Recent Advances in Copper- and Palladium-Catalyzed Carbon–Heteroatom and Carbon-Carbon Bond–Formation

Ryan A. Altman

Submitted to the Department of Chemistry in Partial Fulfillment
of the Requirements for the Degree of Doctor of Philosophy
at the Massachusetts Institute of Technology

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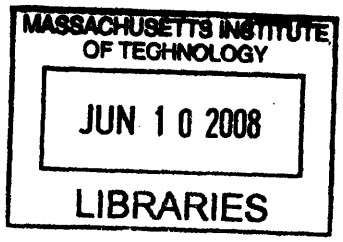

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ABSTRACT

Metal-catalyzed nucleophilic substitution reactions of aryl halides have become one of the most valuable and useful classes of reactions developed in the last 30 years. Foremost among these processes are the classes of palladium- and copper-catalyzed reactions, which employ heteroatom-based nucleophiles. Herein, newly designed catalyst systems are presented for the palladium- and/or copper-catalyzed nucleophilic substitution reactions of aryl halides with a variety of nucleophiles, including (benz)imidazoles, oxindoles, 2-, 3- and 4-hydroxypyridines, anilines, and aliphatic, benzylic, allylic and propargylic alcohols. In many cases, catalyst optimization and ligand structure are discussed and evaluated. Where applicable, the palladium- and copper-based catalyst systems are contrasted to demonstrate the complementary relationships between the employment of these two metals.

Chapter One ***Palladium- and Copper-catalyzed Reactions of Imidazoles and Benzimidazoles with Aryl Halides***

Chapter Two ***Orthogonal Selectivity in Copper- and Palladium-catalyzed Reactions of Aryl Halides with Oxindoles***

Chapter Three ***Copper-catalyzed Reactions of Hydroxypyridines and Related Compounds with Aryl Halides***

Chapter Four ***Pyrrole-2-carboxylic Acid as a Ligand for the Copper-catalyzed Reactions of Primary Anilines with Aryl Halides***

Chapter Five ***An Improved Copper-based Catalyst System for the Reactions of Aryl Halides with Aliphatic Alcohols***

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

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Mom and Dad, your encouragement and support of my academic development has cumulated in the pages bound within this book. Your unconditional love and guidance, has made me the man that I am. Kelly and Kyle, I hope I have been enough of the big brother that I should have been, and I hope that you have learned from my shortcomings. The support from the rest of my family has also helped me arrive at this point on my journey. Thank you, all.

Steve, I am grateful to you for providing me with a home, after the rough experience that was joining a research group. Although you were not in my original list for group selection (and I'm sure that you won't ever forget that, or let me forget that), I would not trade my experience and development as a Buchwaldian for those from another group. Thank you for allowing me the freedom to express myself though my chemistry, but also for steering me in the right direction when I drifted astray.

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PREFACE

Parts of this thesis have been reproduced with permission from the American Chemical Society from the following articles written or co-written by the author:

"4,7-Dimethoxy-1,10-phenanthroline: An Excellent Ligand for the Cu-Catalyzed N-Arylation of Imidazoles"
Altman, R. A.; Buchwald, S. L.
Org. Lett. **2006**, *8*, 2779-2782.

"Cu-Catalyzed *N*- and *O*-Arylation of 2-, 3- and 4-Hydroxypyridines and Hydroxyquinolines"
Altman, R. A.; Buchwald, S. L.
Org. Lett. **2007**, *9*, 643-646.

"Copper-catalyzed *N*-Arylation of Imidazoles and Benzimidazoles"
Altman, R. A.; Koval, E. D.; Buchwald, S. L.
J. Org. Chem. **2007**, *72*, 6190-6199.

"An Improved Cu-Based Catalyst System for the Reactions of Alcohols with Aryl Halides"
Altman, R. A.; Shafir, A.; Choi, A. C.; Lichtor, P. A.; Buchwald, S. L.
J. Org. Chem. **2008**, *73*, 284-286.

"Pyrrole-2-carboxylic Acid as a Ligand for the Cu-catalyzed Reactions of Primary Anilines with Aryl Halides"
Altman, R. A.; Anderson, K. W.; Buchwald, S. L.
Manuscript submitted for publication.

"Orthogonal Pd- and Cu-based Catalyst Systems for the C- and N-Arylation of Oxindoles"
Altman, R. A.; Hyde, A. M.; Huang, X.; Buchwald, S. L.
Manuscript submitted for publication.

Part of this thesis has been adapted from the following article co-written by the author:

"Monodentate Phosphines Provide Highly Active Catalysts for Pd-Catalyzed C–N Bond-forming Reactions of Heteroaromatic Halides/Amines and (H)N–Heterocycles"
Anderson, K. W.; Tundel, R. E.; Ikawa, T.; Altman, R. A.; Buchwald, S. L.
Angew. Chem. Int. Ed. **2006**, *45*, 6523-6527.

RESPECTIVE CONTRIBUTIONS

This thesis contains work that is the result of collaborative efforts between the author and other workers at MIT. An overview of the each authors' contribution is included below.

In Chapter 1, Ms. Erica Koval helped prepare the examples of the Cu-catalyzed reactions of benzimidazoles with aryl bromides, and helped repeat examples of the Cu-catalyzed coupling reactions of imidazoles with aryl bromides and iodides. In Chapter 2, Dr. Xiaohua Huang first observed the chemoselectivity demonstrated by the Pd-based catalyst in the cross-coupling reactions of oxindole with aryl halides. The computational studies of the Cu- and Pd-catalyzed reactions of oxindoles with aryl halides were performed by Mr. Alan Hyde. The crystal structure of **13'** was measured and solved by Dr. Peter Müller. In Chapter 4, Dr. Kevin W. Anderson performed some preliminary screening experiments for the Cu-catalyzed reactions of anilines with aryl halides. In Chapter 5, Dr. Alexandr Shafir and Mr. Phillip A. Lichtor optimized the reaction conditions for the Cu-catalyzed cross-coupling reactions of alcohols with aryl halides, and provided examples. Ms. Alice Choi provided further examples of this reaction.

The balance of the work presented in this thesis was performed by the author.

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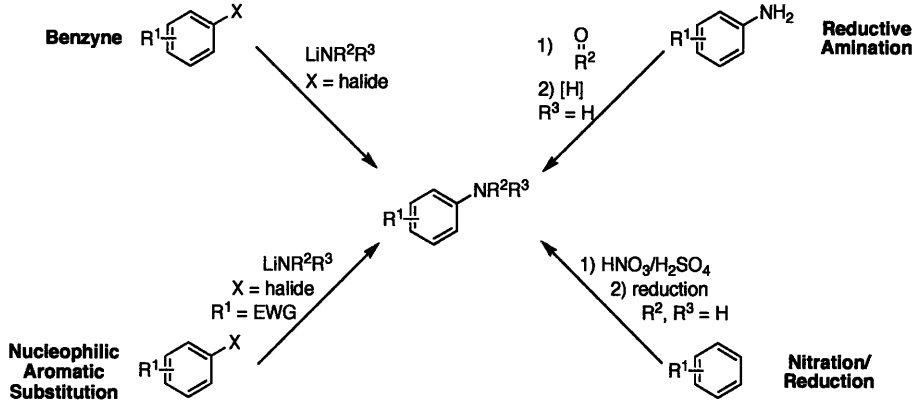
Introduction

Preparations of Aromatic Amines

Aryl amines are a common motif in many biologically active compounds including those with potential therapeutic applications.[1] These structures are also found in conducting and photographic materials as well as electroluminecent devices.[2] Further, *N*-aryl amines serve as intermediates for the synthesis of heterocycles,[3] and for the chemical synthesis of interesting molecules.[1,4]

Non-metal-mediated routes for the preparation of N-substituted anilines involve benzyne chemistry,[5] by reductive amination,[6] by an arene nitration/reduction sequence,[6] and by nucleophilic aromatic substitution of an activated aryl halide (Figure 1).[7]

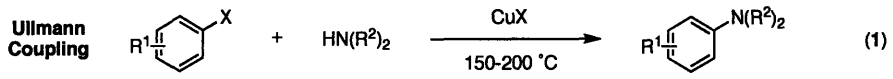
Figure 1. Non-metal-catalyzed Preparations of Aromatic Amines



The stringent conditions required by these methods (strong acid or base, high reaction temperatures, use of stoichiometric metal reagents) and the inherent problems in achieving high regioselectivity render these methods ill-suited for preparing certain targets. Additionally,

employing these strategies makes it difficult to rapidly and directly assemble multiple analogs of a given target (core structure) in a simple fashion using mild conditions.[8-9]

A classical transition-metal mediated approach to form C–heteroatom bonds developed by Ullmann[10] and Goldberg,[11] involves Cu-mediated reactions of amines, phenols or amides with aryl iodides (eq. 1). However, these reactions are severely limited by the harsh conditions often required–exposure of substrates to high temperatures, typically 150-200 °C, for extended periods of time using super-stoichiometric quantities of a copper compound.[12]

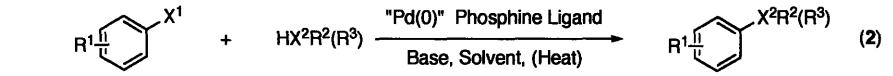


(1)

These limitations have led to the development of new complementary methods based on metal-catalyzed cross-coupling reactions between amines and aryl halides. The newer Cu-[9] and Pd-[8] based methodologies allow for the rapid, direct and efficient preparation of a wide variety of *N*-aryl compounds under conditions that are mild enough to tolerate sensitive functional groups.

Palladium-catalyzed Aryl–Heteroatom Bond Formation

Early reports of Ni-[13] and Pd-catalyzed[14] C-heteroatom bond formation using aryl halides and sulfonate esters remained dormant for decades until extensive work by the groups of Buchwald[8] and Hartwig[15] significantly improved the reliability, generality, functional group tolerance, and substrate scope of these reactions. Currently, these reactions are practiced on a regular basis in industrial[16] and academic laboratories (eq. 2).[3-4]



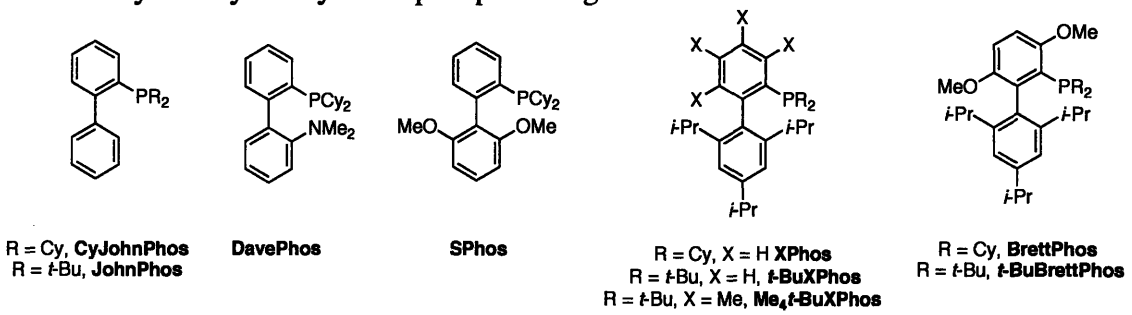
(2)

X^1 = I, Br, Cl, OTs, OTf X^2 = N, O, P, S

Both groups have contributed to the elucidation of the mechanism of Pd-catalyzed C-heteroatom bond-forming reactions.[8,15,17] For the Pd-catalyzed amination of aryl halides using the

dialkyl biarylmonophosphine ligands developed in our laboratory (Figure 2), oxidative addition of an aryl halide to an $L_1Pd(0)$ complex affords the $L_1Pd(II)(Ar)(X)$ complex (Figure 3). A two-step transmetallation reaction occurs, involving coordination of an amine to the metal followed by deprotonation of the acidified N–H bond, to generate an $L_1Pd(II)(Ar)(NR'R'')$ species. Subsequently, reductive elimination provides the N-aryl amine, and regenerates the active $L_1Pd(0)$ species.

Figure 2. Bulky Dialkyl Biarylmonophosphine Ligands



R = Cy, **CyJohnPhos**
R = *t*-Bu, **JohnPhos**

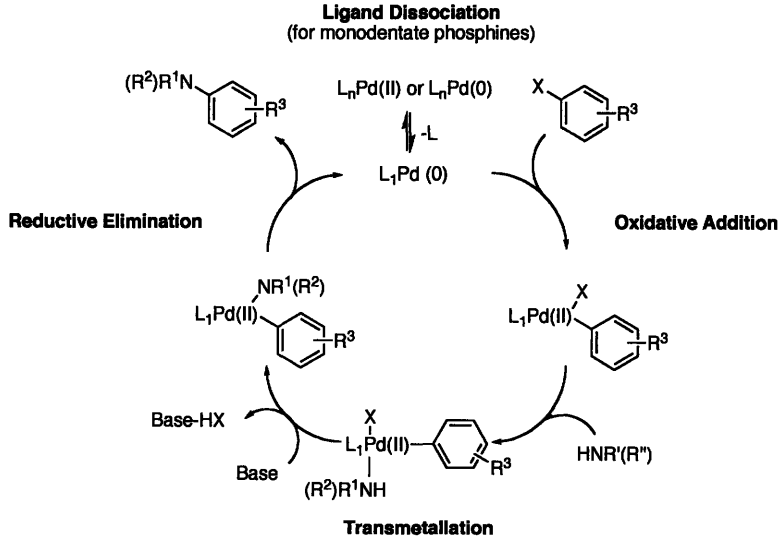
DavePhos

SPhos

R = Cy, X = H **XPhos**
R = *t*-Bu, X = H, ***t*-BuXPhos**
R = *t*-Bu, X = Me, **Me$_4$*t*-BuXPhos**

R = Cy, **BrettPhos**
R = *t*-Bu, ***t*-BuBrettPhos**

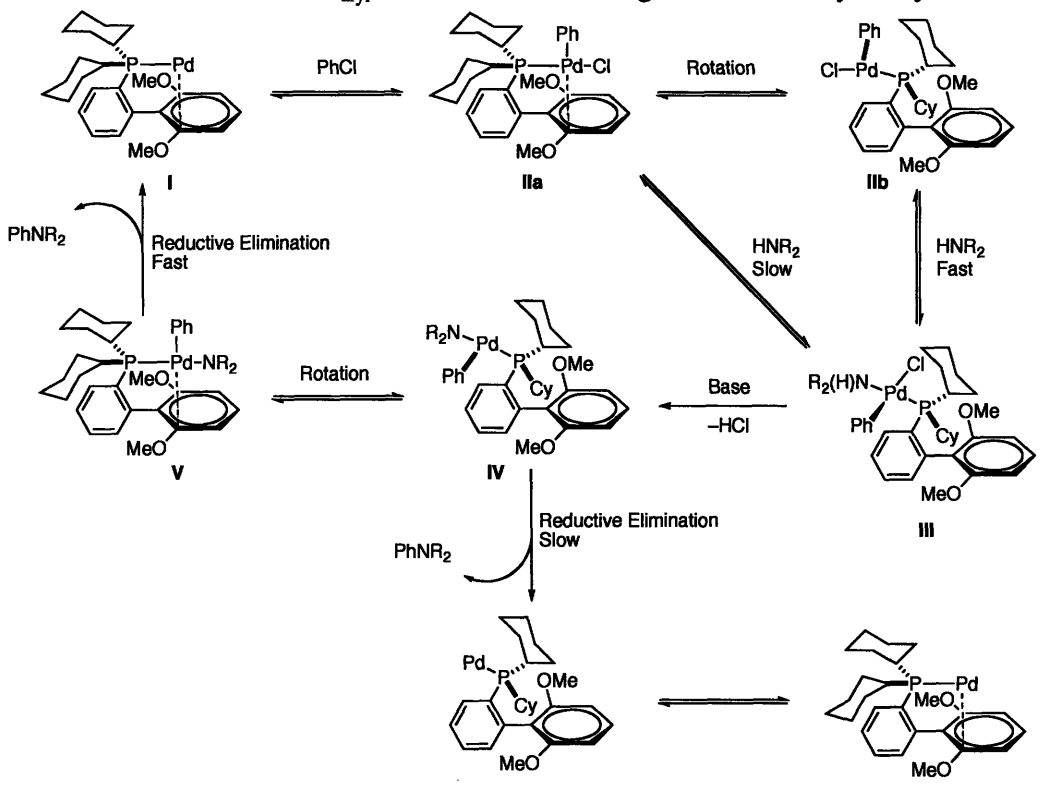
Figure 3. Catalytic Cycle for Palladium-catalyzed Amination Reactions of Aryl Halides



Several properties of dialkylbiarylmonophosphine compounds make this class of ligand attractive for practical use. In general, the crystalline state of the pure compounds and their high stability towards oxidation[18] make them easy for users to manipulate under ambient conditions. Catalytically, when employing bulky biarylmonophosphine ligands, both the oxidative addition, and reductive elimination steps of the catalytic cycle are accelerated due to the electron-donating ability and steric bulk of the ligands, respectively. The size of the ligand encourages formation of the active $L_1Pd(0)$ complex, as opposed to an $L_2Pd(0)$ complex, which resides outside of the catalytic cycle. Further, certain pathways of catalyst decomposition are retarded when employing this class of ligand.[19]

Computational analyses of the metal complexes at various stages of the catalytic cycle have further detailed the participation of the biarylmonophosphine ligands over the course of the reaction.[20-21] Specifically, rotation of the ligand about the P–C_{aryl} bond facilitates the various fundamental organometallic reactions within the catalytic cycle (Scheme 1). First, the $L_1Pd(0)$ species (**I**) and the $L_1Pd(Ar)(X)$ oxidative addition product (**IIa**) are likely stabilized by interactions between the Pd atom and π-electrons from the lower ring of the biaryl moiety (e.g. XPhos), or a substituent on the lower ring (e.g. SPhos).[20] Second, the coordination and deprotonation events of the transmetallation (**IIb→III→IV**) reaction likely occur after the P–C_{aryl} bond rotates so that the metal is distal to the lower biaryl ring, thus preventing the ligand from sterically shielding the electrophilic metal from the nucleophile during the transmetallation step.[21] Most likely, rotation of the P–C_{aryl} bond occurs prior to the reductive elimination step, repositioning the metal above the lower biaryl ring (**V**). This event forces the amine and aryl ligands into a *cis*-relationship, and encourages C–N bond-formation through steric compression.[21]

Scheme 1. Rotation about the P–C_{aryl} Bond at Various Stages of the Catalytic Cycle

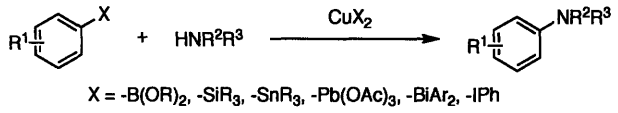


While the preceding discussion considered an amine as the nucleophile, the catalytic cycle is analogous for other substrates, such as alcohols. However, for other nucleophiles, the rate-determining step might be the reductive elimination, as opposed to transmetallation.[22]

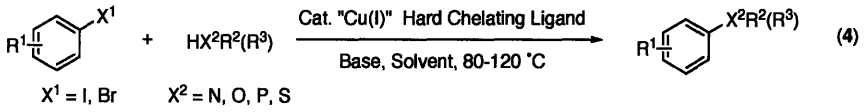
Copper-catalyzed Aryl–Heteroatom Bond Formation

Recent work initiated by Lam, Chan and Evans has employed various stoichiometric reagents as electrophilic components for Cu-mediated heteroatom-arylation reactions including, aryllead triacetates,[23] arylboronic acids,[24] triarylbismuths,[25] hypervalent aryl siloxanes,[26] diaryl iodonium salts,[27] and arylstannanes (eq. 3).[28] While these reactions generally operate at room temperature, as opposed to the high temperatures normally employed in traditional Ullmann reactions, they typically require stoichiometric quantities of copper. A second major drawback of

these methods is the required use of toxic and/or unstable reagents that are generally accessed from aryl iodides or bromides. Furthermore, in some cases, only one of multiple aryl groups is transferred to the nucleophile. The direct use of aryl halides as the electrophilic coupling partner resolves many of these drawbacks.



A plethora of new hard-chelating ligands has been reported in the last decade, which allow the Ullmann and Goldberg reactions to be run under significantly milder conditions– typically rt-120 °C using weak inorganic bases. This development has greatly improved the substrate scope, functional group tolerance and selectivity of these reactions (eq. 4).[9]



Despite the progress in this field, the development of newer, more stable and more active Cu-catalyzed C–heteroatom bond forming reactions has been limited by the poor understanding of the catalytic cycle. Although the Ullmann Reaction is over 100 years old, few formal studies of have shed light into its mechanism.[9,12] The following discussion will consider the arylation of N–H-containing nucleophiles. At this point, it will be assumed that the mechanism is the same for other nucleophiles.

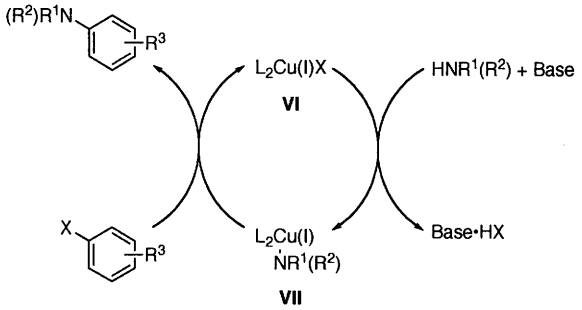
Historically, one reason why Cu-catalyzed arylation reactions of amines with aryl halides have historically been difficult to study is that Cu(0), Cu(I) and Cu(II) salts and complexes all provide active catalysts.[9] Although the crystal structure of an isolated ligated Cu(II) complex, suggests that a Cu(II) species is the catalytically active precursor,[29] more compelling evidence involving electron paramagnetic resonance (EPR) studies and detailed

heterogeneous/homogenous studies run with Cu precursors at 0, +1 and +2 oxidation states suggest that Cu(I) is the active precatalyst.[30-31]

Although mechanisms involving addition-elimination mechanism *via* a Meisenheimer complex have been proposed,[32] the strong trend observed in leaving group reactivity of I > Br >> Cl >> F for Cu-catalyzed processes indicates that the rate limiting step involves the C-halogen bond cleavage, as opposed to rate-limiting addition of the nucleophile.[33]

One plausible proposal has drawn similarities between the Pd(0)/Pd(II)-based catalyst system and a potential Cu(I)/Cu(III)-based catalysts systems–both involving metals with d^{10}/d^8 electronic configurations–and suggested that the individual steps of the Cu catalytic cycle mimic those of the Pd-catalyzed mechanism, that is, oxidative addition, followed by transmetallation and reductive elimination.[34] However, this mechanism is unlikely to occur, as kinetic evidence obtained from catalytic and stoichiometric Cu(I)-catalyzed amidation reactions of aryl iodides indicates that transmetallation precedes aryl halide activation (Figure 4).[35]

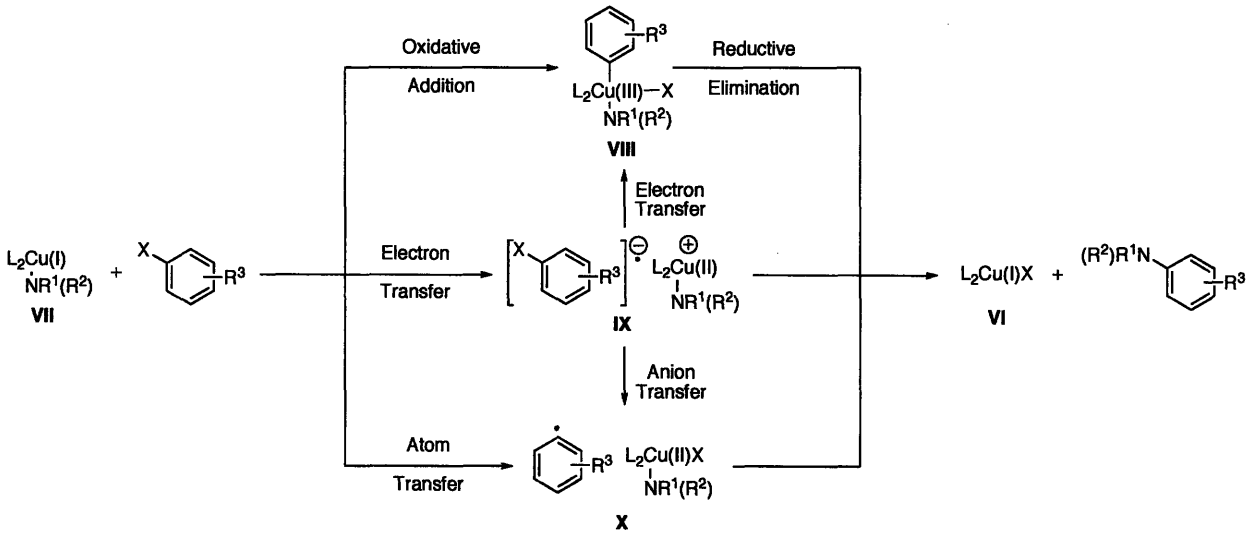
Figure 4. Proposed Cu(I)-Cu(III) Based Mechanism for Amination of Aryl Halides



Several potential mechanisms have been proposed for the aryl halide activation event (Figure 5). After transmetallation, rate-limiting oxidative insertion of Cu(I) into the C–halogen bound could potentially generate a Cu(III) intermediate (**VII**), which would reductively eliminate

the C–N bond to regenerate the $L_2Cu(I)X$ species (**VI**).[36] Critics of this mechanism argue that the existence of an instable Cu(III) intermediate within the catalytic cycle is unlikely. However, Cu(III) complexes have been isolated, characterized and reported, thus reinforcing the possibility of a short-lived, high-energy Cu(III) species.[37] Although the oxidative addition/reductive elimination pathway has been computationally supported,[38] this mechanistic proposal neglects the existence of the Cu(II) and organic radical species that have been observed by EPR in Goldberg reactions.[39-40]

Figure 5. Potential Mechanisms for Aryl Halide Activation During Cu-Catalyzed Amination Reactions



Reasonable mechanisms, which account for this observation, invoke electron transfer and atom transfer processes, which would generate Cu(II) intermediates (**IX**, **X**). An atom transfer reaction between the aryl halide and **VII** would provide a Cu(II) species and an aryl radical (**X**), which can decompose to provide the product by solvolytic, anion transfer, or oxidative substitution (**XI→VIII**) mechanisms.[41] Electron transfer from **VII** to an aryl halide would

generate Cu(II) and an anionic radical halide (**IX**).[40] From complex **IX**, a sequential electron transfer could generate **VIII**. This sequence of reactions would constitute an oxidative addition, and generate a Cu(III) intermediate, albeit by a radical mechanism as opposed to an insertion reaction. Alternatively, decomposition of **IX** into an aryl radical and a halide anion would form **IX**, which could then provide the product.[41-42]

According to these potential mechanisms, the hard-chelating ligands employed for these reactions help control the coordination sphere about the metal throughout the catalytic cycle and provide high concentrations of complex **VII** prior to the rate-determining aryl halide activation step.[43] Further, the electron-donating ability of the ligands drastically lowers the oxidation potential of the Cu(I)-Cu(II) couple, thus, stabilizing higher-oxidation state intermediates, and accelerating the aryl halide activation process.[35,44]

Complementary Pd- and Cu-Based Catalyst Systems

Mechanistically, Pd- and Cu-based catalyst systems can be differentiated by the order of the steps in the catalytic cycle; while oxidative addition is the first step for Pd-catalyzed process, transmetallation precedes the aryl halide activation step for Cu. This suggests that the ideal substrate scopes for the nucleophilic substitution reactions of catalysts derived from each metal might be complementary. For instance, Pd-based catalysts have proven highly efficient in the N-arylation of anilines under generally mild conditions.[8] In contrast, more limited success has been achieved for the N-arylation of N-containing heterocycles.[45] On the other hand, Cu-catalysts typically provide inefficient systems for the N-arylation of anilines with aryl iodides and bromides,[9,46] while they are highly active for the reactions of N–H heterocycles with aryl iodides and bromides.[47]

Foreword

The following thesis will attempt to compare and contrast both Pd- and Cu-based catalyst systems for C–heteroatom bond formation by highlighting the inherent differences in reactivity. In Chapter 1, Pd-based catalyst systems for the N-arylation of imidazoles with aryl halides will be discussed, as well as a newly designed Cu-based catalyst system that provides a highly active and stable system for this transformation. In Chapter 2, the orthogonal chemoselectivity of Pd- and Cu-based catalyst systems in reactions of oxindoles with aryl halides is explored, which generate either the C3- or N1-aryl products, respectively. Chapter 3 details a series of three Cu-based catalysts systems that successfully cross-couple 2-, 3-, and 4-hydroxypyridines and related compounds. Pd-based catalyst systems have historically proven unsuccessful in accomplishing these reactions. In Chapter 4, a general Cu-based catalyst system is developed for the cross-coupling of anilines with aryl iodides and bromides, a reaction that has been dominated by Pd-based catalyst systems for the last 10 years. In Chapter 5, an improved catalyst system is developed for the Cu-catalyzed cross-coupling of aliphatic, benzylic, allylic alcohols with aryl halides, reactions that typically provide high quantities of reduced arene when employing Pd-based catalysts. By studying the following pages, the reader should gain insight into the complementary relationship between Pd- and Cu-based catalyst systems for C-heteroatom bond-forming reactions.

References

(1) (a) Jensen, T. A.; Liang, X.; Tanner, D.; Skjaerbaek, N. *J. Org. Chem.* **2004**, *69*, 4936. (b) Tanoury, G. J.; Hett, R.; Wilkinson, H. S.; Wald, S. A.; Senanayake, C. H. *Tetrahedron: Asymmetry*, **2003**, *14*, 3487. (c) Kink, J. T.; Sorensen, B.; Liu, G.; Pei, Z.; Reilly, E. B.; Leitza, S.; Okasinski, G. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 973. (d) Johns, B. A.; Gudmundsson, K. S.;

Turner, E. M.; Allen, S. H.; Jung, D. K.; Sexton, C. J.; Boyd, F. L.; Peel, M. R. *Tetrahedron* **2003**, *59*, 9001. (e) Lee, J.; Reynolds, C.; Jetter, M. C.; Youngman, M. A.; Hlasta, D. J.; Dax, S. L.; Stone, D. J.; Zhang, S. P; Codd, E. E. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1879. (f) Sun, L. Q.; He, H.; Chen, J.; Wu, Y. J. *Tetrahedron Lett.* **2002**, *43*, 9291. (g) Gillet, L. C. J.; Scharer, O. D. *Org. Lett.* **2002**, *4*, 4205.

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

(3) For representative examples, see: (a) Martín, R.; Rivero, M. R.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2006**, *45*, 7079. (b) Movassaghi, M.; Hill, M. D. *J. Am. Chem. Soc.* **2006**, *128*, 4592. (c) Movassaghi, M.; Hill, M. D. *J. Am. Chem. Soc.* **2006**, *128*, 14254. (d) Martin, R.; Cuenca, A.; Buchwald, S. L. *Org. Lett.* **2007**, *9*, 5521. (e) Zheng, N.; Buchwald, S. L. *Org. Lett.* **2007**, *9*, 4749. (f) Jones, C. P.; Anderson, K. W.; Buchwald, S. L. *J. Org. Chem.* **2007**, *72*, 7968. (g) Martín, R.; Larsen, C. H.; Cuenca, A.; Buchwald, S. L. *Org. Lett.* **2007**, *9*, 3379. (h) Rodriguez Rivero, M.; Buchwald, S. L. *Org. Lett.* **2007**, *9*, 973. (i) Wagaw, S.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 10251.

(4) (a) Movassaghi, M.; Hunt, D. K.; Tjandra, M. *J. Am. Chem. Soc.* **2006**, *128*, 8126. (b) Movassaghi, M.; Ondrus, A. E. *Org. Lett.* **2005**, *7*, 4423. (c) Wang, X.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2003**, *125*, 6040. (d) Andersen, B. M. Andresen, B. M.; Caron, S.; Couturier, M.; DeVries, K. M.; Do, N. M.; Dupont-Gaudet, K.; Ghosh, A.; Girardin, M.; Hawkins, J. M.; Makowski, T. M.; Riou, M.; Sieser, J. E.; Tucker, J. L.; Vanderplas, B. C.; Watson, T. J. N. *Chimia* **2006**, *60*, 554. (e) Wrona, I. E.; Garbarda, A. E.; Evano, G.; Panek, J. S. *J. Am. Chem. Soc.* **2005**, *127*, 15026. (f) Fang, Y. Q.; Karisch, R.; Lautens, M. *J. Org. Chem.* **2007**, *72*, 1341. (g) Damon, D. B.; Dugger, R. W.; Hubbs, S. E.; Scott, J. M.; Scott, R. W. *Org. Process Res. Dev.* **2006**, *10*, 472. (h) Federsel, H.; Hedberg, M.; Qvarnström, F. R.; Sjögren, M. P. T.; Tian,

W. *Acc. Chem. Res.* **2007**, *40*, 1377.

(5) Heaney, H. *Chem. Rev.* **1941**, *28*, 81.

(6) (a) Larock, R. L. *Comprehensive Organic Transformations: A Guide to Functional Group Preparations*. VCH Publishers, Inc.: New York, 1989. (b) Smith, M. B.; March, J. *March's Advanced Organic Chemistry: Reactions, Mechanisms and Structure*. John Wiley & Sons. Inc.: New York, 2001.

(7) (a) Burnett, J. F.; Zahler, R. E. *Tetrahedron*, **1999**, *55*, 11399.

(8) (a) 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. (b) Surry, D. S.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2008**, *47, In Press.*

(9) (a) Monnier, F.; Taillefer, M. *Angew. Chem. Int. Ed.* **2008**, *47*, 3096. (b) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, 2337. (c) Ley, S. V.; Thomas, A. W. *Angew. Chem. Int. Ed.* **2003**, *42*, 5400. (d) Kunz, K.; Scholz, U.; Ganzer, D. *Synlett* **2003**, 2428.

(10) (a) Ullmann, F. *Ber. Dtsch. Chem. Ges.* **1903**, *36*, 2389. (b) Ullmann, F. *Ber. Dtsch. Chem. Ges.* **1904**, *36*, 853.

(11) Goldberg, I. *Ber. Dtsch, Chem. Ges.* **1906**, *39*, 1691.

(12) Lindley, J. *Tetrahedron* **1984**, *40*, 1433.

(13) Cramer, R.; Coulson, D. R. *J. Org. Chem.* **1975**, *40*, 2267.

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

(15) Hartwig, J. F. *Synlett*, **2006**, 1283.

(16) (a) Buchwald, S. L.; Mauger, C.; Mignani, G.; Scholz, U. *Adv. Synth. & Catal.* **2006**, *348*, 23. (b) Schlummer, B.; Scholz, U. *Adv. Synth. Catal.* **2004**, *346*, 1599.

(17) Shekhar, S.; Ryberg, P.; Hartwig, J. F.; Mathew, J. S.; Blackmond, D. G.; Strieter, E. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 3584-3591

(18) Barder, T. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 5096.

(19) (a) Strieter, E. R.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2006**, *45*, 925. (b) Strieter, E. R. Blackmond, D. G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 13978. (c) Singh, U. K., Strieter, E. R.; Blackmond, D. G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 14104.

(20) Barder, T. E.; Biscoe, M. R.; Buchwald, S. L. *Organometallics* **2007**, *26*, 2183.

(21) Barder, T. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 12003.

(22) (a) Hartwig, J. F. *Inorg. Chem.* **2007**, *46*, 1936. (b) Hartwig, J. F. *Angew. Chem. Int. Ed.* **1998**, *37*, 2046.

(23) Alvarado, L. L.; Avedaño, C.; Menéndez. J. C. *J. Org. Chem.* **1995**, *60*, 5678.

(24) (a) Lam, P. Y.; Clark, C. G.; Sauber, S.; Adams, J.; Winters, M. P.; Chan D. M. T.; Combs, A. *Tetrahedron Lett.* **1998**, *39*, 2941. (b) Collman, J. P.; Zhong, M.; Zhang, C.; Costanzo, S.; *J. Org. Chem.* **2001**, 66, 7892. (c) Lan, J. B.; Li, C.; Yu, X.; You, J. S.; Xie, R. G. *Chem. Commun.* **2004**, 188.

(25) Fedorov, A. Y.; Finet, J. P. *Tetrahedron Lett.* **1999**, *40*, 2747.

(26) Lam, P. Y. S.; Deudon, S.; Averill, K. M.; Li, R.; He, M. Y.; DeShong, P.; Clark, C. G. *J. Am. Chem. Soc.* **2000**, *122*, 7600.

(27) Kang, S. K.; Lee, S. H.; Lee, D. *Synlett* **2000**, 1022.

(28) Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Averill, K. M.; Chan, D. M. T.; Combs, A. *Synlett* **2000**, 674.

(29) Pu, Y. M.; Ku, Y. Y.; Grieme, T. Henry, R.; Bhatia, A. B. *Tetrahedron Lett.* **2006**, *47*, 149.

(30) Weingarten H. *J. Org. Chem.* **1964**, *29*, 3624.

(31) Paine, A. J. *J. Am. Chem. Soc.* **1987**, *109*, 1496.

(32) Ma, D.; Zhang, Y.; Yao, J.; Wu, S.; Tao, F. *J. Am. Chem. Soc.* **1998**, *120*, 12459.

(33) Weingarten, H. *J. Org. Chem.* **1964**, *29*, 977.

(34) (a) Ouali, A.; Spindler, J. F.; Jutand, A.; Taillefer, M. *Adv. Synth. Catal.* **2007**, *349*, 1906. (b) Xie, Y. X.; Pi, S. F.; Wang. J.; Yin, D. L.; Li, J. H. *J. Org. Chem.* **2006**, *71*, 8324. (c) Lu, Z.; Twieg, R. J. *Tetrahedron*, **2005**, *61*, 903.

(35) Strieter, E. R.; Bhayana, B.; Buchwald, S. L. *Submitted for publication.*

(36) (a) Bethell, D.; Jenkins, I. L.; Quan, P. M. *J. Chem. Soc., Perkin Trans. II*, **1985**, 1789. (b) Allred, G. D.; Liebeskind, L S. *J. Am. Chem. Soc.* **1996**, *118*, 2748. (c) Cristau, H. J.; Cellier, P. P.; Spindler, J. F.; Taillefer, M. *Chem. Eur. J.* **2004**, *10*, 5607.

(37) (a) Ribas, X.; Jackson, D. A.; Donnadieu, B.; Mahia, J.; Parella, T.; Xifra, R.; Hedman, B.; Hodgson, K. O.; Llobet, A.; Stack, T. D. P. *Angew. Chem. Int. Ed.* **2002**, *41*, 2991. (b) Dubois, J. L.; Mukherjee, P.; Stack, T. D. P.; Hedman, B.; Solomon, E. I.; Hodgson, K. O. *J. Am. Chem. Soc.* **2000**, *122*, 5775.

(38) Zhang, S. L.; Liu, L.; Fu, Y.; Guo, Q. X. *Organometallics*, **2007**, *26*, 4546.

(39) Arai, S.; Hida, M.; Yamagishi, T.; *Bull. Chem. Soc. Jpn.* **1978**, *51*, 277.

(40) Strieter E. R. Mechanistic Studies on Metal-Catalyzed Carbon-Nitrogen Bond Forming Reactions. Ph.D. Thesis, Massachusetts Institute of Technology, Cambridge, MA, June 2005.

(41) (a) Jenkins, C. L. Kochi, J. K. *J. Am. Chem. Soc.* **1972**, *94*, 843. (b) Jenkins, C. L. Kochi, J. K. *J. Am. Chem. Soc.* **1972**, *94*, 856.

(42) (a) Marquez, O. P.; Giulianelli, J. *J. Org. Chem.* **1976**, *41*, 739. (b) Andrieux, C. P.; Blocman, C.; Dumas-Bouchiat, J. M.; M'Halla, F.; Savéant, J. M. *J. Am. Chem. Soc.* **1980**, *102*, 3806.

(43) Strieter, E. R.; Blackmond, D. G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4120.

(44) Ouali, A.; Taillefer, M.; Spindler, J. F.; Jutand, A. *Organometallics*, **2007**, *26*, 65.

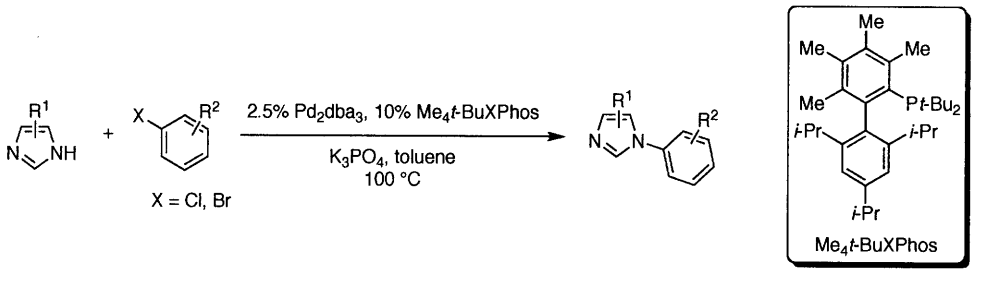
(45) (a) Anderson, K. W.; Tundel, R. E.; Ikawa, T.; Altman, R. A.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2006**, *45*, 6523. (b) Old, D. W.; Harris, M. C.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 1403.

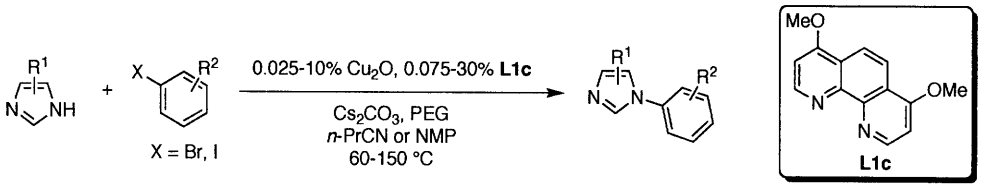
(46) (a) Gujadhur, R.; Venkataraman, D.; Kintigh, J. T. *Tetrahedron Lett.* **2001**, *42*, 4791. (b) Zhang, H.; Cai, Q.; Ma, D. *J. Org. Chem.* **2005**, *70*, 5164. (c) Rao, H.; Fu, H.; Jiang, Y.; Zhao, Y. *J. Org. Chem.* **2005**, *70*, 8107. (d) Guo, X.; Rao, H.; Fu, H.; Jiang, Y.; Zhao, Y. *Adv. Synth. Catal.* **2006**, *348*, 2197. (e) Rao, H.; Jin, Y.; Fu, H.; Jiang, Y.; Zhao, Y. *Chem. Eur. J.* **2006**, *12*, 3636. (f) Liu, Y.; Bai, Y.; Zhang, J.; Li, Y.; Jiao, J.; Qi, X. *Chem. Eur. J.* **2007**, *13*, 6084. (g) Rout, L.; Jammi, S.; Punniyamurthy, T. *Org. Lett.* **2007**, *9*, 3397.

(47) (a) Antilla, J. C.; Baskin, J. M.; Barder, T. E.; Buchwald, S. L. *J. Org. Chem.* **2004**, *69*, 5578. (b) Klapars, A.; Antilla, J.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727.

Chapter One

Palladium and Copper-catalyzed Reactions of Imidazoles and Benzimidazoles with Aryl Halides



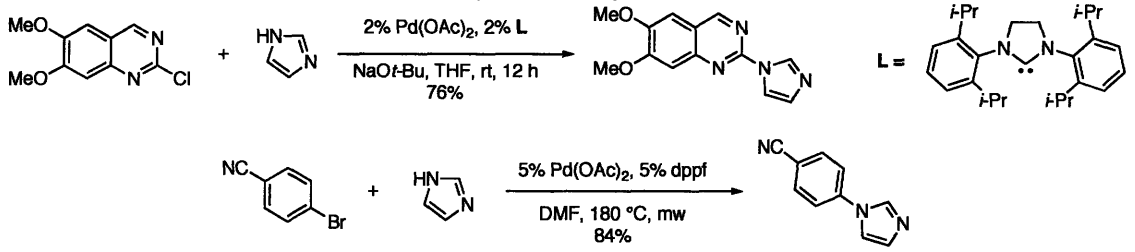


1.1 Introduction

N-Aryl imidazoles and benzimidazoles are found in many biologically active compounds.[1] Although traditional methods for their preparation (nucleophilic aromatic substitution of an activated aryl halide and Cu-mediated coupling of the heterocycle with an aryl iodide) can give access to a wide variety of N-arylated products, these methods suffer from significant limitations. In the former case, the scope of the reaction is confined to the use of aryl halides possessing strongly electron-withdrawing substituents. In the latter case, the range of functional groups tolerated by the long-established Ullmann reaction is severely restricted by the harsh conditions often required (exposure of substrates to high temperatures, typically 150-200 °C, for extended periods of time using stoichiometric quantities of a copper compound).[2]

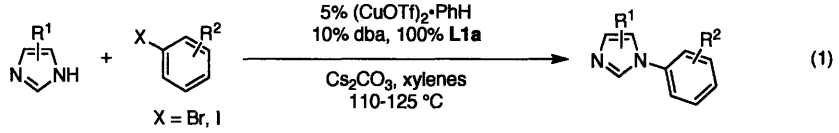
In recent years, mild transition metal-catalyzed cross coupling reactions of aryl halides with N–H heterocycles[3-4] have complemented the traditional preparations of these structures. Despite the continued development of hindered biaryl monophosphines[5] and other ligands[3] for improved Pd-catalyzed C–N bond-forming reactions, only two examples of Pd-catalyzed reactions of imidazoles with aryl halides can be found in the literature (Scheme 1).[6-7] Both examples require the use of activated electrophiles for C–N bond-formation to occur. Thus, Cu-based catalysts have continued to provide the most effective systems for the N-arylation of imidazoles.[4]

Scheme 1. Literature Reports of Pd-Catalyzed N-Arylation Reactions of Imidazole[6-7]



Although the Cu-mediated N-arylation of imidazoles and benzimidazoles has been accomplished using aryllead triacetate,[8] arylboronic acid,[9] triarylbismuth,[10] hypervalent aryl siloxane,[11] diaryl iodonium salt,[12] and arylstannane[13] reagents, these methods generally require the use of toxic and/or unstable reagents that can be difficult to prepare. Furthermore, in many cases, only one of multiple aryl groups is transferred to the heterocycle. In contrast, the use of more stable and readily available aryl halides as the electrophilic coupling partner resolves these issues.

In an early report, 5 mol% bis-[copper(I) triflate] benzene [$(CuOTf)_2 \cdot PhH$] facilitated the coupling of imidazole with aryl iodides under moderate conditions [100% 1,10-phenanthroline, (**L1a**)/10% dba/Cs_2CO_3/xylenes/110–125 °C/24-48 h, eq. 1].[14] However, the scope of the catalyst system was limited to the coupling of unhindered imidazoles with unhindered aryl iodides. The use of the air-sensitive $(CuOTf)_2 \cdot PhH$ as the precatalyst required the use of inconvenient glove box techniques for reaction set-up. The need for stoichiometric quantities of 1,10-phenanthroline ligand and long reaction times were also undesirable.

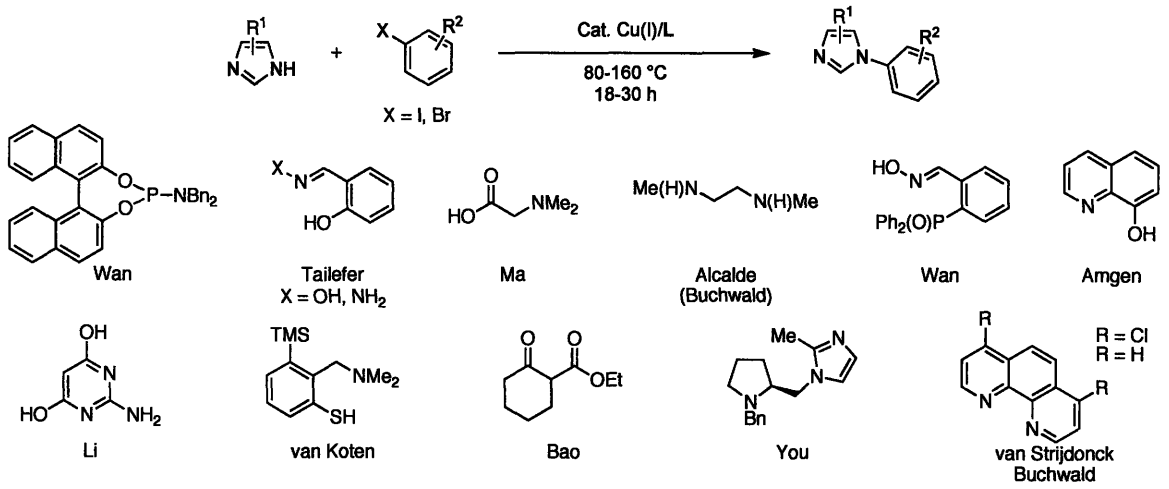


(1)

Subsequently, we developed effective ligands and catalyst systems for the Cu-catalyzed coupling of aryl iodides and bromides with a variety of N-H containing azoles; however, little progress was made with respect to the *N*-arylation of imidazoles.[15] While reports by other groups have disclosed the use of salicylaldoxime derivatives,[16a] amino acid derivatives,[16b-c] *N,N'*-dimethylethylenediamine derivatives (DMEDA),[16d] ligands first reported for C-N couplings by us,[16c-e] 4,7-dichloro-1,10-phenanthroline,[16e] 8-hydroxyquinoline,[16f] aminoarenethiol,[16g] oxime-

phosphine oxides,[16h] phosphoramidites,[16i] 1,10-phenanthroline,[16j] fluoroapetite,[16k] 2-aminopyrimidinediols,[16l] β-ketoesters,[16m] and pyrrolidinylmethylimidazole[16n] as supporting ligands in the Cu-catalyzed *N*-arylation of imidazoles with aryl iodides, very few examples of the coupling of imidazoles with aryl bromides or of even moderately hindered substrates (e.g. a 2-substituted imidazole or a 2-substituted aryl halide) were disclosed until our communication (Figure 1).[17] Furthermore, the use of heteroaryl halides and 4(5)-substituted imidazoles have not been reported.

Figure 1. Reported Ligands for the Cu-Catalyzed N-Arylation Reactions of Imidazole and Benzimidazole



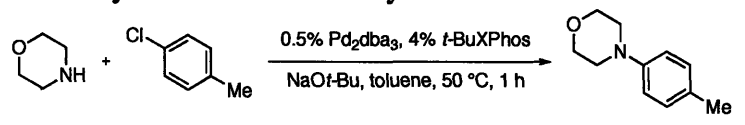
1.2 Results and Discussion

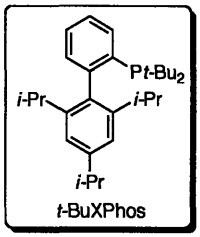
1.2.1 Palladium Catalysis

Imidazole itself acts a catalyst poison for Pd-based C–heteroatom bond-forming reactions. A catalytic amount of this molecule can completely inhibit a simple amination reaction of an aryl halide (Table 1, entries 1-2). Since the replacement of the N–H with an N–Me group provides a more active catalyst (entry 4), the source of catalyst poisoning likely involves the free

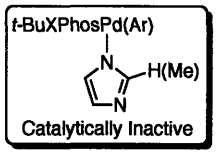
N–H bond. Therefore, the development of a Pd-based catalyst system to cross-couple imidazole with an aryl halide provides a significant challenge.

Table 1. Imidazoles as Catalyst Poisons and Catalyst Enhancers





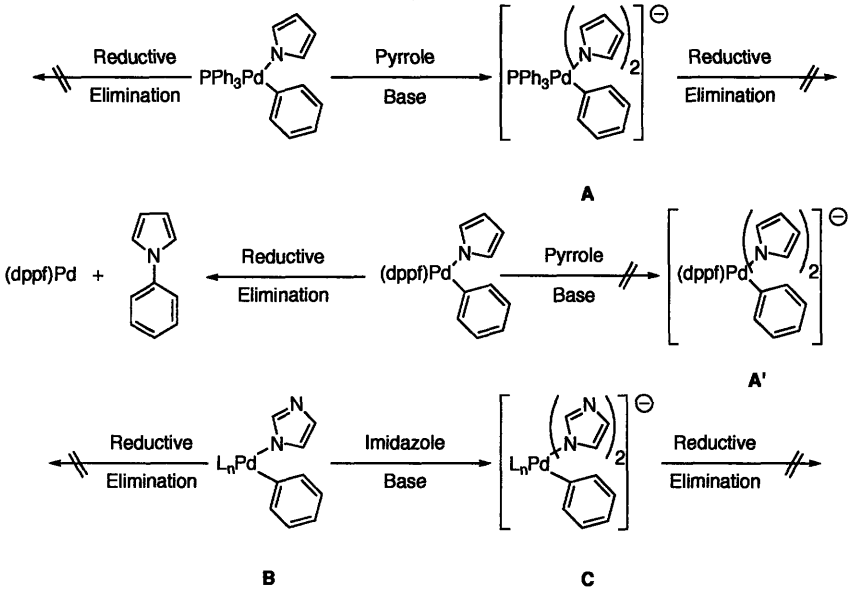
Additive (0.2 eq)	GC Conv. (%)	GC Yield (%)
None	49	48
Imidazole	0	0
2-Methyl imidazole	0	0
1-Methyl imidazole	97	98



Due to the size and structure of pyrrole relative to imidazole (rigid, flat, 5-member ring), insight into the challenge of coupling imidazole with aryl halides using a Pd-based catalyst system can be obtained from Hartwig's studies of the Pd-catalyzed reaction of pyrroles with aryl halides.[18] According to this work, due to the small size of the nucleophile, the slow reductive elimination of the C–N bond from a $(PPh_3)Pd(Ar)(Pyrrole)$ intermediate allowed for the addition of a second equivalent of pyrrole to occur to generate a $Na[PPh_3Pd(Ar)(Pyrrole)_2]$ intermediate (**A**), which resisted reductive elimination (Figure 2). By employing a bidentate ligand (dppf), the authors were able to control the coordination sphere about the metal, inhibiting the formation of the inactive intermediate **A'**, and allow reductive elimination to occur. By analogy, the reductive elimination of an $L_1Pd(Ar)(Imidazole)$ intermediate (**B**) should also be slow. However, the formation of the analogous $[L_1Pd(Ar)(Imidazole)_2]^-$ intermediate (**C**) should be faster, since addition of a second imidazole molecule to **B** involves the sp^2-hybridized lone pair electrons, compared to the reaction of pyrrole with $L_nPd(Ar)(Pyrrole)$ intermediate, where coordination of

the p-hybridized lone pair electrons, prior to deprotonation, results in a loss of aromaticity. Thus, in order to successfully couple imidazole with an aryl halide the slow reductive elimination of complexes complex **B** must be over come, and the formation of complexes of the type **C** must be inhibited.

Figure 2. Potential Formation of Inactive Catalyst



Early attempts to employ a Pd-based catalyst system to cross-couple imidazole with a simple aryl bromide provided no conversion of aryl halide or yield of product (eq. 1). A wide variety of ligands including dialkyl biarylmonophosphino-, bis-phosphinobinaphthyl-, ferrocenyl-, Xantphos-type trialkyl- and triaryl-phosphino-based ligands all provided inactive catalysts for this transformation (Figure 3). In addition to the use of the N–H heterocycle, the reaction of polymeric tri-*n*-butylstannyl imidazole and sodium tetra(imidazoyl) borate provided no yield of product, even at elevated temperatures.

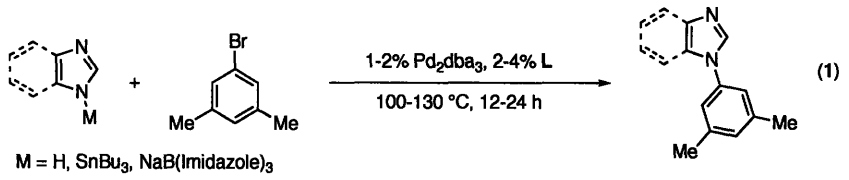
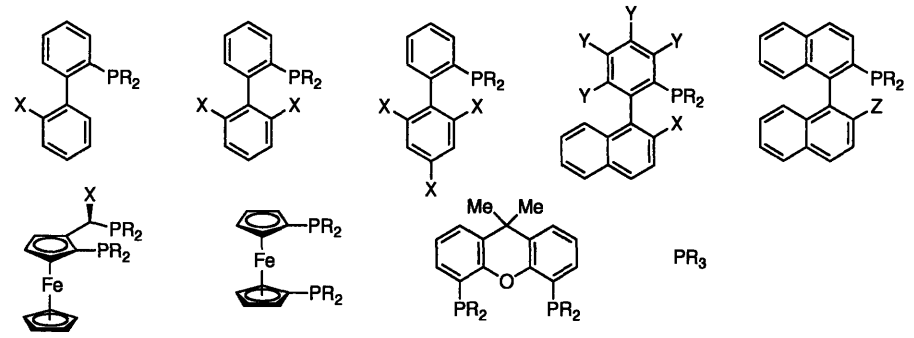
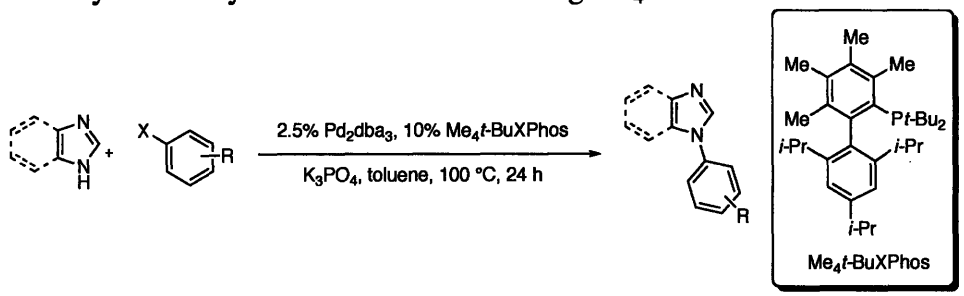


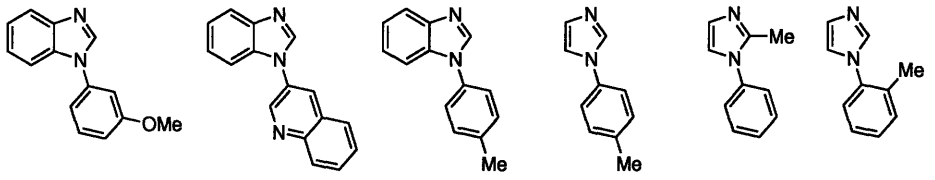
Figure 3. Summary of Unsuccessfully Employed Ligands in the Pd-Catalyzed N-Arylation Reactions of Imidazole



The first success for this methodology came when employing the extremely hindered dialkyl biarylmonophosphine ligand, Me_4t-BuXPhos (Table 2). With a catalyst derived from this ligand, unactivated aryl bromides and chlorides could be coupled with benzimidazoles (**2a-c**), as well as unactivated aryl bromides with imidazole (**2d**). The catalyst system was not very tolerant of steric hindrance, as neither 2-methyl imidazole nor 2-chlorotoluene were not efficiently coupled with simple partners.

Table 2. Pd-Catalyzed N-Arylation of Imidazoles Using Me_4t-BuXPhos[a]





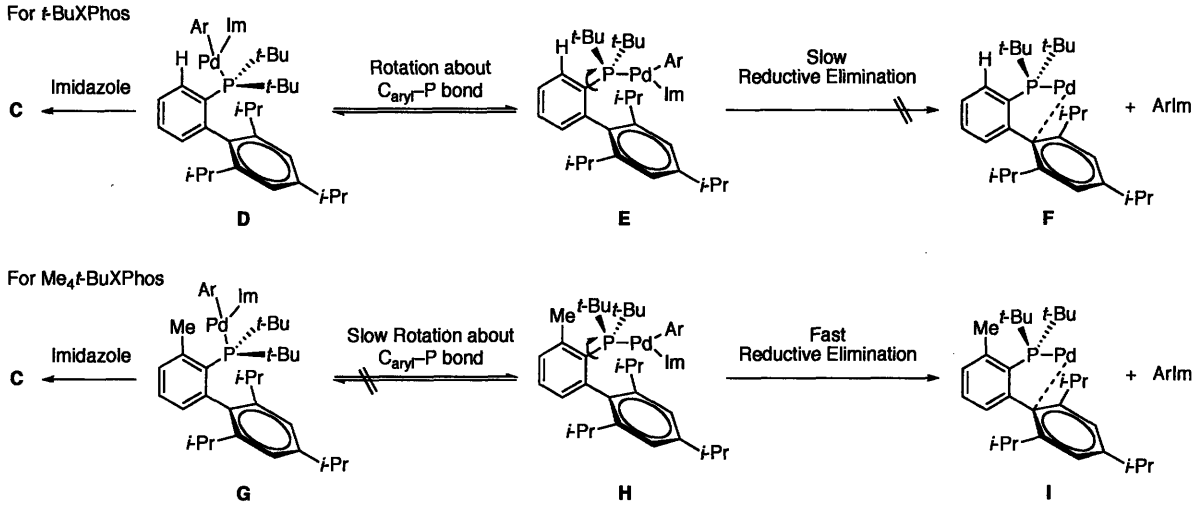
2a 91% (X = Br)	2b 95% (X = Br)	2c 95% (X = Cl)	2d 70% (X = Br, Me_2NPh)	< 15% Conversion	< 10% Conversion

[a] General Reaction Conditions: 1.2 mmol (benz)imidazole, 1.0 mmol ArX, 0.025 mmol Pd_2dba_3, 0.10 mmol Me_4t-BuXPhos, 2.0 mmol K_3PO_4, 1.0 mL toluene under Ar atmosphere at 100 °C for 24 h.

The fact that only Me_4t-BuXPhos serves as an appropriate ligand for this transformation is intriguing. For Me_4t-BuXPhos, the methyl substituent ortho to the phosphorous atom on the biaryl ring resides directly between the *t*-butyl groups on the phosphine. This simple methyl group impedes the rotation about the P–C_{aryl} bond, and thus controls the geometry around the metal center and the coordination of the nucleophile to Pd.[19] For the Pd-catalyzed reaction of imidazole with aryl halides, this phenomenon might have significant implications regarding the formation of the presumed complex **C** (Scheme 2). For dialkyl biarylmonophosphine ligands that lack the methyl-substituted top ring (R = H), transmetallation generally occurs after rotation around the P–C_{aryl} bond places Pd distil to the lower ring of the biaryl system (**D→E**).[20] This, in turn, opens up a free binding site on Pd for a second equivalent of imidazole to coordinate to and form inactive 16 e^- complex **C**. When employing Me_4t-BuXPhos as a ligand (R = Me), the metal is locked directly above the lower biaryl ring, which impedes the transmetallation of a second equivalent of imidazole due to the steric bulk about Pd (**G→H**). This should inhibit the

formation of inactive complex **C**. Thus, from the $L_1Pd(Ar)(Im)$ intermediate **C**, reductive elimination should be the lowest energy pathway (**H→I**).

Scheme 2. Proposed Significance of Methylated Upper Ring in Me_4t-BuXPhos



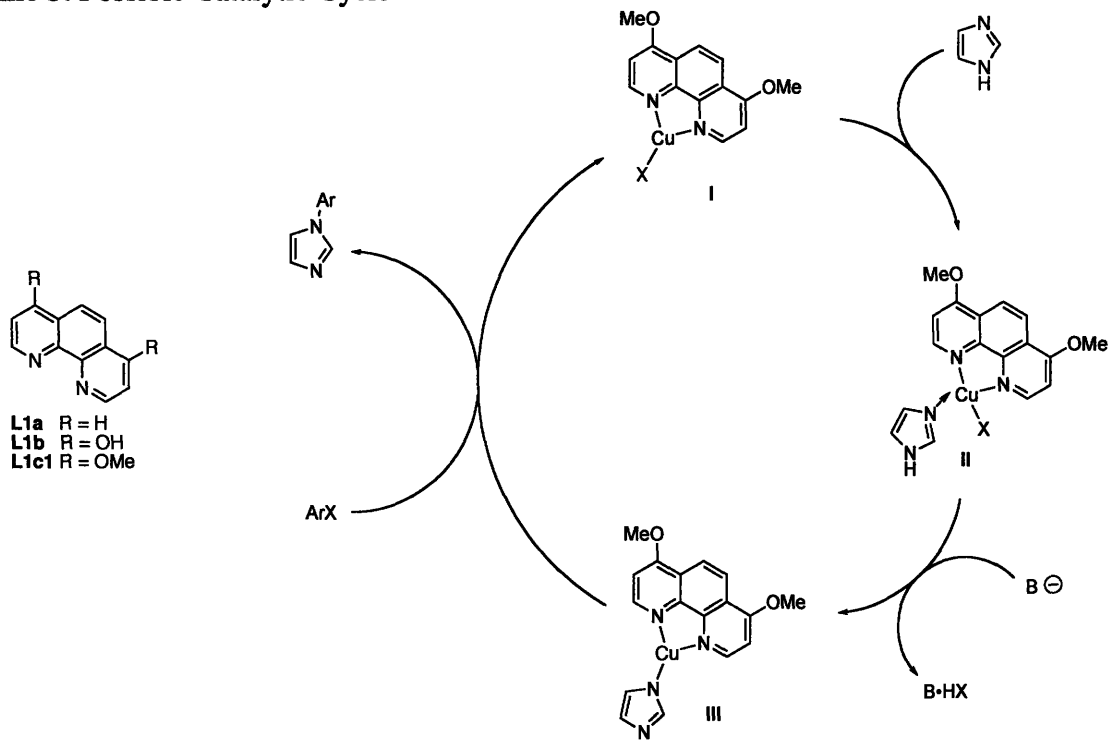
Due to the poor generality of this catalyst system, we sought to develop a more efficient Cu-based catalyst system for the reactions of imidazoles with aryl halides.

1.2.2 Copper Catalysis

1.2.2.1 Method Development and Mechanistic Considerations. Our initial investigations involving the coupling of 2-iodotoluene with imidazole demonstrated that 4,7-dimethoxy-1,10-phenanthroline (**L1c**, Scheme 3)[21] in combination with $(CuOTf)_2{\cdot}PhH$ and Cs_2CO_3 in CH_3CN provided an improved catalyst system for this transformation relative to those previously reported. Compared to that derived from **L1a**, the enhanced reactivity of the catalyst system based on Cu(I)-**L1c** can be attributed to the increased sigma-donating ability of the ligand, as evidenced by the difference in acidities of the corresponding conjugate acids of the free phenanthrolines (pk_a **L1a**-H^+ = 4.86, pk_a **L1c**-H^+ = 6.45).[22] The more electron-rich ligand should

further stabilize a higher oxidation state intermediate (Scheme 3, **III→I**) and lower the oxidation potential for the Cu(I)-Cu(II) or Cu(I)-Cu(III) redox pairs, thus accelerating rate limiting aryl halide activation process.[23]

Scheme 3. Possible Catalytic Cycle



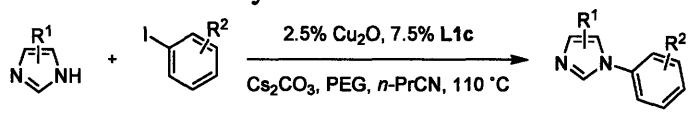
Recent reports have also demonstrated that increasing the solubility of the base can accelerate metal-catalyzed amination reactions of aryl halides. Specifically, cetyltrimethylammonium bromide has been used as a phase transfer catalyst (PTC) in Pd-catalyzed amination reactions[24] and as tetraethylammonium carbonate (TEAC) has been used as a base in the Cu-catalyzed amination reactions[16f] of aryl halides. Therefore, we attempted to employ tetraalkylammonium salts in our own system to increase the solubility of the base. While the use of these reagents did provide increased reaction rates, product yields were low due to alkylation of the starting material and products. Further, TEAC decomposed under the reaction

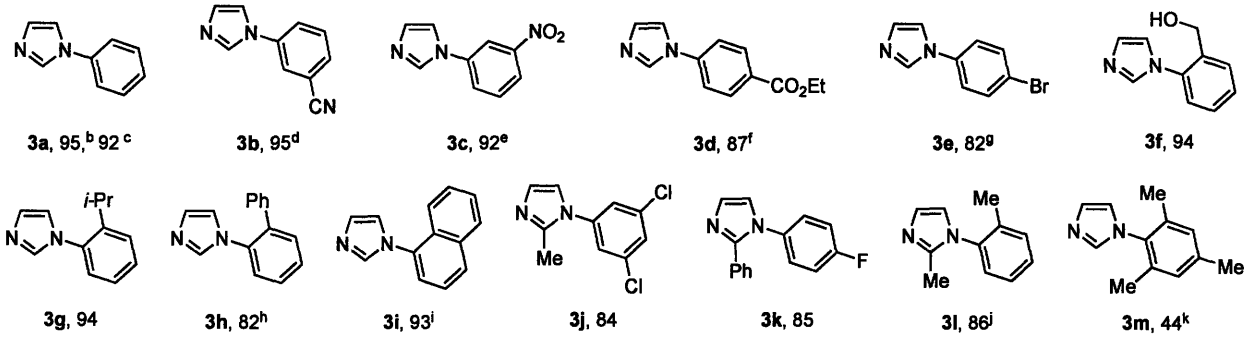
conditions to give NEt_3 and CO_2, which were detected by GCMS and by bubbling the gas produced through 1M HCl, respectively. The problems associated with TEAC could be alleviated while maintaining faster reaction rates by employing non-tetraalkylammonium solid-liquid phase transfer catalysts in combination with Cs_2CO_3.[25] The key choice of poly(ethylene glycol) (PEG) as an additive allowed for the use of inexpensive and stable copper salts (e.g., Cu_2O, CuI) as precatalysts, as opposed to air- and moisture-sensitive copper complexes, such as $[CuOTf]_2 \cdot PhH$.[26]

The use of PEG as a solid-liquid phase transfer catalyst increased the solubility of the carbonate in organic media, increasing the rate of reaction by 10-30%.[27] Without added PEG, the observed reactivity of our system in nitrile solvents decreased in the order MeCN > EtCN > *n*-PrCN at 110 °C–opposite the trend of their boiling points in the same series–suggesting that the relative insolubility of the Cs_2CO_3, or a polar Cu-complex (Scheme 3), in less polar solvents retards the reaction. Reactions carried out in these three solvents in the presence of PEG proceed at comparable rates at 110 °C.[28] However, using PEG as a solvent was less effective, possibly due to poor mass transport in the highly viscous solvent. While most of the chemistry described herein generally uses either *n*-PrCN or NMP, it is also important to note that reactions using the PEG/Cs_2CO_3 combination also show rate enhancements in solvents such as MeCN, EtCN, DMF, DMA and DMSO; however, reactions ducted in these other solvents tend to be slower than those conducted in butyronitrile or NMP. In addition, this imidazole *N*-arylation process is moderately tolerant of water, as evidenced by the fact that our typical procedure involved weighing out a hygroscopic base (Cs_2CO_3) in the air with no protection from ambient moisture. Moreover, by using 2.5-10% Cu_2O as the precatalyst, water is necessarily produced.[29]

1.2.2.2 Substrate Scope. Using the catalyst system based on **L1c**, we explored the scope of the reaction with unhindered aryl iodides (Table 3). Using a catalyst loading of only 0.05% Cu we were able to *N*-arylate imidazole with iodobenzene in 48h at 110 °C (**3a**). To the best of our knowledge, no Cu-based system for C-N bond formation has previously been reported to achieve as many as 2000 turnovers. The reactions of aryl iodides possessing ester and nitrile groups were inefficient under the standard conditions, due to the partial hydrolysis of the ester to benzoic acid, and of the nitrile to benzamide. However, by lowering the reaction temperatures to 80-90 °C, excellent yields of the *N*-arylated products could be obtained (**3b, 3d**). Aryl iodides were selectively coupled in the presence of substrates containing aryl bromides, chlorides and fluorides (**3e**, **3j** and **3k**). Electron-rich, -neutral, and -deficient aryl iodides all provided products in good to excellent yields. The coupling of hindered substrate combinations could also be accomplished using this catalyst system; 2-alkyl and 2-aryl imidazoles (**3j-l**) and ortho-substituted aryl iodides (**3f-i**) were effectively converted to product. The coupling of more hindered substrate combinations (**3l-m**) could be accomplished at higher reaction temperatures (150 °C). When reacting imidazole with mesityl iodide, mesitylene from the reduction of the aryl iodide was the major side-product.

Table 3. Coupling of Imidazoles with Aryl Iodides[a]

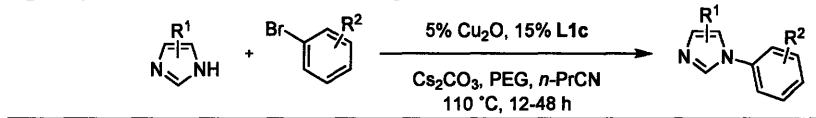


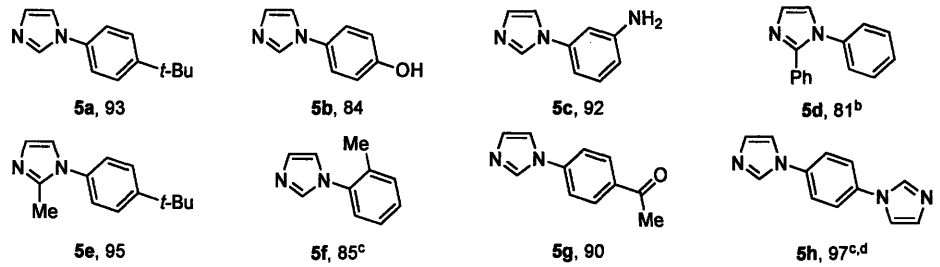


[a] General Reaction Conditions: 1.2 mmol Imidazole, 1.0 mmol ArX, 0.025 mmol Cu_2O, 0.075 mmol **L1c**, 1.4 mmol Cs_2CO_3, 200 mg PEG, 0.25-1.0 mL *n*-PrCN under Ar or N_2 atmosphere at 110 °C for 24-48 h. [b] 12 mmol Imidazole, 10 mmol ArI, 14 mmol Cs_2CO_3, 0.0025 mmol Cu_2O, 0.0075 mmol **L1c**, 2.0 g PEG, 2.5 mL *n*-PrCN. [c] Reaction run in NMP for 3 h. [d] Reaction run at 80 °C in MeCN. [e] Reaction run at 90 °C. [f] Reaction run at 80 °C in MeCN with 3 Å mol. sieves. [g] 1.2 mmol ArI, 1.0 mmol Imidazole. 6 : 1 ratio of iodo- : bromo-substituted arene. [h] 0.05 mmol Cu_2O, 0.15 mmol **L1c**, 120 °C. [i] Reaction run in NMP with no PEG. [j] Reaction run in NMP at 150 °C. [k] Reaction run in DMSO at 150 °C.

Aryl bromides were also successfully coupled under our reaction conditions (Table 4). However, higher quantities of catalyst and longer reaction times were often necessary to provide good yields of product. The combination of 2-substituted imidazoles with aryl bromides provided *N*-arylated products in good yields (**4d-e**). Additionally, the coupling of imidazole and 2-bromotoluene can be successfully accomplished (**4f**). Further, imidazole can be selectively arylated in the presence of a free -OH or $-NH_2$ group (**4b-c**). This selectivity is particularly interesting, as 1,10-phenanthroline derivatives have also been reported as ligands in the Cu-catalyzed syntheses of aryl ethers and aryl amines from aryl halides.[30]

Table 4. Couplings of Imidazoles with Aryl Bromides[a]





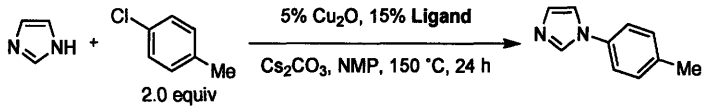
[a] Reaction Conditions: 1.2 mmol imidazole, 1.0 mmol ArX, 0.05 mmol Cu_2O, 0.15 mmol **L1c**, 1.4 mmol Cs_2CO_3, 200 mg PEG, 0.25-1.0 mL *n*-PrCN under Ar at 110 °C for 24-48 hr. [b] 0.10 mmol Cu_2O, 0.30 mmol **L1c** at 120 °C. [c] Reaction run in NMP. [d] 1.0 eq. ArBr and 2.4 eq. imidazole with 2.8 eq. Cs_2CO_3.

For many of the reactions described, butyronitrile was employed as a solvent, since it is relatively volatile, non-polar and easy to remove from products compared to the higher boiling point solvents such as DMF, DMSO and NMP. However, in some cases, the use of NMP as the solvent provided faster reactions. For example, we found that we were able to arylate imidazole with iodobenzene in excellent yields in 3 hours with 5% Cu in NMP (**3a**), while the same reaction required 4 hours using *n*-PrCN. More difficult cases, such as reactions of hindered aryl halides and 2-substituted imidazoles, also reacted more efficiently using NMP as the solvent (**3i**, **3l**, **4f**, **4h** and **6d**). The rate enhancement using NMP will be revisited in Figures 5-8.

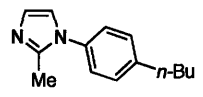
Despite the many reports of Cu-catalyzed methods for the *N*-arylation of heterocycles with aryl iodides and aryl bromides,[16] the inability of Cu(I) to activate the aryl chlorides has traditionally been a major limitation.[4] Since the Cu-catalyzed coupling of N–H-containing heterocycles with activated aryl chlorides has been described,[31] it seemed natural to extend the scope of this reaction to unactivated aryl chlorides. Although 4-chlorotoluene was an unreactive

substrate when employing the general conditions described with aryl bromides and iodides, Cu_2O in combination with 4,7-dihydroxy-1,10-phenanthroline (**L1b**) and **L1c** catalyzed the amination in good yield at 150 °C using a two-fold excess of aryl chloride (Table 5). Due to the high temperatures, O-arylation from residual water in the base was a competing process. Therefore, it was crucial to use anhydrous Cs_2CO_3, and minimize the exposure time of the base to moisture in the air. As previously observed with iodides and bromides, reactions of hindered substrates were significantly slower. Still, due to the commercial availability and relatively low cost compared to iodides and bromides, the use of aryl chlorides in Cu-catalyzed cross-coupling reactions of aryl halides remains a worthy goal.

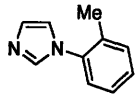
Table 5. Coupling of Imidazoles with Aryl Chlorides[a]



Entry	Ligand	Equiv ArCl Consumed	GC Yield (%)
1	-[b]	0.02	0
2	-	0.34	11
3	**L1c**	0.72	60
4	**L1b**	1.36	86
5	**L1b**[c]	1.10	87
6	**L1c**[d]	1.49	78



22 % GC Yield[a]



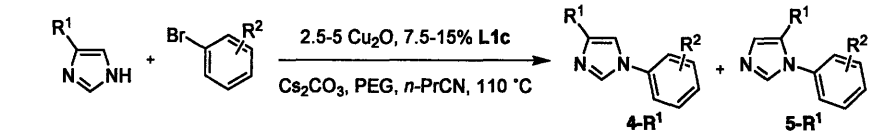
15 % GC Yield[a]

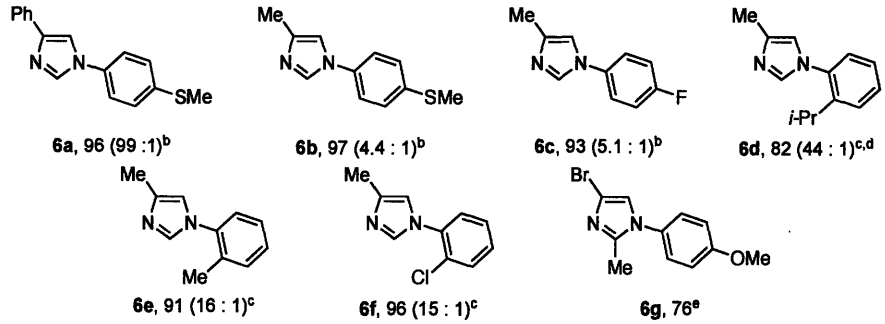
[a] Reaction Conditions: 1.0 mmol Imidazole, 2.0 mmol ArX, 0.05 mmol Cu_2O, 0.15 mmol **L**, 2.0 mmol Cs_2CO_3, 0.25 ml NMP under Ar at 150 °C for 24 h. [b] No Cu. [c] Run with K_2CO_3 as base. [d] Reaction run in microwave (250 W) with Powermax function for 2 h at 150 °C.

The reactions of 4(5)-substituted imidazoles with aryl halides showed varying degrees of regioselectivity, with the preferential formation of 4-substituted imidazoles (Table 6).[32] With 4-

phenyl imidazole, the 1,4-diarylimidazole was the exclusive product observed (**6a**). Reactions of 4-methyl imidazoles with aryl bromides lacking an *ortho*-substituent showed similar selectivity for formation of 1-aryl-4-alkyl imidazoles similar to that previously observed (**6b-c**).[14] As in the study conducted by Collman on the coupling of 4-substituted imidazoles with aryl boronic acids,[32] the preferential selectivity for the 4-regioisomer over the 5-regioisomer is likely due to the greater steric interactions when substituent R^1 resides at the 5-position compared to the 4-position either prior to aryl halide activation (Scheme 4, **V-VI**) or upon activation of the aryl halide (**VII-VIII**). In contrast, reactions of 4(5)-methylimidazole with *ortho*-substituted aryl halides provided the 4-regioisomer with significantly better selectivity (**6d-f**). This increase in regioselectivity when using a hindered aryl halide likely arises due to the additional unfavorable steric interaction between the group *ortho* to the halide (R^2) and R^1 when R^1 is situated in the 5-position (**IX**) as opposed to the 4-position (**X**). The reaction of 4-bromo-2-methylimidazole with 4-iodoanisole provided 4-bromo-1-(4-methoxyphenyl)-2-methyl-1*H*-imidazole as the major product (**6g**). Formation of the 5-bromo-1-(4-methoxyphenyl)-2-methyl-isomer was not detected by GC or ^{1}H NMR techniques. In this case, the selectivity is likely dictated by the increased steric effects that exist on a high-oxidation state intermediate when the large bromide-substituent resides at the 5-position (**XI**) relative to the 4-position (**XII**).

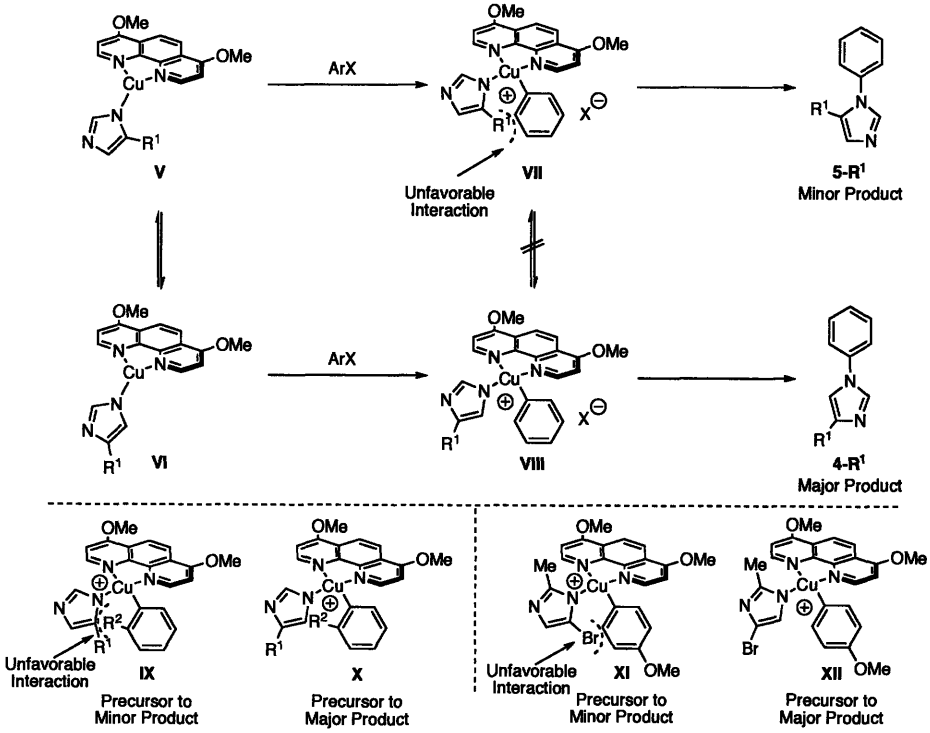
Table 6. Coupling of 4(5)-Substituted Imidazoles[a,b]





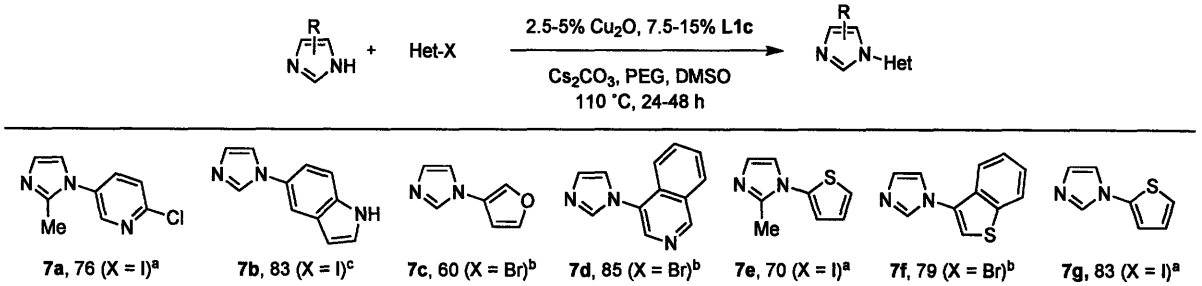
[a] 4-R^1 : 5-R^1 Selectivity is reported in parentheses and was determined by GC analyses of the crude reaction mixtures and/or ^{1}H NMR spectra of the pure products. [b] Reaction Conditions for ArBr: 1.2 mmol imidazole, 1.0 mmol ArBr, 0.05 mmol Cu_2O, 0.15 mmol **L1c**, 1.4 mmol Cs_2CO_3, 200 mg PEG, 0.25-1.0 mL *n*-PrCN under Ar atmosphere at 110 °C for 24-30 h. Isolated yields reported. [c] Reaction Conditions for ArI: 1.2 mmol imidazole, 1.0 mmol ArI, 0.025 mmol Cu_2O, 0.075 mmol **L1c**, with ArI. [d] NMP used as solvent. GC yield reported. [e] 1.2 mmol ArI, 1.0 mmol Imidazole, No PEG, 0.05 mmol CuI, 0.075 mmol **L1c** in 0.5 mL MeCN. Only one regioisomer was detected by GC and ^{1}H NMR.

Scheme 4. Consideration of Steric Effects in Reactions of 4(5)-Substituted Imidazoles



Since *N*-heteroaryl imidazoles are interesting targets in drug discovery and medicinal chemistry,[33] the coupling of imidazoles with unactivated heteroaryl bromides and iodides was examined (Table 7). An interesting result was observed in the reaction of imidazole with 2-chloro-5-iodopyridine, a substrate activated at the 2-position for uncatalyzed S_nAr. In this case, the Cu-catalyzed substitution occurred predominantly at the iodide to provide **7a** in good yield. In the coupling of 5-iodoindole with imidazole (**7b**), the *N*-heteroaryl imidazole was isolated in good yield, with trace amounts of *N*-aryl indole formed as a side product.[34] This selectivity likely arises from the more rapid transmetallation of imidazole with Cu(I) through the sp^2-hybridized lone pair electrons compared to the case of indole, where coordination of the p-hybridized lone pair electrons results in a partial loss of aromaticity. Imidazoles were also successfully combined with a variety of heteroaryl halides including 3-bromofuran (**7c**), 3-bromoisoquinoline (**7d**), 2-iodothiophene (**7e, 7g**),[35] and 3-bromobenzothiophene (**7g**).

Table 7. Couplings of Heteroaryl Halides[a]

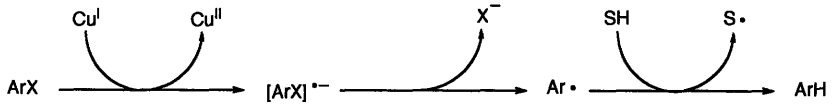


[a] Reaction Conditions (ArI): 1.0 mmol imidazole, 1.2 mmol ArI, 0.025 mmol Cu_2O, 0.075 mmol **L1c**, 1.4 mmol Cs_2CO_3, 200 mg PEG, 0.5 mL DMSO under Ar at 110 °C for 12-24 h. [b] Reaction Conditions (ArBr): 1.0 mmol imidazole, 1.2 mmol ArBr, 0.05 mmol Cu_2O, 0.15 mmol **L1c**, 1.4 mmol Cs_2CO_3, 200 mg PEG, 0.5 mL DMSO under Ar at 110 °C for 24-48 h. [c] 1.2 mmol imidazole, 1.0 mmol ArI, 0.025 mmol Cu_2O, 0.075 mmol **L1c**, 1.4 mmol Cs_2CO_3, 0.5 mL *n*-PrCN under Ar at 110 °C for 16 h.

Generally, isolated yields for reactions of imidazoles with heteroaryl iodides and bromides were slightly lower than those with simple aryl halides due to formation of the reduced

heteroarene as a byproduct.[36] The use of DMSO as a solvent caused an increase in the yield of the desired product and decreased the quantity of the dehalogenated by-product. Although the Cu(I)-catalyzed reduction of aryl halides has been reported,[37] the lack of an obvious hydride source suggests an alternative pathway for the formation of the reduced arene. Since alkali metals have long been known to reduce aryl halides by a radical anionic mechanism,[38] it is plausible that a similar sequence involving the Cu(I)-Cu(II) redox pair might occur (Scheme 5). Single electron transfer (SET) from Cu(I) to the aryl halide, would generate the radical anion, which could homolytically cleave to generate an aryl radical and halogen anion. Abstraction of H· from the solvent[39] would then produce the dehalogenated arene. The observation that more reduction is detected with *N*-containing heteroaryl halides than with aryl halides is consistent with previous reports that SET to halo pyridines is faster than to halobenzenes due to the electron-accepting nature of the imine-like C–N bond.[40] Further, our observation that formation of the reduced arene can be suppressed by using DMSO as a solvent in place of *n*-PrCN agrees with the relative rates of radical anionic aryl halide cleavage in acetonitrile and DMSO.[41] However, the mechanism of the reduction, like the mechanism for the amination itself has yet to be properly elucidated.

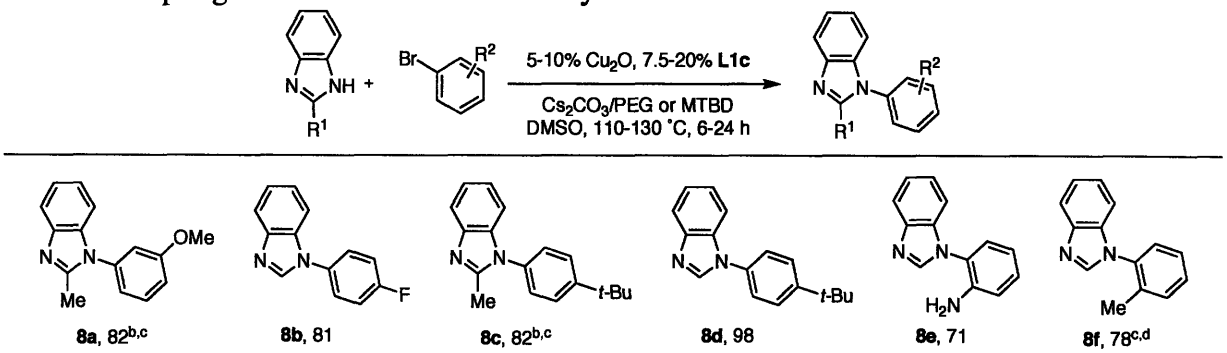
Scheme 5. Possible Reduction Pathway in Cu-Catalyzed Amination Reactions



The use of DMSO and **L1c** also permits the successful coupling of benzimidazoles to unactivated aryl bromides (Table 8), which until recently[16f] had been limited to aryl iodides, and unhindered aryl bromides using Cu-catalyzed methodology.[14,15g,16] As seen previously, substrates

containing a free anilino-NH_2 groups (**8e**) were good substrates under our conditions. Ortho-substituted aryl bromides, as well as 2-substituted benzimidazoles were successfully used as partners (**8a**, **8c**, **8e-f**). In some cases, the use of 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD) as base provided better yields than the Cs_2CO_3/PEG combination (**8a**, **8c**).[42]

Table 8. Coupling of Benzimidazoles with Aryl Bromides[a]



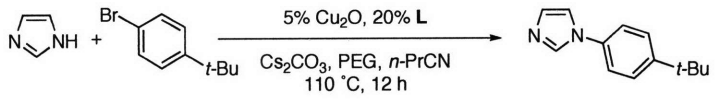
[a] General Reaction Conditions: 1.2 mmol benzimidazole, 1.0 mmol ArBr, 0.10 mmol Cu_2O, 0.20 mmol **L1c**, 1.4 mmol Cs_2CO_3, 200 mg PEG, 0.5 mL DMSO under Ar or N_2 atmosphere at 110 °C for 24 h. [b] MTBD used as base. [c] Reaction run at 130 °C for 24 h. [d] 0.05 mmol Cu_2O, 0.15 mmol **L1c**.

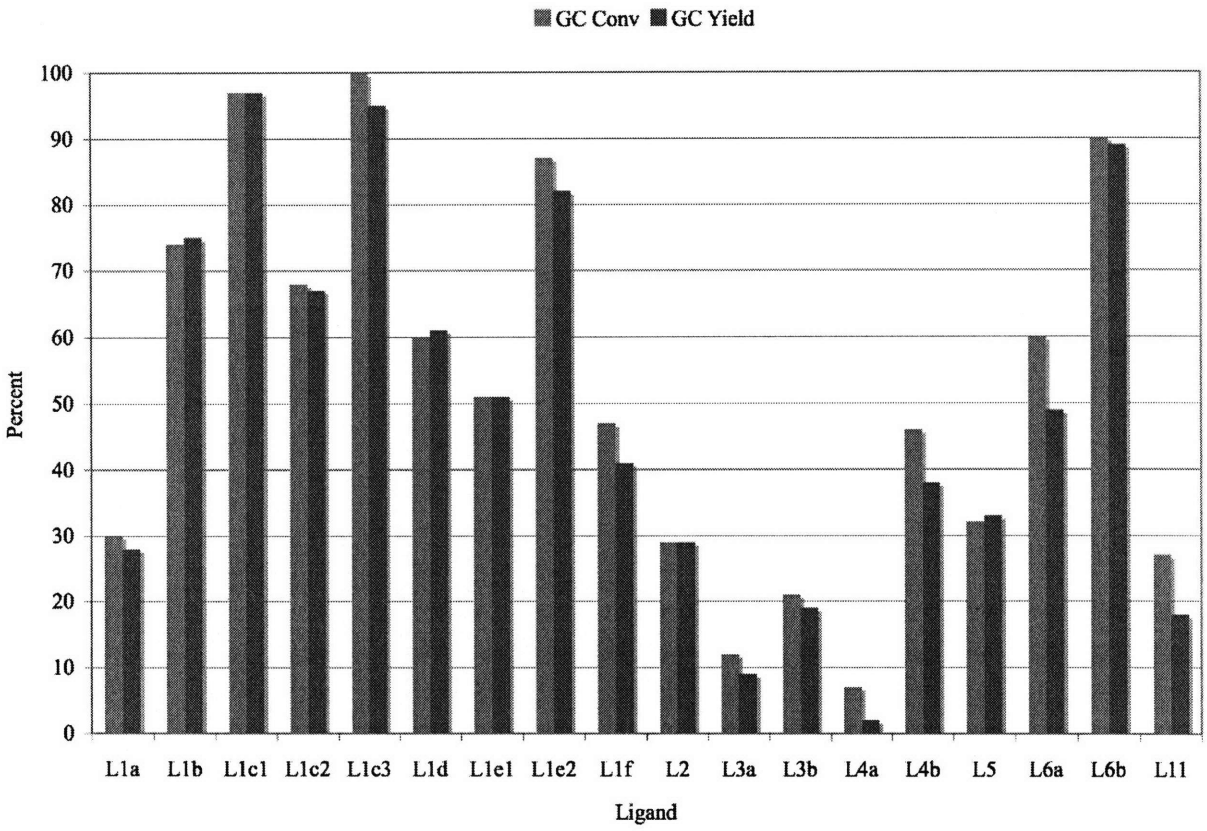
1.2.2.3 Evaluation of the Ligands Commonly Employed for the N-Arylation of Imidazoles.

After most of our work for on this topic was finished, several catalyst systems were reported for the N-arylation of imidazoles and benzimidazoles (Figure 1).[15-16] To evaluate our new catalyst system in light of those previously published, we decided to undertake a study in order to compare our system with those that had been previously reported for this coupling in addition to other 1,10-phenanthroline derivatives (Figures 4-7). While ligands **L1a**, **L1b**, **L1c**, **L2-L6** and **L10** are commercially available, **L7-9** are only accessible through multiple step sequences. Furthermore, the harsh conditions necessary for the use of **L9-10** (145-160 °C) suggest that at the time of the report these ligands were useful only in specific circumstances. For this reason, we focused the following study on **L1-L6**. **L11** was also examined to assess the significance of

ligand rigidity for this transformation. Importantly, no reaction was observed for control reactions in which no ligand or PEG was added.

Figure 4. Reaction of Imidazole with 4-*t*-Butylbromobenzene





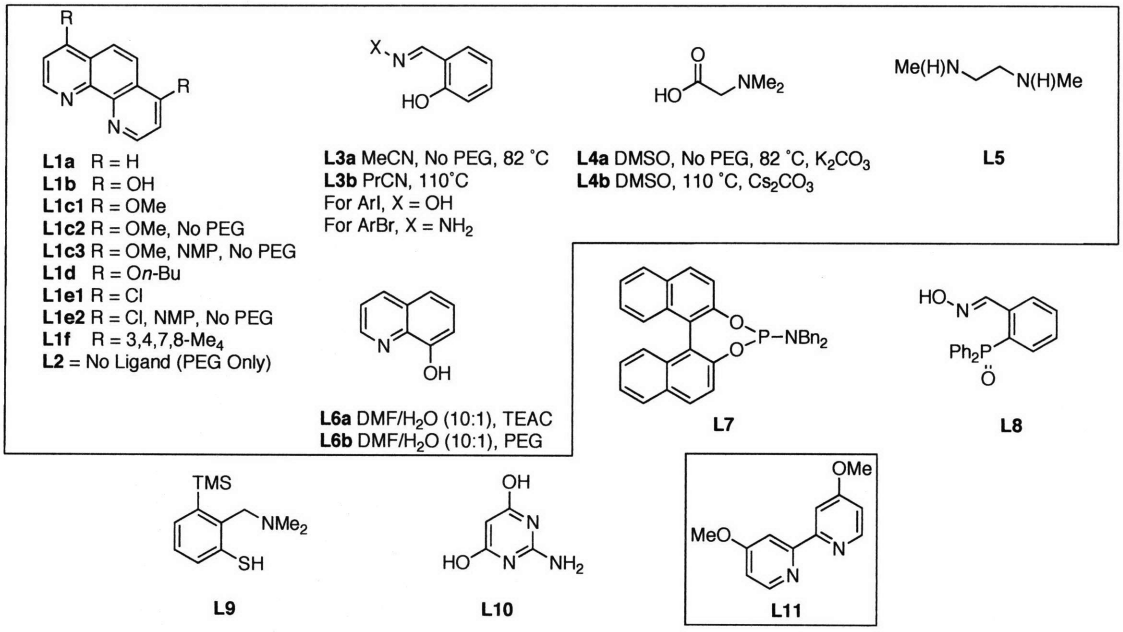


Figure 5. Reaction of 2-Methylimidazole with 4-*n*-Butyliodobenzene

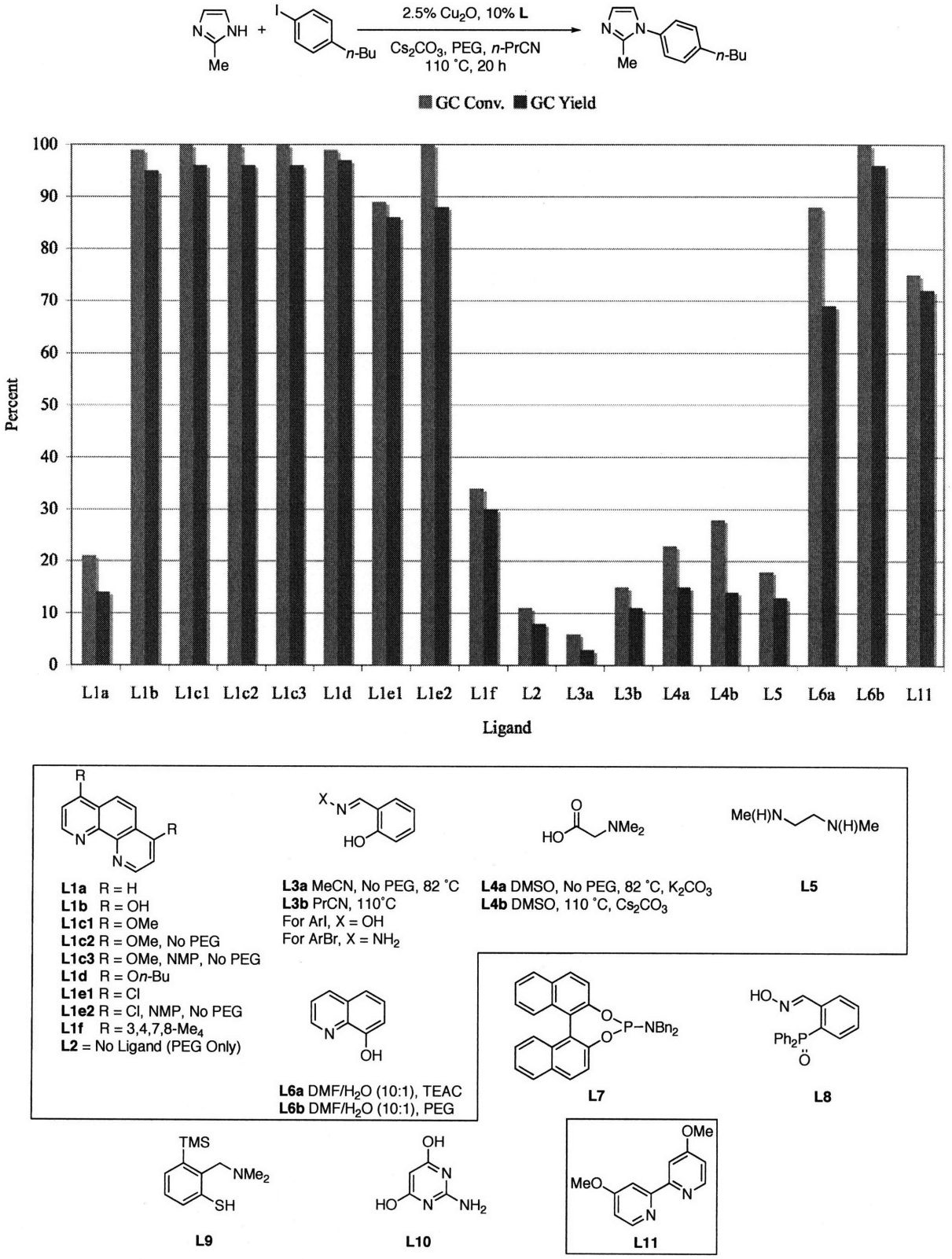


Figure 6. Reaction of Imidazole with 2-Bromotoluene

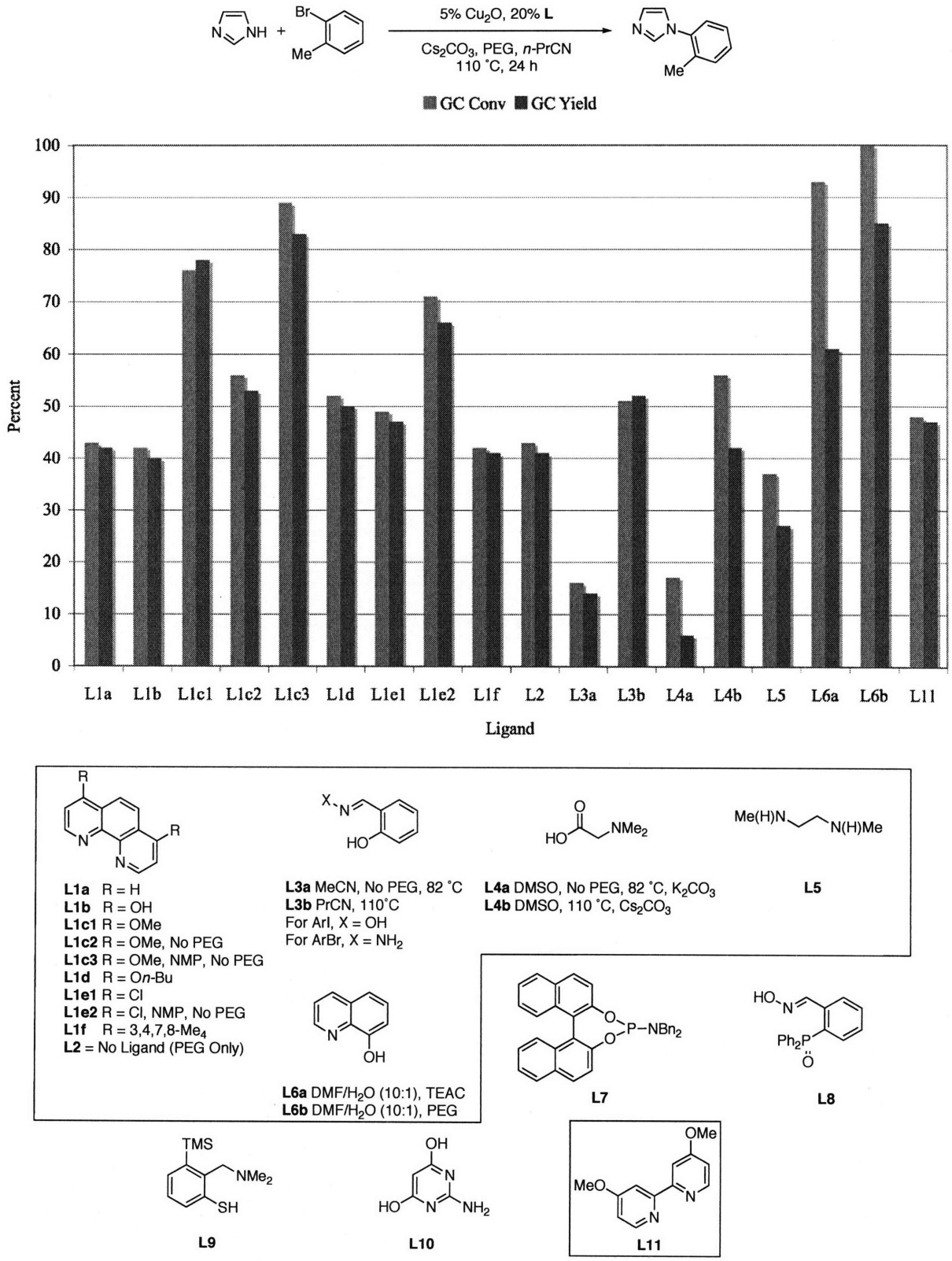
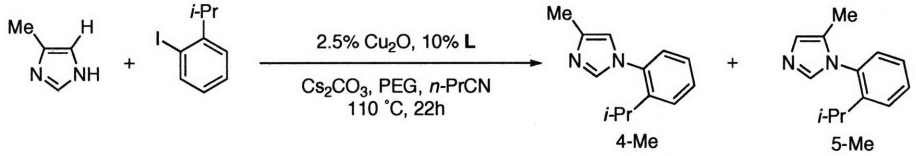
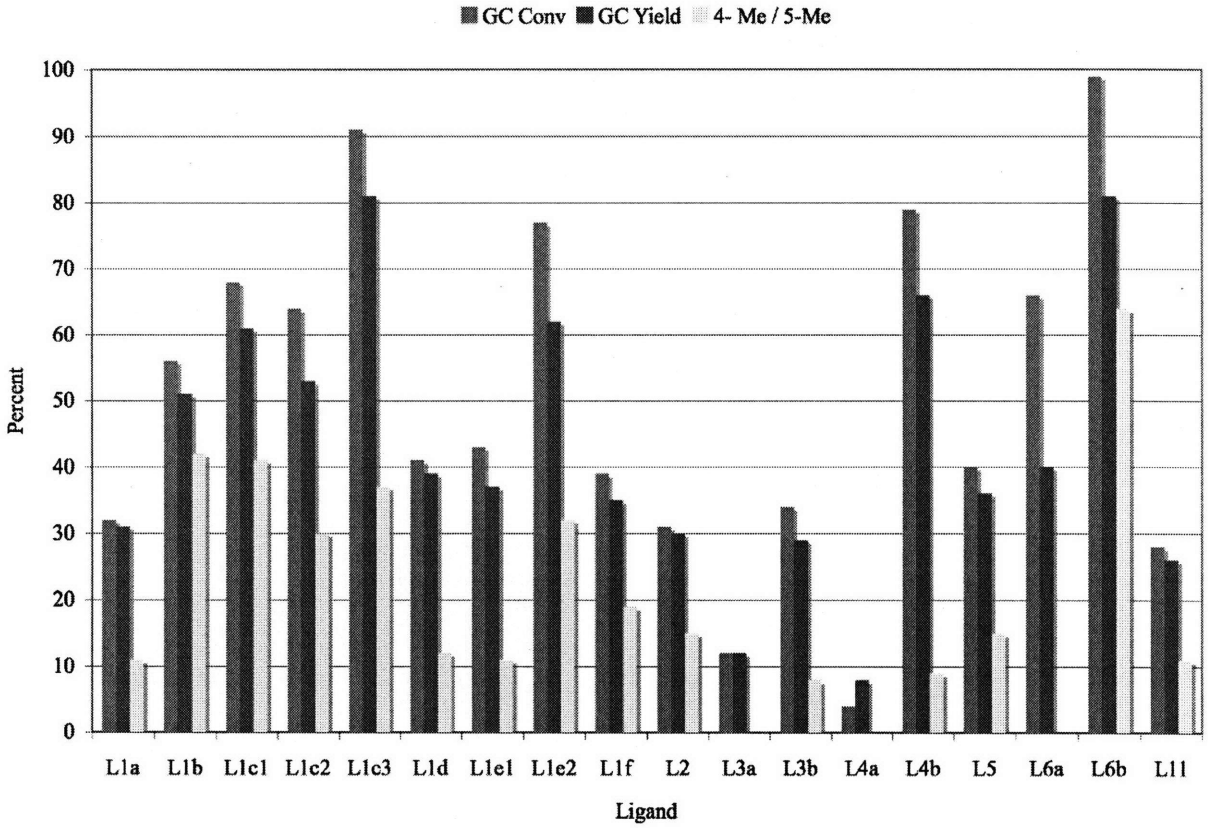
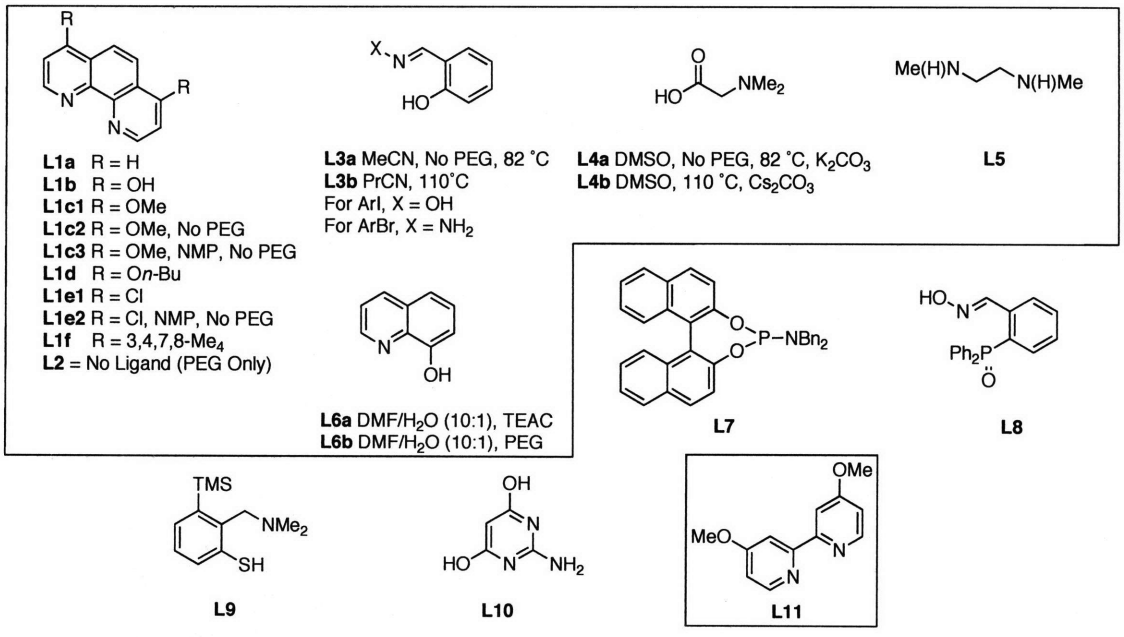


Figure 7. Reaction of 4-Methylimidazole with 2-Isopropyliodobenzene







Case 1–Non-hindered aryl bromide: To examine a process in which steric hindrance was not a significant factor, the reaction of 4-*t*-butylbromobenzene with imidazole was conducted (Figure 4). Of the catalysts examined, only systems derived from the 4,7-disubstituted-1,10-phenanthrolines and **L6** (with PEG/Cs_2CO_3 instead of TEAC) provided reasonable results (> 60% GC yield). Of these, the use of **L1c** provided nearly quantitative yield of N-aryl product, followed by **L1e**, and **L1b** (86% and 76% GC yields, respectively).

