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Palladium Catalyzed C-C Bond Formation at C-H Bonds
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# Palladium Catalyzed C-C bond Formation at C-H Bonds

By

**Louis-Charles Campeau**

B. Sc., University of Ottawa, 2003

A thesis submitted to the Faculty of Graduate and Postdoctoral Studies
In partial fulfillment of the requirements for the
Philosophiae Doctor (Ph.D.) degree in chemistry

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*To my wife…*

It is not the critic who counts: not the man who points out how the strong man stumbles or where the doer of deeds could have done better. The credit belongs to the man who is actually in the arena, whose face is marred by dust and sweat and blood, who strives valiantly, who errs and comes up short again and again, because there is no effort without error or shortcoming, but who knows the great enthusiasms, the great devotions, who spends himself for a worthy cause; who, at the best, knows, in the end, the triumph of high achievement, and who, at the worst, if he fails, at least he fails while daring greatly, so that his place shall never be with those cold and timid souls who knew neither victory nor defeat.

*-Theodore Roosevelt*

# Abstract

The biaryl core has been identified by medicinal chemists as a privileged structure in pharmaceutical compounds as it is found in 4.3% of all drugs. For over a century, synthetic chemists have sought new methods for their preparation. Breakthroughs in synthetic catalytic methodology over the past thirty years gave rise to now routine reactions such as the Suzuki and Stille couplings. Unfortunately, the need for pre-activation of both coupling partners makes for wasteful installation and subsequent removal of activating agents.

Direct arylation reactions are attractive alternatives to traditional cross-coupling methods, as one of the pre-activated partners is replaced with a simple arene. The organometallic coupling partner is typically replaced as it is the most difficult to prepare. Although the advantages of this approach have made it a popular research topic for more than twenty-five years, no general catalysts exist for this transformation, and in a lot of cases reactivity remains a challenge.

This thesis will outline our work in this area of research. First, our efforts toward the development of a general catalyst for the intramolecular direct arylation of aryl halides with simple arenes will be presented. These studies led to the development of three new catalysts for this transformation, affording a process general for aryl chlorides, bromides and iodides. Additionally, mechanistic studies performed on this system have brought to the forefront the concerted metallation-deprotonation mechanistic model for direct arylation. Ultimately, these studies led to the first non-directed intermolecular direct arylation of a simple arene.

In a second section, efforts toward the inclusion of $\pi$-deficient heteocycles as a substrate class in direct arylation will be outlined. These studies led to the development of a novel cross-coupling reaction of azine *N*-oxides with aryl halides. Greater mechanistic understanding, made possible through the use of computational tools, was crucial in extending this methodology to azole *N*-oxides.

Finally, the development of novel direct functionalization reactions with picoline derivatives is described. These substrates are among the first to be suitable for catalyst controlled site-selective functionalization of a $sp^2$ or $sp^3$ C-H bond.

# Acknowledgements

First and foremost an endless debt of gratitude is owed to my loving wife Christine. Over the past four years there have been many nights and weekends of labwork, many conferences and many writing hours at home, but through it all she was by my side supporting me and loving me. Her help in the preparation of this document is also greatly appreciated.

A number of postdoctoral and graduate students of the department have contributed in one shape or form to the work presented in this dissertation. Special thanks to Patrick Crewdson for helping with all the X-Ray diffraction work. Melanie Eelman is thanked for performing all the MALDI-TOF work. Federico Zahariev is thanked for helpful LINUX tricks that enabled some of the computational work presented. To Louis Morency and Mathieu Lemay, thank you for your ears. Our disscusions on chemistry as well as your input on my problems were always appreciated.

I had the wonderful opportunity to supervise four wonderful undergraduates over the course of my Ph. D. To Praew, Annie, Sophie and Ho-Yan, thank you for your enthusiasm and free spirit. I hope you enjoyed your time under my dictatorship ;). I thought this would be a good point in the thesis to properly acknowledge your contributions. Praew worked on reaction development and scope of the second generation catalyst of direct arylation of aryl chlorides. Annie contributed to the scope of the third generation catalyst. Sophie played a pivotal role in the discovery and optimization of the pyridine *N*-oxide and nitroaromatic chemistry. Also, a special thanks to Sophie for "Editing" my thesis. Finally, Ho-Yan contributed to the expanded scope of the pyridine *N*-oxide chemistry.

Over the last four years I've had the chance to share workspace with over 20 graduate students, post-docs and undergraduates. To all of you, thank you for making the Fagnou research labs such a great place to work. To my "original four"; Marc, Mathieu and Méli, I hope we will always keep the close ties that formed during our time together. I know I can always count on you for help, and that means a great deal to me. Special thanks to Mathieu for playing the role of "Head Editor" for this dissertation. To "team *N*-oxide"; Jean-Philippe and Dave, I consider it a privilege to have worked with you and I look forward to keeping in touch with you. To my Second Cup buddies, Megan, Sophie and Nicole, thanks for helping me foster my addiction to caffeine. I really enjoyed our daily walks together and I already miss them. Derek, thanks for all the laughs. I really enjoyed getting to know you and working with you over this past year. To the post-doc's in the group, K, Dan, Ben and Irina, thanks for working late with me! I enjoyed our late night discussions and your breadth of knowledge was always helpful. To the "Sherbrooke Crowd", David, Élisia, Laurence and Mégan, thanks for the support. I enjoyed getting to know you over the past year and hope to have the opportunity to work with some of you in the future. Good luck L-Train and Mégaaan with your projects, I'm counting on you! Dan, thanks for the sarcasm and stolen Simpson jokes (Hi-Oh!). Keep it coming!

A special thanks goes out to my family. To my parents, thanks for always asking what I'm working on, even if the answer will probably make no sense. To my brothers and sisters, thanks for all the love and teasing! Having been a student the better part of the last 24 years, I could always count on their love and support. Now that I have finally reached the job market, I hope to be able to repay some of the favors granted to me over the years.

Last, but certainly not the least, I want to thank Keith. It is truly an honor to be your very first Ph. D. candidate. Over the past four years, I've had the privilege to learn, share my ideas, grow and, on occasion, share a drink with you, and I've enjoyed every second of it. I consider myself lucky to have had the opportunity to know you and work with you. The passion you have for chemistry and research was an inspiration to me and played an important role in the success that we had over the past four years. I can truly say that I am not only a better chemist, but a better man because of you and for that I will forever be in your debt.

# Reasons to Stay the Course

Like in anything worth doing, there are times in a Ph. D. when the going gets tough. I found these few thoughts to be inspirational during those times.

8. We are all stupid, some of us just need it to be pointed out. - *Stupidity Awards*

7. Because chemistry is cool and research is fun. - *Keith Fagnou*

6. It is the mark of an educated mind to entertain a thought without accepting it. -*Aristotle*

5. Chance favors a trained mind. - *Louis Pasteur*

4. Sticking atoms together can actually be really tricky. - *Keith Fagnou*

3. Woodward became interested in organic chemistry when he was ten years old and at some point after that taught himself German so that he could read Beilstein. - *W.v.E. Doering*

2. When you're going through hell, keep going! – *Winston Churchill*

1. À vaincre sans péril on triomphe sans gloire! - *Corneille*

# List of Abbreviations

acac - Acetylacetone
Ar – Generic aromatic ring
B – Generic basic group
BHT - 2,6-di-*t*–butyl-4-methylphenol
Boc – Tert-butyloxy carbamate
Bu - Butyl
*i*Bu - Isobutyl
$^t$Bu - Tertbutyl
Bn - Benzyl
Bz - Benzoyl
Cod – Cyclo-octadiene
COE – Cyclo-ocataene
Cy - Cyclohexyl
dba – Dibenzylideneacetone
DCB - Dichlorobenzene
DCE - Dichloroethane
DCM - Dichloromethane
DIPEA - Diisopropylethylamine
DFT – Density functional theory
DG – Generic directing group
DMA - Dimethylacetamide
DMAP – 4-Dimethylaminopyridine
DMDO - Dimethyldioxirane
DME - Dimethoxyethane
DMF - Dimethylformamide
DMSO - Dimethylsulfoxide
dppb - Diphenylphosphinobutane
dppf - Diphenylphosphinoferrocene
dppm - Diphenylphosphinomethane
dppp - Diphenylphosphinopropane
dtbpy - 4,4'-di-*t*-butyl-2,2'-bipyridine
Et - Ethyl
Et$_2$O – Diethyl ether
EtOAc – Ethyl acetate
FG – Generic functional group
GCMS – Gas chromatography mass spectrometry
h - hours
HMDS - Hexamethyldisalizide
HMPA - Hexamethylphosphoramide
HPLC – High pressure liquid chromatography
HRMS – High resolution mass spectrometry
IMes - 1,3-(2,4,6-mesityl)-imidazol-2-ylidene
IPr - 1,3-(2,6-diisopropylphenyl)-imidazol-2-ylidene
IR – Infra-red spectroscopy
KIE – Kinetic isotope effect
L$_n$ – Generic ligand set
LG – Generic leaving group
M – Generic metal or Molarity
MALDI TOF - Matrix-assisted laser desorption/ionization time of flight spectroscopy
mCBA – *meta*-chlorobenzoic acid
mCPBA – *meta*-chloroperoxybenzoic acid
Me - Methyl
MeCN - Acetonitrile
Mol - Mole
MOM – Methoxymethyl ether
m.p. – Melting point
Ms - Methylsulfonyl
MTO - Methyltrioxorhenium
NEt$_3$ - Triethylamine
NHC – *N*-Heterocyclic carbene
NMP – *N*-methylpyrrolidinone
NMR – Nuclear magnetic resonnance spectroscopy
OAc - Acetate
OPiv - Pivalate
OTs - Toslyate
OTf - Triflate
Ph - Phenyl
Pin - Pinacol
$^i$Pr - Isopropyl
R – Generic organic fragment
S$_E$3 – Type 3 electrophilic aromatic substitution
S$_E$Ar – Electrophilic aromatic substitution
SIMes - 1,3-(2,4,6-mesityl)-dihydroimidazol-2-ylidene
SIPr - 1,3-(2,6-diisopropylphenyl)-dihydroimidazol-2-ylidene
S$_N$Ar – Nucleophilic aromatic substitution
TBAF – Tetrabutylammonium fluoride
TBHP – Tert-butylhydroperoxide
TFA - Trifluoroacetate
THF - Tetrahydrofuran
TMEDA – *N,N*-Tetramethylethyldiamine
TON – Turnover number
TOF – Turnover frequency
Ts - Tosyl
*o*-tolyl – 2-methylphenyl
*p*-Tol – 4-methylphenyl
X – Generic halogen or pseudohalide
Y – Generic atom, except H
°C – Degree Celsius

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# 1

# Direct Arylation in Biaryl Synthesis

## Introduction[1]

Biaryl molecules are important building blocks in both materials and medicinal chemistry (Figure 1.1). In fact, it is estimated that 4.3% of all known drugs contain a biaryl motif.[2] The history of synthetic chemistry directed at the efficient preparation of biaryl molecules is long and rich.[3] From the first report of the Ullmann coupling over a century ago,[4] to the modern transition metal-catalyzed cross-coupling reactions of today,[5] there has been a revolution in our ability to form these once challenging bonds. At present, biaryl molecules can be prepared in high yield under mild conditions with catalysts that exhibit broad functional group tolerance. Given this situation, one may question whether the synthesis of these molecules really

---

[1] Parts of this chapter were published in the form of reviews: (a) Campeau, L.-C.; Fagnou, K. *Chem. Commun.* **2006,** *12*, 1253 (b) Campeau, L.-C.; Stuart, D. R.; Fagnou, K. *Aldrichimica Acta*, **2007**, *40*, 35

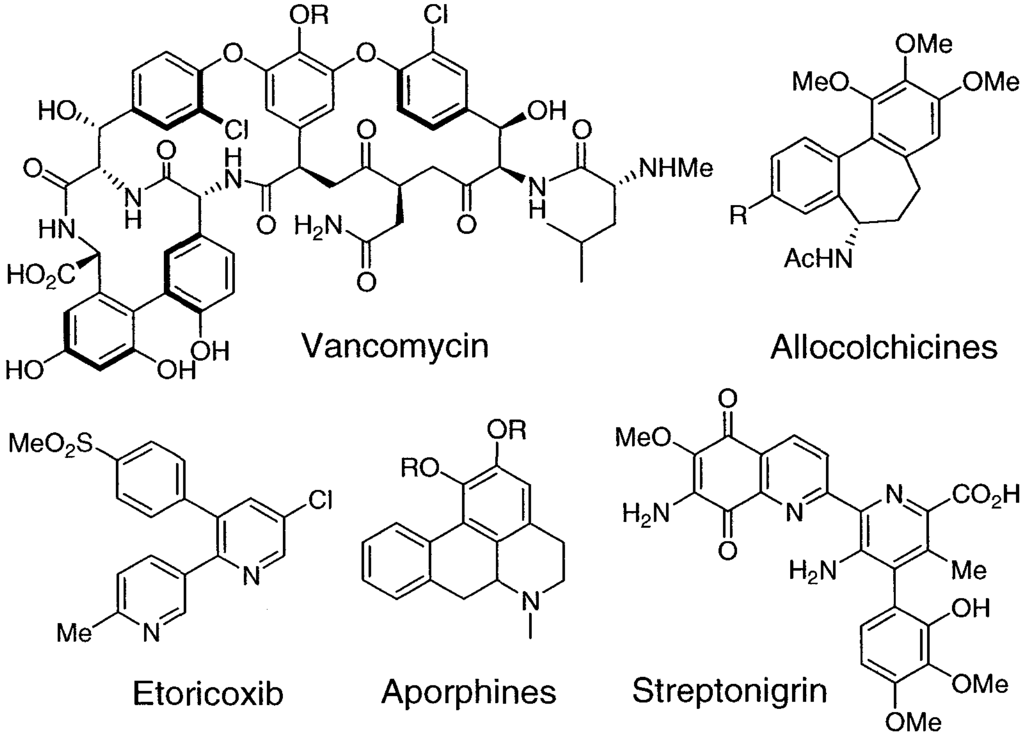
[2] Horton, D.A.; Bourne, G.T.; Smythe, M.L. *Chem. Rev.* **2003**, *103*, 893

[3] Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M.; *Chem. Rev.* **2002**, *102*, 1359.

[4] Ullmann, F.; Bielecki, J.; *Chem. Ber.* **1901**, *34*, 2174.

[5] For a review on this topic, see: *Metal-catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998.

warrants continued methodological attention from the synthetic community. Is there any work left to be done?



Vancomycin

Allocolchicines

Etoricoxib

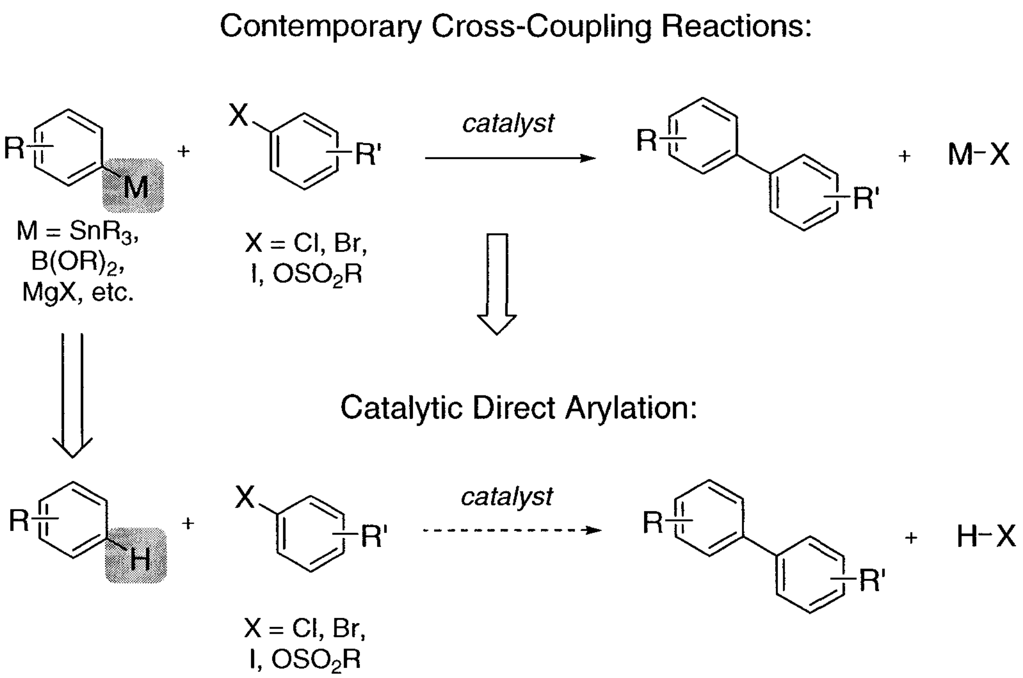
Aporphines

Streptonigrin

**Figure 1.1** - Biologically Relevant Biaryls

When evaluating the efficiency of a chemical process, one must consider not only the final yield, but also the availablility of the starting materials and any steps involved in their synthesis, with particular emphasis on the need to install functional groups that do not appear in the final products. In this light, a common limitation and inefficiency in all modern transition metal-catalyzed cross coupling reactions is the requirement for activating groups on both arene coupling partners. This pre-activation of both substrates is inherently wasteful since the installation of these activating groups can require several steps. This may also be problematic from a synthetic perspective since not all regioisomers of the organometallic or aryl halide may be readily available or easily synthesized. Thus, even though chemists have clearly made major advances in the formation of biaryl molecules, there still remains significant work to be done, particularly in the development of new reactions that do not rely on wasteful substrate pre-activation.

In recent years, reactions that replace one of the pre-activated species with a simple arene have begun to appear.[6] These processes have been described in several ways, including C-H activation, C-H functionalization, C-H arylation and aromatic Heck reaction to name a few. We opt to use the term "direct arylation" to describe these reactions since this name focuses on the arene that is being functionalized and not the bond that is being transformed (which is more in-line with common convention in organic synthesis). Furthermore, it does not convey any mechanistic information which is frequently not known and may change from one substrate class to another. While examples of direct arylation reactions have appeared where the aryl halide is replaced with a simple arene,[7] a more attractive alternative involves the replacement of the organometallic species since it is frequently the pre-activated component that is far less stable and more challenging to prepare (Scheme 1.1).


Contemporary Cross-Coupling Reactions:

Catalytic Direct Arylation:

**Scheme 1.1** - Direct Arylation vs. Cross-Coupling Reactions

---

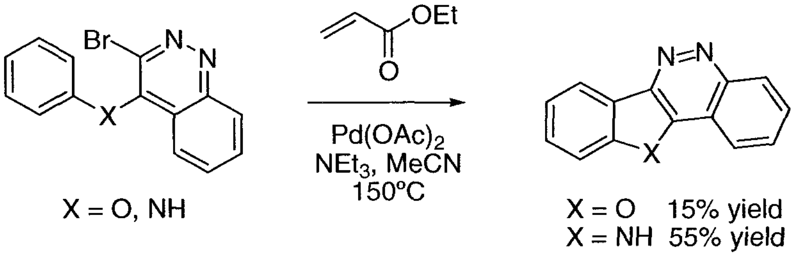
[6] For recent reviews, see: (a) Kakiuchi, F.; Murai, S.; *Acc. Chem. Res.* **2002**, *35*, 826. (b) Ritleng, V.; Sirlin, C.; Pfeffer, M.; *Chem. Rev.* **2002**, *102*, 1731. (c) Miura, M.; Nomura, M. *Top. Curr. Chem.* **2002**, *219*, 211. (d) Kakiuchi, F.; Chatani, N.; *Adv. Synth. Catal.* **2003**, *345*, 1077. (e) *Handbook of C-H Transformations*; Dyker, G., Ed.; Wiley-VCH Velag GmbH & Co. KGaA: Weinheim, 2005; Vols. 1 and 2. (f) see reference 1. (g) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174.

[7] (a) Kakiuchi, F.; Kan, S.; Igi, K.; Chatani, N.; Murai, S. *J. Am. Chem. Soc.*, **2003**, *125*, 1698 (b) Kakiuchi, F.; Matsuura, Y.; Kan, S.; Chatani, N. *J. Am. Chem. Soc.* **2005**, *127*, 5936 and references therein. (c) Oi, S.; Fukita, S.; Inoue, Y.; *Chem. Commun.*, **1998**, 2439

If such direct arylation reactions could be achieved with a wide range of aromatic coupling partners under conditions amenable to the synthesis of complex biaryl molecules, then this would constitute a true advancement in the preparation of this class of compounds.[8] While much work remains to be done to achieve this challenging goal, the field of direct arylation has undergone rapid growth in recent years and continues to garner world wide attention.

## Direct Arylation of Simple Arenes

Simple arenes are much less reactive than their heteroaromatic counterparts in direct arylation reactions (see Chapter 3) – a characteristic attributed to their diminished nucleophilicity. Nonetheless, significant advances in both intra- and intermolecular direct arylation reactions have appeared. An early example by Ames and co-workers described an interesting side reaction observed while attempting a Heck reaction with bromo-cinnolines.[9] Instead of obtaining the Heck-product, they observed direct arylation of the pendant phenyl ring affording the five-membered ring (Equation 1.1).



(1.1)

This discovery prompted additional examinations of the scope of intramolecular direct arylation. Although the formation of a variety of five membered benzofurans was possible with 10% palladium catalyst,[10] the formation of six membered ring benzopyrans proved problematic resulting in only 40% yield of **1.2** along with 35% of the hydrodebromination byproduct **1.3** (Scheme 1.2).[11]

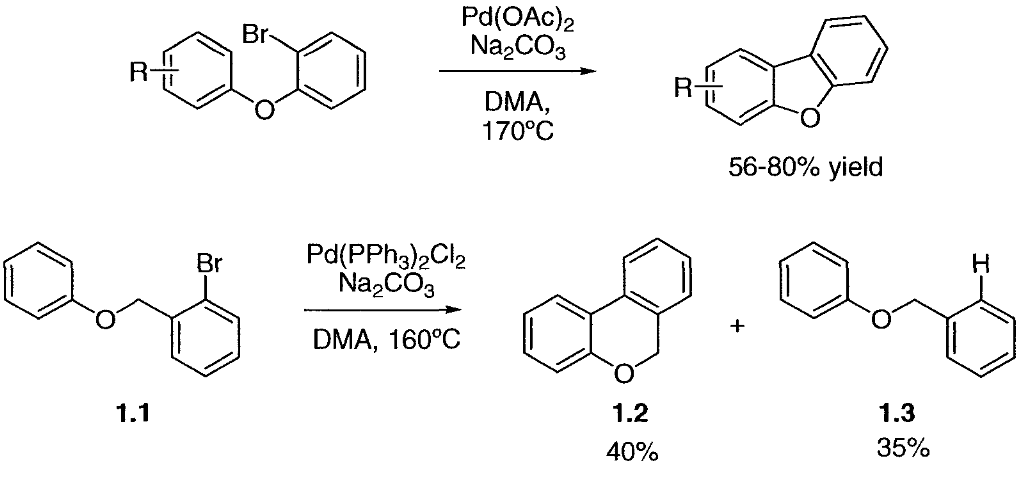
---

[8] Fairlamb, I. J. S. *Tetrahedron*, **2005**, *41*, 9661

[9] Ames, D. E.; Bull, B. *Tetrahedron* **1982**, *38*, 383.

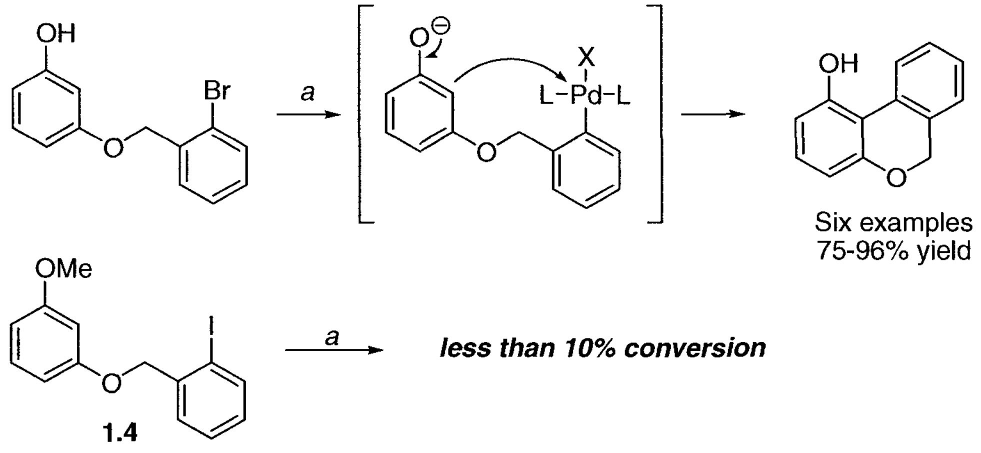
[10] Ames, D. E.; Opalko, A. *Synthesis* **1983**, *39*, 234

[11] Ames, D. E.; Opalko, A. *Tetrahedron* **1984**, *40*, 1919.



**Scheme 1.2** - Ames' first examples with simple arenes

To circumvent the lower nucleophilicity of simple arenes in these reactions, Rawal and co-workers employed substrates bearing a phenol functionality that is deprotonated under the reaction conditions to generate a more reactive coupling partner.[12] Under optimal conditions, direct arylation occurs in high yield with complete selectivity for the ortho–position relative to the hydroxyl group. Evidence for enhanced reactivity of the phenolate anion was obtained from the reaction with methoxy-substituted **1.4** (Scheme 1.3). In this case, less than 10% conversion is observed.



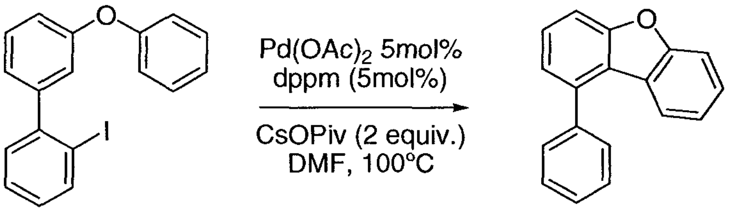
$^a$Conditions: $Pd(OAc)_2$ 5 mol %, (*o*-tolyl)$_3$P 5 mol %, $Cs_2CO_3$ (3 equiv.) in DMA, 85-115°C.

**Scheme 1.3** - Rawal's anion-accelerated intramolecular direct arylation.

---

[12] Hennings, D. D.; Iwasa, S.; Rawal, V. H. *J. Org. Chem.* **1997**, *62*, 2.

The use of intramolecular direct arylation as the terminating event of a migratory cascade has recently been examined by Larock based on his[13] and Gallagher's[14] earlier work on palladium-catalyzed migrations in Heck reactions. For example, reaction with $Pd(OAc)_2$, dppm and cesium pivalate in DMF at 100°C results in the formation of the five membered ring product (Equation 1.2).[15]



Seven examples
40-92% yield

(1.2)

## Directed Reactions with Simple Arenes

Intermolecular direct arylation reactions with simple arenes have also been developed. The necessary substrate-catalyst interactions are promoted by Lewis-basic directing groups that enable metallation by bringing the metal in close proximity to the reactive center. Phenols,[16] amides,[17] ketones,[7a-b] imines[18] and pyridines[19] are commonly used directing groups (Figure 1.2). There have been a number of developments in these types of reactions over the past two years. Selected examples have been chosen for their synthetic value and their conceptual advances.

---

[13] Campo, M. A.; Larock, R. C. *J. Am. Chem. Soc.* **2002**, *124*, 14326.

[14] Karig, G.; Moon, M.-T.; Thasana, N.; Gallagher, T. ; *Org. Lett.* **2002**, *4*, 3115.

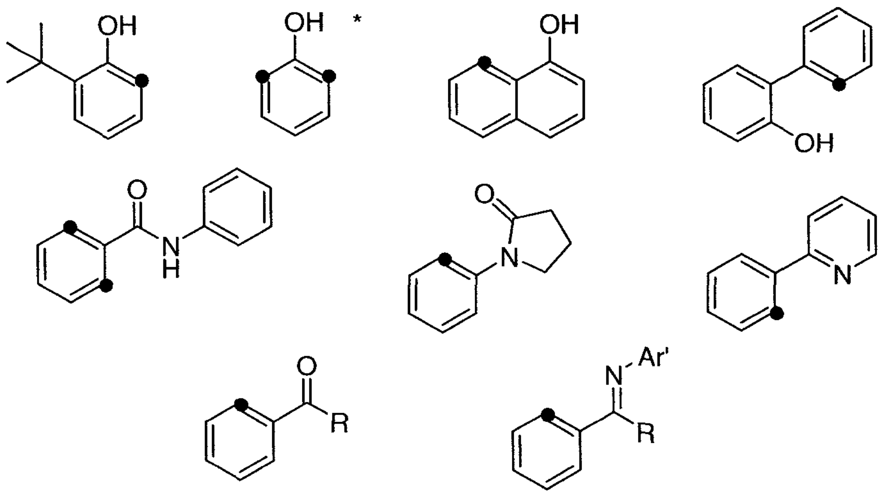
[15] Campo, M. A.; Huang, Q.; Yao, T.; Tian, Q.; Larock, R. C.; *J. Am. Chem. Soc.* **2003**, *125*, 11506.

[16] (a) Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M.; *Angew. Chem. Int. Ed.* **1997**, *36*, 1740. (b) Bedford, R. B.; Coles, S. J.; Hursthouse, M. B.; Limmert, M. E.; *Angew. Chem., Int. Ed.* **2003**, *42*, 112. (c) Kawamura, Y.; Satoh, T.; Miura, M.; Nomura, M.; *Chem Lett.*, **1998**, 961

[17] Kametani, Y.; Satoh, T.; Miura, M.; Nomura, M.; *Tetrahedron Lett.* **2000**, *41*, 2655

[18] Oi, S.; Ogino, Y.; Fukita, S.; Inoue, Y.; *Org. Lett.* **2002**, *4*, 1783.

[19] Oi, S.; Fukita, S.; Hirata, N.; Watanuki, N.; Miyano, S.; Inoue, Y.; *Org. Lett.* **2001**, *3*, 2579.



● denotes the position that is arylated

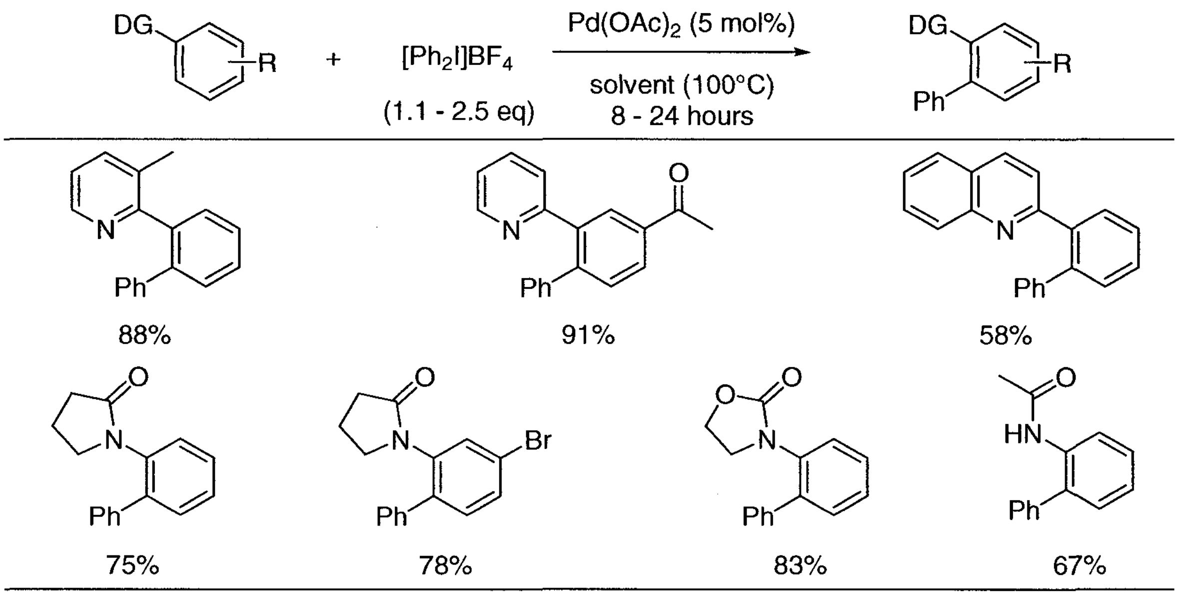
**Figure 1.2** - Substrate Scope in Intermolecular Direct Arylation

*mixtures of polyarylated product obtained

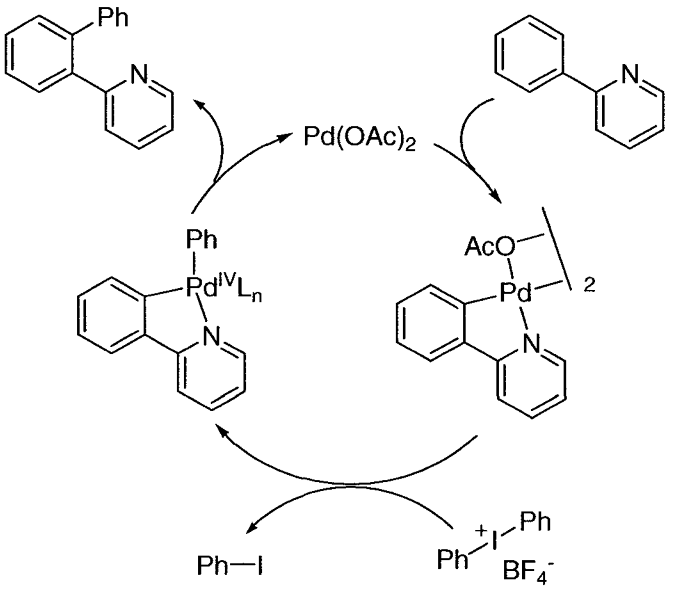
In 2005, Sanford and co-workers reported the use of pyridine moieties as efficient directing groups in the Pd-catalyzed direct arylation of 2-arylpyridines with aryliodonium salts (Scheme 1.4).[20] A wide variety of other directing groups, including quinolines, pyrrolidinones, oxazolidinones, and acetylanilides are compatible with this methodology. Diverse substituents on the pyridine or the aryl moiety that is being functionalized are also tolerated. The reactions can be carried out in the presence of ambient air/moisture and do not require expensive ligands or strong bases. Mechanistic investigations suggest that the process proceeds via a cyclopalladated 2-arylpyridine that is oxidized by the aryliodonium salt to generate a very reactive Pd(IV) intermediate. Reductive elimination of the arylated product regenerates the catalytically active Pd(II) species. A representative catalytic cycle is presented in Scheme 1.5.

---

[20] Kalyani, D.; Deprez, N. R.; Desai, L. V. ; Sanford, M.S. *J. Am. Chem. Soc.* **2005**, *127*, 7330.



**Scheme 1.4** - Scope of Palladium-Catalyzed Direct Arylation with Diaryliodonium Salts



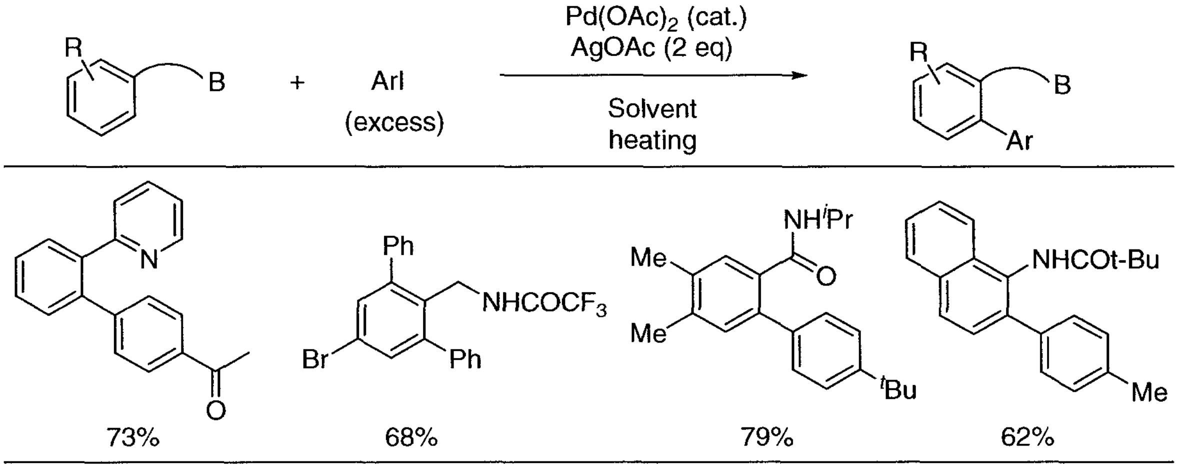
**Scheme 1.5** - Catalytic Cycle of Oxidative Direct Arylation with Diaryliodoium Salts.

Aryl iodides have also been used in direct arylation reactions of simple arenes by Daugulis and co-workers. In 2005, Daugulis reported the di-arylation of acetylanilides with aryl iodides under Pd(II) catalysis.[21] These reactions require stoichiometric amounts of AgOAc for each equivalent of aryl iodide consumed. The use of electron-

---

[21] Zaitsev, V. G.; Daugulis, O. *Angew. Chem. Int. Ed.* **2005**, *44*, 4046.

rich aryl iodides led to faster reactions, in contrast to the typical trend observed in Pd(0)/Pd(II) catalytic cycles. Acetylanilides with donor substituents react faster than their electron-neutral or electron-poor counterparts, which is consistent with an electrophilic aromatic metallation pathway. The proposed mechanism involves a cyclopalladated complex that undergoes oxidative addition of the aryl iodide to produce a Pd(IV) intermediate. Pyridines,[22] benzamides,[23] and benzylamines[24] have all been successfully used as directing groups (Scheme 1.6).



