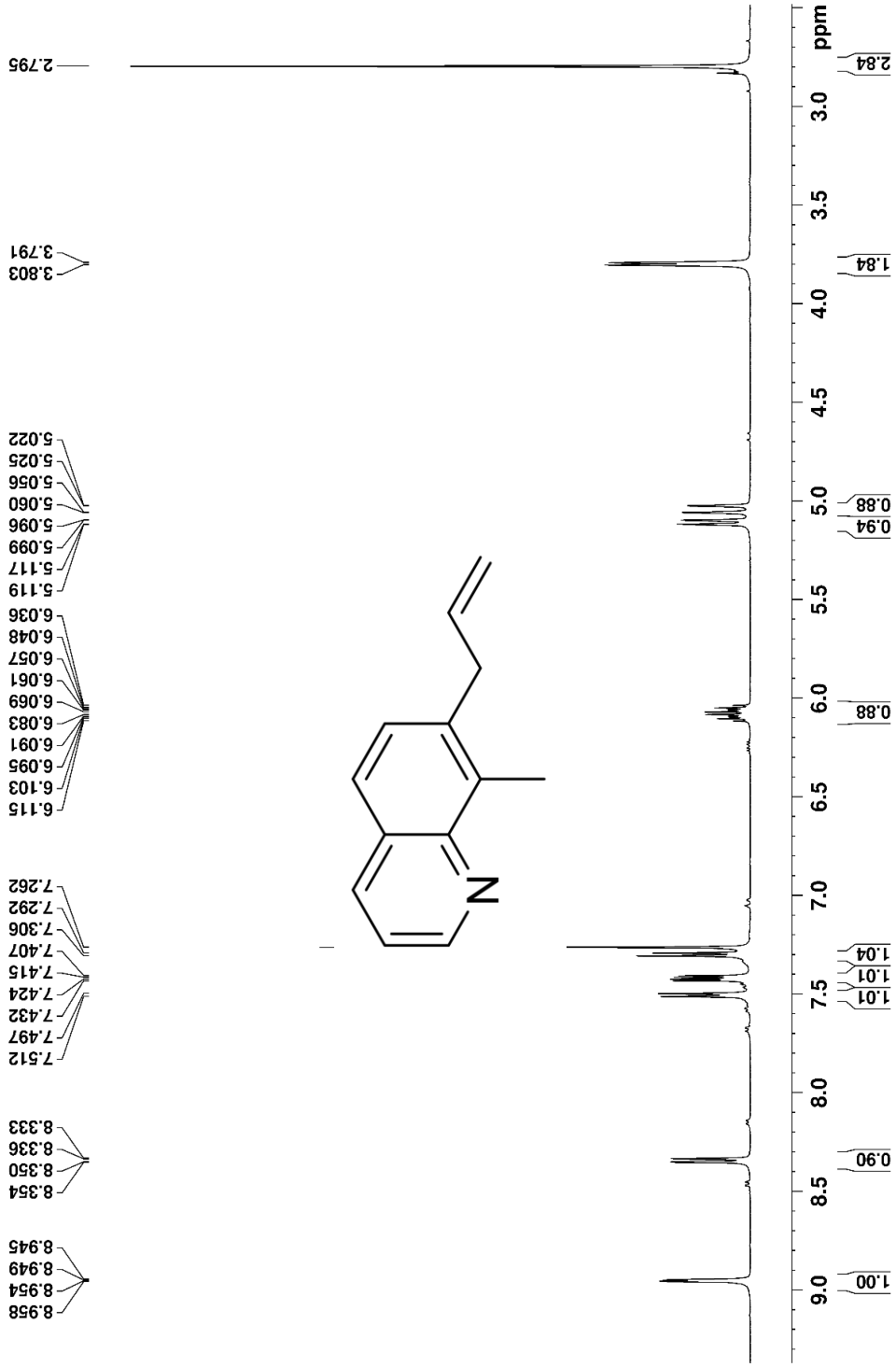


Figure II.48. ^{1}H NMR spectrum of compound **II.19**.

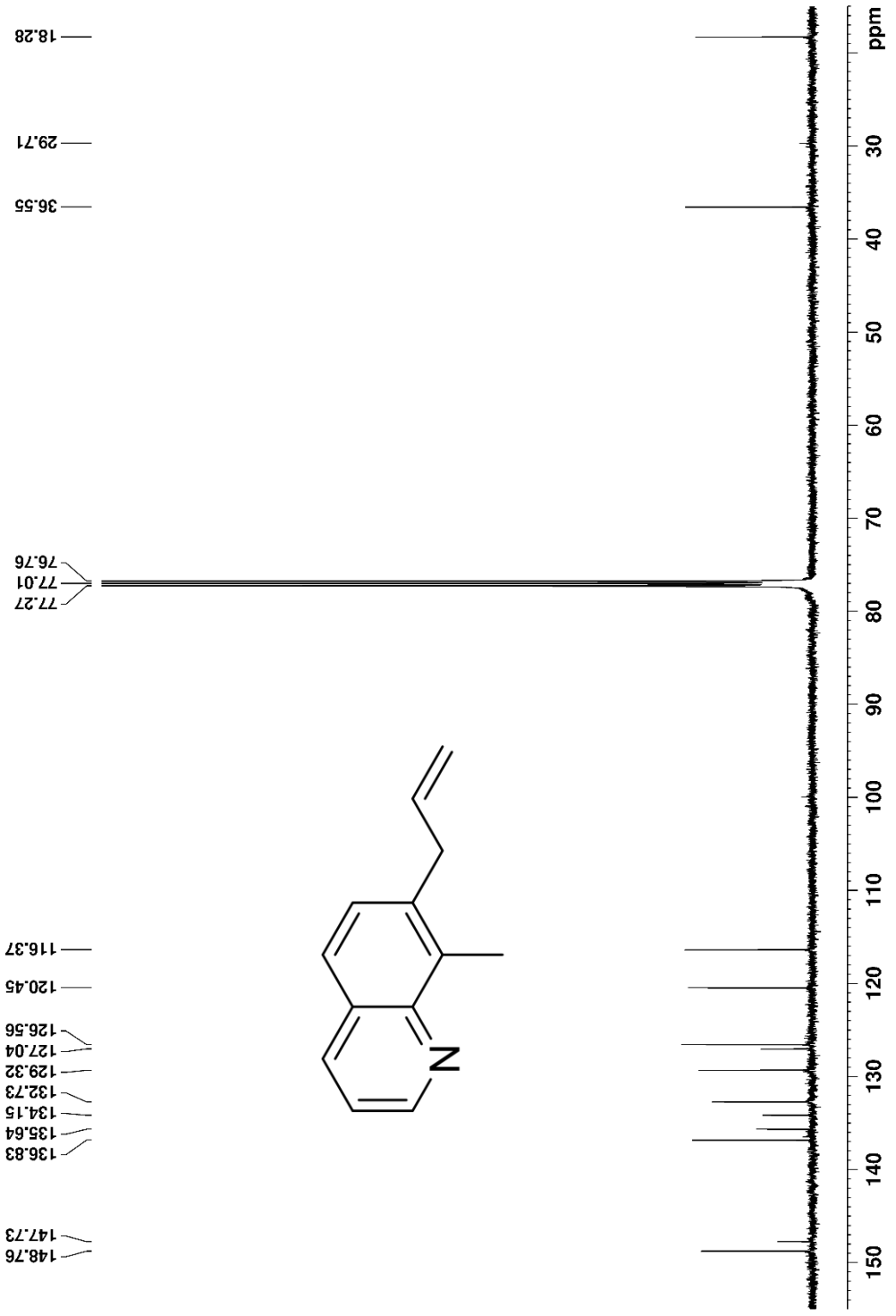


Figure II.49. $^{13}C\{^{1}H\}$ NMR spectrum of compound **II.19**.

