Expanding the Substrate Scope in Palladium-Catalyzed C-N and C-C Bond-Forming Reactions

By Kevin W. Anderson

B. S. Professional Chemistry, Eastern Michigan University, 2000

M. S. Organic Chemistry, Michigan State University, 2002

Submitted to the Department of
Chemistry in Partial Fulfillment of the
Requirements for the Degree of
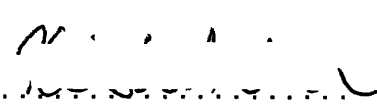
DOCTOR OF PHILOSOPHY IN
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Signature of Author . . . .
Department of Chemistry

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Thesis Supervisor

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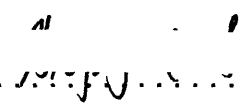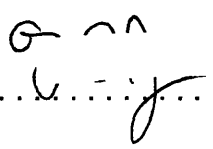Robert W. Field
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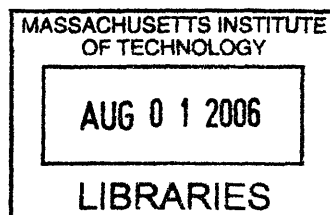
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Abstract

Chapter 1. The first detailed study of the palladium-catalyzed amination of aryl nonaflates is reported. Use of bulky electron-rich monophosphinobiaryl ligands or BINAP allow for the catalytic amination of electron-rich and –neutral aryl nonaflates with both primary and secondary amines. Using XantPhos, the catalytic amination of a variety of functionalized aryl nonaflates resulted in excellent yields of anilines; even 2-carboxymethyl aryl nonaflate is effectively coupled with a primary alkyl amine. Moderate yields were obtained when coupling halo-aryl nonaflates with a variety of amines, where in most cases the aryl nonaflate reacted in preference to the aryl halide. Overall, aryl nonaflates are an effective alternative to aryl triflates in palladium-catalyzed C-N bond-forming processes due to their increased stability under the reaction conditions.

Chapter 2. A catalyst comprised of a Pd precatalyst and 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl is explored in C-N bond-forming processes. This catalyst displayed unprecedented stability and scope allowing, for the first time, the coupling of substrates bearing a carboxylic acid or a primary amide. Also, the more bulky catalyst system Pd/2-*tert*-butylphosphino-2',4',6'-triisopropylbiphenyl was found to be effective for the *N*-arylation of 2-aminoheterocycles and weakly basic HN-heterocycles: pyrazole and indazole. The chemoselectivity for amination using these catalysts was explored where the rough order of reactivity for amines is: aryl amines >> primary and secondary alkyl amines > 2-aminoheterocycles > primary amides ~ HN-heterocycles.

Chapter 3. The palladium-catalyzed Suzuki-Miyaura coupling of haloaminoheterocycles and functionalized organoboronic acids using a highly active and stable monophosphinobiaryl ligand, 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl, efficiently produced aminoheterocyclic biaryl derivatives. This same catalyst was effective in coupling 2-haloaminoaryl compounds with 2-formyl or 2-acetylphenyl boronic acids, providing the fused heterocyclic compounds phenanthridine, benzo[c][1,8]naphthridine and benzo[c][1,5]naphthridine in excellent yields.

Chapter 4. A water-soluble monophosphinobiaryl ligand, sodium 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl-3'-sulfonate, was synthesized by electrophilic sulfonation of the lower-aromatic ring of 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl. This ligand was utilized in the palladium-catalyzed Suzuki-Miyaura reaction of water-soluble aryl/heteroaryl halides and organoboronic acids. The catalyst displays unprecedented reactivity and stability for Suzuki-Miyaura reactions conducted in water.

Chapter 5. A water-soluble monophosphinobiaryl ligand, sodium 2'-(dicyclohexyl-phosphanyl)-2,6-diisopropyl-biphenyl-4-sulfonate, was synthesized by a proposed electrophilic *ipso*-substitution/reverse Friedel-Crafts alkylation of the lower-aromatic ring on 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl. This ligand was utilized in the palladium-catalyzed Heck alkynylation (copper-free Sonogashira coupling) of hydrophobic and hydrophilic aryl halides and terminal alkynes conducted in an aqueous acetonitrile solvent system. For the first time, an electron-deficient terminal alkyne, propiolic acid, was successfully coupled with aryl bromides. We also demonstrated that this catalyst is useful in the reaction of benzyl chlorides and terminal alkynes to provide benzyl alkynes in good yields. We show that by using an excess amount of base (> 1.0 equiv.) and higher reaction temperatures (≥ 80 °C), base-catalyzed isomerization to the corresponding aryl allenes can be achieved in a one-pot process.

Thesis Supervisor: Stephen L. Buchwald
Title: Camille and Henry Dreyfus Professor of Chemistry

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The author gratefully acknowledges: Professor Stephen L. Buchwald for giving me the opportunity to work in his laboratories and develop at my own pace as a scientist. His patience, vision and ethical standards are second to none. Professor Gregory C. Fu for his guidance along this long road to obtaining my degree and for his continued interest and support. Professor Jetze J. Tepe for getting me started in the challenging research area of organic synthesis. Professor William D. Wulff for his suggestion to consider transferring to MIT and facilitating that process. Professor Timothy F. Jamison for proofreading this thesis and for helpful suggestions.

Others who have contributed to this work through helpful conversation and made the laboratory a more pleasant place (in no specific order): Dr. Maria Mendez-Perez, Dr. Julian Priego, Dr. Matthew Rainka, Mr. Joe Martinelli, Dr. Edward Hennessy, Dr. Alex Shafir, Dr. Tom Clark, Dr. Takashi Ikawa, Dr. Catharine H. Larsen, Dr. Nan Zheng, Mr. Ryan Altman, Ms. Rachel Tundel, and Dr. Xiahua Huang (synthesizer of XPhos/*t*-Bu-XPhos).

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Last, but not least, I would like to thank my fiancé Carly S. Carson, D.M.D., who loved, supported, and encouraged me every single second of the day.

To my parents, this thesis is dedicated:

William Gary Anderson and Sharon Rose Anderson

Preface

Parts of this thesis have been adapted from the following articles co-written by the author.

"Palladium-Catalyzed Heck Alkynylation of Benzyl Chlorides" Larsen, C. H.; Anderson, K. W.; Tundel, R. E.; Buchwald, S. L. *Synlett,* **2006**, *submitted.*

"Monodentate Phosphines Provide Highly Active Catalyst for Palladium-Catalyzed C-N Bond-Forming Reactions of Heteroaromatic Halides/Amines and (H)N-Heteroaromatics" Anderson, K. W.; Tundel, R. E.; Ikawa, T.; Altman, R. A.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *submitted.*

"A Highly Active Catalyst for Suzuki-Miyaura Cross-Coupling Reactions of Heteroaryl Compounds" Billingsley, K. L.; Anderson, K. W.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *(Advanced Article).*

"General Catalysts for the Suzuki-Miyaura and Sonogashira Coupling of Aryl Chlorides and for the Coupling of Challenging Substrate Combinations in Water" Anderson, K. W.; Buchwald, S. L *Angew. Chem., Int. Ed.* **2005**, *44*, 6173; *Angew. Chem.* **2005**, *117*, 6329.

"Palladium-Catalyzed Amination of Aryl Nonaflates" Anderson, K. W.; Mendez-Perez, M.; Priego, J.; Buchwald, S. L. *J. Org. Chem.* **2003**, *68*, 9563.

"Expanding Pd-Catalyzed C-N Bond-Forming Processes: The First Amidation of Aryl Sulfonates, Aqueous Amination, and Complementarity with Cu-Catalyzed Reactions" Huang, X.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 6653.

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Introduction

Aryl amines are important structural elements encountered in numerous fields of chemistry. Aryl amines are of interest due to their common occurrence in natural products,[1] pharmaceuticals,[2] xerographic and photographic materials,[3] and conducting polymers.[4] For example, a number of biologically active natural products contain this moiety, including the anti-fungal agent hydroxyitraconazole[5] and anti-cancer compound trichostatin D[6] (Figure 1).

Figure 1: Biologically active natural products containing aryl amines.

Hydroxyitraconazole

Trichostatin D
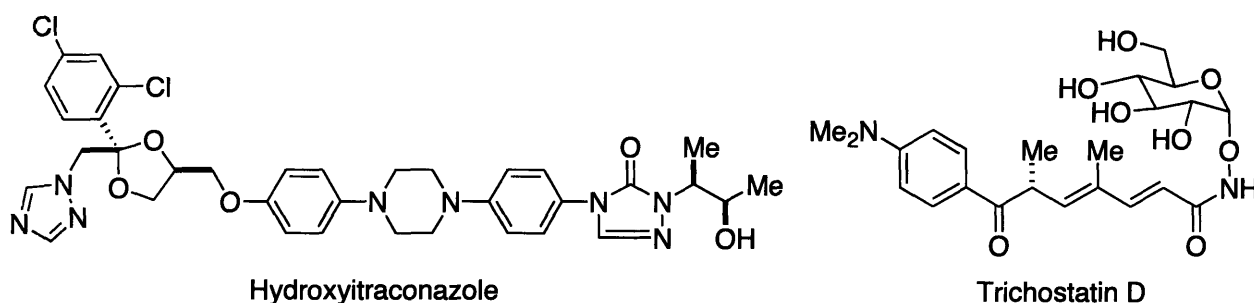
A number of methods have been developed for the synthesis of aryl amines (Scheme 1). One of the most commonly used reactions for the preparation of anilines is nitration of an arene followed by reduction of the nitro group.[7] This method possesses many limitations, which include both the harsh acidic conditions and regioselectivity in the nitration step. Aryl amines have also traditionally been prepared by either reductive amination of aniline derivatives[8,9] or nucleophilic aromatic substitution.[7,10] These processes for the preparation of aryl amines, which are often quite effective, have been plagued by their limited substrate scope and functional group tolerance. Specifically, in reductive amination, the range of substrates is restricted to synthetically available anilines and is limited to the preparation of secondary amines.

Transition metals and their use as catalysts have profoundly changed organic synthesis. In the last few decades, a whole plethora of metal-catalyzed cross-coupling methods have been reported.[11] These methods have been utilized in myriad syntheses both in pharmaceutical and academic pursuits.[12]

Scheme 1. Typical methods for the preparation of aryl amines.
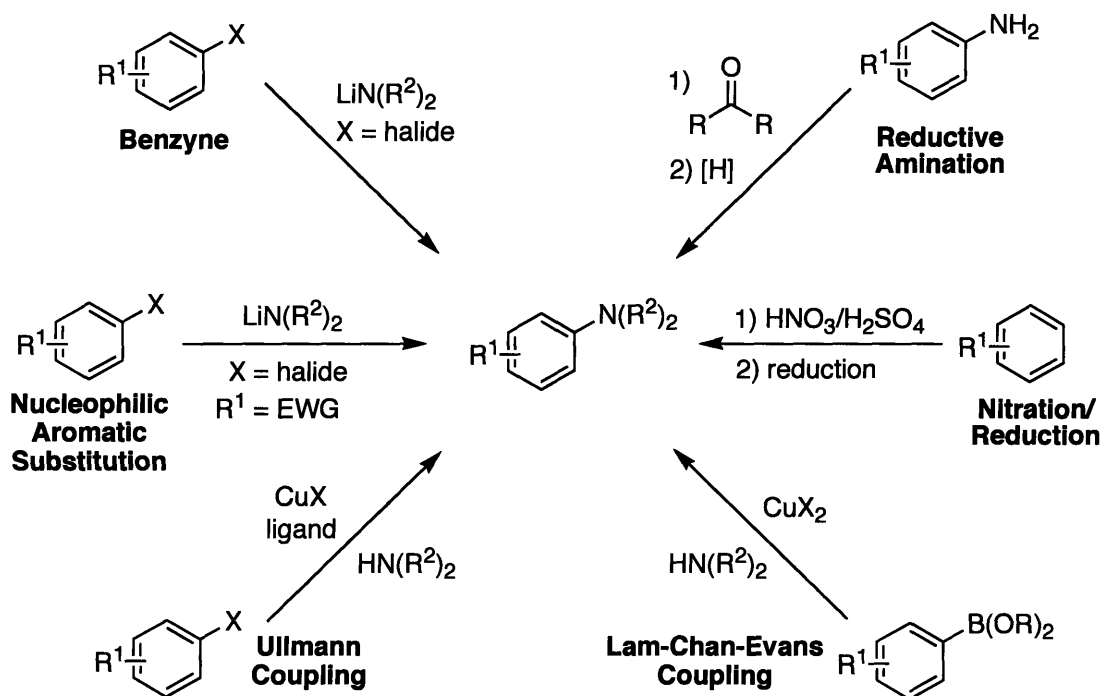
The copper-catalyzed Goldberg and Ullmann coupling of aryl halides and amines for the preparation of aryl amines have been known for over a hundred years (Scheme 1).[13-15] Significant drawbacks with the classically developed conditions are they require extremely high temperatures along with stoichiometric amounts of copper. It was not until recently that more effective copper-based catalysts have been disclosed and shown to be efficient in coupling aryl bromides and iodides with a wide array of amines.[14,15] Some of the more useful ligands that promote catalytic copper cross-coupling reactions are shown in Figure 2. Furthermore, arylboronic acids have also been used as alternative arylating agents in the copper-catalyzed arylation of heterocycles and amines.[16] While this method is very powerful in constructing aryl amines, it is limited in the substrate scope. For example, *ortho*-substituted arylboronic acids react inefficiently.
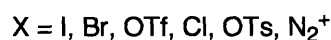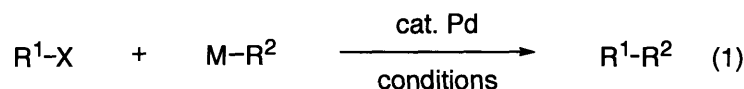
Figure 2. Common ligands used for copper-catalyzed cross-couplings.
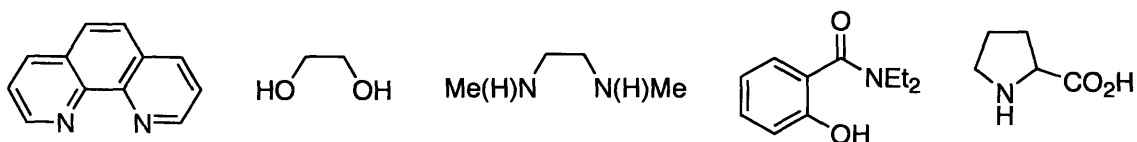
It was evident that conventional methods for the preparation of aryl amines had many limitations. Therefore, it became increasingly important to develop new synthetic methods, for the direct preparation of aryl amines, which are more functional group tolerant and can be conducted under milder conditions.

Of the metals that have been used in cross-coupling reactions, palladium stands out both as the most often used and general of these, which can partially be attributed to its ability (usually in the presence of a supporting ligand) to facilitate formation of a variety of carbon-carbon and carbon-heteroatom bonds (Scheme 2, eq. 1).[17] Another characteristic of palladium catalysts are its high tolerance to functional groups (eg., esters, ketones, etc.) and low sensitivity to moisture and oxygen, greatly enhancing its use to the everyday synthetic chemist.[17] Some of the most universally used methods to construct C-C bonds (sp^2-sp^2 and sp^2-sp) involve the coupling of an aryl or vinyl halide with an organometallic reagent (M-R^2, Scheme 2). The most common of these are the Kumada (M = MgX),[18] Suzuki-Miyaura (M = BX_2),[19] Negishi (M = ZnX),[20] Stille (M = SnR_3),[21] Hiyama (SiX_3)[22] and Sonogashira (M = Cu)[23] reactions.

Scheme 2. Palladium-catalyzed C-C and C-heteroatom bond-forming reactions.

$$R^1\text{-}X \quad + \quad M\text{-}R^2 \quad \xrightarrow[\text{conditions}]{\text{cat. Pd}} \quad R^1\text{-}R^2 \quad (1)$$

$$X = I, Br, OTf, Cl, OTs, N_2^+$$

C-C Bond-Formation

		C-Heteroatom Bond-Formation
R^1 = aryl, vinyl, alkyl	R^1 = aryl, vinyl, alkyl	R^1 = aryl, vinyl
R^2 = aryl, vinyl, alkyl	R^2 = alkyne	R^2 = N, O, S

M = MgX   Kumada
   = BX_2 Suzuki-Miyaura
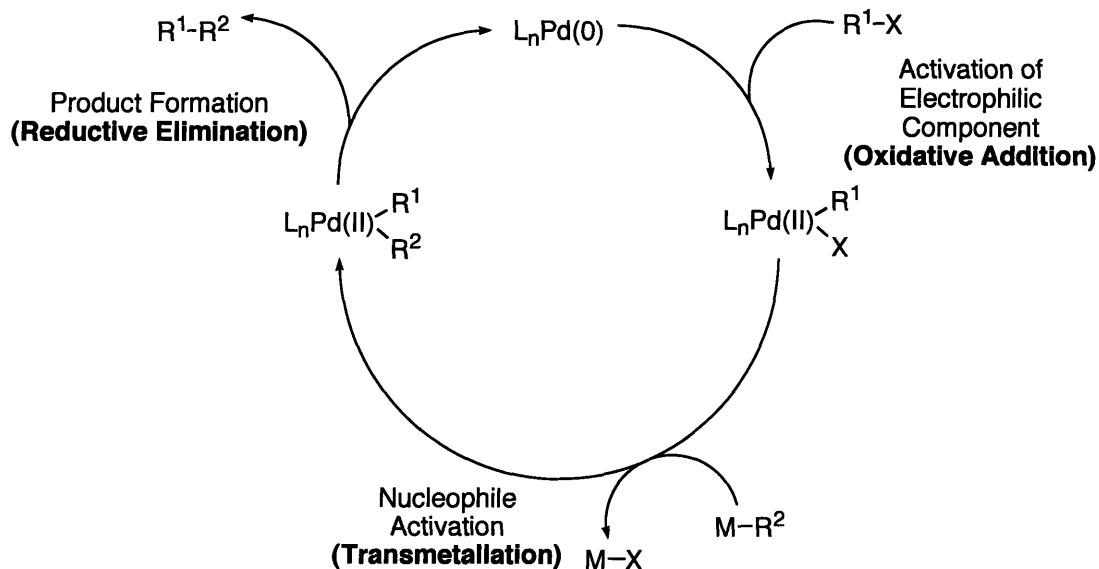   = ZnX   Negishi
   = SnR_3 Stille
   = SiX_3 Hiyama

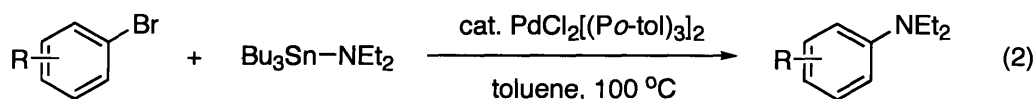M = Cu   Sonogashira

M = H, SnR_3 (R^2 = N)

The generally accepted mechanism for palladium-catalyzed cross-coupling reactions is thought to proceed through three distinct stages (Scheme 3).[24] First, activation of the electrophilic component (R^1-X) occurs via oxidative addition with the $L_nPd(0)$ center to form a $L_nPd(II)R^1X$ species. Next, nucleophile activation or

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transmetallation of M-R^2 occurs to provide the L$_n$Pd(II)R^{1}R^2 species (M must be more electropositive than Pd), which then reductively eliminates to form the desired coupled product (R^1-R^2) and regenerate the active L$_n$Pd(0) catalyst.

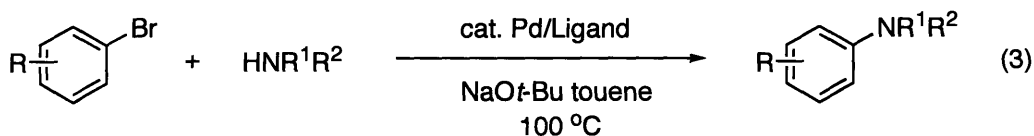**Scheme 3.** General mechanism for Pd-catalyzed cross-coupling reactions.

R^1-R^2 ← L$_n$Pd(0) → R^1-X

Product Formation
(Reductive Elimination)

Activation of
Electrophilic
Component
(Oxidative Addition)

$$L_nPd(II) \overset{R^1}{\underset{R^2}{<}}$$

$$L_nPd(II) \overset{R^1}{\underset{X}{<}}$$

Nucleophile
Activation
(Transmetallation) M–X

M–R^2

While palladium based catalysts have been utilized extensively for C-C bond-forming reactions (sp^2-sp^2, sp^2-sp, etc.), very few reports of the analogous C-N bond-forming reactions had appeared in the literature before 1994. The first of these was a report by Migita in 1983 using a catalyst system comprised of PdCl$_2$/(P(o-tol)$_3$)$_2$ in the coupling of simple aryl bromides and tributyl-N,N-diethylaminostannane to form the corresponding aromatic amines (eq. 2).[25] However, this initial method was plagued by a

R $\overset{}{\underset{}{\bigcirc}}$ Br + Bu$_3$Sn–NEt$_2$ $\xrightarrow[\text{toluene, 100 °C}]{\text{cat. PdCl}_2[(P\textit{o}-tol)_3]_2}$ R $\overset{}{\underset{}{\bigcirc}}$ NEt$_2$ (2)
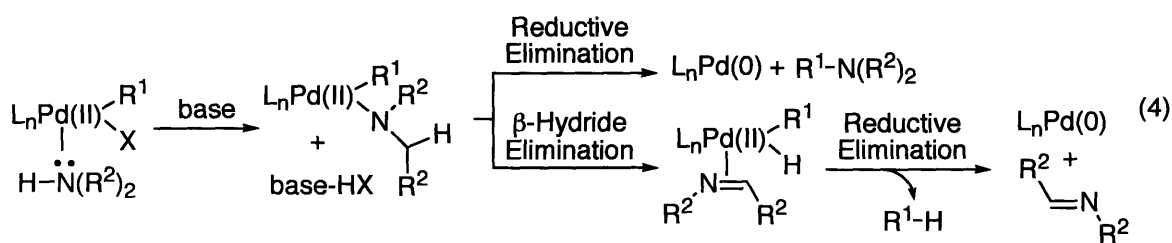
limited substrate scope due to the use of moisture sensitive and toxic tributyl tin amides. Nonetheless, these original reports represented a significant and untouched advance in the literature until the mid 1990's when our group[26] and Hartwig's[27] reported that use of the tin-amide was not necessary. Thus, palladium-catalyzed amination could be carried

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out with the free amine using a Pd/P(o-tol)$_3$ catalyst system in the presence of a
stoichiometric amount of NaOt-Bu (eq. 3).

$$R\text{-}\!\!\overset{Br}{\bigcirc}\quad +\quad HNR^1R^2\quad \xrightarrow[\substack{NaO\text{-}Bu\ touene \\ 100\ ^\circ C}]{cat.\ Pd/Ligand}\quad R\text{-}\!\!\overset{NR^1R^2}{\bigcirc}\qquad (3)$$

This newly developed C-N bond-forming cross-coupling method with free amines
differs mechanistically from the analogous C-C coupling processes, in that there is no
formal transmetallation. Based on mechanistic studies, it was proposed that the
transfer of the heteroatom onto palladium occurs first by coordination of the heteroatom
N-H via the lone-pair of electrons (eq. 4).[28-34] This coordination greatly acidifies the
amine, after which deprotonation by an external base occurs to form the
$L_nPd(II)R^1N(R^2)_2$ species. A competitive side reaction in C-N bond-forming processes is
β-hydride elimination from the amine to form a $L_nPd(II)R^1(H)$ species (eq. 4).[24]
Subsequent reductive elimination provides the reduced arene and imine side-products
with regeneration of the Pd(0) catalyst.

$$\begin{array}{c}
L_nPd(II)\!\!\!\overset{R^1}{\underset{X}{\diagdown}} \\
\overset{\cdot\cdot}{H}\!-\!N(R^2)_2
\end{array}
\xrightarrow{base}
\begin{array}{c}
L_nPd(II)\!\!\!\overset{R^1}{\diagdown}\!\!\overset{R^2}{\underset{N}{\diagdown}}\!\!-\!H \\
+ \\
base\text{-}HX\ \ R^2
\end{array}
\left\{
\begin{array}{l}
\xrightarrow[]{\substack{Reductive \\ Elimination}}\ L_nPd(0) + R^1\text{-}N(R^2)_2 \\
\xrightarrow[]{\substack{\beta\text{-Hydride} \\ Elimination}}\ L_nPd(II)\!\!\overset{R^1}{\underset{\underset{R^2}{\overset{N}{|}}\diagdown R^2}{\diagdown}}\!H \xrightarrow[R^1\text{-}H]{\substack{Reductive \\ Elimination}}\ \begin{array}{c} L_nPd(0) \\ R^2\ + \\ \diagdown\!\!=\!\!N\diagdown R^2 \end{array}
\end{array}
\right.
\qquad (4)$$

Of the many palladium catalyst systems that have been developed, most require
the use of a supporting ligand. Common ligands now used to facilitate cross-coupling
reactions are phosphines and heterocyclic carbenes.[11] These ligands have not only
been shown to stabilize metal-centers, such as palladium, they also can easily be
modified to increase the reactivity of the catalyst. For example, if the aryl groups on
triphenylphosphine (PPh$_3$, the most common ligand used in cross-coupling reactions)

are replaced with bulky alkyl groups (e.g., *t*-Bu, Cy), these more electron-donating bulky phosphines provide a catalyst with Pd that successfully allow the coupling of more challenging substrates such as aryl chlorides using much milder conditions.[17,35] Bulkier electron-rich ligands not only should help facilitate oxidative addition by increasing the electron-density on Pd, they also should speed up reductive elimination, which explains, in part, why they tend to be more efficient and general than previous generations of catalysts.

Figure 3. Bidentate ligands used in Pd-catalyzed C-N bond-formation.

BINAP   DPPF   XantPhos   DPEPhos
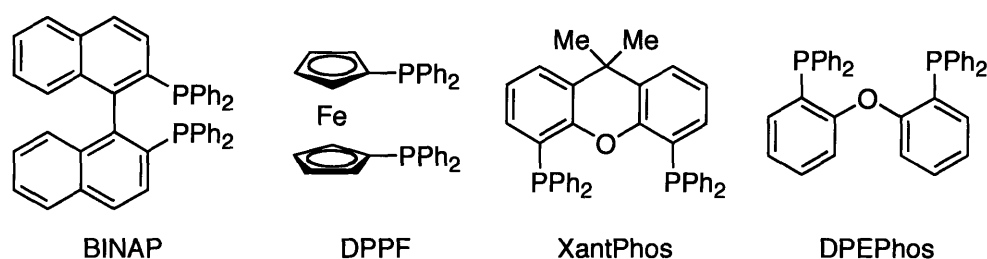
After the initial discovery of the Pd/P(*o*-tol)$_3$ catalyst system for C-N bond-forming reactions, it was found that bidentate ligands, such as BINAP,[36-39] DPPF,[40,41] XantPhos[42-46] and DPEPhos[47-48] were also quite effective. At the time, these catalysts dramatically improved the scope and efficiency of C-N bond-forming reactions, allowing the coupling of a range of aryl bromides and amines/amides. Also, a significant advancement in the reaction conditions was through the discovery that use of inorganic bases, such as Cs$_2$CO$_3$[49] and K$_3$PO$_4$[50], allowed the coupling of more highly functionalized systems (e.g., substrates containing hydrolizable esters, nitriles and enolizable ketones). However, use of these weaker bases increased the reaction times dramatically, presumably due to the fact that deprotonation of the palladium-coordinated amine becomes turnover limiting.

The first proficient use of bulky electron-rich monophosphines as supporting ligands in palladium-catalyzed cross-coupling reactions did not occur until the late 1990's where a catalyst system based on tricyclohexylphosphine PCy$_3$[51,52] and

Pt-Bu$_3$[53,54] were employed in the reaction of aryl chlorides and amines. Since then, Pd/Pt-Bu$_3$ has been shown to be an excellent catalyst for Suzuki-Miyaura,[55,56] Stille,[57,58] Heck[59,60] reactions, α-arylation reactions of ketones, malonates, and silyl enol ethers[61-64], and in additional C-N bond-forming processes.[65-68] Also, a significant amount of work has been reported on the use of trialkylphosphines in cross-coupling reactions of alkyl halides possessing β-hydrogens.[69-76] This work is non-trivial, since the oxidative addition product of alkyl halides can readily undergo β-hydride elimination, resulting in significant amounts of reduced alkane and very little of the desired coupled product.

Figure 4. Supporting ligands used in Pd-catalyzed C-N bond-formation.
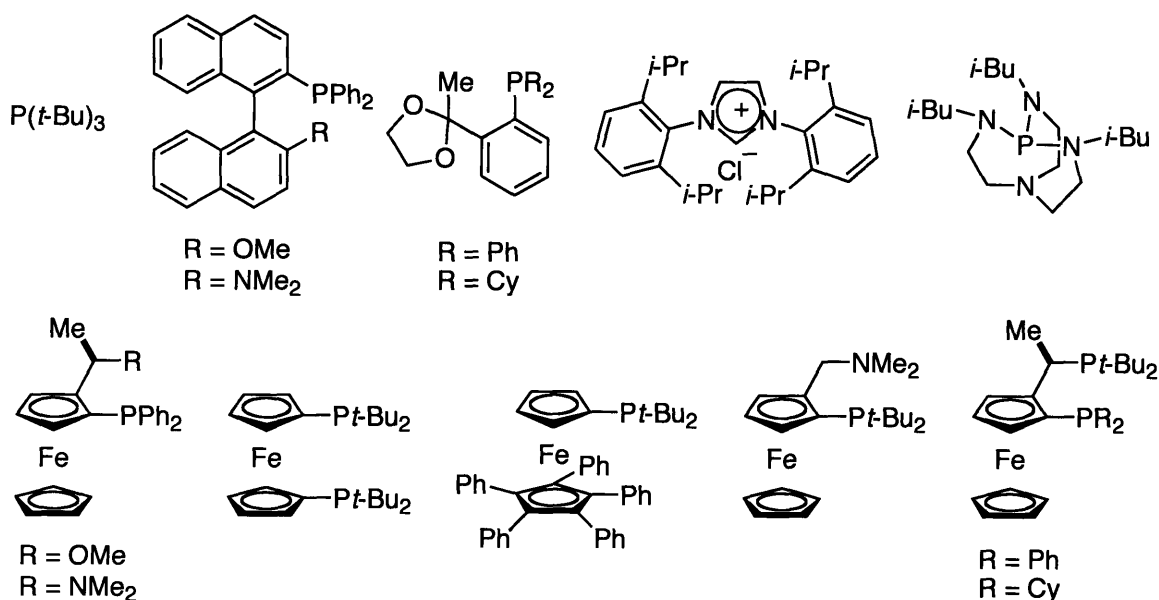
A noteworthy inadequacy of using trialkylphosphines in palladium-catalyzed amination reactions is that the catalyst is much less stable and reacts inefficiently with more basic amines (e.g., primary alkyl amines).[65-68] One possibility is that nucleophilic amines, in the presence of base, have the ability to displace the ligand on palladium, rendering the catalyst inactive. Through extensive procedural advancements, mechanistic studies, and ligand evolution, highly effective and useful catalytic systems have been developed. A large number of catalyst systems based on mono- and

bidentate phosphines or heterocyclic carbenes have been utilized, which display varying degrees of reactivity in palladium-catalyzed C-N bond-forming processes (Figure 4).[77-83]

In our laboratories, we have focused considerable effort towards developing more stable and active palladium catalysts. This work resulted in the synthesis of a series of biphenylmonophosphinobiaryl ligands as shown in Figure 5.[77,78,83,84] Catalysts based on this class of ligands have not only displayed high stability, but also have shown increased reactivity in palladium-catalyzed carbon-carbon, carbon-nitrogen, and carbon-oxygen bond-forming reactions.[77,78,83,84] In some cases these reactions can be conducted at room temperature. The stability of catalysts based on this class of ligands is believed to be due to π-interactions between the lower aromatic ring of the biaryl moiety and the Pd(0) center.[85-88] Therefore, this π-interaction may stabilize any intermediate in the catalytic cycle increasing the overall lifetime of the catalyst. The high activity may be attributed to a number of factors: First, electron-rich ligands should increase the electronic density on Pd, thus facilitating oxidative addition since this process is nucleophilic in nature. Second, the bulkiness of the ligand should favor reductive elimination and facilitate formation of a monoligated Pd(0) species, which is believed to be the active catalystic species. This has been shown by systematically varying the ratio of ligand to Pd. As the L:Pd is increased in the series of monophosphinobiaryl ligands, decreased reaction rates were observed.[89,90]

Figure 5. Monophosphinobiaryl ligands developed prior to the authors work.

R = i-Pr
R = Cy
R = t-Bu

R = Cy
R = t-Bu

R = H
R = Me
R = Et
R = i-Pr

R = H
R = i-Pr

R = Cy
R = t-Bu
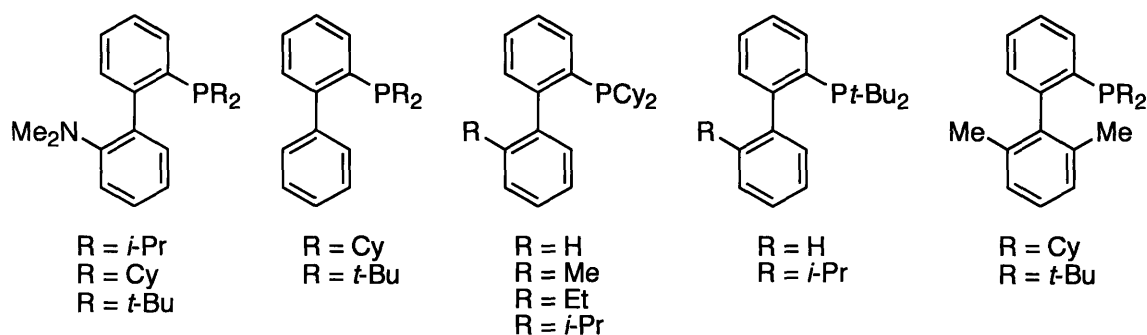
Since its discovery, both academic and industrial chemists have adopted palladium-catalyzed amination methodology in their everyday use, highlighting the large impact this chemistry has had in synthetic ventures.[91] While there was significant

progress in developing more active catalysts for palladium-catalyzed C-N and C-C bond-forming processes, there still remained many obstacles to overcome and substrate classes to explore. This thesis provides a systematic report on the further development and exploration of Pd/monophosphinobiaryl catalysts in C-N and C-C bond-forming reactions of challenging substrate combinations.

References

(1) Buckingham, J. *Dictionary of Natural Products*. University Press, Cambridge, MA, 1994.

(2) Czarnik A. W. *Acc. Chem. Res.* **1996**, *29*, 112.

(3) Law, K-. Y. *Chem. Rev.* **1993**, *93*, 449.

(4) Gospodinova, N.; Terlemezyan, L. *Prog. Polymer Science* **1998**, *23*, 1443.

(5) Tanoury, G. J.; Senanayake, C. H.; Hett. R.; Kuhn, A. M.; Kessler, D. W.; Wald, S. A. *Tetrahedron Lett.* **1998**, *39*, 6845.

(6) Hosokawa, S.; Ogura, T.; Togashi, H.; Tatsuta, K. *Tetrahedron Lett.* **2005**, *46*, 333.

(7) March, J.; Smith, M. B. *Advanced Organic Chemistry: Reactions, Mechanism, and Structure*, 5th Ed.: Eds; John Wiley & Sons, Inc.: New York, 2001.

(8) Patai, S. *The Chemistry of the Carbon-Nitrogen Double Bonds*; Interscience Publishers: London, New York, 1970.

(9) *Comprehensive Organic Synthesis*; Permagon Press: Oxford, 1991; Vol. 8.

(10) Wickham, P. P.; Reuter, K. H.; Senanayake, D.; Guo, H.; Zalesky, M.; Scott. W. J. *Tetrahedron Lett.* **1993**, *34*, 7521.

(11) de Meijere, A.; Diederich, F. Eds; *Metal-Catalyzed Cross-Coupling Reactions*, 2nd Ed.: Wiley-VCH: Weinheim, 2004.

(12) Beller, M.; Bolm, C. Eds; *Transition Metals for Organic Synthesis*, 1st Ed.: Wiley-VCH: Weinheim, 2004.

(13) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337.

(14) Kunz, K.; Scholz, U.; Ganzer, D. *Synlett* **2003**, 2428.

(15) Ley, S. V.; Thomas, A. W. *Angew. Chem. Int. Ed.* **2003**, *42*, 5400.

(16) Chan, D. M. T.; Lam, P. Y. S. Recent Advances in Copper-Promoted C-Heteroatom Bond Cross-Coupling Reactions with Boronic Acids and Derivatives. In *Boronic Acids: Preparation and Applications in Organic Synthesis and Medicine*, 1st Ed.: Hall, D. G. Eds; Wiley-VCH: Weinheim, 2005, Vol. 1st, pp. 205-239.

(17) Tsuji, J. Ed.; *Palladium Reagents and Catalysts: New Perspectives for the 21st Century*, 1st Ed.: Wiley: Weinheim, 2004.

(18) Knochel, P.; Sapountzis, I.; Gommermann, N. Carbon-Carbon Bond-Forming Reactions Mediated by Organomagnesium Reagents. In *Metal-Catalyzed Cross-Coupling Reactions*, 2nd Ed.: de Meijere, A.; Diederich, F. Eds; Wiley-VCH: Weinheim, 2004, pp. 671-698.

(19) Miyaura, N. Metal-Catalyzed Cross-Coupling Reactions of Organoboron Compounds with Organic Halides. In *Metal-Catalyzed Cross-Coupling Reactions*, 2nd Ed.: de Meijere, A.; Diederich, F. Eds; Wiley-VCH: Weinheim, 2004, pp. 41-125.

(20) Negishi, E.; Zeng, X.; Tan, Z.; Qian, M.; Hu, Q.; Huang, Z. Palladium- or Nickel-Catalyzed Cross-Coupling with Organometals Containing Zinc, Aluminum, and Zirconium: The Negishi Coupling. In *Metal-Catalyzed Cross-Coupling Reactions*, 2nd Ed.: de Meijere, A.; Diederich, F. Eds; Wiley-VCH: Weinheim, 2004, pp. 815-890.

(21) Mitchell, T. N. Organotin Reagents in Cross-Coupling Reactions. In *Metal-Catalyzed Cross-Coupling Reactions*, 2nd Ed.: de Meijere, A.; Diederich, F. Eds; Wiley-VCH: Weinheim, 2004, pp. 125-162.

(22) Denmark, S. E.; Sweis, R. F. Organosilicon Compounds in Cross-Coupling Reactions. . In *Metal-Catalyzed Cross-Coupling Reactions*, 2nd Ed.: de Meijere, A.; Diederich, F. Eds; Wiley-VCH: Weinheim, 2004, pp. 163-216.

(23) Marsden, J. A.; Haley, M. M. Cross-Coupling Reactions to sp Carbon Atoms. In *Metal-Catalyzed Cross-Coupling Reactions*, 2nd Ed.: de Meijere, A.; Diederich, F. Eds; Wiley-VCH: Weinheim, 2004, pp. 317-394.

(24) Farina, V. in *Comprehensive Organometallic Chemistry*, 2nd Ed., Pergamon Press: Oxford, 1995, Vol 12, pp. 161-240.

(25) Kosugi, M.; Kameyama, M.; Migita, T. *Chem. Lett.* **1983**, 927.

(26) Guram, A. S.; Rennels, R. A.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **1995**, *34*, 1348.

(27) Louie, J.; Hartwig, J. F. *Tetrahedron Lett.* **1995**, *36*, 3609.

(28) Widenhoefer, R. A.; Buchwald, S. L. *Organometallics* **1996**, *15*, 3534.

(29) Widenhoefer, R. A.; Buchwald, S. L. *Organometallics* **1996**, *15*, 2755.

(30) Widenhoefer, R. A.; Zhong, H. A.; Buchwald, S. L. *Organometallics* **1996**, *15*, 2745.

(31) Widenhoefer, R. A.; Zhong, H. A. **1997**, *36*, 2610.

(32) Singh, U. K.; Strieter, E. R.; Blackmond, D. G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 14104.

(33) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 3694.

(34) Hartwig, J. F. *Synlett* **1997**, 329.

(35) The following pK_a values of conjugate acids of phosphines support the high basicity of $P(t\text{-}Bu)_3$ compared to that of PPh_3: $P(t\text{-}Bu)_3$ (11.4), PCy_3 (9.7), $P(n\text{-}Bu)_3$ (8.4), PPh_3 (2.7). See: Rahman, M. M.; Liu, H, -Y; Eriks, K.; Prock, A.; Giering, W. P. *Organometallics* **1989**, *8*, 1.

(36) Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 715.

(37) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 6066.

(38) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1144.

(39) BINAP = (*R*), (*S*) or *rac*-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl.

(40) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 7217.

(41) DPPF = 1,1'-bis(diphenylphosphino)ferrocene.

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

(43) Kranenburg, M.; Delis, J. G. P.; Kamer, P. C. J.; van Leeuwen, P. W. N.; Vrieze, K.; Veldman, N.; Spek, A. L.; Goubitz, K.; Fraanje, J. *J. Chem. Soc., Dalton Trans.* **1997**, 1839.

(44) Yin, J.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 1101.

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

(46) XantPhos = 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene.

(47) Sadighi, J. P.; Harris, M. C.; Buchwald, S. L. *Tetrahedron Lett.* **1998**, *39*, 5327.

(48) DPEPhos = bis(2-phenylphosphinophenyl)ether.

(49) Wolfe, J. P.; Buchwald, S. L. *Tetrahedron Lett.* **1997**, *38*, 6359.

(50) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722.

(51) Reddy, N. P.; Tanaka, M. *Tetrahedron Lett.* **1997**, *38*, 4807.

(52) Shen, W. *Tetrahedron Lett.* **1997**, *38*, 5575.

(53) Nishiyama, M.; Yamamoto, T.; Koie, Y. *Tetrahedron Lett.* **1998**, *39*, 617.

(54) Yamamoto, T.; Nishiyama, M.; Koie, Y. *Tetrahedron Lett.* **1998**, *39*, 2367.

(55) Littke, A. F.; Fu, G. C. *Angew. Chem. Int. Ed.* **1998**, *37*, 3387.

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

(57) Littke, A. F.; Fu, G. C. *Angew. Chem. Int. Ed.* **1999**, *38*, 2411.

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

(59) Littke, A. F.; Fu, G. C. *J. Org. Chem.* **1999**, *64*, 10.

(60) Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989.

(61) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 1473.

(62) Beare, N. A.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 541.

(63) Hama, T.; Liu, X.; Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 11176.

(64) Liu, X.; Hartwig, J. F. *J. Am. Chem. Soc.* **2004**, *126*, 5182.

(65) Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575.

(66) Kuwano, R.; Utsunomiya, M.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 6479.

(67) Hooper, M. W.; Hartwig, J. F. *Organometallics* **2003**, *22*, 3394.

(68) Hooper, M. W.; Utsunomiya, M.; Hartwig, J. F. *J. Org. Chem.* **2003**, *68*, 2861.

(69) Hills, I. D.; Netherton, M. R.; Fu, G. C. *Angew. Chem. Int. Ed.* **2003**, *42*, 5749.

(70) Zhou, J. –R.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 12527.

(71) Lee, J. –Y.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 5616.

(72) Menzel, K.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 3718.

(73) Kirchhoff, J. H.; Netherton, M. R.; Hills, I. D.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 13662.

(74) Netherton, M. R.; Fu, G. C. *Angew. Chem. Int. Ed.* **2002**, *41*, 3910.

(75) Kirchhoff, J. H.; Dai, C.; Fu, G. C. *Angew. Chem. Int. Ed.* **2002**, *41*, 1945.

(76) Netherton, M. R.; Dai, C..; Neushchutz, K.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 10099.

(77) Hartwig, J. F. in *Handbook on Organopalladium Chemistry for Organic Synthesis*, Negishi, E. Ed., Wiley-Interscience, New York, **2002**, 1051-1096 and references within.

(78) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem. 2002,* 219, 131 and references within.

(79) Harkal, S.; Rataboul, F.; Zapf, A.; Fuhrmann, C.; Riermeier, T.; Monsees, A.; Beller, M. *Adv. Synth. Catal.* **2004**, *346*, 1742.

(80) Nandakumar, M. V.; Verkade, J. G. *Angew. Chem. Int. Ed.* **2005**, *44*, 3115.

(81) Viciu, M. S.; Kissling, R. M.; Stevens, E. D.; Nolan, S. P. *Org. Lett.* **2002**, *4*, 2229.

(82) Urgaonkar, S.; Verkade, J. G. *J. Org. Chem.* **2004**, *69*, 9135.

(83) Jiang, L.; Buchwald, S. L. Palladium-Catalyzed Aromatic Carbon-Nitrogen Bond Formation. In *Metal-Catalyzed Cross-Coupling Reactions*, 2nd Ed.: de Meijere, A.; Diederich, F. Eds; Wiley-VCH: Weinheim, 2004, pp. 699-760 and references within.

(84) Wolfe, J. P.; Wagaw, S.; Marcoux, J. F.; Buchwald, S. L. *Accounts Chem. Res.* **1998**, *31*, 805.

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

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

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

(88) Barder, T. E. *J. Am. Chem. Soc.* **2006**, *128*, 898.

(89) Strieter, E. R. *Unpublished Results*, **2004**.

(90) Alcazar-Roman, L. M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 12905.

(91) Schlummer, B.; Scholz, U. *Adv. Synth. Catal.* **2004**, *346*, 1599.

Chapter 1

Palladium-Catalyzed Amination of Aryl Nonaflates

Introduction

The palladium-catalyzed amination of aryl/heteroaryl halides has become an efficient and useful process for the preparation of various functionalized anilines.[1-6] The scope of this method was enhanced through the use of aryl triflates as compatible substrates due to the wide commercial availability of phenols.[7-12] While aryl triflates have worked well in many cases, base-promoted nucleophilic cleavage of the triflate moiety can occur with competitive rates that often lower the yields of desired product. Significant improvement was made through the use of weaker bases (e.g., Cs_2CO_3, K_3PO_4) or by slow addition of the aryl triflate, however, this protocol is not always successful or practical.[7-12] An attractive alternative to aryl triflates are aryl nonaflates (ArONf = $ArOSO_2(CF_2)_3CF_3$), which can be readily prepared from the corresponding phenol and are stable to chromatography and storage at room temperature.[13-19] Aryl nonaflates have been shown to have reactivity similar to aryl triflates in cross-coupling reactions (Suzuki-Miyuara,[20] Negishi,[21,22] phosphonation,[23,24] reduction,[25] organosilanol coupling[26]) and are more stable towards hydrolysis.[27] Further, alkenyl nonaflates have also shown utility in cross-coupling reactions.[28-38] However, to our knowledge, no detailed study of the palladium-catalyzed amination reactions of aryl nonaflates have been reported.[39,40] Herein we report a detailed study of the palladium-catalyzed amination of aryl nonaflates. In addition, we describe several examples for the selective amination of halo-aryl nonaflates.

Results and Discussion

Catalytic Amination of Electron-Rich and –Neutral Aryl Nonaflates. Initial attempts to couple aryl nonaflates with amines using a catalyst system comprised of Pd_2dba_3, biphenyl phosphine ligand **1** and K_3PO_4 in toluene, THF or DME at 80 °C (Scheme 1) gave little or none of the desired products. Increasing the reaction temperature to 105 °C led to the successful coupling of morpholine with aryl nonaflates. When primary alkyl amines and aromatic amines were used, however, the reaction failed. To our delight,

Scheme 1. Phosphine ligands used in Pd-catalyzed C-N bond-forming reactions.

R—⟨benzene⟩—ONf + HN(R')R" →(Pd catalyst, Ligand / Base, toluene r.t.-110°C / Nf = -SO$_2$(CF$_2$)$_3$CF$_3$ / 59-97 %)→ R—⟨benzene⟩—N(R')R"
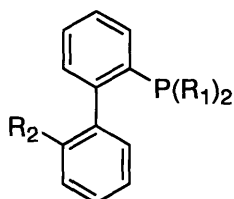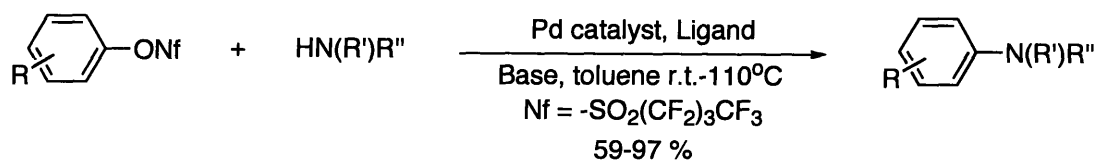
R$_1$ = Ph, R$_2$ = NMe$_2$ (1)
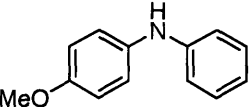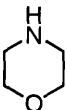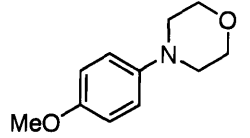R$_1$ = Cy, R$_2$ = NMe$_2$ (2)
R$_1$ = Cy, R$_2$ = H (3)
R$_1$ = ^{t}Bu, R$_2$ = H (4)
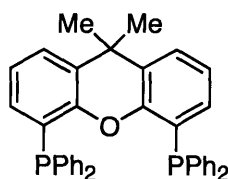
XantPhos (5)
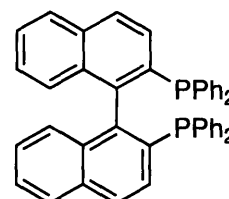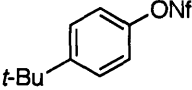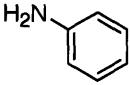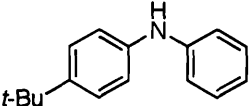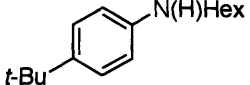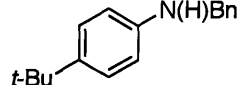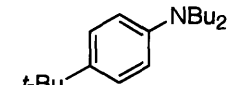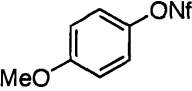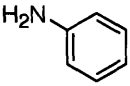
(+/-) BINAP (6)

using the more electron-rich, commercially available ligand **2** provided a catalyst system that proved to be effective in the amination of the majority of electron-rich or -neutral aryl nonaflates that were investigated (Table 1-2). Toluene proved to be the ideal solvent whereas use of more polar and coordinating solvents (e.g., THF or DME) gave much lower yields. Even sterically hindered aryl nonaflates gave excellent yields when utilizing this catalyst system (Table 2, entries 3-5). The ammonia equivalent benzophenone imine[41] proved to be an effective coupling partner when BINAP was used in place of **2** (Table 2, entry 5).

Room-Temperature Catalytic Amination of Aryl Nonaflates. The room temperature catalytic amination of neutral and electron-rich aryl nonaflates were accomplished using ligand **4** and NaOt-Bu as the base (Table 3). In some instances electron-rich aryl nonaflates could not be successfully coupled with primary alkyl amines at elevated temperatures (nonaflate cleavage to the corresponding phenol occurred) using **2**, however, the room temperature amination with **4** proceeded in good yields (Table 3, entries 6,7). Attempts to utilize electron-deficient aryl nonaflates at room temperature were unsuccessful; base-promoted nonaflate cleavage predominated. The use of

weaker bases for reactions carried out at room temperature was unsuccessful; full recovery of the starting aryl nonaflate was realized.

Table 1. Pd-Catalyzed amination of unactivated aryl nonaflates[a]

Entry	Nonaflate	Amine	Product	Ligand	Yield (%)[b]
1	t-Bu—⟨⟩—ONf	H₂N—⟨⟩		2	93[g]
2		H₂NHex		2	78[c,d,g]
3		H₂NBn		4	82[d,e]
4		HNBu₂		3	86[d,e]
5	MeO—⟨⟩—ONf	H₂N—⟨⟩		2	97[g]
6		morpholine		2	80[f,g]

[a]Reaction conditions: 1.0 equiv. of aryl nonaflate, 1.2 equiv. of amine, 1.4 equiv. of NaO*t*-Bu, Pd₂dba₃ (1 mol %), cat. ligand (L/Pd = 1/1), toluene (1.5-3.0 mL/mmol aryl nonaflate), 105 °C, 12-18 h. [b]Yields represent isolated yields of compounds estimated to be ≥ 95% pure as judged by ¹H NMR, GC analysis and combustion analysis. [c]K₃PO₄ used instead of NaO*t*-Bu. [d]Pd(OAc)₂ used in place of Pd₂dba₃. [e]Reaction was run at 80 °C. [f]2 mol % Pd₂dba₃ used. [g]Reactions were conducted by Maria Mendez-Perez and/or Julian Priego.

Catalytic Amination of Electron-Deficient Aryl Nonaflates. Electron deficient aryl nonaflates proved to be viable amination substrates at higher temperatures using the bidentate ligand XantPhos **5**[42-44] with K₃PO₄ as the base, whereas the use of **2** was ineffective (Table 4-5). In some cases it was necessary to increase the ligand/Pd ratio from 1/1 to 2/1 in order to maximize the yields (Table 4, entry 1,3). Using **5**, the coupling of 4-carboxymethylphenyl nonaflate and morpholine gave a 94% yield of the desired product (Table 4, entry 3) whereas under the same reaction conditions, the use of **2** gave a 54% yield. The reaction of this same aryl nonaflate with aniline could be achieved with either **2** or **5** with comparable results. Using **5**, 2-carboxymethyl nonaflate

could be combined with *n*-hexyl amine in excellent yield (Table 5, entry 1). This is in contrast with our results with the corresponding aryl triflate, in which low yields were generally obtained.[9] However, we are unaware of any reports in which the same transformation with a primary alkyl amine can be carried out with a 2-halobenzoic acid ester.

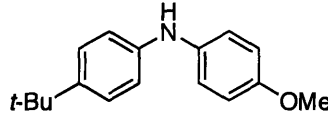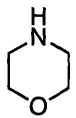**Table 2.** Pd-Catalyzed amination of unactivated 2-substituted aryl nonaflates[a]
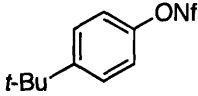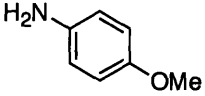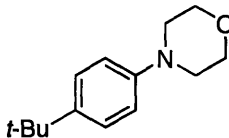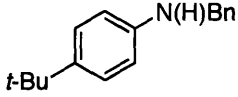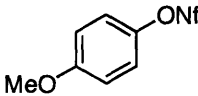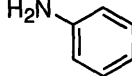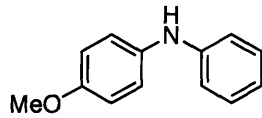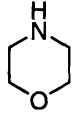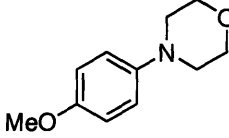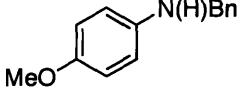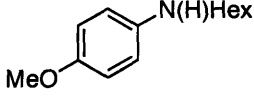
Entry	Nonaflate	Amine	Product	Ligand	Yield (%)[b]
1				2	86[c,f]
2		H₂NHex		2	84[c,f]
3				2	80
4				2	89[d]
5				6	97[e]

[a]Reaction conditions: 1.0 equiv. of aryl nonaflate, 1.2 equiv. of amine, 1.4 equiv. of NaO*t*-Bu, Pd₂dba₃ (1 mol %), cat. ligand (L/Pd = 1/1), toluene (1.5-3.0 mL/mmol aryl nonaflate), 105 °C, 12-18 h. [b]Yields represent isolated yields of compounds estimated to be ≥ 95% pure as judged by ¹H NMR, GC analysis and combustion analysis. [c]K₃PO₄ used instead of NaO*t*-Bu. [d]2 mol % Pd₂dba₃ used. [e]Best results were obtained when 4 Å molecular sieves were included in the reaction mixture. [f]Reactions were conducted by Maria Mendez-Perez and/or Julian Priego.

Using **5**, aryl nonaflates containing nitro and nitrile groups coupled efficiently with various amines, whereas with 4-acetylphenyl nonaflate, only the reaction with aniline was successful (Table 4, entry 6). We believe this is consistent with the notion that aryl triflate/nonaflate cleavage is due to *the combination of the base and amine*, as well as that aryl nonaflates are more stable towards cleavage. In Pd-catalyzed C-N bond-
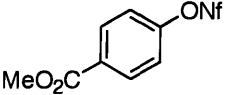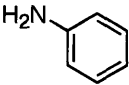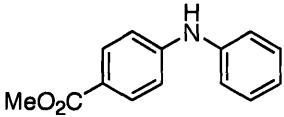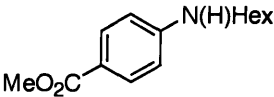
forming processes in general, reactions of anilines are more tolerant of functional groups than those with primary alkyl amines.
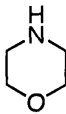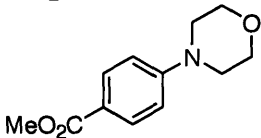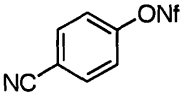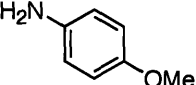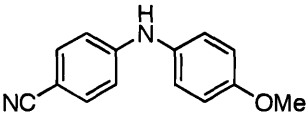
Table 3. Room-temperature catalytic amination of aryl nonaflates[a]

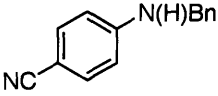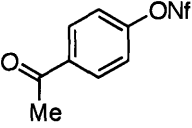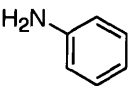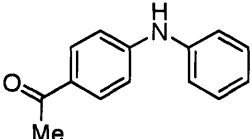| Entry	Nonaflate	Amine	Product	Yield (%)[b]
1	t-Bu—⬡—ONf	H₂N—⬡—OMe	t-Bu—⬡—N(H)—⬡—OMe	87[c]
2		HN(morpholine)	t-Bu—⬡—N(morpholine)	93
3		H₂NBn	t-Bu—⬡—N(H)Bn	88
4	MeO—⬡—ONf	H₂N—⬡	MeO—⬡—N(H)—⬡	91[c]
5		HN(morpholine)	MeO—⬡—N(morpholine)	85
6		H₂NBn	MeO—⬡—N(H)Bn	85
7		H₂NHex	MeO—⬡—N(H)Hex	82

[a]Reaction conditions: 1.0 equiv. of aryl nonaflate, 1.2 equiv. of amine, 1.4 equiv. of NaO*t*-Bu, Pd(OAc)$_2$ (1 mol %), cat. ligand **4** (L/Pd = 2/1), toluene (1.5-3.0 mL/mmol aryl nonaflate), r.t., 18-24 h. [b]Yields represent isolated yields of compounds estimated to be ≥ 95% pure as judged by ^{1}H NMR, GC analysis and combustion analysis. [c]Pd$_2$dba$_3$ used in place of Pd(OAc)$_2$.

Table 4. Pd-Catalyzed amination of functionalized aryl nonaflates[a]

Entry	Nonaflate	Amine	Product	Ligand	Yield (%)[b]
1	MeO₂C—⟨⟩—ONf	H₂N—⟨⟩	MeO₂C—⟨⟩—N(H)—⟨⟩	5	92[c,f]
2		H₂NHex	MeO₂C—⟨⟩—N(H)Hex	2	81[f]
3		morpholine (H–N–O)	MeO₂C—⟨⟩—N-morpholine	5	94[c,d,f]
4	NC—⟨⟩—ONf	H₂N—⟨⟩—OMe	NC—⟨⟩—N(H)—⟨⟩—OMe	5	94
5		H₂NBn	NC—⟨⟩—N(H)Bn	5	88[e]
6	O=C(Me)—⟨⟩—ONf	H₂N—⟨⟩	O=C(Me)—⟨⟩—N(H)—⟨⟩	5	97[f]

[a]Reaction conditions: 1.0 equiv. of aryl nonaflate, 1.2 equiv. of amine, 1.4 equiv. of K₃PO₄, Pd₂dba₃ (1 mol %), cat. ligand (L/Pd = 1/1), toluene (1.5 mL/mmol aryl nonaflate), 105 °C, 24 h. [b]Yields represent isolated yields of compounds estimated to be ≥ 95% pure as judged by ¹H NMR, GC analysis and combustion analysis. [c]L/Pd = 2/1 [d]2 mol %Pd₂dba₃ used. [e]5.0 equiv. of amine used. [f]Reactions were conducted by Maria Mendez-Perez and/or Julian Priego.

Catalytic Amination of Halo-Aryl Nonaflates. We were also interested in determining whether the chemoselective Pd-catalyzed amination of substrates bearing both nonaflate and halide groups could be affected. To this end, we examined reactions of aryl nonaflates bearing either chlorine or bromine substituents (Table 6-7). In many cases, selective substitution of the nonaflate moiety could be achieved in moderate to good yields using either **2** or BINAP **(6)**.[45] The use of other chelating phosphines such as XantPhos **5**, DPEPhos or dppf, proved to be totally ineffective for these substrates.[46,47] While with some aryl nonaflate/amine combinations K₃PO₄ was an effective base, in most cases employing NaO*t*-Bu was necessary to achieve full
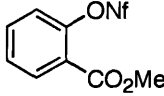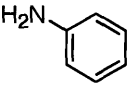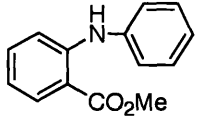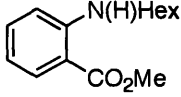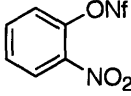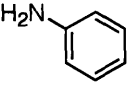
conversion and faster reaction times.[48] However, the use of NaO*t*-Bu generally led to higher degrees of nonaflate cleavage. This was particularly problematic for reactions involving bromo-aryl nonaflates and/or alkyl amines, in which a considerable amount of products resulting from reduction or substitution of both the halide and nonaflate occured.[49] All attempts to minimize these side reactions were met with little success. This included the use of Cs_2CO_3 in THF, the slow addition of NaO*t*-Am, which led to incomplete conversion of aryl nonaflate, as well as employing KO*t*-Bu or LiO*t*-Bu, which gave none of the desired product. Lowering the reaction temperature to 80 °C resulted in slight improvements in yield. Using $Pd(OAc)_2$ as an alternative palladium source resulted in lower reaction rates and selectivity in all cases. The addition of various halides (LiCl, LiBr, NaBr, KBr, NaF) or the use of higher catalyst loadings were either ineffective or produced dele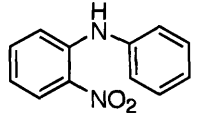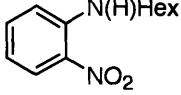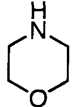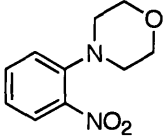terious effects.[50,51] Addition of LiI or various quantities of coordinating solvents (e.g., DMF or NMP) led to complete inhibition of the catalyst activity.

As shown in Table 6, chloro-aryl nonaflates proved to be the best substrates in this class, resulting in chemoselective amination of the nonaflate moiety in reasonable yields using **2** or BINAP **6** (entries 1-6).[52] Bromo-aryl nonaflates proved to be more challenging substrates resulting in much lower yields.

In all but one instance, the selective substitution of the nonaflate was observed. Interestingly when **4** was used, aniline was selectively substituted for the bromide in preference to the nonaflate (Table 7, entry 2).[50a,53]

In conclusion we have described the first detailed study of the Pd-catalyzed amination of a variety of aryl nonaflates. This work complements the existing methodology for amination of aryl triflates, particularly for substrates bearing electron-withdrawing substituents and in some cases allows the selective reaction of halo-aryl nonaflate substrates.
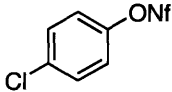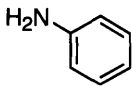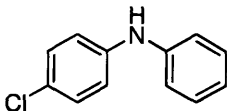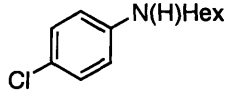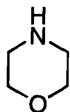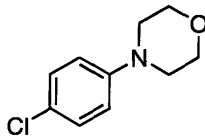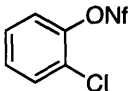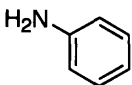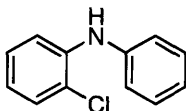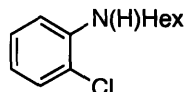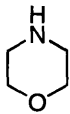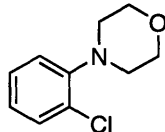
Table 5. Pd-Catalyzed amination of 2-substituted functionalized aryl nonaflates[a]

Entry	Nonaflate	Amine	Product	Ligand	Yield (%)[b]
1	ONf / CO_2Me	H_2N—	N(H)Ph / CO_2Me	**5**	91[c]
2		H_2NHex	N(H)Hex / CO_2Me	**5**	93[c]
3	ONf / NO_2	H_2N—	N(H)Ph / NO_2	**5**	97[c]
4		H_2NHex	N(H)Hex / NO_2	**5**	83[c]
5		morpholine	morpholino / NO_2	**5**	85[c]

[a]Reaction conditions: 1.0 equiv. of aryl nonaflate, 1.2 equiv. of amine, 1.4 equiv. of K_3PO_4, Pd_2dba_3 (1 mol %), cat. ligand (L/Pd = 1/1), toluene (1.5 mL/mmol aryl nonaflate), 105 °C, 24 h. [b]Yields represent isolated yields of compounds estimated to be ≥ 95% pure as judged by ^1H NMR, GC analysis and combustion analysis. [c]Reactions were conducted by Maria Mendez-Perez and/or Julian Priego.

Table 6. Pd-Catalyzed amination of chloro-aryl nonaflates.[a]

Entry	Nonaflate	Amine	Product	Ligand	Yield (%)[b]
1	4-Cl-phenyl ONf	H₂N-phenyl	Cl-C₆H₄-N(H)-phenyl	2	88[c,g]
2		H₂NHex	Cl-C₆H₄-N(H)Hex	2	63[g]
3		morpholine (NH)	Cl-C₆H₄-morpholine	6	77[g]
4	2-Cl-phenyl ONf	H₂N-phenyl	2-Cl-C₆H₄-N(H)-phenyl	2	87[c,e,f,g]
5		H₂NHex	2-Cl-C₆H₄-N(H)Hex	6	69[g]
6		morpholine (NH)	2-Cl-C₆H₄-morpholine	6	85[c,d,g]

[a]Reaction conditions: 1.0 equiv. of aryl nonaflate, 1.2 equiv. of amine, 1.4 equiv. of NaОt-Bu, Pd₂dba₃ (1 mol %), cat. ligand (L/Pd = 1/1), toluene (1.5 mL/mmol aryl nonaflate), 80-105 °C, 18-24 h. [b]Yields represent isolated yields of compounds estimated to be ≥ 95% pure as judged by ¹H NMR, GC analysis and combustion analysis. [c]K₃PO₄ used instead of NaОt-Bu. [d]Reaction took 39 h. [e]L/Pd = 2/1. [f]Reaction carried out at 60 °C. [g]Reactions were conducted by Maria Mendez-Perez and/or Julian Priego.

Table 7. Pd-Catalyzed amination of bromo-aryl nonaflates.[a]

Entry	Nonaflate	Amine	Product	Ligand	Yield (%)[b]
1				6	59[d]
2				4	68[c,d]
3				6	79[d]
4		H₂NHex		6	63[d]
5				6	66[d]

[a]Reaction conditions: 1.0 equiv. of aryl nonaflate, 1.2 equiv. of amine, 1.4 equiv. of NaO*t*-Bu, Pd₂dba₃ (1 mol %), cat. ligand (L/Pd = 1/1), toluene (1.5 mL/mmol aryl nonaflate), 80-105 °C, 18-24 h. [b]Yields represent isolated yields of compounds estimated to be ≥ 95% pure as judged by ¹H NMR, GC analysis and combustion analysis. [c]Reaction complete in 3 h. [d]Reactions were conducted by Maria Mendez-Perez and/or Julian Priego.

Experimental Section

Reagents. $Pd(OAc)_2$, Pd_2dba_3, and Ligands **1-6** were purchased from Strem Chemical Co. and used without further purification. NaOt-Bu was s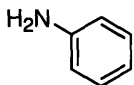tored under nitrogen in a Vacuum Atmosphere glovebox. Small portions (1-2 g) were removed from the glovebox in glass vials, stored in the air in desiccators filled with anhydrous calcium sulfate, and weighed in the air. Toluene, THF and dichloromethane were purchased from J. T. Baker in CYCLE-TAINER® solvent delivery kegs, which were vigorously purged with argon for 2 h, and further purified by passing the solvent through two packed columns of neutral alumina and copper (II) oxide under argon pressure. All other reagents were purchased from commercial sources and used without further purification.

Analytical methods. All reactions were carried out under an argon atmosphere in oven-dried glassware. IR spectra were obtained by placing neat samples directly on the DiComp probe of an ASI REACTIR *in situ* IR instrument. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian XL 300, Varian XL 500, or Bruker 400 MHz with chemical shifts reported in ppm relative to the residual deuterated solvent or the internal standard tetramethylsilane. Yield refers to isolated yields of compounds greater than 95% purity as determined by capillary gas chromatography (GC), and proton Nuclear Magnetic Resonance spectroscopy (^{1}H NMR) analysis. Yields for the preparation of starting materials (nonaflates) refer to a single experiment whereas those reported in Tables 1 to 7 are an average of two or more runs. The procedures described in this section are representative, thus, the yields may differ slightly from those given in Tables 1 to 7. ^{1}H NMR and melting points (where applicable) of all known compounds were taken. All new nonaflates and new amines were further characterized by elemental analysis except for N-[4-(nonafluorobutanesulfonyl)oxy]-phenyl-aniline (Table 7, entry 2) for which a HRMS was obtained. An significant portion of this work was initially conducted by Maria Mendez-Perez and Julian Priego. However, I had repeated and characterized all examples in Tables 1-7.

General Procedure for the Synthesis of Aryl Nonaflates (Method 1). A round bottom flask was charged with diethyl ether (4 mL/mmol phenol) and NaH (1.3 equiv.). The flask was cooled to 0 °C and a solution of phenol (1 equiv.) in diethyl ether (0.5

mL/mmol) was slowly added. After 15 minutes, nonafluorobutanesulfonic fluoride (1.4 equiv.) was added dropwise and the solution was allowed to warm to room temperature and stir for 12 h. To the reaction mixture was added water (30 mL) and diethyl ether (50 mL) and the organic layer was separated. The aqueous layer was extracted twice with diethyl ether (2x 10 mL) and the combined organic extracts were washed with aqueous NaOH (5%) and brine (20 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (eluting with ethyl acetate/hexane mixtures).

General Procedure for the Synthesis of Aryl Nonaflates (Method 2). A solution of phenol (1.0 equiv), cat. DMAP (0.05 equiv.), *i*-Pr$_2$NEt (1.2 equiv., 2.60 mL, 15.5 mmol) in dichloromethane (20 mL) was cooled to 0 °C in an ice bath and nonafluorobutanesulfonic fluoride (1.1 equiv.) was added dropwise. The solution was allowed to warm to room temperature and stir for 12 h after which the solution was poured into water (20 mL/mmol phenol). The organic layer was extracted with dichloromethane, washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/hexanes mixtures).

4-(*tert*-Butylphenyl) nonaflate. With Method 1, 4-*t*-Butyl-phenol (1.50 g, 10.0 mmol), sodium hydride (520 mg, 13.0 mmol, 60% dispersion), nonafluorobutanesulfonic fluoride (3.60 mL, 20.0 mmol) and diethyl ether (40 mL) were used. The crude material was purified by column chromatography on silica gel (eluting with pentanes) to give the title compound as a colorless oil (3.6 g, 84%). ^{1}H NMR (500 MHz, CDCl$_3$) δ: 7.44 (d, J = 8.9 Hz, 2H), 7.20 (d, J = 8.9 Hz, 2H), 1.33 (s, 9H). ^{13}C NMR (125 MHz, CDCl$_3$) δ: 151.7, 147.7, 127.2, 120.7, 109.9-118.3 (m, 4C), 34.7, 31.2. IR (neat, cm^{-1}): 2967, 1503, 1427, 1243, 1205, 1144, 896. Anal. Calcd for C$_{14}$H$_{13}$F$_9$O$_3$S: C, 38.90; H, 3.03. Found: C, 39.13; H, 3.01.

4-(Methoxyphenyl) nonaflate.[54] With Method 1, 4-Methoxyphenol (1.241 g, 10.10 mmol), sodium hydride (525 mg, 13.1 mmol, 60 % dispersion), nonafluorobutanesulfonic fluoride (3.60 mL, 20.2 mmol) and diethyl ether (40 mL) were used. The crude material was purified by column chromatography on silica gel (eluting with ethyl

acetate/hexanes, 1:10) to give the title compound as a colorless oil (3.2 g, 77%). ^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.21-7.25 (m, 2H), 6.98-7.05 (m, 2H), 3.82 (s, 3H). ^{13}C NMR (125 MHz, CDCl$_3$) δ: 159.1, 143.3, 122.4, 114.8, 109.4-118.3 (m, 4C), 55.7.

2-(Methylphenyl) nonaflate.[54] With Method 1, 2-Methylphenol (1.092 g, 10.10 mmol), sodium hydride (525 mg, 13.1 mmol, 60 % dispersion), nonafluorobutanesulfonic fluoride (3.60 mL, 20.2 mmol) and diethyl ether (40 mL) were used. The crude material was purified by column chromatography on silica gel (eluting with pentanes) to give the title compound as a colorless oil (2.5 g, 62%). ^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.25-7.29 (m, 4H), 2.40 (s, 3H). ^{13}C NMR (125 MHz, CDCl$_3$) δ: 148.7, 132.2, 131.0, 128.3, 127.7, 121.3, 109.4-118.3 (m, 4C), 16.4.

2,6-(Dimethylphenyl) nonaflate. With Method 2, 2,6-Dimethylphenol (1.899 g, 15.55 mmol), i-Pr$_2$NEt (3.25 mL, 18.7 mmol), nonafluorobutanesulfonic fluoride (3.07 mL, 17.1 mmol), DMAP (95 mg, 0.70 mmol), and dichloromethane (25 mL) were used. The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/hexanes, 1:9) to give the title compound as a colorless oil (3.7 g, 58%). ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.18-7.12 (m, 3H), 2.4 (s, 6H). ^{13}C NMR (125 MHz, CDCl$_3$) δ: 146.9, 131.9, 130.2, 128.3, 109.3-118.4 (m, 4C), 17.4. IR (neat, cm^{-1}): 1475, 1406, 1353, 1202, 1144, 1079, 1034, 887, 776. Anal. Calcd for C$_{12}$H$_9$F$_9$O$_3$S: C, 35.65; H, 2.24. Found: C, 35.68; H, 2.23.

Methyl 4-[(nonafluorobutanesulfonyl)oxy] benzoate. With Method 1, Methyl (4-hydroxy) benzoate (1.520 g, 10.00 mmol), sodium hydride (520 mg, 13.0 mmol, 60% dispersion), nonafluorobutanesulfonic fluoride (3.60 mL, 20.0 mmol) and diethyl ether (40 mL) were used. The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/hexanes, 1:10) to give the title compound as a as a colorless oil (3.6 g, 83%). ^{1}H NMR (500 MHz, CDCl$_3$) δ: 7.20 (dd, J = 9.2, 1.2 Hz, 2H), 6.92 (dd, J = 9.2, 1.2 Hz, 2H), 3.93 (s, 3H). ^{13}C NMR (125 MHz, CDCl$_3$) δ: 159.1, 143.3, 122.4, 114.8-118.3 (m, 3C), 115.0, 109.7 (m) 55.8. IR (neat, cm^{-1}): 1732, 1601, 1434, 1285, 1203, 1145, 893. Anal. Calcd for C$_{12}$H$_7$F$_9$O$_5$S: C, 33.19; H, 1.62. Found: C, 33.40; H, 1.61.

Methyl 2-[(nonafluorobutanesulfonyl)oxy] benzoate. With Method 1, Methyl (2-hydroxy) benzoate (1.30 mL, 10.0 mmol), sodium hydride (520 mg, 13.0 mmol, 60% dispersion), nonafluorobutanesulfonic fluoride (3.60 mL, 20.0 mmol) and diethyl ether (40 mL) were used. The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/hexanes, 1:10) to give the title compound as a white solid (3.2 g, 74%), Mp = 40-42 °C. ^{1}H NMR (300 MHz, CDCl$_3$) δ: 8.01 (d, J = 7.7 Hz, 1H), 7.64 (ddd, J = 8.2, 7.4, 1.9 Hz, 1H), 7.40 (td, J = 7.4, 1.1 Hz, 1H), 7.24 (d, J = 8.1 Hz, 1H), 3.89 (s, 3H). ^{13}C NMR (125 MHz, CDCl$_3$) δ: 164.2, 148.5, 134.3, 132.7, 128.4, 124.6, 122.8, 107.9-118.2 (m, 4C), 52.6. IR (neat, cm^{-1}): 1732, 1606, 1430, 1240, 1190, 1135, 895. Anal. Calcd for C$_{12}$H$_7$F$_9$O$_5$S: C, 33.19; H, 1.62. Found: C, 33.20; H, 1.60.

2-(Nitrophenyl) nonaflate. With Method 2, 2-Nitrophenol (1.30 g, 10.0 mmol), i-Pr$_2$NEt (2.10 mL, 12.0 mmol), nonafluorobutanesulfonic fluoride (1.90 mL, 11.0 mmol), DMAP (60 mg, 0.50 mmol), and dichloromethane (20 mL) were used. The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/hexanes, 1:6) to give the title compound as a white solid (2.7 g, 64%), Mp = 33-35 °C. ^{1}H NMR (300 MHz, CDCl$_3$) δ: 8.18 (dd, J = 8.0, 1.7 Hz, 1H), 7.67 (ddd, J = 8.2, 7.4, 1.9 Hz, 1H), 7.60 (td, J =7.7, 1.4 Hz, 1H), 7.50 (d, J = 7.7 Hz, 1H). ^{13}C NMR (125 MHz, CDCl$_3$) δ: 141.7, 135.2, 129.2, 126.7, 124.2, 109.0-118.4 (m, 4C), 99.3. IR (neat, cm^{-1}): 2921, 1601, 1538, 1434, 1235, 1200, 1142. Anal. Calcd for C$_{10}$H$_4$F$_9$O$_5$NS: C, 28.52; H, 0.96. Found: C, 28.49; H, 0.97.

4-(Nonafluorobutanesulfonyl)-benzonitrile. With Method 2, 4-Cyanophenol (1.852 g, 15.55 mmol), i-Pr$_2$NEt (3.25 mL, 18.7 mmol), nonafluorobutanesulfonic fluoride (3.07 mL, 17.1 mmol), DMAP (95 mg, 0.70 mmol), and dichloromethane (25 mL) were used. The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/hexanes, 1.5:8.5) to give the title compound as a white solid (5.5 g, 88%), Mp = 111-112 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.80 (d, J = 8.9 Hz, 2H), 7.44 (d, J = 8.8 Hz, 2H). ^{13}C NMR (100 MHz, CDCl$_3$) δ: 152.4, 134.7, 122.8, 117.3, 113.1, 109.2-18.7 (m, 4C). IR (neat, cm^{-1}): 2235, 1599, 1498, 1430, 1237, 1202, 1146, 889, 847. Anal. Calcd for C$_{11}$H$_4$F$_9$O$_3$NS: C, 32.93; H, 1.00. Found: C, 33.09; H, 1.00.

4-(Acetylphenyl) nonaflate. With Method 2, 4-Acetylphenol (1.36 g, 10.0 mmol), *i*-Pr$_2$NEt (2.10 mL, 12.0 mmol), nonafluorobutanesulfonic fluoride (1.90 mL, 11.0 mmol), DMAP (60 mg, 0.50 mmol), and dichloromethane (20 mL) were used. The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/hexanes, 1:4) to give the title compound as a white solid (3.9 g, 92%), Mp = 38-40 °C. ^{1}H NMR (300 MHz, CDCl$_3$) δ: 8.06 (d, *J* = 8.5 Hz, 2H), 7.39 (d, *J* = 8.5 Hz, 2H), 2.63 (s, 3H). ^{13}C NMR (125 MHz, CDCl$_3$) δ: 196.1, 152.7, 136.7, 130.6, 121.6, 96.7-118.1 (m, 4C), 26.7. IR (neat, cm^{-1}): 1694, 1594, 1422, 1356, 1265, 1203. Anal. Calcd for C$_{10}$H$_7$F$_9$O$_4$S: C, 34.46; H, 1.69. Found: C, 34.36; H, 1.70.

4-Chlorophenyl nonaflate.[54] With Method 1, 4-Chlorophenol (1.285 g, 10.00 mmol), sodium hydride (520 mg, 13.0 mmol, 60 % dispersion), nonafluorobutanesulfonic fluoride (3.60 mL, 20.0 mmol) and diethyl ether (40 mL) were used. The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/hexanes, 1:4) to give the title compound as a colorless oil (3.0 g, 73%). ^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.42 (d, *J* = 9.1 Hz, 2H), 7.23 (d, *J* = 9.1 Hz, 2H). ^{13}C NMR (125 MHz, CDCl$_3$) δ: 148.1, 134.3, 130.4, 122.7, 108.5-118.2 (m, 4C).

2-Chlorophenyl nonaflate. With Method 2, 2-Chlorophenol (1.29 g, 10.0 mmol), *i*-Pr$_2$NEt (2.10 mL, 12.0 mmol), nonafluorobutanesulfonic fluoride (1.90 mL, 11.0 mmol), DMAP (60 mg, 0.50 mmol), and dichloromethane (20 mL) were used. The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/hexanes, 1:10) to give the title compound as a colorless oil (3.9 g, 95%). ^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.51-7.55 (m, 3H), 7.31-7.38 (m, 1H). ^{13}C NMR (125 MHz, CDCl$_3$) δ: 145.9, 131.3, 129.2, 128.3, 127.5, 123.0, 107.7-118.2 (m, 4C). IR (neat, cm^{-1}): 1430, 1240, 1203, 1144, 890, 768. Anal. Calcd for C$_{10}$H$_4$F$_9$O$_3$SCl: C, 29.25; H, 0.98. Found: C, 29.05; H, 0.98.

4-Bromophenyl nonaflate. With Method 2, 4-Bromophenol (2.238 g, 12.94 mmol), *i*-Pr$_2$NEt (2.70 mL, 15.5 mmol), nonafluorobutanesulfonic fluoride (2.60 mL, 14.2 mmol), DMAP (79 mg, 0.60 mmol), and dichloromethane (25 mL) were used. The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/hexanes, 1:10) to give the title compound as a colorless oil (5.6 g, 96%). ^{1}H

NMR (300 MHz, CDCl$_3$) δ: 7.17 (d, J = 9.1 Hz, 2H), 7.59 (d, J = 9.3 Hz, 2H). ^{13}C NMR (125 MHz, CDCl$_3$) δ: 148.6, 133.3, 123.0, 121.9, 103.3-118.5 (m, 4C). IR (neat, cm^{-1}): 1481, 1430, 1240, 1204, 1146, 890. Anal. Calcd for C$_{10}$H$_4$F$_9$O$_3$SBr: C, 26.39; H, 0.89. Found: C, 26.19; H, 0.97.

2-Bromophenyl nonaflate. With Method 2, 2-Bromophenol (2.238 g, 12.94 mmol), i-Pr$_2$NEt (2.70 mL, 15.5 mmol), nonafluorobutanesulfonic fluoride (2.60 mL, 14.2 mmol), DMAP (79 mg, 0.60 mmol), and dichloromethane (25 mL) were used. The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/hexanes, 1:10) to give the title compound as a colorless oil (5.7 g, 98%). ^{1}H NMR (500 MHz, CDCl$_3$) δ: 7.51-7.54 (m, 1H), 7.25-7.37 (m, 3H). ^{13}C NMR (125 MHz, CDCl$_3$) δ: 147.3, 134.5, 129.5, 129.1, 122.9, 107.7-118.2 (m, 4C). IR (neat, cm^{-1}): 2926, 1431, 1240, 1202, 1144, 1033, 890. Anal. Calcd for C$_{10}$H$_4$F$_9$O$_3$SBr: C, 26.39; H, 0.89. Found: C, 26.61; H, 0.89.

