The Development and Application of Metal-Catalyzed Processes for Organic Synthesis

by

Edward J. Hennessy

B.A. Chemistry
Northwestern University, 2000

Submitted to the Department of Chemistry in Partial Fulfillment of the Requirements for the Degree of

DOCTOR OF PHILOSOPHY IN ORGANIC CHEMISTRY

at the
Massachusetts Institute of Technology

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ABSTRACT

Chapter 1. ***Copper-Catalyzed Arylation of Stabilized Carbanions***

A mild, general catalytic system for the synthesis of α-aryl malonates has been developed. Aryl iodides bearing a variety of functional groups can be effectively coupled to diethyl malonate in high yields using inexpensive and widely available reagents, making this a superior method to those previously described that employ copper reagents or catalysts. The functional group tolerance of the process developed makes it complementary to analogous palladium-catalyzed couplings. Importantly, a set of mild reaction conditions has been developed that minimize product decomposition, a problem that had not been addressed previously in the literature. In addition, the utilization of aryl bromides as coupling partners has been investigated, as well as the use of other classes of nucleophilic stabilized carbanions.

Chapter 2. ***Synthesis of Oxindoles from α-Haloacetanilides via Palladium-Catalyzed C-H Functionalization***

We have discovered a palladium-catalyzed reaction that efficiently produces oxindoles from α-haloacetanilides through a net functionalization of an arene C-H bond. The high levels of regioselectivity observed in this cyclization obviate the need for highly functionalized aromatic substrates to effect desired ring closure. Moreover, the breadth of functional groups compatible with the reaction conditions is vastly greater than that of analogous Lewis acid-mediated processes. Extensive mechanistic work has been conducted, including kinetic isotope effect and linear free energy relationship studies. A number of plausible pathways are consistent with our data and with previously published examples of palladium-catalyzed C-H functionalization processes.

Chapter 3. ***Synthesis of DAPH Analogs via Palladium-Catalyzed Amination***

DAPH (4,5-dianilinophthalimide) has previously been shown to reverse the formation of neurotoxic fibrils associated with Alzheimer's disease. We have developed a synthetic route to DAPH and structurally-related analogs that employs palladium-catalyzed amination as the key bond-forming step. The requisite substrates are easily obtained, and their coupling with substituted anilines proceeds in generally high yields. Thus, a variety of DAPH analogs can be quickly accessed in a modular fashion. In addition, the route described herein should also be amenable to the incorporation of other classes of nucleophiles into the molecular framework. The results of biological assays conducted thus far will serve as a guide for further lead optimization.

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

ACKNOWLEDGMENTS

Despite this section appearing only a few pages after the title page, it is the last component of the entire thesis to be written. Perhaps this is because in my mind it is the most important part. There are many people who are responsible in some way for helping me to get this point in my life, and I hope this section aptly expresses my gratitude.

I would not be at MIT if not for my undergraduate advisor, Professor SonBinh Nguyen, and his guidance and assistance during my time at Northwestern. Despite my overwhelming lack of knowledge and experience when I first joined his lab, I was encouraged to pursue my own interests in research and was given the chance to explore new areas. I am lucky to have worked with him and am incredibly grateful for the advice and direction I was given.

I am indebted to my graduate advisor, Professor Stephen Buchwald, for the opportunities I have had during my studies at MIT. Steve has given me incredible freedom in deciding the direction of my research since the very first day. He has let me work on difficult problems (often my own ideas) that have had marginal chance for success, and has charitably allowed me to move on without recourse when such projects haven't worked out as planned. I was admittedly naive when I first came to MIT, and Steve has taught me to be a more critical thinker and a more efficient experimentalist. I am grateful to him for an experience that I will carry with me throughout my life.

Of course, there are many people at MIT who have contributed to my development as a scientist. My thesis committee chair, Professor Greg Fu, has been a valuable source of advice and direction in scientific and career-related matters both before and throughout my graduate studies. Likewise, working with Professor Vernon Ingram of the MIT Biology Department has been a refreshing experience, and I am grateful for his assistance in the preparation of pertinent sections of this thesis and for the opportunity to work on a project with the potential for a beneficial impact on society.

I have been fortunate to work with a number of talented graduate students and postdocs during my tenure in the Buchwald group. It would be a disservice to try to name each individual who has been a positive influence because I'm sure I would

mistakenly leave somebody out. However, I would be remiss if I didn't specifically thank my classmates Matt Rainka and Eric Strieter. We all first met during the visitation weekend for prospective graduate students, and thus we have literally been in the same boat since day one. Looking back at the past five years, I realize that I likely would not have gotten to this point if not for their loyal friendship.

It would be an understatement to say that I would not be the person I am today without my family. My brother Andrew has always been there for me, whether it be consistently finding the Nintendo system that had been hidden somewhere in the house by our mother (because we had been grounded), playing baseball or football in the backyard, or serving as the best man in my wedding. I am extremely fortunate to have him as a brother. My parents, Ed and Helene, have been the biggest influences in my life. They have always given me everything I could have ever possibly wanted, and continue to do so to this very day. They consistently put the needs of family above their own, and their values and ideals serve as a model for my own life. It is an honor to be their son, and I hope that someday I will be able to earn a mere fraction of what they've done for me.

Lastly, I would like to thank my wife Portia. We've endured a lot together throughout our relationship, from going to college in cities 800 miles apart to the long hours and stress of graduate school and the recent difficulty and uncertainty of finding a job. Still, through it all, she has been a loving companion and my best friend. I would not have been able to get to the point of writing this thesis without her, and she has earned everything this represents more than I have.

PREFACE

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

"A General and Mild Copper-Catalyzed Arylation of Diethyl Malonate." Hennessy, E. J.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 269-272.

"Synthesis of Oxindoles from α-Chloroacetanilides via Palladium-Catalyzed C-H Functionalization." Hennessy, E. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 12084-12085.

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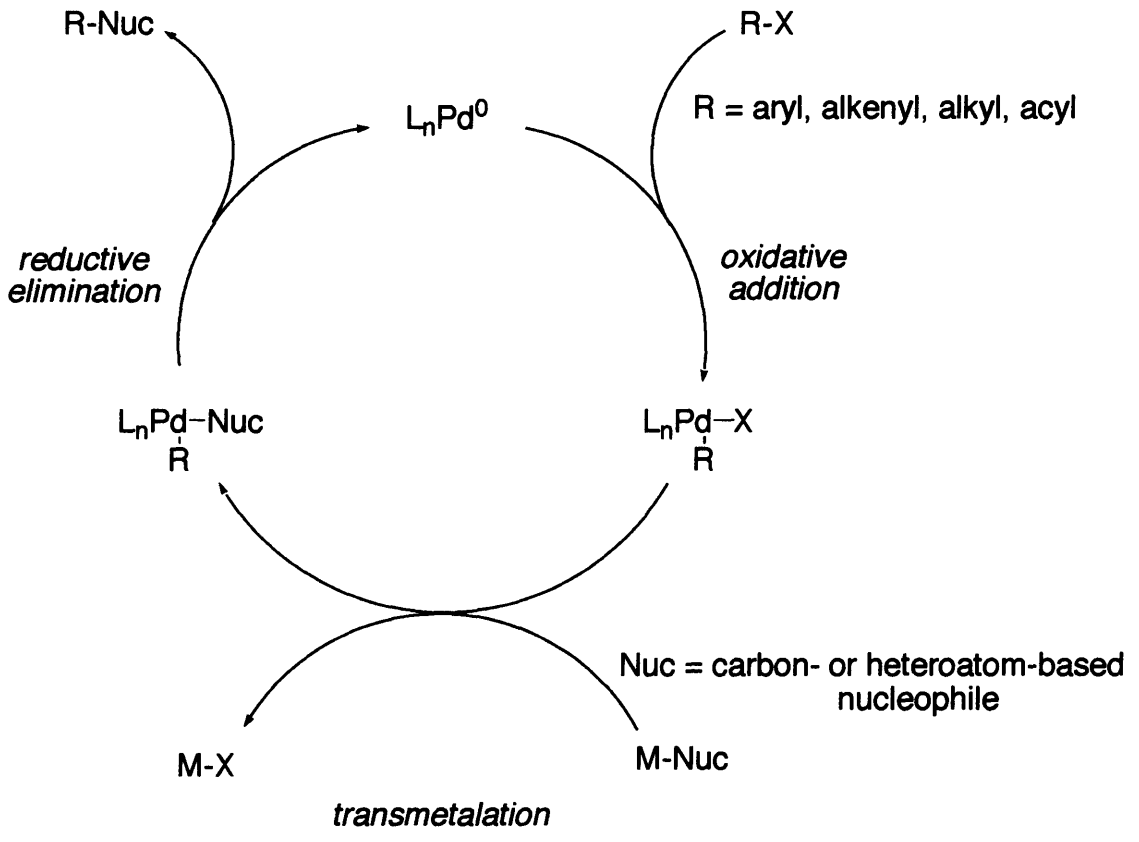
INTRODUCTION

The use of transition metal catalysts and reagents has had a profound impact on the field of organic synthesis. The "toolbox" of reactions available to a synthetic chemist is replete with bond-forming and bond-breaking processes that involve the use of a metal. Moreover, given the extensive research conducted in the field of metal-based synthetic methodology in both academic and industrial laboratories, refinements and improvements to these reactions are occurring on a seemingly daily basis. As a result, the construction of complex natural products, pharmaceutically active compounds, and industrially important materials all increasingly rely on these reagents.[1]

Of the metals commonly employed in organic synthesis, palladium has arguably stood alone as the most versatile for the formation of carbon-carbon and carbon-heteroatom bonds.[2] Both readily accessible oxidation states of palladium (Pd^0 and Pd^{2+}) have extensive and differing reactivity towards a variety of organic groups, and this serves as the basis for the many catalytic cycles known for this metal. For example, Pd(0) undergoes oxidative addition to a number of functional groups, allowing for the initiation of a catalytic cycle, while reductive elimination from Pd(II) intermediates occurs readily to form a new bond between the organic ligands bound to the metal. These steps in particular, in conjunction with transmetalation (the exchange of a ligand covalently bound to palladium for a different group that is bound to another metal) constitute the catalytic cycle of the various cross-coupling processes widely used in organic synthesis (Scheme 1). Specifically, oxidative addition of an aryl, alkenyl, alkyl, or acyl halide to palladium (0) affords a palladium (II) intermediate. Transmetalation between this complex and some

nucleophilic group (which, depending on the reaction, can be carbon- or heteroatom-based) affords a new palladium (II) intermediate. Reductive elimination regenerates the active palladium (0) catalyst while forming the desired bond of the product.



Scheme 1. Generalized Mechanism for Pd-Catalyzed Cross-Coupling Reactions

Another metal that has had a significant impact on the synthesis of organic molecules is copper. The construction of carbon-carbon and carbon-heteroatom bonds using copper-catalyzed or copper-mediated reactions was initially developed many decades ago, and these reactions have found widespread use in numerous synthetic applications.[3] Unfortunately, these classical processes typically employ stoichiometric amounts of copper in conjunction with comparatively harsh reaction conditions (e.g., high temperatures, strong bases). However, many of these well-

known reaction protocols have been recently revisited by a number of research groups and significant improvements to a variety of the reactions have been made, allowing for the use of catalytic quantities of copper and considerably milder reaction conditions.[4]

Interestingly, it seems that the palladium- and copper-catalyzed cross-coupling methodologies are complementary in many respects. While palladium can activate a variety of aryl halides (including aryl chlorides) and aryl sulfonates towards coupling in such reactions, substrates containing certain polar functional groups tend to be problematic in palladium catalysis. Copper, on the other hand, in general only induces coupling reactions with aryl iodides and aryl bromides, although many of the processes exhibit much higher levels of functional group compatibility relative to palladium. The complementary nature of these two metals is further exemplified by the chemoselectivity of reactions involving substrates that contain more than one potentially reactive functional group; it has been demonstrated that changing the metal catalyst from palladium to copper can affect the site at which the coupling occurs.[5]

In this thesis, the continued development of metal-catalyzed processes for carbon-carbon bond formation are described, as is the application of a well-known cross-coupling methodology to the synthesis of a unique class of biologically active compounds. In particular, Chapter 1 discusses our efforts in the modification of the copper-catalyzed coupling of enolates derived from acidic carbonyl compounds with aryl halides, a process that was initially reported in 1929. Significant improvements to previously published processes have been made, resulting in a mild arylation protocol with high levels of functional group compatibility. In Chapter 2, we outline the discovery, development, and mechanistic studies of a novel reaction that generates highly substituted oxindoles from easily accessible substrates employing palladium catalysis. This synthetically useful cyclization features high levels of regioselectivity and functional group tol-

erance. Chapter 3 discusses our efforts in the synthesis of a class of compounds with potential anti-Alzheimer's activity using palladium-catalyzed carbon-nitrogen bond formation. In comparison to the previously described route to these structures, we have found that the use of palladium catalysis allows for systematic modifications in the molecular architecture at a minimal synthetic cost.

References

(1) For recent reviews of metal-catalyzed cross-coupling reactions, see: (a) *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A., Diedrich, F., Eds.; Wiley-VCH: Weinheim, 2004. (b) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359. (c) Miyaura, N. *Top. Curr. Chem.* **2002**, *219*, 1.

(2) For very thorough treatments of the many reactions catalyzed by palladium, see: (a) Tsuji, J. *Palladium Reagents and Catalysts*, 2nd ed.; Wiley: Chichester, 2004. (b) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., de Meijere, A., Eds.; Wiley: Chichester, 2002.

(3) For a review of these "classical" processes, please see: Lindley, J. *Tetrahedron* **1984**, *40*, 1433.

(4) For recent reviews of the advancements made in copper-catalyzed cross-coupling, see: (a) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400. (b) Beletskya, I.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337.

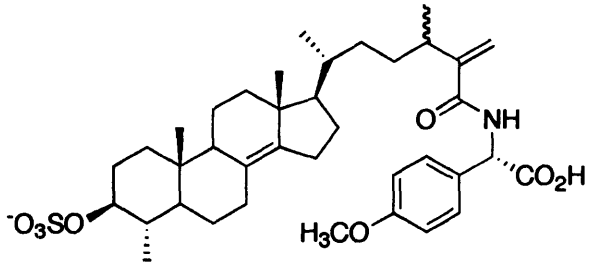
(5) For a relevant example, see: Huang, X.; Anderson, K, W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 6653.

CHAPTER 1

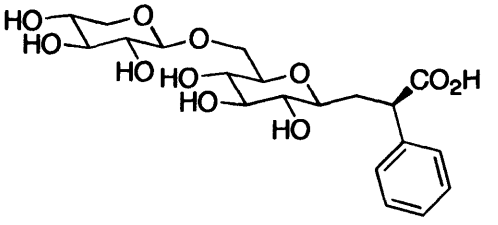
COPPER-CATALYZED ARYLATION OF STABILIZED CARBANIONS

1.1 Introduction

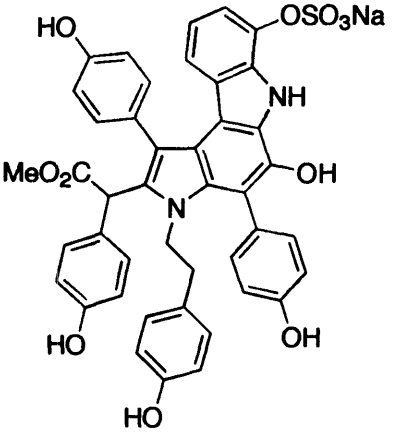
α-Aryl carboxylic acids and acid derivatives comprise an important class of organic molecules. For example, compounds containing α-aryl carboxylic acids are prevalent in nature, such as polymastiamide A, lucuminic acid, vulculic acid, and dictyodendrin A (Figure 1).[1] Moreover, compounds containing such motifs have been widely used in pharmaceutical applications. Indeed, α-aryl acetic acids (e.g., indomethacin, sulindac, ibufenac, diclofenac) and α-aryl propionic acids (e.g., ibuprofen, naproxen, ketoprofen) comprise two of the main classes of non-steroidal antiinflammatory drugs (NSAIDs).[2]



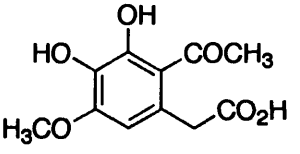
Polymastiamide A
antimicrobial metabolite from *Polymastia boletformis*



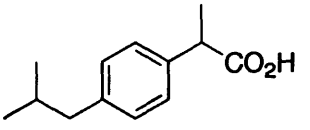
Lucuminic Acid
isolated from seeds of *Calocarpum sapota*



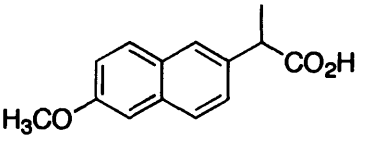
Dictyodendrin A
telomerase inhibitor



Vulculic Acid
inhibitor of pollen germination



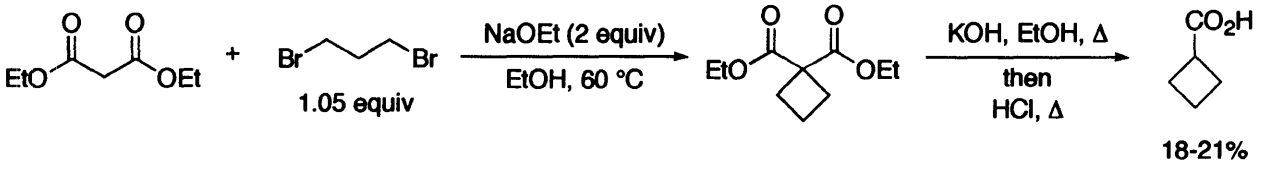
Ibuprofen
antiinflammatory agent



Naproxen
antiinflammatory agent

Figure 1. Examples of Molecules Containing α-Aryl Carboxylic Acids[1]

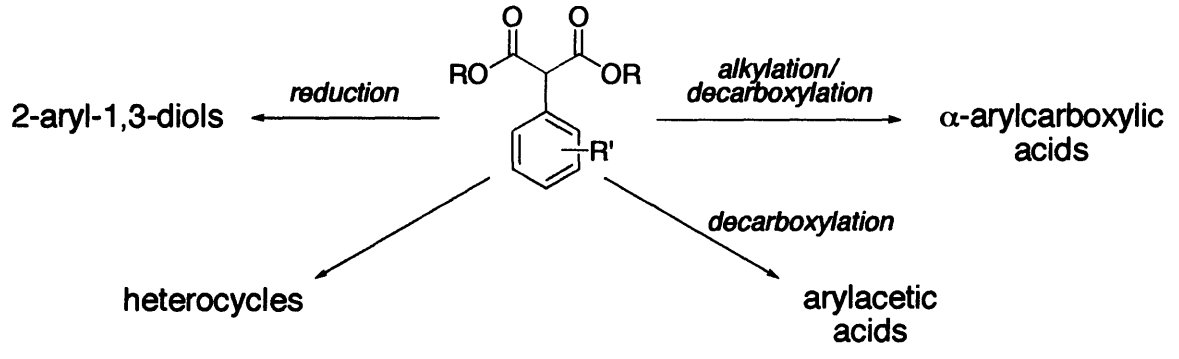
α-Substituted carbonyl derivatives can be accessed by a number of synthetic methods, one of the most common being the functionalization of the corresponding enolate (formed by deprotonation α to the carbonyl group). In particular, the enolates of β-dicarbonyl compounds, which can be generated using relatively weak bases due to the increased acidity of the α-protons, have been used for decades in the synthesis of organic molecules. For example, alkylation of a β-ketoester or a β-diester is typically followed by hydrolysis of the ester group(s) to the corresponding carboxylic acid. Decarboxylation of this intermediate reveals the α-substituted monocarbonyl compound. The utility of this chemistry has been particularly applicable to large-scale syntheses (e.g., the synthesis of cyclobutanecarboxylic acid,[3] Scheme 1). While the advent of very strong, hindered bases (such as lithium diisopropylamide and potassium hexamethyldisilazide) has allowed for the direct deprotonation of essentially any conceivable carbonyl compound, the classical malonate alkylation is still an important tool that finds widespread use in a variety of synthetic applications.



Scheme 1. Synthesis of Cyclobutanecarboxylic Acid[3]

The *arylation* of malonates is, however, less straightforward. Indeed, the direct substitution of aryl halides by malonate esters only occurs with very electron-deficient arenes that are prone to nucleophilic aromatic substitution, although processes employing hypervalent aryl iodides[4] and π-coordinated metal-aryl halide complexes[5] have been developed. α-Aryl malonates have enormous potential as synthetic intermediates, given the plethora of transformations of esters that are known

(Scheme 2). For example, alkylation and hydrolysis followed by decarboxylation would afford α-aryl carboxylic acids (such as ibuprofen and naproxen). Condensation with nucleophiles such as hydrazine or hydroxylamine would generate the heterocyclic 4-aryl-3,5-dihydroxypyrazoles or 4-aryl-3,5-dihydroxyisoxazoles, respectively, both of which have demonstrated interesting reactivity towards carbonyl compounds to form paraionic complexes.[6] Alternatively, reduction of the ester functional groups would afford the corresponding 2-aryl-1,3-diols, which have found numerous applications in organic synthesis as well as in materials chemistry.[7] It is also noteworthy that some α-aryl malonates have demonstrated biological activity. For example, molecules containing this moiety have been reported to be potent tyrosine kinase inhibitors[8] as well as effective modulators of Ca^{2+}-activated K^+ channels in mammalian cell membranes.[9] Therefore, effective and reliable methods for their synthesis are desirable.



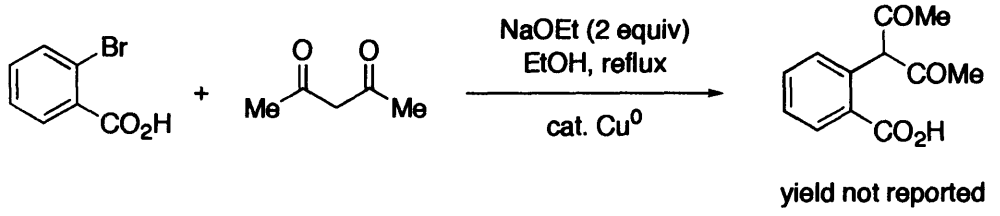
Scheme 2. Synthetic Potential of α-Aryl Malonates

Among the many methods available for the synthesis of α-aryl carbonyl compounds, a great deal of recent attention has focused on the development of the metal-catalyzed coupling of enolates with aryl halides. Research efforts in several laboratories (including our own) have led to effective

methods for the synthesis of α-aryl ketones,[10] amides,[11] and esters.[12] In particular, there have been a number of reports of palladium-catalyzed couplings of aryl halides with enolates of stabilized carbanions. Early work demonstrated that aryl iodides react with malononitrile and cyanoacetates in the presence of a palladium catalyst.[13] Other nucleophiles, such as β-ketoesters, β-diketones, and malonates were initially found to be reactive only in intramolecular cyclizatons.[14] More recently, however, bimolecular couplings with these classes of enolates have been reported.[10g-i,15] In particular, Hartwig and coworkers have systematically explored the scope and mechanism of the palladium-catalyzed arylation of malonates, cyanoacetates, and acetylacetone with a variety of aryl bromides and aryl chlorides.[10g, 15c-d] However, none of the published couplings employing palladium catalysts have been demonstrated to work in the presence of certain aromatic moieties (e.g., $ArNH_2$, ArOH, ArN(H)COR). Indeed, these types of functional groups are often problematic in other types of palladium-catalyzed reactions, whether by inhibiting the reaction by coordination to the metal center or by participating in potentially competitive coupling pathways (i.e., C-N or C-O bond formation).

While recent advances in the field of palladium chemistry have led to new, reliable reactions for the formation of carbon-carbon and carbon-heteroatom bonds, many of the cross-coupling reactions that are associated with modern palladium catalysis have long been known to be promoted or catalyzed by copper salts (such as the Ullman diaryl ether synthesis and the Goldberg amide arylation).[16] These reactions are typically conducted under comparatively harsh conditions (relative to the analogous palladium-catalyzed couplings), commonly using stoichiometric or superstoichiometric amounts of copper. In recent years, however, there has been an explosion of reports detailing vast improvements to these classical processes, allowing for the reactions to occur under significantly milder conditions using only catalytic quantities of copper. Key to the success of these improvements was the realization that inclusion of the appropriate ligand or additive into the reaction

mixture greatly accelerates the rate (presumably due to an increase in solubility of the active catalyst). Effective methods for the arylation of a broad scope of nitrogen, oxygen, carbon, sulfur, and phosphorous (among others) nucleophiles have been disclosed.[17] Interestingly, a significant enhancement in functional group compatibility is generally seen in these copper-catalyzed coupling reactions relative to the analogous palladium-catalyzed processes.



Scheme 3. An Example from Hurtley's 1929 Publication[18]

The arylation of activated methylene compounds mediated by copper salts is a well-established process, dating back to the development of the Hurtley reaction in 1929, in which *ortho*-bromobenzoic acid could be coupled to a variety of stabilized carbanions in the presence of copper powder or $Cu(OAc)_2$ (Scheme 3).[18] There have since been numerous reports of variants of this process,[19] but in general high yields are only obtained with aryl halides bearing electron-withdrawing groups or *ortho*-substituents capable of coordinating to copper. Another limitation of many of these reactions is the need to use non-volatile and/or highly toxic solvents such as DMSO or HMPA. Furthermore, it is often necessary to prepare the enolate (typically using sodium hydride or a sodium alkoxide) prior to coupling. Perhaps least attractive is that in nearly all cases stoichiometric or even excess amounts of copper salts must be used.

At the onset of our studies, some progress had been made in the development of copper-*catalyzed* arylation of stabilized enolates. In 1993, Miura and coworkers reported a copper-catalyzed arylation of malononitrile, ethyl cyanoacetate, and acetylacetone using unhindered aryl iodides.[20] Unfortunately, their system requires forcing conditions (DMSO, 120 °C) under which malonate esters are prone to decomposition (via ester hydrolysis and subsequent rapid decarboxylation, *vide infra*). Konopelski and coworkers have recently disclosed a copper-catalyzed malonate arylation protocol,[21] but the substrate scope is limited (only *ortho*-halophenols are reactive) and the relatively air-sensitive CuBr must be used. Therefore, at the time of our investigations, there were no generally applicable methods for the arylation of malonate esters that employed catalytic amounts of copper.[22]

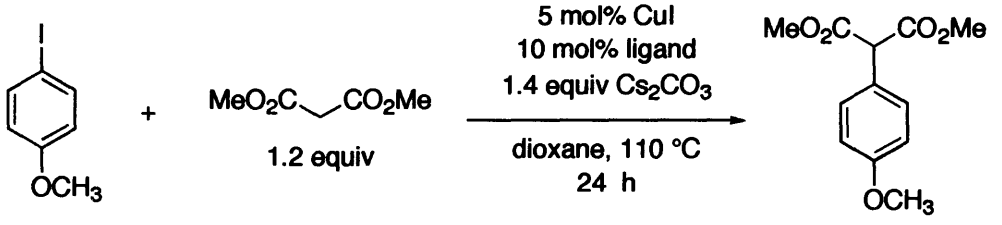
Because of the potential of α-aryl malonates as synthetic intermediates and therapeutic agents, a general and mild catalytic method for their assembly would be valuable to synthetic chemists. Given the functional group tolerance observed in many copper-catalyzed reactions, we set out to develop a process complementary to palladium-catalyzed methodologies that would provide access to a wide variety of α-aryl diesters. In addition, the identification of reaction conditions that would allow for the arylation of other β-dicarbonyl compounds and stabilized carbanions was explored.

1.2 Results and Discussion

1.2.1 Arylation of Malonic Acid Esters

We initially chose the coupling of 4-iodoanisole and dimethyl malonate as a model system upon which reaction conditions could be optimized (Scheme 4). An important early goal of our investigations was to find a base other than sodium hydride or a sodium alkoxide that would effect the

desired reaction. We found that soluble organic bases such as triethylamine, *N*-ethyldiisopropylamine (Hunig's base), and DBU (diazabicyclo[5.4.0]undec-7-ene) completely inhibited the reaction, likely by saturating the coordination sphere of copper.[23] Upon screening commonly used inorganic bases, it was found that the use of Cs_2CO_3 is crucial to the success of the reaction. K_3PO_4 was considerably less effective, while K_2CO_3 and Na_2CO_3 did not afford any reaction at all. This may be due to differences in solubility of these reagents, or possibly due to counterion effects. For example, the facilitation of nucleophilic displacements by cesium reagents (the "cesium effect") is well documented.[24]



Scheme 4. Coupling of 4-Iodoanisole and Dimethyl Malonate

Using 5 mol% CuI and in the absence of any additives, the coupling reaction does proceed to a small extent in refluxing dioxane (17% conversion of aryl iodide). This is not surprising, given the literature precedence for analogous processes stoichiometric in copper. A number of ligands commonly used in copper chemistry were screened for their ability to provide enhanced reaction rates, and in general most additives resulted in faster reactions. Of the compounds examined, 1,10-phenanthroline (Figure 2a) seemed to be optimal (interestingly, the 1,2-diaminocyclohexane-based ligands that are effective for many copper-catalyzed bond-forming processes[17] were less effective). Early on, however, we found that the use of phenanthroline resulted in issues of reproducibility; while in general conversions and yields were very high, they tended to vary from run to run.

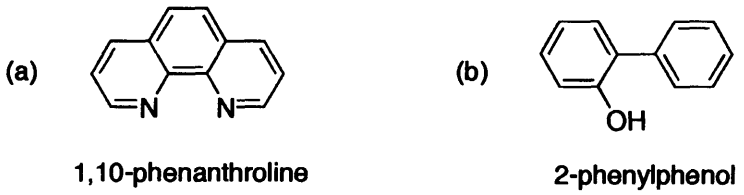
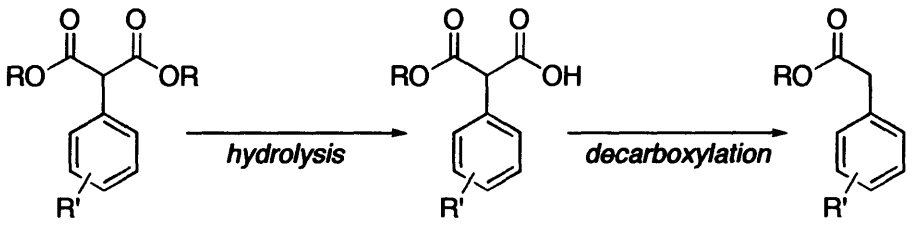


Figure 2. Effective Ligands for Copper-Catalyzed Malonate Arylation

Concurrent with these observations, we had serendipitously discovered that the inclusion of a phenol into the reaction mixture expedites the coupling significantly, even in the absence of a "ligand" for copper. The use of phenol itself resulted in a significant amount of diaryl ether formation,[25] while phenols bearing large *ortho*- substituents (^{t}Bu, ^{i}Pr) slowed the malonate arylation reaction considerably. It was found that 2-phenylphenol (*o*-hydroxybiphenyl, Figure 2b) does not hinder the desired coupling reaction from proceeding, but carbon-oxygen bond formation occurs to only a very small extent. Furthermore, from a practical standpoint, 2-phenylphenol is a practically odorless, crystalline solid that is considerably less toxic than most other phenols. In fact, its sodium salt has been used as a preservative for citrus fruits for decades,[26] and thus it is inexpensive and available from a plethora of commercial sources.

A significant problem that was encountered in our initial work was the apparent instability of the α-aryl malonate products to the reaction conditions being employed. As has been observed in the literature,[15a,f] the reaction products undergo a decarboxylation process to generate the corresponding α-aryl acetate. This most likely occurs via ester hydrolysis (with any water that may be present in the reaction) to give a malonic acid monoester intermediate (Scheme 5). Decarboxylation of the resulting acid is known to be facile, especially with heating.



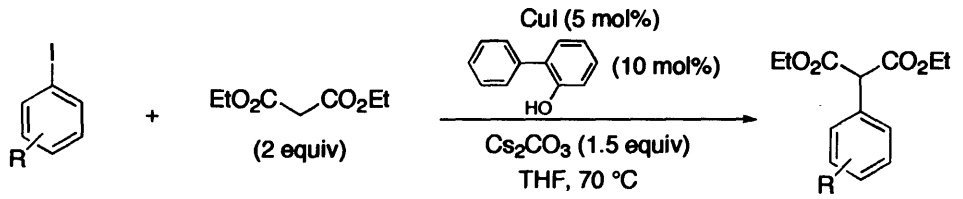
Scheme 5. Decomposition of Reaction Products

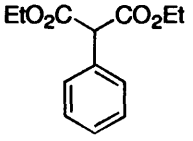
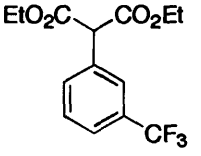
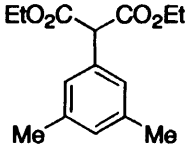
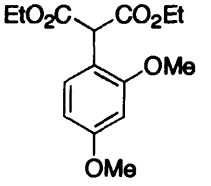
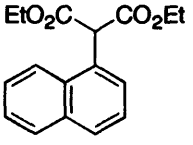
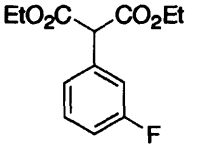
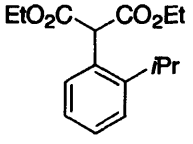
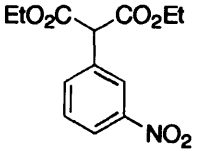
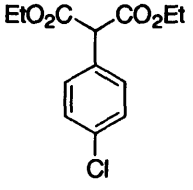
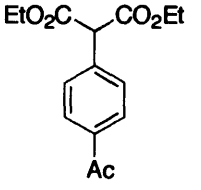
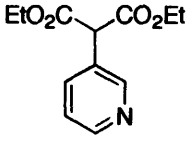
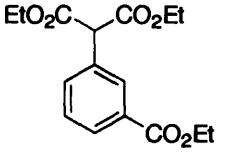
An alternative explanation could be that the cesium iodide that is produced as the reaction proceeds can induce a Krapcho decarboxylation, by which iodide ion would attack the methyl ester, releasing methyl iodide, carbon dioxide, and the α-aryl acetate.[27] It should be pointed out that such a process generally requires considerably higher temperatures and a more polar medium, and so this may not be the dominant pathway for α-aryl acetate formation. In either case, we reasoned that the products containing *ethyl* esters should be less prone to these decomposition processes than the corresponding methyl esters and yet still be synthetically useful compounds. Thus, we shifted the focus of our studies to the coupling of aryl iodides with *diethyl* malonate.

Gratifyingly, reactions employing diethyl malonate as the nucleophile proceed smoothly in refluxing toluene to afford the corresponding α-aryl diesters. However, product decomposition is still problematic under these conditions, with 5-10% decarboxylated product being isolated in cases of electron-neutral aryl iodides. Even more troubling was that this decomposition was considerably more severe in couplings of electron-deficient aryl iodides, likely due to an increase in the electrophilicity of the ester carbonyl groups in these cases. We surmised that for the malonate arylation process to be synthetically useful, further modifications to the reaction needed to be made.

After some brief optimization studies, we found that by simply conducting the reaction at lower temperatures, excessive product decomposition can be circumvented. However, due to the lower reaction rates that naturally result from this modification, we found it necessary to use two full equivalents of diethyl malonate for the reaction to reach completion in an acceptable time period. Thus, by heating a mixture of aryl iodide, Cs_2CO_3 (1.5 equivalents), and diethyl malonate (2 equivalents) in THF (70 °C) in the presence of catalytic amounts of copper (I) iodide and 2-phenylphenol under an inert atmosphere, the corresponding α-aryl malonate can be obtained in good to excellent yields (Table 1). Interestingly, using dimethyl malonate as the nucleophile under these optimized conditions resulted in slower reaction rates, presumably due to a decrease in the solubility of the copper enolate species that may be catalytically active. Moreover, we found that the use of di-*tert*-butyl malonate also resulted in slower reactions, an observation that may be attributable to steric effects.

Table 1. Arylation of Diethyl Malonate



entry	time	product	yield[a]	entry	time	product	yield[a]
1	24 h		91%	7	24 h		89%
2	27 h		95%	8	30 h		90%
3	30 h		98%	9	24 h		87%
4	31 h		84%[b]	10	24 h		84%
5	24 h		94%	11	24 h		86%
6	26.5 h		73%[c]	12	24 h		86%

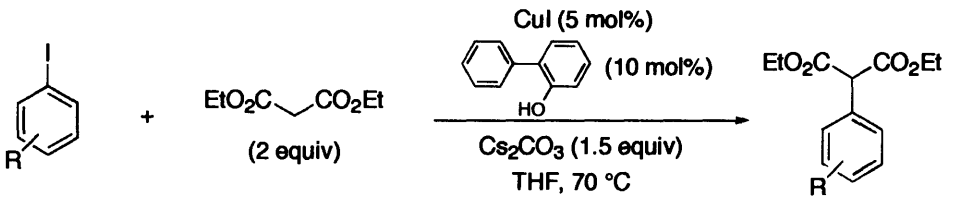
continued on next page...

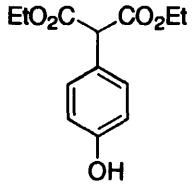
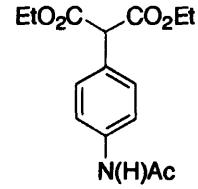
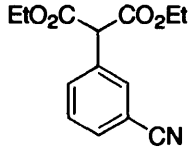
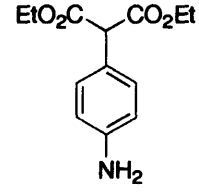
[a] Isolated yields are the average of two runs and are estimated to be >95% pure by ^{1}H NMR and GC analysis. All previously unknown compounds gave satisfactory ^{1}H NMR, ^{13}C NMR, IR, and combustion analysis data.

[b] Using 10 mol % CuI and 15 mol % 2-phenylphenol

[c] Reaction went to only 90% conversion in indicated time

Table 1 (continued)



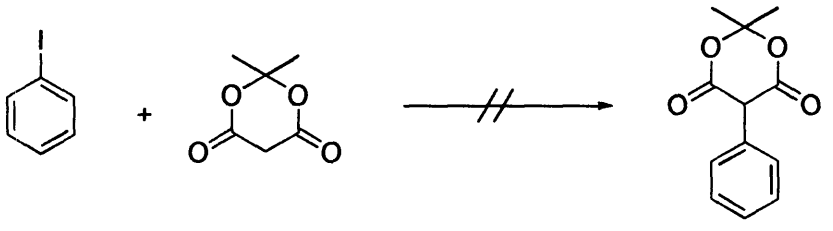
entry	time	product	yield[a]	entry	time	product	yield[a]
continued from previous page							
13	29 h		80%[d]	15	29 h		75%[e]
14	24 h		61%	16	29 h		70%

[a] Isolated yields are the average of two runs and are estimated to be >95% pure by ^1H NMR and GC analysis. All previously unknown compounds gave satisfactory ^1H NMR, ^{13}C NMR, IR, and combustion analysis data.
[d] Using 3 equiv diethyl malonate and 3.5 equiv Cs_2CO_3
[e] Using 3 equiv diethyl malonate and 2.5 equiv Cs_2CO_3

The malonate arylation proceeds smoothly using a diverse array of aryl iodides, including heterocyclic (Entry 6) and electron-rich (Entry 8) iodides. Even the sterically hindered 2-iodoisopropylbenzene (Entry 4) can be converted to the desired product, although 10 mol% CuI and 15 mol% 2-phenylphenol are required to facilitate complete conversion. Importantly, we have found that functional groups expected to be problematic under palladium catalysis (when using basic reaction conditions such as these) are in general well-tolerated using this catalyst system (Entries 13, 15, 16); it would be expected to be difficult to access such products using palladium without appropriate protecting groups. We found that the yields were slightly higher in the cases of Entries 13 and 15 when 3 equivalents of diethyl malonate were used to suppress competing processes, presumably carbon-heteroatom bond formation.

The method is not without its drawbacks, however. For example, aryl bromides are essentially unreactive under these conditions (the use of bromobenzene in place of iodobenzene afforded < 2% of the α-aryl malonate). Additionally, substrates containing certain functional groups in the *ortho-* position (e.g., $-NO_2$, -OH, $-NH_2$) are problematic, possibly because an unreactive copper complex is formed. This is in stark contrast to related processes that require these types of substitution patterns. Furthermore, in select cases, ligand arylation (i.e., carbon-oxygen bond formation) competes with the desired reaction thereby decreasing the overall yield. Lastly, despite the pains taken to avoid product decomposition, α-aryl acetate formation is not completely inhibited; as mentioned above, products having electron-withdrawing substituents on the aromatic ring are more prone to decarboxylation.[28]

It is unclear as to exactly what role the phenol additive plays in the reaction.[29] While it is likely that the catalytically active species is a copper (I) enolate, as proposed by Setsune,[19a,b,e] it is debatable as to whether or not a copper phenoxide species is involved in the chemistry. An alternative explanation is that the phenol acts as a soluble "proton shuttle," i.e., the phenoxide anion serves as the actual base involved in enolate formation. It should be pointed out that when the optimized reaction conditions were applied to the attempted arylation of the cyclic isopropylidene malonate (Meldrum's acid, Scheme 6), 1,3-cyclopentanedione, and 1,3-cyclohexanedione, no desired products were observed. These observations suggest that a bidentate binding of the enolate through the oxygen atoms to copper may be required.



Scheme 6. Attempted Arylation of Meldrum's Acid

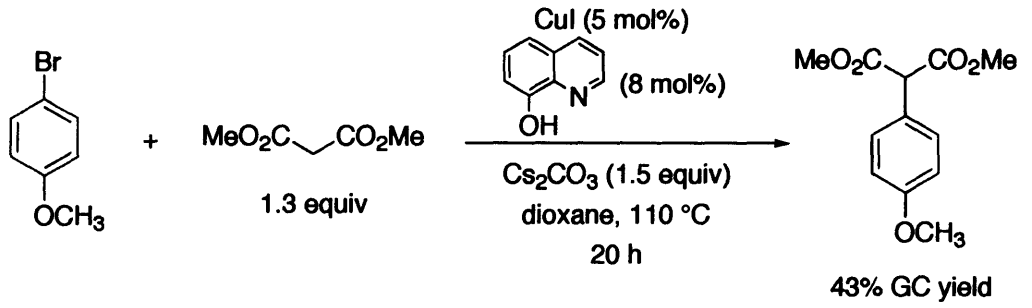
1.2.2 Coupling of Malonate Esters with Aryl Bromides

It is a generally accepted premise that in the direct displacement of electron-deficient aryl halides with nucleophiles (nucleophilic aromatic substitution), the reactivity of the aryl halide component decreases as the halogen atom becomes heavier (i.e., ArF > ArCl > ArBr > ArI). This trend has been attributed to an increase of electron density at the site of attack due to the decreasing electronegativity of the halogen.[30] In contrast, most metal-catalyzed arylation reactions exhibit the opposite trend in reactivity (ArI > ArBr > ArCl >> ArF), mirroring the increasing strengths of the carbon-halogen bonds.[31] Indeed, with the exception of a few reported reactions of aryl chlorides,[32] arylation reactions employing copper reagents or catalysts are in general only applicable to aryl iodides and, to a lesser extent, aryl bromides. Given that aryl bromides are in general more readily available from commercial sources than the corresponding iodides, we explored the possibility of using aryl bromides in malonate arylation reactions.

As mentioned earlier, under the optimized conditions developed for the reaction of aryl iodides with diethyl malonate we observed no conversions of aryl bromides to the desired products. The use of phenols other than 2-phenylphenol afforded the same result. Employing ligands such as 1,10-phenanthroline or aliphatic 1,2-diamines afforded only small conversions (< 10%) of the aryl bromide substrates examined.

In studies subsequent to our work with aryl iodides, we discovered that 8-hydroxyquinoline, a ligand previously found to be effective for copper-catalyzed carbon-oxygen bond formation,[33] promoted the coupling of dimethyl malonate with 4-bromoanisole in refluxing toluene, albeit to a limited extent (Scheme 7). The reaction could be pushed to complete conversion using more electron-deficient aryl bromides, although product decarboxylation is rampant at these temperatures (*vide supra*). It should be noted that 8-hydroxyquinoline is also a competent ligand for reactions of

aryl iodides with diethyl malonate. Unfortunately, beyond these initial results, no further work was done to optimize conditions for couplings with aryl bromides.

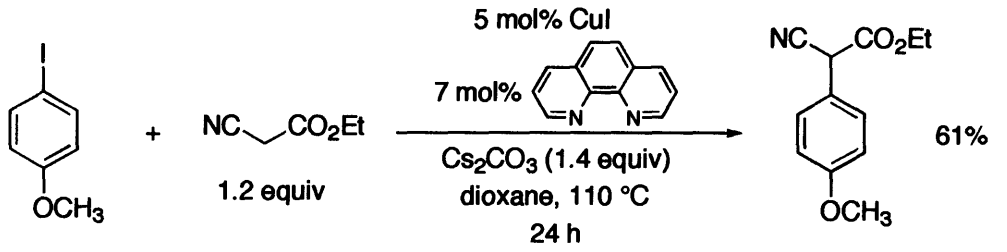


Scheme 7. Coupling Reaction of Malonate Esters and Aryl Bromides

1.2.3 Arylation of Other Stabilized Carbanions

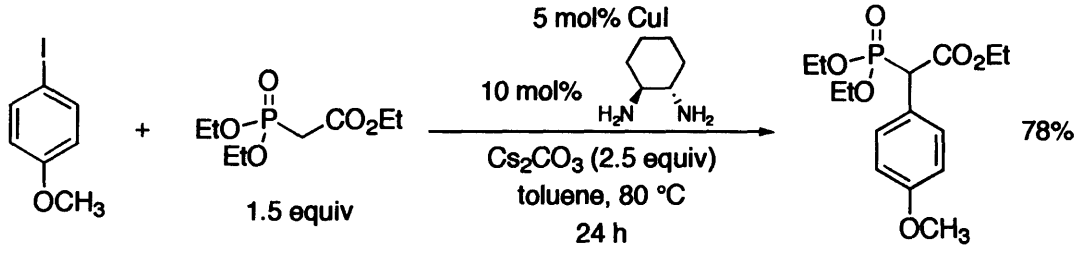
In addition to the arylation of malonate esters, we also briefly explored arylations of other β-dicarbonyl compounds as well as some simple ketones. An effective route to the products derived from these couplings would add to the potential diversity of heterocycles and synthetic intermediates available to a synthetic chemist and thus would be extremely useful. As mentioned in the introduction, examples of these types of couplings abound in the literature. However, a lack of overall generality leaves room for significant improvements in this field.

While our efforts in these types of couplings were relatively perfunctory, we did obtain some promising results. For example, we found that the use of 1,10-phenanthroline as a ligand allows for the use of ethyl cyanoacetate as a nucleophile in a copper-catalyzed arylation reaction (Scheme 8).



Scheme 8. Arylation of Ethyl Cyanoacetate

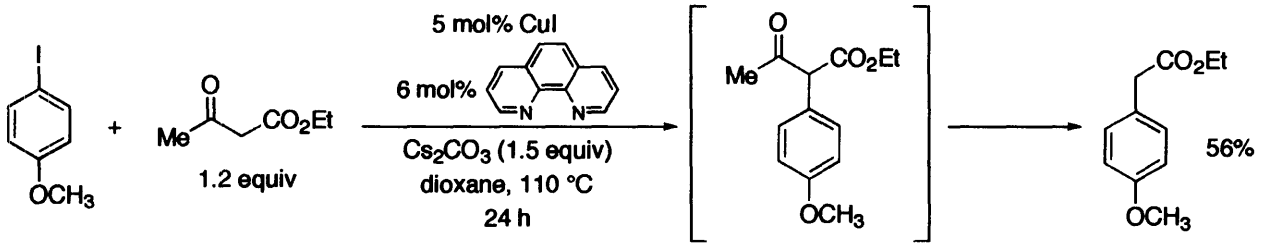
We also conducted preliminary studies on the copper-catalyzed arylation of phosphinyl-stabilized enolates. These carbanions have been previously utilized in similar coupling reactions, although stoichiometric amounts of copper are typically required.[34] We found that the use of *trans*-1,2-diaminocyclohexane as a ligand allows for the catalytic arylation of triethyl phosphonoacetate (Scheme 9), a nucleophile commonly used in Horner-Wadsworth-Emmons olefination reactions.[35] One can envision the reaction of arylated products such as these with aldehydes to access highly substituted styrene derivatives.[36]



Scheme 9. Arylation of Triethyl Phosphonoacetate

An interesting observation was made when we attempted to employ β-ketoesters as nucleophiles in coupling reactions. Instead of the expected α-arylated product, the dominant species pro-

duced was the α-aryl acetate (Scheme 10). Apparently, the initially-formed coupling product undergoes a retro-Claisen deacylation under the reaction conditions.