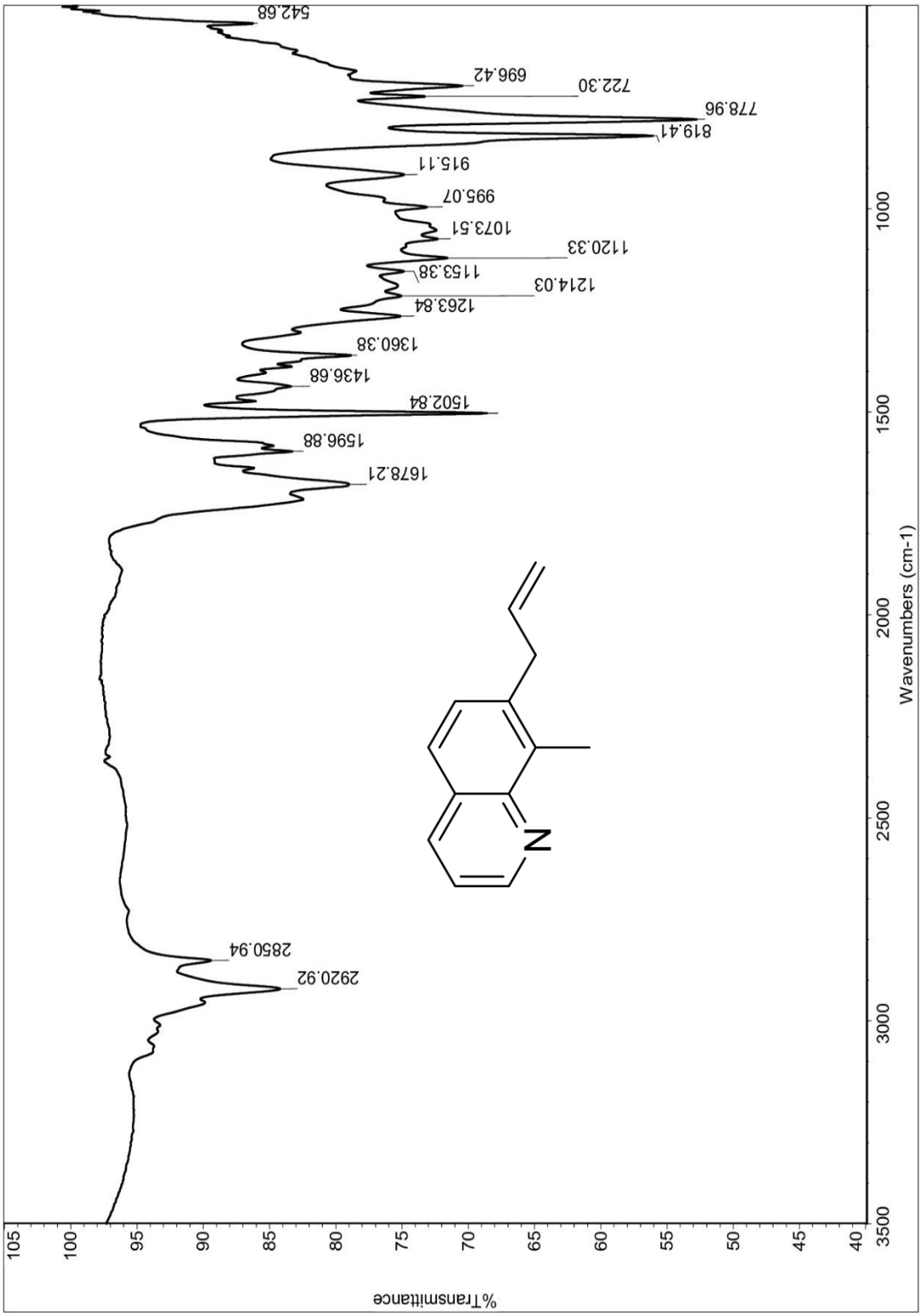


Figure II.50. IR spectrum of compound **II.19**.

Table II.3. Crystal data and structure refinement for compound **II.13b**.

Identification code	22006z	
Empirical formula	$C_{18}H_{25}N_3O_2$	
Formula weight	315.41	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 7.0029(3) Å	α = 90°
	b = 11.6856(5) Å	β = 90°
	c = 20.6588(11) Å	γ = 90°
Volume	1690.57(14) $Å^3$	
Z	4	
Density (calculated)	1.239 Mg/m^3	
Absorption coefficient	0.082 mm^{-1}	
F(000)	680	
Crystal color, morphology	Yellow, Block	
Crystal size	0.260 x 0.190 x 0.120 mm^3	
Theta range for data collection	1.972 to 30.536°	
Index ranges	$-7 \leq h \leq 9$, $-16 \leq k \leq 14$, $-21 \leq l \leq 29$	
Reflections collected	15970	
Independent reflections	5139 [R(int) = 0.0402]	
Observed reflections	4741	
Completeness to theta = 25.242°	99.9%	
Absorption correction	Multi-scan	
Max. and min. transmission	0.7461 and 0.6328	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5139 / 0 / 213	
Goodness-of-fit on F^2	1.045	
Final R indices [I>2sigma(I)]	$R1$ = 0.0370, $wR2$ = 0.0926	
R indices (all data)	$R1$ = 0.0414, $wR2$ = 0.0953	
Absolute structure parameter	0.7(4)	
Largest diff. peak and hole	0.242 and -0.200 $e.Å^{-3}$	

Table II. 4. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for compound **II.13b**. (U_{eq} is defined as one third of the trace of the orthogonalized U_{ij} tensor)

	x	y	z	U_{eq}
O1	8150(2)	6421(1)	4306(1)	49(1)
O2	5425(2)	7288(1)	4233(1)	43(1)
N1	1877(2)	2741(1)	5920(1)	24(1)
N2	807(2)	3209(1)	6464(1)	21(1)
N3	6509(2)	6600(1)	4491(1)	34(1)
C1	973(2)	4433(1)	7425(1)	17(1)
C2	1788(2)	3877(1)	6821(1)	18(1)
C3	3887(2)	4244(1)	6762(1)	19(1)
C4	4052(2)	5046(1)	7364(1)	20(1)
C5	2903(2)	6144(1)	7227(1)	22(1)
C6	797(2)	5724(1)	7254(1)	20(1)
C7	2784(2)	4421(1)	7871(1)	20(1)
C8A	3441(2)	3208(1)	8048(1)	25(1)
C8B	2538(2)	5089(1)	8504(1)	26(1)
C9	-830(2)	3893(1)	7691(1)	21(1)
C10	4502(2)	4792(1)	6135(1)	20(1)
C11	6453(2)	4814(1)	5982(1)	26(1)
C12	7117(2)	5394(1)	5442(1)	29(1)
C13	5816(2)	5958(1)	5053(1)	26(1)
C14	3869(2)	5938(1)	5180(1)	27(1)
C15	3235(2)	5347(1)	5719(1)	25(1)
C16A	2699(3)	1656(2)	6123(1)	34(1)
C16B	482(3)	2535(2)	5405(1)	39(1)

Table II. 5. Bond lengths for compound **II.13b**.

Bond	d/ Å	Bond	d/ Å
O1-N3	1.230(2)	C14-H14A	0.9500
O2-N3	1.227(2)	C15-H15A	0.9500
N1-C16A	1.454(2)	C15-H15A	0.9500
N1-N2	1.4579(17)	C16A-H16A	0.9800
N1-C16B	1.463(2)	C16A-H16B	0.9800
N2-C2	1.2739(18)	C16A-H16C	0.9800
N3-C13	1.466(2)	C16B-H16D	0.9800
C1-C9	1.5144(18)	C16B-H16E	0.9800
C1-C2	1.5193(19)	C16B-H16F	0.9800
C1-C6	1.5548(19)		
C1-C7	1.5668(19)		
C2-C3	1.5359(19)		
C3-C10	1.508(2)		
C3-C4	1.562(2)		
C3-H3A	1.0000		
C4-C5	1.541(2)		
C4-C7	1.554(2)		
C4-H4A	1.0000		
C5-C6	1.555(2)		
C5-H5A	0.9900		
C5-H5B	0.9900		
C6-H6A	0.9900		
C6-H6B	0.9900		
C7-C8B	1.533(2)		
C7-C8A	1.535(2)		
C8A-H8AA	0.9800		
C8A-H8AB	0.9800		
C8A-H8AC	0.9800		
C8B-H8BA	0.9800		
C8B-H8BB	0.9800		
C8B-H8BC	0.9800		
C9-H9A	0.9800		
C9-H9B	0.9800		
C9-H9C	0.9800		
C10-C15	1.395(2)		
C10-C11	1.4024(19)		
C11-C12	1.385(2)		
C11-H11A	0.9500		
C12-C13	1.383(2)		
C12-H12A	0.9500		
C13-C14	1.388(2)		
C14-C15	1.383(2)		

Table II. 6.Bond angles (°) for compound **II.13b**.

