The Development of Palladium-Catalysts for Organic Synthesis

By

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B.S. Chemical Engineering
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at the
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ABSTRACT

Chapter 1.

Suzuki-Miyaura coupling reactions of aryl and heteroaryl halides with aryl-, heteroaryl and vinyl boronic acids proceed in very good to excellent yield with the use of 2-(2',6'-dimethoxybiphenyl)-dicyclohexylphosphine, SPhos. Additionally, a comparison of the reactions with SPhos and with 2-(2',4',6'-triisopropylbiphenyl)-diphenylphosphine is presented that is informative in determining the relative importance of ligand bulk and electron-donating ability in the high activity of catalysts derived from ligands of this type. Further, when the aryl bromide becomes too hindered, an interesting C-H bond functionalization-cross-coupling sequence intervenes to provide product in high yield.

Chapter 2.

The direct transformation of aryl bromides into the corresponding Weinreb amides via Pd-catalyzed aminocarbonylation at atmospheric pressure is described. Electron-deficient, -neutral and -rich aryl bromides were all efficiently transformed to product. Furthermore, the process tolerates a wide variety of functional groups, is mild, and is operationally simple.

Chapter 3.

A general, functional group tolerant, and mild system for the Pd-catalyzed Heck carbonylation of aryl chlorides into the corresponding benzamides has been developed. This catalyst operates at one atmosphere of carbon monoxide using an inexpensive, air-stable and commercially available ligand. A variety of aryl chlorides were all successfully transformed to the corresponding amides using primary, a-branched primary, cyclic secondary, acyclic secondary, or aryl amines. Additionally, the mechanism of this reaction was studied using *in situ* IR spectroscopy and revealed the unique effect of sodium phenoxide in this reaction.

Chapter 4.

Pressurized microreactor systems greatly expand the range of reaction conditions and accelerate gas-liquid mass transfer. Heck aminocarbonylation reactions exemplify the potential for quickly and safely scanning of reagents and reaction conditions (1 to 15 bar and 100 - 160°C). The results reveal a general trend of increased yield of amide with temperature and selectivity for α-ketoamide production at lower temperature and higher pressure.

Thesis Supervisor: Stephen L. Buchwald
Title: Camile Dreyfus Professor of Chemistry

ACKNOWLEDGMENTS

Writing this section is proving to be more difficult than I anticipated. The more I think about it, the more people I want to thank. I suspect that if I thanked all the people that have helped me get to where I am, this would be the longest section of this document. I can't stop thinking of the phrase "standing on the shoulders of giants." I don't recall who coined this phrase, or in what context it was originally stated, but I believe this is an apt description of how I feel.

First of all, I would like to thank my advisor Steve Buchwald. He was willing to accept me into his group even after he found out that I am allergic to cats and, consequently, don't like them much. I learned a great deal about science during my time in his group, including Buchwald's Experiments 1 – 5. I have also been instilled with and appreciate Steve's very high ethical standards. Steve and I bumped heads occasionally, but he taught me a lot and I am grateful for his guidance during my time at MIT. Steve is a great person, as illustrated by numerous gifts of Celtics and Red Sox tickets, and I am proud to have been a "Buchwaldian."

I certainly would never have arrived at MIT had it not been for a number of amazing people I met in the chemistry department at the University of Wisconsin – Madison. My first organic lab T.A., Eric Voight, convinced me to pursue chemistry research and my undergraduate advisor, Prof. Steven D. Burke, was kind enough to accept me into his lab. I owe a considerable debt of gratitude to Prof. Burke. Not only did he make me feel like a valued group member, but also he was available any time I needed advice. I also received a lot of good advice from Lei Jiang, a gentleman I was lucky enough to work with both as an undergraduate and graduate student.

I would also like to acknowledge Prof. Klavs F. Jensen. I had the good fortune of participating in collaboration with Prof. Jensen and two of his co-workers, Ed Murphy and Nick Zaborenko. Prof. Jensen is a great person and I really enjoyed working with him. He, Ed and Nick were all very patient with me and taught me a lot about engineering. Ed Murphy and Nick Zaborenko are both Sci-Fi junkies, like myself, and that really made working with them enjoyable.

I would feel remiss if I did not mention the friends that kept me sane during my time as an undergraduate and graduate student. My long time friends and roommates all through college, Chris Mason and Scott Repa, were instrumental in helping me maintain my sanity. These two formidable minds were also excellent sources of motivation and often provided me with healthy doses of much needed humility. I am also indebted to my long time friend, Conan C., for his infallible abilities to make me laugh and keep me honest with myself. My classmates Tim Barder and Jon Wilson were absolutely essential components of my graduate career. Tim, also my lab mate and roommate, was another constant source of entertainment and humility. On more than one occasion I was sure Tim and I were going to kill each other, but we continue to be, and will remain, close friends. Jon Wilson is a great person and a true friend; with Jon's help I discovered that I am a terrible bowler. Matt Rainka was a great source of comic relief (a la the electric slide) and was a huge help during my time in the Buchwald group. Kelvin "PJ" Billingsley, the southern gentleman that he is, taught me a number of things, three of the most important lessons being that 1) "noon-ball" is amazing, 2) the only thing better than college basketball is college football and 3) Bud Light isn't terrible. The following individuals were all instrumental during my time at MIT and will remain valued friends: Mark Biscoe, Ed Hennessy, Eric Strieter, Mark Charles, John Naber, Tom Clark, Alex Shafir, Ryan Altman, Ana Minatti, Carrie Jones, Rachel Munday, David Surry, Don Watson, Catharine Larsen, Nan Zheng, Xiaohua Huang, Shawn Walker, Jackie Milne, Carlos Burgos, Andreas Kellas, Alan Hyde, Ruben Martin, Gordon Brasche, Nan Zheng, Elaine Lee, Liane Klingensmith, and Daemian Dussault. I apologize to anyone that I may have forgotten to mention.

Finally, I would like to thank my family for being the great people that they are. My parents have always been supportive of me, and I will always be thankful for their love and support. My brothers, Mike and Jeff, have been great friends and are always there when I need them; even if I require several days to return a phone call. My sister-in-law, Kristina, was often in Boston for work during my first few years and she would frequently buy me a nice dinner. The rest of my family, including my little niece and nephew (Maddy and Conner), has all been great. Everyone mentioned in this section has been amazing and I could never have made this journey without you.

PREFACE

This thesis has been adapted from the following published articles co-written by the author:

"Catalysts for Suzuki-Miyaura Coupling Processes: Scope and Studies of the Effect of Ligand Structure" Barder, T.E.; Walker, S.D.; Martinelli, J.R.; Buchwald, S.L. *J. Am. Chem. Soc.* **2005**, *127*, 4685.

"Convenient Preparation of Weinreb Amides via Pd-Catalyzed Aminocarbonylation of Aryl Bromides at Atmospheric Pressure" Martinelli, J.R.; Freckmann, D.M.M.; Buchwald, S.L. *Org. Lett.* ***2006***, *8,* 4843.

"Accelerating Reactions with Microreactors at Elevated Temperature and Pressures: Profiling Aminocarbonylation Reactions" Murphy, E.R.; Martinelli, J.R.; Zaborenko, N.; Buchwald, S.L.; Jensen, K.F. *Angew. Chem. Int. Ed.* **2007**, *46*, 1734.

Respective Contributions

This thesis contains work that is the result of collaborative efforts between the author and other workers at MIT. An overview detailing the specific contributions of the author is included below.

The work described in Chapter 1 was the result of a collaborative between Dr. Shawn Walker, Tim Barder and the author. The specific contributions of the author include the reactions shown in Table 5, the room temperature reactions discussed in the text, and the synthesis of the ligand used in Table 5 (ligand **2**). The other work was conducted by either Tim Barder or Dr. Shawn Walker and was included for the sake of continuity.

The work described in Chapter 2 was the result of collaborative efforts with Dr. Dominique Freckmann. The author is responsible for all but three reactions included in this chapter. Dr. Freckmann conducted the initial experiments using Xantphos for the Pd-catalyzed aminocarbonylation of aryl bromides to make benzamides (not included) and she also synthesized three of the Weinreb amides included in Chapter 2 (Table 1, entries 9 – 11).

Chapter 3 details a project that was a collaborative effort between Dr. Thomas Clark, Dr. Rachel Munday, Dr. Donald Watson and the author. The author initiated this area of research within the group by conducting numerous experiments over a several months testing various ligands and alternative sets of reaction conditions that are not discossed in this chapter. The author was the first person to successfully sythesize the ligand salt used in this chapter using a three-step one-pot procedure. Additionally, the author conducted the initial experiments using the ligand salt for carbonylation reactions with aryl chlorides as well as the first experiments using phenolic additives (phenol and sodium phenoxide) in an effort to improve the overall reaction. Specifically, the author conducted the ligand screen (Table 1), entries 3 – 7 in the base screen (Table 2), and entries 1, 3, and 14 in the Table 5. All other work is included for continuity and was performed by Dr. Clark, Dr. Munday and Dr. Watson.

The work described in Chapter 4 was the result of collaborative efforts with members of Prof. Klavs Jensen's group in the MIT chemical engineering department: Dr. Edward R. Murphy and Nikolay

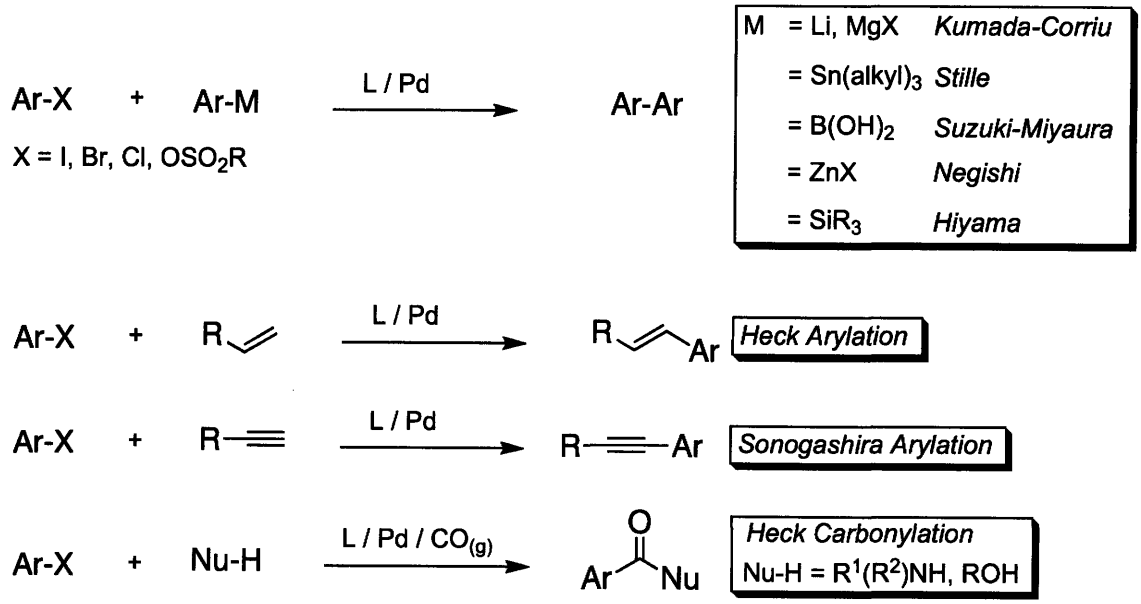
Zaborenko. Dr. Murphy and Mr. Zaborenko were responsible for the fabrication of the microreactors and the periphery connections. The author was responsible for preparing all chemical reagents and isolating and analyzing all products. Dr. Murphy, Mr. Zaborenko and the author equally shared the responsibility of system operation, sample collection and data collection.

TABLE OF CONTENTS

Introduction

Since the discovery of nickel- and palladium-catalyzed cross-coupling processes in the 1970s, these reactions have become extremely important techniques employed by chemists for forming C-C, C-N (Buchwald-Hartwig) and C-O bonds.[1] Advances in catalyst design have fuelled a revolution in cross-coupling chemistry and these reactions have become indispensable to the practicing organic chemist. Many types of aryl nucleophiles have been successfully employed in cross-coupling reactions including aryl lithiums and Grignards (Kumada-Corriu),[2] organotin compounds (Stille),[3] aryl boronic acids and boronate esters (Suzuki-Miyaura),[4] organozinc reagents (Negeshi),[5] aryl silanes (Hiyama),[6] amines and anilines (Buchwald-Hartwig)[7] and alcohols[8] (Scheme 1). In addition, cross-coupling type processes have allowed efficient functionalization of olefins (Heck Arylation),[9] alkynes (Sonogashira)[10] and installation of carbonyl functional groups (Heck Carbonyation).[11]

Scheme 1. General Pd-Catalyzed Cross-Coupling Reactions.



Arguably, one of the most important C-C bond forming reactions is the Suzuki-Miyaura cross-coupling reaction. This Pd-catalyzed reaction between an aryl halide (or sulfonate) and a boron reagent

(typically a boronic acid) allows for the rapid construction of C-C bonds. This reaction possesses several advantages over other cross-coupling reactions due to the benign nature of the boron reagents. Boronic acids are non-volatile, non-toxic, air- and moisture-stable solids that can be stored for long periods of time and handled without special precautions.[12] Additionally, the mild reaction conditions tolerate the presence of many functional groups.[4,13]

The choice of ligand is instrumental in determining the efficacy of Pd-catalyzed Suzuki-Miyaura reactions. The appropriate ligand, such as an electron-rich bulky biaryl-based monophosphine of the type shown in Figure 1, can provide highly active catalyst.[4c,5b,7c] Shown in Scheme 2 is a general catalytic cycle for a Suzuki-Miyaura cross-coupling reaction: 1) the palladium catalyst undergoes oxidative addition with the electrophile (in this case an aryl chloride); 2) the nucleophilic coupling partner undergoes transmetalation (in this case an aryl boronic acid); 3) the biaryl product is formed via reductive elimination of a C-C bond.[4,13] Other cross-coupling reactions proceed through a similar sequence of steps.

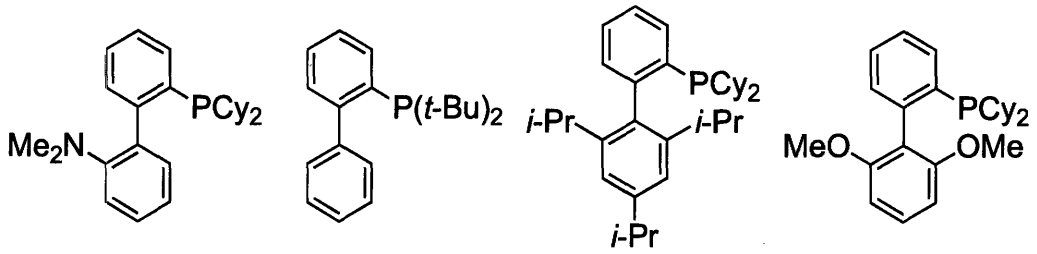
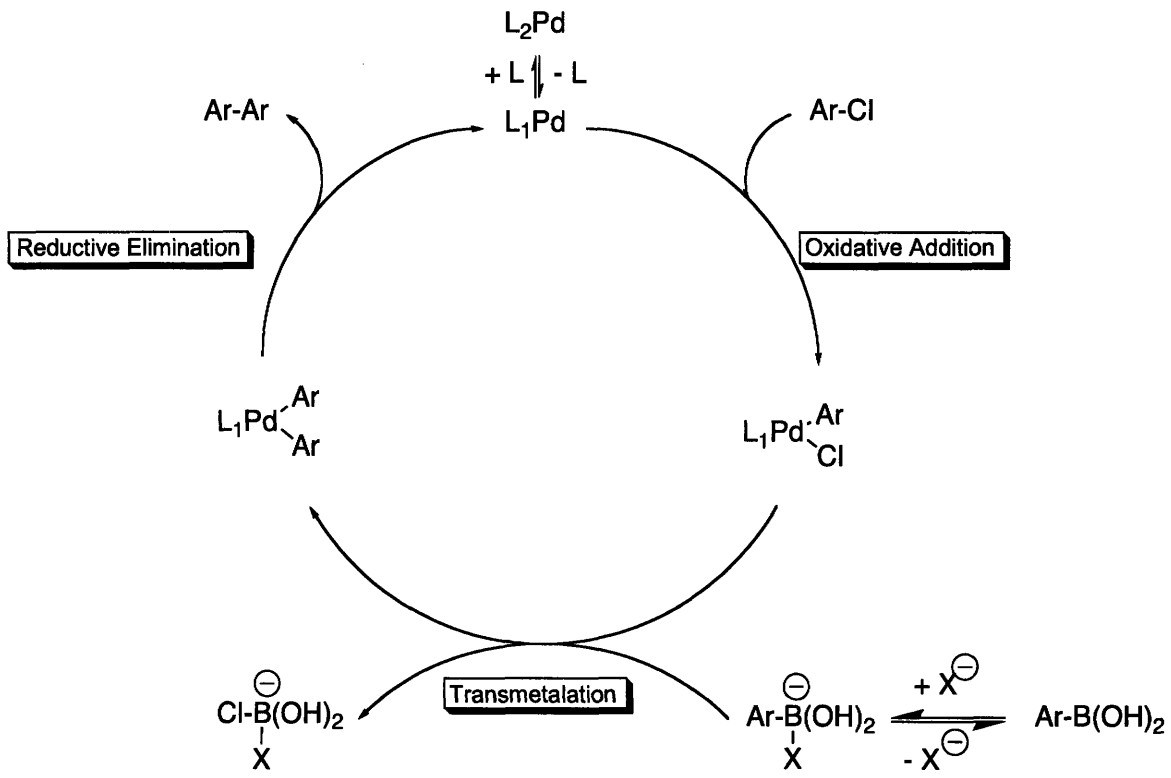


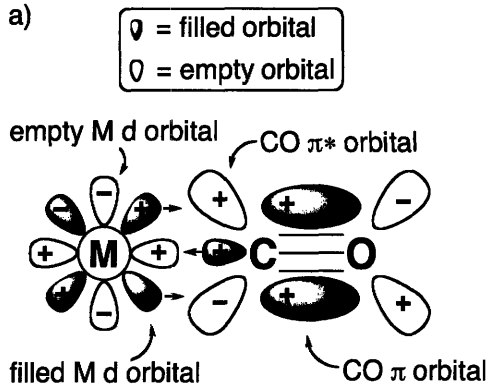
Figure 1. Selected Examples of Biaryl-Based Monophosphines.

Scheme 2. Proposed Catalytic Cycle for the Suzuki-Miyaura Reaction.



Another important Pd-catalyzed reaction is the Heck carbonylation.[11] This three-component coupling reaction of an aryl halide, carbon monoxide (CO), and a nucleophile is a very powerful method for the regioselective installation carbonyl functional groups into target molecules.[14] Although carbon monoxide is a synthetically useful organic molecule, it is an excellent ligand for transition metals which makes it a deadly poison (Scheme 3).[15] CO binds very strongly to metals due to its ability to act as both a σ-donor and a π-acceptor (back-bonding).[16] An analogous catalytic cycle for Pd-catalyzed carbonylation is proposed in Scheme 4.[17]

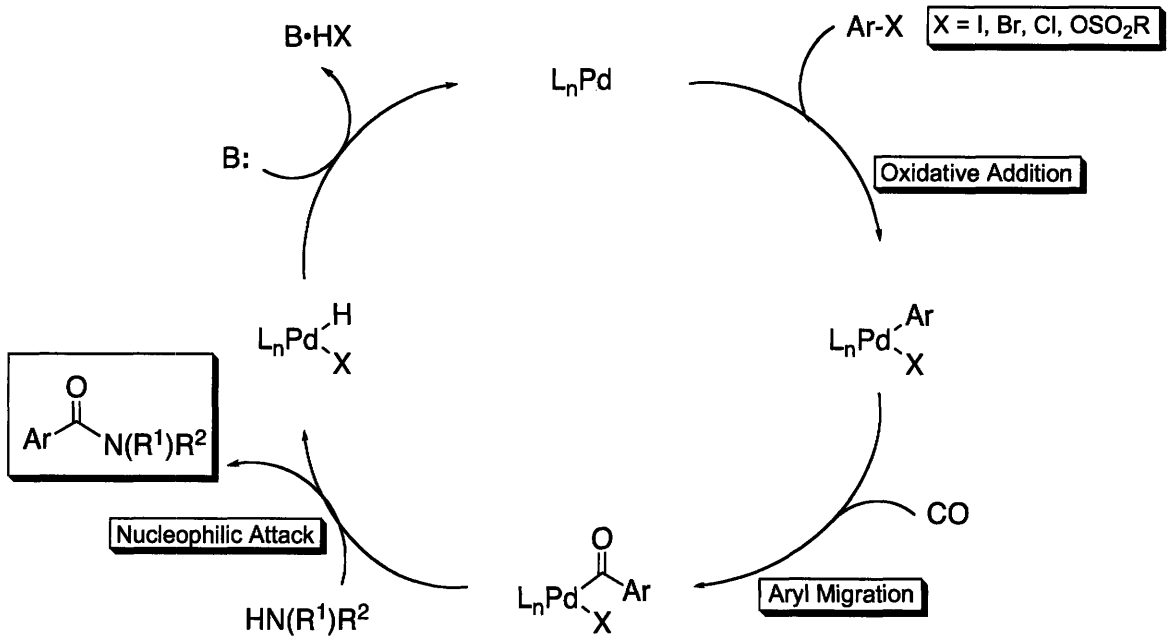
Scheme 3. a) Orbital Interactions Between CO and a Transition Metal. b) Physical Effects of CO.



b)

Concentration of CO in Air and Effect	
0.005%	Tolerable by healthy adults for hours.
0.05%	Tolerable by healthy adults for ~ 1 hour.
0.15%	Dangerous for healthy adults after ~ 1 hour.
0.4%	Fatal for healthy adults in less than 1 hour.

Scheme 4. Proposed Catalytic Cycle for the Heck Carbonylation Reaction.



Cross-coupling reactions have been called on countless number of times to solve ever more challenging problems and each new challenge typically requires a new set of optimized reaction conditions. This has led to great interest in finding ways to speed up the process of reaction optimization. One strategy that has shown great promise is the use of microreactor technology as "micro-total-analysis-systems" (μTAS).[18] These microchemical systems have dimensions ranging from 10 – 1000 μm and are

typically operated in a continuous fashion.[18] Some inherent advantages of these systems are enhanced mass- and energy-transfer due to large surface-to-volume ratios, decreased material requirements per experiment, and greatly increased safety considerations associated with the use of highly toxic or dangerous materials.[18] Such systems have been used successfully in a number of chemical applications fueling further interest and their full potential has yet to be realized.[19]

The work presented in this thesis details recent developments in the areas of Pd-catalyzed Suzuki-Miyaura reactions and Heck Carbonylation reactions that should be of interest to the general organic chemistry community. The work is presented in four chapters. In Chapter 1 work designing new ligands for the improvement of Pd-catalyzed Suzuki-Miyaura cross-coupling reactions is described. Chapters 2 and 3 describe recent developments in the Pd-catalyzed Heck carbonylation reactions. In Chapter 2, a convenient strategy for the synthesis of Weinreb amides by Pd-catalyzed aminocarbonylation of aryl bromides at atmospheric pressure of CO is described. Chapter 3 describes the development of a system for the efficient aminocarbonylation of aryl chlorides at atmospheric pressure of CO. Finally, in Chapter 4, a case study detailing the use of microreactor technology for the optimization of synthetically useful reactions is presented.

References

(1) For reviews see: (a) *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A., Diedrich, F., Eds.; Wiley-VCH: Weinheim, 2004. (b) Tsuji, J. *Palladium Reagents and Catalysts*, 2nd ed.; Wiley: Chichester, 2004. (c) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-I., de Meijere, A., Eds.; Wiley: Chichester, 2002. (d) Tamao, K.; Miyaura, N. *Top. Curr. Chem.* **2002**, *219*, 1.

(2) (a) Corriu, R.J.; Masse, *J.P. Chem. Commun.* **1972**, 144. (b) Tamao, K.; Kiso, Y.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, *94*, 9268. (c) Tamao, K.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, *94*, 4374. (d) Martin, R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 3844.

(3) (a) Kosugi, M.; Sasazawa, K.; Shimizu, Y.; Migitia, T. *Chem. Lett.* **1977**, 1423. (b) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 4992. (c) Littke, A. F.; Schwarz, L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 6343.

(4) (a) Miyaura, N.; Suzuki, A. *Chem. Commun.* **1979**, 866. (b) Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* **1981**, *11*, 513. (c) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550.

(5) (a) Baba, S.; Negishi, E. *J. Am. Chem. Soc.* **1976**, *98*, 6729. (b) Milne, J. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 13028.

(6) (a) Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1988**, *53*, 918. (b) Hatanaka, Y.; Fukushima, S.; Hiyama, T. *Chem. Lett.* **1989**, 1711. (b) Powell, D. A.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 7788.

(7) (a) Kosugi, M.; Kameyama, M.; Migita, T. *Chem. Lett.* **1983**, 927. (b) Guram, A. S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 7901. (c) Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 7215. (d) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 7217. (e) Huang, X.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 6653.

(8) Vorogushin, A. V.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 8146.

(9) (a) Heck, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 5518. (b) Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581.

(10) Sonogashira, K; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467.

(11) (a) Schoenberg, A.; Bartoletti, I.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3318. (b) Schoenberg, A.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3327.

(12) Miyaura, N. *Top. Curr. Chem.* **2002**, *219*, 11.

(13) (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron*, **2002**, *58*, 9633.

(14) (a) Beller, M.; Mägerlein, W.; Indolese, A.; Fischer, C. *Synthesis*, **2001**, *7*, 1098. (b) Skoda-Földes, R.; Kollár, L. *Curr. Org. Chem.* **2002**, *6*, 1097.

(15) *Chemical Hazards of the Workplace*, Proctor, N. H.; Hughes, J. P.; Fischman, M. L., Eds. J.B. Lippincott Co.: Philidelphia, 1988.

(16) Stromnova, T. A.; Moiseev, I. I. *Russ. Chem. Rev.* **1998**, *67*, 485.

(17) (a) Garrou, P. E.; Heck, R. F. *J. Am. Chem. Soc.* **1976**, *98*, 4115. (b) Milstein, D. *Acc. Chem. Res.* **1988**, *21*, 428.

(18) (a) Jensen, K. F. *AIChE J.* **1999**, *45*, 2052. (b) Jensen, K. F. *Chem. Eng. Sci.* **2001**, *56*, 293.

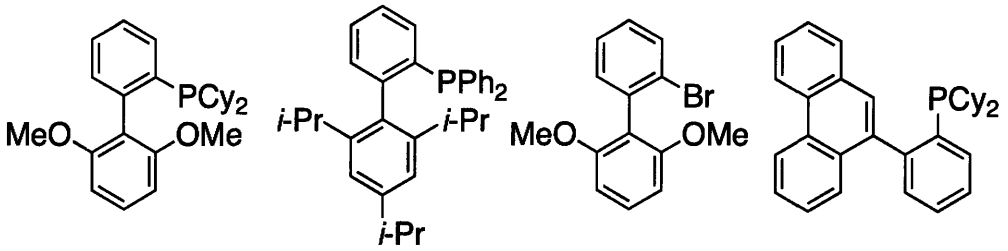
(19) Jähnisch, K.; Hessel, V.; Löwe, H.; Baerns, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 406.

Chapter 1.

Design and Development of Catalysts for Suzuki-Miyaura Cross-Coupling Reactions.

1.1 Introduction

In 1979, the seminal paper of Miyaura, Yamada and Suzuki[1] laid the groundwork for what now is arguably the most important and useful transformation for construction of carbon-carbon bonds in modern day organic chemistry. Although the original paper reported coupling reactions of alkenyl boronates with alkenyl bromides, throughout the past 25 years contributions from myriad research groups[2] have led to vast improvements on what now is known as the Suzuki-Miyaura cross-coupling reaction. Advances have been made in way of reaction scope, including the use of aryl chlorides[3] as substrates and the ability to conduct couplings at very low catalyst loadings[4] and at room temperature.[5] Moreover, it is now possible to couple hindered substrates[6] and even asymmetric variations have been reported.[7] Improvements in Suzuki-Miyaura coupling reactions have relied a great deal on increased reactivity and stability of the metal catalysts by use of increasing efficacious supporting ligands. The most common ligands used today are phosphine-based, although a variety of others, including *N*-heterocyclic carbenes (NHC) have been employed.[5f,h,i,8] Also of great importance are the procedures that utilize so-called "ligandless" conditions.[9] The ability to satisfy the diverse requirements of different Suzuki-Miyaura couplings with a single ligand, however, remains unrealized. Herein, we present a full report of a catalyst system that enables the coupling of heteroaryl, both electron-rich and -poor aryl and vinyl boronic acids with very hindered aryl halides and a variety of heteroaryl halides at exceptionally low catalyst loadings.[10] Additionally, we present crystallographic data and computational studies to help explain the efficacy of catalysts based on **1** impart in Suzuki-Miyaura cross-coupling processes. Further, a simply prepared triarylphosphine, ligand **2**, is described that also demonstrates high activity in the coupling of electron-rich and hindered aryl chloride substrates.



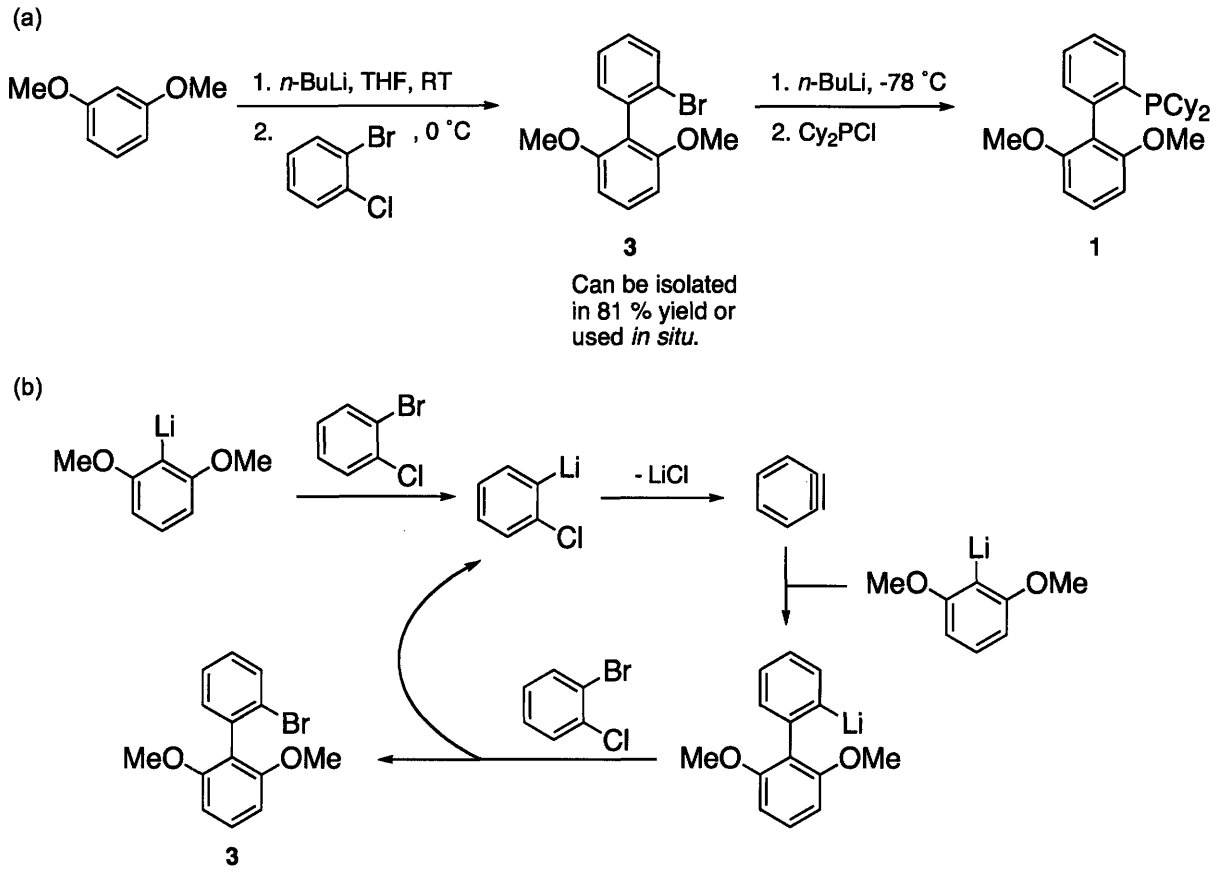
1 (SPhos) **2 (Ph_2XPhos)** **3** **4**

Figure 1. Ligands and a ligand precursor (**3**) for Suzuki-Miyaura Coupling Reactions

1.2 Results and Discussion

1.1.1 Synthesis of 2-(2',6'-dimethoxybiphenyl)-dicyclohexylphosphine (1)

We have developed a direct and experimentally convenient one-pot protocol for the construction of ligand **1**, based upon a procedure developed by Schlosser who had nicely modified our original procedure to provide aryl halides in a simple protocol.[11] Although our previous synthesis of dialkylbiarylphosphine ligands[12] required an aryl halide precursor, the selection of the 1,3-dimethoxybenzene moiety for the bottom (non-phosphine containing) ring, offered the advantage that it can be installed by means of a directed metalation. The directed *ortho*-lithiation of 1,3-dimethoxybenzene with *n*-BuLi in THF at room temperature, followed by cooling the reaction mixture to 0 °C, and slow addition of neat 1-bromo-2-chlorobenzene generated 2-bromo-1',3'-dimethoxybiphenyl (**3**). The latter, produced via a rapid, tandem benzyne condensation-bromine atom transfer sequence, could be isolated in 81% yield. Compound **3**, in THF at -78 °C, could be treated with *n*-BuLi and then chlorodicyclohexylphosphine. However, for expedient access to **1**, **3** was not isolated but was treated sequentially, at -78 °C, with *n*-BuLi and chlorodicyclohexylphosphine followed by warming the reaction to room temperature. Following workup and crystallization, **1** was produced in 59% overall yield. This new procedure allows for the synthesis of **1** in a considerably shorter reaction time and with an easier isolation procedure (no CuCl is required) than the route used previously to access such ligands.



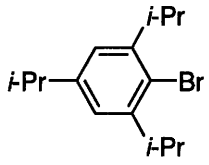
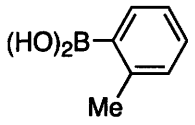
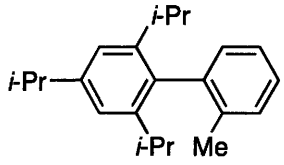
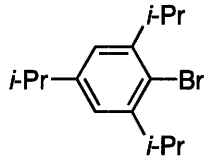
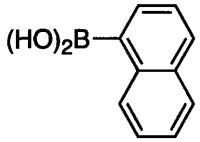
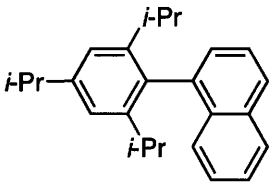
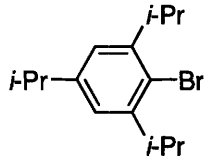
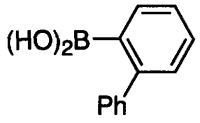
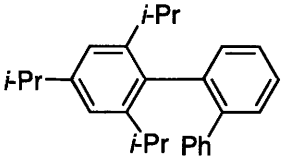
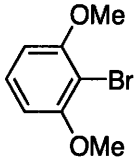
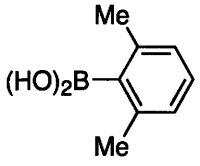
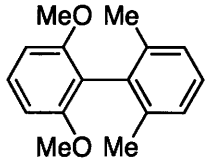
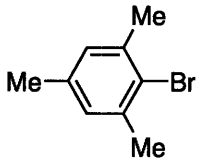
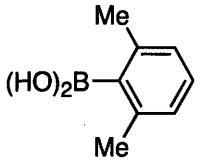
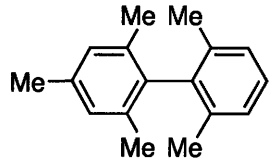
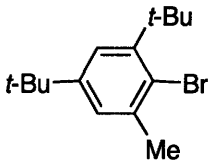
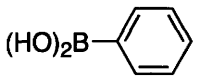
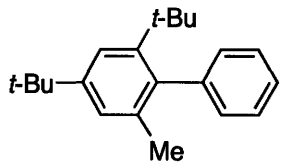
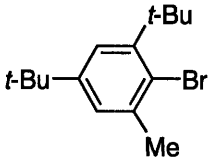
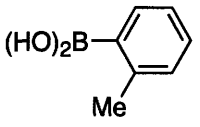
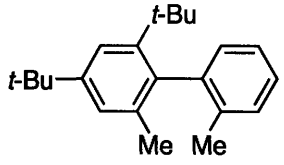
Scheme 1. (a) One-Pot Synthesis of 1. (b) Benzyne Condensation-Bromine Atom Transfer Sequence.

1.1.2 Suzuki-Miyaura Coupling Reactions of Hindered Substrates

The ability to prepare extremely hindered biaryls via Suzuki-Miyaura coupling reactions has historically proven to be a difficult task. Most challenging are examples with substrates that contain large *ortho* substituents and/or *ortho*, *ortho'* substituents. However, with the use of **1**, the coupling of an aryl bromide that possesses two large *ortho, ortho'* substituents, 2,4,6-tri-isopropylbromobenzene, with boronic acids as hindered as 2-biphenylboronic acid proceeded in excellent yield (Table 1, entry 3, 93%). Unfortunately the reaction of 2,4,6-tri-isopropylbromobenzene and 2,6-dimethyl phenyl boronic acid with 1.5% $Pd_2(dba)_3$ and 6% **1** at 100 °C for 14 h provided no desired product. Relatively bulky 1-naphthyl boronic acid required only 0.1% Pd for its efficient combination with 2,4,6-tri-isopropylbromobenzene in 12 h to give product in 96% isolated yield (Table 1, entry 2). We previously reported the preparation of

biaryls possessing a 2,2′,6,6′ tetrasubstituted pattern with a phenanthrene-based phosphine ligand, **4**.[13] However, this system has several disadvantages, including the necessity of using between 4-10% Pd and the fact that **4** is not commercially available. Gratifyingly, the use of ligand **1** allowed for the coupling of 2,6-dimethoxybromobenzene with 2,6-dimethylphenyl boronic acid with 3% Pd in 86% isolated yield (Table 1, entry 4). The difficulty of this particular transformation exists not only from the steric encumberance of both the aryl bromide and boronic acid, but also from the very electron-rich nature of the aryl bromide. Additionally, we were able to couple 2-methyl-4,6-di-*tert*-butylbromobenzene with phenyl- and 2-methylphenyl boronic acid (Table 1, entries 6 and 7). Although 10% $Pd(OAc)_2$ was required to obtain full conversion of the aryl bromide, only a small amount of arene byproduct was observed and isolated yields were greater than 80%. Taken together, the results shown in Table 1 represent, to our knowledge, the most hindered couplings of aryl halides and aryl boronic acids to date.

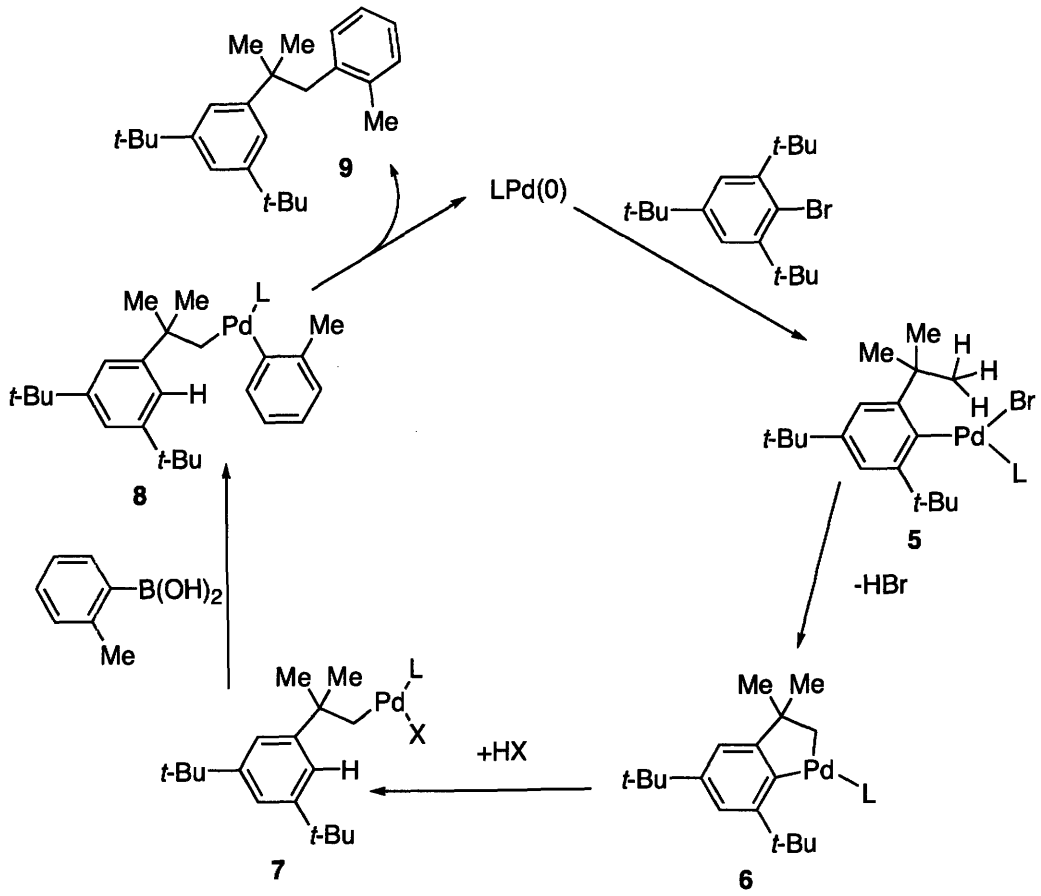
Table 1. Hindered Suzuki-Miyaura Couplings Using Ligand **1**[a]

Entry	Halide	Boronic Acid	Product	mol% Pd	Conditions	Yield (%)[b]
1				3 0.1	100 °C, 2 h 100 °C, 24 h	94 95
2				0.1	100 °C, 12 h	96
3				3	100 °C, 18 h	93
4				3	100 °C, 10 h	86
5				4	110 °C, 18 h	82[c]
6				10	110 °C, 18 h	82
7				10	110 °C, 18 h	89

[a] Reaction conditions: 1 equiv of aryl bromide, 2 equiv of boronic acid, 3 equiv of K_3PO_4, toluene (2 mL/mol halide), cat $Pd_2(dba)_3$, ligand **1**, L:Pd = 2:1. [b] Isolated yield based upon an average of two runs. [c] 4 equiv K_3PO_4 was used.

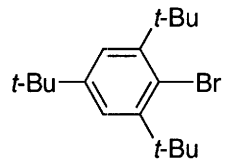
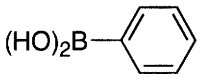
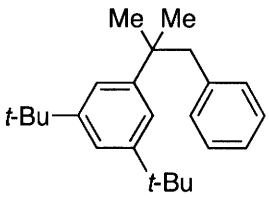
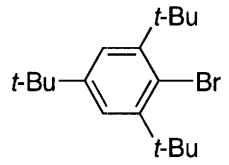
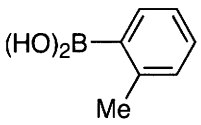
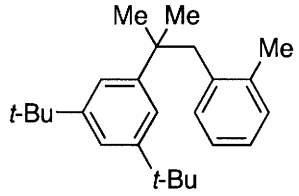
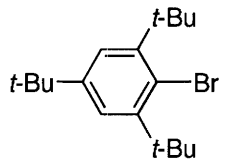
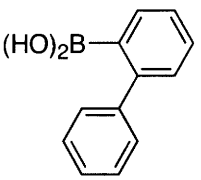
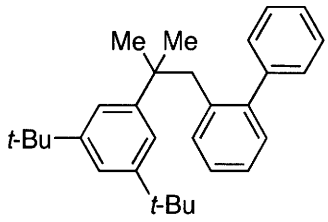
1.1.3 Tandem C-H Functionalization/Suzuki-Miyaura Coupling Reactions

In hope of further pushing the limit of the degree of steric hindrance of the aryl bromide that could be successfully coupled, we examined the reaction of 2,4,6-tri-*tert*-butylbromobenzene with phenyl boronic acid. We were surprised that only 2% Pd was required to promote full conversion of the aryl bromide. The relatively low quantity of catalyst required was initially puzzling, as 10% Pd was needed for the much less hindered 2-methyl-4,6-di-*tert*-butylbromobenzene. Examination of the ^{1}H NMR spectrum of the product from this reaction indicated that instead of the desired biaryl, the α,α-dimethyl-β-aryl hydrostyrene derivative, **9** (Table 2, entry 1), was produced. More hindered boronic acids, such as 2-methylphenyl boronic acid and 2-biphenyl boronic acid also proved to be excellent coupling partners in this type of transformation, with yields >96%. Scheme 2 contains a suggested mechanism for this transformation. Following oxidative addition to the aryl bromide to give **5**, cyclometalation occurs to form a five-membered palladacycle, **6**, via abstraction of one of the hydrogen atoms from the *tert*-butyl group. A mechanism of this type has previously been proposed in the reactions of similar aryl bromides.[14] Selective protonation of the weaker[15] and less hindered sp^2 C-Pd bond of **6** affords the alkyl Pd^{II} species, **7**. This can undergo transmetalation with the boronic acid **8**. Finally, reductive elimination occurs with formation of a carbon-carbon bond to **9** with concomitant regeneration of LPd(0). One possible reason for the efficiency of this reaction is that **7** lacks β-hydrogens and therefore few side reactions are available to it. Further work is ongoing on our laboratories to investigate the scope of this tandem C-H activation/cross-coupling reaction.



Scheme 2. Suggested Mechanism of the Tandem C-H Functionalization Suzuki-Miyaura Coupling

Table 2. C-H Activation Followed by Coupling with Aryl Boronic Acids Using Ligand **1**[a]

Entry	Halide	Boronic Acid	Product	Conditions	Yield (%)[b]
1				100 °C, 18 h	95
2				100 °C, 18 h	96
3				100 °C, 18 h	99

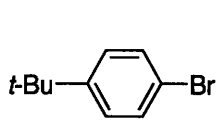
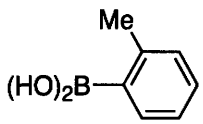
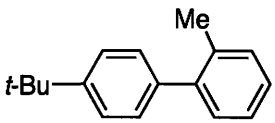
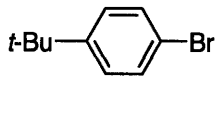
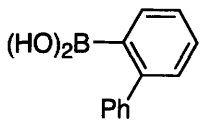
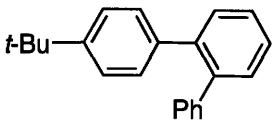
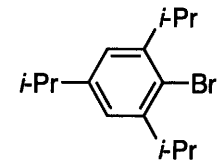
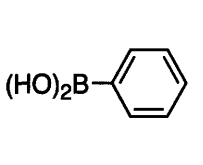
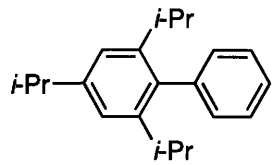
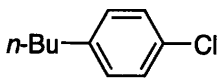
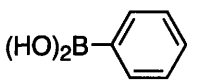
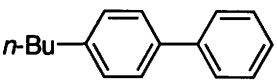
[a] Reaction conditions: 1 equiv of aryl bromide, 2 equiv of boronic acid, 3 equiv of K_3PO_4, toluene (2 mL/mol halide), 1% $Pd_2(dba)_3$, 4% ligand **1**. [b] Isolated yield based upon an average of two runs.

1.1.4 Suzuki-Miyaura Coupling Reactions at Low Catalyst Loadings

The need to perform Suzuki-Miyaura coupling reactions at low catalyst loadings exists not only to minimize the amount of palladium and ligand for reasons of cost, but as well as to allow for these types of coupling processes to be used on large scale while minimizing the effort required for the removal of palladium from the final product.[16] Using **1**, efficient coupling reactions with quantities of palladium at or below the allowable limit[16] can be achieved. For example, the coupling of 4-*tert*-butylbromobenzene with 2-methylphenyl boronic acid using 10 ppm $Pd(OAc)_2$ at 100 °C for 1.5 h provides an 98% isolated yield of product. Using catalyst loadings as low as 10 ppm $Pd(OAc)_2$, the coupling of 4-*tert*-butylbromobenzene with the sterically demanding 2-biphenyl boronic acid proceeds to 85% isolated yield in 24 h at 100 °C. These are, of course, very simple processes. However, these results represent the smallest amount of palladium used in Suzuki-Miyaura couplings of *unactivated* aryl bromides with boronic acids *aside from phenyl boronic acid.* This latter point is important as we find little degree of

extrapolation of results using phenyl boronic acid and those obtained with other aryl boron derivatives. For example, the coupling of 2,4,6-tri-isopropylbromobenzene and phenyl boronic acid proceeded to 97% isolated yield at 0.01% Pd in 16 h (Table 3, entry 3). However, only 50% conversion of aryl bromide was observed under similar conditions when the catalyst loading was lowered to 0.001% Pd. Additionally, we have achieved the coupling of an unactivated aryl chloride, 4-*n*-butylchlorobenzene with phenyl boronic acid using 50 ppm $Pd(OAc)_2$ or 15 ppm $Pd_2(dba)_3$ at 100 °C to give 96% and 93% isolated yield of biaryl, respectively (Table 3, entry 4).

Table 3. Suzuki-Miyaura Couplings at Low Catalyst Loadings Using Ligand **1**[a]

Entry	Halide	Boronic Acid	Product	mol% Pd	Conditions	Yield (%)[b]
1				0.001 0.0005	110 °C, 1.5 h 100 °C, 24 h	98 89
2				0.001	100 °C, 24 h	85[c]
3				0.01	100 °C, 16 h	97[d]
4				0.005 0.003	100 °C, 10 h 100 °C, 24 h	96 93[d,e]

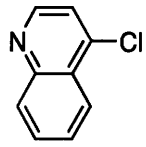
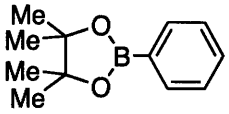
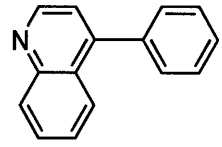
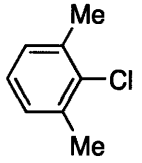
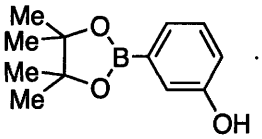
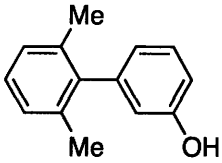
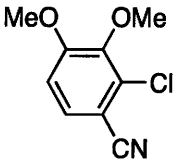
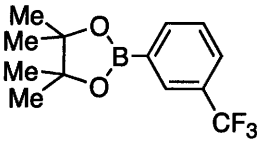
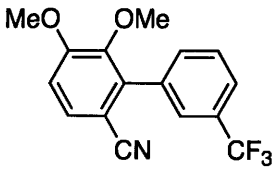
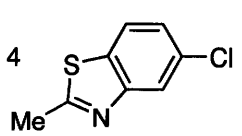
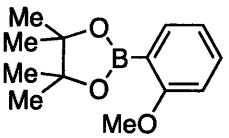
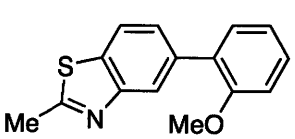
[a] Reaction conditions: 1 equiv of aryl halide, 1.5 equiv of boronic acid, 2 equiv of K_3PO_4, toluene (2mL/mmol halide), cat $Pd(OAc)_2$, ligand **1**, L:Pd = 2.5:1. [b] Isolated yield based upon an average of two runs. [c] L:Pd = 2:1. [d] Cat Pd_2dba_3 used with L:Pd = 2:1. [e] $K_3PO_4 \cdot H_2O$ used as base.

1.1.5 Suzuki-Miyaura Coupling Reactions Using Aryl Pinacol Boronate Esters

Although Suzuki-Miyaura coupling reactions are among the most mild and efficient methods to construct carbon-carbon bonds, a drawback of using boronic acids is the structural ambiguity associated with them. Under anhydrous conditions, boronic acids dimerize and trimerize to form anhydrides and boroxines.[17] In normal laboratory conditions, a mixture of monomer, dimer and boroxine exist. This

drawback can be overcome by use of boronate esters or trifluoroborate salts,[18] both of which are air- and water-stable and exist only in a monomeric form. Further advantages of boronate esters include the ability to purify them via chromatography and the ability to observe them via gas and liquid chromatography. It is our belief that trace water, either from a hydrated base or through the addition of a small amount of water to the reaction mixture, most likely hydrolyzes the boronate ester either partially or fully to allow for transmetalation to occur efficiently.[19] Table 4 illustrates several examples of Suzuki-Miyaura coupling reactions with aryl boronate esters and aryl- and heteroaryl chlorides that all provide product in excellent isolated yield. For example, the coupling of 2-chloro-*m*-xylene with 3-hydoxyphenyl boronic acid was accomplished in 94% isolated yield using 1% $Pd(OAc)_2$ as precatalyst at 100 °C in 30 min (Table 4, entry 2).

Table 4. Suzuki-Miyaura Couplings of Pinacol Aryl Boronates Using Ligand **1**[a]

Entry	Halide	Pinacol Boronate Ester	Product	Conditions	Yield (%)[b]
1				100 °C, 0.5 h	88
2				100 °C, 0.5 h	94
3				100 °C, 0.5 h	94
4				RT, 24 h	91[c]

[a] Reaction conditions: 1 equiv of aryl chloride, 1.5 equiv of boronate ester, 2 equiv of K_3PO_4, toluene:H_2O (10:1) (2 mL/mol halide), 1% $Pd(OAc)_2$, 2% ligand **1**. [b] Isolated yield based upon an average of two runs. [c] 1% $Pd(OAc)_2$ and 1% Ligand **1** in THF:H_2O (10:1) was used.

1.1.6 Suzuki-Miyaura Coupling Reactions at Room Temperature.

Our initial communication describing the activity of **1** included Suzuki-Miyaura couplings at room temperature. Catalyst loadings as low as 0.5% $Pd(OAc)_2$ effected the reaction of *ortho,ortho'* substituted and electron-rich aryl chlorides with *ortho* substituted boronic acids in very good to excellent yield. Little or no effort was made to minimize the quantity of catalyst that was necessary.

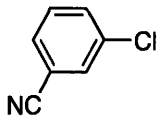
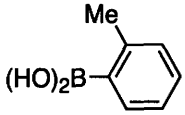
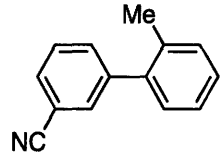
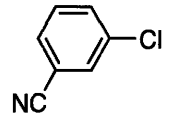
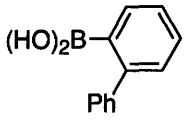
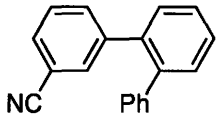
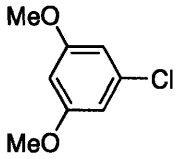
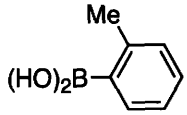
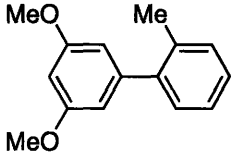
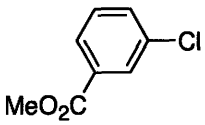
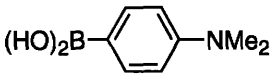
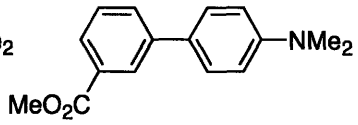
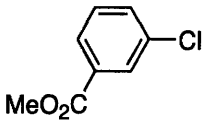
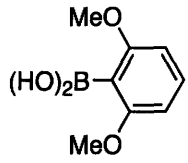
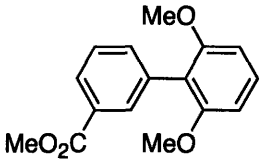
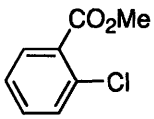
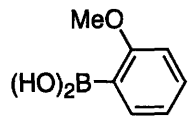
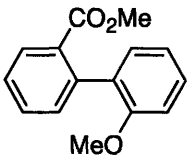
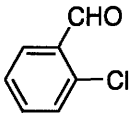
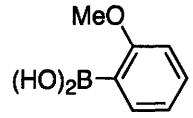
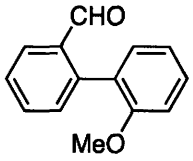
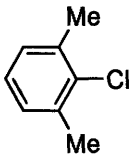
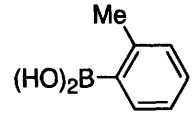
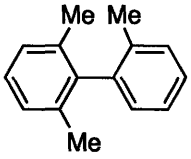
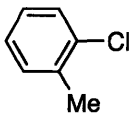
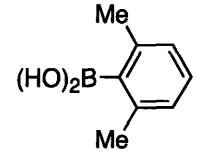
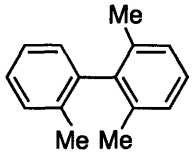
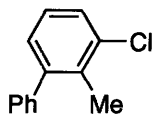
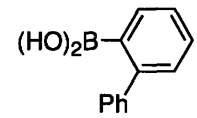
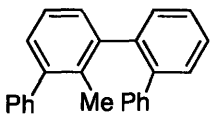
The reason for the efficiency of bulky, electron-rich ligands is often-times ascribed to their proclivity to donate electron-density to the intermediate Pd(0) complex to facilitate the rate of oxidative addition. Alternately, it has been proposed that these ligands cause a reasonable amount of highly reactive L_1Pd species to form.[20] In order to decipher the relative contribution of these two factors, we prepared the triarylphosphine, **2** (**Ph_2XPhos**).[21] Ligand **2** was then employed in various coupling processes and it was ascertained that it was an excellent supporting ligand for Suzuki-Miyaura coupling reactions, particularly those carried out at room temperature.

There have been several accounts of Suzuki-Miyaura coupling reactions of aryl chlorides at room temperature.[5h,5i,6,22] Despite the success that has been realized, limitations still exist. For example, in the report of Nolan, NaO*t*-Bu was required as base and slow addition of the aryl chloride was necessary as dehalogenation was observed as a side reaction.[5i] In a particularly impressive recent paper from Glorius, the use of KOH (from KO*t*-Bu and water) was required for boronic acids possessing two *ortho* methyl substituents.[6] In this work the scope of formation of tetra*ortho* substituted biphenyls was expanded to the highest level reported to date. Fu was able to employ KF, a milder base, in his work; only activated aryl chlorides (heterocyclic and electron-poor), however, were used.[22] Our reaction conditions using **2** allow the use of a mild base, $K_3PO_4 \cdot H_2O$, very hindered boronic acids and electron-rich aryl chlorides, and without slow addition of any reagents. The generality of Suzuki-Miyaura couplings using this ligand is demonstrated by the results shown in Table 5. Catalyst levels as low at 0.05% $Pd(OAc)_2$ effected the reaction of 3-chlorobenzonitrile with 2-biphenyl boronic acid in 93% isolated yield (Table 5, entry 2). Additionally, the formation of previously described 2,2',6-trimethylbiphenyl can be achieved by the coupling of 2-chloro-*m*-xylene with *o*-tolyl boronic acid or 2-chlorotoluene with 2,6-dimethylphenyl

boronic acid using 0.5% $Pd(OAc)_2$ in 94% and 93% isolated yields, respectively (Table 5, entries 8 and 9). In comparison, the reaction of 2-chloro-*m*-xylene with *o*-tolyl boronic acid described by Nolan proceeded in 79% isolated yield with 2% of the preformed Pd complex,[5i] while Glorius used 3% Pd and a reaction temperature of 50 °C to give the product in 85% yield.[5h] Although most coupling reactions using 2-substituted boronic acids proceeded at room temperature in excellent yield with aryl chlorides, a reaction temperature of 40 °C was required for certain electron-rich aryl chlorides (Table 5, entries 14-16). This higher temperature is most likely necessary as oxidative addition is much slower for aryl chlorides that possess an electron donation group in the 2- or 4- positions of the arene relative to the chloride. For example, the coupling of very electron rich 2,6-dimethoxychlorobenzene with 2-biphenyl boronic acid proceeded at 40 °C in 99% isolated yield using 0.5% $Pd(OAc)_2$ (Table 5, entry 15).

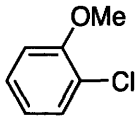
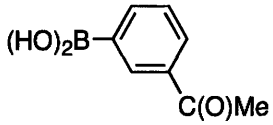
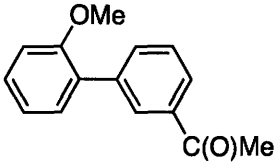
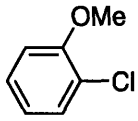
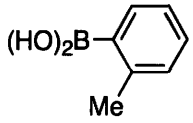
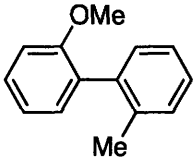
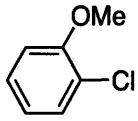
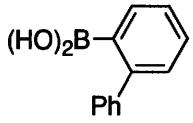
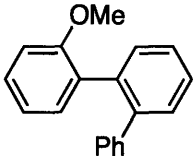
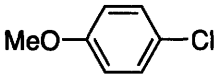
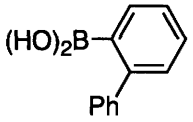
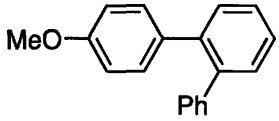
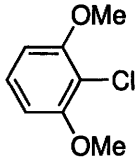
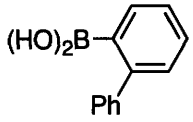
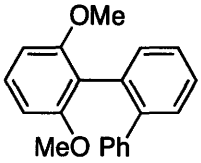
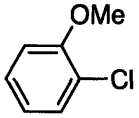
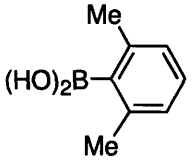
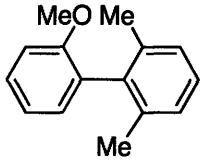
We believe these results illustrate that the primary factor for the efficient Suzuki-Miyaura coupling of unactivated aryl chloride substrates is the ability of biaryl-derived phosphine ligands to maximize the concentration of monoligated palladium species within the catalytic cycle. Ligand **2**, which is nearly isostructural, but substantially less electron-rich than **1**, promotes the reaction of hindered substrates at low temperatures (≤ 40 °C) and relatively low catalyst loadings (down to 0.25 % Pd) in excellent yields. In these studies **1** is superior to **2** as the supporting ligand for all reactions described. As the cost of preparing **2** should be considerably less than that for **1**, **2** may have some advantage for large-scale reactions in cases where the procedure can be optimized to reduce the amount of palladium required. However, in most academic and industrial research laboratories this cost differential is of minimal importance.