Case 2–Aryl iodide, 2-substituted imidazole: The efficient *N*-arylation of 2-substituted imidazoles had not been achieved prior to our earlier communication.[17,43] The reaction of 4-*n*-butyliodobenzene with 2-methylimidazole was chosen to probe the sensitivity of each catalytic system to substitution on the nucleophile (Figure 5). Only catalyst systems based on 4,7-disubstituted-1,10-phenanthrolines (**L1b-e**), **L6** and **L11** were effective for this transformation. Of those mentioned, **L1b**, **L1c,** and **L6b** provided slightly better yields (> 95% GC yield) of product than did **L1e** (86-88% GC yield). All other ligands were ineffective for this transformation within a reasonable time period (< 20% GC yield).

Case 3–Hindered aryl bromide with imidazole: The very few examples of Cu-catalyzed reactions of *ortho*-substituted aryl bromides with imidazole require high temperatures and/or long reaction times.[16b,f,l] We, therefore, chose to examine the reaction of 2-bromotoluene with imidazole (Figure 6). The majority of the ligands screened provided similarly efficacious catalysts (40-60% GC yield). The use of **L1e** provided a slightly higher yield of product (66%). Only the use of dimethoxy **L1c** and **L6** as ligands provided synthetically useful yields (83-85 % GC yield respectively) using PEG/Cs_2CO_3. However, using **L6** and TEAC as the base, 15% of the aryl bromide was lost.

Case 4–Hindered aryl iodide with 4(5)-substituted imidazole: To explore the effect of the ligand employed on the regioselectivity of the coupling process, 4-methylimidazole was combined with 2-isopropyliodobenzene (Figure 7). Systems based on most ligands provided low catalytic activity (< 40% GC yield) and moderate selectivity in favor of the 4-regioisomer. Reactions utilizing **L1b** and **L1e** provided reasonable reaction efficiencies (51 – 62% GC yield) with excellent selectivity for the 4-alkyl imidazole (30 – 42 : 1). Once again, the use of **L1c** provided the best result, giving an 82% GC yield with a selectivity of 37 : 1 in favor of the 4-methyl regioisomer.

Summary of Ligand Comparisons Screens: In general, **L1c** outperformed other 1,10-phenanthroline ligands lacking heteroatoms in the 4- and 7-positions (**L1a** and **L1f**). The catalyst derived from anionic 4,7-dihydroxy derivative **L1b** showed higher reactivity than unsubstituted **L1a**, but was generally less active than that with **L1c**. This may be due to the relative insolubility of **L1b** in the solvents employed. Interestingly, **L1c** outperformed 4,7-dibutoxy-1,10-phenanthroline (**L1d**),[44] which we had postulated might be a better ligand due to its increased solubility. Reactions using chlorinated **L1e** as a ligand demonstrated good conversion to product, which we found surprising considering the electron-deficient nature of the ligand compared to the methoxy counterpart. However using **L1e**, re-isolation of the ligand at the end of the reaction showed that the chlorides had been displaced at the 4- and 7-positions by a mixture of both the residual water and imidazole. Thus, using the Cu/**L1e** combination, it is unclear as to the nature of the actual ligand in the active catalyst. The increased efficiency of catalysts based on **L1c** relative to **L11**, demonstrated the significance of the rigid phenanthroline backbone over the 2,2'-bipyridine structure, which contains conformational freedom about the biaryl bond. While catalysts using ligands **L3-L5** demonstrated sluggish reactivity with more challenging

imidazole/aryl halide substrate combinations under the reported conditions,[16a-d] their use with the PEG/Cs_2CO_3 conditions described here provided higher conversions and yields. The effect of PEG can be further seen as the Cu_2O/PEG combination, **L2**, (without a N-containing ligand) which provided similar reactivity as when unsubstituted 1,10-phenantholine (**L1a**) was used as the ligand. The use of **L6** as ligand for these reactions provided high reactivity; however, the use of TEAC as a base provided low yields as previously mentioned in this text. Using **L6**, the use of PEG/Cs_2CO_3 instead of TEAC as the base provided higher yields of *N*-aryl imidazoles due to the suppression of three side reactions: 1) reduction of the aryl halide, 2) *O*-arylation of the ligand, 3) *N*-alkylation of imidazole by the tetraalkylammonium cation. Due to their low cost, many of these systems might still be attractive for the coupling of more facile substrate combinations; however, there are significant limitations to the scope of imidazoles and aryl halides that can be effectively coupled by these systems compared with **L1c**.

1.3 Conclusion

We have developed the first Pd-based catalyst system for the N-arylation of imidazoles and benzimidazoles using unactivated aryl halides. Due to the poor substrate scope of this catalyst system, a superior Cu-based catalyst system was developed. 4,7-Dimethoxy-1,10-phenanthroline was revealed as an excellent ligand for the Cu-catalyzed arylation of imidazoles and benzimidazoles with aryl and heteroaryl iodides and bromides in combination with PEG and Cs_2CO_3. Not only is this system the most general reported to date, it also allows for the cross-coupling of hindered substrate combinations. The mild conditions employed also manifest a high functional group tolerance.

1.4 Experimental Procedures

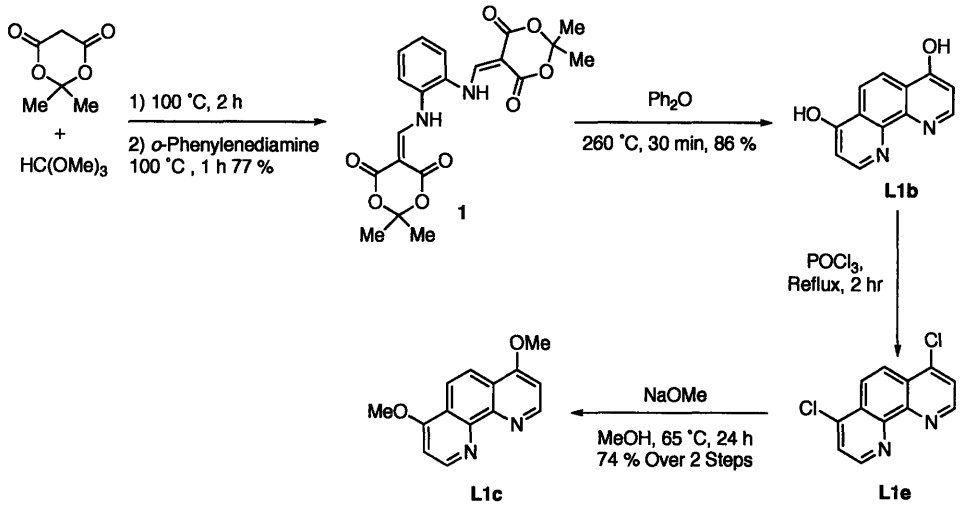
All reactions were carried out in resealable test tubes with teflon septa and run under a dry argon or nitrogen atmosphere. Copper (I) oxide (97%) was purchased from Aldrich as a red powder. Pd_2dba_3 was obtained from Strem, Inc. and stored in a vacuum desiccator filled with anhydrous calcium sulfate. Anhydrous Cs_2CO_3 (99.9%) was purchased from Alfa Aesar. K_3PO_4 (finely milled) was purchased from Fluka. The bulk of the bases were stored under nitrogen in a Vacuum Atmospheres glovebox. Small portions (~5 g) were removed from the glovebox in glass vials, stored in the air in a desiccator filled with anhydrous calcium sulfate, and weighed in the air. Poly(ethylene glycol) (M_n 3,400) was purchased from Aldrich. Generally, aryl halides and imidazoles were purchased from commercial sources and used without further purification. When necessary, aryl halides were filtered through neutral alumina, or distilled. Butyronitrile (≥ 99%) was purchased from Aldrich and used without further purification. Anhydrous solvents (NMP, DMSO, and Acetonitrile) were purchased from Aldrich in Sure-Seal ® bottles. Flash column chromatography was performed with EM Science silica gel 60 (230-400 mesh). In all cases, dichloromethane was used to load the crude reaction material onto a silica gel column. A gradient elution technique was used for column chromatography, beginning with hexane and continuing to the specified concentration of ethyl acetate in hexane.

Yields reported in the publication are isolated (except where noted) and represent an average of at least two independent runs. Yields reported in the supporting information refer to a single experiment. Compounds described in the literature were characterized by comparing their ^1H NMR, and melting point (m.p.) to the previously reported data; their purity was confirmed by gas chromatographic analyses (GC). For known compounds prepared using the new method (conditions) described, a copy of the ^1H NMR spectrum, of each, is included. GC analyses were

performed on a Hewlett Packard 6890 instrument with an FID detector and a Hewlett Packard 10 m x 0.2 mm i.d. HP-1 capillary column using dodecane as an internal standard. Previously unknown compounds were synthesized, purified and analyzed from a single run and were then repeated to determine an average yield. They were characterized by ^{1}H NMR, ^{13}C NMR, m.p., IR and elemental analysis. Elemental analyses were performed by Atlantic Microlabs, Inc., Norcross, GA. For those compounds that did not give a satisfactory elemental analysis, a copy of their ^{1}H NMR spectrum is included. ^{1}H NMR and ^{13}C NMR were recorded on Varian 300 MHz and 500 MHz instruments with chemical shifts reported relative to the deuterated solvent or TMS. IR spectra were recorded on a Perkin-Elmer System 2000 FT-IR instrument for all previously unknown compounds (KBr disc). Melting points (uncorrected) were obtained on a Mel-Temp II capillary melting point apparatus.

Synthesis of Ligands

L1a, **L1f**, **L3**, **L4**, **L5**, **L7** and **L8** were purchased from commercial sources. **L3** was purified by recrystallization from hexane. **L1d**[45] and complex **L6**[46] were prepared according to literature precedent. The synthesis of **L1b**, **L1c** and **L1e** was adapted from literature precedent.[47] A larger scale preparation of **L1b**, **L1c** and **L1e** can be preformed as described in the following text. Alternatively, **L1b** and **L1c** can be purchased in small quantities from commercial sources.



1,2-Bis-[(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidenemethyl)amino]benzene (1). An oven-dried 2 L 2-neck flask equipped with a mechanical stirrer was charged with trimethyl orthoformate (850 mL, 7.8 mol) and Meldrum's acid (101 g, 0.700 mmol). The flask was fitted with a reflux condenser; the contents were flushed with N_2 and brought to a gentle reflux for 2 h. The resulting red solution was cooled (~ 80 °C) and phenylene diamine (32.4 g, 300 mmol) was added portionwise (*exothermic reaction*) resulting in the formation of a yellow solid. The mixture was heated to reflux, stirred vigorously for an additional hour and then cooled to room temperature. The resulting solid was filtered, washed with cold acetone (slightly soluble) and dried to afforded 95 g (77%) of product as a flaky light-yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 11.34 (br d, 2H), 8.50 (d, 2H), 7.41 (m, 4H), 1.74 (s, 12H). m.p. 208-210 °C, decomp. (Lit. 209, decomp.).[47a]

4,7-Dihydroxy-1,10-phenanthroline (L1b). A 5 L 3-neck flask equipped with a mechanical stirrer and a large air-cooled reflux condenser was charged with 3 L of diphenyl ether and was heated to 240 °C using a heating mantle. Precursor **1** was added in small portions resulting in vigorous gas evolution. When the addition was complete, the mixture was brought to reflux (260

°C) for 30 min. The mixture was allowed to cool to 80 °C, and the precipitate was isolated by vacuum filtration and washed with acetone until the filtrate was colorless. The product was further washed with excess hexane and diethyl ether. Drying by vacuum filtration, then under hi-vac at 60 °C, afforded 41.5 g (86%) of a fine dark-brown powder. Although the title compound was essentially insoluble in common NMR solvents, a spectrum could be obtained using NaOH in D_2O. ^1H NMR (D_2O, NaOH, 400 MHz) δ 8.17 (d, 2H, J = 5.6 Hz), 7.75 (s, 2H), 6.43 (d, 2H J = 5.6 Hz). Anal Calc. for $C_{12}H_8N_2$: C 67.92, H 3.80. Found: C 67.60, H 3.59. m.p. stable up to 250 °C (Lit. 471-474, decomp.).[48]

4,7-Dichloro-1,10-phenanthroline (L1e). A 1 L 2-neck round bottom flask equipped with a stir bar, reflux condenser, and distillation apparatus was flame-dried and allowed to cool under an atmosphere of N_2. Phosphorous oxychloride (400 mL) and **L1b** (20.0 g, 94.3 mmol) were added to the flask under a N_2 purge. The apparatus was immersed in an oil bath and heated at reflux for 2 h (the condenser for the distillation apparatus was not filled with water at this time). After this period, the circulation of water for the distillation apparatus was turned on and roughly half of the excess phosphorous oxychloride was removed by gentle vacuum distillation. The solution was cooled to room temperature and crushed ice was slowly added to the reaction mixture (*very exothermic!*) while keeping the temperature below 30 °C with an ice bath. When HCl gas evolution ceased, the acidic solution was stirred for one hour at room temperature to dissolve the black solids that formed. The resulting dark cloudy solution was filtered through activated charcoal (Darco®) to give a translucent-beige solution, which was brought to pH 13 by the slow addition of 20% KOH solution while maintaining the temperature below 25 °C. The white precipitate that formed was collected by suction filtration, washed with excess H_2O, and dried

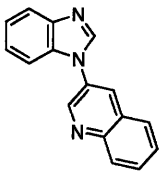
under vacuum overnight at 60 °C affording **L1e** as a white solid. The product was used in the subsequent step without further purification. ^{1}H NMR (DMSO, 400 MHz) δ 9.09 (d, 2H, J = 4.8 Hz), 8.41 (s, 2H), 8.08 (d, 2H, J = 4.8 Hz). m.p. 245-247 (Lit. 249-250).[47c]

4,7-Dimethoxy-1,10-phenanthroline (L1c). An oven-dried 3-neck round bottom flask was cooled under a stream of nitrogen. Anhydrous methanol (1.2 L) was added, and purged with N_2 for 10 min. Sodium metal (9.20 g, 400 mmol) was slowly added in small pieces while the solution was stirred. A reflux condenser was attached, and **L1e** (all that was produced in the previous step) was added. The flask was heated to reflux for 24 hours under an atmosphere of N_2. Concentration of the resulting solution to ~30 mL and addition of cold water (250 mL) resulted in the precipitation of a tan solid. The flask was stored overnight in a refrigerator to allow complete precipitation of the solid. The product was collected by filtration, washed with excess water, and dried under vacuum overnight at 60 °C affording 16.7 g (74% over 2 steps) of a tan solid, which can be recrystallized from benzene. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.93 (d, 2H, J = 5.3 Hz), 8.18 (s, 2H), 7.03 (d, 2H, J = 5.3 Hz), 4.09 (s, 6H). m.p. 210-212 (Lit. 209-210).[47e]

General procedure for the Pd/Me$_4$*t*-BuXPhos *N*-arylation of imidazoles and benzimidazoles.

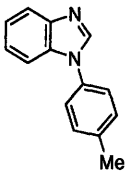
An oven-dried Schlenk tube was charged with a magnetic stir bar, Pd_2dba_3 (0.025 mmol, 5 % Pd), Me$_4$*t*-BuXPhos (0.10 mmol), imidazole/benzimidazole (1.2 mmol) and K_3PO_4 (2.0 mmol). The tube was evacuated and backfilled with argon, and this sequence was two additional times. Aryl halide (1.00 mmol) and solvent (1.0 mL) were then added successively. The reaction tube was sealed, and stirred in a pre-heated oil bath for the designated time period. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (10 mL), and filtered through a plug of celite, eluting with additional ethyl acetate (50 mL). The filtrate was concentrated and the resulting residue

was purified by flash chromatography (100 % CH_2Cl_2 → hexanes : ethyl acetate 3 : 1 → 1 : 3) to provide the desired product.



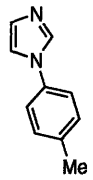
3-benzoimidazol-1-yl-quinoline (2b)

The general procedure was followed using Pd_2dba_3 (23 mg, 0.025 mmol), Me_4t-BuXPhos (48 mg, 0.10 mmol), K_3PO_4 (0.42 g, 2.0 mmol), 3-bromoquinoline (136 μL, 1.0 mmol), and benzimidazole (165 mg, 1.2 mmol) with toluene (1.0 mL) as solvent for 24 h at 100 °C. Chromatographic purification provided the title compound (white crystals, 232 mg, 95 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.02-9.01 (d, 1H, J = 2.3 Hz), 8.20-8.11 (m, 3H), 7.90-7.81 (m, 2H), 7.77-7.71 (m, 1H), 7.63-7.57 (m, 1H), 7.51-7.45 (m, 1H), 7.35-7.27 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.2, 146.3, 144.0, 142.1, 133.6, 130.3, 129.7, 129.6, 129.5, 128.1, 127.8, 127.7, 124.2, 123.2, 120.8, 110.0. m.p. 139-141 °C. (Lit. 136-137).[49]



1-*p*-tolyl-1*H*-benzoimidazole (2c)

The general procedure was followed using Pd_2dba_3 (23 mg, 0.025 mmol), Me_4t-BuXPhos (48 mg, 0.10 mmol), K_3PO_4 (0.42 g, 2.0 mmol), 4-chlorotoluene (120 μL, 1.0 mmol), and benzimidazole (165 mg, 1.2 mmol) with toluene (1.0 mL) as solvent for 24 h at 100 °C. Chromatographic purification provided the title compound (yellow oil, 197 mg, 95 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15-8.11 (m, 1H), 7.91-7.88 (m, 1H), 7.54-7.51 (m, 1H), 7.43-7.32 (m, 6H), 2.48 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.4, 138.1, 130.6, 123.9, 123.6, 122.7, 120.5, 110.5, 21.2.[50]

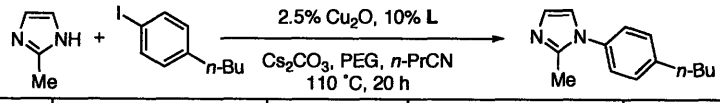


1-*p*-tolyl-1*H*-imidazole (2d)

The general procedure was followed using Pd_2dba_3 (23 mg, 0.025 mmol), Me_4t-BuXPhos (48 mg, 0.10 mmol), K_3PO_4 (0.42 g, 2.0 mmol), 4-bromotoluene (171 mg, 1.0 mmol), and imidazole (82 mg, 1.2 mmol) with N,N-dimethylaniline (1.0 mL) as solvent for 24 h at 100 °C. Chromatographic purification provided the title compound (white crystals, 108 mg, 68 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (bs, 1H), 7.28-7.22 (m, 5H), 7.18 (bs, 1H), 2.40 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.5, 135.7, 130.5, 130.3, 121.5, 118.5, 21.1. m.p. 48-49 °C. (Lit. 49-50).[51]

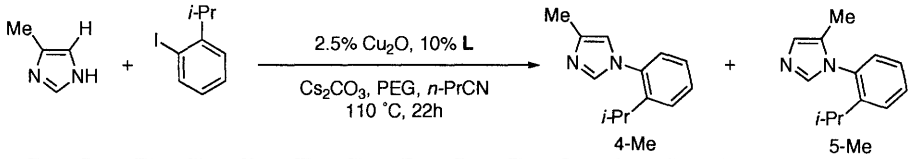
Procedure for screening of the coupling of aryl iodides with imidazoles (Figures 6 and 8)

To a screw-cap test tube, was added copper precatalyst (0.025 mmol), ligand (0.05 mmol, solid), imidazole (0.6 mmol), poly(ethylene glycol) (100 mg), Cs_2CO_3 (0.7 mmol), and a magnetic stir bar. The reaction vessel was fitted with a rubber septum. The vessel was evacuated and back-filled with argon or nitrogen. This was repeated two additional times. Aryl iodide (0.5 mmol), ligand (0.375 mmol, liquid) and solvent (0.25 mL) were added. The reaction tube was sealed and the contents were stirred in a pre-heated oil bath at 110 °C for the designated time period. The reaction mixture was cooled to room temperature, and 113 mL dodecane and dichloromethane (5 mL) were added. This mixture was stirred, then filtered through a small plug of celite into a vial for GC analysis. The average of two experiments is reported.



Ligand	Copper Source	Solvent	Additive	Temperature(°C)	GC Conv. (%)	GC Yield (%)

L1a	Cu_2O	PrCN	PEG	110	21	14
L1b	Cu_2O	PrCN	PEG	110	99	95
L1c1	Cu_2O	PrCN	PEG	110	100	96
L1c1	Cu_2O	PrCN	-	110	100	96
L1c2	Cu_2O	NMP	-	110	100	96
L1d	Cu_2O	PrCN	PEG	110	99	97
L1e1	Cu_2O	PrCN	PEG	110	89	86
L1e2	Cu_2O	NMP	-	110	100	88
L1f	Cu_2O	PrCN	PEG	110	34	30
L2	Cu_2O	PrCN	PEG	110	11	8
L3a	Cu_2O	CH_3CN	-	82	6	3
L3b	CuI	PrCN	PEG	110	15	11
L4a	CuI	DMSO	-	82	23	15
L4b	CuI	DMSO	-	110	28	14
L5	CuI	PrCN	PEG	110	18	13
L6a	CuI	DMF/H2O(10:1)	-	110	88	69
L6b	CuI	PrCN	PEG	110	100	96
L10	CuI	PrCN	PEG	110	75	72

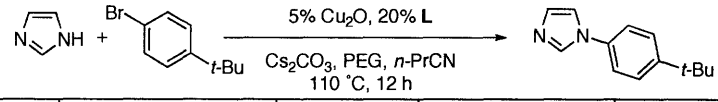


Ligand	Copper Source	Solvent	Additive	Temperature(°C)	GC Conv. (%)	GC Yield (%)	Ratio (4 Me / 5 Me)
L1a	Cu_2O	PrCN	PEG	110	32	31	11
L1b	Cu_2O	PrCN	PEG	110	56	51	42
L1c	Cu_2O	PrCN	PEG	110	68	61	41
L1c	Cu_2O	PrCN	-	110	64	53	30
L1c	Cu_2O	NMP	-	110	91	81	37
L1d	Cu_2O	PrCN	PEG	110	41	39	12
L1e	Cu_2O	PrCN	PEG	110	43	37	11
L1e	Cu_2O	NMP	-	110	77	62	32
L1f	Cu_2O	PrCN	PEG	110	39	35	19
L2	Cu_2O	PrCN	PEG	110	31	30	15
L3a	Cu_2O	CH_3CN	-	82	12	12	n. d.
L3b	CuI	PrCN	PEG	110	34	29	8
L4a	CuI	DMSO	-	82	4	8	n. d.

L4b	CuI	DMSO	-	110	79	66	9
L5	CuI	PrCN	PEG	110	40	36	15
L6a	CuI	DMF/H2O(10:1)	-	110	99	81	64
L6b	CuI	PrCN	PEG	110	66	40	n.d.
L10	CuI	PrCN	PEG	110	28	26	11

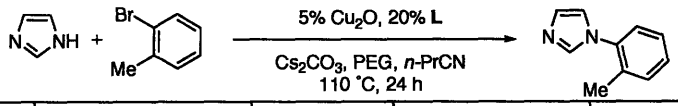
Procedure for screening the coupling of aryl bromides with imidazoles (Figures 5 and 7)

To a screw-cap test tube, was added copper precatalyst (0.05 mmol), ligand (0.01 mmol, solid), imidazole (0.6 mmol), poly(ethylene glycol) (100 mg), Cs_2CO_3 (0.7 mmol), and a magnetic stir bar. The reaction vessel was fitted with a rubber septum. The vessel was evacuated and back-filled with argon or nitrogen. This procedure was repeated two times. Aryl bromide (0.5 mmol), ligand (0.01 mmol, liquid) and solvent (0.25 mL) were then added successively. The reaction tube was sealed and the contents were stirred in a pre-heated oil bath at 110 °C for the designated time period. The reaction mixture was cooled to room temperature and 113 mL dodecane and dichloromethane (5 mL) were added. This mixture was stirred, then filtered through a small plug of celite into a vial for GC analysis. The average of two experiments is reported.



Ligand	Copper Source	Solvent	Additive	Temperature (°C)	GC Conv. (%)	GC Yield (%)
L1a	Cu_2O	PrCN	PEG	110	30	28
L1b	Cu_2O	PrCN	PEG	110	74	75
L1c	Cu_2O	PrCN	PEG	110	97	97
L1c	Cu_2O	PrCN	-	110	68	67
L1c	Cu_2O	NMP	-	110	100	95
L1d	Cu_2O	PrCN	PEG	110	60	61
L1e	Cu_2O	PrCN	PEG	110	51	51
L1e	Cu_2O	NMP	-	110	87	82
L1f	Cu_2O	PrCN	PEG	110	47	41
L2	Cu_2O	PrCN	PEG	110	29	29

L3a	Cu_2O	CH_3CN	-	82	12	9
L3b	CuI	PrCN	PEG	110	21	19
L4a	CuI	DMSO	-	82	7	2
L4b	CuI	DMSO	-	110	46	38
L5	CuI	PrCN	PEG	110	32	33
L6a	CuI	DMF/H2O(10:1)	-	110	60	49
L6b	CuI	PrCN	PEG	110	90	89
L10	CuI	PrCN	PEG	110	27	18



Ligand	Copper Source	Solvent	Additive	Temperature (°C)	GC Conv. (%)	GC Yield (%)
L1a	Cu_2O	PrCN	PEG	110	43	42
L1b	Cu_2O	PrCN	PEG	110	42	40
L1c1	Cu_2O	PrCN	PEG	110	76	78
L1c2	Cu_2O	PrCN	-	110	56	53
L1c3	Cu_2O	NMP	-	110	89	83
L1d	Cu_2O	PrCN	PEG	110	52	50
L1e1	Cu_2O	PrCN	PEG	110	49	47
L1e2	Cu_2O	NMP	-	110	71	66
L1f	Cu_2O	PrCN	PEG	110	42	41
L2	Cu_2O	PrCN	PEG	110	43	41
L3a	Cu_2O	CH_3CN	-	82	16	14
L3b	CuI	PrCN	PEG	110	51	52
L4a	CuI	DMSO	-	82	17	6
L4b	CuI	DMSO	-	110	56	42
L5	CuI	PrCN	PEG	110	37	27
L6a	CuI	DMF/H2O(10:1)	-	110	93	61
L6b	CuI	PrCN	PEG	110	100	85
L10	CuI	PrCN	PEG	110	48	47

General procedure for the *N*-arylation of imidazoles with aryl iodides

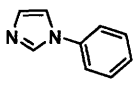
An oven-dried screw-cap test tube was charged with Cu_2O (0.025 mmol), **L1c** (0.075 mmol), imidazole (1.2 mmol), aryl iodide (1.00 mmol, if solid), poly(ethylene glycol) (200 mg), Cs_2CO_3 (1.4 mmol), and a magnetic stir bar. The reaction vessel was fitted with a rubber septum. The

vessel was evacuated and back-filled with argon or nitrogen, and this sequence was repeated an additional time. Aryl iodide (1.00 mmol, if liquid) and solvent (0.5 mL) were then added successively. The reaction tube was sealed, and stirred in a pre-heated oil bath for the designated time period. The reaction mixture was cooled to room temperature, diluted with dichloromethane (10 mL), and filtered through a plug of celite, eluting with additional dichloromethane (50 mL). The filtrate was concentrated and the resulting residue was purified by flash chromatography to provide the desired product.

General procedure for the *N*-arylation of imidazoles with aryl bromides

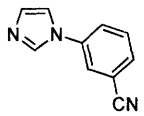
An oven-dried screw-cap test tube was charged with Cu_2O (0.05 mmol), **L1c** (0.15 mmol), imidazole (1.2 mmol), aryl bromide (1.00 mmol, if solid), poly(ethylene glycol) (200 mg), Cs_2CO_3 (1.4 mmol), and a magnetic stir bar. The reaction vessel was fitted with a rubber septum. The vessel was evacuated and back-filled with argon or nitrogen, and this sequence was repeated an additional time. Aryl bromide (1.00 mmol, if liquid), and solvent (0.5 mL) were then added successively. The reaction tube was sealed, immersed, and stirred in a preheated oil bath for the designated time period. The reaction mixture was cooled to room temperature, diluted with dichloromethane (10 mL), filtered through a plug of celite, and eluted with additional dichloromethane (50 mL). The filtrate was concentrated and the resulting residue was purified by flash chromatography to provide the desired product.

Experimental procedures for all compounds contained in Table 1



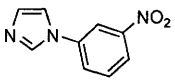
1-phenyl-1*H*-imidazole (3a)

The general procedure was followed using Cu_2O (3.6 mg, 0.025 mmol), **L1c** (18 mg, 0.075 mmol), PEG (200 mg), Cs_2CO_3 (0.45 g, 1.4 mmol), iodobenzene (112 μL, 1.00 mmol), and imidazole (82 mg, 1.2 mmol), with NMP (0.5 mL) as solvent for 3 h at 110 °C. Chromatographic purification (hexane / ethyl acetate 1 : 3) afforded 1-phenyl-1*H*-imidazole (slightly yellow oil, 131 mg, 92%). The low catalyst loading experiment was preformed using the general procedure with Cu_2O (0.4 mg, 0.0025 mmol), **L1c** (1.8 mg, 0.0075 mmol), PEG (2.0 g), Cs_2CO_3 (4.50 g, 14 mmol), iodobenzene (1.12 mL, 10 mmol), and imidazole (820 mg, 12 mmol), in butyronitrile (2.0 mL) as solvent for 48 h at 110 °C. Chromatographic purification (hexane / ethyl acetate 1 : 3) provided 1-phenyl-1*H*-imidazole (slightly yellow oil, 1.34 g, 93%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.47-7.41 (m, 2H), 7.36-7.29 (m, 3H), 7.25 (bs, 1H), 7.18 (bs, 1H).[52]



3-imidazol-1-yl-benzonitrile (3b)

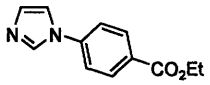
The general procedure was followed using Cu_2O (3.6 mg, 0.025 mmol), **L1c** (18 mg, 0.075 mmol), PEG (200 mg), Cs_2CO_3 (0.45 g, 1.4 mmol), 3-iodobenzonitrile (229 mg, 1.00 mmol), and imidazole (82 mg, 1.2 mmol), with butyronitrile (0.5 mL) as solvent for 24 h at 90 °C. Chromatographic purification (hexane / ethyl acetate 1 : 3) 3-imidazol-1-yl-benzonitrile (white needles, 158 mg, 94%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.71-7.60 (m, 4H), 7.30 (bs, 1H), 7.25 (bs, 1H). m.p. 151-154 °C (Lit. 156-157 °C).[53]



1-(3-nitro-phenyl)-1*H*-imidazole (3c)

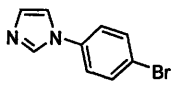
The general procedure was followed using Cu_2O (3.6 mg, 0.025 mmol), **L1c** (18 mg, 0.075 mmol), PEG (200 mg), Cs_2CO_3 (0.45 g, 1.4 mmol), 3-nitroiodobenzene (249 mg, 1.00 mmol),

and imidazole (83 mg, 1.2 mmol) with acetonitrile (0.5 mL) as solvent for 29 h at 80 °C. Chromatographic purification (hexane / ethyl acetate 1 : 3) 1-(3-nitro-phenyl)-1*H*-imidazole (white solid, 177 mg, 93%). ^{1}H NMR (500 MHz, CDCl3) δ 8.25 (t, 1H, J = 1.9), 8.19 (ddd, 1H, J = 1.1, 1.9, 7.9 Hz), 7.94 (s, 1H), 7.75 (ddd, 1H, J = 1.4, 2.2, 8.1 Hz), 7.69 (t, 1H, J = 8.0 Hz), 7.36 (s, 1H), 7.23 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.1, 138.3, 125.5, 131.5, 131.2, 126.9, 122.1, 118.0, 116.2. m.p. 109-110 °C (Lit. 109-110 °C).[54]



4-imidazol-1-yl-benzoic acid ethyl ester (3d)

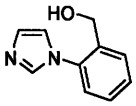
The general procedure was followed using Cu_2O (3.6 mg, 0.025 mmol), **L1c** (18 mg, 0.075 mmol), PEG (200 mg), Cs_2CO_3 (0.45 g, 1.4 mmol), ethyl-4-iodobenzoate (168 μL, 1.00 mmol), and imidazole (82 mg, 1.2 mmol), 3 Å molecular sieves (200 mg, powdered, flame activated) with acetonitrile (0.5 mL) as solvent for 23 h at 80 °C. Chromatographic purification (hexane / ethyl acetate 1 : 3) 4-imidazol-1-yl-benzoic acid ethyl ester (white crystals, 184 mg, 84%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (td, 2H, J = 1.8, 8.5 Hz), 7.96 (s, 1H), 7.48 (td, 2H, J = 1.8, 8.8), 7.37 (s, 1H), 7.26 (s, 1H), 4.43 (q, 2H, J = 7.1 Hz), 1.44 (t, 3H, J = 7.0 Hz). m.p. 101-103 °C (Lit. 100-102 °C).[55]



1-(4-bromo-phenyl)-1*H*-imidazole[56] (3e)

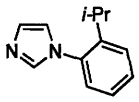
The general procedure was followed using Cu_2O (3.6 mg, 0.025 mmol), **L1c** (18 mg, 0.075 mmol), PEG (200 mg), Cs_2CO_3 (0.45 g, 1.4 mmol), 1-bromo-4-iodobenzene (340 mg, 1.20 mmol), and imidazole (68 mg, 1.0 mmol) with butyronitrile (0.5 mL) as solvent for 24 h at 90 °C. Chromatographic purification (hexane / ethyl acetate 1 : 1) provided 1-(4-bromo-phenyl)-1*H*-

imidazole (white crystals, 171 mg, 78%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (bs, 1H), 7.63 (m, 2H), 7.32-7.20 (m, 4H). m.p. 120-122 °C. GC/MS of the crude material showed an 6.1 : 1 mixture of 1-(4-bromo-phenyl)-1*H*-imidazole to 1-(4-iodo-phenyl)-1*H*-imidazole.



(2-imidazol-1-yl-phenyl)-methanol (3f)

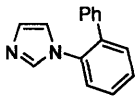
The general procedure was followed using Cu_2O (3.6 mg, 0.025 mmol), **L1c** (18 mg, 0.075 mmol), PEG (200 mg), Cs_2CO_3 (0.45 g, 1.4 mmol), 2-iodobenzylalcohol (234 mg, 1.00 mmol), and imidazole (82 mg, 1.2 mmol) with butyronitrile (0.3 mL) as solvent for 24 h at 110 °C. Chromatographic purification (hexane / ethyl acetate 1 : 1) provided (2-imidazol-1-yl-phenyl)-methanol (clear crystals, 165 mg, 95%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (dd, 2H, J = 1.7, 7.6 Hz), 7.45 (td, 1H, J = 1.4, 7.5 Hz), 7.38 (td, 1H, J = 1.4, 7.4 Hz), 7.23 (dd, 1H, J = 1.1, 7.7 Hz), 7.13 (s, 1H), 7.08 (s, 1H), 4.90 (bs, 1H), 4.46 (s, 1H). m.p. 102-104 °C (Lit. 100.5-102.5 °C).[57]



1-(2-isopropyl-phenyl)-1*H*-imidazole (3g)

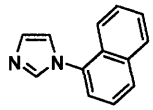
The general procedure was followed using Cu_2O (3.6 mg, 0.025 mmol), **L1c** (18 mg, 0.075 mmol), PEG (200 mg), Cs_2CO_3 (0.45 g, 1.4 mmol), 2-isopropyl iodobenzene (246 mg, 1.00 mmol), and imidazole (82 mg, 1.2 mmol) with butyronitrile (0.5 mL) as solvent for 48 h at 110 °C. Chromatographic purification (hexane / ethyl acetate 1 : 1) provided 1-(2-isopropyl-phenyl)-1*H*-imidazole (white crystals, 171 mg, 92%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (bs, 1H), 7.46-7.42 (m, 2H), 7.31-7.11 (m, 3H), 7.05 (m, bs), 2.74 (heptet, 1H, J = 6.9 Hz), 1.16 (d, 6H, J = 6.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.0, 135.1, 129.4, 129.2, 127.0, 126.7, 126.4, 121.1, 27.4, 24.0. m.p. 76-77 °C (Lit. 67-68 °C).[58] Anal. Calc. for $C_{12}H_{14}N_2$: C 77.38, H 7.58. Found: C 77.42,

H 7.78.



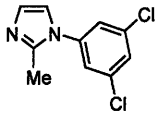
1-biphenyl-2-yl-1*H*-imidazole (3h)

The general procedure was followed using Cu_2O (7.2 mg, 0.05 mmol), **L1c** (36 mg, 0.15 mmol), PEG (200 mg), Cs_2CO_3 (0.45 g, 1.4 mmol), 2-iodobiphenyl (176 μL, 1.00 mmol), and imidazole (82 mg, 1.2 mmol) with butyronitrile (0.6 mL) as solvent for 72 h at 120 °C. Chromatographic purification (hexane / ethyl acetate 1 : 1) provided 1-biphenyl-2-yl-1*H*-imidazole (slightly yellow crystals, 179 mg, 81%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50-7.33 (m, 5H), 7.30-7.24 (m, 3H), 7.02 (bs, 1H), 6.82 (bs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.8, 137.5, 135.2, 131.5, 128.7, 128.7, 128.6, 128.3, 127.8, 126.3. Anal. Calc. for $C_{15}H_{12}N_2$: C 81.79, H 5.49. Found: C 81.50, H 5.46. m.p. 93-95 °C.



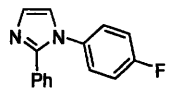
1-naphthalen-1-yl-1*H*-imidazole (3i)

The general procedure was followed using Cu_2O (7.2 mg, 0.05 mmol), **L1c** (36 mg, 0.15 mmol), PEG (200 mg), Cs_2CO_3 (0.45 g, 1.4 mmol), 1-iodonaphthalene (146 μL, 1.00 mmol), and imidazole (82 mg, 1.2 mmol) with NMP (0.3 mL) as solvent for 24 h at 110 °C. The crude reaction mixture was dissolved in 20 mL of water, and extracted with dichloromethane (5 x 30 mL). The combined organic layers were dried with $MgSO_4$, and the solvent was removed *in vacuo*. Chromatographic purification (hexane / ethyl acetate 1 : 1) provided 1-naphthalen-1-yl-1*H*-imidazole (yellow-white solid, 179 mg, 92%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94-7.92 (m, 2H), 7.76, (bs, 1H), 7.61-7.48 (m, 4 H), 7.43 (d, 1H, J = 7.0 Hz), 7.30 (bs, 1H), 7.25 (bs, 1H). m.p. 63-64 °C (Lit. 62 °C).[59]



1-(3,5-dichloro-phenyl)-2-methyl-1*H*-imidazole (3j)

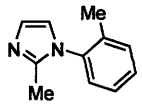
The general procedure was followed using Cu_2O (7.2 mg, 0.05 mmol), **L1c** (36 mg, 0.15 mmol), PEG (200 mg), Cs_2CO_3 (0.45 g, 1.4 mmol), 1,3-dichloro-5-iodobenzene (273 mg, 1.00 mmol), 2-methylimidazole (100 mg, 1.2 mmol) with butyronitrile (0.5 mL) as solvent for 24 h at 110 °C. Chromatographic purification (hexane / ethyl acetate 1 : 3) provided 1-(3,5-dichloro-phenyl)-2-methyl-1*H*-imidazole (white needles, 194 mg, 86%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (t, 1H, J = 1.8), 7.23 (d, 2H, J = 1.9), 7.05 (d, 1H, J = 1.2), 6.99, (d, 1H, J = 1.2), 2.40 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.8, 135.8, 128.5, 128.4, 124.1, 14.0. IR (KBr disc, cm^{-1}) 1534, 1501, 1463, 1451, 1405, 1305, 1176, 1143, 1115, 1099, 985, 850, 781. Anal. Calc. for $C_{10}H_8N_2Cl_2$: C 52.89, H 3.55. Found: C 52.95, H 3.44. m.p. 122-125 °C.



1-(4-fluoro-phenyl)-2-phenyl-1*H*-imidazole (3k)

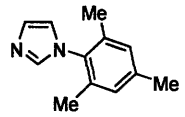
The general procedure was followed using Cu_2O (3.6 mg, 0.025 mmol), **L1c** (18 mg, 0.075 mmol), PEG (200 mg), Cs_2CO_3 (0.45 g, 1.4 mmol), 4-fluoroiodobenzene (222 mg, 1.00 mmol), 2-phenylimidazole (173 mg, 1.2 mmol) with butyronitrile (0.3 mL) as solvent for 24 h at 110 °C. Chromatographic purification (hexane / ethyl acetate 3 : 1) provided 1-(4-fluoro-phenyl)-2-phenyl-1*H*-imidazole (white solid, 211 mg, 89%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.30 (m, 2H), 7.24-7.16 (m, 4H), 7.15-7.09 (m, 2H), 7.06 (s, 1H), 7.03-6.96 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 160.2, 134.5, 129.0, 128.5, 128.4, 128.2, 127.6, 127.5, 116.5, 116.2. IR (KBr disc, cm^{-1}) 1509, 1501, 1466, 1414, 1303, 1285, 1233, 1212, 1151, 1128, 1091, 1068, 970, 915, 840, 775, 747, 715, 697. Anal. Calc. for $C_{15}H_{11}N_2F$: C 75.62, H 4.65. Found: C 75.39, H

4.62. m.p. 112-114 °C.



2-methyl-1-*o*-tolyl-1*H*-imidazole (3l)

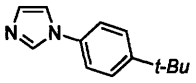
The general procedure was followed using CuI (19 mg, 0.10 mmol), **L1c** (36 mg, 0.15 mmol), PEG (200 mg), Cs_2CO_3 (0.45 g, 1.4 mmol), 2-iodotoluene (127 μL, 1.00 mmol), and imidazole (82 mg, 1.2 mmol) except NMP (0.5 mL) was used as solvent and the reaction was carried out for 48 h at 140 °C. Chromatographic purification (hexane / ethyl acetate 1 : 3) afforded 2-methyl-1-*o*-tolyl-1*H*-imidazole (yellow oil, 149 mg, 86%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.09 (m, 4H), 6.99 (bs, 1H), 6.81 (bs, 1H), 2.12 (s, 3H), 1.99 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.9, 137.6, 135.5, 133.5, 129.6, 129.1, 120.1, 21.1, 17.4. IR (KBr disc, cm^{-1}) 1524, 1501, 1461, 1416, 1303, 1178, 1141, 1093, 1045, 986, 770, 726, 697.



1-(2,4,6-trimethyl-phenyl)-1*H*-imidazole (3m)

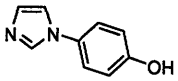
The general procedure was followed using Cu_2O (7.2 mg, 0.05 mmol), **L1c** (36 mg, 0.15 mmol), PEG (200 mg), Cs_2CO_3 (0.45 g, 1.4 mmol), 2-iodotoluene (127 μL, 1.00 mmol), 2-methylimidazole (100 mg, 1.2 mmol) except that DMSO (0.5 mL) was used as solvent and the reaction was carried out for 48 h at 150 °C. Chromatographic purification (hexane / ethyl acetate 1 : 3) afforded 1-(2,4,6-trimethyl-phenyl)-1*H*-imidazole (yellow oil, 96 mg, 51%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (s, 1H), 7.21 (s, 1H), 6.95 (s, 2H), 6.87 (s, 1H), 2.32 (s, 3H), 1.97, (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.1, 136.9, 135.3, 131.1, 129.1, 127.7, 127.4, 126.9, 120.4, 17.2, 13.1. m.p. 107-109 °C (Lit. 107-108 °C).[60]

Experimental procedures for all compounds contained in Table 2



1-(4-*tert*-butyl-phenyl)-1*H*-imidazole[61] (4a)

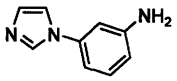
The general procedure was followed using Cu_2O (7.2 mg, 0.05 mmol), **L1c** (36 mg, 0.175 mmol), PEG (200 mg), Cs_2CO_3 (0.45 g, 1.4 mmol), 4-t-butylbromobenzene (173 μL, 1.00 mmol), and imidazole (82 mg, 1.2 mmol) with butyronitrile (0.25 mL) as solvent for 15 h at 110 °C. Chromatographic purification (hexane / ethyl acetate 1 : 3) afforded 1-(4-*tert*-butyl-phenyl)-1*H*-imidazole (white crystals, 174 mg, 87%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.3 (m, 2H), 7.25 (m, 2H), 7.20 (s, 1H), 7.15 (s, 1H), 1.30 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.6, 135.6, 134.8, 130.2, 126.7, 121.1, 118.3, 34.6, 31.3. IR (KBr disc, cm^{-1}) 1525, 1462, 1365, 1302, 1266, 1243, 1120, 1106, 1061, 903. Anal Calc. for $C_{13}H_{16}N_2$: C 77.96, H 8.05. Found: 77.56, H 8.00. m.p. 90-91 °C.



4-imidazol-1-yl-phenol (4b)

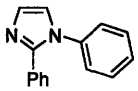
The general procedure was followed using Cu_2O (7.2 mg, 0. 05 mmol), **L1c** (36 mg, 0.15 mmol), PEG (400 mg), Cs_2CO_3 (1.0 g, 3.0 mmol), 4-bromophenol (172 mg, 1.00 mmol), and imidazole (82 mg, 1.2 mmol) with butyronitrile (0.5 mL) as solvent for 15 h at 110 °C. After cooling to ambient temperature, the crude reaction mixture was dissolved in 20 mL 2M $HCl_{(aq)}$, and washed once with diethyl ether. The aqueous layer was brought to pH 8 with Na_2CO_3, and extracted repeatedly with CH_2Cl_2. The combined organic layers were dried with anhydrous $MgSO_4$, and concentrated. Chromatographic purification (1% ethanol in ethyl acetate, dry pack) afforded 4-imidazol-1-yl-phenol (white crystals, 198 mg, 90%). ^{1}H NMR (300 MHz, CD_3OD) δ 7.95 (bs,

1H), 7.41 (bs, 1H), 7.35-7.30 (m, 2H), 7.01 (bs, 1H), 6.92-6.87 (m, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ 158.7, 130.8, 129.8, 124.3, 117.4, 24.0. m.p. 196-198 °C (Lit. 188-190°C [203-205 °C MeOH, H_2O]).[62]



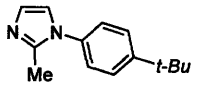
3-imidazol-1-yl-phenylamine (4c)

The general procedure was followed using Cu_2O (7.2 mg, 0.05 mmol), **L1c** (36 mg, 0.15 mmol), PEG (200 mg), Cs_2CO_3 (0.45 g, 1.4 mmol), 3-bromoaniline (109 μL, 1.00 mmol), and imidazole (82 mg, 1.2 mmol) with butyronitrile (0.25 mL) as solvent for 20 h at 110 °C. Chromatographic purification (ethyl acetate) afforded 3-imidazol-1-yl-phenylamine (white powder, 141 mg, 88%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (bs, 1H), 7.21-7.15 (m, 3H), 6.72-6.68 (m, 1H), 6.64-6.60 (m, 2H). 4.01 (bs, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.2, 138.4, 135.6, 130.7, 130.1, 118.4, 114.0, 111.1, 107.7. m.p. 112-114 °C (Lit. 111-113 °C).[63]



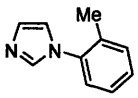
1,2-diphenyl-1*H*-imidazole (4d)

The general procedure was followed using Cu_2O (14.4 mg, 0.10 mmol), **L1c** (72 mg, 0.30 mmol), PEG (200 mg), Cs_2CO_3 (0.45 g, 1.4 mmol), 4-t-butylbromobenzene (173 μL, 1.00 mmol), and imidazole (82 mg, 1.2 mmol) with butyronitrile (0.6 mL) as solvent for 72 h at 120 °C. Chromatographic purification (hexane / ethyl acetate 1 : 1) afforded 1,2-diphenyl-1*H*-imidazole (white crystals, 198 mg, 90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.32 (m, 5H), 7.28-7.16 (m, 6H), 7.14 (d, 1H, J = 1.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6, 130.4, 129.5, 129.1, 128.6, 128.4, 128.2, 128.2, 125.9, 123.0. m.p. 88-89 °C (Lit. 90 °C).[64]



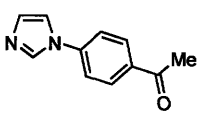
1-(4-*tert*-butyl-phenyl)-2-methyl-1*H*-imidazole (4e)

The general procedure was followed using Cu_2O (7.2 mg, 0.05 mmol), **L1c** (36 mg, 0.15 mmol), PEG (200 mg), Cs_2CO_3 (0.45 g, 1.4 mmol), 4-t-butylbromobenzene (173 μL, 1.00 mmol), 2-methylimidazole (100 mg, 1.2 mmol) with butyronitrile (0.25 mL) as solvent for 48 h at 110 °C. Chromatographic purification (hexane / ethyl acetate 1 : 3) afforded 1-(4-*tert*-butyl-phenyl)-2-methyl-1*H*-imidazole (yellow oil, 207 mg, 97%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (m, 2H), 7.12 (m, 1H), 6.94 (bs, 1H), 6.91 (bs, 1H), 2.28 (s, 3H), 1.29 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.1, 135.3, 127.5, 126.3, 124.9, 12.7, 34.6, 31.3, 13.8. IR (KBr Disc, cm $^{-1}$) 2962, 2870, 1608, 1579, 1513, 1463, 1419, 1365, 1302, 1269, 1178, 1139, 1114, 996, 986, 842, 730, 674, 571.



1-*ortho*-tolyl-1*H*-imidazole (4f)

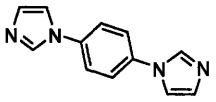
The general procedure was followed using Cu_2O (7.2 mg, 0.05 mmol), **L1c** (36 mg, 0.15 mmol), PEG (200 mg), Cs_2CO_3 (0.45 g, 1.4 mmol), 2-bromotoluene (120 μL, 1.00 mmol), and imidazole (82 mg, 1.2 mmol) with butyronitrile (0.3 mL) as solvent for 28 h at 110 °C. Chromatographic purification (hexane / ethyl acetate 1 : 1) afforded 1-*ortho*-tolyl-1*H*-imidazole (yellow oil, 140 mg, 89%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (bs, 1H), 7.37-7.28 (m, 3H), 7.23-7.20 (m, 2H), 7.06 (bs, 1H), 2.19 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.2, 138.4, 135.6, 130.7, 130.1, 118.4, 114.0, 111.1, 107.7.[65]



1-(4-imidazol-1-yl-phenyl)-ethanone (4g)

The general procedure was followed using Cu_2O (7.2 mg, 0.05 mmol), **L1c** (36 mg, 0.15 mmol),

PEG (200 mg), Cs_2CO_3 (0.45 g, 1.4 mmol), 4-bromoacetophenone (199 mg, 1.00 mmol), and imidazole (82 mg, 1.2 mmol) with butyronitrile (0.4 mL) as solvent for 48 h at 110 °C. Chromatographic purification (hexane / ethyl acetate 1 : 3) afforded 1-(4-imidazol-1-yl-phenyl)-ethanone (white solid, 159 mg, 86%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04, (m, 2H), 7.92 (bs, 1H), 7.46 (m, 2H), 7.33 (bs, 1H), 7.19 (bs, 1H), 2.59 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.6, 140.7, 135.7, 135.4, 131.2, 130.4, 120.7, 117.8, 26.7. m.p. 112-114 °C (Lit. 110-112 °C).[66]



1,4-*bis*(imidazol-1-yl)-benzene[67] (4h)

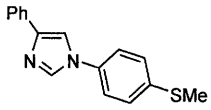
The general procedure was followed using Cu_2O (7.2 mg, 0.05 mmol), **L1c** (36 mg, 0.15 mmol), Cs_2CO_3 (0.90 g, 2.8 mmol), 1,4-dibromobenzene (236 mg, 1.00 mmol), and imidazole (164 mg, 2.4 mmol) with NMP (0.5 mL) as solvent for 30 h at 110 °C. The crude reaction mixture was diluted in excess CH_2Cl_2, and filtered through a celite plug. After removal of the solvent *in vacuo*, the product was crystallized from EtOAc and stored in a freezer at -23 °C overnight, to afford 1,4-*bis*(imidazol-1-yl)-benzene (white solid, 200 mg, 95%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (bs, 2H), 7.54 (s, 4H), 7.32 (bs, 1H), 7.26 (bs, 1H). m.p. 190 °C (dec.). IR (KBr disc, cm^{-1}) 1534, 1485, 1304, 1248, 1105, 1059. Anal Calc. for $C_{12}H_{10}N_4$: C 68.56, H 4.79. Found C 68.49, H 4.90.

Experimental procedures for all compounds contained in Table 5

An oven-dried screw-cap test tube was charged with Cu_2O (0.05 mmol), ligand (0.15 mmol), imidazole (1.0 mmol), Cs_2CO_3 (1.4 mmol), and a magnetic stir bar. The reaction vessel was fitted with a rubber septum. The vessel was evacuated and back-filled with argon, and this sequence was repeated an additional time. Aryl chloride (1.00 mmol, liquid) and NMP (0.25 mL) were then added

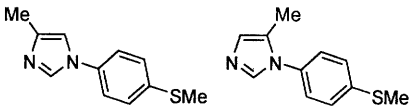
successively by syringe. The reaction tube was sealed, and stirred in a pre-heated oil bath at 150 °C for 24. The reaction mixture was cooled to room temperature. Dichloromethane (10 mL), and 225 μL dodecane were stirred into the reaction mixture, which was subsequently filtered through a short celite plug for GC Analysis.

Experimental procedures for all compounds contained in Table 6



1-(4-methylsulfanyl-phenyl)-4-phenyl-1*H*-imidazole (6a)

The general procedure was followed using Cu_2O (7.2 mg, 0.05 mmol), **L1c** (36 mg, 0.15 mmol), PEG (200 mg), Cs_2CO_3 (0.45 g, 1.4 mmol), 4-bromothioanisole (203 mg, 1.00 mmol), 4-phenylimidazole (173 mg, 1.2 mmol) with butyronitrile (0.4 mL) as solvent for 17 h at 110 °C. Chromatographic purification (hexane / ethyl acetate 1 : 1) afforded 1-(4-methylsulfanyl-phenyl)-4-phenyl-1*H*-imidazole (white crystals, 254 mg, 95%). GC analysis and ^1H NMR showed no trace of a second regioisomer. ^1H NMR (300 MHz, $CDCl_3$) δ 7.87-7.83 (m, 3H), 7.54 (d, 1H, 1.4 Hz), 7.44-7.34 (m, 6H), 7.32-7.26 (m, 2H), 2.53 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 143.3, 138.4, 135.8, 134.5, 133.8, 128.8, 127.8, 127.3, 125.1, 122.0, 113.9, 16.1. IR (KBr disc, cm^{-1}) 1550, 1508, 1443, 1420, 1313, 1252, 1070, 957, 936, 920, 828, 817, 758, 703. Anal. Calc. for $C_{16}H_{14}N_2S$: C 72.15, H 5.30. Found: C 71.98, H 5.34. m.p. 122-124°C.

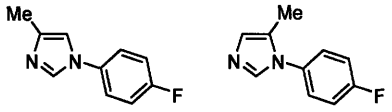


A B

4-methyl-1-(4-methylsulfanyl-phenyl)-1*H*-imidazole (6b)

The general procedure was followed using Cu_2O (7.2 mg, 0.05 mmol), **L1c** (36 mg, 0.15 mmol),

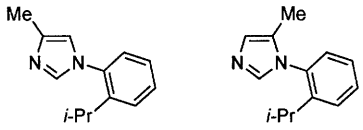
PEG (200 mg), Cs_2CO_3 (0.45 g, 1.4 mmol), 4-bromothioanisole (203 mg, 1.00 mmol), 4-methylimidazole (100 mg, 1.2 mmol) with butyronitrile (0.3 mL) as solvent for 48 h at 110 °C. Chromatographic purification (hexane / ethyl acetate 1 : 1) afforded 4-methyl-1-(4-methylsulfanyl-phenyl)-1*H*-imidazole (yellow oil, 203 mg, 100%). ^{1}HNMR showed a 3.0 : 1 mixture of A : B. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (bs, 1H), 7.28-7.11 (m, 4H), 6.90 (bs, 1H), 2.46 (s, minor regioisomer), 2.43 (s, major regioisomer). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 135.9, 134.6, 133.9, 128.9, 127.9, 125.1, 122.0, 113.9, 16.7, 15.6.. Anal. Calc. for $C_{11}H_{12}N_2S$: C 64.67, H 5.92. Found: C 64.29, H 5.93.



A B

1-(4-fluoro-phenyl)-4-methyl-1*H*-imidazole (6c)

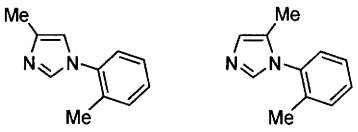
The general procedure was followed using Cu_2O (7.2 mg, 0.05 mmol), **L1c** (36 mg, 0.15 mmol), PEG (200 mg), Cs_2CO_3 (0.45 g, 1.4 mmol), 1-bromo-4-fluorobenzene (109 μL, 1.00 mmol), 4-phenylimidazole (173 mg, 1.2 mmol) with butyronitrile (0.5 mL) as solvent for 15 h at 110 °C. Chromatographic purification (hexane / ethyl acetate 1 : 1) afforded 1-(4-Fluoro-phenyl)-4-methyl-1*H*-imidazole (yellow solid/liquid, 161 mg, 92%). ^{1}HNMR showed a 5.0 : 1 mixture of regioisomers. By GC, the ratio of A : B was determined to be 5.7 : 1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (bs, 1H), 7.31-7.24 (m, 2H), 7.15-7.07 (m, 2H), 6.92 (bs, 1H), 2.26 (s, 1H, major regioisomer), 2.12 (s, 1H, minor regioisomer). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5, 160.5, 139.8, 134.9, 133.9, 123.1, 116.8, 13.7. IR (KBr disc, cm^{-1}) 1519, 1449, 1324, 1293, 1227, 1160, 1101, 1071, 1007, 974, 926, 816. Anal. Calc. for $C_{10}H_9N_2F$: C 68.17, H 5.15. Found: C 68.30, H 5.19. m.p. 22-24 °C



A B

1-(2-isopropyl-phenyl)-4-methyl-1*H*-imidazole (6d)

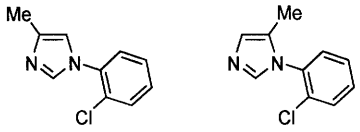
The general procedure was followed using Cu_2O (3.6 mg, 0.025 mmol), **L1c** (18 mg, 0.075 mmol), PEG (200 mg), Cs_2CO_3 (0.45 g, 1.4 mmol), 2-isopropyliodobenzene (160 μL, 1.00 mmol), 4-methylimidazole (100 mg, 1.2 mmol) with butyronitrile (0.3 mL) as solvent for 20 h at 110 °C. GC and GC/MS analysis of the crude material showed an 82% yield and 41 : 1 ratio of A : B. (See GC screens on p. S8) ^{1}H NMR of the purified material showed a 16 : 1 ratio of A : B. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48-7.40 (m, 3H), 7.28-7.15 (m, 2H), 6.75 (t, 1H, J = 0.9 Hz), 2.80 (heptet, 1H, J = 6.9 Hz), 2.31 (d, 3H, J = 0.8 Hz), 1.18 (d, 6H, J = 6.9 Hz).



A B

4-methyl-1-*o*-tolyl-1*H*-imidazole[68] (6e)

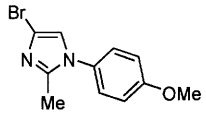
The general procedure was followed using Cu_2O (3.6 mg, 0.025 mmol), **L1c** (18 mg, 0.075 mmol), PEG (200 mg), Cs_2CO_3 (0.45 g, 1.4 mmol), 2-iodotoluene (127 μL, 1.00 mmol), 4-methylimidazole (100 mg, 1.2 mmol), with butyronitrile (0.3 mL) as solvent for 24 h at 110 °C. GC Analysis showed a 23 : 1 ratio of regioisomers. Chromatographic purification (hexane / ethyl acetate 1 : 3) provided 4-methyl-1-*o*-tolyl-1*H*-imidazole (yellow oil, 154 mg, 87%). ^{1}H NMR of the purified material showed a 16 : 1 ratio of A : B. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (bs, 1H), 7.35-7.14 (m, 4H), 6.75 (bs, 1H), 2.28 (s, 3H, major isomer), 2.17 (s, 3H, major isomer), 2.11 (s, minor isomer), 1.97 (s, minor regioisomer). (KBr disc, cm^{-1}) 1507, 1448, 1386, 1364, 1294, 1269, 1231, 1191, 1122, 1073. 1002, 971.



A B

1-(2-chloro-phenyl)-4-methyl-1*H*-imidazole (6f)

The general procedure was followed using Cu_2O (3.6 mg, 0.025 mmol), **L1c** (18 mg, 0.075 mmol), PEG (200 mg), Cs_2CO_3 (0.45 g, 1.4 mmol), 2-chloroiodobenzene (122 μL, 1.00 mmol), 4-methylimidazole (100 mg, 1.2 mmol) with butyronitrile (0.3 mL) as solvent for 15 h at 110 °C. Chromatographic purification (hexane / ethyl acetate 1 : 1) afforded 1-(2-chloro-phenyl)-4-methyl-1*H*-imidazole (yellow oil, 191 mg, 99%). ^{1}HNMR showed a 12.1 : 1 mixture of A : B. By GC, the ratio was determined to be 19 : 1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (bs, 1H), 7.47-7.39 (m, 1H), 7.29-7.18 (m, 3H), 6.78 (bs, 1H), 2.21 (s, major regioisomer), 2.06 (d, minor regioisomer). ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.1, 130.7, 129.4, 129.2, 127.7, 127.4, 13.6. IR (KBr disc, cm^{-1}) 1593, 1570, 1503, 1447, 1392, 1369, 1290, 1232, 1202, 1131, 1084, 1059, 1035, 1004, 973, 819, 761, 633. Anal. Calc. for $C_{10}H_9N_2F$: C 68.17, H 5.15. Found: C 68.30, H 5.19.

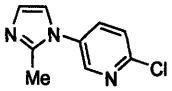


4-bromo-1-(4-methoxy-phenyl)-2-methyl-1*H*-imidazole (6g)

The general procedure was followed using CuI (9.5 mg, 0.05 mmol), **L1c** (18 mg, 0.075 mmol), Cs_2CO_3 (0.45 g, 1.4 mmol), 4-iodoanisole (280 mg, 1.2 mmol), 4-bromo-2-methylimidazole (161 mg, 1.00 mmol) with acetonitrile (1.0 mL) as solvent for 24 h at 110 °C. Chromatographic purification (hexane / ethyl acetate 3 : 1) provided 4-bromo-1-(4-methoxy-phenyl)-2-methyl-1*H*-imidazole (white crystalline solid, 218 mg, 82%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.09 (m, 2H), 6.89, (m, 2H), 6.82 (s, 1H), 3.79, (s, 3H), 2.12 (s, 3H) ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 145.1, 129.6, 126.7, 119.7, 114.6, 113.8, 55.53, 13.4. IR (KBr disc, cm^{-1}) 1559, 1507, 1457,

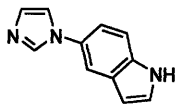
1437, 1419, 1299, 1239, 1181, 1167, 1135, 1108, 1032, 1020, 949, 668. Anal. Calc. for $C_{11}H_{11}BrN_2O$: C 49.46, H 4.15. Found: C 49.51, H 4.03. m.p. 136-137 °C.

Experimental procedures for all compounds contained in Table 7



2-chloro-5-(2-methyl-imidazol-1-yl)-pyridine (7a)

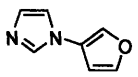
The general procedure was followed using Cu_2O (3.6 mg, 0.025 mmol), **L1c** (18 mg, 0.075 mmol), PEG (200 mg), Cs_2CO_3 (0.45 g, 1.4 mmol), 5-iodo-2-chloropyridine (239 mg, 1.00 mmol), 2-methylimidazole (100 mg, 1.2 mmol) with butyronitrile (1.0 mL) as solvent for 24 h at 110 °C. Chromatographic purification (ethyl acetate) provided 2-chloro-5-(2-methyl-imidazol-1-yl)-pyridine (white solid, 143 mg, 74%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.33, (d, 1H, J = 2.9 Hz), 7.59 (dd, 1H, J = 2.9, 8.7 Hz), 7.43 (d, 1H, 8.7, Hz), 6.99 (d, 1H, 1.2 Hz), 6.95 (d, 1H, J = 1.6 Hz), 2.31 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.9, 136.0, 128.7, 128.5, 124.4, 124.2, 120.5, 120.4, 14.1. IR (KBr disc, cm^{-1}) 1503, 1476, 1415, 1386, 1300, 1177, 1151, 1109, 993, 982. m.p. 147-149 °C.



5-imidazol-1-yl-1*H*-indole (7b)

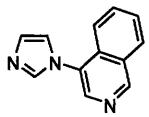
The general procedure was followed using Cu_2O (3.6 mg, 0.025 mmol), **L1c** (18 mg, 0.075 mmol), PEG (200 mg), Cs_2CO_3 (0.45 g, 1.4 mmol), 5-iodoindole (243 mg, 1.00 mmol), and imidazole (82 mg, 1.2 mmol) with butyronitrile (0.3 mL) as solvent for 13 h at 110 °C. Chromatographic purification (ethyl acetate) provided 5-imidazol-1-yl-1*H*-indole (white solid, 152 mg, 83%). ^{1}H NMR (300 MHz, $CDCl_3/CD_3CN$) δ 10.0 (bs, 1H), 7.9 (1H), 7.79-7.65 (1H),

7.60-7.48 (1H), 7.44-7.43 (2H), 7.28 (s, 1H), 7.21 (dd, 1H), 6.68-6.60 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.2, 136.5, 135.4, 129.6 128.4, 126.8, 119.9, 116.8, 114.3, 112.3, 102.6. IR (KBr disc, cm^{-1}) 1541, 1498, 1457, 1436, 1346, 1309, 1268, 1241, 1110, 1055, 916, 870, 725. Anal. Calc. for $C_{11}H_9N_3$: C 72.11, H 4.95. Found: C 72.43, H 4.95. m.p. 144-146 °C.



1-furan-3-yl-1*H*-imidazole (7c)

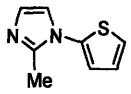
The general procedure was followed using Cu_2O (7.2 mg, 0.05 mmol), **L1c** (36 mg, 0.15 mmol), PEG (200 mg), Cs_2CO_3 (0.45 g, 1.4 mmol), 2-bromofuran (108 μL, 1.2 mmol), and imidazole (68 mg, 1.00 mmol) with DMSO (0.5 mL) as solvent for 24 h at 110 °C. Chromatographic purification (ethyl acetate / hexane 3 : 1) provided 1-furan-3-yl-1*H*-imidazole (white solid, 89 mg, 67%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.71 (bs, 1H), 7.62 (dd, 1H, J = 0.8, 1.7 Hz), 7.42 (dd, 1H, J = 1.7, 1.9 Hz), 7.22-7.06 (bs, 2H), 6.54 (dd, 1H, J = 0.8, 1.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.9, 133.0, 126.0, 106.2. IR (neat, cm^{-1}) 2092, 1523, 1489, 1406, 1317, 1252, 1173, 1025. m.p. 39-41 °C.



4-imidazol-1-yl-isoquinoline (7d)

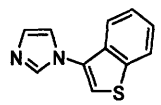
The general procedure was followed using Cu_2O (7.2 mg, 0.05 mmol), **L1c** (36 mg, 0.15 mmol), PEG (200 mg), Cs_2CO_3 (0.45 g, 1.4 mmol), 4-bromoisoquinoline (250 mg, 1.2 mmol), and imidazole (68 mg, 1.00 mmol) with DMSO (0.5 mL) as solvent for 24 h at 110 °C. Chromatographic purification (ethyl acetate / hexane 3 : 1) provided the title compound (clear crystals, 165 mg, 85%). ^1H NMR (300 MHz, $CDCl_3$) δ 9.27 (d, 1H, 0.9 Hz), 8.48 (s, 1H), 8.08 (m, 1H), 7.78-7.62, (m, 4H), 7.30 (bs, 1H), 7.25 (bs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.3,

139.6, 138.2, 132.1, 131.9, 130.2, 129.2, 128.8, 128.4, 127.9, 121.5, 121.2. IR (KBr disc, cm^{-1}) 1589, 1508, 1491, 1406, 1382, 1307, 1260, 1250, 1194, 1107, 1078, 1038, 942, 913, 782, 756, 660, 589. Anal. Calc. for $C_{12}H_9N_3$: C 73.43 H 4.65. Found: C 73.43, H 4.63. m.p. 67-71 °C.



2-methyl-1-thiophen-2-yl-1*H*-imidazole (7e)

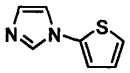
The general procedure was followed using Cu_2O (3.6 mg, 0.025 mmol), **L1c** (18 mg, 0.075 mmol), PEG (200 mg), Cs_2CO_3 (0.45 g, 1.4 mmol), 2-iodothiophene (132 μg, 1.2 mmol), 2-methylimidazole (83 mg, 1.00 mmol) with DMSO (0.3 mL) as solvent for 24 h at 110 °C. Workup was performed under an atmosphere of N_2. Chromatographic purification (ethyl acetate / hexane 3 : 1) provided 2-methyl-1-thiophen-2-yl-1*H*-imidazole (yellow oil, 90 mg, 55%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.25 (dd, 1H, J = 1.4, 5.5 Hz), 7.03-6.99 (m, 3H), 6.96 (dd, 1H, 1.5, 3.7 Hz), 2.39 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 128.0, 126.2, 124.1, 123.5, 122.3, 100.0, 13.7. IR (neat, cm^{-1}) IR (KBr disc, cm^{-1}) 1555, 1496, 1451, 1406, 1305, 1287, 1172, 1137, 987, 941. This compound turns dark brown upon exposure to air or after standing for 2-3 of days as room temperature under an argon atmosphere.



1-benzo[*b*]thiophen-3-yl-1*H*-imidazole (7f)

The general procedure was followed using Cu_2O (7.2 mg, 0.05 mmol), **L1c** (36 mg, 0.05 mmol), PEG (200 mg), Cs_2CO_3 (0.45 g, 1.4 mmol), 3-bromothianaphthene (131 μL, 1.00 mmol), and imidazole (82 mg, 1.2 mmol) with DMSO (0.5 mL) as solvent for 48 h at 110 °C. The crude reaction mixture was dissolved in 20 mL H_2O, and the organic material was extracted repeatedly with CH_2Cl_2. The combined organic extracts were washed once with brine, then dried over

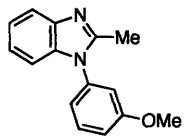
$MgSO_4$ and concentrated to an oil. Chromatographic purification (ethyl acetate / hexane 3 : 1) 1-benzo[*b*]thiophen-3-yl-1*H*-imidazole (yellow oil, 188 mg, 94%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89-7.85 (m, 1H), 7.80 (bs, 1H), 7.68-7.63 (m, 1H), 7.46-7.38 (m, 3H), 7.26 (bs, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.0, 133.8, 130.5, 130.0, 125.8, 125.3, 123.44, 121.0, 119.7. IR (KBr Disc, cm^{-1}) 3114, 1570, 1539, 1509, 1486, 1431, 1385, 1332, 1267, 1254, 1228, 1106, 1081, 1061, 1035, 912, 821, 731, 757, 659. After 2-3 days at room temperature under an argon atmosphere, the compound turned dark brown in color.



1-thiophen-2-yl-1*H*-imidazole (7g)

The general procedure was followed using Cu_2O (3.6 mg, 0.025 mmol), **L1c** (18 mg, 0.075 mmol), PEG (200 mg), Cs_2CO_3 (0.45 g, 1.4 mmol), 2-iodothiophene (132 mg, 1.2 mmol), imidazole (68 mg, 1.00 mmol) with DMSO (0.3 mL) as solvent for 24 h at 110 °C. Chromatographic purification (ethyl acetate / hexane 3 : 1) provided 1-thiophen-2-yl-1*H*-imidazole (yellow oil, 125 mg, 83%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (bs, 1H), 7.15 (bs, 1H), 7.11 (bs, 1H), 7.09 (dd, 1H, J = 2.0, 5.2 Hz), 6.96-6.92 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.0, 137.0, 130.2, 126.4, 121.8, 120.3, 119.0. This oil turned dark brown after 2-3 days as room temperature under an argon atmosphere.

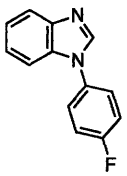
Experimental procedures for all compounds contained in Table 8



1-(3-methoxyphenyl)-2-methyl-1*H*-benzo[*d*]imidazole (8a)

The general procedure was followed using Cu_2O (14.3 mg, 0.10 mmol), **L1c** (48 mg, 0.20

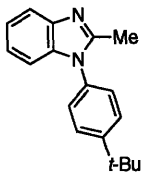
mmol), MTBD (200 μL, 1.4mmol), 3-bromoanisole (126 μL, 1.00 mmol), and 2-methylbenzimidazole (159 mg, 1.2 mmol) with DMSO (0.5 mL) as solvent for 24 h at 130 °C. The crude reaction mixture was dissolved in 20 mL of ammonium hydroxide and extracted with dichloromethane (3 x 30 mL). The combined organic layers were then extracted with 20 mL of brine. The resulting aqueous phase was extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried with anhydrous $MgSO_4$, and the solvent was removed *in vacuo*. Chromatographic purification (hexane / ethyl acetate 1 : 1) afforded 1-(3-methoxyphenyl)-1*H*-benzo[*d*]imidazole (white solid, 192 mg, 81%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (d, 1H, J = 8.0), 7.37 (t, 1H, J = 8.1 Hz), 7.19-7.05 (m, 3H), 6.95 (ddd, 1H, J = 0.9, 2.5, 8.5 Hz), 6.80-6.87 (m, 2H), 3.75 (s, 1H), 2.40 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.7, 151.6, 142.6, 137.2, 136.4, 130.7, 122.6, 122.4, 119.3, 119.0, 114.4, 112.9, 110.1, 55.6, 14.5. IR (KBr disc, cm^{-1}) 1601, 1516, 1492, 1464, 1392, 1322, 1288, 1255, 1222, 1165, 1054, 1024, 928, 879, 830, 786, 751, 697, 435. Anal. Calc. for $C_{15}H_{14}N_2O$: C 75.61, H 5.92. Found C 75.22, H 5.79. m.p. 132.5-133.5 °C.



1-(4-fluroropheyl)-1*H*-benzop[*d*]imidazole (8b)

The general procedure was followed using Cu_2O (14.3 mg, 0.10 mmol), **L1c** (48 mg, 0.20 mmol), PEG (200 mg), Cs_2CO_3 (0.45 g, 1.4 mmol), 1-bromo-4-fluorobenze (109 μL, 1.00 mmol), and benzimidazole (142 mg, 1.2 mmol) with DMSO (0.5 mL) as solvent for 9 h at 110 °C. The crude reaction mixture was dissolved in 20 mL of ammonium hydroxide and extracted with dichloromethane (3 x 30 mL). The combined organic layers were then extracted with 20 mL of brine. The resulting aqueous phase was extracted with dichloromethane (3 x 30 mL). The

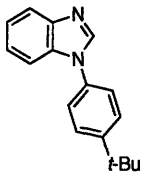
combined organic layers were dried with anhydrous $MgSO_4$, and the solvent was removed *in vacuo*. Chromatographic purification (hexane / ethyl acetate 1 : 2) afforded 1-(4-fluroropheyl)-1*H*-benzop[*d*]imidazole (white solid, 180 mg, 85%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.76-7.72 (m, 1H), 7.34-7.30 (m, 3H), 7.30-7.09 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.9, 160.9, 143.9, 142.3, 133.8, 132.3, 126.0, 125.9, 123.8, 122.9, 120.6. 117.1, 116.9, 110.2. IR (KBr disc, cm^{-1}) 3416, 3061, 1911, 1781, 1734, 1666, 1614, 1511, 1486, 1458, 1317, 1289, 1235, 1217, 1148, 1094, 1010, 980, 936, 887, 868, 845, 823, 815, 783, 766, 750, 716, 668, 647, 619, 589, 567, 531, 483, 436, 411. Anal. Calc. for $C_{13}H_9FN_2$: C 73.57, H 4.27. Found C 73.37, H 4.24. m.p. 118.5-119.5 °C (Lit. 114-115 °C).[69]



1-(4-*tert*-butylphenyl)2-methyl-1*H*-benzo[*d*]imidazole (8c)

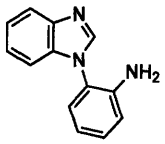
The general procedure was followed using Cu_2O (14.3 mg, 0.10 mmol), **L1c** (48 mg, 0.20 mmol), MTBD (200 μL, 1.4mmol), 1-bromo-4-*t*-butylbenzene (173 μL, 1.00 mmol), and 2-methylbenzimidazole (159 mg, 1.2 mmol) with DMSO (0.5 mL) as solvent for 24 h at 130 °C. The crude reaction mixture was dissolved in 20 mL of ammonium hydroxide and extracted with dichloromethane (3 x 30 mL). The combined organic layers were then extracted with 20 mL of brine. The resulting aqueous phase was extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried with anhydrous $MgSO_4$, and the solvent was removed *in vacuo*. Chromatographic purification (hexane / ethyl acetate 1 : 1) afforded 1-(4-*tert*-butylphenyl)2-methyl-1*H*-benzo[*d*]imidazole (white solid, 191 mg, 72%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (d, 1H, J=7.9Hz), 7.44 (d, 2H, J=8.4), δ 7.15-7.13 (m, 3H), 7.05-7.03 (m, 2H), 2.39 (s, 3H), 1.29 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.9, 151.7, 142.6, 136.6, 133.3,

126.8, 126.5, 122.4, 122.2, 118.9, 110.1, 34.9, 31.4, 14.5. IR (KBr disc, cm^{-1}) 3399, 3050, 3038, 2964, 2868, 2717, 2320, 1924, 1883, 1847, 1806, 1766, 1664, 1612, 1587, 1518, 1477, 1456, 1397, 1367, 1324, 1314, 1285, 1269, 1248, 1204, 1186, 1145, 1122, 1108, 1033, 1011, 998, 973, 942, 875, 860, 842, 764, 741, 704, 678, 644, 633, 593, 566, 534, 497, 429, 406. Anal. Calc. for $C_{18}H_{20}N_2$: C 81.78, H 7.63. Found C 81.69, H 7.62. m.p. 132-133 °C.



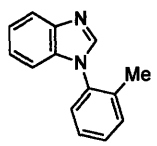
1-(4-*tert*-butylphenyl)-1*H*-benzo[*d*]imidazole (8d)

The general procedure was followed using Cu_2O (14.3 mg, 0.10 mmol), **L1c** (48 mg, 0.20 mmol), PEG (200 mg), Cs_2CO_3 (0.45 g, 1.4 mmol), 1-bromo-4-*t*-butylbeneze (173 μL, 1.00 mmol), and benzimidazole (142 mg, 1.2 mmol) with DMSO (0.5 mL) as solvent for 6 h at 110 °C. The crude reaction mixture was dissolved in 20 mL of ammonium hydroxide and extracted with dichloromethane (3 x 30 mL). The combined organic layers were then extracted with 20 mL of brine. The resulting aqueous phase was extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried with anhydrous $MgSO_4$, and the solvent was removed *in vacuo*. Chromatographic purification (hexane / ethyl acetate 1 : 1) afforded 1-(4-*tert*-butylphenyl)-1*H*-benzo[*d*]imidazole (white crystals, 240 mg, 96%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.77-7.74 (dd, 1H, J = 2.9, 6.2 Hz), 7.43-7.37 (m, 3H), 7.27-7.15 (m, 4H), 1.25 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.2, 144.0, 142.3, 133.8, 133.7, 126.9, 123.6, 123.6, 123.5, 122.6, 120.5, 110.5, 34.7, 31.3. IR (KBr disc, cm^{-1}) 3429, 3112, 3055, 2959, 2902, 2867, 1736, 1609, 1520, 1488, 1461, 1416, 1369, 1361, 1323, 1303, 1267, 1232, 1212, 1162, 1142, 1123, 1107, 1026, 1009, 977, 932, 890, 871, 846, 827, 783, 765, 741, 645, 621, 589, 565, 548, 500, 431. Anal. Calc. for $C_{17}H_{18}N_2$: C 81.56, H 7.25. Found C 81.12, H 7.23. m.p. 150-151.5 °C.



2-(1*H*-benzo[*d*]imidzol-1-yl)aniline (8e)

The general procedure was followed using Cu_2O (14.3 mg, 0.10 mmol), **L1c** (48 mg, 0.20 mmol), PEG (200 mg), Cs_2CO_3 (0.45 g, 1.4 mmol), 2-bromoaniline (109 μL, 1.00 mmol), and benzimidazole (142 mg, 1.2 mmol) with DMSO (0.5 mL) as solvent for 15 h at 110 °C. The crude reaction mixture was dissolved in 20 mL of ammonium hydroxide and extracted with dichloromethane (3 x 30 mL). The combined organic layers were then extracted with 20 mL of brine. The resulting aqueous phase was extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried with anhydrous $MgSO_4$, and the solvent was removed *in vacuo*. Chromatographic purification (with Biotage system with gradient of pure hexane to pure ethyl acetate to hexane / ethyl acetate 1 : 1) afforded 2-(1*H*-benzo[*d*]imidzol-1-yl)aniline (orange crystals, 157 mg, 75%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.73 (dd, 1H, J = 2.2, 6.3 Hz), 7.20-7.11 (m, 4H), 7.03 (dd, 1H, J = 1.4, 7.7 Hz), 6.80-6.71 (m, 2H), 3.67 (s, 2H) ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.5, 143.3, 142.9, 133.9, 130.3, 128.2, 123.6, 122.8, 121.1, 120.4, 118.6, 116.6, 110.9. IR (KBr disc, cm^{-1}) 3227, 3202, 1625, 1507, 1486, 1454, 1308, 1288, 1227, 1157, 977, 890, 785, 744, 503, 442, 428. Anal. Calc. for $C_{13}H_{11}N_3$: C 74.62, H 5.30. Found C 74.45, H 5.25. m.p. 115-116 °C (Lit. 112.5-113 °C).[70]



1-*o*-tolyl-1*H*-benzo[*d*]imidazole[71] (8f)

The general procedure was followed using Cu_2O (7.2 mg, 0.05 mmol), **L1c** (36 mg, 0.15 mmol), PEG (200 mg), Cs_2CO_3 (0.45 g, 1.4 mmol), 2-bromotoluene (120 μL, 1.00 mmol), and

benzimidazole (142 mg, 1.2 mmol) with DMSO (0.5 mL) as solvent for 24 h at 130 °C. The crude reaction mixture was dissolved in 20 mL of ammonium hydroxide and extracted with dichloromethane (3 x 30 mL). The combined organic layers were then extracted with 20 mL of brine. The resulting aqueous phase was extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried with anhydrous $MgSO_4$, and the solvent was removed *in vacuo*. Chromatographic purification (with Biotage system with gradient of pure hexane to hexane / ethyl acetate 1 : 1) afforded 1-*o*-tolyl-1*H*-benzo[*d*]imidazole (yellow oil, 186 mg, 78%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.81 (d, 1H, J = 7.9 Hz), 7.95-7.18 (m, 6H), 7.05 (dd, J = 7.9, 0.6 Hz), 2.01 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.5, 143.1, 135.5, 134.9, 134.8, 131.7, 129.5, 127.8, 127.3, 123.6, 122.6, 120.6, 110.6, 17.8.

RAAIV90

expl s2pul

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np	64000	dseq	
sw	10000.0	dres	1.0
fb	not used	homo	n
bs	8	PROCESSING	
ss	1	wtfile	
tpwr	59	proc	ft
pw	9.8	fn	131072
d1	0	math	f
tof	1498.2		
nt	16	werr	
ct	16	wexp	
alock	n	wbs	
gain	not used	wnt	
FLAGS			
il	n		
in	n		
dp	y		
hs	nn		
DISPLAY			
sp	-998.2		
wp	10000.0		
vs	96		
sc	0		
wc	250		
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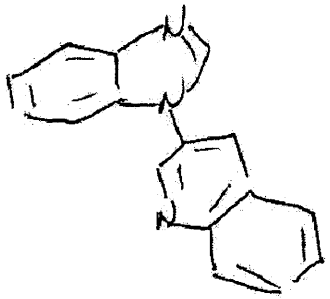
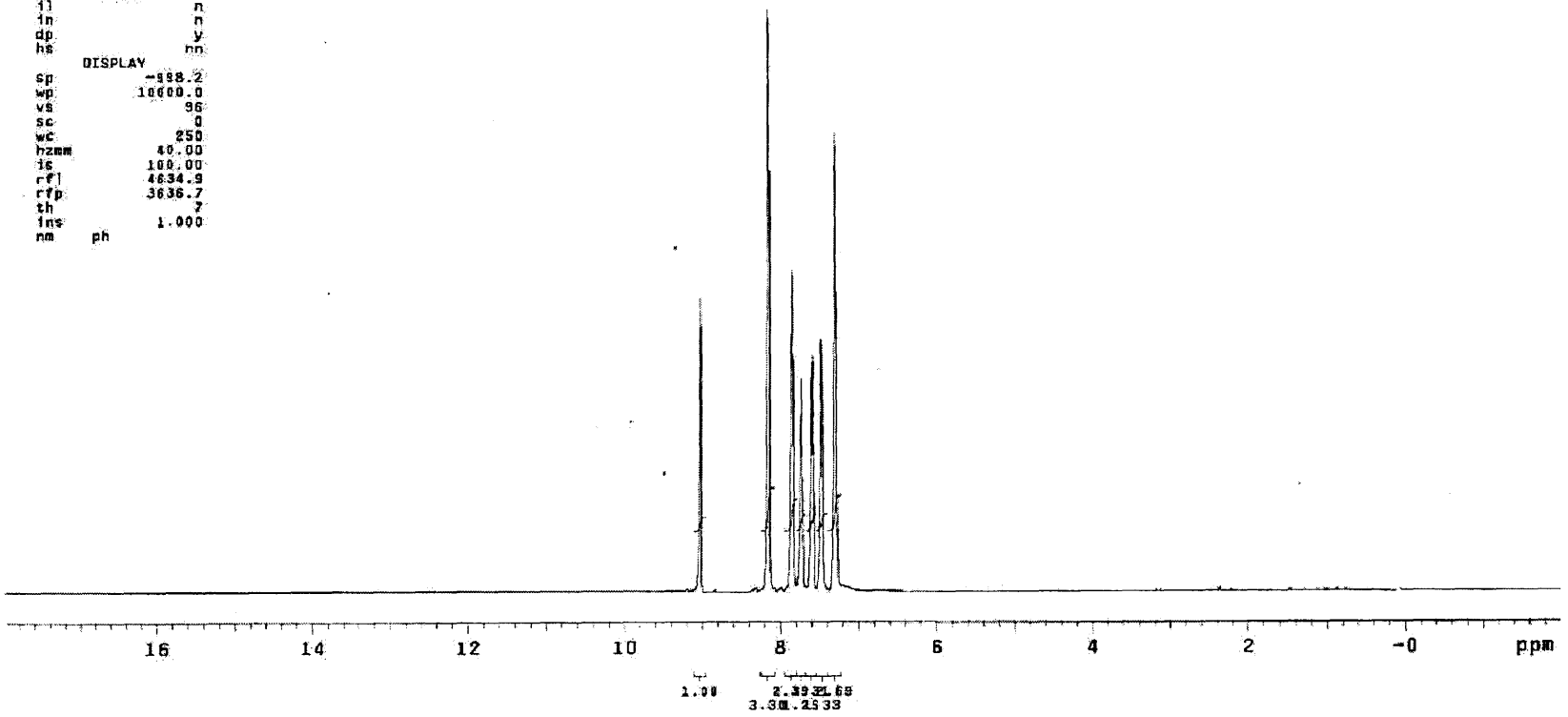
rfp	3636.7		
th	7		
ins	1.000		
nm	ph		





RAAIV92

expl s2pul

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np	64000	dseq	
sw	10000.0	dres	1.0
fb	not used	homo	n
bs	8	PROCESSING	
ss	1	wtfile	
tpwr	59	proc	ft
pw	9.8	fn	131072
d1	0	math	f
tof	1498.2		
nt	16	werr	
ct	16	wexp	
alock	n	wbs	
gain	not used	wnt	
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in	n		
dp	y		
hs	nn		
DISPLAY			
sp	-1003.6		
wp	10000.0		
vs	151		
sc	0		
wc	250		
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is	100.00		
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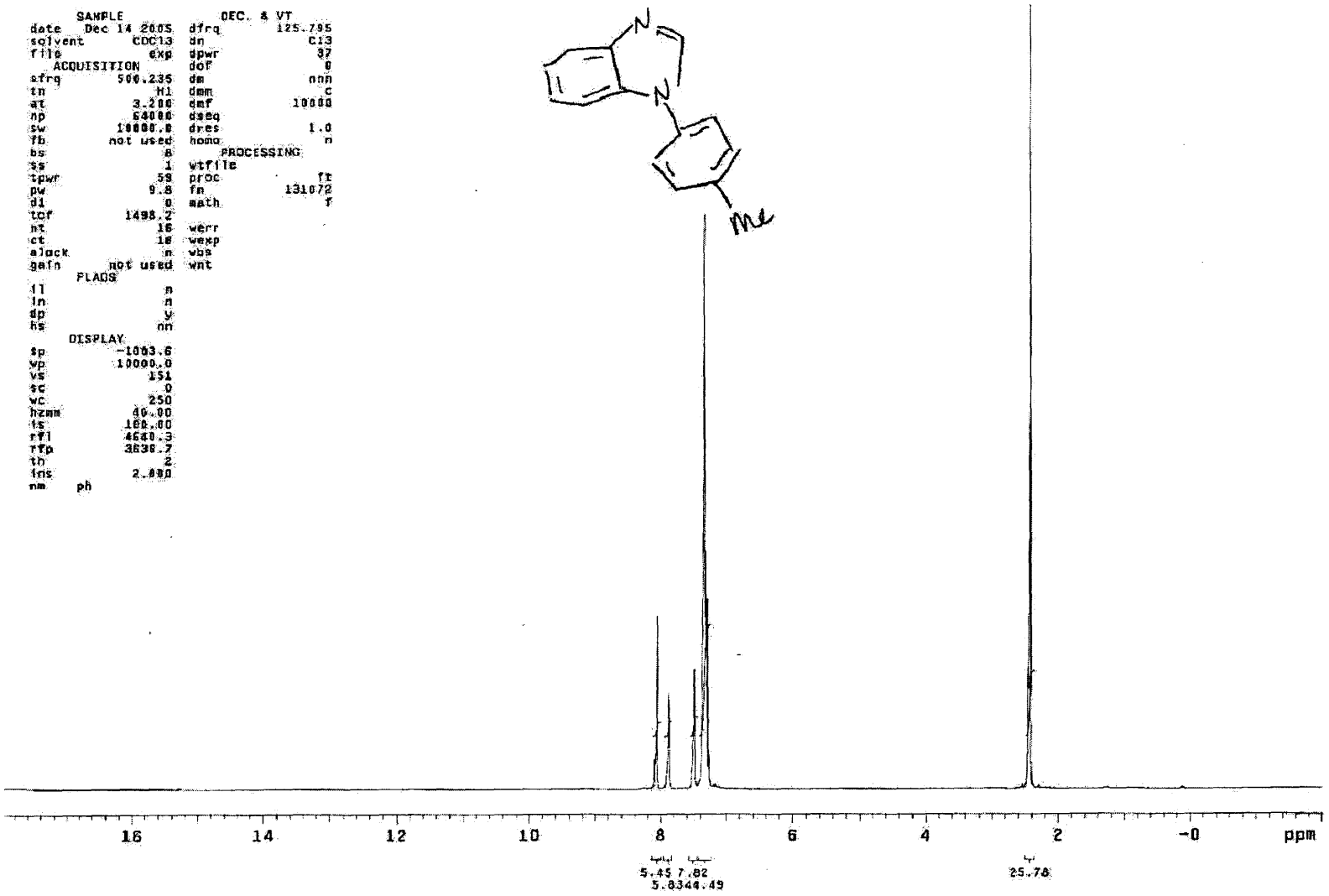
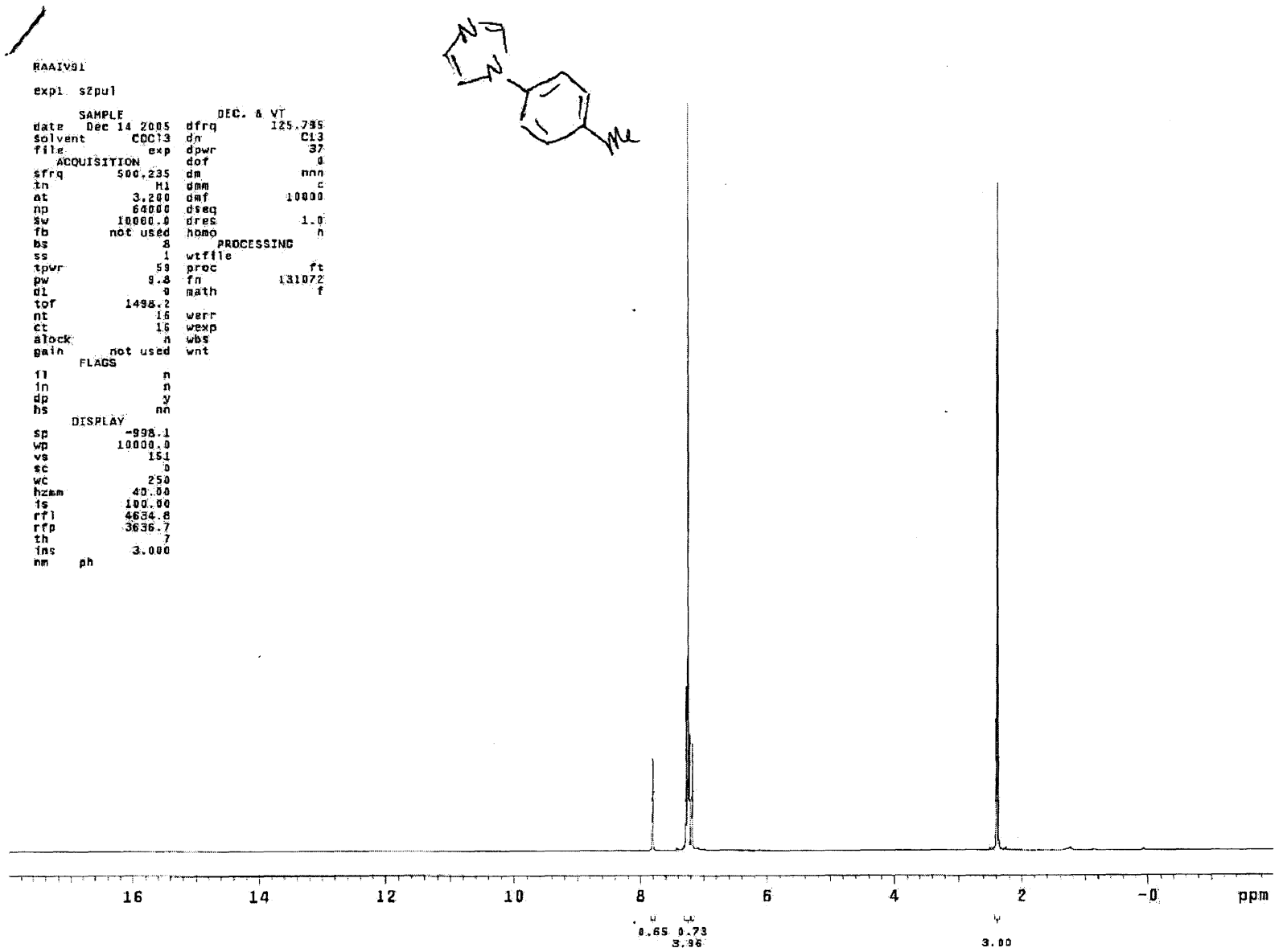
ins	2.000		
nm	ph		

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file exp
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tpwr 59
pw 9.8
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ct 16
alock n
gain not used
FLAGS
il n
in n
dp y
hs nn
DISPLAY
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wp 10000.0
vs 151
sc 0
wc 250
hzmm 40.00
is 100.00
rfl 4634.8
rfp 3636.7
th 7
ins 3.000
nm ph
DEC. & VT
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dn C13
dpwr 37
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dm nnn
dmm c
dmf 10000
dseq
dres 1.0
homo n
PROCESSING
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proc ft
fn 131072
math f
werr
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12
10
8
6
4
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ppm
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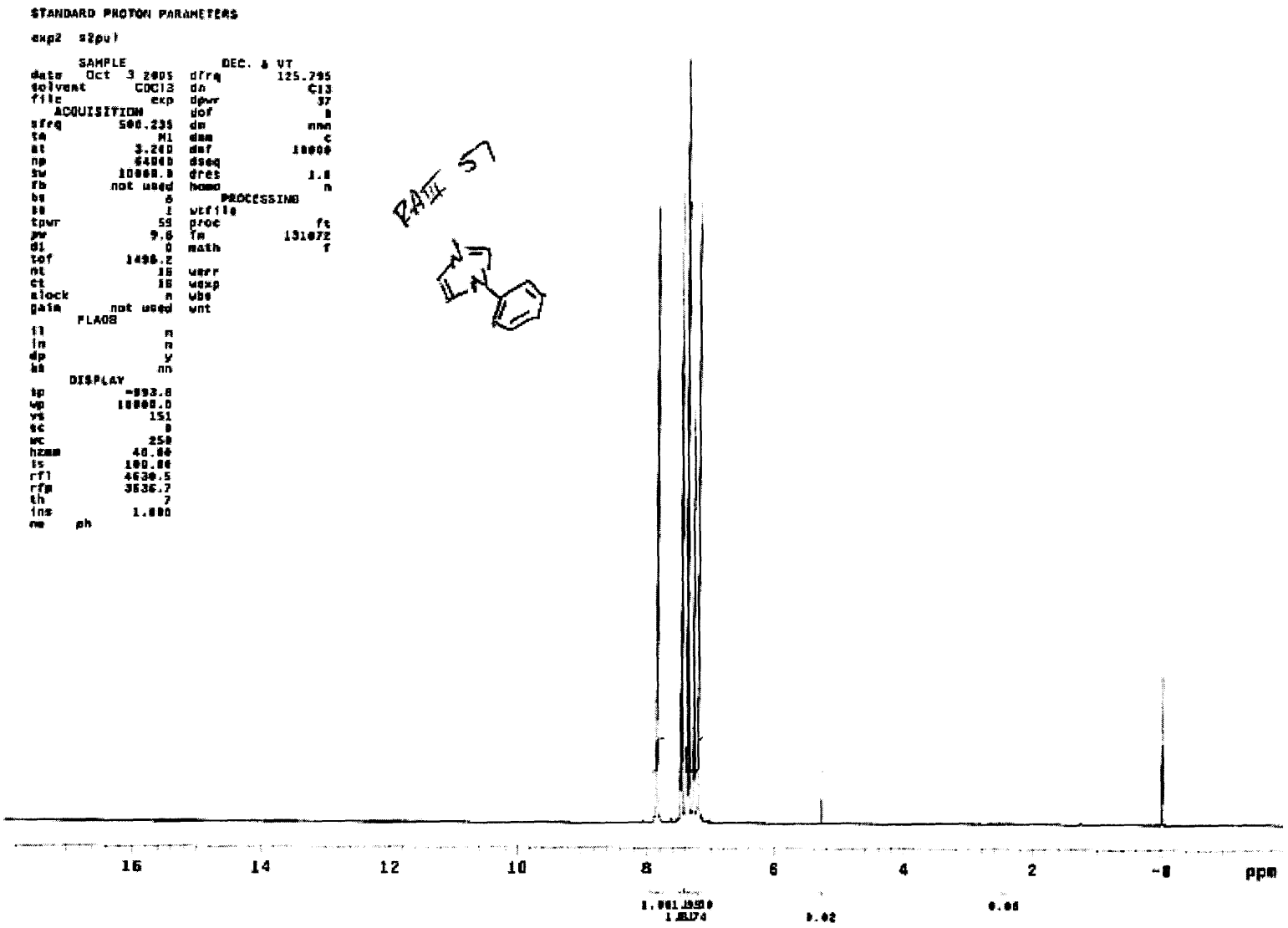
3.96
3.00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date Oct 3 2005
solvent CDCl3
file exp
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at 3.240
np 64808
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bs 8
ss 1
tpwr 59
pw 9.6
dl 0
tof 1498.2
nt 16
ct 16
alock n
gain not used
FLAGS
il n
in n
dp y
hs nn
DISPLAY
sp -893.8
wp 10068.0
vs 151
sc 0
wc 250
hzcm 48.00
is 100.00
rfl 4630.5
rfp 3636.7
th 7
ins 1.000
nm ph
DEC. & VT
dfrq 125.795
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dpwr 37
dof 0
dm nnn
dmm c
dmf 10000
dseq
dres 1.8
homo n
PROCESSING
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proc ft
fn 131072
math f
werr
wexp
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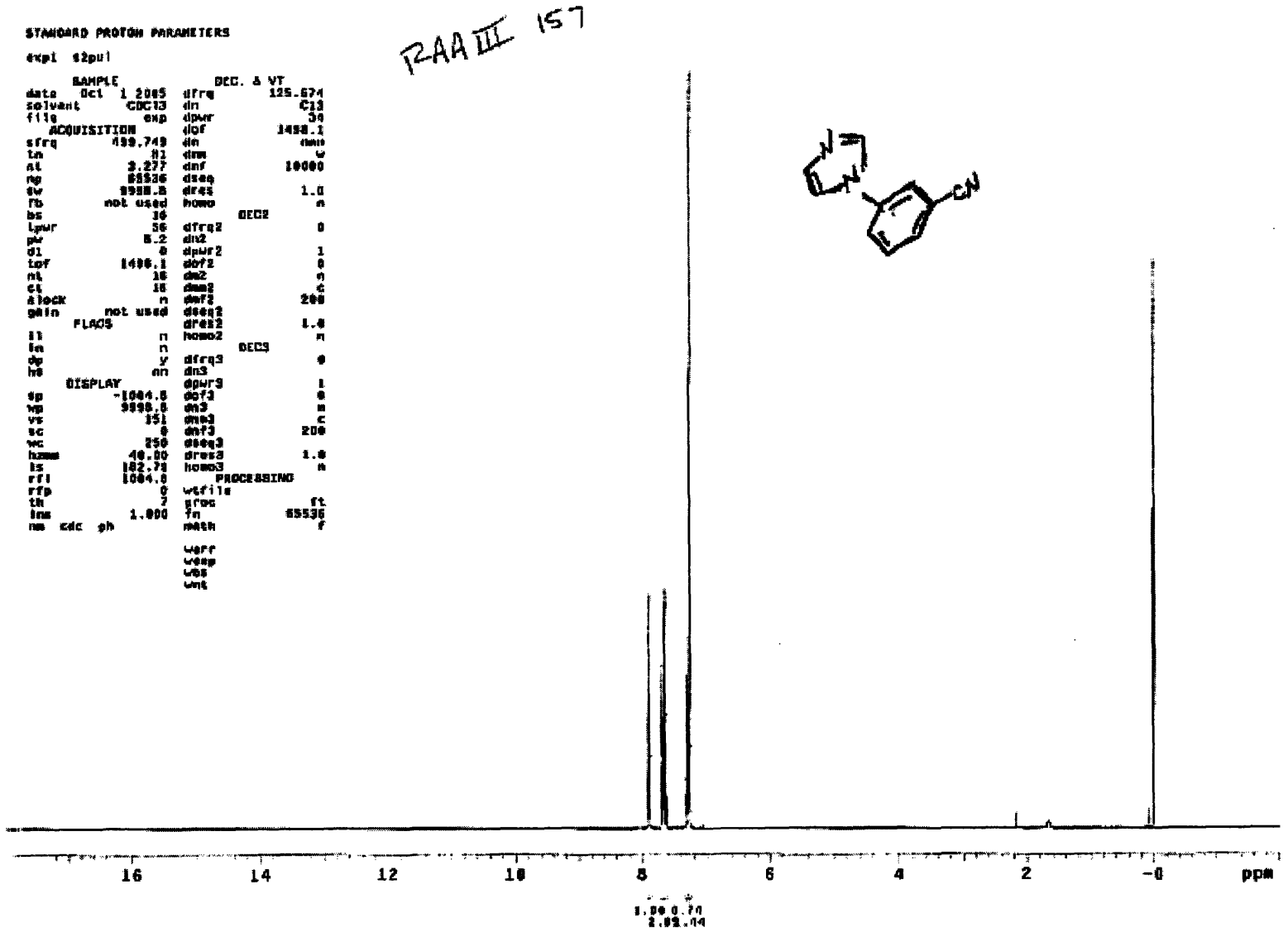
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solvent CDCl3
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at 3.277
np 65536
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d1 0
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ct 16
alock n
gain not used
FLAGS
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in n
dp y
hs nn
DISPLAY
sp -1004.8
wp 9998.0
vs 151
sc 0
wc 250
hzmm 40.00
is 182.7
rfl 1004.8
rfp 0
th 7
ins 1.000
ns cdc ph
DEC. & VT
dfrq 125.674
dn C13
dpwr 34
dof 1498.1
dm w
dmf 10000
dseq
dres 1.0
homo n
DEC2
dfrq2 0
dn2
dpwr2 1
dof2 0
dm2 n
dmm2 c
dmf2 200
dseq2
dres2 1.0
homo2 n
DEC3
dfrq3 0
dn3
dpwr3 1
dof3 0
dm3 n
dmm3 c
dmf3 200
dseq3
dres3 1.0
homo3 n
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fn 65536
math f
werr
wexp
wbs
wnt
RAA III 157
CN
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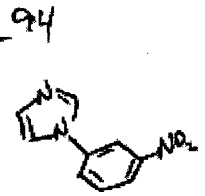
12
10
8
6
4
2
-0
ppm

STANDARD PROTON PARAMETERS

expl s2pul

SAMPLE		DEC. & VT	
date	Nov 20 2005	dfrq	125.674
solvent	CDCl3	dn	C13
file	exp	dpwr	34
ACQUISITION		dof	1498.1
sfrq	499.748	dm	nnn
tn	H1	dmm	w
at	3.277	dmf	10060
np	65536	dseq	
sw	5998.8	drex	1.0
fb	not used	homo	n
bs	16	DEC2	
tpwr	58	dfrq2	0
pw	8.2	dn2	
dl	0	dpwr2	1
dof	1498.1	dof2	0
nt	16	dm2	n
ct	16	dmm2	c
alock	n	dmf2	200
gain	not used	dseq2	
FLAGS		drex2	1.0
il	n	homo2	n
in	n	DEC3	
dp	y	dfrq3	0
hs	nn	dn3	
DISPLAY		dpwr3	1
sp	-1884.5	dof3	0
wp	5958.6	dm3	n
vs	151	dmm3	c
sc	0	dmf3	200
wc	250	dseq3	
hzmm	48.00	drex3	1.0
is	818.95	homo3	n
rfl	4637.6	PROCESSING	
rfp	3633.1	wtfile	
th	7	proc	ft
ins	1.000	fn	65536
nm cdc ph		math	f
		werr	
		wexp	
		wbs	
		wnt	

III-94



STANDARD PROTON PARAMETERS

expl s2pul

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np	65536	dseq	
sw	5938.8	drel	1.0
fb	not used	homo	n
bs	16	DEC2	
tpwr	56	dfrq2	0
pw	8.2	dn2	
dl	0	dpwr2	1
tof	1498.1	dof2	0
nt	16	dm2	n
ct	16	dmm2	c
alock	n	dmf2	200
gain	not used	dseq2	
FLAGS		drel2	1.0
il	n	homo2	n
in	n	DEC3	
dp	y	dfrq3	0
hs	nn	dn3	
DISPLAY		dpwr3	1
sp	-1004.5	dof3	0
wp	8990.8	dm3	n
vs	151	dmm3	c
sc	0	dmf3	200
wc	250	dseq3	
hzmm	40.60	drel3	1.0
is	162.78	homo3	n
rfl	4637.6	PROCESSING	
rfp	3633.1	wtfile	
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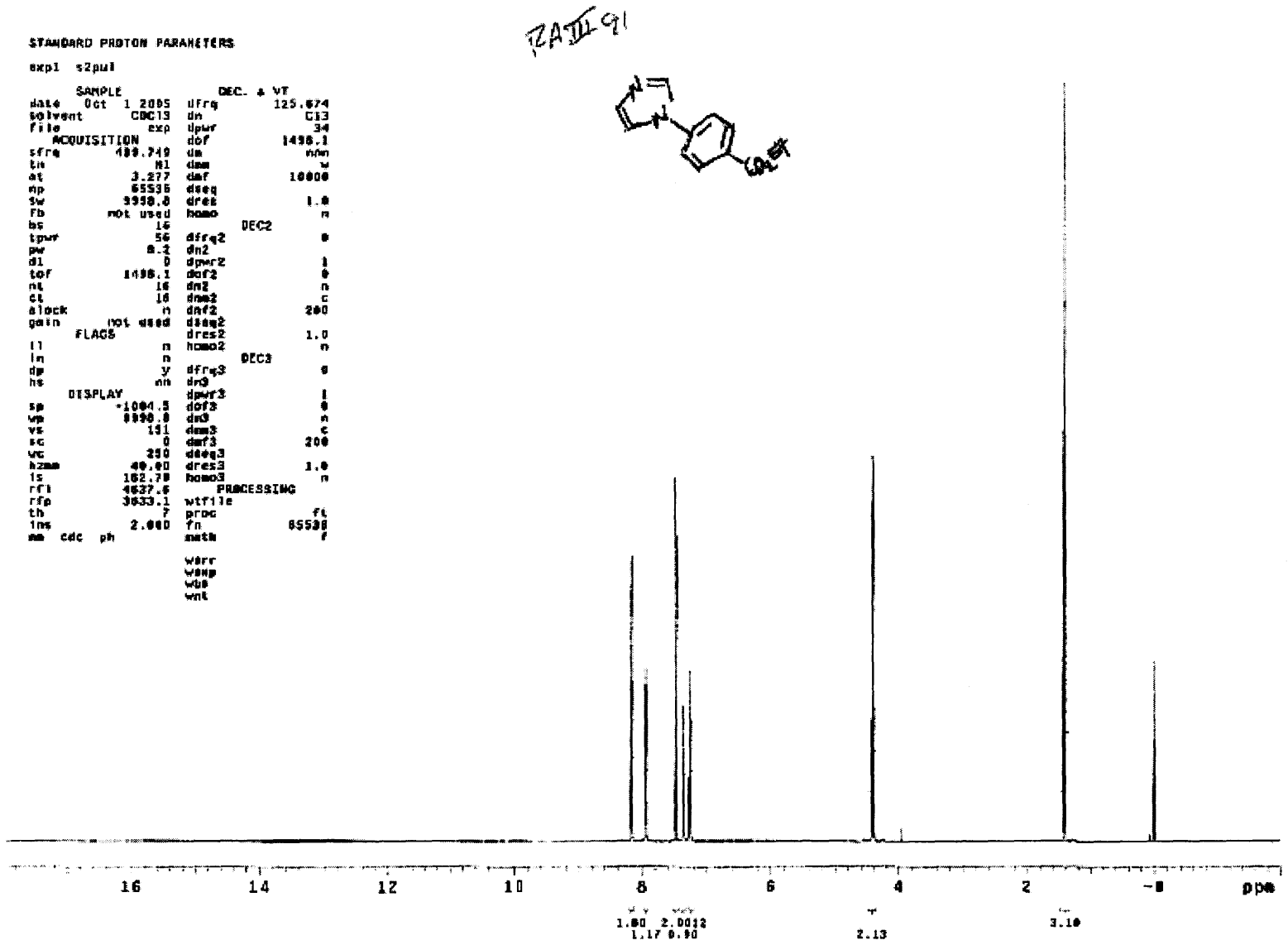
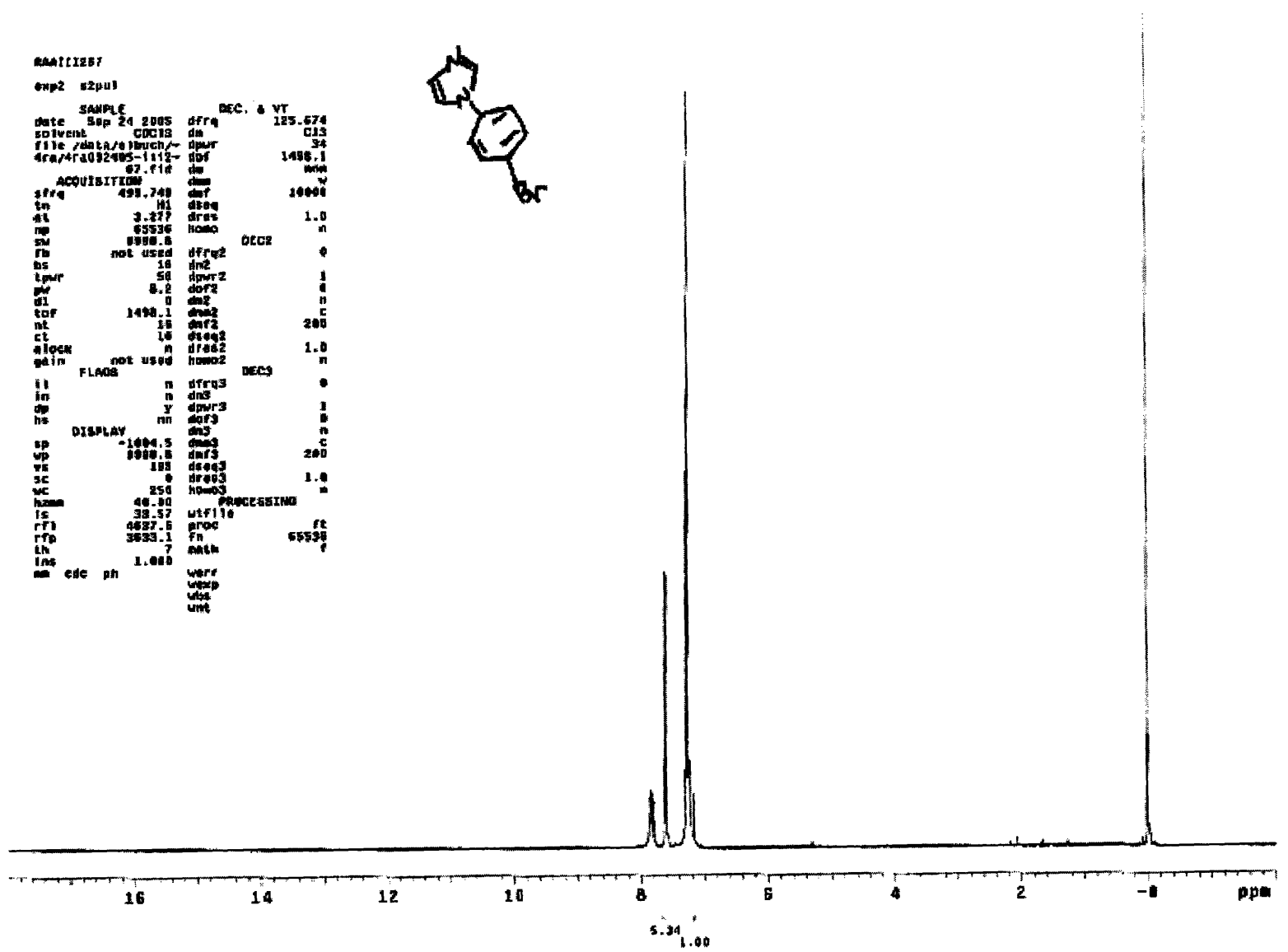
		wexp	
		wbs	
		wnt	