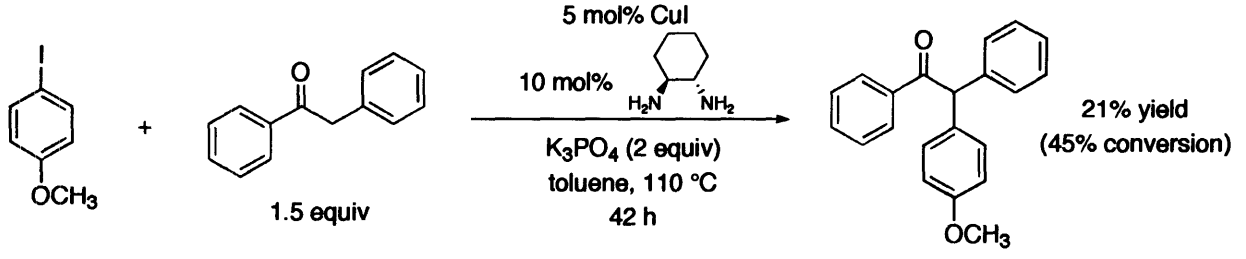
Scheme 10. Formation of α-Aryl Acetates in the Arylation of Ethyl Acetoacetate

Such a phenomenon has been observed in the literature.[15b, 18, 37] Continued optimization of this process revealed that ligands seem to be unnecessary for this coupling, with no variation in GC yields observed between reactions run using only CuI and reactions employing CuI in concert with an additive. Moreover, we found that this process could be conducted under more mild conditions than those used initially. For example, conducting the coupling in refluxing alcohols (*tert*-butanol in particular, due to minimal transesterification) resulted in faster reactions. However, continued work on this process was discontinued before a synthetically useful method could be developed.

In contrast to the smooth α-arylation of simple ketones (i.e., $pK_a > 20$) that takes place in the presence of palladium catalysts, copper salts have been to date ineffective at promoting this process. This may be explained by considering the postulated mechanisms for these reactions. It is accepted that in palladium-catalyzed cross-coupling reactions, oxidative addition of the aryl halide substrate affords an arylpalladium (II) intermediate. This process is for all intents and purposes irreversible, giving a relatively stable species that is in many cases isolable.[38] In the ketone arylation reaction, this palladium (II) species reacts with a ketone enolate to give an arylpalladium enolate; subsequent reductive elimination affords the product.[10h] Given that relatively weak bases can be used in this

process, coordination of the ketone to the arylpalladium (II) halide species likely facilitates deprotonation. While the mechanisms of copper-catalyzed coupling reactions are less well-understood, a common hypothesis is that oxidative addition of an aryl halide to a copper (I)-nucleophile complex affords an unstable copper (III) intermediate, followed by reductive elimination of the coupled product.[16] Since copper (I) is a poor Lewis acid, ketone enolate formation is likely not assisted by coordination (as in the palladium chemistry) and thus only very low concentrations of the requisite copper (I) enolate would be expected to result.

Indeed, all of our attempts to couple ketones such as acetophenone and cyclohexanone with aryl halides were unsuccessful. However, if ketones that are considerably more acidic are used, unassisted enolate formation should occur to a greater extent, thus making the coupling reaction more feasible. We found that 2-phenylacetophenone (deoxybenzoin, pK_a (DMSO) = 17.7[39]) reacts with aryl iodides in the presence of CuI and *trans*-1,2-diaminocyclohexane to afford a small amount of the desired product (Scheme 11). While the reaction proceeds very slowly in the presence of catalytic copper, this result demonstrates the feasibility of the arylation of other enolates.



Scheme 11. Arylation of Deoxybenzoin

1.3 Conclusions

We have developed a mild, general catalytic system for the synthesis of α-aryl malonates. Aryl iodides bearing a variety of functional groups can be effectively coupled to diethyl malonate in

high yields using inexpensive and widely available reagents, making this a superior method to those previously described that employ copper reagents or catalysts. The functional group tolerance of the process described makes it complementary to the analogous palladium-catalyzed couplings. Importantly, a set of mild reaction conditions has been developed that minimize product decomposition, a problem that had not been addressed previously in the literature.

The use of aryl bromides as coupling partners has also been investigated, although considerable work remains in this case to achieve synthetic utility. We have identified a promising lead (8-hydroxyquinoline) for ligands effective for this class of reaction.

We have also surveyed the arylation of other classes of stabilized carbanions, such as β-keto, β-phosphono, and β-cyano esters, as well as acidic "simple" ketones. While reaction conditions for these classes of nucleophiles have not been fully optimized, promising results have been obtained in all cases.

1.4 Experimental Procedures

General Considerations: All reactions were carried out in oven-dried glassware that was cooled under argon. THF and toluene were purchased from J. T. Baker in CYCLE-TAINER® solvent delivery kegs, which were vigorously purged with argon for two hours and further purified by passing through two packed columns of neutral alumina (THF) or one column of neutral alumina and one column of copper (II) oxide (toluene) under argon pressure. Anhydrous 1,4-dioxane was purchased from Aldrich and was used as received. Copper (I) iodide (98%) was purchased from Strem Chemical Company. Cesium carbonate was purchased from both Chemetall and Strem, and the bulk of the reagent was stored under nitrogen in a Vacuum Atmospheres glovebox. Small portions (5-10 g) were removed from the glovebox as needed and stored in a benchtop dessicator in glass vials. Po-

tassium phosphate was purchased from Fluka and was used as received. 2-Phenylphenol was purchased from Fluka and was recrystallized from hexanes prior to use. 4-Iodoaniline (Table 1, Entry 16) was purchased from Aldrich and was recrystallized from hexanes prior to use. 4-Iodoacetanilide (Table 1, Entry 15) was prepared by treatment of a CH_2Cl_2 solution of 4-iodoaniline with acetyl chloride in the presence of triethylamine. All other reagents were obtained from commercial sources and were used as received. Thin layer chromatography was performed using EM Science silica gel 60 F_{254} plates; after development, the plates were stained using a solution prepared from 2 g $KMnO_4$ and 12g Na_2CO_3 in 200 mL H_2O. Column chromatography was done using either Silicycle or EM Science silica gel (230-400 mesh). Melting points were obtained using a Mel-Temp apparatus (Laboratory Devices) and are uncorrected. IR spectra for all previously unreported compounds were obtained by placing the neat sample on the DiComp probe of an ASI ReactIR 1000 instrument. Elemental analyses were performed by Atlantic Microlabs, Inc., Norcross, GA. ^{1}H NMR and ^{13}C NMR were obtained using a Varian 300 MHz spectrometer, with chemical shifts referenced to tetramethylsilane (TMS, internal standard) or to residual protons in the deuterated solvent. Gas chromatographic analysis was performed on a Hewlett Packard 6890 instrument equipped with a FID detector and a Hewlett Packard HP-1 (10 m x 0.2 mm i.d.) capillary column. Mass spectra were obtained using a Hewlett Packard Model G1800B GCD. All yields reported in Table 1 refer to isolated yields (average of two runs) of products estimated to be >95% pure as determined by ^{1}H NMR and GC analysis. The yields reported below may differ from those in Table 1, as they refer to the isolated yields of the single runs whose products were submitted for elemental analysis. In addition to ^{1}H NMR and ^{13}C NMR, all previously unreported compounds were further characterized by elemental analysis and IR. Those compounds described in the literature were positively identified by comparing their ^{1}H NMR spectra to previously reported data.

General Procedure for Malonate Arylation: An oven-dried Schlenk tube equipped with a magnetic stirbar and a Teflon stopcock was evacuated while hot and allowed to cool under argon. The tube was charged sequentially with CuI (9.6 mg, 5.0 mol %), 2-phenylphenol (17.1 mg, 10.0 mol %), Cs_2CO_3 (0.490 g, 1.50 mmol), and the aryl iodide (1.00 mmol), if a solid. The tube was evacuated and backfilled with argon (3 times), and the Teflon stopcock was replaced with a rubber septum. The aryl iodide (if a liquid) was added volumetrically (1.00 mmol), followed by diethyl malonate (304 μL, 2.00 mmol) and anhydrous THF (1.0 mL). The septum was replaced by the Teflon stopcock under a positive pressure of argon, and the sealed tube was placed in an oil bath preheated to 70 °C. After the designated time period, the reaction was allowed to cool to room temperature and was then partitioned between ethyl acetate (20 mL) and saturated aqueous NH_4Cl (10 mL). The organic portion was dried (Na_2SO_4), filtered through a plug of Celite, and concentrated on a rotary evaporator. The material thus obtained was purified by silica gel chromatography to give the product α-aryl malonate.

Diethyl phenylmalonate (Table 1, Entry 1):[40] Reaction time 24 h; silica gel chromatography (60:40 toluene:CH_2Cl_2; $R_f = 0.29$) afforded a colorless oil (92%).

Diethyl (3,5-dimethylphenyl)malonate (Table 1, Entry 2): Reaction time 27 h; silica gel chromatography (60:40 toluene:CH_2Cl_2; $R_f = 0.29$) afforded a colorless oil (96%). ^1H NMR ($CDCl_3$) δ 1.28 (t, $J = 7.2$ Hz, 6H), 2.32 (s, 6H), 4.22 (m, 4H), 4.55 (s, H), 6.98 (s, 1H), 7.01 (s, 2H). ^{13}C NMR ($CDCl_3$) δ 14.14, 21.39, 57.93, 61.83, 127.09, 130.05, 132.67, 138.24, 168.47. Calc. For $C_{15}H_{20}O_4$: C 68.16, H 7.63; Found: C 68.45, H 7.80. IR (neat) ν (cm^{-1}) 1733, 1754.

Diethyl (1-napthyl)malonate (Table 1, Entry 3):[41] Reaction time 30 h; silica gel chromatography (95:5 toluene:acetone; $R_f = 0.60$) afforded a colorless to pale-yellow solid (98%), mp = 60-62 °C.

Diethyl (2-isopropylphenyl)malonate (Table 1, Entry 4): Reaction time 31 h, using 10 mol% CuI and 15 mol% 2-phenylphenol; silica gel chromatography (80:20 hexanes:ethyl acetate; $R_f = 0.43$) afforded a pale yellow oil (86%). ^{1}H NMR ($CDCl_3$) δ 1.26 (d, $J = 6.9$ Hz, 6H), 1.27 (t, $J = 7.2$ Hz, 6H), 3.13 (septet, $J = 6.9$ Hz, 1H), 4.23 (m, 4H), 5.01 (s, 1H), 7.19-7.42 (m, 5H aromatic). ^{13}C NMR ($CDCl_3$) δ 14.19, 23.87, 29.49, 53.69, 61.91, 125.69, 126.11, 128.59, 129.44, 130.40, 146.95, 168.85. Calc. For $C_{16}H_{22}O_4$: C 69.04, H 7.97; Found: C 69.25, H 8.05. IR (neat) ν (cm^{-1}) 1733, 1754.

Diethyl (4-chlorophenyl)malonate (Table 1, Entry 5):[41] Reaction time 24 h; silica gel chromatography (60:35:5 toluene:hexanes:acetone; $R_f = 0.53$) afforded a colorless oil (97%).

Diethyl (3-pyridyl)malonate (Table 1, Entry 6): Reaction time 26.5 h; GC analysis indicated that in this time the reaction had only proceeded to 90% conversion. Silica gel chromatography (1:1 hexanes:ethyl acetate; $R_f = 0.27$) afforded a pale yellow oil (71%). Note: chromatography and analysis should be performed as quickly as possible following reaction workup, as the product slowly decomposes. ^{1}H NMR ($CDCl_3$) δ 1.28 (t, $J = 7.2$ Hz, 6H), 4.24 (m, 4H), 4.63 (s, 1H), 7.33 (m, 1H, aromatic), 7.86 (m, 1H aromatic), 8.59 (m, 2H, aromatic). ^{13}C NMR ($CDCl_3$) δ 14.10, 55.57, 62.33, 123.63, 129.05, 137.00, 149.66, 150.40, 167.57. Calc. For $C_{12}H_{15}NO_4$: C 60.75, H. 6.37; Found: C 60.51, H: 6.35. IR (neat) ν (cm^{-1}) 1731.

Diethyl (3-trifluoromethylphenyl)malonate (Table 1, Entry 7): Reaction time 24 h; silica gel chromatography (1:1:0.03 toluene:hexanes:acetone; $R_f = 0.39$) afforded a colorless oil (88%). ^{1}H NMR ($CDCl_3$) δ 1.28 (t, $J = 7.2$ Hz, 6H), 4.24 (m, 4H), 4.67 (s, H), 7.48-7.68 (m, 5H aromatic). ^{13}C NMR ($CDCl_3$) δ 14.01, 57.74, 62.23, 124.08 (q, $J = 272.3$ Hz), 125.22 (q, $J = 3.8$ Hz), 126.42 (q, $J = 3.9$ Hz), 129.18, 131.01 (q, $J = 32.4$ Hz), 132.97, 133.90, 167.66. Calc. For $C_{14}H_{15}O_4F_3$: C 55.26, H 4.97, F 18.73; Found: C 55.56, H 4.96, F 18.51. IR (neat) ν (cm^{-1}) 1733.

Diethyl (2,4-dimethoxyphenyl)malonate (Table 1, Entry 8): Reaction time 30 h; silica gel chromatography (75:25 hexanes:ethyl acetate; $R_f = 0.38$) afforded a pale yellow solid (91%), mp = 58.5-59.5 °C. ^{1}H NMR ($CDCl_3$) δ 1.27 (t, J = 7.2 Hz, 6H), 3.797 (s, 3H), 3.804 (s, 3H), 4.22 (dq, J = 2.1Hz, 7.2 Hz, 4H), 5.02 (s, H), 6.46 - 6.52 (dt, J = 2.4 Hz, 8.1 Hz, 2H aromatic), 7.26 (d, J = 8.1 Hz, 1H aromatic). ^{13}C NMR ($CDCl_3$) δ 14.21, 50.73, 55.48, 55.75, 61.66, 98.70, 104.63, 114.44, 130.17, 158.05, 160.85, 169.01. Calc. For $C_{15}H_{20}O_6$: C 60.80, H 6.80; Found: C 60.86, H 6.81. IR (neat) ν (cm^{-1}) 1513, 1725, 1748.

Diethyl (3-fluorophenyl)malonate (Table 1, Entry 9): Reaction time 24 h; silica gel chromatography (1:1:0.03 toluene:hexanes:acetone; $R_f = 0.38$) afforded a colorless oil (89%). ^{1}H NMR ($CDCl_3$) δ 1.28 (t, J = 7.2 Hz, 6H), 4.23 (dq, J = 3.3 Hz, 7.2 Hz, 4H), 4.61 (s, 1H), 7.01-7.08 (m, 1H aromatic), 7.16-7.20 (m, 2H aromatic), 7.30-7.37 (m, 1H aromatic). ^{13}C NMR ($CDCl_3$) δ 14.14, 57.70, 62.16, 115.42 (d, J = 21.3 Hz), 116.59 (d, J = 22.7 Hz), 125.26 (d, J = 3.0 Hz), 130.16 (d, J = 8.4 Hz), 135.07 (d, J = 8.1 Hz), 162.84 (d, J = 246.3 Hz), 167.82. Calc. For $C_{13}H_{15}O_4F$: C 61.41, H 5.95, F 7.47; Found: C 61.18, H 5.91, F 7.28. IR (neat) ν (cm^{-1}) 1731.

Diethyl (3-nitrophenyl)malonate (Table 1, Entry 10): Reaction time 24 h; silica gel chromatography (80:20 hexanes:ethyl acetate; $R_f = 0.26$) afforded a pale yellow oil (83%). ^{1}H NMR ($CDCl_3$) δ 1.29 (t, J = 7.2 Hz, 6H), 4.25 (m, 4H), 4.73 (s, 1H), 7.57 (m, 1H aromatic), 7.79 (m, 1H aromatic), 8.22 (m, 1H aromatic), 8.31 (m, 1H aromatic). ^{13}C NMR ($CDCl_3$) δ 14.12, 57.49, 62.50, 123.44, 124.76, 129.66, 134.80, 135.75, 148.38, 167.32. Calc. For $C_{13}H_{15}NO_6$: C 55.51, H 5.38; Found: C 55.56, H 5.46. IR (neat) ν (cm^{-1}) 1530, 1733.

Diethyl (4-acetylphenyl)malonate (Table 1, Entry 11):[40] Reaction time 24 h; silica gel chromatography (70:30 hexanes:EtOAc; $R_f = 0.35$) afforded a yellow oil (87%).

Diethyl (3-carboethoxyphenyl)malonate (Table 1, Entry 12): Reaction time 24 h; silica gel chromatography (7:3 hexanes:diethyl ether; $R_f = 0.34$) afforded a colorless oil (86%). ^{1}H NMR ($CDCl_3$) δ 1.28 (t, $J = 7.2$ Hz, 6H), 1.40 (t, $J = 7.2$ Hz, 3H), 4.23 (dq, $J = 3.0$ Hz, 7.2 Hz, 4H), 4.38 (q, $J = 7.2$ Hz, 2H), 4.68 (s, 1H), 7.46 (m, 1H aromatic), 7.65 (m, 1H aromatic), 8.0-8.1 (m, 2H aromatic). ^{13}C NMR ($CDCl_3$) δ 14.09, 14.42, 57.81, 61.19, 62.08, 128.77, 129.52, 130.66, 130.97, 133.30, 133.76, 166.25, 167.90. Calc. For $C_{16}H_{20}O_6$: C 62.33, H 6.54; Found: C 62.12, H 6.53. IR (neat) ν (cm^{-1}) 1719.

Diethyl (4-hydroxyphenyl)malonate (Table 1, Entry 13): Reaction time 29 h, using 3 equivalents of diethyl malonate and 3.5 equivalents of cesium carbonate; silica gel chromatography (65:35 hexanes:ethyl acetate; $R_f = 0.30$) afforded a colorless oil which crystallized upon standing (76%), mp = 66-68 °C. ^{1}H NMR ($CDCl_3$) δ 1.27 (t, $J = 7.2$ Hz, 6H), 4.22 (m, 4H), 4.56 (s, 1H), 5.71 (s, 1H, chemical shift dependent upon NMR sample concentration), 6.76 (*AB*, J_{AB} = 2.1 Hz, 8.4 Hz, 2H aromatic), 7.24 (*AB*, J_{AB} = 2.1 Hz, 8.4 Hz, 2H aromatic). ^{13}C NMR ($CDCl_3$) δ 14.19, 57.35, 62.12, 115.81, 124.78, 130.69, 156.03, 168.95. Calc. For $C_{13}H_{16}O_5$: C 61.90, H 6.39; Found: C 61.84, H 6.36. IR (neat) ν (cm^{-1}) 1519, 1698, 1737, 3379.

Diethyl (3-cyanophenyl)malonate (Table 1, Entry 14): Reaction time 24 h; silica gel chromatography (80:20 hexanes:ethyl acetate;$R_f = 0.29$) afforded a colorless oil (61%). ^{1}H NMR ($CDCl_3$) δ 1.28 (t, $J = 7.2$ Hz, 6H), 4.24 (m, 4H), 4.64 (s, 1H), 7.46-7.52 (m, 1H aromatic), 7.63-7.69 (m, 1H aromatic), 7.73-7.75 (m, 1H aromatic). ^{13}C NMR ($CDCl_3$) δ 14.04, 57.34, 62.35, 112.82, 118.48, 129.48, 131.97, 133.10, 134.03, 134.31, 167.30. Calc. For $C_{14}H_{15}NO_4$: C 64.36, H 5.79; Found C 64.19, H 5.76. IR (neat) ν (cm^{-1}) 1731, 2232.

Diethyl (4-(*N*-acetyl)-aminophenyl)malonate (Table 1, Entry 15): Reaction time 29 h, using 3 equivalents of diethyl malonate and 2.5 equivalents of cesium carbonate; silica gel chromatography

(crude product loaded onto column as solution in CH_2Cl_2, column eluted with diethyl ether; R_f = 0.24) afforded a colorless solid (78%), mp = 141-144 °C. ^{1}H NMR ($CDCl_3$) δ 1.26 (t, J = 7.2 Hz, 6H), 2.15 (s, 3H), 4.21 (m, 4H), 4.58 (s, 1H), 7.31 (s, 1H, chemical shift dependent upon NMR sample concentration), 7.33 (*AB*, J_{AB} = 7.2 Hz, 2H aromatic), 7.48 (*AB*, J_{AB} = 7.2 Hz, 2H aromatic). ^{13}C NMR ($CDCl_3$) δ 14.21, 16.60, 57.56, 62.08, 120.09, 128.60, 130.07, 138.15, 168.46, 172.64. Calc. For $C_{15}H_{19}NO_5$: C 61.42, H 6.53; Found: C 61.39, H 6.53. IR (neat) ν (cm^{-1}) 1663, 1725, 1744, 3263, 3298.

Diethyl (4-aminophenyl)malonate (Table 1, Entry 16): Reaction time 29 h; silica gel chromatography (3:1 ether:hexanes;R_f = 0.30) afforded a pale yellow oil (69%). Note: chromatography and analysis should be performed as quickly as possible following reaction workup, as the product slowly decomposes. ^{1}H NMR ($CDCl_3$) δ 1.26 (t, J = 7.2 Hz, 6H), 3.70 (s, 2H, chemical shift depends on NMR sample concentration), 4.21 (m, 4H), 4.50 (s, 1H), 6.67 (*AB*, J_{AB} = 2.1 Hz, 6.5 Hz, 2H aromatic), 7.19 (*AB*, J_{AB} = 2.1 Hz, 6.5 Hz). ^{13}C NMR ($CDCl_3$) δ 14.17, 57.30, 61.77, 115.20, 122.60, 130.31, 146.62, 168.85. Calc. For $C_{13}H_{17}NO_4$: C 62.14, H 6.82; Found C 62.17, H 6.88. IR (neat) n (cm^{-1}) 1519, 1625, 1723, 3228, 3379, 3469.

Procedure for the Coupling of Malonate Esters to Aryl Bromides (Scheme 7): An oven-dried Schlenk tube was charged with CuI (10.8 mg, 5.5 mol%), 8-hydroxyquinoline (12.1 mg, 8.0 mol%), and Cs_2CO_3 (460 mg, 1.41 mmol). The tube was evacuated and backfilled with argon (3 times), and 4-bromoanisole (0.13 mL, 1.0 mmol), dimethyl malonate (0.15 mL, 1.3 mmol), and anhydrous dioxane (1.0 mL) were added. The tube was sealed under argon and was placed in an oil bath preheated to 110 °C. After heating for 19.5 h, the mixture was allowed to cool, was treated with *n*-undecane (106 μL, 0.50 mmol, as an internal GC standard), and was partitioned between EtOAc and saturated NH_4Cl (aq). GC analysis indicated a 43% yield of the coupled product.

Ethyl (4-methoxyphenyl)cyanoacetate (Scheme 8):[42] An oven-dried Schlenk tube was charged with CuI (9.6 mg, 5.1 mol%), 1,10-phenanthroline (11.8 mg, 6.7 mol%), Cs_2CO_3 (465 mg, 1.43 mmol), and 4-iodoanisole (230 mg, 0.98 mmol). The tube was evacuated and backfilled with argon (3 times), and ethyl cyanoacetate (0.13 mL, 1.2 mmol) and anhydrous dioxane (1.0 mL) were added. The tube was sealed under argon and was placed in an oil bath preheated to 110 °C. After heating for 20 h, the reaction mixture was allowed to cool and was partitioned between EtOAc and saturated NH_4Cl (aq). The organic layer was dried ($MgSO_4$), filtered, and concentrated via rotary evaporator. The crude material was purified by silica gel chromatography (60:40 hexanes:EtOAc, $R_f = 0.47$) to give the product as a yellow oil (132 mg, 61%).

Triethyl (4-methoxyphenyl)phosphonoacetate (Scheme 9):[34a] A screw-cap test tube was charged with CuI (9.6 mg, 5.0 mol%), 4-iodoanisole (234 mg, 1.00 mmol), and Cs_2CO_3 (813 mg, 2.50 mmol). A Teflon septum cap was applied, and the tube was evacuated and backfilled with argon (3 times). *trans*-1,2-Diaminocyclohexane (12 μL, 10.0 mol%, filtered through a plug of alumina immediately prior to use), triethyl phosphonoacetate (298 μL, 1.50 mmol), and anhydrous toluene (2.0 mL) were added. The resulting mixture was placed in an oil bath preheated to 80 °C. After 24 h, the reaction was allowed to cool and was partitioned between diethyl ether (~20 mL) and 1 N HCl (aq). The aqueous layer was extracted with ether, and the combined organics were washed with brine, dried ($MgSO_4$), filtered, and concentrated via rotary evaporator. The crude oil was purified by silica gel chromatography (ether as eluent; $R_f = 0.31$) to give the product as a colorless oil (257 mg, 78%).

Ethyl (4-methyoxyphenyl)acetate (Scheme 10):[43] An oven-dried Schlenk tube was charged with CuI (9.2 mg, 5.0 mol%), 1,10-phenanthroline (9.8 mg, 5.6 mol%), Cs_2CO_3 (474 mg, 1.45 mmol), and 4-iodoanisole (226 mg, 0.97 mmol). The tube was evacuated and backfilled with argon (3

times), and ethyl acetoacetate (0.15 mL, 1.2 mmol) and anhydrous dioxane (1.0 mL) were added. The tube was sealed under argon and was placed in an oil bath preheated to 110 °C. After heating for 18 h, the reaction mixture was allowed to cool and was partitioned between EtOAc and saturated NH_4Cl (aq). The organic layer was dried ($MgSO_4$), filtered, and concentrated via rotary evaporator. The crude material was purified by silica gel chromatography (85:15 hexanes:EtOAc, $R_f = 0.49$) to give the product as a colorless oil (106 mg, 56%).

2-Phenyl-2-(4-methoxyphenyl)acetophenone (Scheme 11):[44] An oven-dried Schlenk tube was charged with CuI (9.4 mg, 4.9 mol%), K_3PO_4 (435 mg, 2.05 mmol), 4-iodoanisole (235 mg, 1.00 mmol), and deoxybenzoin (295 mg, 1.50 mmol). The tube was evacuated and backfilled with argon (3 times), and *trans*-1,2-diaminocyclohexane (12 μL, 10.0 mol%) was added, followed by anhydrous toluene (1.0 mL) were added. The tube was sealed under argon and was placed in an oil bath pre-heated to 110 °C. After heating for 42 h, the reaction mixture was allowed to cool and was treated with *n*-undecane (106 μL, 0.50 mmol, as an internal GC standard). The mixture was partitioned between EtOAc and saturated NH_4Cl (aq). GC analysis indicated a 45% conversion of the aryl iodide. The organic layer was dried ($MgSO_4$), filtered, and concentrated via rotary evaporator. The crude material was purified by silica gel chromatography (90:10 hexanes:EtOAc, $R_f = 0.25$) to give the product as a pale yellow oil (64 mg, 21%).

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(34) For example, see: (a) Minami, T.; Isonaka, T.; Okada, Y.; Ichikawa, J. *J. Org. Chem.* **1993**, *58*, 7009. (b) Suzuki, H.; Watanabe, K.; Yi, Q. *Chem. Lett.* **1985**, 1779.

(35) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.

(36) For example, see: Geirsson, J. K. F.; Gudmundsson, B. O.; Sigurdardottir, R. *Acta Chem. Scand.* **1993**, *47*, 1112.

(37) For example, see: (a) Bacon, R. G. R.; Murray, J. C. F. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1267. (b) Young, S. D.; Wiggins, J. M.; Huff, J. R. *J. Org. Chem.* **1988**, *53*, 1114.

(38) For a relevant example, see: Paul, F.; Patt, J.; Hartwig, J. F. *Organometallics* **1995**, *14*, 3030.

(39) Bordwell, F. G.; Harrelson, Jr., J. A. *Can. J. Chem.* **1990**, *68*, 1714.

(40) Djakovitch, L.; Kohler, K. *J. Organomet. Chem.* **2000**, *606*, 101.

(41) Guanti, G.; Narisano, E.; Podgorski, T.; Thea, S.; Williams, A. *Tetrahedron* **1990**, *46*, 7081.

(42) You, J.; Verkade, J. G. *J. Org. Chem.* **2003**, *68*, 8003.

(43) Katz, C.; Aubé, J. *J. Am. Chem. Soc.* **2003**, *125*, 13948.

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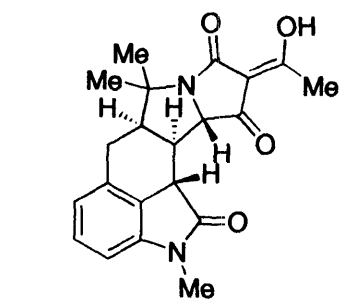
CHAPTER 2

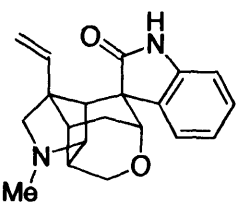
SYNTHESIS OF OXINDOLES FROM α-HALOACETANILIDES VIA PALLADIUM-CATALYZED C-H FUNCTIONALIZATION

2.1 Introduction

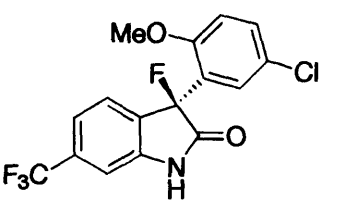
The oxindole ring structure is found in numerous biologically active compounds, ranging from complex alkaloid natural products to synthetic pharmaceutical reagents (Figure 1).[1] Accordingly, the chemistry of oxindoles has garnered considerable attention over the years. Due to the ubiquity of this motif and the biological activity of many molecules in which it is present, efficient methods for the synthesis of oxindoles are highly desirable.



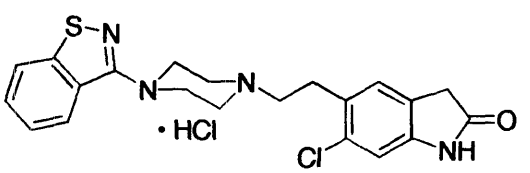
Speradine A
Recently isolated from
Aspergillus tamarii



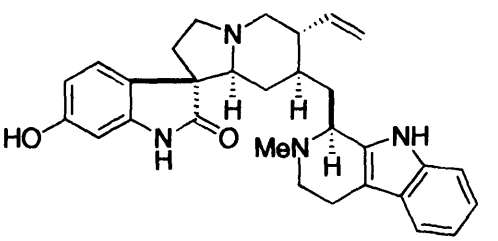
Gelsemine
Major alkaloid component of
Gelsemium sempervirens



BMS-204352 (MaxiPost)
Phase III clinical
trials for treatment of
stroke



Ziprasidone hydrochloride
antipsychotic drug

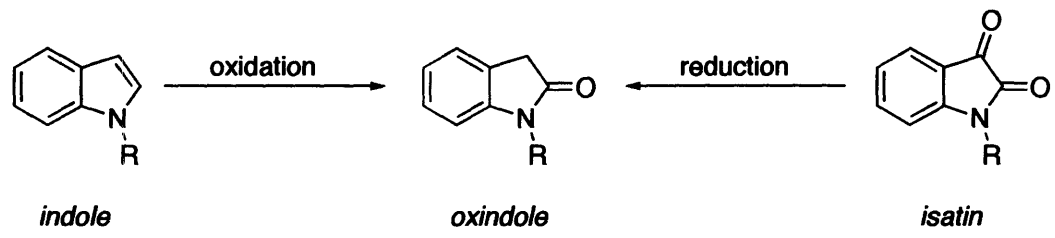


Strychnofoline
Inhibitor of cell mitosis

Figure 1. Examples of Oxindole-Containing Molecules

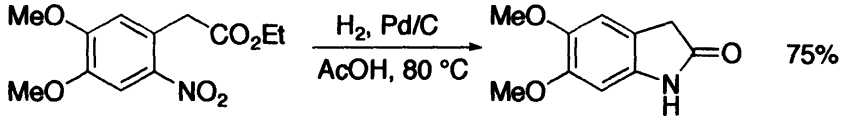
Among the methods commonly used for the synthesis of oxindoles, the most intuitively straightforward involve manipulation of the oxidation state of a preexisting ring system (Scheme 1). For example, 2-H-indoles can be oxidized by a variety of means to the corresponding

oxindoles.[2] Alternatively, partial reduction of substituted isatins (the fully oxidized ring structure) affords the related oxindole.[3] Both of these processes have found widespread use in a variety of synthetic applications, especially those in which the preexisting heterocyclic ring structure is readily available.



Scheme 1. Synthesis of Oxindoles by Oxidation/Reduction of Preexisting Heterocycles

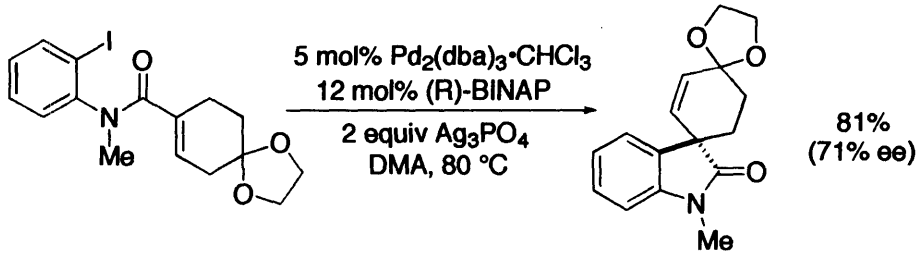
An alternative approach to the synthesis of oxindoles involves ring-closing reactions, most commonly in the formation of the five-membered lactam. A number of processes that effect this ring closure have been developed, and they can be divided into two general classes. In the first, a reactive functional group (such as a nucleophilic component or a suitable leaving



Scheme 2. Oxindoles via Cyclization of *o*-Aminophenylacetic Acid Derivatives[4]

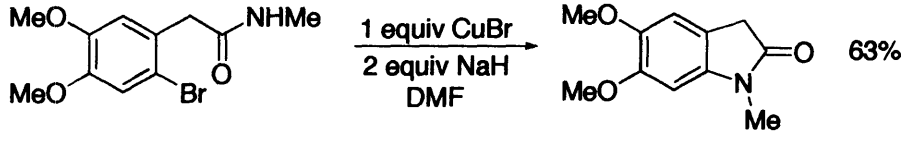
group) is bound directly to the aromatic ring. For example, the cyclization between an aromatic amine (or a precursor thereof) and an appropriately situated carboxylic acid derivative results in the formation of the oxindole lactam ring (Scheme 2).[4] This ring can also be formed when aromatic substrates contain a halogen atom situated *ortho* to a moiety containing a reactive

functional group. For example, intramolecular radical cyclizations[5] and Heck cyclizations[6] have been used to form the C3-C4 bond of the oxindole nucleus (Scheme 3).

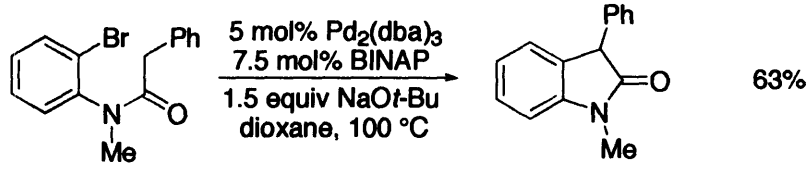


Scheme 3. Asymmetric Heck Cyclization to Construct Chiral Oxindoles[6a]

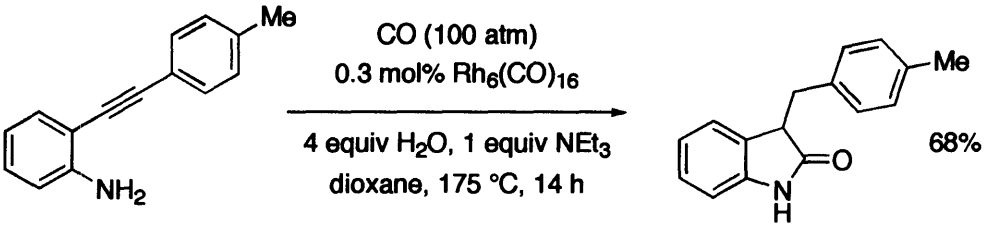
Similarly, metal-catalyzed amide *N*-arylations[7] (Scheme 4) and amide *C*-arylations[8] (Scheme 5) effectively afford the expected oxindole products. Rhodium-catalyzed cyclocarbonylation of 2-alkynylanilines has also been used to access 3-substituted oxindoles (via in situ reduction of the initial cyclization products), although the regioisomeric quinolinones are often produced as well (Scheme 6).[9]



Scheme 4. Oxindoles via Intramolecular Amide-*N*-Arylation[7]



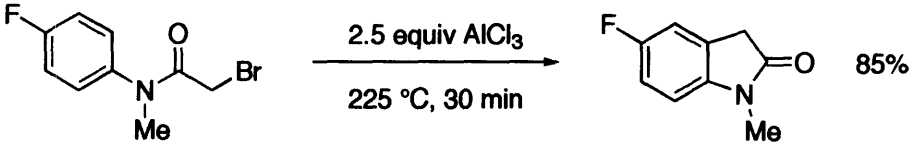
Scheme 5. Oxindoles via Intramolecular Amide Enolate Arylation[8b]



Scheme 6. Oxindoles via Rh-Catalyzed Cyclocarbonylation/Reduction[9]

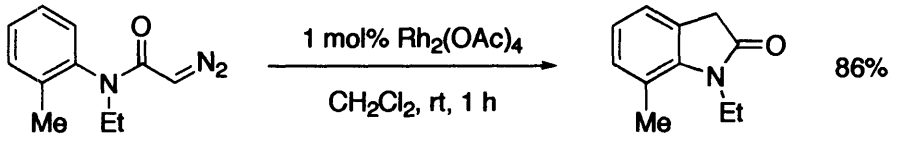
A significant limitation of each of the above methods is the requirement for substrates containing *ortho*-difunctionalized aromatic rings in order to achieve the desired ring closure. In many cases, these compounds may not be readily available, and thus a non-trivial synthetic sequence would be necessary.

In the second class of ring-closing reactions, the reaction to form the oxindole lactam ring occurs at an unfunctionalized position of an arene. Such processes have the obvious advantage that the aromatic ring does not need to be rigged for the cyclization event, thus greatly facilitating the synthesis of substrates. The prototypical example of this type of reaction is the Friedel-Crafts cyclization of α-halo[10] or α-hydroxyacetanilides[11] (Scheme 7). This process, also known as the Stollé reaction,[12] has found widespread use in the synthesis of a variety of oxindoles. Unfortunately, the need to use stoichiometric or superstoichiometric amounts of very strong Lewis acids severely limits the breadth of functional groups that are tolerated.



Scheme 7. Friedel-Crafts Cyclization to Generate Oxindoles[2]

Interesting variants of this process have been developed that offer increased functional group compatibility. For example, the rhodium-catalyzed cyclization of α-diazoacetanilides, which presumably proceeds via rhodium-carbenoid C-H insertion, provides access to substituted oxindoles (Scheme 8).[13] Alternatively, the photochemical cyclization of α-chloroacetanilides has been demonstrated to afford the corresponding oxindoles, although this process appears to be limited to electron-rich aromatic systems.[14]



Scheme 8. Oxindoles via Rh-Catalyzed Decomposition of α-Diazoacetanilides[13a]

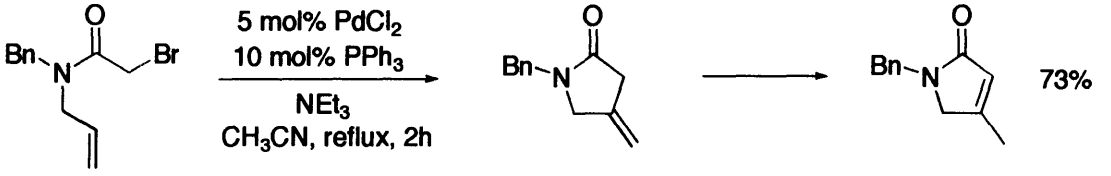
Thus, while many methods are available for the synthesis of substituted oxindoles, a protocol that would be generally applicable to a wide range of substrates and functional groups remains elusive.

2.2 Results and Discussion

2.2.1 Discovery of the Palladium-Catalyzed Oxindole Cyclization

Our initial foray into the synthesis of oxindoles was the result of a serendipitous discovery while exploring the chemistry of palladium enolates, which are known to be generated by the oxidative addition of palladium (0) to α-halo carbonyl compounds.[15] Compared to the richly-developed chemistry based on the intermediacy of arylpalladium complexes, the chemistry of palladium enolates has been largely underexplored. While palladium enolates are considerably more hydrolytically unstable than their arylpalladium counterparts,[15a] they do

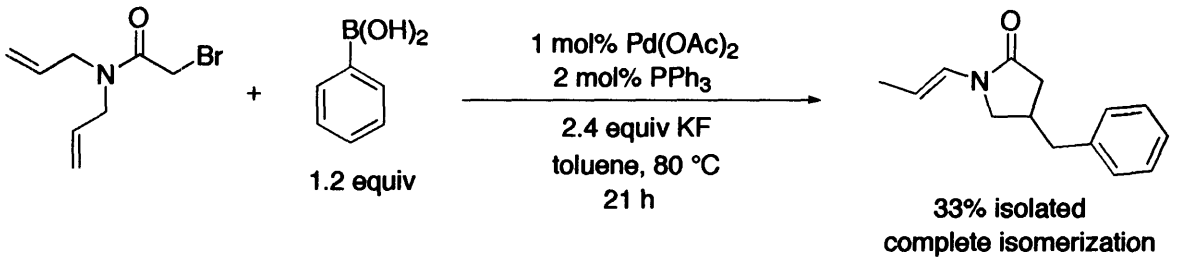
undergo similar reactions. For example, α-halo carbonyl compounds containing appropriately situated olefins undergo Heck-type cyclizations to afford the corresponding ring structure (Scheme 9).[16] Such a cyclization involves the generation of a new stereocenter, although this is ultimately destroyed upon β-hydride elimination (and eventual double bond isomerization). We hypothesized that if the alkylpalladium intermediate could be trapped prior to β-hydride elimination, possibly by some organometallic reagent or carbon monoxide, then the newly-formed stereocenter would be retained. Thus, if the cyclization could be conducted in an asymmetric fashion, then such a process could provide access to a number of enantioenriched heterocycles.



Scheme 9. Cyclization of a Palladium Enolate[16b]

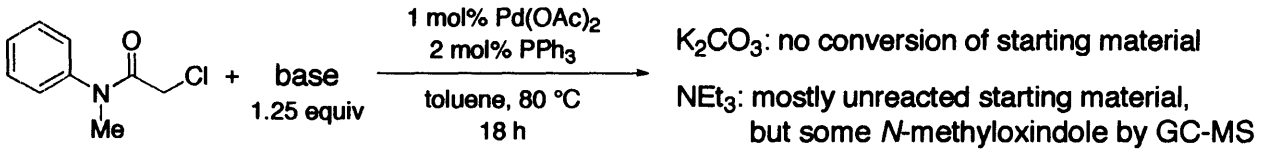
We initially found that reactions of α-halo esters derived from homoallylic alcohols (to form 6-membered lactones) were sluggish, while reactions of substrates derived from allylic alcohols (to form 5-membered lactones) failed due to preferential reaction at the allylic portion. That is, the α-haloacetate moiety served as a leaving group to afford a Pd-π-allyl intermediate. Shifting the focus to α-bromo and α-chloro lactams seemed to be more fruitful, and our initial results in this regard were promising: cyclization of α-bromodiallylacetamide in the presence of stoichiometric phenylboronic acid (using triphenylphosphine as the ligand) afforded at 33% isolated yield of the corresponding lactam in which the alkylpalladium intermediate was

effectively trapped to yield the β-benzyl product (Scheme 10). Not surprisingly, however, the second allyl group in the isolated material had isomerized completely to the more



Scheme 10. Trapping of Cyclization Intermediates with Phenylboronic Acid

thermodynamically stable internal position. We assumed that replacement of this second allyl group would suffice to simplify our initial studies, and we synthesized the *N*-phenyl derivative. Unfortunately, the situation became more complex in this case. A number of reaction products formed, several of which had the desired molecular weight by GC-MS analysis, in addition to several products which had a molecular weight corresponding to a loss of HBr. Interestingly, ^{1}H NMR analysis suggested that some of the isolated reaction products only had four aromatic protons. To test whether there was a competing process occurring at the aromatic ring, *N*-methyl-α-chloroacetanilide was synthesized and subjected to the cyclization conditions (using triphenylphosphine as ligand, Scheme 11). When potassium carbonate was used as the base, no conversion of the starting material was observed. However, employment of triethylamine as the base resulted in a small amount of conversion to what appeared to be *N*-methyloxindole by GC-MS analysis. Isolation of this material revealed that it was in fact this compound. Realizing the potential for a synthetic method that would access oxindoles from this class of substrate employing transition metal catalysis, we abandoned our nascent studies on asymmetric cyclizations of palladium enolates in order to investigate this process.



Scheme 11. Cyclization of *N*-Methyl Chloroacetanilide

2.2.2 Reaction Development

While product formation was observed when using triphenylphosphine as a ligand, the reaction in this case was too slow to be synthetically useful. Therefore, initial experiments were directed at finding ligands that would afford high reaction rates for the cyclization; in particular, a screening of phosphine ligands was conducted (Figure 2). Many of the ligands commonly used in palladium-catalyzed reactions were studied, including a variety of monodentate and bidentate phosphines, triaryl- and trialkylphosphines, and a number of the biaryl-based phosphines developed in the Buchwald group over the past decade.[17] Under reaction conditions with which product formation was initially observed using triphenylphosphine (i.e., $Pd(OAc)_2$ as catalyst precursor, triethylamine as base, toluene, 80 °C), we found that several of the biaryl-based phosphines examined were efficacious at promoting the cyclization. For example, the use of 2-dicyclohexylphosphino-2'-dimethylamino biphenyl (ligand 9), 2-dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl (XPhos, ligand 13), and 2-dicyclohexylphosphino-2'-isopropyl biphenyl (ligand 12) afforded significant enhancement in the rate of cyclization relative to most other phosphines. However, one ligand in particular, 2-di-*tert*-butylphosphinobiphenyl (ligand 7), clearly provided the most rapid reaction of all. In fact, under the conditions employed in the screen, the cyclization is nearly complete within one hour when this ligand is used in twofold excess relative to $Pd(OAc)_2$.

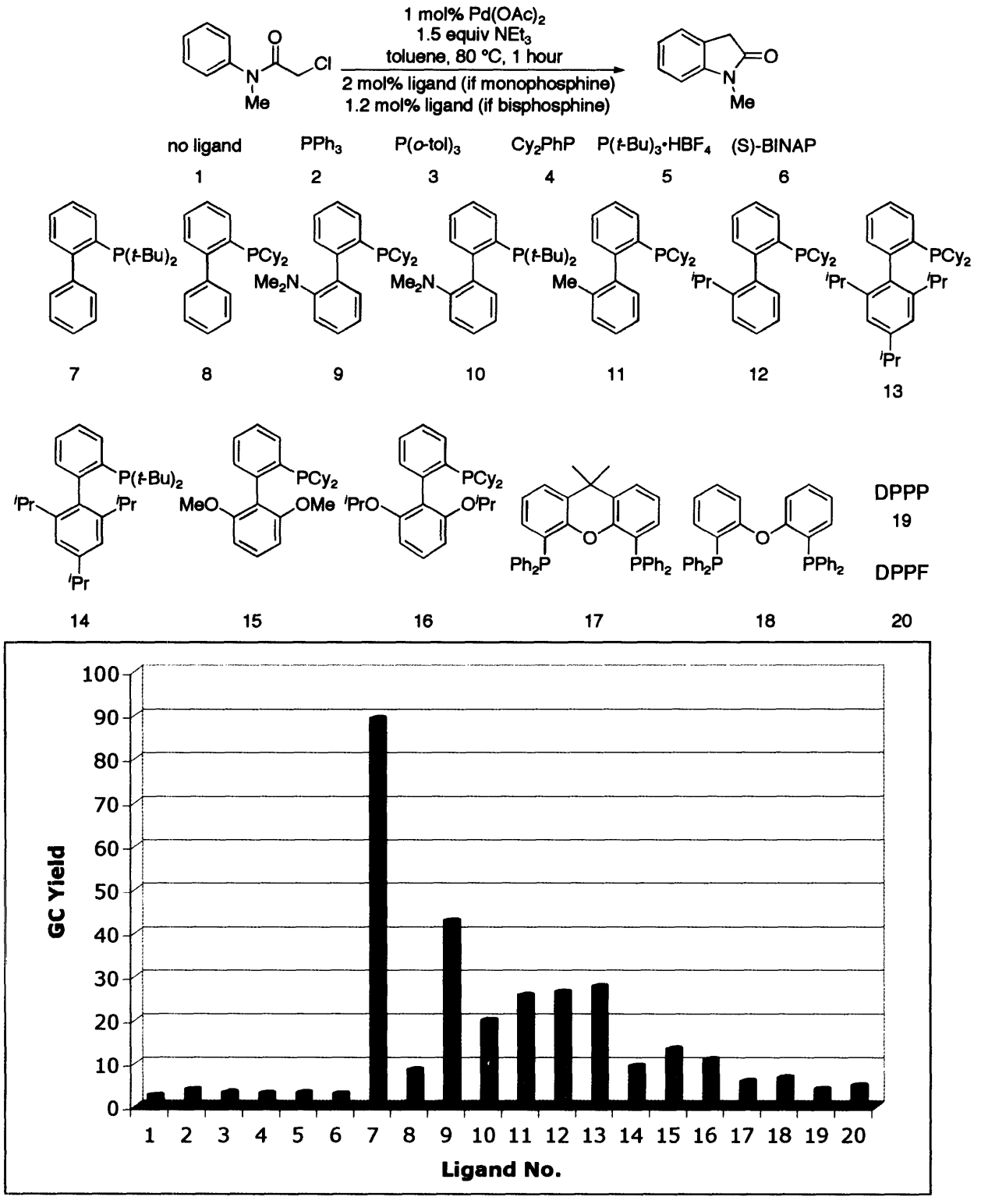


Figure 2. Initial Ligand Screen

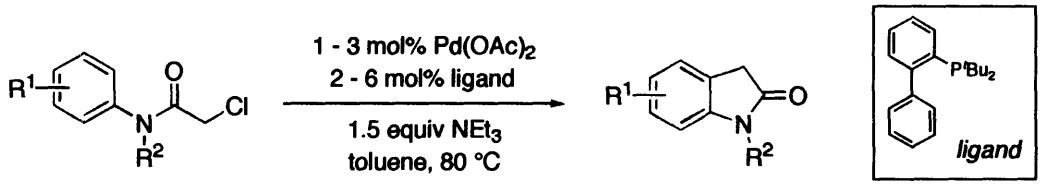
Given the initial failure of the cyclization reaction when potassium carbonate was used as the stoichiometric base, we were not surprised to find that other inorganic bases (which are for the most part insoluble in the reaction mixture) are generally ineffective at promoting the reaction. This may be in large part due to difficulty in generating the active palladium (0) catalyst from $Pd(OAc)_2$ under these conditions, whereas triethylamine is a well-known reducing agent in palladium chemistry.[18] However, we found that when $Pd_2(dba)_3$ (a convenient Pd^0 source) is used as the precatalyst, the reaction is still sluggish when inorganic bases are used. With the exception of Cs_2CO_3, which afforded some noticeable conversion to product, inorganic bases give only trace amounts of oxindole. It appears that a soluble base is necessary for the cyclization to proceed, an observation that has significant mechanistic implications (*vide infra*). Many tertiary amines, such as tributylamine, *N*,*N*-dicyclohexylmethylamine, and *N*-methylmorpholine are effective bases for this process, although detailed comparisons of reaction rates with these different amines have not been conducted. Interestingly, when DBU (diazabicyclo[5.4.0]undec-7-ene) was employed as a base, it appeared that rapid decomposition of the α-chloroamide to unidentified products occurred.