**Scheme 1.6** - Daugalis' Directed Palladium-Catalyzed Arylation

In 2005 and 2006, Ackermann also reported the use of pyridines and other Lewis basic groups in direct arylation reactions. Importantly, with the appropriate ruthenium catalyst, these reactions could be achieved with aryl chlorides and tosylates.[25] While this type of reactivity is now common with other traditional cross-coupling reactions, achieving direct arylation with aryl chlorides and tosylates is exceedingly rare. Both electron-rich and electron-poor aryl chlorides are compatible and afford diarylated products of 2-arylpyridines in good yields (Scheme 1.7).[25a] It is also possible to achieve mono-arylation with this catalyst when ketimines derived from acetophenone are used as substrates. Conveniently, the products are isolated as the corresponding ketones after hydrolysis of the imine (Scheme 1.8).

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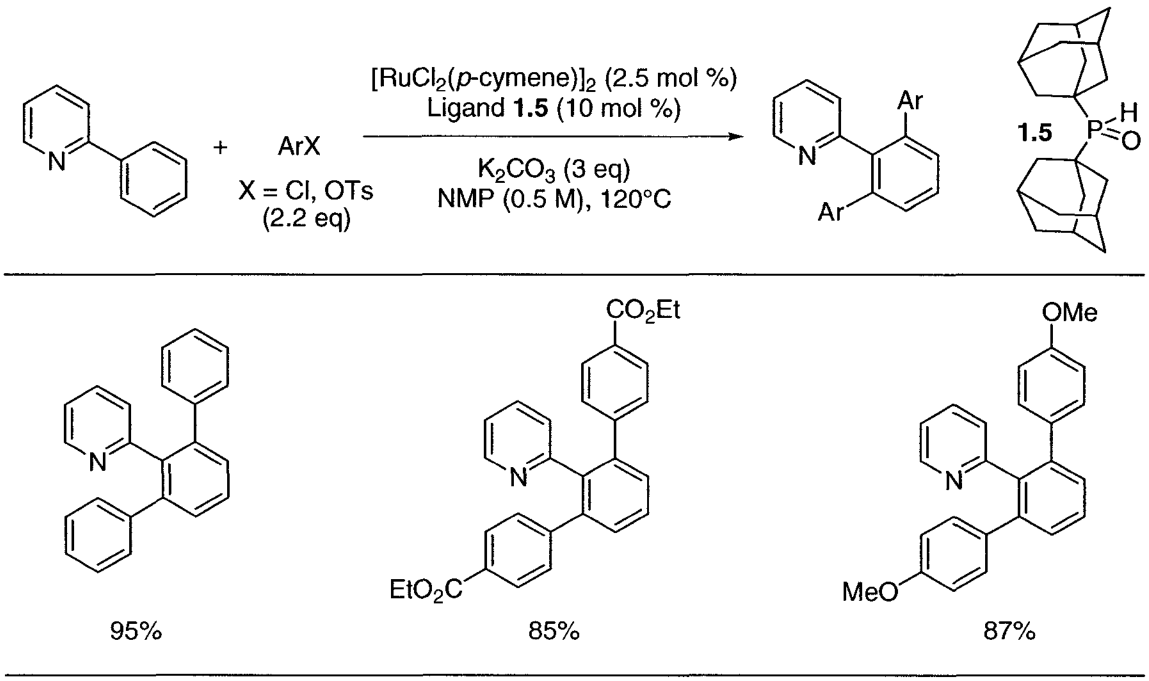
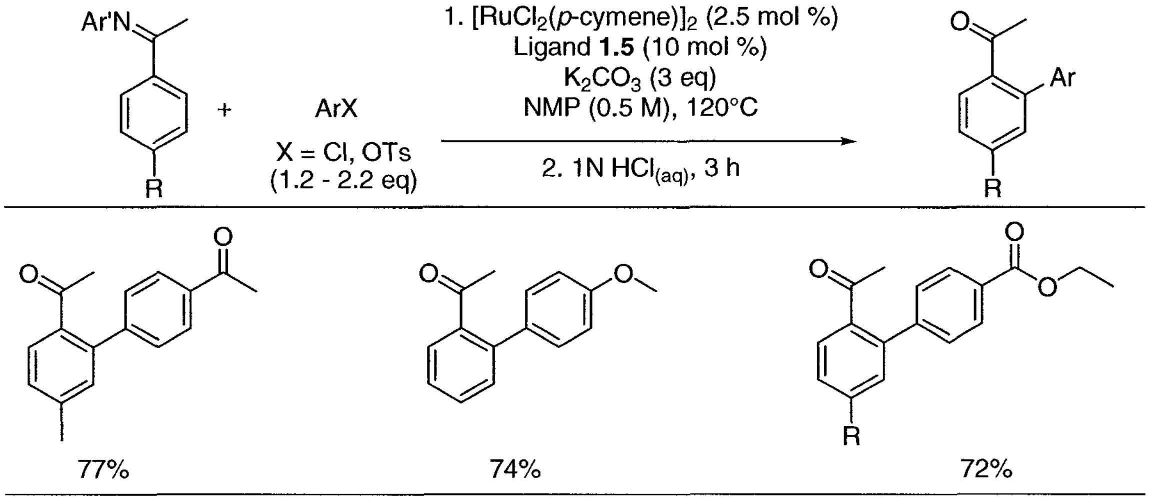
[22] Shabashov, D; Daugulis, O. *Org. Lett.* **2005**, *7*, 3657.
[23] Shabashov, D; Daugulis, O. *Org. Lett.* **2006**, *8*, 4947.
[24] Lazareva, A; Daugulis, O. *Org. Lett.* **2006**, *8*, 5211.
[25] (a) Ackermann, L.; *Org. Lett.* **2005**, *7*, 3123. (b) Born, R.; Althammer, A.; Ackermann, L. *Angew. Chem. Int. Ed.* **2006**, *45*, 2619.

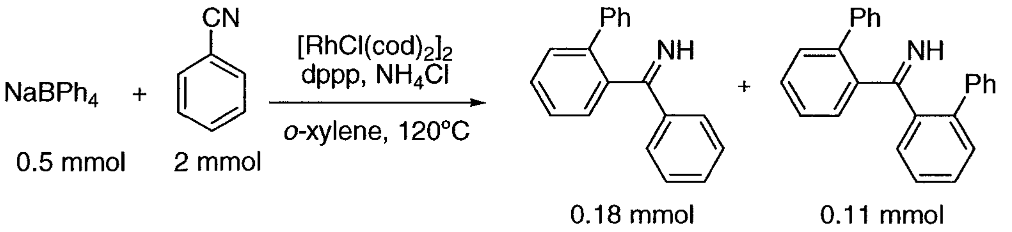


**Scheme 1.7** - Ruthenium-Phosphite Catalyzed Direct Arylation Reactions with Aryl Pyridines



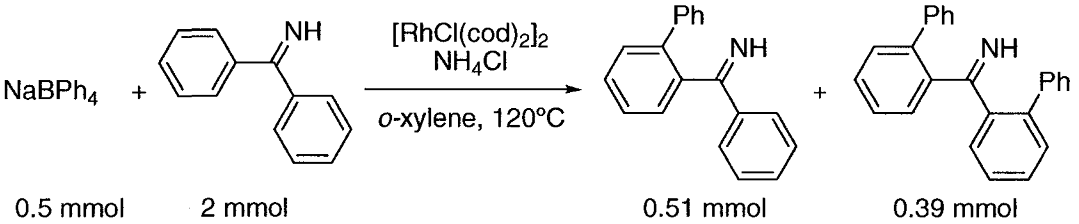
**Scheme 1.8** - Direct Arylation of Ketimines with Aryl Chlorides and Aryl Tosylates

Imines have also been used in rhodium catalyzed direct arylation reactions. In a 2005 report on the development of a rhodium catalyzed Suzuki-type coupling, Miura and co-workers observed that with cyano arenes, benzophenone imines were formed and subsequently arylated *ortho* to the imine (Equation 1.3).[26]



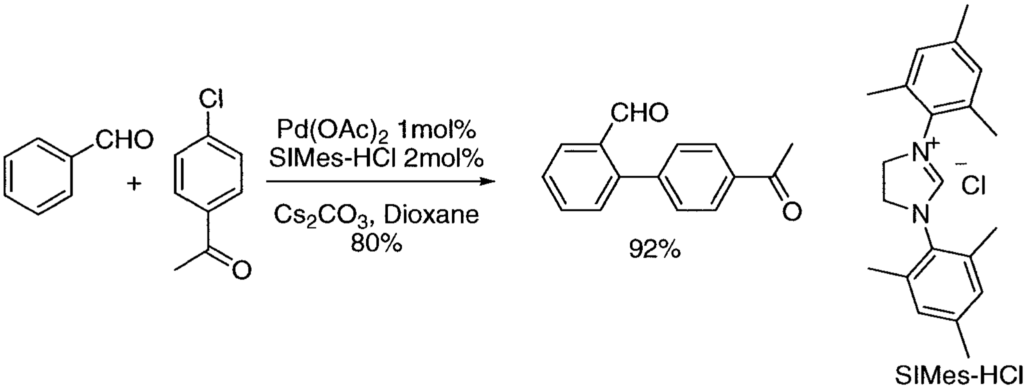
(1.3)

When similar reaction conditions are applied directly to the imine it is possible to isolate a mixture of the mono and diarylated products (Equation 1.4).



(1.4)

In 2005, Çetinkaya and co-workers reported the use of benzaldehydes in direct arylation reactions of aryl chlorides and bromides.[27] Using $Pd(OAc)_2$ in conjuction with an imidazolium salt as a carbene ligand precursor, and $Cs_2CO_3$ in dioxane at 80°C, they obtained *ortho* arylation of benzaldehyde derivatives in good yields (Equation 1.5).



(1.5)

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[26] Ueura, K.; Satoh, T.; Miura, M.; *Org. Lett.* **2005**, *7*, 2229

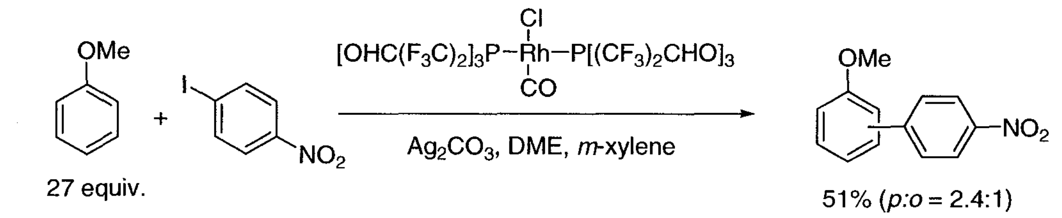
[27] Gürbüz, N.; Özdemir, I.; Çetinkaya, B.; *Tetrahedron Lett.* **2005**, *46*, 2273

The authors postulate that the aldehyde oxygen acts as a directing group resulting in selective *ortho* arylation. When aryl bromides are used, it is possible to achieve diarylation to afford the 2,6-diarylbenzaldehyde derivatives.

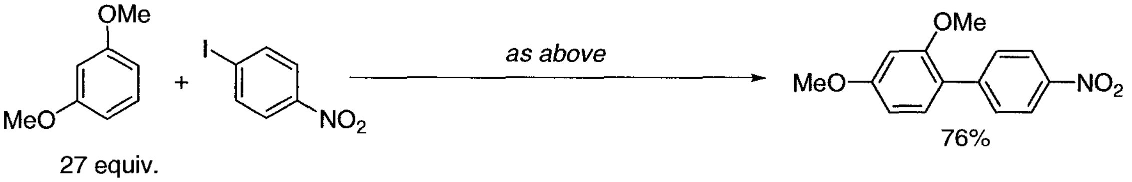
## Non-Directed Reactions with Simple Arenes

Non-directed reactions of simple arenes in direct arylation reactions are exceedingly rare.[28] In fact, when we undertook our investigation, there were no reported direct arylation reactions of simple benzene. In the past year however, there have been a number of reports involving simple benzene rings including three reports by our own group, one of which will be discussed later in this dissertation.

In a 2006 account focusing predominantly on the arylation of heterocycles, Itami and co-workers described direct arylation reactions with anisole and 1,3-dimethoxybenzene.[29] In both cases the regiochemistry is consistent with an electrophilic metallation mechanism occuring preferentially at the *para-* and *ortho*-positions relative to the electron donating methoxy groups (Equations 1.6 and 1.7). Given the small number of non-directed reactions of simple arenes in direct arylation, this result shows significant promise for the development of other rhodium catalyzed direct arylations with simple arenes.



(1.6)



(1.7)

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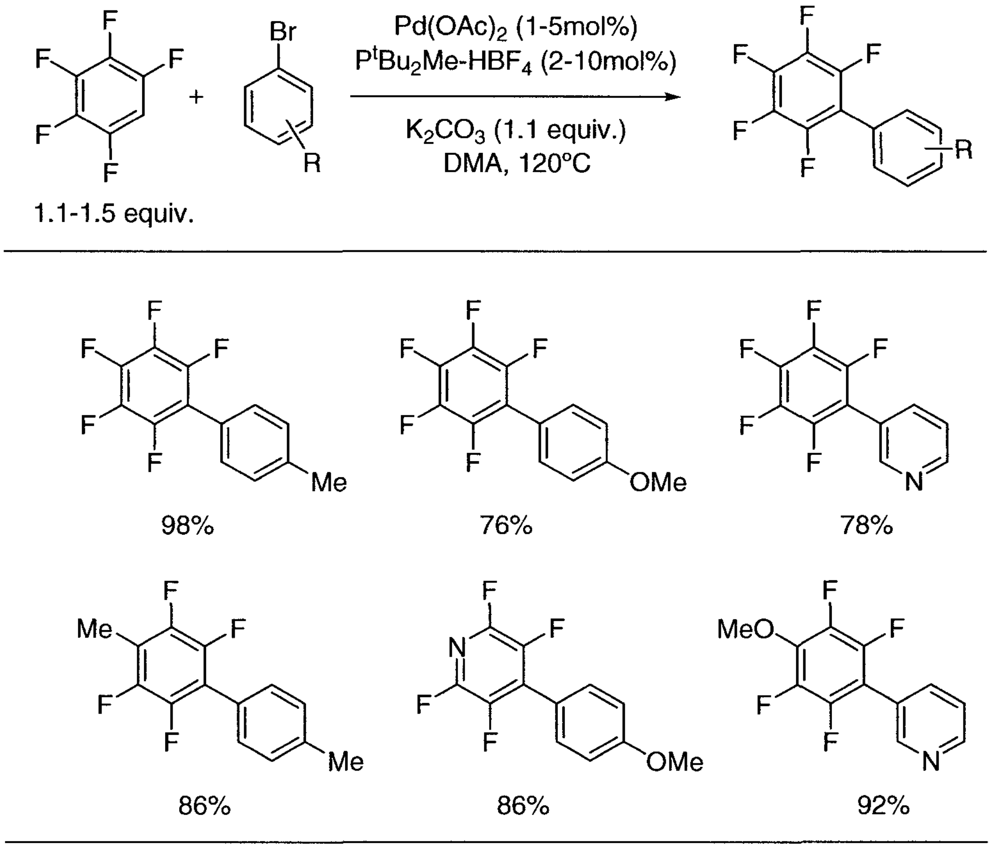
[28] We differentiate these reactions from arylations with aryl radicals whose generation is catalyzed by metals, see: (a) Mukhopadhyay, S.; Rothenberg, G.; Gitis, D.; Baidossi, M.; Ponde, D.E.; Sasson, Y. *J. Chem. Soc., Perkin. Trans. 2* **2000**, 1809. (b) Fujita, K.-i.; Nonogawa, M.; Yamaguchi, R. *Chem. Commun.* **2004**, 1926.

[29] For a rhodium-catalyzed reaction, see: Yanagisawa, S.; Sudo, T.; Noyori, R.; Itami, K. *J. Am. Chem. Soc.* **2006**, *128*, 11748

In 2006, based on our previous observations as well as recent reports from Echevarren and co-workers,[30] our group explored the direct arylation of perfluorinated arenes. The direct arylation of these substrates can occur in high yield with 1-5mol% palladium in conjunction with $P^tBu_2Me\text{-}HBF_4$ (Scheme 1.9). It was even possible to achieve reaction with fluorobenzene, albeit in 8% yield.[31] A key feature in these reactions is thought to be the high acidity of C-H bonds on perfluorinated aromatics.



**Scheme 1.9** - Direct Arylation of Perfluoarenes

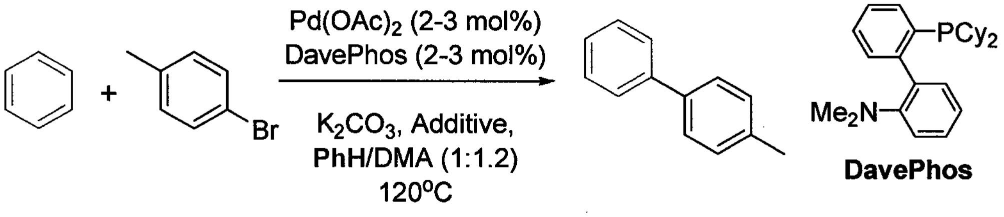
With the goal of expanding the scope of arenes to more challenging arylations with simple benzenes, the use of soluble acid co-catalysts was investigated by Fagnou and Lafrance in conjunction with a stoichiometric amount of insoluble potassium carbonate base. Proper choice of the carboxylic acid is crucial and the use of 30 mol% PivOH

---

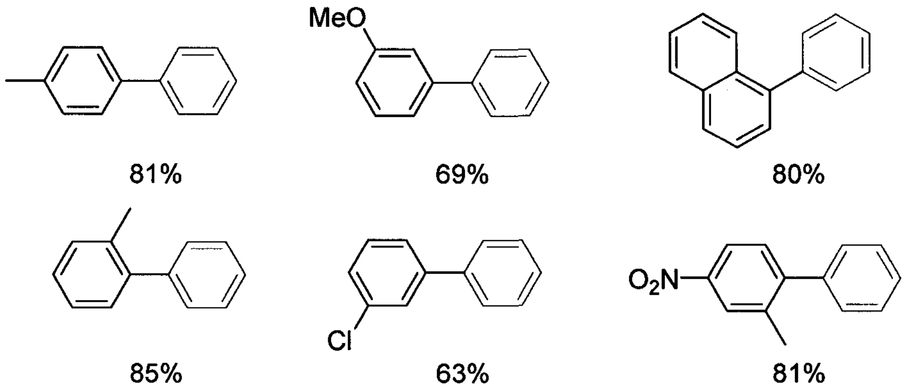
[30] (a) Garcia-Cuadrado, D.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006**, *128*, 1066 (b) Campeau, L.-C.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, 581.

[31] Lafrance, M.; Rowley, C. N.; Woo, T. K.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *127*, 8754.

proved to be optimal.[32] Mechanistic implications of this additive effect will be discussed in great detail in this dissertation. Using this protocol, a number of aryl bromides can be reacted with benzene to afford the biaryl product in high yield (Scheme 1.10).



| Entry | Base | Additive | Conversion | Yield |
|---|---|---|---|---|
| 1 | $K_2CO_3$ | AcOH (30 mol%) | 20 | 11 |
| 2 | $K_2CO_3$ | $^t$BuCO$_2$H (30 mol%) | 100 | 82 |



**Scheme 1.10** - Direct Arylation of Benzene

## Research Plan

At the outset of this research project to develop new direct arylation reactions of simple arenes, we decided to first explore the more precedented intramolecular variant. We were hopeful that investigating the use of the Pd$^0$/Pd$^{II}$ catalytic cycle would potentially allow for cheap aryl chlorides and bromides to be cross coupled with inexpensive simple aromatic compounds. Intramolecular variants involving simple aromatic rings are an important subset of direct arylation reactions, yet have found limited use in organic synthesis due to narrow substrate scope and high[33] (even stoichiometric)[34] catalyst

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[32] Lafrance, M.; Fagnou, K; *J. Am. Chem. Soc.* **2006**, *128*, 16496

[33] With 30 mol % catalyst: (a) Kitamura, M.; Ohmori, K.; Kawase, T.; Suzuki, K. *Angew. Chem., Int. Ed.* **1999**, *38*, 1229. (b) Rice, J. E.; Cai, Z.-W.; He, Z.-M.; LaVaoie, E. J. *J. Org. Chem.* **1995**, *60*, 8101. With 26 mol % catalyst: (c) Hosoya, T.; Takashiro, E.; Matsumoto, T.; Suzuki, K. *J. Am. Chem. Soc.* **1994**, *116*, 1004. With 25 mol % catalyst: (d)

loadings under optimized conditions. Overcoming these hurdles will necessarily require the discovery and development of novel catalysts. Success in this pursuit would allow for a conceptually different approach to molecules such as **1.6** (Figure 1.3, path C) to be generally applied, thereby obviating the need to work with organometallic reagents (paths A and B).

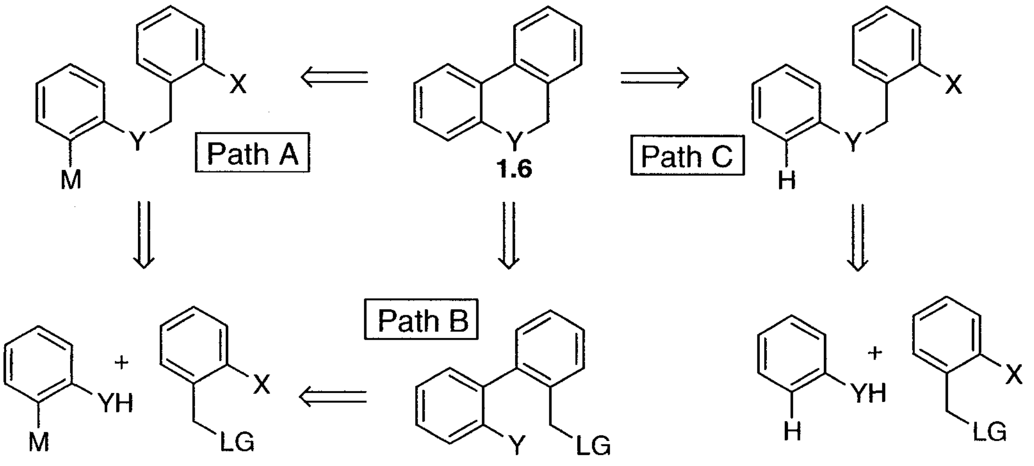

**Figure 1.3** - Routes to Tricyclic Biaryl Compounds

An initial goal was to improve the use of intramolecular direct arlyation as a synthetic tool in the construction of tricyclic biaryl molecules with a wide range of substrates. These advances could then be applied to the synthesis of natural and synthetic target molecules. Also, this newly gained knowledge could then be used for the development of new intermolecular direct arylation reactions (Figure 1.4).

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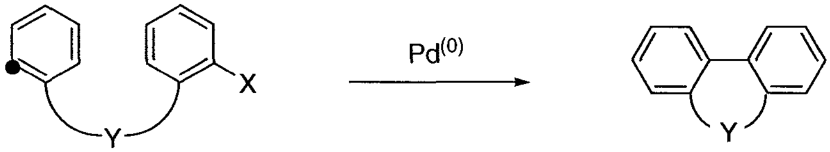
Matsumoto, T.; Hosoya, T.; Suzuki, K. *J. Am. Chem. Soc.* **1992**, *114*, 3568. With 20-25 mol % catalyst: (e) Cuny, G. D. *Tetrahedron Lett.* **2003**, *44*, 8149. (f) Qabaja, G.; Jones, G. B. *J. Org. Chem.* **2000**, *65*, 7187. With as low as 10 mol % catalyst: (g) Bringmann, G.; Heubes, M.; Breuning, M.; Gobel, L.; Ochse, M.; Schoner, B.; Schupp, O. *J. Org. Chem.* **2000**, *65*, 722. (h) Bringmann, G.; Ochse, M.; Gotz, R. *J. Org. Chem.* **2000**, *65*, 2069. (i) Harayama, T.; Yasuda, H. *Heterocycles* **1997**, *46*, 61.

[34] Futagami, S.; Ohashi, Y.; Imura, K.; Hosoya, T.; Ohmori, K.; Matsumoto, T.; Suzuki, K. *Tetrahedron Lett.* **2000**, *41*, 1063.

Intramolecular processes as a viable synthetic strategy...



X = $OSO_2R$, Cl, Br, I
Y = O, NR, $CR_2$

- *new catalysts*
- *improved TON / TOF with less reactive substrates*
- *better selectivity (arylation vs. dehalogenation)*
- *better reactivity (aryl bromides and chlorides)*

... and as a stepping-stone to more challenging intermolecular reactions.

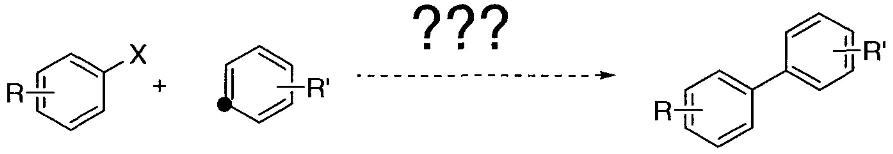


**Figure 1.4 -** Research Objectives

# 2

# Direct Arylation of Simple Arenes

## First Generation Catalyst[35]

While phenolates exhibit enhanced reactivity in intramolecular arylation reactions,[36] ethers such as **2.1** that lack this activating group were known to react poorly and had not previously been shown to undergo selective ring closure prior to our work.[37] With the long-term goal of developing an intermolecular direct arylation of unactiaved arenes, we opted to use aryl bromide **2.1**, which is lacking such activation, as our model substrate in initial screens.[12] Different combinations of ligand, palladium source and solvent were attempted while heating at 95 °C. These screens revealed that 5 mol % $Pd(OAc)_2$ and

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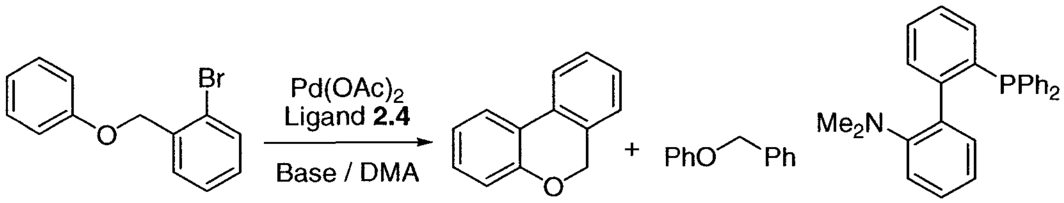
[35] Part of this section was published as a communication, see: Campeau, L.-C.; Parisien, M.; Leblanc, M.; Fagnou, K.; *J. Am. Chem. Soc.*; **2004**, *124*, 9186.

[36] Hennings, D. D.; Iwasa, S.; Rawal, V. H.; *J. Org. Chem.* **1997**, *62*, 2.

[37] Rawal determined that in the absence of a phenolate activating group on the nucleophilic arene, less than 10% of the coupled product was obtained after prolonged reaction; see reference 36. Ames obtained 35% **4** and 40% **5** by reaction with $[(PPh_3)_2PdCl_2]$ in DMA at 160 °C; (b) Ames, D. E.; Opalko, A.; *Tetrahedron* **1984**, *40*, 1919.

10 mol % 2-(diphenylphosphino)-2'-(*N,N*-dimethylamino)biphenyl **2.4**,[38] gave **2.2** in 96 % yield along with 4 % of debrominated ether **2.3** (Table 2.1, Entry 1).

**Table 2.1** - Reaction Optimization[a]



**2.1** **2.2** **2.3** Ligand **2.4**

| Entry | Mol% Pd | Base | Temp. (°C) | Time (h) | Yield **2.2**[b] (%) | Ratio **2.2**:**2.3**[b] |
|---|---|---|---|---|---|---|
| 1 | 5 | $Cs_2CO_3$ | 95 | 10 | 94 | 24:1 |
| 2 | 5 | $Cs_2CO_3$ | 80 | 20 | 44[c] | 7.4:1 |
| 3 | 5 | $K_2CO_3$ | 95 | 4 | 95 | 160:1 |
| 4 | 2 | $K_2CO_3$ | 125 | 2 | 98 | 160:1 |
| 5 | 0.5 | $K_2CO_3$ | 125 | 4 | 94[d] | 165:1 |
| 6 | 0.1 | $K_2CO_3$ | 145 | 10 | 96[d] | 165:1 |

[a]Conditions: **2.1**, $Pd(OAc)_2$, ligand **2.4** (2 equiv. per [Pd]) and base (2 equiv.) dissolved in DMA and heated to indicated temperature until judged complete by GCMS. [b]Yields determined by GCMS analysis. [c]Remainder is unreacted **2.1**. [d]Isolated Yield.

A base screen revealed that substituting $Cs_2CO_3$ with inexpensive $K_2CO_3$ not only resulted in faster reactions, generating **2.2** in 95 % yield after 4 h with 5 mol % catalyst at 95 °C, but also increased the ratio of **2.2**:**2.3** to greater than 160:1. Further investigation of the conditions revealed that the reaction could be run with significantly reduced catalyst loadings. At 125 °C, the reaction gives 100% conversion with as little as 0.5 mol % catalyst within 4 h (TON 200; TOF 50 $h^{-1}$). At 145 °C, 0.1 mol % palladium is sufficient to reach 100% conversion and give **2.2** in 96% isolated yield (TON 1000). This is a rare example for this type of transformation in which such low catalyst loadings have been employed[39,33] and constitutes, to our knowledge, a new benchmark in the formation of biaryls via this approach.

---

[38] Harris, M. C.; Geis, O.; Buchwald, S. L. ; *J. Org. Chem.* **1999**, *64*, 6019. This ligand is commercially available from Strem Chemicals.

[39] Suzuki, K. *Angew. Chem., Int. Ed.* **1999**, *38*, 1229. (b) Rice, J. E.; Cai, Z.-W.; He, Z.-M.; LaVaoie, E. J. *J. Org. Chem.* **1995**, *60*, 8101. With 26 mol % catalyst: (c) Hosoya, T.; Takashiro, E.; Matsumoto, T.; Suzuki, K. *J. Am. Chem. Soc.* **1994**, *116*, 1004. With 25 mol % catalyst: (d) Matsumoto, T.; Hosoya, T.; Suzuki, K. *J. Am. Chem. Soc.* **1992**, *114*, 3568. With 20-25 mol % catalyst: (e) Cuny, G. D. *Tetrahedron Lett.* **2003**, *44*, 8149. (f) Qabaja, G.; Jones, G. B. *J. Org. Chem.* **2000**, *65*, 7187. With as low as 10 mol % catalyst: (g) Bringmann, G.; Heubes, M.; Breuning, M.; Gobel, L.;

A variety of ethers were reacted with varying amounts of catalyst as outlined in Table 2.2. Ortho, meta, and para substituents are compatible, including electron-donating and withdrawing groups. Interestingly, chloro substituents remain intact under the reaction conditions (Entries 9 and 10). Furthermore, the oxygen atom in the tether can be replaced by a carbon or nitrogen atom, as illustrated by reactions with amide and all carbon linked substrates (Entries 12-13). An increase in catalyst loading was required in these cases to ensure complete conversion.[40] Unfortunatly moving the oxygen atom in the tether effectively inverting the electrophilic and nucleophilic partner led to partial conversion and large quantities of dehalogenated product.

Formation of larger ring sizes required further development. For example, while reaction of **2.5** with 5 mol % of a catalyst generated from $Pd(OAc)_2$ and ligand **2.4** gave **2.6** in 77% yield, the use of 2.5 mol% of this same catalyst generated from $Pd(OAc)_2$ and ligand **2.4** gave **2.6** in only 35% yield after 6 hours (Scheme 2.1). Efforts aimed at increasing the reactivity of the catalyst were undertaken by Mathieu Parisien and Mélissa Leblanc and led to the preparation of electron-deficient ligand **2.7**. Gratifyingly, with ligand **2.7** only 1 mol % catalyst is sufficient to induce complete reaction and give **2.6** in 90% yield. Since most ligand development efforts are directed at the preparation of bulky electron-rich systems,[41] our observations that the use of bulky electron-deficient ligands can lead to excellent results should prompt their investigation in other challenging direct arylation reactions. Although no in-depth mechanistic studies were undertaken to study the observed effect, it is plausible that the electron-poor ligand facilitates prerequisite binding of the palladium with the arene being functionalized by making it more electrophilic.

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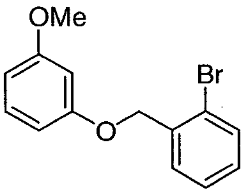
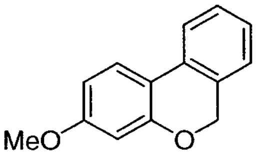
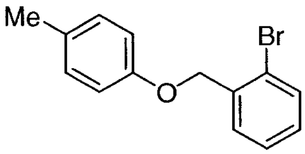
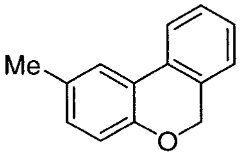
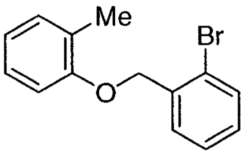
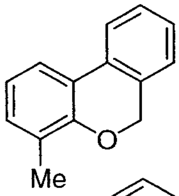
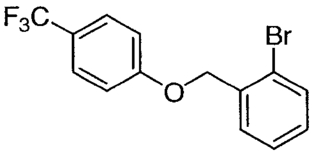
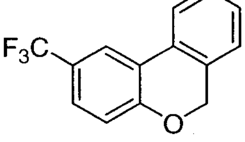
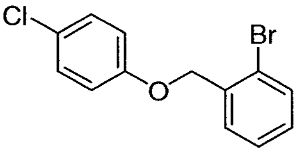
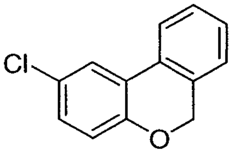
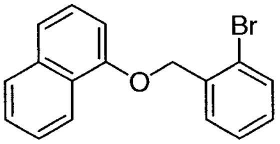
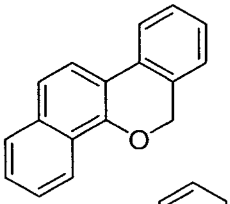
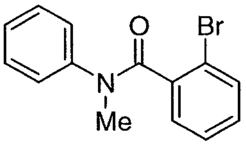
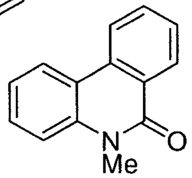
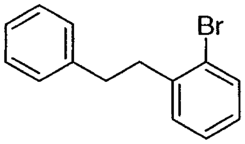
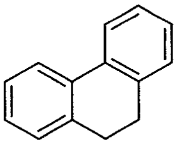
Ochse, M.; Schoner, B.; Schupp, O. *J. Org. Chem.* **2000**, *65*, 722. (h) Bringmann, G.; Ochse, M.; Gotz, R. *J. Org. Chem.* **2000**, *65*, 2069. (i) Harayama, T.; Yasuda, H. *Heterocycles* **1997**, *46*, 61. (j) Larock has reported a catalyst system that has been used with 5 mol % loading in analogous processes: (j) Campo, M. A.; Huang, Q.; Yao, T.; Tian, Q.; Larock, R. C. *J. Am. Chem. Soc.* **2003**, *125*, 11506.

[40] This decreased reactivity in the absence of a heteroatom has previously been observed. See reference 39j

[41] For a recent example, see : Milne, J. E.; Buchwald, S. L.; *J. Am. Chem. Soc.* **2004**, *124*, 13028 and references therein. For a recent highlight on this topic, see: Miura, M. *Angew. Chem. Int. Ed.* **2004**, *43*, 2201 and references therein.

**Table 2.2** - Scope of Biaryl Formation[a]

| Entry | Substrate | Product | Mol % Pd | T (°C) | Yield (%)[b] |
|---|---|---|---|---|---|
| 1 |  |  | 1 | 125 | 91[c] |
| 2 | | | 0.2 | 140 | 94[c] |
| 3 |  |  | 1 | 125 | 90 |
| 4 | | | 0.5 | 140 | 92 |
| 5 |  |  | 1 | 125 | 93 |
| 6 | | | 0.5 | 140 | 94 |
| 7 |  |  | 1 | 125 | 97 |
| 8 | | | 0.2 | 140 | 98 |
| 9 |  |  | 1 | 125 | 93 |
| 10 | | | 0.1 | 140 | 97 |
| 11 |  |  | 0.5 | 125 | 91 |
| 12 |  |  | 2 | 125 | 83 |
| 13 |  |  | 5 | 125 | 79 |

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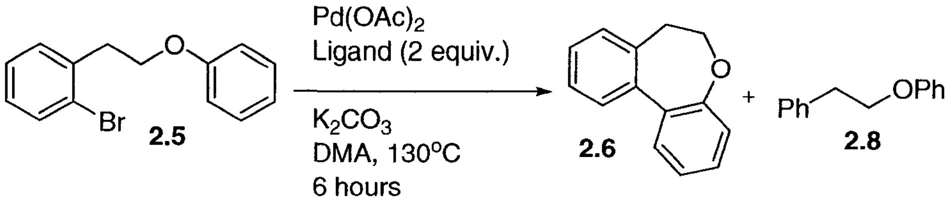
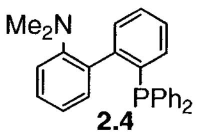
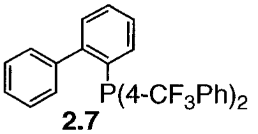
[a] Conditions: Under a nitrogen atmosphere, the substrate, $Pd(OAc)_2$, ligand **2.4** (2 equiv. per [Pd]), $K_2CO_3$ (2 equiv.) were dissolved in DMA (0.2M) and heated to the indicated temperature for 10 to 14 hours. [b] Isolated Yield. [c] *Para/ortho* 21:1.



| Ligand | mol% [Pd] | Yield (%) | 2.6:2.8[a] |
|---|---|---|---|
|  **2.4** | 5 | $77^b$ | 10:1 |
| | 2.5 | $35^a$ | 10:1 |
|  **2.7** | 2.5 | $92^a$ | 14:1 |
| | 1 | $90^b$ | 14:1 |

[a] Determined by GCMS, average of 3 runs. [b] Isolated yield, overnight reaction

**Scheme 2.1** - Ligand Effect on 7-Membered Ring Formation

Little mechanistic information pertaining to the arylation step was collected at this point in our study, but it is noteworthy that we observed an intramolecular $k_H/k_D$ value of 3.5 which is atypical of most electrophilic additions to arenes,[42] but not unprecedented in arylations with palladium.[43] Subsequently, this catalyst system was used in the synthesis of aporphines and their analogues,[44] and was the foundation for an allocolchicinoid synthesis project[45] by our research group.