Bond	Angle/°	Bond	Angle/°
C16A-N1-N2	107.90(12)	C8B-C7-C4	113.55(12)
C16A-N1-C16B	109.28(14)	C8A-C7-C4	115.09(12)
N2-N1-C16B	106.23(12)	C8B-C7-C1	113.91(11)
C2-N2-N1	113.51(12)	C8A-C7-C1	113.03(11)
O2-N3-O1	123.70(16)	C4-C7-C1	93.66(11)
O2-N3-C13	118.36(15)	C7-C8A-H8AA	109.5
O1-N3-C13	117.94(17)	C7-C8A-H8AB	109.5
C9-C1-C2	115.63(11)	H8AA-C8A-H8AB	109.5
C9-C1-C6	114.91(11)	C7-C8A-H8AC	109.5
C2-C1-C6	104.94(11)	H8AA-C8A-H8AC	109.5
C9-C1-C7	117.34(11)	H8AB-C8A-H8AC	109.5
C2-C1-C7	100.04(10)	C7-C8B-H8BA	109.5
C6-C1-C7	101.88(11)	C7-C8B-H8BB	109.5
N2-C2-C1	122.32(12)	H8BA-C8B-H8BB	109.5
N2-C2-C3	129.90(13)	C7-C8B-H8BC	109.5
C1-C2-C3	107.75(11)	H8BA-C8B-H8BC	109.5
C10-C3-C2	117.37(11)	H8BB-C8B-H8BC	109.5
C10-C3-C4	114.11(11)	C1-C9-H9A	109.5
C2-C3-C4	100.13(10)	C1-C9-H9B	109.5
C10-C3-H3A	108.2	H9A-C9-H9B	109.5
C2-C3-H3A	108.2	C1-C9-H9C	109.5
C4-C3-H3A	108.2	H9A-C9-H9C	109.5
C5-C4-C7	102.55(11)	H9B-C9-H9C	109.5
C5-C4-C3	108.29(11)	C15-C10-C11	118.22(14)
C7-C4-C3	102.20(11)	C15-C10-C3	123.00(13)
C5-C4-H4A	114.2	C11-C10-C3	118.63(13)
C7-C4-H4A	114.2	C12-C11-C10	121.13(14)
C3-C4-H4A	114.2	C12-C11-H11A	119.4
C4-C5-C6	103.03(11)	C10-C11-H11A	119.4
C4-C5-H5A	111.2	C13-C12-C11	118.69(14)
C6-C5-H5A	111.2	C13-C12-H12A	120.7
C4-C5-H5B	111.2	C11-C12-H12A	120.7
C6-C5-H5B	111.2	C12-C13-C14	121.96(14)
H5A-C5-H5B	109.1	C12-C13-N3	119.14(15)
C1-C6-C5	103.88(11)	C14-C13-N3	118.90(15)
C1-C6-H6A	111.0	C15-C14-C13	118.41(15)
C5-C6-H6A	111.0	C15-C14-H14A	120.8
C1-C6-H6B	111.0	C13-C14-H14A	120.8
C5-C6-H6B	111.0	C14-C15-C10	121.56(14)
H6A-C6-H6B	109.0	C14-C15-H15A	119.2
C8B-C7-C8A	107.38(12)	C10-C15-H15A	119.2

Bond	Angle/ °
N1-C16A-H16A	109.5
N1-C16A-H16B	109.5
H16A-C16A-H16B	109.5
N1-C16A-H16C	109.5
H16A-C16A-H16C	109.5
N1-C16B-H16D	109.5
N1-C16B-H16E	109.5
H16D-C16B-H16E	109.5
N1-C16B-H16F	109.5
H16D-C16B-H16F	109.5
H16E-C16B-H16F	109.5

Symmetry transformations used to generate equivalent atoms.

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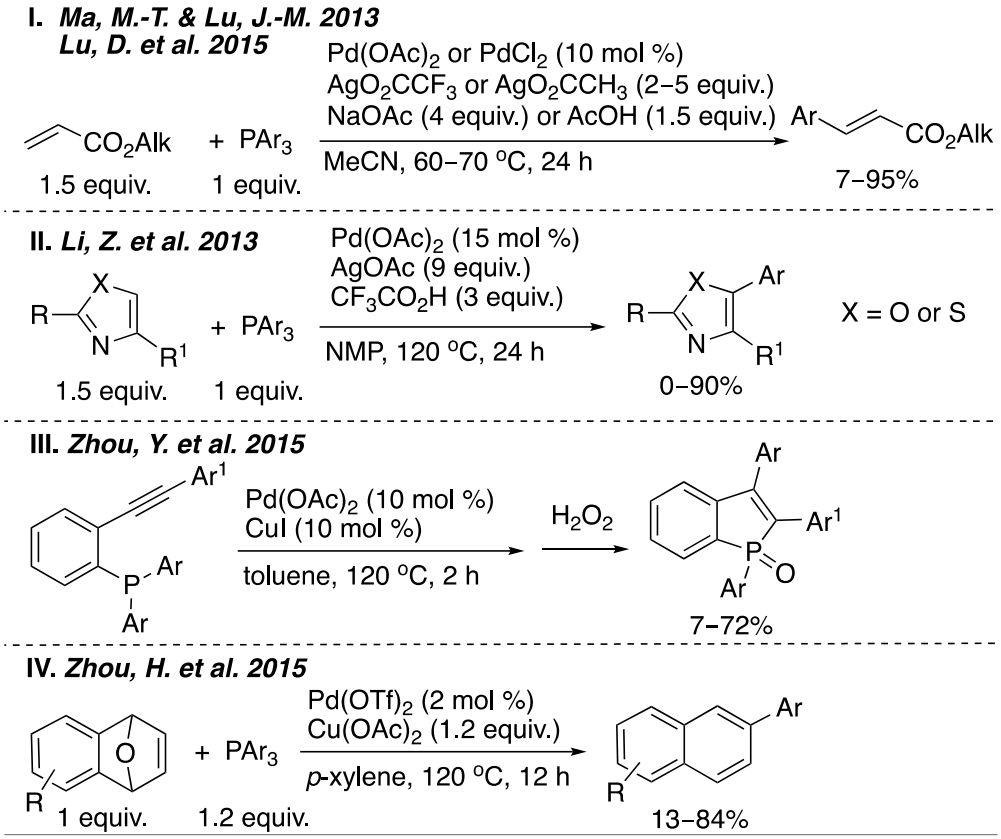
CHAPTER III. PALLADIUM-CATALYZED ARYL GROUP TRANSFER FROM TRIARYLPHOSPHINES TO ARYLBORONIC ACIDS

