2007

Studies Toward Improving the Reactivity and Chemoselectivity of Chloroarenes in Palladium-Catalyzed Cross-Coupling Processes

Joseph P. Simeone
Seton Hall University

STUDIES TOWARD IMPROVING THE REACTIVITY AND CHEMOSELECTIVITY OF CHLOROARENES IN PALLADIUM-CATALYZED CROSS-COUPLING PROCESSES

by

Joseph P. Simeone

Ph.D. DISSERTATION

Submitted in partial fulfillment of the requirements

for the degree of Doctor of Philosophy

in the Department of Chemistry and Biochemistry of

Seton Hall University

August 2007

South Orange, New Jersey

We certify that we have read this thesis and that in our opinion it is sufficient in scientific scope and quality as a dissertation for the degree of Doctor of Philosophy

APPROVED

John R. Sowa, Jr., Ph.D.

Mentor, Seton Hall University

Cecilia Marzabadi, Ph.D.

Member of Dissertation Committee, Seton Hall University

W. Rorer Murphy, Ph.D.

Member of Dissertation Committee, Seton Hall University

Nicholas H. Snow, Ph.D.

Chairperson, Department of Chemistry and Biochemistry, Seton Hall University

To Christine,

because she believes in me.

Life is like riding a bicycle.

To keep your balance you must keep moving.

-Albert Einstein

STUDIES TOWARD IMPROVING THE REACTIVITY AND CHEMOSELECTIVITY OF CHLOROARENES IN PALLADIUM-CATALYZED CROSS-COUPLING PROCESSES

Abstract

Palladium-catalyzed cross-coupling reactions are a powerful tool for the practicing organic chemist. It is a rare occurrence to find an issue of the current organic synthesis literature which does not contain several articles related to this ever expanding field. Recently, much attention has been paid to developing methodology for the use of chloroarenes as substrates for these processes. These efforts are certainly worthwhile when one considers that chloroarenes are easier to obtain and considerably less expensive than other commonly used substrates. However, this task is not without its challenges, due to the inert nature of the carbon-chlorine bond.

We have succeeded in developing a technique which utilizes Pd/C as a precatalyst in combination with a phosphine ligand for the Suzuki cross-coupling reaction. We are the first to demonstrate the broad scope of this process by reacting a variety of chloroarenes and aryl boronic acids which are difficult to couple under ligandless Pd/C conditions. In doing so, we obtain product yields of 30-91% in comparison to the 0-36% yields obtained with Pd/C in the absence of ligand.

We show through catalyst recycling studies that the Pd/C precatalyst can be reused up to four times without any significant loss in efficiency. Analysis of residual palladium levels of several products result in a range from 9 to 30 ppm. Filtration and split tests reveal that product formation continues after the removal of the solid Pd/C from the reaction mixture. Through the use of a combination mercury poisoning and

filtration test we conclude that the reaction is catalyzed by a soluble zero valent molecular palladium species

By instituting an incubation period for the Pd/C precatalyst before the addition of the ligand we are able to significantly reduce the ligand loading. Analysis of soluble palladium levels of a product prepared in this manner result in < 5 ppm palladium. This method is shown to superior to those which use traditional homogeneous precatalysts for the preparation of three biphenyl products. A catalytic cycle is proposed in which ligand free and ligand assisted pathways combine to give practical yields of coupling products but also result in low levels of Pd contamination.

The palladium-catalyzed amination reaction is used to prepare the quinolone antibacterial Norfloxacin from the fluorochloroarene precursor. Selective substitution at the chlorine atom is achieved. This method is shown to have practical advantages over the current methodology for the preparation of these compounds.

The palladium-catalyzed cyanation of bromo and chloroarenes is performed in the presence of tri-*t*-butylphosphine tetrafluoroborate salt. Preliminary results show the complete conversion of bromobenzene at 80 °C in two hours. The rationale behind the preparation of a novel azaphosphine ligand based on a non-biaryl atropisomeric backbone is discussed along with the progress achieved toward that end.

Acknowledgements

My pursuit of the PhD. degree in chemistry began long before I first walked onto the campus at Seton Hall. I will forever be indebted to those who have supported me through the years in this endeavor. It is with great appreciation that I offer my gratitude to all.

To my Dad, Christopher Simeone for opening the door to science and nature and giving me the chance to walk through. To my Mom, Mary Simeone, who laid the foundation for my education that I continue to build upon today. To my Nana, Lucy Trotta, the first best friend I ever had.

To John Javadi for introducing organic chemistry to me with his unique teaching style that still makes me laugh to this day.

To Dr. Brian Humphrey for his invaluable lessons both in the classroom and on the basketball court.

To Dr. Jack Isidor for being the first chemist to let me get my feet wet in the lab.

To Dr. Paul Anderson who first tried to convince me to go to graduate school; even though I wouldn't listen.

To Merck and Co., Inc. for the financial support during my graduate school tenure and to all the brilliant people I've had the honor to work with. To Bob Bugianesi for being an excellent mentor and an even better friend. To my colleagues in the Labeled Compound Synthesis group; Dr. Matthew Braun, Dr. Eric Soli, Dr. Dennis Dean, and Dr. Dave Melillo for giving a medicinal chemist a chance.

To my advisor, Dr. John Sowa for his guidance and direction. I am grateful for the opportunity to have worked in a laboratory where innovation is applauded and no idea is a bad idea.

To the members of my Dissertation Committee; Dr. Rorer Murphy, Dr. Cecilia Marzabadi, and Dr. Nicholas Snow.

To my oldest son, Nicholas Simeone who is always willing to talk science with me. To my youngest son, Luke Simeone for thinking I'm a genius. To my daughter, Lucy Rose Simeone for not crying at night when I was writing this dissertation.

Finally, I thank my wife, Christine Simeone for her unwavering support. Thank you for putting up with the indecision, the expenses, and the endless late nights that plagued me through the years. Without you none of this would have been possible.

Table of Contents

List of Figures

List of Tables

Abbreviations

Ar	aryl group
BINAP	2.2'-Bis(diphenylphosphino)-1,1'-binapthalene
cod	cyclooctadiene
Cy	cyclohexyl
dba	dibenzylideneacetone
DMA	dimethylacetamide
DME	dimethoxyethane
DMF	N,N-dimethylformamide
dppp	diphenylphosphino propane
Et_3N	triethylamine
ICP	Inductively Coupled Plasma
IPA	isopropyl alcohol
NHC	*N*-heterocyclic carbene
9-BBN	9-Borobicyclo[3.3.1]nonane
NMP	1-Methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
OAc	acetate
OTf	triflate
OTs	tosylate
PEG	polyethylene glycol
PTC	phase transfer catalyst
S_E2	bimolecular electrophilic substitution
S_NAr	nucleophilic aromatic substitution
S_N2	bimolecular nucleophilic substitution
TBAB	tetrabutylammonium bromide
TPPh	2,3,4,5-tetraphenylphenyl

Introduction and Rationale

Palladium-catalyzed cross-couplings involving aryl and vinyl halides and pseudohalides as substrates are processes that have been widely studied and extensively developed.[1] Reactions with main group organometallics, which take place via oxidative addition-transmetallation-reductive elimination catalytic cycles result in products with new carbon-carbon bonds. Reactions with amines and alcohols, which occur via oxidative addition-*in situ* deprotonation-reductive elimination pathways, result in carbon-heteroatom bonds.[2] One such example of the remarkable utility of these synthetic methods is the subject of a recent literature review by K.C. Nicolaou[3] of their applicability to the field of total synthesis. Advances in the design of new catalysts have even led to the ability to cross-couple otherwise unreactive substrates such as alkyl halides.[4]

Despite the widespread use and the recent technological advances in the field of palladium-catalyzed cross-couplings, there remains significant opportunity for improvement in certain key areas. One important research topic which has garnished a great deal of attention in recent years is the use of chloroarenes as substrates.[5] What is attractive about their potential use as coupling partners is their low cost and wide availability. In addition, their presence is tolerated by a wide variety of functional groups. However, it is their inert nature which accounts for the fact that they are far less reactive in cross-couplings than other organohalides. Through a series of unique research

---

[1] *Organometallics in Synthesis: A Manual*; (Ed.: M Schlosser) John Wiley & Sons Ltd., Chichester, **1994**.
[2] *Cross-Coupling Reactions: A Practical Guide*; (Ed.: N. Miyuara), Springer, Berlin, **2002** (Series Topics in Current Chemistry, No. 219), pp. 131-211.
[3] Nicolaou, K.C.; Bulger, P.G.; Sarlah, D. *Angew. Chemie. Int. Ed. Engl.* **2005**, *44*, 4442.
[4] Frisch, A.C.; Beller, M. *Angew. Chemie. Int. Ed. Engl.* **2005**, *44*, 674.
[5] Littke, A.F.; Fu, G.C. *Angew. Chemie. Int. Ed. Engl.* **2002**, *41*, 4176.

projects, this dissertation describes our efforts toward improving the scope and utility of chloroarenes in various palladium-catalyzed cross-couplings.

We begin with an examination of palladium on carbon and its utility as a precatalyst for the activation of chloroarenes in the Suzuki cross-coupling reaction with aryl boronic acids. An optimal catalyst and ligand system is described and a survey of different substrates is performed. The properties of this system are then examined through the use of catalyst recycling, filtration, and mercury poisoning tests. This work concludes with a description of methodology which allows for efficient catalysis at low ligand loadings and a proposed catalytic cycle for the process.

The next topic is a systematic study of fluorochloroarenes in the Buchwald-Hartwig palladium-catalyzed amination reaction. A chemoselective synthesis of the quinolone antibacterial Norfloxacin is described using this methodology. The advantages over the current protocol are described along with the potential for additional analog synthesis.

The final chapter describes two novel research topics aimed at activation of chloroarenes for palladium-catalyzed cross-couplings. The first is the application of a known catalyst and ligand system to the preparation of aryl nitriles. Finally, the synthesis of a new azaphosphine ligand is undertaken with a structure based on a non-biaryl atropisomeric backbone.

Review of the Suzuki Cross-Coupling Reaction with Challenging Substrates

The formation of a new bond between two carbon atoms is a fundamental process of synthetic organic chemistry. Over the last three decades the Suzuki-Miyuara cross-coupling reaction has become one of the most important and synthetically useful methods for achieving this transformation.[6] Since the seminal report in 1979[7], an extraordinary amount of effort has been spent in research laboratories around the world to broaden the scope and applicability of this process.

The Suzuki cross-coupling is the transition metal catalyzed reaction between an organic electrophile and a nucleophilic organoboron derivative. This method has several advantages over other metal catalyzed cross-couplings such as the Stille[8] or Kumada[9] reactions. Boronic derivatives are widely available, easy to handle, and exhibit high functional group tolerance. In addition, excellent reactivity and chemoselectivity has been achieved under mild reaction conditions with a wide range of substrates. In recent years, technological advances have allowed for the coupling of substrates which were previously unreactive or nonselective.

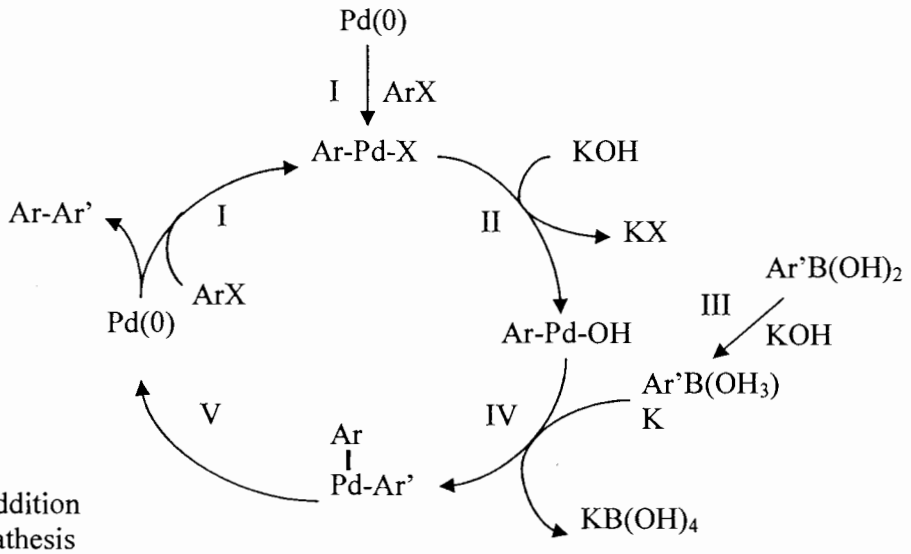
The following review will begin with an examination of the accepted catalytic cycle. As with any reaction, understanding the mechanism is critical to the identification of poorly reactive substrates or possible side products. This will be followed by a discussion of the byproducts which can form under Suzuki conditions. Finally, recent advances in catalyst and substrate design will be detailed.

---

[6] (a) Miyuara, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147. (c) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633. (d) Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* **2004**, *15*, 2419. (e) Dembitsky, V. M.; Abu Ali, H.; Srebnik, M; *Studies in Inorganic Chemistry* **2005**, *22*, 119. (f) Franzen R.; Xu Y. *Canadien Journal of Chemistry* **2005**, *83*, 266.
[7] Miyuara, N.; Yamada, K; Suzuki, A. *Tetrahedron Lett.* **1979**, *20*, 3437.
[8] For a review see: Stille, B.J. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508.
[9] For a review see: Kumada, M. *Pure Appl. Chem.* **1980**, *52*, 669.

The Suzuki Catalytic Cycle

Figure 1 depicts the typical Suzuki cross-coupling catalytic cycle for an aryl halide (X can be I, Br, or Cl) and an aryl boronic acid with potassium hydroxide as the base. The first step in the process is oxidative addition of the electrophile to a Pd(0) complex to form σ-aryl-Pd(II)X species. This may be a preformed catalyst ligand complex or one which is derived from a Pd(0) precatalyst in combination with a ligand. In addition, Pd(II) precatalysts can be reduced *in situ* to Pd(0) by added phosphine ligand[10] or boronic acid[11] present in the reaction mixture.



I Oxidative Addition
II Halide Metathesis
III Formation of Tetrahedral Complex
IV Transmetallation
V Reductive Elimination

Figure 1: The Catalytic Cycle of the Suzuki Cross-Coupling Reaction.

[10] Jutand, A.; Amatore, C.; M'Barki, M.A. *Organometallics* **1992**, *11*, 3009.
[11] Grossman, R.B. *The Art of Writing Reasonable Organic Reaction Mechanisms*; Springer: New York, 2003.

The base present in the reaction mixture can serve a dual role in the catalytic cycle. At a pH > pKa of the boronic acid, the boron atom is quarternized and the aryl boronic acid exists as a hydroxyboronate anion.[12] The coordination of a negatively charged base increases the nucleophilicity of the organic group so that transmetallation can occur via an S_E2(cyclic)transition state. In addition, the halide present in the σ-aryl-Pd(II)X species is readily displaced via ligand exchange by hydroxyl anion; resulting in the aryl-Pd(II)OH species. This accelerates transmetallation[13] due to the formation of stable B-O compounds and the high basicity of [M]-OR complexes. Transmetallation can occur in the absence of the halide metathesis but not in the absence of base. Reductive elimination from the diorganopalladium species yields the product and Pd(0) which reenters the catalytic cycle.

Substrate Properties Which Affect Oxidative Addition

Oxidative addition is a generic term used to describe the reaction of a transition metal with an electrophile resulting in an increase in the formal oxidation state of that metal. The process is favored in coordinatively unsaturated metals in low oxidation states. Such metals are relatively electron rich and nucleophilic. Any ligand which increases the electron density on the metal will increase the rate of oxidative addition. Conversely, the reverse is also true; electron withdrawing ligands will decrease the rate.

Oxidative addition at sp^2 carbons is generally thought to proceed through one of three different mechanisms,[14] two of which involve transition states possessing an ionic character. In the case of the electron transfer mechanism, the metal donates an electron

[12] Norrild, J.C.; Eggert, H. *J. Am. Chem. Soc.* **1995**, *117*, 1479.
[13] Nishikata, T.; Yasunori, Y.; Miyaura, N. *Organometallics* **2004**, *23*, 4317.

to ArX, initiating a series of steps resulting in the σ-aryl-Pd(II)X species (**1**). The nucleophilic aromatic substitution mechanism occurs via attack of the metal on the ipso carbon of the aromatic ring. This forms a transition state (**2**) with a net negative charge on the aromatic ring and a positive charge on X, which collapses to form the oxidative addition product. The third mechanism is concerted and involves either a two or three center neutral transition state (**3**).

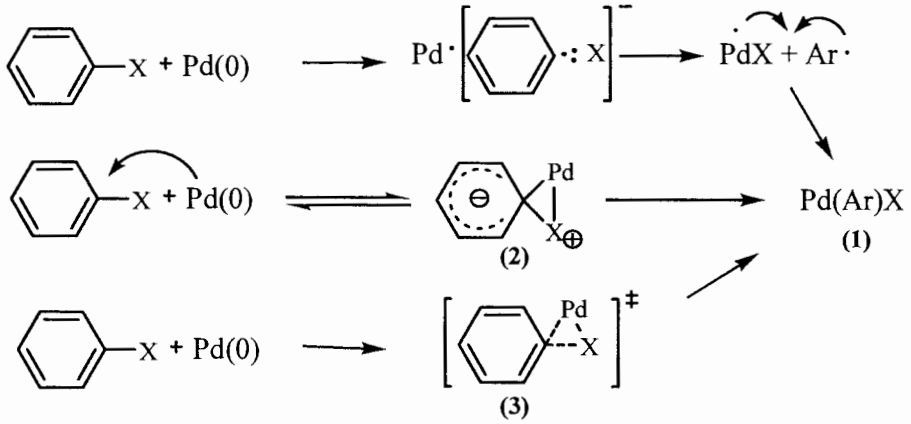


Figure 2: Oxidative Addition at sp^2 Carbon.

The type of mechanism by which oxidative addition at sp^3 carbons take place is strongly dependant upon the substrates involved. For primary and secondary organic halides and tosylates S_N2-like displacement is possible. Among the evidence to support this is the report of Puddephat[15] on the existence of cationic intermediates in the reaction between a d^8 platinum(II) complex with alkyl halides as detected by low temperature NMR spectroscopy. In addition, Stille[16] has reported the inversion of configuration at carbon during the oxidative addition of optically active benzyl-α-*d* chloride with

[14] Amatore, C.; Pflüger, F. *Organometallics* **1990**, *9*, 2276.
[15] Crespo, M.; Puddephatt, R. J. *Organometallics* **1987**, *6*, 2548.
[16] Lau, K. S. Y.; Wong, P. K.; Stille, J. K. *J. Am. Chem. Soc.* **1976**, *98*, 5832.

tetrakis(triphenylphosphine)palladium(0). For some secondary and all tertiary alkyl halides a competing radical chain process is operative.

The rate of oxidative addition is dependant upon the type of leaving group present on the electrophile. For aryl halides with palladium as the nucleophile, the order of reactivity is I > OTf ~ Br > > Cl and is consistent with the strength of the C-X bond.[17] For these substrates, there is experimental evidence to suggest that the mechanism of oxidative addition is nucleophilic aromatic substitution and that the rate limiting step is breakage of the carbon-halogen bond. Electron withdrawing substituents on the aromatic ring increase the overall rate constant by stabilizing the ionic intermediate **(2)** shown in Figure 2.[18] In contrast, electron donating substituents are destabilizing.

For most primary and secondary alkyl halides the rate of reactivity parallels that of aryl halides and is I > Br > OTs > Cl. This is consistent with leaving group ability in S_N2 type reactions, which is dependant upon the basicity of the anion and its ability to stabilize a negative charge. For tertiary alkyl halides which react by a radical type mechanism, the order of reactivity is the same and is related to R-X bond strength. Tosylates and other pseudohalides make very poor leaving groups in radical reactions of $C(sp^3)$ electrophiles.[19]

Electrophiles with chloride as the leaving group are by far the least reactive substrates for oxidative addition. In addition, alkyl halides and pseudohalides are less useful than their aryl counterparts due to a number of factors. From a kinetic standpoint, the rate of oxidative addition to $C(sp^3)$-X is slower than that to $C(sp^2)$-X. This has been

---

[17] Grushin, V.V.; Alper, H., *Chem. Rev.* **1994**, *94*, 1047.
[18] Fitton, P.; Rick, E.A. *J. Organomet. Chem.* **1971**, *28*, 287.
[19] Solomons, T.W.G. *Fundamentals of Organic Chemistry*; John Wiley & Sons, Inc.: New York, 1997; Ch 6, pp. 256-258

attributed to the increased stabilization of the transition state due to availability of the Ar-X π^* orbital for backbonding with the d orbitals of Pd.[20] Such an interaction is not possible with alkyl electrophiles which must rely solely on the interaction between the σ^* orbital and the metal for transition state stabilization.

Thermodynamically, there is a competing side reaction to oxidative addition for substrates which contain hydrogens on the carbon beta to the leaving group. For such compounds beta-hydride elimination is favored over oxidative addition, giving rise to the corresponding olefinic byproducts.

Substrate Properties Which Affect Transmetallation

Transmetallation (eq 1) is most often the rate limiting step in Suzuki cross-coupling reactions.

$$\text{R-M-X} + \text{R'-Y} \rightleftharpoons \text{R-M-R'} + \text{X-Y} \qquad \textbf{(1)}$$

M = transition metal
Y = Zn, Zr, B, Hg, Si, Sn, Ge

A slow transmetallation event will often be the cause of byproduct formation.[21] Among the factors which influence the rate of transmetallation are the electronics of the two coupling partners.

In a study of the mechanism of the Pd/C cross coupling of aryl bromides, Leblond[22] performed a Hammett study which revealed that the reaction rates increase for electron rich aryl boronic acids (ρ =-2.0) and increase slightly with electron poor aryl bromides. The author attributes this phenomenon to increased electronegativity of

[20] Ariafard, A.; Lin, Z. *Organometallics* **2006**, *25*, 4030.
[21] Hegedus, L. S. *Transition Metals in the Synthesis of Complex Organic Molecules;* University Science Books: California, 1994, Ch 4, pp. 87.

palladium in the σ-aryl-Pd(II)OH species when the aryl bromide is electron poor and increased electropositivity of the boron when the aryl boronic acid is electron rich. Nucleophilic transfer of the aryl group of the boronic acid is the rate limiting step in the proposed S_E2(cyclic) mechanism shown in Figure 3.

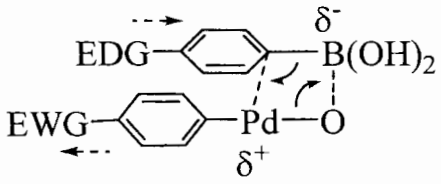
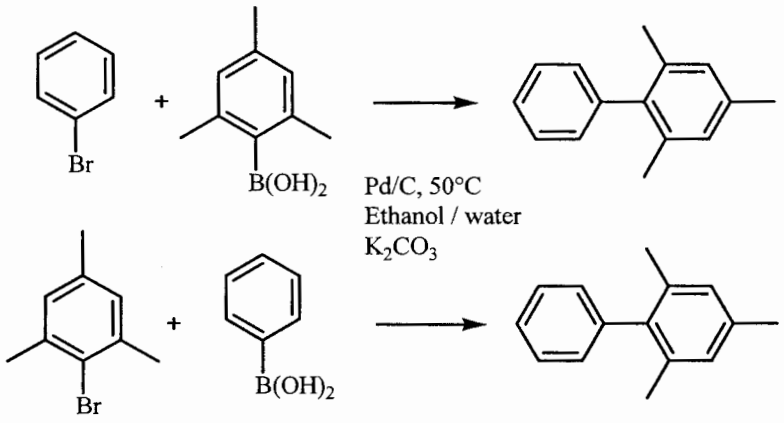


Figure 3. Proposed Mechanism of Transmetallation for Suzuki Cross-Coupling with Pd/C.

In the same study, the effect of steric hinderance on each substrate was also examined. The amount of product formation was compared for two separate aryl bromide and phenyl boronic acid pairs (eq 2).



(2)

The coupling conducted with mesitylbromide and phenylboronic acid resulted in twenty times higher product yield than that conducted with bromobenzene and mesitylboronic acid. Because of the fact that the electronic effects favor the pair that resulted in a lower yield, the author concluded that it is the steric factors which are most important. In

[22] LeBlond, C. *Scope and Mechanistic Studies of the Palladium on Carbon Catalyzed SuzukiCross Coupling Reaction;* PhD dissertation, Seton Hall University, 1994, pp 69-78.

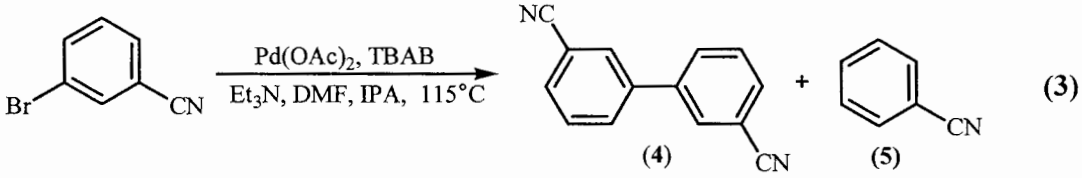
addition, because the boronic acid is most likely involved in the transmetallation step, the findings are consistent with this step being rate limiting.

Byproduct Formation under Suzuki Reaction Conditions

There are several byproducts which can form under the conditions in which the Suzuki coupling reaction is often run. The factors which influence the formation of these byproducts include not only the structural and electronic properties of the coupling partners but also the nature of the catalyst, solvent, and base. In addition the formation of certain byproducts is more facile in air or at higher temperatures.

Haloarene Homocoupling and Hydrodehalogenation

Lemaire[23] has shown that high yields of iodoarene and bromoarene homocoupling products **(4)** can form under conditions typically used for Suzuki couplings (eq 3).



(3)

The reaction also occurs in the absence of TBAB, albeit less efficiently. The role of the quarternary ammonium salt is not mentioned but it has been suggested elsewhere[24] that it may act to stabilize low coordinate Pd(0) species. Biphenyl formation also occurs with an aqueous potassium carbonate system as the base. A single example of an electron deficient aryl chloride was included. There is a competing hydrodehalogenation reaction which forms the corresponding arene product **(5)**.

---

[23] (a) Hassan, J.; Penalva,V.; Lavenot, L. Gozzi, C.; Lemaire, M. *Tetrahedron* **1998**, *54*, 13793. (b) Penalva,V.; Hassan, J.; Lavenot, L.; Gozzi, C.; Lemaire, M. *Tetrahedron Lett.* **1998**, *39*, 2559.

The mechanism of biphenyl formation is proposed by the authors to occur via a catalytic cycle involving two oxidative additions of the haloarene to Pd(0), followed by reductive elimination. Amatore and Jutland[25] have shown through mechanistic studies that the homocoupling of aryl halides can proceed through a catalytic cycle involving an anionic pentacoordinated bisarylpalladium(II) complex and that the halide plays a crucial role in this cycle. Others[26] have suggested that homocoupled products in cross-coupling reactions can arise from the exchange of aryl groups between the σ-aryl-Pd(II)X species formed after oxidative addition and the transmetalating reagent.

Regeneration of Pd(0) in Lemaire's system is said to occur via the concomitant oxidation of isopropanol to acetone. However, DMF could also serve to act as a reducing agent, owing to the fact that the reaction proceeds in the absence of the alcohol. Both Zhang[27] and Sasson[28] have studied the palladium catalyzed homocoupling of aryl halides in the presence of polyethylene glycol and have proposed that the terminal hydroxyl group of PEG may act as a reductant. The requirement for a reducing agent could be satisfied under Suzuki conditions through the presence of the aryl boronic acid.[11]

The homocoupling of haloarenes using Pd/C in oil in water microemulsions[29] led to high chemoselectivity over reduction. Several examples of chloroarenes are also cited. The authors propose that the difference between the reductive coupling and the reduction

---

[24] Ma, N.; Duan, Z; Wu, Y. *J. Organomet. Chem.* **2006**, *691*, 5697.
[25] Amatore, C.; Carre, E.; Jutland, A.; Tanaka, H.; Ren, Q.; Torii, S. *Chemistry – A European Journal* **1996**, *2*, 957.
[26] (a) van Asselt, R.; Elsevier, C. J. *Organometallics* **1994**, *13*, 1972. (b) Casada, A. L.; Casares, J. A.; Espinet, P. *Organometallics* **1997**, *16*, 5730.
[27] Wang, L.; Zhang, Y. Leifang, L. Wang, Y. *J. Org. Chem.* **2006**, *71*, 1284.
[28] Mukhopadhyay, S.; Rothenberg, G.; Gitis, D. Sasson, Y. *Org. Lett.* **2000**, *2*, 211.
[29] Mukhopadhyay, S.; Yaghmur, Y.; Baidossi, M.; Kundu, B.; Sasson, Y. *Org. Proc. Res. Dev.* **2003**, *7*, 641.

to the arene arises from the fact that the homocoupling requires only electrons while the reduction requires hydrogen atoms.

$$\begin{aligned} H_2 + Pd(II) &\longrightarrow Pd(0) + 2H^+ \\ 2Ar\text{-}X + Pd(0) &\longrightarrow Ar\text{-}Ar + PdX_2 \end{aligned} \qquad \textbf{(4)}$$

$$\begin{aligned} H_2 + Pd(0) &\longrightarrow Pd(II)(H^-)_2 \\ Ar\text{-}X + Pd(II)(H^-)_2 &\longrightarrow Ar\text{-}H + Pd(II)(H^-)(X^-) \end{aligned} \qquad \textbf{(5)}$$

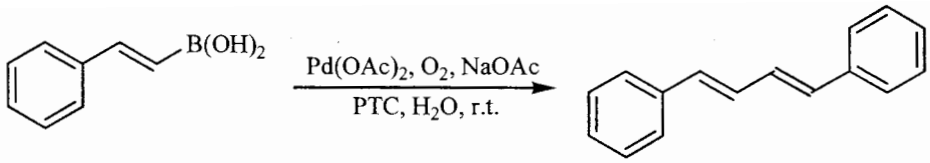
The hydrogen formed in the system arises from the palladium catalyzed decomposition of formate in water. The selectivity of the process is dependant upon the number of vacant Pd(0) sites on the catalyst surface, which reflects the balance between the reduction of Pd(II) (eq 4) and the formation of $Pd(II)(H^-)_2$ (eq 5).[30] Under typical Suzuki cross-coupling conditions, formation of hydrogen[31] is possible from the decomposition of alcoholic solvents.

Boronic Acid Homocoupling

Homocoupling products arising from the reductive coupling of haloarenes are not the only biphenyl byproducts which can form under Suzuki type reaction conditions. The oxidative coupling of the boronic acid substrate is also commonplace.[32] The discovery of this reaction has resulted in the development of synthetic methodology[33,34] (eq 6) which can be used as an alternative to the Suzuki and Ullman coupling reactions for the preparation of symmetrical biaryls and dienes.

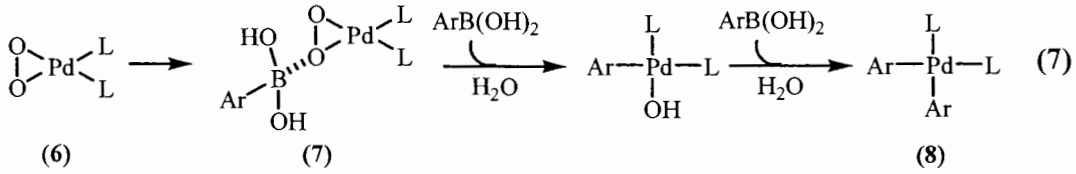
---

[30] Mukhopadhyay, S.; Rothenberg, G.; Gitis, D.; Wiener, H.; Sasson, Y. *J. Chem. Soc., Perkin Trans. 2* **1999,** 2481.
[31] Zoran, A.; Sasson Y.; Blum, J. *J. Mol. Catal.* **1984**, *27*, 347.
[32] (a) Campi, E. M.; Jackson, W.R.; Maruccio, S. M.; Naeslund, G.M. *Chem. Commun.* **1994**, 2395. (b) Wallow, T.I.; Novak, B.M. *J. Org. Chem.* **1994**, *59*, 5034. (c) Moreno-Manas, M.; Pajuelo, F.; Plexats, R. *J. Org. Chem.* **1995**, *60*, 2346.
[33] Parrish, J.P.; Young, J.C.; Floyd, R.J.; Jung, K.W. *Tetraderon Lett.* **2002**, *43*, 7899.



(6)

As mentioned above, homocoupling products have been postulated to arise from aryl exchange between the oxidative addition product and the main group organometallic species.[26] However, it has been observed that the presence of oxygen in the reaction media facilitates the formation of boronic acid homocoupling products. Recently, a detailed mechanistic study[35] has been published which proposes a catalytic cycle (eq 7) involving an η^2-palladium peroxo complex **(6)** derived from tetrakistriphenylphosphine palladium(0) and oxygen. Activation of one of the Pd-O bonds by the aryl boronic acid results in complex **(7)**, which through two consecutive transmetallations yields the diorganopalladium species **(8)**. Reductive elimination results in the homocoupled product.



(6) (7) (8) (7)

A recently published study[36] on the synthesis of a potential Alzheimer's drugs using Suzuki cross-coupling methodology highlights some of the difficulties which can arise using this methodology and validates the mechanisms described above. A byproduct resulting from homocoupling of the boronic acid was produced at

---

[34] (a) Percec, V.; Bae, J.-Y.; Zhao, M.; Hill, D. H. *J. Org. Chem.* **1995**, *60*, 176. (b) Moreno-Manas, M.; Perez, M., Pleixats, R. *J. Org. Chem.* **1996**, *61*, 2346. (c) Wong, M. S.; Zhang, X.L. *Tetrahedron Lett.* **2001**, *42*, 4087.

[35] Adamo, C.; Amatore, C.; Ciofini, I.; Jutland, A.; Lakmini, H. *J. Am. Chem. Soc.* **2006**, *128*, 6829.

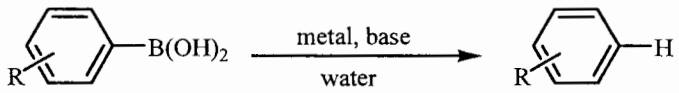
[36] Miller, W.D.; Fray, A.H.; Quatroche, J.T.; Sturgill, S.T. *Org. Proc. Res. Dev.* **2007**, *11*, 359.

unacceptable levels. In order to suppress the formation of this compound, the authors installed two process modifications.

The first involved the addition of potassium formate, to function as a reducing agent for any Pd(II) species which may be in solution from the presence of other oxidants in the reaction. This succeeded in diminishing the amount of boronic acid homocoupling, presumably through reduction of the Pd(II) species (**6**). However, it also resulted in the formation of the haloarene homocoupling and hydrodehalogenation products, which are formed under reducing conditions (see Haloarene Homocoupling and Hydrodehalogenation, pg 23-25). The second successful modification was the exclusion of oxygen by the action of a subsurface nitrogen sparge performed before catalyst addition.

Metal Catalyzed Protodeboronation

In addition to the homocoupling of the boronic acids, protodeboronation (eq 8) can also occur under Suzuki reaction conditions.



(8)

This reaction also takes place in the absence of metal, under acid[37] or base[38] catalysis. The mechanism (eq 9) of the process, as catalyzed by a number of different metals, including the group 10 member nickel, was studied by Kuivila.[39]

$$\begin{aligned} ArB(OH)_2 + M(OH)_2 &\xrightarrow[H_2O]{} ArMOH + B(OH)_3 + H_2O \\ ArMOH + H_2O &\longrightarrow ArH + MOH_2 \end{aligned} \qquad \textbf{(9)}$$

[37] Kuivila, H.G.; Nahabedien, K.V. *J. Am. Chem. Soc.* **1961**, *83*, 2159.
[38] Kuivila, H.G.; Reuwer, J.F.; Mangravite, J.A. *Can. J. Chem.* **1963**,*41*, 3081.
[39] Kuivila, H.G.; Reuwer, J.F.; Mangravite, J.A. *J. Am. Chem. Soc.* **1964**, *86*, 2666.

A kinetic study comparing the rates of cadmium ion catalyzed protodeboronation of several monosubstituted phenylboronic acids at 90 °C and pH 6.7 was performed. The authors found that the overall rate of the reaction increased for most of the substituents (with the exception of *meta* Cl, F, and CH_3). The rate determining step was proposed to be the reaction between boronate anion and a cadmium ion in an electrophilic aromatic substitution process passing through a σ-complex. A Hammett plot of log k/k_0 versus σ+ for the *meta* and *para* substituents revealed that the rate increased for electron rich aryl boronic acids ($\rho = -1.2$).

Protodeboronation is in competition with transmetallation in the Suzuki cross-coupling reaction. Because electron rich phenylboronic acids are favored for the latter process, deboronation may not occur to a large extent for these compounds. However, the slow rate of transmetallation for electron deficient phenylboronic acids may cause protodeboronation to become the favored process.

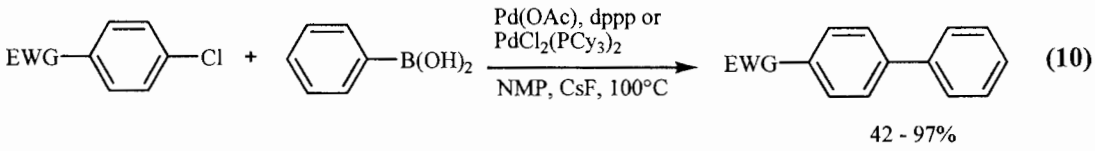
Advances in Catalyst Design

Recent advances in the design of new catalyst and ligand systems have made possible the Suzuki cross-coupling of substrates that were problematic when using the original reaction conditions. In most cases, these systems have been designed to facilitate one or more steps in the catalytic cycle. Cross-coupling reactions involving heterocyclic chloroarenes[40] which are electron poor and thus activated toward oxidative addition have been successful using traditional triarylphosphine based catalysts. However, for the reasons outlined in the previous sections, the Suzuki cross-coupling of unactivated

[40] For a review on palladium-catalyzed chemistry in heterocyclic synthesis see: Kalinin, V. N. *Synthesis* **1992**, 413.

chloroarenes has been a difficult process to achieve. In the past ten years, a great deal of progress has been made in this area.

The first significant breakthrough came in 1997, when Shen[41] reported that palladium complexes of bulky electron rich phosphines catalyzed the coupling (eq 10) of several activated chloroarenes in moderate to good yields.

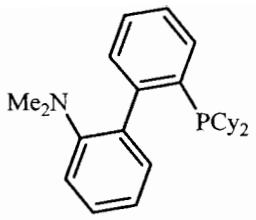


(10)

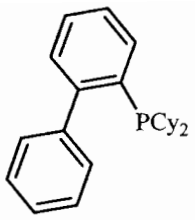
Presumably the advantages of theses types of ligands are twofold. Firstly, the ligand increases the rate of oxidative addition by increasing the nucleophilicity of the metal through donation of electron density. Also, the increased steric bulk of these ligands favor a palladium monophosphine complex through ligand dissociation.

Subsequent to these findings, Buchwald[42] discovered that biphenyl based phosphine **(9)** formed an effective catalyst system with palladium acetate for the formation of biphenyls from electron neutral and electron rich chloroarenes. The efficiency of the process was highlighted by the room temperature cross-couplings of a number of substituted chloroarenes. Shortly thereafter,[43] it was reported that ligands **(10)** and **(11)** were even more efficient and resulted in higher catalyst turnover numbers. Ligands **(9)** and **(11)** were also reported to be effective for the synthesis of hindered biphenyls.

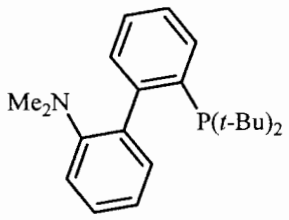
[41] Shen, W. *Tetrahedron Lett.* **1997**, *38*, 5575.
[42] Old, D.W.; Wolfe, J.P.; Buchlwald, S.L. *J. Am. Chem. Soc.* **1998**, *120*, 9722.
[43] Wolfe, J.P.; Buchwald, S.L. *Angew. Chem. Int. Ed.* **1999**, *38*, 2413.



(9)



(10)



(11)

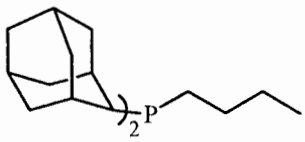
In addition to the electron richness and steric bulk of the phosphines, the authors cited modeling studies which revealed that the catalyst complex may orient itself such that an interaction occurs between the palladium and the *ortho* phenyl ring. This orientation may place the complex in an optimum configuration for reductive elimination to take place.

A concurrent study[44] by Fu and coworkers also resulted in the room temperature cross-coupling of chloroarenes when either $P(Cy)_3$ or $P(t\text{-}Bu)_3$ was used in combination with $Pd_2(dba)_3$ as a precatalyst. Ortho substituents on both the chloroarene and the boronic acid were tolerated and the reaction proceeded regardless of the electronics of the boronic acid. A requirement for an equal ligand to metal ratio was observed. Mechanistic studies[45] using ^{31}P NMR, suggested that the active catalyst is in the monomeric form $Pd[P(t\text{-}Bu)_3]$. The authors postulated that the size of the ligand leads to the monophosphine complex through ligand dissociation and that this form is particularly active for oxidative addition due to the electron rich character of the phosphine.

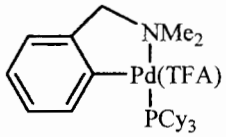
Extremely high palladium turnover numbers were achieved with the use of ligand **(12)** which bears two bulky adamantyl substituents. This ligand proved to be superior to the commercially available trialkylphosphines when used in combination with palladium

[44] Littke, A.F.; Fu, G.C. *Angew. Chem. Int. Ed.* **1998**, *37*, 3387.
[45] Littke, A.F.; Dai, C.; Fu, G.C. *J. Am. Chem. Soc.* **2000**, *122*, 4020.

acetate as a precatalyst.[46] Turnover numbers in excess of 10000 were achieved for electron deficient as well as sterically hindered aryl chlorides.



(12)



(13)

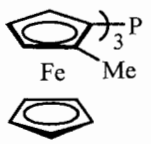
A preformed palladacycle catalyst **(13)** was prepared by Bedford[47] bearing an ortho substituted nitrogen donor ligand. The catalyst was derived from readily available inexpensive starting materials. It showed excellent catalytic activity for unactivated chloroarenes at low Pd loading even under aerobic conditions. The authors postulated that the active catalyst may be a low coordinate Pd(0) species. The formation of which occurs as a result of nucleophilic attack of the aryl boronic acid at the electron deficient metal center, followed by reductive elimination of the phenyl and *N,N*-dimethylbenzylamine groups. They did not address the possibility of palladium nanoparticle formation which can occur upon heating palladacycles at elevated temperatures.[48]

While triarylphosphines in combination with a palladium source can serve as catalysts for the Suzuki couplings of activated chloroarenes, they usually fail with more challenging substrates. However, catalysts that contain phosphines which have at least one ferrocenyl substituent exhibit moderate to excellent catalytic activity for the cross-coupling of electron deficient chloroarenes. Ligands **(14)**[49] and **(15)**[50] in combination with a palladium precatalyst can couple these substrates under mild reaction conditions.

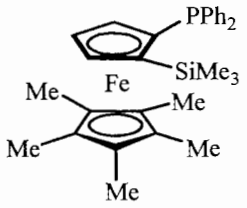
---

[46] Zapf, A.; Ehrentraut, A.; Beller, M. *Angew. Chem. Int. Ed.* **2000**, *39*, 4153.
[47] Bedford, R.B.; Cazin, C.S.J. *Chem. Commun.* **2001**, 1540.
[48] DeVries, J.G. *Dalton Trans.* **2006**, *3*, 421.
[49] Pickett, T.E.; Richards, C.J. *Tet. Lett.* **2001**, *42*, 3767.

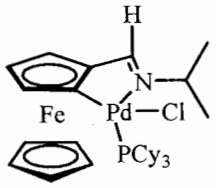
Palladacycle **(16)**[51] is also effective with hindered chloroarenes. The increased efficiency imparted by the ferrocenyl substituent is related to the excellent electron donor ability as well as the increased steric bulk.



(14)

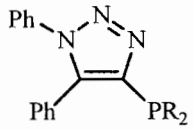


(15)



(16)

Zhang[52] has prepared triazole-based monophosphines via efficient 1,3-dipolar cycloaddition reactions. These ligands were designed to be amenable to modular synthesis so that a wide variety of analogs could be tested for catalytic activity. Ligands based on the core structure **(17)**, in combination with $Pd_2(dba)_3$, have shown effectiveness in the Suzuki cross-coupling of hindered as well as electron deficient chloroarenes at elevated temperatures.



R = Cy, *t*-Bu

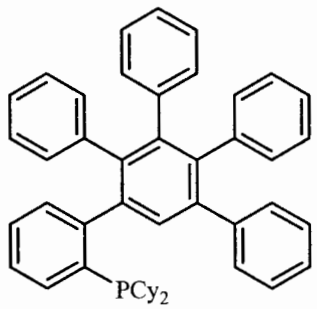
(17)

The 2,3,4,5-tetraphenylphenyl moiety was incorporated into a triarylphosphine framework by Tsuji.[53] The *ortho* derivative **(18)** was an effective catalyst when used in combination with $Pd_2(dba)_3$ for the Suzuki cross-coupling with unactivated chloroarenes. The corresponding *meta* and *para* derivatives were not effective at all as catalysts for this reaction. X-ray crystal analysis of a palladium complex of **(18)** stabilized with maleic

---

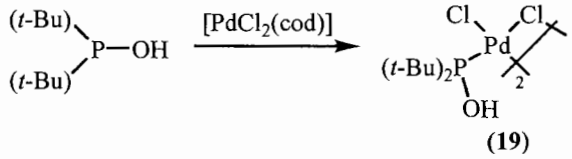
[50] Liu, S.-Y.; Choi, M.J.; Fu, G.C. *Chem. Commun.* **2001**, 2408.
[51] Gong, J.; Liu, G.; Du, C.; Zhu, Y.; Wu, Y. *J. Organomet. Chem.* **2005**, *690*, 3963.
[52] (a) Liu, D.; Gao, W.; Dai, Q.; Zhang, X. *Org. Lett.* **2005**, *7*, 4907. (b) Dai, Q.; Gao, W.; Liu, D.; Kapes, L.M.; Zhang, X. *J. Org. Chem.* **2006**, *71*, 3928.

anhydride revealed an η^2 coordination for the TPPh ligand, resulting in a palladium monophosphine species.



(18)

Li[54] has shown that phosphinous acids can also bind to palladium (eq 10) and after deprotonation yield stable palladium-phosphine complexes of type **(19)**. These are anionic complexes which are relatively electron rich. Because of the favorable electronic properties, they have been successfully employed to prepare products derived from electron rich and sterically hindered chloroarenes.



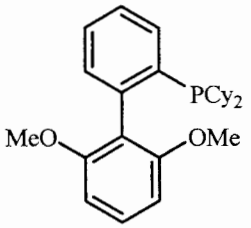
(19) **(10)**

Two remarkably efficient biphenyl based phosphine ligands **(20)** and **(21)** have recently been reported to catalyze the Suzuki coupling of a variety of challenging substrates. Extremely hindered biphenyls have been prepared at low catalyst loading. In addition, the combination of these ligands with palladium acetate constituted the first general catalyst system for the room temperature Suzuki coupling of chloroarenes.[55] Boronic acids and esters derived from pyridine, pyrrole, and indole were also suitable

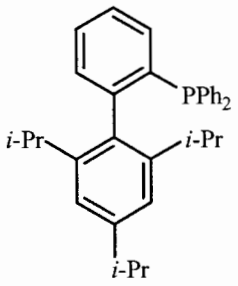
---

[53] Iwasawa, T.; Komano, T.; Tajima,A.; Tokunaga, M.; Obora,Y.; Fujihara,T.; Tsuji, Y. *Organometallics* **2006**, *25*, 4665.
[54] Li, G.Y. *Angew. Chem. Int. Ed.* **2001**, *40*.

coupling partners.[56] In addition these catalyst systems tolerated the presence of highly basic aminopyridines and aminopyrimidines.



(20)



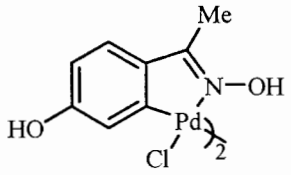
(21)

Based on computational chemistry and X-ray crystallography, the authors concluded that while the electron donating capacity is important, size plays a greater role in the effectiveness of these ligands. Their unprecedented activity is believed to be the result of the steric bulk shifting the $L_2Pd(0)/LPd(0)$ equilibrium toward the monoligated complex. This species would contain either a 12 or 14 electron palladium center, depending on the presence of the palladium interaction with the *ortho* phenyl ring. Facile oxidative addition to the haloarene could then occur.

All of the catalysts described thus far have been based on phosphine ligands. There are other types of ligands and palladacycles which have been successfully employed in Suzuki cross-couplings of chloroarenes. One type is the oxime palladacycle (22) which is both air and water stable. Aqueous reactions have been run on electron rich substrates at elevated temperatures in modest to good yields.[57]

---

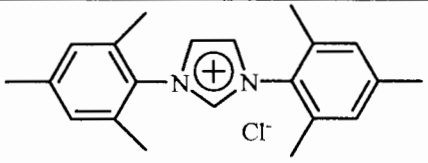
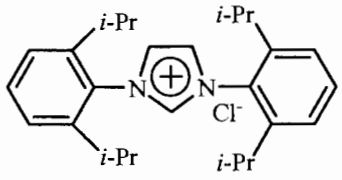
[55] Barder, T.E.; Walker, S.D.; Martinelli, J.R.; Buchwald, S.L. *J. Am. Chem. Soc.* **2005**, *127*, 4685.
[56] Billingsley, K.L.; Anderson, K. W.; Buchwald, S.L. *Angew. Chem. Int. Ed.* **2006**, *45*, 3484.
[57] Botella, L.; Nájera, C. *Angew. Chem. Int. Ed.* **2002**, *41*, 179.



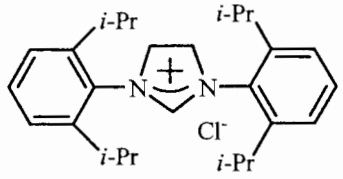
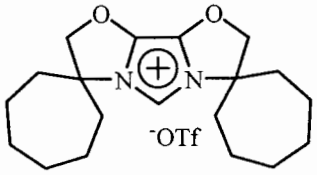
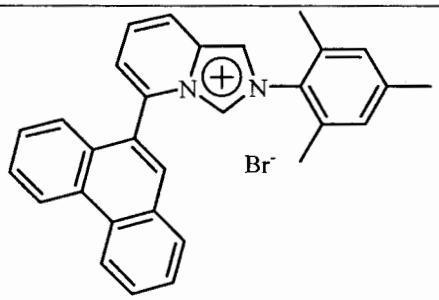
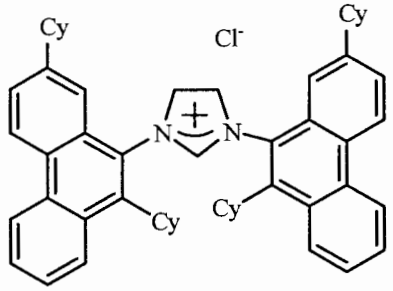
(22)

The class of carbon-based ligands known as N-heterocyclic carbenes are strongly nucleophilic and form tightly bound complexes with palladium. Over the last several years, a large number of variants have been prepared and used as catalysts for metal-catalyzed cross-coupling processes.[58] Their unique structure and geometry allows for many different substitution patterns, resulting in complexes of various sizes and shapes. Table 1 highlights some of the NHC ligands and palladacycles reported in the literature for the Suzuki cross-coupling reaction.

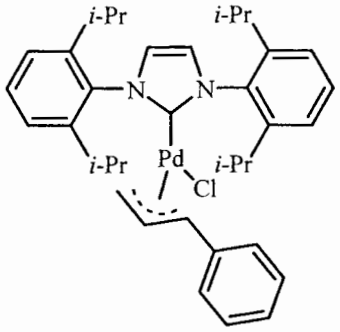
Table 1. N-Heterocyclic Carbenes in the Suzuki Cross-Coupling Reaction

Entry	Catalyst	Conditions	Substrates
1		$Pd_2(dba)_3$, Dioxane, 80 °C	Electron deficient and sterically hindered chloroarenes[59]
2		$Pd(OAc)_2$, THF, reflux	Chloroarenes and allyl or alkyl 9-BBN derivatives[60]

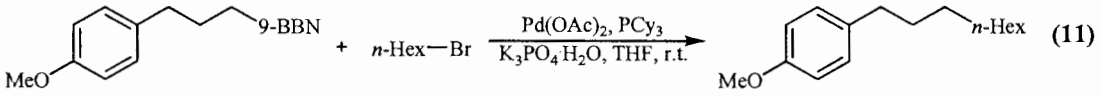
[58] For a review of palladium NHC complexes in cross-coupling reactions see: Kantchev, E.A.B.; O'Brien, C.J.; Organ, M.G. *Angew. Chem. Int. Ed.* **2007**, *46*, 2768.
[59] (a) Zhang, C.; Huang, J.; Trudell, M.L.; Nolan, S.P. *J. Org. Chem.* **1999**, *64*, 3804. (b) Bohm, V.P.W.; Gstottmayr, C.W.K.; Weskamp, T.; Herrmann, W.A. *J. Organomet. Chem.* **2000**, *595*, 186.
[60] Furstner, A.; Leitner, A. *Synlett* **2001**, 290.