Table 5. Suzuki-Miyaura Couplings of Aryl Chlorides at Room Temperature using ligand **2**[a]

Entry	Halide	Boronic Acid	Product	mol% Pd	Yield (%)[b]
1				0.05	94
2				0.05	93
3				0.1	97
4				0.5	97
5				0.5	98[c]
6				0.5	98
7				0.5	98
8				0.5	94
9				0.5	93[c]
10				0.25	99

[a] Reaction conditions: 1 equiv of aryl chloride, 1.5 equiv of boronic acid, 3 equiv. of $K_3PO_4 \cdot H_2O$, THF (1mL/mmol halide), cat $Pd(OAc)_2$, ligand **2**, L:Pd = 3:1. [b] Isolated yield based upon an average of two runs. [c] 3 equiv of boronic acid was used.

Table 5 (cont). Suzuki-Miyaura Couplings of Deactivated Aryl Chlorides using ligand **2**[a]

Entry	Halide	Boronic Acid	Product	mol% Pd	*T* (°C)	Yield (%)[b]
11				0.5	RT	89
12				0.25	RT	97
13				0.25	RT	97
14				0.25	40	93
15				0.5	40	99
16				0.5	40	98[c]

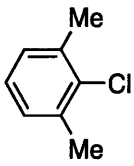
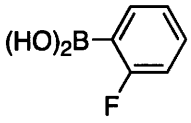
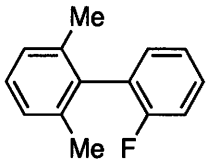
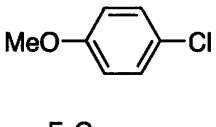
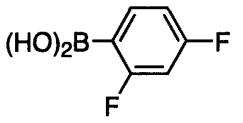
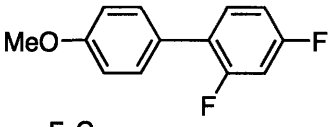
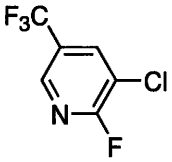
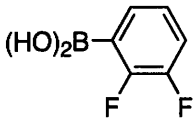
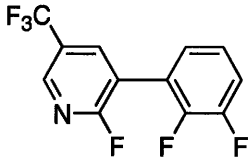
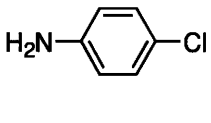
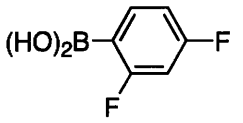
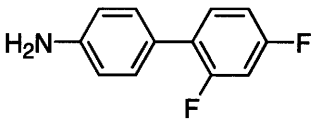
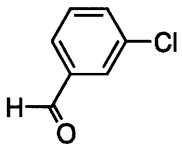
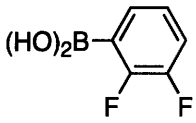
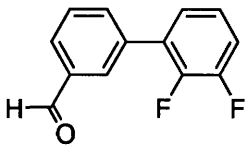
[a] Reaction conditions: 1 equiv of aryl chloride, 1.5 equiv of boronic acid, 3 equiv of $K_3PO_4 \cdot H_2O$, THF (1mL/mmol halide), cat $Pd(OAc)_2$, ligand **2**, L:Pd = 3:1. [b] Isolated yield based upon an average of two runs. [c] 3 equiv of boronic acid was used.

1.1.7 Suzuki-Miyaura Coupling Reactions of Electron-Deficient Aryl Boronic Acids

Our attention next shifted to reactions of mono- and difluoroaryl boronic acids. The interest in the Suzuki-Miyaura coupling of these boronic acids exists, in part, because of the difficulty of coupling electron-poor boronic acids.[23] Fluorinated aromatic rings are often used in medicinally active compounds in which a fluorine is substituted for a hydrogen to help block oxidation of the aromatic ring,[24] alter routes of metabolism,[25] and increase lipophilicity which affects drug distribution.[26] Fortunately, nearly all

combinations of *n*-fluorophenyl boronic acids, where *n*=1 to 5, are commercially available.[27] In spite of the availability of this class of boronic acids, there exist only a few examples of Suzuki-Miyaura coupling reactions, all of which are with aryl bromides or iodides.[28] A particularly challenging example, the coupling of 2,4-difluorophenyl boronic acid with 2,6-dimethylbromobenzene, has previously been reported.[28b] This reaction proceeded in 60% isolated yield; however, a reaction temperature of 130 °C and the use of a non-commercially available ligand were required. In our present work, a wide variety of substrates, including electron-rich, -poor and heterocyclic aryl chlorides, were coupled with fluorophenyl and difluorophenyl boronic acids in very good to excellent yields. Of particular note is the reaction of 4-chloroaniline with 2,4-difluorophenyl boronic acid, which proceeded at 80 °C to give a 96% isolated yield of product (Table 6, entry 4). Although the Suzuki-Miyaura coupling of 4-chloroaniline has been previously reported,[29] all accounts only use phenyl boronic acid as the coupling partner. Hindered aryl chlorides also proved to be excellent coupling partners with 2-fluorophenyl boronic acid (Table 6, entry 1). The reaction with 2-chloro-*m*-xylene gives a 91% isolated yield of product using 0.5 mol% $Pd(OAc)_2$ in only 90 min. Additionally, the coupling of a heteroaryl chloride, 2-fluoro-3-chloro-5-trifluoromethylpyridine, with 2,3-difluorophenyl boronic acid provided a highly fluorinated heteroaromatic compound in 96% isolated yield (Table 6, entry 3). Disappointingly, reactions using 2,6-difluorophenyl boronic acid and 2,4,6-trifluorophenyl boronic acid did not proceed efficiently.

Table 6. Suzuki-Miyaura Couplings of Mono- and Difluorophenyl Boronic Acids Using Ligand 1[a]

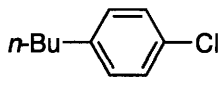
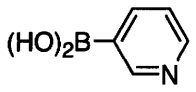
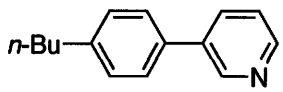
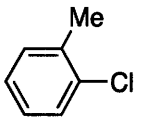
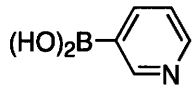
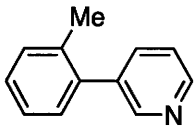
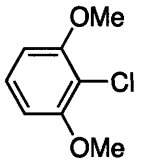
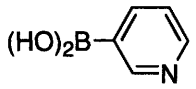
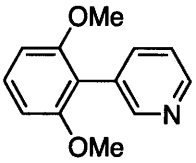
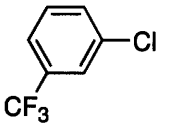
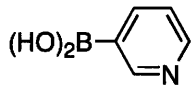
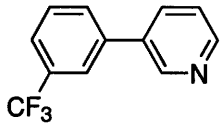
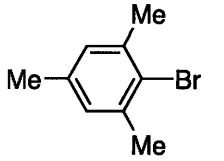
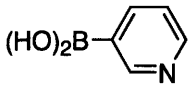
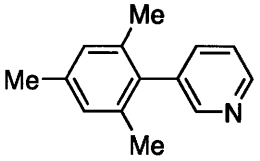
Entry	Halide	Boronic Acid	Product	mol% Pd	Conditions	Yield (%)[b]
1				0.5	90 °C, 1.5 h	91
2				0.5	80 °C, 16 h	99
3				1	90 °C, 16 h	96
4				1	80 °C, 10 h	96
5				0.5	90 °C, 3 h	80

[a] Reaction conditions: 1 equiv of aryl chloride, 1.5 equiv of boronic acid, 2 equiv of K_3PO_4, toluene (2 mL/mol halide), cat $Pd(OAc)_2$, ligand **1**, L:Pd = 2:1. [b] Isolated yield based upon an average of two runs.

We recently reported the coupling of potassium 3-pyridyl trifluoroborate with a variety of aryl- and heteroaryl chlorides using **1**.[30] However, we were unable to efficiently couple this trifluoroborate salt with aryl chlorides possessing one or more *ortho* methyl substituents. Since an improved means for the preparation of 3-pyridyl boronic acid and/or the corrosponding boroxine has been recently reported,[31] the coupling of 3-pyridyl boronic acid with aryl chlorides was attempted. Using conditions similar to what we reported for the coupling of potassium 3-pyridyl trifluoroborate (i.e., 3% $Pd(OAc)_2$, K_2CO_3, ethanol at reflux), low conversion (< 50%) of aryl chloride was observed. However, upon switching from ethanol to 1-butanol and increasing the reaction temperature to 90-100 °C, the coupling of 4-*n*-butylchlorobenzene with 3-pyridyl boronic acid (Table 7, entry 1) produced the desired product in 96% yield. The higher temperature required for the coupling of 3-pyridyl boronic acid is presumably due to the less nucleophilic nature of the boronic acid relative to the trifluoroborate salt.[32] Thus the transmetalation of the ligated

(aryl)PdCl complex is slowed down,[33] which therefore slows down the entire catalytic cycle as transmetalation is usually the rate limiting step for Suzuki-Miyaura couplings. Hindered aryl chlorides,

Table 7. Suzuki-Miyaura Couplings of 3-Pyridyl Boronic Acid Using Ligand **1**[a]

Entry	Halide	Boronic Acid	Product	mol% Pd	Conditions	Yield (%)[b]
1				2	100 °C, 15 h	96
2				2	100°C, 20 h	88
3				3	100 °C, 24 h	81
4				2	90 °C, 24 h	87
5				2	90 °C, 24 h	83

[a] Reaction conditions: 1 equiv of aryl chloride, 1.5 equiv of boronic acid, 2 equiv of K_3PO_4, 1-butanol (2 mL/mmol halide), cat Pd_2dba_3, ligand **1**, L:Pd = 2:1. [b] Isolated yield based upon an average of two runs.

such as 2-chlorotoluene and 2,6-dimethoxychlorobenzene (Table 7, entries 2 and 3) were also excellent coupling partners giving product in isolated yields greater than 80%. The attempted combination of the more hindered 2-chloro-*m*-xylene with 3-pyridyl boronic acid proved to be more difficult and 30% of *m*-xylene, from competitive reduction of the aryl halide, was observed. This limitation could be partially overcome as evidenced by the transformation of 2-bromomesitylene, which could be carried out at 90 °C (Table 7, entry 5). To the best of our knowledge, there are no other examples of the coupling of 3-pyridyl boronic acid with aryl halides possessing an *ortho, ortho'* substitution nor any examples of its successful combination with unactivated aryl chlorides.

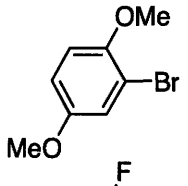
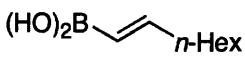
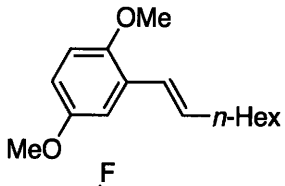
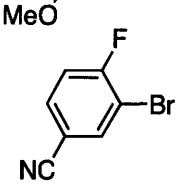
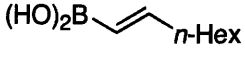
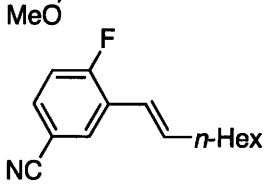
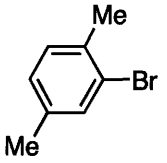
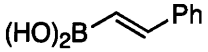
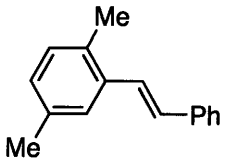
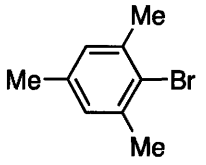
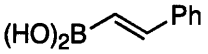
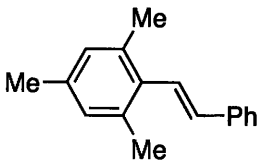
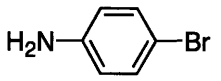
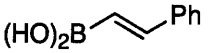
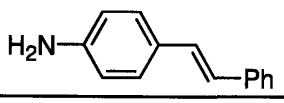
Usually electron-deficient aryl boronic acids (e.g., *n*-fluorophenyl and 3-pyridyl) tend to be difficult coupling partners as they are less nucleophilic and hence, transmetallate more slowly than electron-neutral analogues. Although we have no direct evidence, we believe that the ability of **1** to maximize the concentration of a LPd(aryl)chloride species rather an a L_2Pd(aryl)chloride species is the key for successful coupling of these types of boronic acids. In reactions with poorly nucleophilic aryl boronic acids, transmetalation may well be the rate limiting step in Suzuki-Miyaura coupling reactions. Transmetalation processes are very sensitive to steric factors and should occur much more rapidly to a LPd(aryl)chloride intermediate than to a L'_2Pd(aryl)chloride intermediate, even when L′ is smaller than L. A more detailed discussion on structural features of complexes derived from **1** follows below.

1.1.8 Suzuki-Miyaura Coupling Reactions of Vinyl Boronic Acids

Due to their aforementioned advantages, boronate esters are often the boron reagents of choice for Suzuki-Miyaura coupling reactions. For example, the use of vinyl boronates was recently described in Jacobsen's elegant asymmetric synthesis of quinine,[34] where **1** was utilized in the coupling of an (*E*)-alkenyl pinacol boronate ester with a 4-bromoquinoline derivative in excellent yield. To investigate the generality of **1** in the coupling of vinyl boronate derivatives with aryl halides, we examined the combination of (*E*)-octenyl boronic acid and (*E*)-β-styrene boronic acid with aryl halides. Optimization of reaction conditions proved to be somewhat difficult as reaction at temperatures that we often use (60-100 °C) produced a mixture of *E*- and *Z*-isomers. We found that a reaction temperature of 40 °C was optimal for aryl halide substrates containing an *ortho* substituent and allowed full conversion of aryl halide with no detectable *Z*-isomer. For substrates without an *ortho* substituent as large as methyl, the reactions proceeded at room temperature. For example, 2-fluoro-5-cyanobromobenzene reacted with (*E*)-octenyl boronic acid at room temperature to give product in 97% isolated yield (Table 8, entry 1). However, the coupling of (*E*)-β-styrene boronic acid with 4-bromoaniline also required a reaction temperature of 40 °C, probably due to the very electron-rich nature of the aryl bromide. Aryl bromides possessing an *ortho,ortho′* substitution pattern were also efficient coupling partners as illustrated by the

coupling of 2-bromomesitylene with (*E*)-β-styrene boronic acid (Table 8, entry 4), which proceeded in 99% isolated yield. A similar reaction has been reported by Molander using the potassium trifluoroborate salt of (*E*)-decenyl boronic acid with 2-bromomesitylene.[35] However, under these conditions the product was only isolated in 38% yield. Finally, we attempted to extend these conditions to the coupling of aryl chlorides with vinyl boronic acids; however, reaction temperatures of >40 °C were required to promote full conversion of the aryl chloride and alkene isomerization ensued.

Table 8. Suzuki-Miyaura Couplings of Alkenyl Boronic Acids Using Ligand **1**[a]

Entry	Halide	Boronic Acid	Product	Yield (%)[b]
1				97
2				97[c]
3				98
4				99
5				88

[a] Reaction conditions: 1 equiv of aryl chloride, 1.5 equiv of alkenyl boronic acid, 2 equiv of K_3PO_4, THF (2 mL/mmol halide), 1 % $Pd(OAc)_2$, 2 % ligand **1**, 40 °C, >99:1 trans:cis isomers. [b] Isolated yield based upon an average of two runs. [c] Reaction run at RT.

1.3 Conclusion

In conclusion, we report a new phosphine ligand that that can be used, in combination with a suitable Pd compound to produce a catalyst system which overcomes many of the important limitations in Suzuki-Miyaura coupling processes. Specifically, 2-(2',6'-dimethoxybiphenyl)-dicyclohexylphosphine, **1**,

imparts unprecedented activity in the coupling of extremely hindered aryl boronic acids and aryl halides. Additionally, the coupling of boronic acids with aryl bromides and chlorides can be conducted in excellent yields with only 5 and 30 ppm Pd, respectively. Heterocyclic, electron-deficient and vinyl boronic acids can be coupled with a wide variety of aryl- and heteroaryl chlorides and bromides at minimal catalyst loadings using **1**. This ligand is an air stable crystalline solid which allows for extremely simple and rapid reaction setup. The wide scope and high reactivity that this ligand engenders in Suzuki-Miyaura coupling procesess is unprecedented.

1.4 Experimental

1.4.1 General

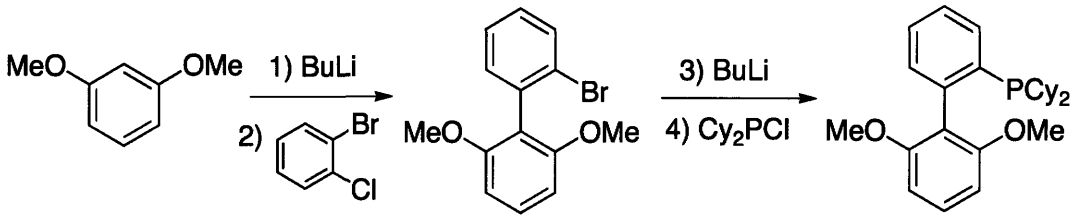
All reactions were carried out under an argon or nitrogen atmosphere, unless otherwise noted. Elemental analyses were performed by Atlantic Microlabs Inc., Norcross, GA. Unless otherwise noted, THF, Et_2O, CH_2Cl_2 and toluene were purchased from J.T. Baker in CYCLE-TAINER® solvent-delivery kegs and vigorously purged with argon for 2 h. The solvents were further purified by passing them under argon pressure through two packed columns of neutral alumina (for THF and Et_2O) or through neutral alumina and copper (II) oxide (for toluene and CH_2Cl_2).[36] Unless otherwise stated, commercially obtained materials were used without further purification. Aryl halides were purchased from Aldrich Chemical Co. Aryl halides were purified by filtration through a thin pad of basic alumina prior to use. $Pd(OAc)_2$ was purchased from Strem, Inc. or supplied by Englehard. Boronic acids were purchased from Aldrich Chemical Co., Alfa Aesar or Frontier Scientific, Inc. Best results were obtained with newly purchased or freshly recrystallized boronic acids. Alkyl boranes were prepared by the reaction of 9-BBN with the requisite alkene in THF at room temperature for 4 h and were used without isolation. Magnesium powder, -50 mesh, (99 %) and 1,2-dibromoethane (99+%) were purchased from Aldrich. 1-Bromo-2,4,6-triisopropylbenzene (95 %) and 2-bromochlorobenzene (99 %) were purchased from Alfa Aesar. Anhydrous CuCl (97 %) was purchased from Strem and stored in a nitrogen-filled glove box. $ClPCy_2$ and $ClPPh_2$ was also purchased from Strem and stored under argon. *Anhydrous tribasic potassium phosphate was purchased from Fluka Chemical Co. and used as supplied. Tribasic potassium phosphate*

monohydrate was purchased from Fluka Chemical Co. and was finely ground (using a mortar and pestle) prior to use. The source (and thus the particle size) of the base employed may be critical for achieving efficient reactions.

All new compounds were characterized by ^{1}H NMR, ^{13}C NMR, and IR spectroscopy, in addition to elemental analysis (Atlantic Microlabs, Inc) and/or low resolution mass spectroscopy. For those new compounds for which a satisfactory elemental analysis was not obtained, copies of the ^{1}H and ^{13}C NMR are attached Nuclear Magnetic Resonance spectra were recorded on a Varian Mercury 300, a Varian Unity 300 or 500, or a Bruker 400 instrument. Infrared spectra were recorded on an ASI Applied Systems ReactIR 1000 (neat samples were placed directly on the DiComp probe). All ^{1}H NMR experiments are reported in δ units, parts per million (ppm) downfield from tetramethylsilane (internal standard) and were measured relative to the signals for residual chloroform (7.26 ppm), methylene chloride (5.32 ppm) or benzene (7.16 ppm) in the deuterated solvents. All ^{13}C NMR spectra are reported in ppm relative to deuterochloroform (77.23 ppm), deuteromethylene chloride (54.00 ppm) or deuterobenzene (128.39 ppm), and all were obtained with ^{1}H decoupling. All ^{31}P NMR spectra are reported in ppm relative to H_3PO_4 (0 ppm). All ^{19}F NMR spectra are reported in ppm relative to trichlorofluoromethane (0 ppm). Melting points (uncorrected) were obtained on a Mel-Temp capillary melting point apparatus. Gas Chromatographic analyses were performed on a Hewlett-Packard 6890 gas chromatography instrument with an FID detector using 25m x 0.20 mm capillary column with cross-linked methyl siloxane as a stationary phase.

The yields in Tables 1-8 refer to isolated yields (average of two runs) of compounds estimated to be ≥95% pure as determined by ^{1}H NMR and GC analysis and/or combustion analysis. The procedures described in this section are representative, and thus the yields may differ from those shown in Tables 1-8.

1.4.2 Preparation of 2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl [S-PHOS (1)]



1

To a cold (0 °C), stirred solution of 1,3-dimethoxybenzene (2.00 mL, 15.3 mmol, 1.1 equiv.) in dry THF (35 mL) was added *n*-BuLi (6.20 mL, 2.5 M solution in hexanes, 15.5 mmol, 1.1 equiv.) dropwise via syringe over 5 min. The reaction mixture was allowed to warm to room temperature and then stirred at room temperature for 3.5 h. The mixture was re-cooled to 0 °C and neat 2-bromochlorobenzene (1.60 mL, 13.7 mmol, 1.0 equiv) was added dropwise via syringe over 15 min with vigorous stirring. The resulting burgundy colored mixture was stirred at 0 °C for an additional 15 min. At this point, GC analysis of an aliquot of the reaction mixture, quenched into ether/water, indicated that complete consumption of the bromochlorobenzene starting material and clean conversion to 2-bromo-2',6'-dimethoxybiphenyl had occurred. The reaction mixture was cooled to -78 °C and *n*-BuLi (6.20 mL, 2.5 M solution in hexanes, 15.5 mmol, 1.1 equiv.) was added dropwise via syringe over 5 min. The resulting mixture was stirred at -78 °C (periodic swirling of the reaction flask by hand was required as stirring with a magnetic stirrer became difficult) for 30 min. Neat chlorodicyclohexylphosphine (3.03 mL, 13.7 mmol, 1.0 equiv) was then added via syringe. The reaction mixture was stirred at -78 °C for 1 h and then allowed to slowly warm to room temperature. The resulting mixture was filtered through a pad of flash silica gel topped with a layer of celite, eluting with ethyl acetate (400 mL). The filtrate was concentrated under reduced pressure to provide a yellow solid. Recrystallization from acetone provided 2.90 g of **1** as a white solid. Concentration of the mother liquor followed by trituration of the residue thus obtained with methanol, provided additional solid material. This material was recrystallized from acetone to afford a further 0.42 g of the title compound. The overall yield of **1** was 3.32 g (59%), a white solid, mp 162-162.5 °C. ^{1}H NMR (300 MHz, C_6D_6) δ: 7.59 (dm, *J* for the doublet = 7.2 Hz, 1H), 7.39-7.42 (m, 1H), 7.15-7.25 (m, 3H), 6.43 (d, *J* = 8.5 Hz, 2H), 3.33 (s, 6H), 1.60-1.94 (m, 12H), 1.06-1.36 (m, 10 H). ^{13}C NMR (75 MHz, C_6D_6) δ:

158.49, 158.48, 144.3, 143.9, 137.3, 137.0, 132.82, 132.77, 132.4, 132.3, 129.2, 128.82, 128.81, 128.2, 126.8, 121.2, 121.1, 104.0, 55.2, 35.0, 34.8, 31.0, 30.8, 30.3, 30.1, 28.22, 28.15, 28.07, 28.05, 27.40, 27.39 (observed complexity due to P-C splitting; definitive assignments have not yet been made). ^{31}P NMR (121 MHz, C_6D_6) δ: −8.6. IR (neat, cm^{-1}): 2921, 2848, 1588, 1470, 1459, 1430, 1245, 1109, 909, 722. Anal. Calcd for $C_{26}H_{35}O_2P$: C, 76.07; H, 8.59. Found: C, 75.97; H, 8.61.

1.4.3 Preparation of 2-Bromo-2',6'-dimethoxybiphenyl

To a cold (0 °C), stirred solution of 1,3-dimethoxybenzene (2.00 mL, 15.3 mmol, 1.2 equiv.) in dry THF (30 mL) was added *n*-BuLi (9.60 mL, 1.6 M solution in hexanes, 15.4 mmol, 1.2 equiv.) dropwise via syringe over 5 min. The reaction mixture was allowed to warm to room temperature and then stirred at room temperature for 5 h. The mixture was recooled to 0 °C and neat 2-bromochlorobenzene (1.50 mL, 12.8 mmol, 1.0 equiv) was added dropwise via syringe over 15 min with vigorous stirring. The resulting burgundy colored mixture was stirred at 0 °C for an additional 15 min. Methanol (0.25 mL) was added via syringe and the resulting mixture was concentrated under reduced pressure. To the residue so obtained was added diethyl ether (50 mL) and water (50 mL). The layers were separated and the aqueous phase was extracted with diethyl ether (2 x 25 mL). The combined organic extracts were washed with brine (1 x 20 mL), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to provide a yellow solid. The crude product was recrystallized from methanol to afford the title compound (3.03 g, 81% yield) as a pale yellow solid, mp = 141-142 °C. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.69 (dd, J = 6.9, 1.1 Hz, 1H), 7.34-7.40 (m, 2H), 7.20-7.28 (m, 2H), 6.68 (d, J = 8.5 Hz, 2H), 3.76 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 157.8, 136.25, 132.52, 132.47, 129.6, 128.8, 127.1, 125.4, 119.0, 104.2, 56.2. IR (neat, cm^{-1}): 2946, 1584, 1472, 1432, 1248, 1108, 1025, 783. Anal. Calcd for $C_{15}H_{25}NO$: C, 57.36; H, 4.47. Found: C, 57.11; H, 4.47.

1.4.4 Preparation of 2,4,6-Triisopropyl-2'-diphenylylphosphinobiphenyl (2)

A flame dried 100 mL, 3 neck, round bottom flask equipped with a Teflon coated magnetic stir bar, reflux condenser, glass stopper, gas inlet adapter and rubber septum was purged with argon and charged with Mg powder, -50 mesh (0.58 g, 24.0 mmol), THF (13 mL) and 2,4,6-triisopropylbromobenzene (2.51 mL,

10.0 mmol). While stirring vigorously under argon, the reaction mixture was then heated to 65 °C in an oil bath and 1,2-dibromoethane (40 μL) was added dropwise via syringe to initiate the reaction. After 40 – 60 min, Grignard formation was complete as judged by G.C. analysis, and 2-bromochlorobenzene (1.3 mL, 11.0 mmol) was added at 65 °C over 1.1 h with the aid of a syringe pump. After an additional 1 h of stirring at 65 °C, the reaction mixture was cooled to room temperature. Then, anhydrous CuCl (0.05 g, 0.5 mmol) was weighed out in a nitrogen-filled glove box and removed from the glove box prior to its addition by removing the septum and adding the CuCl as rapidly as possible. To this, $ClPPh_2$ (1.85 mL, 10 mmol) was then added via syringe; the addition was preformed in a dropwise manner to control the exotherm (Caution!). The resulting mixture was stirred at room temperature for 25 h. The reaction mixture was then placed in an ice bath (as a precaution) prior to quenching with methanol (2 mL). The mixture was transferred to a 500 mL round bottom flask and diluted with ethyl acetate (200 mL), stirred for 15 min, concentrated to one third its original volume in *vacuo* and filtered by gravity through a pad of celite eluting with additional portions of ethyl acetate (400 mL). The solvent was removed from the combined organic layers and the crude product was dissolved in a minimal amount of diethyl ether via sonication. An equal volume of methanol was then added to the homogeneous solution, the flask was sealed and the solution was allowed to stand in a refrigerator (-40 °C) for 24 h. The resulting crystals (2.6 g, 56 %) were collected via vacuum filtration and washed with ice-cold diethyl ether. A second crop of crystals was harvested from the mother liquor using the same procedure that was used to obtain the first crop. The resulting crystals (0.72 g) were collected via vacuum filtration and washed with cold diethyl ether. The crops of crystals were then combined and dried under vacuum for 24 h, yielding 3.3 g of **2** (7.1 mmol, 71 %) as a white crystalline solid, m.p. = 136 - 138 °C. (This procedure has been scaled to 50 mmol providing 14.4 g, 31 mmol, 62 %). ^{1}H NMR (300 MHz, C_6D_6) δ: 7.39 (ddd, J = 7.4, 3.3, 1.1 Hz, 1H), 7.23 – 7.35 (m, 5H), 7.20 (s, 2H), 7.12 (td, J = 7.4, 1.4 Hz), 6.98 – 7.08 (m, 7H), 2.85 (septet, J = 6.9 Hz, 1H), 2.72 (septet, J = 6.6 Hz, 2H), 1.24 (d, J = 6.9 Hz, 6H), 1.14 (d, J = 6.9 Hz, 6H), 1.07 (d, J = 6.9 Hz, 6H). ^{13}C NMR (75 MHz, $C_2D_2Cl_2$) δ: 148.7, 148.2, 147.8, 147.2, 138.4, 138.2, 137.3, 137.1, 136.9, 136.8, 135.9, 134.1, 133.9, 131.6, 131.5, 129.3, 129.0, 128.9, 128.8, 127.6, 121.0, 34.7, 31.3, 25.7, 24.4,

22.7 (observed complexity due to P-C splitting; definitive assignments have not yet been made). ^{31}P NMR (121 MHz, C_6D_6) δ: −17.5. IR (neat, cm^{-1}): 3059, 2958, 2873, 1607, 1460, 1430, 1383, 1313, 1074, 1004. Anal. Calcd for $C_{33}H_{37}P$: C, 85.31; H, 8.03. Found: C, 85.02; H, 8.03. (Pumping on high vacuum at 140 °C for 5 h was required to remove trace solvent trapped in the crystals)

1.4.5 General Procedure A: Pd-Catalyzed Suzuki-Miyaura Coupling of Aryl Halides with Aryl Boronic Acids

An oven-dried resealable Schlenk tube containing a magnetic stir bar was charged with $Pd(OAc)_2$ (2.2 mg, 1.0 mol%), **1** (8.2 mg, 2.0 mol%), the boronic acid (1.5 mmol, 1.5 equiv.) and powdered, anhydrous K_3PO_4 (424 mg, 2.0 mmol, 2.0 equiv.). The Schlenk tube was capped with a rubber septum and then evacuated and backfilled with argon (this sequence was repeated three times). Dry toluene (2.0 mL) was added through the septum via syringe and the resulting mixture was stirred at room temperature for ~2 min. The aryl halide (1.0 mmol, 1.0 equiv.) was added dropwise via syringe (aryl halides which were solids at room temperature were added during the initial charge, prior to the evacuation/backfill cycles). The septum was replaced with a Teflon screwcap and the Schlenk tube was sealed. The reaction mixture was heated at 100 °C with vigorous stirring until the aryl halide had been completely consumed as judged by GC analysis. The reaction mixture was then allowed to cool to room temperature, diluted with diethyl ether (10 mL), filtered through a thin pad of silica gel (eluting with diethyl ether) and concentrated under reduced pressure. The crude material obtained was purified by flash chromatography on silica gel.

For reactions conducted at low catalyst loadings (≤0.1 mol% Pd) the general procedure was followed with the following modification: A separate vial was charged with $Pd(OAc)_2$ (1 mol%) and ligand **1** (2 mol%). The vial was sealed with a Teflon coated screwcap, a needle was inserted through the cap and the vial was then evacuated and backfilled with argon (this sequence was repeated three times). Dry THF (1 mL) was added and the mixture was sonicated for ~1 min to afford a homogeneous solution. 100 μL of this solution (0.1% Pd, 0.2% ligand **1**) was removed via syringe and then added to the Schlenk flask containing the base and boronic acid.

1.4.5 General Procedure B: Pd-Catalyzed Suzuki-Miyaura Coupling of Aryl Halides with Alkylboranes or Alkylboronic acids

Procedure A was used with the following modifications: an alkyl boronic acid or an alkyl borane was used in place of an aryl boronic acid and $K_3PO_4 \bullet H_2O$ was used in lieu of anhydrous K_3PO_4.

1.4.6 General Procedure C: Pd-Catalyzed Suzuki-Miyaura Coupling of Hindered Aryl Halides with Aryl Boronic Acids

Procedure A was used with $Pd_2(dba)_3$ (18 mg, 4.0 mol% Pd) and **1** (33 mg, 8 mol%), and with 3 equiv. of anhydrous K_3PO_4 (636 mg, 3.0 mmol). The reaction temperature was 100-110 °C (as indicated).

1.4.7 General Procedure D: Pd-Catalyzed Suzuki-Miyaura Coupling of Aryl Chlorides with Aryl Boronic Acids at Room Temperature

Procedure A was used with the following changes: a 16 x 100 mm culture tube fitted with a rubber septum was used in place of a Schlenk tube, and the reaction were conducted in THF under nitrogen. Also, for the indicated cases, degassed water (10 μL/mmol halide) was added and the mixture was stirred for ~10 min prior to the addition of the aryl halide

1.4.8 General Procedure E: Pd-Catalyzed Suzuki-Miyaura Coupling of Aryl Chlorides with Aryl Boronate Esters

A screw-cap test tube containing a magnetic stir bar was charged with $Pd(OAc)_2$ (2.2 mg, 1.0 mol%), **1** (8.2 mg, 2.0 mol%), the aryl boronate ester (1.5 mmol, 1.5 equiv.) and K_3PO_4 (424 mg, 2.0 mmol, 2.0 equiv.). The tube was capped with a rubber septum and then evacuated and backfilled with argon (this sequence was repeated three times). Deionized water (200 μL, sparged with argon for 10 min prior to use) and dry toluene (2.0 mL) and were added sequentially via syringe through the septum and the resulting mixture was stirred at room temperature for ~2 min. The aryl halide (1.0 mmol, 1.0 equiv.) was added dropwise via syringe through the septum (solid aryl halides can be added to the test tube during the initial charge). The septum was replaced with a teflon-coated screwcap and the test tube was sealed. The reaction mixture was heated at 100 °C with vigorous magnetic stirring until the aryl halide had been completely consumed as judged by GC analysis (0.5-12 h). The reaction mixture was then allowed to cool

to room temperature, diluted with diethyl ether (10 mL), filtered through a thin pad of silica gel (eluting with diethyl ether) and concentrated under reduced pressure. The crude material obtained was purified by flash chromatography on silica gel.

1.4.9 General Procedure F: Pd-Catalyzed Suzuki-Miyaura Coupling of Aryl Chlorides with Aryl Boronate Esters at Room Temperature

Procedure E was used with the following modification: Dry THF (2.0 mL) was used instead of toluene.

1.4.10 General Proceure G: Pd-Catalyzed Suzuki-Miyaura Couplings of Vinyl Boronic Acids

A screw-cap test tube containing a magnetic stir bar was charged with $Pd(OAc)_2$ (2.2 mg, 1.0 mol%), **1** (8.2 mg, 2 mol%), the boronic acid (1.5 mmol, 1.5 equiv.) and K_3PO_4 (424 mg, 2.0 mmol, 2.0 equiv.). The tube was sealed with a teflon-coated screw cap and then evacuated and backfilled with argon through an 18 gauge needle (this sequence was repeated three times). The aryl halide (1.0 mmol, 1.0 equiv.) and dry THF (2.0 mL) were added sequentially via syringe through the septum. The screwcap was quickly replaced with a non-punctured teflon-coated screwcap. The reaction mixture was vigorously stirred at 40 °C or room temperature until the aryl halide had been completely consumed as judged by GC analysis (12-24 h). The reaction mixture was then diluted with ethyl acetate (10 mL), filtered through a thin pad of silica gel (eluting with ethyl acetate) and concentrated under reduced pressure. The crude material obtained was purified by flash chromatography on silica gel.

1.4.11 General Procedure H: Pd-Catalyzed Suzuki-Miyaura Coupling of 3-Pyridyl Boronic Acid

Procedure G was used with the following modifications: $Pd_2(dba)_3$ was used instead of $Pd(OAc)_2$, *n*-BuOH (2.0 mL) was used instead of THF, and the reaction mixture was heated to either 90 or 100 °C.

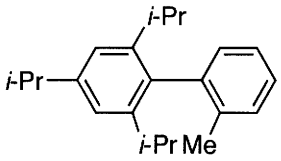
1.4.12 General Procedure I: Pd-Catalyzed Suzuki-Miyaura Couplings of n-Fluorophenyl Boronic Acids

Procedure G was used with the following modification: The reaction mixture was heated to either 80 or 90 °C.

1.4.13 General Procedure J: Pd-Catalyzed Suzuki-Miyaura Coupling of Aryl Chlorides with Aryl Boronic Acids at Room Temperature using Ligand 2

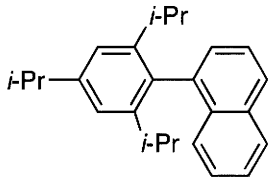
An oven dried 4 mL vial containing a magnetic stir bar was equipped with an open top phenolic screwcap preassembled with a securely seated septum, evacuated while hot, backfilled with nitrogen gas and cooled under nitrogen. The vial was then charged with $Pd(OAc)_2$ (13.5 mg, 0.06 mmol) and **2** (83.6 mg, 0.18 mmol). The vial was then evacuated and backfilled with nitrogen gas (this sequence was repeated three times). Then, dry THF (3 mL) was added via syringe and the catalyst stock solution was allowed to stir for ~30 min. An oven-dried resealable Schlenk tube containing a magnetic stir bar was equipped with a Teflon coated screwcap, evacuated while hot, backfilled with nitrogen gas and cooled under nitrogen. The tube was then charged with the boronic acid (1.5 mmol, 1.5 equiv.) and powdered $K_3PO_4 \bullet H_2O$ (691 mg, 3.0 mmol, 3.0 equiv.). The Schlenk tube was capped with a rubber septum and then evacuated and backfilled with nitrogen gas (this sequence was repeated three times). All liquid reagents were added: the aryl chloride (1.0 mmol, 1.0 equiv.) was added dropwise via syringe (aryl halides which were solids at room temperature were added during the initial charge, prior to the evacuation/backfill cycles), catalyst stock solution (250 μL, 0.5 mol % Pd, 1.5 mol % **2**) was added via micro syringe and dry THF (2 mL) was added via syringe. The septum was replaced with a Teflon screwcap and the Schlenk tube was sealed. The reaction mixture was maintained at room temperature with vigorous stirring until the aryl halide had been completely consumed as judged by GC analysis. The reaction mixture was then diluted with ethyl acetate (10 mL), filtered through a pad of Celite (eluting with ethyl acetate) and concentrated under reduced pressure. The crude material obtained was purified by flash chromatography on silica gel.

1.4.14 Analysis and Characterization

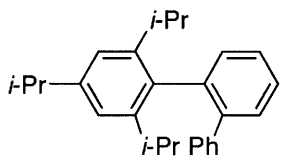


2,4,6-Triisopropyl-2'-methylbiphenyl (Table 1, entry 1) (0.1% Pd). Following general procedure C, a mixture of 2,4,6-triisopropylbromobenzene (251 μL, 1.0 mmol), 2-methyl phenyl boronic acid (272 mg, 2.0 mmol), K_3PO_4 (637 mg 3.0 mmol) and 200 μL of a catalyst solution composed of $Pd_2(dba)_3$ (4.6 mg, 0.005 mmol), **1** (8.2 mg, 0.02 mmol),and THF (2.0 mL) was heated at 100 °C in toluene (2.0 mL) for 24

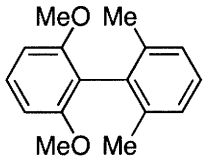
h. The crude product was purified by flash chromatography on silica gel (hexane) to provide the title compound as a white solid (279 mg, 95%), mp 95.5-96.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.13-7.27 (m, 4H), 7.05-7.08 (m, 2H), 2.94 (septet, J = 6.9 Hz, 1H), 2.44 (septet, J = 6.9 Hz, 2H), 1.99 (s, 3H), 1.31 (d, J = 6.9 Hz, 6H), 1.11 (d, J = 6.9 Hz, 6H), 1.03 (d, J = 6.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 147.9, 146.3, 140.6, 136.9, 136.0, 130.3, 129.8, 127.0, 125.6, 120.8, 34.4, 30.5, 25.1, 24.3, 23.7, 20.5. IR (neat, cm^{-1}): 2962, 2869, 1607, 1461, 1362, 1057, 1007. Anal. Calcd for $C_{22}H_{30}$: C, 89.73; H, 10.27. Found: C, 89.61; H, 10.42.



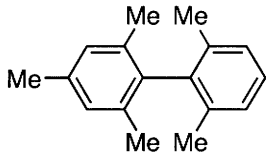
1-(2,4,6-Triisopropylphenyl)naphthalene (Table 1, entry 2) (0.1% Pd). Following general procedure C, a mixture of 2,4,6-triisopropylbromobenzene (251 μL, 1.0 mmol), 1-naphthyl boronic acid (344 mg, 2.0 mmol), K_3PO_4 (637 mg 3.0 mmol) and 200 μL of a catalyst solution composed of $Pd_2(dba)_3$ (4.6 mg, 0.005 mmol), **1** (8.2 mg, 0.02 mmol),and THF (2.0 mL) was heated at 100 °C in toluene (2.0 mL) for 12 h. The crude product was purified by flash chromatography on silica gel (hexane) to provide the title compound as a white solid (324 mg, 98%), mp 169-170 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.92 (d, J = 8.3 Hz, 1H), 7.89 (d, J = 8.3 Hz 1H), 7.30-7.56 (m, 5H), 7.15 (s, 2H), 3.03 (septet, J = 6.9 Hz, 1H), 2.36 (septet, J = 6.9 Hz, 2H), 1.38 (d, J = 6.9 Hz, 6H), 1.06 (d, J = 6.9 Hz , 6H), 0.97 (d, J = 6.9 Hz , 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 148.4, 147.5, 138.8, 134.6, 133.6, 133.5, 128.3, 127.5, 127.2, 126.7, 125.94, 125.85, 125.5, 120.9, 34.5, 30.8, 25.0, 24.4, 24.1. IR (neat, cm^{-1}): 3041, 2960, 2869, 1461, 1071, 907. Anal. Calcd for $C_{22}H_{30}$: C, 90.85 ; H, 9.15. Found: C, 90.96; H, 9.21.



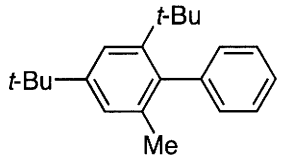
2,4,6-Triisopropyl[1,1';2',1'']terphenyl (Table 1, entry 3). Following general procedure C, a mixture of 2,4,6-triisopropylbromobenzene (251 μL, 1.0 mmol), $Pd_2(dba)_3$ (13.9 mg, 0.015 mmol), **1** (24.6 mg, 0.06 mmol), 2-biphenyl boronic acid (396 mg, 2.0 mmol) and K_3PO_4 (637 mg, 3.0 mmol) in toluene (2.0 mL) was heated at 100 °C with vigorous stirring for 20 h. The crude product was purified by flash chromatography on silica gel (hexane) to provide the title compound as a white solid (333 mg, 93%), mp 140-141.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33-7.52 (m, 3H), 7.23 (dd, J = 7.5, 1.3 Hz, 1H), 7.06-7.14 (m, 5H), 6.91 (s, 2H), 2.88 (septet, J = 6.8 Hz, 1H), 2.55 (septet, J = 6.8 Hz, 2H), 1.26 (d, J = 6.8 Hz, 6H), 1.03 (d, J = 6.8 Hz, 6H), 0.86 (d, J = 6.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.1, 146.4, 141.4, 139.0, 135.8, 131.5, 129.9, 129.6, 127.7, 127.5, 126.9, 126.6, 120.7, 34.4, 30.6, 25.7, 24.3, 23.0. IR (neat, cm^{-1}): 2958, 2869, 1463, 1382, 1007, 911. Anal. Calcd for $C_{27}H_{32}$: C, 90.95; H, 9.05. Found: C, 90.83; H, 9.17.



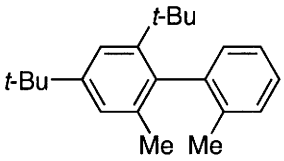
2,6-Dimethoxy-2',6'-dimethylbiphenyl (Table 1, entry 4). Following general procedure C, a mixture of 2-bromo-1,3-dimethoxybenzene (217 mg, 1.0 mmol), $Pd_2(dba)_3$ (13.9 mg, 0.015 mmol), **1** (24.6 mg, 0.06 mmol), 2,6-dimethylphenyl boronic acid (300 mg, 2.0 mmol) and K_3PO_4 (637 mg, 3.0 mmol) in toluene (2.0 mL) was heated at 100 °C with vigorous stirring for 10 h. The crude product was purified by flash chromatography on silica gel (95:5 hexane:diethyl ether) to provide the title compound as a white solid (213 mg, 88%), mp 107-109 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.26-7.36 (m, 1H), 7.09-7.18 (m, 3H), (dm, J for the d = 8.3 Hz, 2H), 3.77 (s, 6H), 2.01 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.6, 137.3, 134.3, 128.9, 127.3, 127.0, 117.7, 104.1, 55.9, 20.3. IR (neat, cm^{-1}): 3012, 2958, 2838, 1590, 1468, 1432, 1283, 1246, 1108. 1003. Anal. Calcd for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49. Found: C, 79.15; H, 7.45.



2,2',4,6,6'-Pentamethylbiphenyl[37] **(Table 1, entry 5).** Following general procedure C, a mixture of 2-bromomesitylene (199 mg, 1.0 mmol), $Pd_2(dba)_3$ (18 mg, 0.020 mmol), **1** (33 mg, 0.08 mmol), 2,6-dimethylphenyl boronic acid (300 mg, 2.0 mmol) and K_3PO_4 (849 mg 4.0 mmol) in toluene (2.0 mL) was heated at 110 °C with vigorous stirring for 10 h. The crude product was purified by flash chromatography on silica gel (hexane) to provide the title compound as a colorless oil (184 mg, 82%). The spectra were in agreement with those described in the literature.

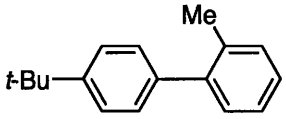


4,6-Di-*tert*-butyl-2-methylbiphenyl (Table 1, entry 6). Following general procedure C, a mixture of 2-Bromo-1,5-di-*tert*-butyl-3-methyl-benzene (59 mg, 0.21 mmol), $Pd_2(dba)_3$ (4.8 mg, 0.053 mmol), **1** (8.6 mg, 0.021 mmol), phenyl boronic acid (51 mg, 0.41 mmol) and K_3PO_4 (177 mg, 0.84 mmol) in toluene (1.0 mL) was heated at 110 °C with vigorous stirring for 18 h. The crude product was purified by flash chromatography on silica gel (hexane) to provide the title compound as a colorless oil (50 mg, 85%). ^1H NMR (300 MHz, $CDCl_3$) δ: 7.03-7.52 (m, 7H), 1.85 (s, 3H), 1.37 (s, 9H), 1.17 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 149.3, 147,3, 143.5, 138.7, 137.3, 131.1, 127.8, 126.5, 124.6, 121.7, 37.1, 34.8, 33.1, 31.7, 22.4. IR (neat, cm^{-1}): 3061, 2967, 2866, 1604, 1478, 1362, 1236, 1009. Anal. Calcd for $C_{21}H_{28}$: C, 89.94; H, 10.06. Found: C, 89.78; H, 10.17.

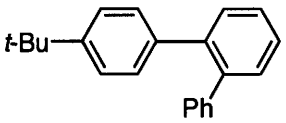


4,6-Di-*tert*-butyl-2,2'-dimethyl-biphenyl (Table 1, entry 7). Following general procedure C, a mixture of 2-Bromo-1,5-di-*tert*-butyl-3-methyl-benzene (59 mg, 0.21 mmol), $Pd_2(dba)_3$ (4.8 mg, 0.053 mmol), **1** (8.6 mg, 0.021 mmol), 2-methylphenyl boronic acid (57 mg, 0.41 mmol) and K_3PO_4 (177 mg, 0.84 mmol) in toluene (1.0 mL) was heated at 110 °C with vigorous stirring for 18 h. The crude product was purified by flash chromatography on silica gel (hexane) to provide the title compound as a colorless oil (55 mg,

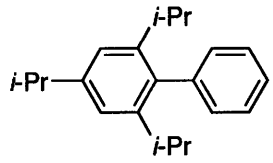
89%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.44 (d, J = 1.9 Hz, 1H), 7.09-7.28 (m, 5 H), 1.98 (s, 3H), 1.78 (s, 3H), 1.37 (s, 9H), 1.15 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 149.1, 146.7, 143.0, 137.3, 137.1, 136.6, 131.0, 129.9, 126.9, 125.3, 124.7, 122.2, 37.1, 34.8, 32.5, 31.7, 21.7, 20.5. IR (neat, cm^{-1}): 3060, 2964, 2868, 1604, 1479, 1361, 1236, 1004. Anal. Calcd for $C_{22}H_{30}$: C, 89.73; H, 10.27. Found: C, 89.50; H, 10.37.



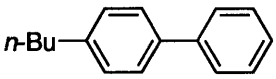
4-*t*-butyl-2'-methylbiphenyl[38] (Table 3, entry 1) (0.0005% Pd). Following general procedure A, a mixture of 4-*tert*-butylbromobenzene (173 μL, 1.0 mmol), 2-methylphenyl boronic acid (204 mg, 1.5 mmol), K_3PO_4 (424 mg, 2.0 mmol) and 4 μL of a catalyst solution composed of $Pd(OAc)_2$ (1.1 mg, 0.005 mmol), **1** (5.2 mg, 0.01 mmol) and THF (4.0 mL) in toluene (3.0 mL) was heated at 100 °C for 24 h. The crude product was purified by flash chromatography on silica gel (hexane) to provide the title compound as a colorless oil (202 mg, 90%). The spectra were in agreement with those described in the literature.



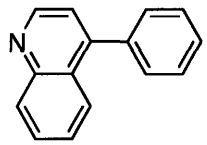
2-(4-*t*-Butylphenyl)biphenyl (Table 3, entry 2) (0.001% Pd). Following general procedure A, a mixture of 4-*tert*-butylbromobenzene (173 μL, 1.0 mmol), 2-biphenylboronic acid (297 mg, 1.5 mmol), K_3PO_4 (424 mg, 2.0 mmol) and 8 μL of a catalyst solution composed of $Pd(OAc)_2$ (1.1 mg, 0.005 mmol), **1** (5.2 mg, 0.01 mmol) and THF (4.0 mL) in toluene (3.0 mL) was heated at 100 °C for 24 h. The crude product was purified by flash chromatography on silica gel (hexane) to provide the title compound as a white solid (276 mg, 96%), mp 55-56 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.48-7.41 (m, 5H), 7.29-7.09 (m, 8H), 1.33 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 149.5, 141.9, 140.7, 140.6, 138.6, 130.9, 130.8, 130.1, 129.7, 128.0, 127.6, 127.4, 126.6, 125.0, 34.6, 31.6. IR (neat, cm^{-1}): 3066, 2988, 1476, 1422, 1266, 896.



2,4,6-Triisopropylbiphenyl (Table 3, entry 3). Following general procedure A, a mixture of 2,4,6-triisopropylbromobenzene (251 μL, 1.0 mmol), phenyl boronic acid (183 mg, 1.5 mmol) and K_3PO_4 (424 mg, 2.0 mmol) and 20 μL of a catalyst solution composed of Pd_2dba_3 (4.6 mg, 0.005 mmol), **1** (8.2 mg, 0.02 mmol) and THF (2.0 mL) in toluene (2.0 mL) was heated at 100 °C with vigorous stirring for 16 h. The crude product was purified by flash chromatography on silica gel (hexane) to provide the title compound as a white solid (278 mg, 99%), mp 120-121 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.32-7.44 (m, 3H), 7.19-7.23 (m, 2H), 7.08 (s, 2H), 2.97 (septet, J = 6.9 Hz, 1H), 2.62 (septet, J = 6.9 Hz, 2H), 1.33 (d, J = 6.9 Hz, 6H), 1.10 (d, J = 6.9 Hz, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 148.0, 146.7, 141.1, 137.3, 130.0, 128.1, 126.6, 120.7, 34.5, 30.5, 24.4, 24.3. IR (neat, cm^{-1}): 2960, 2929, 2867, 1609, 1459, 1362, 1069. Anal. Calcd for $C_{21}H_{28}$: C, 89.94; H, 10.06. Found: C, 89.66; H, 10.01.

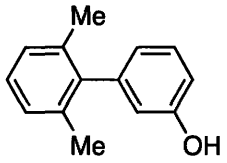


4-*n*-Butylbiphenyl[39] (Table 3, entry 4) (0.003% Pd). Following general procedure A, a mixture of 4-*n*-butylchlorobenzene (165 μL, 1.0 mmol), phenyl boronic acid (183 mg, 1.5 mmol), K_3PO_4 •H_2O(460 mg, 2.0 mmol) and 24 μL of a catalyst solution composed of $Pd(OAc)_2$ (1.1 mg, 0.005 mmol), **1** (10.3 mg, 0.025 mmol) and THF (4.0 mL) in toluene (2.0 mL) was heated at 100 °C for 24 h. The crude product was purified by flash chromatography on silica gel (hexane) to provide the title compound as a colorless oil (195 mg, 93%). The spectra were in agreement with those described in the literature.

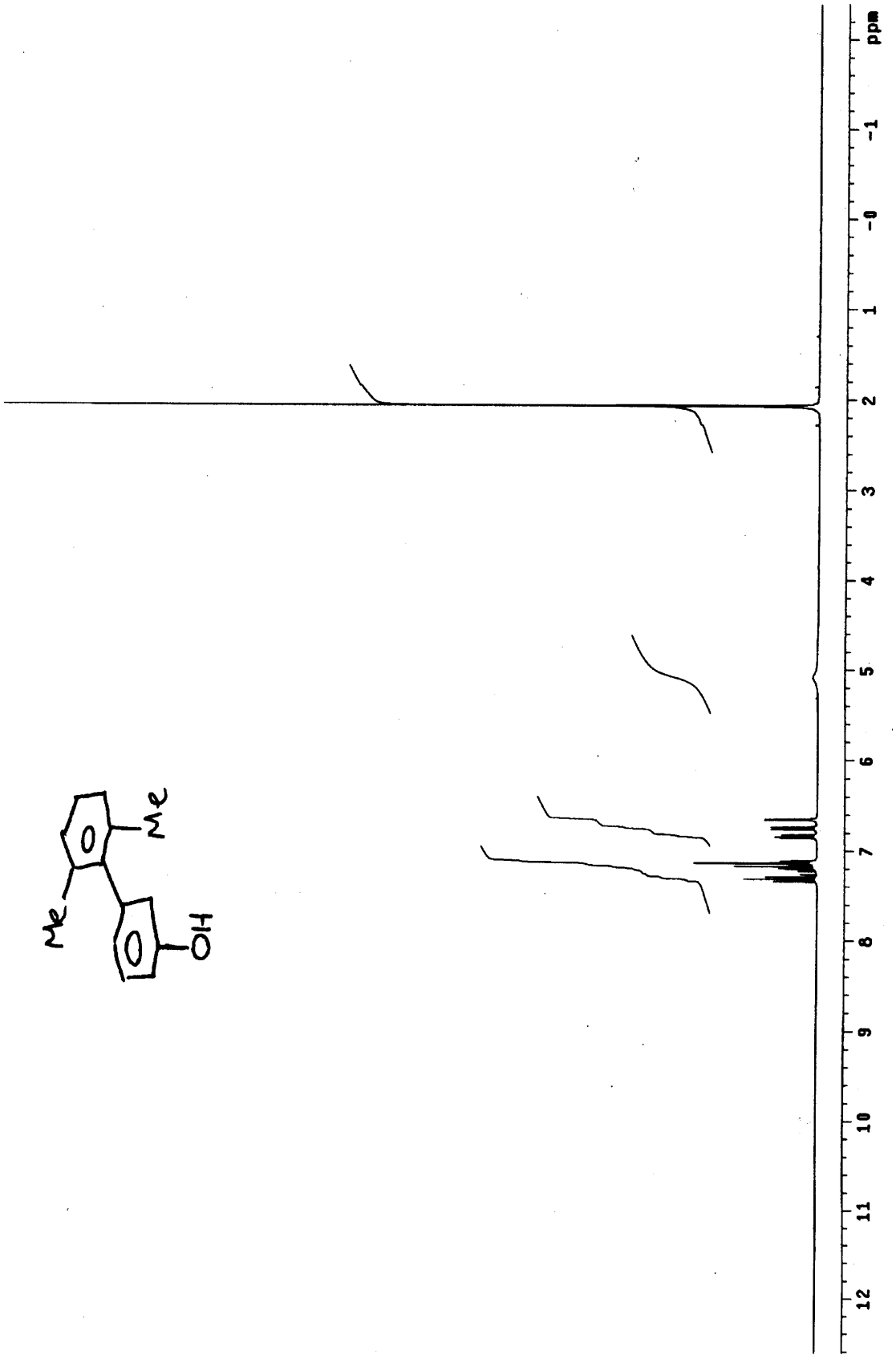


4-phenylquinoline[40] (Table 4, entry 1). Following general procedure E, a mixture of 4-chloroquinoline (82 mg, 0.50 mmol), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol), **1** (4.1 mg, 0.01 mmol), 4,4,5,5-Tetramethyl-2-phenyl-[1,3,2]dioxaborolane (153 mg, 0.75 mmol) and K_3PO_4 (212 mg, 1.0 mmol) in toluene (1.0 mL)

and water (100 μL) was heated at 100 °C with vigorous stirring for 30 min. The crude product was purified by flash chromatography on silica gel (4:1 hexane:ethyl acetate) to provide the title compound as a colorless oil (91 mg, 89 %). The spectra were in agreement with those described in the literature.