RAAIII287
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date Sep 24 2005
solvent CDCl3
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ACQUISITION
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at 3.277
np 65536
sw 9998.8
fb not used
bs 16
tpwr 58
pw 8.2
d1 0
tof 1498.1
nt 16
ct 16
alock n
gain not used
FLAGS
il n
in n
dp y
hs nn
DISPLAY
sp -1004.5
wp 9988.8
vs 183
sc 0
wc 256
hzmm 40.00
is 33.57
rfl 4827.5
rfp 3833.1
th 7
ins 1.000
ap ds ph
DEC. & VT
dfrq 125.674
dn C13
dpwr 34
dof 1498.1
dm nnn
dmm w
dmf 10000
dseq
drss 1.0
homo n
DEC2
dfrq2 0
dn2
dpwr2 1
dof2 0
dm2 n
dmm2 c
dmf2 200
dseq2
drss2 1.0
homo2 n
DEC3
dfrq3 0
dn3
dpwr3 1
dof3 0
dm3 n
dmm3 c
dmf3 200
dseq3
drss3 1.0
homo3 n
PROCESSING
wtfile
proc ft
fn 65536
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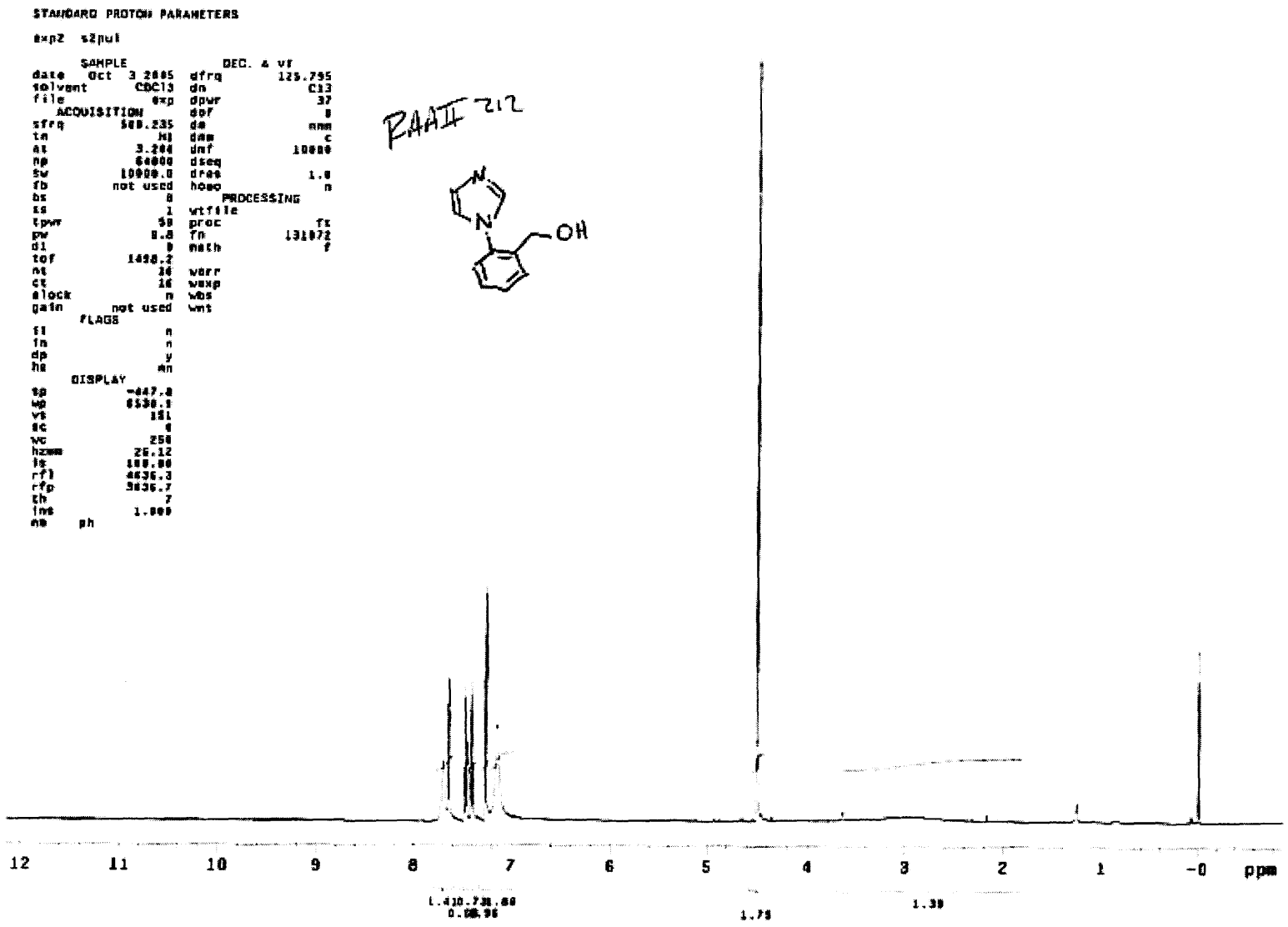
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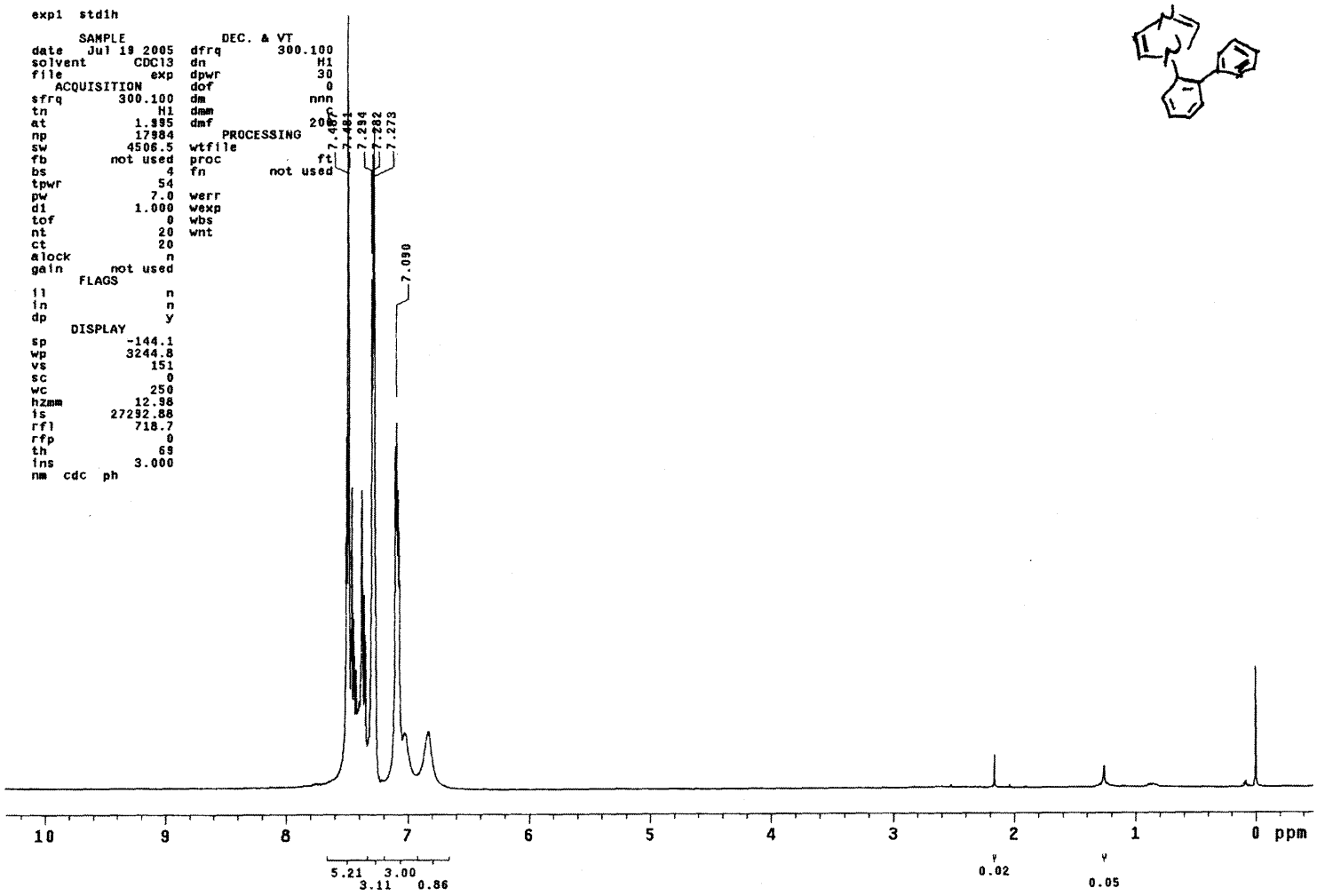
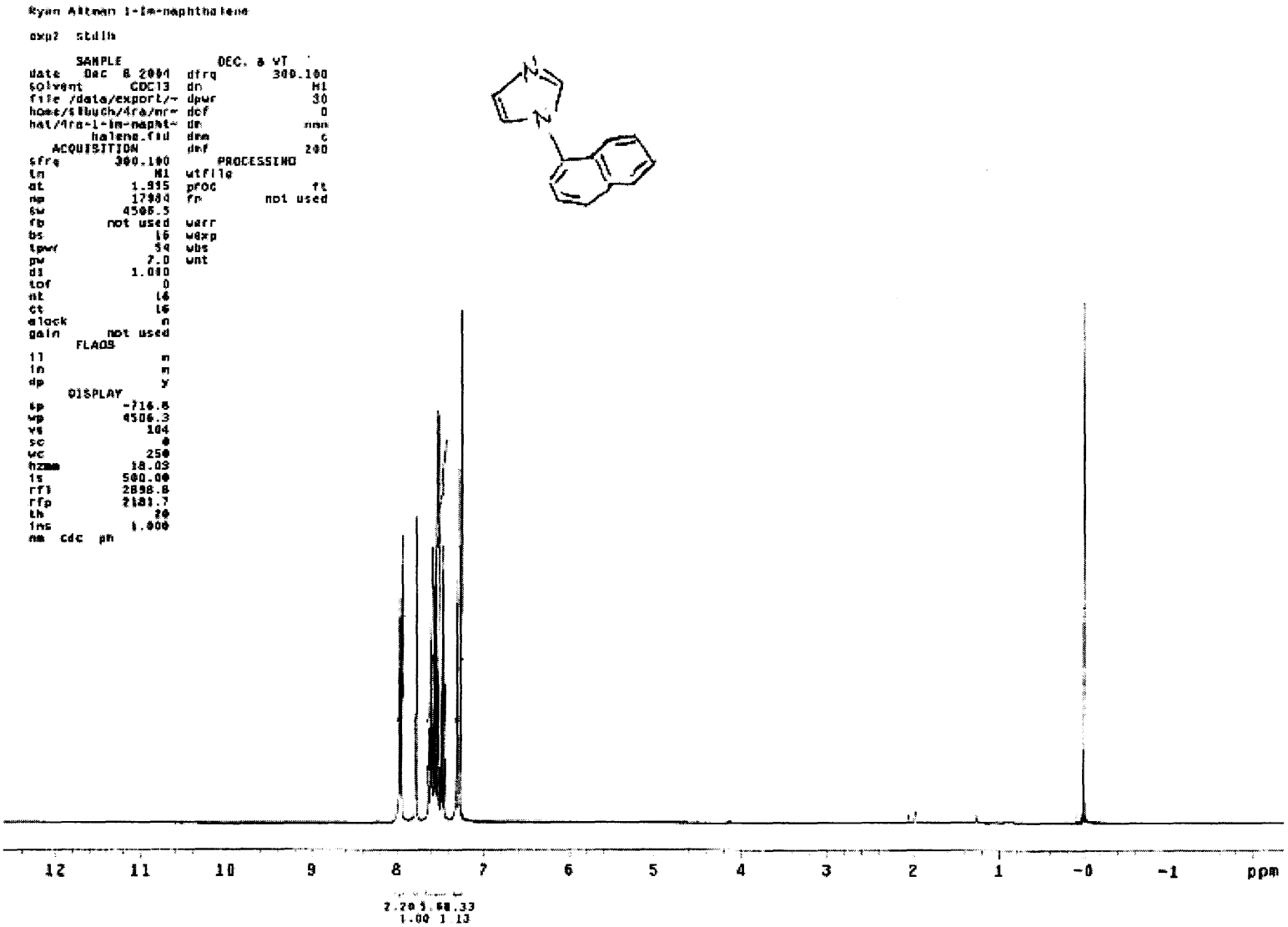
STANDARD 1H OBSERVE




Ryan Altman 1-Im-naphthalene
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date Dec 8 2004
solvent CDCl3
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hat/4ra~1-Im-naph~
halene.fid
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at 1.935
np 17984
sw 4506.5
fb not used
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tpwr 54
pw 7.0
d1 1.000
tof 0
nt 16
ct 16
alock n
gain not used
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il n
in n
dp y
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wc 250
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rf1 2898.8
rfp 2181.7
th 20
ins 1.000
nm cdc pn
DEC. & VT
dfrq 300.100
dn H1
dpwr 30
dcf 0
dm nnn
dmm c
dmf 200
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werr
wexp
wbs
wnt
12
11
10
9
8
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6
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4
3
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ppm
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1.00 1 13

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exp5 std1h

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	60.fid	dmm	c
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sfrq	300.100	PROCESSING	
tn	H1	wtfile	
at	1.997	proc	ft
np	26982	fn	not used
sw	6756.8		
fb	not used	werr	
bs	16	wexp	
tpwr	54	wbs	
pw	7.0	wnt	
d1	1.000		
tof	0		
nt	16		
ct	16		
alock	n		
gain	not used		
FLAGS			
fl	n		
in	n		
dp	y		
DISPLAY			
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wp	6756.3		
vs	151		
sc	0		
wc	250		
hzmm	27.03		
is	500.00		
rfl	4023.8		
rfp	2181.7		
th	20		
ins	3.000		

nm cdc ph

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exp5 stdih

SAMPLE		DEC. & VT	
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solvent	CDCl3	dn	H1
file	exp	dpwr	30
ACQUISITION		dof	0
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np	17984	PROCESSING	
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fb	not used	proc	ft
bs	16	fn	not used
tpwr	54		
pw	7.0	werr	
d1	1.000	wexp	
tof	0	wbs	
nt	16	wnt	
ct	16		
alock	n		
gain	not used		
FLAGS			
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in	n		
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vs	151		
sc	0		
wc	250		
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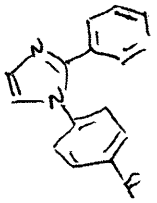
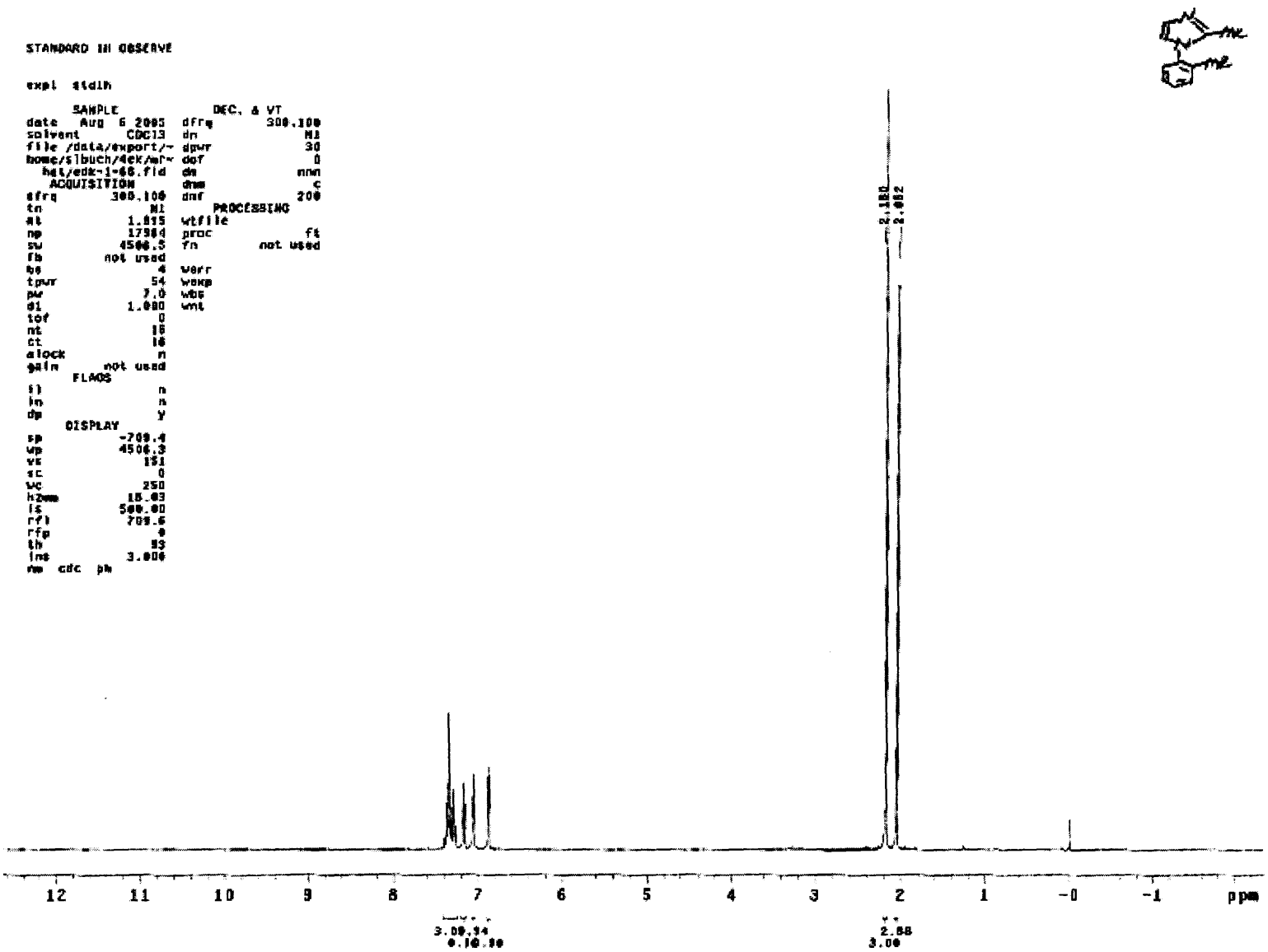
is	500.00		
rfl	2898.8		
rfp	2181.7		
th	5		
ins	2.000		
nm cdc ph			

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solvent CDCl3
file /data/export/~
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hat/edk-1-66.fid
ACQUISITION
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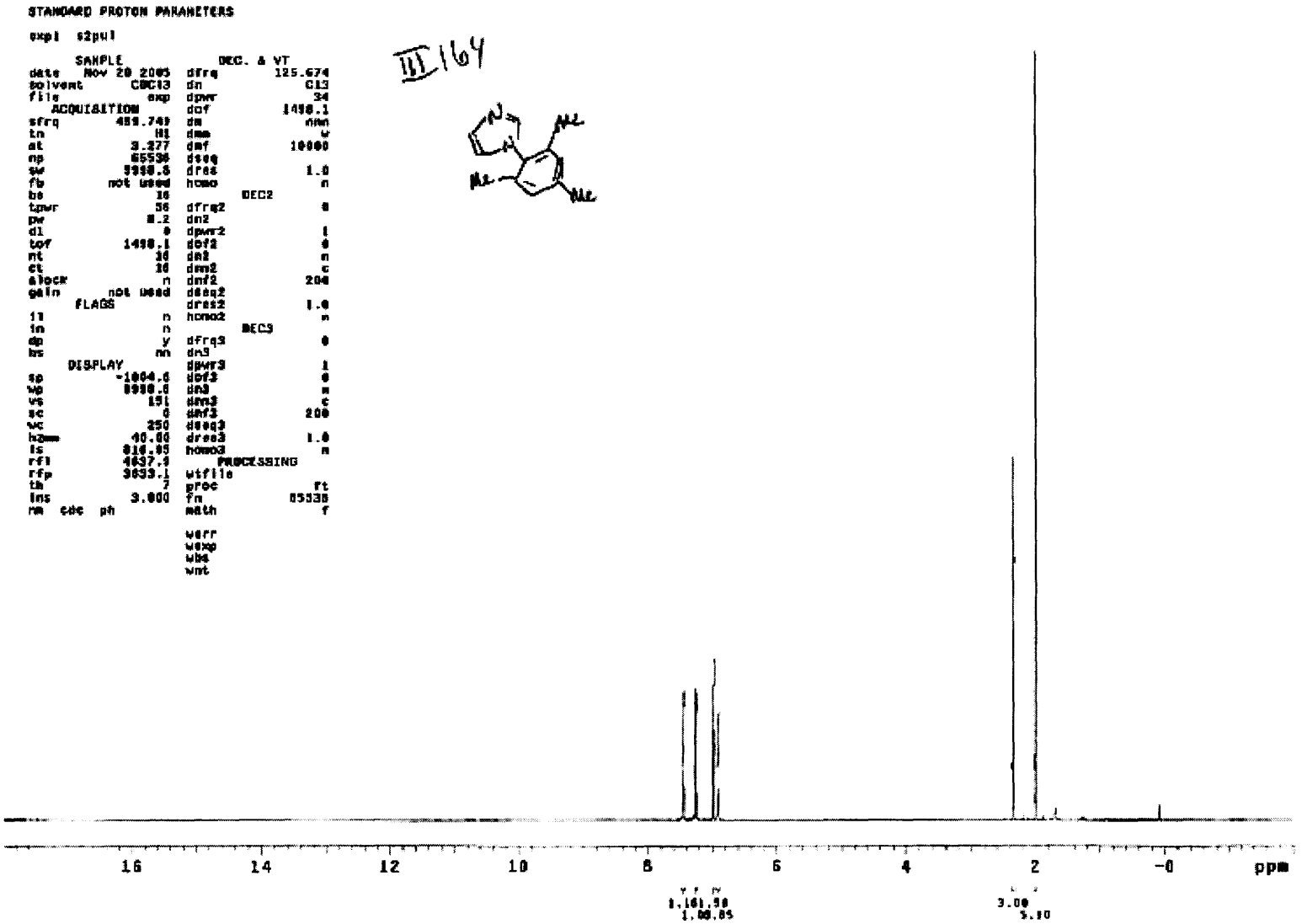
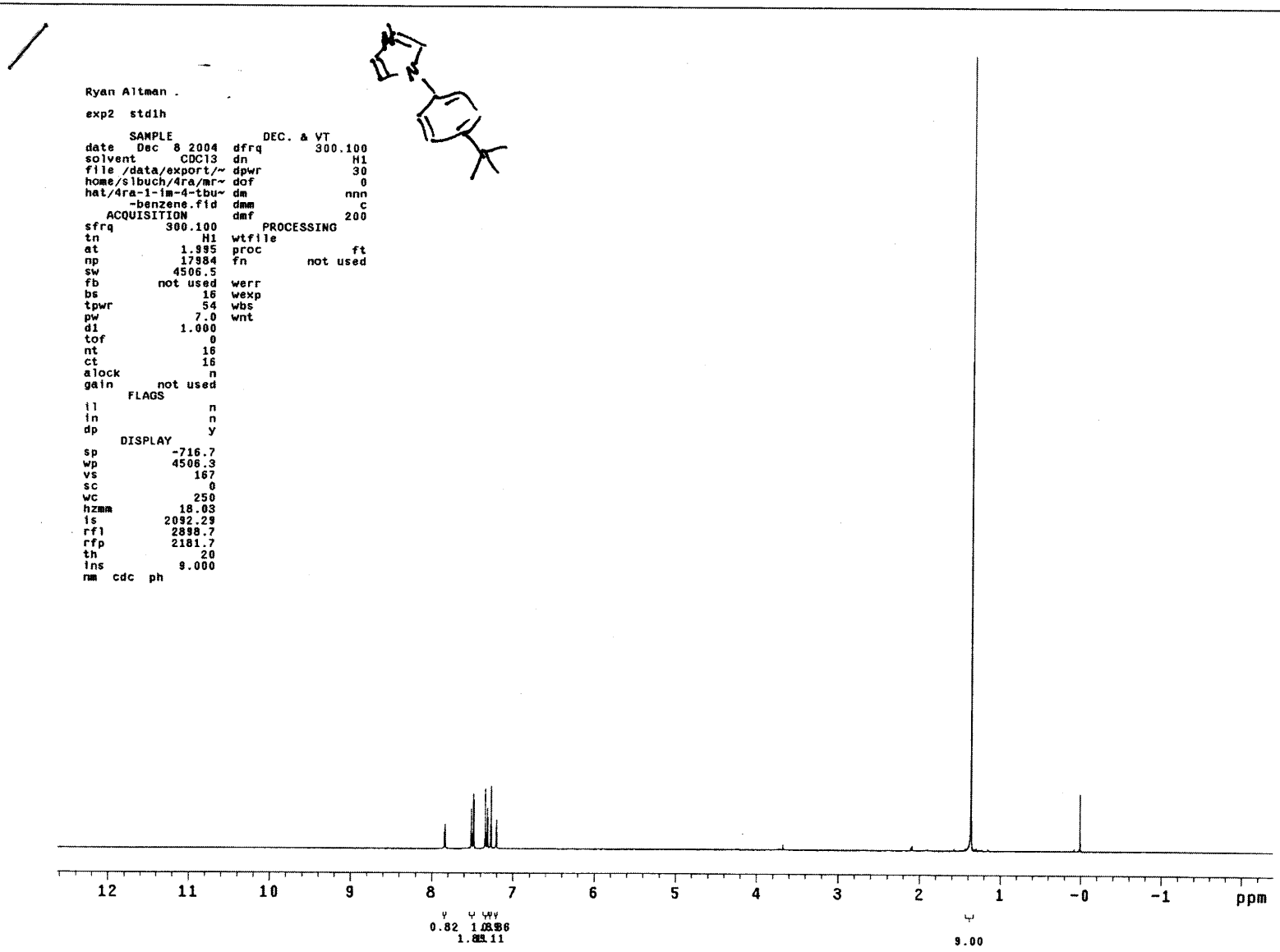
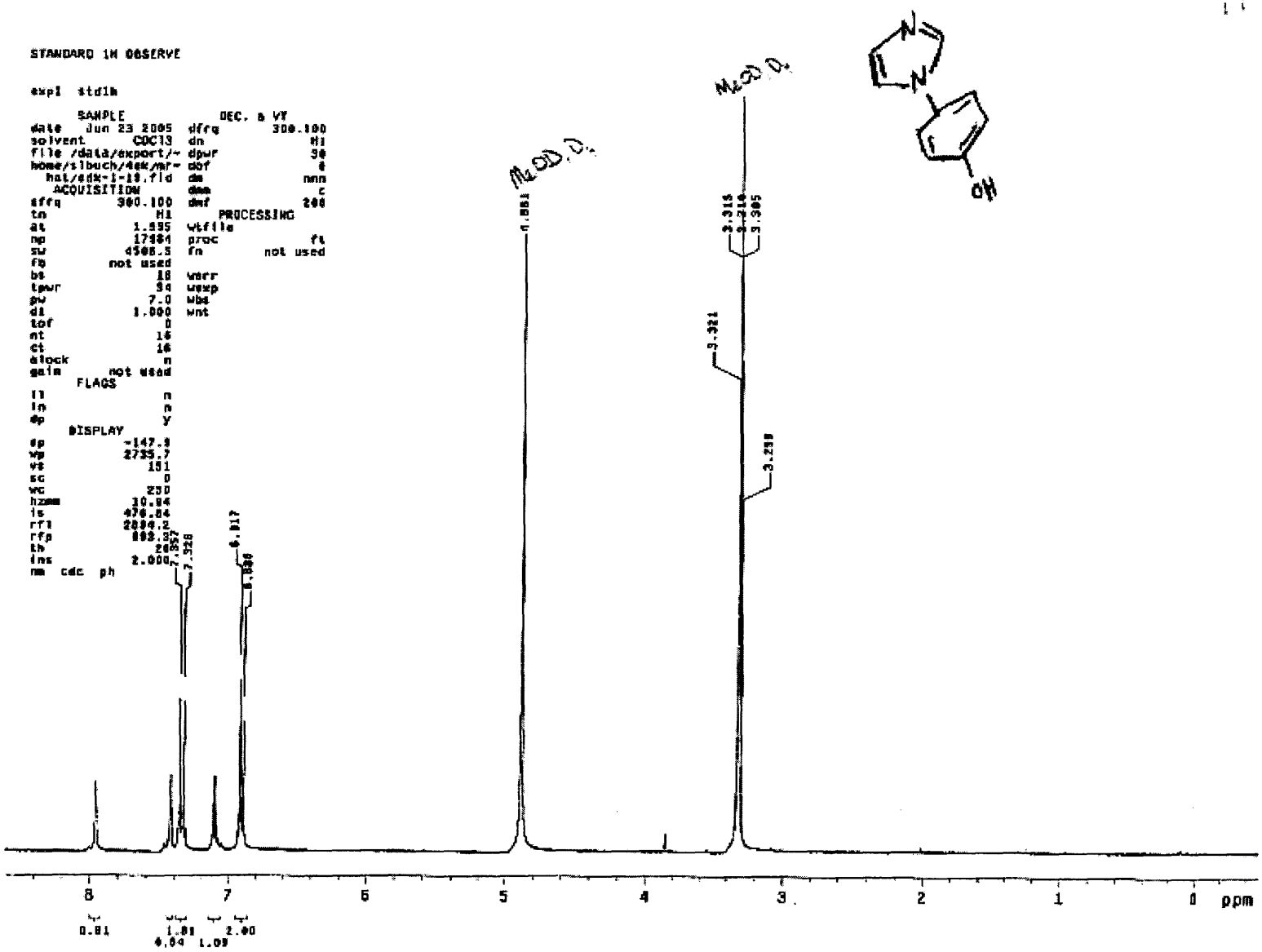
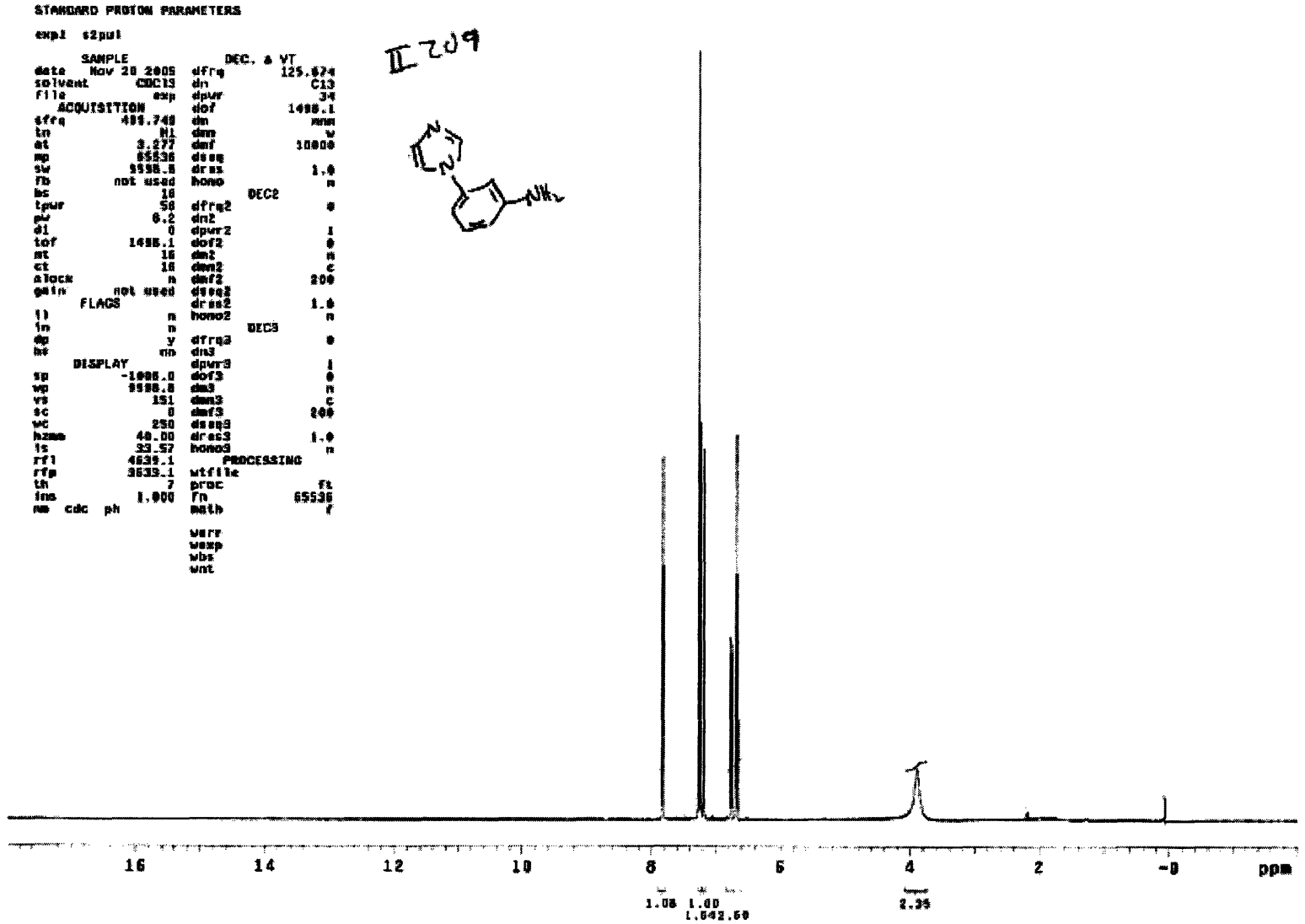
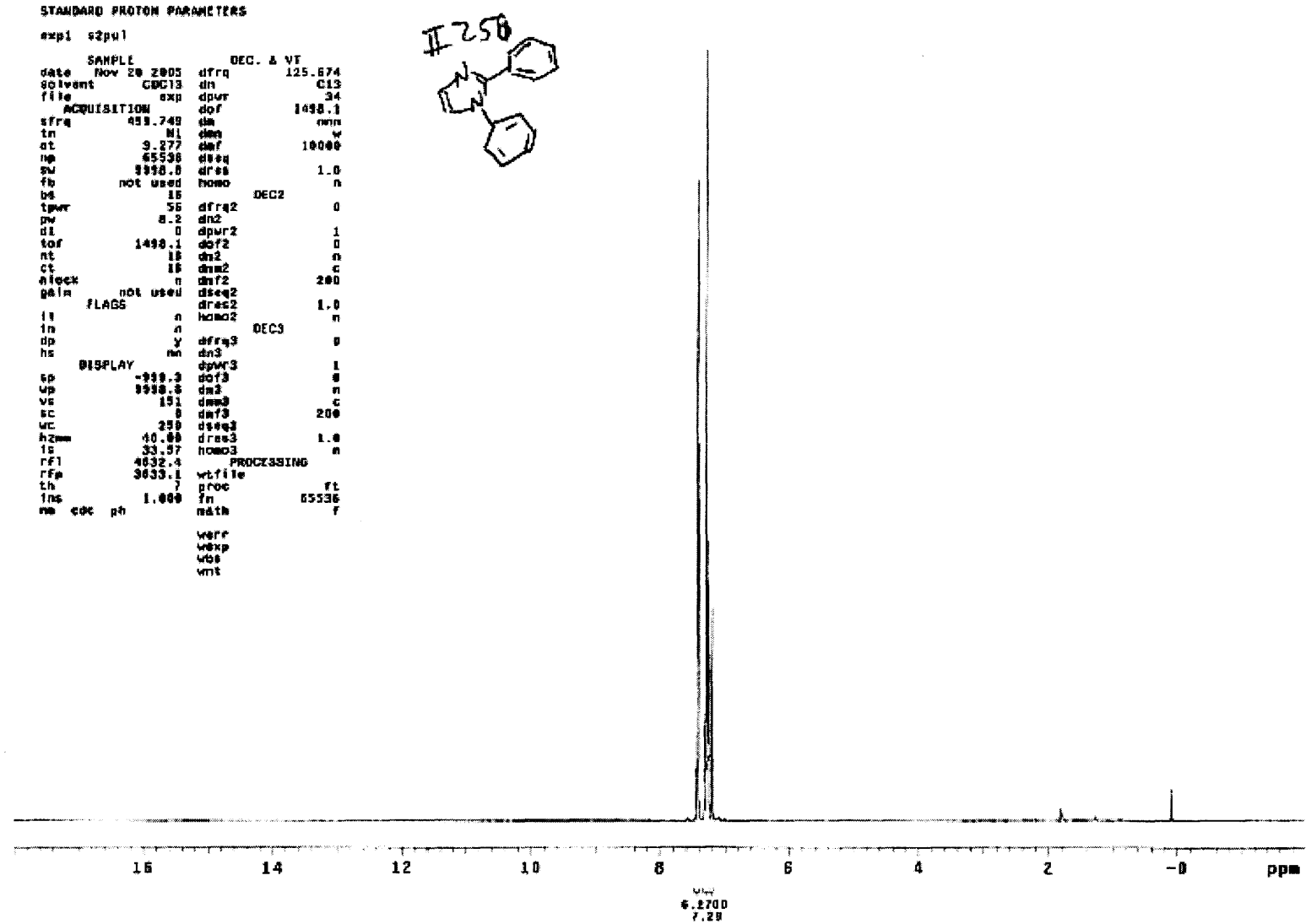
fb not used
bs 4
tpwr 54
pw 7.0
d1 1.000
tof 0
nt 16
ct 16
alock n
gain not used
FLAGS
sl n
in n
dp y
DISPLAY
sp -709.4
wp 4506.3
vs 151
sc 0
wc 250
hzmm 15.03
is 500.00
rfl 709.6
rfp 0
th 53
ins 3.000
nm cdc ph
DEC. & VT
dfrq 300.100
dn H1
dpwr 30
dof 0
dm nnn
dmm c
dmf 200
PROCESSING
wtfile
proc ft
fn not used
werr
wexp
wbs
wnt
2.180
2.002
12
11
10
9
8
7
6
5
4
3
2
1
-0
-1
ppm
3.09,14
0.10.00
2.88
3.00


STANDARD PROTON PARAMETERS
expl s2pul
SAMPLE
date Nov 20 2005
solvent CDCl3
file exp
ACQUISITION
sfrq 499.749
tn H1
at 3.277
np 65536
sw 9998.6
fb not used
bs 16
tpwr 56
pw 8.2
dl 0
tof 1498.1
nt 16
ct 16
alock n
gain not used
FLAGS
il n
in n
dp y
hs nn
DISPLAY
sp -1804.6
wp 9980.8
vs 151
sc 0
wc 250
hzmm 40.00
is 816.85
rfl 4697.4
rfp 3693.1
th 7
ins 3.000
nm cdc ph
DEC. & VT
dfrq 125.674
dn C13
dpwr 34
dof 1498.1
dm nnn
dmm w
dmf 10000
dseq
drss 1.0
homo n
DEC2
dfrq2 0
dn2
dpwr2 1
dof2 0
dm2 n
dmm2 c
dmf2 200
dseq2
drss2 1.0
homo2 n
DEC3
dfrq3 0
dn3
dpwr3 1
dof3 0
dm3 n
dmm3 c
dmf3 200
dseq3
drss3 1.0
homo3 n
PROCESSING
wtfile
proc ft
fn 65536
math f
werr
wexp
wbs
wnt
III 164
16
14
12
10
8
6
4
2
-0
ppm
1.16
1.00
1.98
0.85
3.00
5.10


Ryan Altman .
exp2 stdlh
SAMPLE
date Dec 8 2004
solvent CDCl3
file /data/export/~
home/slbuch/4ra/mr~
hat/4ra-1-im-4-tbu~
-benzene.fid
ACQUISITION
sfrq 300.100
tn H1
at 1.995
np 17984
sw 4506.5
fb not used
bs 16
tpwr 54
pw 7.0
d1 1.000
tof 0
nt 16
ct 16
alock n
gain not used
FLAGS
il n
in n
dp y
DISPLAY
sp -716.7
wp 4506.3
vs 167
sc 0
wc 250
hzmm 18.03
is 2092.29
rfl 2898.7
rfp 2181.7
th 20
ins 9.000
nm cdc ph
DEC. & VT
dfrq 300.100
dn H1
dpwr 30
dof 0
dm nnn
dmm c
dmf 200
PROCESSING
wtfile
proc ft
fn not used
werr
wexp
wbs
wnt
12
11
10
9
8
7
6
5
4
3
2
1
-0
-1
ppm
0.82
9.00


STANDARD 1H OBSERVE
expl stdlh
SAMPLE
date Jun 23 2005
solvent CDCl3
file /data/export/~
home/slbuch/4ek/mr~
hat/edk-1-19.fid
ACQUISITION
sfrq 300.100
tn H1
at 1.595
np 17984
sw 4508.5
fb not used
bs 16
tpwr 54
pw 7.0
d1 1.000
tof 0
nt 16
ct 16
alock n
gain not used
FLAGS
il n
in n
dp y
DISPLAY
sp -147.8
wp 2735.7
vs 151
sc 0
wc 250
hzmm 10.84
is 470.84
rfl 2896.2
rfp 892.9
th 265
ins 2.000
nm cdc ph
DEC. & VT
dfrq 300.100
dn H1
dpwr 30
dof 0
dm nnn
dmm c
dmf 200
PROCESSING
wtfile
proc ft
fn not used
wnr
wexp
wbs
wnt
7.357
7.328
6.917
6.888
4.861
3.315
3.314
3.305
3.321
3.239
8
7
6
5
4
3
2
1
0
ppm
0.81
1.81
2.00
4.04
1.09


STANDARD PROTON PARAMETERS
expl s2pul
SAMPLE
date Nov 28 2005
solvent CDCl3
file exp
ACQUISITION
sfrq 499.749
tn H1
at 3.277
np 65536
sw 9598.5
fb not used
bs 16
tpwr 58
pw 6.2
pl 0
d1 1
tof 1498.1
nt 16
ct 16
alock n
gain not used
FLAGS
il n
in n
dp y
hs nn
DISPLAY
sp -1998.0
wp 9598.8
vs 151
sc 0
wc 250
hzmm 48.00
is 33.57
rfl 4639.1
rfp 3639.1
th 7
ins 1.000
ns cdc ph
DEC. & VT
dfrq 125.624
dn C13
dpwr 34
dof 1498.1
dm nnn
dmm w
dmf 10000
dseq
drss 1.0
homo n
DEC2
dfrq2 0
dn2
dpwr2 1
dof2 0
dm2 n
dmm2 c
dmf2 200
dseq2
drss2 1.0
homo2 n
DEC3
dfrq3 0
dn3
dpwr3 1
dof3 0
dm3 n
dmm3 c
dmf3 200
dseq3
drss3 1.0
homo3 n
PROCESSING
wtfile
proc ft
fn 65536
math f
werr
wexp
wbs
wnt
II-209
NH2
16
14
12
10
8
6
4
2
-0
ppm
1.08
1.00
1.642.60
2.35


STANDARD PROTON PARAMETERS
exp1 s2pul
SAMPLE
date Nov 20 2005
solvent CDCl3
file exp
ACQUISITION
sfrq 499.749
tn H1
at 9.277
np 65536
sw 8998.8
fb not used
bs 16
tpwr 56
pw 8.2
d1 0
tof 1498.1
nt 16
ct 16
alock n
gain not used
FLAGS
il n
in n
dp y
hs nn
DISPLAY
sp -999.3
wp 8998.8
vs 151
sc 0
wc 250
hzmm 40.00
is 33.57
rfl 4032.4
rfp 3033.1
th 7
ins 1.000
nm cdc ph
DEC. & VT
dfrq 125.674
dn C13
dpwr 34
dof 1498.1
dm nnn
dmm w
dmf 10000
dseq
drss 1.0
homo n
DEC2
dfrq2 0
dn2
dpwr2 1
dof2 0
dn2 n
dmm2 c
dmf2 200
dseq2
drss2 1.0
homo2 n
DEC3
dfrq3 0
dn3
dpwr3 1
dof3 0
dm3 n
dmm3 c
dmf3 200
dseq3
drss3 1.0
homo3 n
PROCESSING
wtfile
proc ft
fn 65536
math f
werr
wexp
wbs
wnt
II 258
16
14
12
10
8
6
4
2
-0
ppm
6.2700
7.29

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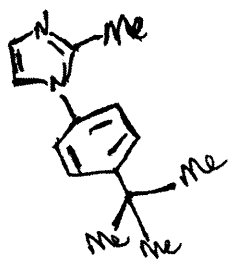
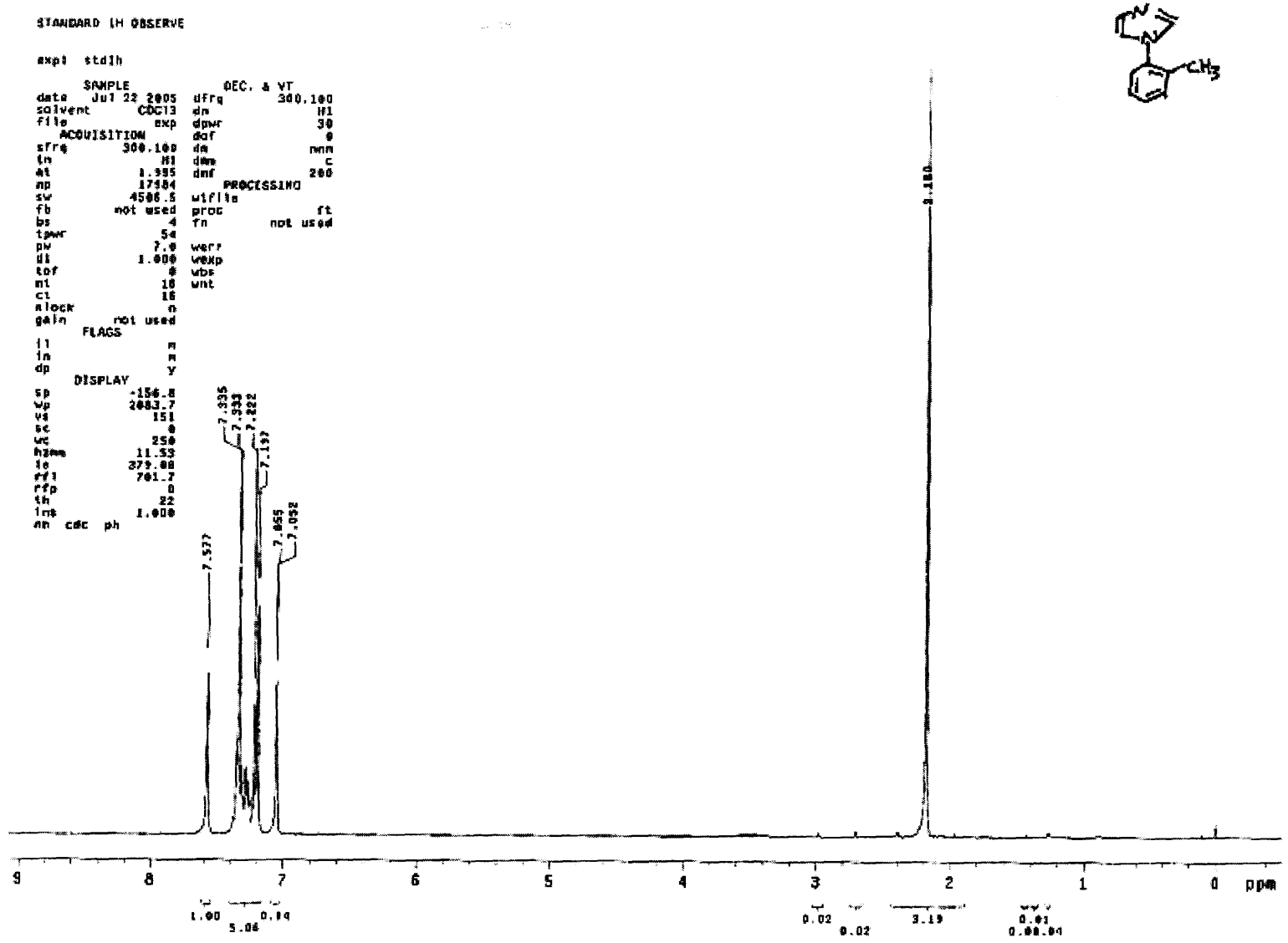
exp5 std1h

SAMPLE		DEC. & VT	
date	Feb 23 2005	dfrq	300.100
solvent	CDCl3	dn	H1
file	exp	dpwr	30
ACQUISITION		dof	0
sfrq	300.100	dm	nnn
tn	H1	dmm	c
at	1.995	dmf	200
np	17984	PROCESSING	
sw	4506.5	wtfile	
fb	not used	proc	ft
bs	16	fn	not used
tpwr	54		
pw	7.0	werr	
d1	1.000	wexp	
tof	0	wbs	
nt	16	wnt	
ct	0		
alock	n		
gain	not used		
FLAGS			
il	n		
in	n		
dp	y		
DISPLAY			
sp	-717.1		
wp	4506.3		
vs	151		
sc	0		
wc	250		
hzmm	18.03		
is	500.00		
rfl	2899.1		
rfp	2181.7		
th	20		
ins	9.000		
nm cdc ph			




STANDARD 1H OBSERVE
expt stdlh
SAMPLE
date Jul 22 2005
solvent CDCl3
file exp
ACQUISITION
sfrq 300.100
tn H1
at 1.995
np 17584
sw 4506.5
fb not used
bs 4
tpwr 54
pw 7.0
d1 1.000
tof 0
nt 16
ct 16
alock n
gain not used
FLAGS
il n
in n
dp y
DISPLAY
sp -156.8
wp 2883.7
vs 151
sc 0
wc 250
hzmm 11.53
is 379.88
rfl 701.7
rfp 0
th 22
int 1.000
nn cdc ph
DEC. & VT
dfrq 300.100
dn H1
dpwr 30
dof 0
da nnn
dmm c
dmf 200
PROCESSING
wtfile
proc ft
fn not used
werr
wexp
wbs
wnt
7.577
7.335
7.333
7.322
7.197
7.055
7.052
2.180
9
8
7
6
5
4
3
2
1
0
ppm
1.00
5.04
0.84
0.02
0.02
3.19
0.01
0.00.04

STANDARD PROTON PARAMETERS

exp1 s2pul

SAMPLE		DEC. & VT	
date	Nov 20 2005	dfrq	125.674
solvent	CDCl3	dn	C13
file	exp	dpwr	34
ACQUISITION		dof	1498.1
sfrq	498.749	dm	nnn
tn	H1	dmm	w
at	3.277	dmf	10000
np	65536	dseq	
sw	8958.8	dres	1.8
fb	not used	homo	n
bs	16	DEC2	
tdav	56	dfrq2	0
pw	8.2	dn2	
pl	0	dpwr2	1
tof	1498.1	dof2	0
nt	16	dm2	n
ct	16	dmm2	c
alock	n	dmf2	200
gain	not used	dseq2	
FLAGS		dres2	1.8
il	n	homo2	n
in	n	DEC3	
dp	y	dfrq3	0
hs	nn	dn3	
DISPLAY		dpwr3	1
sp	-1005.1	dof3	0
wp	8958.8	dm3	n
vs	151	dmm3	c
sc	0	dmf3	200
wc	250	dseq3	
hzmm	40.00	dres3	1.8
is	816.95	homo3	n
rfl	4038.2	PROCESSING	
rfp	3633.1	wtfile	
th	7	proc	ft
ins	1.000	fn	65536
nm cdc ph		math	f
		werr	
		wexp	
		wbs	
		wnt	

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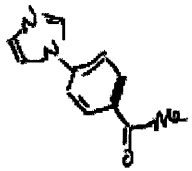

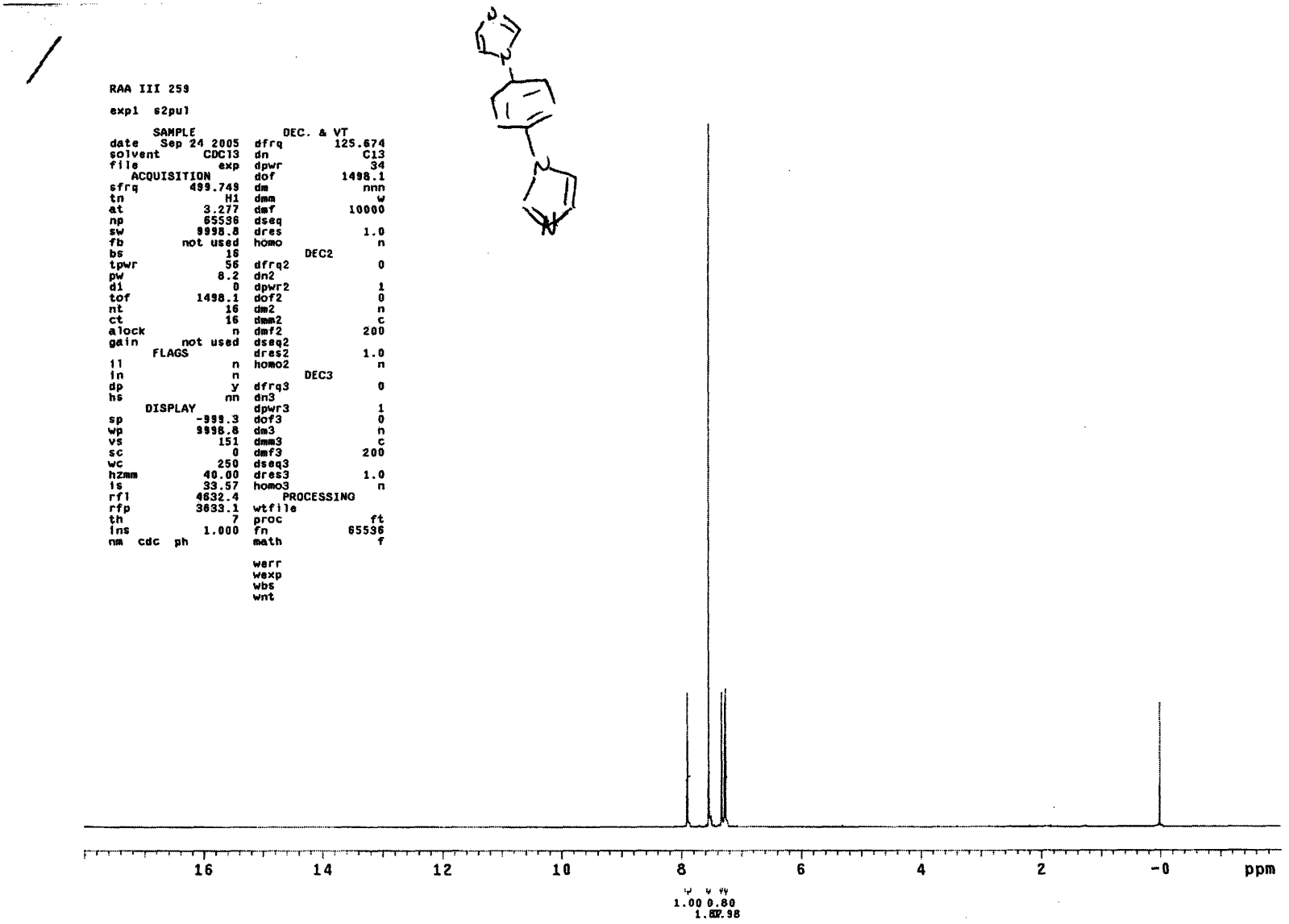

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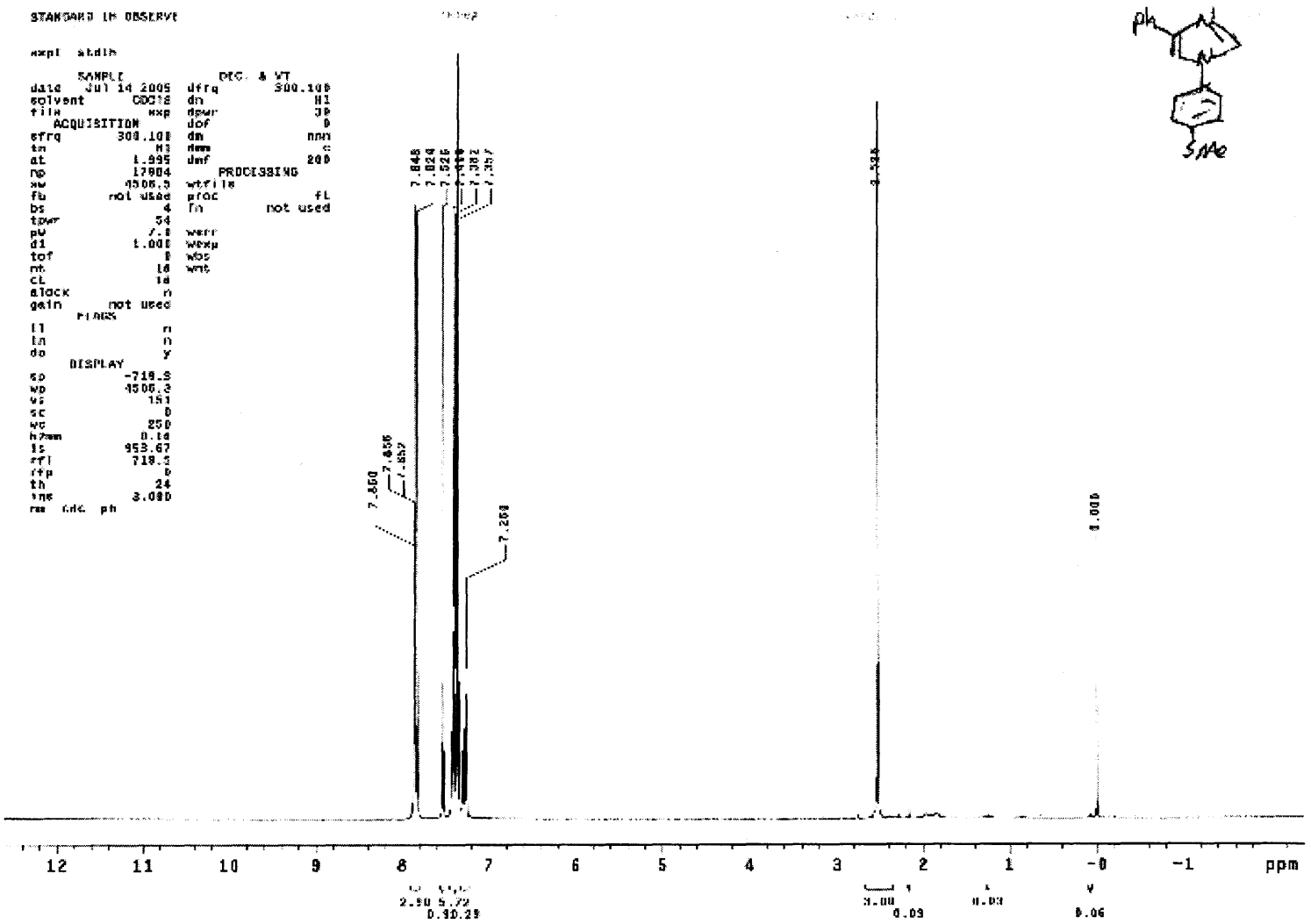
expl s2pul

SAMPLE		DEC. & VT	
date	Sep 24 2005	dfrq	125.674
solvent	CDCl3	dn	C13
file	exp	dpwr	34
ACQUISITION		dof	1498.1
sfrq	499.749	dm	nnn
tn	H1	dmm	w
at	3.277	dmf	10000
np	65536	dseq	
sw	9998.8	dres	1.0
fb	not used	homo	n
bs	16	DEC2	
tpwr	56	dfrq2	0
pw	8.2	dn2	
d1	0	dpwr2	1
tof	1498.1	dof2	0
nt	16	dm2	n
ct	16	dmm2	c
alock	n	dmf2	200
gain	not used	dseq2	
FLAGS		dres2	1.0
il	n	homo2	n
in	n	DEC3	
dp	y	dfrq3	0
hs	nn	dn3	
DISPLAY		dpwr3	1
sp	-999.3	dof3	0
wp	9998.8	dm3	n
vs	151	dmm3	c
sc	0	dmf3	200
wc	250	dseq3	
hzmm	40.00	dres3	1.0
is	33.57	homo3	n
rfl	4632.4	PROCESSING	
rfp	3633.1	wtfile	
th	7	proc	ft
ins	1.000	fn	65536
nm cdc ph		math	f
		warr	
		wexp	
		wbs	
		wnt	


STANDARD IH OBSERVE
expt stdih
SAMPLE
date Jul 14 2005
solvent CDCl3
file exp
ACQUISITION
sfrq 300.108
tn H1
at 1.995
np 17804
sw 4506.5
fb not used
bs 4
tpwr 54
pw 7.8
d1 1.000
tof 0
nt 16
ct 16
alock n
gain not used
FLAGS
il n
in n
dp y
DISPLAY
sp -718.8
wp 4506.2
vs 151
sc 0
wc 250
hzmm 0.16
is 953.67
rfl 719.1
rfp 0
th 24
ins 3.000
ns CDCl3 ph
DEC. & VT
dfrq 300.108
dn H1
dpwr 39
dof 0
dm nnn
dmm c
dmf 200
PROCESSING
wtfile
proc fL
fn not used
wexp
wbs
wnt
7.848
7.824
7.826
7.382
7.357
7.850
7.836
7.819
7.268
3.535
0.000
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
ppm
2.00 5.72
0.90 2.29
3.00
0.09
0.03
0.06
Ph
SiMe

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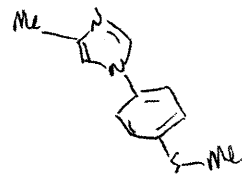
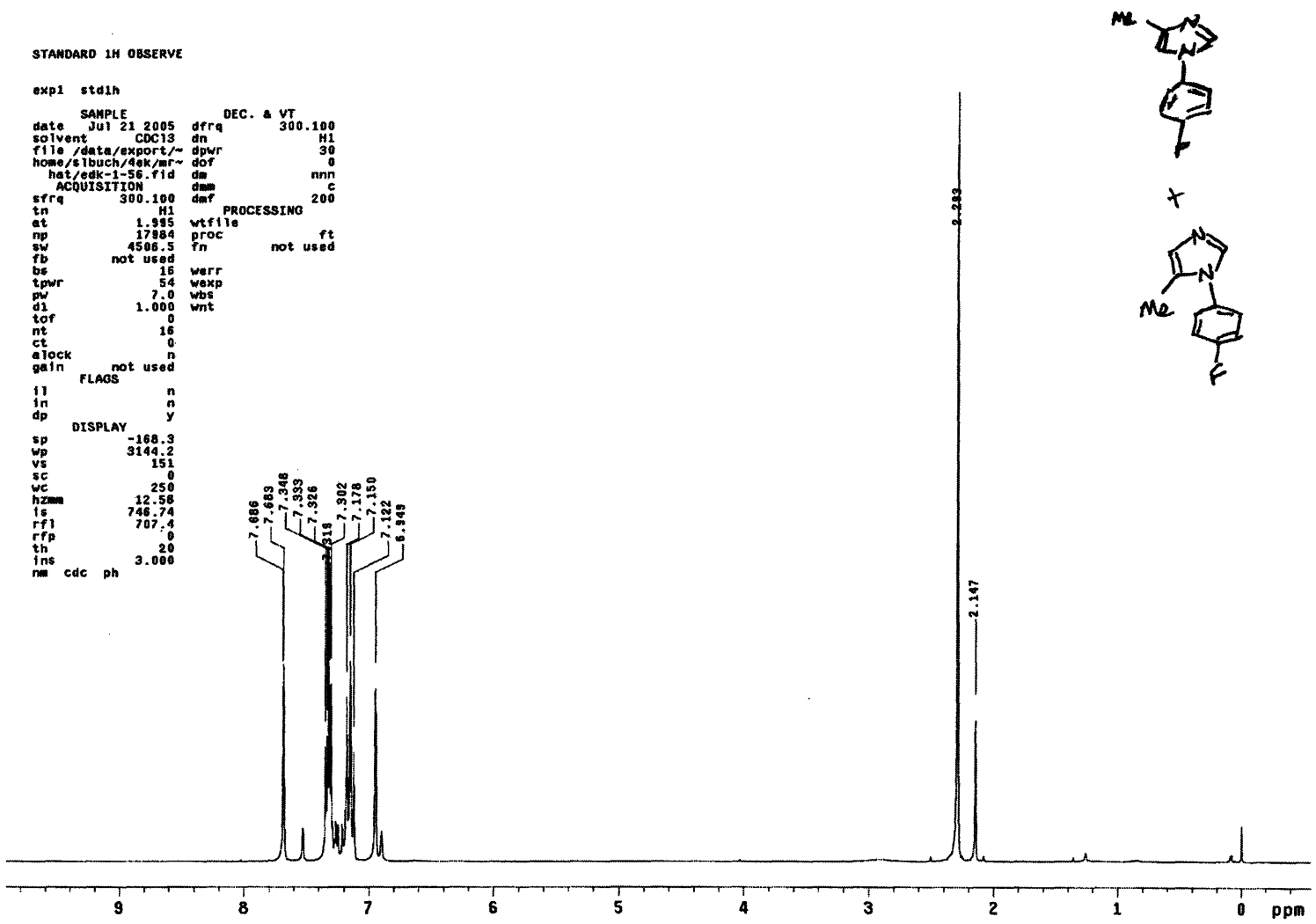
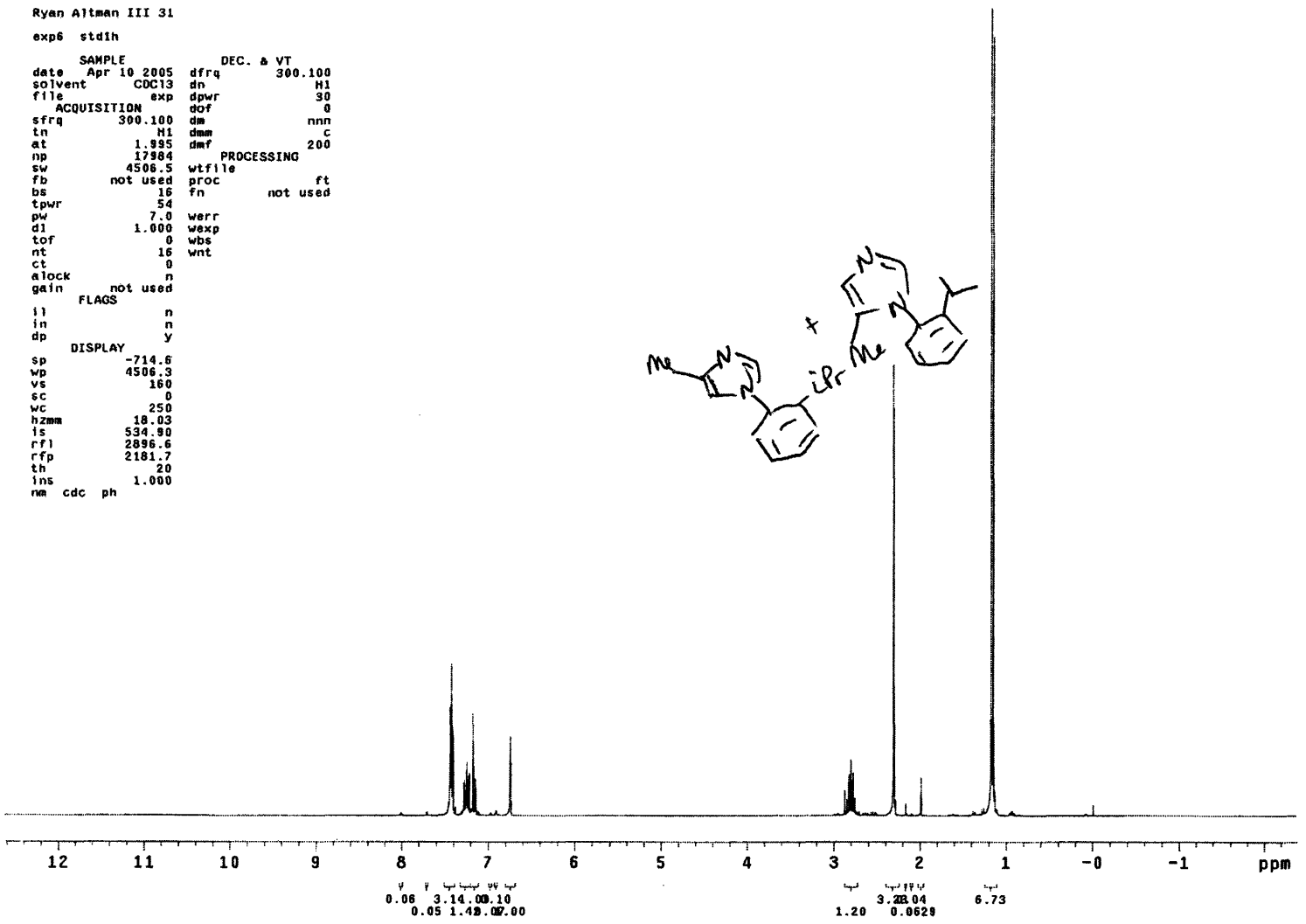
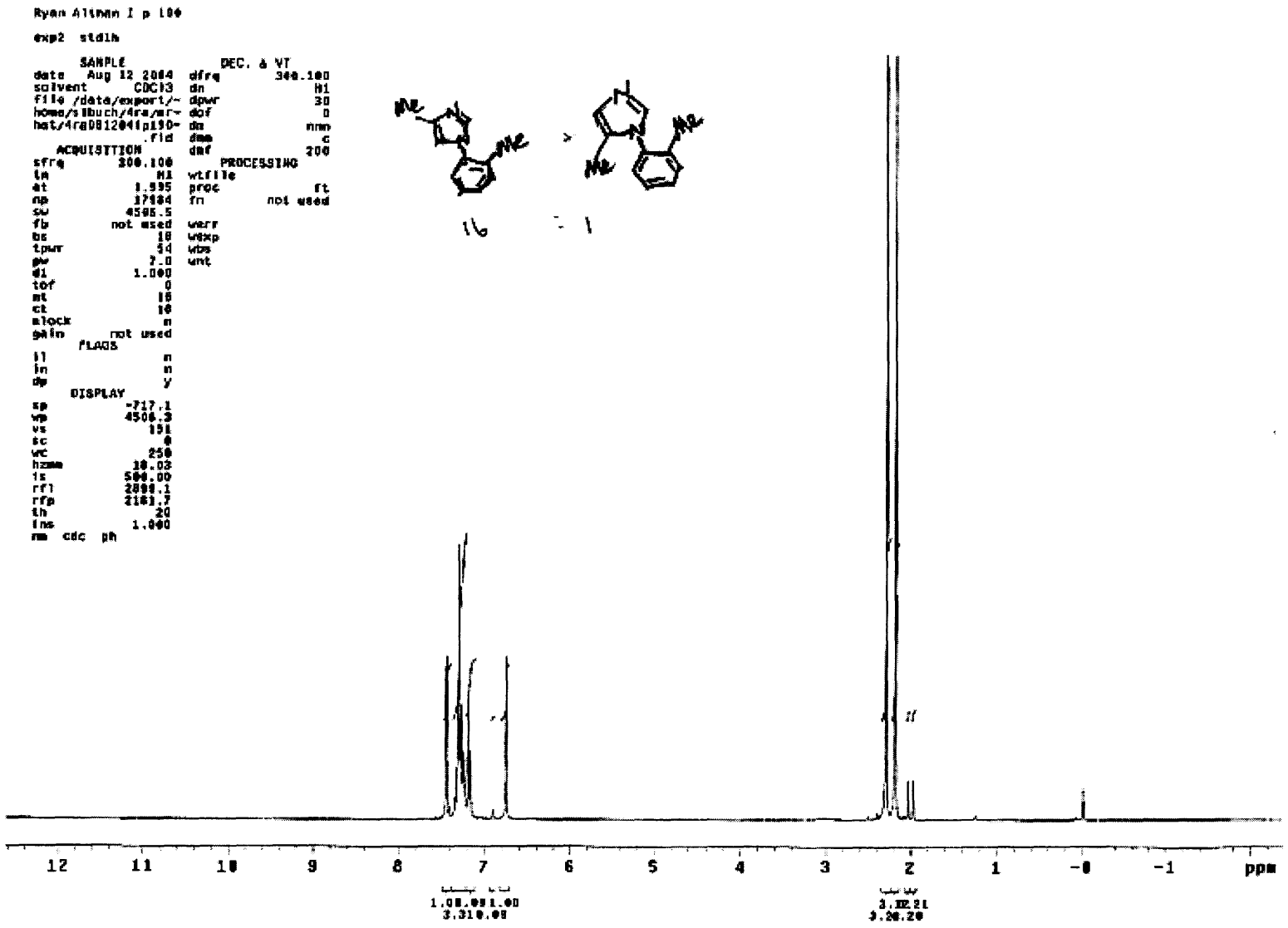
exp5 std1h

SAMPLE		DEC. & VT	
date	Feb 8 2005	dfrq	300.100
solvent	CDCl3	dn	H1
file	exp	dpwr	30
ACQUISITION		dof	0
sfrq	300.100	dm	nnn
tn	H1	dmm	c
at	1.995	dmf	200
np	17984	PROCESSING	
sw	4506.5	wtfile	
fb	not used	proc	ft
bs	16	fn	not used
tpwr	54		
pw	7.0	werr	
d1	1.000	wexp	
tof	0	wbs	
nt	16	wnt	
ct	16		
alock	n		
gain	not used		
FLAGS			
il	n		
in	n		
dp	y		
DISPLAY			
sp	-717.1		
wp	4506.3		
vs	151		
sc	0		
wc	250		
hzmm	18.03		
is	500.00		
rfl	2899.1		
rfp	2181.7		
th	20		
ins	100.000		
nm cdc ph			




STANDARD 1H OBSERVE
expl stdlh
SAMPLE
date Jul 21 2005
solvent CDCl3
file /data/export/~
home/slbuch/4ek/mr~
hat/edk-1-56.fid
ACQUISITION
sfrq 300.100
tn H1
at 1.995
np 17884
sw 4508.5
fb not used
bs 16
tpwr 54
pw 7.0
d1 1.000
tof 0
nt 16
ct 0
alock n
gain not used
FLAGS
il n
in n
dp y
DISPLAY
sp -168.3
wp 3144.2
vs 151
sc 0
wc 250
hzmm 12.56
is 746.74
rfl 707.4
rfp 0
th 20
ins 3.000
nm cdc ph
DEC. & VT
dfrq 300.100
dn H1
dpwr 30
dof 0
dm nnn
dmm c
dmf 200
PROCESSING
wtfile
proc ft
fn not used
werr
wexp
wbs
wnt
7.686
7.683
7.348
7.333
7.326
7.319
7.302
7.178
7.150
7.122
6.949
2.283
2.147
Me
Me
F
F
9
8
7
6
5
4
3
2
1
0
ppm


Ryan Altman III 31
exp6 stdlh
SAMPLE
date Apr 10 2005
solvent CDCl3
file exp
ACQUISITION
sfrq 300.100
tn H1
at 1.995
np 17984
sw 4506.5
fb not used
bs 16
tpwr 54
pw 7.0
dl 1.000
tof 0
nt 16
ct 0
alock n
gain not used
FLAGS
il n
in n
dp y
DISPLAY
sp -714.6
wp 4506.3
vs 160
sc 0
wc 250
hzmm 18.03
is 534.90
rfl 2896.6
rfp 2181.7
th 20
ins 1.000
nm cdc ph
DEC. & VT
dfrq 300.100
dn H1
dpwr 30
dof 0
dm nnn
dmm c
dmf 200
PROCESSING
wtfile
proc ft
fn not used
werr
wexp
wbs
wnt
Me
iPr
Me
12
11
10
9
8
7
6
5
4
3
2
1
-0
-1
ppm
0.06
3.14
0.10
0.05
1.20
3.04
0.06
6.73


Ryan Altman I p 100
exp2 stdih
SAMPLE
date Aug 12 2004
solvent CDCl3
file /data/export/~
home/sbuch/4ra/mr~
hst/4ra0812041p100~
fld
ACQUISITION
sfrq 300.100
tn H1
at 1.995
np 17984
sw 4505.5
fb not used
bs 16
tpwr 54
pw 7.0
d1 1.000
tof 0
mt 15
ct 16
ntock n
gain not used
FLAGS
il n
in n
dp y
DISPLAY
sp -717.1
wp 4506.3
vs 191
sc 0
wc 250
hzmm 18.03
is 500.00
rf1 2898.1
rfp 2161.7
th 20
ins 1.000
nm cdc ph
DEC. & VT
dfrq 300.100
dn H1
dpwr 30
dof 0
dm nnn
dmm c
dmf 200
PROCESSING
wtfile
proc ft
fn not used
werr
wexp
wbs
wnt
Me
Me
Me
Me
16 : 1
12
11
10
9
8
7
6
5
4
3
2
1
-0
-1
ppm
1.00 1.00
3.31 0.09
3.00
3.26 20

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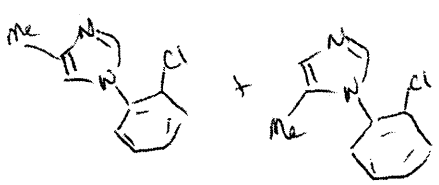
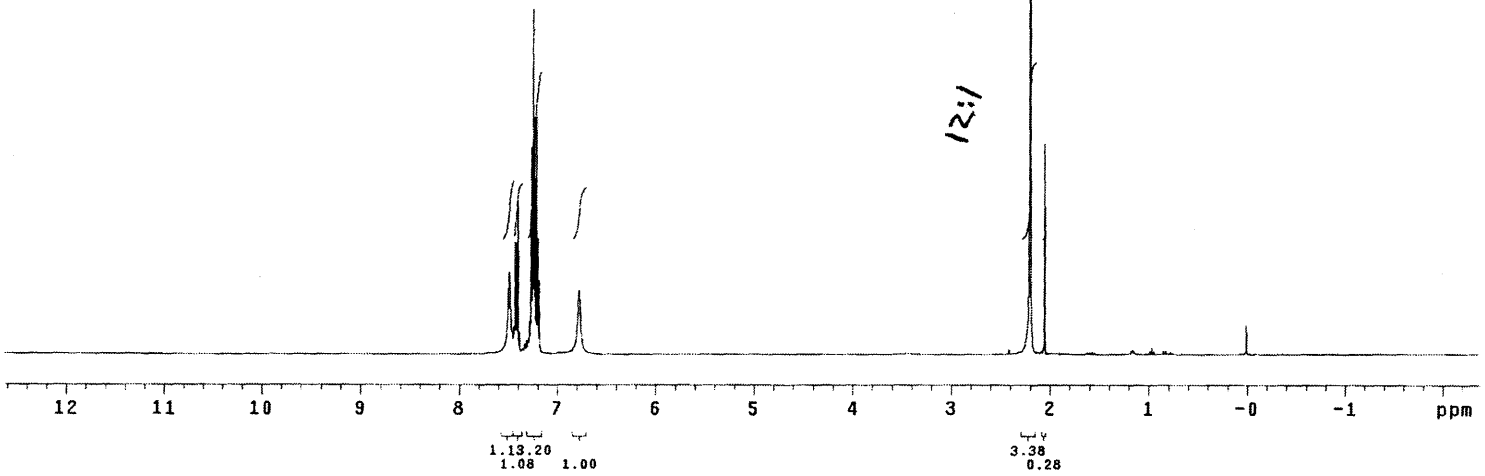
exp6 std1h

SAMPLE		DEC. & VT	
date	Mar 8 2005	dfrq	300.100
solvent	CDCl3	dn	H1
file	exp	dpwr	30
ACQUISITION		dof	0
sfrq	300.100	dm	nnn
tn	H1	dmm	c
at	1.995	dmf	2000
np	17984	PROCESSING	
sw	4506.5	wtfile	
fb	not used	proc	ft
bs	16	fn	not used
tpwr	54		
pw	7.0	werr	
d1	1.000	wexp	
tof	0	wbs	
nt	16	wnt	
ct	16		
alock	n		
gain	not used		
FLAGS			
il	n		
in	n		
dp	y		
DISPLAY			
sp	-715.5		
wp	4506.3		
vs	151		
sc	0		
wc	250		
hzmm	18.03		
is	500.00		
rfl	2897.5		
rfp	2181.7		
th	20		
ins	1.000		
nm cdc ph			



12:1



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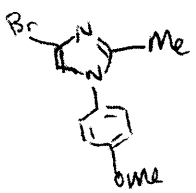
exp3 std1h

SAMPLE		DEC. & VT	
date	Jan 12 2005	dfrq	300.100
solvent	CDCl3	dn	H1
file	/data/slbuch/~	dpwr	30
	4ra/4ra011205-IIp1~	dof	0
	55.fid	dm	nnn
ACQUISITION		dmm	c
sfrq	300.100	dmf	200
tn	H1	PROCESSING	
at	1.995	wtfile	
np	17984	proc	ft
sw	4506.5	fn	not used
fb	not used		
bs	16	werr	
tpwr	54	wexp	
pw	7.0	wbs	
d1	1.000	wnt	
tof	0		
nt	16		
ct	16		
alock	n		
gain	not used		
FLAGS			
il	n		
in	n		
dp	y		
DISPLAY			
sp	-717.7		
wp	4506.3		
vs	151		
sc	0		
wc	250		
hzmm	18.03		
is	500.00		
rfl	2899.7		
rfp	2181.7		
th	20		
ins	3.000		
nm cdc ph			



STANDARD PROTON PARAMETERS

exp1 s2pul

SAMPLE		DEC. & VT	
date	Nov 28 2005	dfrq	125.674
solvent	CDCl3	dn	C13
file	exp	dpwr	34
ACQUISITION		dof	1498.1
sfrq	498.745	dm	nnn
tn	H1	dmm	w
at	3.277	dmf	10060
np	65536	dseq	
sw	9998.8	drss	1.0
fb	not used	homo	n
bs	16	DEC2	
tpwr	58	dfrq2	0
pw	6.2	dn2	
d1	1	dpwr2	1
tof	1498.1	dof2	0
nt	16	dm2	n
ct	16	dmm2	c
alock	n	dmf2	200
gain	not used	dseq2	
FLAGS		drss2	1.0
il	n	homo2	n
in	n	DEC3	
dp	y	dfrq3	0
hs	nn	dn3	
DISPLAY		dpwr3	1
sp	-1805.4	dof3	0
wp	9998.8	dm3	n
vs	151	dmm3	c
sc	0	dmf3	200
wc	200	dseq3	
hzmm	40.00	drss3	1.0
is	5.00	homo3	n
rfl	4638.5	PROCESSING	
rfp	3639.1	wtfile	
th	7	proc	ft
lvl	3.000	fn	65536
nm cdc ph		math	r
		werr	
		wexp	
		wbs	
		wnt	

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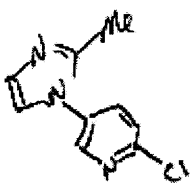
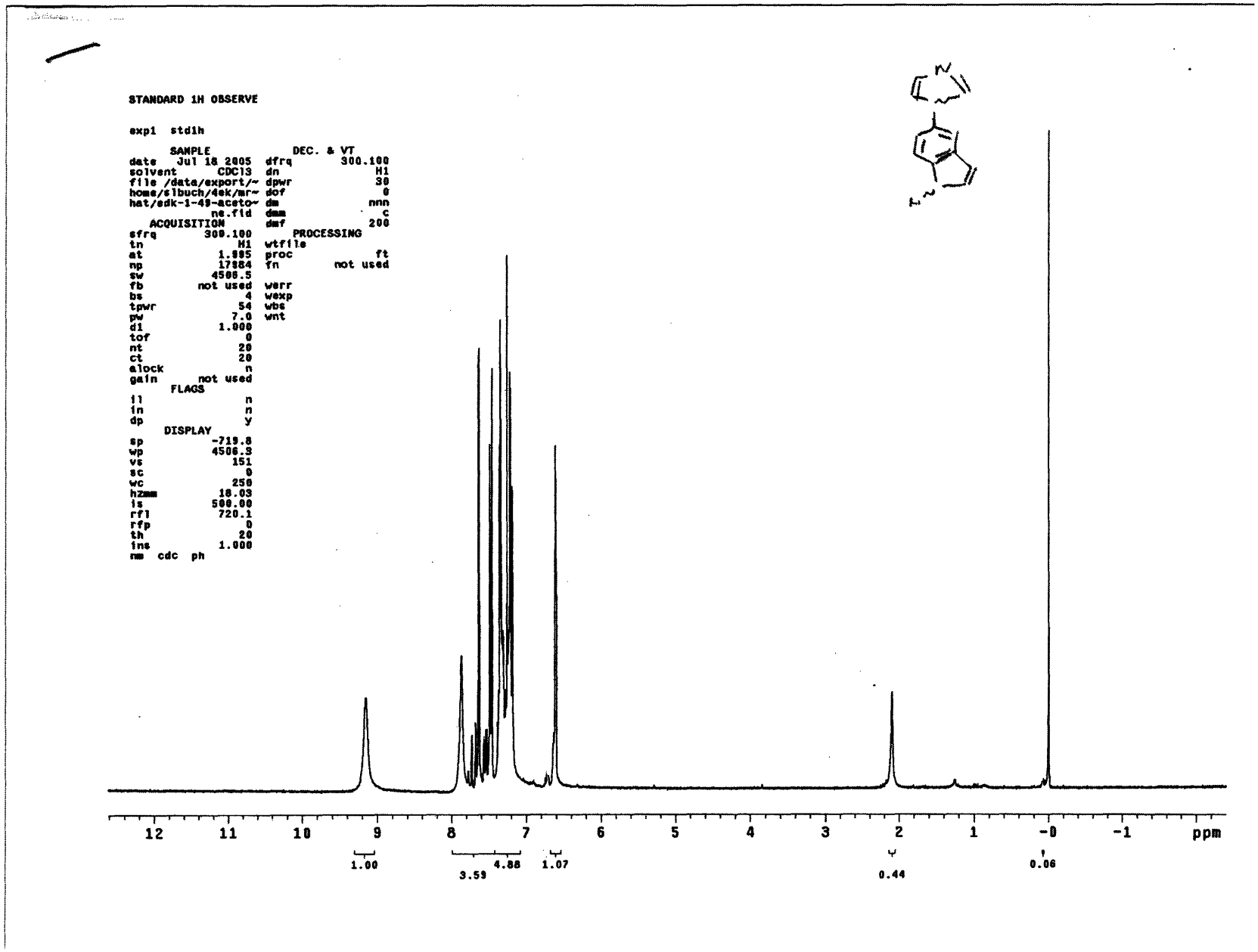
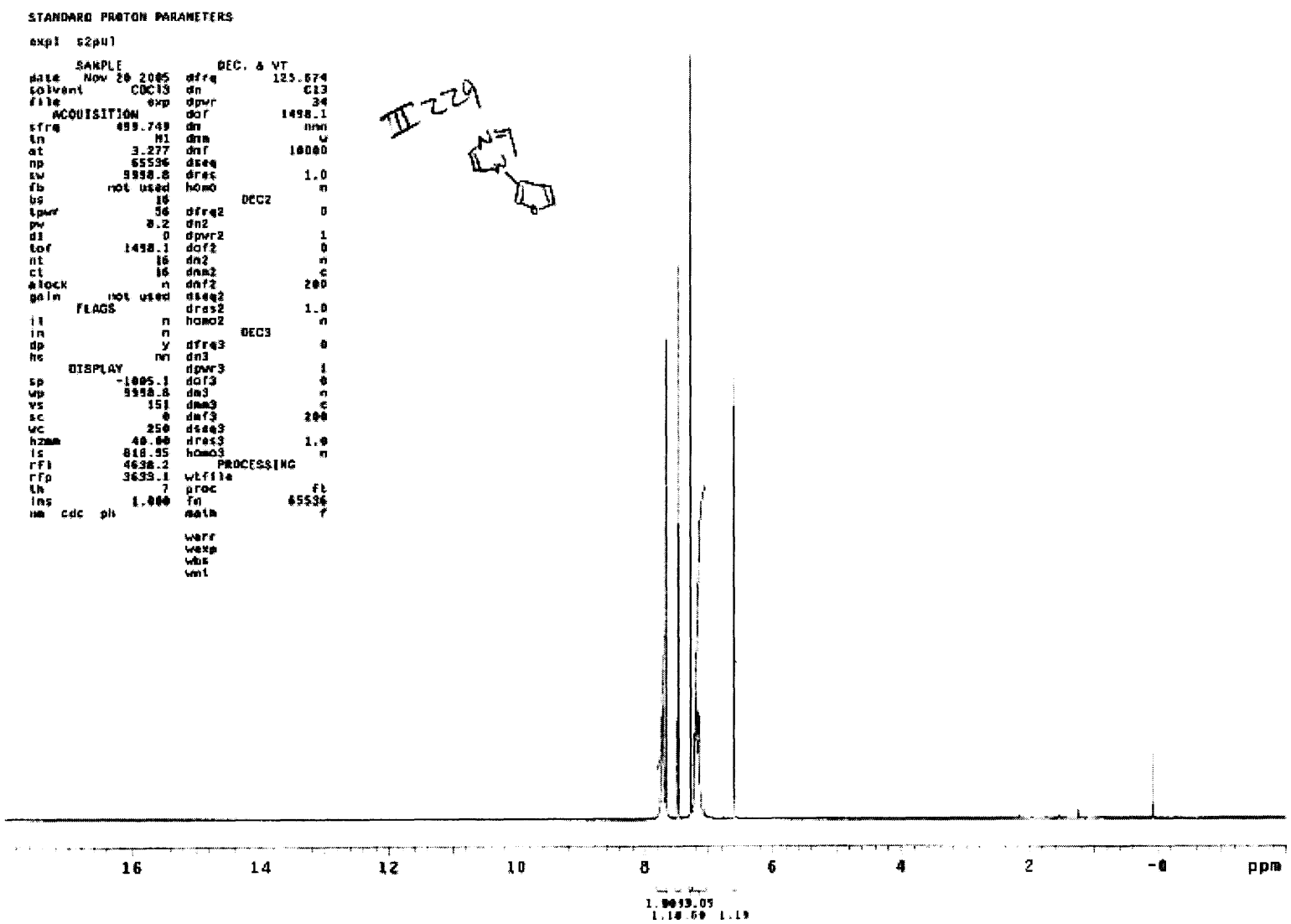



STANDARD 1H OBSERVE
exp1 std1h
SAMPLE
date Jul 18 2005
solvent CDCl3
file /data/export/~
home/slbuch/4sk/mr~
hat/sdk-1-49-aceto~
ne.fid
ACQUISITION
sfrq 300.100
tn H1
at 1.885
np 17984
sw 4506.5
fb not used
bs 4
tpwr 54
pw 7.0
d1 1.000
tof 0
nt 20
ct 20
alock n
gain not used
FLAGS
il n
in n
dp y
DISPLAY
sp -719.8
wp 4506.3
vs 151
sc 0
wc 250
hzmm 18.03
is 500.00
rfl 720.1
rfp 0
th 20
ins 1.000
nm cdc ph
DEC. & VT
dfrq 300.100
dn H1
dpwr 30
dof 0
dm nnn
dmm c
dmf 200
PROCESSING
wtfile
proc ft
fn not used
werr
wexp
wbs
wnt
12
11
10
9
8
7
6
5
4
3
2
1
-0
-1
ppm
1.00
3.59
4.88
1.07
0.44
0.06


STANDARD PROTON PARAMETERS
expl s2pul
SAMPLE
date Nov 20 2005
solvent CDCl3
file exp
ACQUISITION
sfrq 499.749
tn H1
at 3.277
np 65536
sw 9958.8
fb not used
bs 16
tpwr 56
pw 8.2
d1 0
tof 1498.1
nt 16
ct 16
alock n
gain not used
FLAGS
il n
in n
dp y
hs nn
DISPLAY
sp -1005.1
wp 9958.8
vs 151
sc 0
wc 250
hzmm 40.00
is 818.95
rfl 4638.2
rfp 3633.1
th 7
ins 1.000
ns cdc ph
DEC. & VT
dfrq 125.674
dn C13
dpwr 34
dof 1498.1
dm nnn
dmm w
dmf 10080
dseq
drec 1.0
homo n
DEC2
dfrq2 0
dn2
dpwr2 1
dof2 0
dm2 n
dmm2 c
dmf2 200
dseq2
drec2 1.0
homo2 n
DEC3
dfrq3 0
dn3
dpwr3 1
dof3 0
dm3 n
dmm3 c
dmf3 200
dseq3
drec3 1.0
homo3 n
PROCESSING
wtfile
proc ft
fn 65536
math f
werr
wexp
wbs
wnt
II229
16
14
12
10
8
6
4
2
-0
ppm

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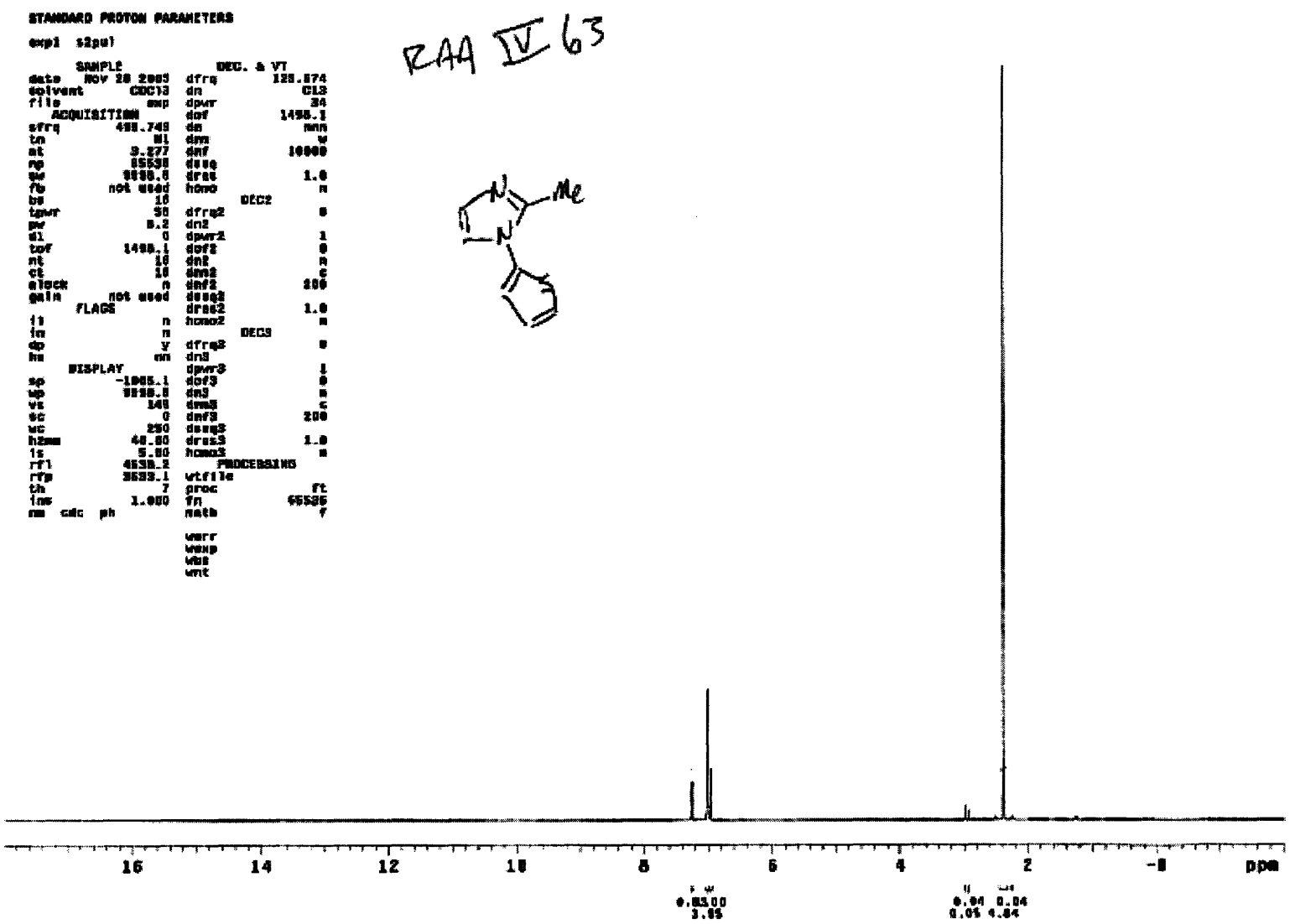
exp5 stdih

SAMPLE		DEC. & VT	
date	Feb 16 2005	dfrq	300.100
solvent	CDCl3	dn	H1
file	exp	dpwr	30
ACQUISITION		dof	0
sfrq	300.100	dm	nnn
tn	H1	dmm	c
at	1.995	dmf	200
np	17984	PROCESSING	
sw	4506.5	wtfile	
fb	not used	proc	ft
bs	16	fn	not used
tpwr	54		
pw	7.0	werr	
dl	1.000	wexp	
tof	0	wbs	
nt	16	wnt	
ct	16		
alock	n		
gain	not used		
FLAGS			
il	n		
in	n		
dp	y		
DISPLAY			
sp	-716.8		
wp	4506.3		
vs	151		
sc	0		
wc	250		
hzmm	18.03		
fs	500.00		
rfl	2898.8		
rfp	2181.7		
th	20		
ins	1.000		
nm cdc ph			


STANDARD PROTON PARAMETERS
exp1 s2pul
SAMPLE
date Nov 28 2003
solvent CDCl3
file exp
ACQUISITION
sfrq 499.749
tn H1
at 3.277
np 65536
sw 9998.0
fb not used
bs 16
tpwr 58
pw 9.2
pl 0
tof 1498.1
nt 16
ct 16
alock n
gain not used
FLAGS
il n
in n
dp y
hs nn
DISPLAY
sp -1965.1
wp 9998.8
vs 148
sc 0
wc 250
hzmm 40.80
is 5.00
rfl 4538.2
rfp 3633.1
th 7
ins 1.000
nm cdc ph
DEC. & VT
dfrq 125.674
dn C13
dpwr 34
dof 1498.1
dm nnn
dmm w
dmf 10000
dseq
drat 1.0
homo n
DEC2
dfrq2 0
dn2
dpwr2 1
dof2 0
dm2 n
dmm2 c
dmf2 200
dseq2
drat2 1.0
homo2 n
DEC3
dfrq3 0
dn3
dpwr3 1
dof3 0
dm3 n
dmm3 c
dmf3 200
dseq3
drat3 1.0
homo3 n
PROCESSING
wtfile
proc ft
fn 65536
math f
werr
wexp
wbs
wnt
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Me
N
N
16
14
12
10
8
6
4
2
-0
ppm
0.83 0.00
3.05
0.84 0.84
0.05 4.84

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STANDARD PROTON PARAMETERS

expl s2pul

SAMPLE		DEC. & VT			
date	Nov 28 2005	dfrq	125.674		
solvent	CDCl3	dn	C13		
file	exp	dpwr	36		
ACQUISITION		dof	1498.1		
sfrq	499.749	dm	nnn		
tn	H1	dmm	w		
at	3.277	dmf	10000		
np	65536	dseq			
sw	9998.8	dres	1.0		
fb	not used	homo	n		
bs	16	DEC2			
tpwr	56	dfrq2	0		
pw	8.2	dn2			
pl	0	dpwr2	1		
tof	1498.1	dof2	0		
nt	16	dm2	n		
ct	16	dmm2	c		
alock	n	dmf2	200		
gain	not used	dseq2			
FLAGS		dres2	1.0		
il	n	homo2	n		
in	n	DEC3			
dp	y	dfrq3	0		
hs	nn	dn3			
DISPLAY		dpwr3	1		
sp	-1005.1	dof3	0		
wp	9998.8	dm3	n		
vs	151	dmm3	c		
sc	0	dmf3	200		
wc	250	dseq3			
hzmm	40.00	dres3	1.0		
is	5.00	homo3	n		
rfl	4038.2	PROCESSING			
rfp	3833.1	wtfile			
th	7	proc	ft		
lvl	1.000	fn	65536		
wm	exc ph	math	f		
		werr			
		wexp			
		wbs			
		wnt			

STANDARD PROTON PARAMETERS

```
exp1  s2pul

      SAMPLE                    DEC. & VT
date    Nov 28 2003     dfrq          125.674
solvent       CDCl3     dn              C13
file           exp      dpwr              34
   ACQUISITION          dof           1498.1
sfrq        499.749      dm                nnn
tn               H1     dmm               w
at             3.277     dmf           10000
np            65536     dseq
sw          9998.8      drst              1.0
fb          not used    homo                n
bs               16                DEC2
tpwr             50     dfrq2               0
pw             5.2      dn2
d1               0      dpwr2               1
tof           1498.1    dof2                0
nt               16     dn2                 n
ct               16     dmm2                c
alock             n     dmf2              200
gain        not used    dseq2
      FLAGS             drst2             1.0
il                n     homo2               n
in                n                 DEC3
dp                y     dfrq3               0
hs               nn     dn3
      DISPLAY           dpwr3               1
sp            -1985.1   dof3                0
wp            9998.8    dn3                 n
vs               149    dmm3                c
sc                 0     dmf3              200
wc               250    dseq3
hzmm           48.80    drst3             1.0
is              5.00    homo3               n
rfl           4638.2          PROCESSING
rfp           3633.1    wtfile
th                 7    proc                ft
lnw           1.000     fn              65536
nm  cdc  ph             math                f

                        werr
                        wexp
                        wbs
                        wnt
```

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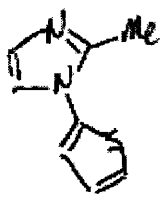


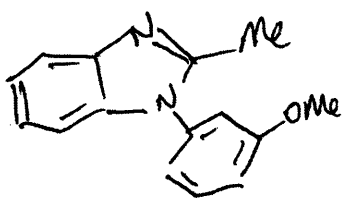
STANDARD 1H OBSERVE

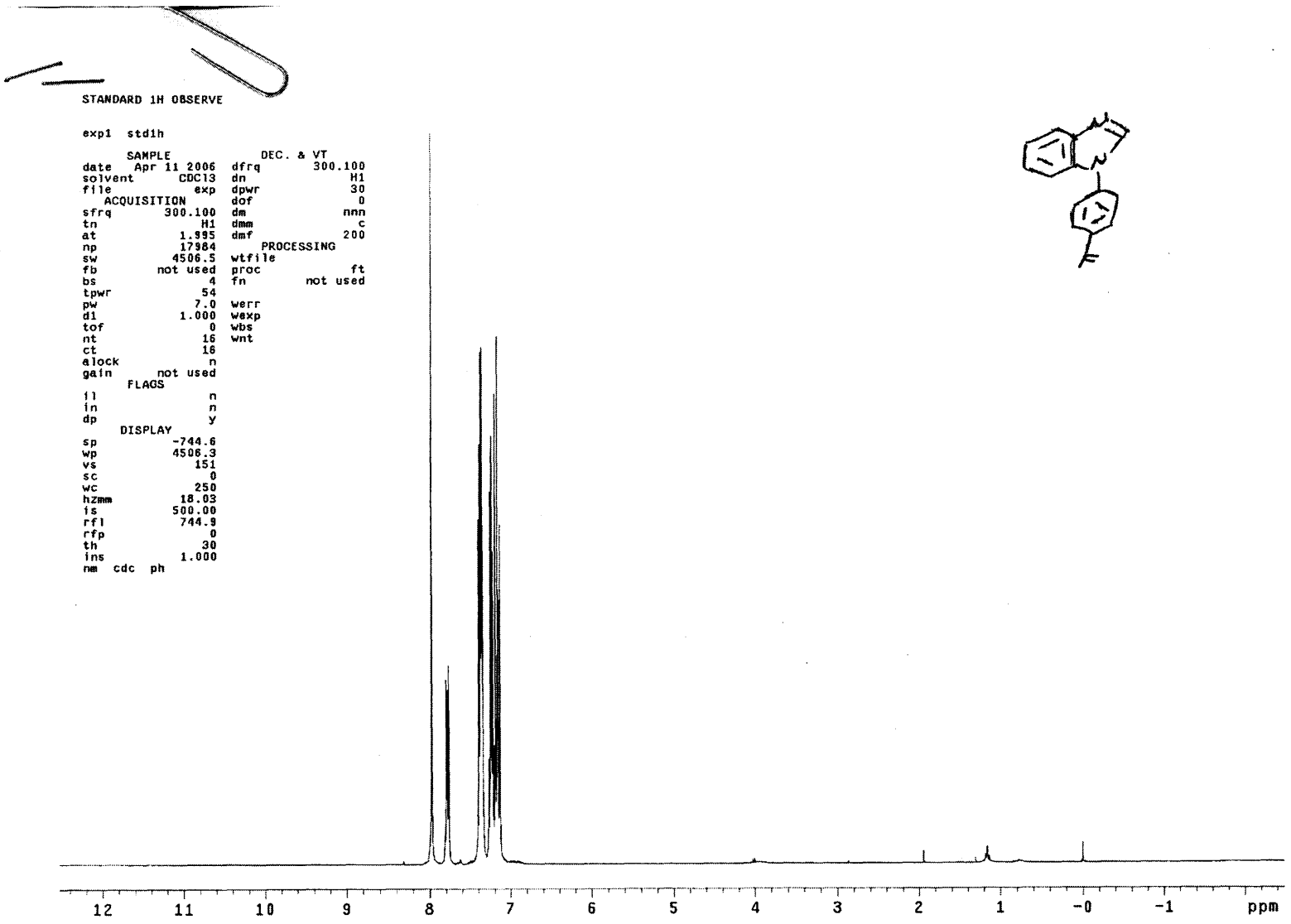
```
exp1  std1h

      SAMPLE
date   Jun 21 2006
solvent      CDCl3
file /data/s1buch/~
 4ek/edk-1-146.fid
   ACQUISITION
sfrq         300.100
tn               H1
at             1.995
np             17984
sw            4506.5
fb         not used
bs                 4
tpwr              54
pw               7.0
d1             1.000
tof                0
nt                16
ct                16
alock              n
gain       not used
      FLAGS
il                 n
in                 n
dp                 y
     DISPLAY
sp            -133.7
wp            3132.3
vs               151
sc                 0
wc               250
hzmm           12.53
is             500.00
rfl            749.5
rfp                0
th                20
ins            3.000
nm  cdc  ph

      DEC. & VT
dfrq         300.100
dn               H1
dpwr             30
dof               0
dm              nnn
dmm               c
dmf             200
     PROCESSING
wtfile
proc             ft
fn         not used

werr
wexp
wbs
wnt
```

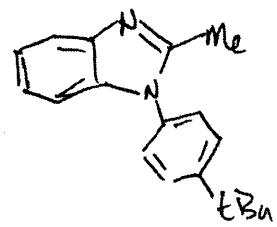


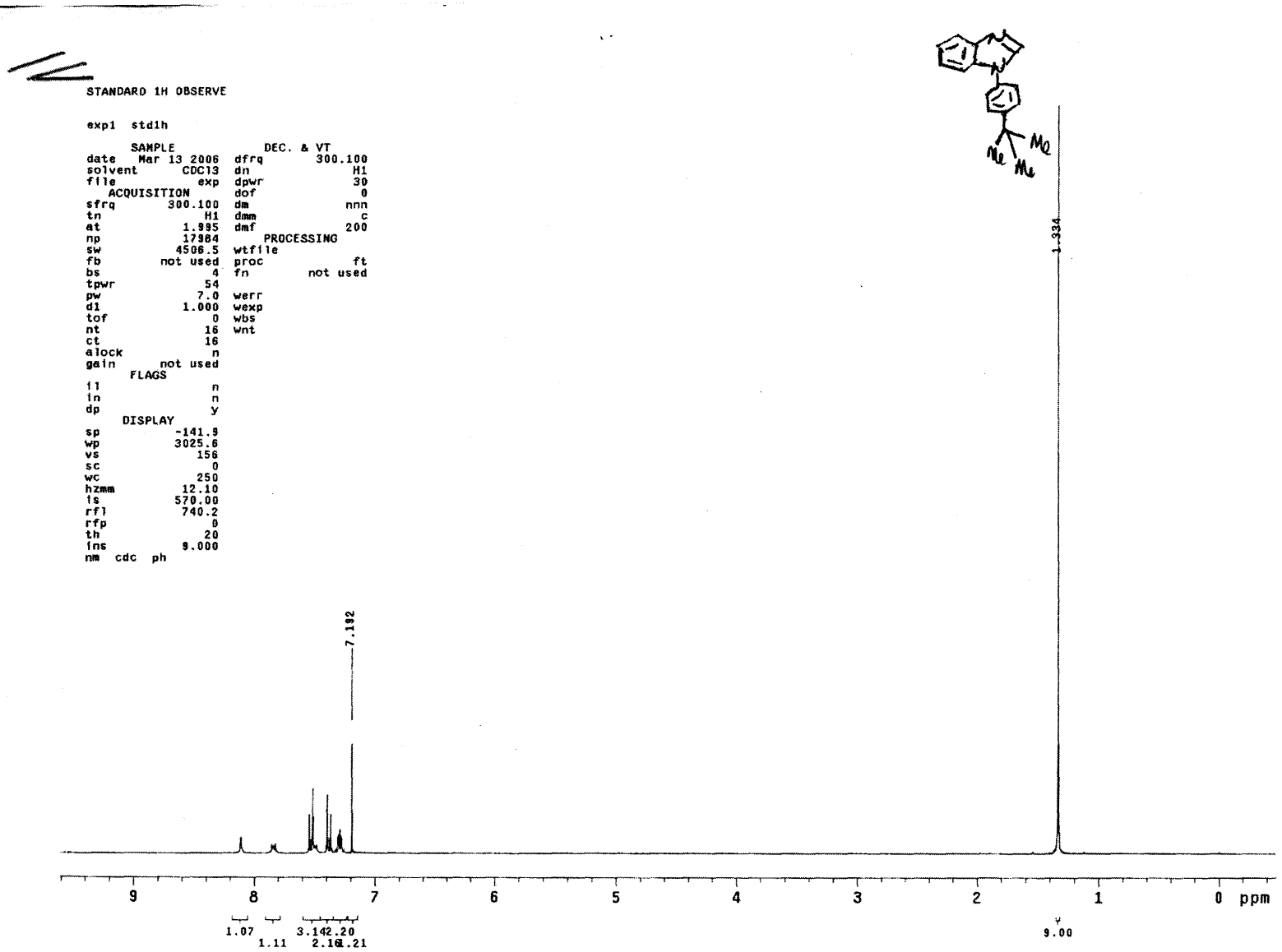

STANDARD 1H OBSERVE
exp1 std1h
SAMPLE
date Apr 11 2006
solvent CDCl3
file exp
ACQUISITION
sfrq 300.100
tn H1
at 1.995
np 17984
sw 4506.5
fb not used
bs 4
tpwr 54
pw 7.0
d1 1.000
tof 0
nt 16
ct 16
alock n
gain not used
FLAGS
il n
in n
dp y
DISPLAY
sp -744.6
wp 4506.3
vs 151
sc 0
wc 250
hzmm 18.03
is 500.00
rfl 744.9
rfp 0
th 30
ins 1.000
nm cdc ph
DEC. & VT
dfrq 300.100
dn H1
dpwr 30
dof 0
dm nnn
dmm c
dmf 200
PROCESSING
wtfile
proc ft
fn not used
werr
wexp
wbs
wnt
12
11
10
9
8
7
6
5
4
3
2
1
-0
-1
ppm

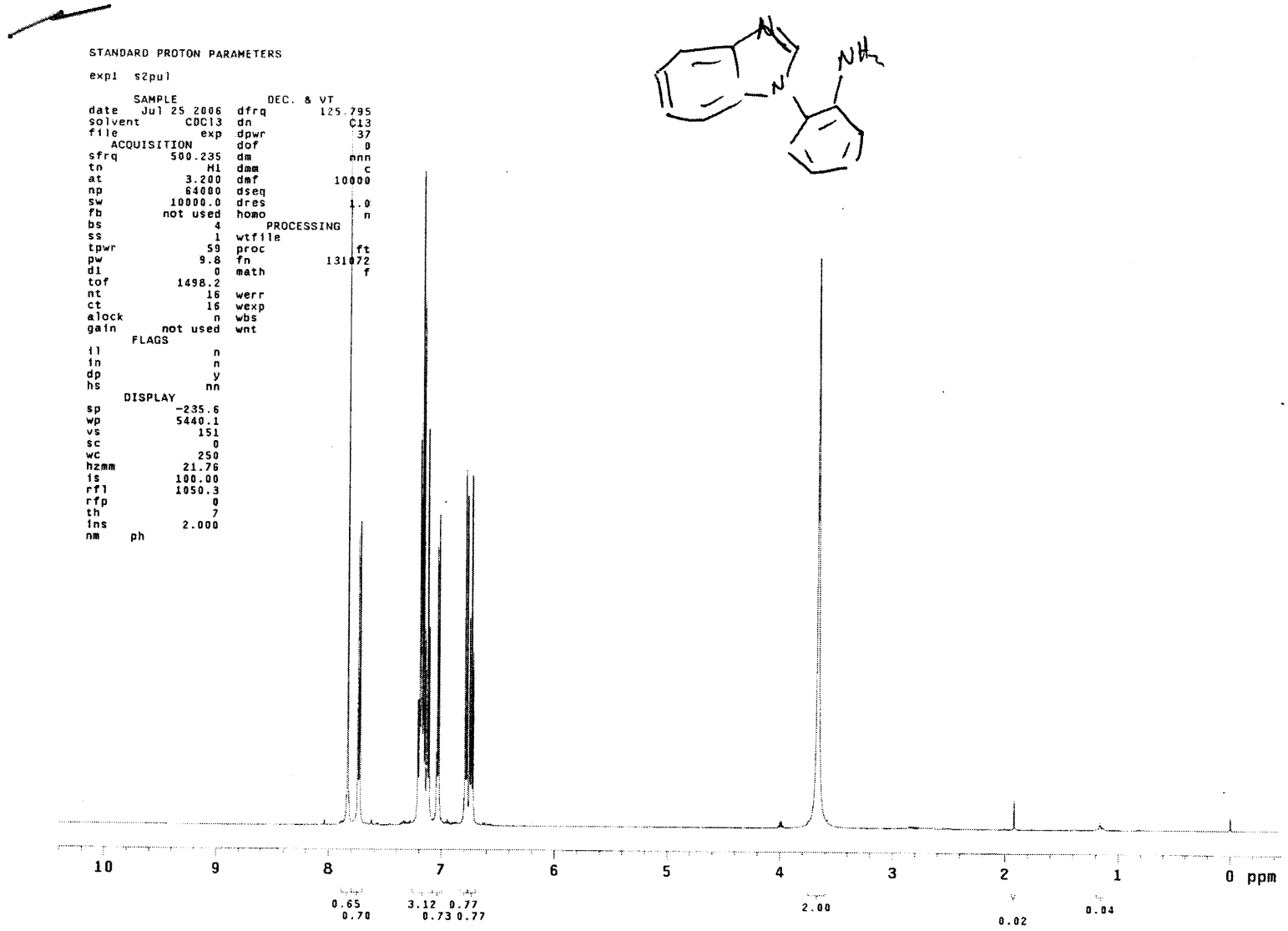
STANDARD PROTON PARAMETERS

expl s2pul

SAMPLE		DEC. & VT	
date	Jul 25 2006	dfrq	125.795
solvent	CDCl3	dn	C13
file	exp	dpwr	37
ACQUISITION		dof	0
sfrq	500.235	dm	nnn
tn	H1	dmm	c
at	3.200	dmf	10000
np	64000	dseq	
sw	10000.0	dres	1.0
fb	not used	homo	n
bs	4	PROCESSING	
ss	1	wtfile	
tpwr	59	proc	ft
pw	9.8	fn	131072
dl	0	math	f
tof	1498.2		
nt	16	werr	
ct	16	wexp	
alock	n	wbs	
gain	not used	wnt	
FLAGS			
il	n		
in	n		
dp	y		
hs	nn		
DISPLAY			
sp	-244.9		
wp	4691.1		
vs	151		
sc	0		
wc	250		
hzmm	18.76		
is	100.00		
rfl	1046.5		
rfp	0		
th	7		
ins	3.000		
nm	ph		




STANDARD 1H OBSERVE
exp1 std1h
SAMPLE
date Mar 13 2006
solvent CDCl3
file exp
ACQUISITION
sfrq 300.100
tn H1
at 1.995
np 17984
sw 4506.5
fb not used
bs 4
tpwr 54
pw 7.0
d1 1.000
tof 0
nt 16
ct 16
alock n
gain not used
FLAGS
il n
in n
dp y
DISPLAY
sp -141.9
wp 3025.6
vs 156
sc 0
wc 250
hzmm 12.10
is 570.00
rfl 740.2
rfp 0
th 20
ins 9.000
nm cdc ph
DEC. & VT
dfrq 300.100
dn H1
dpwr 30
dof 0
dm nnn
dmm c
dmf 200
PROCESSING
wtfile
proc ft
fn not used
werr
wexp
wbs
wnt
7.192
1.334
Me
Me
Me
9
8
7
6
5
4
3
2
1
0 ppm
1.07
1.11
3.14
2.20
2.16
1.21
9.00


STANDARD PROTON PARAMETERS
exp1 s2pul
SAMPLE
date Jul 25 2006
solvent CDCl3
file exp
ACQUISITION
sfrq 500.235
tn H1
at 3.200
np 64000
sw 10000.0
fb not used
bs 4
ss 1
tpwr 59
pw 9.8
d1 0
tof 1498.2
nt 16
ct 16
alock n
gain not used
FLAGS
il n
in n
dp y
hs nn
DISPLAY
sp -235.6
wp 5440.1
vs 151
sc 0
wc 250
hzmm 21.76
is 100.00
rf1 1050.3
rfp 0
th 7
ins 2.000
nm ph
DEC. & VT
dfrq 125.795
dn C13
dpwr 37
dof 0
dm nnn
dmm c
dmf 10000
dseq
dres 1.0
homo n
PROCESSING
wtfile
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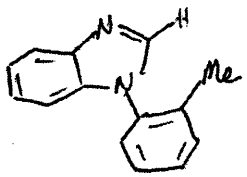


1.5 References and Notes

(1) (a) Quan, M. L.; Lam, P. Y. S.; Han, Q.; Pinto, D. J. P.; He, M. Y.; Li, R.; Ellis, C. D.; Clark, C. G.; Teleha, C. A.; Sun, J. H.; Alexander, R. S.; Bai, S.; Luettgen, J. M.; Knabb, R. M.; Wong, P. C.; Wexler, R. R. *J. Med. Chem.* **2005**, *48*, 1729. (b) Dyck, B.; Goodfellow, V. S.; Phillips, T.; Grey, J.; Haddach, M.; Rowbottom, M.; Naeve, G. S.; Brown, B.; Saunders, J. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1151. (c) Smallheer, J. M.; Alexader, R. S.; Wang, J.; Wang, S.; Nakajima, S.; Rossi, K. A.; Smallwod, A.; Barbera, F.; Burdick, D.; Luettgen, J. M.; Knabb, R. M.; Wexler, R. R.; Jadhav, P. K. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5263. (d) Venkatesan, A. M.; Gu, Y.; Santos, O. D.; Abe, T.; Agarwal, A.; Yang, Y.; Petersen, P. J.; Weiss, W. J.; Mansour, T. S.; Nukaga, M.; Hujer, A. M.; Bonomo, R. A.; Knox, J. R. *J. Med. Chem.* **2004**, *47*, 6556. (e) Lange, J. H. M.; van Stuivenberg, H. H.; Coolen, H. K. A. C.; Adolfs, T. J. P.; McCreary, A. C.; Keizer, H. G.; Wals, H. C.; Veerman, W.; Borst, A. J. M.; de Looff, W.; Verveer, P. C.; Kruse, C. G. *J. Med. Chem.* **2005**, *48*, 1823. (f) Barchechath, S. D.; Tawatao, R. I.; Corr, M.; Carson, D. A.; Cottam, H. B. *J. Med. Chem.* **2005**, *48*, 6409. (g) Mano, T.; Stevens, R. W.; Kazuo, A.; Nakao, Y. O.; Sakakibara, M.; Okumura, T. T.; Miyamoto, K. *Bioorg. Med. Chem.* **2003**, *11*, 3879. (h) Mano, T.; Okumura, Y.; Sakakibara, M.; Okumura, T.; Tamura, T.; Miyamoto, K.; Stevens, R. W. *J. Med Chem.* **2004**, *47*, 720. (k) Roppe, J.; Smith, N. D.; Huang, D.; Tehrani, L.; Wang, B.; Anderson, J.; Brodkin, J.; Chung, J.; Jiang, X.; King, C.; Munoz, B.; Varney, M. A.; Prasit, P.; Cosford, N. D. P. *J. Med. Chem.* **2004**, *47*, 4645. (i) Voets, M.; Antes, I.; Scherer, C.; Muller-Viera, U.; Biemel, K.; Barassin, C.; Marchais-Oberwinkler, S.; Hartmann, R. W. *J. Med. Chem.* **2005**, *48*, 6632.