3		$Pd_2(dba)_3$, CsF, DME, Dioxane, reflux	Chloroarenes and alkynyltrimethylborates[61]
4		$Pd(OAc)_2$, KO*t*-Bu, KH, K_3PO_4, toluene, 100 °C	Sterically hindered chloroarenes and aryl boronic acids[62]
5		$[Pd(C_3H_5)Cl]_2$, K_3PO_4, dioxane, 80 °C	Sterically hindered chloroarenes and aryl boronic acids[63]
6		$Pd(OAc)_2$, KF, 18-crown-6, THF, rt or 50 °C	Sterically hindered chloroarenes, vinyl and benzyl chlorides[64]

[61] Torres, G.H.; Choppin, S.; Colobert, F. *Eur. J. Org. Chem.* **2006**, 1450.
[62] Altenhoff, G.; Goddard, R.; Lehmann, C.W.; Glorius, F. *J. Am. Chem. Soc.* **2004**, *126*, 15195.
[63] Burstein, C.; Lehmann, C.W.; Glorius, F. *Tetrahedron* **2005**, *61*, 6207.
[64] Song, C.; Ma, Y.; Chai, Q.; Ma,C.; Jiang, W. Andrus, M.B. *Tetrahedron* **2005**, *61*, 7438.

7		KO*t*-Bu, isopropanol, 80 °C	Sterically hindered chloroarenes[65]

The Suzuki cross-coupling of alkyl halides with organoboron nucleophiles is an area which has garnered attention in recent years. Alkyl boranes and primary alkyl halides and tosylates have been successfully coupled in the presence of bulky electron rich phosphine ligands. Fu has reported[66] that PCy_3 was the only effective ligand for the room temperature cross-coupling of alkyl bromides with alkyl boranes (eq 11).



(11)

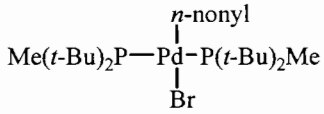
The same group later reported that this ligand in combination with $Pd_2(dba)_3$ provided an effective catalyst system for the cross-coupling of alkyl chlorides[67] with alkyl 9-BBN derivatives. Higher reaction temperatures were needed but the methodology tolerated a wide variety of functional groups.

In addition to the type of electrophile that was used, the nature of the nucleophile and the base greatly influenced the choice of catalyst systems. Cross-couplings involving alkyl bromides and alkyl boronic acids[68] worked significantly better in the presence of the less bulky phosphine ligand P(*t*-Bu)$_2$Me. This ligand also provided an efficient

[65] Marion, N.; Navarro, O.; Mei, J.; Stevens, E.D.; Scott, N.M.; Nolan, S.P. *J. Am. Chem. Soc.* **2006**, *128*, 4101.
[66] Netherton, M.R.; Dai, C.; Neuschutz, K.; Fu, G.C. *J. Am. Chem. Soc.* **2001**, *123*, 10099.
[67] Kirchhoff, J.H.; Dai, C.; Fu, G.C. *Angew. Chem. Int. Ed.* **2002**, *41*, 1945.
[68] Kirchhoff, J.H.; Netherton, M.R.; Hills, I.D.; Fu, G.C. *J. Am. Chem. Soc.* **2002**, *124*, 13662.

catalyst system with palladium acetate for cross-couplings involving alkyl tosylates[69], provided sodium hydroxide was used as the base.

Experiments aimed at elucidating the mechanism for this process[70] revealed that in the absence of a nucleophile, the oxidative addition product **(23)** could be isolated and crystallographically characterized.



(23)

Through kinetic investigations it was revealed that the alkyl bromide oxidatively adds to $L_2Pd(0)$ via an associative S_N2 pathway. The effect of the sterics of the electrophile was also studied and it was determined that branching in the γ and β positions significantly decreased the rate of oxidative addition. Through computational chemistry, the authors concluded that the cross-coupling efficiency correlates with the propensity of $L_2Pd(0)$ to undergo oxidative addition. The lower reactivity of certain phosphine ligands was attributed to conformational restriction of the L_2Pd complex, resulting in an unfavorable steric environment around the palladium.

Successful alkyl-alkyl Suzuki cross-coupling using palladium NHC catalysis is limited to a single literature example. Caddick and Cloke[71] have shown that primary alkyl bromides can be coupled with alkyl 9-BBN derivatives in low to moderate yields. The protocol involved the use of a system comprised of a palladium precatalyst and 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride with potassium *t*-butoxide as the base and silver triflate as an additive.

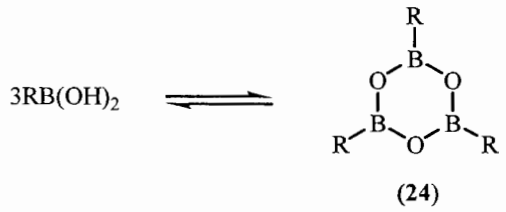
---

[69] Netherton, M.R.; Fu, G.C. *Angew. Chem. Int. Ed.* **2002**, *41*, 3910.
[70] Hills, I.D.; Netherton, M.R.; Fu, G.C. *Angew. Chem. Int. Ed.* **2003**, *42*, 5749.
[71] Arentsen, K.; Caddick, S.; Cloke, G.N.; Herring, A.P.; Hitchcock, P.B. *Tet. Lett.* **2004**, *45*, 3511.

Advances in the Design of New Coupling Partners

Aside from the efforts directed toward discovering new catalyst systems for the Suzuki cross-coupling of challenging substrates, in recent years much attention has been placed on finding new and improved coupling partners. Both the nucleophilic boron derivative and the electrophile have been the subject of this research. The following section will examine some of the advances published in the recent literature.

Despite the many advantages of boronic acids as substrates for cross-coupling processes, the use of these compounds does reveal two significant drawbacks. The first problem with boronic acids is their inherent instability. These compounds exist in equilibrium with boroxine **(24)** which is a trimeric cyclic anhydride (eq 12). Prolonged storage can result in significant formation of boroxine. The presence of **(24)** does not inhibit the cross-coupling. However, because there is no known assay to determine the relative concentrations of the two forms, the stoichiometry is uncertain. This often makes it a necessity to use the boronic acid in excess, which is sometimes undesirable due to the cost associated with their preparation.



(12)

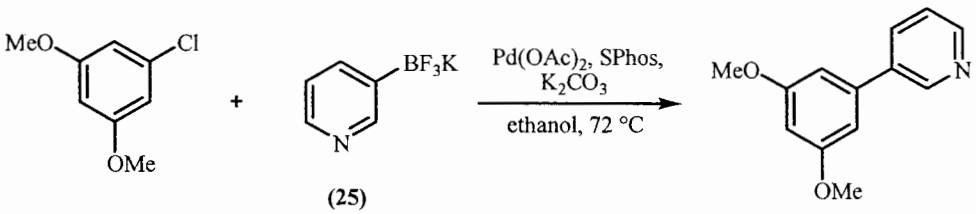
(24)

Another problem inherent in the use of boronic acids is that their presence is often not tolerated by other chemical reagents. Because of this, the boronic acid functionality is seldom carried through multiple synthetic steps. In fact, this drawback is also an issue with boronate esters or oxygen sensitive alkyl 9-BBN derivatives, which are often used as

surrogates for boronic acids. In addition, the preparation of boronate esters involves multistep syntheses from expensive diols.[72]

The use of organotrifluoroborates has become a viable alternative to these types of boron derivatives described above. These are air stable, crystalline compounds which are readily available from cheap starting materials. Their preparation usually involves treatment of a boronic acid or similar derivative with KHF_2 with the organoboron derivative itself readily available from metallation of a haloarene. Alternatively they are accessible from a variety of hydroborating reagents.[73] The first report of these compounds in cross-couplings with arenediazonium salts was reported by Genêt in 1997.[74]

Buchwald reported the Suzuki cross-coupling of aryl- and heteroarylchlorides with potassium aryl- and heteroaryltrifluoroborates using a catalyst system comprised of $Pd(OAc)_2$ and the SPhos ligand **(20)**.[75] Of particular importance were the couplings involving potassium 3-pyridyltrifluoroborate **(25)** (eq 13) because of the ease with which these compounds are prepared[76] relative to their boronic acid counterparts.

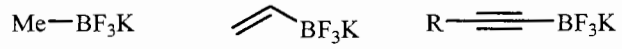


(13)

[72] For the preparation of boronic acids and their derivatives see: *Boronic Acids: Preparations and Applications in Organic Synthesis and Medicine*; (Ed.: D. G. Hall), Wiley-VCH, Weinheim, **2005**, Ch. 1, pp. 1-100.
[73] For the preparation and synthetic applications of organotrifluoroborates see: Molander, G.A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275.
[74] Genêt, J-P.; Darses, S.; Brayer, J-L.; Demoute, J-P. *Tetrahedron Lett.* **1997**, *25*, 4393.
[75] Barder, T.E.; Buchwald, S.L. *Org. Lett.* **2004**, *6*, 2649.
[76] Molander, G.A.; Biolatto, B. *J. Org. Chem.* **2003**, *68*, 4302.

The advent of organotrifluoroborates has allowed for the Suzuki cross-coupling methodology to be used in lieu of other cross-coupling techniques. As an alternative to Kumada and Negishi type couplings involving alkylmetallics, alkyltrifluoroborates can be used in the synthesis of arenes.[77] One particularly useful reagent is potassium methyltrifluoroborate **(26)** because it is readily prepared on a large scale and has a long shelf life. Methyl substituents can be incorporated into a large variety of functionalized aromatics rings as well as alkenyl halides and triflates[78] using this reagent.

As an alternative to Stille couplings, potassium vinyltrifluoroborate **(27)** has been used to introduce vinyl groups in much the same manner.[79] Like **(26)**, large quantities can be prepared and stored for long time periods. In place of the Sonogashira reaction, Suzuki methodology can be used with alkynyltrifluoroborates such as **(28)** for cross-couplings with bromo and chloarenes and triflates.



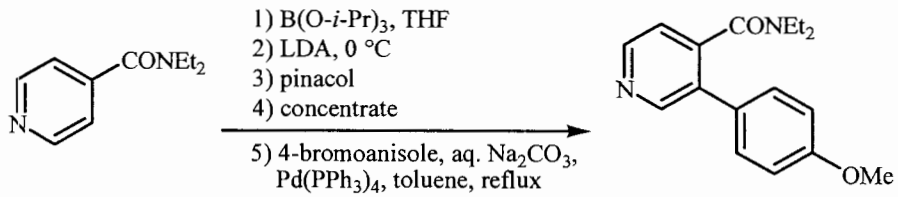
(26) **(27)** **(28)**

Perhaps the most powerful attribute of organotrifluoroborates is the ability to use them as a protected form of a boronic acid. Because of the inert nature of the trifluoroborate functional group, a myriad of different compounds can be prepared through direct synthetic modification while this group remains intact. While a complete treatment of this area is beyond the scope of this review,[73] organotrifluoroborates have been successfully subjected to metal-halogen exchange, cycloaddition, oxidation, and Wittig reactions, to name a few.

---

[77] Molander, G.A.; Yun, C-S.; Ribagorda, M.; Biolatto, B. *J. Org. Chem.* **2003**, *68*, 5534.
[78] Molander, G.A.; Ham, J.; Seapy, D.G. *Tetrahedron* **2007**, *63*, 768.
[79] Molander, G.A.; Brown, A. *J. Org. Chem.* **2006**, *71*, 9681.

Though there are many commercially available boronic acids, a general route to obtaining pyridylboronic acids has been met with some difficulty. While 3-pyridylboronic acid is a relatively stable compound, preparation of substituted pyridylboronic acids usually requires careful control of the pH during preparation in order to control protodeboronation.[80] The preparation of functionalized azabiaryls was reported by Snieckus[81] via a directed ortho metallation and Suzuki cross-coupling procedure (eq 14). This procedure circumvented the use of pyridylboronic acids. The stable pyridylboronate intermediates were isolated whereas the more sensitive analogs were used *in situ.*



(14)

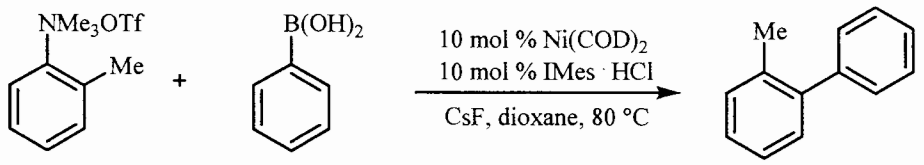
Research aimed at discovering new electrophiles for the Suzuki cross-coupling reaction has been rather limited. In 2003, MacMillan reported the first Suzuki cross-coupling of aryltrimethylammonium triflates.[82] These compounds were derived from dialkylanilines via a simple nitrogen quartenization step. The cross-couplings were catalyzed by a nickel precatalyst in combination with a NHC ligand (eq 15). Both electron poor and electron rich ammonium triflates and arylboronic acids were tolerated.

---

[80] (a) Bouillon, A.; Lancelot, J.-C.; Collot, V.; Bovy, P.R.; Rault, S. *Tetrahedron* **2002**, *58*, 2885. (b) Bouillon, A.; Lancelot, J.-C.; Collot, V.; Bovy, P.R.; Rault, S. *Tetrahedron* **2002**, *58*, 3323. (c) Bouillon, A.; Lancelot, J.-C.; Bovy, P.R.; Rault, S. *Tetrahedron* **2002**, *58*, 4369. (d) Bouillon, A.; Lancelot, J.-C.; Sopkova, J.; de Santos, O.; Collot, V.; Bovy, P.R.; Rault, S. *Tetrahedron* **2003**, *59*, 10043. (e) Cailly, T.; Fabis, F.; Bouillon, A.; Lemaître, S.; Sopkova, J.; de Santos, O.; Rault, S. *Synlett* **2006**, 53.

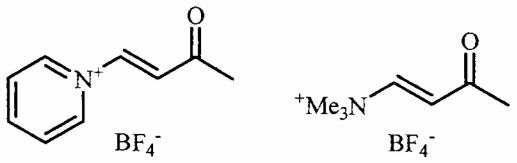
[81] Alessi, M.; Larkin, A.L.; Ogilvie, K.A.; Green, L.A.; Lai, S.; Lopez, S.; Snieckus, V. *J. Org. Chem.* **2007**, *72*, 1589.

[82] Blakey, S.B.; MacMillan, D.W.C. *J. Am. Chem. Soc.* **2003**, *125*, 6046.



(15)

In a similar study, Buszek reported that both *N*-vinylpyrimidine **(29)** and ammonium tetrafluoroborate **(30)** salts could be cross-coupled with a wide variety of arylboronic acids.[83] These electrophiles were reported to be air stable, crystalline compounds that were easily prepared in one step from activated acetylenes and the corresponding tetrafluroborate. Although high catalyst loadings (5 mol % Pd, 20 mol% ligand) and microwave heating (150 °C) were required for activation of these substrates, this study represents a novel approach to carbon-carbon bond formation under Suzuki reaction conditions.



(29) **(30)**

[83] Buszek, K.R.; Brown, N. *Org. Lett.* **2007**, *9*, 707.

Pd/C as a Catalyst for the Suzuki Coupling of Chloroarenes

Catalysts play a unique role in synthetic organic chemistry. Their presence in a reaction medium often makes possible transformations that would otherwise be unattainable due to high activation energy and a slow reaction rate. Very often these catalysts are metals because of their unique physical and chemical properties. Palladium, in particular, can catalyze a large number of organic transformations; from the reduction of unsaturated compounds and organic groups to the formation of carbon-carbon bonds.

Properties of Supported Metal Catalysts

For a catalyst to be effective, it is imperative to ensure adequate interaction with the reactant molecules. One way to achieve this and to expose the maximum amount of surface area is by using the catalyst as a fine powder. With metals, this can present several problems. Safety can become an issue with some metals when they are used in this form because they are pyrophoric in ambient conditions. In addition, when heat is applied to metal powders, sintering may occur. This phenomenon is essentially the agglomeration of small particles into larger, less effective ones. It occurs because of the close proximity of the metal particles to one another.[84]

Due to these drawbacks, metals are often dispersed onto stable supports. These supports act to separate the active catalytic species and prevent agglomeration from occurring. Common supports for palladium include alumina, silica, and carbon. Other less common ones include calcium carbonate and barium sulfate. The term Pd/C denotes

[84] Augustine, R.A. *Heterogeneous Catalysis for the Synthetic Chemist*; Marcel Dekker: New York, 1996; Ch 9, pp 153-160.

palladium supported on activated carbon. It is also common to supply the supported metal in water-wet form as this form reduces the pyrophoric properties of the catalyst.

There are several properties of these supported metals which are important to the reactivity and usefulness of the catalyst. For palladium, commercial supported catalysts are available in reduced [mostly Pd(0)], or unreduced [mostly Pd(II)], forms. For the Suzuki cross-coupling reaction, reports which included a discussion of the effective difference between the two forms are somewhat contradictory. Both Buchecker[85] and Nishida[86] suggest that either form is capable of catalyzing the process with approximately the same efficiency. However, Köhler[87] has shown through analysis of both turnover rates and frequencies, that the unreduced form is far superior.

Physical characteristics of the support are extremely important for the efficiency of the catalyst. In order for proper performance to be achieved, the catalyst particles must be sufficiently hard to withstand the fast stirring rates which are often used. Hardness is related to the porosity of the support. The more porous the catalyst particles, the higher the surface area; however, this must be balanced with the density which will decrease as porosity increases.[84]

The dispersion of the metal on the surface of the catalyst can also serve to increase surface area. Palladium is typically available in loadings from 0.1 to 20 %. A typical dispersion can have anywhere from 10 – 60 % of the palladium atoms exposed. The distribution of the palladium on the catalyst particle is often referred to as either uniform, eggshell, or thick shell loading. A uniform distribution is one in which the metal is homogeneously distributed throughout the catalyst particle. Eggshell and thick

[85] Marck, G.; Villiger, A.; Buchecker, R. *Tetrahedron Lett.* **1994**, *35*, 3277.
[86] Tagata, T.; Nishida, M. *J. Org. Chem.* **2003**, *68*, 9412.

shell are surface loaded particles with varying depths (50-150 nm from the surface for eggshell and 200-500 nm for thick shell).[88]

The preparation of palladium on carbon usually begins from natural organic material such as wood or nutshells. The material is then heated under air free conditions at 700-900 °C. Activation of the carbon can be done by one of two methods, physical or chemical. Physical activation involves treating the material with carbon dioxide or steam at 400-600 °C. Chemical activation is performed by treatment with an activating agent such as zinc chloride prior to the pyrolysis. The result of this activation process is the burning away of the carbon and the resulting formation of the charcoal-like pore structure. The surface area of the carbon depends largely on the starting material, with wood resulting in a range of 300-900 m^2/g, nutshell 700-1500 m^2/g, and coal carbon 300-1000 m^2/g. Carbon prepared in this fashion has many oxygen containing functionalities present including phenols, carboxylic acids, and ketones.[89]

There are a large number of methods available for the introduction of the active palladium catalyst onto the carbon support.[90] Most of these methods involve the treatment of the support with an aqueous solution containing the metal cation. A sufficiently high interaction between the support and the metal must exist, especially during the washout procedure, in order to ensure adequate dispersion. Typical palladium solutions include $PdCl_2$ or $Pd(NO_3)_2$, which are followed by a washout step or solvent removal, and sometimes a reducing agent.

---

[87] Heidenreich, R.G.; Köhler, K.; Krauter, J.G.E.; Pietsch, J. *Synlett* **2002**, 1118.
[88] Felpin, F.-X.; Ayad, T.; Mitra, S. *Eur. J. Org. Chem.* **2006**, 2679.
[89] Augustine, R.A. *Heterogeneous Catalysis for the Synthetic Chemist*; Marcel Dekker: New York, 1996; Ch 9, pp 167-175.
[90] For a review on the preparation of supported palladium catalysts see: Toebes, M.L.; van Dillen, J.A.; de Jong, K.P. *J. Mol. Catal. A* **2001**, *173*, 75.

The support is not simply an inert surface on which the catalyst lies. Interactions between the metal and the functional groups present on the charcoal not only result in changes in the reactivity of the metal but these interactions can also affect the adsorption properties. The nature of catalyst-support interactions is beyond the scope of this discussion [89] however, factors such as support type, particle size, and the identity of the metal, all play a role.

The adsorption of the substrate to the palladium surface is a crucial aspect of the catalytic process. For chloroarenes, Richardson[91] studied the surface interactions of chlorobenzene with a platinum surface at room temperature using angle-resolved photoemission measurements. The orientation of the phenyl ring to the metal surface was shown to be nearly parallel. LeBlond, Sowa and co-workers[92] have suggested that a combination of anchimeric and electronic effects are responsible for the unique reactivity of chloroarenes on palladium surfaces. The adsorption of the chloroarene on the metal surface serves as an anchor which enhances the chemical interaction of the C-Cl bond with nearby palladium sites. In addition, during the adsorption process the arene donates electrons to the metal resulting in the activation of the C-Cl bond.

Supported metal catalysts offer additional advantages other than increased safety and the prevention of sintering. Most solid supports onto which metals are dispersed are insoluble in solvents which are used to run organic reactions. This allows for easy removal of the catalyst by simple filtration and low residual metal contamination in the product. This can be an enormous advantage over those which form homogeneous mixtures with the reaction medium. Compounds prepared through the use of these

---

[91] Richardson, N.V.; Palmer, N.R. *Surf. Sci.* **1982**, *114*, L1.
[92] LeBlond, C.R.; Andrews, A.; Sun, Y.; Sowa, J.R. *Org. Lett.* **2001**, *3*, 1555.

soluble catalysts are usually plagued with high levels of residual metal which can only be removed through the performance of a subsequent purification step.[93]

In addition to easy removal, supported metal catalysts can often be recycled. It is sometimes possible to reuse them several times with little or no reactivation required. While soluble catalysts can sometimes be used at very low loadings, there are few reports in the literature dealing with the recycling of homogeneous catalysts.[94] From a manufacturing standpoint, the ability to reuse a catalyst can often result in a significant cost savings, while at the same time reducing waste.

The Scope of Pd/C-Catalyzed Suzuki Coupling of Chloroarenes

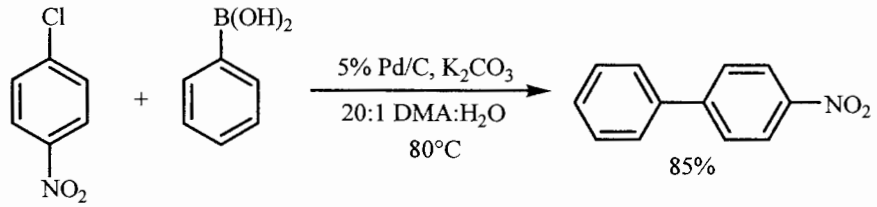
The earliest example of the Pd/C-catalyzed Suzuki cross-coupling reaction was a study utilizing bromoarenes as substrates published in 1994.[85] Since then, a great number of experiments involving the cross-coupling of iodo- and bromoarenes have been reported in the literature.[95] However, the use of chloroarenes has been somewhat limited because of the difficulty associated with the activation of the C-Cl bond toward oxidative addition.[96] Most of the reactions that are reported in the literature are those which make use of activated chloroarenes.

The first general method for the Pd/C-catalyzed Suzuki cross-coupling of chloroarenes was introduced by Leblond, Sowa and coworkers.[92] The use of the polar solvent dimethylacetamide, in a 20:1 ratio with water, was crucial for the efficient

---

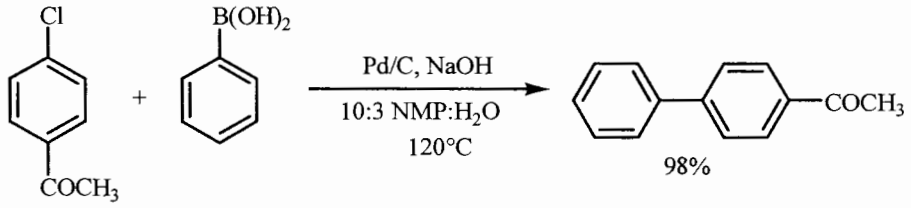
[93] For a review on methods used to remove palladium impurities from organic compounds see: Garret, C.E.; Prasad, K. *Adv. Synth. Catal.* **2004**, *346*, 889.
[94] (a) Matthews, C.J.; Smith, P.J.; Welton, T. *Chem. Commun.* **2000**, *14*, 1249. (b) Nobre, S.M.; Wolke, S.I.; da Rosa, R.G.; Monteiro, A.L. *Tetrahedron Lett.* **2004**, *45*, 6527.
[95] For a review on the use of Pd/C for the Suzuki cross-coupling reaction see ref [88].

coupling of activated substrates with phenylboronic acid (eq 16). Higher water concentrations or the use of alcohol solvents resulted in greater yields of chloroarene homocoupling products. Electron rich substrates could also be coupled, albeit in lower yields. As mentioned earlier (see: Properties of Supported Metal Catalysts, pg 44-45), they attributed this unexpected reactivity to the unique adsorption characteristics of Pd/C.



(16)

In 2002, Köhler[87] reported turnover numbers as high as 1600 for the cross-coupling of *p*-chloroacetophenone with phenylboronic acid (eq 17). The author also found that the choice of solvent and base played a critical role in the outcome of the reaction. Sodium hydroxide in combination with a 10:3 ratio of NMP:water was effective at a relatively high reaction temperature of 120 °C. The author attributed the reactivity to soluble palladium species present in the reaction solution and pointed to the requirement for high temperatures as evidence for the presence of a dissolution re-precipitation process.



(17)

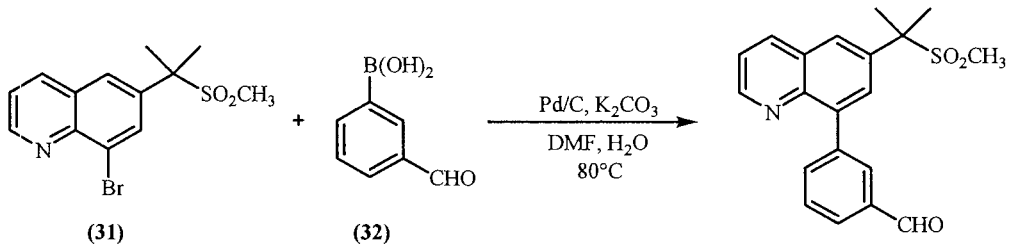
The question of whether palladium on carbon acts as a heterogeneous or homogeneous catalyst has been somewhat controversial. Earlier studies concluded that

---

[96] For examples of the Suzuki cross-coupling of chloroarenes using ligandless homogeneous catalysts see: a) Bumagin, N.A.; Bykov, V.V. *Tetrahedron* **1997**, *53*, 14437. b) Zim, D.; Monteiro, A.L.; Dupont, J. *Tetrahedron Lett.* **2000**, *41*, 8199.

the Pd/C-catalyzed Suzuki reaction was solely heterogeneous in nature.[85,92] However, there are a number of reports in the current literature suggesting that there is a dominant homogeneous component to most Pd/C catalyzed coupling processes.[97]

A study which provided significant evidence to support that homogeneous palladium species are responsible for the catalytic activity of Pd/C in the Suzuki cross-coupling of bromoarenes was published in 2003. [98] The reaction between a bromoquinoline derivative **(31)** and 3-formylphenylboronic acid **(32)** (eq 18) was followed over time by ICP-MS to determine the level of soluble palladium species. The authors found that these levels correlated with the concentration of the bromoquinoline and that a maximum level was achieved at approximately 90 % conversion. As **(31)** was consumed, the solution phase palladium decayed to less than 4 ppm at the conclusion of the reaction.



(31) **(32)** **(18)**

Based on these findings, along with the fact that no soluble palladium is present in mixtures of Pd/C and DMF in the absence of the reactants, the authors concluded that oxidative addition of the palladium to **(31)** was responsible for the metal desorption process. This hypothesis is consistent with the observation of Davies who found that the

[97] For a review on the subject of homogeneous versus heterogeneous Suzuki and Heck reactions see: Phan, N.T.S.; Van Der Sluys, M.; Jones, C.W. *Adv. Synth. Catal.* **2006**, *348*, 609.
[98] Conlon, D.A.; Pipik, B.; Ferdinand, S.; LeBlond, C.R.; Sowa, J.R.; Izzo, B.; Collins, P.; Ho, G.; Williams, J.M.; Shi, Y.; Sun, Y. *Adv. Synth. Catal.* **2003**, *345*, 931.

Pd/C-catalyzed carbonylation of an aryl halide on a solid support did not proceed unless another aryl halide was present in the reaction solution.[99]

The kinetic data obtained also led to the conclusion that the buildup of solution phase palladium was a result of the difference between the rate of oxidative addition and the rate of palladium precipitation. These rates were found to be reliant upon the base, the amount and type of carbon support used, and the time period in which the reaction finished and the product was isolated. Because the rate of palladium solubilization was affected by the base but the palladium concentration did not correlate with the overall reaction rate, the authors concluded that transmetallation and not oxidative addition was most likely the rate determining step.

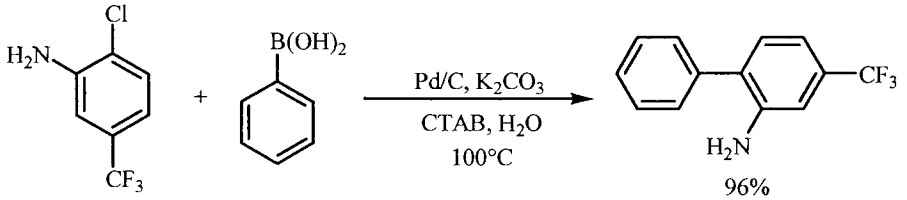
The precipitation of the palladium after the haloarene is consumed has been observed to result in a re-deposition of the metal onto the support. This phenomenon was studied for the Heck reaction with iodobenzene in NMP.[100] There are two possible sites for the re-deposition of the palladium to occur; this could be on the bare surface of the support or on the surface of the nonleached palladium that remained on the support.

A comparison of the size of the immobilized palladium particles of a 10 wt % Pd/C catalyst, both before and after the reaction, was performed by x-ray diffraction and electron microscopy. The authors reported that the palladium particles did indeed grow after the reaction was complete, indicating that the re-deposition occurred preferentially onto the surface of the supported palladium particles. However, the authors also warned that the site of the re-deposited palladium may differ, depending on the type of support used or the amount and location of the supported palladium particles.

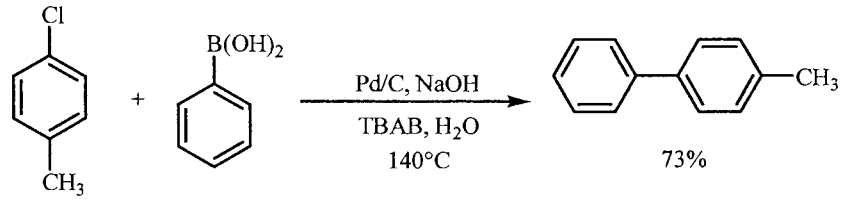
---

[99] Davies, I.W.; Matty, L.; Hughes, D.L.; Reider, P.J. *J. Am. Chem. Soc.* **2001**, *123*, 10139.
[100] Zhao, F.; Shirai, M.; Ikushima, Y.; Arai, M. *J. Mol. Cat. A.* **2002**, *180*, 211.

In order to enhance the reactivity of Pd/C, a number of authors have turned toward the use of additives. The surfactant cetyltrimethylammonium bromide (CTAB) was used in combination with Pd/C for the Suzuki cross-coupling of activated chloroarenes (eq 19).[101] The formation of palladium nanoparticles was proposed as a result of the surfactant interacting with the palladium dispersed on the catalyst surface. In a similar report, tetrabutylammonium bromide (TBAB) in combination with Pd/C, successfully coupled both electron neutral and electron rich chloroarenes (eq 20) at high temperatures but without the need for the exclusion of oxygen.[102]



(19)

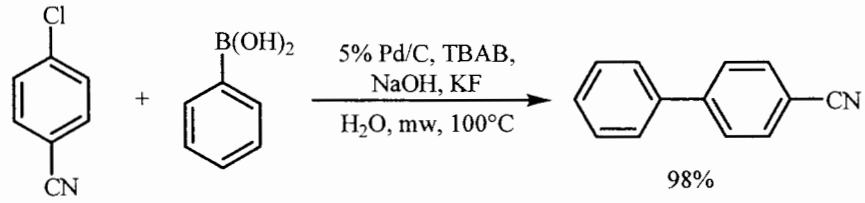


(20)

In addition to the use of additives, Leadbeater has subjected the Suzuki cross-coupling of chloroarenes to microwave irradiation.[103] By using a 10 wt % Pd/C catalyst in the presence of TBAB, the author was able to obtain excellent yields of substituted biphenyls arising from the reaction of electron poor chloroarenes with phenylboronic acid (eq 21). It was necessary to use a microwave apparatus which could simultaneously cool the samples, in order to avoid the decomposition of the chloroarenes.

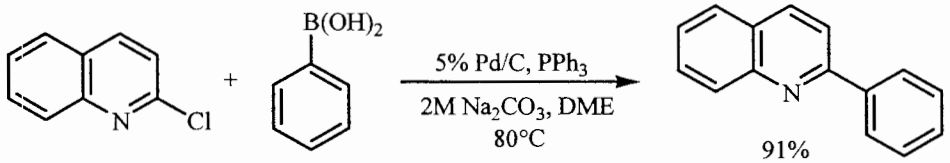
---

[101] Arcadi, A.; Cerichelli, G.; Chiarini, M.; Correa, M.; Zorzan, D. *Eur. J. Org. Chem.* **2003**, 4080.
[102] Lysèn, M.; Köhler, K. *Synlett* **2005**, 1671.
[103] Arvela, R.K.; Leadbeater, N.E. *Org. Lett.* **2005**, *7*, 2101.



(21)

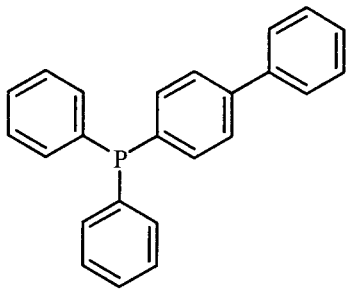
The use of phosphines as additives for the Pd/C-catalyzed Suzuki cross-coupling was first reported by Buchecker.[85] Small amounts of triphenylphosphine were added to the reaction between a bromoarene and an electron deficient aryl boronic acid to mimic the effects of the homogeneous catalyst $Pd(PPh_3)_4$. Several years later, a report was published[86] which highlighted the use of triphenylphosphine as an additive for Suzuki cross-couplings involving chloropyridines and chloroquinolines (eq 22). Improvements in product yields were realized when the phosphine was added to the Pd/C catalyst system. Within this report, there is a single example of an electron deficient chloroarene used as a substrate. The catalyst for this reaction was unreduced 5% Pd/C with the addition of the biphenyl based phosphine ligand 2-(dicyclohexylphosphino)biphenyl **(10)**.



(22)

In 2006, Joshaghani described the synthesis of several bulky triarylphosphine ligands of type **(33)**.[104] These phosphines made efficient catalysts for the Suzuki cross-coupling of chloroarenes when used in combination with $Pd(OAc)_2$. However, when Pd/C was used, only activated bromoarenes could be successfully cross-coupled.

[104] Joshaghani, M.; Faramarzi, E.; Rafiee, E.; Daryanavard, M.; Xiao, J.; Baillee, C. *J. Mol. Cat. A.* **2006**, *259*, 35.



(33)

Results and Discussion

The widespread use of palladium-catalyzed cross-couplings has created a need for new synthetic methods that can be executed efficiently, while keeping costs low, and have a minimal impact on the environment. Because many chloroarenes are commercially available, the use of these compounds as substrates can help to minimize costs and reduce the amount of waste associated with the preparation of haloarenes. In addition, employing recyclable catalysts in these processes also helps the organic chemist achieve these goals. However, it is a significant challenge to develop methodology which allows for the successful implementation of these concepts.

Our contributions to this area are discussed in the following chapters. We began by studying the impact of phosphine ligands on the Suzuki cross-coupling of chloroarenes. Through the optimization of a model reaction we have discovered a general method for the cross-coupling of substrates that are difficult to couple under ligand free conditions. These include electron rich and sterically hindered chloroarenes as well as electron deficient and sterically hindered boronic acids.

In order for this process to be practical, we needed to demonstrate that our system retained the desirable characteristics of an immobilized catalyst. Therefore we performed recycling experiments to determine if the Pd/C remained catalytically active after several uses. We also determined the level of residual palladium contamination after removal of the Pd/C from our products by simple filtration techniques.

We examined the active catalytic species by performing experiments designed to discriminate between homogeneous and heterogeneous catalysis. Filtration and split tests were used to separate the heterogeneous component from any soluble species during the

course of a reaction. Also a novel mercury poisoning test was conceived and successfully executed. This allowed us to unambiguously reach a conclusion as to the true nature of the catalytically active species.

Finally, we were able to implement a protocol that allowed us to significantly reduce the amount of ligand that was necessary to successfully catalyze these processes. We prepared a number of compounds using this new methodology. We were then able to use the insights gained from all of these experiments to propose a catalytic cycle for what we have termed the ligand assisted Suzuki cross-coupling of chloroarenes.

In a separate project, we studied the palladium catalyzed amination of fluorochloroarenes. After the initial experiments determined that these compounds could be selectively substituted at the chlorine atom, we developed methodology that allowed preparation of the quinolone antibacterial Norflaxacin. We performed a battery of optimization experiments with the goal of minimizing the amount of side product formed from nucleophilic aromatic substitution.

We also discuss our progress in two other areas of palladium-catalyzed cross couplings. The cyanation of bromo and chloroarenes was explored utilizing a known catalyst system. Also, an effort was undertaken to prepare a novel azaphosphine ligand with a structure based on a non-biaryl atropisomeric backbone.

Ligand Assisted Pd/C-Catalyzed Suzuki Coupling of Chloroarenes

Our interest in the Pd/C-catalyzed Suzuki cross-coupling stems from our desire to develop an efficient procedure that is more economical, environmentally friendly, and results in products with lower metal-based contaminants than one obtains with homogeneous catalysts. Extensive research on this topic has been published from our laboratory as well as others (see: The Scope of Pd/C-Catalyzed Suzuki Coupling of Chloroarenes, pg 48-54, and references therein).

Previously, we have obtained evidence suggesting that Pd/C works as a quasi-heterogeneous catalyst where the initial solid material leaches a catalytic species that is eventually re-deposited on the carbon surface as the reaction nears completion.[98] While we initially could not rule out a heterogeneous component to the reaction, we found mounting evidence in the current literature suggesting that there is a dominant homogeneous component to most Pd/C-catalyzed coupling processes.[97,99] Thus, this well known catalyst has been proven to be a practical catalyst for the coupling of bromoarenes, resulting in high yields and very low palladium contamination.

Pd/C is also an excellent catalyst for the coupling of chloroarenes, provided that they contain electron withdrawing groups.[92] Unfortunately, coupling reactions using electron neutral and electron donating chloroarenes were found to be both low yielding and to contain significant homocoupling byproducts. Thus, we became interested in the challenge of developing a Suzuki-Miyaura reaction using Pd/C with chloroarenes containing electron neutral and donating groups.

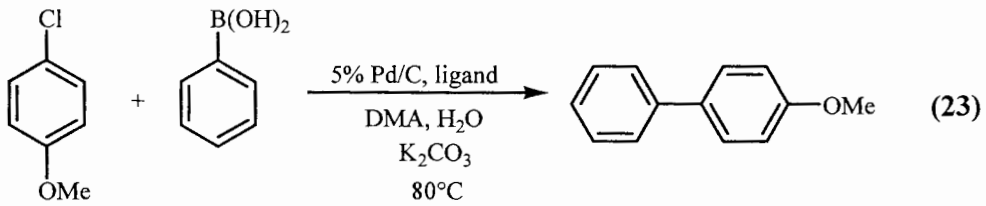
We were attracted by the possibility of exploiting the soluble palladium component of the Pd/C-catalyzed Suzuki reaction in such a way as to increase catalyst reactivity with chloroarenes. We were also interested to see if in doing so, we could

continue to reap the benefits which are inherent in a heterogeneous catalyst. Our hypothesis was that the addition of low levels of ligand could form a palladium complex in solution, similar to that present in the reactions of homogeneous palladium catalysts.

At the time we were performing optimization studies, we were unaware of the concurrent study reported by Nishida in which he described increased yields for the Pd/C-catalyzed Suzuki-Miyuara coupling when biphenyl based phosphine ligands were added to the reaction mixture.[86] However, this report focused mainly on the use of heteroaromatic chloroarenes; with only a single example of an electron rich chloroarene reported. There was also no mention of recycling studies or palladium contamination and no insight was given into the nature of the active catalytic species. Thus we continued our efforts toward a goal of developing a general synthetic methodology while fully examining the properties of the active catalyst.

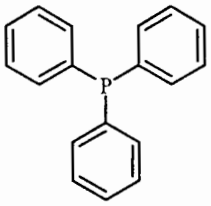
Reaction Optimization Studies

We first set out to find the optimal ligand, using the reaction between 4-chloroanisole **(34)** and phenylboronic acid **(35)** in the presence of Degussa 5 % Pd/C as a model reaction (eq 23). From the initial study,[92] we knew that a 32 % isolated yield of 4-methoxybiphenyl **(36)** could be obtained using the ligandless procedure.

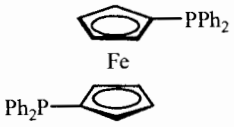


(34) **(35)** **(36)** **(23)**

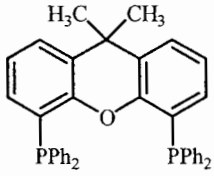
We screened a number of phosphine ligands that were reported in the literature to be effective in Pd-catalyzed cross-couplings. There structures are shown in Figure 4.



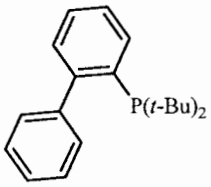
triphenylphosphine



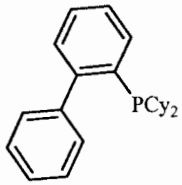
1,1'-bis(diphenylphosphino)ferrocene(dppf)



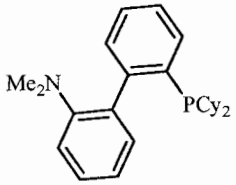
9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene
(Xantphos)



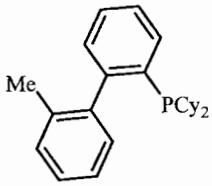
2-(di-*t*-butylphosphino)biphenyl



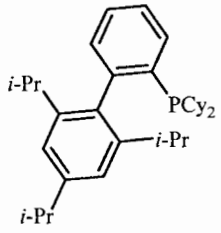
2-(dicyclohexylphosphino)biphenyl



2-dicyclohexylphosphino-2'-(*N,N*-dimethylamino)biphenyl



2-dicyclohexylphosphino-2'-methylbiphenyl (MePhos)



2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (XPhos)

Figure 4: The Structure of Phosphines Used in Ligand Screening Studies

This study was conducted by monitoring the percentage of the chloroarene that was converted to product after a 24 h reaction period. This was determined by analyzing a reaction aliquot by HPLC with the UV-Vis detector set at 220 nm and calculating the

concentration of the reactant and product. To compensate for differences in the molar absorptivity of each compound, calibrated curves of concentration versus absorbance were constructed with a minimum of three data points for each compound.

The results of the study indicated that the monodentate ligand triphenylphosphine (Table 2, entries 2-3) as well as the bidentate ligands dppf and Xantphos (entries 4-7), completely inhibited the cross-coupling and resulted in no conversion to product when as little as 2.5 mol % relative to the chloroarene was added. This came as somewhat of a surprise to us due to the fact that triphenylphospine has been reported in the past as an additive for Pd/C-catalyzed Suzuki reactions.[85, 86] However, it has also been shown that phosphine inhibition plays a role in limiting the catalytic efficiency of Suzuki cross-couplings.[32b]

Biphenyl based phosphines 2-(dicyclohexylphosphino)biphenyl (entry 8) and 2-(di-*t*-butylphosphino)biphenyl (entry 10) exhibited mild inhibition or no significant effect at the 10 mol % level. However, decreasing the amount of ligand resulted in increased conversion to product (entries 9 and 11). Maximal conversion was observed at 2.5 mol %, with respect to chloroarene, for 2-(dicyclohexylphosphino)biphenyl (entry 12). The most effective ligands were the multisubstituted biphenylphosphines (entries 14-17), giving product conversions as high as 91 %.

Table 2. Effect of Ligand on the Pd/C-Catalyzed Suzuki Cross-Coupling of 4-Chloroanisole and Phenylboronic acid.[a]

Entry	Ligand	Mol (%)	Conversion (%)[b]
1	None	NA	37[c]
2	triphenylphosphine	10	0
3	triphenylphosphine	2.5	1
4	dppf	10	0
5	dppf	2.5	3
6	Xantphos	10	0
7	Xantphos	2.5	0
8	2-(di-*t*-butylphosphino)biphenyl	10	14
9	2-(di-*t*-butylphosphino)biphenyl	2.5	58
10	2-(dicyclohexylphosphino)biphenyl	10	36
11	2-(dicyclohexylphosphino)biphenyl	5	47
12	2-(dicyclohexylphosphino)biphenyl	2.5	56
13	2-(dicyclohexylphosphino)biphenyl	1.0	18
14	2-dicyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl	2.5	88
15	MePhos	2.5	91
16	MePhos	1.25	71
17	XPhos	2.5	79

[a] All reactions were performed with 0.8 mmol 4-chloroanisole, 0.96 mmol phenylboronic acid, 1.6 mmol K_2CO_3, 0.02 mmol 5% Pd/C, and 0.02 mmol ligand, in 5 mL of 20:1 (v:v) DMA:H_2O at 80°C for 24 h.
[b] Corrected HPLC conversions are defined as (mmol 4-methoxybiphenyl)/ (mmol 4-chloroanisole + mmol 4-methoxybiphenyl) x 100.
[c] See reference 92.

Most of the phosphines used for this study were obtained from commercial sources, except for 2-dicyclohexylphosphino-2'-(*N,N*-dimethylamino)biphenyl (entry 14), which at the time required synthetic preparation.[42] As can be seen from Figure 5, this ligand was obtained in five steps starting from 2-bromoaniline **(37)**. Reductive alkylation [105] of this compound with aqueous formaldehyde and sodium cyanoborohydride resulted in 2-bromo(*N,N*-dimethylamino)aniline **(38)**.

Metal-halogen exchange using n-butyllithium followed by quenching with triisopropyl borate gave the boronate ester which was hydrolyzed during workup to yield

the arylboronic acid (**39**). After Suzuki cross-coupling with 2-bromoiodobenzene using the homogeneous catalyst tetrakis(triphenylphoshine)palladium(0), biphenyl (**41**) was obtained. Another metal-halogen exchange with n-butyllithium was followed by quenching with chlorodicyclohexylphosphine to give the final product (**11**).

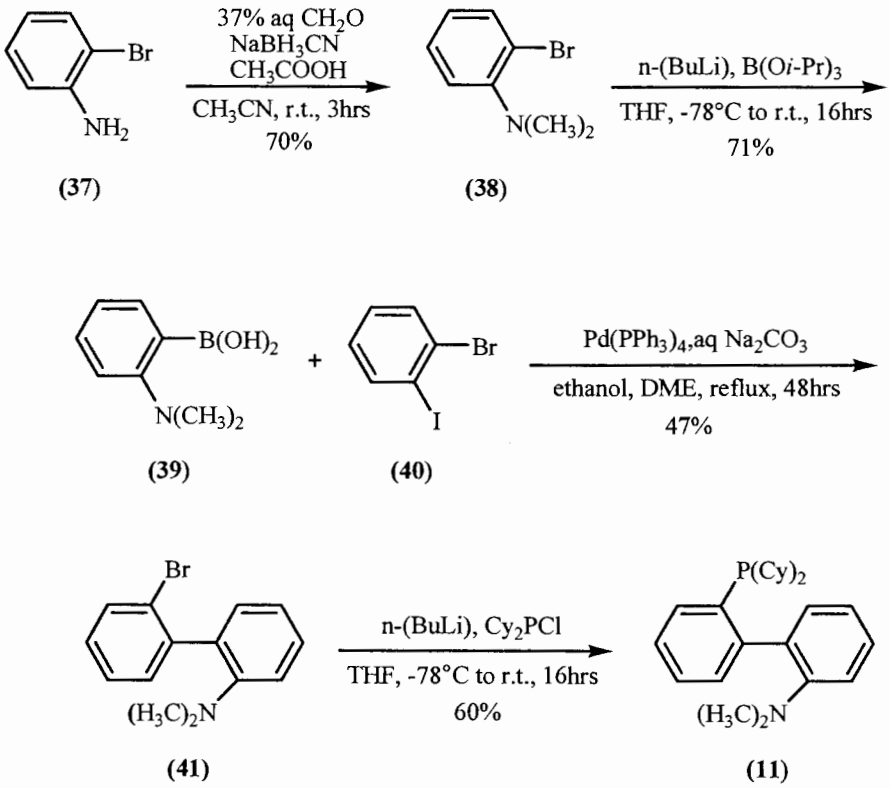


Figure 5: The Preparation of 2-Dicyclohexylphosphino-2'-(*N,N*-dimethylamino)biphenyl

With a comprehensive picture of the ligand effects in hand; we turned toward an examination of the other reaction conditions to determine if the presence of a phosphine affected these variables. From the initial study with ligandless Pd/C, [92] we knew that not only was it crucial to have DMA as the organic solvent but it was also essential to minimize the amount of water present in the mixture. The use of ethanol as a solvent or

[105] Borch, R.F.; Hassid, A.I. *J. Org. Chem.* **1972**, *37*, 1673.

the presence of high concentrations of water resulted in mostly chloroarene homocoupling products.

Table 3 is a comparison of some common solvents and their effect on the Suzuki cross-coupling of our model reaction in the presence of 2.5 mol % MePhos. Just like with ligandless Pd/C, the new system worked well only in the presence of DMA. Unlike the ligandless system, no 4-chloroanisole homocoupling product was detected. There was biphenyl present in low amounts in all the reactions from the homocoupling of the phenylboronic acid. We chose not to change the composition of the solvent and water mixture because of the fact that the 20:1 ratio resulted in no 4-chloroanisole homocoupling product.

Table 3. Effect of Solvent on the Ligand Assisted Pd/C-Catalyzed Suzuki-Miyuara Cross Coupling of 4-chloroanisole and Phenylboronic acid.[a]

Entry	Solvent	Conversion (%)[b]
1	DMA	91
2	Ethanol	48
3	Dimethoxyethane	55
4	N-Methylpyrrolidone	31

[a] All reactions were performed with 0.8 mmol 4-chloroanisole, 0.96 mmol phenylboronic acid, 1.6 mmol K_2CO_3, 0.02 mmol 5% Pd/C, and 0.02 mmol ligand, in 5 mL of 20:1 (v:v) Solvent:H_2O at 80°C for 24 h.
[b] Corrected HPLC conversions are defined as (mmol 4-methoxybiphenyl)/(mmol 4-chloroanisole + mmol 4-methoxybiphenyl) x 100.

We then studied the effect of different bases on our model system. As can be seen from Table 4, the choice of base is also crucial to the success of the reaction. Mild bases such as sodium carbonate (entry 2) and potassium acetate (entry 3) were not effective for the conversion of 4-chloroanisole to 4-methoxybiphenyl. Sodium hydroxide (entry 4) was more effective but still not as efficient as potassium carbonate.

The base plays a dual role in the Suzuki cross-coupling catalytic cycle (see: The Suzuki Catalytic Cycle, pg. 17). It controls the pH of the reaction mixture which is essential for the formation of the hydroxyboronate anion. Also, it plays a role in halide metathesis. Both of these reactions affect the rate of transmetallation, which is believed to be the rate limiting step in the catalytic cycle.

Conlon, Sowa and coworkers[98] have also shown that the type of base which is used can have an impact on the amount of palladium which leaches from the carbon support. By monitoring soluble palladium levels during the Suzuki cross-coupling of a bromoarene and an aryl boronic acid, they determined that the maximum palladium concentration was greater for potassium fluoride than for potassium carbonate. This buildup of soluble palladium was attributed to slow transmetallation, due to the efficiency with which the base can form the species involved in this step.