General Procedure for Catalytic Amination of Aryl Nonaflates. An oven-dried resealable Schlenk flask was charged with Pd$_2$dba$_3$ (1 mol %, 2 mol % Pd) or Pd(OAc)$_2$ (2 mol % Pd), ligand (2-4 mol %) and base (1.4 equiv.). The flask was evacuated and backfilled with argon; this sequence was repeated two additional times. The flask was capped with a rubber septum and toluene (1.5 mL/mmol aryl nonaflate), the aryl nonaflate (1.0 equiv.) and the amine (1.2 equiv.) were added through the septum via syringe (aryl nonaflates or amines that were solids at room temperature were added prior to addition of the base). The septum was replaced with a Teflon screwcap, the flask was sealed, and the mixture was allowed to stir at room temperature or heated in an oil bath (80 °C or 105 °C) with stirring until the starting aryl nonaflate had been completely consumed as judged by GC analysis. The mixture was cooled to room temperature, diluted with diethyl ether (20 mL), filtered through Celite, and concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/hexane mixtures).

N-(4-*tert*-Butylphenyl)-aniline (Table 1, entry 1).[55] Using the general procedure, 4-(*tert*-Butylphenyl) nonaflate (432 mg, 1.00 mmol), Pd$_2$dba$_3$ (9.2 mg, 0.010 mmol), ligand **2** (7.8 mg, 0.020 mmol), aniline (0.109 mL, 1.20 mmol), and NaO*t*-Bu (135 mg, 1.40

mmol) in toluene (3 mL) was heated at 105 °C for 12 h. The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/hexane, 1:10) to give the title compound as a white solid (210 mg, 93%), Mp = 65-66 °C (lit.[55] 67 °C). ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.50 (d, J = 8.4 Hz, 2H), 7.46 (t, J = 7.2 Hz, 2H), 7.22 (m, 4H), 7.09 (t, J = 7.6 Hz, 1H), 5.76 (br-s, 1H), 1.55 (s, 9H).

N-(4-*tert*-Butylphenyl)-*n*-hexylamine (Table 1, entry 2).[56] Using the general procedure, 4-(*tert*-Butylphenyl) nonaflate (432 mg, 1.00 mmol), Pd$_2$dba$_3$ (9.2 mg, 0.010 mmol), ligand **2** (15.6 mg, 0.0400 mmol), *n*-hexylamine (0.159 mL, 1.20 mmol), and K$_3$PO$_4$ (297 mg, 1.40 mmol) in toluene (3 mL) was heated at 105 °C for 24 h. The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/hexane, 1:10) to give the title compound as a colorless oil (183 mg, 78%). ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.34 (d, J = 8.8 Hz, 2H), 6.68 (d, J = 8.8 Hz, 2H), 3.62 (br-s, 1H), 3.30 (t, J = 7.0 Hz, 2H), 1.72 (m, 2H), 1.36-1.54 (m, 6H), 1.41 (s, 9H), 1.04 (t, J = 6.8 Hz, 3H).

Benzyl-(4-*tert*-butylphenyl)-amine (Table 1, entry 3).[7] Using the general procedure, 4-(*tert*-Butylphenyl) nonaflate (216 mg, 0.500 mmol), Pd(OAc)$_2$ (1.1 mg, 0.0050 mmol), ligand **4** (3.0 mg, 0.010 mmol), benzyl amine (0.065 mL, 0.60 mmol), and NaO*t*-Bu (67 mg, 0.700 mmol) in toluene (1 mL) was heated at 80 °C for 21 h. The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/hexane, 1:9) to give the title compound as a colorless oil (94 mg, 78%). ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.38-7.51 (m, 5H), 7.33 (d, J = 8.8 Hz, 2H), 6.71 (d, J = 8.8 Hz, 2H), 4.40 (s, 2H), 4.02 (br-s, 1H), 1.40 (s, 9H).

Dibutyl-(4-*tert*-butylphenyl)-amine (Table 1, entry 4).[57] Using the general procedure, 4-(*tert*-Butylphenyl) nonaflate (216 mg, 0.500 mmol), Pd(OAc)$_2$ (1.1 mg, 0.0050 mmol), ligand **3** (3.5 mg, 0.010 mmol), di-*n*-butyl amine (0.101 mL, 0.600 mmol), and NaO*t*-Bu (67 mg, 0.70 mmol) in toluene (1 mL) was heated at 80 °C for 19 h. The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/hexane, 1:19) to give the title compound as a colorless oil (105 mg, 81%). ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.30 (d, J = 8.8 Hz, 2H), 6.66 (d, J = 8.8 Hz, 2H), 3.29 (t, J = 7.6 Hz, 4H), 1.62 (m, 4H), 1.41-1.44 (m, 4H), 1.39 (s, 9H), 1.04 (t, J = 7.2 Hz, 6H).

(4-Methoxyphenyl)-phenyl-amine (Table 1, entry 5).[58] Using the general procedure, 4-(Methoxyphenyl) nonaflate (203 mg, 0.500 mmol), Pd_2dba_3 (4.6 mg, 0.0050 mmol), ligand **2** (4.0 mg, 0.010 mmol), aniline (0.054 mL, 0.60 mmol), and NaO*t*-Bu (67 mg, 0.70 mmol) in toluene (1.5 mL) was heated at 105 °C for 20 h. The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/hexane, 1:9) to give the title compound as a white solid (96 mg, 98%), Mp = 99-101 °C (lit.[58] 98-100 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.12-7.18 (m, 2H), 7.00 (d, J = 8.9 Hz, 2H), 6.74-6.84 (m, 5H), 5.41 (br-s, 1H), 3.72 (s, 3H).

4-(4-Methoxyphenyl)-morpholine (Table 1, entry 6).[59] Using the general procedure, 4-(Methoxyphenyl) nonaflate (203 mg, 0.500 mmol), Pd_2dba_3 (4.6 mg, 0.0050 mmol), ligand **2** (8.0 mg, 0.020 mmol), morpholine (0.052 mL, 0.60 mmol), and NaO*t*-Bu (67 mg, 0.70 mmol) in toluene (0.75 mL) was heated at 105 °C for 20 h. The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/hexane, 1:4) to give the title compound as a white solid (76 mg, 80%), Mp = 72 °C (lit.[59] 73.3 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.84-6.91 (m, 4H), 3.86 (t, J = 4.8 Hz, 4H), 3.78 (s, 3H)., 3.06 (t, J = 4.5 Hz, 4H).

Phenyl-*o*-tolyl-amine (Table 2, entry 1).[58] Using the general procedure, 2-(Methylphenyl) nonaflate (200 mg, 0.510 mmol), Pd_2dba_3 (4.6 mg, 0.0050 mmol), ligand **2** (4.0 mg, 0.010 mmol), aniline (0.056 mL, 0.60 mmol), and K_3PO_4 (151 mg, 0.710 mmol) in toluene (1.5 mL) was heated at 105 °C for 24 h. The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/hexane, 1:10) to give the title compound as a white solid (81 mg, 86%), Mp = 37 °C (lit.[58] 38 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.20-7.30 (m, 4H), 7.17 (dd, J = 8.0 Hz, J = 7.0 Hz, 1H), 6.90-7.00 (m, 4H), 5.40 (br-s, 1H), 2.29 (s, 3H).

Hexyl-*o*-tolyl-amine (Table 2, entry 2).[60] Using the general procedure, 2-(Methylphenyl) nonaflate (200 mg, 0.510 mmol), Pd_2dba_3 (4.6 mg, 0.0050 mmol), ligand **2** (4.0 mg, 0.010 mmol), *n*-hexylamine (0.081 mL, 0.60 mmol), and K_3PO_4 (151 mg, 0.710 mmol) in toluene (1.5 mL) was heated at 105 °C for 24 h. The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/hexane, 1:10) to give the title compound as a yellow oil (82 mg, 84%). ^{1}H NMR (400 MHz,

CDCl$_3$) δ: 7.16-7.21 (m, 1H), 7.11 (d, J = 6.6 Hz, 1H), 6.66-6.73 (m, 2H), 3.44 (br-s, 1H), 3.21 (t, J = 7.1 Hz, 2H), 2.20 (s, 3H), 1.68-1.78 (m, 2H), 1.34-1.55 (m, 6H), 0.96-1.04 (m, 3H).

4-(2,6-Dimethylphenyl)-morpholine (Table 2, entry 3).[7] Using the general procedure, 2,6-(Dimethylphenyl) nonaflate (202 mg, 0.500 mmol), Pd$_2$dba$_3$ (4.6 mg, 0.0050 mmol), ligand **2** (4.0 mg, 0.010 mmol), morpholine (0.053 mL, 0.60 mmol), and NaO*t*-Bu (67 mg, 0.70 mmol) in toluene (1.5 mL) was heated at 105 °C for 24 h. The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/hexane, 1:9) to give the title compound as a light brown solid (76 mg, 80%): Mp = 86 °C (lit.[7] 86-87 °C). ^{1}H NMR (400 MHz, CDCl$_3$) δ: 6.99-7.06 (m, 3H), 3.85 (t, J = 4.4 Hz, 4H), 3.14 (t, J = 4.4 Hz, 4H), 2.40 (s, 6H).

(2,6-Diisopropylphenyl)-(2,6-dimethyl-phenyl)-amine (Table 2, entry 4).[7] Using the general procedure, 2,6-(Dimethylphenyl) nonaflate (202 mg, 0.500 mmol), Pd$_2$dba$_3$ (9.2 mg, 0.010 mmol), ligand **2** (8.0 mg, 0.020 mmol), 2,6-di-isopropyl aniline (0.113 mL, 0.600 mmol), and NaO*t*-Bu (67 mg, 0.70 mmol) in toluene (1.0 mL) was heated at 105 °C for 24 h. The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/hexane, 1:10) to give the title compound as a colorless oil (130 mg, 93%). ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.23-7.28 (m, 3H), 7.07 (d, J = 7.6 Hz, 2H), 6.86 (t, J = 7.6 Hz, 1H), 4.93 (br-s, 1H), 3.29 (m, 2H), 2.12 (s, 6H), 1.25 (d, J = 7.2 Hz, 12H).

Benzhydrylidene-(2,6-dimethylphenyl)-amine (Table 2, entry 5).[61] Using the general procedure, 2,6-(Dimethylphenyl) nonaflate (300 mg, 0.740 mmol), Pd$_2$dba$_3$ (6.8 mg, 0.0074 mmol), ligand **6** (18.5 mg, 0.0296 mmol), freshly distilled benzophenone imine (0.149 mL, 0.897 mmol), and NaO*t*-Bu (99 mg, 1.0 mmol) in toluene (2.5 mL) was heated at 105 °C for 24 h. The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/hexane, 1:19) to give the title compound as a yellow oil (206 mg, 97%). ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.77 (d, J = 8.4 Hz, 2H), 7.37-7.50 (m, 3H), 7.18-7.28 (m, 3H), 7.10 (d, J = 8.0 Hz, 2H), 6.88 (d, J = 7.2 Hz, 2H), 6.78 (t, J = 8.0 Hz, 1H), 2.04 (s, 6H).

(4-*tert*-Butylphenyl)-(4-methoxy-phenyl)-amine (Table 3, entry 1).[7] Using the general procedure, 4-(*tert*-Butylphenyl) nonaflate (432 mg, 1.00 mmol), Pd$_2$dba$_3$ (9.2 mg, 0.010 mmol), ligand **4** (7.5 mg, 0.025 mmol), 4-methoxy aniline (148 mg, 1.20 mmol), and NaO*t*-Bu (135 mg, 1.40 mmol) in toluene (3 mL) was stirred at room temperature for 28 h. The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/hexane, 1:10) to give the title compound as a white solid (222 mg, 87%), Mp = 80-81 °C (lit.[7] 80-82 °C). ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.40 (d, J = 8.6 Hz, 2H), 7.17 (d, J = 8.8 Hz, 2H), 7.03 (d, J = 8.6 Hz, 2H), 6.98 (d, J = 8.8 Hz, 2H), 5.60 (br-s, 1H), 3.90 (s, 3H), 1.46 (s, 9H).

4-(4-*tert*-Butylphenyl)-morpholine (Table 3, entry 2).[7] Using the general procedure, 4-(*tert*-Butylphenyl) nonaflate (432 mg, 1.00 mmol), Pd(OAc)$_2$ (2.2 mg, 0.010 mmol), ligand **4** (6.0 mg, 0.020 mmol), morpholine (0.106 mL, 1.20 mmol), and NaO*t*-Bu (135 mg, 1.40 mmol) in toluene (1.5 mL) was stirred at room temperature for 24 h (usually formed a gel within 1 h). The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/hexane, 1:10) to give the title compound as a white solid (198 mg, 90%), Mp = 58 °C (lit.[7] 59 °C). ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.40 (d, J = 8.8 Hz, 2H), 6.96 (d, J = 8.8 Hz, 2H), 3.94 (t, J = 4.8 Hz, 4H), 3.22 (t, J = 5.2 Hz, 4H), 1.41 (s, 9H).

Benzyl-(4-*tert*-butylphenyl)-amine (Table 3, entry 3).[7] Using the general procedure, 4-(*tert*-Butylphenyl) nonaflate (216 mg, 0.500 mmol), Pd(OAc)$_2$ (1.1 mg, 0.0050 mmol), ligand **4** (3.0 mg, 0.010 mmol), benzyl amine (0.065 mL, 0.60 mmol), and NaO*t*-Bu (67 mg, 0.70 mmol) in toluene (0.7 mL) was stirred at room temperature for 21 h (usually formed a gel within 1 h). The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/hexane, 1:9) to give the title compound as a colorless oil (105 mg, 88%). ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.38-7.51 (m, 5H), 7.33 (d, J = 8.8 Hz, 2H), 6.71 (d, J = 8.8 Hz, 2H), 4.40 (s, 2H), 4.02 (br-s, 1H), 1.40 (s, 9H).

(4-Methoxyphenyl)-phenyl-amine (Table 3, entry 4).[58] Using the general procedure, 4-(Methoxyphenyl) nonaflate (406 mg, 1.00 mmol), Pd$_2$dba$_3$ (9.2 mg, 0.010 mmol), ligand **2** (6.0 mg, 0.020 mmol), aniline (0.109 mL, 1.20 mmol), and NaO*t*-Bu (135 mg, 1.40 mmol) in toluene (1.5 mL) was stirred at room temperature (usually formed a gel

within 1h) for 24 h. The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/hexane, 1:9) to give the title compound as a white solid (182 mg, 92%), Mp = 100 °C (lit.[58] 98-100 °C). ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.12-7.18 (m, 2H), 7.00 (d, J = 8.9 Hz, 2H), 6.74-6.84 (m, 5H), 5.41 (br-s, 1H), 3.72 (s, 3H).

4-(4-Methoxy-phenyl)-morpholine (Table 3, entry 5).[59] Using the general procedure, 4-(Methoxyphenyl) nonaflate (406 mg, 1.00 mmol), Pd(OAc)$_2$ (2.2 mg, 0.010 mmol), ligand **2** (6.0 mg, 0.020 mmol), morpholine (0.106 mL, 1.20 mmol), and NaOt-Bu (135 mg, 1.40 mmol) in toluene (1.5 mL) was stirred at room temperature (usually formed a gel within 1h) for 24 h. The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/hexane, 3:7) to give the title compound as a white solid (170 mg, 88%), Mp = 71-72 °C (lit.[59] 73.3 °C). ^{1}H NMR (400 MHz, CDCl$_3$) δ: 6.84-6.91 (m, 4H), 3.86 (t, J = 4.8 Hz, 4H), 3.78 (s, 3H)., 3.06 (t, J = 4.5 Hz, 4H).

Benzyl-(4-methoxyphenyl)-amine (Table 3, entry 6).[62] Using the general procedure, 4-(Methoxyphenyl) nonaflate (406 mg, 1.00 mmol), Pd(OAc)$_2$ (2.2 mg, 0.010 mmol), ligand **2** (6.0 mg, 0.020 mmol), benzyl amine (0.131 mL, 1.20 mmol), and NaOt-Bu (135 mg, 1.40 mmol) in toluene (1.5 mL) was stirred at room temperature (usually formed a gel within 1h) for 24 h. The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/hexane, 1:9) to give the title compound as a colorless oil (181 mg, 85%). ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.38-7.46 (m, 5H), 6.91 (d, J = 8.8 Hz, 2H), 6.71 (d, J = 8.8 Hz, 2H), 4.38 (s, 2H), 3.91 (br-s, 1H), 3.84 (s, 3H).

N-(4-methoxyphenyl)-n-hexylamine (Table 3, entry 7). Using the general procedure, 4-(Methoxyphenyl) nonaflate (406 mg, 1.00 mmol), Pd(OAc)$_2$ (2.2 mg, 0.010 mmol), ligand **2** (6.0 mg, 0.020 mmol), n-hexylamine (0.159 mL, 1.20 mmol), and NaOt-Bu (135 mg, 1.40 mmol) in toluene (1.5 mL) was stirred at room temperature (usually formed a gel within 1 h) for 24 h. The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/hexane, 1:9) to give the title compound as a colorless oil (174 mg, 84%). ^{1}H NMR (300 MHz, CDCl$_3$) δ: 6.83 (d, J = 8.9 Hz, 2H), 6.63 (d, J = 8.9 Hz), 3.79 (s, 3H), 3.36 (br-s, 1H), 3.10 (t, J = 7.2 Hz, 2H), 1.64 (m, J = 7.7 Hz, 2H), 1.47-1.37 (m, 6H), 0.97 (t, J = 6.8 Hz, 3H). ^{13}C NMR (125 MHz, CDCl$_3$) δ: 151.9, 142.9, 114.9, 114.0, 55.8, 45.1, 31.8, 29.7, 27.0, 22.8, 14.2. IR (neat, cm^{-1}):

3393, 1619, 1514, 1294, 1236, 1179, 1040, 818. Anal. Calcd. For $C_{13}H_{21}NO$: C, 75.32; H, 10.21. Found: C, 75.58; H, 10.25.

N-(4-Methoxycarbonylphenyl)-aniline (Table 4, entry 1). Using the general procedure, Methyl 4-[(nonafluorobutanesulfonyl)oxy] benzoate (200 mg, 0.480 mmol), Pd_2dba_3 (4.2 mg, 0.0046 mmol), ligand 5 (11.0 mg, 0.0180 mmol), aniline (0.051 mL, 0.55 mmol), and K_3PO_4 (137 mg, 0.640 mmol) in toluene (1.5 mL) was stirred at 105 °C for 15 h. The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/hexane, 1:3) to give the title compound as a pale yellow solid (92 mg, 89%), Mp = 108-110 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.92 (dt, J = 8.8, 2.5 Hz, 2H), 7.33 (tt, J = 7.5, 1.6 Hz, 2H), 7.18 (d, J =7.4 Hz, 2H), 7.05 (t, J = 7.2 Hz, 1H), 6.97 (dt, J = 8.8, 2.5 Hz, 2H), 6.10 (br-s, 1H), 3.86 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.8, 147.9, 140.7, 131.3, 129.4, 122.9, 120.9, 120.3, 114.4, 51.7. IR (neat, cm^{-1}): 3343, 1695, 1592, 1280, 1170, 1109, 747. Anal. Calcd. For $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77. Found: C, 73.93; H, 5.92.

N-(4-Methoxycarbonylphenyl)-n-hexylamine (Table 4, entry 2).[7] Using the general procedure, Methyl 4-[(nonafluorobutanesulfonyl)oxy] benzoate (200 mg, 0.480 mmol), Pd_2dba_3 (4.2 mg, 0.0046 mmol), ligand 2 (3.6 mg, 0.0092 mmol), n-hexylamine (0.073 mL, 0.55 mmol), and K_3PO_4 (138 mg, 0.650 mmol) in toluene (0.9 mL) was stirred at 105 °C for 16 h. The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/hexane, 1:10) to give the title compound as a white solid (86 mg, 79%), Mp = 93-94 °C (lit.[7] 93-94 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.85 (d, J = 8.7 Hz, 2H), 6.52 (d, J= 8.7 Hz, 2H), 4.20 (br-s, 1H), 3.86 (s, 3H), 3.15 (t, J = 6.9 Hz, 2H), 1.50-1.70 (m, 3H), 1.25-1.46 (m, 5H), 0.90 (t, J = 6.6 Hz, 3H).

N-(4-Methoxycarbonylphenyl)-morpholine (Table 4, entry 3).[63] Using the general procedure, Methyl 4-[(nonafluorobutanesulfonyl)oxy] benzoate (200 mg, 0.480 mmol), Pd_2dba_3 (4.2 mg, 0.0046 mmol), ligand 5 (10.6 mg, 0.0184 mmol), morpholine (0.049 mL, 0.55 mmol), and K_3PO_4 (137 mg, 0.640 mmol) in toluene (1.5 mL) was stirred at 105 °C for 16 h. The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/hexane, 1:2) to give the title compound as a white solid (96 mg, 94%), Mp = 154-156 °C (lit.[63] 152-154 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.94 (d, J =

8.6 Hz, 2H), 6.86 (d, J = 8.8 Hz, 2H), 3.87 (s, 3H), 3.86 (t, J = 4.8 Hz, 4H), 3.29 (t, J = 4.8 Hz, 4H).

4-(4-Methoxyphenylamino)-benzonitrile. (Table 4, entry 4).[65] Using the general procedure, 4-(Nonafluorobutanesulfonyl)-benzonitrile (401 mg, 1.00 mmol), Pd$_2$dba$_3$ (9.2 mg, 0.010 mmol), ligand **5** (11.6 mg, 0.0200 mmol), p-anisidine (148 mg, 1.20 mmol), and K$_3$PO$_4$ (297 mg, 1.40 mmol) in toluene (3 mL) was stirred at 105 °C for 24 h. The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/hexane, 3:7) to give the title compound as a light yellow solid (206 mg, 92%), Mp = 100 °C (lit.[65] 99-100 °C). ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.39 (d, J = 8.8 Hz, 2H), 7.11 (d, J = 8.8 Hz, 2H), 6.91 (d, J = 8.9 Hz, 2H), 6.81 (d, J = 8.8 Hz, 2H), 6.31 (br-s, 1H), 3.81 (s, 3H).

4-Benzylamino-benzonitrile.[66] **(Table 4, entry 5).** Using the general procedure, 4-(Nonafluorobutanesulfonyl)-benzonitrile (401 mg, 1.00 mmol), Pd$_2$dba$_3$ (9.2 mg, 0.010 mmol), ligand **5** (11.6 mg, 0.0200 mmol), benzylamine (0.327 mL, 3.00 mmol), and K$_3$PO$_4$ (297 mg, 1.40 mmol) in THF (4 mL) was stirred at 65 °C for 24 h. The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/hexane, 1:4) to give the title compound as a light yellow solid (185 mg, 88%), Mp = 66 °C (lit.[66] 65 °C). ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.31-7.42 (m, 7H), 6.60 (d, J = 8.8 Hz, 2H), 5.01 (br-s, 1H), 4.39 (s, 2H).

N-(4-Acetylphenyl)-aniline (Table 4, entry 6).[67] Using the general procedure, 4-(Acetylphenyl) nonaflate (200 mg, 0.470 mmol), Pd$_2$dba$_3$ (4.4 mg, 0.0048 mmol), ligand **5** (5.5 mg, 0.0096 mmol), aniline (0.053 mL, 0.57 mmol), and K$_3$PO$_4$ (143 mg, 0.670 mmol) in toluene (0.75 mL) was stirred at 105 °C for 14 h. The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/hexane, 1:6) to give the title compound as a yellow solid (92 mg, 91%), Mp = 104-105 °C (lit.[67] 106 °C). ^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.86 (d, J = 8.8 Hz, 2H), 7.35 (t, J = 7.4 Hz, 2H), 7.18 (d, J = 7.4 Hz, 2H), 7.09 (t, J = 7.4 Hz, 1H), 6.99 (m, J = 8.8 Hz, 2H), 6.15 (br-s, 1H), 2.53 (s, 3H).

N-(2-Methoxycarbonylphenyl)-aniline (Table 5, entry 1).[64] Using the general procedure, Methyl 2-[(nonafluorobutanesulfonyl)oxy] benzoate (200 mg, 0.480 mmol),

Pd$_2$dba$_3$ (4.2 mg, 0.0046 mmol), ligand **5** (5.3 mg, 0.0092 mmol), aniline (0.051 mL, 0.55 mmol), and K$_3$PO$_4$ (137 mg, 0.640 mmol) in toluene (1.5 mL) was stirred at 105 °C for 14 h. The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/hexane, 1:10) to give the title compound as a pale yellow solid (95 mg, 91%), Mp = 52-54 °C (lit.[64] 54-56 °C). ^{1}H NMR (300 MHz, CDCl$_3$) δ: 9.49 (br-s, 1H), 7.98 (d, J = 8.4 Hz, 1H), 7.38-7.25 (m, 6H), 7.10 (m, 1H), 6.77-6.71 (m, 1H), 3.91 (s, 3H).

N-(2-Methoxycarbonylphenyl)-n-hexylamine (Table 5, entry 2). Using the general procedure, Methyl 2-[(nonafluorobutanesulfonyl)oxy] benzoate (200 mg, 0.480 mmol), Pd$_2$dba$_3$ (4.2 mg, 0.0046 mmol), ligand **5** (5.3 mg, 0.0092 mmol), n-hexylamine (0.073 mL, 0.55 mmol), and K$_3$PO$_4$ (137 mg, 0.640 mmol) in toluene (1.5 mL) was stirred at 105 °C for 15 h. The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/hexane, 1:20) to give the title compound as a colorless oil (100 mg, 93%): ^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.89 (dd, J = 7.9, 1.7 Hz, 1H), 7.69 (br-s, 1H), 7.35 (m, 1H), 6.68 (d, J = 7.7 Hz, 1H), 6.57 (t, J = 7.2 Hz, 1H), 3.86 (br-s, 3H), 3.19 (t, J = 6.9 Hz, 2H), 1.65-1.75 (m, 2H), 1.31-1.49 (m, 6H), 0.52 (t, J = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, CDCl$_3$) δ: 169.0, 151.1, 134.5, 131.5, 114.0, 111.1, 109.4, 51.4, 42.9, 31.7, 29.2, 26.9, 22.7, 14.2. IR (neat, cm^{-1}): 3365, 1686, 1581, 1518, 1450, 1259, 1169, 749. Anal. Calcd. For C$_{14}$H$_{21}$NO$_2$: C, 71.46; H, 8.99. Found: C, 71.26; H, 9.03.

N-(2-Nitrophenyl)-aniline (Table 5, entry 3). Using the general procedure, 2-(Nitrophenyl) nonaflate (200 mg, 0.470 mmol), Pd$_2$dba$_3$ (4.3 mg, 0.0047 mmol), ligand **5** (5.4 mg, 0.0094 mmol), aniline (0.052 mL, 0.56 mmol), and K$_3$PO$_4$ (140 mg, 0.660 mmol) in toluene (1.8 mL) was stirred at 105 °C for 13 h. The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/hexane, 1:6) to give the title compound as a orange oil (98 mg, 97%). ^{1}H NMR (300 MHz, CDCl$_3$) δ: 9.49 (br-s, 1H), 8.20 (dd, J = 8.5, 1.6 Hz, 1H), 7.34-7.44 (m, 3H), 7.21-7.33 (m, 4H), 6.74-6.79 (m, 1H). ^{13}C NMR (75 MHz, CDCl$_3$) δ: 142.9, 138.5, 135.6, 133.0, 129.6, 126.5, 125.5, 124.2, 117.4, 115.9. IR (neat, cm^{-1}): 3352, 3063, 1614, 1573, 1504, 1348, 1263, 1148, 741. Anal. Calcd. For C$_{12}$H$_{10}$N$_2$O$_2$: C, 67.28; H, 4.71. Found: C, 67.52; H, 4.71.

N-(2-Nitrophenyl)-n-hexylamine (Table 5, entry 4). Using the general procedure, 2-(Nitrophenyl) nonaflate (200 mg, 0.470 mmol), Pd_2dba_3 (4.3 mg, 0.0047 mmol), ligand **5** (5.4 mg, 0.0094 mmol), n-hexylamine (0.075 mL, 0.56 mmol), and K_3PO_4 (140 mg, 0.660 mmol) in toluene (1.8 mL) was stirred at 105 °C for 13 h. The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/hexane, 1:10) to give the title compound as a bright orange oil (86 mg, 83%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.15 (d, J = 8.8 Hz, 1H), 8.10 (br-s, 1H), 7.38-7.45 (m, 1H), 6.84 (d, J = 8.8 Hz, 1H), 5.59-6.64 (m, 1H), 3.29 (t, J = 7.1 Hz, 2H), 1.68-1.78 (m, 2H), 1.25-1.49 (m, 6H), 0.75-0.93 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 145.6, 136.2, 131.7, 126.9, 115.0, 113.8, 43.0, 31.5, 28.9, 26.3, 22.5, 14.0. IR (neat, cm^{-1}): 3381, 1618, 1510, 1350, 1260, 1156, 1038. Anal. Calcd. For $C_{12}H_{18}N_2O_2$: C, 64.84; H, 8.16. Found: C, 65.07; H, 8.20.

N-(2-Nitrophenyl)-morpholine (Table 5, entry 5). Using the general procedure, 2-(Nitrophenyl) nonaflate (200 mg, 0.470 mmol), Pd_2dba_3 (4.3 mg, 0.0047 mmol), ligand **5** (5.4 mg, 0.0094 mmol), morpholine (0.049 mL, 0.56 mmol), and K_3PO_4 (140 mg, 0.660 mmol) in toluene (1.8 mL) was stirred at 105 °C for 13 h. The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/hexane, 1:4) to give the title compound as a bright yellow oil (83 mg, 85%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.78 (dt, J = 7.9, 1.2 Hz, 1H), 7.50 (d, J = 6.4 Hz, 1H), 7.16 (d, J = 7.4 Hz, 1H), 7.09 (t, J = 6.1 Hz, 1H), 3.85 (t, J = 4.6 Hz, 4H), 3.06 (t, J = 4.6 Hz, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 145.8, 143.3, 133.6, 125.9, 122.3, 120.8, 66.8, 52.1. IR (neat, cm^{-1}): 2961, 2856,1605, 1520, 1344, 1115, 936, 754. Anal. Calcd. For $C_{10}H_{12}N_2O_3$: C, 57.68; H, 5.81. Found: C, 57.59; H, 5.84.

N-(4-Chlorophenyl)-aniline (Table 6, entry 1).[68] Using the general procedure, 4-(Chlorophenyl) nonaflate (200 mg, 0.490 mmol), Pd_2dba_3 (4.5 mg, 0.0049 mmol), ligand **2** (3.4 mg, 0.0097 mmol), aniline (0.054 mL, 0.59 mmol), and K_3PO_4 (146 mg, 0.690 mmol) in toluene (1.5 mL) was stirred at 105 °C for 13 h. The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/hexane, 1:4) to give the title compound as a yellow solid (95 mg, 95%), Mp = 72-74 °C (lit.[68] 74 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.19-7.29 (m, 4H), 6.96-7.15 (m, 5H), 5.64 (br-s, 1H).

N-(4-Chlorophenyl)-n-hexylamine (Table 6, entry 2).[68] Using the general procedure, 4-(Chlorophenyl) nonaflate (200 mg, 0.490 mmol), Pd$_2$dba$_3$ (4.5 mg, 0.0049 mmol), ligand **2** (3.9 mg, 0.0010 mmol), n-hexylamine (0.078 mL, 0.60 mmol), and NaOt-Bu (66 mg, 0.680 mmol) in toluene (1.5 mL) was stirred at 105 °C for 16 h. The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/hexane, 1:10) to give the title compound as a colorless oil (60 mg, 59%). ^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.00 (d, J = 8.8 Hz, 2H), 6.41 (d, J = 8.8 Hz, 2H), 3.50 (br-s, 1H), 2.97 (t, J = 7.1 Hz, 2H), 1.49-1.52 (m, 2H), 1.22-1.28 (m, 6H), 0.82 (t, J = 6.6 Hz, 3H).

N-(4-Chlorophenyl)-morpholine (Table 6, entry 3).[69] Using the general procedure, 4-(Chlorophenyl) nonaflate (200 mg, 0.490 mmol), Pd$_2$dba$_3$ (9.0 mg, 0.0098 mmol), ligand **6** (24.0 mg, 0.0392 mmol), morpholine (0.052 mL, 0.59 mmol), and K$_3$PO$_4$ (146 mg, 0.690 mmol) in toluene (1.5 mL) was stirred at 105 °C for 21 h. The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/hexane, 1:10) to give the title compound as a pale yellow solid (66 mg, 68%), Mp = 69-70 °C (lit.[69] 71-72 °C). ^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.21 (d, J = 6.9 Hz, 2H), 6.81 (d, J = 6.9 Hz, 2H), 3.84 (t, J = 6.6 Hz, 4H), 3.11 (t, J = 6.6 Hz, 4H).

N-(2-Chlorophenyl)-aniline (Table 6, entry 4). Using the general procedure, 2-(Chlorophenyl) nonaflate (200 mg, 0.490 mmol), Pd$_2$dba$_3$ (4.5 mg, 0.0049 mmol), ligand **2** (8.0 mg, 0.020 mmol), aniline (0.054 mL, 0.59 mmol), and K$_3$PO$_4$ (146 mg, 0.690 mmol) in toluene (1.5 mL) was stirred at 60 °C for 24 h. The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/hexane, 1:6) to give the title compound as a colorless oil (82 mg, 83%). ^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.02-7.35 (m, 8H), 6.75-6.99 (m, 1H), 6.08 (br-s, 1H). ^{13}C NMR (75 MHz, CDCl$_3$) δ: 141.5, 140.2, 129.4, 127.4, 122.6, 121.5, 120.3, 120.1, 115.5. IR (neat, cm^{-1}): 3401, 1587, 1503, 1311, 1090, 750. Anal. Calcd. For C$_{12}$H$_{10}$ClN: C, 70.77; H, 4.95. Found: C, 70.83; H, 4.98.

N-(2-Chlorophenyl)-n-hexylamine (Table 6, entry 5). Using the general procedure, 2-(Chlorophenyl) nonaflate (200 mg, 0.490 mmol), Pd$_2$dba$_3$ (4.5 mg, 0.0049 mmol), ligand **6** (12.3 mg, 0.0200 mmol), n-hexylamine (0.078 mL, 0.60 mmol), and NaOt-Bu (66 mg, 0.70 mmol) in toluene (1.5 mL) was stirred at 105 °C for 24 h. The crude material was

purified by column chromatography on silica gel (eluting with ethyl acetate/hexane, 1:10) to give the title compound as a colorless oil (78 mg, 75 %). ^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.09-7.25 (m, 2H), 6.57-6.65 (m, 2H), 4.25 (br-s, 1H), 3.14 (t, J = 7.0 Hz, 2H), 1.61-1.69 (m, 2H), 1.00-1.44 (m, 6H), 0.91 (t, J = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, CDCl$_3$) δ: 128.9, 127.7, 116.7, 111.0, 43.7, 31.7, 29.3, 26.9, 22.7, 14.1. IR (neat, cm^{-1}): 3421, 2927, 2856, 1599, 1514, 1328, 1033, 739. Anal. Calcd. For C$_{12}$H$_{18}$ClN: C, 68.07; H, 8.57. Found: C, 68.15; H, 8.60.

N-(2-Chlorophenyl)-morpholine (Table 6, entry 6).[70] Using the general procedure, 2-(Chlorophenyl) nonaflate (200 mg, 0.490 mmol), Pd$_2$dba$_3$ (4.5 mg, 0.0049 mmol), ligand **6** (12.3 mg, 0.0200 mmol), morpholine (0.052 mL, 0.59 mmol), and K$_3$PO$_4$ (146 mg, 0.690 mmol) in toluene (1.5 mL) was stirred at 105 °C for 40 h. The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/hexane, 1:10) to give the title compound as a colorless oil (96 mg, 78%). ^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.36 (dd, J = 2.0 Hz, J = 10.4 Hz, 1H), 7.21-7.26 (m, 1H), 7.04 (dd, J = 2.0 Hz, J = 10.8 Hz, 1H), 6.97-7.02 (m, 1H), 4.09 (t, J = 4.5 Hz, 4H), 3.27 (t, J = 4.5 Hz, 4H).

N-(4-Bromophenyl)-aniline (Table 7, entry 1).[68] Using the general procedure, 4-(Bromophenyl) nonaflate (200 mg, 0.440 mmol), Pd$_2$dba$_3$ (4.0 mg, 0.0046 mmol), ligand **6** (12.3 mg, 0.0200 mmol), aniline (0.048 mL, 0.53 mmol), and NaOt-Bu (60 mg, 0.62 mmol) in toluene (1.5 mL) was stirred at 105 °C for 24 h. The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/hexane, 1:10) to give the title compound as a tan solid (53 mg, 49%), Mp = 87-89 °C (lit.[68] 88 °C). ^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.31-7.34 (m, 2H), 6.99-7.29 (m, 7H), 5.70 (br-s, 1H).

N-[4-(Nonafluorobutanesulfonyl)oxy]-phenyl-aniline (Table 7, entry 2). Using the general procedure, 4-(Bromophenyl) nonaflate (200 mg, 0.440 mmol), Pd$_2$dba$_3$ (8.0 mg, 0.0088 mmol), ligand **4** (5.2 mg, 0.0176 mmol), aniline (0.048 mL, 0.53 mmol), and NaOt-Bu (60 mg, 0.62 mmol) in toluene (2.0 mL) was stirred at 80 °C for 15 h. The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/hexane, 1:4) to give the title compound as a yellow oil (102 mg, 50%). ^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.31-7.34 (m, 2H), 6.99-7.29 (m, 7H). ^{13}C NMR (75 MHz, CDCl$_3$) δ: 143.6, 142.7, 141.5, 129.4, 122.4, 122.3, 119.2, 117.2. IR (neat, cm^{-1}): 3419, 3060,

1593, 1504, 1422, 1350, 1240, 1144, 1035, 1010, 890, 751. HRMS (EI) calculated for $C_{16}H_{10}NF_9O_3S$: 467.2038. Found: 467.2039.

N-(4-Bromophenyl)-morpholine (Table 7, entry 3).[71] Using the general procedure, 4-(Bromophenyl) nonaflate (200 mg, 0.440 mmol), Pd_2dba_3 (4.0 mg, 0.0044mmol), ligand **6** (5.6 mg, 0.009 mmol), morpholine (0.046 mL, 0.53 mmol), and NaOt-Bu (60 mg, 0.62 mmol) in toluene (1.5 mL) was stirred at 105 °C for 12 h. The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/hexane, 1:10) to give the title compound as a white solid (79 mg, 75%), Mp = 111-112 °C (lit.[71] 112-113 °C). ^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.34 (d, J = 8.8 Hz, 2H), 6.67 (d, J = 9.0 Hz, 2H), 3.85 (t, J = 4.8 Hz, 4H), 3.12 (t, J = 4.8 Hz, 4H).

N-(4-Bromophenyl)-n-hexylamine (Table 7, entry 4).[71] Using the general procedure, 4-(Bromophenyl) nonaflate (200 mg, 0.440 mmol), Pd_2dba_3 (4.0 mg, 0.0044mmol), ligand **6** (5.6 mg, 0.009 mmol), n-hexylamine (0.070 mL, 0.53 mmol), and NaOt-Bu (60 mg, 0.62 mmol) in toluene (1.5 mL) was stirred at 105 °C for 24 h. The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/hexane, 1:6) to give the title compound as a colorless oil (48 mg, 52%). ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.27 (d, J = 8.8 Hz, 2H), 6.50 (d, J = 8.8 Hz, 2H), 3.66 (br-s, 1H), 3.08 (t, J = 7.2 Hz, 2H), 1.63 (m, 2H), 1.40-1.44 (m, 6H), 0.94 (t, J = 6.9 Hz, 3H).

N-(2-Bromophenyl)-morpholine (Table 7, entry 5).[72] Using the general procedure, 2-(Bromophenyl) nonaflate (200 mg, 0.440 mmol), Pd_2dba_3 (4.0 mg, 0.0044 mmol), ligand **6** (11.0 mg, 0.0176 mmol), morpholine (0.047 mL, 0.53 mmol), and NaOt-Bu (60 mg, 0.62 mmol) in toluene (2.0 mL) was stirred at 105 °C for 24 h. The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/hexane, 1:10) to give the title compound as a colorless oil (84 mg, 78%). ^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.55 (d, J = 8.0 Hz, 1H), 7.27 (t, J = 8.0 Hz, 1H), 7.04 (d, J = 8.0 Hz, 1H), 6.92 (t, J = 8.0 Hz, 1H), 3.88 (t, J = 4.5 Hz, 4H), 3.06 (t, J = 4.6 Hz, 4H).
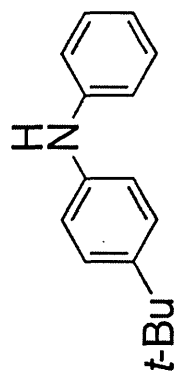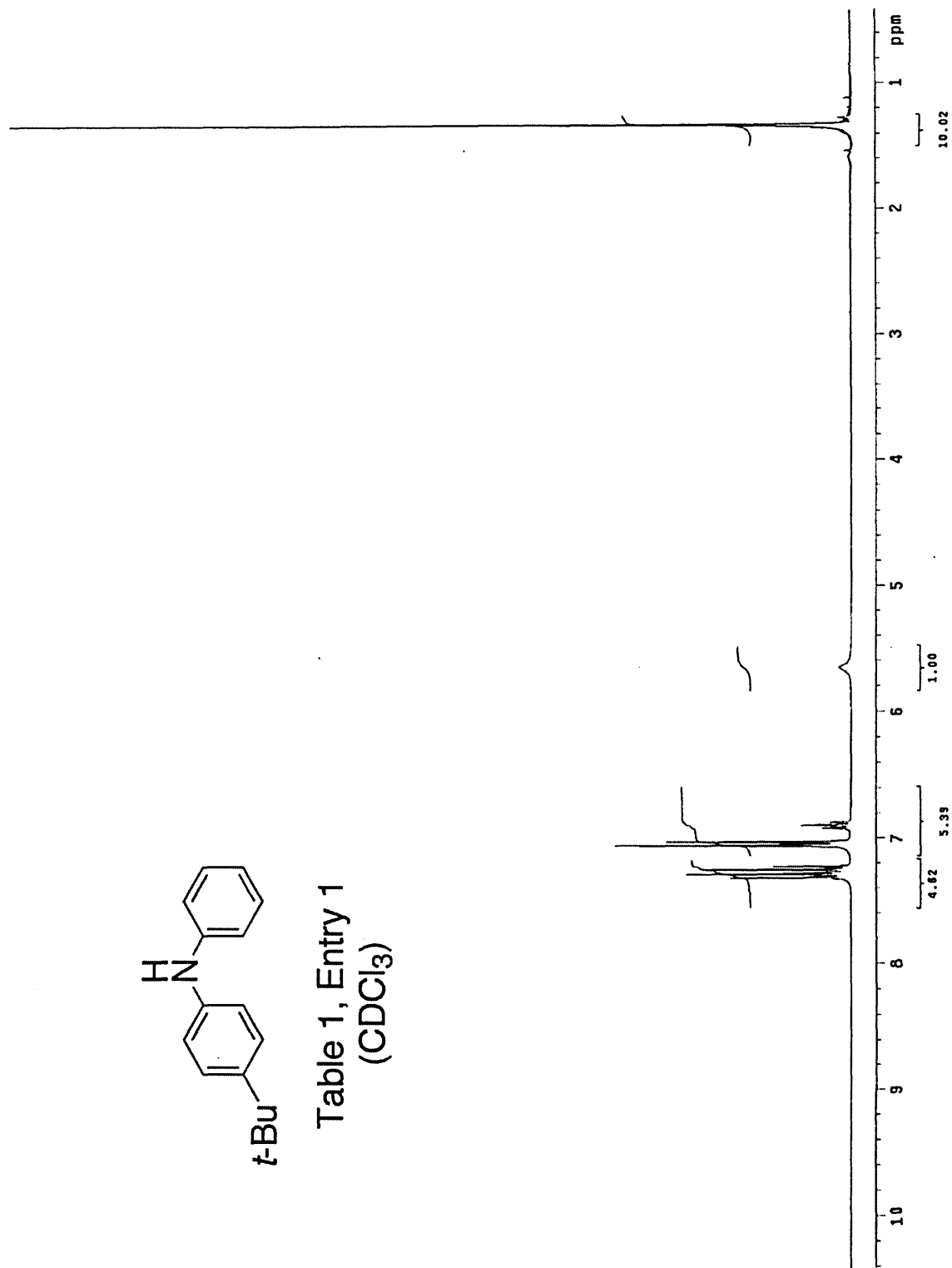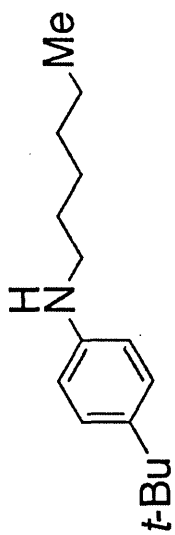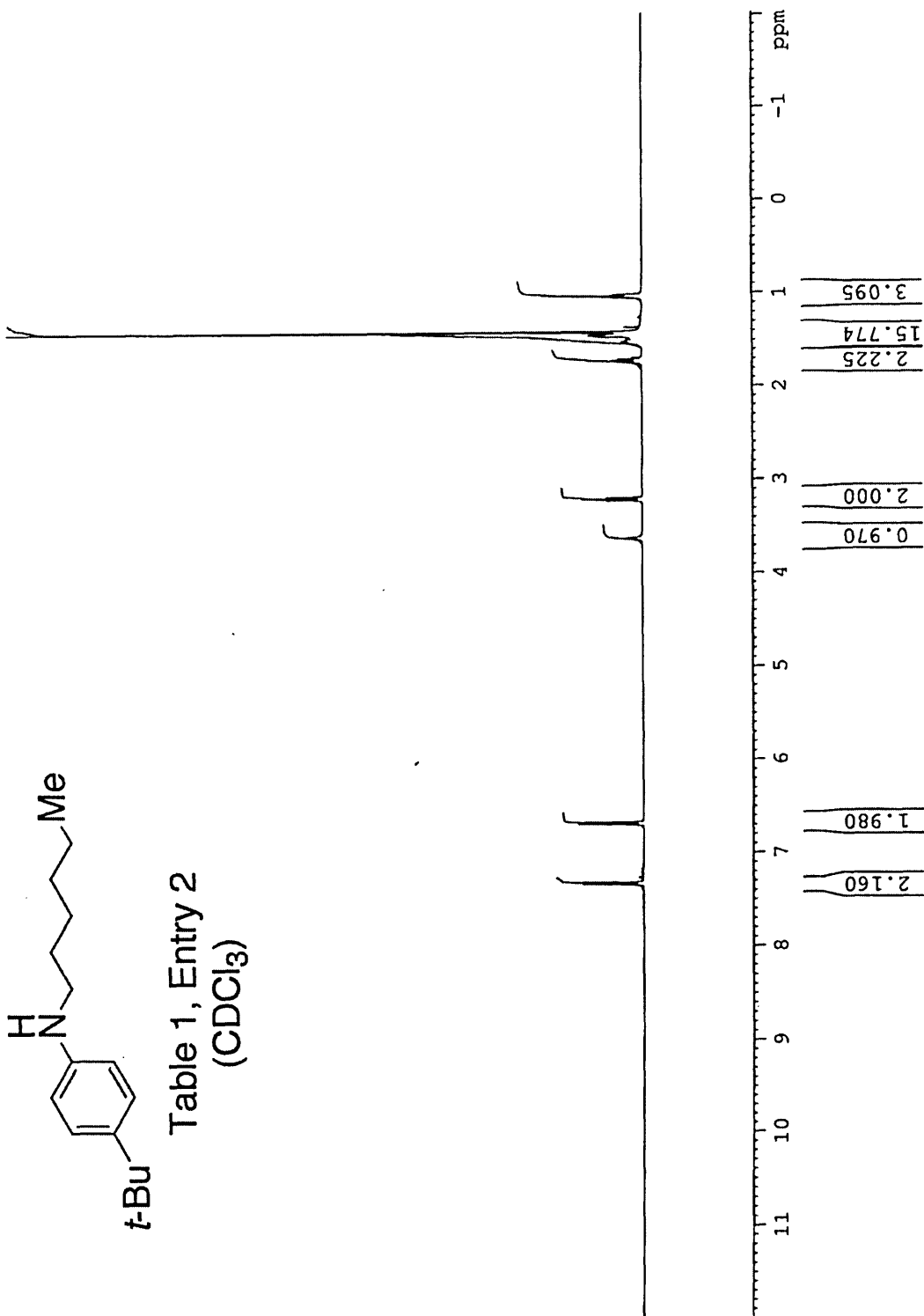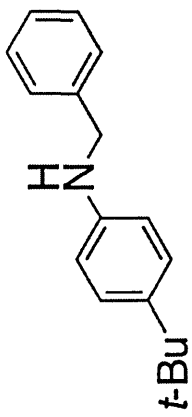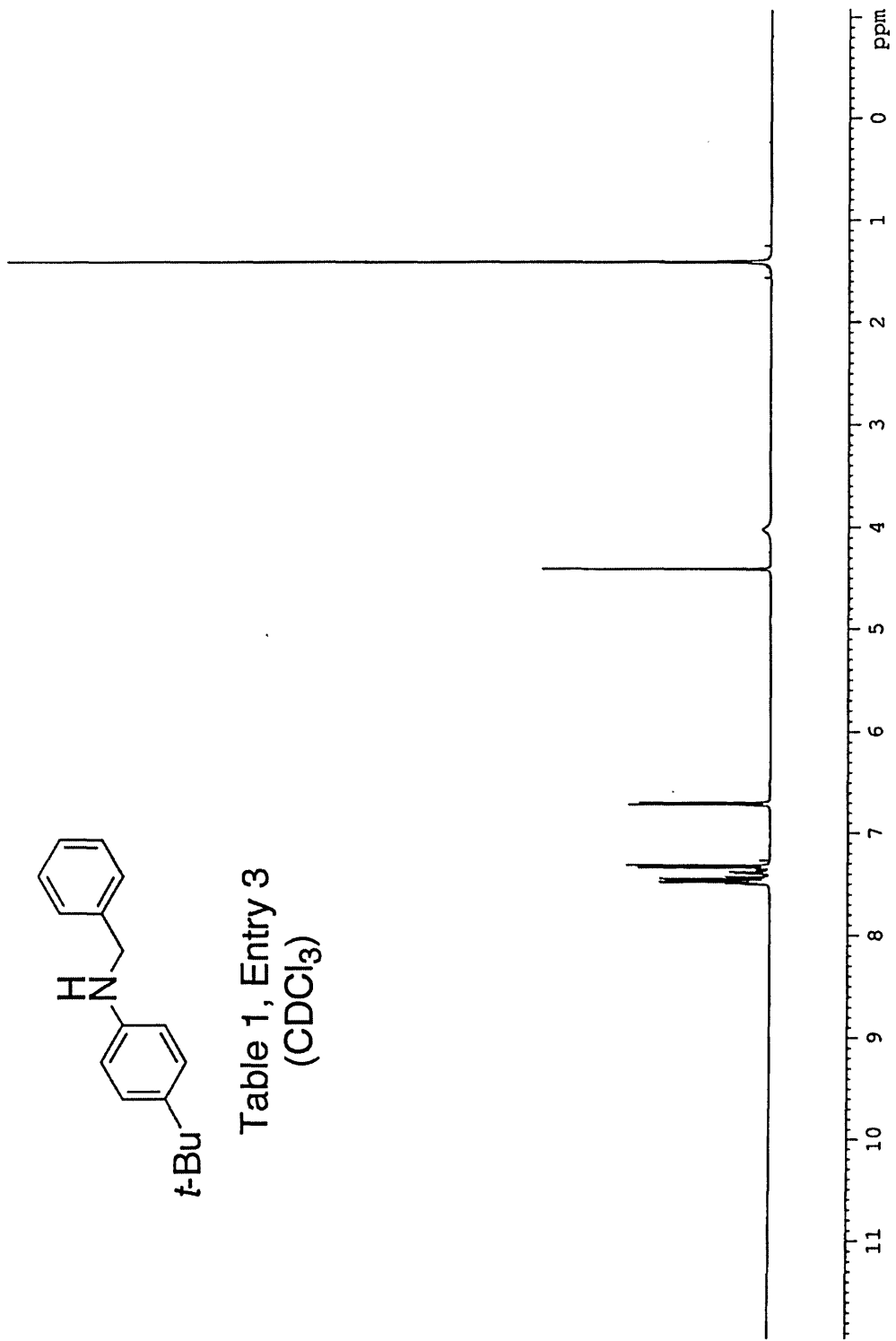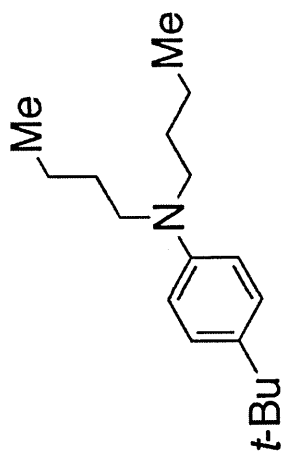
Table 1, Entry 1
(CDCl$_3$)

53

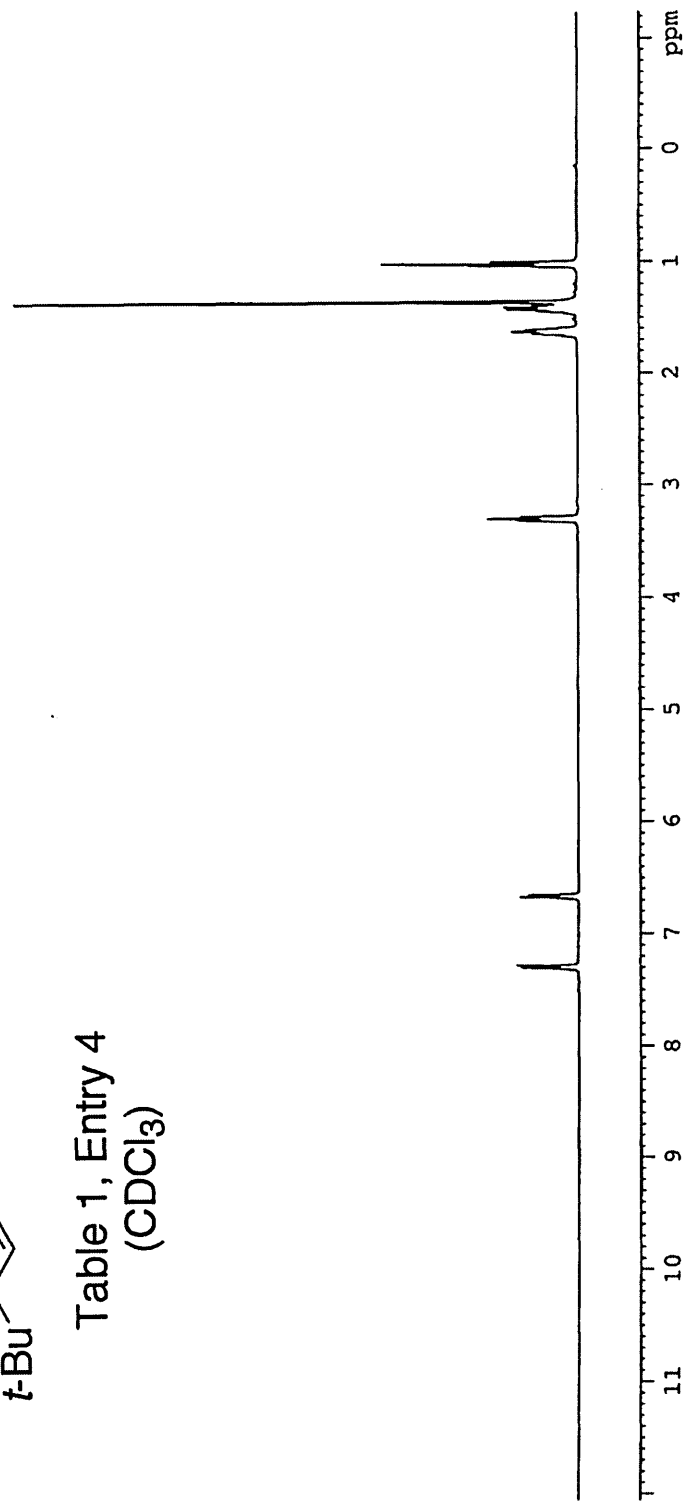Table 1, Entry 2
(CDCl$_3$)

54

Table 1, Entry 3
(CDCl$_3$)

Table 1, Entry 4
(CDCl$_3$)

56

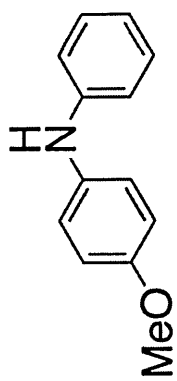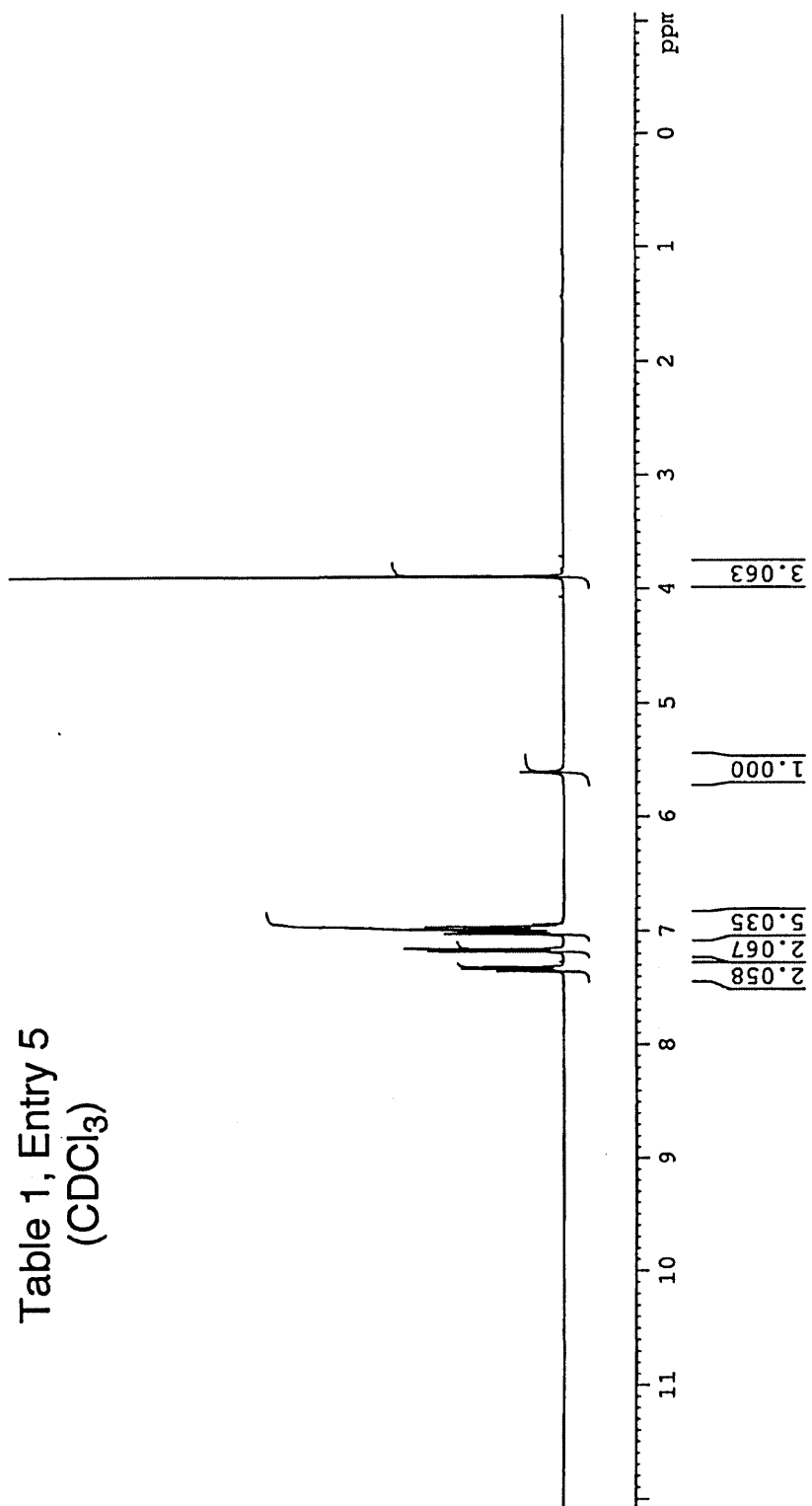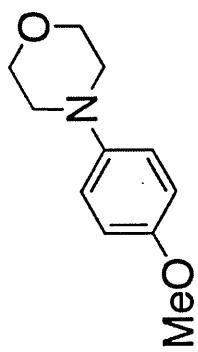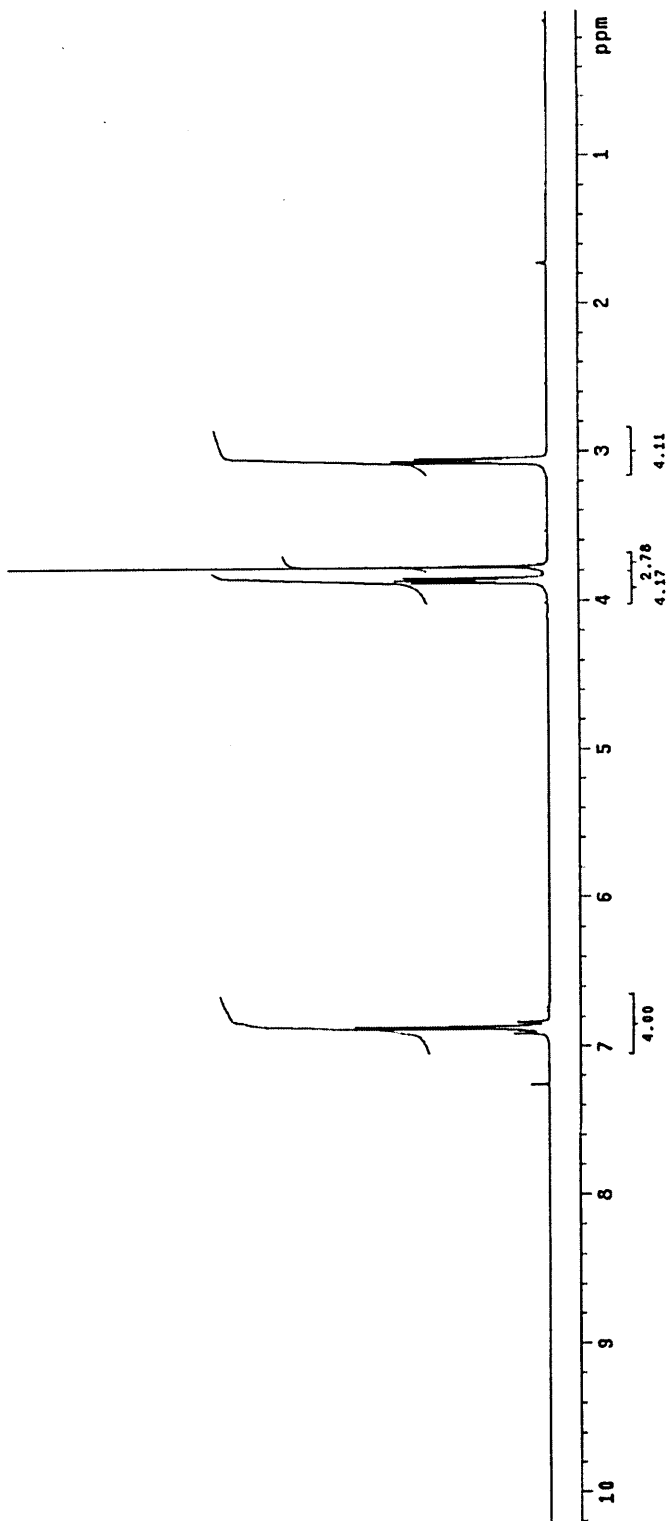Table 1, Entry 5
(CDCl$_3$)

Table 1, Entry 6
(CDCl₃)

58

Table 2, Entry 1
(CDCl₃)

Table 2, Entry 2
(CDCl$_3$)

2.398

3.128
3.140
3.151
3.835
3.847
3.858

6.993
7.005
7.015
7.028
7.042
7.056
7.064
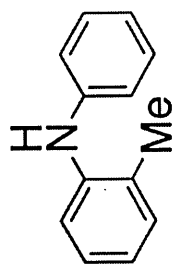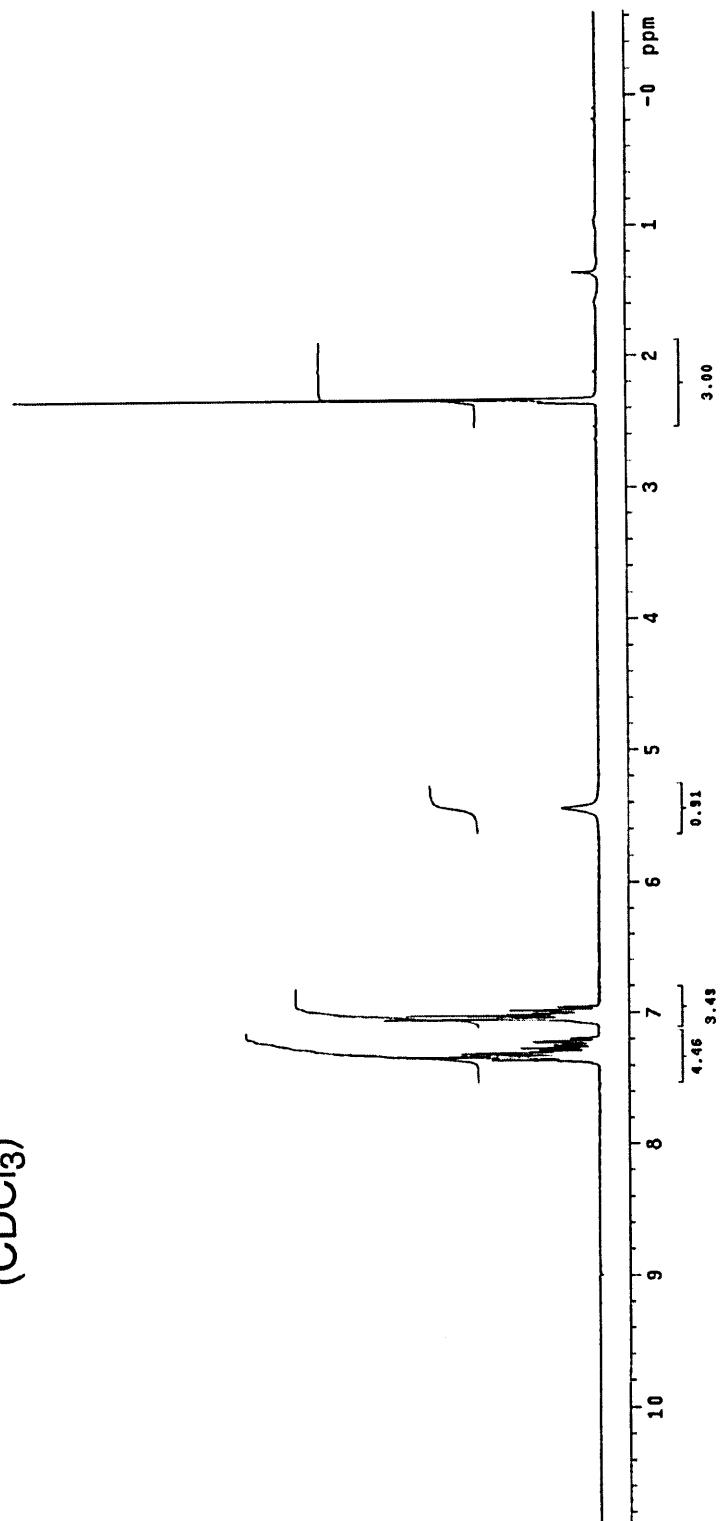
Table 2, Entry 3
(CDCl₃)

Table 2, Entry 4
(CDCl₃)

62

Table 2, Entry 5
(CDCl$_3$)

6.000

0.978
1.987
5.034
3.069
2.011

1.496

3.926
5.611
7.003
7.009
7.020
7.026
7.031
7.039
7.044
7.055
7.060
7.068
7.184
7.189
7.200
7.206
7.417
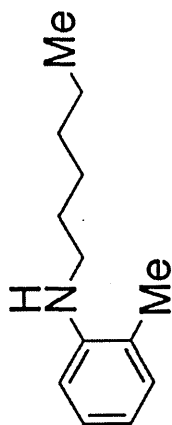7.422
7.434
7.439

Table 3, Entry 1
(CDCl$_3$)

9.144

3.000

0.959

3.984
2.026
2.003

Table 3, Entry 2
(CDCl₃)

65
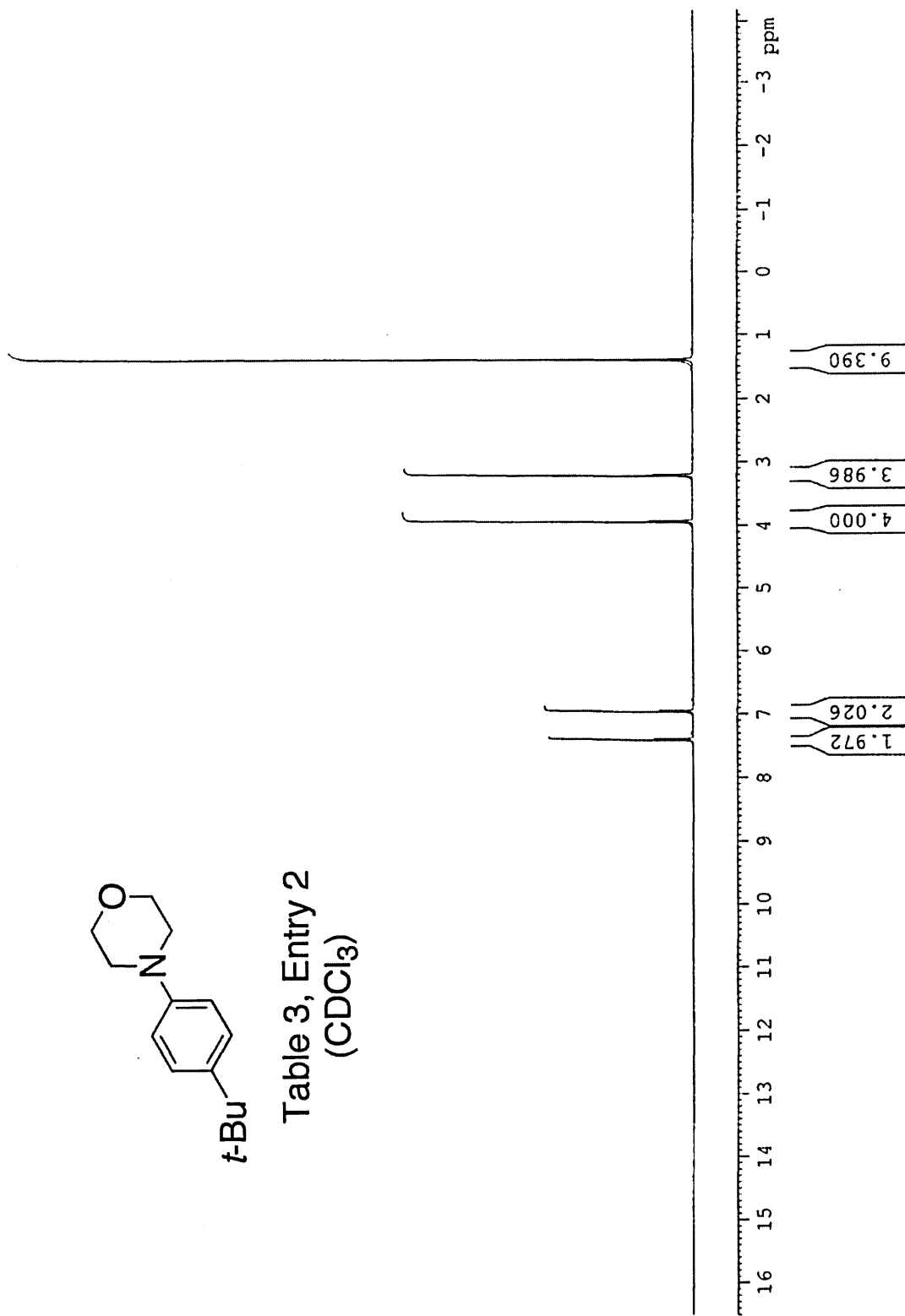
Table 3, Entry 3
(CDCl$_3$)

66

Table 3, Entry 4
(CDCl$_3$)

67
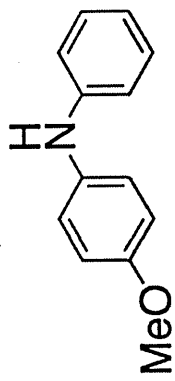
Table 3, Entry 5
(CDCl$_3$)

Table 3, Entry 6
(CDCl$_3$)
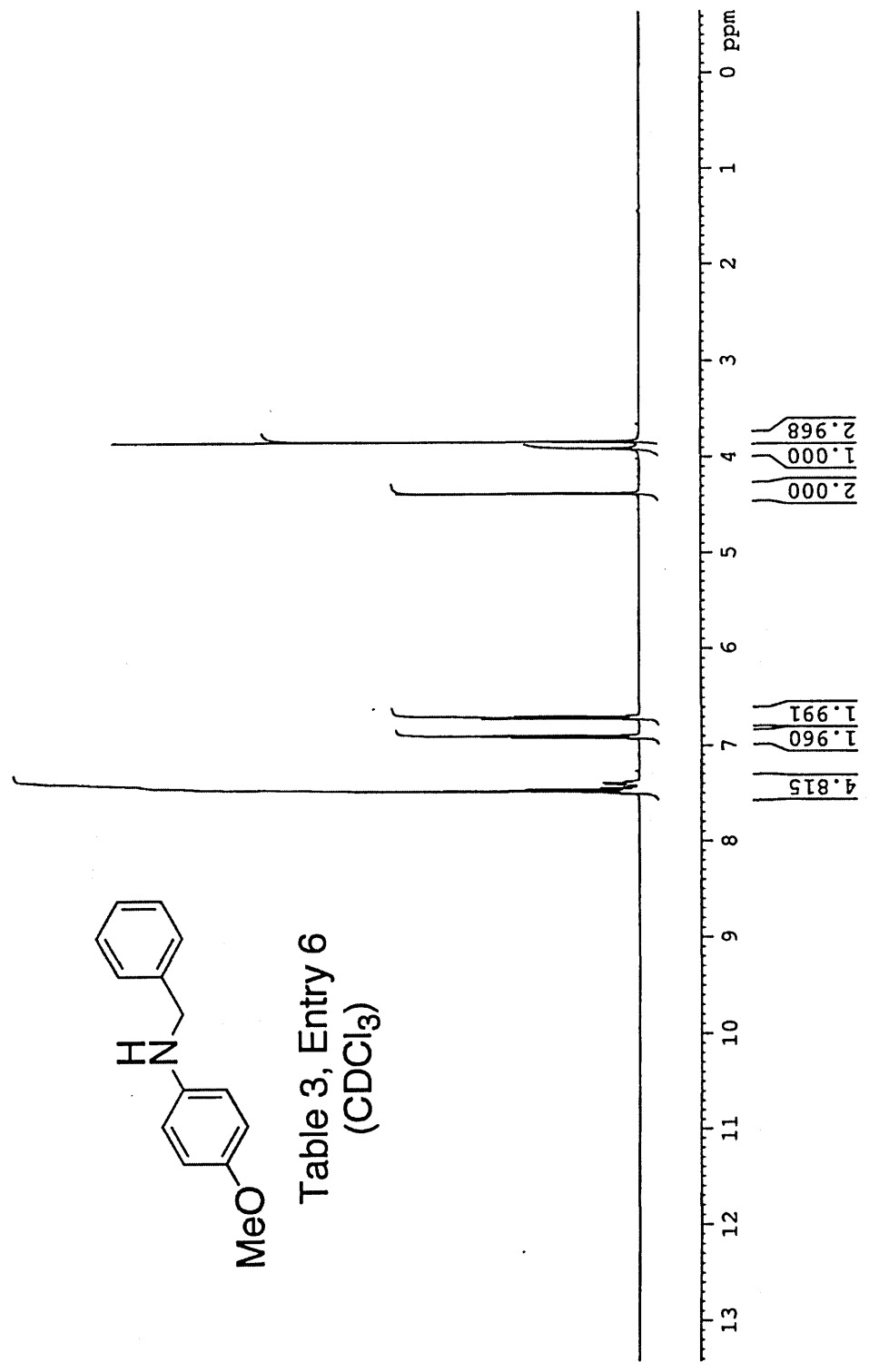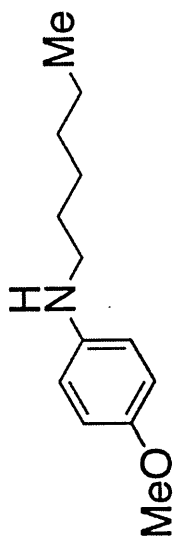
Table 3, Entry 7
(CDCl$_3$)

70
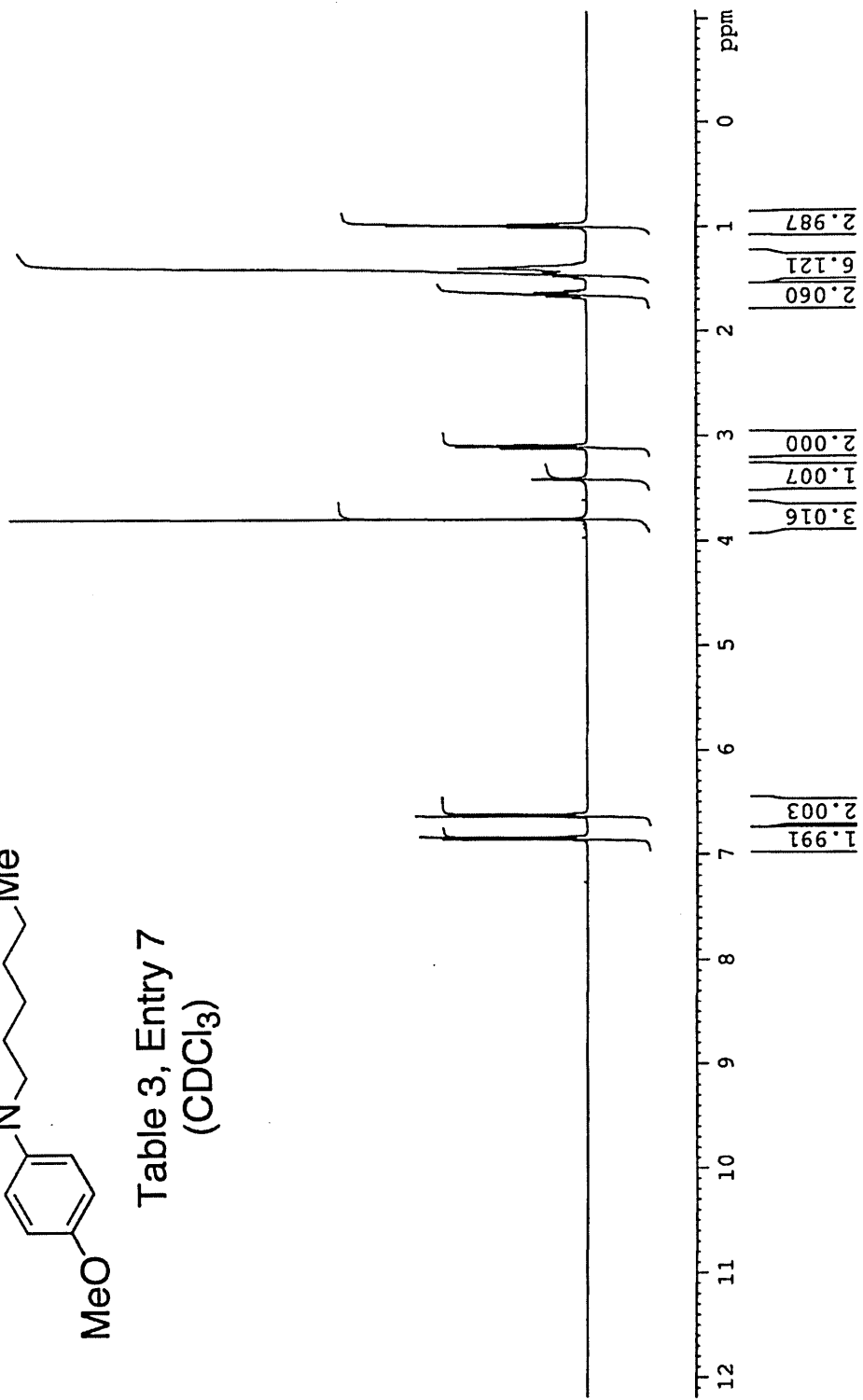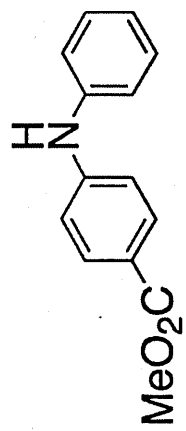
Table 4, Entry 1
(CDCl₃)

Table 4, Entry 2
(CDCl₃)