(2) Lindley, J. *Tetrahedron* **1984**, *40*, 1433.

(3) (a) Surry, D. S.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2008**, *In Press*. (b) 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. (c) Hartwig, J. F. *Synlett*. **2006**, 1283.

(4) (a) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, 2337. (b) Ley, S. V.; Thomas, A. W. *Angew. Chem. Int. Ed.* **2003**, *42*, 5400. (c) Kunz, K.; Scholz, U.; Ganzer, D. *Synlett* **2003**, 2428. (d) Monnier, F.; Taillefer, M. *Angew. Chem. Int. Ed.* **2008**, *47*, 3096.

(5) Anderson, K. W.; Tundel, R. E.; Ikawa, T.; Altman R. A.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2006**, *45*, 6523.

(6) Wan, Y.; Alterman, M.; Hallberg, A. *Synthesis* **2002**, 1597.

(7) Andrus, M. B.; Mettath, S. N.; Song, C. *J. Org. Chem.* **2002**, *67*, 8284.

(8) Alvarado, L. L.; Avedaño, C.; Menéndez. J. C. *J. Org. Chem.* **1995**, *60*, 5678.

(9) (a) Lam, P. Y.; Clark, C. G.; Sauber, S.; Adams, J.; Winters, M. P.; Chan D. M. T.; Combs, A. *Tetrahedron Lett.* **1998**, *39*, 2941. (b) Collman, J. P.; Zhong, M.; Zeng, L.; Costanzo, S.; *J. Org. Chem.* **2001**, 66, 1528. (c) Lan, J. B.; Li, C.; Yu, X.; You, J. S.; Xie, R. G. *Chem. Commun.* **2004**, 188.

(10) Fedorov, A. Y.; Finet, J. P. *Tetrahedron Lett.* **1999**, *40*, 2747.

(11) Lam, P. Y. S.; Deudon, S.; Averill, K. M.; Li, R.; He, M. Y.; DeShong, P.; Clark, C. G. *J. Am. Chem. Soc.* **2000**, *122*, 7600.

(12) Kang, S. K.; Lee, S. H.; Lee, D. *Synlett* **2000**, 1022.

(13) Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Averill, K. M.; Chan, D. M. T.; Combs, A. *Synlett* **2000**, 674.

(14) Kiyomori, A.; Marcoux, J. F.; Buchwald, S. L. *Tetrahedron Lett.* **1999**, *40*, 2657.

(15) (a) Kwong, F. Y.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 581. (b) Kwong, F. Y.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 793. (c) Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421. (d) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727. (e) Antilla, J. C.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 11684. (f) Klapars, A.; Parris, S.; Anderson, K. W.; Buchwald, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 3529. (g) Antilla, J. C.; Baskin, J. M.; Barder, T. E.; Buchwald, S. L. *J. Org. Chem.* **2004**, *69*, 5578. (h) Shafir, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 8742.

(16) (a) Cristau, H. J.; Cellier, P. P.; Spindler, J. F.; Taillefer, M. *Chem.-Eur. J.* **2004**, *10*, 5607. (b) Zhang, H.; Cai, Q.; Ma, D. *J. Org. Chem.* **2005**, *70*, 5164. (c) Ma, D.; Cai, Q. *Synlett* **2004**, 128. (d) Alcalde, E.; Dinarès, I.; Rodríguez, S.; Garcia de Miguel, C. *Eur. J. Org. Chem.* **2005**, 1637. (e) Kuil, M.; Bekedam, L.; Visser, G. M.; van den Hoogenband, A.; Terpstra, J. W.; Kamer, P. C. J.; Kamer, van Leeuwen, P. W. N. M.; van Strijdonck, G. P. F. *Tetrahedron Lett.* **2005**, *46*, 2405. (f) Liu, L.; Frohn, M.; Xi, N.; Donminguez, C.; Hungate, R.; Reider, P. J. *J. Org. Chem.* **2005**, *70*, 10135. (g) Jerphagnon, T.; van Klink, G. P. M.; de Vries, J. G.; van Koten, G. *Org. Lett.* **2005**, *7*, 5241. (h) Xu, L.; Zhu, D.; Wang, R.; Wan, B. *Tetrahedron* **2005**, *61*, 6553. (i) Zhang, Z.; Mao, J.; Zhu, D.; Wu, F.; Chen, H.; Wan, B. *Tetrahedron* **2006**, *62*, 4435. (j) Hosseinzadeh, R.; Tajbakhsh, M.; Alikarami, M. *Tetrahedron Lett.* **2006**, *47*, 5203. (k) Kantam, M. L.; Venkanna, G. T.; Sridhar, C.; Kumar, K. B. *Tetrahedron Lett.* **2006**, *47*, 3897. (l) Xie, Y., X.; Pi, S. F.; Yin, D. L.; Li, J. H. *J. Org. Chem.* **2006**, *71*, 8324. (m) Lv, X.; Bao, W. *J. Org. Chem.* **2007**, *72*, 3863. (n) Zhu, L.; Cheng, L.; Zhang, Y.; Xie, R.; You, J. *J. Org. Chem.* **2007**, *72*, 2737.

(17) Altman, R. A.; Buchwald, S. L. *Org. Lett.* **2006**, *8*, 2779.

(18) Mann, G.; Hartwig, J. F.; Driver, M. S.; Fernandez-Rivas, C. *J. Am. Chem. Soc.* **1998**, *120*, 827.

(19) Ikawa, T.; Barder, T. E.; Biscoe, M. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 13001.

(20) Barder, T. E.; Bucwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 120039

(21) **L1c** is available from Aldrich, or can been prepared on large scale in a four-step procedure. For details of the synthesis, see Ref. 15.

(22) Schilt, A. A.; Smith, G. F. *J. Phys. Chem.* **1956**, *60*, 1546.

(23) (a) Ouali, A.; Spindler, J. F.; Jutand, A.; Taillefer, M. *Adv. Synth. Catal.* **2007**, *349*, 1906. (b) Similarly, $(\mathbf{L1a})_3Fe(PF_6)_2$ has a higher oxidation potential than $(\mathbf{L1c})_3Fe(PF_6)_2$ (0.69 V and 0.38 V *vs.* SCE, respectively). Lewis, M.; Lüning, U.; Müller, M.; Schmittel, M.; Wöhrle, C. *Zeitschrift für Naturforschung: B Chemical Sciences* **1994**, *49*, 675.

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

(25) 18-Crown-6 has been used to accelerate the coupling of diarylamines with aryl iodides using Cu (stoichiometric)/K_2CO_3/*o*-dichlorobenzene/reflux: Gauthier, S.; Fréchet, J. M. J. *Synthesis* **1987**, 383.

(26) Recent examples of the use of PEG as a solvent in transition metal-catalyzed processes include: (a) Nobre, S. M.; Wolke, S. I.; da Rosa, R. G.; Monteiro, A. L. *Tetrahedron Lett.* **2004**, *45*, 6527. (b) Reed, N. N.; Dickerson, T. J.; Boldt, G. E.; Janda, K. D. *J. Org Chem.* **2005**, *70*, 1728. (c) Svennebring, A.; Garg, N.; Nilsson, P.; Hallberg, A.; Larhed, M. *J. Org. Chem.* **2005**, *70*, 4720. (d) Liu, L.; Zhang, Y.; Wang, Y. *J. Org. Chem.* **2005**, *70*, 6122. (e) Wang, L.; Zhang, Y.; Liu, L.; Wang, Y. *J. Org. Chem.* **2006**, *71*, 1284.

(27) This phenomenon is likely similar to the recently reported use of the more soluble carbonate base, TEAC, in which the amount of the base in solution increases due to the enhanced "greasiness" of the cation.[16f]

(28) Increased rates involving acetonitrile and propionitrile may be partially due to the elevation of the boiling points of these solvents.

(29) The addition of small quantities of water to accelerate solid/liquid phase-transfer catalysis processes is well documented. See: (a) Albanese, D.; Landini, D.; Maia, A.; Penso, M. *Ind. Eng. Chem. Res.* **2001**, *40*, 2396. (b) Yadav, G. D.; Jadhav, Y. B. *Langmuir*, **2002**, *18*, 5595.

(30) (a) Gujadhur, R. K.; Bates, C. G.; Venkataraman, D. *Org. Lett.* **2001**, *3*, 4315. (b) Wolter, M.; Nordmann, G.; Job, G. E.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 973. (c) Nordmann, G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 4978.

(31) (a) Son, S. U.; Park, I. K.; Park, J.; Hyeon, T. Chem. Comm. **2004**, 7, 778. (b) Choudary, B. M.; Sridhar, C.; Kantam, M. L.; Venkanna, G. T.; Sreedhar, B. *J. Am. Chem. Soc.* **2005**, *127*, 9948. (c) Xie, Y. X.; Pi, S. F.; Wang, J.; Yin, D, L., Li, J. H. *J. Org. Chem.* **2006**, 71

(32) The increased selectivity for the preferential formation of the 4-substituted *N*-aryl imidazole over the 5-regioisomer, due to increased steric effects has also been observed in the Cu-catalyzed coupling of 4(5)-substituted imidazoles with aryl boronic acids. See: Collman, J. P.; Zhong, M.; Zhang, C.; Costanzo, S. *J. Org. Chem.* **2001**, *66*, 7892.

(33) Representative examples: (a) Maekawa, T.; Sakai, N.; Tawada, H.; Murase, K.; Hazama, M.; Sugiyama, Y.; Momose, Y. *Chem. Pharm Bull.* **2003**, *51*, 565. (b) Hoffmann-La Roche Inc. Heteroaryl-substituted Imidazole Derivatives. U.S. Patent 20,040,254,179. December 16, 2004. (c) Smithkline Beecham Corporation. Thiophene Compounds. WO 2004/014899 A1. February 19, 2004. (d) Chen, P.; Doweyko, A. M.; Norris, D.; Gu, H. H.; Spergel, S. H.; Das, J.; Moquin,

R. V.; Lin, J.; Wityak, J.; Iwanowicz, E. J.; McIntyre, K. W.; Shuster, D. J.; Behnia, K.; Chong, S.; de Fex, H.; Pang, S.; Pitt, S.; Shen, D. R.; Thrall, S.; Stanley, P.; Kocy, O. R.; Witmer, M. R.; Kanner, S. B.; Schieven, G. L.; Barrish, J. C. *J. Med. Chem.* **2004**, *47*, 4517.

(34) The Cu-catalyzed *N*-arylation of indole under mild conditions has been previously reported by our group.[15e]

(35) 2-Aminothiophenes are unstable to air oxidation, and decompose readily upon exposure to air. See Lu, Z.; Twieg, R. J. *Tetrahedron* **2005**, *61*, 903.

(36) Significant quantities of reducted arene has been observed in the Cu-catalyzed amination of heteroaryl halides. See Arterburn, J. B.; Pannala, M.; Gonzalez, A. M. *Tetrahedron Lett.* **2001**, *42*, 1475.

(37) Narisada, M.; Horibe, I. Watanabe, W.; Takeda, K. *J. Org. Chem.* **1989**, *54*, 5308.

(38) de Marquez, O. P.; Giulianelli, J. *J. Org. Chem.* **1976**, *41*, 739.

(39) Grimshaw, J.; Trocha-Grimshaw, J. *J. Chem. Soc. Perkin II* **1975**, 215.

(40) Andrieux, C. P.; Blocman, C.; Dumas-Bouchiat, J. M.; Savéant, J. M. *J. Am. Chem. Soc.* **1979**, *101*, 3431.

(41) M'Halla, F.; Pinson, J.; Savéant J. M. *J. Am. Chem. Soc.* **1980**, *102*, 4120.

(42) MTBD has been previously used as a soluble base for the Pd-catalyzed amination of aryl nonaflates using microwave irradiation. Tundel, R. E.; Anderson, K. W.; Buchwald, S. L. *J. Org. Chem.* **2006**, *71*, 430.

(43) The coupling of 2-methylimidazole with 4-iodoanisole proceeds to 65% conversion in 48 h (10% $(CuOTf)_2$•PhH/10% dba/100% **L1a**/xylenes/125 °C/48 h).[14] The coupling of 2-methylimidazole with 5-bromo-*m*-xylene (10% CuI, 10% **L6**/TEAC/10 : 1 DMF : H_2O/ 130 °C, 16 h) yields 64 percent of *N*-aryl imidazole.[16f]

(44) 4,7-diethoxy-1,10-phenanthroline was also found to be more effective than **L1d**, but less effective than **L1c** for this transformation.

(45) Åkermark, B.; Frisell, H. *Organometallics* **1995**, *14*, 561.

(46) Venkataraman, D.; Gujadhur, R. K.; Bates, C. G. *Org. Lett.* **2001**, *3*, 435.

(47) The synthesis of **L1b**, **L1c** and **L1e** was preformed according to a combination of the following procedures. (a) Graf, I. G.; Jastreiter, D.; da Silva, L. E.; Rebelo, R. A.; Montalban, A. G.; McKillop, A. *Tetrahedron* **2002**, *58*, 9095. (b) Schmittel, M.; Ammon, H. *Eur. J. Org. Chem.* **1998**, 785. (c) Snyder, H. R.; Freier, H. E. *J. Am. Chem. Soc.* **1946**, *68*, 1320. d) Wehman, P.; Kaasjager, de Lange, W. G.; Jartl, F.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Organometallics* **1995**, *14*, 3751. (e) Zacharias, D. E.; Case, F. H. *J. Am. Chem. Soc.* **1962**, *27*, 3878.

(48) Molock, F. F. *J. Heterocyclic Chemistry* **1983**, *20*, 681.

(49) Kauffmann, T.; Tigler, D.; Woltermann, A. *Tetrahedron Lett.* **1977**, *17*, 741.

(50) Collman, J. P.; Zhong, M.; Zeng, L.; Constanzo, S. *J. Org. Chem.* **2001**, *66*, 1528.

(51) Begg, et al. *Aus. J. Chem.* **1973**, *26*, 2435.

(52) Sezen, B.; Sames, D. *J. Am. Chem. Soc.* **2003**, *125*, 5274.

(53) Wang, L.; Chen, Z. C. *J. Chem. Res. Synop.* **2000**, *8*, 367.

(54) Khan, M. A.; Polya J. B. *J. Chem. Soc. C* **1970**, 85.

(55) Artico, M.; Silvestri, R.; Stefancich, G.; Avigliano, L.; Di Giulio, A. *Eur. J. Med. Chem. Chim. Ther.* **1992**, *27*, 219.

(56) Wang, L.; Chen, Z. C. *J. Chem. Res. Synop.* **2000**, *8*, 367.

(57) Du Pont de Nemours, E. I., and Co. "1-Substituted Imidazoles Useful in ACTH [Adrenocorticotrophin] Reserve Assay." US 3541109. 1970.

(58) Du Pont de Nemours, E. I., and Co. "1-(Alkyl-Substituted Phenyl)Imidazoles Useful in ACTH Reserve Assay." US 3637731. 1972.

(59) Perry, M. C.; Cui, X.; Powell, M. T.; Hou, D. R.; Reibenspies, J. H.; Burgess, K. *J. Am. Chem. Soc.* **2003**, *125*, 113.

(60) Liu, J.; Chen, J.; Zhao, J.; Zhao, Y.; Li, L.; Zhang, H. *Synthesis* **2003**, 2661.

(61) Kiyomori, A.; Marcoux, J. F.; Buchwald, S. L. *Tetrahedron Lett.* **1999**, *40*, 2657.

(62) Tashiro, M.; Itoh, T.; Fukata, G. Synthesis **1982**, 217.

(63) Paul, R.; Hallett, W. A.; Hanifin, J. W.; Reich, M. F.; Johnson, B. D. *J. Med. Chem.* **1993**, *36*, 2716.

(64) Sezen, B.; Sames, D. *J. Am. Chem. Soc.* **2003**, *125*, 10580.

(65) Collman, J. P.; Zhong, M.; Zeng, L.; Costanzo, S. *J. Org. Chem.* **2001**, *66*, 1528.

(66) Liu, J.; Chen, J.; Zhao, J.; Zhao, Y.; Li, L.; Zhang, H. *Synthesis* **2003**, 2661.

(67) Pozharskii et al. *Chem. Heterocycl. Compd.* **1970**, *6*, 194.

(68) Collman, J. P.; Zhong, M. *Org. Lett.* **2000**, *2*, 1233.

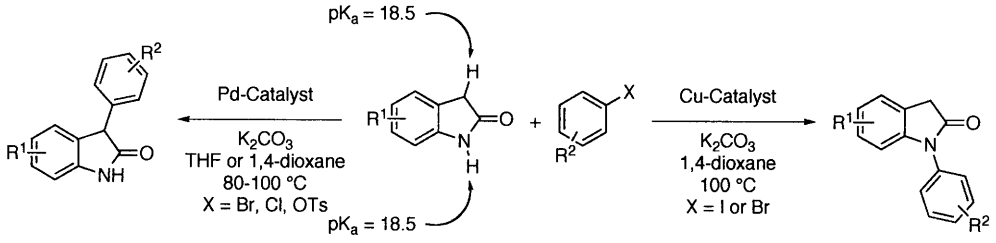
(69) Zhao, Z., Peng, Y., Dalley, N. K.; Cannon, J. F.; Peterson, M. A. *Tetrahedron Lett.* **2004**, 45, 3621.

(70) Palmer, B. D.; Smaill, J. B.; Boyd, M.; Boschelli, D. H.; Doherty, A. M.; Hamby, J. M.; Khatana, S. S.; Kramer, J. B.; Kraker, A. J.; Panek, R. L.; Lu, G. H.; Dahring, T. K.; Winters, R. T.; Showalter, H. D. H.; Denny, W. A. *J. Med. Chem.* **1998**, *41*, 5457.

(71) Zhang, Z., Mao, J., Zhu, D., Wu, F., Chen, H., Wan, B. *Tetrahedron* **2006**, *62*, 4435.

Chapter Two

Orthogonal Selectivity in Palladium- and Copper-catalyzed Reactions of Aryl Halides with Oxindoles

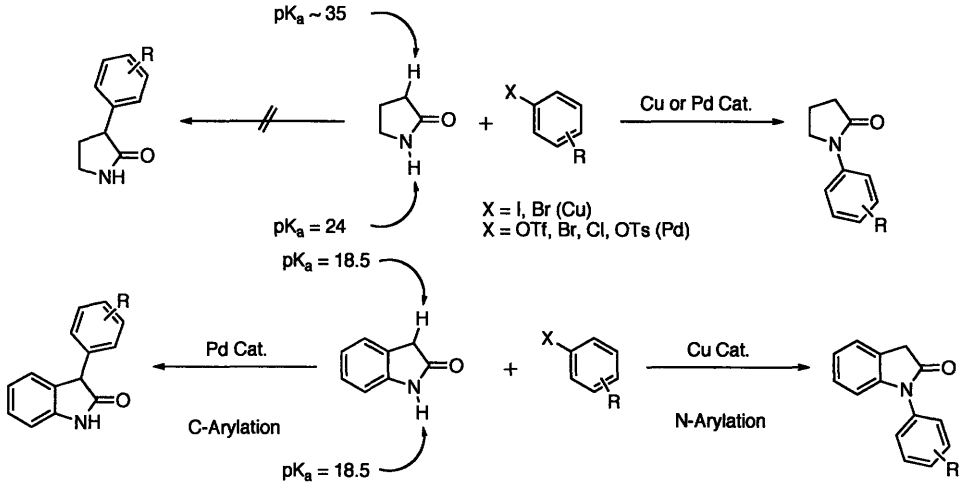


2.1 Introduction

In recent years, Pd-[1] and Cu-[2] catalyzed nucleophilic substitution reactions of aryl halides have been areas of intensive research. Our laboratory has been intimately involved in designing and developing highly-efficient and user-friendly Pd- and Cu-based catalyst systems to cross-couple aryl halides with a wide variety of nucleophiles, including amides[3-4] and ketone enolate derivatives.[5-6]

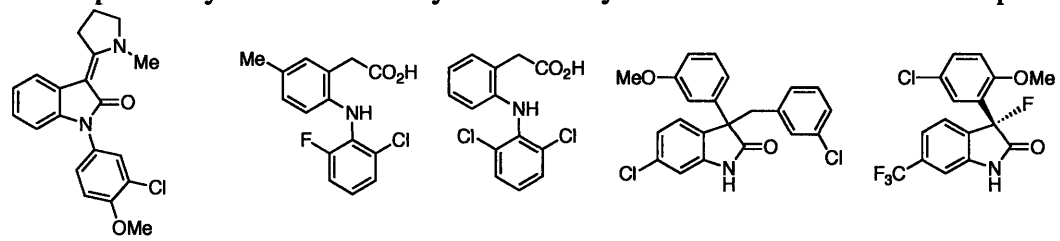
Generally, the Cu- and Pd-catalyzed arylation reactions of both linear and cyclic aliphatic amides react at the more acidic N–H moiety as opposed to the less acidic C–H_α position. For instance, when reacting 2-pyrrolidinone with aryl halides, both Cu-diamine- and Pd-biarylmonophosphine-based catalyst systems provide the *N*-aryl amide in excellent yield (Scheme 1).[3-4] Ongoing work in our and other laboratories[7] has identified oxindole as a unique substrate for chemoselective metal-catalyzed cross-coupling reactions with aryl halides. Due to the identical acidities of the protons in positions C3 and N1 (pK_a = 18.5),[8] the cross-coupling reactions of oxindole with aryl halides might provide either the *C*-aryl or *N*-aryl products.

Scheme 1. Pd- and Cu-Catalyzed C- and N-Arylation of 2-Pyrrolidinone and Oxindole



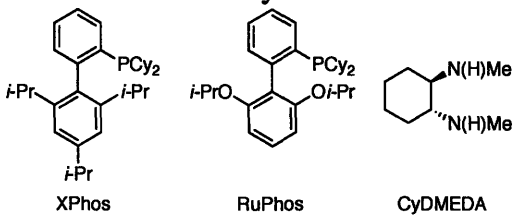
Importantly, *N1*-aryl and *C3*-aryl oxindole products of the type generated from the reactions described in this manuscript display interesting biological activities with therapeutic applications (Figure 1).[9] In addition, the amide of the *N*-aryl oxindole can be cleaved to provide access to a variety of derivatives of 2-(2-phenylamino)-phenyl)ethanoic acid non-steroidal anti-inflammatory agents, such as Lumiracoxib[10] and diclofenac.[11]

Figure 1. Therapeutically Relevant *C3*-Aryl and *N1*-Aryl Oxindoles and Related Compounds



Herein, we describe improved reaction conditions for the Cu-catalyzed N1-arylation reaction with aryl iodides and bromides, and general reaction conditions for the Pd-catalyzed C3-arylation reaction of unprotected oxindoles with aryl chlorides and tosylates. Further, we report computational studies that suggest reasonable explanations for the observed selectivity.

Figure 2. Ligands Employed for the Metal-Catalyzed C3- and N1-Arylation of Oxindole



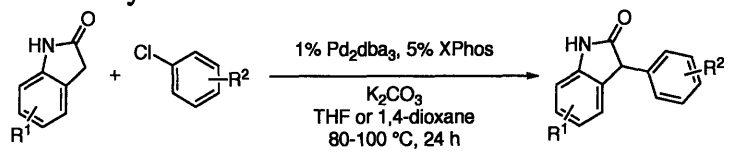
2.2 Results and Discussion

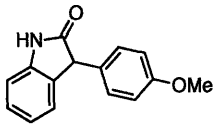
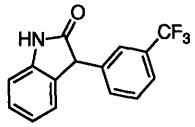
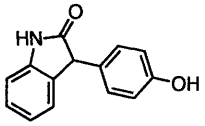
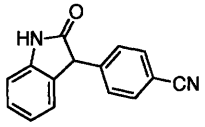
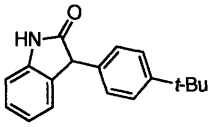
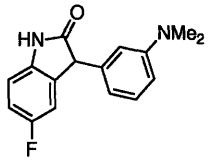
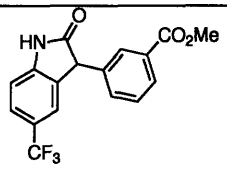
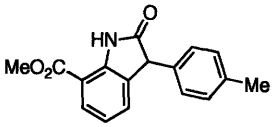
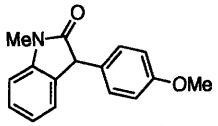
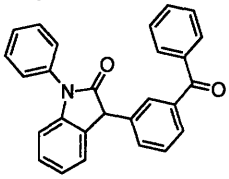
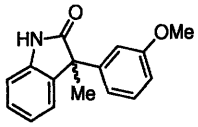
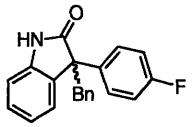
2.2.1 Palladium-Catalyzed C3-Arylation of Oxindole

The use of 1% $Pd_2(dba)_3$ and 5% XPhos (Figure 2) was found to facilitate the cross-coupling of aryl chlorides with oxindoles unsubstituted at C3 using K_2CO_3 as the base in THF or 1,4-dioxane at temperatures ranging between 80 and 100 °C (Table 1). The use of bidentate or other dialkylbiarylmonophosphine ligands provided low conversion of starting material and yield of products. The Pd-catalyzed C3-arylation reaction of oxindoles with aryl chlorides tolerated a variety of functional groups on the *meta*- and *para*-positions of the electrophile (entries 1-10); however, *ortho*-substituted aryl chlorides provided low conversion of reactants (> 5%) even at slightly elevated temperatures (up to 120 °C) with a variety of biarylmonophosphine ligands. Under the standard reaction conditions, the use of 3-chlorobenzonitrile provided low yields of coupled product due to partial hydrolysis of the nitrile functional group to an amide (entry 4). This side reaction could be partially impeded by the addition of activated 4 Å molecular sieves to the reaction vessel. Using *t*-BuOH as a solvent, an unactivated aryl benzenesulfonate could be successfully cross-coupled to provide the *C*-aryl product in modest yield (entry 5). Substrates possessing substituents on the benzannulated backbone as well as on the nitrogen atom provided more highly substituted products (entries 6-10). Using XPhos as a ligand, the reaction of a 3-substituted oxindole was unsuccessful;[7b] however, using re-optimized reaction conditions (RuPhos/NaO*t*-Bu/toluene), the cross-coupling reactions of 3-methyl- and 3-benzyl-oxindole were successfully accomplished to generate quaternary stereocenters at the C3 positions to produce racemic products (entries 11-12). In contrast to the previously reported catalyst systems for the C3-vinylation of unprotected oxindoles and –arylation of protected oxindoles, which

required strong bases such as KHMDS and LHMDS, respectively, for the reactions to proceed,[7b-c] K_2CO_3 and NaO*t*-Bu were found to be suitable bases with our catalyst system.

Table 1. Pd-Catalyzed C3-Arylation of Oxindoles[a]



entry	product	solvent	temp. (°C)	% yield
1		THF	80	92
2		1,4-dioxane	100	81
3		1,4-dioxane	100	89[b]
4		THF	80	55[c]
5		*t*-BuOH	110	67[d]
6		1,4-dioxane	100	80
7		THF	80	77
8		THF	80	63
9		THF	80	82
10		1,4-dioxane	80	94[e]
11		toluene	100	90[f]
12		toluene	100	90[g]

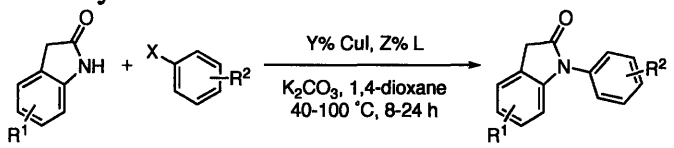
[a] Reactions Conditions: 1.0-1.2 mmol oxindole, 1.2-1.0 mmol ArCl, 2.0 mmol K_2CO_3, 0.010 mmol Pd_2dba_3, 0.050 mmol XPhos, 1.0 mL solvent, in a sealed tube under an Ar atmosphere. Yields reported are an average of at least two runs determined to be > 95% pure by elemental analysis or ^1H NMR. [b] 3.0 mmol K_2CO_3. [c] 4 Å mol Sieves. [d] From $ArOSO_2Ph$. [e] K_3PO_4 used as base. [f] From ArBr. RuPhos and NaO*t*-Bu employed as ligand and base. 9 h reaction time. [g] From ArBr. RuPhos and NaO*t*-Bu employed as ligand and base. 20 h reaction time.

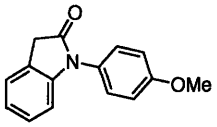
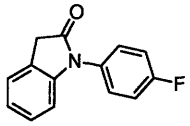
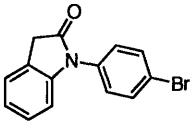
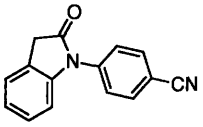
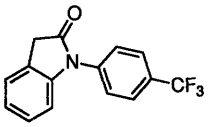
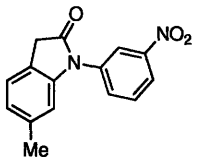
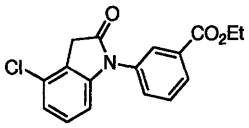
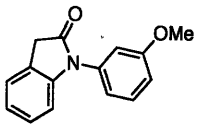
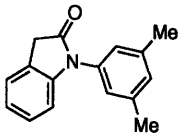
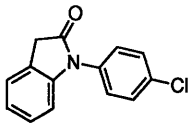
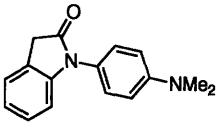
2.2.2 Copper-Catalyzed N1-Arylation of Oxindole

The Cu-catalyzed N-arylation reactions of *meta*- and *para*-substituted aryl iodides generally proceeded smoothly at temperatures ranging from 80 to 100 °C using 1-5% catalyst loading, 4-10% CyDMEDA (Figure 2) as the ligand, K_2CO_3 as the base, and 1,4-dioxane as the solvent (Table 2, entries 1-8). In these reactions, the *C3*-aryl product was not detected by GCMS analysis of the crude reaction mixtures. Using this catalyst system, *ortho*-substituted aryl iodides were unreactive, even at temperatures up to 150 °C in high boiling-point solvents. This serves to reinforce the notion that *ortho*-substituted aryl halides can be quite difficult to activate in Cu-catalyzed C-heteroatom bond-forming reactions. At 60-100 °C, the cross-coupling reaction of 1-bromo-4-iodobenzene with oxindole provided a complex mixture of products; however, by lowering the reaction temperature to 40 °C, the iodo-substituted product could be isolated in acceptable yield (entry 3). The addition of activated 4 Å molecular sieves to the reaction mixtures was necessary for substrates containing hydroxide- or water-sensitive functional groups (entries 4 and 7). As anticipated, substituents on the nucleophile were also tolerated (entries 6-7).

Aryl bromides also proved to be reactive in the Cu-catalyzed cross-coupling reactions with oxindoles (entries 8-11), though higher catalyst loadings were necessary to ensure full conversion of the substrates within a 24 h time period. Although the *C3*-aryl oxindole product was not observed, up to 5% of the N1,C3-*bis*-arylated product (10% of aryl halide consumption) was isolated in the reaction of 5-bromo-*m*-xylene (entry 9). A second common side product, when using aryl bromides, was the reduced arene.

Table 2. Cu-Catalyzed N1-Arylation of Oxindoles[a]



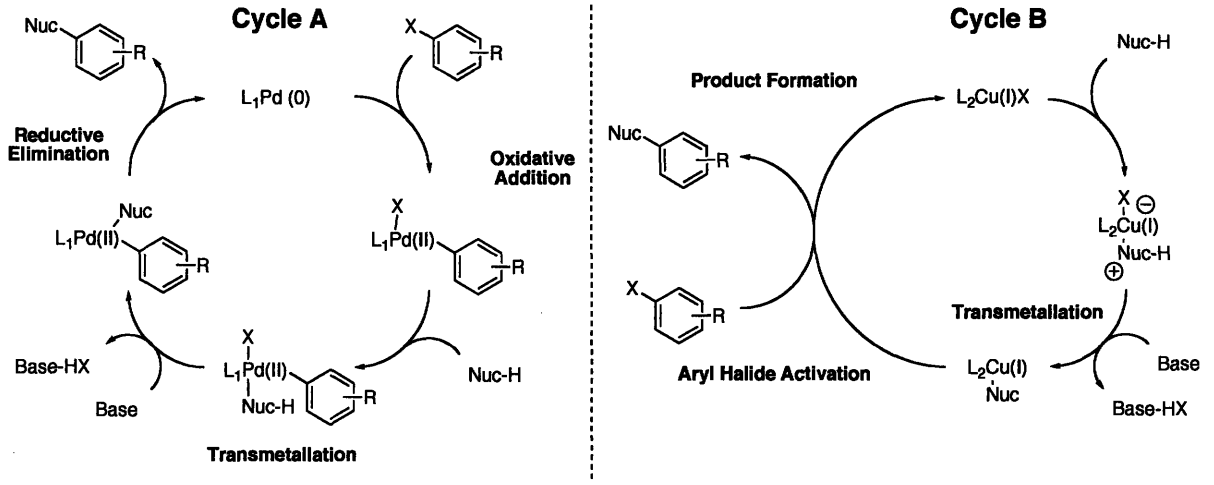
entry	product	Y	X	Z	temp. (°C)	% yield
1		5	I	10	100	86
2		1	I	4	100	94
3		5	I	10	40	61
4		5	I	10	80	72[b]
5		1	I	4	80	85
6		5	I	10	80	69
7		5	I	10	80	87[b]
8		10	Br	20	100	62
9		10	Br	20	100	71
10		10	Br	20	100	77
11		10	Br	20	100	72

[a] Reactions Conditions: 1.0-1.2 mmol oxindole, 1.2-1.0 mmol ArI, 2.0 mmol K_2CO_3, 1.0 mL 1,4-dioxane, in a sealed tube under an Ar atmosphere. Yields reported are an average of at least two runs determined to be > 95% pure by elemental analysis or ^{1}H NMR. [b] 4 Å mol Sieves.

2.2.3 Computational Studies of Palladium- and Copper-Catalyzed Reactions

The catalytic cycle of Pd-catalyzed nucleophilic substitution reactions of aryl halides involve three steps: 1) oxidative-addition; 2) transmetallation; 3) reductive-elimination (Scheme 2, Cycle A).[1]

Scheme 2. Mechanisms of Pd- and Cu-Catalyzed Nucleophilic Substitution Reactions of Aryl Halides

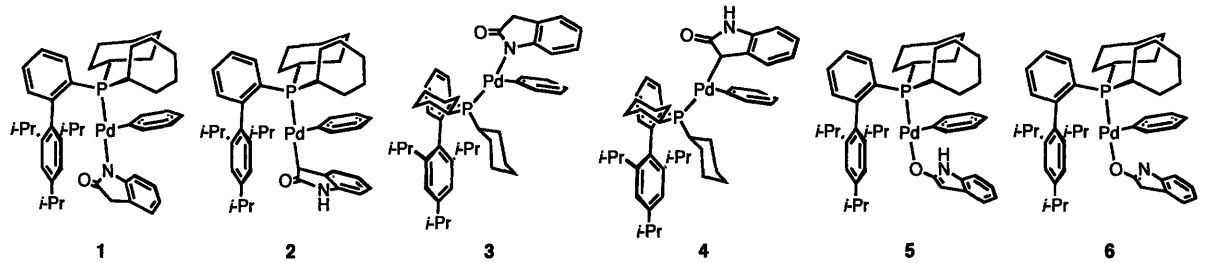


Since oxindole does not participate in the oxidative addition step of the cycle, the selectivity-controlling feature for the Pd-based catalyst system must involve either the transmetallation or reductive-elimination steps. To gain further insight into the observed selectivity, the relative energies and structures of various L_1Pd(Ph)(oxindolate) complexes were calculated by DFT methods.

In light of the experimental findings that catalysts derived from XPhos were the only ones that produced high yields of the C3-arylation of oxindole product, it was critical to model structures that contained the entire ligand without any approximations. The geometry of the XPhos·Pd(Ph)(oxindolate) complex formed following transmetallation was minimized with the Pd bound to either the nitrogen or α-carbon of the oxindole (Figure 3). This minimization was performed with structures in which the Pd points towards or away from the lower biaryl ring. Consistent with previous computational studies from our group,[12] three-coordinate Pd(II)/dialkylbiarylmonophosphine intermediates prefer the orientation shown in structures **1** and **2** with the Pd sitting above the lower biaryl ring. In both cases, the C-bound oxindolate was

significantly higher in energy than the N-bound complex. This energy difference was 4.8 kcal/mol between **1** and **2** and 7.0 kcal/mol between **3** and **4**.

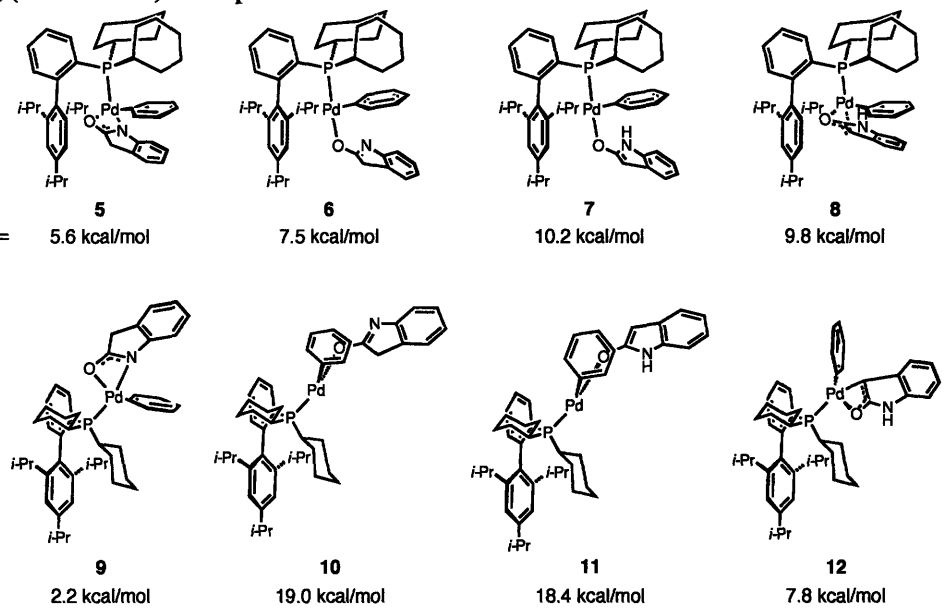
Figure 3. Calculated Geometries and Energies of XPhos·Pd(Ph)(oxindolate) Complexes with B3LYP[a]



[a] Calculated at 298 K in THF.

We then determined the energies of the κ^2-amidate (**5**,**9**), O-bound amidate and enolate (**6**-**7**, **10**-**11**), and η^3-oxyallyl (**8**,**12**) structures as, they may be intermediates in the N to C isomerization process (Figure 4). As expected, the three-coordinate O-bound enolate and amidate structures are lower in energy when the Pd is pointing towards the lower ring. However, the four-coordinate κ^2-amidate and η^3-oxyallyl bound structures are lower in energy when the Pd is distal to the lower ring.

Figure 4. Calculated Geometries and Energies of the κ^2- O- and η^3-oxyallyl-bound XPhos·Pd(Ph)(oxindolate) Complexes with B3LYP.[a,b]



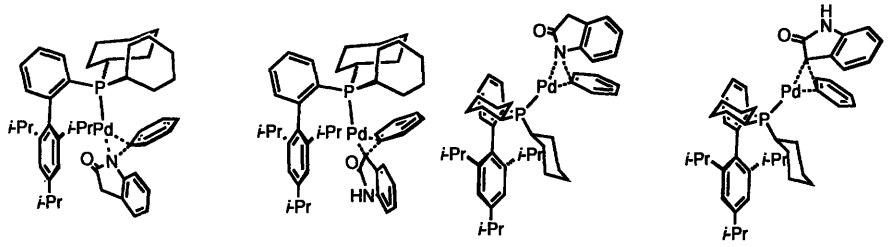
[a] Calculated at 298 K in THF. [b] ΔE_{rel} values are relative to complex **1** in Figure 3.

If the N-bound and C-bound structures exist in rapid equilibrium, then the barriers for reductive elimination should be product determining. Thus, transition states for both C–C and C–N reductive elimination processes were calculated. The mechanism for reductive elimination from Pd-bound enolates has not been well studied, and could occur by different mechanisms involving O-bound, C-bound, or η^3-oxyallyl Pd intermediates. Hartwig and Culkin[13] have put forth circumstantial evidence in support of a simple reductive-elimination between an η^1-bound enolate and the arene. However, these studies were primarily performed using bidentate ligands, which may prevent η^3-bound intermediates and relevant transition states. Several reports have appeared, which indicate η^3-oxyallyl Pd intermediates may be involved in some Pd-enolate based processes.[14]

Reasonable starting geometries for the transition states of enolate C–C reductive elimination were arrived at by examining calculations reported by others for methyl-methyl

reductive elimination from Pd.[15] A prior publication by our group on the mechanism of aryl amination provided us with reasonable starting geometries for amidate C–N reductive-elimination.[12] We were then able to quickly find transition states for both C–C and C–N reductive elimination towards and away from the lower biaryl ring (Figure 5). The $\Delta E^{\ddagger}$ for **1→1-TS** was calculated to be 21.7 kcal/mol while the $\Delta E^{\ddagger}$ for **2→2-TS** was significantly less at 14.5 kcal/mol. For the structures with the Pd swung away, the $\Delta E^{\ddagger}$ of **3→3-TS** was calculated to be 20.9 kcal/mol and the $\Delta E^{\ddagger}$ of **4→4-TS** was 12.6 kcal/mol. Although these barriers are lower than when the Pd is pointed towards the lower biaryl ring, their absolute energies are much higher. Therefore, it is unlikely that **3-TS** and **4-TS** contribute to the reaction course. We also attempted to find a transition state for C–C reductive elimination, which proceeds through an η^3 pathway, but one could not be located.

Figure 5. Calculated Reductive-Elimination Transition States for XPhos·Pd(Ph)(oxindolate) with B3LYP[a,b]

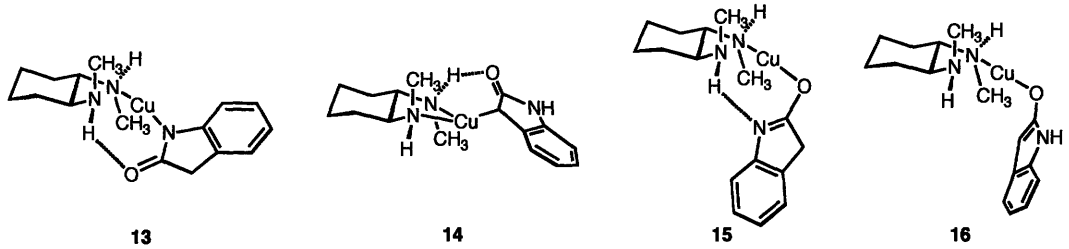


[a] Calculated at 298 K in THF. [b] ΔE_{rel} values are relative to complex **1** in Figure 3.

Cu-catalyzed amidation reactions of aryl halides initiate by addition of the nucleophile to a $L_2Cu(I)X$ complex to provide an $L_2Cu(I)$amidate, followed by aryl halide activation and subsequent product formation (Scheme 2, Cycle B).[16-17] Although the Guo group has recently published a computational study that calculates the transition states and intermediates of the

catalytic cycle for the Goldberg reaction,[18] this study only considered a mechanism based on an insertion reaction between an $L_2Cu(I)$(amidate) and an aryl halide to generate an $L_2Cu(III)$ (Ar)(X)(amidate) species, and neglects to evaluate evidence that an electron-transfer mechanism might be occurring, as suggested by Hida.[19] Therefore, we will assume that the mechanism of the rate-limiting aryl halide activation step is yet to be fully elucidated. According to this paradigm, reaction of a molecule of oxindole with the CyDMEDA-CuI complex and base may provide multiple regioisomeric products, which could react with aryl halides to provide the *N*-aryl and *C3*-aryl products, respectively. In order to gain insight into the features that control the selectivity of the reaction, the energies of relevant CyDMEDA·Cu(I)(oxindolate) complexes were examined (Figure 6).

Figure 6. Calculated Geometries and Energies of CyDMEDA·Cu(Oxindolate) Complexes with B3LYP[a]



	13	14	15	16
ΔE_{rel} =	0 kcal/mol	14.1 kcal/mol	9.7 kcal/mol	19.6 kcal/mol

[a] Calculated at 298 K.

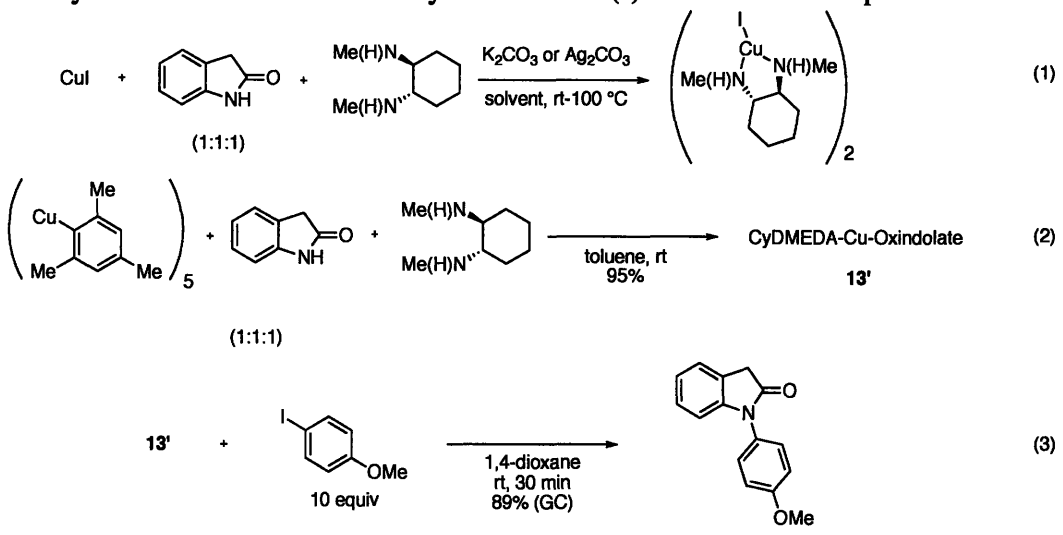
As observed with the Pd-based catalyst system, the N-bound (CyDMEDA)·Cu(oxindolate) **13** was found to be significantly lower in energy than both C3-bound and O-bound structures. In this structure, the geometry around Cu is a distorted T-shape, consistent with known neutral tricoordinate Cu(I) structures.[20] Interestingly, the calculation predicts a hydrogen-bonding interaction between the carbonyl and one hydrogen of the amine (O–H distance of 1.9 Å). The C3-bound oxindolate **14** is significantly higher in energy by 14.1

kcal/mol. It is noteworthy that the geometry about Cu is no longer planar but trigonal pyramidal and equidistant to both nitrogen atoms. There also appears to be a hydrogen bond between the carbonyl oxygen and amine hydrogen (O–H distance of 2.0 Å). The O-bound amidate **15** and enolate **16** are 9.3 kcal/mol and 19.2 kcal/mol higher in energy respectively than the N-bound structure. We also optimized κ^2-amidate and η^3-oxyallyl bound structures but no reasonable stationary points could be found.

2.2.4 Synthesis and Isolation of Diamine-Cu(I)-Oxindolate Complex

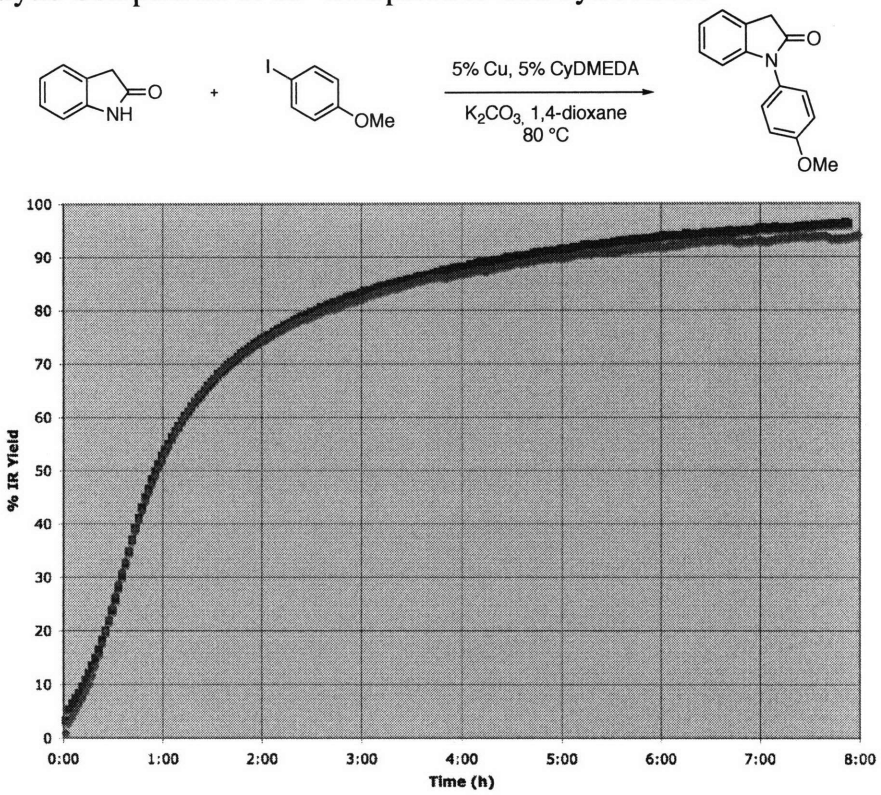
Although ligated-Cu(I)-amidate complexes relevant to the Goldberg reaction have been generated and studied *in situ*, these species have not been isolated and characterized.[17,21] Our initial attempt to prepare the computationally predicted CyDMEDA-Cu-oxindolate complex (**7**) involved reacting CuI with stoichiometric quantities of CyDMEDA, oxindole and K_2CO_3 (eq. 1). Under these conditions, transmetallation did not occur, and a diamine-CuI dimer was formed.[22] Even with the use of Ag_2CO_3 as a base to facilitate the removal of the halogen atom from copper, **13'** was not observed. Complex **13'** was successfully prepared by mixing equimolar quantities of $(Cu\text{-mesityl})_5$,[23] oxindole and CyDMEDA in toluene (eq. 2). The ^1H NMR spectrum of this species in both toluene-d_8 shows a two-proton singlet signal at 3.20 ppm corresponding to the C3-protons. No amide N-H peak was detected near 9 ppm. This complex proved to be sensitive to oxygen, changing colors from off-white to blue upon exposure to the air.

Scheme 3. Synthesis and Reactions of CyDMEDA-Cu(I)-Oxindolate Complex **13'**



The reactivity of **13'** was examined to evaluate the competency of this species in amidation reactions of aryl halides. Complex **13'** was reacted with an excess of 4-iodoanisole at room temperature to provide the *N*-aryl oxindole in 89% yield (eq. 3). The catalytic activity of **13'** was compared to the activity of the CuI/CyDMEDA combination generally employed in amidation reactions of aryl halides[3] by monitoring the formation of the *N*-aryl product using *in-situ* IR spectroscopy. A graphical plot of product formation *vs.* time for the cross-coupling reaction of 4-iodoanisole with oxindole in 1,4-dioxane at 80 °C at 5% catalyst loading (1:1, metal:ligand) using **13'** or CuI/CyDMEDA demonstrated that both catalyst precursors were equally efficient at promoting the amidation process (Figure 7).

Figure 7. Catalytic Competence of **13'** Compared to CuI/CyDMEDA[a]

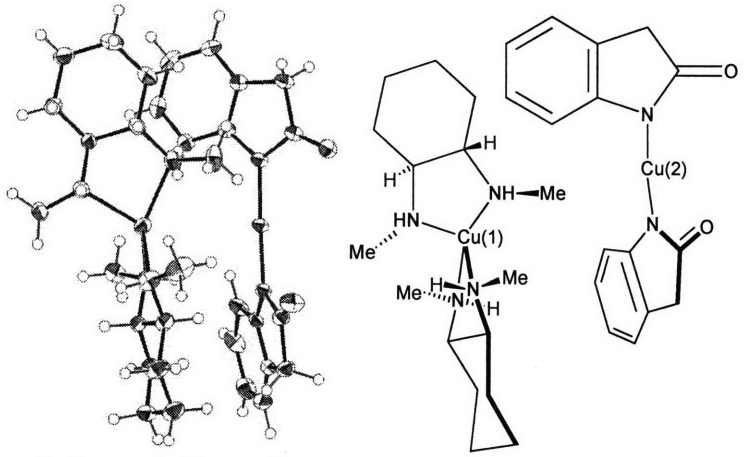


[a] Reaction Conditions: 1.0 mmol Oxindole, 2.0 mmol 4-iodoanisole, 2.0 mmol K_2CO_3, and 1.0 mL 1,4-dioxane, under Ar at 80 °C. (■) 0.050 mmol **13'**. (◆) 0.050 mmol CuI and 0.050 mmol CyDMEDA. Reactions monitored by *in situ* IR spectroscopy. Product observed at 1514 nm^{-1}. Data recorded at 2 min intervals.

Complex **13'** proved difficult to recrystallize, due to the propensity of the complex to disproportionate into Cu(0) and Cu(II) under a variety of standard recrystallization techniques.[24] However, crystals of **13'**, suitable for X-Ray analysis, were obtained by recrystallizing the material from a saturated solution of acetonitrile, layered with pentane at -15 °C in the glovebox. The material obtained in this fashion provided an unexpected dinuclear Cu-complex, with disproportionated ligands (Figure 8). While to CyDMEDA ligands were bound to Cu(1) in a pseudo-tetrahedral arrangement (CyDMEDA bite angle = 85.0 °, average bond length = 2.05 and 2.12 Å), two anionic oxindole ligands were bound to Cu(2) in a nearly linear geometry (bond angle = 176.3 °, average bond length = 1.85 Å). No hydrogen-bonding interactions were present

in the complex. The methyl groups on each diamine ligand were arranged in a trans fashion, presumably to minimize steric interactions.

Figure 8. ORTEP Diagram[a] and Rendition of Crystallized **13'**[a]



[a] *ORTEP Diagram with thermal ellipsoids at 30% probability*

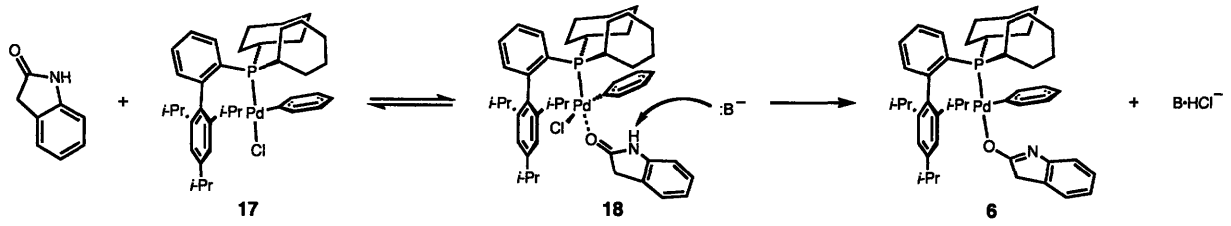
2.2.5 Discussion

In metal-catalyzed amidation reactions of aliphatic amides, such as 2-pyrrolidinone, coordination and deprotonation of the nucleophile during the transmetallation step of the catalytic cycle occur at the more acidic N–H position as opposed to the less acidic C–H_α position (Scheme 1). In the case of oxindole, both the N–H and the C–H_α protons are significantly acidified due to the conjugation of the deprotonated anion with the aromatic ring. Further, the predisposition for the anion to reside on the more electronegative nitrogen atom is overcome by the aromatic stabilization gained from isomerization of the anion to generate an enolate.[8] Thus, a 1:1 ratio of amidate:enolate exists in solution. As such, the difference in reactivity between typical aliphatic amides and oxindole demonstrated by Cu- and Pd-based catalyst systems might not be entirely unexpected.

Since a weak base was employed (K_2CO_3), the large pK_a difference (~5) between

oxindole and the base indicates that appreciable quantities of an anionic amidate species do not exist in solution; thus, an intermolecular ligand exchange between an oxindolate anion and XPhos·Pd(Ar)(Cl) **17** is unlikely. As such, it is likely that the oxindole is further acidified by reversible coordination of Pd(II) intermediate **17** to the oxindole carbonyl to form **18** (Scheme 4). Deprotonation of the acidified oxindole should occur at N as opposed to C3, since deprotonation is kinetically faster from N–H than from C–H bonds, in which rehybridization must occur at the carbon atom.[25] Thus, deprotonation of **18** would initially lead to **6**, followed by an intramolecular migration of Pd from O to either N or C. If intramolecular isomerization is the preferred pathway, then a plausible reaction sequence to form a C-bound Pd enolate that does not involve formation a Pd–N bond may be **17→18→6→7→8→2**. If a Pd–N bond does transiently form, then the reaction pathway might proceed as such, **17→18→6→5→1→5→6→7→8→2**.

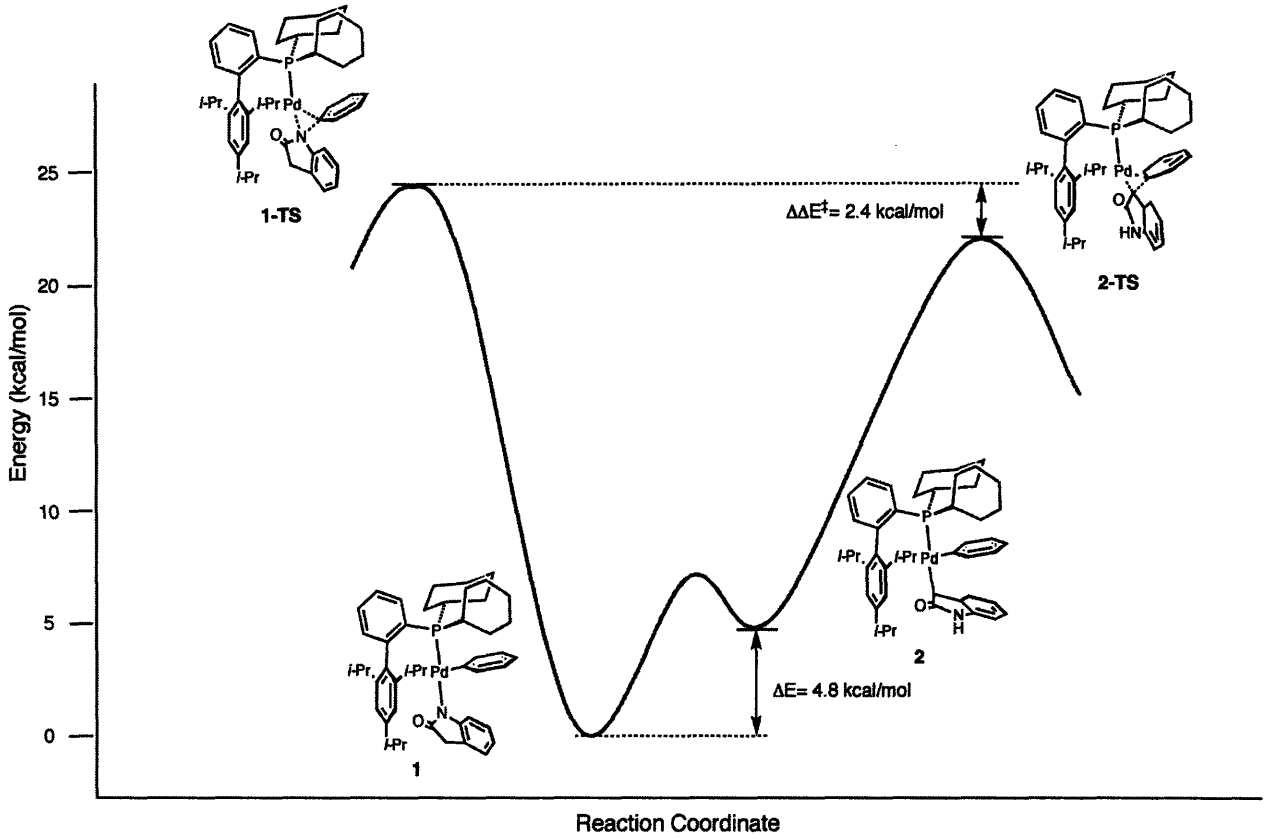
Scheme 4. Transmetallation of oxindole to XPhos·Pd(Ph)(Cl).



For the Pd-catalyzed C-arylation reaction of oxindole with aryl halides, transmetallation of a molecule of oxindole to the $L_1Pd(Ar)(X)$ complex can provide multiple isomeric species. Two of these isomers, namely **1** and **2**, would reductively eliminate to provide the *N*-aryl and *C3*-aryl oxindole products, respectively. The energy profile illustrating the reaction course with the relative energies of the key intermediates and transition states is shown in Figure 9. The *C3*-aryl product, which is exclusively observed in the Pd-catalyzed reaction, must result from a rapid

reductive elimination from the higher-energy Pd-C-bound enolate, **2**, as opposed to the more-stable Pd-N-bound amidate, **1**. Therefore, the selectivity demonstrated by the Pd-catalyzed reaction is kinetically governed according to the Curtin-Hammett principle.[26] The 2.4 kcal/mol difference in energy between **1-TS** and **2-TS** is consistent with the observed selectivity of the catalytic reaction. This difference in energy is likely a reflection of the relative electronegativities of nitrogen and carbon and the overlap of the relevant molecular orbitals with those of Pd.[27]

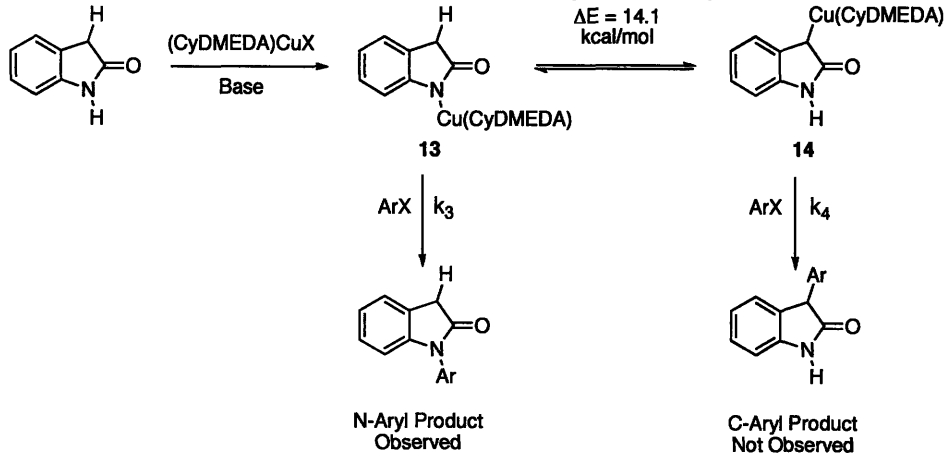
Figure 9. Energy Diagram for XPhos·Pd(Ph)(oxindolate) Reductive-elimination.



For the Cu-catalyzed N-arylation reaction, the computational studies of the relevant CyDMEDA·Cu(oxindolate) species suggest that N-bound species **13** is favored by 14.1 kcal/mol

over the C-bound isomer **14** (Scheme 5). Therefore, the selectivity observed for the Cu-catalyzed N-arylation of oxindole might be governed by two different factors: (1) aryl halide activation from **13** proceeds faster than from **14**, or (2) aryl halide activation proceeds faster than the isomerization process. If the first factor is selectivity-determining, there could be a dynamic equilibrium in solution between **13** and **14**. The nature of the aryl halide activation step in Cu-catalyzed C-heteroatom bond-forming substitution reactions of aryl halides is not well understood.[17-19] Kinetic studies for the reaction of 2-pyrrolidinone with 4-iodo-m-xylene estimate $\Delta G^{\ddagger}$ to be 19.4 kcal/mol.[17] Therefore, it is plausible that the C-bound enolate does exist in small portions in solution, and that the selectivity is governed by the aryl halide activation processes ($k_3 > k_4$). If the second factor is selectivity-determining, then the absence of a low energy pathway for the interconversion of **13** and **14** determines the reaction's outcome. A better understanding of the mechanism of aryl halide activation is required to properly estimate the transition state energies to gain a full understanding for the observed chemoselectivity of the Cu-catalyzed reaction.

Scheme 5. Mechanistic Considerations for the Cu-Catalyzed N-Arylation of Oxindole.



The stoichiometric (eq. 3) and catalytic (Figure 7) reactions of 4-iodoanisole with

isolated complex **13'** confirm that **13'** is an active coupling agent possessing the nucleophilic component to react with an aryl halide, thus providing evidence that **13** may be a possible intermediate of the catalytic cycle.

Although the crystal structure of **13'** does not match the computationally predicted complex **13**, several interesting features of **13'** are worth considering. The linear geometry of the Cu(2)(oxindolate)$_2$ species is consistent with a previously reported crystal structure of a linear anionic $[Cu\{N(SiMePh_2)_2\}_2]^-$ bis-amide complex containing tetrahedral-ligated Li-based cation,[28] and suggests that Cu(2) in **13'** exist in the +1 oxidation state. However, the "cation" of **13'** contains a transition metal-based species, and thus allows for speculation as to the oxidation states of each Cu atom of the complex. Although disproportionation of the Cu atoms could generate a Cu(0)(CyDMEDA)$_2$ complex and the corresponding Cu(II)(oxindolate)$_2$ species, the linear geometry of the Cu-bis-oxindolate species suggest that Cu(2) is a Cu(I) species.[28] Further, disproportionation of the Cu atoms is unlikely, as the tetrahedral Cu(0)(CyDMEDA)$_2$ complex would possess 19 valence shell electrons.

The crystal structure obtained for **13'** may be misleading, and likely does not accurately represent the structure of the active complex. While Cu-catalyzed amination reactions of aryl halides using diamine ligands are 1st order in Cu,[17] a reaction based on a bimetallic Cu-complex would involve a reaction that is 2nd order in Cu. Therefore, an active species based on the structure of **13** is more likely. At a bare minimum, the crystallization of **13'** reconfirms the understanding of the lability of the amide and diamine ligands in solution,[21] and reminds us that crystal structures might not always adequately represent the actual structures of active catalysts in solution.

2.3 Conclusion

In summary, we have reported efficient and complementary Pd- and Cu-based catalyst systems for the C3- and N-arylation reactions of unprotected oxindoles using aryl halides. The use of a weak base allows for the presence of a wide variety of functional groups and substitution patterns that are not tolerated with stronger bases.[7b-c] Theoretical calculations suggest that for both the Pd- and Cu-based catalyst systems, the respective metallated oxindoles have a strong preference for the oxindole moiety to coordinate as an N-bound amidate as opposed to a C3-bound enolate. For the Pd-based catalyst system, the energy difference between the Pd-amide and Pd-enolates is ~ 5 kcal/mol, however, the selectivity is governed by a rapid C–C reductive elimination compared to C–N reductive elimination based on calculated transition state energies. For the Cu-based catalyst system, the preference for the metal to bind at N1 is stronger (~ 14 kcal/mol). In this case, the selectivity might be governed by rapid aryl halide activation from the diamine-Cu(I)-amidate complex compared to the diamine-Cu(I)-enolate. Alternatively, a low energy pathway for Cu to isomerize from N to C may not exist, and the C-bound enolate might never form. The implications of this study should be useful for those chemists interested in understanding the inherent differences between Pd- and Cu-based catalyst systems for nucleophilic substitution reactions of aryl halides.

2.4 Experimental Procedures

All reactions were carried out in resealable test tubes with Teflon septa under a dry argon or nitrogen atmosphere. Copper(I) iodide (98%) and Pd_2dba_3 were purchased from Strem. Copper(I) mesityl was prepared according to literature precedent and stored in a -20 °C freezer in a nitrogen-filled glovebox.[29] Diamine ligands were purchased from Aldrich and used without

further purification. XPhos was generously provided by Saltigo. RuPhos was prepared according to literature precedent.[30] Anhydrous K_2CO_3 (99%) and NaO*t*-Bu (98%) were purchased from Aldrich and stored under nitrogen in a Vacuum Atmospheres glovebox. Small portions (~5 g) were removed from the glovebox in glass vials, stored in the air in a desiccator filled with anhydrous calcium sulfate, and weighed in the air. Oxindoles were purchased from commercial sources and used without further purification. Aryl halides were purchased from commercial sources and, when necessary, filtered through neutral alumina or distilled. Anhydrous 1,4-dioxane was purchased from Aldrich in Sure-Seal® bottles. Anhydrous THF was purchased from J. T. Baker in CYCLE-TRAINER® solvent delivery kegs and vigorously purged with argon for 2 h. The solvent was further purified by passing it through two packed columns of neutral alumina under argon. The solvents were transferred by syringe from the solvent purification system or bottle to the reaction flask. Flash column chromatography was performed using a Biotage SP4 Flash Purification System using KP-Sil silica cartridges. In all cases, dichloromethane was used to transfer the crude reaction material onto the silica gel samplet, which was subsequently air-dried before usage. A gradient elution technique was performed, based on the recommendation from the Biotage TLC Wizard. *In situ* monitoring of reactions using infrared spectroscopy was performed with a Mettler Toledo iC10 ReactIR instrument equipped with a C1Fiber with a diamond-tipped probe.

Yields reported in the publication are of the isolated material and represent an average of at least two independent runs. Yields reported in the supporting information refer to a single experiment. Compounds described in the literature were characterized by comparing their ^1H NMR and ^{13}C NMR spectra, and melting points (m.p.) to the previously reported data; their purity was confirmed by gas chromatography (GC) or elemental analysis. GC analyses were performed on a Hewlett Packard 6890 instrument with an FID detector and a Hewlett Packard 10

m x 0.2 mm i.d. HP-1 capillary column using dodecane as an internal standard. Elemental analyses were performed by Atlantic Microlabs, Inc., Norcross, GA. Previously unknown compounds were synthesized, purified and analyzed from a single run and were then repeated to determine an average yield. They were characterized by ^{1}H NMR, ^{13}C NMR, m.p., IR and elemental analysis. For those compounds that did not give a satisfactory elemental analysis, a copy of their ^{1}H NMR spectra is included. ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian 500 MHz instruments with chemical shifts reported relative to the deuterated solvent or TMS. IR spectra were recorded on a Perkin-Elmer System 2000 FT-IR instrument for all previously unknown compounds (KBr disc). Melting points (uncorrected) were obtained on a Mel-Temp II capillary melting point apparatus.

All calculations were performed with the Gaussian '03[31] suite of programs. DFT calculations employed the B3LYP functional[32] using the 6-31G(d) basis set for all atoms in the Cu complexes. Due to the size of the XPhos-Pd complexes, geometry optimization was first performed using a two-layered ONIOM[33] calculation (B3LYP/6-31g(d):UFF) with the oxindole, phenyl, Pd and P at a high level and the rest of the ligand at the low level. The resulting structures were then reoptimized using all atom DFT B3LYP/6-31g(d) with the LANL2DZ basis set and the Hay-Wadt effective core potential[34] (ECP) for Pd. To obtain the final ΔE values, single point energy calculations were performed with the 6-311g(d,p) basis set with implicit solvation included. Frequency calculations were performed on all optimized structures to confirm that the minima had no negative frequencies and transition states had a single imaginary frequency. The Gibbs free energies were calculated at 298.15 K and 1 atm.

General procedure for the C3-arylation of oxindoles

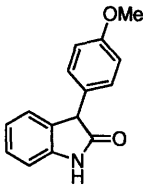
An oven-dried screw-cap test tube was charged with Pd_2dba_3 (0.010-0.020 mmol), XPhos (0.04-0.08 mmol), oxindole (1.00 mmol), aryl halide (1.20 mmol, if solid), K_2CO_3 (2.0 mmol), and a magnetic stir bar. The reaction vessel was fitted with a rubber septum. The test tube was evacuated and back-filled with dry argon twice. Aryl halide (1.20 mmol, if liquid), and solvent (0.50-1.0 mL) were then added successively. The rubber septum was removed and the reaction tube was quickly sealed with a Teflon-lined septum. The vessel was immersed in a pre-heated oil bath and stirred vigorously until TLC and/or GC analysis of the crude reaction mixture indicated that the limiting reagent had been completely consumed. The reaction mixture was cooled to room temperature, diluted with dichloromethane (15 mL), and filtered through a plug of celite, eluting with additional ethyl acetate (50 mL). The filtrate was concentrated and the resulting residue was purified by flash chromatography (hexanes/ethyl acetate or hexanes/dichloromethane) to provide the desired product.

General procedure for the N1-arylation of oxindoles

An oven-dried screw-cap test tube was charged with CuI (0.010-0.10 mmol), oxindole (1.00 mmol), aryl halide (1.20 mmol, if solid), K_2CO_3 (2.0 mmol), and a magnetic stir bar. The reaction vessel was fitted with a rubber septum. The test tube was evacuated and back-filled with dry argon. Aryl halide (1.20 mmol, if liquid), *rac-trans-N,N'*-dimethylcyclohexane-1,2-diamine (0.040-0.20 mmol) and 1,4-dioxane (0.50-1.0 mL) were then added successively. The rubber septum was removed and the reaction tube was quickly sealed with a Teflon-lined septum. The vessel was immersed in a pre-heated oil bath and stirred vigorously until TLC and/or GC analysis of the crude reaction mixture indicated that the limiting reagent had been completely consumed. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (15

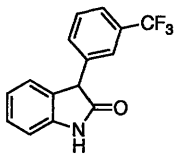
mL), and filtered through a plug of silica, eluting with additional ethyl acetate (50 mL). The filtrate was concentrated and the resulting residue was purified by flash chromatography (hexanes/ethyl acetate) to provide the desired product.

Experimental procedures for compounds in Table 1



3-(4-methoxyphenyl)indolin-2-one (entry 1)

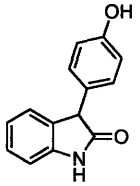
The general procedure was followed using Pd_2dba_3 (9.1 mg, 0.010 mmol), XPhos (24 mg, 0.050 mmol), K_2CO_3 (0.28 g, 2.0 mmol), 4-chloroanisole (128 mg, 1.20 mmol), and oxindole (133 mg, 1.00 mmol) with THF (1.0 mL) as solvent for 24 h at 80 °C. Isolation and chromatographic purification (hexane / ethyl acetate) afforded the title compound as white solid (226 mg, 94%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.53 (s, 1H), 7.25-6.86 (m, 8H), 4.60 (s, 1H), 3.80 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.7, 159.2, 142.0, 130.1, 129.7, 128.7, 128.5, 125.3, 122.8, 114.6, 110.3, 55.4, 52.2. m.p. 161-163 °C. (Lit. 163-165 °C).[35]



3-(3-(trifluoromethyl)phenyl)indolin-2-one (entry 2)

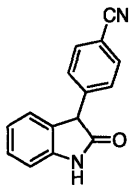
The general procedure was followed using Pd_2dba_3 (9.1 mg, 0.010 mmol), XPhos (24 mg, 0.050 mmol), K_2CO_3 (0.28 g, 2.0 mmol), (136 μL, 1.00 mmol), and oxindole (146 mg, 1.10 mmol) with 1,4-dioxane (1.0 mL) as solvent for 24 h at 100 °C. Isolation and chromatographic purification (hexane / ethyl acetate) afforded the title compound as white solid (228 mg, 82 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.29 (s, 1H), 7.58 (d, 1H, J = 7.5 Hz), 7.52 (s, 1H), 7.47 (t, 1H, J = 7.8 Hz), 7.28 (td, 1H, J = 0.6 Hz, 7.8 Hz), 7.12 (d, 1H, J = 7.3 Hz), 7.07 (m, 1H), 6.96 (d, 1H, J = 7.9 Hz), 4.71 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.3, 141.9, 137.6, 132.2, 131.4, 129.6, 129.0, 128.7, 128.1, 125.5, 125.4, 124.8, 123.2, 110.6, 52.5. IR (KBr disc, cm^{-1}) 3226, 1712, 1621, 1472, 1332, 1221, 1167, 1127, 1075, 751, 700, 671, 592. Anal. Calc. for $C_{15}H_{10}F_3NO$: C 64.98, H 3.64. Found: C 65.08, H 3.89. m.p. 169-171 °C.



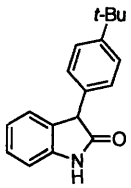
3-(4-hydroxyphenyl)indolin-2-one (entry 3)

The general procedure was followed using Pd_2dba_3 (9.1 mg, 0.010 mmol), XPhos (24 mg, 0.050 mmol), K_2CO_3 (0.42 g, 3.0 mmol), (129 mg, 1.00 mmol), and oxindole (160 mg, 1.20 mmol) with 1,4-dioxane (1.0 mL) as solvent for 24 h at 100 °C. After cooling to room temperature, the reaction mixture was dissolved in 2M HCl (5mL) and extracted with EtOAc (3 x 15 mL). The combined organic fractions were dried over $MgSO_4$ and concentrated. The residue was stirred in 5 mL CH_2Cl_2 to dissolve the soluble impurities. The product was then isolated by filtration and washed with hexane to provide the title compound as an orange solid (240 mg, 90%). ^{1}H NMR (500 MHz, CD_3OD) δ 7.13 (tt, 1H, J = 0.9, 7.6 Hz), 6.98 (m, 1H), 6.92-6.89 (m, 3H), 6.85 (d, 1H, J = 7.8 Hz), 6.67-6.89 (m, 2H), 3.27 (s, 1H). ^{13}C NMR (125 MHz, CD_3OD) δ 180.7, 157.3, 143.0, 131.4, 130.3, 128.9, 128.5, 125.7, 123.3, 116.4, 110.6, 54.4. IR (KBr disc, cm^{-1}) 3266, 1700, 1616, 1559, 1541, 1512, 1471, 1219, 824, 751. m.p. 234-239 °C.



4-(2-oxoindolin-3-yl)benzonitrile (entry 4)

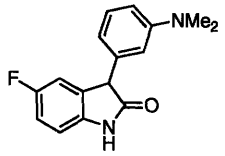
The general procedure was followed using Pd_2dba_3 (9.1 mg, 0.010 mmol), XPhos (24 mg, 0.050 mmol), K_2CO_3 (0.28 g, 2.0 mmol), 4-chlorobenzonitrile (166 mg, 1.20 mmol), oxindole (133 mg, 1.00 mmol), and 200 mg flame activated 4Å mol sieves with THF (1.0 mL) as solvent for 24 h at 80 °C. Isolation and chromatographic purification (hexane / ethyl acetate) afforded the title compound as white solid (135 mg, 58 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.29 (s, 1H), 7.66-7.64 (m, 2H), 7.38-7.36 (m, 2H), 7.31-7.28 (m, 1H), 7.12-7.06 (m, 2H), 6.97 (d, 1H, J = 7.8 Hz), 4.71 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.7, 141.9, 132.9, 129.5, 129.2, 128.2, 125.4, 124.7, 123.3, 118.7, 111.8, 110.6, 52.7. IR (KBr disc, cm^{-1}) 3250 (br), 2230, 1711, 1620, 1471, 1328, 1219, 1097, 1019, 914, 818, 752, 678. m.p. 176-178 °C.



3-(4-*tert*-butylphenyl)indolin-2-one (entry 5)

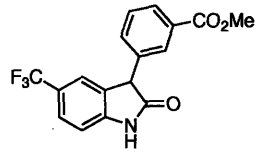
The general procedure was followed using Pd_2dba_3 (9.1 mg, 0.010 mmol), XPhos (24 mg, 0.050 mmol), K_2CO_3 (0.28 g, 2.0 mmol), 4-*t*-butyl-4-methylbenzenesulfonate (334 mg, 1.10 mmol), and oxindole (133 mg, 1.00 mmol) with *t*-BuOH (1.0 mL) as solvent for 24 h at 80 °C. Isolation and chromatographic purification (hexane / ethyl acetate) afforded the title compound as white solid (164 mg, 64%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.21 (s, 1H), 7.38-7.35 (m, 2H), 7.23 (t, 1H, J = 7.8 Hz), 7.21-7.13 (m, 3H), 7.02, (1H, td, J = 7.9, 1.0 Hz) 6.88 (d, 1H, 7.8 Hz), 4.62 (s, 1H),

1.31 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.6, 141.9, 133.5, 130.0, 128.5, 128.2, 126.1, 125.4, 122.8, 110.2, 52.4, 34.9, 31.5. IR (KBr disc, cm^{-1}) 3211 (br), 2963, 1709, 1620, 1515, 1471, 1328, 1269, 1220, 1018, 910, 818, 751, 677, 564. m.p. 170-172 °C.



3-(3-(Dimethylamino)phenyl)-5-fluoroindolin-2-one (entry 6)

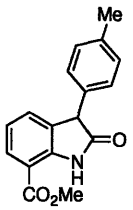
The general procedure was followed using Pd_2dba_3 (9.1 mg, 0.010 mmol), XPhos (24 mg, 0.050 mmol), K_2CO_3 (0.28 g, 2.0 mmol), (171 mg, 1.10 mmol), and 5-fluorooxindole (157 mg, 1.00 mmol) with 1,4-dioxane (1.0 mL) as solvent for 24 h at 100 °C. Isolation and chromatographic purification (hexane / ethyl acetate) afforded the title compound as white solid (203 mg, 75 %). ^1H NMR (500 MHz, $CDCl_3$) δ 9.44 (s, 1H), 7.22 (dd, 1H, J = 7.5, 8.2 Hz), 6.94-6.82 (m, 3H), 6.69 (dd, 1H, J = 2.3, 5.9 Hz), 6.56 (t, 1H, J = 1.6 Hz), 6.50 (d, 1H, J = 7.6 Hz), 4.57, (s, 1H), 2.94 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.0, 159.8, 151.7, 138.4, 137.4, 132.4, 132.3, 130.4, 116.9, 115.3, 113.7, 113.1, 112.7, 111.3, 54.4, 41.2. IR (KBr disc, cm^{-1}) 3219 (br), 3085, 2877, 2808, 1712, 1601, 1501, 1486, 1356, 1302, 1231, 1194, 1126, 999, 910, 815, 761, 732, 694, 592. Anal. Calc. for $C_{16}H_{15}FN_2O$: C 71.10, H 5.59. Found: C 70.87, H 5.61. m.p. 126-128 °C.



Methyl 3-(2-oxo-5-(trifluoromethyl)indolin-3-yl)benzoate (entry 7)

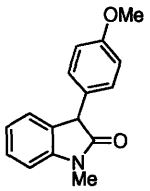
The general procedure was followed using Pd_2dba_3 (9.1 mg, 0.010 mmol), XPhos (24 mg, 0.050 mmol), K_2CO_3 (0.28 g, 2.0 mmol), methyl 3-chlorobenzoate (153 μL, 1.10 mmol), and 5-

trifluoromethyloxindole (120 mg, 1.00 mmol) with THF (2.0 mL) as solvent for 24 h at 80 °C. Isolation and chromatographic purification (dichloromethane / ethyl acetate, 1:0 → 9:1) afforded the title compound as a slightly yellow foam (265 mg, 79%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.94 (s, 1H), 8.01 (dt, 1H, J = 1.4, 7.8 Hz), 7.92 (t, 1H, J = 1.7 Hz), 7.52 (dt, 1H, J = 0.9, 8.2 Hz), 7.45 (m, 1H), 7.39 (dt, 1H, J = 1.4, 7.6 Hz) 7.34 (s, 1H), 7.01 (d, 1H, J = 8.2 Hz), 4.74 (s, 1H), 3.90 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.9, 166.8, 145.0, 136.0, 133.1, 131.3, 129.9, 129.8, 129.6, 129.5, 126.6, 125.6, 122.3, 121.8, 110.5, 52.5, 36.3. IR (KBr disc, cm^{-1}) 3256, 2957, 1722, 1631, 1499, 1415, 1330, 1303, 1264, 1221, 1159, 1117, 1060, 91,0 829, 732, 695, 635, 543. m.p. 132-136 °C.



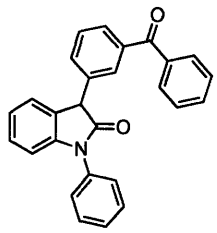
methyl 2-oxo-3-*p*-tolylindoline-7-carboxylate (entry 8)

The general procedure was followed using Pd_2dba_3 (9.1 mg, 0.010 mmol), XPhos (24 mg, 0.050 mmol), K_2CO_3 (0.28 g, 2.0 mmol), 4-chlorotoluene (130 μL, 1.10 mmol), and methyl oxindole-7-carboxylate (191 mg, 1.00 mmol) with THF (2.0 mL) as solvent for 24 h at 80 °C. Isolation and chromatographic purification (hexane / ethyl acetate) afforded the title compound as a white solid (160 mg, 57%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.22 (s, 1H), 7.86 (dt, 1H, J = 0.9, 8.1 Hz.), 7.29 (dd, 1H, J = 0.5, 7.3 Hz), 7.16 (d, 2H, J = 7.9 Hz), 7.01-7.03 (m, 3H), 4.60 (s, 1H), 3.96 (s, 3H), 2.34 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.4, 166.6, 144.3, 137.7, 133.0, 131.1, 129.9, 129.8, 129.2, 128.4, 122.1, 111.6, 52.4, 51.5, 21.3. IR (KBr disc, cm^{-1}) 3267 (br), 3024, 3004, 2952, 1707, 1608, 1514, 1454, 1430, 1312, 1285, 1198, 1133, 1060, 993, 941, 916, 804, 774, 753, 737, 661, 496, 460. m.p. 155-163 °C.



3-(4-methoxyphenyl)-1-methylindolin-2-one (entry 9)

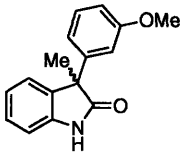
The general procedure was followed using Pd_2dba_3 (9.1 mg, 0.010 mmol), XPhos (24 mg, 0.050 mmol), K_2CO_3 (0.28 g, 2.0 mmol), 4-chloroanisole (134 μL, 1.00 mmol), and 1-methyl oxindole (147 mg, 1.10 mmol) with THF (1.0 mL) as solvent for 24 h at 80 °C. Isolation and chromatographic purification (hexane / ethyl acetate) afforded the title compound as white solid (201 mg, 79%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (tt, 1H, J = 0.8, 7.6 Hz), 7.20-7.12 (m, 4H), 7.08 (dt, 1H, J = 0.8, 8.5 Hz), 9.91-6.81 (m, 3H), 4.57 (s, 1H), 3.79 (s, 3H), 3.26 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.5, 159.2, 144.6, 129.6, 129.2, 128.8, 128.5, 125.2, 122.8, 114.5, 108.3, 55.5, 51.4, 26.6. Anal. Calc. for $C_{16}H_{15}NO_2$: C 75.97, H 5.97. Found: C 75.58, H 6.00. m.p. 85-88 °C. (Lit. 90-91°C).[36]



1-phenyl-3-(3-(phenylcarbonyl)phenyl)indolin-2-one (entry 10)

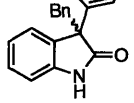
The general procedure was followed using Pd_2dba_3 (9.1 mg, 0.010 mmol), XPhos (24 mg, 0.050 mmol), K_3PO_4 (0.42 g, 2.0 mmol), 3-chlorobenzophenone (217 mg, 1.00 mmol), and 1-phenyloxindole (251 mg, 1.20 mmol) with 1,4-dioxane (1.0 mL) as solvent for 24 h at 80 °C. Isolation and chromatographic purification (hexane / ethyl acetate) afforded the title compound as white solid (341 mg, 88 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95-7.81 (m, 3H), 7.75 (dt, 1H, J = 1.6, 7.4 Hz), 7.62-7.41 (m, 10H), 7.30-7.25 (m, 2H), 7.12 (td, 1H, J = 0.8, 7.5 Hz), 6.90 (d,

1H, J = 7.8 Hz), 4.89 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.5, 175.0, 144.6, 138.3, 137.5, 137.3, 134.5, 132.7, 132.6, 130.4, 130.3, 129.8, 129.7, 129.0, 128.8, 128.5, 128.4, 128.1, 126.8, 125.5, 123.5, 109.9, 52.1. IR (KBr disc, cm^{-1}) 1722, 1658, 1612, 1596, 1500, 1465, 1369, 1320, 1283, 1219, 1176, 911, 754, 722, 714, 698, 603. Anal. Calc. for $C_{27}H_{19}NO_2$: C 83.27, H 4.92. Found: C 83.62, H 4.92. m.p. 133-135 °C.



3-(3-methoxyphenyl)-3-methylindolin-2-one (entry 11)

The general procedure was followed using Pd_2dba_3 (9.1 mg, 0.010 mmol), RuPhos (23 mg, 0.050 mmol), NaO*t*-Bu (0.20 g, 2.0 mmol), 3-bromoanisole (152 μL, 1.20 mmol), and 3-methyloxindole (146 mg, 1.00 mmol) with toluene (1.0 mL) as solvent for 9 h at 100 °C. Isolation and chromatographic purification (CH_2Cl_2 / ethyl acetate) afforded the title compound as yellow solid (228 mg, 90 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.60 (s, 1H), 7.26-7.20 (m, 2H), 7.13 (td, 1H, J = 0.6, 7.5 Hz), 7.04 (td, 1H, J = 0.9, 7.65 Hz), 76.97 (d, 1H, J = 7.6 Hz), 6.93-6.90 (m, 2H), 6.81 (ddd, 1H, J = 0.9, 2.5, 8.2 Hz), 3.77 (s, 3H), 1.83 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.0, 159.7, 143.9, 143.6, 129.7, 129.4, 128.0, 128.0, 120.1, 113.1, 112.5, 55.3, 43.3, 37.9, 20.4. IR (KBr disc, cm^{-1}) 3215, 1710, 1618, 1599, 1485, 1472, 1372, 1324, 1259, 1204, 1167, 1118, 1043, 912, 754, 696, 660. m.p. 131-133 °C.

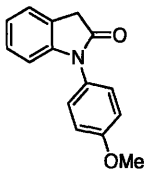


3-(4-fluorophenyl)-3-benzylindolin-2-one (entry 12)

The general procedure was followed using Pd_2dba_3 (9.1 mg, 0.010 mmol), RuPhos (19 mg, 0.040

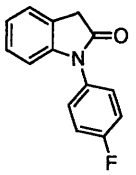
mmol), NaO*t*-Bu (0.20 g, 2.0 mmol), 1-bromo-3-fluorobenzene (132 μL, 1.20 mmol), and 3-benzyloxindole (223 mg, 1.00 mmol) with toluene (1.0 mL) as solvent for 20 h at 100 °C. Isolation and chromatographic purification (hexane / ethyl acetate) afforded the title compound as yellow solid (253 mg, 80 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (bs 1H), 7.49-7.42 (m, 2H), 7.20-7.15 (m, 2H), 7.10-6.88 (m, 5H), 6.86-6.63 (m, 2H), 6.73-6.70 (m, 2H), 3.66 (d, 1H, J = 12.8 Hz), 3.44 (d, 1H, J = 12.8 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.3, 164.0, 141.0, 135.5, 131.7, 130.2, 129.1, 129.1, 128.6, 127.8, 126.9, 126.0, 122.5, 115.8, 110.2, 58.2, 44.0. IR (KBr disc, cm^{-1}) 3198, 1697, 1617, 1507, 147, 1225, 1201, 1163, 1014, 855, 815, 754, 697. m.p. 189-191 °C.

Experimental procedures for compounds in Table 2



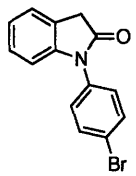
1-(4-methoxyphenyl)indolin-2-one (entry 1)

The general procedure was followed using CuI (9.5 mg, 0.050 mmol), *rac-trans-N,N'*-dimethylcyclohexane-1,2-diamine (16 μL, 0.10 mmol), K_2CO_3 (0.28 g, 2.0 mmol), 4-iodoanisole (234 mg, 1.00 mmol), and oxindole (160 mg, 1.20 mmol) with 1,4-dioxane (1.0 mL) as solvent for 24 h at 100 °C. Isolation and chromatographic purification (hexane / ethyl acetate) afforded the title compound as white solid (204 mg, 85%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33-7.30 (m, 3H), 7.21 (td, J = 1.2, 7.8 Hz), 7.09-7.04 (m, 3H), 6.74 (dd, 1H, J = 0.3, 7.9 Hz), 3.87 (s, 3H), 2.71 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.9, 159.3, 145.88, 128.1, 127.9, 127.2, 124.7, 124.4, 122.8, 115.9, 109.4, 55.7, 36.1. Anal. Calc. for $C_{15}H_{13}NO_2$: C 75.30, H 5.48. Found: C 75.17, H 5.41. m.p. 131-132 °C. (Lit. 118-122 °C).[37]



1-(4-fluorophenyl)indolin-2-one (entry 2)

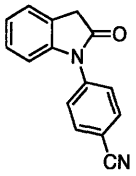
The general procedure was followed using CuI (1.9 mg, 0.010 mmol), *rac-trans-N,N'*-dimethylcyclohexane-1,2-diamine (6.4 μL, 0.040 mmol), K_2CO_3 (0.28 g, 2.0 mmol), 4-fluoroiodobenzene (115 μL, 1.00 mmol), and oxindole (160 mg, 1.20 mmol) with 1,4-dioxane (1.0 mL) as solvent for 24 h at 100 °C. Isolation and chromatographic purification (hexane / ethyl acetate) afforded the title compound an orange solid (221 mg, 97 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42-7.39 (m, 2H), 7.34-7.32 (m, 1H), 7.25-7.21 (m, 2H), 7.10 (td, 1H, J = 0.9, 7.3 Hz), 6.75 (dd, J = 0.5, 7.9 Hz), 3.72 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.7, 163.0, 161.1, 145.3, 128.7, 128.0, 124.9, 123.1, 116.9, 116.8, 109.4, 36.1. IR (KBr disc, cm^{-1}) 1710, 1612, 1602, 1512, 1481, 1461, 1371, 1322, 1244, 1222, 1201, 1174, 1100, 952, 840, 814, 746. Anal. Calc. for $C_{14}H_{10}FNO$: C 74.00, H 4.44. Found: C 73.68, H 4.37. m.p. 129-132 °C.



1-(4-bromophenyl)indolin-2-one (entry 3)

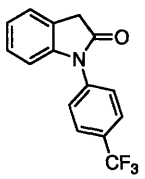
The general procedure was followed using CuI (9.5 mg, 0.050 mmol), *rac-trans-N,N'*-dimethylcyclohexane-1,2-diamine (16 μL, 0.10 mmol), K_2CO_3 (0.28 g, 2.0 mmol), 1-bromo-4-iodobenzene(340 mg, 1.20 mmol), and oxindole (133 mg, 1.00 mmol) with 1,4-dioxane (1.0 mL) as solvent for 24 h at 40 °C. Isolation and chromatographic purification (hexane / ethyl acetate) afforded the title compound as white solid (148 mg, 57%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67-7.65 (m, 2H), 7.33-7.30 (m, 2H), 7.25-7.18 (m, 2H), 7.10 (t, 1H, J = 7.6 Hz), 6.81 (d, 1H, J =

7.8 Hz), 3.72 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.3, 144.7, 138.9, 133.0, 128.3, 128.0, 124.9, 124.4, 123.2, 121.8, 109.4, 36.1. IR (KBr disc, cm^{-1}) 1722, 1612, 1493, 1464, 1370, 1324, 1240, 1172, 1094, 1070, 1012, 821, 751, 673. m.p. 115-117 °C.



4-(2-oxoindolin-1-yl)benzonitrile (entry 4)

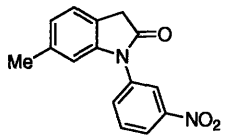
The general procedure was followed using CuI (9.5 mg, 0.050 mmol), *rac-trans-N,N'*-dimethylcyclohexane-1,2-diamine (16 μL, 0.10 mmol), K_2CO_3 (0.28 g, 2.0 mmol), 4-iodobenzonitrile (343 mg, 1.20 mmol), oxindole (133 mg, 1.00 mmol) and 200 mg 4Å flame activated mol sieves with 1,4-dioxane (1.0 mL) as solvent for 24 h at 80 °C. Isolation and chromatographic purification (hexane / ethyl acetate) afforded the title compound as white solid (167 mg, 71%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.85-7.82 (m, 2H), 7.64-7.61 (m, 2H), 7.37-7.34 (m, 1H), 7.26 (td, 1H, J = 1.3, 8.0 Hz), 7.14 (td, 1H, J = 0.9 7.5, Hz), 6.90 (dd, 1H, J = 0.5, 8.0 Hz), 3.776 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.1, 143.7, 138.8, 133.7, 128.1, 126.9, 125.2, 124.4, 123.8, 118.4, 111.4, 109.5, 39.7. IR (KBr disc, cm^{-1}) 2231, 1714, 1607, 1513, 1463, 1365, 1242, 1167, 743, 630. m.p. 190-192 °C.



1-(4-(trifluoromethyl)phenyl)indolin-2-one (entry 5)

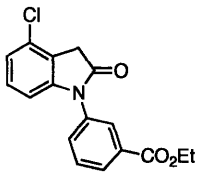
The general procedure was followed using CuI (1.9 mg, 0.010 mmol), *rac-trans-N,N'*-dimethylcyclohexane-1,2-diamine (6.4 μL, 0.04 mmol), K_2CO_3 (0.28 g, 2.0 mmol), 4-iodobenzotrifluoride (176 μL, 1.20 mmol), and oxindole (133 mg, 1.00 mmol) with 1,4-dioxane

(1.0 mL) as solvent for 24 h at 100 °C. Isolation and chromatographic purification (hexane / ethyl acetate) afforded the title compound as white solid (242 mg, 87%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, 2H, *J* = 8.3 Hz), 7.61 (d, 2H, *J* = 8.2 Hz), 7.36 (dd, 1H, J= 0.5, 7.3 Hz), 7.26 (td, 1H, *J* = 1.0, 7.7 Hz), 7.14 (td, 1H, *J* = 0.8, 7.5 Hz), 6.88 (d, 1H, *J* = 8.0 Hz), 3.76 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.3, 144.2, 137.9, 129.9, 128.0, 127.0, 126.9, 126.8, 125.1, 124.4, 123.5, 109.5, 36.1. IR (KBr disc, cm^{-1}) 1724, 1613, 1483, 1370, 1324, 1240, 1169, 1123, 1068, 1019, 750. Anal. Calc. for $C_{15}H_{10}F_3NO$: C 64.98, H 3.64. Found: C 64.83, H 3.57. m.p. 125-125 °C.



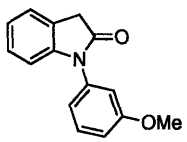
6-methyl-1-(3-nitrophenyl)indolin-2-one (entry 6)

The general procedure was followed using CuI (9.5 mg, 0.050 mmol), *rac-trans-N,N'*-dimethylcyclohexane-1,2-diamine (16 μL, 0.10 mmol l), K_2CO_3 (0.28 g, 2.0 mmol), 3-iodonitrobenzene (275 mg, 1.1 mmol), and 6-methyloxindole (147 mg, 1.00 mmol) with 1,4-dioxane (0.5 mL) as solvent for 24 h at 80 °C. Isolation and chromatographic purification (hexane / ethyl acetate) afforded the title compound as red/brown solid (196 mg, 73%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35-8.32 (m, 2H), .84-7.77 (m, 2H), 7.65 (d, 1H, *J* = 7.7 Hz), 7.07-7.04 (m, 1H), 6.75 (s, 1H), 2.43 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.1, 157.9, 151.5, 150.8, 149.3, 134.4, 132.4, 131.2, 126.4, 123.6, 121.2, 115.77, 111.8, 39.8, 17.1. IR (KBr disc, cm^{-1}) 3093, 2922, 2865, 1728, 1626, 1533, 1369, 1352, 1242, 1179, 1112, 912, 805, 738, 690, 602. m.p. 170-180 °C (dec.).



methyl 3-(4-chloro-2-oxoindolin-1-yl)benzoate (entry 7)

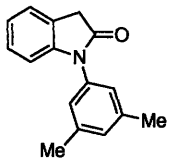
The general procedure was followed using CuI (9.5 mg, 0.050 mmol), *rac-trans-N,N'*-dimethylcyclohexane-1,2-diamine (16 μL, 0.10 mmol), K_2CO_3 (0.28 g, 2.0 mmol), ethyl 3-iodobenzoate (202 μL, 1.20 mmol), and 4-chlorooxindole (168 mg, 1.00 mmol) with 1,4-dioxane (0.5 mL) as solvent for 24 h at 80 °C. Isolation and chromatographic purification (hexane / ethyl acetate) afforded the title compound as white solid (276 mg, 88 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13-8.08 (m, 2H), 7.65-7.60 (m, 2H), 7.17 (tt, 1H, J = 0.8, 8.0 Hz), 7.09 (dd, 1H, J = 0.8, 8.2 Hz), 6.68 (dd, 1H, J = 0.5, 7.9 Hz), 4.40 (q, 2H, J = 7.1 Hz), 3.73 (s, 2H), 1.40 (t, 3H, J = 7.1 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.5, 165.7, 145.9, 134.7, 132.5, 131.2, 131.0, 130.5, 129.6, 129.4, 127.8, 123.4, 123.1, 107.8, 61.6, 35.7, 14.5. IR (KBr disc, cm^{-1}) 1726, 1609, 1587, 1491, 1456, 1366, 1262, 1182, 1164, 1142, 1105, 1081, 1023, 755, 717, 687, 614. Anal. Calc. for $C_{16}H_{12}ClNO_3$: C 64.67, H 4.47. Found: C 64.41, H 4.48. m.p. 114-116 °C.



1-(3-methoxyphenyl)indolin-2-one (entry 8)

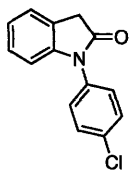
The general procedure was followed using CuI (19 mg, 0.10 mmol), *rac-trans-N,N'*-dimethylcyclohexane-1,2-diamine (32 μL, 0.20 mmol), K_2CO_3 (0.28 g, 2.0 mmol), 3-bromoanisole (152 μL, 1.20 mmol), and oxindole (133 mg, 1.00 mmol) with 1,4-dioxane (1.0 mL) as solvent for 24 h at 100 °C. Isolation and chromatographic purification (hexane / ethyl acetate) afforded the title compound as a slightly orange solid (139 mg, 58 %). ^{1}H NMR (500

MHz, $CDCl_3$) δ 7.46-7.43 (m, 1H), 7.32 (dd, J = 0.6, 7.2 Hz), 7.22 (td, 1H, J = 1.1, 7.9 Hz), 7.07 (td, 1H, J = 1.1, 7.5 Hz), 7.02-6.96 (m, 3H), 6.83 (dd, 1H, J = 0.3, 7.9 Hz), 3.84 (s, 3H), 3.72 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.5, 160.7, 145.3, 135.7, 130.5, 127.9, 124.7, 124.4, 122.9, 118.9, 114.2, 112.4, 109.6, 55.6, 36.2. m.p. 101-104 °C (Lit. 104-106 °C).[38]



1-(3,5-dimethylphenyl)indolin-2-one (entry 9)

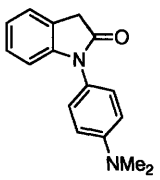
The general procedure was followed using CuI (19 mg, 0.10 mmol), *rac-trans-N,N'*-dimethylcyclohexane-1,2-diamine (32 μL, 0.20 mmol), K_2CO_3 (0.28 g, 2.0 mmol), 5-bromo-m-xylene (163 μL, 1.20 mmol), and oxindole (133 mg, 1.00 mmol) with 1,4-dioxane (0.5 mL) as solvent for 24 h at 100 °C. Isolation and chromatographic purification (hexane / ethyl acetate) afforded the title compound as slightly yellow solid (143 mg, 60%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.31 (dd, 1H, J = 0.4, 7.3 Hz), 7.21 (td, 1H, J = 1.1, 7.6 Hz), 7.09-7.04 (m, 2H), 7.03 (d, 2H, J = 0.5 Hz), 6.7 (d, 1H, J = 7.6 Hz), 3.73 (s, 2H), 2.39 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.7, 145.7, 139.6, 134.4, 130.1, 127.9, 124.6, 124.5, 124.4, 122.8, 109.6, 36.2, 21.5. IR (KBr disc, cm^{-1}) 1725, 1614, 1593, 1489, 1465, 1369, 1325, 1304, 1240, 1197, 176, 1095, 848, 750, 733, 696, 619. m.p. 92-94 °C.