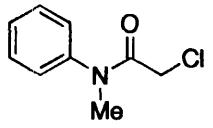
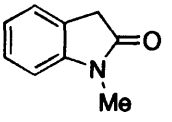
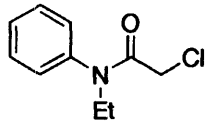
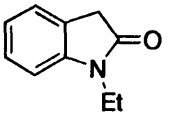
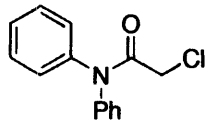
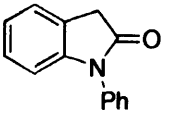
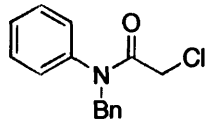
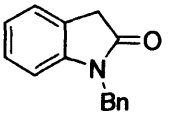
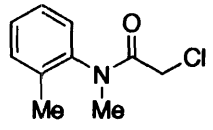
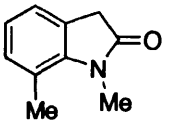
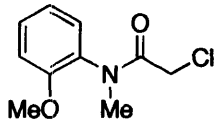
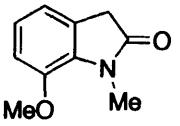
The synthesis of the cyclization substrates is generally straightforward and uneventful. *N*-Substituted anilines can constructed by alkylation of protected primary anilines (e.g., *N*-acyl, *N*-alkoxycarbonyl) followed by deprotection of the alkylated product. Similarly, reductive amination can be used to monoalkylate primary anilines, and we have found this methodology to be particularly applicable to the synthesis of anilines containing *N*-benzylic groups. Alternatively, the palladium-catalyzed amination of aryl halides[19] is a reliable method to access substituted anilines, in particular diarylamines (which could be potentially difficult to access by more conventional methods). Then, with the requisite substituted anilines in hand, acylation

with chloroacetyl chloride affords the desired α-chloroacetanilides in high yields, often as crystalline solids. While a number of acylation protocols have proven successful in the synthesis of these substrates, we have found that employing biphasic (Schotten-Baumann) conditions in general results in cleaner reactions. In contrast, the use of triethylamine as a base for acylation often results in the formation of dark, tarry side-products (likely due to the rapid formation of chloroketene and its subsequent reactions). It should be noted that another convenient method to synthesize the α-chloroamides involves simply heating a solution of the aniline and chloroacetyl chloride in an inert solvent (e.g., toluene, ethyl acetate) in the absence of any base. While not amenable to substrates containing acid-sensitive moieties (due to the unabated evolution of HCl), this method allows for the acylation of more hindered or less nucleophilic anilines such as diarylamines and nitro-substituted anilines.

Employing the conditions used in the preliminary ligand screen, a variety of simple α-chloroacetanilides are smoothly converted to the corresponding oxindoles in very high yields (Table 1). Noteworthy is that benzylic groups on the nitrogen do not participate in any cyclization process (Entry 4); we observe exclusive five-membered oxindole formation, with no formation of the six-membered tetrahydroisoquinolinone. This selectivity may be attributable to the more favorable formation of a 6-membered versus 7-membered palladacyclic intermediate (see section 2.2.3). Employing Lewis acids to conduct a similar cyclization (i.e., Friedel-Crafts conditions), it is possible that a mixture of these two possible products would result.[20] Thus a broad array of well-known benzylic-based nitrogen protecting groups is available for this chemistry.

Table 1. Synthesis of Unfunctionalized Oxindoles



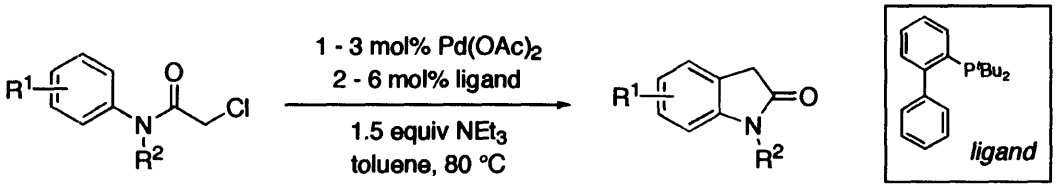
Entry	Substrate	Product	Time	Pd (mol%)	Yield[a]
1			2.5 h	1	94%
2			3 h	1	99%
3			3 h	2	96%
4			3 h	2	97%
5			6 h	2	90%
6			6 h	2	90%

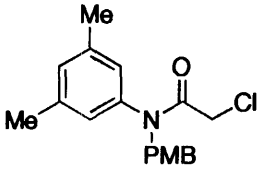
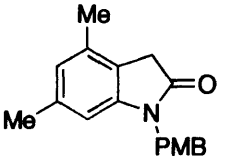
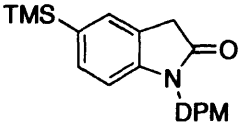
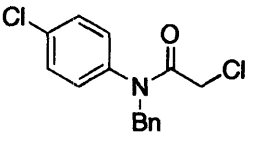
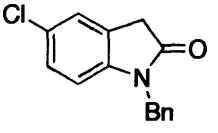
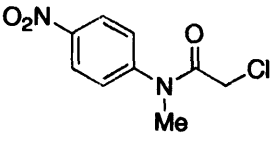
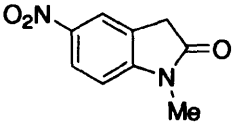
[a] Isolated yield (average of two runs); estimated to be >95% pure by ^{1}H NMR and combustion analysis

Oxindoles containing 7-substituents, derived from *ortho*-subtituted chloroacetanilides, are also accessible using this methodology (Table 1, Entries 5 and 6). Not surprisingly, the rates

are somewhat slower in these cases. However, simply raising the catalyst loading and increasing the reaction times results in complete conversions to the desired products.

Table 2. Synthesis of Functionalized Oxindoles



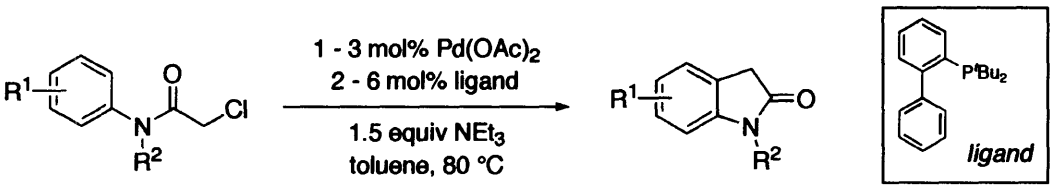
Entry	Substrate	Product	Time	Pd (mol%)	Yield[a]
1			3 h	2	84%
2			19 h	2	78%[b]
3			3 h	3	76%
4			3 h	1	91%

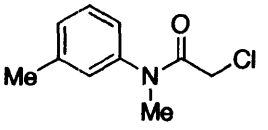
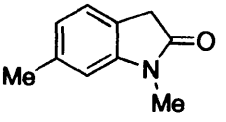
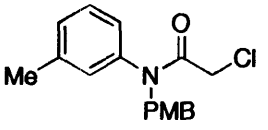
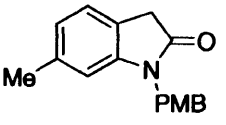
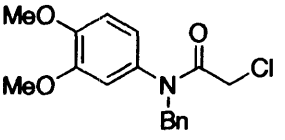
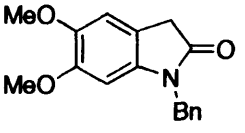
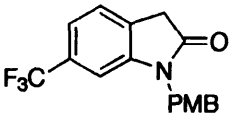
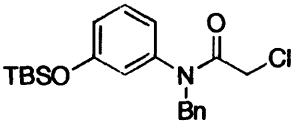
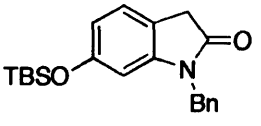
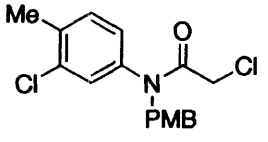
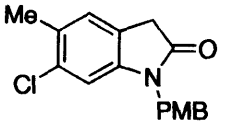
[a] Isolated yield (average of two runs); estimated to be >95% pure by ^{1}H NMR and combustion analysis
[b] Reaction conducted at 100 °C
PMB = *p*=methoxybenzyl, TMS = trimethylsilyl, DPM = diphenylmethyl

Substrates containing a variety of other substitution patterns and functional groups undergo the cyclization as well (Table 2). For instance, oxindoles containing substituents in the 4- and 6-positions are accessible, as exemplified by Entry 1. While the relevance of this result

may not be immediately apparent, the fact that 4-substituted oxindoles can be constructed by this reaction is of interest (*vide infra*). Notably, aryl-trimethylsilyl groups and *N*-diphenylmethyl groups are tolerant of the reaction conditions (Table 2, Entry 2); these groups are generally considered to be acid-sensitive, and may quite possibly not survive the strongly acidic conditions of the Friedel-Crafts reaction. The cyclization of this substrate is somewhat slower than the other examples, however, most likely due to the steric bulk of the diphenylmethyl group. Aryl chlorides are also stable under the reaction conditions (Table 2, Entry 3), despite the fact that the catalyst system used is known to activate aryl chlorides in other classes of coupling reactions.[17] Thus, by taking advantage of the relative reactivity of Pd(0) towards the α-chloroamide and the aryl chloride, good yields of the chloroarene-containing oxindole can be generated. However, since reactions employing 1-2 mol% Pd tended to cease after ~90% conversion, slightly increased catalyst loadings are necessary (presumably due to a non-productive, competitive oxidative addition at the aryl chloride). Interestingly, electron-deficient substrates, such as a *para*-nitro substituted chloroacetanilide (Table 2, Entry 4), undergo smooth cyclization with rates comparable to the more electron-rich cases. In contrast, a nitro-substituted oxindole should be a difficult compound to synthesize using conventional Friedel-Crafts methodology (indeed, these compounds are typically made by nitration of a preexisting oxindole).[21]

Table 3. Regioselective Synthesis of Oxindoles

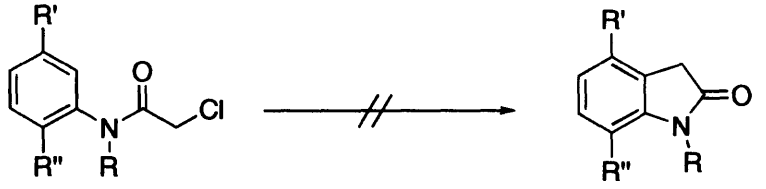


Entry	Substrate	Product	Time	Pd (mol%)	Yield[a]
1			3 h	1	95%[b]
2			3 h	2	97%[c]
3			3 h	2	94%[d]
4			3 h	2	96%[d]
5			3 h	2	93%[d]
6			3 h	3	78%[d]

[a] Isolated yield (average of two runs); estimated to be >95% pure by ^{1}H NMR and combustion analysis
[b] 15:1 regioselectivity
[c] 14:1 regioselectivity
[d] > 20:1 regioselectivity
PMB = *p*-methoxybenzyl, TBS = *tert*-butyldimethylsilyl

A very interesting observation was made in the cyclization of the chloroacetanilide dervied from *m*-toluidine (Table 3, Entry 1). While two products can theoretically be formed in

this process, the reaction exhibits a high selectivity for 6-methyloxindole as opposed to the 4-methyloxindole (15:1 regioselectivity). This is presumably attributable to steric interactions in the cyclization transition state raising the $\Delta G^{\ddagger}$ for the 4-substituted regioisomer. Increasing the bulk of the other nitrogen substituent (e.g., *p*-methoxybenzyl), however, seems to have little effect on the regioselectivity (Table 3, Entry 2). Other unsymmetrically substituted substrates cyclize with a similarly high bias, favoring aromatic substituents in the 6-position rather than the 4-position of the product oxindole (Table 3, Entries 3-6). In fact, in most cases only a single product is obtained from the reaction. By contrast, mixtures of products are often obtained from *meta*-substituted substrates under classical Friedel-Crafts conditions.[22] Thus, a number of 6- and 5,6-substituted oxindoles can be readily accessed without the need for *ortho*-difunctionalized aromatic systems. Additionally, the functional group tolerance of the cyclization is further evidenced by the compatibility of trifluoromethyl groups (Table 3, Entry 4), which are known to react with strong acids such as $AlCl_3$,[23] as well as aryl-TBS ethers (Table 3, Entry 5), which are prone to cleavage in the presence of palladium salts.[24]

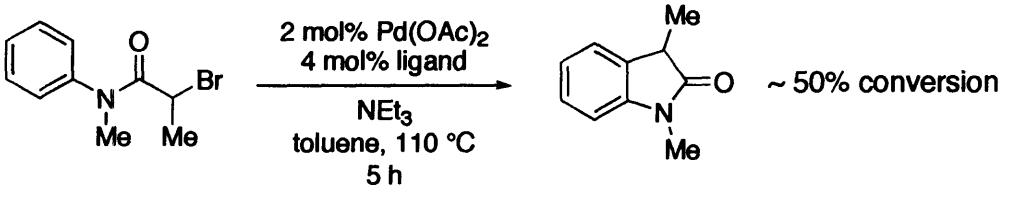


Scheme 12. Lack of Reactivity in 2,5-Disubstituted Substrates

An interesting dilemma we encountered during these studies was that chloroacetanilides containing substituents in both the 2- and 5-positions are essentially inert under all reaction conditions explored (Scheme 12). Thus, 4,7-disubstituted oxindoles are not accessible using this chemistry. As mentioned earlier, one can access 7-substituted oxindoles (Table 1, Entries 5 and

6), although the cyclization seems to be somewhat slower than for the less hindered substrates. Likewise, 4-substituted oxindoles can be synthesized from *meta*-substituted anilines (Table 2, Entry 1), although there is a strong preference to direct aromatic substituents to the 6-position if possible. Since these observations can be rationalized in terms of steric interactions between the ring substituents and the palladium enolate (to which the bulky phosphine ligand is presumably bound), it is likely that the recalcitrance of the 2,5-disubstituted chloroamides is due to a prohibitively costly combination of steric interactions in the cyclization transition state. Aside from being a mechanistically interesting problem, there are numerous natural products that contain 4,7-disubstituted indole fragments (such as lyngbyatoxin A and teliocidin B[25]) and thus a reliable method to access such structures would be valuable. Unfortunately, despite extensive experimentation, to date we have not been able to solve this shortcoming.

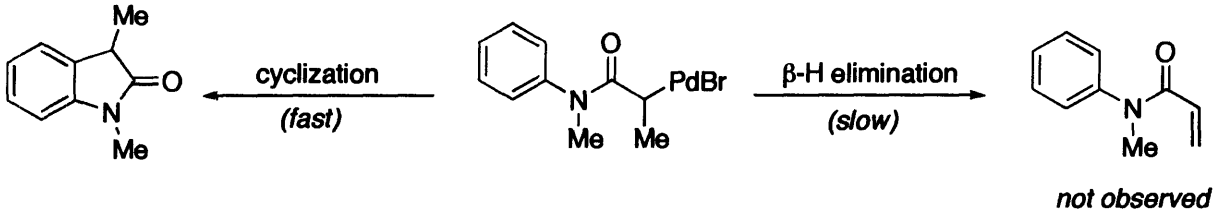
We also investigated the possibility of conducting the cyclization on α-haloamides that contain additional α-substituents. If successful, such reactions would afford 3-substituted oxindoles directly. Unfortunately, little (if any) conversion of several of such α-substituted chloroacetanilides was observed under reaction conditions we explored. This was not



Scheme 13. Cyclization to Afford 3-Substituted Oxindoles

completely unexpected, however; since the oxidative addition of alkyl halides to low-valent metals often occurs by an S_N2-type pathway,[26] hindered electrophiles would be expected to react with the palladium catalyst more slowly than the simple α-chloroamides previously examined.

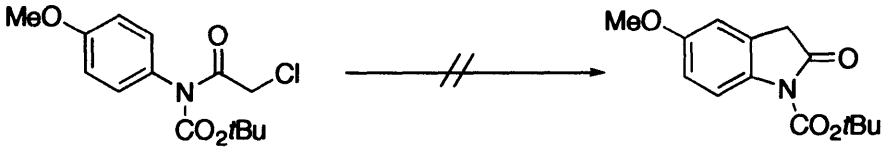
We do observe some reaction (albeit sluggish) with the corresponding α-*bromoamides*, however. Thus, in the cyclization of *N*-methyl-*N*-phenyl-α-bromopropionamide, a ~50% conversion of the substrate is achieved after 5 hours in refluxing toluene, affording what appears to be the 3-methyl oxindole by ^{1}H NMR analysis (Scheme 13). Unfortunately, increasing the duration of the reaction did not seem to facilitate higher conversions. While there are obviously better ways to access 3-methyl oxindoles than through this process, it is an interesting observation from a mechanistic standpoint. This result implies that once the palladium enolate is formed, the cyclization to the oxindole occurs faster than β-hydride elimination (Scheme 14). Indeed, no resonances attributable to olefinic protons are observed in the ^{1}H NMR of the crude reaction mixture (see Section 2.4). While no further progress beyond these preliminary experiments was made, the potential remains for an interesting route to access more highly substituted oxindoles.



Scheme 14. Cyclization vs. β-Hydride Elimination from a Pd-Enolate

A key drawback to the oxindole cyclization reaction is that substrates containing a free N-H do not undergo the cyclization. Attempted reactions employing unprotected chloroacetanilides resulted in the formation of an insoluble, oily, unidentified material (possibly oligimers resulting from intramolecular or intermolecular amide alkylation). While there are established procedures to remove alkyl and benzylic moieties from amide nitrogen atoms,[27] it would be advantageous to be able to use some protecting groups more commonly employed in

organic synthesis. For example, we found that the acid-labile *tert*-butoxycarbonyl (BOC) group can be introduced onto a secondary chloroacetanilide. However, the attempted cyclization of this substrate failed, yielding only unreacted starting material (Scheme 15). An acetyl-protected chloroacetanilide likewise fails to undergo cyclization at 80 °C, and decomposes under more forcing conditions.



Scheme 15. Lack of Reactivity of BOC-Protected Substrates

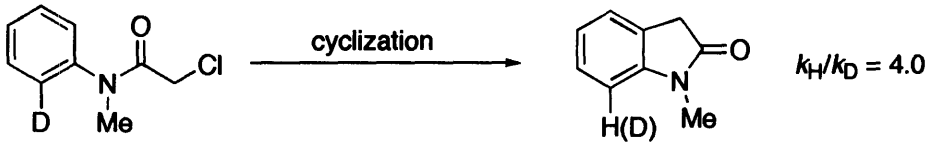
While several other classes of protecting groups have been explored, the results obtained have been either inconclusive or disappointing. Indeed, the protection of amide nitrogen atoms in general remains a underdeveloped field in organic synthesis.[27] Nevertheless, given the known methods available for the removal of benzylic protecting groups from amides, the oxindole cyclization reaction described herein will likely find use in a variety of synthetic applications.

2.2.3 Mechanistic Studies

Central to our studies on the palladium-catalyzed oxindole cyclization was the intent to learn about the mechanism of the reaction. We hypothesized that determining intimate details of how the reaction occurs could potentially solve some of the difficulties encountered with certain substrates, in addition to possibly leading to new classes of related reactions.

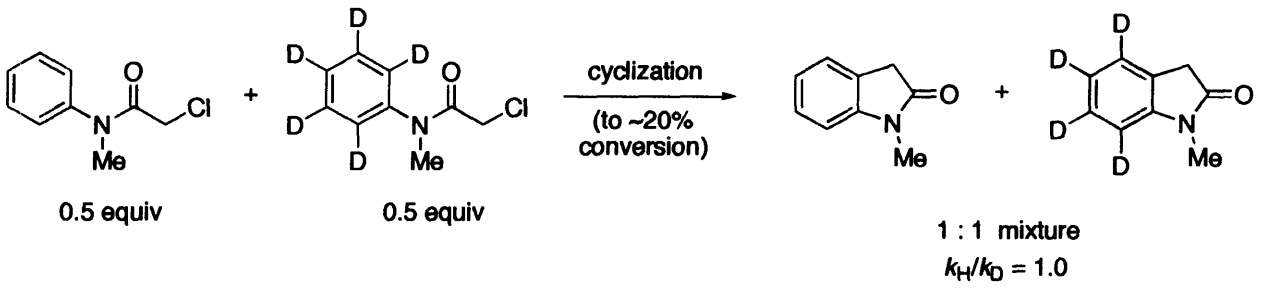
One of the central goals of our mechanistic studies was to determine if any kinetic isotope effects were present in the cyclization. In particular, strategic incorporation of deuterium

atoms into the substrates would allow for observation of isotope effects associated with the C-H bond cleavage that occurs in this process. We initially envisioned two experiments that were expected to provide the desired information. In the first, a substrate containing a deuterium atom *ortho*-to the amide nitrogen would be subjected to the cyclization. The amount of deuterium present in the resulting product would be indicative of any kinetic isotope effects present in the cyclization step. The second experiment would be an *intermolecular* competition experiment between a substrate containing a perdeuterated aromatic ring and one with an unlabelled ring. The resulting distribution of labelled and unlabelled products would provide information on the overall catalytic cycle, not just the cyclization event.



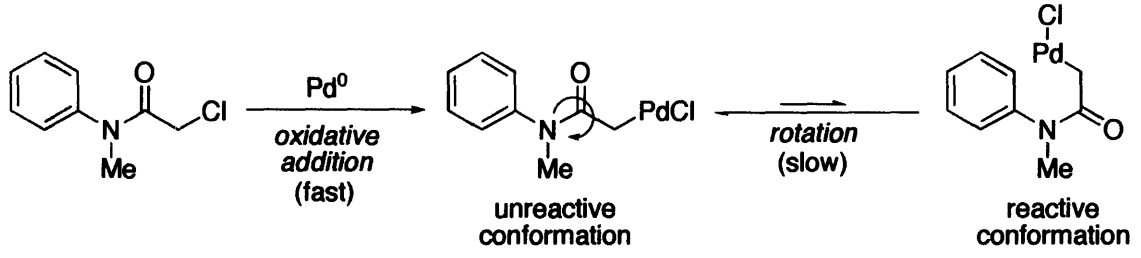
Scheme 16. Observation of an Intramolecular Kinetic Isotope Effect

After the *ortho*-deuterated substrate is subjected to the standard reaction conditions, analysis of the isolated oxindole indicates that there is a primary kinetic isotope effect of 4.0 (Scheme 16).[28] This means that once the palladium enolate is formed, cyclization occurs at the *ortho*-proteo site four times faster that at the *ortho*-deutero site. However, if a 1:1 mixture of the perdeuterated *N*-methyl chloroamide and the corresponding nondeuterated substrate is subjected to the cyclization, and the reaction is stopped at ~20% conversion (to assure the reaction is pseudo-first order in both substrates), an equal amount of oxindole derived from both substrates is observed (Scheme 17). That is, the cyclization occurs at an equal rate for both substrates.



Scheme 17. Competitive Cyclization of Unlabelled and Labelled Substrates

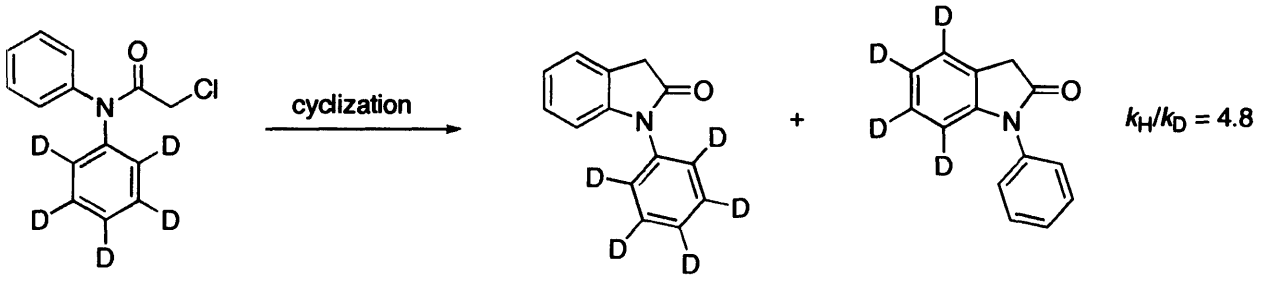
Taken together, these observations imply that the oxidative addition to form the palladium enolate would be the rate-limiting step overall. If the cyclization event were the slow step, a kinetic isotope effect would be observed in the competitive reaction of the fully deuterated and nondeuterated substrates. While none is observed in this case, an isotope effect is observed in the cyclization of the *ortho*-deuterated substrate because the discrimination step (i.e., protonated site vs. deuterated site) must occur *after* the palladium enolate has already formed.



Scheme 18. Potentially Slow Rotation of a Pd-Enolate

An alternative explanation for these observations is that the oxidative addition is in fact a fast step, but that rotation of the palladium enolate about the carbon-nitrogen bond into a reactive conformation is rate-limiting (Scheme 18). Similar phenomena have been observed in other systems.[29] However, in the cyclization of a diaryl chloroacetanilide in which one of the aromatic rings is fully deuterated, a kinetic isotope effect of 4.8 is observed (Scheme 19). While rotation

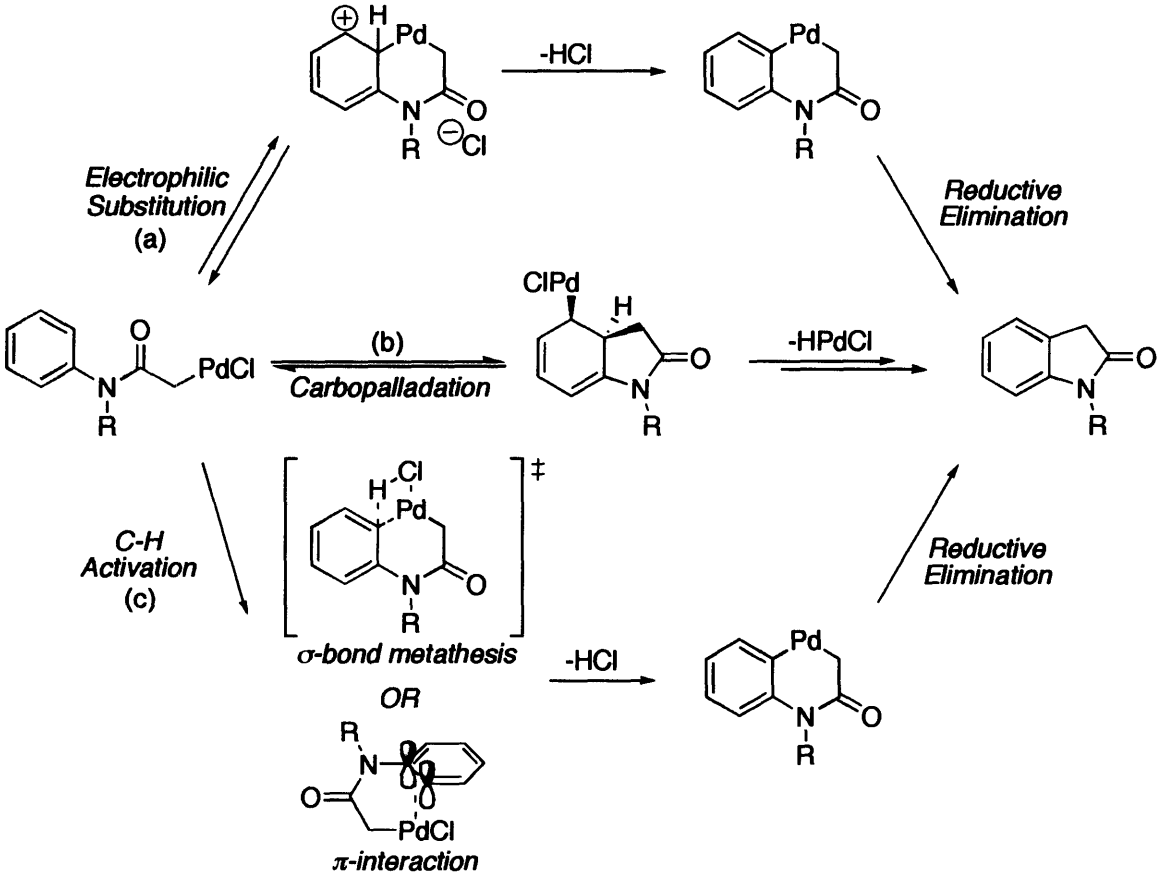
about the C-N bond in this substrate should be more facile than in the *N*-methyl substituted substrates, this result suggests that rotation is faster than cyclization and that oxidative addition is the slowest step overall.



Scheme 19. Observation of a Second Intramolecular Isotope Effect

Based on these observations and previously reported examples of palladium-catalyzed C-H functionalization, we propose several possible mechanistic pathways that may be operative in this reaction (Scheme 20). The first step, common to all possible mechanisms, is the oxidative addition of palladium (0) to the α-chloroamide, affording a palladium enolate. One potential mechanistic possibility is an electrophilic aromatic substitution onto palladium (II), forming an intermediate σ-complex (path a).[30] Loss of a proton from the arene would yield a six-membered palladacycle; subsequent reductive elimination would yield the product oxindole and regenerate the palladium (0) catalyst. Since a primary kinetic isotope effect of 4.0 is observed in the cyclization of a pre-formed palladium enolate (Scheme 16), the C-H bond cleavage must necessarily be slower than the electrophilic palladation step. This conclusion seems somewhat counterintuitive based on what is known about Friedel-Crafts reactions in general; it is often found that aromatic substitution to form a σ-complex is the slow step, followed by a rapid proton loss.[31] However, most Friedel-Crafts reactions exhibit negligible deuterium isotope effects.[32] In

fact, *inverse secondary* isotope effects are commonly observed in these reactions, as changing from sp^2 hybridization to sp^3 hybridization should occur faster at a deuterated site relative to a protonated site. Thus, the palladation step would have to be a reversible process prior to C-H bond cleavage, and the observed primary isotope effect would be a result of a partitioning effect (that is, there is an equilibrium between the Pd enolate and the σ-complex).[33] This might serve to explain the apparent need for a soluble base to drive the reaction towards the product.



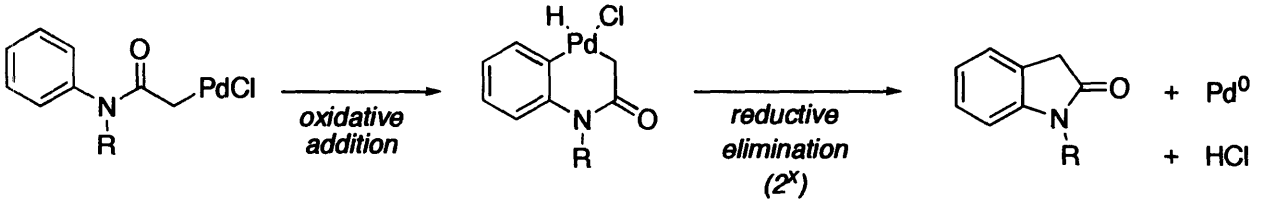
Scheme 20. Potential Mechanisms for the Pd-Catalyzed Oxindole Cyclization

A second possible mechanism that could be occurring is a carbopalladation process (path b), in which the palladium enolate participates in a Heck-type addition across one of the "double-bonds" of the aromatic ring.[34] β-Elimination from this intermediate would afford the oxindole along with hydrogen chloride and the palladium (0) catalyst. Again, since a primary kinetic isotope effect of 4.0 is observed, the carbopalladation should be a reversible process that is followed by a slow cleavage of the C-H bond. It should be pointed out that such a carbopalladation would be a *syn*-addition of the enolate carbon and the palladium across the aromatic ring, and so a *syn*-β-hydride elimination in the conventional sense would be impossible. More likely, an *anti*-β-hydride elimination (essentially an E_2-type elimination) could be occurring in the presence of the stoichiometric base.[35] This would again explain the apparent need for a soluble base and the very slow rates observed for inorganic bases.[35a] Interestingly, the isotope effect we observe is intermediate to the values commonly associated with *syn*-β-hydride (typically 2-3) and *anti*-β-hydride (typically 5-7) eliminations.[36]

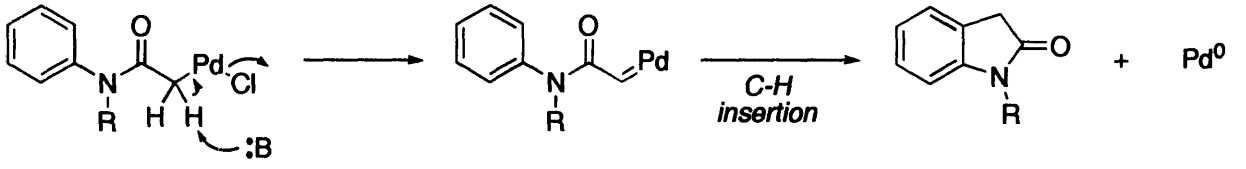
A third mechanistic possibility would be a *bona fide* "C-H activation," a term which on its own invokes a number of potential mechanistic manifolds (path c).[37] For example, a σ-bond metathesis between the palladium enolate and the arene would afford a six-membered palladacycle and hydrogen chloride.[38] Alternatively, the aromatic ring could serve as a Lewis base towards the palladium enolate by interaction of its π-electrons with unfilled orbitals of the metal. Such a π-type of interaction is known to activate the arene C-H bonds by increasing their acidity, such that deprotonation by exogenous base is feasible thus generating palladacyclic intermediates.[39] Therefore, a π-interaction between the palladium enolate and the arene would allow for palladacycle formation upon deprotonation by triethylamine (again explaining the need for a soluble base). In effect, this would be indistinguishable from an electrophilic aromatic

substitution process involving a rapid equilibration between a free Pd-enolate and a σ-complex (Scheme 20, path a).

Another "C-H activation" mechanistic possibility consistent with the observed isotope effects could proceed by a second oxidative addition following palladium enolate formation to give a palladium (IV) intermediate (Scheme 21); two reductive elimination steps would afford the oxindole and hydrogen chloride. While the invocation of Pd(IV) intermediates into catalytic cycles is relatively rare,[40] an analogous redox cycle is the accepted pathway for *platinum*-catalyzed C-H activation.[41] Yet another mechanistic possibility would involve deprotonation of the α-position of the palladium enolate to generate a palladium-alkylidene complex (Scheme 22).[42] Insertion into an aromatic C-H bond (in analogy to the rhodium-carbenoid chemistry mentioned in the introduction[13]) would yield the product oxindole.



Scheme 21. Possible Palladium (IV) Intermediate



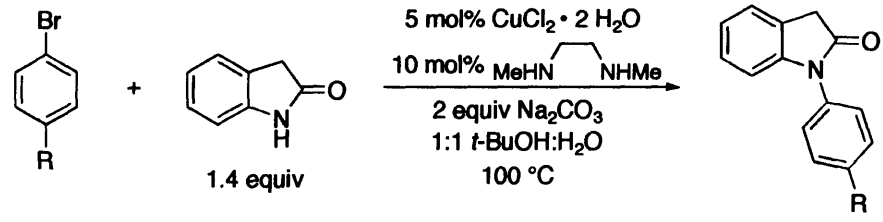
Scheme 22. A Potential Pathway Involving a Palladium Alkylidene

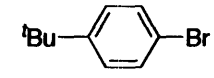
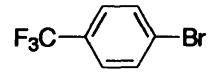
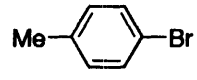
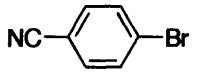
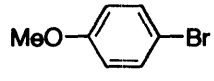
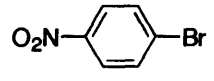
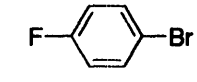
To further gain some insights into the reaction mechanism, we were interested in learning how the electronic nature of aromatic substituents affects the reaction. In particular, we designed a sequence of intramolecular competition experiments on unsymmetrically substituted diaryl chloroacetanilides, in which one of the arenes has a *para*-substitutent and the other is a simple phenyl ring. Given that rotation about the carbonyl carbon-nitrogen bond is fast relative to the cyclization, as demonstrated by the presence of a kinetic isotope effect in the cyclization of a diaryl chloroacetanilide (Scheme 19), the ratio of products obtained should be solely influenced by the electronic nature of the arene substituent.

However, before conducting the desired competition experiments, we needed a way to access the authentic *N*-aryl oxindoles that would be produced by these cyclizations in order to differentiate the reaction products spectroscopically. Our initial plan was to simply conduct a copper-catalyzed amide *N*-arylation[43] of commercially available oxindole with a variety of *para*-substituted aryl halides. Given the ease with which other 5-membered lactams react in this process, we were surprised to find no reaction occurring between oxindole and 4-bromoanisole under previously published conditions. In retrospect, this may be due in part to the fact that oxindole is equally acidic at the 3-position (carbon) as it is at the 1-position (nitrogen), and thus deprotonation results in an anion that is conceivably delocalized over the entire lactam.[44] For example, previously reported attempts to selectively alkylate oxindole discuss complications in reaction at both of these positions.[45] Moreover, we were unable to find a single report of oxindole *N*-arylation in which the 3-position contains hydrogen atoms.[46] However, we were encouraged by the observation that the only reaction conditions we had initially examined that afforded any conversion to product involved the use of potassium carbonate which had been exposed to atmospheric moisture numerous times. Interestingly, the use of anhydrous potassium

carbonate resulted in no reaction. Based on this apparent need for water in the reaction, we were eventually able to develop a set of conditions that allowed for the selective *N*-arylation of 3-H oxindoles by using biphasic aqueous/organic media. Specifically, heating oxindole, an aryl bromide, and sodium carbonate in a 1:1 mixture of *tert*-butanol and H_2O in the presence of catalytic $CuCl_2$ and *N,N'*-dimethylethylenediamine results in the formation of the *N*-aryloxindole (Table 4).

Table 4. Copper-Catalyzed *N*-Arylation of Oxindole



entry	aryl bromide	time	yield[a]	entry	aryl bromide	time	yield[a]
1		17 h	76%	5		19 h	35%
2		19.5 h	46%	6		20 h	4%
3		17 h	40%	7		20 h	15%
4		19.5 h	49%				

[a] Isolated yield (one run)

The yields for this reaction vary depending on the aryl bromide used, with more electron-deficient aryl bromides resulting in modest to very poor isolated yields. The necessity for

aqueous reaction conditions is likely the reason for these poor yields, as the *para*-substituent may be hydrolytically unstable at elevated temperatures. Alternatively, lactam hydrolysis would be expected to be more problematic in the cases of products derived from electron-deficient aryl bromides. Nevertheless, while this arylation protocol requires considerable modification to be generally applicable, it was sufficient to access enough material for our purposes at the time.

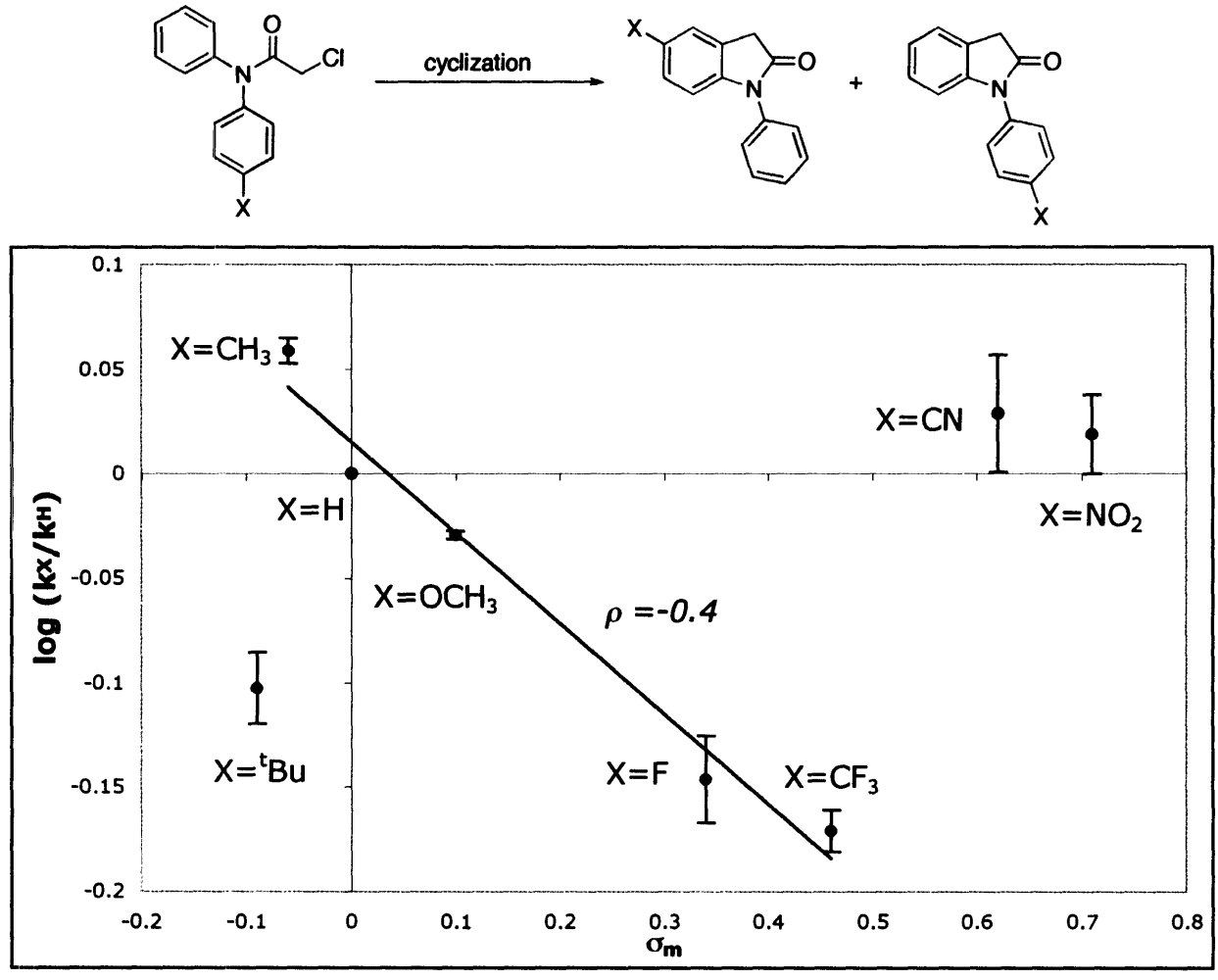


Figure 3. Hammett Plot for Cyclization of Diaryl Chloroacetanilides

With the authentic *N*-aryloxindoles at hand, we were in a position conduct the intramolecular competition experiments. The diarylchloroacetanilides were subjected to the generalized reaction conditions and allowed to react to completion. Analysis of the ^{1}H NMR spectrum of the crude reaction mixture indicated the ratio of rates of reaction on either ring, which was plotted against the Hammett σ_m constant for the arene substitutent (σ_m is used because the substituent is *meta*- to the site of reaction).[47] The results obtained have several interesting features (Figure 3). Firstly, an expected trend is observed for cases in which the substituted arene contains electron-releasing groups: the cyclization proceeds more quickly on the more electron-rich arene, suggesting an electrophilic attack of the palladium enolate onto the aromatic ring. It should be noted that the ρ value of this trend (-0.4) is relatively small in comparison to other examples of aromatic palladation reactions (the maximum ratio of rates we observe is 1.16:1, in the case of the *p*-methyl substituted substrate). For example, observed ρ values of -1.4[48] and -2.16[28a] have been used to support an electrophilic aromatic substitution mechanism for palladation. However, we also observe that as the substituted ring becomes severely electron-deficient, a reversal of this trend occurs and reaction on the more electron-poor ring becomes more facile. For example, in the cases of the *p*-cyano and *p*-nitro substituted substrates, the electron-deficient rings reproducibly react at essentially equal or slightly higher rates than the phenyl ring. This non-linear free energy relationship is suggestive of either a change in mechanism or a change in rate determining step as the electronic nature of the substrate varies.

Even more astounding is that in the case of the *p-tert*-butyl substituted substrate, the relative reaction rates are opposite of what was expected based solely on electronic considerations. While *para*-substituents were chosen for these experiments to avoid the effects

of any potential steric interactions, this seemingly incongruous observation suggests steric effects may be involved for this particular substrate. One potential explanation for this result can be derived by consideration of the carbopalladation mechanism described earlier (Scheme 20, Path b). If this process were operative, the palladium atom (which is coordinated by a very bulky phosphine ligand) would be transferred to a position *ortho*- to the *tert*-butyl group; such an interaction would be expected to raise the energy of the transition state relative to cyclization onto the unsubstituted phenyl ring, resulting in the ratio of products observed.

Thus, while it appears that the cyclization reaction exhibits behavior similar to that of an electrophilic palladation reaction (at least in part), the situation is considerably more complex than initially expected. Unfortunately, these results as well as others obtained over the course of our studies do not serve to definitively rule out or support any of the hypothesized mechanisms described above. Therefore, at this time we are unable to indicate which mechanism is the one most likely operative under the reaction conditions explored, or if it is possible that several pathways are occurring simultaneously.

2.3 Conclusions

While studying the cyclization chemistry of palladium enolates, we were fortunate to discover an interesting side reaction that produces oxindoles from α-haloacetanilides. Reaction optimization studies were conducted, and they have led to a reliable method for the synthesis of oxindoles from readily available starting materials that proceeds through a net functionalization of an arene C-H bond. In contrast to many of the well-known protocols to access oxindoles, this method does not require highly functionalized aromatic systems to allow for regioselective ring

closure. Rather, an inherent preference for directing arene substituents away from the site of cyclization allows for the facile formation of 5,6- and 6-substituted oxindoles directly from *meta*-substituted anilines. Moreover, we have demonstrated the breadth of functional groups that are compatible with the cyclization reaction conditions, in contrast to previous methods that require strongly acidic reagents to achieve ring closure.

We have also conducted extensive mechanistic work on this reaction, including kinetic isotope effect and linear free energy relationship studies. Despite our efforts, however, a clear picture of how this cyclization proceeds remains elusive. We suggest a number of plausible pathways that are consistent with our data and with previously published examples of palladium-catalyzed C-H functionalization processes.