MeO₂C
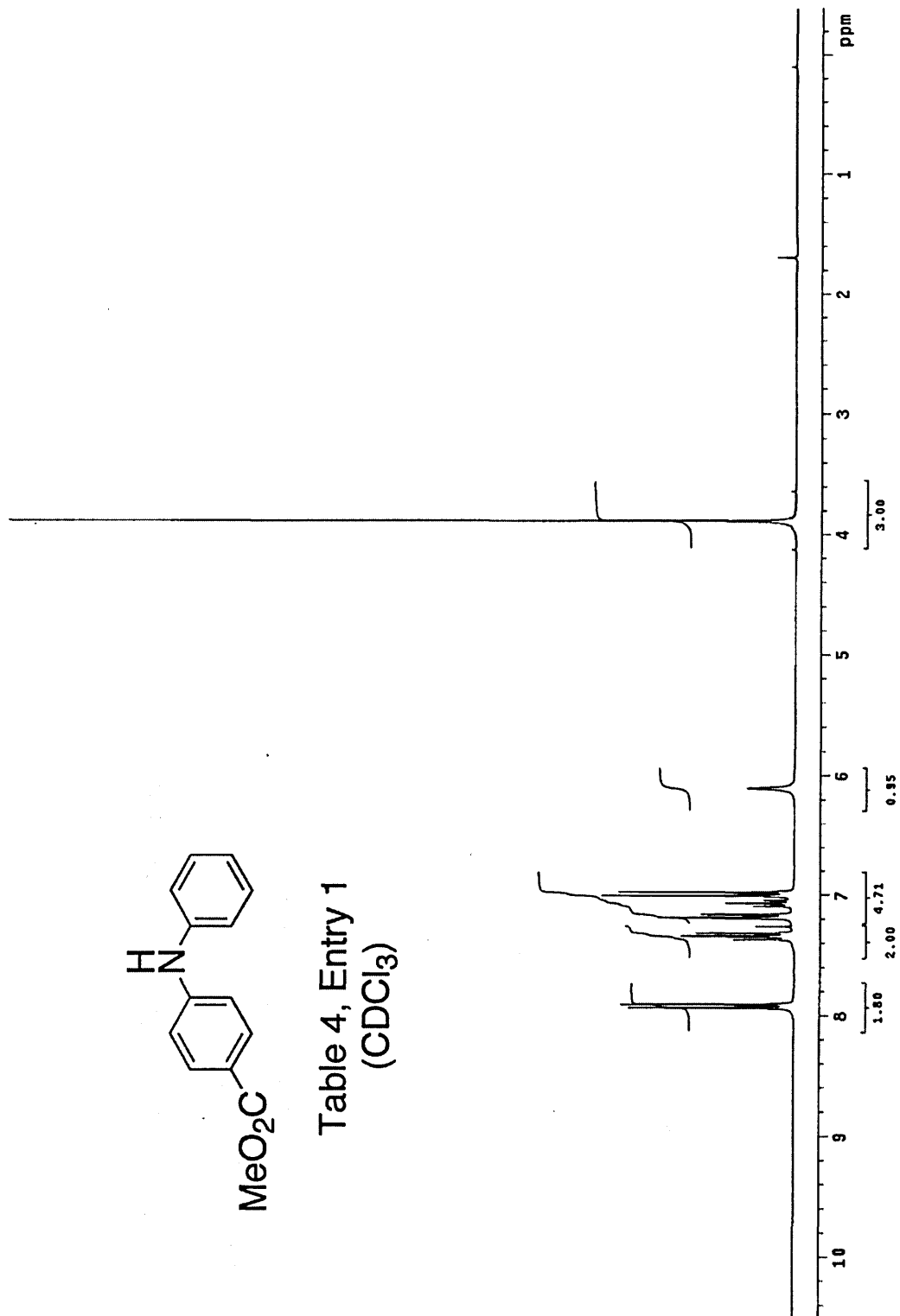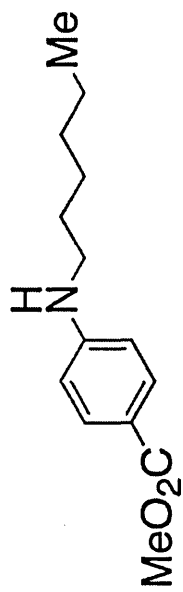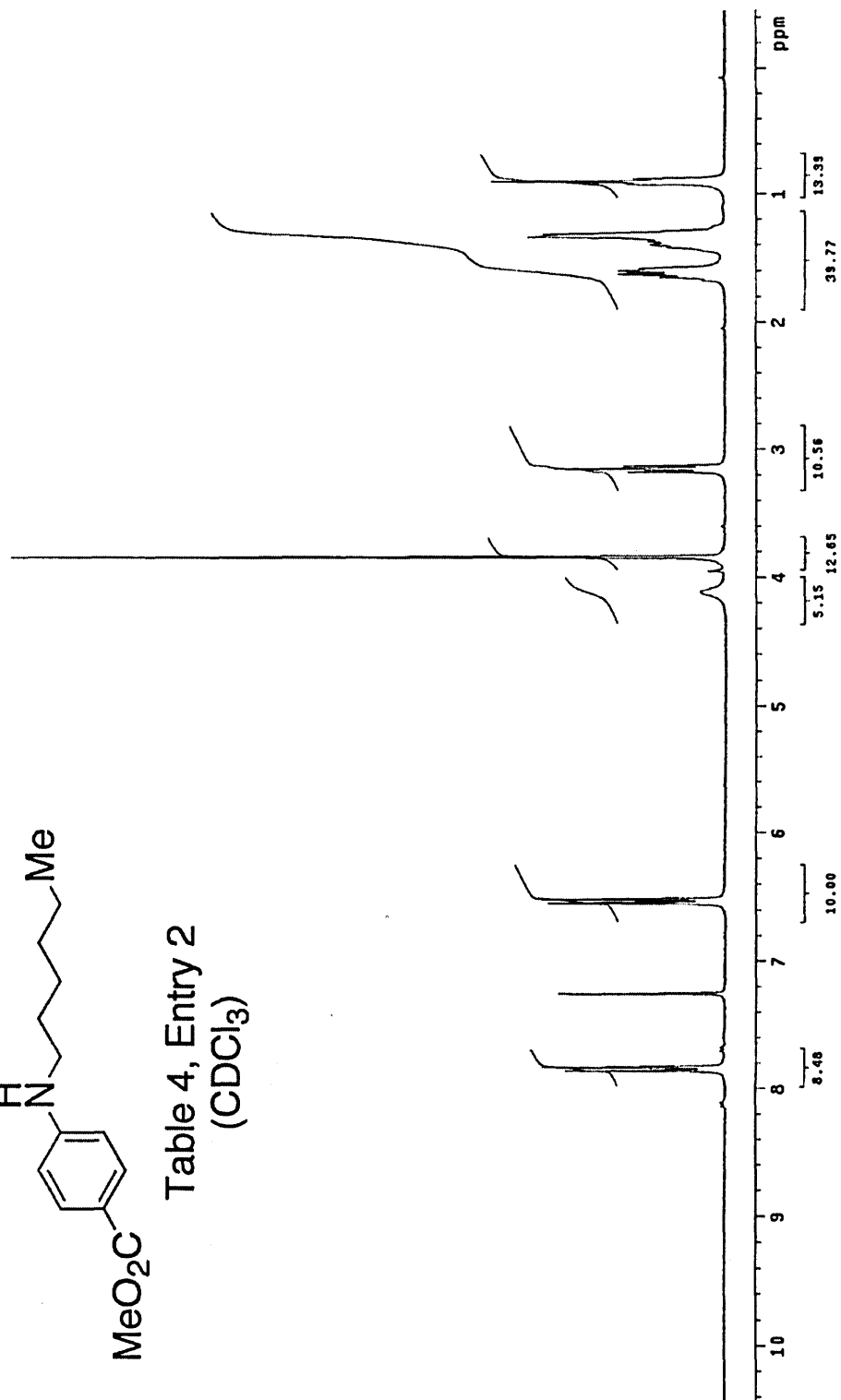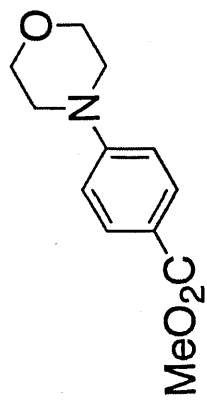
Table 4, Entry 3
(CDCl₃)

Table 4, Entry 4
(CDCl₃)

2.979

0.995

3.981
2.029
2.000
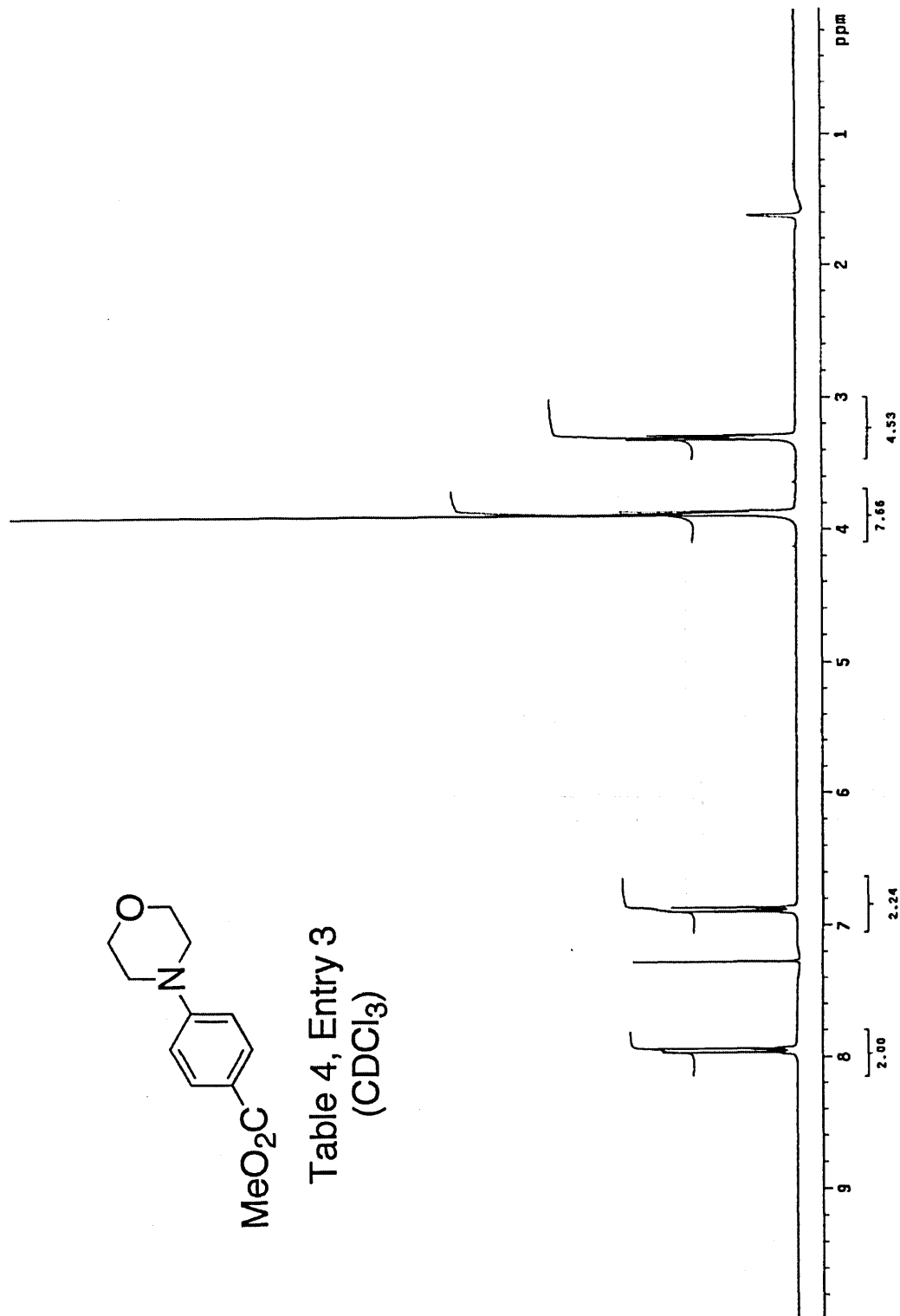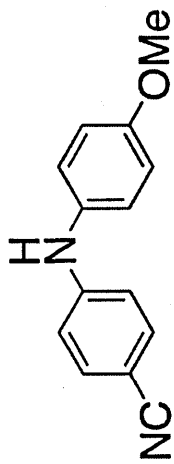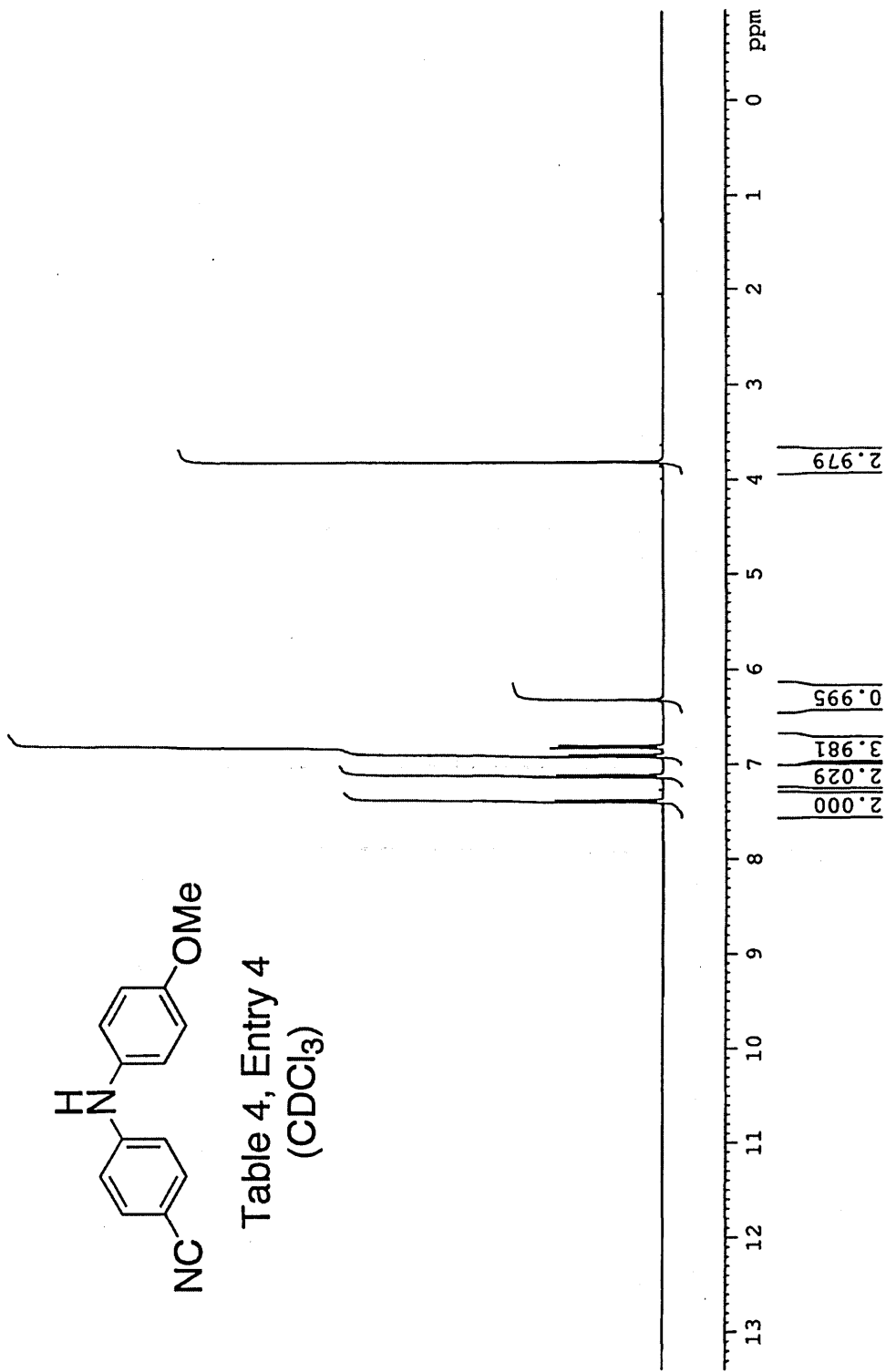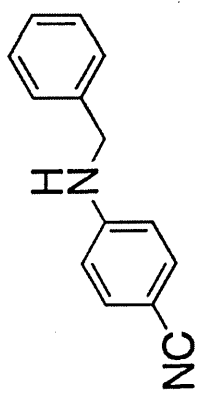
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(CDCl₃)
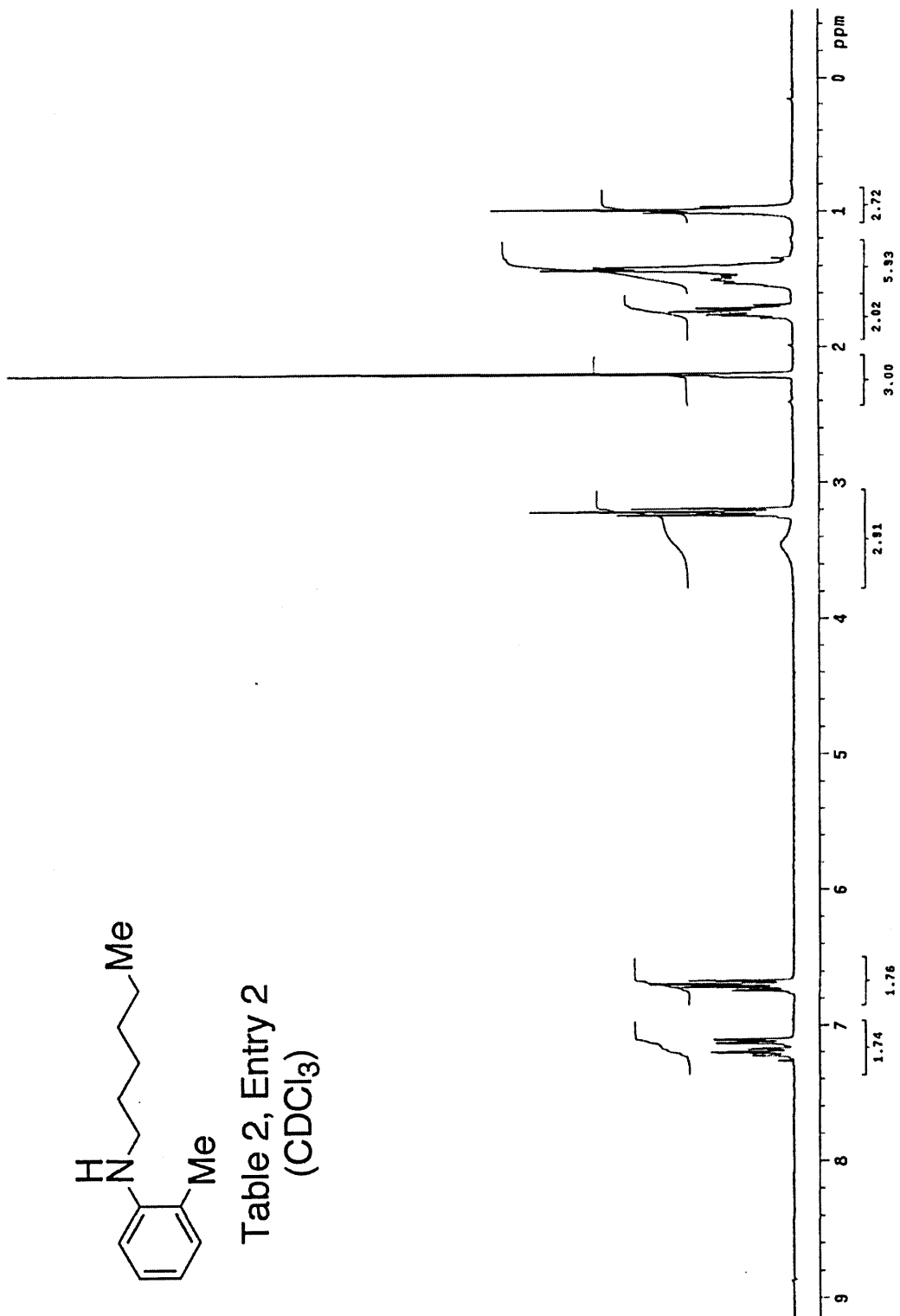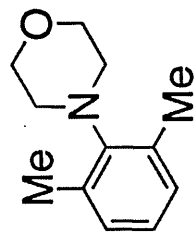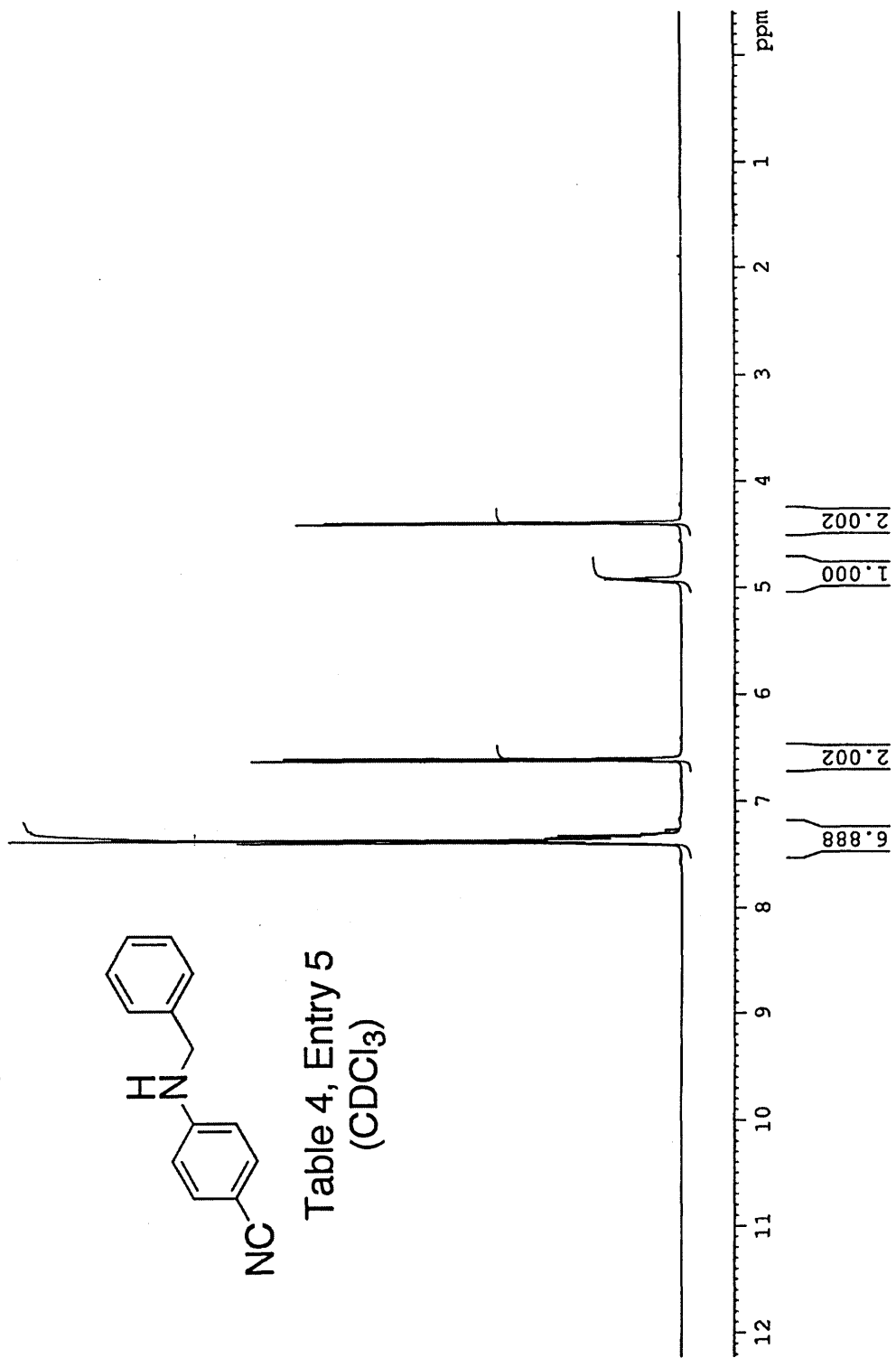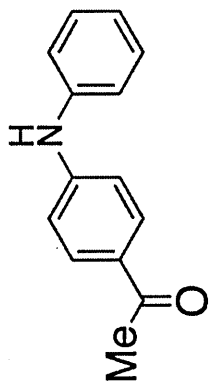
Table 4, Entry 6
(CDCl$_3$)
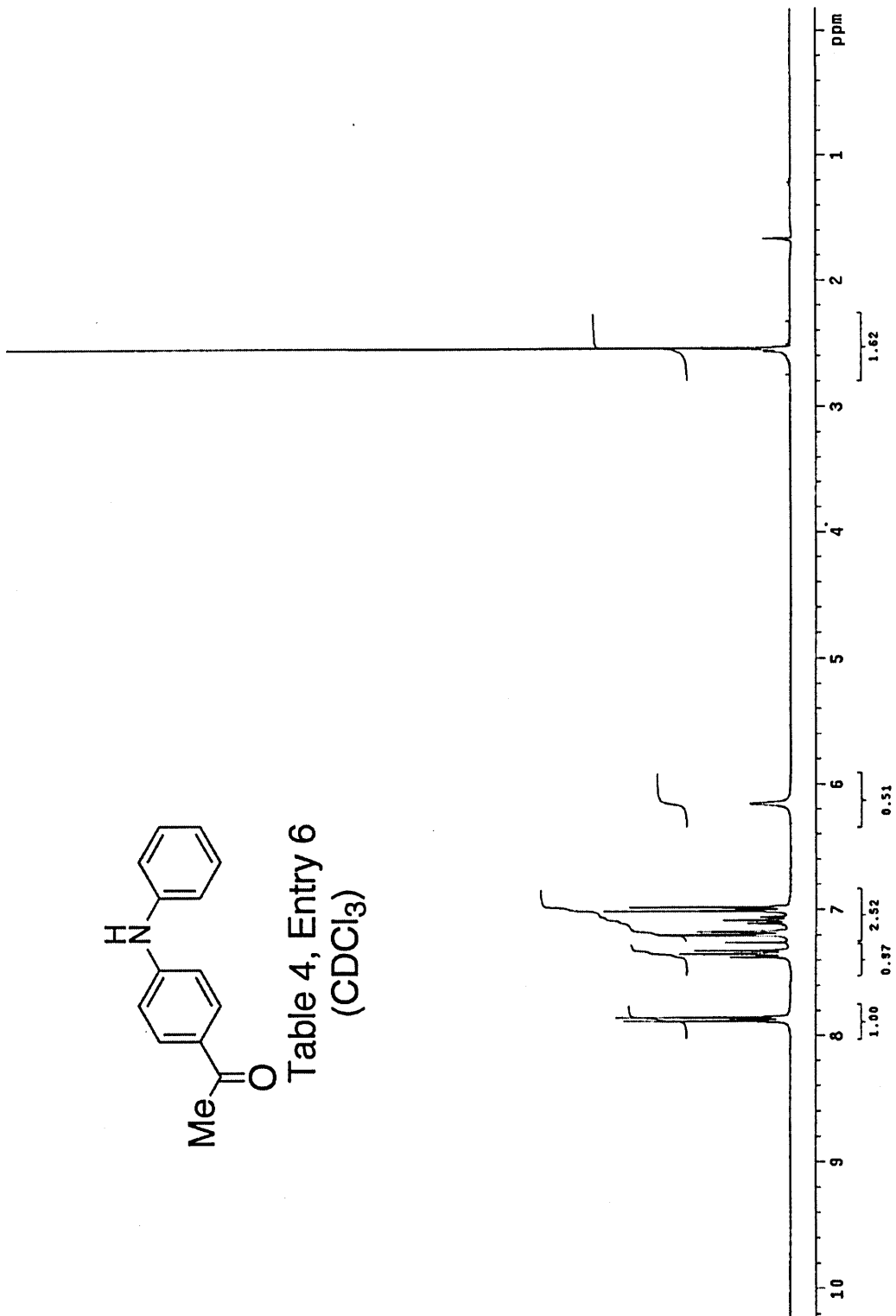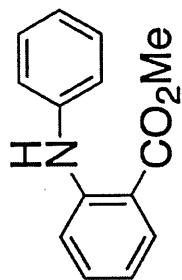
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(CDCl₃)
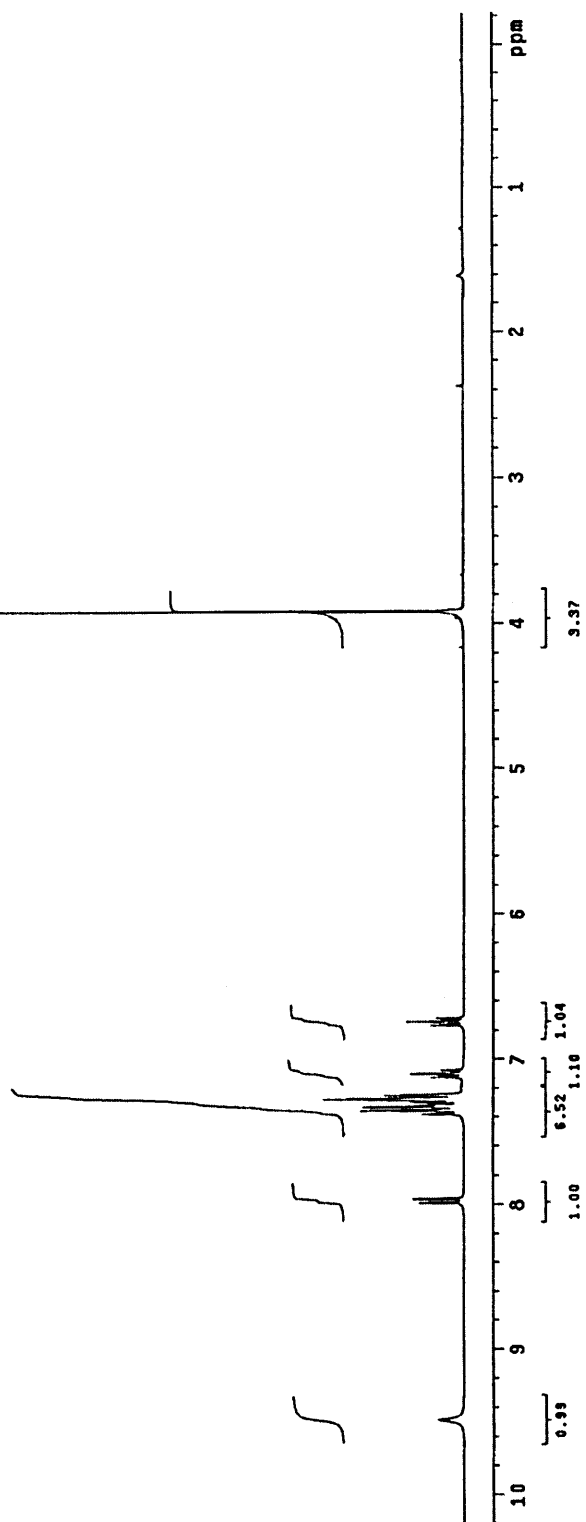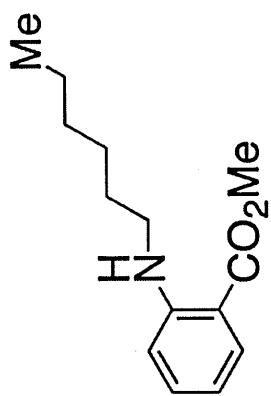
Table 5, Entry 2
(CDCl₃)
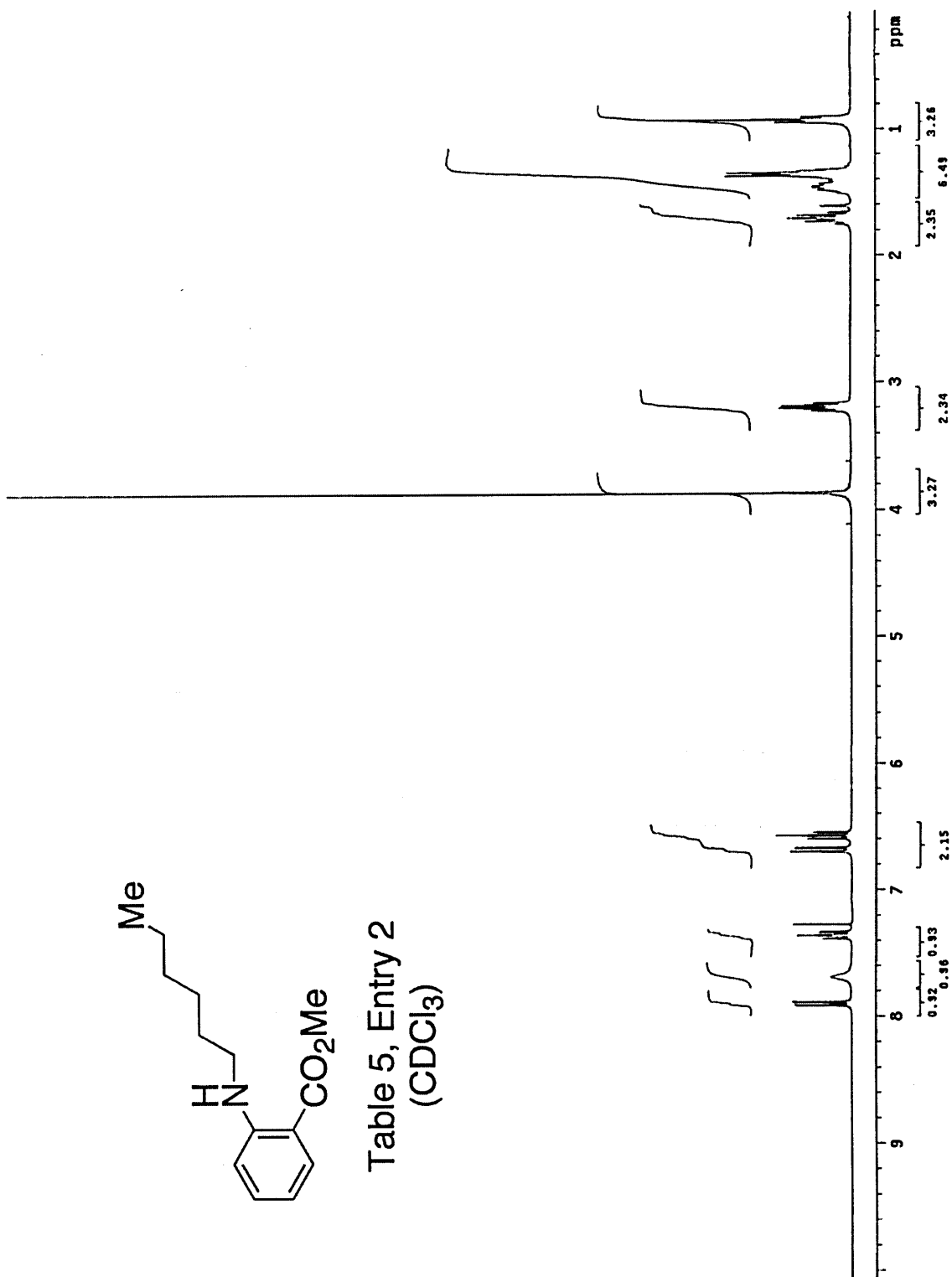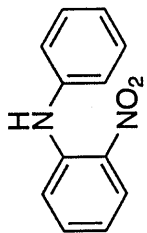
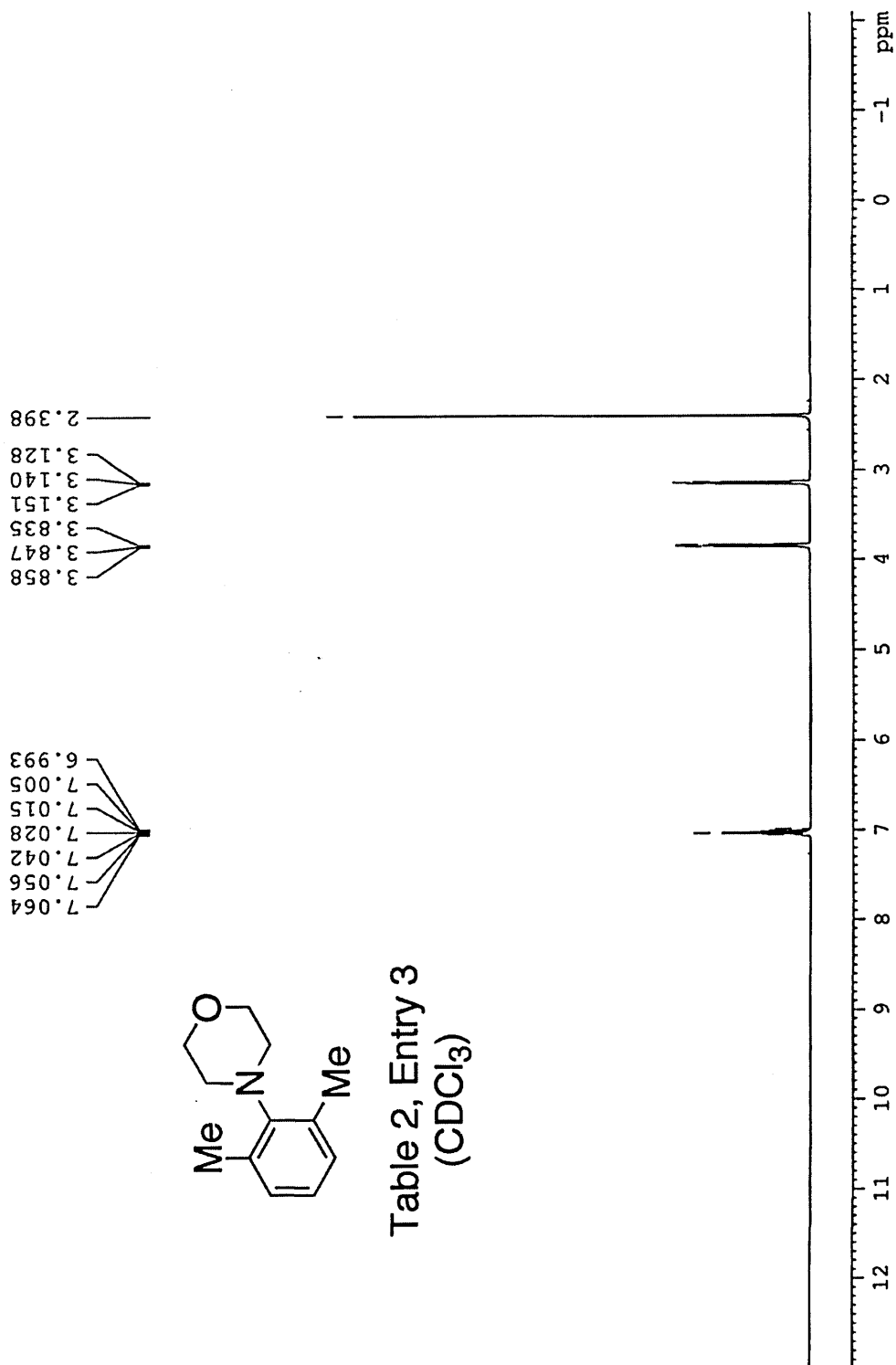Table 5, Entry 3
(CDCl₃)

79

Me

H
N
NO$_2$
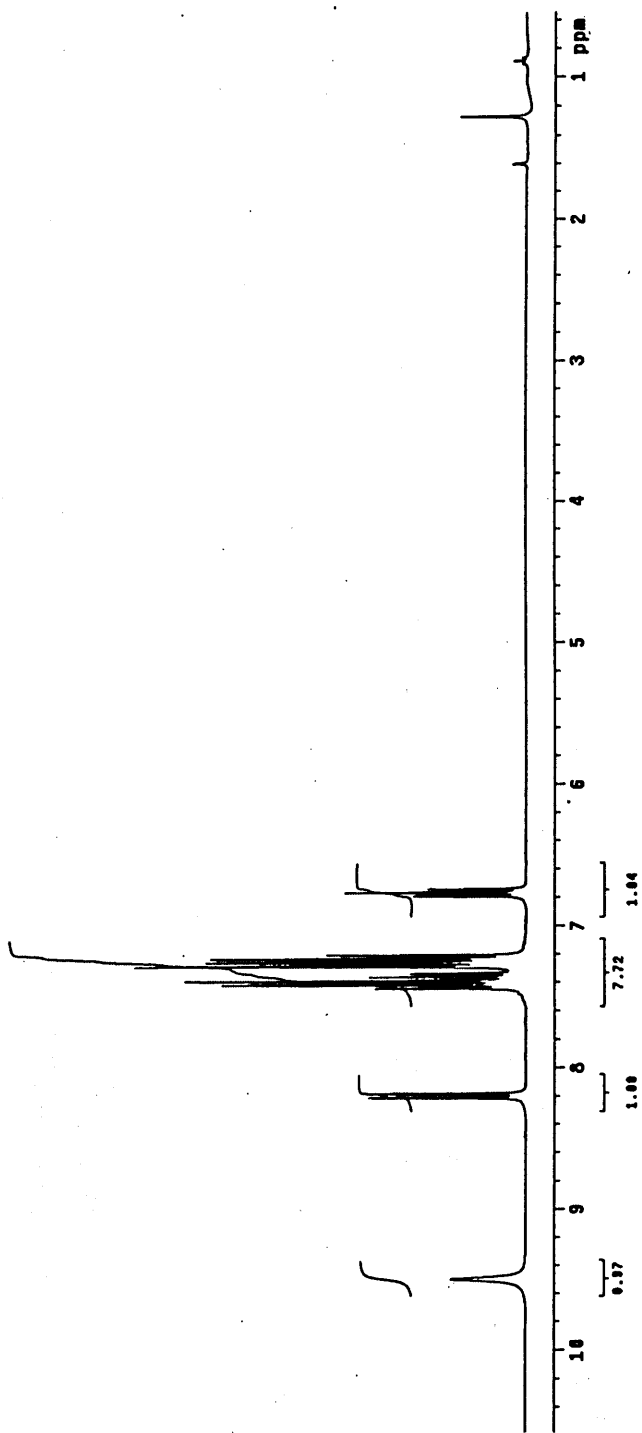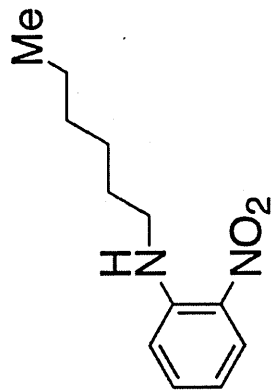
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(CDCl$_3$)
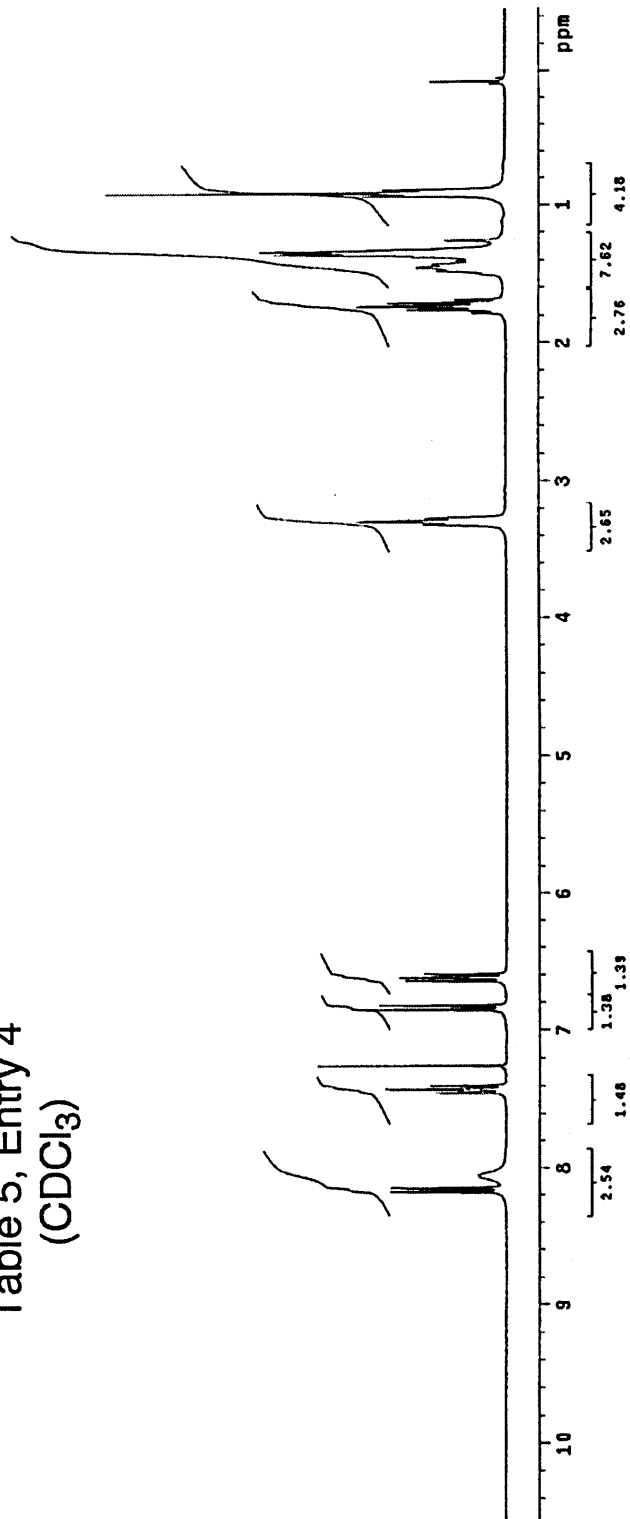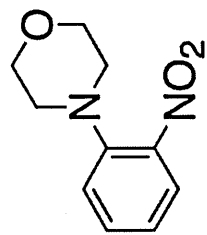
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(CDCl$_3$)
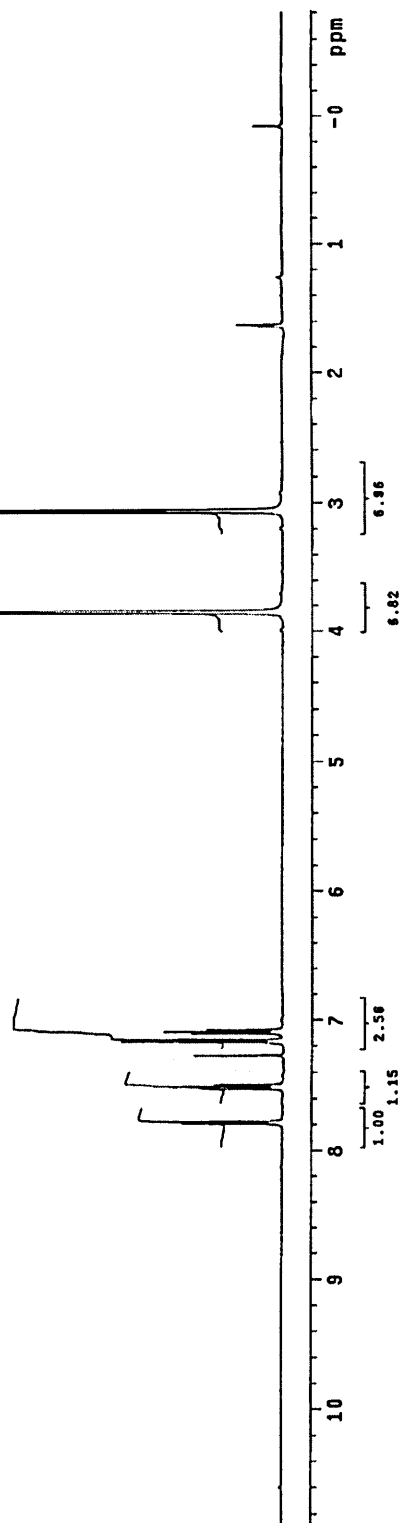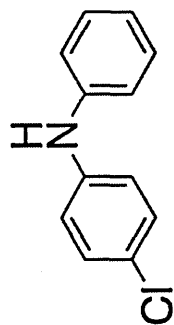
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(CDCl₃)
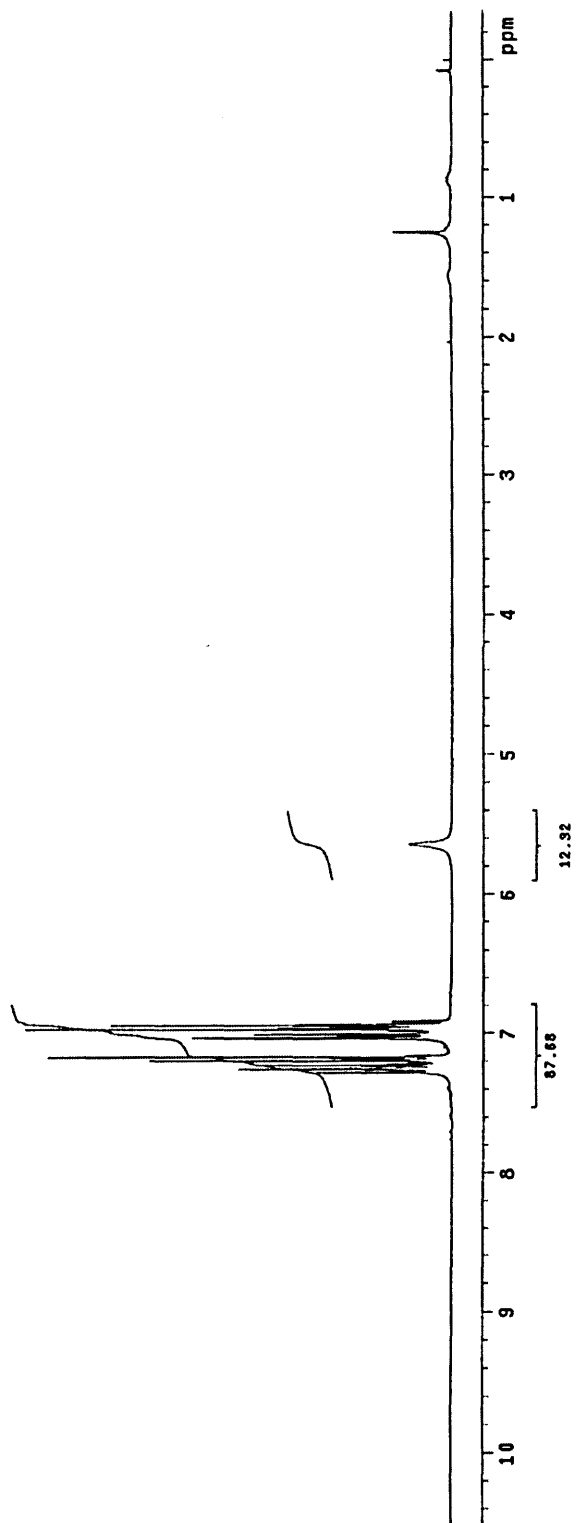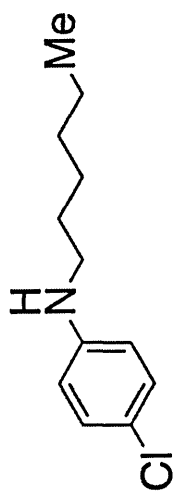
Table 6, Entry 2
(CDCl$_3$)

Table 6, Entry 3
(CDCl₃)

84
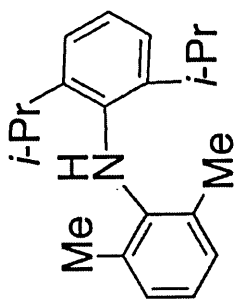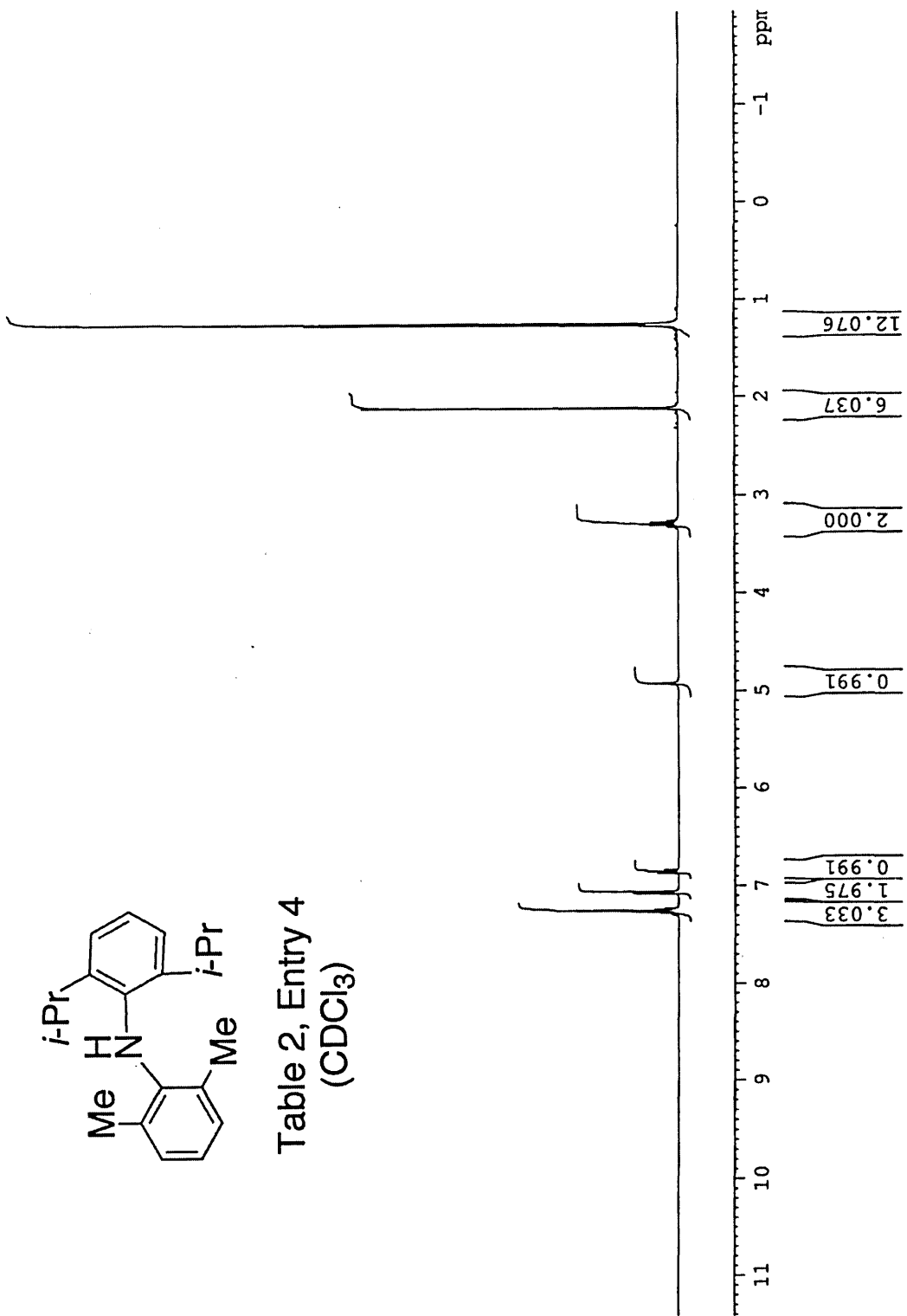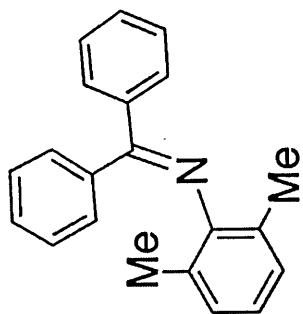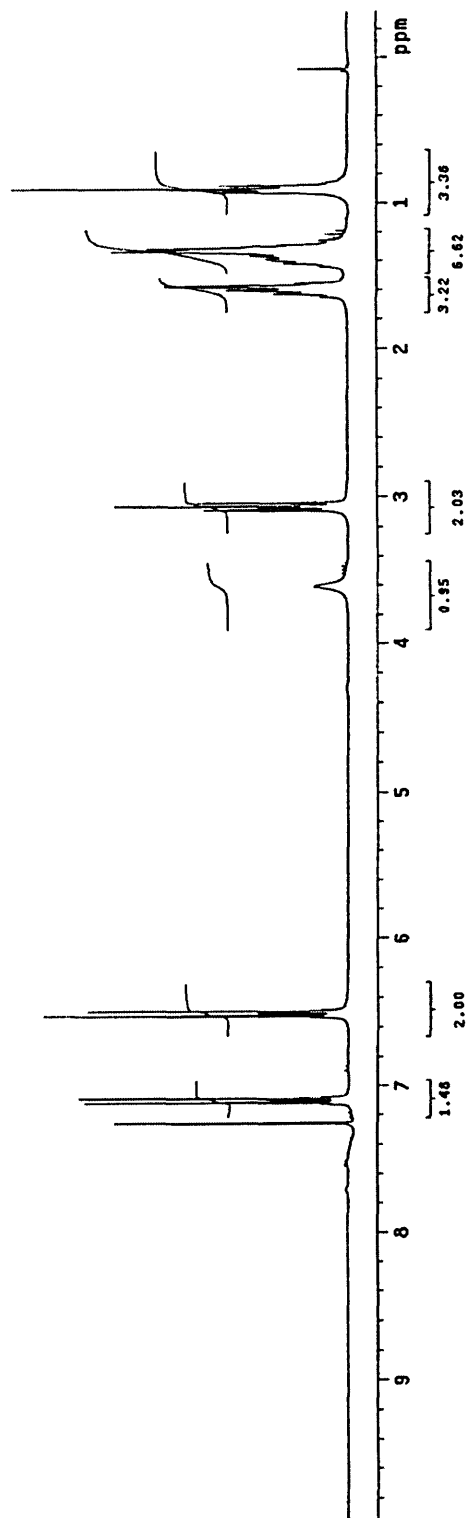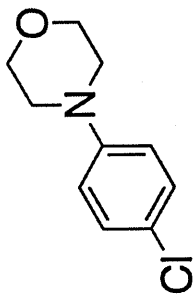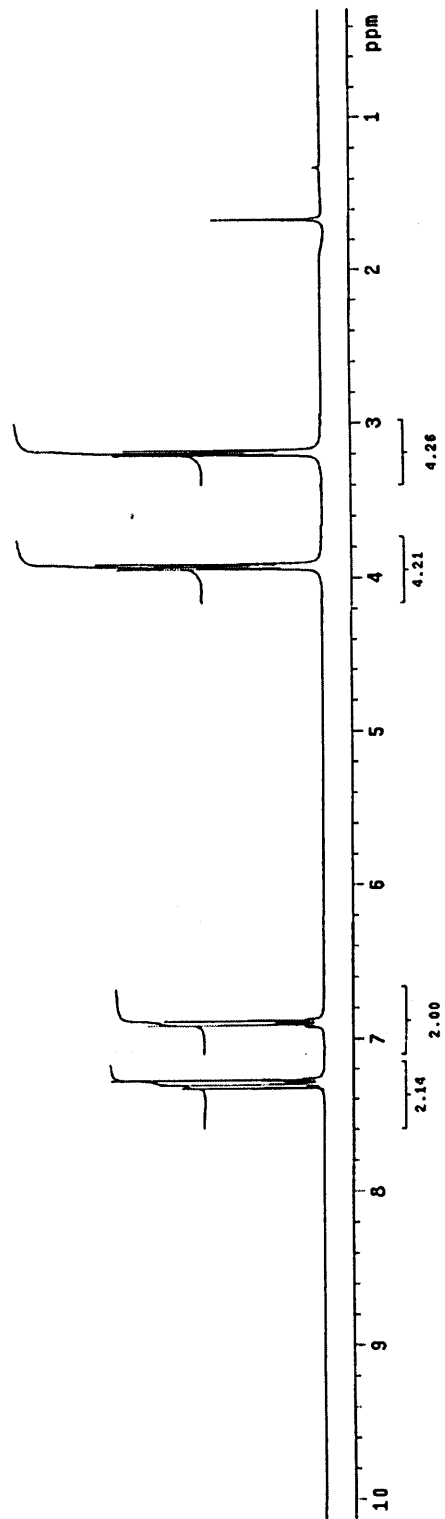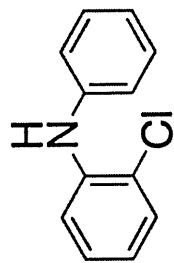
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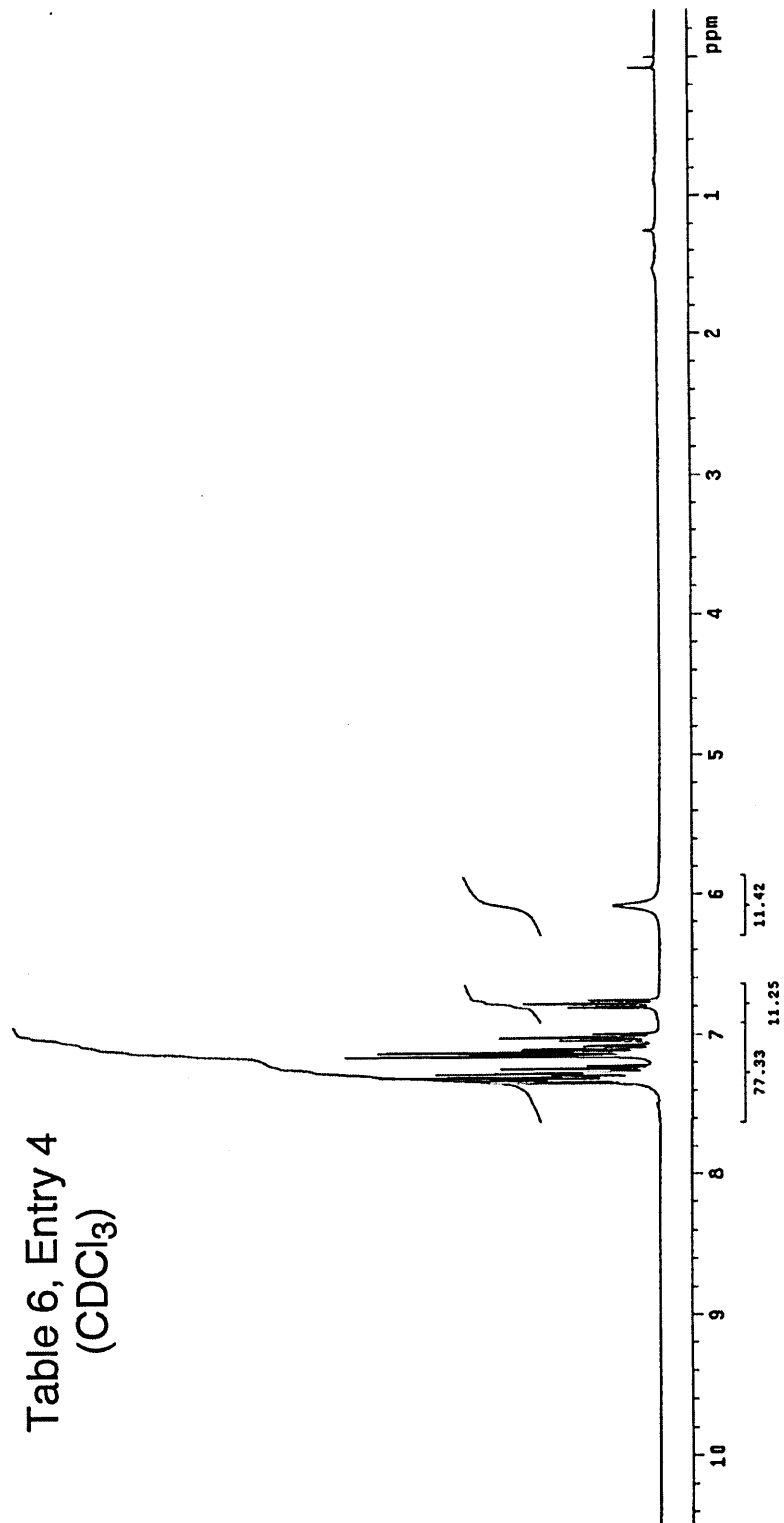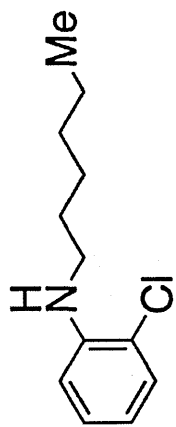
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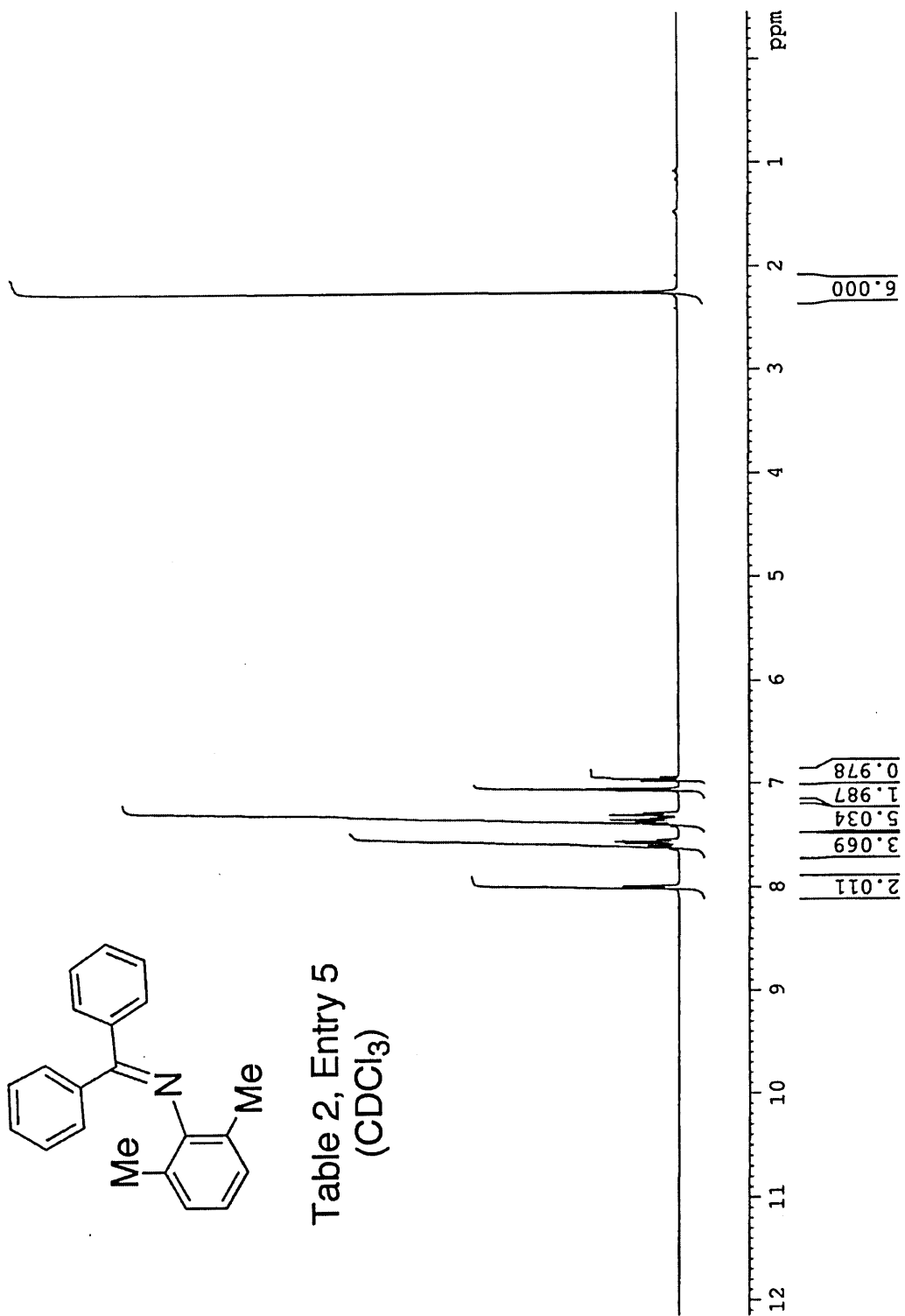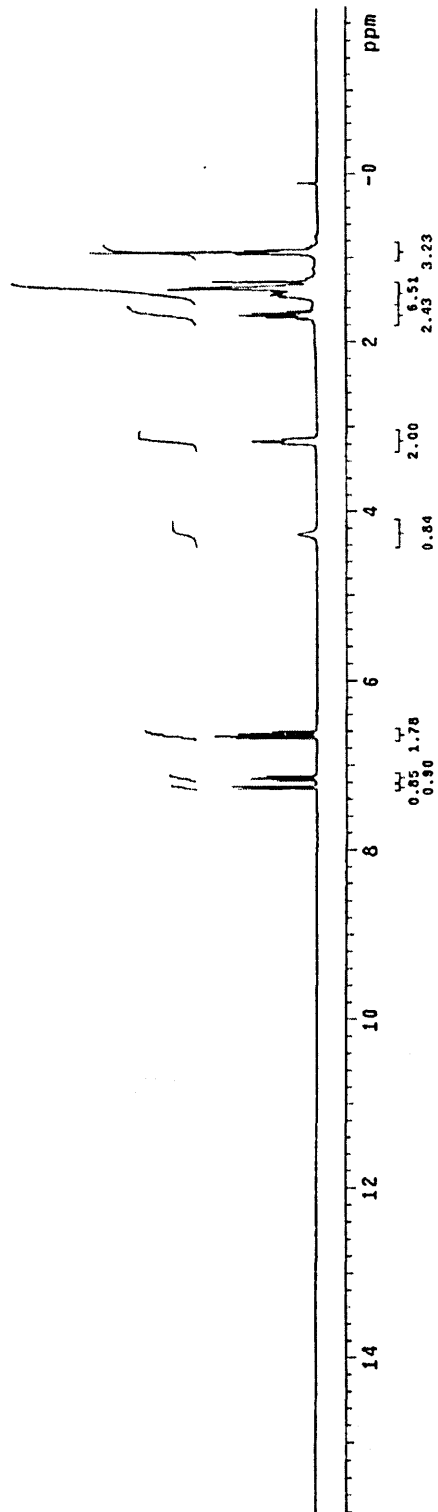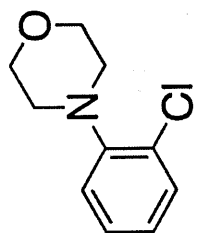
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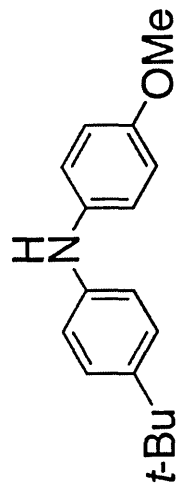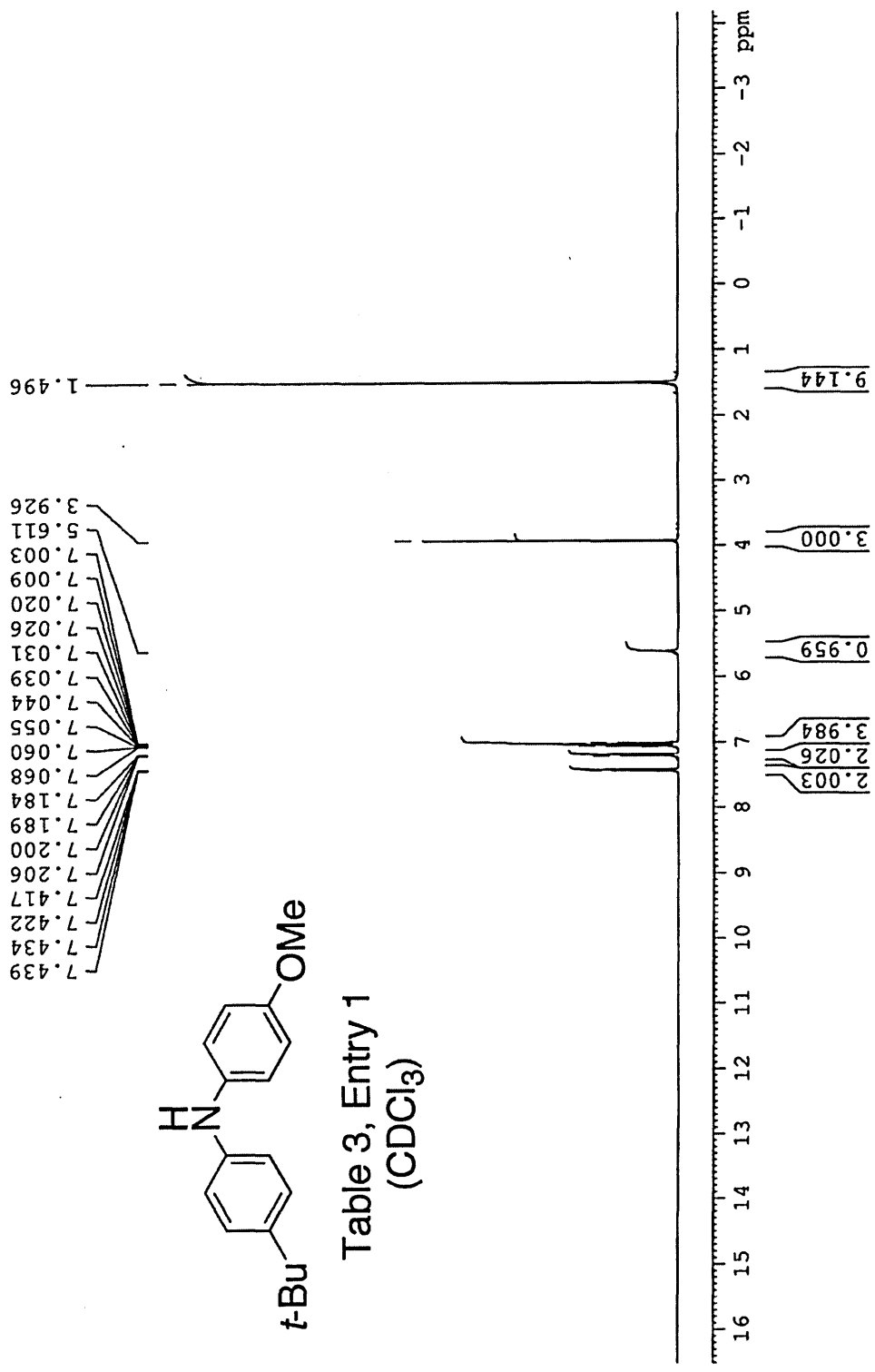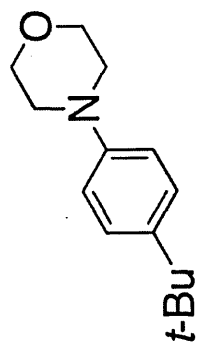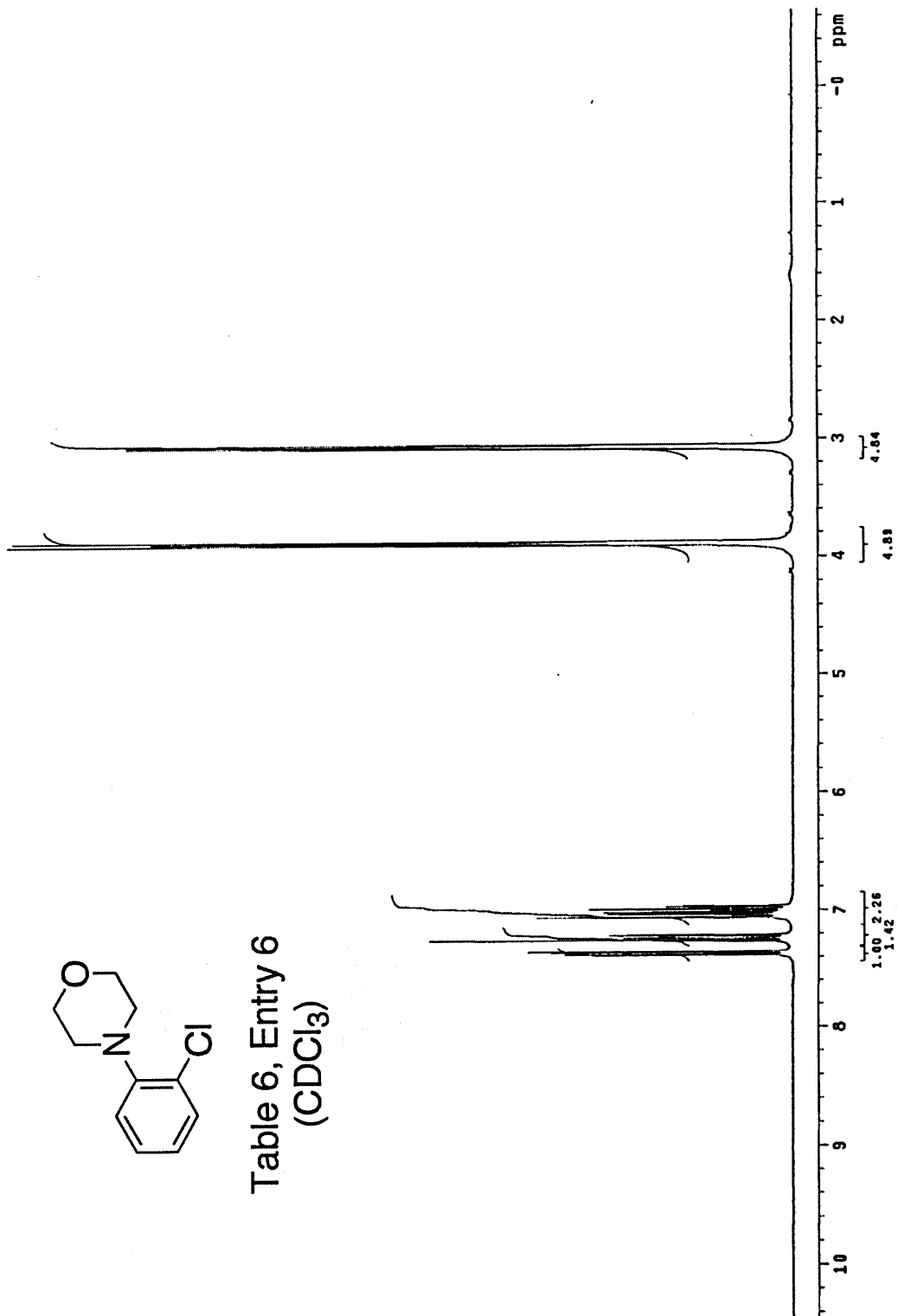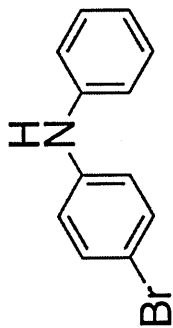
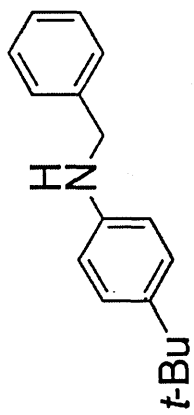Table 7, Entry 1
(CDCl₃)
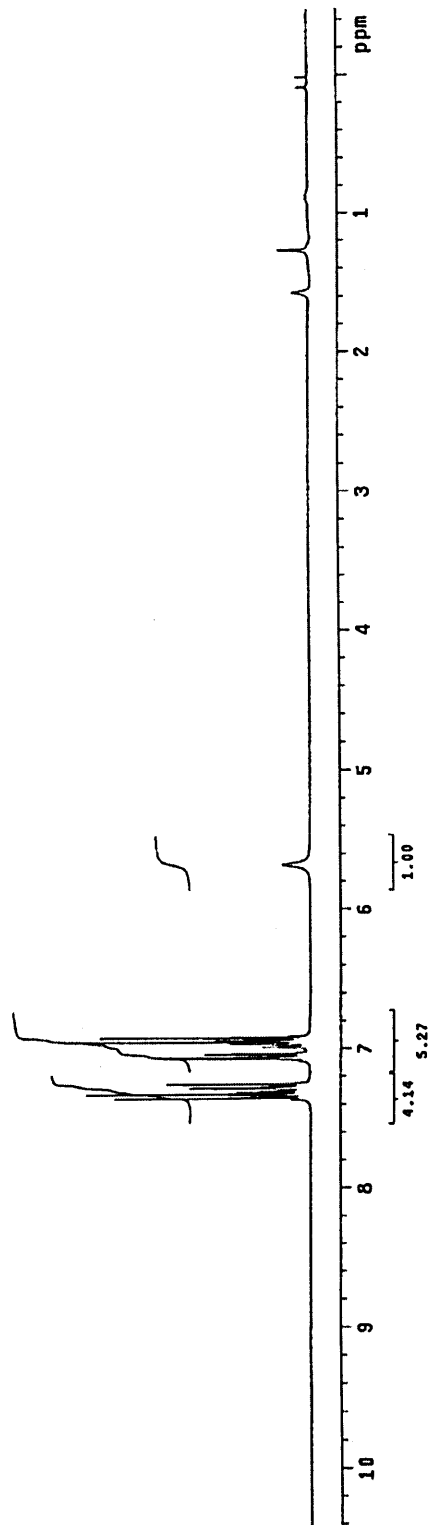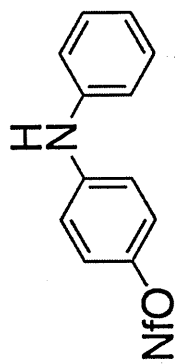
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(CDCl$_3$)
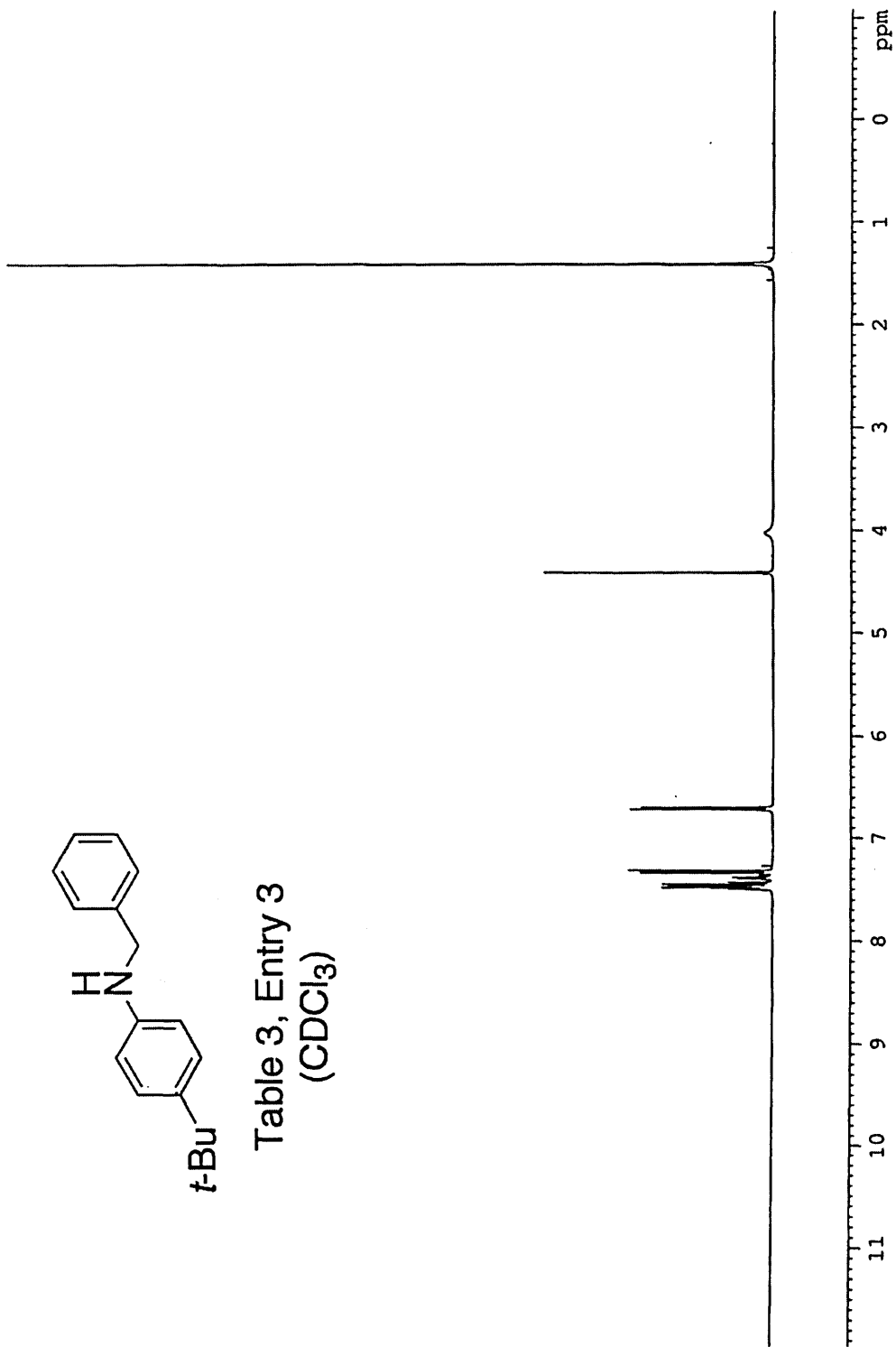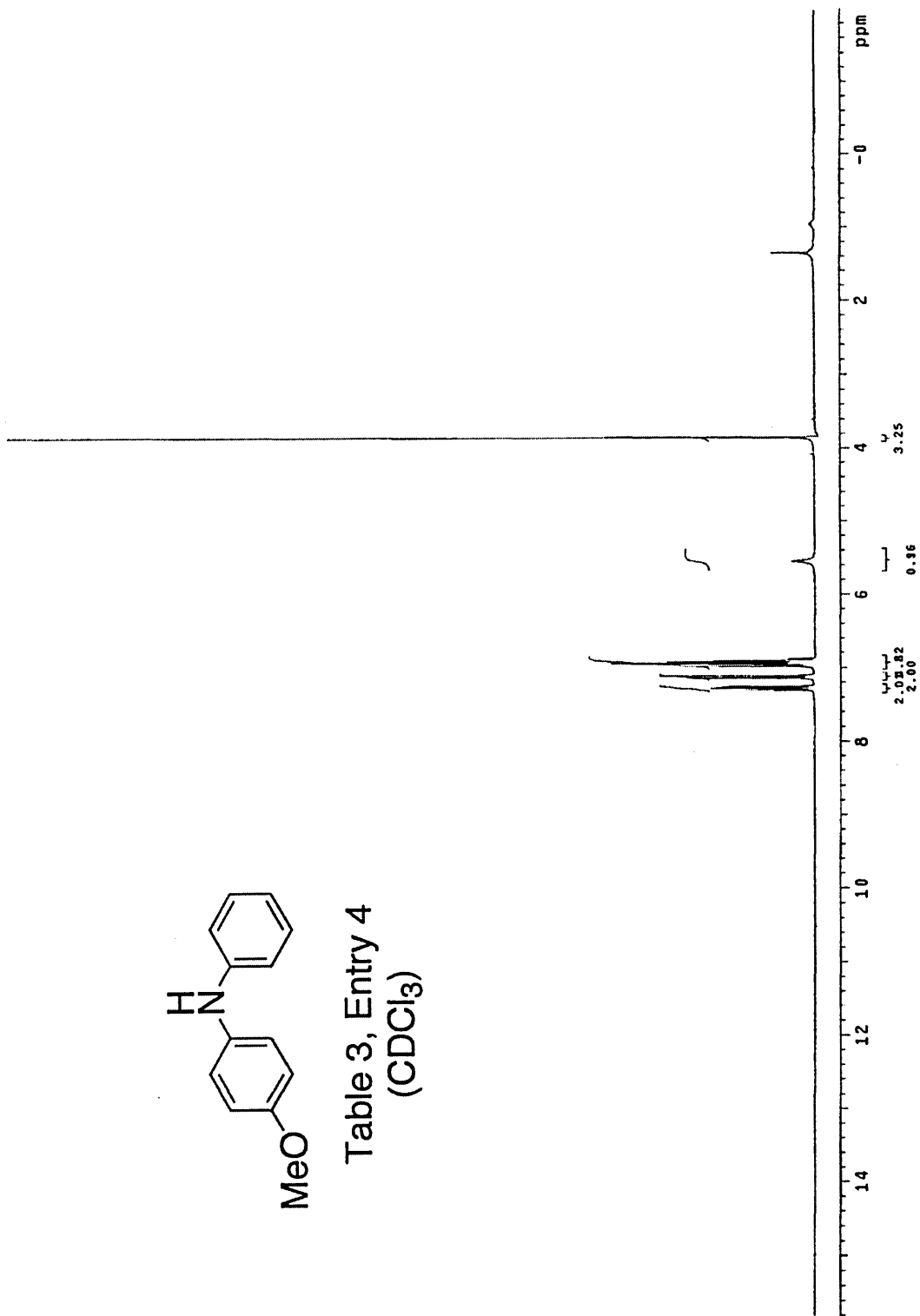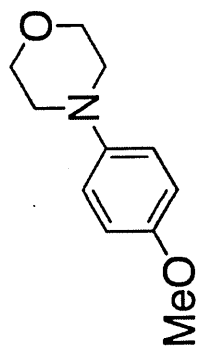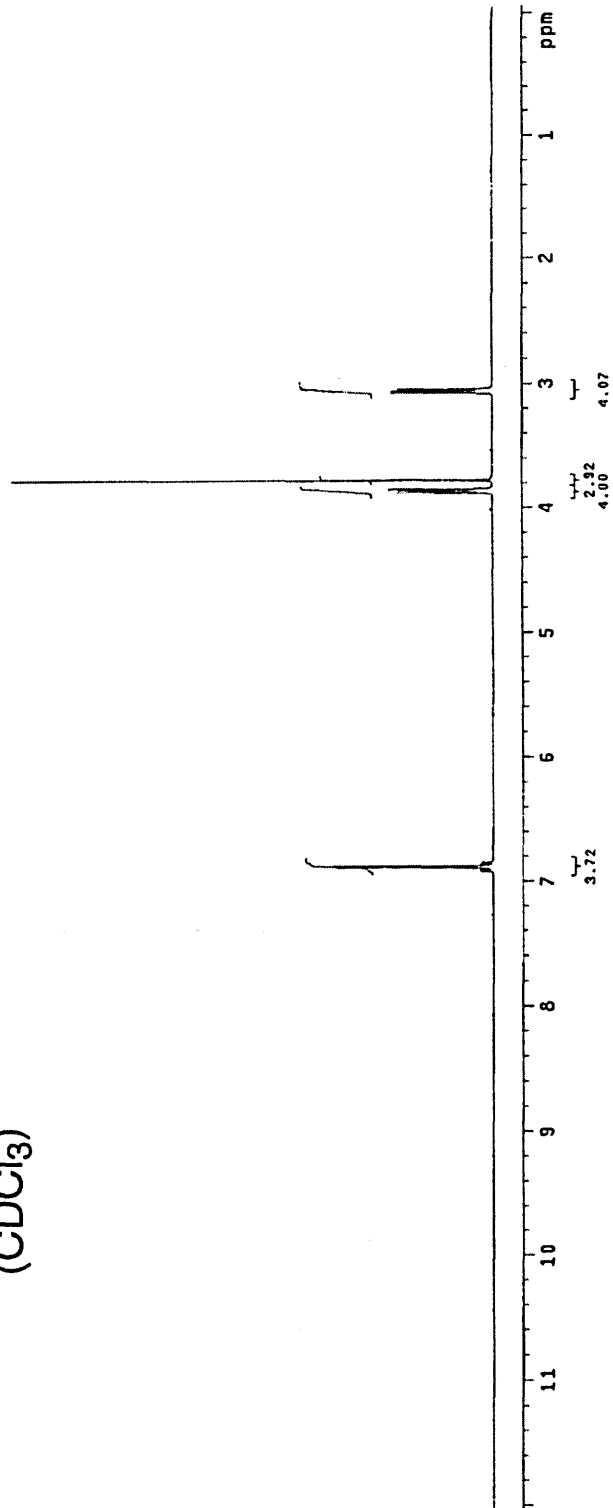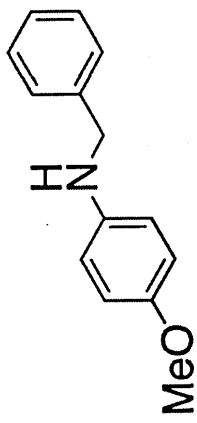
Nf = -SO$_2$(CF$_2$)$_3$CF$_3$