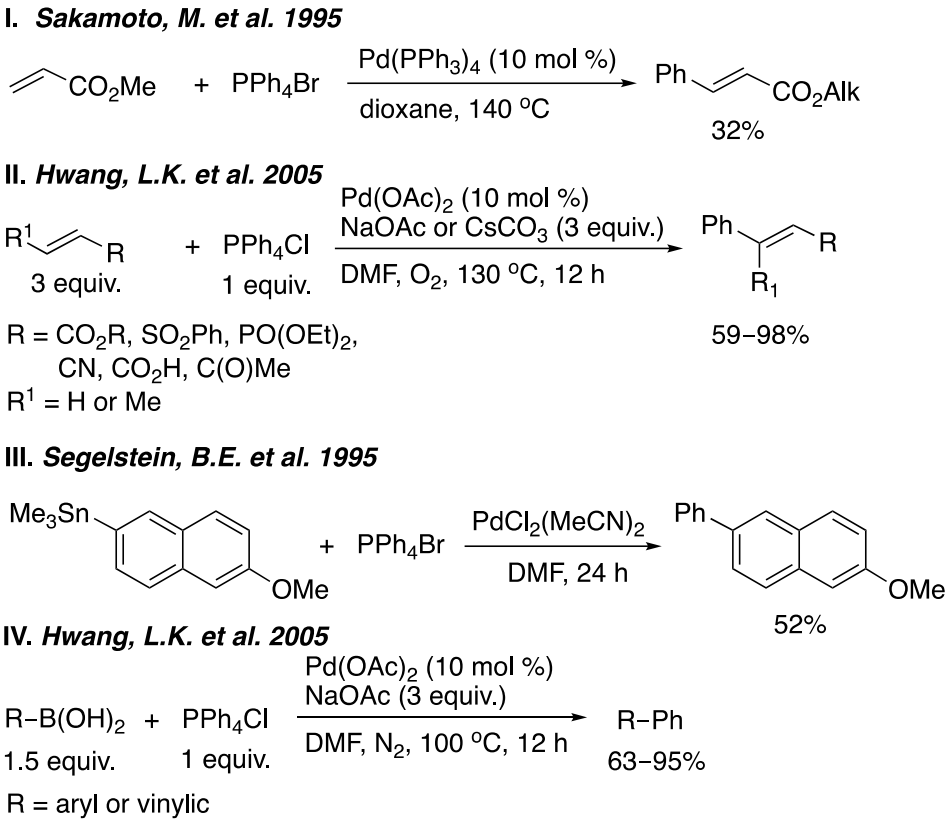
III.1. Background

A possibility of the C–P bond cleavage in PPh_3 in the presence of Pd salts has been known since 1968 when D. R. Coulson[1] reported the formation of a trinuclear PPh_2-bridged complex.[1,2] After his discovery, the Matsuda group described the arylation of alkenes using equimolar amounts of $Pd(OAc)_2(PAr_3)_2$ in AcOH at 50-60 ^oC.[3–5] A similar study was reported by R. Asano et al.[6] They used equimolar amounts of styrene, PPh_3, and $Pd(OAc)_2$ in dioxane-AcOH under reflux. Three decades later, catalytic versions of the Ph-transfer from PAr_3 to styrenes, esters of acrylic acid and related compounds were developed by two groups, M.-T. Ma & J.-M. Lu[7] and D. Lu et al.[8] (Scheme III.1, reaction I). Three more studies reported the use of PAr_3 as a source of the aryl group in Pd-catalyzed transformations (Scheme III.1, reactions II–IV).[9–11]



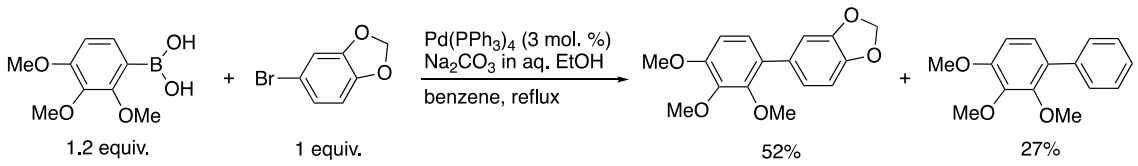
Scheme III.1. Pd-catalyzed aryl group transfer from PAr_3.

Tetraphenylphosphonium halides, PAr_4Hal, can also arylate esters of acrylic acid and related compounds (Scheme III.2, reactions I and II).[12–13] The transformations require 10 molar percent of either $Pd(PPh_3)_4$ or $Pd(OAc)_2$. One example of the Ph group transfer from Ph_4PBr to an organostannane was disclosed by Segelstein et al. (Scheme III.2, reaction III).[14] Phenylation of aryl and vinylic boronic acids using PPh_4Cl in the presence of a catalytic amount of $Pd(OAc)_2$ has been reported as well (Scheme III.2, reaction IV).[13]



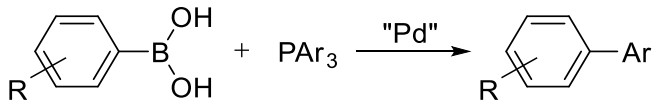
Scheme III.2. Pd-catalyzed aryl group transfer from PPh_4Hal.

Breaking of a C-P bond in phosphine molecules in the presence of Pd salts followed by arylation of different substrates has been reported as a *side* reaction in various organic reactions.[15,16] Specifically, there are several publications in which the Ph group transfer from PPh_3 to boronic acids was mentioned as an undesirable side process[17–21] in Pd-catalyzed Suzuki-Miyaura reactions of $ArB(OH)_2$ with aryl halides performed in the presence of phosphines, see an example in Scheme III.3.[22,23]



Scheme III.3. Example of a competition between the Suzuki-Miyaura reaction and Ph-transfer from PPh_3 to boronic acid.[17]

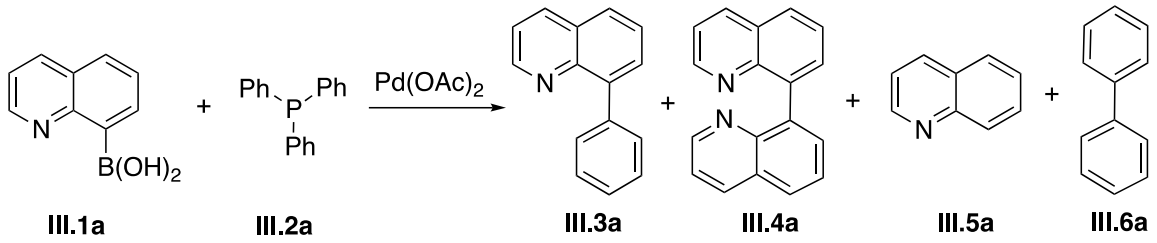
It appears that there are no studies i) on the possibility of converting this side reaction to the desired transformation, in which inexpensive PAr_3 is used in the arylation of boronic acids or ii) on conditions favoring this transformation. In this work, we investigated the factors affecting the Pd-catalyzed aryl group transfer from PAr_3 to boronic acids (Scheme III.4).



Scheme III.4. Pd-catalyzed arylation of arylboronic acids using triarylphosphines.

III.2. Results and Discussion

The reaction of 8-quinolineboronic acid (**III.1a**) with PPh_3 (**III.2a**) in the presence of $Pd(OAc)_2$ was used as a model reaction to determine the best conditions for the phenyl group transfer. The possible products are shown in Scheme III.5. Trial experiments were performed in MeCN under an argon atmosphere at 35 and 80 ^oC using 0.1–0.3 molar equiv. of $Pd(OAc)_2$ and did not provide any expected products. However, the formation of 8-phenylquinoline (**III.3a**) was observed when the reaction mixture was stirred at 35 ^oC in Ar for 24 h and then exposed to the air for an additional 24 h before purification. This result suggests that oxygen plays a vital role in the phenyl group transfer from PPh_3. Performing the reaction in the air resulted in a further increase in the yield of compound **III.3a**. All reactions described below were performed in the air.



Scheme III.5. Possible products in the reaction of 8-quinolineboronic acid with PPh_3 in the presence of $Pd(OAc)_2$.

Then, we tested several solvents using a 1:1 ratio of $RB(OH)_2$:PPh_3 and $Pd(OAc)_2$ (30 mol%) at 35 ^oC (Table III.1). Acetone and acetonitrile produced similar results among the absolute solvents tried (entries 1 and 2). Compound **III.4a**, the self-coupled product of boronic acid **III.1a**, was dominant when DMF was used (Table III.1, entry 6). Other solvents tested under these conditions were toluene, 1,4-dioxane and acetic acid. These reactions provided less than 5% of product **III.3a**. Interestingly, the reaction on SiO_2 without any solvent at 35^o C afforded 9% of **III.3a**. However, the highest yield of compound **III.3a** was obtained when the experiment was carried out in a 4:1 mixture of MeCN and H_2O. In this study, all other reactions were performed in abs. MeCN or a 4:1 mixture of MeCN-H_2O.

Table III.1. Solvent and temperature effect on the aryl transfer.[a]

Entry	Solvent	Temp. (°C)	Yield (%)[b]			
			III.3a	**III.4a**	**III.5a**	**III.6a**
1	acetone	35	18	0	6	0
2	MeCN	35	19	0	0	traces
3	MeCN-H_2O (4:1)	35	31	13	0	0
4	PhMe	35	5	0	traces	traces
5	DMF	35	8	53	0	0
6	PhMe	reflux	17	6	33	4
7	MeCN	22	11	0	0	0
8	MeCN	55	24	41	15	traces
9	SiO_2	35	9	traces	0	0

[a] Reaction conditions: **III.1a** (1.0 equiv.), PPh_3 (1.0 equiv.), $Pd(OAc)_2$ (30 mol%), 24 h at 35 °C, air.
[b] All yields reported in this study are isolated and represented an average of three experiments.