2.4 Experimental Procedures

General Considerations: Toluene, tetrahydrofuran, and diethyl ether were purchased from J. T. Baker in CYCLE-TAINER® solvent delivery kegs, which were vigorously purged with argon for two hours and further purified by passing through two packed columns of neutral alumina (for THF and ether) or one column of neutral alumina followed by a column of copper (II) oxide (for toluene) under argon pressure. Anhydrous DMF was purchased from Aldrich in a Sure/Seal™ bottle. Palladium acetate was purchased from Strem Chemical Company and was recrystallized from benzene prior to use. 2-(Di-*tert*-butylphosphino)biphenyl was purchased from Strem and was used as received. Triethylamine (purchased from EM Science) was distilled from calcium hydride under nitrogen and was stored under nitrogen in an oven-dried Strauss

flask. d_7-Aniline and d_5-bromobenzene were purchased from Aldrich. $CDCl_3$, CD_2Cl_2, and CD_3OD were purchased from Cambridge Isotope Laboratories. *n*-BuLi (~1.6 M in hexanes) was purchased from Aldrich and was titrated using diphenylacetic acid directly prior to use. All other reagents were purchased from commercial sources and were used without further purification (unless otherwise indicated). Thin layer chromatography was performed using EM Science silica gel 60 F_{254} plates. Column chromatography was done using EM Science silica gel (230-400 mesh). Melting points were obtained using a Mel-Temp apparatus (Laboratory Devices) and are uncorrected. IR spectra for all previously unreported compounds were obtained either by placing the neat sample on the DiComp probe of an ASI ReactIR 1000 instrument or by analysis of a thin film on a NaCl plate using a Perkin-Elmer System 2000 FT-IR. Elemental analyses were performed by Atlantic Microlabs, Inc., Norcross, GA. ^{1}H NMR and ^{13}C NMR spectra were obtained using either a Varian Mercury 300 MHz spectrometer, a Varian Inova 500 MHz spectrometer, or a Varian Inova 501 MHz spectrometer; chemical shifts for ^{1}H NMR are referenced to tetramethylsilane (TMS) as an internal standard, while chemical shifts for ^{13}C NMR are referenced to the solvent used. Gas chromatographic analyses were performed on a Hewlett Packard 6890 instrument equipped with a FID detector and a HP-1 (either a 10m x 0.2mm i.d. or a 25m x 0.2mm i.d.) capillary column. Low-resolution mass spectra were obtained using a Hewlett Packard Model G1800B GCD. High-resolution mass spectra were obtained in the MIT Department of Chemistry Instrumentation Facility. Yields reported in Tables 1-3 refer to isolated yields of >95% purity (as determined by ^{1}H NMR and/or elemental analysis) and are the average of two runs. Yields mentioned in this section refer to single runs, and thus may differ slightly from the yields in Tables 1-3. Yields mentioned in Table 4 refer to single runs.

Synthesis of *N*-Substituted Anilines:

N-Benzyl (and Derivative) Anilines: These can be conveniently prepared from a primary aniline and a benzaldehyde derivative following a reductive amination protocol: a solution of primary aniline (1 equiv) and aldehyde (1.05 equiv) in methanol (1 mL per mmol) is treated with 3 drops of acetic acid at room temperature. If the imine precipitates from the reaction, it may be isolated prior to reduction, although yields are generally higher for a "one-pot" reaction. Once GC analysis indicates >95% conversion to imine (typically 1-3 h), $NaBH_4$ (1 equiv) is *carefully* added in small portions (CAUTION: initial gas evolution is very vigorous due to water formed during the reaction and residual acetic acid – performing the reaction in a round bottomed flask ~5-6 times larger than the reaction volume minimizes the chances of the solution frothing from the flask). Once gas evolution has ceased (~ 1 h), the methanol is removed with the aid of a rotary evaporator. The resulting residue is partitioned between ethyl acetate and water. The aqueous portion is extracted with ethyl acetate, and the combined organics are washed with brine, dried ($MgSO_4$), filtered, and concentrated via rotary evaporator. The crude amine is purified by recrystallization or distillation.

Commercially available anilines (Aldrich, unless otherwise noted): *N*-methyl aniline (Table 1, Entry 1), *N*-ethyl aniline (Table 1, Entry 2), diphenylamine (Table 1, Entry 3), *N*-phenylbenzylamine (Table 1, Entry 4), *N*-methyl-*o*-toluidine (Table 1, Entry 5), *N*-methyl-*o*-anisidine (Table 1, Entry 6), 4-nitro-*N*-methylaniline (Table 2, Entry 4), *N*-methyl-*m*-toluidine (Acros Organics, Table 3, Entry 1).

***N*-(*p*-Methoxybenzyl)-3,5-dimethyl aniline (Table 2, Entry 1):** Obtained as a colorless solid, recrystallized from MeOH (84%, 2 crops), mp = 47.5-49 °C. ^{1}H NMR ($CDCl_3$) δ 2.23 (s, 6H, ArCH_3), 3.79 (s, 3H, -OCH_3), 3.79 (broad s, 1H, -N*H*), 4.21 (s, 2H, benzylic CH_2), 6.27

(apparent s, 2H, aromatic), 6.38 (apparent s, 2H, aromatic), 6.87 (d, J_{AB} = 8.4 Hz, 2H, aromatic), 7.27 (d, J_{AB} = 8.4 Hz, 2H, aromatic). ^{13}C NMR ($CDCl_3$) δ 21.70, 48.01, 55.46, 110.91, 114.14, 119.70, 129.02, 131.80, 139.09, 148.54, 158.96. Calc. for $C_{16}H_{19}NO$: C 79.63, H 7.94; Found: C 79.54, H 7.96. IR (neat) ν (cm^{-1}) 3379.

***N*-Diphenylmethyl-4-trimethylsilyl aniline (Table 2, Entry 2):** A solution of *N*-diphenylmethylene-4-trimethylsilyl aniline[49] (3.3 g, 10 mmol) in MeOH (40 mL) was treated in small portions with excess $NaBH_4$ at room temperature until GC-MS analysis indicated complete conversion of the imine. The MeOH was removed via rotary evaporator, and the resulting residue was partitioned between ethyl acetate (20 mL) and water (40 mL). The aqueous portion was extracted with 2 x 10 mL ethyl acetate, and the combined organics are washed with brine, dried (K_2CO_3), filtered, and concentrated via rotary evaporator to a yellow oil which crystallized upon standing. The product was recrystallized from EtOH to give pale yellow crystals (1.69, 51%), mp = 95-98.5 °C. ^{1}H NMR ($CDCl_3$) δ 0.19 (s, 9H, -Si(C*H*$_3$)$_3$), 4.29 (d, J = 3.3 Hz, 1H, -N*H*), 5.50 (d, J = 3.3 Hz, 1H, benzylic –C*H*), 6.55 (d, J_{AB} = 8.7 Hz, 2H, aromatic), 7.25-7.37 (m, 12H, aromatic). ^{13}C NMR ($CDCl_3$) δ -0.67, 63.10, 113.20, 127.48, 127.60, 127.64, 128.98, 134.61, 143.02, 148.10. Calc. for $C_{22}H_{25}NSi$: C 79.70, H 7.60; Found: C 79.62, H 7.60. IR (neat) ν (cm^{-1}) 3408.

***N*-Benzyl-4-chloro aniline (Table 2, Entry 3):**[50] The imine formation reaction mixture was filtered after 1.5 h at room temperature, and the filter cake was washed with cold methanol and dried in air to give the corresponding imine. This material was suspended in methanol at room temperature, and $NaBH_4$ was added in small portions. After workup, the product was obtained as a colorless solid (51%), mp = 44-46 °C (lit.[51] 47-48 °C).

***N*-(*p*-Methoxybenzyl)-3-methyl aniline (Table 3, Entry 2):** Obtained as a pale yellow oil (85%) by Kugelrohr distillation (oven at 180 °C @ 0.5 Torr). ^{1}H NMR ($CDCl_3$) δ 2.24 (s, 3H, ArCH_3), 3.75 (s, 3H, -OCH_3), 3.83 (broad s, 1H, -N*H*), 4.18 (s, 2H, benzylic CH_2), 6.38-6.41 (m, 2H, aromatic), 6.50 (apparent d, 1H, aromatic), 6.83 (d, J_{AB} = 8.7 Hz, 2H, aromatic), 7.02 (apparent t, 1H, aromatic), 7.23 (d, J_{AB} = 8.7 Hz, 2H, aromatic). ^{13}C NMR ($CDCl_3$) δ 21.92, 47.95, 55.43, 109.98, 113.64, 114.01, 118.45, 128.83, 129.15, 131.52, 138.98, 148.24, 158.73. Calc. for $C_{15}H_{17}NO$: C 79.26, H 7.54; Found: C 79.43, H 7.68. IR (neat) ν (cm^{-1}) 3411.

***N*-Benzyl-3,4-dimethoxy aniline (Table 3, Entry 3):** Obtained as a pale yellow oil (83%) by Kugelrohr distillation (oven at 200 °C @ 0.4 Torr). This compound has been reported in the literature several times,[52] but no spectral data has been presented. The compound decomposes slowly over time and should be used promptly. ^{1}H NMR ($CDCl_3$) δ 3.80 (s, 3H, -OCH_3), 3.81 (s, 3H, -OCH_3), 4.29 (s, 2H, benzylic CH_2), 6.17 (apparent d, 1H, aromatic), 6.28 (apparent s, 1H, aromatic), 6.74 (apparent d, 1H, aromatic), 7.25-7.39 (m, 5H, aromatic). ^{13}C NMR ($CDCl_3$) δ 49.19, 55.73, 56.72, 98.99, 103.54, 113.20, 127.28, 127.63, 128.68, 139.66, 141.63, 143.17, 150.00. Calc. for $C_{15}H_{17}NO_2$: C 74.05, H 7.04; Found: C 73.99, H 7.01. IR (neat) ν (cm^{-1}) 3392.

***N*-(*p*-Methoxybenzyl)-3-trifluoromethyl aniline (Table 3, Entry 4):** Obtained as a colorless oil (69%) by Kugelrohr distillation (oven at 180 °C @ 0.6 Torr). ^{1}H NMR ($CDCl_3$) δ 3.79 (s, 3H, -OCH_3), 4.13 (broad s, 1H, -N*H*), 4.24 (s, 2H, benzylic CH_2), 6.73 (apparent d, 1H, aromatic), 6.82 (apparent s, 1H, aromatic), 6.88 (d, J_{AB} = 8.7 Hz, 2H, aromatic), 6.93 (apparent d, 1H, aromatic), 7.21 (apparent d, 1H, aromatic), 7.26 (d, J_{AB} = 8.7 Hz, 2H, aromatic). ^{13}C NMR ($CDCl_3$) δ 47.74, 55.46, 109.16 (q, J = 4.0 Hz), 113.99 (q, J = 3.85 Hz), 114.30, 115.88 (q, J = 1.2 Hz), 128.14 (q, J = 272.4 Hz), 129.03, 129.82, 130.69, 131.67 (q, J = 31.9 Hz), 148.42,

159.20. Calc. for $C_{15}H_{14}F_3NO$: C 64.05, H 5.02; Found: C 64.07, H 5.12. IR (neat) ν (cm^{-1}) 3409.

***N*-Benzyl-3-(*tert*-butyldimethylsiloxy) aniline (Table 3, Entry 5):** A 50 mL round-bottomed flask was charged with 3-aminophenol (3.32 g, 30.4 mmol), imidazole (2.60 g, 38.2 mmol), and *tert*-butyldimethylsilyl chloride (5.04 g, 33.4 mmol). Anhydrous DMF (8 mL) was added under N_2, and with stirring the mixture eventually became a light brown solution. After 4 hours at room temperature, the reaction was partitioned between ethyl acetate (15 mL) and H_2O (20 mL). The aqueous portion was extracted with an additional 2 x 5 mL ethyl acetate, and the combined organics were washed with H_2O and brine, dried ($MgSO_4$), filtered through cotton, and concentrated to a pale brown oil. This material was subjected to the reductive amination conditions described above. The more volatile components of the crude product were removed via short-path vacuum distillation; the remaining material was purified by Kugelrohr distillation (oven at 210 °C @ 0.5 Torr) to give a pale yellow oil (6.23 g, 65%). ^{1}H NMR ($CDCl_3$) δ 0.13 (s, 6H, Si^{t}Bu(CH_3)$_2$), 0.94 (s, 9H, SiMe$_2$(C(CH_3)$_3$)), 3.95 (broad s, 1H, -N*H*), 4.25 (d, J = 4.5 Hz, 2H, benzylic CH_2), 6.09 (apparent s, 1H, aromatic), 6.17-6.24 (m, 2H, aromatic), 6.97 (apparent t, 1H, aromatic), 7.22-7.33 (m, 5H, aromatic). ^{13}C NMR ($CDCl_3$) δ -4.06, 18.50, 26.01, 48.56, 104.81, 106.60, 109.51, 127.26, 127.55, 128.67, 129.85, 139.42, 149.47, 156.73. Calc. for $C_{19}H_{27}NOSi$: C 72.79, H 8.68; Found: C 72.50, H 8.74. IR (neat) ν (cm^{-1}) 3417.

***N*-(*p*-Methoxybenzyl)-3-chloro-4-methyl aniline (Table 3, Entry 6):** The product was crystallized from EtOH/H_2O in two crops to give a tan solid (79%), mp = 40-41.5 °C. ^{1}H NMR ($CDCl_3$) δ 2.23 (s, 3H, ArCH_3), 3.78 (s, 3H, -OCH_3), 3.85 (broad s, 1H, -N*H*), 4.18 (s, 2H, benzylic CH_2), 6.41 (apparent d, 1H, aromatic), 6.61 (apparent s, 1H, aromatic), 6.85 (d, J_{AB} = 9.0 Hz, 2H, aromatic), 6.95 (apparent d, 1H, aromatic), 7.23 (d, J_{AB} = 9.0 Hz, 2H, aromatic). ^{13}C

NMR ($CDCl_3$) δ 19.23, 48.09, 55.53, 111.73, 113.18, 114.15, 124.37, 128.85, 131.05, 131.32, 134.85, 147.30, 158.90. Calc. for $C_{15}H_{16}ClNO$: C 68.83, H 6.16; Found: C 68.68, H 6.14. IR (neat) ν (cm^{-1}) 3408.

Synthesis of Chloroacetanilides:

General Procedure: Unless otherwise noted, a biphasic mixture of the aniline (1 equiv) and KOH (3 equiv) in 1:1 to 2:1 ethyl acetate:water (1-2 mL EtOAc per mmol of aniline) is cooled to 0 °C using an ice/water bath. To the vigorously stirred mixture, chloroacetyl chloride (1.5 equiv) is added in small portions over 5 min. Stirring is continued at 0 °C for 20-30 min, at which point the reaction mixture is transferred to a separatory funnel. The organic layer is washed with brine, dried ($MgSO_4$), filtered, and concentrated with the aid of a rotary evaporator. The crude product is purified by recrystallization or by silica gel chromatography.

***N*-Methylchloroacetanilide (Table 1, Entry 1):**[53] Colorless solid (84%), recrystallized from aqueous ethanol, mp = 69-71 °C (lit[54] 69-70 °C).

***N*-Ethylchloroacetanilide (Table 1, Entry 2):**[55] Colorless oil (86%), obtained by silica gel chromatography (75:25 hexanes:ethyl acetate; $R_f = 0.24$).

***N*-Phenylchloroacetanilide (Table 1, Entry 3):**[55] A solution of diphenylamine (4.66 g, 27.5 mmol) and chloroacetyl chloride (4.39 mL, 55.1 mmol) in toluene (30 mL) was heated at 100 °C for 2 hours. The reaction was allowed to cool to room temperature, and the toluene and unreacted acid chloride were removed via rotary evaporator. The residue remaining was recrystallized from ethanol to afford a colorless solid (6.25 g, 92%), mp = 119-120 °C (lit.[55] 120-121 °C).

***N*-Benzylchloroacetanilide (Table 1, Entry 4):**[56] Colorless solid (81%), recrystallized from EtOH, mp = 77-79 °C (lit.[57] 79-80 °C).

***N*-Methyl-2-methylchloroacetanilide (Table 1, Entry 5):** Colorless solid (81%), obtained by recrystallization from EtOH/H_2O, mp = 45-47 °C. By ^{1}H NMR, the compound is a ~40:1 mixture of rotamers. ^{1}H NMR ($CDCl_3$) δ 2.27 (s, 3H, -ArCH_3), 3.24 (s, 3H, -NRCH_3), 3.76 (apparent q, 2H, -COCH_2Cl), 7.17 (apparent d, 1H, aromatic), 7.25-7.34 (m, 3H, aromatic). ^{13}C NMR ($CDCl_3$) δ 17.47, 36.77, 41.63, 127.83, 128.04, 129.23, 131.89, 135.55, 141.17, 166.47. Calc. for $C_{10}H_{12}ClNO$: C 60.76, H 6.12; Found: C 60.89, H 6.20. IR (neat) ν (cm^{-1}) 1671.

***N*-Methyl-2-methoxychloroacetanilide (Table 1, Entry 6):**[58] Colorless solid (94%), obtained by silica gel chromatography (75:25 hexanes:ethyl acetate; R_f = 0.21), mp = 49-50 °C (lit.[58] 49-50 °C).

***N*-(*p*-Methoxybenzyl)-3,5-dimethylchloroacetanilide (Table 2, Entry 1):** Colorless solid (88%), recrystallized from aqueous methanol, mp = 56-58 °C. ^{1}H NMR ($CDCl_3$) δ 2.26 (s, 6H, -ArCH_3), 3.77 (s, 3H, -OCH_3), 3.84 (s, 2H, -COCH_2Cl), 4.78 (s, 2H, benzylic CH_2), 6.58 (apparent s, 2H, aromatic), 6.77 (d, J_{AB} = 8.4 Hz, 2H, aromatic), 6.95 (apparent s, 1H, aromatic), 7.11 (d, J_{AB} = 8.4 Hz, 2H, aromatic). ^{13}C NMR ($CDCl_3$) δ 21.40, 42.50, 53.29, 53.39, 113.70, 125.75, 128.99, 130.30, 130.37, 139.58, 140.67, 158.93, 165.90. Calc. for $C_{18}H_{20}ClNO_2$: C 68.03, H 6.34; Found: C 68.14, H 6.33. IR (neat) ν (cm^{-1}) 1665.

***N*-Diphenylmethyl-4-(trimethylsilyl)chloroacetanilide (Table 2, Entry 2):** *N*-Diphenylmethyl-4-(trimethylsilyl)-aniline (1.66 g, 5.01 mmol) and pyridine (607 mL, 7.51 mmol) were dissolved in anhydrous toluene (7 mL). Chloroacetyl chloride (600 mL, 7.53 mmol) was added, forming a yellow, heterogeneous mixture. Additional toluene (3 mL) was added, and the mixture was heated to 60 °C. After 1 h, the mixture was allowed to cool was filtered through

a plug of cotton. The reaction flask and filter cake were washed well with ethyl acetate, and the combined filtrates were concentrated via rotary evaporator. The crude material was purified by silica gel chromatography (90:10 hexanes:ethyl acetate; $R_f = 0.11$) to give a colorless oil. This material was dissolved in EtOH (6-7 mL) and cooled to 0 °C. The material that crystallized was collected via filtration (810 mg), followed by a second crop (560 mg) of colorless solid (67% overall), mp = 88.5-89.5 °C. ^{1}H NMR ($CDCl_3$) δ 0.21 (s, 9H, -Si(CH_3)$_3$), 3.88 (s, 2H, -COCH_2Cl), 6.79 (d, J_{AB} = 8.4 Hz, 2H, aromatic), 7.08 (s, 1H, benzylic C*H*), 7.13-7.15 (m, 4H, aromatic), 7.21-7.24 (m, 6H, aromatic), 7.28 (d, J_{AB} = 8.4 Hz, 2H, aromatic). ^{13}C NMR ($CDCl_3$) δ -0.86, 43.14, 65.38, 127.65, 128.19, 129.25, 129.62, 134.16, 138.30, 139.30, 141.85, 166.44. Calc. for $C_{24}H_{26}ClNOSi$: C 70.65, H 6.42; Found: C 70.39, H 6.44. IR (neat) ν (cm^{-1}) 1671.

***N*-Benzyl-4-(chloro)chloroacetanilide (Table 2, Entry 3):** Colorless solid (99%), recrystallized from EtOH, mp = 96-97 °C. ^{1}H NMR ($CDCl_3$) δ 3.82 (s, 2H, -COCH_2Cl), 4.86 (s, 2H, benzylic CH_2), 6.94 (d, J_{AB} = 8.7 Hz, 2H, aromatic), 7.13-7.17 (m, 2H, aromatic), 7.24-7.26 (m, 3H, aromatic), 7.30 (d, J_{AB} = 8.7 Hz, 2H, aromatic). ^{13}C NMR ($CDCl_3$) δ 42.05, 53.86, 127.92, 128.65, 129.01, 129.75, 130.12, 134.80, 136.23, 139.22, 165.99. Calc. for $C_{15}H_{13}Cl_2NO$: C 61.24, H 4.45; Found: C 61.23, H 4.43. IR (neat) ν (cm^{-1}) 1671.

***N*-Methyl-4-nitrochloroacetanilide (Table 2, Entry 4):** A suspension of 4-nitro-*N*-methyl aniline (2.92 g, 19.2 mmol) and chloroacetyl chloride (3.00 mL, 37.7 mmol) in toluene (20 mL) was heated to 100 °C. After 2 hours, the reaction was allowed to cool, and the toluene and excess acid chloride were removed via rotary evaporator. The resulting residue was recrystallized from ethanol to give the title compound as a colorless to pale yellow solid (4.09 g, 93%), mp = 109-110.5 °C. ^{1}H NMR ($CDCl_3$) δ 3.40 (s, 3H, -NRCH_3), 3.96 (s, 2H, -COCH_2Cl), 7.49 (d, J_{AB} = 8.7 Hz, 2H, aromatic), 8.31 (d, J_{AB} = 8.7 Hz, 2H, aromatic). ^{13}C NMR ($CDCl_3$)

δ 38.22, 41.49, 125.35, 127.67, 146.84, 148.30, 165.90. Calc. for $C_9H_9ClN_2O_3$: C 47.28, H 3.97; Found: C 47.40, H 3.99. IR (neat) ν (cm^{-1}) 1519, 1667.

***N*-Methyl-3-methylchloroacetanilide (Table 3, Entry 1):** Colorless solid (79%), obtained by recrystallization from EtOH/H_2O, mp = 71-72 °C. ^1H NMR ($CDCl_3$) δ 2.39 (s, 3H, -ArCH_3), 3.29 (s, 3H, -NRCH_3), 3.85 (s, 2H, -COCH_2Cl), 7.00-7.03 (m, 2H, aromatic), 7.18 (apparent d, 1H, aromatic), 7.31 (apparent t, 1H, aromatic). ^{13}C NMR ($CDCl_3$) δ 21.60, 38.25, 41.89, 124.07, 127.67, 129.40, 129.91, 140.33, 142.64, 166.25. Calc. for $C_{10}H_{12}ClNO$: C 60.76, H 6.12; Found: C 60.87, H 6.11. IR (neat) ν (cm^{-1}) 1671.

***N*-(*p*-Methoxybenzyl)-3-methylchloroacetanilide (Table 3, Entry 2):** Colorless solid (73%), obtained by recrystallization from EtOH, mp = 56-57.5 °C. ^1H NMR ($CDCl_3$) δ 2.32 (s, 3H, -ArCH_3), 3.77 (s, 3H, -OCH_3), 3.84 (s, 2H, -COCH_2Cl), 4.81 (s, 2H, benzylic CH_2), 6.76 (apparent d, 1H, aromatic), 6.79 (d, J_{AB} = 8.7 Hz, 2H, aromatic), 6.84 (apparent s, 1H, aromatic), 7.12 (d, J_{AB} = 8.7 Hz, 2H, aromatic), 7.15 (apparent d, 1H, aromatic), 7.22 (apparent t, 1H, aromatic). ^{13}C NMR ($CDCl_3$) δ 21.36, 42.35, 53.22, 55.32, 113.83, 125.43, 128.84, 128.98, 129.57, 129.64, 130.50, 140.09, 140.82, 159.15, 166.09. Calc. for $C_{17}H_{18}ClNO_2$: C 67.21, H 5.97; Found: C 67.20, H 5.95. IR (neat) ν (cm^{-1}) 1673.

***N*-Benzyl-3,4-dimethoxychloroacetanilide (Table 3, Entry 3):** Colorless solid (94%), recrystallized from EtOH, mp = 94-95.5 °C. ^1H NMR ($CDCl_3$) δ 3.70 (s, 3H, -OCH_3), 3.87 (s, 3H, -OCH_3), 3.87 (s, 2H, -COCH_2Cl), 4.86 (s, 2H, benzylic CH_2), 6.39 (apparent s, 1H, aromatic), 6.59 (apparent d, 1H, aromatic), 6.79 (apparent d, 1H, aromatic), 7.19-7.28 (m, 5H, aromatic). ^{13}C NMR ($CDCl_3$) δ 42.31, 53.91, 56.12, 56.19, 111.27, 111.46, 120.52, 127.77, 128.53, 129.30, 133.43, 136.86, 149.11, 149.36, 166.41. Calc. for $C_{17}H_{18}ClNO_3$: C 63.85, H 5.67; Found: C 63.82, H 5.62. IR (neat) ν (cm^{-1}) 1677.

***N*-(*p*-Methoxybenzyl)-3-trifluoromethylchloroacetanilide (Table 3, Entry 4):** Colorless solid (82%), obtained by recrystallization from EtOH, mp = 78-79 °C. ^{1}H NMR ($CDCl_3$) δ 3.78 (s, 3H, -OC*H*$_3$), 3.80 (s, 2H, -COC*H*$_2$Cl), 4.85 (s, 2H, benzylic C*H*$_2$), 6.80 (d, J_{AB} = 8.7 Hz, 2H, aromatic), 7.09 (d, J_{AB} = 8.7 Hz, 2H, aromatic), 7.19 (apparent d, 1H, aromatic), 7.31 (apparent s, 1H, aromatic), 7.51 (apparent t, 1H, aromatic), 7.64 (apparent d, 1H, aromatic). ^{13}C NMR ($CDCl_3$) δ 41.95, 53.24, 55.35, 114.09, 123.36 (q, J = 272.6 Hz), 125.71 (apparent q), 128.20, 130.52, 130.61, 132.44 (q, J = 33.2 Hz), 141.38, 159.45, 165.90 (remaining two resonances are likely occluded behind larger peaks). Calc. for $C_{17}H_{15}ClF_3NO_2$: C 57.07, H 4.23; Found: C 56.97, H 4.20. IR (neat) ν (cm^{-1}) 1671.

***N*-Benzyl-3-(*tert*-butyldimethylsiloxy)chloroacetanilide (Table 3, Entry 5):** Obtained as a colorless to pale yellow oil of ~90 % purity (88% yield) by Kugelrohr distillation (oven at 220 °C @ 0.6 Torr). Redistillation, discarding the initial ~30% of the distillate, afforded analytically pure material. ^{1}H NMR ($CDCl_3$) δ 0.10 (s, 6H, Si^{t}Bu(C*H*$_3$)$_2$), 0.93 (s, 9H, SiMe$_2$(C(C*H*$_3$)$_3$)), 3.87 (s, 2H, -COC*H*$_2$Cl), 4.86 (s, 2H, benzylic C*H*$_2$), 6.43 (apparent s, 1H, aromatic), 6.63 (apparent d, 1H, aromatic), 6.80 (apparent d, 1H, aromatic), 7.16-7.25 (m, 6H, aromatic). ^{13}C NMR ($CDCl_3$) δ -4.22, 18.39, 25.79, 42.20, 53.73, 120.10, 120.75, 120.99, 127.69, 128.49, 128.95, 130.52, 136.56, 141.60, 156.56, 166.00. Calc. for $C_{21}H_{28}ClNO_2Si$: C 64.67, H 7.24; Found: C 64.88, H 7.02. IR (neat) ν (cm^{-1}) 1671.

***N*-(*p*-Methoxybenzyl)-3-chloro-4-methylchloroacetanilide (Table 3, Entry 6):** Pale yellow, viscous oil (89%), purified by Kugelrohr distillation (oven at 230 °C @ 0.5 Torr). This oil eventually solidified upon standing for several weeks (mp = 45-48 °C). ^{1}H NMR ($CDCl_3$) δ 2.37 (s, 3H, ArC*H*$_3$), 3.78 (s, 3H, -OC*H*$_3$), 3.82 (s, 2H, -COC*H*$_2$Cl), 4.78 (s, 2H, benzylic C*H*$_2$), 6.74 (apparent d, 1H, aromatic), 6.78 (d, J_{AB} = 8.7 Hz, 2H, aromatic), 7.03 (apparent s, 1H, aromatic),

7.09 (d, J_{AB} = 8.7 Hz, 2H, aromatic), 7.17 (apparent d, 1H, aromatic). ^{13}C NMR ($CDCl_3$) δ 20.16, 42.26, 53.36, 55.48, 113.97, 126.83, 128.53, 128.82, 130.46, 131.87, 135.17, 137.14, 139.42, 159.18, 165.94. Calc. for $C_{17}H_{17}Cl_2NO_2$: C 60.37, H 5.07; Found: C 60.33, H 5.04. IR (neat) ν (cm^{-1}) 1684.

General Procedure for Palladium-Catalyzed Oxindole Formation: An oven-dried Schlenk tube equipped with a magnetic stir bar and a Teflon stopcock was evacuated while hot and cooled under nitrogen. The tube was charged with palladium acetate (1.0 to 3.0 mol%), 2-(di-*tert*-butylphosphino)biphenyl (Pd:ligand = 1:2), and the chloroacetanilide substrate (1.00 mmol). The tube was evacuated and backfilled with nitrogen (this sequence was repeated 3 times), and the Teflon stopcock was replaced with a rubber septum. Anhydrous triethylamine (0.21 mL, 1.50 mmol) was added, followed by anhydrous toluene (1.0 mL). The septum was replaced by the Teflon stopcock under a positive pressure of nitrogen, and the sealed tube was placed in an oil bath preheated to 80 °C. After the designated time period, the reaction was allowed to cool to room temperature and was diluted with ethyl acetate (10 mL). The mixture was filtered through a plug of Celite and concentrated on a rotary evaporator. The crude material thus obtained was purified by silica gel chromatography to give the product oxindole.

1-Methyl oxindole (Table 1, Entry 1):[59] Reaction time: 2.5 h, using 1 mol% Pd; the product was obtained as a colorless solid (93%) by silica gel chromatography (75:25 hexanes:ethyl acetate; R_f = 0.19), mp = 87-88 °C (lit.[59] 86.5–87 °C).

1-Ethyl oxindole (Table 1, Entry 2):[60] Reaction time: 3 h, using 1 mol% Pd; the product was obtained as a colorless solid (99%) by silica gel chromatography (80:20 hexanes:ethyl acetate; R_f = 0.16), mp = 95-96.5 °C (lit.[61] 93-94 °C).

1-Phenyl oxindole (Table 1, Entry 3):[62] Reaction time: 3 h, using 2 mol% Pd; the product was obtained as a colorless solid (95%) by silica gel chromatography (85:15 hexanes:ethyl acetate; R_f = 0.16), mp = 122-123 °C (lit.[62] 119-121 °C).

1-Benzyl oxindole (Table 1, Entry 4):[63] Reaction time: 3 h, using 2 mol% Pd; the product was obtained as a colorless solid (98%) by silica gel chromatography (80:20 hexanes:ethyl acetate; R_f = 0.32), mp = 66-68 °C (lit.[63] 66.5-67 °C).

1,7-Dimethyl oxindole (Table 1, Entry 5): Reaction time: 6 h, using 2 mol% Pd; the product was obtained as a colorless to pale yellow solid (86%) by silica gel chromatography (75:25 hexanes:ethyl acetate; R_f = 0.17), mp = 118-119.5 °C. ^{1}H NMR ($CDCl_3$) δ 2.56 (s, 3H, ArC*H*$_3$), 3.46 (s, 2H, -COC*H*$_2$Ar), 3.47 (s, 3H, -NRC*H*$_3$), 6.89 (apparent t, 1H, aromatic), 6.98 (apparent d, 1H, aromatic), 7.04 (apparent d, 1H, aromatic). ^{13}C NMR ($CDCl_3$) δ 19.22, 29.77, 35.85, 119.74, 122.27, 122.29, 125.01, 131.57, 142.93, 175.67. Calc. for $C_{10}H_{11}NO$: C 74.51, H 6.88; Found: C 74.20, H 6.74. IR (neat) ν (cm^{-1}) 1694.

1-Methyl-7-methoxy oxindole (Table 1, Entry 6):[58] Reaction time: 6 h, using 2 mol% Pd; the product was obtained as a colorless solid (88%) by silica gel chromatography (75:25 hexanes:ethyl acetate; R_f = 0.18), mp = 101-101.5 °C (lit.[58] 101-102 °C).

1-(*p*-Methoxybenzyl)-4,6-dimethyl oxindole (Table 2, Entry 1): Reaction time: 3 h, using 2 mol% Pd; the product was obtained as a colorless to pale yellow solid (81%) by silica gel chromatography (75:25 hexanes:ethyl acetate; R_f = 0.25), mp = 124-126 °C. ^{1}H NMR ($CDCl_3$) δ 2.21 (s, 3H, ArC*H*$_3$), 2.26 (s, 3H, ArC*H*$_3$), 3.43 (s, 2H, -COC*H*$_2$Ar), 3.76 (s, 3H, -OC*H*$_3$), 4.80 (s, 2H, benzylic C*H*$_2$), 6.40 (apparent s, 1H, aromatic), 6.63 (apparent s, 1H, aromatic), 6.81 (d, J_{AB} = 8.7 Hz, 2H, aromatic), 7.22 (d, J_{AB} = 8.7 Hz, 2H, aromatic). ^{13}C NMR ($CDCl_3$) δ 18.81, 22.02, 34.83, 43.44, 55.48, 107.53, 114.15, 120.27, 124.30, 128.31, 128.71, 133.73, 137.80,

144.18, 158.92, 175.48. Calc. for $C_{18}H_{19}NO_2$: C 76.84, H 6.81; Found: C 76.71, H 6.76. IR (neat) ν (cm^{-1}) 1702.

1-Diphenylmethyl-5-(trimethylsilyl)oxindole (Table 2, Entry 2): Reaction time: 19 h (at 100 °C), using 3 mol% Pd; the product was obtained as a colorless solid (79%) by silica gel chromatography (90:10 hexanes:ethyl acetate; R_f = 0.14), mp = 156-159 °C. ^{1}H NMR ($CDCl_3$) δ 0.21 (s, 9H, - Si(CH_3)$_3$), 3.64 (s, 2H, -COCH_2Ar), 6.41 (apparent d, 1H, aromatic), 7.02 (s, 1H, benzylic C*H*), 7.10 (apparent d, 1H, aromatic), 7.24-7.32 (m, 10H, aromatic), 7.36 (apparent s, 1H, aromatic). ^{13}C NMR ($CDCl_3$) δ -0.61, 35.78, 58.35, 111.58, 124.11, 127.80, 128.59, 128.63, 129.08, 132.60, 133.15, 137.83, 144.56, 175.29. Calc. for $C_{24}H_{25}NOSi$: C 77.58, H 6.78; Found: C 77.85, H 6.87. IR (neat) ν (cm^{-1}) 1708.

1-Benzyl-5-chloro oxindole (Table 2, Entry 3): Reaction time: 3 h, using 3 mol% Pd; the product was obtained as a colorless solid (74%) by silica gel chromatography (80:20 hexanes:ethyl acetate; R_f = 0.19), mp = 103-104.5 °C. ^{1}H NMR ($CDCl_3$) δ 3.62 (s, 2H, - COCH_2Ar), 4.90 (s, 2H, benzylic CH_2), 6.61 (apparent d, 1H, aromatic), 7.13 (apparent d, 1H, aromatic), 7.22 (apparent s, 1H, aromatic), 7.26-7.34 (m, 5H, aromatic). ^{13}C NMR ($CDCl_3$) δ 35.84, 44.02, 110.11, 125.07, 126.25, 127.48, 127.95, 127.97, 129.04, 135.59, 143.00, 174.69 (only 12 resonances, not 13, were observed). Calc. for $C_{15}H_{12}ClNO$: C 69.91, H 4.69; Found: C 69.56, H 4.72. IR (neat) ν (cm^{-1}) 1702.

1-Methyl-5-nitro oxindole (Table 2, Entry 4):[64] Reaction time: 3 h, using 1 mol% Pd; the product was obtained as a colorless to pale yellow solid (92%) by silica gel chromatography (60:40 hexanes:ethyl acetate; R_f = 0.26), mp = 195-196 °C (lit.[10b] 198 °C).

1-Methyl-6-methyl oxindole (Table 3, Entry 1):[65] Reaction time: 3 h, using 1 mol% Pd; the product was obtained as a colorless to pale yellow solid (93%) by silica gel chromatography

(80:20 hexanes:ethyl acetate; $R_f = 0.18$). The isolated material was a 15:1 mixture of regioisomers, mp = 85-88 °C (lit.[65] 94.5-96 °C).

1-(*p*-Methoxybenzyl)-6-methyl oxindole (Table 3, Entry 2): Reaction time: 3 h, using 2 mol% Pd; the product was obtained as a colorless solid (97%) by silica gel chromatography (75:25 hexanes:ethyl acetate; $R_f = 0.27$). The isolated material was a 14:1 mixture of regioisomers, mp = 101-105 °C. ^{1}H NMR ($CDCl_3$) δ 2.29 (s, 3H, ArC*H*$_3$), 3.55 (s, 2H, -COC*H*$_2$Ar), 3.77 (s, 3H, -OC*H*$_3$), 4.83 (s, 2H, benzylic C*H*$_2$), 6.57 (apparent s, 1H, aromatic), 6.80 (apparent d, 1H, aromatic), 6.84 (d, J_{AB} = 8.7 Hz, 2H, aromatic), 7.10 (apparent d, 1H, aromatic), 7.25 (d, J_{AB} = 8.7 Hz, 2H, aromatic). ^{13}C NMR ($CDCl_3$) δ 21.97, 35.71, 43.27, 55.42, 110.04, 114.27, 121.61, 123.02, 124.25, 128.30, 128.84, 137.99, 144.62, 159.16, 175.69. Calc. for $C_{17}H_{17}NO_2$: C 76.38, H 6.41; Found: C 76.09, H 6.36. IR (neat) ν (cm^{-1}) 1710.

1-Benzyl-5,6-dimethoxy oxindole (Table 3, Entry 3):[60] Reaction time: 3 h, using 2 mol% Pd; the product was obtained as a colorless solid (94%) by silica gel chromatography (60:40 hexanes:ethyl acetate; $R_f = 0.17$), mp = 119-120 °C (lit.[60] 118-120 °C).

1-(*p*-Methoxybenzyl)-6-trifluoromethyl oxindole (Table 3, Entry 4): Reaction time: 3 h, using 2 mol% Pd; the product was obtained as a colorless to pale yellow solid (97%) by silica gel chromatography (75:25 hexanes:ethyl acetate; $R_f = 0.18$), mp = 153-155 °C. ^{1}H NMR ($CDCl_3$) δ 3.64 (s, 2H, -COC*H*$_2$Ar), 3.78 (s, 3H, -OC*H*$_3$), 4.87 (s, 2H, benzylic C*H*$_2$), 6.86 (d, J_{AB} = 8.7 Hz, 2H, aromatic), 6.96 (apparent s, 1H, aromatic), 7.26 (d, J_{AB} = 8.7 Hz, 2H, aromatic), 7.28 (apparent d, 1H, aromatic), 7.34 (apparent d, 1H, aromatic). ^{13}C NMR ($CDCl_3$) δ 35.78, 43.56, 55.45, 105.68 (q, J = 3.8 Hz), 114.46, 119.59 (q, J = 4.2 Hz), 124.09 (q, J = 272.2 Hz), 124.76, 127.45, 128.63 (apparent q), 129.04, 130.57 (q, J = 32.3 Hz), 145.09, 159.43, 174.75. Calc. for $C_{17}H_{14}F_3NO_2$: C 63.55, H 4.39; Found: C 63.28, H 4.38. IR (neat) ν (cm^{-1}) 1715.

1-Benzyl-6-(*tert*-butyldimethylsiloxy)oxindole (Table 3, Entry 5):[3] Reaction time: 4 h, using 2 mol% Pd; the product was obtained as a colorless oil (93%), obtained by silica gel chromatography (85:15 hexanes:ethyl acetate; $R_f = 0.17$).

1-(*p*-Methoxybenzyl)-5-methyl-6-chloro oxindole (Table 3, Entry 6): Reaction time: 4 h, using 3 mol% Pd; the product was obtained as a colorless solid (74%) by silica gel chromatography (75:25 hexanes:ethyl acetate; $R_f = 0.25$), mp = 147-149 °C. ^{1}H NMR ($CDCl_3$) δ 2.29 (s, 3H, ArCH_3), 3.53 (s, 2H, -COCH_2Ar), 3.77 (s, 3H, -OCH_3), 4.79 (s, 2H, benzylic CH_2), 6.71 (apparent s, 1H, aromatic), 6.83 (d, J_{AB} = 8.4 Hz, 2H, aromatic), 7.07 (apparent s, 1H, aromatic), 7.21 (d, J_{AB} = 8.4 Hz, 2H, aromatic). ^{13}C NMR ($CDCl_3$) δ 19.98, 35.64, 43.57, 55.49, 109.92, 114.30, 123.04, 126.75, 127.63, 128.80, 129.54, 133.17, 143.31, 159.12, 174.85. Calc. for $C_{17}H_{16}ClNO_2$: C 67.66, H 5.34; Found: C 67.63, H 5.30. IR (neat) ν (cm^{-1}) 1704.

***N*-Methyl-*N*-phenyl-2-bromopropionamide (Scheme 13):**[66] A biphasic mixture of NaOH (5.32 g, 133 mmol) and *N*-methylaniline (4.40 mL, 40.6 mmol) in EtOAc (40 mL) and H_2O (40 mL) was cooled to 0 °C. To the vigorously stirred reaction, 2-bromopropionyl bromide (5.50 mL, 52.5 mmol) was added in small portions. After 25 minutes at 0 °C, the reaction layers were separated using a separatory funnel. The organic layer was dried ($MgSO_4$), filtered, and concentrated. The resulting oil was purified by silica gel chromatography (80:20 hexanes:EtOAc; $R_f = 0.21$) to give an oil. The product was crystallized from CH_2Cl_2/hexanes to give colorless crystals (5.44 g, 55%), mp = 43.5-46 °C. (lit.[67] 46 °C)

Cyclization of *N*-Methyl-*N*-phenyl-2-bromopropionamide: The oxindole cyclization procedure described above was followed, using 2 mol% $Pd(OAc)_2$ and 4 mol% ligand. The reaction was conducted at 110 °C. After 5 h of reaction, the mixture was allowed to cool, and was diluted with EtOAc, filtered through Celite, and concentrated via rotary evaporator. ^{1}H

NMR analysis of the residue indicated a ~50% conversion of the starting bromoamide to what appears to be the desired oxindole. Trace (if any) resonances due to vinylic protons are observed (see Figures 4 and 5).

***N-tert*-Butoxycarbonyl-4-Methoxychloroacetanilide (Scheme 15):** A roundbottom flask was charged with 4-methoxychloroacetanilide[68] (2.05 g, 10.3 mmol), and 4-dimethylaminopyridine (DMAP, 60 mg, 5 mol%). The flask was evacuated and backfilled with N_2, and anhydrous THF (10 mL) was added. The resulting suspension was treated with di-*tert*-butyldicarbonate (2.83 mL, 12.3 mmol) and additional THF (5 mL), and was allowed to stir at rt. After 10 h, GC-MS analysis indicated incomplete conversion, so additional DMAP (250 mg, 25 mol% total) in THF (2 mL) was added. After another hour, the reaction was partitioned between EtOAc and H_2O. The organic layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated via rotary evaporator. The crude material was purified by silica gel chromatography (90:10 hexanes: EtOAc; $R_f = 0.22$) to give a colorless solid. Recrystallization from hexanes afforded the title compound as colorless needles (1.29 g, 42%), mp = 108.5-110.5 °C. ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 9H, -C(CH_3)$_3$), 3.84 (s, 3H, -OCH_3), 4.80 (s, 2H, -COCH_2Cl), 6.92 (d, J = 9.0 Hz, 2H, aromatic), 7.02 (d, J = 9.0 Hz, 2H, aromatic). ^{13}C NMR ($CDCl_3$) δ 28.08, 46.38, 55.67, 84.28, 114.40, 129.03, 130.72, 152.68, 159.13, 169.24. Calc. for $C_{14}H_{18}ClNO_4$: C 56.10, H 6.05; Found: C 55.97, H 6.12. IR (CH_2Cl_2) ν (cm^{-1}) 1743, 1715.

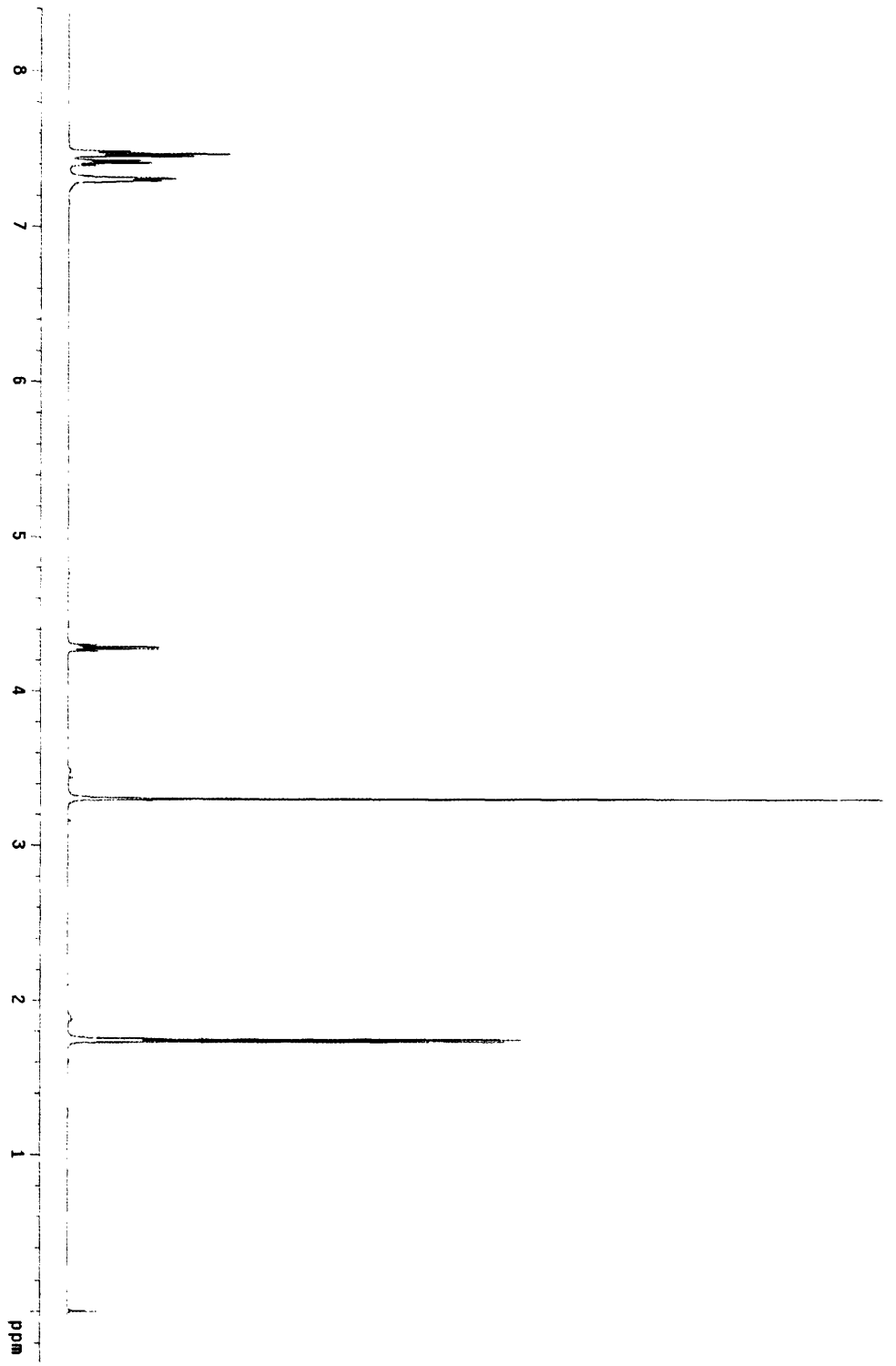


Figure 4. ^{1}H NMR Spectrum of *N*-Methyl-*N*-Phenyl-α-Bromopropionamide

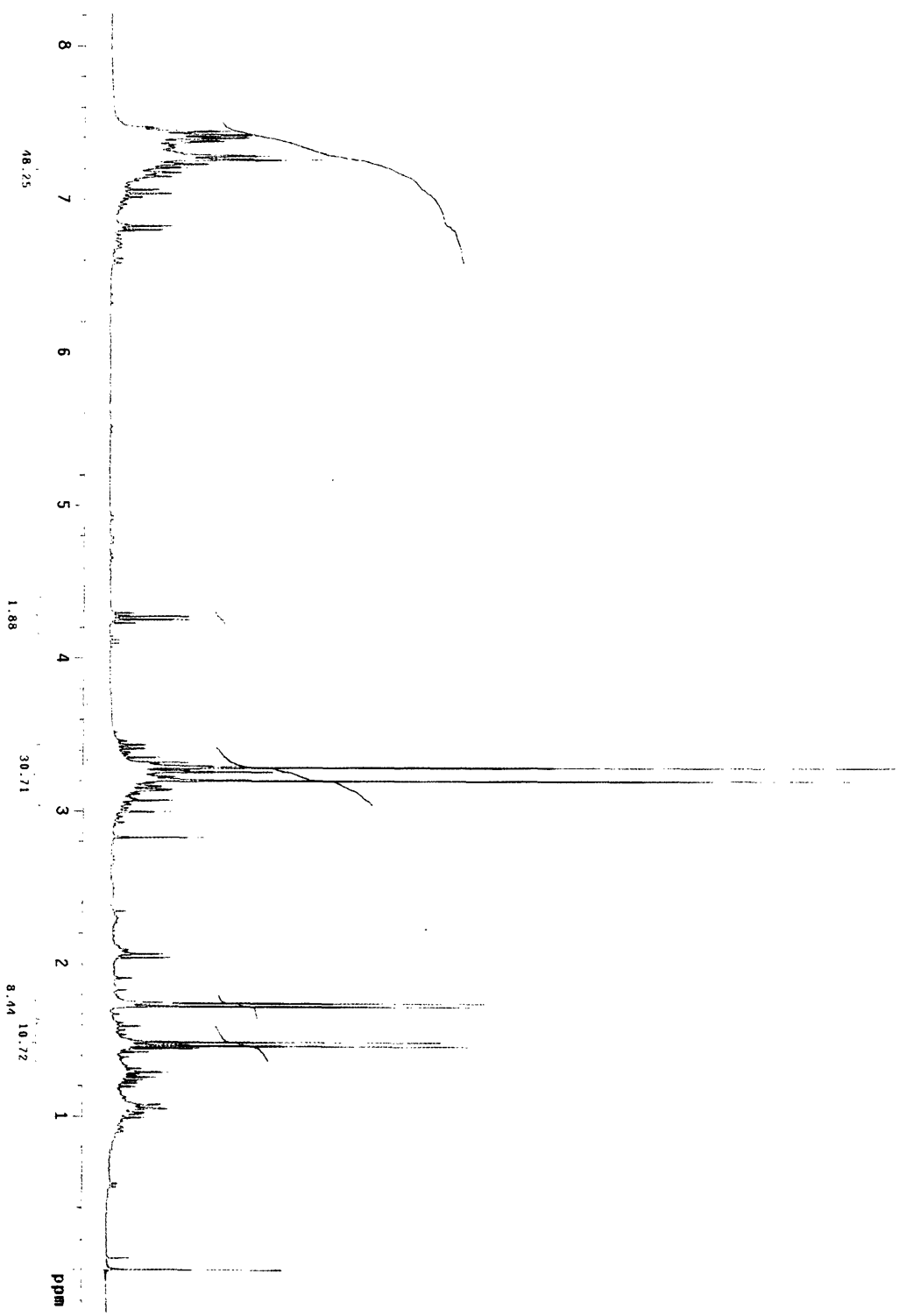


Figure 5. Reaction Mixture of Cyclization of *N*-Methyl-*N*-Phenyl-α-Bromopropionamide

Determination of Kinetic Isotope Effects

Intermolecular Case:

***d_5*-Acetanilide**: A 250 mL Erlenmeyer flask containing a solution of *d_7*-aniline (5.0g, 50 mmol) in glacial acetic acid (10 mL) was treated with acetic anhydride (7.1 mL, 75 mmol). After standing at room temperature for 20 min, the solution was treated with cold H_2O (125 mL) in one portion, causing crystallization of a colorless solid. The flask was stored in the refrigerator for 30 min, and the solid was filtered via suction, washed thoroughly with cold water, and dried *in vacuo* to afford the title compound (5.26 g, 75%), mp = 115-116 °C. ^{1}H NMR ($CDCl_3$) δ 2.14 (s, 3H, -COC*H*$_3$), 8.01 (broad s, 1H, -N*H*). ^{13}C NMR ($CDCl_3$) δ 24.61, 119.82 (apparent t), 123.92 (apparent t), 128.57 (apparent t), 138.02, 169.07. HRMS (ESI) Calc. for $C_8H_4D_5NO$ $[M+H]^+$: 141.1071, Found 141.1078. IR (neat) ν (cm^{-1}) 1661, 3286.