In the hope that this catalytic system would be general for aryl iodides and chlorides, we investigated the reactions of **2.9** and **2.10**. Unfortunately, both of these reactions gave unsatisfactory yields at 1 mol % Pd (Equation **2.1** and **2.2**). Although it was possible to circumvent these shortcomings by increasing catalyst loadings, we decided to undertake a catalyst optimization study that would allow for the discovery of a highly efficient and general catalyst.

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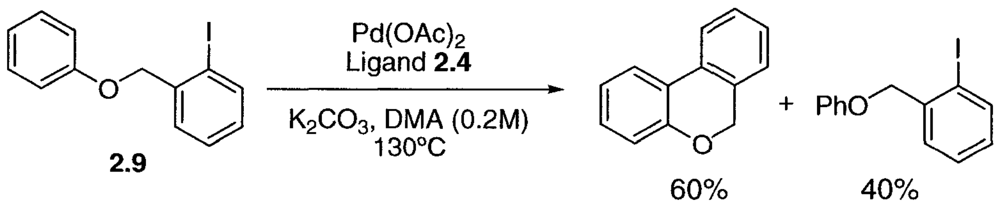
[42] (a) Martin-Matute, B.; Mateo, C.; Cardenas, D. J.; Echavarren, A. M.; *Chem. Eur. J.* **2001**, *7*, 2341; (b) Catellani, M.; Chiusoli, G. P.; *J. Organomet. Chem.* **1992**, *425*, 151; (c) Park, C.-H.; Ryabova, V.; Seregin, I.V.; Sromek, A.W.; Gevorgyan, V.; *Org. Lett.* **2004**, *6*, 1159.

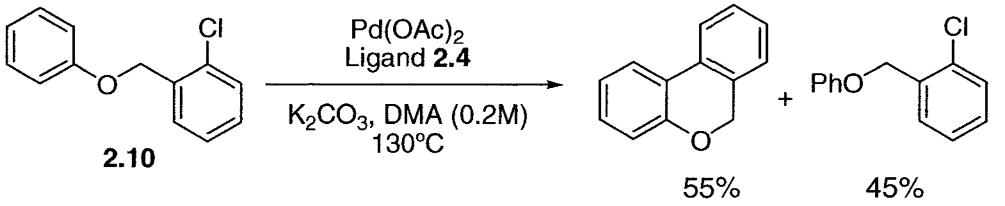
[43] For example, see Hennessy, E. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003** *125*, 12084 and references therein.

[44] Lafrance, M.; Blaquiere, N.; Fagnou, K.; *Chem. Commun.* **2004**, 2874

[45] Leblanc, M.; Fagnou, K.; *Org. Lett.* **2005**, *7*, 2849



(2.1)



(2.2)

## Second Generation Catalyst[46]

While traditional cross-coupling methods are now more frequently carried out with aryl chlorides,[47] direct arylation processes commonly require the use of aryl iodides or bromides, with near complete exclusion of aryl chlorides.[48] In an initial broad screening of various ligands for $Pd(OAc)_2$ for the intramolecular direct arylation of substrate **2.10**, we identified *N*-heterocyclic carbenes (NHC) as potential leads. Results from NHC catalyst screening are outlined in Scheme 2.2.

All reactions were carried out with 1 mol % [Pd] and allowed to react until catalyst deactivation had occurred. Both *in situ* generated catalysts and isolated NHC palladium complexes were examined. Mono-NHC complexes **2.13** and **2.14** were prepared according to previously reported methods,[49] including previously unreported **2.14**-IPr and **2.14**-SIPr. Optimal results were achieved with **2.14**-IPr, which gave a TON of 66.

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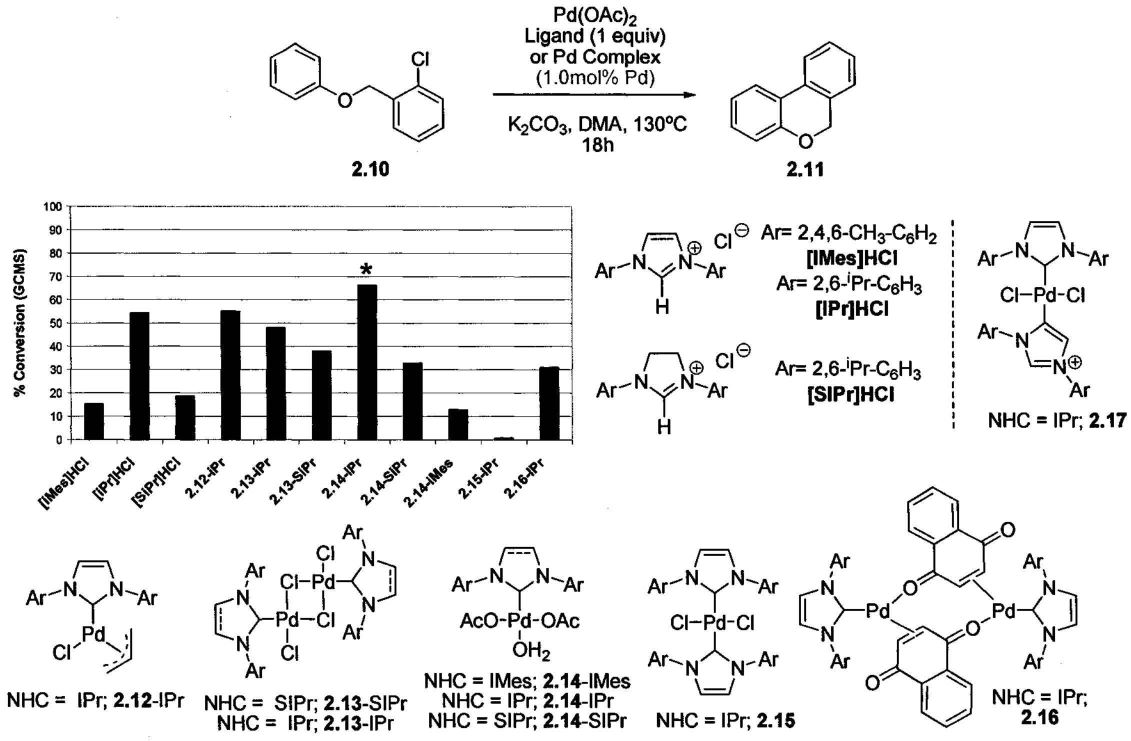
[46] Part of this work was performed with the aid of a summer undergraduate researcher and was published as a letter, see : Campeau, L.-C.; Thansandote, P.; Fagnou, K.; *Org. Lett.* **2005**, *7*, 1857.

[47] For a review of palladium-catalyzed cross-coupling reactions of aryl chlorides, see: Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176.

[48] Successful reaction with simple aryl chlorides has been achieved in intermolecular reactions with electron-rich zinc pyrrole anions[a] and in the formation of five-membered rings in moderate yield.[b] (a) Rieth, R. D.; Mankad, N. P.; Calimano, E.; Sadighi, J. P.; *Org. Lett.* **2004**, *6*, 3981. (b) Bedford, R. B.; Cazin, C. S. J.; *Chem. Commun.* **2002**, 2310. To our knowledge, no intramolecular examples with larger ring sizes have appeared.

[49] (a) Jensen, D. R.; Schultz, M. J.; Mueller, J. A.; Sigman, M. S. *Angew. Chem., Int. Ed.* **2003**, *42*, 3810. (b) Viciu, M. S.; Stevens, E. D.; Petersen, J. L.; Nolan, S. P. *Organometallics* **2004**, *23*, 3752.



[a]Conditions: Substrate **2.10**, catalyst (1mol%), $K_2CO_3$ (2 equiv.) was dissolved in DMA (0.2 M) and heated to 130°C until catalyst deactivation has occurred. Pre-catalysts **2.12** react irreproducibly giving as much as 48 TON for 2.12-IPr.

**Scheme 2.2** - Screening of Various NHC/Pd Systems for Direct Arylation of 2.10[a]

The Cl precatalysts **2.12** were found to react irreproducibly. While a TON of up to 48 can be achieved, we also frequently observed inferior TON or even no reaction under identical conditions. Wondering if catalyst activation is influenced by the catalyst counterion, we tested the use of different silver additives to promote anionic ligand exchange prior to reaction. When 4 equivalents of silver acetate is added to **2.12**-IPr, activation occurs reproducibly, giving results similar to those obtained with the acetate catalyst **2.14**-IPr. The IPr catalysts give dramatically better TON than IMes analogues despite showing similar initial rates. This may point to an important steric component in preventing catalyst death.

Despite the impressive reactivity of NHC catalysts, they can be prone to decomposition after insertion of the aryl halide.[50] Cavell, Caddick, and Grushin have shown that in the absence of a good nucleophile, NHC aryl palladium(II) species are

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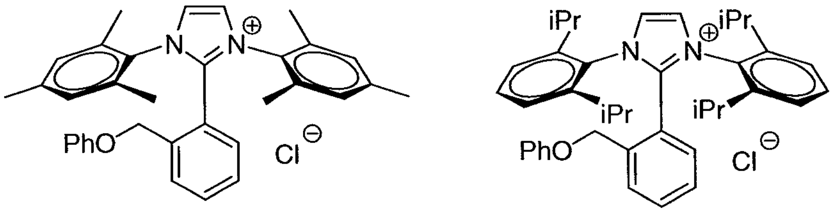
[50] For a review, see: Crudden, C. M.; Allen, A. P. *Coord. Chem. Rev.* **2004**, *248*, 2247.

unstable and undergo facile aryl-NHC reductive elimination to give the arylimidazolium salts and catalyst death.[51] MALDI TOF-MS analysis[52], following catalyst deactivation of the crude reaction mixtures with **2.14**-IMes and **2.14**-IPr, revealed the presence of mass peaks at 485.687 and 569.728 corresponding to catalyst decomposition products **2.18** and **2.19** (Scheme 2.3), indicating that reductive elimination of the aryl and NHC ligands is a contributing factor to catalyst death. The study of these NHC catalysts in the context of direct arylation reactions could therefore not only enable the general use of aryl chlorides in these reactions but also provide an opportunity to circumvent NHC catalyst decomposition in other reactions.



**2.18** **2.19**

**Scheme 2.3** – Imidazolium Decomposition Products Detected by MALDI TOF-MS

Studies of *N*-heterocyclic carbene ligands employed in palladium catalysis[53,54] have revealed that 1:1 NHC-metal complexes typically exhibit enhanced reactivity compared to analogous 2:1 species.[55] These observations have prompted the development of several methods to prepare NHC metal complexes with a well defined 1:1 ligand to metal ratio.[56] Deliberate addition of NHC hydrochloride salts (pre-NHC ligands) to

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[51] (a) Marshall, W. J.; Grushin, V. V. *Organometallics* **2003**, *22*, 1591. (b) McGuinness, D. S.; Green, M. J.; Cavell, K. J.; Skeleton, B. W.; White, A. H. *J. Organomet. Chem.* **1998**, *565*, 165. (c) McGuinness, D. S.; Cavell, K. J.; Skeleton, B. W.; White, A. H. *Organometallics* **1999**, *18*, 1596. (d) Caddick, S.; Cloke, F. G. N.; Hitchcock, P. B.; Leonard, J.; Lewis, A. K.; McKerrecher, D.; Titcomb, L. R. *Organometallics* **2002**, *21*, 4318.

[52] We thank Prof. Deryn Fogg and Dr. Melanie Eelman for assistance with MALDI TOF-MS analysis.

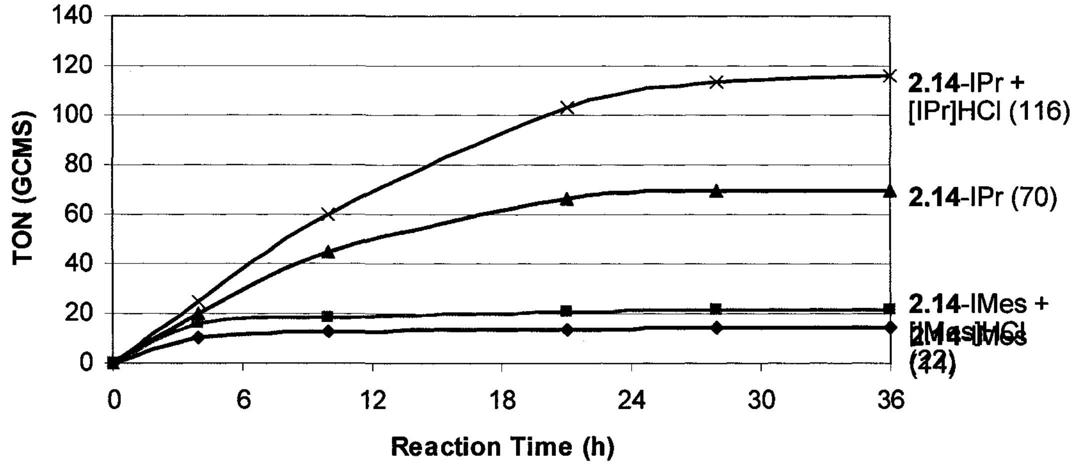
[53] Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1290.

[54] Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. In *Principles and Applications of Organotransition Metal Chemistry*; University Science: Mill Valley, CA, 1987.

[55] For example see: (a) Hillier, A. C.; Grasa, G. A.; Viciu, M. S.; Lee, H. M.; Yang, C.; Nolan, S. P. *J. Organomet. Chem.* **2002**, *653*, 69. (b) Huang, J.; Nolan, S. P. *J. Am. Chem. Soc.* **1999**, *121*, 9889. (c) Huang, J.; Grasa, G. A.; Nolan, S. P. *Org. Lett.* **1999**, *1*, 1307. (d) Lee, H. M.; Nolan, S. P. *Org. Lett.* **2000**, *2*, 119. (e) Grasa, G. A.; Viciu, M. S.; Huang, J.; Nolan, S. P. *J. Org. Chem* **2001**, *66*, 7729. (f) Grasa, G. A.; Viciu, M. S.; Huang, J.; Zhang, C.; Trudell, M. L.; Nolan, S. P. *Organometallics* **2002**, *21*, 2866. (g) Viciu, M. S.; Kissling, R. M.; Stevens, E. D.; Nolan S. P. *Org. Lett.* **2002**, *4*, 2229. (h) Viciu, M. S.; Germaneau, R. F.; Navarro- Fernandez, O.; Stevens E. D.; Nolan, S. P. *Organometallics* **2002**, *21*, 5740.

[56] (a) Viciu, M. S.; Navarro, O.; Germaneau, R. F.; Kelly, R. A., III; Sommer, W.; Marion, N.; Stevens, E. D.; Cavallo, L.; Nolan, S. P. *Organometallics* **2004**, *23*, 1629. (b) Jensen, D. R.; Schultz, M. J.; Mueller, J. A.; Sigman, M. S. *Angew.*

mono-NHC catalyst **2.14**-IPr should produce slower reactions due to the *in situ* formation of bis-NHC complexes. Nonetheless, when we explored the use of [IPr]HCl and [IMes]HCl as additives in reactions with the palladium IPr and IMes complexes **2.14**, substantial improvements in TON were obtained with no loss in reactivity (Figure 2.1).[57,58]



[a]Conditions: **2.10**, $K_2CO_3$ (2 equiv.), Pd catalyst **2.14** (0.5 mol %) and imidazolium salt additive if used (0.5 mol%) were dissolved in DMA (0.2 M) and heated to 130°C in a screw capped vial for 36 hours. Aliquots were periodically removed via syringe to determine % conversion by GCMS analysis.

**Figure 2.1** - Effect of Added Imidazolium Salts on Catalyst TON[a]

The addition of 0.5 mol % [IMes]HCl to **2.14**-IMes led to a modest, but reproducible, TON enhancement of approximately 10. More significantly, the TON with **2.14**-IPr increased from 70 to 116 when 0.5 mol % [IPr]HCl was added. The catalyst combination of **2.14**-IPr/[IPr]HCl, was consequently employed to investigate the scope of these reactions. Selected examples are outlined in Table 2.3.

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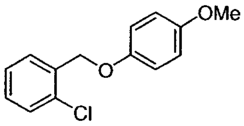
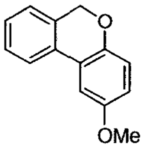
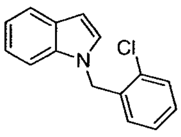
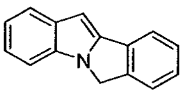
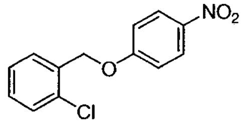
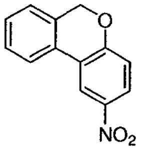
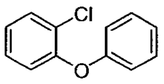
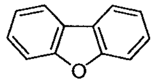
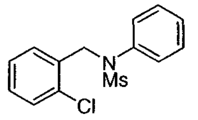
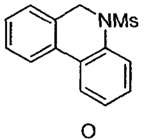
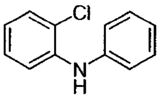
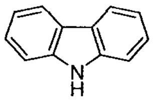
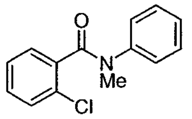
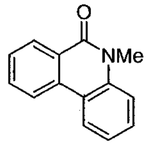
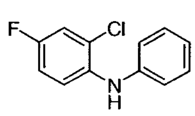
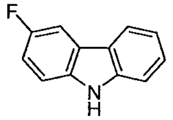
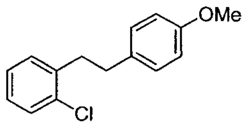
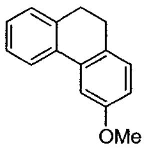
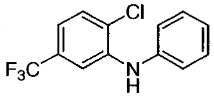
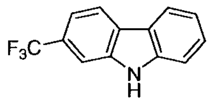
*Chem., Int. Ed.* **2003**, *42*, 3810. (c) Frisch, A. C.; Rataboul, F.; Zapf, A.; Beller, M. *J. Organomet. Chem.* **2003**, *687*, 403. (d) Viciu, M. S.; Stevens, E. D.; Petersen, J. L.; Nolan, S. P. *Organometallics* **2004**, *23*, 3752. **2004**, *248*, 2247.

[57] Addition of [IPr]HCl to **2.13**-IPr only leads to modest increases in TON.

[58] TON increase upon NHC-HCl addition was also observed in telomerization of dienes with alcohols, but increased reaction rates were observed with higher imidazolium salt additive concentrations: Jackstell, R.; Harkal, S.; Jiao, H.; Spannenberg, A.; Borgmann, C.; Roëttger, D.; Nierlich, F.; Elliot, M.; Niven, S.; Cavell, K.; Navarro, O.; Viciu, M. S.; Nolan, S. P.; Beller, M. *Chem. Eur. J.* **2004**, *10*, 3891

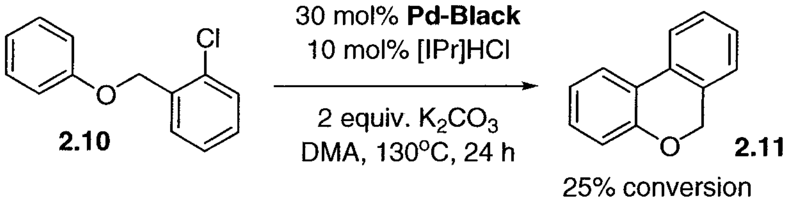
**Table 2.3** - Scope of Intramolecular Biaryl Formation[a]

| Entry | Substrate | Product | Yield(%)[b] | Entry | Substrate | Product | Yield (%)[b] |
|---|---|---|---|---|---|---|---|
| 1 |  |  | 91 | 6 |  |  | 89 |
| 2 |  |  | 88 | 7 |  |  | 86 |
| 3 |  |  | 82 | 8 |  |  | 99 |
| 4 |  |  | 97 | 9 |  |  | 89 |
| 5 |  |  | 84[c] | 10 |  |  | 92 |

[a] Conditions: Substrate, **2.14**-IPr (1-3 mol %), [IPr]HCl (1-3 mol %), $K_2CO_3$ (2 equiv.) dissolved in DMA (0.2 M) and heated to 130 °C for 10-16 hours. [b] Isolated yield. [c] Conducted using an *in situ* generated catalyst from $Pd(OAc)_2$ and 2 equivalents of [IPr]HCl.

Hydrodehalogenation can be a severely limiting side reaction in intramolecular processes, resulting in nonproductive consumption of starting material. While this can be effectively overcome in intermolecular couplings through the use of an excess of the aryl halide, intramolecular reactions must rely on catalyst selectivity. We were therefore gratified to find that, in all cases, only trace amounts of hydrodechlorination (<1%) were detected by GCMS analysis of the crude reaction mixtures. The catalyst system of **2.14**-IPr/[IPr]HCl was found to be highly reactive and selective for the formation of five- and six-membered rings. A variety of tethers can be employed, as illustrated in the formation of six-membered rings with an ether (Entries 1, 2), amine (Entry 3), amide (Entry 4), or alkyl (Entry 5) tether. Cyclization of *N*-2'-chlorobenzylindole occurs rapidly to close the five membered ring (Entry 6), underlining the superior reactivity associated with heteroaromatic coupling partners. Biaryl ethers can also be efficiently arylated in high yield (Entry 7). This methodology enables carbazole synthesis (Entries 8-10) without the protection of the nitrogen functionality and is a very efficient route to this class of molecule, which has demonstrated medicinal importance.[59]

We have conducted initial experiments to probe the imidazolium additive's influence on catalyst TON. Under some conditions, unusual palladium NHC complexes[60] that possess different activity can be formed *in situ*. Consequently, we prepared the previously uncharacterized complex **2.17** (Scheme 2.3).[61] Complex **2.17** is a poor catalyst, giving only 10 turnovers after 18 h. Bis-carbene complex **2.15** also gave inferior results, essentially giving trace amounts of **2.11**. Furthermore, we have ruled out that the [IPr]HCl is simply behaving as a chloride additive, since added $Bu_4NCl$ does not induce the same beneficial effects. Alternatively it is possible that the reactivity of the **2.14**-IPr catalyst, once reduced to palladium(0), is not diminished by the presence of a slight excess of IPr. Once catalyst decomposition has occurred and the bound IPr ligand has been consumed by the formation of **2.19**, the excess IPr may intercept the unligated palladium(0) prior to the formation of palladium black, thereby regenerating an active NHC catalyst. We have obtained support for this notion in reactions using palladium black as the palladium source, which is otherwise completely inactive. Treatment of **2.10** with 30 mol % palladium black and 10 mol % [IPr]HCl in the presence of $K_2CO_3$ in DMA at 130 °C results in 25% conversion to **2.11**, proving that catalyst recovery is viable even after palladium black formation has occurred (Equation 2.3). MALDI TOF-MS analysis of the crude reaction mixture shows peaks corresponding to IPr-Pd complexes and aryl-imidazolium salt **2.19** proving that discrete palladium NHC catalysts can be produced under the reaction conditions.



**2.10**

**2.11**

25% conversion

(2.3)

Additional evidence for a catalyst rescue pathway was obtained from crossover experiments. When **2.14**-IPr/[IMes]HCl is used as a catalyst, 79 TON are observed

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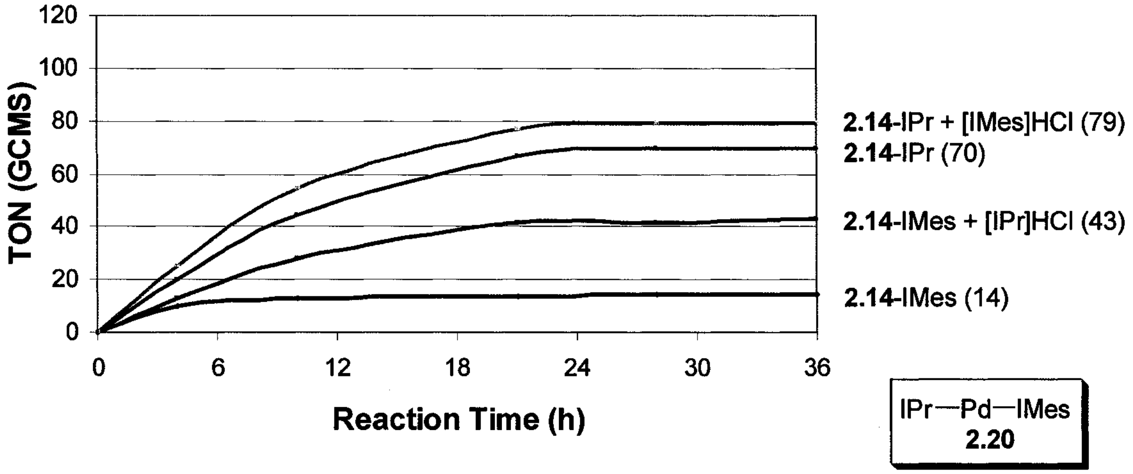
[59] Knolker, H.-J.; Reddy, K. R.; *Chem. Rev.* **2002**, *102*, 4303.

[60] Lebel, H.; Janes, M. K.; Charette, A. B.; Nolan, S. P.; *J. Am. Chem. Soc.* **2004**, *126*, 5046-5047.

[61] We thank Patrick Crewdson for performing X-Ray structures for various Pd-NHC complexes

whereas when **2.14**-IMes/[IPr]HCl is used, only 43 TON are obtained (Figure 2.2). This suggests the reaction does not involve a biscarbene palladium catalyst such as **2.20**. If a hybrid catalyst was formed we would expect as similar TON with both catalyst/additive mixtures.

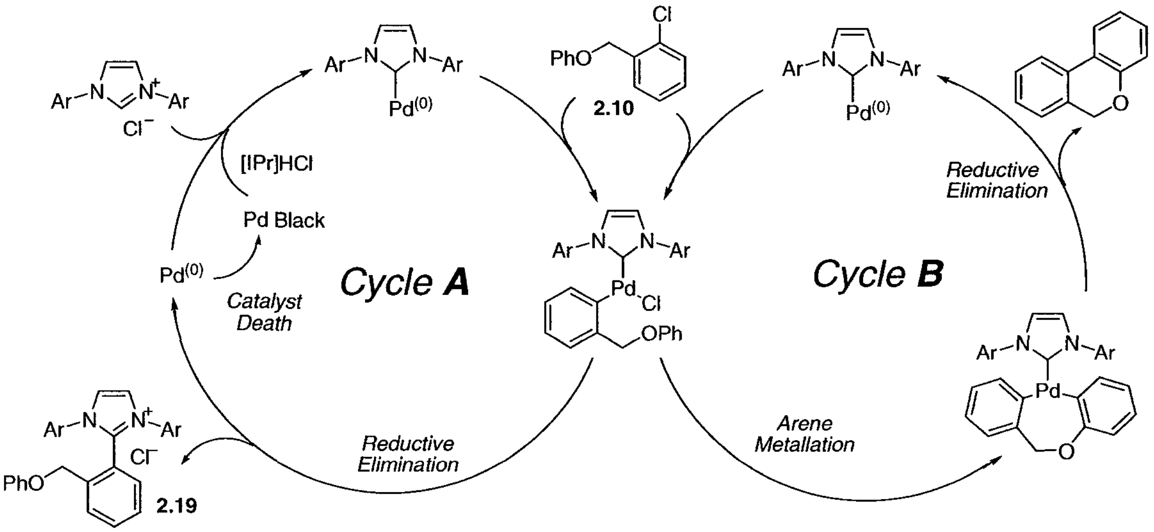


IPr—Pd—IMes
**2.20**

$^a$Conditions: **2.10**, $K_2CO_3$ (2 equiv.), Pd catalyst **2.14** (0.5 mol %) and imidazolium salt additive if used (0.5 mol %) were dissolved in DMA (0.2 M) and heated to 130 °C in a screw capped vial for 36 hours. Aliquots were periodically removed via syringe to determine % conversion by GCMS analysis.

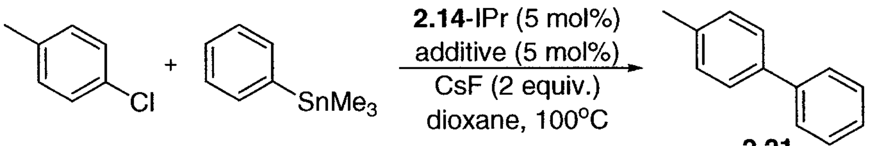
**Figure 2.2** – Cross-over Effect of Added Imidazolium Salts on Catalyst TON $^a$

The proposed mechanism for reversing/preventing catalyst death is presented in Scheme 2.4. Cycle **B** represents the productive catalytic cycle while cycle **A** represents catalyst decomposition via imidazolium reductive elimination followed by rescue by the [IPr]HCl additive.



**Scheme 2.4** – Mechanism For Preventing/Reversing Catalyst Decomposition

To investigate the pertinence of these discoveries to other reaction classes, we selected the Stille coupling.[62] For these reactions, it is known that transmetallation is rate-determining, making NHC catalysts prone to decomposition via reductive elimination to the imidazolium salt. Preliminary results indicate that the use of imidazolium salt additives can increase the TON in Stille couplings (Equation 2.4). In the absence of additive, biaryl **2.21** is obtained in 19% isolated yield. When 5 mol % [IPr]HCl is added, 55% yield is obtained.



**2.21**

(2.4)

| **Additive** | **Yield (%)** |
|---|---|
| none | 19 |
| [IPr]HCl | 55 |

While this catalyst system proved very efficient for the direct arylations of various aryl chloride substrates, it was still unable to catalyze reactions using aryl iodides. Additionally, subsequent studies revealed this catalyst to be very sensitive to steric encumbrance near the reactive site, leading to low yields of the tri-substituted biaryls (Equation 2.5).

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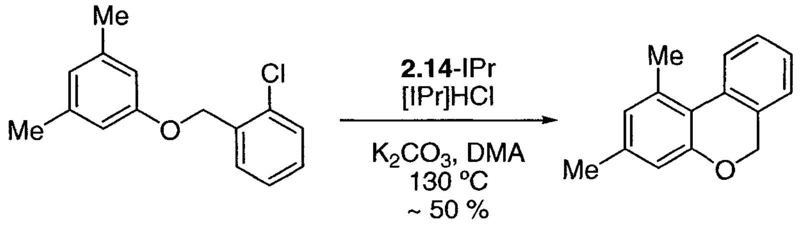
[62] For a review, see: Espinet, P.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4704.



(2.5)

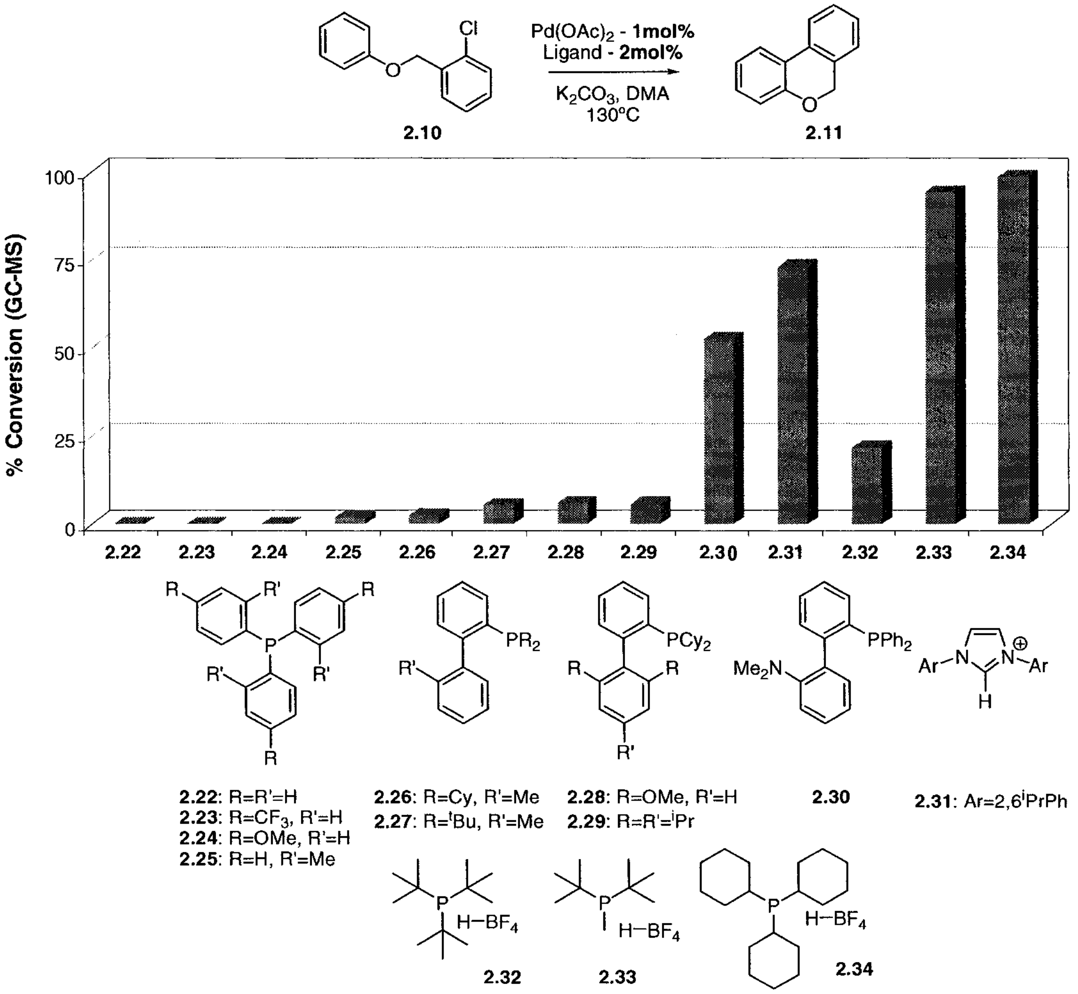
## Third Generation Catalyst[63]

In the previous section, the use of *N*-heterocyclic carbene (NHC) ligands for the direct arylation of aryl chlorides was described. In subsequent studies, we discovered that these catalysts did not lead to complete reactions when more sterically encumbered substrates were employed. This limitation prompted a reinvestigation of the potential catalysts capable of performing direct arylation with aryl chlorides. Catalyst screens were performed with aryl chloride **2.10** in the presence of 1 mol % $Pd(OAc)_2$, 2 mol % ligand and two equivalents of $K_2CO_3$ in dimethylacetamide (DMA) at 130 °C. Results are outlined in Scheme 2.5. Triarylphosphines (Entries **2.22** to **2.25**) as well as *ortho*-biaryl phosphines (Entries **2.26** to **2.30**) gave inferior reactivity while better results were obtained with some trialkylphosphines (Entries **2.32** to **2.34**) as well as *N*-heterocyclic carbenes (Entry **2.31**). Tricyclohexylphosphine (**2.34**) and di-*tert*-butylmethylphosphine (**2.33**) (added as the air-stable $HBF_4$ salts[64]) showed increased reactivity and robustness compared to the NHC system, affording complete conversion with only 1 mol% $Pd(OAc)_2$.

---

[63] Part of the scope presented in this section was performed with the aid of an undergraduate researcher (Annie Jean) and fellow graduate student (Mathieu Parisien) and was published as an article, see : Campeau, L.-C.; Parisien, M.; Jean, A.; Fagnou, K.; *J. Am. Chem. Soc.*. **2006**, *128*, 581

[64] This allows for this otherwise air sensitive phosphine to be weighed in air as a cristaline solid, see: Netherton, M. R.; Fu, G. C.; *Org. Lett.* **2001**, *3*, 4295-4298



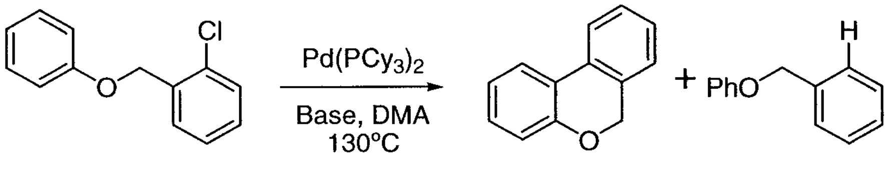
[a]Conditions: Substrate 2.10, $Pd(OAc)_2$ (1mol %), Ligand (2mol %) and $K_2CO_3$ (2 equiv.) are dissolved in DMA (0.2M) and heated to 130 °C until catalyst deactivation has occurred.

**Scheme 2.5** - Screen of Various Ligands for Direct Arylation of 2.10[a]

The influence of base was also examined (Table 2.4). The nature of the base and its counter ion has a significant impact on catalyst reactivity and selectivity. For example, while $K_2CO_3$ gives optimal results (Entry 2), both $Na_2CO_3$ and $Cs_2CO_3$ are ineffective, giving low conversions and inferior ratios of coupling vs. hydrodechlorination products (Entries 1 and 3). Alkoxide bases such as KO$^t$Bu also lead to an increase in dehalogenation (Entry 4). KOAc gives good selectivity but lower conversion (Entry 6). The same counterion effect is also observed with acetate bases since NaOAc gives lower conversion and selectivity than KOAc (Entries 6 and 7). Organic bases such as

$Et_3N$, $Cy_2MeN$ and diisopropylethylamine (DIPEA) lead to increased hydrodechlorination and very low conversion (Entries 8 to 10).