3-(2',6'-Dimethylphenyl)phenol (Table 4, entry 2). Following general procedure E, a mixture of 2-chloro-*m*-xylene (133 μL, 1.0 mmol), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), **1** (8.2 mg, 0.02 mmol), 3-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenol (330 mg, 1.50 mmol) and K_3PO_4 (424 mg, 2.0 mmol) in toluene (2.0 mL) and water (200 μL)was heated at 100 °C with vigorous stirring for 30 min. The crude product was purified by flash chromatography on silica gel (9:1 hexane:diethyl ether) to provide the title compound as a colorless oil (189 mg, 95%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.33 (t, J = 7.7 Hz, 1H), 7.12-7.23 (m, 3H), 6.85 (ddd, J = 8.3, 2.8, 1.1 Hz), 6.76 (ddd, J = 7.4, 1.2, 1.2 Hz), 6.65-6.67 (m, 1H), 5.09 (br s, 1H), 2.08 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 155.6, 143.0, 141.6, 136.2, 129.9, 127.4, 127.3, 121.9, 116.1, 113.8, 20.9. IR (neat, cm^{-1}): 3320, 3060, 2920, 1581, 1446, 1289, 1187, 999. A satisfactory elemental analysis was not obtained for this compound. The ^{1}H and ^{13}C NMR spectra follow.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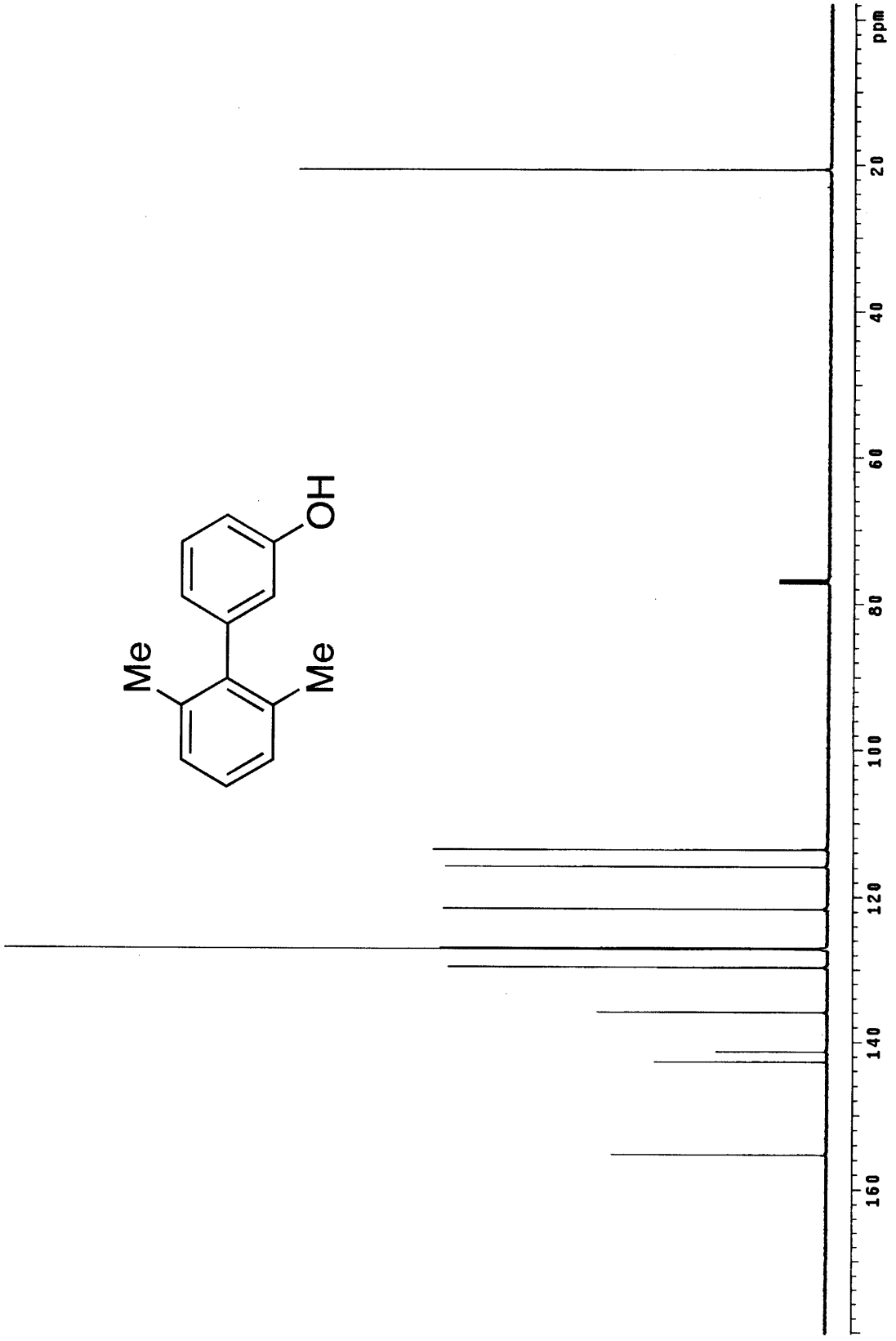
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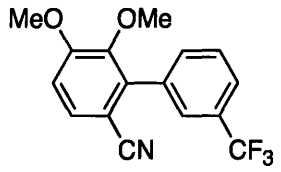
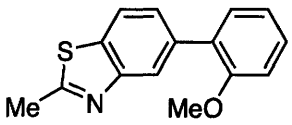
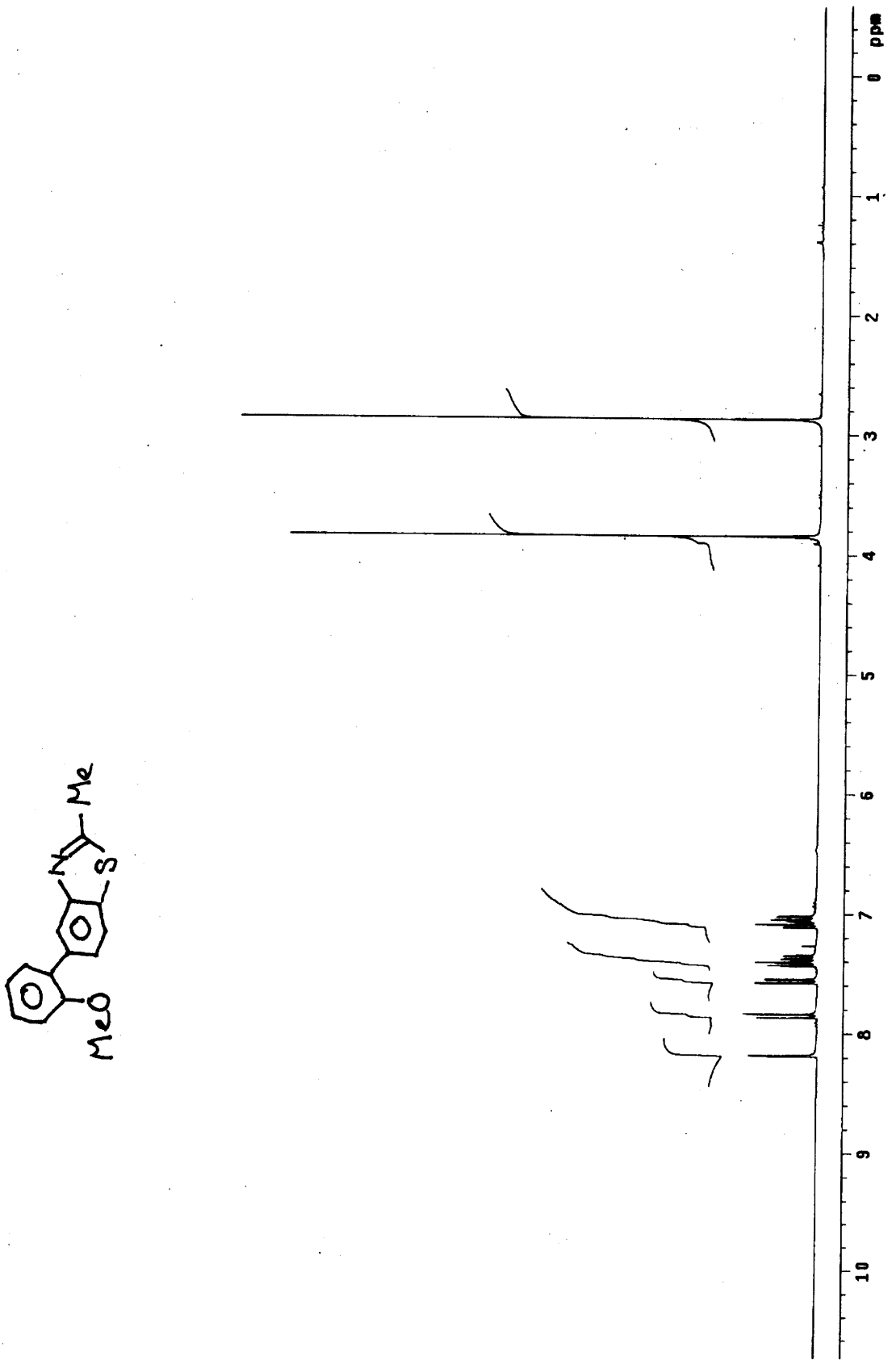


5,6-Dimethoxy-3'-trifluoromethyl-2-cyano-biphenyl (Table 4, entry 3). Following general procedure E, a mixture of 2-chloro-3,4-dimethoxybenzonitrile (99 mg, 0.50 mmol), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol), **1** (4.1 mg, 0.01 mmol), 4,4,5,5-Tetramethyl-2-(3-trifluoromethyl-phenyl)-[1,3,2]dioxaborolane (204 mg, 0.75 mmol) and K_3PO_4 (212 mg, 1.0 mmol) in toluene (1.0 mL) and water (100 μL)was heated at 100 °C with vigorous stirring for 30 min. The crude product was purified by flash chromatography on silica gel (4:1 hexane:diethyl ether) to provide the title compound as a white solid (151 mg, 98%), mp 87-88 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.59-7.75 (m, 3H), 7.54 (d, J = 8.6 Hz, 1H), 7.02 (d, J = 8.6 Hz, 1H), 3.99 (s, 3H), 3.58 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 157.2, 147.1, 138.3, 135.0, 133.3, 131.0, 130.6, 130.4, 129.0, 127.0, 126.9, 126.0, 125.53, 125.48, 122.4, 118.26, 112.32, 105.0, 61.1, 56.3 (observed complexity due to F-C splitting). IR (neat, cm^{-1}): 3061, 2948, 2846, 2228, 1590, 1484, 1332, 1126, 1031. Anal. Calcd for $C_{16}H_{12}F_3NO_2$: C, 62.54; H, 3.94. Found: C, 62.55; H, 3.87.



5-(2-Methoxyphenyl)-2-methyl-benzothioazole (Table 4, entry 4). Following general procedure F, a mixture of 5-chloro-2-methyl-benzothiazole (184 mg, 1.0 mmol), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), **1** (4.1 mg, 0.01 mmol), 2-(2-methoxy-phenyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (351 mg, 1.5 mmol) and K_3PO_4 (424 mg, 2.0 mmol) in THF (2.0 mL) and water (200 μL) was vigorously stirred at room temperature for 30 min. The crude product was purified by flash chromatography on silica gel (9:1 to 9:2 hexane:diethyl ether) to provide the title compound as a thick colorless oil (244 mg, 96%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.19 (dd, J = 1.7, 0.5 Hz, 1H), 7.86 (dd, J = 8.3, 0.5 Hz, 1H), 7.57 (dd, J = 8.3, 1.7 Hz, 1H), 7.34-7.44 (m, 2H), 7.02-7.12 (m, 2H), 3.84 (s, 3H), 2.87 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 167.3, 156.6, 153.6, 136.7, 134.4, 131.2, 130.2, 128.9, 126.7, 123.4, 121.1, 120.8, 111.3, 55.6, 20.3. IR

(neat, cm^{-1}): 3072, 2957, 2834, 1598, 1496, 1241, 1026. A satisfactory elemental analysis was not obtained for this compound. The ^{1}H and ^{13}C NMR spectra follow.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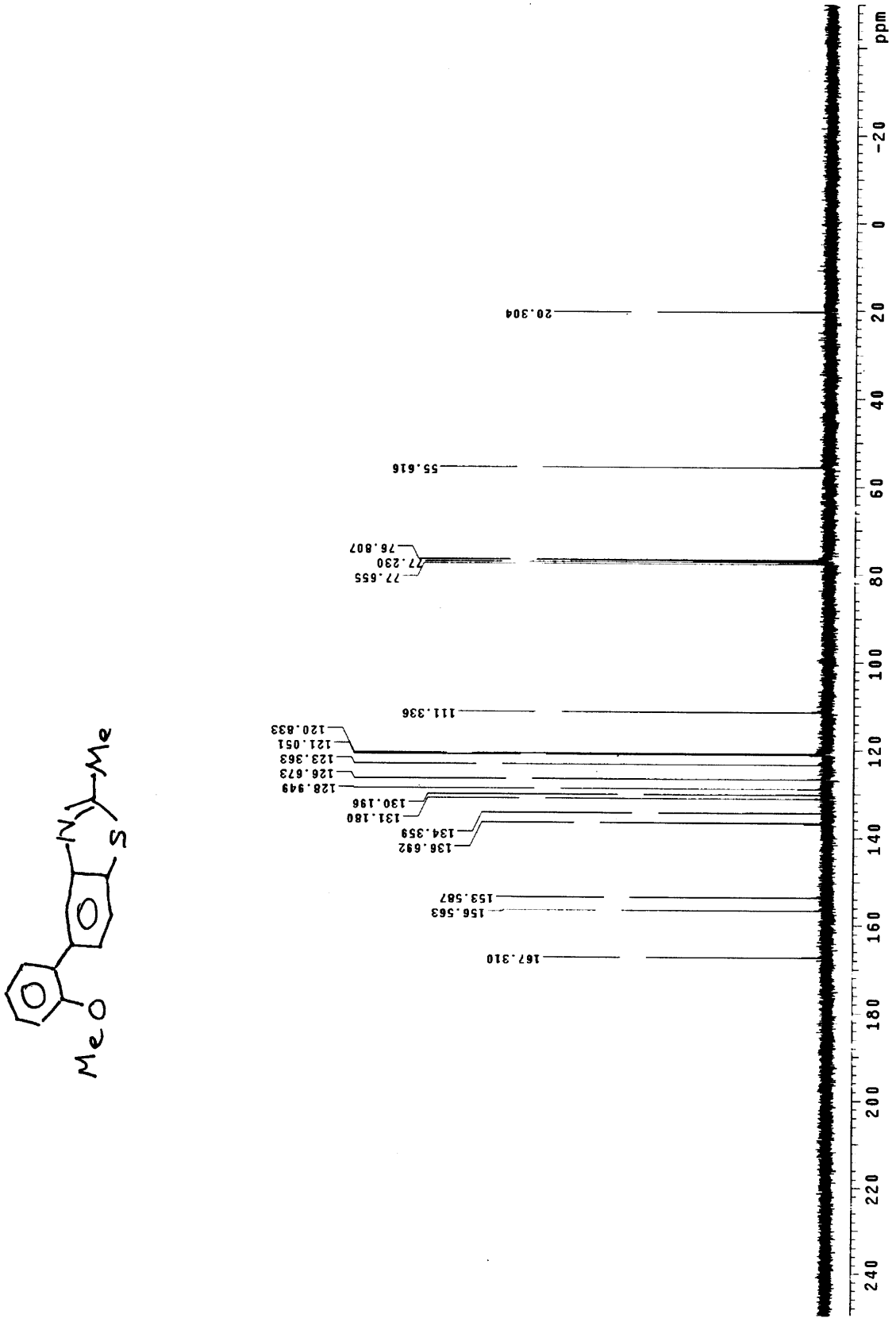
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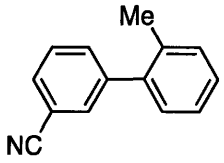
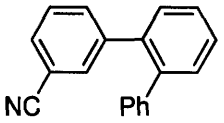
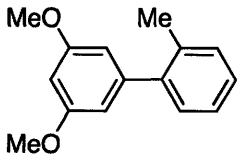


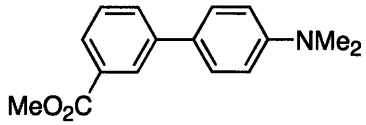
3-Cyano-2'-methylbiphenyl[41] **(Table 5, entry 1).** Following general procedure J, a mixture of 3-chlorobenzonitrile (137 mg, 1.0 mmol), 2-methylphenyl boronic acid (204 mg, 1.5 mmol), $K_3PO_4 \bullet H_2O$ (691 mg, 3.0 mmol), $Pd(OAc)_2$ (0.11 mg, 0.0005 mmol) and **2** (0.7 mg, 0.0015 mmol) was maintained at room temperature with vigorous stirring for 24 h. The crude product was purified via flash column chromatography on silica gel (hexanes to 9:1 hexanes: ethyl acetate) to provide the title compound as a colorless oil (182 mg, 94%). ^1H NMR (300 MHz, CD_2Cl_2) δ: 7.51-7.70 (m, 4H), 7.17-7.38 (m, 4H), 2.26 (s, 3H). The spectra were in agreement with those described in the literature.



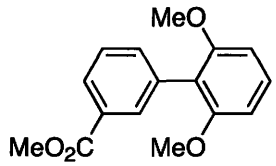
3-Cyano-2'-phenylbiphenyl (Table 5, entry 2). Following general procedure J, a mixture of 3-chlorobenzonitrile (137 mg, 1.0 mmol), 2-biphenyl boronic acid (297 mg, 1.5 mmol), $K_3PO_4 \bullet H_2O$ (691 mg, 3.0 mmol), $Pd(OAc)_2$ (0.11 mg, 0.0005 mmol) and **2** (0.7 mg, 0.0015 mmol) was maintained at room temperature with vigorous stirring for 24 h. The crude product was purified via flash column chromatography on silica gel (hexanes) to provide the title compound as a white solid (237 mg, 93%), mp 108-110 °C. ^1H NMR (300 MHz, CD_2Cl_2) δ: 7.30-7.55 (m, 8H), 7.22-7.29 (m, 3H), 7.09-7.17 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 143.3, 141.2, 138.8, 134.9, 133.7, 131.3, 130.8, 130.6, 130.4, 129.2, 128.9, 128.6, 128.3, 127.4, 119.2, 112.6. IR (neat, cm^{-1}): 3063, 3053, 2985, 1601, 1577, 1487, 1476, 1471, 1450, 1435, 1411, 1266, 1173, 1075, 1009 (-CN obscured by diamond probe). Anal. Calcd for $C_{19}H_{13}N$: C, 89.38; H, 5.13. Found: C, 89.40; H, 5.16.



3,5-Dimethoxy-2'-methylbiphenyl (Table 5, entry 3). Following general procedure J, a mixture of 3,5-dimethoxychlorobenzene (173 mg, 1.0 mmol), 2-methylphenyl boronic acid (204 mg, 1.5 mmol), $K_3PO_4 \bullet H_2O$ (691 mg, 3.0 mmol), $Pd(OAc)_2$ (0.22 mg, 0.001 mmol) and **2** (1.4 mg, 0.003 mmol) was maintained at room temperature with vigorous stirring for 24 h. The crude product was purified via flash column chromatography on silica gel (hexanes to 95:5 hexanes: ethyl acetate) to provide the title compound as a colorless oil (221 mg, 97%). ^1H NMR (300 MHz, CD_2Cl_2) δ: 7.22-7.30 (m, 4H), 6.47-6.50 (m, 3H), 3.82 (s, 6H), 2.30 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 161.1, 144.5, 142.5, 135.9, 130.8, 129.9, 127.9, 126.2, 107.8, 99.3, 55.9, 20.7. IR (neat, cm^{-1}): 2927, 2858, 1599, 1460, 1421, 1344, 1267, 1205, 1159, 1066, 1035. Anal. Calcd for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06. Found: C, 78.88; H, 7.06.

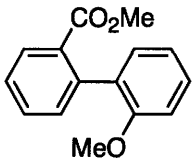


Methyl-3-(4'-N,N-dimethylphenyl)benzoate[42] **(Table 5, entry 4).** Following general procedure J, a mixture of 3-chloromethylbenzoate (171 mg, 1.0 mmol), 4-N,N-dimethylphenyl boronic acid (248 mg, 1.5 mmol), $K_3PO_4 \bullet H_2O$ (691 mg, 3.0 mmol), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol) and **2** (6.9 mg, 0.015 mmol) was maintained at room temperature with vigorous stirring for 24 h. The crude product was purified via flash column chromatography on silica gel (hexanes to 95:5 hexanes:ethyl acetate) to provide the title compound as an off-white solid (247 mg, 97%), mp 140-142 °C. ^1H NMR (300 MHz, CD_2Cl_2) δ: 8.20-8.26 (m, 1H), 7.85-7.92 (m, 1H), 7.73-7.81 (m, 1H), 7.38-7.60 (m, 3H), 6.74-6.86 (m, 2H), 3.91 (s, 3H), 2.99 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 167.6, 150.9, 141.9, 131.2, 130.8, 129.3, 128.0, 127.9, 127.4, 127.3, 113.1, 52.5, 40.8. The spectra were in agreement with those described in the literature.

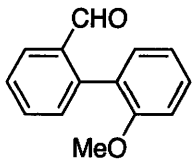


Methyl-3-(2',6'-dimethoxyphenyl)benzoate (Table 5, entry 5). Following general procedure J, a mixture of 3-chloromethylbenzoate (171 mg, 1.0 mmol), 2,6-dimethoxyphenyl boronic acid (364 mg, 3.0

mmol), $K_3PO_4 \cdot H_2O$ (691 mg, 3.0 mmol), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol) and **2** (6.9 mg, 0.015 mmol) was maintained at room temperature with vigorous stirring for 24 h. The crude product was purified via flash column chromatography on silica gel (hexanes to 9:1 hexanes:ethyl acetate) to provide the title compound as an off-white solid (267 mg, 98%), mp 91-93 °C. ^{1}H NMR (300 MHz, CD_2Cl_2) δ: 7.95-8.30 (m, 2H), 7.45-7.57 (m, 2H), 7.33 (t, J = 8.4 Hz, 1H), 6.69 (d, J = 8.4 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 167.5, 158.1, 136.2, 135.5, 132.7, 130.4, 129.8, 128.3, 118.7, 104.6, 56.2, 52.4. IR (neat, cm^{-1}): 3066, 3012, 2958, 2920, 2850, 1716, 1591, 1476, 1437, 1298, 1244, 1112, 1035. Anal. Calcd for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found: C, 70.65; H, 6.02.

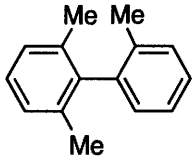


Methyl-2-(2'-methoxyphenyl)benzoate[43] (Table 5, entry 6). Following general procedure J, a mixture of 2-chloromethylbenzoate (171 mg, 1.0 mmol), 2-methoxyphenyl boronic acid (228 mg, 1.5 mmol), $K_3PO_4 \cdot H_2O$ (691 mg, 3.0 mmol), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol) and **2** (6.9 mg, 0.015 mmol) was maintained at room temperature with vigorous stirring for 24 h. The crude product was purified via flash column chromatography on silica gel (hexanes to 9:1 hexanes:ethyl acetate) to provide the title compound as a colorless oil (237 mg, 98%). ^{1}H NMR (300 MHz, CD_2Cl_2) δ: 7.83 (dd, J = 7.7, 1.4 Hz, 1H), 7.56 (td, J = 7.7, 1.7, 1H), 7.43 (dd, J = 7.7, 1.4 Hz, 1H), 7.31-7.40 (m, 2H), 7.25 (dd, J = 7.4, 1.9 Hz, 1H), 7.05 (td, J = 7.4, 1.1 Hz, 1H), 6.93 (d, J = 8.3 Hz, 1H), 3.71 (s, 3H), 3.66 (s, 3H). The spectra were in agreement with those described in the literature.

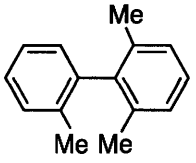


2-Formyl-2'-methoxybiphenyl[44] (Table 5, entry 7). Following general procedure J, a mixture of 2-chlorobenzaldehyde (141 mg, 1.0 mmol), 2-methoxyphenyl boronic acid (228 mg, 1.5 mmol), $K_3PO_4 \cdot H_2O$ (691 mg, 3.0 mmol), $Pd(OAc)_2$ (0.22 mg, 0.001 mmol) and **2** (1.4 mg, 0.003 mmol) was maintained at

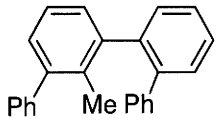
room temperature with vigorous stirring for 24 h. The crude product was purified via flash column chromatography on silica gel (hexanes to 9:1 hexanes:ethyl acetate) to provide the title compound as a colorless oil (208 mg, 98%). ^{1}H NMR (300 MHz, CD_2Cl_2) δ: 9.76 (d, J = 0.8 Hz, 1H), 7.95 (dd, J = 1.4, 0.5 Hz, 1H), 7.66 (td, J = 7.4, 1.4 Hz, 1H), 7.51 (dt, J = 7.7, 0.8 Hz, 1H), 7.44 (ddd, J = 8.3, 7.4, 1.7 Hz, 1H), 7.29 (dd, J = 7.4, 1.7 Hz, 1H) 7.09 (td, J = 7.4, 1.1 Hz, 1H), 7.01 (dd, J = 8.3, 0.8 Hz, 1H), 3.74 (s, 3H). The spectra were in agreement with those described in the literature.



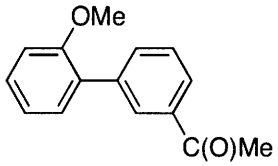
2,2',6-trimethylbiphenyl[45] (Table 5, entry 8). Following general procedure J, a mixture of 2-chloro-*m*-xylene (141 mg, 1.0 mmol), 2-methylphenyl boronic acid (204 mg, 1.5 mmol), K_3PO_4•H_2O (691 mg, 3.0 mmol), $Pd(OAc)_2$ (0.22 mg, 0.001 mmol) and **2** (1.4 mg, 0.003 mmol) was maintained at room temperature with vigorous stirring for 24 h. The crude product was purified via flash column chromatography on silica gel (hexanes) to provide the title compound as a colorless oil (185 mg, 94%). ^{1}H NMR (300 MHz, CD_2Cl_2) δ: 7.12-7.42 (m, 6H), 7.01-7.11 (m, 1H), 2.02 (s, 3H), 1.99 (s, 6H). The spectra were in agreement with those described in the literature.



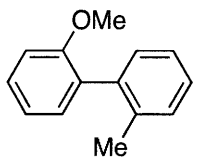
2,2',6-trimethylbiphenyl[45] (Table 5, entry 9). Following general procedure J, a mixture of 2-chlorotoluene (127 mg, 1.0 mmol), 2,6-dimethylphenyl boronic acid (450 mg, 3.0 mmol), K_3PO_4•H_2O (691 mg, 3.0 mmol), $Pd(OAc)_2$ (0.22 mg, 0.001 mmol) and **2** (1.4 mg, 0.003 mmol) was maintained at room temperature with vigorous stirring for 24 h. The crude product was purified via flash column chromatography on silica gel (hexanes) to provide the title compound as a colorless oil (182 mg, 93%). ^{1}H NMR (300 MHz, CD_2Cl_2) δ: 7.12-7.42 (m, 6H), 7.01-7.11 (m, 1H), 2.02 (s, 3H), 1.99 (s, 6H). The spectra were in agreement with those described in the literature.



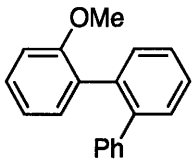
2'-Methyl-[1,1';3',1'';2'',1''']quaterphenyl (Table 5, entry 10). Following general procedure J, a mixture of 3-chloro-2-methylbiphenyl (203 mg, 1.0 mmol), 2-biphenyl boronic acid (298 mg, 1.5 mmol), $K_3PO_4 \bullet H_2O$ (691 mg, 3.0 mmol), $Pd(OAc)_2$ (0.56 mg, 0.0025 mmol) and **2** (3.5 mg, 0.0075 mmol) was maintained at room temperature with vigorous stirring for 24 h. The crude product was purified via flash column chromatography on silica gel (hexanes) to provide the title compound as a white solid (318 mg, 99%), mp 105-108 °C. ^{1}H NMR (300 MHz, CD_2Cl_2) δ: 7.26-7.52 (m, 7H), 7.10-7.25 (m, 10H), 1.74 (s, 3H). ^{13}C NMR (75 MHz, CD_2Cl_2) δ: 143.1, 142.9, 142.7, 142.1, 141.7, 141.4, 133.9, 131.7, 130.5, 130.3, 130.1, 129.8, 129.2, 128.6, 128.3, 128.2, 127.8, 127.3, 127.1, 125.6, 18.8. IR (neat, cm^{-1}): 3059, 3028, 2927, 1576, 1460, 1429, 1074, 1004. Anal. Calcd for $C_{25}H_{20}$: C, 93.71; H, 6.29. Found: C, 93.89; H, 6.31.



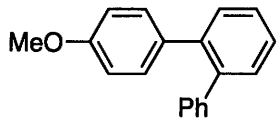
3-Acetyl-2'-methoxybiphenyl[46] **(Table 5, entry 11).** Following general procedure J, a mixture of 2-chloroanisole (143 mg, 1.0 mmol), 3-acetylphenyl boronic acid (246 mg, 1.5 mmol), $K_3PO_4 \bullet H_2O$ (691 mg, 3.0 mmol), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol) and **2** (6.9 mg, 0.015 mmol) was maintained at room temperature with vigorous stirring for 24 h. The crude product was purified via flash column chromatography on silica gel (hexanes to 9:1 hexanes:ethyl acetate) to provide the title compound as a light yellow oil (201 mg, 89%). ^{1}H NMR (300 MHz, CD_2Cl_2) δ: 8.07-8.15 (m, 1H), 7.92 (dq, J = 7.7, 1.1 Hz, 1H), 7.74 (dq, J = 7.7, 1.1 Hz, 1H), 7.52 (td, J = 7.7, 0.6 Hz, 1H), 7.31-7.43 (m, 2H), 7.0-7.12 (m, 2H). The spectra were in agreement with those described in the literature.



2-methoxy-2'-methylbiphenyl[47] **(Table 5, entry 12).** Following general procedure J, a mixture of 2-chloroanisole (143 mg, 1.0 mmol), 2-methylphenyl boronic acid (204 mg, 1.5 mmol), $K_3PO_4 \cdot H_2O$ (691 mg, 3.0 mmol), $Pd(OAc)_2$ (0.56 mg, 0.0025 mmol) and **2** (3.6 mg, 0.0075 mmol) was maintained at room temperature with vigorous stirring for 24 h. The crude product was purified via flash column chromatography on silica gel (hexanes to 9:1 hexanes:ethyl acetate) to provide the title compound as a white crystalline solid (192 mg, 97%), mp 42-44 °C. ^1H NMR (300 MHz, CD_2Cl_2) δ: 7.37-7.46 (m, 1H), 7.17-7.35 (m, 5H), 7.01-7.12 (m, 2H), 3.81 (s, 3H), 2.18 (s, 3H). The spectra were in agreement with those described in the literature.

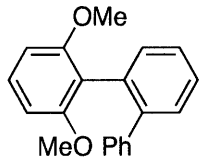


2-methoxy-2'-phenylbiphenyl[48] **(Table 5, entry 13).** Following general procedure J, a mixture of 2-chloroanisole (143 mg, 1.0 mmol), 2-biphenyl boronic acid (298 mg, 1.5 mmol), $K_3PO_4 \cdot H_2O$ (691 mg, 3.0 mmol), $Pd(OAc)_2$ (0.56 mg, 0.0025 mmol) and **2** (3.6 mg, 0.0075 mmol) was maintained at room temperature with vigorous stirring for 24 h. The crude product was purified via flash column chromatography on silica gel (hexanes) to provide the title compound as a thick oil (252 mg, 97%). ^1H NMR (300 MHz, CD_2Cl_2) δ 7.36-7.51 (m, 4H), 7.14-7.32 (m, 7H), 6.96 (t, J = 7.4, 1H), 6.77 (d, J = 8.3 Hz, 1H), 3.42 (s, 3H). The spectra were in agreement with those described in the literature.

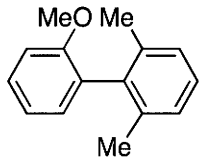


4-methoxy-2'-phenylbiphenyl[49] **(Table 5, entry 14).** Following general procedure J, a mixture of 4-chloroanisole (143 mg, 1.0 mmol), 2-biphenyl boronic acid (298 mg, 1.5 mmol), $K_3PO_4 \cdot H_2O$ (691 mg, 3.0 mmol), $Pd(OAc)_2$ (0.56 mg, 0.0025 mmol) and **2** (3.6 mg, 0.0075 mmol) was heated to 40 °C with vigorous stirring for 24 h. The crude product was purified via flash column chromatography on silica gel (hexanes) to provide the title compound as a viscous oil (241 mg, 93%). ^1H NMR (300 MHz, CD_2Cl_2) δ

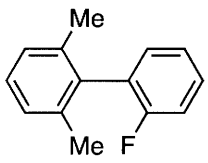
7.39-7.47 (m, 4H), 7.16-7.32 (m, 5H), 7.10 (d, J = 8.8 Hz, 2H), 6.79 (d, J = 8.8 Hz, 2H), 3.78 (s, 3H). The spectra were in agreement with those described in the literature.



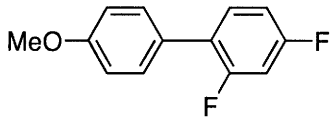
2,6-dimethoxy-2'-phenylbiphenyl[50] **(Table 5, entry 15).** Following general procedure J, a mixture of 2,6-dimethoxychlorobenzene (173 mg, 1.0 mmol), 2-biphenyl boronic acid (298 mg, 1.5 mmol), $K_3PO_4 \bullet H_2O$ (691 mg, 3.0 mmol), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol) and **2** (6.9 mg, 0.015 mmol) was heated to 40 °C with vigorous stirring for 24 h. The crude product was purified via flash column chromatography on silica gel (hexanes) to provide the title compound as a white solid (287 mg, 99%), mp 102-103 °C. ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.34-7.48 (m, 3H), 7.23-7.29 (m, 1H), 7.08-7.22 (m, 6H), 6.48 (d, J = 8.5 Hz, 2H), 3.54 (s, 3H). The spectra were in agreement with those described in the literature.



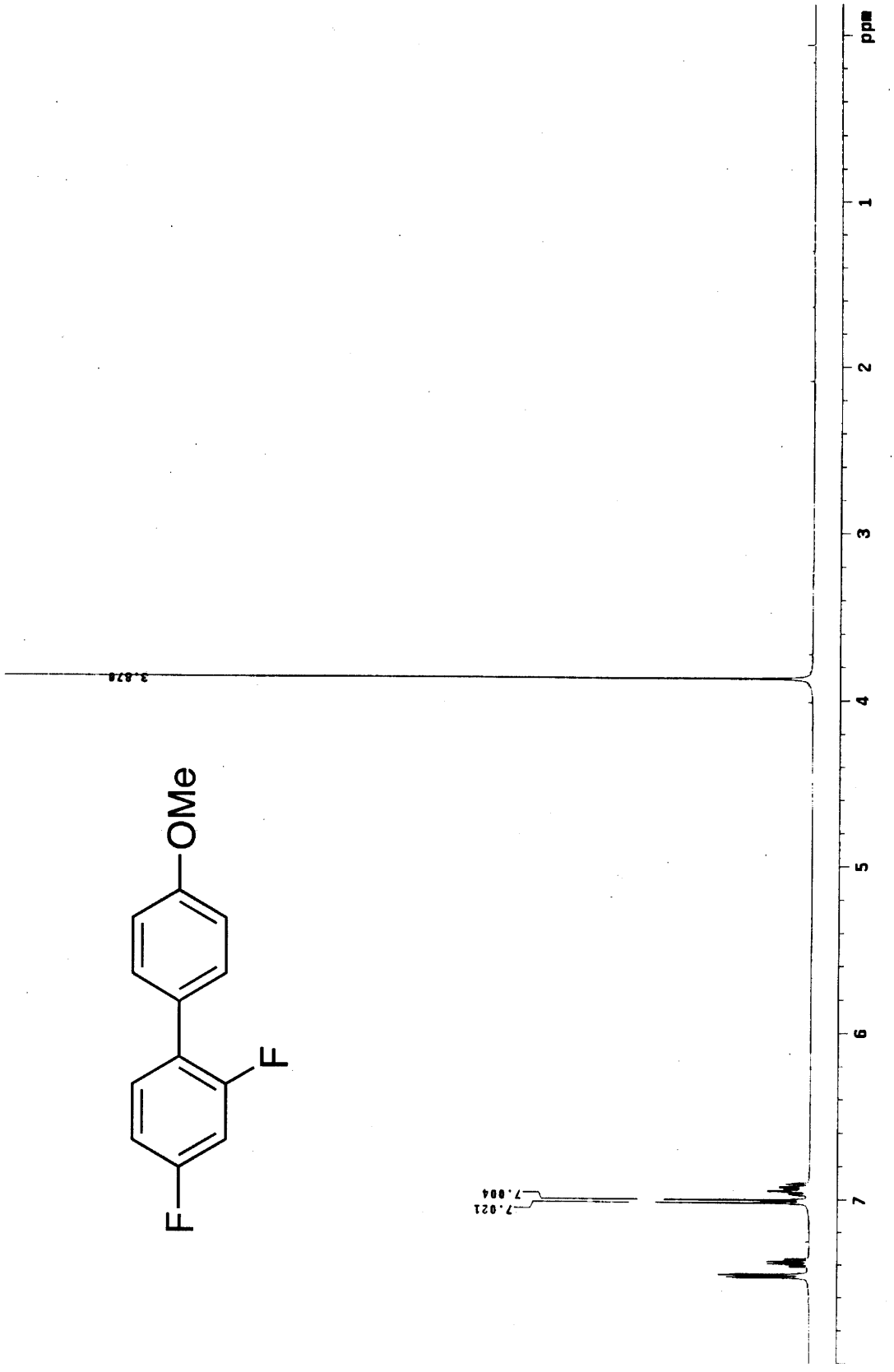
2,6-dimethyl-2'-methoxybiphenyl[51] **(Table 5, entry 16).** Following general procedure J, a mixture of 2-chloroanisole (143 mg, 1.0 mmol), 2,6-dimethylphenyl boronic acid (450 mg, 3.0 mmol), $K_3PO_4 \bullet H_2O$ (691 mg, 3.0 mmol), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol) and **2** (6.9 mg, 0.015 mmol) was heated to 40 °C with vigorous stirring for 24 h. The crude product was purified via flash column chromatography on silica gel (hexanes) to provide the title compound as a colorless oil (207 mg, 98%). ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.34-7.44 (m, 1H), 7.08-7.22 (m, 3H), 7.01-7.08 (m, 3H), 3.77 (s, 3H), 2.02 (s, 6H). The spectra were in agreement with those described in the literature.



2-Fluoro-2',4'-dimethylbiphenyl (Table 6, entry 1). Following general procedure I, a mixture of 2-chloro-*m*-xylene (141 mg, 1.0 mmol), 2-fluorophenyl boronic acid (210 mg, 1.5 mmol), K_3PO_4 (425 mg, 2.0 mmol), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol), and **1** (4.1 mg, 0.01 mmol) in toluene (2.0 mL) was heated to 90 °C with stirring for 90 min. The crude product was purified via flash column chromatography on silica gel (hexanes) to provide the title compound as a colorless oil (184 mg, 92%). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.31-7.36 (m, 2H), 7.11-7.21 (m, 5H), 2.05 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 160.4, 158.5, 136.7, 135.2, 131.3, 131.3, 129.0, 128.9, 128.0, 127.9, 127.7, 127.2, 124.1, 124.1, 115.8, 115.6, 20.5. ^{19}F NMR (282 MHz, $CDCl_3$) δ: -115.4. IR (neat, cm^{-1}): 3064, 2923, 2863, 1577, 1447, 1208, 1110, 1006. Anal. Calcd for $C_{14}H_{13}F$: C, 83.97; H, 6.54. Found: C, 83.74; H, 6.52.



2,4-Difluoro-4'-methoxybiphenyl (Table 6, entry 2). Following general procedure I, a mixture of 4-chloroanisole (143 mg, 1.0 mmol), 2,4-difluorophenyl boronic acid (237 mg, 1.5 mmol), K_3PO_4 (425 mg, 2.0 mmol), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol), and **1** (4.1 mg, 0.01 mmol) in toluene (2.0 mL) was heated to 80 °C with stirring for 16 h. The crude product was purified via flash column chromatography on silica gel (2% ethyl acetate in hexanes) to provide the title compound as a white solid (219 mg, 99%), mp 78-79 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.47 (d, J = 7 Hz, 2H), 7.37-7.41 (m, 1H), 7.01 (d, J = 9 Hz, 2H), 6.91-6.97 (m, 2H), 3.87 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 162.9, 162.8, 160.9, 160.8, 160.6, 160.5, 159.2, 158.6, 158.5, 131.1, 131.0, 131.0, 130.9, 130.0, 129.9, 127.3, 127.2, 125.0, 124.9, 124.9, 124.8, 113.9, 111.5, 111.4, 111.3, 111.2, 104.4, 104.2, 104.2, 104.0, 55.2. ^{19}F NMR (282 MHz, $CDCl_3$) δ: -112.7 (t, J = 6 Hz, 1F), -114.1 (d, J = 6 Hz, 1F). IR (neat, cm^{-1}): 3056, 2840, 1611, 1496, 1266, 1140, 965. A satisfactory elemental analysis was not obtained for this compound. The ^{1}H and ^{13}C NMR spectra follow.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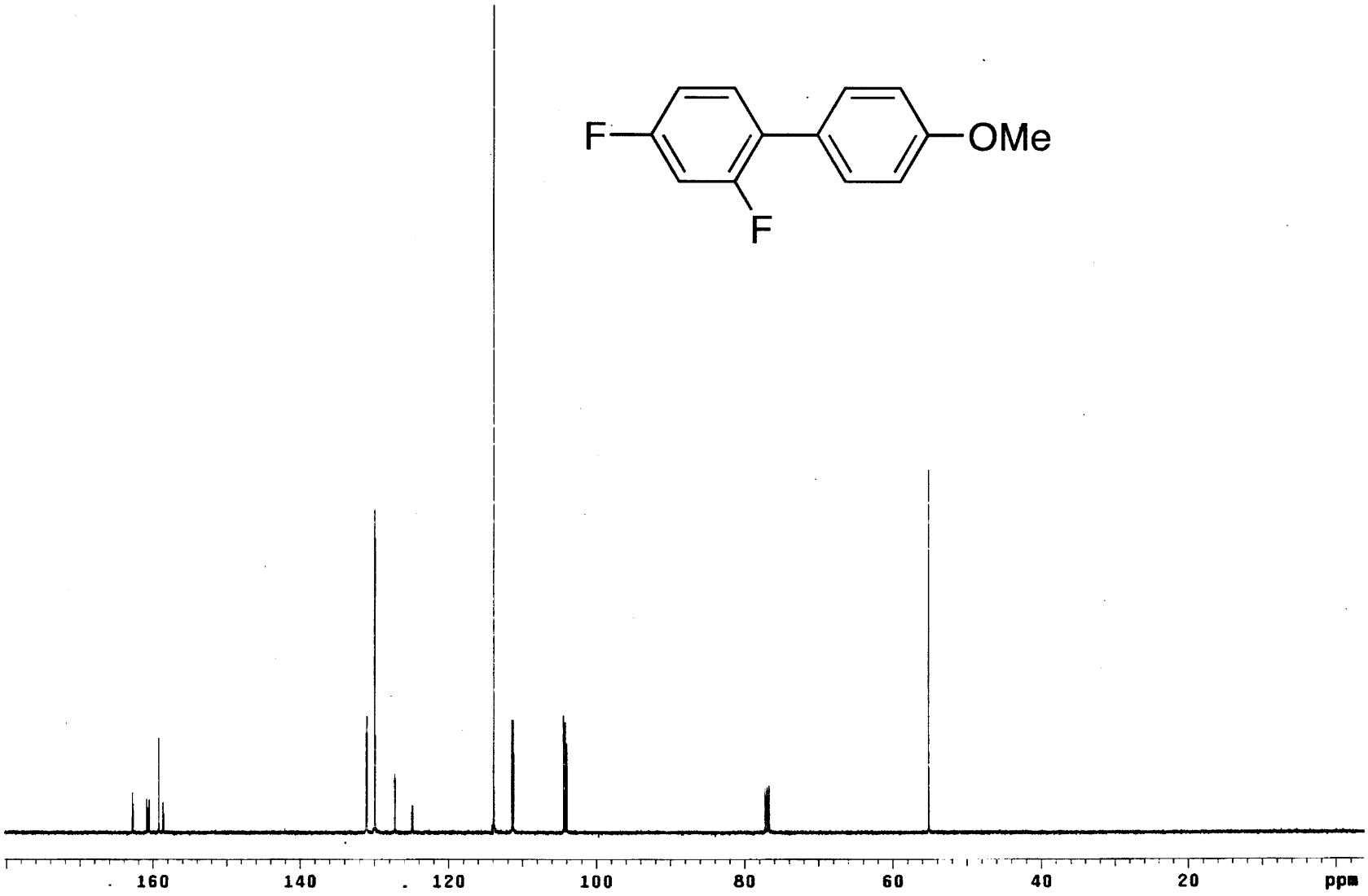
7.021
7.084
ppm
1
2
3
4
5
6
7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OMe
F
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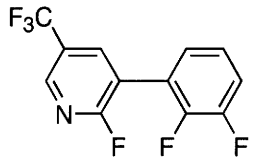
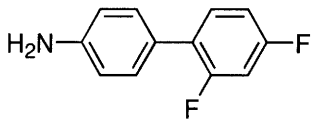
140
120
100
80
60
40
20
ppm

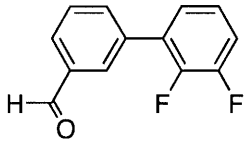


3-(2,3-Difluorophenyl)-2-fluoro-5-trifluoromethylpyridine (Table 6, entry 3). Following general procedure I, a mixture of 2-fluoro-3-chloro-5-(trifluoromethyl)pyridine (199 mg, 1.0 mmol), 2,3-difluorophenyl boronic acid (316 mg, 2.0 mmol), K_3PO_4 (637 mg, 3.0 mmol), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), and **1** (8.2 mg, 0.02 mmol) in toluene (2 mL) was heated to 90 °C with stirring for 16 h. The crude product was purified via flash column chromatography on silica gel (3% ethyl acetate in hexanes) to provide the title compound as a pale yellow oil (265 mg, 96%). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.59 (s, 1H), 8.11 (d, J = 8 Hz, 1H), 7.17-7.34 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 163.5, 160.2, 152.6, 152.4, 149.8, 149.6, 149.2, 149.1, 146.5, 146.3, 145.6, 145.5, 145.4, 145.4, 145.3, 145.3, 145.2, 145.1, 139.4, 139.3, 139.3, 139.3, 139.2, 125.8, 125.6, 125.5, 125.1, 125.1, 124.7, 124.7, 124.6, 124.6, 122.4, 122.3, 122.2, 122.2, 121.1, 118.6, 118.4, 118.2, 118.1, 117.8, 117.7. ^{19}F NMR (282 MHz, $CDCl_3$) δ: -62.1 (s, 3F), -63.8 (q, J = 6 Hz, 1F), -136.8 (q, J = 6 Hz, 1F), -139.8 (m, 1F). IR (neat, cm^{-1}): 3086, 1598, 1496, 1483, 1454, 1418, 1343, 1293, 1260, 1160, 1132, 1092. Anal. Calcd for $C_{12}H_5F_6N$: C, 52.00; H, 1.82. Found: C, 52.03; H, 1.83.

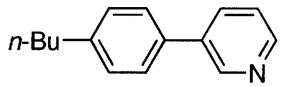


2,4-Difluoro-4'-aminobiphenyl (Table 6, entry 4). Following general procedure I, a mixture of 4-chloroaniline (128 mg, 1.0 mmol), 2,4-difluorophenyl boronic acid (237 mg, 1.5 mmol), K_3PO_4 (425 mg, 2 mmol), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), and **1** (8.2 mg, 0.02 mmol) in toluene (2.0 mL) was heated to 80 °C with stirring for 10 h. The crude product was purified via flash column chromatography on silica gel (1:4 ethyl acetate:hexanes) to provide the title compound as a pale brown solid (197 mg, 96%), mp 110-111 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.34-7.40 (m, 3H), 6.89-6.96 (m, 2H), 6.77 (d, J = 8 Hz, 2H), 3.78 (bs, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 162.5, 162.4, 160.6, 160.5, 160.5, 160.4, 158.5,

158.4, 146.1, 130.9, 130.8, 130.7, 130.7, 129.8, 129.7, 125.3, 125.3, 125.2, 125.1, 124.8, 124.8, 114.9, 111.3, 111.3, 111.2, 111.1, 104.3, 104.1, 104.0, 103.9. ^{19}F NMR (282 MHz, $CDCl_3$) δ: -113.3 (quintet, J = 6 Hz, 1F), -114.2 (t, J = 6 Hz, 1F). IR (neat, cm^{-1}): 3487, 3397, 3039, 1626, 1606, 1490, 1412, 1263, 1138, 1103. Anal. Calcd for $C_{12}H_9F_2N$: C, 70.24; H, 4.42. Found: C, 70.04; H, 4.34.

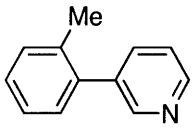


3-(2,3-Difluorophenyl)-benzaldehyde (Table 6, entry 5). Following general procedure I, a mixture of 3-chlorobenzaldehyde (141 mg, 1.0 mmol), 2,3-difluorophenyl boronic acid (237 mg, 1.5 mmol), K_3PO_4 (425 mg, 2.0 mmol), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol), and **1** (4.1 mg, 0.01 mmol) in toluene (2.0 mL) was heated to 90 °C with stirring for 3 h. The crude product was purified via flash column chromatography on silica gel (5% ethyl acetate in hexanes) to provide the title compound as a white solid (175 mg, 80%), mp 42-43 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 10.0 (s, 1H), 8.01 (s, 1H), 7.89 (d, J = 8 Hz, 1H), 7.78 (d, J = 7 Hz, 1H), 7.60 (t, J = 8 Hz, 1H), 7.13-7.22 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 191.8, 152.7, 125.5, 149.6, 149.4, 149.3, 149.2, 146.2, 146.1, 136.6, 135.5, 135.4, 134.7, 134.6, 130.0, 129.9, 129.7, 129.6, 129.2, 125.1, 125.1, 125.0, 125.0, 124.4, 124.3, 124.3, 124.2, 116.8, 116.6. ^{19}F NMR (282 MHz, $CDCl_3$) δ: -137.7 (quintet, J = 6 Hz, 1F), -143.9 (t, J = 6 Hz, 1F). IR (neat, cm^{-1}): 3067, 2830, 1699, 1593, 1579, 1482, 1468, 1266, 1189, 1100, 986. Anal. Calcd for $C_{13}H_8F_2O$: C, 71.56; H, 3.70. Found: C, 71.35; H, 3.61.

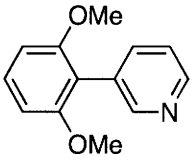


3-(4-*n*-Butylphenyl)-pyridine[52] **(Table 7, entry 1)**. Following general procedure H, a mixture of 4-*n*-butylchlorobenzene (169 mg, 1.0 mmol), 3-pyridyl boronic acid (185 mg, 1.5 mmol), K_3PO_4 (425 mg, 2.0 mmol), $Pd_2(dba)_3$ (9.2 mg, 0.01 mmol), and **1** (16.4 mg, 0.04 mmol) in *n*-butanol (2.0 mL) was heated to 100 °C with stirring for 15 h. The crude product was purified via flash column chromatography on silica

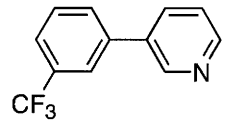
gel (5% ethyl acetate in hexanes to 10% ethyl acetate in hexanes) to provide the title compound as a pale yellow oil (209 mg, 99%). The spectra were in agreement with those described in the literature.



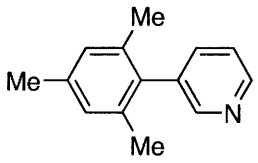
3-(2-Methylphenyl)-pyridine[45] **(Table 7, entry 2)**. Following general procedure H, a mixture of 2-chlorotoluene (127 mg, 1.0 mmol), 3-pyridyl boronic acid (185 mg, 1.5 mmol), K_3PO_4 (425 mg, 2.0 mmol), $Pd_2(dba)_3$ (9.2 mg, 0.01 mmol), and **1** (16.4 mg, 0.04 mmol) in *n*-butanol (2.0 mL) was heated to 100 °C with stirring for 20 h. The crude product was purified via flash column chromatography on silica gel (10% ethyl acetate in hexanes to 1:3 ethyl acetate:hexanes) to provide the title compound as a pale yellow oil (149 mg, 88%). The spectra were in agreement with those described in the literature.



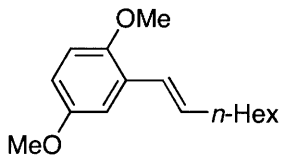
3-(2,6-Dimethoxyphenyl)-pyridine (Table 7, entry 3). Following general procedure H, a mixture of 2,6-dimethoxychlorobenzene (173 mg, 1.0 mmol), 3-pyridyl boronic acid (185 mg, 1.5 mmol), K_3PO_4 (425 mg, 2.0 mmol), $Pd_2(dba)_3$ (13.7 mg, 0.015 mmol), and **1** (24.6 mg, 0.06 mmol) in *n*-butanol (2.0 mL) was heated to 100 °C with stirring for 24 h. The crude product was purified via flash column chromatography on silica gel (1:3 ethyl acetate:hexanes) to provide the title compound as a off-white solid (177 mg, 82%), mp 87-88 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.60 (d, J = 2 Hz, 1H), 8.52 (d, J = 5 Hz, 1H), 7.69 (d, J = 8 Hz, 1H), 7.30-7.33 (m, 2H), 6.67 (d, J = 8 Hz, 2H), 3.74 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 157.6, 151.8, 147.6, 138.4. 129.9, 129.5, 122.6, 120.2, 115.6, 55.8. IR (neat, cm^{-1}): 3004, 2939, 2837, 1588, 1473, 1407, 1260, 1102, 998. Anal. Calcd for $C_{13}H_{16}NO_2$: C, 72.54; H, 6.09. Found: C, 72.23; H, 6.08.



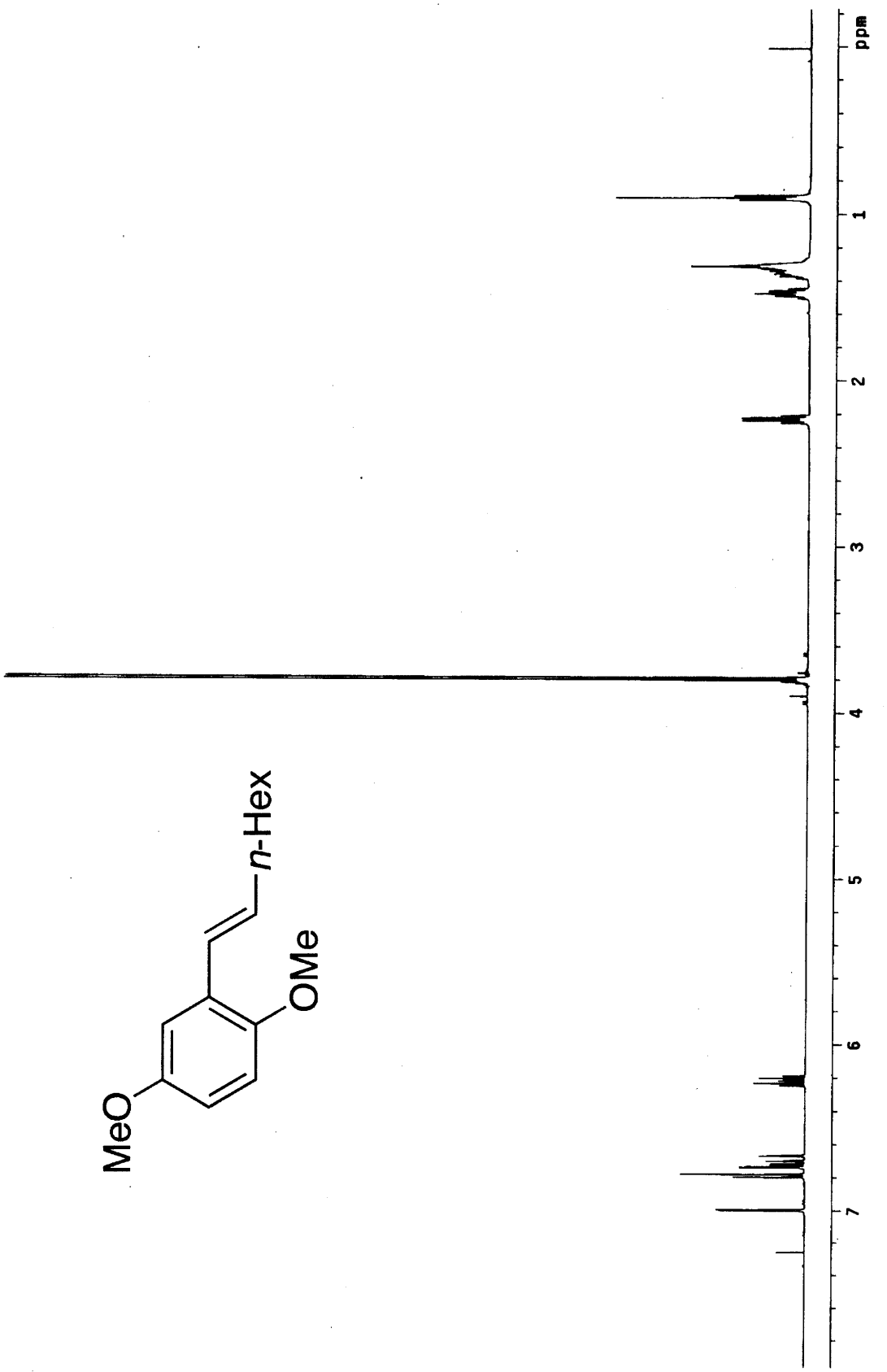
3-(3-Trifluoromethylphenyl)-pyridine[53] (Table 7, entry 4). Following general procedure H, a mixture of 3-(trifluoromethyl)chlorobenzene (181 mg, 1.0 mmol), 3-pyridyl boronic acid (185 mg, 1.5 mmol), K_3PO_4 (425 mg, 2.0 mmol), $Pd_2(dba)_3$ (9.2 mg, 0.01 mmol), and **1** (16.4 mg, 0.04 mmol) in *n*-butanol (2.0 mL) was heated to 90 °C with stirring for 24 h. The crude product was purified via flash column chromatography on silica gel (1:4 ethyl acetate:hexanes) to provide the title compound as a pale yellow oil (200 mg, 90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.85 (d, J = 5 Hz, 1H), 8.64 (dd, J = 2, 5 Hz, 1H), 7.88 (ddd, J = 2, 5, 8 Hz, 1H), 7.81 (s, 1H), 7.75 (d, J = 8 Hz, 1H), 7.57-7.67 (m, 2H), 7.39 (dd, J = 5, 8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 149.5, 148.5, 138.9, 135.5, 134.7, 132.0, 131.5, 130.7, 130.6, 129.9, 126.0, 125.1, 125.0, 125.0, 124.2, 124.1, 123.9, 122.4. ^{19}F NMR (282 MHz, $CDCl_3$) δ: -63.0. IR (neat, cm^{-1}): 3039, 1571, 1437, 1402, 1333, 1266, 1166, 1121, 1028, 1017.



3-(2,4,6-Trimethylphenyl)-pyridine (Table 7, entry 5). Following general procedure H, a mixture of 2-bromomesitylene (199 mg, 1.0 mmol), 3-pyridyl boronic acid (185 mg, 1.5 mmol), K_3PO_4 (425 mg, 2.0 mmol), $Pd_2(dba)_3$ (9.2 mg, 0.01 mmol), and **1** (16.4 mg, 0.04 mmol) in *n*-butanol (2.0 mL) was heated to 90 °C with stirring for 24 h. The crude product was purified via flash column chromatography on silica gel (1:4 ethyl acetate:hexanes) to provide the title compound as a white solid (168 mg, 85%), mp 46-47 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.60 (dd, J = 2, 5 Hz, 1H), 8.44 (d, J = 2 Hz, 1H), 7.50 (dt, J = 2, 8 Hz, 1H), 7.36 (dd, J = 5, 8 Hz, 1H), 6.98 (s, 2H), 2.35 (s, 3H), 2.01 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 150.3, 148.0, 137.4, 136.9, 136.6, 136.1, 134.9, 128.2, 123.3, 21.0, 20.7. IR (neat, cm^{-1}): 3024, 2920, 2860, 1614, 1563, 1470, 1406, 999. Anal. Calcd for $C_{14}H_{15}N$: C, 85.24; H, 7.66. Found: C, 84.90; H, 7.67.