1-(4-chlorophenyl)indolin-2-one[39] (entry 10)

The general procedure was followed using CuI (19 mg, 0.10 mmol), *rac-trans-N,N'*-dimethylcyclohexane-1,2-diamine (32 μL, 0.20 mmol), K_2CO_3 (0.28 g, 2.0 mmol), 1-bromo-4-

chlorobenzene (287, 1.50 mmol), and oxindole (133 mg, 1.00 mmol) with 1,4-dioxane (1.0 mL) as solvent for 24 h at 100 °C. Isolation and chromatographic purification (hexane / ethyl acetate) afforded the title compound as white solid (192 mg, 79%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52-7.49 (m, 2H), 7.40-7.37 (m, 2H), 7.334-7.31 (m, 1H), 7.23 (td, 1H, J = 0.8, 7.7 Hz), 7.10 (td, 1H, J = 0.9, 7.5 Hz), 76.80 (dd, 1H, J = 0.6, 7.9 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.5, 144.8, 133.8, 133.1, 133.0, 130.0, 128.0, 124.9, 124.4, 123.2, 109.4, 36.1. m.p. 123-125 °C.



1-(4-(dimethylamino)phenyl)indolin-2-one (entry 11)

The general procedure was followed using CuI (19 mg, 0.10 mmol), *rac-trans-N,N'*-dimethylcyclohexane-1,2-diamine (32 μL, 0.20 mmol), K_2CO_3 (0.28 g, 2.0 mmol), 4-bromo-*N,N*-dimethylaninline (200 mg, 1.00 mmol), and oxindole (160 mg, 1.20 mmol) with 1,4-dioxane (1.0 mL) as solvent for 24 h at 100 °C. Isolation and chromatographic purification (hexane / ethyl acetate) afforded the title compound as a tan solid (127 mg, 50%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (dt, 1H, J = 0.5, 7.3 Hz), 7.24 (m 2H), 7.20 (td, 1H, J = 0.4, 7.8 Hz), 7.06 (td, 1H, J = 0.9, 7.5 Hz), 6.8 (d, 2H, J = 8.8 Hz), 6.74 (d, 1H, J = 7.8 Hz), 3.70 (s, 2H), 3.02 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.2, 150.4, 146.4, 127.9, 127.7, 124.6, 124.5, 122.5, 113.2, 109.6, 105.3, 40.8, 36.2. IR (KBr disc, cm^{-1}) 1712, 1610, 1524, 1483, 1462, 1354, 1241, 1168, 1095, 950, 8821, 763, 631. Anal. Calc. for $C_{16}H_{16}N_2O$: C 76.16, H 6.39. Found: C 75.83, H 6.37. m.p. 171-172 °C.

Preparation of complex 13'

In a nitrogen-filled glovebox, oxindole (1.33 g, 10.0 mmol) and *rac-trans-N,N'*-dimethylcyclohexane-1,2-diamine (1.42 g, 10.0 mmol) were stirred in dry toluene (50 mL). To this solution was slowly added copper(I) mesityl (1.82g, 10.0 mmol) dissolved in toluene (20 mL). After a short time period (< 5 min) a tan solid began to precipitate. The solution was allowed to stir for an additional 15 min, after which time pentane (30 mL) was added. After stirring for an additional 10 min, complete precipitation was achieved by storing the solution at -15 °C overnight. The resulting solid was filtered, washed with additional pentane and dried under vacuum to provide 3.2 g (95%) of a white (slightly pink) solid. ^{1}H NMR (500 MHz, C_6D_6) δ. 7.28 (br s, 1H), 7.19 (br s, 1H), 7.02 (br s, 1H), 6.90 (br t, 1H), 3.42 (s, 2H), 2.31 (s, 6H), 2.14 (br s, 2H), 1.85 (d, 2H, J = 13.4 Hz), 1.80 (m, 2H), 1.49 (m, 2H), 0.91 (m, 2H), 0.73 (m, 2H). ^{13}C NMR (125 MHz, DMF-d_7) δ 185.7, 130.5, 127.8, 123.9, 118.8, 112.6, 67.9, 64.5, 38.4, 30.8, 26.0. This compound was stored in a refrigerator at -15 °C in a nitrogen-filled glovebox. Although thermally stable, this complex was found to be sensitive to O_2. Crystals of **13'** suitable for X-ray diffraction analysis were grown in a nitrogen-filled glovebox by preparing a near-saturated solution of **13'** in acetonitrile at rt. Pentane was layered on top of the acetonitrile solution, and the biphasic mixture was stored in a freezer at -15 °C. Crystals grew from the biphasic membrane downward into the acetonitrile layer.

Stoichiometric reaction of 13' with 4-iodoanisole

In a nitrogen-filled glovebox, a dry schlenk tube was charged with **13'** (33.5 mg, 0.100 mmol), 4-iodoanisole (234 mg, 1.00 mmol), 1,4-dioxane (1.00 mL), and a magnetic stir bar. The vessel was sealed, removed from the glovebox, and stirred at rt for 30 min. Dodecane (22.5 mL, 0.100 mmol), ethyl acetate (20 mL), and $NH_4OH_{(aq)}$ (2 mL) were stirred into the reaction mixture.

Analysis of the organic layer by GC confirmed an 88% corrected yield of 1-(4-methoxyphenyl)indolin-2-one.

Cross coupling of 4-iodoanisole with oxindole monitored by IR spectroscopy (Figure 6)

In a nitrogen-filled glovebox, a dry 25 mL reaction vessel designed for use with the IR probe was charged with either **13'** (17 mg, 0.050 mmol) or CuI (9.5 mg, 0.050 mmol), oxindole (133 mg, 1.00 mmol), 4-iodoanisole (351 mg, 1.50 mmol), K_2CO_3 (278 mg, 2.00 mmol), and a magnetic stir bar. The vessel was sealed, removed from the glovebox, and attached to a vacuum manifold. The tube was evacuated and back-filled with Ar. CyDMEDA (7.9 μL, 0.050 mmol, if necessary), and 1,4-dioxane (1.00 mL) were added successively. Under a purge of Ar, the reaction vessel was attached to a Mettler Toledo iC10 ReactIR, sealed and stirred in an oil bath at 80 °C, until the reaction was completed by IR monitoring. The reaction was cooled to room temperature. Dodecane (225 mL) and ethyl acetate (20 ml) were added, and the reaction mixture was sampled for GC analysis. The corrected GC yield was used to standardize the data obtained from the IR.

Crystal data and structure refinement for 13'

Identification code	07067	
Empirical formula	C32 H48 Cu2 N6 O2	
Formula weight	675.84	
Temperature	100(2) K	
Wavelength	0.71073 ≈	
Crystal system	Monoclinic	
Space group	Cc	
Unit cell dimensions	a = 25.053(16) ≈	α= 90∞.
	b = 8.747(6) ≈	β= 95.236(10)∞.
	c = 14.682(10) ≈	γ = 90∞.
Volume	3204(4) ≈^{3}	
Z	4	

Density (calculated)	1.401 Mg/m^3
Absorption coefficient	1.366 mm^{-1}
F(000)	1424
Crystal size	0.50 x 0.23 x 0.05 mm^3
Theta range for data collection	2.47 to 29.57∞.
Index ranges	-34<=h<=34, -12<=k<=12, -20<=l<=20
Reflections collected	32316
Independent reflections	8810 [R(int) = 0.0342]
Completeness to theta = 29.57∞	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9349 and 0.5484
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	8810 / 257 / 488
Goodness-of-fit on F^2	1.019
Final R indices [I>2sigma(I)]	R1 = 0.0232, wR2 = 0.0575
R indices (all data)	R1 = 0.0265, wR2 = 0.0589
Absolute structure parameter	0.008(6)
Largest diff. peak and hole	0.350 and -0.173 $e.\approx^{-3}$

Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($\approx^2$x 10^3) for 13'. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor

	x	y	z	U(eq)
Cu(1)	5714(1)	3379(1)	9689(1)	25(1)
N(1)	4986(1)	3463(1)	8939(1)	25(1)
C(1)	4961(1)	4560(2)	8181(1)	39(1)
N(2)	5255(1)	3635(1)	10836(1)	24(1)
C(2)	5499(1)	2881(2)	11659(1)	27(1)
C(11)	4564(1)	3772(2)	9565(1)	23(1)
C(12)	4010(1)	3224(2)	9178(1)	33(1)
C(13)	3585(1)	3584(2)	9824(1)	35(1)
C(14)	3736(1)	2890(2)	10763(1)	35(1)
C(15)	4289(1)	3410(2)	11151(1)	29(1)
C(16)	4721(1)	3086(2)	10510(1)	21(1)
N(3)	6353(1)	1922(2)	9645(2)	22(1)
C(3)	6302(2)	437(3)	10117(2)	30(1)
N(4)	6296(1)	5128(2)	9848(2)	33(1)
C(4)	6149(2)	6515(3)	9319(3)	47(1)
C(21)	6838(1)	2786(3)	9991(2)	24(1)
C(22)	7358(1)	1991(3)	9779(2)	30(1)
C(23)	7854(1)	2938(4)	10069(3)	37(1)
C(24)	7810(1)	4540(3)	9661(2)	39(1)
C(25)	7305(1)	5314(3)	9921(2)	36(1)
C(26)	6795(1)	4420(3)	9592(2)	27(1)
N(3A)	6336(3)	1831(7)	10089(6)	19(1)
C(3A)	6249(6)	212(12)	9855(8)	18(2)
N(4A)	6367(2)	4812(6)	9383(5)	16(1)
C(4A)	6270(6)	6413(12)	9688(9)	29(3)
C(21A)	6835(4)	2434(10)	9772(7)	16(2)
C(22A)	7347(3)	1693(8)	10245(6)	21(1)
C(23A)	7848(5)	2457(11)	9949(11)	25(2)
C(24A)	7862(3)	4146(9)	10138(7)	25(2)
C(25A)	7378(3)	4875(10)	9622(7)	21(2)
C(26A)	6848(3)	4179(10)	9891(6)	14(1)
Cu(2)	5831(1)	1493(1)	7189(1)	20(1)
N(5)	6574(1)	1587(1)	7310(1)	20(1)
C(31)	6854(1)	2872(2)	7142(1)	25(1)
O(1)	6663(1)	4160(1)	6994(1)	37(1)
C(32)	7451(1)	2487(2)	7150(1)	30(1)
C(33)	7464(1)	805(2)	7353(1)	23(1)
C(34)	7874(1)	-250(2)	7462(1)	34(1)
C(35)	7752(1)	-1767(2)	7631(1)	37(1)
C(36)	7229(1)	-2215(2)	7697(1)	34(1)
C(37)	6812(1)	-1150(2)	7613(1)	28(1)

C(38)	6933(1)	360(2)	7430(1)	20(1)
N(6)	5091(1)	1295(1)	7015(1)	21(1)
C(41)	4792(1)	2026(2)	6324(1)	22(1)
O(2)	4965(1)	2909(1)	5770(1)	28(1)
C(42)	4201(1)	1589(2)	6339(1)	26(1)
C(43)	4213(1)	537(2)	7154(1)	24(1)
C(44)	3815(1)	-248(2)	7551(1)	29(1)
C(45)	3956(1)	-1161(2)	8316(1)	32(1)
C(46)	4484(1)	-1262(2)	8682(1)	30(1)
C(47)	4889(1)	-461(2)	8281(1)	25(1)
C(48)	4748(1)	427(2)	7512(1)	21(1)

Bond lengths [≈] and angles [∞] for 13'

Cu(1)-N(1)	2.0448(19)
Cu(1)-N(3)	2.052(2)
Cu(1)-N(3A)	2.106(7)
Cu(1)-N(4)	2.111(2)
Cu(1)-N(2)	2.1359(17)
Cu(1)-N(4A)	2.141(6)
N(1)-C(1)	1.467(2)
N(1)-C(11)	1.486(2)
N(2)-C(2)	1.461(2)
N(2)-C(16)	1.462(2)
C(11)-C(12)	1.529(3)
C(11)-C(16)	1.529(2)
C(12)-C(13)	1.520(3)
C(13)-C(14)	1.522(3)
C(14)-C(15)	1.518(3)
C(15)-C(16)	1.524(2)
N(3)-C(21)	1.481(3)
N(3)-C(3)	1.483(4)
N(4)-C(4)	1.469(4)
N(4)-C(26)	1.474(3)
C(21)-C(22)	1.536(3)
C(21)-C(26)	1.545(4)
C(22)-C(23)	1.521(4)
C(23)-C(24)	1.524(4)
C(24)-C(25)	1.515(4)
C(25)-C(26)	1.538(3)
N(3A)-C(3A)	1.469(10)
N(3A)-C(21A)	1.471(10)
N(4A)-C(26A)	1.467(9)
N(4A)-C(4A)	1.496(10)
C(21A)-C(26A)	1.536(11)
C(21A)-C(22A)	1.544(10)
C(22A)-C(23A)	1.520(12)
C(23A)-C(24A)	1.503(10)
C(24A)-C(25A)	1.510(10)
C(25A)-C(26A)	1.544(11)
Cu(2)-N(5)	1.8547(18)
Cu(2)-N(6)	1.8557(18)
N(5)-C(31)	1.359(2)
N(5)-C(38)	1.402(2)
C(31)-O(1)	1.235(2)
C(31)-C(32)	1.534(2)
C(32)-C(33)	1.501(3)
C(33)-C(34)	1.378(2)

C(33)-C(38)	1.401(2)
C(34)-C(35)	1.389(3)
C(35)-C(36)	1.381(3)
C(36)-C(37)	1.397(3)
C(37)-C(38)	1.387(2)
N(6)-C(41)	1.365(2)
N(6)-C(48)	1.401(2)
C(41)-O(2)	1.2295(19)
C(41)-C(42)	1.529(2)
C(42)-C(43)	1.508(2)
C(43)-C(44)	1.381(2)
C(43)-C(48)	1.397(2)
C(44)-C(45)	1.397(3)
C(45)-C(46)	1.385(3)
C(46)-C(47)	1.406(2)
C(47)-C(48)	1.390(2)

N(1)-Cu(1)-N(3)	131.77(7)
N(1)-Cu(1)-N(3A)	140.7(2)
N(3)-Cu(1)-N(3A)	18.24(19)
N(1)-Cu(1)-N(4)	127.36(7)
N(3)-Cu(1)-N(4)	85.47(9)
N(3A)-Cu(1)-N(4)	87.11(19)
N(1)-Cu(1)-N(2)	84.41(7)
N(3)-Cu(1)-N(2)	124.55(8)
N(3A)-Cu(1)-N(2)	106.5(2)
N(4)-Cu(1)-N(2)	104.62(8)
N(1)-Cu(1)-N(4A)	121.85(17)
N(3)-Cu(1)-N(4A)	75.17(17)
N(3A)-Cu(1)-N(4A)	82.8(2)
N(4)-Cu(1)-N(4A)	20.91(18)
N(2)-Cu(1)-N(4A)	125.5(2)
C(1)-N(1)-C(11)	111.56(13)
C(1)-N(1)-Cu(1)	113.88(12)
C(11)-N(1)-Cu(1)	108.85(11)
C(2)-N(2)-C(16)	115.08(12)
C(2)-N(2)-Cu(1)	113.00(10)
C(16)-N(2)-Cu(1)	104.49(9)
N(1)-C(11)-C(12)	112.71(13)
N(1)-C(11)-C(16)	110.62(13)
C(12)-C(11)-C(16)	111.25(13)
C(13)-C(12)-C(11)	111.55(15)
C(12)-C(13)-C(14)	110.60(15)
C(15)-C(14)-C(13)	111.32(15)
C(14)-C(15)-C(16)	112.71(14)
N(2)-C(16)-C(15)	114.66(13)

N(2)-C(16)-C(11)	108.63(12)
C(15)-C(16)-C(11)	110.50(13)
C(21)-N(3)-C(3)	112.9(2)
C(21)-N(3)-Cu(1)	106.86(15)
C(3)-N(3)-Cu(1)	115.4(2)
C(4)-N(4)-C(26)	112.9(2)
C(4)-N(4)-Cu(1)	113.8(2)
C(26)-N(4)-Cu(1)	105.07(15)
N(3)-C(21)-C(22)	112.6(2)
N(3)-C(21)-C(26)	108.4(2)
C(22)-C(21)-C(26)	111.9(2)
C(23)-C(22)-C(21)	112.5(2)
C(22)-C(23)-C(24)	111.3(3)
C(25)-C(24)-C(23)	110.1(2)
C(24)-C(25)-C(26)	112.5(2)
N(4)-C(26)-C(25)	113.9(2)
N(4)-C(26)-C(21)	108.9(2)
C(25)-C(26)-C(21)	108.9(2)
C(3A)-N(3A)-C(21A)	112.5(8)
C(3A)-N(3A)-Cu(1)	117.7(7)
C(21A)-N(3A)-Cu(1)	108.0(5)
C(26A)-N(4A)-C(4A)	110.5(7)
C(26A)-N(4A)-Cu(1)	106.3(5)
C(4A)-N(4A)-Cu(1)	109.7(7)
N(3A)-C(21A)-C(26A)	109.3(7)
N(3A)-C(21A)-C(22A)	113.7(7)
C(26A)-C(21A)-C(22A)	110.9(7)
C(23A)-C(22A)-C(21A)	111.1(8)
C(24A)-C(23A)-C(22A)	112.7(9)
C(23A)-C(24A)-C(25A)	108.5(9)
C(24A)-C(25A)-C(26A)	112.0(7)
N(4A)-C(26A)-C(21A)	108.0(7)
N(4A)-C(26A)-C(25A)	114.0(7)
C(21A)-C(26A)-C(25A)	111.9(7)
N(5)-Cu(2)-N(6)	176.29(6)
C(31)-N(5)-C(38)	108.67(14)
C(31)-N(5)-Cu(2)	123.32(11)
C(38)-N(5)-Cu(2)	127.23(10)
O(1)-C(31)-N(5)	126.05(16)
O(1)-C(31)-C(32)	124.28(14)
N(5)-C(31)-C(32)	109.66(14)
C(33)-C(32)-C(31)	102.73(12)
C(34)-C(33)-C(38)	120.49(16)
C(34)-C(33)-C(32)	132.95(14)
C(38)-C(33)-C(32)	106.55(13)
C(33)-C(34)-C(35)	119.16(17)

C(36)-C(35)-C(34)	120.58(16)
C(35)-C(36)-C(37)	120.80(17)
C(38)-C(37)-C(36)	118.51(17)
C(37)-C(38)-C(33)	120.41(14)
C(37)-C(38)-N(5)	127.20(14)
C(33)-C(38)-N(5)	112.38(13)
C(41)-N(6)-C(48)	108.58(13)
C(41)-N(6)-Cu(2)	122.22(10)
C(48)-N(6)-Cu(2)	129.19(11)
O(2)-C(41)-N(6)	125.60(15)
O(2)-C(41)-C(42)	124.57(14)
N(6)-C(41)-C(42)	109.83(13)
C(43)-C(42)-C(41)	102.41(13)
C(44)-C(43)-C(48)	120.78(15)
C(44)-C(43)-C(42)	132.45(16)
C(48)-C(43)-C(42)	106.77(14)
C(43)-C(44)-C(45)	118.94(16)
C(46)-C(45)-C(44)	120.70(15)
C(45)-C(46)-C(47)	120.44(16)
C(48)-C(47)-C(46)	118.58(16)
C(47)-C(48)-C(43)	120.55(14)
C(47)-C(48)-N(6)	127.06(15)
C(43)-C(48)-N(6)	112.39(14)

Symmetry transformations used to generate equivalent atoms:

Anisotropic displacement parameters ($\approx^2$x 10^3) for 13'. The anisotropic displacement factor exponent takes the form: $-2p^2[\ h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Cu(1)	22(1)	24(1)	28(1)	3(1)	5(1)	-1(1)
N(1)	32(1)	22(1)	22(1)	1(1)	2(1)	3(1)
C(1)	60(1)	31(1)	26(1)	8(1)	7(1)	7(1)
N(2)	25(1)	24(1)	23(1)	-2(1)	0(1)	1(1)
C(2)	29(1)	30(1)	22(1)	-1(1)	0(1)	5(1)
C(11)	25(1)	21(1)	21(1)	-4(1)	-1(1)	2(1)
C(12)	30(1)	35(1)	31(1)	-3(1)	-6(1)	0(1)
C(13)	24(1)	37(1)	44(1)	-5(1)	-3(1)	3(1)
C(14)	25(1)	43(1)	38(1)	-7(1)	5(1)	-4(1)
C(15)	25(1)	35(1)	27(1)	-4(1)	5(1)	-2(1)
C(16)	22(1)	21(1)	20(1)	-1(1)	1(1)	1(1)
N(3)	23(1)	20(1)	22(1)	-4(1)	2(1)	-2(1)
C(3)	31(1)	22(1)	37(2)	1(1)	-2(2)	-2(1)
N(4)	33(1)	22(1)	45(1)	-9(1)	12(1)	-3(1)

C(4)	47(2)	19(1)	78(3)	4(1)	17(2)	-6(1)
C(21)	22(1)	30(1)	20(1)	-6(1)	2(1)	-6(1)
C(22)	26(1)	33(1)	32(1)	0(1)	1(1)	1(1)
C(23)	22(1)	54(2)	33(1)	-5(2)	0(1)	-7(1)
C(24)	31(1)	44(2)	43(1)	-10(1)	11(1)	-15(1)
C(25)	31(1)	35(1)	43(1)	-12(1)	11(1)	-14(1)
C(26)	29(1)	24(1)	29(2)	-8(1)	7(1)	-8(1)
N(3A)	24(3)	23(3)	12(3)	2(3)	7(3)	-3(2)
C(3A)	20(5)	18(3)	15(5)	10(3)	-1(4)	4(3)
N(4A)	17(2)	8(2)	24(3)	-2(2)	7(2)	3(2)
C(4A)	30(6)	12(3)	44(6)	-4(4)	3(5)	8(3)
C(21A)	25(3)	15(2)	9(4)	9(3)	4(3)	5(2)
C(22A)	25(3)	19(3)	17(3)	8(3)	-2(3)	3(2)
C(23A)	24(3)	18(3)	33(5)	-2(4)	-1(4)	3(3)
C(24A)	19(3)	21(3)	34(4)	-4(3)	-3(3)	3(2)
C(25A)	20(3)	17(3)	27(4)	-4(3)	3(3)	4(2)
C(26A)	16(2)	16(2)	9(4)	-2(3)	1(2)	3(2)
Cu(2)	16(1)	20(1)	24(1)	1(1)	-1(1)	-2(1)
N(5)	19(1)	21(1)	21(1)	0(1)	-1(1)	-2(1)
C(31)	22(1)	26(1)	26(1)	5(1)	0(1)	-4(1)
O(1)	30(1)	24(1)	57(1)	9(1)	-1(1)	-1(1)
C(32)	21(1)	34(1)	36(1)	12(1)	4(1)	-3(1)
C(33)	20(1)	30(1)	20(1)	2(1)	0(1)	-1(1)
C(34)	22(1)	45(1)	33(1)	7(1)	2(1)	6(1)
C(35)	39(1)	38(1)	33(1)	0(1)	-3(1)	18(1)
C(36)	41(1)	23(1)	36(1)	0(1)	-11(1)	1(1)
C(37)	27(1)	24(1)	32(1)	0(1)	-9(1)	-3(1)
C(38)	20(1)	23(1)	16(1)	-2(1)	-3(1)	0(1)
N(6)	18(1)	18(1)	26(1)	3(1)	-3(1)	-2(1)
C(41)	20(1)	17(1)	29(1)	1(1)	-3(1)	0(1)
O(2)	29(1)	24(1)	31(1)	7(1)	-2(1)	-5(1)
C(42)	19(1)	25(1)	34(1)	4(1)	-5(1)	0(1)
C(43)	22(1)	20(1)	29(1)	-1(1)	1(1)	0(1)
C(44)	21(1)	26(1)	41(1)	-2(1)	7(1)	-2(1)
C(45)	33(1)	26(1)	41(1)	0(1)	19(1)	-2(1)
C(46)	42(1)	21(1)	26(1)	1(1)	10(1)	4(1)
C(47)	26(1)	22(1)	26(1)	0(1)	1(1)	3(1)
C(48)	21(1)	15(1)	27(1)	-3(1)	2(1)	0(1)

Hydrogen coordinates (x 10^4) and isotropic displacement parameters (≈^{2}x 10^3) for 13'

	x	y	z	U(eq)
H(1)	4909(8)	2478(18)	8709(12)	30

H(1A)	4601	4550	7858	58
H(1B)	5225	4277	7757	58
H(1C)	5042	5588	8422	58
H(2)	5237(8)	4723(16)	10933(12)	28
H(2A)	5273	3039	12162	40
H(2B)	5855	3314	11825	40
H(2C)	5532	1783	11543	40
H(11)	4544	4905	9642	27
H(12A)	3913	3725	8582	39
H(12B)	4020	2107	9074	39
H(13A)	3235	3169	9569	42
H(13B)	3549	4705	9882	42
H(14A)	3468	3195	11184	42
H(14B)	3731	1761	10714	42
H(15A)	4384	2883	11741	34
H(15B)	4279	4522	11274	34
H(16)	4743	1952	10435	25
H(3)	6383(10)	1750(30)	9053(12)	26
H(3A)	6597	-236	9981	45
H(3B)	5960	-40	9903	45
H(3C)	6317	607	10779	45
H(4)	6355(11)	5290(30)	10447(12)	39
H(4A)	6435	7277	9427	71
H(4B)	5814	6930	9512	71
H(4C)	6101	6264	8667	71
H(21)	6840	2867	10671	29
H(22A)	7386	993	10098	36
H(22B)	7345	1791	9113	36
H(23A)	8175	2423	9867	44
H(23B)	7899	3012	10745	44
H(24A)	8127	5150	9890	47
H(24B)	7802	4476	8987	47
H(25A)	7283	6353	9653	43
H(25B)	7325	5421	10595	43
H(26)	6774	4344	8910	32
H(3AN)	6380	1872	10710	23
H(3A1)	6251	78	9192	27
H(3A2)	5903	-119	10045	27
H(3A3)	6536	-404	10170	27
H(4AN)	6403	4795	8772	19
H(4A1)	6522	6660	10217	43
H(4A2)	5902	6503	9857	43
H(4A3)	6323	7124	9188	43
H(21A)	6827	2213	9102	19
H(22C)	7343	1782	10916	25
H(22D)	7352	592	10088	25

H(23C)	8167	1973	10275	30
H(23D)	7865	2288	9285	30
H(24C)	8195	4596	9937	30
H(24D)	7857	4333	10802	30
H(25C)	7400	4736	8957	25
H(25D)	7381	5986	9750	25
H(26A)	6824	4401	10554	17
H(32A)	7586	2704	6550	36
H(32B)	7667	3069	7631	36
H(34)	8235	57	7421	40
H(35)	8032	-2503	7702	44
H(36)	7151	-3260	7801	41
H(37)	6453	-1454	7679	34
H(42A)	3976	2499	6422	31
H(42B)	4066	1055	5769	31
H(44)	3452	-168	7307	35
H(45)	3687	-1718	8588	39
H(46)	4573	-1876	9207	35
H(47)	5252	-526	8530	30

Hydrogen bonds for 13' [≈ and ∞]

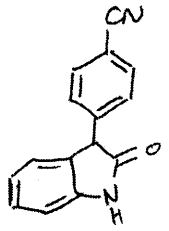
D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(2)-H(2)...O(2)#1	0.964(14)	2.187(15)	3.109(3)	159.6(16)
N(3)-H(3)...N(5)	0.892(16)	2.650(17)	3.535(3)	171(2)
N(4)-H(4)...O(1)#1	0.891(16)	2.380(17)	3.261(3)	170(2)

Symmetry transformations used to generate equivalent atoms:
#1 x,-y+1,z+1/2

RAAVI279

exp9 std1h

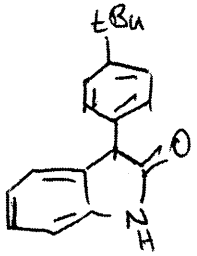
SAMPLE		DEC. & VT	
date	May 7 2007	dfrq	300.100
solvent	CDCl3	dn	H1
file	exp	dpwr	30
ACQUISITION		dof	0
sfrq	300.101	dm	nnn
tn	H1	dmm	c
at	4.003	dmf	200
np	48052	PROCESSING	
sw	6002.4	wtfile	
fb	not used	proc	ft
bs	4	fn	131072
tpwr	54		
pw	8.0	werr	
d1	0.050	wexp	
tof	867.7	wbs	
nt	16	wnt	
ct	16		
alock	n		
gain	not used		
FLAGS			
fl	n		
in	n		
dp	y		
DISPLAY			
sp	-13.4		
wp	3076.0		
vs	151		
sc	0		
wc	250		
hzmm	12.30		
is	500.00		
rfl	2778.8		
rfp	2181.7		
th	20		
ins	1.000		
nm	ph		

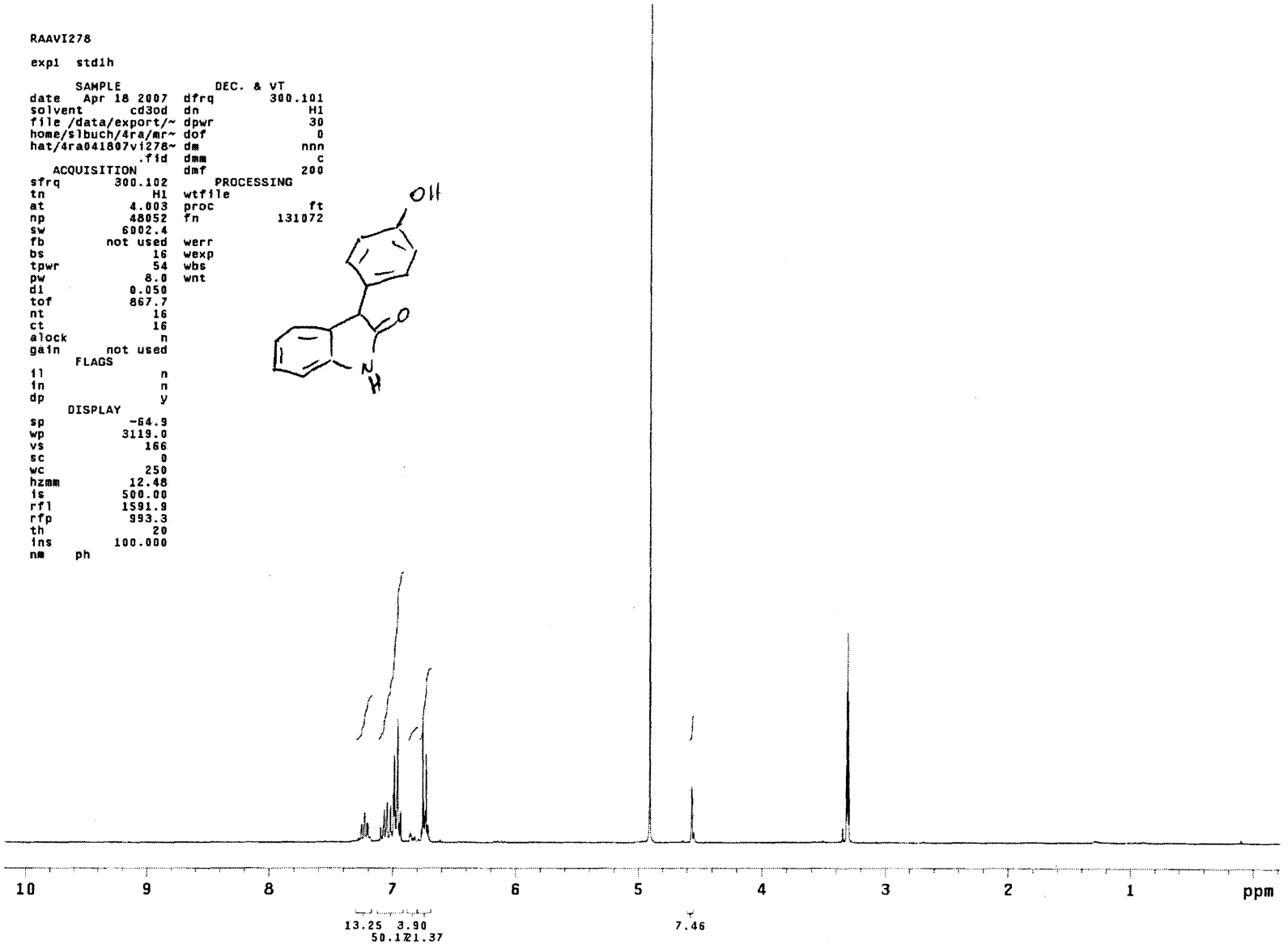


RAAVI280

exp3 s2pul

SAMPLE		DEC. & VT	
date	Apr 13 2007	dfrq	125.672
solvent	CDCl3	dn	C13
file	exp	dpwr	30
ACQUISITION		dof	0
sfrq	499.746	dm	nnn
tn	H1	dmm	w
at	3.001	dmf	10000
np	63050	dseq	
sw	10504.2	dres	1.0
fb	not used	homo	n
bs	8	DEC2	
tpwr	56	dfrq2	0
pw	8.6	dn2	
d1	2.000	dpwr2	1
tof	1519.5	dof2	0
nt	16	dm2	n
ct	16	dmm2	c
alock	n	dmf2	200
gain	not used	dseq2	
FLAGS		dres2	1.0
il	n	homo2	n
in	n	DEC3	
dp	y	dfrq3	0
hs	nn	dn3	
DISPLAY		dpwr3	1
sp	-198.1	dof3	0
wp	5314.1	dm3	n
vs	14	dmm3	c
sc	0	dmf3	200
wc	250	dseq3	
hzmm	21.26	dres3	1.0
is	33.57	homo3	n
rfl	4866.5	PROCESSING	
rfp	3633.1	wtfile	
th	7	proc	ft
ins	1.000	fn	262144
ai cdc ph		math	f
		werr	
		wexp	
		wbs	
		wnt	wft




RAAVI278
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SAMPLE
date Apr 18 2007
solvent cd3od
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hat/4ra041807vi278~
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ACQUISITION
sfrq 300.102
tn H1
at 4.003
np 48052
sw 6002.4
fb not used
bs 16
tpwr 54
pw 8.0
dl 0.050
tof 867.7
nt 16
ct 16
alock n
gain not used
FLAGS
il n
in n
dp y
DISPLAY
sp -64.9
wp 3119.0
vs 166
sc 0
wc 250
hzmm 12.48
is 500.00
rfl 1591.9
rfp 993.3
th 20
ins 100.000
nm ph
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dfrq 300.101
dn H1
dpwr 30
dof 0
dm nnn
dmm c
dmf 200
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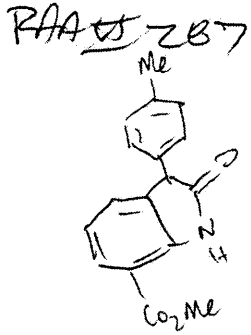
wnt
OH
O
N
H
10
9
8
7
6
5
4
3
2
1
ppm
13.25
3.90
50.12
21.37
7.46

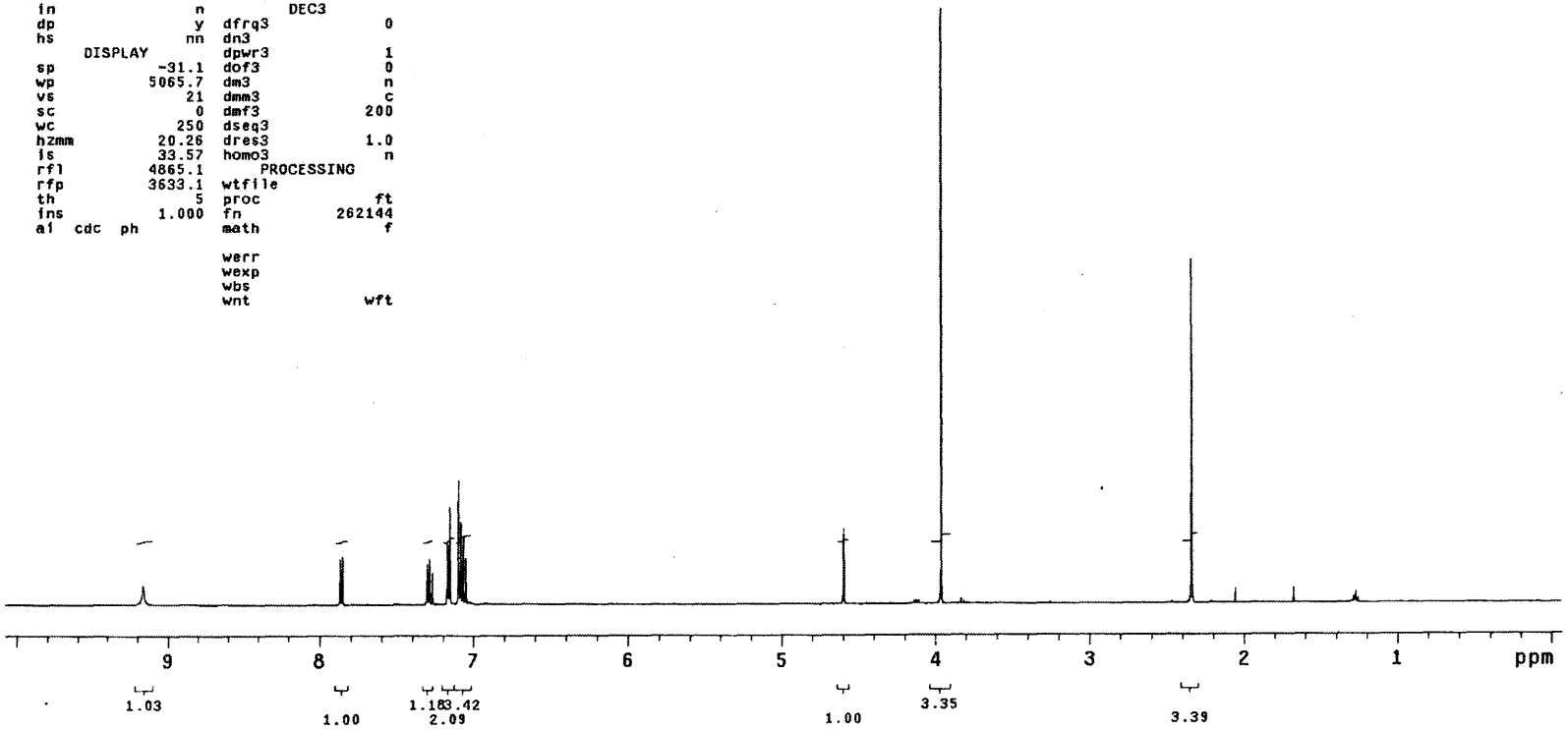
STANDARD PROTON PARAMETERS

exp3 s2pul

SAMPLE		DEC. & VT	
date	Apr 6 2007	dfrq	125.672
solvent	CDCl3	dn	C13
file	exp	dpwr	30
ACQUISITION		dof	0
sfrq	499.746	dm	nnn
tn	H1	dmm	w
at	3.001	dmf	10000
np	63050	dseq	
sw	10504.2	dres	1.0
fb	not used	homo	n
bs	8	DEC2	
tpwr	56	dfrq2	0
pw	8.6	dn2	
d1	2.000	dpwr2	1
tof	1519.5	dof2	0
nt	16	dm2	n
ct	16	dmm2	c
alock	n	dmf2	200
gain	not used	dseq2	
FLAGS		dres2	1.0
il	n	homo2	n
in	n	DEC3	
dp	y	dfrq3	0
hs	nn	dn3	
DISPLAY		dpwr3	1
sp	-31.1	dof3	0
wp	5065.7	dm3	n
vs	21	dmm3	c
sc	0	dmf3	200
wc	250	dseq3	
hzmm	20.26	dres3	1.0
is	33.57	homo3	n
rfl	4865.1	PROCESSING	
rfp	3633.1	wtfile	
th	5	proc	ft
ins	1.000	fn	262144
ai cdc ph		math	f
		werr	
		wexp	
		wbs	
		wnt	wft

RAA-II-287

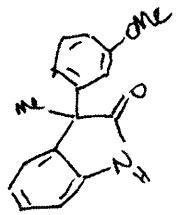


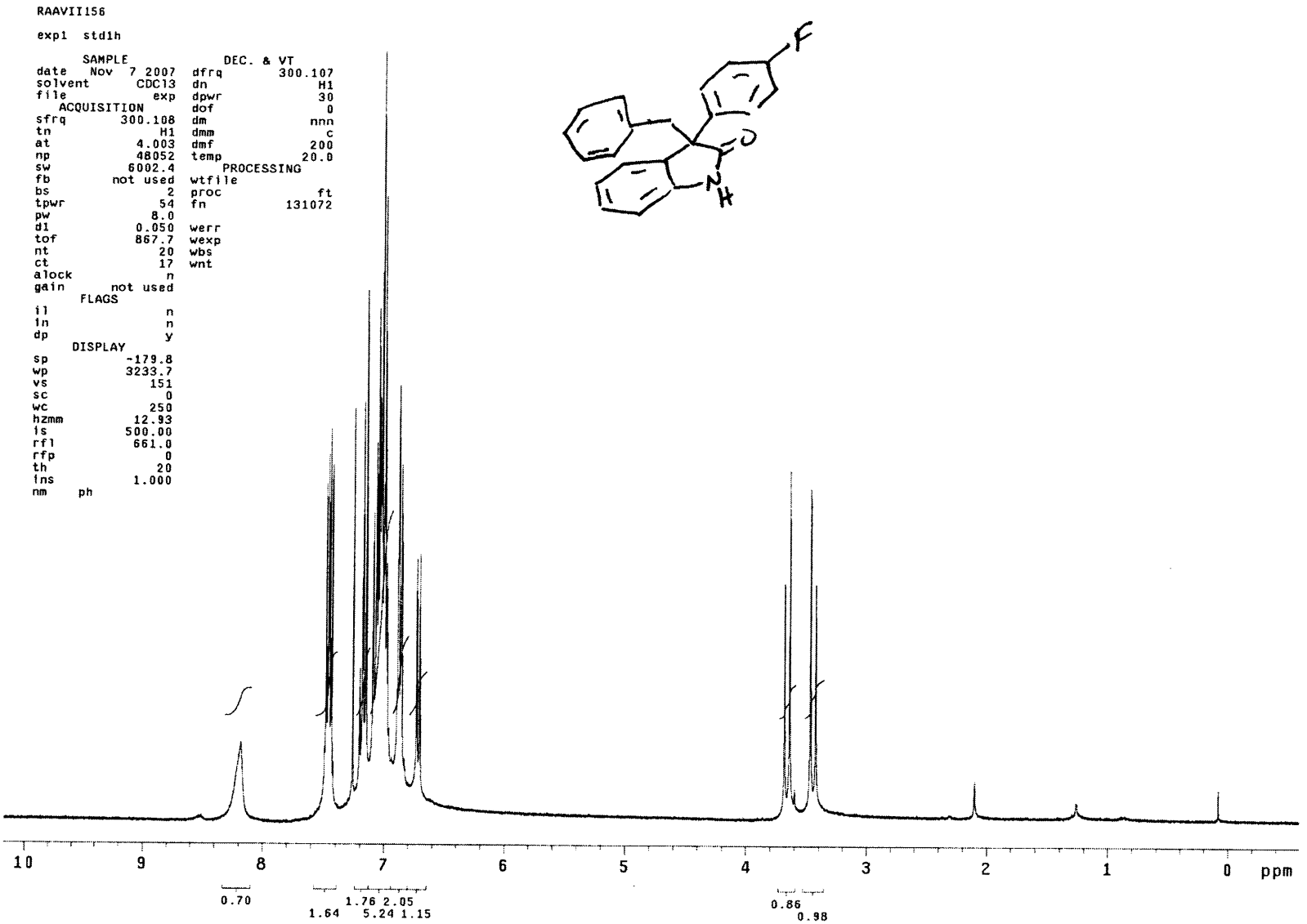


RAAVII86d

exp3 s2pul

SAMPLE		DEC. & VT	
date	Jul 26 2007	dfrq	125.795
solvent	CDCl3	dn	C13
file	exp	dpwr	44
ACQUISITION		dof	0
sfrq	500.235	dm	nnn
tn	H1	dmm	c
at	3.200	dmf	10000
np	64000	dseq	
sw	10000.0	dres	1.0
fb	not used	homo	n
bs	1	PROCESSING	
ss	1	wtfile	
tpwr	63	proc	ft
pw	9.0	fn	131072
dl	0	math	f
tof	1498.2		
nt	16	werr	
ct	0	wexp	
alock	n	wbs	
gain	not used	wnt	
FLAGS			
il	n		
in	n		
dp	y		
hs	nn		
DISPLAY			
sp	-225.5		
wp	5466.4		
vs	151		
sc	0		
wc	250		
hzmm	21.87		
is	342.18		
rfl	4622.3		
rfp	3621.7		
th	7		
ins	3.000		
nm	ph		




RAAVII156
exp1 std1h
SAMPLE
date Nov 7 2007
solvent CDCl3
file exp
ACQUISITION
sfrq 300.108
tn H1
at 4.003
np 48052
sw 6002.4
fb not used
bs 2
tpwr 54
pw 8.0
d1 0.050
tof 867.7
nt 20
ct 17
alock n
gain not used
FLAGS
il n
in n
dp y
DISPLAY
sp -179.8
wp 3233.7
vs 151
sc 0
wc 250
hzmm 12.93
is 500.00
rfl 661.0
rfp 0
th 20
ins 1.000
nm ph
DEC. & VT
dfrq 300.107
dn H1
dpwr 30
dof 0
dm nnn
dmm c
dmf 200
temp 20.0
PROCESSING
wtfile
proc ft
fn 131072
werr
wexp
wbs
wnt
F
O
N
H
10
9
8
7
6
5
4
3
2
1
0
ppm
0.70
1.64
1.76
5.24
2.05
1.15
0.86
0.98

STANDARD PROTON PARAMETERS

expl s2pul

SAMPLE		DEC. & VT	
date	Jan 30 2007	dfrq	125.795
solvent	CDCl3	dn	C13
file	exp	dpwr	38
ACQUISITION		dof	0
sfrq	500.235	dm	nnn
tn	H1	dmm	c
at	3.200	dmf	10060
np	64000	dseq	
sw	10000.0	dres	1.0
fb	not used	homo	n
bs	8	PROCESSING	
ss	1	wtfile	
tpwr	59	proc	ft
pw	9.8	fn	131072
dl	0	math	f
tof	1498.2		
nt	16	werr	
ct	16	wexp	
alock	n	wbs	
gain	not used	wnt	
FLAGS			
il	n		
in	n		
dp	y		
hs	nn		
DISPLAY			
sp	-113.5		
wp	5216.8		
vs	151		
sc	0		
wc	250		
hzmm	20.87		
is	834.47		
rfl	4630.5		
rfp	3636.7		
th	7		
ins	3.000		
nm	ph		

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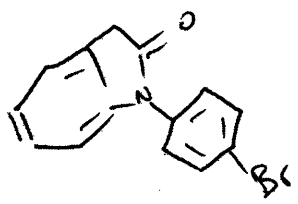
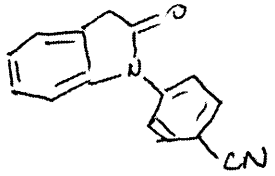
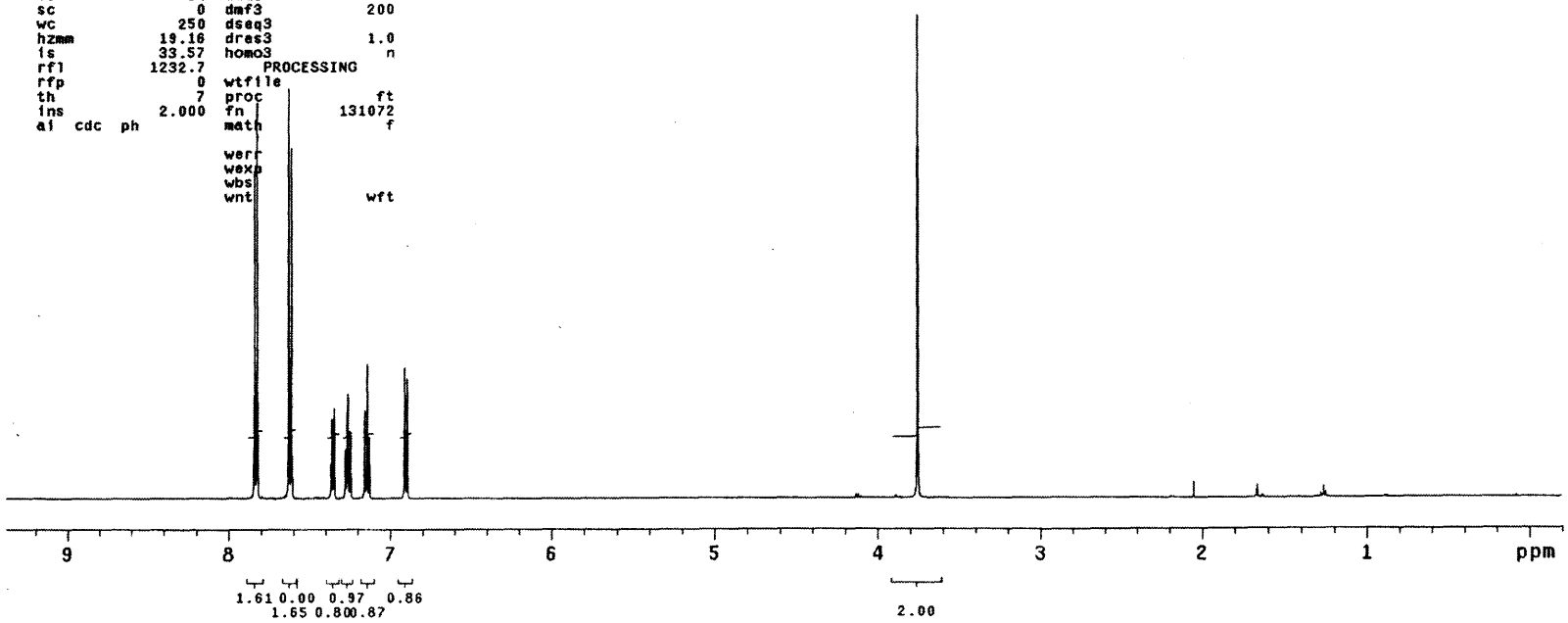


RAAVI245

exp1 s2pul

SAMPLE		DEC. & VT	
date	Feb 25 2007	dfrq	125.672
solvent	CDCl3	dn	C13
file	exp	dpwr	30
ACQUISITION		dof	0
sfrq	499.746	dm	nnn
tn	H1	dmm	w
at	3.001	dmf	10000
np	63050	dseq	
sw	10504.2	dres	1.0
fb	not used	homo	n
bs	8	DEC2	
tpwr	56	dfrq2	0
pw	8.9	dn2	
d1	2.000	dpwr2	1
tof	1519.5	dof2	0
nt	16	dm2	n
ct	16	dmm2	c
alock	n	dmf2	200
gain	not used	dseq2	
FLAGS		dres2	1.0
il	n	homo2	n
in	n	DEC3	
dp	y	dfrq3	0
hs	nn	dn3	
DISPLAY		dpwr3	1
sp	-100.8	dof3	0
wp	4789.5	dm3	n
vs	34	dmm3	c
sc	0	dmf3	200
wc	250	dseq3	
hzmm	19.16	dres3	1.0
is	33.57	homo3	n
rfl	1232.7	PROCESSING	
rfp	0	wtfile	
th	7	proc	ft
ins	2.000	fn	131072
ai cdc ph		math	f
		werr	
		wexp	
		wbs	
		wnt	wft

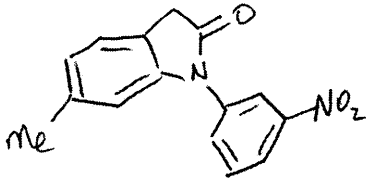


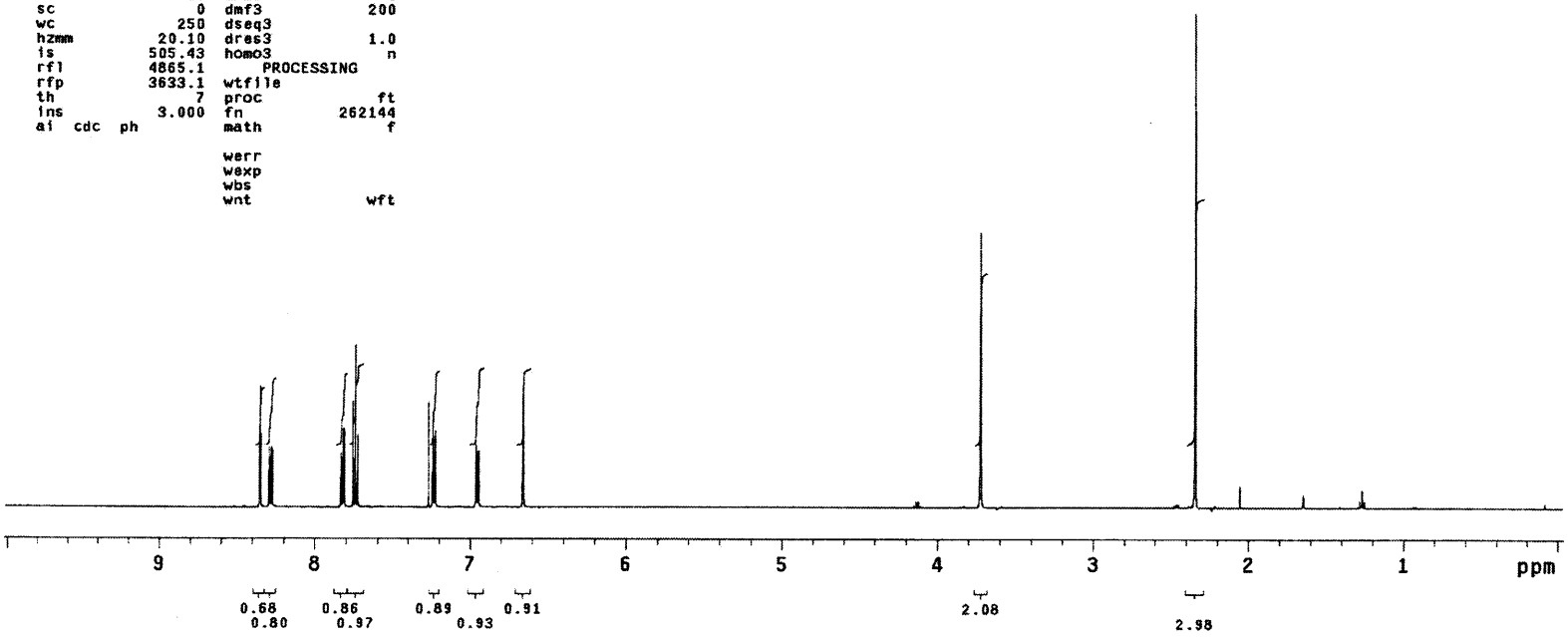


RAAVI283

exp2 s2pul

SAMPLE		DEC. & VT	
date	May 9 2007	dfrq	125.672
solvent	CDCl3	dn	C13
file	exp	dpwr	30
ACQUISITION		dof	0
sfrq	499.746	dm	nnn
tn	H1	dmm	w
at	3.001	dmf	10000
np	63050	dseq	
sw	10504.2	dres	1.0
fb	not used	homo	n
bs	2	DEC2	
tpwr	56	dfrq2	0
pw	8.6	dn2	
d1	2.000	dpwr2	1
tof	1519.5	dof2	0
nt	16	dm2	n
ct	16	dmm2	c
alock	n	dmf2	200
gain	not used	dseq2	
FLAGS		dres2	1.0
fl	n	homo2	n
in	n	DEC3	
dp	y	dfrq3	0
hs	nn	dn3	
DISPLAY		dpwr3	1
sp	-17.3	dof3	0
wp	5024.3	dm3	n
vs	16	dmm3	c
sc	0	dmf3	200
wc	250	dseq3	
hzmm	20.10	dres3	1.0
is	505.43	homo3	n
rfl	4865.1	PROCESSING	
rfp	3633.1	wtfile	
th	7	proc	ft
ins	3.000	fn	262144
ai cdc ph		math	f
		werr	
		wexp	
		wbs	
		wnt	wft



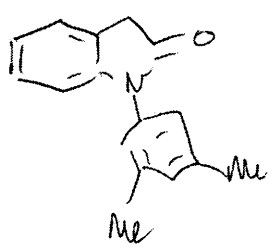


RAA VI 273

STANDARD PROTON PARAMETERS

exp3 s2pul

SAMPLE		DEC. & VT	
date	Apr 6 2007	dfrq	125.672
solvent	CDCl3	dn	C13
file	exp	dpwr	30
ACQUISITION		dof	0
sfrq	499.746	dm	nnn
tn	H1	dmm	w
at	3.001	dmf	10000
np	63050	dseq	
sw	10504.2	dres	1.0
fb	not used	homo	n
bs	8	DEC2	
tpwr	56	dfrq2	0
pw	8.6	dn2	
d1	2.000	dpwr2	1
tof	1519.5	dof2	0
nt	16	dm2	n
ct	16	dmm2	c
alock	n	dmf2	200
gain	not used	dseq2	
FLAGS		dres2	1.0
il	n	homo2	n
in	n	DEC3	
dp	y	dfrq3	0
hs	nn	dn3	
DISPLAY		dpwr3	1
sp	-362.7	dof3	0
wp	4582.6	dm3	n
vs	15	dmm3	c
sc	0	dmf3	200
wc	250	dseq3	
hzmm	18.33	dres3	1.0
is	33.57	homo3	n
rfl	4865.3	PROCESSING	
rfp	3633.1	wtfile	
th	7	proc	ft
ins	2.000	fn	262144
ai cdc ph		math	f
		werr	
		wexp	
		wbs	
		wnt	wft



Cartesian Coordinates for Complexes 1-16 and Transition States 1-TS-4-TS

Complex 1

C -0.610381 2.338797 -0.191842
C -1.205948 2.173304 -1.477423
C -2.574743 1.904434 -1.550257
C -3.386951 1.813495 -0.415244
C -2.787394 1.984173 0.833708
C -1.419580 2.251393 0.973850
C 0.778703 2.925792 -0.108323
C 1.989253 2.196228 -0.047975
C 3.206258 2.903506 -0.093313
C 3.249588 4.294298 -0.153380
C 2.057475 5.015976 -0.160884
C 0.845291 4.331700 -0.145143
H -3.027399 1.757751 -2.526400
H -3.398691 1.922058 1.728481
H 4.146157 2.363585 -0.088523
H 4.207648 4.805495 -0.189126
H 2.068373 6.101993 -0.194242
H -0.085748 4.889936 -0.177700
P 1.982067 0.351523 0.189316
Pd -0.183536 -0.557184 -0.208372
C 3.466187 -0.214449 -0.818764
C 3.882280 -1.679336 -0.559450
C 3.210341 0.027788 -2.323464
H 4.310491 0.418067 -0.511301
C 5.106369 -2.058700 -1.411597
H 3.053062 -2.349674 -0.800105
H 4.114372 -1.830262 0.500536
C 4.426851 -0.376409 -3.173576
H 2.336742 -0.557323 -2.636153
H 2.967539 1.081736 -2.503261
C 4.846185 -1.828741 -2.906637
H 5.365603 -3.108490 -1.225924
H 5.974855 -1.460368 -1.096107
H 4.193451 -0.232747 -4.236098
H 5.269278 0.293965 -2.945285
H 5.739004 -2.081327 -3.492711
H 4.045629 -2.504692 -3.238932
C 2.462274 0.227157 2.024295
C 2.047231 -1.118817 2.653706
C 3.925124 0.573978 2.371929
H 1.826197 1.002331 2.475742
C 2.291677 -1.129153 4.172015

H 2.607017 -1.940827 2.189786
H 0.989612 -1.307148 2.441660
C 4.157106 0.553443 3.894720
H 4.602302 -0.150549 1.900543
H 4.189810 1.561922 1.982077
C 3.747590 -0.788446 4.516461
H 2.020125 -2.110675 4.580642
H 1.624532 -0.396417 4.649730
H 5.212104 0.769927 4.106140
H 3.573265 1.362190 4.358201
H 3.887280 -0.761789 5.604439
H 4.406892 -1.582011 4.134628
C 0.429784 -2.419713 -0.653392
C 0.651887 -3.403825 0.313089
C 0.574285 -2.734021 -2.009718
C 1.075770 -4.681553 -0.074733
H 0.488100 -3.199889 1.365274
C 1.000437 -4.012345 -2.388969
H 0.320171 -2.004506 -2.771080
C 1.264229 -4.986488 -1.423265
H 1.249435 -5.438830 0.686628
H 1.109851 -4.245673 -3.445748
H 1.593461 -5.978818 -1.720470
C -0.864503 2.554223 2.366787
C -1.162226 1.442645 3.388891
C -1.382811 3.913391 2.881392
H 0.224515 2.639261 2.284375
H -0.766573 0.479034 3.052480
H -0.705423 1.684384 4.356534
H -2.237636 1.316442 3.554607
H -1.122699 4.726444 2.195117
H -2.473477 3.904014 2.990896
H -0.947998 4.144752 3.861346
C -0.413606 2.389633 -2.769056
C -0.642111 3.816434 -3.314821
C -0.722655 1.356908 -3.867882
H 0.650352 2.299992 -2.525981
H -0.344628 4.586082 -2.595761
H -0.061195 3.969308 -4.232610
H -1.700281 3.971297 -3.557775
H -0.719355 0.335341 -3.482857
H -1.710583 1.524476 -4.312980
H 0.014401 1.450268 -4.675049
C -4.888371 1.607299 -0.583888
C -5.589733 2.966395 -0.794517
C -5.552570 0.827236 0.561455

H -5.024898 1.023457 -1.504616
H -5.164592 3.507121 -1.647298
H -6.661852 2.826119 -0.978549
H -5.478886 3.601033 0.093493
H -5.052892 -0.128821 0.746005
H -5.549151 1.398830 1.497659
H -6.601092 0.622865 0.315151
C -2.774274 -2.076119 0.629983
C -3.885170 -2.775443 0.103900
N -2.079142 -1.379800 -0.363771
C -3.900019 -2.527878 -1.378643
H -3.812871 -3.436719 -1.986182
C -4.717069 -3.508283 0.936370
H -5.571635 -4.044718 0.529091
C -4.443519 -3.558839 2.312718
H -5.087173 -4.132687 2.973735
C -3.343207 -2.871072 2.829433
H -3.135744 -2.913461 3.896319
C -2.500116 -2.122574 1.999010
H -1.648683 -1.585663 2.405929
C -2.647810 -1.647526 -1.586137
O -2.237274 -1.258517 -2.678039
H -4.791087 -1.992393 -1.730842

Complex 2

C 0.939518 -2.357536 -0.263768
C 1.521942 -2.055544 -1.529013
C 2.885006 -1.743613 -1.585645
C 3.700099 -1.720363 -0.450134
C 3.104412 -1.991560 0.785803
C 1.747369 -2.311888 0.906259
C -0.398764 -3.061125 -0.221911
C -1.673581 -2.458445 -0.107273
C -2.814677 -3.282167 -0.163272
C -2.724235 -4.665390 -0.296476
C -1.467870 -5.263235 -0.371995
C -0.328941 -4.463465 -0.338934
H 3.327686 -1.506563 -2.548608
H 3.717208 -1.975394 1.682699
H -3.802186 -2.838297 -0.108484
H -3.628255 -5.266828 -0.337059
H -1.372170 -6.341385 -0.467690
H 0.650660 -4.925903 -0.419149
P -1.842304 -0.627968 0.184285
Pd 0.239060 0.558808 -0.241123

C -3.413186 -0.196759 -0.761122
C -3.940606 1.225355 -0.468311
C -3.184401 -0.394401 -2.276205
H -4.192141 -0.901299 -0.438897
C -5.217771 1.513182 -1.277582
H -3.176177 1.965280 -0.721574
H -4.152967 1.342611 0.600014
C -4.454358 -0.082180 -3.085713
H -2.370700 0.266195 -2.600741
H -2.861133 -1.422002 -2.481077
C -4.988009 1.325072 -2.783408
H -5.556867 2.535428 -1.068162
H -6.023264 0.840453 -0.945032
H -4.241684 -0.190666 -4.156906
H -5.230054 -0.824904 -2.844797
H -5.918058 1.506758 -3.337193
H -4.260121 2.071848 -3.130212
C -2.281166 -0.596244 2.032521
C -1.995974 0.777907 2.676368
C -3.685846 -1.106548 2.414573
H -1.551175 -1.304367 2.451704
C -2.195779 0.736311 4.201059
H -2.657857 1.540059 2.245449
H -0.973362 1.089487 2.437060
C -3.871566 -1.139615 3.943369
H -4.451803 -0.450674 1.979475
H -3.855859 -2.109786 2.009664
C -3.593857 0.228525 4.580126
H -2.022878 1.735102 4.621417
H -1.437769 0.074798 4.646416
H -4.888901 -1.475801 4.181894
H -3.187248 -1.886467 4.372472
H -3.696097 0.168187 5.671086
H -4.349219 0.949622 4.234020
C -0.548234 2.362485 -0.702094
C -0.869848 3.308908 0.277031
C -0.825582 2.647458 -2.045853
C -1.507750 4.503734 -0.078977
H -0.617973 3.133628 1.318111
C -1.460604 3.844789 -2.397177
H -0.527278 1.956261 -2.828587
C -1.813790 4.772599 -1.414323
H -1.757280 5.227060 0.694564
H -1.666560 4.052858 -3.445149
H -2.307317 5.701700 -1.688323
C 1.198425 -2.693696 2.281485

C 1.456094 -1.610322 3.345312
C 1.756901 -4.053929 2.747716
H 0.113292 -2.807940 2.189012
H 1.041714 -0.643798 3.038880
H 0.992596 -1.895522 4.297632
H 2.526822 -1.469870 3.532488
H 1.522033 -4.848111 2.031192
H 2.846583 -4.016428 2.862151
H 1.326622 -4.333814 3.716825
C 0.724223 -2.151932 -2.830637
C 0.948750 -3.515945 -3.518572
C 1.033377 -1.012083 -3.819806
H -0.337482 -2.084523 -2.571122
H 0.649090 -4.353242 -2.880993
H 0.366371 -3.571986 -4.446225
H 2.006201 -3.647586 -3.778178
H 1.057173 -0.031663 -3.336249
H 2.007413 -1.151689 -4.304028
H 0.279265 -1.003609 -4.616256
C 5.194620 -1.451517 -0.582664
C 5.991156 -2.770402 -0.503165
C 5.725445 -0.428982 0.437516
H 5.354215 -1.029938 -1.583911
H 5.654310 -3.484687 -1.262710
H 7.061179 -2.586688 -0.657935
H 5.869808 -3.244084 0.478883
H 5.168898 0.512770 0.390738
H 5.659205 -0.808316 1.464305
H 6.781238 -0.211189 0.238779
C 2.400198 2.490415 0.784108
C 2.606862 3.766556 0.206255
C 2.838377 4.900820 0.976272
H 2.991992 5.873012 0.515153
C 2.879465 4.750544 2.369106
H 3.062029 5.622115 2.992423
C 2.697997 3.497874 2.961499
H 2.744621 3.399928 4.042962
C 2.455729 2.365230 2.170680
H 2.311989 1.393593 2.636606
C 2.360627 2.304465 -1.570696
O 2.372448 1.930381 -2.739502
N 2.562235 3.629333 -1.178972
H 2.662538 4.375267 -1.852110
C 2.145021 1.521699 -0.308319
H 2.710337 0.586737 -0.284587

Complex 3

H 5.791211 1.193580 -0.909510
C 5.527752 -0.895805 -0.497671
C 5.177878 0.453764 -0.402689
H 5.018116 -2.868682 0.149995
C 4.742335 -1.818497 0.195312
C 4.073571 0.887634 0.339266
C 3.625798 -1.442303 0.954207
C 3.266870 -0.070022 1.003513
P -0.015979 0.675735 -0.185884
C 2.117774 0.357177 1.886763
C 0.758910 0.537708 1.505645
H 3.490867 0.415659 3.531155
C 2.449283 0.528244 3.244657
C -0.192678 0.789055 2.519454
H -1.245271 0.880114 2.256551
C 1.501385 0.820095 4.222668
C 0.162440 0.929304 3.858952
H 1.809325 0.941726 5.257736
H -0.607530 1.124600 4.599481
C 1.059150 -0.145915 -1.488712
C 0.842231 -1.673251 -1.479365
C 0.816425 0.404593 -2.911495
H 2.098916 0.065841 -1.217928
C 1.751927 -2.377993 -2.498924
H -0.205705 -1.887248 -1.719715
H 1.009904 -2.078536 -0.477549
C 1.727517 -0.297444 -3.935107
H -0.233831 0.245053 -3.194526
H 1.000698 1.483502 -2.954098
C 1.544436 -1.820438 -3.914004
H 1.550235 -3.456785 -2.482890
H 2.802661 -2.248890 -2.203267
H 1.523062 0.100375 -4.937369
H 2.775490 -0.053248 -3.707446
H 2.237256 -2.296022 -4.619828
H 0.528724 -2.067573 -4.256141
C 0.046822 2.541703 -0.572590
C -1.100284 2.910294 -1.546810
C -0.035276 3.450770 0.672483
H 1.008025 2.731707 -1.069753
C -1.056809 4.395628 -1.944318
H -2.065043 2.708283 -1.051358
H -1.081315 2.285241 -2.443961
C 0.008698 4.939239 0.282486

H -0.969359 3.246862 1.213984
H 0.777275 3.230517 1.370760
C -1.100394 5.307602 -0.712095
H -1.893395 4.618576 -2.618124
H -0.135302 4.589121 -2.513675
H -0.070884 5.553399 1.188267
H 0.988278 5.166968 -0.164170
H -1.011388 6.359515 -1.011209
H -2.078065 5.202056 -0.219958
C 3.815786 2.388566 0.471281
C 3.950926 3.157495 -0.856130
C 4.740901 3.005873 1.541277
H 2.788289 2.522213 0.822179
H 3.352262 2.703055 -1.653619
H 3.615906 4.193409 -0.726574
H 4.989242 3.197355 -1.204613
H 4.595652 2.529180 2.516125
H 5.794472 2.885966 1.261859
H 4.539999 4.078165 1.654817
C 2.885390 -2.517381 1.758052
C 3.595353 -2.776076 3.105826
C 2.723044 -3.858914 1.016624
H 1.880637 -2.142656 1.980013
H 3.647155 -1.874573 3.721940
H 3.060292 -3.544339 3.676983
H 4.619810 -3.130981 2.939939
H 2.311207 -3.733211 0.011824
H 3.676548 -4.392134 0.924063
H 2.043242 -4.508700 1.578990
C 6.733669 -1.352019 -1.308920
C 8.049980 -0.773583 -0.754879
C 6.575625 -1.024926 -2.806227
H 6.789689 -2.445117 -1.215359
H 8.186071 -1.036931 0.299750
H 8.908389 -1.160150 -1.317115
H 8.067988 0.320197 -0.831288
H 5.661846 -1.470191 -3.215401
H 6.524755 0.057604 -2.973662
H 7.428126 -1.410283 -3.378186
Pd -2.333998 0.238590 -0.071139
C -2.233292 -1.728530 0.263691
C -2.702298 -2.597461 -0.725027
C -1.769611 -2.228187 1.481564
C -2.669664 -3.979236 -0.502753
H -3.107236 -2.214781 -1.656477
C -1.747324 -3.612594 1.695005

H -1.435815 -1.559962 2.267766
C -2.188715 -4.490576 0.703979
H -3.033830 -4.651483 -1.276214
H -1.389103 -3.997578 2.647163
H -2.170707 -5.563701 0.875116
N -4.363642 0.283580 0.260172
C -4.749513 0.456590 1.573640
C -5.466131 -0.120510 -0.496708
C -6.265317 0.188794 1.692048
O -4.007492 0.774860 2.500956
C -6.640457 -0.196555 0.286409
C -5.508016 -0.399241 -1.864795
H -6.773716 1.090827 2.055284
H -6.441201 -0.598331 2.435571
C -7.847888 -0.557789 -0.290918
C -6.731680 -0.769533 -2.434893
H -4.609449 -0.318874 -2.471289
C -7.893320 -0.851919 -1.663066
H -8.753145 -0.614450 0.310026
H -6.776654 -0.991843 -3.498511
H -8.833924 -1.139091 -2.124994

Complex 4

H 5.899073 0.721299 -0.868346
C 5.412931 -1.325692 -0.445980
C 5.204762 0.053722 -0.365704
H 4.687366 -3.229602 0.201853
C 4.523621 -2.155889 0.238360
C 4.139910 0.606460 0.354260
C 3.441402 -1.658581 0.977038
C 3.228909 -0.255691 1.013564
P 0.043953 0.835453 -0.207644
C 2.124605 0.297817 1.883723
C 0.796581 0.621397 1.488486
H 3.484371 0.219412 3.538252
C 2.462325 0.439620 3.243610
C -0.129670 0.971320 2.495695
H -1.163479 1.167893 2.218584
C 1.543325 0.834343 4.213140
C 0.225843 1.080439 3.837909
H 1.854279 0.928027 5.250197
H -0.525027 1.357378 4.572164
C 1.029697 -0.122744 -1.490281
C 0.623079 -1.610556 -1.454014
C 0.853436 0.428089 -2.922491

H 2.088446 -0.037562 -1.224902
C 1.433649 -2.441251 -2.462180
H -0.444824 -1.694270 -1.688655
H 0.742255 -2.015772 -0.444571
C 1.667243 -0.399140 -3.934150
H -0.209448 0.394056 -3.202170
H 1.168667 1.475682 -2.983117
C 1.293263 -1.886301 -3.886629
H 1.100060 -3.486351 -2.427629
H 2.493569 -2.437175 -2.170439
H 1.513476 0.003917 -4.943468
H 2.738124 -0.285634 -3.709757
H 1.918125 -2.457656 -4.584938
H 0.253214 -2.008774 -4.222794
C 0.338422 2.675307 -0.611442
C -0.749109 3.161853 -1.600633
C 0.346001 3.602558 0.622722
H 1.319132 2.751974 -1.100899
C -0.536630 4.628622 -2.012534
H -1.734372 3.072563 -1.111052
H -0.792090 2.527362 -2.490313
C 0.566724 5.071347 0.218759
H -0.613206 3.515151 1.152105
H 1.117227 3.298094 1.335885
C -0.483300 5.554524 -0.790507
H -1.337109 4.938365 -2.696166
H 0.404867 4.709464 -2.575922
H 0.551643 5.701961 1.116676
H 1.569901 5.178025 -0.220712
H -0.269824 6.585087 -1.100900
H -1.470568 5.570923 -0.306031
C 4.031357 2.127069 0.464441
C 4.263972 2.858567 -0.870704
C 4.995795 2.666317 1.541771
H 3.015940 2.364418 0.795018
H 3.633317 2.456153 -1.671516
H 4.035912 3.925378 -0.760173
H 5.305962 2.785852 -1.202607
H 4.787423 2.223561 2.521069
H 6.036586 2.436817 1.283591
H 4.902004 3.755209 1.635203
C 2.575744 -2.643910 1.770809
C 3.222455 -2.963934 3.136957
C 2.292018 -3.966897 1.032945
H 1.610160 -2.165509 1.966673
H 3.349283 -2.067661 3.749618

H 2.598135 -3.670093 3.697730
H 4.209428 -3.421927 2.998725
H 1.927077 -3.806477 0.015088
H 3.184659 -4.600828 0.973743
H 1.529327 -4.534440 1.577813
C 6.578415 -1.911950 -1.232607
C 7.937428 -1.498429 -0.635364
C 6.501607 -1.554012 -2.728946
H 6.503619 -3.005023 -1.151958
H 8.011005 -1.786090 0.419138
H 8.760322 -1.978072 -1.178845
H 8.086007 -0.413643 -0.696822
H 5.551754 -1.881293 -3.166343
H 6.586490 -0.471937 -2.884620
H 7.316332 -2.034504 -3.283743
Pd -2.385129 0.619535 -0.133591
C -2.578894 -1.339752 0.254365
C -3.074141 -2.195757 -0.734056
C -2.155452 -1.859078 1.481409
C -3.105353 -3.576894 -0.505955
H -3.452855 -1.800651 -1.671660
C -2.202452 -3.240931 1.704822
H -1.792997 -1.203290 2.266264
C -2.668425 -4.103690 0.710879
H -3.485307 -4.236693 -1.282756
H -1.876130 -3.636960 2.664222
H -2.701611 -5.175838 0.887225
C -4.749135 0.696722 1.569124
C -5.464612 0.106150 -0.607319
O -4.262910 1.237158 2.557964
C -6.164742 -0.669183 0.348336
C -5.785094 -0.033620 -1.955569
C -7.146951 -1.582008 -0.017277
C -6.781823 -0.942043 -2.339360
H -5.263320 0.556885 -2.705931
C -7.447644 -1.710235 -1.380335
H -7.673669 -2.172556 0.727784
H -7.036557 -1.050592 -3.390226
H -8.214900 -2.414869 -1.690412
C -4.471903 0.930593 0.111107
N -5.703952 -0.320564 1.617761
H -6.030297 -0.706848 2.491768
H -4.424527 1.995977 -0.155309

Complex 5

H 2.604766 1.727180 -2.962061
C 2.993218 2.542381 -1.018881
C 2.156225 2.083583 -2.040517
H 3.027436 3.409858 0.934682
C 2.391956 3.027390 0.140295
C 0.762912 2.078138 -1.922289
C 1.002359 3.054623 0.314907
C 0.173928 2.540470 -0.715291
P -1.999714 -0.014169 0.354419
C -1.322222 2.717374 -0.587899
C -2.274651 1.792374 -0.085694
H -1.057093 4.703314 -1.348911
C -1.782374 4.003330 -0.946709
C -3.600991 2.241251 0.103781
H -4.335310 1.574586 0.543616
C -3.101349 4.411188 -0.786706
C -4.020055 3.523470 -0.231963
H -3.400575 5.415180 -1.075048
H -5.051682 3.819287 -0.062516
C -3.445050 -0.787175 -0.601709
C -3.260793 -0.636339 -2.126183
C -3.774406 -2.245534 -0.220020
H -4.317799 -0.184514 -0.317745
C -4.479999 -1.170239 -2.898101
H -2.368713 -1.190284 -2.436957
H -3.097316 0.416536 -2.382074
C -4.991530 -2.763504 -1.009493
H -2.912769 -2.890049 -0.417127
H -3.992733 -2.319276 0.850894
C -4.791327 -2.625264 -2.523893
H -4.296240 -1.080913 -3.976420
H -5.355723 -0.541283 -2.677693
H -5.176413 -3.811047 -0.740171
H -5.888530 -2.200379 -0.709737
H -5.682663 -2.975310 -3.060087
H -3.957252 -3.268201 -2.839204
C -2.572145 -0.113828 2.162163
C -2.122227 -1.436066 2.827774
C -2.085501 1.075272 3.018752
H -3.672884 -0.094560 2.130909
C -2.663190 -1.549103 4.263331
H -1.024668 -1.454891 2.850840
H -2.435266 -2.305392 2.241689
C -2.608717 0.971887 4.462494
H -0.988165 1.082191 3.025626
H -2.411260 2.024422 2.582439

C -2.219687 -0.357865 5.122994
H -2.321152 -2.491572 4.709628
H -3.762486 -1.595875 4.238111
H -2.224984 1.816089 5.049303
H -3.705202 1.068158 4.457607
H -2.655930 -0.426760 6.127747
H -1.128108 -0.392581 5.249104
C -0.081229 1.654082 -3.126832
C 0.610197 0.618365 -4.033140
C -0.487040 2.869427 -3.990489
H -1.001423 1.197961 -2.745107
H 1.078730 -0.184347 -3.457080
H -0.119912 0.174425 -4.720043
H 1.389386 1.080120 -4.651081
H -1.091211 3.589007 -3.432735
H 0.405054 3.388847 -4.361123
H -1.071440 2.541771 -4.859368
C 0.443050 3.727669 1.572514
C 0.462684 5.265029 1.421175
C 1.176816 3.333111 2.868901
H -0.601579 3.421687 1.684799
H -0.126095 5.604588 0.563757
H 0.054604 5.742168 2.320891
H 1.489460 5.625924 1.286077
H 1.279460 2.249412 2.954393
H 2.180020 3.775171 2.914021
H 0.623037 3.715510 3.735513
C 4.508286 2.555803 -1.176171
C 4.953707 3.556727 -2.260686
C 5.083520 1.154267 -1.452296
H 4.926423 2.901773 -0.220549
H 4.584816 4.565741 -2.044993
H 6.047946 3.598346 -2.323779
H 4.573927 3.265933 -3.247592
H 4.797294 0.440340 -0.672889
H 4.727258 0.757148 -2.410154
H 6.178757 1.190673 -1.496771
Pd 0.173177 -0.929802 0.327336
C -0.257250 -2.561400 -0.746529
C -0.214314 -2.604183 -2.143167
C -0.446299 -3.756318 -0.035904
C -0.374870 -3.819677 -2.822118
H -0.051447 -1.697824 -2.713168
C -0.610165 -4.967581 -0.716643
H -0.458888 -3.751839 1.050250
C -0.578359 -5.004029 -2.112820

H -0.335042 -3.833635 -3.909151
H -0.756061 -5.884387 -0.149790
H -0.702757 -5.946119 -2.640322
N 2.143258 -1.518811 0.785745
C 2.335283 -0.615559 1.751840
C 3.292115 -2.303974 0.639693
C 3.729218 -0.745604 2.364441
O 1.417842 0.200563 2.050374
C 4.291131 -1.894283 1.555869
C 3.519118 -3.353586 -0.248001
H 3.659132 -0.950525 3.440137
H 4.285078 0.193438 2.251419
C 5.520563 -2.534236 1.581761
C 4.765860 -3.990974 -0.208611
H 2.747247 -3.663515 -0.945152
C 5.758323 -3.592765 0.690378
H 6.293332 -2.224200 2.281992
H 4.961765 -4.812680 -0.893207
H 6.717515 -4.102978 0.701579

Complex 6

C 0.284678 2.499120 0.298059
C 0.163307 2.965712 -1.045551
C -1.091640 3.365655 -1.509637
C -2.236559 3.326112 -0.710483
C -2.110523 2.827043 0.587319
C -0.878817 2.427408 1.118753
C 1.658292 2.469566 0.931236
C 2.514285 1.348129 1.026508
C 3.794568 1.514529 1.587158
C 4.230271 2.746389 2.069292
C 3.378730 3.847693 2.001292
C 2.114720 3.702479 1.435286
H -1.182502 3.738130 -2.526552
H -2.990403 2.772791 1.221611
H 4.473312 0.670847 1.645641
H 5.225650 2.841060 2.494330
H 3.697349 4.816242 2.376802
H 1.456267 4.563570 1.366420
P 1.924792 -0.324397 0.483921
Pd -0.064095 -0.064040 -0.694339
C 3.470492 -1.139049 -0.207324
C 3.300985 -2.645171 -0.508641
C 3.987622 -0.385376 -1.452630
H 4.231358 -1.053380 0.581184

C 4.618433 -3.249830 -1.024136
H 2.517670 -2.786622 -1.258325
H 2.979259 -3.183908 0.388844
C 5.292832 -1.006091 -1.979752
H 3.221612 -0.426721 -2.236347
H 4.148912 0.673451 -1.218547
C 5.134450 -2.506450 -2.264033
H 4.465325 -4.311970 -1.252084
H 5.379264 -3.205957 -0.229901
H 5.610389 -0.474712 -2.885916
H 6.090489 -0.858388 -1.236168
H 6.089602 -2.933098 -2.595584
H 4.421304 -2.646468 -3.088838
C 1.545111 -1.163247 2.142978
C 0.541564 -2.328251 2.004999
C 2.774071 -1.569013 2.984072
H 1.027135 -0.361002 2.686769
C 0.138547 -2.875932 3.384307
H 0.984527 -3.138054 1.410087
H -0.350048 -1.986316 1.469383
C 2.346289 -2.120316 4.357466
H 3.349407 -2.342104 2.457514
H 3.443078 -0.713621 3.130049
C 1.357893 -3.286730 4.220327
H -0.542366 -3.726095 3.253041
H -0.428619 -2.103650 3.924573
H 3.236725 -2.432541 4.918367
H 1.877832 -1.312664 4.938864
H 1.044216 -3.635261 5.212493
H 1.863550 -4.135133 3.735354
C 0.166607 -1.727245 -1.801862
C -0.378072 -2.953177 -1.411559
C 0.779411 -1.609772 -3.054812
C -0.282732 -4.061923 -2.261746
H -0.903209 -3.042363 -0.467790
C 0.866004 -2.721460 -3.902404
H 1.187184 -0.660382 -3.387502
C 0.343357 -3.953171 -3.504723
H -0.710676 -5.011284 -1.947488
H 1.340810 -2.615937 -4.875525
H 0.413545 -4.816266 -4.161680
C -0.805569 2.036177 2.594874
C -1.866695 0.992638 2.993896
C -0.907608 3.281319 3.501099
H 0.180490 1.593840 2.772856
H -1.890376 0.143786 2.303114

H -1.663931 0.626497 4.008205
H -2.872375 1.429394 3.007774
H -0.108490 4.000968 3.294191
H -1.867062 3.791966 3.356970
H -0.837003 2.990905 4.556287
C 1.377392 3.128751 -1.960519
C 1.797180 4.609123 -2.073294
C 1.147087 2.531914 -3.361591
H 2.212279 2.583579 -1.508579
H 2.044105 5.034281 -1.095223
H 2.678923 4.709107 -2.717906
H 0.991726 5.211874 -2.509519
H 0.786536 1.500717 -3.297755
H 0.409860 3.106006 -3.934382
H 2.083104 2.541835 -3.932934
C -3.566393 3.837231 -1.246806
C -4.136425 4.975932 -0.379702
C -4.588471 2.699026 -1.415113
H -3.369719 4.251990 -2.244934
H -3.421833 5.801262 -0.283689
H -5.056962 5.371990 -0.824654
H -4.381833 4.625942 0.629898
H -4.182072 1.912152 -2.056442
H -4.840553 2.246850 -0.448482
H -5.515889 3.076762 -1.862598
C -3.858727 -2.041465 0.578282
C -4.800000 -2.002222 -0.477493
N -2.701536 -1.291343 0.310871
C -4.186628 -1.143699 -1.550705
C -6.007323 -2.675704 -0.380248
H -6.732336 -2.643786 -1.191289
C -6.285173 -3.409306 0.785096
H -7.225938 -3.946002 0.875309
C -5.353940 -3.452074 1.826300
H -5.580371 -4.023466 2.723816
C -4.133577 -2.770854 1.736666
H -3.413079 -2.801036 2.549818
C -2.857557 -0.754115 -0.885663
O -2.011939 0.001247 -1.497388
H -3.982507 -1.679989 -2.486523
H -4.780404 -0.260224 -1.811649

Complex 7

C 0.322192 2.499608 -0.033323
C -0.020168 2.699387 -1.403237

C -1.353117 2.957770 -1.735404
C -2.367039 3.031701 -0.780149
C -2.016397 2.827826 0.558518
C -0.700356 2.576634 0.957613
C 1.775790 2.588152 0.376157
C 2.664311 1.500807 0.549425
C 4.008064 1.768686 0.872744
C 4.477753 3.068348 1.047603
C 3.597524 4.139299 0.903905
C 2.268357 3.892775 0.569652
H -1.614250 3.109797 -2.778807
H -2.788618 2.900985 1.319943
H 4.710566 0.950543 0.985317
H 5.521896 3.238806 1.294848
H 3.942766 5.160414 1.040806
H 1.584373 4.726762 0.440697
P 2.048875 -0.246487 0.408623
Pd -0.047922 -0.213488 -0.615672
C 3.512271 -1.169671 -0.328714
C 3.356545 -2.707101 -0.303798
C 3.805879 -0.670848 -1.760453
H 4.379934 -0.925140 0.299908
C 4.598699 -3.393324 -0.899862
H 2.469990 -3.000611 -0.873408
H 3.205121 -3.061380 0.721387
C 5.036868 -1.373687 -2.358078
H 2.931463 -0.871807 -2.390539
H 3.960041 0.414667 -1.763094
C 4.888797 -2.901217 -2.324323
H 4.449938 -4.480208 -0.893789
H 5.471970 -3.192551 -0.260459
H 5.192708 -1.025520 -3.387048
H 5.933578 -1.081358 -1.790998
H 5.794801 -3.380030 -2.716841
H 4.060960 -3.200468 -2.982673
C 1.935270 -0.765079 2.229974
C 0.982015 -1.960142 2.445648
C 3.283588 -0.983108 2.949205
H 1.459585 0.113281 2.688983
C 0.794707 -2.266137 3.941078
H 1.371859 -2.851647 1.938467
H 0.014232 -1.742850 1.981774
C 3.073509 -1.291827 4.443313
H 3.823130 -1.820820 2.487701
H 3.919718 -0.097141 2.847640
C 2.137365 -2.490213 4.650267

H 0.147260 -3.144170 4.056537
H 0.269444 -1.425960 4.419006
H 4.045613 -1.476007 4.918326
H 2.646820 -0.406917 4.937927
H 1.978998 -2.667823 5.721333
H 2.613720 -3.396989 4.249070
C 0.002228 -2.096731 -1.334828
C -0.550845 -3.167010 -0.626718
C 0.493756 -2.308941 -2.628552
C -0.576208 -4.446814 -1.194272
H -0.987100 -3.015726 0.355056
C 0.459171 -3.589169 -3.194653
H 0.894582 -1.485049 -3.211832
C -0.065924 -4.663997 -2.474681
H -1.010150 -5.270389 -0.631953
H 0.837648 -3.738685 -4.203662
H -0.091118 -5.657817 -2.914083
C -0.384702 2.500409 2.451940
C -1.237221 1.452482 3.191190
C -0.531466 3.883298 3.120009
H 0.663855 2.204211 2.560378
H -1.120124 0.457638 2.747089
H -0.936665 1.389521 4.243929
H -2.302933 1.709161 3.174655
H 0.115426 4.626789 2.642541
H -1.563704 4.246502 3.055584
H -0.259405 3.828505 4.180993
C 1.035657 2.726305 -2.509896
C 1.317089 4.171714 -2.970764
C 0.657757 1.843757 -3.714542
H 1.967799 2.329205 -2.095319
H 1.666734 4.798246 -2.143520
H 2.087723 4.181018 -3.751016
H 0.413676 4.634582 -3.385085
H 0.412111 0.825581 -3.397432
H -0.209726 2.239334 -4.254598
H 1.493484 1.800359 -4.423394
C -3.790548 3.386909 -1.187765
C -4.171534 4.793391 -0.681254
C -4.824183 2.338573 -0.739202
H -3.809221 3.417072 -2.285375
H -3.463699 5.552056 -1.034433
H -5.172433 5.069548 -1.033496
H -4.182889 4.830593 0.415000
H -4.588970 1.347426 -1.136924
H -4.872549 2.261645 0.353757

H -5.823489 2.622209 -1.090394
C -4.336717 -1.555366 0.824766
C -4.786832 -2.096286 -0.419594
N -3.193744 -0.817000 0.558639
C -3.896357 -1.622210 -1.436787
C -5.922335 -2.924650 -0.412691
H -6.287367 -3.359087 -1.340512
C -6.580275 -3.177247 0.789613
H -7.461667 -3.814155 0.794091
C -6.126308 -2.621609 1.998779
H -6.660281 -2.829819 2.922359
C -4.993104 -1.805008 2.028021
H -4.635757 -1.378072 2.962880
C -2.946926 -0.813032 -0.827529
O -1.986879 -0.090042 -1.335393
H -2.807895 -0.103636 1.159576
H -3.920612 -1.851958 -2.492751

Complex 8

H -1.988651 2.758101 -2.894183
C -2.474623 3.361344 -0.894174
C -2.259246 2.414641 -1.900509
H -3.041294 3.617886 1.150888
C -2.855839 2.894262 0.361524
C -2.403046 1.041088 -1.678564
C -3.012788 1.531746 0.643399
C -2.756151 0.586702 -0.381230
P -0.328711 -1.799439 0.412486
C -3.084644 -0.866235 -0.122296
C -2.202554 -1.899124 0.291720
H -5.125215 -0.392112 -0.578104
C -4.455704 -1.178912 -0.244566
C -2.761382 -3.150104 0.633667
H -2.118275 -3.940518 1.006436
C -4.977935 -2.429948 0.063606
C -4.120872 -3.423966 0.530071
H -6.042847 -2.617739 -0.043603
H -4.500231 -4.403546 0.807872
C 0.120023 -3.377931 -0.546038
C -0.236616 -3.237074 -2.040569
C 1.577050 -3.851120 -0.361938
H -0.521877 -4.165148 -0.129096
C 0.052570 -4.531804 -2.819694
H 0.347908 -2.418496 -2.474823
H -1.295545 -2.975963 -2.149010

C 1.845545 -5.144587 -1.154244
H 2.271444 -3.072540 -0.691362
H 1.782158 -4.039237 0.697714
C 1.507990 -4.983971 -2.641905
H -0.175467 -4.376608 -3.882084
H -0.621706 -5.327468 -2.468491
H 2.897017 -5.432257 -1.028302
H 1.243578 -5.963968 -0.732202
H 1.683241 -5.926431 -3.176646
H 2.179097 -4.235222 -3.085623
C 0.011588 -2.277617 2.219210
C 1.465314 -1.933005 2.617206
C -0.961103 -1.604425 3.210471
H -0.120672 -3.368752 2.286902
C 1.772400 -2.359361 4.063015
H 1.600883 -0.847119 2.520626
H 2.184138 -2.390482 1.931627
C -0.659186 -2.014807 4.663272
H -0.870055 -0.514811 3.110552
H -1.996793 -1.862151 2.968934
C 0.793998 -1.717684 5.055765
H 2.806264 -2.088381 4.313333
H 1.709333 -3.454959 4.143238
H -1.351275 -1.496719 5.339373
H -0.853869 -3.091368 4.782490
H 0.994436 -2.070861 6.075410
H 0.949739 -0.628788 5.062936
C -2.273283 0.078926 -2.860088
C -1.255351 0.532590 -3.921453
C -3.639829 -0.156169 -3.541093
H -1.929994 -0.883403 -2.467832
H -0.313149 0.853261 -3.468384
H -1.043972 -0.290114 -4.614569
H -1.637925 1.366488 -4.522018
H -4.368690 -0.596919 -2.855425
H -4.051317 0.790877 -3.910893
H -3.529635 -0.833822 -4.396973
C -3.532075 1.133358 2.027933
C -5.053556 1.376935 2.131601
C -2.814438 1.851237 3.187742
H -3.363675 0.060018 2.157658
H -5.612252 0.809099 1.380982
H -5.422177 1.081668 3.121912
H -5.286622 2.439160 1.989294
H -1.729038 1.780536 3.092285
H -3.078300 2.915106 3.228496

H -3.123955 1.408503 4.142907
C -2.332852 4.854428 -1.160694
C -3.373773 5.351718 -2.182799
C -0.906181 5.233878 -1.599881
H -2.531889 5.370286 -0.211411
H -4.393369 5.123819 -1.852518
H -3.293662 6.436847 -2.321248
H -3.226561 4.879328 -3.161557
H -0.166180 4.915770 -0.857416
H -0.645803 4.764948 -2.556547
H -0.816594 6.319537 -1.727998
Pd 0.875157 0.261034 0.006710
C 2.361879 -0.443117 -1.164039
C 2.256330 -0.568613 -2.555412
C 3.585832 -0.774077 -0.559824
C 3.332391 -1.039518 -3.319647
H 1.334246 -0.302299 -3.060125
C 4.658484 -1.249856 -1.321372
H 3.714826 -0.661801 0.513676
C 4.535687 -1.389693 -2.705655
H 3.224350 -1.127088 -4.398959
H 5.594055 -1.504684 -0.827895
H 5.370174 -1.756227 -3.298046
O 0.094198 1.845232 1.688028
C 1.235739 2.250004 1.345688
N 2.272892 2.553200 2.211072
C 3.453022 2.792888 1.494989
C 4.712481 3.146653 1.966385
C 3.171596 2.648101 0.113034
C 5.720205 3.367579 1.020876
H 4.908457 3.255634 3.029962
C 4.190464 2.887380 -0.810381
C 5.461379 3.244594 -0.349910
H 6.715663 3.642007 1.359418
H 3.999748 2.779090 -1.874452
H 6.260145 3.423339 -1.064438
C 1.761554 2.280218 -0.018655
H 2.205605 2.417188 3.209622
H 1.138670 2.653948 -0.827285

Complex 9

H 5.778881 1.384538 -0.628112
C 5.613832 -0.722011 -0.257721
C 5.180430 0.603543 -0.167839
H 5.185960 -2.729943 0.338692

C 4.845463 -1.698544 0.377949
C 4.010910 0.962171 0.511607
C 3.665652 -1.398976 1.072750
C 3.222519 -0.051116 1.112574
P -0.062896 0.584999 -0.220047
C 2.007388 0.297712 1.941505
C 0.658769 0.430015 1.504197
H 3.305288 0.368359 3.644436
C 2.272286 0.442903 3.317952
C -0.338077 0.612122 2.487745
H -1.375603 0.678279 2.169306
C 1.274787 0.661025 4.264056
C -0.050471 0.724863 3.845167
H 1.534025 0.763386 5.314346
H -0.857191 0.868191 4.558304
C 1.114108 -0.212798 -1.459354
C 0.979061 -1.748326 -1.472290
C 0.976991 0.337671 -2.896512
H 2.118250 0.044471 -1.104737
C 2.010349 -2.397222 -2.410164
H -0.027549 -2.018043 -1.807531
H 1.076510 -2.150601 -0.460093
C 1.996283 -0.322499 -3.843727
H -0.039860 0.152790 -3.270311
H 1.135980 1.419873 -2.916382
C 1.884378 -1.851442 -3.838674
H 1.871252 -3.485993 -2.405401
H 3.024705 -2.205290 -2.033130
H 1.854447 0.071972 -4.858103
H 3.010949 -0.032684 -3.533318
H 2.651856 -2.291196 -4.488469
H 0.910946 -2.146872 -4.256609
C 0.033177 2.449939 -0.589306
C -0.932180 2.856377 -1.732300
C -0.248148 3.333171 0.647125
H 1.067116 2.631579 -0.916379
C -0.775897 4.347035 -2.082417
H -1.960588 2.674377 -1.403851
H -0.771137 2.251818 -2.627897
C -0.116474 4.828732 0.305720
H -1.266081 3.132447 1.003802
H 0.434645 3.088296 1.466466
C -1.028820 5.235763 -0.858287
H -1.472178 4.603151 -2.891169
H 0.237410 4.534184 -2.470301
H -0.345413 5.424208 1.198901

H 0.929450 5.050311 0.042994
H -0.875151 6.292824 -1.111504
H -2.077740 5.129253 -0.549077
C 3.661058 2.443486 0.651995
C 3.860747 3.251094 -0.643907
C 4.462996 3.084113 1.804887
H 2.603040 2.513407 0.921864
H 3.365628 2.779266 -1.499994
H 3.447393 4.259437 -0.525636
H 4.920900 3.366447 -0.896411
H 4.267248 2.579371 2.756403
H 5.540475 3.027483 1.608875
H 4.194343 4.141132 1.920997
C 2.951280 -2.526558 1.826826
C 3.624197 -2.778716 3.194644
C 2.884120 -3.858763 1.054688
H 1.921485 -2.207144 2.017798
H 3.614984 -1.887843 3.828185
H 3.104673 -3.580642 3.733053
H 4.668570 -3.085154 3.059139
H 2.488121 -3.734753 0.043908
H 3.868700 -4.333876 0.974265
H 2.231766 -4.559435 1.588096
C 6.889987 -1.095918 -1.000402
C 8.136823 -0.462787 -0.353149
C 6.807699 -0.744195 -2.498129
H 6.998331 -2.186480 -0.924404
H 8.218437 -0.738890 0.703867
H 9.048103 -0.795185 -0.864539
H 8.103765 0.631759 -0.411311
H 5.942363 -1.222221 -2.970609
H 6.715639 0.338048 -2.648676
H 7.710606 -1.077228 -3.023694
Pd -2.359651 0.071136 -0.144856
C -2.097298 -1.905525 -0.153238
C -2.584574 -2.641428 -1.242353
C -1.578524 -2.584480 0.954984
C -2.541114 -4.040099 -1.223569
H -3.008381 -2.131746 -2.103357
C -1.545087 -3.984701 0.971529
H -1.196826 -2.033723 1.810153
C -2.020517 -4.716458 -0.117531
H -2.921445 -4.599200 -2.075690
H -1.144952 -4.500103 1.842063
H -1.990796 -5.802863 -0.103808
N -4.483273 0.104584 -0.017698

C -4.572629 1.430284 0.111699
C -5.766714 -0.455230 0.025002
C -6.025011 1.883257 0.249863
O -3.525208 2.143076 0.112528
C -6.745366 0.555391 0.180901
C -6.129781 -1.797282 -0.064181
H -6.289463 2.576841 -0.558308
H -6.171307 2.421256 1.194917
C -8.089768 0.224210 0.244537
C -7.491952 -2.116832 0.002335
H -5.373502 -2.566679 -0.182120
C -8.464820 -1.125805 0.153869
H -8.847212 0.995996 0.363898
H -7.794984 -3.158921 -0.065192
H -9.515325 -1.398966 0.202784

Complex 10

C -3.366826 -0.921406 -0.936542
C -3.383415 -2.215050 -0.360209
C -4.474672 -2.582081 0.438298
C -5.555704 -1.728760 0.670156
C -5.526351 -0.465114 0.072854
C -4.460396 -0.043301 -0.730188
C -2.296719 -0.558545 -1.934805
C -1.056451 0.088926 -1.687664
C -0.206027 0.325789 -2.794410
C -0.536302 -0.041469 -4.095692
C -1.750652 -0.678004 -4.332093
C -2.603814 -0.925074 -3.260509
H -4.494369 -3.574633 0.881247
H -6.365723 0.208222 0.224157
H 0.750893 0.814071 -2.628843
H 0.157909 0.161702 -4.905638
H -2.033104 -0.985210 -5.335202
H -3.552601 -1.422092 -3.440111
P -0.280258 0.715343 -0.096630
Pd 1.942741 0.062117 -0.514920
C -0.790919 2.528494 0.008877
C -0.136097 3.252776 1.207649
C -0.501749 3.312596 -1.289303
H -1.879413 2.511533 0.161518
C -0.648580 4.698918 1.324058
H 0.949456 3.264283 1.069010
H -0.324323 2.720263 2.145470
C -0.993800 4.767209 -1.179622

H 0.580724 3.307562 -1.476826
H -0.977651 2.830944 -2.149349
C -0.391195 5.488275 0.033647
H -0.160927 5.189396 2.175741
H -1.727198 4.691161 1.541639
H -0.749668 5.303834 -2.105122
H -2.090998 4.770263 -1.097472
H -0.801472 6.502590 0.116255
H 0.693364 5.596228 -0.110408
C -1.012906 -0.145321 1.421120
C 0.088510 -0.366896 2.487054
C -2.255436 0.507662 2.062410
H -1.307095 -1.129674 1.039007
C -0.432676 -1.175316 3.687525
H 0.452611 0.605993 2.843247
H 0.948795 -0.873820 2.034311
C -2.766578 -0.316548 3.259450
H -2.003535 1.514294 2.417862
H -3.056677 0.613801 1.328728
C -1.673850 -0.527899 4.314395
H 0.367248 -1.277435 4.431777
H -0.682095 -2.194535 3.357980
H -3.634465 0.190076 3.700792
H -3.123589 -1.290380 2.898108
H -2.051768 -1.146870 5.137830
H -1.396407 0.442072 4.753423
C 2.889826 1.582385 0.366581
C 3.131701 1.613857 1.742658
C 3.417624 2.578136 -0.461947
C 3.890508 2.656039 2.290775
H 2.740200 0.839547 2.393331
C 4.169782 3.618426 0.096873
H 3.266543 2.542994 -1.536335
C 4.404891 3.662516 1.472447
H 4.077551 2.673158 3.361933
H 4.581217 4.386871 -0.553156
H 4.993396 4.469098 1.901131
C -4.542857 1.324514 -1.412405
C -4.944500 2.462576 -0.454666
C -5.507290 1.279119 -2.615997
H -3.549133 1.565678 -1.804262
H -4.291466 2.507174 0.423838
H -4.882854 3.427247 -0.972134
H -5.974367 2.353641 -0.096230
H -5.194112 0.530943 -3.351216
H -6.524655 1.027466 -2.293408

H -5.543311 2.253365 -3.118164
C -2.288771 -3.246511 -0.649457
C -2.741269 -4.228204 -1.751662
C -1.833433 -4.036040 0.592583
H -1.413479 -2.710573 -1.032909
H -2.984063 -3.705848 -2.681938
H -1.947369 -4.952615 -1.968707
H -3.631298 -4.785229 -1.435270
H -1.533450 -3.375821 1.413351
H -2.620640 -4.698934 0.969353
H -0.974492 -4.666631 0.336738
C -6.732937 -2.179539 1.525621
C -8.040144 -2.241188 0.712225
C -6.905049 -1.301782 2.780078
H -6.510360 -3.199905 1.866399
H -7.931415 -2.888475 -0.164846
H -8.858706 -2.633660 1.327099
H -8.337376 -1.246394 0.359433
H -5.990106 -1.285905 3.382298
H -7.146902 -0.266282 2.511906
H -7.720312 -1.681084 3.407593
C 6.781276 -1.901018 -0.772783
C 6.369632 -2.029778 0.575466
N 5.778106 -1.396654 -1.613903
C 4.939155 -1.565620 0.613660
C 7.241857 -2.496692 1.545670
H 6.928020 -2.593203 2.583487
C 8.547854 -2.850549 1.168287
H 9.244114 -3.222786 1.915443
C 8.954223 -2.727603 -0.164110
H 9.968696 -3.005500 -0.441171
C 8.079297 -2.252937 -1.148125
H 8.391630 -2.154127 -2.183633
C 4.720257 -1.206062 -0.864937
O 3.581946 -0.798705 -1.340070
H 4.226559 -2.340218 0.927656
H 4.775288 -0.692385 1.257199

Complex 11

C 3.406345 -0.730628 0.973803
C 3.381402 -2.110568 0.655240
C 4.393057 -2.632219 -0.161909
C 5.436233 -1.847009 -0.657284
C 5.452717 -0.493239 -0.309311
C 4.465656 0.082745 0.498568

C 2.426972 -0.176606 1.977389
C 1.156737 0.406374 1.721549
C 0.396331 0.839112 2.833412
C 0.845526 0.730440 4.146346
C 2.092101 0.162642 4.391779
C 2.855654 -0.280875 3.315876
H 4.380575 -3.691035 -0.408123
H 6.266043 0.131849 -0.667522
H -0.585454 1.273362 2.660341
H 0.218611 1.079210 4.961799
H 2.467201 0.057446 5.406047
H 3.826881 -0.730131 3.501851
P 0.243580 0.742654 0.113565
Pd -1.976294 0.252960 0.762542
C 0.787672 2.479102 -0.383855
C 0.041364 2.985058 -1.640348
C 0.635065 3.504679 0.759712
H 1.856860 2.391203 -0.622303
C 0.565019 4.365137 -2.074005
H -1.027399 3.057696 -1.416920
H 0.137855 2.278785 -2.470963
C 1.136986 4.895325 0.330911
H -0.424539 3.571956 1.039996
H 1.181056 3.177393 1.650366
C 0.436065 5.391976 -0.941127
H 0.011589 4.701616 -2.959531
H 1.620042 4.281328 -2.375404
H 0.987284 5.605604 1.153985
H 2.221812 4.847798 0.153271
H 0.850716 6.359548 -1.251065
H -0.629609 5.557523 -0.727667
C 0.820612 -0.414411 -1.271483
C -0.383890 -0.793766 -2.168225
C 2.007027 0.058174 -2.138775
H 1.133945 -1.319057 -0.737205
C 0.000145 -1.833229 -3.234660
H -0.768383 0.105847 -2.667061
H -1.204032 -1.171746 -1.546495
C 2.381193 -0.995462 -3.198679
H 1.741830 0.988113 -2.655706
H 2.878215 0.270862 -1.516443
C 1.185871 -1.362315 -4.086704
H -0.870701 -2.043326 -3.868492
H 0.262057 -2.781161 -2.741579
H 3.210371 -0.614328 -3.808750
H 2.753853 -1.896489 -2.693117

H 1.469534 -2.139363 -4.807725
H 0.884121 -0.483480 -4.675742
C -2.957511 1.646995 -0.293585
C -3.434580 1.373685 -1.577868
C -3.264749 2.864372 0.323255
C -4.202066 2.331288 -2.252548
H -3.226735 0.422142 -2.056430
C -4.032832 3.816050 -0.358626
H -2.923824 3.075403 1.332599
C -4.497624 3.554637 -1.649033
H -4.572762 2.111046 -3.250954
H -4.272276 4.758611 0.128594
H -5.095287 4.294046 -2.175445
C 4.598807 1.555496 0.894474
C 4.918100 2.481840 -0.294475
C 5.658883 1.731698 2.001999
H 3.639354 1.880548 1.310574
H 4.199238 2.359365 -1.111891
H 4.889518 3.529312 0.028175
H 5.918419 2.297029 -0.702324
H 5.407812 1.148391 2.893640
H 6.646014 1.404820 1.653823
H 5.736417 2.785069 2.297179
C 2.333581 -3.060481 1.242697
C 2.904775 -3.811506 2.464657
C 1.772406 -4.074081 0.227394
H 1.491758 -2.456238 1.598056
H 3.238733 -3.118649 3.242957
H 2.143564 -4.469072 2.901281
H 3.761547 -4.431481 2.174329
H 1.385519 -3.584012 -0.672427
H 2.529554 -4.800435 -0.088768
H 0.951943 -4.640168 0.682978
C 6.531515 -2.461492 -1.520127
C 7.892367 -2.453805 -0.796219
C 6.636716 -1.784193 -2.899093
H 6.256326 -3.511489 -1.689670
H 7.831885 -2.971406 0.167416
H 8.656454 -2.952377 -1.404502
H 8.234716 -1.429785 -0.604519
H 5.679678 -1.815876 -3.431088
H 6.933898 -0.732751 -2.806739
H 7.388690 -2.287302 -3.518410
C -5.926640 -2.440514 -0.099337
C -6.833473 -1.615396 0.637825
N -4.647781 -2.022212 0.218896

C -6.046827 -0.714642 1.420541
C -8.213788 -1.827524 0.470354
H -8.929977 -1.214332 1.012271
C -8.653416 -2.830457 -0.389374
H -9.720131 -2.997526 -0.517332
C -7.740630 -3.635246 -1.096273
H -8.110096 -4.413904 -1.758505
C -6.364371 -3.446289 -0.959490
H -5.657426 -4.065685 -1.507224
C -4.708634 -0.991405 1.168546
O -3.629165 -0.480870 1.692645
H -3.792963 -2.508627 -0.004978
H -6.397502 0.057997 2.090129

Complex 12

H 5.712383 -0.095514 -1.201419
C 5.006686 -1.949416 -0.382436
C 4.986332 -0.561039 -0.540696
H 4.109898 -3.589372 0.654878
C 4.086369 -2.513481 0.502440
C 4.070472 0.253247 0.134789
C 3.148658 -1.747447 1.208333
C 3.117901 -0.344372 0.997763
P -0.008304 0.981211 -0.175548
C 2.178752 0.504801 1.822919
C 0.875564 0.957052 1.470253
H 3.667393 0.497075 3.363469
C 2.663514 0.822381 3.106860
C 0.117221 1.621878 2.456074
H -0.897151 1.921545 2.221834
C 1.909734 1.516334 4.049767
C 0.612928 1.902656 3.726056
H 2.329371 1.733730 5.028360
H -0.015763 2.414756 4.448664
C 0.775713 -0.275501 -1.338361
C 0.223104 -1.680859 -1.019326
C 0.546515 0.047950 -2.831874
H 1.853510 -0.270685 -1.148716
C 0.850148 -2.758541 -1.918661
H -0.866589 -1.670989 -1.164576
H 0.389606 -1.924073 0.034892
C 1.185425 -1.027005 -3.730209
H -0.530042 0.104125 -3.037639
H 0.974896 1.023413 -3.087913
C 0.656714 -2.430445 -3.405416

H 0.409851 -3.736724 -1.684010
H 1.923872 -2.835119 -1.696970
H 0.994954 -0.781048 -4.782822
H 2.277335 -1.011819 -3.596520
H 1.155944 -3.181533 -4.031075
H -0.414588 -2.478359 -3.651995
C 0.454686 2.681380 -0.901148
C -0.631167 3.154566 -1.895502
C 0.701221 3.789385 0.144248
H 1.394765 2.524110 -1.449270
C -0.231463 4.470895 -2.582626
H -1.566841 3.302647 -1.338440
H -0.853756 2.393296 -2.645803
C 1.102864 5.112229 -0.533903
H -0.214697 3.948750 0.730286
H 1.475957 3.494727 0.857985
C 0.060022 5.576169 -1.559674
H -1.030917 4.782074 -3.266723
H 0.661780 4.302269 -3.203015
H 1.256314 5.882506 0.233010
H 2.071975 4.977366 -1.037624
H 0.402046 6.488933 -2.064191
H -0.871184 5.837500 -1.035658
C 4.171456 1.770344 -0.025849
C 4.364720 2.223158 -1.484866
C 5.298909 2.336169 0.863055
H 3.233824 2.207390 0.330190
H 3.607191 1.791790 -2.148575
H 4.294392 3.315263 -1.552461
H 5.348465 1.939729 -1.876343
H 5.132408 2.095484 1.918060
H 6.271194 1.920456 0.572464
H 5.355168 3.427528 0.768867
C 2.249429 -2.445757 2.235086
C 2.994175 -2.630284 3.576110
C 1.712459 -3.815344 1.774418
H 1.385096 -1.800250 2.423736
H 3.313739 -1.675391 4.001364
H 2.344502 -3.124872 4.308338
H 3.885310 -3.254816 3.438683
H 1.244114 -3.770765 0.787298
H 2.504749 -4.571869 1.734402
H 0.963099 -4.175196 2.488871
C 6.006807 -2.823486 -1.128133
C 7.459671 -2.504894 -0.725925
C 5.824541 -2.730531 -2.655118

H 5.806023 -3.863176 -0.835420
H 7.602928 -2.607461 0.355344
H 8.157802 -3.184550 -1.229168
H 7.734925 -1.480334 -1.003585
H 4.800844 -2.987900 -2.949132
H 6.032175 -1.717299 -3.019489
H 6.509702 -3.415425 -3.168929
H -7.286039 -4.197359 -0.694443
C -6.749620 -3.252457 -0.680815
C -5.842998 -2.965106 -1.707155
C -6.976457 -2.339116 0.356580
C -5.171611 -1.748817 -1.651786
H -5.675243 -3.667390 -2.519626
C -6.296020 -1.118800 0.400116
H -7.687466 -2.584747 1.140659
C -5.373596 -0.816258 -0.603127
N -4.246468 -1.203059 -2.552158
H -6.465862 -0.420758 1.215193
C -4.514948 0.338733 -0.865037
C -3.830472 0.041871 -2.118280
H -3.765157 -1.710762 -3.280763
H -4.823439 1.355457 -0.637038
O -2.874900 0.706932 -2.612262
Pd -2.390150 0.590527 -0.275689
C -2.756367 0.191186 1.657865
C -3.469799 1.100572 2.454479
C -2.348923 -1.022170 2.230173
C -3.751242 0.810075 3.794818
H -3.812995 2.044174 2.036040
C -2.638348 -1.314745 3.567577
H -1.801297 -1.749065 1.635765
C -3.336068 -0.398636 4.356986
H -4.302964 1.530381 4.395801
H -2.315122 -2.263365 3.991416
H -3.558128 -0.626092 5.396563

Transition State 1-TS

C -0.556715 2.567021 -0.425372
C -1.190641 2.211590 -1.643748
C -2.567920 1.959315 -1.637623
C -3.345179 2.063346 -0.481732
C -2.699973 2.419507 0.705432
C -1.324750 2.673481 0.759965
C 0.876878 3.037191 -0.449920
C 2.028435 2.226000 -0.284154

C 3.293061 2.831300 -0.422752
C 3.444769 4.191457 -0.682692
C 2.312860 4.993403 -0.808418
C 1.052776 4.412391 -0.696435
H -3.054941 1.684958 -2.569824
H -3.284514 2.518566 1.616035
H 4.190214 2.229837 -0.333557
H 4.440053 4.616164 -0.782677
H 2.406384 6.058446 -1.003116
H 0.166236 5.029259 -0.813225
P 1.914471 0.415689 0.168575
Pd -0.130341 -0.699601 -0.225750
C 3.398505 -0.333811 -0.718683
C 3.659348 -1.795353 -0.295916
C 3.204242 -0.245144 -2.248138
H 4.290393 0.248070 -0.449735
C 4.858272 -2.390391 -1.056150
H 2.768183 -2.399905 -0.493708
H 3.850645 -1.856250 0.780995
C 4.401183 -0.844334 -3.005873
H 2.290866 -0.791477 -2.518865
H 3.054163 0.796810 -2.554908
C 4.673214 -2.292715 -2.576412
H 4.994580 -3.436848 -0.755313
H 5.777032 -1.857818 -0.766170
H 4.214444 -0.793518 -4.086287
H 5.296273 -0.232886 -2.815088
H 5.557545 -2.685191 -3.094915
H 3.824077 -2.923793 -2.874165
C 2.372349 0.487037 2.014228
C 1.897623 -0.767033 2.780641
C 3.842362 0.810394 2.351279
H 1.761100 1.329507 2.368820
C 2.117116 -0.618648 4.295679
H 2.434967 -1.653979 2.421150
H 0.838335 -0.945088 2.564800
C 4.052904 0.951690 3.870672
H 4.494680 0.009543 1.977044
H 4.156064 1.735969 1.857784
C 3.579909 -0.295375 4.629810
H 1.802064 -1.537592 4.806915
H 1.472553 0.187816 4.675765
H 5.112658 1.148801 4.078271
H 3.495602 1.829097 4.230722
H 3.702744 -0.152453 5.711022
H 4.213635 -1.151055 4.352882

C -0.111479 -2.814364 -0.492306
C 0.212769 -3.629243 0.608937
C 0.308812 -3.199526 -1.782538
C 0.988344 -4.774786 0.422419
H -0.123076 -3.375288 1.605360
C 1.079880 -4.351823 -1.943306
H 0.025370 -2.607131 -2.641100
C 1.431337 -5.146964 -0.848808
H 1.243749 -5.380460 1.289103
H 1.405203 -4.626406 -2.944349
H 2.028864 -6.043745 -0.985301
C -0.711563 3.119101 2.087472
C -1.038800 2.154537 3.243054
C -1.138436 4.557453 2.444911
H 0.377190 3.129894 1.968443
H -0.756825 1.126085 2.993586
H -0.499943 2.451223 4.151405
H -2.108237 2.155069 3.482946
H -0.845205 5.265588 1.662447
H -2.225701 4.627153 2.568415
H -0.671629 4.877749 3.384548
C -0.434188 2.185431 -2.973246
C -0.672324 3.492392 -3.759615
C -0.777978 0.968999 -3.850876
H 0.635654 2.132943 -2.747748
H -0.351182 4.372343 -3.192622
H -0.116135 3.477515 -4.705046
H -1.736103 3.614515 -3.997137
H -0.716444 0.029808 -3.294576
H -1.791911 1.035852 -4.262661
H -0.088257 0.921153 -4.702735
C -4.854464 1.863554 -0.548763
C -5.584917 3.222227 -0.536685
C -5.398102 0.941356 0.556132
H -5.070816 1.385058 -1.514093
H -5.238026 3.866284 -1.352354
H -6.667584 3.083904 -0.646611
H -5.407908 3.753429 0.406639
H -4.892708 -0.029829 0.556438
H -5.269614 1.383171 1.551371
H -6.471784 0.768898 0.413300
C -2.615093 -2.351825 0.688948
C -3.870003 -2.818647 0.257077
N -1.777782 -2.029020 -0.412508
C -3.898586 -2.761940 -1.242375
H -3.999626 -3.742064 -1.726773

C -4.844112 -3.177612 1.179319
H -5.815984 -3.531240 0.843298
C -4.563560 -3.072525 2.548168
H -5.315432 -3.355778 3.279200
C -3.325720 -2.583753 2.971340
H -3.121343 -2.480992 4.033883
C -2.342963 -2.205867 2.049224
H -1.402263 -1.782397 2.384492
C -2.523930 -2.177703 -1.594175
O -2.129745 -1.922675 -2.718677
H -4.690584 -2.121188 -1.647567

Transition State 2-TS

C 0.454677 2.617400 -0.576890
C -0.501793 2.451653 -1.609330
C -1.845022 2.744718 -1.341347
C -2.278942 3.199395 -0.094054
C -1.317991 3.349349 0.910836
C 0.037917 3.076194 0.696796
C 1.922144 2.503340 -0.911362
C 2.711659 1.328680 -0.818920
C 4.048970 1.390614 -1.257536
C 4.618765 2.563419 -1.748420
C 3.849799 3.723408 -1.809925
C 2.520297 3.681283 -1.398423
H -2.578079 2.634692 -2.137335
H -1.628667 3.710502 1.887642
H 4.666445 0.500082 -1.224146
H 5.654622 2.566568 -2.077053
H 4.274886 4.651052 -2.183847
H 1.911088 4.578828 -1.461957
P 2.045433 -0.258813 -0.092674
Pd -0.308609 -0.566927 0.113855
C 2.897373 -1.586478 -1.123315
C 2.656453 -2.998203 -0.545250
C 2.405155 -1.513225 -2.585653
H 3.980627 -1.403807 -1.112979
C 3.298134 -4.085237 -1.425239
H 1.579059 -3.182647 -0.465719
H 3.061759 -3.070389 0.470046
C 3.043755 -2.606290 -3.459221
H 1.312963 -1.633261 -2.594975
H 2.619228 -0.525046 -3.010308
C 2.803773 -4.005634 -2.875437
H 3.077668 -5.072716 -1.000568

H 4.393028 -3.973060 -1.407620
H 2.643009 -2.541843 -4.479194
H 4.126343 -2.424668 -3.537435
H 3.300177 -4.766665 -3.491380
H 1.727551 -4.229004 -2.899663
C 2.887126 -0.254877 1.612862
C 2.144649 -1.150295 2.630169
C 4.402858 -0.533835 1.632917
H 2.739270 0.785556 1.936826
C 2.735470 -0.997760 4.042451
H 2.214048 -2.202088 2.322773
H 1.076951 -0.902416 2.638065
C 4.981336 -0.385130 3.052836
H 4.597180 -1.554857 1.276802
H 4.929308 0.147109 0.955768
C 4.245239 -1.274995 4.063640
H 2.211291 -1.669155 4.734102
H 2.549723 0.025421 4.401133
H 6.053315 -0.622118 3.040122
H 4.897631 0.666064 3.365892
H 4.649906 -1.119623 5.072021
H 4.423949 -2.331525 3.813429
C -1.229510 -2.430255 0.142046
C -0.862470 -3.323999 1.162816
C -1.526638 -2.939759 -1.134326
C -0.732997 -4.688212 0.888287
H -0.679773 -2.954179 2.166137
C -1.379195 -4.303298 -1.401791
H -1.870510 -2.277909 -1.922095
C -0.980536 -5.184955 -0.393919
H -0.437753 -5.364605 1.687516
H -1.592653 -4.676087 -2.401161
H -0.882917 -6.247399 -0.600560
C 1.031371 3.345221 1.826752
C 0.619664 2.682004 3.154762
C 1.250257 4.859845 2.020434
H 1.996537 2.918815 1.533198
H 0.424961 1.611971 3.028708
H 1.415199 2.804041 3.900073
H -0.286964 3.134418 3.572940
H 1.615245 5.331264 1.101394
H 0.316185 5.358990 2.304873
H 1.985880 5.045603 2.812591
C -0.104946 2.030588 -3.024761
C -0.207325 3.218114 -4.003295
C -0.917112 0.827603 -3.537771

H 0.943336 1.718706 -3.001852
H 0.427343 4.051947 -3.684068
H 0.108359 2.917206 -5.009732
H -1.237344 3.588520 -4.070448
H -0.836260 -0.016773 -2.844154
H -1.979405 1.072184 -3.658215
H -0.542709 0.506806 -4.517625
C -3.739392 3.569541 0.136597
C -3.899708 5.085521 0.367595
C -4.381659 2.767591 1.283349
H -4.284049 3.318285 -0.783781
H -3.478962 5.660860 -0.464629
H -4.959057 5.351567 0.466449
H -3.388973 5.402808 1.284749
H -4.338773 1.691604 1.085749
H -3.877106 2.957024 2.238219
H -5.435118 3.047911 1.403225
C -3.695761 -1.082915 0.002711
C -4.600366 -1.694269 0.899012
C -5.890566 -2.045312 0.520690
H -6.575569 -2.515680 1.220861
C -6.285210 -1.761657 -0.793718
H -7.289173 -2.026431 -1.114392
C -5.413140 -1.137287 -1.688349
H -5.743728 -0.916537 -2.699440
C -4.112656 -0.793513 -1.292106
H -3.436131 -0.304168 -1.987146
C -2.703296 -1.267701 2.151211
O -1.987440 -1.166588 3.137484
N -3.978479 -1.819348 2.144435
H -4.408141 -2.178566 2.984962
C -2.418938 -0.845931 0.727239
H -2.122889 0.229057 0.725203

Transition State 3-TS

H -5.828729 1.011747 1.035861
C -5.462191 -1.079481 0.728094
C -5.198901 0.279599 0.538444
H -4.875615 -3.054359 0.158211
C -4.662307 -1.994954 0.042811
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Complex 13

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N -1.743168 0.007502 -0.067024
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H -3.681769 -2.375782 -0.612929

Complex 16

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H -2.312348 -2.708805 1.956202
H -2.189342 -0.984764 2.313932

2.5 References and Notes

(1) (a) Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234. (b) 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. (c) Surry, D. S.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2008**, *47*, *In Press*.