The reaction carried out in MeCN at 55 °C increased the yield of **III.3a** to 24%; however, undesired compounds **III.4a** and **III.5a** were formed in 41 and 15%, respectively (entry 8 in Table III.1). Similarly, using toluene at reflux provided **3a** in 17% yield while compounds **III.4** and **III.5** were isolated in 6 and 33%, respectively (entry 6).

As expected, the phenyl group transfer from PPh_3 to 8-quinolineboronic acid was highly dependent on the amounts of $Pd(OAc)_2$ used (Table III.2, entries 1, 2, 4 and 5). Other Pd sources were also tested in the reaction. The utilization of $PdCl_2(MeCN)_2$ in MeCN provided no desired product. When $Pd(PPh_3)_4$ was used as a palladium source in MeCN, compound **III.3a** was isolated in 8–10% even without free PPh_3 (entries 10 and 11). The same two reactions carried out in MeCN with H_2O (4:1) did not give **III.3a** at all. Attempts to replace $Pd(OAc)_2$ with $Pd_2(dba)_3$ were unsuccessful under all conditions tested (e.g., entries 8 and 9).

Table III.2. The use of different Pd salts in the reaction of boronic acid **III.1a** with PPh_3 in abs. MeCN (35 °C, 24 h).

Entry	Pd salt	Mol of Pd%	Additive	Yield (%) of **III.3a**
1	$Pd(OAc)_2$	0.1	none	5
2	$Pd(OAc)_2$	0.3	none	19
3	$Pd(OAc)_2$	0.3	NaOAc [a]	27
4	$Pd(OAc)_2$	0.5	none	26
5	$Pd(OAc)_2$	0.75	none	43
6	$PdCl_2(MeCN)_2$	0.3	none	0
7	$PdCl_2(MeCN)_2$	0.3	NaOAc [a]	0
8	$Pd_2(dba)_3$	0.3	NaOAc [a]	0
9	$Pd_2(dba)_3$	0.3	none	0
10	$Pd(PPh_3)_4$	0.3	none	8
11	$Pd(PPh_3)_4$ [b]	0.3	none	10
12	$Pd(PPh_3)_4$	0.3	NaOAc [a]	traces

[a] 2 equiv. of NaOAc was used.
[b] The reaction was carried out without free PPh_3.

In some of the experiments (e.g., entries 2, 4, 6 and 8 in Table 1), a tiny amount of biphenyl (**III.6a**) was isolated, suggesting that two phenyl groups from PPh_3 can be attached to the Pd in some of the intermediates of the reaction. Based on this observation, we attempted to improve the yield of **III.3a** by keeping the phosphine quantities constant and varying the amounts of boronic acid **III.1a**. An increase in molar equivalents of **III.1a** (1.5, 2 and 5) in the reaction did not improve the yield of **III.3a,** suggesting that the aryl group transfer from $ArB(OH)_2$ to Pd is not the rate-limiting step under the conditions used.

In an attempt to improve the yield of compound **III.3a**, several additives were tested using a 1:1 ratio of PPh_3 and $ArB(OH)_2$ and 0.3 mol% of $Pd(OAc)_2$ in MeCN at 35 °C (Table III.3). The addition of 2 molar equiv. of NaOAc increased the yield of **III.3a** from 19 to 24% (entry 1). When the same reaction was carried out at 65 °C, 34% of the self-coupling product **III.4a** was isolated (entry 2), while only 4% of this compound was formed at 35 °C. Other additives such as $Cu(OAc)_2 \cdot H_2O$, $Cu(OAc)_2$,[11] trimethylamine-*N*-

oxide,[24] and AgOAc,[8,9] which were used in related reactions, inhibited the formation of compound **III.3a**.

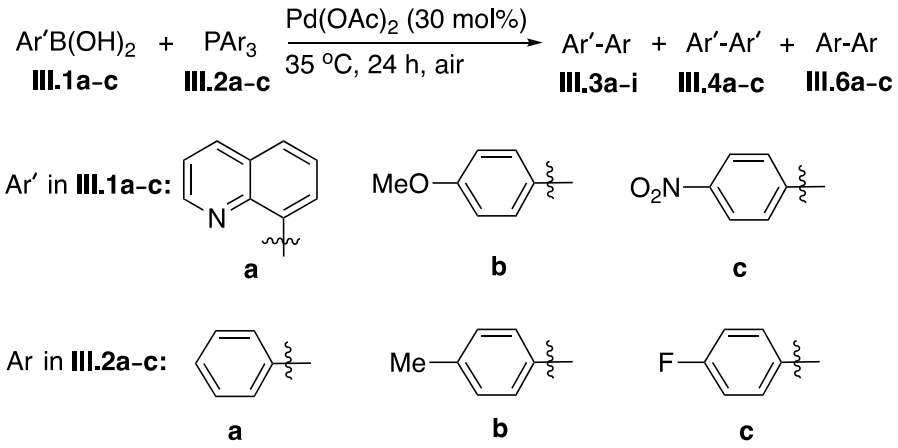
Table III.3. Effect of additives on the yield of compounds **III.3a–III.6a**.

Entry	Additive	Mol.equiv. of additive	Solvent	Temp. (°C)	Yield (%)			
					III.3a	**III.4a**	**III.5a**	**III.6a**
1	NaOAc	2.0	MeCN	35	24	4	0	0
2	NaOAc	2.0	MeCN-H_2O (4:1)	35	31	13	0	0
3	NaOAc	2.0	MeCN	65	22	34	4	0
4	NaOAc	2.0	Acetone	35	21	10	0	0
5	AcOH	2.0	MeCN	35	18	4	traces	0
6	$Cu(OAc)_2 \cdot H_2O$	2.0	MeCN	35	17	8	0	0
7	$Cu(OAc)_2$	2.0	MeCN	35	13	3	5	0
8	Me_3NO	3.0	MeCN	35	0	0	0	0
9	Me_3NO TBAF	3.0 2.0	1,4-dioxane	100	13	27	31	11
10	AgOAc TFA	6.0 2.0	NMP	120	10	62	6	15

The influence of electron-withdrawing and electron-donating groups in both PAr_3 and $Ar'B(OH)_2$ on the aryl transfer was studied using three phosphines, **III.2a**–**c** [Ar = *p*-MeC_6H_4 (**b**) and *p*-FC_6H_4 (**c**)] and three arylboronic acids, **III.1a**–**c** [Ar' = *p*-$MeOC_6H_4$ (**b**) and *p*-$NO_2C_6H_4$ (**c**)]. Three different reaction conditions were used: (*i*) abs. MeCN, (*ii*) abs. MeCN with 2 equiv. of NaOAc, and (*iii*) a 4:1 mixture of MeCN-H_2O with 2 equiv. of NaOAc (Table III.4). The obtained data for all three reaction conditions suggest a prominent electronic effect in the studied transformation. As a rule, the use of $Ar'B(OH)_2$ and PAr_3 with an electron-withdrawing substituent either on the Ar' or Ar group resulted in higher yields of products of type **III.3**. For example, the highest yield, 62%, of the aryl-group transfer product **III.3i** was obtained when *p*-$NO_2C_6H_4B(OH)_2$ and $(p\text{-}FC_6H_4)_3P$ were

used (entry 9). In contrast, boronic acids and phosphines with electron-donation groups provided lower yields of Ar'-Ar (e.g., entry 5).