Table 4. Effect of Base on the Ligand Assisted Pd/C-Catalyzed Suzuki-Miyuara Cross Coupling of 4-Chloroanisole and Phenylboronic acid.[a]

Entry	Base	Conversion (%)[b]
1	K_2CO_3	91
2	Na_2CO_3	38
3	KOAc	27
4	NaOH	69

[a] All reactions were performed with 0.8 mmol 4-chloroanisole, 0.96 mmol phenylboronic acid, 1.6 mmol base, 0.02 mmol 5% Pd/C, and 0.02 mmol ligand, in 5 mL of 20:1 (v:v) DMA:H_2O at 80°C for 24 h.
[b] Corrected HPLC conversions are defined as (mmol 4-methoxybiphenyl)/(mmol 4-chloroanisole + mmol 4-methoxybiphenyl) x 100.

No attempt was made by us to study reaction rates in the presence of different bases. The purpose of these optimization studies was to find a system with which we could apply to a broad range of substrates in order to develop a general synthetic

methodology for the preparation of biphenyls using Pd/C. Both the solvent and base screening studies showed that the conditions of the model reaction were the most efficient for meeting this goal.

We then decided to examine different commercial sources of Pd/C, knowing that each vendor uses slightly different methods for the preparation of this catalyst. We screened Pd/C from four different companies, while keeping the type of catalyst constant (5 % Pd/C, unreduced, eggshell dispersion, approximately 50 % water wetted). We also attempted to lower the concentration of Pd/C, while keeping the metal:ligand ratio the same.

Table 5. Effect of Pd Source and Loading on the Ligand Assisted Pd/C-Catalyzed Suzuki-Miyuara Cross Coupling of 4-Chloroanisole and Phenylboronic acid.[a]

Entry	Pd Source	Pd Mol (%)	Ligand Mol (%)	Conversion (%)[b]
1	Degussa	2.5	2.5	88(66)
2	Alfa Aesar	2.5	2.5	78(70)
3	Englehard	2.5	2.5	57(53)
4	PMC	2.5	2.5	68(57)
5	Degussa	1.25	1.25	30
6	Degussa	0.125	0.125	4

[a] All reactions were performed with 0.8 mmol 4-chloroanisole, 0.96 mmol phenylboronic acid, 1.6 mmol base, 5% Pd/C, and **11** as the ligand, in 5 mL of 20:1 (v:v) DMA:H_2O at 80°C for 24 h.
[b] Corrected HPLC conversions are defined as (mmol 4-methoxybiphenyl)/(mmol 4-chloroanisole + mmol 4-methoxybiphenyl) x 100.
Numbers in parentheses represent isolated yields

The Pd/C from two of the vendors performed equally well (Table 5, entries 1 and 2) while the other two gave slightly worse results (entries 3 and 4). Reducing the concentration of catalyst and ligand by half resulted in approximately two thirds less product formation, while a twentyfold reduction gave only a trace of product.

Taking the results of all the optimization studies together, we decided on a system composed of Degussa 5% Pd/C with MePhos as the ligand, both at a loading of 2.5 mol

% with respect to the chloroarene. We also decided to continue to run the reactions in 20:1 DMA:water with potassium carbonate as the base. The reaction temperature was kept at eighty degrees because it resulted in significant product formation in a reasonable amount of time. As our research on this system progressed, we would reexamine this variable.

By examining the data collected over the course of these studies, it would seem that the original hypothesis is a valid one. There is evidence for a significant homogeneous component to the Pd/C-catalyzed Suzuki reaction. If the reaction were heterogeneous, it would seem unlikely that adding a phosphine would result in such a large difference in reactivity. However, if there is palladium in solution as a result of oxidative addition, the phosphine could ligate to the metal and considerably change its properties.

The fact that high concentrations of ligand effectively shut down the reaction is something that was examined further as the research progressed. However, at the time of the optimization studies we assumed that coordination of the phosphine to the palladium would effectively remove it from the catalytic cycle if the metal:ligand ratio was not optimal. For ligands such as triphenylphosphine, Xantphos, or dppf the reaction was inhibited at all concentrations. To us, this was further evidence to suggest that a discrete palladium-ligand interaction was occurring because of the fact that the biphenyl-based ligands were so effective.

However, without further studies we could not completely rule out a heterogeneous reaction pathway. It is possible that the phosphine is interacting with surface bound palladium and that the chloroarene then reacts with this metal-ligand complex on the carbon surface. Indeed, Buchwald has shown that a biphenyl-based

phosphine ligand anchored on a solid support could effectively sequester solution phase palladium.[106] This surface bound ligand-palladium complex could then be reused in subsequent reactions.

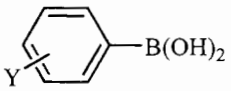
Substrate Scope

Encouraged by the large increase in product conversion in the presence of ligand, we screened additional substrates that were difficult to couple under ligandless conditions. We took our optimized conditions and applied them to the Suzuki cross-coupling of the substrates shown in Table 6. We also compared the reactions run in the presence of ligand to the analogous reactions run under ligandless conditions. Each pair of substrates was reacted for 24 h and then worked up by filtration to remove the catalyst, followed by extraction between ethyl acetate and water. The crude products thus obtained were purified by chromatography on silica to afford the pure biphenyl products.

Each reaction showed a significant increase in yield in the presence of ligand. Each pair of substrates was chosen because of the difficulty with which they couple under ligandless conditions. Electron rich chloroarenes (entries 1-3 and 5) could be coupled along with electron poor phenylboronic acids (entries 2, 4, and 5). Of particular interest were the couplings involving 4-formylphenylboronic acid (entries 2 and 4). This substrate gave particularly poor results under ligandless conditions resulting in no product (entry 2) or very low yield (entry 4).

[106] Parrish, C.A.; Buchwald, S.L. *J. Org. Chem.* **2001**, *66*, 3820.

Table 6. Ligand Free Versus MePhos Assisted Pd/C-Catalyzed Suzuki Cross-Couplings of Chloroarenes.[a]

Entry			Ligand Assisted Yield (%)[b]	Ligand Free Yield (%)[b]
1	4-OCH_3	H	66	32[c]
2	4-OCH_3	4-CHO	30	0
3	4-CH_3	H	61	36[c]
4	H	4-CHO	80	8
5	4-CH_3	2-F	71	27

[a] All reactions were performed with 0.8 mmol 4-chloroanisole, 0.96 mmol phenylboronic acid, 1.6 mmol K_2CO_3, 0.02 mmol 5% Pd/C, and 0.02 mmol MePhos in 5 mL of 20:1 (v:v) DMA:H_2O at 80°C for 24 h.
[b] Isolated yield.
[c] See reference 92.

From this limited data set it would appear as though the addition of ligand has the greatest effect on the couplings involving electron deficient aryl boronic acids (entries 2, 4, and 5). This suggests that the ligand is having the largest effect on the steps in the catalytic cycle which involve the aryl boronic acid. This includes transmetallation and reductive elimination. It is known that electron deficient boronic acids transmetallate slowly because they are poorly nucleophilic (see: Substrate Properties Which Affect Transmetallation, pg 21-23).

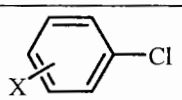
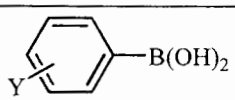
This finding is consistent with that of Buchwald, who reported that the phosphine ligand S-Phos (**20**) efficiently cross-couples electron deficient aryl boronic acids. He proposed that the relative size of this ligand favors a PdL complex and that this accelerates the transmetallation step which is known to be very sensitive to steric effects.[55] It is possible that the MePhos ligand is operating in the same way.

A major advantage of Buchwald's biphenyl based ligands is the ability to catalyze the Suzuki cross-coupling of sterically hindered aryl halides and boronic acids.[55] With this in mind, we explored the coupling of a number of sterically hindered substrates using

our optimized conditions. Unfortunately, this system showed little catalytic activity for these types of substrates and these reactions suffered from low conversion. However, replacing MePhos with XPhos allowed us to obtain a variety of biphenyls in good yields, as seen in Table 7.

In contrast, the ligandless reactions resulted in only trace amounts of product and in most cases only unreacted starting materials were recovered. The efficiency of this process is highlighted by the Suzuki cross-coupling of 2-chloro-*m*-xylene and *o*-tolylboronic acid (entry 5) which proceeded in 71% yield in the presence of XPhos and failed to yield any isolable product under ligandless conditions. In all cases studied the ligand assisted Pd/C reactions were superior to ligandless conditions.

Table 7. Ligand Free Versus XPhos Assisted Pd/C-Catalyzed Suzuki Cross-Couplings of Chloroarenes.[a]

Entry			Ligand Assisted Yield (%)[b]	Ligand Free Yield (%)[b]
1	4-CH_3	2-CH_3	91	27
2	2-CH_3	H	71	15
3	2-CH_3	2-CH_3	80	7
4	2-OCH_3	2-CH_3	30	0
5	2,6-dimethyl	2-CH_3	71	0
6	2-CH_3	4-CHO	86	n.d.
7	2,6-dimethyl	4-CHO	77	n.d.
8	2,6-dimethyl	2-F	70	n.d.
9	4-OCH_3	2-F	75	n.d.

[a] All reactions were performed with 0.8 mmol 4-chloroanisole, 0.96 mmol phenylboronic acid, 1.6 mmol K_2CO_3, 0.02 mmol 5% Pd/C, and 0.02 mmol XPhos, in 5 mL of 20:1 (v:v) DMA:H_2O at 80°C for 24 hrs.
[b] Isolated yield.

As mentioned above, the transmetallation step is very sensitive to steric effects. It is reasonable to assume that there is an equilibrium between PdL and PdL_2 complexes in

solution during the course of the reaction. It is possible that the increased steric bulk of XPhos over MePhos may result in a higher solution concentration of the PdL complex when XPhos is used. This PdL complex could more easily accommodate larger substrates during the transmetallation step. This may explain the increased efficiency for XPhos with hindered substrates.

Recycling Experiments

Having determined that the ligand assisted Pd/C-catalyzed Suzuki coupling of chloroarenes is applicable to a wide variety of substrates, we then needed to explore if this methodology provides any advantages over traditional homogeneous palladium catalysts. It was important to explore whether the Pd/C used in the ligand-assisted process retains any of the desirable characteristics of an immobilized catalyst.

A significant advantage of supported metal catalysts is that they can be easily removed from reaction mixtures. Simple filtration often leads to high recovery of the Pd/C catalyst which can be reused in subsequent reactions. However, it is possible that palladium leaching caused by the presence of the ligand may render the catalyst inactive if the metal does not re-deposit onto the carbon support or if the re-deposition itself reduces the catalytic activity.

To address this issue, several experiments were run using the same batch of catalyst which was recovered from the reaction mixture by filtration. After 24 h of heating, product conversions for the reaction between 2-chlorotoluene and *o*-tolylboronic acid were measured by HPLC and the catalyst was removed and recycled into new reactions. No special precautions were taken to reactivate the Pd/C, except for the addition of 2.5 mol % fresh ligand. We found that the catalyst could be used twice

without any loss in product conversion (Table 8, entries 1 and 2) and up to four times with only a 10-20 % (entries 3 and 4) loss. On the fifth use, a significant drop-off occurred resulting in a mere 19 % conversion to product.

Table 8. The Effect of Catalyst Recycling on the X-Phos Assisted Pd/C-Catalyzed Suzuki-Miyuara Cross Coupling.[a]

Number of Times Used	Conversion (%)[b]
1	75
2	71
3	59
4	53
5	19

[a] All reactions were performed with 1 equiv 2-chlorotoluene, 1.2 equiv *o*-tolylboronic acid, 2 equiv K_2CO_3, 0.025 equiv 5% Pd/C, and 0.025 equiv ligand, in 20:1 (v:v) DMA:H_2O at 80°C.
[b] Corrected HPLC conversions are defined as (mol. of 2,2'-dimethylbiphenyl)/(mol. of 2-chlorotoluene + mol. of 2,2'-dimethylbiphenyl) x 100.

Köhler has reported that Pd/C used for the ligandless Suzuki cross-coupling of bromo and chloroarenes lost more than 50 % of its catalytic activity when it was reused one time.[87] He attributed this loss in efficiency to changes in the distribution and dispersion of the recycled Pd/C, although no experimental evidence was offered to support this. However, during a study of the Heck reaction with iodobenzene,[100] X-ray diffraction and electron microscopy revealed that the re-deposition of solution palladium occurred preferentially onto the surface of the supported palladium particles (see: The Scope of Pd/C-Catalyzed Suzuki Coupling of Chloroarenes, pg 48-49). This finding supports Köhler's hypothesis.

Our study has shown that the Pd/C used in combination with MePhos, can be effectively recycled, provided ligand is added during each subsequent reuse. Until the fifth use, the catalyst retains much of its activity. It is possible that this marked decrease

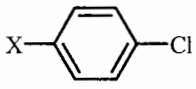
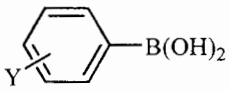
in efficiency during the fifth run is due to an accumulation of leaching in the preceding reactions. This leaching, followed by the repeated re-deposition process could have a number of effects on the metal. It could change the distribution of the metal to a more uniform loading, leaving less palladium at the catalyst surface. It could also cause a change in the distribution as discussed above or it could simply leave the palladium in a different oxidation state, possibly decreasing its activity.

Residual Palladium Analysis of Biphenyl Products

An important characteristic of supported metal catalysts is the low contamination of residual metal in the isolated products. Palladium contamination can become an issue when preparing products for certain applications, such as pharmaceutically active ingredients. Therefore, to probe the issue of palladium leaching, three separate reactions were run. In each case the catalyst was filtered, the products were isolated via simple precipitation or solvent removal, and the residual amount of palladium present was measured by atomic absorption spectroscopy.

As shown in Table 9, the palladium levels in the final products are substantially lower than those observed in reactions which use traditional homogeneous catalysts.[93] For such systems, the potential exists for all of the palladium used in the reaction to remain in the product after isolation. Moreover, palladium levels for the products of the ligand-assisted reactions are near those which have been observed for ligandless Pd/C reactions. This study and that of the above catalyst recycling study suggests that the low palladium contamination is due to a combination of leached palladium that is washed away in the filtrate during workup and significant quantities that are re-deposited back onto the carbon support.

Table 9. Residual Palladium Levels Present in Products Obtained from the Ligand Assisted Pd/C-Catalyzed Suzuki Cross-Coupling.[a]

Entry			Ligand Mol (%)	Pd (ppm)	Yield (%)
1	4-CN	4-CH_3	2.5[b]	9	95
2	2-CH_3	2-CH_3	2.5[c]	11	95
3	4-OCH_3	H	2.5[b]	30	58

[a] All reactions were performed with 3.0 mmol aryl chloride, 3.6 mmol boronic acid, 6.0 mmol K_2CO_3, and 0.075 mmol 5% Pd/C in 20 mL of 20:1 (v:v) DMA:H_2O, in the presence of the stated amount of ligand at 80°C for 24 hrs, except where noted.
[b] MePhos.
[c] XPhos

Tests for Catalyst Homogeneity

When Pd/C is used for carbon-carbon bond forming reactions it is often referred to as the catalyst for the reaction. This terminology is correct if the reaction is taking place heterogeneously, that is, if the palladium active site remains bound to the carbon support throughout the course of the reaction. However, there is mounting evidence in the literature that indicates the active catalytic species is solubilized palladium (see: The Scope of Pd/C-Catalyzed Suzuki Coupling of Chloroarenes, pg 48-50). In this case, the Pd/C is acting as a precatalyst which undergoes an *in situ* transformation to the active catalyst under the reaction conditions.

We believe this to be the case for the Pd/C used in the ligand assisted process. The marked increase in the activity of the Pd/C in the presence of ligand suggests that a soluble form of palladium is interacting with the ligand present in the reaction solution. However, the fact that the Pd/C can be reused, along with the finding that low residual palladium is present in the reaction products, makes it difficult to rule out a

heterogeneous component to the reaction. The situation is further complicated by the fact that we could not initially rule out a surface bound palladium-ligand complex.

There are a number of tests available to the organic chemist for the determination of catalyst homogeneity. Kinetic studies can be performed whereby the concentration of the dissolved palladium can be measured and correlated with the reaction rate.[107] While this provides powerful evidence for homogeneous catalysis, it requires the ability to monitor *in situ* palladium levels by techniques such as ICP or atomic absorption.

Quantifying the amount of recovered catalyst at the end of a reaction is another option. While this may appear to be a logical experiment to run, when one considers that part per million levels of palladium are often all that is required for catalytic activity; it is apparent that such a small loss in mass could not be accurately measured. However, catalyst recovery experiments may confirm the presence of a homogeneous reaction mechanism if a significant amount of palladium is lost from the recovered solid.

The design and execution of the 3-Phase Test is an excellent method for determining catalyst homogeneity. Davies and coworkers,[99] recently applied this test to the Suzuki and Heck reactions. The basic premise of this test is to immobilize one reagent on a solid support, in this case an iodoarene. The palladium is then immobilized on a different support and the rest of the reactants are introduced into the solution. For the reaction to occur there must be soluble palladium species present. There are, however, drawbacks to this methodology. First, there is the requirement to have one of the reagents on a solid support; the preparation of which may not be a trivial task. Also,

---

[107] (a) Zhao, F.Y.; Bhanage, B.M.; Shirai, M.; Arai, M. *Chem. Eur. J.* **2000**, *6*, 843. (b) Heidenreich, R.G.; Krauter, J.G.E.; Pietsch, J.; Köhler, K. *J. Mol. Catal. A* **2002**, *182*, 499.(c) Köhler, K.; Heidenreich, R.G.; Krauter, J.G.E.; Pietsch, J. *Chem. Eur. J.* **2002**, *8*, 622.

one must consider the possibility of changes in reaction kinetics when one reagent is immobilized.

Catalyst poisons are often used as indicators of reaction homogeneity. Some common poisons for soluble catalysts are carbon disulfide, triphenylphosphine, and thiophene.[108] Jones and coworkers,[109] have developed an approach which introduces an insoluble solid material, which is filled with binding sites, to a reaction mixture. They used cross-linked poly(vinylpyridine) as a soluble palladium poison during reactions of immobilized palladium pincer complexes. However, the use of these additives as poisons for the Pd/C-catalyzed Suzuki reaction may not be ideal because the concentration of soluble palladium species has been observed to change during the course of the reaction.[98] This makes it difficult to choose the proper stoichiometry for addition of the poison.

In an effort to determine the true nature of the active catalytic species present during the ligand assisted Pd/C-catalyzed Suzuki cross-coupling, we employed two operationally simple tests. First we performed filtration and split tests to determine if cross-coupling could occur when the solid material was separated from the reaction. We then used the mercury poisoning test to determine the extent of homogeneous catalysis and to gain insight into the properties of the active catalyst.

Filtration and Split Tests

The use of a filtration test to rule out catalysis by a homogeneous species can often be misleading. A recently published study demonstrates the uncertainty which can

[108] Widegren, J.A.; Finke, R.G. *J. Mol. Catal. A.* **2003**, *198*, 317

accompany such tests.[110] Arai and coworkers designed experiments whereby homogeneous palladium compounds were used as catalysts for the Heck reaction in the presence of either a carbon or silica support. After complete conversion of the iodoarene to product, no solution phase palladium could be detected. The support was then reused in subsequent reactions without adding a palladium source and all of the catalytic activity remained. In a separate experiment, they found that palladium leached from a silica support into solution and preferentially re-deposited onto a carbon support. If the soluble palladium concentrations were determined at the completion of these reactions by someone with no knowledge of the experimental design, this person would undoubtedly conclude that the reaction was heterogeneously catalyzed.

However, the use of a filtration test to determine the presence of homogeneous species is valid. If, after removal of the solid Pd/C from the reaction solution, the reaction continues to proceed, one can conclude that soluble palladium species are present. Of course, this would not rule out the possibility that colloidal palladium could pass through a filter and catalyze the coupling. The presence of palladium colloids can be detected using a suitable analytic technique, such as X-Ray diffraction or transmission electron microscopy, but this experiment was not done.

Two different filtration tests were designed and run using the experimental setup depicted in Figure 6, with 4-chloroanisole and phenylboronic acid as substrates (see: Experimental Section, pg 129-132).

---

[109] Sommer, W.J.; Yu, K.Q.; Sears, J.S.; Ji, Y.Y.; Zheng, X.L.; Davis, R.J.; Sherrill, C.D.; Jones, C.W.; Weck, M. *Organometallics* **2005**, *24*, 4351.
[110] Zhao, F.; Murakami, K.; Shirai, M. Arai, M. *J. Catal.* **2000**, *194*, 479.

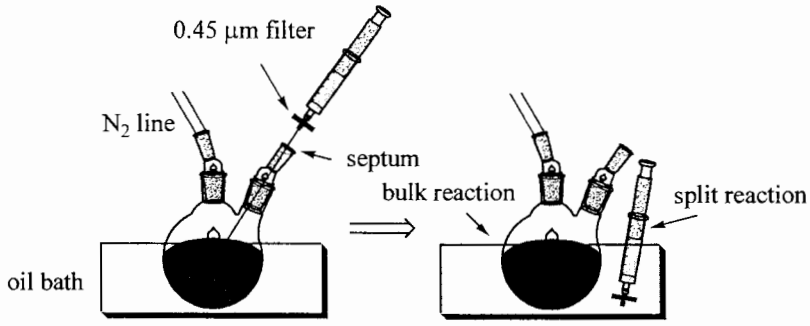


Figure 6: Schematic Representation of the Apparatus Used for Filtration and Split Tests

In the first, an aliquot was removed by using a syringe after 6 h at 80 °C and the solid Pd/C was removed through a 0.45 μm filter. To ensure that any soluble palladium would not become deactivated, additional quantities of potassium carbonate, phenylboronic acid, and 4-chloroanisole were present inside the syringe. The filtered sample was heated for a further 18 h.

Product yield was determined by HPLC for the bulk reaction at 6 h and the split reaction at 24 h by measuring the reactant and product concentrations against a calibration curve, using hexamethylbenzene as an internal standard to account for variations in injection volume. If the reaction had stopped after the filtration, a yield of 30 % should have been obtained for the split reaction based on the amount of additional 4-chloroanisole added. In contrast, an HPLC yield of 64 % was obtained.

In the second experiment, an aliquot was removed after 3 h and filtered. This time additional reagents were not added and the reaction was heated for another 19 h. The aliquot taken immediately before the filtration showed 4 % conversion to product. After 22 h, the filtered reaction had proceeded to 27 % as measured by HPLC, whereas the bulk reaction had a conversion of 33 %. The low yields were attributed to boronic acid homocoupling, which was most likely a result of oxygen introduction into the

system[35] when the aliquots were taken. However, the fact that the product conversions were similar for the bulk and the filtered split reaction clearly demonstrates that the reaction proceeded even after the Pd/C was filtered off.

The results of these filtration tests suggest a homogeneous reaction pathway is operative. In addition, the prior results obtained during the reaction optimization and substrate scope studies, point toward catalysis by a homogeneous palladium-ligand complex. Such a complex may dissociate to liberate molecular palladium which can re-deposit onto the support at the end of the reaction when no chloroarene is present.

Mercury Poisoning Experiments

While the product formation for the split reaction was close to that of the bulk reaction in the second filtration test, the split reaction was less efficient. The reason for this was somewhat unclear. It is possible that there is a heterogeneous component to the cross-coupling that could not operate in the split reaction after the Pd/C was removed. Another explanation could be that without the Pd/C present in the reaction mixture the re-deposition of the metal could not occur and this resulted in the solution phase palladium becoming deactivated. Finally, it is possible that during the course of the bulk reaction the concentration of soluble palladium increased after the split was taken. This would result in a lower palladium concentration for the split reaction because no Pd/C was present to act as a "palladium reservoir".

We set out to explore these possibilities through the use of the mercury poisoning test. Mercury can amalgamate most metals and destroy their catalytic activity. The first

example of this was reported in 1918.[111] It was discovered that colloidal palladium solutions used for catalyzing detonating gas or reducing organic nitro compounds were rendered inactive when they were employed in gas burets with mercury as the confining liquid. Through a series of experiments the authors concluded that mercury and mercuric oxide inhibited palladium from adsorbing hydrogen gas and catalyzing reactions such as the reduction of unsaturated compounds. Reactions such as the decomposition of hydrogen peroxide, which take place via a homogeneous pathway, were unaffected.

The ability of mercury to inhibit such heterogeneous processes was later used to distinguish between homogeneous and heterogeneously catalyzed reactions. The original test was developed to determine the presence of homogeneous transition metal species during the course of hydrogenation reactions.[112] This was done by simply mixing the reaction with an excess of mercury and determining the effect on the catalytic activity of the metal.

To further address the issue of catalyst homogeneity we designed a series of experiments to determine the effect of mercury added to the reaction mixture. Both the ligandless Pd/C catalyzed reaction between 4-chloroanisole and phenylboronic acid and the reaction run with 2.5 mol % MePhos (Table 10, entries 1 and 2) were inhibited by the presence of excess mercury. In addition, to make certain that a palladium-ligand complex formed, the ligand assisted reaction (entry 3) was run for 3 hours before the mercury was added. This protocol also resulted in catalyst poisoning.

---

[111] Paal, C.; Hartman, W. *Ber. Dtsch. Chem. Ges.* **1918**, *51*, 711.
[112] Foley, P.; Dicoismo, R.; Whitesides, G.M. *J. Am. Chem. Soc.* **1980**, *102*, 6713.

Table 10. The Effect of Mercury on the Pd/C-Catalyzed Suzuki Cross-Coupling of 4-chloroanisole and Phenylboronic acid.[a]

Entry	Procedure	Mol % Ligand	Control Conversion (%)[b]	Hg Treated Conversion (%)
1	A	0	37	7
2	A	2.5	91	2
3	B	2.5	n.d.	1
4	C	2.5	38[c]	2

[a] See Experimental Section for procedural details.
[b] Corrected HPLC conversions are defined as (mmol 4-methoxybiphenyl)/(mmol. 4-chloroanisole + mmol. 4-methoxybiphenyl) x 100.
[c] The conversion of the control reaction without mercury was equal to the conversion of the bulk reaction at three hours (38%).

According to the traditional interpretation of the mercury poisoning test, the results above imply that a heterogeneous reaction mechanism is operative. However, there can also be another explanation. The original poisoning tests were performed on metals in high oxidation states surrounded by large, tightly bound ligands. The likelihood of such a species being affected by mercury, even while in solution, is low.

Weck and Jones have demonstrated this phenomenon by studying palladium(II) pincer catalysts. They have shown that these compounds are unaffected by mercury in reactions where the ligands stay intact and the metal remains as palladium(II). On the contrary, these catalysts are quenched by mercury in the Heck reaction, a process which is known to occur via a catalytic cycle involving palladium in the zero oxidation state.[113] Based on this type of evidence, it has been suggested [97] that a positive mercury poisoning test can only lead to the conclusion that the reaction is occurring via a cycle that involves a palladium(0) intermediate.

[113] Yu, K.; Sommer, W.; Richardson, J.M.; Weck, M.; Jones, C.W. *Adv. Synth. Catal.* **2005**, *347*, 161.

To remove the ambiguity from our experimental results, a novel mercury poisoning experiment was designed (entry 4) utilizing the reaction apparatus depicted in Figure 7. Aliquots of an ongoing reaction were filtered through a 0.25 μM filter into gas tight syringes (to minimize contamination by oxygen) after one hour at 100 °C. One aliquot was heated in the presence of excess mercury, while the other was heated without mercury to serve as a control. The control aliquot continued to form product at the same rate and in the same amount as the unfiltered bulk reaction. However, the aliquot treated with mercury failed to provide significant amounts of product (2 % conversion) after the filtration.

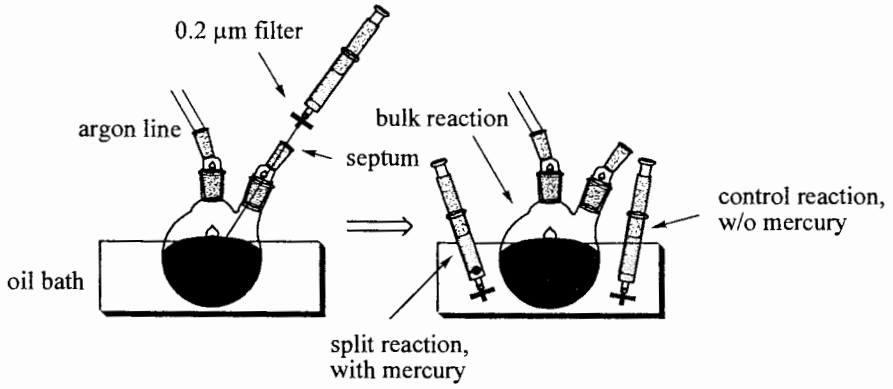


Figure 7: Schematic Representation of the Apparatus Used for Mercury Split Test

Because of the fact that there is no solid Pd/C present in the filtered control sample, this proves that a solubilized form of the catalyst is responsible for the catalysis. However, the fact that the filtered mercury treated sample ceases to form product suggests that the solubilized catalyst is a weakly ligated palladium(0) species. In addition, because the product conversion in the filtered control sample is equal to that of the unfiltered bulk reaction this indicates that there is minimal or no cross-coupling

occurring at the surface bound palladium atoms. Taken in their entirety, we believe these experiments provide proof that the reaction takes place via a homogeneous pathway.

In summary, we have successfully shown that unreduced, water wetted, Pd/C can be used as a precatalyst for the Suzuki reaction of chloroarenes and phenylboronic acids. Addition of a phosphine ligand allows for the preparation of a wide variety of biphenyl products with low residual palladium contamination. The precatalyst can be removed by simple filtration and reused multiple times. Despite the fact that Pd/C retains many of the advantages of a heterogeneous catalyst, the reaction is taking place via a homogeneous pathway.

Pd/C-Catalyzed Suzuki Couplings of Chloroarenes at Low Ligand Loadings

We have successfully demonstrated that Pd/C can be used as an efficient precatalyst in the Suzuki cross-coupling of chloroarenes and aryl boronic acids. Our ligand assisted method has many advantages over both ligandless Pd/C-catalyzed reactions and those which employ traditional homogeneous catalysts. We have shown that the addition of ligand can greatly expand the scope of the substrates that can be coupled using Pd/C. Unlike traditional homogeneous catalysts, our method also allows for easy removal and reuse of the Pd/C as well as low palladium contamination of the final products.

However, the cost associated with the preparation or purchase of the phosphine ligand is a significant drawback. When we first developed this methodology we envisioned that very small concentrations of ligand would be sufficient to successfully catalyze these reactions. Unfortunately, initial experiments designed to lower the phosphine loading in our model study resulted in suboptimal results when less than 2.5 mol % of ligand was employed (see: Reaction Optimization Studies, pg 58-62).

From the work on ligandless Pd/C systems we were aware that for most substrates extremely low levels of soluble palladium are present throughout the time course of the reaction.[114] In addition, Conlon, Sowa and coworkers[98] have shown that soluble palladium levels increase during the Pd/C-catalyzed Suzuki coupling, as long as aryl halide is present. From our ligand screening studies we knew that higher ligand levels are detrimental to the process, perhaps due to overcoordination of the ligand to the metal. We then reasoned that at the onset of the reaction, when soluble palladium levels are low,

[114] LeBlond, C. *Scope and Mechanistic Studies of the Palladium on Carbon Catalyzed Suzuki Cross Coupling Reaction;* PhD dissertation, Seton Hall University, 1994.

the ligand is actually inhibiting the reaction. One way to overcome this problem would be to wait until the soluble palladium concentration increases before adding the ligand.

Pd/C Incubation Studies

We designed experiments whereby low levels of ligand (0.3 mol %) were added to the reaction mixture after a short incubation period. We determined the optimum amount and time for addition of the ligand by studying the model reaction between 2-chlorotoluene and phenylboronic acid in the presence of XPhos. We determined that when this reaction was run at 100 °C, a 15 min incubation period was sufficient for successful catalysis and running the incubation at 80 °C required 3 h.

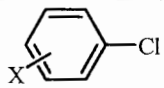
Initially, we had difficulty adding the ligand because it was insoluble in dimethylacetamide. We were able to dissolve it in a minimal amount of dichloromethane or tetrahydrofuran. However, we abandoned this practice in favor of solid addition under a positive counter current of argon.

As can be seen from Table 11, this protocol allows for coupling reactions under low ligand loadings. The reaction between 4-chloroanisole and phenylboronic acid (entries 1-3) is equally as effective at a ligand loading of 0.3 mol % with respect to chloroarene as it is at 2.5 mol %, (see Table 6, entry 1) provided an incubation time of 3 h at 80 °C is used. Without the incubation period the yield is similar to the ligandless reaction. In addition, palladium analyses of the product prepared from the conditions listed in entry 1, resulted in < 5 ppm by atomic absorption spectroscopy.

Even more remarkable are the results for the coupling between 2-chlorotoluene and phenylboronic acid (entries 4-8). Incorporating an incubation time of either 15 min

at 100 °C or 3h at 80 °C results in a fourfold increase in product yield (90 %) vs. reaction without an incubation period (~20 % yield).

Table 11. The Effect of Incubation Time on the Pd/C-Catalyzed Suzuki Cross-Couplings of Chloroarenes and Aryl Boronic Acids[a]

Entry		Ar-B(OH)$_2$	Ligand	Temp (°C)	Incubation Time (h)	Post Incubation Time (h)	Yield (%)[b]
1	4-OCH_3	phenyl	MePhos	80	3	21	63
2	4-OCH_3	phenyl	MePhos	80	0	24	31
3	4-OCH_3	phenyl	none	80	n/a	24	32
4	2-CH_3	phenyl	XPhos	80	3	21	89
5	2-CH_3	phenyl	XPhos	80	0	24	22
6	2-CH_3	phenyl	none	80	n/a	24	15
7	2-CH_3	phenyl	XPhos	100	0.25	2	90
8	2-CH_3	phenyl	XPhos	100	0	2	24
9	2-CH_3	3-pyridyl	XPhos	100	0.25	23	53
10	2-CH_3	3-pyridyl	XPhos	100	0	23	45
11	2-CH_3	3-pyridyl	none	100	n/a	23	0
12[c]	4-OCH_3	2,4-difluorophenyl	XPhos	100	0.25	2	64
13[c]	4-OCH_3	2,4-difluorophenyl	XPhos	100	0	2	66
14[c]	4-OCH_3	2,4-difluorophenyl	none	100	n/a	2	0

[a] Reactions mixtures were incubated with 2.8 mmol aryl chloride, 3.4 mmol boronic acid, 5.6 mmol K_2CO_3, and 0.07 mmol 5% Pd/C in 20 mL of 20:1 (v:v) DMA:H_2O at 100°C for 15 min, followed by continued heating in the presence of 0.3 mol% ligand.
[b] Isolated yield.
[c] 5.6 mmol of boronic acid was used.

Coupling of heteroaromatic compounds is desirable. Thus, we successfully prepared 3-(2-methylphenyl)pyridine (entries 9-11) in yield of 53 % after 23 h at 100 °C. However, this reaction does not appear to require an incubation period. Remarkably, the ligandless reaction failed to yield any product, instead only unreacted 2-chlorotoluene was observed by HPLC. Protodeboronation of the 3-pyridylboronic acid occurred in all reactions studies and likely limited the overall yield of this reaction.

Similar results were obtained for the cross-coupling of 4-chloroanisole with 2,4-difluorophenylboronic acid (entries 12-14). There was essentially no difference

between the reactions run with or without the incubation period. However, because of the ease with which electron deficient phenylboronic acids protodeboronate,[39] we were pleased to be able to prepare this biphenyl product in up to 66 % yield. Indeed, in the ligandless reaction, only protodebornation occurs; while in the ligand assisted reactions, the competing protodeboronation reaction only became dominant after the 2 h. Fortunately, the volatile 1,3-difluorobenzene is easily separated from the product.

We believe these results demonstrate our ability to exploit the unique property of Pd/C to leach catalytically active species into solution over time, thereby making it possible to greatly reduce the phosphine loading. By instituting an incubation period for the Pd/C, product yields were increased for two of the reactions. However, for the other two reactions an incubation period was not necessary to achieve coupling at low ligand loading.

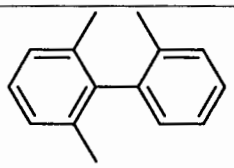
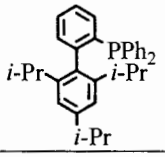
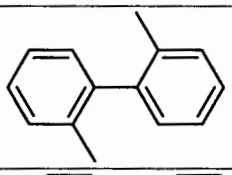
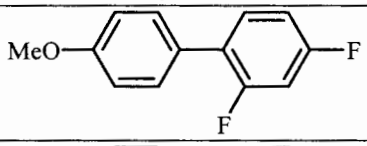
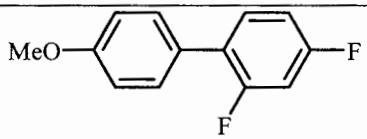
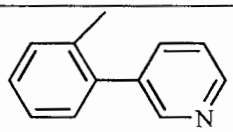
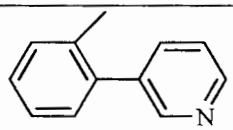
This finding demonstrates that consideration of the properties of the haloarene and the boronic acid may be effective in predicting the length of the incubation period and the ligand loading necessary for Suzuki couplings using Pd/C as a precatalyst. It is possible that the use of a model system is insufficient and that the optimal time differs for each reactant pair. As can be seen in Table 11, for two electron donating chloroarenes (entries 1-8) an incubation time was crucial. However, it was not when these substrates were coupled with two strongly electron withdrawing boronic acids (entries 9-14) Therefore, it may be necessary to determine the appropriate incubation period by studying either product conversion or palladium concentration over time for each set of reactants.

While the results we have obtained using Pd/C incubation times seem to validate our hypothesis that the phosphine is acting as an inhibitor at high concentrations, there may be another explanation. It is possible that when the ligand is added at low loading before the start of the reaction, it preferentially adsorbs on the carbon support. As discussed previously, (see: Properties of Supported Metal Catalysts, pg 44) the surface of the charcoal contains functionalities which can interact with a phosphine group. Allowing the reaction to initiate before adding the ligand may provide high enough levels of soluble palladium to effectively compete for the ligand over the carbon support. To date we have not been able to rule this possibility out.

As displayed in Table 12, utilizing an incubation period for the Pd/C significantly reduces the cost associated with the phosphine ligand by decreasing the amount needed for successful catalysis. This table compares ligand turnover numbers for the preparation of four biphenyl products using different palladium precatalysts. This data shows that Pd/C has the potential to be a more cost effective precatalyst than traditional homogeneous palladium sources.

Entries 1 and 2 compare two structurally related compounds; one of which was prepared using a state of the art homogeneous catalyst system while the other was prepared using the ligand assisted Pd/C methodology. Entries 3 to 6 compare the same compounds prepared using both methods. The data clearly shows that the use of Pd/C as a precatalyst allows for significantly higher ligand turnover numbers.

Table 12. Comparison of Ligand Turnover Numbers for the Preparation of Biaryls Using Palladium Precatalysts[a]

Entry	Product	Catalyst System	Ligand Loading (mol %)	Yield (%)	Ligand TON
1		$Pd(OAc)_2$/ 	1.5	94	63
2		5 % Pd/C XPhos	0.3	90	300
3		$Pd(OAc)_2$/ SPhos	1.0	99	99
4		5 % Pd/C XPhos	0.3	66	220
5		$Pd_2(dba)_3$/ SPhos	4.0	81	20
6		5 % Pd/C XPhos	0.3	53	177

[a] For entries 2,4, and 6 see Table 11, for entries 1,3, and 5 see ref. 55

Proposed Catalytic Cycle for the Ligand Assisted Process

Based on the results presented in this dissertation and building upon previously published findings, we propose the mechanism depicted in Figure 8 for the ligand assisted process.

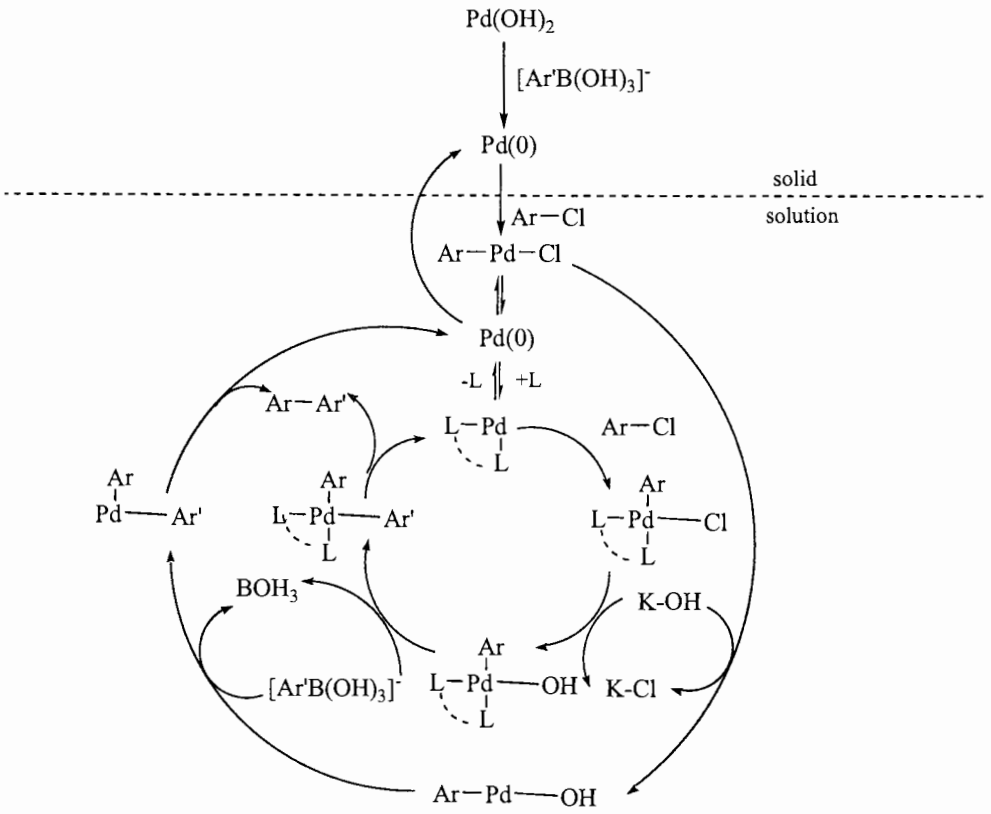


Figure 8: Proposed Catalytic Cycle for the Ligand Assisted Suzuki Reaction with Pd/C.

The initial palladium in Pd/C exists in the form of palladium hydroxide or oxide on the surface of the carbon support. It is reduced to Pd(0) by concomitant oxidation of the boronic acid [32b, 35] or by the DMA solvent. Oxidative addition to the aryl chloride results in the σ-aryl-Pd(II) chloride species, thereby desorbing the palladium from the carbon support.[97]

In the absence of ligand or at low ligand concentrations, this species can undergo reaction via the outer cycle shown in blue. Excess base present in the aqueous reaction mixture provides a source of hydroxide ions which can displace the chloride to give the aryl-Pd(II) hydroxide species.[115] Transmetallation with the aryl boronic acid[116] and

[115] Miyuara, N.; Yamada, K.; Suginome, H.; Suzuki, A. *J. Am. Chem. Soc.* **1985**, *107*, 972.

reductive elimination provide the product and regenerate Pd(0) which can either continue to react or readsorb onto the carbon support.

Mercury poisoning studies provide evidence for the presence of a labile palladium ligand complex. We interpret this result to mean that the ligand association to Pd(0) is a reversible process. Ligand association results in the palladium ligand complex which may be monodentate or bidentate. This complex then proceeds via the inner cycle shown in red. This cycle also results in product and Pd(0) which, as we have shown through palladium contamination studies, also undergoes the redeposition process.

One or both of the cycles may be operative at a time. For the ligand assisted reactions, the contribution of the outer cycle to product formation is likely minimal and the inner cycle is most likely the dominant pathway.

In summary, the use of a Pd/C incubation period can significantly increase ligand turnover numbers, thereby reducing the overall cost of the process. Based on our work and previously published findings, a catalytic cycle is proposed in which ligand free and ligand assisted pathways combine to give practical yields of coupling products but also result in low levels of Pd contamination.

---

[116] Aliprantis, A.O.; Canary, J.W. *J. Am. Chem. Soc.* **1994**, *116*, 6985.

Synthesis of Norfloxacin via Palladium-Catalyzed Amination

Currently there is considerable interest in fluoroquinolone antibacterials as these pharmaceuticals are used for the treatment of infections resulting from exposure to *Bacillus anthracis* (anthrax).[117] In particular, Ciprofloxacin is specifically recommended; however, utilization of other fluoroquinolones such as Levaquin and Tequin is under investigation.[118] The first fluoroquinolone to establish clinical usage was Norfloxacin (**42**).[119] This pharmaceutical also serves as an excellent example of the typical synthesis of fluoroquinolones which are almost invariably prepared via nucleophilic addition (S_NAr) of an amine to a fluorochloroquinolone (**43**) as the final step (Figure 9).[120] However, it is known that this step may produce 10 – 25 % of an undesired fluoro-substituted byproduct (**44**).[121,122]

---

[117] (a) Kelly, D.J.; Chulay, J.D.; Mikesell, P.; Friedlander, A.M. *J. Infect. Dis.* **1992**, *166*, 1184. (b) Terriff, C.M.; Tee, A.M. *Am. J. Health-Syst. Pharm.* **2001**, *58*, 233.

[118] Silverman, E. "Bioterrorism anxieties may spell end of red tape." The Sunday Star-Ledger: Newark, NJ, Oct 28, 2001, p. 11.

[119] (a) Koga, H.; Itoh, A.; Murayama, S.; Suzue, S.; Irikura, T. *J. Med. Chem.* **1980**, *23*, 1358. (b) *Quinolone Antimicrobial Agents, 2nd ed.*; Hooper, D.C. Wolfson, J.S., Eds. American Society for Microbiology: Washington DC, 1993; Ch 1, 3.

[120] Chu, D.T.W. In *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications*, Filler, R. et al. Eds. Fluoroquinolone carboxylic acids and antibacterial drugs. Elsevier: New York, 1993.

[121] (a) Kalkote, U.R.; Sathe, V.T.; Kharul, R.K.; Chavan, S.P.; Ravindranathan, T. *Tetrahedron Lett.*, **1996**, *37*, 6785. (b) Hermecz, I.; Vasvari-Debreczy, L.; Podanyi, B.; Kereszturi, G.; Balogh, M.; Horvath, A.; Varkonyi, P. *Heterocycles*, **1998**, *48*, 1111. (c) Preiss, M. *Eur. Patent Appl.* 0,461,501,A1 Jan 6. 1991.

[122] Although the chemoselectivity is not discussed, the following patents claim > 90 % yield of fluoroquinolone products using protected piperazines: (a) Park, S.W.; Kim, Y.S.; Jin J.H. *US Patent* 5051505, 1991. (b) V. Scherrer-Pangka *CA Patent* 1326239, 1994.

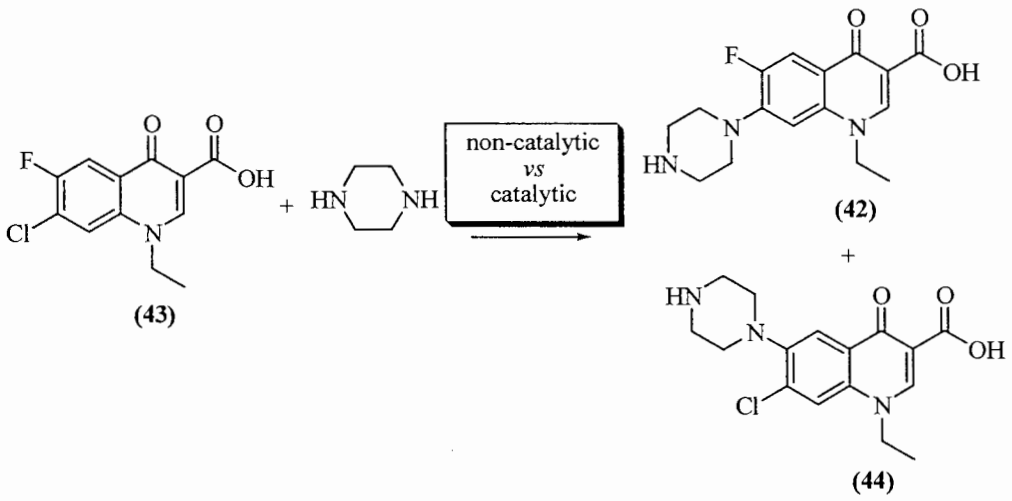


Figure 9: The Final Step in the Synthesis of Fluoroquinolones

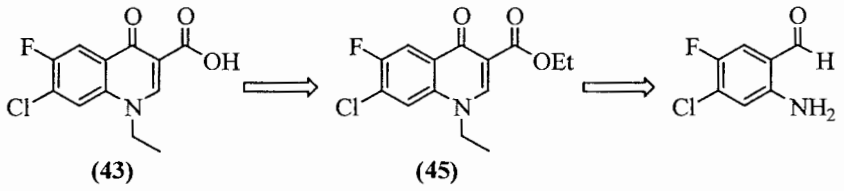
Palladium-catalyzed amination[123] is an attractive alternative strategy to the current synthesis of fluoroquinolones because the reaction goes through an oxidative addition step in which aryl-fluoride bonds are inert.[124] This reaction involves an efficient coupling of haloarenes and amines and is successful for haloarenes with a broad range of functionalities. Herein, we demonstrate that the palladium-catalyzed amination methodology can be extended toward chemoselective syntheses of fluoroquinolones.

Preparation of Norfloxacin

The synthesis of fluoroquinoline antibacterials almost invariably involves substitution of the chlorofluoroquinolone with an amine as the final step. Earlier model studies[123] on the palladium-catalyzed amination of simple fluorohaloarenes indicated excellent potential for the palladium-catalyzed amination reaction to succeed. However,

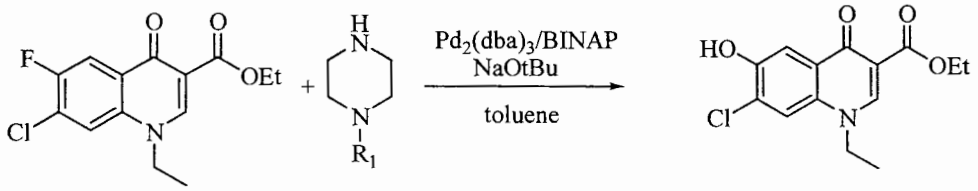
[123] For reviews see: a) Hartwig, J.F. *Angew. Chem. Int. Ed. Engl.*, **1998**, *37*, 2046. b) Wolfe, J.P.; Wagaw, S.; Marcoux, J. –F.; Buchwald, S.L. *Acc. Chem. Res.*, **1998**, *31*, 805. c) Hartwig, J.F. *Synlett*, **1997**, 329.
[124] For a preliminary communication of this work see: Hayden, S. Sowa, Jr., J. R. In *Catalysis of Organic Reactions*, Herkes, F. E., Ed. Synthesis of fluoroaniline derivatives by selective palladium-catalyzed coupling of N-methylpiperazine and fluorhaloarenes. Marcel Dekker: New York, 1998; pp. 627-632.

initial attempts to couple the chlorofluoroquinolone derivative (**43**) with piperazine using a Pd_2dba_3/BINAP catalyst system and NaOtBu in toluene solvent resulted only in the recovery of unreacted starting material. Changing to more polar solvents (DMSO, DMF) or the addition of iodide salts (in an attempt to generate the iodo derivative) had no effect. It was believed that the insolubility of the carboxylic acid (**43**) played a role in its failure to react and that the ethyl ester would be a more productive substrate. Conveniently, the ethyl ester of (**43**) is an intermediate in the standard synthesis of Norfloxacin, thus, the synthesis of (**45**) was readily accomplished (eq 24).[118a]



(43) (45) **(24)**

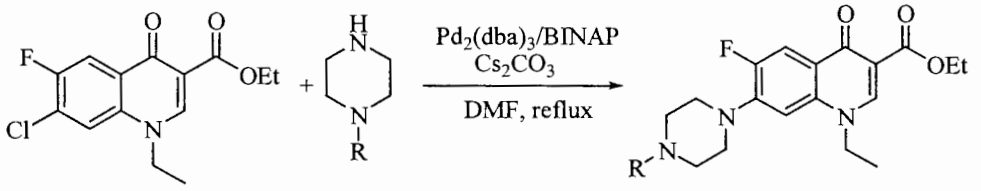
With this compound in hand, the original conditions were repeated. However the nucleophilic character of the NaOtBu base resulted in a product from a non-catalytic attack of the t-butoxide anion at the fluorine and subsequent hydrolysis of the t-butyl ether (eq 25) during workup to give phenol (**46**).



(45) (46) **(25)**

The first signs of the desired product (**47**) were obtained in 29% yield by switching to the non-nucleophilic base, cesium carbonate, after 48 hours in refluxing

toluene.[125] Further optimization was achieved by switching to the higher boiling DMF and increasing the amount of piperazine to five equivalents. These modifications gave yields that ranged from 58 - 66 % after three hours at reflux for the piperazine (**47a**) and 72 - 75% for the N-methylpiperazine (**47b**) analogs (eq 26).