(2) (a) Monnier, F.; Taillefer, M. *Angew. Chem. Int. Ed.* **2008**, *47*, 3096. (b) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, 2337. (c) Ley, S. V.; Thomas, A. W. *Angew. Chem. Int. Ed.* **2003**, *42*, 5400. (d) Kunz, K.; Scholz, U.; Ganzer, D. *Synlett* **2003**, 2428.

(3) For Cu-catalyzed N-arylation of amides using *N,N'*-dimethyl-1,2-ethylenediamine-derived ligands, See: (a) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727. (b) Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421.

(4) For Pd-catalyzed amidation of aryl halides using Xantphos and dialkylbiarylmonophosphine ligands, see: (a) Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 6043. (b) Huang, X.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 6653. (c) Ikawa, T.; Barder, T. E.; Biscoe, M. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 13001.

(5) (a) Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 11108. (b) Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360. (c) Hamada, T.; Chieffi, A.; Ahman, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1261. (d) Nguyen, H. N.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 11818.

(6) Hennessy, E. J.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 269.

(7) (a) Phillips, D. P.; Hudson, A. R.; Nguyen, B.; Lau T. L.; McNeill, M. H.; Dalgard, J. E.; Chen, J. H.; Penuliar, R. J.; Miller T. A.; Zhi, L. *Tetrahedron Lett.* **2006**, *47*, 7137. (b) Huang, J.; Bunel, E.; Faul, M. M. *Org. Lett.* **2007**, *9*, 4343. (c) Durbin, M. J.; Willis, M. C. *Org. Lett. ASAP Article*.

(8) Bordwell, F. G.; Fried, H. E. *J. Org. Chem.* **1991**, *56*, 4218.

(9) (a) Luk, K. C.; So, S. S.; Zhang, J.; Zhang, Z. (F. Hoffman-LaRoche AG) Oxindole Derivatives. WO 2006/136606 A3. December 28, 2006. (b) Hewawasam, P.; Gribkoff, V. K.; Pendri, Y.; Dworetzky, S. I.; Meanwell, N. A.; Martinez, E.; Boissard, C. G.; Post-Munson, D. J.; Trojnacki, J. T.; Yeleswaram, K.; Pajor, L. M.; Knipe, J.; Gao, Q.; Perrone, R.; Starrett, J. E., Jr. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1023. (c) Sarges, R.; Howard, H. R.; Koe, K.; Weissman, A. *J. Med. Chem.* **1989**, *32*, 437.

(10) Karnachi, A. A.; Bateman, S. D. (Novartis-AG) Pharmaceutical Composition Comprising Lumiracoxib. WO 03/020261 A1. March 13, 2003.

(11) Acemoglu, M.; Allmendinger, T.; Calienni, J.; Cercus, J.; Loiseleur, O.; Sedelmier, G. H.; Xu, D. *Tetrahedron*, **2004**, *60*, 11571.

(12) Barder, T. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 12003.

(13) (a) Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 5816. (b) Culkin, D. A.; Hartwig, J. F. *Organometallics* **2004**, *23*, 3398.

(14) (a) Ito, Y.; Nakatsuka, M.; Kise, N.; Saegusa, T. *Tetrahedron Lett.* **1980**, *21*, 2873. (b) Sodeoka, M.; Ohrai, K.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 2648. (c) Albéniz, A. C.; Catalina, N. M.; Espinet, P.; Redón, R. *Organometallics* **1999**, *18*, 5571. For a DFT study which reports an η^3-oxyallyl Pd transition state between O-bound and C-bound enolates, see: (d) Cámpora, J.; Maya, C. M.; Palma, P.; Carmona, E.; Gutiérrez, E.; Ruiz, C.; Graiff, C.; Tiripicchio, A. *Chem.—Eur. J.* **2005**, *11*, 6889.

(15) (a) Low, J. J.; Goddard, W. A. III. *J. Am. Chem. Soc.* **1984**, *106*, 8321. (b) Ananikov, V. P.; Musaev, D. G.; Morokuma, K. *Organometallics* **2005**, *24*, 715.

(16) Paine, A. J. *J. Am. Chem. Soc.* **1987**, *109*, 1496.

(17) Strieter, E. R.; Bhayana, B.; Buchwald, S. L. *Submitted for publication.*

(18) Zhang, S. L.; Liu, L.; Fu, Y.; Guo, Q. X. *Organometallics*, **2007**, *26*, 4546.

(19) Arai, S.; Hida, M.; Yamagishi, T.; *Bull. Chem. Soc. Jpn.* **1978**, *51*, 277.

(20) (a) Jazdzewski, B. A.; Young, V. G., Jr.; Tolman, W. B. *Chem. Comm.* **1998**, 2521. (b) Näther, C.; Beck, A. *Acta Crystallogr., Sect. E: Struct. Rep. Online* **2004**, *60*, m1008. (c) Blue, E. D.; Davis, A.; Conner, D.; Gunnoe, T. B.; Boyle, P. D.; White, P. S. *J. Am. Chem. Soc.* **2003**, *125*, 9435.

(21) Strieter, E. R.; Blackmond, D. G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4120.

(22) Strieter E. R. Mechanistic Studies on Metal-Catalyzed Carbon-Nitrogen Bond Forming Reactions. Ph.D. Thesis, Massachusetts Institute of Technology, Cambridge, MA, June 2005.

(23) Meyer, E. M.; Gambarotta, S.; Floriani, C.; Chiesi-Villa, A.; Guastini, C. *Organometallics* **1989**, *8*, 1067.

(24) Müller, P. MIT Department of Chemistry X-Ray Diffraction Facility: Growing Quality Crystals, http://web.mit.edu/x-ray/cystallize.html (accessed March 2007).

(25) (a) Eigen, M. *Angew. Chem. Int. Ed.* **1964**, *3*, 1. (b) Borwell, F. G.; Boyle, W. J.; Hautala, J. A.; Yee, K. C. *J. Am. Chem. Soc.* **1969**, *91*, 4002. (c) Kresge, A. J. *Acc. Chem. Res.* **1975**, *8*, 354.

(26) Anslyn, E. V.; Dougherty, D. A. *Modern Physical Organic Chemistry* 3rd Ed.; University Science Books: Sausalito, CA, 2006; pp 378-379.

(27) Hartwig, J. F. *Inorganic Chemistry* **2007**, *46*, 1936.

(28) Power, P. P.; Ruhlandt-Senge, K.; Shoner, S. C. *Inorg. Chem.* **1991**, *30*, 5013.

(29) Meyer, E. M.; Gambarotta, S.; Floriani, C.; Chiesi-Villa, A.; Guastini, C. *Organometallics* **1989**, *8*, 1067.

(30) Milne, J. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 13028.

(31) Frisch, M. J.; et al. *Gaussian 03*, revision D.01; Guassian Inc.: Wallingford, CT, 2004.

(32) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.

(33) (a) Svensson, M.; Humbel, S.; Froese, R. D. J.; Matsubara, T.; Sieber, S.; Morokuma, K. *J. Phys. Chem.* **1996**, *100*, 19357. (b) Vreven, T.; Morokuma, K.; Farkas, O.; Schlegel, H. B.; Frisch, M. J. *J. Comput. Chem.* **2003**, *24*, 760.

(34) Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 299.

(35) Angyal et al. *J. Chem. Soc.* **1957**, 1592.

(36) Hino et al. *Chem. Pharm. Bull.* **1973**, *21*, 2739.

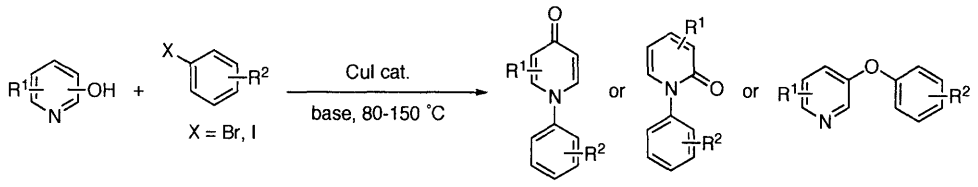
(37) Bergmann; Bille-Same *Bull.* Soc. *Chim. Fr.* **1968**, 1090.

(38) Przheval'skii, N. M.; Grandberg, I. I. *Chem. Heterocycl. Compd.* (Engl. Transl.) **1982**, *18*, 716.

(39) Ting, P. C.; Kaminski, J. J.; Sherlock, M. H.; Tom, W. C.; Lee, J. F.; et al. *J. Med. Chem.* **1990**, *33*, 2697.

Chapter Three

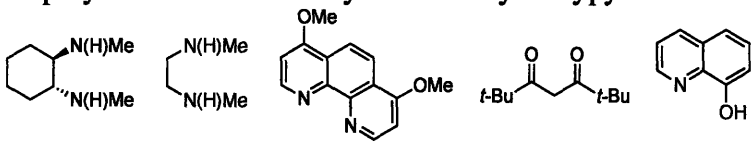
Copper-catalyzed Reactions of Hydroxypyridines and Related Compounds with Aryl Halides



3.1 Introduction

N-Aryl 2-, 4-hydroxypyridines, and *O*-aryl 3-hydroxypyridines manifest significant biological activities[1] and exhibit interesting photochemical properties.[2] The successful *N*- or *O*-arylation of 2-, 3-, and 4-hydroxypyridines with aryl halides have not been reported with the use of Pd-based methods;[3,4] however, the use of Cu for this transformation has been described.[5] Although the Cu-mediated cross-coupling of 2-hydroxypyridines with aryl boronic acids,[6] aryl stannanes,[7] and aryl bismuth reagents[8] has been previously reported, aryl halides are preferred substrates as these electrophiles tend to be more stable, easier to prepare, and/or less toxic than the corresponding B, Sn, and Bi counterparts. Several accounts of the Cu-catalyzed N-arylation of 2-hydroxypyridines with aryl halides have been reported without the use of added ligand and with ligands **1**, **2**, and **5**.[9] However, the Cu-catalyzed N- and O-arylations of 4- and 3-hydroxypyridines, respectively, are yet to be disclosed. Herein, we describe our recent progress in coupling hydroxypyridines and hydroxyquinolines with aryl halides.

Figure 1. Ligands Employed for *N*- and *O*-Arylation of Hydroxypyridines.



1 **2** **3** **4** **5**

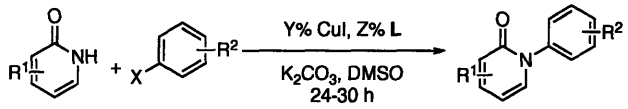
Previous accounts of the Cu-catalyzed N-arylation of 2-hydroxypyridine with *N*-containing aryl halides reported that many substrates were incompatible with the methods.[9] First, *N*-containing heteroaryl halides could not be utilized. Li proposed that the coordination of the sp^2-hybridized nitrogen lone pair electrons of these electrophiles to the copper catalyst impeded the cross-coupling reaction.[9d] Second, ortho-substituted aryl halides were unreactive, as a

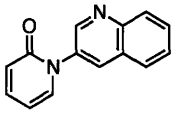
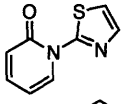
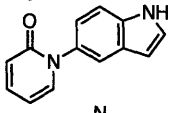
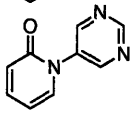
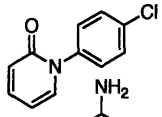
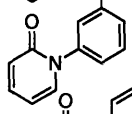
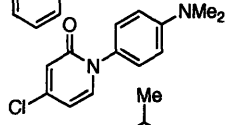
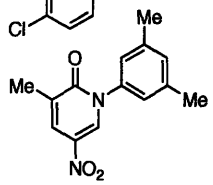
maximum yield of 2% was reported for the reactions of 2-hydroxypyridines with such substrates.[9] This finding agrees with the well-established notion that Cu-catalyzed C-heteroatom bond-forming reactions of aryl halides are particularly sensitive to steric hindrance on the electrophilic component.[6] Finally, 2-hydroxypyridines bearing strongly electron-withdrawing groups or containing substituents at the 6-position were also unreactive.[9d-f]

3.2 Results and Discussion

While ligands **1** and **2** were first designed and reported for reactions of Cu-catalyzed *N*-arylations of indoles[10] and amides[11] (pK_a = 21-26), using aryl iodides and bromides, 2-hyroxypyridine is significantly more acidic (pK_a = 17).[12] Since the pK_a of imidazole (pK_a = 19) is closer to that of the hydroxypyridine, we felt that a good catalyst system for the *N*-arylation of imidazoles[13] might also be effective for the *N*-arylation 2-hydroxypyridines. We recently reported that a catalytic system based on Cu_2O, 4,7-dimethoxy-1,10-phenanthroline (**3**) as a ligand, and poly(ethylene glycol) as an additive was efficient for promoting the *N*-arylation of imidazoles. Using a combination of CuI and **3**, we found that *N*-containing heterocyclic aryl halides could be coupled to 2-hydroxypyridine in modest to good yields (Table 1 entries 1-4). The reactions of 2-hydroxypyridine with aryl iodides and bromides can be successfully accomplished even in the presence of free N–H groups (Table 1, entries 3 and 6). By using this catalyst system, a nonconjugated electron-withdrawing group at the 5-position was tolerated (Table 1, entry 7). However, 2-hydroxy-3-methyl-5-nitropyridine was unreactive, presumably due to the decreased coordinating ability (nucleophilicity) of the hydroxypyridine (Table 1, entry 8).

Table 1. *N*-Arylation of 2-Hydroxypyridines[a]

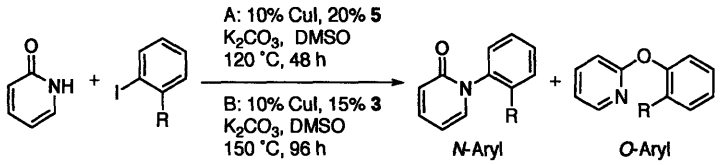


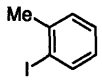
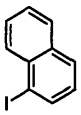
entry	product	X	L	Y/Z	temperature (°C)	yield[b] (%)
1		Br	**3**	5/7.5	110	82[c]
2		Br	**3**	5/7.5	110	85[c]
3		I	**1**	10/20	100	75
4		I	**3**	5/7.5	110	47
5		I	**3**	10/15	110	80
6		Br	**3**	5/7.5	110	78
7		Br	**3**	10/15	120	71
8		I	**3**	10/15	80-150	0

[a] General reaction conditions: 1.2 mmol of 2-hydroxypyridine, 1.0 mmol of ArX, 2.0 mmol of K_2CO_3, 1.0 mL of DMSO under Ar or N_2 atmosphere. [b] Isolated yield. [c] DMF used as solvent.

In our own attempts to improve the reaction of 2-hydroxypyridine with hindered aryl iodides, we discovered that a mixture of *N*- and *O*-aryl products was produced under the reaction conditions, with the latter being the major product. This phenomenon had not been previously reported for reactions of this type.[9] Using **5** as a ligand, we were able to achieve modest selectivity for coupling the 2-substituted aryl halides with 2-hydroxypyridine to afford moderate yields of 2-pyridylaryl ethers (Table 2). Under more forcing conditions, the selectivity changed from O to N, providing the *N*-aryl product in poor yield with **3** as a ligand. Interestingly, although N-arylation is the preferential pathway for the Cu-catalyzed arylation of 2-hydroxypyridines with unhindered aryl halides, the milder conditions for achieving the *O*-aryl product when using hindered aryl iodides suggest that the inherent preference for C–N bond-formation over C–O can be overcome by steric effects. While the procedures are not very selective, they do provide access to usable amounts of both the *N*-aryl and *O*-aryl products.

Table 2. Arylation of 2-Hydroxypyridine with Hindered Aryl Iodides[a]



entry	ArI	conditions[a]	*N*-Aryl : *O*-Aryl[b]	yield of major product[c] (%)
1		A	1.0 : 4.8	67
2		B	1.8 : 1.0	40
3		A	1.0 : 4.0	64
4		B	1.6 : 1.0	42

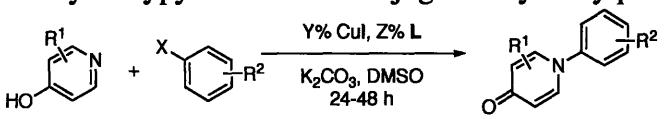
[a] Conditions A: 1.2 mmol of 2-hydroxypyridine, 1.0 mmol of ArI, 0.10 mmol of CuI, 0.15 mmol of **3**, 2.0 mmol of K_2CO_3, 1.0 mL of DMSO at 150 °C for 96 h under Ar or N_2 atmosphere. Conditions B: 1.2 mmol of 2-hydroxypyridine, 1.0 mmol of ArI, 0.10 mmol of CuI, 0.20 mmol of **5**, 2.0 mmol of K_2CO_3, 1.0 mL of DMSO at 120 °C for 48 h under Ar or N_2 atmosphere. [b] Detected by GC Analysis. [c] Isolated yield.

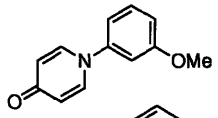
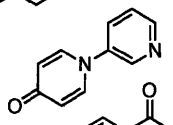
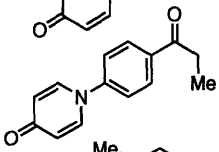
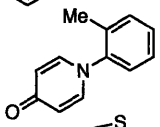
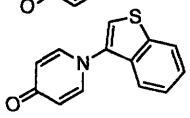
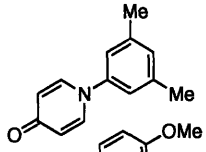
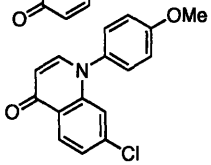
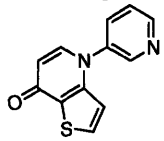
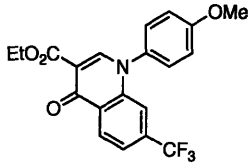
Although we have shown that **3** is a better ligand than diamines **1** and **2** for Cu-catalyzed reactions of 2-hydroxypyridine with *N*-containing heteroaryl halides and with 2-substituted aryl iodides, commercially available ligands **1**-**2** and **5** are still viable alternatives for other coupling transformations of 2-hydroxypyridines with aryl halides. Attempts to arylate 2-hydroxy-6-methylpyridine were met with limited success, even under forcing conditions. Presumably, the hindered amide coordinates too poorly to Cu(I) for the catalytic reaction to proceed. If the substrate does coordinate at N1, the methyl presumably impedes the aryl halide from interacting with the metal. On the other hand, if the methyl group provides too much hindrance to coordinate at nitrogen, the resulting **L**-Cu(I)-O species might not react with the aryl halide, to form the *O*-aryl product.

Since with Cu-catalysis 2-hydroxypyridines reacted preferentially with aryl halides at nitrogen instead of at oxygen, we became interested in exploring the selectivity difference between the N- and the O-positions for 4-hydroxypyridines. Previous investigations have shown

that, depending on the nature of the electrophile, reactions of 4-hydroxypyridine with an electrophile can form the *O*-substituted product as the major product, the *N*-substituted product as the major product, or mixtures of the *N*- and *O*-substituted products.[14] No O-arylation was detected in reports of the uncatalyzed N-arylation of 4-hydroxypyridine with activated aryl chlorides,[14] or in the Cu(II)-mediated vinylation with tetravinyl tin[15] or arylation with arylboronic acids.[16] Similarly, we have found that the Cu(I)-catalyzed coupling of 4-hydroxypyridine with a variety of aryl and heteroaryl iodides and bromides showed complete selectivity for reaction at nitrogen using ligands **3** and **4** (Table 3).[17] The use of other *N*- and *O*-based chelating ligands, including **1**, **2**, and **5**, provided significantly lower yields of the *N*-substituted product. Only when using 2-iodotoluene as the electrophile did we detect trace amounts of *O*-aryl product as identified by GC/MS (Table 3, entry 4). However, we were unable to achieve selectivity for formation of the aryl 4-pyridyl ether as the major product using a variety of conditions and ligands. Reactions of 4-hydroxyquinolines were accomplished by employing a stronger base and slightly higher temperatures (Table 3, entries 7 and 8). As with 2-hydroxypyridines, a 4-hydroxyquinoline with an electron-withdrawing group conjugated with the nitrogen was unreactive toward an aryl iodide under a variety of conditions (Table 3, entry 9).

Table 3. *N*-Arylation of 4-Hydroxypyridines and Conjugated Hydroxyquinolines[a]

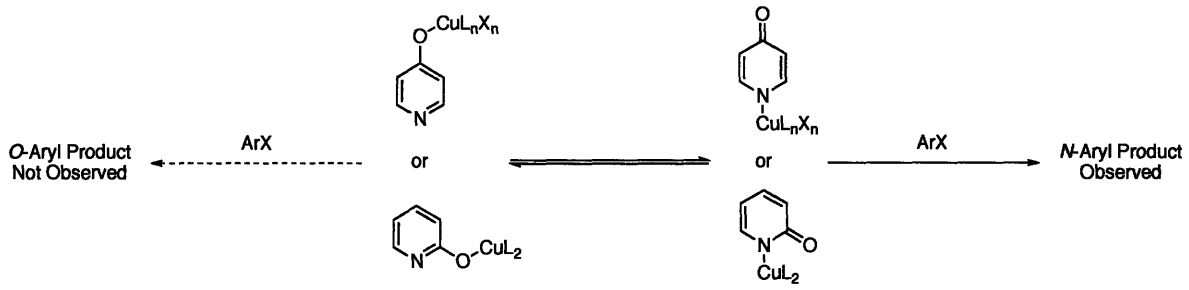


entry	product	X	L	Y/Z	temperature (°C)	yield[b] (%)
1		Br	**3**	5/7.5	110	95
2		Br	**3**	7/7.5	110	89
3		Br	**4**	5/20	110	92
4		I	**4**	10/40	110	63
5		Br	**4**	10/40	110	76
6		I	**4**	2/8	110	90
7		I	**4**	10/40	120	68[c]
8		I	**4**	10/40	120	65[c]
9		I	**4**	10/40	140	0

[a] General reaction conditions: 1.2 mmol of hydroxypyridine, 1.0 mmol of ArX, 2.0 mmol of K_2CO_3, 1.0 mL of DMSO under Ar or N_2 atmosphere. [b] Isolated yield. [c] K_3PO_4 used as base.

For the 2- and 4-hydroxypyridines, we tentatively propose that the selectivity favoring *N*-arylation occurs due to one of two factors. If the Cu–N binding affinity is significantly stronger than that for the Cu–O bond, isomerization from Cu–N to Cu–O might be slower than aryl halide activation (Scheme 1). Thus, the *N*-aryl product would form selectively. In the case that a non-negligible amount of the Cu–O species is present in solution, the selectivity might be due to a lower activation barrier for oxidative addition to the Cu–N species. Further work is necessary to interrogate these hypotheses.

Scheme 1. Selectivity of Cu-Catalyzed Reactions of 2- and 4-Hydroxypyridines with Aryl Halides.

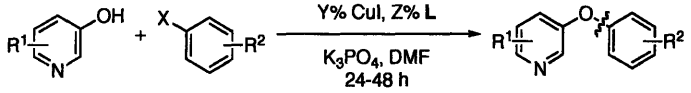


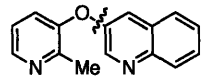
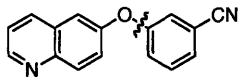
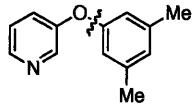
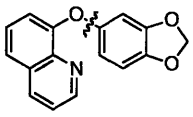
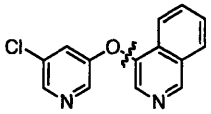
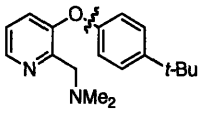
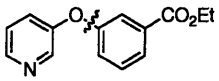
For 3-hydroxypyridine and related compounds, N-arylation is not a viable reaction pathway, and exclusive O-arylation might be possible. In our previous attempts to O-arylate 3-hydroxypyridines with aryl halides (using Pd catalysts), none of the desired product was observed.[4] To construct the aryl-3-pyridyl ether structure, it was necessary to cross-couple the 3-halopyridine with a phenol.

We have found that using a system based on CuI and 2,2,6,6-tetramethylheptane-3,5-dione, **4**,[18] 3-hydroxypyridines were successfully coupled with aryl bromides. The use of other *N*- and *O*-based chelating ligands in this reaction, including those depicted in Figure 1 and other β-diketones,[19] provided lower conversions and yields of product. Reactions of 3-hydroxypyridines with aryl halides containing water and/or base-sensitive functional groups could be accomplished at a lower temperature (80 °C) with the addition of molecular sieves to prevent hydrolysis of the nitrile and ester groups (Table 4, entries 2 and 7). The reaction of an aryl bromide was successful with a catalyst loading of 1% Cu, making this one of the most efficient Cu-catalyzed N- or O-arylation reaction of an aryl bromide reported to date (Table 4, entry 3). To O-arylate 8-hydroxyquinoline (Table 4, entry 4), ligand was not necessary, although more forcing conditions were required to achieve complete conversion of the aryl halide. In contrast, the presence of a neighboring coordinating group on the nucleophile has been

demonstrated to accelerate the N-arylation of R-amino acids significantly.[20] The requirement for more strenuous conditions to O-arylate 8-hydroxyquinoline is not surprising since it is an effective ligand for Cu-catalyzed *O*-arylation reactions of phenols.[21] Reactions of 3-hydroxypyridines with 3-bromoquinoline and 4-bromoisoquinoline were successful (Table 4, entries 2 and 6). This is notable, since the 3-pyridyl-3-(iso)quinolinyl ether structure cannot be accessed by other direct routes such as Pd-catalyzed methods or S_nAr of the corresponding 3-halopyridine under mild conditions without further activation (e.g., using 3-hydroxypyridine *N*-oxide). Under standard reaction conditions, the use of an aryl iodide gave significant amounts of diaryl ether as a byproduct. However, by using 4 Å molecular sieves and Cs_2CO_3 as a base,[22] a higher yield of aryl-pyridyl ether could be obtained (Table 4, entry 8).

Table 4. *O*-Arylation of 3-Hydroxypyridine and Nonconjugated Hydroxyquinolines[a]



entry	product	X	L	Y/Z	temperature (°C)	yield[b] (%)
1		Br	4	5/20	110	82
2		Br	4	10/40	80	78[c]
3		Br	4	1/4	120	91
4		Br	4	10/40	130	56[d]
5		Br	4	10/40	120	69
6		Br	-	10/0	110	77
7		I	4	10/40	80	91[e]

[a] General reaction conditions: 1.2 mmol of hydroxypyridine, 1.0 mmol of ArX, 2.0 mmol of K_3PO_4, 1.0 mL of DMF under Ar or N_2 atmosphere. [b] Isolated yield. [c] MeCN used as solvent with 3 Å molecular sieves. [d] DMSO used as solvent. [e] Cs_2CO_3 used as base with 3 Å molecular sieves.

3.3 Conclusion

In conclusion, we have developed a series of catalysts for the N- and O-arylation of hydroxypyridines and hydroxyquinolines. Future efforts will be devoted both to maximizing the efficiency and scope of this method as well as to determining the mechanistic basis behind the observed selectivity.

3.4 Experimental Procedures

All reactions were carried out in resealable test tubes with teflon septa under a dry argon or nitrogen atmosphere. Copper(I) iodide (99.99%) was purchased from Strem as an off-white solid. Ligands **1**, **2**, **4** and **5** were purchased from commercial sources and used without further purification. Ligand **3** was prepared according to our previously reported procedure.[23] Anhydrous K_2CO_3 (99.99%) was purchased from Aldrich in glass ampules. Powdered K_3PO_4 was purchased from Riedel-de Haën. Cs_2CO_3 (99.9%) was purchased from Alfa Aesar. The bulk of the bases were stored under nitrogen in a Vacuum Atmospheres glovebox. Small portions (~5 g) were removed from the glovebox in glass vials, stored in the air in a desiccator filled with anhydrous calcium sulfate, and weighed in the air. Hydroxypyridines and hydroxyquinolines were purchased from commercial sources and used without further purification. Aryl halides were purchased from commercial sources and filtered through neutral alumina or distilled. Anhydrous solvents were purchased from Aldrich in Sure-Seal® bottles. Flash column chromatography was performed using a Biotage SP4 Flash Purification System using KP-Sil silica cartridges. In all cases, dichloromethane was used to transfer the crude reaction material onto the silica gel samplet. A gradient elution technique was performed, based on the recommendation from the Biotage TLC Wizard.

Yields reported in the publication are of the isolated material and represent an average of

at least two independent runs. Yields reported in the supporting information refer to a single experiment. Compounds described in the literature were characterized by comparing their ^{1}H NMR and ^{13}C NMR spectra, and melting points (m.p.) to the previously reported data; their purity was confirmed by gas chromatography (GC) or elemental analysis. GC analyses were performed on a Hewlett Packard 6890 instrument with an FID detector and a Hewlett Packard 10 m x 0.2 mm i.d. HP-1 capillary column using dodecane as an internal standard. Previously unknown compounds were synthesized, purified and analyzed from a single run and were then repeated to determine an average yield. They were characterized by ^{1}H NMR, ^{13}C NMR, m.p., IR and elemental analysis. Elemental analyses were performed by Atlantic Microlabs, Inc., Norcross, GA. For those compounds that did not give a satisfactory elemental analysis, a copy of their ^{1}H NMR spectra is included. ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian 500 MHz instruments with chemical shifts reported relative to the deuterated solvent or TMS. IR spectra were recorded on a Perkin-Elmer System 2000 FT-IR instrument for all previously unknown compounds (KBr disc). Melting points (uncorrected) were obtained on a Mel-Temp II capillary melting point apparatus.

General procedure for the *N*- and *O*-Arylation of hydoxypyridines and hydroxyquinolines

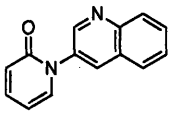
An oven-dried screw-cap test tube was charged with CuI, ligand (if solid), hydroxypyridine (1.2 mmol), aryl halide (1.00 mmol, if solid), base (2.0 mmol), and a magnetic stir bar. The reaction vessel was fitted with a rubber septum. The test tube was evacuated and back-filled with dry argon or nitrogen. Aryl halide (1.00 mmol, if liquid), ligand (if liquid) and solvent were then added successively. The rubber septum was removed and the reaction tube was quickly sealed with a Teflon septum. The vessel was immersed in a pre-heated oil bath and stirred vigorously

for the designated time period.

Workup A: The reaction mixture was cooled to room temperature, diluted with ethyl acetate (15 mL), and filtered through a plug of silica, eluting with additional ethyl acetate (50 mL). The filtrate was concentrated and the resulting residue was purified by flash chromatography to provide the desired product.

Workup B: The crude reaction mixture was diluted in CH_2Cl_2 (15 mL) and filtered through a celite plug eluting with additional CH_2Cl_2 (20 mL). The filtrate was washed successively with aqueous NH_4OH then brine. The combined aqueous layers were extracted twice with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and then concentrated. The resulting residue was purified by flash chromatography to provide the desired product.

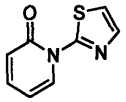
Experimental procedures for compounds in Table 1



1-(quinolin-3-yl)pyridin-2(1H)-one (entry 1)

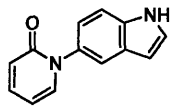
The general procedure was followed using CuI (9.5 mg, 0.05 mmol), **3** (36 mg, 0.15 mmol), K_2CO_3 (0.28 g, 2.0 mmol), 3-bromoquinoline (136 μL, 1.00 mmol), 2-hydroxypyridine (114 mg, 1.2 mmol) with DMF (0.5 mL) as solvent for 24 h at 110 °C. Workup B, followed by chromatographic purification (hexane / ethyl acetate) provided the title compound as a white solid (177 mg, 80%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.95 (d, 1H, J = 2.4 Hz), 8.21 (d, 1H, J = 2.3 Hz), 8.16 (d, 1H, J = 8.5 Hz), 7.85 (d, 1H, J = 8.4 Hz), 7.78 (m, 1H), 7.61 (m, 1H), 7.47-7.40 (m,

3H), 6.72 (d, 1H, J = 9.7 Hz), 6.33 (td, 1H, J = 6.7, 1.2 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.6, 148.5, 147.5, 140.6, 137.7, 134.5, 133.0, 130.6, 129.6, 128.2, 127.8, 122.3, 106.9. IR (KBr disc, cm^{-1}) 1661, 1584, 1535, 1148, 927, 767, 759, 747. Anal. Calc. for $C_{14}H_{10}N_2O$: C 75.66, H 4.54. Found: C 75.34, H 4.71. m.p. 145-146 °C. (Lit. 145-146 °C).[24]



1-(thiazol-2-yl)pyridin-2(1H)-one (entry 2)

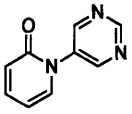
The general procedure was followed using CuI (19 mg, 0.10 mmol), **3** (36 mg, 0.15 mmol), K_2CO_3 (0.28 g, 2.0 mmol), 2-bromothiazole (90 μL, 1.00 mmol), 2-hydroxypyridine (114 mg, 1.2 mmol) with DMF (1.0 mL) as solvent for 24 h at 110 °C. Workup A followed by chromatographic purification (hexane / ethyl acetate) provided the title compound (white solid, 142 mg, 80%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.74 (ddd, 1H, J = 0.6, 1.9, 8.2 Hz), 7.59 (d, 1H, J = 3.5 Hz), 7.37-7.34 (m, 1H), 7.17 (d, 1H, 3.5 Hz), 6.68 (dt, 1H, J = 1.0, 9.2 Hz), 6.33 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.6, 156.1, 139.8, 137.9, 131.9, 121.6, 118.8, 107.5. IR (KBr disc, cm^{-1}) 3118, 1670, 1543, 1500, 1275, 1138, 981, 867, 844, 771, 717, 621. Anal. Calc. for $C_8H_6N_2OS$: C 53.92, H 3.39. Found: C 53.94, H 3.42. m.p. 89-90 °C. (Lit. 85.5-86 °C).[25]



1-(1H-indol-5-yl)pyridin-2(1H)-one (entry 3)

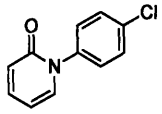
The general procedure was followed using CuI (19 mg, 0.10 mmol), **1** (32 mL, 0.40 mmol), K_2CO_3 (0.28 g, 2.0 mmol), 5-iodoindole (243 mg, 1.00 mmol), 2-hydroxypyridine (114 mg, 1.2 mmol) with DMSO (0.5 mL) as solvent for 24 h at 110 °C. Workup A followed by chromatographic purification (CH_2Cl_2 / ethyl acetate), and then recrystallization from CH_2Cl_2, provided 165 mg of the product as a white solid (78%). ^{1}H NMR (500 MHz, DMSO-D_6) δ 11.3

(bs, 1H), 7.65 (dd, J = 1.6, 6.8 Hz), 7.51-7.45 (m 3H), 7.03 (dd, 1H, J = 4.3, 6.1 Hz), 6.50-6.45 (m, 2H), 6.28 (td, 1H, J = 6.7, 1.7 Hz). ^{13}C NMR (125 MHz, DMSO-D_6) δ 161.8, 140.3, 140.0, 135.0, 133.0, 127.5, 126.9, 120.4, 119.9, 118.0, 111.5, 105.1, 101.6. m.p. 218-220 °C.



1-(pyrimidin-5-yl)pyridin-2(1H)-one (entry 4)

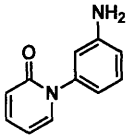
The general procedure was followed using CuI (19 mg, 0.10 mmol), **3** (36 mg, 0.15 mmol), K_2CO_3 (0.28 g, 2.0 mmol), 5-bromopyrimidine (159 mg, 1.00 mmol), 2-hydroxypyridine (114 mg, 1.2 mmol) with DMSO (0.5mL) as solvent for 24 h at 110 °C. The crude reaction mixture was diluted with CH_2Cl_2 and filtered. The filtrate was concentrated to a white/yellow solid. The product was recrystallized from hot EtOAc to provide 1-(pyrimidin-5-yl)pyridin-2(1H)-one as a white solid (83.5 mg, 48%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.26 (s, 1H), 8.91 (s, 2H), 7.47 (m, 1H), 7.31 (m, 1H), 6.70 (m, 1H), 7.36 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.9, 158.0, 154.6, 141.1, 136.5, 122.4, 107.5, 100.0. IR (KBr disc, cm^{-1}) 1664, 1591, 1415, 1299, 1147, 994, 847, 765, 721. Anal. Calc. for $C_9H_7N_3O$: C 62.42, H 4.07. Found: C 62.63, H 4.03. m.p. 201-202 °C.



1-(4-chlorophenyl)pyridin-2(1H)-one (entry 5)

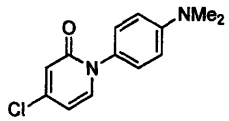
The general procedure was followed using CuI (19 mg, 0.10 mmol), **3** (36 mg, 0.15 mmol), K_2CO_3 (0.28 g, 2.0 mmol), 1-chloro-4-iodobenzene (243 mg, 1.00 mmol), 2-hydroxypyridine (114 mg, 1.2 mmol) with DMSO (0.5 mL) as solvent for 24 h at 110 °C. Workup B, followed by chromatographic purification (hexane / ethyl acetate) provided the title compound (white solid,

169 mg, 82%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49-7.45 (m, 2H), 7.43-7.39 (m, 1H), 7.35-7.25 (m, 2H), 7.30 (ddd, J = 0.8, 2.1, 6.9 Hz), 6.66 (m, 1H), 6.26 (td, 1H, J = 6.7, 1.3 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.4, 140.2, 139.5, 137.8, 1344.6, 129.7, 128.1, 122.2, 106.4. Anal. Calc. for $C_{11}H_8NOCl$: C 64.25, H 3.92. Found: C 64.09, H 3.92. m.p. 122-124 °C. (Lit. 133 °C)[26]



1-(3-aminophenyl)pyridin-2(1H)-one (entry 6)

The general procedure was followed using CuI (19 mg, 0.10 mmol), **3** (36 mg, 0.15 mmol), K_2CO_3 (0.28 g, 2.0 mmol), 3-bromoaniline (109 μL, 1.00 mmol), 2-hydroxypyridine (114 mg, 1.2 mmol) with DMSO (0.5 mL) as solvent for 24 h at 110 °C. Workup A followed by chromatographic purification (ethyl acetate / isopropanol) provided the title compound (off-white solid, 162 mg, 87%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41-7.19 (m, 3H), 6.70-6.21 (m, 3H), 62.1 (td, 1H, J = 1.1, 6.9 Hz), 3.54 (bs, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.7, 147.8, 142.0, 140.0, 138.3, 130.3, 121.8, 116.1, 115.4, 113.4, 105.9. m.p. 180-182 °C. (Lit. 182.5-184.5°C).[27]

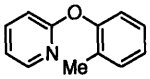


4-chloro-1-(4-(dimethylamino)phenyl)pyridin-2(1H)-one (entry 7)

The general procedure was followed using CuI (19 mg, 0.10 mmol), **3** (36 mg, 0.15 mmol), K_2CO_3 (0.28 g, 2.0 mmol), *N*,*N*-dimethyl-4-bromoanilne (200 mg, 1.00 mmol), 5-chloro-2-hydroxypyridine (156 mg, 1.2 mmol) with DMSO (1.0 mL) as solvent for 24 h at 110 °C. Workup B, followed by chromatographic purification (hexane / ethyl acetate) provided the product as a pale yellow solid (193 mg, 78%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, 1H, J = 2.9 Hz), 7.32 (dd, 2.9, J = 9.8 Hz), 7.21-7.18 (m, 2H), 6.77-6.74 (m, 2H), 6.61 (d, 1H, J = 9.8 Hz),

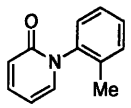
3.00 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.5, 150.6, 140.6, 136.4, 129.2, 126.9, 122.5, 112.5, 112.1. IR (KBr disc, cm^{-1}) 1664, 1363, 1266, 1120, 1062, 944, 782, 728, 646. Anal. Calc. for $C_{13}H_{13}ClN_2O$: C 62.78, H 5.27. Found: C 62.52, H 5.24. m.p. 159-160 °C.

Experimental procedures for compounds in Table 2



2-(o-tolyloxy)pyridine[28] (entry 1)

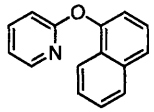
The general procedure was followed using CuI (19 mg, 0.10 mmol), **5** (29 mg, 0.20 mmol), K_2CO_3 (0.28 g, 2.0 mmol), 2-iodotoluene (127 μL, 1.00 mmol), 2-hydroxypyridine (114 mg, 1.2 mmol) with DMSO (1.0 mL) as solvent for 48 h at 120 °C. GC analysis of the crude reaction mixture showed full conversion of the aryl iodide and a 1.0 : 4.7 ratio of *N*- to *O*-arylated products. Workup B, followed by chromatographic purification (hexane / ethyl acetate) provided the *O*-arylated product (white solid, 135 mg, 73%). ^1H NMR (500 MHz, $CDCl_3$) δ 8.09 (dd, J = 1.2, 4.9 Hz), 7.59-7.56 (m, 1H), 7.20-7.14 (m, 2H), 7.06 (td, 1H, J = 0.8, 7.5 Hz), 6.98 (dd, 1H, J = 1.2, 7.9 Hz), 6.87 (ddd, 1H, J = 0.9, 5.0, 7.2 Hz), 6.77 (m, 1H), 2.10 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.9, 152.4, 148.0, 139.5, 133.3, 131.6, 131.0, 130.7, 127.3, 125.4, 122.0, 118.1, 110.8, 16.6. m.p. 44-45.5 °C.



1-o-tolylpyridin-2(1H)-one[29] (entry 2)

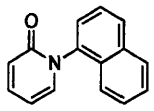
The general procedure was followed using CuI (19 mg, 0.10 mmol), **3** (36 mg, 0.15 mmol), K_2CO_3 (0.28 g, 2.0 mmol), 2-iodotoluene (153 μL, 1.20 mmol), 2-hydroxypyridine (96 mg, 1.0 mmol) with DMSO (0.5 mL) as solvent for 96 h at 150 °C. GC analysis of the crude reaction

mixture showed full conversion of the aryl iodide and a 1.6 : 1 ratio of *N*- to *O*-arylated products. Workup B, followed by chromatographic purification (hexane / ethyl acetate) provided the *N*-arylated product as a slightly yellow solid (79 mg, 43%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45-7.42 (m, 1H), 7.36-7.30 (m, 3H), 7.21-7.18 (m, 2H), 6.69-6.67 (m, 1H), 6.27-6.24 (m, 1H), 2.16 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.21, 140.3, 140.1, 138.1, 135.1, 131.2, 129.2, 127.2, 127.1, 121.9, 105.9, 17.7. Anal. Calc. for $C_{12}H_{11}NO$: C 77.81, H 77.19. Found: C 77.49, H 6.03. m.p. 71-72.5 °C.



2-(naphthalen-1-yloxy)pyridine (entry 3)

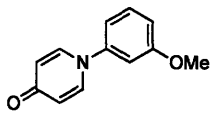
The general procedure was followed using CuI (19 mg, 0.10 mmol), **5** (36 mg, 0.15 mmol), K_2CO_3 (0.28 g, 2.0 mmol), 1-iodonaphthalene (260 μL, 1.00 mmol), 2-hydroxypyridine (114 mg, 1.2 mmol) with DMSO (1.0 mL) as solvent for 48 h at 120 °C. GC analysis of the crude reaction mixture showed full conversion of the aryl iodide and a 1.0 : 3.7 ratio of *N*- to *O*-arylated products. Workup B, followed by chromatographic purification (hexane / ethyl acetate) provided 137 mg of the *O*-arylated product (white solid, 62%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.2 (dd, 1H, J = 1.3, 4.6 Hz), 8.04-8.02 (m, 1H), 7.91 (dd, 1H, J = 0.6, 8.2 Hz), 7.76 (d, 1H, J = 8.2 Hz), 7.53-7.46 (m, 3H), 7.26 (dd, 1H, J = 0.9, 7.5 Hz), 7.02-6.99 (m, 1H), 6.96 (d, 1H, J = 8.2 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.2, 148.2, 139.7, 125.2, 128.2, 127.7, 126.6, 126.3, 126.0, 125.2, 122.2, 118.6, 117.3, 111.1. IR (KBr disc, cm^{-1}) 1592, 1465, 1426, 1387, 1282, 1156, 1070, 1037, 1013, 890, 839, 799, 773, 672, 534. Anal. Calc. for $C_{15}H_{11}NO$: C 81.43, H 5.01. Found: C 81.27, H 4.98. m.p. 80.5-82 °C.



1-(naphthalen-1-yl)pyridin-2(1H)-one (entry 4)

The general procedure was followed using CuI (19 mg, 0.10 mmol), **3** (36 mg, 0.15 mmol), K_2CO_3 (0.28 g, 2.0 mmol), 1-iodonaphthalene (175 μL, 1.20 mmol), 2-hydroxypyridine (96 mg, 1.0 mmol) with DMSO (0.5 mL) as solvent for 96 h at 150 °C. GC analysis of the crude reaction mixture showed full conversion of the aryl iodide and a 1.7 : 1.0 ratio of *N*- to *O*-arylated products. Workup B, followed by chromatographic purification (hexane / ethyl acetate) provided 97 mg of the *N*-arylated product (yellow solid, 44%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98-7.89 (m, 1H), 7.60-7.46 (m, 7H), 7.33-7.31 (m, 1H), 6.77 (dd, 1H, J = 0.8, 9.3 Hz), 6.32 (td, 1H, J = 6.7, 1.2 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.9, 140.5, 139.1, 137.8, 134.5, 129.7, 129.4, 128.1, 127.6, 126.9, 125.6, 125.2, 122.5, 122.0, 106.0. IR (KBr disc, cm^{-1}) 3062, 1660, 1590, 1571, 1394, 1284, 1136, 964, 773. Anal. Calc. for $C_{15}H_{11}NO$: C 81.43, H 5.01. Found: C 81.05, H 5.00. m.p. 132-134 °C.

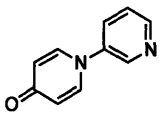
Experimental procedures for compounds in Table 3



1-(3-methoxyphenyl)pyridin-4(1H)-one (entry 1)

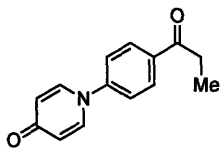
The general procedure was followed using CuI (19 mg, 0.10 mmol), **3** (36 mg, 0.15 mmol), K_2CO_3 (0.28 g, 2.0 mmol), 3-bromoanisole (125 μL, 1.00 mmol), 4-hydroxypyridine (114 mg, 1.2 mmol) with DMF (0.5 mL) as solvent for 24 h at 110 °C. Workup B, followed by chromatographic purification (ethyl acetate/ isopropanol) provided 197 mg of product (white

solid, 98%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64-7.59 (m, 2H), 7.43 (t, 1H, J = 8.3 Hz), 7.00-6.91 (m, 2H), 6.85 (t, 1H, J = 2.5 Hz), 6.52 (m, 2H), 3.88 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.1, 160.0, 144.3, 139.2, 131.1, 119.0, 114.8, 113.8, 109.0, 55.8. IR (KBr disc, cm^{-1}) 3034, 2954, 16.6, 1569, 1347, 1286, 1051, 845, 762, 679. Anal. Calc. for $C_{12}H_{11}NO_2$: C 71.63, H 5.51. Found: C 71.85, H 5.43. m.p. 151-152 °C.



1-(pyridin-3-yl)pyridin-4(1H)-one (entry 2)

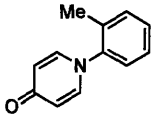
The general procedure was followed using CuI (19 mg, 0.10 mmol), **3** (36 mg, 0.15 mmol), K_2CO_3 (0.28 g, 2.0 mmol), 3-bromopyridine (98 μL, 1.00 mmol), 4-hydroxypyridine (114 mg, 1.2 mmol) with DMSO (0.5 mL) as solvent for 24 h at 110 °C. Workup A followed by chromatographic purification (ethyl acetate/ isopropanol) provided 1-(pyridin-3-yl)pyridin-4(1H)-one (white solid, 167 mg, 97%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.71-8.69 (m, 2H), 7.74 (m, 1H), 7.59 (m, 2H), 7.30 (m, 1H), 6.52 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.9, 149.8, 144.1, 141.0, 139.0, 130.4, 124.6, 119.5. m.p. 205-206 °C. (Lit. 189-191 °C)[30]



1-(4-propanoylphenyl)pyridin-4(1H)-one (entry 3)

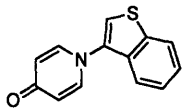
The general procedure was followed using CuI (9.5 mg, 0.05 mmol), **4** (20 mL, 0.20 mmol), K_2CO_3 (0.28 g, 2.0 mmol), 4'-bromopropiophenone (213 mg, 1.00 mmol), 4-hydroxypyridine (114 mg, 1.2 mmol) with DMSO (0.5 mL) as solvent for 24 h at 110 °C. Workup B, followed by chromatographic purification (ethyl acetate/ methanol) provided the title compound as a white solid (199 mg, 87%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (m, 2H), 7.65 (m, 2H), 7.44 (m, 2H),

6.48 (m, 2H), 3.02 (q, 2H, J = 7.2 Hz), 1.22 (t, 3H, J = 7.2 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.2. 179.0. 146.1. 138.6. 138.3. 130.2. 122.5. 119.3. 32.0. 8.1. IR (KBr disc, cm^{-1}) 1636, 1412, 1342, 1281, 1192, 1017, 952. m.p. 182-184 °C.



1-o-tolylpyridin-4(1H)-one (entry 4)

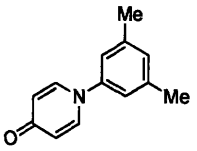
The general procedure was followed using CuI (19 mg, 0.10 mmol), 4 (40 mL, 0.40 mmol), K_2CO_3 (0.28 g, 2.0 mmol), 2-iodotoluene (127 μL, 1.00 mmol), 4-hydroxypyridine (114 mg, 1.2 mmol) with DMSO (1.0 mL) as solvent for 24 h at 110 °C. Workup B, followed by chromatographic purification (ethyl acetate/ methanol) provided a white solid (121 mg, 65%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41-7.31 (m, 4H), 7.24 (dd, 1H, J = 1.2, 7.8 Hz), 6.48-6.45 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.9, 142.4, 140.5, 133.9, 132.0, 129.9, 127.7, 126.3, 118.7, 17.6. m.p. 149-150 °C. (Lit. 148 °C).[31]



1-(benzo[b]thiophen-3-yl)pyridin-4(1H)-one (entry 5)

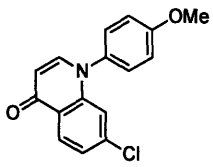
The general procedure was followed using CuI (19 mg, 0.10 mmol), 4 (42 mL, 0.40 mmol), K_2CO_3 (0.28 g, 2.0 mmol), 3-bromothianaphthene (131 μL, 1.00 mmol), 4-hydroxypyridine (114 mg, 1.2 mmol) with DMSO (0.5 mL) as solvent for 24 h at 110 °C. Workup B followed by chromatographic purification (ethyl acetate/ methanol) provided the title product as an oil, which was then triturated with CH_2Cl_2 and hexane (white solid, 164 mg, 72%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95-7.93 (m, 1H), 7.66-7.49 (m, 6H), 6.56-6.53 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.1, 140.4, 139.1, 135.7, 133.2, 126.3, 125.8, 123.8, 121.5, 120.6, 119.1. IR (KBr disc, cm^{-1})

1632, 1558, 1402, 1367, 1191, 939, 855, 760, 586, 564. Anal. Calc. for $C_{13}H_9NOS$: C 68.70, H 3.99. Found: C 68.44, H 4.12. m.p. 188.5-190 °C.



1-(3,5-dimethylphenyl)pyridin-4(1H)-one (entry 6)

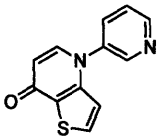
The general procedure was followed using CuI (3.8 mg, 0.020 mmol), **4** (8 mL, 0.08 mmol), K_2CO_3 (0.28 g, 2.0 mmol), 5-iodo-*m*-xylene (144 μL, 1.00 mmol), 4-hydroxypyridine (114 mg, 1.2 mmol) with DMSO (0.5 mL) as solvent for 24 h at 110 °C. Workup B followed by chromatographic purification (ethyl acetate/ methanol) provided the product as a white solid (175 mg, 88%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59-7.57 (m, 2H), 7.07 (s, 1H), 6.95 (s, 2H), 6.49-6.47 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.1, 143.3, 140.4, 139.4, 130.2, 120.6, 119.0, 21.4. IR (KBr disc, cm^{-1}) 1650, 1617, 1555, 1457, 1333, 1203, 846, 696. Anal. Calc. for $C_{13}H_{13}NO$: C 78.36, H 6.58 Found: C 77.96 H 6.49. m.p. 138-139 °C.



7-chloro-1-(4-methoxyphenyl)quinolin-4(1H)-one (entry 7)

The general procedure was followed using CuI (19 mg, 0.10 mmol), **4** (40 mL, 0.15 mmol), K_3PO_4 (0.42 g, 2.0 mmol), 4-iodoanisole (234 mg, 1.00 mmol), 7-chloro-4-hydroxyphenanthroline (216 mg, 1.2 mmol) with DMSO (1.0 mL) as solvent for 24 h at 120 °C. Workup B followed by chromatographic purification (hexane / ethyl acetate) provided 198 mg of the title compound as a white solid (69%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (dd, 1H, J = 0.5, 8.7 Hz), 7.47 (d, 1H, J = 7.8 Hz), 7.24-7.20 (m, 3H), 7.03-7.00 (m, 2H), 6.88 (d, 1H, J = 3.3 Hz),

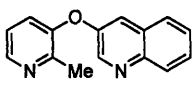
6.24 (d, 1H, J = 7.8 Hz), 3.84 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.7, 160.5, 143.6, 142.6, 138.4, 133.6, 128.7, 128.4, 125.0, 124.6, 117.1, 115.7, 110.7, 55.9. IR (KBr disc, cm^{-1}) 1603, 1510, 1449, 1252, 1169, 1032, 909, 813, 734, 646. Anal. Calc. for $C_{16}H_{12}NO_2Cl$: C 67.26, H 4.23. Found: C 66.99, H 4.19. m.p. 173-176 °C.



4-(pyridin-3-yl)thieno[3,2-b]pyridin-7(4H)-one (entry 8)

The general procedure was followed using CuI (9.5 mg, 0.05 mmol), **4** (21 mL, 0.20 mmol), K_3PO_4 (0.42 g, 2.0 mmol), 2-bromopyridine (49 μL, 1.00 mmol), thieno[3,2-b]pyridin-7-ol (90 mg, 1.2 mmol) with DMSO (0.5 mL) as solvent for 24 h at 110 °C. Workup B followed by chromatographic purification (ethyl acetate/ methanol) provided the product (white solid, 83 mg, 73%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.76-8.74 (m, 2H), 7.87 (ddd, 1H, J = 1.5, 2.6, 8.1 Hz), 7.61 (d, 1H, J = 5.5 Hz), 7.56 (dd, 1H, J = 4.7, 8.1 Hz), 7.49 (d, 1H, J = 7.6 Hz), 6.76 (d, J = 5.5 Hz), 6.33 (d, 1H, J = 7.6 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.1, 150.6, 147.1, 144.5, 139.9, 133.7, 132.5, 130.7, 129.7, 124.7, 117.3, 112.1. IR (KBr disc, cm^{-1}) 1610, 1493, 1425, 1291, 1221, 1124, 877, 820, 711. m.p. 189-190 °C.

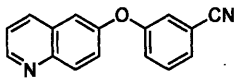
Experimental procedures for compounds in Table 4



3-(2-methylpyridin-3-yloxy)quinoline (entry 1)

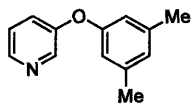
The general procedure was followed using CuI (9.5 mg, 0.05 mmol), **4** (20 mL, 0.20 mmol), K_3PO_4 (0.42 g, 2.0 mmol), 3-bromoquinoline (136 μL, 1.00 mmol), 3-hydroxy-2-methylpyridine

(131 mg, 1.2 mmol) with DMF (1.0 mL) as solvent for 24 h at 110 °C. Workup B followed by chromatographic purification (hexane / ethyl acetate) provided the title compound as a white solid (184 mg, 78%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.84 (d, 1H, J = 2.7 Hz), 8.42 (dd, 1H, J = 1.2, 4.7 Hz), 8.12 (d, 1H, J = 8.4 Hz), 7.69-7.52 (m, 3H), 7.37 (d, 1H, J = 2.7 Hz), 7.30 (m, 1H), 7.21 (m, 1H), 2.56 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.7, 150.7, 150.5, 145.4, 144.9, 144.6, 129.4, 128.6, 128.3, 127.7, 127.2, 126.9, 122.6, 119.1, 19.6. IR (KBr disc, cm^{-1}) 1602, 1497, 1424, 1342, 1246, 1175, 984, 911, 783, 754. Anal. Calc. for $C_{15}H_{12}N_2O$: C 76.25, H 5.12. Found: C 76.36, H 5.09. m.p. 67-69 °C.



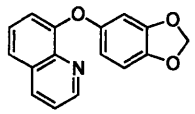
3-(quinolin-3-yloxy)benzonitrile (entry 2)

The general procedure was followed using CuI (19 mg, 1.0 mmol), **4** (42 mL, 0.40 mmol), K_3PO_4 (0.42 g, 2.0 mmol), 3-bromobenzonitrile (182 mg, 1.00 mmol), 6-hydroxyquinoline (174 mg, 1.2 mmol) and 3Å mol. sieves (200 mg flame activated under vacuum) with DMF (1.0 mL) as solvent for 24 h at 110 °C. Workup A followed by chromatographic purification (hexane / ethyl acetate) provided 191 mg of the title compound as a white solid (78%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.85 (s, 1H), 8.10 (d, 1H, J = 9.2 Hz), 8.02 (dd, 1H, J = 1.4, 8.2 Hz), 7.45-7.37 (m, 4H), 7.28-7.24 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.5, 153.9, 149.9, 145.7, 135.5, 132.1, 131.0, 127.3, 123.5, 123.3, 122.0, 118.2, 115.1, 114.8, 113.8. IR (KBr disc, cm^{-1}) 2232, 1622, 1579, 1500, 1480, 1326, 1216, 1156, 967, 795, 682. Anal. Calc. for $C_{16}H_{10}N_2O$: C 78.03, H 4.11. Found: C 77.99, H 4.11. m.p. 85-87 °C.



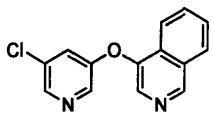
3-(3,5-dimethylphenoxy)pyridine (entry 3)

The general procedure was followed using CuI (1.9 mg, 0.01 mmol), **4** (4 mL, 0.04 mmol), K_3PO_4 (0.42 g, 2.0 mmol), 5-iodo-*m*-xylene (145 μL, 1.00 mmol), 2-hydroxypyridine (114 mg, 1.2 mmol) with DMF (1.0 mL) as solvent for 24 h at 110 °C. Workup A followed by chromatographic purification (hexane / ethyl acetate) provided the title compound as a yellow oil (177 mg, 89%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.40 (s, 1H), 8.34 (d, 1H, J = 3.6 Hz), 7.29-7.23 (m, 2H), 6.79 (m, 1H), 6.64 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.3, 144.2, 141.5, 140.0, 125.9, 125.5, 124.1, 116.8, 21.4. IR (KBr disc, cm^{-1}) 1615, 1573, 1475, 1422, 1297, 1137, 1022, 950, 853, 803, 709. Anal. Calc. for $C_{13}H_{13}NO$: C 78.36, H 6.58. Found: C 78.55, H 6.80.



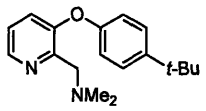
8-(benzo[d][1,3]dioxol-5-yloxy)quinoline (entry 4)

The general procedure was followed using CuI (19 mg, 0.10 mmol), **4** (42 mL, 0.40 mmol), K_3PO_4 (0.42 g, 2.0 mmol), 4-bromo-1,2-methylenedioxybenzene (120 μL 1.00 mmol), 8-hydroxyquinoline (174 mg, 1.2 mmol) with DMSO (1.0 mL) as solvent for 48 h at 130 °C. Workup B followed by chromatographic purification (hexane / ethyl acetate) provided 145 mg of the title compound (yellow oil, 56%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.99 (dd, 2H, J = 1.7, 4.1 Hz), 8.18 (dd, 1H, J = 1.7, 8.4 Hz), 7.50 (dd, 1H, J = 1.2, 8.2 Hz), 7.39 (t, 1H, J = 7.9 Hz), 7.01 (dd, 1H, J = 1.2, 7.8 Hz), 6.80 (d, 1H, J = 8.3 Hz), 6.72 (d, 1H, J = 2.2.3 Hz), 6.65 (dd, 1H, J = 2.3, 8.4 Hz), 5.99 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.0, 151.1, 150.2, 148.5, 144.4, 140.6, 136.2, 129.8, 126.7, 122.1, 121.8, 114.0, 113.2, 108.6, 103.1, 101.7. IR (KBr disc, cm^{-1}) 1614, 1500, 1373, 1315, 1181, 1125, 1037, 930, 792, 770. Anal. Calc. for $C_{16}H_{11}NO_3$: C 72.45, H 4.18. Found: C 72.16, H 4.39.



4-(5-chloropyridin-3-yloxy)isoquinoline (entry 5)

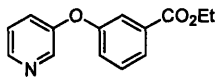
The general procedure was followed using CuI (19 mg, 0.05 mmol), **4** (40 mL, 0.40 mmol), K_3PO_4 (0.42 g, 2.0 mmol), 4-bromoisoquinoline (229 mg, 1.00 mmol), 5-chloro-3-hydroxypyridine (130 mg, 1.2 mmol) with DMF (0.8 mL) as solvent for 24 h at 120 °C. Workup B followed by chromatographic purification (hexane / ethyl acetate) provided a yellow solid (180 mg, 70%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.19 (bs, 1H), 8.37-8.15 (m, 3H), 8.07 (dd, 1H, J = 0.7, 8.2 Hz), 8.00 (d, 1H, J = 8.4 Hz), 7.77-7.68 (m, 2H), 7.23 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.7, 149.7, 143.7, 138.4, 133.2, 131.2, 130.5, 129.5, 128.6, 127.9, 126.7, 124.5, 120.8. IR (KBr disc, cm^{-1}) 1627, 1574, 1499, 1417, 1386, 1305, 1252, 1164, 1092, 1064, 1051, 920, 872, 783, 626. Anal. Calc. for $C_{14}H_9N_2OCl$: C 65.51, H 3.53. Found: C 65.65, H 3.57. m.p. 153-155 °C.



1-(3-(4-*tert*-butylphenoxy)pyridin-2-yl)-*N*,*N*-dimethylmethanamine (entry 6)

The general procedure was followed using CuI (19 mg, 0.05 mmol), K_3PO_4 (0.42 g, 2.0 mmol), 4-*tert*-butylbromobenzene (173 μL, 1.00 mmol), 2(dimethylaminomethyl)-3-hydroxypyridine (182 mg, 1.2 mmol) with DMF (0.8 mL) as solvent for 24 h at 110 °C. Workup B followed by chromatographic purification (ethyl acetate/ methanol) provided the product as a brown oil (214 mg, 75%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (dd, 1H, J = 1.5, 4.5 Hz), 7.36-7.34 (m, 2H), 7.19-7.12 (m, 2H), 6.91-6.89 (m, 2H), 3.68 (s, 2H), 2.34 (s, 6H), 1.31 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.5, 152.5, 150.4, 146.7, 144.1, 128.9, 125.8, 123.1, 118.2, 59.3, 45.9, 34.5, 31.6. IR

(KBr disc, cm^{-1}) 1575, 1508, 1364, 1211, 1179, 1105, 1014, 853, 728, 608, 550.



ethyl 3-(pyridin-3-yloxy)benzoate (entry 7)

The general procedure was followed using CuI (9.5 mg, 0.05 mmol), **4** (20 mL, 0.20 mmol), Cs_2CO_3 (0.65 g, 2.0 mmol), ethyl-3-iodobenzoate (140 μL, 1.00 mmol), 3-hydroxypyridine (114 mg, 1.2 mmol) and 3Å mol sieves (200 mg flame activated under vacuum) with DMF (1.0 mL) as solvent for 36 h at 80 °C. Workup A followed by chromatographic purification (hexane / ethyl acetate) provided the title compound (yellow oil, 260 mg, 89%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (bs, 1H), 8.40 (bs, 1H), 7.84 (m, 1H), 7.68 (dd, 1H, J = 1.5, 10.1 Hz), 7.44 (td, 1H, J = 7.8, 0.5 Hz), 7.31-7.28 (m, 2H), 7.23-7.21 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.9, 156.6, 144.9, 141.7, 132.8, 130.8, 130.2, 125.8, 125.4, 124.4, 123.5, 119.9, 61.5, 14.5. IR (KBr disc, cm^{-1}) 1717, 1575, 1444, 1161, 1100, 1021, 940, 756, 692, 621. Anal. Calc. for $C_{14}H_{14}NO_3$: C 69.12, H 5.39. Found: C 68.86, H 5.45.

RAAV161

exp1 s2pul

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at	3.001	dres	1.0
np	63050	homo	n
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fb	not used	dfrq2	0
bs	8	dn2	
tpwr	56	dpwr2	1
pw	8.9	dof2	0
d1	2.000	dm2	n
tof	1519.5	dmm2	c
nt	16	dmf2	200
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gain	not used	homo2	n
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in	n	dn3	
dp	y	dpwr3	1
hs	nn	dof3	0
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wp	6418.3	dmf3	200
vs	151	dseq3	
sc	0	dres3	1.0
wc	250	homo3	n
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rfl	2482.6	proc	ft
rfp	1248.4	fn	131072
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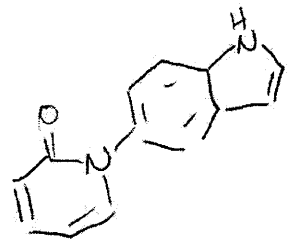
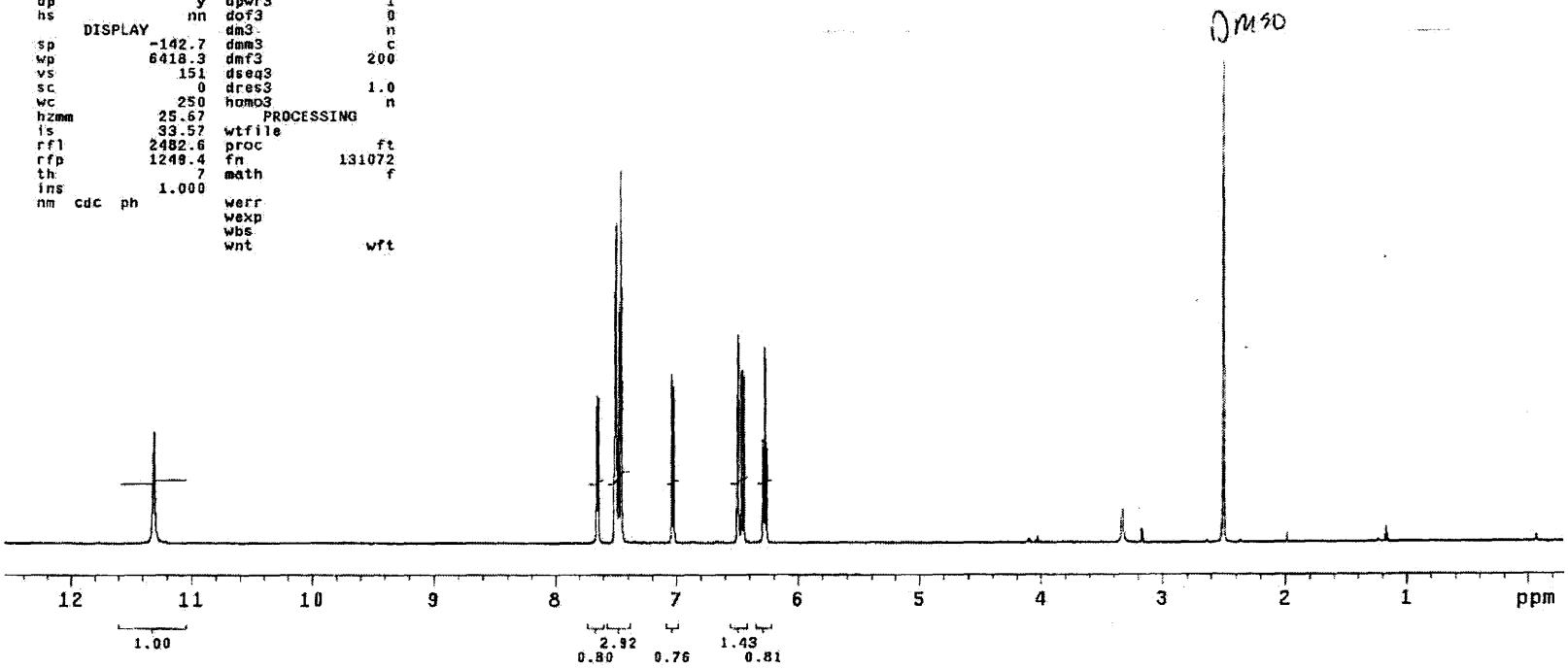
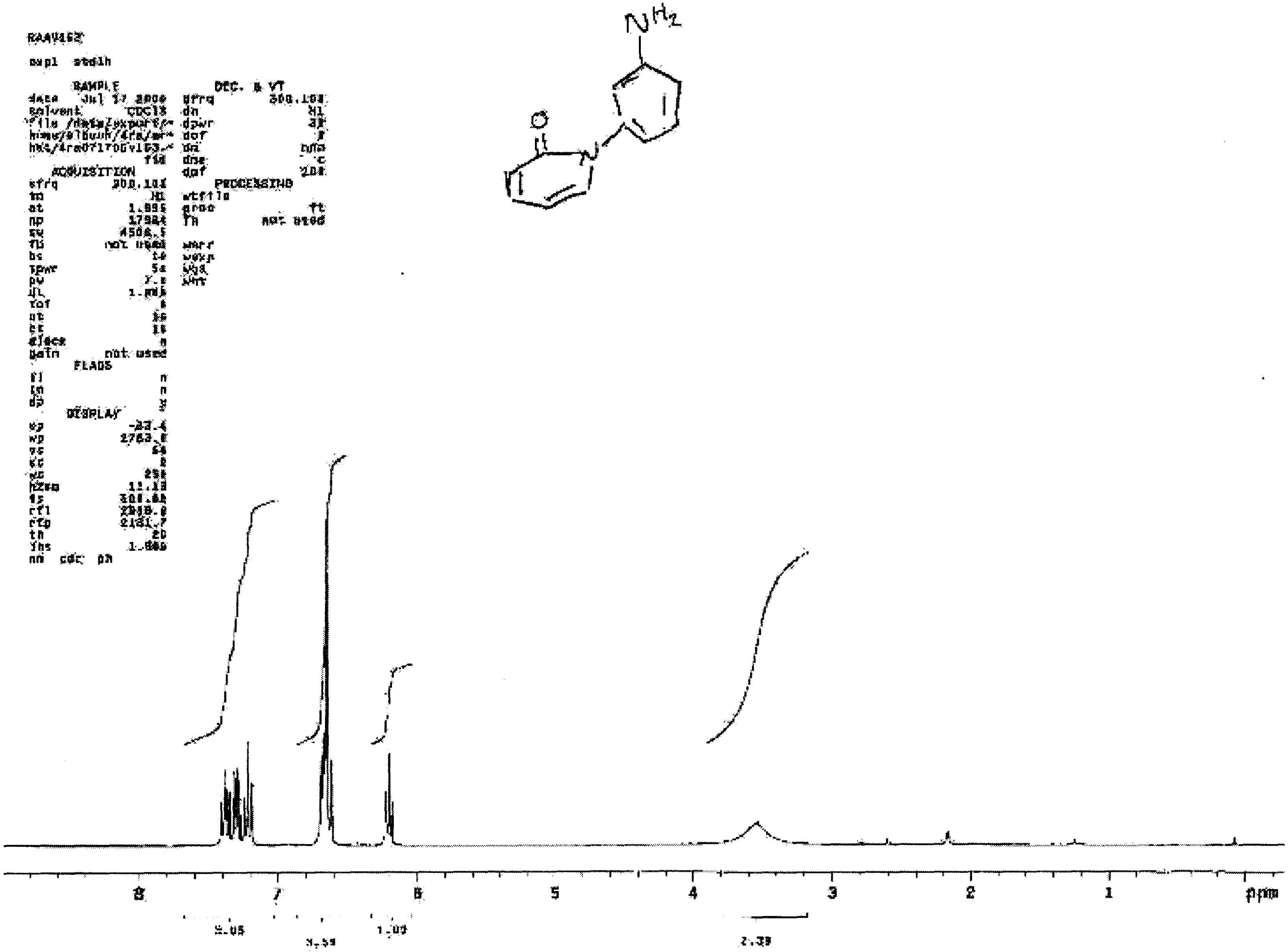
nm cdc ph		werr	
		wexp	
		wbs	
		wnt	wft







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5
4
3
2
1
ppm

RAAV172

expl s2pul

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d1	2.000	dpwr2	1
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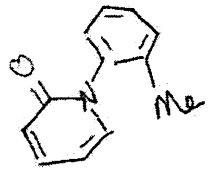

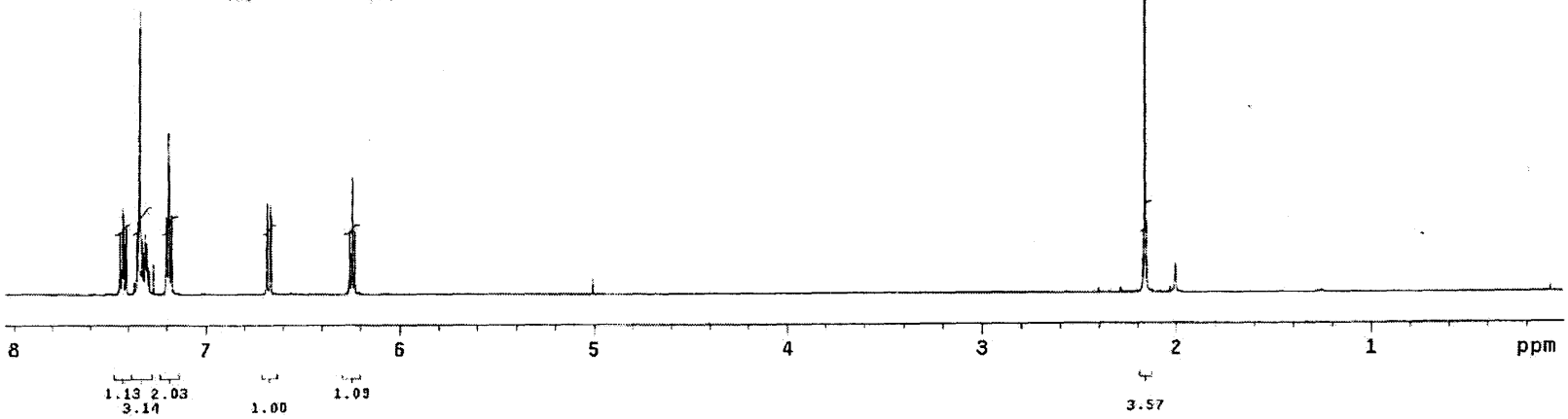

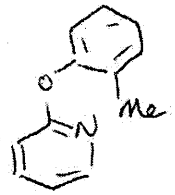

RAAV173

exp5 s2pul

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np	64000	dseq	
sw	10000.0	dres	1.0
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bs	8	**PROCESSING**	
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tof	1498.2		
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ct	16	wexp	
alock	n	wbs	
gain	not used	wnt	

FLAGS	
il	n
in	n
dp	y
hs	nn

DISPLAY	
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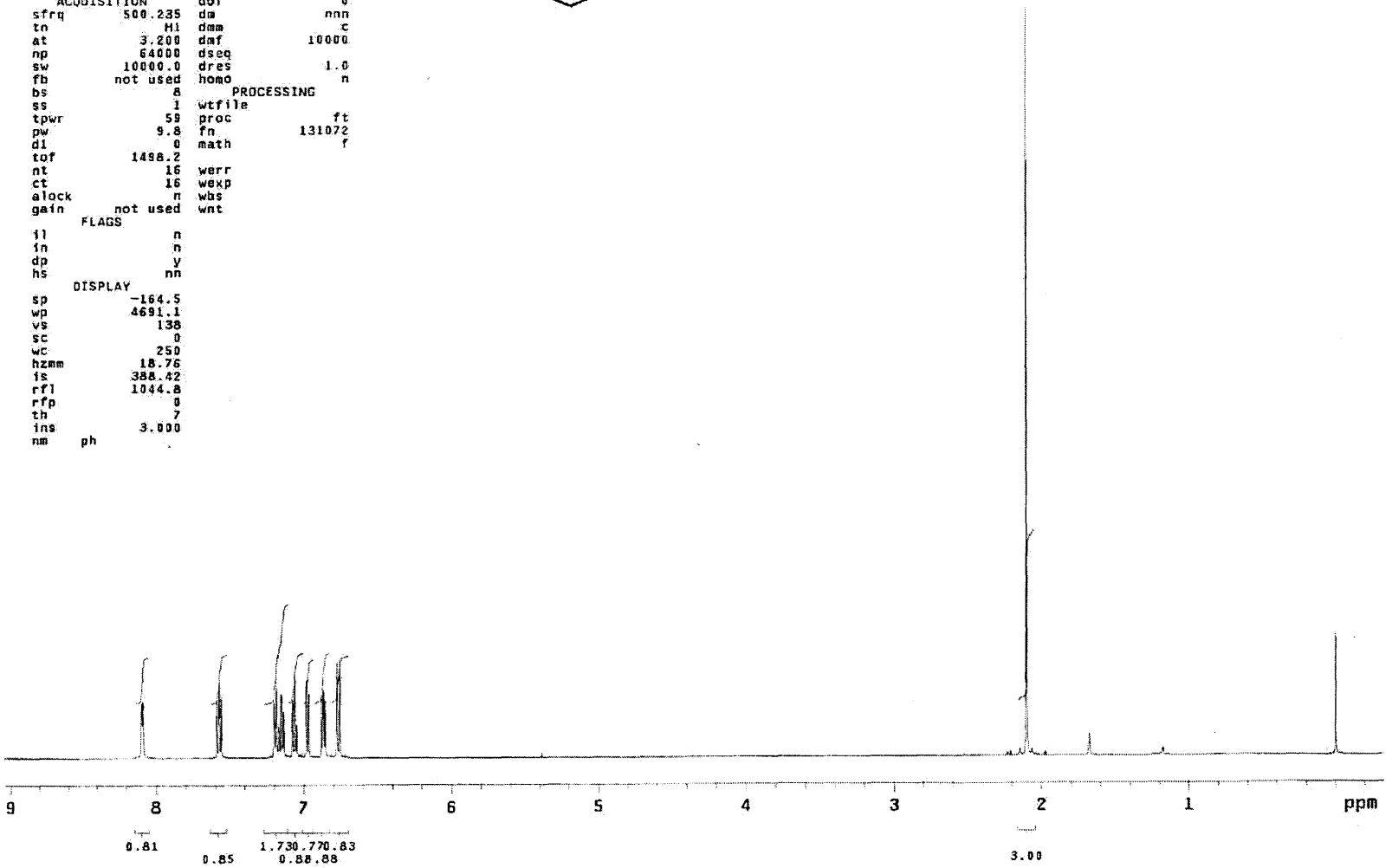
nm ph	



RAA V 184

STANDARD 1H OBSERVE

expl std1h

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d1	1.000	wexp	
tof	0	wbs	
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ct	16		
alock	n		
gain	not used		
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dp	y		
DISPLAY			
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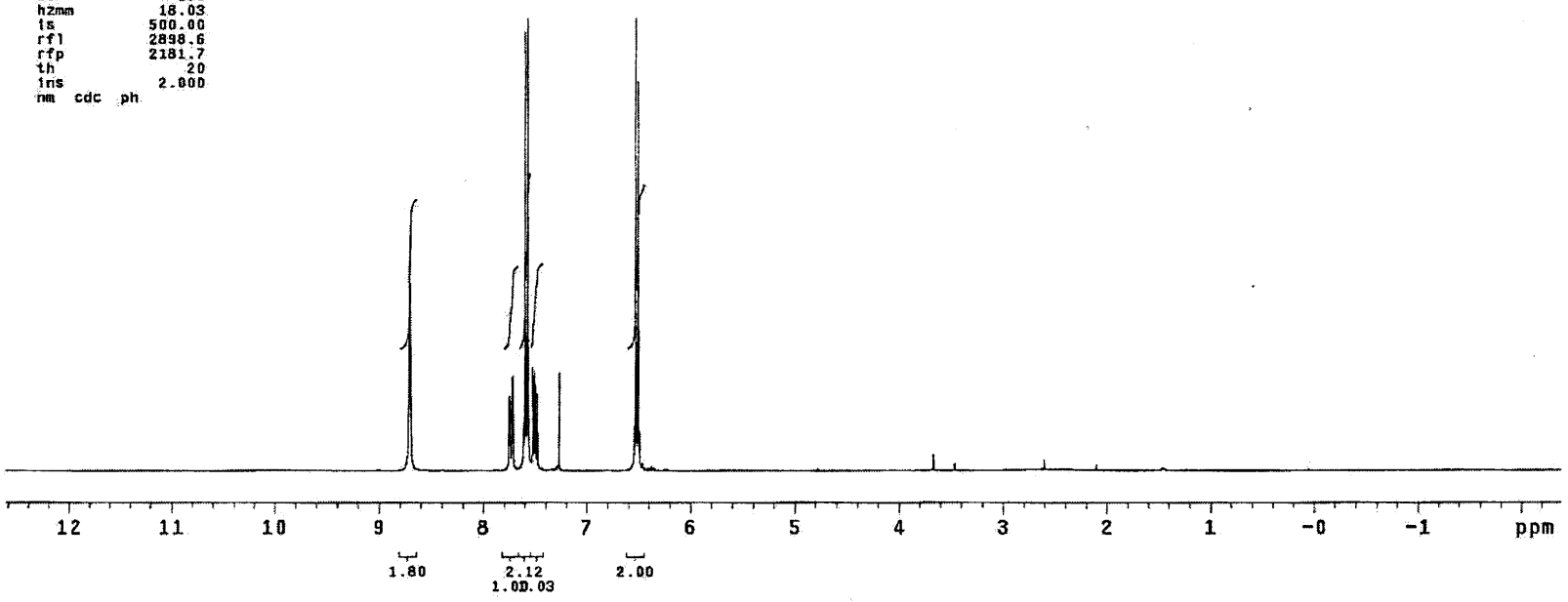
nm cdc ph			



RAAV96

exp1 stdlh

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d1	1.000	wexp	
tof	0	wbs	
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dp	y		
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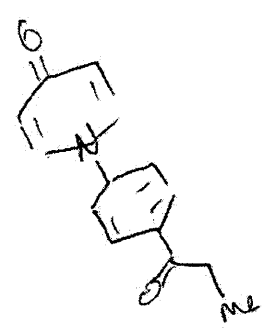
nm cdc ph			



RAAVS1

exp4 s2pul

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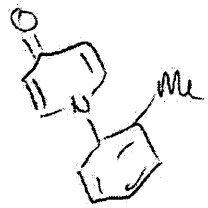

RAAV82

exp5 s2pul

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np	64000	dseq	
sw	10000.0	dres	1.0
fb	not used	homo	n
bs	8	PROCESSING	
ss	1	wtfile	
tpwr	59	proc	ft
pw	9.8	fn	131072
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tof	1498.2		
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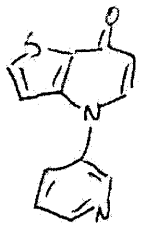

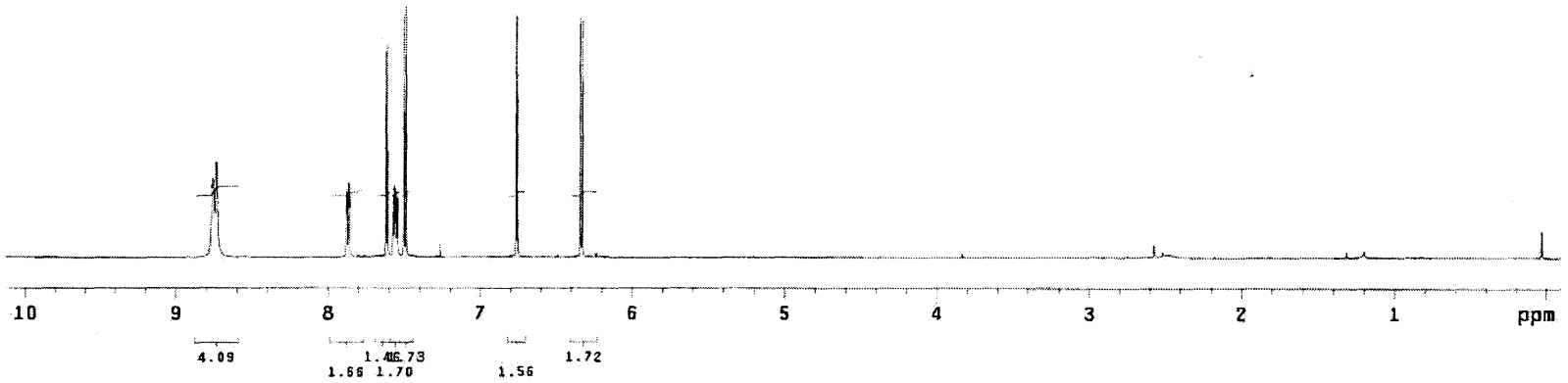

RAAVI308

expl s2pul

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gain	not used	wnt	
FLAGS			
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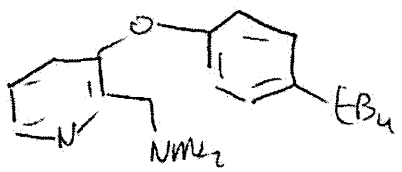
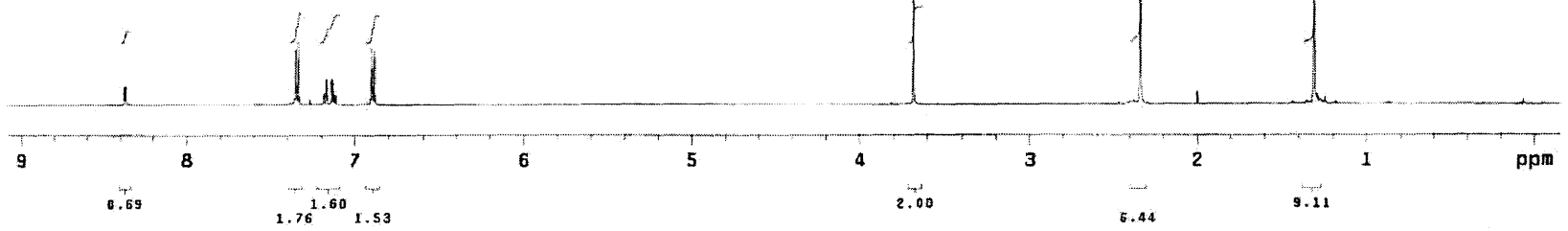




3.5 References and Notes

(1) (a) Julemont, F.; de Leval, X.; Michaux, C.; Renard, J. F.; Winum, J. Y.; Montero, J. L.; Damas, J.; Donge, J. M.; Pirotte, B. *J. Med. Chem.* **2004**, *47*, 6749. (b) Zhu, G. D.; Arendsen, D. L.; Gunawardana, I. W.; Boyd, S. A.; Steward, A. O.; Fry, D. G.; Cool, B. L.; Kifle, L.; Schaefer, B.; Meuth, J.; Marsh, K. D.; Kemph-Grote, A. J.; Kilgannon, P.; Gallatin, W. M.; Okasinski, G. F. *J. Med. Chem.* **2001**, *44*, 3469. (c) Baker, W. R.; Cai, S.; Dimitroff, M.; Fang, L.; Huh, K. K.; Ryckman, D. R.; Shang, X.; Shawar, R. M.; Therrien, J. H. *J. Med. Chem.* **2004**, *47*, 4693. (d) Wallace & Tiernan, Inc. Substituted 1-(*m*-aminophenyl)-2-pyridones. U.S. Patent 2,947,755, August 2, 1960. (e) Satoshi, N.; Nagato, S.; Ueno, K.; Kawano, K.; Norimine, Y.; Ito, K.; Hanada, T.; Ueno, M.; Amino, H.; Ogo, M.; Hatakeyama, S.; Urawa, Y.; Naka, H.; Groom, A. J.; Rivers, L.; Smith, Terrence (Esiai Co. Ltd.). 1,2-Dihydropyridine Compounds, Process for Preparation of the Same and Use Thereof. Patent WO0196308, December 20, 2001. (f) Alonso-Alija, C.; Michels, M.; Schirok, H.; Schlemmer, K. H.; Bell, J.; Gitzgerald, M. F.; Dodd, S.; Gill, A. (Bayer AG). Monocyclic Aroylpyridinones as Antiinflammatory Agents. Patent WO03076405, September 18, 2003. (g) Young, S. D.; Anthony, N. J.; Gomez, R. P.; Tran, L. O. (Merck & Co. Inc.). Inhibitors of Farnesyl-Protein Transferase. Patent WO9828980, July 9, 1998.

(2) (a) Qu, J.; Kohl, C.; Potek, M.; Mu¨llen, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1528. (b) Joule, J. A., Mills, K. *Heterocyclic Chemistry*, 4th ed.; Blackwell Science Ltd.: Oxford, UK, 2000; pp 86-88. (c) Mehta, G.; Singh, V. *Chem. Rev.* **1999**, *99*, 881. (d) Afarinkia, K.; Vinader, V.; Nelson, T. D.; Posner, G. H. *Tetrahedron* **1992**, *48*, 9111.

(3) Burgos, C. H.; Barder, T. E.; Huang, X.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*,

4321.

(4) 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, Germany, 2004; pp 699-760.

(5) For reviews of Cu-catalyzed nucleophilic substitution reactions of aryl halides, see: (a) Monnier, F.; Taillefer, M. *Angew. Chem. Int. Ed.* **2008**, *47*, 3096. (b) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, 2337. (c) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400. (d) Kunz, K.; Scholz, U.; Ganzer, D. *Synlett* **2003**, 2428. (e) Lindley, J. *Tetrahedron* **1984**, *40*, 1433.

(6) (a) Mederski, W. W. K. R.; Lefort, M.; Germann, M.; Kux, D. *Tetrahedron* **1999**, *55*, 12757. (b) Lam, Y. S. P.; Clark, C. G.; Sauber, S.; Adams, J.; Averill, K. M.; Chan, D. M. T.; Combs, A. *Synthesis* **2000**, 674.

(7) Lam, P. Y. S.; Vincent, G.; Bonne, D.; Clark, C. G. *Tetrahedron Lett.* **2002**, *43*, 3091.

(8) Ikegai, K.; Nagata, Y.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **2006**, *79*, 761.

(9) (a) Renger, B. *Synthesis* **1985**, 856. (b) Sugahara, M.; Ukita, T. *Chem. Pharm. Bull.* **1997**, *45*, 719. (c) Cristau, H. J.; Cellier, P. P.; Spindler, J. F.; Taillefer, M. *Chem. Eur. J.* **2004**, *10*, 5607. (d) Li, C. S.; Dixon, D. D. *Tetrahedron Lett.* **2004**, *45*, 4257. (e) Wang, P. S.; Liang, C. K.; Leung, M. *Tetrahedron* **2005**, *61*, 2931. (f) Filipski, K. J.; Kohrt, J. T.; Casimiro-Garcia, A.; Van, Huis, C. A.; Dudley, d. A.; Cody, W. L.; Bigge, C. F.; Desiraju, S.; Sun, S.; Maiti, S. N.; Jaber, M. R.; Edmunds, J. J. *Tetrahedron Lett.* **2006**, *47*, 7677.

(10) Antilla, J. C.; Klapars, A.; Buchwald, S. L. *J Am. Chem. Soc.* **2002**, *124*, 11684.

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

(12) p*k*a data: (a) Bordwell, F. G.; Bartmess, J. E.; Hautala, J. A. *J. Org. Chem.* **1978**, *43*, 3095. (b) Olmstead, W. M.; Margolin, Z.; Bordwell, F. G. *J. Org. Chem.* **1980**, *45*, 3295. (c) Bordwell, F. G.; Drucker, G. E.; Fried, H. E. *J. Org. Chem.* **1981**, *46*, 632. (d) Bordwell, F. G.; Ji, G. Z. *J. Am. Chem. Soc.* **1991**, *113*, 8398.

(13) Altman, R. A.; Buchwald, S. L. *Org. Lett.* **2006**, *8*, 2779.

(14) For a brief summary, see: You, F.; Twieg, R. J. *Tetrahedron Lett.* **1999**, *40*, 8759.

(15) Blouin, M.; Frenette, R. *J. Org. Chem.* **2001**, *66*, 9043.

(16) Mederski, W. W. K. R.; Lefort, M.; Germann, M.; Kux, D. *Tetrahedron* **1999**, *55*, 12757.

(17) An authentic sample of 4-(3-methoxyphenoxy)pyridine was independently synthesized by uncatalyzed nucleophilic substitution of 4-chloropyridine with 3-methoxyphenol and compared to 1-(3-methoxyphenyl)- 1*H*-pyridin-4-one (Table 5, entry 1) to verify that the product of Cu-catalysis was not the *O*-aryl compound.

(18) This ligand was originally reported by Merck chemists for the Cu-catalyzed *O*-arylation of phenol. See: Buck, E.; Song, Z. J.; Tschaen, D.; Dormer, P. G.; Volante, R. P.; Reider, P. J. *Org. Lett.* **2002**, *4*, 1623.

(19) Shafir, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 8742.

(20) For an example, see: Ma, D.; Yongda, Z.; Yao, J.; Wu, S.; Tao, F. *J. Am. Chem. Soc.* **1998**, *120*, 12459.

(21) Fagan, P. J.; Hauptman, E.; Shapiro, R.; Casalnuovo, A. *J. Am. Chem. Soc.* **2000**, *122*, 5043.

(22) Cristau, H. J.; Cellier, P. P.; Hamada, S.; Spindler, J. S.; Taillefer, M. *Org. Lett.* **2004**, *6*, 913.

(23) Altman, R. A.; Buchwald, S. L. *Org. Lett.* **2006**, *8*, 2779.

(24) Sugahara, M.; Ukita, T. *Chem. Pharm. Bull.* **1997**, *45*, 719.

(25) Wang, P. S.; Liang, C. K.; Leung, M. K. *Tetrahedron* **2005**, *61*, 2931.

(26) Firl, J.; Kresze, G. *Chem. Ber.* **1966**, *99*, 3695.

(27) Wallace & Tiernan Inc. Substituted 1-(m-aminophenyl)-2-pyridones. US 2947755. February 5, 1959.

(28) Renshaw, R. R.; Conn R. C. *J. Am. Chem. Soc.* **1937**, *59*, 297.

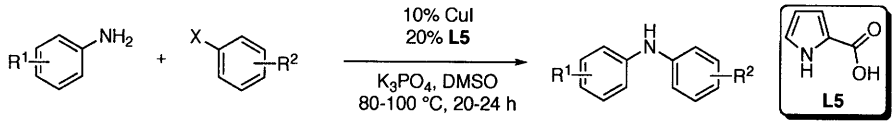
(29) Lawrence, R.; Waight, E. S. *J. Chem. Soc. B* **1968**, 1.

(30) Fleet, G. W. J.; Fleming, I.; Philippides D. *J. Chem. Soc. C* **1971**, 3948.

(31) Smirnoff, A. P. *Helv. Chim. Acta* **1921**, *4*, 604.

Chapter Four

Pyrrole-2-carboxylic Acid as a Ligand for the Cu-catalyzed Reactions of Primary Anilines with Aryl Halides



4.1 Introduction

The diaryl amine moiety can be found in a variety of biologically active pharmaceuticals, natural products, and materials.[1] Metal-catalyzed cross-coupling reactions of anilines with aryl halides are among the foremost methods for assembling this substructure.[1,2] For reactions of poorly nucleophilic primary anilines with aryl halides, Pd-based catalyst systems are highly efficient.[1] This is due, in great part, to the rapid transmetallation of anilines to Pd(II), a phenomenon that arises from the large increase in acidity of the nucleophile when coordinated to Pd(II).[3] The complementary nature of Pd- and Cu-catalyzed C–N bond-forming processes, and the issues involving removal of the trace Pd from the products encourage the development of Cu-based catalyst systems for the preparation of diaryl amines.

In recent years, Cu-catalyzed C–N bond-forming reactions have evolved as reliable alternatives to Pd-catalyzed reactions.[2] However, Cu-based catalyst systems for the synthesis of diaryl amines are less general and useful than the Pd-based protocols.[4] The Cu-catalyzed reactions of anilines with aryl halides are slow enough that a wide variety of N–H and O–H nucleophiles, including amides, nitrogen heterocycles, aliphatic, benzylic and allylic amines, as well as aliphatic and benzylic alcohols are selectively arylated in the presence of an anilino-NH_2 group.[5] In the absence of a competing reactant, the poor nucleophilicity of the aniline, when employing Cu-based catalysts, further manifests itself in the need to use high catalyst loadings (> 20% Cu),[4a,f] long reaction times (> 30 h),[4b-c,e] strong bases that preclude the presence of many common functional groups,[4g] and/or anilines with strong electron-withdrawing groups in the para-position.[4b] Further, the few examples of Cu-catalyzed reactions of anilines with ortho-substituted aryl halides require even higher catalyst loadings (35-50% Cu).[4f] Finally, when employing Cu-based catalysts, the propensity of the diaryl amine product to undergo further N-

arylation to form a triarylamine provides an added level of complexity to developing a suitable catalyst system.[6]

4.2 Results and Discussion

We began our investigation into the Cu-catalyzed reactions of aromatic amines with aryl iodides, by evaluating previously reported catalysts for this transformation.[4] Since the more successful systems employed proline-type ligands,[4b-e] we sought to evaluate the use of new ligands that would provide a more active and generally applicable catalyst for the reaction of aniline with an aryl iodide (Table 1). While several heterocyclic-2-carboxylic acids, including some previously reported as ligands for Cu-catalyzed and -mediated nucleophilic substitution reactions of aryl halides,[7] provided poor results for this transformation (entries 1-4), pyrrole-2-carboxylic acid, **L5**, manifested good catalytic activity (entry 5). Both the N–H and carboxylate functional groups of this ligand are important to the activity of the catalysts derived from it. This can be seen as modification of these groups provided less-active catalysts (entries 6-8). Benzannulated analogs **L9** and **L10** also provided less-active catalyst (entries 9-10); presumably because they are too hindered. Finally, **L5** provided a more active catalyst system than those derived from commercially-available ligands previously reported for this transformation (i.e., 11-14).[4a-b,d,f]

Figure 1. Ligands Examined for N-Arylation Reactions of Aniline

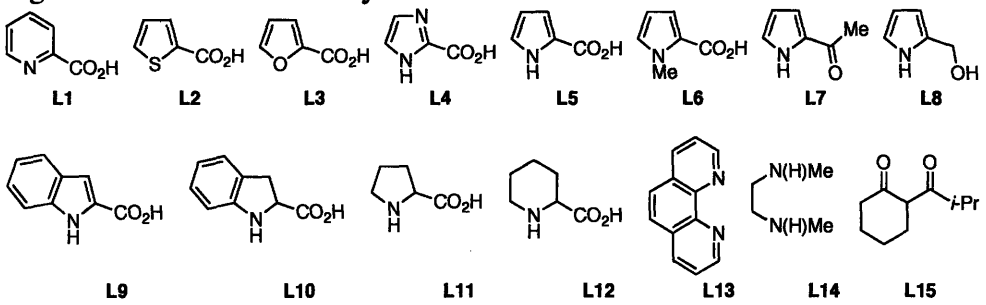
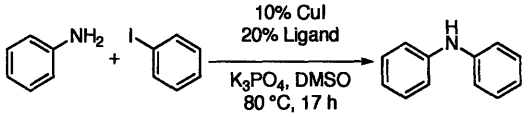


Table 1. Cu-Catalyzed Reaction of Aniline with Iodobenzene



Entry	Ligand	GC Conversion (%)	GC Yield (%)
1	**L1**	58	35
2	**L2**	46	27
3	**L3**	47	27
4	**L4**	0	0
5	**L5**	94	68
6	**L6**	57	37
7	**L7**	55	22
8	**L8**	66	0
9	**L9**	62	26
10	**L10**	60	22
11	**L11**	64	34
12	**L12**	64	29
13	**L13**	48	15
14	**L14**	64	19
15	**L15**	51	30

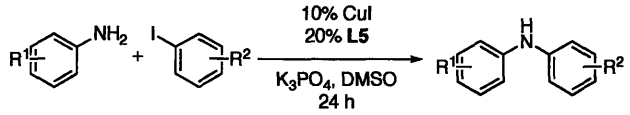
[a] Reactions Conditions: 1.0 mmol $ArNH_2$, 0.5 mmol ArI, 1.0 mmol K_3PO_4, 0.050 mmol CuI, 0.10 mmol ligand, 0.25 mL DMSO, at 80 °C in a sealed tube under an N_2 atmosphere for 17 h.