(*E*)-1-(2,4-Dimethoxyphenyl)-octene (Table 8, entry 1). Following general procedure G, a mixture of 2,5-dimethoxybromobenzene (217 mg, 1.0 mmol), (*E*)-1-octenyl boronic acid (234 mg, 1.5 mmol), K_3PO_4 (425 mg, 2.0 mmol), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), and **1** (8.2 mg, 0.02 mmol) in THF (2.0 mL) was heated to 40 °C with stirring for 24 h. The crude product was purified via flash column chromatography on silica gel (4% ethyl acetate in hexanes) to provide the title compound as pale yellow oil (241 mg, 97%). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.00 (d, J = 3 Hz, 1H), 6.79 (d, J = 9 Hz, 1H), 6.73 (dd, J = 3, 9 Hz, 1H), 6.69 (d, J = 16 Hz, 1H), 6.22 (dt, J = 7, 16 Hz, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 2.23 (q, J = 4 Hz, 2H), 1.48 (quintet, J = 7 Hz, 2H), 1.29-1.38 (m, 4H), 0.90 (t, J = 7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 153.7, 150.7, 132.3, 127.9, 124.0, 112.5, 112.1, 111.8, 56.2, 55.7, 33.4, 31.7, 29.4, 28.9, 22.6, 14.1. IR (neat, cm^{-1}): 2996, 2926, 2864, 1583, 1496, 1282, 1218, 1060. A satisfactory elemental analysis was not obtained for this compound. The ^{1}H and ^{13}C NMR spectra follow.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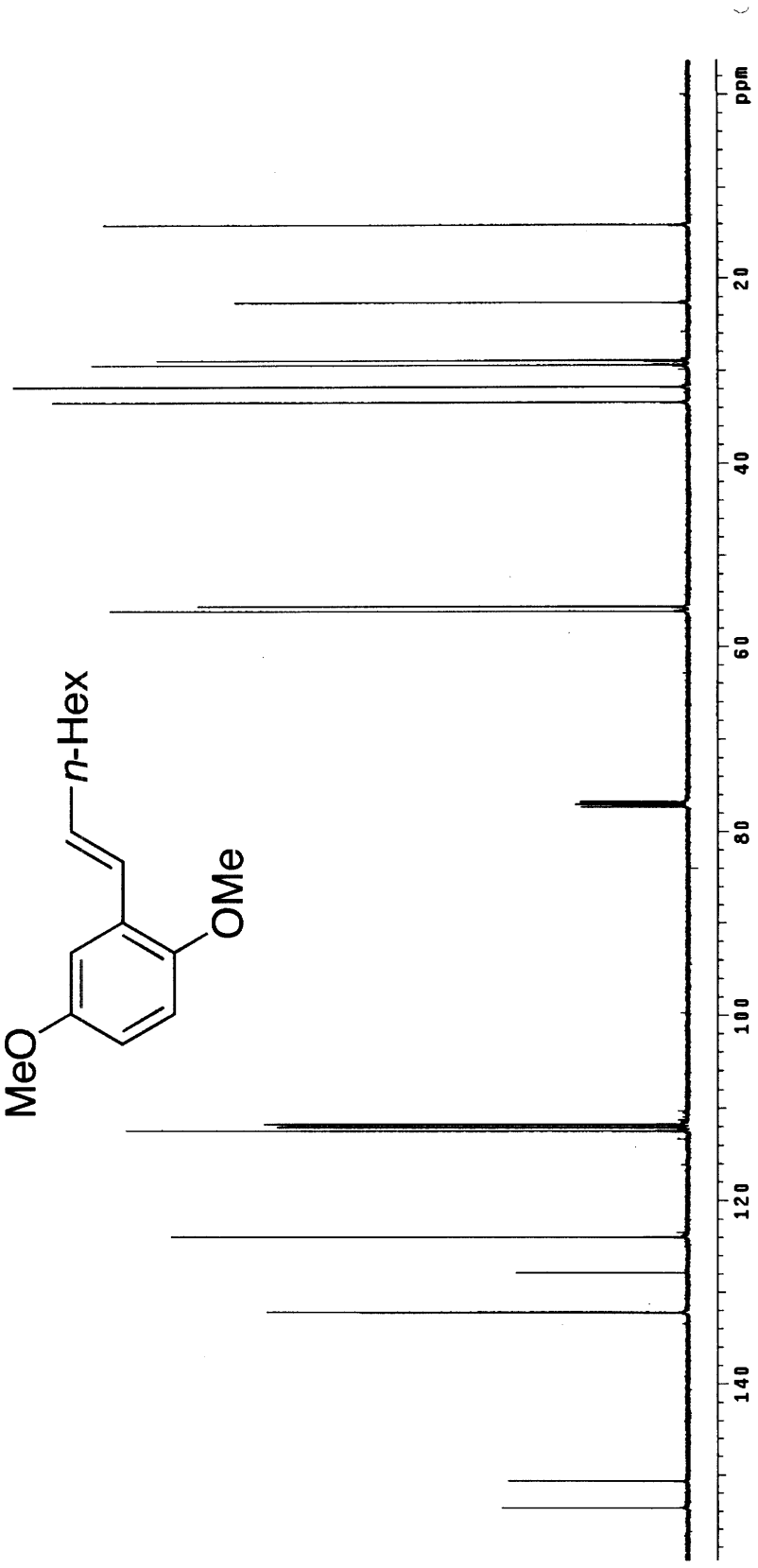
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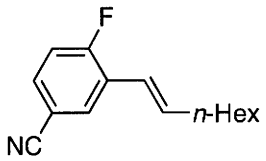
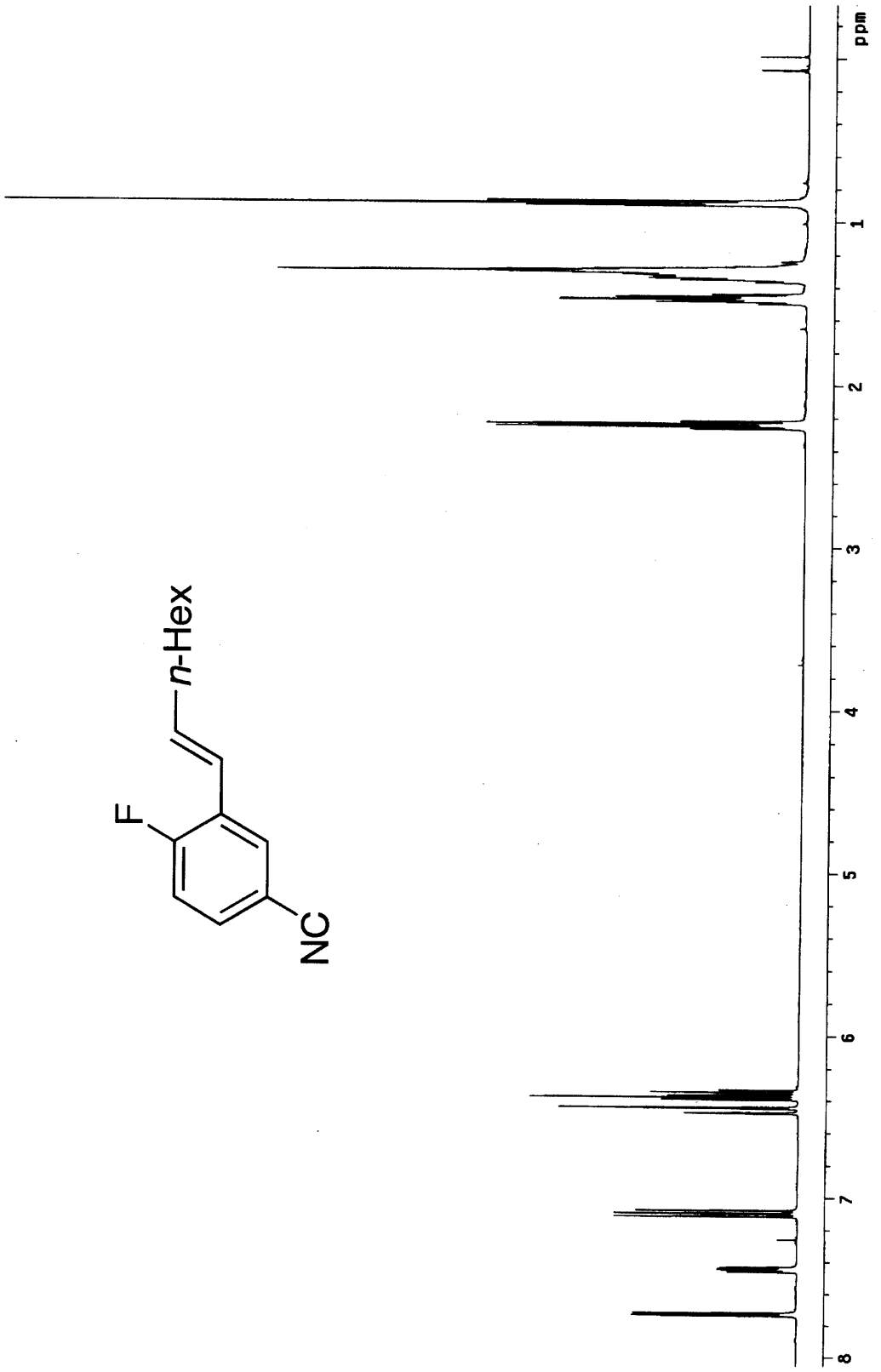


(*E*)-1-(2-Fluoro-5-cyanophenyl)-octene (Table 8, entry 2). Following general procedure G, a mixture of 3-bromo-4-fluorobenzonitrile (200 mg, 1.0 mmol), (*E*)-1-octenyl boronic acid (234 mg, 1.5 mmol), K_3PO_4 (425 mg, 2.0 mmol), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), and **1** (8.2 mg, 0.02 mmol) in THF (2.0 mL) was stirred at RT for 24 h. The crude product was purified via flash column chromatography on silica gel (4% ethyl acetate in hexanes) to provide the title compound as a yellow oil (224 mg, 97%). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.74 (dd, J = 3, 7 Hz, 1H), 7.46 (m, 1H), 7.11 (dd, J = 9, 10 Hz, 1H), 6.47 (d, J = 16 Hz, 1H), 6.37 (dt, J = 7, 16 Hz, 1H), 2.25 (q, J = 7 Hz, 2H), 1.47 (quintet, J = 7 Hz, 2H), 1.26-1.37 (m, 4H), 0.89 (t, J = 7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 162.8, 160.8, 136.9, 136.8, 131.7, 131.6, 131.3, 131.2, 127.4, 127.3, 120.0, 119.9, 118.2, 117.0, 116.8, 108.5, 108.4, 33.3, 31.6, 28.9, 28.8, 22.5, 14.0. ^{19}F NMR (282 MHz, $CDCl_3$) δ: -109.4. IR (neat, cm^{-1}): 2967, 2927, 2868, 2234, 1606, 1488, 1246, 1104, 969. A satisfactory elemental analysis was not obtained for this compound. The ^{1}H and ^{13}C NMR spectra follow.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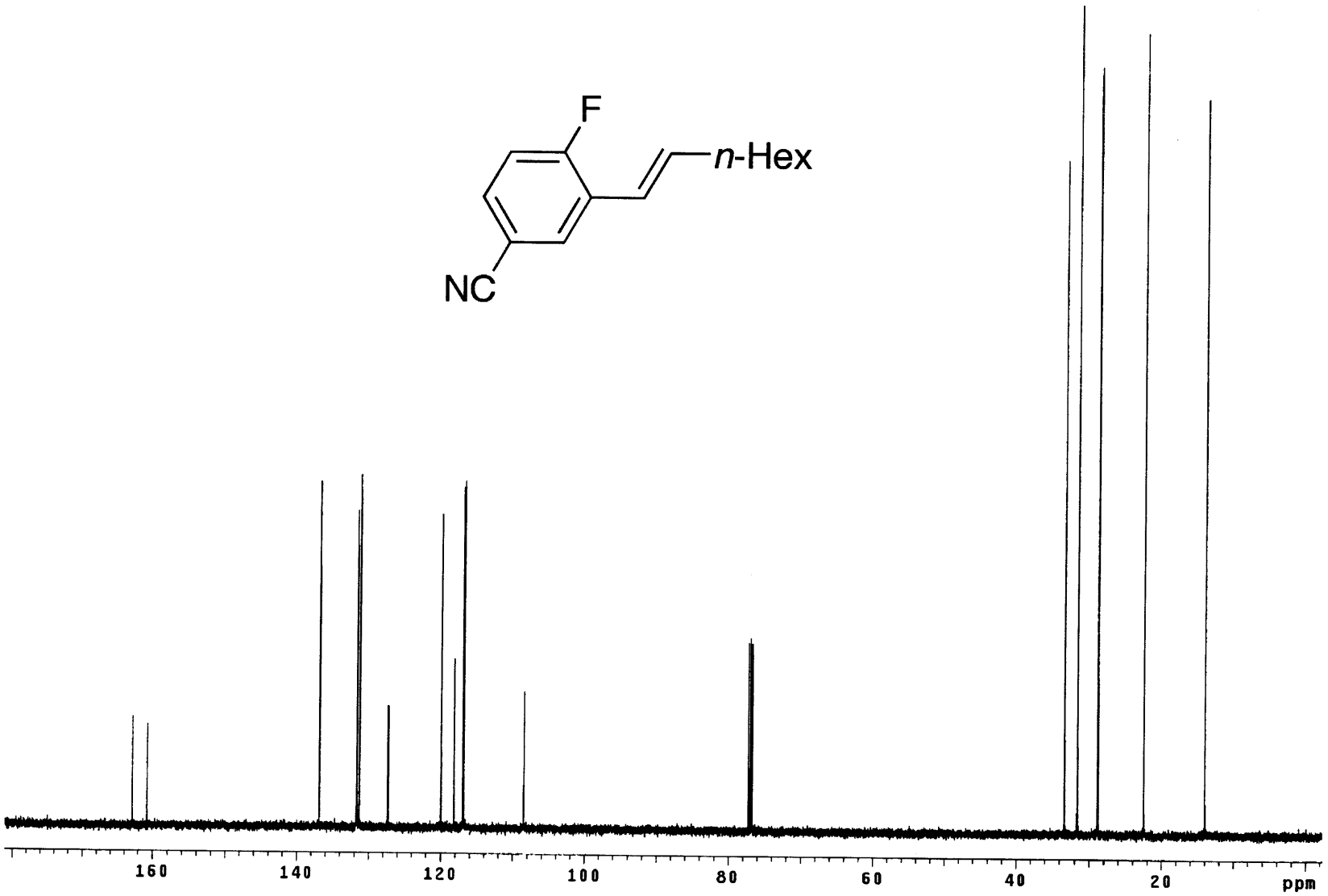
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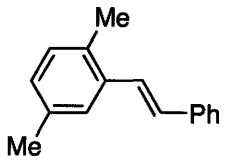
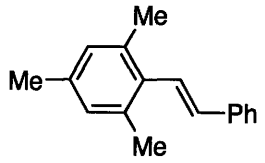
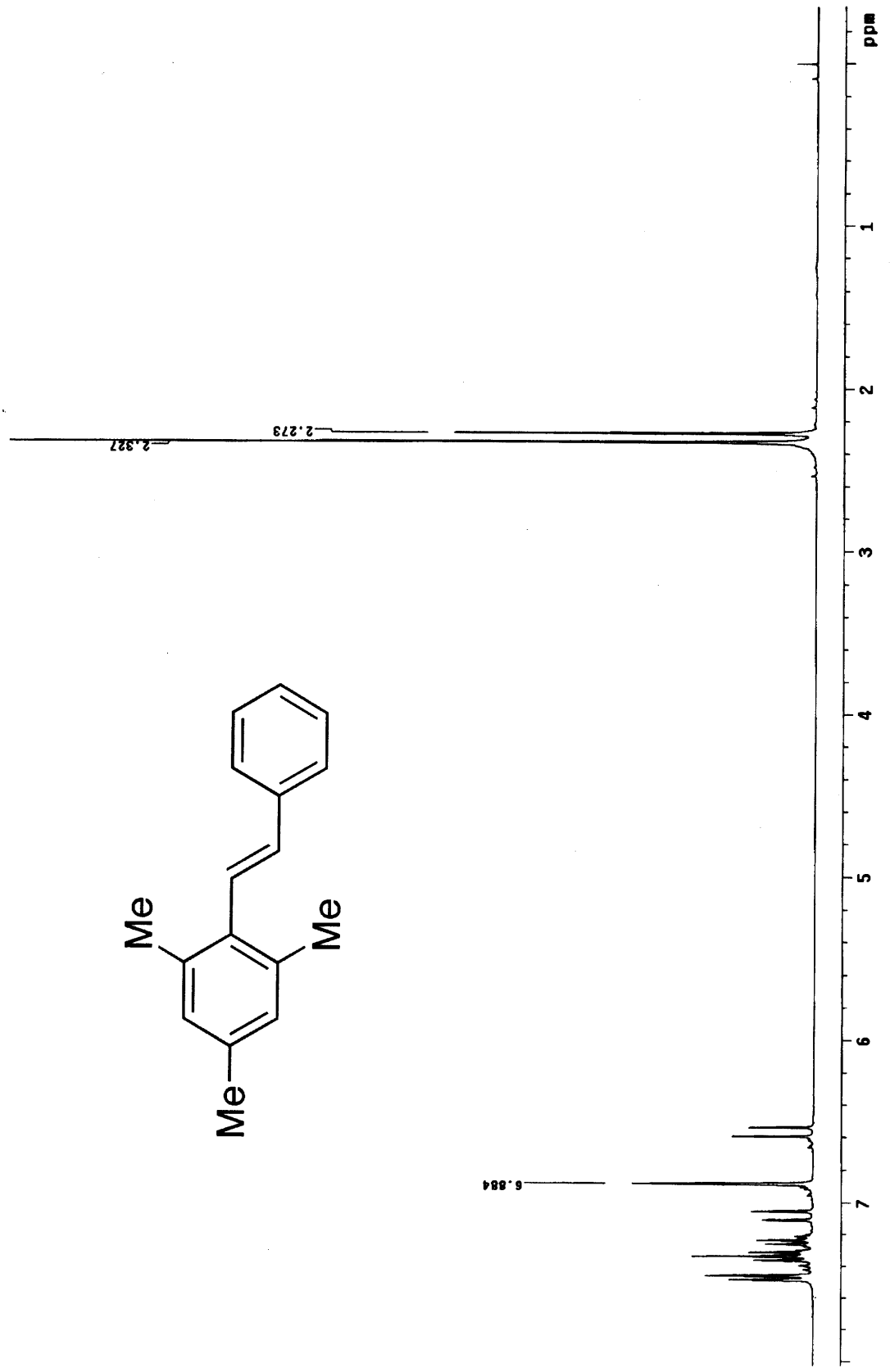


***trans*-2,5-Dimethylstilbene (Table 8, entry 3).** Following general procedure G, a mixture of 2-bromo-*p*-xylene (185 mg, 1.0 mmol), (*E*)-β-styrene boronic acid (225 mg, 1.5 mmol), K_3PO_4 (425 mg, 2.0 mmol), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), and **1** (8.2 mg, 0.02 mmol) in THF (2.0 mL) was heated to 40 °C with stirring for 24 h. The crude product was purified via flash column chromatography on silica gel (hexanes to 5% ethyl acetate in hexanes) to provide the title compound as a white solid (211 mg, 97%), mp 42-43 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.50(d, J = 8 Hz, 2H), 7.28-7.40(m, 3H), 7.23 (d, J = 8 Hz, 2H), 6.96-7.06 (m, 3H), 2.36 (s, 3H), 2.33 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 137.7, 136.0, 135.4, 132.7, 130.3, 130.0, 128.6, 128.3, 127.4, 126.5, 126.4, 125.9, 21.0, 19.4. IR (neat, cm^{-1}): 3026, 2922, 1599, 1499, 1448, 1266, 961. Anal. Calcd for $C_{16}H_{16}$: C, 92.26; H, 7.74. Found: C, 92.00; H, 7.70.



***trans*-2,4,6-Trimethylstilbene (Table 8, entry 4).** Following general procedure G, a mixture of 2-bromomesitylene (199 mg, 1.0 mmol), (*E*)-β-styrene boronic acid (225 mg, 1.5 mmol), K_3PO_4 (425 mg, 2.0 mmol), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), and **1** (8.2 mg, 0.02 mmol) in THF (2.0 mL) was heated to 40 °C with stirring for 24 h. The crude product was purified via flash column chromatography on silica gel (hexanes to 1% ethyl acetate in hexanes) to provide the title compound as a white solid (219 mg, 99%), mp 49-50 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.47 (d, J = 7 Hz, 2H), 7.34 (t, J = 7 Hz, 2H), 7.25 (d, J = 7 Hz, 1H), 7.08 (d, J = 16 Hz, 1H), 6.88 (s, 2H), 6.58 (d, J = 16 Hz, 1H), 2.33 (s, 6H), 2.27 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 137.7, 136.2, 136.1, 133.9, 133.6, 128.7, 128.6, 127.4, 126.9, 126.2, 21.0, 20.9. IR (neat, cm^{-1}): 3024, 2917, 1598, 1496, 1449, 1377, 1266, 970. A satisfactory elemental analysis was not obtained for this compound. The ^{1}H and ^{13}C NMR spectra follow.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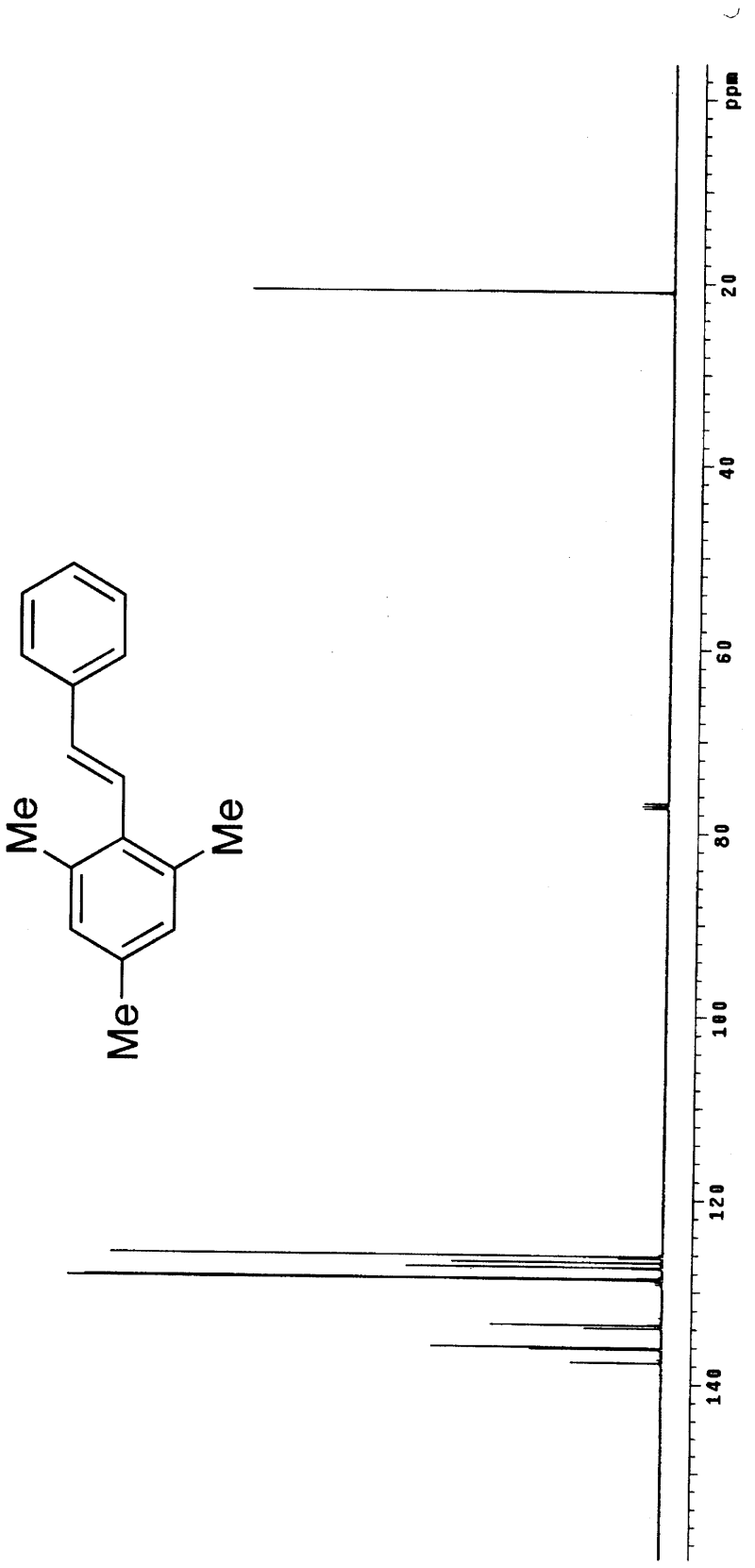
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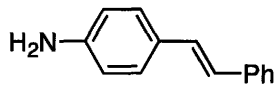
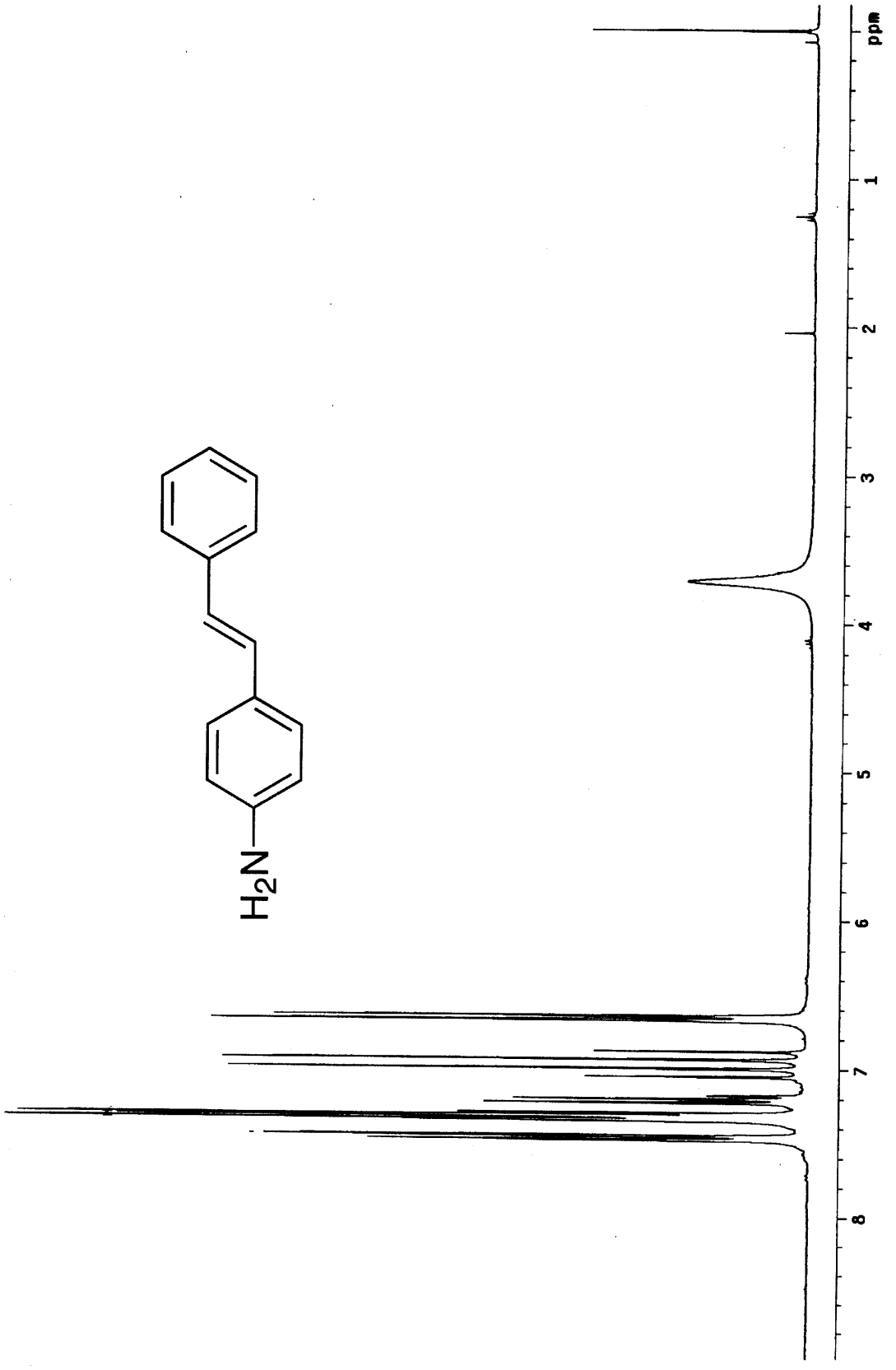


***trans*-4-Aminostilbene (Table 8, entry 5)**. Following general procedure G, a mixture of 4-bromoaniline (172 mg, 1.0 mmol), (*E*)-β-styrene boronic acid (225 mg, 1.5 mmol), K_3PO_4 (425 mg, 2.0 mmol), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), and **1** (8.2 mg, 0.02 mmol) in THF (2.0 mL) was heated to 40 °C with stirring for 24 h. The crude product was purified via flash column chromatography on silica gel (1:4 ethyl acetate:hexanes) to provide the title compound as a orange solid (171 mg, 88%), mp 147-148 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.47 (d, J = 7 Hz, 2H), 7.32 (t, J = 7 Hz, 4H), 7.20 (t, J = 7 Hz, 1H), 6.97 (q, J = 16 Hz, 2H), 6.66 (d, J = 8 Hz, 2H), 3.71 (bs, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 146.1, 137.9, 128.6, 128.5, 127.9, 127.7, 126.8, 126.1, 125.0, 115.1. IR (neat, cm^{-1}): 3453, 3362, 3029, 1616, 1591, 1517, 1286, 1180, 969. A satisfactory elemental analysis was not obtained for this compound. The ^{1}H and ^{13}C NMR spectra follow.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1.5 References

(1) Miyaura, N.; Yamada, K.; Suzuki, A. *Tetrahedron Lett.* **1979**, *36*, 3437.

(2) (a) Miyaura, N.; Suzuki, A. *Chem Rev.* **1995**, *95*, 2457. (b) Suzuki, A. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F.; Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, 1998; Chapter 2. (c) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147-168. (d) Miyaura, N. *Top. Curr. Chem.* **2002**, *219*, 11. (e) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359. (f) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633. (g) Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* **2004**, *15*, 2419.

(3) For a review on Pd-catalyzed couplings of aryl chlorides see: Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176.

(4) (a) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550. (b) Zapf, A.; Ehrentraut, A.; Beller, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 4153. (c) Alonso, D. A.; Nájera, C.; Pacheco, M. C. *J. Org. Chem.* **2002**, *67*, 5588. (d) Bedford, R. B.; Cazin, C. S. J.; Hazelwood, S. L. *Angew. Chem., Int. Ed.* **2002**, *41*, 4120. (e) Bedford, R. B.; Hazelwood, S. L.; Limmert, M. E. *Chem. Commun.* **2002**, 2610. (f) Bedford, R. B.; Hazelwood, S. L.; Limmert, M. E.; Albisson, D. A.; Draper, S. M.; Scully, P. N.; Coles, S. J.; Hursthouse, M. B. *Chem. Eur. J.* **2003**, *9*, 3216.

(5) (a) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722. (b) Zim, D.; Gruber, A. S.; Ebeling, G.; Dupont, J.; Monteiro, A. L. *Org. Lett.* **2000**, *2*, 2881. (c) Netherton, M. R.; Dai, C.; Neuschutz, K.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 10099. (d) Colacot, T. J.; Gore, E. S.; Kuber, A. *Organometallics* **2002**, *21*, 3301. (e) Kirchhoff, J. H.; Netherton, M. R.; Hills, I. D.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 13662. (f) Gstöttmayr, C. W. K.; Böhm, V. P. W.; Herdtweck, E.; Grosche, M.; Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1363. (g) Hu, Q.-S.; Lu, Y.; Tang, Z.-Y.; Yu, H.-B. *J. Am. Chem. Soc.* **2003**, *125*, 2856. (h) Altenhoff, G.; Goddard, R.; Lehmann, C. W.; Glorius, F. *Angew. Chem., Int. Ed.* **2003**, *42*, 3690. (i) Navarro, O.; Kelly, R. A., III; Nolan, S. P. *J. Am.*

Chem. Soc. **2003**, *125*, 16194. (j) Kwong , F. Y.; Chan, K. S.; Yeung, C. H.; Chan, A. S. C. *Chem. Commun.* **2004**, 2336.

(6) Altenhoff, G.; Goddard, R.; Lehmann, C. W.; Glorius, F. *J. Am. Chem. Soc.* **2004**, *126*, 15195.

(7) (a) Cho, S. Y.; Shibasaki, M. *Tetrahedron: Asymmetry* **1998**, *9*, 3751. (b) Cammidge, A. N.; Crépy, K. V. L. *Chem. Commun.* **2000**, 1723. (c) Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 12051. (d) Castanet, A. S.; Colobert, F.; Broutin, P. E.; Obringer, M. *Tetrahedron: Asymmetry* **2002**, *13*, 659. (e) Herrbach, A.; Marinetti, A.; Baudoin, O.; Guenard, D.; Gueritte, F. *J. Org. Chem.* **2003**, *68*, 4897. (f) Cammidge, A. N.; Crépy, K. V. L. *Tetrahedron* **2004**, *60*, 4377. (g) Mikami, K.; Miyamoto, T.; Hatano, M. *Chem. Commun.* **2004**, 2082.

(8) (a) Böhm, V. P. W.; Gstöttmayr, C. W. K.; Weskamp, T.; Herrmann, W. A. *J. Organomet. Chem.* **2000**, *595*, 186. (b) Andrus, M. B.; Song, C. *Org. Lett.* **2001**, *3*, 3761. (c) Zhao, Y. H.; Zhou, Y. Y.; Ma, D. D.; Liu, J. P.; Li, L.; Zhang, T. Y.; Zhang, H. B. *Org. Biomol. Chem.* **2003**, *1*, 1643.

(9) (a) Wallow, T. I.; Novak, B. M. *J. Org. Chem.* **1994**, *59*, 5034. (b) Campi, E. M.; Jackson, W. R.; Marcuccio, S. M.; Naeslund, C. G. M. *Chem. Commun.* **1994**, 2395. (c) Darses, S.; Jeffery, T.; Genêt, J.-P.; Brayer, J.-L.; Demoute, J.-P. *Tetrahedron Lett.* **1996**, *37*, 3857. (d) Bumagin, N. A.; Bykov, V. V. *Tetrahedron* **1997**, *53*, 14437. (e) Badone, D.; Baroni, M.; Cardamone, R.; Ielmini, A.; Guzzi, U. *J. Org. Chem.* **1997**, *62*, 7170. (f) Goodson, E. F.; Wallow, T. I.; Novak, B. M. *Org. Synth.* **1998**, *75*, 61. (g) Blettner, C. G.; König, W. A.; Stenzel, W.; Schotten, T. *J. Org. Chem.* **1999**, *64*, 3885. (h) Bussolari, J. C.; Rehborn, D. C. *Org. Lett.* **1999**, *1*, 965. (i) Kabalka, G. W.; Pagni, R. M.; Hair, C. M. *Org. Lett.* **1999**, *1*, 1423. (j) Chi, S. M.; Choi, J.-K.; Yum, E. K.; Chi, D. Y. *Tetrahedron Lett.* **2000**, *41*, 919. (k) Zim, D.; Monteiro, A. L.; Dupont, J. *Tetrahedron Lett.* **2000**, *41*, 8199. (l) Ma, D.; Wu, Q. *Tetrahedron Lett.* **2001**, *42*, 5279. (m) Kabalka, G. W.; Namboodiri, V.; Wang, L. *Chem. Commun.* **2001**, 775. (n) LeBlond, C. R.; Andrews, A. T.; Sun, Y.; Sowa, J. R. *Org. Lett.* **2001**, *3*, 1555. (o) Sakurai, H.; Tsukuda, T.; Hirao, T. *J. Org. Chem.* **2002**, *67*, 2721. (p) Molander, G. A.; Biolatto, B. *Org. Lett.* **2002**, *4*, 1867. (q) Molander, G. A.; Biolatto, B. *J. Org. Chem.* **2003**, *68*, 4302.

(10) A portion of this work has previously been communicated: Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1871.

(11) Leroux, F.; Schlosser, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4272.

(12) Tomori, H.; Fox, J. M.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 5334.

(13) Yin, J.; Rainka, M. P.; Zhang, X.-X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1162.

(14) For reviews of C-H activation, see: (a) Shilov, A. E.; Shul'pin, G. B. *Chem. Rev.* **1997**, *97*, 2879. (b) Dyker, G. *Agnew. Chem., Int. Ed.* **1999**, *38*, 1698. (c) Miura, M.; Nomura, M. *Top. Curr. Chem.* **2002**, *219*, 211.

(15) There is precedent for such chemoselectivity: Cámpora, J.; López, J. A.; Palma, P.; Valerga, P.; Spillner, E.; Carmona, E. *Angew. Chem., Int. Ed.* **1999**, *38*, 147.

(16) (a) Garrett, C. E.; Prasad, K. *Adv. Synth. Catal.* **2004**, *346*, 889. (b) Bien, J. T.; Lane, G. C.; Oberholzer, M. R. Removal of Metals from Process Streams: Methodologies and Applications. *Topics in Organometallic Chemisty,* **2004**, *6*, 263.

(17) Onak, T. *Organoborane Chemistry*; Academic Press: New York, New York 1975.

(18) Vedejs, E.; Chapman, R. W.; Fields, S. C.; Lin, S.; Schrimpf, M. R. *J. Org. Chem.* **1995**, *60*, 3020.

(19) We were under the impression that studies were conducted demonstrating the necessity of water for the efficient coupling of aryl boronate esters. We were, however, unable to locate any reports directly illustrating this theory.

(20) (a) Paul, F.; Hartwig, J. F. *J. Am. Chem. Soc.* **1994**, *116*, 5969. (b) Hartwig, J. F.; Paul, F. *J. Am. Chem. Soc.* **1995**, *117*, 5373. (c) Galardon, E.; Ramdeehul, S.; Brown, J. M.; Cowley, A.; Hii, K. K.; Jutand, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1760. (d) Hills, I. D.; Netherton, M. R.; Fu, G. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 5749. (e) Strieter, E. R.; Blackmond, D. G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 13978.

(21) Liu, S.-H.; Choi, M. J.; Fu, G. C. *Chem. Commun.* **2001**, 2408.

(22) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020.

(23) Electron-poor aryl boronic acids are less nucleophilic and undergo transmetalation at a slower rate than electron-neutral and -rich aryl boronic acids. Additionally, electron-poor boronic acids are prone to homocoupling. For a recent report, see: Wong, M. S.; Zhang, X. L. *Tetrahedron Lett.* **2001**, *42*, 4087. Electron-poor aryl boronic acids are more susceptible to metal-catalyzed protodeboronation. For a report, see: Kuivila, H. G.; Reuwer, J. F.; Mangravite, J. A. *J. Am. Chem. Soc.* **1964**, *86*, 2666.

(24) For an example of aryl fluorides blocking oxidation, see: Rosenblum, S. B.; Huynh, T.; Afonso, A.; Davis, H. R. Jr.; Yumibe, N.; Clader, J. W.; Burnett, D. A. *J. Med. Chem.* **1998**, *41*, 973.

(25) (a) Bush, I. E.; Mahesh, V. B. *Biochem. J.* **1964**, *93*, 236-255. (b) Abel, S. M.; Back. D. J.; Maggs, J. L.; Park, B. K. *J. Steriod Biochem. Mol. Biol.* **1993**, *46*, 833.

(26) Park, B. K.; Kitteringham, N. R. *Drug Metab. Rev.* **1994**, *26*, 605.

(27) Prices from Sigma-Aldrich Co.: 2,3-difluorophenyl boronic acid, $52.40/5g; 4-fluorophenyl boronic acid, $16.20/1g.

(28) For examples of Suzuki-Miyaura couplings with 2,4-difluorophenyl boronic acid, see: (a) Thiemann, T.; Umeno, K. Wang, J.; Tabuchi, Y.; Arima, K.; Wantabe, M.; Tanaka, Y.; Gorohmaru, H.; Mataka, S. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2090. (b) Feuerstein, M.; Berthiol, F.; Doucet, H.; Santelli, M. *Synlett* **2002**, *11*, 1807.

(29) (a) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 3387. (b) Botella, L.; Nájera, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 179.

(30) Barder, T. E.; Buchwald, S. L. *Org. Lett.* **2004**, *6*, 2649.

(31) Li, W.; Nelson, D. P.; Jensen, M. S.; Hoerrner, R. S.; Cai, D.; Larsen, R. D.; Reider, P. J. *J. Org. Chem.* **2002**, *67*, 5394.

(32) (a) Batey, R. A.; Thadani, A. N.; Smil, D. V. *Org. Lett.* **1999**, *1*, 1683. (b) Batey, R. A.; Thadani, A. N.; Smil, D. V. *Tetrahedron Lett.* **1999**, *40*, 4289. (c) Batey, R. A.; MacKay, D. B.; Santhakumar, V. *J. Am. Chem. Soc.* **1999**, *121*, 5075. (d) Batey, R. A.; Thadani, A. N.; Smil, D. V.; Lough, A. J. *Synthesis* **2000**, 990. (e) Molander, G. A.; Ito, T. *Org. Lett.* **2001**, *3*, 393.

(33) Matos, K.; Soderquist, J. A. *J. Org. Chem.* **1998**, *63*, 461.

(34) Raheem, I. T.; Goodman, S. N.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 706.

(35) Molander, G. A.; Bernardi, C. R. *J. Org. Chem.* **2002**, *67*, 8424.

(36) (a) Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518. (b) Alaimo, P. J.; Peters, D. W.; Arnold, J.; Bergman, R. G. *J. Chem. Ed.* **2001**, *78*, 64.

(37) Yin, J.; Rainka, M. P.; Zhang, X.-X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1162.

(38) Wolfe, J. P; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 2413.

(39) Littke, A. F.; Schwarz, L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 6343.

(40) Curran, D. P.; Kuo, S.-C. *J. Org. Chem.* **1984**, *49*, 2063.

(41) Huang, W., et al. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 561.

(42) Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1871.

(43) Cram, D. J.; Bryant, J. A.; Doxsee, K. M. *Chem. Lett.* **1987**, 19.

(44) Zhao, Y., et al. *Org. Biomol. Chem.* **2003**, *1*, 1643.

(45) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020.

(46) Jung, Y. C.; Mishra, R. K.; Yoon, C. H.; Jung, K.W. *Org. Lett.* **2003**, *5*, 2231.

(47) Widdowson, D. A.; Zhang, Y.-Z. *Tetrahedron* **1986**, *42*, 2111.

(48) Hori, M., et al. *Chem. Pharm. Bull.* **1974**, *22*, 2004.

(49) Sato, T., et al. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 766.

(50) Kamikawa, T.; Uozumi, Y.; Hayashi, T. *Tett. Lett.* **1996**, *37*, 3161.

(51) Saa, J. M.; Martorell, G. *J. Org. Chem.* **1993**, *58*, 1963.

(52) Barder, T. E.; Buchwald, S. L. *Org. Lett.* **2004**, *6*, 2649.

(53) Nguyen, H. N.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 11818.

Chapter 2.

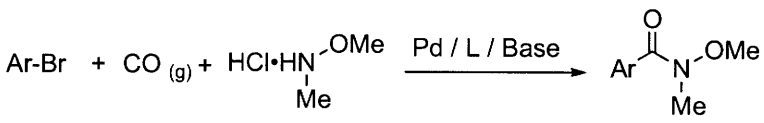
Synthesis of Weinreb Amides via Palladium-Catalyzed Aminocarbonylation of Aryl Bromides.

2.1 Introduction

N-Methoxy-*N*-methyl amides (Weinreb amides) are well-established acylating agents.[1] Since the original report by Nahm and Weinreb in 1981,[2] significant effort has been devoted toward the development of mild and general methods for their preparation. The ability of Weinreb amides to undergo selective addition of one equivalent of a variety of organometallic reagents is key to their utility. The importance of these amides as reliable and general acylating agents is reinforced by the frequency with which they appear in advanced synthetic intermediates.[1,3]

To access complex structures containing Weinreb amides more readily, new, mild and general means for their preparation are required. The conversion of acid chlorides[1c,2] to Weinreb amides is straightforward. In addition, esters[4] are also commonly employed precursors. Carboxylic acids can also be converted into the corresponding Weinreb amides by a number of one-pot protocols.[5] Furthermore, methods have been reported for the conversion of lactones, amides and anhydrides to Weinreb amides.[1c] Murakami has also developed a strategy for the synthesis of vinyl and aryl Weinreb amides using a Stille-type cross-coupling of *N*-methoxy-*N*-methylcarbamoyl chloride with vinyl or aryl stannanes.[6]

Since its initial discovery by Heck in 1974,[7] the three component coupling of an aryl halide, carbon monoxide and a nucleophile has been developed to allow the selective synthesis of benzannulated heterocycles[8] and aromatic acyl derivatives such as esters,[7a,9a] β-ketoesters,[9b] amides,[7b,9c,9d] α-ketoamides,[9e] ketones,[9f] aldehydes,[9g] and anhydrides.[9h] Despite the considerable attention that aminocarbonylation reactions have received, there is, to our knowledge, only one example of a Weinreb amide synthesized in such a way. This reaction was reported, but not highlighted in the main text, by Zhuang and coworkers at Merck.[10] Herein, we report a general Pd-catalyzed process for the conversion of aryl bromides to Weinreb amides that can be carried out at one atmosphere of carbon monoxide.

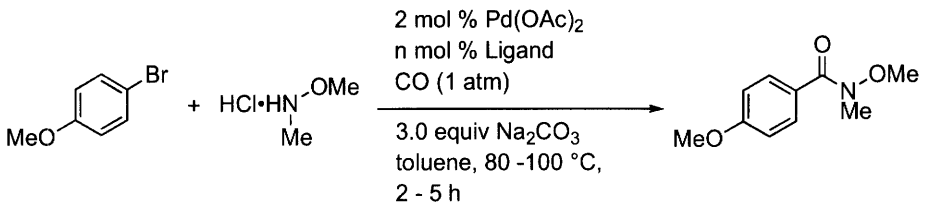


Scheme 1. Synthesis of Weinreb Amides via Aminocarbonylation of Aryl Bromides.

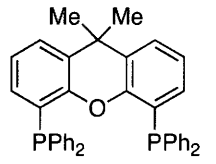
2.2 Results and Discussion

Guided by the literature and our own results, we expected the most efficient ligands for the aminocarbonylation process to be bidentate phosphines possessing a large bite angle.[9a] Thus, we began our studies by examining the reaction shown in Table 1 using a series of bidentate phosphines as ligands. In addition, based on our success using biaryl monophosphines in a variety of Pd-catalyzed processes,[11] we also included SPhos as a representative of this ligand class. Despite the success of PPh_3 at higher pressures, reactions that employed PPh_3 or SPhos (Table 1, entries 1 and 2) were both ineffective under the atmospheric aminocarbonylation reaction conditions examined. A number of bidentate ligands that have been shown to be useful for other Pd-catalyzed processes were completely ineffective as supporting ligands as well. These included (*S*)-BINAP,[9a,12a] dppp,[12b] dppb,[12c] dppf[9c, 9f] and DPEphos.[12d] These are ligands whose bite angles span a range from 92° to 108°.[13] Only van Leeuwen's Xantphos ligand,[14] with the largest bite angle (110°), was effective for the synthesis of Weinreb amides from the corresponding aryl bromides. We began our work using a Pd: Xantphos ratio of 1:1 based on previous work in our labratory that showed excess Xantphos to be deleterious in Pd-catalyzed C-N bond forming reactions.[15] Using Xantphos as the supporting ligand, the reaction at 100 °C resulted in 36% conversion and 30% of the desired product after only 2 hours. Unfortunately, allowing the reaction to run for 5 hours at 100 °C resulted in only 90% conversion and 87% of the desired product. Surprisingly, lowering the temperature to 80 °C and allowing the reaction to run for 5 hours led to the complete consumption of the aryl bromide and 89% isolated yield of the desired product. This unexpected result may be attributed to enhanced catalyst stability at lower temperatures. With these conditions in hand, we explored the range of this method.

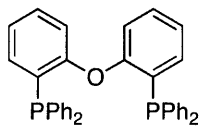
Table 1. Aminocarbonylation of 4-Bromoanisole using Various Ligands.[a]



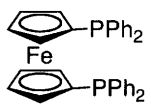
entry	n mol %	Ligand	Bite Angle	T (°C)	time	% Conversion[b]	% Yield[b]
1	8	PPh_3	145[c]	100	2 h	< 1	0
2	5	SPhos	217[c,d]	100	2 h	< 1	0
3	2.2	(*S*)-BINAP	92	100	2 h	< 1	0
4	2.2	dppp	95	100	2 h	< 1	0
5	2.2	dppb	99	100	2 h	< 1	0
6	2.2	dppf	106	100	2 h	< 1	0
7	2.2	DPEphos	108	100	2 h	< 1	0
8	2	Xantphos	110	100	2 h	36	30
9	2	Xantphos	110	100	5 h	90	87
10[e]	2	Xantphos	110	80	5 h	100	89[f]



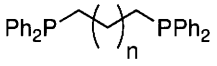
Xantphos



DPEphos

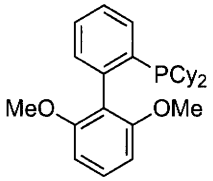


dppf

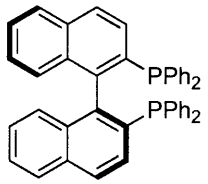


dppp: n = 1

dppb: n = 2



SPhos



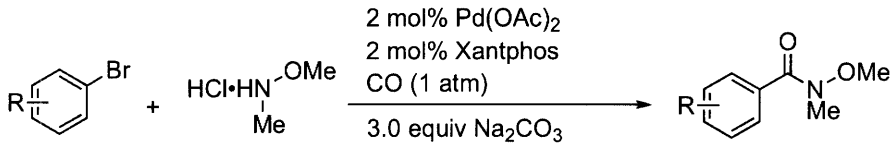
(*S*)-BINAP

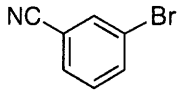
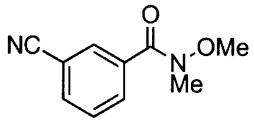
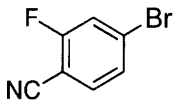
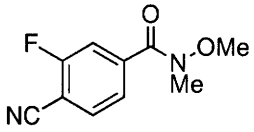
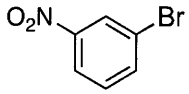
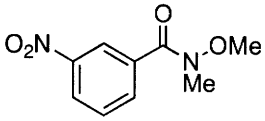
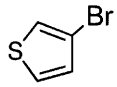
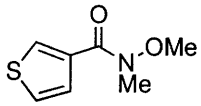
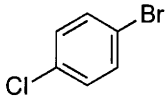
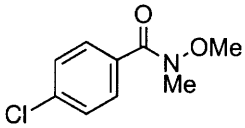
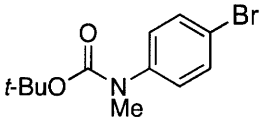
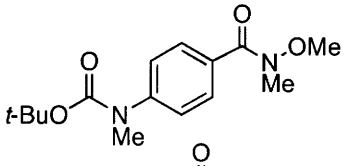
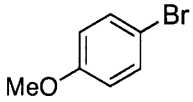
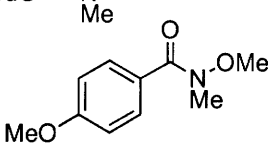
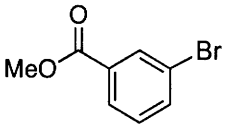
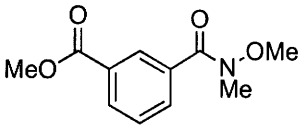
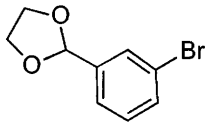
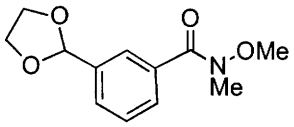
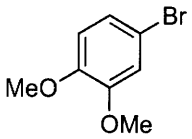
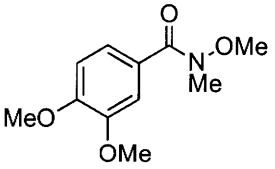
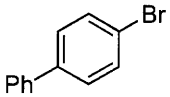
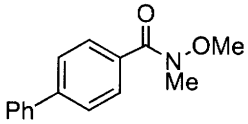
[a]Reaction conditions: 2 mol % $Pd(OAc)_2$, n mol % ligand, 1 mmol 4-bromoanisole, 1.5 mmol amine, 3 mmol base in toluene (2 mL) at 100 °C. [b]Determined by G.C., average of 2 runs. [c]Cone angles. [d]See reference 10c. [e]Reaction was run at 80 °C for 5 h. [f]Isolated yield, average of 2 runs.

To determine the scope of this process, a set of aryl bromides were examined as substrates with which the method demonstrated good generality. This was exemplified by the high-yield transformation of 3-bromonitrobenzene, 3-bromobenzonitrile and 4-bromo-2-fluorobenzonitrile to the corresponding Weinreb amides (Table 2, entries 1-3). Similarly, a *tert*-butyl carbamate group was untouched during the aminocarbonylation of *tert*-butyl *N*-(4-bromophenyl)carbamate (Table 2, entry 6). The high yield realized with a methyl ester-containing substrate was surprising (Table 2, entry 8); no product resulting from addition of the hydroxylamine to the ester group was detected. It is also important to note that the selective aminocarbonylation of aryl bromides can be achieved in the presence of aromatic fluoride and chloride groups (Table 2, entries 2 and 5). Electron-rich aryl bromides were also cleanly converted into the corresponding Weinreb amides (Table 2, entries 4, 6, 7 and 10). The reaction of 3-bromothiophene was of particular interest due to the common occurrence of the thiophene moiety in organic electronic materials.[16] Though sodium carbonate was employed as the base in most reactions shown in Table 2, it is also possible to use organic bases such as triethylamine (Table 2, entries 9 – 11).

Despite the wide scope indicated by the results described in Table 2, there were several substrates that were not successfully converted to the corresponding Weinreb amides using this procedure. Specifically, *ortho*-substituted aryl bromides were not satisfactorily converted to product. Given that (Xantphos)Pd-based catalyst systems can be used to transform *ortho*-substituted aryl bromides in C-N coupling reactions,[17] it is likely that the problematic step in this reaction involves the nucleophilic addition of the amine to the Pd-acyl intermediate.[18] If this process is sluggish, the Pd-acyl intermediate could be vulnerable to putative decomposition processes leading to an inefficient overall transformation.

Table 2. Conversion of Aryl Bromides to Weinreb Amides via Pd-Catalyzed Aminocarbonylation at 1 atm.[a]

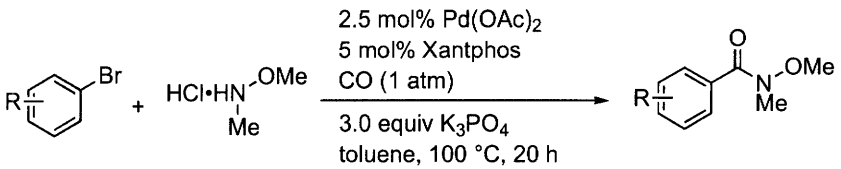


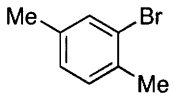
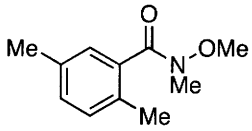
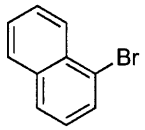
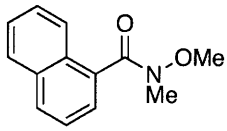
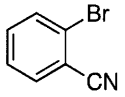
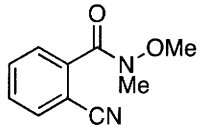
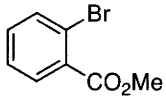
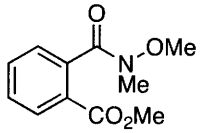
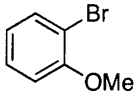
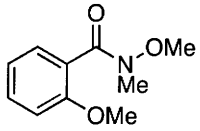
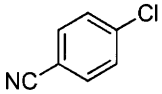
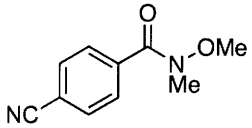
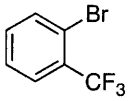
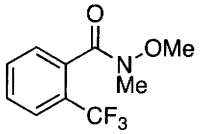
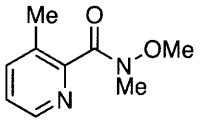
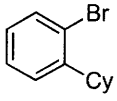
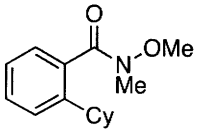
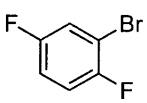
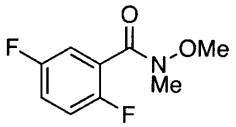
entry	ArBr	Product	% yield[b]
1			88
2			90
3			87
4			91
5			87
6			95
7			89
8			88
9			93[c]
10			89[c]
11			94[c]

[a]Reaction conditions: 2 mol % $Pd(OAc)_2$, 2 mol % Xantphos, 1 mmol aryl bromide, 1.5 mmol amine, 3 mmol Na_2CO_3 in toluene (2 mL) at 80 °C. [b]Yields are an average of 2 runs. [c]3 mmol of Et_3N was used as base.

In an effort to overcome this limitation, the reaction conditions were reevaluated. During optimization of the transformation of the test substrate, 2-bromo-*p*-xylene (Table 3, entry 1), it was found that use of potassium phosphate as the base with a Pd:Xantphos ratio of 1:2 at 100 °C led to complete conversion of the starting aryl bromide with formation of a high yield of the desired product. This new procedure was also effective for a variety of other *ortho*-substituted substrates. Both 1-bromonaphthalene and 2-bromobenzonitrile were efficiently converted to the corresponding Weinreb amides (Table 3, entries 2 and 3). A slightly higher quantity of catalyst (3 mol % Pd, 6 mol % Xantphos) was required to achieve full conversion in the case of (2-bromo)methylbenzoate and 2-bromoanisole (Table 3, entries 4 and 5). In the former case, the lower reactivity may possibly be attributed to the ability of the *ortho*-substituent to coordinate to the Pd center. The same quantity of catalyst at a slightly higher temperature (105 °C) was also effective for the aminocarbonylation of the electron-poor aryl chloride, 4-chlorobenzonitrile (Table 3, entry 6).

Table 3. Conversion of *ortho*-Substituted Aryl Bromides to Weinreb Amides via Pd-Catalyzed Aminocarbonylation at 1 atm.[a]



entry	ArBr	Product	% yield[b]
1			87
2			97
3			84
4			80[c]
5			81[c]
6			74[d]
7			94[e]
8			78[e]
9			90[f]
10			65[g]

[a]Reaction conditions: 2.5 mol % $Pd(OAc)_2$, 5 mol % Xantphos, 1 mmol aryl bromide, 1.5 mmol amine, 3 mmol K_3PO_4 in toluene (2 mL) at 100 °C. [b]Yields are an average of 2 runs. [c]3 mol % $Pd(OAc)_2$ was used. [d]3 mol % $Pd(OAc)_2$ was used at 105 °C. [e]3 mol % $Pd(OAc)_2$ was used in *m*-xylene (2 mL) at 110 °C. [f]3 mol % $Pd(OAc)_2$ was used in *m*-xylene (2 mL) at 120 °C. [g]2.5 mol % $Pd(OAc)_2$ was used in *m*-xylene (2 mL) at 110 °C.

While these conditions were effective for most *ortho*-substituted aryl bromides, substrates with large *ortho*-substituents and/or certain functional groups remained unreactive. The simplest way to overcome this lack of reactivity was to use *m*-xylene as solvent and increase the reaction temperature to 110 or 120 °C. In this way substrates such as 2-bromobenzotrifluoride, 2-bromo-3-methylpyridine, 2-cyclohexylbromobenzene and 2,5-difluorobromobenzene were successfully transformed into the corresponding Weinreb amides (Table 3, entries 7 – 10).

2.3 Conclusion

In conclusion, a protocol for the direct transformation of aryl bromides into the corresponding Weinreb amides via an aminocarbonylation protocol at atmospheric pressure has been developed. Electron-deficient, -neutral and -rich aryl bromides were all efficiently transformed to product. Furthermore, the process tolerates a wide variety of functional groups, is mild, and is operationally simple.

2.4 Experimental

2.4.1 General

All reactions were carried out under a carbon monoxide atmosphere, Air Gas. Elemental analyses were performed by Atlantic Microlabs Inc., Norcross, GA. Unless otherwise noted, THF, Et_2O, CH_2Cl_2 and toluene were purchased from J.T. Baker in CYCLE-TAINER® solvent-delivery kegs and vigorously purged with argon for 2 h. The solvents were further purified by passing them under argon pressure through two packed columns of neutral alumina (for THF and Et_2O) or through neutral alumina and copper (II) oxide (for toluene and CH_2Cl_2).[19] Unless otherwise stated, commercially obtained materials were used without further purification. The following aryl bromides were purchased form Acros: 3-

bromothiophene (filtered through basic alumina prior to use) and 2-bromo-3-methylpyridine. The following aryl bromides were purchased from Lancaster: 3-bromonitrobenzene, 4-bromo-2-fluorobenzonitrile, methyl 3-bromobenzoate and 1-bromo-2-cyclohexylbenzene. The following aryl bromides were purchased from Alfa Aesar: 3-bromobenzonitrile (Avocado Organics), 4-chloro-bromobenzene (Avocado Organics), 4-bromoanisole (filtered through basic alumina prior to use), 1-bromonaphthalene (Avocado Organics), 2-bromobenzonitrile, 2-bromobenzotrifluoride (filtered through basic alumina prior to use) and 2-bromoanisole (Avocado Organics; filtered through basic alumina prior to use). The following aryl bromides were purchased from Aldrich: 4-bromoveratrole (filtered through basic alumina prior to use), 4-bromobiphenyl, 2-(3-bromophenyl)-1,3-dioxolane (filtered through basic alumina prior to use), 2-bromo-*p*-xylene, methyl 2-bromobenzoate and 4-chlorobenzonitrile. The following compound was purchased from PCR Inc.: 2,5-difluorobromobenzene (filtered through basic alumina prior to use). *tert*-Butyl *N*-(4-bromophenyl)carbamate was prepared following literature procedures[20] using 4-bromoaniline (Aldrich), Di-*tert*-butyl dicarbonate (Aldrich) and Iodomethane (Alfa). *N, O*-dimethylhydroxylamine hydrochloride was purchased from Aldrich and Alfa Aesar. Xantphos was purchased form Strem and used without further purification. $Pd(OAc)_2$ was purchased from Strem, Inc. or supplied by Englehard. Sodium Carbonate was purchased from Mallinckrodt. *Anhydrous tribasic potassium phosphate was purchased from Fluka Chemical Co. and used as supplied.* The source (and thus the particle size) of the base employed may be critical for achieving efficient reactions.

All products of aminocarbonylation reactions were characterized by ^{1}H NMR, ^{13}C NMR, and IR spectroscopy, as well as elemental analysis (Atlantic Microlab, Inc). Two new compounds failed to give satisfactory elemental analyses. For these copies of ^{1}H and ^{13}C NMR spectra are included. Nuclear Magnetic Resonance spectra were recorded on a Varian Mercury 300 Infrared spectra were recorded using a Perkin-Elmer 2000 FT-IR. All ^{1}H NMR experiments are reported in δ units, parts per million (ppm) downfield from tetramethylsilane (internal standard) and were measured relative to the signals for residual chloroform (7.26 ppm), methylene chloride (5.32 ppm) or benzene (7.16 ppm) in the deuterated solvents. All ^{13}C NMR spectra are reported in ppm relative to deuterochloroform (77.23 ppm),

deuteromethylene chloride (54.00 ppm) or deuterobenzene (128.39 ppm), and all were obtained with ^{1}H decoupling. All ^{31}P NMR spectra are reported in ppm relative to H_3PO_4 (0 ppm). All ^{19}F NMR spectra are reported in ppm relative to trichlorofluoromethane (0 ppm). Melting points (uncorrected) were obtained on a Mel-Temp capillary melting point apparatus. Gas Chromatographic analyses were performed on a Hewlett-Packard 6890 gas chromatography instrument with an FID detector using 25 m x 0.20 mm capillary column with cross-linked methyl siloxane as a stationary phase.

The conversions in Table 1 were determined by G.C. using dodecane as an internal standard, added during reaction workup. The yields in Table 1, entries 1 – 9 were also determined by G.C. using dodecane as an internal standard. The yield in Table 1, entry 10, is an isolated yield (average of two runs) and the procedure is given below. The yields in Tables 2 and 3 are isolated yields (average of two runs). All compounds isolated were estimated to be ≥95% pure as determined by ^{1}H NMR and GC analysis and/or combustion analysis. The procedures described in this section are representative, and thus the yields may differ from those shown in Tables 1 - 3.