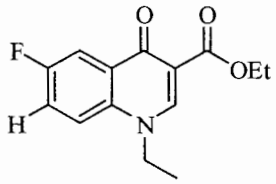


(45)

(47a) R=H, 58-66 %
(47b) R=Me, 72-75 %

(26)

Detailed analysis of the reaction mixtures revealed that the reaction occurs with quantitative chemoselectivity as no fluoro-substituted products are observed. However, further analysis of the synthesis of (**47a**) revealed 22 % of the known hydrodechlorinated product[126] (**48**). Although the reducing agent has not been identified, reductions in palladium-catalyzed aminations have been observed where the amine acts as the reducing agent via a β-hydrogen elimination pathway.[127]



(48)

Although this byproduct is removed by chromatography in the work-up, efforts to eliminate its formation during the reaction were unsuccessful. Attempts to improve yield and eliminate (**48**) with biphenyl based ligands such as (**9**) and (**10**) or $P(tBu_3)$ were

---

[125] Wolfe, J.P.; Buchwald, S.L. *J. Org. Chem.*, **2000**, *65*, 1144.
[126] Tsou, T.–L.; Tang, S.–T.; Wu, J.–R.; Hung, JY.-W.; Liu, Y.-T. *Eur. J. Med. Chem.*, **1999**, 34, 255.
[127] (a) Hamann, B.C.; Hartwig, J.F. *J. Am. Chem. Soc.*, **1998**, *120*, 12706. (b) Hamann, B.C.; Hartwig, J.F. *J. Am. Chem. Soc.*, **1998**, *120*, 7369. (c) Hamann, B.C.; Hartwig, J.F. *J. Am. Chem. Soc.*, **1998**, *120*, 3694. (d) Hartwig, J.F.; Richards, S.; Baranano, D.; Paul, F. *J. Am. Chem. Soc.*, **1996**, *118*, 3626.

fruitless. When the non-catalytic reaction was run under the same conditions, the desired **(47a)** formed in 24 h which is much longer than the reaction with catalyst present. However, the formation of the undesired fluoro-substituted product was inconclusive. Nevertheless, the substantially shorter reaction time (3 h) when catalyst is present suggests that a catalytic reaction is indeed occurring.

The syntheses of the fluoroquinolones were completed by subjecting the corresponding esters to basic hydrolysis. Treatment of **(47a)** and **(47b)** with 2N sodium hydroxide solution for two hours at reflux resulted in near quantitative yields of Norfloxacin **(42)** and the N-methylpiperazine derivative **(49)**.

Another strategy employed to enhance the chemoselectivity of fluoroquinolone syntheses has been the use of boron reagents to increase the electrophilicity of the C-7 position by chelating to the β-ketoacid but ~ 5% side-product **(44)** formation is still observed.[120b] Our study shows that the palladium-catalyzed pathway completely eliminates the formation of this by-product. Although palladium-catalyzed amination has been extensive developed for simple as well as moderately complex substrates, its compatibility with fluoroquinolones is noteworthy because of the complex functionality these substrates possess.

Additional and Preliminary Investigations

This chapter is dedicated to the discussion of two research projects that were undertaken with the aim of improving the reactivity and selectivity of chloroarenes in palladium catalyzed processes. For both projects the results are preliminary and more work should be done to further this research. This is especially true of the second project, which is essentially a proposal for a new type of azaphosphine ligand. Because of time constraints the desired compound was never successfully prepared.

Preparation of Aryl Nitriles via Pd Catalyzed Cyanation

Aryl nitriles are found in a number of pharmaceuticals and natural products and are also among the most versatile functionalities in synthetic organic chemistry. They can be transformed into a variety of other moieties including: carboxylic acids, amides, aldehydes, and tetrazoles. Several methods have been reported for their preparation including: the Sandmeyer reaction of aryl diazonium salts,[128] electrophilic aromatic substitution of anilines,[129] phenols,[130] and phenolic ethers,[131] cyanide displacement of aryl sulfonates, [132] and conversion of primary nitro compounds into nitriles. [133] Haloarenes can be converted to nitriles via the Rosemund-von Braun reaction,[134] however this procedure employs stoichiometric amounts of copper cyanide and high reaction temperatures. In recent years, haloarene cyanation using transition metal catalysts, most

[128] Kochi, J.K. *J. Am. Chem. Soc.* **1957,** *79*, 2942.
[129] Adachi, M.; Sugasawa, T. *Synth. Commun.* **1990**, *20*, 71.
[130] Bigi, F.; Maggi, R.; Sartori, G.; Casnati, G.; Bocelli, G. *Gazz. Chim. Ital.* **1992**, 283.
[131] Jones, M.; Froussios, C.; Evans, D.A. *J. Chem. Soc. Chem. Commun.* **1976**, 472.
[132] Maffei, S. *Gazz. Chim. Ital.* **1950**, 651.
[133] (a) Wehrli, P.A.; Schaer, B. *J. Org. Chem.* **1977**, *42*, 3956. (b) Urpf, F.; Vilarrasa, J.; *Tetrahedron Lett.* **1990** *31*, 7497. (c) Olah, G.A.; Narang, S.C.; Field, L.D.; Fung, A.P. *J. Org. Chem.* **1983**, *48*, 2766.

[134] Rosemund, K.W.; Struck, E. *Chem. Ber.* **1919**, *52*, 1749.

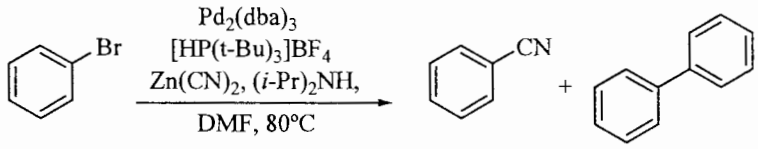
notably copper,[135] nickel,[136] and palladium,[137] has emerged as the method of choice for aryl nitrile synthesis.

Due to its wider functional group stability, palladium is often utilized for reactions involving pharmacologically active substrates. Despite this, there are still a number of drawbacks to the current palladium catalyzed cyanation methodology. High reaction temperatures are often required to drive the reaction to completion and the catalyst systems most commonly employed often give unreliable results. In addition, catalyst activity is affected by the concentration of cyanide ions in solution[138] and this often leads to low turnover numbers due to catalyst poisoning. Also, a milder and more general method for the cyanation of chloroarenes[139] is needed due to the economy and availabilty of these substrates.

Fu and Netherton[140] recently reported the use of air stable trialkyl phosphonium salts for the room temperature cross couplings of chloroarenes. The unique combination of electron richness and steric bulk of some trialkylphosphines, most notably tri-*tert*-butylphosphine, has been shown to enhance the rate of oxidative addition, while also facilitating reductive elimination. We decided to apply this methodology to the synthesis of aryl nitriles (eq 27) and were pleased to find that with 1.5 mol% $Pd_2(dba)_3$ and $[HP(t\text{-}Bu)_3]BF_4$, in the presence of 0.6 molar equivalents of zinc cyanide and 1 equivalent of base, bromobenzene **(50)** can be converted to benzonitrile **(51)** in 2 hours at 80 °C.

---

[135] Buchwald, S.L.; Klapars, A.; Zanon, J. *J. Am. Chem. Soc.* **2003**, *125*, 2890
[136] (a) Van Soolingen, J.; Brandsma, L. *Synth. Comm.* **1990**, *20*, 3153 (b) Sakakibara, Y.; Ido, Y.; Sasaki, K.; Sakai, M.; Uchino, N. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 2776.
[137] Maligres, P.E.; Waters, M.S.; Fleitz, F. Askin, D. *Tetrahedron Lett.*, **1999**, *40*, 8193.
[138] Sundermeier, M.; Zapf, A.; Beller, M. *Angew. Chem. Int. Ed.* **2003**, *42*, 1661.
[139] (a) Sundermeier, M.; Zapf, A.; Beller, M.; Sans, J. *Tetrahedron Lett.* **2001**, *42*, 6707. (b) Confalone, P.N.; Jin, F. *Tetrahedron Lett.* **2000**, *40*, 3271.
[140] Netherton, M.R.; Fu. G.C. *Org. Lett.* **2001**, *3*, 4295.



(27)

(50) (51) (52)

The bromobenzene homocoupling product (**52**) was also observed by HPLC. Nevertheless, the moderate reaction temperature and short reaction time for this conversion suggests that this catalyst system may be promoting oxidative addition at an accelerated rate over the more commonly used $Pd(PPh_3)_4$ (6 mol %, 6 h @80 °C)[141] and $Pd_2(dba)_3$ and dppf (0.05 mol % Pd, 20 h @ 120 °C).[136] Unfortunately, when this system was applied to the cyanation of a simple chloroarene, no reaction occurred. The use of other phosphine ligands was planned but never pursued. We believe this is a promising area for future experimentation.

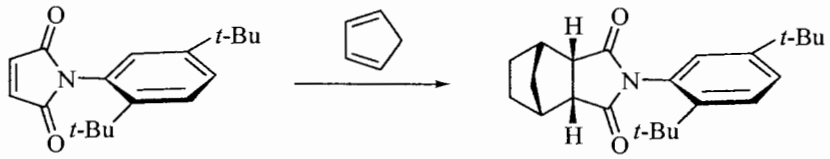
Non-Biaryl Atropisomeric Azaphosphine Ligands

Biaryl based phosphine ligands are unique in their ability to facilitate palladium-catalyzed cross-coupling processes. In addition to Buchwald's biphenyl based phosphines (see: Advances in Catalyst Design pg 28-29 and 32-33 and Reaction Optimization Studies pg 58-62), BINAP has also been shown to be an effective ligand for palladium-catalyzed aminations (see: Preparation of Norfloxacin pg 92-95 and references therein). However, BINAP is best known for its use as a ligand for metals which act as hydrogenation catalysts. Because of the restricted rotation about the carbon-carbon bond between the two naphthalene rings, this compound exists as a mixture of atropisomers.

[141] Tschaen, D.M.; Desmond, R.; King, A.O., Fortin, M.C. Pipik, B., King, S. Verhoeven, T.R. *Synth. Comm.* **1994**, *24*, 887.

Enantiopure BINAP has been successfully employed in chiral hydrogenation reactions.[142] There have also been reports detailing the use of BINAP for the growing field of enantioselective allylic amination reactions.[143]

In 1994 Curran and coworkers published a report [144] detailing the use of maleimides bearing *ortho*-substituted aryl groups as "atroposelective" reagents. They prepared an axially chiral compound containing two trigonal centers linked by a rotationally restricted single bond **(53)** and subjected it to a Diels Alder reaction (eq 28). Remarkably, this resulted in a 97:3 diastereomeric ratio favoring one atropisomer product **(54)**. This study made us wonder whether structures which exhibit this type of atropisomerism could be modified into ligands for palladium and used to catalytically induce chirality during cross-couplings. We explored whether such compounds were ever used as ligands for palladium.[145] To our surprise, we found no examples in the literature.

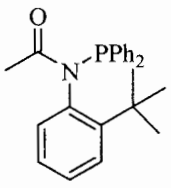


(53) **(54)** **(28)**

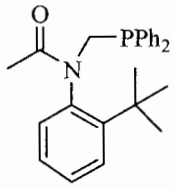
We then set out to design novel structures based on a nonbiaryl atropisomeric backbone and arrived at the azaphosphine compounds **(55)** and **(56)**. We intended to prepare these ligands and test their effectiveness in palladium catalyzed cross-couplings. If successful we would then resolve them and determine if they could be used to induce

[142] Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994.
[143] (a) Kodamo, H.; Taiji, T.; Ohta, T.; Furukawa, I. *Synlett* **2001**, 385. (b) Faller, J.W.; Wilt, J.C. *Tetrahedron Lett.* **2004**, *45*, 7613. (c) Faller, J.W.; Wilt, J.C. *Org. Lett.* **2005**, *7*, 633.
[144] Curran, D.P.; Qi, H.; Geib, S.J.; DeMello, N.C. *J. Am. Chem. Soc.* **1994**, *116*, 3131.
[145] For a review on non-biaryl atropisomers as chiral reagents, auxiliaries, and ligands see: Clayden, J. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 949.

chirality in palladium-catalyzed asymmetric allylic aminations and Suzuki cross-coupling reactions.



(55)



(56)

We envisioned that ligand **(55)** could possibly monoligate to palladium in the manner depicted in Figure 10. The extra carbon present in ligand **(56)** may allow the bidentate complex shown on the right through interaction of the palladium with the ipso carbon of the benzene ring.[146]

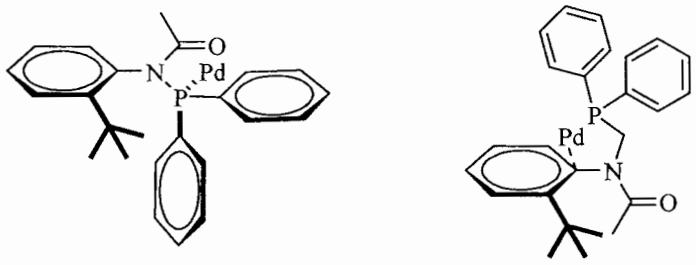


Figure 10: Possible Binding Modes for Azaphosphine Ligands with Palladium

We designed a synthesis of both compounds as depicted in Figure 11 and set out to prepare ligand **(55)**. We could easily prepare gram quantities of compound **(58)** from the commercially available 2-*tert*-butylaniline **(57)**. However, we could not successfully phosphorylate the aniline via metallation and quenching with chlorodiphenylphosphine. Using sodium hydride as the base we were able to detect a mass corresponding to the phosphine oxide of **(55)** but this accounted for less than 10 % of the total crude product. The remainder was unreacted **(58)** and contained two unidentified products. Butyllithium

[146] A similar type of interaction has been observed for the SPhos ligand in the presence of Pd(dba). See ref 55.

gave similar results but was complicated by additional byproducts. It is possible that compound **(55)** is unstable and readily oxidizes in air.

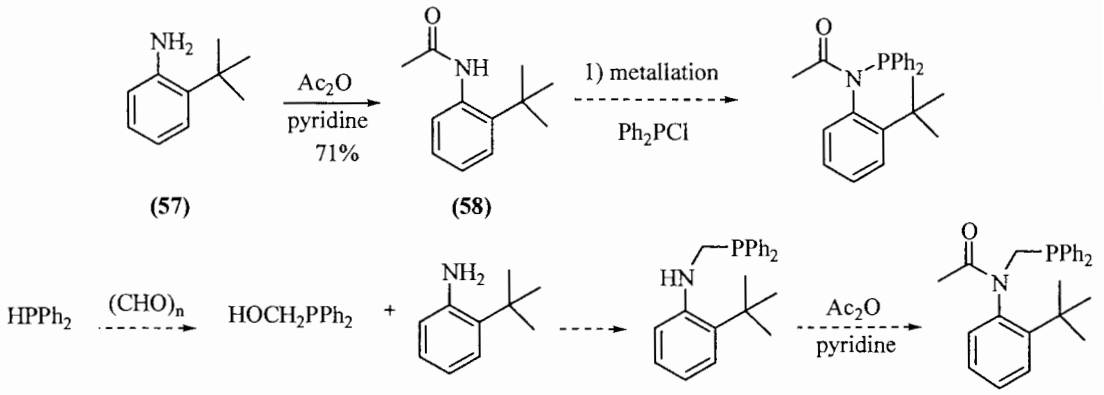


Figure 11: The Proposed Synthesis of Two Non Biaryl Atropisomeric Azaphosphines

The synthesis of ligand **(56)** was never started due to the difficulty encountered with the preparation of **(55)**. Time constraints forced us to shift focus away from this project. However, we still believe this is an area which warrants further research because of the novelty of the idea.

Future Experimentation

The use of Pd/C as a precatalyst for the Suzuki cross-coupling reaction shows great promise. We have shown through the use of Pd/C incubation periods that the ligand loading can be greatly reduced relative to the amount that is commonly employed for this reaction. More research in this area is recommended.

For instance, it may be useful to monitor the concentration of soluble palladium species over time using a suitable analytical technique, such as atomic absorption spectroscopy. This could be helpful in determining the proper length of time for the incubation period. Also this may provide insight into the optimal ligand loading through determination of the palladium to ligand ratio.

We suggest an alternative approach to the ligand assisted method for the activation of the Pd/C. Because it has been shown that oxidative addition of the palladium to the chloroarene is responsible for the palladium leaching, it may be possible to use a surrogate to initiate this process. For instance, small amounts of a compound which is more prone to oxidative addition could be added to the reaction in the presence of ligandless Pd/C. One example is iodomethane and another possibility is the bromo or iodoarene of the corresponding chloroarene starting material. Catalytic concentrations may be sufficient to begin the palladium solubilization and possibly allow for lower reaction temperatures or shorter reaction times.

Finally, we suggest expanding the use of Pd/C as a precatalyst to other cross-coupling processes. Many of the ligands used for Suzuki cross-coupling have been successfully employed in Buchwald-Hartwig aminations. Also, developing Pd/C for use in cyanation reactions would have great appeal from an industrial standpoint.

Conclusions

Unreduced, water wetted, Pd/C was shown to be an efficient precatalyst for the Suzuki reaction of chloroarenes and phenylboronic acids. With the appropriate choice of ligand, substituted biphenyls were prepared from substrates that gave little or no yield under ligandless conditions. A particularly active catalyst system resulting from Pd/C and XPhos was utilized for the preparation of sterically hindered biphenyls. In some cases, by delaying the introduction of the ligand until palladium solubilization occurred, ligand turnover numbers could be significantly increased.

The ligand assisted system was examined through a series of experiments designed to determine if the catalyst retains any characteristics of ligandless heterogeneous systems or if it is simply a source of soluble palladium. The results of catalyst recycling experiments indicated that the Pd/C could be reused multiple times but rapidly became deactivated with the fifth reuse. Mercury poisoning tests implied the presence of a soluble zero valent molecular palladium species formed as a result of ligand dissociation. We propose a catalytic cycle in which ligand free and ligand assisted pathways combine to give practical yields of coupling products but also result in low levels of Pd contamination.

In addition, we developed a relatively high yielding chemoselective synthesis of the quinolone antibacterial Norfloxacin. By utilizing palladium-catalyzed amination methodology we were able to completely suppress the formation of the byproduct resulting from substitution at the fluorine atom. Our technique also provides a synthetic avenue for further exploration through structure activity relationship studies.

In the area of palladium-catalyzed cyanation we applied a known catalyst system for the preparation of benzonitrile from bromobenzene. The moderate reaction temperature and short reaction time for this conversion implied that this catalyst system may be promoting oxidative addition at an accelerated rate over the more commonly used palladium complexes. However, the reaction was complicated by the formation of biphenyl resulting from bromobenzene homocoupling. In addition, we were not able to apply this technique to the cyanation of chloroarenes.

Finally, we proposed the synthesis of two novel azaphosphines to be used as ligands for palladium catalyzed cross-coupling processes. These structures are based on a non biaryl atropisomeric backbone. The synthesis of one of the ligands was commenced but was not completed because of time constraints and unexpected byproduct formation.

Through a series of novel research projects we have demonstrated the enormous synthetic potential in the use of chloroarenes for palladium-catalyzed cross-coupling processes. With the aid of an environmentally friendly catalyst system we were able to meet and sometimes exceed the performance of state of the art catalyst systems for Suzuki cross-couplings. We were also able to demonstrate a new use of palladium-catalyzed amination technology through the chemoselective preparation of Norfloxacin. Finally, we proposed two novel research projects and reported preliminary results in the areas of palladium-catalyzed cyanation and non biaryl atropisomeric ligand synthesis.

Experimental Section

Ligand Assisted Pd/C-Catalyzed Suzuki Couplings of Chloroarenes

Materials

All reagents and solvents were purchased from commercial sources and used without further purification. HPLC mobile phases were comprised of acetonitrile (Fisher or Pharmco HPLC grade) and water (Fisher or Pharmco HPLC grade), with either trifluoroacetic acid (Aldrich) or phosphoric acid (Aldrich) as the mobile phase modifier. Palladium on carbon (5 wt %) was either purchased from PMC (1610) or Alfa Aesar, or obtained from Degussa (E 101 CA) or Engelhard (EUW-741) corporations. Unreduced, 50 % water-wet with egg-shell dispersion performed best in these reactions. The materials used for the couplings were as follows: aryl chlorides (Aldrich), aryl boronic acids (Aldrich or Frontier Scientific), DMA (Aldrich or Acros), potassium carbonate (Aldrich), and water (Fisher). The ligands used for the couplings were as follows: triphenylphosphine, dppf, xantphos (Aldrich), 2-(di-*t*-butylphosphino)biphenyl, 2-(dicyclohexylphosphino)biphenyl, MePhos, and XPhos (Strem).

Instrumentation

^{1}H and ^{13}C NMR (400 or 500 MHz) were recorded on Varian Inova Spectrometers. Chemical shifts are reported as δ parts per million (ppm) downfield from tetramethylsilane. Either Agilent series 1090 or 1100 HPLC systems were used to monitor reactions and check for purity. Conversions were calculated by HPLC using calibrated curves of concentration versus absorbance of the appropriate reference.

Preparative chromatography was either performed on a simple glass column packed with silica gel or on an Argonaut Flashmaster Solo using Isolute silica gel columns. Palladium analyses were performed by Schwarzkopf Microanalytical Laboratory.

Reaction Optimization Studies

Typical Ligand Screening Procedure - A 10 mL recovery flask containing a magnetic stir bar was charged with Pd/C (Degussa, 5 wt %, 50 % water-wet, 85 mg, 0.02 mmol total Pd), phenyl boronic acid (120 mg, 0.96 mmol), K_2CO_3 (221 mg, 1.60 mmol), ligand, and 20:1 v/v DMA:H_2O (5 mL). The mixture was degassed and purged with nitrogen and 4-chloroanisole was added (97 μL, 0.8 mmol). The reaction was heated at 80 °C for 24 h. A 100 μL sample was removed via pipette and diluted with 1 mL of acetonitrile. The sample was then filtered through a 0.45 μM filter and a 50 μL aliquot was removed and diluted with 1 mL of acetonitrile for HPLC analysis (Zorbax XDB C8 column, 4.6 x 150 mm, 50 % acetonitrile:H_2O (0.1 % TFA) to 100 % acetonitrile, 15 min linear gradient, 1 mL/min). Percent conversion to product was determined using the following equation: (mmol 4-methoxybiphenyl)/ (mmol. 4-chloroanisole + mmol. 4-methoxybiphenyl) x 100.

Triphenylphosphine (Table 2, entry 2) - 10 mol % (21 mg, 0.08 mmol)

4-chloroanisole	LC Area = 7704	mmol = 0.0022
4-methoxybiphenyl	LC Area = 0	mmol = 0

Conversion = 0 %

Triphenylphosphine (Table 2, entry 3) - 2.5 mol % (5.3 mg, 0.02 mmol)

4-chloroanisole LC Area = 9444 mmol = 0.0027

4-methoxybiphenyl LC Area = 156 mmol = 3.818E-05

Conversion = 1 %

1,1'-Bis(diphenylphosphino)ferrocene (dppf) (Table 2, entry 4) -

10 mol % (44 mg, 0.08 mmol)

4-chloroanisole LC Area = 10023 mmol = > 0.0027

4-methoxybiphenyl LC Area = 0 mmol = 0

Conversion = 0 %

1,1'-Bis(diphenylphosphino)ferrocene (dppf) (Table 2, entry 5) -

2.5 mol % (11 mg, 0.02 mmol)

4-chloroanisole LC Area = 7197 mmol = 0.0026

4-methoxybiphenyl LC Area = 1415 mmol = 9.080E-05

Conversion = 3 %

9,9-Dimethyl-4,5-bis(diphenylphosphino)xanthene (Xantphos) (Table 2, entry 6) -

10 mol % (40 mg, 0.08 mmol)

4-chloroanisole LC Area = 9760 mmol = > 0.0027

4-methoxybiphenyl LC Area = 0 mmol = 0

Conversion = 0 %

9,9-Dimethyl-4,5-bis(diphenylphosphino)xanthene (Xantphos) (Table 2, entry 7) -

2.5 mol % (10 mg, 0.02 mmol)

4-chloroanisole LC Area = 9791 mmol = > 0.0027

4-methoxybiphenyl LC Area = 0 mmol = 0

Conversion = 0 %

2-(Di-*t*-butylphosphino)biphenyl (Table 2, entry 8) - 10 mol % (24 mg, 0.08 mmol)

4-chloroanisole LC Area = 7197 mmol = 0.0021

4-methoxybiphenyl LC Area = 1415 mmol = 3.463E-04

Conversion = 14 %

2-(Di-*t*-butylphosphino)biphenyl) (Table 2, entry 9) - 2.5 mol % (6.0 mg, 0.02 mmol)

4-chloroanisole LC Area = 4877 mmol = 0.0014

4-methoxybiphenyl LC Area = 7852 mmol = 0.0019

Conversion = 58 %

2-(Dicyclohexylphosphino)biphenyl) (Table 2, entry 10) -

10 mol % (28 mg, 0.08 mmol)

4-chloroanisole LC Area = 6858 mmol = 0.0020

4-methoxybiphenyl LC Area = 4499 mmol = 0.0011

Conversion = 36 %

2-(Dicyclohexylphosphino)biphenyl) (Table 2, entry 11) -

5 mol % (14 mg, 0.04 mmol)

4-chloroanisole LC Area = 6151 mmol = 0.0018

4-methoxybiphenyl LC Area = 6503 mmol = 0.0016

Conversion = 47 %

2-(Dicyclohexylphosphino)biphenyl) (Table 2, entry 12) -

2.5 mol % (7.0 mg, 0.02 mmol)

4-chloroanisole LC Area = 4807 mmol = 0.0014

4-methoxybiphenyl LC Area = 7276 mmol = 0.0018

Conversion = 56 %

2-(Dicyclohexylphosphino)biphenyl) (Table 2, entry 13) -

1 mol % (2.8 mg, 0.008 mmol)

4-chloroanisole LC Area = 8488 mmol = 0.0025

4-methoxybiphenyl LC Area = 2274 mmol = 5.565E-04

Conversion = 18 %

2-Dicyclohexylphosphino-2'-(*N,N*-dimethylamino)biphenyl (Table 2, entry 14) -

2.5 mol % (7.9 mg, 0.02 mmol)

4-chloroanisole LC Area = 944 mmol = 2.733E-04

4-methoxybiphenyl LC Area = 8560 mmol = 0.0021

Conversion = 88 %

2-Dicyclohexylphosphino-2'-methylbiphenyl (MePhos) (Table 2, entry 15) -

2.5 mol % (7.3 mg, 0.02 mmol)

4-chloroanisole LC Area = 214 mmol = 6.196E-05

4-methoxybiphenyl LC Area = 8948 mmol = 0.0022

Conversion = 97 %

4-chloroanisole LC Area = 1968 mmol = 5.698E-04

4-methoxybiphenyl LC Area = 9106 mmol = 0.0022

Conversion = 80 %

Average Conversion = 89 %

2-Dicyclohexylphosphino-2'-methylbiphenyl (MePhos) (Table 2, entry 16) -

1.25 mol % (3.7 mg, 0.01 mmol)

4-chloroanisole LC Area = 2943 mmol = 8.522E-04

4-methoxybiphenyl LC Area = 8486 mmol = 0.0021

Conversion = 71%

2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (XPhos) (Table 2, entry 17) -

2.5 mol % (9.5 mg, 0.02 mmol)

4-chloroanisole LC Area = 1980 mmol = 5.733E-04

4-methoxybiphenyl LC Area = 9005 mmol = 0.0022

Conversion = 79 %

2-Bromo-*N,N*-dimethylaniline (38) – To a solution of 2-bromoaniline (4.3 g, 0.025 mol) in acetonitrile (100 mL) was added aqueous formaldehyde (20 mL, 0.250 mol), followed by $NaBH_3CN$ (4.75 g, 0.075 mol). Acetic acid (2.5 mL) was then added dropwise over 10 min and the mixture was allowed to stir for 2 h. At this time additional acetic acid (2.5 mL) was added and stirring was continued for a further 75 min. The reaction mixture was then poured into diethyl ether (300 mL) and washed with 1N potassium hydroxide solution and brine. The organic layer was dried over potassium carbonate, filtered, and concentrated *in vacuo*. The resulting residue was purified on silica gel (eluting with 2 % ethyl acetate in hexane) to provide the title compound as a colorless oil (3.50 g, 70 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (dd, J = 0.9 Hz, 7.8 Hz, 1H), 7.26-7.23 (m, 1H), 7.10-7.08 (m, 1H), 6.87 (t, J = 7.5 Hz, 1H), 2.80 (br s, 6H).

2-(*N,N*-Dimethylamino)phenylboronic acid (39) – To a solution of 2-bromo-*N,N*-dimethylaniline (661 mg, 3.30 mmol) in THF (3.3 mL) under a nitrogen atmosphere at -78 °C was added a solution of 1.6 M n-butyllithium in hexanes (2.2 mL, 3.47 mmol) dropwise. After 75 min, additional THF (11.5 mL) was added and the solution was cannulated into a precooled (-78 °C) solution of triisopropylborate (1.5 mL, 6.60 mmol) in THF (3.3 mL). After 1 h the mixture was allowed to warm to room temperature and age overnight. The resulting white suspension was quenched with the addition of 1 N HCl solution (30 mL) and stirrer for 1 h. The pH was adjusted to 7 with the addition of sodium hydroxide solution and the mixture was extracted into diethyl ether. The organic layer was washed with additional 1N sodium hydroxide solution. The aqueous washings were combined and adjusted to pH = 7 with the addition of 1N sodium hydroxide solution and extracted with diethyl ether. The combined organics were dried over

magnesium sulfate, filtered, and concentrated *in vacuo* to provide a brown oil (389 mg, 71 %) which was taken on without further purification.

2'-Bromo-*N,N,*-dimethylbiphenyl-2-amine (41) – To a solution of 2-bromoiodobenzene (772 mg, 2.73 mmol) in dimethoxyethane (19 mL) under an argon atmosphere was added $Pd(PPh_3)_4$ (131mg, 0.113 mmol), a solution of sodium carbonate (1.2 g, 11.4 mmol) in degassed water (5.6 mL), and a solution of 2-(*N,N*-dimethylamino)phenylboronic acid (375 mg, 2.27 mmol) in ethanol (1 mL). The reaction was heated under reflux for 48 h and cooled to room temperature. Diethyl ether (50 mL) was then added and the mixture was transferred to a separatory funnel. The organic layer was separated and washed with 1N sodium hydroxide solution (40 mL), followed by extraction with 1N HCl (3 x 40 mL). The pH of the aqueous extracts was adjusted to 14 with the addition of 5N sodium hydroxide solution and then extracted into diethyl ether. The combined organics were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The resulting residue was purified on silica gel (eluting with 3 % ethyl acetate in hexane) to provide the title compound as a colorless oil (300 mg, 47 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, J = 8 Hz, 1H), 7.35-6.96 (m, 8H), 2.50 (br s, 6H).

2-Dicyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl (11) – To a solution of 2'-bromo-*N,N,*-dimethylbiphenyl-2-amine (300 mg, 1.08 mmol) in THF (15 mL) under an argon atmosphere at -78 °C was added a solution of 1.6 M n-butyllithium in hexanes (744 μL, 1.19 mmol) dropwise. After 35 min a solution of chlorodicyclohexylphosphine (298 μL, 1.35 mmol) in THF (4 mL) was added dropwise. The mixture was allowed to warm

to room temperature and age overnight. The reaction was quenched with the addition of saturated ammonium chloride solution (50 mL) and extracted into diethyl ether. The combined organics were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The resulting residue was recrystallized from ethanol to provide the title compound as a white solid (255 mg, 60 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, J = 6.8 Hz, 1H), 7.40-7.26 (m, 4H), 7.05-7.02 (m, 1H), 6.98-6.93 (m, 3H), 2.44 (s, 6H), 2.05-1.98 (m, 1H), 1.82-1.40 (m, 11H), 1.38-0.75 (m, 10H). ^{1}H NMR spectrum was in agreement with that described in the literature (see: reference 42).

Typical Solvent Screening Procedure - A 10 mL recovery flask containing a magnetic stir bar was charged with Pd/C (Degussa, 5 wt %, 50 % water-wet, 85 mg, 0.02 mmol total Pd), phenyl boronic acid (120 mg, 0.96 mmol), K_2CO_3 (221 mg, 1.60 mmol), MePhos (7.3 mg, 0.02 mmol) and 20:1 v/v solvent:H_2O (5 mL). The mixture was degassed, purged with nitrogen, and 4-chloroanisole added (97 μL, 0.8 mmol). The reaction was heated at 80 °C for 24 h. A 100 μL sample was removed via pipette and diluted with 1 mL of acetonitrile. The sample was then filtered through a 0.45 μM filter and a 50 μL aliquot was removed and diluted with 1 mL of acetonitrile for HPLC analysis (Zorbax XDB C8 column, 4.6 x 150 mm, 5% acetonitrile:H_2O (0.1 % TFA) to 100 % acetonitrile, 15 min linear gradient, 1 mL/min). Percent conversion to product was determined using the following equation: (mmol 4-methoxybiphenyl)/ (mmol. 4-chloroanisole + mmol. 4-methoxybiphenyl) x 100.

Ethanol (Table 3, entry 2) -

4-chloroanisole	LC Area = 4460	mmol = 0.0013
4-methoxybiphenyl	LC Area = 4887	mmol = 0.0012

Conversion = 48 %

Dimethoxyethane (Table 3, entry 3) -

4-chloroanisole	LC Area = 6160	mmol = 0.0018
4-methoxybiphenyl	LC Area = 9006	mmol = 0.0022

Conversion = 55 %

N-Methylpyrrolidone (Table 3, entry 4) -

4-chloroanisole	LC Area = 8210	mmol = 0.0023
4-methoxybiphenyl	LC Area = 4284	mmol = 0.0011

Conversion = 31 %

Typical Base Screening Procedure - A 10 mL recovery flask containing a magnetic stir bar was charged with Pd/C (Degussa, 5 wt %, 50 % water-wet, 85 mg, 0.02 mmol total Pd), phenyl boronic acid (120 mg, 0.96 mmol), base, MePhos (7.3 mg, 0.02 mmol) and 20:1 v/v DMA:H_2O (5 mL). The mixture was degassed and purged with nitrogen and 4-chloroanisole was added (97 μL, 0.8 mmol). The reaction was heated at 80 °C for 24 h. A 100 μL sample was removed via pipette and diluted with 1 mL of acetonitrile. The sample was then filtered through a 0.45 μM filter and a 50 μL aliquot was removed and diluted with 1 mL of acetonitrile for HPLC analysis (Zorbax XDB C8 column, 4.6 x 150

mm, 5% acetonitrile:H_2O (0.1 % TFA) to 100 % acetonitrile, 15 min linear gradient, 1 mL/min). Percent conversion to product was determined using the following equation: (mmol 4-methoxybiphenyl)/ (mmol. 4-chloroanisole + mmol. 4-methoxybiphenyl) x 100.

Sodium carbonate (Table 4, entry 2) - (127 mg, 1.60 mmol)

4-chloroanisole	LC Area = 8472	mmol = 0.0024
4-methoxybiphenyl	LC Area = 6261	mmol = 0.0015

Conversion = 38 %

Potassium acetate (Table 4, entry 3) - (157 mg, 1.60 mmol)

4-chloroanisole	LC Area = 7491	mmol = 0.0022
4-methoxybiphenyl	LC Area = 3248	mmol = 0.0008

Conversion = 27 %

Sodium Hydroxide (Table 4, entry 4) - (64 mg, 1.60 mmol)

4-chloroanisole	LC Area = 3366	mmol = 0.0010
4-methoxybiphenyl	LC Area = 8806	mmol = 0.0022

Conversion = 69 %

Typical Palladium Source and Loading Study - A 10 mL recovery flask containing a magnetic stir bar was charged with Pd/C (5 wt %, 50 % water-wet with egg-shell dispersion), phenyl boronic acid (120 mg, 0.96 mmol), K_2CO_3 (221 mg, 1.60 mmol), 2-dicyclohexylphosphino-2'-(*N,N*-dimethylamino)biphenyl and 20:1 v/v solvent:H_2O (5 mL). The mixture was degassed, purged with nitrogen, and 4-chloroanisole added (97

μL, 0.8 mmol). The reaction was heated at 80 °C for 24 h. A 100 μL sample was removed via pipette and diluted with 1 mL of acetonitrile. The sample was then filtered through a 0.45 μM filter and a 50 μL aliquot was removed and diluted with 1 mL of acetonitrile for HPLC analysis (Zorbax XDB C8 column, 4.6 x 150 mm, 5% acetonitrile:H_2O (0.1 % TFA) to 100 % acetonitrile, 15 min linear gradient, 1 mL/min). Percent conversion to product was determined using the following equation: (mmol 4-methoxybiphenyl)/ (mmol. 4-chloroanisole + mmol. 4-methoxybiphenyl) x 100. The remaining reaction mixture was then filtered over celite and washed with ethyl acetate. The ethyl acetate was then transferred to a separatory funnel and washed with water and brine. The organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification of the residue by silica gel chromatography yielded 4-methoxybiphenyl, which was identical to an authentic sample by ^{1}H NMR and HPLC.

Alfa Aesar (38299) (Table 5, entry 2) – 2.5 mol % (85 mg, 0.02 mmol)

2-dicyclohexylphosphino-2'-(*N,N*-dimethylamino)biphenyl (7.9 mg, 0.02 mmol).

4-chloroanisole LC Area = 1953 mmol = 0.0006

4-methoxybiphenyl LC Area = 8436 mmol = 0.0021

Conversion = 78 %

Yield = 103 mg (70 %)

Engelhard (EUW-741) (Table 5, entry 3) – 2.5 mol % (85 mg, 0.02 mmol)

2-dicyclohexylphosphino-2'-(*N,N*-dimethylamino)biphenyl (7.9 mg, 0.02 mmol).

4-chloroanisole LC Area = 4106 mmol = 0.0011

4-methoxybiphenyl LC Area = 6478 mmol = 0.0016

Conversion = 57 %

Yield = 78 mg (53 %)

PMC (1610) (Table 5, entry 4) – 2.5 mol % (85 mg, 0.02 mmol)

2-dicyclohexylphosphino-2'-(*N,N*-dimethylamino)biphenyl (7.9 mg, 0.02 mmol).

4-chloroanisole LC Area = 3953 mmol = 0.0011

4-methoxybiphenyl LC Area = 7862 mmol = 0.0019

Conversion = 63 %

Yield = 84 mgs (57 %)

Degussa (E 101 CA) (Table 5, entry 5) – 1.25 mol % (43 mg, 0.01 mmol)

2-dicyclohexylphosphino-2'-(*N,N*-dimethylamino)biphenyl (3.8 mg, 0.01 mmol).

4-chloroanisole LC Area = 8735 mmol = 0.0025

4-methoxybiphenyl LC Area = 4510 mmol = 0.0011

Conversion = 30 %

Degussa (E 101 CA) (Table 5, entry 5) – 0.125 mol % (4.3 mg, 0.001 mmol)

2-dicyclohexylphosphino-2'-(*N,N*-dimethylamino)biphenyl (0.4 mg, 0.001 mmol).

4-chloroanisole LC Area = 7279 mmol = 0.0025

4-methoxybiphenyl LC Area = 361 mmol = 8.836E-05

Conversion = 30 %

Substrate Scope

Standard Procedure for Table 6 Substrates - A 10 mL recovery flask containing a magnetic stir bar was charged with Pd/C (5 wt %, 50 % water-wet, 85 mg, 0.02 mmol total Pd), aryl boronic acid (0.96 mmol), K_2CO_3 (221 mg, 1.60 mmol), MePhos (7.3 mg, 0.02 mmol), and 20:1 v/v DMA:H_2O (5 mL). The mixture was degassed, purged with nitrogen, and the chloroarene added (0.8 mmol). The reaction was heated at 80 °C for 24 h. The reaction mixture was filtered over celite and washed with ethyl acetate. The ethyl acetate was transferred to a separatory funnel and washed with water and brine. The organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo*.

4-Methoxybiphenyl (Table 6, entry 1) – The standard procedure was followed with phenylboronic acid (120 mg, 0.96 mmol) and 4-chloroanisole (97 μL, 0.8 mmol). The product was purified on silica gel (eluting with 2 % ethyl acetate in hexane) to provide the title compound as a white powder (97 mg, 66 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.56-7.51 (m, 4H), 7.43-7.40 (m, 2H), 7.32-7.28 (tt, J = 1.3 Hz, 7.3 Hz, 1H), 7.00- 6.97 (m, 2H), 3.86 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.1, 140.8, 133.7, 128.7, 128.1, 126.7, 126.6, 114.2, 55.3. The ^{1}H NMR spectrum was identical with that of a sample purchased from Sigma-Aldrich, Inc.

4- Methoxybiphenyl, ligandless procedure (Table 6, entry 1) – see reference 92.

4'-Methoxybiphenyl-4-carbaldehyde (Table 6, entry 2) – The standard procedure was followed with 4-formylphenylboronic acid (144 mgs, 0.96 mmol) and 4-chloroanisole (97

μL, 0.8 mmol). The product was purified on an Isolute silica gel column using the Argonaut Flashmaster Solo (eluting with 0 – 100 % methylene chloride in hexanes, linear gradient over 23 min) to provide the title compound as a white solid (50 mg, 30 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.03 (s, 1H), 7.92 (dd, J = 1.7 Hz, 6.5 Hz, 2H), 7.71 (d, J = 8.2 Hz, 2H), 7.59 (dd, J = 1.9 Hz, 6.7 Hz, 2H), 7.00 (dd, J = 2 Hz, 6.7 Hz, 2H), 3.86 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 191.9, 160.1, 146.8, 134.7, 132.0, 130.3, 128.4, 127.0, 114.4, 55.4.

The ^{1}H NMR spectrum was in agreement with that described in the literature (see: Mutule, I.; Suna, E. *Tetrahedron* **2005**, *61*, 11168).

4'-Methoxybiphenyl-4-carbaldehyde, ligandless (Table 6, entry 2) – No product was obtained.

4-Methylbiphenyl (Table 6, entry 3) - The standard procedure was followed with 4-chlorotoluene (95 μL, 0.8 mmol). The product was purified on silica gel (eluting with hexanes) to provide the title compound as a white solid (82 mg, 61 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.61-7.55 (m, 2H), 7.51-7.47 (m, 2H), 7.44-7.39 (m, 2H), 7.31 (tt, J = 1.2 Hz, 7.4 Hz, 1H), 7.24 (d, J = 7.9 Hz, 2H), 2.39 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 141.1, 138.3, 137.0, 129.5, 128.7, 127.2, 127.0, 21.1. The ^{1}H NMR spectrum was identical with that of a sample purchased from Sigma-Aldrich, Inc.

4-Methylbiphenyl, ligandless (Table 6, entry 3) – see reference 92.

4-Formylbiphenyl (Table 6, entry 4) - The standard procedure was followed with chlorobenzene (95 μL, 0.8 mmol) and 4-formylphenylboronic acid (144 mgs, 0.96 mmol). The product was purified on an Isolute silica gel column using the Argonaut Flashmaster Solo (eluting with 0 – 100 % methylene chloride in hexanes, linear gradient over 23 min) to provide the title compound as a crystalline solid (116 mg, 80 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.07 (s, 1H), 8.19 (d, 8.3 Hz, 2H), 7.70 (d, 8.3 Hz, 2H), 7.65 (d, 7.4 Hz, 2H), 7.52-7.46 (m,3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 191.9, 147.2, 135.2, 130.3, 129.0, 128.4, 127.7, 127.3. The ^{1}H NMR spectrum was identical with that of a sample purchased from Sigma-Aldrich, Inc.

4-Formylbiphenyl, ligandless (Table 6, entry 4) – A white solid was obtained (12 mg, 8 %).

2-Fluoro-4'-methylbiphenyl (Table 6, entry 5) - The standard procedure was followed with 4-chlorotoluene (95 μL, 0.8 mmol) and 2-Fluorophenylboronic acid (134 mgs, 0.96 mmol). The product was purified on an Isolute silica gel column using the Argonaut Flashmaster Solo (eluting with 0 – 2 % methylene chloride in hexanes, linear gradient over 20 min) to provide the title compound as a colorless oil (105 mg, 70 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.47-7.44 (m, 2H), 7.42 (dd, J = 1.8 Hz, 7.8 Hz, 1H), 7.32-7.25 (m, 3H), 7.22-7.12 (m, 2H), 2.41 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 137.5, 130.7, 129.14, 128.9, 128.7, 128.6, 124.3, 116.1, 115.9, 21.2. The ^{1}H NMR spectrum was in agreement with that described in the literature (see: Mino, T.; Shirae, Y.; Sakomoto, M.; Fujita, T. *J. Org. Chem.* **2005**, *70*, 2191).

2-Fluoro-4'-methylbiphenyl, ligandless (Table 6, entry 5) – A colorless oil was obtained (40 mg, 27 %).

Standard Procedure For Table 7 Substrates - A 10 mL recovery flask containing a magnetic stir bar was charged with Pd/C (5 wt %, 50 % water-wet, 85 mg, 0.02 mmol total Pd), aryl boronic acid (0.96 mmol), K_2CO_3 (221 mg, 1.60 mmol), XPhos (9.5 mg, 0.02 mmol), and 20:1 v/v DMA:H_2O (5 mL). The mixture was degassed and purged with nitrogen and chloroarene was added (0.8 mmol). The reaction was heated at 80 °C for 24 h. The reaction mixture was filtered over celite and washed with ethyl acetate. The ethyl acetate was then transferred to a separatory funnel and washed with water and brine. The organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo*.

2,4'-Dimethylbiphenyl (Table 7, entry 1) – The standard procedure was followed with 2-methylphenylboronic acid (130 mg, 0.96 mmol) and 4-chlorotoluene (95 μL, 0.8 mmol). The product was purified on silica gel (eluting with hexanes) to provide the title compound as a colorless oil (132 mg, 91 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.26-7.21 (m, 8H), 2.40 (s, 3H), 2.27 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 141.8, 139.0, 136.3, 135.4, 130.2, 129.8, 129.0, 128.7, 127.0, 125.7, 21.1, 20.4.

2,4'-Dimethylbiphenyl, ligandless (Table 7, entry 1) – A colorless oil was obtained (39 mg, 27 %).

2-Methylbiphenyl (Table 7, entry 2) - The standard procedure was followed with phenylboronic acid (120 mg, 0.96 mmol) and 2-chlorotoluene (95 μL, 0.8 mmol). The product was purified on silica gel (eluting with hexanes) to provide the title compound as a colorless oil (95 mg, 70 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.43-7.38 (m, 2H), 7.35-7.31 (m, 3H), 7.27-7.21 (m, 4H), 2.23 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 141.9, 135.3, 130.3, 129.8, 129.2, 128.0, 127.2, 126.7, 125.7, 20.4. The ^{1}H NMR spectrum was in agreement with that described in the literature (see: Mino, T.; Shirae, Y.; Sakomoto, M.; Fujita, T. *J. Org. Chem.* **2005**, *70*, 2191).

2-Methylbiphenyl, ligandless (Table 7, entry 2) – A colorless oil was obtained (20, mg, 15 %).

2,2'-Dimethylbiphenyl (Table 7, entry 3) - The standard procedure was followed with 2-methylphenylboronic acid (130 mg, 0.96 mmol) and 2-chlorotoluene (95 μL, 0.8 mmol). The product was purified on silica gel (eluting with hexanes) to provide the title compound as a colorless oil (116 mg, 80 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.27-7.20 (m, 6H), 7.10 (d, J = 6.8 Hz), 2.06 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 141.6, 135.8, 129.8, 129.3, 127.1, 125.5, 19.8. The ^{1}H NMR spectrum was in agreement with that described in the literature (see: Percec, V.; Bae, J-Y.; Zhao, M.; Hill, D.H. *J. Org. Chem.* **1995**, *60*, 176).

2,2'-Dimethylbiphenyl, ligandless (Table 7, entry 3) – A colorless oil was obtained (10 mg, 7 %).

2-Methoxy-2'-Methylbiphenyl (Table 7, entry 4) - The standard procedure was followed with 2-methylphenylboronic acid (130 mg, 0.96 mmol) and 2-chloroanisole (102 μL, 0.8 mmol). The product was purified on an Isolute silica gel column using the Argonaut Flashmaster Solo (eluting with 0 – 3 % methylene chloride in hexanes, linear gradient over 20 min) to provide the title compound as a colorless oil (48 mg, 30 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.36-7.31 (m, 1H), 7.26-7.12 (m, 5H), 7.03-6.94 (m, 2H), 3.68 (s, 3H), 2.15 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 131.0, 130.8, 129.6, 128.5, 127.3, 125.4, 120.4, 110.6, 55.4, 19.9. The ^{1}H NMR spectrum was in agreement with that described in the literature (see: reference 55).

2-Methoxy-2'-Methylbiphenyl, ligandless (Table 7, entry 4) –No product was obtained.

2,2',6-Trimethylbiphenyl (Table 7, entry 5) - The standard procedure was followed with 2-methylphenylboronic acid (130 mg, 0.96 mmol) and 2-chloro-*m*-xylene (112 mg, 0.8 mmol). The product was purified on silica gel (eluting with hexanes) to provide the title compound as a colorless oil (112 mg, 71 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.33-7.23 (m, 3H), 7.11-7.21 (m, 3H), 7.06-7.02 (m, 1H) 1.99 (s, 3H), 1.97 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 141.0, 140.5, 135.9, 135.6, 130.0, 128.8, 127.2, 127.0, 126.9, 126.0, 20.3, 19.4. The ^{1}H NMR spectrum was in agreement with that described in the literature (see: reference 55).

2,2',6-Trimethylbiphenyl, ligandless (Table 7, entry 5) – No product was obtained.

2'-Methylbiphenyl-4-carbaldehyde (Table 7, entry 6) – The standard procedure was followed with 4-formylphenylboronic acid (144 mgs, 0.96 mmol) and 2-chlorotoluene (94 μL, 0.8 mmol). The product was purified on an Isolute silica gel column using the Argonaut Flashmaster Solo (eluting with 0 – 100 % methylene chloride in hexanes, linear gradient over 23 min) to provide the title compound as a white crystalline solid (135 mg, 86 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.08 (s, 1H), 7.94 (d, J = 8.0 Hz, 2H), 7.50 (d, J = 8.0 Hz, 2H), 7.35-7.22 (m, 4H), 2.28 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 192.3, 148.7, 140.8, 135.4, 135.2, 130.8, 130.2, 130.0, 129.7, 128.3, 126.2, 20.6. The ^{1}H NMR spectrum was in agreement with that described in the literature (see: Kataoka, N.; Shelby, Q.; Stambuli, J.P.; Hartwig, J.F. *J. Org. Chem.* **2002**, *67*, 5553).

2',6'-Dimethylbiphenyl-4-carbaldehyde (Table 7, entry 7) – The standard procedure was followed with 4-formylphenylboronic acid (144 mgs, 0.96 mmol) and 2-chloro-*m*-xylene (112 mg, 0.8 mmol). The product was purified on an Isolute silica gel column using the Argonaut Flashmaster Solo (eluting with 0 – 100 % methylene chloride in hexanes, linear gradient over 23 min) to provide the title compound as a white crystalline solid (130 mg, 77 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.1 (s, 1H), 8.22 (d, J = 8.1 Hz, 2H), 7.30 (d, J = 8.1 Hz, 2H), 7.22-7.19 (m, 1H), 7.18-7.15 (m, 2H), 2.04 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 192.1, 172.1, 147.2, 140.7, 135.5, 130.5, 130.0, 129.9, 129.4, 127.7, 127.6, 127.5, 127.4, 20.7.

2',6'-Dimethyl-2-fluorobiphenyl (Table 7, entry 8) – The standard procedure was followed with 2-fluorophenylboronic acid (134 mgs, 0.96 mmol) and 2-chloro-*m*-xylene (112 mg, 0.8 mmol). The product was purified on silica gel (eluted with hexanes) to provide the title compound as a colorless oil (140 mg, 70 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.38-7.30 (m,2H), 7.24-7.10 (m, 5H), 2.06 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.7, 136.6, 135.3, 131.3, 129.0, 128.9, 127.7, 127.2, 124.1, 115.8, 115.6, 20.4. ^{1}H NMR spectrum was in agreement with that described in the literature (see: reference 55).

2-Fluoro-4'-methoxybiphenyl (Table 7, entry 9) – The standard procedure was followed with 2-fluorophenylboronic acid (134 mgs, 0.96 mmol) and 4-chloroanisole (97 μL, 0.8 mmol). The product was purified on silica gel (eluted with methylene chloride) to provide the title compound as a colorless oil (153 mg, 75 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.52-7.48 (m, 2H), 7.42 (td, J = 1.9 Hz, 7.7 Hz, 1H), 7.32-7.15 (m, 3H), 7.02-6.96 (m, 2H), 3.86 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.0, 159.2, 158.5, 130.5, 130.4, 130.1, 128.4, 128.3, 128.2, 124.3, 124.2, 116.1, 115.9, 115.2, 114.0, 113.9, 55.3. ^{1}H NMR spectrum was in agreement with that described in the literature (see: Lourak, M.; Vanderesse, R.; Fort, Y.; Caubere, P. *J. Org. Chem.* **1989**, *54*, 4844).