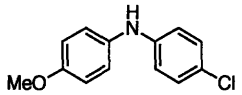
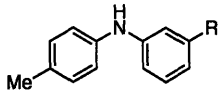
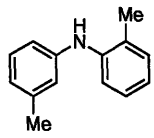
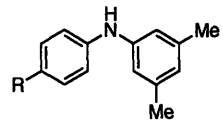
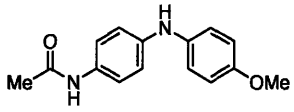
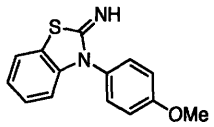
Further optimization of the reaction conditions using **L5** revealed that the base/solvent combination of K_3PO_4/DMSO typically provided a superior system than combinations involving K_2CO_3, Cs_2CO_3, KOH, and NaO*t*-Bu in DMF, 1,4-dioxane, toluene, and acetonitrile. Since diaryl ether and phenolic products (up to 20% of ArX consumption) were frequently produced under

the reaction conditions and observed by GC/MS,[8] the base was flame-dried under reduced pressure then cooled under a positive pressure of N_2 prior to use.

The reaction conditions we developed (1.0 equiv ArX/2.0 equiv $ArNH_2$/10% CuI/20% **L5**/K_3PO_4/DMSO/80-90 °C) could be used to couple aryl iodides with anilines in moderate to good yields (Table 2). For the reaction of *p*-anisidine with 4-chloroiodobenzene, the catalyst loading and reaction temperature could be reduced to 5% CuI and 70 °C, respectively (entry 1). Substrates containing base-sensitive functional groups such as benzoic esters and benzonitriles, which do not tolerate heating in the presence of hydroxide,[5c] were transformed to the desired product in respectable yields (entries 2-3). In addition, the presence of an ortho substituent on the aryl halide was tolerated (entry 4). Using the standard conditions, reactions of anilines containing strongly electron-withdrawing substituents at the 4-position provided the diaryl amine product in lower yields (entries 5-7). In these reactions, significant quantities of triarylamine byproducts were observed.[4d] Although the reaction of 4-nitroaniline with an aryl iodide provided the triarylamine as the major product, an aryl halide could be coupled with *N*-(4-aminophenyl)acetamide to provide a product with a similar substitution pattern (entry 8). As previously noted, the Cu-catalyzed coupling of an anilino-NH_2 group in the presence of an amide is unusual for a Cu-catalyzed reaction of this type.[6a-b] In this case, the observed chemoselectivity is likely due to the slow reaction of secondary amides.[9] In contrast to this result, the reaction of 4-aminobenzamide with 4-iodoanisole provided a complex mixture of products. Lastly, the Cu/**L5**-catalyzed reaction of 2-aminobenzothiazole with 4-iodoanisole arylated the heterocyclic nitrogen as opposed to the anilino-NH_2 (entry 9).[10] This result is noteworthy, since the Pd-catalyzed reactions of this nucleophile with aryl bromides selectively react at the anilino-NH_2 position.[11]

Table 2. Cu-Catalyzed Reactions of Anilines with Aryl Iodides[a]

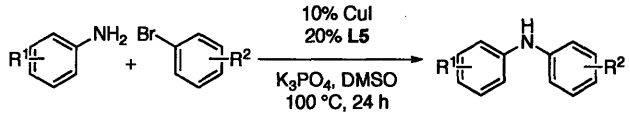


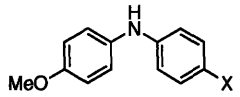
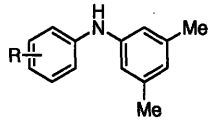
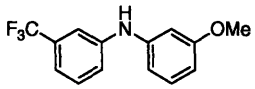
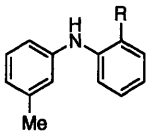
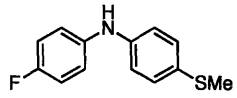
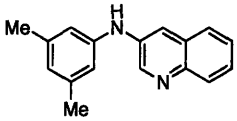
entry	product	temperature (°C)	yield (%)[b]
1		70	82[c]
2	 R = CO_2Et	80	78
3	CN	80	73
4		80	71
5	 R = Ac	90	60
6	CO_2Et	90	50
7	CN	90	52
8		80	82
9		90	68

[a] General reactions conditions: 2.0 mmol $ArNH_2$, 1.0 mmol ArI, 2.0 mmol K_3PO_4, 0.10 mmol CuI, 0.20 mmol **L5**, 0.5 mL DMSO, in a sealed tube under an N_2 atmosphere for 24 h. [b] Yields reported are the average of at least two runs determined to be > 95% pure by elemental analysis or ^1H NMR. [c] 5% CuI, 10% **L5**, 1.5 mmol $ArNH_2$

Aryl bromides were also successfully coupled using the CuI/L catalyst system (Table 3), although higher temperatures were required (100 °C). Increasing the reaction temperature to 110 °C provided significant quantities of N-arylated and decarboxylated pyrrole, and low yields of the diarylamine products. Electron-donating and -withdrawing substituents were tolerated on both the nucleophile and electrophile (entries 1-4). In addition, anilines and aryl bromides containing ortho-substituents were effectively combined (entries 5-8). When employing 3-bromoquinoline as a substrate, a significant quantity of reduced heteroarene was observed (entry 9). The formation of this byproduct is common for Cu-catalyzed reactions of heteroaryl halides with amines.[5c]

Table 3. Cu-Catalyzed Reactions of Anilines with Aryl Bromides[a]



entry	product		yield (%)[b]	entry	product		yield (%)[b]
1		X = Cl	76	5		R = 2,5-Me_2	75[c]
2		F	72	6		2-OMe	70
3			55	7		R = Me	74[d]
4			71	8		OMe	67[d]
				9			51

[a] General reactions conditions: 2.0 mmol $ArNH_2$, 1.0 mmol ArBr, 2.0 mmol K_3PO_4, 0.10 mmol CuI, 0.20 mmol **L5**, 0.5 mL DMSO, in a sealed tube under an N_2 atmosphere for 24 h. [b] Yields reported are the average of at least two runs determined to be > 95% pure by elemental analysis or ^1H NMR. [c] 20% **L15** employed as a ligand in DMF at 110 °C. [d] 30 h.

4.3 Conclusion

In conclusion, pyrrole 2-carboxylic acid was employed as a suitable ligand for the Cu-catalyzed monoarylation of anilines with aryl iodides and bromides. Anilines and aryl halides possessing diverse electronic properties and useful functional groups were all tolerated. In many cases, the relatively low catalyst loading (10% Cu), the breadth of functional groups tolerated by the catalyst system, and the cost and commercial availability of the metal and ligand, might offset the required use of two equivalents of amine, and the moderate yields obtained. We are continuing our investigations to develop newer and more active Cu-based catalyst systems for this transformation.

4.4 Experimental Procedures

All reactions were carried out in resealable test tubes with Teflon septa under an argon or

nitrogen atmosphere. Copper(I) iodide (98%) was purchased from Strem. Pyrrole-2-carboxylic acid was purchased from Aldrich. Finely milled K_3PO_4 was purchased from Fluka. The base was flame-dried under vacuum and cooled under nitrogen immediately before usage. The base is hygroscopic and excessive amounts of water lead to the formation of phenol and diaryl ether byproducts. Anilines were purchased from commercial sources and, when necessary, purified by distillation or sublimation. Aryl halides were purchased from commercial sources and, when necessary, were distilled or filtered through a plug of alumina before use. Anhydrous dimethylsulfoxide (DMSO) and *N,N'*-dimethylformamide (DMF) were purchased from Aldrich in SureSeal® bottles and used as received. Flash column chromatography was performed using a Biotage SP4 Flash Purification System using SNAP 10g silica cartridges. In all cases, dichloromethane was used to transfer the crude reaction material onto the silica gel samplet. The samplet was then air-dried before usage. A gradient elution using hexanes and ethyl acetate was performed, based on the recommendation from the Biotage TLC Wizard.

Yields reported in the publication are of isolated material and represent an average of at least two independent runs. Yields reported in the supporting information refer to a single experiment. Compounds described in the literature were characterized by comparing their ^1H NMR and ^{13}C NMR spectra, and melting points (m.p.) to the previously reported data; their purity was confirmed by gas chromatography (GC) or elemental analysis. GC analyses were performed on a Hewlett Packard 6890 instrument with an FID detector and a Hewlett Packard 10 m x 0.2 mm i.d. HP-1 capillary column using dodecane as an internal standard. Elemental analyses were performed by Atlantic Microlabs, Inc., Norcross, GA. Previously unknown compounds were synthesized, purified and analyzed from a single run and the reactions used to form them were then repeated to determine an average yield. They were characterized by ^1H

NMR, ^{13}C NMR, m.p., IR and elemental analysis. ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian 500 MHz instruments with chemical shifts reported relative to the deuterated solvent or TMS. IR spectra were recorded on a Perkin-Elmer System 2000 FT-IR instrument for all previously unknown compounds (KBr disc). Melting points (uncorrected) were obtained on a Mel-Temp II capillary melting point apparatus.

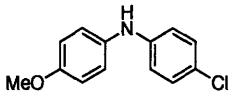
General procedure for the Cu-catalyzed cross-coupling of anilines with aryl halides

An oven-dried screw-cap test tube was charged with K_3PO_4 (424 mg, 2.0 mmol). The tube was sealed and the base was flame-dried under vacuum, and cooled under a purge of N_2. CuI (19 mg, 0.10 mmol), Pyrrole-2-carboxylic acid (22 mg, 0.20 mmol), aryl halide (1.0 mmol, if solid), amine (2.0 mmol, if solid) and a magnetic stir bar were added to the cooled vessel. The tube was then evacuated and back-filled with nitrogen. The evacuation/backfill sequence was repeated two additional times. Aryl halide (1.0 mmol, if liquid), amine (2.0 mmol, if liquid) and DMSO (0.50 mL) were then added by syringe. The vessel was immersed in a preheated oil bath and the reaction mixture was stirred vigorously until TLC and/or GC analysis of the crude reaction mixture indicated that the aryl halide had been completely consumed. The reaction mixture was cooled to room temperature. Ethyl acetate (15 mL), $NH_4Cl_{(aq)}$ (2 mL), and H_2O (1mL) were added and the mixture was stirred. The organic layer was separated, and filtered through a plug of silica. The aqueous layer was extracted twice more with ethyl acetate (10 mL), and each extract was sequentially filtered through the pad of silica gel. The filtrate was concentrated and the resulting residue was purified by flash chromatography (hexanes/ethyl acetate, gradient elution) to provide the desired product.

Experimental procedure for the reactions described in Table 1

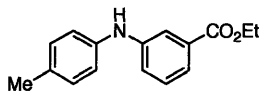
An oven-dried screw-cap test tube was charged with CuI (9.5 mg, 0.050 mmol), ligand (0.20 mmol, if solid), and a magnetic stir bar. The tubes were transferred into a nitrogen-filled glove box where flame-dried anhydrous K_3PO_4 (212 mg, 1.0 mmol) was added. The tubes were sealed with a Teflon septum and removed from the glovebox, where iodobenzene (56 μL, 0.5 mmol), aniline (92 mL, 1.0 mmol) and DMSO (0.25 mL) were successfully added by syringe. The vessel was immersed in a pre-heated oil bath and stirred vigorously for 12 h at 80 °C. The reaction mixture was cooled to room temperature. Dodecane (112 μL), ethyl acetate (15 mL), $NH_4Cl_{(aq)}$ (2 mL), and H_2O (1mL) were added and stirred. The organic layer was sampled for GC analysis.

Experimental procedures for compounds in Table 2



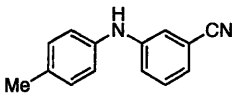
4-chloro-*N*-(4-methoxyphenyl)aniline (Entry 1)

The general procedure was followed using CuI (19 mg, 0.10 mmol), pyrrole-2-carboxylic acid (22 mg, 0.20 mmol), K_3PO_4 (424 mg, 2.0 mmol), 4-chloroiodobenzene (238 mg, 1.00 mmol), and *p*-anisidine (182 mg, 1.5 mmol) with DMSO (0.50 mL) as solvent for 20 h at 80 °C. Workup and chromatographic purification (hexanes / ethyl acetate 1:0 → 4:1) afforded the title compound as an off-white solid (188 mg, 81 %). m.p. 49-50.5 °C (lit. 50-51°C).[12] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18-7.13 (2H, m), 7.09-7.03 (2H, m), 6.90-6.80 (m, 4H), 5.48 (1H, bs), 3.81 (3H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.8, 144.1, 135.4, 129.4, 124.5, 122.7, 116.8, 114.9, 55.8.



ethyl 3-(*p*-tolylamino)benzoate (Entry 2)

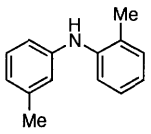
The general procedure was followed using CuI (9.5 mg, 0.05 mmol), pyrrole-2-carboxylic acid (11 mg, 0.10 mmol), K_3PO_4 (424 mg, 2.0 mmol), ethyl-3-iodobenzoate (167 μL, 1.00 mmol), and *p*-toluidine (214 mg, 2.0 mmol) with DMSO (0.50 mL) as solvent for 24 h at 80 °C. Workup and chromatographic purification (hexanes / ethyl acetate 1:0 → 4:1) afforded the title compound as a tan solid (199 mg, 78 %). m.p. 95-96 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (1H, dd, J = 1.8, 2.0 Hz), 7.54 (1H, ddd, J = 1.1, 1.5, 7.6 Hz), 7.29 (1H, t, J = 7.8 Hz), 7.20 (1H, ddd, J = 0.9, 2.5, 8.1 Hz), 7.13-7.11 (2H, m), 7.04-7.01 (2H, m), 5.73 (1H, bs), 4.37 (2H, q, J = 7.1 Hz), 2.33 (3H, s), 1.39 (3H, t, J = 7.1 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9, 144.4, 139.8, 131.8, 130.2, 120.4, 121.2, 120.6, 119.5, 117.5, 61.1, 20.9, 14.5. IR (KBr disc, cm^{-1}) 3356, 1701, 1604, 1589, 1526, 1487, 1367, 1280, 1219, 1106, 1025, 829, 801, 752. Anal. Calc. for $C_{16}H_{17}NO_2$: C 75.27, H 6.71. Found: C 75.51, H 6.74.



3-(*p*-tolylamino)benzonitrile (Entry 3)[13]

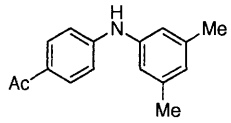
The general procedure was followed using CuI (9.5 mg, 0.05 mmol), pyrrole-2-carboxylic acid (11 mg, 0.10 mmol), K_3PO_4 (424 mg, 2.0 mmol), 3-iodobenzonitrile (229 mg, 1.00 mmol), and *p*-toluidine (214 mg, 2.0 mmol) with DMSO (0.50 mL) as solvent for 24 h at 90 °C. Workup and chromatographic purification (hexanes / ethyl acetate 1:0 → 4:1) afforded the title compound as an tan solid (150mg, 72 %). m.p. 71-73°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30-7.28 (1H, m), 7.20-7.15 (2H, m), 7.13 (1H, ddd, J = 0.9, 2.4, 7.4 Hz), 7.09 (1H, ddd, J = 1.1, 1.4, 7.5 Hz), 7.05-7.02 (2H, m), 5.78 (1H, bs), 2.35 (3H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.5, 138.4, 133.3, 130.4, 130.3, 123.1, 120.1, 119.3, 118.1, 113.2, 21.0. IR (KBr disc, cm^{-1}) 3398, 2226, 1598, 1523, 1489, 1312, 996, 867, 818, 780, 681. Anal. Calc. for $C_{14}H_{12}N_2$: C 80.74, H 5.81. Found: C

80.49, H 5.74.



2-methyl-*N*-*m*-tolylaniline (Entry 4)[14]

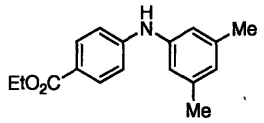
The general procedure was followed using CuI (19 mg, 0.10 mmol), pyrrole-2-carboxylic acid (22 mg, 0.20 mmol), K_3PO_4 (424 mg, 2.0 mmol), 2-iodotoluene (127 μL, 1.00 mmol), and *m*-toluidine (216 μL, 2.0 mmol) with DMSO (0.50 mL) as solvent for 30 h at 80 °C. Workup and chromatographic purification (hexanes / ethyl acetate 1:0 → 4:1) afforded the title compound as a tan oil (144 mg, 75 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (1H, d, J = 6.9 Hz), 7.22 (1H, d, J = 7.5 Hz), 7.17 (2H, m), 6.97-6.94 (1H, m), 6.81-6.75 (m, 3H), 5.36 (1H, bs), 2.33 (3H, s), 2.28 (3H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.0, 141.5, 139.3, 131.1, 129.3, 128.3, 126.9, 122.0, 122.5, 118.9, 118.3, 114.7, 21.7, 18.1.



1-(4-(3,5-dimethylphenylamino)phenyl)ethanone (Entry 5)

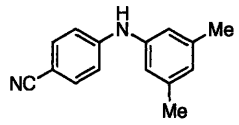
The general procedure was followed using CuI (19 mg, 0.10 mmol), pyrrole-2-carboxylic acid (22 mg, 0.20 mmol), K_3PO_4 (424 mg, 2.0 mmol), 5-iodo-*m*-xylene (144 μL, 1.00 mmol), and 1-(4-aminophenyl)ethanone (270 mg, 2.0 mmol) with DMSO (0.50 mL) as solvent for 24 h at 90 °C. Workup and chromatographic purification (hexanes / ethyl acetate 1:0 → 4:1) afforded the title compound as a yellow solid (136 mg, 57 %). m.p. 131-134 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90-7.86 (2H, m), 7.01-6.97 (2H, m), 6.81 (2H, s), 6.74 (1H, s), 6.02 (1H, bs), 2.54 (3H, s), 2.32 (6H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.6, 148.8, 140.6, 139.5, 130.8, 129.0, 125.4, 118.7, 114.6, 26.4, 21.6. IR (KBr disc, cm^{-1}) 3331, 1653, 1570, 1342, 1274, 1181, 1168, 827.

Anal. Calc. for $C_{16}H_{17}NO$: C 80.30, H 7.16. Found: C 80.22, H 7.18.



ethyl 4-(3,5-dimethylphenylamino)benzoate (Entry 6)

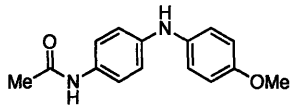
The general procedure was followed using CuI (19 mg, 0.10 mmol), pyrrole-2-carboxylic acid (22 mg, 0.20 mmol), K_3PO_4 (424 mg, 2.0 mmol), 5-iodo-*m*-xylene (144 μL, 1.00 mmol), and ethyl-4-aminobenzoate (330 mg, 2.0 mmol) with DMSO (0.50 mL) as solvent for 24 h at 90 °C. Workup and chromatographic purification (hexanes / ethyl acetate 1:0 → 4:1) afforded the title compound as a white solid (138 mg, 51%). m.p. 119-120 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94-7.91 (2H, m), 7.00-6.96 (2H, m), 6.81 (2H, m), 6.72 (1H, m), 5.96 (1H, s), 4.35 (2H, q, J = 7.1 Hz), 2.31 (3H, s), 1.38 (3H, t, J = 7.1 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 148.3, 141.0, 139.4, 131.6, 125.1, 121.4, 118.3, 114.8, 60.6, 21.6, 14.6. IR (KBr disc, cm^{-1}) 2241, 1697, 1595, 1509, 1352, 1285, 1170, 830, 769. Anal. Calc. for $C_{17}H_{19}NO_2$: C 75.81, H 7.11. Found: C 76.13, H 6.94.



4-(3,5-dimethylphenylamino)benzonitrile (Entry 7)[15]

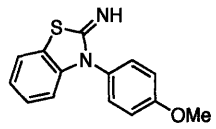
The general procedure was followed using CuI (19 mg, 0.10 mmol), pyrrole-2-carboxylic acid (22 mg, 0.20 mmol), K_3PO_4 (424 mg, 2.0 mmol), 5-iodo-*m*-xylene (144 μL, 1.00 mmol), and 4-aminobenzonitrile (236 mg, 2.0 mmol) with DMSO (0.50 mL) as solvent for 24 h at 90 °C. Workup and chromatographic purification (hexanes / ethyl acetate 1:0 → 4:1) afforded the title compound as a yellow solid (113 mg, 51%). m.p. 154-155 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.32 (3H, S)7.49-7.46 (2H, m), 6.97-6.94 (2H, m), 6.80 (2H, s), 6.77 (1H, s), 6.00 (1H, bs). ^{13}C

NMR (125 MHz, $CDCl_3$) δ 148.1, 139.7, 139.4, 133.7, 125.7, 120.0, 118.9, 114.8, 101.1, 21.3. IR (KBr disc, cm^{-1}) 3335, 2214, 1591, 1532, 1350, 1170, 826. Anal. Calc. for $C_{15}H_{14}N_2$: C 81.05, H 6.35. Found: C 80.76, H 6.33.



N-(4-(4-methoxyphenylamino)phenyl)acetamide (Entry 8)

The general procedure was followed using CuI (19 mg, 0.10 mmol), pyrrole-2-carboxylic acid (22 mg, 0.20 mmol), K_3PO_4 (424 mg, 2.0 mmol), 4-iodoanisole (234 mg, 1.00 mmol), and *N*-(4-aminophenyl)acetamide (300 mg, 2.0 mmol) with DMSO (0.70 mL) as solvent for 24 h at 80 °C. Workup and chromatographic purification (hexanes / ethyl acetate 1:0 → 4:1) afforded the title compound as a white solid (212 mg, 83 %). m.p. 138-139 °C (lit. 138 °C).[16] ^1H NMR (500 MHz, $CDCl_3$) δ 7.33-7.30 (2H, m), 7.16 (1H, bs), 7.10-7.02 (2H, m), 6.90-.84 (m, 4H), 5.47 (1H, bs), 3.80 (3H, s), 2.15 (3H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.4, 155.2, 142.1, 136.3, 130.4, 122.2, 121.7, 116.7, 114.9, 55.8, 24.6. IR (KBr disc, cm^{-1}) 3270, 1653, 1512, 1297, 1248, 1035, 819. Anal. Calc. for $C_{16}H_{15}N_2O_2$: C 70.29, H 6.29. Found: C 70.55, H 6.32.

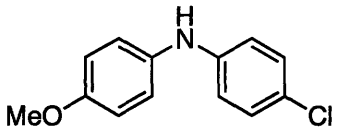


3-(4-methoxyphenyl)benzo[*d*]thiazol-2(3*H*)-imine (Entry 9)

The general procedure was followed using CuI (19 mg, 0.10 mmol), pyrrole-2-carboxylic acid (22 mg, 0.20 mmol), K_2CO_3 (280 mg, 2.0 mmol), 4-iodoanisole (234 mg, 1.00 mmol), and 2-aminobenzothiazole (298 mg, 2.0 mmol) with DMSO (0.80 mL) as solvent for 24 h at 90 °C. Workup and chromatographic purification (hexanes / ethyl acetate 1:0 → 4:1) afforded the title compound as a white solid (169 mg, 66 %). m.p. 91.5-92 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 7.53

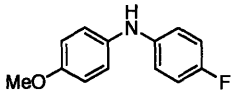
(1H, td, J = 0.6, 7.8 Hz), 7.-7.41 (1H, m), 7.31 (1H, dd, J = 0.6, 8.2 Hz), 7.13-7.07 (3H, m), 6.07 (1H, bs), 6.84-6.82 (2H, bs), 3.78 (3H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.3, 139.0, 136.6, 131.2, 130.7, 125.0, 124.2, 119.9, 115.4, 115.3, 110.4, 55.6. IR (KBr disc, cm^{-1}) 3220, 2235, 1591, 1580, 1493, 1404, 1289, 1246, 1175, 1021, 824, 753. Anal. Calc. for $C_{14}H_{12}N_2OS$: C 65.60, H 54.72. Found: C 65.64, H 4.75.

Experimental procedures for compounds in Table 3



4-chloro-*N*-(4-methoxyphenyl)aniline (Entry 1)

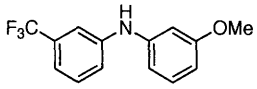
The general procedure was followed using CuI (19 mg, 0.10 mmol), pyrrole-2-carboxylic acid (22 mg, 0.20 mmol), K_3PO_4 (424 mg, 2.0 mmol), 1-bromo-4-chlorobenzene (191 mg, 1.00 mmol), and *p*-anisidine (248 mg, 2.0 mmol) with DMSO (0.50 mL) as solvent for 24 h at 100 °C. Workup and chromatographic purification (hexanes / ethyl acetate 1:0 → 4:1) afforded the title compound as a tan solid (180 mg, 77 %). m.p. 50-51 °C (lit. 50-51°C).[17] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18-7.13 (2H, m), 7.09-7.03 (2H, m), 6.90-6.80 (m, 4H), 5.48 (1H, bs), 3.81 (3H, s).



4-fluoro-*N*-(4-methoxyphenyl)aniline (Entry 2)

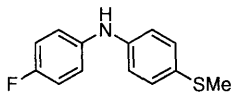
The general procedure was followed using CuI (19 mg, 0.10 mmol), pyrrole-2-carboxylic acid (22 mg, 0.20 mmol), K_3PO_4 (424 mg, 2.0 mmol), 1-bromo-4-fluorobenzene (109 μL, 1.00 mmol), and *p*-anisidine (248 mg, 2.0 mmol) with DMSO (0.50 mL) as solvent for 24 h at 80 °C. Workup and chromatographic purification (hexanes / ethyl acetate 1:0 → 4:1) afforded the title

compound as a tan solid (155 mg, 71 %). m.p. 57-59 °C (lit. 59 °C).[18] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.03-7.00 (2H, m), 6.96-6.85 (6H, m), 5.40 (1H, bs), 3.81 (3H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.3, 155.2, 141.3 (d), 136.7, 121.4, 117.9 (d), 116.1, 115.9, 114.9, 55.8.



3-methoxy-*N*-(3-(trifluoromethyl)phenyl)aniline (Entry 3)[19]

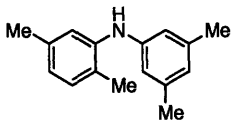
The general procedure was followed using CuI (19 mg, 0.10 mmol), pyrrole-2-carboxylic acid (22 mg, 0.20 mmol), K_3PO_4 (424 mg, 2.0 mmol), 3-bromoanisole (127 μL, 1.00 mmol), and 3-aminobenzotrifluoride (250 μL, 2.0 mmol) with DMSO (0.50 mL) as solvent for 24 h at 100 °C. Workup and chromatographic purification (hexanes / ethyl acetate 1:0 → 4:1) afforded the title compound as an orange oil (153 mg, 57%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (1H, t, J = 7.9 Hz), 7.30 (1H, s), 7.26-7.20 (2H, m), 7.16 (1H, d, J = 7.8 Hz), 6.70 (1H, dd, J = 1.2, 8.1 Hz), 6.67 (1H, s), 6.59 (1H, d, J = 8.2 Hz), 5.85 (1H, bs), 3.81 (3H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.9, 143.9, 143.4, 132.1, 130.5, 130.0, 129.9, 120.4, 117.3 (q), 113.0 (t), 111.4 (d), 107.6 (d), 104.7, 55.4.



4-fluoro-*N*-(4-(methylthio)phenyl)aniline (Entry 4)

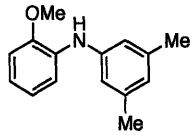
The general procedure was followed using CuI (19 mg, 0.10 mmol), pyrrole-2-carboxylic acid (22 mg, 0.20 mmol), K_3PO_4 (424 mg, 2.0 mmol), 4-bromothioanisole (203 mg, 1.00 mmol), and 4-fluoroaniline (189 μL, 2.0 mmol) with DMSO (0.50 mL) as solvent for 24 h at 100 °C. Workup and chromatographic purification (hexanes / ethyl acetate 1:0 → 4:1) afforded the title compound as a brown oil (170 mg, 73 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21-7.17 (2H, m), 7.02-6.92 (4H, m), 6.89-6.86 (2H, m), 5.56 (1H, bs), 2.41 (3H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ

159.2, 142.4, 139.0 (d), 130.3, 129.7, 120.6 (d), 117.7, 116.1 (d), 18.2. IR (KBr disc, cm^{-1}) 3396, 1595, 1508, 1314, 1223, 817, 506. Anal. Calc. for $C_{11}H_{12}F_3NS$: C 66.93, H 5.18. Found: C 67.16, H 5.20.



N-(3,5-dimethylphenyl)-2,5-dimethylaniline (Entry 5)

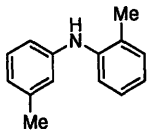
The general procedure was followed using CuI (19 mg, 0.10 mmol), 2-isobutyrylcyclohexanone (33 μL, 0.20 mmol), K_3PO_4 (424 mg, 2.0 mmol), 5-bromo-*m*-xylene (136 μL, 1.00 mmol), and 2,5-dimethylaniline (249 μL, 2.0 mmol) with DMF (0.50 mL) as solvent for 24 h at 110 °C. Workup and chromatographic purification (hexanes / ethyl acetate 1:0 → 4:1) afforded the title compound as a yellow oil (166 mg, 74 %). ^1H NMR (500 MHz, $CDCl_3$) δ 7.05-7.02 (2H, s), 6.72 (1H, td, J = 0.4, 7.6 Hz), 6.56 (2H, d, J = 0.6 Hz), 6.53 (1H, t, J = 0.6 Hz), 5.22 (1H, bs), 2.26 (3H, s), 2.23 (6H, s), 2.17 (3H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.2, 141.3, 139.2, 136.6, 130.9, 125.4, 122.8, 122.4, 119.9, 116.8, 115.4, 21.6, 21.4, 17.7. IR (KBr disc, cm^{-1}) 3383, 3020, 2919, 1601, 1578, 1522, 1466, 1221, 1177, 829, 802. Anal. Calc. for $C_{14}H_{12}F_3NO$: C 62.92, H 4.53. Found: C 63.13, H 4.46.



N-(2-methoxyphenyl)-3,5-dimethylaniline (Entry 6)[20]

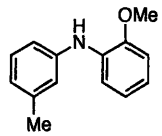
The general procedure was followed using CuI (19 mg, 0.10 mmol), pyrrole-2-carboxylic acid (22 mg, 0.20 mmol), K_3PO_4 (424 mg, 2.0 mmol), 5-bromo-*m*-xylene (136 μL, 1.00 mmol), and *o*-anisidine (225 μL, 2.0 mmol) with DMSO (0.50 mL) as solvent for 24 h at 100 °C. Workup and chromatographic purification (hexanes / ethyl acetate 4:1 → 1:0) afforded the title compound

as an orange oil (155 mg, 68%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33-7.31 (1H, m), 6.91-6.84 (3H, m), 6.81 (2H, d, J = 0.6 Hz), 6.62 (1H, t, J = 0.6 Hz), 6.10 (1H, s), 3.89 (3H, s), 2.30 (3H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.4, 142.8, 139.1, 123.2, 121.0, 119.8, 118.7, 116.5, 115.0, 110.6, 55.8, 21.6.



2-methyl-*N*-*m*-tolylaniline (Entry 7)[3]

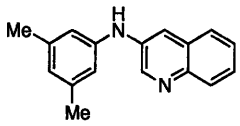
The general procedure was followed using CuI (19 mg, 0.10 mmol), pyrrole-2-carboxylic acid (22 mg, 0.20 mmol), K_3PO_4 (424 mg, 2.0 mmol), 2-bromotoluene (120 μL, 1.00 mmol), and *m*-toluidine (216 μL, 2.0 mmol) with DMSO (0.50 mL) as solvent for 30 h at 100 °C. Workup and chromatographic purification (hexanes / ethyl acetate 1:0 → 4:1) afforded the title compound as a tan oil (129 mg, 66 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (1H, d, J = 6.9 Hz), 7.22 (1H, d, J = 7.5 Hz), 7.17 (2H, m), 6.97-6.94 (1H, m), 6.81-6.75 (3H, m), 5.36 (1H, bs), 2.33 (3H, s), 2.28 (3H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.0, 141.5, 139.3, 131.1, 139.3, 128.3, 126.9, 122.0, 122.5, 118.9, 118.3, 114.7, 21.7, 18.1.



2-methoxy-*N*-*m*-tolylaniline (Entry 8)[21]

The general procedure was followed using CuI (19 mg, 0.10 mmol), pyrrole-2-carboxylic acid (22 mg, 0.20 mmol), K_3PO_4 (424 mg, 2.0 mmol), 2-bromoanisole (125 μL, 1.00 mmol), and *m*-toluidine (216 μL, 2.0 mmol) with DMSO (0.50 mL) as solvent for 30 h at 100 °C. Workup and chromatographic purification (hexanes / ethyl acetate 1:0 → 4:1) afforded the title compound as an orange oil (142 mg, 66%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.33 (1H, m), 7.23-7.18 (1H,

m), 7.02-6.87 (5H, m), 6.81 (1H, d, J = 7.5 Hz), 6.16 (1H, bs), 3.29 (3H, s), 2.36 (3H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.4, 142.8, 139.3, 133.2, 129.3, 122.2, 121.0, 119.9, 119.4, 115.8, 114.9, 110.6, 55.8, 21.7.



N-(3,5-dimethylphenyl)quinolin-3-amine (Entry 9)

The general procedure was followed using CuI (19 mg, 0.10 mmol), pyrrole-2-carboxylic acid (22 mg, 0.20 mmol), K_3PO_4 (424 mg, 2.0 mmol), 3-bromoquinoline (136 μL, 1.00 mmol), and 3,5-dimethylaniline (248 μL, 2.0 mmol) with DMSO (0.50 mL) as solvent for 24 h at 100 °C. Workup and chromatographic purification (hexanes / ethyl acetate 4:1 → 1:0) afforded the title compound as a green oil (135 mg, 54 %). ^1H NMR (500 MHz, $CDCl_3$) δ 8.72 (1H, d, J = 2.8 Hz), 8.02 (1H, dd, J = 0.6, 8.2 Hz), 7.70 (1H, d, J = 2.8 Hz), 7.65 (1H, dd, J = 1.2, 8.1 Hz), 7.54-7.46 (2H, m), 6.82 (2H, s), 6.71 (1H, d, J = 0.6 Hz), 6.12 (1H, s), 2.32 (6H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.3, 143.7, 141.9, 139.6, 137.4, 120.2, 129.1, 127.2, 126.6, 126.5, 124.4, 117.2, 116.5, 21.6. IR (KBr disc, cm^{-1}) 3265, 3038, 1596, 1491, 1470, 1361, 1215, 1140, 908, 834, 781, 749, 732.

RAAVII284g

expl stdlh

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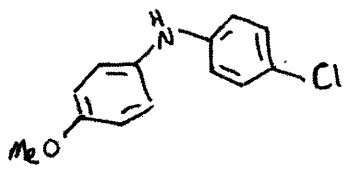

RAAVIII9c

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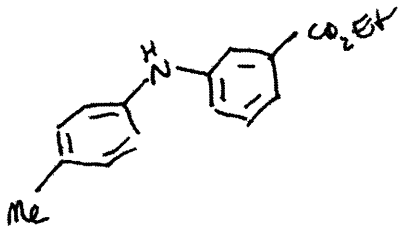

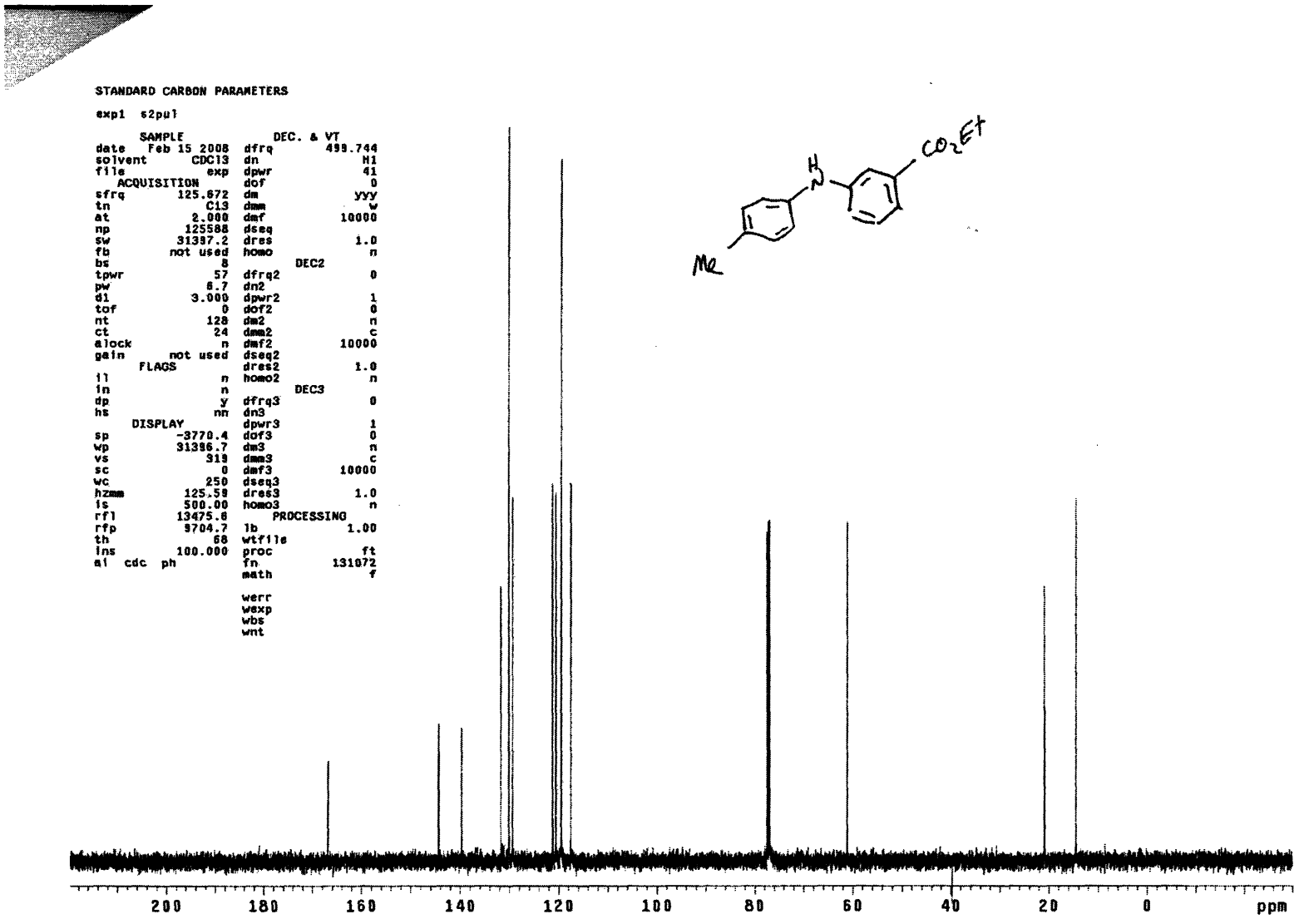
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RAAVIII8c

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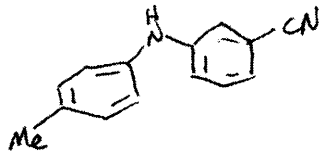

RAAVIII46b

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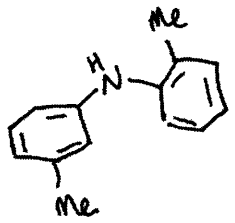

RAAVIII17A

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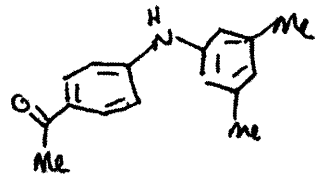

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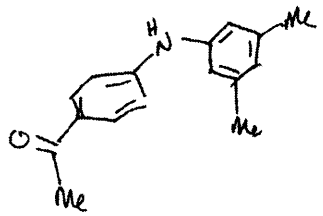

RAAVIII17b

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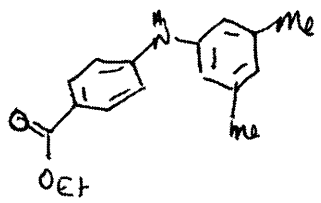

STANDARD CARBON PARAMETERS

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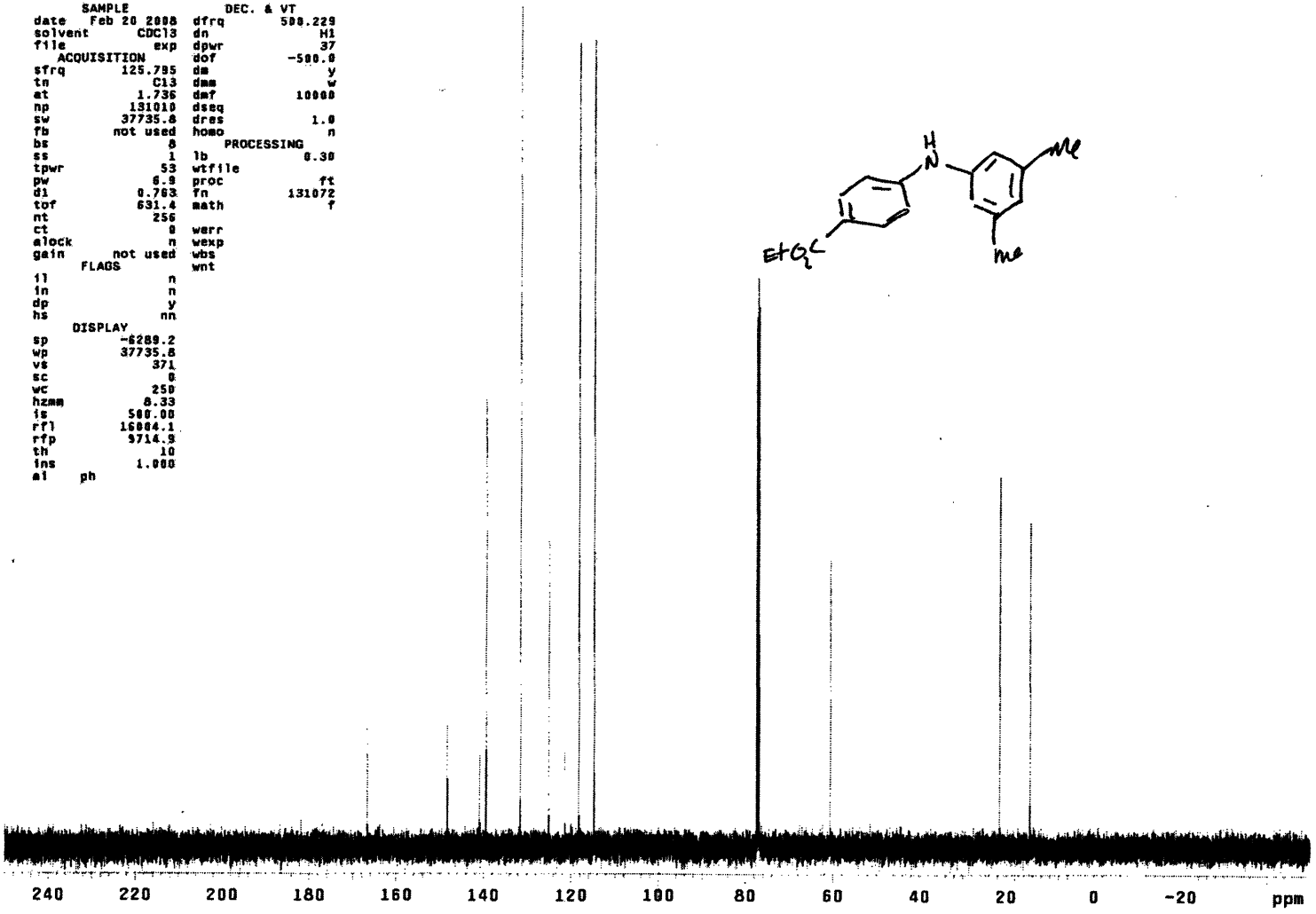

RAAVIII17c

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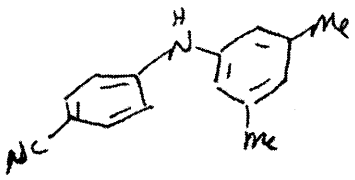
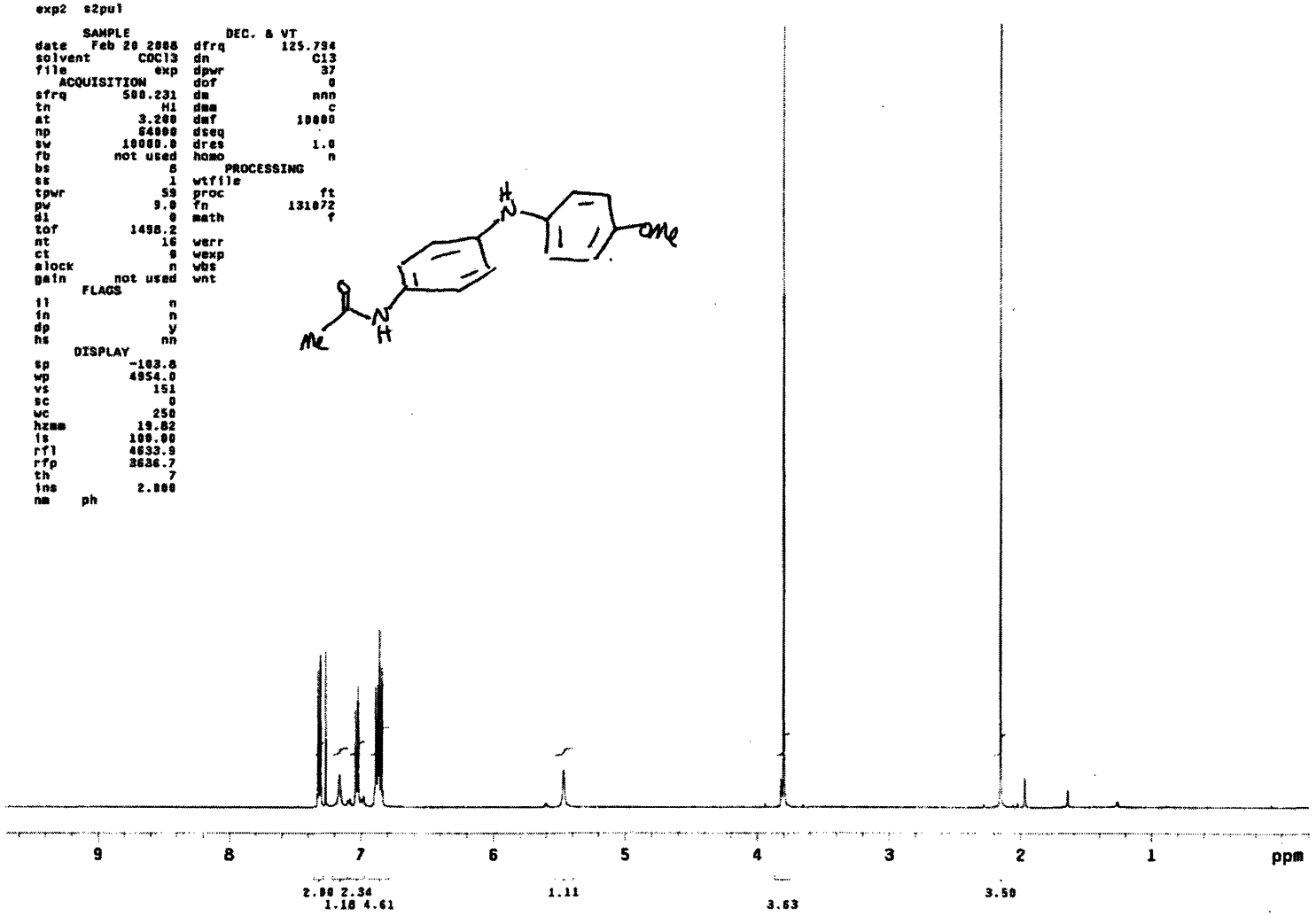
np	64000	dseq	
sw	10000.0	dres	1.0
fb	not used	homo	n
bs	1	PROCESSING	
ss	1	wtfile	
tpwr	59	proc	ft
pw	9.0	fn	131072
d1	0	math	f
tof	1498.2		
nt	16	werr	
ct	0	wexp	
alock	n	wbs	
gain	not used	wnt	
FLAGS			
il	n		
in	n		
dp	y		
hs	nn		
DISPLAY			
sp	-12.5		
wp	5124.7		
vs	151		
sc	0		
wc	250		
hzmm	20.50		
is	400.00		
rfl	4634.6		
rfp	3836.7		
th	5		
ins	6.000		
nm	ph		

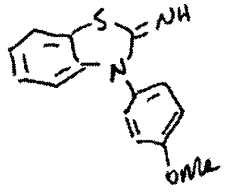



RAAVI16A
exp2 s2pul
SAMPLE
date Feb 20 2006
solvent CDCl3
file exp
ACQUISITION
sfrq 500.231
tn H1
at 3.280
np 64000
sw 10000.0
fb not used
bs 8
ss 1
tpwr 59
pw 9.0
dl 0
tof 1498.2
nt 16
ct 0
alock n
gain not used
FLAGS
il n
in n
dp y
hs nn
DISPLAY
sp -183.8
wp 4954.0
vs 151
sc 0
wc 250
hzmm 19.82
is 100.00
rfl 4633.9
rfp 3636.7
th 7
ins 2.000
nm ph
DEC. & VT
dfrq 125.794
dn C13
dpwr 37
dof 0
dm nnn
dmm c
dmf 10000
dseq
dres 1.0
homo n
PROCESSING
wtfile
proc ft
fn 131072
math f
werr
wexp
wbs
wnt
NH
NH
OMe
Me
9
8
7
6
5
4
3
2
1
ppm
2.00 2.34
1.18 4.61
1.11
3.63
3.50

RAAVIII25B

exp2 s2pul

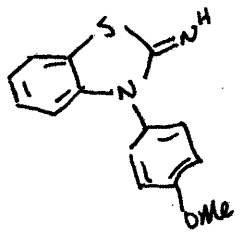
SAMPLE		DEC. & VT	
date	Feb 25 2008	dfrq	125.672
solvent	CDCl3	dn	C13
file	exp	dpwr	30
ACQUISITION		dof	0
sfrq	499.746	dm	nnn
tn	H1	dmm	w
at	3.001	dmf	10000
np	63050	dseq	
sw	10504.2	dres	1.0
fb	not used	homo	n
bs	1	DEC2	
tpwr	59	dfrq2	0
pw	8.6	dn2	
dl	2.000	dpwr2	1
tof	1519.5	dof2	0
nt	16	dm2	n
ct	16	dmm2	c
alock	n	dmf2	200
gain	not used	dseq2	
FLAGS		dres2	1.0
il	n	homo2	n
in	n	DEC3	
dp	y	dfrq3	0
hs	nn	dn3	
DISPLAY		dpwr3	1
sp	-85.2	dof3	0
wp	4595.5	dm3	n
vs	34	dmm3	c
sc	0	dmf3	200
wc	250	dseq3	
hzmm	18.38	dres3	1.0
is	33.57	homo3	n
rfl	4884.1	PROCESSING	
rfp	3633.1	wtfile	
th	7	proc	ft
ins	3.000	fn	262144
ai cdc ph		math	f
		werr	
		wexp	
		wbs	
		wnt	wft



STANDARD CARBON PARAMETERS

exp2 s2pul

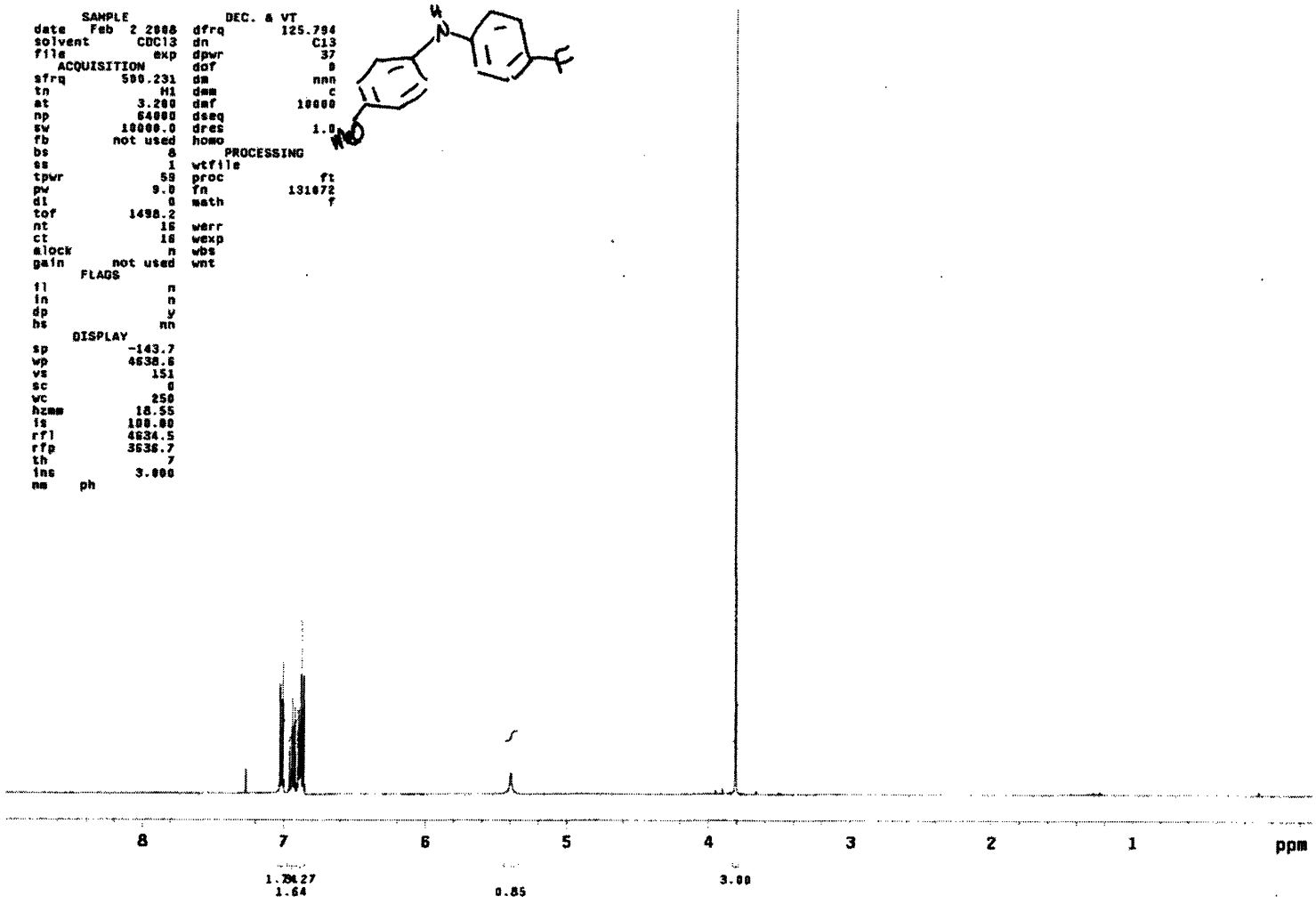
SAMPLE		DEC. & VT	
date	Feb 14 2008	dfrq	500.229
solvent	CDCl3	dn	H1
file	exp	dpwr	37
ACQUISITION		dof	-500.0
sfrq	125.795	dm	y
tn	C13	dmm	w
at	1.736	dmf	10040
np	131010	dseq	
sw	37735.8	dres	1.0
fb	not used	homo	n
bs	8	PROCESSING	
ss	1	lb	0.30
tpwr	53	wtfile	
pw	6.9	proc	ft
dl	0.763	fn	131072
tof	531.4	math	f
nt	256		
ct	170	werr	
alock	n	wexp	
gain	not used	wbs	
FLAGS		wnt	
il	n		
in	n		
dp	y		
hs	nn		
DISPLAY			
sp	-6292.7		
wp	37735.8		
vs	356		
sc	0		
wc	250		
hzmm	158.94		
is	500.00		
rfl	16087.6		
rfp	9714.9		
th	8		
ins	1.000		
ai	ph		



RAAVII246

expl s2pul

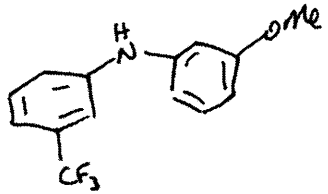
SAMPLE		DEC. & VT	
date	Feb 2 2008	dfrq	125.794
solvent	CDCl3	dn	C13
file	exp	dpwr	37
ACQUISITION		dof	0
sfrq	500.231	dm	nnn
tn	H1	dmm	c
at	3.280	dmf	10000
np	64000	dseq	
sw	10000.0	dres	1.0
fb	not used	homo	
bs	8	PROCESSING	
ss	1	wtfile	
tpwr	59	proc	ft
pw	9.0	fn	131072
dl	0	math	f
tof	1498.2		
nt	16	werr	
ct	16	wexp	
alock	n	wbs	
gain	not used	wnt	
FLAGS			
fl	n		
in	n		
dp	y		
hs	nn		
DISPLAY			
sp	-143.7		
wp	4538.6		
vs	151		
sc	0		
wc	250		
hzmm	18.55		
is	100.00		
rfl	4634.5		
rfp	3538.7		
th	7		
ins	3.000		
nm ph			

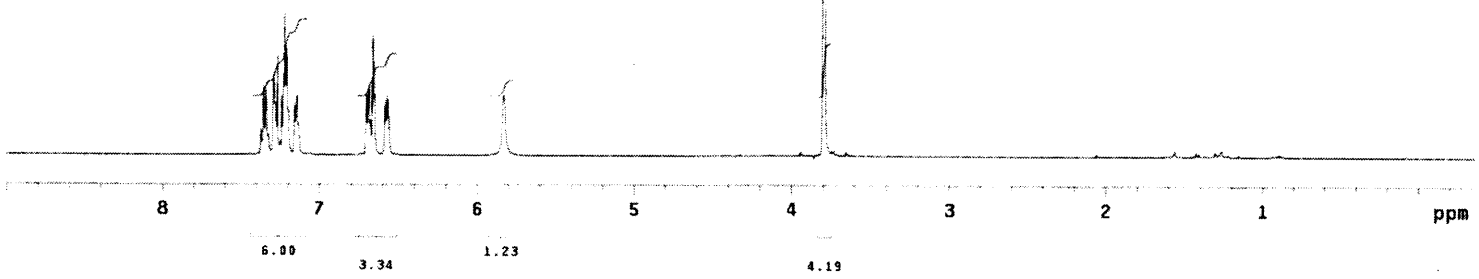


RAAVIII57

exp2 s2pul

SAMPLE		DEC. & VT	
date	Mar 20 2008	dfrq	125.794
solvent	CDCl3	dn	C13
file	exp	dpwr	37
ACQUISITION		dof	0
sfrq	500.231	dm	nnn
tn	H1	dmm	c
at	3.200	dmf	10000
np	64000	dseq	
sw	10000.0	dres	1.0
fb	not used	homo	n
bs	1	PROCESSING	
ss	1	wtfile	
tpwr	59	proc	ft
pw	9.0	fn	131072
dl	0	math	f
tof	1498.2		
nt	16	werr	
ct	16	wexp	
alock	n	wbs	
gain	not used	wnt	
FLAGS			
il	n		
in	n		
dp	y		
hs	nn		
DISPLAY			
sp	-182.5		
wp	4691.1		
vs	151		
sc	0		
wc	250		
hzmm	18.76		
is	100.00		
rf1	4633.9		
rfp	3636.7		
th	12		
ins	2.000		
nm	ph		

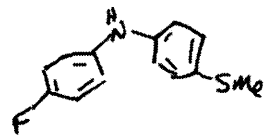




RAAVIII56

expz s2pul

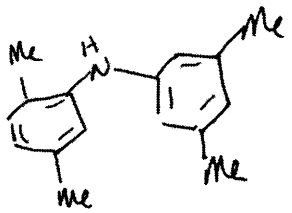
SAMPLE		DEC. & VT	
date	Mar 20 2008	dfrq	125.794
solvent	CDCl3	dn	C13
file	exp	dpwr	37
ACQUISITION		dof	0
sfrq	500.231	dm	nnn
tn	H1	dmm	c
at	3.200	dmf	10000
np	64000	dseq	
sw	10000.0	dres	1.0
fb	not used	homo	n
bs	1	PROCESSING	
ss	1	wtfile	
tpwr	59	proc	ft
pw	9.0	fn	131072
d1	0	math	f
tof	1498.2		
nt	16	werr	
ct	16	wexp	
alock	n	wbs	
gain	not used	wnt	
FLAGS			
il	n		
in	n		
dp	y		
hs	nn		
DISPLAY			
sp	-169.4		
wp	5045.9		
vs	151		
sc	0		
wc	250		
hzmm	20.18		
is	100.00		
rfl	4633.9		
rfp	3636.7		
th	7		
ins	2.000		
nm	ph		

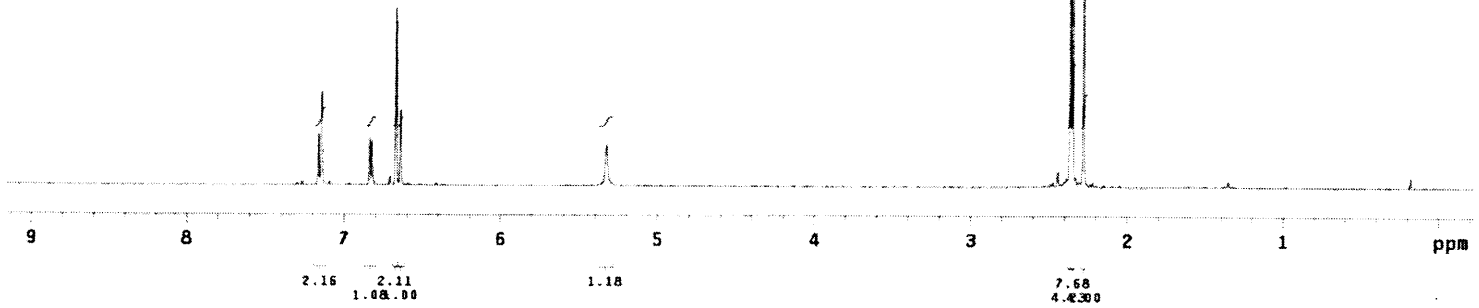


RAAVII254a

exp2 s2pul

SAMPLE		DEC. & VT	
date	Feb 2 2008	dfrq	125.794
solvent	CDCl3	dn	C13
file	exp	dpwr	37
ACQUISITION		dof	0
sfrq	500.231	dm	nnn
tn	H1	dmm	c
at	3.200	dmf	10000
np	64000	dseq	
sw	10000.0	dres	1.0
fb	not used	homo	n
bs	8	PROCESSING	
ss	1	wtfile	
tpwr	59	proc	ft
pw	9.0	fn	131072
d1	0	math	f
tof	1498.2		
nt	16	werr	
ct	16	wexp	
alock	n	wbs	
gain	not used	wnt	
FLAGS			
il	n		
in	n		
dp	y		
hs	nn		
DISPLAY			
sp	-118.3		
wp	4704.2		
vs	151		
sc	0		
wc	250		
hzmm	18.82		
is	100.00		
rfl	4635.2		
rfp	3636.7		
th	7		
ins	1.000		
nm	ph		

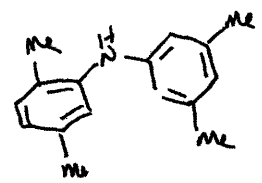




STANDARD CARBON PARAMETERS

expl s2pul

SAMPLE		DEC. & VT	
date	Feb 2 2008	dfrq	500.229
solvent	CDCl3	dn	H1
file	exp	dpwr	37
ACQUISITION		dof	-500.0
sfrq	125.795	dm	y
tn	C13	dmm	w
at	1.736	dmf	10000
np	131010	dseq	
sw	37735.8	dres	1.0
fb	not used	homo	n
bs	8	**PROCESSING**	
ss	1	lb	0.30
tpwr	53	wtfile	
pw	6.9	proc	ft
dl	0.763	fn	131072
tof	631.4	math	f
nt	256		
ct	104	werr	
alock	n	wexp	
gain	not used	wbs	
FLAGS		wnt	
tl	n		
fn	n		
dp	y		
hs	nn		
DISPLAY			
sp	-6301.9		
wp	37735.8		
vs	106		
sc	0		
wc	250		
hzmm	150.94		
is	500.00		
rfl	16816.8		
rfp	9714.9		
th	9		
ins	1.000		
ai	ph		



RAAVIII63

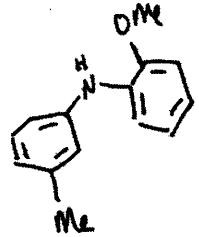
exp2 s2pul

SAMPLE		DEC. & VT	
date	Mar 28 2008	dfrq	125.794
solvent	CDCl3	dn	C13
file	exp	dpwr	37
ACQUISITION		dof	0
sfrq	500.231	dm	nnn
tn	H1	dmm	c
at	3.280	dmf	10000
np	64000	dseq	
sw	10000.0	dres	1.0
fb	not used	homo	n
bs	1	PROCESSING	
ss	1	wtfile	
tpwr	59	proc	ft
pw	9.0	fn	131072
d1	0	math	f
tof	1498.2		
nt	64	werr	
ct	26	wexp	
alock	n	wbs	
gain	not used	wnt	
FLAGS			
il	n		
in	n		
dp	y		
hs	nn		
DISPLAY			
sp	-54.4		
wp	4783.1		
vs	151		
sc	0		
wc	250		
hzmm	19.13		
is	100.00		
rfl	4634.0		
rfp	3636.7		
th	4		
ins	6.000		
nm	ph		

RAAVIII45a

expl s2pul

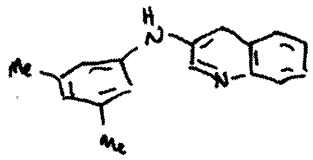
SAMPLE		DEC. & VT	
date	Mar 6 2008	dfrq	125.794
solvent	CDCl3	dn	C13
file	exp	dpwr	37
ACQUISITION		dof	0
sfrq	500.231	dm	nnn
tn	H1	dmm	c
at	3.200	dmf	10000
np	64000	dseq	
sw	10000.0	dres	1.0
fb	not used	homo	n
bs	2	PROCESSING	
ss	1	wtfile	
tpwr	59	proc	ft
pw	9.8	fn	131072
d1	0	math	f
tof	1498.2		
nt	16	werr	
ct	16	wexp	
alock	n	wbs	
gain	not used	wnt	
FLAGS			
il	n		
in	n		
dp	y		
hs	nn		
DISPLAY			
sp	-63.9		
wp	5137.9		
vs	151		
sc	0		
wc	250		
hzmm	20.55		
is	100.00		
rfl	4633.6		
rfp	3636.7		
th	7		
ins	3.000		
nm	ph		

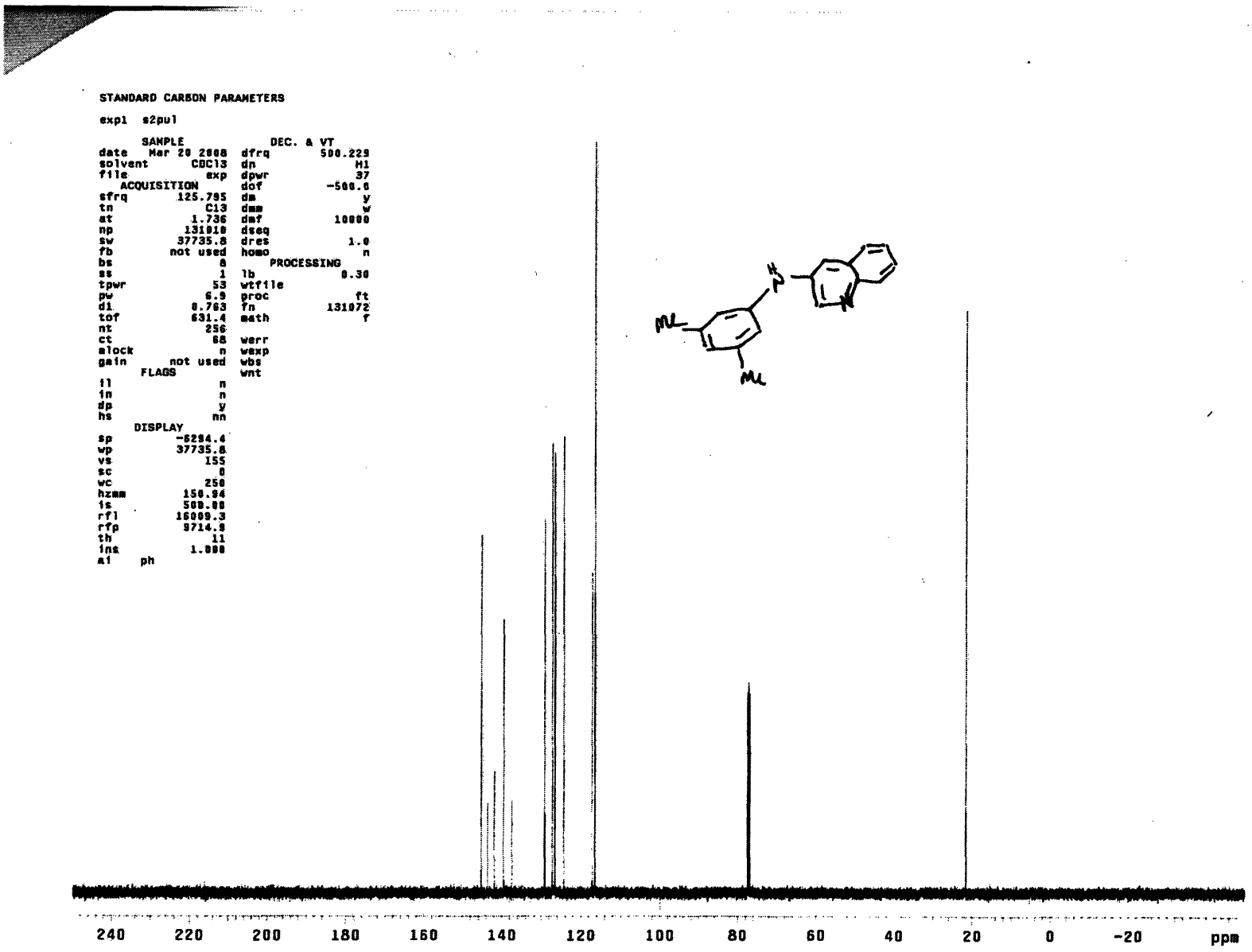


RAAVIII58

exp2 s2pul

SAMPLE		DEC. & VT	
date	Mar 20 2008	dfrq	125.794
solvent	CDCl3	dn	C13
file	exp	dpwr	37
ACQUISITION		dof	0
sfrq	500.231	dm	nnn
tn	H1	dmm	c
at	3.200	dmf	10000
np	64000	dseq	
sw	10000.0	dres	1.0
fb	not used	homo	n
bs	1	PROCESSING	
ss	1	wtfile	
tpwr	59	proc	ft
pw	9.0	fn	131072
d1	0	math	f
tof	1498.2		
nt	16	werr	
ct	16	wexp	
alock	n	wbs	
gain	not used	wnt	
FLAGS			
il	n		
in	n		
dp	y		
hs	nn		
DISPLAY			
sp	-116.9		
wp	5289.2		
vs	151		
sc	0		
wc	250		
hzmm	21.08		
is	100.00		
rfl	4633.9		
rfp	3636.7		
th	5		
ins	6.000		
nm	ph		




STANDARD CARBON PARAMETERS
exp1 s2pul
SAMPLE
date Mar 28 2008
solvent CDCl3
file exp
ACQUISITION
sfrq 125.795
tn C13
at 1.736
np 131010
sw 37735.8
fb not used
bs 8
ss 1
tpwr 53
pw 6.9
d1 0.763
tof 631.4
nt 256
ct 68
alock n
gain not used
FLAGS
il n
in n
dp y
hs nn
DISPLAY
sp -6284.4
wp 37735.6
vs 155
sc 0
wc 250
hzmm 150.94
is 500.00
rfl 16009.3
rfp 9714.9
th 11
ins 1.000
ai ph
DEC. & VT
dfrq 500.229
dn H1
dpwr 37
dof -500.0
dm y
dmm w
dmf 10000
dseq
dres 1.0
homo n
PROCESSING
lb 0.30
wtfile
proc ft
fn 131072
math f
werr
wexp
wbs
wnt
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

4.5 References and Notes

(1) (a) Surry, D. S.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2008**, Manuscript Accepted. (b) 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.

(2) (a) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, 2337. (b) Ley, S. V.; Thomas, A. W. *Angew. Chem. Int. Ed.* **2003**, *42*, 5400. (c) Kunz, K.; Scholz, U.; Ganzer, D. *Synlett* **2003**, 2428.

(3) Biscoe, M. B.; Barder, T. E.; Bucwhald, S. L. *Angew. Chem. Int. Ed.* **2007**, *46*, 7232.

(4) (a) Gujadhur, R.; Venkataraman, D.; Kintigh, J. T. *Tetrahedron Lett.* **2001**, *42*, 4791. (b) Zhang, H.; Cai, Q.; Ma, D. *J. Org. Chem.* **2005**, *70*, 5164. (c) Rao, H.; Fu, H.; Jiang, Y.; Zhao, Y. *J. Org. Chem.* **2005**, *70*, 8107. (d) Guo, X.; Rao, H.; Fu, H.; Jiang, Y.; Zhao, Y. *Adv. Synth. Catal.* **2006**, *348*, 2197. (e) Rao, H.; Jin, Y.; Fu, H.; Jiang, Y.; Zhao, Y. *Chem. Eur. J.* **2006**, *12*, 3636. (f) Liu, Y.; Bai, Y.; Zhang, J.; Li, Y.; Jiao, J.; Qi, X. *Chem. Eur. J.* **2007**, *13*, 6084. (g) Rout, L.; Jammi, S.; Punniyamurthy, T. *Org. Lett.* **2007**, *9*, 3397.

(5) (a) Huang, X.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.*, **2003**, *125*, 6653. (b) Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421. (c) Altman, R. A.; Koval, E. D.; Buchwald, S. L. *J. Org. Chem.* **2007**, *72*, 6190. (d) Antilla, J. C.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 11684. (e) Shafir, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 8742. (f) Shafir, A.; Lichtor, P. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 3490. (g) Altman, R. A.; Shafir, A.; Choi, A.; Lichtor, P. A.; Buchwald, S. L. *J. Org. Chem.* **2008**, *73*, 284.

(6) (a) Goodbrand, H. B.; Hu, N. X. *J. Org. Chem.* **1999**, *64*, 670. (b) Kelkar, A. A.; Patil, N. M.; Chaudhari, R. V. *Tetrahedron Lett.* **2002**, *43*, 7143. (c) Patil, N. M.; Kelkar, A. A.; Chaudhari, R. V. *J. Mol. Catal. A: Chem.* **2004**, *223*, 45.

(7) (a) Allred, G. D; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748. (b) Yip, S. F.; Cheung, H. Y.; Zhou, Z.; Kwong, F. Y. *Org. Lett.* **2007**, *9*, 3469.

(8) Cristau, H. J.; Cellier, P. P.; Hamada, S.; Spindler, J. F.; Taillefer, M. *Org. Lett.* **2004**, *6*, 913.

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

(10) Authentic *N*-(4-methoxyphenyl)benzo[*d*]thiazol-2-amine was independently prepared from the reaction of 2-chlorobenzothiazole and *p*-anisidine according to the procedure in Cossey, H. D.; Judd, J.; Stephens, F. F. *J. Chem. Soc.* **1965**, 954. The product of this uncatalyzed reaction was found to be different than the product obtained from the reaction described in Table 2, entry 9.

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

(12) Nordiff, E. A.; Hausman, M. *J. Org. Chem.* **1964**, *29*, 2453.

(13) Toyama, T.; Toyama, I.; Nimura, M.; Kamiyama, N.; Yokota, M. Biaryl compounds and diaryl ethers as uricosuric agents. Jpn. Kokai Tokkyo Koho, JP/2000001431 A 20000107, 2000.

(14) Spagnolo, P.; Zanirato, P. *Tetrahedron Lett.* **1987**, *28*, 961.

(15) Buchwald, S. L.; Klapars, A.; Antilla, J. C.; Job, G. E.; Wolter, M.; Kwong, F. Y.; Nordmann, G.; Hennessy, E. J. Copper-catalyzed formation of carbon-heteroatom and carbon-carbon bonds by arylation and vinylation of amines, amides, hydrazides, heterocycles, alcohols, enolates, and malonates, using aryl, heteroaryl, and vinyl halides and analogs. WO/2002085838 A1, 2002.

(16) Erdley, et Al. *Acta Chim. Acad. Sci Hung.* **1957**, *12*, 251.

(17) Zhang, Hui; Cai, Qian; Ma, D. *J. Org. Chem.* **2005**, *70*, 5164.

(18) Thu-Cuc, T., et al. *J. Heterocycl. Chem.* **1964**, *1*, 28.

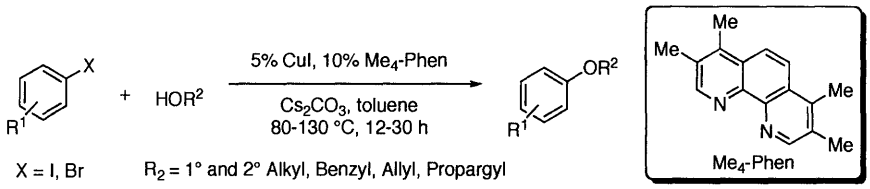
(19) Nodiff, E. A.; Craig, P. N. *J. Org. Chem.* **1961**, *26*, 824.

(20) Zhang, X. X.; Harris, M. C.; Sadighi, J. P.; Buchwald, S. L. *Can. J. Chem.* **2001**, *79*, 1799.

(21) Sridharan, V.; Karthikeyan, K.; Muthusubramanian, S. *Tetrahedron Lett.* **2006**, *47*, 4221.

Chapter Five

An Improved Copper-based Catalyst System for the Reactions of Aryl Halides with Aliphatic Alcohols



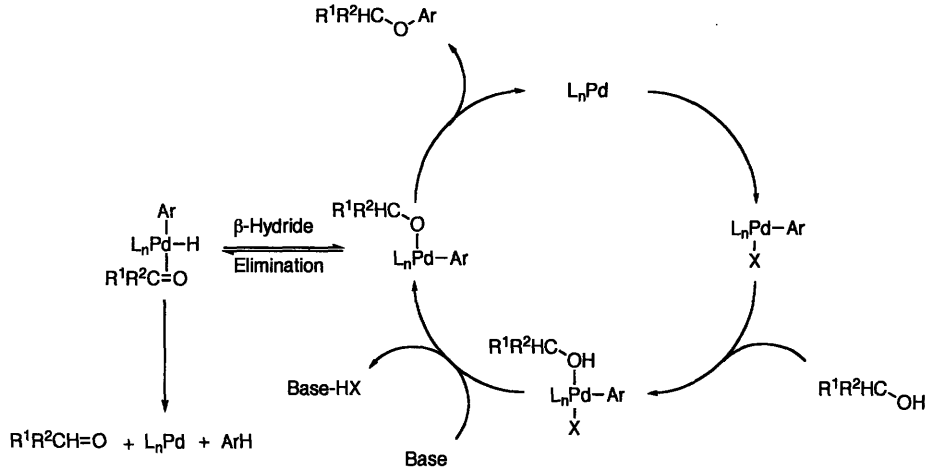
X = I, Br R_2 = 1° and 2° Alkyl, Benzyl, Allyl, Propargyl

5.1 Introduction

Recently developed transition metal-catalyzed nucleophilic substitution reactions of aryl halides have complemented traditional approaches for synthetic organic chemists to prepare C-heteroatom bonds. For the synthesis of alkyl aryl ethers, a traditional preparation might involve nucleophilic displacement of an alkyl halide by a phenol,[1] while the complementary metal-catalyzed variant would involve displacement of an aryl halide with an aliphatic alcohol. While the scope of products that can be accessed by the former method might be limited by the nucleophilicity of the phenol and the steric hindrance at the electrophilic carbon atom, the latter reaction can be limited by the activation of the aryl halide or reductive elimination processes.

In our continuing quest to improve metal-catalyzed C- heteroatom bond-forming reactions, we have developed several Pd- and Cu-based catalyst systems for the intermolecular coupling reactions of aliphatic alcohols with aryl halides to prepare alkyl aryl ethers.[2-3] Using Pd-based catalysts, the low yields observed in the coupling of certain substrates have been attributed to the slow rate of CO reductive elimination relative to β-hydride elimination from the $L_nPd(II)(Ar)(alkoxide)$ intermediate.[1a,b,4] In these cases, Cu-based catalyst systems can provide complementary reactivities, as the analogous intermediates derived from these catalysts do not readily undergo β-hydride elimination reactions.[5]

Figure 1. Competitive β-Hydride Elimination Pathway in Pd-Catalyzed Arylation of Aliphatic Alcohols

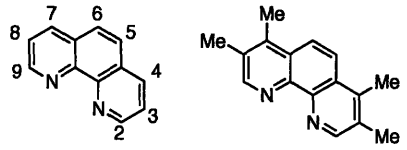


The substrate scopes and the overall utility of the traditional Cu-based methods for the synthesis of alkyl aryl ether are severely limited by (1) the use of superstoichiometric quantities of Cu, (2) high reaction temperatures, and (3) the use of strong alkoxide bases.[6] Currently, few generally applicable Cu-based catalyst systems, which facilitate the reaction under mild conditions, have been reported for the cross-coupling of aliphatic alcohols with aryl halides.[2,7-8]

In 2002, we reported that 10 mol % of CuI in conjunction with 20 mol % of 1,10-phenanthroline (Phen, Figure 1) could facilitate CO bond formation between aryl iodides and aliphatic alcohols under mild reaction conditions (Cs_2CO_3/ 110 °C/18-38 h); however, in most cases, the use of the alcohol as a solvent was required to achieve satisfactory yields, thus rendering the procedure impractical for the use of precious or highly functionalized alcohols.[2] In certain simple cases, toluene could be utilized as a solvent to reduce the quantity of alcohol required for the reactions. Recently developed catalysts systems that employ amino acids as ligands or KF/Al_2O_3 as the base have also failed to overcome the required use of excess quantities of alcohols for these reactions.[7] In addition, reactions of both secondary (2°) cyclic and acyclic alcohols provided the corresponding products in low yields due to incomplete conversion

of the aryl iodides in reasonable time periods (24 h).[2,7] More recently, we reported that the use of a commercially available ligand, 3,4,7,8-tetramethyl-1,10-phenanthroline (Me_4-Phen, Figure 2), improved the Cu-catalyzed nucleophilic substitution reactions of aryl iodides and alkyl-substituted vinyl iodides with amino alcohols and allylic alcohols, respectively; however, the scope of the reaction was not investigated/explored beyond these selected substrates.[9-10] Herein, we report an in-depth account of the use of Me_4-Phen in Cu-catalyzed CO bond-forming reactions that presents the scope and limitations of this catalyst system.

Figure 2. 1,10-Phenanthroline-based Ligands for Cu-catalyzed C–O Bond-formation



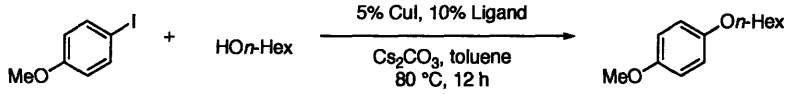
Phen Me_4-Phen

5.2 Results and Discussion

A variety of 1,10-phenanthroline-substituted ligands were tested in the reaction of 4-iodoanisole with *n*-hexanol using the following catalyst system: 5 mol % CuI/10 mol % ligand/Cs_2CO_3/toluene/80 °C/12 h (Table 1). The data presented suggest that the presence of methyl and phenyl substituents in positions 3-5 of the phenanthroline backbone increase the activity of the catalyst (entries 17). More specifically, the catalytic activity of the methyl-substituted ligands increases as a function of the number of methyl substituents present on the Phen core: Phen 4-Me-Phen 5-Me-Phen 4,7-Me_2-Phen 5,6-Me_2-Phen Me_4-Phen. Two hypotheses to explain the high activity of the catalyst systems, which employ methyl-substituted Phen ligands, are (1) the alkyl substituents might increase the solubility of the metal catalyst in a nonpolar organic solvent, thus raising the effective concentration of catalyst in solution, and/or

(2) the presence of the alkyl substituents on the ligand increases the σ-donating ability of the nitrogen atoms[11] and accelerates the rate-limiting aryl halide activation step. Neocuproine (2,9-Me_2-Phen) is not a good ligand for this transformation and reinforces the notion that Cu-catalyzed C-heteroatom bond-forming reactions are extremely sensitive to steric hindrance.[4] When 4,7-$(MeO)_2$-Phen is employed as a ligand for this transformation, 1,4-dimethoxybenzene is produced as a byproduct (15% GC yield), presumably due to nucleophilic displacement of the methoxy groups of the ligand by *n*-hexanol, followed by cross-coupling of the resulting methoxide nucleophile with the aryl iodide (entry 9). Interestingly, the combined yield of methoxy- and *n*-hexyloxy-substituted products (81%) when employing the dimethoxy-substituted ligand is comparable to the yield of product observed when Me_4-Phen is used (79%), suggesting that these two catalyst systems facilitate C–O bond formation at comparable rates. Other 4,7-bis-heteroatom-substituted-Phen derivatives provide relatively inactive catalysts (entries 10, 11).

Table 1. Cu-Catalyzed Reaction of 4-Iodoanisole with *n*-Hexanol Using 1,10-Phenanthroline-derived Ligands[a]



entry	ligand	conversion (%)	yield (%)
1	1,10-phenanthroline (Phen)	50	44
2	4-Me-Phen	56	54
3	5-Me-Phen	55	51
4	4,7-Me_2-Phen	68	57
5	5,6-Me_2-Phen	64	54
6	Me_4-Phen	82	79
7	4,7-Ph_2-Phen	63	64
8	neocuproine	10	0
9	4,7-$(MeO)_2$-Phen	83	66
10	4,7-$(NMe)_2$-Phen	37	19
11	4,7-Cl_2-Phen	35	33

[a] Reaction conditions: 1.0 mmol of 4-iodoanisole, 1.5 mmol of *n*-hexanol, 0.050 mmol of CuI, 0.10 mmol of ligand, 1.5 mmol of Cs_2CO_3, and 0.5 mL of toluene under Ar atmosphere at 80 °C for 12 h. Corrected conversion and yield data were calculated from GC analyses of the crude reaction mixtures using dodecane as an internal standard.

Using the optimized reaction conditions, a wide variety of substrates containing useful functional groups can be success- fully cross-coupled (Table 2). The reaction of our model substrates (*n*-hexanol with 4-iodoanisole) proceeds in excellent yield at temperatures as low as 80 °C using 5% catalyst (entry 1). At 110 °C using 2% and 5% catalyst loading, this same reaction proceeds in 24 and 12 h, respectively (entries 2, 3).

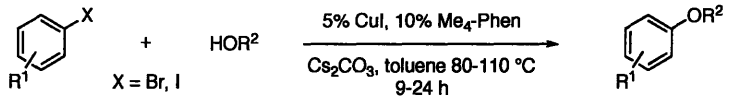
The catalyst system is tolerant of ortho-substituents on the aryl halide (entries 4-6), as well as both electron-donating and withdrawing substituents on the aromatic ring. Aryl iodides can be selectively cross-coupled in the presence of aryl bromides, chlorides, and fluorides (entries 8-10). Low-boiling point alcohols, as well as allyl, propargyl, and benzyl alcohols, furnish the corresponding aryl ethers in good to excellent yields (entries 7, 8, 10-13). The latter example

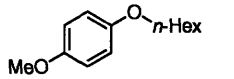
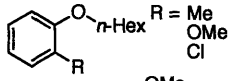
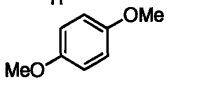
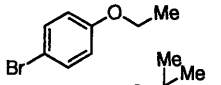
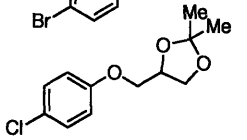
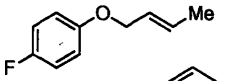
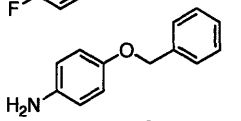
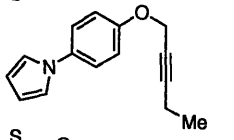
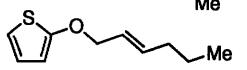
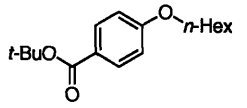
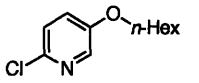
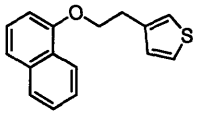
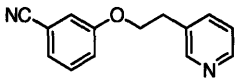
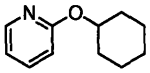
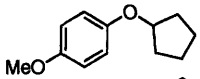
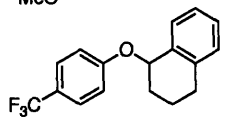
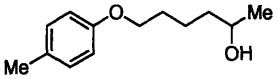
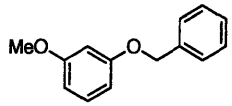
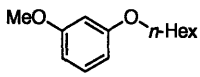
provides ready access to the corresponding phenols, as the resulting aryl benzyl ether can be readily cleaved.[12] Remarkably, the catalyst system can selectively cross-couple alcohols in the presence of an unprotected aniline (entry 11) or aliphatic amines.[9]

Although the Cu-catalyzed reaction of ethyl 4-iodobenzoate with *n*-hexanol provides a complex mixture of transesterified and cross-coupled products, the formation of the transesterified product can be drastically reduced by employing the *tert*-butyl ester (entry 14). Heterocyclic compounds can be employed either as the electrophilic or nucleophilic reactant (entries 12, 13, 15-18). Products containing water-sensitive functional groups can be provided in good yields by adding activated molecular sieves to the reaction mixtures. (entries 17, 18).

The Cu-catalyzed cross-coupling reactions of secondary alcohols with aryl halides are particularly important reactions, due to the increased propensity for 2° alcohols to undergo β-hydride elimination using Pd-based catalyst systems.[1] Further, the complementary uncatalyzed Williamson reactions of 2° alkyl halides with poorly nucleophilic phenols typically provide low yields of the aryl alkyl ether products.[13] The CuI/Me_4-Phen- catalyzed reactions of 2° cyclic alcohols with aryl iodides are generally slower than the respective primary (1°) alcohol counterparts (entries 18-20), requiring higher reaction temperatures (110 °C compared to 80 °C). However, the reactions of secondary acyclic alcohols (e.g., isopropyl alcohol and 3-pentanol) with simple aryl iodides are unsuccessful, unless the reactions are run in neat alcohol. This difference in reactivity can be exploited to selectively cross-couple a 1° alcohol in the presence of a 2° alcohol (entry 21). We speculate that this selectivity difference occurs due to the poor coordinating ability of the 2° alcohol relative to the 1° alcohol.

Table 2. CuI/Me_4-Phen-Catalyzed Cross-coupling Reactions of Alcohols with Aryl Iodides and Bromides[a]



entry	product	X =	temperature (°C)	time (h)	yield (%)
1		I	80	20	87[b]
2		I	110	24	99[b,c]
3		I	110	12	95[b]
4	 R = Me	I	110	24	83
5	OMe	I	110	30	94
6	Cl	I	110	24	80
7		I	80	20	82
8		I	80	24	72[d]
9		I	80	16	75
10		I	80	20	74
11		I	80	16	81
12		I	80	20	92
13		I	80	16	59
14		I	80	24	92[e]
15		I	80	16	86
16		I	110	24	95
17		I	80	24	78[f]
18		I	110	24	85[f]
19		I	110	24	88
20		I	110	24	75
21		I	80	24	73[g]
22		Br	110	24	94[h]
23		Br	130	24	77[i]

[a] Reaction conditions: 1.0 mmol of ArX, 1.5 of mmol alcohol, 0.050 of mmol CuI (5%), 0.10 mmol of Me_4-Phen (10%), 1.5 mmol of Cs_2CO_3, and 0.50 mL of toluene under an Ar atmosphere. The isolated yields reported are averages of two or more runs of material judged to be 95% pure by ^{1}H NMR and/or elemental analysis. [b] GC yield reported. [c] 2% CuI, 4% Me_4-Phen. [d] GC analysis: 14:1 mixture of I- to Br-substituted products that were separated by column chromatography. [e] Inseparable 7:1 mixture of depicted product and *n*-hexyl 4-(hexyloxy)benzoate. [f] 200 mg of 4 Å mol sieves added to reaction mixture. [g] One regioisomer detected by GCMS and ^{1}H NMR. [h] 10% CuI, 20% Me_4-Phen. [i] 130 °C, 0.50 mL of *n*-hexanol used as solvent.

The cross-coupling reactions of aryl bromides are less successful than their iodide counterparts. At a 10% catalyst loading, the reaction of benzyl alcohol with 3-bromoanisole

proceeds smoothly (entry 22). However, the Cu-catalyzed reactions of other aliphatic alcohols are more challenging for this catalyst system. An aryl bromide can be successfully cross-coupled in neat *n*-hexanol at an elevated temperature (130 °C, entry 23). However, the reactions of both 2° cyclic and acyclic alcohols do not proceed to full conversion under these and more rigorous conditions. These data suggest that the efficacy of Cu- catalyzed cross-coupling reactions of various alcohols with aryl halides follows the trend benzylic 1° alkyl 2° cyclic alkyl 2° acyclic alkyl. We suspect that the efficiency of reactions that employ benzylic alcohols is due, in large part, to their enhanced acidity relative to other aliphatic alcohols.[14]

5.3 Conclusion

In summary, we have explored the utility of Me_4-Phen as a ligand in the Cu-catalyzed cross-coupling reactions of aryl iodides and bromides with alcohols. With this protocol, the cross-coupling reactions of aryl iodides with alcohols can be run under mild conditions without the required use of excess quantities of nucleophile in the reaction. This catalyst system complements Pd-based catalyst systems, as well as traditional Williamson reactions, and nucleophilic substitution reactions of activated aryl halides for the preparation of alkyl aryl ethers. We believe that chemists in both academic and industrial laboratories will find this improved catalyst system useful in their work.

5.4 Experimental Procedures

All reactions were carried out in resealable test tubes with teflon septa under a dry argon or nitrogen atmosphere. Copper(I) iodide (98%) was purchased from Strem. Me_4-Phen was purchased from Acros. The *Anhydrous finely powdered* Cs_2CO_3 was a generous gift from

Chemetall. This base was stored under nitrogen in a Vacuum Atmospheres glovebox. (The base is hygroscopic and excessive amounts of water lead to the formation of phenol and diaryl ether byproducts.) Small portions of the base (~5 g) were removed from the glovebox in glass vials, stored in the air in a desiccator filled with anhydrous calcium sulfate, and weighed in the air. Alcohols were purchased from commercial sources and used without further purification. Aryl halides were purchased from commercial sources and, when necessary, filtered through neutral alumina or distilled. Anhydrous toluene was purchased from J. T. Baker in CYCLE-TRAINER® solvent delivery kegs and vigorously purged with argon for 2 h. The solvent was further purified by passing it through two packed columns of neutral alumina under argon. The solvents were transferred by syringe from the solvent purification system to the reaction flask. Flash column chromatography was performed using a Biotage SP4 Flash Purification System using KP-Sil silica cartridges. In all cases, dichloromethane was used to transfer the crude reaction material onto the silica gel samplet. The samplet was dried in an oven before usage. A gradient elution using hexane and ethyl acetate was performed, based on the recommendation from the Biotage TLC Wizard.

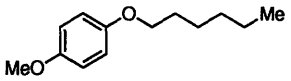
Unless specified, yields reported in the publication are of the isolated material and represent an average of at least two independent runs. Yields reported in the supporting information refer to a single experiment. Compounds described in the literature were characterized by comparing their ^{1}H NMR and ^{13}C NMR spectra, and melting points (m.p.) to the previously reported data; their purity was confirmed by gas chromatography (GC) or elemental analysis. GC analyses were performed on a Hewlett Packard 6890 instrument with an FID detector and a Hewlett Packard 10 m x 0.2 mm i.d. HP-1 capillary column using dodecane as an internal standard. Elemental analyses were performed by Atlantic Microlabs, Inc., Norcross, GA.

Previously unknown compounds were synthesized, purified and analyzed from a single run and were then repeated to determine an average yield. They were characterized by ^{1}H NMR, ^{13}C NMR, m.p., IR and elemental analysis. For those compounds that did not give a satisfactory elemental analysis, a copy of their ^{1}H NMR spectra is included. ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian 500 MHz instruments with chemical shifts reported relative to the deuterated solvent or TMS. IR spectra were recorded on a Perkin-Elmer System 2000 FT-IR instrument for all previously unknown compounds (KBr disc). Melting points (uncorrected) were obtained on a Mel-Temp II capillary melting point apparatus.

General procedure for the Cu-catalyzed cross-coupling of alcohols with aryl halides

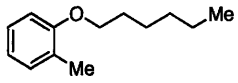
An oven-dried screw-cap test tube was charged with CuI (9.5 mg, 0.050 mmol), Me_4-Phen (24 mg, 0.10 mmol), aryl halide (1.0 mmol, if solid), Cs_2CO_3 (490 mg, 1.5 mmol), and a magnetic stir bar. The reaction vessel was fitted with a rubber septum. The test tube was evacuated and back-filled with dry argon. Aryl halide (1. 0 mmol, if liquid), and toluene (0.50 mL) were then added by syringe. The rubber septum was removed and the reaction tube was quickly sealed with a Teflon-lined septum. The vessel was immersed in a pre-heated oil bath and stirred vigorously until TLC and/or GC analysis of the crude reaction mixture indicated that the aryl halide had been completely consumed. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (15 mL), and filtered through a plug of silica, eluting with additional ethyl acetate (30 mL). The filtrate was concentrated and the resulting residue was purified by flash chromatography (hexane/ethyl acetate) to provide the desired product.

Experimental procedures for compounds in Table 2



4-(hexyloxy)-anisole (Entries 1-3)

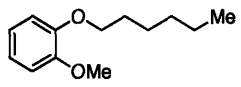
The general procedure was followed using CuI (9.5 mg, 0.050 mmol), Me_4-Phen (24 mg, 0.10 mmol), Cs_2CO_3 (391 mg, 1.2 mmol), 4-iodoanisole (234 mg, 1.00 mmol), and *n*-hexanol (186 μL, 1.50 mmol) with toluene (0.50 mL) as solvent for 15 h at 80 °C. After cooling to room temperature, dodecane (225 mL, 1.0 mmol) and ethyl acetate (20 mL) were stirred into the reaction mixture. The mixture was filtered through a small plug of silica gel, and sampled for GC analysis. In order to standardize this compound for GC analysis, the product was purified by flash chromatography (hexane / ethyl acetate 1:0 → 9:1) to afford the title compound as a colorless oil (162 mg, 78%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.85 (4H, s), 3.94-3.89 (3H, t, J = 6.6 Hz), 3.78 (3H, s), 1.79-1.72 (2H, m), 1.49-1.37 (2H, m), 1.36-1.32 (4H, m), 0.94-0.90 (3H, t, J = 7.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.9, 153.5, 115.6, 115.0, 68.9, 56.0, 31.9, 29.6, 26.0, 22.9, 14.3. IR (KBr disc, cm^{-1}) 2937, 1510, 1466, 1290, 1235, 1113, 1036, 827, 726, 532. Anal. Calc. for $C_{13}H_{20}O_2$: C 74.96, H 9.68. Found: C 74.78, H 9.74.



2-(hexyloxy)-toluene (entry 4)[1]

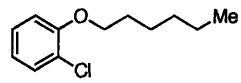
The general procedure was followed using CuI (9.5 mg, 0.050 mmol), Me_4-Phen (24 mg, 0.10 mmol), Cs_2CO_3 (490 mg, 1.5 mmol), 2-iodotoluene (127 μL, 1.00 mmol), and *n*-hexanol (187 μL, 1.50 mol) with toluene (0.50 mL) as solvent for 24 h at 110 °C. Chromatographic purification (hexane / ethyl acetate 1:0 → 9:1) afforded the title compound as a clear oil (159 mg, 83%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16-7.12 (2H, m), 6.85-6.80 (2H, m), 3.96 (2H, t, J =

6.4 Hz), 2.23 (3H, s), 1.85-1.76 (2H, m), 1.56-1.32 (6H, m), 0.94-0.88 (3H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.6, 130.9, 127.1, 127.0, 120.3, 111.1, 68.1, 32.0, 29.7, 26.2, 23.0, 16.6, 14.4. IR (KBr disc, cm^{-1}) 2955, 2931, 2860, 1603, 1496, 1463, 1379, 1245, 119, 1122, 1050, 749, 713. Anal. Calc. for $C_{13}H_{20}O$: C 81.20, H 10.48. Found: C 81.41, H 10.33.



2-(hexyloxy)-anisole (entry 5)[15]

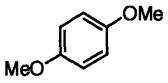
The general procedure was followed using CuI (9.5 mg, 0.050 mmol), Me_4-Phen (24 mg, 0.10 mmol), Cs_2CO_3 (490 mg, 1.5 mmol), 2-iodoanisole (130 μL, 1.00 mmol), and *n*-hexanol (187 μL, 1.50 mol) with toluene (0.50 mL) as solvent for 30 h at 110 °C. Chromatographic purification (hexane / ethyl acetate 1:0 → 9:1) afforded the title compound as a clear oil (195 mg, 94%). ^1H NMR (500 MHz, $CDCl_3$) δ 6.92-6.90 (4H, m), 4.03 (2H, t, J = 7.0 Hz), 3.88 (3H, s), 1.86 (2H, m), 7.49-1.34 (8H, m), 0.93-0.90 (3H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.6, 148.8, 121.0, 121.0, 113.2, 112.0, 69.2, 56.2, 31.9, 29.4, 25.9, 22.8, 14.3. IR (KBr disc, cm^{-1}) 2932, 2860, 1593, 1507, 1456, 1253, 1228, 1180, 1125, 1030, 740. Anal. Calc. for $C_{13}H_{20}O_2$: C 74.96, H 9.68. Found: C 74.69, H 9.68.



1-chloro-2-(hexyloxy)benzene (entry 6)[16]

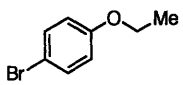
The general procedure was followed using CuI (9.5 mg, 0.050 mmol), Me_4-Phen (24 mg, 0.10 mmol), Cs_2CO_3 (490 mg, 1.5 mmol), 1-chloro-2-iodobenzene (122 μL, 1.00 mmol), and *n*-hexanol (187 μL, 1.50 mol) with toluene (0.50 mL) as solvent for 24 h at 110 °C. Chromatographic purification (hexane / ethyl acetate 1:0 → 1:3) afforded the title compound as a clear oil (185 mg, 87%). ^1H NMR (500 MHz, $CDCl_3$) d 7.36 (1H, dd, J = 1.7, 7.9 Hz), 7.20

(1H, m), 6.94-6.85 (2H, m), 4.03 (2H, t, J = 6.5 Hz), 1.85 (2H, m), 1.54-1.31 (m, 6H), 0.94-0.89 (m, 3H).



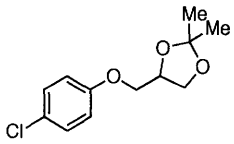
1,4-dimethoxybenzene (entry 7)[17]

The general procedure was followed using CuI (9.5 mg, 0.050 mmol), Me_4-Phen (24 mg, 0.10 mmol), Cs_2CO_3 (391 mg, 1.2 mmol), 4-iodoanisole (234 mg, 1.00 mmol), and methanol (81 μL, 2.00 mmol) with toluene (0.50 mL) as solvent for 15 h at 80 °C. Chromatographic purification (hexane / ethyl acetate 1:0 → 9:1) afforded the title compound as a colorless oil (108 mg, 78%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.84 (4H, s), 3.77 (6H, s). IR (KBr disc, cm^{-1}) 2933, 2860, 1509, 1467, 1233, 1181, 1107, 1042, 824, 742, 724, 523.



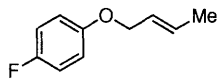
1-bromo-4-ethoxybenzene (entry 8)[18]

The general procedure was followed using CuI (9.5 mg, 0.050 mmol), Me_4-Phen (24 mg, 0.10 mmol), Cs_2CO_3 (490 mg, 1.5 mmol), 1,bromo-4-iodobenzene (283 mg, 1.00 mmol), and ethanol (116 μL, 2.0 mol) with toluene (0.50 mL) as solvent for 24 h at 80 °C. Chromatographic purification (hexane / ethyl acetate 1:0 → 9:1) afforded the title compound as a clear oil (130 mg, 65%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39-7.36 (2H, m), 6.80-6.77 (2H, m), 4.00 (2H, q, J = 7.0 Hz), 1.42 (t, 3H, J = 7.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.2, 132.4, 116.4, 112.8, 63.9, 14.9. IR (KBr disc, cm^{-1}) 2981, 2927, 1592, 1579, 1489, 1475, 1393, 1286, 1245, 1172, 1115, 1072, 1048, 1002, 923, 820, 639, 507. Anal. Calc. for C_8H_9BrO: C 47.79, H 4.51. Found: C 47.62, H 4.55.



4-((4-chlorophenoxy)methyl)-2,2-dimethyl-1,3-dioxolane (entry 9)

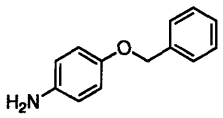
The general procedure was followed using CuI (9.5 mg, 0.050 mmol), Me_4-Phen (24 mg, 0.10 mmol), Cs_2CO_3 (650 mg, 2.0 mmol), 4-chloro-1-iodobenzene (238 mg, 1.00 mmol), and solketal (249 μL, 2.00 mmol) with toluene (0.50 mL) as solvent for 15 h at 80 °C. Chromatographic purification (hexane / ethyl acetate 1:0 → 9:1) afforded the title compound as a colorless oil (202 mg, 83%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.268-7.209 (2H, m), 6.872-6.819 (2H, m), 4.512-4.434 (1H, m), 4.192-4.143 (1H, dd, J = 6.4, 8.5 Hz), 4.046-3.996 (1H, dd, J = 5.5, 9.5 Hz), 3.938-3.868 (2H, m), 1.465 (3H, s), 1.407 (3H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.3, 129.5, 126.2, 116.0, 110.0, 74.1, 69.2, 66.9, 27.0, 25.5. IR (KBr disc, cm^{-1}) 2980, 2932, 1489, 1451, 1371, 1240, 1203, 1169, 1152, 1075, 1051, 1000, 973, 893, 831, 658. Anal. Calc. for $C_{12}H_{15}ClO_3$: C 59.39, H 6.23. Found: C 59.57, H 6.30.



(*E*)-1-(but-2-enyloxy)-4-fluorobenzene (entry 10)[19]

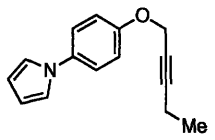
The general procedure was followed using CuI (9.5 mg, 0.050 mmol), Me_4-Phen (24 mg, 0.10 mmol), Cs_2CO_3 (490 mg, 1.5 mmol), 1-fluoro-4-iodobenzene (115 μL, 1.00 mmol), and (E)-crotyl alcohol (127 μL, 1.50 mol) with toluene (0.50 mL) as solvent for 24 h at 80 °C. Chromatographic purification (hexane / ethyl acetate 1:0 → 9:1) afforded the title compound as a clear oil (117 mg, 70%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.00-6.95 (2H, m), 6.89-6.83 (2H, m), 5.90-5.83 (1H, m), 5.75-5.70 (1H, m), 4343 (2H, dd, J = 0.9, 6.2 Hz), 1.77 (3H, d, J = 6.4 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.4, 155.0, 130.9, 126.1, 116.0, 115.8, 69.5, 18.1. IR (KBr

disc, cm^{-1}) 3025, 2941, 2919, 2859, 1506, 1463, 1379, 1293, 1246, 1208, 1097, 1009, 967, 828, 780, 741, 514. Anal. Calc. for $C_{10}H_{11}FO$: C 72.27, H 6.67. Found: C 72.00, H 6.81.



4-(benzyloxy)aniline (entry 11)[20]

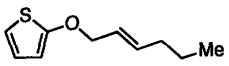
The general procedure was followed using CuI (9.5 mg, 0.050 mmol), Me_4-Phen (24 mg, 0.10 mmol), Cs_2CO_3 (391 mg, 1.2 mmol), 4-iodoaniline (219 mg, 1.00 mmol), and benzyl alcohol (210 μL, 2.00 mmol) with toluene (0.50 mL) as solvent for 15 h at 80°C. Chromatographic purification (hexane / ethyl acetate 1:0 → 9:1) afforded the title compound as a red solid (158 mg, 79%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45-7.32 (5H, m), 6.86-6.80 (2H, m), 6.68-6.63 (2H,m), 3.428 (2H, b s). ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.1, 140.4, 137.7, 128.7, 128.0, 127.7, 116.5, 116.2, 70.9. IR (KBr disc, cm^{-1}) 2932, 2960, 1585, 1568, 1462, 1382, 1274, 1228, 1127, 1109, 1014, 829, 727, 673, 627, 423. m.p. 45-46.5 °C.



1-(4-(pent-2-ynyloxy)phenyl)-1*H*-pyrrole (entry 12)

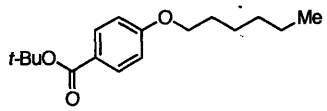
The general procedure was followed using CuI (9.5 mg, 0.050 mmol), Me_4-Phen (24 mg, 0.10 mmol), Cs_2CO_3 (391 mg, 1.2 mmol), 1-(4-iodophenyl)pyrrole (269 mg, 1.00 mmol), and 2-pentyn-1-ol (139 μL, 1.50 mmol) with toluene (0.50 mL) as solvent for 24 h at 80 °C. Chromatographic purification (hexane / ethyl acetate 1:0 → 9:1) afforded the title compound as a white solid (209 mg, 92%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.30 (2H, m), 7.06-7.01 (4H, m), 6.34-6.33 (2H, t, J = 2.2 Hz), 4.71-4.70 (2H, , J = 2.2 Hz), 2.31-2.22 (2H, m), 1.19-1.14 (3H, t, J = 7.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.0, 122.2, 119.9, 115.9, 110.1, 90.0, 74.1, 57.0,

44.8, 13.8, 12.7. IR (KBr disc, cm^{-1}) 3132, 2977, 1522, 1325, 1258, 1243, 1190, 1070, 1018, 1006, 920, 824, 734. m.p. 57.5-59.0 °C.