***d_5*-*N*-Methylacetanilide:** A round bottomed flask was charged with *d_5*-acetanilide (4.54 g, 32.4 mmol) and NaH (60% dispersion in mineral oil, 1.64 g, 41.0 mmol). The flask was evacuated and backfilled with nitrogen, and anhydrous THF (25 mL) was added (Caution: the deprotonation results in vigorous gas evolution, and a sufficient vent for the reaction should be provided). The resulting suspension was allowed to stir at room temperature for 15 min. Dimethyl sulfate (3.8 mL, 40 mmol, passed through a plug of alumina immediately prior to use) was added dropwise. After 3 h at room temperature, the reaction mixture was treated with ethyl acetate (10 mL) and H_2O (20 mL). The aqueous layer was extracted with ethyl acetate (5 mL), and the combined organics were washed with brine, dried ($MgSO_4$), filtered through cotton, and concentrated. The crude material obtained was purified by recrystallization from EtOH/hexanes to give the title compound as a colorless solid (4.07 g, 81%), mp = 99-100 °C. ^{1}H NMR ($CDCl_3$) δ 1.88 (s, 3H, -COC*H*$_3$), 3.27 (s, 3H, -NRC*H*$_3$). ^{13}C NMR ($CDCl_3$) δ 22.40, 37.15, 126.62

(apparent t), 127.21 (apparent t), 129.25 (apparent t), 144.40, 170.58. HRMS (ESI) Calc. for $C_9H_6D_5NO$ $[M+H]^+$: 155.1227, Found 155.1231. IR (neat) ν (cm^{-1}) 1656.

***d_5*-*N*-Methylchloroacetanilide:** A mixture of *d_5*-*N*-methylacetanilide (2.06 g, 14.7 mmol), NaOH (1.66 g, 41.5 mmol), and H_2O (20 mL) was heated at 100 °C for 6 h. The mixture was allowed to cool, and was extracted with ethyl acetate (2 x 10 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered through cotton, and concentrated. Distillation of the crude material (43 °C @ 0.7 Torr) gave *d_5*-*N*-methylaniline as a pale yellow oil (1.18 g, 72%). This material was treated with KOH (1.35 g, 21.2 mmol), ethyl acetate (20 mL), and H_2O (10 mL). The biphasic mixture was cooled to 0 °C, and chloroacetyl chloride (1.26 mL, 15.8 mmol) was added in small portions. After 15 minutes at 0 °C, the reaction layers were separated, and the organic portion was dried ($MgSO_4$), filtered through cotton, and concentrated to an oil which crystallized on standing. Recrystallization from EtOH/H_2O afforded the title compound as colorless crystals (1.81 g, 91%), mp = 69-70 °C. ^1H NMR ($CDCl_3$) δ 3.32 (s, 3H, -NC*H_3*), 3.86 (s, 2H, -COC*H_2*Cl). ^{13}C NMR ($CDCl_3$) δ 38.13, 41.70, 126.77 (apparent t), 128.21 (apparent t), 129.73 (apparent t), 142.64, 166.39. HRMS (ESI) Calc. for $C_9H_5D_5ClNO$ $[M+H]^+$: 189.0838, Found 189.0841. IR (neat) ν (cm^{-1}) 1679.

Determination of Intermolecular Isotope Effect: An oven-dried Schlenk tube equipped with a magnetic stir bar and a Teflon stopcock was evacuated while hot and cooled under nitrogen. The tube was charged with palladium acetate (2.3 mg, 1.0 mol%), 2-(di-*tert*-butylphosphino)biphenyl (6.0 mg, 2.0 mol%), *N*-methylchloroacetanilide (92.3 mg, 0.50 mmol), and *d_5*-*N*-methylchloroacetanilide (94.6 mg, 0.50 mmol). The tube was evacuated and backfilled with nitrogen (this sequence was repeated 3 times), and the Teflon stopcock was replaced with a rubber septum. Anhydrous triethylamine (0.21 mL, 1.50 mmol) was added, followed by

anhydrous toluene (1.0 mL). The septum was replaced by the Teflon stopcock under a positive pressure of nitrogen, and the sealed tube was placed in an oil bath preheated to 80 °C. After 10.0 minutes, the reaction tube was cooled to room temperature using running tap water, and the reaction mixture was diluted with ethyl acetate (10 mL). The mixture was filtered through a plug of Celite and concentrated on a rotary evaporator. The crude material was analyzed by ^{1}H NMR spectroscopy (500 MHz, allowing 30 sec between each transient to ensure complete relaxation of all protons, Figure 6). Comparing this data with the spectra of *N*-methylchloroacetanilide (Figure 7), and *N*-methyloxindole (Figure 8), it can be seen the cyclization proceeded to ~20% conversion in 10 minutes. The ratio of the aromatic oxindole proton integrals to the benzylic oxindole proton integral is what is expected in the absence of an isotope effect; that is, half of the oxindole formed comes from the deuterated substrate.

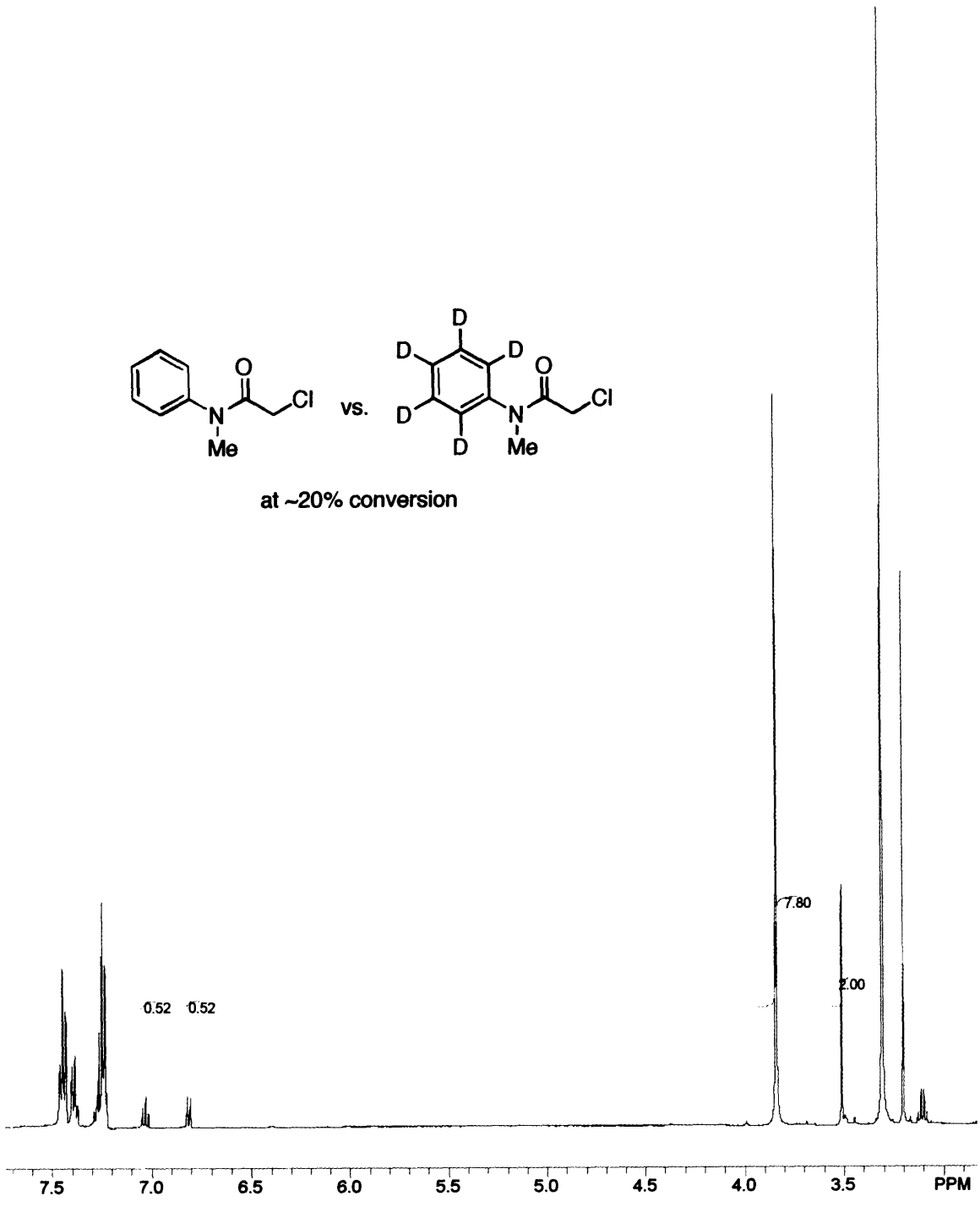


Figure 6. Reaction Mixture of Intermolecular Competition Experiment at ~20% Conversion

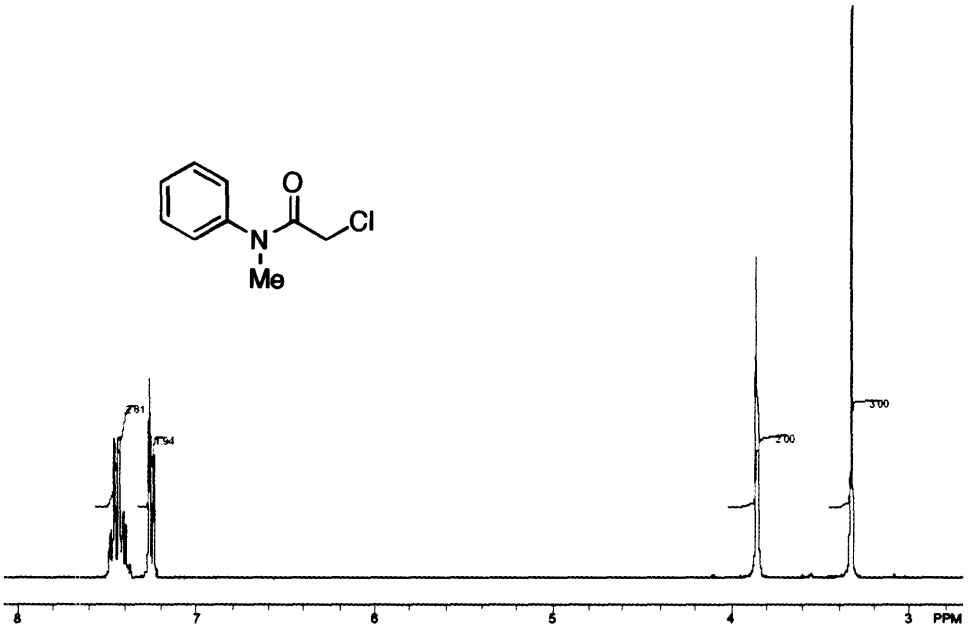


Figure 7. *N*-Methylchloroacetanilide

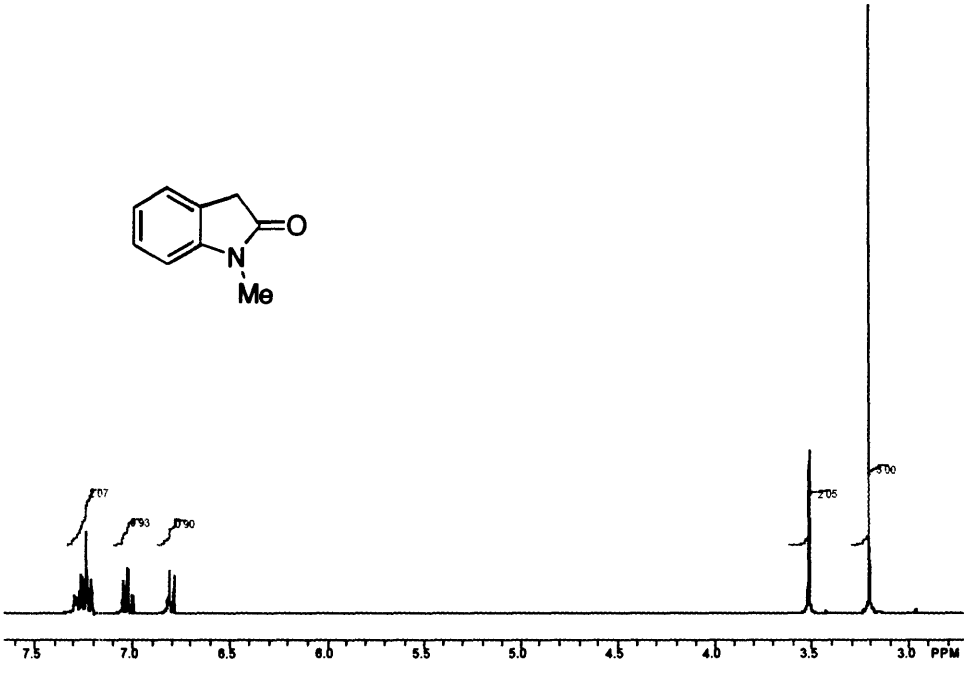


Figure 8. *N*-Methyloxindole

Intramolecular Cases:

***N*-(2-Bromophenyl)-*O*-benzyl carbamate:** A solution of 2-bromoaniline (5.05 g, 29.4 mmol) and pyridine (3.25 mL, 40.2 mmol) in ethyl acetate (30 mL) was treated dropwise with benzyl chloroformate (5.0 mL, 35 mmol) at room temperature, taking care to minimize the rate of the exothermic reaction. After 2 h, the colorless suspension was washed with H_2O (20 mL), 1 N HCl (10 mL), saturated aqueous $NaHCO_3$ (10 mL), and brine (10 mL). The solution was dried ($MgSO_4$), filtered through cotton, and concentrated via rotary evaporator. The resulting oil was dissolved in hexanes (30 mL), and the solution was stored in the refrigerator overnight. At this point a solid had formed which was filtered via suction, washed with cold hexanes, and dried in air to afford 6.96 g (77 %) of colorless needles, mp = 50-51 °C. ^{1}H NMR ($CDCl_3$) δ 5.20 (s, 2H, benzylic C*H*$_2$), 6.90 (apparent t, 1H, aromatic), 7.18 (broad s, 1H, -N*H*), 7.28 (apparent t, 1H, aromatic), 7.32-7.42 (m, 5H, aromatic), 7.48 (apparent d, 1H, aromatic), 8.15 (apparent d, 1H, aromatic). ^{13}C NMR ($CDCl_3$) δ 67.53, 112.64, 120.26, 124.40, 128.49, 128.52, 128.56, 128.73, 132.37, 135.79, 135.81, 153.04. Calc. for $C_{14}H_{12}BrNO_2$: C 54.92, H 3.95; Found: C 55.09, H 3.86. IR (neat) ν (cm^{-1}) 1698, 3292.

***N*-(2-Bromophenyl)-*N*-methyl-*O*-benzyl carbamate:** A round bottomed flask was charged with *N*-(2-bromophenyl)-*O*-benzyl carbamate (6.39 g, 20.9 mmol) and NaH (60% dispersion in mineral oil, 1.04 g, 26.0 mmol). The flask was evacuated and backfilled with nitrogen, and anhydrous THF (20 mL) was added (Caution: the deprotonation results in vigorous gas evolution, and a sufficient vent for the reaction should be provided). The resulting suspension was allowed to stir at room temperature for 15 minutes. Dimethyl sulfate (2.6 mL, 28 mmol, passed through a plug of alumina immediately prior to use) was added dropwise, followed by additional THF (10 mL). After 4.5 h at room temperature, the reaction mixture was treated with

ethyl acetate (10 mL) and H_2O (30 mL). The aqueous layer was extracted with ethyl acetate (10 mL), and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered through cotton, and concentrated. Purification by silica gel chromatography (80:20 hexanes:ethyl acetate; $R_f = 0.32$) afforded the title compound as a colorless oil (6.51 g, 97%); at room temperature in $CDCl_3$, the product is a ~3:1 mixture of rotamers. ^1H NMR ($CDCl_3$) δ 3.21 (s, 3H, -NC*H*$_3$ of major rotamer), 3.22 (s, 3H, -NC*H*$_3$ of minor rotamer), 5.09 (s, 2H, benzylic C*H*$_2$ of major rotamer), 5.22 (s, 2H, benzylic C*H*$_2$ of minor rotamer), 7.10-7.41 (m, 8H, aromatic), 7.59 (apparent d, 1H, aromatic). ^{13}C NMR ($CDCl_3$, peaks corresponding to major rotamer) δ 37.31, 67.45, 123.25, 127.39, 127.72, 128.06, 128.29, 128.49, 129.08, 129.52, 133.34, 136.57, 141.72, 155.24. Calc. for $C_{15}H_{14}BrNO_2$: C 56.27, H 4.41; Found: C 56.31, H 4.37. IR (neat) ν (cm^{-1}) 1706.

***N*-(2-Deuteriophenyl)-*N*-methyl-*O*-benzyl carbamate:** An oven-dried 100 mL round bottomed flask equipped with a rubber septum was evacuated while hot and allowed to cooled under N_2. The flask was charged with *N*-(2-bromophenyl)-*N*-methyl-*O*-benzyl carbamate (5.24 g, 16.4 mmol), and the flask was again evacuated and backfilled with N_2. Anhydrous THF (30 mL) was added, and the colorless solution was cooled to -78 °C. A solution of freshly titrated *n*-BuLi in hexanes (1.65 M, 11.0 mL, 18.2 mmol) was added dropwise, forming a dark red solution. After 1 h at -78 °C, CD_3OD (1.20 mL, 29.5 mmol) was added, forming an orange suspension. After warming to room temperature, the mixture was washed with H_2O (20 mL). The aqueous fraction was extracted with ethyl acetate (10 mL), and the combined organics were washed with brine, dried ($MgSO_4$), filtered through cotton, and concentrated to an oil. Purification by silica gel chromatography (90:10 hexanes:ethyl acetate; $R_f = 0.14$) afforded the title compound as a yellow oil (3.30 g, 83%). ^1H NMR ($CDCl_3$) δ 3.32 (s, 3H, -NC*H*$_3$), 5.16 (s, 2H, -benzylic C*H*$_2$), 7.19-

7.38 (m, 9H, aromatic. ^{13}C NMR ($CDCl_3$) δ 37.98, 67.46, 125.92, 126.31, 127.88, 128.09, 128.62, 128.94, 129.04, 136.82, 143.32, 155.67. HRMS (ESI) Calc. for $C_{15}H_{14}DNO_2$ $[M+H]^+$: 243.1238, Found 243.1246. IR (neat) ν (cm^{-1}) 1698.

***N*-Methyl-2-deuteriochloroacetanilide:** A flask containing *N*-(2-deuteriophenyl)-*N*-methyl-*O*-benzyl carbamate (2.95 g, 12.2 mmol) and 5% Pd/C (121 mg, 0.5 mol %) was evacuated and backfilled with H_2 via a filled balloon. Ethyl acetate (15 mL) was added, and the reaction was allowed to stir at room temperature under 1 atm of H_2. The reaction progress was monitored by GC. Once all of the starting carbamate had been consumed, the reaction mixture was filtered through a plug of Celite. Concentration of the filtrate afforded the crude aniline, which was treated with KOH (2.43 g, 38.1 mmol), ethyl acetate (25 mL), and H_2O (20 mL). The biphasic mixture was cooled to 0 °C, and chloroacetyl chloride (1.99 mL, 25.0 mmol) was added in small portions. After 25 minutes at 0 °C, the reaction layers were separated, and the organic portion was dried ($MgSO_4$), filtered through cotton, and concentrated to an oil. Crystallization of the product from $EtOH/H_2O$ afforded the title compound as pale yellow crystals (1.73 g, 77%), mp = 67-70 °C. ^1H NMR ($CDCl_3$) δ 3.32 (s, 3H, -NC*H*$_3$), 3.86 (s, 2H, -COC*H*$_2$Cl), 7.24-7.28 (m, 1 H, aromatic), 7.38-7.49 (m, 3H, aromatic). ^{13}C NMR ($CDCl_3$) δ 38.16, 41.72, 127.20, 128.74, 130.14, 130.24, 142.74, 166.42. HRMS (ESI) Calc. for C_9H_9DClNO $[M+H]^+$: 185.0586, Found 185.0589. IR (neat) ν (cm^{-1}) 1671.

Determination of Intramolecular Isotope Effect: An oven-dried Schlenk tube equipped with a magnetic stir bar and a Teflon stopcock was evacuated while hot and cooled under nitrogen. The tube was charged with palladium acetate (1.0 mol%), 2-(di-*tert*-butylphosphino)biphenyl (2.0 mol%), *N*-methyl-2-deuteriochloroacetanilide (184 mg, 1.00 mmol). The tube was evacuated and backfilled with nitrogen (this sequence was repeated 3 times), and the Teflon stopcock was

replaced with a rubber septum. Anhydrous triethylamine (0.21 mL, 1.50 mmol) was added, followed by anhydrous toluene (1.0 mL). The septum was replaced by the Teflon stopcock under a positive pressure of nitrogen, and the sealed tube was placed in an oil bath preheated to 80 °C. After 2.5 h, the reaction was allowed cooled to room temperature, and the mixture was diluted with ethyl acetate (10 mL). The mixture was filtered through a plug of Celite and concentrated on a rotary evaporator. The crude material was purified by silica gel chromatography (75:25 hexanes:ethyl acetate; $R_f = 0.19$) to give a colorless solid. Inspection of the aromatic region of the ^1H NMR spectrum indicated that the 7-position of the product oxindole was only 20% protonated, indicating an intramolecular isotope effect of $k_H/k_D = 4.0$ (compare Figures 9 and 10).

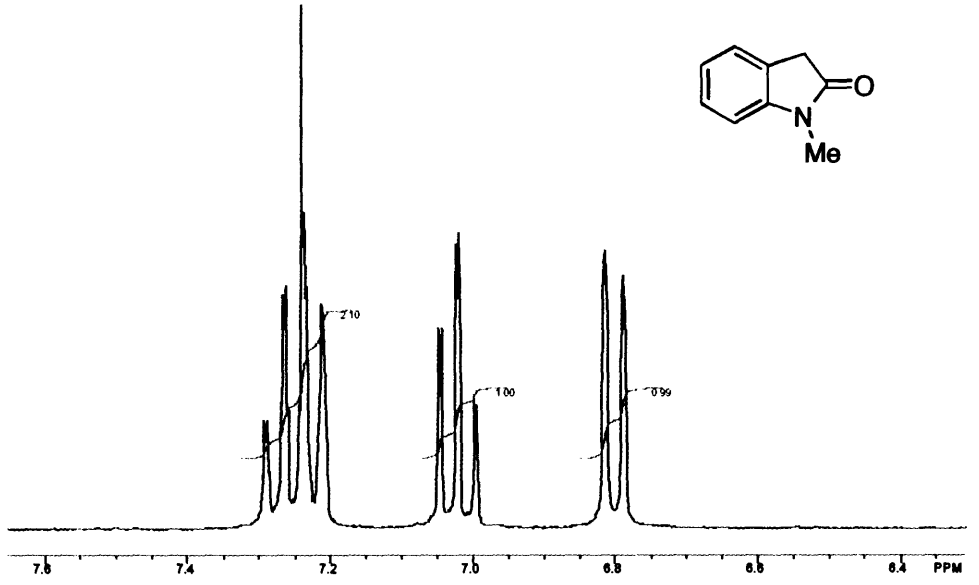


Figure 9. Aromatic Region of *N*-Methyloxindole

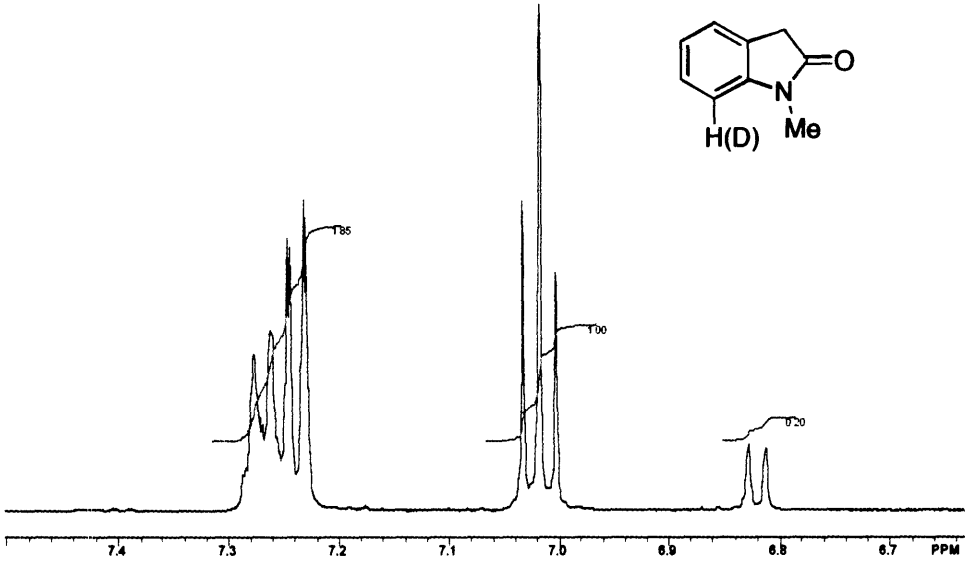


Figure 10. Aromatic Region of Isolated Material from Cyclization of *N*-Methyl-2-deuteriochloroacetanilide

***N*-(1,2,3,4,5-Pentadeuteriophenyl) aniline:** An oven-dried Schlenk tube was evacuated while hot and allowed to cool under N_2. The tube was charged with $Pd_2(dba)_3$ (11.3 mg, 0.5 mol%), XPhos (23.6 mg, 1.0 mol%), and sodium *tert*-butoxide (680 mg, 1.4 equiv). The tube was evacuated and backfilled with N_2 (3 times), and anhydrous toluene (5 mL) was added. The mixture was allowed to stir at rt for 5 min, and then d_5-bromobenzene (0.53 mL, 5.03 mmol), aniline (0.55 mL, 6.04 mmol) and additional toluene (2.5 mL) were added. The tube was sealed under N_2, and was placed in an oil bath preheated to 80 °C. After 3 h, the reaction was allowed to cool and was partitioned between ethyl acetate and H_2O. The organic layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated. The crude material was purified by silica gel chromatography (95:5 hexanes:EtOAc; $R_f = 0.22$) to give a pale yellow solid, (856 mg, 98%) mp = 55.5-57.5 °C. ^{1}H NMR δ 5.63 (s, 1H, -N*H*), 6.91 (m, 1H, aromatic), 7.05 (m, 2H, aromatic), 7.24 (m, 2H, aromatic). ^{13}C NMR δ 117.52 (t, $J = 24.1$ Hz), 117.87, 120.61 (t, $J = 24.3$ Hz), 121.09, 19.00 (t, $J = 24.0$ Hz), 129.51, 143.08, 143.24. HRMS (ESI) Calc. for $C_{12}H_6D_5N$ $[M+H]^+$: 174.1200, Found 174.1203. IR (CH_2Cl_2) ν (cm^{-1}) 3384, 3407.

***N*-(1,2,3,4,5-Pentadeuteriophenyl) chloroacetanilide:** A solution of *N*-(1,2,3,4,5-pentadeuteriophenyl) aniline (741 mg, 4.25 mmol) and pyridine (0.71 mL, 8.8 mmol) in anhydrous toluene (6 mL) was cooled to 0 °C. Chloroacetyl chloride (0.68 mL, 8.5 mmol) was added dropwise over 5 min, followed by additional toluene (2 mL). After 1 h at 0 °C, 1 N NaOH (~10 mL) and EtOAc (~15 mL) were added, and the layers were separated. The aqueous portion was extracted with EtOAc, and the combined organics were washed with brine, dried ($MgSO_4$), filtered, and concentrated via rotary evaporator. The product was crystallized from 95% EtOH to give a pale yellow solid (886 mg, 83%), mp = 120-121 °C. ^{1}H NMR δ 4.03 (s, 2H, -COC*H*$_2$Cl), 7.20-7.48 (broad m, 5H, aromatic). ^{13}C NMR δ 42.87, 126.1-130.2 (aromatic), 141.9 (aromatic),

166.27. HRMS (ESI) Calc. for $C_{14}H_7D_5ClNO$ $[M+H]^+$: 251.0994, Found 251.0982. IR (CH_2Cl_2) ν (cm^{-1}) 1688.

Cyclization of *N*-(1,2,3,4,5-Pentadeuteriophenyl) chloroacetanilide: An oven-dried Schlenk tube equipped with a magnetic stir bar and a Teflon stopcock was evacuated while hot and cooled under nitrogen. The tube was charged with palladium acetate (4.8 mg, 2.0 mol%), 2-(di-*tert*-butylphosphino)biphenyl (12.6 mg, 4.0 mol%), and *N*-(1,2,3,4,5-pentadeuteriophenyl) chloroacetanilide (246 mg, 0.98 mmol). The tube was evacuated and backfilled with nitrogen (this sequence was repeated 3 times), and the Teflon stopcock was replaced with a rubber septum. Anhydrous triethylamine (0.21 mL, 1.50 mmol) was added, followed by anhydrous toluene (1.0 mL). The septum was replaced by the Teflon stopcock under a positive pressure of nitrogen, and the sealed tube was placed in an oil bath preheated to 80 °C. After 3 h, the reaction was allowed cooled to room temperature, and the mixture was diluted with ethyl acetate (10 mL). The mixture was filtered through a plug of Celite and concentrated on a rotary evaporator. The crude material was purified by silica gel chromatography (85:15 hexanes:ethyl acetate; R_f = 0.18) to give a colorless solid. Inspection of the aromatic region of the ^1H NMR spectrum (CD_2Cl_2, 30 seconds between each transient to ensure complete relaxation) indicated that the cyclization occurred on the phenyl ring 4.8 times faster than at the pentadeuteriophenyl ring (k_H/k_D = 4.8, compare Figures 11 and 12).

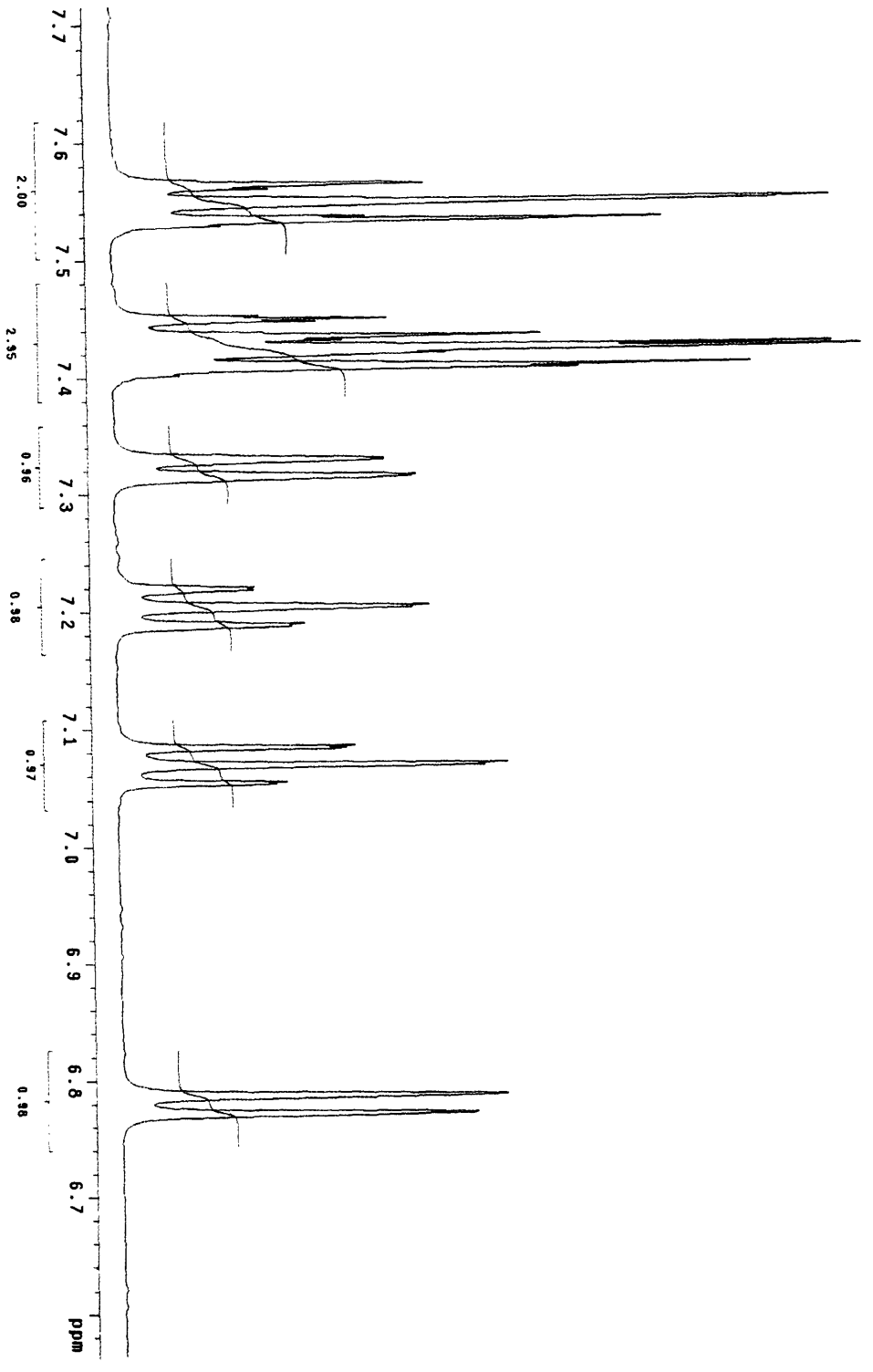


Figure 11. Aromatic Region of *N*-Phenyloxindole

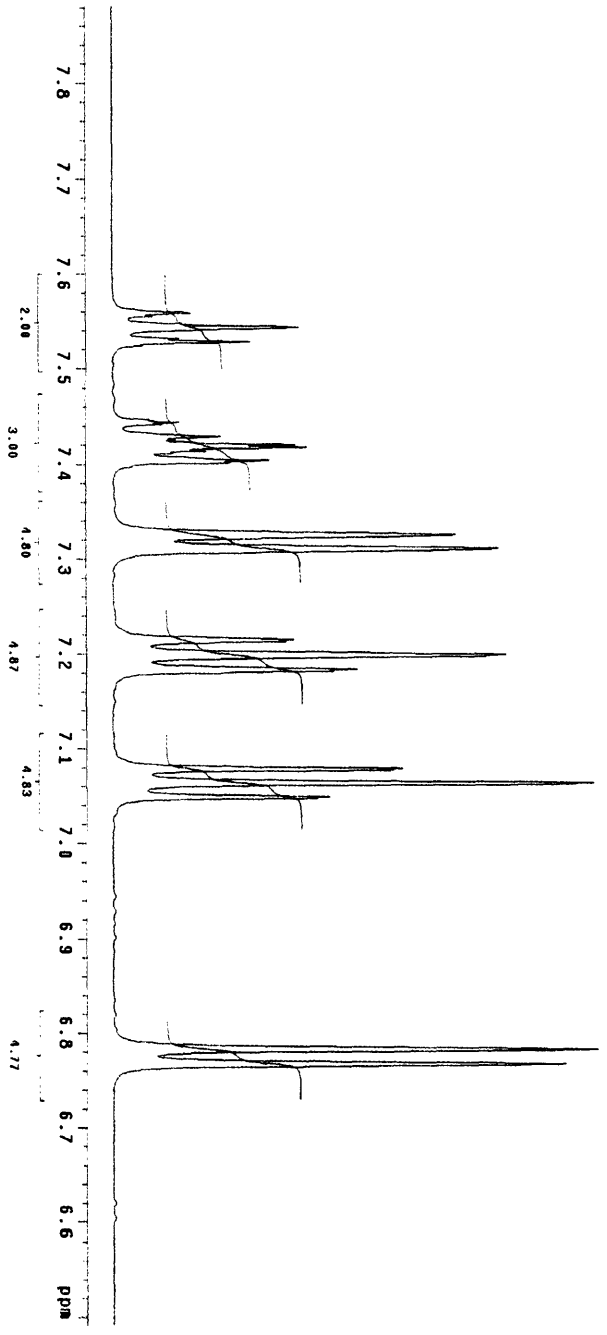


Figure 12. Aromatic Region of Isolated Material from Cyclization of *N*-(Pentadeuteriophenyl)chloroacetanilide

General Procedure for the Synthesis of Diarylamines: Unless otherwise noted, an oven-dried Schlenk tube was evacuated while hot and allowed to cool under N_2. The tube was charged with $Pd_2(dba)_3$ (0.5 mol%), XPhos (1.0 mol%), and sodium *tert*-butoxide (1.4 equiv). The tube was evacuated and backfilled with N_2 (3 times), and aryl halide (1 equiv), aniline (1.2 equiv), and anhydrous toluene (1.5 mL per mmol aryl halide) were added. The tube was sealed under N_2, and was placed in an oil bath preheated to 80 °C. After the indicated time, the reaction was allowed to cool and was partitioned between ethyl acetate and H_2O. The organic layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated. The crude material was purified by silica gel chromatography.

***N*-(4-*tert*-Butylphenyl) aniline:**[69] After 3 h of reaction using 4-*tert*-butylbromobenzene as substrate, silica gel chromatography (95:5 hexanes:EtOAc; $R_f = 0.24$) afforded a pale yellow solid (100%), mp = 66-67 °C (lit.[69] 66-67 °C).

***N*-(4-Methylphenyl) aniline:**[70] After 3 h of reaction using 4-chlorotoluene as substrate, silica gel chromatography (95:5 hexanes:EtOAc; $R_f = 0.26$) afforded a colorless to pale yellow solid (97%), mp = 88.5-89.5 °C (lit.[70] 87-88 °C).

***N*-(4-Methoxyphenyl) aniline:**[71] After 3 h of reaction using 4-bromoanisole as substrate, silica gel chromatography (95:5 hexanes:EtOAc; $R_f = 0.23$) afforded a pale yellow solid (96%), mp = 105-106.5 °C (lit.[72] 104-105 °C).

***N*-(4-Fluorophenyl) aniline:**[73] After 3 h of reaction using 4-fluorobromobenzene as substrate, silica gel chromatography (95:5 hexanes:EtOAc; $R_f = 0.22$) afforded a yellow oil (99%) which eventually crystallized on standing, mp = 36-38 °C (lit.[74] 34 °C).

***N*-(4-Trifluoromethylphenyl) aniline:** The general procedure was followed, using 4-chlorobenzotrifluoride as substrate and 1.4 equiv powdered K_3PO_4 as base in anhydrous 1,4-

dioxane at 110 °C. After 20 h of reaction, silica gel chromatography (95:5 hexanes:EtOAc; R_f = 0.16) afforded a colorless to pale yellow solid (93%), mp = 63.5-65 °C. ^{1}H NMR δ 5.90 (broad s, 1H, -*N*H), 7.05 (m, 3H, aromatic), 7.14 (m, 2H, aromatic), 7.33 (m, 2H, aromatic), 7.46 (m, 2H, aromatic). ^{13}C NMR δ 115.52, 120.21, 121.82 (q, J = 32.5 Hz), 123.13, 124.82, (q, J = 270.9 Hz), 126.90 (q, J = 3.8 Hz), 129.75, 141.32, 146.94. Calc. for $C_{13}H_{10}F_3N$: C 65.82, H 4.25; Found: C 65.81, H 4.11. IR ($CDCl_3$) ν (cm^{-1}) 3399.

***N*-(4-Cyanophenyl) aniline:**[75] The general procedure was followed using 4-bromobenzonitrile as substrate, with 1 mol% $Pd_2(dba)_3$, 4 mol% XPhos, and 6.2 equiv Cs_2CO_3 in anhydrous 1,4-dioxane at 100 °C. After 18 h of reaction, silica gel chromatography (85:15 hexanes:EtOAc; R_f = 0.21) afforded a pale yellow solid (91%), mp = 99-101.5 °C (lit.[75] 101-102 °C).

***N*-(4-Nitrophenyl)-aniline:** Commerically available (Aldrich).

General Procedure for the Synthesis of Diarylchloroacetanilides: Unless otherwise noted, a roundbottom flask was charged with the diarylamine and anhydrous toluene (2 mL per mmol diarylamine). Chloroacetyl chloride (2 equiv) was added, and the flask was placed in an oil bath preheated to 100 °C. After 2 hours, the mixture is allowed to cool and is concentrated via rotary evaporator. The resulting residue is purified by silica gel chromatography or crystallization. Note: due to the presence of amide rotamers, the aromatic regions in both the ^{1}H and ^{13}C NMR spectra of these compounds are broad and poorly resolved (especially in cases where the aromatic *para*-substituent is electron-donating). As such, ranges of observed resonances are reported when not well-defined.

***N*-(4-*tert*-Butylphenyl)-*N*-phenylchloroacetanilide:** Silica gel chromatography (80:20 hexanes:EtOAc; R_f = 0.35) afforded a viscous, pale yellow oil (100%) that eventually crystallized on standing, mp = 80.5-82 °C. ^{1}H NMR δ 1.31 (s, 9H, -C(C*H*$_3$)$_3$), 4.03 (s, 2H,

COCH_2Cl), 7.21-7.39 (m, 9H, aromatic). ^{13}C NMR δ 31.46, 42.97, 126.0-130.0 (aromatic), 141.7-142.1 (aromatic), 166.40. Calc. for $C_{18}H_{20}ClNO$: C 71.63, H 6.68; Found: C 71.79, H 6.73. IR ($CDCl_3$) ν (cm^{-1}) 1684.

***N*-(4-Methylphenyl)-*N*-phenylchloroacetanilide:** Crystallization from absolute EtOH afforded a colorless solid (83%), mp = 73-75 °C. ^{1}H NMR δ 2.36 (broad s, 3H, -CH_3), 4.02 (s, 2H, -COCH_2Cl), 7.19-7.42 (m, 9H, aromatic). ^{13}C NMR δ 21.22, 42.88, 125.9-142.2 (aromatic region), 166.33. Calc. for $C_{15}H_{14}ClNO$: C 69.36, H 5.43; Found: C 69.41, H 5.44. IR ($CDCl_3$) ν (cm^{-1}) 1689.

***N*-(4-Methoxyphenyl)-*N*-phenylchloroacetanilide:** Silica gel chromatography (75:25 hexanes:EtOAc; R_f = 0.23) afforded a viscous, pale tan oil (97%). ^{1}H NMR δ 3.81 (s, 3H, -OCH_3), .4.02 (s, 2H, -COCH_2Cl), 6.91 (broad m, 2H, aromatic), 7.20-7.44 (broad m, 7H, aromatic). ^{13}C NMR δ 42.90, 55.72, 115.3-142.0 (aromatic region), 166.53. Calc. for $C_{15}H_{14}ClNO_2$: C 65.34, H 5.12; Found: C 65.30, H 5.13. IR (CH_2Cl_2) ν (cm^{-1}) 1686.

***N*-(4-Fluorophenyl)-*N*-phenylchloroacetanilide:** Silica gel chromatography (80:20 hexanes:EtOAc; R_f = 0.29) afforded a viscous, pale yellow oil (90%) that eventually crystallized on standing, mp = 79-81 °C. ^{1}H NMR δ 4.02 (s, 2H, COCH_2Cl), 7.07 (broad m, 2H, aromatic), 7.26-7.50 (m, 7H, aromatic). ^{13}C NMR δ 42.69, 116.0-142.0 (aromatic region), 166.43. Calc. for $C_{14}H_{11}ClFNO$: C 63.77, H 4.20; Found: C 63.97, H 4.09. IR (CH_2Cl_2) ν (cm^{-1}) 1681.

***N*-(4-Trifluoromethylphenyl)-*N*-phenylchloroacetanilide:** The general procedure was followed, except at 80 °C with the inclusion of pyridine (2 equiv) as a reagent. After 2 hours, the reaction was allowed to cool and was partitioned between ethyl acetate and H_2O. The organic layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated. Silica gel chromatography (85:15 hexanes:EtOAc; R_f = 0.11) afforded a pale yellow oil (71%). The

product was crystallized from aqueous ethanol, mp = 65.5-67.5 °C. ^{1}H NMR δ 4.03 (s, 2H, COC*H*$_2$Cl), 7.32 (d, *J* = 8.1 Hz, 2H, aromatic), 7.40-7.51 (m, 5H, aromatic), 7.61 (d, *J* = 8.1 Hz, 2H, aromatic). ^{13}C NMR δ 42.90, 126.5-145.1 (aromatic region), 166.45. Calc. for $C_{15}H_{11}ClF_3NO$: C 57.43, H 3.53; Found: C 57.18, H 3.48. IR (CH_2Cl_2) ν (cm^{-1}) 1691.

***N*-(4-Cyanophenyl)-*N*-phenylchloroacetanilide:** Silica gel chromatography (80:20 hexanes:EtOAc; R_f = 0.11) afforded a yellow oil. This material was crystallized from MeOH (53%), mp = 90-92.5 °C. ^{1}H NMR δ 4.01 (s, 2H, COC*H*$_2$Cl), 7.31 (apparent d, 2H, aromatic), 7.40 (d, *J* = 8.5 Hz, 2H, aromatic), 7.46-7.53 (m, 3H, aromatic), 7.62 (d, *J* = 8.5 Hz, 2H, aromatic). ^{13}C NMR δ 43.08, 109.75, 118.48, 125.93, 128.77, 129.54, 130.68, 133.08, 140.32, 145.92, 166.44. Calc. for $C_{15}H_{11}ClN_2O$: C 66.55, H 4.10; Found: C 66.45, H 4.02. IR (CH_2Cl_2) ν (cm^{-1}) 1693.

***N*-(4-Nitrophenyl)-*N*-phenylchloroacetanilide:**[76] The general procedure was followed using 4-nitrodiphenylamine (Aldrich), except that the reaction was conducted for a total of 5 hours. The crude material was recrystallized from absolute EtOH to give pale green/yellow crystals (67%), mp = 115-117 °C (lit.[76] 113.5-116 °C).