**Table 2.4** - Base Effects in Direct Arylation of Aryl Chlorides[a]



**2.10** **2.2** **2.3**

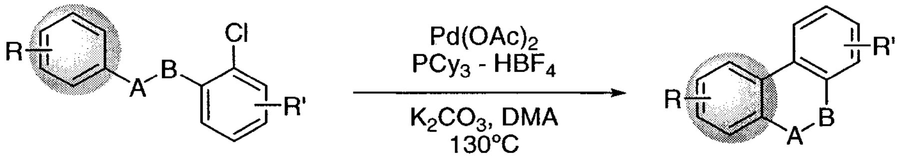
| Entry | Base | Conversion (%)[b] | Ratio **2.2**:**2.3**[b] |
|---|---|---|---|
| 1 | $Na_2CO_3$ | 11 | 20:1 |
| 2 | $K_2CO_3$ | 100 | >99:1 |
| 3 | $Cs_2CO_3$ | 25 | 15:1 |
| 4 | KOtBu | 84 | 2.3:1 |
| 5 | $K_3PO_4$ | 13 | 5:1 |
| 6 | KOAc | 81 | >99:1 |
| 7 | NaOAc | 41 | 28:1 |
| 8 | $Et_3N$ | 3 | 2:1 |
| 9 | DIPEA | 2 | 1.8:1 |
| 10 | $Cy_2MeN$ | 4 | 3:1 |

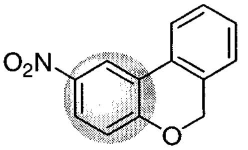
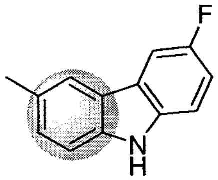
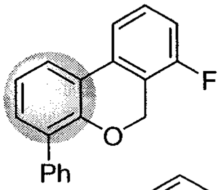
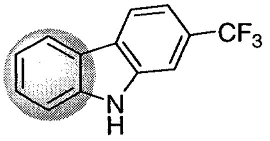
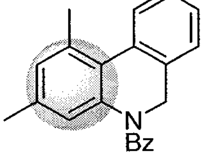
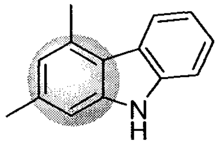
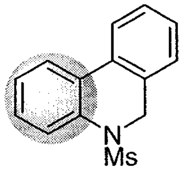
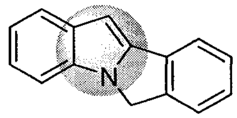
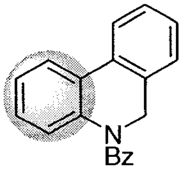
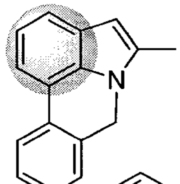
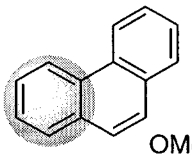
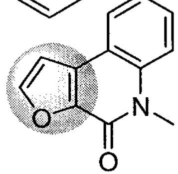
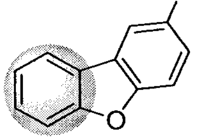
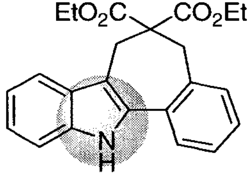
[a] Conditions: **2.10**, $Pd(PCy_3)_2$ and base (2 equiv.) are dissolved in DMA (0.2M) and heated to 130 °C until catalyst deactivation has occurred. [b] Determined by GC-MS.

To probe the origin of the base counterion effect, we compared the relative solubility of sodium, potassium and cesium carbonate. Mimicking the reaction conditions, we heated the base in DMA at 130°C for 30 minutes then filtered the hot solution. Distillation of the DMA from the filtrate revealed that in all three cases, only trace amounts (1 to 2%) of the carbonate base was dissolved. In light of the dramatic halide effect observed with the use of aryl iodide substrates (*vide infra*), we also evaluated the relative solubility of sodium, potassium and cesium chloride, which are generated as a byproduct of the reaction as it progresses. Again, all of the salts were insoluble under the reaction conditions, indicating that this cannot account for the observed base counterion effect. While the reason for the base effect remains elusive when aryl chlorides are employed, the observation that potassium bases provide superior reaction outcomes should be of use in the development of other arylation processes.

Various palladium sources such as $PdBr_2$, $PdCl_2$, $Pd(acac)_2$, $Pd(TFA)_2$ and $Pd_2(dba)_3$ were also examined. These studies reconfirmed that $Pd(OAc)_2$ is the optimal palladium catalyst source. The optimal reaction concentration remained 0.2M and heating to temperatures lower than 130 °C necessitated an increase in catalyst loading with certain substrates. These conditions, ($Pd(OAc)_2$, $PCy_3{\cdot}HBF_4$ (two equivalents of ligand per [Pd]) and two equivalents of $K_2CO_3$ in DMA (0.2M) at 130 °C), were therefore selected for further study.

**Table 2.5** - Scope of Intramolecular Direct Arylation of Aryl Chlorides[a]



| Entry | Product | mol% Pd | Yield[b] | Entry | Product | mol% Pd | Yield[b] |
|---|---|---|---|---|---|---|---|
| 1 |  | 1 | 97 | 8 |  | 3 | 88 |
| 2 |  | 1 | 92 | 9 |  | 3 | 87 |
| 3 |  | 5 | 89 | 10 |  | 5 | 78 |
| 4 |  | 3 | 94 | 11 |  | 3 | 91 |
| 5 |  | 3 | 97 | 12 |  | 3 | 82 |
| 6 |  | 3 | 87 | 13 |  | 3 | 83 |
| 7 |  | 5 | 81 | 14 |  | 10 | 80 |

[a]Conditions: Substrate, Pd(OAc)$_2$, PCy$_3$ – HBF$_4$ (2 equiv. per Pd) and K$_2$CO$_3$ (2 equiv.) are dissolved in DMA (0.2M) and heated to 130 °C for 8-16 h. [b]Isolated Yields.

The scope of the reaction with aryl chlorides is outlined in Table 2.5. Typically reactions were left to react overnight, but in some cases were done within 8 hours. Various tethers including carbon (Entries 6, 11, 12 and 14), oxygen (Entries 1, 2 and 7) and nitrogen (Entries 3, 4, 5, 8, 9, 10 and 13) can be effectively employed in these transformations. In the formation of six-membered rings with a nitrogen atom in the tether, an amide or a sulfonamide protecting group can be employed (Entries 3, 4 and 5). Leaving the nitrogen unprotected or simply using an aryl group leads to partial conversion and increased dehalogenation. We also found that acetyl and trifluoroacetyl were unsuitable as protecting groups. Five-membered ring carbazole products can be obtained without the installation of a nitrogen protecting group (Entries 8, 9 and 10). The synthesis of hindered biaryls is also facilitated by this catalyst as demonstrated by Entries 3 and 10. This is an improvement over our previously reported conditions which fail to induce complete reactions.[45,46] Z-Alkenes selectively undergo intramolecular direct arylation over a possible competitive intermolecular Heck pathway (Entry 6). Substitution is also tolerated on the aryl halide moiety with fluoro (Entries 2 and 8) and trifluoromethyl (Entry 9) aryl chlorides reacting readily. Additional catalyst is needed in the case of deactivated aryl chlorides as illustrated with methoxy substituted substrate (Entry 7). This catalyst system also allows the use of heterocycles in these processes (Entries 11 to 14). *N*-alkyl indole reacts at the 2-position to afford the biaryl product in high yield (Entry 11). Methyl substitution at the 2-position leads to arylation on the adjacent phenyl ring of indole to afford the structural core of the pyrrolophenanthridine class of natural products[65] (Entry 12). Furans can also be arylated as illustrated by the synthesis of a furoquinolinone product (Entry 13). Unprotected indoles also react (Entry

---

[65] (a) Martin, S. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1987; Vol. 30, Chapter 3, pp 252-369. (b) Cook, J. W.; Loudon, J. D. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1952; Vol. 2, Chapter 11, p 331. (c) Lewis, J. R. *Nat. Prod. Rep.* **1995**, *12*, 339.

14), in this case to form a seven membered ring which has been scarcely explored in direct arylation reactions.[66]

The generality of this catalyst system was then tested on aryl bromide substrates. Gratifyingly, this can be achieved without modification to the protocol developed for aryl chlorides. The scope of reactions employing aryl bromides is outlined in Table 2.6. Selective arylation in the presence of a chloride functionality is possible, providing a useful handle for further cross-coupling reactions (Entry 1). Electron-rich, as well as electron-poor, arenes are compatible (Entries 2 and 3). Deactivated aryl bromides can be used although increased catalyst loading is required for complete reactions (Entry 4). Tosyl protecting groups are compatible when a nitrogen atom is in the tether (Entry 5). Activated aryl bromides react to provide the corresponding phenanthredinone product in good yield (Entry 6).

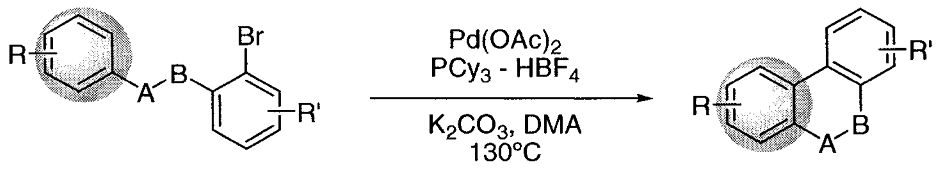
Recent advances in catalyst development for biaryl synthesis have been directed at the formation of sterically hindered biaryls.[67] In the context of these challenging cross-coupling reactions, we were interested in determining whether this catalyst system could achieve direct arylation reactions of more sterically demanding substrates such as tetra-*ortho*-substituted substrates. We were pleased to find that under our optimized conditions, the synthesis of tri- (Entries 9 and 10) and tetra-*ortho*-substitued (Entries 11 to 13) biaryls was feasible. Mesylate and benzoyl protecting groups can be used when a nitrogen atom is in the tether (Entries 9 and 11). Ester groups also remain intact under reaction conditions (Entry 13).

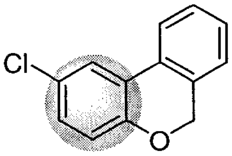
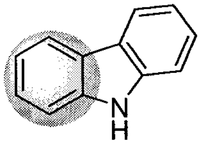
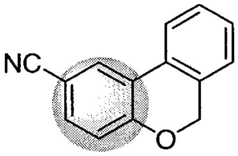
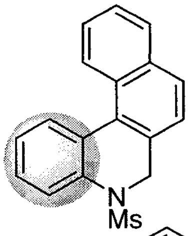
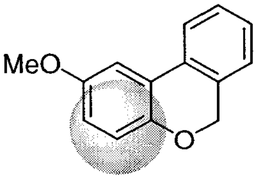
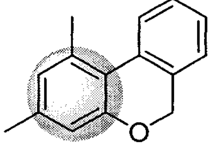
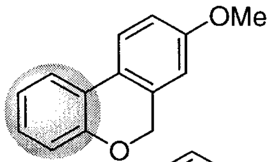
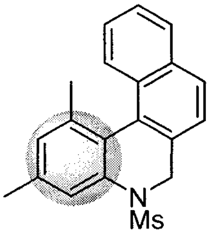
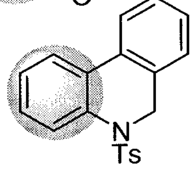
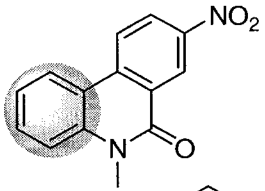
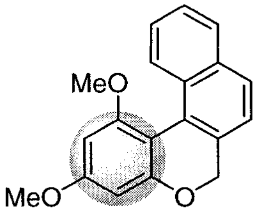
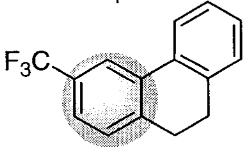
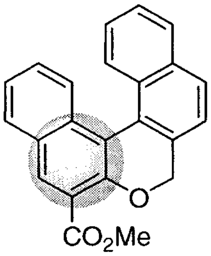
---

[66] For examples using heterocyclic arenes, see: (a) Kozikowski, A. P.; Ma, D. *Tetrahedron Lett.* **1991**, *32*, 3317. (b) Hughes, C. C.; Trauner, D. *Angew. Chem., Int. Ed.* **2002**, *41*, 1569. For examples using non-heteroaromatic arenes, see: (c) reference 35. (d) reference 45.

[67] For recent advances, see: (a) Milne, J. E.; Buchwald, S. L.; *J. Am. Chem. Soc.* **2005**, *126*, 13028; (b) Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1871-1876.

**Table 2.6** - Scope of Intramolecular Direct Arylation of Aryl Bromides[a]

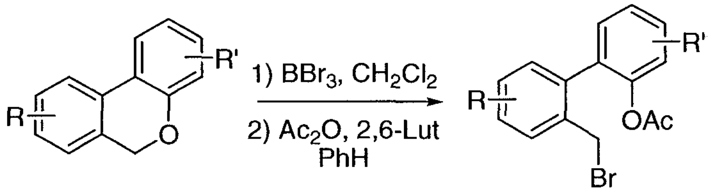


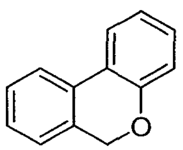
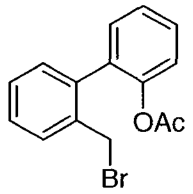
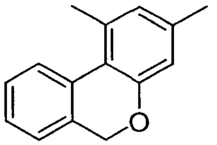
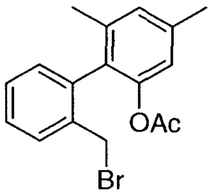
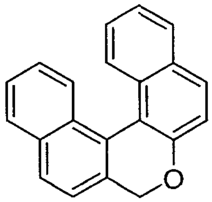
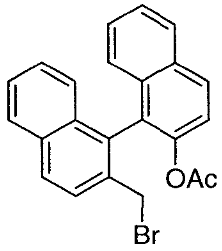
| Entry | Product | mol% Pd | Yield[b] | Entry | Product | mol% Pd | Yield[b] |
|---|---|---|---|---|---|---|---|
| 1 |  | 1 | 90 | 8 |  | 3 | 94 |
| 2 |  | 1 | 99 | 9 |  | 5 | 98[d] |
| 3 |  | 1 | 92 | 10 |  | 5 | 86 |
| 4 |  | 5 | 75 | 11 |  | 5 | 97[d] |
| 5 |  | 3 | 97 | | | | |
| 6 |  | 3 | 84 | 12 |  | 5 | 90[d] |
| 7 |  | 5 | 87[c] | 13 |  | 5 | 85[d] |

[a]Conditions: Substrate, $Pd(OAc)_2$, $PCy_3 - HBF_4$ (2 equiv. per Pd) and $K_2CO_3$ (2 equiv.) are dissolved in DMA (0.2M) and heated to 130 °C for 8-16hrs. [b]Isolated Yields. [c]Heated to 145 °C. [d]Entry performed by Annie Jean

Ring opening reactions were explored in order to obtain acyclic biaryl molecules. Treatment of the direct arylation products with 1.1 equivalents of $BBr_3$ in $CH_2Cl_2$ at room temperature, followed by trapping with acetic anhydride, yields the acyclic biaryl products in good yield (Table 2.7).[68] This sequence of direct arylation/ring cleavage is a complimentary entry point to these challenging biaryl substrates and may offer an attractive alternative to cross-coupling protocols in some cases.

**Table 2.7** - Scope of Ring Opening Reactions[a]



| Entry | Starting | Product | Yield[b] |
|---|---|---|---|
| 1 |  |  | 83 |
| 2 |  |  | 84[c] |
| 3 |  |  | 85[c] |

[a]Conditions: (1) Biaryl, $BBr_3$ 1.0M solution in heptane (1 equiv.), $CH_2Cl_2$, rt. (2) Crude benzyl bromide from step 1, $Ac_2O$ (excess), 2,6-Lutidine (2 equiv.), PhH, 0 °C to rt. [b]Isolated Yields. [c]Reaction performed by Annie Jean

While regioselectivity is an important factor when considering the application of a methodology in synthesis, it is an issue that has been scarcely studied in direct

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[68] Punna, S.; Meunier, S.; Finn, M. G.; *Org. Lett.* **2004**, *6*, 2777

arylation.[69,70] Consequently, various ether substrates were synthesized to study the influence of sterics and electronics on arylation regioselectivity of non-symmetrical arenes (Table 2.8). In general, we have determined that arylation preferentially occurs at the most sterically accessible site to give regioisomer **A**. In the case of large alkyl substituents (Entry 3 and 4) only one product is detected by NMR. Diminished yet synthetically useful selectivity is obtained when using a smaller alkyl substituent such as a methyl group (Entry 2) or a methoxy group[71] (Entry 1). In the case of electron withdrawing groups (Entries 5 to 7), arylation is very selective, giving only one product by NMR. Halide substituents give poorer regioselectivities. For example, a chlorine substituent gives a 3.2:1 ratio in favor of isomer **A**. Interestingly, when the arene is substituted with a fluorine atom, isomer **B** is produced as the major product in a 1:4.3 ratio.[72] It is worth noting that this reversal contrasts recent reports in palladium-catalyzed C-H activation/oxygenation reactions.[69]

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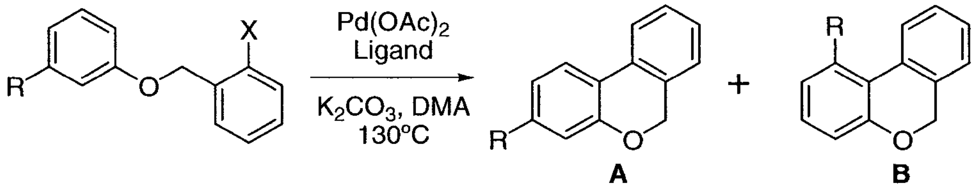
[69] For examples of such studies in other types of arene functionalization reactions see: (a) Kalyani, D.; Sanford, M.S.; *Org. Lett.* **2005**, *7*, 4149.

[70] For stoichiometric studies dealing with palladacycle formation see: (a) Teijido, B.; Fernandez, A.; Lopez-Torres, M.; Castro-Juiz, S.; Suarez, A.; Ortigueira, J. M.; Vila, J. M.; Fernandez, J. J. *J.Organomet. Chem.* **2000**, *598*, 71. (b) Gutierrez, M. A.; Newkome, G. R.; Selbin, J. *J. Organomet. Chem.* **1980**, *202*, 341. (c) Holton, R. A.; Davis, R. G. *J. Am. Chem. Soc.* **1977**, *99*, 4175.

[71] We had previously reported a ratio of 20:1 for this substrate which might be an indication of the increased reactivity of this system see reference 35.

[72] This type of effect with fluorine has also been observed in direct borylation of aromatic C-H bonds (a) and ruthenium catalyzed C-H/olefin coupling (b) : (a) Chotana, G.A.; Rak, M.A.; Smith III, M.R.; *J. Am. Chem. Soc.* **2005**, *127*, 10539. (b) Sonoda, M.; Kakiuchi, F.; Chatani, N.; Murai, S.; *Bull. Chem. Soc. Jpn.* **1997**, *70*, 3117

**Table 2.8** - Catalyst Selectivity in Direct Arylation[a]



| Entry | Substituent | Halide | Ligand | Ratio A:B[b] |
|---|---|---|---|---|
| 1 | OMe | Br | $PCy_3$ - $HBF_4$ | 10:1 |
| 2 | Me | Br | $PCy_3$ - $HBF_4$ | 15:1 |
| 3 | iPr | Br | $PCy_3$ - $HBF_4$ | >30:1 |
| 4 | tBu | Br | $PCy_3$ - $HBF_4$ | >30:1 |
| 5 | $CF_3$ | Br | $PCy_3$ - $HBF_4$ | >30:1 |
| 6 | $NO_2$ | Br | $PCy_3$ - $HBF_4$ | >30:1 |
| 7 | $CO_2Me$ | Br | $PCy_3$ - $HBF_4$ | >30:1 |
| 8 | Cl | Br | $PCy_3$ - $HBF_4$ | 3.2:1 |
| 9 | F | Br | $PCy_3$ - $HBF_4$ | 1:4.3 |
| 10 | F | Cl | $PCy_3$ - $HBF_4$ | 1:8.3 |
| 11 | F | Br | $P^tBu_3$ - $HBF_4$ | 1:1.3 |
| 12 | F | Br | $P^tBu_2Me$ - $HBF_4$ | 1:6.9 |

[a]Conditions: Aryl halide, $Pd(OAc)_2$ (3 mol %), Ligand (6 mol %) and $K_2CO_3$ (2 equiv.) are dissolved in DMA (0.2M) and heated to130 °C for 8-16 h. [b]Ratio determined by $^1H$ NMR. All reactions reached 100% conversion as determined by crude $^1H$ NMR analysis.

The next step in our investigation was the optimization of the reactions with aryl iodide **2.9**. The use of aryl iodides in direct arylation is well precedented.[73] The disproportionate focus on the use of aryl iodides compared to aryl bromides and especially aryl chlorides may be rationalized, at least in part, by the desire to reduce catalytic demand. Oxidative insertion into a C-X bond is most facile for aryl iodides.[74] The use of aryl iodides allows the chemist to focus their reaction/catalyst development

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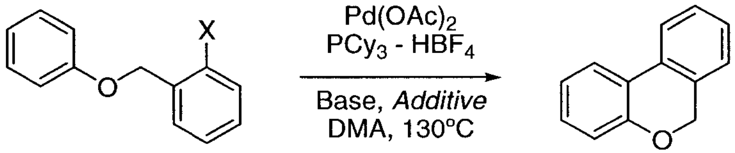
[73] Catalytic direct arylation of aryl iodides can be achieved using heterogenous catalysts, see: (a) Parisien, M.; Valette, D.; Fagnou, K. *J. Org. Chem.* **2005**, *70*, 7578 and references therein; With rhodium, see: (b) Wang, X. ; Lane, B.S. ; Sames, D. ; *J. Am. Chem. Soc.* **2005**, *127*, 4996.

[74] For a discussion, see (a) Grushin, V. V.; Alper, H. in Activation of Unreactive Bonds and Organic Synthesis, (Ed.: S. Murai), Springer, Berlin, **1999**, pp. 193 - 226; (b) Grushin, V. V.; Alper, H.; *Chem. Rev.* **1994**, *94*, 1047.

efforts on the challenging arylation step of the catalytic cycle. Given the strong precedent for the use of aryl iodides in direct arylation reactions, we were surprised to find that aryl iodides reacted very poorly under our optimized conditions. For example, reaction of aryl iodide **2.9** under the optimized conditions for aryl chlorides gave only 64% conversion, even after prolonged reaction times.[75] We have established that this poor reactivity is due to the accumulation of iodide anions in the reaction mixture, poisoning the catalyst. Although bromide **2.1** and iodide **2.9** react at similar rates at early conversions, the reaction of iodide **2.9** reaches a plateau at 64% conversion (Table 2.9, entries 1 and 2). Furthermore if one equivalent of KI is added to the reaction of bromide **2.1**, the arylation reaction is completely inhibited (Table 2.9, entry 3).

**Table 2.9 -** Halide Effect in Direct Arylation Reactions[a]



X=I **2.9**
X=Br **2.1**

**2.2**

| Entry | Halide | Base | Additive | Yield[b] |
|---|---|---|---|---|
| 1 | Br | $K_2CO_3$ | none | 99 |
| 2 | I | $K_2CO_3$ | none | 64[c] |
| 3 | Br | $K_2CO_3$ | KI[d] | <5 |
| 4 | I | $Cs_2CO_3$ | none | 89[e] |
| 5 | I | $K_2CO_3$ | AgOTf[d] | 99 |
| 6 | I | $K_2CO_3$ | $Ag_2CO_3$[f] | 99 |

[a]Conditions: Substrate, $Pd(OAc)_2$ (1 mol %), Ligand (2 equiv. per Pd) and $K_2CO_3$ (2 equiv.) are dissolved in DMA (0.2M) and heated to 130 °C for 12 h.[b]GC-MS Yields. [c]**2.2**:**2.3** = 8:1. [d]1 equiv. [e]**2.2**:**2.3** = 8.5:1. [f]0.5 equiv.

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[75] Similarly this diminished reactivity was observed with benzothiophene : Chabert, J. F. D.; Joucla, L. ; David, E. ; Lemaire, M. ; *Tetrahedron*, **2004**, *60*, 3221.

To sequester iodide, we explored the use of different bases and silver additives. In some cases, superior results can be achieved by using $Cs_2CO_3$ instead of $K_2CO_3$.[76] With the reaction of **2.9**, the use of $Cs_2CO_3$ was ineffective, resulting in an erosion of selectivity for cyclization to hydrodehalogenation from greater than 99:1 with $K_2CO_3$ to 8.5:1 with $Cs_2CO_3$. (Table 2.9, entry 4). Of the silver sources tested, AgOTf and $Ag_2CO_3$ gave the best results (Table 2.9, entries 5 and 6). We opted to use silver carbonate because of its increased ease of handling and lower cost.[77] These observations warn against the presumption of increased reactivity with aryl iodides in catalyst/reaction development efforts in direct arylation processes. Catalyst and substrate screens in the search for new reactions may best be performed with aryl bromides and/or chlorides, and not with aryl iodides as is commonly the case.

With these new reaction conditions, other reaction parameters were reinvestigated, including solvent and temperature. We also found that silver additives accelerated reaction times and allowed reactions to be carried out at temperatures as low as 80 °C in DMA with 5 mol % catalyst. Use of $Ag_2CO_3$ also provides complete conversion of aryl iodide **2.9** with 5 mol % catalyst in refluxing dioxane. In contrast, no reaction is observed in dioxane in the absence of $Ag_2CO_3$. It is also possible to achieve good conversion in refluxing THF if five equivalents of HMPA are used as an additive. The scope of direct arylation with aryl iodides is outlined in Table 2.10. Pivaloyl (Entries 4 and 5) and MOM ethers (Entry 2) can be used as protecting groups for amine and alcohol functional groups. Thiophenes are suitable reaction partners for the transformation (Entry 7). Five-membered ring biaryls can also be formed to afford the carbazole (Entry 8), benzopyrane (Entry 9) and fluorene (Entry 10) products.

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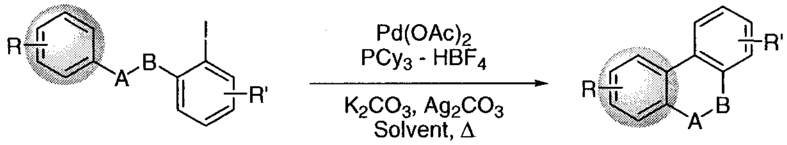
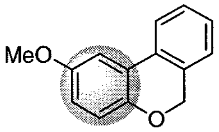
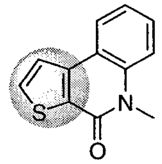
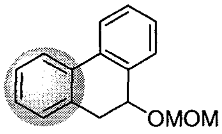
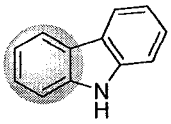
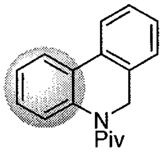
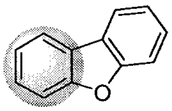
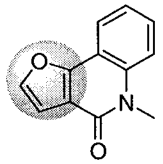
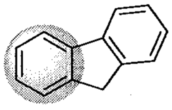
[76] Pivsa-Art, S.; Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M.; *Bull. Chem. Soc. Jpn.* **1998**, *71*, 467.

[77] $Ag_2CO_3$ (272CAD$/100g-Aldrich 2005) 377CAD$/mol Ag ; AgOTf (196CAD$/25g-Aldrich 2005) 2008CAD$/mol Ag

**Table 2.10** - Scope of Intramolecular Direct Arylation of Aryl Iodides[a]



| Entry | Product | Solvent | mol% Pd | Yield[b] | Entry | Product | Solvent | mol% Pd | Yield[b] |
|---|---|---|---|---|---|---|---|---|---|
| 1 |  | THF[c] | 5 | 86 | 7 |  | DMA | 5 | 88 |
| 2 | | Dioxane | 5 | 93 | | | | | |
| 3 |  | DMA | 5 | 85 | 8 |  | DMA | 3 | 83 |
| 4 |  | DMA | 3 | 94 | 9 |  | DMA | 3 | 99 |
| 5 | | Dioxane | 5 | 86 | | | | | |
| 6 |  | DMA | 5 | 81 | 10 |  | DMA | 3 | 81 |

[a] Conditions: Substrate, Pd(OAc)$_2$, Ligand (2 equiv. per Pd), Ag$_2$CO$_3$ (0.5 equiv.) and K$_2$CO$_3$ (2 equiv.) are dissolved in solvent (0.2M) and heated (DMA – 130 °C;Dioxane – 100 °C;THF – 70 °C) for 8-16 h. [b] Isolated Yields. [c] 5 equivalents HMPA added.

## *Mechanistic Investigations*

Having achieved our goal of developing a generally applicable catalyst for intramolecular direct arylation, we turned our attention to the mechanism of the reaction. To probe for the presence of an electronic bias, competition experiments were devised to ascertain if the catalyst would selectively react with an electron-rich or electron-poor aromatic ring. Two amide substrates were synthesized. With amide **2.35**, reaction can occur at the "activated" ring bearing a methoxy substituent or at the unactivated ring. With amide **2.36**, the catalyst can select for reaction with the unactivated ring or with the nitro substituted "deactivated" ring. With both substrates, slight selectivity is obtained for reaction at the more electron-rich ring (Scheme 2.6).[78]

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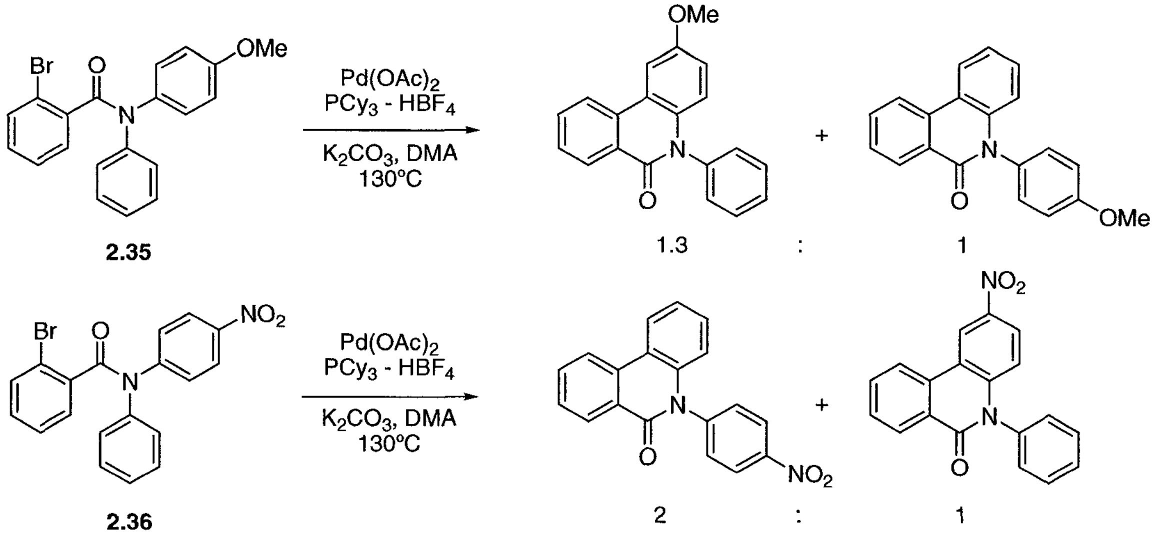
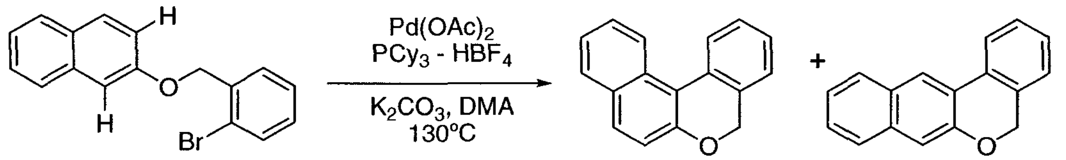
[78] High temperature $^1$H NMR experiments confirmed the absence of any conformational restriction.



**Scheme 2.6** – Electronic Preference in Direct Arylation

Reaction of naphthyl substrate **2.37** is also informative. In this case, two regioisomeric products are possible. It is well documented that electrophilic additions to naphthalenes occur preferentially at the 1-position.[79] When **2.37** is reacted under the standard arylation conditions, a 1.3:1 ratio of **2.38**:**2.39** is obtained (Equation 2.6). While it is important not to over interpret the reaction preference when such low selectivities are obtained, the ratio observed is informative since it is not characteristic of electrophilic aromatic substitutions on this substrate class.



(2.6)

**2.37**

**2.38**/**2.39** = 1.3:1

The presence of kinetic isotope effects can provide valuable information about the rate determining steps in complex chemical processes. With the first generation catalyst we observed a primary intramolecular kinetic isotope effect (KIE) of 3.5.[35] A larger primary

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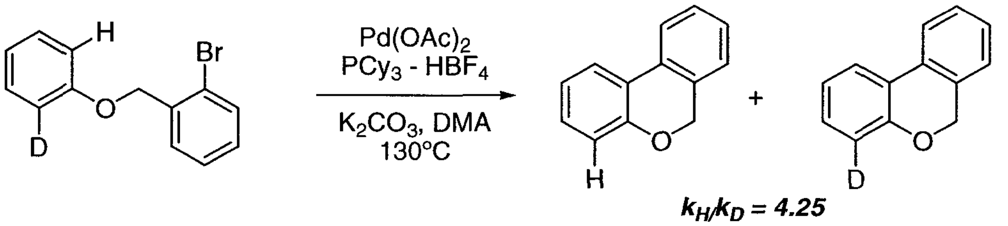
[79] For a discussion on the preferred site of attack of many ring systems, see: de la Mare, P.B.D.; Ridd, J.H. *Aromatic Substitution Nitration and Halogenation*; Academic Press: NY, **1959**, p.169

kinetic isotope effect of 4.25 is observed with the third generation catalyst (Equation 2.7). This value is not affected by the presence of silver additives.



(2.7)

Several mechanistic scenarios have been proposed for direct arylation reactions. The pathway with the strongest experimental support is electrophilic palladation.[80,81] Oxidative C-H insertion to palladium (IV) has also been proposed[82] as has a carbo-palladation (Heck type) pathway requiring a formal anti β-hydride elimination.[83] Carbene intermediates have been demonstrated with other metals such as rhodium,[84] but analogous reactivity in palladium arylations has not appeared.

While it cannot be ruled out, the carbo-palladation or Heck-type route is unlikely, given the high barrier for dearomatization and anti β-hydridd elminiation required. Additionally, it is reasonable that the mechanism of direct arylation should parallel that involved in the preparation of palladacycles.[85] In these cases, there exists ample evidence pointing to an electrophilic metallation or C-H oxidative insertion. The oxidative C-H insertion pathway fits with our experimental observations, but recently reported computational studies indicate that C-H insertion is higher in energy and less favorable than an alternative σ-bond methathesis pathway that does not require the intermediacy of a

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[80] With simple arenes: (a) Martin-Matute, B.; Matea, C.; Cardenas, D.J.; Echavarren, A.M.; *Chem. Eur. J.* **2001**, *7*, 234; (b) Echavarren, A.M.; Gòmez-Lor, B.; Gonzàlez, J.J.; de Fruto, O.; *Synlett* **2003**, *5*, 585; (c) Gonzalez, J.J.; Garcia, N.; Gomez-Lor, B. ; Echavarren, A.M. *J. Org. Chem.* **1997**, *62*, 1286. (d) Hennessy, E. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003** *125*, 12084 (e) Boele, M.D.K.; van Strijdonck, G.P.F.; de Vries, A.H.M.; Kamer, P.C.J.; de Vries, J.G.; van Leeuwen, P.W.N.M.; *J. Am. Chem. Soc.*, **2002**, *124*, 1586. (f) Shue, R.S.; *J. Am. Chem. Soc.*, **1971**, *93*, 7116. (g) Parshall, G.W.; *Acc. Chem. Res.* **1970**, *3*, 139;

[81] With heteroaromatics: (a) Lane, B.S.; Brown, M.A.; Sames, D.; *J. Am. Chem. Soc.* **2005**, *127*, 8050; (b) Park, C.-H.; Ryabova, V.; Seregin, I. V.; Sromek, A. W.; Gevorgyan, V. *Org. Lett.* **2004**, *6*, 1159. ; (c) Trauner, D.; Hughes, C.C.; *Angew. Chem. Int. Ed.* **2002**, *41*,1569; (d) Glover, B.; Harvey, K.A.; Liu, B.; Sharp, M.J.; Tymoschenko, M.F.; *Org. Lett.* **2003**, *5*, 301;

[82] Campo, M. A.; Huang, Q.; Yao, T.; Tian, Q.; Larock, R. C. *J. Am. Chem. Soc.* **2003**, *125*, 11506.

[83] This pathway has been proposed as a possibility before: (a) Toyata, M.; Ilangovan, A.; Okamoto, R.; Masaki, T.; Arakawa, M.; Ihara, M.; *Org. Lett.* **2002**, *4*, 4293; reference 80(d).; Proposed but dimissed: ref 81(c)

[84] Tan. K.L.; Bergman, R.G.; Ellman, J.A. *J. Am. Chem. Soc.* **2002**, *124*, 3203.

[85] For a review, see: Ryabox, A.D.; *Chem. Rev.* **1990**, *90*, 403.

palladium(IV) species.[86] Thus, while a C-H insertion pathway cannot be definitively ruled out, evidence does not favor it.