Recycling Experiment

The procedure for the initial reaction in this section is described above (see: Substrate Scope, Standard Procedure for Table 7 Substrates, pg 120). All additional reactions were scaled according to the amount of Pd/C that was recovered. A Schlenk flask containing a

magnetic stir bar was charged with Pd/C (5 wt %, 50 % water-wet, 0.025 equiv total Pd), *o*-tolylboronic acid (1.2 equiv.) K_2CO_3 (2 equiv.), XPhos (0.025 equiv.), and 20:1 v/v DMA:H_2O. The mixture was degassed and purged with nitrogen and 2-chlorotoluene was added (1 equiv). The reaction was heated at 80 °C for 24 h. A 100 μL sample was removed via pipette and diluted with 1 mL of acetonitrile. The sample was then filtered through a 0.45 μM filter and a 50 μL aliquot was removed and diluted with 1 mL of acetonitrile for HPLC analysis (Phenomenex Luna C18 column, 4.6 x 150 mm, 50 % acetonitrile:H_2O (0.1 % H_3PO_4) to 100 % acetonitrile, 15 min linear gradient, 1 mL/min). Percent conversion to product was determined using the following equation: (mmol 2,2'-dimethylbiphenyl)/ (mmol. 2-chlorotoluene + mmol. 2,2'-dimethylbiphenyl) x 100. The remaining reaction mixture was filtered through filter paper, washed with water and acetone, and allowed to air dry for 1 h. The Pd/C was then carefully scraped from the filter paper and used as is in the next reaction.

First Run (Table 8, entry 1) -

2-chlorotoluene LC Area = 787 mmol = 0.0004

2,2'-dimethylbiphenyl LC Area = 6602 mmol = 0.0012

Conversion = 75 %

Second Run (Table 8, entry 2) -

2-chlorotoluene LC Area = 1487 mmol = 0.0008

2,2'-dimethylbiphenyl LC Area = 11078 mmol = 0.0020

Conversion = 71 %

Third Run (Table 8, entry 3) -

2-chlorotoluene LC Area = 2405 mmol = 0.0014

2,2'-dimethylbiphenyl LC Area = 11117 mmol = 0.0020

Conversion = 59 %

Fourth Run (Table 8, entry 4) -

2-chlorotoluene LC Area = 1528 mmol = 0.0009

2,2'-dimethylbiphenyl LC Area = 5343 mmol = 0.0010

Conversion = 53 %

Fifth Run (Table 8, entry 5) -

2-chlorotoluene LC Area = 3817 mmol = 0.0022

2,2'-dimethylbiphenyl LC Area = 2648 mmol = 0.0005

Conversion = 19 %

Residual Palladium Analysis of Biphenyl Products

4'-Methylbiphenyl-4-carbonitrile (Table 9, entry 1) - A 100 mL round bottom flask containing a magnetic stir bar was charged with Pd/C (5 wt %, 50 % water-wet, 340 mg, 0.08 mmol total Pd), toluene-4-boronic acid (516 mg, 3.8 mmol) K_2CO_3 (884 mg, 6.40 mmol), MePhos (29 mg, 0.08 mmol), and 20:1 v/v DMA:H_2O (20 mL). The mixture was degassed, purged with nitrogen, and 4-chlorobenzonitrile added (440 mg, 3.2 mmol). The reaction was heated at 80 °C for 24 h. The reaction mixture was filtered through filter paper and washed water and acetone. The solution was filtered again through a

0.45 μM filter and the filtrate was poured into 250 mL of water. The precipitate was collected on filter paper and washed with water yielding a white solid (587 mg, 95 %). After drying under high vacuum the sample was sent for analysis by atomic absorption and the residual palladium level was determined to be 9 ppm. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.67 (q, J = 8.5 Hz, 17.2 Hz, 4H), 7.49 (d, J = 8.1 Hz, 2H), 7.28 (d, J = 8.5 Hz, 2H), 2.41 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 145.84, 139.0, 136.5, 132.8, 130.1, 127.7, 127.3, 119.3, 110.8, 21.4. The ^{1}H NMR spectrum was in agreement with that described in the literature (see: Ueda, M.; Saitoh, A.; Oh-tani, S.; Miyuara, N. *Tetrahedron* **1998**, *54*, 13079).

2,2'-Dimethylbiphenyl (Table 9, entry 2) - A 100 mL round bottom flask containing a magnetic stir bar was charged with Pd/C (5 wt %, 50 % water-wet, 318 mg, 0.075 mmol total Pd), *o*-tolylboronic acid (489 mg, 3.6 mmol) K_2CO_3 (829 mg, 6.0 mmol), XPhos (36 mg, 0.075 mmol), and 20:1 v/v DMA:H_2O (20 mL). The mixture was degassed, purged with nitrogen, and 2-chlorotoluene added (380 mg, 3.0 mmol). The reaction was heated at 80 °C for 24 h. The reaction mixture was filtered twice through a 0.45 μM filter and partitioned between diethyl ether and water. The organic layer was washed with brine and dried over sodium sulfate. The solution was filtered and concentrated *in vacuo* yielding a yellow oil (520 mg, 95 %). After drying under high vacuum the sample was sent for analysis by atomic absorption and the residual palladium level was determined to be 11 ppm. ^{1}H NMR and HPLC were consistent with an authentic sample of the title compound.

4-Methoxybiphenyl (Table 9, entry 3) - A 100 mL round bottom flask containing a magnetic stir bar was charged with Pd/C (5 wt %, 50 % water-wet, 340 mg, 0.08 mmol total Pd), phenylboronic acid (463 mg, 3.8 mmol) K_2CO_3 (884 mg, 6.40 mmol), MePhos (29 mg, 0.08 mmol), and 20:1 v/v DMA:H_2O (20 mL). The mixture was degassed, purged with nitrogen, and 4-chloroanisole added (388 μL, 3.2 mmol). The reaction was heated at 80 °C for 24 h. The reaction mixture was filtered through filter paper and washed water and acetone. The solution was filtered again through a 0.45 μM filter and the filtrate was poured into 250 mL of water. The precipitate was collected on filter paper and washed with water yielding a white solid (384 mg, 65 %). After drying under high vacuum the sample was sent for analysis by atomic absorption and the residual palladium level was determined to be 30 ppm. ^{1}H NMR and HPLC were consistent with an authentic sample of the title compound.

Tests for Catalyst Homogeneity

Catalyst Filtration and Split Test 1 - A 100 mL two-necked Schlenk flask containing a magnetic stir bar was charged with Pd/C (5 wt %, 50 % water-wet, 340 mg, 0.08 mmol total Pd), phenyl boronic acid (463 mg, 3.8 mmol), K_2CO_3 (884 mg, 6.40 mmol), MePhos (29 mg, 0.08 mmol), and 20:1 v/v DMA:H_2O (20 mL). The mixture was degassed, purged with nitrogen, and 4-chloroanisole added (388 μL, 3.2 mmol). The reaction was heated at 80 °C for 6 h.

At this time a 1.5 mL aliquot was removed and drawn into a syringe containing phenylboronic acid (46 mg, 0.38 mmol), K_2CO_3 (88 mg, 0.64 mmol) and 4-chloroanisole

(39 μL, 0.32 mmol); which was fitted with a long tipped needle and 0.45 μM filter. The needle was removed and the syringe was capped and sealed with Parafilm and placed in an oil bath at 80 °C for an additional 16 h.

Another aliquot totaling 100 μL was removed at the same time as the first (6 h) and diluted with 1 mL of acetonitrile. The sample was then filtered through a 0.45 μM filter and a 50 μL aliquot of this was removed and diluted with 1 mL of a solution of 0.3 mg hexamethylbenzene in acetonitrile for HPLC analysis (Phenomenex Luna C18 column, 4.6 x 150 mm, 50 % acetonitrile:H_2O (0.1 % H_3PO_4) to 100 % acetonitrile, 15 min linear gradient, 1 mL/min) to give a baseline value for HPLC yield.

After 24 h a sample was taken from the syringe totaling 50 μL and diluted with 1 mL of acetonitrile. It was then filtered through a 0.45 μM filter and a 50 μL aliquot of this was removed and diluted with 1 mL of a solution of 0.3 mg hexamethylbenzene in acetonitrile. HPLC yield was determined.

Sample @ 6 h – hexamethylbenzene correction factor = 0.27/0.30 = 0.9
4-methoxybiphenyl LC Area = 1704 x 0.9 = 1534
4-methoxybiphenyl concentration = 0.09 mg/mL x 231 (dil. factor)
= 20.8 mg/mL

Sample @ 24 h – hexamethylbenzene correction factor = 0.27/0.30 = 0.9
4-methoxybiphenyl LC Area = 1824 x 0.9 = 1642
4-methoxybiphenyl concentration = 0.1 mg/ml x 441 (dil factor)
= 44.1 mg/mL

Amount of 4-chloroanisole added @ 6h = 30.4 mg/mL
If all this converted to product @ 24 h = 39.2 mg/mL of 4-methoxybiphenyl

Amount of 4-chloroanisole added @ 0h = 22.8 mg/mL
If all this converted to product @ 24 h = 29.5 mg/mL of 4-methoxybiphenyl

theoretical yield of 4-methoxybiphenyl @ 24 h = 39.2 + 29.5 mg/mL
= 68.7 mg/mL

HPLC yield @ 24 h if reaction stopped @ 6 h = 20.8/68.7 x 100 = 30 %

Actual HPLC yield @ 24 h = 44.1/68.7 = 64 % thus, the reaction continued.

Catalyst Filtration and Split Test 2- A 100 mL two-necked Schlenk flask containing a magnetic stir bar was charged with Pd/C (5 wt %, 50 % water-wet, 340 mg, 0.08 mmol total Pd), phenyl boronic acid (463 mg, 3.8 mmol), K_2CO_3 (884 mg, 6.40 mmol), MePhos (29 mg, 0.08 mmol), and 20:1 v/v DMA:H_2O (20 mL). The mixture was degassed, purged with nitrogen, and 4-chloroanisole added (388 μL, 3.2 mmol). The reaction was heated at 80 °C for 3 h, at which time two aliquots were removed. One sample was removed via a syringe fitted with a long tipped needle and 0.45 μM filter. The needle was removed and the syringe was capped and sealed with Parafilm and placed in an oil bath at 80 °C for an additional 19 h. The second aliquot that was removed was analyzed to give a baseline measurement of reactant conversion to product by HPLC

Bulk Reaction @ 3 h -

4-chloroanisole	LC Area = 4060	mmol = 0.0018
4-methoxybiphenyl	LC Area = 230	mmol = 7.548E-05

Conversion = 4 %

Bulk Reaction @ 24 h -

4-chloroanisole	LC Area = 2178	mmol = 0.0010
4-methoxybiphenyl	LC Area = 1538	mmol = 0.0005

Conversion = 33 %

Split Reaction @ 24 h -

4-chloroanisole LC Area = 2310 mmol = 0.0011

4-methoxybiphenyl LC Area = 1190 mmol = 0.0004

Conversion = 27 %

Mercury Poisoning Test: Procedure A (Table 10, entry 1) - A 500 mL baffled flask equipped with an overhead stirrer was charged with Pd/C (5 wt %, 50 % water-wet, 340 mg, 0.08 mmol total Pd), phenylboronic acid (463 mg, 3.8 mmol), K_2CO_3 (884 mg, 6.40 mmol), mercury (approximately 500 mg), and 20:1 v/v DMA:H_2O (20 mL). The mixture was degassed, purged with argon, and 4-chloroanisole added (388 μL, 3.2 mmol). The reaction was stirred at 1000 rpm and heated to 80 °C for 24 h. Product conversion was determined by HPLC.

4-chloroanisole LC Area = 1291 mmol = 0.0006

4-methoxybiphenyl LC Area = 141 mmol = 4.627E-05

Conversion = 7 %

Mercury Poisoning Test: Procedure A (Table 10, entry 2) - A 500 mL baffled flask equipped with an overhead stirrer was charged with Pd/C (5 wt %, 50 % water-wet, 340 mg, 0.08 mmol total Pd), phenylboronic acid (463 mg, 3.8 mmol), K_2CO_3 (884 mg, 6.40 mmol), MePhos (29 mg, 0.08 mmol), mercury (approximately 500 mg), and 20:1 v/v DMA:H_2O (20 mL). The mixture was degassed, purged with argon, and 4-chloroanisole added (388 μL, 3.2 mmol). The reaction was stirred at 1000 rpm and heated to 80 °C for 24 h. Product conversion was determined by HPLC.

4-chloroanisole LC Area = 1651 mmol = 0.0008

4-methoxybiphenyl LC Area = 53 mmol = 1.739E-05

Conversion = 2 %

Mercury Poisoning Test: Procedure B (Table 10, entry 3) - A 500 mL baffled flask equipped with an overhead stirrer was charged with Pd/C (5 wt %, 50 % water-wet, 340 mg, 0.08 mmol total Pd), phenylboronic acid (463 mg, 3.8 mmol), K_2CO_3 (884 mg, 6.40 mmol), MePhos (29 mg, 0.08 mmol), and 20:1 v/v DMA:H_2O (20 mL). The mixture was degassed, purged with argon, and 4-chloroanisole added (388 μL, 3.2 mmol). The reaction was stirred at 1000 rpm and heated at 80 °C for 3 h. While keeping positive argon pressure, mercury (approximately 500 mg) was added. The reaction was heated for a further 21 h at 80 °C. Product conversion was determined by HPLC.

4-chloroanisole LC Area = 1841 mmol = 0.0008

4-methoxybiphenyl LC Area = 32 mmol = 1.050E-05

Conversion = 1 %

Mercury Poisoning Split Test: Procedure C (Table 10, entry 4) - A 500 mL baffled flask equipped with an overhead stirrer was charged with Pd/C (5 wt %, 50 % water-wet, 340 mg, 0.08 mmol total Pd), phenylboronic acid (463 mg, 3.8 mmol), K_2CO_3 (884 mg, 6.40 mmol), MePhos (29 mg, 0.08 mmol) and 20:1 v/v DMA:H_2O (20 mL). The mixture was degassed, purged with argon, and 4-chloroanisole added (388 μL, 3.2 mmol). The reaction was stirred at 1000 rpm and heated at 100 °C for 1 h. Two aliquots were removed via syringes fitted with a 0.25 μM filter. One aliquot was heated at 100 °C in the presence of excess mercury (~50 mgs) and the other was heated at 100 °C without

mercury. Both aliquots and the bulk reaction were heated for an additional 3 h at 100 °C. Product conversion was determined by HPLC.

Bulk Reaction @ time = 1 h -

4-chloroanisole LC Area = 1585 mmol = 0.0007

4-methoxybiphenyl LC Area = 240 mmol = 7.877E-05

Conversion = 10 %

Split Reaction without Mercury @ time = 4 h -

4-chloroanisole LC Area = 1164 mmol = 0.0005

4-methoxybiphenyl LC Area = 784 mmol = 0.0003

Conversion = 38 %

Split Reaction with Mercury @ time = 4 h -

4-chloroanisole LC Area = 1598 mmol = 0.0007

4-methoxybiphenyl LC Area = 278 mmol = 9.123E-05

Conversion = 12 %

Bulk Reaction @ time = 4 h -

4-chloroanisole LC Area = 1164 mmol = 0.0005

4-methoxybiphenyl LC Area = 842 mmol = 0.0003

Conversion = 38 %

Pd/C-Catalyzed Suzuki Couplings of Chloroarenes at Low Ligand Loadings

4-Methoxybiphenyl (Table 11, entry 1) – A 100 mL Schlenk flask containing a magnetic stir bar was charged with Pd/C (340 mg, 5 wt %, 0.08 mmol total Pd, obtained from

Degussa E 101 CA), phenylboronic acid (463 mg, 3.8 mmol) K_2CO_3 (884 mg, 6.40 mmol), and 20:1 v/v DMA:H_2O (20 mL). The mixture was degassed, purged with argon, and 4-chloroanisole added (388 μL, 3.2 mmol). The reaction was heated to 80 °C for 3 h, and then MePhos (3 mg, 0.008 mmol) was added as a solid, while keeping positive argon pressure and heating was continued for a further 21 h. The reaction mixture was filtered over celite and washed with ethyl acetate. The ethyl acetate was then transferred to a separatory funnel and washed with water and brine. The organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification of the residue by silica gel chromatography yielded 371 mgs (63 % yield) of 4-methoxybiphenyl. After drying under high vacuum the sample was sent for analysis by atomic absorption and the residual palladium level was determined to be < 5 ppm. ^{1}H NMR and HPLC were consistent with an authentic sample of the title compound.

4-Methoxybiphenyl (Table 11, entry 2) – This compound was prepared according to the procedure above, except the MePhos was added at the onset of the reaction. After purification a white solid was obtained (183 mg, 31 %).

2-Methylbiphenyl (Table 11, entry 4) – A 100 mL Schlenk flask containing a magnetic stir bar was charged with Pd/C (318 mg, 5 wt %, 0.075 mmol total Pd, obtained from Degussa E 101 CA), phenylboronic acid (489 mg, 3.6 mmol) K_2CO_3 (829 mg, 6.0 mmol), and 20:1 v/v DMA:H_2O (20 mL). The mixture was degassed, purged with argon, and 2-chlorotoluene was added (380 mg, 3.0 mmol). The reaction was heated to 80 °C for 3 h, and then XPhos (4 mg, 0.0084 mmol) was added as a solid, while keeping positive argon pressure and heating was continued for a further 21 h. The reaction mixture was filtered

over celite and washed with ethyl acetate. The ethyl acetate was then transferred to a separatory funnel and washed with water and brine. The organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification of the residue by silica gel chromatography yielded 450 mgs (89 % yield). ^{1}H NMR and HPLC were consistent with an authentic sample of the title compound.

2-Methylbiphenyl (Table 11, entry 5) – This compound was prepared according to the procedure above, except the XPhos was added at the onset of the reaction. After purification a colorless oil was obtained (111 mg, 22 %).

2-Methylbiphenyl (Table 11, entry 7) – This compound was prepared according to the procedure above, except at a temperature of 100 °C with the XPhos added at 15min and the reaction heated for a further 2 h. After purification a colorless oil was obtained (454 mg, 90 %).

2-Methylbiphenyl (Table 11, entry 8) – This compound was prepared according to the procedure above, except at a temperature of 100 °C with the XPhos added the onset of the reaction. After purification a colorless oil was obtained (121 mg, 24 %).

3-(2-methylphenyl)pyridine (Table 11, entry 9) - A 100 mL Schlenk flask containing a magnetic stir bar was charged with Pd/C (298 mg, 5 wt %, 0.07 mmol total Pd, obtained from Degussa E 101 CA), 3-pyridylboronic acid (516 mg, 4.2 mmol) K_2CO_3 (774 mg, 5.6 mmol), and 20:1 v/v DMA:H_2O (20 mL). The mixture was degassed, purged with argon, and 2-chlorotoluene added (328 μL, 2.8 mmol). The reaction was heated to 100

°C for 15 min, and then XPhos (4 mg, 0.0084 mmol) was added as a solid, while keeping positive argon pressure and heating was continued for a further 23 h. The reaction mixture was filtered over celite and washed with ethyl acetate. The ethyl acetate was then transferred to a separatory funnel and washed with water and brine. The organic layer was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The resulting residue was purified on silica gel (eluting with 10 % ethyl acetate in hexane, followed by 33 % ethyl acetate in hexane) to provide the title compound as a colorless oil (249 mg, 53 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (dd, J = 1.6 Hz, 4.9 Hz, 2H), 7.65 (dt, J = 7.8 Hz, 1.9 Hz, 1H), 7.36-7.26 (m, 4H), 7.21 (d, 7 Hz), 2.28 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 149.9, 148.1, 136.4, 135.5, 130.5, 129.8, 128.1, 126.1, 123.0, 20.3. ^{1}H NMR spectrum was in agreement with that described in the literature (see: reference 55).

3-(2-methylphenyl)pyridine (Table 11, entry 10) - This compound was prepared according to the procedure above, except the XPhos was added at the onset of the reaction. After purification a colorless oil was obtained (215 mg, 45 %).

3-(2-methylphenyl)pyridine (Table 11, entry 11) - This compound was prepared according to the procedure above, except under ligandless conditions. No product was obtained.

2,4-Difluoro-4'-methoxybiphenyl (Table 11, entry 12) - A 100 mL Schlenk flask containing a magnetic stir bar was charged with Pd/C (298 mg, 5 wt %, 0.07 mmol total Pd, obtained from Degussa E 101 CA), 2,4-difluorophenylboronic acid (884 mg, 5.6

mmol) K_2CO_3 (774 mg, 5.6 mmol), and 20:1 v/v DMA:H_2O (20 mL). The mixture was degassed, purged with argon, and 4-chloroanisole added (340 μL, 2.8 mmol). The reaction was heated to 100 °C for 15 min, and then XPhos (4 mg, 0.0084 mmol) was added as a solid, while keeping positive argon pressure and heating was continued for a further 2 h. The reaction mixture was filtered over celite and washed with ethyl acetate. The ethyl acetate was then transferred to a separatory funnel and washed with water and brine. The organic layer was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The resulting residue was purified on silica gel (eluting with 2 % ethyl acetate in hexane) to provide the title compound as a colorless oil (392 mg, 64 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, J = 8.5 Hz, 2H), 7.38 (q, J = 15.0 Hz, 8.4 Hz, 1H), 6.99 (d, 8.7Hz, 2H), 6.97-6.90 (m, 2H), 3.86 (s, 3H). ^{13}C NMR 163.2, 163.1, 160.7, 160.6, 159.2, 158.2, 131.2, 131.1, 131.0, 130.0, 129.7, 129.3, 127.3, 115.2, 115.1, 114.0, 111.5, 111.4, 111.3, 104.5, 104.2, 104.0, 55.3. ^{1}H NMR spectrum was in agreement with that described in the literature (see: reference 55).

2,4-Difluoro-4'-methoxybiphenyl (Table 11, entry 13) - This compound was prepared according to the procedure above, except the XPhos was added at the onset of the reaction. After purification a colorless oil was obtained (407 mg, 66 %).

2,4-Difluoro-4'-methoxybiphenyl (Table 11, entry 14) - This compound was prepared according to the procedure above, except under ligandless conditions. No product was obtained.

Synthesis of Norflaxacin via Palladium-Catalyzed Amination

Materials

Reagents, solvents and chromatographic media were purchased from commercial sources and were used without further purification. Toluene and N,N-dimethylformamide (DMF) were purchased as anhydrous, nitrogen purged solvents from Aldrich (SureSeal^{TM}). Fluorochloroquinolone **43** was a gift from Merck & Co., Inc. and fluorochloroquinolone ethyl ester **45** was prepared by a method of Koga and co-workers. Catalytic reactions were performed under an inert atmosphere of nitrogen with use of Schlenk techniques.

Instrumentation

Nuclear magnetic resonance (NMR) spectra were obtained on a Varian Unity 500 MHz instrument. The chemical shifts for the ^{1}H (TMS standard, δ = 0.00 ppm) and ^{13}C ($CDCl_3$ standard, δ = 77.00 ppm) NMR spectra are reported in ppm. Gas chromatography/mass spectrometry (GC/MS) analyses were performed on an HP 5890 Series II gas chromatograph (DB-1, 30m column, Baker) with a HP 5971A mass spectrometer. High pressure liquid chromatographic analyses were performed on a Beckman System Gold 126 instrument (column: ARMOR C18, 5 cm x 4.6 mm; solvent gradient: 10% acetonitrile (0.01 % TFA)/water (0.01 % TFA) to 100 % acetonitrile (0.01 % TFA) over a period of 5 min and a 2 mL/min flow rate) with a Beckman 166 UV/Vis detector (210 nm). Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory, Inc. (Woodside, NY) and Microlit Laboratories, Inc. (Madison, NJ).

1-Ethyl-6-hydroxy-1,4-dihydro-4-oxo-7-chloroquinoline-3-carboxylic acid ethyl ester (46). To a dry 15 mL recovery flask equipped with a reflux condenser was added **43** (0.25 mmol), (R)-BINAP (0.008 mmol), NaOtBu (0.475 mmol), piperazine (0.55 mmol), $Pd_2(dba)_3$ (0.005 mmol) and 1 mL of toluene. The reaction vessel was purged with nitrogen and heated to 75 °C. After 90 min, the reaction mixture was cooled to room temperature, and the solvent was removed under reduced pressure. The residue was chromatographed on a 500 micron silica gel prep plate using an elution solvent of 90:10 methylene chloride:methanol to give a yellow solid (39 mg, 53 %). ^{1}H NMR ($CDCl_3$) δ 1.53, (t, 3H, CH_3, J = 6.9 Hz), 1.59 (t, 3H, CH_3, J = 7.3 Hz), 4.27 (q, 2H, CH_2, J = 14.2 Hz), 4.33 (q, 2H, CH_2, J = 14.7 Hz), 7.67 (s, 1H, ArH), 7.91, (s, 1H, ArH), 8.70 (s, 1H, CH). MS m/z 296.1 (M+1).

Catalytic synthesis of 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-quinoline-3-carboxylic acid ethyl ester (Norfloxacin ethyl ester) (47a). To a dry 15 mL recovery flask equipped with a reflux condenser was added **43** (150 mg, 0.5 mmol), (R)-BINAP (10 mg, 0.017 mmol), cesium carbonate (360 mg, 0.950 mmol), piperazine (215 mg, 2.5 mmol), $Pd_2(dba)_3$ (10 mg, 0.010 mmol), and 1.5 mL of DMF. The reaction vessel was purged with nitrogen and heated to reflux. After three hours, the reaction mixture was cooled to room temperature, and the solvent was removed under reduced pressure. The residue was purified by thin-layer chromatography on a 500 micron silica gel preparative plate with an elution mixture of chloroform : methanol : water : ammonia (80:20:2:0.2) to give 101 mg of **47a** as an off-white solid in 58% yield and 29 mg of **48** as a light brown solid in 22% yield. Using this procedure, the yield of **47a** ranged as high as 66 %.

*Characterization of **47a***: ^{1}H NMR ($CDCl_3$) δ 1.39 (t, 3H, CH_3, J = 7.2 Hz), 1.53 (t, 3H, CH_3, J = 7.2 Hz), 3.07 (dd, 4H, CH_2, J = 4.6, 3.0 Hz), 3.20 (dd, 4H, CH_2, J = 3.0, 4.6 Hz), 4.18 (q, 2H, CH_2, J = 14.4 Hz), 4.37 (q, 2H, CH_2, J = 14.4 Hz), 6.72 (d, 1H, ArH, J = 6.6 Hz), 8.08 (d, 1H, ArH, J = 13.2 Hz), 8.41(s, 1H, ArH). MS m/z 348.2 (M+1).

Characterization of **1-ethyl-6-fluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid ethyl ester (48)**: ^{1}H NMR ($CDCl_3$) δ 1.43 (t, 3H, CH_3, J = 7.1 Hz), 1.57 (t, 3H, CH_3, J = 7.3 Hz), 4.28 (q, 2H, CH_2, J = 14.4 Hz), 4.42 (q, 2H, CH_2, J = 14.2 Hz), 7.45 (m, 1H, ArH,), 7.48 (dd, 1H, ArH, J = 2.5, 2.8 Hz), 8.21(d, 1H, ArH, J = 2.8 Hz), 8.51(s, 1H, CH). MS m/z 264.3 (M+1).

1-Ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-quinoline-3-carboxylic acid (Norfloxacin) (42). To a 15 mL recovery flask equipped with a reflux condenser was added **47a** (68 mg, 0.2 mmol) and 2 N NaOH (550 μL, 1.1 mmol). The reaction vessel was purged with nitrogen and heated to reflux. After 2 hours, the reaction mixture was cooled to room temperature and neutralized with 2 N HCl. Insoluble material was filtered away, and the filtrate was evaporated under reduced pressure. The resulting solid was triturated with a mixture of chloroform:methanol (3:1) and filtered. Evaporation of the filtrate under reduced pressure resulted in 61 mg of a light-brown solid in 96% yield. The ^{1}H NMR spectrum was identical with that of a sample purchased from Sigma-Aldrich, Inc.

Catalytic synthesis of 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-methyl-piperazinyl)-quinoline-3-carboxylic acid ethyl ester (47b) To a dry 15 mL recovery flask equipped with a reflux condenser was added **43** (150 mg, 0.5 mmol), (R)-BINAP (10 mg, 0.017 mmol), cesium carbonate (360 mg, 0.95 mmol), N-methylpiperazine (122 μL, 1.1 mmol), $Pd_2(dba)_3$ (10 mg, 0.01 mmol), and 1.5 mL of DMF. The reaction vessel was purged with nitrogen and heated to reflux. After three hours, the reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure. The residue was purified by thin-layer chromatography on a 500 micron silica gel preparative plate with an elution mixture of methylene chloride:methanol (9:1) to give 131 mg of an off-white solid in 72% yield. Using this procedure, the yields ranged as high as 75 %. ^{1}H NMR ($CDCl_3$) δ 1.39 (t, 3H, CH_3, J = 7.1 Hz), 1.52 (t, 3H, CH_3, J = 7.3 Hz), 1.61 (broad, NH), 2.36 (s, 3H, CH_3), 2.61 (dd, 4H, CH_2, J = 4.8 Hz), 3.25 (dd, 4H, CH_2, J = 4.8 Hz), 4.18 (q, 2H, CH_2, J = 14.4 Hz), 4.37 (q, 2H, CH_2, J = 14.4 Hz), 6.72 (d, 1H, ArH, J = 6.9 Hz), 8.08 (d, 1H, ArH, J = 13.3 Hz), 8.40(s, 1H, ArH). MS m/z 362.2 (M+1).

Anal. Calcd for $C_{19}H_{24}N_3O_3F$: C, 63.14; H, 6.69; N, 11.63;. Found: C, 62.99; H, 7.00; N, 11.43.

1-Ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-methylpiperazinyl)-quinoline-3-carboxylic acid (49) To a 15 mL recovery flask equipped with a reflux condenser was added 72 mg (0.2 mmol) of **47b** and 2N NaOH (550 mL, 1.1 mmol). The reaction vessel was purged with nitrogen and heated to reflux. After 2 hours, the reaction mixture was cooled to room temperature and neutralized with 2 N HCl. Insoluble material was filtered away and the filtrate was evaporated under reduced pressure. The resulting solid was triturated with a mixture of

chloroform:methanol (3:1) and filtered. Evaporation of the filtrate under reduced pressure resulted in 64 mg of a light-brown solid in 96% yield.

Additional and Preliminary Investigations

Materials

All reagents and solvents were purchased from commercial sources and used without further purification. HPLC mobile phases were comprised of acetonitrile (Fisher or Pharmco HPLC grade) and water (Fisher or Pharmco HPLC grade), with either trifluoroacetic acid (Aldrich) or phosphoric acid (Aldrich) as the mobile phase modifier.

Instrumentation

^{1}H and ^{13}C NMR (400 or 500 MHz) were recorded on Varian Inova Spectrometers. Chemical shifts are reported as δ parts per million (ppm) downfield from tetramethylsilane. Either Agilent series 1090 or 1100 HPLC systems were used to monitor reactions and check for purity.

General Procedure for the Cyanation of Bromobenzene (50) - A 10 mL recovery flask containing a magnetic stir bar was charged with $Pd_2(dba)_3$ (13.7 mg, 0.015 mmol), zinc cyanide (70 mg, 0.6 mmol), $[(t\text{-}Bu)_3PH]BF_4$ (4.3 mg, 0.015 mmol), DMF (1 mL), and bromobenzene (105 μL, 1 mmol). The mixture was degassed, purged with nitrogen, and diisopropylamine (140 μL, 1.0 mmol) added. The reaction was heated at 80 °C for 2 h. HPLC analysis (Zorbax XDB C8 column, 4.6 x 150 mm, 50 % acetonitrile:H_2O (0.1 %

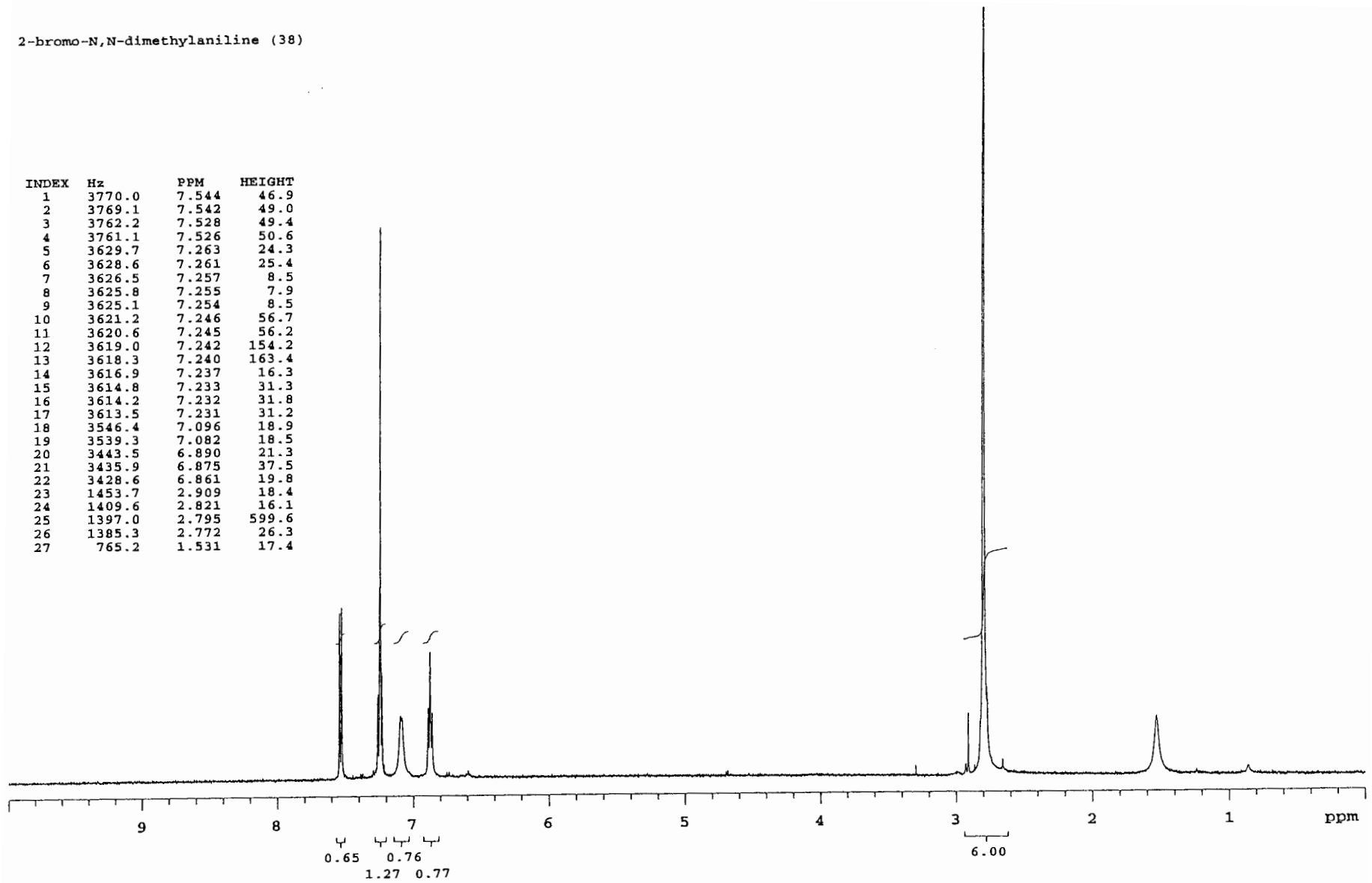
TFA) to 100 % acetonitrile, 15 min linear gradient, 1 mL/min, detection a 220 nm) of the reaction mixture showed 100 % conversion of the bromobenzene and a peak which corresponded to an authentic sample of benzonitrile.

***N*-(2-*tert*-butylphenyl)acetamide (58)** – In a 50 mL roundbottom flask was added pyridine (9 mL) and *tert*-butylaniline (1.4 mL, 9 mmol). The solution was cooled to 0 °C in an ice water bath and acetic anhydride (918 μL, 9.3 mmol) was added. The reaction was allowed to warm to room temperature and age overnight. The resulting milky white suspension was diluted with ethyl acetate (50 mL) and washed with 1N HCl and brine. The organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo* to yield a white foam which was recrystallized from methylene chloride. Obtained white crystals (1.2 g, 71 %). %). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.46 (d, J = 7.7 Hz, 1H), 7.39 (d, 7.7 Hz, 1H), 7.05-7.34 (m, 2H), 2.19 (s, 3H), 1.38 (s, 9H) ^{13}C NMR (100 MHz, $CDCl_3$) δ: 128.6, 126.7, 126.5, 126.4, 30.6, 30.5, 24.3.

Appendix I – ^{1}H NMR Spectra

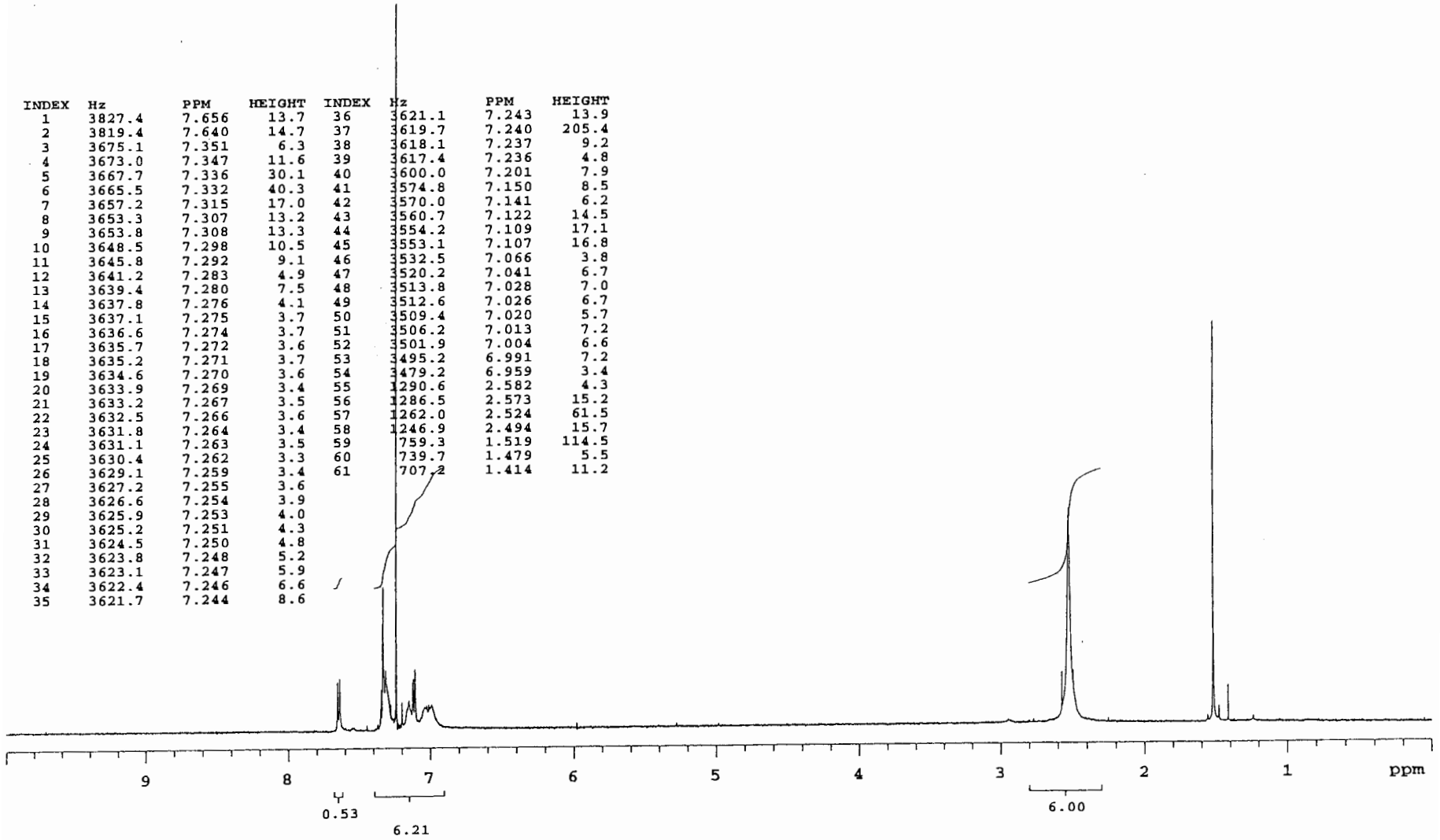
2-bromo-N,N-dimethylaniline (38)

INDEX	Hz	PPM	HEIGHT
1	3770.0	7.544	46.9
2	3769.1	7.542	49.0
3	3762.2	7.528	49.4
4	3761.1	7.526	50.6
5	3629.7	7.263	24.3
6	3628.6	7.261	25.4
7	3626.5	7.257	8.5
8	3625.8	7.255	7.9
9	3625.1	7.254	8.5
10	3621.2	7.246	56.7
11	3620.6	7.245	56.2
12	3619.0	7.242	154.2
13	3618.3	7.240	163.4
14	3616.9	7.237	16.3
15	3614.8	7.233	31.3
16	3614.2	7.232	31.8
17	3613.5	7.231	31.2
18	3546.4	7.096	18.9
19	3539.3	7.082	18.5
20	3443.5	6.890	21.3
21	3435.9	6.875	37.5
22	3428.6	6.861	19.8
23	1453.7	2.909	18.4
24	1409.6	2.821	16.1
25	1397.0	2.795	599.6
26	1385.3	2.772	26.3
27	765.2	1.531	17.4

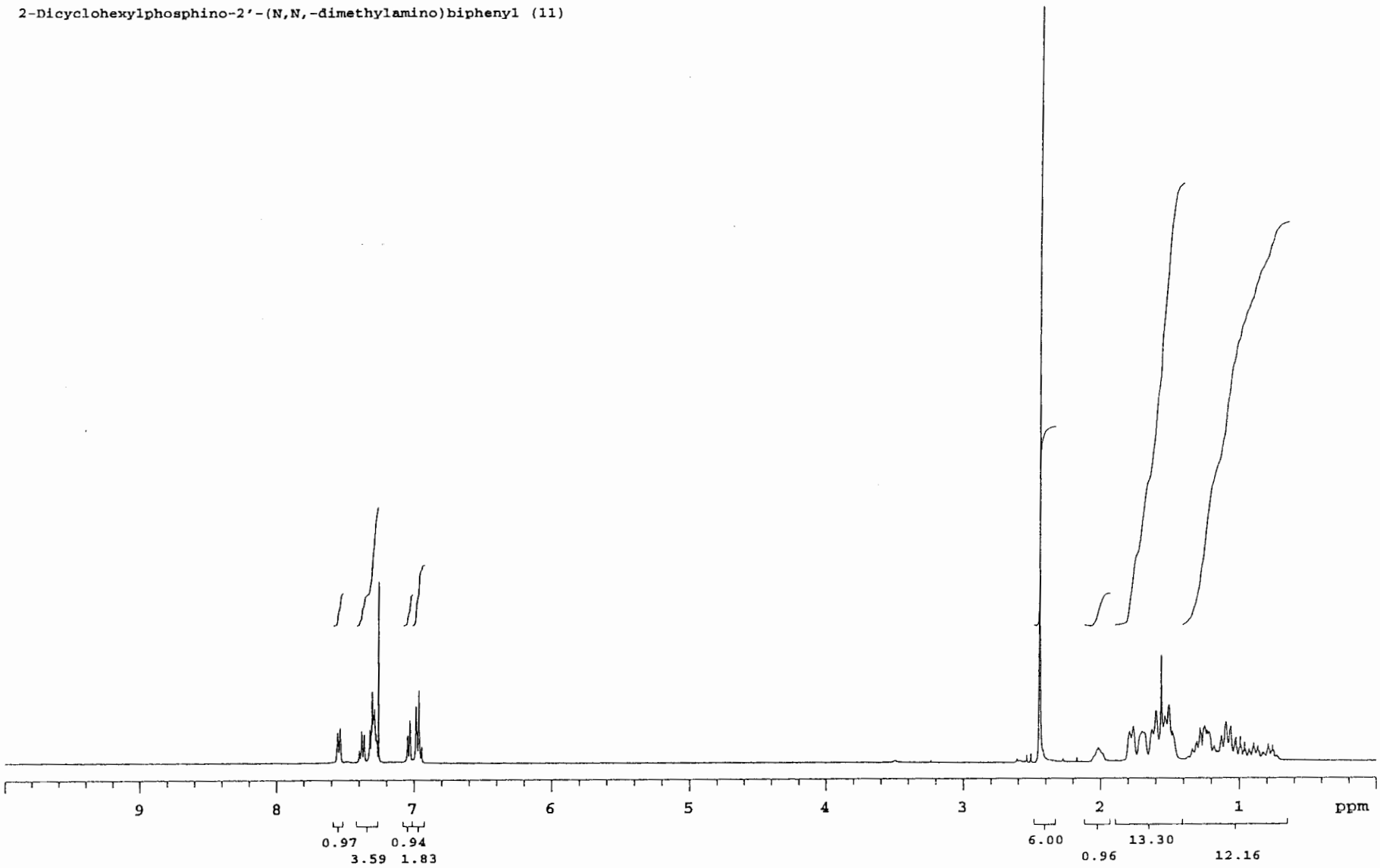


2'-bromo-N,N-dimethylbiphenyl-2-amine (41)

INDEX	Hz	PPM	HEIGHT	INDEX	Hz	PPM	HEIGHT
1	3827.4	7.656	13.7	36	3621.1	7.243	13.9
2	3819.4	7.640	14.7	37	3619.7	7.240	205.4
3	3675.1	7.351	6.3	38	3618.1	7.237	9.2
4	3673.0	7.347	11.6	39	3617.4	7.236	4.8
5	3667.7	7.336	30.1	40	3600.0	7.201	7.9
6	3665.5	7.332	40.3	41	3574.8	7.150	8.5
7	3657.2	7.315	17.0	42	3570.0	7.141	6.2
8	3653.3	7.307	13.2	43	3560.7	7.122	14.5
9	3653.8	7.308	13.3	44	3554.2	7.109	17.1
10	3648.5	7.298	10.5	45	3553.1	7.107	16.8
11	3645.8	7.292	9.1	46	3532.5	7.066	3.8
12	3641.2	7.283	4.9	47	3520.2	7.041	6.7
13	3639.4	7.280	7.5	48	3513.8	7.028	7.0
14	3637.8	7.276	4.1	49	3512.6	7.026	6.7
15	3637.1	7.275	3.7	50	3509.4	7.020	5.7
16	3636.6	7.274	3.7	51	3506.2	7.013	7.2
17	3635.7	7.272	3.6	52	3501.9	7.004	6.6
18	3635.2	7.271	3.7	53	3495.2	6.991	7.2
19	3634.6	7.270	3.6	54	3479.2	6.959	3.4
20	3633.9	7.269	3.4	55	1290.6	2.582	4.3
21	3633.2	7.267	3.5	56	1286.5	2.573	15.2
22	3632.5	7.266	3.6	57	1262.0	2.524	61.5
23	3631.8	7.264	3.4	58	1246.9	2.494	15.7
24	3631.1	7.263	3.5	59	759.3	1.519	114.5
25	3630.4	7.262	3.3	60	739.7	1.479	5.5
26	3629.1	7.259	3.4	61	707.2	1.414	11.2
27	3627.2	7.255	3.6				
28	3626.6	7.254	3.9				
29	3625.9	7.253	4.0				
30	3625.2	7.251	4.3				
31	3624.5	7.250	4.8				
32	3623.8	7.248	5.2				
33	3623.1	7.247	5.9				
34	3622.4	7.246	6.6				
35	3621.7	7.244	8.6				

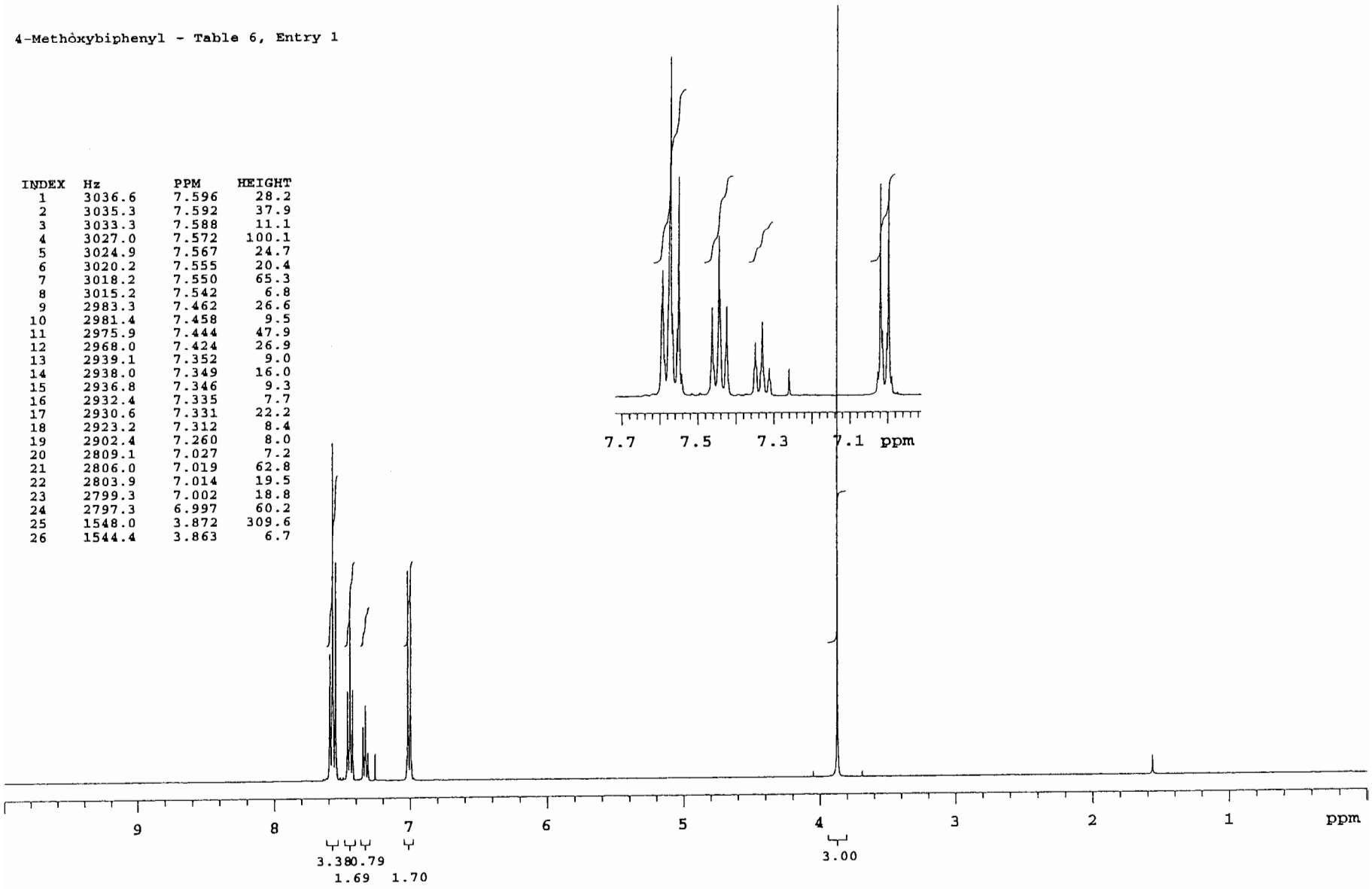


2-Dicyclohexylphosphino-2'-(N,N,-dimethylamino)biphenyl (11)