General Procedure for the Copper-Catalyzed *N*-Arylation of Oxindole: A screw-cap test tube was charged with $CuCl_2 \cdot 2\ H_2O$ (5.0 mol%), Na_2CO_3 (2.0 equiv), oxindole (1.4 equiv), and aryl bromide, if a solid (1 equiv). *N*,*N*′-Dimethylethylenediamine (10.0 mol%) was added, followed by aryl bromide, if a liquid (1 equiv). H_2O (0.5 mL per mmol aryl bromide) and *tert*-butanol (0.5 mL per mmol aryl bromide) were added, and the tube was capped and placed in an oil bath preheated to 100 °C. After the indicated time, the reaction was partitioned between EtOAc and H_2O. The organic portion was washed with brine, dried ($MgSO_4$), filtered, and

concentrated via rotary evaporator. The crude product was purified by silica gel chromatography.

***N*-(4-*tert*-Butylphenyl) oxindole:** After 17 h of reaction, silica gel chromatography (85:15 hexanes: EtOAc; $R_f = 0.17$) afforded a yellow oil that crystallized on standing (76%), mp = 102-104 °C. ^{1}H NMR ($CDCl_3$) δ 1.36 (s, 9H, -C(CH_3)$_3$), 3.70 (s, 2H, -COCH_2Ar), 6.80 (apparent d, 1H, aromatic), 7.05 (apparent t, 1H, aromatic), 7.19 (apparent t, 1H, aromatic), 7.31 (m, 3H, aromatic), 7.53 (apparent d, 2H, aromatic). ^{13}C NMR ($CDCl_3$) δ 31.48, 34.89, 36.22, 109.64, 122.82, 124.46, 124.69, 126.20, 126.77, 127.88, 131.84, 145.57, 151.19, 174.74. IR (CH_2Cl_2) ν (cm^{-1}) 1717.

***N*-(4-Methylphenyl) oxindole:** After 19.5 h of reaction, silica gel chromatography (80:20 hexanes: EtOAc; $R_f = 0.21$) afforded a pink oil that crystallized on standing (46%), mp = 90-92 °C. ^{1}H NMR ($CDCl_3$) δ 2.41 (s, 3H, -CH_3), 3.69 (s, 2H, -COCH_2Ar), 6.75 (apparent d, 1H, aromatic), 7.05 (apparent t, 1H, aromatic), 7.18 (apparent t, 1H, aromatic), 7.27-7.33 (m, 5H, aromatic). ^{13}C NMR ($CDCl_3$) δ 21.37, 36.17, 109.49, 122.80, 124.44, 124.69, 126.60, 127.89, 130.43, 131.92, 138.23, 145.57, 174.70. IR (CH_2Cl_2) ν (cm^{-1}) 1718.

***N*-(4-Methoxyphenyl) oxindole:** After 17 h of reaction, silica gel chromatography (75:25 hexanes: EtOAc; $R_f = 0.17$) afforded a pink solid (40%), mp = 131-133 °C. ^{1}H NMR ($CDCl_3$) δ 3.69 (s, 2H, -COCH_2Ar), 3.85 (s, 3H, -OCH_3), 6.72 (apparent d, 1H, aromatic), 7.02-7.08 (m, 3H, aromatic), 7.19 (apparent t, 1H, aromatic), 7.28-7.32 (m, 3H, aromatic). ^{13}C NMR ($CDCl_3$) δ 36.22, 55.74, 109.51, 115.18, 122.85, 124.47, 124.75, 127.28, 128.00, 128.22, 145.91, 159.40, 174.96. IR (CH_2Cl_2) ν (cm^{-1}) 1717.

***N*-(4-Fluorophenyl) oxindole:** After 19.5 h of reaction, silica gel chromatography (80:20 hexanes: EtOAc; $R_f = 0.18$) afforded a pale yellow solid (49%), mp = 140-141 °C. ^{1}H NMR

($CDCl_3$) δ 3.71 (s, 2H, -COCH_2Ar), 6.74 (apparent d, 1H, aromatic), 7.09 (apparent t, 1H, aromatic), 7.19-7.26 (m, 3H, aromatic), 7.32 (apparent d, 1H, aromatic), 7.37-7.41 (m, 2H, aromatic). ^{13}C NMR ($CDCl_3$) δ 36.19, 109.41, 116.90 (d, J = 22.9 Hz), 123.16, 124.43, 124.92, 128.09, 128.76 (d, J = 8.6 Hz), 145.31, 160.47, 163.75, 174.73. IR (CH_2Cl_2) ν (cm^{-1}) 1712.

***N*-(4-Trifluoromethylphenyl) oxindole:** After 19 h of reaction, silica gel chromatography (85:15 hexanes: EtOAc; R_f = 0.19) afforded a colorless solid (35%), mp = 128-129 °C. ^{1}H NMR ($CDCl_3$) δ 3.675 (s, 2H, -COCH_2Ar), 6.86 (apparent d, 1H, aromatic), 7.12 (apparent t, 1H, aromatic), 7.24 (apparent t, 1H, aromatic), 7.34 (apparent d, 1H, aromatic), 7.59 (d, J = 8.4 Hz, 2H, aromatic), 7.80 (d, J = 8.4 Hz, 2H, aromatic). ^{13}C NMR ($CDCl_3$) δ 36.24, 109.53, 123.55, 124.48, 125.13, 126.86, 127.00 (q, J = 3.8 Hz), 128.15, 144.41, 174.40 (not all resonances could be observed due to C-F coupling of low-intensity signals). Calc. for $C_{15}H_{10}F_3NO$: C 64.98, H 3.64; Found: C 65.07 H 3.57. IR (CH_2Cl_2) ν (cm^{-1}) 1716.

***N*-(4-Cyanophenyl) oxindole:** After 20 h of reaction, silica gel chromatography (70:30 hexanes: EtOAc; R_f = 0.27) afforded a yellow solid (4%), mp = 186-190 °C. ^{1}H NMR ($CDCl_3$) δ 3.75 (s, 2H, -COCH_2Ar), 6.89 (apparent d, 1H, aromatic), 7.14 (apparent t, 1H, aromatic), 7.26 (apparent t, 1H, aromatic), 7.35 (apparent d, 1H, aromatic), 7.61 (d, J = 8.1 Hz, 2H, aromatic), 7.83 (d, J = 8.1 Hz, 2H, aromatic). ^{13}C NMR ($CDCl_3$) δ 36.19, 109.53, 111.47, 118.40, 123.83, 124.43, 125.25, 126.90, 128.17, 133.68, 138.86, 143.76, 174.21. IR (CH_2Cl_2) ν (cm^{-1}) 1714.

***N*-(4-Nitrophenyl) oxindole:** After 20 h of reaction, silica gel chromatography (70:30 hexanes: EtOAc; R_f = 0.28) afforded a pink solid (15%), mp = 168-172 °C. ^{1}H NMR ($CDCl_3$) δ 3.77 (s, 2H, -COCH_2Ar), 6.94 (apparent d, 1H, aromatic), 7.15 (apparent t, 1H, aromatic), 7.28 (apparent t, 1H, aromatic), 7.36 (apparent d, 1H, aromatic), 7.69 (d, J = 9.3 Hz, 2H, aromatic), 8.41 (d, J =

9.3 Hz, 2H, aromatic). ^{13}C NMR ($CDCl_3$) δ 36.21, 109.62, 123.96, 124.47, 125.20, 125.32, 126.72, 128.23, 140.57, 143.66, 146.55, 174.16. IR (CH_2Cl_2) ν (cm^{-1}) 1726.

General Procedure for Conducting Intramolecular Competition Experiments: An oven dried Schlenk tube was evacuated while hot and allowed to cool under N_2. The tube was charged with $Pd(OAc)_2$ (2-4 mol%), 2-di-*tert*-butylphosphinobiphenyl (4-8 mol%), and the diarylchloroacetanilide (1 equiv). The tube was evacuated and backfilled with N_2 (3 times), and anhydrous triethylamine (1.5-2 equiv) was added , followed by anhydrous toluene (1 mL per mmol substrate). The tube was sealed under N_2, and was placed in an oil bath preheated to 80 °C. After the specified time, the reaction was allowed to cool and was diluted with EtOAc (~10 mL per mmol substrate). The mixture was filtered through a plug of Celite and was concentrated via rotary evaporator. The crude material was analyzed by ^1H NMR spectroscopy to determine the ratio of products formed, by comparison to the spectra of the authentic *N*-aryl oxindoles. Each cyclization was repeated either two or three times to derive the values of k_X/k_H and the error bars used in Figure 3. Values of k_X/k_H for representative single experiments are given in Figures 13-25.

Cyclization of *N*-(*p*-*tert*-butylphenyl) chloroacetanilide: Product ratio determined by comparison of the apparent doublet centered at δ 6.80 (authentic *N*-(*p*-*tert*-butylphenyl) oxindole) and the apparent doublet centered at δ 6.74. These resonances indicate $k_{tBu}/k_H = 0.82$.

Cyclization of *N*-(*p*-methylphenyl) chloroacetanilide: Product ratio determined by comparison of the apparent doublet centered at δ 6.76 (authentic *N*-(*p*-methylphenyl) oxindole) and the apparent doublet centered at δ 6.69. These resonances indicate $k_{Me}/k_H = 1.16$.

Cyclization of *N*-(*p*-methoxyphenyl) chloroacetanilide: Product ratio determined by comparison of the singlet at δ 3.86 (authentic *N*-(*p*-methoxyphenyl) oxindole) and the singlet at δ 3.80. These resonances indicate $k_{OMe}/k_H = 0.93$.

Cyclization of *N*-(*p*-fluorophenyl) chloroacetanilide: Product ratio determined by comparison of the apparent doublet centered at δ 7.31 (authentic *N*-(*p*-fluorophenyl) oxindole) and the apparent triplet centered at δ 6.90 (which is not present in spectrum of authentic product). These resonances indicate $k_F/k_H = 0.75$.

Cyclization of *N*-(*p*-trifluoromethylphenyl) chloroacetanilide: Product ratio determined by comparison of the singlet at δ 3.75 (authentic *N*-(*p*-trifluoromethylphenyl) oxindole) and the singlet at δ 3.77. These resonances indicate $k_{CF3}/k_H = 0.66$.

Cyclization of *N*-(*p*-cyanophenyl) chloroacetanilide: Product ratio determined by comparison of the apparent doublet centered at δ 6.90 (authentic *N*-(*p*-cyanophenyl) oxindole) and the apparent doublet centered at δ 6.84. These resonances indicate $k_{CN}/k_H = 1.03$.

Cyclization of *N*-(*p*-nitrophenyl) chloroacetanilide: Product ratio determined by comparison of the singlet at δ 3.76 (authentic *N*-(*p*-nitrophenyl) oxindole) and the singlet at δ 3.82. These resonances indicate $k_{NO2}/k_H = 1.00$.

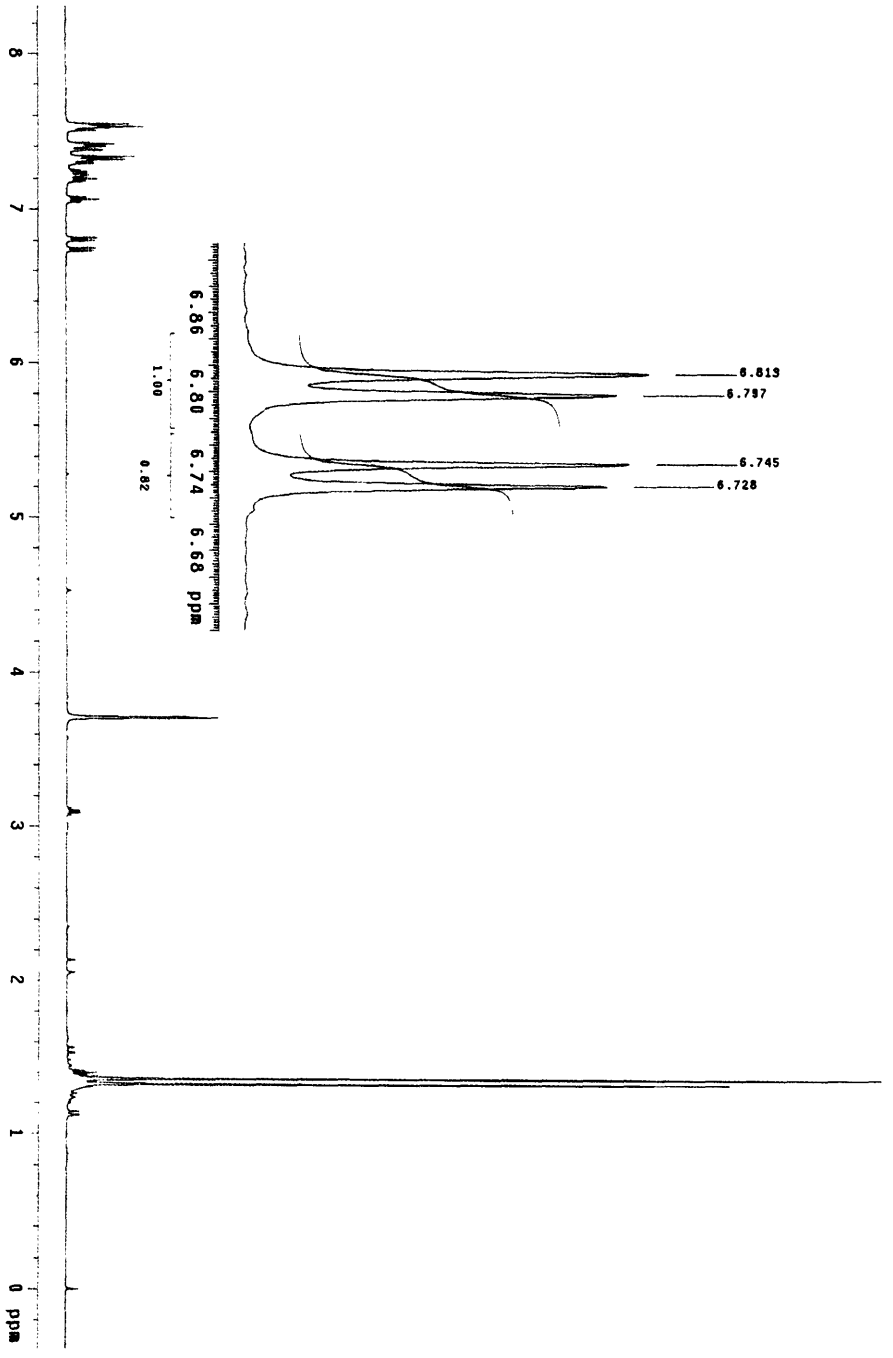


Figure 13. Cyclization of (*p-tert*-butylphenyl) chloroacetanilide ($CDCl_3$, 500 MHz)

$$k_{t\mathrm{Bu}} / k_{\mathrm{H}} = 0.82$$

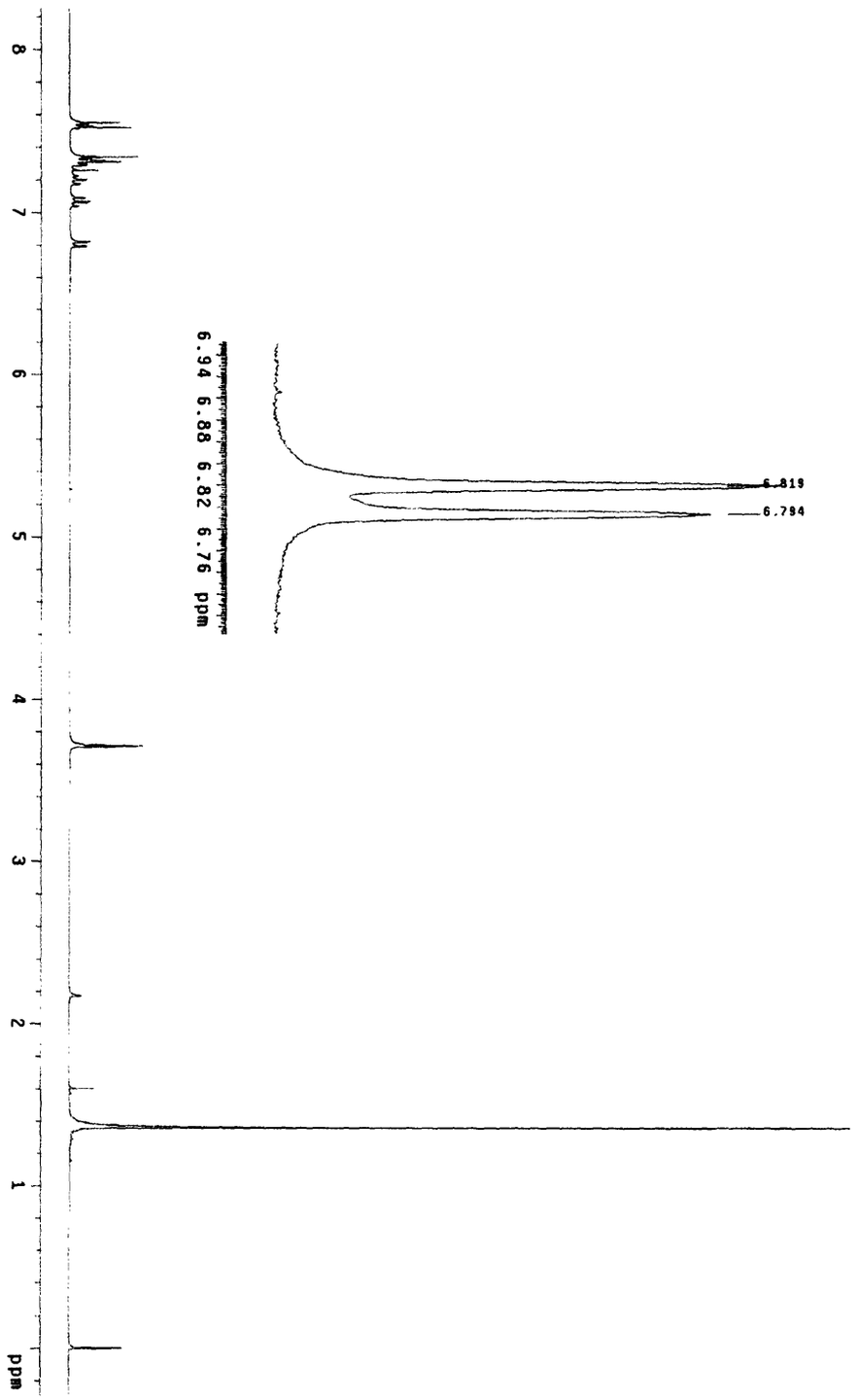


Figure 14. Authentic *N*-(*p-tert*-butylphenyl)oxindole ($CDCl_3$, 300 MHz)

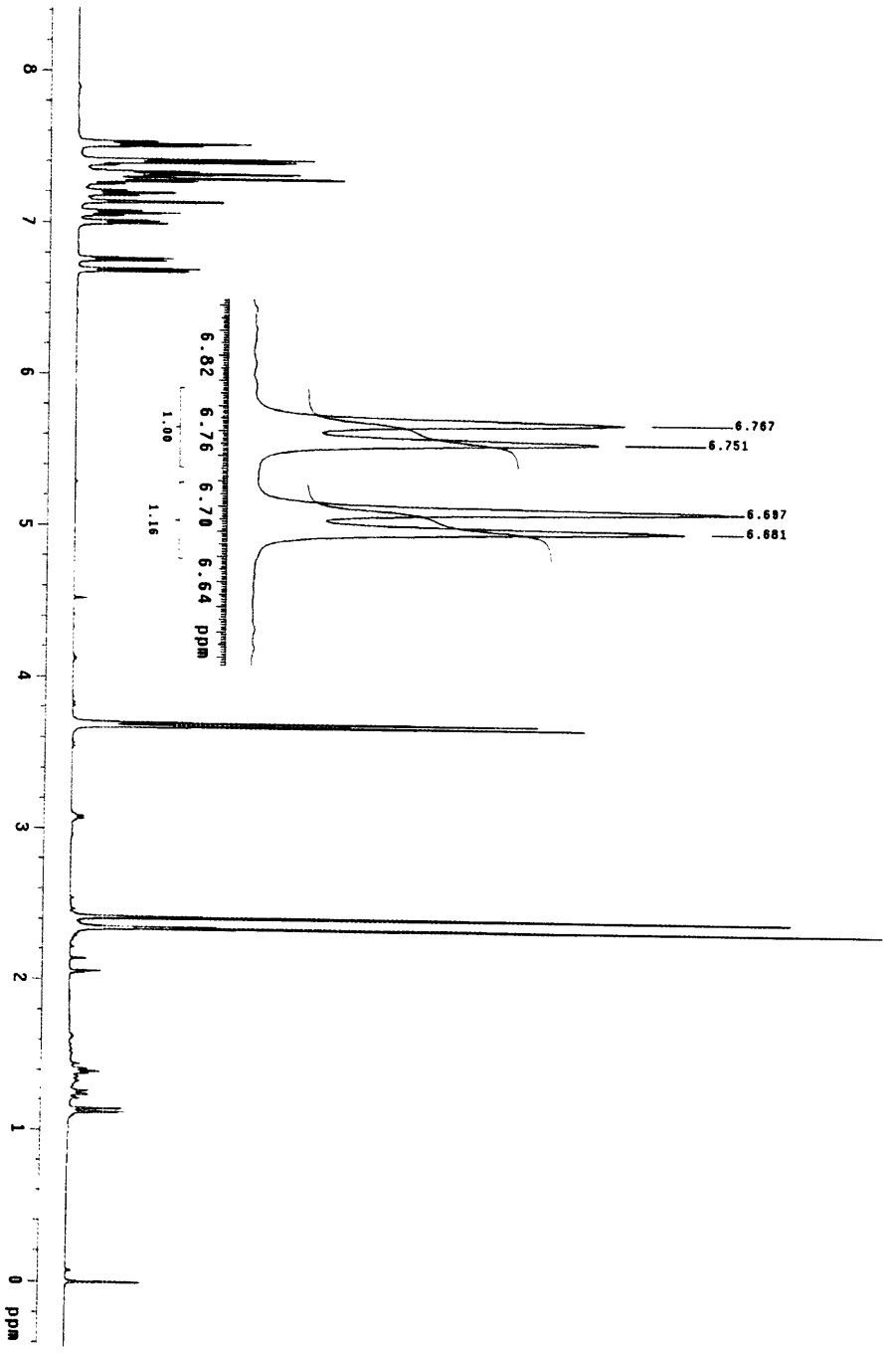


Figure 15. Cyclization of (*p*-methylphenyl) chloroacetanilide ($CDCl_3$, 500 MHz)

$$k_{Me} / k_{H} = 1.16$$

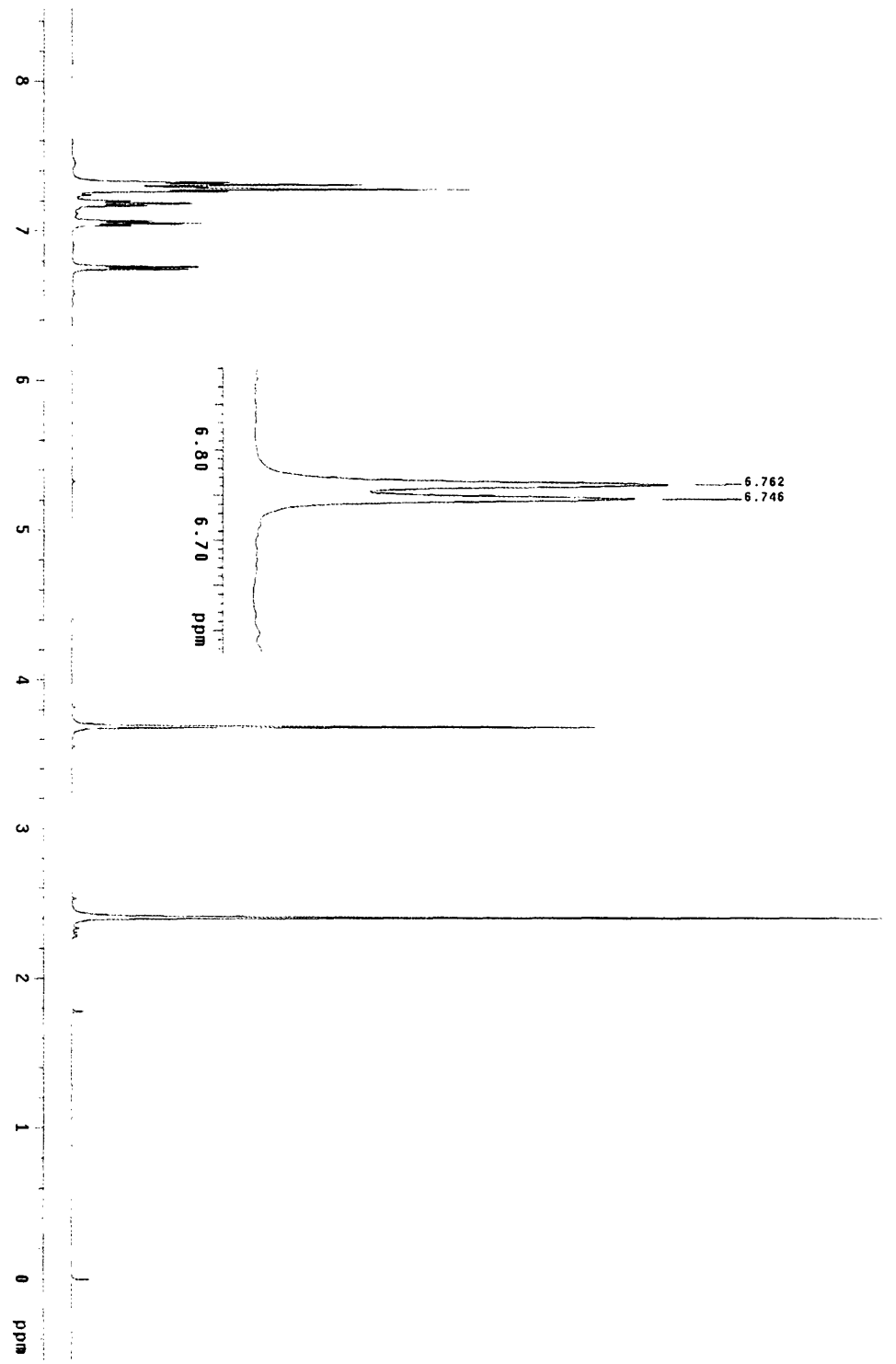


Figure 16. Authentic *N*-(*p*-methylphenyl)oxindole ($CDCl_3$, 500 MHz)

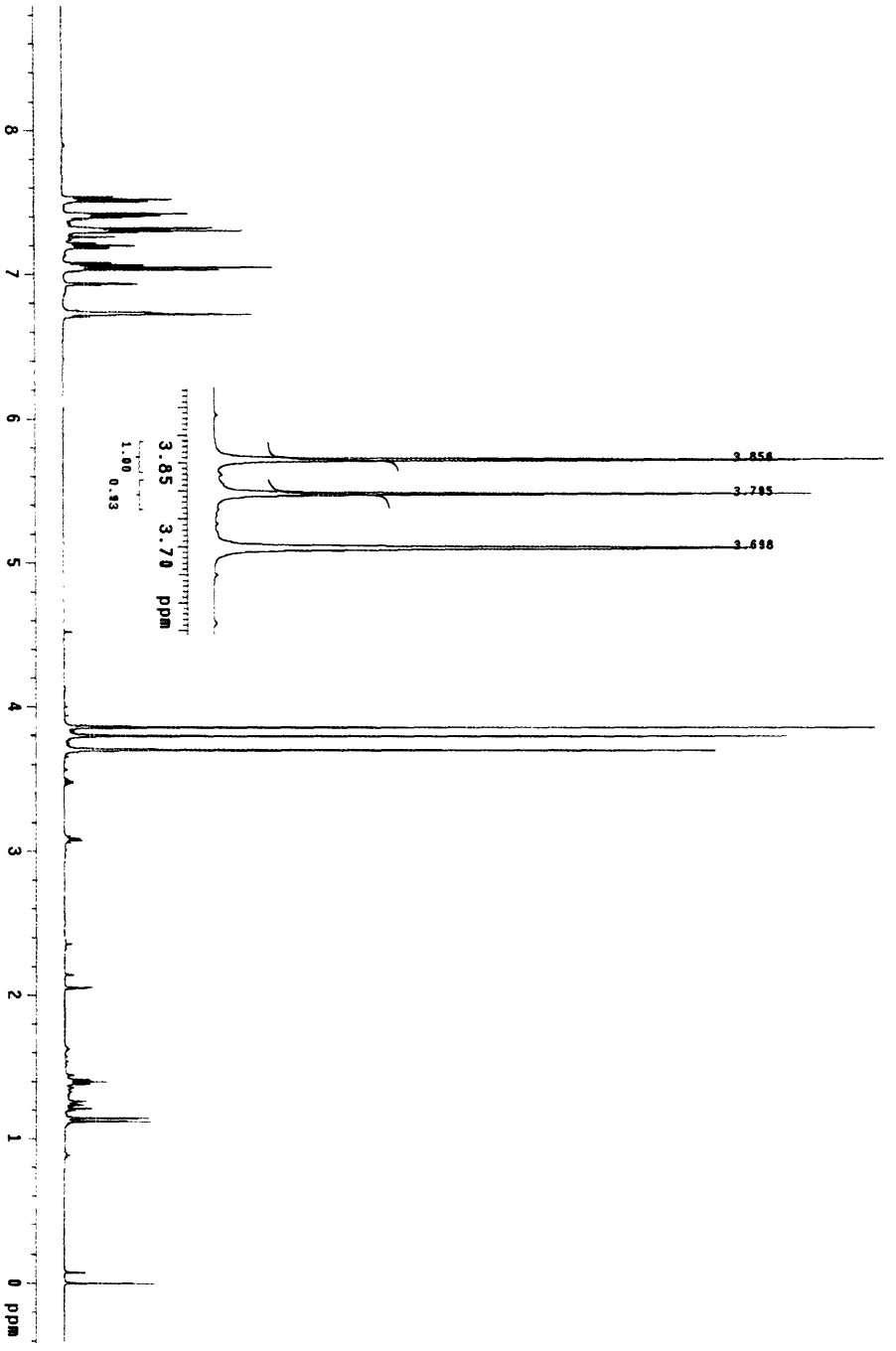


Figure 17. Cyclization of (*p*-methoxyphenyl) chloroacetanilide ($CDCl_3$, 500 MHz)

$$k_{OMe} / k_H = 0.93$$

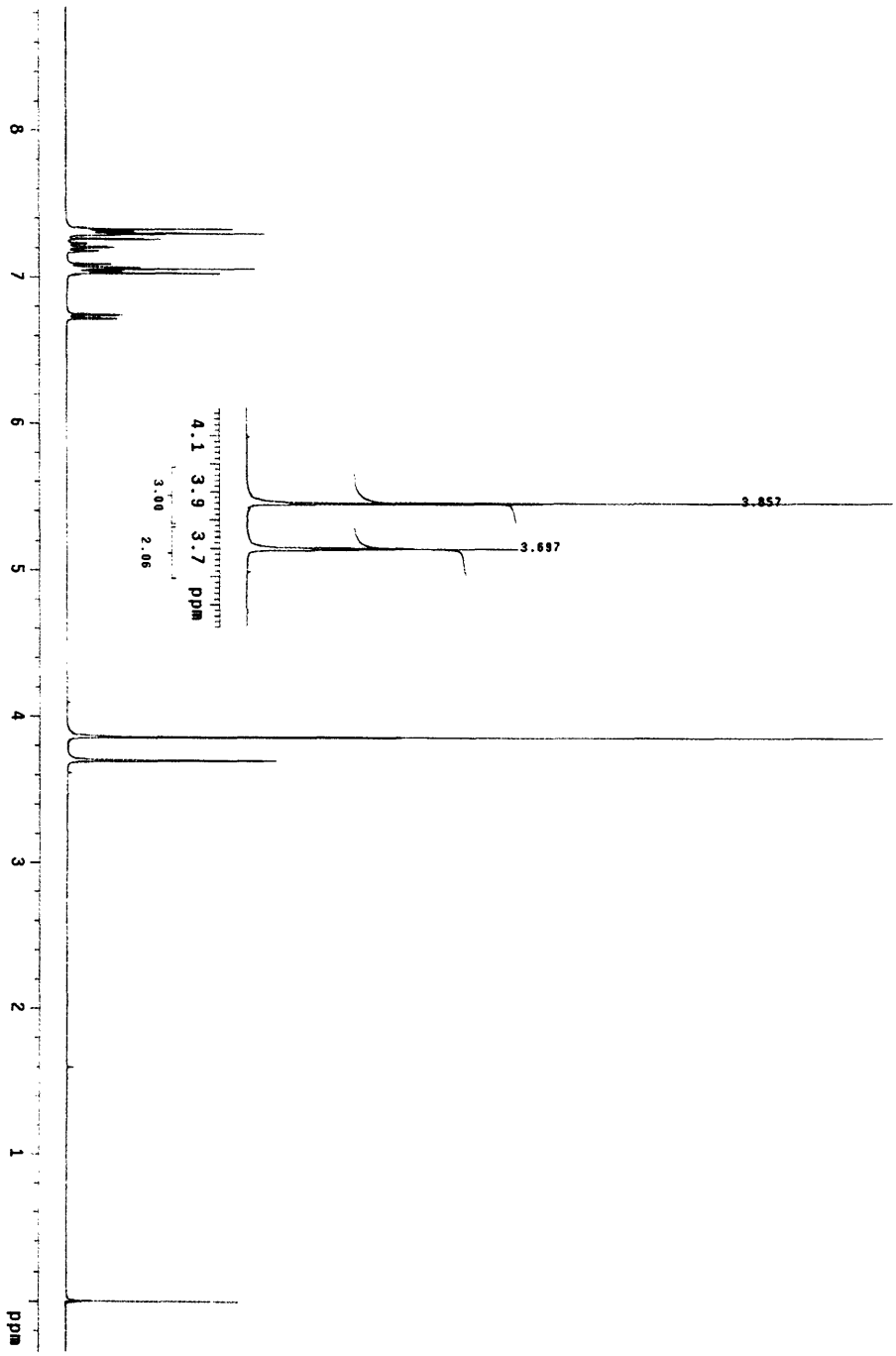


Figure 18. Authentic *N*-(*p*-methoxyphenyl)oxindole ($CDCl_3$, 300 MHz)

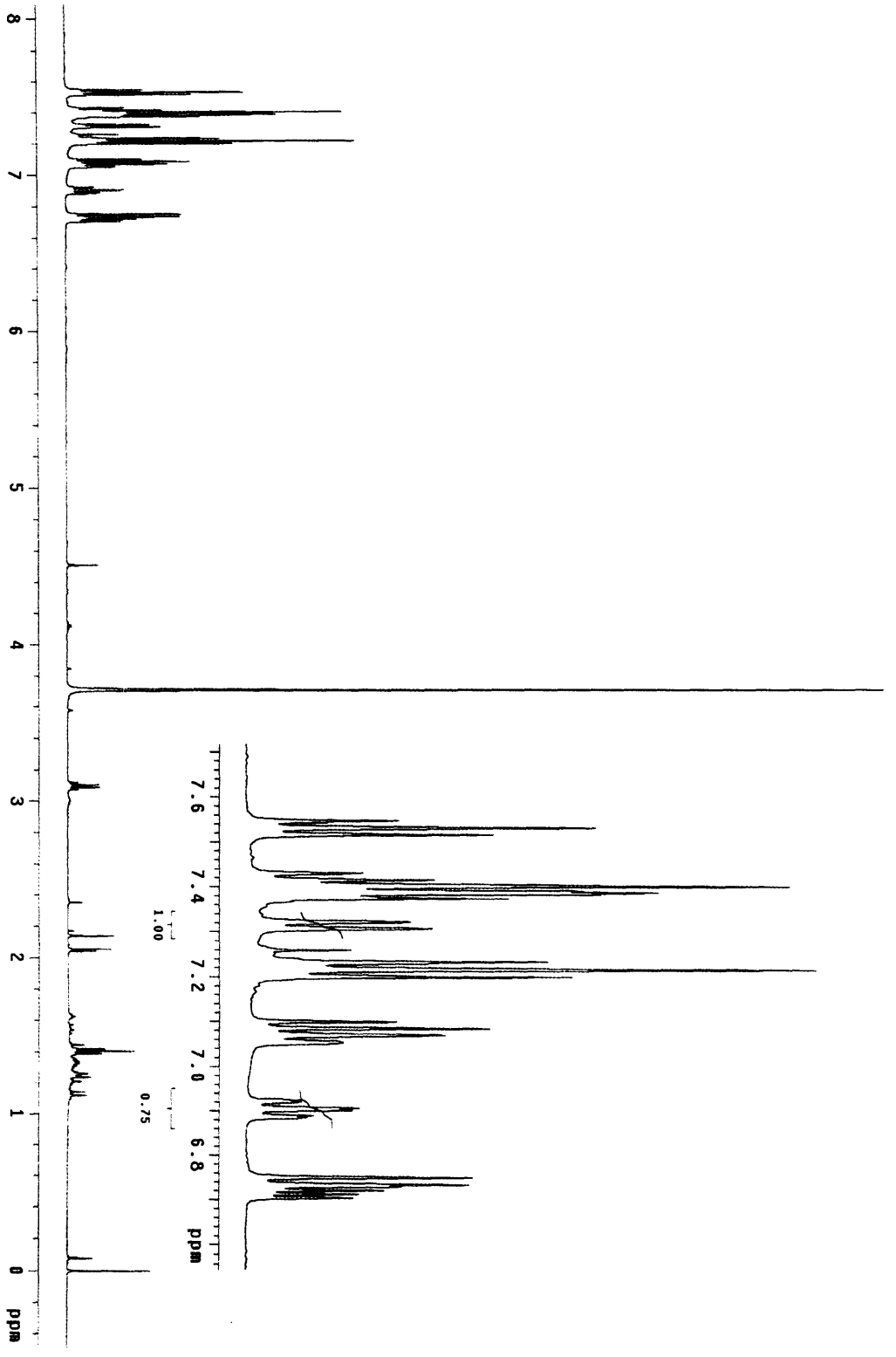


Figure 19. Cyclization of (*p*-fluorophenyl) chloroacetanilide ($CDCl_3$, 500 MHz)

$$k_F / k_H = 0.75$$

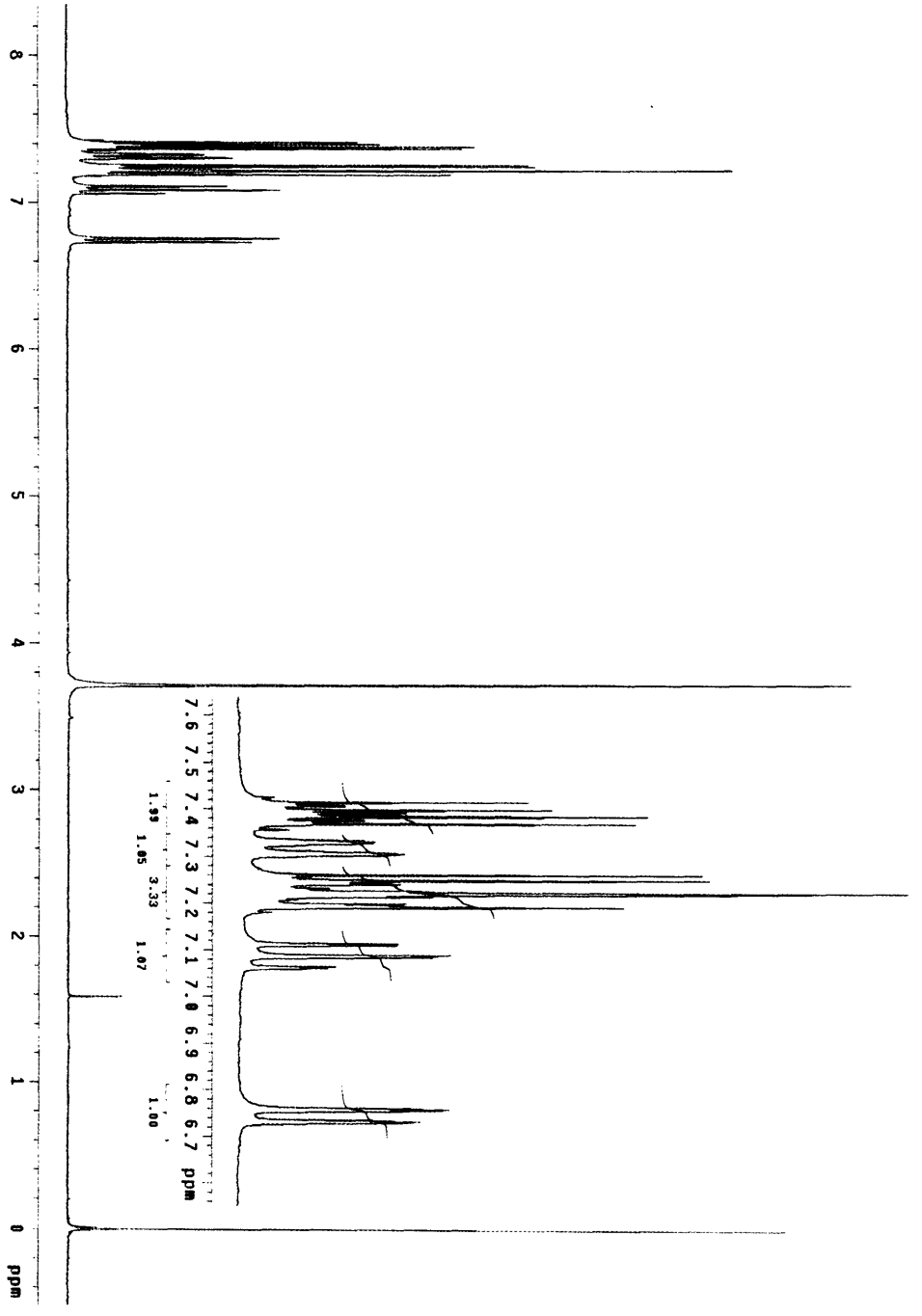


Figure 20. Authentic *N*-(*p*-fluorophenyl)oxindole ($CDCl_3$, 300 MHz)

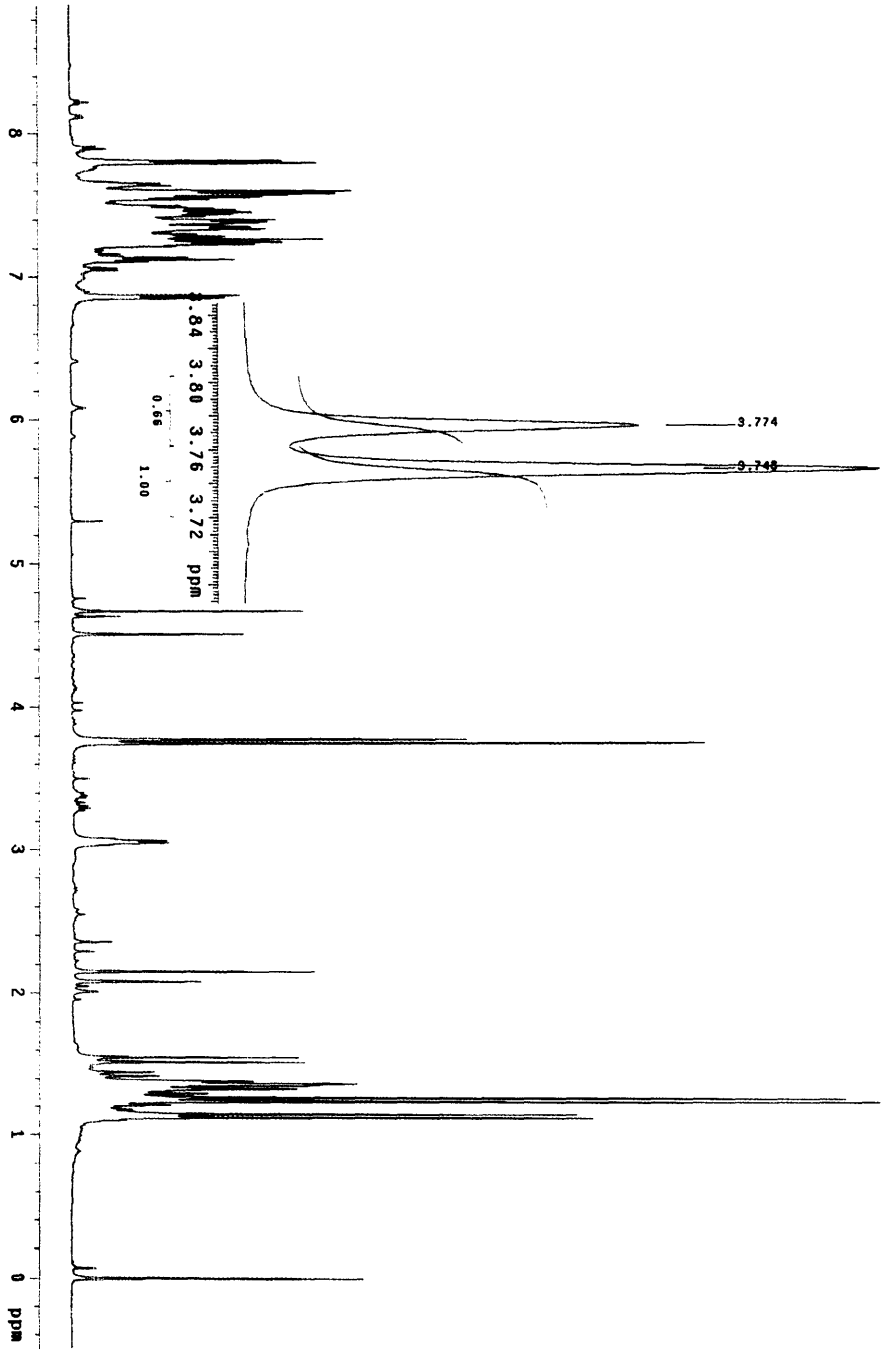


Figure 21. Cyclization of (*p*-trifluoromethylphenyl) chloroacetanilide ($CDCl_3$, 500 MHz)

$$k_{CF3} / k_H = 0.66$$

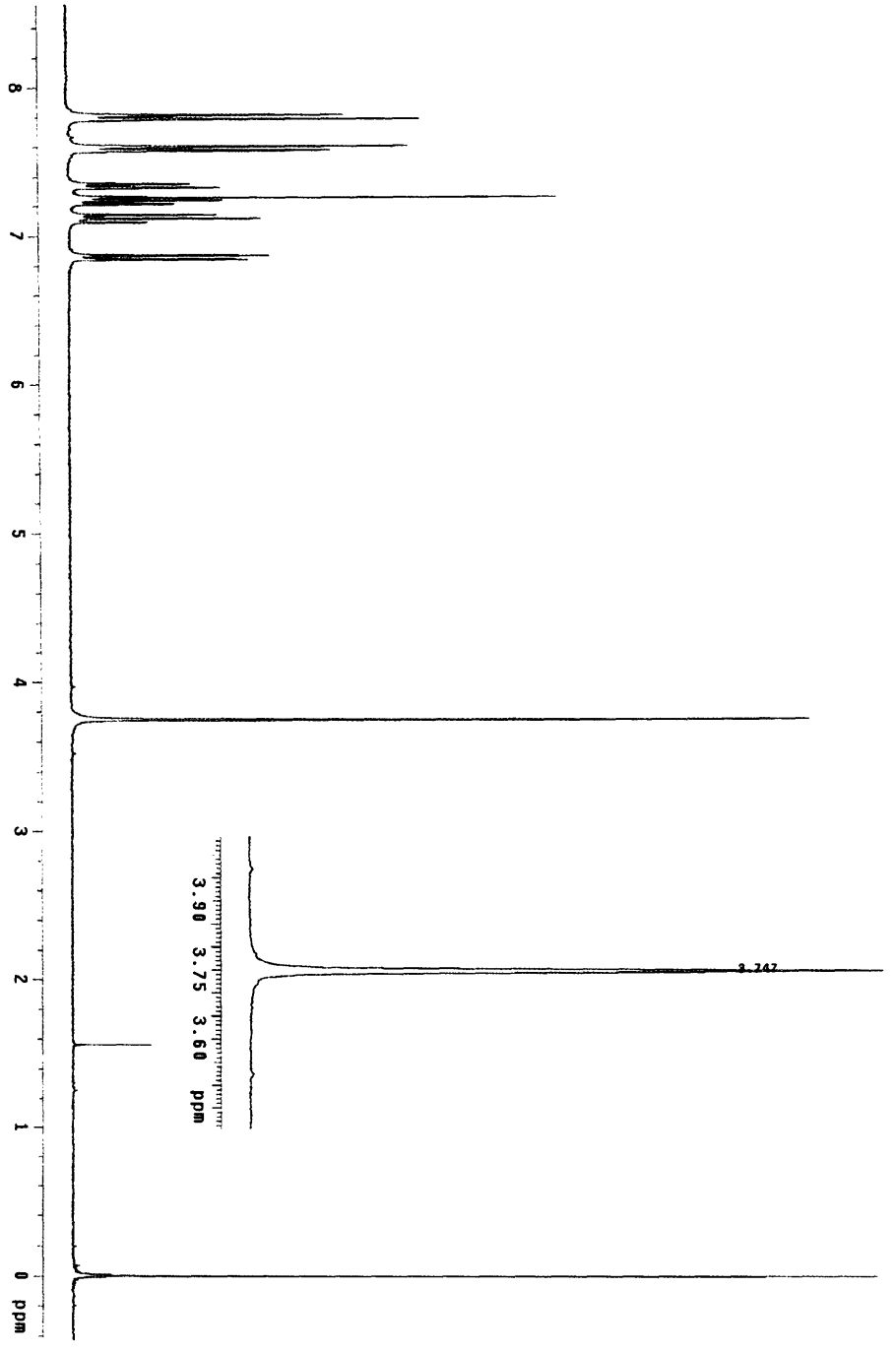


Figure 22. Authentic *N*-(*p*-trifluoromethylphenyl)oxindole ($CDCl_3$, 300 MHz)