On the other hand, concerted aromatic substitution pathways can rationalize the current experimental observations and have significant mechanistic support in the direct arylation of other classes of arenes. Many electrophilic aromatic substitution reactions do not exhibit KIEs since deprotonation is fast relative to the formation of the arenium σ-complex.[87] However, this is not always the case, as exemplified by electrophilic mercurations for which KIEs of up to six have been documented.[88] The presence of a primary kinetic isotope effect in palladium-catalyzed direct arylations[89] can be rationalized by considering the relative rates for the formation of $\pi,\eta^2$-**2.41** and/or $\pi,\eta^1$-**2.41**[90] from the palladium(II) arene intermediate **2.40** ($k_1$ and $k_{-1}$) and deprotonation ($k_2$). The presence of a KIE implies that $k_1$ and $k_{-1}$ are fast and reversible compared to $k_2$. As a consequence, [π-**2.41**]$k_2$ becomes kinetically significant and would result in the observed KIE (Scheme 2.7). A concerted metallation deprotonation pathway is consistent with our experimental observations. Either an $S_E3$-type process, where an external base deprotonates the arene as the palladium-carbon bond is being formed,[87] or a σ-bond metathesis mechanism, where a ligand on the palladium metal serves as the base, could be occurring.[80(d), 91]

In this mechanism, the electronic properties of the arene ring will influence $k_1$, $k_{-1}$ and $k_2$. Our competition experiments (Scheme 2.6) as well as reactions with 2-naphthol derived substrates (Equation 2.6) reveal a small but reproducible bias for functionalization of the more electron-rich arene (or site). These results are in accord with the qualitative kinetics reported by Echavarren who found no strong electronic bias in direct arylation.[80(a)] The absence of a strong electronic bias may point to a lack of cationic arenium character at the rate determining step, which may be anticipated in a concerted palladium-carbon/carbon-hydrogen bond formation/cleavage process.

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[86] Mota, A.J.; Dedieu, A.; Bour, C.; Suffert, J.; *J. Am. Chem. Soc.* **2005**, *127*, 7171

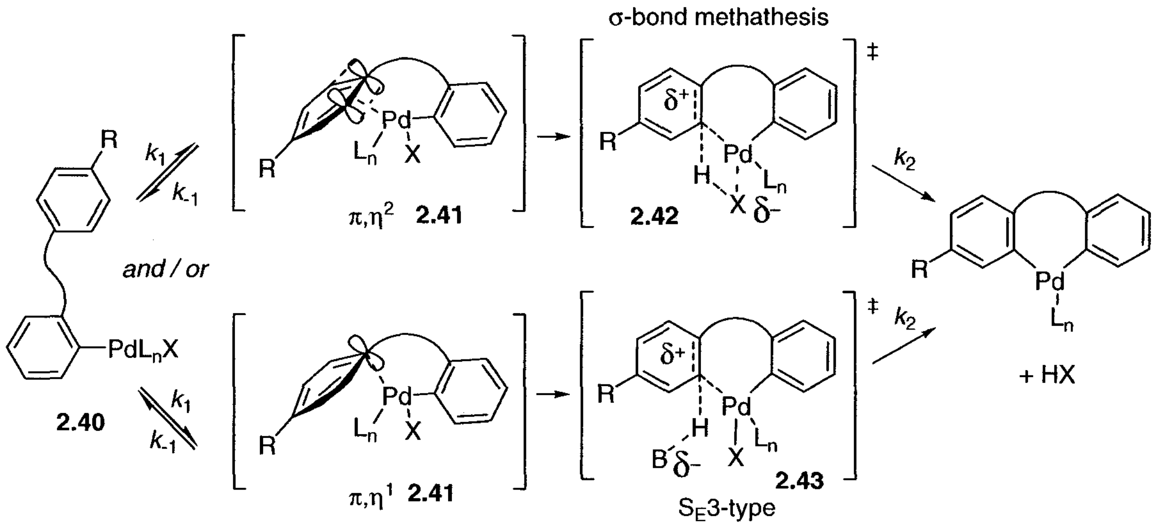
[87] Zollinger, H. *Adv.* Phys. *Org. Chem.* **1964**, *2*, 162-200.

[88] Kresge, A.J.; Brennan, J.F.; *J. Org. Chem.*, **1967**, *32*, 752.

[89] (a) reference 80(e); (b) Shue, R.S.; *J.* Am. *Chem. Soc.*, **1971**, *93*, 7116. (c) ref. 27(d)

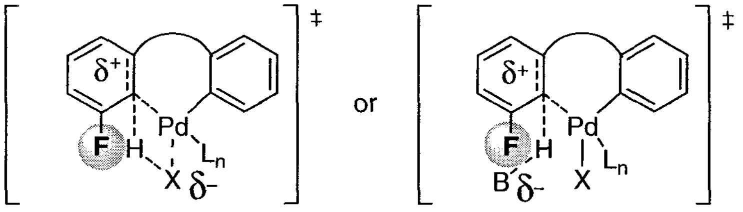
[90] (a) Càmpora, J.; Gutiérrez-Puebla, E.; Lòpez, J. A.; Monge, A.; Palma, P.; del Rý'o, D.; Carmona, E. *Angew. Chem., Int. Ed.* **2001**, *40*, 3641. (b) Càmpora, J.; Lòpez, J. A.; Palma, P.; Valerga, P.; Spillner, E.; Carmona, E. *Angew. Chem., Int. Ed.* **1999**, *38*, 147.

[91] This type of mechanistic dichotomy has been proposed before with Hg[88] and Rh: Wang, X.; Lane, B. S.; Sames. D.; *J. Am. Chem. Soc.* **2005**, *127*, 4996.



**Scheme 2.7** – Proposed Concerted Metallation/Deprotonation Pathways for Direct Arylation

In the context of our previous experimental observations on regioselectivity of the reaction, the current mechanistic model might be affected by acidity of the C-H bond at the position of arylation. Hydorgens *ortho* to fluorine atoms are known to be more acidic, the observed regioselectivity was our first indication that C-H bond acidity would be a cruicial factor in reaction development (Scheme 2.8).



**Scheme 2.8** – Effect of Fluorine in Concerted Metallation/Deprotonation Pathways

Other research groups have also been investigating the mechanism of direct arylation. During the submission of our manuscript,[63] a paper appeared suggesting a similar type of process for cyclometallation reactions with palladium acetate.[92] Following the appearance of our manuscript, an elegant study on intramolecular direct arylation using

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[92] Davies, D. L.; Donald, S. M. A.; Macgregor, S. A.; *J. Am. Chem. Soc.* **2005**, *127*, 13754

our first generation catalyst was reported by Echavarren and Maseras.[93] Their study matched competition experiments similar to those performed in Scheme 2.6 with DFT analysis. Of note, their competition experiments showed an important bias for fluorinated arenes which is in accord with our experiental observation fluorinated aromatics. They also identified the mechanism as occurring via concerted metallation/deprotonation, more specifically they propose an internal deprotonation by a carbonate anion (**2.42** with X = $CO_3H^-$).

## *Novel Intermolecular Direct Arylation Processes*[94]

In addition to improving the use of intramolecular direct arylation reactions with aryl chlorides, bromides and iodides, these studies were conducted to gain a better understanding of the catalyst, substrate and reaction parameters necessary to achieve high levels of reactivity. We hoped that knowledge garnered from these efforts would ultimately lead to the establishment of new *intermolecular* reactions with previously unknown substrate classes, thus opening new doors in the direct arylation methodology. Progress in this area is being made as illustrated by the first examples of intermolecular direct arylation of benzodioxole with aryl bromides and chlorides (*vide infra*). To achieve the substrate-catalyst interactions necessary to induce intermolecular direct arylation, researchers have previously employed very basic directing groups in the absence of which no reaction occurs.[95] The examples below constitute the first instance of ethers on simple arenes in this type of reactions. From a synthetic perspective, these reactions generate products that are regio-complementary to those readily accessible from commercially available aryl halides and organometallics with traditional cross coupling techniques.[96] Importantly, these results lay the foundation for the establishment of direct

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[93] (a) Garcia-Cuadrado, D.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006**; *128,* 1066; (b) Garcia-Cuadrado, D.; de Mendoza, P.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M.; *J. Am. Chem. Soc.*; **2007**, *129*, 6880.

[94] Part of this section was published as an article, see reference 63

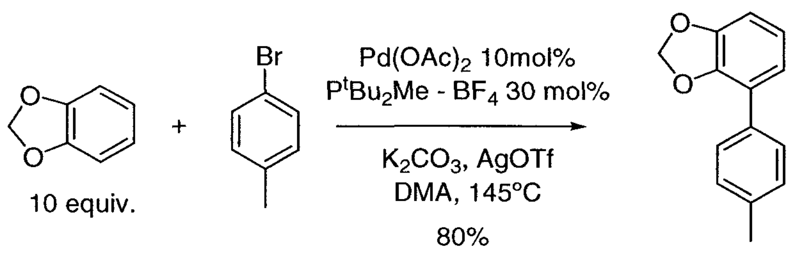
[95] See Chapter 1, section 1.3 – Directed Reactions

[96] For recent the use of 1,3-benzodioxl-5-yl boronic acid in Suzuki coupling, see: (a) Gurjar, M. K.; Cherian, J.; Ramana, C. V.; *Org. Lett.* **2004**, *6*, 317. (b) Savarin, C.; Liebeskind, L. S.; *Org. Lett.* **2004**, *3*, 2149. Cross-coupling reactions with 4-bromo-1,3-benzodioxle[(c)] or 4-(1,3-benzodioxolyl)-boronic acid[(d)] are exceedingly rare. See: (c) Thibonnet, J.; Abarbri, M.; Parrain, J.-L.; Duchêne, A.; *Tetrahedron* **2003**, *59*, 4433; (d) Wu, T.Y.H.; Schultz, P.G.; *Org. Lett.* **2002**, *4*, 4033

arylation reactions with significantly improved scope; a focus of continued study in our group.

## *Benzodioxole*

To validate the intermolecular reactivity of benzodioxole, reactions were performed with 10 mol % $Pd(OAc)_2$, 10-30 mol % of either $P^tBu_2Me{\cdot}HBF_4$ or $PCy_3{\cdot}HBF_4$, one equivalent AgOTf, and two equivalents $K_2CO_3$ in DMA at 145 °C. While $Ag_2CO_3$ performed well in intramolecular reactions, its use led to more homocoupling of aryl bromide in these intermolecular processes compared to AgOTf. Initial screens were executed with 4-bromotoluene and ten equivalents of benzodioxole. Reaction concentrations, ranging from 0.1 to 0.8 M, were also evaluated. From this screening of reaction conditions, a 3:1 ligand to palladium ratio was deemed optimal with the $P^tBu_2Me{\cdot}HBF_4$ pre-ligand performing slightly better than the tricyclohexylphosphine salt. Optimal results are also achieved under very concentrated conditions. Reactions are typically performed at 0.8 M. Under these conditions, we were gratified to find that an 80% isolated yield of **2.44** can be obtained as exclusively one regioisomer (Equation 2.8).

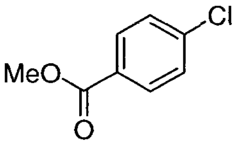
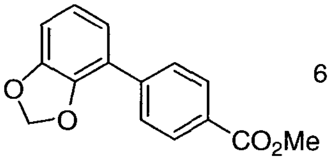
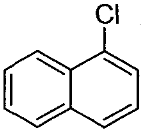
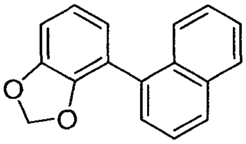
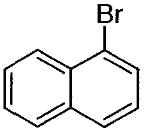
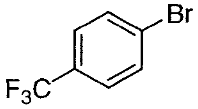
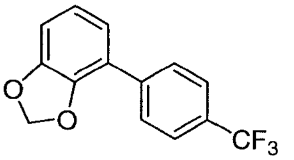
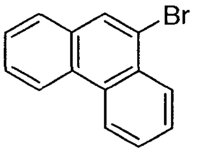
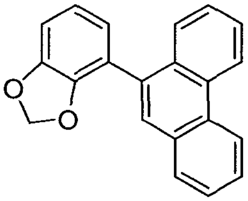
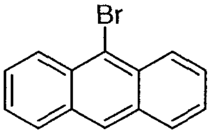
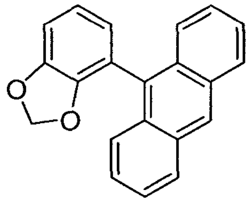


**2.44**

(2.8)

These reaction conditions were used to investigate the intermolecular direct arylation of benzodioxole (Table 2.11) with a range of aryl chlorides and bromides. Both activated and non-activated aryl chlorides can be employed (Entries 1 and 2). More sterically encumbered aryl bromides can also be employed in good yield as illustrated by reaction with bromoanthracene (Entry 6). Interestingly, no cross-coupled direct arylation product is obtained when these reactions are run with iodobenzene. In this case, the major product as determined by GC-MS analysis of the crude reaction mixture is biphenyl arising from homocoupling of the iodobenzene. This result underlines our findings that aryl iodides can frequently exhibit inferior reactivity in direct arylation reactions with simple arenes and thus should not be used exclusively as model substrates in the development of new direct arylation processes.

**Table 2.11** – Direct Arylation of 1,3-Benzodioxole[a]

| Entry | Aryl Halide | Product | Yield[b] |
|---|---|---|---|
| 1 |  |  | 62 |
| 2 |  |  | 78 |
| 3 |  | | 83 |
| 4 |  |  | 86 |
| 5 |  |  | 81 |
| 6 |  |  | 80 |

[a]Conditions: Aryl halide, $Pd(OAc)_2$ (10 mol %), Ligand (30 mol %), AgOTf (1 equiv.) and $K_2CO_3$ (2 equiv.) are dissolved in DMA (0.8M) and heated to145 °C for 8-16 h. [b]Isolated yield.

Regiochemistry can also be indicative of the mechanism of direct arylation in this case. Electrophilic aromatic substitutions typically occur at the 5-position with benzodioxole. Reaction at the 4-position implies either that binding of the neighbouring oxygen plays an important role in regiochemistry or that another mechanistic manifold is operating under these conditions. We hypothesized that this intermolecular direct arylation reaction may proceed via a concerted metallation/deprotonation. DFT analysis of the direct arylation step was undertaken to verify this hypothesis.[97]

Three stationary points were identified including the starting η-2 complex **2.45** as well as the two final complexes **2.46** and **2.47**. The reaction was judged to be energetically equivalent. We then examined the relative energies of transition states **2.48** and **2.49**. As can be seen from figure 2.3, the DFT model for concerted metallation/deprotonation accurately predicts the observed regiochemistry as **2.49** is ~2.8 kcal/mol lower in energy. It is also important to note that no binding effect of the oxygen is observed in any of the ground or transition state structure suggesting that this is a non-directed intermolecular direct arylation reaction.

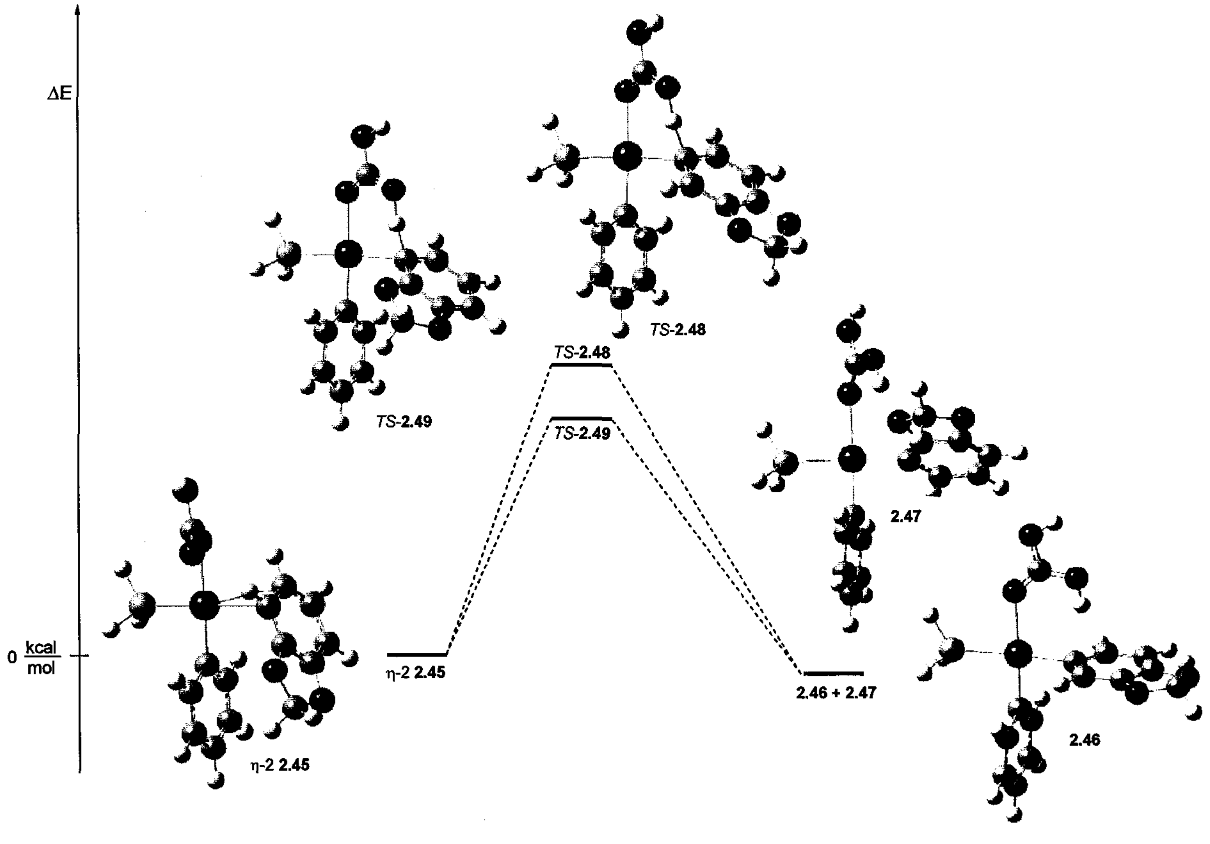


**Figure 2.3** – Relative Energies Calculated for Concerted Metallation/Deprotonation of 1,3-Benzodioxole

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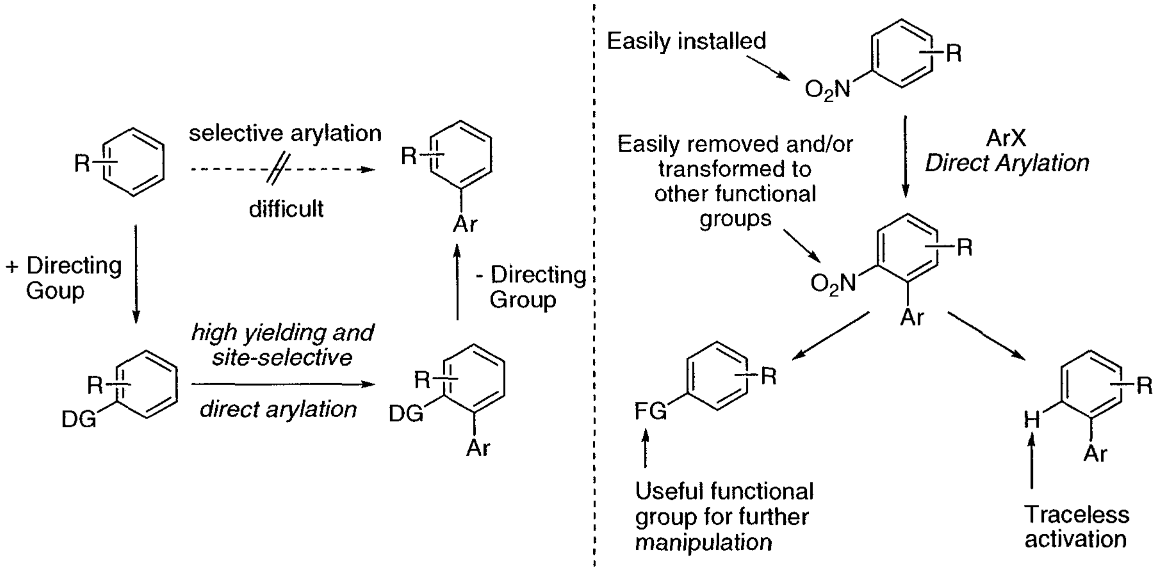
[97] B3LYP density-functional theory calculations were performed with the Jaguar 6.0 package with the LACV3P** basis set and pseudopotential combination of Jaguar. Please see computational details section of the supporting information (Chapter 7).

## Nitrobenzene

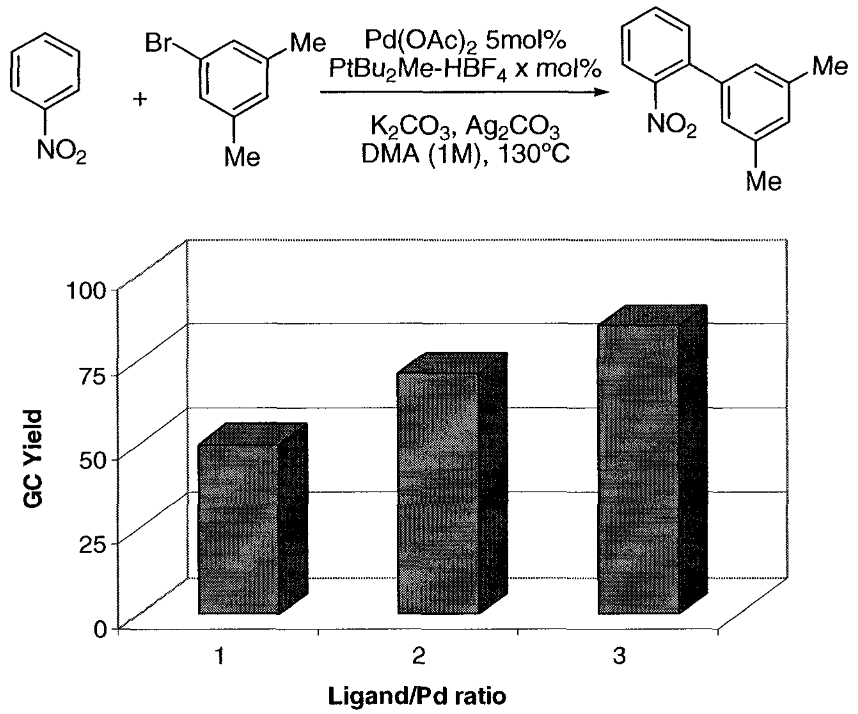
Bearing in mind our goal of devising a versatile and broadly applicable direct arylation reaction of simple arenes, we focused our attention on reactions using an adaptable directing group which could then be easily removed or transformed into other functionalities. The nitro functional group is ideal for such a process since (1) nitroarenes are easily accessible due to their low cost and ease of synthesis, (2) the nitro group could act as a directing group, facilitating approach of the metal centre in close proximity of the reacting site, (3) the strong electron withdrawing nature of the nitro group would facilitate C-H bond functionalization and (4) the wide range of known methods for deriving this functional group allows for its removal or for further transformations of the product obatined. The following section will disclose preliminary conditions for the direct arylation of nitroarenes which allow for the facile regioselective synthesis of *ortho*-nitrobiaryls (Scheme 2.9).



**Scheme 2.9** – Direct Arylation of Nitroarenes

In a preliminary investigation for the direct arylation of nitrobenzene with bromobenzene, we surveyed the use of the conditions developed for the reaction of 1,3-benzodioxole. To our delight, reaction at the 2-position is favoured in a 7:1 ratio. Di-*t*-butylmethylphosphine (used as its air-stable tetrafluoroborate salt) proved to be an effective lead catalyst while the use of silver carbonate proved crucial to achieve high yields at this time in reaction development. However, it is possible to use only 0.5

equivalents of $Ag_2CO_3$ when used in conjunction with less expensive $K_2CO_3$. While initial scans were performed with 20 equivalents of nitrobenzene, only 5-10 equivalents are necessary to obtain reproducibly good yields. To reduce the catalyst loading, a more extensive optimization of the reaction conditions was undertaken at 5 mol % Pd. First, ligand equivalents were examined. As with 1,3-benzodioxole, three equivalents of phosphine per palladium proved superior, resulting in better yield and selectivity for the 2-position (Scheme 2.10).



**Scheme 2.10** – Ligand/Pd ratio effect on Direct Arylation of Nitroarenes

The use of higher concentration was also deemed beneficial as was the case in previous studies (Scheme 2.11). Reaction optimization work is ongoing and with be reported in due course.[98]

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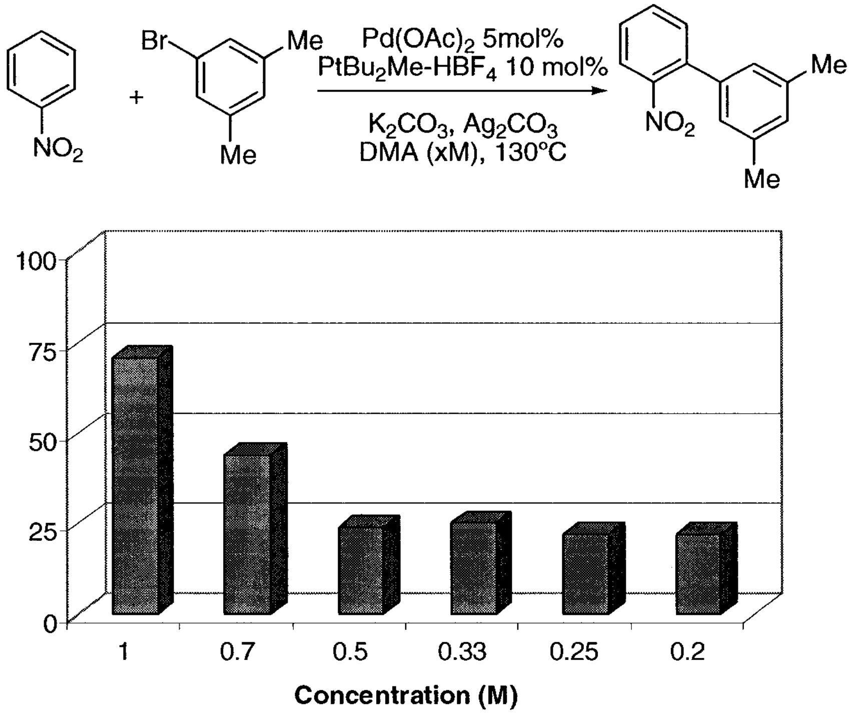
[98] This work was passed on to another graduate student; Laurence Caron, January 2007



**Scheme 2.11** – Concentration effects on Direct Arylation of Nitroarenes

The adaptability of the nitro function reveals the significance of this transformation. Scheme 2.12 demonstrates functional groups and structures that can be obtained from *ortho*-nitrobiphenyls. This method would allow for short and effective synthesis of carbazoles[99] and phenanthridinones[100] from the corresponding nitroarene and aryl halide. The nitro group can also be a precursor to anilines[101] which can in turn serve as versatile building blocks, particularly via diazonium intermediates. This reaction manifold thus allows for complete removal of the nitro group[102] or further transformations via Sandmeyer,[103] Heck[104] and Suzuki[105] couplings of the corresponding diazonium salts. Bartoli reactions[106] of these *ortho*-nitrobiaryls yield the corresponding aryl indoles which can be difficult to synthesize via other means.

---

[99] Freeman, A. W.; Urvoy, M.; Criswell, M. E.; *J. Org. Chem.* **2005**, *70*, 5014. For indole synthesis via Bartoli reaction, see: Mudadu, M. S.; Singh, A.; Thummel, R. P.; *J. Org. Chem.* **2006**, *71*, 7615

[100] (a) Pizzotti, M.; Cenini, S.; Quici, S.; Tollari, S.; *J. Chem. Soc. Perkin Trans. 2*, **1994**, *4*, 913. (b) Banwell, M. G. ; Lupton, D. W. ; Ma, X. ; Renner, J. ; Sydnes, M. O. ; *Org. Lett.* **2004**, *6*, 2741

[101] Mendenhall, G. D.; Smith, P. A. S.; *Org. Syn.* **1966**, *46*, 85

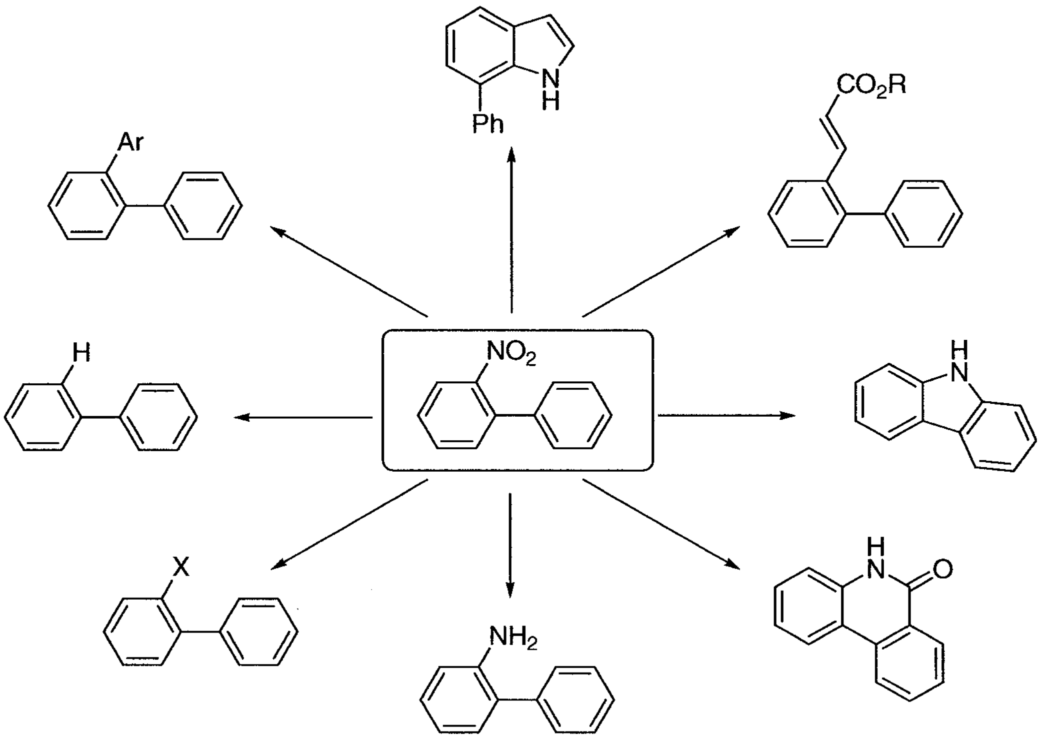
[102] Adams, R.; Kornblum, N.; *J. Am. Chem. Soc.* **1941**, *63*, 188

[103] Doyle, M. P.; Siegfried, B.; Dellaria Jr. J. F.; *J. Org. Chem.* **1977**, *42*, 2426

[104] Andrus, M. B. ; Song, C. ; Zhang, J. ; *Org. Lett.* **2002**, *4*, 2079

[105] Andrus, M. B. ; Song, C. ; *Org. Lett.* **2001**, *3*, 3761

[106] Knepper, K.; Brase, S. *Org. Lett.* **2003**, *5*, 2829



**Scheme 2.12** - Versatility of Nitro Functional Groups in Organic Synthesis

Given the versatility of the nitro function in organic synthesis, this method would be a highly desirable direct arylation reaction. Once optimized, this method should find use in the preparation of important building blocks for organic synthesis and medicinal chemistry.

# 3

# Heterocycles in Direct Arylation

## *Introduction*[107]

Since the organometallic compound typically reacts as a nucleophile in cross-coupling reactions, one would assume that more electron-rich substituted nucleophilic arenes will exhibit enhanced reactivity. In this context, π-electron-rich heteroaromatics have featured prominently in these transformations.[108] While the heteroatoms in the aromatic ring may also be acting as directing groups, the benefit of enhanced nucleophilicity has been clearly demonstrated. It is commonly accepted that π-electron rich substrates react via an electrophilic palladation in direct arylation reactions and that the reactions are facilitated by the highly nucleophilic nature of these arenes.[109] This section will review these processes with special emphasis on recent advances.

---

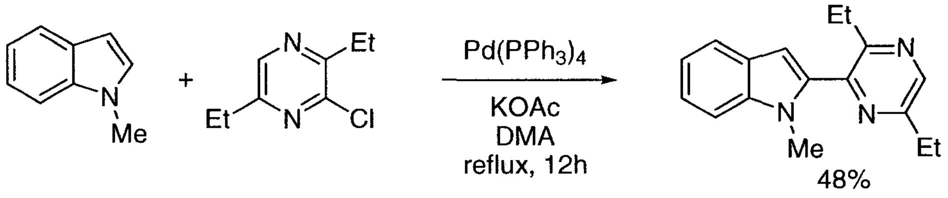
[107] Parts of this chapter were published in the form of reviews: (a) Campeau, L.-C.; Fagnou, K.; *Chem. Commun.* **2006**, *12*, 1253 (b) Campeau, L.-C.; Stuart, D. R.; Fagnou, K.; *Aldrichimica Acta*, **2007**, *40*, 35.

[108] Miura, M.; Nomura, M. *Top. Curr. Chem.*, **2002**, *219*, 211.

[109] Lane, B. S.; Brown, M. A.; Sames, D.; *J. Am. Chem. Soc.* **2005**, *127*, 8050 and references therein

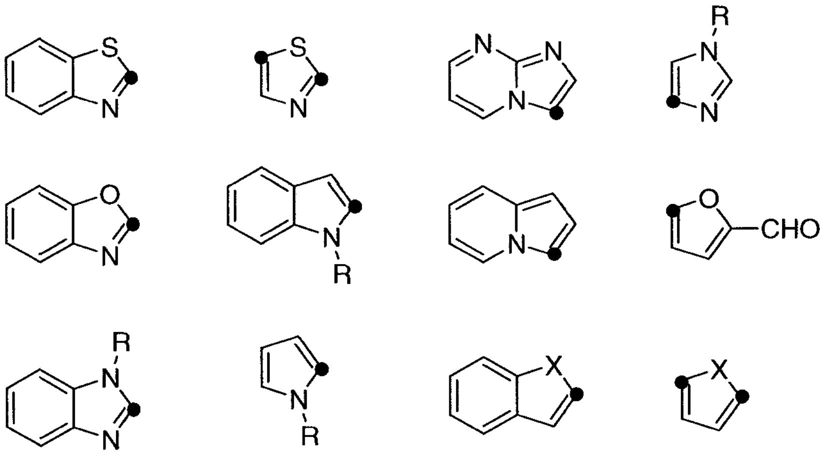
## Reactions of π-Electron-Rich Heterocycles

One of the first examples of heterocycles used in direct arylation was reported by Ohta and co-workers in 1989.[110] *N*-Alkylindole could be arylated at the 2- or 3-positions depending on the nature of the *N*-substituent (Equation 3.1).



(3.1)

This result set the stage for numerous examples of such coupling reactions using other aryl halides and many arylation reactions of heteroaromatic substrates have since appeared.[111] Figure 3.1 shows a variety of heteroaromatic compounds that have been shown to undergo direct arylation.



X = S or O

● denotes the position that is arylated

**Figure 3.1** – Examples of Heteroaromatic Compounds Used in Direct Arylation

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[110] Akita, Y.; Itagaki, Y.; Takizawa, S. Ohta, A.; *Chem. Pharm. Bull.* **1989**, *37*, 1477

[111] For a recent report on benzothiazole and benzoxazole, see: Alagille, D.; Baldwin, R. M.; Tamagnan, G. D.; *Tetrahedron Lett.* **2005**, *46*, 1349; For recent reports on azoles, see: (a) Bellina, F.; Cauteruccio, S.; Mannina, L.; Rossi, R.; Viel, S.; *Eur. J. Org. Chem.* **2006**, 693; (b) Bellina, F.; Cauteruccio, S.; Rossi, R.; *Eur. J. Org. Chem.* **2006**, 1379; For recent reports on oxazole, see: Hoarau, C.; Du Fou de Kerdaniel, A.; Bracq, N.; Grandclaudon, P.; Couture, A.; Marsais, F. ; *Tetrahedron Lett.* **2005**, *46*, 8573 ; For recent reports on thiophene and benzothiophene, see: (a) Kobayashi, K. Sugie, A. Takahashi, M.; Masui, K. ; Mori, A. ; *Org. Lett.* **2005**, *7*, 5083 ; (b) David, E.; Perrin, J.; Pellet-Rostaing, S.; Fournier dit Chabert, J.; Lemaire, M. ; *J. Org. Chem.* **2005**, *70*, 3569.

In recent years, researchers have sought to develop novel strategies that might allow for milder reaction conditions as well as broaden the substrate scope. In 2005, Sames and co-workers reported the development of C-2 selective indole arylation reactions with palladium and rhodium catalysts. Of note, the rhodium catalyzed reactions are compatible with unprotected indoles and aryl iodides to afford moderate to good yields of the C-2 aryl indoles.[112] Selected examples and the proposed catalytic cycle are outlined in Scheme 3.1. The rhodium catalyst first inserts the aryl iodide to afford a rhodium (III) intermediate. This species could be isolated and was found to be a competent catalyst for the reactions, further validating this as the first step in the catalytic cycle. This arylrhodium (III) intermediate can then bind and metallate the indole to afford the diarylrhodium (III) species which can reductively eliminate the product and regenerate the rhodium (I) catalyst. Use of cesium pivalate as the base is key to obtaining high yields. While no insight into the intimate details of the indole metallation step could be provided, the authors postulated that the pivlalate may be serving as an intramolecular base.