89

Table 7, Entry 3
(CDCl₃)

90
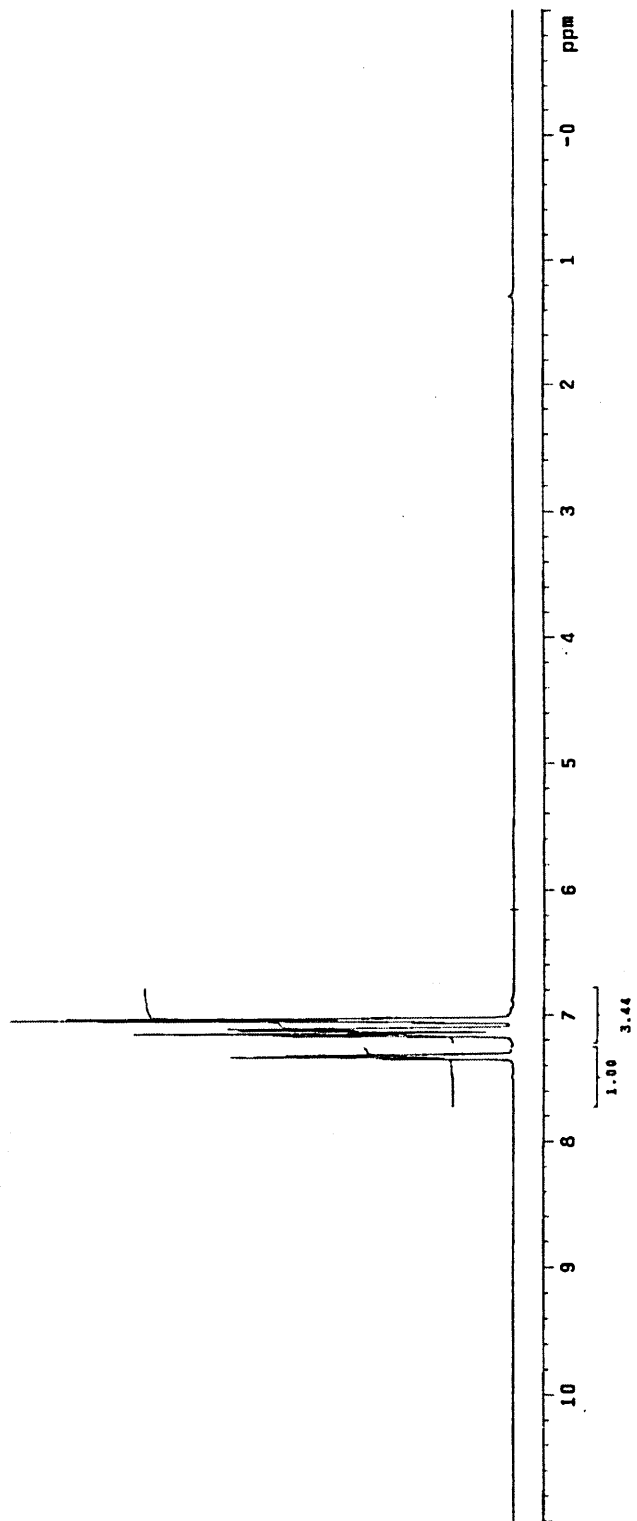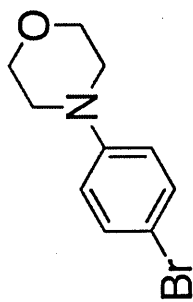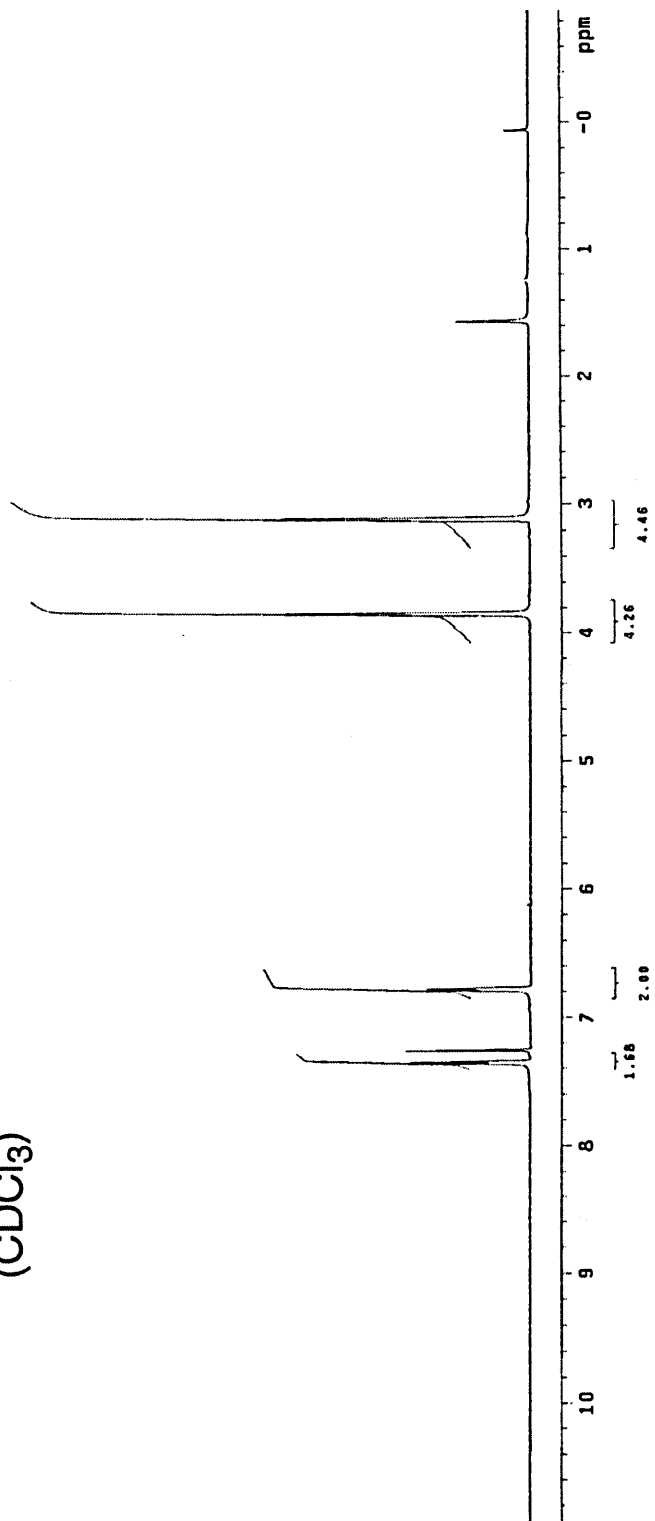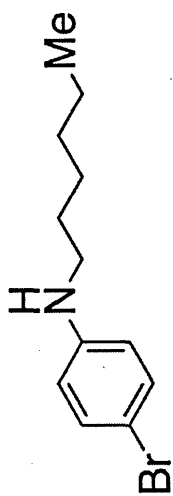
Table 7, Entry 4
(CDCl$_3$)

91
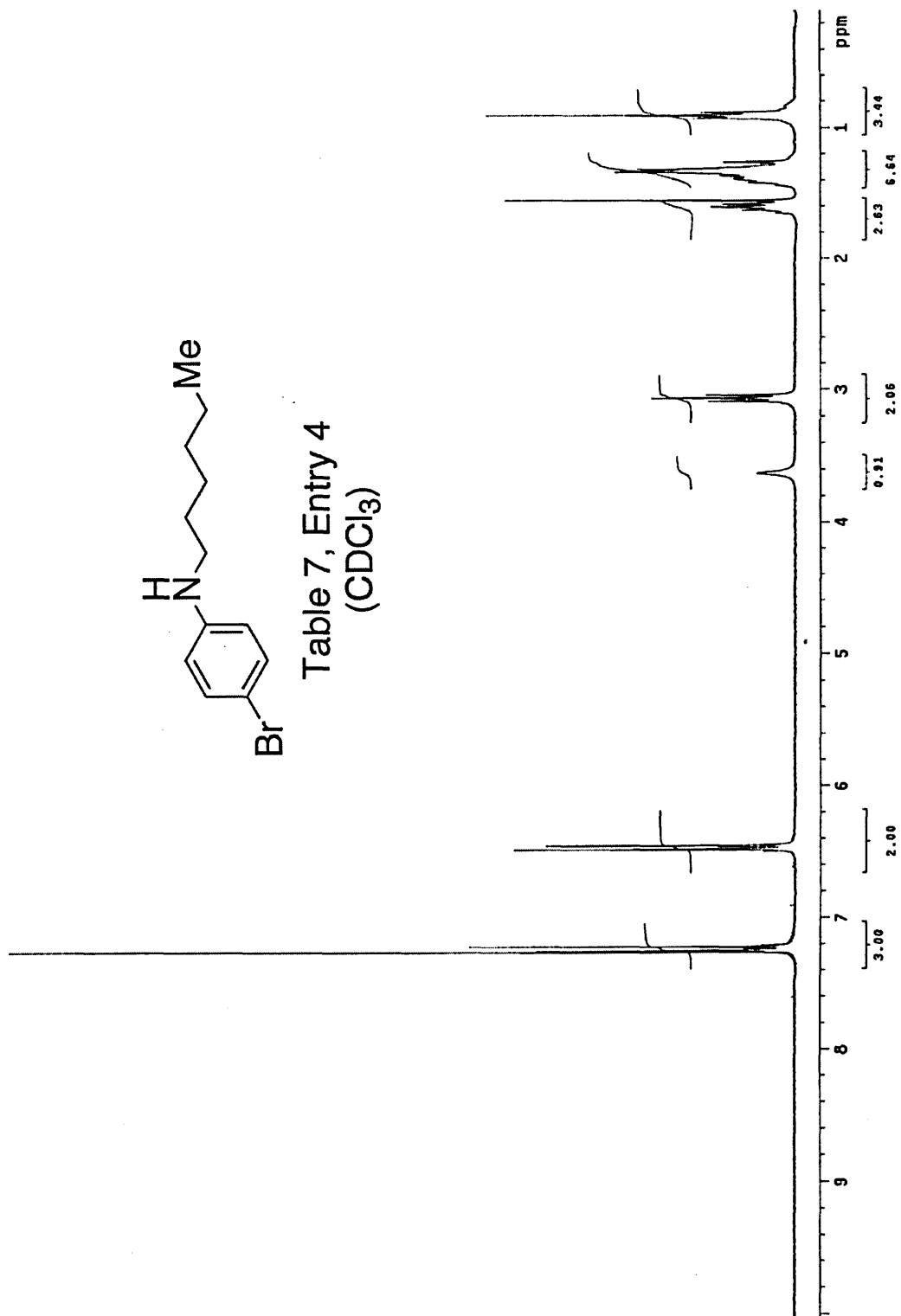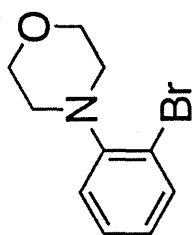
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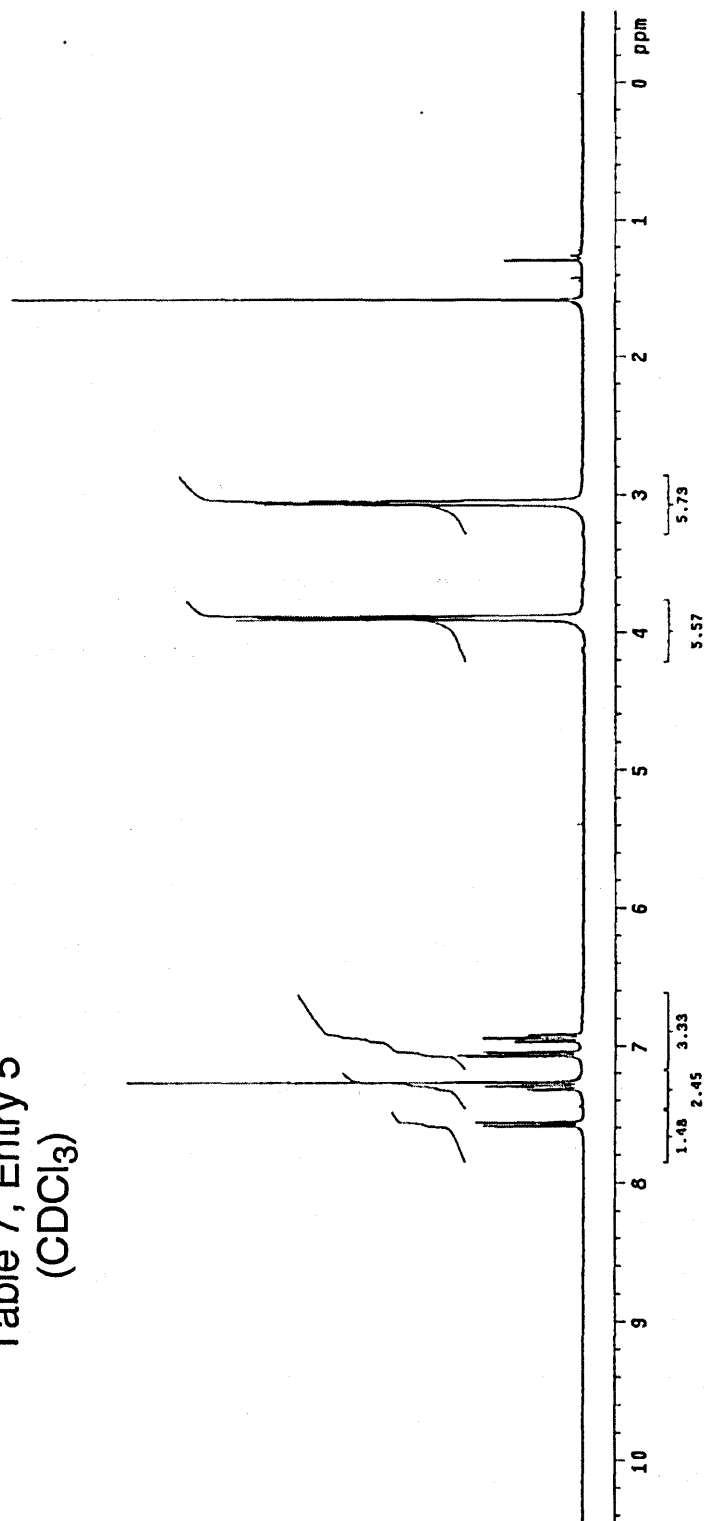
References

(1) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125.

(2) Wolfe, J. P.; Wagaw, J. –F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805.

(3) Hartwig, J. F. *Angew. Chem. Int. Ed.* **1998**, *37*, 2046.

(4) Muci, A. R.; Buchwald, S. L. *Topics in Current Chem.* **2002**, *219*, 131.

(5) Hartwig, J. F. *Pure Appl. Chem.* **1999**, *71*, 1417.

(6) Hartwig, J. F. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed; Wiley-Interscience: New York, 2002; p 1051.

(7) Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158.

(8) Singer, R. A.; Buchwald, S. L. *Tetrahedron Lett.* **1999**, *40*, 1095.

(9) Ahman, J.; Buchwald, S. L. *Tetrahedron Lett.* **1997**, *38*, 6363.

(10) Wolfe, J. P.; Ahman, J.; Sadighi, J. P.; Singer, R. A.; Buchwald, S. L. *Tetrahedron Lett.* **1997**, *38*, 6367.

(11) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 1264.

(12) Louie, J.; Driver, M. S.; Hamann, B. C.; Hartwig, J. *J. Org. Chem.* **1997**, *62*, 1268.

(13) Niederprum, H.; Voss, P.; Beyl, V. *Liebigs Ann. Chem.* **1973**, 20.

(14) Subramanian, L. R.; Bentz, H.; Hanack, M. *Synthesis* **1973**, 293.

(15) Zhu, J.; Bigot, A.; Tran Huu Dau, M. E. *Tetrahedron Lett.* **1997**, *38*, 1181.

(16) Boisnard, S.; Chastanet, J.; Zhu, J. *Tetrahedron Lett.* **1999**, *40*, 7469.

(17) Neuville, L.; Bigot, A.; Tran Huu Dau, M. E.; Zhu, J. *J. Org. Chem.* **1999**, *64*, 7638.

(18) For reviews on the synthesis of triflates and nonaflates, see: (a) Stang, P. J.; Hanack, M.; Subramanian, L. R. *Synthesis* **1982**, 85. (b) Ritter, K. *Synthesis* **1993**, 735.

(19) Aryl nonaflates are prepared using perfluoro-1-butanesulfonyl fluoride (Aldrich Chem. Co.), which is comparable in price to triflic anhydride (Aldrich Chem. Co.).

(20) Blettner, C. G.; Konig, W. A.; Stenzel, W.; Schotten, T. *J. Org. Chem.* **1999**, *64*, 3885.

(21) Rottlander, M.; Knochel, P.; *J. Org. Chem.* **1998**, *63*, 203.

(22) Jensen, A. E.; Dohle, W.; Knochel, P. *Tetrahedron* **2000**, *56*, 4197.

(23) Lipshutz, B. H.; Buzard, D. J.; Yun, C. S. *Tetrahedron Lett.* **1999**, *40*, 201

(24) Al-Masum, M.; Livinghouse, T. *Tetrahedron Lett.* **1999**, *40*, 7731.

(25) Lipshutz, B. H.; Buzard, D. J.; Vivian, R. W. *Tetrahedron Lett.* **1999**, *40*, 6871.

(26) Denmark, S. E.; Sweis, R. F. *Org. Lett.* **2002**, *4*, 3771.

(27) Zhang, X.; Sui, Z. *Tetrahedron Lett.* **2003**, *44*, 3071.

(28) Webel, M.; Reissig, H. U. *Synlett* **1997**, 1141.

(29) Bellina, F.; Ciucii, D.; Rossi, R.; Vergamini, P. *Tetrahedron* **1999**, *55*, 2103.

(30) Okauchi, T.; Yano, T.; Fukamachi, T.; Ichikawa, J.; Minami, T. *Tetrahedron Lett.* **1999**, *40*, 5337.

(31) Brase, S. *Synlett* **1999**, 1654.

(32) Bellina, F.; Ciucci, D.; Vergamini, P.; Rossi, R. *Tetrahedron* **2000**, *56*, 2533.

(33) Lyapkalo, I. M.; Webel, M.; Reissig, H.-U. *Synlett* **2001**, 1293.

(34) Lyapkalo, I. M.; Webel, M.; Reissig, H. –U. *Eur. J. Org. Chem.* **2001**, 4189.

(35) Lyapkalo, I. M.; Webel, M.; Reissig, H.-U. *Eur. J. Org. Chem.* **2002**, 1015.

(36) Wada, A.; Leki, Y.; Ito, M. *Synlett* **2002**, 1061.

(37) Lyapkalo, I. M.; Webel, M.; Reissig, H. –H. *Eur. J. Org. Chem.* **2002**, 3646.

(38) Li, S.; Dieter, R. K. *J. Org. Chem.* **2003**, *68*, 969.

(39) Amination reactions utilizing sulfoximines and aryl nonaflates has been reported: Bolm, C.; Hildebrand, J. P.; Rudolph, J. *Synthesis* **2000**, *7*, 911.

(40) Louie, J.; Hartwig, J. F. *Macromolecules* **1998**, *31*, 6737.

(41) Wolfe, J. P.; Ahman, J.; Sadighi, J. P.; Singer, R. A.; Buchwald, S. L. *Tetrahedron Lett.* **1997**, *38*, 6367.

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

(43) Previous uses of XantPhos in C-N bond-forming reactions: (a) Guari, Y.; van Es, D. S.; Reek, J. N. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Tetrahedron Lett.* **1999**, *40*, 3789. (b) Wagaw, S.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 10251. (c) Harris, M. C.; Geis, O.; Buchwald, S. L. *J. Org. Chem.* **1999**, *64*, 6019. (d) Yin, J.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 1101. (e) Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 6043.

(44) For a kinetic study of XantPhos/Pd-catalyzed amine arylation reactions, see: Guari, Y.; van Strijdonck, G. P. F.; Boele, M. D. K.; Reek, J. N. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Chem. Eur. J.* **2001**, *7*, 475.

(45) Surprisingly, reactions of 4-bromophenyl nonaflate with either morpholine or aniline in the presence of **2** and K_3PO_4 as the base, led preferentially to amination at bromine along with the diamination products. No reaction was observed with *n*-hexylamine.

(46) DPEphos = bis[2-(diphenylphosphino)phenyl]-ether; dppf = 1,1'-Bis(diphenylphosphino)ferrocene.

(47) This is the same behavior observed with the corresponding aryl triflate (see Ref. 11).

(48) Most reactions using K_3PO_4 as base did not proceed beyond 65% conversion.

(49) Cleavage of the nonaflate was observed in the presence of amine and alkoxide in the absence of Pd. This side reaction had also been observed with the corresponding triflates (See Ref. 12).

(50) These halide additives are often necessary to obtain high yields of coupled products with aryl triflates in Stille reactions: (a) Echavarren, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1987**, *109*, 5478. (b) Farina, V.; Krishnan, B.; Marshall, D. R.; Roth, G. P. *J. Org. Chem.* **1993**, *58*, 5434 and references therein.

(51) It has been reported that the addition of halides inhibits the amination of aryl halides: (a) Louie, J.; Hartwig, J. F. *Tetrahedron Lett.* **1995**, *36*, 3609. (b) Guram, A. S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 7901.

(52) In these reactions only trace amounts of phenol or diamination products were detected by GC analysis.

(53) For recent Pd-catalyzed reactions where an aryl halide (Br, Cl) reacts in preference to an aryl triflate, see: (a) Littke, A. F.; Schwarz, L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 6343. (b) Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989. (c) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020.

(54) Subramanian, L. R.; Garcia Martinez, A.; Herrero Fernandez, A.; Martinez Alvarez, R. *Synthesis* **1984**, 481.

(55) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1144.

(56) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 1264.

(57) Marcoux, J. F.; Wagaw, S.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 1568.

(58) Louie, J.; Driver, M. S.; Hamann, B. C.; Hartwig, J. F. *J. Org. Chem.* **1997**, *62*, 1268.

(59) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 1133.

(60) Pandey, G.; Sudha, Rani, R.; Bhalerau, V. T. *Tetrahedron Lett.* **1990**, *31*, 1199.

(61) Strekowski, L.; Cegla, M. T.; Harden, D. B.; Kong, S.-B. *J. Org. Chem.* **1989**, *54*, 2464.

(62) Watanabe, Y.; Tsuji, Y.; Ige, H.; Ohsugi, Y.; Ohta, T. *J. Org. Chem.* **1984**, *49*, 3359.

(63) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722.

(64) Hellwinkel, D.; Hemann. *Chem. Ber.* **1986**, *119*, 3165.

(65) Burger, D.; Darby. *J. Am. Chem. Soc.* **1955** *77*, 5733.

(66) Kanie, K.; Mizuno, K.; Kuroboshi, M.; Hiyama, T. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 1973.

(67) Wullner, G.; Jansch, H.; Kauueuberg, S.; Schubert, F.; Boche, G. *Chem. Commun.* **1998**, *15*, 1509.

(68) Takeuchi, H.; Takano, K. *J. Chem. Soc. Perkin Trans. 1* **1986**, 611.

(69) Pearson, A. J.; Gelormini, A. M. *J. Org. Chem.* **1994**, *59*, 4561.

(70) Tsuji, Y.; Huh, K.-T.; Ohsugi, Y.; Watanabe, Y. *J. Org. Chem.* **1985**, *50*, 1365.

(71) Beletskaya, I. P.; Bessmertnykh, A. G.; Guillard, R. *Tetrahedron Let.* **1999**, *40*, 6393.

(72) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 6066.

Chapter 2

**Palladium-Catalyzed C-N Bond-Forming Reactions of Difficult Substrate
Combinations Using Bulky Monophosphinobiaryl Ligands**

Introduction

While significant progress has been made in palladium-catalyzed C-N bond-forming processes, many common functional groups have been incompatible with the typical reaction protocols.[1-3] A significant improvement was made through the use of weaker inorganic bases (e.g., K_3PO_4, Cs_2CO_3), which allowed the successful coupling of substrates bearing base-sensitive functional groups, such as nitriles, enolizable ketones and esters.[4,5] As a result, reactions using these weak bases were much slower than those employing NaO*t*-Bu and usually required higher palladium loadings to push to completion. Alternatively, the use of $LiN(TMS)_2$ as a base increased the substrate scope to include substrates bearing free hydroxyl groups.[6]

In recent years, we have placed considerable effort on developing more stable and active palladium catalysts based on a series of biphenylmonophosphinobiaryl ligands.[7,8] Catalysts based on this class of ligands have not only displayed high stability, but also have shown increased reactivity in palladium-catalyzed carbon-carbon, carbon-nitrogen, and carbon-oxygen bond-forming reactions.[1-3,7,8] Through empirical and mechanistic studies, we discovered a structural derivative of these ligands that produced a catalytic system with both a greater degree of activity and stability than our previous generations of ligands.[9]

Figure 1. Substitution affects on the activity/stability of phosphinobiaryl phosphines.

Increased Steric Bulk = Increased Reactivity
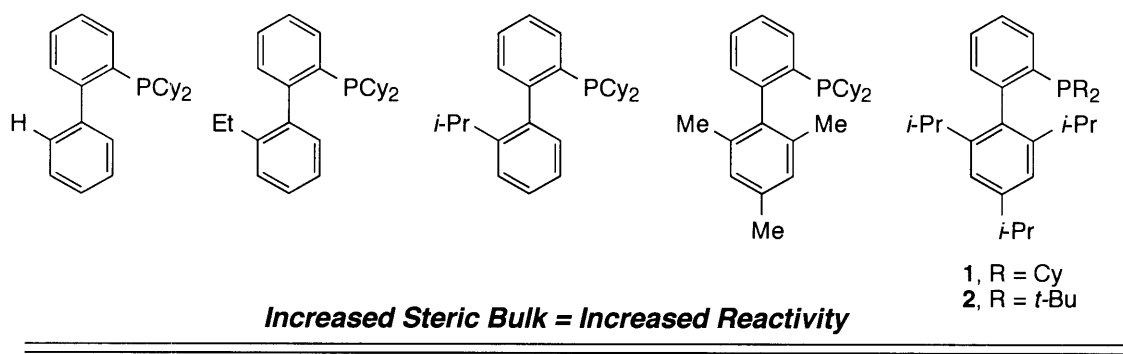
The evolution of this catalyst system was based on a number of observations with previous generations of biarylmonophosphines. First, more electron-rich

dialkylbiarylmonophosphines (e.g., alkyl = cyclohexyl or *tert*-butyl) displayed extremely high reactivity in cross-coupling reactions, specifically for the reaction of more challenging substrates, such as aryl chlorides.[3,8] Second, biarylmonophosphines bearing no substitution on the 2',2'-positions of the lower aromatic ring, have the ability to form a palladacycle when mixed with Pd(OAc)$_2$, a common palladium precatalyst used in cross-coupling reactions.[10,11] Since palladacycle formation is not preferred, because it resides outside of the catalytic cycle, substitution of these positions by an alkyl group would prevent its formation. Third, substituting the 2',2'-positions provides a more bulky ligand, which should shift the ligand/Pd equilibrium from L$_2$Pd(0) to L$_1$Pd(0) allowing more of the active catalyst in the catalytic cycle.[12,13] Finally, a bulkier phosphine should favor reductive elimination with less basic amines, which may allow the coupling of a wider range of nitrogen nucleophiles, since the electron-donating ability of the nucleophile is thought to play a role in this process.[14]

$$R \overset{\text{OSO}_2\text{Ph}}{\bigcirc} \quad + \quad \text{HNR}^1\text{R}^2 \quad \xrightarrow[\substack{\text{toluene, } t\text{-BuOH} \\ \text{Cs}_2\text{CO}_3, \ 90\text{-}110\,^\circ\text{C}}]{\text{Pd(OAc)}_2, \ \mathbf{1}} \quad R \overset{\text{NR}^1\text{R}^2}{\bigcirc} \qquad (1)$$

86-99% yields
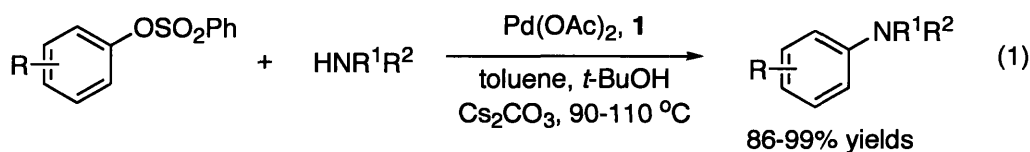
Combining all of these observations led to the discovery that catalyst systems based on Pd/2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl **1**, XPhos, provided high activity and unprecedented stability for C-N bond-forming processes.[15,16] In fact, for the first time, aryl phenylsulfonates were effectively coupled with a variety of amines and amides using this monophosphine catalyst (eq. 1).[15,16] Since this finding, catalysts based on Pd/**1** have been shown to be valuable in Suzuki-Miyaura,[17] Sonogashira[18] and α-arylation reactions of ketones[17] with aryl tosylates or aryl phenylsulfonates. These studies have led us to try reactions and substrate combinations, using Pd/**1** and its analogous phosphine derivatives, which have been futile in the application of previous catalysts.

Results and Discussion

During the course of our work we had reason to examine the palladium-catalyzed coupling reactions using 3-aminobenzamide as a nucleophile. This was despite the fact that amine substrates containing primary amides had not, to our knowledge, been successfully arylated. Interestingly, the reaction of 3-aminobenzamide and 4-aminobenzamide with 4-*tert*-butyl bromobenzene and 4-*n*-butylchlorobenzene, respectively, proceeded in excellent yield with nearly complete selectivity (>20:1) for reaction at the aniline NH_2 group (eq. 2 and 3). This result was not too surprising since catalyst systems based on the monophosphinobiaryl ligands reacted inadequately with primary amides, usually resulting in low conversion and/or decomposition of the catalyst. Of importance is that this result is complementary to that seen using the Cu-catalyzed methodology developed in our laboratories, where exclusive C-N coupling on the amide NH_2 is observed.[19] This provides the ability to switch the chemoselectivity of the coupling reactions by changing the catalyst employed, something not previously possible with reactions of this type. There are a variety of instances where Cu- and Pd-catalyzed processes provide complementary products.[15,16]
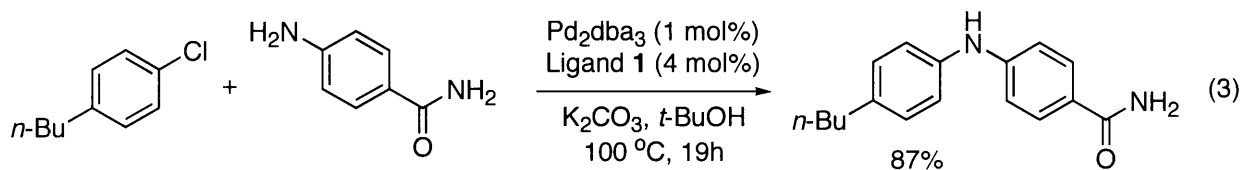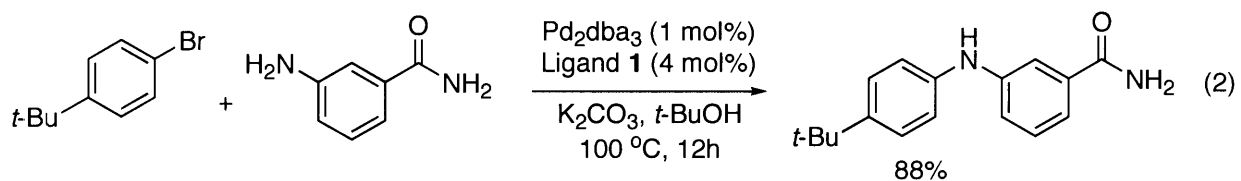
Of note, this catalyst system also had the ability to couple aniline, an aliphatic primary and cyclic secondary amine with a substrate containing a primary amide (3-chlorobenzamide), which has been problematic with previous catalyst systems (Table 1). Substrates containing free carboxylic acid groups had previously failed to be

transformed to coupling products by palladium-catalyzed amination. As can be seen, this now can be accomplished for aromatic carboxylic acids with the carboxylic acid group being either on the aryl halide, the aniline, or both. We believe, in this case, that the key is to have sufficient solubility of the carboxylic acid-containing substrates under the basic reaction conditions that are employed.

Table 1. Pd-catalyzed amination of substrates bearing amides or carboxylic acids.[a,b]

79%[c]
82%[d]

81%[e]

83%[e]

85%[f]

78%[f]

91%[g,h]
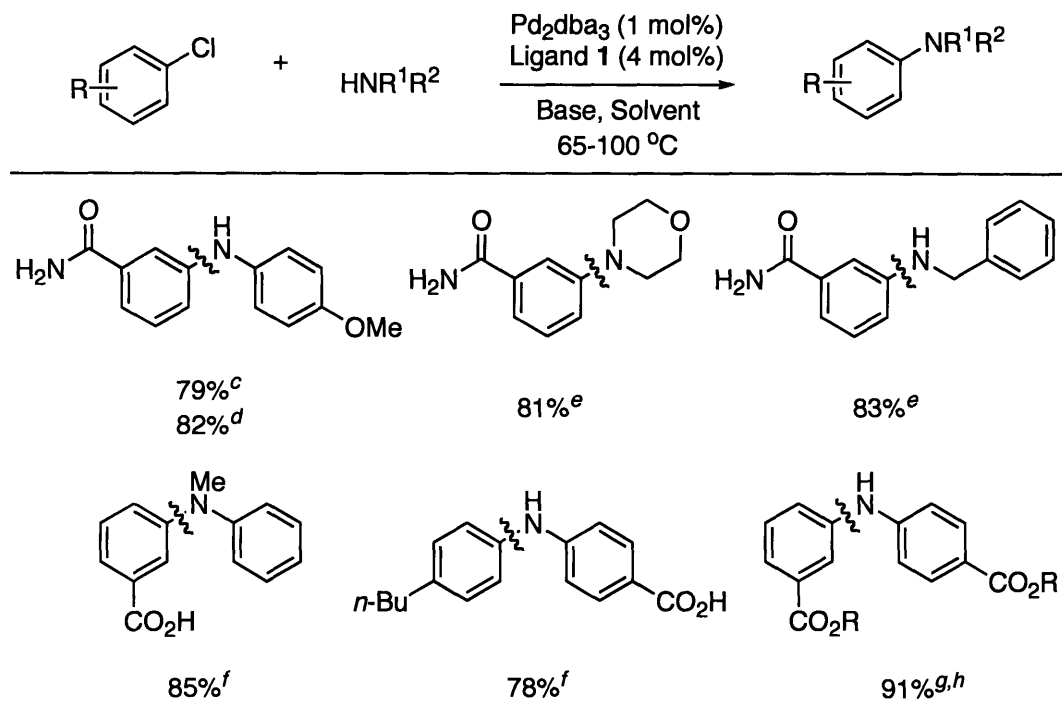
[a]Reaction conditions: 1.0 equiv. of aryl chloride, 1.2-1.4 equiv. of amine. [b]Yields represent isolated yields of compounds estimated to be ≥ 95% pure as judged by ^{1}H NMR, GC analysis and combustion analysis. [c]K_2CO_3 as base in t-BuOH, 100 °C, 20h. [d]NaOt-Bu as base in toluene, 100 °C, 18h. [e].LiN(TMS)$_2$ as base in THF, 65 °C, 16h. [f]KOH as base in t-BuOH, 110 °C, 3h. [g]KOH as base in t-BuOH, 100 °C, 24h. [h]Starting materials with R = H were used; the product (R = Me) was isolated after treatment with TMSCl in MeOH at 0 °C to room temperature for 12h.

As the use of KOH in t-BuOH oftentimes gave superior results, we decided to examine the use of water as a "solvent" for aminations using no cosolvent.[20] The use of Pd$_2$dba$_3$/1 and KOH in water in many cases gives excellent results (eq. 4).

101

HNR^{1}R^2

Pd$_2$dba$_3$ (0.5 mol%)
Ligand 1 (2 mol%)
————————————
KOH, water, 3-6 h
110 °C

R—Cl → R—NR^{1}R^2

93%   Me   84%   (4)
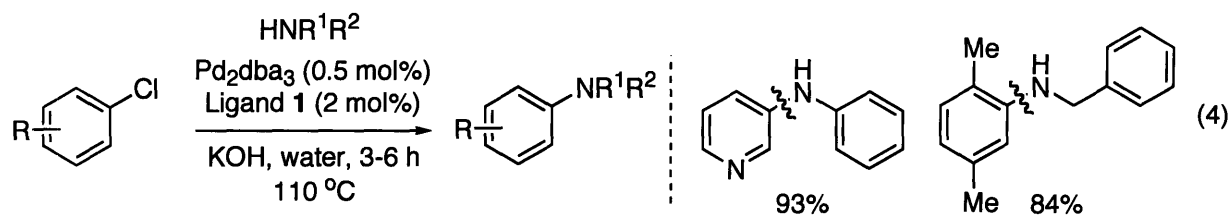
2-Aminoheterocycles have previously been inefficient electrophilic components for C-N bond-forming processes using monophosphine ligands. Thus, we examined the coupling of 2-amino-5-chloropyridine with aniline and morpholine (with 1) and benzyl amine (with 2) and were pleased to find that these reactions proceeded in good yield.

Table 2. Palladium-catalyzed amination of 5-chloro-2-aminopyridine.[a,b]

2 mol% Pd$_2$dba$_3$
8 mol% ligand 1 or 2
————————————
LiHMDS, THF
65 °C, 18 h

H_2N—Cl + HN(R')R" → N(R')R"

89%   79%   77%[c]
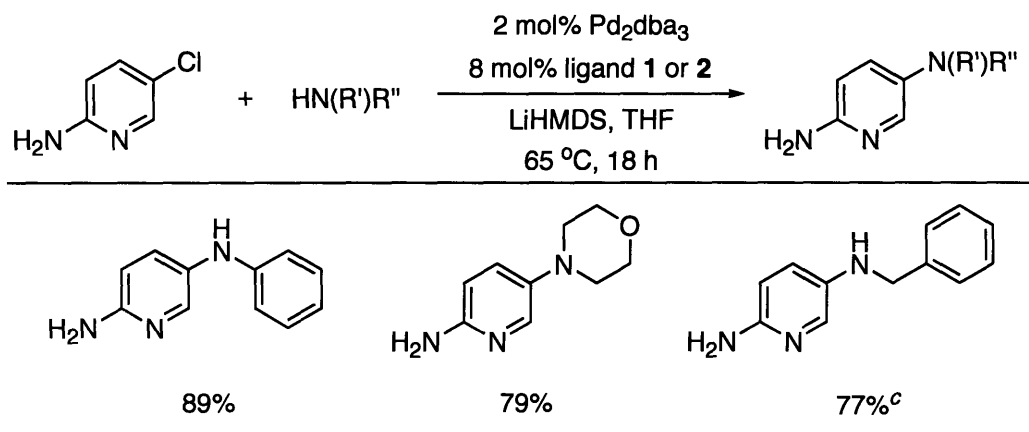
[a]Reaction conditions: 1.0 equiv. of aryl chloride, 1.4 equiv. of amine, 3.0 equiv. LiHMDS, Pd$_2$dba$_3$ (2 mol% Pd), ligand 1 (8 mol%), THF, 65 °C. [b]Yields represent isolated yields of compounds estimated to be ≥ 95% pure as judged by ^{1}H NMR, GC analysis and combustion analysis. [c]Ligand 2 was used.

The observed chemoselectivity in many of these processes may arise from the fact that the more basic amines (e.g., anilines, primary and secondary aliphatic amines) bind much more tightly to Pd than the weakly basic 2-aminoheteroaromatics, primary amides or HN-heteroaromatics, thus deprotonation of this species would provide the product. This is in contrast to what is observed for the competition reaction of anilines and primary aliphatic amines (Figure 2).[15] In this case, the aniline reacts faster than the primary alkyl amine. Thus, there must be a cutoff point with respect to the basicity and/or binding ability of the amine to Pd and the rate for deprotonation of the Pd-coordinated amine (binding affinity K_b vs. rate of deprotonation k_d of the Pd-bound

amine), if the chemoselectivity is determined in this step of the catalytic cycle.[21] Alternatively, the same selectivity would be observed if reductive elimination of the weakly basic Pd-amides were slow enough to allow associative amine exchange on palladium with the more basic amines.

Figure 2. Hypothesis for chemoselectivity in Pd-catalyzed amination.

$$L_nPd(II){<}^{Ar}_{X} \ + \ H{-}\overset{\cdot\cdot}{N}(R^2)_2 \ \overset{K_b}{\rightleftharpoons} \ L_nPd(II){<}^{Ar}_{X} \ \underset{H{-}\overset{\cdot\cdot}{N}(R^2)_2}{|} \ \overset{k_d}{\underset{Base}{\longrightarrow}} \ L_nPd(II){<}^{Ar}_{N(R^2)_2} \ + \ Base{-}H$$

Binding to $L_nPd(II)ArX$: K_b (aniline) < K_b (1° alkyl amine)
Deprotonation of $L_nPd(II)Ar(HNR^1R^2)$: k_d (aniline) >> k_d (1° alkyl amine) ◄ - - - - - - | Deprotonation controls selectivity |

Binding to $L_nPd(II)ArX$: K_b (2-aminopyridine) << K_b [HN(R')R"] ◄ - - - - - - - - - - - | Binding or nucleophilic attack controls selectivity |
Deprotonation of $L_nPd(II)Ar(HNR^1R^2)$: k_d (2-aminopyridine) >> k_d [HN(R')R"]

Successful coupling of 2-aminoheterocycles, as a nucleophilic component, with aryl bromides had only been accomplished utilizing Pd/XantPhos[22] or BINAP[23] catalyst systems.[24,25] A common belief is that using a bidentate ligand would prevent any coordination to a Pd(II) species of the "guanidine-like" moiety of these substrates. Thus, the discovery that a catalyst comprised of Pd$_2$dba$_3$ and **2** was effective in the N-arylation of 2-aminopyridine, was somewhat surprising. An assortment of other biarylmonophosphine based catalysts worked to a lesser degree for this challenging reaction, as shown in Table 3. We postulate that the more sterically encumbered ligands prevent any unwanted coordination of 2-aminoheterocycles to the Pd(II) center,

thus allowing the catalyst to remain active throughout the course of the reaction. Also, such a bulky ligand could avert ligand decomposition by preventing substitution of the ligand on palladium by the aminoheterocycle. Since aminoheterocycles are not as basic as other aryl amines,[26] it is possible that the bulkier ligand may also facilitate reductive elimination of the palladium-coordinated amide complex. Interestingly, if the steric bulk of the ligand is increased too much, the reaction slows down dramatically, which may be due to decomposition of the catalyst since it would be more difficult for the metal to be coordinated to the ligand.

Table 3. Ligand effects in the N-arylation of a 2-aminoheterocycle.[a,b]

Ligand:	1	2	3	4	5	6	7
Conversion:	52%	74%	32%	20%	56%	27%	20%
Yield (GC):	48%	70%	32%	20%	52%	27%	20%

[a]Reaction conditions: 1.0 equiv. of aryl chloride, 1.2-1.4 equiv. of amine, 1.4 equiv. NaOt-Bu, Pd₂dba₃ (4 mol % Pd), ligands 1-7 (8 mol %), toluene, 100 °C, 5 h. [b]Yields represent GC-yields calculated by using an internal standard (n-dodecane).

We explored the use of the Pd/2 catalyst for a diverse array of substrate combinations. Substrates bearing a free hydroxyl group and a indole -NH react well with 2-aminopyridine and 2-aminopyrimidine, respectively, providing 92% and 90% of the resultant diarylamines (Table 4). In accord with the previous result, reaction at the

heteroaromatic $-NH_2$ group prevails over reaction at a primary amide providing 94%

yield in the coupling of 5-bromonicotinamide and 2-aminopyridine. A variety of other

heteroaryl halides react proficiently with heteroaryl amines, such as aminopyrazine, 2-

amino-5-chloropyridine and 5-amino-N-ethyl-pyrazole. Unfortunately,

aminoheterocycles, such as 2-aminobenzothiazole or 2-aminothiazole, fail to N-arylate

using Pd/2 and other monophosphine catalysts. In fact, these aminoheterocycles inhibit

this process, indicating their role as a catalyst poison.

Table 4. Palladium-catalyzed N-arylation of aminoheterocycles.[a,b]
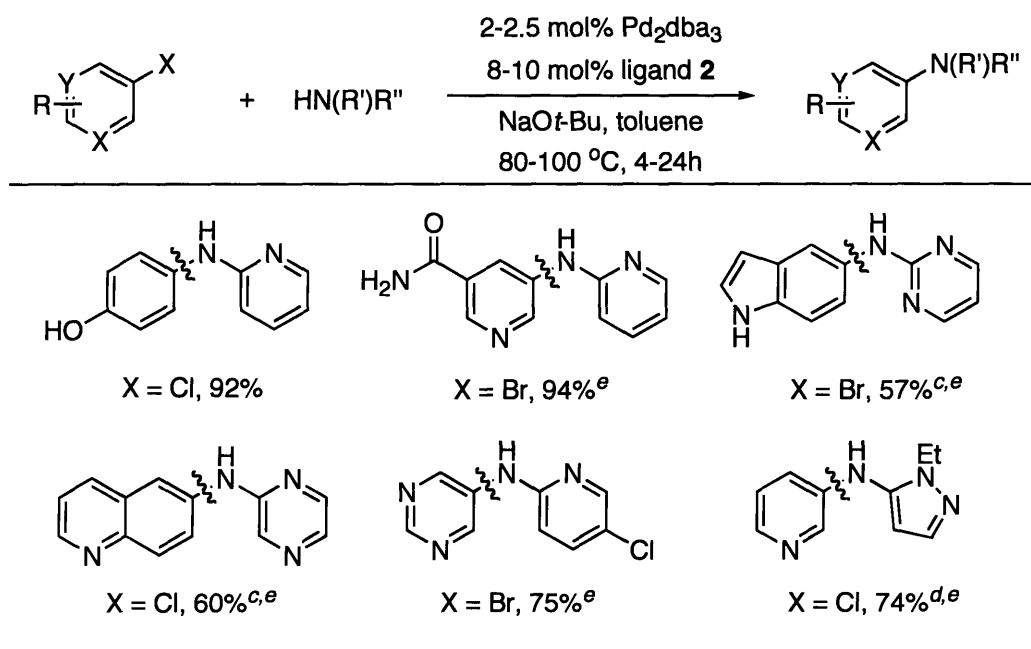
X = Cl, 92%   X = Br, 94%[e]   X = Br, 57%[c,e]

X = Cl, 60%[c,e]   X = Br, 75%[e]   X = Cl, 74%[d,e]

[a]Reaction conditions: 1.0 equiv. of aryl chloride, 1.2-1.4 equiv. of amine, 1.5-3.5 equiv. NaOt-Bu, toluene, Pd_2dba_3 (4-5 mol% Pd), ligand **2** (8-10 mol %), 80-100 °C. [b]Yields represent isolated yields of compounds estimated to be ≥ 95% pure as judged by ^{1}H NMR, GC analysis and combustion analysis. [c]Cs_2CO_3 and N,N-dimethylformamide were used. [d]1,4-Dioxane was used as the solvent. [e]Reactions were conducted by Rachel E. Tundel.

Prior work on the N-arylation of indoles and pyrroles revealed that catalytic

systems based on monophosphinobiaryl ligands were somewhat effective.[27] In contrast,

more acidic heterocycles, such as indazole or pyrazole have not been reported to be

coupling partners in palladium based methods.[28] Given our success with the Pd/2

combination for the coupling of less basic 2-aminoheterocycles, we felt that it might also

be quite effective for the coupling of these nitrogen heterocycles. Indazole/pyrazole are

expected to be less basic than their indole/pyrrole counterparts, thus a more bulky phosphine might speed up reductive elimination from a Pd aryl/amido intermediate and/or prevent coordination of more than one heterocycle to any Pd intermediates. Based on earlier mechanistic work, heterocycles have been shown to over-saturate Pd, thus inactivating such catalysts.[29] Our hypothesis led us in the right direction; however, it is still unclear whether this ligand significantly prevents any inhibitory effects of nitrogen heterocycles or speeds up reductive elimination, since higher palladium loadings are necessary.

Table 5. Ligand effects in the N-arylation of indazole.[a,b]

Ligand:	1	2	3	4	8
Conversion:	0%	52%	17%	57%	30%
Yield (GC):	0%	48%	14%	52%	22%

[a]Reaction conditions: 1.0 equiv. of aryl bromide, 1.2 equiv. of amine, 1.5 equiv. K_3PO_4, 1,4-dioxane, Pd_2dba_3 (4 mol% Pd), ligand 1-8 (8 mol %), 100 °C. [b]Yields represent GC-yields calculated by using an internal standard (n-dodecane).

As is shown in Table 5, ligands 2 and 4 provided moderate conversion in the reaction of 3-bromoanisole and indazole with K_3PO_4 and 1,4-dioxane at 100 °C, resulting in formation of the N-1 arylated product exclusively.[30] This result is observed in Cu-catalyzed methodology. It contrasts, however, that seen for the reaction with aryl

bromides with the copper system, where a mixture of N-1 and N-2 arylated products is observed.[31] Optimization of the reaction conditions revealed that use of bases NaOt-Bu (toluene, 80 °C) or Cs_2CO_3 (1,4-dioxane,105 °C) provided the N-1 arylated indazole in excellent yields using $Pd_2dba_3/2$. Interestingly, when NaOt-Bu is used as the base at 100 °C, mixtures of N-1 and N-2 arylated products are observed. One explanation for this is that I is the kinetically formed species, as binding of the N-1 lone-pair of electrons would disrupt aromaticity (I', Scheme 1). At 80 °C (with NaOt-Bu) or at 105 °C (with Cs_2CO_3), conversion to II occurs faster than deprotonation. This system effectively coupled 3-chloroanisole and indazole, displaying another advantage of palladium over copper-based methods where aryl chlorides are generally nonproductive coupling partners (Table 6). Further, for the first time, pyrazoles are reacted with both an aryl bromide and aryl chloride using palladium as the metal.

Scheme 1. Hypothesis for chemoselectivity for N-arylation of indazole.
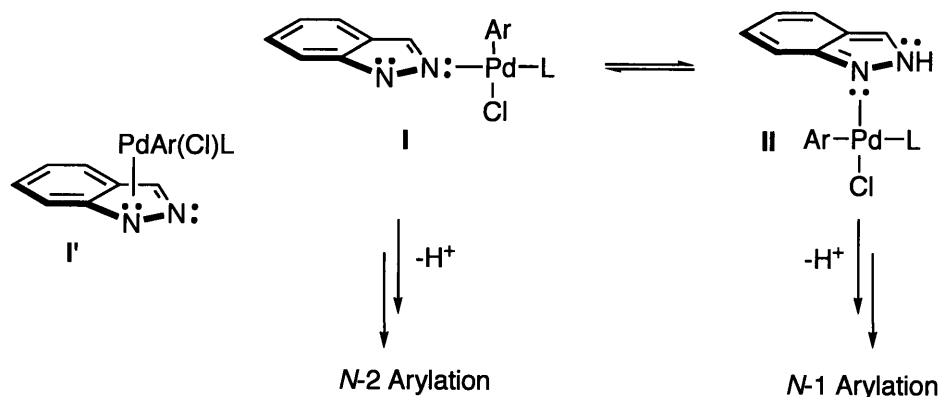
We have also explored the coupling of some aminoheterocycles and/or pyrazole substrates (Table 7). The results that we have obtained, in some cases, complement those previously obtained with Cu-catalyzed protocols. Not surprising, chemoselectivity of the aniline $-NH_2$ reacts in preference to indazole –NH providing 67% yield in the reaction of 5-aminoindazole with 5-bromo-m-xylene. We were particularly surprised to find that 5-amino-3-phenylpyrazole could be selectively arylated at the primary amino

group, which represents the first time, to our knowledge, that an unprotected aminopyrazole has ever reacted with this mode of chemoselectivity in a metal-catalyzed C-N bond-forming process. For instance, we have previously shown with Cu-catalysts, that aminopyrazoles react preferentially at the pyrazole -NH, again representing complementarity between Pd- and Cu-based methods.[31] Finally, for the first time a free (H)N-bromopyrazole can be successfully aminated, in this case with aniline as shown.

Table 6. Palladium-catalyzed N-arylation of indazole and pyrazole.[a,b]

$$
\begin{array}{ccc}
\text{R} \overset{Y}{\underset{X}{\bigodot}} X + \text{H-Het} & \xrightarrow[\substack{\text{NaO}t\text{-Bu, toluene} \\ 60\text{-}100\ ^\circ\text{C, 12-24h}}]{\substack{\text{2-2.5 mol\% Pd}_2\text{dba}_3 \\ \text{8-10 mol\% ligand 2}}} & \text{R} \overset{Y}{\underset{X}{\bigodot}} \text{Het}
\end{array}
$$

X = Cl, 97%	X = Br, 62%	X = Br, 88%[c]	X = Cl, 76%[c]
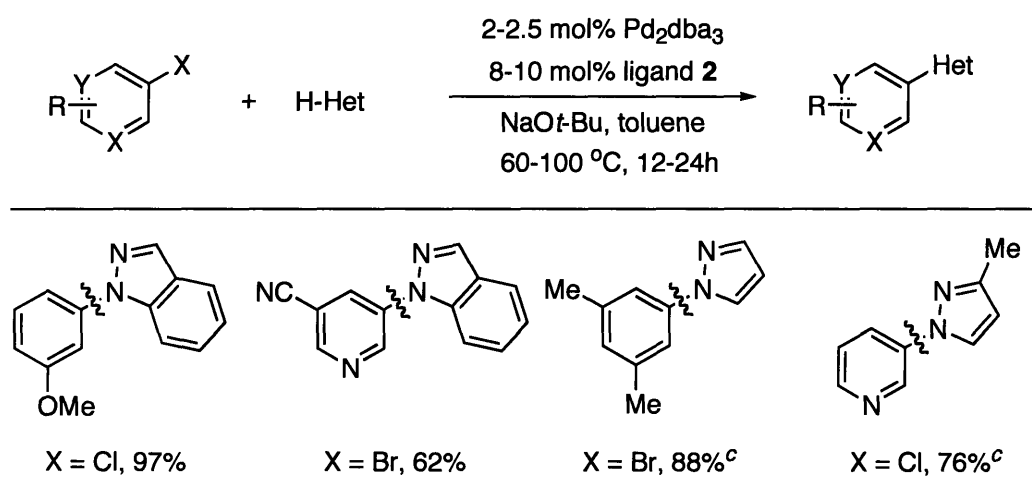
[a]Reaction conditions: 1.0 equiv. of aryl halide, 1.2 equiv. of amine, 1.5 equiv. NaOt-Bu, toluene, Pd₂dba₃ (4-5 mol% Pd), ligand 2 (8-10 mol %), 60-100 °C. [b]Yields represent isolated yields of compounds estimated to be ≥ 95% pure as judged by ¹H NMR, GC analysis and combustion analysis. [c]Reactions were conducted at 105 °C.

Table 7. Interesting chemoselectivity in palladium-catalyzed C-N bond-formation.[a,b]

72%   67%   94%

88%

Our previous work using CuI:

88% (ArI)[c]
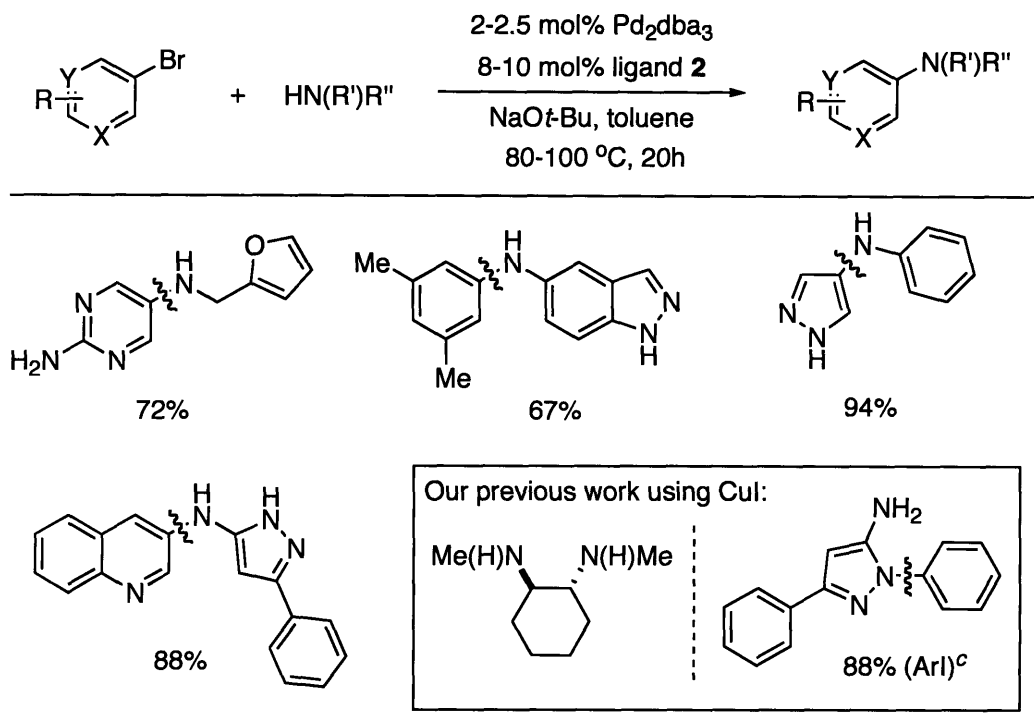
[a]Reaction conditions: 1.0 equiv. of aryl halide, 1.2-1.4 equiv. of amine, 1.5-3.5 equiv. NaOt-Bu, toluene, Pd$_2$dba$_3$ (4-5 mol% Pd), ligand **2** (8-10 mol %), 80-100 °C. [b]Yields represent isolated yields of compounds estimated to be ≥ 95% pure as judged by ^{1}H NMR, GC analysis and combustion analysis. [c]See: Ref. 31.

In conclusion, we have developed highly reactive catalysts based on Pd and dialkylbiaryphosphino ligands, particularly **1** or **2**. These provide unprecedented reactivity and selectivity in C-N bond-forming processes. The bulky monophosphine catalyst Pd/**1** was effective for the reaction of aryl/heteroaryl halides bearing primary amides and 2-aminoheterocycles. Also, the more sterically encumbered catalyst systems based on Pd and ligand **2** were found to be more proficient for the *N*-arylation of 2-aminoheterocycles and weakly basic HN-heterocycles: pyrazole and indazole. The chemoselectivity of these catalysts was explored and the rough order of reactivity for amines follows the general trend: aryl amines > > primary and secondary aliphatic amines > 2-aminoheteroaromatics > primary amides ≈ HN-heterocycles. We hypothesize that the efficacy of palladium catalysts based on ligands **1** or **2** is attributed to a combination of factors: 1) A maximization of the amount of L$_1$Pd intermediates. This speeds the desired catalytic process relative to different modes of catalyst

decomposition. 2) Providing a quasi-stable L_1Pd, $L_1Pd(Ar)X$ and $L_1Pd(Ar)Amine$ intermediates because the size of these complexes slows bimolecular decomposition processes and because of stabilizing Pd/arene interactions. 3) Providing $L_1Pd(Ar)Amine$ intermediates with especially sterically demanding L_1 facilitates the rate of reductive elimination to form product. Further, this work demonstrates that monodentate ligands are viable alternatives to and sometimes superior to chelating ones' in Pd-catalyzed C-N bond-forming processes.

Experimental

Reagents: All reactions were carried out under an argon atmosphere. $Pd(OAc)_2$ and Pd_2dba_3 were obtained from Engelhard and used without further purification. Ligands **1** and **2** were prepared according to literature procedure and are also commercially available from Strem and Aldrich Chemical Company. Ligands **3-8** were prepared according to literature procedures. NaO*t*-Bu was stored under nitrogen in a Vacuum Atmosphere glovebox. Small portions (1-2 g) were removed from the glovebox in glass vials, stored in the air in desiccators filled with anhydrous calcium sulfate, and weighed in the air. Anhydrous granular potassium phosphate and potassium carbonate were purchased from Mallinckrodt Chemicals and ground with a mortar and pestle and stored in a bench-top dessicator. Toluene was purchased from J. T. Baker in CYCLE-TAINER solvent delivery kegs, which were vigorously purged with argon for 2 h, and further purified by passing the solvent through two packed columns of neutral alumina and copper (II) oxide under argon pressure. Anhydrous *t*-BuOH was purchased from Aldrich Chemical Co. and used without further purification. Water was used after degassing by sonicating under high vacuum for 30 seconds. All other reagents were purchased from commercial sources and used without further purification.

Analytical Methods. IR spectra were obtained on a Perkin-Elmer Model 2000 FT-IR using NaCl plates (thin film). ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker 400 MHz instrument with chemical shifts reported in ppm relative to the residual deuterated solvent or the internal standard tetramethylsilane. Yield refers to isolated yields of compounds greater than 95% purity as determined by capillary gas chromatography (GC), and proton Nuclear Magnetic Resonance spectroscopy (^1H NMR) analysis. Yields of products reported in Tables 1-8 are an average of two or more runs. The procedures described in this section are representative, thus, the yields may differ slightly from those given in Tables 1-8. ^1H NMR and melting points (where applicable) of all known compounds were taken. All new amines were further characterized by elemental analysis. Experiments and characterization data for compounds in Table 5 (entries 2-6) were carried out by Rachel E. Tundel and can be found in *Angew. Chem. Int. Ed* **2006** or her undergraduate thesis (MIT, 2006).

3-(4-*tert*-Butylphenylamino)benzamide (eq. 2). An oven-dried resealable Schlenk tube was evacuated and backfilled with argon. The Schlenk tube was charged with Pd_2dba_3 (4.6 mg, 0.0050 mmol, 1 mol % Pd), ligand **1** (9.4 mg, 0.020 mmol, 2 mol %), ground K_2CO_3 (193 mg, 1.40 mmol) and 3-aminobenzamide (204 mg, 1.49 mmol). The Schlenk tube was evacuated and backfilled with argon (this sequence was repeated three times) and then capped with a rubber septum. To the Schlenk tube was added 4-*t*-butyl-1-bromobenzene (0.173 mL, 1.00 mmol) and *t*-BuOH (2 mL). The septum was replaced with a Teflon screwcap, the Schlenk tube was sealed, and the mixture was heated to 100 °C (the reaction mixture was heterogeneous) with stirring until the starting aryl bromide was consumed according to GC analysis (12 h; 25:1 selectivity by GC analysis). The reaction was cooled to room temperature, diluted with ethyl acetate, filtered through Celite, and concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/hexanes, 9:1) to give the desired product as a white solid (233 mg, 87%), Mp = 187-188 °C. ^{1}H NMR (400 MHz, d^6-DMSO) δ: 8.22 (s, 1H), 7.95 (s, 1H), 7.63 (s, 1H), 7.36-7.24 (m, 5H), 7.16 (d, J = 7.8 Hz, 1H), 7.07 (d, J = 8.55 Hz, 2H), 1.26 (s, 9H). ^{13}C NMR (100 MHz, d^6-DMSO) δ: 168.5, 144.2, 142.7, 140.3, 135.5, 128.9, 125.9, 118.6, 117.9, 117.5, 114.8, 38.8, 31.4. IR (neat, cm^{-1}): 3450, 3344, 1639, 1600, 1575, 1525, 1485, 1432, 830. 751. Anal. Calcd. For $C_{17}H_{20}N_2O$: C, 76.09; H, 7.51. Found: C, 75.80; H, 7.67.

4-(4-*n*-Butylphenylamino)benzamide (eq. 3). An oven-dried resealable Schlenk tube was evacuated and backfilled with argon. The Schlenk tube was charged with Pd_2dba_3 (4.6 mg, 0.0050 mmol, 1 mol % Pd), ligand **1** (9.4 mg, 0.020 mmol, 2 mol %), ground K_2CO_3 (193 mg, 1.40 mmol) and 4-aminobenzamide (163 mg, 1.20 mmol). The Schlenk tube was evacuated and backfilled with argon (this sequence was repeated three times) and then capped with a rubber septum. To the Schlenk tube was added 4-*n*-butylchlorobenzene (168 mg, 1.00 mmol) and *t*-BuOH (2 mL). The septum was replaced with a Teflon screwcap, the Schlenk tube was sealed, and the mixture was heated to 100 °C (the reaction mixture was heterogeneous) with stirring until the starting aryl chloride was consumed according to GC analysis (19 h; 20:1 selectivity by GC

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analysis). The reaction was cooled to room temperature, diluted with ethyl acetate, filtered through Celite, and concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/hexanes, 8:2) to give the desired product as a white solid (235 mg, 88%), Mp = 135-136 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.70 (d, J = 8.6 Hz, 2H), 7.15 (d, J = 8.2 Hz, 2H), 7.08 (d, J = 8.2 Hz, 2H), 6.96 (d, J = 8.6 Hz, 2H), 6.04 (s, 1H), 5.98 (s, 2H), 2.60 (t, J = 7.7 Hz, 2H), 1.61 (m, J = 7.8 Hz, 2H), 1.37 (m, J = 7.4 Hz, 2H), 0.95 (t, J = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ: 169.4, 148.2, 138.6, 138.2, 129.6, 129.4, 123.7, 121.0, 114.6, 35.2, 33.9, 22.6, 14.2. IR (neat, cm^{-1}): 3410, 3300, 3204, 1652, 1605, 1525, 1514, 1405, 1326, 822. Anal. Calcd. For C$_{17}$H$_{20}$N$_2$O: C, 76.09; H, 7.51. Found: C, 75.90; H, 7.54.

3-(4-Methoxyphenylamino)benzamide (Table 1, Entry 1). An oven-dried resealable Schlenk tube was evacuated and backfilled with argon. The Schlenk tube was charged with Pd$_2$dba$_3$ (9.2 mg, 0.010 mmol, 2 mol % Pd), ligand 1 (19.0 mg, 0.040 mmol, 4 mol %), ground K$_2$CO$_3$ (304 mg, 2.19 mmol), 3-chlorobenzamide (156 mg, 1.00 mmol) and 4-methoxyaniline (148 mg, 1.20 mmol). The Schlenk tube was evacuated and backfilled with argon (this sequence was repeated three times) and then capped with a rubber septum. To the Schlenk tube was added *t*-BuOH (2.5 mL). The septum was replaced with a Teflon screwcap, the Schlenk tube was sealed, and the mixture was heated to 100 °C (the reaction mixture was heterogeneous) with stirring until the starting aryl chloride was consumed according to TLC analysis (20 h). The reaction mixture was cooled to room temperature, diluted with ethyl acetate, filtered through Celite, and concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/hexanes, 8.5:1.5) to give the desired product which was recrystallized from ethyl acetate/hexanes (14/1) to give white flaky crystals (191 mg, 79%), Mp = 153 °C. ^{1}H NMR (400 MHz, d^6-DMSO) δ: 7.99 (s, 1H), 7.86 (s, 1H), 7.43 (s, 1H), 7.28 (s, 1H), 7.20 (d, J = 5.1 Hz, 2H), 7.07 (d, J = 8.8 Hz, 2H), 7.03 (m, 1H), 6.88 (d, J = 8.8 Hz, 2H), 3.72 (s, 3H). ^{13}C NMR (100 MHz, d^6-DMSO) δ: 168.5, 154.2, 145.4, 135.7, 135.5, 128.9, 120.9, 117.4, 114.6, 113.7, 55.2. IR (neat, cm^{-1}): 3409, 3373, 3346, 3172, 1657, 1607, 1578, 1528, 1113, 1033. Anal. Calcd. For

$C_{14}H_{14}N_2O_2$: C, 69.41; H, 5.82. Found: C, 69.42; H, 5.83. The title compound was obtained after a reaction time of 18h in 81% yield if toluene (3 mL) was used as the solvent instead of *t*-BuOH, and NaO*t*-Bu (211 mg, 2.20 mmol) was used as the base.

3-Morpholin-4-yl-benzamide (Table 1, Entry 2).[32] An oven-dried resealable Schlenk tube was evacuated and backfilled with argon. The Schlenk tube was charged with Pd_2dba_3 (9.2 mg, 0.010 mmol, 2 mol % Pd), ligand 1 (19.0 mg, 0.040 mmol, 4 mol %) and 3-chlorobenzamide (156 mg, 1.00 mmol). The Schlenk tube was evacuated and backfilled with argon (this sequence was repeated three times) and then capped with a rubber septum. To the Schlenk tube was added morpholine (0.105 mL, 1.20 mmol) and $LiN(TMS)_2$ (3.0 mL, 1.0 M in THF, 3.00 mmol)). The septum was replaced with a Teflon screwcap, the Schlenk tube was sealed, and the mixture was heated to 65 °C with stirring until the starting aryl chloride was consumed according to TLC analysis (16 h). The reaction mixture was cooled to room temperature, quenched with water, extracted with ethyl acetate, filtered through Celite, and concentrated under reduced pressure. The crude material was purified by recrystallizing from hot ethyl acetate/hexanes to provide the title compound as a white solid (168 mg, 81%), Mp = 154 °C. ^1H NMR (400 MHz, d^6-DMSO) δ: 7.93 (br-s, 1H), 7.41 (s, 1H), 7.32-7.28 (m, 3H), 7.08 (d, J = 7.6 Hz, 1H), 3.74 (t, J = 4.8 Hz, 4H), 3.14 (t, J = 4.8 Hz, 4H). ^{13}C NMR (100 MHz, d^6-DMSO) δ: 168.2, 150.9, 134.9, 128.9, 118.3, 117.8, 113.9, 66.0, 48.4.

3-Benzylamino-benzamide (Table 1, Entry 3).[32] An oven-dried resealable Schlenk tube was evacuated and backfilled with argon. The Schlenk tube was charged with Pd_2dba_3 (9.2 mg, 0.010 mmol, 4 mol % Pd), ligand 1 (19.0 mg, 0.040 mmol, 8 mol %) and 3-chlorobenzamide (78 mg, 0.500 mmol). The Schlenk tube was evacuated and backfilled with argon (this sequence was repeated three times) and then capped with a rubber septum. To the Schlenk tube was added benzyl amine (0.082 mL, 0.75 mmol) and $LiN(TMS)_2$ (2.0 mL, 1.0 M in THF, 2.00 mmol). The septum was replaced with a Teflon screwcap, the Schlenk tube was sealed, and the mixture was heated to 65 °C with stirring until the starting aryl chloride was consumed according to TLC analysis (24 h). The reaction mixture was cooled to room temperature, quenched with water, extracted with ethyl acetate, filtered through Celite, and concentrated under reduced

pressure. The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate) to give the desired product as a white solid (94 mg, 83%), Mp = 125-126 °C. ^{1}H NMR (400 MHz, d^4-MeOH) δ: 7.35 (d, J = 7.6 Hz, 2H), 7.28 (t, J = 7.6 Hz, 2H), 7.19 (t, J = 7.2 Hz, 1H), 7.15-7.11 (m, 2H), 7.05 (d, J = 7.2 Hz, 1H), 6.75 (dd, J = 2.4 Hz, J = 5.6 Hz, 1H), 4.33 (s, 2H). ^{13}C NMR (100 MHz, d^6-DMSO) δ: 168.6, 148.6, 140.1, 135.1, 128.6, 128.3, 127.2, 126.7, 115.1, 114.8, 111.3, 46.3.

3-(Methylphenylamino)benzoic acid (Table 1, Entry 4). An oven-dried resealable Schlenk tube was evacuated and backfilled with argon. The Schlenk tube was charged with Pd$_2$dba$_3$ (9.2 mg, 0.010 mmol, 2 mol % Pd), ligand 1 (19.0 mg, 0.040 mmol, 4 mol %), pulverized KOH (168 mg, 3.00 mmol) and 3-chlorobenzoic acid (156 mg, 1.00 mmol). The Schlenk tube was evacuated and backfilled with argon (this sequence was repeated three times) and then capped with a rubber septum. To the Schlenk tube was added t-BuOH (2 mL), N-methylaniline (0.163 mL, 1.50 mmol) and t-BuOH (0.5 mL). The septum was replaced with a Teflon screwcap, the Schlenk tube was sealed, and the mixture was heated to 100 °C (the reaction mixture became totally homogeneous) with stirring until the starting aryl chloride was consumed according to GC analysis (3h, monitored by converting small aliquots of the reaction mixture to the corresponding methyl ester). The reaction mixture was cooled to room temperature, diluted with 5% aqueous NaOH and extracted with diethyl ether. The aqueous layer was cooled to 0 °C and acidified with HCl (12.0 M) to pH ~ 4. The aqueous layer was extracted with diethyl ether, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to give the crude product (233 mg). The product was purified by recrystallizing from hot hexanes/chloroform (5:1) to give a light yellow solid (191 mg, 84%), Mp = 114-115 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ: 12.96 (s, 1H), 7.78 (s, 1H), 7.71 (d, J = 7.6 Hz, 1H), 7.43-7.35 (m, 3H), 7.24-7.12 (m, 4H), 3.42 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ: 173.4, 149.7, 148.9, 130.7, 130.0, 129.6, 124.1, 123.6, 123.2, 122.2, 119.6, 40.8. IR (neat, cm^{-1}): 1685, 1605, 1582, 1491, 1453, 1294, 751. HRMS Calcd. For C$_{14}$H$_{13}$NO$_2$: 227.0941. Found: 227.0945.

4-(4-n-Butylphenylamino)benzoic acid (Table 1, Entry 5). An oven-dried resealable Schlenk tube was evacuated and backfilled with argon. The Schlenk tube was charged

with Pd$_2$dba$_3$ (9.2 mg, 0.010 mmol, 2 mol % Pd), ligand 1 (19.0 mg, 0.040 mmol, 4 mol %), pulverized KOH (168 mg, 3.00 mmol) and 4-aminobenzoic acid (165 mg, 1.20 mmol). The Schlenk tube was evacuated and backfilled with argon (this sequence was repeated three times) and then capped with a rubber septum. To the Schlenk tube was added *t*-BuOH (2 mL), 4-*n*-butylchlorobenzene (168 mg, 1.00 mmol) and *t*-BuOH (0.5 mL). The septum was replaced with a Teflon screwcap, the Schlenk tube was sealed, and the mixture was heated to 100 °C (the reaction mixture became totally homogeneous) with stirring until the starting aryl chloride was consumed according to GC analysis (3h). The reaction mixture was cooled to room temperature, diluted with 5% aqueous NaOH and extracted with diethyl ether. The aqueous layer was cooled to 0 °C and acidified with HCl (12.0 M) to pH ~ 4. The aqueous layer was extracted with diethyl ether, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to give the crude product (248 mg). The product was purified by recrystallizing from hot hexanes/chloroform to give faint brown platelets (209 mg, 78%), Mp = 138-140 °C. ^{1}H NMR (400 MHz, d^6-DMSO) δ: 12.25 (s, 1H), 8.61 (s, 1H), 7.75 (d, J = 7.8 Hz, 2H), 7.13 (d, J = 8.4 Hz, 2H), 7.08 (d, J = 8.4 Hz, 2H), 6.98 (d, J = 7.8 Hz, 2H), 2.49 (t, J = 7.2 Hz, 2H), 1.50 (m, J = 6.8 Hz, 2H), 1.27 (m, J = 7.2 Hz, 2H), 0.87 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, d^6-DMSO) δ: 167.4, 148.8, 139.1, 136.1, 131.3, 129.1, 119.9, 119.8, 113.6, 34.4, 33.5, 21.9, 13.9. IR (neat, cm^{-1}): 3406, 1668, 1601, 1515, 1309. HRMS Calcd. For C$_{17}$H$_{19}$NO$_2$ (M+H): 268.1343. Found: 268.1336.

Methyl 3-(4-methoxycarbonylphenylamino)benzoate (Table 1, Entry 6). An oven-dried resealable Schlenk tube was evacuated and backfilled with argon. The Schlenk tube was charged with Pd$_2$dba$_3$ (9.2 mg, 0.010 mmol, 2 mol % Pd), ligand 1 (19.0 mg, 0.040 mmol, 4 mol %), pulverized KOH (224 mg, 4.00 mmol), and 4-aminobenzoic acid (165 mg, 1.20 mmol) and 3-chlorobenzoic acid (224 mg, 1.00 mmol). The Schlenk tube was evacuated and backfilled with argon (this sequence was repeated three times) and then capped with a rubber septum. To the Schlenk tube was added *t*-BuOH (4 mL). The septum was replaced with a Teflon screwcap, the Schlenk tube was sealed, and the mixture was heated to 100 °C (the reaction was heterogeneous) with stirring until the starting aryl chloride was consumed according to GC analysis (24h). The reaction

mixture was cooled to room temperature, diluted with 5% aqueous NaOH and extracted with diethyl ether. The aqueous layer was cooled to 0 °C and acidified with HCl (12.0 M) to pH ~ 4. The aqueous layer was extracted with ethyl acetate, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to give the crude product. The crude material was diluted with methanol (4 mL), cooled to 0 °C under a N_2 atmosphere and TMSCl (1 mL) was added. The solution was allowed to warm to room temperature and stir for 24 h. The reaction mixture was concentrated under reduced pressure and purified by column chromatography on silica gel (eluting with ethyl acetate/hexanes, 2.5:7.5) to give the desired product as a white solid (259 mg, 90%), Mp = 118 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.91 (d, J = 8.4 Hz, 2H), 7.83 (s, 1H), 7.67 (s, 1H), 7.35 (m, 2H), 7.02 (d, J = 8.4 Hz, 2H), 6.77 (s, 1H), 3.89 (s, 3H), 3.86 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ: 167.1, 166.9, 147.6, 141.5, 131.5 131.4, 129.5, 123.9, 123.5, 121.4, 120.6, 115.0, 52.3, 51.8. IR (neat, cm^{-1}): 3356, 1713, 1592, 1530, 1435, 1282, 1176, 1107, 752. Anal. Calcd. For $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30. Found: C, 67.27; H, 5.33.

General procedure for reactions in water (eq. 4). An oven-dried resealable Schlenk tube was evacuated and backfilled with argon. The Schlenk was charged with Pd$_2$dba$_3$ (4.6 mg, 0.0050 mmol, 1 mol% Pd), ligand 1 (9.4 mg, 0.020 mmol, 2 mol%), and KOH (78 mg, 1.40 mmol). The Schlenk tube was evacuated and backfilled with argon (this sequence was repeated three times) and then capped with a rubber septum. To the reaction mixture was added amine (1.20 mmol), aryl chloride (1.00 mmol), and degassed water (0.5 mL). The septum was replaced with a Teflon screwcap, the Schlenk tube was sealed, and the mixture was heated to 110 °C (the reaction mixture was biphasic) with stirring until the starting aryl chloride was consumed according to CG analysis. The reaction mixture was cooled to room temperature, extracted with diethyl ether, filtered through Celite, and concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/hexane mixtures) to give the desired product.

Benzyl-(2,5-dimethylphenyl)amine (eq. 4).[33] Following the general procedure with a reaction time of 12 h, 2-chloro-*p*-xylene (0.134 mL, 1.00 mmol) was coupled with benzyl

amine (0.130 mL, 1.23 mmol). After chromatography on silica gel (eluting with ethyl acetate/hexanes, 1:20), the desired product was obtained as a colorless oil (179 mg, 85%). ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.51 (m, 4H), 7.43 (t, J = 7.2 Hz, 1H), 7.28 (d, J = 8.0 Hz, 1H), 6.78 (d, J = 8.0 Hz, 1H), 6.67 (m, 1H), 4.58 (s, 2H), 3.99 (br-s, 1H), 2.55 (s, 3H), 2.34 (s, 3H).

N-Phenyl-N-pyridin-3-yl-amine (eq. 4).[34] Following the general procedure with a reaction time of 6 h, 3-chloro-pyridine (0.095 mL, 1.00 mmol) was coupled with aniline (0.109 mL, 1.14 mmol). After chromatography on silica gel (eluting with ethyl acetate/hexanes, 8:2), the desired product was obtained as a white solid (162 mg, 95%), Mp = 140-141 °C (lit[34] 141-142 °C). ^{1}H NMR (400 MHz, CDCl$_3$) δ: 8.30 (d, J = 2.8 Hz, 1H), 8.07 (dd, J = 8.6, 1.2 Hz, 1H), 7.35 (m, 1H), 7.19-7.24 (m, 2H), 7.00-7.11 (m, 3H), 6.91 (t, J = 7.2 Hz, 1H), 5.87 (br-s, 1H).