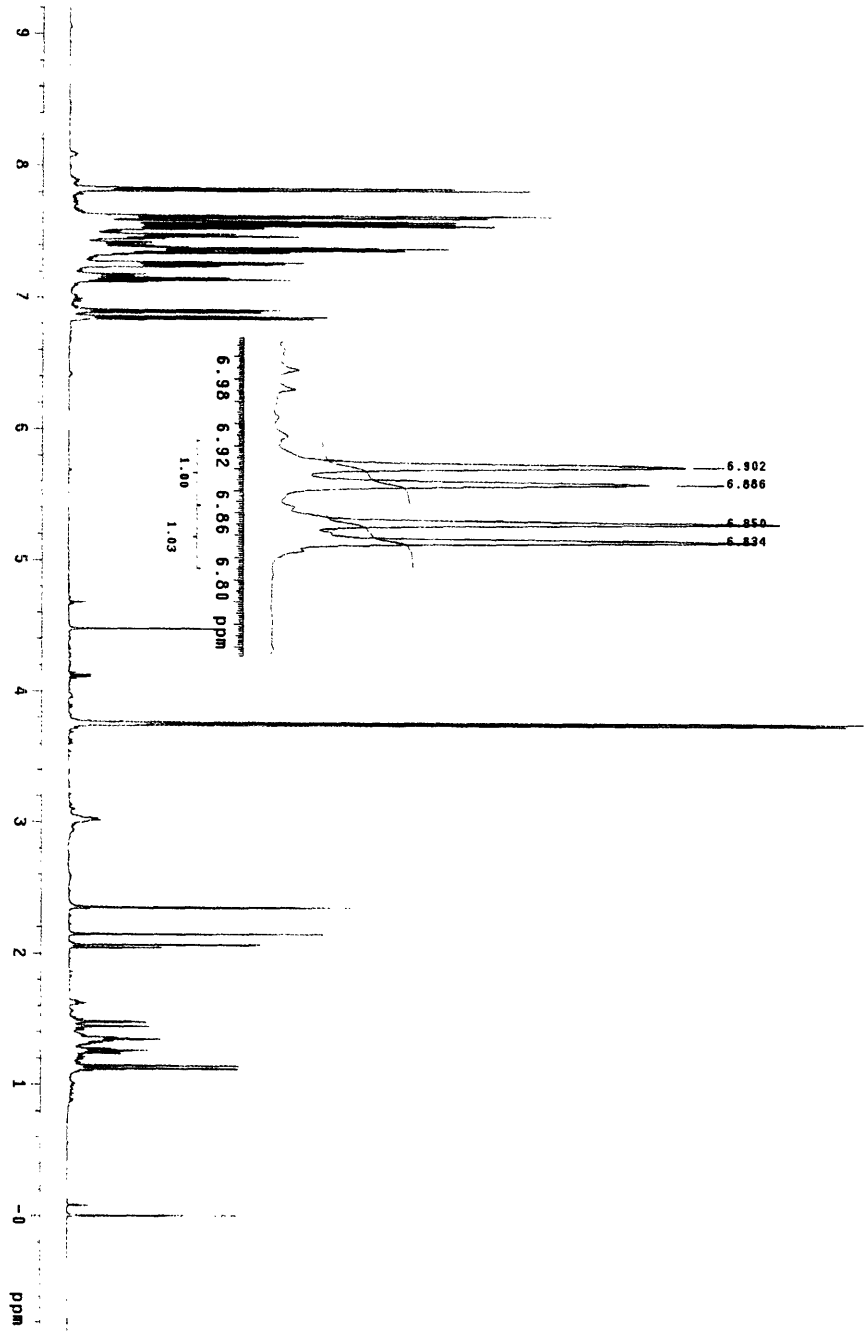


Figure 23. Cyclization of (*p*-cyanophenyl) chloroacetanilide ($CDCl_3$, 500 MHz)

$$k_{CN} / k_H = 1.03$$

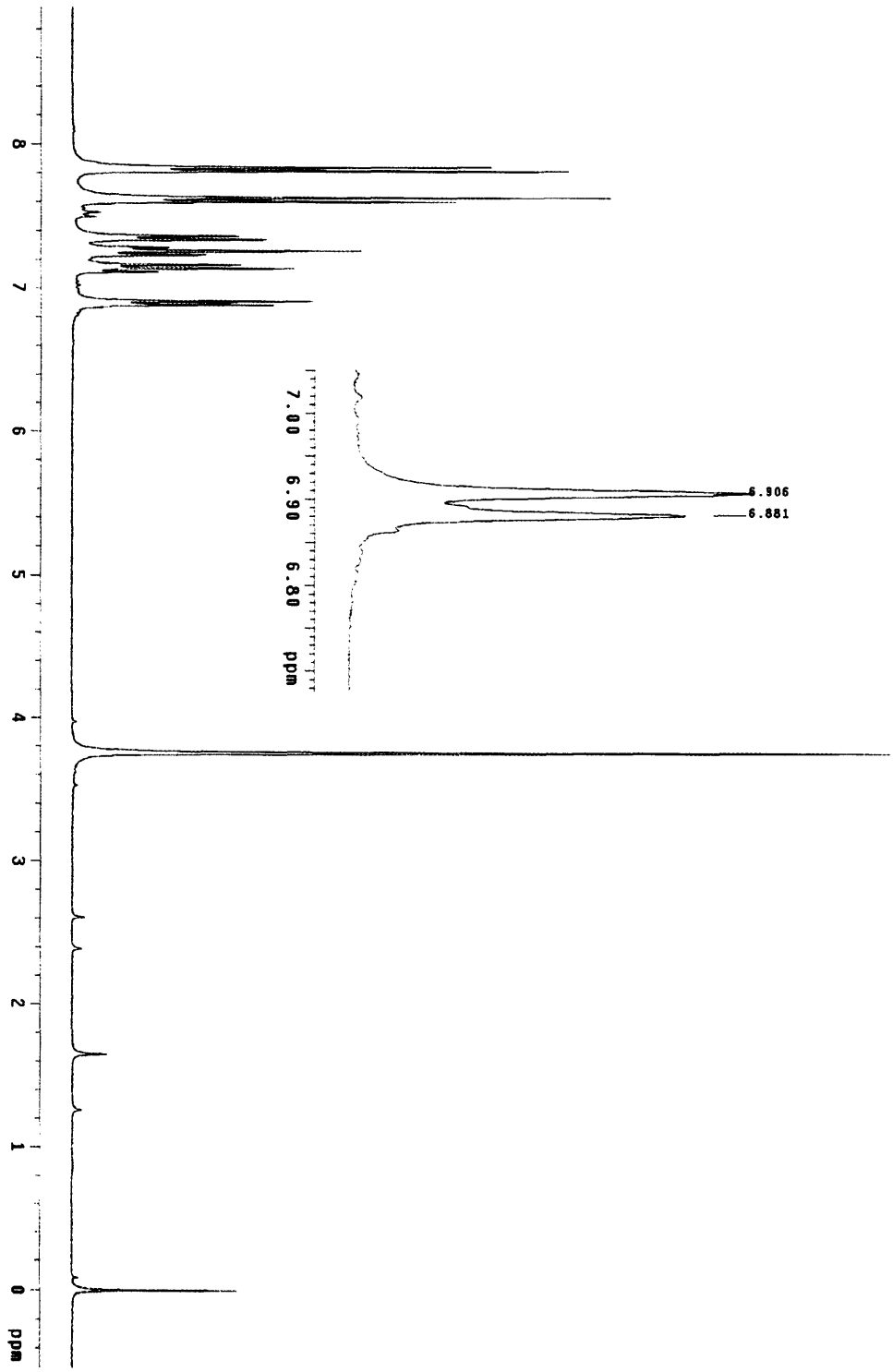


Figure 24. Authentic *N*-(*p*-cyanophenyl)oxindole ($CDCl_3$, 300 MHz)

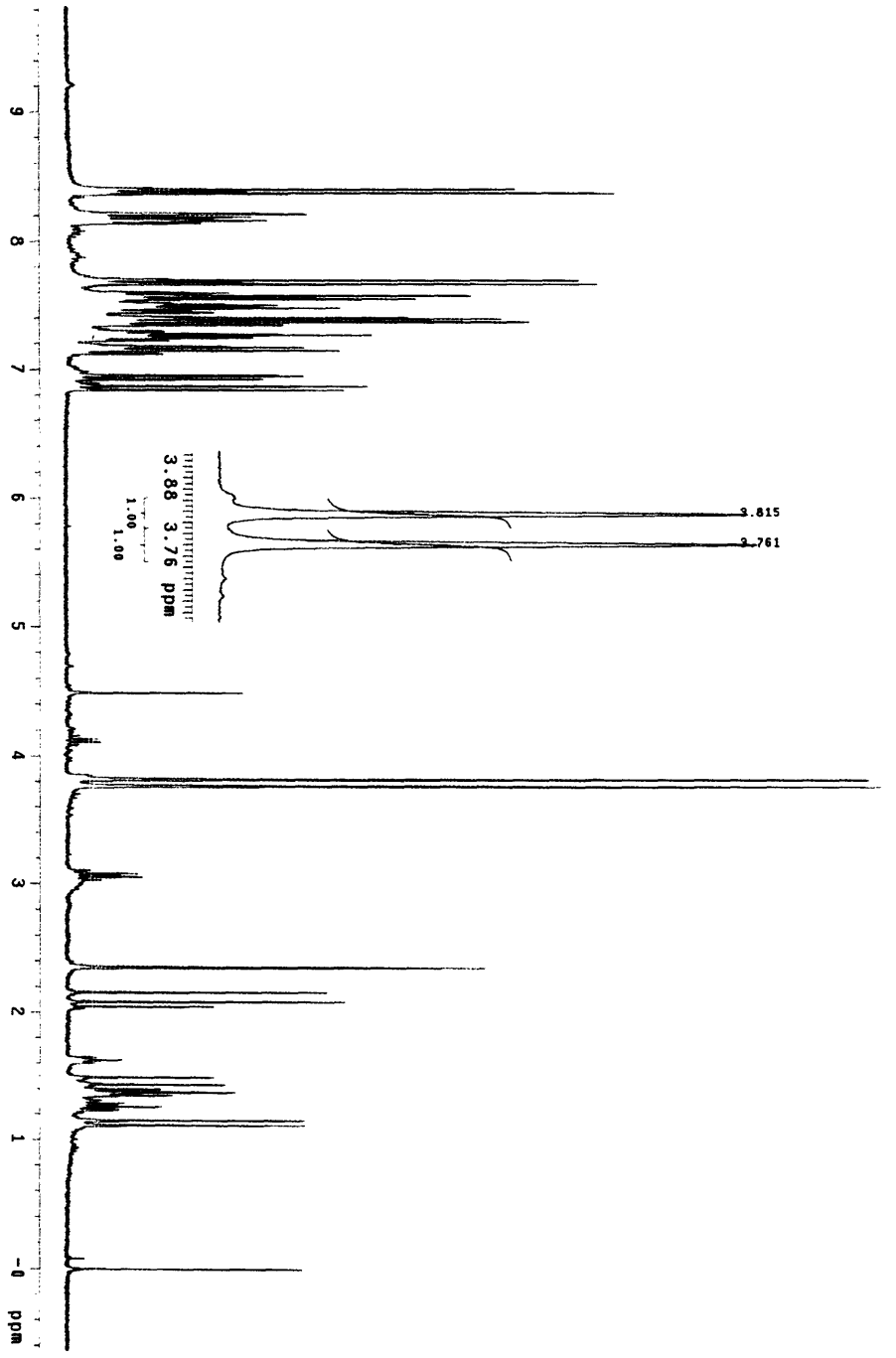


Figure 25. Cyclization of (*p*-nitrophenyl) chloroacetanilide ($CDCl_3$, 300 MHz)

$$k_{NO2} / k_H = 1.00$$

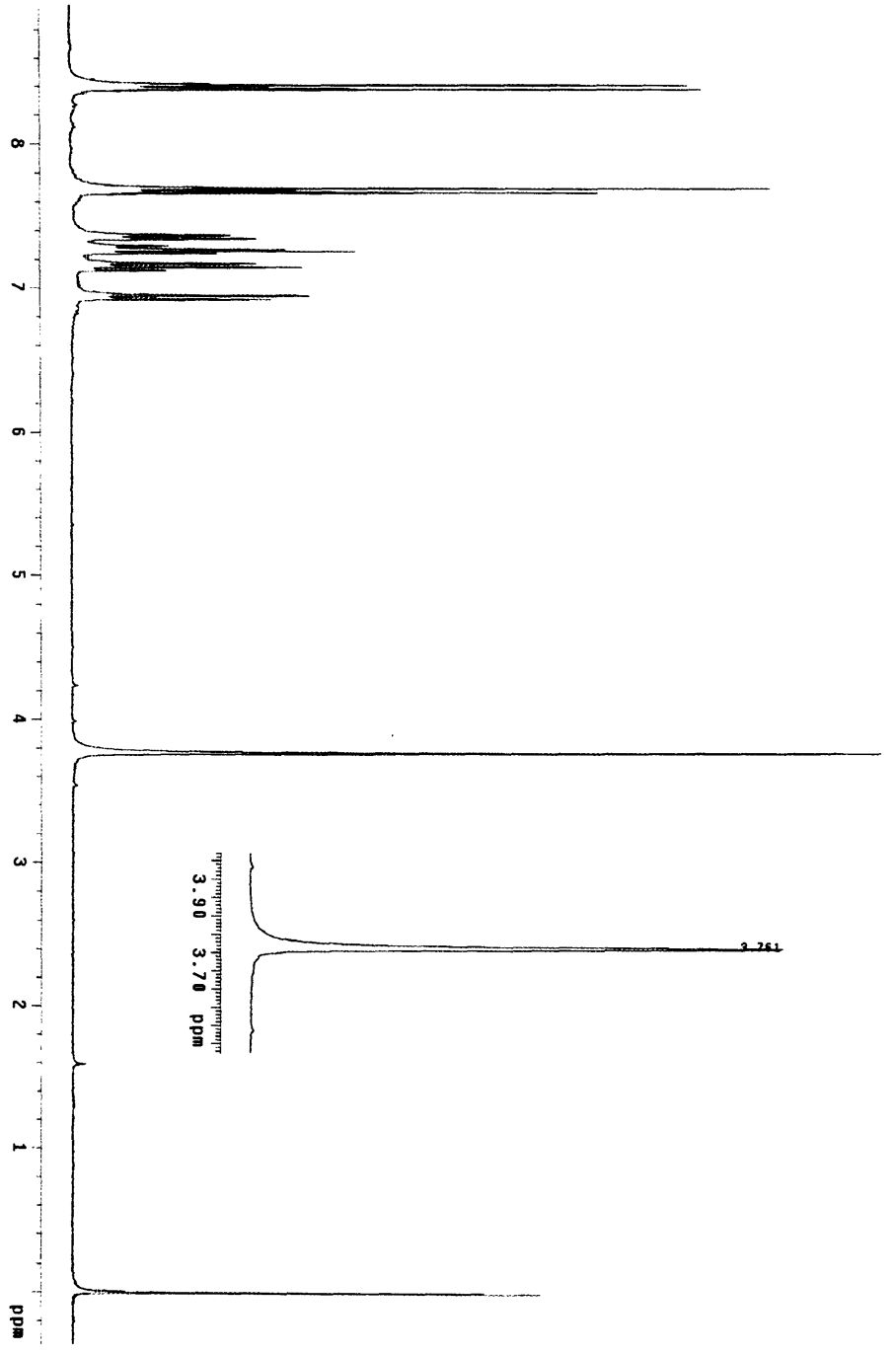


Figure 26. Authentic *N*-(*p*-nitrophenyl)oxindole ($CDCl_3$, 300 MHz)

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CHAPTER 3

SYNTHESIS OF DAPH ANALOGS VIA PALLADIUM-CATALYZED AMINATION

3.1 Introduction

Despite intensive research efforts over recent decades, Alzheimer's disease is still an incurable affliction that affects many elderly patients. The trademark pathological markers of Alzheimer's, observed in post-mortem analysis of the brains of affected patients, are β-amyloid plaques and neurofibrillary tangles.[1] While the exact role of these lesions in the pathogenesis of the disease (or whether they are merely symptomatic of the underlying illness) is unknown, several hypotheses have been put forth to explain their formation.

The β-amyloid plaques are primarily composed of short peptides (denoted Aβ) that are derived from a much larger transmembrane protein, amyloid precursor protein (APP). It has been found that normal APP catabolism occurs at a site within the Aβ region, and thus the intact Aβ produced in patients with Alzheimer's disease is derived from abnormal APP processing.[2]

The neurotoxicity of Aβ peptides, which are typically comprised of 40 to 42 amino acids (Aβ40 and Aβ42, respectively), has been documented.[3] These short peptides aggregate into a fibrillar form with high β-sheet content, and it is these fibrils that are believed to be toxic (through their interaction with receptors on neurons). For example, it has been demonstrated that Aβ fibrils cause an influx of Ca^{2+} ions into neuronal cells.[4] This disruption of calcium homeostasis can have many deleterious effects within the cell, eventually leading to cell death. Moreover, aggregated Aβ42 has been shown to cause prolonged depolarization of neuronal cell membranes.[5] This drastically affects the excitability of the neurons and may be an underlying cause for the cognitive deterioration associated with Alzheimer's.

Among the many potential therapies aimed at curing Alzheimer's disease, biologists at MIT (led by Professor Vernon Ingram) have hypothesized that by preventing or reversing the

formation of β-sheets in the short peptides Aβ40 and Aβ42, the toxicity associated with the fibrillar forms will not manifest itself. Indeed, they have found that Aβ42 must be preincubated for at least 24 hours before being able to induce Ca^{2+} ion influx into neuronal cells, an occurrence that correlates with the β-sheet content of the peptide.[6] Accordingly, this group has explored the use of physiologically stable "decoy peptides," derived from D-amino acids, that interfere with the aggregation of Aβ peptides into their neurotoxic forms.[7] Several of these decoy peptides have been identified that exhibit promising activity in this regard.

More recently, the MIT biology team has expanded their focus to small molecule inhibitors of β-sheet formation as potential therapeutic agents for Alzheimer's disease. In particular, a screen of a number of compounds known to have other types of biological activity was conducted, monitoring for a decrease in the β-sheet content of preaggregated Aβ-42.[6] Of the molecules studied, the most promising lead was 4,5-dianilinophthalimide (DAPH, Figure 1). This compound demonstrated a strong reversal of β-sheet formation ($IC_{50} \sim 15$ μm), as well as the ability to shut down the Ca^{2+} ion influx associated with Aβ fibrils ($IC_{50} \sim 0.7$ μm).

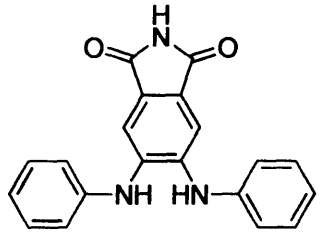
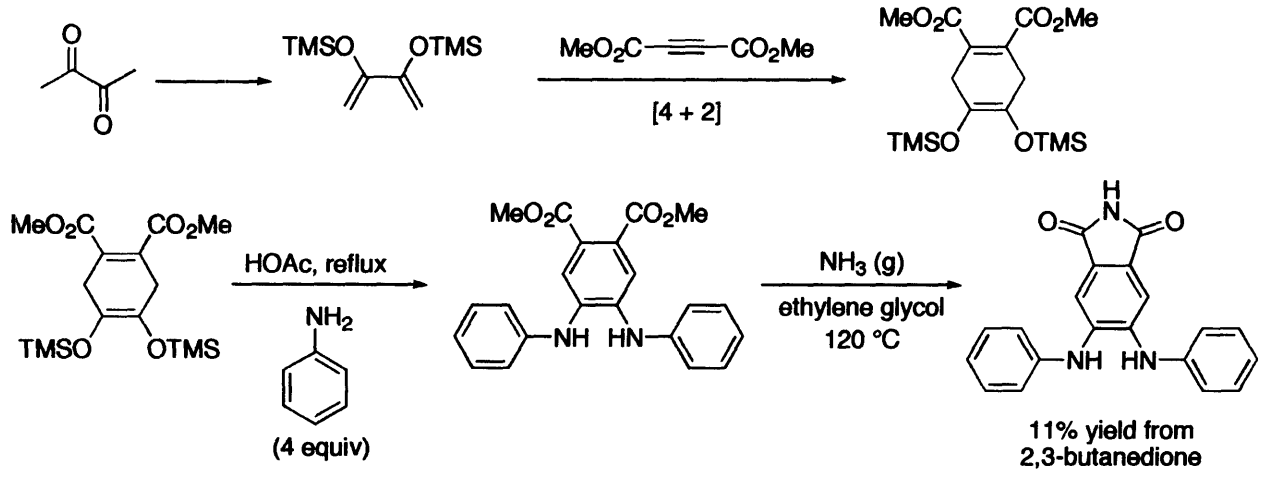


Figure 1. 4,5-Dianilinophthalimide (DAPH)

4,5-Dianilinophthalimide was first synthesized at CIBA Pharmaceuticals as a part of a study on tyrosine kinase inhibitors.[8] In this work, DAPH and its related analogs were assembled as shown in Scheme 1. Bis-silylation of 2,3-butanedione followed by [4+2] cycloaddition with

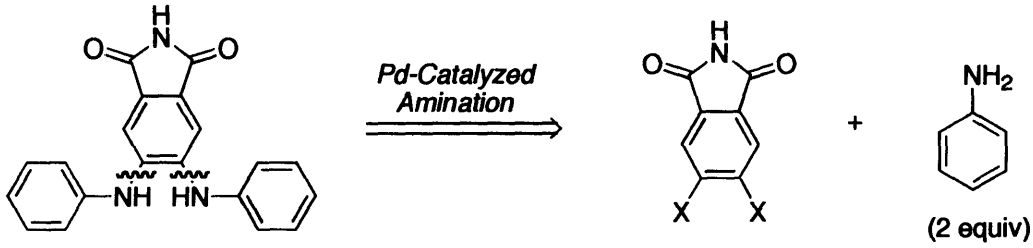
dimethylacetylene dicarboxylate has been shown to afford the dienyl diester shown.[9] Treatment of this compound with an excess of aniline in refluxing acetic acid afforded a relatively low yield of the dimethyl dianilinophthalate, which upon treatment with gaseous ammonia in hot ethylene glycol affords the desired compound. Overall, this process is relatively low-yielding (11% from the starting dione for DAPH), and more importantly only allows for the introduction of nitrogenous nucleophiles onto the aromatic ring. Other groups (such as thiols) cannot be installed by direct reaction with the diene,[8b] and thus a separate synthetic sequence must be used.



Scheme 1. Prior Synthesis of DAPH

Given the promising result obtained by the MIT biologists, it was obvious that there would be need for lead optimization to identify a drug-like small molecule for potential Alzheimer's therapy. However, the initially published synthetic sequence to this class of compounds is not amenable to significant variations in terms of introduction of other nucleophiles at the 4- and 5-positions. Moreover, the number of steps and overall low yields further detract from the applicability of this route.

An alternative route to dianilinophthalimides that would be considerably more attractive is the formation of the C-N bonds through palladium-catalyzed aryl amination, a reaction pioneered and developed in our group over the past decade.[10] Specifically, the target compounds could be constructed from a 4,5-dihalophthalimide derivative and the corresponding aniline (Scheme 2). Moreover, given the precedence for formation of aromatic C-C, C-O, and C-S bonds using palladium catalysis, the potential exists for a diversity of related analogs that are readily accessible from convenient starting materials.



Scheme 2. Retrosynthetic Disconnection of C-N Bonds in DAPH

Given our experience and understanding of the palladium-catalyzed amination process, we entered into a collaborative effort with the MIT biology group headed by Professor Ingram. It is our hope that the work presented herein is only the beginning of a fruitful relationship, one which may very well have an impact on future research into potential Alzheimer's therapies.

3.2 Results and Discussion

3.2.1 Amination on 4,5-Dichlorophthalic Acid Dimethyl Ester

Our initial ventures into the synthesis of DAPH analogs using palladium-catalyzed amination focused on a more expedient synthesis of the dimethyl 4,5-dianilinophthalate intermediates used in the originally published route. We hypothesized that these would be easily accessi-

ble from commercially available 4,5-dichlorophthalic acid, and that the subsequent closure of the phthalimide ring could be performed a number of ways.

The palladium-catalyzed amination has been conducted under a wide variety of reaction conditions, with seemingly countless permutations of palladium precatalyst, phosphine ligand, stoichiometric base, and solvent.[10] However, based on the considerable research efforts expended by our group on both synthetic[11] and mechanistic[12] aspects of the amination, we chose to start our studies using 2-dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl (XPhos, Figure 2) as the ligand for palladium. This phosphine has proven to be superior for amination in most synthetic applications. We also chose $Pd_2(dba)_3$, a convenient Pd^0 source, as the precatalyst since the substrate combinations we planned to employ were not amenable to *in situ* reduction of a Pd(II) precatalyst. Lastly, we decided to avoid the use of sodium *tert*-butoxide as the stoichiometric base due to the potential for transesterification, which would hamper subsequent formation of the phthalimide ring.

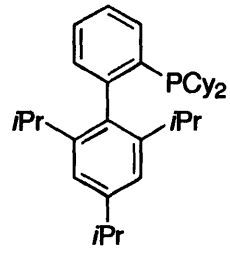
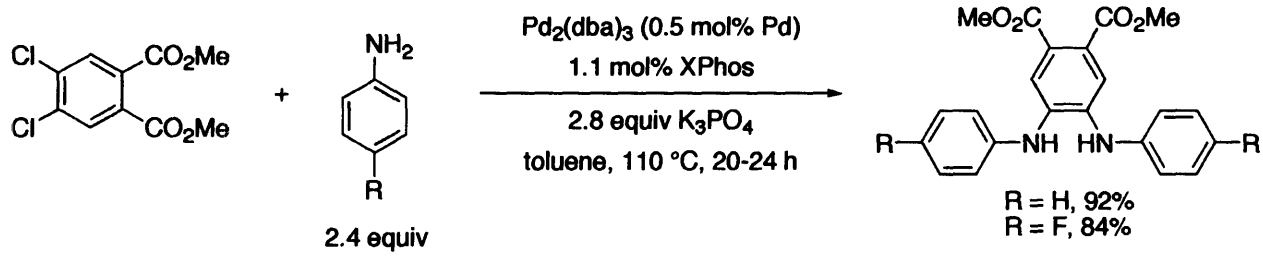


Figure 2. XPhos (2-Dicyclohexylphosphino-2',4',6'-Triisopropylbiphenyl)

Gratifyingly, by heating a toluene solution of 4,5-dichlorophthalic acid dimethyl ester (obtained in high yield by treatment of the diacid with thionyl chloride in methanol) and aniline in the presence of potassium phosphate and catalytic quantities of $Pd_2(dba)_3$ and XPhos, the de-

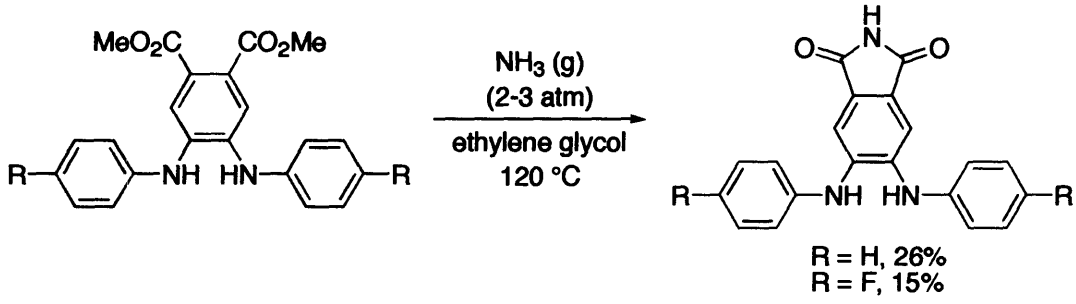
sired dimethyl 4,5-dianilinophthalate can be obtained in excellent yield (Scheme 3). Due to the low solubility of the product in nonpolar organic media as well as water, isolation is simplified by pouring the entire reaction into a mixture of diethyl ether and water (to dissolve any unreacted starting reagents as well as any inorganic material) and filtration of the insoluble product. The *para*-fluoroanilino analog can be made in an analogous fashion (Scheme 3).



Scheme 3. Amination Reactions on 4,5-Dichlorophthalic Acid Dimethyl Ester

Given the ease with which dimethyl 4,5-dianilinophthalates could be assembled, we were disappointed to find that the closure of the phthalimide ring was a nontrivial problem despite the variety of protocols examined. For example, heating a solution of the diester with urea and sodium methoxide, a procedure commonly used for this transformation in cases of more simple phthalates,[13] was not successful when applied to these compounds (nor was it when conducted under acid-catalyzed conditions). Alternatively, no desired phthalimides were observed when heating the diesters in the presence of excess hexamethyldisilazane (commonly used as an ammonia equivalent)[14] and Lewis acids. Difficulties in the formation of this ring were also discussed in the initially published synthesis (Scheme 1).[8b] When applying a modification of the published ammonolysis protocol, we were pleased to observe formation of the desired phthalimides albeit in disappointingly low yields (Scheme 4). While the published procedure typically affords yields of 40-60% for this step, it requires larger quantities of gaseous ammonia

(a steady stream for a duration of 16 hours) that were not immediately available in our lab at the time of this work. Instead, we conducted the reactions in sealed reaction vessels pressurized with ammonia gas under otherwise identical conditions.



Scheme 4. Synthesis of Phthalimide Ring via Ammonlysis

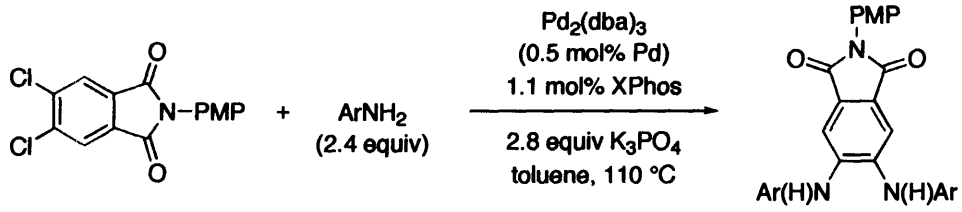
Due to the difficulties encountered in formation of the phthalimide ring (in both our hands and in the previously published route), we sought to develop an alternative approach to the desired DAPH analogs by conducting the palladium-catalyzed amination reactions on substrates that already contained the phthalimide ring.

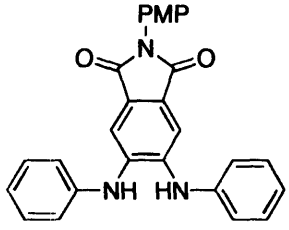
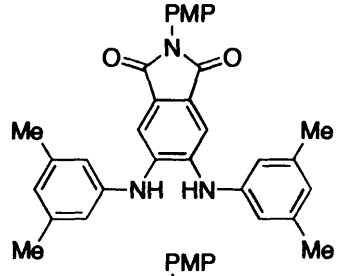
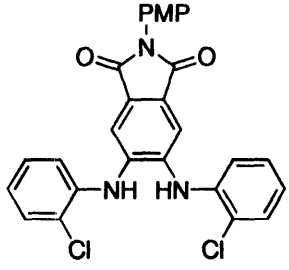
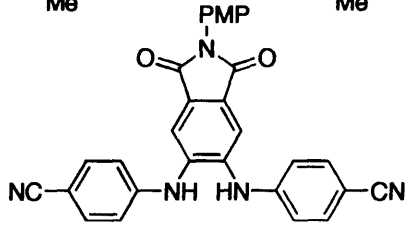
3.2.2 Amination on 4,5-Dichlorophthalimide Derivatives

The most attractive and intuitively straightforward protocol for the synthesis of DAPH analogs would be to conduct the palladium-catalyzed amination directly on commercially available 4,5-dichlorophthalimide. Such a route would obviate the need to use protecting groups for the acidic phthalimide nitrogen and would afford the desired compounds directly. However, while a variety of reaction conditions were explored for this coupling, we were unable to effect the amination on the unprotected substrate.

We were pleased to observe that the amination reaction does proceed on 4,5-dichlorophthalimides in which the nitrogen is protected. For example, amination on the *p*-methoxyphenyl (PMP)-protected substrate proceeds cleanly under the aforementioned conditions to give the corresponding DAPH analogs (Table 1).

Table 1. Synthesis of *p*-Methoxyphenyl-Protected DAPH Analogs



Entry	Product	Yield	Entry	Product	Yield
1		97%[a]	3		68%[b]
2		55%[b]	4		74%[c]

[a] Product isolated by silica gel chromatography
[b] Product isolated by recrystallization of crude material
[c] Product isolated by direct crystallization from reaction mixture

Unfortunately, we were unable to find a way to effectively remove the *p*-methoxyphenyl group from these protected phthalimides under standard conditions. In hindsight, however, a PMP protecting group is far from ideal for this class of products. Since removal of this moiety is

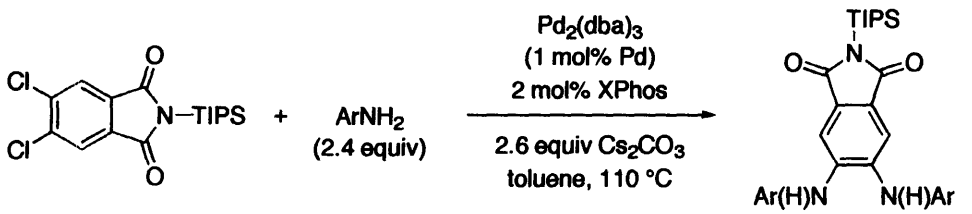
typically performed under oxidative conditions (for example, using ceric ammonium nitrate),[15] one can imagine a host of unwanted side reactions occurring at the diarylamino motif instead, especially in cases where the DAPH analogs are derived from electron-rich anilines.

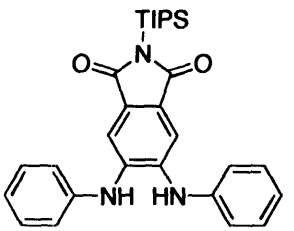
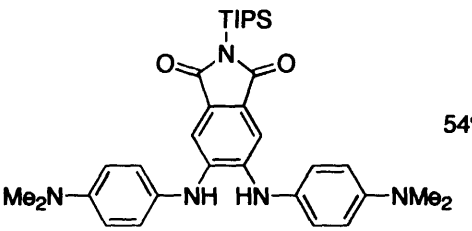
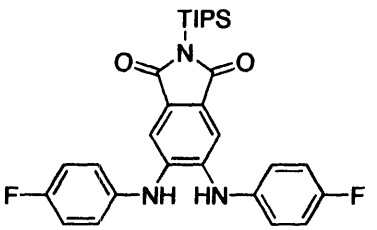
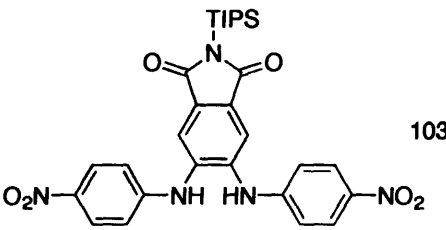
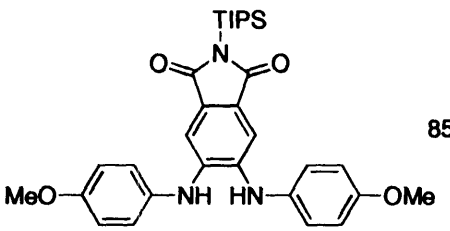
Given the difficulty in liberating the desired compounds from the PMP-protected analogs, we set about surveying other types of commonly used nitrogen protecting groups. Unfortunately, there is little precedent for the protection of the phthalimide nitrogen; usually the phthalimide ring *itself* is the protecting group that is cleaved![15] We found that the amination reaction proceeds cleanly on *N*-benzyl-4,5-dichlorophthalimide, although again we encountered difficulties in removing the protecting group. Hydrogenolysis (Pd/C) was ineffective, and we worried that more forcing reductive conditions would also result in the reduction of one of the carbonyl groups of the phthalimide ring (which are known to be reduced under relatively mild conditions).[16] We also ruled out the possibility of using carbonyl-based protecting groups, as phthalimide ring-opening (with the aniline used in the amination) should be facile at the temperatures employed.[17]

The logical solution to the problem seemed to reside in the use of silicon-based protecting groups. While silicon reagents are more commonly used to protect hydroxyl groups in organic synthesis, bulkier groups have found applications in protection of the amide nitrogen.[15] Moreover, the weak N-Si bond was expected to translate into easy removal of the protecting group. Indeed, we were encouraged by the report of a stable, crystalline *N*-*tert*-butyldimethylsilyl (TBS)-protected phthalimide, from which the parent N-H compound is easily liberated by treatment with a fluoride source.[18] The analogous *N*-TBS-protected 4,5-dichlorophthalimide is easily synthesized, but unfortunately the amination reaction fails (presumably due to desilylation of the substrate). We were able to synthesize the analogous *N*-triisopropylsilyl (TIPS)-protected 4,5-

dichlorophthalimide, and this substrate undergoes the amination reaction without any noticeable decomposition. Thus, employing reaction conditions similar to those described above (with the exception that Cs_2CO_3 was used as the stoichiometric base), the TIPS-protected DAPH analogs can be accessed in short order (Table 2).

Table 2. Synthesis of TIPS-Protected DAPH Analogs

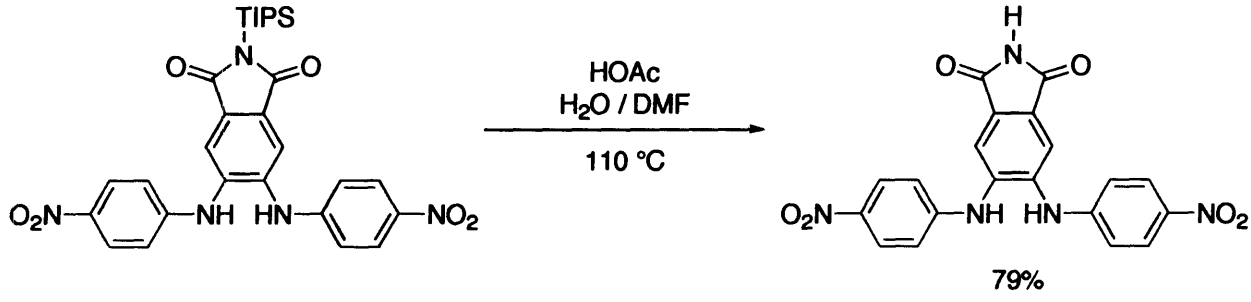


Entry	Product	Yield	Entry	Product	Yield
1		92%	4		54%
2		80%	5		103%[a,b]
3		85%			

[a] 2.6 equiv K_2CO_3 used as base

[b] Product crystallizes directly from reaction mixture; reported yield includes solvent that could not be removed *in vacuo*

It should be pointed out that the amination reaction employing 4-nitroaniline as the nucleophile requires the use of a weaker base (K_2CO_3); employing Cs_2CO_3 or K_3PO_4 resulted in ineffective coupling. Also noteworthy about this particular example is that the product is insoluble in toluene and crystallizes as it is formed. As a result, the crystallization trapped some toluene that could not be removed under high vacuum, resulting in an observed yield higher than the theoretical maximum. As expected, the silicon protecting group is easily removed from the desired DAPH analogs, either by heating with aqueous acetic acid or by treatment with methanolic KF (Scheme 5).

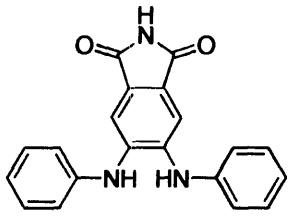
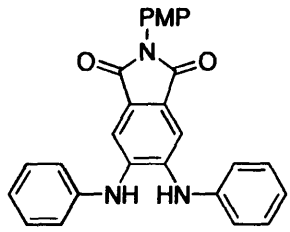
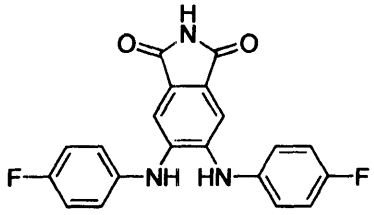
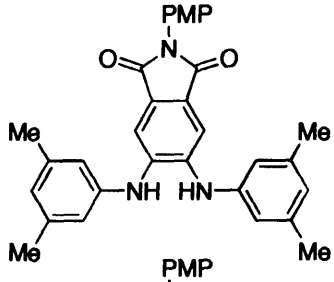
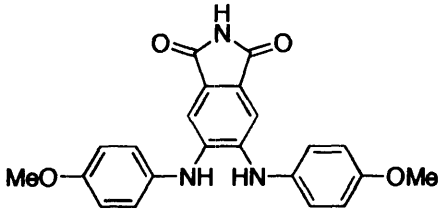
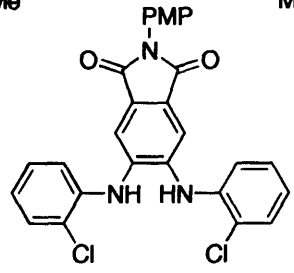
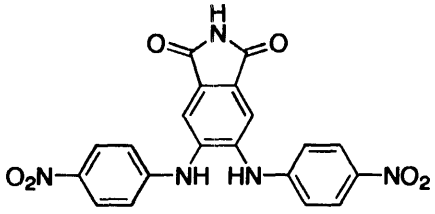
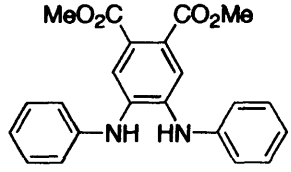


Scheme 5. Deprotection of TIPS-Protected DAPH Analogs

Thus, we have developed an effective route to DAPH analogs employing palladium-catalyzed amination to form the 4,5- carbon-nitrogen bonds. A number of previously known as well as novel compounds have been accessed through this methodology, and have been subjected to screening in their ability to reverse β-sheet formation of aggregated Aβ42 (see Section 3.2.3).

3.2.3 Efficacy of DAPH Analogs in Reversal of β-Sheet Formation

Table 3. Efficacy of DAPH Analogs in Reversal of β-Sheet Formation

Compound	Fibril Reversal[a]	Compound	Fibril Reversal[a]
	60%[b]		21%
	68%		13%
	80%		16%
	12%		40%

[a] Measured reversal of β-sheet content of preformed Aβ42 fibrils
[b] Value is the average of three measurements

Key to the rational design of new DAPH analogs is a knowledge of how variations in the molecular framework affect the desired biological activity (i.e., structure-activity relationships). Many of the compounds prepared in the above sections have been tested by biologists at MIT for

efficacy in reversing the β-sheet content of Aβ42. Gratifyingly, several of the analogs we have synthesized have demonstrated an increase in activity relative to the parent DAPH compound (Table 3).[19]

It appears that the presence of a free phthalimide N-H is necessary for the desired activity (the PMP-protected analogs are considerably less effective). The results also suggest that electron-releasing groups on the aniline rings are beneficial, although more data is necessary to verify this assertion. Interestingly, the compound that has thus far exhibited the greatest activity in the reversal of β-sheet formation, 4,5-bis-(4-methoxyanilino) phthalimide, has been shown to be a poor tyrosine kinase inhibitor ($IC_{50} > 50$ μm), in contrast to the *para*-fluoro analog ($IC_{50} = 0.7$ μm) and DAPH itself ($IC_{50} = 0.3$ μm).[8] Thus, these preliminary results indicate that selectivity in terms of biological activity can be achieved.

3.3 Conclusions

We have developed a synthetic route to 4,5-dianilinophthalimide (DAPH) and structurally-related analogs that employs palladium-catalyzed amination as the key bond-forming step. The requisite dihalogenated substrates are easily obtained, often in a single step, from commercially available materials. The coupling of these precursors with a host of substituted anilines proceeds in generally high yields. In the case of *N*-TIPS-protected compounds, subsequent removal of the silicon protecting group has proven to be facile. Thus, a variety of DAPH analogs can be quickly accessed in a modular fashion.

In addition to the related analogs synthesized thus far, the route described herein should be amenable to the incorporation of other classes of nucleophiles at the DAPH 4- and 5-

positions, given the wealth of palladium-catalyzed cross coupling reactions developed in the recent decades. For example, one can imagine the installment of carbon, oxygen, and sulfur-based motifs into the DAPH structure using these reactions.

The results of biological assays conducted using many of the DAPH analogs synthesized suggest structural features that are important to biological activity, and further lead optimization is currently underway. While a small molecule-based therapy for Alzheimer's disease based on the reversal of β-sheet formation is likely years away, these promising results validate the concept of such a treatment and will serve as a foundation for future work in the area.

3.4 Experimental Procedures

General Considerations: Toluene was purchased from J. T. Baker in a CYCLE-TAINER® solvent delivery keg, which was vigorously purged with argon for two hours and further purified by passing through one column of neutral alumina followed by a column of copper (II) oxide under argon pressure. $Pd_2(dba)_3$ was purchased from Strem Chemical Company and was used as received. 2-(Dicyclohexylphosphino)-2',4',6'-triisopropylbiphenyl (XPhos) was synthesized following the published procedure.[11a] $CDCl_3$ and d_6-DMSO were purchased from Cambridge Isotope Laboratories. *N*, *N*-Dimethyl-*p*-phenylenediamine was purchased from Alfa Aesar and was distilled immediately prior to use. All other reagents were purchased from commercial sources and were used without further purification. Thin layer chromatography was performed using EM Science silica gel 60 F_{254} plates. Column chromatography was done using EM Science silica gel (230-400 mesh). Melting points were obtained using a Mel-Temp apparatus (Laboratory Devices) and are uncorrected. IR spectra for all previously unreported compounds were obtained

(by analysis of a thin film on a NaCl plate) using a Perkin Elmer System 2000 FT-IR spectrometer. Elemental analyses were performed by Atlantic Microlabs, Inc., Norcross, GA. ^{1}H NMR and ^{13}C NMR spectra were obtained using either a Varian Mercury 300 MHz spectrometer, a Varian Inova 500 MHz spectrometer, or a Varian Inova 501 MHz spectrometer; chemical shifts for ^{1}H NMR are referenced to tetramethylsilane (TMS) as an internal standard, while chemical shifts for ^{13}C NMR are referenced to the solvent used. Yields reported in Tables 1 and 2 refer to isolated yields of >95% purity (as determined by ^{1}H NMR and/or elemental analysis), unless otherwise noted. ^{1}H NMR spectra for compounds whose elemental analyses were unsatisfactory are included in Figures 3-10.

Amination on 4,5-Dichlorophthalic Acid Dimethyl Ester

4,5-Dichlorophthalic acid dimethyl ester:[13] A solution of 4,5-dichlorophthalic acid (23.53 g, 100.1 mmol) in MeOH (200 mL) was treated with thionyl chloride (30 mL, 410 mmol) dropwise over 2 h. The resulting solution was allowed to stir at rt for 72 h (reaction time unoptimized) and was then concentrated using a rotary evaporator. The resulting oil was dissolved in EtOAc (100 mL), and the solution was washed with H_2O, saturated $NaHCO_3$ (aq), and brine, and was then dried ($MgSO_4$), filtered, and concentrated to a colorless oil. This material was dissolved in hexanes (50 mL), and the title compound crystallized at room temperature. A first crop of 23.48 g was collected, followed by a second crop of 1.20 g (24.68 total, 94%), mp = 46-49 °C.

Procedure for the Synthesis of Dimethyl 4,5-Dianilinophthalate Derivatives: A roundbottom flask is charged with $Pd_2(dba)_3$ (0.5 mol%), XPhos (1.1 mol%), K_3PO_4 (2.8 equiv), and 4,5-dichlorophthalic acid dimethyl ester (1 equiv). The flask is evacuated and backfilled with N_2 (this process is repeated 3 times), and then anhydrous toluene (1 mL / mmol of substrate) is

added. The mixture is allowed to stir at room temperature for 5 min, and then the substituted aniline (2.4 equiv) is added, followed by additional toluene (0.5 mL / mmol substrate). The mixture is heated at 110 °C overnight (~20-24 h), and is then allowed to cool. The entire reaction is then poured into a flask containing diethyl ether and H_2O (ca. 2 mL each per mmol substrate), and the mixture is allowed to stir vigorously at room temperature for 10 min before being filtered via suction. The filter cake is washed with H_2O and ether, and is then dried in air to afford analytically pure product.

Dimethyl-4,5-Dianilinophthalate:[8b] Obtained as a pale green solid (92%), mp = 177-180 °C (lit. 177-180 °C)[8b].