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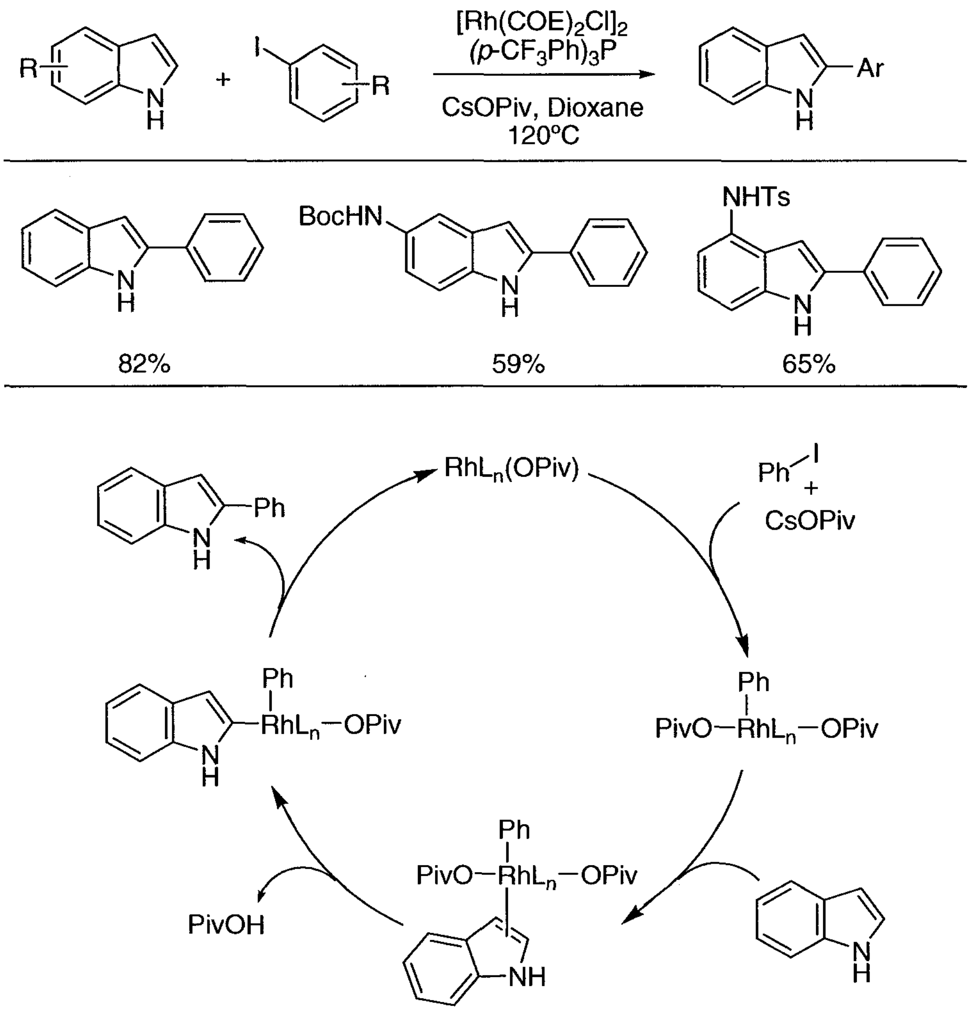
[112] Wang, X.; Lane, B. S.; Sames. D.; *J. Am. Chem. Soc.* **2005**, *127*, 4996



**Scheme 3.1** - C-2 Selective Rhodium-Catalyzed Arylation of Indoles

In 2005, Sames also reported further studies dealing with palladium-catalyzed indole arylation reactions enabling a wide range of *N*-substituted indole substrates to be employed.[109,113] Most of the transformations are typically selective for reaction at C-2, but a remarkable base effect was observed with free *N*-H indoles. The proper selection of the base counterion allows for the selective formation of either the C-2 or the C-3 arylation isomer (Equations 3.2 and 3.3).

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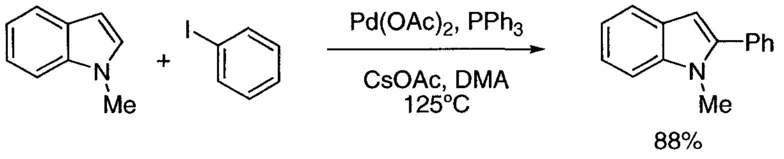
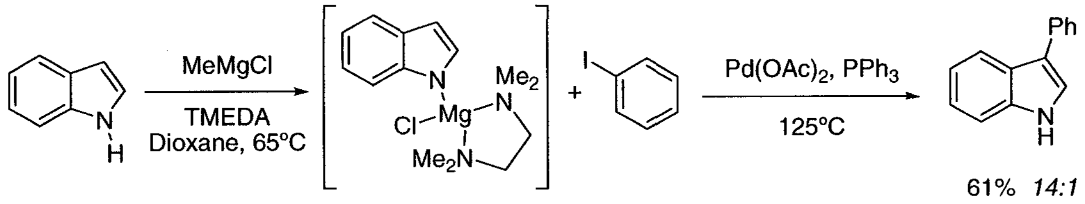
[113] Touré, B. B.; Lane, B. S.; Sames, D.; *Org. Lett.* **2006**, *8*, 1979

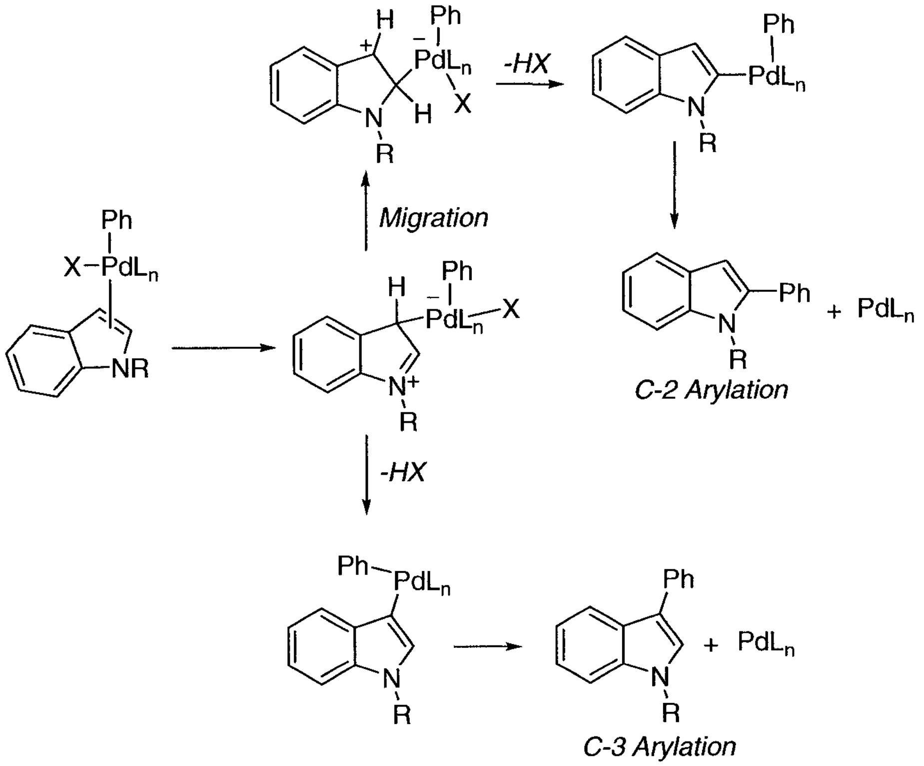


(3.2)



(3.3)

The authors postulate that the selectivity arises from a migration of palladium during the metallation event (Scheme 3.2). Kinetic data and isotope effects support an electrophilic palladation at C-3 followed by deprotonation to give the C-3 isomer. Conversely, migration of the aryl palladium moiety to C-2 may occur prior to deprotonation, yielding the C-2 isomer.



**Scheme 3.2** - Mechanistic Rationale for Regioselectivity in the Arylation of Indoles

Sanford and co-workers have established an alternative strategy for the site-selective arylation of indoles at the C-2 position.[114] Instead of exploiting the Pd(0)/Pd(II) catalytic manifold, they developed reactions functioning under a Pd(II)/Pd(IV) redox couple. In these reactions, the initial metallation of an indole by a palladium (II) salt is followed by an oxidation with a diaryliodonium salt to generate a diarylpalladium (IV) intermediate. This intermediate can reductively eliminate the final product and regenerate the catalytically active palladium(II) species (see, Scheme 1.5). Unlike previous reports which commonly require heating to very elevated temperatures, these reactions can be carried out under remarkably mild conditions in acetic acid at 25 °C (Scheme 3.3). A number of substituted indoles were shown to participate in the reaction. When the C-2 position is blocked, reaction at the C-3 position occurs in lower yields. It is also possible to perform the reaction with a number of functionalized diaryl iodonium salts.

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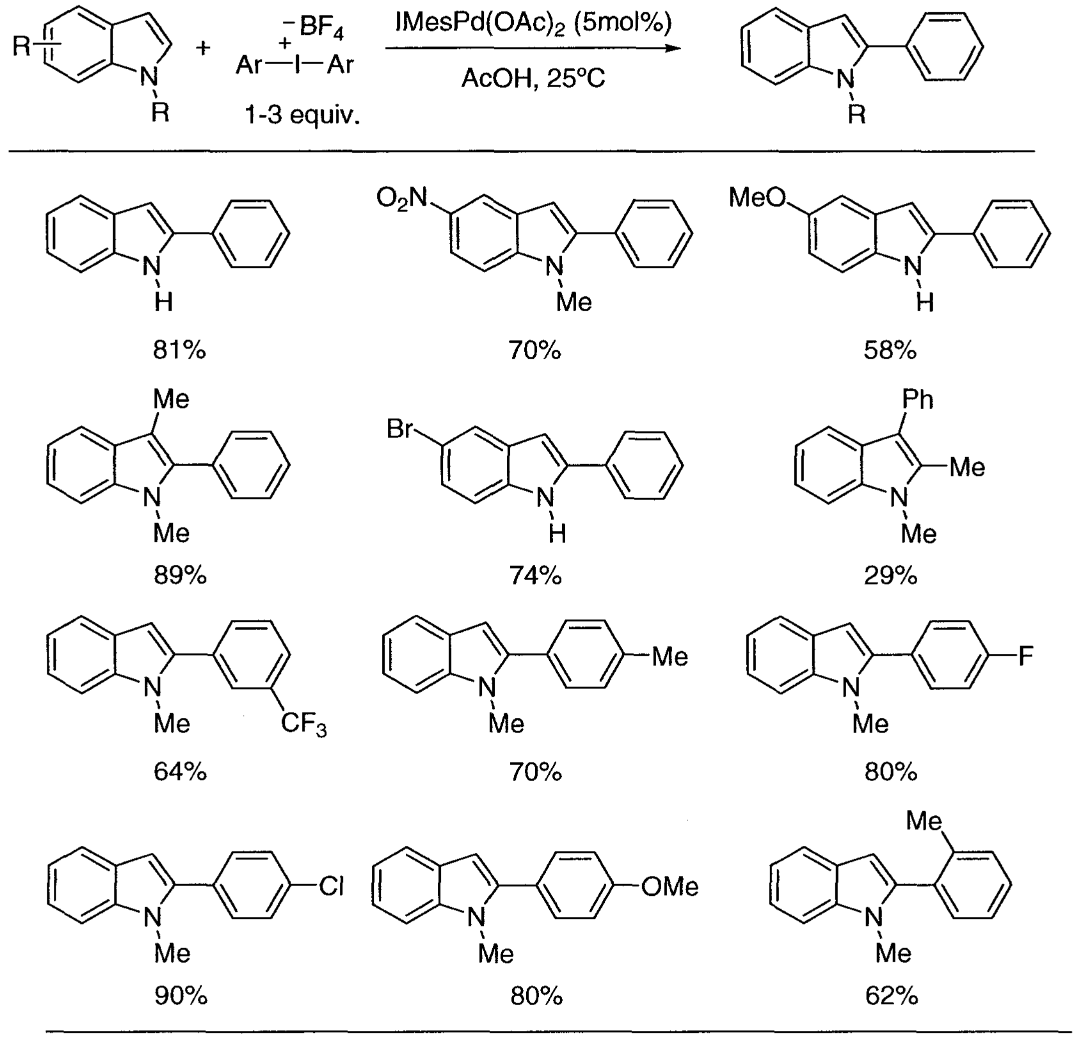
[114] Deprez, N. R.; Kalyani, D.; Krause, A.; Sanford, M. S.; *J. Am. Chem. Soc.* **2006**, *128*, 4972



**Scheme 3.3** - Scope of the Direct Arylation of Indoles with Diaryliodonium Salts

Another class of heterocycles that have been studied in direct arylation reactions is the azoles. Bergman, Ellman and co-workers found that rhodium can form carbene complexes of azoles.[115] This reactivity profile has provided a valuable mechanistic entry point for the development of rhodium catalyzed direct arylation reactions. The rhodium carbene intermediates (**3.1**) have been isolated and are postulated to be crucial to the reactivity (Scheme 3.4). Following the formation of the rhodium carbene, oxidative addition of the aryl iodide leads to the formation of a diarylrhodium (III) species which can undergo reductive elimination to give the corresponding aryl azole.

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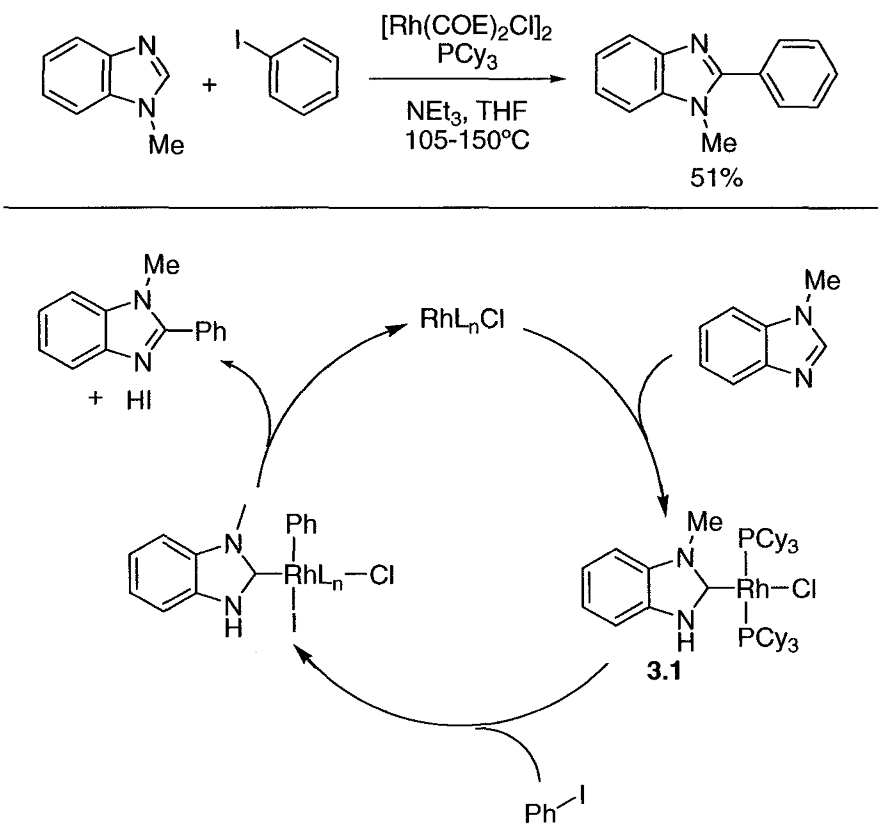
[115] Lewis, J. C.; Wiedemann, S. H.; Bergman, R. G.; Ellman, J. A.; *Org. Lett.* **2004**, *6*, 35



**Scheme 3.4** - Proposed Catalytic Cycle for the Rhodium Catalyzed Arylation of Azoles

In 2006, Bergman and Ellman also described studies leading to the development of a new catalytic system for the arylation of azoles.[116] The new reaction conditions allow for the use of aryl bromides which have been scarcely employed in azole direct arylation. Under microwave-heating at 250 °C, a number of different azole substrates can be used with various aryl bromides to give the aryl azoles in good to excellent yields (Scheme 3.5).

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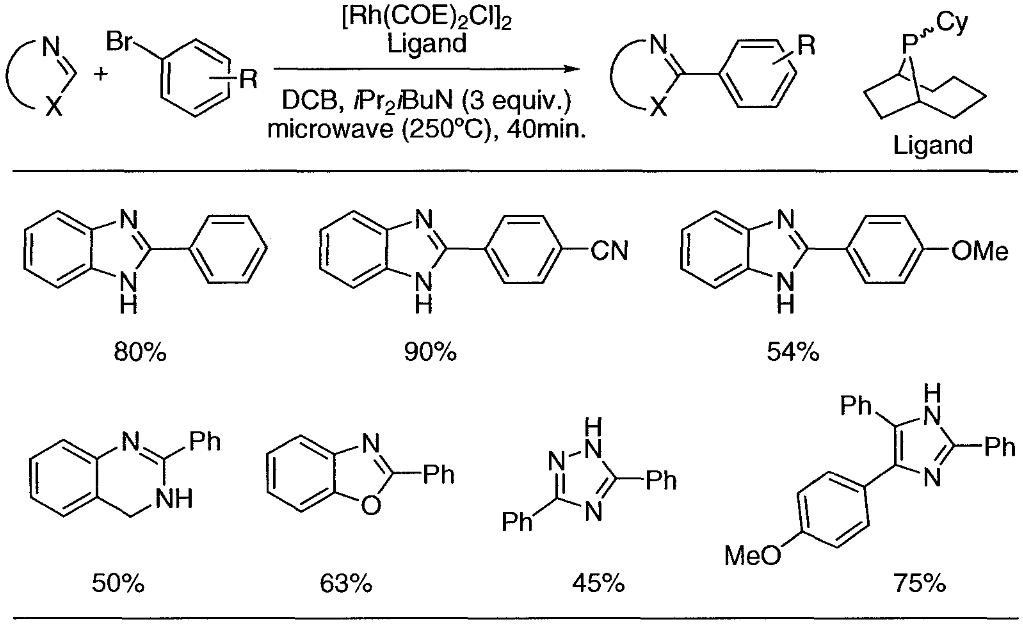
[116] Lewis, J. C.; Wu, J.Y.; Bergman, R. G.; Ellman, J. A.; *Angew. Chem. Int. Ed.* **2006**, *45*, 1589



**Scheme 3.5** - Scope of the Rhodium Catalyzed Direct Arylation of Azoles with Aryl Bromides

Another rhodium catalyzed transformation of π-rich heterocycles was reported by Itami and co-workers in 2006.[117] An electron-deficient rhodium complex bearing strong π-accepting perfluoroalkylphosphite ligands was employed, which is postulated to favor the electrophilic rhodation of the electron-rich heterocycle. Aryl iodides participate in the reaction with various heterocycles such as thiophenes, furans, pyrroles and indoles (Scheme 3.6).

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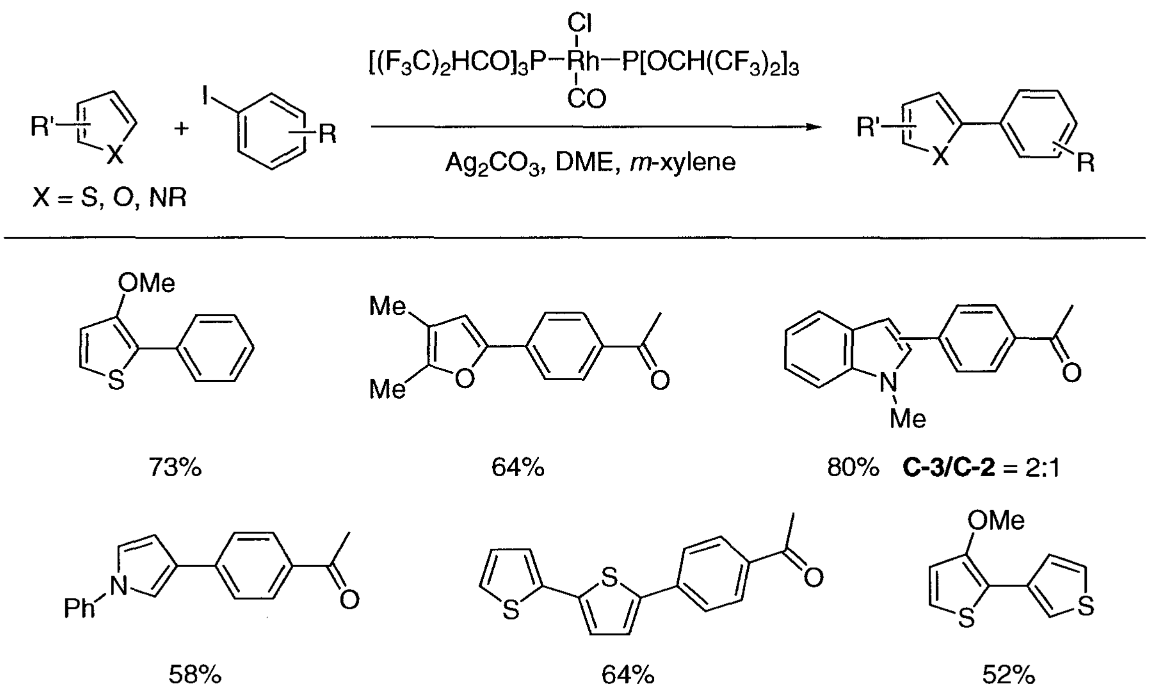
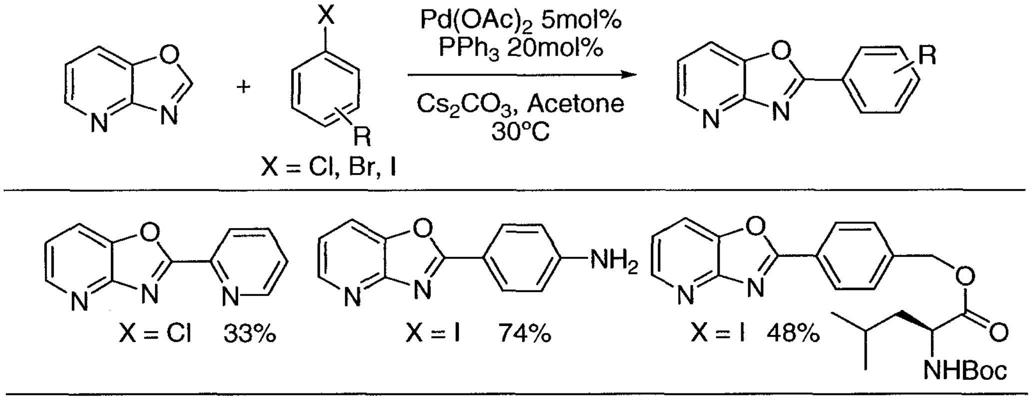
[117] Yanagisawa, S.; Sudo, T.; Noyori, R.; Itami, K.; *J. Am. Chem. Soc.* **2006**, *128*, 11748



**Scheme 3.6** - Scope of the Rhodium Catalyzed Direct Arylation of Heterocycles with Aryl Iodides

Recently, Zhuravlev reported a very mild direct arylation reaction between aryl halides and oxazolo[4,5-*b*]pyridines.[118] Reactions are carried out with $Pd(OAc)_2/PPh_3$ in acetone at 30 °C yielding the products in moderate to good yields (Scheme 3.7). The superior reactivity of these substrates is attributed to the high acidity of the hydrogen where the arylation reaction occurs.



**Scheme 3.7** - Direct Arylation of Oxazolo[4,5-*b*]pyridine

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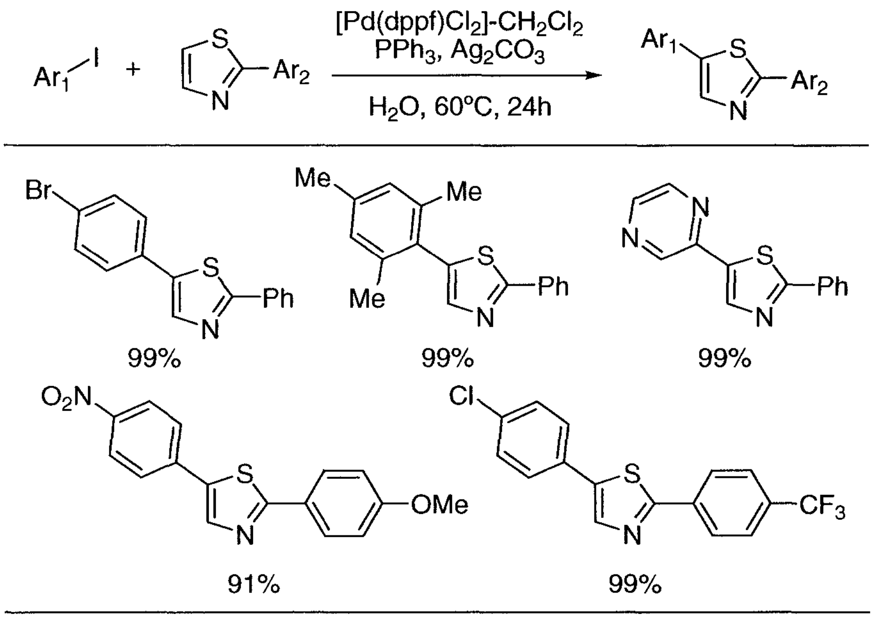
[118] Zhuravlev, F. A. ; *Tetrahedron Lett.* **2006**, *47*, 2929

Very recently, papers re-examining the formation of previously described substrates through direct arylation have appeared. Greaney and co-workers have reported that direct arylation reactions of thiazole can be performed under milder conditions than typically required for this type of arylation.[119] Using $Ag_2CO_3$ as the base and 0.5 mol % Pd in water as the solvent, 2-phenylthiazole was effectively arylated at C-5 in good yield in 24 hours at 60 °C (Scheme 3.8). Though the reaction scope seems to be limited to aryl iodides, the authors briefly explored their newly developed conditions on other heterocycles such as oxazole, thiophene, benzimidazole, benzoxazole and benzothiazole, providing a good precedent for a more extensive study into these substrate classes.



**Scheme 3.8** – Greaney's Direct Arylation on Water

The increased reactivity in this system has been attributed to the use of the silver additive, which had previously been demonstrated to accelerate direct arylation reactions,[120] as well as the fact that the reactions are performed in water. The authors point out that performing the reactions neat provided similar results as those using water as the solvent. This suggests that effective concentration of the substrates and catalyst

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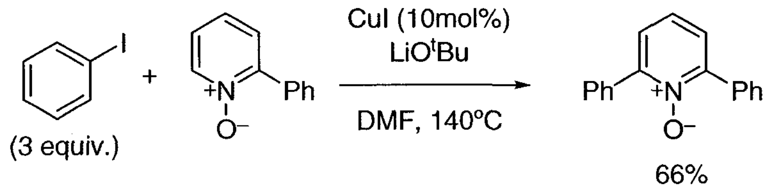
[119] Turner, G. M.; Morris, J. A.; Greaney, M. F.; *Angew. Chem. Int. Ed.* **2007**,*46*, 1

[120] (a) Masui, K.; Mori, A.; Okano, K.; Takamura, K.; Kinoshita, M.; Ikeda T.; *Org. Lett.* **2004**, *6*, 2011. (b) Campeau, L.-C.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, 128, 581.

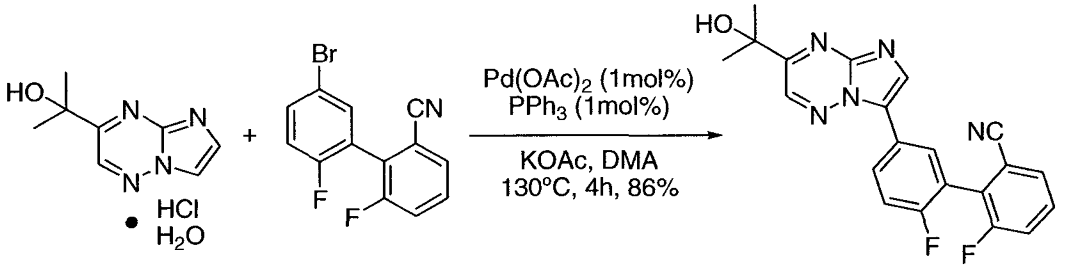
system is the main driving force for the observed rate acceleration, prompting the authors to name their paper “Direct Arylation of Thiazoles *on* Water”.

Daugulis and Do have recently reported their development of a copper catalyzed direct arylation reaction.[121] This protocol uses the inexpensive CuI in conjuction with LiO$^t$Bu in DMF at 140 °C to effect the coupling of various azoles with aryl iodides. The authors discovered that when KOtBu was used as the base, benzyne intermediates were formed, which justified the use of the less common LiO$^t$Bu. The reaction conditions were amenable to the use of a variety of aryl iodides and azoles and were even compatible with 2-phenylpyridine *N*-oxide as a substrate (Equation 3.4).



(3.4)

A clear indication that direct arylation methodology has become increasingly accepted by the synthetic community is its use in industrial contexts. For example, researchers at Merck & Co. reported in 2005 that the direct arylation of imidazo[1,2-*b*][1,2,4]triazine can be successfully employed as an alternative to the Suzuki cross-coupling reaction in a key fragment coupling for the preparation of a selective GABA agonist. (Equation 3.5).[122]



(3.5)

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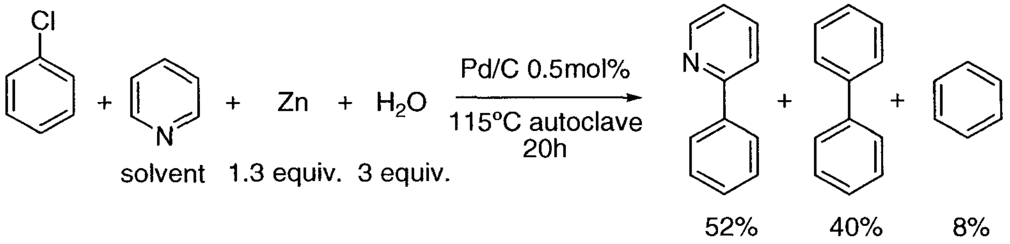
[121] Do, H.-Q.; Daugulis, O.; *J. Am. Chem. Soc.* **2007**, *129*, ASAP – DOI: 10.1021/ja0758202

[122] (a) Jensen, M. S.; Hoerrner, R. S.; Li, W.; Nelson, D. P.; Javadi, G. J.; Dormer, P. G.; Cai, D.; Larsen, R. D. ; *J. Org. Chem.* **2005**, *70*, 6034; (b) Gauthier, D. R., Jr.; Limanto, J.; Devine, P. N.; Desmond, R. A.; Szumigala, R. H., Jr.; Foster, B. S.; Volante, R. P. *J. Org. Chem.* **2005**; *70*, 5938 ; (c) Cameron, M. ; Foster, B. S. ; Lynch, J. L. Shi, Y.-J.; Dolling, U.-H.; *Org. Proc. Res. Dev.*; **2006**, *10*, 398.

## Reactions of π-Electron-Deficient Heterocycles

In contrast to the number of reports of π-rich heterocycles in direct arylation, the use of π-deficient heteroarenes such as azines and diazines remains a challenging goal. In 2000, Sasson and co-workers prepared 2-phenylpyridine using a Pd/C, zinc, water catalyst system in conjunction with chlorobenzene and pyridine (Scheme 3.9).[123] Addition of 5% 2,6-di-*t*-butyl-4-methylphenol (BHT) to the reaction leads to a reduction of the reaction rate by two orders of magnitude. The authors suggest the participation of free-radicals in the rate-determining step, although the observation that no chlorobiphenyls are detected suggests that these radicals would only exist in close proximity to the catalyst surface. The use of the zinc-water-palladium system was demonstrated to produce hydrogen *in situ* which is critical for catalytic turnover.[124]



**Scheme 3.9** - Direct Arylation of Pyridine with Chlorobenzene

To our knowledge, this constitutes the only example of the direct arylation of an azine with an aryl halide.[125] In fact, most biaryls containing a pyridine or other azine ring are synthesized using pathway **A** (Figure 3.2). The complimentary strategy using pathway **B** is infrequently used.

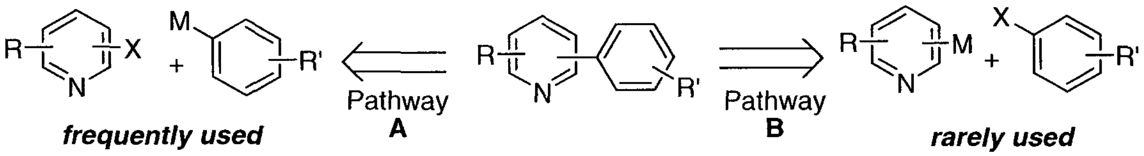


**Figure 3.2** – Strategies in Azine Biaryl Synthesis

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[123] Mukhopadhyay, S.; Rothenberg, G.; Gitis, S.; Baidossi, M.; Ponde, D. E.; Sasson, Y.; *J. Chem. Soc., Perkin Trans. 2*, **2000**, *9*, 1809

[124] Mukhopadhyay, S.; Rothenberg, G.; Wiener, H.; Sasson, Y.; *New. J. Chem.* **2000**, *24*, 305

[125] A report from 2005 was retracted, see : Godula, K.; Sezen, B.; Sames, D.; *J. Am. Chem. Soc.* **2006**, *128*, 3102

The next section will highlight the synthesis of these important biaryls via azine organometallics in palladium catalyzed cross-coupling reactions, with a focus on pyridyl organometallics (Pathway **B**). Emphasis has been placed on the most recent examples and on emerging alternatives to traditional cross-couplings. This section is divided into two parts. The first part describes cross-coupling reactions of 3- and 4-pyridyl organometallics. The second deals with the use of 2-metallapyridines, which are typically more challenging to use.

## *π-Electron-Deficient Azine Organometallics in Metal Catalyzed Cross-coupling Reactions*[126]

Pyridines are among the most prevalent heterocycles in bioactive compounds and have been claimed to be the most common heterocycle in pharmaceutically active compounds (Scheme 3.10).[127] Heterobiaryls, a sub-class of biaryls, have one or both of the aryl units replaced by heteroaromatic rings. Examples with azines include micrococcin P1,[128] Streptonigrin[129] and Nemerelline.[130] Etoricoxib,[131] Rosuvastatin[132] and Glivec[133] are three examples of commercialized drugs bearing an arylpyridine motif. This motif is also found in seretonin receptor agonists[134] and MAP kinase inhibitors.[135] Many P,N ligands, such as QUINAP, are based on arylazine frameworks.[136]

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[126] Campeau, L.-C.; Fagnou, K.; *Chem. Soc. Rev.* **2007**, *36*, 1058;

[127] (a) Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T.; *Org. Biomol. Chem.*, **2006**, *4*, 2337. (b) Bonnet, V. ; Mongin, F. ; Trécourt, F. ; Breton, G. ; Marsais, F. ; Knochel, P. ; Quéquiner, G.; *Synlett*, **2002**, *6*, 1008 – Footnote 1.

[128] Pestka, S.; In *Antibiotics*; Corcoran, J. W.; Hahn, F. E.; Eds.; Springer-Verlag: New York, **1975**; Vol. 3, p 480 ff

[129] (a) Ming, L.-J.; *Med. Res. Rev.*, **2003**, *23*, 697; (b) Lewis, A. M.; Ough, M.; Hinkhouse, M. M.; Tsao, M.-S.; Oberley, L. W.; Cullen, J. J.; *Molecular Carcinogenesis*, **2005**, *43*, 215

[130] Ken, W. R.; Soti, R.: Rittschof, D.; *Biomolecular Engineering*, **2003**, *20*, 355

[131] Friesen, R. W.; Brideau, C.; Chan, C. C.; Charleson, S.; Deschênes, D.; Dubé, D.; Ethier, D.; Fortin, R.; Gauthier, J. Y.; Girard, Y.; Gordon, R.; Greig, G. M.; Riendeau, D.; Savoie, C.; Wang, Z.; Wong, E.; Visco, D.; Xu, L. J.; Young, R. N.; *Biorg. & Med. Chem. Lett.*, **1998**, *8*, 2777

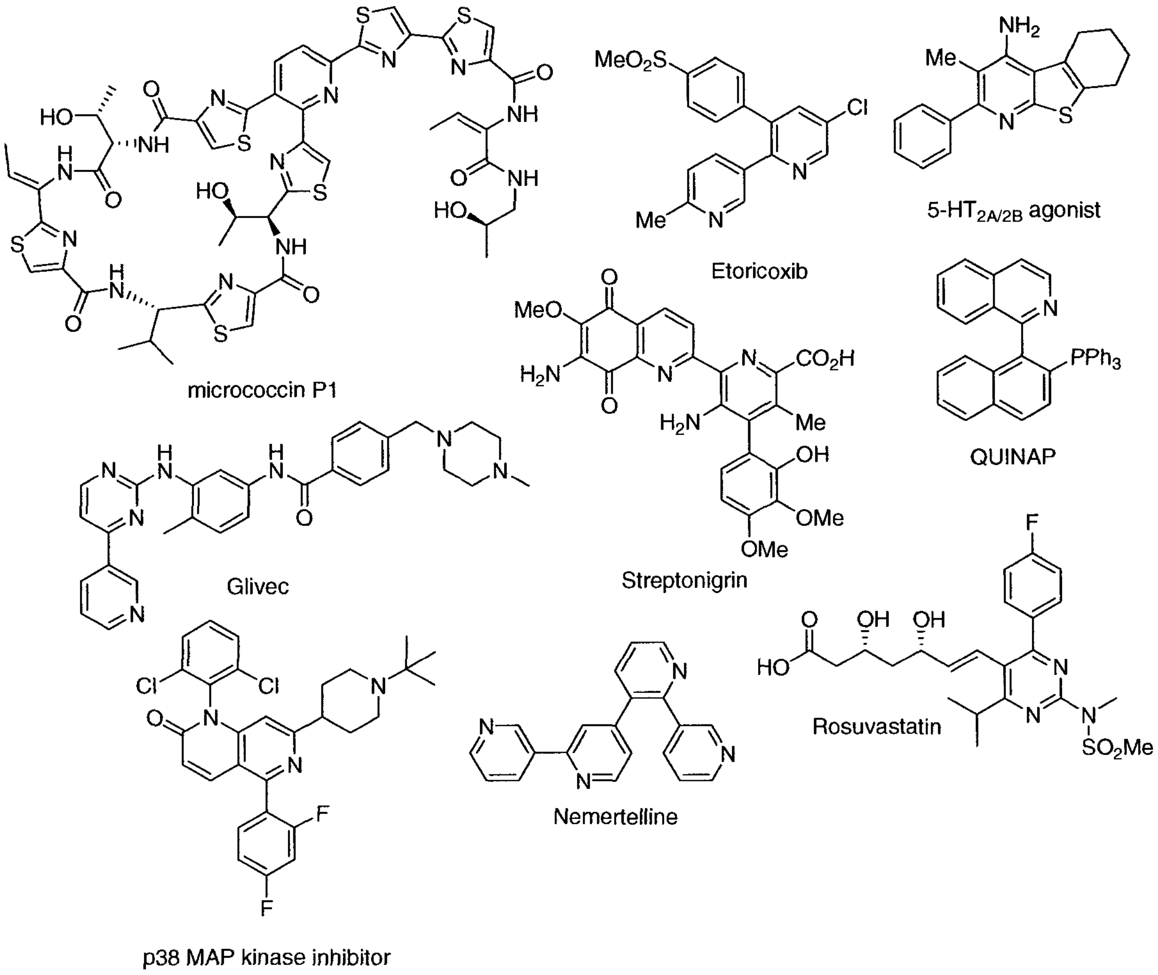
[132] Quirk, J.; Thornton, M.; Kirkpatrick, P.; *Nature*, **2003**, *2*, 769

[133] Capdeville, R.; Buchdunger, E.; Zimmermann, J.; Matter, A.; *Nature*, **2002**, *1*, 493

[134] Bush, E.; Fielitz, J.; Melvin, L.; Martinez-Arnold, M.; McKinsey, T. A.; Plichta, R.; Olson, E. O.; *Proc. Nat. Acad. Sci.* **2004**, *101*, 2870

[135] Chung, J. Y. L.; Cvetovich, R. J.; McLaughlin, M.; Amato, J.; Tsay, F.-R.; Jensen, M.; Weissman, S .; Zewge, D.; *J. Org. Chem.* **2006**, *71*, 8602

[136] (a) For a reveiw on P,N Ligands with pyridyl donors see Chelucci, G.; Orru, G.; Pinna, G. A.; *Tetrahedron*, **2003**, *59*, 9471 (b) Alcock, N. W.; Brown, J. M.; Hulmes, D. I.; *Tetrahedron: Asymmetry*, **1993**, *4*, 743.