2.4.2 General Procedure A: Synthesis of Wienreb Amides via Pd-Catalyzed Aminocarbonylation

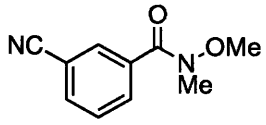
An oven-dried culture tube (18 x 150 mm, VWR) equipped with a Teflon® coated magnetic stir bar was sealed with a 14/20 rubber septum (inverted), evacuated, backfilled with nitrogen and cooled under nitrogen. All solid reagents were added by briefly removing the rubber septum: $Pd(OAc)_2$ (2 mol %, 0.02 mmol, 0.02 equiv., 4.5 mg), Xantphos (2 mol %, 0.02 mmol, 0.02 equiv., 11.6 mg), *N, O*-dimethylhydroxylamine hydrochloride (1.5 mmol, 1.5 equiv., 146 mg), and Na_2CO_3 (3 mmol, 3 equiv., 318 mg). Then, all liquid reagents were added dropwise via syringe: aryl bromide (1 mmol, 1 equiv.; aryl bromides which were solids at room temperature were added during the initial charge) and toluene (2 mL). After the addition of all reagents, the rubber septum was secured with several wrappings of electrical tape. Then, the reaction was purged for ~ 30 seconds with $CO_{(g)}$; following the gas purge a balloon was connected to the reaction using a short length of rubber tubing (~ 1 in.), a needle adapter and a 20 G needle. This balloon was then inflated with $CO_{(g)}$ and the reaction tube was submerged in a 80 °C preheated oil bath. The reaction mixture was heated at 80 °C with vigorous stirring until the aryl halide

had been completely consumed as judged by GC analysis. The reaction mixture was then allowed to cool to room temperature, diluted with ethyl acetate (~ 10 mL), filtered through a plug of celite (eluting with ethyl acetate) and concentrated under reduced pressure. The crude material obtained was purified by flash chromatography on silica gel.

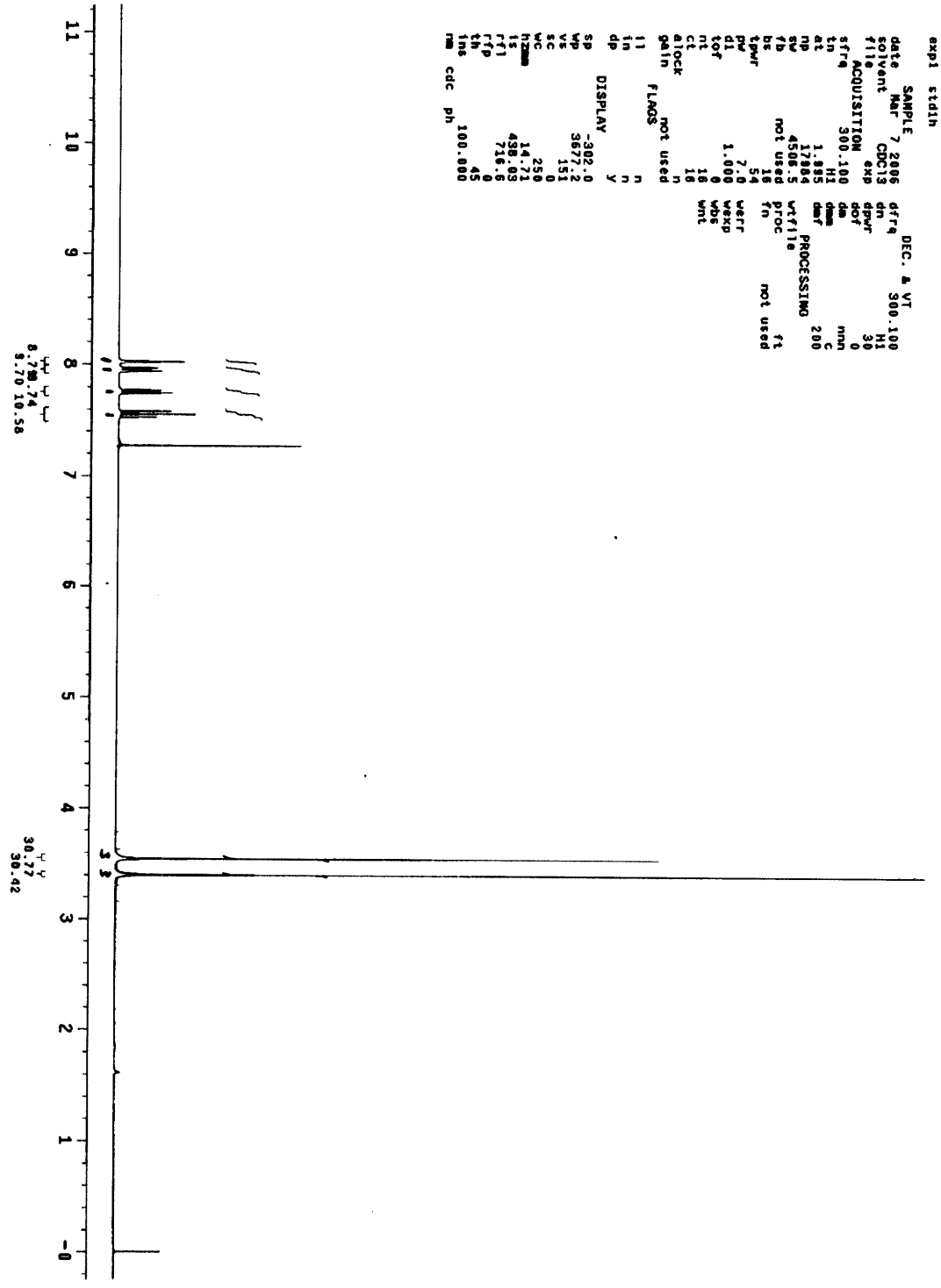
2.4.3 General Procedure B: Synthesis of Wienreb Amides via Pd-Catalyzed Aminocarbonylation of ortho-Substituted Aryl Halides

An oven-dried culture tube (18 x 150 mm, VWR) equipped with a Teflon® coated magnetic stir bar was sealed with a 14/20 rubber septum (inverted), evacuated, backfilled with nitrogen and cooled under nitrogen. All solid reagents were added by briefly removing the rubber septum: $Pd(OAc)_2$ (2.5 mol %, 0.025 mmol, 0.025 equiv., 5.6 mg), Xantphos (5 mol %, 0.05 mmol, 0.05 equiv., 28.9 mg), *N, O*-dimethylhydroxylamine hydrochloride (1.5 mmol, 1.5 equiv., 146 mg), and K_3PO_4 (3 mmol, 3 equiv., 637 mg). Then, all liquid reagents were added dropwise via syringe: aryl bromide (1 mmol, 1 equiv.; aryl bromides which were solids at room temperature were added during the initial charge) and solvent (2 mL, toluene or *m*-xylene). After the addition of all reagents, the rubber septum was secured with several wrappings of electrical tape. Then, the reaction was purged for ~ 30 seconds with $CO_{(g)}$; following the gas purge a balloon was connected to the reaction using a short length of rubber tubing (~ 1 in.), a needle adapter and a 20 G needle. This balloon was then inflated with $CO_{(g)}$ and the reaction tube was submerged in a 100 - 120 °C preheated oil bath. The reaction mixture was heated at 100 - 120 °C with vigorous stirring until the aryl halide had been completely consumed as judged by GC analysis. The reaction mixture was then allowed to cool to room temperature, diluted with ethyl acetate (~ 10 mL), filtered through a plug of celite (eluting with ethyl acetate) and concentrated under reduced pressure. The crude material obtained was purified by flash chromatography on silica gel.

2.4.4 Analysis and Characterization



3-Cyano-*N*-methoxy-*N*-methyl-benzamide (Table 2, entry 1). Following general procedure A, a mixture of 3-bromobenzonitrile (1 mmol, 0.182 g), $Pd(OAc)_2$ (2 mol %, 0.02 mmol, 0.02 equiv., 4.5 mg), Xantphos (2 mol %, 0.02 mmol, 0.02 equiv., 11.6 mg), *N, O*-dimethylhydroxylamine hydrochloride (1.5 mmol, 1.5 equiv., 146 mg), Na_2CO_3 (3 mmol, 3 equiv., 318 mg), and toluene (2 mL) was heated at 80 °C for 8 hours. The crude product mixture was purified by flash column chromatography on silica gel (50 % ethyl acetate in hexanes) to provide the title compound as a viscous light orange oil (181 mg, 95 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.04-8.01 (m, 1H), 7.97-7.93 (dm, *J* for the d = 7.98 Hz, 1H), 7.78-7.73 (dm, *J* for the d = 7.70 Hz, 1H), 7.55 (ddd, *J* = 0.55, 7.70, 7.98 Hz, 1H), 3.54 (s, 3H), 3.39 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 167.06, 135.02, 133.74, 132.48, 131.84, 128.93, 118.01, 112.10, 61.19, 33.06. IR (neat, cm^{-1}): 3075, 2975, 2938, 2821, 2232, 1647,1602, 1578, 1486, 1460, 1436, 1412, 1384, 1178, 986, 799, 734, 684. A satisfactory elemental analysis was not obtained for this compound: Anal. Calcd for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30. Found: C, 62.74; H, 5.22. The ^{1}H and ^{13}C NMR spectra follow.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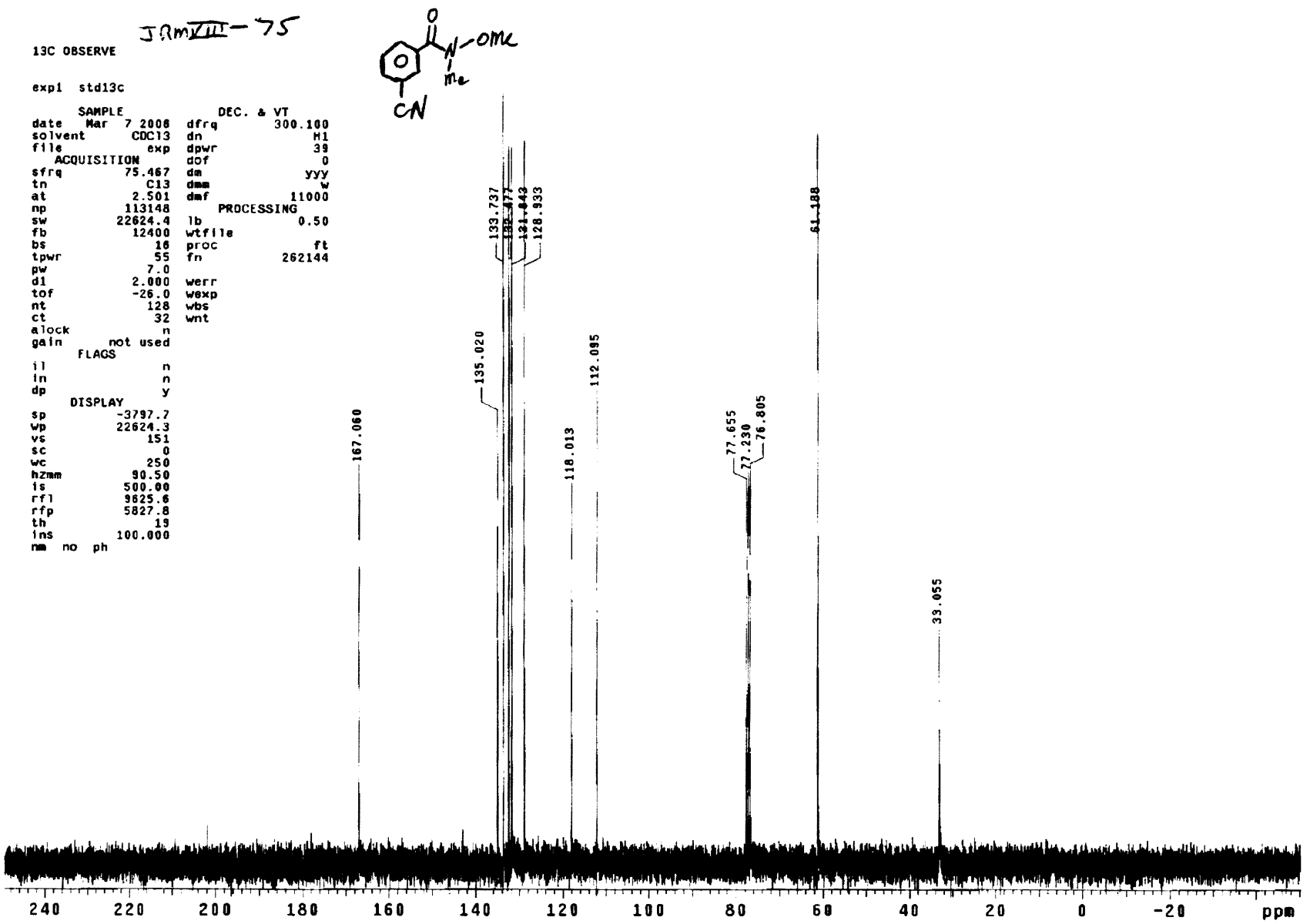
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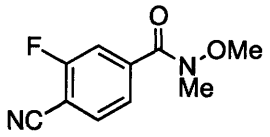
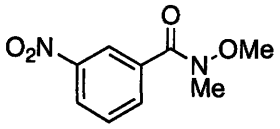
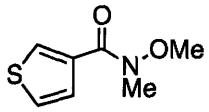


4-Cyano-3-fluoro-*N*-methoxy-*N*-methyl-benzamide (Table 2, entry 2). Following general procedure A, a mixture of 4-bromo-2-fluorobenzonitrile (1 mmol, 0.200 g), $Pd(OAc)_2$ (2 mol %, 0.02 mmol, 0.02 equiv., 4.5 mg), Xantphos (2 mol %, 0.02 mmol, 0.02 equiv., 11.6 mg), *N, O*-dimethylhydroxylamine hydrochloride (1.5 mmol, 1.5 equiv., 146 mg), Na_2CO_3 (3 mmol, 3 equiv., 318 mg), and toluene (2 mL) was heated at 80 °C for 18 hours. The crude product mixture was purified by flash column chromatography on silica gel (20 % - 50 % ethyl acetate in hexanes) to provide the title compound as a light yellow-orange solid (181 mg, 95 %), mp 43 - 44 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.71-7.66 (m, 1H), 7.60-7.52 (m, 2H), 3.54 (s, 3H), 3.38 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.38, 164.23, 160.79, 140.84, 140.74, 133.36, 124.70, 124.65, 116.64, 116.35, 113.42, 103.26, 103.06, 61.59, 33.17 (observed complexity due to C-F splitting; definitive assignments have not yet been made). ^{19}F NMR (282 MHz, $CDCl_3$) δ: -106.1. IR (neat, cm^{-1}): 3090, 2977, 2940, 2823, 2239, 1652, 1622, 1566, 1503, 1459, 1428, 1386, 1251, 1198, 1182, 1115, 990, 941, 887, 835, 750, 733, 714, 682, 668. Anal. Calcd for $C_{10}H_9FN_2O_2$: C, 57.69; H, 4.36. Found: C, 57.64; H, 4.37.

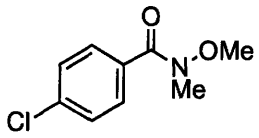


3-Nitro-*N*-methoxy-*N*-methyl-benzamide (Table 2, entry 3). Following general procedure A, a mixture of 3-bromonitrobenzene (1 mmol, 0.202 g), $Pd(OAc)_2$ (2 mol %, 0.02 mmol, 0.02 equiv., 4.5 mg), Xantphos (2 mol %, 0.02 mmol, 0.02 equiv., 11.6 mg), *N, O*-dimethylhydroxylamine hydrochloride (1.5 mmol, 1.5 equiv., 146 mg), Na_2CO_3 (3 mmol, 3 equiv., 318 mg), and toluene (2 mL) was heated at 80 °C for 8 hours. The crude product mixture was purified by flash column chromatography on silica gel (50 % ethyl acetate in hexanes) to provide the title compound as a tan colored solid (185 mg, 88 %), mp 41 – 43 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.60-8.58 (t, J = 19 Hz, 1H), 8.35-8.31 (ddd, J = 1.1, 2.5, 8.2 Hz, 1H), 8.07-8.03 (dt, J = 1.4, 7.7 Hz, 1H), 7.65-7.59 (t, J = 8 Hz, 1H), 3.57 (s, 3H), 3.41 (s, 3H). ^{13}C NMR (75

MHz, $CDCl_3$) δ: 167.02, 147.62, 135.43, 134.29, 129.22, 125.17, 123.41, 61.31, 33.13. IR (neat, cm^{-1}): 3087, 2974, 2938, 2822, 1648, 1616, 1577, 1532, 1485, 1459, 1438, 1417, 1383, 1351, 1215, 1170, 1099, 983, 918, 858, 815, 715. Anal. Calcd for $C_9H_{10}N_2O_4$: C, 51.43; H, 4.80. Found: C, 51.43; H, 4.70.

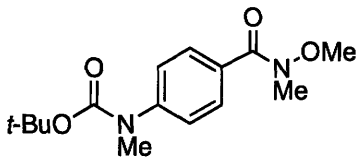


Thiophene-3- ***N*****-methoxy-*N*-methyl carboxamide (Table 2, entry 4).** Following general procedure A, a mixture of 3-bromothiophene (1 mmol, 0.163 g, 94 μL, filtered through basic alumina prior to use), $Pd(OAc)_2$ (2 mol %, 0.02 mmol, 0.02 equiv., 4.5 mg), Xantphos (2 mol %, 0.02 mmol, 0.02 equiv., 11.6 mg), *N, O*-dimethylhydroxylamine hydrochloride (1.5 mmol, 1.5 equiv., 146 mg), Na_2CO_3 (3 mmol, 3 equiv., 318 mg), and toluene (2 mL) was heated at 80 °C for 21 hours. The crude product mixture was purified by flash column chromatography on silica gel (50 % ethyl acetate in hexanes) to provide the title compound as a very light yellow oil (155 mg, 90 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.09-8.06 (dd, J = 1.1, 3.0 Hz, 1H), 7.59-7.57 (dd, J = 1.1, 5.1, 1H), 7.31-7.27 (dd, J = 3.0, 5.2 Hz, 1H), 3.66 (s, 3H), 3.37 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 163.57, 134.37, 130.79, 128.95, 124.77, 61.10, 33.17. IR (neat, cm^{-1}): 3109, 2970, 2936, 2819, 1627, 1518, 1458, 1427, 1387, 1350, 1217, 1182, 1153, 1078, 985, 931, 881, 851, 816, 792, 733, 707, 667, 621. Anal. Calcd for $C_7H_9NO_2S$: C, 49.10; H, 5.30. Found: C, 49.40; H, 5.40.

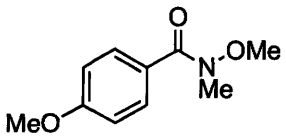


4-Chloro-*N*-methoxy-*N*-methyl-benzamide (Table 2, entry 5). Following general procedure A, a mixture of 4-chloro-bromobenzene (1 mmol, 0.191 g), $Pd(OAc)_2$ (2 mol %, 0.02 mmol, 0.02 equiv., 4.5 mg), Xantphos (2 mol %, 0.02 mmol, 0.02 equiv., 11.6 mg), *N, O*-dimethylhydroxylamine hydrochloride (1.5 mmol, 1.5 equiv., 146 mg), Na_2CO_3 (3 mmol, 3 equiv., 318 mg), and toluene (2 mL) was heated at 80 °C for 19 hours. The crude product mixture was purified by flash column chromatography on silica gel (50 % ethyl acetate in hexanes) to provide the title compound as a colorless oil (173 mg, 87 %). ^{1}H NMR

(300 MHz, $CDCl_3$) δ: 7.79-7.64 (m, 2H), 7.41-7.36 (m, 2H), 3.54 (s, 3H), 3.37 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 168.53, 136.62, 132.27, 129.82, 128.21, 61.06, 33.43. IR (neat, cm^{-1}): 3067, 2970, 2935, 2818, 1917, 1643, 1594, 1567, 1490, 1460, 1416, 1380, 1275, 1213, 1176, 1148, 1111, 1091, 1016, 995, 979, 887, 840, 746, 691, 656, 627. Anal. Calcd for $C_9H_{10}ClNO_2$: C, 54.15; H, 5.05. Found: C, 54.23; H, 4.92.

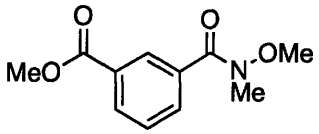


***tert*-Butyl *N*-methyl-*N*-(4- *N*-methoxy-*N*-methyl-benzamide)carbamate (Table 2, entry 6).** Following general procedure A, a mixture of *tert*-Butyl *N*-(4-bromophenyl)carbamate (1 mmol, 0.285 g), $Pd(OAc)_2$ (2 mol %, 0.02 mmol, 0.02 equiv., 4.5 mg), Xantphos (2 mol %, 0.02 mmol, 0.02 equiv., 11.6 mg), *N, O*-dimethylhydroxylamine hydrochloride (1.5 mmol, 1.5 equiv., 146 mg), Na_2CO_3 (3 mmol, 3 equiv., 318 mg), and toluene (2 mL) was heated at 80 °C for 13 hours. The crude product mixture was purified by flash column chromatography on silica gel (50 % ethyl acetate in hexanes) to provide the title compound as a light brown oil (210 mg, 95 %). ^1H NMR (300 MHz, $CDCl_3$) δ: 7.73-7.66 (m, 2H), 7.33-7.28 (m, 2H), 3.57 (s, 3H), 3.37 (s, 3H), 3.29 (s, 3H), 1.48 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 169.01, 154.18, 145.69, 130.13, 128.71, 124.15, 80.58, 60.89, 36.83, 33.62, 28.14, 27.70. IR (neat, cm^{-1}): 2976, 2934, 2819, 1791, 1703, 1644, 1607, 1569, 1512, 1477, 1456, 1422, 1367, 1315, 1300, 1279, 1254, 1216, 1153, 1109, 1065, 1018, 995, 977, 889, 851, 807, 770, 758, 734, 700. Anal. Calcd for $C_{15}H_{22}N_2O_4$: C, 61.21; H, 7.53. Found: C, 60.91; H, 7.75.

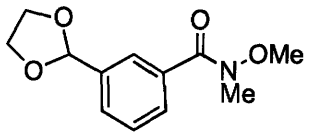


4-*N*-Dimethoxy-*N*-methyl-benzamide (Table 2, entry 7). Following general procedure A, a mixture of 4-bromoanisole (1 mmol, 0.187 g, 125 μL, filtered through basic alumina prior to use), $Pd(OAc)_2$ (2 mol

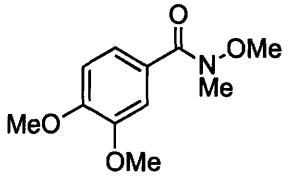
%, 0.02 mmol, 0.02 equiv., 4.5 mg), Xantphos (2 mol %, 0.02 mmol, 0.02 equiv., 11.6 mg), *N, O*-dimethylhydroxylamine hydrochloride (1.5 mmol, 1.5 equiv., 146 mg), Na_2CO_3 (3 mmol, 3 equiv., 318 mg), and toluene (2 mL) was heated at 80 °C for 8 hours. The crude product mixture was purified by flash column chromatography on silica gel (50 % ethyl acetate in hexanes) to provide the title compound as a colorless oil (210 mg, 95 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.77-7.70 (m, 2H), 6.94-6.88 (m, 2H), 3.85 (s, 3H), 3.57 (s, 3H), 3.36 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 169.21, 161.39, 130.39, 125.84, 113.11, 60.73, 55.16, 33.74. IR (neat, cm^{-1}): 3074, 3002, 2966, 2936, 2840, 2559, 2048, 1639, 1608, 1575, 1512, 1462, 1421, 1375, 1304, 1255, 1216, 1173, 1112, 1064, 1029, 994, 977, 888, 842, 796, 756, 703, 676, 631, 593. Anal. Calcd for $C_{10}H_{13}NO_3$: C, 61.53; H, 6.71. Found: C, 61.29; H, 6.69.



***N*-Methoxy-*N*-methyl-isophthalamic acid methyl ester (Table 2, entry 8).** Following general procedure A, a mixture of methyl 3-bromobenzoate (1 mmol, 0.215 g), $Pd(OAc)_2$ (2 mol %, 0.02 mmol, 0.02 equiv., 4.5 mg), Xantphos (2 mol %, 0.02 mmol, 0.02 equiv., 11.6 mg), *N, O*-dimethylhydroxylamine hydrochloride (1.5 mmol, 1.5 equiv., 146 mg), Na_2CO_3 (3 mmol, 3 equiv., 318 mg), and toluene (2 mL) was heated at 80 °C for 24 hours. The crude product mixture was purified by flash column chromatography on silica gel (50 % ethyl acetate in hexanes) to provide the title compound as a colorless oil (196 mg, 88 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.38-8.33 (t, J = 1.7 Hz, 1H), 8.17-8.10 (ddd, J = 1.4, 1.7, 7.9 Hz, 1H), 7.91-7.84 (ddd, J = 1.4, 1.7, 7.7 Hz, 1H), 7.54-7.46 (dt, J = 1.7, 7.7 Hz, 1H), 3.94 (s, 3H), 3.56 (s, 3H), 3.39 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 168.69, 166.18, 134.32, 132.41, 131.37, 129.88, 129.19, 128.13, 60.99, 52.13, 33.30. IR (neat, cm^{-1}): 3072, 2953, 1725, 1645, 1582, 1487, 1435, 1381, 1300, 1278, 1208, 1170, 1109, 1085, 991, 972, 922, 824, 772, 724, 665, 633, 575. Anal. Calcd for $C_{11}H_{13}NO_4$: C, 59.19; H, 5.87. Found: C, 58.98; H, 5.78.

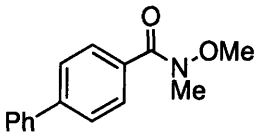


3-[1,3]Dioxolan-2-yl-*N*-methoxy-*N*-methyl-benzamide (Table 2, entry 9). Following general procedure A (a screw-capped test tube with a Teflon-lined septum was used in place of the culture tube and rubber septum), a mixture of 2-(3-bromophenyl)-1,3-dioxolane (1 mmol, 151 μL, filtered through basic alumina prior to use), $Pd(OAc)_2$ (2 mol %, 0.02 mmol, 0.02 equiv., 4.5 mg), Xantphos (2 mol %, 0.02 mmol, 0.02 equiv., 11.6 mg), *N, O*-dimethylhydroxylamine hydrochloride (1.5 mmol, 1.5 equiv., 146 mg), triethylamine (3 mmol, 3 equiv., 420 mL), and toluene (1 mL) was heated at 80 °C for 15 hours. The crude product mixture was purified by flash column chromatography on silica gel (67 % ethyl acetate in hexanes) to provide the title compound as a colorless oil (220 mg, 93 %). ^{1}H NMR (400 MHz, $CDCl_3$) 7.78 (s, 1 H), 7.67 (d, 1 H, J = 7.5 Hz), 7.56 (d, 1 H, J = 7.5 Hz), 7.41 (dd, 1 H, J = 7.5 Hz), 5.83 (s, 1 H), 4.00-4.14 (m, 4 H), 3.53 (s, 3 H), 3.33 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) d 169.4, 138.0, 134.1, 128.8, 128.6, 128.0, 126.3, 103.1, 65.2, 60.9, 33.6. IR ($CDCl_3$, cm^{-1}) 2972, 2937, 2892, 1639. Anal. Cald. for $C_{12}H_{15}NO_4$; C: 60.75, H: 6.37; Found C: 60.37, H: 6.35.

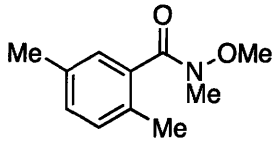


3,4,*N*-Trimethoxy-*N*-methyl-benzamide (Table 2, entry 10). Following general procedure A (a screw-capped test tube with a Teflon-lined septum was used in place of the culture tube and rubber septum), a mixture of 4-bromoveratrole (1 mmol, 144 μL, filtered through basic alumina prior to use), $Pd(OAc)_2$ (2 mol %, 0.02 mmol, 0.02 equiv., 4.5 mg), Xantphos (2 mol %, 0.02 mmol, 0.02 equiv., 11.6 mg), *N, O*-dimethylhydroxylamine hydrochloride (1.5 mmol, 1.5 equiv., 146 mg), triethylamine (3 mmol, 3 equiv., 420 mL), and toluene (1 mL) was heated at 80 °C for 15 hours. The crude product mixture was purified by flash column chromatography on silica gel (67 % ethyl acetate in hexanes) to provide the title compound as a colorless solid (202 mg, 90 %), mp 55 – 57 °C. ^{1}H NMR (400 MHz, $CDCl_3$) 7.39 (dd, 1 H,

J = 2 Hz, 8 Hz), 7.32 (d, 1 H, J = 2 Hz), 6.87 (d, 1 H, J = 8 Hz), 3.92 (s, 3 H), 3.91 (s, 3 H), 3.58 (s, 3 H), 3.36 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) d 168.9, 150.8, 148.0, 125.9, 121.8, 111.7, 109.9, 60.7, 55.7, 55.6, 33.7. IR ($CDCl_3$, cm^{-1}) 2966, 2937, 1631, 1517. m. p. 56 - 57 °C. Anal. Cald. for $C_{11}H_{15}NO_4$; C: 58.66, H: 6.71; Found C: 58.61, H: 6.77.

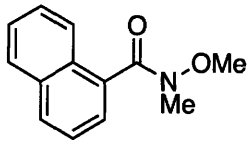


Biphenyl-4- *N*-methoxy-*N*-methyl carboxamide (Table 2, entry 11).[21] Following general procedure A (a screw-capped test tube with a Teflon-lined septum was used in place of the culture tube and rubber septum), a mixture of 4-bromobiphenyl (1 mmol, 0.233 g), $Pd(OAc)_2$ (2 mol %, 0.02 mmol, 0.02 equiv., 4.5 mg), Xantphos (2 mol %, 0.02 mmol, 0.02 equiv., 11.6 mg), *N, O*-dimethylhydroxylamine hydrochloride (1.5 mmol, 1.5 equiv., 146 mg), triethylamine (3 mmol, 3 equiv., 420 mL), and toluene (1 mL) was heated at 80 °C for 15 hours. The crude product mixture was purified by flash column chromatography on silica gel (40 % ethyl acetate in hexanes) to provide the title compound as a colorless solid (226 mg, 94 %), mp 80 – 82 °C, lit. mp 77 – 78 °C. ^{1}H NMR (400 MHz, $CDCl_3$) 7.77-7.81 (m, 2 H), 7.61-7.67 (m, 4 H), 7.37-7.50 (m, 3 H), 3.61 (s, 3 H), 3.40 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) d 169.5, 143.2, 140.0, 132.7, 128.8, 128.7, 127.8, 127.1, 126.6, 61.0, 33.7. IR ($CDCl_3$, cm^{-1}) 2971, 2936, 1632.

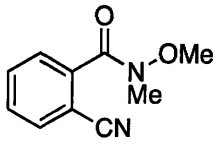


***N*-Methoxy-2,5,*N*-trimethyl-benzamide (Table 3, entry 1).** Following general procedure B, a mixture of 2-bromo-*p*-xylene (1 mmol, 0.185 g, 138 μL), $Pd(OAc)_2$ (2.5 mol %, 0.025 mmol, 0.025 equiv., 5.6 mg), Xantphos (5 mol %, 0.05 mmol, 0.05 equiv., 28.9 mg), *N, O*-dimethylhydroxylamine hydrochloride (1.5 mmol, 1.5 equiv., 146 mg), K_3PO_4 (3 mmol, 3 equiv., 637 mg), and toluene (2 mL) was heated at 100 °C for 20 hours. The crude product mixture was purified by flash column chromatography on silica gel (50 % ethyl acetate in hexanes) to provide a mixture of rotamers (ratio not determined) of the title

compound as a colorless oil (166 mg, 86 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.12-7.06 (m, 3H), 3.56 (brs, 3H), 3.31 (brs, 3H), 2.32 (s, 3H), 2.29 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 169.8, 134.5, 133.9, 130.6, 129.2, 129.2, 129.0, 125.8, 59.9, 31.9, 19.8, 17.7. IR (neat, cm^{-1}): 3018, 2969, 2932, 2818, 2736, 1903, 1844, 1651, 1612, 1577, 1502, 1459, 1422, 1375, 1287, 1242, 1181, 1157, 1126, 1062, 1041, 998, 980, 922, 887, 838, 816, 777, 746, 706, 694, 642, 597. Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82. Found: C, 68.28; H, 7.86.

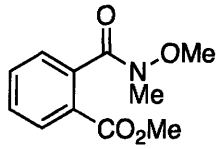


Naphthalene-1- *N*-methoxy-*N*-methyl carboxamide (Table 3, entry 2). Following general procedure B, a mixture of 1-bromonaphthalene (1 mmol, 0.207 g, 139 μL), $Pd(OAc)_2$ (2.5 mol %, 0.025 mmol, 0.025 equiv., 5.6 mg), Xantphos (5 mol %, 0.05 mmol, 0.05 equiv., 28.9 mg), *N, O*-dimethylhydroxylamine hydrochloride (1.5 mmol, 1.5 equiv., 146 mg), K_3PO_4 (3 mmol, 3 equiv., 637 mg), and toluene (2 mL) was heated at 100 °C for 20 hours. The crude product mixture was purified by flash column chromatography on silica gel (50 % ethyl acetate in hexanes) to provide a mixture of rotamers (ratio not determined) of the title compound as a light orange oil (208 mg, 97 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.94-7.85 (m, 3H), 7.58-7.47 (m, 4H), 3.4 (brs, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 169.1, 132.7, 129.1, 128.9, 127.8, 126.3, 125.3, 124.3, 124.2, 123.7, 60.5, 32.4. IR (neat, cm^{-1}): 3280, 3056, 3005, 2971, 2935, 2817, 1947, 1820, 1651, 1592, 1580, 1508, 1474, 1439, 1422, 1374, 1266, 11232, 1183, 1167, 1102, 1027, 1014, 975, 891, 865, 801, 779, 740, 697, 647, 629, 580. Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09. Found: C, 72.16; H, 6.12.

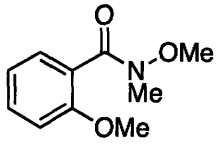


2-Cyano-*N*-methoxy-*N*-methyl-benzamide (Table 3, entry 3). Following general procedure B, a mixture of 2-bromobenzonitrile (1 mmol, 0.182 g), $Pd(OAc)_2$ (2.5 mol %, 0.025 mmol, 0.025 equiv., 5.6

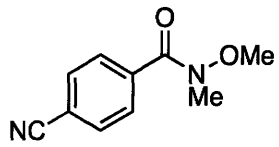
mg), Xantphos (5 mol %, 0.05 mmol, 0.05 equiv., 28.9 mg), *N, O*-dimethylhydroxylamine hydrochloride (1.5 mmol, 1.5 equiv., 146 mg), K_3PO_4 (3 mmol, 3 equiv., 637 mg), and toluene (2 mL) was heated at 100 °C for 20 hours. The crude product mixture was purified by flash column chromatography on silica gel (50 % ethyl acetate in hexanes) to provide a mixture of rotamers (ratio not determined) the title compound as a colorless oil (161 mg, 84 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.74-7.70 (ddd, J = 0.55, 1.38, 7.7 Hz, 1H), 7.69-7.50 (m, 3H), 3.52 (brs, 3H), 3.40 (brs, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.5, 138.2, 132.4, 132.3, 129.7, 127.3, 116.6, 109.9, 61.0, 32.3. IR (neat, cm^{-1}): 3292, 3071, 2976, 2938, 2822, 2229, 1657, 1595, 1572, 1492, 1459, 1445, 1421, 1385, 1289, 1219, 1191, 1168, 1117, 1062, 1036, 982, 891, 772, 759, 720, 687, 634. Anal. Calcd for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30. Found: C, 63.42; H, 5.29.



***N*-Methoxy-*N*-methyl-phthalamic acid methyl ester (Table 3, entry 4).** Following general procedure B, a mixture of methyl 2-bromobenzoate (1 mmol, 0.215 g, 140 μL), $Pd(OAc)_2$ (3.0 mol %, 0.03 mmol, 0.03 equiv., 6.7 mg), Xantphos (6 mol %, 0.06 mmol, 0.06 equiv., 34.7 mg), *N, O*-dimethylhydroxylamine hydrochloride (1.5 mmol, 1.5 equiv., 146 mg), K_3PO_4 (3 mmol, 3 equiv., 637 mg), and toluene (2 mL) was heated at 100 °C for 20 hours. The crude product mixture was purified by flash column chromatography on silica gel (20 - 50 % ethyl acetate in hexanes) to provide the title compound as a colorless oil (186 mg, 83 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.04-7.97 (d, J = 7.7 Hz, 1H), 7.63-7.55 (dt, J = 1.4, 7.4 Hz, 1H), 7.52-7.45 (dt, J = 1.4, 7.7 Hz, 1H), 7.45-7.38 (d, J = 7.4 Hz), 3.91 (s, 3H), 3.74 (brs, 3H), 3.35 (brs, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 172.0, 166.1, 137.2, 132.3, 129.7, 128.9, 127.7, 126.9, 60.9, 52.4, 33.1. IR (neat, cm^{-1}): 3067, 2953, 2939, 2904, 2820, 2845, 1726, 1662, 1599, 1578, 1492, 1459, 1413, 1435, 1379, 1280, 1211, 1192, 1166, 1130, 1091, 1062, 1040, 991, 964, 883, 828, 802, 777, 739, 723, 703, 667, 631, 576. Anal. Calcd for $C_{11}H_{13}NO_4$: C, 59.19; H, 5.87. Found: C, 59.17; H, 5.90.

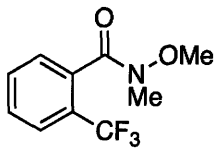


2,*N*-Dimethoxy-*N*-methyl-benzamide (Table 3, entry 5).[22] Following general procedure B, a mixture of 2-bromoanisole (1 mmol, 0.187 g, 125 μL, filtered through basic alumina prior to use), $Pd(OAc)_2$ (3.0 mol %, 0.03 mmol, 0.03 equiv., 6.7 mg), Xantphos (6 mol %, 0.06 mmol, 0.06 equiv., 34.7 mg), *N, O*-dimethylhydroxylamine hydrochloride (1.5 mmol, 1.5 equiv., 146 mg), K_3PO_4 (3 mmol, 3 equiv., 637 mg), and toluene (2 mL) was heated at 100 °C for 20 hours. The crude product mixture was purified by flash column chromatography on silica gel (50 % ethyl acetate in hexanes) to provide a mixture of rotamers (ratio not determined) of the title compound as a colorless plates (174 mg, 89 %), mp 47 – 49 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.40-7.32 (ddd, J = 1.6, 7.4, 8.2 Hz, 1H), 7.30-7.24 (dd, J = 1.4, 7.4 Hz, 1H), 7.01-6.95 (dt, J = 0.8, 7.4 Hz, 1H), 6.95-6.90 (d, J = 8.3 Hz, 1H), 3.84 (s, 3H), 3.49 (brs, 3H), 3.33 (brs, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 168.8, 155.2, 130.1, 126.9, 124.7, 119.9, 110.6, 60.4, 55.1, 31.6. IR (neat, cm^{-1}): 3067, 3003, 2970, 2938, 2939, 1651, 1601, 1584, 1495, 1465, 1437, 1418, 1381, 1284, 1249, 1209, 1182, 1164, 1116, 1064, 1045, 1022, 987, 940, 884, 795, 758, 697, 630. Anal. Calcd for $C_{10}H_{13}NO_3$: C, 61.53; H, 6.71. Found: C, 61.46; H, 6.76.

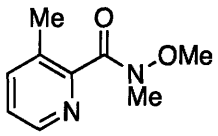


4-Cyano-*N*-methoxy-*N*-methyl-benzamide (Table 3, entry 6). Following general procedure B, a mixture of 4-chlorobenzonitrile (1 mmol, 0.146 g), $Pd(OAc)_2$ (3.0 mol %, 0.03 mmol, 0.03 equiv., 6.7 mg), Xantphos (6 mol %, 0.06 mmol, 0.06 equiv., 34.7 mg), *N, O*-dimethylhydroxylamine hydrochloride (1.5 mmol, 1.5 equiv., 146 mg), K_3PO_4 (3 mmol, 3 equiv., 637 mg), and toluene (2 mL) was heated at 105 °C for 20 hours. The crude product mixture was purified by flash column chromatography on silica gel (50 % ethyl acetate in hexanes) to provide the title compound as a colorless oil (149 mg, 78 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.81-7.64 (m, 4H), 3.53 (s, 3H), 3.38 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 167.7,

138.2, 131.7, 128.6, 118.0, 113.8, 61.2, 33.0. IR (neat, cm^{-1}): 3093, 3066, 2974, 2938, 2821, 2230, 1937, 1651, 1609, 1560, 1507, 1461, 1422, 1383, 1286, 1215, 1180, 1149, 1115, 1065, 1020, 980, 889, 851, 7777, 754, 703, 668, 638, 575. Anal. Calcd for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30. Found: C, 63.12; H, 5.33.



2-trifluoromethyl-*N*-Methoxy-*N*-methy-benzamide (Table 3, entry 7). Following general procedure B, a mixture of 2-bromobenzotrifluoride (1 mmol, 0.225 g, 136 μL, filtered through basic alumina prior to use), $Pd(OAc)_2$ (3.0 mol %, 0.03 mmol, 0.03 equiv., 6.7 mg), Xantphos (6 mol %, 0.06 mmol, 0.06 equiv., 34.7 mg), *N, O*-dimethylhydroxylamine hydrochloride (1.5 mmol, 1.5 equiv., 146 mg), K_3PO_4 (3 mmol, 3 equiv., 637 mg), and *m*-xylene (2 mL) was heated at 110 °C for 20 hours. The crude product mixture was purified by flash column chromatography on silica gel (20 - 50 % ethyl acetate in hexanes) to provide the title compound as a colorless oil and a 1.1:1 mixture of rotamers (214 mg, 92 %). ^1H NMR (300 MHz, $CDCl_3$) δ: 7.75-7.67 (d, J = 7.4 Hz, 1H), 7.65-7.50 (m, 2H), 7.46-7.40 (m, 1H), 3.89 (brs, 0.6H), 3.42 (s, 2.4H), 3.37 (s, 2.3H), 3.05 (brs, 0.7H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 169.1, 164.4, 133.7, 132.1, 131.3, 129.5, 128.9, 127.2, 126.8, 126.2, 1259, 125.3, 121.6, 118.0, 60.4, 59.7, 36.1, 31.9 (observed complexity due to C-F splitting; definitive assignments have not yet been made). ^{19}F NMR (282 MHz, $CDCl_3$) δ: -60.2. IR (neat, cm^{-1}): 3071, 2977, 2941, 2823, 1667, 1606, 1584, 1503, 1426, 1445, 1416, 1384, 1317, 1272, 1213, 1171, 1130, 1077, 1049, 1034, 991, 961, 891, 879, 772, 742, 708, 655, 632. Anal. Calcd for $C_{10}H_{10}F_3NO_2$: C, 51.51; H, 4.32. Found: C, 51.61; H, 4.36.



3-Methyl-pyridine-2- *N*-methoxy-*N*-methyl carboxamide (Table 3, entry 8). Following general procedure B, a mixture of 2-bromo-3-methylpyridine (1 mmol, 0.172 g, 111 μL), $Pd(OAc)_2$ (3.0 mol %, 0.03 mmol, 0.03 equiv., 6.7 mg), Xantphos (6 mol %, 0.06 mmol, 0.06 equiv., 34.7 mg), *N, O*-

dimethylhydroxylamine hydrochloride (1.5 mmol, 1.5 equiv., 146 mg), K_3PO_4 (3 mmol, 3 equiv., 637 mg), and *m*-xylene (2 mL) was heated at 110 °C for 20 hours. The crude product mixture was purified by flash column chromatography on silica gel (50 - 60 % ethyl acetate in hexanes) to provide the title compound as a light yellow oil and a 1:1 mixture of rotamers (140 mg, 77 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.44-8.36 (dd, J = 0.8, 4.7 Hz, 1H), 7.60-7.48 (d, J = 7.1 Hz, 1H), 7.27-7.16 (dd, J = 4.9, 7.7 Hz, 1H), 3.89 (brs, 0.6H), 3.52 (s, 2.4H), 3.37 (s, 2.4H), 3.13 (brs, 0.6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 168.8, 153.3, 145.7, 137.5, 129.8, 123.4, 61.1, 31.4, 17.1. IR (neat, cm^{-1}): 3055, 2977, 2938, 2821, 1655, 1575, 1485, 1446, 1407, 1384, 1274, 1260, 1238, 1186, 1169, 1119, 1072, 983, 896, 889, 818, 800, 743, 692, 639, 580. A satisfactory elemental analysis was not obtained for this compound: Anal. Calcd for $C_9H_{12}N_2O_2$: C, 59.99; H, 6.71. Found: C, 59.53; H, 6.72. The ^{1}H and ^{13}C NMR spectra follow.

STANDARD 1H OBSERVE

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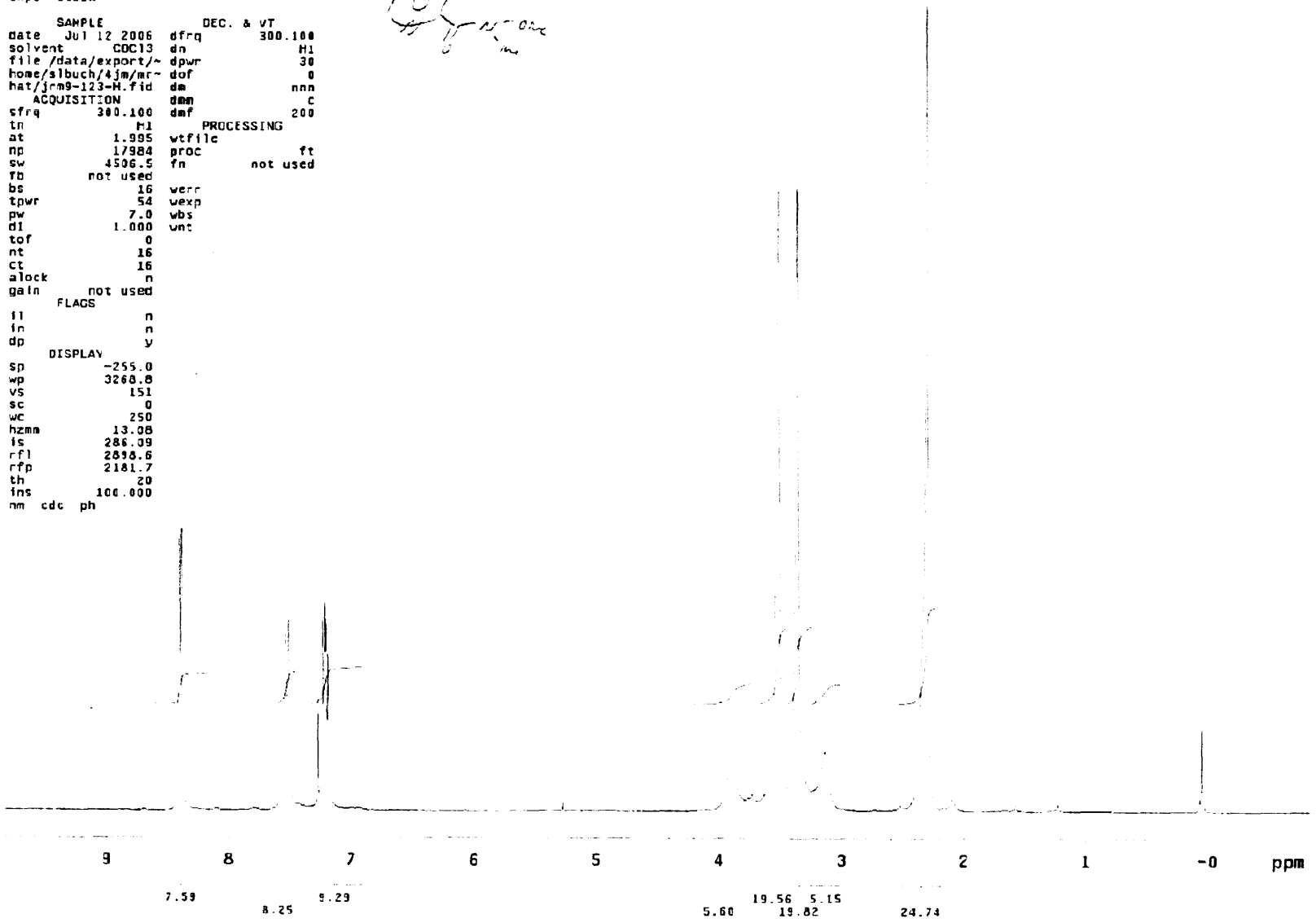

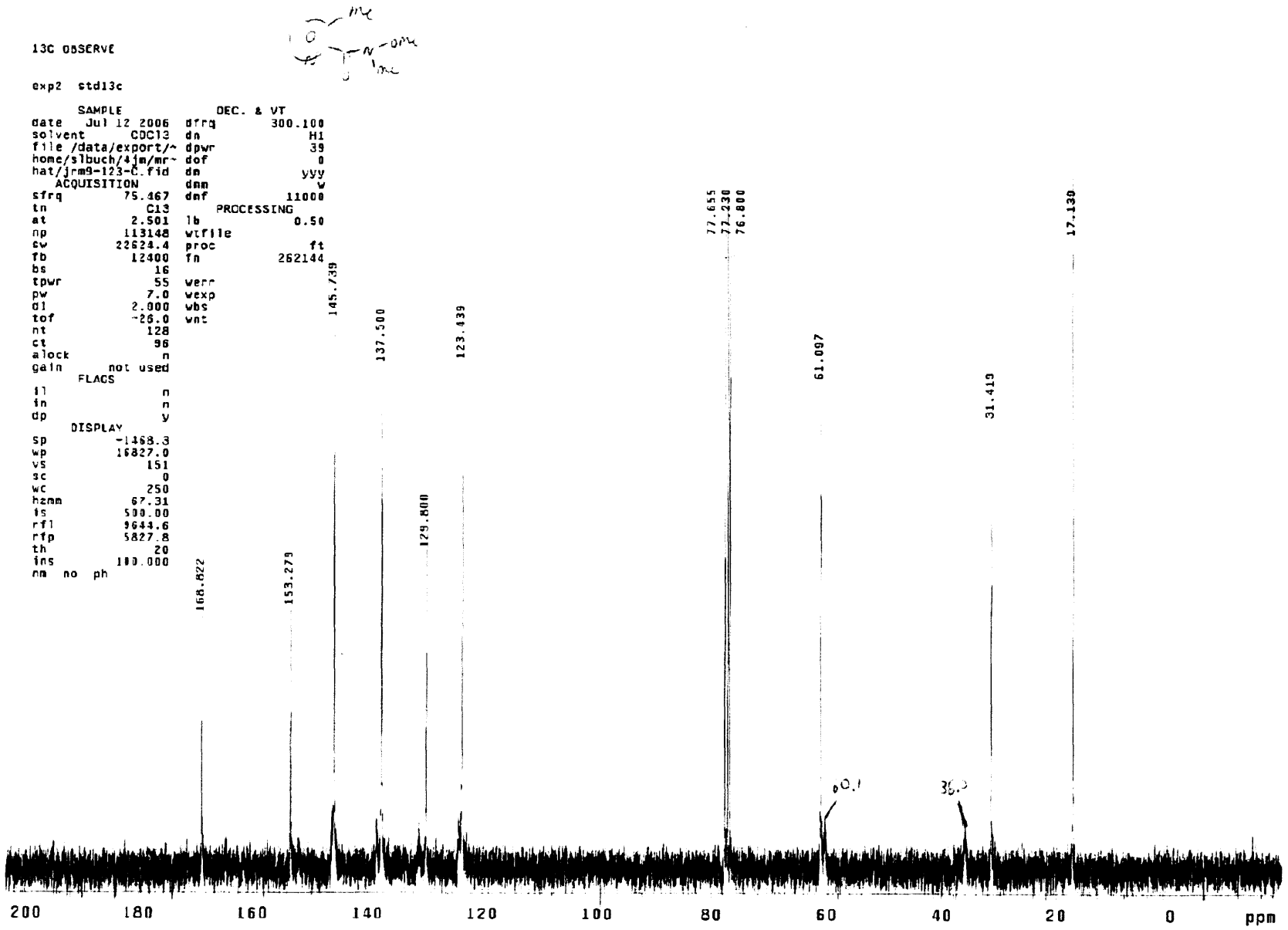
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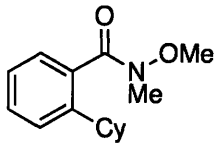
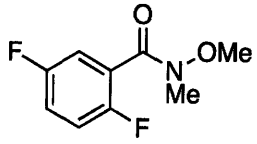


2-Cyclohexyl-*N*-methoxy-*N*-methyl-benzamide (Table 3, entry 9). Following general procedure B, a mixture of 1-bromo-2-cyclohexylbenzene (1 mmol, 0.239 g), $Pd(OAc)_2$ (3.0 mol %, 0.03 mmol, 0.03 equiv., 6.7 mg), Xantphos (6 mol %, 0.06 mmol, 0.06 equiv., 34.7 mg), *N, O*-dimethylhydroxylamine hydrochloride (1.5 mmol, 1.5 equiv., 146 mg), K_3PO_4 (3 mmol, 3 equiv., 637 mg), and *m*-xylene (2 mL) was heated at 120 °C for 20 hours. The crude product mixture was purified by flash column chromatography on silica gel (30 - 50 % ethyl acetate in hexanes) to provide a mixture of rotamers (ratio not determined) of the title compound as a viscous colorless oil (213 mg, 86 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.41-7.30 (m, 2H), 7.24-7.14 (m, 2H), 3.85 (brs, 1H), 3.38 (brs, 5H), 2.75 (brs, 1H), 1.60-1.95 (m, 5H), 1.2-1.58 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.1, 143.9, 134.2, 128.7, 125.6, 125.4, 124.8, 60.2, 41.0, 33.6, 31.6, 26.3, 25.5. IR (neat, cm^{-1}): 3292, 3061, 3025, 2926, 2851, 2817, 2668, 1651, 1599, 1575, 1489, 1448, 1410, 1378, 1264, 1218, 1193, 1168, 1140, 1117, 1093, 1060, 1044, 989, 893, 884, 863, 829, 771, 755, 705, 644, 634, 625, 577, 530. Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56. Found: C, 72.66; H 8.54.



2,5-Difluoro-*N*-methoxy-*N*-methyl-benzamide (Table 3, entry 10). Following general procedure B, a mixture of 2,5-difluorobromobenzene (1 mmol, 0.193 g, filtered through basic alumina prior to use), $Pd(OAc)_2$ (2.5 mol %, 0.025 mmol, 0.025 equiv., 5.6 mg), Xantphos (5 mol %, 0.05 mmol, 0.05 equiv., 28.9 mg), *N, O*-dimethylhydroxylamine hydrochloride (1.5 mmol, 1.5 equiv., 146 mg), K_3PO_4 (3 mmol, 3 equiv., 637 mg), and *m*-xylene (2 mL) was heated at 110 °C for 20 hours. The crude product mixture was purified by flash column chromatography on silica gel (50 % ethyl acetate in hexanes) to provide the title

compound as a colorless oil (140 mg, 70 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.19-7.03 (m, 3H), 3.56 (brs, 3H), 3.36 (brs, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 164.7, 159.7, 156.4, 156.1, 152.9, 124.7, 124.6, 124.4, 124.3, 117.9, 117.6, 117.1, 117.0, 116.8, 116.7, 115.4, 115.1, 61.1, 31.9 (observed complexity due to C-F splitting; definitive assignments have not yet been made). ^{19}F NMR (282 MHz, $CDCl_3$) δ: -118.8, -120.4. IR (neat, cm^{-1}): 3074, 2977, 2940, 2823, 1659, 1599, 1495, 1437, 1405, 1383, 1266, 1251, 1205, 1149, 1104, 1059, 992, 939, 879, 851, 822, 786, 735, 706, 690, 640, 604. Anal. Calcd for $C_9H_9F_2NO_2$: C, 53.73; H, 4.51. Found: C, 53.50; H, 4.55.

2.5 References

(1) For reviews, see (a) Khlestkin, V. K.; Mazhukin, D. G. *Curr. Org. Chem.* **2003**, *7*, 967. (b) Singh, J.; Satyamurthi, N.; Aidhen, I. S. *J. Prakt. Chem.* **2000**, *342*, 340. (c) Sibi, M. P. *Org. Prep. Proc. Int.* **1993**, *25*, 15.

(2) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.

(3) (a) Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001. (b) Sha, C.-K.; Huang, S.-J; Zhan, Z.-P. *J. Org. Chem.* **2002**, *67*, 831.

(4) (a) Colobert, F. C.; Des Mazery, R.; Solladié, G.; Carreño, M. C. *Org. Lett.* **2002**, *4*, 1723. (b) Williams, J. M.; Jobson, R. B.; Yasuda, N.; Marchesini, G.; Dolling, U.-H.; Grabowski, E. J. J. *Tetrahedron Lett.* **1995**, *36*, 5461.

(5) (a) Woo, J. C. S.; Fenster, E.; Dake, G. R. *J. Org. Chem.* **2004**, *69*, 8984. (b) De Luca, L.; Giacomelli, G.; Taddei, M. *J. Org. Chem.* **2001**, *66*, 2534. (c) Banwell, M.; Smith, J. *Synth. Commun.* **2001**, *31*, 2011. (d) Tunoori, A. R.; White, J. M.; Georg, G. I. *Org. Lett.* **2000**, *2*, 4091. (e) Gibson, C. L.; Hanada, S. *Tetrahedron: Asymmetry* **1996**, *7*, 1281. (f) Einhorn, J.; Einhorn, C.; Luche, J.-L. *Synth. Commun.* **1990**, *20*, 1105.

(6) Murakami, M.; Hoshino, Y.; Ito, H.; Ito, Y. *Chem. Lett.* **1998**, 163.

(7) (a) Schoenberg, A.; Bartoletti, I.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3318. (b) Schoenberg, A.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3327.

(8) (a) Perry, R. J.; Wilson, B. D. *Organometallics* **1994**, *13*, 3346. (b) Perry, R. J.; Wilson, B. D. *J. Org. Chem.* **1993**, *58*, 7016. (c) Perry, R. J.; Wilson, B. D.; Miller, R. J. *J. Org. Chem.* **1992**, *57*, 2883.

(9) (a) Albaneze-Walker, J.; Bazaral, C.; Leavey, T.; Dormer, P. G.; Murry, J. A. *Org. Lett.* **2004**, *6*, 2097. (b) Lapidus, A. L.; Eliseev, O. L.; Bondarenko, T. N.; Sizan, O. E.; Ostapenko, A. G.; Beletskaya, I. P. *Synthesis* **2002**, *3*, 317. (c) Kumar, K.; Zapf, A.; Michalik, D.; Tillack, A.; Heinrich, T.; Böttcher, H.; Arlt, M.; Beller, M. *Org. Lett.* **2004**, *6*, 7. (d) Atkins, R. J.; Banks, A.; Bellingham, R. K.; Breen, G. F.; Carey, J. S.; Etridge, S. K.; Hayes, J. F.; Hussain, N.; Morgan, D. O.; Oxley, P.; Passey, S. C.; Walsgrove, T. C.; Wells, A. S. *Org. Process Res. Dev.* **2003**, *7*, 663. (e) Iizuka, M.; Kondo, Y. *Chem. Commun.* **2006**, *16*, 1739. (f) Ishiyama, T.; Kizaki, H.; Hayashi, T.; Suzuki, A.; Miyaura, N. *J. Org. Chem.* **1998**, *63*, 4726. (g) Klaus, S.; Neumann, H.; Zapf, A.; Strübing, D.; Hübner, S.; Almena, J.; Riermeier, T.; Grob, P.; Sarich, M.; Krahnert, W.-R.; Rossen, K.; Beller, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 154. (h) Pri-Bar, I.; Alper, H. *J. Org. Chem.* **1989**, *54*, 36.

(10) Zhuang, L.; Wai, J. S.; Embrey, M. W.; Fisher, T. E.; Egbertson, M. S.; Payne, L. S.; Guare, J. P., Jr.; Vacca, J. P.; Hazuda, D. J.; Felock, P. J.; Wolfe, A. L.; Stillmock, K. A.; Witmer, M. V.; Moyer, G.; Schleif, W. A.; Gabryelski, L. J.; Leonard, Y. M.; Lynch, J. J., Jr.; Michelson, S. R.; Young, S. D. *J. Med. Chem.* **2003**, *46*, 453.

(11) (a) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685. (b) Strieter, E. R.; Blackmond, D. G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 13978. (c) Barder, T. E.; Buchwald, S. L. *unpublished results*.

(12) (a) Sadighi, J. P.; Singer, R. A.; Buchwald, S. B. *J. Am. Chem. Soc.* **1998**, *120*, 4960. (b) Scalone, M.; Vogt, P. (Hoffmann – La Roche) EP 385210 A2, **1990**. (c) Beller, M.; Mägerlein, W.; Indolese, A. F.; Fischer, C. *Synthesis* **2001**, 1098. (d) Sadighi, J. P.; Harris, M. C.; Buchwald, S. L. *Tetrahedron Lett.* **1998**, *39*, 5327.

(13) (a) Casey, C. P.; Whiteker, G. T. *Isr. J. Chem.* **1990**, *30*, 299. (b) Tolman, C. A. *Chem. Rev.* **1977**, *77*, 313.

(14) Kranenburg, M.; van der Burgt, Y. E. M.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Organometallics* **1995**, *14*, 3081.