Dimethyl-4,5-bis-(4-fluoroanilino) phthalate:[8b] Obtained as a pale green/yellow solid (84%), mp = 165-166 °C (lit. 164-166 °C).[8b]

Amination on N-PMP-Protected-4,5-Dichlorophthalimide

***N*-*p*-Methoxyphenyl-4,5-Dichlorophthalimide:** A mixture of 4,5-dichlorophthalic anhydride (10.84 g, 50.0 mmol) and *p*-anisidine (6.62 g, 53.8 mmol) in glacial acetic acid (75 mL) was heated at reflux for 2 h. The reaction mixture was then allowed to cool to ensure complete crystallization of the product, which was isolated by suction filtration. The filter cake was washed with acetic acid (50 mL) and then ether (50 mL). After drying briefly, the solid material was transferred to a flask along with ether (50 mL), and the suspension was allowed to stir vigorously for 10 min. The solid material was isolated by suction filtration and dried in air to afford the title compound as a pale yellow solid (14.95 g, 93%), mp = 213.5-215 °C. ^{1}H NMR ($CDCl_3$) δ 3.85 (s, 3H, -OCH_3), 7.02 (d, J = 9.3 Hz, 2H, aromatic), 7.31 (d, J = 9.3 Hz, 2H, aromatic), 8.02 (s, 2H). ^{13}C NMR ($CDCl_3$) δ 53.74, 114.76, 123.93, 125.95, 127.97, 131.09, 139.49, 159.68,

165.82. Calc. for $C_{15}H_9Cl_2NO_3$: C 55.93, H 2.82. Found: C 55.79, H 2.66. IR (CH_2Cl_2) ν (cm^{-1}) 1717, 1707.

Procedure for the Synthesis of *N-p*-Methoxyphenyl-4,5-Dianilinophthalimide Derivatives: A screw-cap test tube is charged with $Pd_2(dba)_3$ (0.5 mol%), XPhos (1.1 mol%), K_3PO_4 (2.8 equiv), and *N-p*-methoxyphenyl-4,5-dichlorophthalimide (1 equiv). A Teflon septum/cap is applied, and the tube is evacuated and backfilled with N_2 (this process is repeated 3 times) and treated with anhydrous toluene (1 mL / mmol of substrate). The mixture is allowed to stir at room temperature for 5 min, and then the substituted aniline (2.4 equiv) is added, followed by additional toluene (0.5 mL / mmol substrate). The mixture is heated at 110 °C overnight and is then allowed to cool to room temperature. The reaction mixture is diluted with EtOAc (~10 mL per mmol substrate) and filtered through a plug of Celite, and the filtrate is concentrated using a rotary evaporator. The product is isolated either by silica gel chromatography or by crystallization.

***N-p*-Methoxyphenyl-4,5-Dianilinophthalimide (Table 1, Entry 1):** Using the general procedure (21 h), the product was purified by silica gel chromatography (75:25 hexanes:EtOAc; R_f = 0.22) to give an orange solid (97%), mp = 172-174 °C. ^{1}H NMR ($CDCl_3$, Figure 3) δ 3.83 (s, 3H, -OC*H*$_3$), 5.93 (s, 2H, -N*H*), 6.98 (d, *J* = 9.0 Hz, 2H, aromatic), 7.04-7.10 (m, 6H, aromatic), 7.26-7.37 (m, 6H, aromatic), 7.68 (s, 2H, aromatic). ^{13}C NMR ($CDCl_3$) δ 55.69, 112.58, 114.59, 119.92, 123.40, 124.94, 125.76, 128.14, 130.03, 140.10, 141.51, 159.19, 167.91. IR (CH_2Cl_2) ν (cm^{-1}) 3342, 1762, 1705.

***N-p*-Methoxyphenyl-4,5-Bis-(2-chloroanilino) phthalimide (Table 1, Entry 2):** Using the general procedure (20 h), the product was purified by recrystallization from CH_2Cl_2/MeOH to give a yellow solid (55%), mp = 168-170 °C. ^{1}H NMR ($CDCl_3$, Figure 4) δ 3.84 (s, 3H, -OC*H*$_3$),

6.35 (s, 2H, -N*H*), 6.99-7.05 (m, 4H, aromatic), 7.17-7.32 (m, 6H, aromatic), 7.43-7.46 (m, 2H, aromatic), 7.68 (s, 2H, aromatic). ^{13}C NMR ($CDCl_3$) δ 55.71, 114.01, 114.64, 119.87, 123.84, 124.70, 126.61, 128.14, 128.22, 130.42, 138.41, 139.59, 159.29, 167.60. IR (CH_2Cl_2) ν (cm^{-1}) 3350, 1766, 1711.

***N*-*p*-Methoxyphenyl-4,5-Bis-(3,5-dimethylanilino) phthalimide (Table 1, Entry 3):** Using the general procedure (20 h), the product was purified by recrystallization from CH_2Cl_2/MeOH to give an orange solid (68%), mp = 205-207 °C. ^1H NMR ($CDCl_3$) δ 2.30 (s, 12H, -C*H*$_3$), 3.83 (s, 3H, -OC*H*$_3$), 5.79 (s, 2H, -N*H*), 6.67 (s, 4H, aromatic), 6.72 (s, 2H, aromatic), 6.98 (d, *J* = 9.0 Hz, 2H, aromatic), 7.29 (d, *J* = 9.0 Hz, 2H, aromatic) 7.64 (s, 2H, aromatic). ^{13}C NMR ($CDCl_3$) δ 21.61, 55.69, 112.76, 114.56, 117.84, 125.03, 125.28, 125.55, 128.17, 139.76, 140.31, 141.46, 159.15, 168.03. Calc. for $C_{31}H_{29}N_3O_3$: C 75.74, H 5.95. Found: C 75.79, H 5.86. IR (CH_2Cl_2) ν (cm^{-1}) 3343, 1765, 1705.

***N*-*p*-Methoxyphenyl-4,5-Bis-(4-cyanoanilino) phthalimide (Table 1, Entry 4):** Using the general procedure (20 h), the reaction mixture was diluted with CH_2Cl_2 (10 mL per mmol substrate) and H_2O (2 mL per mmol substrate). The mixture was filtered via suction, and the filter cake was washed with H_2O and ether and then dried in air to give the product as a pale yellow solid (74%), mp = >260 °C. Due to the rapid crystallization of the product from the reaction, a small amount (~5%) of unidentified contaminant is present in the solid. ^1H NMR (d_6-DMSO, Figure 5) δ 3.80 (s, 3H, -OC*H*$_3$), 7.06 (d, *J* = 8.5 Hz, 2H, aromatic), 7.16 (d, *J* = 8.5 Hz, 4H, aromatic), 7.32 (d, *J* = 8.5 Hz, 2H, aromatic), 7.67 (d, *J* = 8.5 Hz, 4H, aromatic), 7.72 (s, 2H, aromatic), 8.92 (broad s, 2H, -N*H*). ^{13}C NMR (d_6-DMSO) δ 55.40, 92.26, 101.23, 114.14, 114.87, 116.69, 119.69, 126.07, 128.61, 133.59, 138.40, 147.08, 158.74, 166.69. IR (acetone) ν (cm^{-1}) 3313, 1769, 1709.

Amination on N-TIPS-Protected-4,5-Dichlorophthalimide

***N*-Triisopropylsilyl-4,5-Dichlorophthalimide:** A 100 mL roundbottom flask was charged with 4,5-dichlorophthalimide (6.50 g, 30.1 mmol) and was evacuated and backfilled with Ar. Anhydrous CH_2Cl_2 (20 mL) was added, and the suspension was treated with anhydrous triethylamine (6.0 mL, 43 mmol) and triisopropylsilyl chloride (7.00 mL, 32.7 mmol). Additional CH_2Cl_2 (10 mL) was added, and the resulting mixture was heated to reflux under Ar. After heating overnight, the reaction mixture was allowed to cool and was partitioned between CH_2Cl_2 and H_2O. The aqueous portion was extracted with CH_2Cl_2 and the combined organics were washed with H_2O, brine, dried ($MgSO_4$), filtered, and concentrated to a yellow solid. This material was recrystallized from hot EtOAc/hexanes (with a hot filtration prior to cooling) to afford the title compound as colorless crystals (5.58 g, 50%), mp = 164-166 °C. ^{1}H NMR ($CDCl_3$) δ 1.12 (d, J = 7.8 Hz, 18 H, -SiCH(C*H*$_3$)$_2$), 1.81 (septet, J = 7.5 Hz, 3H, -SiC*H*(CH$_3$)$_2$), 7.90 (s, 2H, aromatic). ^{13}C NMR ($CDCl_3$) δ 11.98, 18.31, 125.29, 133.25, 139.06, 172.21. Calc. for $C_{17}H_{23}Cl_2NO_2Si$: C 54.83, H 6.23. Found: C 54.78, H 6.21. IR (CH_2Cl_2) ν (cm^{-1}) 1765, 1711.

Procedure for the Synthesis of *N*-Triisopropylsilyl-4,5-Dianilinophthalimide Derivatives: A screw-cap test tube is charged with $Pd_2(dba)_3$ (1 mol%), XPhos (2 mol%), Cs_2CO_3 (2.6 equiv), and *N*-triisopropylsilyl-4,5-dichlorophthalimide (1 equiv). A Teflon septum/cap is applied, and the tube is evacuated and backfilled with N_2 (this process is repeated 3 times), and then anhydrous toluene (1 mL / mmol of substrate) is added. The mixture is allowed to stir at room temperature for 5 min, and then the substituted aniline (2.4 equiv) is added, followed by additional toluene (0.5 mL / mmol substrate). The mixture is heated at 110 °C overnight and is then allowed to cool to room temperature. The reaction mixture is partitioned between EtOAc and

H_2O, and the organic layer is washed with brine, dried ($MgSO_4$), filtered, and concentrated using a rotary evaporator. The product is isolated by silica gel chromatography or crystallization.

***N*-Triisopropylsilyl-4,5-Dianilinophthalimide (Table 2, Entry 1):** Using the general procedure (23 h), the product was obtained by silica gel chromatography (85:15 hexanes:EtOAc; $R_f = 0.29$) to give a yellow solid (92%), mp = 133-136 °C. ^{1}H NMR ($CDCl_3$, Figure 6) δ 1.13 (d, $J = 7.5$ Hz, 18H, -SiCH(CH_3)$_2$), 1.79 (septet, $J = 7.5$ Hz, 3H, -SiC*H*(CH_3)$_2$), 5.89 (s, 2H, -N*H*), 7.07 (m, 6H, aromatic), 7.34 (m, 4H, aromatic), 7.59 (s, 2H, aromatic). ^{13}C NMR ($CDCl_3$) δ 12.07, 18.42, 111.56, 119.93, 123.24, 128.11, 129.94, 140.01, 141.61, 174.42. IR ($CDCl_3$) ν (cm^{-1}) 3351, 1752, 1686.

***N*-Triisopropylsilyl-4,5-bis-(4-fluoroanilino) phthalimide (Table 2, Entry 2):** Using the general procedure (19 h), the product was obtained by silica gel chromatography (85:15 hexanes:EtOAc; $R_f = 0.22$) to give a yellow solid (85%), mp = 172-173 °C. ^{1}H NMR ($CDCl_3$, Figure 7) δ 1.11 (d, $J = 7.5$ Hz, 18H, -SiCH(CH_3)$_2$), 1.77 (septet, $J = 7.5$ Hz, 3H, -SiC*H*(CH_3)$_2$), 5.82 (s, 2H, -N*H*), 7.00-7.05 (m, 8H, aromatic), 7.41 (s, 2H, aromatic). ^{13}C NMR ($CDCl_3$) δ 12.03, 18.39, 110.91, 116.68 (d, $J = 22.4$ Hz), 122.23 (d, $J = 8.0$ Hz), 127.99, 137.47, (d, $J = 2.9$ Hz), 140.27, 159.24 (d, $J = 242.9$ Hz), 174.41. IR ($CDCl_3$) ν (cm^{-1}) 3369, 1752, 1685.

***N*-Triisopropylsilyl-4,5-bis-(4-methoxyanilino) phthalimide (Table 2, Entry 3):** Using the general procedure (19 h), the product was obtained by silica gel chromatography (80:20 hexanes:EtOAc; $R_f = 0.27$) to give a yellow solid (85%), mp = 166-168 °C. ^{1}H NMR ($CDCl_3$, Figure 8) δ 1.10 (d, $J = 8.0$ Hz, 18H, -SiCH(CH_3)$_2$), 1.76 (septet, $J = 8.0$ Hz, 3H, -SiC*H*(CH_3)$_2$), 3.81 (s, 6H, -OC*H*$_3$), 5.66 (s, 2H, -N*H*), 6.90 (d, $J = 9.0$ Hz, 4H, aromatic), 7.02 (d, $J = 9.0$ Hz, 4H, aromatic), 7.33 (s, 2H, aromatic). ^{13}C NMR ($CDCl_3$) δ 12.06, 18.41, 55.82, 109.83, 115.27, 123.15, 127.35, 134.34, 140.91, 156.46, 174.71. IR (CH_2Cl_2) ν (cm^{-1}) 3369, 1750, 1685.

***N*-Triisopropylsilyl-4,5-bis-[(4-dimethylamino)anilino] phthalimide (Table 2, Entry 4):** Using the general procedure (27 h) with *freshly distilled* aniline, the product was obtained by silica gel chromatography (70:30 hexanes:EtOAc; $R_f = 0.26$) to give a red/orange solid (54%), mp = 170 °C (decomposes). ^{1}H NMR ($CDCl_3$) δ 1.09 (d, J = 7.5 Hz, 18H, -SiCH(CH_3)$_2$), 1.75 (septet, J = 7.5 Hz, 3H, -SiC*H*(CH_3)$_2$), 2.94 (s, 12H, -N(CH_3)$_2$), 5.57 (s, 2H, -N*H*), 6.75 (d, J = 9.0 Hz, 4H, aromatic), 7.00 (d, J = 9.0 Hz, 4H, aromatic), 7.26 (s, 2H, aromatic). ^{13}C NMR ($CDCl_3$) δ 12.06, 18.43, 41.30, 108.93, 114.28, 123.79, 126.76, 130.83, 141.40, 148.18, 174.95. Calc. for $C_{33}H_{45}N_5O_2Si$: C 69.31, H 7.93. Found: C 69.17, H 7.85. IR (CH_2Cl_2) ν (cm^{-1}) 3372, 1749, 1696.

***N*-Triisopropylsilyl-4,5-bis-(4-nitroanilino) phthalimide (Table 2, Entry 5):** Using the general procedure (24 h) with 2.6 equiv powdered K_2CO_3 as base, the reaction mixture was allowed to cool to room temperature and was diluted with ether (5 mL per mmol substrate) and H_2O (5 mL per mmol substrate). The biphasic mixture was allowed to stir vigorously at room temperature for 15 min and the solid material was then isolated by suction filtration. The filter cake was washed with H_2O and ether and was dried in air to give a yellow solid (103%), from which not all solvents could be removed *in vacuo*. A pure sample was obtained by recrystallization from EtOAc, mp = 260 °C (decomposes). ^{1}H NMR (d_6-DMSO, Figure 9) δ 1.08 (d, J = 7.5 Hz, 18H, -SiCH(CH_3)$_2$), 1.74 (septet, J = 7.5 Hz, 3H, -SiC*H*(CH_3)$_2$), 7.17 (d, J = 9.0 Hz, 4H, aromatic), 7.73 (s, 2H, aromatic), 8.12 (d, J = 9.0 Hz, 4H, aromatic), 9.24 (s, 2H, -N*H*). ^{13}C NMR (d_6-DMSO) δ 11.27, 18.01, 115.56, 115.65, 125.75, 128.54, 138.63, 139.43, 149.57, 172.76. IR ($CDCl_3$) ν (cm^{-1}) 3319, 1704.

Synthesis of DAPH and Analogs From Dimethyl Dianilinophthalates: A pressure reaction vessel (either a Fischer-Porter bottle or a stainless steel Parr bomb) was charged with the di-

methyl dianilinophthalate and ethylene glycol (3 mL per mmol substrate). The vessel was sealed and charged with ammonia gas (20-45 psi). The reaction was allowed to stir at 120 °C for ~24 h, at which point the reaction was allowed to cool. The mixture was treated with EtOAc and water, and the entire mixture was filtered to remove insoluble materials (the solids were washed well with EtOAc to ensure all product was recovered). The layers were separated (difficult due to darkness of both layers), and the aqueous phase was extracted twice with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated using a rotary evaporator. The resulting material was purified by silica gel chromatography to afford the desired product.

4,5-Dianilinophthalimide:[8b] Silica gel chromatography (70:30 hexanes:EtOAc; $R_f = 0.26$) gave a yellow-orange powder (26%), mp = 199-201.5 °C (lit. 205-207 °C).[8b]

4,5-Bis-(4-fluoroanilino) phthalimide:[8b] Silica gel chromatography (70:30 hexanes:EtOAc; $R_f = 0.19$) gave a bright orange powder (15%), mp = 238-240 °C (decomposes, lit. 244-246 °C).[8b]

Synthesis of DAPH and Analogs From *N*-Triisopropylsilyldianilinophthalimides: A mixture of the *N*-triisopropylsilyldianilinophthalimide in 2:1 HOAc:H_2O was heated at 100 °C until TLC analysis indicated complete conversion of the starting material (DMF can be added to improve solubility if necessary). The volatile components are removed using a rotary evaporator, and the crude material is purified by silica gel chromatography or crystallization.

4,5-Bis-(4-methoxyanilino) phthalimide:[8b] Silica gel chromatography (60:40 hexanes:EtOAc; $R_f = 0.28$) gave an orange powder (38%), mp = 182-183.5 °C (decomposes, lit. 191-193 °C).[8b]

4,5-Bis-(4-nitroanilino) phthalimide: The product crystallized directly from the reaction mixture, and was isolated by suction filtration. The filter cake was washed with H_2O and then ether, and was dried *in vacuo* to give an orange solid (79%), mp = >260 °C. ^1H NMR (d_6-DMSO, Fig-

ure 10) δ 7.12 (d, J = 9.0 Hz, 4H, aromatic), 7.71 (s, 2H, aromatic), 8.12 (d, J = 9.0 Hz, 4H, aromatic), 9.22 (broad s, 2H, aromatic), 11.24 (broad s, 1H, aromatic). ^{13}C NMR (d_6-DMSO) δ 115.45, 115.97, 125.77, 128.06, 138.10, 139.33, 149.62, 168.55. IR (acetone) ν (cm^{-1}) 3261, 1766, 1720.

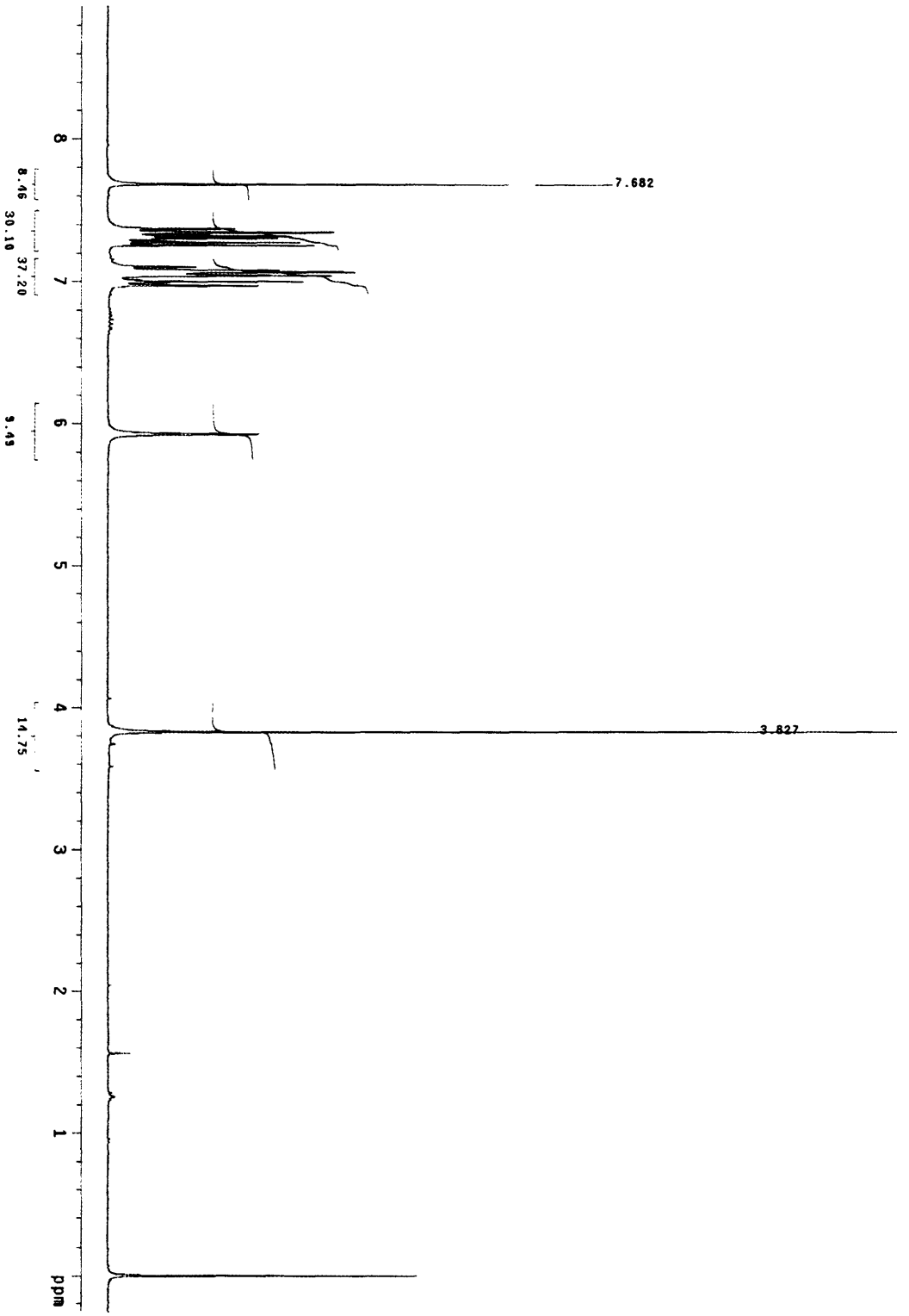


Figure 3. *N*-PMP-4,5-dianilinophthalimide ($CDCl_3$, 300 MHz)

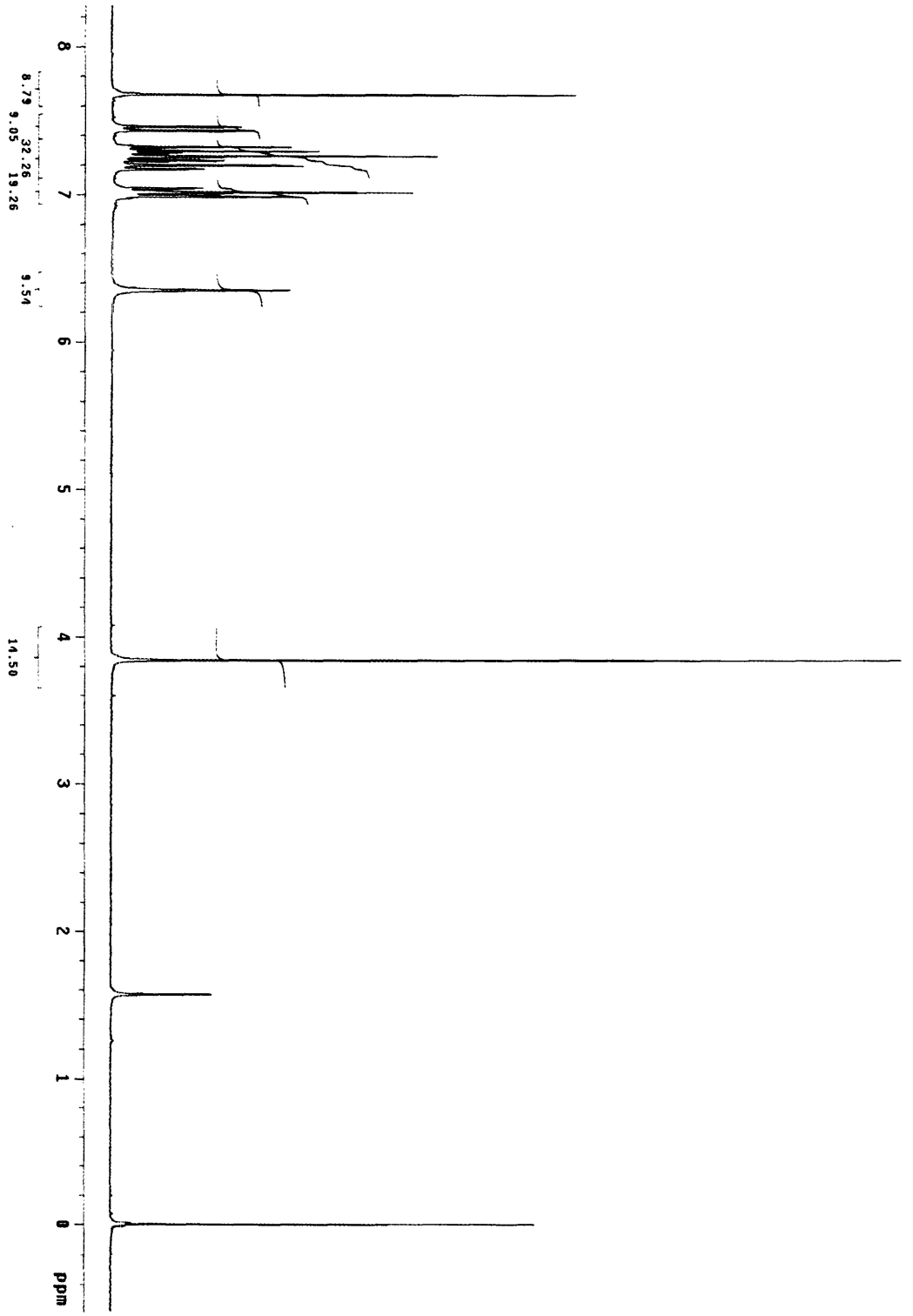


Figure 4. *N*-PMP-4,5-Bis-(2-chloroanilino) phthalimide ($CDCl_3$, 300 MHz)

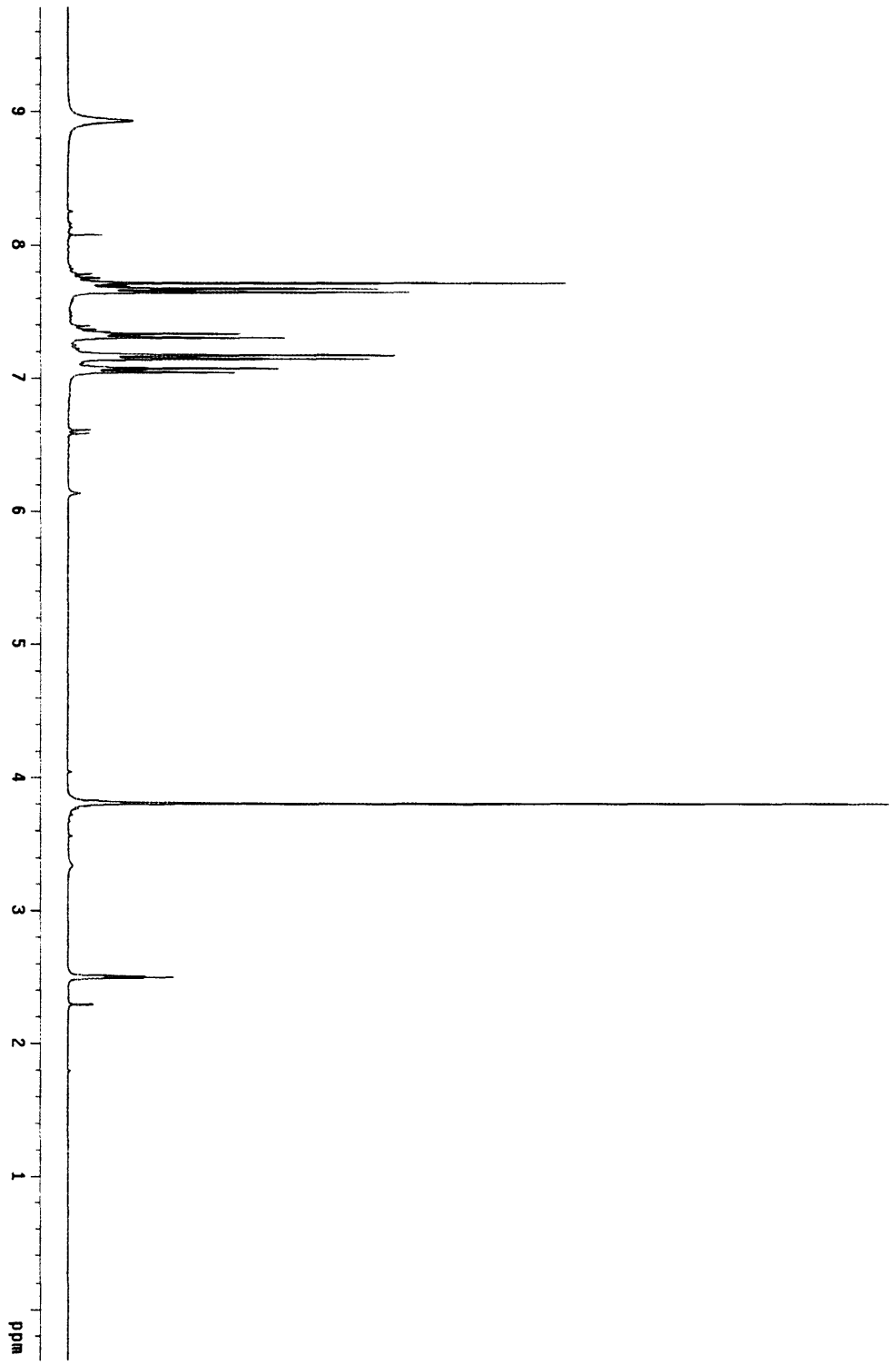


Figure 5. *N*-PMP-4,5-Bis-(4-cyanoanilino) phthalimide (d_6-DMSO, 300 MHz, ~95% pure)

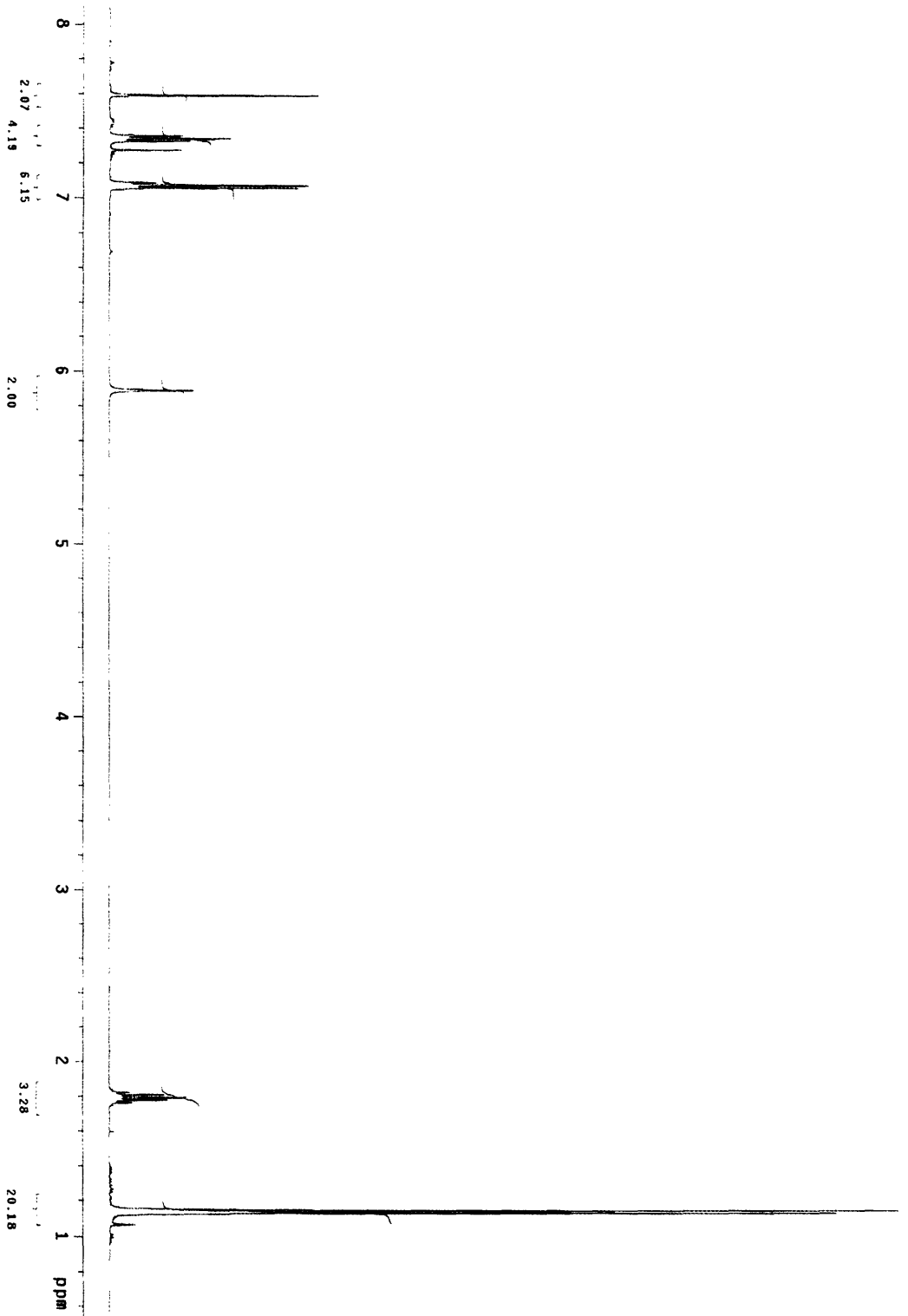


Figure 6. *N*-TIPS-4,5-Dianilinophthalimide ($CDCl_3$, 500 MHz)

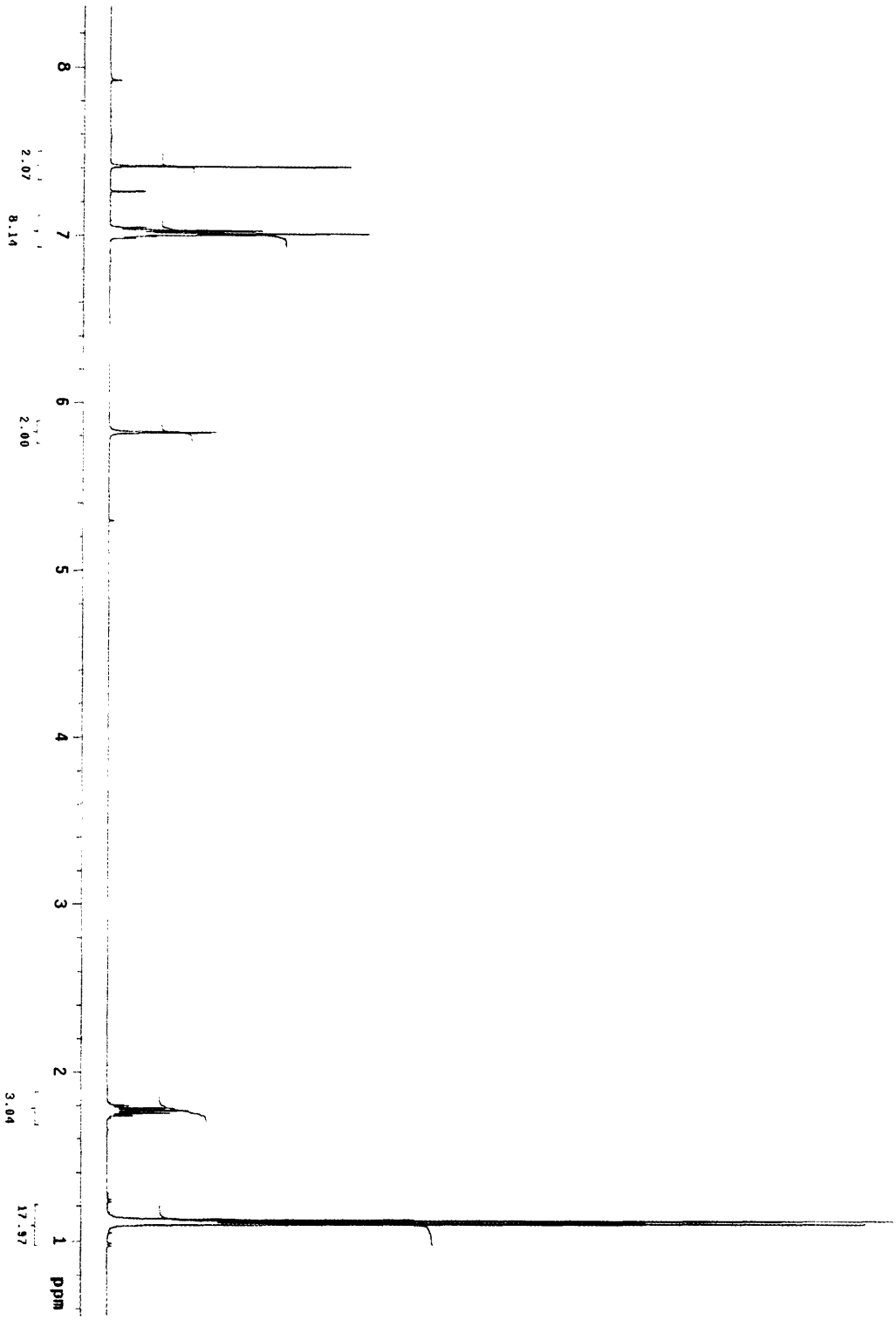


Figure 7. *N*-TIPS-4,5-Bis-(4-fluoroanilino) phthalimide ($CDCl_3$, 500 MHz)

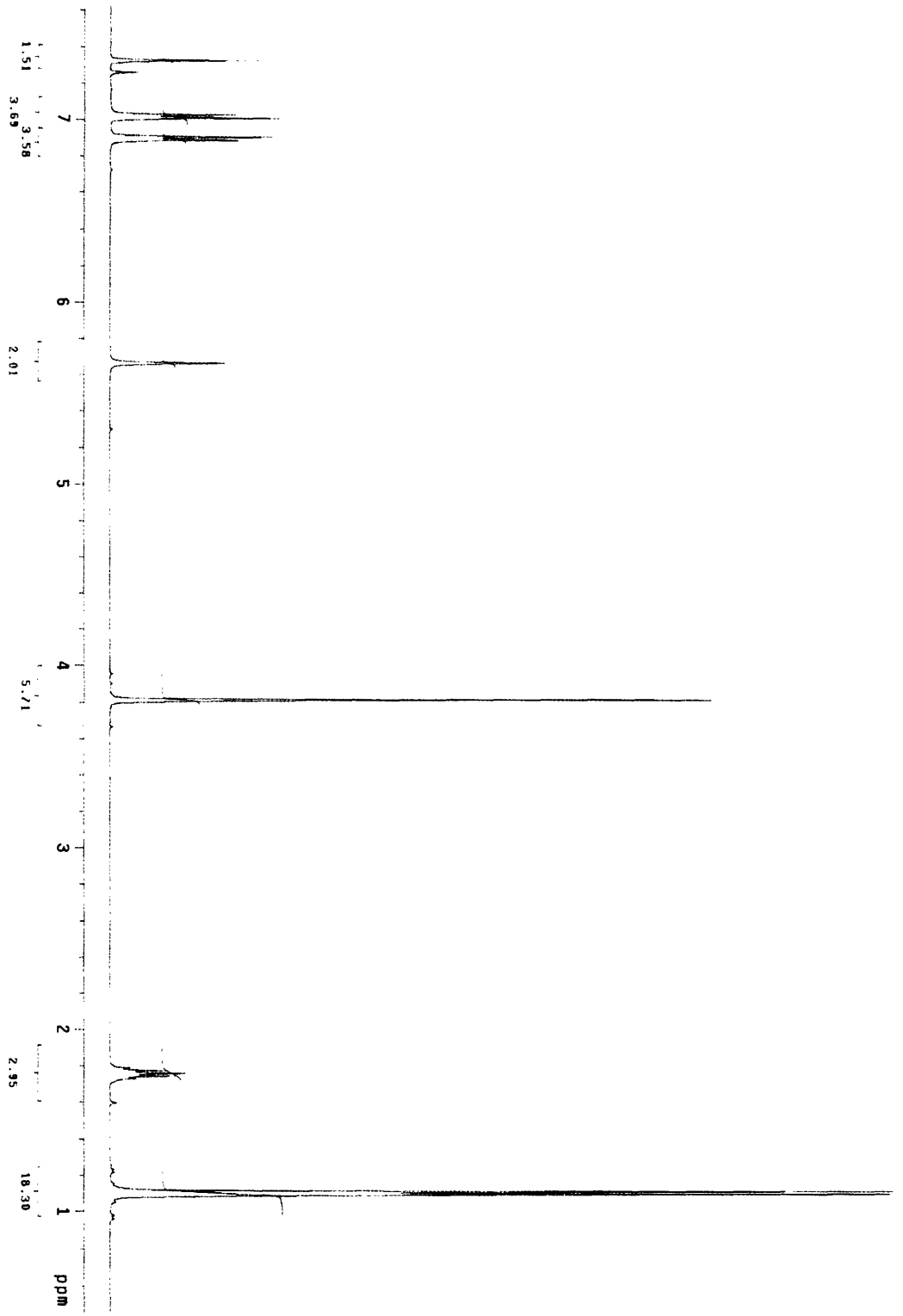


Figure 8. *N*-TIPS-4,5-Bis-(4-methoxyanilino) phthalimide ($CDCl_3$, 500 MHz)

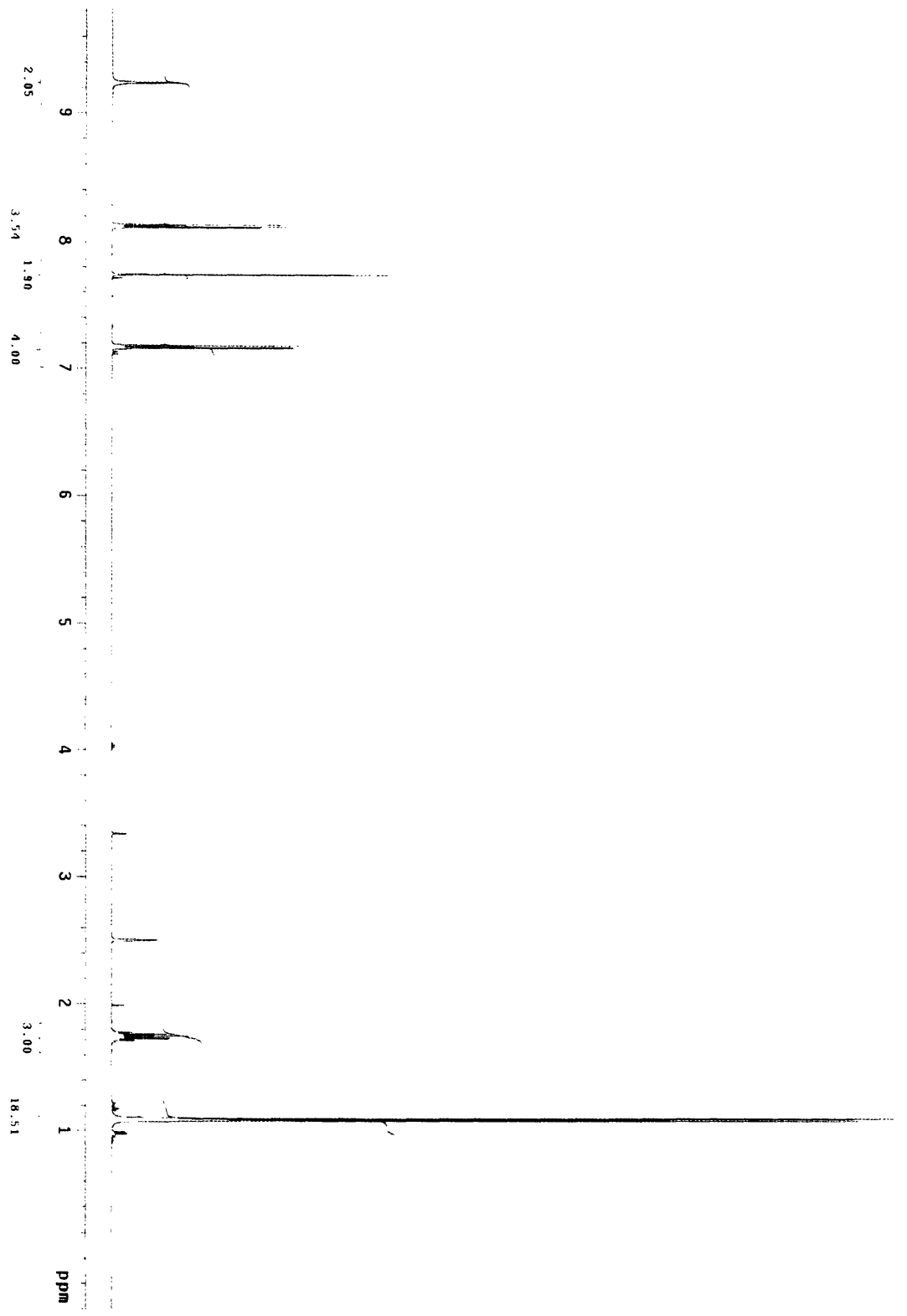


Figure 9. *N*-TIPS-4,5-Bis-(4-nitroanilino) phthalimide (d_6-DMSO, 500 MHz)

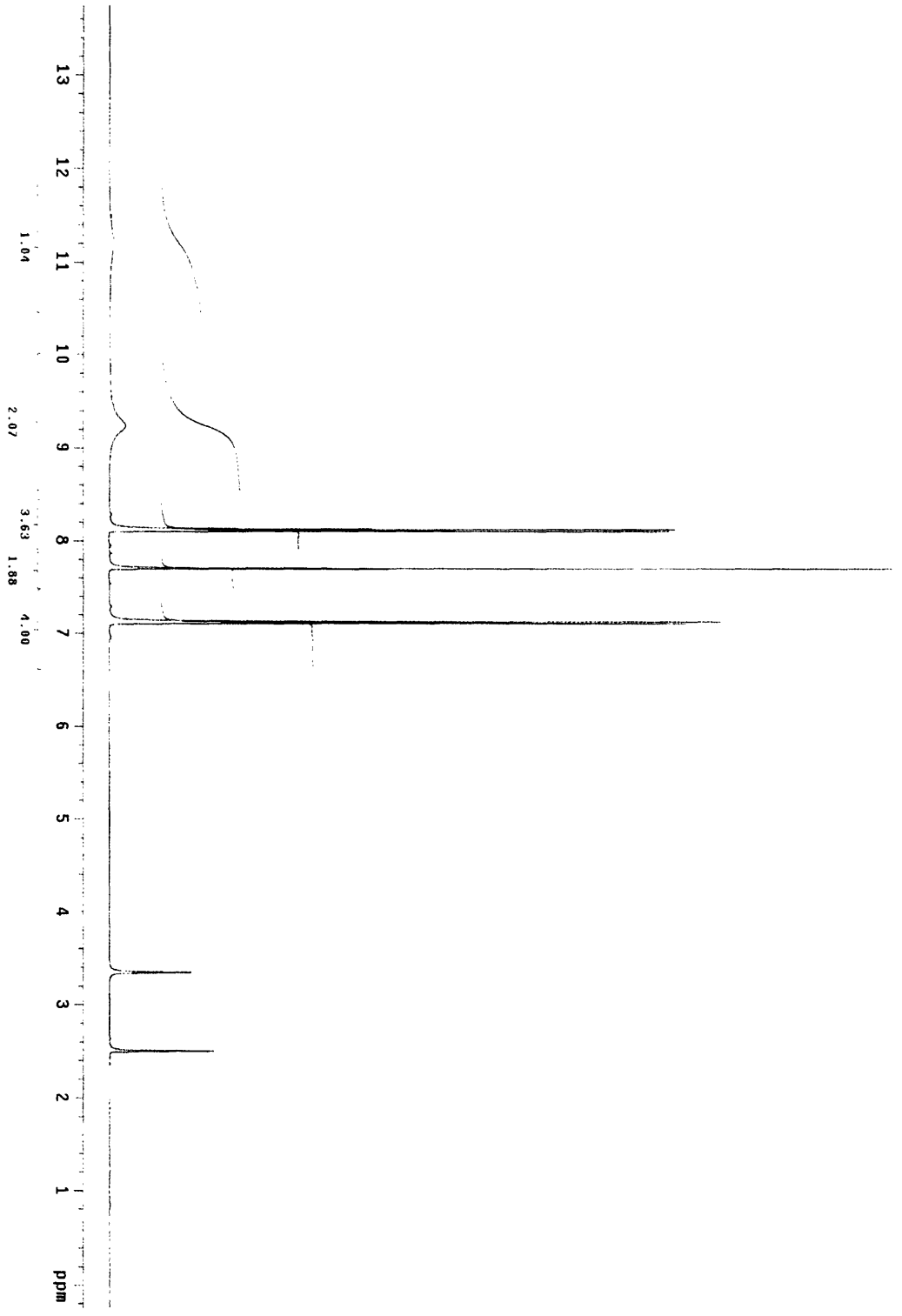


Figure 10. 4,5-Bis-(4-nitroanilino) phthalimide (d_6-DMSO, 500 MHz)

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Curriculum Vitae

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PUBLICATIONS

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Phi Beta Kappa, Northwestern University — 2000

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