**Scheme 3.10** – Important Arylazines

The development of palladium catalyzed cross-coupling methods has had the greatest impact on the synthesis of these compounds. The Suzuki, Stille, Kumada-Corriu, Negishi and Hiyama couplings are among the most powerful and versatile tools in biaryl synthesis, exhibiting high functional group compatibility and broad reaction scope.[137]

Although reaction conditions and the nature of the organometallic component vary from one type of cross-coupling reaction to another, all of these reactions are mechanistically related (Scheme 3.11). The first step of the catalytic cycle involves the oxidative addition of a Pd$^{(0)}$ catalyst into a carbon-halide bond (or equivalent) to generate an electrophilic aryl-palladium(II) intermediate. Reaction of this species with the

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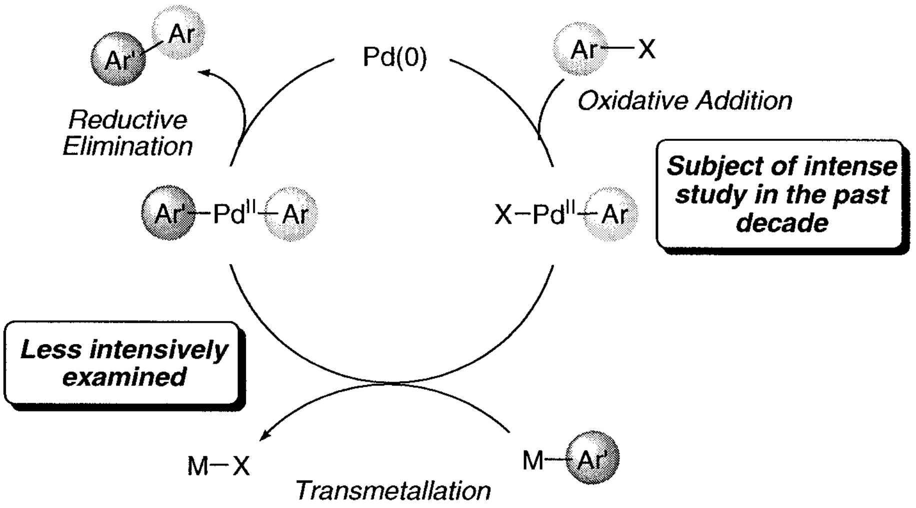
[137] For reviews on this topic, see: *Metal-catalyzed Cross-coupling Reactions*; Diederich, F.; Stang, P. J.; Eds.; Wiley-VCH: New York, **1998**.

nucleophilic organometallic component via transmetallation provides a diaryl-palladium(II) species which undergoes reductive elimination to form the biaryl carbon-carbon bond and regenerate the Pd$^{(0)}$ catalyst



**Scheme 3.11** - Catalytic Cycle of Palladium Catalyzed Cross-Coupling Reactions

Important progress has been made over the last decade in catalyst development leading to mild, high yielding processes that can be performed with low catalyst loadings.[137] The majority of catalyst development efforts have been directed at the first step of the catalytic cycle, oxidative addition, which in many cases can be the most challenging. Notably, this work has enabled extension of these reactions to include very challenging aryl halides including deactivated aryl chlorides[138] and very sterically hindered bis *ortho*-substituted aryl halides.[139]

In contrast, the transmetallation step has been less extensively studied and optimized. This reduced attention compared to oxidative insertion is reasonable because transmetallation is typically not problematic and in many cases not rate-determining. However, there are important organometallic classes that tend to be less frequently employed due to their sluggish or poor reactivity. This is the case for π-electron deficient azine organometallics such as metallapyridines which, in addition to exhibiting diminished stability, are less nucleophilic and undergo transmetallation more slowly.[139]

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[138] Littke, A. F.; Fu, G. C.; *Angew. Chem. Int. Ed.* **2002**, *41*, 4176

[139] For a recent report see : Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L.; *J. Am. Chem. Soc.* **2005**, *127*, 4685 and references therein

In some cases, transmetallation can even be the rate determining step of the catalytic cycle.[140] Nonetheless, important advances have recently been made with these challenging substrates.

## 3- and 4-Azine Organometallics

Cross-coupling reactions using 3- and 4-pyridyl organometallics are more challenging than those with simple arene organometallics. As previously mentioned, they are less nucleophilic and transmetallate the arylPdX complex at slower rates.[139] They are also more prone to dimerization[141] and protodeboronation.[142] In spite of these hurdles, reliable methods exist for the use of these compounds in cross-coupling methodology. For example, the robustness and reliability of the Stille reaction make it a good tool for the coupling of 3- and 4-stannylpyridines with aryl and heteroaryl bromides and iodides. Recent advances in the synthesis (commercial availability) and use of pyridyl boronic acids and esters have also made Suzuki couplings a very attractive choice. While Negishi, Kumada and Hiyama couplings are less prevalent, good precedent exists for their use. Alternatively, interesting reactions of pyridine *N*-oxides and benzyne can be used to access 3-arylpyridines. For an in-depth discussion of methods of cross-coupling with 3- and 4-azine organometallics, the reader is directed to a recent review.[126]

## 2-Azine Organometallics

2-Azine organometallics are less commonly employed in cross-couplings, likely due to their greater instability. In particular, the instability of 2-metallapyridines makes the preparation of the organometallic and the cross-coupling reactions very problematic except in special cases. Nevertheless, chemists have been developing methods to circumvent these limitations by either carefully choosing coupling partners or by investigating novel methodologies. Although there are fewer examples of these species used in cross-coupling, the following section represents a collection of successful applications with emphasis on methodological studies whenever possible. The dominance of the Stille coupling reaction should be noted, as it is likely the most reliable

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[140] Smith, G. B.; Dezeny, G. C.; Hughes, D. L.; King, A. O.; Verhoeven, T. R.; *J. Org. Chem.* **1994**, *59*, 8151; For a theoretical study of transmetallation in Suzuki coupling, see: Braga, A. A. C.; Morgon, N. H.; Ujaque, G.; Maseras, F.; *J. Am. Chem. Soc.* **2005**, *127*, 9298; For a theoretical study of transmetallation in Stille coupling, see: Alvarez, R.; Faza, O. N.; Lopez, C. S.; de Lera, A. R.; *Org. Lett.* **2006**, *8*, 35

[141] Wong, M. S.; Zhang, X. L.; *Tetrahedron Lett.*, **2001**, *42*, 4087

[142] Kuivila, H. G.; Reuwer, J. F.; Mangravite, J. A.; *J. Am. Chem. Soc.* **1964**, *86*, 2666

use of 2-metallapyridines in cross-couplings. Recent advances in the synthesis of stabilized boron species have allowed for the use of these in Suzuki couplings, albeit in limited scope.

## Common Methods

### *Stille Coupling*

As with the other regioisomers, the prevalence of Stille cross-couplings with 2-stannylpyridines is likely attributable to the relatively high stability of the stannane. Generally, it can be anticipated that reactions of 2-pyridylstannanes with aryl iodides and some aryl bromides will occur in synthetically useful yields.

In 1993, Gronowitz and co-workers reported that addition of cupric oxide to Stille reactions using 2-tributylstannylpyridine led to much faster reaction times and higher yields.[143] The beneficial effect of copper additives in Stille reactions has been studied extensively and could operate via various mechanisms. It may accelerate reactions by binding free phosphine that would otherwise bind palladium and increase steric congestion around the metal center, therefore slowing transmetallation.[144] Alternatively, copper additives have also been proposed to transmetallate the organostannane generating organocuprates *in-situ* which are more nucleophilic than the corresponding stannanes.[145] Using 5 mol % Pd(dppb)$Cl_2$ and 1 equivalent of CuO in DMF, 2-pyridyltributylstannane (**3.2**) can be coupled with aryl and heteroaryl iodides and bromides in good yields (Scheme 3.12). In contrast, they were unable to achieve reactions with unactivated aryl chlorides, and the more activated 4-chloropyridine was coupled in a modest 44% yield. 2-Stannylpyridines have also been extensively used in the synthesis of functionalized bis- and tris-pyridyl ligands.[146]

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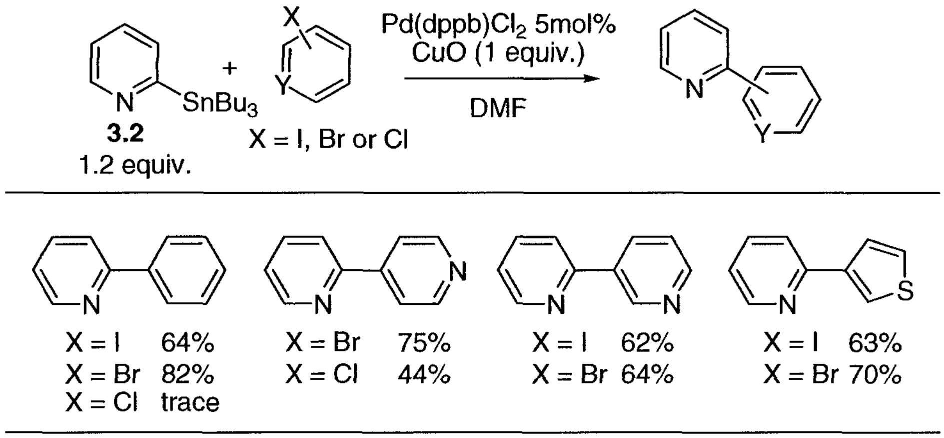
[143] Gronowitz, S.; Björk, P.; Malm, J.; Hörnfeldt, A.-B.; *J. Organomet. Chem.* **1993**, *460*, 127

[144] For an in-depth discussion, see: (a) Casado, A. L.; Espinet, P.; *Organometallics*, **2003**, *22*, 1305 and references therein; (b) Allred, G. D; Liebeskind, L. S.; *J. Am. Chem. Soc.* **1996**, *118*, 2748.

[145] For an in-depth discussion of this effect, see: Crawforth, C. M.; Fairlamb, I. J. S.; Kapdi, A. R.; Serrano, J. L.; Taylor, R. J. K.; Sanchez, G.; *Adv. Synth. Catal.* **2006**, *348*, 405 and references therein.

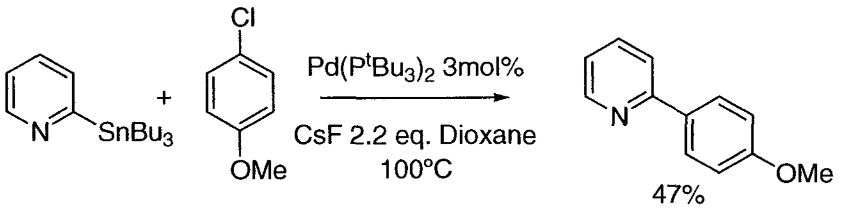
[146] For recent examples see : (a) Schubert, U. S.; Eschbaumer, C.; Heller, M.; *Org. Lett.* **2000**, *2*, 3373; (b) Shcubert, U. S.; Eschbaumer, C.; *Org. Lett.* **1999**, *1*, 1027; (c) Heller, M.; Schubert, U. S.; *J. Org. Chem.* **2002**, *67*, 8269; (d) Berghian, C.; Darabantu, M.; Turck, A.; Plé, N.; *Tetrahedron,* **2005**, *61*, 9637; (e) Gros, P.; Fort, Y.; *Synthesis,* **1999**, *5*, 754 ; (f) Lehmann, U.; Henze, O.; Schlüter, A. D.; *Chem. Eur. J.* **1999**, *5* 854.



**Scheme 3.12** - CuO Mediated Palladium Catalyzed Stille Coupling of 2-Pyridyltributylstannane

It is also possible to synthesize and use certain 2-stannyl diazines in Stille couplings.[147] Yields for the synthesis of the organometallic vary from 9% to 98% and the Stille coupling of these reagents with heteroaromatic aryl halides or iodobenzene is achieved using $Pd(PPh_3)_4$ in refluxing toluene over 2 days with yields ranging from 21% to 82% depending on the substrates.

A rare example of a cross-coupling with an aryl chloride and 2-tributylstannylpyridine was reported by Littke, Schwarz and Fu.[148] Their highly active catalyst, based on $Pd(P^tBu_3)_2$ and CsF, promotes the Stille coupling of aryl chlorides and bromides at room temperature. In this report, they describe a single example employing 2-stannylpyridine and 4-chloroanisole in refluxing dioxane, resulting in a 47% yield (Equation 3.6).



(3.6)

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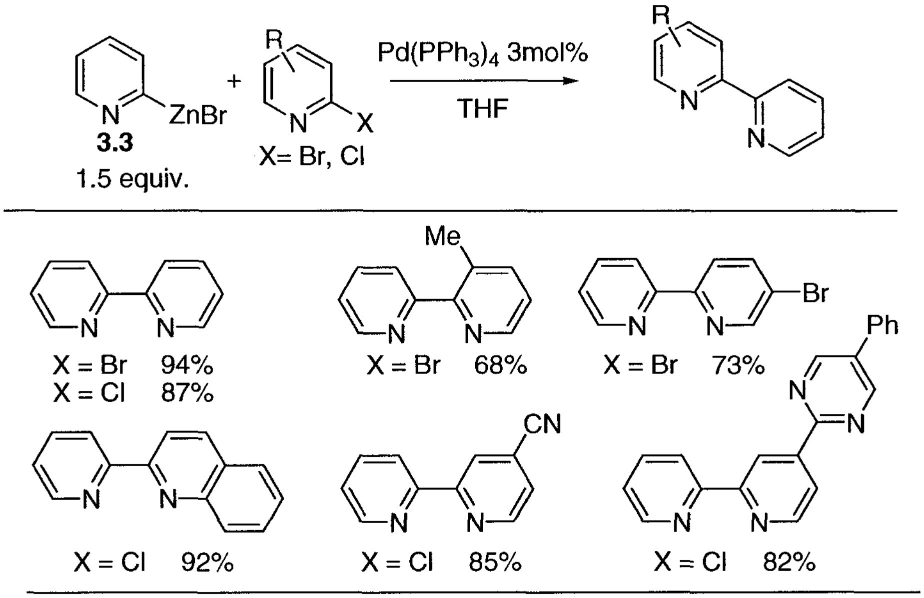
[147] Darabantu, M.; Boully, L.; Turck, A.; Plé, N.; *Tetrahedron*, **2005**, *61*, 2897

[148] Littke, A. F.; Schwarz, L.; Fu, G. C.; *J. Am. Chem. Soc.* **2002**, *124*, 6343

### *Negishi Coupling*

The use of 2-pyridylzinc reagents in Negishi couplings can also be a reliable method for the synthesis of these heterobiaryls. The increased stability and *in situ* formation of these species facilitates their application in cross-coupling reactions.[149] An added advantage is the establishment of well developed techniques for the generation of organozinc reagents.[150] The 2-pyridylzinc halides are usually synthesized either by transmetallation of 2-lithiopyridines or by direct insertion of 2-halopyridines with Rieke zinc.[151] In general, reaction conditions used for Negishi couplings with regular aryl zinc halides can be used without modification, and the efficiency of the reaction relies predominantly on the nature of the coupling partners.

In 2003, Fang and Hanan demonstrated that 2-pyridylzinc bromide (**3.3**) could be efficiently coupled with various 2-bromo and 2-chloroazines to give functionalized bipyridines.[152] A slight excess (1.5 equivalents) of the organozinc reagent is used in conjunction with $Pd(PPh_3)_4$ in THF. Reactions with bromides can be performed at room temperature, whereas the reactions of chlorides require heating to 60 °C (Scheme 3.13).



**Scheme 3.13** - Bipyridine Synthesis via Negishi Coupling of 2-Pyridylzinc Bromide

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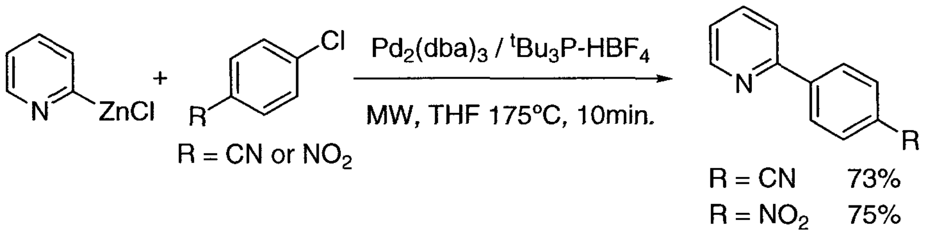
[149] For two early reports, see : (a) Deshayes, K.; Broene, R. D.; Chao, I.; Knobler, C. B.; Diederich, F.; *J. Org. Chem.* **1991**, *56*, 6787; (b) Trécourt, F. ; Gervais, B. ; Mallet, M.; Quéguiner, G. ;*J. Org. Chem.* **1996**, *61*, 1673

[150] Knochel, P.; Almena Perea, J. J.; Jones, P.; *Tetrahedron*, **1998**, *54*, 8275

[151] Prasad, A. S. B.; Stevenson, T. M.; Citineni, J. R.; Nyzam, V.; Knochel, P.; *Tetrahedron*, **1997**, *53*, 7237

[152] Fang, Y.-Q.; Hanan, G. S.; *Synlett*, **2003**, *6*, 852

Kappe and Walla reported two examples of microwave accelerated Negishi cross-coupling with activated aryl chlorides and 2-pyridylzinc chloride using $Pd_2(dba)_3$ in conjunction with tri-*t*-butylphosphine as the supporting ligand (Equation 3.7).[153]



(3.7)

## Uncommon Methods

### *Suzuki Coupling*

Progress in the use of 2-pyridylboron species in Suzuki cross-coupling has been slower to appear. This can be attributed to the instability of the boron functionality at the 2-position of the pyridine ring,[154] making their use in coupling reactions challenging.

In 2003, Rault and co-workers reported that 5- and 6-halopyridin-2-ylboronic acids and esters could be synthesized and isolated in modest yields.[155] In a series of four papers related to the synthesis of halogenated pyridyl boron reagents, they reported that the halogenated species were more stable than their non-halogenated counterparts.[156,155] Eleven halo-2-pyridyl boron compounds were synthesized, five of which were shown to be suitable cross-coupling partners in the Suzuki reaction. The choice of solvent and base for the cross-coupling depend on the nature of the boron reagent. When boronic acids are employed, dimethoxyethane and $Na_2CO_3$ are optimal, whereas for boronic esters, *N,N*-dimethylformamide and $K_3PO_4$ are best. A single example with the dioxazaborocane **3.4** was conducted using a toluene-ethanol mixture and $Na_2CO_3$ (Scheme 3.14). Although no explanation is given regarding the increased stability of

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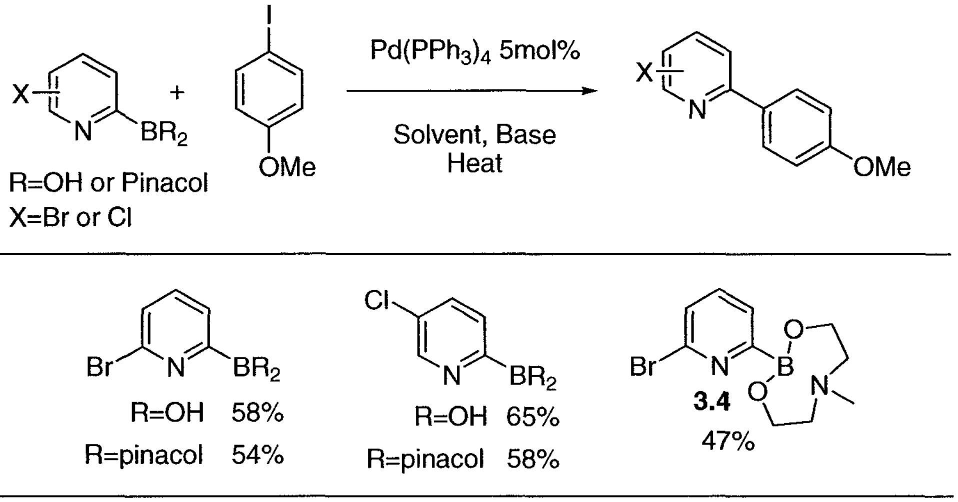
[153] Walla, P.; Kappe, C. O.; *Chem. Commun.* **2004**, 564

[154] Fischer, F. C.; Havinga, E.; *Recl. Trav. Chim. Pays-Bas*, **1974**, *93*, 21

[155] Bouillon, A.; Lancelot, J.-C.; de Oliveira santos, J. S.; Collot, V.; Bovy, P. R.; Rault, S.; *Tetrahedron*, **2003**, *59*, 10043.

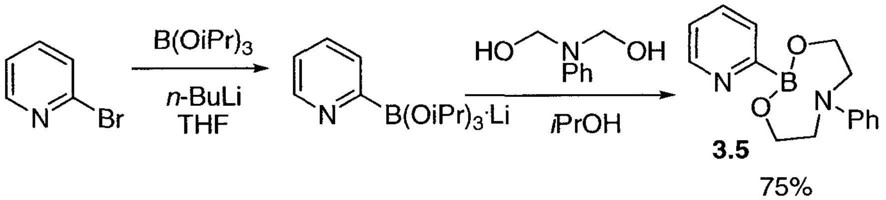
[156] (a) Bouillon, A.; Lancelot, J.-C.; Collot, V.; Bovy, P. R.; Rault, S.; *Tetrahedron*, **2002**, *58*, 2885 (b) Bouillon, A.; Lancelot, J.-C.; Collot, V.; Bovy, P. R.; Rault, S.; *Tetrahedron*, **2002**, *58*, 3323 (c) Bouillon, A.; Lancelot, J.-C.; Collot, V.; Bovy, P. R.; Rault, S.; *Tetrahedron*, **2002**, *58*, 4369

these halogenated pyridylboron species compared to the non-halogenated compounds, it is plausible that attenuated nitrogen basicity, as a result of the electronegative halide atoms, will diminish protodeboronation.



**Scheme 3.14** - Suzuki Coupling of Halogenated 2-Pyridylboron Species

In the following year, Hodgson and Salingue reported the use of *N*-phenyldiethanolamine derived 2-pyridyl dioxazaborocanes (**3.5**) in Suzuki cross-coupling reactions.[157] The one-pot synthesis provides the boronic ester in 75% yield (Scheme 3.15).



**Scheme 3.15** - Synthesis of Dioxazaborocane

Studies of the reaction conditions revealed that **3.5** is suitable for cross-coupling reactions with activated aryl bromides and iodides as well as non-activated aryl iodides.[157] In contrast, deactivated aryl iodides and non-activated aryl bromides are poor substrates for this reaction. The added stability of **3.5** likely results from

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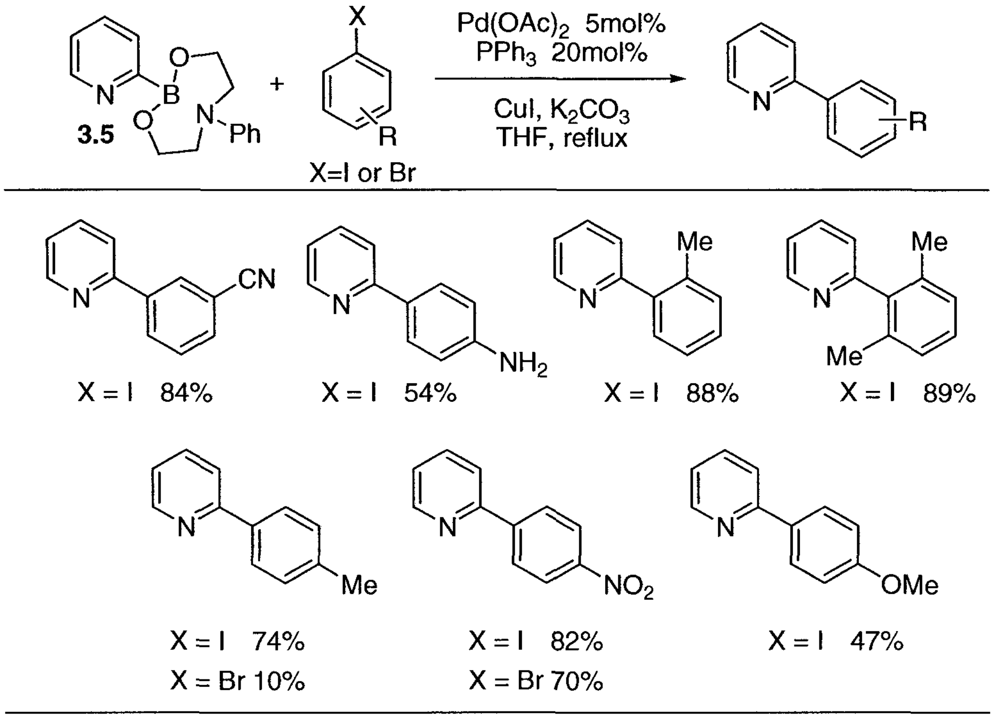
[157] Hodgson, P. B.; Salingue, F. H.; *Tetrahedron Lett.* **2004**, *45*, 685

donation of the nitrogen lone pair onto the boron atom which in turn diminished Lewis acidity (Scheme 3.16).



**Scheme 3.16** - Suzuki Cross-Coupling using Dioxazaborocane **3.5**

Marder and co-workers achieved the direct borylation of pyridines via iridium-catalysis.[158] For the reaction to succeed, the pyridine must bear a substituent at the 2-position to inhibit its unproductive binding to the iridium catalyst via the nitrogen atom. In one example, 4,4'-di-*t*-butyl-2,2'-bipyridine (**3.6**, dtbpy) reacts with the catalyst to provide the bis 2-pyridylboronate pinacol ester **3.7**, which was then reacted without purification with 3 equivalents of iodobenzene and a palladium catalyst to provide the bis-arylated product in 67% yield. When only 1.2 equivalents of iodobenzene are used, monoarylation is obtained along with protodeboronation of the second boronate ester (Scheme 3.17).

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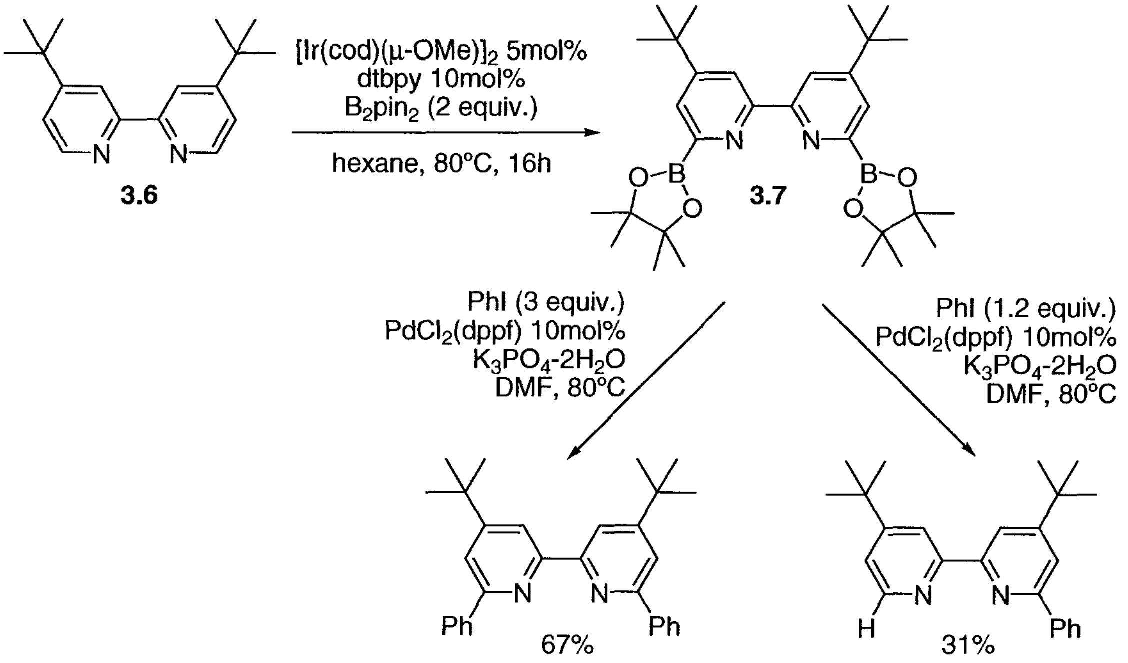
[158] Mkhalid, I. A. I.; Coventry, D. N.; Albesa-Jove, D.; Batsanov, A. S.; Howard, J. A. K.; Perutz, R. N.; Marder, T. B. *Angew. Chem. Int. Ed.* **2006**, *45*, 489



**Scheme 3.17** - Iridium-Catalyzed Borylation of 4,4'-di-t-butyl-2,2'-bipyridine (**3.6**, dtbpy)

The *in situ* generation of an organoboron species has also been applied to the total synthesis of Cytisine (Scheme 3.18).[159] O'Neill and co-workers explored the possibility of using a Suzuki coupling to provide **3.8**. Unfortunately, isolation of the requisite 2-pyridyl boron compound was problematic, leading to low yields (20-30%). To circumvent this limitation, they opted to generate the lithium 2-pyridyltrimethoxyborate *in situ* and subject it to the Suzuki cross-coupling conditions without isolation. Using this approach they were able to obtain the cross-coupled compound **3.8** in 50-55% yield. An alternative synthetic route employing 3-pyridyltributyltin gave similar results.

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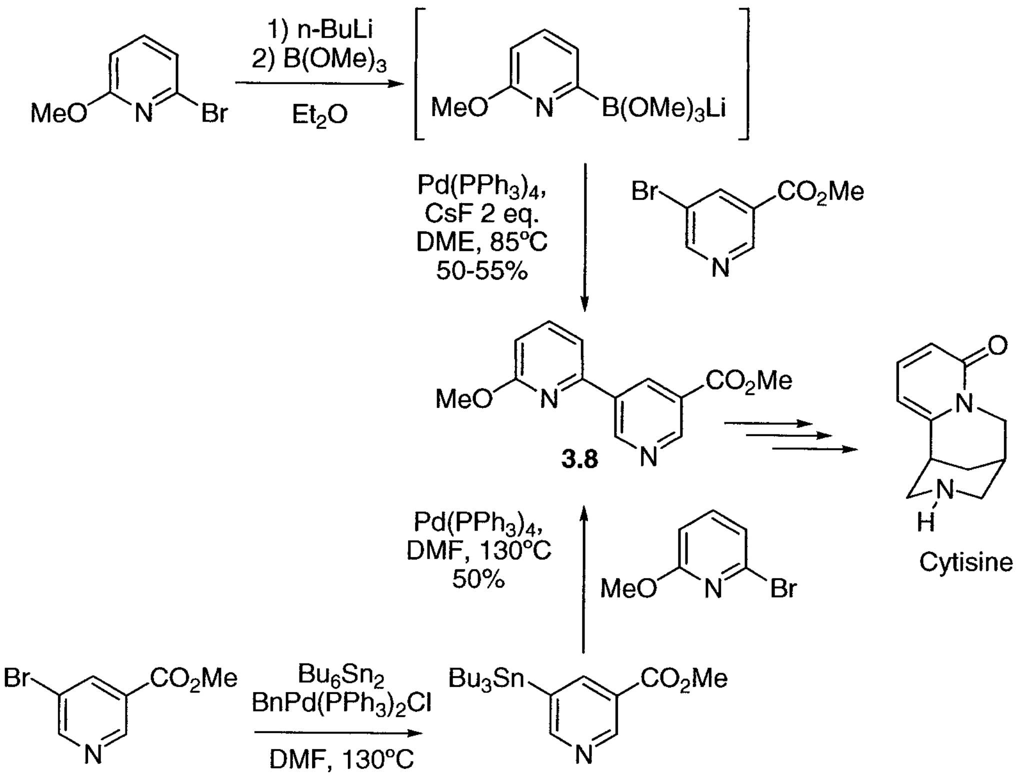
[159] O'Neill, B. T.; Yohannes, D.; Bundesmann, M. W.; Arnold E. P.; *Org. Lett.* **2000**, *2*, 4201



**Scheme 3.18** – Biaryl Strategies in the Total Synthesis of Cytisine

*Hiyama and Kumada Coupling*

In 2005, Gros and co-workers reported that chloropyridyltrimethylsilanes are stable enough to be isolated and used in Hiyama cross-couplings. For example, 3- and 4-chloro-2-pyridylsilanes can be reacted with aryl iodides and heteroarylbromides in good yields using 10 mol % $PdCl_2(PPh_3)_2$ in the presence of 20 mol % $PPh_3$, 2 equivalents CuI and 4 equivalents TBAF (Scheme 3.19).[160] 3-Methoxy-2-pyridylsilane, as well as 3- and 6-fluoro-2-pyridylsilanes, can also be cross-coupled in useful yields. The authors propose that the heteroatom substituent on the pyridyl ring plays a dual role. First, it may increase the polarization of the carbon-silicon bond, which can aid in the formation of a silicate species by reaction with a fluoride anion, thus facilitating transmetallation. Second, the substituent can attenuate the basicity of the pyridyl nitrogen atom, which could reduce its propensity to bind the palladium catalyst in unproductive modes. This type of substitution appears to be necessary for the cross-coupling to occur, as illustrated by the lack of reactivity observed with 2-trimethylsilylpyridine.

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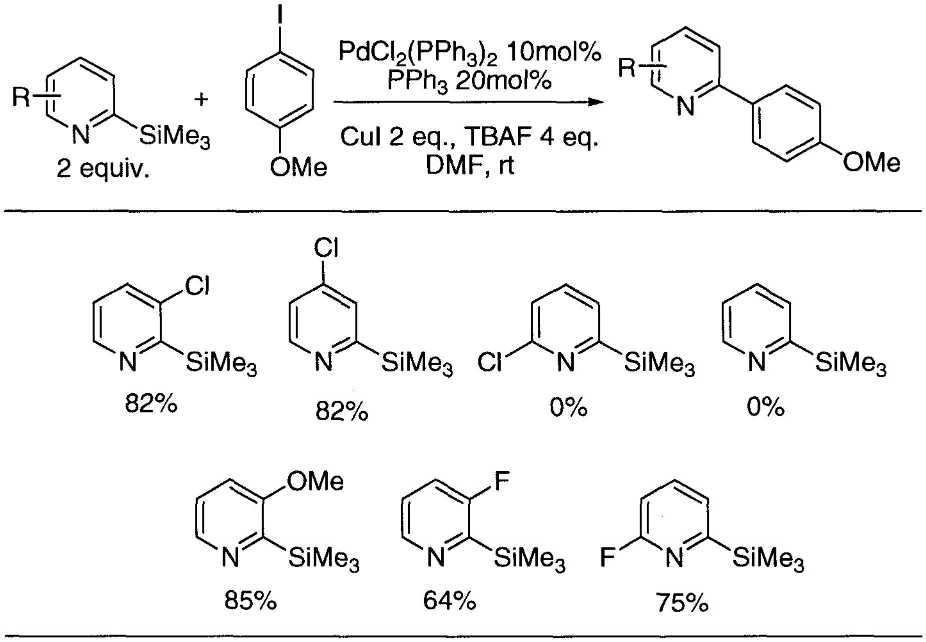
[160] Pierrat, P.; Gros, P.; Fort, Y.; *Org. Lett.* **2005**, *7*, 697.