(*E*)-2-(hex-2-enyloxy)thiophene (entry 13)

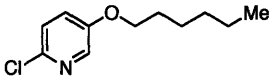
The general procedure was followed using CuI (9.5 mg, 0.050 mmol), Me_4-Phen (24 mg, 0.10 mmol), Cs_2CO_3 (650 mg, 2.0 mmol), 3-iodothiophene (102 μL, 1.00 mmol), and (*E*)-hex-2-en-1-ol (236 μL, 2.00 mmol) with toluene (0.50 mL) as solvent for 15 h at 80 °C. Chromatographic purification (hexane / ethyl acetate 1:0 → 12.5:1) afforded the title compound as a yellow oil (125 mg, 69%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.191-7.163 (1H, dd, J = 3.1, 5.3 Hz), 6.789-6.767 (1H, dd, J = 1.6, 5.3 Hz), 6.274-6.258 (1H, q, J = 1.6 Hz), 5.906-5.811 (1H, m), 5.765-5.666 (1H, m), 4.461-4.438 (2H, dd, J = 1.0, 6.0 Hz), 2.119-2.045 (2H, m), 1.507-1.384 (2H, m), 0.951-0.902 (3H, t, J = 7.3 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.7, 136.1, 124.9, 124.7, 119.8, 97.6, 71.1, 34.6, 22.3, 13.9. IR (KBr disc, cm^{-1}) 3118, 2959, 2929, 2871, 1544, 1421, 1366, 1234, 1177, 1010, 970, 873, 831, 752, 627. Anal. Calc. for $C_{10}H_{14}OS$: C 65.89, H 7.74. Found: C 66.05, H 7.92.



tert-butyl 4-(hexyloxy)benzoate (entry 14)

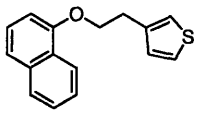
The general procedure was followed using CuI (9.5 mg, 0.050 mmol), Me_4-Phen (24 mg, 0.10 mmol), Cs_2CO_3 (490 mg, 1.5 mmol), *tert*-butyl-4-iodo benzoate[21] (304 mg, 1.00 mmol), and *n*-hexanol (187 μL, 1.50 mol) with toluene (0.50 mL) as solvent for 24 h at 80 °C. Chromatographic purification (hexane / ethyl acetate 1:0 → 19:1) afforded a mixture of the title compound and *n*-hexyl 4-(hexyloxy)benzoate (7:1 by ^{1}H NMR and GC) as a clear oil (264 mg,

95%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98-7.92 (2H, m), 6.92-6.87 (2H, m), 4.00 (2H, t, *J* = 6.6 Hz), 1.83-1.76 (2H, m), 1.49-1.44 (2H, m), 1.35-1.30 (2H, m), 0.92 (3H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.9 ,162.8, 131.5, 124.4, 114.0, 80.6, 68.3, 31.8, 29.3, 28.5, 25.9, 22.8, 14.2. IR (KBr disc, cm^{-1}) 2933, 2872, 1710, 1607, 1510, 1368, 1293, 1253, 1160, 1116, 1010, 848, 771, 696.



2-chloro-5-(hexyloxy)pyridine (entry 15)

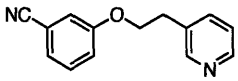
The general procedure was followed using CuI (9.5 mg, 0.050 mmol), Me_4-Phen (24 mg, 0.10 mmol), Cs_2CO_3 (391 mg, 1.2 mmol), 2-chloro-5-iodopyridine (239 mg, 1.00 mmol), and *n*-hexanol (249 μL, 2.00 mol) with toluene (0.50 mL) as solvent for 15 h at 80 °C. Chromatographic purification (hexane / ethyl acetate 1:0 → 9:1) afforded the title compound as a colorless oil (179 mg, 84%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03-8.02 (1H, dd, *J* = 0.8, 2.9 Hz), 7.22-7.19 (1H, dd, *J* = 0.8, 8.7 Hz), 7.17-7.14 (1H, dd, *J* = 2.9, 8.7 Hz), 3.99-3.94 (2H, t, *J* = 6.4), 1.80-1.73 (2H, m), 1.47-1.30 (6H, m), 0.92-0.87 (3H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.9, 142.6, 137.0, 125.2, 124.7, 69.3, 31.9, 29.4, 26.0, 23.0, 14.4. IR (KBr disc, cm^{-1}) 2902, 2863, 1516, 1454, 1245, 1016, 917, 814, 736, 697, 517. Anal. Calc. for $C_{11}H_{16}ClNO$: C 61.82, H 7.55. Found: C 62.02, H 7.65.



3-(2-(naphthalen-1-yloxy)ethyl)thiophene (entry 16)

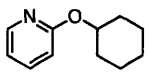
The general procedure was followed using CuI (9.5 mg, 0.050 mmol), Me_4-Phen (24 mg, 0.10 mmol), Cs_2CO_3 (490 mg, 1.5 mmol), 1-iodonaphthalene (175 μL, 1.00 mmol), and 2-(3-thieno)-ethanol (168 μL, 1.50 mol) with toluene (0.50 mL) as solvent for 24 h at 110 °C.

Chromatographic purification (hexane / ethyl acetate 1:0 → 9:1) afforded the title compound as a tan oil (252 mg, 99%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31-8.29 (1H, m), 7.82 (1H, dd, *J* = 2.1, 6.4 Hz), 7.53-7.48 (1H, m), 7.45 (1H, d, *J* = 8.2 Hz), 7.39 (1H, d, *J* = 8.0 Hz), 7.31 (1H, dd, *J* = 2.9, 4.9 Hz), 7.19-7.18 (1H, m), 7.14 (1H, dd, *J* = 1.2, 4.9 Hz), 6.83 (1H, d, *J* = 7.5 Hz), 4.38 (2H, d, *J* = 6.7 Hz), 3.31 (2H, d, *J* = 6.4 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.7. 138.9. 134.7. 128.7. 127.7. 126.6. 126.0. 125.9. 125.7. 125.4. 122.2. 121.8. 120.5. 104.8. 68.4. 30.5. IR (KBr disc, cm^{-1}) 3052, 2928, 2873, 1594, 1580, 1508, 1460, 1405, 1269, 1240, 1100, 1071, 1020, 790. Anal. for $C_{16}H_{14}OS$: C 75.55, H 5.55. Found: C 75.28, H 5.50.



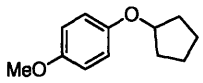
3-(2-(pyridin-3-yl)ethoxy)benzonitrile (entry 17)

The general procedure was followed using CuI (9.5 mg, 0.050 mmol), Me_4-Phen (24 mg, 0.10 mmol), Cs_2CO_3 (490 mg, 1.5 mmol), 3-iodobenzonitrile (229 mg, 1.00 mmol), and 2-(3-pyridyl)ethanol (172 μL, 1.50 mol) with toluene (0.50 mL) as solvent for 24 h at 80 °C. Chromatographic purification (hexane / ethyl acetate 1:0 → 3:1) afforded the title compound as a clear oil (174 mg, 78%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.56 (1H, d, *J* = 2.2 Hz), 8.22 (1H, dd, *J* = 1.6, 4.7 Hz), 7.65-7.60 (1H, m), 7.40-7.33 (1H, m), 7.29-7.23 (2H, m), 7.13-7.09 (2H, m), 4.20 (2H, t, *J* = 6.5 Hz), 3.12 (2H, t, *J* = 6.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.8, 150.5, 148.5, 136.6, 133.6, 130.6, 125.0, 123.6, 119.9, 118.8, 117.6, 113.4, 68.5, 33.0. IR (KBr disc, cm^{-1}) 3033, 2934, 2878, 2230, 1597, 1578, 1480, 1431, 1328, 1292, 1148, 1033, 971, 715, 682. Anal. Calc. for $C_{14}H_{12}N_2O$: C 74.98, H 5.39.



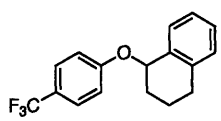
2-(cyclohexyloxy)pyridine (entry 18)

The general procedure was followed using CuI (9.5 mg, 0.050 mmol), Me_4-Phen (24 mg, 0.10 mmol), Cs_2CO_3 (490 mg, 1.5 mmol), 4 Å molecular sieves (200 mg, flame activated under vacuum) 2-iodopyridine (106 μL, 1.00 mmol), and cyclohexanol (158 μL, 1.50 mmol) with toluene (0.50 mL) as solvent for 24 h at 110 °C. Chromatographic purification (hexane / ethyl acetate 1:0 → 9:1) afforded the title compound as a clear oil (164 mg, 93%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (1H, ddd, J = 0.8, 2.1, 5.0 Hz), 7.54 (1H, ddd, J = 2.0, 7.2, 8.4 Hz), 6.81 (1H, ddd, J = 0.9, 5.0, 7.1 Hz), 6.69 (1H, dt, J = 8.4, 0.8 Hz), 5.06-5.00 (1H, m), 2.05-2.01 (2H, m), 1.82-1.76 (2H, m), 1.66-1.39 (4H, m), 1.34-1.25 (2H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.7, 147.1, 138.7, 116.4, 111.9, 73.2, 32.1, 25.9, 24.2. IR (KBr disc, cm^{-1}) 3025, 2942, 1614, 1516, 1328, 1249, 1161, 1110, 1061, 961, 837, 749. Anal. Calc. for $C_{11}H_{15}NO$: C 74.54, H 8.53. Found: C 74.50, H 8.63.



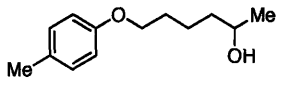
1-(cyclopentyloxy)-4-methoxybenzene (entry 19)[22]

The general procedure was followed using CuI (9.5 mg, 0.050 mmol), Me_4-Phen (24 mg, 0.10 mmol), Cs_2CO_3 (490 mg, 1.5 mmol), 4-iodoanisole (234 mg, 1.00 mmol), and cyclopentanol (136 μL, 1.50 mol) with toluene (0.50 mL) as solvent for 24 h at 110 °C. Chromatographic purification (hexane / ethyl acetate 1:0 → 9:1) afforded the title compound as a clear oil (168 mg mg, 88%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.83 (4H, s), 4.71-4.66 (1H, m), 3.78 (3H, s), 1.90-1.76 (6H, m), 1.65-1.56 (2H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.3, 116.8, 114.8, 80.0, 55.9, 33.0, 24.2. IR (KBr disc, cm^{-1}) 2960, 2872, 1833, 1507, 1465, 1441, 1231, 1173, 1106, 1040, 990, 824. Anal. Calc. for $C_{12}H_{16}O_2$: C 74.97, H 8.39. Found: C 74.56, H 8.25.



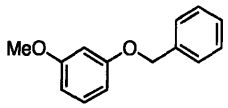
1-(4-(trifluoromethyl)phenoxy)-1,2,3,4-tetrahydronaphthalene (entry 20)

The general procedure was followed using CuI (9.5 mg, 0.050 mmol), Me_4-Phen (24 mg, 0.10 mmol), Cs_2CO_3 (490 mg, 1.5 mmol), 4-iodobenzotrifluoride (147 μL, 1.00 mmol), and (±)-1-tetralol (222 mg, 1.50 mol) with toluene (0.50 mL) as solvent for 24 h at 110 °C. Chromatographic purification (hexane / ethyl acetate 1:0 → 9:1) afforded the title compound as a clear oil (217 mg, 75%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (2H, d, J = 8.8 Hz), 7.36-7.19 (4H, m), 7.10 (d, J = 8.8 Hz), 5.47 (1H, t, J = 4.3 Hz), 2.96-2.91 (1H, m), 2.84-2.78 (1H, m), 2.21-2.15 (1H, m), 2.09-1.99 (2H, m), 1.87-1.80 (1H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.0, 135.1, 129.6, 129.4, 128.4, 127.3, 127.2, 127.1, 126.4, 116.1, 74.2, 29.2, 28.0, 18.9. IR (KBr disc, cm^{-1}) 3024, 2942, 1614, 1516, 1328, 1250, 1161, 1110, 1061, 961, 837, 749. Anal. Calc. for $C_{17}H_{15}F_3OX$: C 69.85, H 5.17. Found: C 69.74, H 5.24.



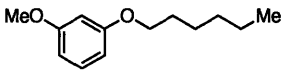
1-(*p*-tolyloxy)hexan-5-ol (entry 21)

The general procedure was followed using CuI (9.5 mg, 0.050 mmol), Me_4-Phen (24 mg, 0.10 mmol), Cs_2CO_3 (490 mg, 1.5 mmol), 4-iodotoluene (218 mg, 1.00 mmol), and 1,5-hexanediol (181 μL, 1.50 mol) with toluene (0.50 mL) as solvent for 24 h at 80 °C. Chromatographic purification (hexane / ethyl acetate 1:0 → 4:1) afforded the title compound as a clear oil (156 mg, 75%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.09-7.07 (2H, m), 6.82-6.79 (2H, m), 3.95 (2H, t, J = 6.5 Hz), 6.87-3.81 (1H, m), 2.30 (3H, t), 1.83-1.78 (2H, m), 1.61-1.47 (6H, m), 1.22 (3H, dd, J = 0.6, 6.3 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.1, 130.0, 129.9, 114.5, 68.2, 68.0, 39.2, 29.5, 23.7, 22.6, 20.7. IR (KBr disc, cm^{-1}) 3363 (br), 3031, 2940, 2867, 1614, 1584, 1512, 1474, 1376, 1291, 1244, 1176, 1111, 1037, 952, 818, 511.



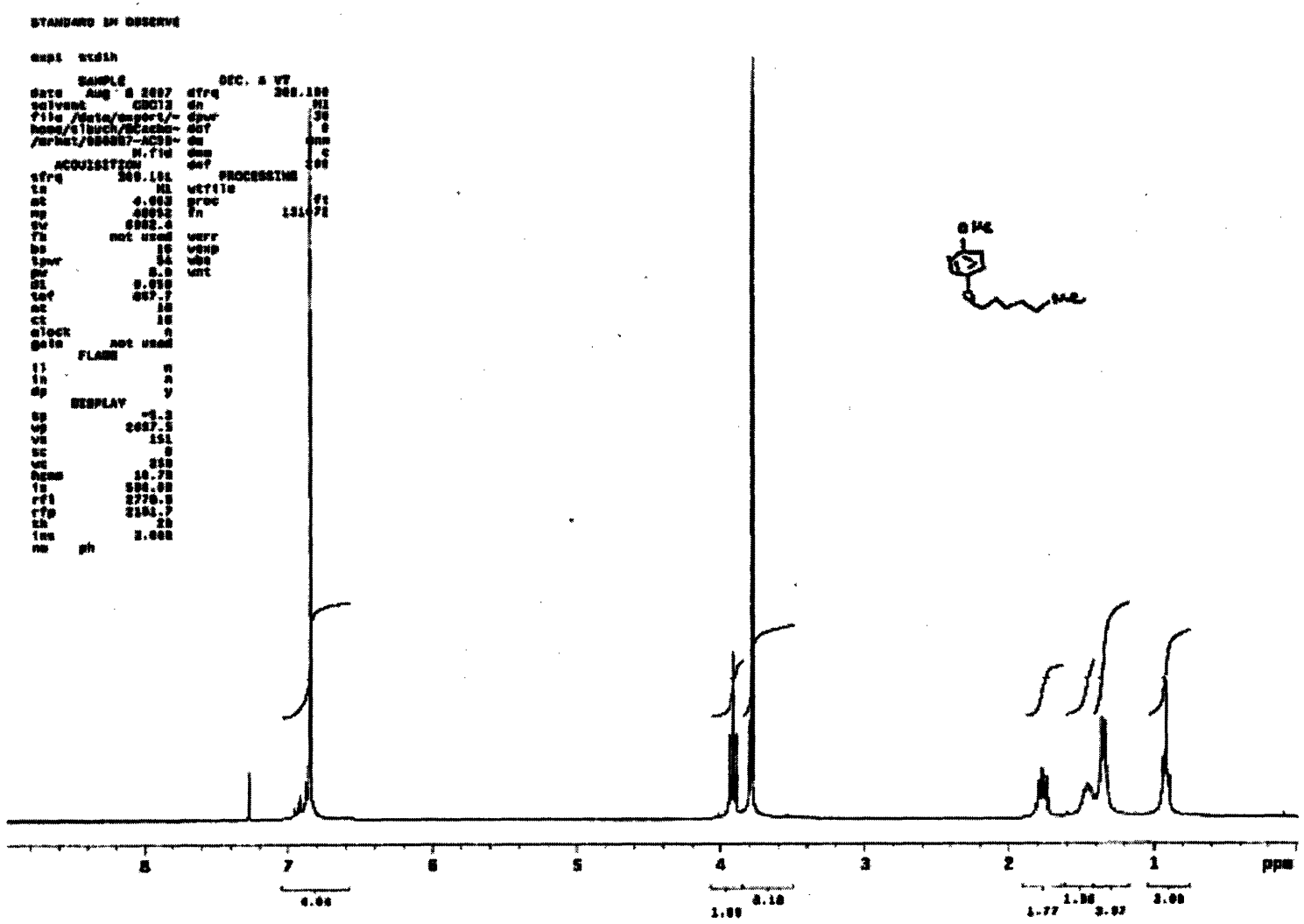
1-(benzyloxy)-3-methoxybenzene (entry 22)[23]

The general procedure was followed using CuI (19 mg, 0.050 mmol), Me_4-Phen (48 mg, 0.10 mmol), Cs_2CO_3 (490 mg, 1.5 mmol), 3-bromoanisole (127 μL, 1.00 mmol), and benzyl alcohol (155 μL, 1.50 mol) with toluene (0.50 mL) as solvent for 24 h at 110 °C. Chromatographic purification (hexane / ethyl acetate 1:0 → 9:1) afforded the title compound as a clear oil (199 mg, 93%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51-7.36 (5H, m), 7.23 (1H, m), 6.64-6.57 (3H, m), 5.08 (2H, s), 3.82 (3H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.0, 160.2, 137.1, 130.1, 128.8, 128.1, 127.7, 107.1, 106.7, 101.5, 70.2, 55.4. IR (KBr disc, cm^{-1}) 3032, 2939, 2835, 1592, 1492, 1453, 1381, 1288, 1264, 1199, 1151, 1082, 1045, 835, 761, 734, 697. Anal. Calc. for $C_{14}H_{14}O_2$: C 78.48, H 6.59. Found: C 78.39, H 6.59.



3-(hexyloxy)-anisole (entry 23)[24]

The general procedure was followed using CuI (9.5 mg, 0.050 mmol), Me_4-Phen (24 mg, 0.10 mmol), Cs_2CO_3 (490 mg, 1.5 mmol), 3-bromoanisole (127 μL, 1.00 mmol), and *n*-hexanol (0.5 μL) as solvent for 24 h at 130 °C. Chromatographic purification (hexane / ethyl acetate 1:0 → 9:1) afforded the title compound as a clear oil (160 mg, 77%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 (1H, t, J = 4.5 Hz), 6.53-6.48 (3H, m), 3.95 (2H, t, J = 6.7 Hz), 3.79 (3H, s), 1.81-1.76 (2H, m), 1.49-1.45 (2H, m), 1.38-1.33 (4H, m), 0.94-0.91 (3H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.0, 160.6, 130.0, 106.8, 106.3, 101.1, 77.0, 55.5, 31.8, 29.5, 26.0, 22.8, 14.3. IR (KBr disc, cm^{-1}) 3000, 2933, 28871, 1599, 1493, 1468, 1455, 1334, 1287, 1265, 1201, 1153, 1046, 835, 762, 687.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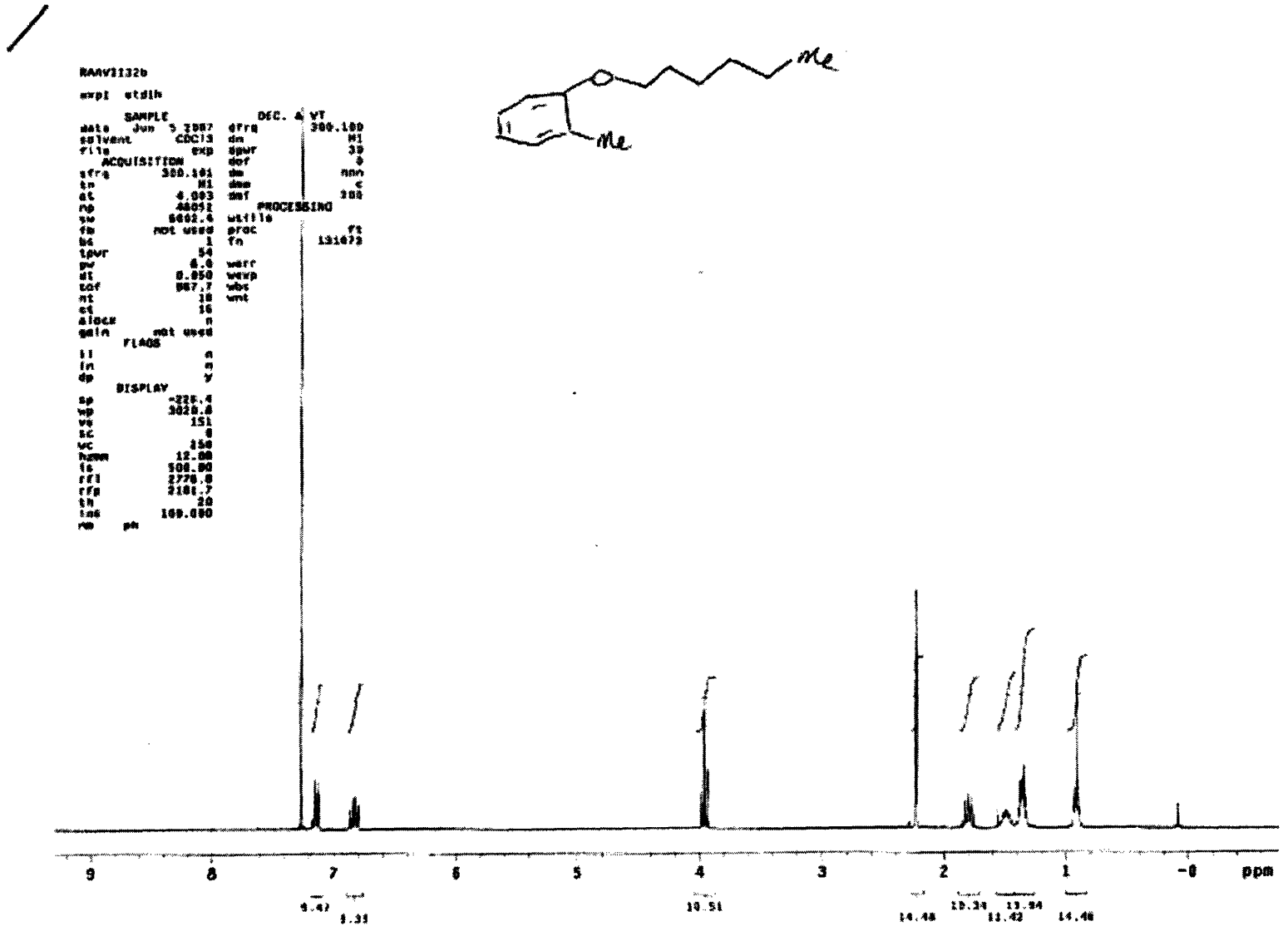
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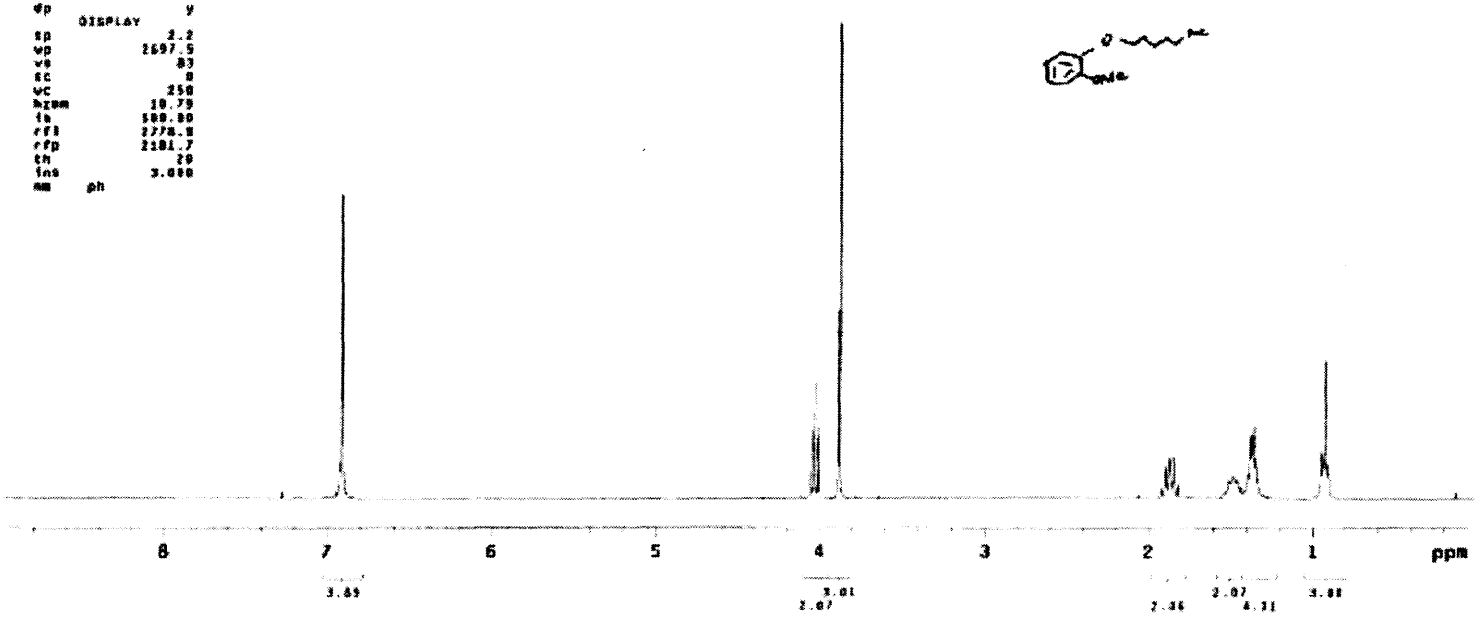

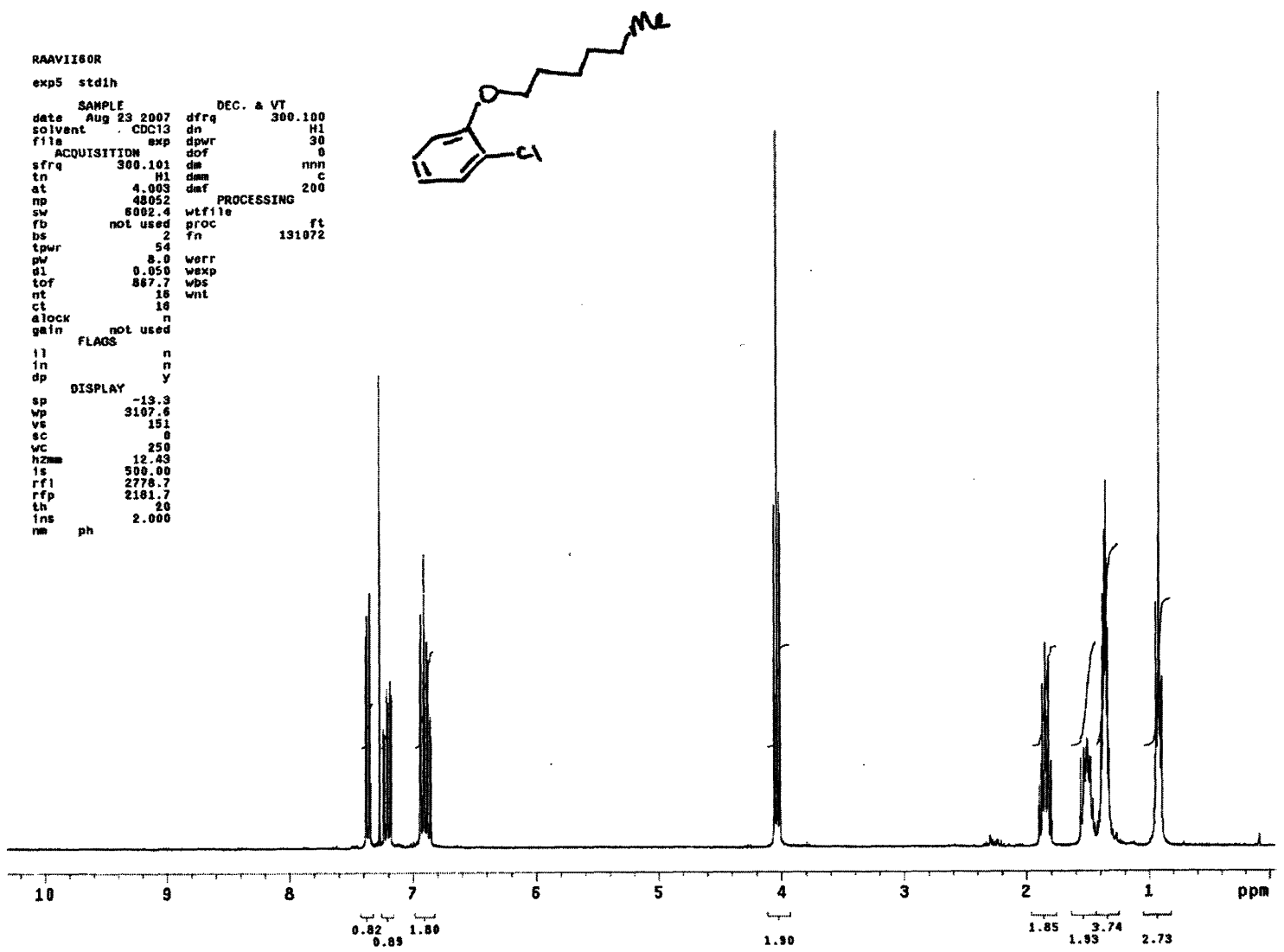
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STANDARD 1H OBSERVE

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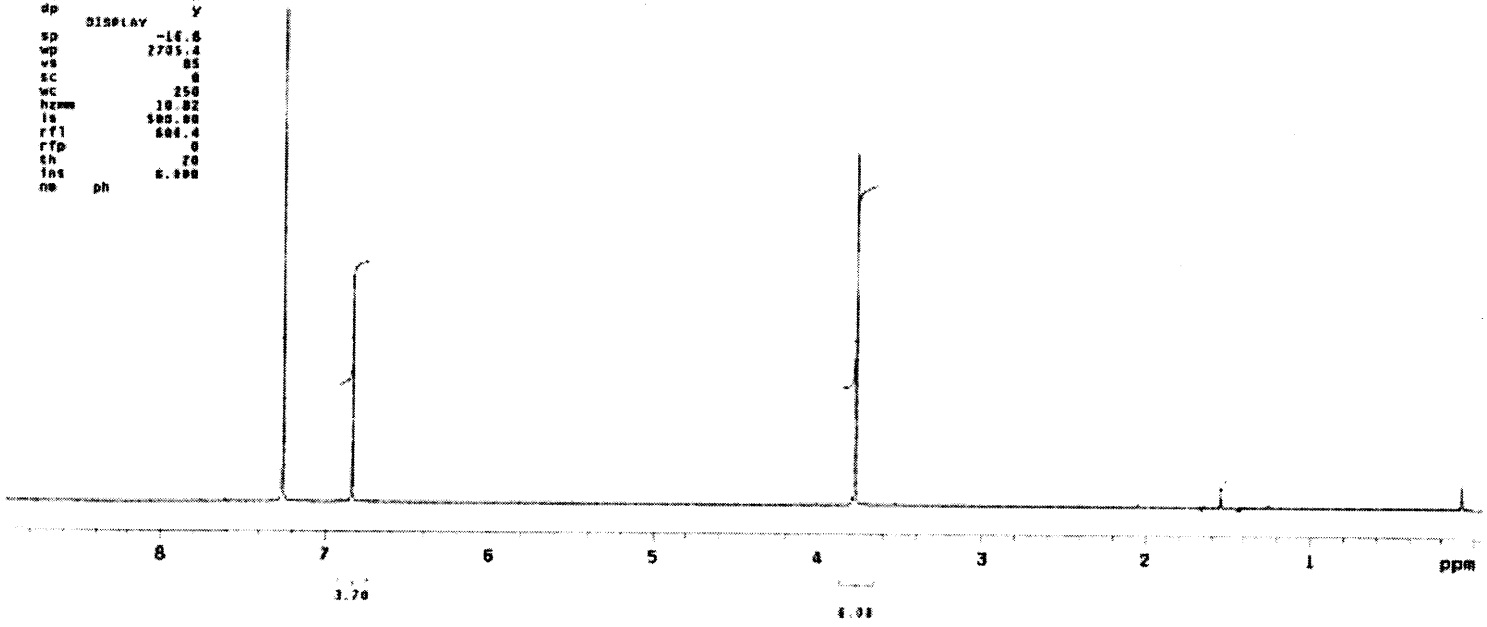

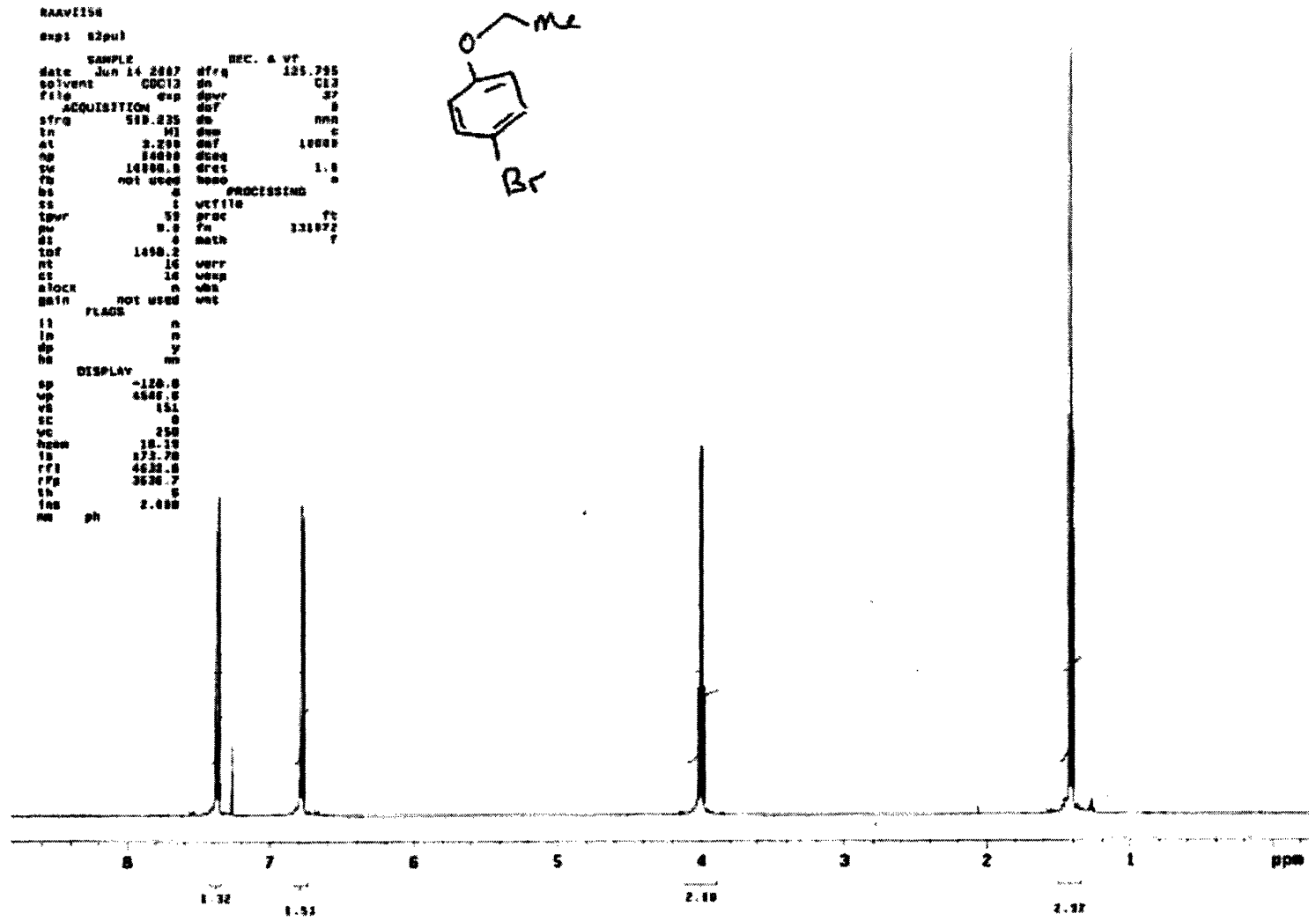
RAAVE156
expt s2pul
SAMPLE
date Jun 14 2007
solvent CDCl3
file exp
ACQUISITION
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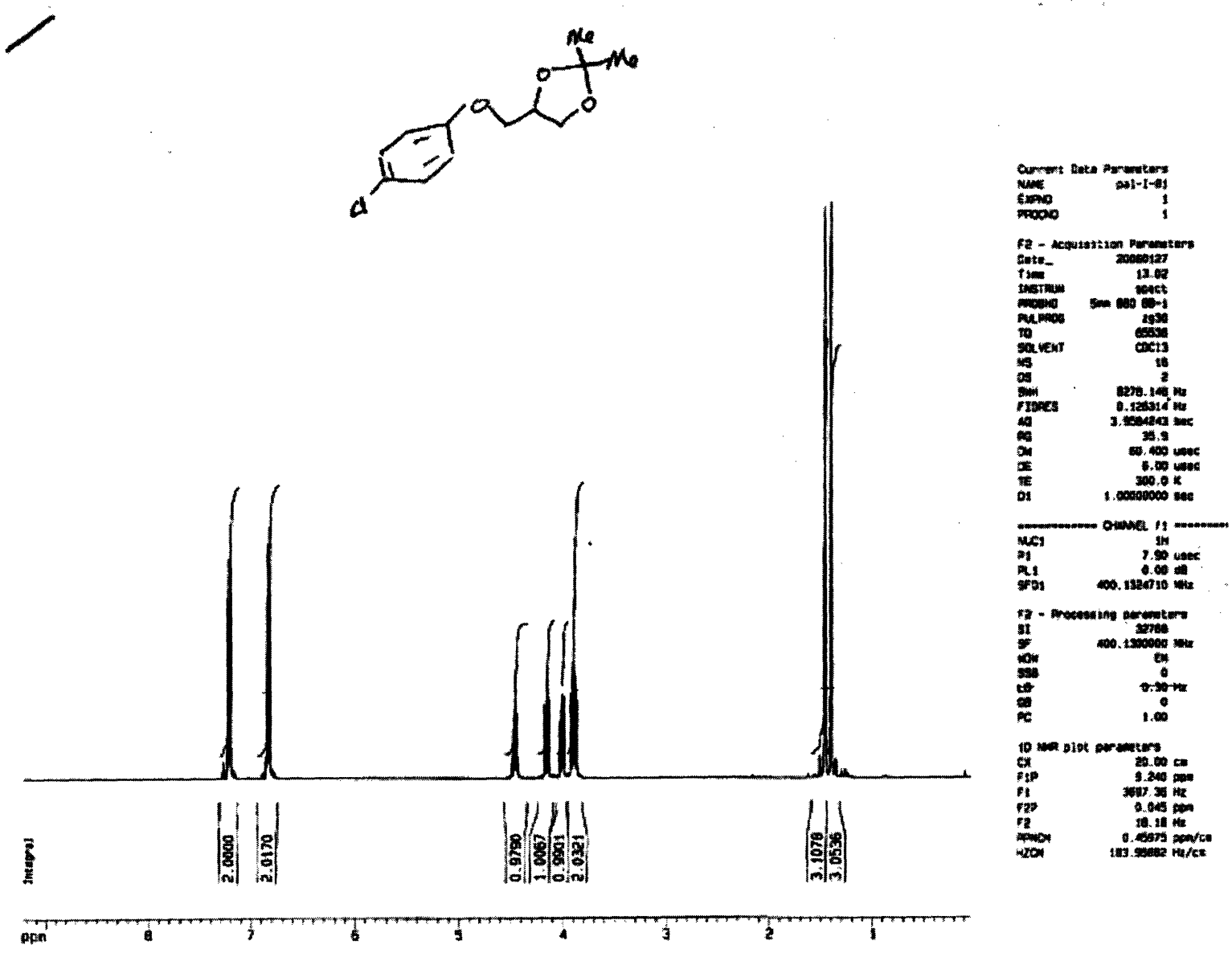
tn H1
at 3.298
np 64896
sw 14598.8
fb not used
bs 8
ss 1
tpwr 59
pw 9.8
d1 4
tof 1458.2
nt 16
ct 16
alock n
gain not used
FLAGS
il n
in n
dp y
hs nn
DISPLAY
sp -128.8
wp 4646.5
vs 151
sc 0
wc 250
hzcm 18.19
hz 173.78
rfl 4632.8
rfp 3636.7
th 5
ins 2.000
nm ph
DEC. & VT
dfrq 125.795
dn C13
dpwr 37
dof 0
dm nnn
dmm c
dmf 10000
dseq
drel 1.5
homo n
PROCESSING
wtfile
proc ft
fn 131072
math f
vserr
vsmp
vsm
vnt
Me
O
Br
8
7
6
5
4
3
2
1
ppm
1.32
1.51
2.18
2.97



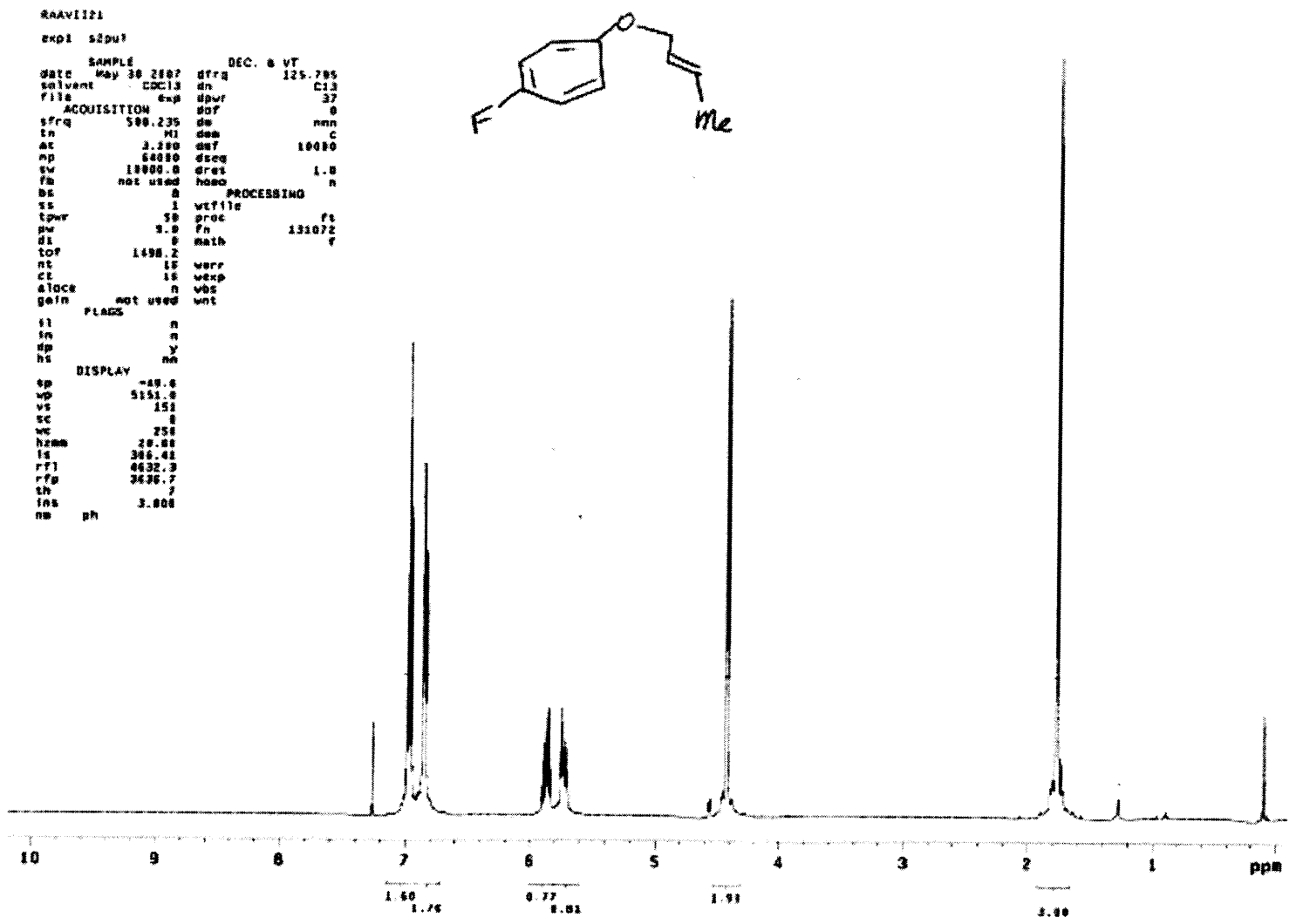
Current Data Parameters
NAME pal-I-81
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20080127
Time 13.02
INSTRUM spect
PROBHD 5mm BBO BB-1
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 35.9
DW 60.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec

======== CHANNEL f1 ========
NUC1 1H
P1 7.90 usec
PL1 0.00 dB
SFO1 400.1324710 MHz

F2 - Processing parameters
SI 32768
SF 400.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 20.00 cm
F1P 9.240 ppm
F1 3697.36 Hz
F2P 0.045 ppm
F2 18.18 Hz
PPMCM 0.45975 ppm/cm
HZCM 183.95882 Hz/cm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date May 30 2007
solvent CDCl3
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at 3.280
np 64080
sw 10000.0
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bs 8
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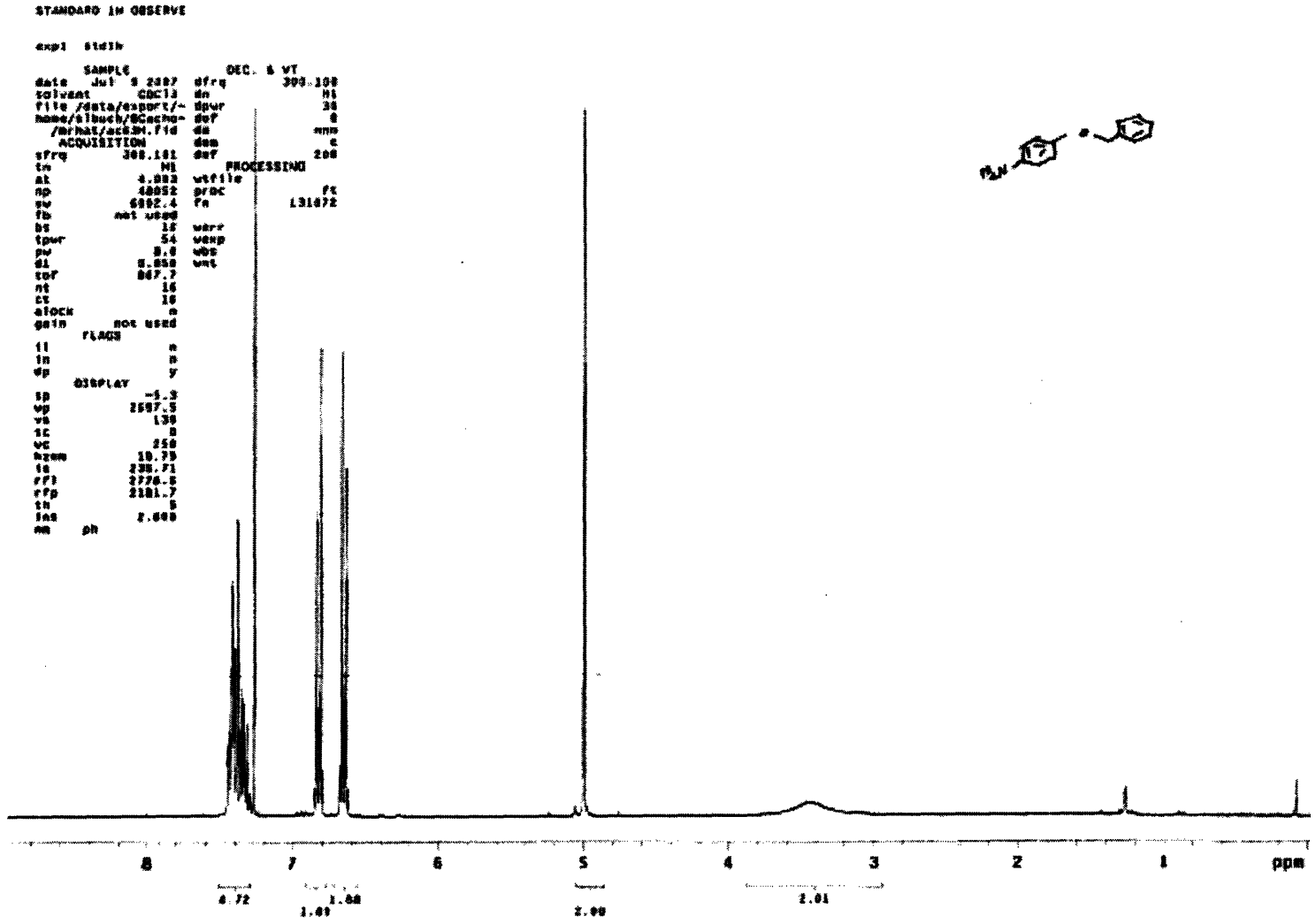
tpwr 58
pw 9.0
dl 0
tof 1498.2
nt 16
ct 16
alock n
gain not used
PLOTS
fl n
fn n
dp y
hs nn
DISPLAY
sp -49.6
wp 5151.8
vs 151
sc 8
wc 256
hzmm 20.88
is 386.41
rfl 4632.3
rfp 3636.7
th 7
ins 3.808
nm ph
DEC. & VT
dfrq 125.795
dn C13
dpwr 37
dof 0
dm nnn
dmm c
dmf 10080
dseq
dres 1.8
homo n
PROCESSING
wtfile
proc ft
fn 131072
math f
werr
wexp
wbs
wnt
F
Me
10
9
8
7
6
5
4
3
2
1
ppm
1.60
1.76
0.77
0.81
1.91
3.00


STANDARD in OBSERVE
expl stdih
SAMPLE
date Jul 8 2007
solvent CDCl3
file /data/export/~
home/slbuch/@Cache-
/mrhat/ac83M.fid
ACQUISITION
sfrq 300.181
tn H1
at 4.883
np 48052
sw 6892.4
fb not used
bs 16
tpwr 54
pw 8.0
d1 5.000
tof 867.7
nt 16
ct 16
alock n
gain not used
FLAGS
il n
in n
dp y
DISPLAY
sp -5.3
wp 2597.5
vs 138
sc 0
wc 250
hzcm 10.79
hz 230.71
rfl 2776.5
rfp 2181.7
th 5
ins 2.000
nm ph
DEC. & VT
dfrq 300.138
dn H1
dpwr 36
dof 0
da nnn
dm c
dmf 208
PROCESSING
wtfile
proc ft
fn 131072
werr
wexp
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wnt
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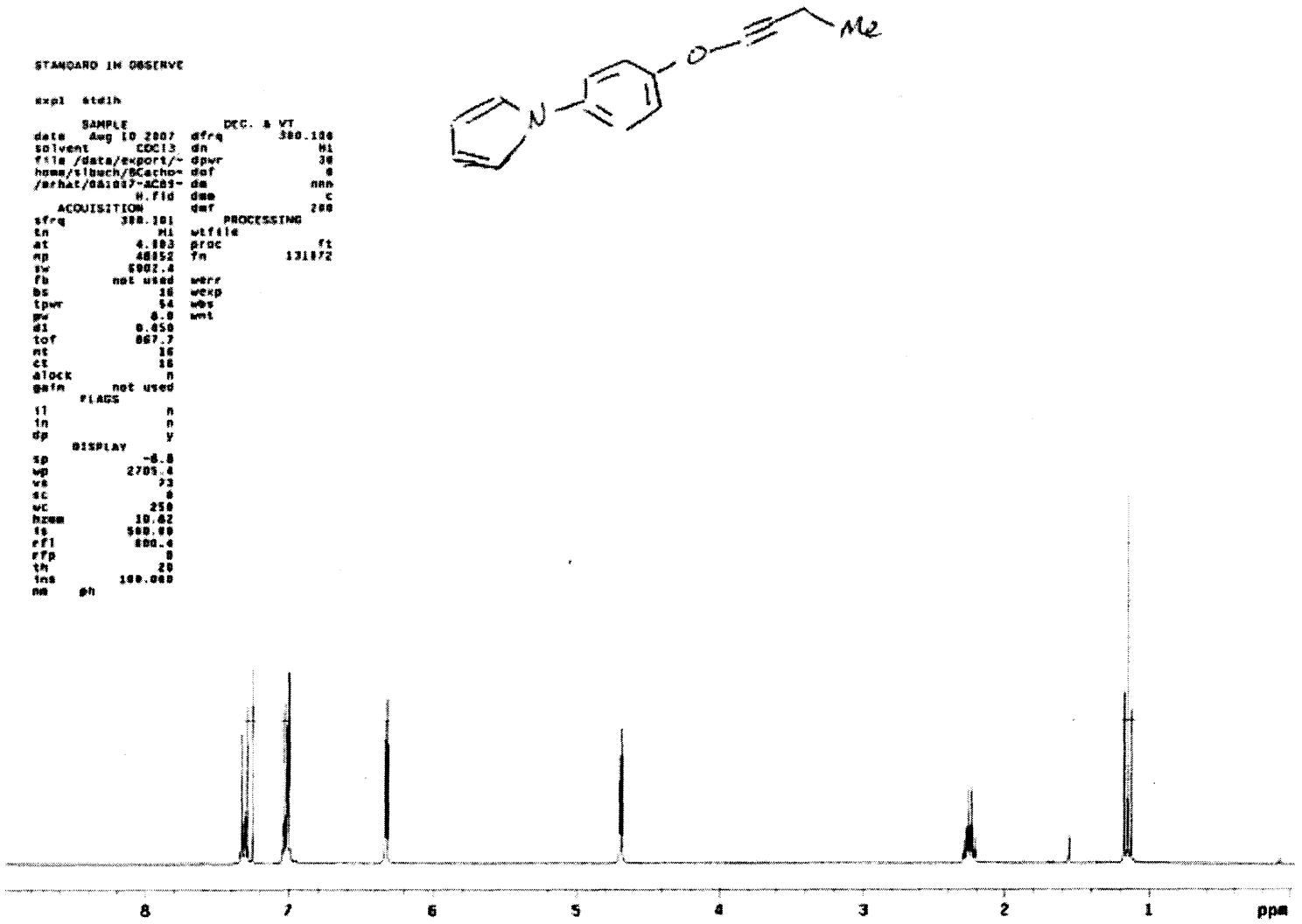
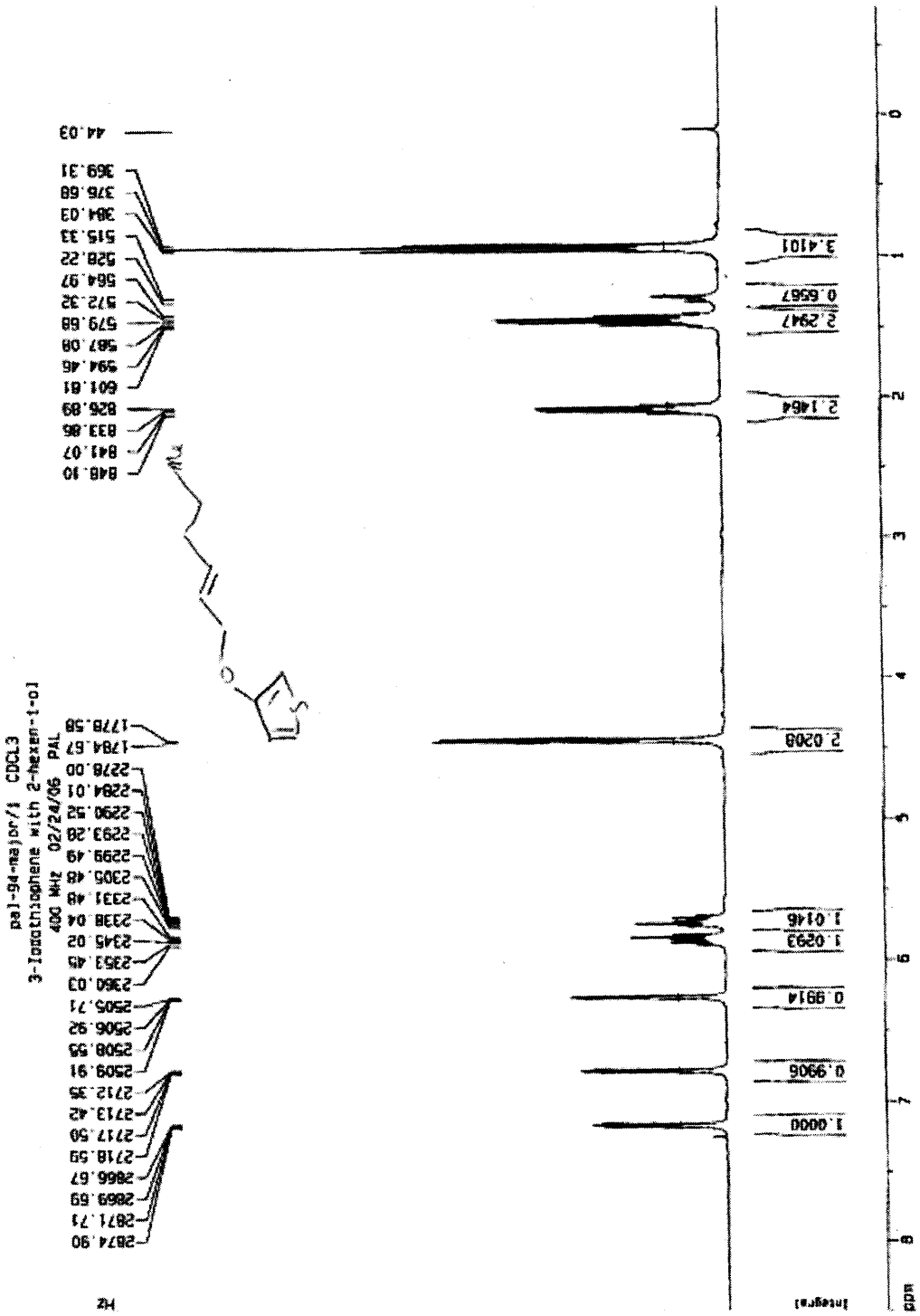
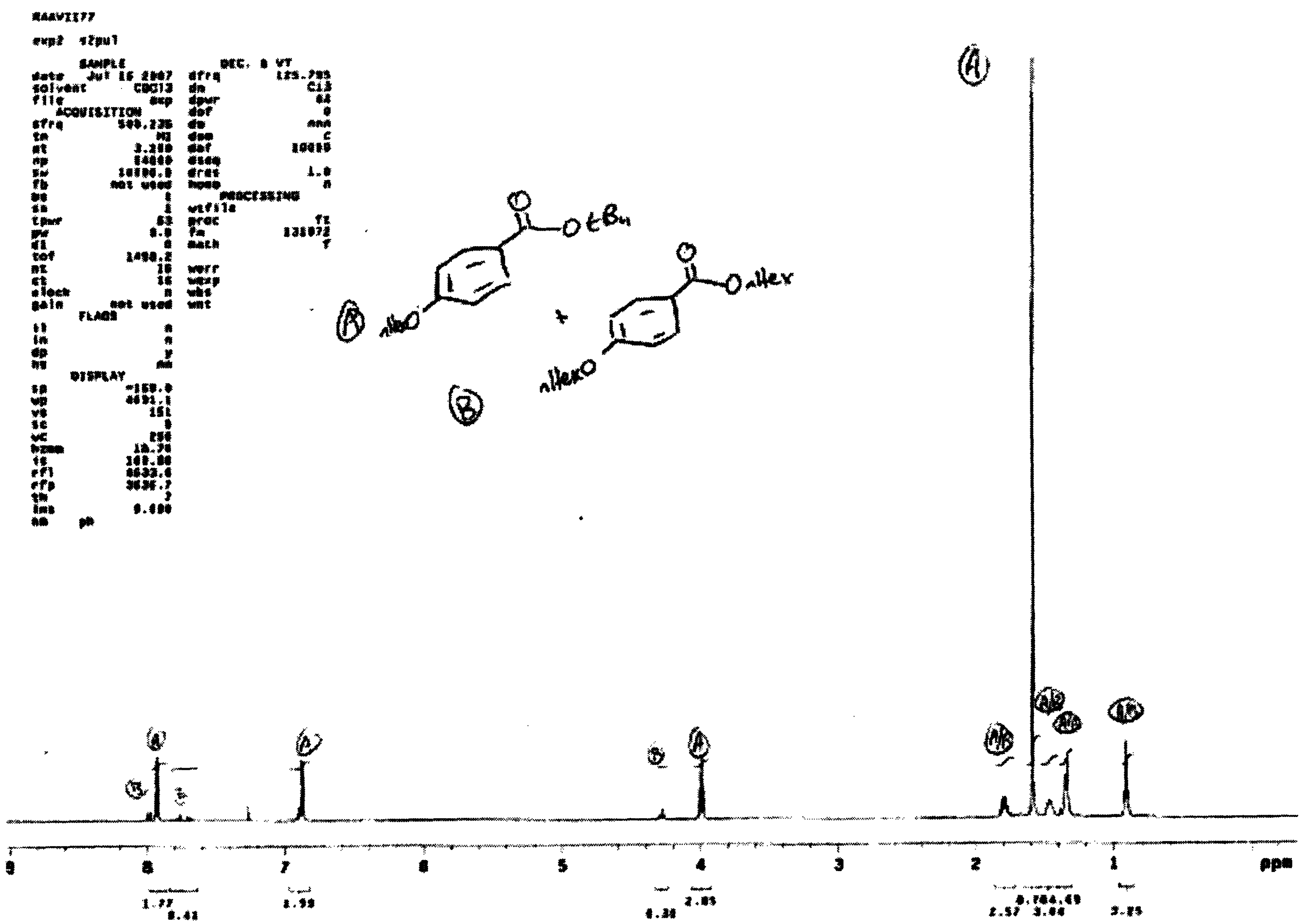
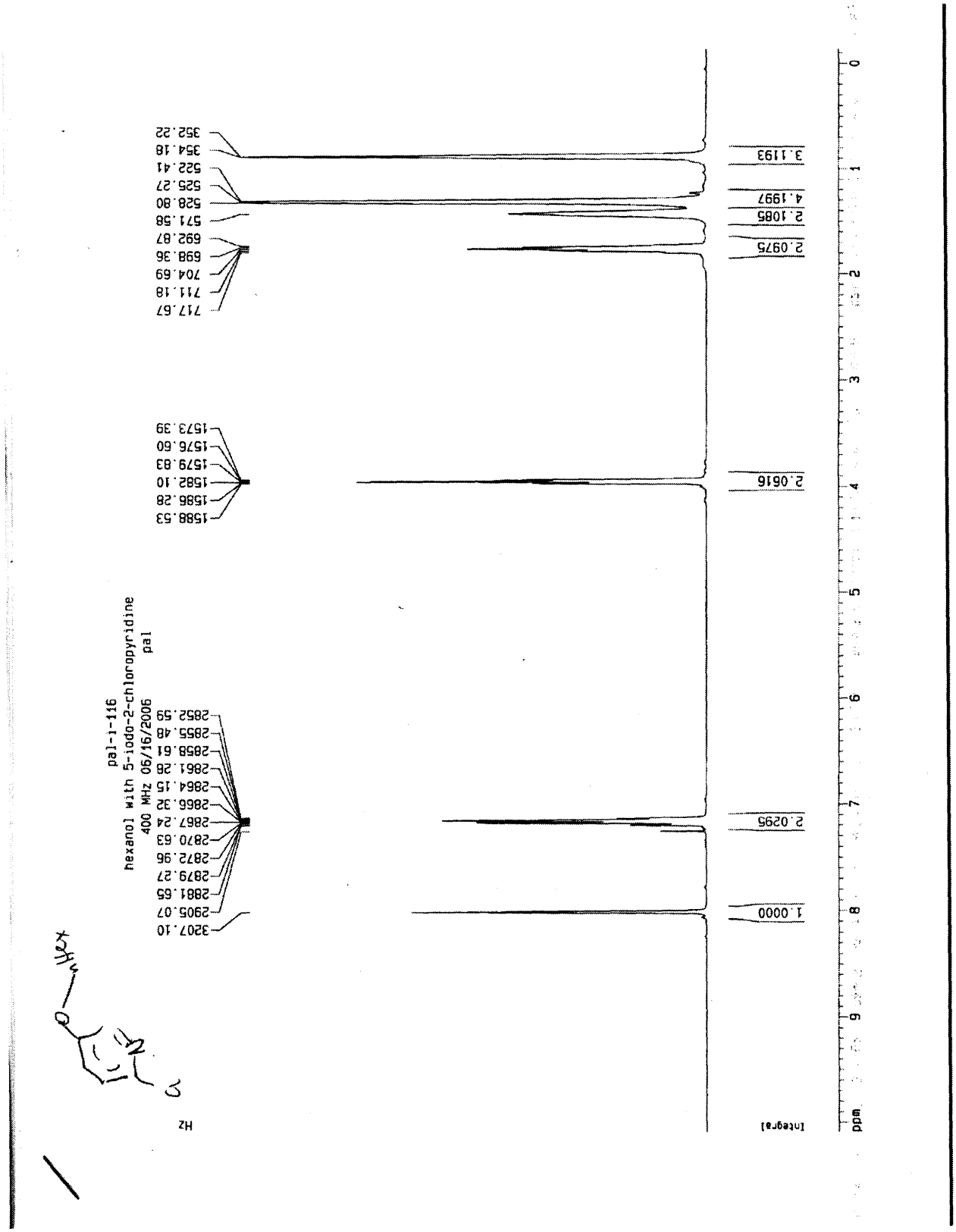
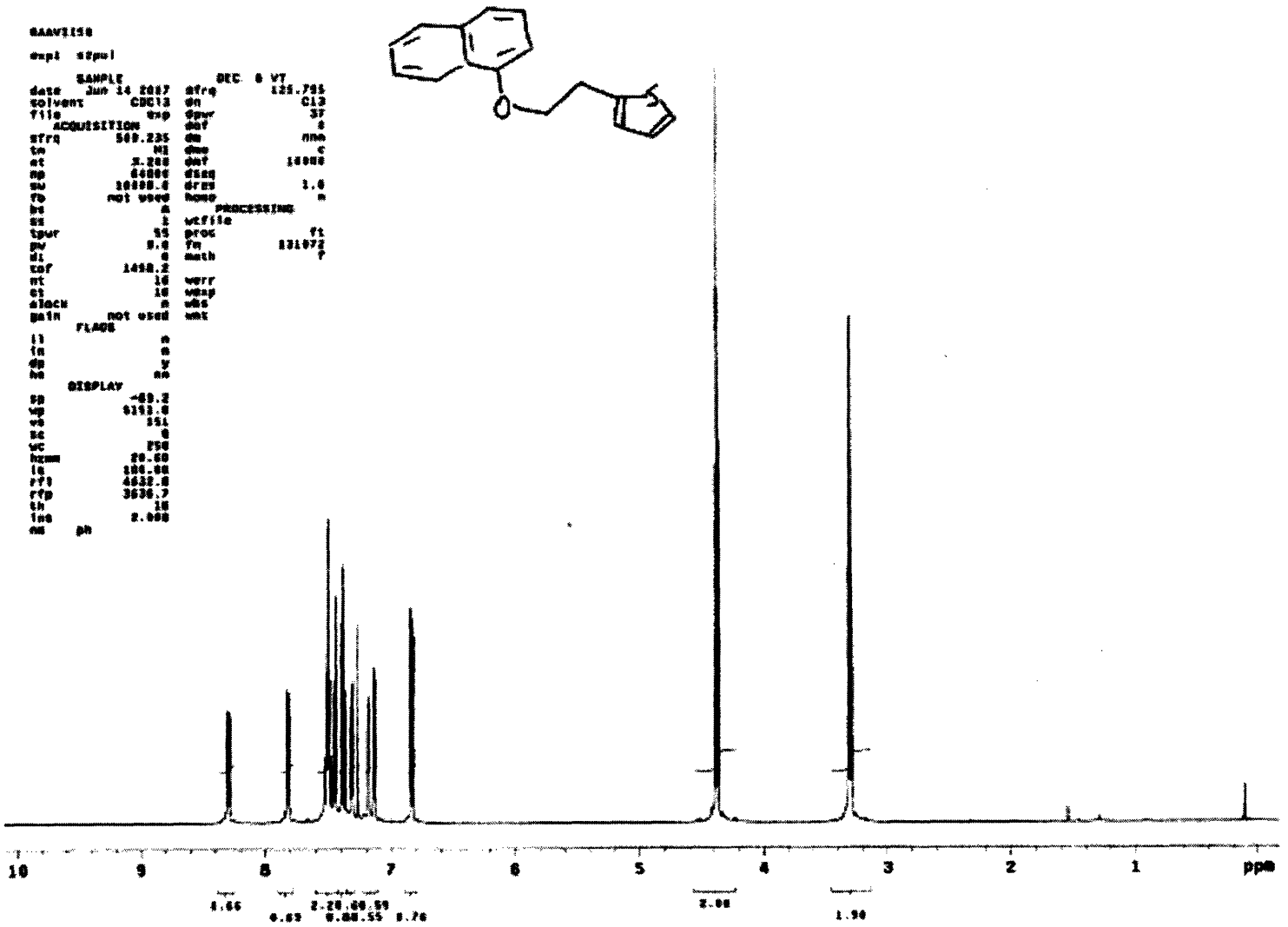
ppm
0.72
1.00
1.68
2.00
2.01

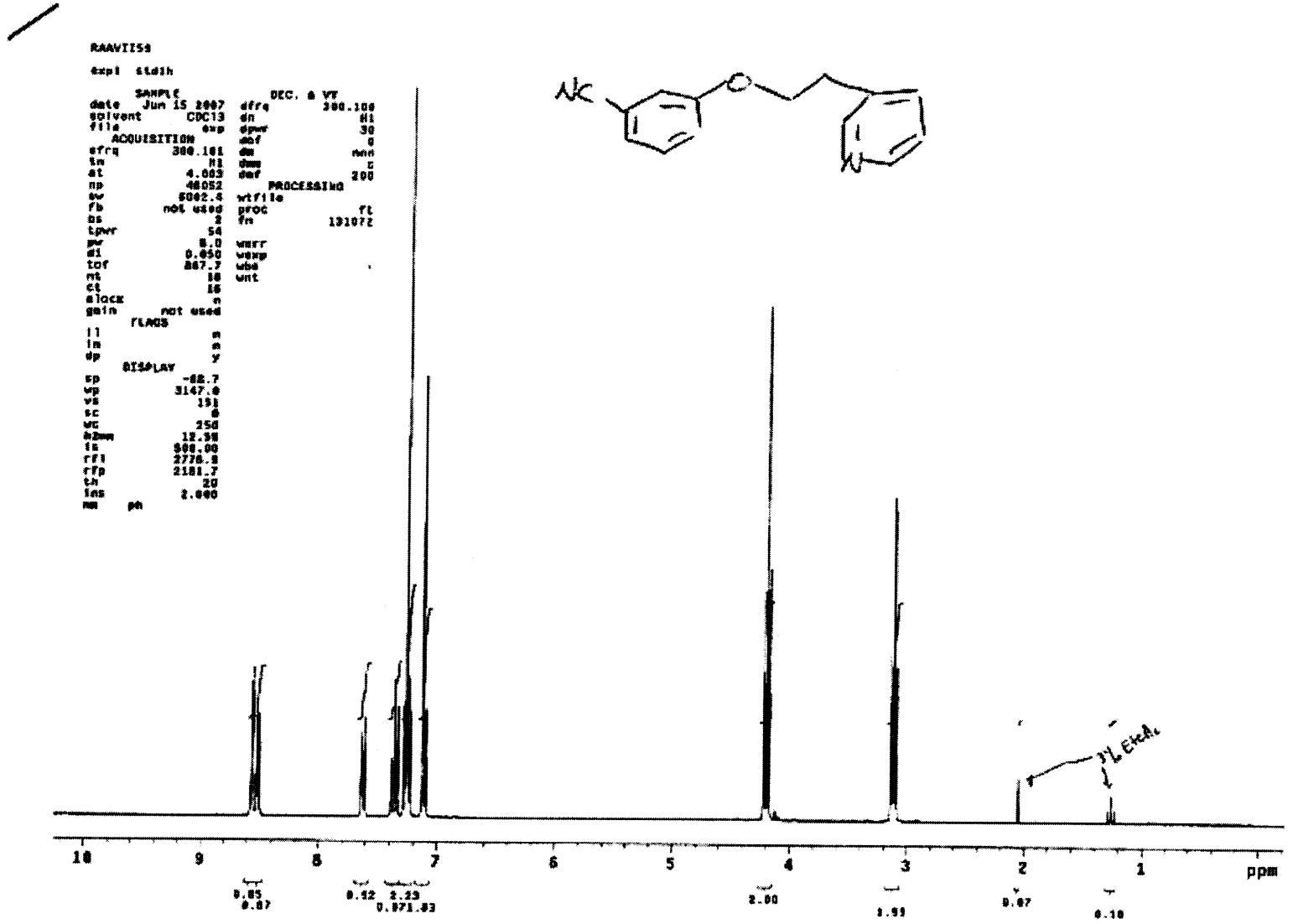

STANDARD IN OBSERVE
expl stdih
SAMPLE
date Aug 10 2007
solvent CDCl3
file /data/export/~
home/tlbuch/BCacho~
/brhat/BA1007-ACB3~
H.fid
ACQUISITION
sfrq 388.181
tn H1
at 4.883
np 48852
sw 9982.4
fb not used
bs 16
tpwr 54
pw 8.8
d1 0.050
tof 867.7
nt 16
ct 16
alock n
gain not used
FLAGS
il n
in n
dp y
DISPLAY
sp -6.8
wp 2705.4
vs 73
sc 0
wc 250
hzmm 10.62
is 500.00
rfl 800.4
rfp 0
th 20
ins 100.000
nm ph
DEC. & VT
dfrq 388.186
dn H1
dpwr 38
dof 0
dm nnn
dmm c
dmf 200
PROCESSING
wtfile
proc ft
fn 131072
werr
wexp
wbs
wnt
N
O
Me
8
7
6
5
4
3
2
1
ppm


pal-94-major/1 CDCl3
3-Isoxthiophene with 2-hexen-1-ol
400 MHz 02/24/96 PAL
Hz
Integral
ppm
3.4101
0.6567
2.2947
2.1464
2.0208
1.0146
1.0293
0.9914
0.9906
1.0000


RAAVII77
exp2 s2pul
SAMPLE
DEC. & VT
ACQUISITION
PROCESSING
FLAGS
DISPLAY
A
B
OtBu
OHex
nHexO
+
9
8
7
6
5
4
3
2
1
ppm


pal-i-116
hexanol with 5-iodo-2-chloropyridine
400 MHz 06/16/2006 pal
Hz
3207.10
2905.07
2881.65
2879.27
2872.96
2870.63
2867.24
2866.32
2864.15
2861.28
2858.61
2855.48
2852.59
1588.53
1586.28
1582.10
1579.83
1576.60
1573.39
717.67
711.18
704.69
698.36
692.87
571.58
528.80
525.27
522.41
354.18
352.22
Integral
1.0000
2.0295
2.0616
2.0975
2.1085
4.1997
3.1193
ppm


10
9
8
7
6
5
4
3
2
1
ppm
1.66
0.83
2.00
1.90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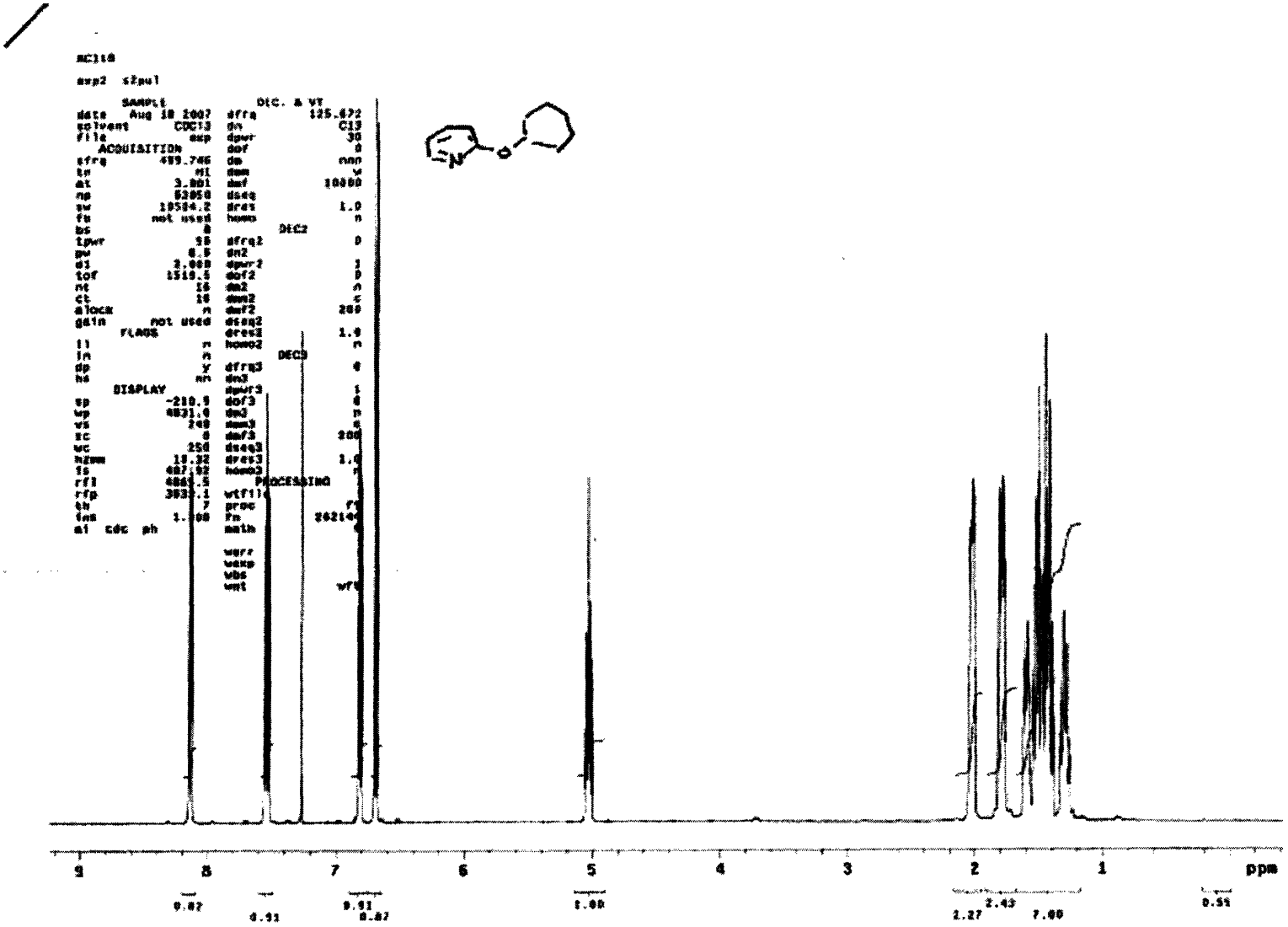
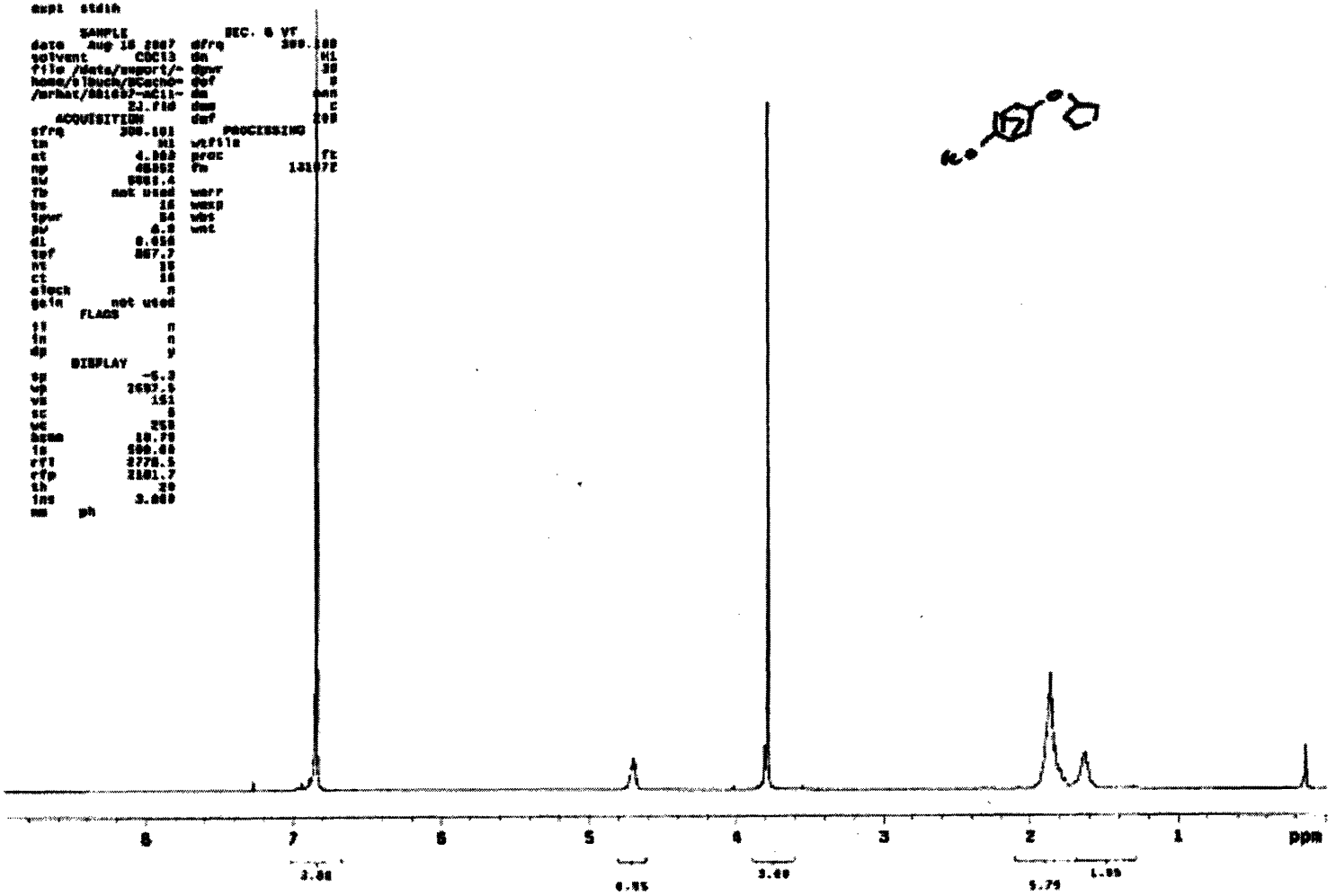
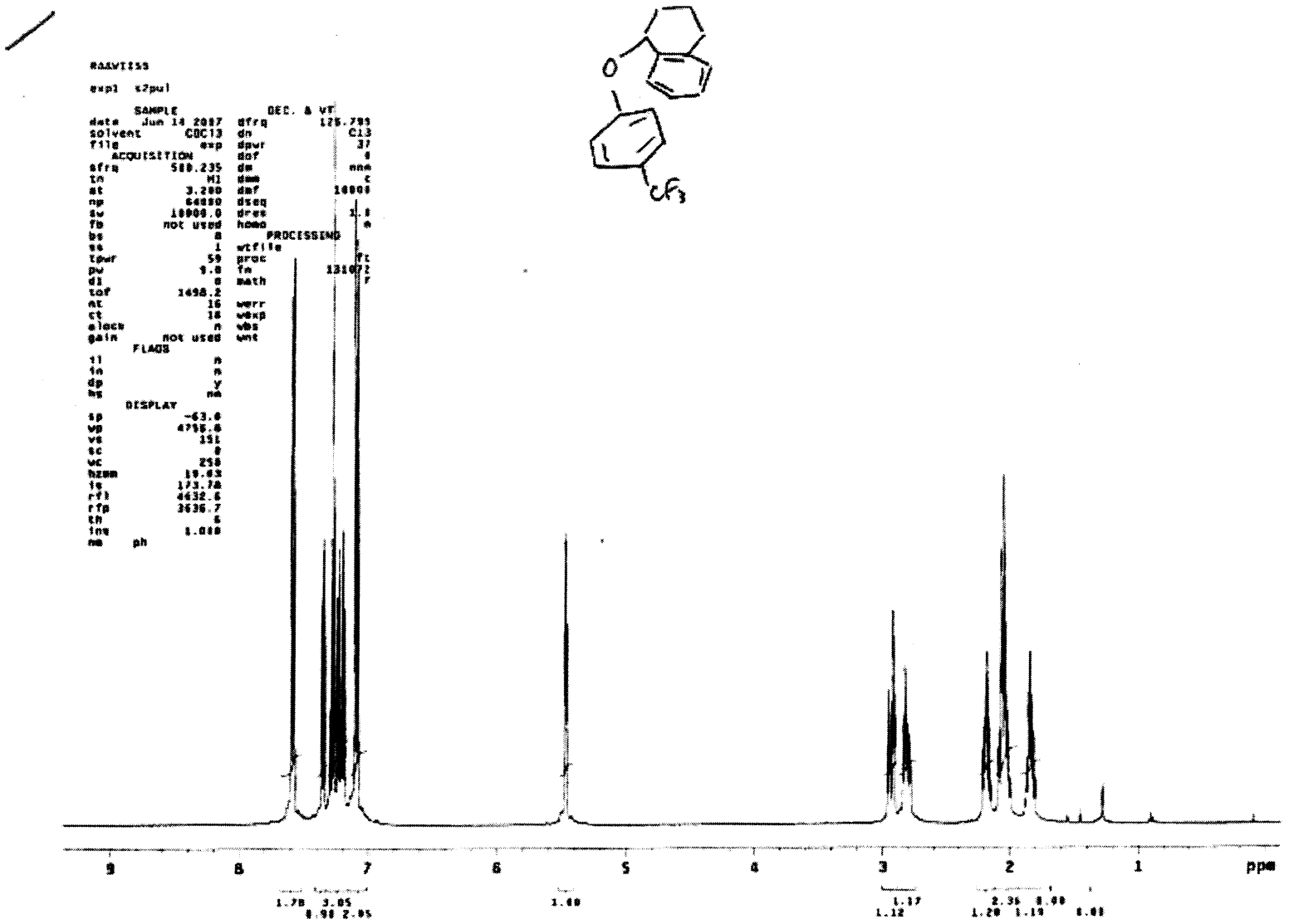
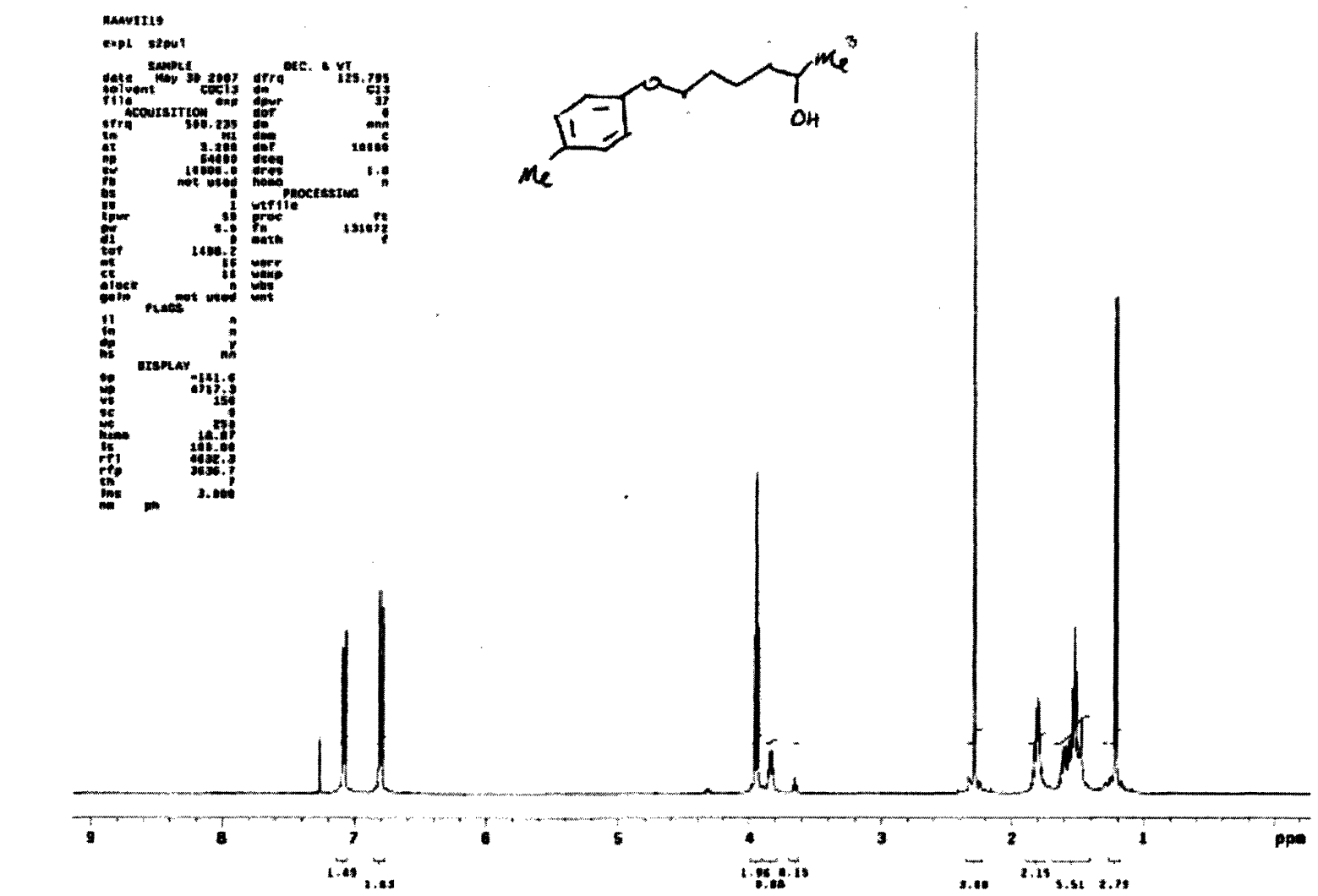
expl stdih
SAMPLE
date Jun 15 2007
solvent CDCl3
file exp
ACQUISITION
sfrq 300.101
tn H1
at 4.083
np 48052
sw 5002.4
fb not used
bs 2
tpwr 54
pw 8.0
d1 0.050
tof 887.7
nt 16
ct 16
alock n
gain not used
FLAGS
il n
in n
dp y
DISPLAY
sp -88.7
wp 3147.0
vs 151
sc 0
wc 250
hzmm 12.58
fn 8K.00
rfl 2778.8
rfp 2181.7
th 20
ins 2.000
nm ppm
DEC. & VT
dfrq 300.100
dn H1
dpwr 30
dof 0
dm nnn
dmm c
dmf 200
PROCESSING
wtfile
proc ft
fn 131072
wnrr
wexp
wbs
wnt
NC
3'L Et2O
10
9
8
7
6
5
4
3
2
1
ppm
0.85
0.87
0.92
2.23
0.971.03
3.00
2.99
0.87
0.18


MC110
exp2 s2pul
SAMPLE
date Aug 10 2007
solvent CDCl3
file exp
ACQUISITION
sfrq 499.746
tn H1
at 3.801
np 65858
sw 10504.2
fb not used
bs 8
tpwr 58
pw 8.5
d1 2.000
tof 1519.5
nt 16
ct 16
alock n
gain not used
FLAGS
ii n
in n
dp y
hs nn
DISPLAY
sp -210.9
wp 4831.6
vs 248
sc 0
wc 250
hzmm 19.32
is 487.92
rfl 4861.5
rfp 3933.1
th 7
ins 1.00
ai cdc ph
DEC. & VT
sfrq 125.672
dn C13
dpwr 38
dof 0
dm nnn
dmm w
dmf 10060
dseq
drat 1.0
homo n
DEC2
sfrq2 0
dn2
dpwr2 1
dof2 0
dm2 n
dmm2 s
dmf2 200
dseq2
drat2 1.0
homo2 n
DEC3
sfrq3 0
dn3
dpwr3 1
dof3 0
dm3 n
dmm3 s
dmf3 200
dseq3
drat3 1.0
homo3 n
PROCESSING
wtfile
proc ft
fn 262144
math
wnr
wexp
wbs
wnt wft
9
8
7
6
5
4
3
2
1
ppm
0.82
0.91
0.87
1.00
2.27
2.43
7.00
0.51

AC112-1


STANDARD 1H OBSERVE
expl stdih
SAMPLE
date Aug 15 2007
solvent CDCl3
file /data/expert/...
home/blouch/DCache...
/orbat/881657-AC11...
21.fid
ACQUISITION
sfrq 300.101
tn H1
at 4.882
np 48852
fb not used
bs 16
tdav 64
pw 6.0
d1 0.656
tof 887.7
nt 16
ct 16
alock n
gain not used
FLAGS
ii n
in n
dp y
DISPLAY
sw -5.2
wp 2697.5
sp 151
rfl 8
rfp 253
th 10.78
lb 590.48
rtl 2778.5
rtp 2181.7
lvl 20
tm 3.869
wc ph
REC. & VT
dfrq 300.100
dn H1
dpwr 38
dof 0
dm nnn
dmm c
dmf 208
PROCESSING
wtfile
proc ft
fn 131072
wexp
wbs
wnt
ppm
3.88
0.95
3.40
5.79
1.99


RAAVIISS
expl s2pul
SAMPLE
date Jun 14 2007
solvent CDCl3
file exp
ACQUISITION
sfrq 500.235
tn H1
at 3.280
np 64880
sw 10000.0
fb not used
bs 8
ss 1
tpwr 59
pw 9.8
dl 0
tof 1498.2
nt 16
ct 16
alock n
gain not used
FLAGS
il n
in n
dp y
hs nn
DISPLAY
sp -63.6
wp 4755.6
vs 151
sc 0
wc 258
hzmm 19.63
is 173.78
rfl 4632.6
rfp 3636.7
th 6
ins 1.000
ph
DEC. & VT
dfrq 125.795
dn C13
dpwr 37
dof 0
dm nnn
dmm c
dmf 10000
dseq
dres 1.0
homo n
PROCESSING
wtfile
proc ft
fn 131072
math f
wnt
9
8
7
6
5
4
3
2
1
ppm
1.78 3.05
8.98 2.95
1.00
1.17
1.12
2.35 8.00
1.20 1.19 0.83


RAMVII19
expl szpul
SAMPLE
date May 30 2007
solvent CDCl3
file exp
ACQUISITION
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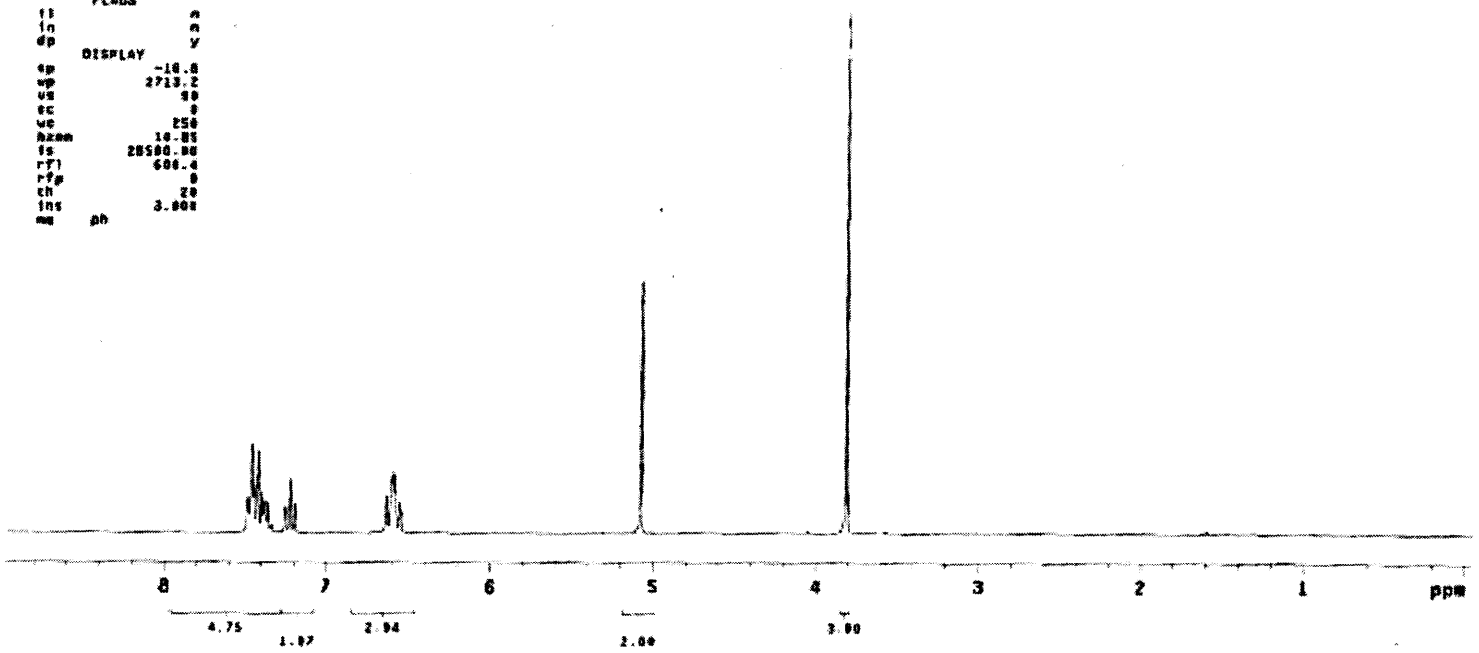
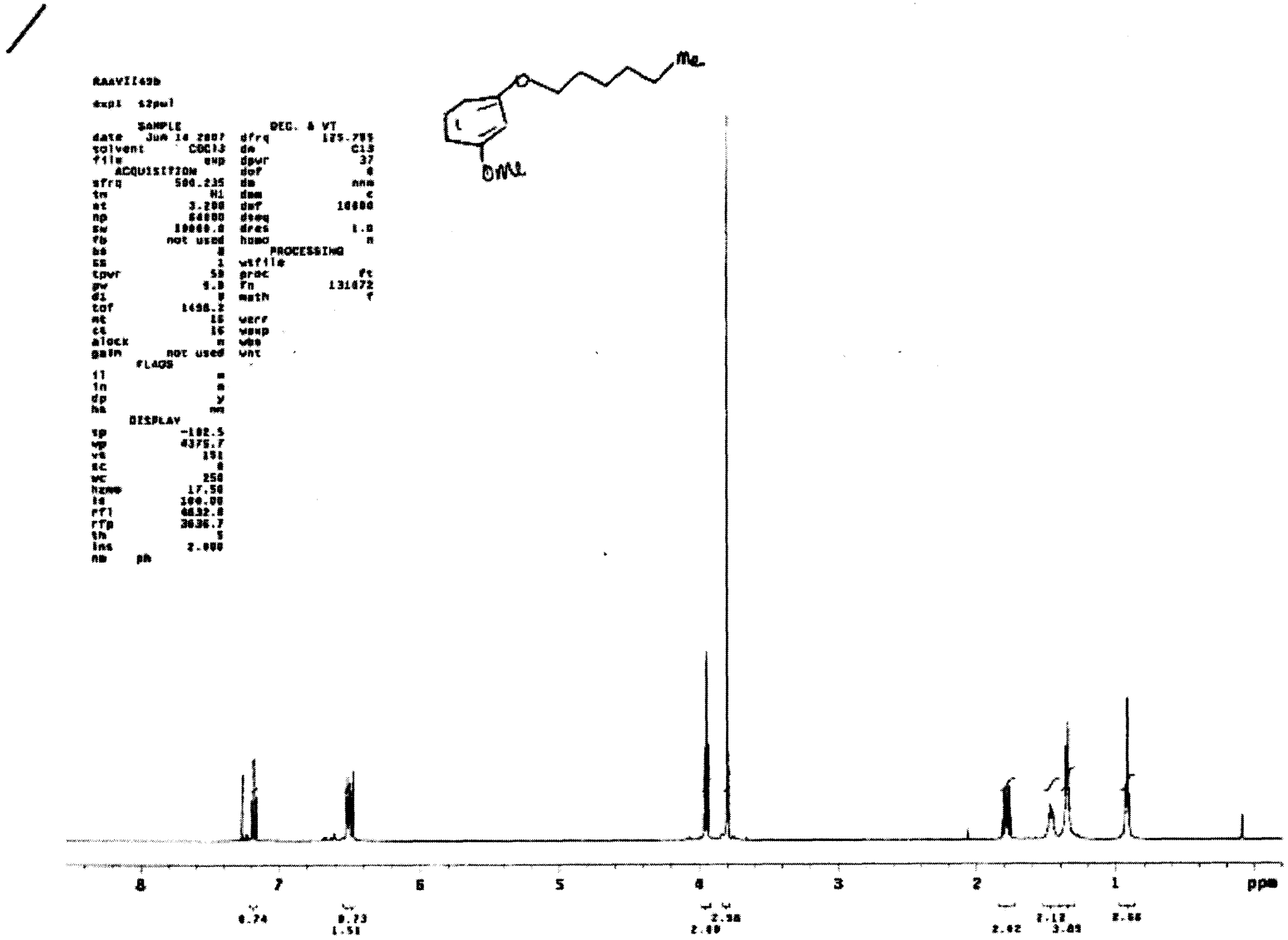
tn H1
at 3.288
np 64000
sw 14008.4
fb not used
bs 8
ss 1
tpwr 58
pw 8.9
dl 0
tof 1498.2
nt 16
ct 16
alock n
gain not used
FLAGS
il n
in n
dp y
hs nn
DISPLAY
sp -151.6
wp 6717.9
vs 156
sc 0
wc 250
hzmm 10.87
is 189.00
rfl 4482.8
rfp 3636.7
th 7
ins 3.000
nm ppm
DEC. & VT
dfrq 125.795
dn C13
dpwr 37
dof 0
dm nnn
dmm c
dmf 10180
dseq
drgs 1.0
homo n
PROCESSING
wtfile
proc ft
fn 131072
math f
werr
wexp
wbs
wnt
Me
OH
Me
9
8
7
6
5
4
3
2
1
ppm
1.49
1.63
1.96
0.88
0.15
3.00
2.15
5.51
2.79

STANDARD 1H OBSERVE

expl stdih

SAMPLE		DEC. & VT	
date	Aug 10 2007	dfrq	300.189
solvent	CDCl3	dn	H1
file	/data/export/-	dpwr	38
home/stbuch/BCacho-		dof	0
/mrhat/081507-AC10-		dm	nnn
	8H.fid	dmm	c
ACQUISITION		dmf	2500
sfrq	300.181	PROCESSING	
tn	H1	wtfile	
at	4.083	proc	ft
np	48852	fn	131072
sw	8992.4		
fb	not used	werr	
bs	16	wexp	
tpwr	54	wbs	
pw	8.0	wnt	
d1	2.000		
tof	867.7		
nt	16		
ct	16		
alock	n		
gain	not used		
FLAGS			
fl	n		
in	n		
dp	y		
DISPLAY			
sp	-18.8		
wp	2713.2		
vs	90		
sc	0		
wc	250		
hzcm	10.85		
is	28580.00		
rfl	606.4		
rfp	0		
th	20		
ins	3.000		
ns	8		




RAAVII49b
expt s2pul
SAMPLE
date Jun 14 2007
solvent CDCl3
file exp
ACQUISITION
sfrq 500.235
tn H1
at 3.280
np 64880
sw 19860.8
fb not used
bs 8
ss 1
tpwr 58
pw 9.8
dl 0
tof 1498.2
nt 16
ct 16
alock n
gain not used
FLAGS
il n
in n
dp y
hs nn
DISPLAY
sp -182.5
wp 4375.7
vs 151
sc 0
wc 250
hzmm 17.50
is 100.00
rfl 4832.8
rfp 3636.7
th 5
ins 2.000
ap ph
DEC. & VT
dfrq 125.795
dn C13
dpwr 37
dof 0
dm nnn
dmm c
dmf 16808
dseq
drec 1.0
homo n
PROCESSING
wtfile
proc ft
fn 131072
math f
werr
wexp
wbs
wnt
Me
OMe
8
7
6
5
4
3
2
1
ppm
0.74
0.73
1.51
2.58
2.69
2.02
2.12
3.89
2.66

5.5 References and Notes

(1) Smith, M. B.; March J. *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, 5th ed.* John Wiley & Sons, Inc.: New York, USA, 2001; p 477.

(2) (a) Vorogushin, A. V.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 8146. (b) Torraca, K. E.; Huang, X.; Parrish, C.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 10770. (c) Parrish, C. A.; Buchwald, S. L. *J. Org. Chem.* **2001**, *66*, 2498.

(3) Wolter, M.; Normann, G.; Job, G. E.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 973.

(4) For reviews including Pd-catalyzed C–O bond formation, see: (a) Schlummer, B.; Scholz, U. *Ad. Synth. Catal.* **2004**, *346*, 11599. (b) Mucci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 133.

(5) For reviews including Cu-catalyzed C–O bond formation, see: (a) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Re.* **2004**, 2337. (b) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400.

(6) Lindley, J. *Tetrahedron* **1984**, *40*, 1433.

(7) Fagan, P. J.; Hauptman, E.; Shapiro, R.; Casalnuovo, A. *J. Am. Chem. Soc.* **2000**, *122*, 5043.

(8) (a) Zhang, H.; Ma, D.; Cao, W. *Synlett* **2007**, 243. (b) Hosseinzadeh, R.; Tajbakhsh, M.; Mohadjerani, M.; Alikarami, M. *Synlett* **2005**, 1101.

(9) Nordmann, G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 4978.

(10) Shafir, A.; Lichtor, P. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 3490.

(11) pK_a in H_2O: H-Me_4-Phen 6.31, H-Phen, 4.86. Schilt, A. A.; Smith, G. F. *J. Phys. Chem.* **1956**, *60*, 1546.

(12) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis,* 3rd ed.; John Wiley

& Sons, Inc.: New York, 1999; pp 266-269.

(13) Smith, M. B.; March J. *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure,* 5th ed.; John Wiley & Sons, Inc.: New York, 2001; p 477.

(14) p*K*a in DMSO: BnOH 26.9, EtOH 29.8. (a) Bordewll, F. G.; Liu, W. Z. *J. Am. Chem. Soc.* **1996**, *118*, 8777. (b) Olmstead, W. N.; Margolin, Z.; Bordwell, F. B. *J. Org. Chem.* **1980**, *45*, 3295.

(15) Stewart, D.; McHattie, G. S.; Imrie, C. T. *J. Mater. Chem.* **1998**, *8*, 47.

(16) Dalal et al. *J. Indian Chem. Soc.* **1958**, *35,* 745.

(17) Robbins, T. A.; Knobler, C. B.; Bellew, D. *R.*; Cram, D. J. *J. Am. Chem. Soc.* **1994**, *116*, 111.

(18) Lajis, N. H.; Khan, M. N.; Hassan, H. A. *Tetrahedron* **1993**, *49*, 3405.

(19) Sharma, G. V. M.; Ilangovan, A.; Sreenivas, P.; Mahalingam, A. K. *Syn. Lett.* **2000**, 615.

(20) Chandrasekhar, S.; Prakash, S. J.; Rao, C. L. *J. Org. Chem.* **2006**, *71*, 2196.

(21) Prepared using the procedure described in the following paper: Zhang, Xin-Ge; Zhang, Hui-Jie; Wang, Zhen; Li, Chao-Xing, *Jiegou Huaxue*, **2006**, *25*, 300.

(22) Wolter, M.; Nordmann, G.; Job, G. E.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 973.

(23) Torraca, K. E.; Huang, X.; Parrish, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 10770.

(24) Ruhland, T.; Andersen, K.; Pedersen, H. *J. Org. Chem.* **1998**, *63*, 9204.

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EDUCATION

Massachusetts Institute of Technology, Ph.D., Organic Chemistry	June 2008
Creighton University, B.S. Chem., Chemistry, *Summa Cum Laude*	June 2003

EXPERIENCE

Massachusetts Institute of Technology	2003-2008
Graduate Student with Professor Stephen Buchwald	2004-2008
Project: Transition metal-catalyzed C–heteroatom and C–C bond-forming reactions	
Environmental Health and Safety Representative for the Buchwald Laboratory	2004-2008
Mentor for MIT Undergraduate Research Opportunity Program (UROP) Students	2005-2007
Member of the Committee for the Implementation and Analysis of ChemTracker	2005-2006
Teaching Assistant for 5.12 and 5.13 (Organic Chemistry I and II)	2003-2004
Creighton University	1999-2003
Research Assistant with Professor Mark Kearley (currently employed at Florida State University)	2002
Project: Synthesis of small molecules aimed at understanding the chemical basis of alcohol induced liver injury	
Tutor for Athletic Department (Chemistry and Spanish)	2001-2003

ACADEMIC HONORS AND AWARDS

NIH Ruth L. Kirschstein National Research Service Award Predoctoral Fellow	2007-2008
Pfizer Diversity in Organic Chemistry Predoctoral Fellow	2006-2007
MIT Institute Fellow	2003-2004
Omaha World Herald Presidential Scholar	2002-2003
Creighton University Presidential Scholar	1999-2002
American Institute of Chemists Award–for the outstanding senior chemistry major	2003
Department of Chemistry Award–for distinguished academic achievement	2003
Phi Lambda Upsilon–National Chemistry Honor Society	2003
Missouri Valley Conference (NCAA Division I) President's Academic Excellence Award	2003
•In recognition of outstanding academic achievement as a Student-Athlete	
The POLYED Award in Organic Chemistry	2001
•For the outstanding chemistry major in organic chemistry (given by the American Chemical Society Polymer Education Committee, Division of Polymer Chemistry, Division of Polymeric Materials: Science and Engineering and The Industrial Sponsors)	
National Dean's List	2001-2003
National Society of Collegiate Scholars	2000-2003
Dean's List (8 Semesters)	1999-2003

PUBLICATIONS

1) "4,7-Dimethoxy-1,10-phenanthroline: An Excellent Ligand for the Cu-Catalyzed *N*-Arylation of Imidazoles" Altman, R. A.; Buchwald, S. L. *Org. Lett.* **2006**, *8*, 2779-2782.

2) "Monodentate Phosphines Provide Highly Active Catalysts for Pd-Catalyzed C–N Bond-forming Reactions of Heteroaromatic Halides/Amines and (H)N-Heterocycles" Anderson, K. W.; Tundel, R. E.; Ikawa, T.; Altman, R. A.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2006**, *45*, 6523-6527.

3) "Cu-Catalyzed *N*- and *O*-Arylation of 2-, 3- and 4-Hydroxypyridines and Hydroxyquinolines" Altman, R. A.; Buchwald, S. L. *Org. Lett.* **2007**, *9*, 643-646.

4) "Copper-Catalyzed N-Arylation of Imidazoles and Benzimidazoles" Altman, R. A.; Koval, E. D.; Buchwald, S. L. *J. Org. Chem.* **2007**, *72*, 6190-6199.

5) "Cu-Catalyzed Goldberg and Ullmann Reactions of Aryl Halides Using Diamine and β-Diketone Ligands" Altman, R. A.; Buchwald, S. L. *Nature Prot.* **2007**, *2*, 2474-2479.

6) "Pd-Catalyzed Amination Reactions of Aryl Halides Using Bulky Biarylmonophosphine Ligands" Altman, R. A.; Buchwald, S. L. *Nature Prot.* **2007**, *2*, 2881-2887.

7) "Pd-Catalyzed Suzuki-Miyaura Reactions of Aryl Halides Using Bulky Biarylmonophosphine Ligands" Altman, R. A.; Buchwald, S. L. *Nature Prot.* **2007**, *2*, 3115-3121.

8) "An Improved Cu-Based Catalyst System for the Reactions of Alcohols with Aryl Halides" Altman, R. A.; Shafir, A.; Choi, A. C.; Lichtor, P. A.; Buchwald, S. L. *J. Org. Chem.* **2008**, *73*, 284-286.

9) "1,10-Phenanthroline, 4,7-Dimethoxy-" Altman, R. A. *Electronic Encyclopedia of Reagents Organic Synthesis, in press*.

10) "Pyrrole-2-carboxylic Acid as a Ligand for the Cu-Catalyzed Reactions of Primary Anilines with Aryl Halides" Altman, R. A.; Anderson, K. W.; Buchwald, S. L. *Manuscript submitted for publication*.

11) "Orthogonal Pd- and Cu-Based Catalyst Systems for the C- and N-arylation of Oxindoles" Altman, R. A.; Hyde, A. M.; Huang, X.; Buchwald, S. L. *Manuscript submitted for publication*.

PRESENTATIONS

Poster: "Cu-Catalyzed C-Heteroatom Bond-Formation: A New 1,10-Phenanthroline Ligand and the Application of Solid/Liquid Phase Transfer Catalysis for the *N*-Arylation of Imidazoles and Benzimidazoles and the *N*- and *O*-arylation of 2-, 3- and 4-Hydroxypyridines" Pfizer Symposium Supporting Diversity in Organic Chemistry, Groton, CT. October 13, 2006.

Oral: "Orthogonal Pd- and Cu-Based Catalyst Systems for the *C*- and *N*-Arylation of Oxindoles" Pfizer Symposium Supporting Diversity in Organic Chemistry, Groton, CT. September 28, 2007.

Oral: "Metal-Catalyzed N-Arylation of Heterocycles: Pd- and Cu-Based Catalyst Systems for Amination Reactions of Aryl Halides Can Provide Complementary and Orthogonal Reactivities" Massachusetts Institute of Technology, Cambridge, MA. May 2007.