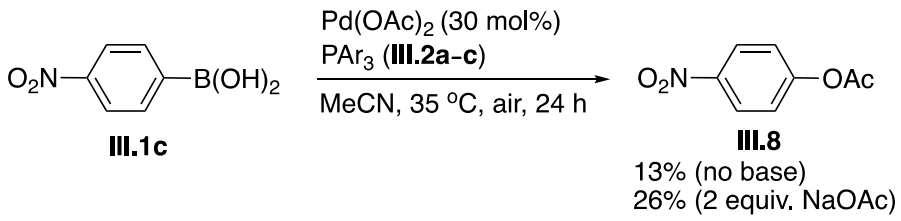
Table III.4. Electronic effect on the aryl transfer



Entry	Ar'	Ar	Yield (%) of **III.3a–i**		Yield (%) of **III.4a–c**[b]		Yield (%) of **III.6a–c**[b]	
1	**III.1a**	**III.2a**	**III.3a**	19 (24) [31][a]	**III.4a**	0 (4) [13]	**III.6a**	traces (0) [0]
2	**III.1a**	**III.2b**	**III.3b**	20 (29) [0]	**III.4a**	0 (traces) [0]	**III.6b**	6 (0) [0]
3	**III.1a**	**III.2c**	**III.3c**	27 (24) [38]	**III.4a**	0 (0) [0]	**III.6c**	0 (0) [0]
4	**III.1b**	**III.2a**	**III.3d**	18 (15) [37]	**III.4b**	14 (22) [21]	**III.6a**	68 (24) [21]
5	**III.1b**	**III.2b**	**III.3e**	8 (10) [12]	**III.4b**	21 (16) [30]	**III.6b**	48 (70) [35]
6	**III.1b**	**III.2c**	**III.3f**	22 (26) [54]	**III.4b**	10 (18) [20]	**III.6c**	39 (35) [27]
7	**III.1c**	**III.2a**	**III.3g**	23 (31) [44]	**III.4c**	8 (29) [40]	**III.6a**	52 (30) [traces]
8	**III.1c**	**III.2b**	**III.3h**	23 (21) [13]	**III.4c**	14 (53) [60]	**III.6b**	33 (48) [30]
9	**III.1c**	**III.2c**	**III.3i**	37 (49) [62]	**III.4c**	10 (35) [54]	**III.6c**	41 (50) [21]

[a] The first yield number for all compounds represents the data for the reactions in abs. MeCN; the numbers in parentheses are given for the experiments in abs. MeCN using 2 molar equiv. of NaOAc; the numbers in brackets are the yields in the reactions in a 4:1 mixture of MeCN-H_2O with 2 equiv. of NaOAc.
[b] Yields of products **III.4** and **III.6** are calculated by considering that 2 moles of the boronic acid produce 1 mole of **III.4** and 2 moles of PAr_3 produce 1 mole of **III.6**.

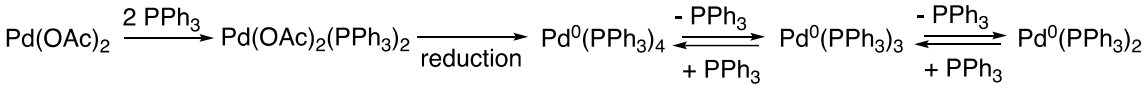
Interestingly, in addition to products of type **III.3**–**III.6**, an unexpected compound, 4-nitrophenyl acetate (**III.8**), was isolated in 13% yield in the reactions of 4-nitrophenylboronic acid **III.1c**, regardless of PAr_3 used (Scheme III.6). The yield of this compound was increased to 26% when the reaction was performed in the presence of NaOAc (2.0 equiv.). The aryl acetate formation was not observed in the experiments carried out using arylboronic acids **III.1a,b**. Product **III.8** was not detected in the reactions without PAr_3, suggesting the involvement of Pd(0) intermediates in this process.



Scheme III.6. The acetylated product formed in the reaction of 4-nitrophenylboronic acid.

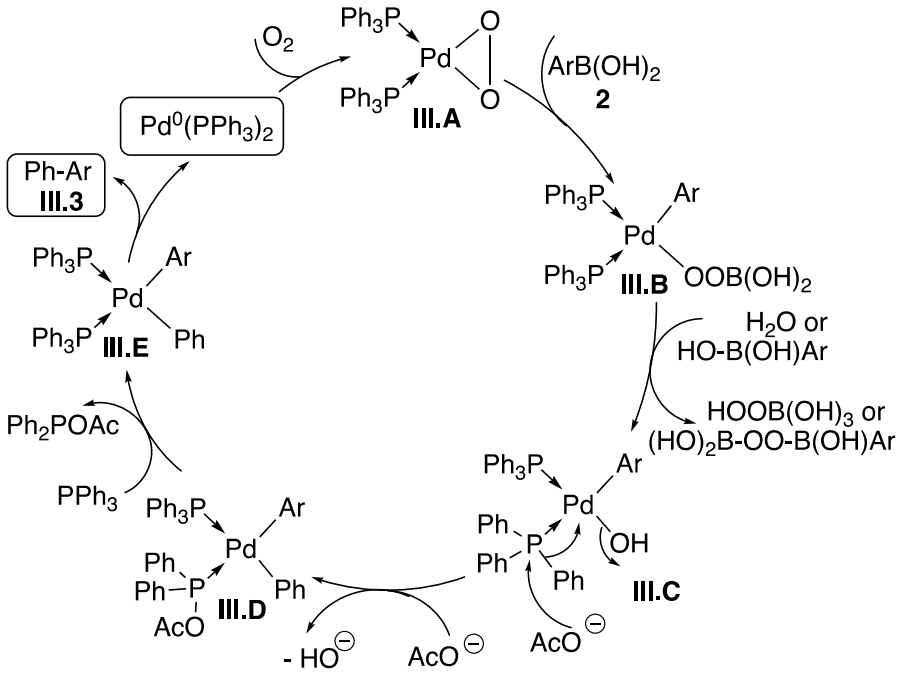
III.3. Mechanism Hypothesis

A plausible mechanism of the Ar group transfer is expected to include the addition of oxygen to Pd because the aryl group transfer from PAr_3 does not occur in the argon atmosphere. There are reported transformations when oxygen oxidizes Pd(0) to Pd(II). At the same time, Pd(II) oxidation to Pd(IV) species by O_2 is unlikely.[25] Also, the reaction of boronic acid with PPh_3 in the presence of 30% $Pd(MeCN)_2Cl_2$ in the air did not provide expected products **III.3**–**III.6**. Therefore, it is reasonable to propose that oxygen reacts with a Pd(0) species and, therefore, the reaction starts with the conversion of $Pd(OAc)_2$ to $Pd(PPh_3)_n$ in the presence of PPh_3 (Scheme III.7).[26] Most likely, the active species to start the next step of the transformation is $Pd(PPh_3)_2$.



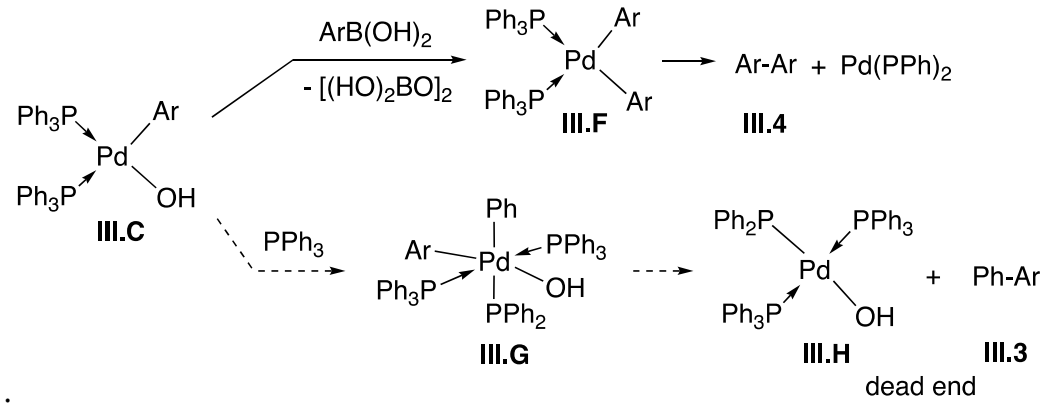
Scheme III.7. Reduction of $Pd(OAc)_2$ by PPh_3 as reported by Amatore et al.[26]

$Pd(PPh_3)_2$ is oxidized by oxygen in the air to give $Pd(PPh_3)_2O_2$ (**A**, Scheme III.8) as reported by Adamo et al.[27] It appears that this step is the only one that includes a single electron transfer. When the $Pd(OAc)_2$-catalyzed reaction of boronic acid **III.1a** with PPh_3 was carried out in the presence of TEMPO, the yield of **III.3a** was 9%. No TEMPO-derived products were isolated. It strongly suggests that boronic acids and PPh_3 do not participate in single-electron steps during the Ph-group transfer.



Scheme III.8. A proposed catalytic cycle of the Ph-group transfer in the presence of acetate ion.