(15) Klingensmith, L. M.; Strieter, E. R.; Barder, T. E.; Buchwald, S. L. *Organometallics* **2006**, *25*, 82.

(16) Wong, K.-T.; Hwu, T.-Y.; Balaiah, A.; Chao, T.-C.; Fang, F.-C.; Lee, C.-T.; Peng, Y.-C. *Org. Lett.* **2006**, *8*, 1415.

(17) Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 6043.

(18) (a) Milstein, D. *Acc. Chem. Res.* **1988**, *21*, 428. (b) Ozawa, F.; Sugimoto, T.; Yuasa, Y.; Santra, M.; Yamamoto, T.; Tamamoto, A. *Organometallics* **1984**, *3*, 683. (c) Ozawa, F.; Suglmoto, T.; Yamamoto, T.; Tamamoto, A. *Organometallics* **1984**, *3*, 692.

(19) (a) Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518. (b) Alaimo, P. J.; Peters, D. W.; Arnold, J.; Bergman, R. G. *J. Chem. Ed.* **2001**, *78*, 64.

(20) (a) Seganish, W. M.; DeShong, P. *J. Org. Chem.* **2004**, *64*, 6790. (b) Deetz, M. J.; Forbes, C. C.; Jonas, M.; Malerich, J. P.; Smith, B. D.; Wiest, S. *J. Org. Chem.* **2002**, *67*, 3949.

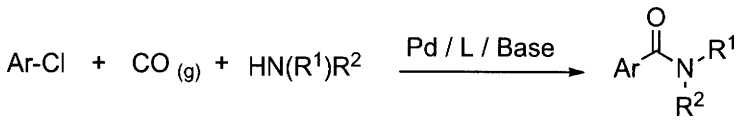
(21) De Voss, J. J.; Sui, Z.; DeCamp, D. L.; Salto, R.; Babé, L. M.; Craik, C. S.; Ortiz de Montellano, P. R. *J. Med. Chem.* **1994**, *37*, 665.

(22) Einhorn, J.; Einhorn, C.; Luche, J.-L. *Synth. Commun.* **1990**, *20*, 1105.

Chapter 3.
Palladium-Catalyzed Aminocarbonylation of Aryl Chlorides.

3.1 Introduction

Carbonylation is a powerful method for the direct and regioselective incorporation of carbonyl groups into molecules using carbon monoxide (CO).[1,2] However, despite the development of several highly effective Pd catalysts for the efficient carbonylation of aryl bromides,[3] and recent developments in the area of cross-coupling and Heck arylation processes,[4] few catalysts are capable of carbonylation reactions with unactivated aryl chlorides (Scheme 1).[5] In particular, there is no general method for the aminocarbonylation of unactivated aryl chlorides at atmospheric pressure. To the best of our knowledge, Beller has reported the only example of such a reaction (chlorobenzene and di-*n*-propylamine).[5b] Milstein has also reported the Pd-catalyzed aminocarbonylation of unactivated aryl chlorides with secondary amines at 150 °C under 70 psig of CO.[5a] Herein we describe our efforts towards the development of a general and mild catalyst system for the aminocarbonylation of aryl chlorides under atmospheric pressure of CO.



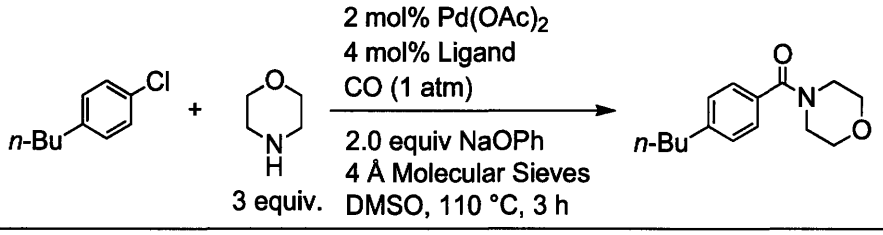
Scheme 1. Synthesis of Benzamides via Aminocarbonylation of Aryl Chlorides.

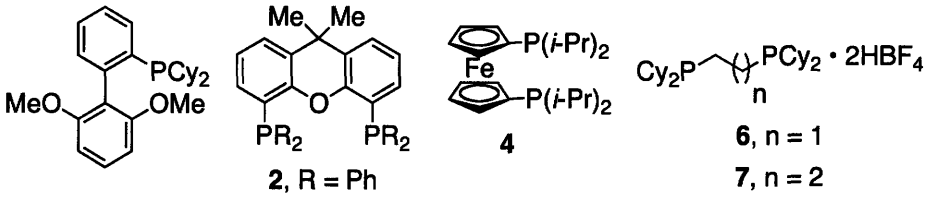
3.2 Results and Discussion

Based on results reported in the literature,[3,4] we decided to focus our investigation on electron-rich bidentate ligands. These ligands presumably aid in preventing catalyst poisoning resulting from the coordination of multiple equivalents of CO to Pd.[6] For the initial experiments, 4-*n*-butylchlorobenzene and morpholine were chosen as test substrates, and the reactions were conducted under balloons filled with CO (Table 1). The most effective ligand was 1,3-bis(dicyclohexylphosphino)propane[7] (dcpp), which is similar to the ligand reported by Milstein and coworkers.[5a,8] In our case, however, we elected to introduce the ligand as the commercially available and air-stable tetrafluoroborate salt. Further optimization studies revealed that the use of anhydrous DMSO was the best solvent for this reaction. In

general, exclusion of extraneous water, accomplished through the use of activated 4 Å molecular sieves, was necessary to obtain high yields.

Table 1. Optimization of Atmospheric Pressure Aminocarbonylation of 4-*n*-Butylchlorobenzene.





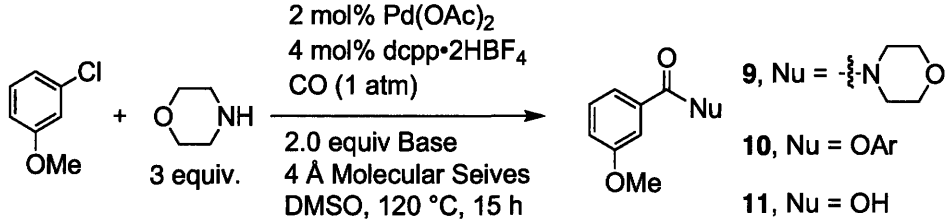
1 **2**, R = Ph; **3**, R = *t*-Bu **4** **5**, $(Cy_3P)_2PdCl_2$ **6**, n = 1; **7**, n = 2; **8**, n = 3

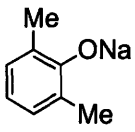
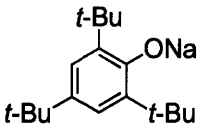
Ligand:	1	2	3	4	5	6	7	8
Conversion:	6%	1%	6%	8%	7%	61%	92%	14%
Yield (GC):	0%	0%	0%	4%	0%	57%	91%	7%

Unexpectedly, the identity of the base proved critical to the success of the carbonylation reaction (Table 2). The use of anhydrous organic bases, such as tri-*n*-propylamine, resulted in very low conversion of the aryl chloride (Table 2, entry 1). The use of Na_2CO_3, K_3PO_4 (stored in air), or Cs_2CO_3 (stored in a nitrogen filled glove box) resulted in the formation of a significant amount of carboxylic acid due to moisture contained in the salt (Table 2, entries 2-4). Surprisingly, the use of the nucleophilic[9] base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) resulted in a low yield of the desired product possibly due to decomposition of the amidine base[10] (Table 2, entry 5). In an effort to circumvent the side reaction with water, 25 mol% phenol was added to a reaction in which Na_2CO_3 was used as the base and an increase in the yield (>10%) of the desired product was observed (Table 2, entry 6). As this result suggests, employment of anhydrous sodium phenoxide as base provided complete conversion of the aryl chloride and an excellent yield of the desired amide was realized. More sterically encumbered derivatives of

sodium phenoxide provided less promising results (Table 2, entry 7 and 8). Interestingly, the use of sodium *tert*-butoxide as the base provided the aromatic amine[11] product exclusively over products derived from CO insertion.

Table 2. Effect of Base on the Aminocarbonylation of 3-Chloroanisole.

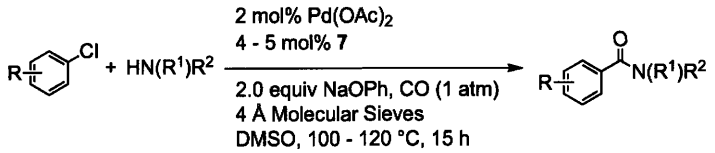


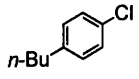
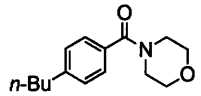
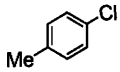
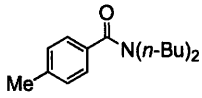
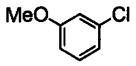
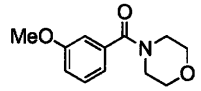
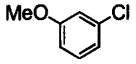
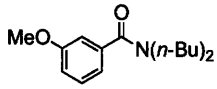
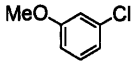
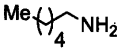
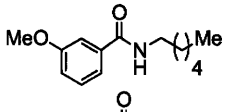
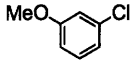
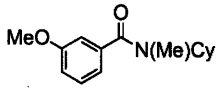
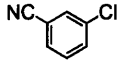
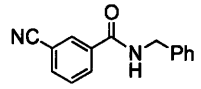
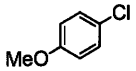
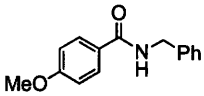
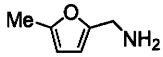
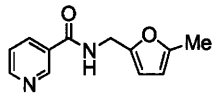
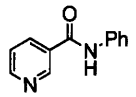
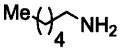
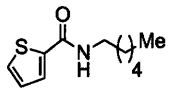
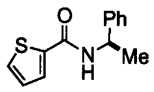
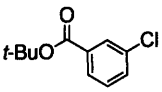
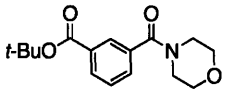
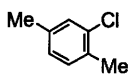
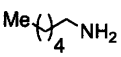
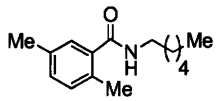
Entry	Base	Conv. ArCl	Yield **9**	Yield **10**	Yield **11**
1	*n*-Pr_3N	11%	11%	--	--
2	Na_2CO_3	94%	52%	--	38%
3	Cs_2CO_3	> 99%	8%	--	n.d.
4	K_3PO_4	> 99%	62%	--	n.d.
5	DBU	78%	25%	--	n.d.
6	Na_2CO_3/ 25% PhOH	> 99%	70%	--	n.d.
7	NaOPh	> 99%	> 99%	--	--
8		> 99%	76%	22%	--
9		80%	60%	< 2%	n.d.

To determine the scope of this process, a range of aryl chlorides and amines were employed as substrates (Table 3). Primary, secondary and aromatic amines are all readily converted to amides. Additionally, electron-rich, -neutral, and -poor aryl chlorides are all compatible with these aminocarbonylation conditions. The combination of a primary amine and an electron-poor aryl chloride

can be successfully transformed to the corresponding benzamide in 4h using only 0.5 mol% catalyst (Table 3, entry 6). Not surprisingly, acyclic secondary amines require higher temperatures to afford complete transformation to the desired amide (Table 3, entries 2, 4 and 7). It is also worth noting that functional groups, such as the *t*-butyl ester and nitrile groups (Table 3, entries 8 and 14), and heteroaryl chlorides, such as 3-chloropyridine and 3-chlorothiophene (Table 3, entries 10 – 13), were also amenable to these reaction conditions.

Table 3. Substrate Scope of Atmospheric Pressure Aminocarbonylation with **7**.[a,b]

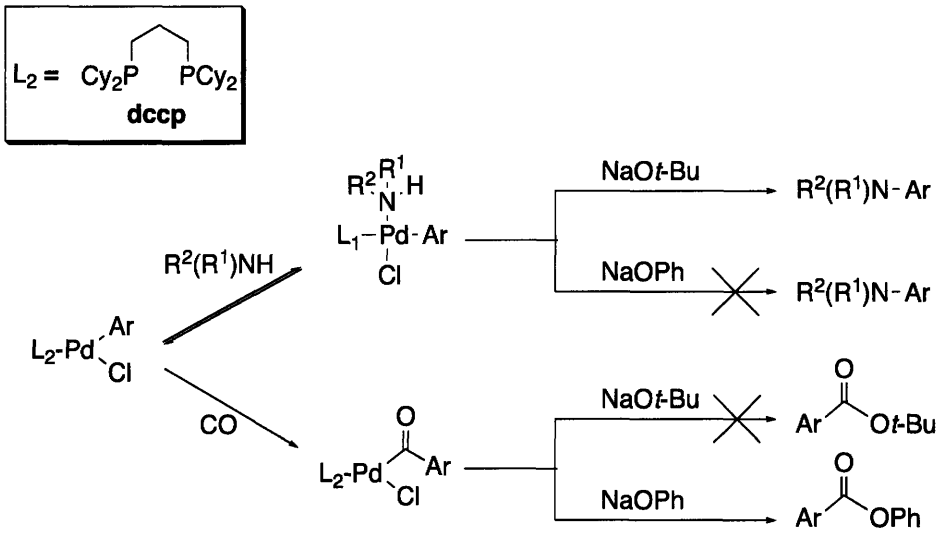


entry	ArCl	amine	product	yield
1				88%[c,d]
2		$(n\text{-Bu})_2NH$		79%[e]
3				88%
4		$(n\text{-Bu})_2NH$		85%[e]
5				93%[f]
6				97%[c,g]
7		Cy(Me)NH		93%[e,h]
8				65%
9				98%
10				92%
11				92%
12				99%
13		 99% ee		94% 99% ee
14				75%
15				86%[c]

[a]Reaction conditions: 2 mol% $Pd(OAc)_2$, 4 -5 mol% **7**, 1 mmol aryl chloride, 3 mmol amine, 2 mmol NaOPh, 150 mg 4 Å molecular sieves in DMSO (1 mL) at 100 °C for 15 h. [b]Yields are an average of 2 runs (isolated). [c]Reaction

time 4 h. [d]Reaction temperature 110 °C. [e]Reaction temperature 120 °C. [f]Reaction time 3 h. [g]Less catalyst used: 0.5 mol% $Pd(OAc)_2$, 2 mol% **7**. [h]4 equiv. of amine used.

We were intrigued by the high reactivity of sodium phenoxide as base in this reaction. We reasoned that its effectiveness was due either to its basicity or greater nucleophilicity amongst the bases screened (Scheme 2). On one hand, phenoxide might be sufficiently basic (in DMSO) to achieve catalyst turnover at an appreciable rate (unlike the less basic trialkyl amines) but not so basic as to substantially deprotonate the amine and trigger direct C-N coupling (such as with the more basic *tert*-butoxide). On the other hand, being both relatively small and negatively charged, phenoxide might be sufficiently nucleophilic to react directly with acyl palladium intermediates and result in the initial formation of phenyl esters. These phenyl esters might later be converted to the observed amide under the reaction conditions.



Scheme 2. Potential Effect of Different Bases on Possible Intermediates in the Aminocarbonylation Reaction.

In an attempt to distinguish between the possible scenarios outlined above, the reaction of 3-chloroanisole and di-*n*-butylamine was monitored using in situ IR spectroscopy. In the initial kinetic experiments, the combination of $Pd(OAc)_2$ (2 mol%) and **7** (4 mol%) were used as the catalytic additives.

These reactions displayed an irreproducible initiation period that ranged over a period of minutes to more than an hour. We assume that this initiation period is due to the reduction of $Pd(OAc)_2$ to Pd(0). In order to improve reproducibility in the kinetics experiments, we prepared (dcpp)PdPhCl (**12**) from dcpp and $(Ph_3P)_2PdPhCl$ as the mono-toluene solvate. Using the combination of **12** (2 mol%) and **7** (2 mol %) as the precatalyst eliminated the initiation period.

Figure 1 shows the reaction profile from the combination of 3-chloroanisole (0.33 M), di-*n*-butylamine (1.0 M), phenoxide (0.66 M), **12** (0.66 mM) and **7** (0.66 mM) in DMSO at 120 °C. A signal at 1736 cm^{-1} (corresponding to phenyl 3-methoxybenzoate **13**) was observed at the beginning of the reaction. Shortly thereafter, a signal at 1632 cm^{-1} (corresponding to amide **14**) was observed to increase in intensity. After approximately 1 hour, the concentration of the ester ceased to increase and began to decrease; the concentration of the amide continued to increase. At the end of the reaction, the ester had been completely consumed and the amide was formed in 88% yield (determined by GC). Thus, the phenyl ester appears to be an intermediate in the formation of amide **14**. It should be noted that, despite the initiation period, transient ester has also been observed with similar kinetic behavior in reactions employing $Pd(OAc)_2$ as the precatalyst.

In order to further confirm the intermediacy of the ester, we examined the kinetic competence of the conversion of ester **13** to amide **14**. Combining ester **13** (0.33 M) and di-*n*-butylamine (1.0 M) in DMSO and heating to 120 °C did result in very slow formation of amide **14** ($t_{1/2} \approx 10$ h). However, when the same reaction was conducted in the presences of PhONa (0.33 M), rapid conversion ($t_{1/2} \approx 12$ m) of ester **13** to amide **14** was observed.[12]

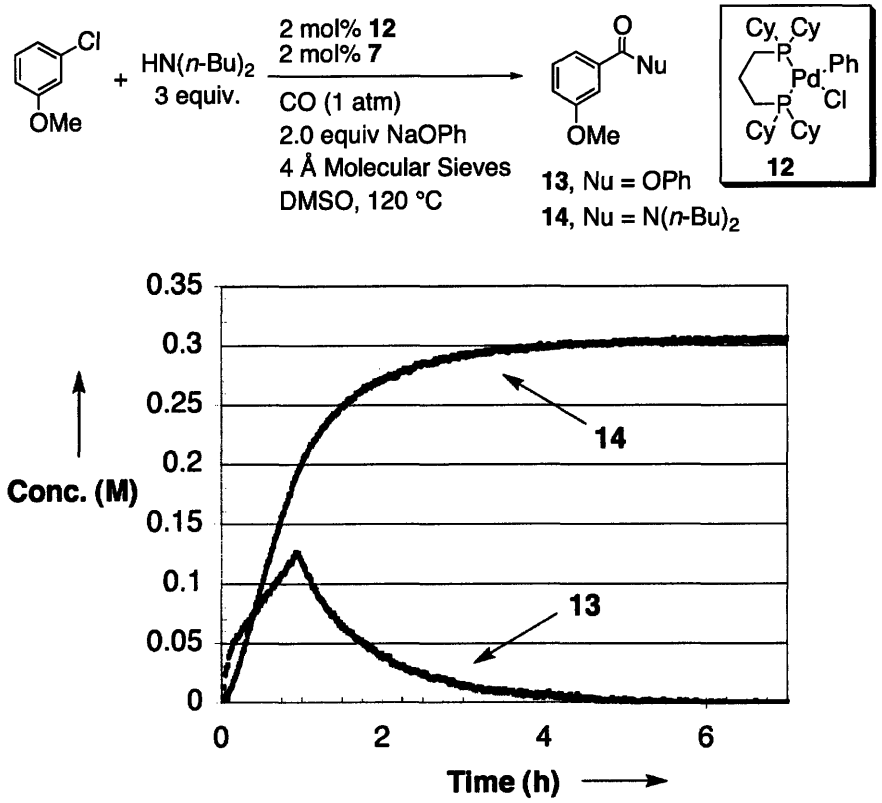
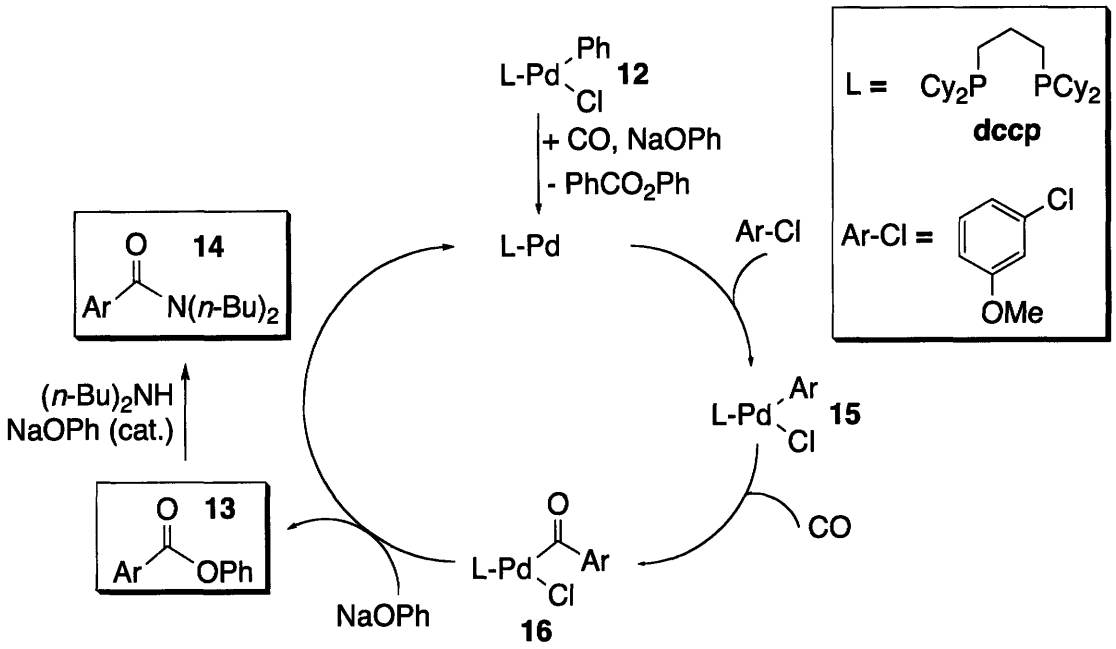


Figure 1. Kinetic Profile for the Reaction of Di-*n*-Butylamine and 3-Chloroanisole as Determined by in situ Reaction IR Spectroscopy.

The above observations suggest that sodium phenoxide is playing a dual role in the formation of amide **14** (Scheme 3). First, due to its greater nucleophilicity compared to di-*n*-butylamine, phenoxide intercepts the acyl palladium species resulting from oxidative addition of the aryl chloride and migratory insertion of CO[13] and leads to the formation of phenyl ester **13**.[14,15] Subsequently, phenoxide acts as a basic catalyst in the conversion of the intermediate ester to the observed amide product.



Scheme 3. Proposed reaction pathway for reactions involving acyclic 2° amines.

3.3 Conclusion

In conclusion, an efficient protocol for the aminocarbonylation of aryl chlorides at atmospheric pressure of CO has been developed using an inexpensive, air-stable and commercially available ligand. Electron-deficient, -neutral and –rich aryl chlorides were all successfully transformed to the corresponding amides. Primary, α-branched primary, cyclic secondary, acyclic secondary, and aryl amines were all productive in the reaction. Furthermore, the process tolerates a variety of functional groups and is relatively mild. Additionally, in these studies we have discovered that sodium phenoxide is a uniquely active basic additive, which can result in the formation of phenyl esters as intermediates in route to amide products. Future studies will be directed at exploring the generality of this base in other carbonylation protocols. Additional mechanistic studies will also be conducted to determine if phenyl ester intermediates are also present in reactions with more nucleophilic amines, such as *n*-hexyl amine.

3.4 Experimental

4.4.1 General

All reactions were carried out under a carbon monoxide atmosphere, purchased from Airgas. Elemental analyses were performed by Atlantic Microlabs Inc., Norcross, GA. Unless otherwise noted, THF, Et_2O, CH_2Cl_2 and toluene were purchased from J.T. Baker in CYCLE-TAINER® solvent-delivery kegs and vigorously purged with argon for 2 h. The solvents were further purified by passing them under argon pressure through two packed columns of neutral alumina (for THF and Et_2O) or through neutral alumina and copper (II) oxide (for toluene and CH_2Cl_2).[16] Dimethyl Sulfoxide was purchased from Aldrich in a Sure/Seal™ bottle, used as received and stored under Argon. Also, 4Å molecular sieves were purchased from Aldrich and activated (heat-gun or Bunsen burner heating under vacuum) prior to use. The following aryl chlorides were purchased from the following companies and used as received or purified as described: 4-*n*-butylchlorobenzene (Alfa Aesar, filtered through basic alumina prior to use), 4-chlorotoluene (Aldrich, filtered through basic alumina prior to use), 3-chloroanisole (Acros, filtered through basic alumina prior to use), 3-chlorobenzonitrile (Alrich, used as received), 3-chlorobenzotrifluoride (Aldrich, distilled over CaH_2), 4-chloroanisole (Acros, filtered through basic alumina prior to use), 3-chloropyridine (Aldrich, filtered through basic alumina prior to use), 2-chlorothiophene (Alfa Aesar, filtered through basic alumina prior to use), and 2-chloro-*p*-xylene (Aldrich, used as received). 3-Chloro-*tert*-butylbenzoate was synthesized from 3-chlorobenzoic acid via the acid chloride and following literature procedures.[17] The following amines were purchased from the following companies and used as received or purified as described: morpholine (Aldrich or Alfa Aesar, used as received from both sources), di-*n*-butylamine (Aldrich, distilled over CaH_2), cyclohexanemethylamine (Aldrich, distilled over CaH_2), aniline (Aldrich, distilled over CaH_2), 5-methylfurfurylamine (Aldrich, distilled over CaH_2), (*R*)-(+)-α-methylbenzylamine (Aldrich, distilled over NaOH), and *n*-hexylamine (Aldrich, distilled over CaH_2). The following ligands were purchased from the following companies, or received as gifts, and used as received: 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (Xantphos,

Strem), 9,9-dimethyl-4,5-bis(di-*t*-butylphosphino)xanthene (*t*-Bu-Xantphos, Strem), $(Cy_3P)_2PdCl_2$ (Strem), 1,2-bis(dicyclohexylphosphino)ethane (dcpe•2HBF$_4$; Nippon), 1,3-bis(dicyclohexylphosphino)propane (dcpp•2HBF$_4$; Nippon), 1,4-bis(dicyclohexylphosphino)butane (dcpb•2HBF$_4$; Nippon), 1,1'-bis(di-*iso*propyl-phosphino)ferrocene (dippf; Strem). SPhos was synthesized following the published procedure.[18] $Pd(OAc)_2$ was purchased from Strem, Inc. or supplied by Englehard. Sodium phenoxide, sodium 2,6-dimethylphenolate and sodium 2,4,6-tri-*tert*-butylphenolate were all synthesized from the parent phenols using either Na(0) or NaH using modified literature procedures and then stored in a glove box under nitrogen.[19] The following phenols were used as received: phenol (Acros), 2,6-dimethylphenol (Acros) and 2,4,6-tri-*tert*-butylphenol (Aldrich). The aryl esters used in the control experiments presented in Table S3 were all synthesized from 3-methoxybenzoyl chloride (Aldrich, used as received) using modified literature procedures.[20] The bis-HBF$_4$ salt of 1,3-Bis(dicyclohexylphosphino)propane (dcpp•2HBF$_4$) was also synthesized using modified literature procedures from dicyclohexylphosphine (Strem), 1,3-dibromopropane (Aldrich), *n*-butyl lithium (Aldrich) and 48 wt % tetrafluoroboric acid (Aldrich).[21]

All new compounds were characterized by ^{1}H NMR, ^{13}C NMR, and IR spectroscopy, in addition to elemental analysis (Atlantic Microlabs, Inc) and/or low resolution mass spectroscopy. Nuclear Magnetic Resonance spectra were recorded on a Varian Mercury 300 or Bruker 400 instrument. Infrared spectra were recorded using a Perkin-Elmer 2000 FT-IR. All ^{1}H NMR experiments are reported in δ units, parts per million (ppm) downfield from tetramethylsilane (internal standard) and were measured relative to the signals for residual chloroform (7.26 ppm), methylene chloride (5.32 ppm), benzene (7.16 ppm) or acetone (2.05 ppm) in the deuterated solvents. All ^{13}C NMR spectra are reported in ppm relative to deuterochloroform (77.23 ppm), deuteromethylene chloride (54.00 ppm), deuterobenzene (128.39 ppm) or deuteroacetone (29.84 ppm), and all were obtained with ^{1}H decoupling. All ^{19}F NMR spectra are reported in ppm relative to trichlorofluoromethane (0 ppm). All ^{31}P NMR spectra are reported in ppm relative to H_3PO_4 (0 ppm). All analyses by ReactIR were made using a Mettler Toledo iC10 with a 6.3 mm 1-piece diamond (DiComp) tipped probe. Melting points (uncorrected) were obtained on a Mel-

Temp capillary melting point apparatus. Gas Chromatographic analyses were performed on a Hewlett-Packard 6890 gas chromatography instrument with an FID detector using 25 m x 0.20 mm capillary column with cross-linked methyl siloxane as a stationary phase.

The conversions and yields in Tables 1, 2, 3, S1, and S2 were determined by G.C. using dodecane as an internal standard, added during reaction workup. The conversions in Table 3 were also determined using dodecane as an internal standard, added during reaction workup, and are uniformly > 99%. The yields in Tables 3 are isolated yields (average of two runs). All compounds isolated were estimated to be ≥95% pure as determined by ^{1}H NMR and GC analysis and/or combustion analysis. The procedures described in this section are representative, and thus the yields may differ from those shown in Table 3.

3.4.2 General Procedure: Pd-Catalyzed Aminocarbonylation of ArCl at Atmospheric Pressure

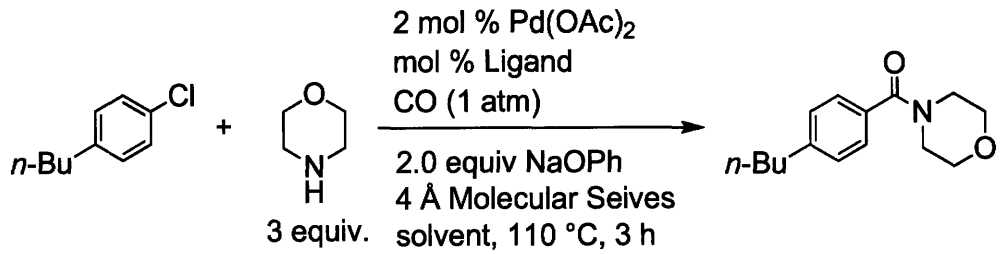
An oven-dried culture tube (18 x 150 mm, VWR) or screw-cap test tube equipped with a Teflon® coated magnetic stir bar was charged with 4Å molecular sieves then sealed with a 14/20 rubber septum (inverted) or screw-cap and Teflon-lined septum. The tube was then evacuated, heated for ~ 1 min with a Bunsen burner or for ~ 2-3 min with a heat gun to activate the molecular sieves, then the tube was backfilled with argon and allowed to cool under argon. Then, the tube was taken into a glovebox (a needle was inserted in the septum or the septum was removed upon entering the antechamber) and the tube was charged with anhydrous NaOPh (2 mmol, 2 equiv., 232 mg). The tube was resealed inside the glovebox and removed from the glovebox. All solid reagents were added, in the air, by briefly removing the rubber septum: $Pd(OAc)_2$ (2 mol %, 0.02 mmol, 0.02 equiv., 4.5 mg) and 1,3-bis(dicyclohexylphosphino)propane (dcpp•2HBF$_4$) (4 - 5 mol %, 0.04 – 0.05 mmol, 0.04 – 0.05 equiv., 24.5 – 30.6 mg). After the addition of all solid reagents, the rubber septum was secured by wrapping with electrical tape. Next, all liquid reagents were added via syringe: DMSO (1 mL), aryl chloride (1 mmol, 1 equiv.; aryl chlorides which were solids at room temperature were added during the initial charge), and amines (3 mmol, 3 equiv.). Once all reagents were added, a balloon was connected to the reaction vessel using a short length of rubber tubing (~ 1 in.), a needle adapter and a 20 G needle. The inert atmosphere was then exchanged for carbon monoxide by briefly exposing the reaction vessel to vacuum (~ 1-2 sec)

and backfilling with carbon monoxide; the balloon was inflated with $CO_{(g)}$ directly following this atmosphere exchange. The reaction tube was then submerged in a preheated oil bath (100 – 120 °C). The reaction mixture was heated with vigorous stirring for 15 h or until the aryl halide had been completely consumed as judged by GC analysis. The reaction mixture was then allowed to cool to room temperature, diluted with methylene chloride or ethyl acetate (~ 10 mL), filtered through a plug of celite (eluting with methylene chloride or ethyl acetate) and concentrated under reduced pressure. The crude material obtained was purified by flash chromatography on silica gel.

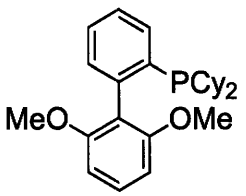
3.4.3 Reaction Optimization: Effect of Ligands and Solvents

Following the general procedure, a mixture of 4-*n*-butylchlorobenzene (1 mmol, 169 mg), $Pd(OAc)_2$ (2 mol %, 0.02 mmol, 4.5 mg), DCPP (4 - 5 mol %, 0.04 – 0.05 mmol, 25 - 32 mg), morpholine (3 mmol, 262 μl), NaOPh (2 mmol, 230 mg), 4Å molecular sieves (150 mg) and solvent (1 mL) was heated under CO at 110 °C for 15 h. The reaction mixture was then allowed to cool to room temperature and dodecane was added as an internal standard and the reaction mixture was diluted with methylene chloride (~ 10 mL) and an aliquot was filtered through a plug of celite (eluting with methylene chloride) and analyzed by GC. Some of this data is presented in the main text in Table 1.

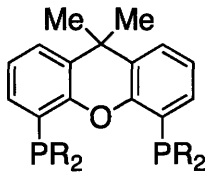
Table S1. Effects of ligands and solvents on the atmospheric pressure aminocarbonylation of 4-*n*-butylchlorobenzene with morpholine.



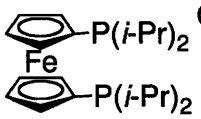
entry	Ligand	Solvent	% Ligand	% Conversion	% Yield
1	SPhos	DMSO	4	6	0
2	Xantphos	DMSO	4	1	0
3	*t*-Bu-Xantphos	DMSO	4	6	0
4	$(Cy_3P)_2PdCl_2$	DMSO	4	7	0
5	dcpe	DMSO	4	61	57
6	dcpp	DMSO	4	92	91
7	dcpp	DMSO	5	92	90
8	dcpb	DMSO	4	14	7
9	dippf	DMSO	4	8	4
10	dcpp	Sulfolane	5	72	54
11	dcpp	dioxane	5	26	15
12	dcpp	NMP	5	22	11
13	dcpp	*m*-xylene	5	11	10
14	dcpp	DMF	5	83	62[a]



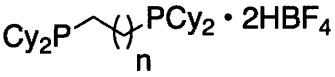
SPhos



Xantphos: R = Ph
t-Bu-Xantphos: R = *t*-Bu



dippf



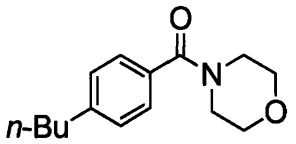
dcpe: n = 1
dcpp: n = 2
dcpb: n = 3

[a]14 % n-butylbenzene, 6 % aryl amine product (no CO insertion).

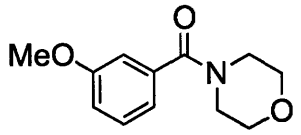
3.4.4 Reaction Optimization: Effect of Bases

Following the general procedure, a mixture of 3-chloroanisole (1 mmol, 123 mL), $Pd(OAc)_2$ (2 mol %, 0.02 mmol, 4.5 mg), DCPP (4 mol %, 0.04 mmol, 25 mg), morpholine (3 mmol, 262 μl), base (2 mmol), 4Å molecular sieves (150 mg) and DMSO (1 mL) was heated under CO at 120 °C for 15 - 18 h. The reaction mixture was then allowed to cool to room temperature and dodecane was added as an internal standard. Then the reaction mixture was diluted with methylene chloride (~ 10 mL) and an aliquot was filtered through a plug of celite (eluting with methylene chloride) and analyzed by GC.

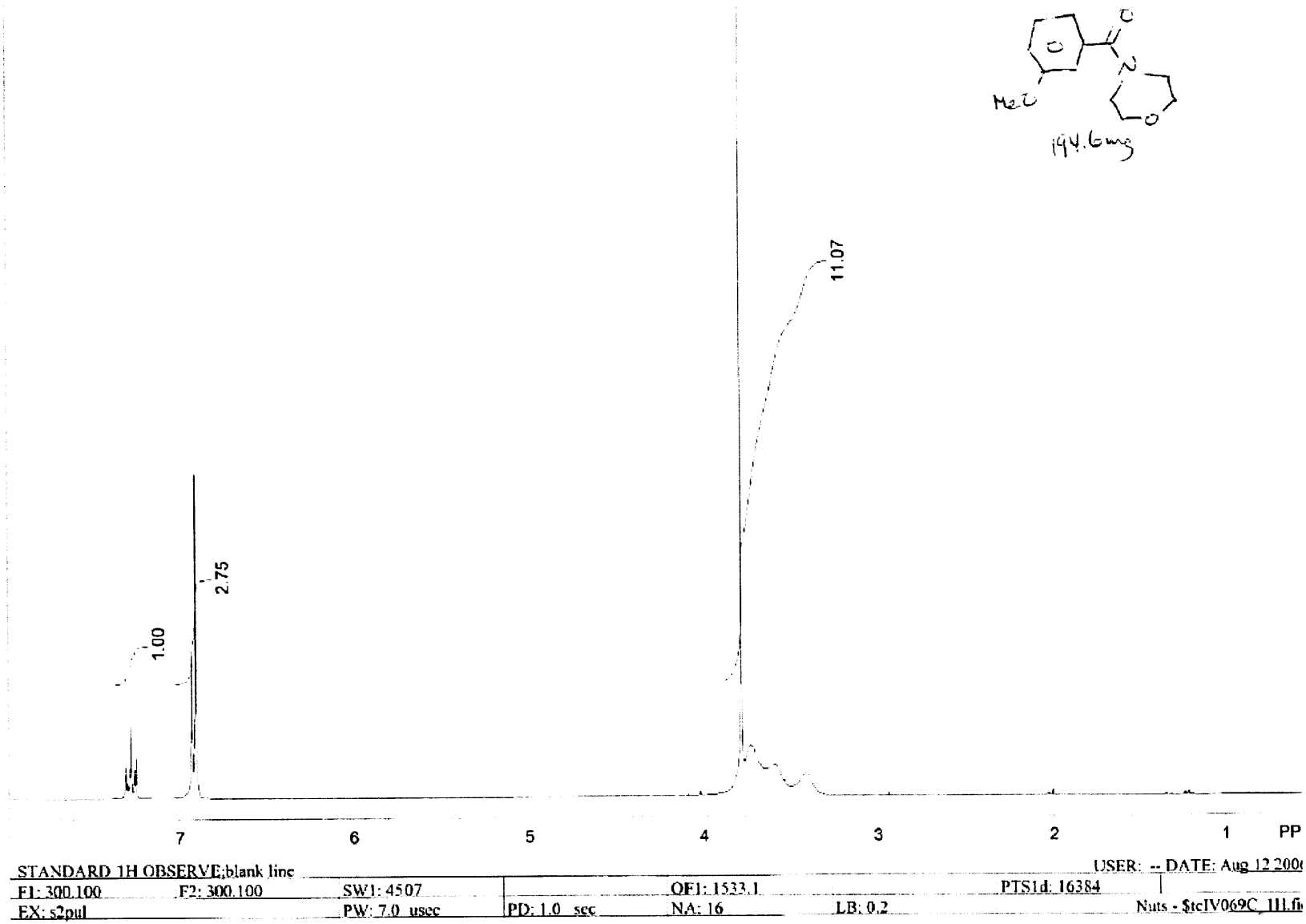
3.4.5 Analysis and Characterization



***N*-(4-*n*-Butylbezoyl)morpholine (Table 3, entry 1).** Following the general procedure, a mixture of 4-*n*-butylchlorobenzene (1 mmol, 0.168 g), morpholine (3.0 mmol, 3.0 equiv., 0.262 mL), $Pd(OAc)_2$ (2 mol %, 0.02 mmol, 0.02 equiv., 4.5 mg), dcpp•$2HBF_4$ (5 mol %, 0.04 mmol, 0.04 equiv., 25 mg), sodium phenoxide (2 mmol, 2 equiv., 0.32 g), 4Å molecular sieves (150 mg), and DMSO (1.0 mL) was heated at 110 °C for 4 h. The crude product mixture was purified by flash chromatography on silica gel (50% ethyl acetate in hexanes) to provide a mixture of rotamers of the title compound as a viscous oil (247 mg, 90%). ^{1}H NMR (300 MHz, CD_2Cl_2) d: 7.32-7.26 (m, 2H), 7.25-7.19 (m, 2H), 3.92-3.30 (brm, 8H), 2.67-2.59 (m, 2H), 1.66-1.52 (m, 2H), 1.43-1.25 (m, 2H), 0.92 (t, J = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, CD_2Cl_2) d: 170.3, 145.1, 133.3, 128.7, 127.7, 67.1, 48.3, 42.8, 35.7, 33.8, 22.7, 14.2. IR (neat, cm^{-1}): 2957, 2928, 2857, 1633, 1567, 1511, 1455, 1427, 1362, 1300, 1278, 1258, 1204, 1182, 1155, 1115, 1067, 1067, 1026, 1013, 934, 894, 841, 759, 586, 556. Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56. Found: C, 72.78 ;H, 8.56.



***N*-(3-Methoxybezoyl)morpholine (Table 3, entry 3).** Following the general procedure, a mixture of 3-chloroanisole (0.98 mmol, 0.12 mL), morpholine (3.09 mmol, 3.09 equiv., 0.27 mL), $Pd(OAc)_2$ (2 mol %, 0.02 mmol, 0.02 equiv., 4.5 mg), dcpp•$2HBF_4$ (4 mol %, 0.04 mmol, 0.04 equiv., 25 mg), sodium phenoxide (2 mmol, 2 equiv., 0.23 g), 4Å molecular sieves (150 mg), and DMSO (1.0 mL) was heated at 100 °C for 15 h. The crude product mixture was purified by flash chromatography on silica gel (50% ethyl acetate in hexanes) to provide the title compound as a viscous oil (194.6 mg, 90%). ^{1}H NMR (300 MHz, $CDCl_3$) d: 7.38-7.27 (m, 1H), 7.03-6.90 (m, 3H), 3.83 (s, 3H), 3.90-3.69 (bs, 4H), 3.69-3.55 (bs, 2H), 3.55-3.30 (bs, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) d: 170.2, 159.8, 136.7, 129.8, 119.1, 115.7, 112.6, 67.0, 55.5, 48.3, 42.7. IR (neat, cm^{-1}): 2855, 1636, 1462, 1432, 1289, 1114, 1023, 749. A satisfactory elemental analysis was not obtained for this compound:Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83. Found: C, 64.27; H, 6.85. The ^{1}H NMR spectrum follows.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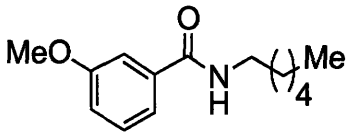
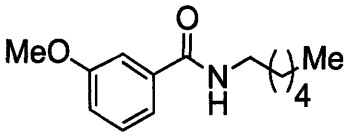
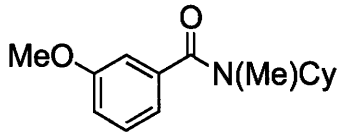


***N*-Hexyl-3-methoxybenzamide (Table 3, entry 5).** Following the general procedure, a mixture of 3-chloroanisole (0.98 mmol, 0.120 mL), *n*-hexylamine (3.03 mmol, 3.03 equiv., 0.40 mL), $Pd(OAc)_2$ (**2 mol %,** 0.02 mmol, 0.02 equiv., 4.5 mg), dcpp•2HBF_4 (4 mol %, 0.04 mmol, 0.04 equiv., 25 mg), sodium phenoxide (2 mmol, 2 equiv., 0.23 g), 4Å molecular sieves (150 mg), and DMSO (1.0 mL) was heated at 100 °C for 3 h. The reaction mixture was filtered through Celite with methylene chloride. The solution was rinsed with 1M NaOH and the solvent was removed *in vacuo*. The residue was purified by flash chromatography on silica gel (Biotage, 6-50% ethyl acetate in hexane gradient) to provide the title compound as a viscous oil (217.5 mg, 94%). ^{1}H NMR (300 MHz, $CDCl_3$) d: 7.38-7.33 (m, 1H), 7.31-7.22 (m, 2H), 7.04-6.93 (m, 1H), 6.60-6.40 (bm, 1H), 3.80 (s, 3H), 3.44-3.34 (m, 2H), 1.64-1.49 (m, 2H), 1.40-1.19 (m, 6H), 0.86 (t, J = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) d: 167.6, 159.9, 136.5, 129.7, 118.9, 117.6, 112.5, 55.5, 40.3, 31.7, 29.7, 26.8, 22.7, 14.2. IR (neat, cm^{-1}): 3315, 2930, 1637, 1583, 1544, 1488, 1310, 1245, 1044, 754, 690. Anal. Calcd for $C_{14}H_{21}NO_2$: C, 71.46; H, 8.99. Found: C, 71.49; H, 9.12.

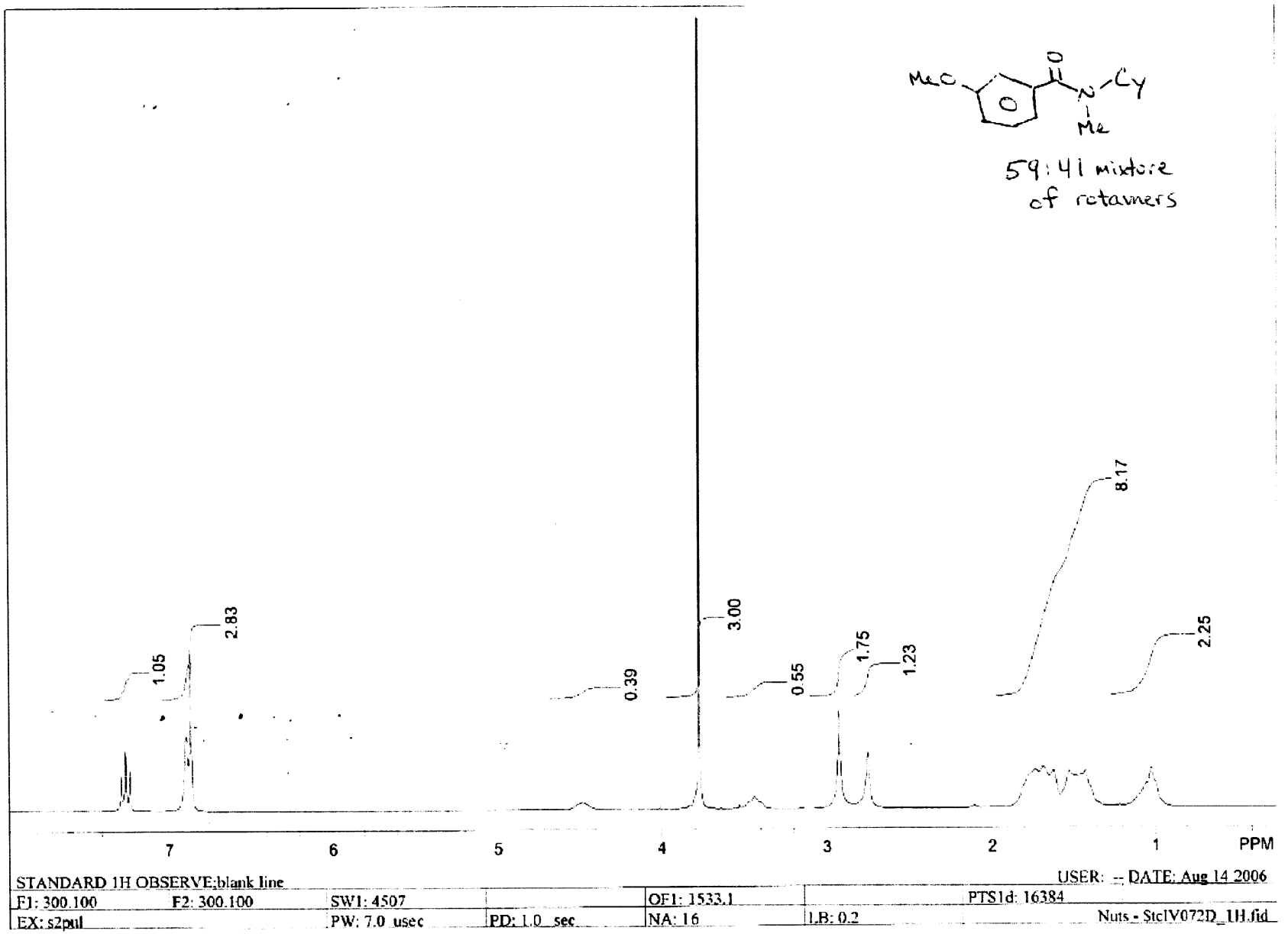


***N*-Hexyl-3-methoxybenzamide (Table 3, entry 6).** Following the general procedure, a mixture of 3-chloroanisole (1 mmol, 123 μl), $Pd(OAc)_2$ (**0.5 mol %,** 0.005 mmol, 1.1 mg), dcpp•2HBF_4 (2 mol %, 0.025 mmol, 12.5 mg), *n*-hexylamine (3 mmol, 396 μl), NaOPh (2 mmol, 230 mg), 4Å molecular sieves (150 mg), and DMSO (1 mL) was heated under CO at 120 °C for 4 h. The crude product was filtered through celite and purified by flash column chromatography on silica gel (20 % EtOAc in hexanes) to

provide the title compound as a colorless oil (228 mg, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) d: 7.39-7.36 (m, 1H), 7.35- 7.32 (d, J = 7.95, 1H), 7.30- 7.26 (m, 1H), 7.06- 7.03 (ddd, J = 8.07, 2.64, 1.03, 1H), 6.15 (br s, 1H), 3.89 (s, 3H), 3.49 – 3.44 (q, J = 6.73, 2H), 1.66- 1.59 (quintet, J = 7.44, 2H), 1.42-1.31 (m, 6H), 0.93-0.90 (t, J = 6.94, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) d: 167.29, 159.76, 136.34, 129.48, 118.44, 117.46, 112.21, 55.38, 40.09, 31.47, 29.58, 26.63, 22.54, 14.01; IR (KBr, cm^{-1}) 3316, 2930, 1638, 1583; Anal. Calcd. for $C_{14}H_{21}NO_2$: C, 71.46; H, 8.99. Found: C, 71.47; H, 9.09.



***N*-cyclohexyl-3-methoxy-*N*-methylbenzamide (Table 3, entry 7).** Following the general procedure, a mixture of 3-chloroanisole (0.98 mmol, 0.120 mL), *N*-methylcyclohexylamine (3.83 mmol, 3.83 equiv., 0.50 mL), $Pd(OAc)_2$ (2 mol %, 0.02 mmol, 0.02 equiv., 4.5 mg), dcpp•2HBF_4 (4 mol %, 0.04 mmol, 0.04 equiv., 25 mg), sodium phenoxide (2 mmol, 2 equiv., 0.23 g), 4Å molecular sieves (150 mg), and DMSO (1.0 mL) was heated at 120 °C for 15 h. The crude product was dissolved in methylene chloride and filtered through Celite. Solvent was removed and the residue was purified by flash chromatography on silica (Biotage, 8-66% ethyl acetate in hexane gradient) to provide a mixture of rotamers (59:41 ratio) of the title compound as a viscous oil (221.0 mg, 91%). ^{1}H NMR (300 MHz, $CDCl_3$) d: 7.32-7.19 (m, 1H), 6.97-6.80 (m, 3H), 6.64-6.33 (bm, 0.36H), 3.79 (s, 3H), 3.56-3.32 (bm, 0.55H), 2.93 (bs, 1.76H), 2.75 (bs, 1.27H), 1.91-1.30 (bm, 8H), 1.18-0.89 (bm, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) d: 171.5, 159.6, 138.8, 138.5, 129.6, 118.9, 118.3, 115.1, 112.1, 111.6, 58.3, 55.4, 52.8, 32.0, 30.9, 29.7, 27.6, 25.7, 25.5, 25.2 (observed complexity due to presence of rotamers, final assignments have not been made). IR (neat, cm^{-1}): 2930, 1632, 1453, 1404, 1324, 1258, 1044, 797, 753. A satisfactory elemental analysis was not obtained for this compound: Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56. Found: C, 72.24; H, 8.56. The ^{1}H NMR spectrum follows.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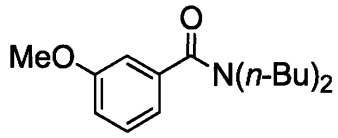
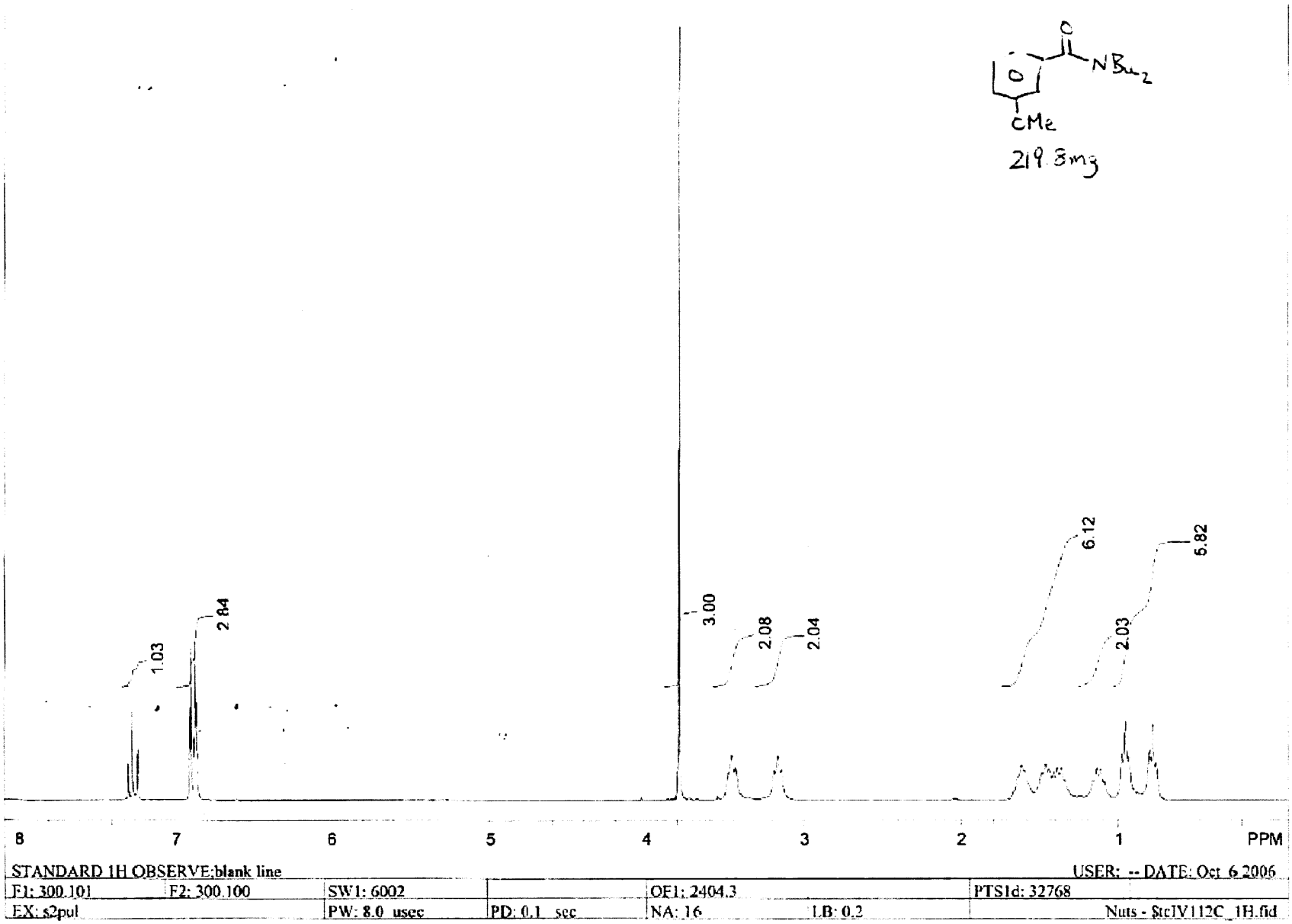


***N,N*-dibutyl-3-methoxybenzamide (Table 3, entry 4).** Following the general procedure, a mixture of 3-chloroanisole (0.98 mmol, 0.120 mL), dibutylamine (2.97 mmol, 2.97 equiv., 0.50 mL), $Pd(OAc)_2$ (2 mol %, 0.02 mmol, 0.02 equiv., 4.5 mg), dcpp•$2HBF_4$ (4 mol %, 0.04 mmol, 0.04 equiv., 25 mg), sodium phenoxide (2 mmol, 2 equiv., 0.23 g), 4Å molecular sieves (150 mg), and DMSO (1.0 mL) was heated at 120 °C for 15 h. The crude product was dissolved in methylene chloride and filtered through Celite. The organic solution was rinsed with 1M NaOH and the solvent was removed *in vacuo*. The residue was purified by flash chromatography on silica gel (Biotage, 5-44% ethyl acetate in hexane) to provide the title compound as a viscous oil (219.8 mg, 85%). ^{1}H NMR (300 MHz, $CDCl_3$) d: 7.31-7.22 (m, 1H), 6.93-6.82 (m, 3H), 3.79 (s, 3H), 3.53-3.35 (bm, 2H), 3.26-3.05 (bm, 2H), 1.74-1.25 (m, 6H), 1.22-1.03 (m, 2H), 1.03-0.87 (bm, 3H), 0.86-0.66 (bm, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) d: 171.4, 159.6, 138.7, 129.6, 118.7, 115.0, 111.9, 55.4, 48.8, 44.5, 30.9, 29.7, 20.4, 19.9, 14.1, 13.8. IR (neat, cm^{-1}): 2958, 1635, 1580, 1466, 1429, 1289, 1267, 1223, 1103, 1046, 792, 753. A satisfactory elemental analysis was not obtained for this compound: Anal. Calcd for $C_{16}H_{25}NO_2$: C, 72.96; H, 9.57. Found: C, 71.91; H, 9.54. The ^{1}H NMR spectrum follows.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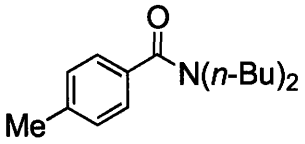
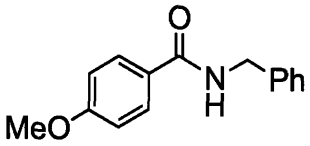
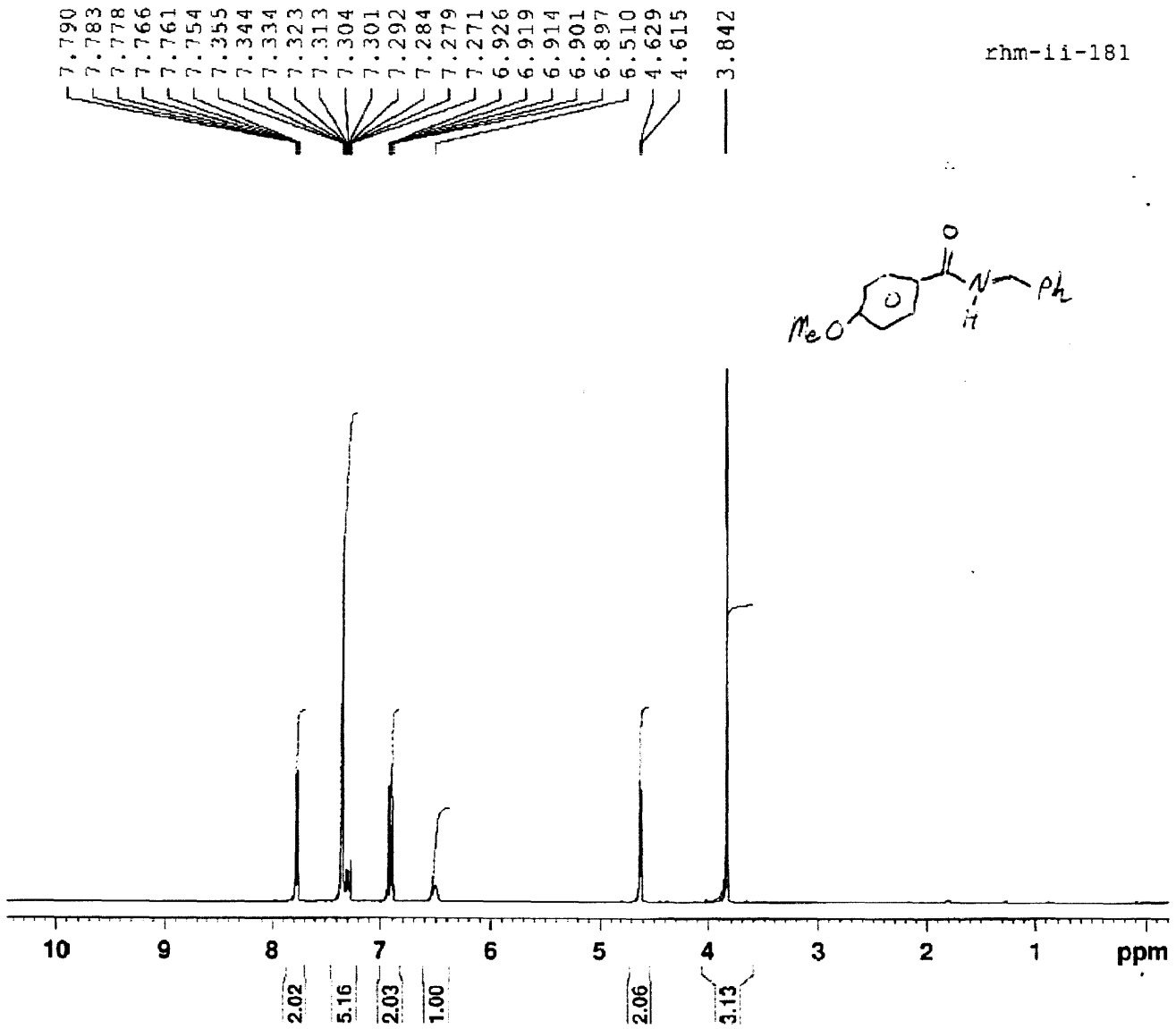


***N,N*-dibutyl-4-methylbenzamide (Table 3, entry 2).** Following the general procedure, a mixture of 4-chlorotoluene (1.01 mmol, 0.120 mL), dibutylamine (2.97 mmol, 2.97 equiv., 0.50 mL), $Pd(OAc)_2$ (2 mol %, 0.02 mmol, 0.02 equiv., 4.5 mg), dcpp•$2HBF_4$ (4 mol %, 0.04 mmol, 0.04 equiv., 25 mg), sodium phenoxide (2 mmol, 2 equiv., 0.23 g), 4Å molecular sieves (150 mg), and DMSO (1.0 mL) was heated at 120 °C for 15 h. The crude product was dissolved in dichloromethane and rinsed with a 1M NaOH solution. Solvent was removed in vacuo and the residue was purified by flash chromatography on silica (Biotage, 3-28% ethyl acetate in hexanes) to provide the title compound as a viscous oil (200.7 mg, 80%). ^1H NMR (300 MHz, $CDCl_3$) d: 7.26-7.19 (m, 2H), 7.19-7.10 (m, 2H), 3.61-3.31 (bm, 2H), 3.31-3.00 (bm, 2H), 2.33 (s, 3H), 1.76-1.03 (bm, 8H), 1.02-0.86 (bm, 3H), 0.86-0.61 (bm, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) d: 171.9, 139.0, 134.5, 129.0, 126.6, 48.9, 44.5, 30.9, 29.7, 21.4, 20.4, 19.8. 14.0, 13.8. IR (neat, cm^{-1}): 2958, 1635, 1466, 1424, 1297, 829, 754. Anal. Calcd for $C_{16}H_{25}NO$: C, 77.68; H, 10.19. Found: C, 77.41; H, 10.15.