General procedure for the examples given in Tables 2, 4, 6, and 7. An oven-dried resealable Schlenk tube was evacuated and backfilled with argon. The Schlenk tube was charged with Pd$_2$dba$_3$ (1-4 mol% Pd), ligands **1** or **2** (2-8 mol%). If the aryl halide (1.0 mmol), amine (1.1-1.5 mmoL) or base (1.5-4.0 mmol) were solids, they were also added at this time. The Schlenk tube was evacuated and backfilled with argon or nitrogen (this sequence was repeated three times) and then capped with a rubber septum. If the aryl halide, amine or base were liquids, they were added to the Schlenk tube at this time along with the solvent. The septum was replaced with a Teflon screwcap, the Schlenk tube was sealed, and the mixture was stirred in a pre-heated oil bath until the aryl halide was consumed as judged by TLC, LC-MS or GC analysis. The reaction mixture was cooled to room temperature, quenched with water and extracted with ethyl acetate. The organic layer was either filtered through Celite or dried over anhydrous MgSO$_4$, filtered and concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/hexane mixtures) or by crystallization.

N5-Phenyl-pyridine-2,5-diamine (Table 2, Entry 1).[35] Using the general procedure, 2-amino-5-chloropyridine (128 mg, 1.00 mmol), Pd$_2$dba$_3$ (18.3 mg, 0.020 mmol, 4 mol % Pd), ligand **1** (34.0 mg, 0.080 mmol, 8 mol %), aniline (0.137 mL, 1.50 mmol) and

LiN(TMS)$_2$ (3.0 mL, 1.0 M in THF, 3.00 mmol) were heated to 65 °C for 20 h. The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate) to give the desired product as a light brown solid (165 mg, 89%), Mp = 117 °C (lit.[35] 118-119°C). ^{1}H NMR (400 MHz, d^4-MeOH) δ: 7.74 (d, J = 2.8 Hz, 1H), 7.35 (dd, J = 2.8 Hz, J = 8.8 Hz, 1H), 7.13 (t, J = 7.2 Hz, 2H), 6.80 (d, J = 7.6 Hz, 2H), 6.72 (t, J = 7.6 Hz, 1H), 6.60 (d, J = 8. 8 Hz, 1H).

5-Morpholin-4-yl-pyridin-2-ylamine (Table 2, Entry 2).[36] Using the general procedure, 2-amino-5-chloropyridine (64.0 mg, 0.500 mmol), Pd$_2$dba$_3$ (9.2 mg, 0.010 mmol, 4 mol % Pd), ligand 1 (19.0 mg, 0.040 mmol, 8 mol %), morpholine (0.066 mL, 0.75 mmol) and LiN(TMS)$_2$ (1.5 mL, 1.0 M in THF, 1.50 mmol) were heated to 65 °C for 20 h. The crude material was purified by column chromatography on silica gel (eluting with methanol/ethyl acetate, 0.5: 9.5) to give the desired product as a light brown solid (71 mg, 79%), Mp = 143 °C. ^{1}H NMR (400 MHz, d^4-MeOH) δ: 7.60 (d, J = 2.8 Hz, 1H), 7.30 (dd, J = 2.8 Hz, J = 8.8 Hz, 1H), 6.58 (d, J = 8.8 Hz, 1H), 3.81 (t, J = 4.4 Hz, 4H), 2.98 (t, J = 4.4 Hz, 4H).

*N*5-Benzyl-pyridine-2,5-diamine (Table 2, Entry 3). Using the general procedure, 2-amino-5-chloropyridine (64.0 mg, 0.500 mmol), Pd$_2$dba$_3$ (9.2 mg, 0.010 mmol, 4 mol % Pd), ligand 2 (17.0 mg, 0.040 mmol, 8 mol %), benzyl amine (0.082 mL, 0.75 mmol) and LiN(TMS)$_2$ (1.5 mL, 1.0 M in THF, 1.50 mmol) were heated to 65 °C for 20 h. The crude material was purified by column chromatography on silica gel (eluting with methanol/ethyl acetate, 0.5: 9.5) to give the desired product as a light brown solid (76 mg, 77%). Mp = 93-94 °C. ^{1}H NMR (400 MHz, d^4-MeOH) δ: 7.33-7.36 (m, 3H), 7.29 (t, J = 7.2 Hz, 2H), 7.20 (t, J = 7.2 Hz, 1H), 7.03 (dd, J = 2. 8 Hz, J = 8.8 Hz, 1H), 6.51 (d, J = 8.8 Hz, 1H), 4.22 (s, 2H). ^{13}C NMR (100 MHz, CDCl$_3$) δ: 151.4, 139.4, 137.7, 133.3, 128.8, 127.7, 127.5, 124.9, 109.7, 49.5. IR (neat, cm^{-1}): 3326, 3027, 1613, 1602, 1577, 1500, 1452, 1392, 1285, 112, 822, 732, 697.

General procedure for the examples give in Table 3. An oven-dried resealable Schlenk tube was evacuated and backfilled with argon. The Schlenk tube was charged with Pd$_2$dba$_3$ (9.2 mg, 0.010 mmol, 4 mol % Pd), ligand 1-7 (0.040 mmol, 8 mol %), 2-amino-pyridine (61.0 mg, 0.650 mmol), and NaO*t*-Bu (96.0 mg, 1.00 mmol). The

Schlenk tube was evacuated and backfilled with argon (this sequence was repeated three times) and then capped with a rubber septum. To the Schlenk tube was added 3-chloroanisole (0.061 mL, 0.500 mmol) and toluene (1.5 mL). The septum was replaced with a Teflon screwcap, the Schlenk tube was sealed, and the mixture was heated to 100 °C with stirring for 5 h. The reactions were cooled to room temperature, after which n-dodecane (0.113 mL, 0.500 mmol), water, and ethyl acetate were added. The reactions were analyzed by GC and the results are shown in Table 3.

Pyridin-2-yl-m-methoxyphenyl-amine (Table 3).[37] ^{1}H NMR (400 MHz, CDCl₃) δ: 8.12 (dd, J = 5.2, 1.2 Hz, 1H), 7.39 (m, 1H), 7.27 (br s, 1H), 7.13 (m, 1H), 6.79-6.87 (m, 3H), 6.63 (m, 1H), 6.50 (dd, J = 9.2, 2.0 Hz, 1H).

4-Pyridin-2-ylaminophenol (Table 4, Entry 1).[38] Using the general procedure, 4-chlorophenol (65.0 mg, 0.500 mmol), Pd₂dba₃ (9.2 mg, 0.010 mmol, 4 mol % Pd), ligand 2 (17.0 mg, 0.040 mmol, 8 mol %), 2-aminopyridine (61.0 mg, 0.650 mmol) and NaOt-Bu (144 mg, 1.50 mmol) in toluene (2.0 mL) were heated to 100 °C for 18 h. The reaction mixture was cooled to room temperature, quenched carefully with 1.0 M aqueous HCl, neutralized with saturated aqueous NaHCO₃, extracted with ethyl acetate, filtered through Celite, and concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/hexanes, 1:1) to give the desired product as a light yellow solid (93 mg, 90%). Mp = 184 °C (lit.[38] 186 °C). ^{1}H NMR (400 MHz, d⁶-DMSO) δ: 9.07 (s, 1H), 8.69 (s, 1H), 8.14 (m, 1H), 7.54 (m, 1H), 7.47 (d, J = 8.8 Hz, 2H), 6.79-6.76 (m, 3H), 6.69 (t, J = 5.6 Hz, 1H). ^{13}C NMR (100 MHz, d⁶-DMSO) δ: 156.6, 151.9, 147.4, 136.9, 133.2, 120.8, 115.2, 113.2, 109.4.

General procedure for the examples given in Table 5. An oven-dried resealable Schlenk tube was evacuated and backfilled with argon. The Schlenk tube was charged with Pd₂dba₃ (9.2 mg, 0.010 mmol, 4 mol % Pd), ligand 1-4,8 (17.0 mg, 0.040 mmol, 8 mol %), indazole (73.0 mg, 0.650 mmol) and K₃PO₄ (151 mg, 0.75 mmol). The Schlenk tube was evacuated and backfilled with argon (this sequence was repeated three times) and then capped with a rubber septum. To the Schlenk tube was added 3-

bromoanisole (0.064 mL, 0.500 mmol) and 1,4-dioxane (1.0 mL). The septum was replaced with a Teflon screwcap, the Schlenk tube was sealed, and the mixture was heated to 100 °C with stirring for 14 h. The reactions were cooled to room temperature, after which n-dodecane (0.113 mL, 0.500 mmol), water, and ethyl acetate were added. The reactions were analyzed by GC and the results are shown in Table 5.

1-(3-Methoxy-phenyl)-1H-indazole (Table 5 and Table 6, Entry 1).[31] Using the general procedure, 3-chloroanisole (0.061 mL, 0.500 mmol), Pd_2dba_3 (11.4 mg, 0.0125 mmol, 5 mol % Pd), ligand **2** (21.0 mg, 0.050 mmol, 10 mol %), indazole (73.0 mg, 0.650 mmol) and NaOt-Bu (72 mg, 0.75 mmol) in toluene (1.0 mL) were heated to 80 °C for 18 h. The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/hexanes, 4:1) to give the desired product as a clear oil (109 mg, 97%). ^{1}H NMR (400 MHz, CDCl$_3$) δ: 8.19 (s, 1H), 7.77 (dd, J = 4.0 Hz, J = 8.0 Hz, 2H), 7.41 (t, J = 7.6 Hz, 2H), 7.32-7.29 (m, 2H), 7.21 (t, J = 7.6 Hz, 1H), 6.89 (dd, J = 2.4 Hz, J = 8.0 Hz, 1H), 3.86 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ: 160.6, 141.4, 138.9, 135.5, 130.3, 127.3, 125.5, 121.7, 121.5, 114.8, 112.7, 110.7, 108.5, 55.6.

5-Indazol-1-yl-nicotinonitrile (Table 6, Entry 2). Using the general procedure, 3-bromonicotinonitrile (92.0 mg, 0.500 mmol), Pd_2dba_3 (11.4 mg, 0.0125 mmol, 5 mol % Pd), ligand **2** (21.0 mg, 0.050 mmol, 10 mol %), , indazole (72.0 mg, 0.650 mmol) and NaOt-Bu (72 mg, 0.750 mmol) in toluene (1.5 mL) were heated to 80 °C for 13 h. The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/hexanes, 3:7) to give the desired product as a light yellow solid (67 mg, 62%), Mp = 134 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ: 9.32 (d, J = 2.4 Hz, 1H), 8.80 (d, J = 1.6 Hz, 1H), 8.38 (t, J = 2.4 Hz, 1H), 8.29 (s, 1H), 7.85 (d, J = 8.0 Hz, 1H), 7.78 (d, J = 8.4 Hz, 1H), 7.55 (t, J = 7.6 Hz, 1H), 7.33 (t, J = 7. 6 Hz, 1H). ^{13}C NMR (100 MHz, CDCl$_3$) δ: 149.0, 145.9, 138.6, 138.2, 137.2, 131.4, 128.7, 126.2, 123.0, 122.2, 116.1, 110.7, 109.9. IR (neat, cm^{-1}): 3065, 2232, 1591, 1563, 1503, 1466, 1436, 1353, 1188, 1127, 1025, 899, 736, 696.

1-(3,5-Dimethyl-phenyl)-1H-pyrazole (Table 6, Entry 3).[39] Using the general procedure, 5-bromo-m-xylene (0.068 mL, 0.500 mmol), Pd_2dba_3 (11.4 mg, 0.0125 mmol, 5 mol % Pd), ligand **2** (21.0 mg, 0.050 mmol, 10 mol %), pyrazole (44.0 mg, 0.650

mmol) and NaO*t*-Bu (72 mg, 0.750 mmol) in toluene (1.0 mL) were heated to 80 °C for 22 h. The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/hexanes, 0.5:9.5) to give the desired product as a light yellow oil (76 mg, 88%). ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.87 (d, J = 2.4 Hz, 1H), 7.69 (d, J = 1.2 Hz, 1H), 7.30 (s, 2H), 6.91 (s, 1H), 6.41 (t, J = 2.4 Hz, 1H), 2.35 (s, 6H). ^{13}C NMR (100 MHz, CDCl$_3$) δ: 140.9, 140.2, 139.4, 128.2, 126.9, 117.2, 107.4, 21.5.

3-(3-Methyl-pyrazol-1-yl)-pyridine (Table 6, Entry 4). Using the general procedure, 3-chlorpyridine (0.048 mL, 0.500 mmol), Pd$_2$dba$_3$ (11.4 mg, 0.0125 mmol, 5 mol % Pd), ligand **2** (21.0 mg, 0.050 mmol, 10 mol %), 3-methylpyrazole (0.052 mL, 0.650 mmol) and NaO*t*-Bu (72 mg, 0.750 mmol) in toluene (1.0 mL) were heated to 100 °C for 21 h. The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/hexanes, 7:3) to give the desired product as a light yellow solid (60 mg, 76%). Mp = 68-69 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ: 8.94 (m, 1H), 8.49 (m, 1H), 8.00 (m, 1H), 7.85 (m, 1H), 7.35 (m, 1H), 6.29 (m, 1H), 2.38 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ: 151.6, 147.0, 140.1, 136.6, 127.4, 126.0, 123.9, 108.5, 13.8. IR (neat, cm^{-1}): 3101, 3060, 2924, 1585, 1537, 1499, 1487, 1446, 1364, 1057, 946, 814, 768, 701, 616.

N-Furan-2-ylmethyl-pyrimidine-2,5-diamine (Table 7, Entry 1). Using the general procedure, 2-amino-5-bromopyrimidine (87.0 mg, 0.500 mmol), Pd$_2$dba$_3$ (11.4 mg, 0.0125 mmol, 5 mol % Pd), ligand **2** (21.0 mg, 0.050 mmol, 10 mol %), 2-furyl-methylamine (0.066 mL, 0.750 mmol) and NaO*t*-Bu (192 mg, 2.00 mmol) in toluene (1.5 mL) were heated to 100 °C for 24 h. The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate) to give the desired product as a light yellow solid (68 mg, 72%). Mp = 79-80 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.90 (s, 2H), 7.36 (m, 1H), 6.31 (d, J = 2.4 Hz, 1H), 6.26 (d, J = 2.4 Hz, 1H), 4.83 (br-s, 2H), 4.24 (s, 2H), 3.69 (br-s, 1H). ^{13}C NMR (100 MHz, CDCl$_3$) δ: 157.7, 152.0, 145.4, 142.4, 134.5, 110.5, 107.8, 42.5. . IR (neat, cm^{-1}): 3313, 3192, 1638, 1564, 1488, 1399, 1289, 1198, 1146, 1065, 1016, 926, 911, 811, 790, 733.
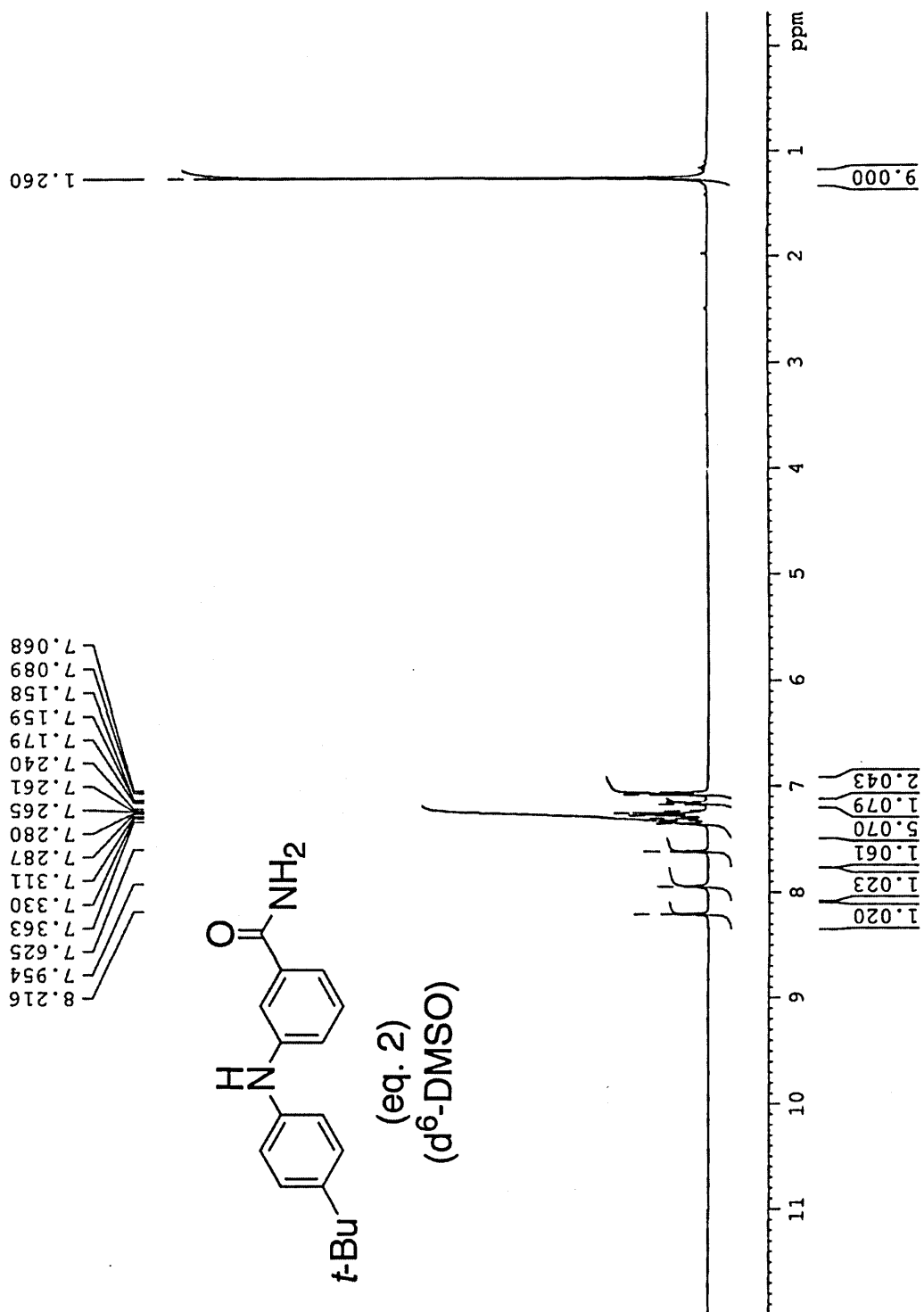
(3,5-Dimethyl-phenyl)-(1*H*-indazol-5-yl)-amine (Table 7, Entry 2). Using the general procedure, 5-bromo-*m*-xylene (0.068 mL, 0.500 mmol), Pd$_2$dba$_3$ (11.4 mg, 0.0125 mmol, 5 mol % Pd), ligand **2** (21.0 mg, 0.050 mmol, 10 mol %), 5-aminoindazole (87.0 mg,

0.650 mmol) and NaO*t*-Bu (144 mg, 1.50 mmol) in toluene (1.0 mL) were heated to 110 °C for 24 h. The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/hexanes, 1:1) to give the desired product as a light brown solid (68 mg, 72%). Mp = 175-176 °C. ^{1}H NMR (400 MHz, d^6-DMSO) δ: 12.90 (br-s, 1H), 7.94 (s, 1H), 7.80 (s, 1H), 7.48 (d, J = 8.8 Hz, 1H), 7.42 (s, 1H), 7.17 (d, J = 8.8 Hz, 1H), 6.63 (s, 2H), 6.37 (s, 1H), , 2.17 (s, 6H). ^{13}C NMR (100 MHz, d^6-DMSO) δ: 145.4, 137.9, 136.5, 136.3, 132.7, 123.5, 121.9, 120.4, 113.0, 110.7, 107.7, 21.2. IR (neat, cm$^-$^{1}): 3393, 1598, 1515, 1328, 1228, 1176, 1148, 1082, 954, 823, 768, 750.

Phenyl-(1*H*-pyrazol-4-yl)-amine (Table 7, Entry 3). Using the general procedure, 4-bromopyrazole (73.0 mg, 0.500 mmol), Pd$_2$dba$_3$ (9.2 mg, 0.0100 mmol, 4 mol % Pd), ligand **2** (17.0 mg, 0.040 mmol, 8 mol %), aniline (0.060 mL, 0.650 mmol) and NaO*t*-Bu (120 mg, 1.25 mmol) in toluene (1.0 mL) were heated to 110 °C for 24 h. The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/hexanes, 7:3) to give the desired product as a white solid (68 mg, 72%). Mp = 107-108 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ: 11.40 (br-s, 1H), 7.54 (m, 2H), 7.20 (t, J = 8.0 Hz, 2H), 6.79-6.75 (m, 3H), 5.14 (br-s, 1h). ^{13}C NMR (100 MHz, d^6-DMSO) δ: 147.0, 133.4 129.1, 124.4, 120.2, 116.7, 112.8. IR (neat, cm$^-$^{1}): 3392, 3121, 2934, 2515, 1602, 1499, 1458, 1375, 1301, 1128, 969, 874, 830, 752, 691, 631.

(5-Phenyl-2*H*-pyrazol- 3-yl)-quinolin-3-yl-amine (Table 7, Entry 4). Using the general procedure, 3-bromoquinoline (0.068 mL, 0.500 mmol), Pd$_2$dba$_3$ (11.4 mg, 0.0125 mmol, 5 mol % Pd), ligand **2** (21.0 mg, 0.050 mmol, 10 mol%), 5-Phenyl-2*H*-pyrazol-3-ylamine (111.0 mg, 0.700 mmol) and NaO*t*-Bu (168 mg, 1.75 mmol) in toluene (1.5 mL) were heated to 110 °C for 20 h. The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/hexanes, 4:1) to give the desired product as a yellow solid (103 mg, 72%). Mp = 213-215 °C ^{1}H NMR (400 MHz, d^6-DMSO) δ: 12.79 (br-s, 1H), 9.23 (s, 1H), 8.82 (s, 1H), 8.44 (br-s, 1H), 7.88-7.76 (m, 4H), 7.48-7.34 (m, 5H), 6.41 (s, 1H). ^{1}H NMR (400 MHz, d^4-MeOH) δ: 8.63 (d, J = 2. 8 Hz, 1H), 8.11 (s, 1H), 7.86 (m, 1H), 7.67-7.62 (m, 3H), 7.44-7.37 (m, 4H), 7.31 (t, J = 7.6 Hz, 1H), 6.30 (s, 1H). ^{13}C NMR (100 MHz, d^6-DMSO) δ: 151.6, 143.9, 142.3, 141.8,

137.4, 137.3, 129.5, 129.1, 129.0, 128.5, 128.2, 126.8, 126.6, 125.2, 113.4, 91.2. IR (neat, cm^{-1}): 1607, 1554, 1518, 1436, 1376, 747.

1.260

7.068
7.089
7.158
7.159
7.179
7.240
7.261
7.265
7.280
7.287
7.311
7.330
7.363
7.625
7.954
8.216

NH$_2$

O

N
H

(eq. 2)
(d^6-DMSO)

t-Bu

ppm

1
2
3
4
5
6
7
8
9
10
11

9.000

2.043
1.079
5.070
1.061
1.023
1.020

125

(eq. 3)
(CDCl$_3$)

3.0359

2.0428

2.0477

2.0000

3.0038

1.9976

3.9470

1.9890

[Integral]

ppm

126

Table 1, Entry 1
(d[6]-DMSO)

Table 1, Entry 2
(d^6-DMSO)

2.500

3.123
3.135
3.147
3.729
3.741
3.753

7.071
7.090
7.263
7.282
7.302
7.310
7.415
7.934

3.866
3.883
0.998
2.805
1.067
1.000

ppm

Table 1, Entry 3
(d⁴-MeOH)

3.297
3.300

4.327

4.888

6.743
6.749
6.763
6.768
7.043
7.061
7.111
7.115
7.130
7.150
7.177
7.195
7.213
7.263

2.000

0.979

1.050
1.961
1.062
2.017
1.928

ppm

3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5

3.417

7.122
7.140
7.158
7.173
7.192
7.224
7.229
7.245
7.249
7.270
7.270
7.346
7.366
7.380
7.385
7.399
7.419
7.701
7.720
7.782

13.029

Me
N
CO₂H

Table 1, Entry 4
(CDCl₃)

3.000

4.078
3.027
1.041
0.985
0.045

1.014

ppm

Table 1, Entry 5
(d6-DMSO)

131

Table 1, Entry 6
(CDCl$_3$)

132

eq. 4a
(CDCl₃)

eq. 4b
(CDCl$_3$)

1.036
2.066
3.083
1.030
0.991
2.034

ppm
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
10.0
10.5
11.0
11.5

134

3.302
3.306
3.310
3.314
3.318
4.903
6.590
6.591
6.612
6.613
6.698
6.701
6.717
6.719
6.733
6.735
6.737
6.790
6.792
6.811
6.813
7.112
7.116
7.130
7.133
7.146
7.151
7.353
7.360
7.375
7.382
7.749
7.756

Table 2, Entry 1
(d⁴-MeOH)

1.056
1.337
1.740
2.092
1.043
0.999

H₂N

Table 2, Entry 2
(d⁴-MeOH)

2.966
2.978
2.989
3.302
3.306
3.310
3.314
3.318
3.795
3.807
3.818

4.807

6.572
6.594

7.286
7.293
7.308
7.315
7.596
7.603

4.056

4.050

0.968

1.000

1.000

8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

3.302
3.306
3.310
3.314
3.318

4.220

4.916

6.503
6.526
7.022
7.029
7.044
7.051
7.191
7.209
7.227
7.274
7.293
7.311
7.337
7.352
7.358

CD4-MeOH

CD4-MeOH

2.069

3.834

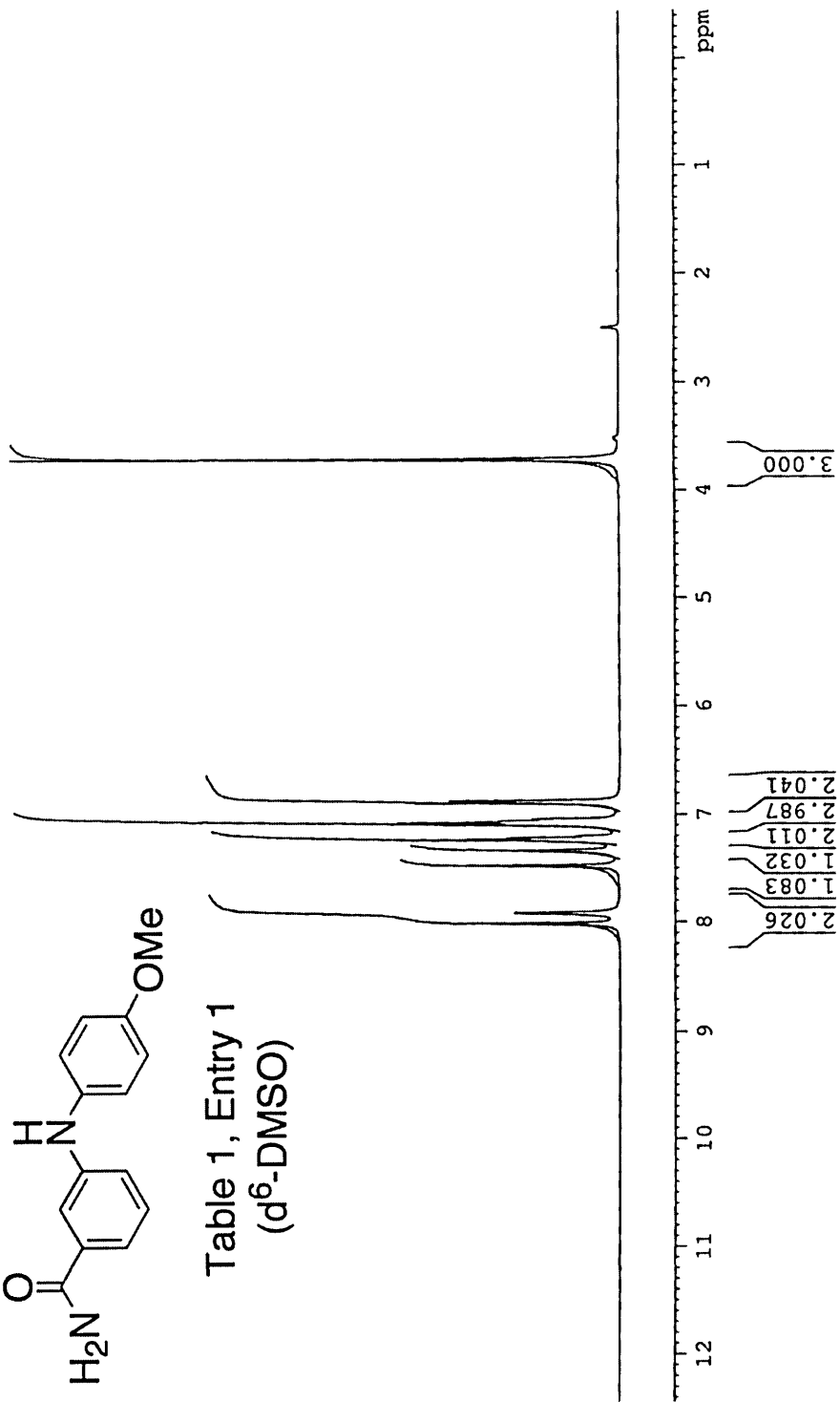1.000

1.022
1.044
2.078
2.973

Table 2, Entry 3
(d⁴-MeOH)

ppm
1
2
3
4
5
6
7
8
9
10
11

Table 4, Entry 1
(d⁶-DMSO)

2.588
2.592
3.258
3.271

6.682
6.698
6.712
6.761
6.775
6.781
6.797
7.462
7.484
7.520
7.525
7.542
7.545
7.559
7.563
8.132
8.140
8.144
8.690
9.072

1.000
3.055
1.933
1.117
0.996
0.998
1.000

16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3 ppm

138

Table 6, Entry 1
(CDCl₃)

7.880
7.884
7.886
7.900
7.906
7.190
7.208
7.227
7.294
7.299
7.305
7.325
7.327
7.391
7.412
7.427
7.431
7.759
7.770
7.780

3.858
3.872

3.000

1.016
1.215
2.056
1.993
1.954
0.930

Table 6, Entry 2
(CDCl₃)

7.186
7.238
7.256
7.275
7.455
7.458
7.476
7.479
7.494
7.497
7.699
7.720
7.767
7.787
8.214
8.304
8.310
8.315
8.730
8.734
9.252
9.258

1.084
1.040
1.029
1.004
0.970
0.981
0.981
1.000

Table 6, Entry 3
(CDCl₃)

2.354

6.413
6.417
6.423

6.906

7.305

7.691
7.694
7.870
7.876

6.133

0.954

0.964

1.947

0.956

1.000

ppm 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0 6.5 7.0 7.5 8.0

2.328
2.331
2.377
2.428

6.285
6.291
7.321
7.339
7.351
7.359
7.371
7.847
7.853
7.981
7.984
7.987
7.990
8.001
8.005
8.008
8.011
8.485
8.496
8.948

Me

Table 6, Entry 4
(CDCl$_3$)

3.109

0.974

1.064

0.977
1.005

0.992
1.000

ppm

Table 7, Entry 1
(CDCl₃)

143

2.147
2.179
2.197

6.383
6.533
7.077
7.082
7.099
7.103
7.333
7.337
7.345
7.367
7.821
7.823

Table 7, Entry 2
(CDCl$_3$/d^6-DMSO)

6.031

1.860
2.000
1.038
2.111
1.004

0.966

ppm

Table 7, Entry 3
(CDCl$_3$)

5.140

6.754
6.776
6.797
7.169
7.188
7.208
7.244
7.545

0.973

2.939
2.144
2.000

0.822

Table 7, Entry 4
(d⁶-DMSO)

2.500

12.740

6.417
7.340
7.357
7.375
7.452
7.466
7.484
7.755
7.777
7.797
7.862
7.880
8.441
8.822
8.864
9.233

1.000
4.985
3.992
0.969
0.978
0.903
0.958

ppm

146

References

(1) Hartwig, J. F. in *Handbook on Organopalladium Chemistry for Organic Synthesis*, Negishi, E. Ed., Wiley-Interscience, New York, **2002**, 1051-1096 and references within.

(2) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, 219, 131 and references within.

(3) Jiang, L.; Buchwald, S. L. Palladium-Catalyzed Aromatic Carbon-Nitrogen Bond Formation. In *Metal-Catalyzed Cross-Coupling Reactions*, 2nd Ed.: de Meijere, A.; Diederich, F. Eds; Wiley-VCH: Weinheim, 2004, pp. 699-760.

(4) Wolfe, J. P.; Buchwald, S. L. *Tetrahedron Lett.* **1997**, 38, 6359.

(5) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, 120, 9722.

(6) While we previously reported the use of the strong base LiN(TMS)$_2$ could offer a partial solution to this problem, this was both experimentally complicated and still had a fairly narrow substrate scope (e.g., no primary aliphatic amines, no acyclic secondary amines): Harris, M. C.; Huang, X.; Buchwald, S. L. *Org. Lett.* **2002**, 4, 2885.

(7) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, 120, 9722.

(8) Wolfe, J. P.; Wagaw, S.; Marcoux, J. F.; Buchwald, S. L. *Accounts Chem. Res.* **1998**, 31, 805.

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

(10) Zim, D.; Buchwald, S. L. *Org. Lett.* **2003**, 5, 2413.

(11) Strieter, E. R.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2006**, 45, 925.

(12) Strieter, E. R. *Unpublished Results*, **2004**.

(13) Alcazar-Roman, L. M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, 123, 12905.

(14) Tsuji, J. Ed.; *Palladium Reagents and Catalysts: New Perspectives for the 21st Century*, 1st Ed.: Wiley: Weinheim, 2004.

(15) Huang, X.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, 125, 6653

(16) Huang, X.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, 125, 10767.

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

(18) Gelman, D.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2003**, 42, 5993.

(19) Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421.

(20) Aqueous hydroxide as a base for palladium-catalyzed amination has been reported; however, a phase transfer catalyst and toluene co-solvent were required: (a) Kuwano, R.; Utsunomiya, M.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 6479. (b) Wullner, G.; Jansch, H.; Kannenberg, S.; Schubert, F.; Boche, S. *Chem. Commun.* **1998**, 1509. For the use of solid NaOH in dioxane, see: (c) Grasa, G.; Viciu, M. S.; Huang, J.; Nolan, S. P. *J. Org. Chem.* **2001**, *66*, 7729.

(21) For a detailed study of the binding affinity of various amines to Pd[P(*o*-tol)$_3$](p-C$_6$H$_4$Me)Cl, see: Widenhoefer, R. A.; Buchwald, S. L. *Organometallics* **1996**, *15*, 2755.

(22) Yin, J.; Zhao, M. M.; Huffman, M. A.; McNamara, J. M. *Org. Lett.* **2002**, *4*, 3481.

(23) (a) Jonckers, T. H. M.; Maes, B. U. W.; Lemiere, G. L. F.; Dommisse, R. *Tetrahedron* **2001**, *57*, 7027. (b) Kosmrlj, J.; Maes, B. U. W.; Lemiere, G. L. F.; Haemers, A. *Synlett* **2000**, 1581.

(24) For Pd coupling reactions of heteroarylamines not substituted in the 2-position, see: (a) Wagaw, S.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 7240. (b) Iwaki, T.; Yashara, A.; Sakamoto, T. *J. Chem. Soc., Perkin Trans 1* **1999**, 1505. (c) Khan, M. M.; Ali, H.; van Lier, J. E. *Tetrahedron Lett.* **2001**, *42*, 1615. (d) Yang, J. –S.; Lin, Y. –H.; Yang, C. – S.; *Org. Lett.* **2002**, *4*, 777. (e) Ogawa, K.; Radke, K. R.; Rothstein, S. D.; Rasmussen, S. C. *J. Org. Chem.* **2001**, *66*, 9067. For an example of Ni- or Cu-catalyzed couplings between a protected 5-iodouracil and heteroarylamines, see: Arterburn, J. B.; Pannala, M.; Gonzales, A. M. *Tetrahedron Lett.* **2001**, *42*, 1475.

(25) Direct reaction of 2-aminothiazoles with highly activated aryl halides in refluxing PhOH or EtOH has been very limited in scope and often resulted in low yields in the absence of a 4-substituent on thiazole. For examples, see: (a) Sarkar, B. R.; Pathak, B.; Dutta, S.; Lahiri, S. C. *J. Ind. Chem. Soc.* **1984**, *61*, 151. (b) Forlani, L.; Guastadisegni, G.; Raffellini, L.; Todesco, P. E. Foresti, E. *Gazz. Chim. Ital.* **1990**, *120*, 493. (c) Chauhan, P. M. S.; Pratap, R.; Sharma, S. *Ind. J. Chem.* **1985**, *15B*, 1154. (d) El-Bayouki, K. A. M.; Basyouni, W. M. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3794. (e) Pande, A.; Pramilla, S.; Saxena, V. K.; Khan, M. N. A. A.; Verma, H. N. *Acta Pharm. Jugosl.* **1984**, *34*, 61.

(26) pK_a of aniline (30.6, DMSO) and 2-aminopyridine (27.7, DMSO): Bordwell, F. G.; Algrim, D. J. *J. Am. Chem. Soc.* **1988**, *110*, 2964.

(27) (a) Mann, G.; Hartwig, J. F.; Driver, M. S.; Fernandez-Rivas, C. *J. Am. Chem. Soc.* **1998**, *120*, 827. (b) Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575. (c) Old, D. W.; Harris, M. C.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 1403. (d) Movassaghi, M.; Ondrus, A. E. *Org. Lett* **2005**, *7*, 4423. (e) Movassaghi, M.; Ondrus, A. E. *J. Org. Chem.* **2005**, *70*, 8638.

(28) pK_a of pyrrole (23.0, DMSO), indole (20.95, DMSO), pyrazole (19.8, DMSO): Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456.

(29) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852.

(30 We chose to use ligand **2** over ligand **4**, since it is commercially available from Aldrich and Strem Chemical Co.

(31) Antilla, J. C.; Baskin, J. M.; Barder, T. E.; Buchwald, S. L. *J. Org. Chem.* **2004**, *69*, 5578.

(32) Willoughby, C. A.; Chapman, K. T. *Tetrahedron Lett.* **1996**, *37*, 7181.

(33) Schliemann, W.; Buege, A. *Pharmazie* **1980**, *35*, 203.

(34) Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158.

(35) Peterson, L. H.; Douglas, A. W.; Tolman, R. L. *J. Heterocyclic Chem.* **1981**, *18*, 659.

(36) Toogood, P. L.; Harvey, P. J.; Repine, J. T.; Sheehan, D. J.; VanderWel, S. N.; Zhou, H.; Keller, P. R.; McNamara, D. J.; Sherry, D.; Zhu, T.; Brodfuehrer, J.; Choi, C.; Barvian, M. R.; Fry, D. W. *J. Med. Chem.* **2005**; *48*, 2388.

(37) Hirota, M.; Kobayashi, K. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1583.

(38) Jerchel, D.; Jakob, L. *Chem. Ber.* **1959**, *92*, 724.

(39) Klapars, A.; Antilla, J. C; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727.

Chapter 3

Suzuki-Miyaura Coupling of Haloaminoheterocycles and Organoboronic Acids
using a Monophosphinobiaryl Ligand

Introduction

In the past two decades, the Suzuki-Miyaura cross-coupling reaction has evolved into one of the most widely employed carbon-carbon bond-forming processes.[1-4] The Suzuki-Miyaura reaction is the metal-catalyzed (most often palladium) cross-coupling of substituted boronic acids or esters with aryl, vinyl and now alkyl halides (eq. 1).[2]

$$R^1\text{-}X \ + \ (R^3O)_2B\text{-}R^2 \xrightarrow[\text{base, } \Delta]{\text{Pd cat.}} R^1\text{-}R^2 \quad (1)$$

R^1 = aryl, vinyl, alkyl R^3 = H, alkyl
R^2 = aryl, vinyl, alkyl   X = halide, -OSO$_2$R, N$_2^+$
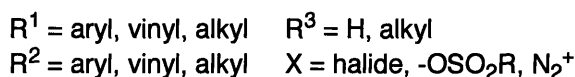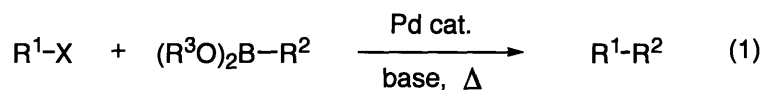
Its impact on organic synthesis is largely attributed to the fact that it provides a general and applicable method for the formation of biaryls, which are found in polymers,[5] biologically active compounds,[6] ligands[7] and various materials.[8] For example, a number of biologically active compounds contain this moiety, including the anti-tumor agent NU7441[9] and DNA repair enzyme inhibitor diazonamide A[10] (Figure 1).

Figure 1. Biologically active biaryl compounds.

NU7441   Diazonamide A
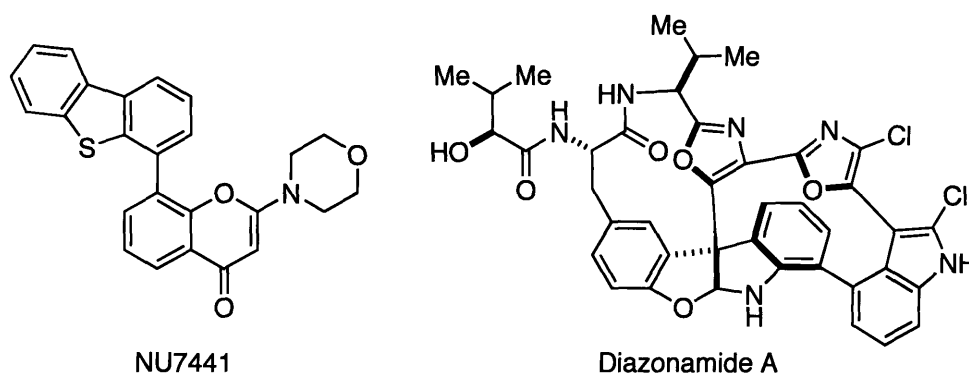
The mechanism for the coupling of organoboron compounds follows an analogous catalytic cycle to most palladium cross-coupling methods: oxidative addition of the R^1-X electrophile to a L$_n$Pd(0) species, followed by transmetallation of the R^2 group from boron to palladium, and reductive elimination to form the desired product and regenerate the Pd(0) catalyst (Scheme 1).[2,11,12] A base is generally required for these reactions, as transmetallation of the organoboron species is believed to take place from a four-coordinate ate complex (Scheme 2, Pathway A).[2]

Scheme 1. General catalytic cycle for palladium-catalyzed Suzuki-Miyaura couplings.
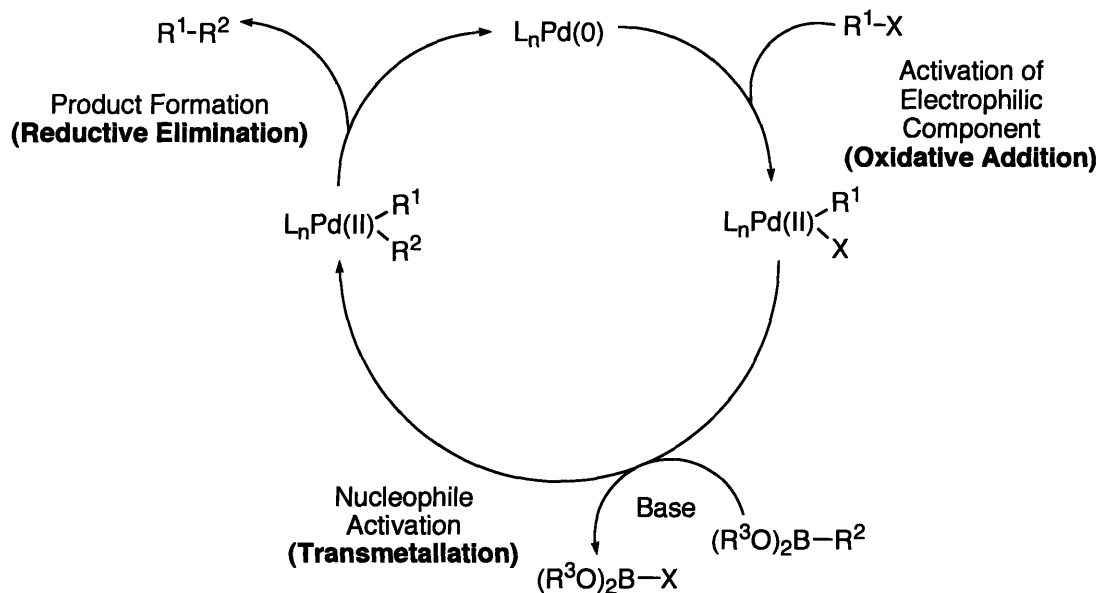
Some mechanistic studies suggest that transmetallation occurs to a palladium hydroxide complex rather than a halide complex (Scheme 2, Pathway B).[2,13] Recently, a theoretical study using DFT (density functional theory) calculations concluded that the main mechanism of transmetallation in the catalytic cycle starts with the reaction of the base and the organoborane (Scheme 2, Pathway A).[14]

Scheme 2. Proposed transmetallation pathways in Suzuki-Miyaura reactions.
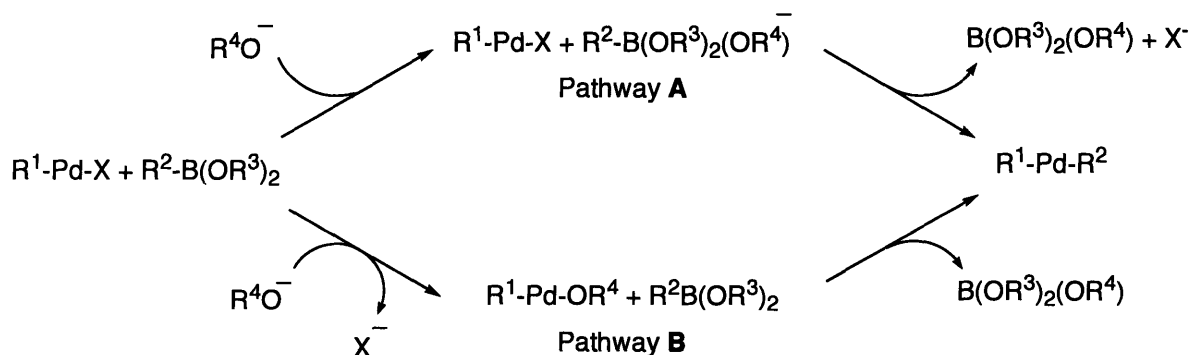
Over the years, a wide array of bases have been shown to be effective in facilitating this process, including Na_2CO_3, K_3PO_4, NaOH, KOH, CsF and KF.[2] Too

many to discuss in detail here, a myriad of ligands have been shown to promote Suzuki-Miyaura couplings.[2,3] The most often used ligand for this process is triphenylphosphine, however it is somewhat limited in the fact that aryl iodides or bromides are only successfully coupled.[2] Also, these triarylphosphine systems cannot be conducted using low catalyst loadings, at room temperature or with very sterically hindered substrate combinations. Couplings of organoboron reagents have also been demonstrated under ligandless conditions, however these suffer the same limitations.[2,15] In recent years, work by numerous groups has resulted in the production of highly active catalyst systems, which allow for couplings to occur with more challenging substrates, under lower catalyst loadings and with substrates which include unactivated aryl chlorides and hindered organoboronic acids.[16]

In our group, we have focused our attention on developing electron-rich dialkyl-monophosphinobiaryl ligands for a variety of cross-coupling processes. The most effective of the biphenyl based ligands for Suzukui-Miyaura reactions are shown in Figure 2. First generation catalyst systems based on Pd/**6-9** displayed high reactivity for organoboron couplings of aryl chlorides using relatively low catalyst loadings and could be conducted at room temperature.[17] The use of axially chiral ligand **5** promoted the first enantioselective cross-coupling for the preparation of functionalized biaryls.[18] Furthermore, a catalyst comprised of Pd and ligand **4** allowed for the preparation of tetra-*ortho*-substituted unsymmetrical biaryls using this process.[16e]

The most recent generation of Suzuki catalysts Pd/**1-3** have displayed unprecedented reactivity and stability in cross-coupling processes.[16a-d] For example, use of ligand **3** allowed the coupling of aryl chlorides at room temperature, representing the first time a triarylphosphine has ever accomplished this feat.[16a] Also, use of ligand **2** promotes, for the first time, efficient reactions of aryl arenesulfonates and aryl boronic acids.[16d] Finally, one of the most active biaryl ligands, **1**, proficiently facilitates reactions of a wide range of substituted aryl bromides/chlorides and aryl/vinyl/alkyl boronic acids using as low as 0.0005% Pd loading in one case.[16a-c]

Despite these major advances, limitations in Suzuki-Miyaura reactions, to date, include its inability to maintain the efficacy exhibited in simple aryl-aryl bond formation

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when employing nitrogen heterocycles as one or both of the coupling partners (e.g., heteroarylhalides and/or heteroarylboronic acids/esters).[16,19] Nitrogen-based heterocycles are ubiquitous in biologically-active compounds, but inclusion of these heterocyclic motifs have been particularly detrimental to catalyst activity when palladium is used.[6] In addition, for exceptionally challenging substrates such as chloroaminopyridines and chloroaminopyrimidines, protection of the free $-NH_2$ or the need to employ chelating ligands, which prevent competitive binding of the substrate, have been reported to be essential to the success of the transformation.[20,21] Given the importance of the Suzuki-Miyaura reaction, particularly in the area of drug development, an efficient method for the coupling of nitrogen-containing heterocyclic substrates would make a significant impact.

Figure 2. Biaryl-based ligands used in Suzuki-Miyaura reactions.
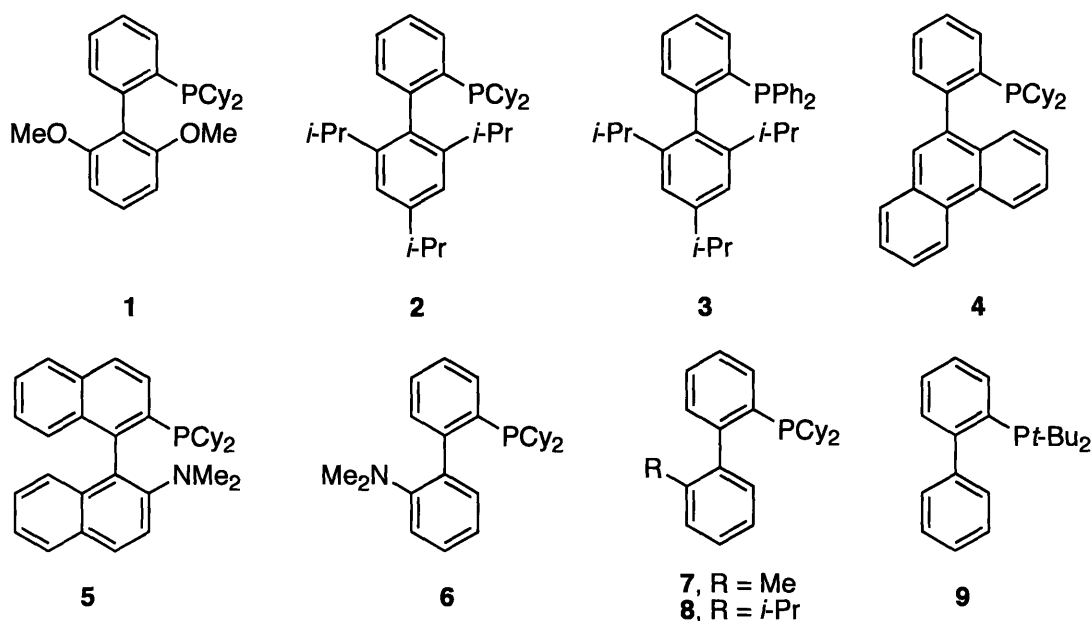
Herein, we report that an extremely active catalyst composed of Pd and 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl **1** provides a general system for the Suzuki-Miyaura reaction of challenging amino-heteroaryl halides (chloroaminopyridines and chloroaminopyrimidines).

Results and Discussion

Only a few reports can be found on the successful Suzuki-Miyaura coupling of substrates that possess unprotected-amino groups on a heteroaryl moiety.[20] Traditionally, in order to circumvent the problems associated with this functional group array, the free amino group is protected prior to the cross-coupling process and must, correspondingly, be deprotected following the organometallic reaction.[21] Past studies suggest that binding of the free $-NH_2$ group to the metal can retard the catalytic cycle; therefore, the basicity of the amino-heteroaryl moiety should directly correlate to the efficacy of the Pd-catalyzed process (Scheme 1).[20a,22]

Scheme 3. Basicity of selected aminopyridines.

pKa: 1.8   2.1   2.8   4.5   4.8

Increasing Basicity → Increased Basicity = Increased Propensity for Coordination to Pd
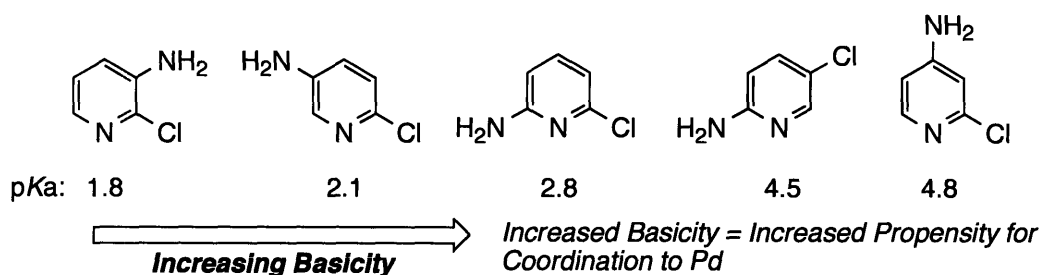
Although previous reports suggest that chelating ligands are a necessity for the efficient coupling of unprotected amino-heteroaromatics,[20a] our group has established that Suzuki-Miyaura reactions employing the dialkylmonophosphino biaryl, **1**, as the supporting ligand display unprecedented reactivity while maintaining a broad substrate scope. Thus, in our initial studies, we utilized a catalyst based upon $Pd(OAc)_2$/**1** for the coupling of aryl boronic acids with chloroaminoheterocycles.

A catalyst system employing **1** as the supporting ligand proved to be highly active for the cross-coupling of a range of chloroaminopyridines and chloroaminopyrimidines with aryl boronic acids that possess functional groups. For example, the reaction of 3-amino-2-chloropyridine with 2-methoxyphenyl boronic acid smoothly produced the desired biaryl in 99% yield (Table 1, Entry 1). In addition, the sterically hindered 2,6-dimethylphenyl boronic acid reacted in 82% yield with 5-amino-2-chloropyridine (Table 1, Entry 2), and similarly electron-deficient boronic acids also react in good yield under the derived conditions (Table 1, Entry 4). Also, it is interesting to note that 4-amino-2-

Table 1. Suzuki-Miyaura coupling of chloroaminoheterocycles using ligand 1.[a]

Reaction scheme: H₂N-heterocycle-Cl + (HO)₂B-Ar-R → Pd(OAc)₂ (0.5-2.0 %), 1 (1.0-2.0%), K₂CO₃, CH₃CN/H₂O → H₂N-heterocycle-Ar-R

Entry	Aryl-Cl	Ar-B(OH)₂	Product	Yield (%)[b]
1				99
2				82
3				95
4				79[c]
5				92
6				97
7				96
8				92[c]

[a]Reaction Conditions: 1.0 equiv. of heteroaryl halide, 1.2-1.5 equiv. arylboronic acid, 2.0-3.0 equiv. K₂CO₃, CH₃CN (1.5 mL/mmol aryl halide), H₂O (1.0 mL/mmol aryl halide), cat. Pd(OAc)₂, L:Pd = 2/1. [b]Isolated yield based upon an average of two runs. [c]Reaction was conducted using K₃PO₄ and 1,4-dioxane (2.5 mL/mmol aryl halide).

chloropyridine, which is the most basic among these substrates, reacts in excellent yield with phenyl boronic acid (Table 1, Entry 5). To the best of our knowledge, this represents the highest yielding Suzuki-Miyaura coupling with a highly basic chloroaminopyridine.[20a]

Table 2. Suzuki-Miyaura coupling to form fused heterocycles.[a,b]

Entry	Aryl-Cl	Ar-B(OH)$_2$	Product	Yield (%)
1				99
2				95
3				94
4				94
5				74

[a]Reaction Conditions: 1.0 equiv. of heteroaryl halide, 1.2-1.5 equiv. arylboronic acid, 2.0-3.0 equiv. K$_2$CO$_3$, CH$_3$CN (1.5 mL/mmol aryl halide), H$_2$O (1.0 mL/mmol aryl halide), cat. Pd(OAc)$_2$, L:Pd = 2/1. [b]Isolated yield based upon an average of two runs.

Similar to the results found for chloroaminopyridines, the $Pd(OAc)_2$/1 catalyst system was highly active for the coupling of chloroaminopyrimidines (Table 1, Entries 6-8). These reactions proceed in greater than 90% yield for both sterically encumbered heteroaryl halides and aryl boronic acids. In addition, the reaction of the electron deficient boronic acid, 3-acetylphenyl boronic acid, with 4-amino-5-chloro-2,6-dimethylpyrimidine proceeds smoothly to produce the highly substituted heterobiaryl in 96% yield (Table 1, Entry 7). This protocol corresponds to the only method whereby chloroaminopyrimidines are coupled to hindered aryl boronic acids.

This method was also used successfully in the preparation of fused heterocyclic systems. As shown in Table 2, 2-chloroaniline can be combined with 2-formylphenyl boronic acid to form phenanthridine in 99% yield, where either the coupling occurs prior to dehydrative cyclization or vise versa (Table 2, Entry 1).[23] Using the same protocol, 6-methylphenanthridine is formed in 95% yield using 2-acetylphenyl boronic acid as the coupling partner (Table 2, Entry 2). This method can be extended to the use of haloaminoheterocycles to form benzo[c][1,8]naphthridines and benzo[c][1,5]naphthridines both in 94% yield, respectively (Table 2, Entries 3,4). Finally, using 2-bromochlorobenzene and 2-aminophenyl boronic acid, carbazole is productively synthesized in 74% yield (Table 2, Entry 5).

In summary, palladium-catalyzed Suzuki-Miyaura couplings of haloaminoheterocycles and functionalized organoboronic acids using a highly active and stable monophosphinobiaryl ligand, 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl 1, efficiently produced aminoheterocyclic biaryl derivatives. This same catalyst was effective in coupling 2-haloaminoaryl compounds with 2-formyl or 2-acetylphenyl boronic acids, providing the fused heterocyclic compounds phenanthridine, benzo[c][1,8]naphthridine and benzo[c][1,5]naphthridine in excellent yields

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Experimental

Reagents. All reactions were carried out under an argon atmosphere. $Pd(OAc)_2$ and Pd_2dba_3 were obtained from Engelhard and used without further purification. Acetonitrile (anhydrous) was purchased from Aldrich. Commercially available materials were used without further purification unless otherwise noted. Ligand **1** was synthesized in our laboratory, but is commercially available from Aldrich Chemical Co. or Strem Chemicals, Inc. Aryl halides were purchased from Aldrich Chemical Co. Liquid aryl bromides were purified through a pad of basic alumina prior to use. Boron reagents were purchased from Aldrich or Frontier Scientific. Anhydrous granular potassium phosphate and potassium carbonate were purchased from Mallinckrodt Chemicals and ground with a mortar and pestle and stored in a bench-top dessicator.

Analytical Methods. All new compounds were characterized by ^1H NMR, ^{13}C NMR, IR spectroscopy and elemental analysis. Known compounds were characterized by ^1H NMR and melting points (for solids) and compared to their literature values. ^1H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 MHz or Bruker 400 MHz. Infrared spectra were recorded on a Perkin-Elmer Model 2000 FT-IR using NaCl plates (thin film). Elemental analyses were preformed by Atlantic Microlabs Inc., Norcros, GA. All ^1H NMR experiments are reported in $\geq$ units, parts per million (ppm) downfield of TMS and were measured relative to the signals for the residual benzene (7.16 ppm), chloroform (7.26 ppm), dimethylsulfoxide (2.50 ppm) or methanol (3.31 ppm). All ^{13}C NMR spectra were reported in ppm relative to residual chloroform (77 ppm), dimethylsulfoxide (39.5 ppm) or methanol (49 ppm) and were obtained with ^1H decoupling. Melting points were obtained on a Mel-Temp capillary melting point apparatus. Gas chromatographic analyses were preformed on Hewlett-Packard 6890 gas chromatography instrument with a FID detector using 25m x 0.20 mm capillary column with cross-linked methyl siloxane as a stationary phase. The yields in Tables 1-2 refer to isolated yields (average of two runs) of compounds estimated to be $\geq$ 95% pure as determined by ^1H NMR and GC analysis and/or combustion analysis.

Table 1: General Procedure A for Suzuki-Miyaura coupling. A disposable tube with a screw cap, Teflon septum and stir bar was charged with $Pd(OAc)_2$ (2.2 mg, 0.010 mmol, 1 mol %), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl **1** (8.3 mg, 0.0200 mmol, 2 mol %), aryl halide (1.00 mmol), boronic acid (1.20-1.50 mmol) and K_2CO_3 (276-690 mg, 2.00-5.00 mmol). The tube was evacuated and back-filled with argon (this was repeated two additional times). The solvent/solvents were added (when degassed water was used, it was sonicated under vacuum for 2 min. prior to addition) and the reaction mixture was allowed to stir at the noted temperature for the indicated period of time. After cooling to room temperature, the products were extracted from the water layer with diethyl ether or ethyl acetate, dried over $MgSO_4$, filtered through celite and concentrated to dryness and purified by column chromatography on silica gel (eluting with hexanes/ethyl acetate mixtures).

2-(2-Methoxy-phenyl)-pyridin-3-ylamine (Table 1, Entry 1). The general procedure was used with 3-amino-2-chloro-pyridine (128 mg, 1.00 mmol), 2-methoxyphenylboronic acid (225 mg, 1.50 mmol), $Pd(OAc)_2$ (2.3 mg, 0.010 mmol, 1 mol %), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl **1** (8.3 mg, 0.020 mmol, 2 mol %), K_2CO_3 (414 mg, 3.00 mmol), water (1.0 mL), acetonitrile (1.5 mL), 12 h, 100 °C. The product was purified by column chromatography on silica gel (eluting with ethyl acetate) to provide the title compound as a light yellow solid (177 mg, 95%). Mp = 97-98 °C. ^1H NMR (400 MHz, $CDCl_3$) δ: 8.12 (dd, J = 1.2 Hz, J = 4.4 Hz, 1H), 7.36-7.40 (m, 2H), 7.04-7.09 (m, 2H), 6.99-7.01 (m, 2H), 3.79 (s, 3H), 3.76 (br-s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.6, 144.1, 141.2, 139.8, 131.7, 129.9, 127.8, 123.1, 122.5, 121.5, 111.4, 55.9. IR (neat, cm^{-1}): 3452, 3325, 3200, 3056, 3009, 2964, 2934, 2836, 1632, 1600, 1580, 1494, 1456, 1310, 1273, 1238, 1179, 1140, 1123, 1070, 1052, 1018, 796, 755. Anal. Calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04. Found: C, 71.67; H, 6.10.

6-(2,6-Dimethyl-phenyl)-pyridin-3-ylamine (Table 1, Entry 2). The general procedure was used with 3-amino-6-chloro-pyridine (128 mg, 1.00 mmol), 2,6-dimethylphenylboronic acid (300 mg, 2.00 mmol), $Pd(OAc)_2$ (4.6 mg, 0.020 mmol, 2 mol %), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl **1** (16.8 mg, 0.040 mmol, 4 mol %), K_2CO_3 (414 mg, 3.00 mmol), water (1.0 mL), acetonitrile (1.5 mL), 14 h, 100 °C. The

product was purified by column chromatography on silica gel (eluting with ethyl acetate/hexanes, 9:1) to provide the title compound as a light beige solid (163 mg, 82%). Mp = 129-130 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ: 8.20 (d, J = 2.8 Hz, 1H), 7.15 (m, 1H), 6.99-7.08 (m, 4H), 3.72 (br-s, 2H), 2.05 (s, 6H). ^{13}C NMR (100 MHz, CDCl$_3$) δ: 149.9, 140.9, 140.6, 137.2, 136.6, 127.6, 127.5, 124.5, 122.2, 20.4. IR (neat, cm^{-1}): 3446, 3322, 3194, 1631, 1596, 1565, 1494, 1466, 1407, 1297, 838, 772.

6-(2-Amino-phenyl)-pyridin-2-ylamine (Table 1, Entry 3). The general procedure was used with 2-amino-6-chloropyridine (128 mg, 1.00 mmol), 2-amino-phenylboronic acid (205 mg, 1.50 mmol), Pd(OAc)$_2$ (2.3 mg, 0.010 mmol, 1.0 mol %), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl 1 (8.3 mg, 0.020 mmol, 2 mol %), K$_2$CO$_3$ (414 mg, 3.00 mmol), water (2.0 mL), acetonitrile (2.0 mL), 10 h, 100 °C. The product was purified by column chromatography on silica gel (eluting with ethyl acetate/hexanes, 4:1) to provide the title compound as a light brown solid (177 mg, 95%). Mp = 119-120 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.53 (t, J = 7.6 Hz, 1H), 7.44 (dd, J = 1.6 Hz, J = 8.0 Hz, 1H), 7.14 (td, J = 1.6 Hz, J = 8.4 Hz, 1H), 6.98 (d, J = 7.6 Hz, 1H), 6.73-7.79 (m, 2H), 6.42 (d, J = 8.0 Hz, 1H), 5.41 (br-s, 2H), 4.30 (br-s, 2H).). ^{13}C NMR (100 MHz, CDCl$_3$) δ: 158.0, 157.1, 145.9, 138.9, 129.7, 129.6, 123.4, 117.9, 117.1, 113.1, 106.2. IR (neat, cm^{-1}): 3429, 3371, 3194, 1652, 1597, 1563, 1467, 1453, 1420, 1269, 759.

2-(6-Amino-pyridin-3-yl)-benzonitrile (Table 1, Entry 4). The general procedure was used with 2-amino-5-chloro-pyridine (64 mg, 0.500 mmol), 2-cyanophenylboronic acid (110 mg, 0.750 mmol), Pd(OAc)$_2$ (2.3 mg, 0.010 mmol, 2 mol %), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl 1 (8.3 mg, 0.020 mmol, 4 mol %), K$_3$PO$_4$ (212 mg, 1.00 mmol), 1,4-dioxane (2.5 mL), 14 h, 100 °C. The product was purified by column chromatography on silica gel (eluting with ethyl acetate) to provide the title compound as a white solid (77 mg, 79%). Mp = 144-145 °C ^{1}H NMR (400 MHz, CDCl$_3$/d^4-MeOH) δ: 8.08 (d, J = 2.0 Hz, 1H), 7.73 (dd, J = 0.8 Hz, J = 7.6 Hz, 1H), 7.64 (m, 2H), 7.46 (d, J = 8.0 Hz, 1H), 7.42 (td, J = 0.8 Hz, J = 7.6 Hz, 1H), 6.65 (d, J = 8.4 Hz, 1H). ^{13}C NMR (100 MHz, CDCl$_3$) δ: 160.4, 147.7, 143.4, 139.3, 134.7, 134.3, 130.5,

128.4, 124.2, 119.6, 111.4, 109.7. IR (neat, cm⁻¹): 3450, 3362, 2224, 1624, 1510, 1480, 1440, 1393, 823, 762.

2-Phenyl-pyridin-4-ylamine (Table 1, Entry 5).[20a] The general procedure was used with 4-amino-2-chloropyridine (129 mg, 1.00 mmol), phenylboronic acid (181 mg, 1.50 mmol), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol, 0.5 mol %), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl **1** (4.1 mg, 0.010 mmol, 1 mol %), K_2CO_3 (414 mg, 3.00 mmol), water (1.0 mL), acetonitrile (1.5 mL), 13 h, 100 °C. The product was purified by column chromatography on silica gel (eluting with methanol/ethyl acetate, 0.3:9.7) to provide the title compound as a light beige solid (158 mg, 92%). Mp = 123 °C. ¹H NMR (400 MHz, CDCl₃) δ: 8.32 (d, J = 5.6 Hz, 1H), 7.91 (d, J = 7.2 Hz, 2H), 7.45 (t, J = 7.2 Hz, 2H), 7.39 (t, J = 7.2 Hz, 1H), 6.96 (d, J = 2.4 Hz, 1H), 6.50 (dd, J = 2.4 Hz, J = 5.6 Hz, 1H), 4.22 (br-s, 2H). ¹³C NMR (100 MHz, CDCl₃) δ: 158.4, 153.7, 150.2, 139.9, 128.9, 128.7, 127.0, 108.5, 106.7.

2,6-Dimethyl-5-o-tolyl-pyrimidin-4-ylamine (Table 1, Entry 6). The general procedure was used with 5-Chloro-2,6-dimethyl-pyrimidin-4-ylamine (156 mg, 1.00 mmol), 2-methylphenylboronic acid (203 mg, 1.50 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 2 mol %), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl **1** (16.4 mg, 0.040 mmol, 4 mol %), K_2CO_3 (552 mg, 4.00 mmol), water (2.0 mL), acetonitrile (2.0 mL), 16 h, 100 °C. The product was purified by column chromatography on silica gel (eluting with methanol/ethyl acetate, 0.5:9.5) to provide the title compound as a light yellow solid (207 mg, 97%). Mp = 204-205 °C. ¹H NMR (400 MHz, CDCl₃) δ: 7.29-7.34 (m, 3H), 7.11 (d, J = 8.4 Hz, 1H), 4.55 (br-s, 2H), 2.55 (s, 3H), 2.11 (s, 3H), 2.08 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ: 165.9, 162.7, 161.1, 137.3, 133.8, 130.9, 130.0, 128.8, 113.7, 25.8, 22.0, 19.4. IR (neat, cm⁻¹): 3382, 3303, 3174, 2919, 2543, 2487, 2352, 1635, 1562, 1420, 998, 761.

1-[3-(4-Amino-2,6-dimethyl-pyrimidin-5-yl)-phenyl]-ethanone (Table 1, Entry 7). The general procedure was used with 5-Chloro-2,6-dimethyl-pyrimidin-4-ylamine (156 mg, 1.00 mmol), 3-acetylphenylboronic acid (246 mg, 1.50 mmol), $Pd(OAc)_2$ (2.3 mg, 0.01 mmol, 1 mol %), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl **1** (8.3 mg, 0.020 mmol, 2 mol %), K_2CO_3 (414 mg, 3.00 mmol), water (1.5 mL), acetonitrile (2.0 mL), 10 h,

100 °C. The product was purified by column chromatography on silica gel (eluting with methanol/ethyl acetate, 0.1:9.9) to provide the title compound as a white solid (231 mg, 96%). Mp = 197-198 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ: 8.01 (dt, J = 7.6 Hz, J = 1.2 Hz, 1H), 7.87 (t, J = 1.6 Hz, 1H), 7.62 (t, J = 7.6 Hz, 1H), 7.47 (dt, J = 7.6 Hz, J = 1.6 Hz, 1H), 4.69 (br-s, 2H), 2.64 (s, 3H), 2.54 (s, 3H), 2.14 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ: 197.7, 166.2, 162.8, 161.1, 138.4, 135.6, 134.7, 130.0, 129.7, 128.3, 113.6, 26.9, 25.8, 22.4. IR (neat, cm^{-1}): 3416, 3309, 3157, 1678, 1646, 1560, 1465, 1422, 1370, 1358, 1290, 1227.

4-Methyl-6-naphthalen-1-yl-pyrimidin-2-ylamine (Table 1, Entry 8).[24] The general procedure was used with 2-amino-4-chloro-6-methylpyrimidine (144 mg, 1.00 mmol), 1-naphthylboronic acid (258 mg, 1.50 mmol), Pd(OAc)$_2$ (4.6 mg, 0.020 mmol, 2 mol %), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl **1** (16.8 mg, 0.040 mmol, 4 mol %), K$_3$PO$_4$ (424 mg, 2.00 mmol), 1,4-dioxane (3.0 mL), 14 h, 100 °C. The product was purified by column chromatography on silica gel (eluting with ethyl acetate/hexanes, 4:1) to provide the title compound as a white solid (218 mg, 92%). Mp = 157 °C (lit.[24] = 158-161 °C). ^{1}H NMR (400 MHz, CDCl$_3$) δ: 8.15-8.17 (m, 1H), 7.89-7.94 (m, 2H), 7.50-7.61 (m, 4H), 6.80 (s, 1H), 5.17 (br-s, 2H), 2.46 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ: 168.5, 167.7, 163.2, 136.8, 133.9, 130.7, 129.7, 128.5, 127.0, 126.8, 126.2, 125.6, 125.3, 111.9, 24.2.

Phenanthridine (Table 2, Entry 1).[25] The general procedure was used with 2-chloroaniline (0.105 mL, 1.00 mmol), 2-formylphenylboronic acid (225 mg, 1.50 mmol), Pd(OAc)$_2$ (2.3 mg, 0.010 mmol, 1 mol %), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl **1** (8.3 mg, 0.020 mmol, 2 mol %), K$_2$CO$_3$ (552 mg, 4.00 mmol), water (2.0 mL), acetonitrile (2.0 mL), 12 h, 100 °C. The product was purified by column chromatography on silica gel (eluting with ethyl acetate/hexanes, 1:1) to provide the title compound a light yellow solid (178 mg, 99%). Mp = 106 °C (lit.[25] 107-108 °C) ^{1}H NMR (400 MHz, CDCl$_3$) δ: 9.31 (s, 1H), 8.62 (dd, J = 8.4 Hz, J = 3.6 Hz, 2H), 8.21 (d, J = 8.0 Hz, 1H), 8.07 (d, J = 8.0 Hz, 1H), 7.89 (td, J = 7.2 Hz, J = 1.2 Hz, 1H), 7.69-7.79 (m, 3H).
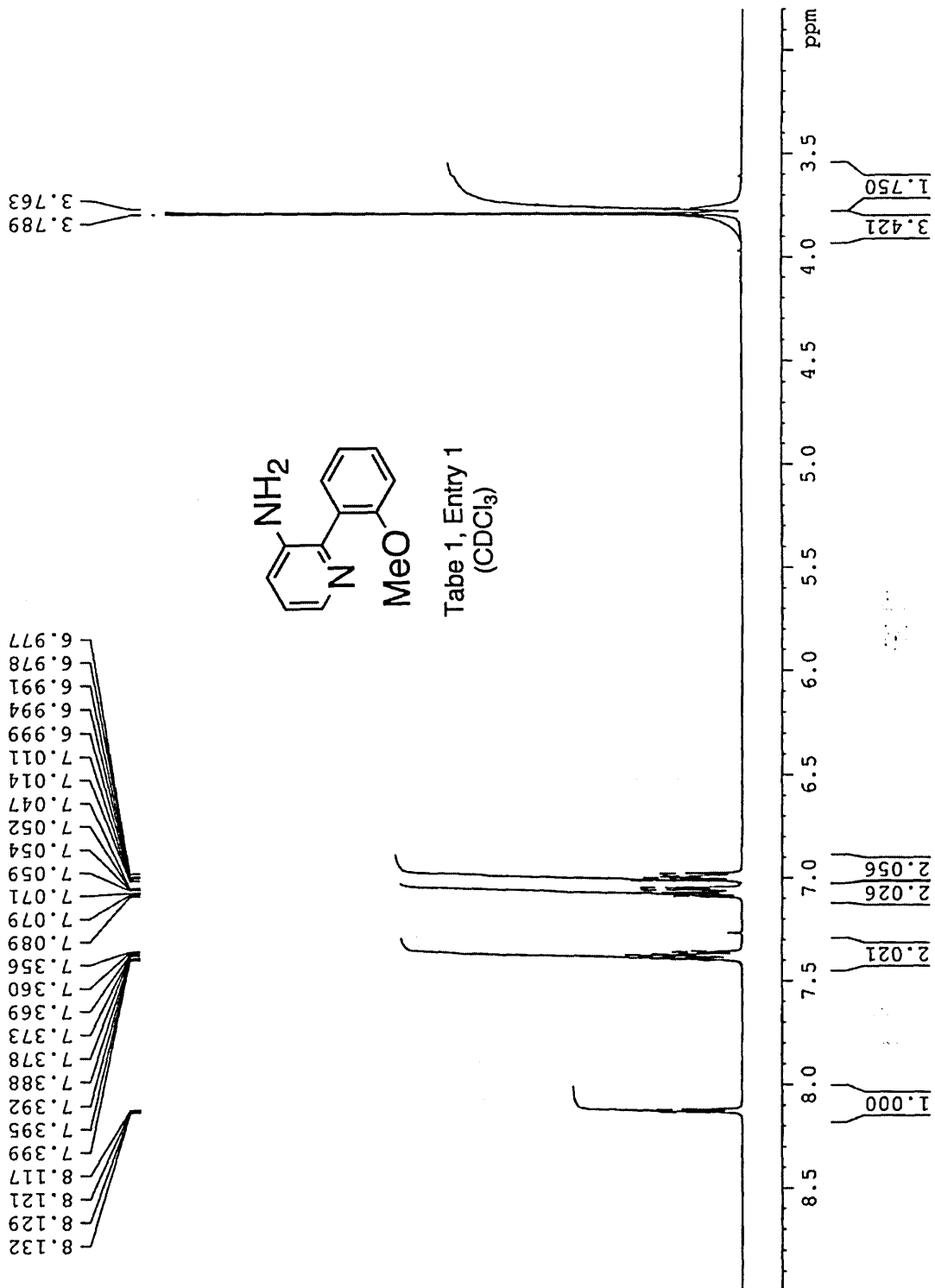
6-Methyl-phenanthridine (Table 2, Entry 2).[26] The general procedure was used with 2-chloroaniline (0.105 mL, 1.00 mmol), 2-acetylphenylboronic acid (246 mg, 1.50 mmol), Pd(OAc)$_2$ (2.3 mg, 0.010 mmol, 1 mol %), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl **1** (8.3 mg, 0.020 mmol, 2 mol %), K$_2$CO$_3$ (552 mg, 4.00 mmol), water (1.0 mL), acetonitrile (1.5 mL), 8 h, 100 °C. The product was purified by column chromatography on silica gel (eluting with ethyl acetate/hexanes, 3:2) to provide the title compound as a white solid (185 mg, 95%). Mp = 85 °C (lit.[26] = 84-85 °C) ^{1}H NMR (400 MHz, CDCl$_3$) δ: 8.63 (d, J = 8.4 Hz, 1H), 8.55 (d, J = 8.0 Hz, 1H), 8.23 (d, J = 8.4 Hz, 1H), 8.11 (d, J = 8.0 Hz, 1H), 7.85 (td, J = 7.2 Hz, J = 1.2 Hz, 1H), 7.69-7.75 (m, 2H), 7.62 (t, J = 8.0 Hz, 1H), 3.06 (s, 3H).

6-Methyl-2-trifluoromethyl-benzo[c][1,8]naphthyridine (Table 2, Entry 3). The general procedure was used with 3-Chloro-5-trifluoromethyl-pyridin-2-ylamine (197 mg, 1.00 mmol), 2-acetylphenylboronic acid (246 mg, 1.50 mmol), Pd(OAc)$_2$ (2.3 mg, 0.010 mmol, 1 mol %), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl **1** (8.3 mg, 0.020 mmol, 2 mol %), K$_2$CO$_3$ (552 mg, 4.00 mmol), water (1.0 mL), acetonitrile (1.5 mL), 13 h, 100 °C. The product was purified by column chromatography on silica gel (eluting with ethyl acetate) to provide the title compound as a white solid (246 mg, 94%). Mp = 151-152 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ: 9.25 (s, 1H), 9.10 (s, 1H), 8.62 (d, J = 8.4 Hz, 1H), 8.33 (d, J = 8.4 Hz, 1H), 7.96 (t, J = 7.2 Hz, 1H), 7.84 (t, J = 8.0 Hz, 1H), 3.16 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ: 166.1, 154.5, 147.2, 131.8, 131.7, 129.0, 127.0, 126.1, 125.1, 124.5, 124.1, 123.8, 123.1, 122.5, 122.4, 117.3, 23.9. IR (neat, cm^{-1}): 2918, 1614, 1588, 1566, 1435, 1376, 1356, 1286, 1165, 1115, 1089, 911, 808, 759, 722. Anal. Calcd for C$_{14}$H$_9$F$_3$N$_2$: C, 64.12; H, 3.46. Found: C, 63.93; H, 3.36.

Benzo[c][1,5]naphthyridine (Table 2, Entry 4).[27] The general procedure was used with 3-amino-2-chloro-pyridine (129 mg, 1.00 mmol), 2-formylphenylboronic acid (225 mg, 1.50 mmol), Pd(OAc)$_2$ (2.3 mg, 0.010 mmol, 1 mol %), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl **1** (8.3 mg, 0.020 mmol, 2 mol %), K$_2$CO$_3$ (552 mg, 4.00 mmol), water (1.0 mL), acetonitrile (1.5 mL), 12 h, 100 °C. The product was purified by column chromatography on silica gel (eluting with ethyl acetate/hexanes, 8.5/1.5) to provide the title compound as a white solid (170 mg, 94%). Mp = 92 °C (lit.[27] = 93-93.5 °C) ^{1}H NMR

(400 MHz, CDCl$_3$) δ: 9.37 (s, 1H), 9.19 (d, J = 8.0 Hz, 1H), 9.03 (dd, J = 1.6 Hz, J = 4.4 Hz, 1H), 8.48 (dd, J = 1.6 Hz, J = 8.4 Hz, 1H), 8.11 (d, J = 8.0 Hz, 1H), 7.98 (t, J = 7.2 Hz, 1H), 7.85 (t, J = 8.0 Hz, 1H), 7.71 (dd, J = 4.0 Hz, J = 8.0 Hz, 1H).