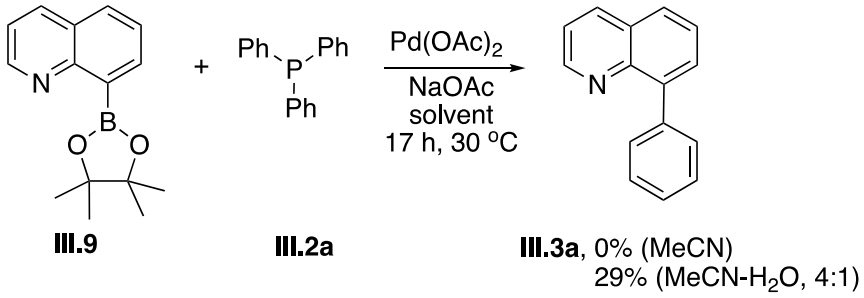
Adamo et al. thoroughly investigated the reaction of complex **III.A** with $ArB(OH)_2$.[27] They postulated the formation of complex **III.B** as the next intermediate (Scheme III.8). According to that study, complex **III.B** can react with the second equivalent of an aryl boronic acid to furnish intermediate **III.C**. The same group[27] ascertained that this species forms $(PPh_3)_2PdAr_2$ (**III.F**, Scheme III.9) in the presence of an additional equivalent of $ArB(OH)_2$. In its turn, $(PPh_3)_2PdAr_2$ can provide the self-coupling products of type **III.4**, Ar-Ar.



Scheme III.9. The formation of the self-coupling product **III.4** and the structure of the ostensible intermediate **III.G**.

To yield the Ph-group transfer products **III.3**, a key intermediate must have both the Ar group from $ArB(OH)_2$ and the Ph ligand from PPh_3. The oxidative addition of PPh_3 to intermediate **III.C** affording a Pd(IV) species (**III.G**, Scheme III.9) is unlikely. In addition, the reductive elimination step to get product **III.3** from the Pd(IV) intermediate **III.G** would be terminal and cannot be a part of a catalytic cycle. The results of the experiments using $Ar'B(OH)_2$, PAr_3 and 30% of $Pd(OAc)_2$ (Table III.4) implies that a catalytic cycle is involved in the formation of Ar'-Ar (**III.3**) since this type of product was isolated in some of the reactions in the yields greater than 30%. (The highest yield of **III.3i** was 62%, entry 9).

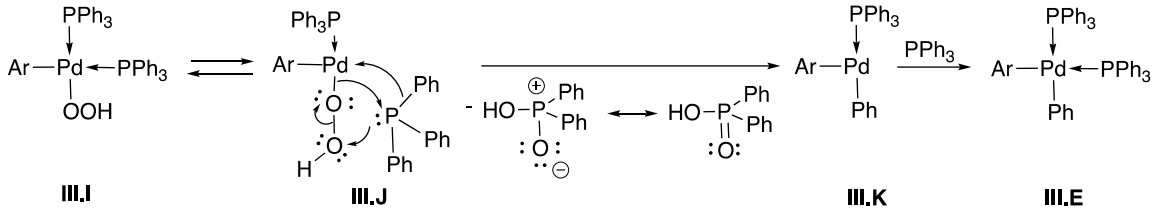
We would also like to stress that the transformation of intermediate **III.B** to **III.C** requires the presence of a Brønsted-Lowry acid, i.e., $ArB(OH)_2$ [pK_a 8.83 for $PhB(OH)_2$] or water. The necessity of a proton donor in the product **III.3** formation is supported by the results of two experiments shown in Scheme III.10. In the reaction of boronic ester **III.9** with PPh_3 in the presence of 30% $Pd(OAc)_2$, compound **III.3** was obtained in 29% yield when the solvent contained water. No compound **III.3** was formed in the reaction carried out in abs. MeCN.



Scheme III.10. The reaction of boronic ester **III.9** with PPh_3.

According to Ma and Lu[7] acetate ion is capable of nucleophilic attack at the PPh_3 ligand coordinated to Pd. If so, complex **III.C** can be converted to the putative intermediate **III.D**, which is expected to form **III.E** (Scheme 8). The final reductive elimination step affords Ph-Ar (**III.3**) and $Pd(PPh_3)_2$ to complete the catalytic cycle. The possible involvement of acetate ion in the catalytic cycle of the Ph-Ar formation is supported by a yield increase for products **III.3a,b,f,g,i** in the experiments with $Pd(OAc)_2$ and 2 equivalents of NaOAc.

The mechanism depicted in Scheme III.8 can be operational only in the presence of acetate ions. It cannot explain the formation of compounds of type **III.3** in the reactions with $Pd(PPh_3)_4$ without NaOAc (Table III.2, entries 10 and 11). We hypothesize that complex **III.B** reacts with a Brønsted-Lowry acid, i.e., $ArB(OH)_2$ or water, to afford not only intermediate **III.C** but also the critical hydroperoxo complex **III.I** (Scheme III.11). Oxidation of PPh_3 by the Pd(II) hydroperoxide is expected to form intermediate **III.E** necessary for the effective catalytic cycle producing product **III.3**.



Scheme III.11. A plausible formation of intermediate **III.E** from the proposed hydroperoxo complex **III.I.**

As shown above, 4-nitrophenylboronic acid **III.1c** reacted with PAr_3 (**III.2a**–**c**) in the presence of 30% $Pd(OAc)_2$ with and without NaOAc to give 26 and 13% of 4-nitrophenyl acetate **III.8**, respectively (Scheme III.6). Ester **III.8** is likely formed as a result of reductive elimination from the intermediate $[(PAr_3)_2Pd(p\text{-}NO_2C_6H_4)(OAc)]$, which can be formed from **III.C** in the presence of excess acetate ions by replacing the OH ligand with OAc.

The mechanistic schemes presented in this study include only neutral mononuclear intermediates. However, we cannot exclude the existence of additional intermediates in the studied reactions, specifically cyclic Pd_3 clusters[28] binuclear *m*-AcO-Pd(II), or charged *k*-AcO-Pd(II) species. It appears that the mechanism of the studied reactions is multifarious, and the treatment of arylboronic acids with PAr_3 in the presence of $Pd(OAc)_2$ can give various products depending on the conditions used and the nature of aryl groups in the reagents.

III.4. Conclusions

The formation of an $(sp^2)C–(sp^2)C$ bond was achieved in the reactions of arylboronic acids with triarylphosphines using $Pd(OAc)_2$ or $Pd(PPh_3)_4$ with or without NaOAc. However, the overall yield of the desired products of type **III.3** was rather low and did not exceed 37% for the model reaction of 8-quinolineboronic acid **III.1a** with PPh_3.

Our study suggests that oxygen plays a vital role in the aryl group transfer from PAr_3 to $RB(OH)_2$. Bronsted-Lowry acids, e.g., H_2O or $ArB(OH)_2$ instead of the corresponding ester, are necessary to produce **III.3**. These compounds were formed in acetone and MeCN (with or without H_2O) at 20–35 ^oC practically as single products, while at higher temperatures, the self-coupling compounds **III.4** became major products. In many reactions, the addition of NaOAc increased the yield of **III.3**. Electron-withdrawing groups in both $ArB(OH)_2$ and PAr_3 further enhanced the production of **III.3**. Finally, the unusual transfer of the acetate group from $Pd(OAc)_2$ to *p*-nitrophenylboronic acid was discovered.

The researchers performing Suzuki reactions and wishing to avoid the formation of type **III.3** compounds as side products are recommended to carry out reactions using boronic esters instead of $ArB(OH)_2$ and in the absence of water or do purification as soon as possible after completing the reaction as the exposure of the reaction mixture to the air may facilitate the aryl group transfer from PPh_3 to unreacted boronic acid. The use of $ArB(OH)_2$ and PAr_3 with electron-donating substituents on both aryl groups is expected to minimize the formation of side product **III.3** in Suzuki reactions.

III.5. Experimental

III.5.1 General Methods and Instrumentation

Reactions under an argon atmosphere were carried out using Schlenk techniques. Purifications by column chromatography were completed using Natland silica gel 60 (230 mesh). Preparative thin-layer chromatography (TLC) was carried out using 200 × 250 mm glass plates with an unfixed layer of Natland or Merck silica gel 60 (230 mesh). Analytical TLC was performed on Whatman silica gel 60 (F_{254}) 250 μm precoated plates. Compounds were visualized on TLC plates using UV light (254 nm) and iodine stains. Routine ^{1}H (500 MHz) and $^{13}C\{^{1}H\}$ (126 MHz) spectra were recorded on a Bruker AVANCE 500 NMR spectrometer. Spectra of the products obtained were recorded in $CDCl_3$. Melting points were measured on a Laboratory Devices Mel-Temp apparatus and are uncorrected.