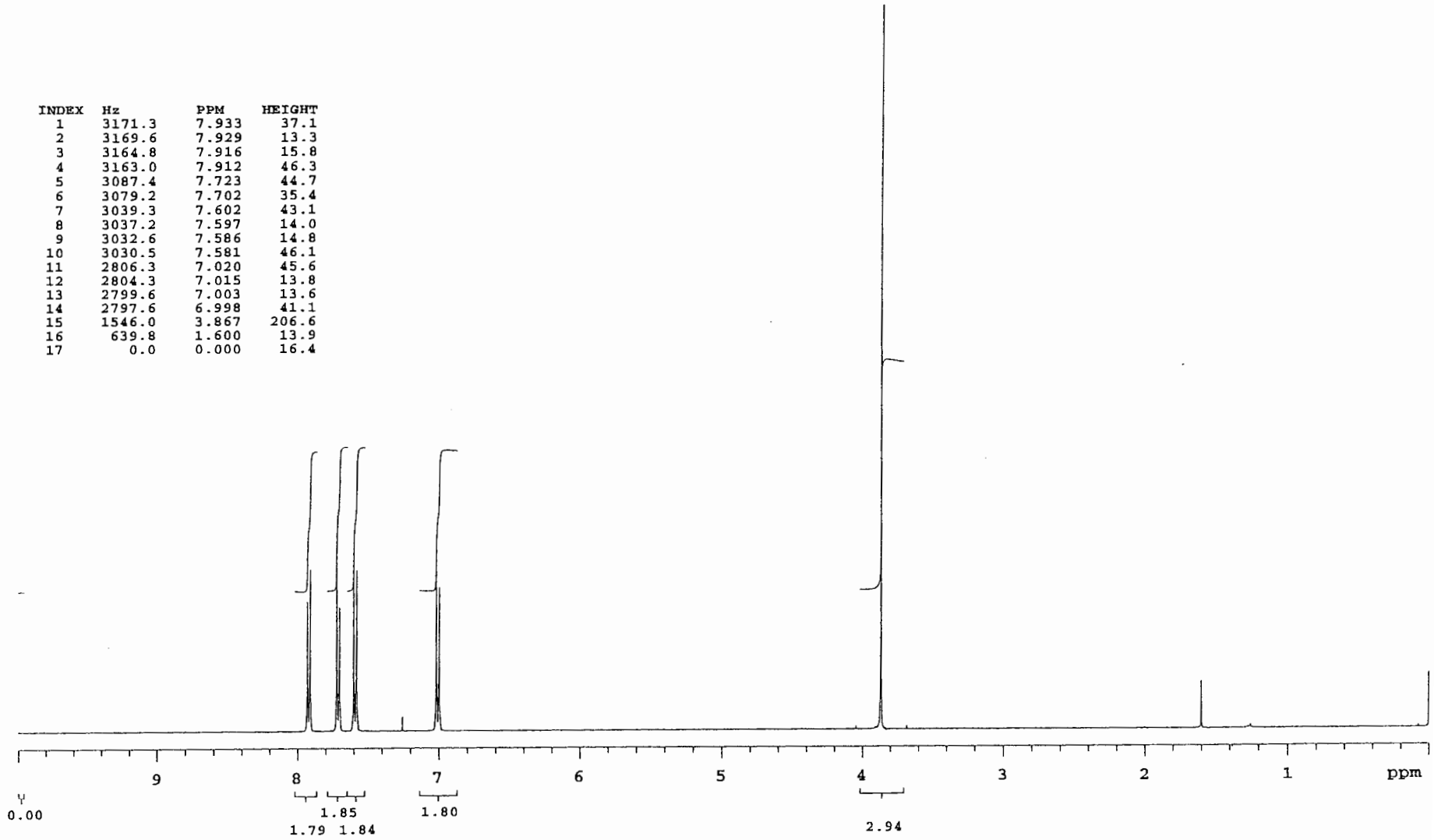
4-Methoxybiphenyl - Table 6, Entry 1

INDEX	Hz	PPM	HEIGHT
1	3036.6	7.596	28.2
2	3035.3	7.592	37.9
3	3033.3	7.588	11.1
4	3027.0	7.572	100.1
5	3024.9	7.567	24.7
6	3020.2	7.555	20.4
7	3018.2	7.550	65.3
8	3015.2	7.542	6.8
9	2983.3	7.462	26.6
10	2981.4	7.458	9.5
11	2975.9	7.444	47.9
12	2968.0	7.424	26.9
13	2939.1	7.352	9.0
14	2938.0	7.349	16.0
15	2936.8	7.346	9.3
16	2932.4	7.335	7.7
17	2930.6	7.331	22.2
18	2923.2	7.312	8.4
19	2902.4	7.260	8.0
20	2809.1	7.027	7.2
21	2806.0	7.019	62.8
22	2803.9	7.014	19.5
23	2799.3	7.002	18.8
24	2797.3	6.997	60.2
25	1548.0	3.872	309.6
26	1544.4	3.863	6.7



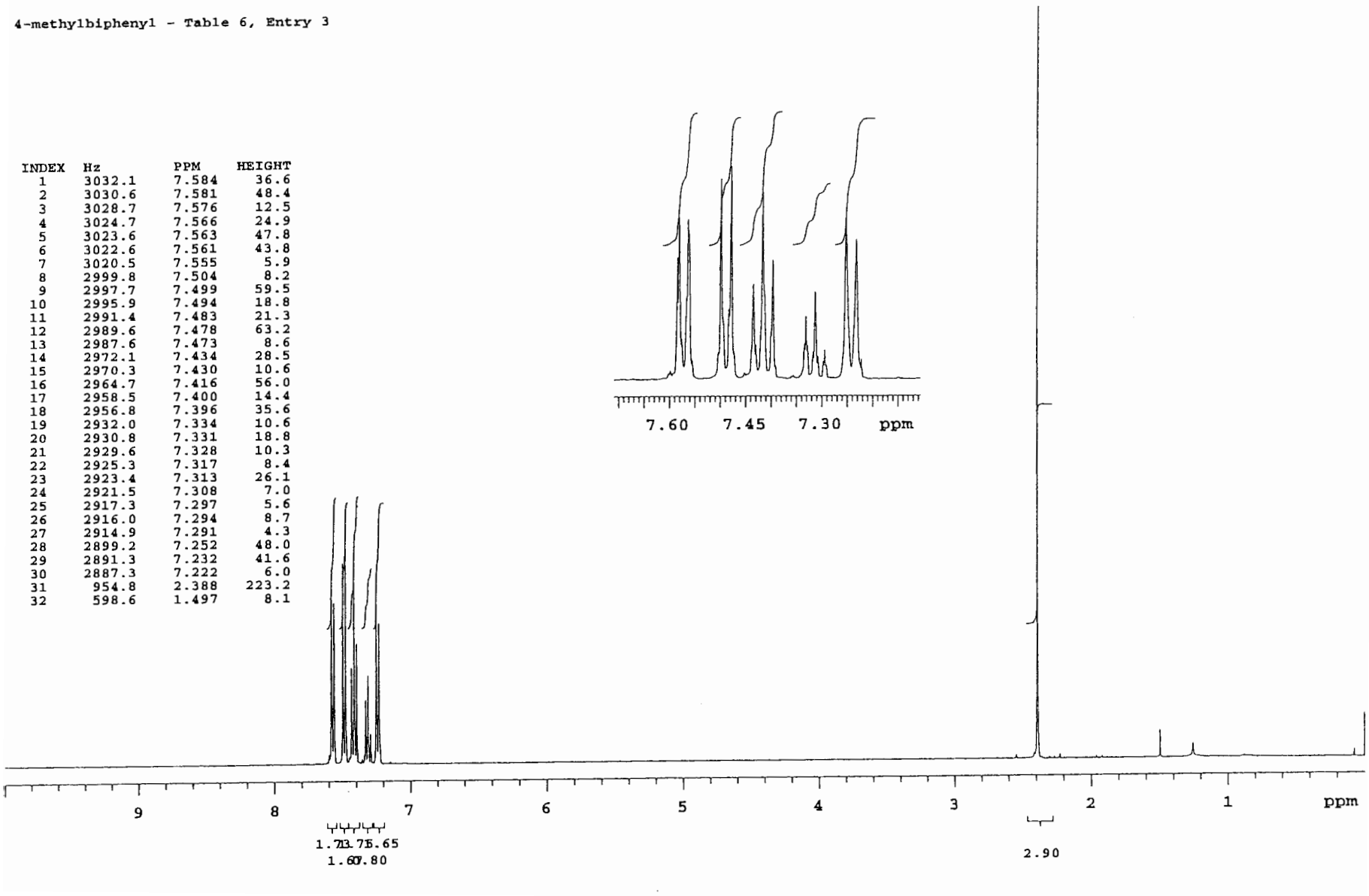
4'-methoxybiphenyl-4-carbaldehyde - Table 6, Entry 2

INDEX	Hz	PPM	HEIGHT
1	3171.3	7.933	37.1
2	3169.6	7.929	13.3
3	3164.8	7.916	15.8
4	3163.0	7.912	46.3
5	3087.4	7.723	44.7
6	3079.2	7.702	35.4
7	3039.3	7.602	43.1
8	3037.2	7.597	14.0
9	3032.6	7.586	14.8
10	3030.5	7.581	46.1
11	2806.3	7.020	45.6
12	2804.3	7.015	13.8
13	2799.6	7.003	13.6
14	2797.6	6.998	41.1
15	1546.0	3.867	206.6
16	639.8	1.600	13.9
17	0.0	0.000	16.4



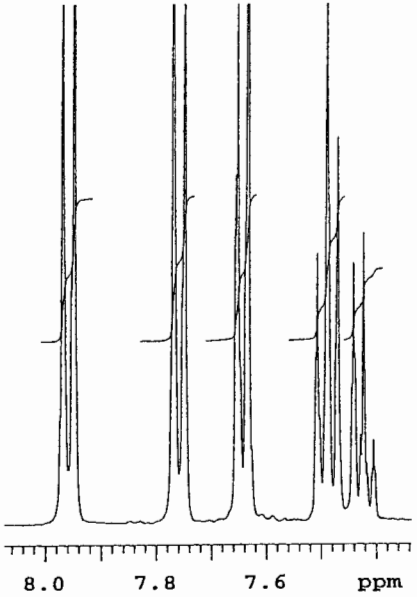
4-methylbiphenyl - Table 6, Entry 3

INDEX	Hz	PPM	HEIGHT
1	3032.1	7.584	36.6
2	3030.6	7.581	48.4
3	3028.7	7.576	12.5
4	3024.7	7.566	24.9
5	3023.6	7.563	47.8
6	3022.6	7.561	43.8
7	3020.5	7.555	5.9
8	2999.8	7.504	8.2
9	2997.7	7.499	59.5
10	2995.9	7.494	18.8
11	2991.4	7.483	21.3
12	2989.6	7.478	63.2
13	2987.6	7.473	8.6
14	2972.1	7.434	28.5
15	2970.3	7.430	10.6
16	2964.7	7.416	56.0
17	2958.5	7.400	14.4
18	2956.8	7.396	35.6
19	2932.0	7.334	10.6
20	2930.8	7.331	18.8
21	2929.6	7.328	10.3
22	2925.3	7.317	8.4
23	2923.4	7.313	26.1
24	2921.5	7.308	7.0
25	2917.3	7.297	5.6
26	2916.0	7.294	8.7
27	2914.9	7.291	4.3
28	2899.2	7.252	48.0
29	2891.3	7.232	41.6
30	2887.3	7.222	6.0
31	954.8	2.388	223.2
32	598.6	1.497	8.1



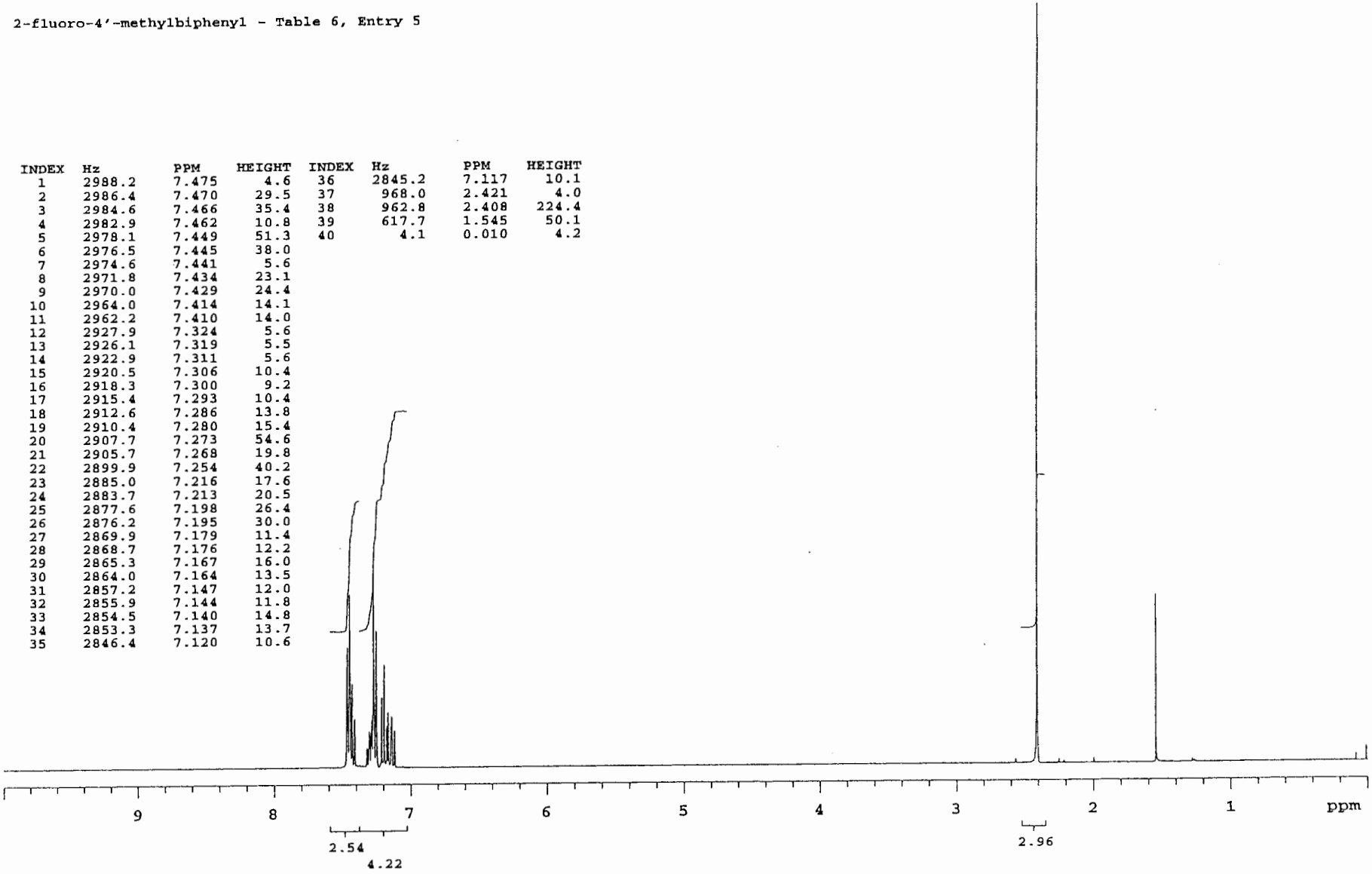
4-Formylbiphenyl - Table 6, Entry 4

INDEX	Hz	PPM	HEIGHT
1	3185.8	7.969	142.6
2	3181.7	7.959	11.9
3	3179.4	7.953	56.0
4	3177.6	7.948	184.1
5	3106.0	7.769	173.7
6	3097.8	7.749	141.9
7	3060.7	7.656	77.2
8	3059.2	7.652	118.1
9	3052.0	7.634	126.2
10	3051.3	7.633	124.9
11	3049.0	7.627	16.3
12	3002.3	7.510	36.2
13	3001.1	7.507	59.5
14	2999.5	7.503	23.5
15	2994.1	7.489	137.7
16	2992.7	7.486	71.4
17	2986.4	7.470	85.5
18	2976.1	7.444	30.5
19	2974.8	7.441	57.3
20	2973.7	7.439	37.3
21	2969.8	7.429	19.4
22	2967.6	7.423	64.0
23	2965.1	7.417	13.1
24	2961.5	7.408	11.1
25	2960.3	7.405	18.1
26	2902.4	7.260	28.2



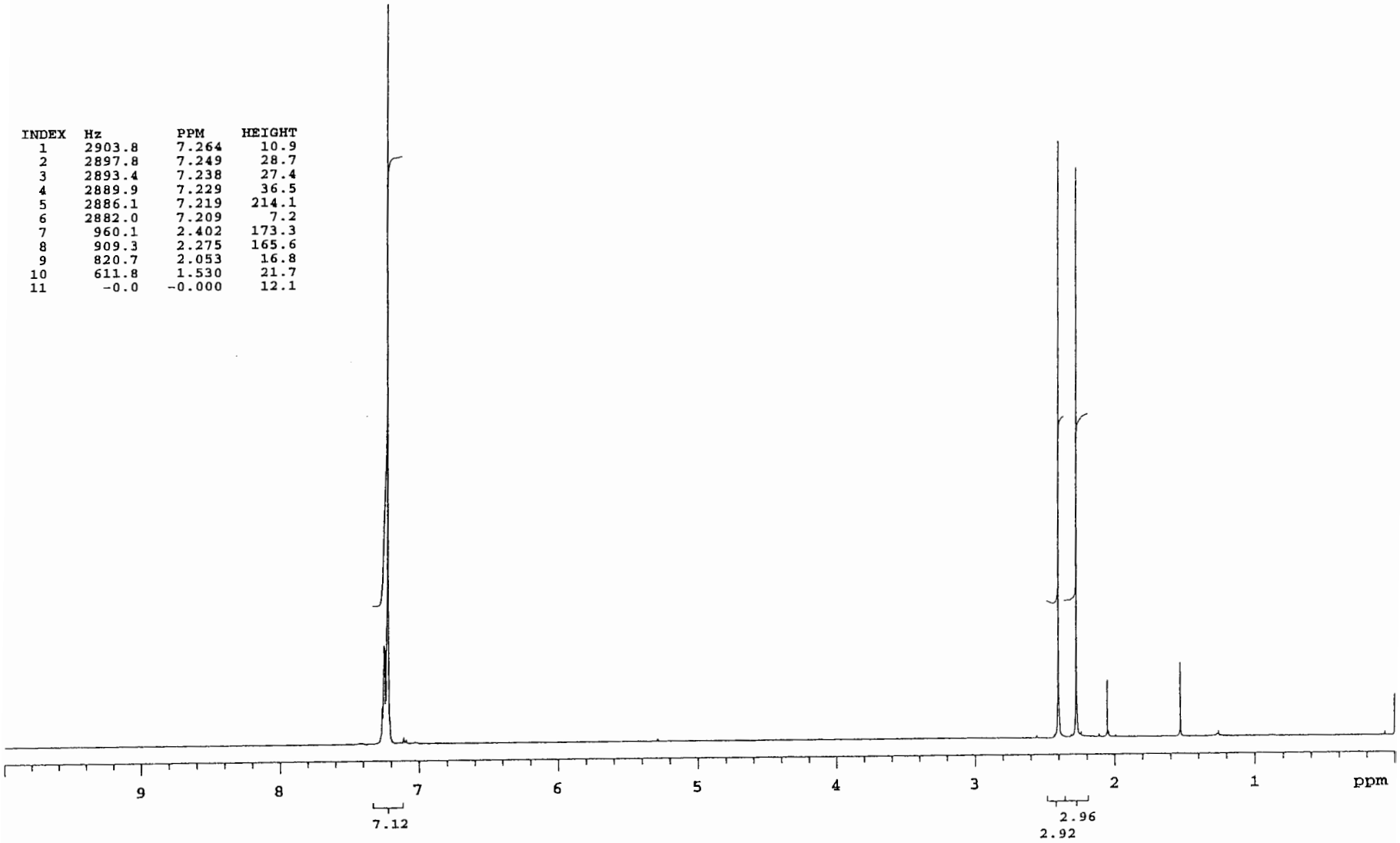
2-fluoro-4'-methylbiphenyl - Table 6, Entry 5

INDEX	Hz	PPM	HEIGHT	INDEX	Hz	PPM	HEIGHT
1	2988.2	7.475	4.6	36	2845.2	7.117	10.1
2	2986.4	7.470	29.5	37	968.0	2.421	4.0
3	2984.6	7.466	35.4	38	962.8	2.408	224.4
4	2982.9	7.462	10.8	39	617.7	1.545	50.1
5	2978.1	7.449	51.3	40	4.1	0.010	4.2
6	2976.5	7.445	38.0				
7	2974.6	7.441	5.6				
8	2971.8	7.434	23.1				
9	2970.0	7.429	24.4				
10	2964.0	7.414	14.1				
11	2962.2	7.410	14.0				
12	2927.9	7.324	5.6				
13	2926.1	7.319	5.5				
14	2922.9	7.311	5.6				
15	2920.5	7.306	10.4				
16	2918.3	7.300	9.2				
17	2915.4	7.293	10.4				
18	2912.6	7.286	13.8				
19	2910.4	7.280	15.4				
20	2907.7	7.273	54.6				
21	2905.7	7.268	19.8				
22	2899.9	7.254	40.2				
23	2885.0	7.216	17.6				
24	2883.7	7.213	20.5				
25	2877.6	7.198	26.4				
26	2876.2	7.195	30.0				
27	2869.9	7.179	11.4				
28	2868.7	7.176	12.2				
29	2865.3	7.167	16.0				
30	2864.0	7.164	13.5				
31	2857.2	7.147	12.0				
32	2855.9	7.144	11.8				
33	2854.5	7.140	14.8				
34	2853.3	7.137	13.7				
35	2846.4	7.120	10.6				



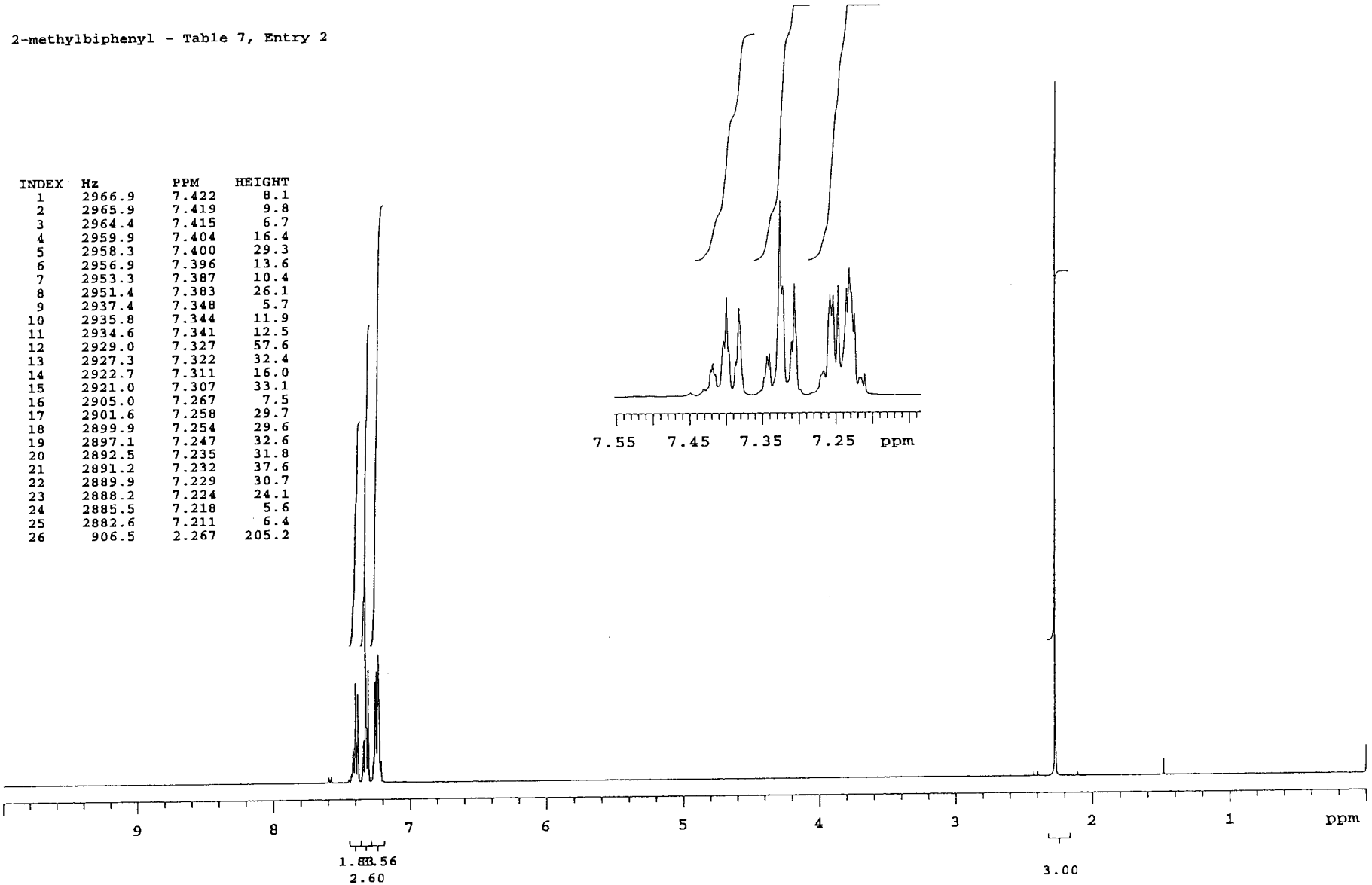
2,4'-dimethylbiphenyl - Table 7, Entry 1

INDEX	Hz	PPM	HEIGHT
1	2903.8	7.264	10.9
2	2897.8	7.249	28.7
3	2893.4	7.238	27.4
4	2889.9	7.229	36.5
5	2886.1	7.219	214.1
6	2882.0	7.209	7.2
7	960.1	2.402	173.3
8	909.3	2.275	165.6
9	820.7	2.053	16.8
10	611.8	1.530	21.7
11	-0.0	-0.000	12.1



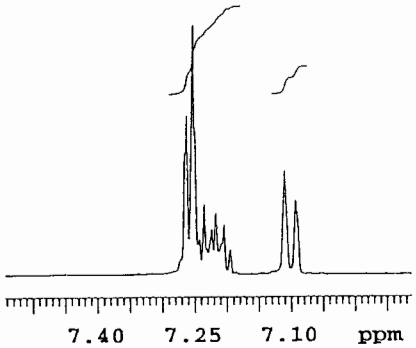
2-methylbiphenyl - Table 7, Entry 2

INDEX	Hz	PPM	HEIGHT
1	2966.9	7.422	8.1
2	2965.9	7.419	9.8
3	2964.4	7.415	6.7
4	2959.9	7.404	16.4
5	2958.3	7.400	29.3
6	2956.9	7.396	13.6
7	2953.3	7.387	10.4
8	2951.4	7.383	26.1
9	2937.4	7.348	5.7
10	2935.8	7.344	11.9
11	2934.6	7.341	12.5
12	2929.0	7.327	57.6
13	2927.3	7.322	32.4
14	2922.7	7.311	16.0
15	2921.0	7.307	33.1
16	2905.0	7.267	7.5
17	2901.6	7.258	29.7
18	2899.9	7.254	29.6
19	2897.1	7.247	32.6
20	2892.5	7.235	31.8
21	2891.2	7.232	37.6
22	2889.9	7.229	30.7
23	2888.2	7.224	24.1
24	2885.5	7.218	5.6
25	2882.6	7.211	6.4
26	906.5	2.267	205.2



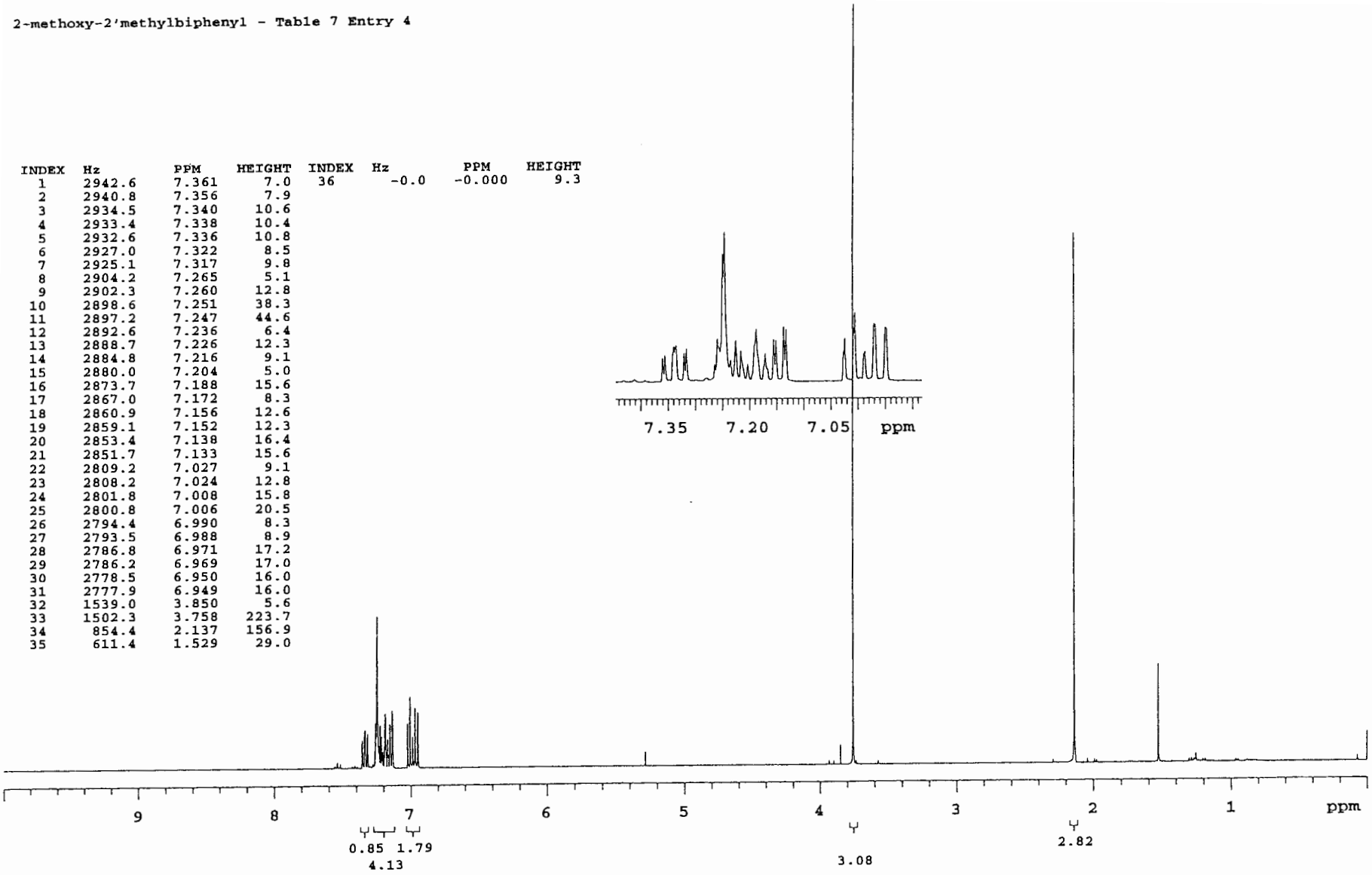
2,2'-dimethylbiphenyl - Table 7, Entry 3

INDEX	Hz	PPM	HEIGHT
1	2904.7	7.266	27.1
2	2903.7	7.263	35.2
3	2899.9	7.254	55.3
4	2898.5	7.250	32.2
5	2895.6	7.243	7.9
6	2892.6	7.236	15.2
7	2890.9	7.231	5.7
8	2888.0	7.224	9.9
9	2885.4	7.218	13.5
10	2882.2	7.210	6.7
11	2881.4	7.208	7.0
12	2880.4	7.205	10.9
13	2876.5	7.195	5.4
14	2842.6	7.111	22.8
15	2835.8	7.093	16.1
16	820.7	2.053	225.0
17	608.5	1.522	10.7
18	-0.0	-0.000	7.9



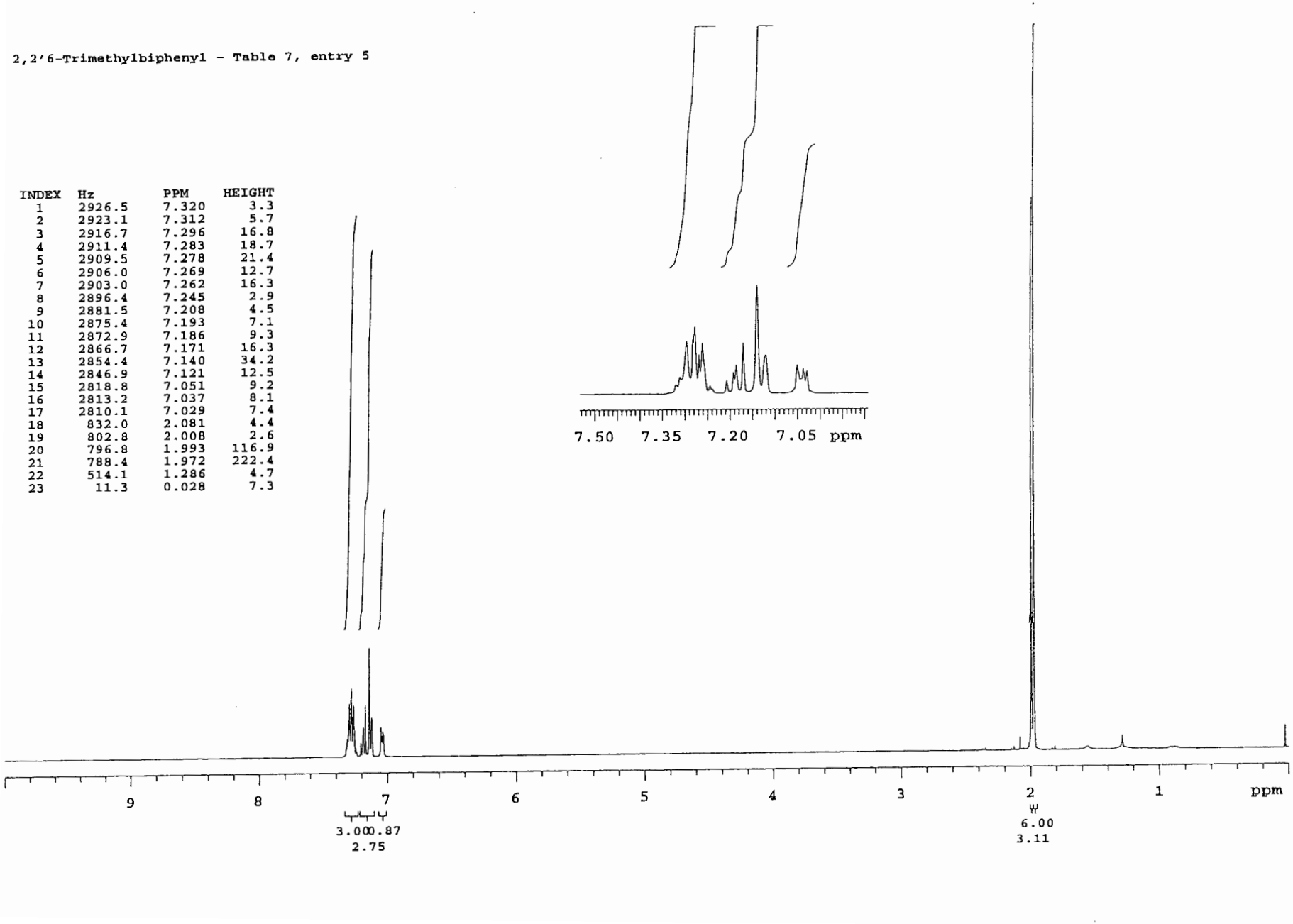
2-methoxy-2'methylbiphenyl - Table 7 Entry 4

INDEX	Hz	PPM	HEIGHT	INDEX	Hz	PPM	HEIGHT
1	2942.6	7.361	7.0	36	-0.0	-0.000	9.3
2	2940.8	7.356	7.9				
3	2934.5	7.340	10.6				
4	2933.4	7.338	10.4				
5	2932.6	7.336	10.8				
6	2927.0	7.322	8.5				
7	2925.1	7.317	9.8				
8	2904.2	7.265	5.1				
9	2902.3	7.260	12.8				
10	2898.6	7.251	38.3				
11	2897.2	7.247	44.6				
12	2892.6	7.236	6.4				
13	2888.7	7.226	12.3				
14	2884.8	7.216	9.1				
15	2880.0	7.204	5.0				
16	2873.7	7.188	15.6				
17	2867.0	7.172	8.3				
18	2860.9	7.156	12.6				
19	2859.1	7.152	12.3				
20	2853.4	7.138	16.4				
21	2851.7	7.133	15.6				
22	2809.2	7.027	9.1				
23	2808.2	7.024	12.8				
24	2801.8	7.008	15.8				
25	2800.8	7.006	20.5				
26	2794.4	6.990	8.3				
27	2793.5	6.988	8.9				
28	2786.8	6.971	17.2				
29	2786.2	6.969	17.0				
30	2778.5	6.950	16.0				
31	2777.9	6.949	16.0				
32	1539.0	3.850	5.6				
33	1502.3	3.758	223.7				
34	854.4	2.137	156.9				
35	611.4	1.529	29.0				



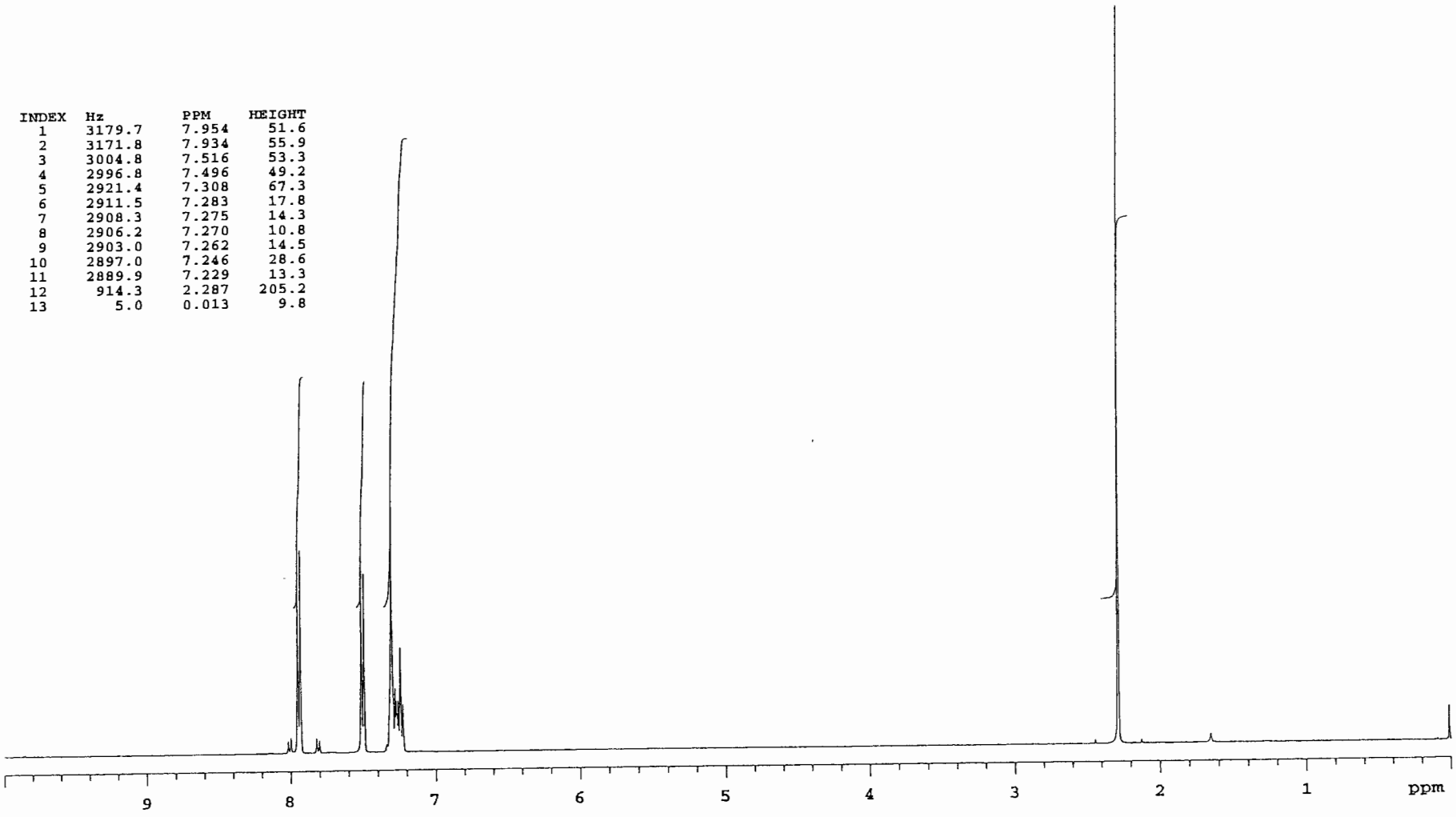
2,2'6-Trimethylbiphenyl - Table 7, entry 5

INDEX	Hz	PPM	HEIGHT
1	2926.5	7.320	3.3
2	2923.1	7.312	5.7
3	2916.7	7.296	16.8
4	2911.4	7.283	18.7
5	2909.5	7.278	21.4
6	2906.0	7.269	12.7
7	2903.0	7.262	16.3
8	2896.4	7.245	2.9
9	2881.5	7.208	4.5
10	2875.4	7.193	7.1
11	2872.9	7.186	9.3
12	2866.7	7.171	16.3
13	2854.4	7.140	34.2
14	2846.9	7.121	12.5
15	2818.8	7.051	9.2
16	2813.2	7.037	8.1
17	2810.1	7.029	7.4
18	832.0	2.081	4.4
19	802.8	2.008	2.6
20	796.8	1.993	116.9
21	788.4	1.972	222.4
22	514.1	1.286	4.7
23	11.3	0.028	7.3



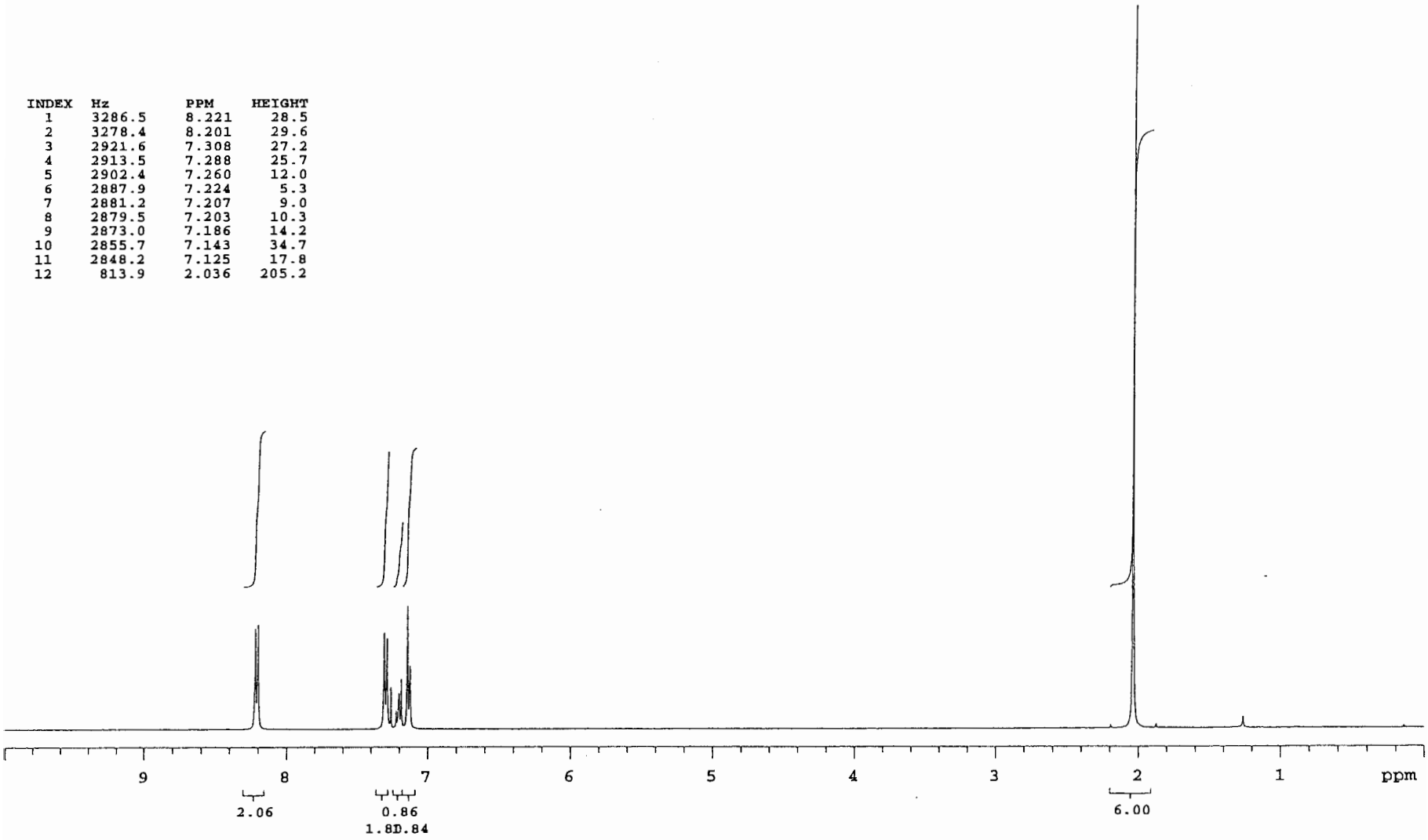
2'-Methylbiphenyl-4-carbaldehyde - Table 7, entry 6

INDEX	Hz	PPM	HEIGHT
1	3179.7	7.954	51.6
2	3171.8	7.934	55.9
3	3004.8	7.516	53.3
4	2996.8	7.496	49.2
5	2921.4	7.308	67.3
6	2911.5	7.283	17.8
7	2908.3	7.275	14.3
8	2906.2	7.270	10.8
9	2903.0	7.262	14.5
10	2897.0	7.246	28.6
11	2889.9	7.229	13.3
12	914.3	2.287	205.2
13	5.0	0.013	9.8



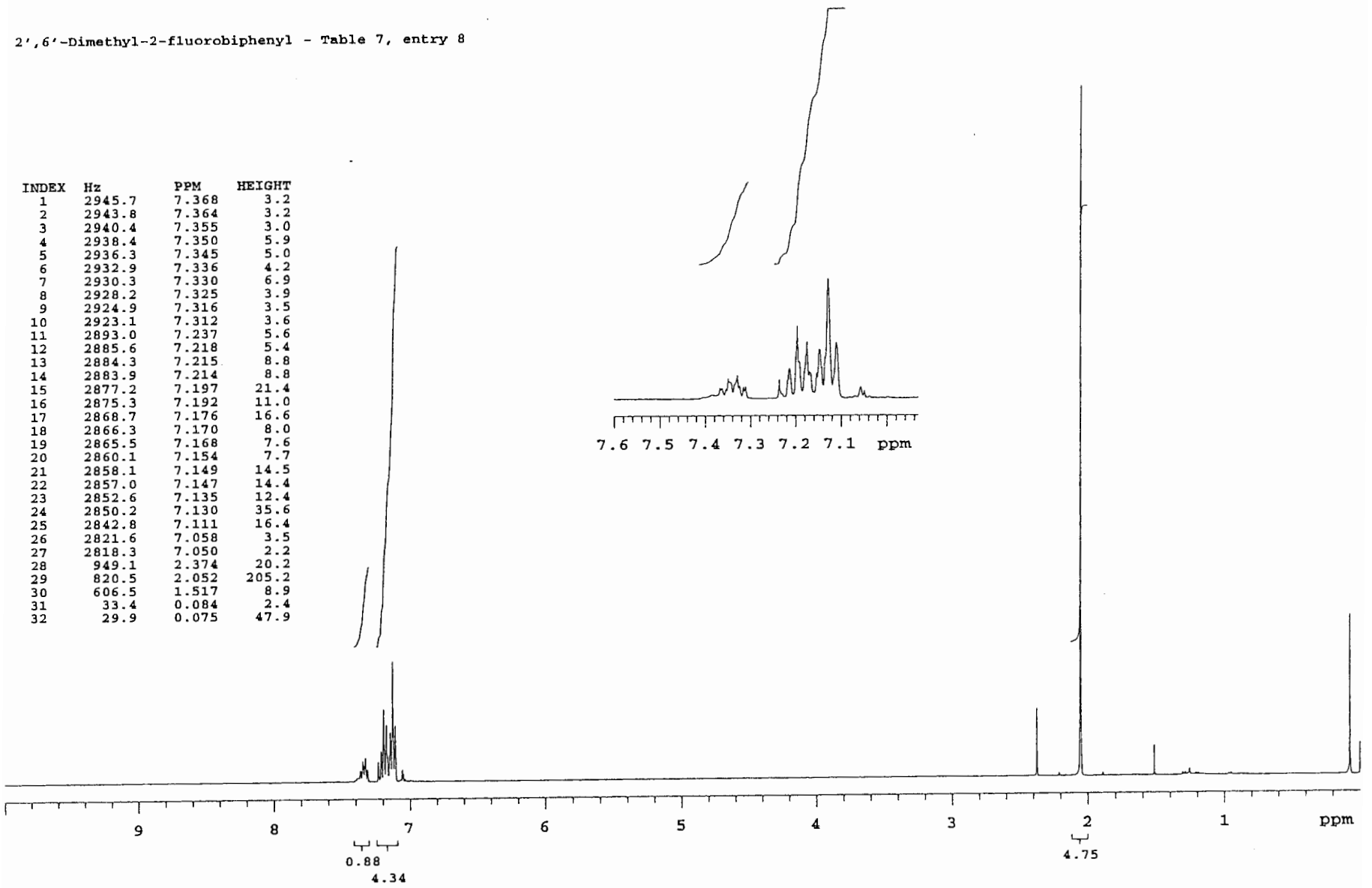
2′,6′-Dimethylbiphenyl-4-carbaldehyde - Table 7, Entry 7

INDEX	Hz	PPM	HEIGHT
1	3286.5	8.221	28.5
2	3278.4	8.201	29.6
3	2921.6	7.308	27.2
4	2913.5	7.288	25.7
5	2902.4	7.260	12.0
6	2887.9	7.224	5.3
7	2881.2	7.207	9.0
8	2879.5	7.203	10.3
9	2873.0	7.186	14.2
10	2855.7	7.143	34.7
11	2848.2	7.125	17.8
12	813.9	2.036	205.2



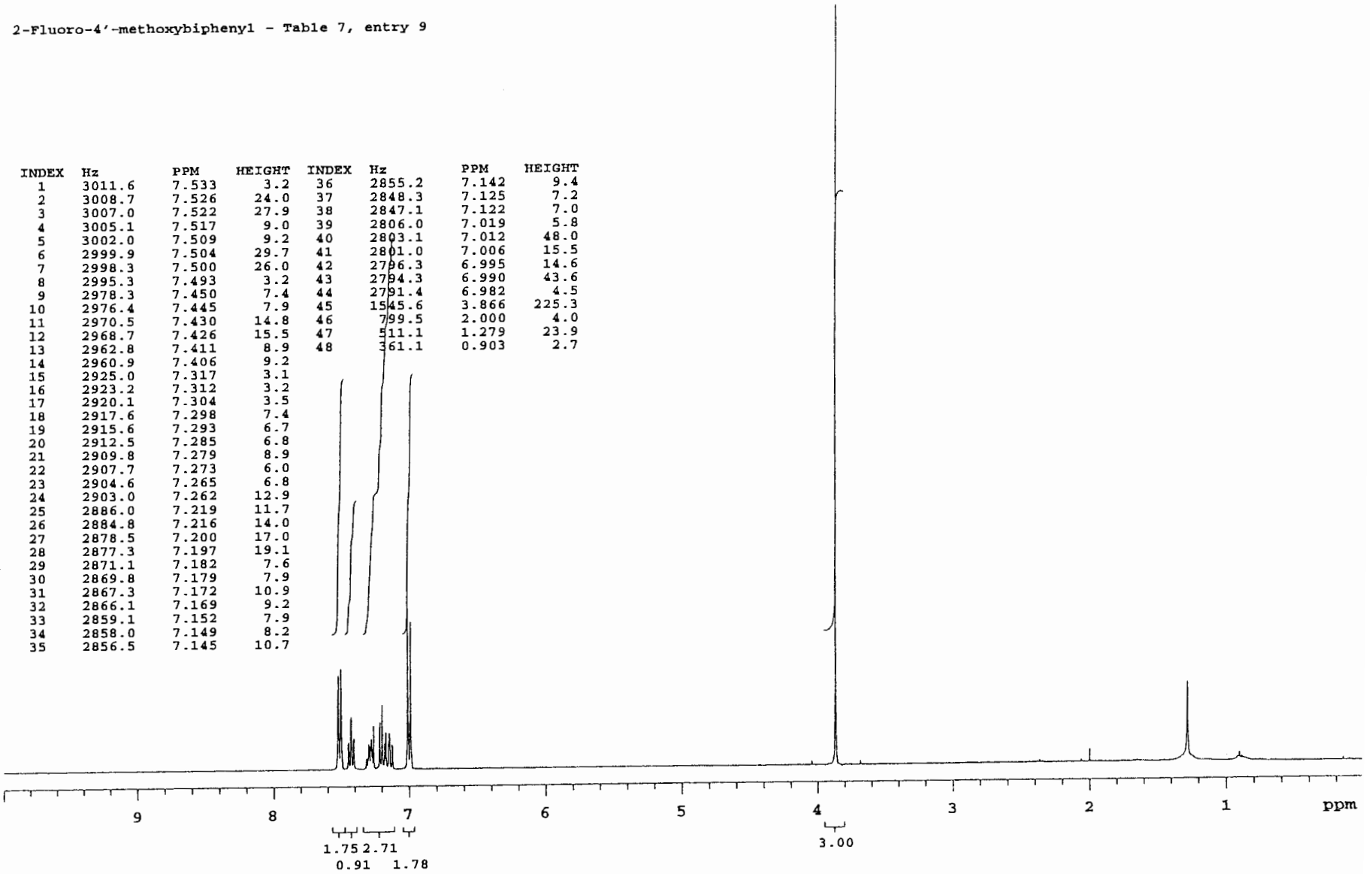
2',6'-Dimethyl-2-fluorobiphenyl - Table 7, entry 8