Carbazole (Table 2, Entry 5).[28] The general procedure was used with 2-bromochlorobenzene (0.060 mL, 0.500 mmol), 2-aminophenylboronic acid (102 mg, 0.75 mmol), Pd(OAc)$_2$ (1.1 mg, 0.005 mmol, 1 mol %), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl 1 (4.1 mg, 0.010 mmol, 2 mol %), K$_2$CO$_3$ (275 mg, 2.00 mmol), water (1.0 mL), acetonitrile (1.0 mL), 24 h, 100 °C. The product was purified by column chromatography on silica gel (eluting with ethyl acetate/hexanes, 1/9) to provide the title compound as a white solid (79 mg, 79%). Mp = >230 °C (lit.[28] = 240 °C) ^{1}H NMR (400 MHz, CDCl$_3$) δ: 8.11 (d, J = 8.0 Hz, 2H), 8.06 (br-s, 1H), 7.42-7.47 (m, 4H), 7.24-7.31 (m, 2H).
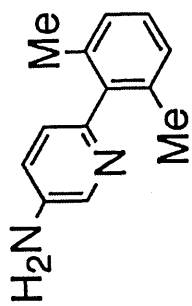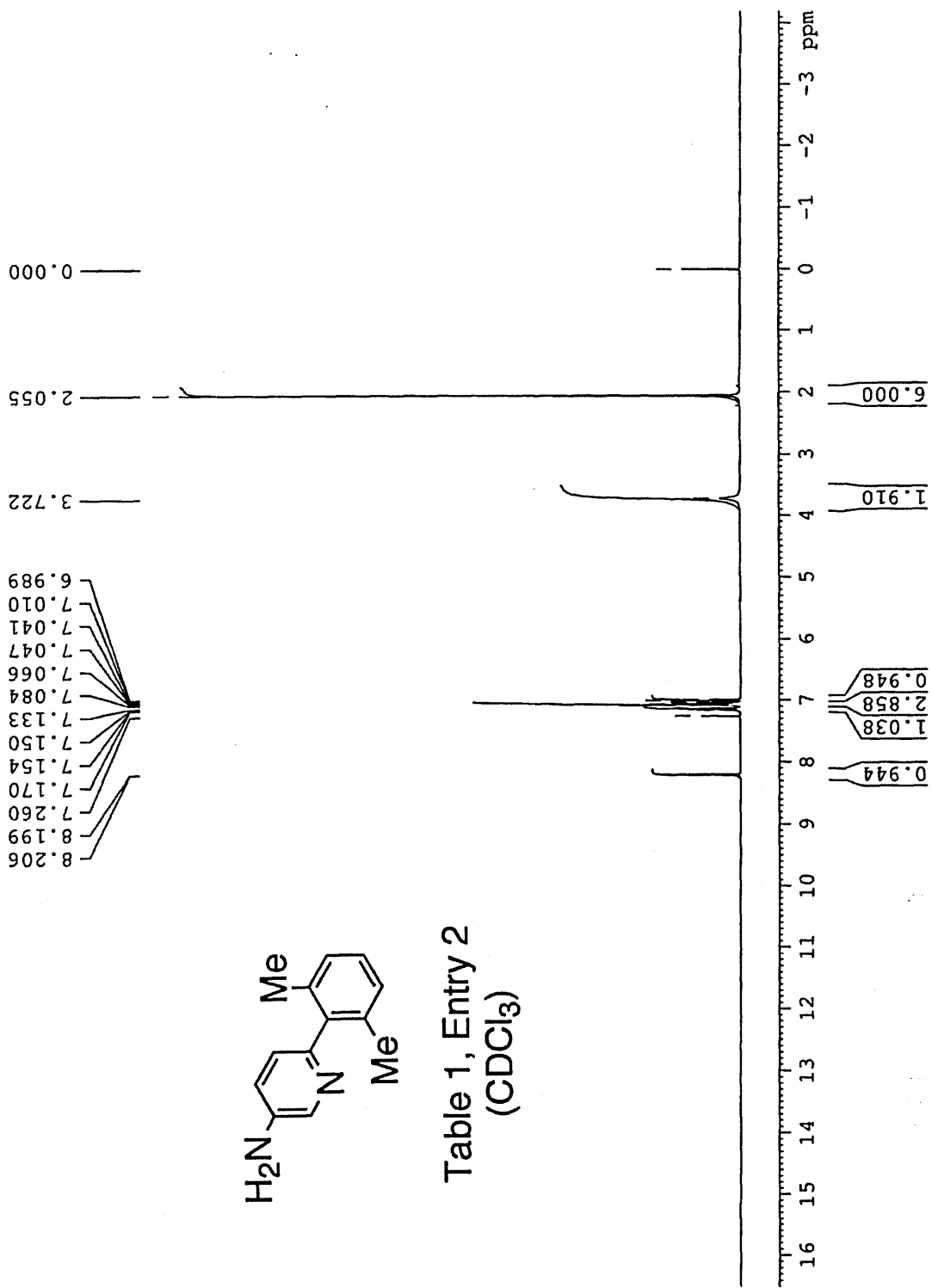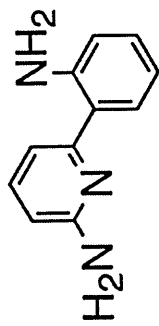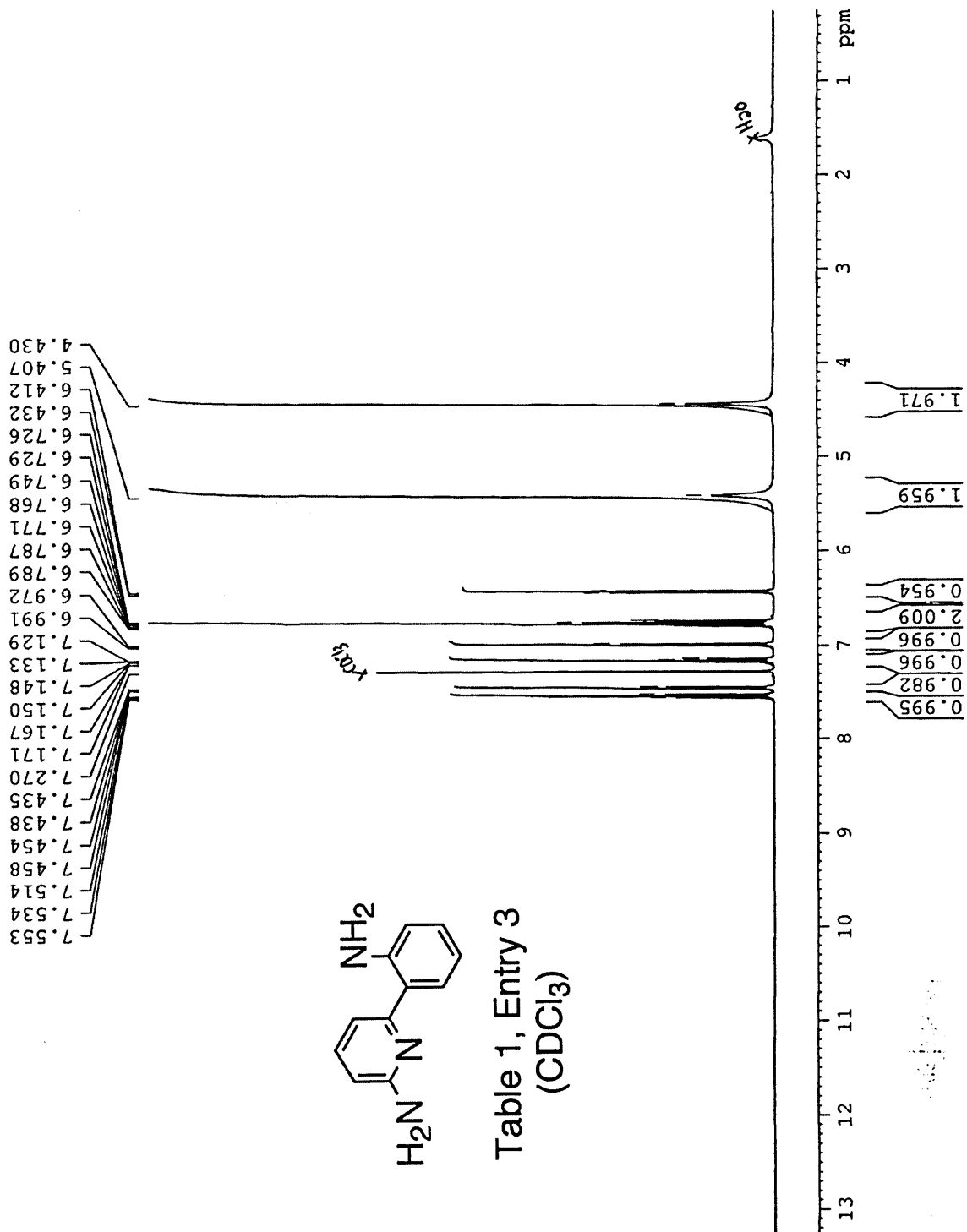
Tabe 1, Entry 1
(CDCl₃)

0.000

2.055

3.722

6.989
7.010
7.041
7.047
7.066
7.084
7.133
7.150
7.154
7.170
7.260
8.199
8.206

6.000

1.910

0.948
2.858
1.038

0.944

Me

H₂N

Me

N

Table 1, Entry 2
(CDCl₃)

16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3 ppm

167

4.430
5.407
6.412
6.432
6.726
6.729
6.749
6.768
6.771
6.787
6.789
6.972
6.991
7.129
7.133
7.148
7.150
7.167
7.171
7.270
7.435
7.438
7.454
7.458
7.514
7.534
7.553

XH₂O

CHCl₃

1.971

1.959

0.954
2.009
0.996
0.996
0.982
0.995

Table 1, Entry 3
(CDCl₃)

168

ppm 1 2 3 4 5 6 7 8 9 10 11 12 13

Table 1, Entry 4
(d⁶-DMSO)

2.500

6.315
6.553
6.574
7.458
7.478
7.497
7.550
7.569
7.609
7.614
7.631
7.635
7.700
7.719
7.739
7.766
7.868
7.887
8.138

0.426
1.040

1.140
0.979
1.083
1.040
1.099
1.000

4.247

6.356
6.361
6.369
6.375
6.815
6.820
7.174
7.289
7.295
7.303
7.307
7.310
7.326
7.341
7.344
7.357
7.362
7.365
7.790
7.792
7.805
7.810
7.814
8.191
8.205

2.119

1.008

1.028

3.089

2.074

1.000

ppm

Table 1, Entry 5
(CDCl₃)

170

1.985
2.032

2.430

4.846

7.022
7.026
7.042
7.187
7.193
7.204
7.210
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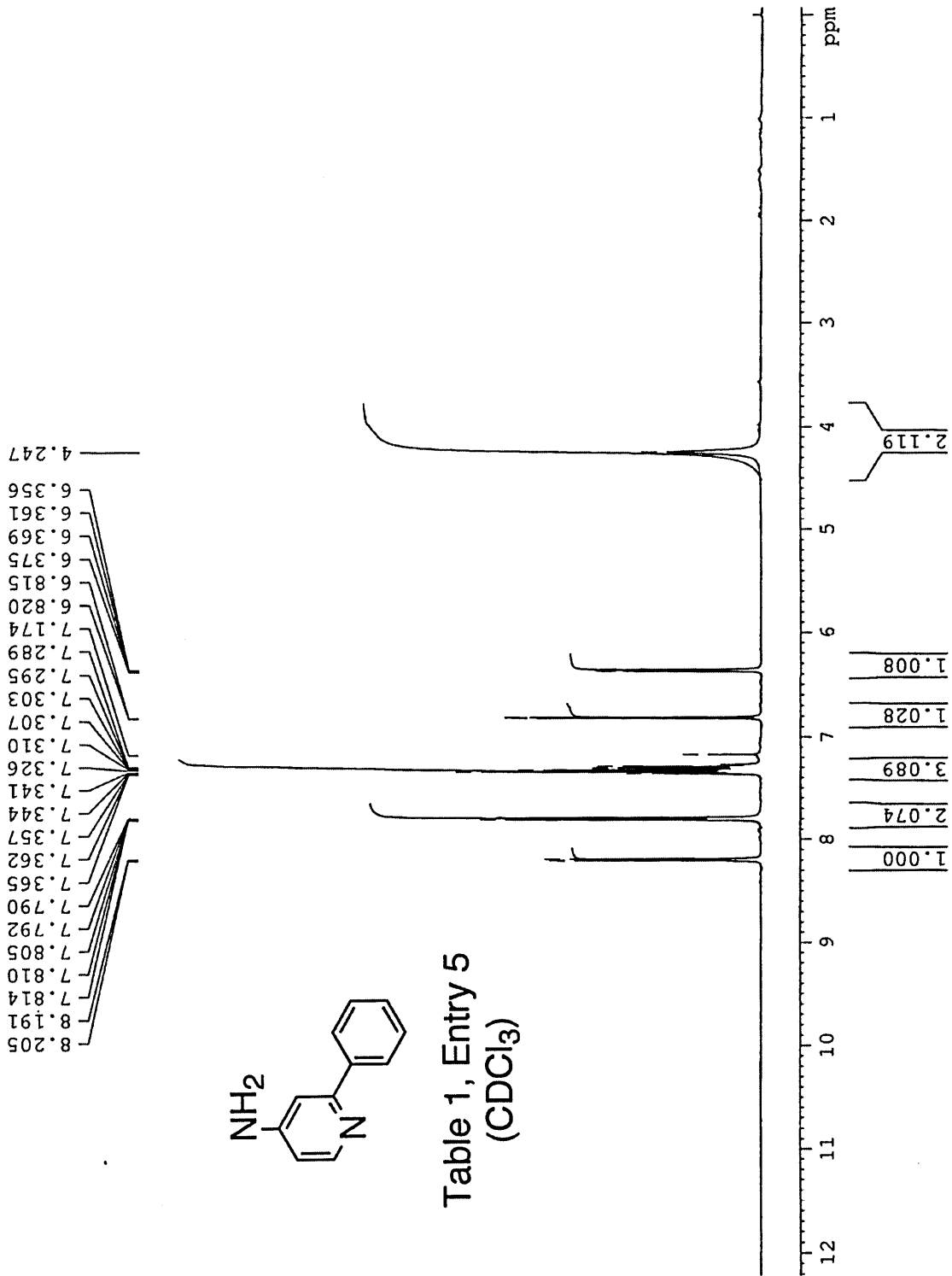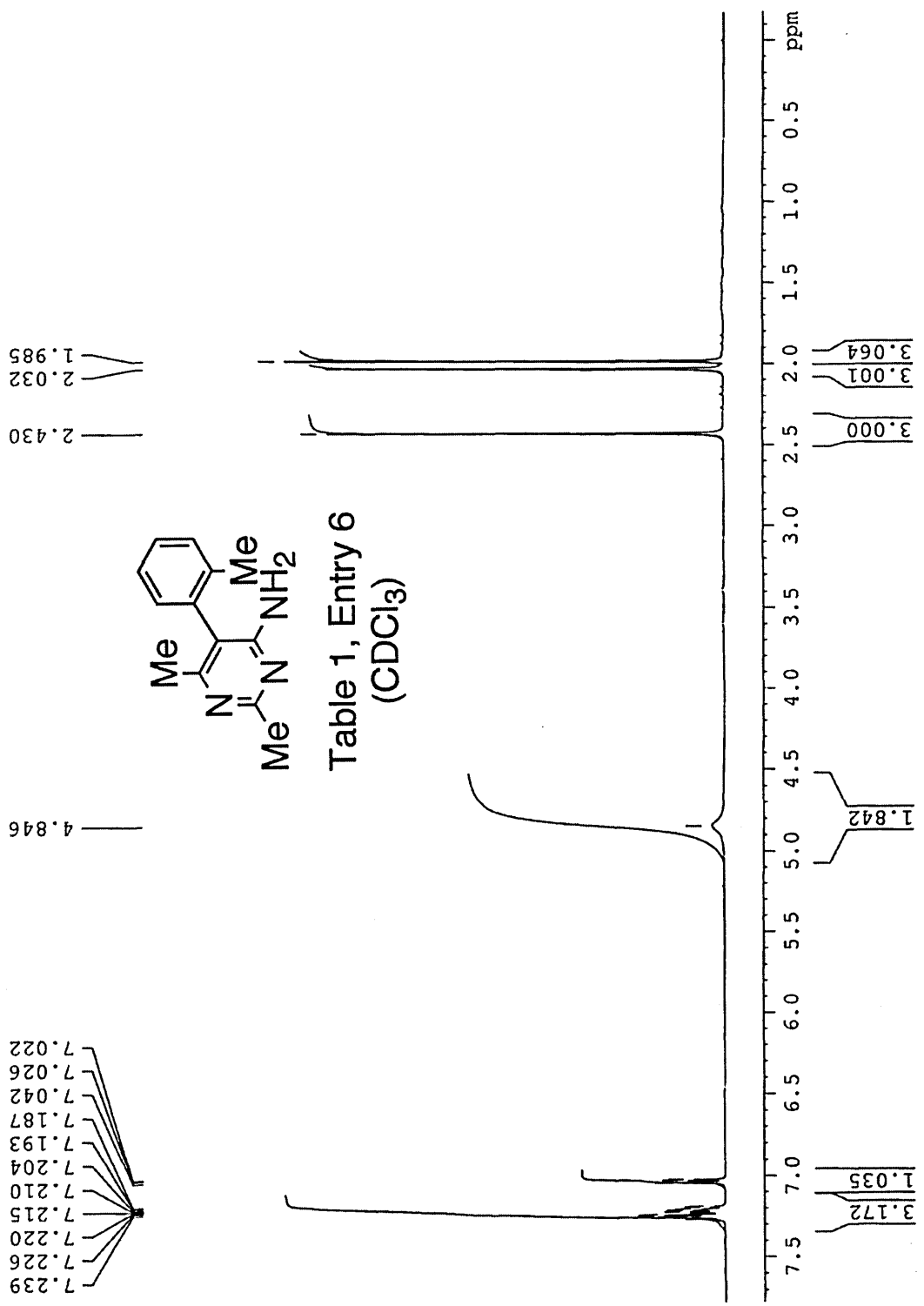
Table 1, Entry 6
(CDCl$_3$)

3.064
3.001

3.000

1.842

1.035
3.172

ppm

0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5

171

Table 1, Entry 7
(CDCl₃)

7.270
7.472
7.475
7.487
7.491
7.494
7.597
7.616
7.635
7.866
7.870
7.873
7.993
7.997
8.000
8.013
8.016

4.686

2.141
2.536
2.641

ppm
1.0
1.5
2.0
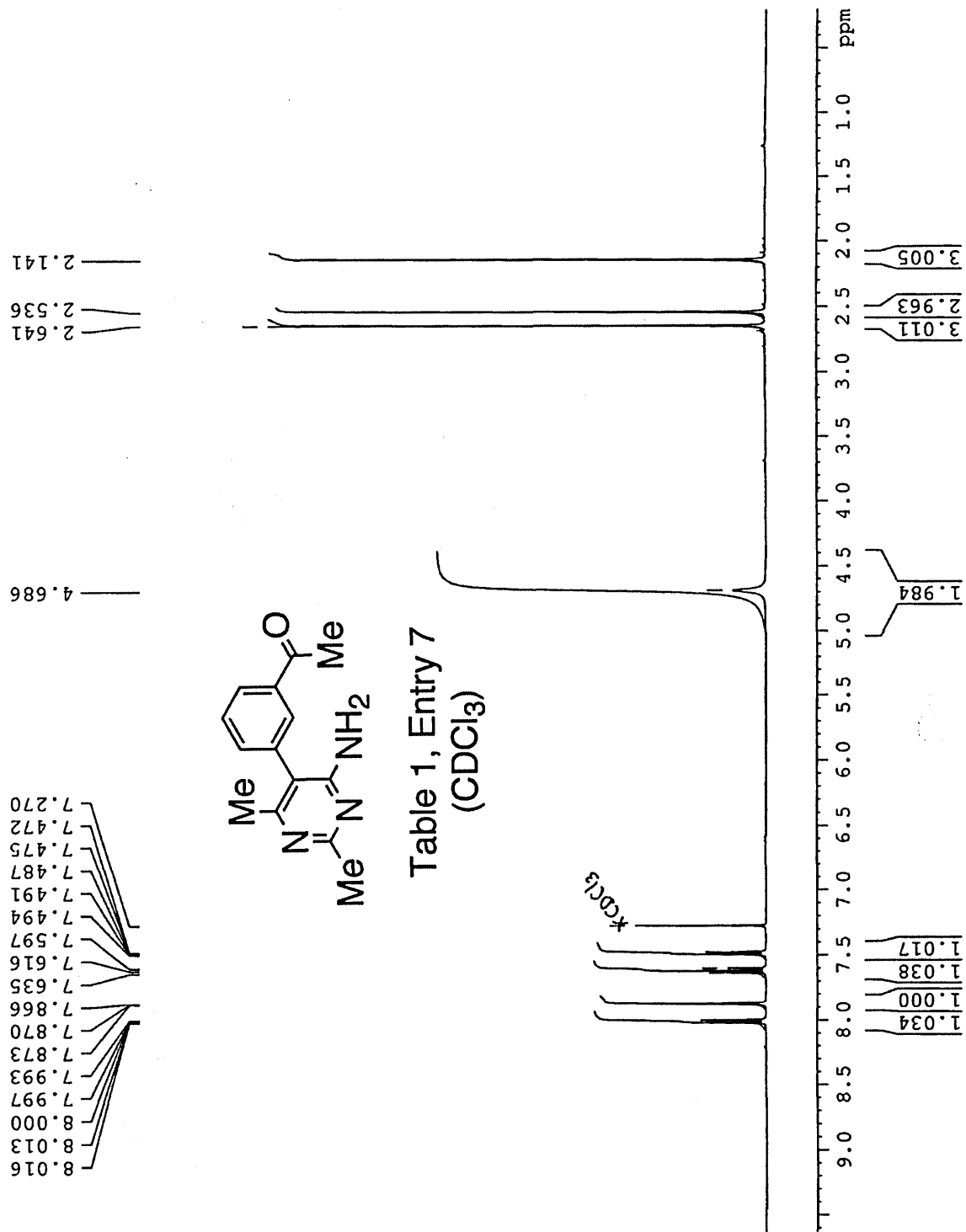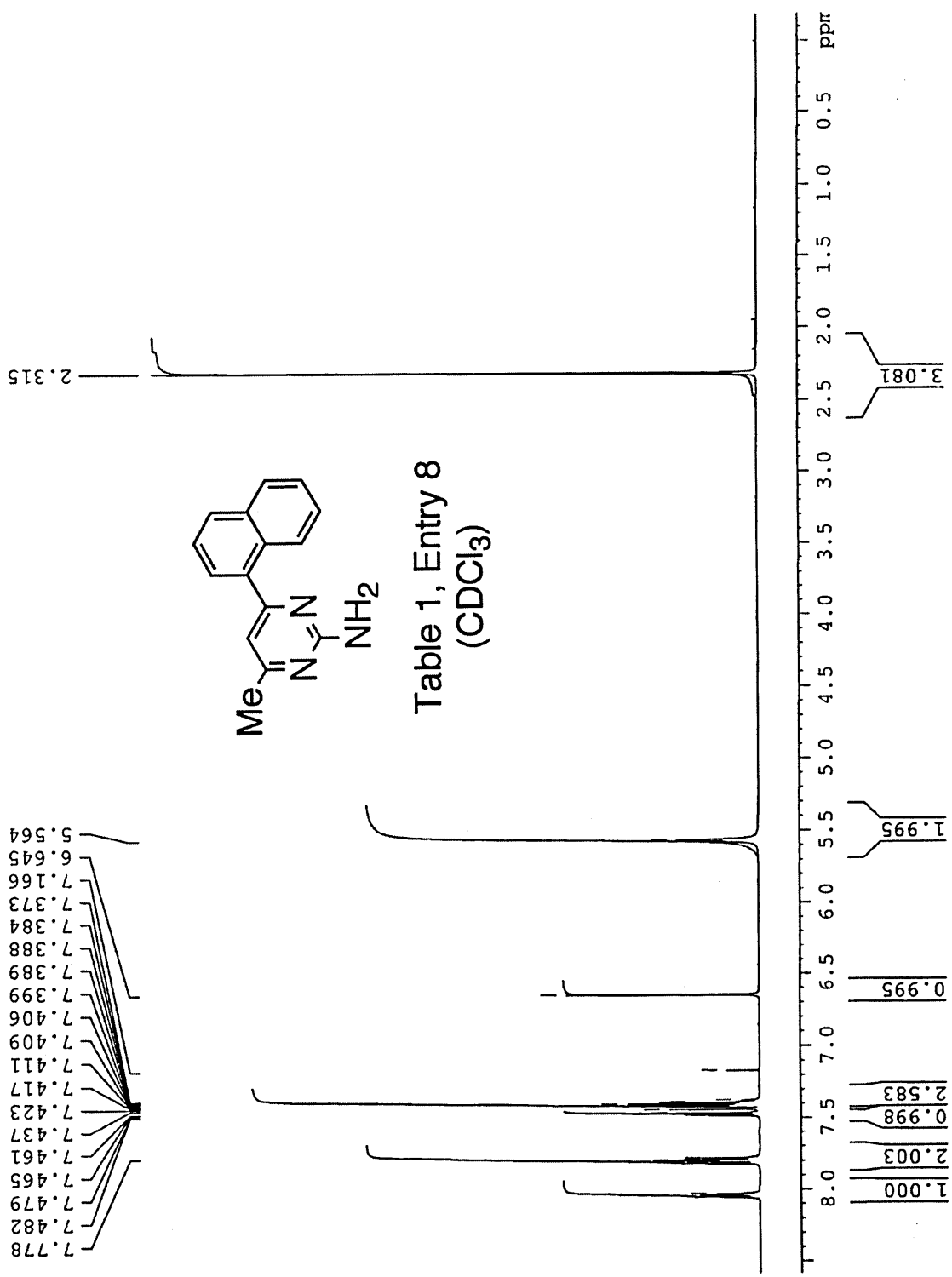2.5
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3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0

3.005
2.963
3.011

1.984

1.017
1.038
1.000
1.034

CDCl₃

Table 1, Entry 8
(CDCl$_3$)

2.315

5.564
6.645
7.166
7.373
7.384
7.388
7.389
7.399
7.406
7.409
7.411
7.417
7.423
7.437
7.461
7.465
7.479
7.482
7.778

3.081
1.995
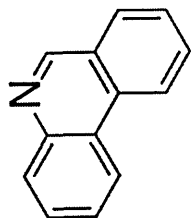0.995
2.583
0.998
2.003
1.000

ppm
0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0 6.5 7.0 7.5 8.0

Me, N, N, NH$_2$

Table 2, Entry 1
(CDCl$_3$)

7.540
7.559
7.574
7.576
7.591
7.593
7.658
7.661
7.679
7.699
7.717
7.720
7.877
7.896
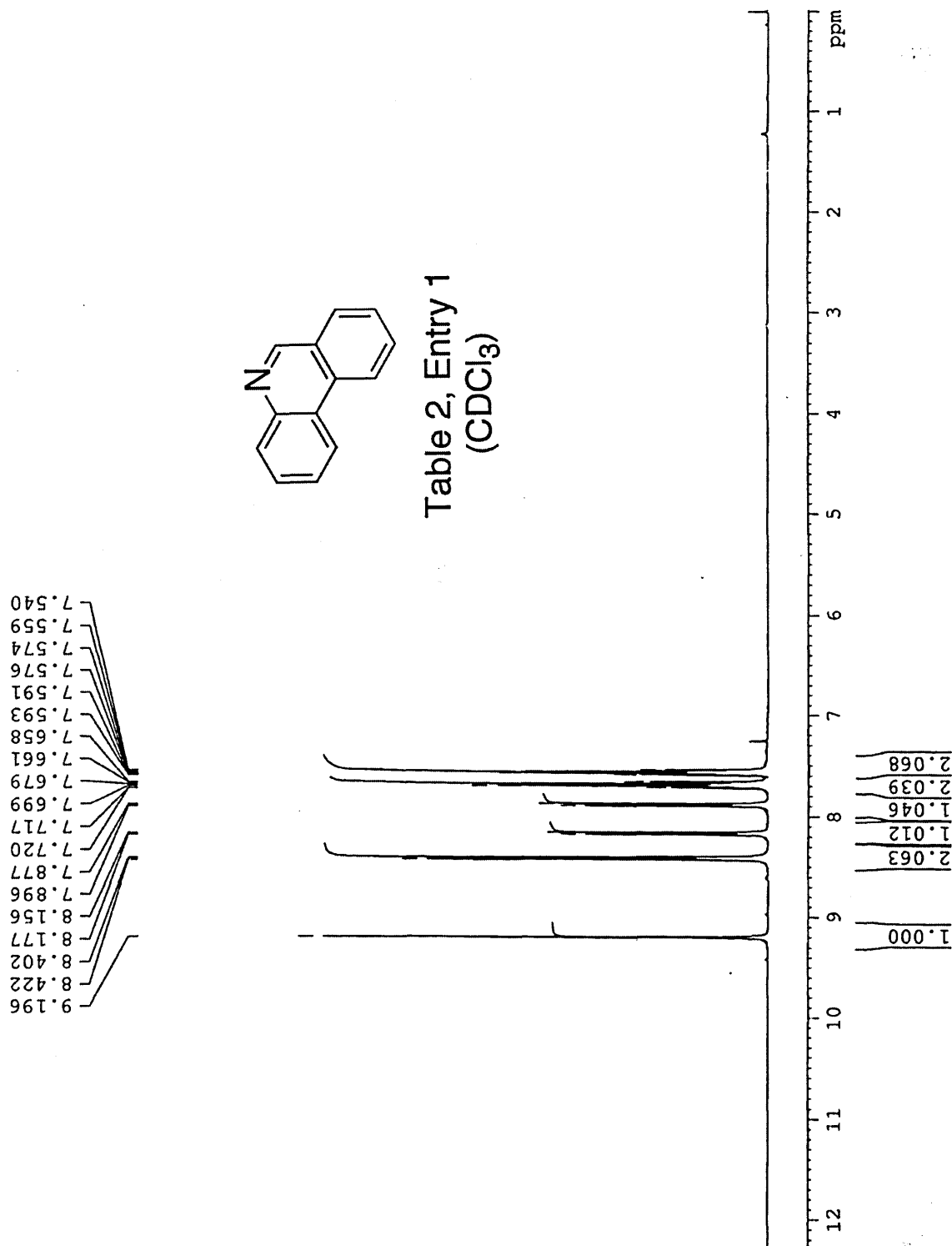8.156
8.177
8.402
8.422
9.196

2.068
2.039
1.046
1.012
2.063

1.000

ppm
1 2 3 4 5 6 7 8 9 10 11 12

Table 2, Entry 2
(CDCl₃)

7.270
7.612
7.615
7.633
7.650
7.653
7.688
7.691
7.705
7.708
7.725
7.728
7.742
7.745
7.832
7.835
7.852
7.855
7.870
7.873
8.101
8.103
8.121
8.123
8.223
8.244
8.543
8.563
8.629
8.650

3.061

3.000

0.994
1.977
1.004
0.966
0.984
1.006
1.006

ppm

7.333
7.741
7.758
7.776
7.865
7.870
7.883
7.901
8.204
8.223
8.488
8.508
8.982
9.202

3.089

F₃C

Me

N

N

Table 2, Entry 3
(CDCl₃)

3.099

1.003
1.047
1.031
1.036

1.020
1.000

1.678

7.270
7.694
7.705
7.715
7.725
7.828
7.831
7.848
7.866
7.868
7.960
7.963
7.981
7.983
7.998
8.001
8.104
8.124
8.470
8.474
8.491
8.495
9.030
9.034
9.041
9.045
9.188
9.208
9.373

Table 2, Entry 4
(CDCl$_3$)

CDCl$_3$

CH$_3$

1.000
0.976
1.001
0.964
0.965

0.933
0.937
0.946

ppm
1   2   3   4   5   6   7   8   9   10   11   12

177

Table 2, Entry 5
(CDCl₃)

0.025
0.033
0.041

7.239
7.252
7.259
7.266
7.272
7.279
7.284
7.292
7.305
7.427
7.429
7.447
7.449
7.454
7.455
7.460
7.463
7.474
8.065
8.106
8.126

16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3 ppm

178
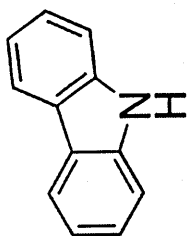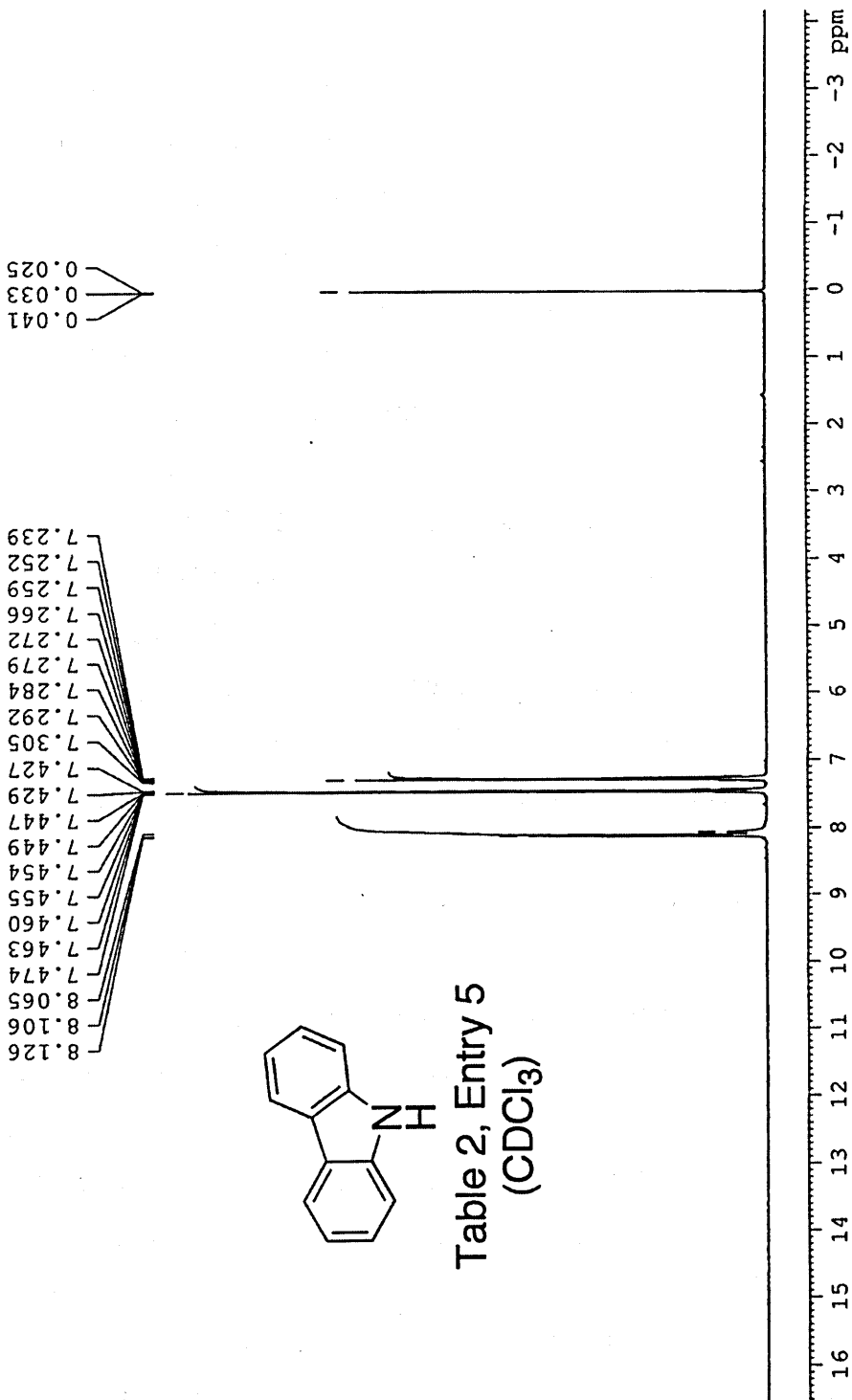
References

(1) de Meijere, A.; Diederich, F. Eds. *Metal-Catalyzed Cross-Coupling Reactions*, Vol. 2: Wiley-VCH, Weinheim, 2004.

(2) Miyaura, N. Metal-Catalyzed Cross-Coupling Reactions of Organoboron Compounds with Organic Halides. In *Metal-Catalyzed Cross-Coupling Reactions*, 2nd Ed.: de Meijere, A.; Diederich, F. Eds; Wiley-VCH: Weinheim, 2004, pp. 41-125.

(3) Miyaura, N. *Topics in Current Chem.* **2002**, *219*, 11.

(4) Suzuki, A. *Organomet. Chem.* **1999**, *576*, 147.

(5) Kertesz, M.; Choi, C. H.; Yang, S. *Chem. Rev.* **2005**, *105*, 3448.

(6) (a) Markham, A.; Goa, K. L. *Drugs* **1997**, *54*, 299. b) Capdeville, R.; Buchdunger, E.; Zimmermann, J.; Matter, A. *Nat. Rev. Drug Discovery* **2002**, *1*, 493. (c) Boren, J.; Cascante, M.; Marin, S.; Comin-Anduix, B.; Centelles, J. J.; Lim, S.; Bassilian, S.; Ahmed, S.; Lee, W. N.; Boros, L. G. *J. Biol. Chem.* **2001**, *276*, 37747.

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

(8) Lightowler, S.; Hird, M. *Chem. Mater.* **2005**, *17*, 5538.

(9) (a) Leahy, J. J. J.; Golding, B. T.; Griffin, R. J.; Hardcastle, I. R.; Richardson, C.; Rigoreau, L.; Smith, G. C. M. *Bioorg. & Med. Chem. Lett.* **2004**, 14, 6083. (b) Hardcastle, I. R.; Cockcroft, X.; Curtin, N. J.; El-Murr, M. -D.; Leahy, J. J. J.; Stockley, M.; Golding, B. T.; Rigoreau, L.; Richardson, C.; Smith, G. C. M.; Griffin, R. J. *J. Med. Chem.* **2005**, *48*, 7829.

(10) Cruz-Monserrate Z.; Vervoort, H. C.; Bai, R.; Newman, D. J.; Howell, S. B.; Los, G.; Mullaney, J. T.; Williams, M. D.; Pettit, G. R.; Fenical, W.; Hamel, E. *Mol. Pharm.* **2003**, *63*, 1273.

(11) Amatore, C.; Jutand, A. *J. Organomet. Chem.* **1999**, *576*, 254.

(12) Tsuji, J. Ed.; *Palladium Reagents and Catalysts: New Perspectives for the 21st Century*, 1st Ed.: Wiley: Weinheim, 2004.

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

(14) Braga, A. A. C.; Morgon, N. H.; Ujaque, G.; Maseras, F. *J. Am. Chem. Soc.* **2005**, *127*, 9298.

(15) (a) Bandgar, B. P.; Patil, A. V. *Tetrahedron Lett.* **2005**, *46*, 7627. (b) Leadbeater,

N. E. *Chem. Comm.* **2005**, 2881.

(16) (a) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685. (b) Barder, T. E.; Buchwald, S. L. *Org. Lett.* **2004**, *6*, 2649. (c) Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2004**, *43*, 1871. (d) Nguyen, H. N.; Huang, X.; Buchwald S. L. *J. Am. Chem. Soc.* **2003**, *125*, 11818. (e) Yin, J.; Rainka, M. P.; Zhang, X. -X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1162. (f) Singh, R.; Viciu, M. S.; Kramareva, N.; Novarro, O.; Nolan, S. P *Org. Lett.* **2005**, *7*, 1829. (g) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020. (h) Kudo, N.; Perseghini, M.; Fu, G. C. *Angew. Chem. Int. Ed.* **2006** (Advanced Article).

(17) (a) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722 (b) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550.

(18) Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 12051.

(19) (a) Kondolff, I.; Doucet, H.; Santelli, M. *Synlett* **2005**, 2057. (b) Thompson, A. E.; Hughes, G.; Batsanov, A. S.; Bryce, M. R.; Parry, P. R.; Tarbit, B. *J. Org. Chem.* **2005**, *70*, 388.

(20) A few direct cross-coupling reactions involving H_2N-unprotected heteroaryl moieties have been disclosed, see: 19b and (a) Itoh, T.; Mase, T. *Tetrahedron Lett.* **2005**, *46*, 3573. (b) Itoh, T.; Sato, K.; Mase, T. *Adv. Synth. Catal.* **2004**, *346*, 1859. (c) Gunda, P.; Russon, L. M.; Lakshman, M. K. *Angew. Chem. Int. Ed.* **2004**, *43*, 6372. (d) Agrofoglio, L. A.; Gillaizeau, I.; Saito, Y. *Chem. Rev.* **2003**, *103*, 1875. (e) Tagata, T.; Nishida, M.; *J. Org. Chem.* **2003**, *68*, 9412. (f) Feuerstein, M.; Doucet, H.; Santelli, M. *J. Organomet. Chem.* **2003**, *687*, 327.

(21) For examples where it was essential to protect the aminoheterocycle, see: (a) Caron, S.; Massett, S. S.; Bogle, D. E.; Castaldi, M. J.; Braish, T. F. *Org. Process. Res. Dev.* **2003**, *5*, 254. (b) Miller, J. A.; Farrell, R. P. *Tetrahedron Lett.* **1998**, *39*, 6441.

(22) Wagaw, S.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 7240.

(23) Gronowitz, S.; Hoernfeldt, A. B.; Yang, Y. H. *Chemica Scripta* **1986**, *26*, 311.

(24) *Collect Czech. Commun.* **1961**, *26*, 2865.

(25) (a) Ibrahim, Y. A.; Al-Awadi, N. A.; Kual, K. *Tetrahedron* **2003**, *59*, 5425. (b)

Murahashi, S. –I.; Oda, T.; Sugahara, T.; Masui, Y. *J. Org. Chem.* **1990**, *55*, 1744.

(26) Leardini, R.; McNab, H.; Minozzi, M.; Nanni, D. *J. Chem. Soc., Perkin Trans. 1*

2001, 1072.

(27) Ninomiya, I.; Kiguchi, T.; Yamauchi, S.; Naito, T. *J. Chem. Soc., Perkin Trans 1*

1976, 1861.

(28) Appler, H. *J. Organomet. Chem.* **1988** *350*, 217.

Chapter 4

**Synthesis and Utilization of a Water-Soluble Monophosphinobiaryl Ligand in the
Suzuki-Miyaura Coupling of Aryl/Heteroaryl Halides and Organoboronic Acids**

Introduction

Metal-catalyzed cross-coupling methodology to form carbon-carbon bonds has inarguably advanced organic synthesis.[1] The Suzuki-Miyaura coupling is one of the preeminent methods for formation of carbon-carbon bonds and has been used in numerous synthetic ventures.[2] We recently reported a new catalyst system that manifested high activity paired with extremely broad scope.[3] There remained, however, a need to develop reaction conditions for the coupling of water-soluble aryl chlorides and for the combination of difficult coupling partners in aqueous conditions. Additionally, compounds containing hydrophilic functional groups, which are insoluble in organic solvents and are present in many pharmaceutically interesting compounds, may be transformed, obviating the need for additional protection/deprotection steps. Further, conducting reactions in water is attractive since it is easily separated from organic products, nontoxic, nonflammable, renewable, and inexpensive.[4]

Very few examples have been reported concerning palladium-catalyzed cross-coupling reactions of hydrophilic aryl chlorides with aryl boronic acids using purely aqueous reaction conditions.[5-9] Several sulfonated phosphine derivatives have been prepared and used in cross-coupling reactions conducted in water or water/organic biphasic solvent systems.[10,11] Shaughnessy reported that use of sterically demanding, water-soluble, alkylphosphine salts in the Suzuki-Miyaura, Sonogashira, and Heck coupling of unactivated aryl bromides provided excellent yields of products derived from carbon-carbon bond formation.[12] Limitations to this methodology include a lengthy synthesis and poor thermal and air stability of the ligand. Furthermore, only a single example of a substituted aryl chloride was described. This was an activated aryl chloride (4-chlorobenzonitrile) that was combined with phenylboronic acid in a coupling that required 4 mol % of the palladium catalyst. Very recently, a Pd/glucosamine-based dicyclohexylarylphosphine catalyst was reported that displayed modest activity in Suzuki-Miyaura couplings of activated aryl chlorides when conducted in an water/toluene/ethanol solvent system.[13] This system, as reported, was not general and the ligand was not readily available.

We felt that the electron-rich lower aromatic ring on **1** would be readily amenable to the incorporation of a water-solublizing sulfonate group. In fact, treatment of **1** with concentrated H_2SO_4 at 40 °C for 24 h gave **2** with exclusive mono-sulfonation at the 3'-position in 99% yield after treatment with NaOH and workup (eq. 1). With **2** in hand, excellent yields were obtained in Suzuki-Miyaura couplings of highly functionalized aryl chlorides and heterocyclic chlorides/bromides (containing carboxylic acids, amines, alcohols, sulfonamides and sulfonic acids) and aryl/alkyl-boronic acids in aqueous media.

$$1) \ H_2SO_4, \ CH_2Cl_2 \quad 0 \ °C \ to \ 40 \ °C, \ 24h$$

$$2) \ NaOH, \ H_2O \quad 0 \ °C \quad 99\% \ yield$$

(1)
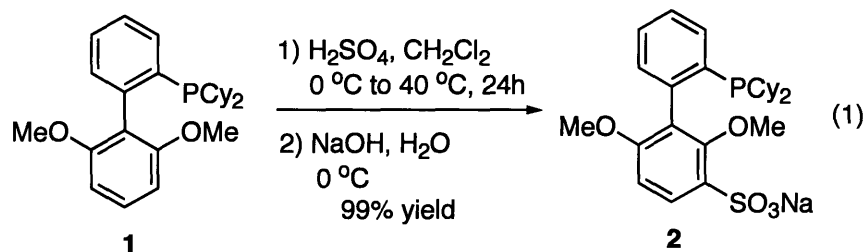
Results and Discussion

Using a catalyst system based on **2**, we investigated the coupling of hydrophobic and hydrophilic substrates; a summary of our initial results is shown in Table 1. The coupling of electronically neutral 1-chloro-3,4-dimethylbenzene and phenylboronic acid at room temperature using water as the solvent provided the corresponding biaryl in 99% yield (Table 1, entry 1). A temperature of 100 °C was necessary for successful coupling of 3-chlorobenzamide and hindered 2,6-dimethylphenylboronic acid resulting in 99% yield of the biaryl amide (Table 1, entry 2). Using microwave irradiation (150 °C), the same coupling product was obtained in 94% yield in 10 minutes (Table 1, entry 2).[14,15] This result indicates that the catalyst system based on 2 exhibits high thermal stability. We found that coupling of 3-chlorobenzoic acid with phenylboronic acid proceeds at room temperature using 0.5% Pd and at 100 °C using 0.1% Pd, providing the coupled product in 97% yield for both cases (Table 1, entry 3). Similar catalytic activity was observed in the coupling of 3-chlorobenzoic acid and 2-methylphenylboronic acid using 0.5% Pd at room temperature and 0.1% Pd at 100 °C giving the desired product in 95% and 96% yield, respectively (Table 1, entry 4). Using

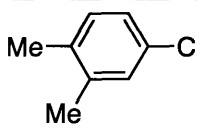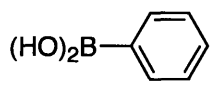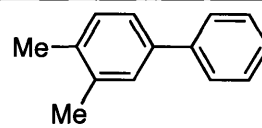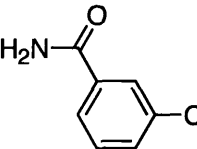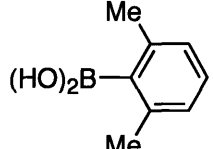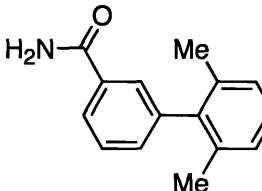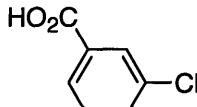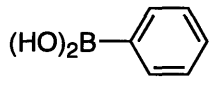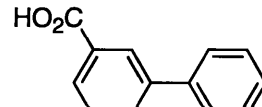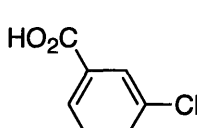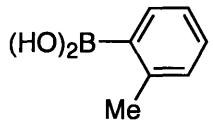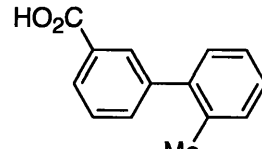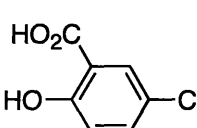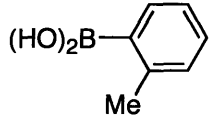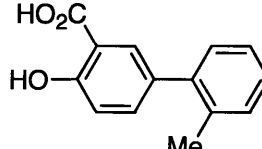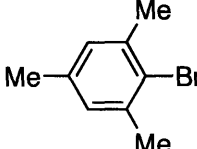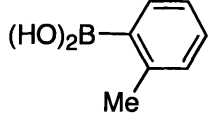microwave irradiation (150 °C) and 0.1% Pd, the same coupling product was obtained in 98% yield in 10 minutes (Table 1, entry 4). The combination of 5-chloro-2-hydroxybenzoic acid and 2-methylphenylboronic acid, while slower, provided an excellent yield of the biaryl product at 2% Pd (RT) or 0.1% Pd (100 °C) (Table 1, entry 5).

The Suzuki-Miyaura coupling of hydrophobic aryl bromides in aqueous media has been reported to occur with an assortment of catalysts including those that operate without a supporting ligand. Successful application to moderately hindered substrate combinations, however, have not been disclosed or possible.[11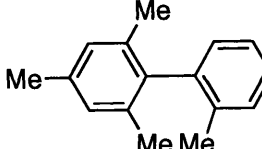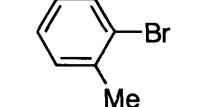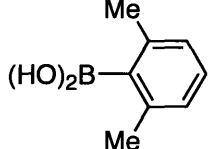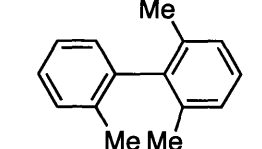,12,15] To ascertain whether or not our Pd(OAc)$_2$/**2** catalyst system could address this limitation, we examined two reasonably hindered substrate combinations using water as the solvent at room temperature: The reaction of 2-bromomesitylene with 2-methylphenylboronic acid and 2-bromotoluene with 2,6-dimethylphenylboronic acid to form a biaryl that contains three substituents *ortho* to the aryl-aryl connection (Table 1, entries 6-7).[16] To our knowledge, this represents the first successful coupling of a hindered substrate combination conducted using a water or water/organic biphasic solvent at room temperature.
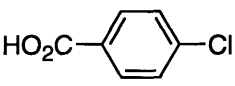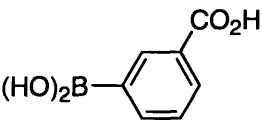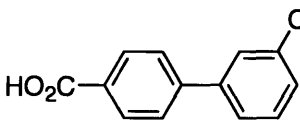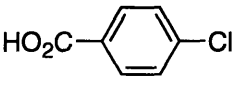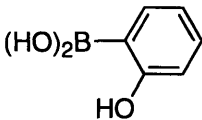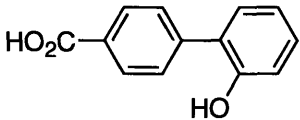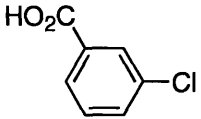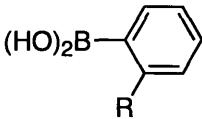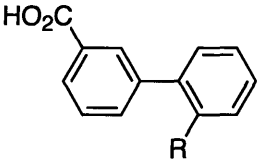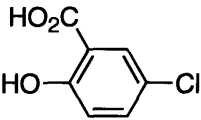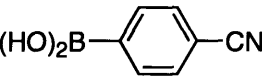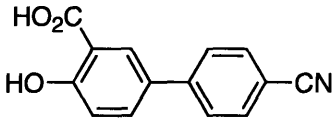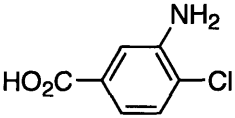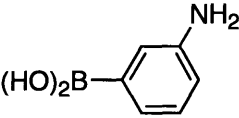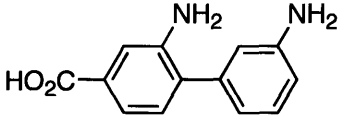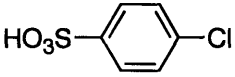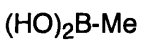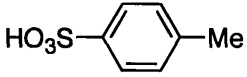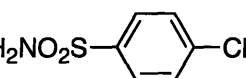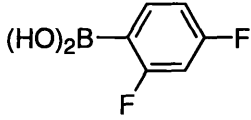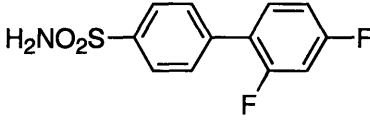
To determine the scope of this process, we examined the reaction of chlorobenzoic acids with 3-carboxyphenylboronic acid, 2-hydroxyphenylboronic acid, 2-aminophenylboronic acid, 2-acetylphenylboronic acid and 2-formylphenylboronic acid; these coupling processes all proceeded in excellent yield (Table 2, entries 1-3) using 1% catalyst. Using microwave irradiation (150 °C), 4-chlorobenzoic acid and 3-carboxyphenylboronic acid were coupled in 10 minutes with 1% Pd providing the product in 95% yield (Table 2, entry 1), again demonstrating catalyst stability at higher temperatures.

Table 1. Suzuki-Miyaura coupling of aryl halides using ligand **2**.[a]

Entry	Halide	Boronic Acid	Product	Pd (mol %)	Conditions	Yield (%)[b]
1				2	RT, 10 h	99
2				1	100 °C, 8 h	99
				1	150 °C (μW), 10 min.	94[c]
3				2	RT, 2 h	96
				0.5	RT, 8 h	97
				0.1	100 °C, 5 h	97
				0.1	150 °C (μW), 10 min.	98[c]
4				0.5	RT, 8 h	95
				0.1	100 °C, 6 h	96
5				2	RT, 12 h	99[d]
				0.1	100, 12 h	96[d]
6				2	RT, 22 h	94
7				2	RT, 22 h	97
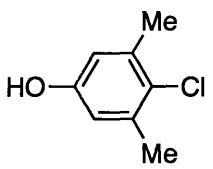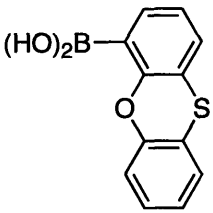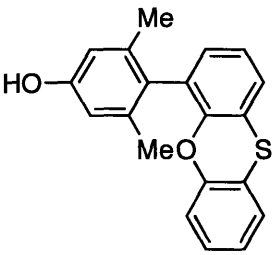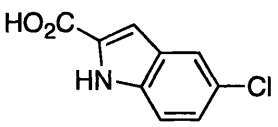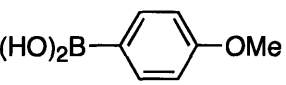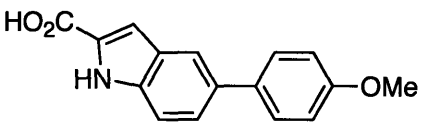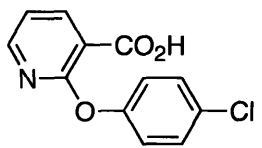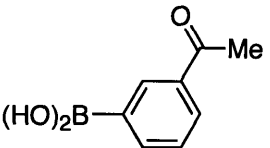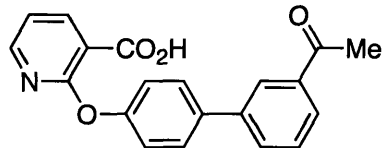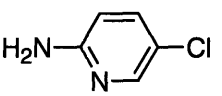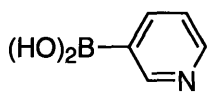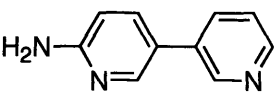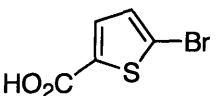
[a]Reaction conditions: 1.0 equiv aryl chloride, 1.2 equiv boronic acid, 3.0 equiv K_2CO_3, degassed water (1.5 mL mmol⁻¹), cat. $Pd(OAc)_2$, ligand **2**, L:Pd = 2:1. [b]Yield of isolated product (average of 2 runs). [c]Conducted using microwave irradiation with cooling. [d]4.0 equiv K_2CO_3 was used.

Table 2. Suzuki-Miyaura coupling of aryl chlorides using ligand **2**.[a]

Entry	Halide	Boronic Acid	Product	Yield (%)[b]
1	HO_2C—⬡—Cl	$(HO)_2B$—⬡(CO_2H)	HO_2C—⬡—⬡(CO_2H)	99[c] / 95[d]
2	HO_2C—⬡—Cl	$(HO)_2B$—⬡(HO)	HO_2C—⬡—⬡(HO)	99
3	HO_2C⬡Cl	$(HO)_2B$—⬡(R)	HO_2C⬡—⬡(R)	R = NH_2 94 / C(O)Me 97 / CHO 87[e]
4	HO_2C/HO⬡Cl	$(HO)_2B$—⬡—CN	HO_2C/HO⬡—⬡—CN	92[f]
5	HO_2C—⬡(NH_2)—Cl	$(HO)_2B$—⬡(NH_2)	HO_2C—⬡(NH_2)—⬡(NH_2)	93
6	HO_3S—⬡—Cl	$(HO)_2B$-Me	HO_3S—⬡—Me	97
7	H_2NO_2S—⬡—Cl	$(HO)_2B$—⬡(F)(F)	H_2NO_2S—⬡—⬡(F)(F)	96

[a]Reaction conditions: 1.0 equiv aryl chloride, 1.3-1.5 equiv boronic acid, 3.0 equiv K_2CO_3, degassed water (2.0 mL mmol⁻¹), $Pd(OAc)_2$ (1.0 mol %), ligand **2** (2.0 mol %), 100 °C, 2-8 h. Reaction times and temperatures conducted were not optimized. [b]Yield of isolated product (average of 2 runs). [c]The reaction was conducted at 50 °C. [d]The reaction was conducted using microwave irradiation with cooling, 150 °C for 10 min. [e]The reaction was conducted at 80 °C. [f]The reaction was conducted at 80 °C.

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Table 3. Suzuki-Miyaura coupling of heterocyclic halides using ligand **2**.[a]

Entry	Halide	Boronic Acid	Product	Yield (%)[b]
1	HO–(ring)–Cl, Me, Me	(HO)₂B–(dibenzo ring, O, S)	HO–(ring with Me, MeO)–(dibenzo ring O, S)	93
2	HO₂C–(indole, HN)–Cl	(HO)₂B–(phenyl)–OMe	HO₂C–(indole, HN)–(phenyl)–OMe	93[c]
3	(pyridine, N)–CO₂H, O–(phenyl)–Cl	(HO)₂B–(phenyl)–C(O)–Me	(pyridine, N)–CO₂H, O–(phenyl)–(phenyl)–C(O)–Me	92[c]
4	H₂N–(pyridine, N)–Cl	(HO)₂B–(pyridine, N)	H₂N–(pyridine, N)–(pyridine, N)	93
5	HO₂C–(thiophene, S)–Br	(HO)₂B–(furan, O)	HO₂C–(thiophene, S)–(furan, O)	97 / 95[d]

[a]Reaction conditions: 1.0 equiv aryl halide, 1.3-1.5 equiv boronic acid, 3.0 equiv K₂CO₃, degassed water (4.0 mL mmol⁻¹), Pd(OAc)₂ (1.0 mol %), ligand **2** (2.0 mol %), 100 °C, 10-12 h. Reaction times and temperatures were not optimized. [b]Yield of isolated product (average of 2 runs). [c]The reaction was conducted at 80 °C. [d]The reaction was conducted using microwave irradiation with cooling, 150 °C for 10 min.

We next shifted our attention to Suzuki-Miyaura couplings of functionalized hydrophilic aryl chlorides and substituted arylboronic acids. Chlorobenzoic acids containing phenolic (Table 2, entry 4) and amino (Table 2, entry 5) groups on the aromatic ring were effectively coupled with substituted arylboronic acids (4-cyanophenylboronic acid and 3-aminophenylboronic acid, respectively) generating the biaryl products in high yields (92% and 99%, respectively). Of interest, 4-chlorobenzenesulfonic acid successfully coupled with methylboronic acid giving the sulfonic acid derivative in 96% yield, (Table 2, entry 6). To the best of our knowledge, this is the first reported Suzuki-Miyaura coupling of an aryl halide bearing an unprotected sulfonic acid.[17]

Applications of heterocyclic compounds (which are commonplace in numerous natural products) in cross-coupling processes remain a challenge. To the best of our knowledge, very few examples of aqueous-phase Suzuki-Miyaura couplings of water-soluble heterocyclic halides have been published.[18] We have examined the use of **2** as a supporting ligand in the Suzuki-Miyaura coupling with a variety of challenging hydrophilic heterocyclic halides; our results are shown in Table 3. As is shown, the method worked well for a number of different carboxylic acid containing heterocyclic chlorides and bromides including indole (possessing a free -NH), pyridine and thiophene (Table 3, entries 2-3, 5). Even 2-amino-5-chloropyridine, which can potentially chelate to metal centers such as Pd(II), is successfully coupled with 3-pyridylboronic acid in 93% yield (Table 3, entry 4).[19]

The Suzuki-Miyaura coupling of 3-chlorobenzoic acid and phenylboronic acid employing **1** provided efficient conversion and yield of the desired product using an water/organic biphasic solvent system at 100 °C (Table 4, entries 3,4). However at room temperature, under these conditions, the reaction was sluggish (Table 4, entry 5). A dramatic increase in activity was observed when using the amphiphilic ligand **2**, as compared to **1**, in water at room temperature providing the biaryl product in 97% yield (Table 4, entry 7). Although a catalyst system using **1** in a similar biphasic solvent system may work in many instances, this has not yet been explored.

In conclusion, a water-soluble monophosphinobiaryl ligand, sodium 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl-3'-sulfonate **2**, was synthesized by electrophilic sulfonation of the lower-aromatic ring of 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl **1**. This ligand was utilized in the palladium-catalyzed Suzuki-Miyaura reaction of water-soluble aryl/heteroaryl halides and organoboronic acids. The catalyst displays unprecedented reactivity and stability for Suzuki-Miyaura reactions conducted in water.

Table 4. Screening of conditions for Suzuki-Miyaura coupling with **1** and **2**.[a]

$$HO_2C\text{—}C_6H_4\text{—}Cl \; + \; (HO)_2B\text{—}C_6H_5 \; \xrightarrow[\substack{\text{Ligand (4\%)} \\ K_2CO_3}]{Pd(OAc)_2\ (2\%)} \; HO_2C\text{—}C_6H_4\text{—}C_6H_5 \quad (2)$$

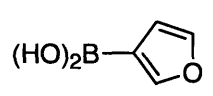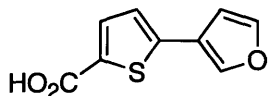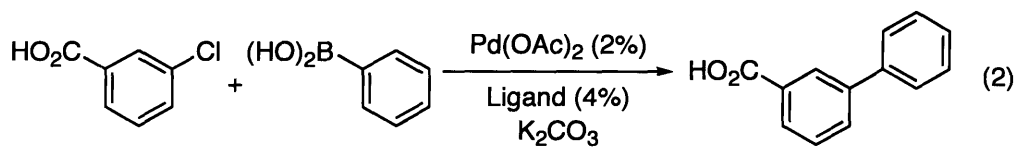| Entry	Ligand	Solvent	$T\,(^oC)$	Conv. (%)	Yield (%)[b]
1	1	n-BuOH	100	77	75
2	1	n-BuOH/H$_2$O (5:1)	100	27	26
3	1	propionitrile/H$_2$O (1:1)	100	>99	96
4	1	N,N-DMF/H$_2$O (1:1)	100	>99	94
5	1	CH$_3$CN/H$_2$O (1:1)	RT	17	12
6	1	H$_2$O	100	22	20
7	2	H$_2$O	RT	>99	97[c]

[a]Reaction conditions: 1.0 equiv aryl chloride, 1.2 equiv boronic acid, 3.0 equiv K$_2$CO$_3$, solvent (2.0 mL mmol^{-1}), cat. Pd(OAc)$_2$, ligand **1** or **2**, L:Pd = 2:1, 14 h. [b]NMR yield of product. [c]The reaction was complete in 2 h.

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Experimental

Reagents. Pd(OAc)$_2$ was obtained from Engelhard and used without further purification. Ligand **1** was synthesized in our laboratory, but is commercially available from Strem Chemical Co. and Aldrich Chemical Co. Dichloromethane was purchased from J. T. Baker in CYCLE-TAINER® solvent delivery kegs, which were vigorously purged with argon for 2 h, and further purified by passing the solvent through two packed columns of neutral alumina and copper (II) oxide under argon pressure. All other reagents were purchased from commercial sources and used without further purification.

Analytical methods. All reactions were carried out under an argon atmosphere. IR spectra were obtained on a Perkin-Elmer Model 2000 FT-IR using NaCl plates (thin film). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 400 MHz NMR with chemical shifts reported in ppm relative to the residual deuterated solvent or the internal standard tetramethylsilane. Yield refers to isolated yields of compounds greater than 95% purity as determined by capillary gas chromatography (GC) and proton Nuclear Magnetic Resonance spectroscopy (^{1}H NMR) analysis. ^{1}H NMR and melting points (where applicable) of all known compounds were compared with those reported. All new compounds were further characterized by elemental analysis.

Preparation of Water-Soluble Ligand (eq. 1):

Sodium 2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl-3'-sulfonate (eq. 1), (2). To an oven-dried 25 mL round bottom flask equipped with a Teflon-coated magnetic stir bar and rubber septum was added 2-dicyclohexylphosphino-2'6'dimethoxybiphenyl **1** (5.13 g, 12.5 mmol) and CH$_2$Cl$_2$ (5 mL). The solution was cooled to 0 °C using an ice/water bath and then concentrated H$_2$SO$_4$ (32.5 mL, 625 mmol) was added dropwise. The solution slowly turned yellow in color. The solution was heated to 40 °C in a preheated oil bath and was allowed stir for 24 h. At this time it was cooled to 0 °C using an ice/water bath and crushed ice (~50 g) was added. The solution turned cloudy and white in color. An aqueous solution of NaOH (6.0 M, ~200 mL) was then added dropwise to the cooled solution until it became neutral (pH ~7.0 as judged by pH paper). The aqueous solution was extracted with CH$_2$Cl$_2$ (3 x 300 mL) and concentrated under reduced pressure to give a light yellow solid. The crude

material was then dissolved in a minimum amount of cold methanol (~20 mL), filtered and concentrated (this cycle was repeated) to give the desired product as a light yellow solid (6.35 g, 99%). Mp = 165 °C (turned red, dec.) ^{1}H NMR (400 MHz, CD_3OD) δ: 7.88 (d, 1H, J = 8.8 Hz), 7.60 (m, 1H), 7.36 (m, 2H), 7.22 (m, 1H), 6.76 (d, 1H, J = 8.8 Hz) 3.70 (s, 3H), 3.39 (s, 3H), 1.14-2.01 (m, 22H). ^{13}C NMR (125 MHz, CD_3OD) δ: 161.3, 157.1, 143.3, 142.9, 137.9, 137.8, 133.7, 133.6, 133.3, 133.2, 131.9, 130.0, 129.3, 128.0, 127.9, 127.8, 105.9, 61.6, 56.1, 50.0, 37.0, 36.9, 34.8, 34.6, 31.7, 31.6, 31.5, 31.2, 31.0, 30.8, 30.7, 28.9, 28.8, 28.7, 28.4, 28.34, 28.31, 28.2, 27.8, 27.7. ^{31}P NMR (162 MHz, CD_3OD) δ: -8.02. IR (neat, cm^{-1}): 3453, 2925, 2849, 1577, 1462, 1448, 1400, 1229, 1191, 1099, 1053, 736. Anal. Calcd for $C_{26}H_{34}NaO_5PS$: C, 60.92; H, 6.69. Found: C, 60.40; H, 6.85.

¹H NMR (d⁴-MeOH/D₂O):
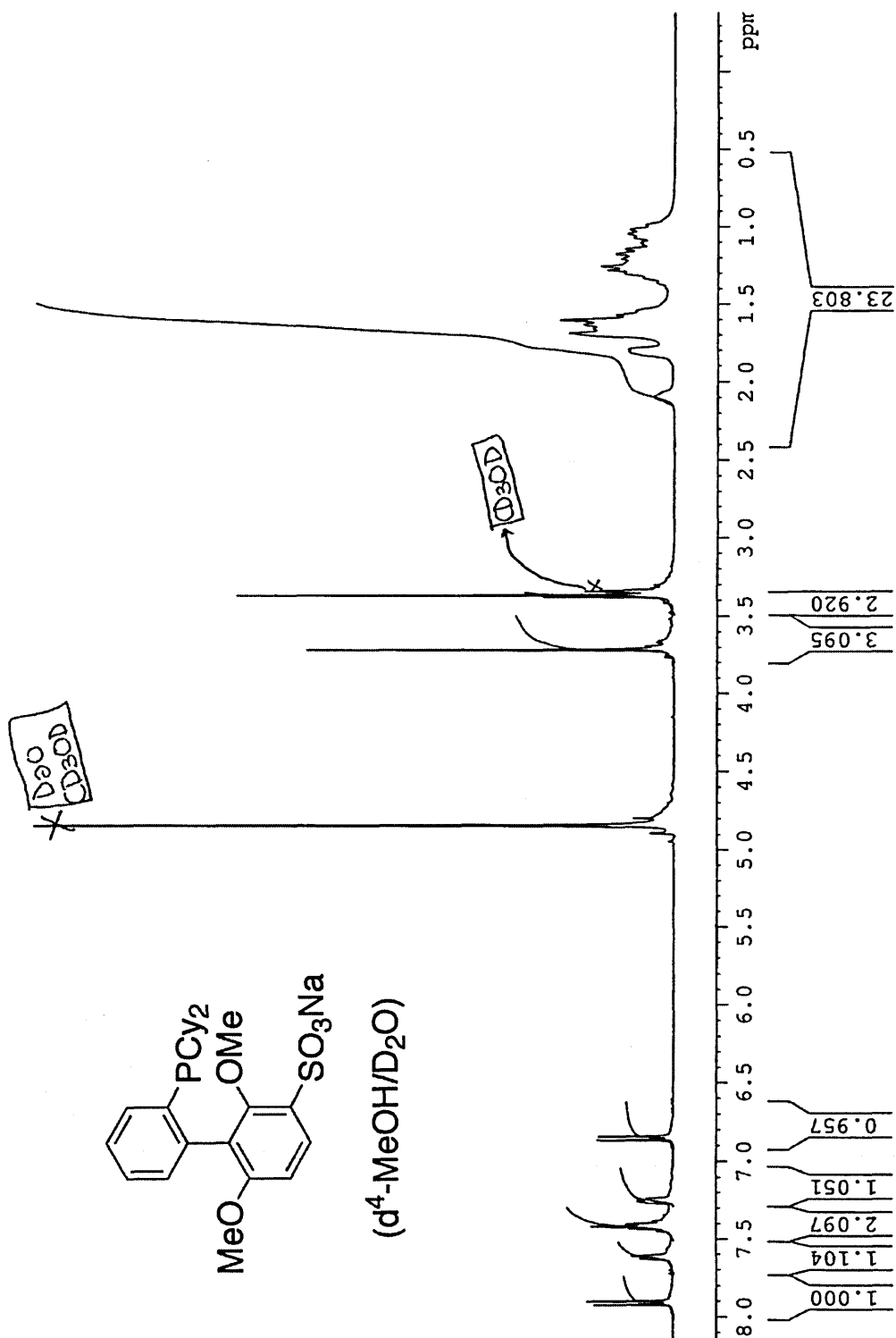
¹H NMR (d⁴-MeOH):
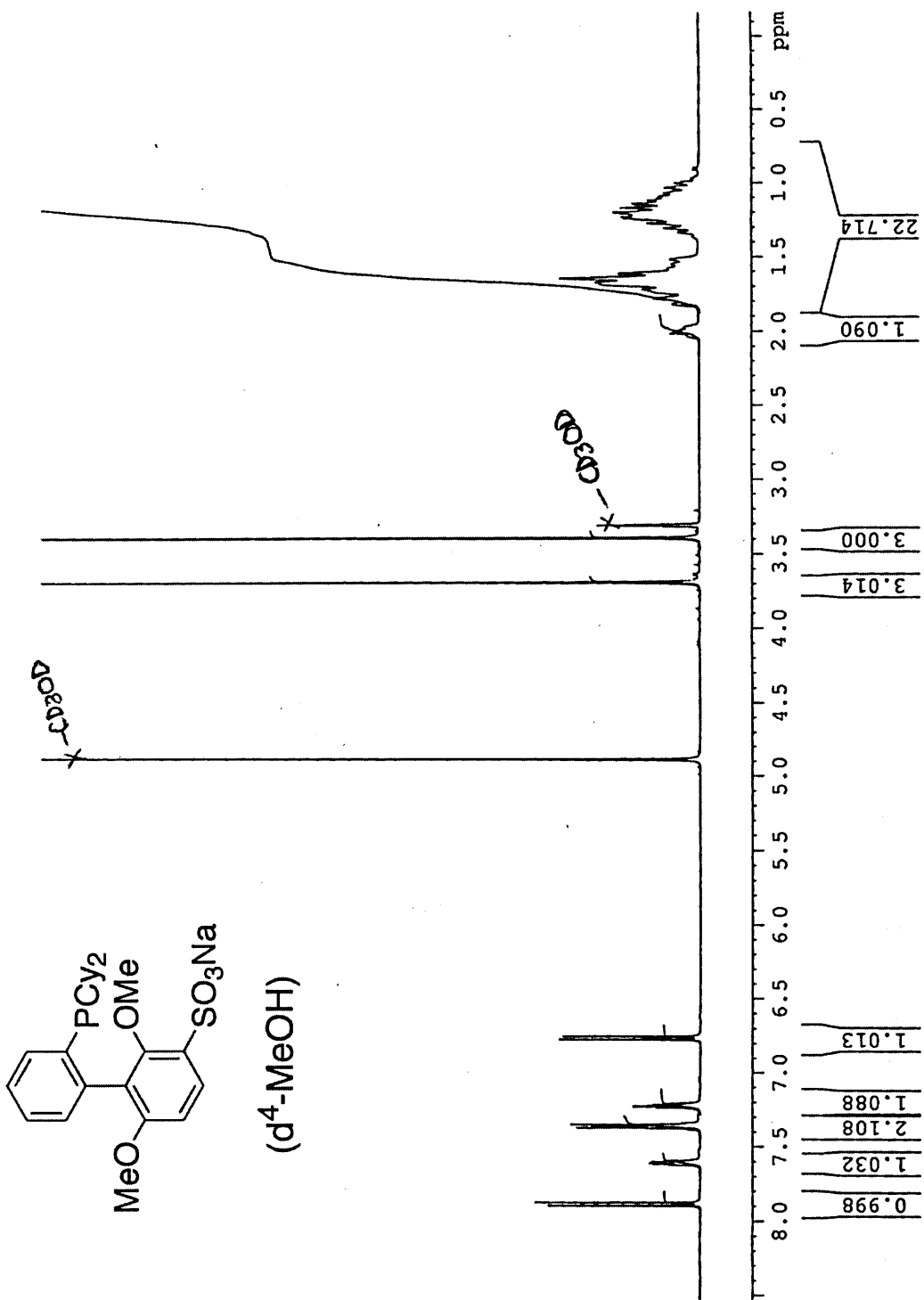
³¹P NMR (d⁴-MeOH):

Current Data Parameters
NAME   4ka-5-205p31
EXPNO   1
PROCNO   1

F2 - Acquisition Parameters
Date_   20041211
Time   11.54
INSTRUM   spect
PROBHD   5mm BBO BB-1
PULPROG   zgpg30
TD   65536
SOLVENT   Aceton
NS   4
DS   4
SWH   64935.066 Hz
FIDRES   0.990830 Hz
AQ   0.5046772 sec
RG   4597.6
DW   7.700 usec
DE   6.00 usec
TE   300.0 K
D1   2.00000000 sec
d11   0.03000000 sec
d12   0.00002000 sec

======== CHANNEL f1 ========
NUC1   31P
P1   8.20 usec
PL1   0.00 dB
SFO1   161.9672941 MHz

======== CHANNEL f2 ========
CPDPRG2   waltz16
NUC2   1H
PCPD2   107.50 usec
PL2   0.00 dB
PL12   24.00 dB
PL13   24.00 dB
SFO2   400.1316005 MHz

F2 - Processing parameters
SI   32768
SF   161.9753930 MHz
WDW   EM
SSB   0
LB   1.00 Hz
GB   0
PC   1.40

1D NMR plot parameters
CX   20.00 cm
F1P   150.447 ppm
F1   24360.66 Hz
F2P   -250.448 ppm
F2   -40566.40 Hz
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HZCM   3246.75342 Hz/cm

8.0286
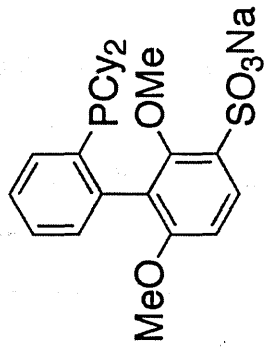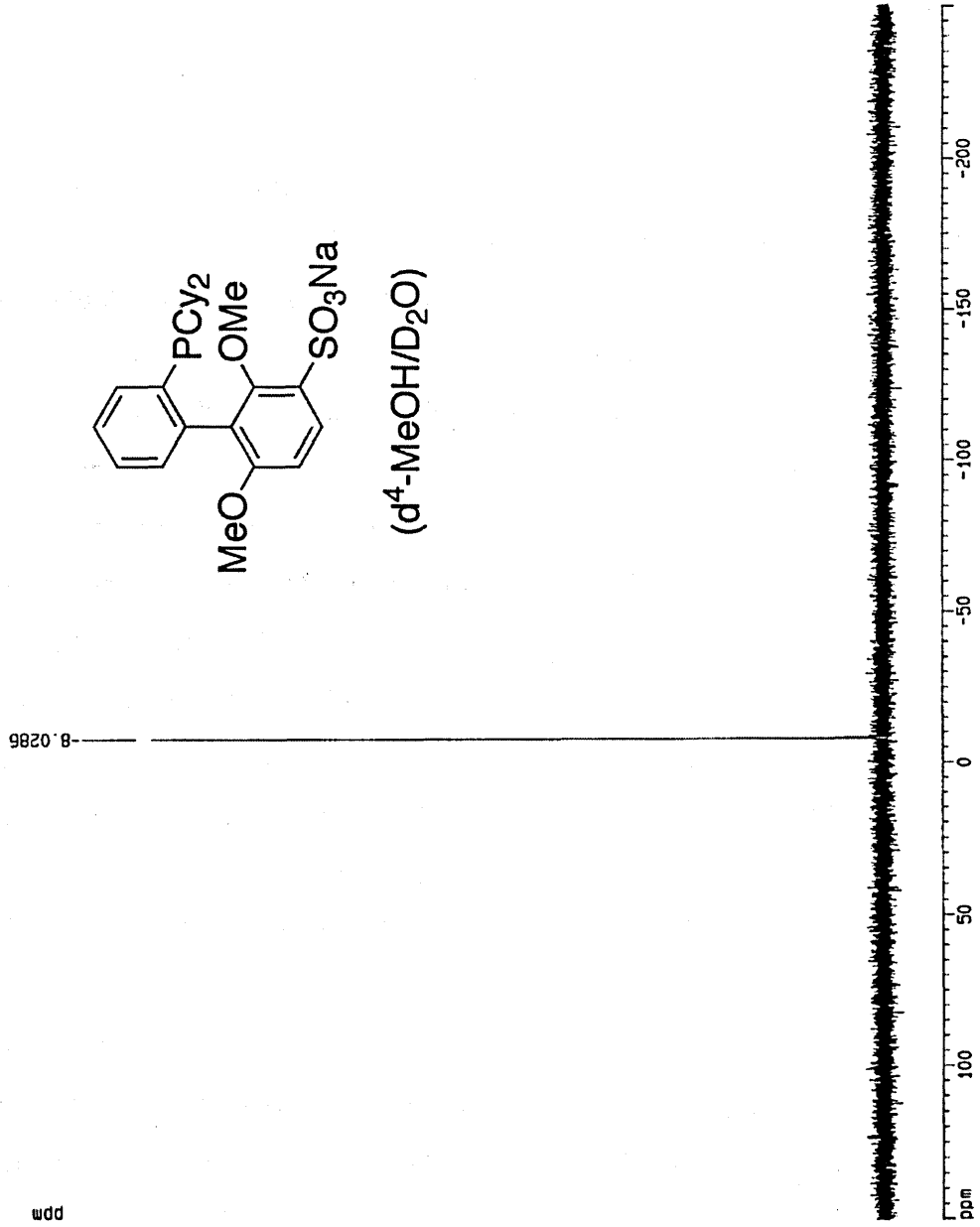
General Procedure for Suzuki-Miyaura coupling in Water. A disposable tube with a screw cap, Teflon septum and stir bar was charged with $Pd(OAc)_2$ (2.2 mg, 0.010 mmol, 1 mol %), sodium 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl-3'-sulfonate **2** (10.0 mg, 0.0200 mmol, 2 mol %), aryl halide (1.00 mmol), boronic acid (1.20-1.50 mmol) and K_2CO_3 (276-690 mg, 2.00-5.00 mmol). The tube was evacuated and back-filled with argon (this was repeated two additional times). Degassed water (1.5-3.0 mL, sonicated under vacuum for 2 min) was added and the reaction mixture was allowed to stir at the noted temperature or submitted to microwave irradiation using a CEM Discover® LabMate microwave (300W, 150 °C, with cooling to optimize the power). After cooling to room temperature, the hydrophilic products were isolated by acidifying the reaction mixture with HCl (2.0 M) to pH~5 and extraction with ethyl acetate or diethyl ether. The organic layer was dried over anhydrous $MgSO_4$, filtered through celite and concentrated to give the crude product. The products were purified by crystallization from water to give pure compounds (as judged by ^1H NMR and elemental analysis). Hydrophobic products were extracted from the water layer with diethyl ether, dried over $MgSO_4$, filtered through celite and concentrated to dryness and purified by column chromatography on silica gel (eluting with hexanes).

Table 1: Suzuki-Miyaura coupling of aryl chlorides using ligand 2.

3,4-Dimethyl-biphenyl (Table 1, Entry 1)[20] The general procedure was used with 3,4-dimethyl-chlorobenzene (0.140 mL, 1.00 mmol), phenylboronic acid (157 mg, 1.20 mmol), $Pd(OAc)_2$ (4.5 mg, 0.020 mmol, 2 mol %), sodium 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl-3'-sulfonate **2** (20.0 mg, 0.040 mmol, 4 mol %), K_2CO_3 (276 mg, 2.00 mmol), water (1.0 mL), 10 h, room temperature. The product was isolated as a colorless oil (151 mg, 99%). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.82 (d, 2H, J = 7.6 Hz), 6.81-7.55 (m, 6H), 2.24 (s, 6H).

2',6'-Dimethyl-biphenyl-3-carboxylic acid amide (Table 1, Entry 2). The general procedure was used with 3-chlorobenzamide (0.132 mL, 1.00 mmol), 2,6-dimethylphenylboronic acid (180 mg, 1.20 mmol), $Pd(OAc)_2$ (2.2 mg, 0.010 mmol, 1 mol %), sodium 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl-3'-sulfonate **2** (10.0 mg,

0.020 mmol, 2 mol %), K_2CO_3 (414 mg, 3.00 mmol), water (2.0 mL),12 h, 100 °C. The product was isolated as a white solid (225 mg, 99%).

Using microwave irradiation: The general procedure was used with 3-chlorobenzamide (156 mg, 1.00 mmol), 2,6-dimethylphenylboronic acid (180 mg, 1.20 mmol), $Pd(OAc)_2$ (4.5 mg, 0.020 mmol, 2 mol %), sodium 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl-3'-sulfonate **2** (20.0 mg, 0.0391 mmol, 4 mol %), K_2CO_3 (345 mg, 2.50 mmol), water (3.0 mL), 10 min, 150 °C (microwave irradiation with cooling). The product was isolated as a white solid (207 mg, 92%). Mp = 123-125 °C. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.85 (d, 1H, J = 7.6 Hz), 7.67 (s, 1H), 7.50 (t, 1H, J = 7.6 Hz), 7.33 (d, 1H, J = 7.6 Hz), 7.20 (t, 1H, J = 7.4 Hz), 7.13 (d, 2H, J = 7.2 Hz), 6.87 (br-s, 1H), 6.69 (br-s, 1H), 2.03 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.1, 141.6, 140.8, 135.9, 133.8, 132.8, 128.9, 128.1, 127.5, 126.0, 20.96. IR (neat, cm^{-1}): 3347 (br), 3197 (br), 1657, 1602, 1578, 1379, 1102, 770, 737, 703. Anal. Calcd for $C_{15}H_{15}NO$: C, 79.97; H, 6.71. Found: C, 79.98; H, 6.48.

Biphenyl-3-carboxylic acid (Table 1, Entry 3)[21]

2 mol % Pd: The general procedure was used with 3-chlorobenzoic acid (157 mg, 1.00 mmol), phenylboronic acid (145 mg, 1.20 mmol), $Pd(OAc)_2$ (4.5 mg, 0.020 mmol, 2 mol %), sodium 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl-3'-sulfonate **2** (20.0 mg, 0.040 mmol, 4 mol %), K_2CO_3 (345 mg, 2.50 mmol), water (1.5 mL), 2 h, room temperature. The product was isolated as a white solid (190 mg, 96%).

0.5 mol % Pd: The general procedure was used with 3-chlorobenzoic acid (157 mg, 1.00 mmol), phenylboronic acid (145 mg, 1.20 mmol), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol, 0.5 mol %), sodium 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl-3'-sulfonate **2** (5.0 mg, 0.010 mmol, 1 mol %), K_2CO_3 (345 mg, 2.50 mmol),water (1.5 mL), 8 h, room temperature. The product was isolated as a white solid (192 mg, 97%).

0.1 mol % Pd: The general procedure was used with 3-chlorobenzoic acid (157 mg, 1.00 mmol), phenylboronic acid (145 mg, 1.20 mmol), K_2CO_3 (345 mg, 2.50 mmol), water (1.5 mL), Pd/L solution (0.200 mL of a $Pd(OAc)_2$ (1.1 mg, 0.005 mmol, 0.5 mol %), sodium 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl-3'-sulfonate **2** (5.0 mg, 0.010

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mmol, 1 mol) in 1.0 mL water), 5 h, 100 °C. The product was isolated as a white solid (192 mg, 97%).