III.5.2. Materials

1,4-Dioxane was dried by refluxing over Na/benzophenone ketyl and distilled under Ar. Acetone and acetonitrile of the HPLC grade and anhydrous DMF and DMSO were used as purchased from MilliporeSigma. Other solvents were distilled over CaH_2.

Boronic acids (98 % purity, Combi-Blocks) and PAr_3 (Ar = *p*-Tol and *p*-FC_6H_4) were used without additional purification. PPh_3 (MilliporeSigma) was recrystallized from ethanol/water. $Pd(OAc)_2$ (98 % purity, Strem Chemicals), $Pd(PPh_3)_4$ (99 % purity, MilliporeSigma), $PdCl_2(MeCN)_2$ (99%, Aldrich Chem Co.), $Pd_2(dba)_3$ (97%, Aldrich Chem Co.) were used as purchased.

III.5.3 Typical Procedure

A solution of aryl boronic acid (1 molar equiv.) and PAr_3 (1 molar equiv.) in acetonitrile (8.0 mL per 0.38 mmol of $RB(OH)_2$) was placed in a Schlenk flask. Then $Pd(OAc)_2$ (0.3 molar equiv.) was added. The reaction mixture was stirred at 35 °C for 24 h. The reaction progress was monitored by TLC (1:4 EtOAc-hexanes). The reaction mixture was filtered through celite to remove insoluble materials, celite was washed with dichloromethane. The filtrate was concentrated under reduced pressure. The resulting residue was dissolved in MeOH-CH_2Cl_2 (1:20) and loaded on to preparative TLC plate. A 3:7 mixture of EtOAc-hexanes was used as an eluent for the purification unless otherwise mentioned.

III.5.4. Procedure for the Reaction on SiO_2

Triphenylphosphine and **III.1a** were dissolved in *i*-PrOH at 40–45 °C. Then SiO_2 (2.0 g per 0.38 mmol of PPh_3, 60 Å, 40–75 μm) was added to the solution. In a separate flask, $Pd(OAc)_2$ was mixed with SiO_2 (0.350 g per 0.114 mmol of $Pd(OAc)_2$) and MeCN (2.0 mL). The solvents were evaporated from each mixture, and the resulting powders were combined in one flask. The mixture was stirred at 35 °C for 24 h. Then the reaction mixture was transferred to a fritted glass filter and washed with CH_2Cl_2. The crude product was purified using preparative TLC (3:7 EtOAc-hexanes).

III.5.5. Compounds Obtained in the Study

8-Phenylquinoline (**III.3a**). The compound was obtained as a pale-yellow oil in 19% yield in the reaction using the typical procedure. R_f 0.61 (1:4 EtOAc-hexanes). ^{1}H and ^{13}C NMR spectra of the isolated compound matched those reported previously.[29,30]

8-(4-Methylphenyl)quinoline (III.3b). The compound was obtained as a pale-yellow oil in 20% yield in the reaction using the typical procedure described above. R_f 0.65 (1:4 EtOAc-hexanes). ^{1}H and ^{13}C{^{1}H} NMR spectral data of the isolated compound were identical to those reported previously.[29]

8-(4-Fluorophenyl)quinoline (III.3c). The compound was isolated as an off-white solid in 27% yield using the typical procedure described above. M.p. 85.5–87 °C. R_f 0.50 (1:4 EtOAc-hexanes). ^{1}H and ^{13}C{^{1}H} NMR spectra of the isolated compound matched those reported previously.[29]

4-Methoxy-1,1'-biphenyl (III.3d). The compound was obtained as an off-white solid in 18% yield in the reaction using the typical procedure described above. A 1:9 mixture of EtOAc-hexanes was used as an eluent for the purification. M.p. 85–86 °C. R_f 0.44 (1:9 EtOAc-hexanes). ^{1}H and ^{13}C{^{1}H} NMR spectral data of the isolated compound were identical to those reported previously.[31,32]

4-Methoxy-4'-methyl-1,1'-biphenyl (III.3e). The compound was obtained as an off-white solid in 8% yield in the reaction using the typical procedure described above. A 1:9 mixture of EtOAc-hexanes was used as an eluent for the purification. M.p. 106–108 °C. R_f 0.37 (1:9 EtOAc-hexanes). ^{1}H and ^{13}C{^{1}H} NMR spectra of the isolated compound matched those reported previously.[31]

4-Fluoro-4'-methoxy-1,1'-biphenyl (III.3f). The compound was prepared as an off-white solid in 22% yield in the reaction using the typical procedure described above. A 1:9 mixture of EtOAc-hexanes was used as an eluent for the purification. M.p. 89.2–91.1°C. R_f 0.33 (1:9 EtOAc-hexanes). ^{1}H and ^{13}C{^{1}H} NMR spectral data of the isolated compound were identical to those reported previously.[32]

4-Nitro-1,1'-biphenyl (III.3g). The compound was isolated as an off-white solid in 23% yield in the reaction using the typical procedure described above. A 1:9 mixture of EtOAc-hexanes (1:9) was used as an eluent for the purification. M.p. 113–114°C. R_f 0.51 (1:9 EtOAc-hexanes). ^{1}H and ^{13}C{^{1}H} NMR spectra of the isolated compound matched those reported previously.[31]

4-Methyl-4'-nitro-1,1'-biphenyl (III.3h). The compound was obtained as a pale yellow fluffy solid in 23% yield in the reaction using the typical procedure described above. A 1:9 mixture of EtOAc-hexanes (1:9) was used as an eluent for the purification. M.p. 136–138 °C. R_f 0.54 (1:9 EtOAc-hexanes). ^{1}H and ^{13}C{^{1}H} NMR spectral data of the isolated compound were identical to those reported previously.[33]

4-Fluoro-4'-nitro-1,1'-biphenyl (III.3i). The compound was isolated as a pale-yellow crystalline solid in 37% yield in the reaction using the typical procedure described above. A 1:9 mixture of EtOAc-hexanes was used as an eluent for the purification. M.p. 124–125 °C. R_f 0.46 (1:9 EtOAc-hexanes). ^{1}H and ^{13}C{^{1}H} NMR spectra of the isolated compound matched those reported previously.[34]

4,4'-Dimethoxy-1,1'-biphenyl (III.4b). The compound was isolated as an off-white solid. R_f 0.61 (1:9 EtOAc-hexanes). ^{1}H and ^{13}C{^{1}H} NMR spectral data of the isolated compound were identical to those reported previously.[35]

4,4'-Dinitro-1,1'-biphenyl (III.4c). The compound was isolated as a pale-yellow solid. R_f 0.47 (1:4 EtOAc-hexanes). ^{1}H and ^{13}C{^{1}H} NMR spectra of the isolated compound matched those reported previously.[35]

Biphenyl (III.6a). The compound was isolated as an off-white solid. M.p. 68–69 °C. R_f 0.49 (hexanes). ^{1}H and ^{13}C{^{1}H} NMR spectral data of the isolated compound were identical to those reported previously.[35]

4,4'-Dimethy-1,1'-biphenyl (III.6b). The compound was isolated as an off-white solid. M.p. 86–88 °C. R_f 0.41 (hexanes). ^{1}H and ^{13}C{^{1}H} NMR spectra of the isolated compound matched those reported previously.[35]

4,4'-Difluoro-1,1'-biphenyl (III.6c). The compound was isolated as an off-white solid. M.p. 114–116 °C. R_f 0.38 (hexanes). ^{1}H and ^{13}C{^{1}H} NMR spectral data of the isolated compound were identical to those reported previously.[35]

4-Nitrophenyl acetate (III.8). The compound was obtained as a pale-yellow solid in 13% yield in the reaction using the typical procedure described above. A 1:9 mixture of EtOAc-hexanes was used as an eluent for the purification. ^{1}H and ^{13}C{^{1}H} NMR spectra of the isolated compound matched those reported previously.[36]

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