INDEX	Hz	PPM	HEIGHT
1	2945.7	7.368	3.2
2	2943.8	7.364	3.2
3	2940.4	7.355	3.0
4	2938.4	7.350	5.9
5	2936.3	7.345	5.0
6	2932.9	7.336	4.2
7	2930.3	7.330	6.9
8	2928.2	7.325	3.9
9	2924.9	7.316	3.5
10	2923.1	7.312	3.6
11	2893.0	7.237	5.6
12	2885.6	7.218	5.4
13	2884.3	7.215	8.8
14	2883.9	7.214	8.8
15	2877.2	7.197	21.4
16	2875.3	7.192	11.0
17	2868.7	7.176	16.6
18	2866.3	7.170	8.0
19	2865.5	7.168	7.6
20	2860.1	7.154	7.7
21	2858.1	7.149	14.5
22	2857.0	7.147	14.4
23	2852.6	7.135	12.4
24	2850.2	7.130	35.6
25	2842.8	7.111	16.4
26	2821.6	7.058	3.5
27	2818.3	7.050	2.2
28	949.1	2.374	20.2
29	820.5	2.052	205.2
30	606.5	1.517	8.9
31	33.4	0.084	2.4
32	29.9	0.075	47.9



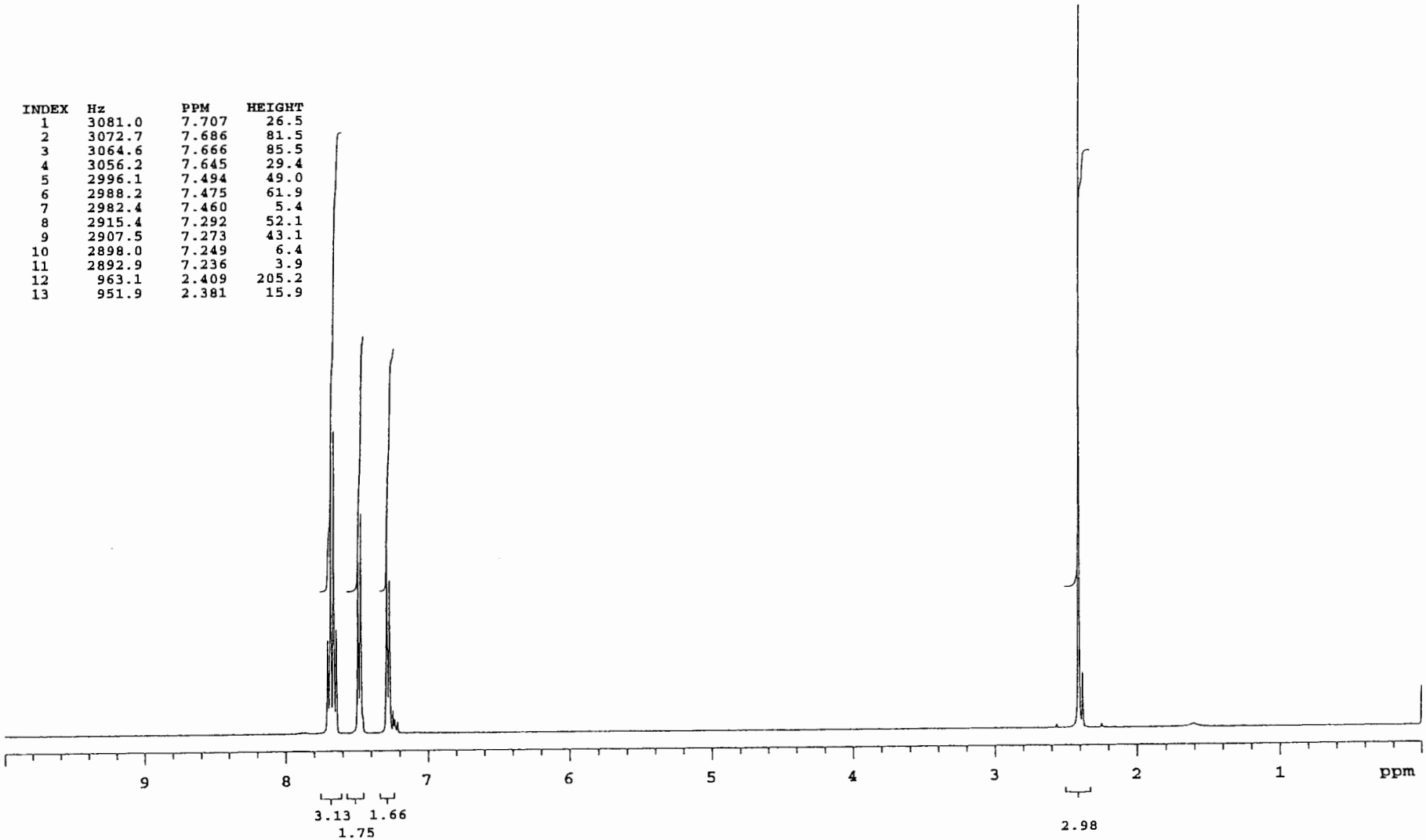
2-Fluoro-4'-methoxybiphenyl - Table 7, entry 9

INDEX	Hz	PPM	HEIGHT	INDEX	Hz	PPM	HEIGHT
1	3011.6	7.533	3.2	36	2855.2	7.142	9.4
2	3008.7	7.526	24.0	37	2848.3	7.125	7.2
3	3007.0	7.522	27.9	38	2847.1	7.122	7.0
4	3005.1	7.517	9.0	39	2806.0	7.019	5.8
5	3002.0	7.509	9.2	40	2803.1	7.012	48.0
6	2999.9	7.504	29.7	41	2801.0	7.006	15.5
7	2998.3	7.500	26.0	42	2796.3	6.995	14.6
8	2995.3	7.493	3.2	43	2794.3	6.990	43.6
9	2978.3	7.450	7.4	44	2791.4	6.982	4.5
10	2976.4	7.445	7.9	45	1545.6	3.866	225.3
11	2970.5	7.430	14.8	46	799.5	2.000	4.0
12	2968.7	7.426	15.5	47	511.1	1.279	23.9
13	2962.8	7.411	8.9	48	361.1	0.903	2.7
14	2960.9	7.406	9.2				
15	2925.0	7.317	3.1				
16	2923.2	7.312	3.2				
17	2920.1	7.304	3.5				
18	2917.6	7.298	7.4				
19	2915.6	7.293	6.7				
20	2912.5	7.285	6.8				
21	2909.8	7.279	8.9				
22	2907.7	7.273	6.0				
23	2904.6	7.265	6.8				
24	2903.0	7.262	12.9				
25	2886.0	7.219	11.7				
26	2884.8	7.216	14.0				
27	2878.5	7.200	17.0				
28	2877.3	7.197	19.1				
29	2871.1	7.182	7.6				
30	2869.8	7.179	7.9				
31	2867.3	7.172	10.9				
32	2866.1	7.169	9.2				
33	2859.1	7.152	7.9				
34	2858.0	7.149	8.2				
35	2856.5	7.145	10.7				



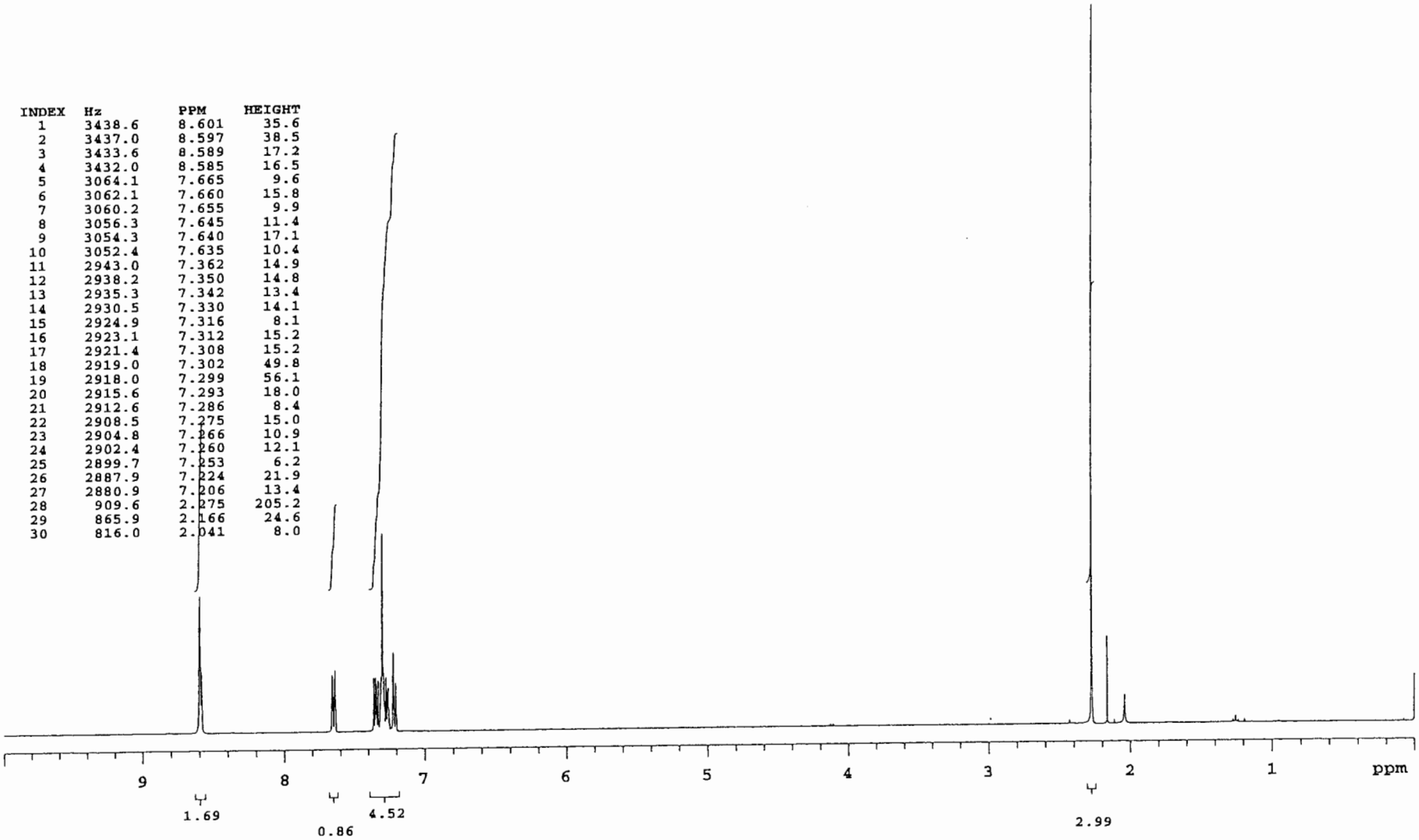
4-Methylbiphenyl-4-carbonitrile - Table 9, entry 1

INDEX	Hz	PPM	HEIGHT
1	3081.0	7.707	26.5
2	3072.7	7.686	81.5
3	3064.6	7.666	85.5
4	3056.2	7.645	29.4
5	2996.1	7.494	49.0
6	2988.2	7.475	61.9
7	2982.4	7.460	5.4
8	2915.4	7.292	52.1
9	2907.5	7.273	43.1
10	2898.0	7.249	6.4
11	2892.9	7.236	3.9
12	963.1	2.409	205.2
13	951.9	2.381	15.9



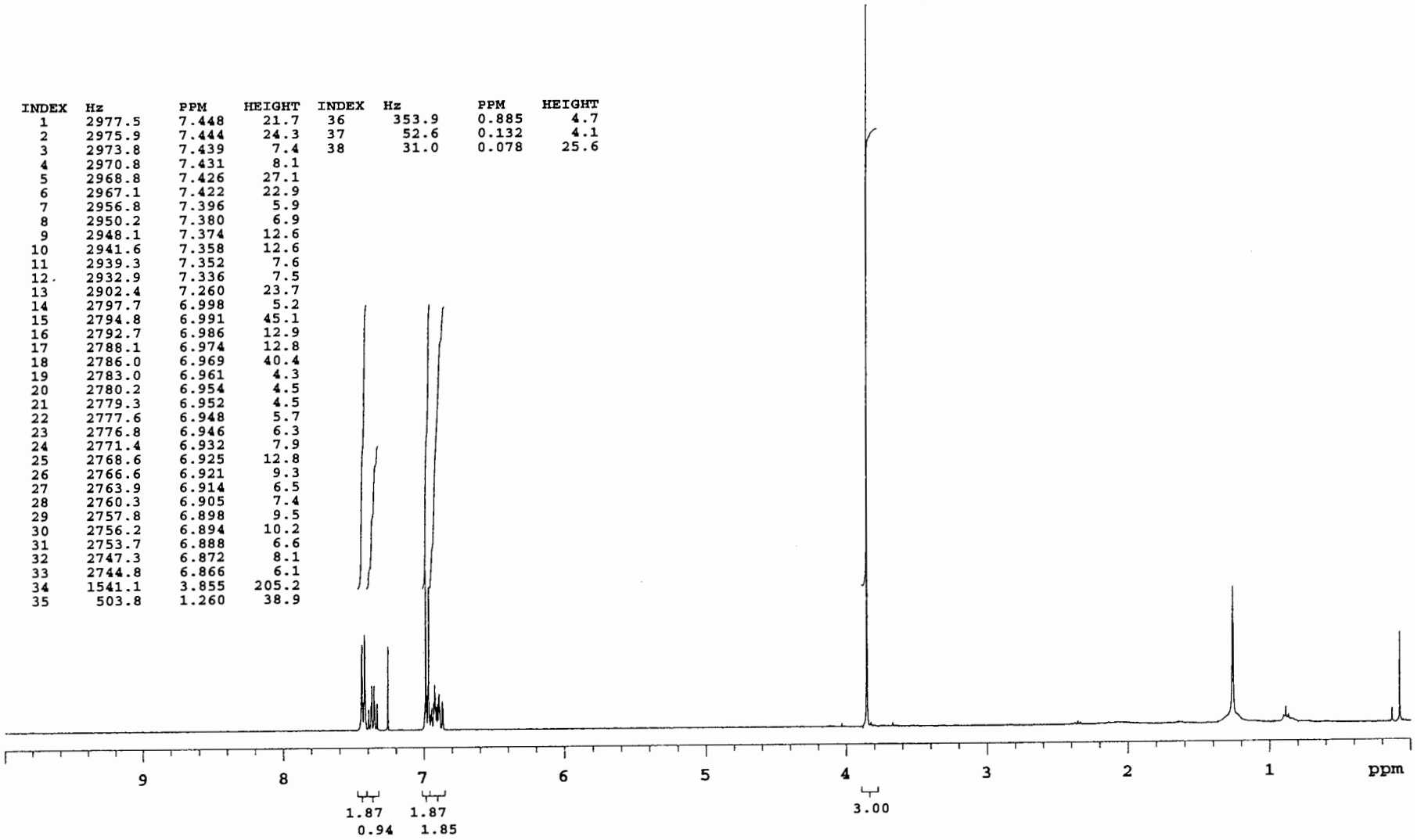
3-(2-methylphenyl)pyridine - Table 11, Entry 9

INDEX	Hz	PPM	HEIGHT
1	3438.6	8.601	35.6
2	3437.0	8.597	38.5
3	3433.6	8.589	17.2
4	3432.0	8.585	16.5
5	3064.1	7.665	9.6
6	3062.1	7.660	15.8
7	3060.2	7.655	9.9
8	3056.3	7.645	11.4
9	3054.3	7.640	17.1
10	3052.4	7.635	10.4
11	2943.0	7.362	14.9
12	2938.2	7.350	14.8
13	2935.3	7.342	13.4
14	2930.5	7.330	14.1
15	2924.9	7.316	8.1
16	2923.1	7.312	15.2
17	2921.4	7.308	15.2
18	2919.0	7.302	49.8
19	2918.0	7.299	56.1
20	2915.6	7.293	18.0
21	2912.6	7.286	8.4
22	2908.5	7.275	15.0
23	2904.8	7.266	10.9
24	2902.4	7.260	12.1
25	2899.7	7.253	6.2
26	2887.9	7.224	21.9
27	2880.9	7.206	13.4
28	909.6	2.275	205.2
29	865.9	2.166	24.6
30	816.0	2.041	8.0

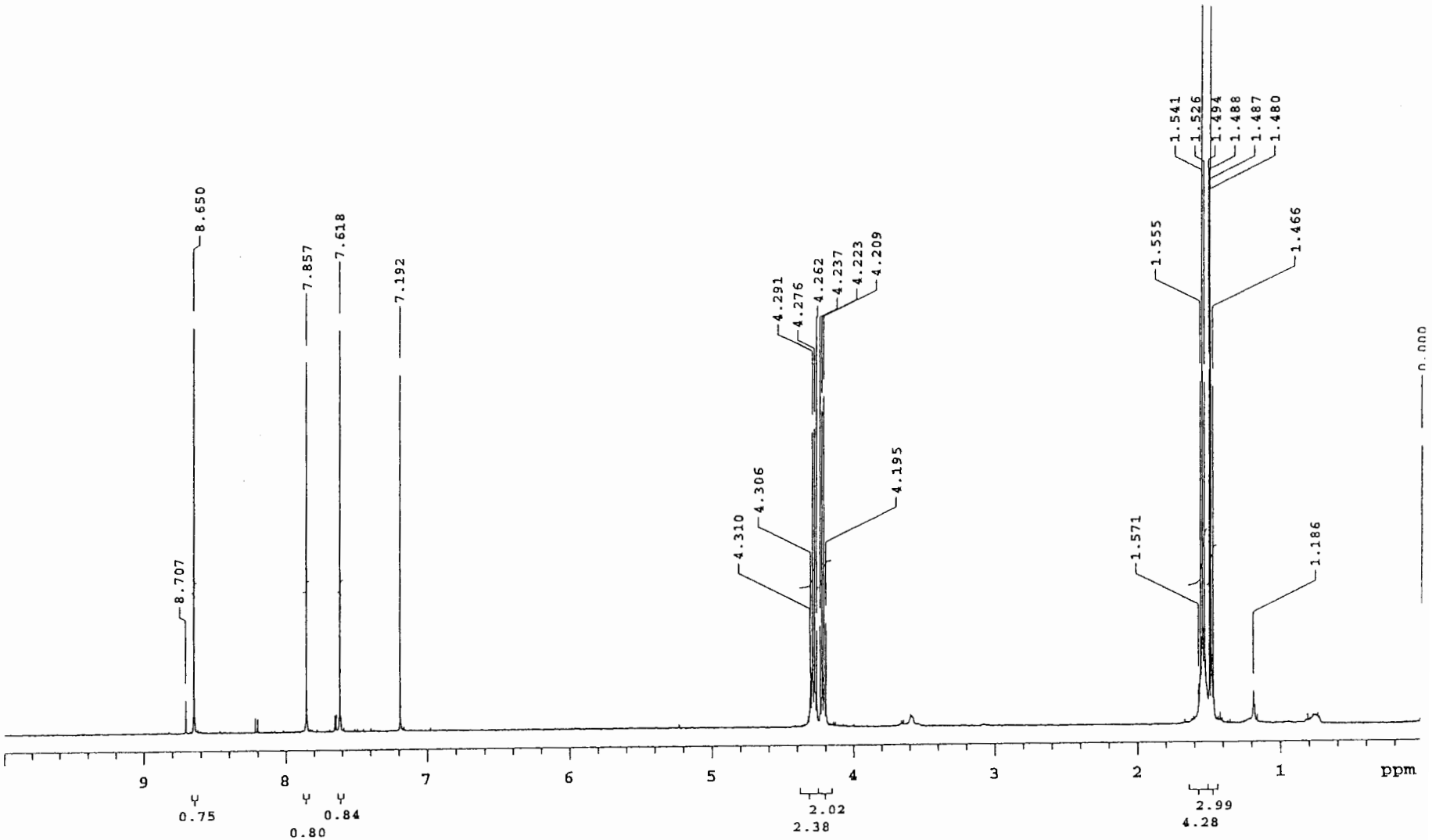


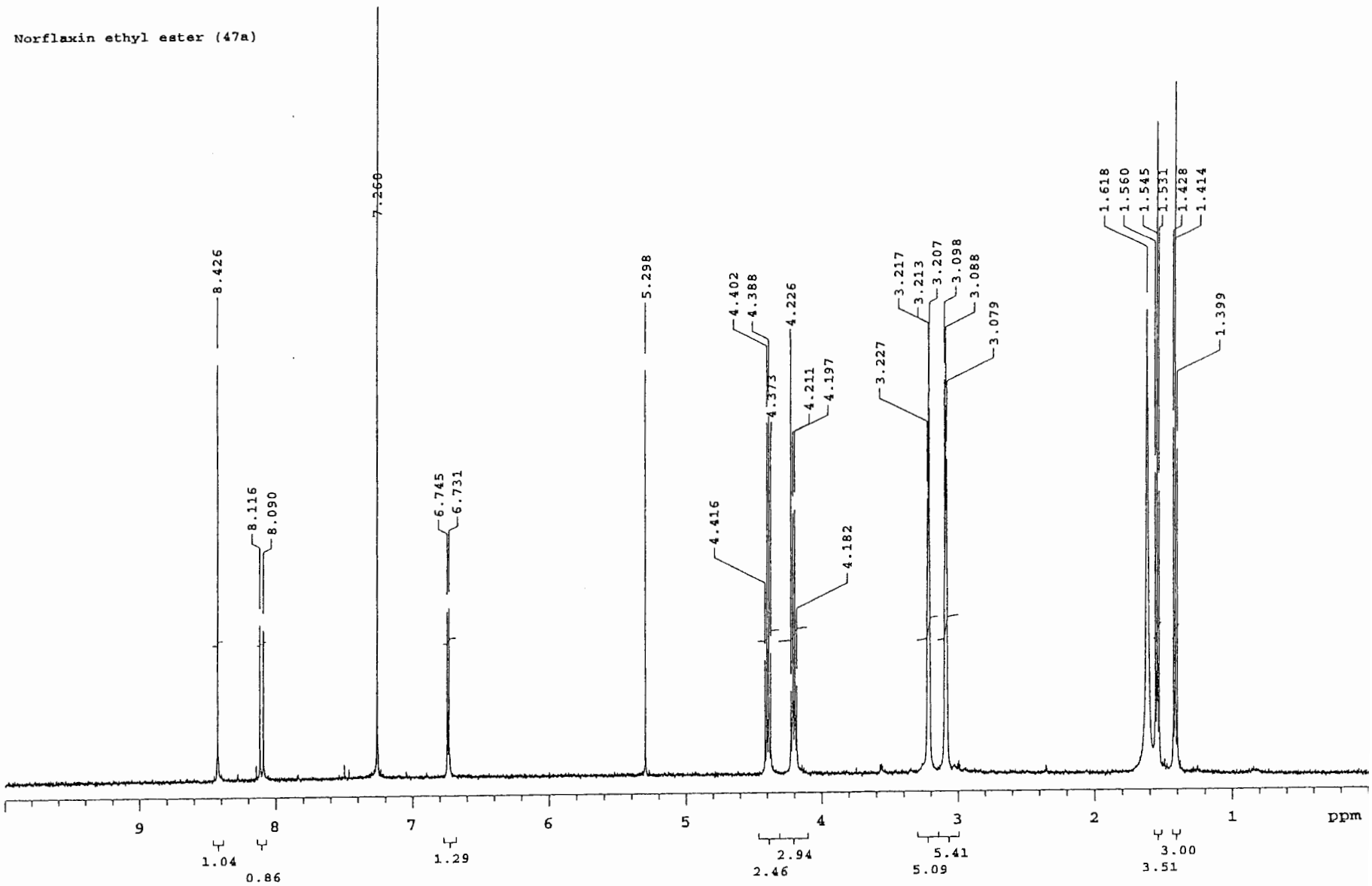
2,4-Difluoro-4'-methoxybiphenyl - Table 11, Entry 12

INDEX	Hz	PPM	HEIGHT	INDEX	Hz	PPM	HEIGHT
1	2977.5	7.448	21.7	36	353.9	0.885	4.7
2	2975.9	7.444	24.3	37	52.6	0.132	4.1
3	2973.8	7.439	7.4	38	31.0	0.078	25.6
4	2970.8	7.431	8.1				
5	2968.8	7.426	27.1				
6	2967.1	7.422	22.9				
7	2956.8	7.396	5.9				
8	2950.2	7.380	6.9				
9	2948.1	7.374	12.6				
10	2941.6	7.358	12.6				
11	2939.3	7.352	7.6				
12	2932.9	7.336	7.5				
13	2902.4	7.260	23.7				
14	2797.7	6.998	5.2				
15	2794.8	6.991	45.1				
16	2792.7	6.986	12.9				
17	2788.1	6.974	12.8				
18	2786.0	6.969	40.4				
19	2783.0	6.961	4.3				
20	2780.2	6.954	4.5				
21	2779.3	6.952	4.5				
22	2777.6	6.948	5.7				
23	2776.8	6.946	6.3				
24	2771.4	6.932	7.9				
25	2768.6	6.925	12.8				
26	2766.6	6.921	9.3				
27	2763.9	6.914	6.5				
28	2760.3	6.905	7.4				
29	2757.8	6.898	9.5				
30	2756.2	6.894	10.2				
31	2753.7	6.888	6.6				
32	2747.3	6.872	8.1				
33	2744.8	6.866	6.1				
34	1541.1	3.855	205.2				
35	503.8	1.260	38.9				

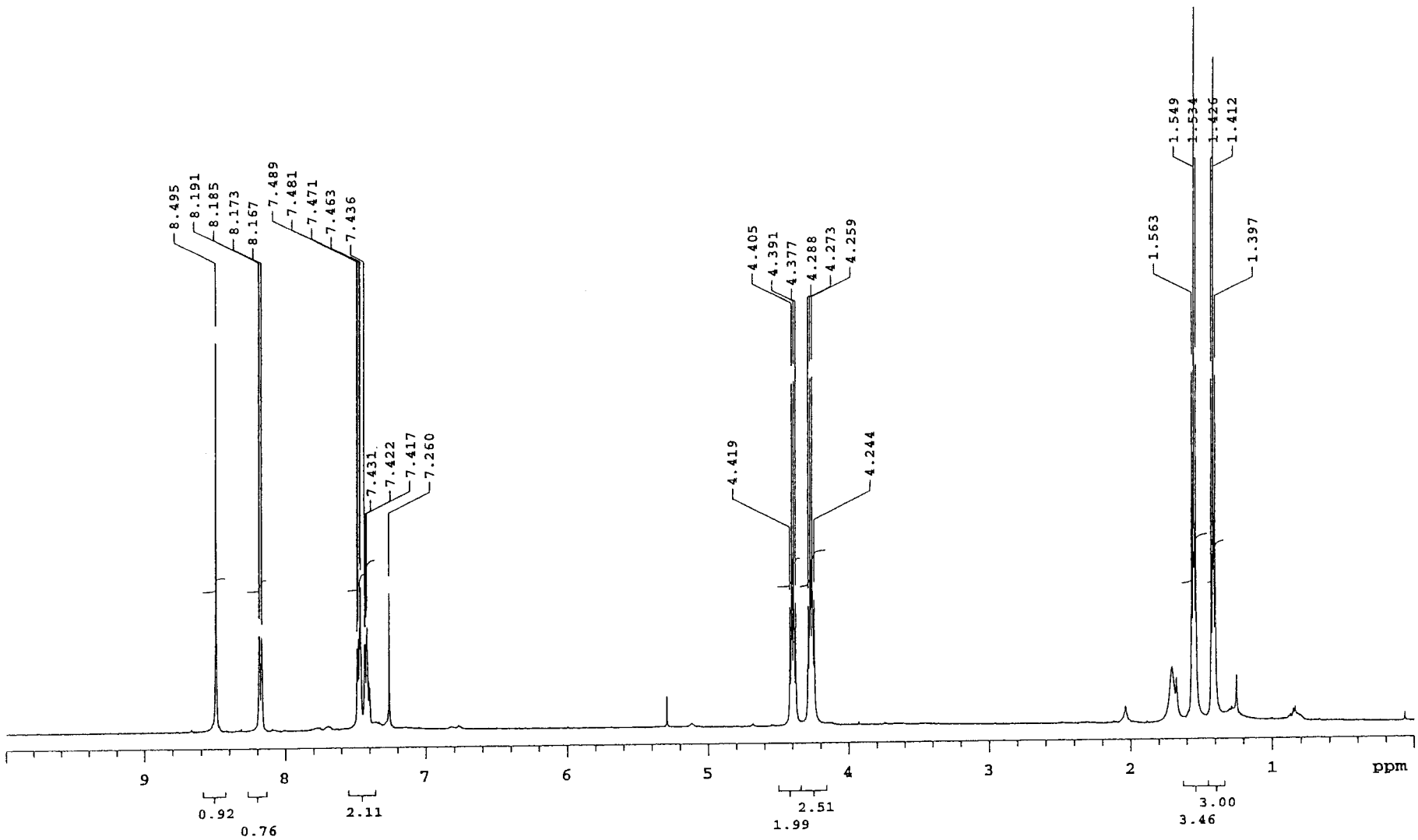


1-Ethyl-6-hydroxy-1,4-dihydro-4-oxo-7-chloroquinoline-3-carboxylic acid ethyl ester (46)

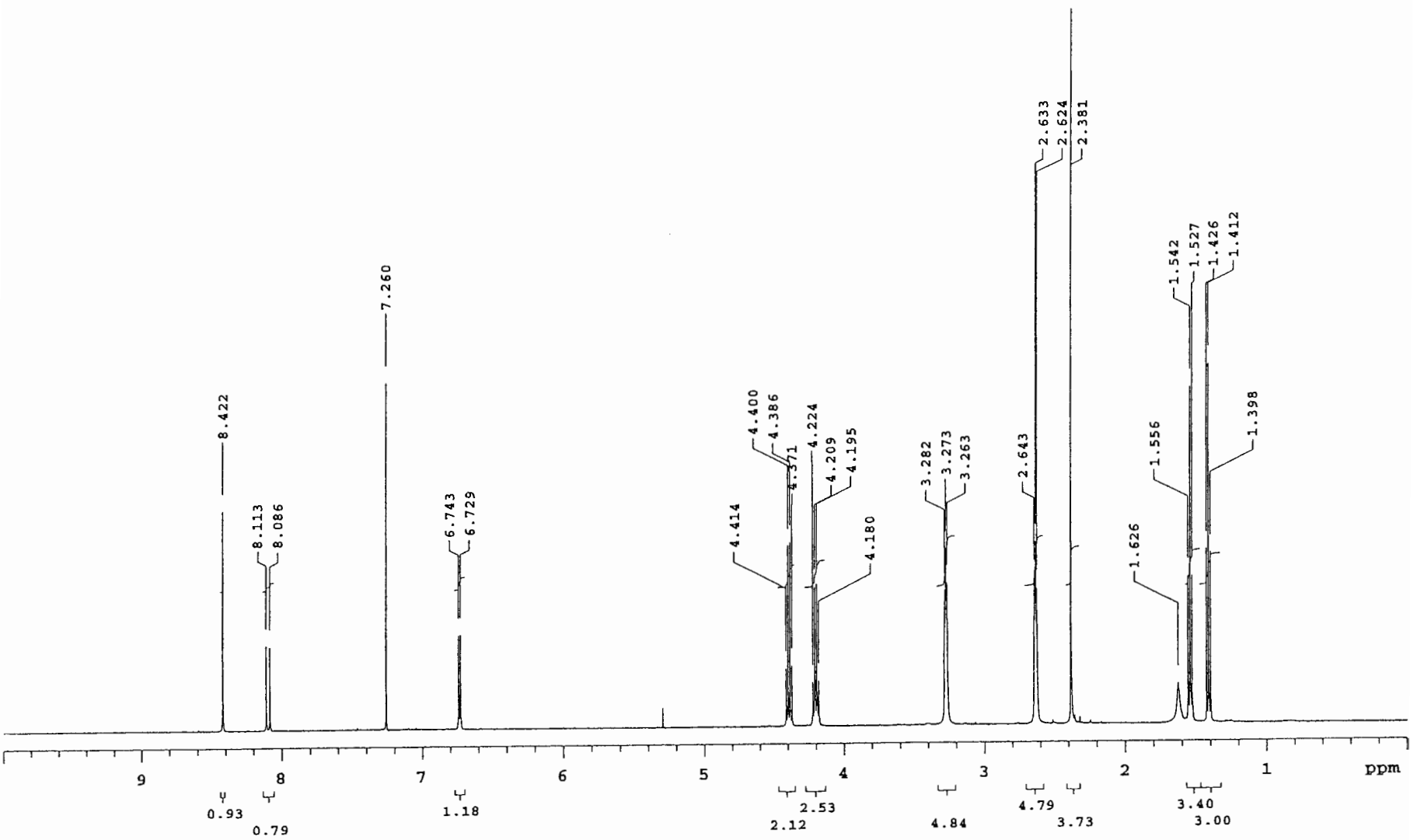



Norflaxin ethyl ester (47a)
8.426
8.116
8.090
7.260
6.745
6.731
5.298
4.416
4.402
4.388
4.373
4.226
4.211
4.197
4.182
3.227
3.217
3.213
3.207
3.098
3.088
3.079
1.618
1.560
1.545
1.531
1.428
1.414
1.399
9
8
7
6
5
4
3
2
1
ppm
1.04
0.86
1.29
2.46
2.94
5.09
5.41
3.51
3.00

1-Ethyl-6-fluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid ethyl ester (48)

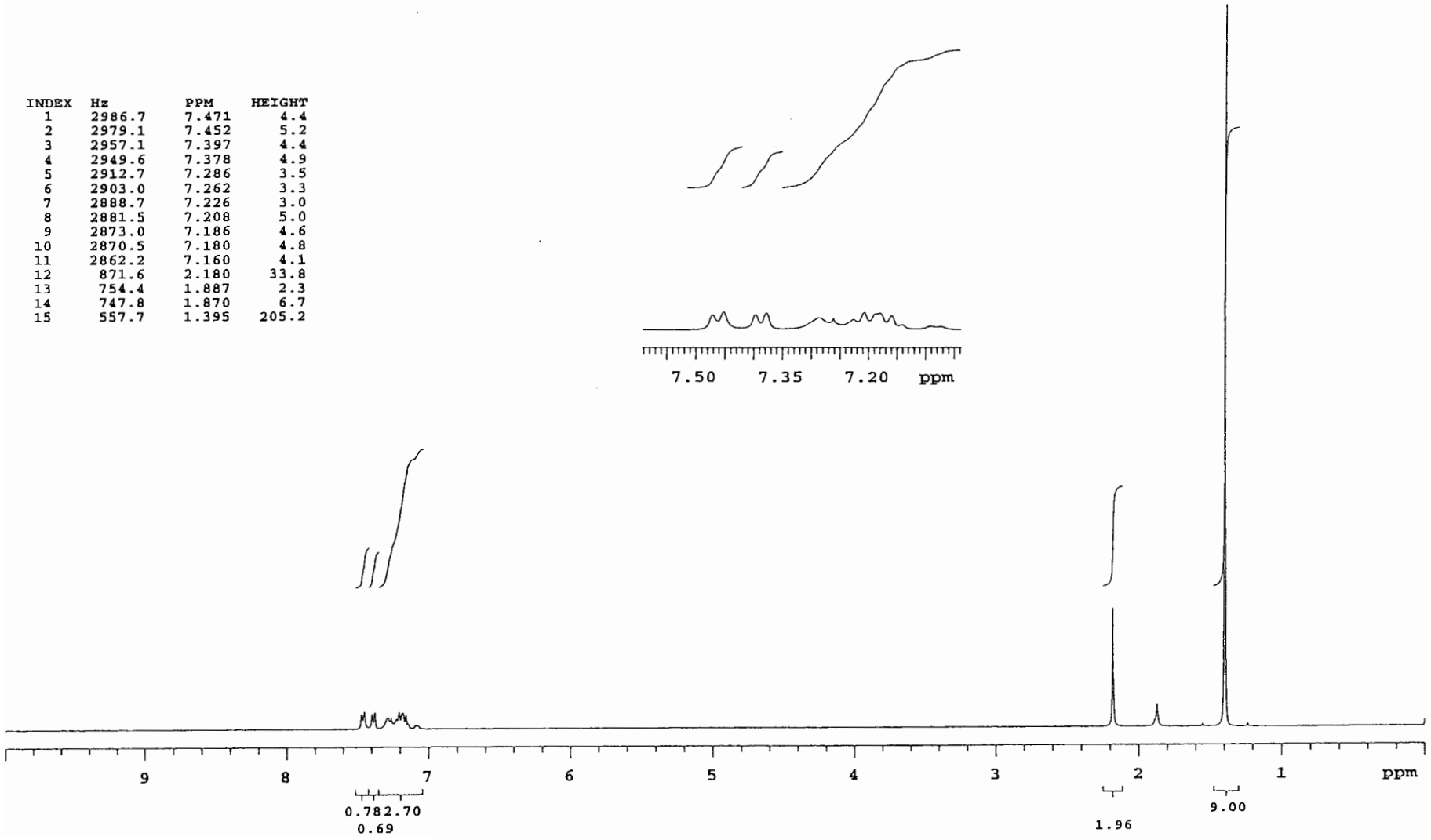


1-Ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-methyl-piperazinyl)-quinoline-3-carboxylic acid ethyl ester (47b)



N-(2-tert-butylphenyl)acetamide (58)

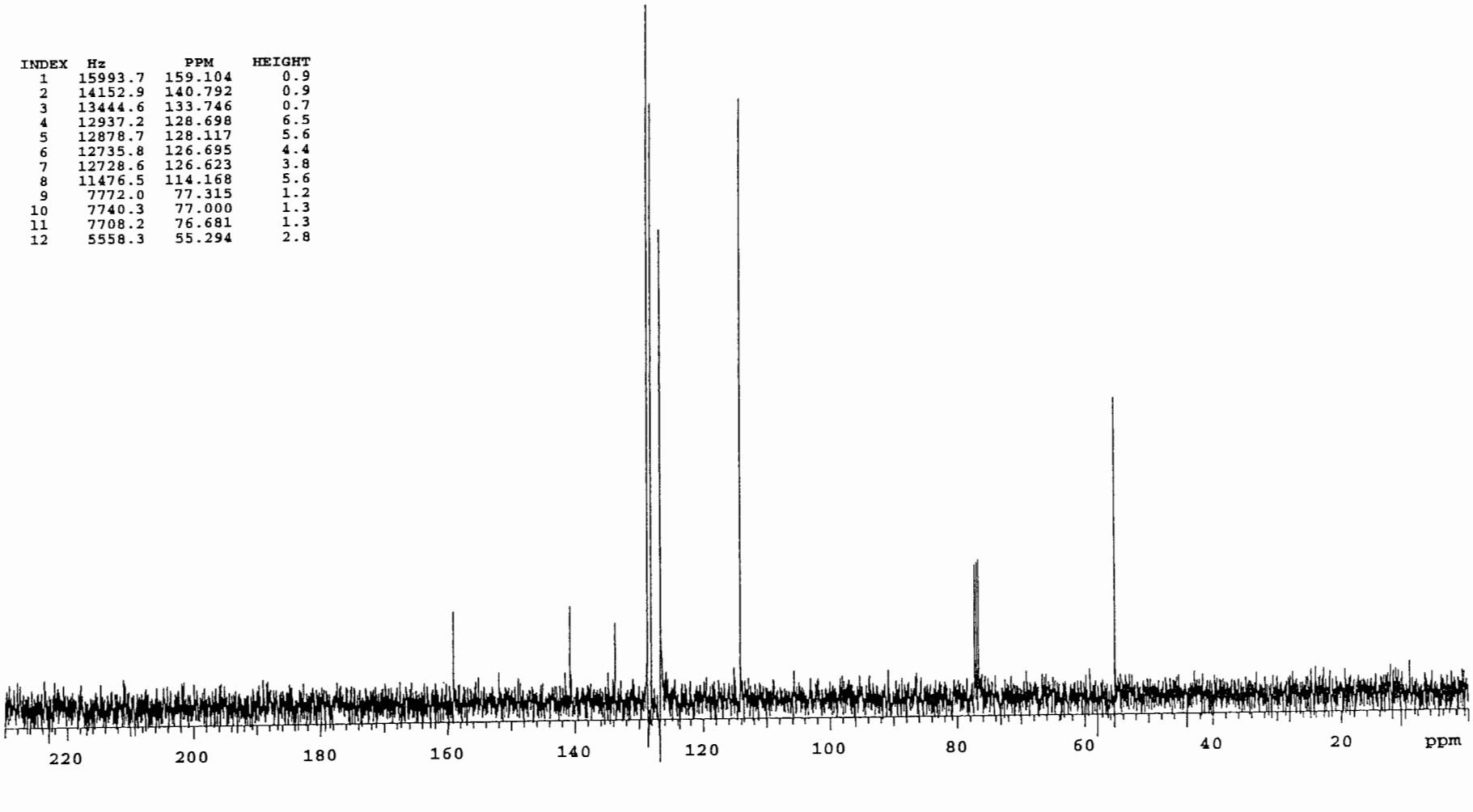
INDEX	Hz	PPM	HEIGHT
1	2986.7	7.471	4.4
2	2979.1	7.452	5.2
3	2957.1	7.397	4.4
4	2949.6	7.378	4.9
5	2912.7	7.286	3.5
6	2903.0	7.262	3.3
7	2888.7	7.226	3.0
8	2881.5	7.208	5.0
9	2873.0	7.186	4.6
10	2870.5	7.180	4.8
11	2862.2	7.160	4.1
12	871.6	2.180	33.8
13	754.4	1.887	2.3
14	747.8	1.870	6.7
15	557.7	1.395	205.2



Appendix II – ^{13}C NMR Spectra

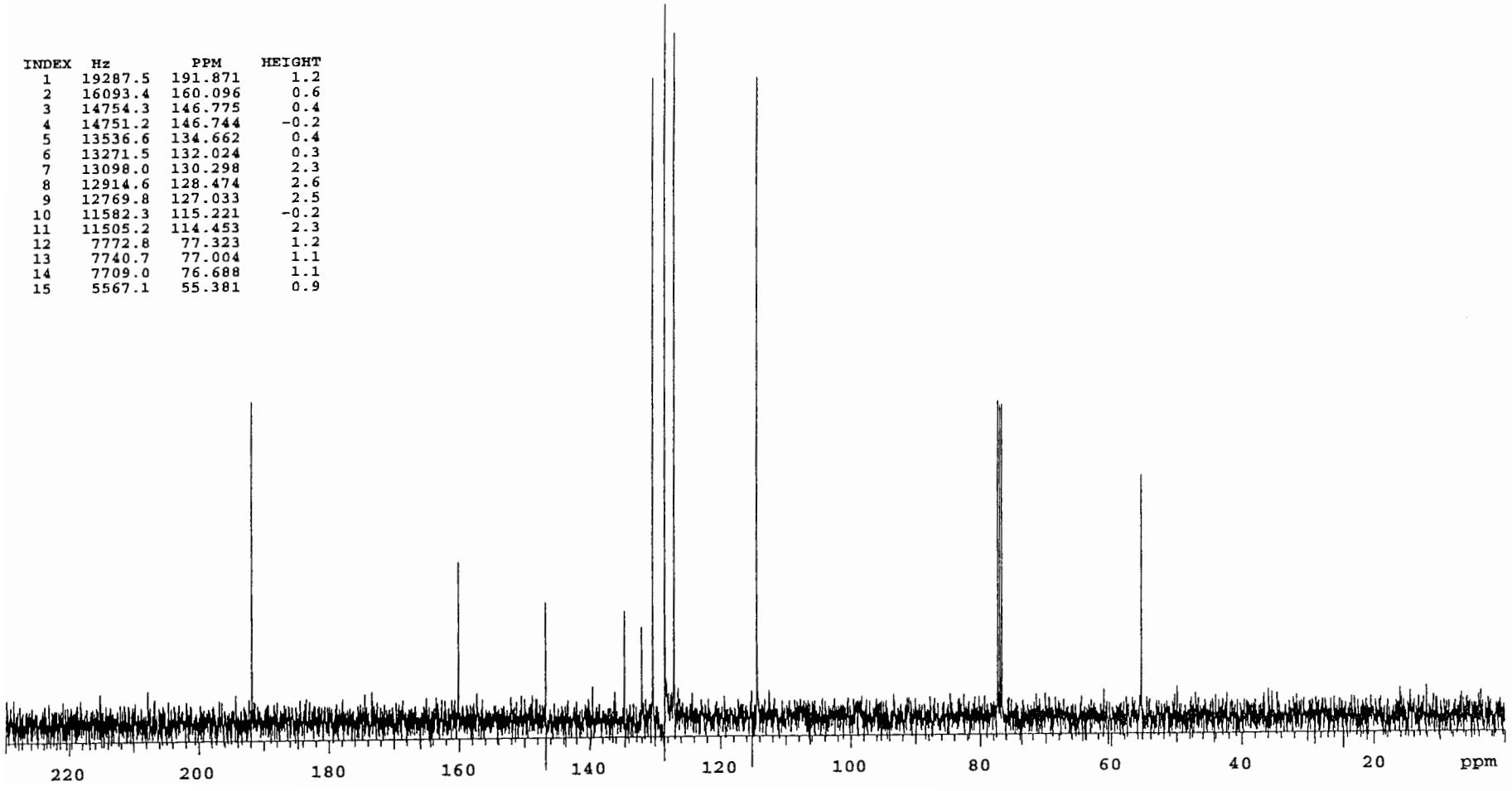
4-Methoxybiphenyl - Table 6, entry 1

INDEX	Hz	PPM	HEIGHT
1	15993.7	159.104	0.9
2	14152.9	140.792	0.9
3	13444.6	133.746	0.7
4	12937.2	128.698	6.5
5	12878.7	128.117	5.6
6	12735.8	126.695	4.4
7	12728.6	126.623	3.8
8	11476.5	114.168	5.6
9	7772.0	77.315	1.2
10	7740.3	77.000	1.3
11	7708.2	76.681	1.3
12	5558.3	55.294	2.8



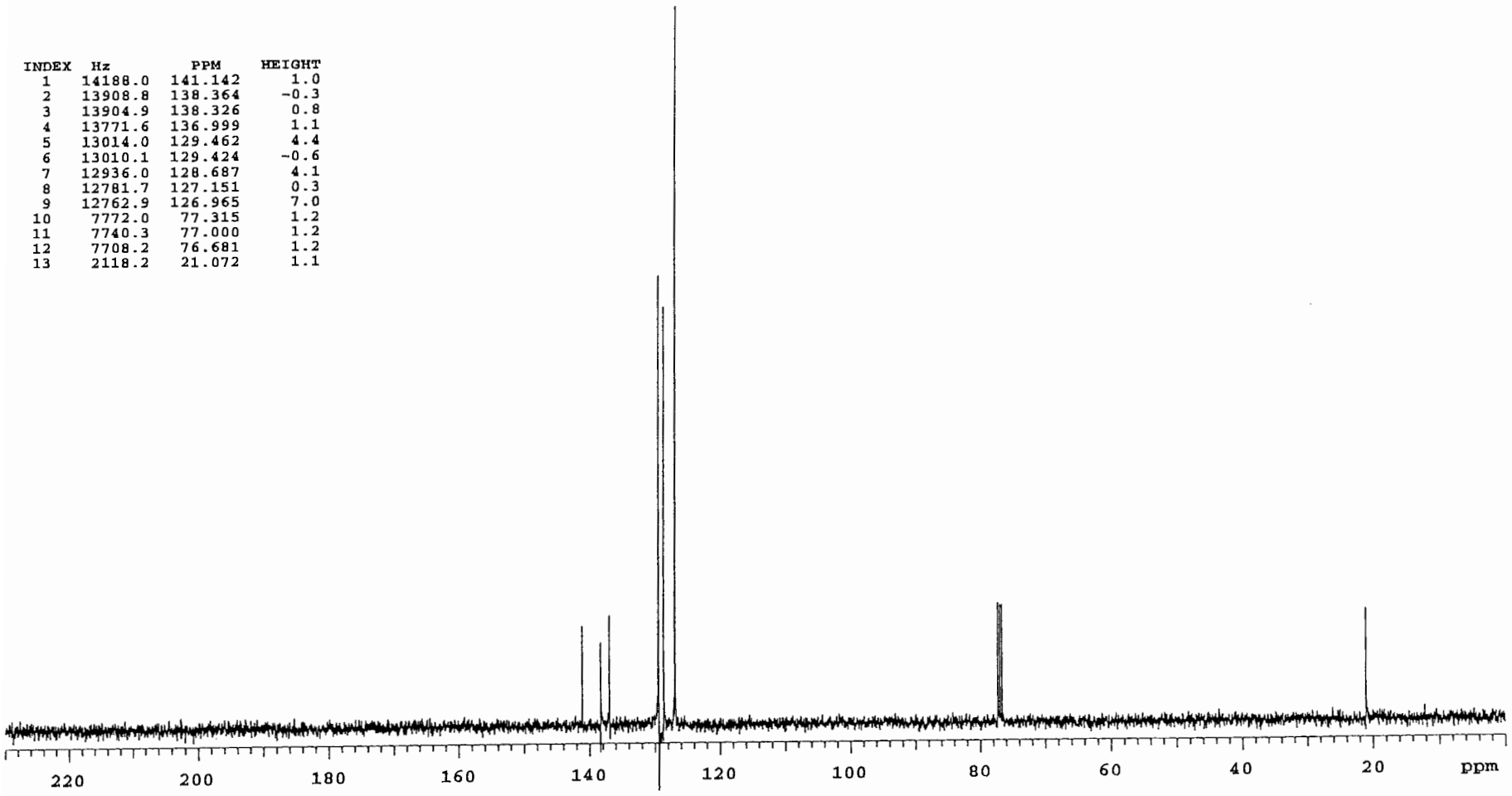
4'-methoxybiphenyl-4-carbaldehyde - Table 6, Entry 2

INDEX	Hz	PPM	HEIGHT
1	19287.5	191.871	1.2
2	16093.4	160.096	0.6
3	14754.3	146.775	0.4
4	14751.2	146.744	-0.2
5	13536.6	134.662	0.4
6	13271.5	132.024	0.3
7	13098.0	130.298	2.3
8	12914.6	128.474	2.6
9	12769.8	127.033	2.5
10	11582.3	115.221	-0.2
11	11505.2	114.453	2.3
12	7772.8	77.323	1.2
13	7740.7	77.004	1.1
14	7709.0	76.688	1.1
15	5567.1	55.381	0.9