0.1 mol % Pd using microwave irradiation: The general procedure was used with 3-chlorobenzoic acid (157 mg, 1.00 mmol), phenylboronic acid (145 mg, 1.20 mmol), K_2CO_3 (345 mg, 2.50 mmol), water (1.5 mL), Pd/L solution (0.200 mL of a $Pd(OAc)_2$ (1.1 mg, 0.005 mmol, 0.5 mol %), sodium 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl-3'-sulfonate **2** (5.0 mg, 0.010 mmol, 1 mol %) solution in 1.0 mL water), 10 min, 150 °C (microwave irradiation with cooling). The product was isolated as a white solid (192 mg, 97%). Mp = 164 °C (lit.[22] = 165-166 °C) ^{1}H NMR (400 MHz, CDCl$_3$) δ: 11.90 (br-s, 1H), 8.41 (s, 1H), 8.15 (d, 1H, J = 7.6 Hz), 7.88 (d, 1H, J = 7.6 Hz), 7.68 (d, 2H, J = 7.2 Hz), 7.60 (t, 1H, J = 6.4 Hz), 7.52 (t, 2H, J = 7.6 Hz), 7.43 (t, 1H, J = 7.2 Hz). ^{13}C NMR (125 MHz, CDCl$_3$) δ: 172.6, 141.8, 140.1, 132.7, 130.0, 129.3, 129.2, 129.1, 129.0, 128.0, 127.4.

2'-Methyl-biphenyl-3-carboxylic acid (Table 1, Entry 4).

0.5 mol % Pd: The general procedure was used with 3-chlorobenzoic acid (157 mg, 1.00 mmol), *o*-tolylboronic acid (163 mg, 1.20 mmol), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol, 0.5 mol %), sodium 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl-3'-sulfonate **2** (5.0 mg, 0.010 mmol, 1 mol %), K_2CO_3 (345 mg, 2.50 mmol), water (1.5 mL), 8 h, room temperature. The product was isolated as a white solid (201 mg, 95%).

0.1 mol % Pd: The general procedure was used with 3-chlorobenzoic acid (157 mg, 1.00 mmol), *o*-tolylboronic acid (163 mg, 1.20 mmol), K_2CO_3 (345 mg, 2.50 mmol), water (1.5 mL), Pd/L solution (0.200 mL of a $Pd(OAc)_2$ (1.1 mg, 0.005 mmol, 0.5 mol %), sodium 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl-3'-sulfonate (5.0 mg, 0.010 mmol, 1 mol %) solution in 1.0 mL water), 6 h,100 °C. The product was isolated as a white solid (203 mg, 96%). Mp = 127 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ: 12.9 (br-s, 1H), 8.01 (m, 2H), 7.46 (d, 1H, J = 7.6 Hz), 7.40 (t, 1H, J = 7.6 Hz), 7.20-7.14 (m, 4H), 2.17 (s, 3H). ^{13}C NMR (125 MHz, CDCl$_3$) δ: 172.8, 142.5, 140.8, 135.5, 134.8, 131.1, 130.7, 129.9, 129.4, 128.8, 128.5, 127.9, 125.2, 20.6. IR (neat, cm^{-1}): 2962, 1689, 1309, 1258, 747. Anal. Calcd for $C_{14}H_{12}O_2$: C, 79.22; H, 5.70. Found: C, 79.12; H, 5.62.

4-Hydroxy-2'-methyl-biphenyl-3-carboxylic acid (Table 1, Entry 5)[23]

2 mol % Pd: The general procedure was used with 5-chloro-2-hydroxy-benzoic acid (173 mg, 1.00 mmol), 2-methylphenylboronic acid (163 mg, 1.20 mmol), Pd(OAc)$_2$ (4.5 mg, 0.020 mmol, 2 mol %), sodium 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl-3'-sulfonate (20.0 mg, 0.040 mmol, 4 mol %), K$_2$CO$_3$ (483 mg, 3.50 mmol), water (2.0 mL), 12 h, room temperature. The product was isolated as a white solid (227 mg, 99%).

0.1 mol % Pd: The general procedure was used with 5-chloro-2-hydroxy-benzoic acid (173 mg, 1.00 mmol), 2-methylphenylboronic acid (163 mg, 1.20 mmol), K$_2$CO$_3$ (345 mg, 2.50 mmol), water (2.0 mL), Pd/L solution (0.200 mL of a Pd(OAc)$_2$ (1.1 mg, 0.005 mmol, 0.5 mol %), sodium 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl-3'-sulfonate 2 (5.0 mg, 0.010 mmol, 1 mol %) solution in 1.0 mL water),12 h,100 °C. The product was isolated as a white solid (217 mg, 96%). Mp = 151 °C (lit.[23] 150-152 °C). ^{1}H NMR (400 MHz, CDCl$_3$) δ: 11.91 (br-s, 1H), 10.28 (br-s, 1H), 7.83 (d, 1H, J = 2.0 Hz), 7.42 (dd, 1H, J = 2.4 Hz, J = 8.6 Hz), 7.20-7.13 (m, 4H), 6.98 (d, 1H, J = 8.4 Hz), 2.20 (s, 3H). ^{13}C NMR (125 MHz, CDCl$_3$) δ: 175.4, 161.3, 140.4, 138.2, 135.6, 133.7, 131.4, 130.7, 129.9, 127.4, 126.2, 117.9, 111.2, 20.7 IR (neat, cm^{-1}): 3062, 1664, 1614, 1583, 1478, 1440, 1229, 1190, 728.

2,4,6,2'-Tetramethyl-biphenyl (Table 1, Entry 6)[23].The general procedure was used with 2-bromo-mesitylene (0.153 mL, 1.00 mmol), 2-methylphenylboronic acid (203 mg, 1.50 mmol), Pd(OAc)$_2$ (4.5 mg, 0.020 mmol, 2 mol %), sodium 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl-3'-sulfonate 2 (20.0 mg, 0.040 mmol, 4 mol %), K$_2$CO$_3$ (276 mg, 2.00 mmol), water (1.5 mL), 22 h, room temperature. The product was isolated as a colorless oil (197 mg, 94%). ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.30-7.19 (m, 3H), 7.05-7.00 (m, 1H), 6.92 (s, 2H), 2.30 (2, 3H), 1.99 (s, 3H), 1.89 (s, 6H). ^{13}C NMR (125 MHz, CDCl$_3$) δ: 140.9, 138.2, 136.4, 136.0, 135.9, 130.0, 129.2, 128.1, 127.1, 126.2, 21.4, 20.6, 19.9.

2,6,2'-Trimethyl-biphenyl (Table 1, Entry 7)[23]. The general procedure was used with 2-bromotoluene (0.120 mL, 1.00 mmol), 2,6-dimethylphenylboronic acid (225 mg, 1.50 mmol), Pd(OAc)$_2$ (4.5 mg, 0.020 mmol, 2 mol %), sodium 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl-3'-sulfonate 2 (20.0 mg, 0.040 mmol, 4 mol %), K$_2$CO$_3$ (276 mg, 2.00

mmol), water (1.5 mL), 22 h, room temperature. The product was isolated as a colorless oil (190 mg, 97%). ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.30-7.10 (m, 6H), 7.02-7.00 (m, 1H), 1.99 (s, 3H), 1.96 (s, 6H). ^{13}C NMR (125 MHz, CDCl$_3$) δ: 141.1, 140.7, 136.1, 135.9, 130.0, 129.1, 127.4, 127.1, 127.1, 126.1, 20.7, 19.7.

Table 2. Suzuki-Miyaura coupling of chlorobenzoic acids using ligand 2.

Biphenyl-3,4'-dicarboxylic acid (Table 2, Entry 1)[24] The general procedure was used with 4-chlorobenzoic acid (157 mg, 1.00 mmol), 3-carboxyphenylboronic acid (199 mg, 1.20 mmol), Pd(OAc)$_2$ (2.2 mg, 0.010 mmol, 1 mol %), sodium 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl-3'-sulfonate **2** (10.0 mg, 0.020 mmol, 2 mol %), K$_2$CO$_3$ (414 mg, 3.00 mmol), water (3.0 mL), 8 h, 50 °C. The product was isolated as a white solid (241 mg, 99%).

Using microwave irradiation: The general procedure was used with 4-chlorobenzoic acid (157 mg, 1.00 mmol), 3-carboxyphenylboronic acid (199 mg, 1.20 mmol), Pd(OAc)$_2$ (2.2 mg, 0.010 mmol, 1 mol %), sodium 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl-3'-sulfonate **2** (10.0 mg, 0.020 mmol, 2 mol %), K$_2$CO$_3$ (414 mg, 3.00 mmol), water (3.0 mL), 10 min at 150 °C (using microwave irradiation with cooling). The product was isolated as a white solid (229 mg, 95%). Mp = >250 °C (lit.[24] mp = 295 °C). ^{1}H NMR (400 MHz, d^6-DMSO/D$_2$O) δ: 8.22 (s, 1H), 8.42 (d, 2H, J = 7.6 Hz), 7.98 (d, 1H, J = 7.6 Hz), 7.91 (d, 1H, J = 7.6 Hz), 7.79 (d, 2H, J = 7.6 Hz), 7.59 (t, 1H, J = 7.2 Hz). ^{13}C NMR (125 MHz, d^6-DMSO/D$_2$O) δ: 167.5, 143.6, 139.7, 131.9, 131.7, 130.4, 130.3, 129.8, 129.4, 127.8, 127.2.

2'-Hydroxy-biphenyl-4-carboxylic acid (Table 2, Entry 2)[25] The general procedure was used with 4-chlorobenzoic acid (157 mg, 1.00 mmol), 2-hydroxyphenylboronic acid (166 mg, 1.20 mmol), Pd(OAc)$_2$ (2.2 mg, 0.010 mmol, 1 mol %), sodium 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl-3'-sulfonate **2** (10.0 mg, 0.020 mmol, 2 mol %), K$_2$CO$_3$ (414 mg, 3.00 mmol), water (2.0 mL), 12 h, 100 °C. The product was isolated as a white solid (203 mg, 95%). Mp = 186 °C. ^{1}H NMR (400 MHz, d^4-MeOH) δ: 8.04 (d, 2H, J = 8.4 Hz), 7.65 (d, 2H, J = 8.4 Hz), 7.25 (dd, 1H, J = 7.6 Hz, 1.6 Hz), 7.16 (td, 1H, J = 7.6 Hz, 1.6 Hz), 6.89 (m, 2H). ^{13}C NMR (125 MHz, d^4-MeOH) δ: 170.2,

155.6, 145.4, 131.7, 130.5 (2), 130.48, 130.4, 129.8, 128.7, 121.2, 117.2. IR (neat, cm^{-1}): 3391, 2529, 1683, 1274, 1008, 753.

2'-Amino-biphenyl-3-carboxylic acid (Table 2, Entry 3)[26] The general procedure was used with 3-chlorobenzoic acid (157 mg, 1.00 mmol), 2-aminophenylboronic acid (205 mg, 1.50 mmol), Pd(OAc)$_2$ (2.2 mg, 0.010 mmol, 1 mol %), sodium 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl-3'-sulfonate **2** (10.0 mg, 0.020 mmol, 2 mol %), K$_2$CO$_3$ (414 mg, 3.00 mmol), water (2.0 mL), 12 h, 100 °C. The product was isolated as a white solid (203 mg, 95%). Mp = 170 °C (lit.[26] = 173-175 °C) ^{1}H NMR (400 MHz, d^4-MeOH) δ: 8.07 (m, 1H), 7.99 (d, 1H, J = 7.6 Hz), 7.65 (d, 1H, J = 8.0 Hz), 7.53 (t, 1H, J = 7.6 Hz), 7.13 (td, 1H, J = 1.6 Hz, J = 7.6 Hz), 6.84 (d, 1H, J = 8.0 Hz), 6.77 (t, 1H, J = 7.6 Hz). ^{13}C NMR (125 MHz, d^4-MeOH) δ: 169.9, 145.1, 141.7, 134.8, 132.6, 131.4, 131.4, 130.1, 129.9, 129.5, 128.3, 120.0, 117.6.

2'-Acetyl-biphenyl-3-carboxylic acid (Table 2, Entry 3). The general procedure was used with 3-chlorobenzoic acid (157 mg, 1.00 mmol), 2-acetylphenylboronic acid (179 mg, 1.20 mmol), Pd(OAc)$_2$ (2.2 mg, 0.010 mmol, 1 mol %), sodium 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl-3'-sulfonate **2** (10.0 mg, 0.020 mmol, 2 mol %), K$_2$CO$_3$ (414 mg, 3.00 mmol), water (2.0 mL), 10 h, 100 °C. The product was isolated as a light yellow solid (233 mg, 97%). Mp = 143 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ: 12.60 (br-s, 1H), 8.05 (m, 1H), 7.65 (d, 1H, J = 7.2 Hz), 7.58-7.55 (m, 3H), 7.49 (d, 1H, J = 7.2 Hz), 7.42 (d, 1H, J = 7.6 Hz), 2.16 (s, 3H). ^{13}C NMR (125 MHz, CDCl$_3$) δ: 204.3, 172.2, 141.7, 140.7, 139.9, 134.7, 131.5, 131.0, 130.7, 130.3, 129.9, 129.2, 128.7, 128.4, 30.8. IR (neat, cm^{-1}): 3419, 2517, 1686, 1018. Anal. Calcd for C$_{15}$H$_{12}$O$_3$: C, 74.99; H, 5.03. Found: C, 75.04; H, 5.06.

2'-Formyl-biphenyl-3-carboxylic acid monohydrate (Table 2, Entry 3)[27] The general procedure was used with 3-chlorobenzoic acid (157 mg, 1.00 mmol), 2-formylphenylboronic acid (225 mg, 1.50 mmol), Pd(OAc)$_2$ (2.2 mg, 0.010 mmol, 1 mol %), sodium 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl-3'-sulfonate **2** (10.0 mg, 0.020 mmol, 2 mol %), K$_2$CO$_3$ (414 mg, 3.00 mmol), water (2.0 mL), 10 h, 80 °C. The product was isolated as a white solid (192 mg, 85%). Mp = 164-167 °C. ^{1}H NMR (400 MHz, d^4-MeOH, d^6-DMSO) δ: 8.07 (m, 2H), 7.68 (m, 1H), 7.63-7.52 (m, 2H), 7.46 (m,

2H), 7.30 (m, 1H), 5.10 (s, 1H), 4.98 (br-s, 2H). ^{13}C NMR (125 MHz, d^4-MeOH, d^6-DMSO) δ: 169.4, 142.1. 142.0, 137.0, 135.0, 131.9, 131.7, 131.2, 129.9, 129.8, 129.6, 128.9, 127.8, 103.6 [Ar-CH(OH)$_2$] IR (neat, cm^{-1}): 3066, 1694, 1260, 754.

4'-Cyano-4-hydroxy-biphenyl-3-carboxylic acid (Table 2, Entry 4). The general procedure was used with 5-chloro-2-hydroxy-benzoic acid (173 mg, 1.00 mmol), 4-cyanophenylboronic acid (176 mg, 1.20 mmol), Pd(OAc)$_2$ (2.2 mg, 0.010 mmol, 1 mol %), sodium 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl-3'-sulfonate **2** (10.0 mg, 0.020 mmol, 2 mol %), K$_2$CO$_3$ (552 mg, 4.00 mmol), water (2.0 mL), 12 h, 80 °C. The product was isolated as a white solid (220 mg, 92%). Mp = 227 °C. ^{1}H NMR (400 MHz, d^4-MeOH) δ: 8.11 (d, 1H, J = 2.4 Hz), 7.81-7.70 (m, 5H), 7.02 (d, 1H, J = 8.4 Hz). ^{13}C NMR (125 MHz, d^4-MeOH) δ: 173.2, 163.5, 145.5, 135.4, 134.0, 131.2, 130.1, 128.3, 120.1, 119.4, 114.6, 111.5. IR (neat, cm^{-1}): 3429, 2229, 1667, 750. Anal. Calcd for C$_{14}$H$_9$NO$_3$: C, 70.29; H, 3.79. Found: C, 69.96; H, 3.52.

2,3'-Diamino-biphenyl-4-carboxylic acid (Table 2, Entry 5). The general procedure was used with 3-Amino-4-chloro-benzoic acid (172 mg, 1.00 mmol), 3-aminophenylboronic acid (190 mg, 1.40 mmol), Pd(OAc)$_2$ (2.2 mg, 0.010 mmol, 1 mol %), sodium 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl-3'-sulfonate **2** (10.0 mg, 0.020 mmol, 2 mol %), K$_2$CO$_3$ (552 mg, 4.00 mmol), water (3.0 mL), 12 h, 100 °C. The product was isolated as a light brown oil (254 mg, 99%). ^{1}H NMR (400 MHz, CDCl$_3$/d^4-MeOH) δ: 7.35 (m, 2H), 7.10 (t, 1H, J = 7.6 Hz), 7.02 (d, 1H, J = 8.0 Hz), 6.70-6.60 (m, 3H). ^{13}C NMR (125 MHz, CDCl$_3$/d^4-MeOH) δ: 169.4, 146.6, 143.4, 139.4, 132.4, 129.9, 129.7, 129.0, 119.8, 118.9, 115.8, 115.5, 114.8. IR (neat, cm^{-1}): 3419, 1645, 1016. EI-MS for C$_{13}$H$_{12}$N$_2$O$_2$: Theoretical [M + H] = 229.0977. Found: 229.0982. Anal. Calcd for C$_{13}$H$_{12}$N$_2$O$_2$: C, 68.41; H, 5.30. Found: C, 68.29; H, 5.29.

Toluene-4-sulfonic acid monohydrate (Table 2, Entry 6)[28] The general procedure was used with 4-chlorobenzenesulfonic acid (192 mg, 1.00 mmol), methylboronic acid (90 mg, 1.50 mmol), Pd(OAc)$_2$ (2.2 mg, 0.010 mmol, 1 mol %), sodium 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl-3'-sulfonate **2** (10.0 mg, 0.020 mmol, 2 mol %), K$_2$CO$_3$ (414 mg, 3.00 mmol), water (2.0 mL), 12 h, 100 °C. The product was isolated as a white solid (207 mg, 99%). Mp = 104 °C (lit.[28] = 106 °C). ^{1}H NMR (400

MHz, d^4-MeOH) δ: 7.71 (d, 2H, J = 8.4 Hz), 7.24 (d, 2H, J = 8.4 Hz), 5.08 (s, H$_2$O), 2.37 (s, 3H).). ^{13}C NMR (125 MHz, d^4-MeOH) δ: 143.3, 142.0, 130.0, 127.1, 21.4.

2',4'-Difluoro-biphenyl-4-sulfonic acid amide (Table 2, Entry 7). The general procedure was used with 4-chloro-benzenesulfonamide (192 mg, 1.00 mmol), 2,4-difluorophenylboronic acid (205 mg, 1.30 mmol), Pd(OAc)$_2$ (2.2 mg, 0.010 mmol, 1 mol %), sodium 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl-3'-sulfonate **2** (10.0 mg, 0.020 mmol, 2 mol %), K$_2$CO$_3$ (414 mg, 3.00 mmol), water (2.0 mL), 12 h, 80 °C. The product was isolated as a white solid (258mg, 96%). Mp = 143 °C. ^{1}H NMR (400 MHz, d^4-MeOH) δ: 7.98 (d, 2H, J = 8.4 Hz), 7.87 (d, 1H, J = 8.4 Hz), 7.63 (d, 2H, J = 7.2 Hz), 7.49 (d, 2H, J = 8.4 Hz), 7.05-6.99 (m, 2H). ^{13}C NMR (125 MHz, d^4-MeOH) δ: 165.5 (d), 163.0 (d), 162.3 (d), 159.8 (d), 144.0, 143.6, 140.0, 139.3, 133.1 (d), 133.0 (d), 130.5 (d), 130.2, 128.9, 127.4, 125.1 (d), 124.9 (d), 113.2 (d), 113.0 (d), 105.4 (t). IR (neat, cm^{-1}): 3362, 3257, 1619, 1599, 1516, 1487, 1302, 1103, 965, 849, 809. Anal. Calcd for C$_{12}$H$_9$F$_2$NO$_2$S: C, 53.53; H, 3.37. Found: C, 53.34; H, 3.36.

Table 3. Suzuki-Miyaura coupling of heterocyclic halides using ligand 2.

3,5-Dimethyl-4-phenoxathiin-4-yl-phenol (Table 3, Entry 1). The general procedure was used with 4-chloro-3,5-dimethyl-phenol (156 mg, 1.00 mmol), 4-phenoxathiineboronic acid (293 mg, 1.20 mmol), Pd(OAc)$_2$ (2.2 mg, 0.010 mmol, 1 mol %), sodium 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl-3'-sulfonate **2** (10.0 mg, 0.020 mmol, 2 mol %), K$_2$CO$_3$ (414 mg, 3.00 mmol), water (3.0 mL), 12 h, 100 °C. The product was isolated as a colorless oil (277 mg, 85%), which became a white solid upon standing. Mp = 116 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.20 (m, 2H), 7.01-7.16 (m, 3H), 6.96 (d, 1H, J = 7.6 Hz), 6.73 (m, 3H), 5.64 (s, 1H), 2.04 (s, 6H). ^{13}C NMR (125 MHz, CDCl$_3$) δ: 154.6, 152.6, 149.9, 138.3, 130.2, 129.9, 129.5, 127.8, 126.8, 126.1, 124.7, 124.6, 121.2, 121.1, 118.2, 114.2, 20.9. IR (neat, cm^{-1}): 3367, 1593, 1471, 1419, 1311, 1265, 1223, 1154, 1026, 752. Anal. Calcd for C$_{20}$H$_{16}$O$_2$S: C, 74.97; H, 5.03. Found: C, 74.88; H, 4.99.

5-(4-Methoxy-phenyl)-1H-indole-2-carboxylic acid (Table 3, Entry 2). The general procedure was used with 5-chloro-1H-indole-2-carboxylic acid (194 mg, 1.00 mmol), 4-methoxyphenylboronic acid (207 mg, 1.50 mmol), Pd(OAc)$_2$ (2.2 mg, 0.010 mmol, 1 mol

%), sodium 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl-3'-sulfonate **2** (10.0 mg, 0.020 mmol, 2 mol %), K_2CO_3 (414 mg, 3.00 mmol), water (2.0 mL), 12 h, 80 °C. The product was isolated as a light yellow solid (246 mg, 93%). Mp = >230 °C. ^{1}H NMR (400 MHz, d^6-DMSO) δ: 11.81 (s, 1H), 7.84 (s, 1H), 7.58 (d, 2H, J = 8.8 Hz), 7.49 (m, 2H), 7.13 (d, 1H, J = 1.6 Hz), 6.99 (d, 2H, J = 8.4 Hz), 3.78 (s, 3H). ^{13}C NMR (125 MHz, d^6-DMSO) δ: 162.7, 158.3, 136.3, 133.7, 132.2, 129.0, 127.7, 127.5, 123.7, 119.1, 114.3, 112.8, 107.7, 55.1. IR (neat, cm^{-1}): 4320, 1700, 1183. Anal. Calcd for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90. Found: C, 71.94; H, 4.93.

2-(3'-Acetyl-biphenyl-4-yloxy)-nicotinic acid (Table 3, Entry 3). The general procedure was used with 2-(4-chloro-phenoxy)-nicotinic acid (250 mg, 1.00 mmol), 3-acetylphenylboronic acid (246 mg, 1.50 mmol), Pd(OAc)$_2$ (2.2 mg, 0.010 mmol, 1 mol %), sodium 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl-3'-sulfonate **2** (10.0 mg, 0.020 mmol, 2 mol %), K_2CO_3 (414 mg, 3.00 mmol), water (2.0 mL), 12 h, 80 °C. The product was isolated as a white solid (305 mg, 92%). Mp = 188 °C. ^{1}H NMR (400 MHz, d^6-DMSO) δ: 8.27 (m, 2H), 8.20 (s, 1H), 7.93 (d, 2H, J = 7.6 Hz), 7.77 (d, 2H, J = 8.8 Hz), 7.61 (t, 1H, J = 7.6 Hz), 7.23 (m, 3H), 2.66 (s, 3H). ^{13}C NMR (125 MHz, d^6-DMSO) δ: 198.0, 166.0, 160.7, 153.9, 150.3, 141.5, 140.0, 137.5, 135.6, 131.3, 129.4, 128.2, 126.9, 126.4, 121.9, 119.1, 117.2, 26.9. IR (neat, cm^{-1}): 3000-4000 (br), 1674, 1651, 1585, 1418, 1231, 896, 770. Anal. Calcd for $C_{20}H_{15}NO_4$: C, 72.06; H, 4.54. Found: C, 71.68; H, 4.41.

[2,3']Bipyridinyl-6-ylamine (Table 3, Entry 4). The general procedure was used with 6-chloro-pyridin-2-ylamine (129 mg, 1.00 mmol), 3-pyridylboronic acid (184 mg, 1.50 mmol), Pd(OAc)$_2$ (2.2 mg, 0.010 mmol, 1 mol %), sodium 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl-3'-sulfonate **2** (10.0 mg, 0.020 mmol, 2 mol %), K_2CO_3 (414 mg, 3.00 mmol), water (2.0 mL), 12 h, 100 °C. The product was purified by column chromatography on silica gel (eluting with ethyl acetate/methanol, 9.5/0.5) to give the desired product as a white solid (145 mg, 85%). Mp = 108 °C. ^{1}H NMR (400 MHz, d^4-MeOH) δ: 8.69 (d, 1H, J = 4.8 Hz), 8.43 (dd, 1H, J = 4.8 Hz, 1.6 Hz), 8.19 (d, 1H, J = 4.8 Hz), 7.96 (dq, 1H, J = 8.0 Hz, 1.6 Hz, 0.4 Hz), 7.75 (dd, 1H, J = 8.8 Hz, 2.4 Hz), 7.44 (qd, 1H, J = 4.8 Hz, 8.8 Hz), 6.68 (d, 1H, J = 8.4 Hz). ^{13}C NMR (125 MHz, d^4-MeOH) δ:
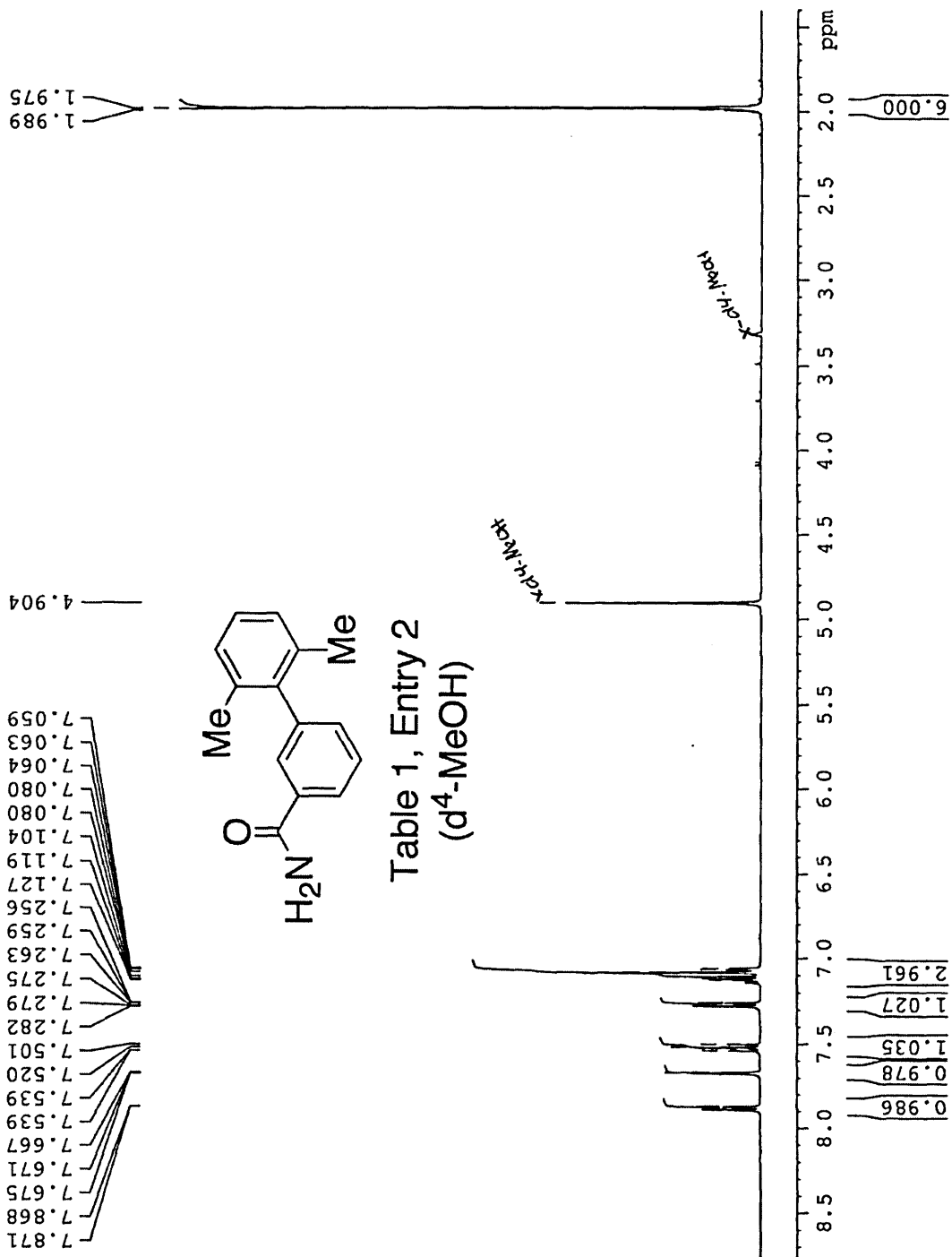
161.0, 148.2, 147.4, 146.5, 137.9, 136.0, 135.4, 125.6, 123.4, 110.6. IR (neat, cm^{-1}):
3396 (br), 2522, 1633, 1018. EI-MS: Theoretical [M + H] = 172.0869. Found: 172.0868.
Anal. Calcd for $C_{10}H_9N_3$: C, 70.16; H, 5.30. Found: C, 69.89; H, 5.25.

5-Furan-3-yl-thiophene-2-carboxylic acid (Table 3, Entry 5). The general procedure
was used with 5-bromothiophene carboxylic acid (206 mg, 1.00 mmol), 3-furanboronic
acid (168 mg, 1.50 mmol), Pd(OAc)$_2$ (2.2 mg, 0.010 mmol, 1 mol %), sodium 2-
dicyclohexylphosphino-2',6'-dimethoxybiphenyl-3'-sulfonate **2** (10.0 mg, 0.020 mmol, 2
mol %), K$_2$CO$_3$ (414 mg, 3.00 mmol), water (5.0 mL), 12 h, 100 °C. The product was
isolated as a white solid (181 mg, 94%).

Using microwave irradiation: The general procedure was used with 5-bromothiophene
carboxylic acid (206 mg, 1.00 mmol), 3-furanboronic acid (168 mg, 1.50 mmol),
Pd(OAc)$_2$ (2.2 mg, 0.010 mmol, 1 mol %), sodium 2-dicyclohexylphosphino-2',6'-
dimethoxybiphenyl-3'-sulfonate **2** (10.0 mg, 0.020 mmol, 2 mol %), K$_2$CO$_3$ (414 mg, 3.00
mmol), water (5.0 mL), 10 min, 150 °C (using microwave irradiation with cooling). The
product was isolated as a white solid (183 mg, 95%). Mp = 147 °C. ^{1}H NMR (400 MHz,
d^4-MeOH) δ: 7.89 (m, 1H), 7.65 (d, 1H, J = 4.0 Hz), 7.54 (t, 1H, J = 1.6 Hz), 7.15 (d, 1H,
J = 4.0 Hz), 6.69 (m, 1H). ^{13}C NMR (125 MHz, d^4-MeOH) δ: 165.4, 145.6, 143.7, 140.9,
135.5, 132.9, 125.2, 121.5, 109.9. IR (neat, cm^{-1}): 3200 (br), 1672, 1287. Anal. Calcd for
C$_9$H$_6$O$_3$S: C, 55.66; H, 3.11. Found: C, 55.50; H, 3.32.

Table 4. Screening of conditions of Suzuki-Miyaura coupling.

Biphenyl-3-carboxylic acid[21] The general procedure was used with 3-chlorobenzoic
acid (157 mg, 1.00 mmol), phenylboronic acid (145 mg, 1.20 mmol), Pd(OAc)$_2$ (4.5 mg,
0.020 mmol, 2 mol %), sodium 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl-3'-
sulfonate (20.0 mg, 0.040 mmol, 4 mol %), K$_2$CO$_3$ (345 mg, 2.50 mmol), solvent (see
Table 4) (2.0 mL), 14 h, temperature. The conversion and yield were determined using
^{1}H NMR.

1.975
1.989

4.904

7.059
7.063
7.064
7.080
7.080
7.104
7.119
7.127
7.256
7.259
7.263
7.275
7.279
7.282
7.501
7.520
7.539
7.539
7.667
7.671
7.675
7.868
7.871

Me

Me

O

H₂N

Table 1, Entry 2
(d⁴-MeOH)

x₄ʰₓ·MₑOₕ

x₄ʰₓ·MₑOₕ

6.000

2.961
1.027
1.035
0.978
0.986

ppm
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5

7.284
7.413
7.431
7.449
7.467
7.516
7.534
7.576
7.595
7.614
7.670
7.688
7.876
7.895
8.143
8.162
8.411

CDCl3

ppm

1.043
2.085
1.013
2.040
1.000
1.147

0.978

0.735

Table 1, Entry 3
(CDCl$_3$)

HO$_2$C

Me

HO₂C

Table 1, Entry 4
(CDCl₃)

0.177

2.350

7.303
7.316
7.322
7.334
7.343
7.354
7.358
7.364
7.571
7.591
7.611
7.643
7.646
7.658
7.662
8.176
8.179
8.192
8.196

2938.27
2942.67
2944.33
2946.70
3029.29
3037.26
3045.19
3058.02
3059.32
3064.21
3065.60
3271.34
3272.50
3277.89

3.000

4.135
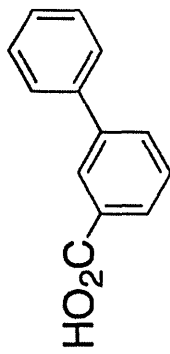2.100
2.022

1.010

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4.135
2.100
2.022

208

Table 1, Entry 5
(CDCl₃)

209

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DS   2
SWH   8278.146 Hz
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RG   128
DW   60.400 usec
DE   6.00 usec
TE   300.0 K
D1   1.00000000 sec

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SFO1   400.1324710 MHz

F2 - Processing parameters
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WDW   EM
SSB   0
LB   0.30 Hz
GB   0
PC   1.00

1D NMR plot parameters
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F1   5384.66 Hz
F2P   7.150 ppm
F2   2861.05 Hz
PPMCM   0.31535 ppm/cm
HZCM   126.18059 Hz/cm

Table 2, Entry 1
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1.1776
2.0011
2.1734
1.9906
1.0000

2.1208

3.305
3.310
3.348
6.865
6.868
6.884
6.886
6.900
6.902
6.920
6.922
7.143
7.147
7.161
7.163
7.165
7.167
7.181
7.186
7.245
7.249
7.264
7.268
7.648
7.652
7.665
7.670
8.031
8.035
8.048
8.052
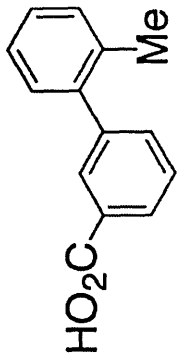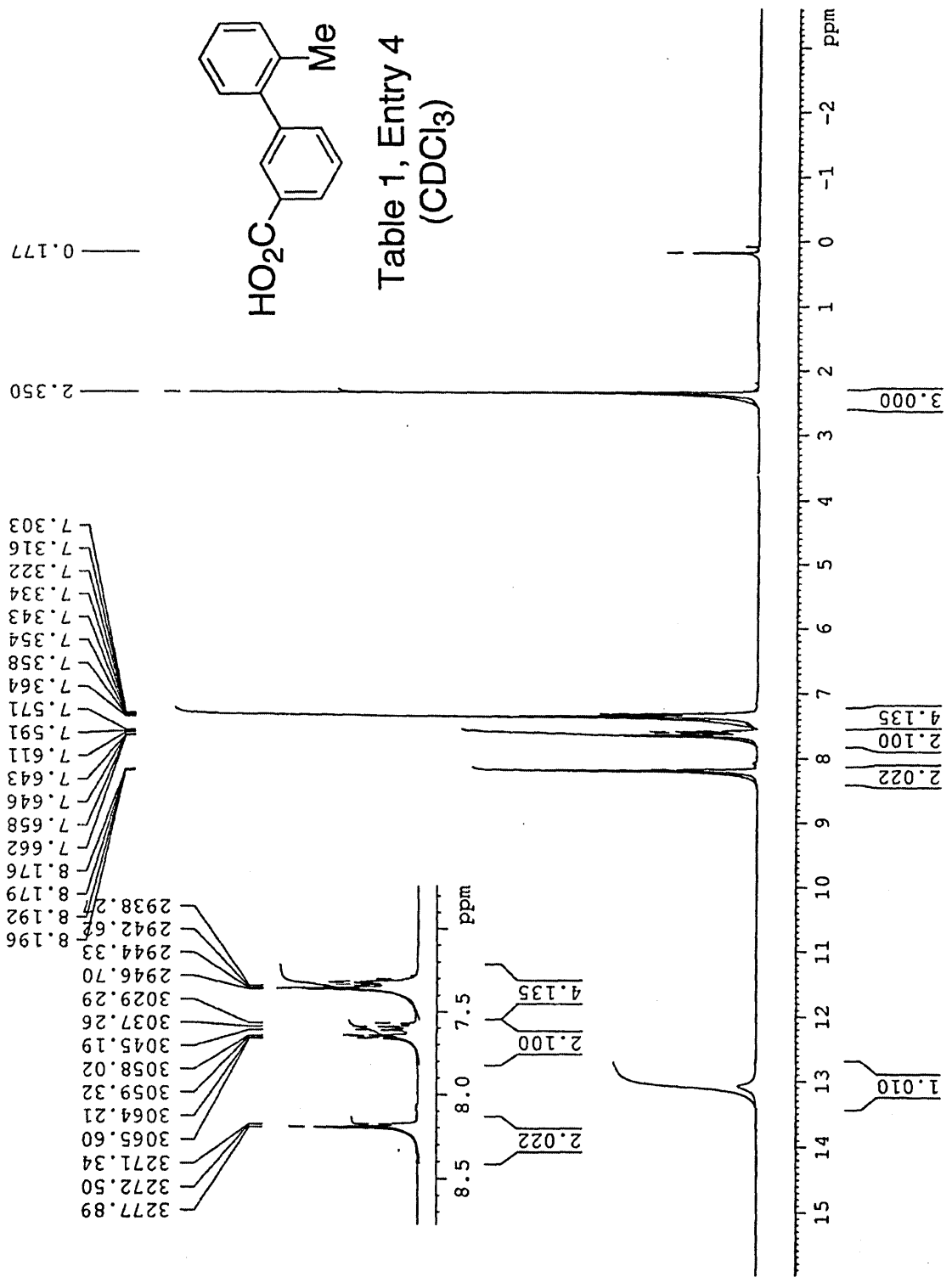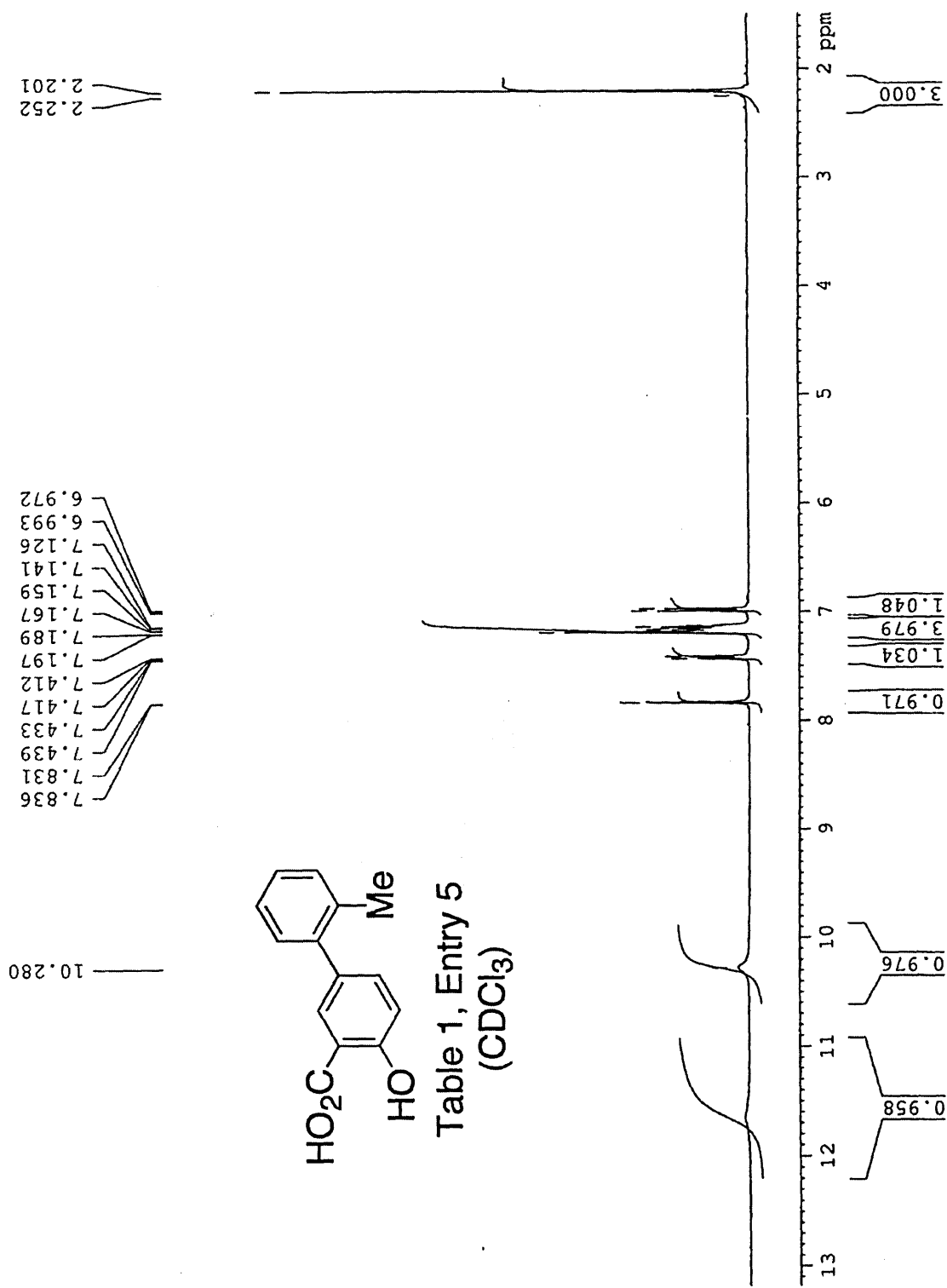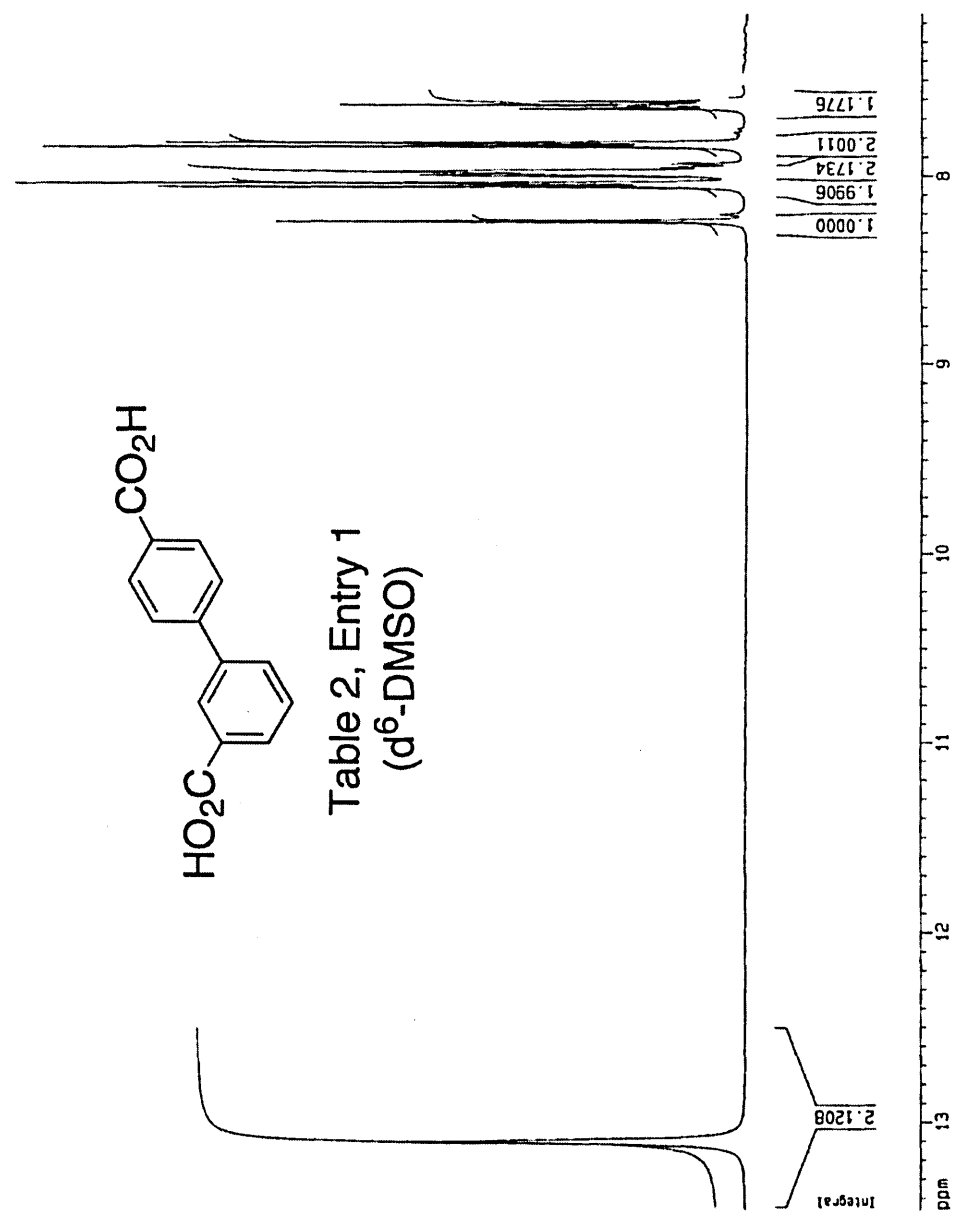
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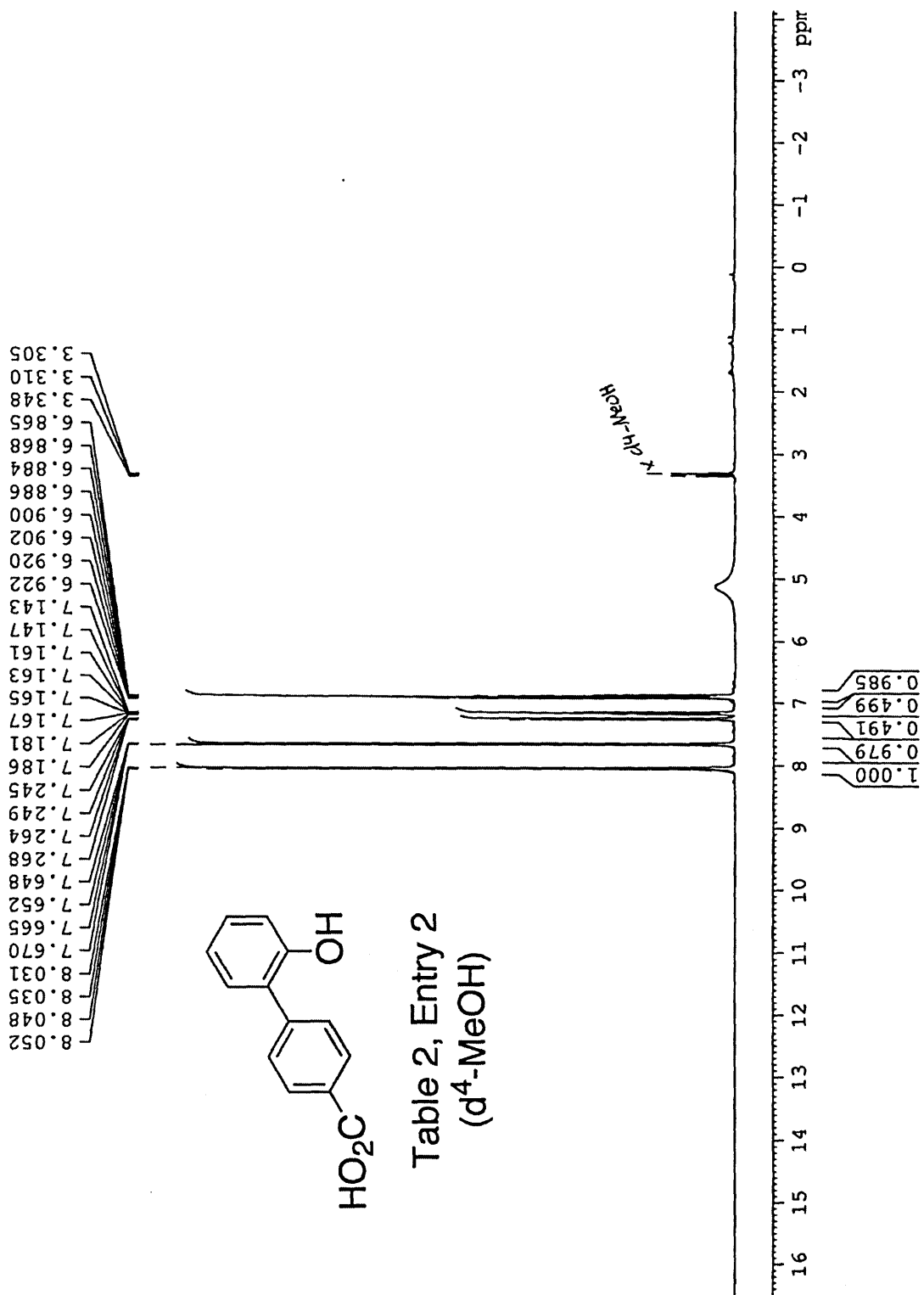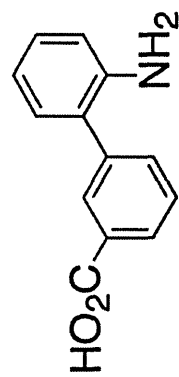
Table 2, Entry 3a
(d⁴-MeOH)

x d4-MeOH

x d4-MeOH

2.146

3.303
3.307
3.311
3.315
3.319

Me

O

HO2C

Table 2, Entry 3b
(d⁴-MeOH)

7.393
7.395
7.412
7.414
7.454
7.457
7.473
7.476
7.492
7.495
7.520
7.523
7.528
7.533
7.535
7.549
7.553
7.568
7.571
7.587

d⁴-MeOH

d⁴-MeOH

3.000

1.065
1.079
1.936
1.188
1.044
1.067
1.068

ppm 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0 6.5 7.0 7.5 8.0

Table 2, Entry 4
(d^4-MeOH/d^6-DMSO)

Table 2, Entry 5
(CDCl$_3$/d^6-DMSO)

Me

HO$_3$S
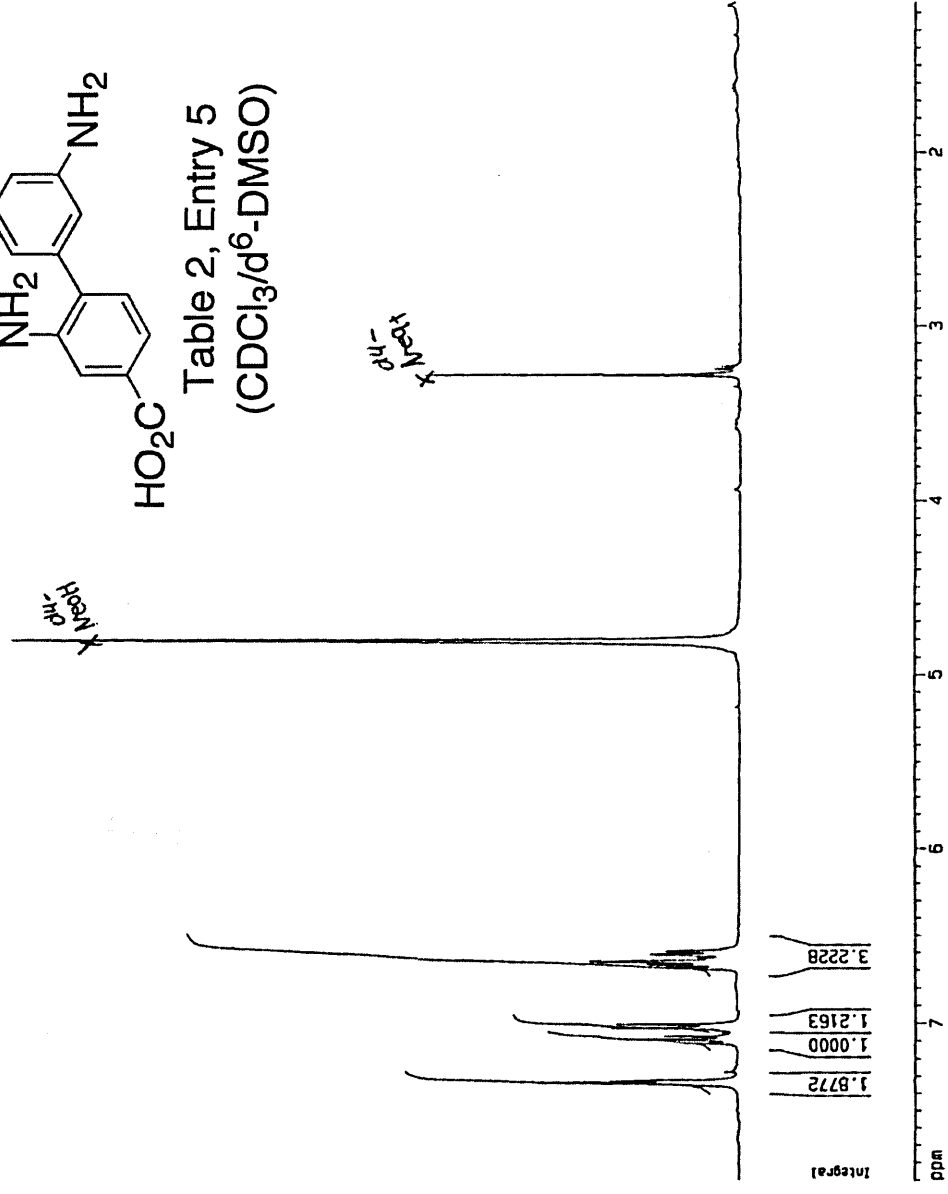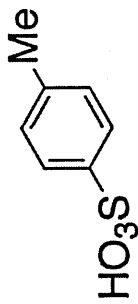
Table 2, Entry 6
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PROCNO   1

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DS   2
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SFO1   400.1324710 MHz

F2 - Processing parameters
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WDW   EM
SSB   0
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GB   0
PC   1.00

1D NMR plot parameters
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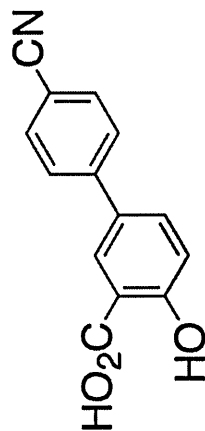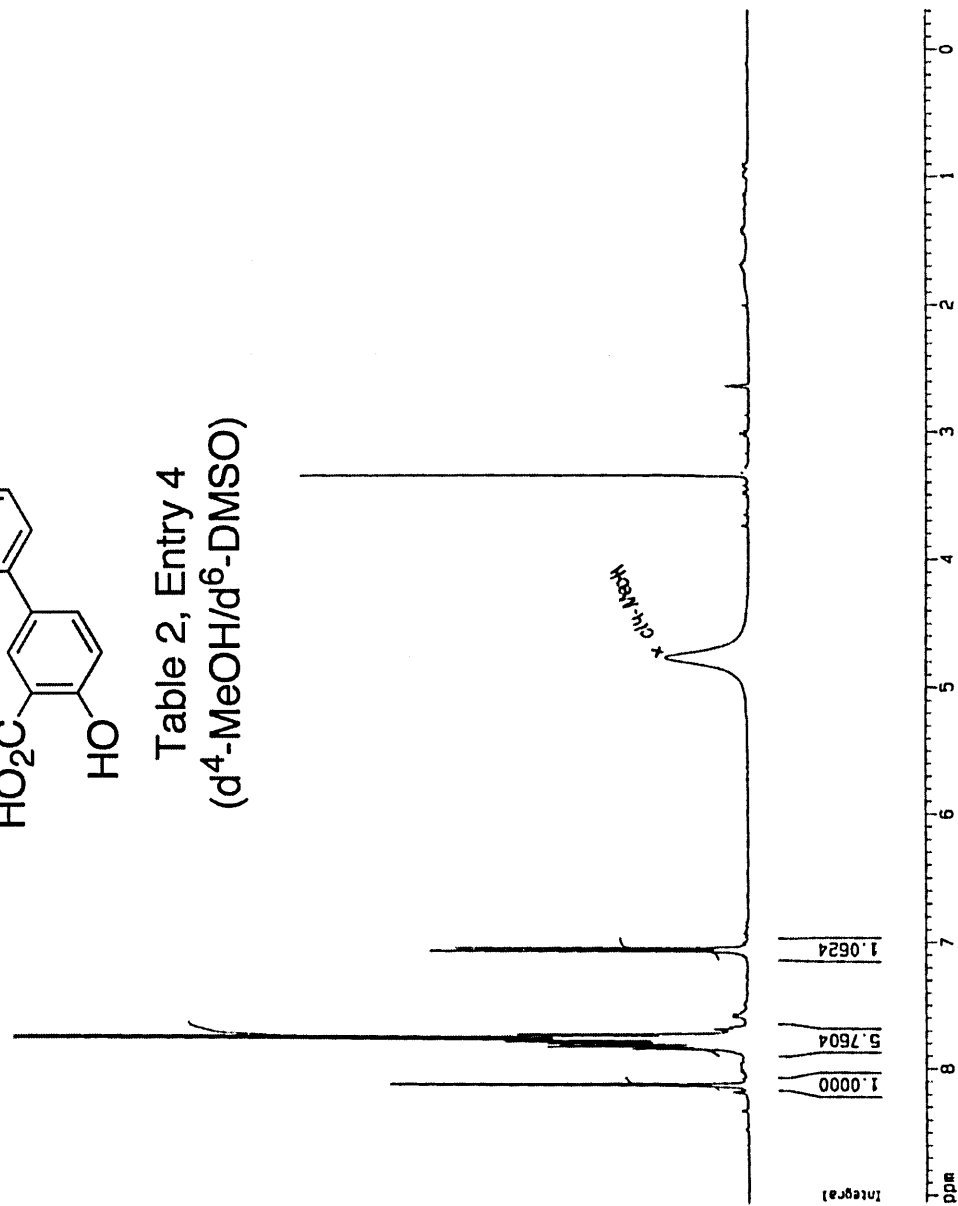F2P   -0.247 ppm
F2   -98.96 Hz
PPMCM   0.51666 ppm/cm
HZCM   206.73041 Hz/cm

2.9987

1.9560

1.9187

[Integral]

ppm
0   2   4   6   8

216

3.312

4.849

F

F

H₂NO₂S

Table 2, Entry 7
(d⁴-MeOH)

6.997
7.003
7.018
7.025
7.035
7.046
7.054
7.468
7.485
7.506
7.528
7.629
7.647
7.864
7.885
7.971
7.992

HOH, d4-MeOH
x, d4-MeOH

ppm

9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5

1.989
2.202
2.016
1.192
2.000

Table 3, Entry 1
(CDCl$_3$)

2.046

5.640

6.650
6.732
6.761
6.960
6.962
6.979
7.014
7.032
7.050
7.069
7.088
7.099
7.118
7.136
7.165

6.000

1.134

3.000
1.013
3.122
1.993

ppm

2.496
2.500
2.505

3.762
3.778

6.952
6.975
6.985
6.990
7.003
7.007
7.015
7.136
7.140
7.476
7.498
7.503
7.507
7.516
7.525
7.529
7.566
7.573
7.578
7.590
7.595
7.602
7.842

x d6-DMSO

Table 3, Entry 2
(d6-DMSO)

OMe

HO_2C

N
H

3.000
2.060
0.930
2.347
1.922
0.985
1.095

ppm
3 4 5 6 7 8 9 10 11 12 13

2.502
2.505
2.664

7.219
7.226
7.240
7.258
7.595
7.614
7.633
7.758
7.780
7.925
7.929
7.944
7.948
8.203
8.243
8.248
8.262
8.268
8.273
8.281
8.285

DMSO-d6

3.000

2.782
1.058
1.824
1.844
0.932
1.908

Me

CO₂H

O

O

N

Table 3, Entry 3
(d⁶-DMSO)

Table 3, Entry 4
(d⁶-DMSO)

1.9675   0.9874   1.0000   1.0073   1.0061   0.9646   0.9734   0.9898

Integral

ppm   9.0   8.5   8.0   7.5   7.0   6.5   6.0

6.694
6.697

7.146
7.156

7.533
7.537
7.542

7.654
7.664

7.891

HO_2C

Table 3, Entry 5
(d^4-MeOH)

ppm
6.4
6.6
7.0
7.2
7.4
7.6
7.8
8.0
8.2
8.4

1.010
1.017
1.001
1.123
1.000

References

(1) de Meijere, A.; Diederich, F. Eds. *Metal-Catalyzed Cross-Coupling Reactions*, Vol. 2: Wiley-VCH, Weinheim, 2004.

(2) a) Miyaura, N. *Topics in Current Chem.* 2002, *219*, 11. b) Suzuki, A. *Organomet. Chem.* **1999**, *576*, 147.

(3) (a) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685. (b) Barder, T. E.; Buchwald, S. L. *Org. Lett.* **2004**, *6*, 2649. (c) Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem.* **2004**, *116*, 1907; *Angew. Chem. Int. Ed.* **2004**, *43*, 1871.

(4) (a) Li, C.-J.; Chan, T. –H. In *Organic Reactions in Aqueous Media*; Wiley: New York, 1997. b) *Organic Synthesis in Water*; Grieco, P. A. Ed.; Academic: Dordrecht, The Netherlands, 1997. (c) *Aqueous-Phase Organometallic Catalysis*; Cornils, B.; Herrmann, W. A. Eds., 2nd ed.; Wiley-VCH: Weinheim, 2004. (d) Shaughnessy, K. H.; DeVasher, R. B. *Curr. Org. Chem.* **2005**, *9*, 585. (e) Leadbeater, N. E. *Chem. Comm.* **2005**, 2881.

(5) With a $NiCl_2$/dppe/trisulfonated triphenylphosphine system: Galland, J.-C.: Savignac, M.; Genet, J. P. *Tetrahedron Lett.* **1999**, *40*, 2323.

(6) With oxime-derived palladacycles: a) Botella, L.; Najera, C. *Angew. Chem. Int. Ed.* **2002**, *41*, 179. b) Botella, L.; Najera, C. *J. Organomet. Chem.* **2002**, *663*, 46.

(7) With di-2-pyridylmethylamine-based palladium complexes: Najera, C.; Gil-Molto, J.; Karlstrom, S.; Falvello, L. R. *Org. Lett.* **2003**, *5*, 1451.

(8) With palladium *N*-heterocyclic carbene complexes: a) Ozdemir, I.; Gok, Y.; Gurbuz, N.; Cetinkaya, E.; Cetinkaya, B.; *Heterat. Chem.* **2004**, *15*, 419. b) Osdemir, I.; Demir, S.; Yaser, S.; Cetinkaya, B. *Appl. Organomet. Chem.* **2005**, *19*, 55.

(9) With TBAB-water mixtures: Bedford, R. B.; Blake, M. E.; Butts, C. P.; Holder, D. *Chem. Comm.* **2003**, 466.

(10) (a) Gulyas, H.; Szollosy, A.; Szabo, P.; Halmos, P.; Bakos, J. *Eur. J. Org. Chem.* **2003**, 2775. (b) Mul, W. P.; Ramkisoensing, K.; Kamer, P. C. J.; Reek, J. N. H.; van der Linder, A. J.; Marson, A.; van Leeuwen, P. W. M. N. *Adv. Syn. Catal.* **2002**, *344*, 293. (c)

Gulyas, H.; Szollosy, A.; Hanson, B. E.; Bakos, J. *Tetrahedron Lett.* **2002**, *43*, 2543. (d) Schwab, E.; Mecking, S. *Organometallics* **2001**, *20*, 5504.

(11) (a) Moore, L. R.; Shaughnessy, K. H. *Org. Lett.* **2004**, *6*, 225. (b) Western, E. C.; Daft, J. R.; Johnson II, E. M.; Gannett, P. M.; Shaughnessy, K. H. *J. Org. Chem.* **2003**, *68*, 6767. (c) Sollewijn Gelpke, A. E.; Veerman, J. J. N.; Goedheijt, M. S.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Hiemstra, H. *Tetrahedron* **1999**, *55*, 6657. (d) Bahrmann, H.; Bergrath, K.; Kleiner, H. –J.; Lappe, P.; Naumann, C.; Peters, D.; Regnat, D. *J. Organomet. Chem.* **1996**, *520*, 97. (e) Genet, J. P.; Linquist, A.; Blart, E.; Mouries, V.; Savignac, M. *Tetrahedron Lett.* **1995**, *36*, 1443.

(12) (a) DeVasher, R. B.; Moore, L. R.; Shaughnessy, K. H. *J. Org. Chem.* **2004**, *69*, 7919. (b) DeVasher, R. B.; Spruell, J. M.; Dixon, D. A.; Broker, G. A.; Griffin, S. T.; Rogers, R. D.; Shaughnessy, K. H. *Organometallics* **2005**, *24*, 962.

(13) Konovets, A.; Penciu, A.; Framery, E.; Percina, N.; Goux-Henry, C.; Sinou, D. *Tetrahedron Lett.* **2005**, *46*, 3205.

(14) Arvela, R. K.; Leadbeater, N. E. *Org. Let.* **2005**, *7*, 2101.

(15) For an excellent review on catalyst systems used in Suzuki-Miyaura couplings conducted in aqueous media and using microwave irradiation: See refs. (4d), (4e) and references within.

(16) Our attempts to effect the coupling of 2-bromomesitylene with 2,6-dimethylphenylboronic acid in water at 100 °C, to form a biaryl with four substituents *ortho* to the aryl-aryl connection, provided none of the desired product. This is in contrast to what is observed with a catalytic system using 1. See ref. (2c).

(17) The sulfonic acid is undoubtedly rapidly transformed to the sulfonate under the reaction conditions. For examples of Suzuki-Miyaura couplings of aryl halides with protected sulfonic acids: (a) Avitabile, B. G.; Smith, C. A.; Judd, D. B. *Org. Lett.* **2005**, *7*, 843. (b) Hari, A.; Miller, B. L. *Org. Lett.* **1999**, *1*, 2109. (c) Baxter, E. W.; Rueter, J. K.; Nortey, S. O.; Reitz, A. B. *Tetrahedron Lett.* **1998**, *39*, 979.

(18) See ref (4) and (10b).

(19) The authors report that monodentate phosphines are poor ligands for the Suzuki-Miyaura coupling of 2-amino pyridines and pyrimidines. This result suggests that use of

a highly active catalyst system such as Pd/**2** at least in some instances overcomes this limitation: Itoh, T.; Mase, T. *Tetrahedron Lett.* **2005**, *46*, 3573.

(20) Gavina, F.; Costero, A. M.; Gonzalez. A. M. *J. Org. Chem.* **1990**, 2060.

(21) Leadbeater, N. E.; Resouly, S. M. *Tetrahedron* **1999**, *55*, 11889.

(22) 1988 107/27, Patent; Merck US DE 1801300, 1968.

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

(24) (a) Lawson Daku, K. M.; Newton, R. F.; Pearce, S. P.; Vile, J.; Williams, J. M. J. *Tetrahedron Lett.* **2003**, *44*, 5095. b) Bapat, J. B.; Brown, R. F. C.; Bulmer, G. H.; Childs, T.; Coulston, K. J.; Eastwood, F. W.; Taylor, D. K. *Australian J. Chem.* **1997**, *50*, 1159.

(25) Yanagisawa, H.; Sakurai, M.; Takamura, M.; Fujiwara, T. PCT Int. Appl. **1999**, 720 pp.

(26) Nesloney, C. L.; Kelly, J. W. *J. Org. Chem.* **1996**, *61*, 3127.

(27) (a) Blettner, C. G.; Konig, W. A.; Ruhter, G.; Stenzel, W.; Schotten, T. *Synlett* **1999** 307. (b) Blettner, C. G.; Konig, W. A.; Stenzel, W.; Schotten, T. *Synlett* **1998** 295.

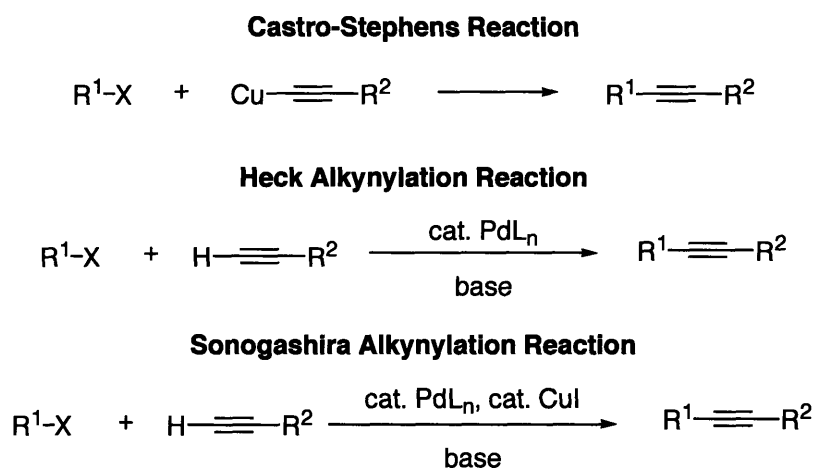(28) Jones, J. H.; Wood, M. E. *Syn. Comm.* **1986**, *16*, 1515.

Chapter 5

Synthesis and Utilization of a Water-Soluble Monophosphinobiaryl Ligand in the Palladium-Catalyzed Heck Alkynylation of Aryl/Benzyl/Heteroaryl Halides

Introduction

Among the approaches that are available for the introduction of an alkynyl moiety in organic molecules, by far the most convenient and simple method is the palladium-catalyzed cross-coupling reaction of terminal alkynes with organic electrophiles.[1] The most widely used of these is a cross between the Cu-promoted Castro-Stephens reaction[2] and the Heck alkynylation reaction,[3] which is now known as the Sonogashira reaction (Scheme 1).[1,4]

Scheme 1. Synthetic methods for the reaction of terminal alkynes.

Castro-Stephens Reaction

$$R^1\text{-}X \quad + \quad Cu\text{—}\equiv\text{—}R^2 \quad \longrightarrow \quad R^1\text{—}\equiv\text{—}R^2$$

Heck Alkynylation Reaction

$$R^1\text{-}X \quad + \quad H\text{—}\equiv\text{—}R^2 \quad \xrightarrow[\text{base}]{\text{cat. PdL}_n} \quad R^1\text{—}\equiv\text{—}R^2$$

Sonogashira Alkynylation Reaction

$$R^1\text{-}X \quad + \quad H\text{—}\equiv\text{—}R^2 \quad \xrightarrow[\text{base}]{\text{cat. PdL}_n,\ \text{cat. CuI}} \quad R^1\text{—}\equiv\text{—}R^2$$

The generally accepted mechanism for the Sonogashira reaction follows the prototypical catalytic cycle for palladium-catalyzed cross-couplings: oxidative addition of a $L_n Pd(0)$ complex with an organic electrophile, transmetallation to generate diorganopalladium derivatives, and their reductive elimination to produce the desired alkynes with concomitant regeneration of the $L_n Pd(0)$ complex (Scheme 2).[1,5,6]

An alternative catalytic cycle has been proposed consisting of the same oxidative addition as in Scheme 2, carbopalladation, and reductive β-dehydropalladation (Scheme 3).[7,8] Carbopalladation of alkynes is a widely observed process occurring with both terminal and internal alkynes and is expected to be a fundamentally favorable process with electron-rich metalated alkynes, provided that it can compete with transmetallation involving the alkyne-M σ-bond.[9] Furthermore, the β-metaloorganopalladium derivative formed is expected to undergo facile reductive β-elimination to produce the desired

alkyne with concomitant regeneration of the $L_nPd(0)$ species. However, this pathway is not as well accepted due to the fact that hindered terminal alkynes, in many cases, react efficiently which can only be explained by the first pathway.

Scheme 2. General catalytic cycle for Sonogashira reactions.
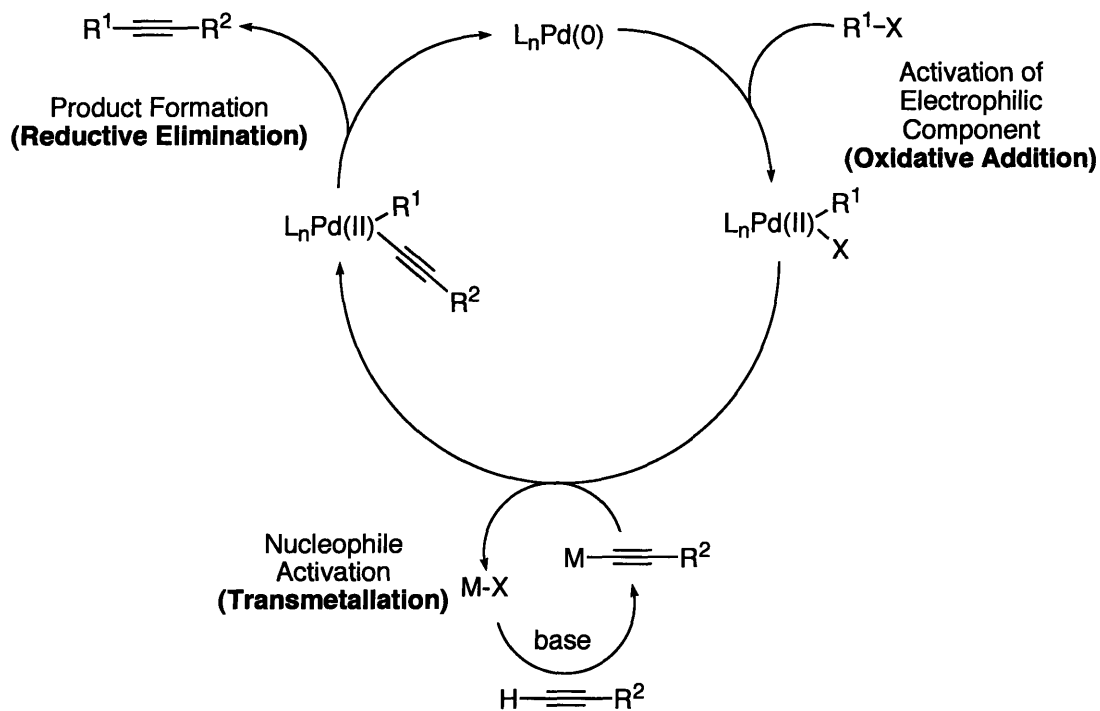
Scheme 3. Alternative mechanism for Sonogashira reactions.
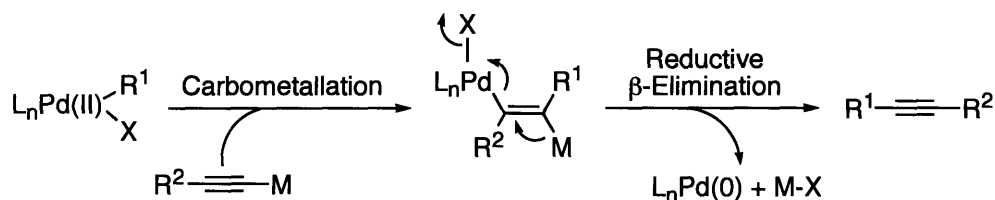
The most widely employed co-catalysts (M) are copper salts, which mediate homocoupling of terminal alkynes when the copper acetylide is exposed to oxidative agents or air.[10] The use of other co-catalysts such as zinc, tin, boron, aluminum, Ag_2O and AgOTf have been developed to address this issue, but additional steps are needed to prepare these reagents.[11,12]

Recently, a palladium system modified by a bulky, electron-rich phosphine ligand, such as Pt-Bu$_3$, has been reported to display unusually high activity in the Sonogashira reaction of aryl bromides.[13] Furthermore, catalysts derived from Na$_2$PdCl$_4$/CuI and bis(adamantyl)benzylphosphane allowed the coupling of electron-deficient aryl chlorides and terminal alkynes, representing, at the time the most general method for coupling these more difficult electrophiles.[14] Even unactivated alkyl electrophiles are suitable substrates for coupling to terminal alkynes using a Pd/N-heterocyclic carbene-based catalyst.[15]

We previously disclosed that a catalyst system based on PdCl$_2$(CH$_3$CN)$_2$/2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl 1 provided excellent reactivity in the Heck alkynylation (copper-free Sonogashira coupling) of aryl chlorides/tosylates and terminal alkynes.[16] While this method was superior to other catalyst systems for the coupling of unactivated and hindered aryl chlorides, it also possessed some limitations. This catalyst system was successful in reactions of aryl alkynes only when the alkyne was added slowly over the course of the reaction. This is presumably due to competing non-productive oligomerization of the alkyne at higher concentrations in the presence of the catalyst. Interestingly, copper salts were shown to inhibit the coupling process when using Pd/1, where the alkyne is again consumed deleteriously. We felt that by incorporating a water-solubilizing sulfonate group on 1 would provide an amphiphilic alkynylation catalyst that might address the limitations that were previously reported and allow for the coupling of hydrophilic substrate combinations.[17]

We found that treatment of 1 with fuming sulfuric acid (H$_2$SO$_4$/20% SO$_3$) at room temperature for 24 h provided 2, with selective mono-sulfonation at the 4'-position, in 93% yield after treatment with NaOH and workup (Scheme 4). We believe this sulfonation occurs by electrophilic $ipso$-substitution of SO$_3$ at the 4'-position of the aromatic ring followed by elimination.[18] Alternatively, this could proceed by proto-deisopropylation of the 4'-isopropyl group and then electrophilic sulfonation.
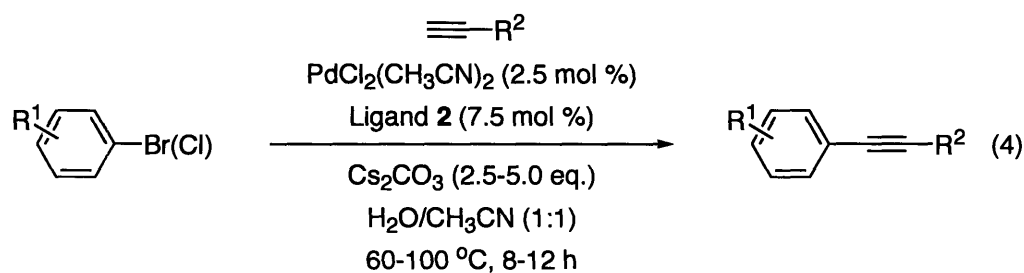
229

Scheme 4. Synthesis and proposed formation of a water-soluble version of ligand **1**.
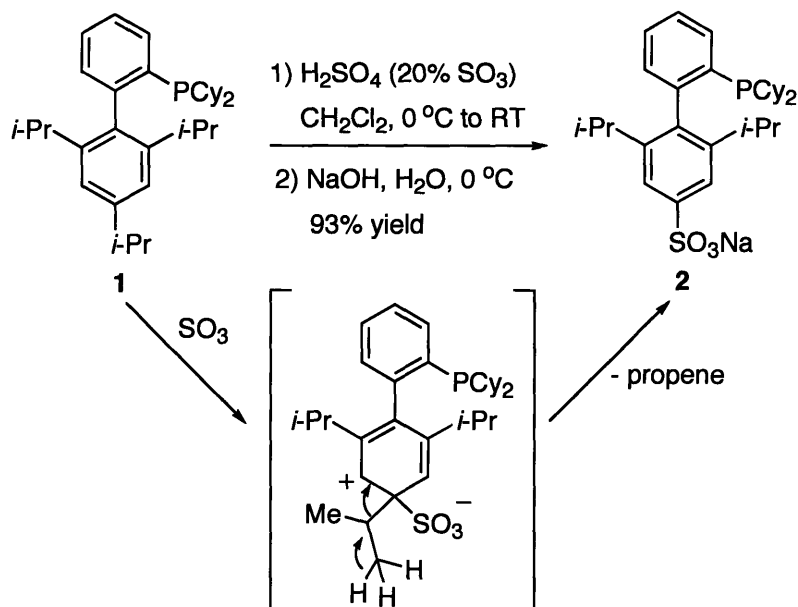
Results and Discussion

For the first time, using a catalyst system based on $PdCl_2(CH_3CN)_2$/**2** and a water/acetonitrile biphasic solvent system, propiolic acid was successfully coupled with 3-bromoanisole and 3-bromobenzoic acid providing 70% and 69% yields of aryl alkynoic acids, respectively (Table 1, entries 1-2). This result represents a significant advancement in aryl alkynylation reactions, since electron-deficient propiolate esters have been problematic coupling partners due to their increased reactivity towards nucleophilic attack and their propensity to polymerize in the presence of Pd catalysts.[19]

Good yields were obtained for the coupling of hydrophilic aryl chlorides bearing carboxylic acids (Table 1, entries 3, 5) and an alkyne containing an aliphatic carboxylic acid (Table 1, entry 4). Interestingly, use of **2** and a water/acetonitrile solvent system, the coupling of aryl chlorides and aryl alkynes proceeds obviating the need to employ slow addition of the aryl alkyne (Table 1, entries 6-8). This result may be attributed to the lower effective concentration of the alkyne in proximity to the catalyst, which resides at the water/organic interface.

Table 1. Palladium-catalyzed coupling of aryl halides and alkynes using ligand 2.[a]

$$\equiv\!\!-R^2$$

$$R^1\!-\!\text{Ar}\!-\!Br(Cl) \xrightarrow[\substack{Cs_2CO_3\ (2.5\text{-}5.0\ eq.)\\ H_2O/CH_3CN\ (1:1)\\ 60\text{-}100\ ^\circ C,\ 8\text{-}12\ h}]{\substack{PdCl_2(CH_3CN)_2\ (2.5\ mol\ \%)\\ Ligand\ 2\ (7.5\ mol\ \%)}} R^1\!-\!\text{Ar}\!-\!\equiv\!\!-R^2 \quad (4)$$

Entry	Halide	Alkyne	Product	Yield (%)[b]
1	3-MeO-C6H4-Br	$\equiv\!\!-CO_2H$	3-MeO-C6H4-C≡C-CO2H	70[c,d]
2	3-HO2C-C6H4-Br	$\equiv\!\!-CO_2H$	3-HO2C-C6H4-C≡C-CO2H	69[c,d]
3	4-HO2C-C6H4-Cl	$\equiv\!\!-C_8H_{17}$	4-HO2C-C6H4-C≡C-C8H17	86
4	3-MeO-C6H4-Cl	$\equiv\!\!-(CH_2)_3CO_2H$	3-MeO-C6H4-C≡C-(CH2)3CO2H	85[d]
5	4-F-2-F-3-HO2C-C6H2-Cl	$\equiv\!\!-C_8H_{17}$	4-F-2-F-3-HO2C-C6H2-C≡C-C8H17	71
6	3-MeO-C6H4-Cl	$\equiv\!\!-C_6H_5$	3-MeO-C6H4-C≡C-C6H5	88
7	3-Cl-pyridine	$\equiv\!\!-$thiophen-3-yl	3-(thiophen-3-ylethynyl)pyridine	93
8	4-HO2C-C6H4-Cl	$\equiv\!\!-C_6H_5$	4-HO2C-C6H4-C≡C-C6H5	96[d]

[a]Reaction conditions: 1.0 equiv aryl halide, 1.3-1.5 equiv terminal alkyne, 2.5-5.0 equiv Cs₂CO₃, degassed water (2.0 mL mmol⁻¹), CH₃CN (2.0 mL mmol⁻¹), PdCl₂(CH₃CN)₂ (2.5 mol %), ligand 2 (7.5 mol %), 100 °C, 8-12 h. Reaction times were not optimized. [b]Yield of isolated product (average of 2 runs). [c]The alkyne was added to the reaction at 0 °C and heated to 60 °C. [d]To ease in purification, the product was converted to the methyl ester using trimethylsilyldiazomethane.