***N*-benzyl-4-methoxybenzamide (Table 3, entry 9).** Following the general procedure, a mixture of 4-chloroanisole (1 mmol, 123 μl), $Pd(OAc)_2$ (2 mol %, 0.02 mmol, 4.5 mg), dcpp•$2HBF_4$ (4 mol %, 0.04 mmol, 25 mg), benzylamine (3 mmol, 328 μl), NaOPh (2 mmol, 230 mg), 4Å molecular sieves (150 mg), and DMSO (1 mL) was heated under CO at 110 °C for 15 h. The crude product was filtered through celite and purified by flash column chromatography on silica gel (20% EtOAc in hexanes) to provide the title

compound as a white solid (237 mg, 98 %). mp 129-130 °C. ^{1}H NMR (400 MHz, $CDCl_3$) d: 7.79-7.75 (dt, J = 8.87, 2.47, 2H), 7.36- 7.27 (m, 5H), 6.93- 6.90 (dt, J = 8.79, 2.38, 2H), 6.51 (br s, 1H), 4.63-4.62 (d, J = 5.68, 2H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) d: 166.90, 162.14, 138.41, 128.79, 128.69, 127.84, 127.46, 126.57, 113.68, 55.38, 43.97; IR (KBr, cm^{-1}) 3267, 1632, 1256, 1030. A satisfactory elemental analysis was not obtained for this compound: Anal. Calcd for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27. Found: C, 72.04; H, 6.07. The ^{1}H NMR spectrum follows.

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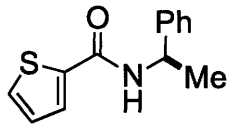
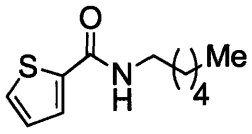
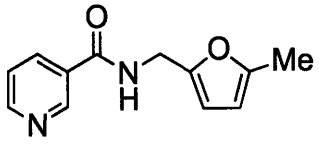


(*S*)-*N*-(1-phenylethyl)thiophene-2-carboxamide (Table 3, entry 13). Following the general procedure, a mixture of 2-chlorothiophene (1 mmol, 92 μl), $Pd(OAc)_2$ (2 mol %, 0.02 mmol, 4.5 mg), dcpp•2HBF_4 (4 mol %, 0.04 mmol, 25 mg), (*R*)-*N*-a-methylbenzylamine (99% ee) (3 mmol, 382 μl), NaOPh (2 mmol, 230 mg), 4Å molecular sieves (150 mg), and DMSO (1 mL) was heated under CO at 100 °C for 15 h. The crude product was filtered through celite and purified by flash column chromatography on silica gel (20% EtOAc in hexanes) to provide the title compound as a white solid (217 mg, 94 %). mp 127-128 °C. ^1H NMR (400 MHz, d6-acetone) d: 8.20- 8.18 (br d, *J* = 7.17, 1H), 7.83-7.82 (dd, *J* = 3.74, 1.1, 1H), 7.66-7.65 (dd, *J* = 5.01, 1.1, 1H), 7.46- 7.44 (m, 2H), 7.35- 7.31 (t, *J* = 7.56, 2H), 7.26 – 7.22 (tt, *J* = 7.32, 1.25, 1H), 7.11 – 7.09 (dd, *J* = 5.01, 3.75, 1H), 5.32- 5.28 (quin, *J* = 7.46, 1H), 1.55 – 1.53 (d, *J* = 7.07, 3H); ^{13}C NMR (100 MHz, d6-acetone) d: 160.61, 144.52, 140.46, 130.24, 128.27, 127.57, 127.53, 126.76, 126.18, 48.84, 21.49; IR (KBr, cm^{-1}) 3281, 3085, 2979, 1620, 1548. Anal. Calcd. for $C_{13}H_{13}NOS$: C, 67.50; H, 5.66. Found: C 67.45; H, 5.63. The product was found to be of > 99% ee as determined by HPLC analysis using a Chiracel OJ column with a 15% IPA/ hexane mobile phase, and a flow rate of 1 mL/min $[a]^{21}$ +11.7 (*c* 0.62, $CHCl_3$).

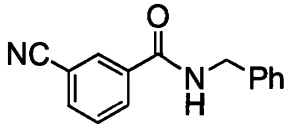


***N*-hexylthiophene-2-carboxamide (Table 3, entry 12).** Following the general procedure, a mixture of 2-chlorothiophene (1 mmol, 92 μl), $Pd(OAc)_2$ (2 mol %, 0.02 mmol, 4.5 mg), dcpp•2HBF_4 (4 mol %, 0.04 mmol, 25 mg), hexylamine (3 mmol, 396 μl), NaOPh (2 mmol, 230 mg), 4Å molecular sieves (150 mg), and DMSO (1 mL) was heated under CO at 100 °C for 15 h. The crude product was filtered through celite and purified by flash column chromatography on silica gel (20 % EtOAc in hexanes) to provide the title

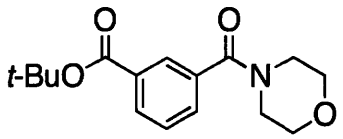
compound as a colorless oil (209 mg, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) d: 7.51-7.50 (dd, J = 3.72, 1.17, 1H), 7.48- 7.47 (dd, J = 5.00, 1.17, 1H), 7.10- 7.08 (dd, J = 4.98, 3.69, 1H), 6.01 (br s, 1H), 3.47- 3.42 (q, J = 6.76, 2H), 1.66-1.59 (m, 2H), 1.41-1.31 (m, 6H), 0.93- 0.89 (t, J = 6.78, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) d: 161.77, 139.13, 129.56, 127.74, 127.52, 40.01, 31.45, 29.62, 26.58, 22.52, 14.00; IR (KBr, cm^{-1}) 3310, 2956, 1625, 1551, 1307; Anal. Calcd. for $C_{11}H_{17}NOS$: C, 62.52; H, 8.11. Found: C 62.55; H, 8.21.



***N*-((5-methylfuran-2-yl)methyl)pyridine-3-carboxamide (Table 3, entry 10).** Following the general procedure, a mixture of 3-chloropyridine (1 mmol, 94 μl), $Pd(OAc)_2$ (2 mol %, 0.02 mmol, 4.5 mg), dcpp•2HBF_4 (4 mol %, 0.04 mmol, 25 mg), 5-methylfurfurylamine (3 mmol, 334 μl), NaOPh (2 mmol, 230 mg), 4Å molecular sieves (150 mg), and DMSO (1 mL) was heated under CO at 100 °C for 15 h. The crude product was filtered through celite and purified by flash column chromatography on silica gel (EtOAc) to provide the title compound as a white solid (198 mg, 92 %). mp 94-95 °C. ^{1}H NMR (400 MHz, $CDCl_3$) d: 8.93 (d, J = 2.15, 1H), 8.57-8.56 (dd, J = 4.80, 1.42, 1H), 8.12- 8.10 (dt, J = 7.96, 1.83, 1H), 7.73-7.71 (t, J = 4.72, 1H), 7.29- 7.26 (dd, J = 7.90, 4.86, 1H), 6.09 (d, J = 2.99, 1H), 5.82 (d, J = 2.87, 1H), 4.51 (d, J = 5.36, 2H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) d: 165.44, 151.92, 151.85, 148.91, 148.12, 135.29, 130.02, 123.33, 108.73, 106.28, 37.02, 13.42; IR (KBr, cm^{-1}) 3305, 3072, 1642, 1545; Anal. Calcd. for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59. Found: C 66.43; H, 5.61.

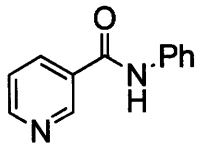


***N*-benzyl-3-cyanobenzamide (Table 3, entry 8).** Following the general procedure, a mixture of 3-chlorobenzonitrile (1.00 mmol, 0.137 g), benzylamine (3.02 mmol, 3.02 equiv., 0.33 mL), $Pd(OAc)_2$ (2 mol %, 0.02 mmol, 0.02 equiv., 4.5 mg), dcpp•$2HBF_4$ (4 mol %, 0.04 mmol, 0.04 equiv., 25 mg), sodium phenoxide (2 mmol, 2 equiv., 0.23 g), 4Å molecular sieves (150 mg), and DMSO (1.0 mL) was heated at 100 °C for 15 h. The crude product was purified by flash chromatography on silica gel (Biotage, 8-66% ethyl acetate in hexane gradient) to provide the title compound as a white solid (151.9 mg, 64%). m.p.= 119 °C. ^{1}H NMR (300 MHz, $CDCl_3$) d: 8.09-8.05 (m, 1H), 8.05-7.97 (m, 1H), 7.77-7.69 (m, 1H), 7.52 (t, J = 7.8 Hz, 1H), 7.37-7.24 (m, 5H), 7.16-7.00 (bt, 1H), 4.59 (d, J = 5.6 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) d: 165.5, 137.8, 135.6, 134.8, 131.6, 131.0, 129.7, 128.9, 128.0, 127.9, 118.2, 112.8. IR (neat, cm^{-1}): 3308, 3066, 2232, 1645, 1541, 1301, 750, 699, 684. Anal. Calcd for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12. Found: C, 76.01; H, 5.04.

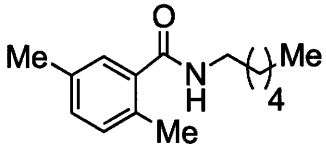


***tert*-butyl 3-(morpholine-4-carbonyl)benzoate (Table 3, entry 14).** Following the general procedure, a mixture of 3-chloro-*tert*-butylbenzoate (1.00 mmol, 0.213 g), morpholine (3.0 mmol, 3.0 equiv., 0.262 mL), $Pd(OAc)_2$ (2 mol %, 0.02 mmol, 0.02 equiv., 4.5 mg), dcpp•$2HBF_4$ (5 mol %, 0.05 mmol, 0.05 equiv., 32 mg), sodium phenoxide (2 mmol, 2 equiv., 0.23 g), 4Å molecular sieves (150 mg), and DMSO (1.0 mL) was heated at 100 °C for 15 h. The crude product was purified by flash chromatography on silica gel (25% ethyl acetate in hexane, gradient) to provide the title compound as a viscous, colorless oil (246 mg, 84%). ^{1}H NMR (300 MHz, CD_2Cl_2) d: 8.06-8.01 (m, 1H), 7.99-7.96 (m, 1H), 7.58-7.52 (m, 1H), 7.51 (m, 1H), 3.93-3.29 (brm, 8H), 1.79 (s, 9H). ^{13}C NMR (75 MHz, CD_2Cl_2) d: 169.5, 165.1, 136.2, 132.9, 131.3, 130.8, 128.9, 128.4, 81.7, 67.1, 48.6, 42.9, 28.3. IR (neat, cm^{-1}): 2976, 2929, 2867, 1714, 1638, 1582, 1481, 1457, 1437, 1421, 1393, 1368, 1308, 1272, 1250, 1155, 1115, 1082, 1069, 1026, 946,

912, 867, 849, 125, 775, 761, 736, 696, 669, 637, 603, 563. Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.27. Found: C, 65.99; H, 7.21.



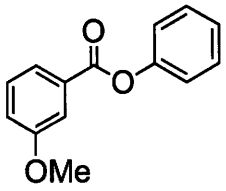
***N*-phenylpyridine-3-carboxamide (Table 3, entry 11).** Following the general procedure, a mixture of 3-chloropyridine (1 mmol, 94 μl), $Pd(OAc)_2$ (2 mol %, 0.02 mmol, 4.5 mg), dcpp•2HBF$_4$ (4 mol %, 0.04 mmol, 25 mg), aniline (3 mmol, 273 μl), NaOPh (2 mmol, 230 mg), 4Å molecular sieves (150 mg), and DMSO (1 mL) was heated under CO at 100 °C for 15 h. The crude product was filtered through celite and purified by flash column chromatography on silica gel (gradient elution: 50% EtOAc in hexanes - EtOAc) to provide the title compound as a white solid (185 mg, 94 %). Mp 119 -120 °C. ^{1}H NMR (400 MHz, $CDCl_3$) d: 9.05 (s, 1H), 8.76 - 8.69 (m, 2H), 8.17 - 8.16 (d, J = 6.68, 1H), 7.65 - 7.63 (d, J = 7.89, 2H), 7.36- 7.32 (m, 3H), 7.18- 7.15 (t, J = 7.37, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) d: 164.22, 152.21, 147.99, 137.55, 135.46, 130.85, 129.07, 125.01, 123.63, 120.65; IR (KBr, cm^{-1}) 3346, 1652, 1524; Anal. Calcd. for $C_{12}H_{10}N_2O$: C, 72.71; H, 5.08. Found: C, 72.39; H, 5.00.



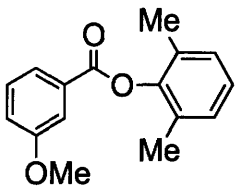
***N*-hexyl-2,5-dimethylbenzamide (Table 3, entry 15).** Following the general procedure, a mixture of 2-chloro-1,4-dimethylbenzene (1.01 mmol, 0.135 mL), *n*-hexylamine (3.03 mmol, 3.03 equiv., 0.40 mL), $Pd(OAc)_2$ (2 mol %, 0.02 mmol, 0.02 equiv., 4.5 mg), dcpp•2HBF$_4$ (4 mol %, 0.04 mmol, 0.04 equiv., 25 mg), sodium phenoxide (2 mmol, 2 equiv., 0.23 g), 4Å molecular sieves (150 mg), and DMSO (1.0 mL) was heated at 110 °C for 15 h. The crude product was dissolved in dichloromethane and rinsed with a 1M NaOH solution. Solvent was removed in vacuo and the residue was purified by flash chromatography on

silica (Biotage, 5-40% ethyl acetate in hexanes) to provide the title compound as a white solid (200.3 mg, 85%). mp = 87 °C. ^{1}H NMR (300 MHz, $CDCl_3$) d: 7.10 (s, 1H), 7.10-7.00 (m, 2H), 6.04 (bt, 1H), 3.34 (q, J = 7.4 Hz, 2H), 2.34 (s, 3H), 2.28 (s, 3H), 1.62-1.45 (m, 2H), 1.41-1.21 (m, 6H), 0.89 (t, J = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) d: 170.4, 136.8, 135.2, 132.6, 130.8, 130.3, 127.3, 39.8, 31.6, 29.7, 26.7, 22.7, 20.9, 19.3, 14.1. IR (neat, cm^{-1}): 3289, 2926, 1638, 1540, 1318, 816, 726. Anal. Calcd for $C_{15}H_{23}NO$: C, 77.21; H, 9.93. Found: C, 77.27; H, 9.98.

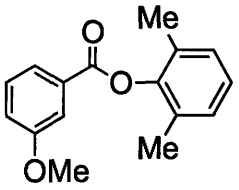
3.4.6 Synthesis of Aryl Esters



Phenyl 3-methoxybenzoate. Following a modified literature procedure:[20] An oven-dried 300 mL round bottom flask equipped with a Teflon® coated magnetic stir bar was sealed with a rubber septum, then purged with and cooled under nitrogen gas and then charged with 3-methoxybenzoyl chloride (33.8 mmol, 5.77 g, 4.75 mL), triethylamine (37.2 mmol, 6.84 g, 9.4 mL), methylene chloride (40 mL) and cooled to 0 °C in an ice water bath. Next, phenol (37.2 mmol, 3.5 g) was added to the cooled reaction mixture as a solid in three equal portions by briefly removing the septum. The reaction mixture was stirred over night and allowed to slowly warm to room temperature over this time. After approximately 12 h, water was added; the organic phase was separated and extracted with methylene chloride (2 x 50 mL). The combined organics were dried over $MgSO_4$ and purified by flash column chromatography on silica gel (5 % EtOAc in hexanes) to provide the title compound as a slightly orange solid (5.3 g, 69 %). mp = 53-54 °C ^{1}H NMR (300 MHz, $CDCl_3$) d: 7.85-7.80 (m, 1H), 7.73-7.71 (m, 1H), 7.48-7.39 (m, 3H), 7.32-7.17 (m, 4H), 3.89 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) d: 165.2, 159.8, 151.1, 131.0, 129.8, 129.7, 126.1, 122.7, 121.8, 120.3, 114.6, 55.6. IR (neat, cm^{-1}): 1729, 1599, 1486, 1467, 1457, 1431, 1327, 1278, 1221, 1196, 1165, 1085, 1038, 993, 925, 899, 872, 841, 806, 788, 749, 743, 691, 679.

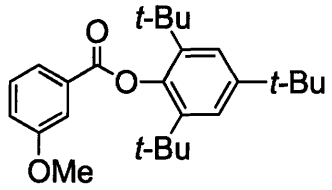


2,6-Dimethylphenyl 3-methoxybenzoate. Following the general aminocarbonylation procedure, a mixture of 3-chloroanisole (0.98 mmol, 0.120 mL), dibutylamine (2.97 mmol, 2.97 equiv., 0.50 mL), $Pd(OAc)_2$ (2 mol %, 0.02 mmol, 0.02 equiv., 4.5 mg), dcpp•2HBF$_4$ (4 mol %, 0.04 mmol, 0.04 equiv., 25 mg), sodium 2,6-dimethylphenoxide (2 mmol, 2 equiv., 0.29 g), and DMSO (1.0 mL) was heated at 120 °C for 15 h. The crude product was dissolved in methylene chloride and filtered through Celite. The product was purified by flash chromatography on silica gel (Biotage, 2-18% ethyl acetate in hexane gradient) to provide the title compound as a white solid (207.2 mg, 82%). mp = 65 °C. ^{1}H NMR (300 MHz, $CDCl_3$) d: 7.94-7.85 (m, 1H), 7.82-7.75 (m, 1H), 7.47 (t, J = 8.1 Hz, 1H), 7.26-7.19 (m, 1H), 7.19-7.07 (m, 3H), 3.92 (s, 3H), 2.24 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) d: 164.4, 159.9, 148.5, 130.7, 130.5, 129.8, 128.8, 126.1, 122.7, 120.3, 114.7, 55.7, 16.6. IR (neat, cm^{-1}): 2925, 1733, 1586, 1488, 1276, 1221, 1170, 1096, 1041, 770, 751. Anal. Calcd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 74.81; H, 6.25.



2,6-Dimethylphenyl 3-methoxybenzoate. This compound was also synthesized following a modified literature procedure:[20] An oven-dried 50 mL round bottom flask equipped with a Teflon® coated magnetic stir bar and reflux condenser was sealed with a rubber septum, then purged with and cooled under nitrogen gas and then charged with 3-methoxybenzoyl chloride (15 mmol, 2.56 g, 2.11 mL), triethylamine (30 mmol, 3.04 g, 4.18 mL), THF (15 mL) and cooled to 0 °C in an ice water bath. Next, 2,6-dimethyl phenol (22.5 mmol, 2.75 g) was added to the cooled reaction mixture as a solid in three equal portions by briefly removing the septum. The reaction vessel was then placed in a preheated oil bath (c.a. 70 °C) and

the reaction mixture was stirred over night at reflux. After approximately 12 h, the reaction mixture was cooled and water was added; the organic phase was separated and extracted with ethyl acetate (2 x 50 mL). The combined organics were dried over $MgSO_4$ and purified by flash column chromatography on silica gel (5 % EtOAc in hexanes) to provide the title compound as an off-white solid (2.9 g, 77 %). mp = 64-65 °C. ^{1}H NMR (300 MHz, $CDCl_3$) d: 7.94-7.85 (m, 1H), 7.82-7.75 (m, 1H), 7.47 (t, J = 8.1 Hz, 1H), 7.26-7.19 (m, 1H), 7.19-7.07 (m, 3H), 3.92 (s, 3H), 2.24 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) d: 164.4, 159.9, 148.5, 130.7, 130.5, 129.8, 128.8, 126.1, 122.7, 120.3, 114.7, 55.7, 16.6. IR (neat, cm^{-1}): 2925, 1733, 1586, 1488, 1276, 1221, 1170, 1096, 1041, 770, 751.



2,4,6-tri-*tert*-butylphenyl 3-methoxybenzoate. Following a modified literature procedure:[20] An oven-dried 100 mL round bottom flask equipped with a Teflon® coated magnetic stir bar and reflux condenser was sealed with a rubber septum, then purged with and cooled under nitrogen gas. This glassware was then brought into a glove box under nitrogen and was charged with NaH (24 mmol, 0.61 g, 95 % Aldrich). Then, 2,4,6-tri-*tert*-butyl phenol (22.5 mmol, 5.91 g) was added to the reaction mixture as a solid in three equal portions by briefly removing the septum; THF (20 mL) was then added and the reaction mixture was stirred under nitrogen until bubble evolution ceased. Next, 3-methoxybenzoyl chloride (15 mmol, 2.56 g, 2.11 mL) was added via syringe and rinsed down the condenser with additional THF (10 mL); the reaction vessel was then placed in a preheated oil bath (c.a. 70 °C) and the reaction mixture was stirred over night at reflux. After approximately 12 h, the reaction mixture was cooled and water was added; the organic phase was separated and extracted with ethyl acetate (2 x 50 mL). The combined organics were dried over $MgSO_4$ and purified by flash column chromatography on silica gel (5 % EtOAc in hexanes) to provide the title compound as an off-white solid (2.7 g, 46 %). mp =

154-155 °C ^{1}H NMR (300 MHz, $CDCl_3$) d: 7.89-7.84 (m, 1H), 7.77-7.75 (m, 1H), 7.51-7.44 (m, 1H), 7.39 (s, 2H), 7.24-7.17 (m, 1H), 3.91 (s, 3H), 1.36 (s, 9H), 1.35 (s, 18H). ^{13}C NMR (75 MHz, $CDCl_3$) d: 172.3, 166.9, 160.0, 147.4, 145.9, 141.6, 132.2, 130.0, 123.6, 123.0, 119.8, 115.2, 55.7, 35.8, 35.0, 31.9, 31.8. IR (neat, cm^{-1}): 2963, 1734, 1600, 1587, 1487, 1465, 1428, 1394, 1363, 1322, 1275, 1209, 1190, 1109, 1043, 995, 906, 879, 844, 751, 734, 682, 668, 648. Anal. Calcd for $C_{26}H_{36}O_3$: C, 78.75; H, 9.15. Found: C, 78.66; H, 9.19.

3.4.7 Preparation of the Ligand Salt 1,3-bis(dicyclohexylphosphino)propane•2HBF$_4$ (7)

The ligand obtained from Nippon Chemical Co. was used for the experiments published in the main text; however, **7** can also be prepared following modified literature procedures:[21] A 200 mL round bottom flask equipped with a Teflon® coated magnetic stir bar was evacuated, flame dried under vacuum, back filled with nitrogen gas and cooled under nitrogen gas. Once cool, the flask, a 24/ 40 rubber septum, 10 mL plastic disposable syringe (Normject) and 21 G disposable needle were taken into a glove box under nitrogen. In the glove box, the flask was charged with dicyclohexylphosphine (34.6 mmol, 2.2 equiv., 7 mL) using the syringe, the flask was sealed with the rubber septum and removed from the glove box. The flask was kept under a positive pressure of nitrogen, THF (70 mL) was added and the flask was cooled to 0 °C in an ice water bath. Next, *n*-butyl lithium (36.3 mmol, 2.31 equiv., 14.8 mL of a 2.45 M solution in hexanes) was added to the stirring, cooled solution drop-wise via syringe over ~10 min and the solution was allowed to stir for 1 h. Then, 1,3-dibromopropane (15.7 mmol, 1 equiv., 3.18 g, 1.6 mL; filtered through a plug of basic Alumina immediately prior to use) was added to the stirring, cooled solution drop wise via syringe. The solution was allowed to stir and slowly warm to 10 °C; then, the ice water bath was removed and the solution was stirred at room temperature for an additional 5.5 h. Next, the solution was cooled to 0 °C using an ice water bath and HBF_4 (5 mL, 7g of 48 wt% solution in water, 3.36 g HBF_4, 38.3 mmol, 2.4 equiv.) was added *SLOWLY* via syringe to the stirring, cooled solution. This solution was allowed to stir for ~5 min after the addition was complete, then the bath was removed and the solution was allowed to stir for an additional 20 - 30 min at room temperature. Then the crude reaction mixture was transferred to a 500 mL sparatory funnel, CH_2Cl_2 (~150 mL) was added and deionized water (~150

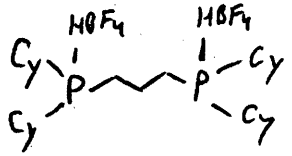
mL) was added. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 100 mL). The organics were combined, dried over $MgSO_4$, filtered and concentrated in vacuo. This crude material was transferred to a 200 mL round bottom; significant foaming occurred upon exposure to high vacuum and care was taken to avoid over filling the flask. After extended exposure to the high vacuum (~48 h), the foam solidified and the crude material could be scraped from the flask to provide the *crude* bis-HBF_4 salt of the ligand as an off-white solid (8.16 g, 85%; crude) mp = 154-155 °C ^{1}H NMR (300 MHz, $CDCl_3$) d: 5.9 (brd, J_{P-H} = 471 Hz, 2H; the individual peaks are broad singlets located at 6.75 ppm and 5.18 ppm), 2.80-2.35 (brm, 6H), 2.35-2.1 (brm, 2H), 2.35-1.6 (brm, 22H), 1.6-1.1 (brm, 20H). ^{13}C NMR (75 MHz, $CDCl_3$) d: 28.9, 28.4, 27.7, 27.6, 27.5, 27.3, 26.9, 26.7, 26.5, 26.4, 26.3, 26.3, 25.9, 25.4. ^{31}P NMR (121 MHz, C_6D_6) δ: 25.1.

JRM VII-279

31P

CD_2Cl_2

(CRUDE)



P-31 STANDARD PARAMETERS
PHOSPHATE REGION

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at	0.640	dmf	11000
np	128000	PROCESSING	
sw	100000.0	lb	1.00
fb	55000	wtfile	
bs	16	proc	ft
tpwr	62	fn	not used
pw	10.0		
d1	0.250	werr	
tof	2337.3	wexp	
nt	100	wbs	
ct	0	wnt	
alock	n		
gain	not used		
FLAGS			
il	n		
in	n		
dp	y		
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sc	0		
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rfp	0		
th	78		
ins	100.000		
nm	ph		

3.4.8 General Procedures for Kinetic Experiments

The glovebox (Vacuum Atmospheres Nexus One) was nitrogen filled and the internal atmosphere maintained below 0.5 ppm O_2 and 0.1 ppm H_2O. Glassware and stirbars were dried in a convection oven 200 °C under air for a minimum of 24 h and transferred into the glovebox while still hot. Toluene was received and purified as described above, then further deoxygenated by transferring to a 1 L an oven-dried Strauss flask under argon and purging with nitrogen for one hour before being taken into the glovebox. Toluene was stored in the glovebox over activated Linde Type 3Å molecular sieves. DMSO was purchased anhydrous (Aldrich Sure-Seal®), transferred via cannula to an oven-dried Strauss flask under nitrogen and purged with nitrogen for 2 h before being taken into the glovebox. Molecular sieves were activated by heating approximately 200 g in 1 L round bottom flask equipped with a vacuum adapter at 200 °C under high vacuum for 48 h and transferred into the glovebox under vacuum. Sodium phenoxide was prepared as described above. Di-*n*-butylamine (Aldrich) was distilled from CaH_2 and degassed via freeze-pump-thaw technique before being transferred into the glovebox. 3-chloroanisole (Aldrich) was passed though a plug of neutral alumina and degassed via freeze-pump-thaw technique before being transferred into the glovebox. The standard solution of 3-chloroanisole in DMSO was prepared from the above materials in the glovebox using standard volumetric techniques. 1,3-bis(dicyclohexylphosphino)propane (dccp; Aldrich) was used as received. 1,3-bis(dicyclohexylphosphino)propane tetrafluoroborate salt (dcpp•2HBF_4; Nippon) was used as received. $(Ph_3P)_2PdPhCl$ was prepared using slightly modified literature procedures.[22]

3.4.9 Preparation of (DCCP)PdPhCl

In the glovebox, $(Ph_3P)_2PdPhCl$ (910 mg, 1.22 mmol), 1,3-bis(dicyclohexylphosphino)propane (563 mg, 1.37 mmol) and toluene (10 mL) were combined in an 20 mL scintillation vial containing a small Teflon coated stirbar. The vial was capped and the resulting colorless suspension was rapidly stirred atop a magnetic stirplate in the glovebox for 12 h. During this time, ligand exchange occurs converting the insoluble $(Ph_3P)_2PdPhCl$ to insoluble (DCPP)PdPhCl. The resulting colorless suspension was filtered on a medium porosity fritted glass Buchner funnel, and the solids were washed with toluene (5 mL). Upon

washing, the solids were removed from the glovebox, transferred to a round bottom flask under air and dried under high-vacuum to provide 852 mg (93%) of 1,3-bis(dicyclohexylphosphino)propane palladium phenylchloride ((DCPP)PdPhCl) as the toluene mono-solvate (^{1}H NMR). Attempts to remove the solvating toluene by exposing the material to prolonged vacuum failed. The complex was characterized and used as the mono-solvate ((DCPP)PdPhCl•tol): ^{1}H NMR (400 MHz, CD_2Cl_2) d 7.34 (t, J = 7.6 Hz, 2H), 7.23 (t, J = 7.6 Hz, 2H), 7.10-719 (m, 3H), 7.13 (td, J = 7.2, 2 Hz, 2H), 6.89 (t, J = 7.2 Hz, 1H), 2.33 (s, 3H), 2.10-2.30 (m, 6H), 1.10-2.02 (m, 42 H), 0.97 (qt, J = 9.6, 3.2 Hz, 2H); ^{13}C NMR (100 MHz, CD_2Cl_2) d161.2, 160.0, 138.1, 136.9 (t, J = 2.1 Hz), 128.7 (d, J = 80.9 Hz) , 126.9 (d, J = 8.3 Hz), 125.4, 122.9, 36.1 (d, J = 28 Hz), 34.6 (d, J = 20 Hz), 30.4 (d, 2H), 30.3 (d, J = 5 Hz), 28.8 (d, 2H), 28.6 (d, J = 3 Hz), 27.7 (d, J = 2Hz), 27.6 (d, J = 2 Hz), 27.2 (m), 26.5, 26.2, 22.6 (d, J = 6Hz), 21.3, 19.4 (m), 18.3, 18.2; ^{31}P NMR (162 MHz, CD_2Cl_2) d 24.9 (d, J = 40.5 Hz), 5.2 (d, J = 40.5 Hz); IR (film from CH_2Cl_2, cm^{-1}) 3045, 2925, 2851, 1563, 1447. Anal. Calcd for $C_{40}H_{63}ClP_2Pd$: C, 64.25; H, 8.49. Found: C, 64.45; H, 8.36.

3.4.10 General Procedure for Kinetic Measurements

In the glovebox, solids materials were were added to a 10 mL round bottom flask equipped with a 14/20 ground glass joint and containing an teflon coated 5/16 X 1/2 inch polygon stirbar. Liquid reagents and solvents were then added using auto-pipet with plastic dispensing tips. The flask was then fitted with a gas adapter (Chemglass model AF-0500-01) and the resulting apparatus sealed with a 14/20 ground glass plug. Ground glass joints were sealed with a light coating of high-vacuum silicon grease and secured with standard taper joint clips. The sealed reactor was then removed from the glovebox while maintaining an upright position.

In a well-ventilated fume-hood, the reactor was then attached to a standard vacuum/gas double manifold (Shlenk line) using 1/4 inch ID rubber tubing. For reactions involving carbon monoxide, the gas supply on this manifold was attached to a carbon monoxide (CO) source regulated to 0.5 psig (0-2 psig AirGas regulator, part number Y12N175A350). For other reactions, the gas supply was attached to an argon source regulated at ca. 0.5 psig. The gas-inlet to the reactor was evacuated and refilled with the

working gas three times prior to opening the stopcock. Under positive backpressure of the working gas, the ground glass stopper was removed and the reactor was attached to an in situ IR spectrometer (Mettler Toledo ReactIR-iC10 with a C1 Fiber and a diamond tip) by passing the probe though the ground glass joints of the gas-adapter and into the 10 mL flask. The reactor was secured to the probe using fitted with a 14/20 Teflon ground glass joint adapter (J-Chem model number 1414) and a standard taper joint clip. The probe depth was adjusted to place the sensor approximately 1/8 inch below the surface of the DMSO suspension before both the probe and the reactor were secured to a tall ring-stand using standard three-prong clamps.

For reactions involving CO, the reactor was then quickly evacuated (vacuum achieved in reactor approximately 0.5 torr as measured by a vacuum gauge attached to the manifold) and refilled with CO at room temperature. This procedure was repeated four times for a total of five backfills. After the final backfill, the reactor left open to the CO supply and the regulator pressure was adjusted (if needed) to bring pressure in the reactor back to 0.5 psig CO. For other reactions, the reactor was maintained under positive pressure of argon for the duration of the reaction once attached to the probe.

Once the atmosphere over the suspension was properly adjusted, an oil bath (pre-equilibrated to 120 °C) atop a magnetic stirplate was then raised to the reactor using a laboratory jack, such that the bottom of the flask was position over the center of the stirplate about 1/4 inch from the bottom of the oil bath to insure efficient stirring. The oil bath was stirred using a small paper clip and the temperature of the bath was maintained via thermal-couple controlled heating at 120 ± 1 °C . The timer for the kinetic run was triggered within 30 seconds of the flask entering the oil bath. IR spectra were collected every minute for the duration of the amide formation, about 7 hours. At the end of the reaction, the oil bath was lowered and the reactor was allowed to cool to room temperature and then opened. Docecane (227 μL, 1.0 mmol) was added and the suspension was diluted with CH_2Cl_2 (10 mL). A sample of this suspension was filter through celite for GC analysis using the dodecane as an internal standard for yield determination.

The data from the in situ IR spectroscopy was processed in the following manner. Solvent subtraction was applied using a reference sample of DMSO at 120 °C. Baseline offset functions were also applied using 1680 cm^{-1} as a reference (a region devoid of IR absorption peaks) to correct for baseline fluctuations during the initial warming period. Phenyl 3-methoxybenzoate (**13**) concentrations were measured by following the carbonyl absorption at 1735-1737 cm^{-1}. *N,N*-dibutyl-3-methoxybenzamide (**14**) concentrations were measured by following the carbonyl absorption at 1631-1633 cm^{-1}. Concentrations of both **13** and **14** were obtained by conversion of absorbance to concentration using a correction factor derived from absorbance measurements using samples of each material at known concentrations in DMSO at 120 °C and correlated well (within 5%) to measured GC yields.

3.4.11 In situ Monitoring of the Formation of N,N-Dibutyl-3-methoxybenzamide (14) from 3-Chloroanisole

Using the general procedure for kinetic experiments, (DCPP)PdPhCl•tol (15.0 mg, 0.02 mmol), DCPP•2HBF$_4$ (12.3 mg, 0.02 mmol), 4Å molecular sieves (powdered, activated, 150 mg), NaOPh (232 mg, 2.0 mmol), a solution of 3-chloroanisole in DMSO (0.25 mL, 1.0 mmol, 4 M), Bu_2NH (neat, 0.5 mL, 3.0 mmol) and DMSO (2.25 mL) were combined to give a colorless slurry and reacted under an atmosphere of CO. The concentration vs. time data for **13** and **14** from this experiment is presented in Table S2. Data was plotted using Excel and is shown in Figure 1 in the main text. The measured GC yield for **14** was 88%.

Table S2.

Time	[13]	[14]	0.082	0.032	0.005	0.165	0.052	0.021
(h)	(M)	(M)	0.099	0.039	0.009	0.182	0.052	0.023
0.032	0.013	0.005	0.115	0.043	0.012	0.199	0.056	0.026
0.049	0.024	0.005	0.132	0.046	0.014	0.215	0.056	0.030
0.066	0.029	0.007	0.149	0.050	0.018	0.232	0.057	0.033

0.249	0.059	0.037	0.665	0.099	0.137	1.082	0.107	0.211
0.265	0.063	0.041	0.682	0.101	0.139	1.099	0.106	0.214
0.282	0.062	0.045	0.699	0.103	0.143	1.115	0.103	0.216
0.299	0.065	0.049	0.715	0.103	0.146	1.132	0.098	0.216
0.315	0.067	0.051	0.732	0.105	0.150	1.149	0.098	0.219
0.332	0.067	0.057	0.749	0.108	0.155	1.165	0.095	0.221
0.349	0.069	0.061	0.765	0.109	0.158	1.182	0.094	0.222
0.365	0.068	0.064	0.782	0.109	0.160	1.199	0.091	0.224
0.382	0.073	0.068	0.799	0.111	0.164	1.215	0.089	0.225
0.399	0.074	0.072	0.815	0.113	0.167	1.232	0.088	0.227
0.415	0.076	0.077	0.832	0.115	0.169	1.249	0.087	0.230
0.432	0.078	0.082	0.849	0.118	0.174	1.265	0.086	0.231
0.449	0.077	0.084	0.866	0.117	0.175	1.282	0.084	0.232
0.465	0.080	0.088	0.882	0.118	0.180	1.299	0.081	0.233
0.482	0.083	0.093	0.899	0.122	0.184	1.315	0.079	0.235
0.499	0.083	0.097	0.915	0.123	0.186	1.332	0.078	0.237
0.516	0.086	0.102	0.932	0.126	0.189	1.349	0.077	0.237
0.532	0.088	0.105	0.949	0.124	0.193	1.365	0.074	0.239
0.549	0.087	0.109	0.965	0.125	0.195	1.382	0.074	0.241
0.565	0.090	0.114	0.982	0.122	0.197	1.399	0.075	0.242
0.582	0.092	0.118	0.999	0.119	0.199	1.415	0.073	0.242
0.599	0.093	0.120	1.015	0.116	0.202	1.432	0.069	0.243
0.615	0.093	0.124	1.032	0.115	0.205	1.449	0.070	0.244
0.632	0.097	0.128	1.049	0.112	0.207	1.465	0.066	0.245
0.649	0.097	0.132	1.065	0.107	0.208	1.482	0.067	0.248

1.499	0.064	0.249	1.915	0.044	0.270	2.332	0.028	0.280
1.515	0.065	0.249	1.932	0.042	0.269	2.349	0.026	0.278
1.532	0.062	0.251	1.949	0.041	0.269	2.365	0.027	0.281
1.549	0.062	0.251	1.965	0.041	0.271	2.382	0.027	0.281
1.565	0.061	0.253	1.982	0.039	0.270	2.399	0.026	0.281
1.582	0.060	0.254	1.999	0.041	0.272	2.415	0.026	0.283
1.599	0.060	0.255	2.015	0.038	0.271	2.432	0.027	0.284
1.615	0.059	0.255	2.032	0.038	0.272	2.449	0.026	0.283
1.632	0.059	0.255	2.049	0.038	0.273	2.465	0.025	0.284
1.649	0.056	0.256	2.065	0.039	0.273	2.482	0.025	0.283
1.665	0.055	0.257	2.082	0.037	0.274	2.499	0.024	0.285
1.682	0.054	0.259	2.099	0.039	0.275	2.515	0.025	0.286
1.699	0.054	0.259	2.115	0.033	0.274	2.532	0.023	0.285
1.715	0.053	0.260	2.132	0.035	0.274	2.549	0.025	0.286
1.732	0.052	0.261	2.149	0.033	0.273	2.565	0.022	0.285
1.749	0.052	0.262	2.165	0.033	0.276	2.582	0.021	0.285
1.765	0.049	0.263	2.182	0.032	0.274	2.599	0.021	0.286
1.782	0.050	0.265	2.199	0.032	0.276	2.615	0.021	0.285
1.799	0.048	0.263	2.215	0.031	0.278	2.632	0.021	0.286
1.815	0.050	0.265	2.232	0.030	0.278	2.649	0.020	0.286
1.832	0.046	0.266	2.249	0.032	0.278	2.665	0.021	0.288
1.849	0.048	0.265	2.265	0.031	0.278	2.682	0.021	0.286
1.865	0.046	0.265	2.282	0.029	0.281	2.699	0.022	0.287
1.882	0.045	0.267	2.299	0.028	0.279	2.715	0.021	0.287
1.899	0.044	0.267	2.315	0.028	0.280	2.732	0.020	0.289

2.749	0.020	0.289	3.165	0.011	0.293	3.582	0.010	0.298
2.765	0.020	0.288	3.182	0.012	0.295	3.599	0.010	0.297
2.782	0.020	0.290	3.199	0.013	0.293	3.615	0.010	0.297
2.799	0.019	0.289	3.215	0.012	0.293	3.632	0.008	0.298
2.815	0.019	0.289	3.232	0.012	0.294	3.649	0.008	0.297
2.832	0.017	0.288	3.249	0.010	0.294	3.665	0.007	0.296
2.849	0.016	0.289	3.265	0.010	0.294	3.682	0.008	0.298
2.865	0.019	0.290	3.282	0.011	0.294	3.699	0.009	0.297
2.882	0.018	0.292	3.299	0.010	0.296	3.715	0.010	0.299
2.899	0.016	0.291	3.315	0.010	0.296	3.732	0.007	0.297
2.915	0.016	0.290	3.332	0.012	0.294	3.749	0.007	0.296
2.932	0.016	0.291	3.349	0.011	0.295	3.765	0.007	0.298
2.949	0.016	0.290	3.365	0.010	0.294	3.782	0.009	0.296
2.965	0.015	0.293	3.382	0.011	0.296	3.799	0.007	0.297
2.982	0.014	0.292	3.399	0.009	0.296	3.815	0.007	0.299
2.999	0.015	0.293	3.415	0.010	0.297	3.832	0.007	0.298
3.015	0.014	0.292	3.432	0.009	0.296	3.849	0.007	0.298
3.032	0.014	0.291	3.449	0.011	0.297	3.865	0.007	0.299
3.049	0.015	0.293	3.465	0.009	0.296	3.882	0.007	0.299
3.065	0.014	0.292	3.482	0.010	0.297	3.899	0.005	0.298
3.082	0.014	0.293	3.499	0.010	0.296	3.915	0.008	0.298
3.099	0.013	0.293	3.515	0.011	0.297	3.932	0.006	0.298
3.115	0.013	0.292	3.532	0.009	0.296	3.949	0.007	0.300
3.132	0.012	0.293	3.549	0.009	0.296	3.965	0.007	0.301
3.149	0.012	0.293	3.565	0.009	0.295	3.982	0.008	0.298

3.999	0.006	0.298	4.415	0.007	0.301	4.832	0.002	0.302
4.015	0.007	0.299	4.432	0.005	0.302	4.850	0.004	0.302
4.032	0.006	0.299	4.449	0.004	0.302	4.865	0.002	0.303
4.049	0.008	0.298	4.465	0.004	0.301	4.882	0.001	0.304
4.065	0.009	0.301	4.482	0.004	0.302	4.899	0.002	0.303
4.082	0.006	0.299	4.499	0.003	0.300	4.915	0.002	0.303
4.099	0.007	0.299	4.515	0.004	0.301	4.932	0.002	0.302
4.115	0.006	0.300	4.532	0.004	0.301	4.949	0.002	0.301
4.132	0.006	0.300	4.549	0.004	0.302	4.965	0.000	0.303
4.149	0.005	0.299	4.565	0.004	0.302	4.982	0.002	0.304
4.165	0.005	0.299	4.582	0.004	0.302	4.999	0.003	0.302
4.182	0.005	0.299	4.599	0.003	0.302	5.015	0.001	0.302
4.199	0.007	0.301	4.615	0.004	0.301	5.032	0.001	0.302
4.215	0.007	0.301	4.632	0.004	0.302	5.049	0.002	0.303
4.232	0.006	0.301	4.649	0.002	0.301	5.065	0.002	0.304
4.249	0.004	0.301	4.665	0.003	0.301	5.082	0.003	0.304
4.265	0.005	0.302	4.682	0.003	0.302	5.099	0.000	0.302
4.282	0.005	0.302	4.699	0.002	0.302	5.115	0.002	0.303
4.299	0.004	0.301	4.715	0.002	0.302	5.132	0.001	0.304
4.315	0.003	0.300	4.732	0.001	0.301	5.149	0.000	0.303
4.332	0.007	0.303	4.749	0.002	0.302	5.165	0.000	0.303
4.349	0.004	0.300	4.765	0.002	0.302	5.182	0.000	0.302
4.365	0.004	0.301	4.782	0.001	0.301	5.199	0.001	0.304
4.382	0.004	0.301	4.799	0.002	0.301	5.215	0.000	0.304
4.399	0.004	0.302	4.815	0.002	0.302	5.232	0.002	0.304

5.249	0.001	0.303	5.665	0.000	0.303	6.082	0.000	0.303
5.265	0.000	0.303	5.682	0.002	0.304	6.099	0.000	0.304
5.282	0.000	0.304	5.699	0.000	0.304	6.115	0.000	0.303
5.299	0.002	0.303	5.715	0.001	0.305	6.132	0.000	0.304
5.315	0.002	0.302	5.732	0.000	0.305	6.149	0.000	0.302
5.332	0.001	0.303	5.749	0.000	0.303	6.165	0.000	0.305
5.349	0.000	0.303	5.765	0.001	0.303	6.182	0.000	0.305
5.365	0.000	0.304	5.782	0.000	0.304	6.199	0.000	0.304
5.382	0.001	0.303	5.799	0.000	0.305	6.215	0.000	0.305
5.399	0.001	0.303	5.815	0.000	0.304	6.232	0.001	0.305
5.415	0.000	0.303	5.832	0.000	0.304	6.249	0.000	0.306
5.432	0.000	0.303	5.849	0.000	0.303	6.265	0.000	0.305
5.449	0.001	0.303	5.865	0.000	0.304	6.282	0.000	0.304
5.465	0.002	0.302	5.882	0.001	0.305	6.299	0.000	0.304
5.482	0.002	0.304	5.899	0.000	0.305	6.315	0.000	0.306
5.499	0.000	0.302	5.915	0.000	0.304	6.332	0.000	0.304
5.515	0.001	0.304	5.932	0.000	0.304	6.349	0.000	0.304
5.532	0.000	0.304	5.949	0.000	0.305	6.365	0.000	0.305
5.549	0.000	0.304	5.965	0.000	0.305	6.382	0.000	0.305
5.565	0.001	0.303	5.982	0.000	0.303	6.399	0.000	0.305
5.582	0.000	0.303	5.999	0.000	0.304	6.415	0.000	0.304
5.599	0.000	0.305	6.015	0.000	0.303	6.432	0.000	0.303
5.615	0.000	0.306	6.032	0.000	0.306	6.449	0.000	0.304
5.632	0.000	0.302	6.049	0.000	0.304	6.465	0.000	0.305
5.649	0.000	0.303	6.065	0.001	0.304	6.482	0.000	0.306

6.499	0.000	0.305	6.682	0.000	0.305	6.865	0.000	0.304
6.515	0.000	0.305	6.699	0.000	0.306	6.882	0.000	0.305
6.532	0.000	0.305	6.715	0.000	0.305	6.899	0.000	0.303
6.549	0.000	0.305	6.732	0.000	0.306	6.915	0.000	0.306
6.565	0.000	0.305	6.749	0.000	0.304	6.932	0.000	0.304
6.582	0.000	0.304	6.765	0.000	0.305	6.949	0.000	0.304
6.599	0.000	0.304	6.782	0.000	0.306	6.965	0.000	0.305
6.615	0.001	0.305	6.799	0.000	0.304	6.982	0.000	0.304
6.632	0.000	0.305	6.815	0.000	0.305	6.999	0.000	0.305
6.649	0.000	0.304	6.832	0.000	0.305			
6.665	0.000	0.305	6.849	0.000	0.306			

3.4.12 In Situ Monitoring of the Reaction of Di-n-butyl-amine with Phenyl 3-methoxybenzoate in the Absence of Sodium Phenoxide

Using the general procedure for kinetic experiments, phenyl 3-methoxybenzoate (228.2 mg, 1.0 mmol), Bu_2NH (neat, 0.5 mL, 3.0 mmol) and DMSO (2.5 mL) were combined and reacted under an atmosphere of argon. The concentration vs. time data for **13** and **14** from this experiment is presented in Table S3. Data was plotted using Excel and is shown in Figure S1 (p. 169). At the end of the experiment (105 min), the reactor the conversion (GC) of **13** was 2% and the yield (GC) of **14** was 4%.

Table S3.

Time (h)	[**13**] (M)	[**14**] (M)
0.0153	0.3455	0.0000
0.0319	0.3294	0.0000
0.0483	0.3231	0.0000
0.0653	0.3170	0.0000
0.0819	0.3184	0.0000
0.0994	0.3154	0.0000
0.1153	0.3147	0.0000
0.1322	0.3173	0.0000
0.1486	0.3154	0.0000
0.1656	0.3154	0.0000
0.1817	0.3145	0.0000

0.1989	0.3121	0.0000	0.6153	0.3082	0.0047	1.0319	0.3057	0.0114
0.2153	0.3131	0.0000	0.6317	0.3077	0.0049	1.0483	0.3041	0.0111
0.2319	0.3123	0.0000	0.6486	0.3093	0.0051	1.0656	0.3051	0.0109
0.2486	0.3113	0.0000	0.6653	0.3093	0.0049	1.0822	0.3014	0.0117
0.2650	0.3136	0.0011	0.6819	0.3092	0.0063	1.0986	0.3028	0.0113
0.2825	0.3135	0.0000	0.6983	0.3076	0.0059	1.1153	0.3032	0.0114
0.2986	0.3122	0.0000	0.7153	0.3061	0.0066	1.1319	0.3021	0.0125
0.3153	0.3097	0.0000	0.7317	0.3082	0.0060	1.1486	0.3032	0.0133
0.3319	0.3107	0.0001	0.7483	0.3068	0.0064	1.1650	0.3037	0.0132
0.3486	0.3102	0.0012	0.7653	0.3087	0.0080	1.1825	0.3035	0.0127
0.3650	0.3113	0.0021	0.7817	0.3075	0.0080	1.1983	0.3029	0.0143
0.3819	0.3105	0.0002	0.7994	0.3075	0.0073	1.2153	0.3023	0.0127
0.3983	0.3094	0.0007	0.8153	0.3065	0.0076	1.2317	0.3003	0.0134
0.4153	0.3116	0.0009	0.8319	0.3054	0.0073	1.2486	0.3034	0.0138
0.4319	0.3116	0.0024	0.8486	0.3064	0.0090	1.2653	0.3021	0.0139
0.4486	0.3093	0.0018	0.8653	0.3065	0.0087	1.2822	0.3027	0.0138
0.4653	0.3095	0.0027	0.8819	0.3058	0.0092	1.2986	0.3035	0.0152
0.4828	0.3101	0.0029	0.8983	0.3065	0.0075	1.3156	0.3018	0.0156
0.4983	0.3106	0.0025	0.9153	0.3068	0.0103	1.3319	0.3001	0.0152
0.5153	0.3093	0.0028	0.9317	0.3045	0.0097	1.3486	0.3021	0.0168
0.5317	0.3096	0.0030	0.9486	0.3070	0.0110	1.3650	0.3003	0.0155
0.5486	0.3086	0.0031	0.9653	0.3053	0.0098	1.3819	0.3009	0.0163
0.5661	0.3080	0.0031	0.9819	0.3074	0.0109	1.3983	0.3002	0.0166
0.5819	0.3090	0.0048	0.9986	0.3045	0.0103	1.4153	0.3010	0.0168
0.5986	0.3097	0.0036	1.0153	0.3049	0.0111	1.4317	0.3008	0.0156

1.4486	0.3030	0.0181	1.5653	0.2999	0.0184	1.6817	0.2984	0.0194
1.4661	0.3011	0.0176	1.5819	0.3002	0.0190	1.6986	0.2986	0.0208
1.4819	0.3008	0.0171	1.5986	0.2994	0.0198	1.7153	0.2988	0.0211
1.4986	0.3014	0.0186	1.6150	0.2993	0.0176	1.7319	0.2977	0.0210
1.5150	0.3010	0.0180	1.6319	0.2977	0.0193	1.7486	0.2982	0.0220
1.5319	0.3008	0.0180	1.6492	0.3003	0.0197			
1.5483	0.3003	0.0180	1.6653	0.2971	0.0193			

3.4.13 In Situ Monitoring of the Reaction of Di-n-butyl-amine with Phenyl 3-Methoxybenzoate in the Presence of Sodium Phenoxide

Using the general procedure for kinetic experiments, phenyl 3-methoxybenzoate (228.2 mg, 1.0 mmol), NaOPh (232 mg, 2.0 mmol), Bu_2NH (neat, 0.5 mL, 3.0 mmol) and DMSO (2.5 mL) were combined and reacted under an atmosphere of argon. The concentration vs. time data for **13** and **14** from this experiment is presented in Table S4. Data was plotted using Excel and is shown in Figure S1 (p. 169). The measured GC yield for **14** was 93%.

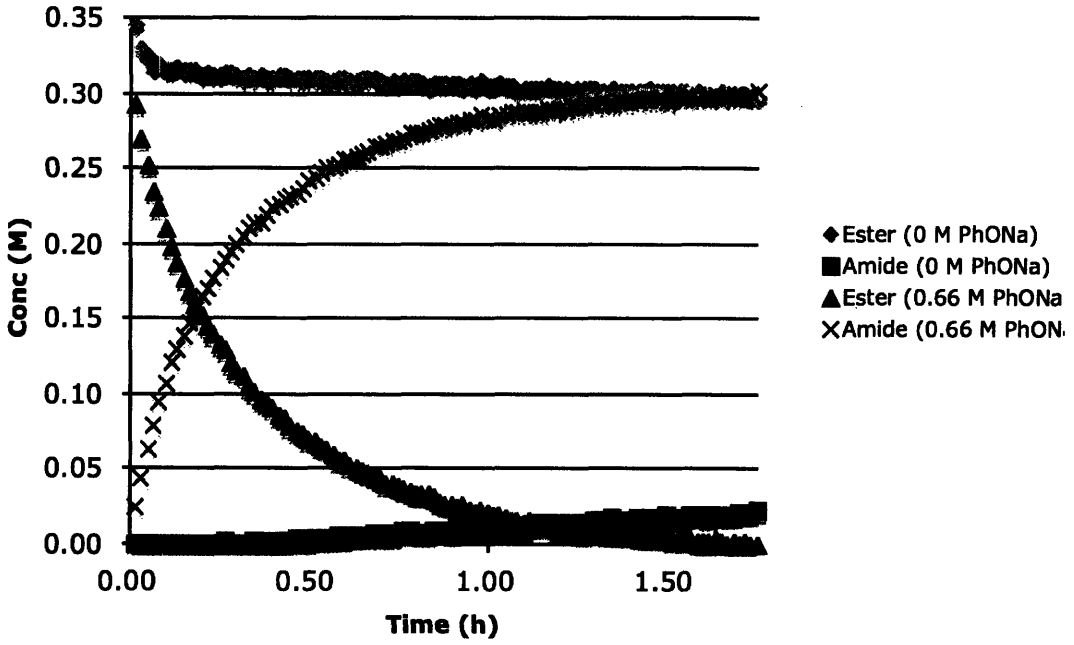
Table S4.

Time (h)	[**13**] (M)	[**14**] (M)
0.032	0.293	0.024
0.049	0.269	0.043
0.065	0.251	0.063
0.082	0.235	0.078
0.099	0.224	0.094
0.115	0.211	0.108
0.132	0.198	0.121
0.149	0.187	0.129
0.165	0.177	0.139
0.183	0.168	0.146
0.199	0.158	0.156
0.215	0.152	0.164
0.232	0.145	0.169
0.249	0.140	0.178
0.265	0.133	0.183
0.282	0.129	0.189
0.299	0.121	0.194
0.315	0.115	0.199
0.332	0.113	0.205
0.349	0.105	0.210
0.365	0.101	0.213
0.382	0.096	0.214
0.399	0.094	0.218

0.415	0.090	0.224	0.832	0.033	0.273	1.249	0.009	0.291
0.432	0.086	0.226	0.849	0.033	0.274	1.266	0.010	0.291
0.449	0.083	0.230	0.865	0.031	0.277	1.283	0.008	0.291
0.465	0.078	0.231	0.882	0.028	0.278	1.299	0.010	0.292
0.483	0.076	0.233	0.899	0.026	0.279	1.315	0.010	0.292
0.499	0.073	0.236	0.915	0.027	0.278	1.332	0.009	0.293
0.515	0.070	0.242	0.932	0.025	0.280	1.349	0.008	0.292
0.532	0.068	0.242	0.949	0.026	0.280	1.365	0.007	0.292
0.549	0.064	0.246	0.965	0.023	0.281	1.382	0.007	0.293
0.565	0.062	0.250	0.982	0.022	0.281	1.399	0.007	0.293
0.582	0.059	0.251	0.999	0.023	0.284	1.415	0.007	0.295
0.599	0.056	0.253	1.015	0.020	0.283	1.432	0.005	0.293
0.615	0.056	0.255	1.032	0.019	0.282	1.449	0.008	0.295
0.632	0.053	0.256	1.049	0.019	0.285	1.465	0.006	0.295
0.649	0.050	0.258	1.065	0.018	0.285	1.482	0.006	0.296
0.666	0.048	0.259	1.082	0.017	0.286	1.499	0.004	0.295
0.682	0.047	0.261	1.099	0.016	0.287	1.515	0.005	0.295
0.699	0.046	0.264	1.115	0.014	0.286	1.532	0.004	0.296
0.715	0.043	0.263	1.132	0.015	0.287	1.549	0.005	0.296
0.732	0.040	0.265	1.149	0.013	0.287	1.565	0.003	0.297
0.749	0.040	0.268	1.165	0.012	0.287	1.582	0.003	0.297
0.765	0.039	0.268	1.182	0.013	0.289	1.599	0.002	0.296
0.782	0.038	0.269	1.199	0.013	0.289	1.615	0.001	0.297
0.799	0.035	0.272	1.215	0.010	0.289	1.632	0.001	0.298
0.815	0.033	0.273	1.232	0.011	0.289	1.649	0.003	0.298

1.665	0.001	0.298	2.082	0.000	0.301	2.499	0.000	0.303
1.682	0.000	0.299	2.099	0.000	0.301			
1.699	0.001	0.299	2.115	0.000	0.300			
1.715	0.000	0.298	2.132	0.000	0.302			
1.732	0.001	0.298	2.149	0.000	0.302			
1.749	0.000	0.299	2.165	0.000	0.303			
1.765	0.000	0.300	2.182	0.000	0.302			
1.782	0.000	0.300	2.199	0.000	0.304			
1.799	0.000	0.299	2.215	0.000	0.302			
1.815	0.000	0.300	2.232	0.000	0.303			
1.832	0.000	0.300	2.249	0.000	0.303			
1.849	0.000	0.301	2.265	0.000	0.301			
1.865	0.000	0.300	2.282	0.000	0.301			
1.882	0.000	0.300	2.299	0.000	0.301			
1.899	0.000	0.300	2.315	0.000	0.302			
1.916	0.000	0.302	2.332	0.000	0.302			
1.932	0.000	0.300	2.349	0.000	0.301			
1.949	0.000	0.301	2.365	0.000	0.302			
1.966	0.000	0.300	2.382	0.000	0.303			
1.982	0.000	0.300	2.399	0.000	0.303			
1.999	0.000	0.301	2.415	0.000	0.301			
2.015	0.000	0.299	2.432	0.000	0.303			
2.032	0.000	0.302	2.449	0.000	0.304			
2.049	0.000	0.302	2.466	0.000	0.303			
2.065	0.000	0.301	2.482	0.000	0.304			

Figure S1. Plot of Conc vs. Time for Conversion of 13 to 14 With and Without Phenoxide.