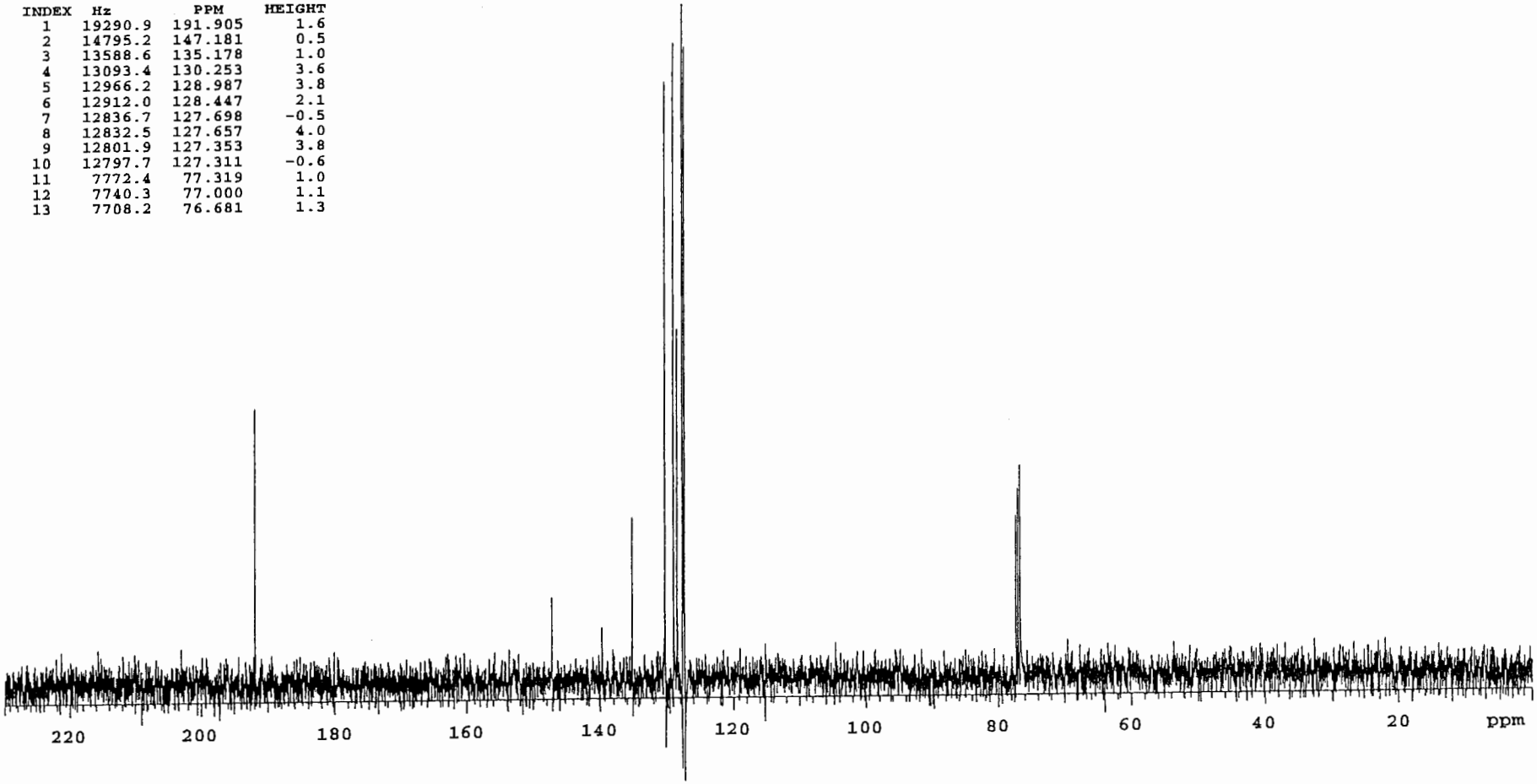
4-methylbiphenyl - Table 6, Entry 3

INDEX	Hz	PPM	HEIGHT
1	14188.0	141.142	1.0
2	13908.8	138.364	-0.3
3	13904.9	138.326	0.8
4	13771.6	136.999	1.1
5	13014.0	129.462	4.4
6	13010.1	129.424	-0.6
7	12936.0	128.687	4.1
8	12781.7	127.151	0.3
9	12762.9	126.965	7.0
10	7772.0	77.315	1.2
11	7740.3	77.000	1.2
12	7708.2	76.681	1.2
13	2118.2	21.072	1.1



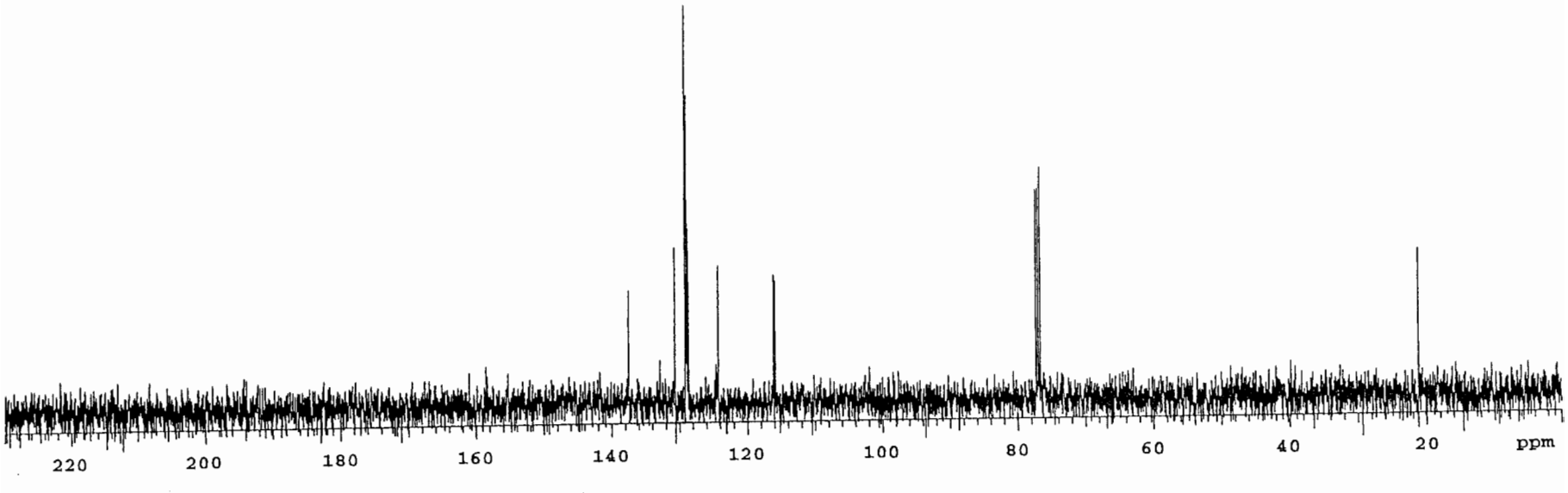
4-Formylbiphenyl - Table 6, Entry 4

INDEX	Hz	PPM	HEIGHT
1	19290.9	191.905	1.6
2	14795.2	147.181	0.5
3	13588.6	135.178	1.0
4	13093.4	130.253	3.6
5	12966.2	128.987	3.8
6	12912.0	128.447	2.1
7	12836.7	127.698	-0.5
8	12832.5	127.657	4.0
9	12801.9	127.353	3.8
10	12797.7	127.311	-0.6
11	7772.4	77.319	1.0
12	7740.3	77.000	1.1
13	7708.2	76.681	1.3



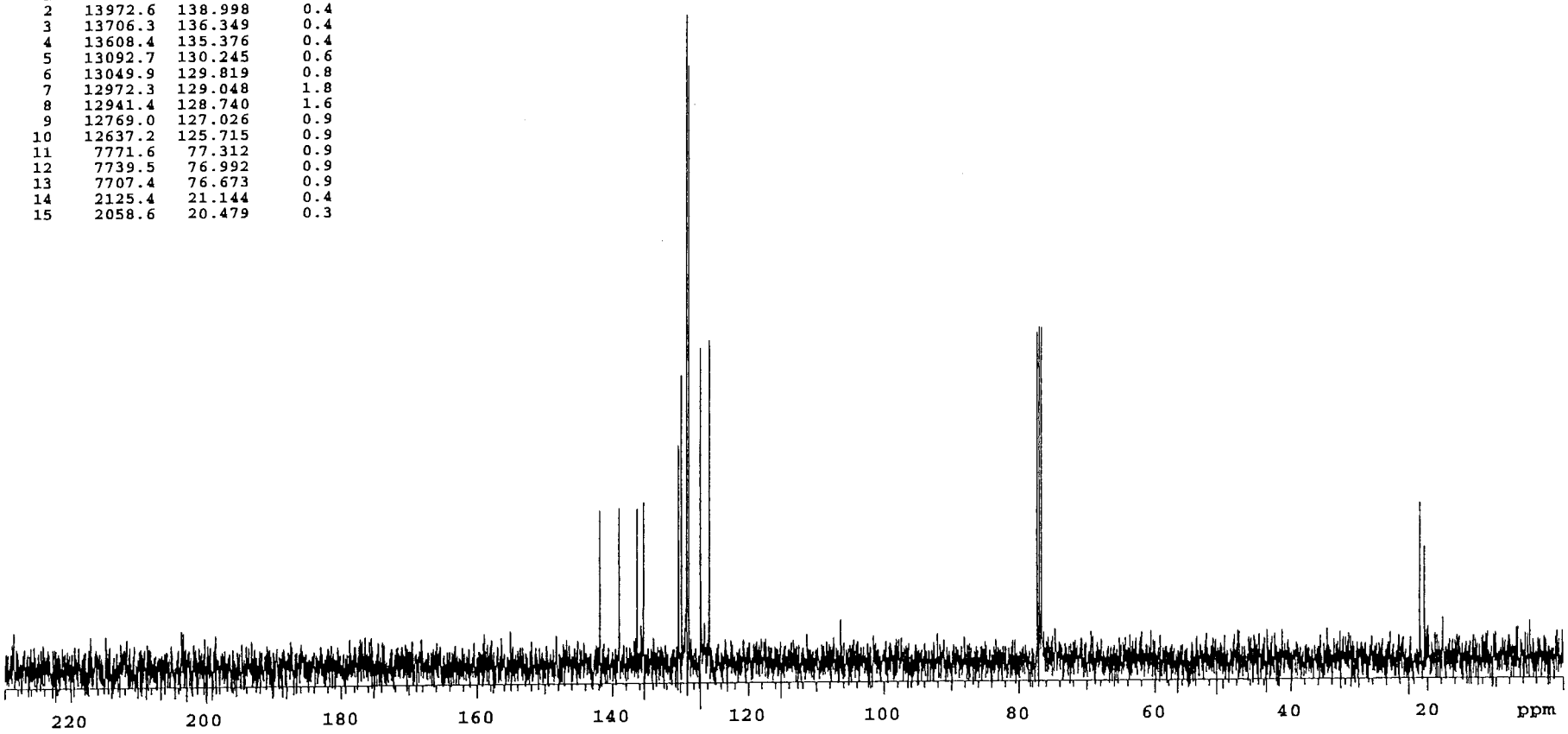
2-fluoro-4'-methylbiphenyl - Table 6, Entry 5

INDEX	Hz	PPM	HEIGHT
1	13819.0	137.470	0.3
2	13135.5	130.671	0.5
3	12981.5	129.139	1.2
4	12956.3	128.888	0.9
5	12936.0	128.687	0.5
6	12926.8	128.596	0.4
7	12494.0	124.289	0.4
8	11675.2	116.144	0.4
9	11651.1	115.905	0.4
10	7772.4	77.319	0.6
11	7740.3	77.000	0.6
12	7708.2	76.681	0.7
13	2128.9	21.178	0.4



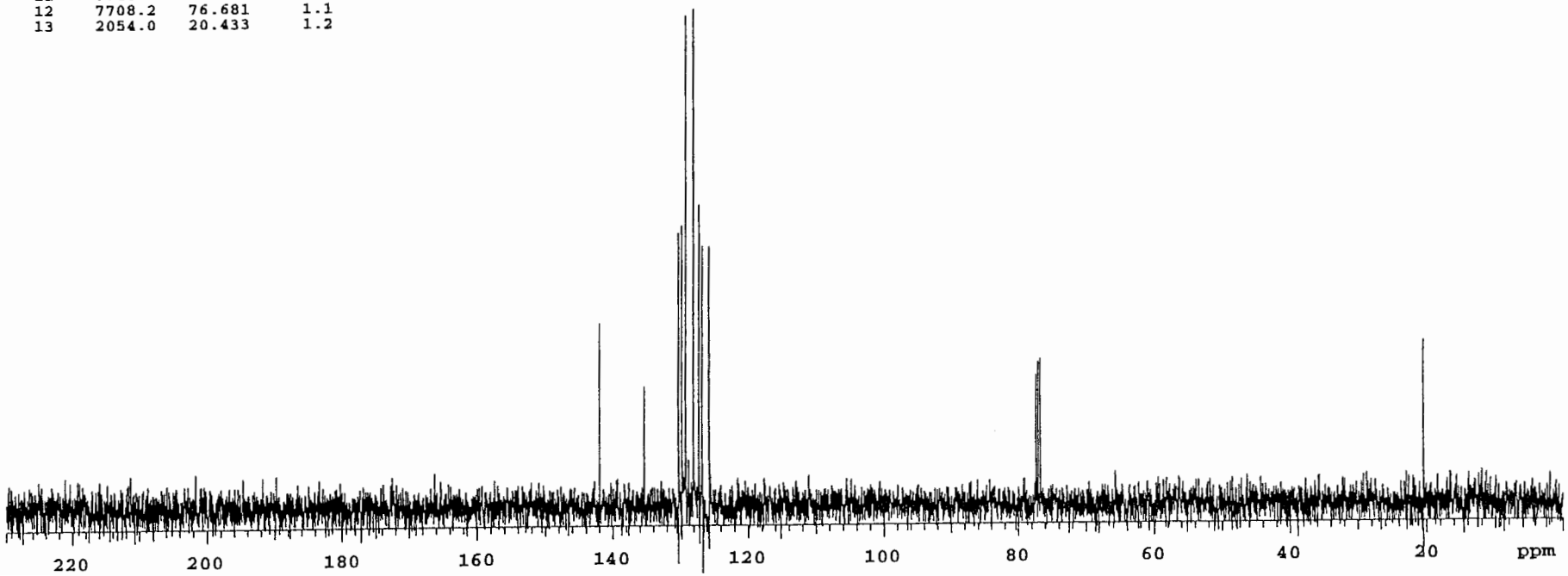
2,4'-dimethylbiphenyl - Table 7, Entry 1

INDEX	Hz	PPM	HEIGHT
1	14259.1	141.849	0.4
2	13972.6	138.998	0.4
3	13706.3	136.349	0.4
4	13608.4	135.376	0.4
5	13092.7	130.245	0.6
6	13049.9	129.819	0.8
7	12972.3	129.048	1.8
8	12941.4	128.740	1.6
9	12769.0	127.026	0.9
10	12637.2	125.715	0.9
11	7771.6	77.312	0.9
12	7739.5	76.992	0.9
13	7707.4	76.673	0.9
14	2125.4	21.144	0.4
15	2058.6	20.479	0.3



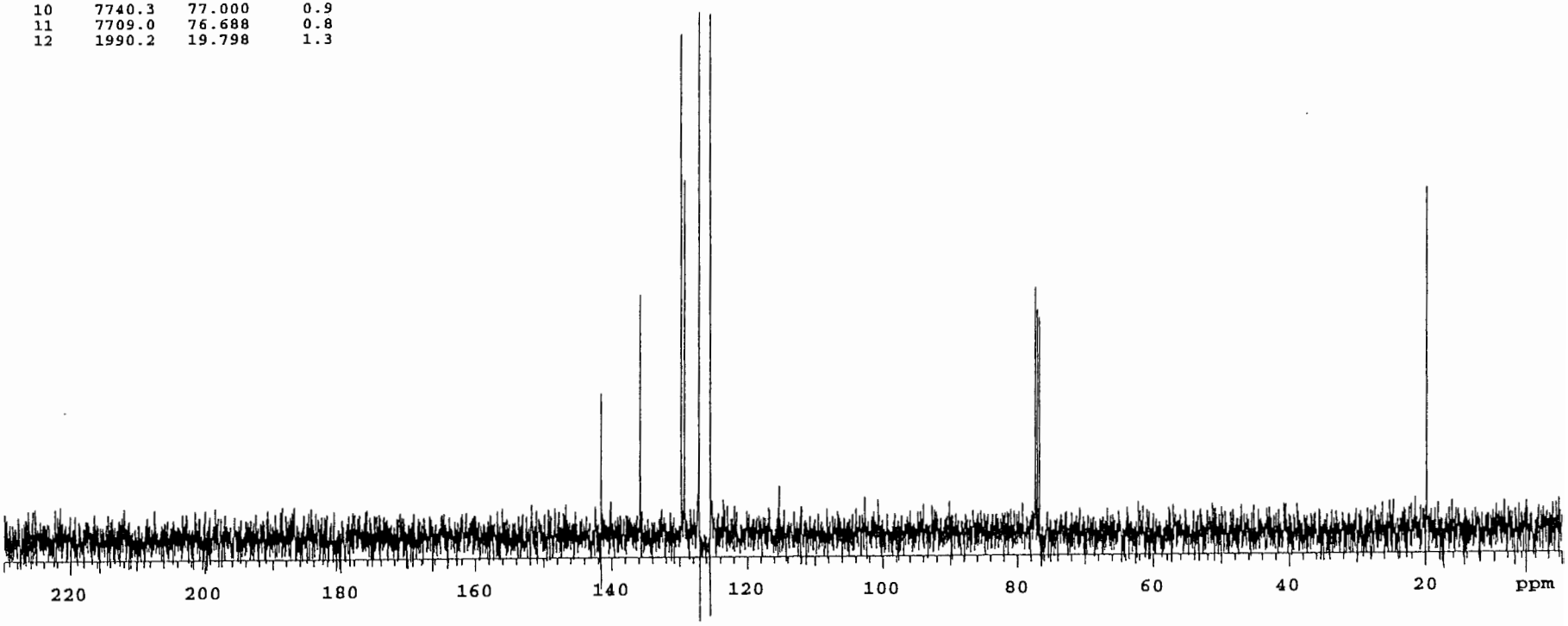
2-methylbiphenyl - Table 7, Entry 2

INDEX	Hz	PPM	HEIGHT
1	14266.4	141.921	1.3
2	13602.7	135.319	0.9
3	13095.0	130.268	2.0
4	13044.2	129.762	2.1
5	12984.9	129.173	3.6
6	12870.3	128.033	3.6
7	12789.3	127.227	2.2
8	12740.4	126.741	1.9
9	12638.4	125.726	1.9
10	7772.4	77.319	1.0
11	7740.3	77.000	1.0
12	7708.2	76.681	1.1
13	2054.0	20.433	1.2



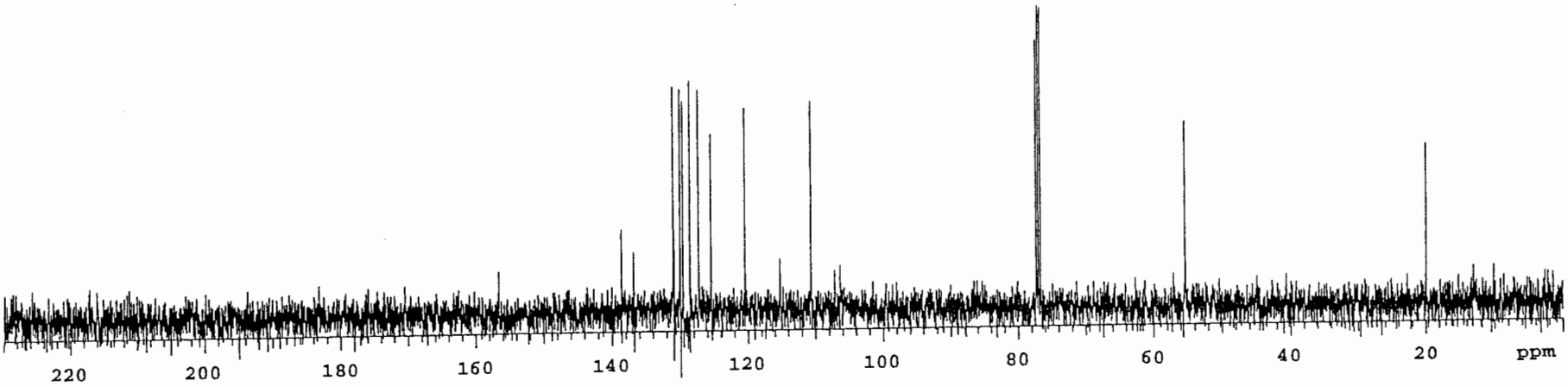
2,2'-dimethylbiphenyl - Table 7, Entry 3

INDEX	Hz	PPM	HEIGHT
1	14229.7	141.556	0.5
2	13650.5	135.794	0.9
3	13044.9	129.770	1.9
4	12993.3	129.257	1.4
5	12779.0	127.125	2.0
6	12774.8	127.083	-0.3
7	12619.7	125.540	-0.3
8	12615.5	125.498	2.0
9	7772.4	77.319	0.9
10	7740.3	77.000	0.9
11	7709.0	76.688	0.8
12	1990.2	19.798	1.3



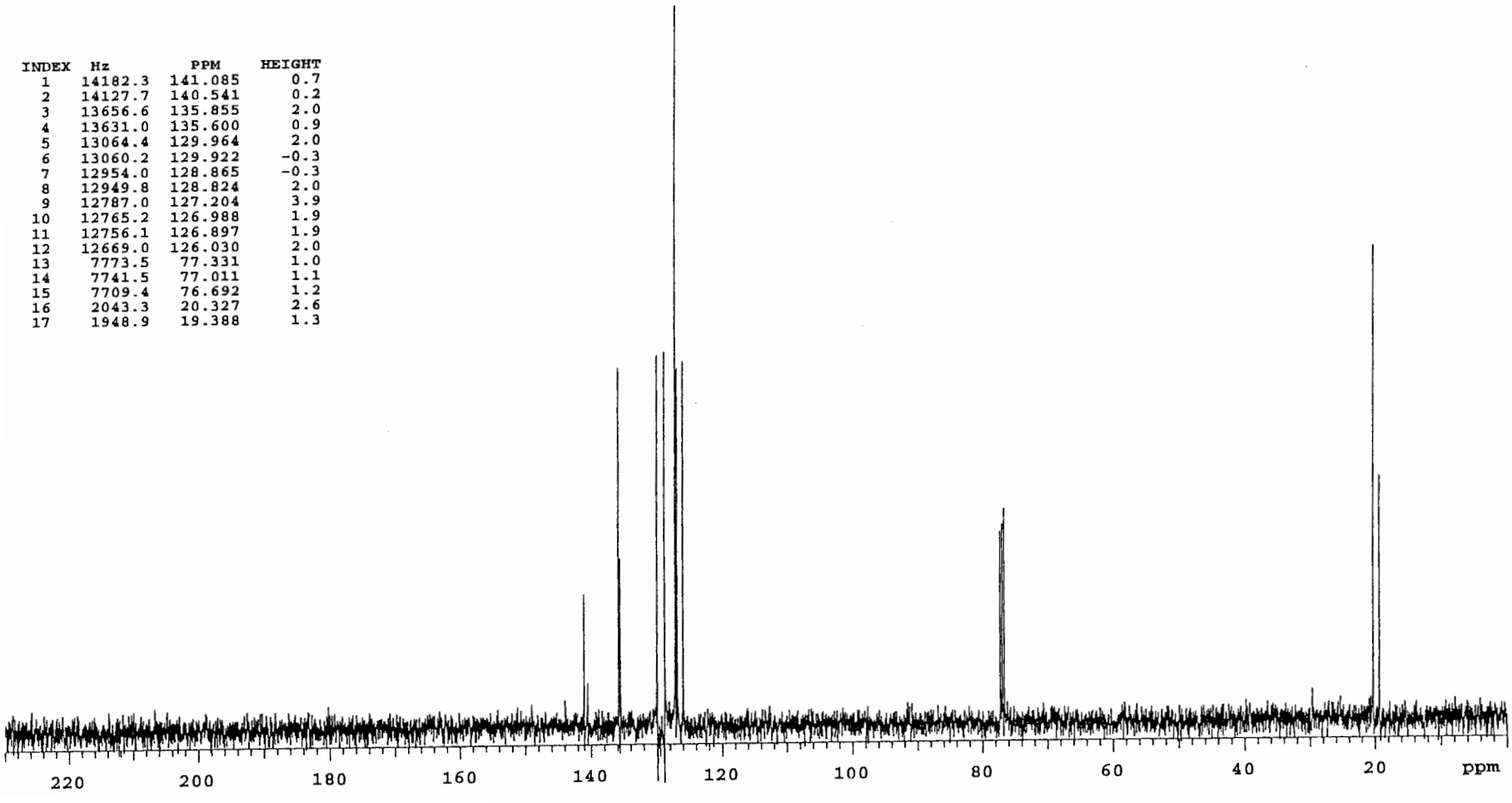
2-methoxy-2'methylbiphenyl - Table 7 Entry 4

INDEX	Hz	PPM	HEIGHT
1	13932.1	138.595	0.1
2	13753.6	136.820	0.1
3	13167.9	130.994	0.4
4	13151.5	130.830	0.1
5	13066.7	129.987	0.4
6	13062.9	129.949	-0.1
7	13023.1	129.553	0.4
8	12919.6	128.523	0.4
9	12793.1	127.265	0.4
10	12607.4	125.418	0.3
11	12104.3	120.413	0.4
12	11120.4	110.626	0.4
13	7772.0	77.315	0.5
14	7740.3	77.000	0.5
15	7708.2	76.681	0.5
16	5566.3	55.374	0.3
17	2000.5	19.901	0.3



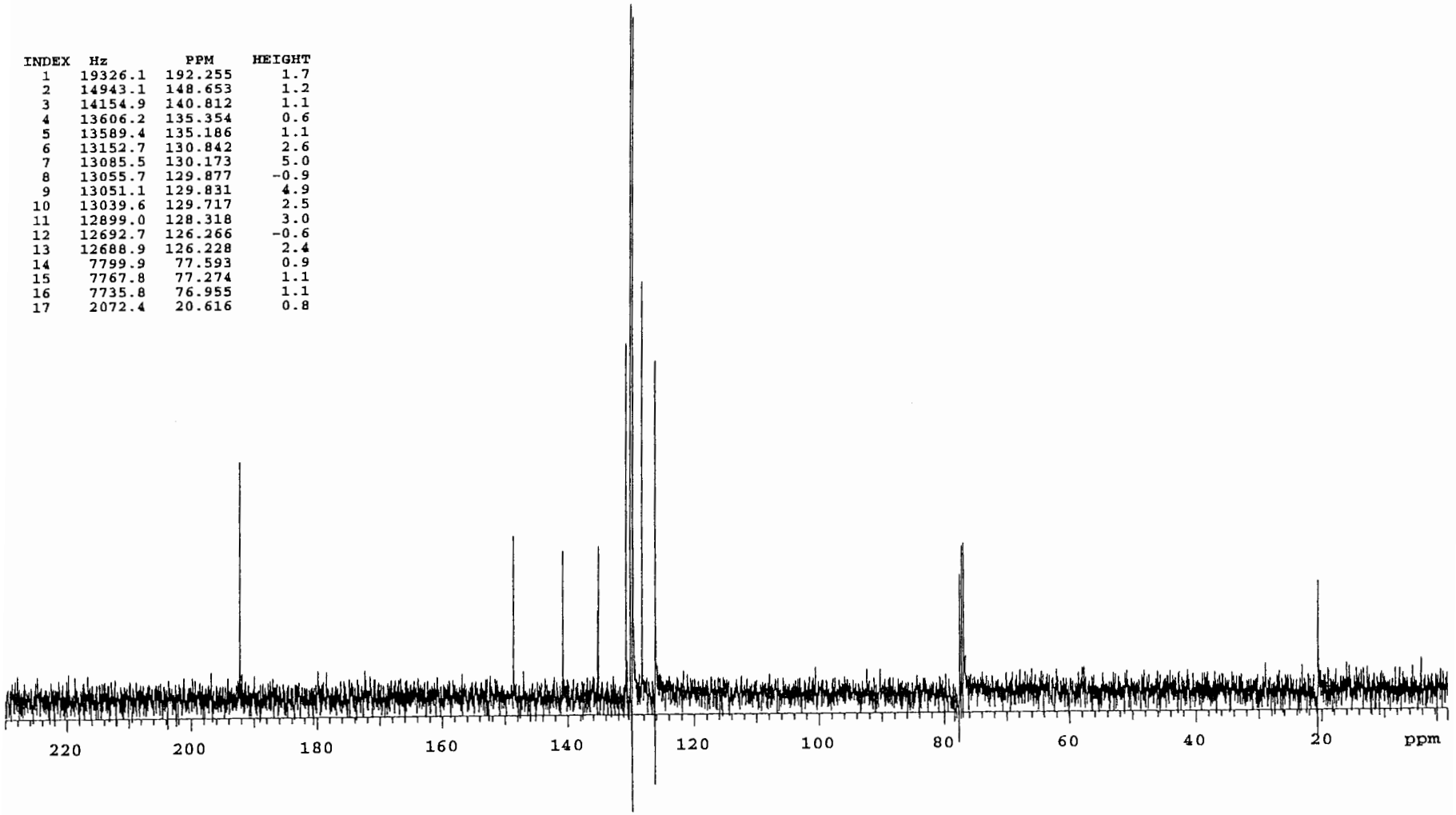
2,2',6-Trimethylbiphenyl - Table 7, Entry 5

INDEX	Hz	PPM	HEIGHT
1	14182.3	141.085	0.7
2	14127.7	140.541	0.2
3	13656.6	135.855	2.0
4	13631.0	135.600	0.9
5	13064.4	129.964	2.0
6	13060.2	129.922	-0.3
7	12954.0	128.865	-0.3
8	12949.8	128.824	2.0
9	12787.0	127.204	3.9
10	12765.2	126.988	1.9
11	12756.1	126.897	1.9
12	12669.0	126.030	2.0
13	7773.5	77.331	1.0
14	7741.5	77.011	1.1
15	7709.4	76.692	1.2
16	2043.3	20.327	2.6
17	1948.9	19.388	1.3



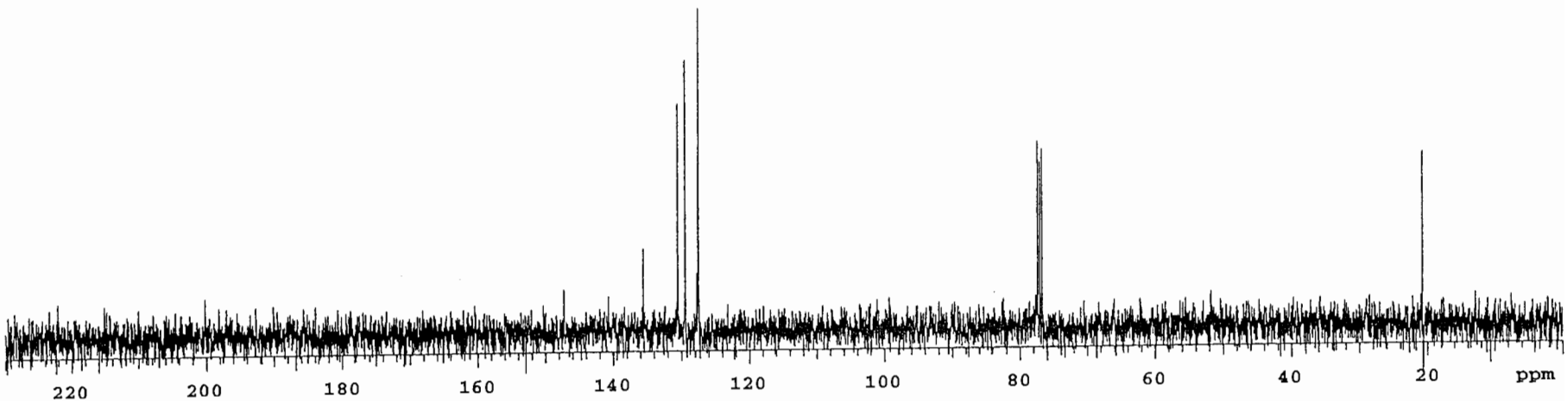
2′-Methylbiphenyl-4-carbaldehyde - Table 7, entry 6

INDEX	Hz	PPM	HEIGHT
1	19326.1	192.255	1.7
2	14943.1	148.653	1.2
3	14154.9	140.812	1.1
4	13606.2	135.354	0.6
5	13589.4	135.186	1.1
6	13152.7	130.842	2.6
7	13085.5	130.173	5.0
8	13055.7	129.877	-0.9
9	13051.1	129.831	4.9
10	13039.6	129.717	2.5
11	12899.0	128.318	3.0
12	12692.7	126.266	-0.6
13	12688.9	126.228	2.4
14	7799.9	77.593	0.9
15	7767.8	77.274	1.1
16	7735.8	76.955	1.1
17	2072.4	20.616	0.8



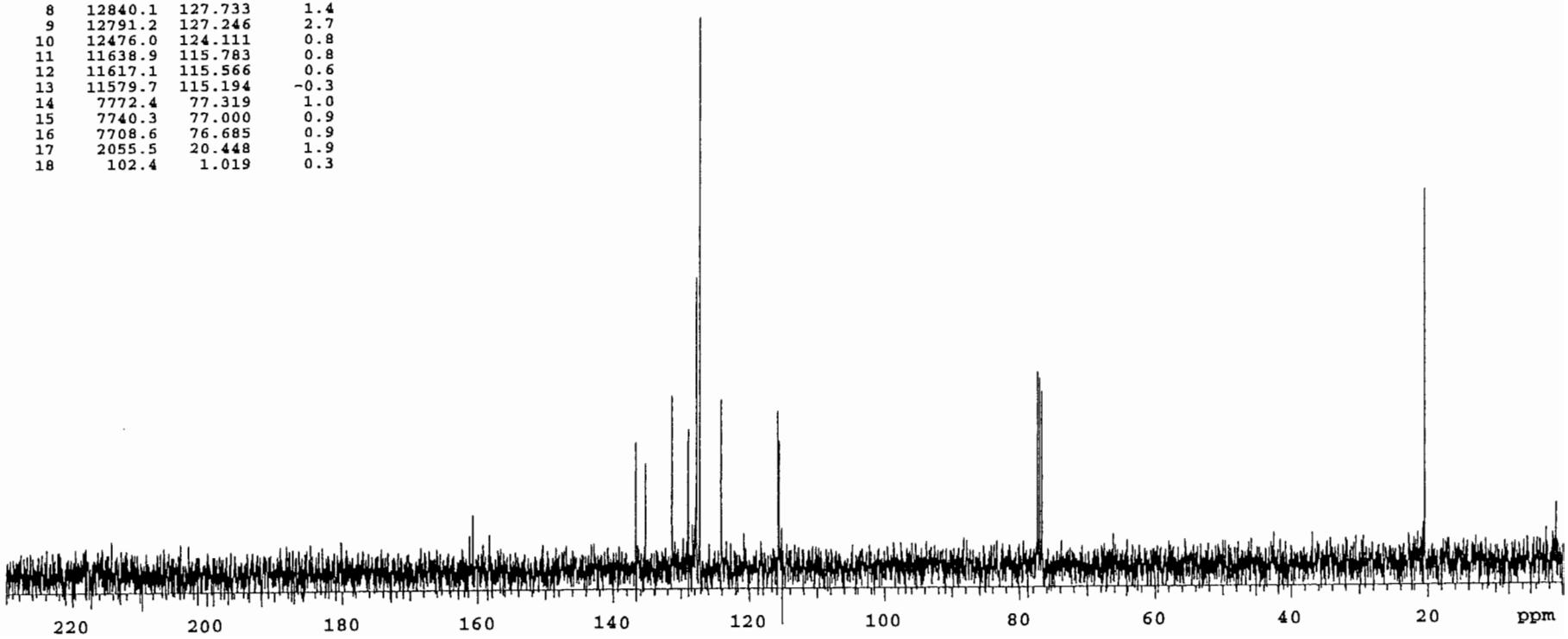
2',6'-Dimethylbiphenyl-4-carbaldehyde - Table 7, Entry 7

INDEX	Hz	PPM	HEIGHT
1	13625.9	135.550	0.2
2	13116.6	130.483	0.7
3	13008.5	129.408	0.8
4	12842.7	127.758	0.2
5	12821.7	127.549	0.5
6	12811.0	127.443	1.0
7	7772.3	77.318	0.6
8	7740.6	77.002	0.5
9	7708.5	76.683	0.5
10	2083.7	20.728	0.5



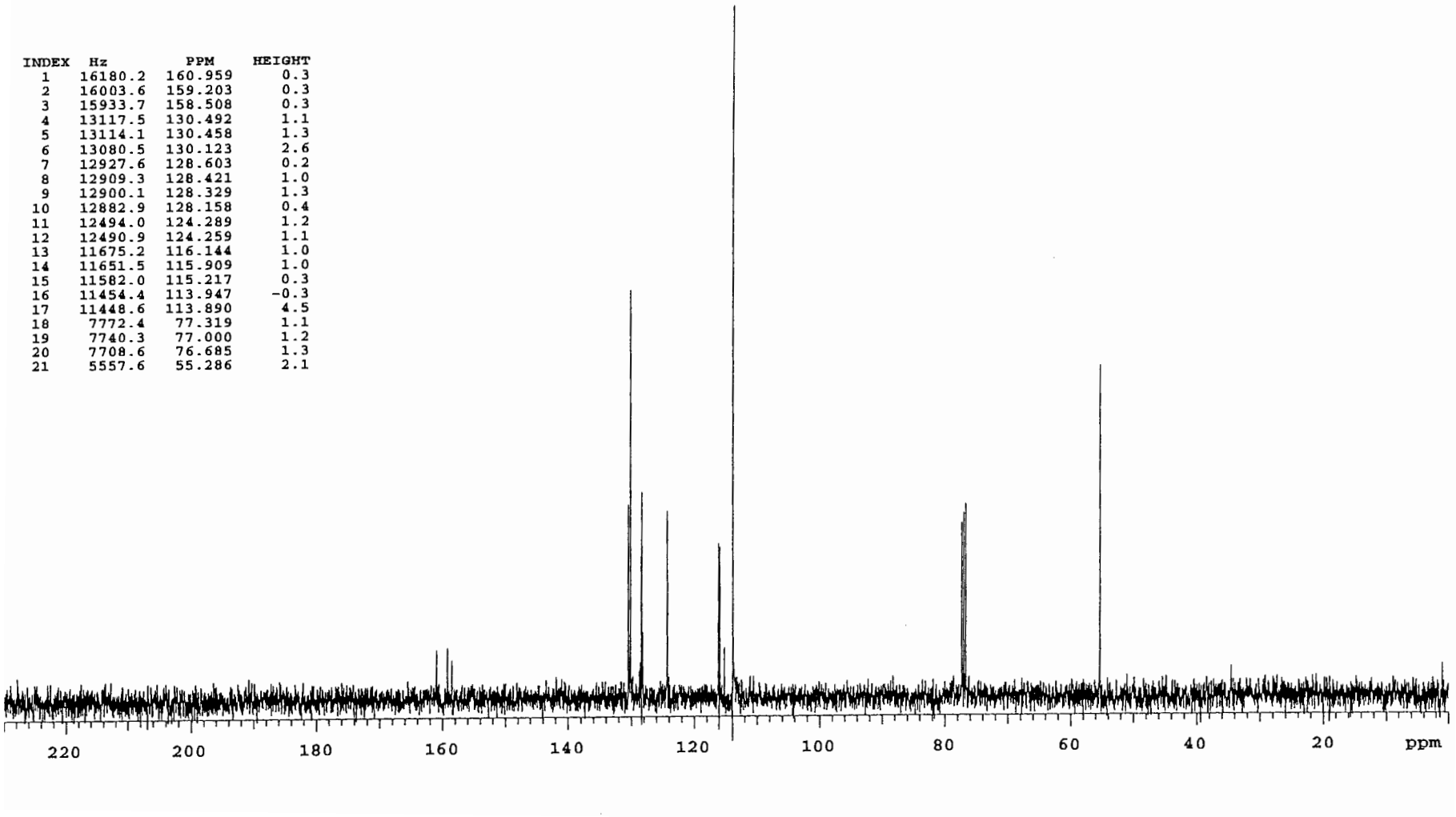
2',6'-Dimethyl-2-fluorobiphenyl - Table 7, entry 8

INDEX	Hz	PPM	HEIGHT
1	16156.1	160.720	0.3
2	13738.8	136.672	0.6
3	13595.9	135.251	0.5
4	13200.8	131.321	0.9
5	12967.0	128.995	0.6
6	12957.8	128.903	0.7
7	12856.2	127.892	0.3
8	12840.1	127.733	1.4
9	12791.2	127.246	2.7
10	12476.0	124.111	0.8
11	11638.9	115.783	0.8
12	11617.1	115.566	0.6
13	11579.7	115.194	-0.3
14	7772.4	77.319	1.0
15	7740.3	77.000	0.9
16	7708.6	76.685	0.9
17	2055.5	20.448	1.9
18	102.4	1.019	0.3



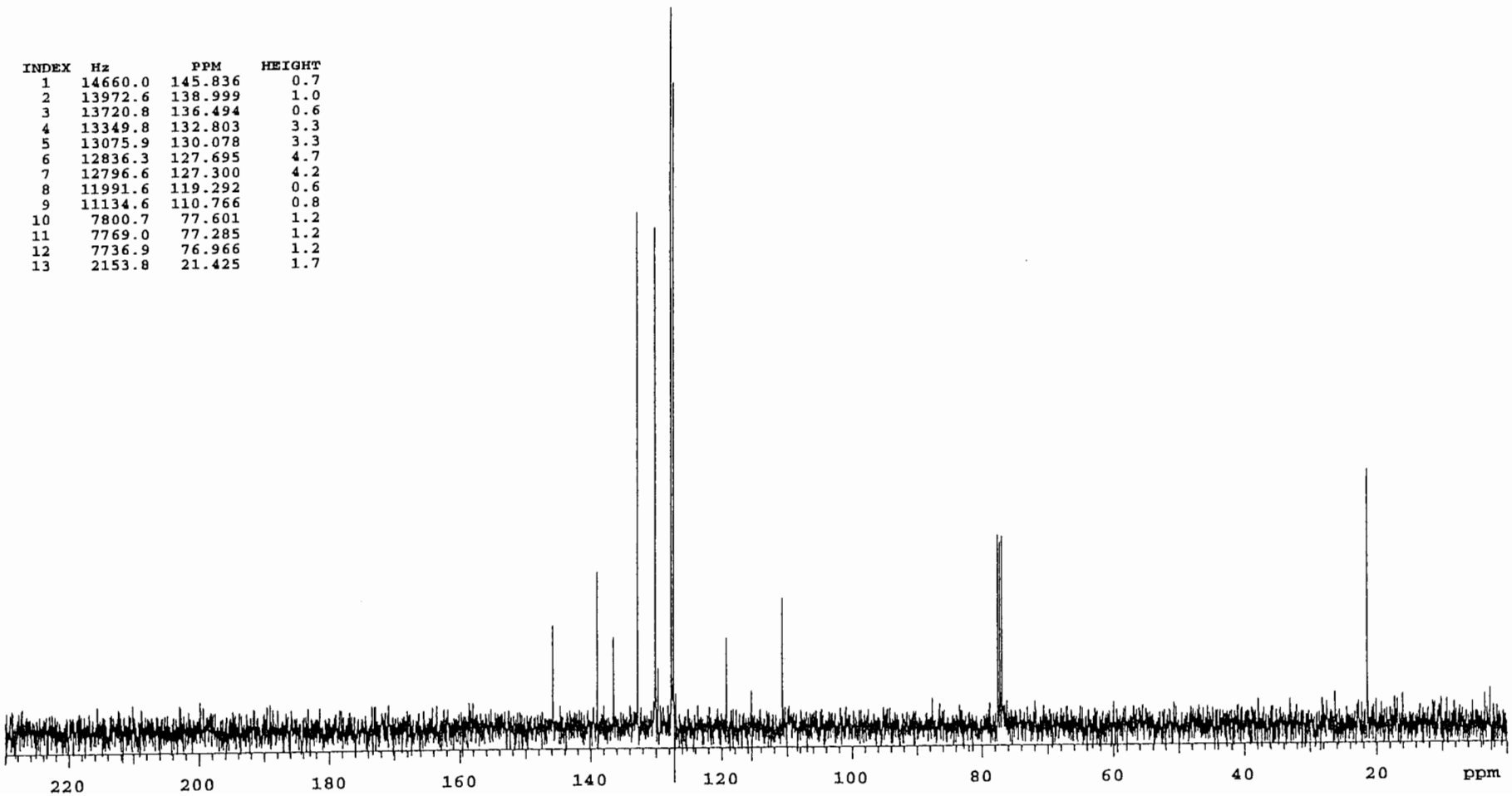
2-Fluoro-4'-methoxybiphenyl - Table 7, entry 9

INDEX	Hz	PPM	HEIGHT
1	16180.2	160.959	0.3
2	16003.6	159.203	0.3
3	15933.7	158.508	0.3
4	13117.5	130.492	1.1
5	13114.1	130.458	1.3
6	13080.5	130.123	2.6
7	12927.6	128.603	0.2
8	12909.3	128.421	1.0
9	12900.1	128.329	1.3
10	12882.9	128.158	0.4
11	12494.0	124.289	1.2
12	12490.9	124.259	1.1
13	11675.2	116.144	1.0
14	11651.5	115.909	1.0
15	11582.0	115.217	0.3
16	11454.4	113.947	-0.3
17	11448.6	113.890	4.5
18	7772.4	77.319	1.1
19	7740.3	77.000	1.2
20	7708.6	76.685	1.3
21	5557.6	55.286	2.1



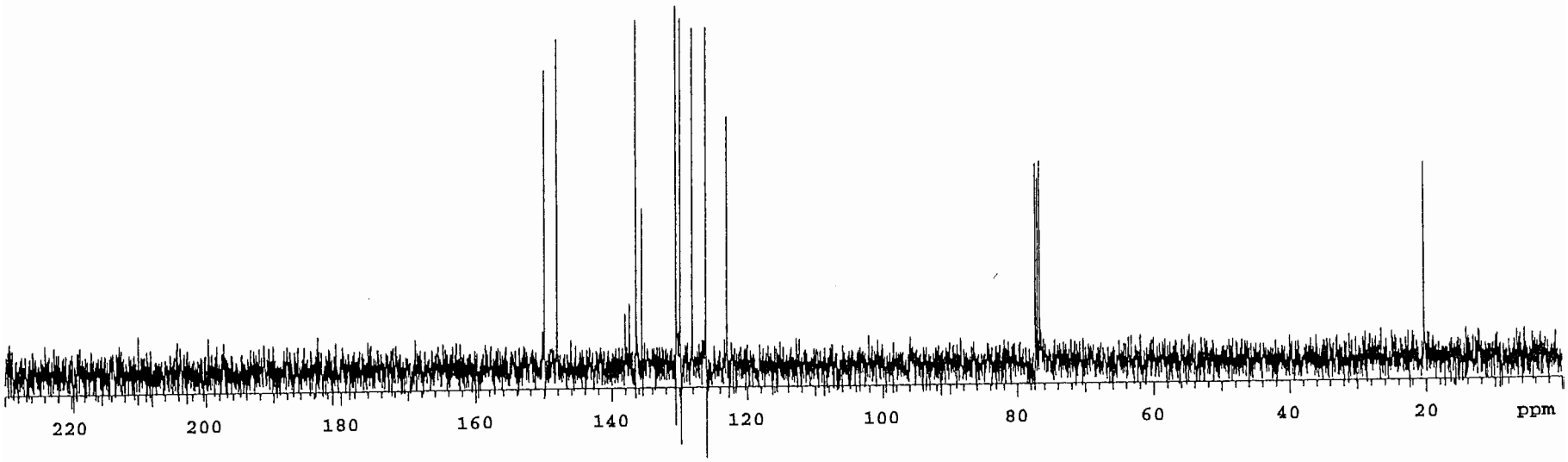
4-Methylbiphenyl-4-carbonitrile - Table 9, entry 1

INDEX	Hz	PPM	HEIGHT
1	14660.0	145.836	0.7
2	13972.6	138.999	1.0
3	13720.8	136.494	0.6
4	13349.8	132.803	3.3
5	13075.9	130.078	3.3
6	12836.3	127.695	4.7
7	12796.6	127.300	4.2
8	11991.6	119.292	0.6
9	11134.6	110.766	0.8
10	7800.7	77.601	1.2
11	7769.0	77.285	1.2
12	7736.9	76.966	1.2
13	2153.8	21.425	1.7



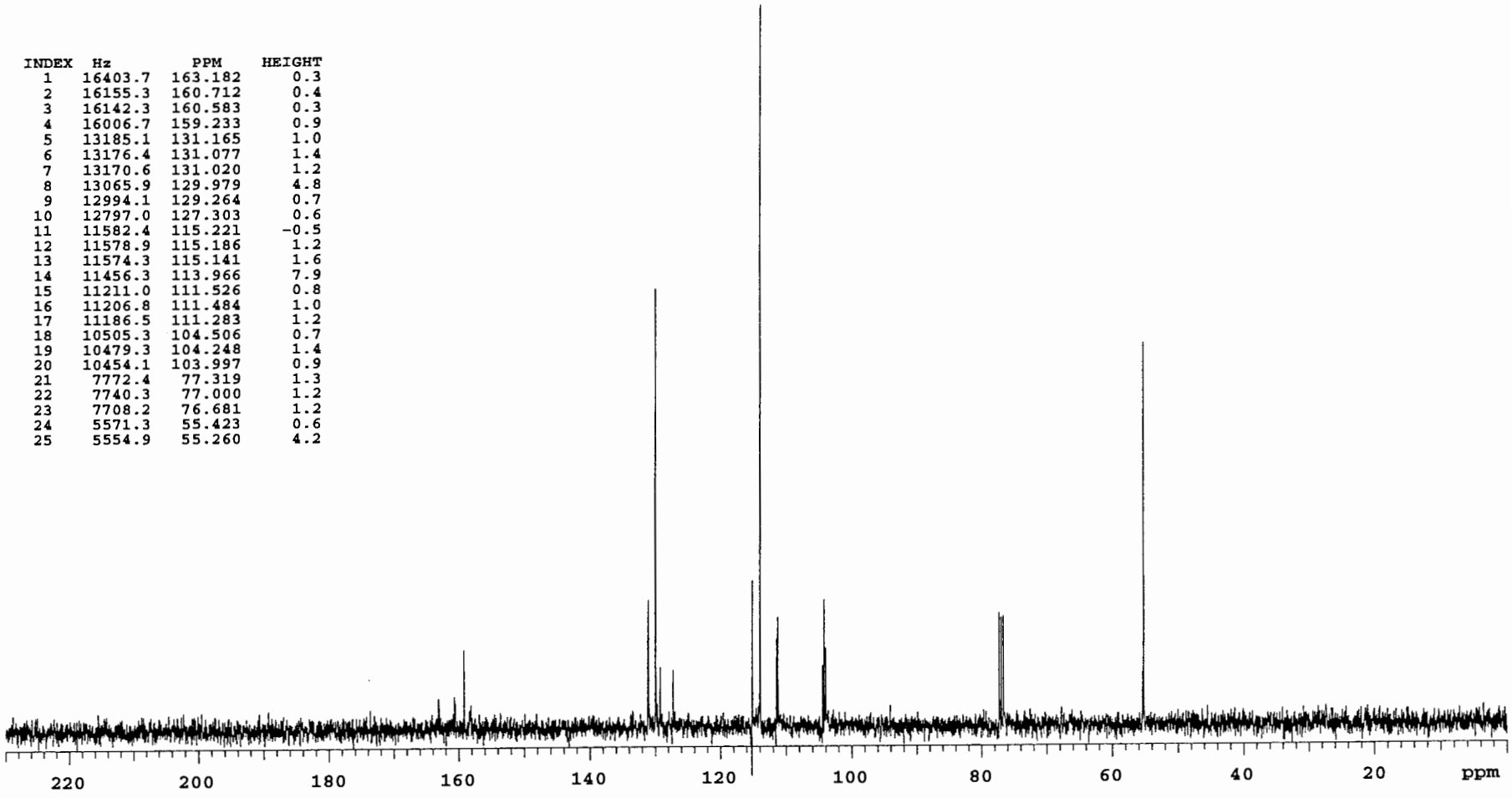
3-(2-methylphenyl)pyridine - Table 11, Entry 9

INDEX	Hz	PPM	HEIGHT
1	15071.8	149.933	1.0
2	14886.9	148.093	1.1
3	13876.7	138.044	0.2
4	13812.1	137.402	0.2
5	13712.4	136.410	1.2
6	13625.3	135.543	0.5
7	13123.6	130.553	-0.2
8	13119.8	130.515	1.2
9	13051.4	129.835	1.2
10	13047.6	129.797	-0.3
11	12873.4	128.063	1.1
12	12670.9	126.049	1.1
13	12666.7	126.007	-0.3
14	12360.6	122.963	0.8
15	7772.0	77.315	0.7
16	7740.3	77.000	0.6
17	7708.6	76.685	0.7
18	2042.2	20.315	0.7



2,4-Difluoro-4'-methoxybiphenyl - Table 11, Entry 12

INDEX	Hz	PPM	HEIGHT
1	16403.7	163.182	0.3
2	16155.3	160.712	0.4
3	16142.3	160.583	0.3
4	16006.7	159.233	0.9
5	13185.1	131.165	1.0
6	13176.4	131.077	1.4
7	13170.6	131.020	1.2
8	13065.9	129.979	4.8
9	12994.1	129.264	0.7
10	12797.0	127.303	0.6
11	11582.4	115.221	-0.5
12	11578.9	115.186	1.2
13	11574.3	115.141	1.6
14	11456.3	113.966	7.9
15	11211.0	111.526	0.8
16	11206.8	111.484	1.0
17	11186.5	111.283	1.2
18	10505.3	104.506	0.7
19	10479.3	104.248	1.4
20	10454.1	103.997	0.9
21	7772.4	77.319	1.3
22	7740.3	77.000	1.2
23	7708.2	76.681	1.2
24	5571.3	55.423	0.6
25	5554.9	55.260	4.2



N-(2-tert-butylphenyl)acetamide (58)

INDEX	Hz	PPM	HEIGHT
1	12931.4	128.641	1.7
2	12740.4	126.741	1.7
3	12720.9	126.547	1.8
4	12704.9	126.387	2.0
5	7772.0	77.315	1.2
6	7740.3	77.000	1.3
7	7707.8	76.677	1.3
8	3084.4	30.684	5.7
9	3062.7	30.467	1.3
10	2439.5	24.268	0.8