We were also interested in exploring the use of ligand **1** or **2** in alkynylation reactions of readily available and activated benzylic halides. To the best of our knowledge, except two examples describing the palladium-catalyzed reaction of tris(alkynyl)indiums or alkynyl zinc reagents with benzyl bromide, alkynylation of readily available benzyl halides in the absence of a stoichiometric co-catalyst appears to be unprecedented.[6,20] Interestingly, a reported attempt to couple benzyl halides with terminal alkynes using a $PdCl_2(PPh_3)_2$/CuCl catalyst only provides small amounts of the desired benzyl-substituted alkyne. Instead, highly substituted enynes are produced via a tandem Sonogashira-carbopalladation-Sonogashira sequence as shown in Scheme 5.[21]

Scheme 5. Proposed catalytic-cycle for Sonogashira reaction to form enynes.
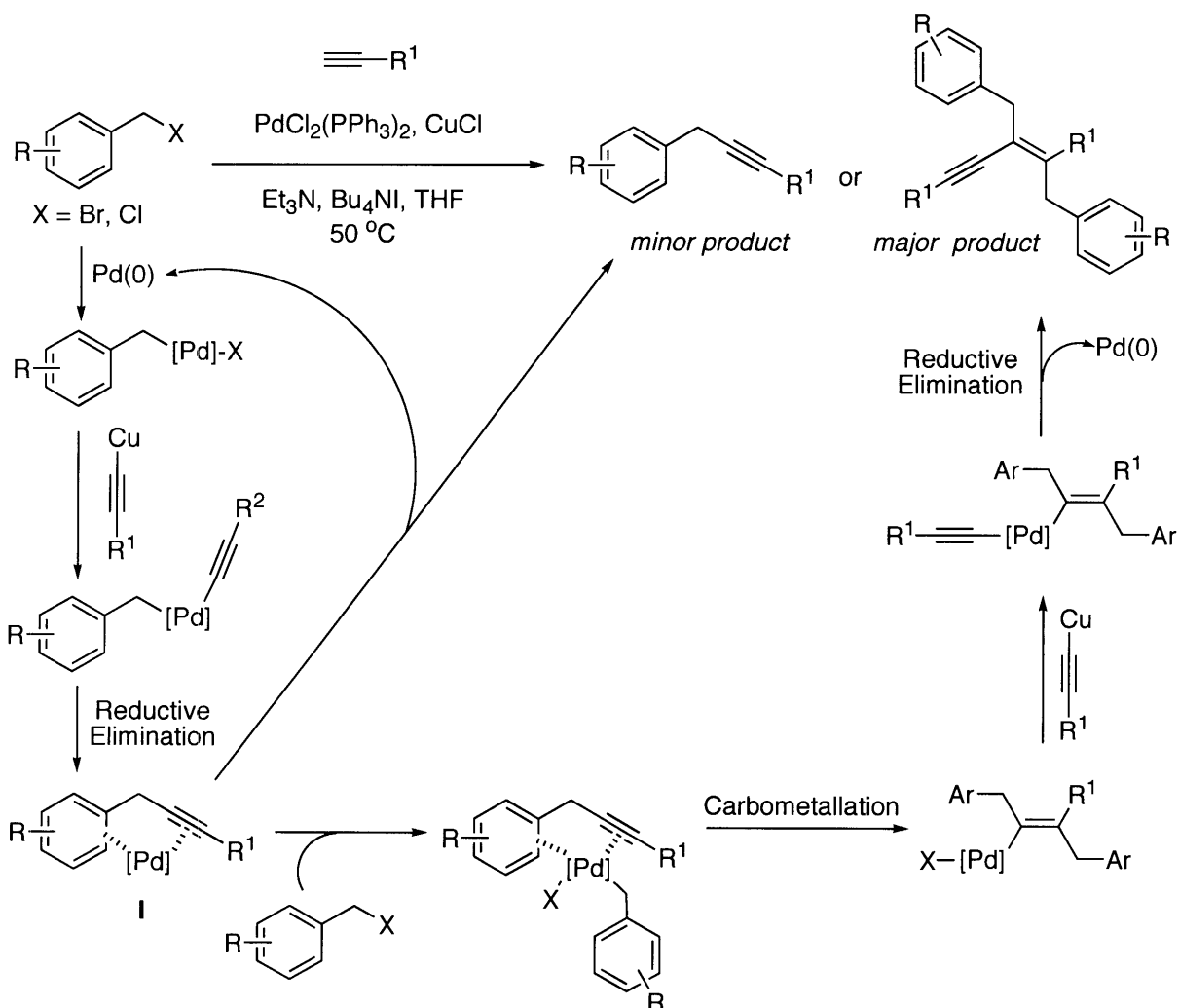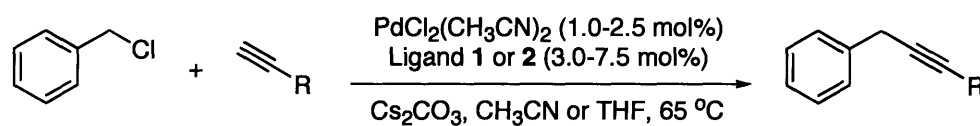
We postulated that the use of an electron-rich bulky ligand (XPhos, **1**) would suppress formation of the proposed Pd-bound benzyl alkynyl species (**I**) and prevent formation of the enyne product. Indeed, using catalytic $PdCl_2(CH_3CN)_2$/**1** and 2.5 equiv. Cs_2CO_3 as the base in acetonitrile, benzyl chloride and 1-decyne were efficiently combined providing the benzyl allkyne in 96% yield (eq. 1). Note that this transformation proceeds in the absence of a copper co-catalyst and without isomerization to the undesired aryl allene. Exploration of these initial catalytic conditions revealed that while KOAc provides a faster initial reaction rate than Cs_2CO_3, it also consumes the terminal alkyne leaving significant amounts of unreacted benzyl chloride. The use of most other bases is unproductive, but NaOAc and $K_3PO_4 \bullet H_2O$ do provide 50% conversion to product in the same time frame in which the reaction with Cs_2CO_3 is complete. While the process is water-tolerant, if it is not carried out under an inert atmosphere, the rate is 4-5 times slower. Utilization of $Pd(OAc)_2$ as the pre-catalyst is just as efficacious as $PdCl_2(CH_3CN)_2$ with either CH_3CN or THF as the solvent.
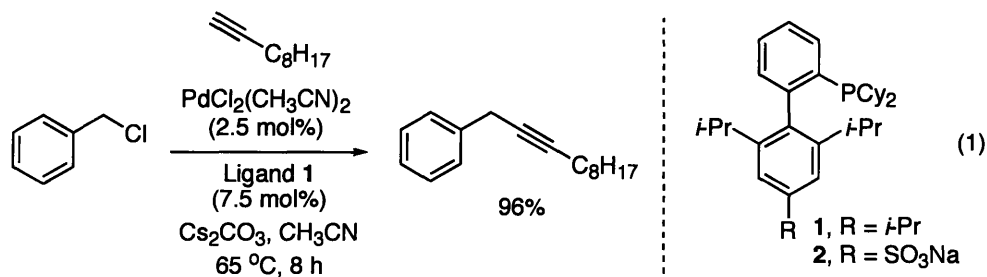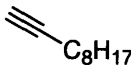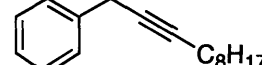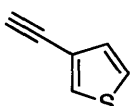

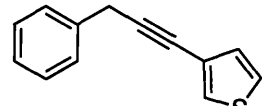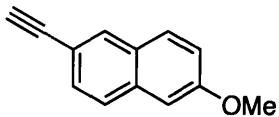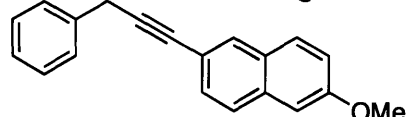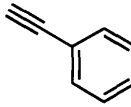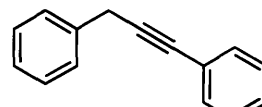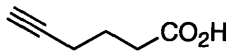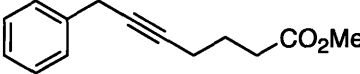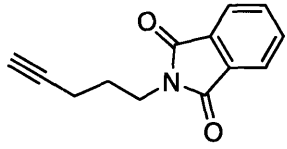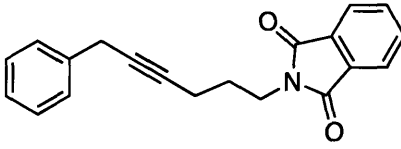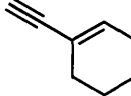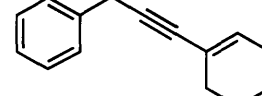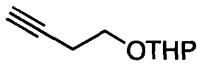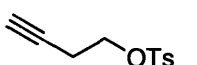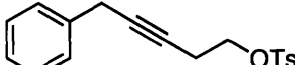Unfortunately, when the same conditions were applied to the coupling of 4-fluorobenzyl chloride and 4-cyano-1-butyne, an inseparable mixture of alkyne and allene products were formed, with the allene predominating. Lowering the stoichiometry of base to 1.5 equiv. gave a 1:2 ratio of alkyne to allene and to 1.1 equiv. finally provided a majority of the desired alkyne product in a 5:1 ratio. Switching the solvent to THF, toluene, or 1,4-dioxane is the key to obtaining solely the alkynyl Heck product for this more highly functionalized set of substrates, with the reactions in both THF and 1,4-dioxane proceeding to completion. If the alkynyl Heck product is not prone to

isomerization to the allene, then the original conditions in acetonitrile also cleanly provide the coupled product.

Table 2. Palladium-catalyzed coupling of benzyl chloride and terminal alkynes.[a]

PdCl$_2$(CH$_3$CN)$_2$ (1.0-2.5 mol%)
Ligand **1** or **2** (3.0-7.5 mol%)

Cs$_2$CO$_3$, CH$_3$CN or THF, 65 °C

Entry	Alkyne	Product	Time (h)	Yield (%)[b]
1	C$_8$H$_{17}$	C$_8$H$_{17}$	8	96[c]
2	(thiophene)	(thiophene)	2	88[c,f]
3	(naphthalene-OMe)	(naphthalene-OMe)	1.5	96[c,f]
4	(phenyl)	(phenyl)	10	94[d]
5	CO$_2$H	CO$_2$Me	10	81[d,e]
6	(phthalimide)	(phthalimide)	17	94[f]
7	(cyclohexenyl)	(cyclohexenyl)	1.5	91[f]
8	OTHP	OTHP	4	82[f]
9	OTs	OTs	12	95[f]

[a]Reaction Conditions: 1.0 equiv. benzyl chloride, 1.3-1.5 equiv. alkyne, 1.05 equiv. Cs$_2$CO$_3$, THF (2.5 mL/mmol), PdCl$_2$(CH$_3$CN)$_2$ (2.0 mol%), ligand **1** (6.0 mol%), 65 °C. [b]Yield of isolated product (average of 2 runs). [c]CH$_3$CN used as the solvent. [d]Ligand **2** and a H$_2$O/CH$_3$CN solvent system were used. [e]To ease in purification, the product was converted to the methyl ester using trimethylsilyldiazomethane. [f]Reactions were performed by Dr. Catharine H. Larsen and/or Rachel E. Tundel.
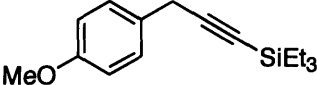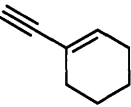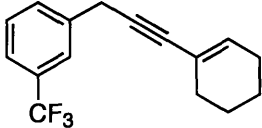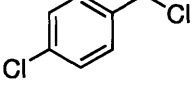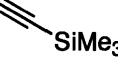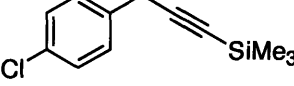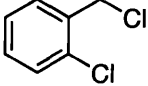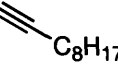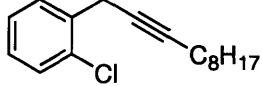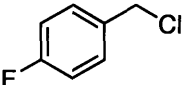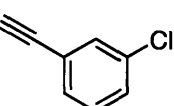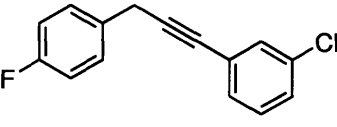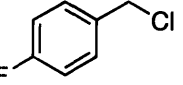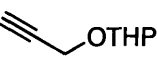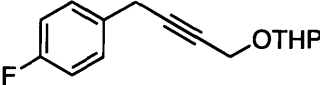
As is illustrated in Table 2, a wide variety of terminal alkynes can be successfully coupled with benzyl chloride using this catalyst system derived from $PdCl_2(CH_3CN)_2$ and 1. Aryl and heteroaryl alkynes are effective coupling partners as shown with 3-ethynylthiophene and 2-ethynyl-6-methoxynaphthalene where, in contrast to the Heck alkynylation of aryl chlorides using this same catalyst system, slow addition of the aryl/heteroaryl alkyne is not necessary (Table 2, Entries 2, 3). This may be attribu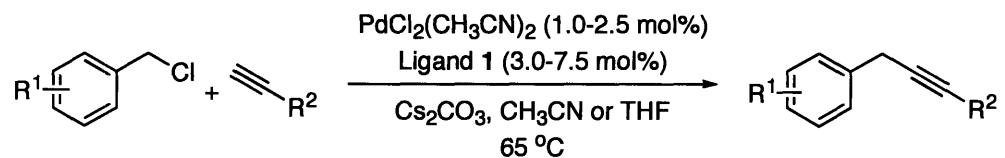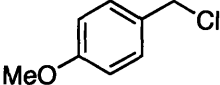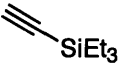ted to the fact that oxidative addition to benzyl chloride occurs much faster than non-productive alkyne polymerization. However, it should be noted that the reaction of 3-ethynylthiophene must be halted after 2 hours as the alkynyl product begins to isomerize to the allene upon consumption of the benzyl chloride starting material. Interestingly, the water-soluble sodium sulfonate version of XPhos (2) in biphasic mixture of H_2O/CH_3CN is proficient in the coupling of benzyl chloride with both phenylacetylene and the water-soluble terminal alkyne, 5-hexynoic acid, where 94% and 81% of the disubstituted alkynes are obtained, respectively (Table 2, Entries 4, 5).[11] Phthalimide-protected 5-aminohexyne is smoothly coupled with benzyl chloride in good yield only in THF (Table 2, Entry 6). Terminal aliphatic alkynes possessing either tetrahydropyran- or tosyl-protected alcohols are well tolerated and provide the corresponding benzyl alkynes in 82% and 95% yield, respectively (Table 2, Entries 8, 9).

The substrate scope was expanded further by varying the type, and position of substituents on the benzyl halide. As shown in Table 3, electron-rich 4-methoxybenzyl chloride and triethylsilyl-protected acetylene react to form the corresponding benzyl alkyne in nearly quantitative yield (Table 3, Entry 1). Electron-deficient 3-trifluoromethylbenzyl chloride is combined with 1-ethynylcyclohexene with high fidelity (Table 3, Entry 2). Complete selectivity of a benzyl chloride over an aryl chloride is achieved when coupling both 4-chloro and 2-chloro benzyl chloride with terminal alkynes (Table 3, Entries 3, 4). The coupling products of 4-fluorobenzyl chloride and either tetrahydropyran-protected propynol or 3-chlorophenylacetylene are also produced in good yields (Table 3, Entry 5, 6). While primary benzyl chlorides were suitable coupling partners using this catalyst system, reactions conducted with secondary benzyl

chlorides resulted in significant amounts of styrene (presumably formed via β-hydride elimination).

Table 3. Pd-Catalyzed coupling of substituted benzyl chlorides and terminal alkynes.[a]

$$\text{R}^1 \text{-benzyl-Cl} + \text{alkyne-R}^2 \xrightarrow[\substack{\text{Cs}_2\text{CO}_3,\ \text{CH}_3\text{CN or THF} \\ 65\ ^\circ\text{C}}]{\substack{\text{PdCl}_2(\text{CH}_3\text{CN})_2\ (1.0\text{-}2.5\ \text{mol}\%) \\ \text{Ligand 1 (3.0-7.5 mol}\%)}} \text{R}^1 \text{-product-R}^2$$

Entry	Benzyl Chloride	Alkyne	Product	Yield (%)[b]
1	MeO-benzyl-Cl	≡-SiEt₃	MeO-product-SiEt₃	99[c]
2	CF₃-benzyl-Cl	≡-cyclohexenyl	CF₃-product-cyclohexenyl	99[d]
3	Cl-benzyl-Cl	≡-SiMe₃	Cl-product-SiMe₃	82[d]
4	Cl-benzyl-Cl	≡-C₈H₁₇	Cl-product-C₈H₁₇	71[c,d]
5	F-benzyl-Cl	≡-phenyl-Cl	F-product-phenyl-Cl	95[c,d]
6	F-benzyl-Cl	≡-OTHP	F-product-OTHP	94[d]

[a]Reaction Conditions: 1.0 equiv. benzyl chloride, 1.3-1.5 equiv. alkyne, 1.05 equiv. Cs₂CO₃, THF (2.5 mL/mmol), PdCl₂(CH₃CN)₂ (2.0 mol %), ligand 1 (6.0 mol %), 65 °C. [b]Yield of isolated product (average of 2 runs). [c]CH₃CN used as the solvent. [d]Reactions were conducted by Dr. Catharine H. Larsen and/or Rachel E. Tundel
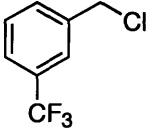
In the initial optimization studies, we found that if we heated the reaction to greater than 65 °C for the simple combination of benzyl chloride and 1-decyne, instead of only forming the desired benzyl alkyne, a significant amount of aryl allene is produced. In fact, heating the reaction at 90 °C for 12 hours with excess Cs_2CO_3 (2.5 equiv.) produced aryl allene in a modest 68% yield (eq. 2).
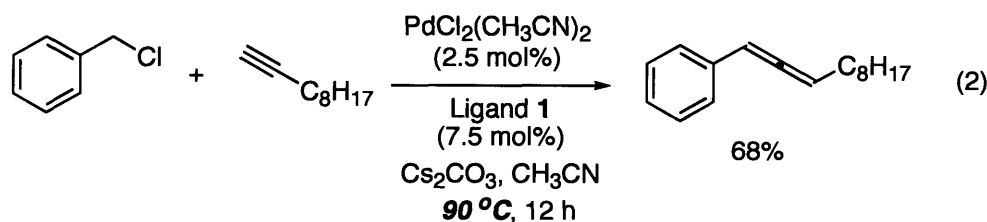
To determine whether the isomerization was mediated by the metal or by the base, we subjected the octyl-benzyl alkyne product from Table 2, Entry 1 to 2.5 equiv. Cs_2CO_3 in CH_3CN at 90 °C for 10 hours. Under these conditions, the product is completely converted to the corresponding aryl allene, confirming the role of the base in this reaction. As is seen in Table 4, by changing the amount of base used, as well as the solvent, and temperature, one can predictably convert benzyl chlorides to either the benzyl alkyne (65 °C, 1.05 equiv. Cs_2CO_3) or the aryl allene (≥80 °C, 2.50 equiv. Cs_2CO_3) in a one-pot protocol. For substrates in which the reaction in CH_3CN gives a mixture of alkyne and allene even at 65 °C with only 1.05 eq. of base, switching the solvent to THF provides solely the alkyne product.

In conclusion, we have demonstrated that use of water-soluble sulfonated ligand 2 provides a highly active catalyst system for Cu-free Sonogashira cross-coupling reactions, with unprecedented scope, reactivity, and stability for aqueous-phase processes. Also, use of ligands 1 and 2 provide an extremely active system for coupling primary benzyl chlorides and terminal alkynes. We also found that by using this same catalyst, an excess of base and more forcing reaction conditions, the coupling of benzyl chlorides and terminal alkynes produces aryl allenes via a base-catalyzed isomerization of the resultant benzyl alkyne.

Table 4. Palladium-catalyzed coupling of benzyl chlorides with terminal alkynes to form benzyl alkynes or aryl allenes.[a]

Entry	Benzyl Chloride	Alkyne	Condition	Product	Yield (%)[b]
1			A		96
2			B		68
3			A		93[d]
4			B		72
5			A		91[c,d]
6			B		70

[a]Reaction Conditions: 1.0 equiv. benzyl chloride, 1.3-1.5 equiv. alkyne, $PdCl_2(CH_3CN)_2$ (2.0 mol %), ligand **1** (6.0 mol %). (**A**) 1.05 equiv. Cs_2CO_3, THF (2.5 mL/mmol), 65 °C, 4-25 h. (**B**) 2.50 equiv. Cs_2CO_3, CH_3CN (2.5 mL/mmol), 80-90 °C, 12 h. [b]Yield of isolated product (average of 2 runs). [c]1,4-dioxane was used as the solvent. [d]Reactions were conducted by Dr. Catharine H. Larsen and/or Rachel E. Tundel.

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Experimental

Reagents. PdCl$_2$(CH$_3$CN)$_2$ was obtained from Engelhard and used without further purification. Ligand **1** was synthesized in our laboratory, but is commercially available from Strem Chemical Co. and Aldrich Chemical Co. Dichloromethane was purchased from J. T. Baker in CYCLE-TAINER® solvent delivery kegs, which were vigorously purged with argon for 2 h, and further purified by passing the solvent through two packed columns of neutral alumina and copper (II) oxide under argon pressure. All other reagents were purchased from commercial sources and used without further purification.

Analytical methods. All reactions were carried out under an argon atmosphere. IR spectra were obtained on a Perkin-Elmer Model 2000 FT-IR using NaCl plates (thin film). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 400 MHz NMR with chemical shifts reported in ppm relative to the residual deuterated solvent or the internal standard tetramethylsilane. Yield refers to isolated yields of compounds greater than 95% purity as determined by capillary gas chromatography (GC) and proton Nuclear Magnetic Resonance spectroscopy (^{1}H NMR) analysis. ^{1}H NMR and melting points (where applicable) of all known compounds were compared with those reported. All new compounds were further characterized by elemental analysis.

Preparation of Water-Soluble Ligand (Scheme 3):

Sodium 2'-(Dicyclohexyl-phosphanyl)-2,6-diisopropyl-biphenyl-4-sulfonate (2). To an oven-dried 25 mL round bottom flask equipped with a Teflon-coated magnetic stir bar and rubber septum was added dicyclohexyl-(2',4',6'-triisopropyl-biphenyl-2-yl)-phosphane (476 mg, 1.00 mmol) and CH$_2$Cl$_2$ (1.0 mL). The solution was cooled to 0 °C using an ice/water bath and then concentrated H$_2$SO$_4$ (1.00 mL) and fuming sulfuric acid (3.0 mL, 20% SO$_3$) were added dropwise. The solution was allowed to warm to room temperature and stir for 24 h. At this time it was cooled to 0 °C using an ice/water bath and crushed ice (~10 g) was added. The solution turned cloudy and white in color. An aqueous solution of NaOH (6.0 M, ~20.0 mL) was then added dropwise to the cooled solution until it became neutral (pH ~7.0 as judged by pH paper). The aqueous solution was extracted with CH$_2$Cl$_2$ (3 x 50 mL) and concentrated under reduced pressure to give

a beige solid. The crude material was then dissolved in a minimum amount of cold methanol (~20 mL), filtered and concentrated (this cycle was repeated) to give the desired product as a beige solid (503 mg, 94%). Mp = >250 °C ^{1}H NMR (400 MHz, CD$_3$OD) δ: 7.52 (s, 2H), 7.46 (m, 1H), 7.22 (m, 2H), 6.90 (m, 1H), 2.24 (m, 1H), 0.71-1.83 (34H). ^{13}C NMR (125 MHz, CD$_3$OD) δ: 148.4, 147.9, 147.8, 147.5, 145.6, 142.8, 137.4, 137.2, 133.92, 133.91, 132.43, 132.42, 129.3, 128.1, 121.3, 121.0, 40.1, 39.9, 39.7, 39.5, 39.3, 38.8, 35.8, 35.7, 32.5, 32.3, 31.9, 30.8, 30.6, 28.7, 28.6, 28.4, 28.3, 27.7, 26.0, 25.9, 23.3, 23.1. ^{31}P NMR (162 MHz, CD$_3$OD) δ: -10.7. IR (neat, cm^{-1}): 3459, 2927, 2851, 1634, 1463, 1447, 1184, 1078, 1040. Anal. Calcd for C$_{30}$H$_{42}$NaO$_3$PS: C, 67.14; H, 7.89. Found: C, 66.93; H, 7.77.

¹H NMR (d⁴-MeOH):

Peak list (ppm):

1.137
1.154
1.168
1.178
1.208
1.224
1.247
1.264
1.344
1.557
1.581
1.655
1.679
1.756
1.764
1.871
1.895
2.463
2.480
2.497
2.514
3.306
3.310
3.314
3.318
4.885

7.105
7.112
7.118
7.123
7.127
7.381
7.387
7.395
7.405
7.410
7.424
7.428
7.645
7.656
7.662
7.668
7.697

Integrations:

22.286
12.768
1.853
1.068
2.000
2.701

Structure label: PCy₂, i-Pr, i-Pr, SO₃Na (d⁴-MeOH)

^{31}P NMR (d^4-MeOH):

10.693

(d^4-MeOH)

ppm

-200   -100   0   100

General Procedure for Heck Alkynylation in Water/Acetonitrile (Table 1). A disposable tube with a screw cap, Teflon septum and stir bar was charged with $PdCl_2(CH_3CN)_2$ (3.2 mg, 0.0125 mmol, 1.25 mol %), sodium 2'-(dicyclohexyl-phosphanyl)-2,6-diisopropyl-biphenyl-4-sulfonate **2** (20.0 mg, 0.0375 mmol, 3.75 mol %), aryl halide (0.500 mmol) and Cs_2CO_3 (406-813 mg, 1.25-2.50 mmol). The tube was evacuated and back-filled with argon (this was repeated two additional times). Acetonitrile (3.0 mL) was added and the reaction mixture was allowed to stir at room temperature for 20 minutes. The alkyne (0.650 mmol) and degassed water (1.0-1.5 mL, sonicated under vacuum for 2 min) were added and the reaction mixture was allowed to stir at the noted temperature. After cooling to room temperature the following work-up procedure was followed:

Table 1, entries 1,2,4,8: The reaction mixture was acidified with HCl (2.0 M) to pH~5 (as judged by pH paper) and extracted out with ethyl acetate. The organic layer was dried over anhydrous $MgSO_4$, filtered through celite and concentrated to give the crude product. To the crude material was added diethyl ether (10.0 mL), methanol (5.0 mL) and then trimethylsilyldiazomethane (2.0 mL, 2.0 M solution in diethyl ether, 4.0 mmol). The solution was allowed to stir for 5 minutes after which it was filtered and concentrated. The product was purified by column chromatography on silica gel (eluting with ether/hexane mixtures).

Table 1, entries 6,7: The products were extracted out of the water layer with ethyl acetate, dried over $MgSO_4$, filtered through celite and concentrated to dryness. The product was purified by column chromatography on silica gel (eluting with hexanes).

Table 1, entries 3,5: The reaction was acidified with HCl (2.0 M) to pH~5 (as judged by pH paper) and extracted out with ethyl acetate. The organic layer was dried over anhydrous $MgSO_4$, filtered through celite and concentrated to give the crude product. The product was purified by crystallization from water.

(3-Methoxy-phenyl)-propynoic acid methyl ester (Table 1, entry 1).[22] The general procedure was used with 3-bromoanisole (0.063 mL, 0.50 mmol), propiolic acid (added at 0 °C) (0.050 mL, 0.65 mmol), $PdCl_2(CH_3CN)_2$ (3.2 mg, 0.0125 mmol, 1.25 mol %), sodium 2'-(dicyclohexyl-phosphanyl)-2,6-diisopropyl-biphenyl-4-sulfonate **2** (20.0 mg,

0.0375 mmol, 3.75 mol %), Cs_2CO_3 (650 mg, 2.00 mmol), water (1.0 mL), acetonitrile (1.0 mL), 12 h, 60 °C. The product was isolated as a colorless oil (66 mg, 69%). ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.28 (t, 1H, J = 7.6 Hz, 8.4 Hz), 7.17 (dt, 1H, J = 1.2 Hz, 7.6 Hz), 7.09 (m, 1H), 7.00 (qd, 1H, J = 1.2 Hz, 2.4 Hz, 8.4 Hz), 3.84 (s, 3H), 3.80 (s, 3H). ^{13}C NMR (125 MHz, CDCl$_3$) δ: 159.4, 154.6, 129.9, 125.6, 120.5, 117.7, 117.6, 86.6, 80.2, 55.5, 52.9.

3-Methoxycarbonylethynyl-benzoic acid methyl ester (Table 1, entry 2). The general procedure was used with 3-bromobenzoic acid (101 mg, 0.50 mmol), propiolic acid (added at 0 °C) (0.050 mL, 0.65 mmol), PdCl$_2$(CH$_3$CN)$_2$ (3.2 mg, 0.0125 mmol, 1.25 mol %), sodium 2'-(dicyclohexyl-phosphanyl)-2,6-diisopropyl-biphenyl-4-sulfonate **2** (20.0 mg, 0.0375 mmol, 3.75 mol %), Cs_2CO_3 (813 mg, 2.50 mmol), water (1.0 mL), acetonitrile (1.0 mL), 12 h, 60 °C. The product was isolated as a white solid (77 mg, 70%). Mp = 96-97 °C ^{1}H NMR (400 MHz, CDCl$_3$) δ: 8.19 (m, 1H), 8.04 (d, 1H, J = 8.0 Hz), 7.68 (d, 1H, J = 7.6 Hz), 7.41 (t, 1H, J = 7.6 Hz), 3.87 (s, 3H), 3.79 (s, 3H). ^{13}C NMR (125 MHz, CDCl$_3$) δ: 165.9, 154.3, 136.9, 134.2, 131.7, 130.9, 128.9, 120.1, 85.1, 81.0, 53.0, 52.6. IR (neat, cm^{-1}): 3022, 2963, 2231, 1738, 1718, 1437, 1290, 1259, 1197, 1173, 1101, 749. Anal. Calcd for $C_{12}H_{10}O_4$: C, 66.05; H, 4.62. Found: C, 65.95; H, 4.60

4-Dec-1-ynyl-benzoic acid (Table 1, entry 3). The general procedure was used with 4-chlorobenzoic acid (79 mg, 0.50 mmol), 1-decyne (0.136 mL, 0.75 mmol), PdCl$_2$(CH$_3$CN)$_2$ (3.2 mg, 0.0125 mmol, 1.25 mol %), sodium 2'-(dicyclohexyl-phosphanyl)-2,6-diisopropyl-biphenyl-4-sulfonate **2** (20.0 mg, 0.0375 mmol, 3.75 mol %), Cs_2CO_3 (650 mg, 2.00 mmol), water (1.0 mL), acetonitrile (1.0 mL), 12 h, 100 °C. The product was isolated as a white solid (111 mg, 86%). Mp = 103 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ: 11.0 (br-s, 1H), 8.04 (d, 2H, J = 8.4 Hz), 7.49 (d, 2H, J = 8.4 Hz), 2.46 (t, 2H, J = 6.8 Hz), 1.64 (p, 2H, J = 6.8 Hz), 0.89-1.49 (m, 13H). ^{13}C NMR (125 MHz, CDCl$_3$) δ: 169.3, 132.6, 130.9, 130.8, 130.4, 94.6, 81.2, 33.2, 30.5, 30.4, 30.2, 29.9, 23.9, 20.2, 14.6 IR (neat, cm^{-1}): 3402 (br), 2920, 2849, 2214, 1686, 1607, 1428, 1319, 1283, 1178, 1112, 929, 862, 769. Anal. Calcd for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58. Found: C, 78.84; H, 8.48.

6-(3-Methoxy-phenyl)-hex-5-ynoic acid methyl ester (Table 1, entry 4). The general procedure was used with 3-chloroanisole (0.061 mL, 0.50 mmol), 5-hexynoic acid (0.072 mL, 0.65 mmol), $PdCl_2(CH_3CN)_2$ (3.2 mg, 0.0125 mmol, 1.25 mol %), sodium 2'-(dicyclohexyl-phosphanyl)-2,6-diisopropyl-biphenyl-4-sulfonate **2** (20.0 mg, 0.0375 mmol, 3.75 mol %), Cs_2CO_3 (650 mg, 2.00 mmol), water (1.0 mL), acetonitrile (1.0 mL), 10 h, 100 °C. The product was isolated as a colorless oil (60 mg, 85%). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.16 (t, 1H, J = 8.0 Hz), 6.96 (dt, 1H, J = 1.2 Hz, 7.6 Hz), 6.89 (m, 1H), 6.80 (qd, 1H, J = 1.2 Hz, 2.4 Hz, 8.4 Hz), 3.76 (s, 3H), 3.66 (s, 3H), 2.48 (t, 2H, J = 7.2 Hz), 2.45 (t, 2H, J = 6.8 Hz), 1.90 (q, 2H, J = 6.8 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 173.8, 159.4, 129.5, 124.9, 124.3, 116.6, 114.5, 88.9, 81.6, 55.4, 51.8, 33.1, 24.1, 19.1. IR (neat, cm^{-1}): 2952, 2232, 1737, 1598, 1574, 1481, 1434, 1316, 1287, 1206, 1164, 1045, 854, 786, 688. Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.22; H, 6.85

3-Dec-1-ynyl-2,4-difluoro-benzoic acid (Table 1, entry 5). The general procedure was used with 3-chloro-2,4-difluoro-benzoic acid (97 mg, 0.50 mmol), 1-decyne (0.136 mL, 0.75 mmol), $PdCl_2(CH_3CN)_2$ (3.2 mg, 0.0125 mmol, 1.25 mol %), sodium 2'-(dicyclohexyl-phosphanyl)-2,6-diisopropyl-biphenyl-4-sulfonate **2** (20.0 mg, 0.0375 mmol, 3.75 mol %), Cs_2CO_3 (650 mg, 2.00 mmol), water (1.0 mL), acetonitrile (1.0 mL), 12 h, 100 °C. The product was isolated as a white solid (102 mg, 70%). Mp = 117 °C. ^1H NMR (400 MHz, d^6-DMSO) δ: 10.1 (br-s, 1H), 7.88 (q, 1H, J = 8.8 Hz), 7.26 (t, 1H, J = 8.4 Hz), 2.51 (t, 2H, J = 6.8 Hz), 1.57 (p, 2H, J = 6.8 Hz), 0.80-1.43 (m, 13H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.7, 167.9, 165.3, 162.6, 132.3, 132.2, 114.1, 111.7, 111.5, 104.8, 103.1, 66.7, 32.0, 29.4, 29.3, 28.9, 28.5, 22.9, 20.0, 14.3. IR (neat, cm^{-1}): 3428 (br), 2922, 2848, 2235, 1689, 1611, 1406, 1268, 1242, 1051, 1036. Anal. Calcd for $C_{17}H_{20}F_2O_2$: C, 69.37; H, 6.85. Found: C, 69.13; H, 6.80.

1-Methoxy-3-(phenethynyl)-benzene (Table 1, entry 6).[23] The general procedure was used with 3-chloroanisole (0.063 mL, 0.50 mmol), phenylacetylene (0.072 mL, 0.65 mmol), $PdCl_2(CH_3CN)_2$ (3.2 mg, 0.0125 mmol, 1.25 mol %), sodium 2'-(dicyclohexyl-phosphanyl)-2,6-diisopropyl-biphenyl-4-sulfonate **2** (20.0 mg, 0.0375 mmol, 3.75 mol %), Cs_2CO_3 (650 mg, 2.00 mmol), water (1.0 mL), acetonitrile (1.5 mL), 12 h, 100 °C.

The product was isolated as a white solid (99 mg, 95%). Mp = 70 °C (lit.[23] 72-74 °C). [1]H

NMR (400 MHz, CDCl$_3$) δ: 7.62 (m, 2H), 7.41 (m, 3H), 7.32 (t, 1H, J = 7.6 Hz), 7.23 (dt,

1H, J = 1.2 Hz, 7.6 Hz), 7.15 (m, 1H), 6.96 (qd, 1H, J = 1.2 Hz, 2.4 Hz, 7.6 Hz). [13]C

NMR (125 MHz, CDCl$_3$) δ: 159.5, 131.8, 129.6, 128.5, 128.48, 124.4, 124.3, 123.3,

116.5, 115.1, 89.5, 89.4, 55.4.

3-(3-Thienylethynyl)-pyridine (Table 1, entry 7).[24] The general procedure was used

with 3-chloropyridine (0.050 mL, 0.50 mmol), 3-ethynylthiophene (0.074 mL, 0.75

mmol), PdCl$_2$(CH$_3$CN)$_2$ (3.2 mg, 0.0125 mmol, 1.25 mol %), sodium 2'-(dicyclohexyl-

phosphanyl)-2,6-diisopropyl-biphenyl-4-sulfonate **2** (20.0 mg, 0.0375 mmol, 3.75 mol

%), Cs$_2$CO$_3$ (650 mg, 2.00 mmol), water (1.0 mL), acetonitrile (1.5 mL), 10 h, 100 °C.

The product was isolated as a white solid (86 mg, 93%). Mp = 62 °C (lit.[24] 65.5-64.0 °C).

^{1}H NMR (400 MHz, CDCl$_3$) δ: 8.75 (d, 1H, J = 1.6 Hz), 8.54 (dd, 1H, J = 2.0 Hz, 5.2 Hz),

7.79 (dt, 1H, J = 8.0 Hz, 2.0 Hz), 7.57 (dd, 1H, J = 2.8 Hz, 1.2 Hz), 7.32 (dd, 1H, J = 5.2

Hz, 2.8 Hz), 7.27 (qd, 1H, J = 0.8 Hz, 4.8 Hz, 3.2 Hz), 7.21 (dd, 1H, J = 1.2 Hz, 5.2 Hz).

^{13}C NMR (125 MHz, CDCl$_3$) δ: 152.4, 148.7, 138.5, 129.9, 129.6, 125.9, 123.2, 121.8,

120.6, 87.9, 85.7.

Methyl-4-(phenethynyl) benzoate (Table 1, entry 8).[25] The general procedure was

used with 4-chlorobenzoic acid (79 mg, 0.50 mmol), phenylacetylene (0.072 mL, 0.65

mmol), PdCl$_2$(CH$_3$CN)$_2$ (3.2 mg, 0.0125 mmol, 1.25 mol %), sodium 2'-(dicyclohexyl-

phosphanyl)-2,6-diisopropyl-biphenyl-4-sulfonate **2** (20.0 mg, 0.0375 mmol, 3.75 mol

%), Cs$_2$CO$_3$ (650 mg, 2.00 mmol), water (1.0 mL), acetonitrile (1.5 mL), 12 h, 100 °C.

The product was isolated as a white solid (101 mg, 86%). Mp = 114 °C (lit.[25] 113-115

°C). ^{1}H NMR (400 MHz, CDCl$_3$) δ: 8.04 (d, 2H, J = 8.4 Hz), 7.61 (d, 2H, J = 8.4 Hz), 7.57

(m, 2H), 7.39 (m, 3H). ^{13}C NMR (125 MHz, CDCl$_3$) δ: 166.6, 131.9, 131.6, 129.64,

129.56, 128.9, 128.6, 128.1, 122.8, 92.5, 88.8, 52.3.

General Procedure for Heck Alkynylation of Benzylic Halides (Table 2-3). A

disposable tube with a screw cap, Teflon septum and stir bar was charged with

PdCl$_2$(CH$_3$CN)$_2$ (6.5 mg, 0.025 mmol, 2.5 mol %), 2-dicyclohexylphosphino-2',4',6'-

triisopropylbiphenyl (36.0 mg, 0.0750 mmol, 7.5 mol %) and Cs$_2$CO$_3$ (813 mg, 2.50

mmol). If the benzylic halide (1.00 mmol) is a solid, it was also added at this time. The

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tube was evacuated and back-filled with argon (this was repeated two additional times). The benzyl halide (1.00 mmol, liquid) and solvent/solvents were added (when degassed water was used, it was sonicated under vacuum for 2 min. prior to addition) and the reaction mixture was allowed to stir at the room temperature for 20 minutes. The alkyne (1.30 mmol) was added all at once and the solution was heated to the noted temperature for the indicated period of time. After cooling to room temperature, the products were extracted from the water layer with diethyl ether or ethyl acetate, dried over $MgSO_4$, filtered through celite and concentrated to dryness and purified by column chromatography on silica gel (eluting with hexanes/ethyl acetate mixtures).

Undec-2-ynyl-benzene (Table 2, Entry 1).[26] The general procedure was used with benzyl chloride (0.138 mL, 1.00 mmol), 1-decyne (0.234 mL, 1.30 mmol), $PdCl_2(CH_3CN)_2$ (6.5 mg, 0.025 mmol, 2.5 mol %), 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl **1** (36.0 mg, 0.0750 mmol, 7.5 mol %), Cs_2CO_3 (813 mg, 2.50 mmol), acetonitrile (2.5 mL), 5 h, 60 °C. The product was purified by column chromatography on silica gel (eluting with hexanes) to provide the title compound as a clear oil (220 mg, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.33 (d, J = 7.2 Hz, 2H), 7.28 (t, J = 7.2 Hz, 2H), 7.17 (t, J = 6.8 Hz, 1H), 3.56 (br-t, J = 2.4 Hz, 2H), 2.20 (tt, J = 4.8 Hz, J = 2.4 Hz, 2H), 1.52 (m, 2H), 1.28-1.42 (m, 10H), 0.88 (t, J = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 137.8, 128.5, 128.0, 126.5, 82.9, 77.7, 32.0, 29.5, 29.4, 29.2, 29.1, 25.3, 22.9, 19.0, 14.3.

1,3-diphenyl-propyne (Table 2, Entry 4).[27] The general procedure was used with benzyl chloride (0.069 mL, 0.50 mmol), phenyl acetylene (0.083 mL, 0.75 mmol), $PdCl_2(CH_3CN)_2$ (3.2 mg, 0.0125 mmol, 2.5 mol %), Sodium 2-dicyclohexylphosphino-2',4'-diisopropylbiphenyl-6'-sulfonate **2** (20.0 mg, 0.0375 mmol, 7.5 mol %), Cs_2CO_3 (206 mg, 1.25 mmol), acetonitrile (1.0 mL), H_2O (1.0 mL), 12 h, 65 °C. The product was purified by column chromatography on silica gel (eluting with hexanes) to provide the title compound as a clear oil (92 mg, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.40-7.46 (m, 4H), 7.33 (t, J = 7.2 Hz, 2H), 7.22-7.30 (m, 4H), 3.82 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 136.9, 131.8, 128.7, 128.4, 128.2, 128.0, 126.8, 123.8, 87.7, 82.8, 25.9.

7-Phenyl-hept-5-ynoic acid methyl ester (Table 2, Entry 5).[28] The general procedure was used with benzyl chloride (0.069 mL, 0.50 mmol), 5-hexynoic acid (0.072 mL, 0.65 mmol), $PdCl_2(CH_3CN)_2$ (3.2 mg, 0.0125 mmol, 2.5 mol %), Sodium 2-dicyclohexylphosphino-2',4'-diisopropylbiphenyl-6'-sulfonate **2** (20.0 mg, 0.0375 mmol, 7.5 mol %), Cs_2CO_3 (650 mg, 2.00 mmol), acetonitrile (1.0 mL), H_2O (1.0-mL), 12 h, 65 °C. The reaction mixture was cooled to room temperature and acidified with aq. HCl (1.0 N). The aqueous layer was extracted with ethyl acetate, dried over anhydrous $MgSO_4$, filtered and concentrated to dryness. The crude material was dissolved in Et_2O (5.0 mL) and MeOH (5.0 mL) and cooled to 0 °C in a ice/water bath. At this time, trimethylsilyldiazomethane (2.0 mL, 1.0 M solution in Et_2O) was added and the flask was allowed to stir for 10 min. The reaction mixture was concentrated to dryness. The product was purified by column chromatography on silica gel (eluting with diethyl ether/hexanes, 1:9) to provide the title compound as a clear oil (108 mg, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.19-7.36 (m, 5H), 3.66 (s, 3H), 3.56 (t, J = 2.4 Hz, 2H), 2.45 (t, J = 7.2 Hz, 2H), 2.29 (tt, J = 2.4 Hz, J = 6.8 Hz, 2H), 1.85 (p, J = 7.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.8, 137.5, 128.7, 128.6, 127.9, 126.6, 81.3, 78.7, 51.7, 33.0, 25.2, 24.3, 18.5.

Triethyl-[3-(4-methoxy-phenyl)-prop-1-ynyl]-silane (Table 3, Entry 1). The general procedure was used with 4-methoxybenzyl chloride (0.140 mL, 1.00 mmol), triethyl-ethynyl-silane (0.232 mL, 1.30 mmol), $PdCl_2(CH_3CN)_2$ (6.5 mg, 0.025 mmol, 2.5 mol %), 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl **1** (36.0 mg, 0.0750 mmol, 7.5 mol %), Cs_2CO_3 (813 mg, 2.50 mmol), acetonitrile (2.5 mL), 16 h, 65 °C. The product was purified by column chromatography on silica gel (eluting with diethyl ether/hexanes, 0.3:9.7) to provide the title compound as a clear oil (259 mg, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.32 (d, J = 8.4 Hz, 2H), 6.90 (d, J = 8.4 Hz, 2H), 3.84 (s, 3H), 3.67 (s, 2H), 1.06 (t, J = 8.0 Hz, 9H), 0.68 (q, J = 8.0 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.4, 128.9, 128.7, 113.9, 105.9, 83.9, 55.4, 25.5, 7.7, 4.7. IR (neat, cm^{-1}): 2955, 2911, 2874, 2174, 1612, 1586, 1512, 1462, 1417, 1333, 1302, 1247, 1175, 1039, 1020, 815, 807, 726.

1-Chloro-2-undec-2-ynyl-benzene (Table 3, Entry 4). The general procedure was used with 2-chlorobenzyl chloride (0.127 mL, 1.00 mmol), 1-decyne (0.220 mL, 1.20 mmol), $PdCl_2(CH_3CN)_2$ (6.5 mg, 0.025 mmol, 2.5 mol %), 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl **1** (36.0 mg, 0.0750 mmol, 7.5 mol %), Cs_2CO_3 (813 mg, 2.50 mmol), acetonitrile (2.5 mL), 22 h, 65 °C. The product was purified by column chromatography on silica gel (eluting with hexanes) to provide the title compound as a light yellow oil (259 mg, 99%). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.69 (d, J = 7.6 Hz, 1H), 7.37 (dd, J = 1.6 Hz, J = 8.0 Hz, 1H), 7.30 (td, J = 1.6 Hz, J = 5.6 Hz, 1H), 7.21 (td, J = 2.0 Hz, J = 6.0 Hz, 1H), 3.71 (t, J = 2.4 Hz, 2H), 2.30 (tt, J = 2.4 Hz, J = 4.8 Hz, 2H), 1.52 (q, J = 2.4 Hz, 2H), 1.51-1.35 (m, 10H), 0.95 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 135.4, 133.6, 129.7, 129.2, 127.9, 126.9, 83.9, 76.2, 32.1, 29.5, 29.4, 29.2, 29.1, 23.5, 22.9, 19.0, 14.3. IR (neat, cm^{-1}): 2955, 2927, 2855, 1705, 1593, 1573, 1468, 1444, 1322, 1050, 1038, 748.

General Procedure for Heck Alkynylation of Benzylic Halides to form Benzyl Allenes (Table 4). A disposable tube with a screw cap, Teflon septum and stir bar was charged with $PdCl_2(CH_3CN)_2$ (5.2 mg, 0.020 mmol, 2.0 mol %), 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl **1** (28.6 mg, 0.060 mmol, 6.0 mol %) and Cs_2CO_3 (2.5 equiv.). If the benzyl chloride (1.00 mmol) is a solid, it was also added at this time. The tube was evacuated and back-filled with argon (this was repeated two additional times). The benzyl chloride (1.00 mmol, liquid) and solvent was added and the reaction mixture was allowed to stir at room temperature for 3 minutes. The alkyne (1.30 mmol) was added all at once and the solution was heated to the noted temperature until the reaction was complete by GC analysis. After cooling to room temperature, the products were extracted from the water layer with diethyl ether or ethyl acetate, dried over $MgSO_4$, filtered through celite and concentrated to dryness and purified by column chromatography on silica gel.
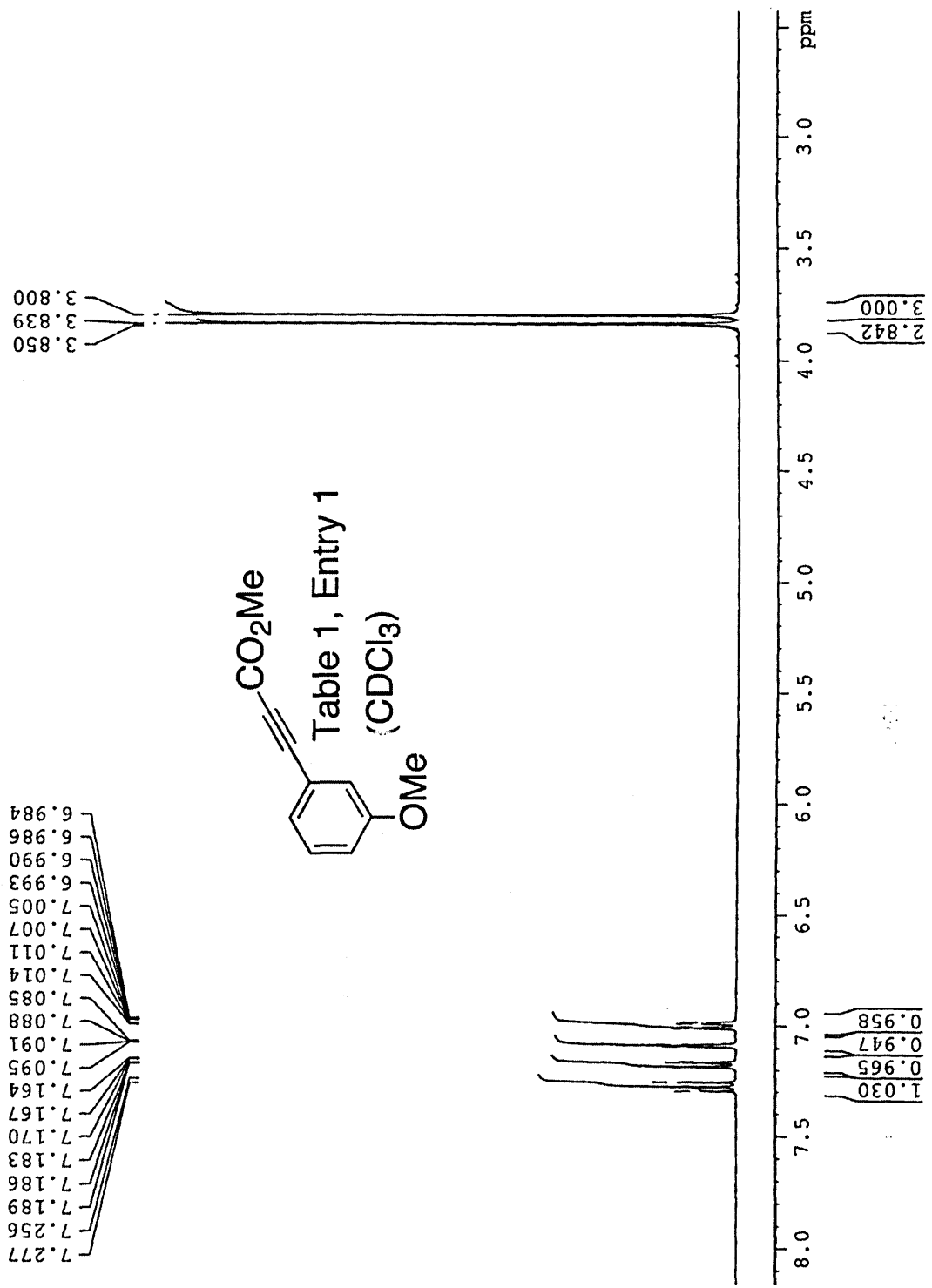
Undeca-1,2-dienyl-benzene (Table 4, Entry 2).[29] The general procedure was used with benzyl chloride (0.138 mL, 1.00 mmol), 1-decyne (0.234 mL, 1.30 mmol), $PdCl_2(CH_3CN)_2$ (6.5 mg, 0.025 mmol, 2.5 mol %), 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl **1** (36.0 mg, 0.0750 mmol, 7.5 mol %), Cs_2CO_3 (813 mg, 2.50 mmol),

acetonitrile (2.5 mL), 16 h, 90 °C. The product was purified by column chromatography on silica gel (eluting with hexanes) to provide the title compound as a clear oil (130 mg, 60%). ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.25-7.32 (m, 4H), 7.14-7.19 (m, 1H), 6.11 (m, 1H), 5.55 (q, J = 3.2 Hz, 1H), 2.11 (qd, J = 3.2 Hz, J = 7.2 Hz, 2H), 1.25-1.51 (m, 15H), 0.87 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ: 205.3, 135.4, 128.7, 126.79, 126.77, 95.3, 94.7, 32.0, 29.6, 29.5, 29.4, 29.3, 28.9, 22.9, 14.3.

1-Trifluoromethyl-2-undeca-1,2-dienyl-benzene (Table 4, Entry 4). The general procedure was used with 2-trifluorometylbenzyl chloride (0.146 mL, 1.00 mmol), 1-decyne (0.234 mL, 1.30 mmol), PdCl$_2$(CH$_3$CN)$_2$ (6.5 mg, 0.025 mmol, 2.5 mol %), 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl 1 (36.0 mg, 0.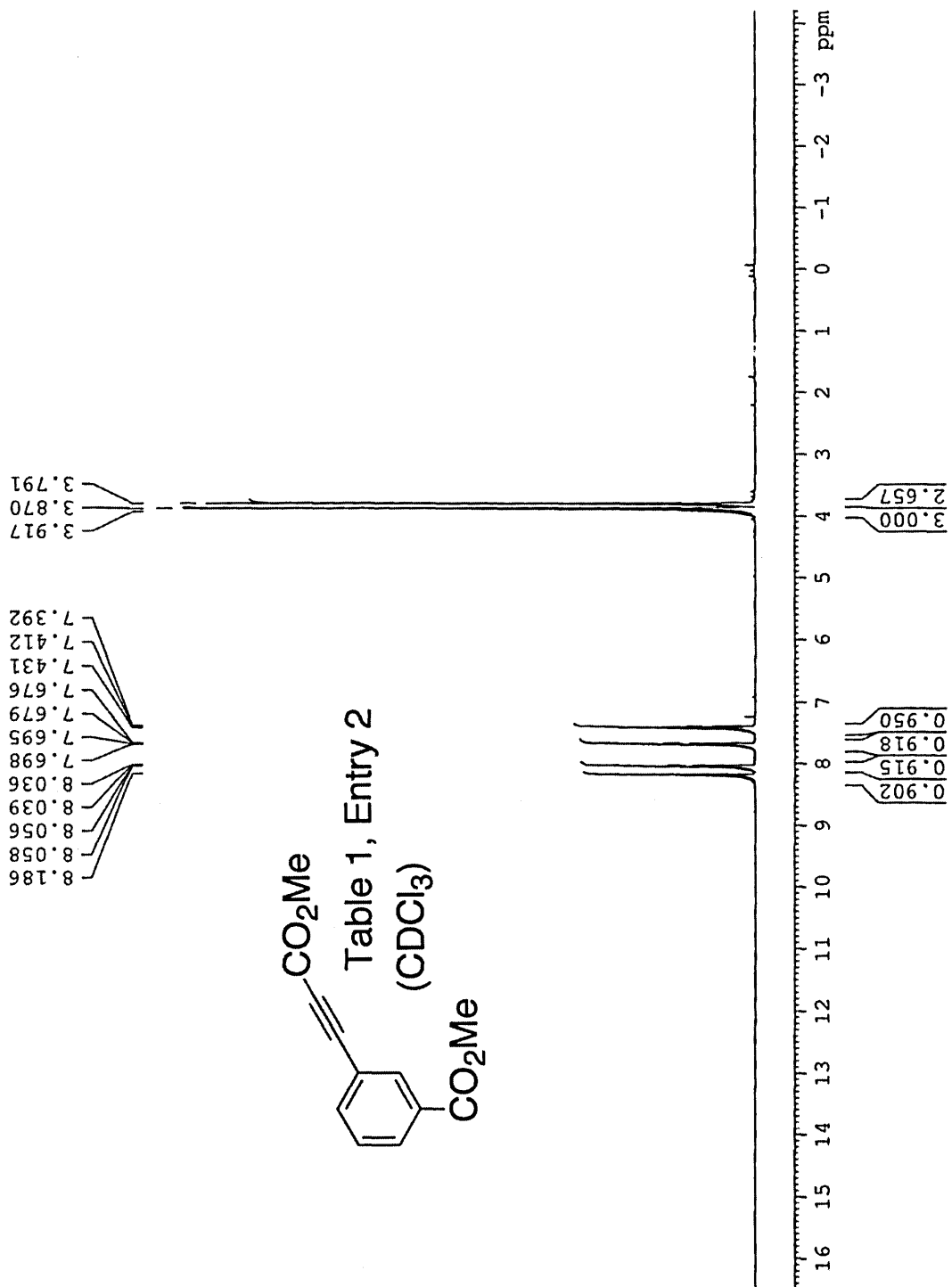0750 mmol, 7.5 mol %), Cs$_2$CO$_3$ (813 mg, 2.50 mmol), acetonitrile (2.0 mL), 12 h, 80 °C. The product was purified by column chromatography on silica gel (eluting with hexanes) to provide the title compound as a clear oil (214 mg, 72%). ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.52 (t, J = 8.0 Hz, 2H), 7.36 (t, J = 7.6 Hz, 1H), 7.15 (t, J = 7.6 Hz, 1H), 6.41 (m, 1H), 5.52 (q, J = 6.8 Hz, 1H), 2.06 (qd, J = 2.8 Hz, J = 7.6 Hz, 2H), 1.39 (m, 2H), 1.10-1.28 (m, 10H), 0.79 (m, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ: 206.7, 134.1, 131.8, 128.7, 126.7 (q, J = 30.1 Hz), 126.5, 126.0 (q, J = 26.7 Hz), 123.3, 120.6, 32.1, 29.6, 29.5, 29.4, 29.3, 28.7, 22.9, 14.3. IR (neat, cm^{-1}): 2927, 2856, 1950, 1605, 1579, 1493, 1455, 1316, 1159, 1124, 1035, 763.

6-(4-Fluoro-phenyl)-hexa-4,5-dienenitrile (Table 4, Entry 6). The general procedure was used with 4-fluorobenzyl chloride (0.146 mL, 1.00 mmol), 1-decyne (0.234 mL, 1.30 mmol), PdCl$_2$(CH$_3$CN)$_2$ (6.5 mg, 0.025 mmol, 2.5 mol %), 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl 1 (36.0 mg, 0.0750 mmol, 7.5 mol %), Cs$_2$CO$_3$ (813 mg, 2.50 mmol), acetonitrile (2.0 mL), 12 h, 80 °C. The product was purified by column chromatography on silica gel (eluting with diethyl ether/hexanes, 1:1) to provide the title compound as a yellow oil (130 mg, 70%). ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.17 (q, J = 5.6 Hz, 2H), 6.90 (t, J = 8.4 Hz, 2H), 6.17 (m, 1H), 5.54 (q, J = 6.0 Hz, 1H), 2.32-3.47 (m, 4H). ^{13}C NMR (100 MHz, CDCl$_3$) δ: 204.9, 162.1 (163.3, 160.9, d, J = 246.4 Hz), 129.6 (129.77, 129.73, d, J = 4.0 Hz), 128.4 (128.45, 128.38, d, J = 7.0 Hz), 119.3, 115.6

(115.8, 115.5, d, J = 21.9 Hz), 96.2, 92.4, 24.7, 16.6. IR (neat, cm^{-1}): 2927, 2246, 1951, 1603, 1507, 1224, 1156, 879, 838.

3.800
3.839
3.850

3.000
2.842

6.984
6.986
6.990
6.993
7.005
7.007
7.011
7.014
7.085
7.088
7.091
7.095
7.164
7.167
7.170
7.183
7.186
7.189
7.256
7.277

0.958
0.947
0.965
1.030

CO$_2$Me

Table 1, Entry 1
(CDCl$_3$)

OMe

ppm

3.0   3.5   4.0   4.5   5.0   5.5   6.0   6.5   7.0   7.5   8.0

3.791
3.870
3.917

7.392
7.412
7.431
7.676
7.679
7.695
7.698
8.036
8.039
8.056
8.058
8.186

CO$_2$Me

Table 1, Entry 2

(CDCl$_3$)

CO$_2$Me

2.657
3.000

0.950
0.918
0.915
0.902

16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3 ppm

253

(CDCl₃)
Table 1, Entry 3

Table 1, Entry 4
(CDCl₃)

0.922
1.274
1.311
1.325
1.332
1.496
1.629
1.646
1.665
1.678
1.694
1.701
2.507
2.524
2.542

6.975
6.978
6.997
7.017
7.020
7.284
7.297
7.931
7.947
7.953
7.968
7.973
7.989

Me

Table 1, Entry 5
(CDCl$_3$)

F

F

CO$_2$H

ppm

1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5

3.663
11.725
2.016

2.060

1.039

1.000

256

Table 1, Entry 6
(CDCl$_3$)

3.867

6.948
6.951
6.955
6.957
6.969
6.971
6.976
6.978
7.148
7.152
7.154
7.158
7.208
7.211
7.214
7.227
7.230
7.233
7.302
7.322
7.341
7.388
7.392
7.394
7.400

3.000

0.969
0.982
1.016
1.046
2.981
1.981

ppm

0.000

7.207
7.210
7.220
7.223
7.259
7.261
7.266
7.271
7.273
7.279
7.281
7.291
7.293
7.317
7.324
7.330
7.337
7.569
7.572
7.576
7.579
7.775
7.780
7.785
7.795
7.800
7.804
8.535
8.539
8.547
8.552
8.752
8.756
8.757

(CDCl₃)

Table 1, Entry 7

1.029
1.249
1.033
1.000
1.022
1.012
1.001

16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 −1 −2 −3 ppm

3.941

7.378
7.385
7.394
7.568
7.574
7.579
7.583
7.592
7.603
7.624
8.037
8.041
8.058

MeO₂C

(CDCl₃)
Table 1, Entry 8

3.000

3.071
3.898
1.964

16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3 ppm

259

Table 2, Entry 1
(CDCl₃)

260

7.203
7.223
7.241
7.260
7.272
7.273
7.278
7.285
7.288
7.298
7.312
7.332
7.350
7.402
7.421
7.436
7.440
7.449
7.455
7.458

3.824

Table 2, Entry 4
(CDCl₃)

3.862
2.042
3.927

2.000

ppm
3
4
5
6
7
8
9
10
11
12

CO₂Me

Table 2, Entry 5 (CDCl₃)

2.0000
2.0450
2.0528
1.9433
2.5816
5.7710

[Integral]

Table 3, Entry 1
(CDCl$_3$)

0.673
0.682
0.702
1.009
1.029
1.050
1.060
1.069
1.089

3.671
3.836

6.897
6.919
7.301
7.310
7.331

5.825
8.682
1.747
3.060
2.000
1.936

ppm

7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0

263

1.471
1.477
1.493
1.498
1.508
1.569
1.587
1.605
1.618
1.624
1.640
1.642
2.278
2.284
2.291
2.296
2.302
2.308
2.314
2.320
2.326
3.708
3.713
3.719

7.198
7.201
7.203
7.218
7.221
7.236
7.241
7.282
7.285
7.295
7.301
7.304
7.309
7.319
7.323
7.369
7.372
7.388

Me

Table 3, Entry 4
(CDCl$_3$)

Cl

ppm

1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0

3.095
10.534
2.108
2.059
2.000
1.051
1.176
0.944
0.967

Peaks around 1.3-2.1 ppm region:
1.352, 1.368, 1.389, 1.405, 1.418, 1.423, 1.429, 1.437, 1.455, 1.474, 1.480, 1.494, 1.508, 1.512, 2.086, 2.093, 2.103, 2.111, 2.122, 2.129, 2.139, 2.147

Peaks around 5.5-6.1 ppm region:
5.528, 5.544, 5.561, 5.578, 6.096, 6.103, 6.111, 6.119, 6.127

Peaks around 7.1-7.3 ppm region:
7.141, 7.152, 7.163, 7.173, 7.184, 7.194, 7.213, 7.224, 7.226, 7.234, 7.237, 7.253, 7.256, 7.261, 7.276

Integration values: 3.880, 15.411, 2.348, 1.000, 0.966, 1.027, 4.333

Structure label: Me

Table 4, Entry 2
(CDCl₃)

Chemical shift axis: 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0 ppm

0.755
0.773
0.789
1.088
1.160
1.189
1.225
1.241
1.249
1.264
1.331
1.345
1.363
1.381
1.396
1.401
1.414
2.008
2.015
2.026
2.033
2.044
2.051
2.061
2.069

5.475
5.491
5.508
5.525
6.397
6.401
6.404
6.408
6.412
7.100
7.117
7.136
7.304
7.324
7.342
7.475
7.495
7.507
7.527

C_8H_{17}

CF_3

Table 4, Entry 4
(CDCl_3)

3.363
10.895
2.124
2.000
0.939
0.899
1.038
0.971
1.889

ppm
0
1
2
3
4
5
6
7
8
9
10

1.336
2.320
2.322
2.340
2.347
2.357
2.368
2.377
2.393
2.403
2.444
2.454
2.461
2.463
2.471

5.522
5.535
5.550
5.565
6.166
6.175
6.182
6.190
6.879
6.883
6.900
6.918
6.922
7.150
7.156
7.161
7.170
7.178
7.187
7.191
7.205

CN

F

Table 4, Entry 6
(CDCl$_3$)

4.000

0.901

0.831

1.934

1.923

ppm

0

1

2

3

4

5

6

7

8

9
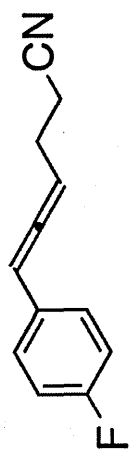
References

(1) Marsden, J. A.; Haley, M. M. Cross-Coupling Reactions to sp Carbon Atoms. In *Metal-Catalyzed Cross-Coupling Reactions*, 2nd Ed.: de Meijere, A.; Diederich, F. Eds; Wiley-VCH: Weinheim, 2004, pp. 317-394.

(2) Castro, C. E.; Stephens, R. D. *J. Org. Chem.* **1963**, *28*, 2163.

(3) Dieck, H. A.; Heck, F. R. *J. Organomet. Chem.* **1975**, *93*, 259.

(4) (a) Sonogashira, K. *J. Organomet. Chem.* **2002**, *653*, 46. (b) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron* **1975**, *16*, 4467. (c) Sonogashira, K.; Yatake, T.; Tohda, Y.; Takahashi, S.;. Hagihara, N. *J. Chem. Soc., Chem. Commun.* **1977**, 291. (d) Tohda, Y.; Sonogashira, K.; Hagihara, N. *Synthesis* **1977**, 777. (e) Takahashi, S.; Kuroyama, Y.; So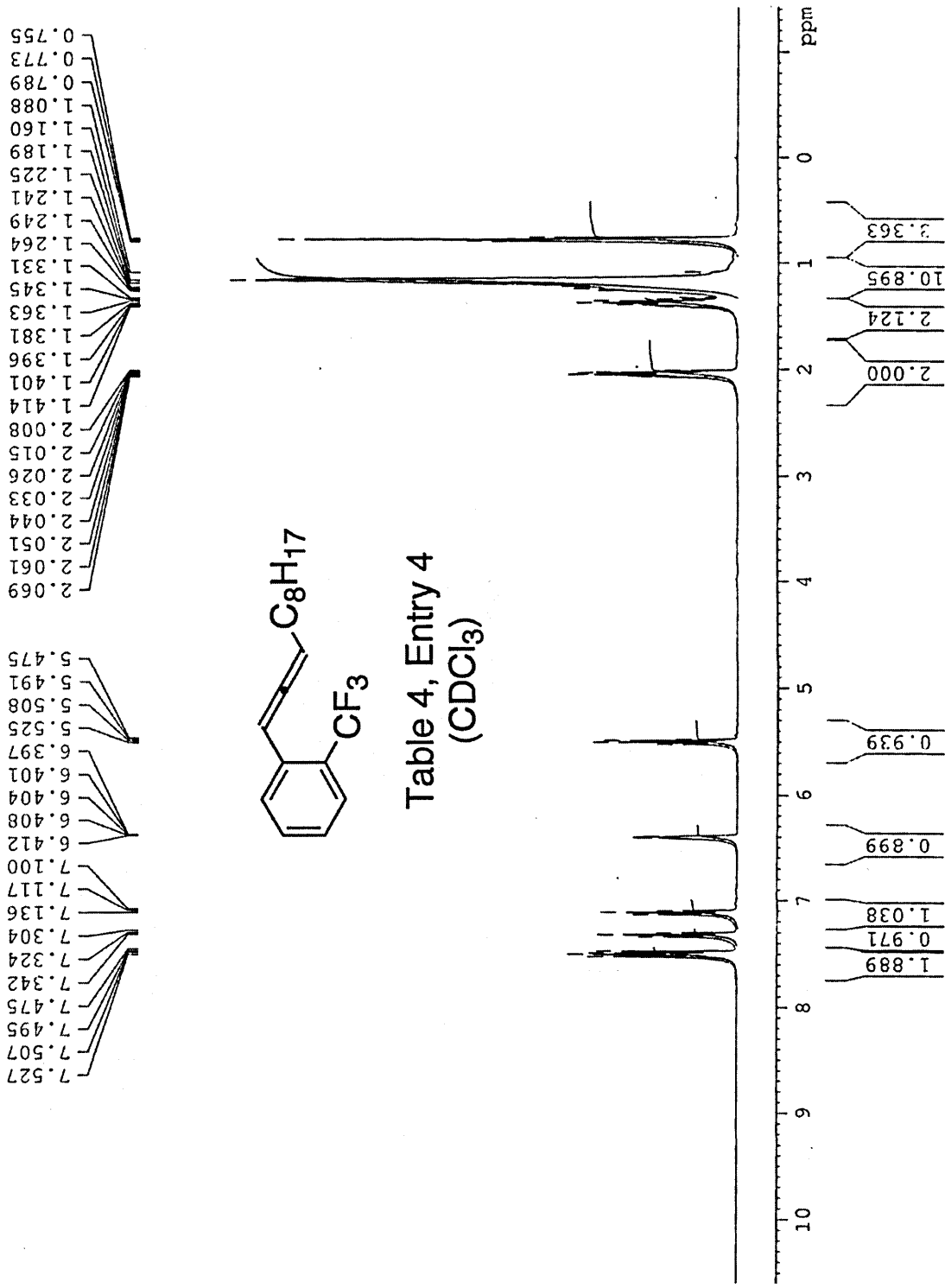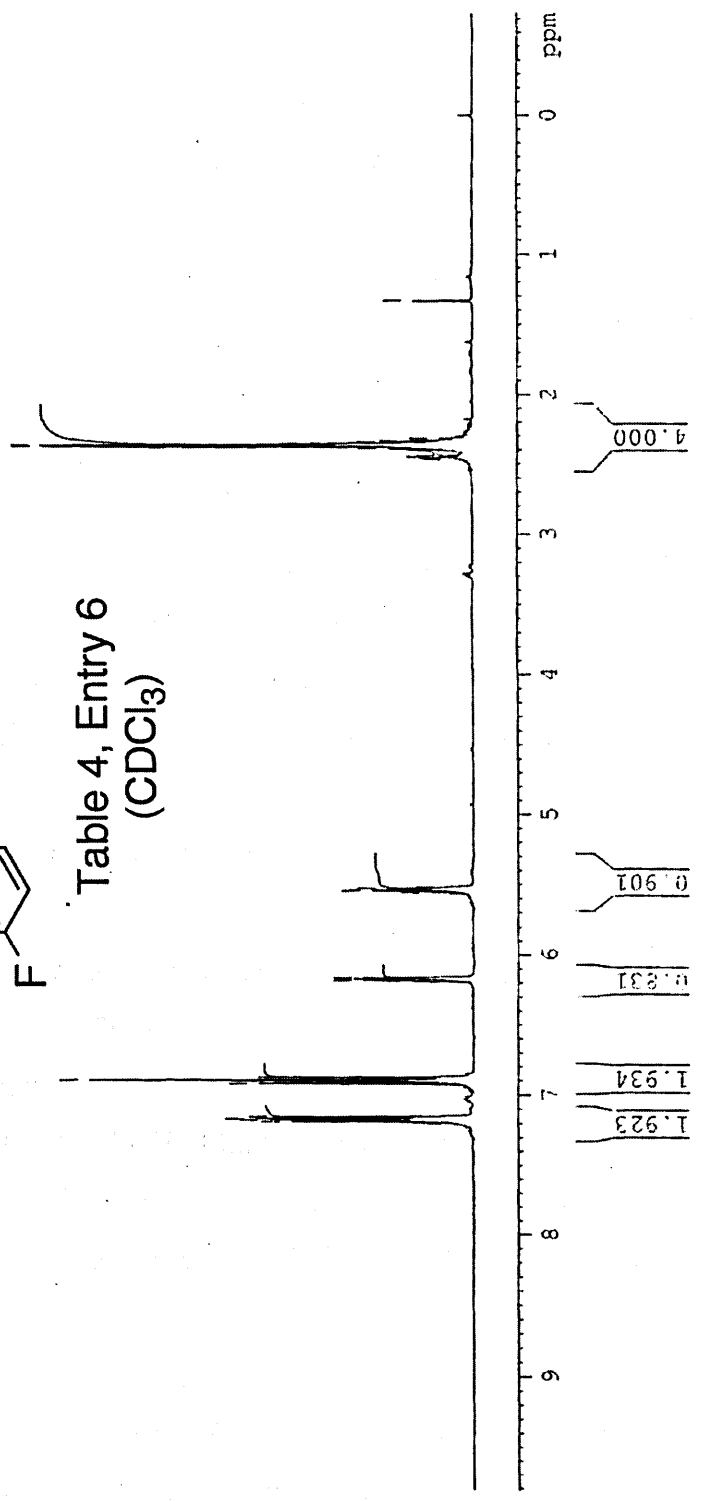nogashira, K.; Hagihara, N. *Synthesis*, **1980**, 627. (f) Sonogashira, K. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F. Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998, pp. 203-229. (g) Sonogashira, K. In *Handbook on Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley-Interscience: New York, 2002; pp. 493-529. (h) Rotovelomanana, V.; Linstrumelle, G. *Tetrahedron Lett.* **1981**, *22*, 315.

(5) Amatore, C.; Jutand, A. *J. Organomet. Chem.* **1999**, *576*, 254.

(6) Negishi, E.; Anastasia, L. *Chem. Rev.* **2003**, *103*, 1979.

(7) Negishi, E. In *Aspects of Mechanism and Organometallic Chemistry*; Brewster, J. H., Ed.; Plenum Press: New York, 1978; pp. 285-317.

(8) Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340.

(9) Negishi, E.; Coperet, C.; Liou, S. –Y.; Liu, F.; Ma, S. *Chem. Rev*, **1996**, *96*, 365.

(10) (a) Glaser, C. *Ber. Dtsch. Chem. Ges.* **1969**, *2*, 42. (b) Hay, A. S. *J. Org. Chem.* **1962**, *27*, 3320. (c) Siemsen, P.; Livingston, R. C.; Diederich, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 2632.

(11) (a) Sonogashira, K. *J. Organomet. Chem.* **2002**, *653*, 46. (b) Tykwinski, R. R. *Angew. Chem., Int. Ed.* **2003**, *42*, 1566. (c) Mori, A.; Kawashima, J.; Shimada, T.; Suguor, M.; Hirabayashi, K.; Nishihara, Y. *Org. Lett.* **2000**, *2*, 2935. (d) Liao, Y.; Fathi, R.; Yang, Z. *Org. Lett.* **2003**, *5*, 909.

(12) For metal-free Sonogashira-type couplings, see: (a) Leadbeater, N. E.; Marco, M.; Tominack, B. J. *Org. Lett.* **2003**, *5*, 3919. (b) Cheng, J.; Sun, Y.; Wang, F.; Guo, M.; Xu, J.; Pan, Y.; Zhang, Z. *J. Org. Chem.* **2004**, *69*, 5428. (c) Urgaonkar, S.; Verkade, J. G. *J. Org. Chem.* **2004**, *69*, 5752.

(13) (a) Bohm, V. P. W.; Herrmann, W. A. *Eur. J. Org. Chem.* **2000**, *22*, 3679. (b) Hundertmark, T.; Littke, A. F.; Buchwald, S. L.; Fu, G. C. *Org. Lett.* **2000**, *2*, 1729.

(14) Kollhofer, A.; Pullmann, T.; Plenio, H. *Angew. Chem., Int. Ed.* **2003**, *42*, 1056.

(15) Eckhardt, M.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 13642.

(16) Gelman, D.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2003**, *42*, 5993.

(17) For recent reports of alkynylation reactions conducted in water or water/organic biphasic reaction solvents: (a) Liang, B. Dai, M.; Chen, J.; Yang, A. *J. Org. Chem.* **2005**, *70*, 391. (b) Zhang, G. *Synlett* **2005**, *4*, 619. (c) Mohamed Ahmed, M. S.; Mori, A. *Tetrahedron* **2004**, *60*, 9977. (d) Wolf, C.; Lerebours, R. *Org. Biomol. Chem.* **2004**, *2*, 2161. (e) Bhattacharya, S.; Sengupta, S. *Tetrahedron Lett.* **2004**, *45*, 8733.

(18) For some examples of electrophilic ipso-substitution reactions, see: (a) Bartlett, P. D.; Roha, M.; Stiles, R. M. *J. Am. Chem. Soc.* **1954**, *76*, 1954. (b) Kurashov, M. V.; Perchenko, V. N.; Abubakirov, R. Sh.; Filatova, M. F. *Neftekhimiya* **1989**, *29*, 707. (c) Colonna, Martino; Greci, Lucedio; Poloni, Marino. J. Chem. Soc., Perkin Trans. 2 **1981**, 628.

(19) (a) Use of electron-deficient zinc acetylides allows coupling with aryl halides: Negishi, E.; Anastasia, L. *Chem. Rev.* **2003**, *103*, 1979 and references within. (b) Use of K_2CO_3 allows the coupling of electron-deficient terminal alkynes and electron-deficient or neutral aryl iodides: Eckert, T.; Ipaktschi, J. *Syn. Comm.* **1998**, *28*, 327. (c) Use of K_2CO_3 allows the coupling of electron-deficient terminal alkynes and diphenyliodonium salts: Radhakrishnan, U.; Stang, P. J. *Org. Lett.* **2001**, *3*, 859. (d) Water was essential to the coupling reaction of aryl iodides and various alkynoates: Uozumi, Y.; Kobayashi, Y. *Heterocycles* **2003**, *59*, 71.

(20) a) Perez, I.; Sestelo, J. P.; Sarandeses, L. A. *J. Am. Chem. Soc.* **2001**, *123*, 4155. b) Qian, M.; Negishi, E. *Tetrahedron Lett.* **2005**, *46*, 2927.

(21) Pottier, L. R.; Peyrat, J. –F.; Alami, M.; Brion, J. –D. *Synlett* **2004**, *9*, 1503.

(22) S. –T. Lin, L. –C. Chen *J. Chem. Res. Synop.* **2004**, *5*, 353.

(23) Shen, W.; Le, W. *J. Org. Chem.* **1999**, *64*, 8873.

(24) Novak, I.; Ng, S. –C.; Mok, C. –Y.; Huang, H. –H.; Fang, J.; Wang, K. K. T. *J. Chem. Soc. Perkin Trans 2* **1994**, 1771.

(25) Yang, U. –C.; Luh, T. –Y. *J. Org. Chem.* **2003**, *68*, 9870.

(26) Kunishima, M.; Nakata, D.; Tanaka, S.; Hioki, K.; Tani, S. *Tetrahedron* **2000**, *56*, 9927.

(27) Qian, M.; Negishi, E. *Tetrahedron Lett.* **2005**, *46*, 2927.

(28) Friary, R.; Seidl, V. *J. Org. Chem.* **1986**, *51*, 3214.

(29) Elsevier, C. J.; Vermeer, P. *Journal of Organic Chemistry* **1989**, *54*, 3726.

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HONORS, AWARDS, AFFILIATIONS

Wyeth Pharmaceutical Scholar Award   2005
American Chemical Society   2004-Present
National Institutes of Health Cancer Training Grant   2004-2005
Excellence in Teaching by a Graduate Student at MIT   2002-2003
Sigma Xi-The University of Michigan Chapter   2000-2003
Parke-Davis Colleague Recognition Award for Technical Assistance   2000

PATENTS

Buchwald, S. L. Anderson, K. W. "Transition-Metal-Catalyzed Carbon-Nitrogen and Carbon-Carbon Bond-Forming Reactions" US Patent Application # 11/328,426 (2006).

PUBLICATIONS

Anderson, K. W. Ikawa, T. Tundel, R. E. Buchwald, S. L. "Palladium-Catalyzed C-O Bond-Formation: The Synthesis of Phenols and Oxygen Heterocycles from Aryl Halides" J. Am. Chem. Soc. **2006**, in preparation.

Larsen, C. H. Anderson, K. W. Tundel, R. E. Buchwald, S. L. "Palladium-Catalyzed Heck Alkynylation of Benzyl Chlorides" Synlett **2006**, submitted.

Anderson, K. W. Tundel, R. E. Ikawa, T. Altman, R. A. Buchwald, S. L. "Monodentate Phosphines Provide Highly Active Catalyst for Palladium-Catalyzed C-N Bond-Forming Reactions of Heteroaromatic Halides/Amines and (H)N-Heteraromatics" Angew. Chem. Int. Ed. **2006**, submitted.

Billingsley, K. L. Anderson, K. W. Buchwald, S. L. "A Highly Active Catalyst for Suzuki-Miyaura Cross-Coupling Reactions of Heteroaryl Compounds" Angew. Chem. Int. Ed. **2006**, (Advanced Article).

Tundel, R. E. Anderson, K. W. Buchwald, S. L. "Expedited Palladium-Catalyzed Amination of Aryl Nonaflates through the use of Microwave Irradiation and Soluble Organic Amine Bases " J. Org. Chem. **2006**, 71, 430.

Anderson, K. W. Buchwald, S. L. "General Catalysts for the Suzuki-Miyaura and Sonogashira Coupling of Aryl Chlorides and for the Coupling of Challenging Substrate Combinations in Water" Angew. Chem. Int. Ed. **2005**, 44, 6173; Angew. Chem. **2005**, 117, 6329.

Klapars, A. Parris, S. Anderson, K. W. Buchwald, S. L. "Synthesis of Medium Ring Nitrogen Heterocycles via a Tandem Copper-Catalyzed C-N Bond Formation-Ring-Expansion Process." J. Am. Chem. Soc. **2004**, 126, 3529.

Anderson, K. W. Mendez-Perez, M. Priego, J. Buchwald, S. L. "Palladium-Catalyzed Amination of Aryl Nonaflates" J. Org. Chem. **2003**, 68, 9563.

Huang, X. Anderson, K. W. Zim, D. Jiang, L. Klapars, A. Buchwald, S. L. "Expanding Pd-Catalyzed C-N Bond-Forming Processes: The First Amidation of Aryl Sulfonates, Aqueous Amination, and Complementarity with Cu-Catalyzed Reactions" J. Am. Chem. Soc. **2003**, 125, 6653.

Anderson K. W. Tepe, J. J. "Trifluoromethanesulfonic Acid Catalyzed Friedel-Crafts Acylation of Aromatics with β-Lactams" Tetrahedron, **2002**, 58, 8475.

Anderson, K. W. Tepe, J. J. "First Intermolecular Friedel-Crafts Acylations with β-Lactams" Org. Lett. **2002**, 4, 459.

Anderson, K. W. Benedict, K. "Conducting a Flammable and Combustible Liquid Survey in Pharmaceutical Research Laboratories" Chemical Health and Safety, **2000**, 7, 20.