3.5 References

(1) (a) Schoenberg, A.; Bartoletti, I.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3318. (b) Schoenberg, A.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3327.

(2) Colquhoun, H. M.; Thompson, D. J.; Twigg, M. V. *Carbonylation, Direct Synthesis of Carbonyl Compounds*; Plenum Press: New York, **1991**.

(3) (a) Ishiyama, T.; Kizaki, H.; Hayashi, T.; Suzuki, A.; Miyaura, N. *J. Org. Chem.* **1998**, *63*, 4726. (b) Kaiser, N.-F. K.; Hallberg, A.; Larhed, M. *J. Comb. Chem.* **2002**, *4*, 109. (c) Kumar, K.; Zapf, A.; Michalik, D.; Tillack, A.; Heinrich, T.; Böttcher, H.; Arlt, M.; Beller, M. *Org. Lett.* **2004**, *6*, 7. (d) Albaneze-Walker, J.; Bazaral, C.; Leavey, T.; Dormer, P. G.; Murry, J. A. *Org. Lett.* **2004**, *6*, 2097. (e) Klaus, S.; Neumann, H.; Zapf, A.; Strübing, D.; Hübner, S.; Almena, J.; Riermeier, T.; Grob, P.; Sarich,

M.; Krahnert, W.-R.; Rossen, K.; Beller, M. *Angew. Chem. Int. Ed.* **2006**, *45*, 154. (f) Martinelli, J. R.; Freckmann, D. M. M.; Buchwald, S. L. *Org. Lett.* **2006**, *8*, 4843.

(4) Littke, A. F.; Fu, G. C. *Angew. Chem. Int. Ed.* **2002,** *41*, 4176.

(5) (a) Ben-David, Y.; Portnoy, M.; Milstein, D. *J. Am. Chem. Soc.* **1989**, *111*, 8742. (b) Mägerlein, W.; Indolese, A. F.; Beller, M. *Angew. Chem. Int. Ed.* **2001**, *40*, 2856. (c) Mägerlein, W.; Indolese, A. F.; Beller, M. *J. Organomet. Chem.* **2002**, *641*, 30. (d) Lagerlund, O.; Larhed, M. *J. Comb. Chem.* **2006**, *8*, 4.

(6) Strmnova, T. A.; Moiseev, I. I. *Russ. Chem. Rev.* **1998**, *67*, 485.

(7) (a) Commercially available from Nippon Chemical Co. (b) For a convenient synthesis see the experimental section.

(8) The complex reported by Milstein[5a] and the ferrocene-based ligand reported by Beller[5b,5c] can be employed and afford similar results. However, due to the air-sensitivity[5a] or relative cost[5b,5c] of these systems, our conditions that employ the air-stable phosphine salt **7** offer considerable practical advantages.

(9) Shieh, W.-C.; Dell, S.; Repič, O. *J. Org. Chem.* **2002**, *67*, 2188.

(10) Kers, A.; Kers, I.; Stawinski, J. *J. Chem. Soc., Perkin Trans. 2*, **1999**, 2071.

(11) Strieter, E. R.; Blackmond, D. G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 13978.

(12) Although kinetic investigations of **14** were conducted under homogenous conditions (excluding 4Å MS), quantification of the kinetic order of the reagents involved in the production of **14** was not possible using our experimental apparatus: the reactions proved very sensitive to the rate of stirring and other factors, and measured rate constants varied too greatly to determine reagent order.

(13) (a) Garrou, P. E.; Heck, R. F. *J. Am. Chem. Soc.* **1976**, *98*, 4115. (b) Milstein, D. *Acc. Chem. Res.* **1988**, *21*, 428.

(14) For previous examples of aryl ester synthesis from aryl bromides and aryl iodides via carbonylation see: (a) Kubota, Y.; Hanaoka, T.; Takeuchi, K.; Sugi, Y. *Synlett* **1994**, 515. (b) Kubota, Y.; Hanaoka, T.; Takeuchi, K.; Sugi, Y. *J. Mol. Catal. A* **1996**, *111*, L187.

(15) For an example of reductive elimination of aryl carboxylates see: Komiya, S.; Akai, Y.; Tanaka, K. *Organometallics* **1985**, *4*, 1130.

(16) (a) Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518. (b) Alaimo, P. J.; Peters, D. W.; Arnold, J.; Bergman, R. G. *J. Chem. Ed.* **2001**, *78*, 64.

(17) (a) Morley, J. A.; Woolsey, N. F. *J. Org. Chem.* **1992**, *57*, 6487. (b) Carini, D. J.; Dunica, J. V.; Aldrich, P. E.; Chiu, A. T.; Johnson, A. L.; Pierce, M. E.; Price, W. A.; Santella, J. B.; Wells, G. J.; Wexler, R. R.; Wong, P. C.; Yoo, S.-E.; Timmermans, P. B. M. W. M. *J. Med. Chem.* **1991**, *34*, 2525.

(18) Barder, T. E.; Walker, S. D.; Martinelli, J. R. *J. Am. Chem. Soc.* **2005**, *127*, 4685.

(19) Aranyos, A.; Old, D. W.; Kiyomori, A.; Wolfe, J. P.; Sadighi, J. P.; Buchwald, S.L. *J. Am. Chem. Soc.* **1999**, *121*, 4369.

(20) Sasse, A.; Ligneau, X.; Sadek, B.; Elz, S.; Pertz, H. H.; Ganellin, C. R.; Arrang, J.-M.; Schwartz, J.-C.; Schunack, W.; Stark, H. *Arch. Pharm. (Weinheim, Ger.)* **2001**, *334*, 45.

(21) (a) Issleib, K.; Müller, D.-W. *Chem. Ber.* **1959**, *92*, 3175. (b) Netherton, M. R.; Fu, G. C. *Org. Lett.* **2001**, *3*, 4295.

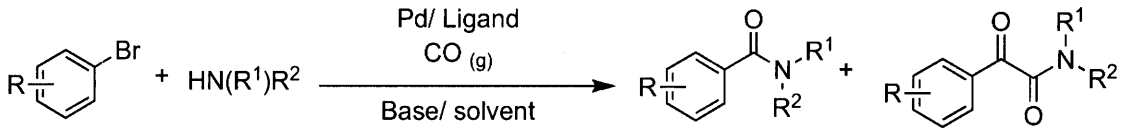
(22) Herrmann, W. A.; Broßmer, C.; Priermeier, T.; Öfele, K. *J. Organomet. Chem.* **1994**, *481*, 97.

Chapter 4.

Microchemical Systems for the Rapid Analysis of Aminocarbonylation Reactions.

4.1 Introduction

The use of microreactors can greatly accelerate scanning and optimization of reaction conditions because of enhanced heat and mass transfer, reduced reaction volumes, and the ability to run several experiments within a sealed system (minimizing contamination by oxygen and water). These advantages have been demonstrated in several studies over the past decade at conditions typically used in bench scale synthesis.[1-10] A major advantage of microreactors is the ability to perform reactions at conditions not easily realized in conventional glassware, such as the use of standard solvents (e.g., toluene) at elevated temperatures and pressures.[4,9] Performing reactions under such circumstances is also one of the major benefits of microwave synthesis.[11,12] Microreactors offer many of the advantages of microwave reactors and have the additional advantages of continuous flow and not requiring a microwave generator.



Scheme 1. Pd-Catalyzed Heck Aminocarbonylation.

Realizing high pressure in glass-based microreactors has been complicated by difficulties in interfacing with fluid inlet and exit tubes. For example, typical compression sealing techniques of glass and silicon devices are cumbersome and typically limited to moderate pressures (~10 bar) to avoid breaking the device. In this paper we used a recently developed solder based sealing technique[5] to construct microreactors capable of reaching pressures exceeding 100 bar[13] to demonstrate potential advantages of operating above the boiling point of toluene in Heck aminocarbonylation[14] reactions (Scheme 1). The microreactor approaches enable rapid evaluation of effects of modifications to reaction conditions on yield and selectivity as well as the use of experiments with several reagent solutions in rapid succession. The ability to rapidly change reactants and conditions would be a powerful strategy for high throughput synthesis of a diverse array of compounds as well as for catalyst screening. Chemical parameters such as functional groups, ligand properties, and base strength could be rapidly varied along

with reaction conditions. The continuous operation and scanning of reaction parameters provides information that can lead to improved insight over typical batch or array based processes, which are often limited to one-variable-at-a-time experimentation. The case study also illustrates the advantages of a closed system in handling elevated pressures of a toxic gas (carbon monoxide) and air-sensitive Pd catalysts.

4.2 Results and Discussion

The microreactor (Figure 1) is formed in silicon by defining the mixer and channel layout by lithography and then etching channels in silicon.[4] Subsequent oxidation of the silicon forms a glass layer on the surface, so that when the channels are capped by bonding a Pyrex glass wafer to the oxidized silicon device, the reaction channels become functionally equivalent to a glass reaction vessel. Moreover, the top glass layer provides visual access to the reaction medium, which is particularly useful in monitoring gas-liquid contact and detecting formation of solid by-products.

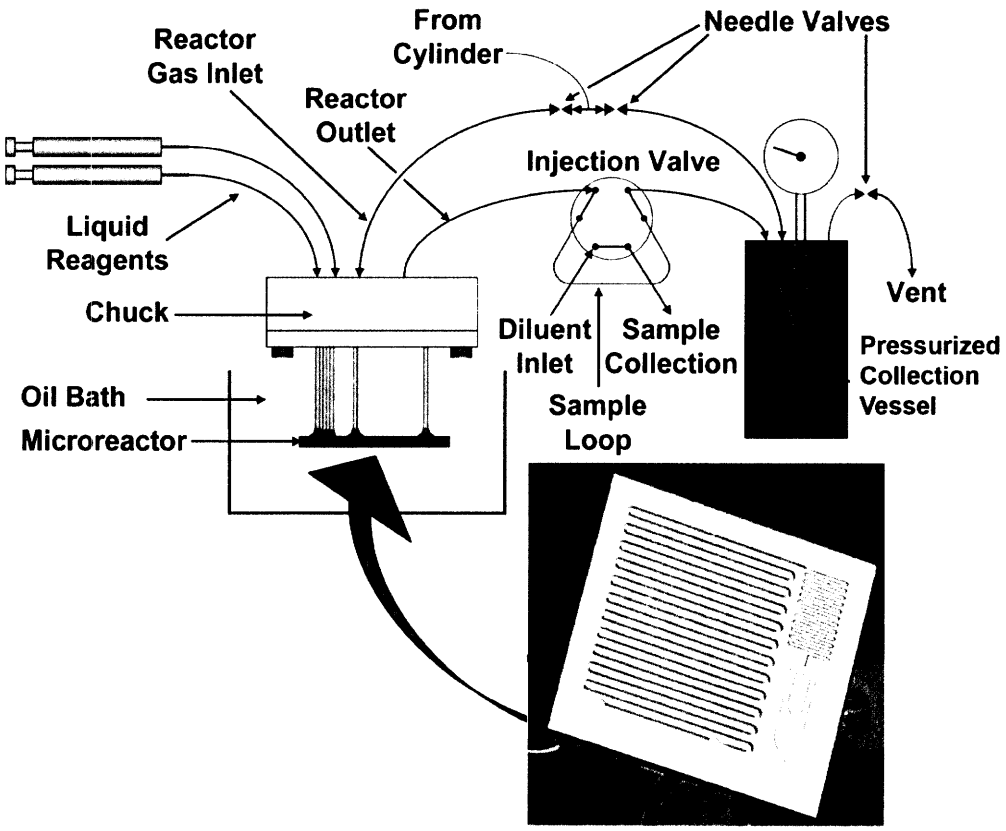
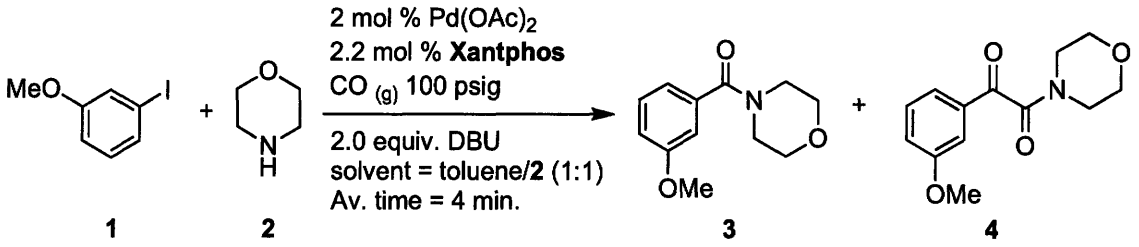


Figure 1. Pressurized Microreactor Setup.

In the initial studies with the reactor shown in Figure 1, a Xantphos-Pd catalyst[15] was used with a silicon microreactor we previously designed for general organic synthesis.[5] The small dimensions of the reactor channels required that the generation of precipitates be controlled and their potential to clog the reactor minimized. The solid by-products of chief concern were palladium black, palladium carbonyl complexes[16] and protonated amine salts. While some precipitation was observed, the formation of solids was minimal and occurred primarily along the reactor walls. Rinsing the microreactor daily with methanol was sufficient to avoid any blockage of the flow.

The first Pd-catalyzed aminocarbonylation reaction explored was that of 3-iodoanisole, **1**, and morpholine, **2** (Scheme 2). The carbonylation was performed by delivering CO by syringe pump at 7.9 bar. The pulsation of the syringe pump induced minor changes in the residence times, but the average reaction times (~ 4 min) could still be determined from the active reactor volume (78 μL) divided by the averaged volumetric flow rate (Q_L = 4 μL/min per syringe; Q_G = 12 μL/min).



Scheme 2. Aminocarbonylation of 3-Iodoanisole.

In contrast to conventional bench-top reactions at near-atmospheric pressure, the aminocarbonylation in the microreactor at elevated CO pressures produced significant quantities of the α-ketoamide, **4**, in addition to the amide, **3**.[14] This shift in product distribution is attributed to the superior gas-liquid contact area, the resulting improvement in mass transfer and the greater amount of CO in solution.[17] Figure 2 shows measured yields of **3** and **4**, for samples with greater than 90% conversion of

3-iodoanisole and an average reaction time of 4 min. The amide yield increases with temperature. In particular, temperatures above the normal boiling point of the solvent (toluene, 110°C) produce a significant shift towards the amide, underscoring the advantage of being able to conduct experiments at elevated pressures. These initial results suggest that in addition to achieving faster reaction rates at elevated temperatures, it could be possible to manipulate the relative yields of amide and α-ketoamide by varying temperature and pressure. Increasing temperature will favor the amide whereas elevated CO pressures will enhance α-ketoamide formation.

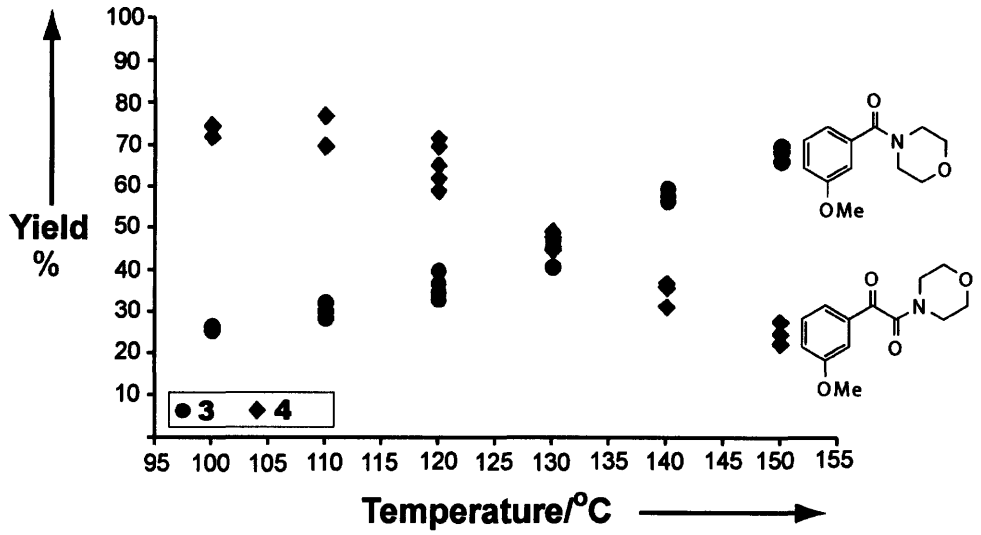
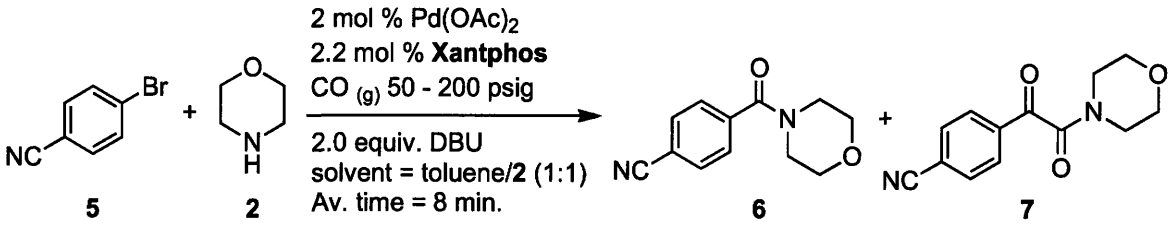


Figure 2. Aminocarbonylation Product Yields for Samples with Greater than 90 % Conversion of 3-Iodoanisole. Each Data Point Represents Individual Experiments.

In order to further demonstrate the flexibility of the microreactor to rapidly scan pressures and temperatures and explore their effect on α-ketoamide formation, the selectivity of the aminocarbonylation reaction of 4-bromobenzonitrile, **5**, was profiled. Though carbonylation reactions of aryl bromides are more challenging than those with aryl iodides, the greater diversity and lower cost of commercially available substrates make the aryl bromide reactions more attractive. To accommodate the longer reaction times required when using the less reactive aryl bromides, the selectivity study was performed using the original microreactor design and a volume extension consisting of a 300 mm length of stainless

steel tubing (0.046" internal diameter). The volume extension was connected to the reactor via the same solder bonding technique used for the other connections and added a volume of 322 μL, which was submerged alongside the reactor into the oil bath, for a total heated reactor volume of 400 μL. Rather than using the syringe pump with its complication of pulsating flow, the carbon monoxide was delivered directly from the tank and controlled using needle valves.



Scheme 3. Aminocarbonylation of 4-Bromobenzonitrile.

Reaction data were collected at temperatures between 98°C and 160°C and carbon monoxide pressures of 4.5, 7.9 and 14.8 bar. For each sample, overall selectivity for the α-ketoamide **7** was calculated as the ratio of α-ketoamide to amide and plotted in Figure 3. The expected increase in selectivity for formation of amide with increased temperature was observed along with enhanced selectivity for production of α-ketoamide with increasing pressure, corresponding to larger amounts of dissolved carbon monoxide.

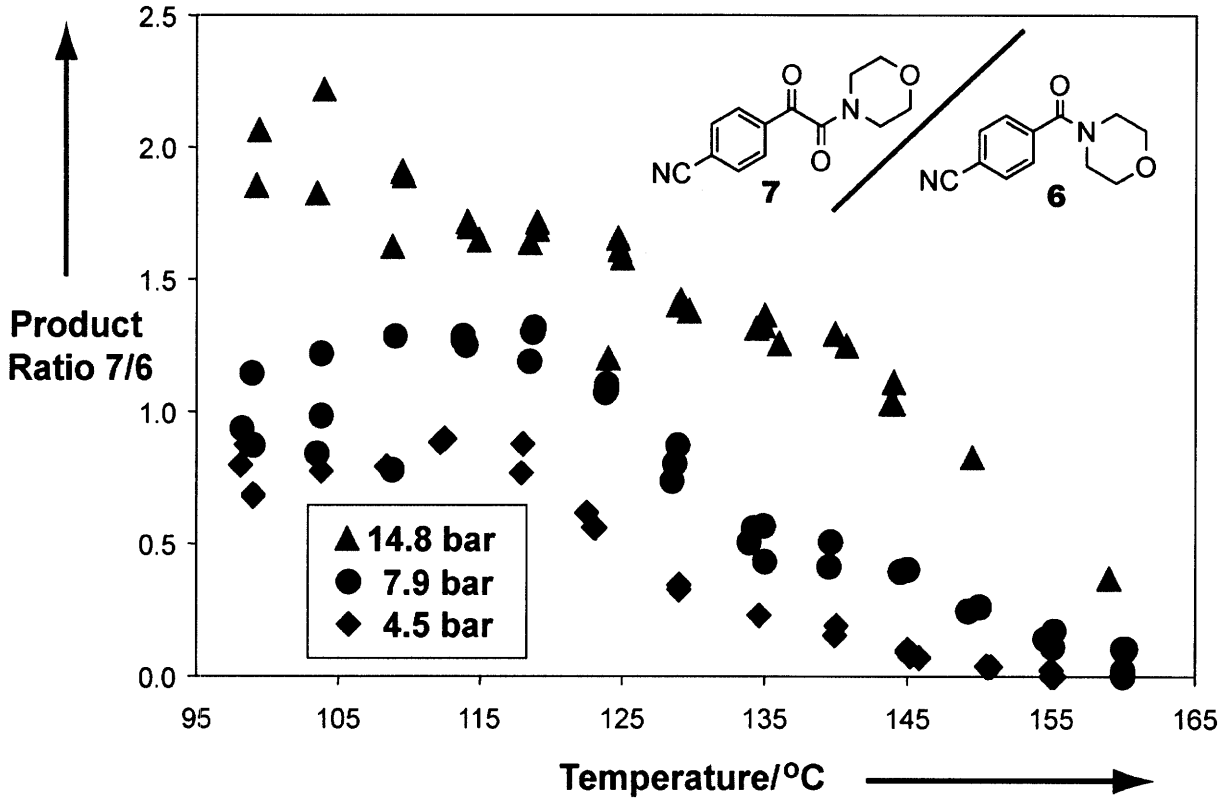


Figure 3. Product Ratio of α-Ketoamide (**7**) to Amide (**6**) for the Aminocarbonylation of 4-Bromobenzonitrile (**5**). Each Data Point Represents Individual Experiments.

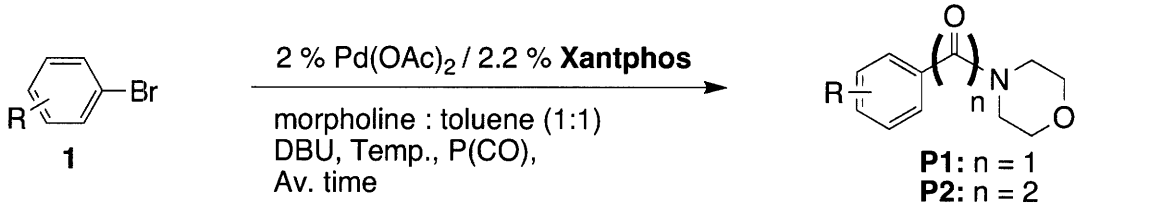
In addition to using the microreactor to rapidly scan the effect of reaction conditions on yield and selectivity, several reagent solutions could be tested in rapid succession by installing injection valves to the liquid reagent inlet lines. Thus, if one desired to run several combinations of substrates at the same conditions, this could be accomplished by simply varying the solutions loaded into the inlet-sample loops. This ability to rapidly change reactants and conditions is a powerful strategy for fast synthesis of a diverse array of compounds as well as for catalyst screening.

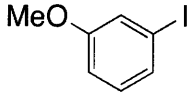
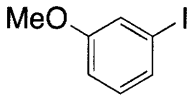
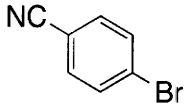
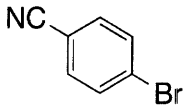
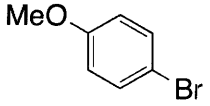
We demonstrated this by switching between 4-bromobenzonitrile and 4-bromoanisole without stopping the flow into the reactor. The system was brought to pressure with toluene loaded in the each syringe and the sample loops were loaded with reagent stock solutions; $Pd(OAc)_2$, Xantphos and toluene

in one and Ar-Br, DBU, dodecane (internal standard) and morpholine in the other. This system was successfully used to test the aminocarbonylation of 4-bromoanisole (Table 1, entry 5).

The use of a pressurized microreactor system greatly expands the range of reaction conditions available to the bench chemist. In this study, pressures from 4.5 to 14.8 bar and temperatures from 98 - 160°C were examined with greater flexibility, in terms of loading and sampling, than would be possible with traditional high pressure chemical equipment such as a Parr® bomb or autoclave. In addition, the use of injection valves on the inlet lines offers the possibility of using a wide range of substrates to efficiently produce a library of products. Furthermore, with the microreactor system, the reaction conditions themselves are improved. The significantly greater mass transfer area resulting from segmented gas-liquid flow enables very rapid reaction times from the accelerated mass transfer.[18]

Table 1. Maximum Yields for Various Carbonylation Reactions.



1	P (bar)	Temp. (°C)	Av. time (min.)	Conv.	Yield **P1**	Yield **P2**
	7.9	146	3.3	100	68	28
	7.9	116	4.2	100	35	65
	2.7	160	7.1	100	83	0
	14.8	109	6.6	99	32	57
	2.7	150	12.7	48	35	0

4.3 Conclusion

The carbonylation case study demonstrates the considerable potential of continuous flow, microreactor-based experiments at conditions not easily achieved in conventional bench experiments. In particular, the technique provides a useful tool for quickly and safely scanning reaction conditions and reagents. Using this technique we were able to test multiple aryl halides over a wide range of temperatures and pressures much more rapidly than could be accomplished with batch experiments. For instance, in the study of the effects of pressure and temperature on the aminocarbonylation of 4-bromobenzonitrile, **5**, up to 36 samples were collected and analyzed in a single day. Table 1 summarizes the conditions where the maximum amide and α-ketoamide yields for each reaction were observed. These results reveal the general trend of increased yield of amide with temperature and selectivity for α-ketoamide production at lower temperature and higher pressure.

4.4 Experimental

4.4.1 General

All chemicals were reagent grade and used as supplied. 1,8-Diazabicyclo [5.4.0] undec-7-ene (DBU) 98% was purchased from Acros Organics (New Jersey). Pentadecane 99%, 4-Bromobenzonitrile 99%, and 3-Bromoanisole 98% were purchased from Sigma-Aldrich in St. Louis, MO. Morpholine 99% and 3-Iodoanisole 98% were purchased from Alfa-Aesar Lancaster in Pelham, NJ. 9,9-Dimethyl-4,5-bis (diphenyphosphino) xanthene 98% (Xantphos) was purchased from Strem Chemicals in Newburyport, Massachusetts. Palladium (II) acetate was obtained from the Engelhard Corporation in Iselin, New Jersey and n-dodecane 99% was purchased from Avocado Research Chemicals Ltd. in Heysham, Lancashire UK. Carbon monoxide cylinders were purchased from Airgas Inc in Radnor, PA. Toluene was purchased in CYCLE-TAINER® solvent delivery kegs from Malinckrodt Baker Inc. in Phillipsburg, New Jersey. Before use, the toluene was vigorously purged with argon for two hours. The toluene was further purified by passing it under argon pressure through two packed columns of neutral alumina.[19]

4.4.2 Characterization

All products of aminocarbonylation reactions were isolated by flash column chromatography on silica gel and characterized by ^{1}H NMR, ^{13}C NMR, and IR spectroscopy, as well as elemental analysis (Atlantic Microlab, Inc). Two new compounds failed to give satisfactory elemental analyses. For these copies of ^{1}H and ^{13}C NMR spectra are included. Nuclear Magnetic Resonance spectra were recorded on a Varian Mercury 300. Infrared spectra were recorded using a Perkin-Elmer 2000 FT-IR. All ^{1}H NMR experiments are reported in δ units, parts per million (ppm) downfield from tetramethylsilane (internal standard) and were measured relative to the signal for residual chloroform (7.26 ppm) or dichloromethane (5.32 ppm) in the deuterated solvent. All ^{13}C NMR spectra are reported in ppm relative to residual chloroform (77.23 ppm) or dichloromethane (54.00 ppm) in the deuterated solvent and all were obtained with ^{1}H decoupling. Melting points (uncorrected) were obtained on a Mel-Temp capillary melting point apparatus. Gas Chromatographic analyses were performed on a Hewlett-Packard 6890 gas chromatography instrument with an FID detector using 25 m x 0.20 mm capillary column with cross-linked methyl siloxane as a stationary phase.

4.4.3 Liquid Reagent Preparation

Liquid reagent mixtures were prepared under nitrogen in oven-dried glassware such that, once the two inlet streams were combined, the concentrations of each component in the reactor would be 0.5 M aryl halide, 1.5 M DBU, 0.5 M internal standard (dodecane or pentadecane), 0.01 M (2 mol % relative to aryl halide) $Pd(OAc)_2$ and 0.011 M (2.2 mol % relative to aryl halide) Xantphos. The first reagent mixture was 1 M aryl halide, 3 M DBU, and 1 M dodecane or pentadecane dissolved in morpholine. For example, a typical experiment would require 546 mg 4-bromobenzonitrile, 900 μL DBU and 829 μL pentadecane dissolved in 3 mL morpholine. The catalyst solution was 0.02 M palladium(II) acetate and 0.02 M ligand dissolved in neat toluene. For example, a typical experiment would require 13.5 mg $Pd(OAc)_2$ and 34.8 mg Xantphos dissolved in 3 mL toluene. If particles were observed in either solution, the mixture was filtered before loading. Filtration was performed by syringe over glass wool inserted into

the luer end of an 18 Gauge needle. This filtered solution was transferred to a second dried flask under nitrogen from which the mixture was drawn into the stainless steel syringe.

4.4.4 Gas Delivery via Syringe-Pump

Liquid reagents were loaded into high pressure stainless steel syringes (Harvard Apparatus 702267) and delivered by a syringe pump. A third stainless steel syringe was placed into a separate syringe pump. All syringes were connected to the reactor chuck with 1/16" OD, 0.009" ID stainless steel tubing. To control the pressure in the reaction zone, the outlet of the reactor was connected to a pressure bomb. The gas cylinder outlet was split, with one branch connected to the microreactor gas inlet and the second branch connected to the bomb makeup inlet. The bomb inlet was regulated by an on/off valve; the syringe inlet was regulated by two three-way valves, with the first one (counting from the syringe) regulating flow either to the reactor or to the tank (3-way #1), and the second one either flowing from the tank to the syringe or venting the tank regulator to the atmosphere (3-way #2). The pressure bomb was set up with outlet capillary tubing to allow for a slow constant leak from the headspace of the bomb and permit gas flow through the system.

The syringes loaded with liquid reagents were placed into their syringe pump and the rear plate of the pump was advanced into contact with the syringe plungers. The syringe pump was then run at 500 μL/min with a tissue held to the tip of the syringes until material was observed to flow from both syringes. At this point, the syringes were attached to the inlet tubing and the reactor was primed with 100 μL to 150 μL of material at a flow rate of 70 μL/min.

The gas syringe was emptied of air and installed into its syringe pump, with the rear plate of the pump secured in place where the plunger was expected to be at 8 mL of syringe volume. The gas cylinder was then opened slowly and brought to 120 psi, allowing 8 mL of the syringe to fill with pressurized gas before shutting off the regulator. The 3-way #2 was then vented to the atmosphere and closed. The valve to the bomb was opened to allow for simultaneous pressurization of the bomb, the reactor, and the gas syringe. Liquid reagent flow was started at the desired flow rate. Gas was brought up to the desired pressure gradually while monitoring optically the liquid flow through the reactor to ensure

its forward progress. The 3-way #1 was set from syringe to reactor and allowed to equilibrate with the gas pressure of the bomb, then closed. The sample loop (see Operation and Sample Collection) was flushed with diluent and set to "Load." The 3-way #1 was again set from syringe to reactor, the gas flow was turned on to 500 μL/min until gas slugs were observed, then set to the desired gas flow rate.

4.4.5 Gas Delivery Directly from Gas Tank

The delivery of carbon monoxide directly from the source cylinder was found to be more reliable than syringe delivery. In this case, the system pressure was controlled by three needle valves (Upchurch P-445). The cylinder outlet was split and each branch was connected to a needle valve. One branch was connected to the microreactor gas inlet and the second branch was connected to the pressure bomb makeup inlet. To compensate for the flow path's pressure drop and maintain sufficient pressure within the system, the cylinder regulator was set to a pressure 5% higher than the desired system pressure as measured by the pressure gauge on the bomb. The third needle valve was connected to the bomb outlet tubing such that there was a controlled constant leak from the headspace of the pressure bomb.

Once loaded, the liquid reagent syringes were set up, prepared, and the reactor primed as described in the previous procedure. Next, the carbon monoxide cylinder was opened and the delivery pressure adjusted to the desired reactor pressure. The reactor gas inlet valve was opened slightly to allow gas flow into the reactor. The bomb inlet valve was then opened to allow pressurization of the bomb. The flow through the reactor was monitored and both the bomb and reactor inlet valves were adjusted to ensure that the reagent flow progressed forward during pressurization.

When the bomb reached the desired pressure, all needle valves were closed and the cylinder delivery pressure was raised an additional 5%. The liquid reagent flow rate was next set to the desired reaction conditions and the reactor gas inlet was partially opened to allow gas flow and begin slug flow equilibration. Additionally, the leak valve was slightly opened to allow the microsystem to come to steady state. During operation, these two valves were used to maintain the desired flow rate as observed in the reactor by measuring the speed of the slugs on a stopwatch (VWR Traceable® 4-Channel Alarm Timer).

The bomb inlet valve remained fully closed unless the pressure in the bomb dropped below the desired operating pressure, in which case the valve was opened to allow repressurization.

4.4.6 Operation and Sample Collection

To operate the system in slug flow large changes in the pressure drop across the system had to be avoided. In addition to destabilizing the slug flow, large fluctuations in pressure could force reagents backwards into the reactor gas inlet. In order to facilitate sampling of the system without interrupting the flow through the reactor, an HPLC injection valve (Upchurch V-451) was connected to the reactor outlet.

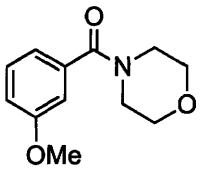
The injection valve was plumbed such that it operated in reverse of that on a standard HPLC system. Thus, when the valve was in the "Load" position (the position illustrated in Figure 1), flow from the reactor outlet proceeded through the sample loop before flowing into the pressure bomb. When the valve was turned to the "Inject" position, the reactor outlet flow bypassed the sample loop and proceeded directly into the bomb, the sample loop would then be connected to the diluent inlet and sample outlet ports. To prevent back-flow into the diluent supply, a check valve (Upchurch CV-3301) was installed to the diluent inlet. Thus, upon decompression, the sample would flow into a collection vial, placed at the outlet of the injection valve. The diluent was a 50 vol% mixture of dichloromethane and isopropanol. This choice of solvents was compatible with the GC analysis method and the viscosity of this mixture approximated the apparent viscosity of the slug flow through the sample loop. By matching the viscosity, disturbances to the reactor flow were minimized.

After a stable slug flow had been achieved, the temperature of the oil bath was raised. The temperature was controlled by a temperature controller with a K-type thermocouple and the actual bath temperature was measured by an alcohol thermometer. Once equilibrated to the desired operating point, the reactor was allowed to run until a full reactor volume had flowed through (78 μL or 400 μL combined flow). The sample loop was then flushed with diluent and set to the "Load" position to begin collecting a sample. Sample sizes were collected in a 322 μL sample loop at liquid volumes between 100 μL and 160 μL as determined by the liquid flow rate from the syringe pump. Samples were collected by turning the sample valve to "Inject" and delivering 1.5 mL of diluent through the sample loop into the collection vial,

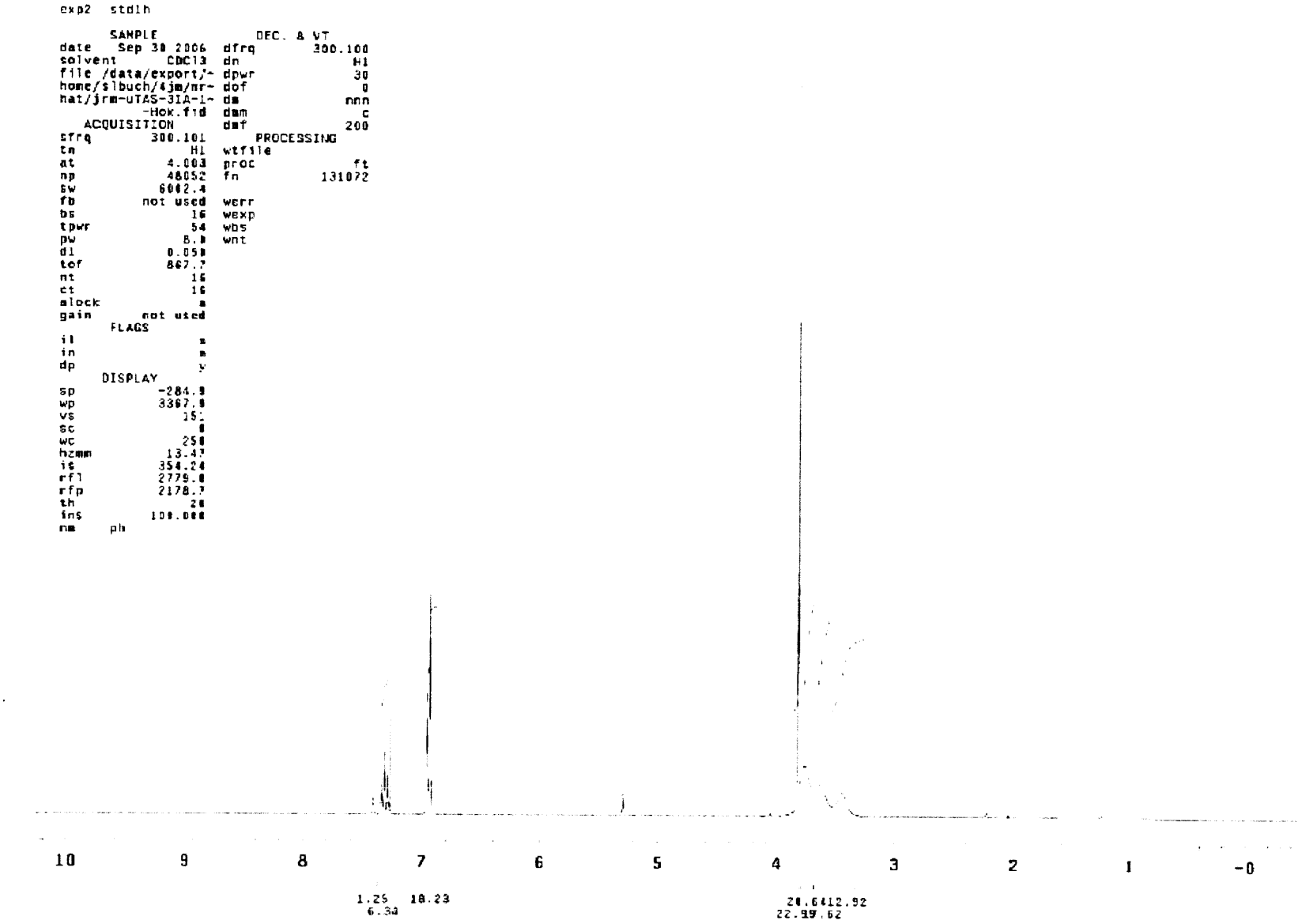
thus collecting properly diluted GC samples and rinsing the sample loop simultaneously. The valve was then returned to the "Load" position to collect the next sample. Multiple samples were collected at each set of reaction conditions before adjusting the temperature to the next data point. After the oil bath reached the next temperature, the reactor was again flushed with a reactor volume of slug flow before collecting the next set of samples.

4.4.7 Sample Analysis and Characterization

The samples were analyzed by gas chromatography on an Agilent 6890 Series gas chromatograph with an FID detector. The samples were injected by an Agilent 7683 automatic liquid sampler, onto a 10 meter Agilent HP-1 capillary column (200 μm I.D. 0.11 μm film thickness) with a 1mL/min flow rate of nitrogen. The oven temperature was raised from 70°C to 240°C over 6.5 minutes. Sample peak areas were normalized to the peak area of the internal standard and multiplied by the response factor for the compound divided by the response factor for the internal standard to determine the sample concentrations. Compounds were isolated by column chromatography on the residue resulting from combining several samples from a series of experiments using the same stock-solutions and removing the solvent.



N-(3-methoxybezoyl)morpholine (3). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.35-7.27 (m, 1H), 6.98-6.91 (m, 3H), 3.98-3.36 (m, 11H; slow rotation of amide) ^{13}C NMR (75 MHz, $CDCl_3$) δ: 168.9, 158.8, 136.0, 128.8, 118.2, 114.6, 111.7, 65.9, 54.4, 47.3, 41.6 (observed complexity due to slow rotation of amide; definitive assignments have not yet been made). IR (neat, cm^{-1}): 3063, 2965, 2917, 2855, 1635, 1580, 1490, 1462, 1432, 1363, 1320, 1301, 1289, 1264, 1237, 1185, 1141, 1114, 1070, 1044, 1023, 946, 915, 862, 818, 794, 749, 709, 691, 634, 580, 488, 425. A satisfactory elemental analysis was not obtained for this compound: Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83. Found: C, 64.70; H, 6.89. The ^{1}H and ^{13}C NMR spectra follow.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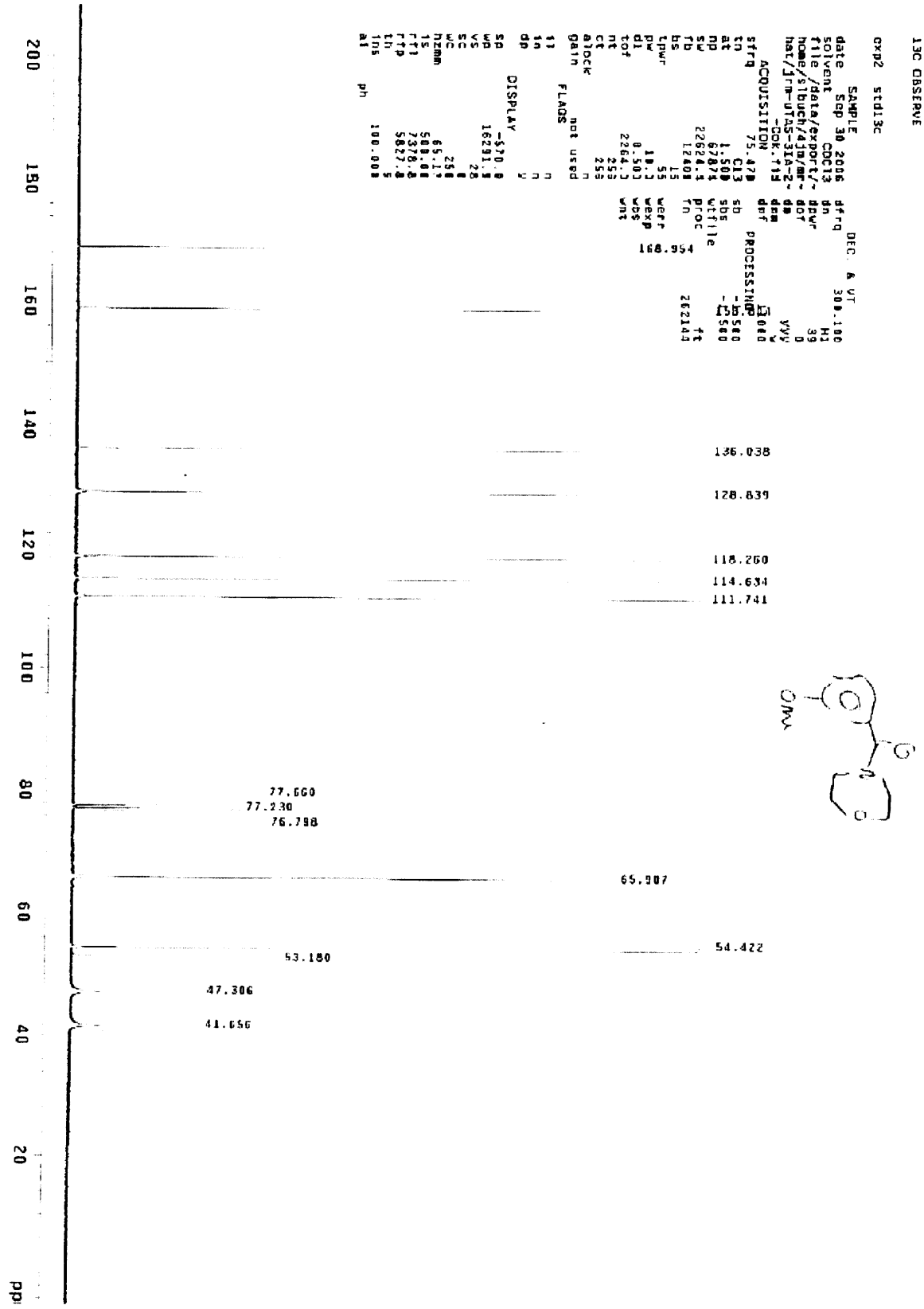
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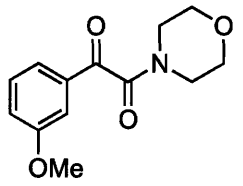
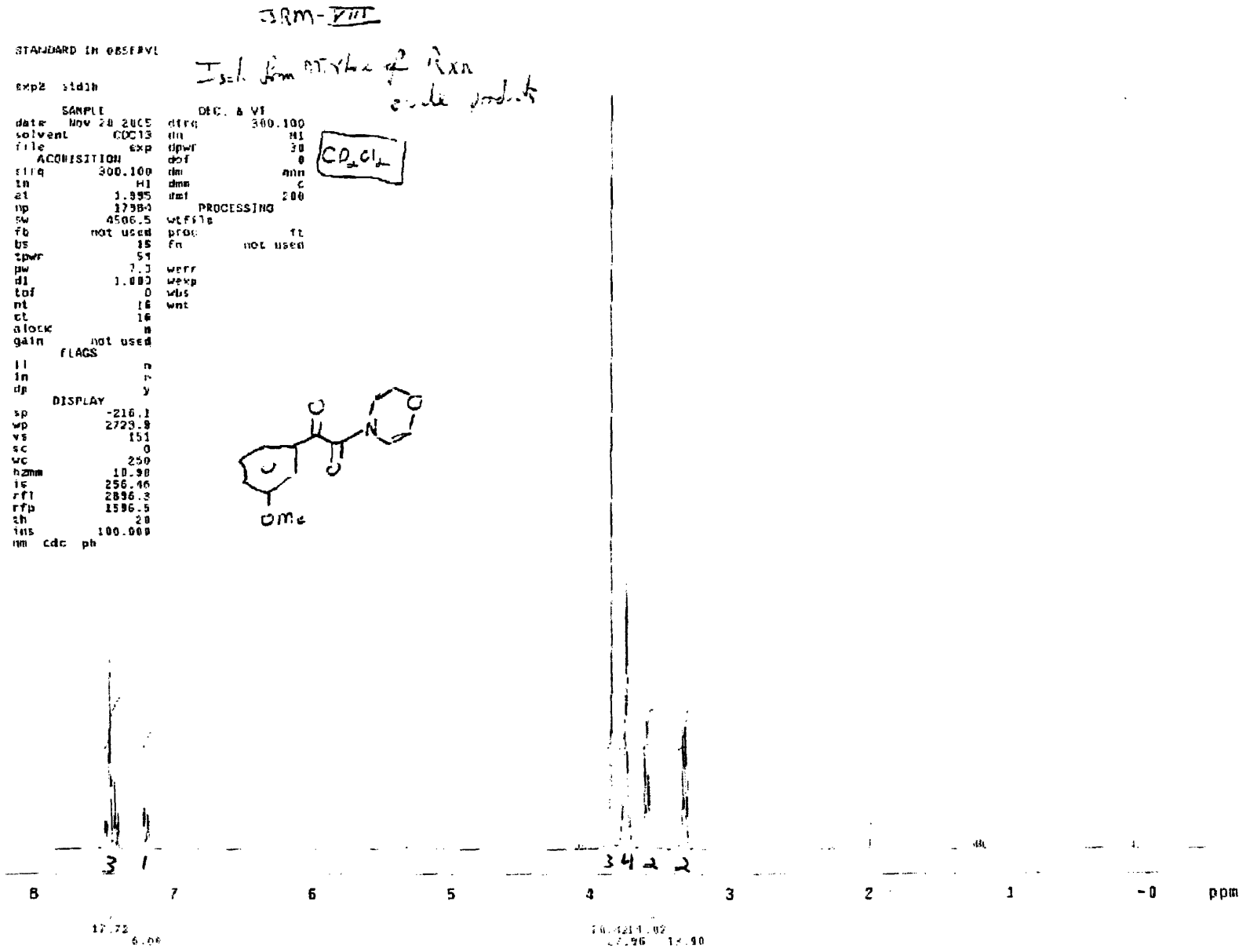


1-(3-methoxyphenyl)-2-morpholinoethane-1,2-dione (4). ^{1}H NMR (300 MHz, CD_2Cl_2) δ: 7.52-7.40 (m, 3H), 7.18-7.24 (m, 1H), 3.84 (s, 3H), 3.79-3.69 (m, 4H), 3.63-3.57 (dd, J = 4.9, 4.7 Hz, 2H), 3.36-3.30 (dd, J = 4.9, 4.7 Hz, 2H). ^{13}C NMR (75 MHz, CD_2Cl_2) δ: 191.8, 165.7, 160.6, 134.8, 130.6, 123.0, 121.8, 113.3, 67.1, 67.0, 55.9, 46.6, 41.9. IR (neat, cm^{-1}): 2969, 2920, 2856, 1680, 1646, 1596, 1582, 1486, 1465, 1445, 1388, 1362, 1291, 1272, 1250, 1174, 1196, 1114, 1068, 1038, 1014, 991, 933, 889, 876, 847, 820, 798, 759, 741, 682, 651, 588, 560, 437. A satisfactory elemental analysis was not obtained for this compound: Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07. Found: C, 61.50; H, 6.15. The ^{1}H and ^{13}C NMR spectra follow.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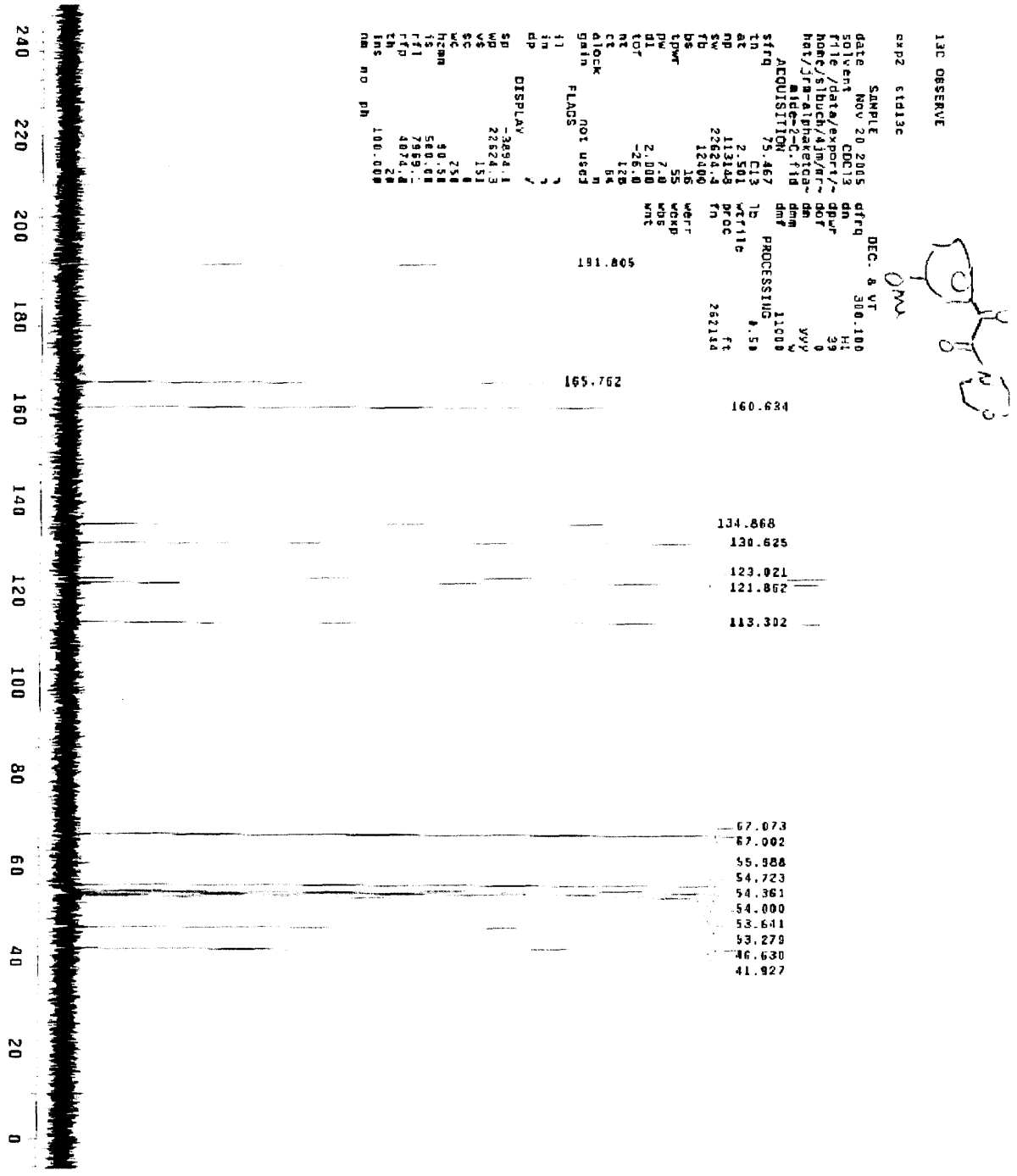
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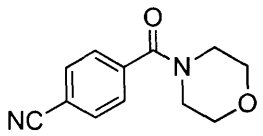
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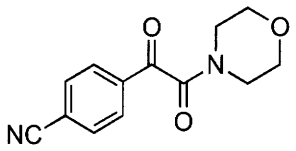
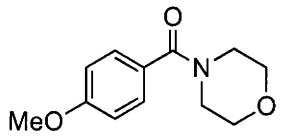
N-(4-cyanobezoyl)morpholine (6). mp 143 - 145 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.72-7.65 (dd, J = 7.9, 1.1 Hz, 2H), 7.52-7.44 (dd, J = 7.9, 1.1 Hz, 2H), 3.86-3.48 (m, 6H; slow rotation of amide), 3.33 (brs, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 167.6, 139.2, 131.9, 127.3, 117.6, 112.8, 66.1, 47.4, 41.9 (observed complexity due to slow rotation of amide; definitive assignments have not yet been made). IR (neat, cm^{-1}): 3119, 3087, 3035, 2982, 2931, 2905, 2862, 2228, 1950, 1625, 1607, 1507, 1463, 1442, 1401, 1364, 1332, 1301, 1281, 1261, 1195, 1182, 1155, 1112, 1026, 1014, 972, 933, 911, 897, 855, 841, 759, 733, 677, 647, 636, 612, 574, 534, 515, 481, 415. Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59. Found: C, 66.69; H, 5.49.



1-(4-cyanophenyl)-2-morpholinoethane-1,2-dione (7). mp 112 - 115 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ:8.14-8.04 (m, 2H), 7.88-7.80 (m, 2H), 3.86-3.77 (m, 3H), 3.73-3.66 (m, 4H), 3.45-3.38 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 189.1, 163.9, 135.7, 132.7, 132.5, 129.8, 124.8, 117.5, 66.3, 45.9, 41.5. IR (neat, cm^{-1}): 2973, 2923, 2859, 2231, 1689, 1645, 1607, 1568, 1502, 1467, 1445, 1407, 1363, 1297, 1269, 1212, 1176, 1114, 1067, 1031, 1016, 982, 918, 856, 835, 780, 734, 663, 649, 576, 546, 483, 428. Anal. Calcd for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.95. Found: C, 63.95; H, 5.11.



N-(4-methoxybezoyl)morpholine[20] (Table 1, entry 5). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.43-7.34 (m, 2H), 6.95-6.88 (m, 2H), 3.83 (s, 3H), 3.80-3.40 (m, 8H; slow rotation of amide) ^{13}C NMR (75 MHz, $CDCl_3$) δ: 169.3, 160.1, 128.5, 126.6, 112.9, 65.9, 54.5, 47.2, 42.7 (observed complexity due to slow rotation of amide; definitive assignments have not yet been made). IR (neat, cm^{-1}): 2964, 2916, 2855, 1610, 1576, 1514, 1456, 1428, 1362, 1302, 1279, 1251, 1175, 1158, 1114, 1067, 1022, 1007, 934, 894, 841, 795, 763, 729, 681, 631, 612, 585, 553, 486.

4.5 References

(1) Ehrfeld, W.; Hessel, V.; Löwe, H. *Microreactors: New Technology for Modern Chemistry*, Wiley-VCH., Weinheim, Germany, **2000**.

(2) Jähnisch, K.; Hessel, V.; Löwe, H.; Baerns, M. *Angew. Chem. Int. Ed.* **2004**, *43*, 406.

(3) Fletcher, P. D. I.; Haswell, S. J.; Pombo-Villar, E.; Warrington, B. H.; Watts, P.; Wong, S. Y. F.; Zhang, X. L. *Tetrahedron* **2002**, **58**, 4735.

(4) Jensen, K. F. *Mat. Res. Soc. Bulletin* **2006**, *31*, 101

(5) Ratner, D. H.; Murphy, E. R.; Jhunjhunwala, M.; Snyder, D. A.; Jensen, K. F.; Seeberger, P. H. *Chem. Commun.* **2005**, 578.

(6) Mauger, C.; Buisine, O.; Caravieilhes, S.; Mignani, G. *J. Organomet. Chem.* **2005**, *690*, 3627.

(7) Miller, P. W.; Long, N. J.; de Mello, A. J.; Vilar, R.; Passchier, J.; Gee, A. *Chem. Commun.* **2005**, 546.

(8) Pennemann, H.; Watts, P.; Haswell, S. J.; Hessel, V.; Löwe, H. *Org. Process Res. Dev.* **2004**, *8*, 422.

(9) Hessel, V.; Hofmann, C.; Löb, P.; Löhndorf, J.; Löwe, H.; Ziogas, A. *Org. Process Res. Dev.* **2005**, *9*, 479.

(10) Yen, B. K. H.; Günther, A.; Schmidt, M. A.; Jensen, K. F.; Bawendi, M. G. *Angew. Chem. Int. Ed.* **2005**, *44*, 5447.

(11) Kappe, C. O. *Angew. Chem. Int. Ed.* **2004**, *43*, 6250.

(12) Tundel, R. E.; Anderson, K. A.; Buchwald, S. L. *J. Org. Chem.* **2006**, *71*, 430.

(13) Timko, M. T.; Smith, K. A.; Danheiser, R. L.; Steinfeld, J. I.; Tester, J. W. *AIChE J.* **2006**, *52*, 1127.

(14) Schoenberg, R.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3327.

(15) Martinelli, J. R.; Freckmann, D. M. M.; Buchwald, S. L. *Org. Lett.* **2006**, *8*, 4843.

(16) Stromnova, T. A.; Moiseev, I. I. *Russ. Chem. Rev.* **1998**, *67*, 485.

(17) Ozawa, F.; Soyama, H.; Yanagihara, H.; Aoyama, I.; Takino, H.; Izawa, K.; Yamamoto, T.; Yamamoto, A. *J. Am. Chem. Soc.* **1985**, *107*, 3235.

(18) Günther, A.; Jensen, K. F. *Lab Chip* **2006**, DOI: 10.1039/b6

(19) (a) Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518. (b) Alaimo, P. J.; Peters, D. W.; Arnold, J.; Bergman, R. G. *J. Chem. Ed.* **2001**, *78*, 64.

(20) Tillaack, A.; Rudloff, I.; Beller, M. *Eur. J. Org. Chem.* **2001**, 523.

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Publications

"Dioxolane-to-Bridged Acetal-to-Spiroketal via Ring-Closing Metathesis and Rearrangement: A Novel Route to 1,7-Dioxaspiro [5.5]undecanes" Keller, V.A.; Martinelli, J.R.; Strieter, E.R.; Burke, S.D. *Org. Lett.* **2002**, *4*, 467.

"A Practical Synthesis of the F-Ring of Halichondrin B via Ozonolytic Desymmetrization of a C_2-Symmetric Dihydroxycyclohexene" Jiang, L.; Martinelli, J.R.; Burke, S.D. *J. Org. Chem.* **2003**, *68*, 1150.

"A Rationally Designed Universal Catalyst for Suzuki-Miyaura Coupling Processes" Walker, S.D.; Barder, T.E.; Martinelli, J.R.; Buchwald, S.L. *Angew. Chem. Int. Ed.* **2004**, *43*, 1871.

"Catalysts for Suzuki-Miyaura Coupling Processes: Scope and Studies of the Effect of Ligand Structure" Barder, T.E.; Walker, S.D.; Martinelli, J.R.; Buchwald, S.L. *J. Am. Chem. Soc.* **2005**, *127*, 4685.

"Convenient Preparation of Weinreb Amides via Pd-Catalyzed Aminocarbonylation of Aryl Bromides at Atmospheric Pressure" Martinelli, J.R.; Freckmann, D.M.M.; Buchwald, S.L. *Org. Lett.* **2006**, *8*, 4843.

"Accelerating Reactions with Microreactors at Elevated Temperature and Pressures: Profiling Aminocarbonylation Reactions" Murphy, E.R.; Martinelli, J.R.; Zaborenko, N.; Buchwald, S.L.; Jensen, K.F. *Angew. Chem. Int. Ed.* **2007**, *46*, 1734.