**Scheme 3.19** - Hiyama Cross-Coupling with 2-Pyridylsilanes

There are very few examples of Kumada coupling reactions using 2-pyridyl Grignard reagents largely due to their inherent instability.[161] These, along with 2-pyridyl organolithiums, are usually handled at very low temperature and under very anhydrous conditions to avoid protodemetallation and/or decomposition. In a recent communication dealing with low temperature Kumada coupling reactions, Buchwald and co-workers indicated that pyridyl Grignard reagents resulted in low yields ranging from 0-30% with various aryl iodides.[162]

## Research Plan

In light of the greater challenge associated with the use of 2-metalla-azines in cross-coupling reactions, new methods for their preparation and use are warranted. Given our previous experience with direct arylation reactions, we sought to develop a novel direct arylation of pyridines which would eliminate the need for the unstable organometallic component and replace it with an inexpensive and bench stable alternative.

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[161] Tamao, K.; Kodama, S.; Nakajima, I.; Kumada, M.; Minato, A.; Suzuki, K.; *Tetrahedron*, **1982**, *38*, 3347

[162] Martin, R.; Buchwald, S. L.; *J. Am. Chem. Soc.* **2007**, *129*, 3844

All our initial attempts to develop a direct arylation of pyridines were met with failure. Not only is pyridine π-electron-deficient, making an electrophilic palladation manifold impossible, it is also a very good ligand for palladium and was found to be a poison for our intramolecular direct arylation reaction. In an effort to circumvent this poisoning effect and increase its reactivity, we turned to pyridine *N*-oxides. Pyridine *N*-oxides are commercially available (or easily prepared),[163,164] inexpensive and bench stable. Additionally, the amphoteric nature of their reactivity with electrophiles and nucleophiles and the increased C-H bond acidity are all factors that could be exploited in the development of a direct arylation reaction (Figure 3.3).

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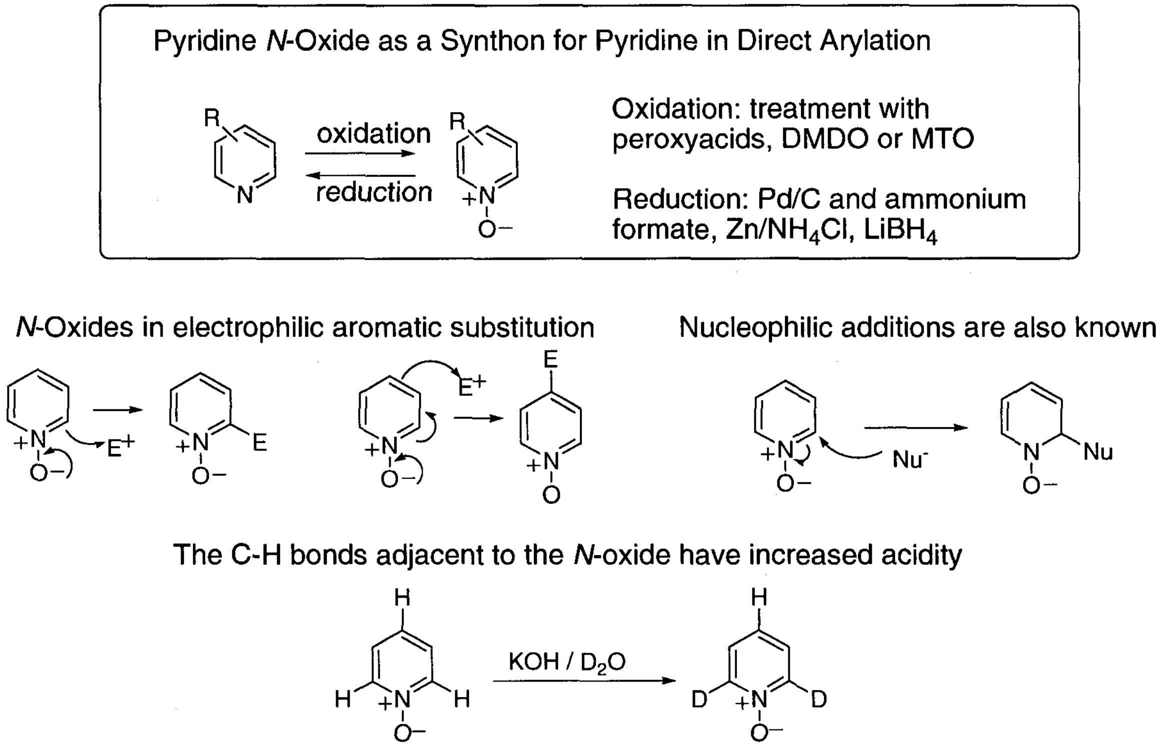
[163] For a review on oxidation of pyridines, see: Ochiai, E. *Aromatic Amine Oxides*; Elsevier: Amsterdam, 1967; Albini, A.; Pietra, S. *Heterocyclic N-Oxides*; CRC Press: Boca Raton, FL, 1991.

[164] (a) For some examples of *N*-oxidation using peracids: Edwards, D. C.; Gillespie *Tetrahedron Lett.* **1966**, 4867; (b) For oxidation with a combination of hydrogen peroxides and acids/anhydrides: Chivers, G. E.; Suschitzky, H. *J. Chem. Soc., Chem. Commun.* **1971**, 28. Takabe, K.; Yamada, T.; Katagiri, T. *Chem. Lett.* **1982**, 1987. Tortorella, V. *J. Chem. Soc., Chem. Commun.* **1966**, 308. Kaczmarek; Balicki, R.; Nantka-Namirski, P. *Chem. Ber.* **1992**, *125*, 1965; (c) For oxidation with DMDO: Murray, R. W.; Jeyaraman, R. *J. Org. Chem.* **1985**, *50*, 2847; (d) MTO: Coperet, C.; Adolfsson, H.; Khuong, T.-A. V.; Yudin, A. K.; Sharpless, K. B. *J. Org. Chem.;* **1998**; *63*, 1740; (e) Vanadium/$H_2O_2$ : Rout, L; Punniyamurthy, T.; *Adv. Synth. Catal.* **2005**, *347*, 1958; (f) $RuCl_3/O_2$ : Sain, B.; Jain, S.L.; *Chem. Commun.* **2002**, 1040; (g) HOF·MeCN: Rozen, S.; Kol, M.; Dayan, S.; *Synthesis*, **1999**, 1427; (h)Cobalt (II) Schiff base complex/$O_2$: Sain, B.; Jain, S.L.; *Angew. Chem. Int. Ed.* **2003**, *42*, 1265



Pyridine *N*-Oxide as a Synthon for Pyridine in Direct Arylation

Oxidation: treatment with peroxyacids, DMDO or MTO

Reduction: Pd/C and ammonium formate, Zn/$NH_4Cl$, $LiBH_4$

*N*-Oxides in electrophilic aromatic substitution

Nucleophilic additions are also known

The C-H bonds adjacent to the *N*-oxide have increased acidity

**Figure 3.3** – Features of Pyridine *N*-Oxides

# 4

# Direct Arylation of Heterocycles

## *Direct Arylation of Azines*[165]

While transition metal catalyzed cross couplings have been successfully employed with a wide range of halides and organometallics, some substrate classes still pose significant challenges. As illustrated in the previous chapter, this is the case with 2-pyridyl organometallics, whose frequent instability and difficult synthesis severely limits their application. For example, while the coupling of 2-halopyridines with aryl boronic acids is well precedented,[166] the inherent instability of 2-pyridyl boronic acid makes successful cross-couplings with this nucleophile rare. As a solution to this problem, chemists have resorted to the use of 2-pyridylstannanes which have been used in cross-coupling of aryl iodides and bromides. The modest reactivity observed with aryl chlorides and high toxicity associated with their use has pushed chemists to develop new methodologies to circumvent this problem. Advances in the use of stabilized boronate esters were discussed in the previous chapter as an alternative to the use of organostannanes. Unfortunately, these do not appear to be compatible with non-

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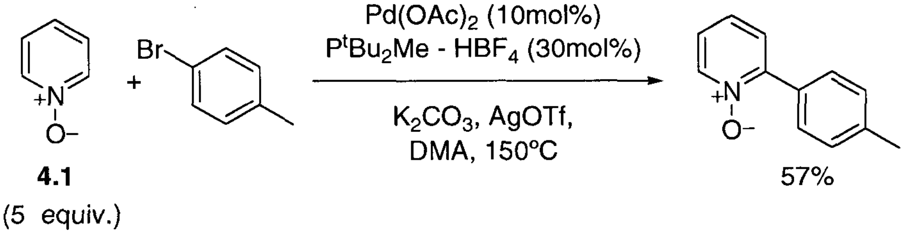
[165] Part of this section was published as a communication, see: Campeau, L.-C.; Rousseaux, S.; Fagnou, K.; *J. Am. Chem. Soc.*; **2005**, *127*, 18020.

[166] For an example using $P^tBu_3$, see: Littke, A. F.; Dai, C.; Fu, G. C.; *J. Am. Chem. Soc.*; **2000**, *122*, 4020

activated aryl bromides or aryl chlorides. Additionally, the need for dual pre-activation in traditional cross-coupling methods is inherently wasteful since these groups may require multiple steps for their installation, and none of the pre-activation groups appear in the final product. Given the importance of 2-arylpyridines in materials[167] and medicinal chemistry,[168] the development of a readily available, bench stable replacement for 2-pyridyl organometallics in cross coupling reactions would be an important advance. To do so we turned to direct arylation of pyridine *N*-oxides which, if widely applicable, would be of significant use in the preparation of these important molecules.

Reaction development was carried out with pyridine *N*-oxide and 4-bromotoluene. Initial experiments using conditions optimized for 1,3-benzodioxole arylation revealed not only the reaction to be possible, but highly regioselective, affording the 2-arylpyridine *N*-oxide exclusively. Given the large number of biologically active compounds displaying this motif, the high regioselectivity observed was encouraging (see Scheme 3.10). Preliminary optimization was undertaken.



(4.1)

From these studies, palladium acetate in combination with tri-*tert*-butylphosphine (added to the reaction mixture as the commercially available and air-stable $HBF_4$ salt) emerged as a good metal-ligand combination. Potassium carbonate was deemed the superior base, and toluene as a suitable solvent.[169] The reactions were run under concentrated conditions (0.3M), with two to four equivalents of pyridine *N*-oxide. Under these conditions (4-bromotoluene, 2 to 4 equiv. pyridine *N*-oxide, 5 mol % $Pd(OAc)_2$, 15 mol% $P^tBu_3{\cdot}HBF_4$, 2 equiv. $K_2CO_3$ in toluene at 110 °C), 2-tolylpyridine *N*-oxide is obtained in 91% isolated yield as exclusively one regioisomer (Table 4.1, Entry 1).[170]

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[167] For example, see: Fang, A.G.; Mello, J.V.; Finney, N.S. *Org. Lett.* **2003**, *5*, 967.

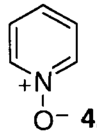
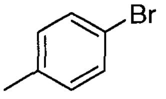
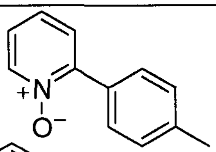
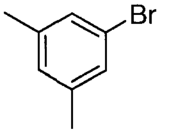
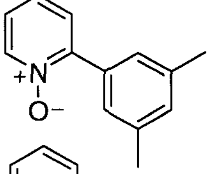
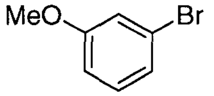
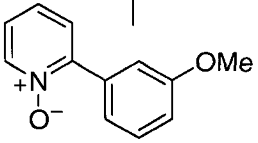
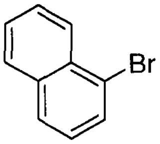
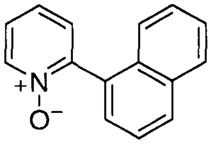
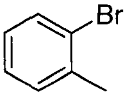
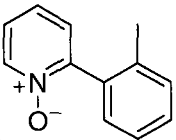
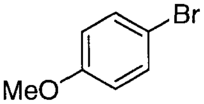
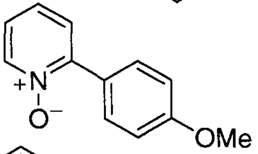
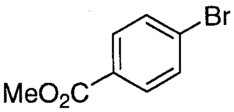
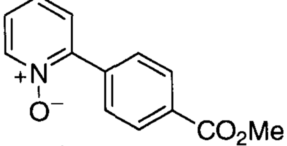
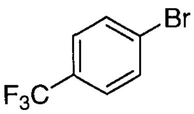
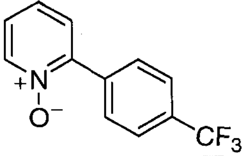
[168] For example, see: (a) Davies, I.W.; Marcoux, J.F.; Reider, P.J. *Org. Lett.* **2001**, *3*, 209. (b) Roppe, J.R.; wang, B.; Huang, D.; Tehrani, L.; Kamenecka, T.; Schweiger, E.J.; Anderson, J.J.; Brodkin, J.; Jiang, X.; cramer, M.; Chung, J.; Reyes-Manalo, G.; Munoz, B.; Cosford, N.D.P. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3993.

[169] Other solvents such as dioxane, mesitylene and *N,N*-dimethylacetamide can also be employed, but result in lower yields.

[170] Free pyridine is unreactive under these conditions.

While four equivalents of the *N*-oxide are not required, under the present conditions a decrease to one equivalent leads to diminished yields (Entries 2 to 5). Importantly, when one equivalent **4.1** is employed, greater than 95% of the unreacted *N*-oxide can be recovered by silica gel chromatography demonstrating that oxide decomposition does not occur.

**Table 4.1** - Regioselective Direct Arylation of Pyridine *N*-Oxides[a]

| Entry | *N*-Oxide | Aryl Halide | Product | Yield[b] |
|---|---|---|---|---|
| 1 |  **4.1** |  |  | 91 |
| 2 | **4.1** |  |  | 95 |
| 3 | **4.1** | | | $89^c$ |
| 4 | **4.1** | | | $76^d$ |
| 5 | **4.1** | | | $45^e$ |
| 6 | **4.1** |  |  | 97 |
| 7 | **4.1** | | | $93^c$ |
| 8 | **4.1** | | | $75^d$ |
| 9 | **4.1** |  |  | 88 |
| 10 | **4.1** |  |  | 87 |
| 11 | **4.1** |  |  | 80 |
| 12 | **4.1** |  |  | 74 |
| 13 | **4.1** |  |  | 76 |

[a]Conditions: Aryl halide (1 equiv.), pyridine *N*-oxide (4 equiv.), $K_2CO_3$ (2 eq.), $Pd(OAc)_2$ (0.05 equiv.) and $P^tBu_3$ – $HBF_4$ (0.15 equiv.) in toluene (0.3M) at 110 °C overnight. [b]Isolated Yields. [c]With 3 equivalents **4.1**. [d]With 2 equivalents **4.1**. [e]With 1 equivalent **4.1**.

Illustrative examples of the reaction scope with pyridine *N*-oxide are included in Table 4.1. (Caution: Pyridine N-oxides have been shown to exothermically decompose at very high temperatures.[171] Uncontrolled heating of the reaction media should be avoided.) A variety of substitution types and positions can be employed in these transformations. Both electron-rich (Entries 5-7 and 10) and electron-poor (Entries 11 and 12) aryl bromides are compatible, as are more sterically encumbered ortho-substituted arenes (Entries 8 and 9). However, reactions of diortho-substituted aryl bromides were unsuccessful. In contrast to reactions performed with many types of organometallics, these reactions are insensitive to the presence of water since five equivalents of water added at the reaction outset has no deleterious impact on the outcome.

A number of different pyridine *N*-oxides were subsequently shown to undergo reaction. Illustrative examples are presented in Tables 4.2 and 4.3. First, functional group compatibility was investigated with *para*-substituted *N*-oxides (Table 4.2). We found the reaction to be compatible with a wide range of substituents including ester (Entries 1,2 & 7), alkyl (Entries 3, 4 & 8) and aryl (Entries 9 and 10) groups affording the products in high yield with both electron rich and electron poor aryl halides. Alkoxy and nitro substitution is also tolerated leading to modest to good yields of the aryl pyridine products (Entries 5, 6, 11 & 12). C-6 arylation of 2-substituted pyridine *N*-oxide was then investigated (Table 4.3). We found 2-alkyl pyridines such as picoline *N*-oxide and 2,3-lutidine *N*-oxide to be less reactive under these conditions affording the corresponding products in poor to modest yeilds. However, adding an electron-withdrawing substitutent at C-5 increased the reactivity of the substrates as demonstrated by reactions of 5-cyano-2-methylpyridine *N*-oxide (Entry 3). Benzyl (Entry 4) as well as aryl (Entry 5) substitutents were well tolerated. In contrast to 2-picoline *N*-oxide, we found that 2-cyanopyridine *N*-oxide was an excellent substrate for the reaction affording good yields with a range of aryl bromide substitutents (Entries 6-8). We also found that 2,3-dimethyl pyrazine *N*-oxide, as well as 3-methyl isoquinoline *N*-oxide were very reactive affording high yields of the reaction. It was even possible to use 1.1 equivalents of *N*-oxide with the isoquinoline substrate.

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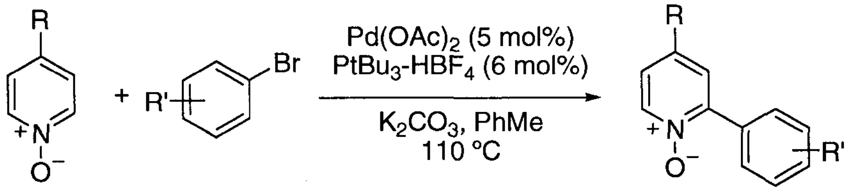
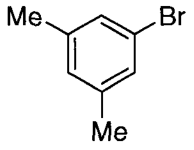
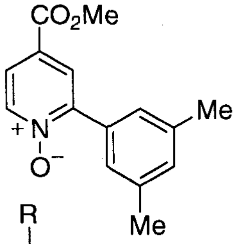
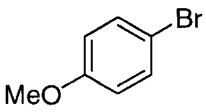
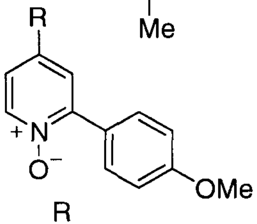
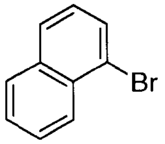
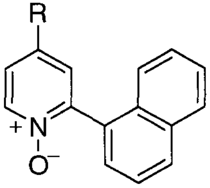
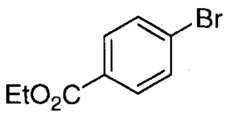
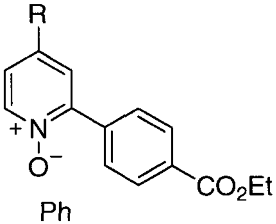
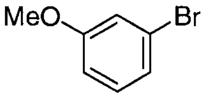
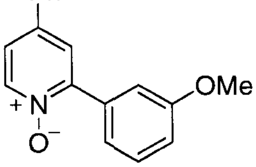
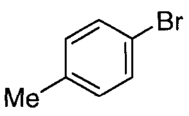
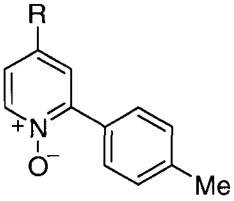
[171] Examples of exothermic onset temperatures ($T_o$): Pyridine *N*-oxide: 288 °C; 2,6-Lutidine *N*-oxide: 288 °C; Nicotinic acid *N*-oxide: 302 °C; γ-Picoline *N*-oxide: 285 °C; Picolinic acid *N*-oxide: 307 °C. From : Ando, T.; Fujimoto, Y.; Morisaki, S.; *J. Haz. Mat.* **1991**, *28*, 251.

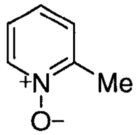
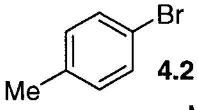
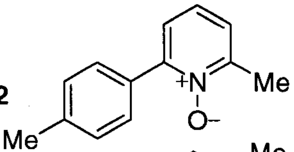
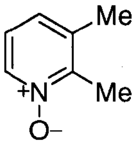
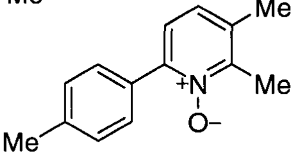
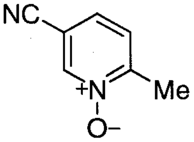
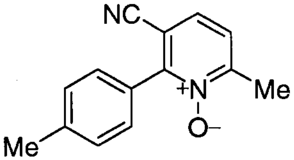
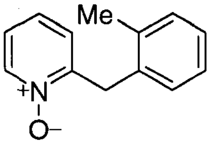
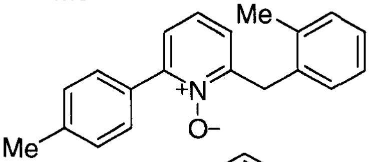
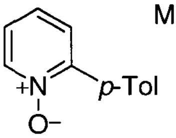
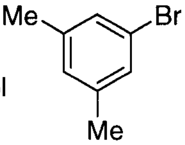
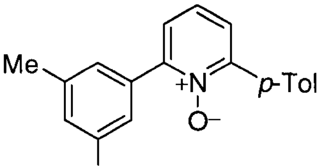
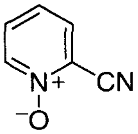
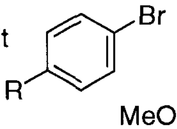
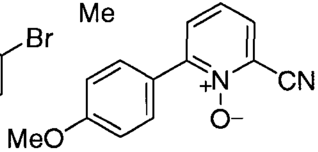
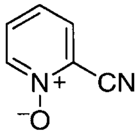
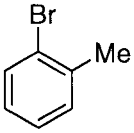
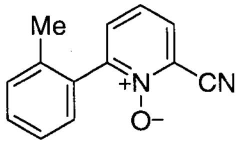
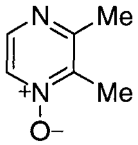
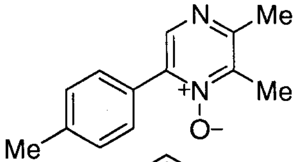
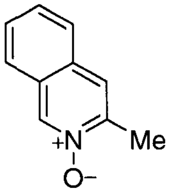
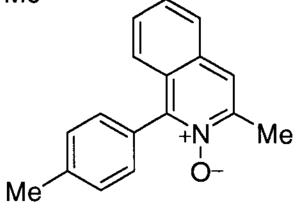
**Table 4.2** – Direct Arylation of 4-Substituted Pyridine N-Oxides



| Entry | Pyridine *N*-oxide | Aryl Halide | Product | Yield (%)[b] |
|---|---|---|---|---|
| 1 | R = $CO_2Me$ |  |  | 97 |
| 2 | R = $CO_2Me$ |  |  | 88 |
| 3 | R = Me | | | 95 |
| 4 | R = Me |  |  | 85 |
| 5 | R = $NO_2$ | | | 64[c] |
| 6 | R = OMe | | | 54[c] |
| 7 | R = $CO_2Me$ |  |  | 85[c] |
| 8 | R = Me | | | 76[c] |
| 9 | R = Ph | | | 90[c] |
| 10 | R = Ph |  |  | 85[c] |
| 11 | R = $NO_2$ |  |  | 78 |
| 12 | R = OMe | | | 80 |

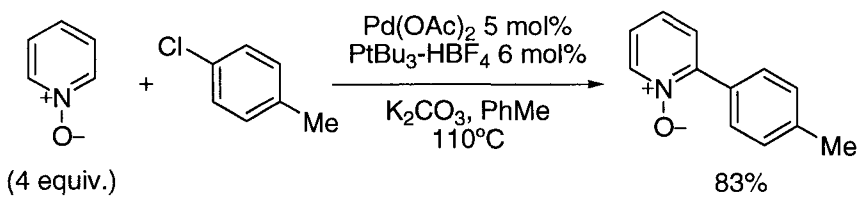
[a]Conditions: Aryl halide (1 equiv.), pyridine *N*-oxide (4 equiv.), $K_2CO_3$ (2 equiv.), $Pd(OAc)_2$ (0.05 equiv.) and $P^tBu_3$ – $HBF_4$ (0.15 equiv.) in toluene (0.3M) at 110 °C overnight. [b]Isolated Yields. [c]Reaction performed by Ho-Yan Sun

**Table 4.3** – Direct Arylation of 2-Substituted Pyridine N-Oxides

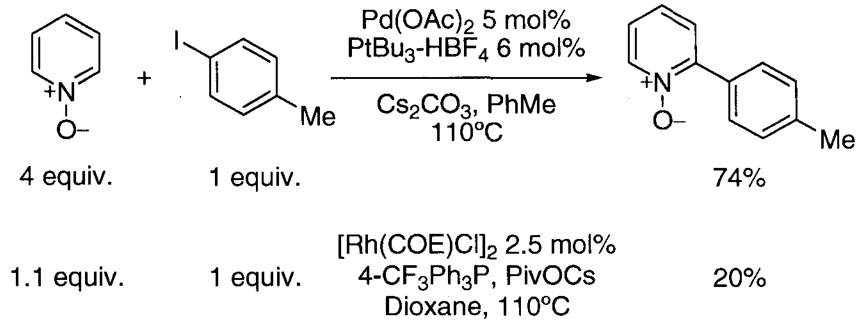
| Entry | *N*-Oxide | Aryl Halide | Product | Yield[b] |
|---|---|---|---|---|
| 1 |  |  **4.2** |  | 56 |
| 2 |  | **4.2** |  | 34 |
| 3 |  | **4.2** |  | 74 |
| 4 |  | **4.2** |  | 59 |
| 5 |  |  |  | 74 |
| 6<br>7 |  | R=CO$_2$Et<br>R=OMe  |  | 81[c,e]<br>81[c,e] |
| 8 |  |  |  | 68[c,e] |
| 9 |  | **4.2** |  | 89 |
| 10 |  | **4.2** |  | 90[d] |

[a] Conditions: Aryl halide (1 equiv.), pyridine *N*-oxide (2-3 equiv.), $K_2CO_3$ (2 equiv.), $Pd(OAc)_2$ (0.05 equiv.) and $P^tBu_3$ – $HBF_4$ (0.06 equiv.) in toluene (0.15M) at 110 °C overnight. [b] Isolated Yields. [c] With 4 equiv. of *N*-oxide and 15 mol% $P^tBu_3$ – $HBF_4$. [d] With 1.1 equiv. of *N*-oxide. [e] Reaction performed by Ho-Yan Sun

A brief investigation of aryl iodides and aryl chlorides as substrates was also performed. We found that it was possible to achieve good yields with both 4-chlorotoluene using the newly optimized (*vide infra*) conditions for arylation on large scale (Equation 4.2). Aryl iodide substrates were compatible when $K_2CO_3$ was replaced by $Cs_2CO_3$ as the base affording the product in 74% yield. Interestingly, aryl iodide substrates also showed promise using other metal catalysts such as rhodium. This observation should prompt the investigation of other metals using these substrates which seem predisposed to arylation reactions.[172]



(4.2)



(4.3)

These reaction conditions were also tested on quinoline *N*-oxides as substrates. Using the reaction conditions developed for pyridine *N*-oxide, we found that a modest yield for arylation of the C-2 position was obtained (Scheme 4.1). Following this lead result, David R. Stuart developed a high yielding protocol for the arylation of quinoline *N*-oxide.[173] Using the newly optimized protocol he was able obtain high yields for the coupling of a number of quinolines and aryl bromides.

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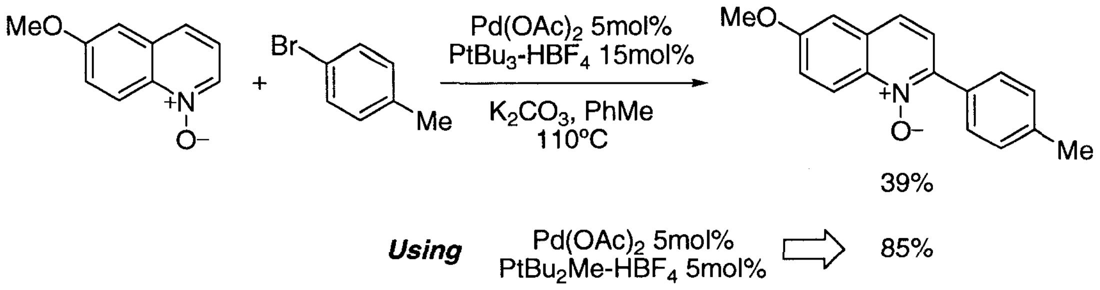
[172] Daugulis has since shown that CuI can catalyze the arylation of 2-phenylpyridine *N*-oxide, when an excess of ArI is used: Do, H.-Q.; Daugulis, O.; *J. Am. Chem. Soc.* **2007**, *129*, 12404

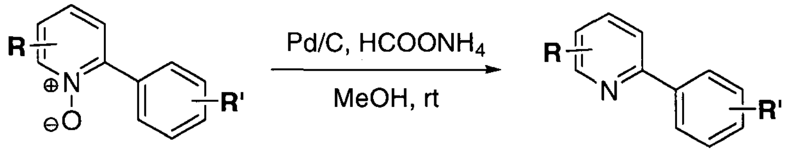
[173] Stuart, D. R.; Campeau, L.-C.; Sun, H.-Y.; Lecavalier, M.; Leclerc, J.-P.; Gorelsky, S.; Fagnou, K. *submitted for publication*



**Scheme 4.1** – Direct Arylation of Quinoline *N*-Oxide

The 2-arylpyridine *N*-oxide products can easily be converted to the corresponding 2-aryl pyridines under mild conditions and in high yields *via* palladium-catalyzed reduction with ammonium formate (Table 4.4).[174]

**Table 4.4** – Deoxygenation of Arylpyridine *N*-Oxides[a]



| R | R' | Yield (%) | R | R' | Yield (%) |
|---|---|---|---|---|---|
| H | 4-$CH_3$ | 95 | 4-OMe | 4-$CH_3$ | 84 |
| H | 3-OMe | 87 | H | 4-$CO_2CH_3$ | 87 |

[a]Conditions: Pyridine *N*-oxide (1 equiv.), Pd/C (0.1 equiv.), $HCOONH_4$ (10 equiv.) MeOH (0.2M), rt.

### Oxidation Methods for the Synthesis of Azine and Diazine *N*-Oxides

Over the course of ongoing studies, efficient methods for rapid access to a variety of pyridine *N*-oxides from commercailly available pyridines were needed. A number of methods were identified.[175] While oxidation with peracids such as mCPBA[176] or acetic acid/hydrogen peroxide[177] mixtures proved effective, tedious isolation protocols and the

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[174] Balicki, R.; *Synthesis*, **1989**, *8*, 645; Similar yield were also obtained using zinc mediated reduction, see: Aoyagi, Y.; Abe, T.; Ohta, A.; *Synthesis*, **1997**, *8*, 891

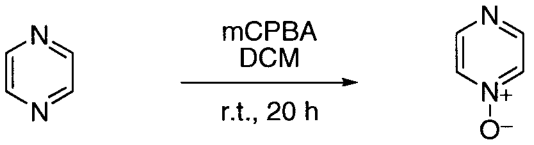
[175] (a) Ochiai, E. *Aromatic Amine Oxides*; Elsevier: Amsterdam, 1967; Albini, A.; Pietra, S. *Heterocyclic N-Oxides*; CRC Press: Boca Raton, FL, 1991. (b) For oxidation with DMDO: Murray, R. W.; Jeyaraman, R. *J. Org. Chem.* **1985**, *50*, 2847. (c) MTO: Coperet, C.; Adolfsson, H.; Khuong, T.-A. V.; Yudin, A. K.; Sharpless, K. B. *J. Org. Chem.*; **1998**; *63*, 1740. (d) Vanadium/$H_2O_2$ : Rout, L; Punniyamurthy, T.; *Adv. Synth. Catal.* **2005**, *347*, 1958. (e) $RuCl_3/O_2$ : Sain, B.; Jain, S.L.; *Chem. Commun.* **2002**, 1040. (f) HOF·MeCN: Rozen, S.; Kol, M.; Dayan, S.; *Synthesis*, **1999**, 1427. (g) Cobalt (II) Schiff base complex/$O_2$: Sain, B.; Jain, S.L.; *Angew. Chem. Int. Ed.* **2003**, *42*, 1265.

[176] Edwards, D. C.; Gillespie *Tetrahedron Lett.* **1966**, 4867.

[177] Chivers, G. E.; Suschitzky, H. *J. Chem. Soc., Chem. Commun.* **1971**, 28. Takabe, K.; Yamada, T.; Katagiri, T. *Chem. Lett.* **1982**, 1987. Tortorella, V. *J. Chem. Soc., Chem. Commun.* **1966**, 308. Kaczmarek; Balicki, R.; Nantka-Namirski, P. *Chem. Ber.* **1992**, *125*, 1965.

high solubility of pyridine *N*-oxides in water led us to identify a better method for their synthesis. Ultimately, a catalytic oxidation with methyltrioxorhenium and hydrogen peroxide developed by Sharpless and co-workers was chosen as the optimal reaction.[175c] This method allows for easy isolation of the final products by simple extraction and filtration of the reaction mixture, often giving access to analytically pure samples without chromatography. The high efficacy of this method prompted us to investigate its use in the synthesis of mono diazine *N*-oxides. At the time of these studies, the highest yielding protocol for the isolation of diazine *N*-oxides called for a *m*CPBA oxidation followed by silica adsorption and lengthy chromatography. Alternatively, extraction and filtration of the *m*-chlorobenzoic acid (*m*CBA) led to consistently lower yields (Table 4.5).[178]

**Table 4.5**– Oxidation of Pyrazine Using mCPBA



| Entry | Conversion | Work-Up/Purification | Yield |
|---|---|---|---|
| 1 | 100 % | Extraction with NaOH 10 %<br>followed by silica gel chromatography | 41 % |
| 2 | 100% | Direct filtration of reaction followed by<br>silica gel chromatography of filtrate | 60 % |
| 3 | 100 % | Absorption of reaction mixture onto<br>silica gel followed by chromatography | 79 % |

Initial attempts to carry-out the Sharpless protocol with pyrazine *N*-oxide led to complete consumption of starting material. However, no mono pyrazine *N*-oxide was observed. Isolation of a white precipitate from the reaction confirmed the formation of pyrazine di-*N*-oxide. Measures were then undertaken to reduce the formation of this unwanted byproduct (Table 4.6). Reduction of $H_2O_2$ equivalents from 2 to 1 only led to 43% product yield (Entry 3). The reaction was then diluted from 2.5M to 1M. This resulted in an improved yield of 77% (Entry 4). It is also possible to perfom the reaction in a 1:1 mixture of MeOH:DCM for less soluble substrates (Entry 5). Though it was not possible to completely supress dioxidation with pyrazines, the yields obtained through

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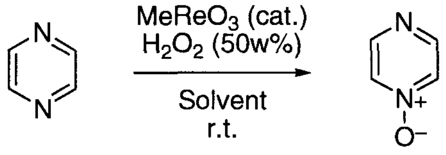
[178] This phase of the experimentation was carried out by Jean-Philippe Leclerc, M. Sc. Thesis, 2005-2007

this method are comparable to those obtained with the use of *m*CPBA. However, this method eliminates the tedious separation of the *m*CBA byproduct.[179]

**Table 4.6** – Oxidation of Pyrazine with $MeReO_3/H_2O_2$



**4.3**

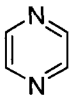
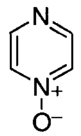
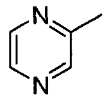
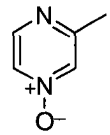
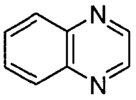
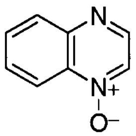
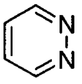
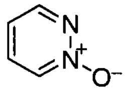
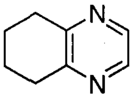
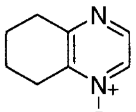
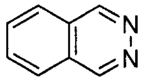
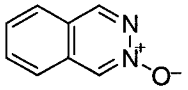
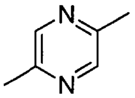
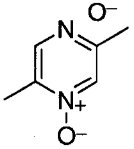
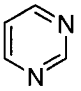
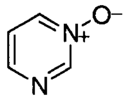
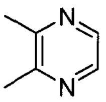
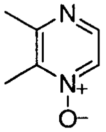
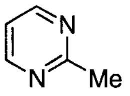
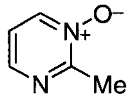
| Entry | mol% Re | equiv. $H_2O_2$ | Solvent | Conc. (M) | Yield **4.3**(%) |
|---|---|---|---|---|---|
| 1 | 1 | 2 | $CH_2Cl_2$ | 2.5 | Trace |
| 2 | 1 | 1.5 | $CH_2Cl_2$ | 2.5 | 10 |
| 3 | 1 | 1 | $CH_2Cl_2$ | 2.5 | 46 |
| 4 | 1 | 1 | $CH_2Cl_2$ | 1 | 77 |
| 5 | 1 | 1 | $CH_2Cl_2$:MeOH | 1 | 76 |

Screening pyrimidines and pyridazines revealed that these were more resistant to dioxidation. Substituted pyrazines were also less prone to dioxidation than pyrazine itself. Nonetheless, careful monitoring of reactions is recommended in order to minimize the formation of these side products. The reaction conditions are amenable to a broad scope of diazines and are compatible with a variety of substrates (Table 4.7)[180]. A number of pyrazines, including those with *ortho*-substitution, undergo the reaction in good yield. The process is also compatible with quinoxaline, pyridazine, pyrimidine and phthalazine. In most cases the reaction produces analytically pure material by simple filtration and extraction. This high yielding, selective and operationally simple oxidation procedure represents an attractive alternative to tedious mCPBA oxidations and should find use for the synthesis of mono diazine *N*-oxides.

---

[179] Campeau, L.-C.; Leclerc, J.-P.; Fagnou, K.; *unpublished results*
[180] mCPBA oxidations performed by Jean-Philippe Leclerc

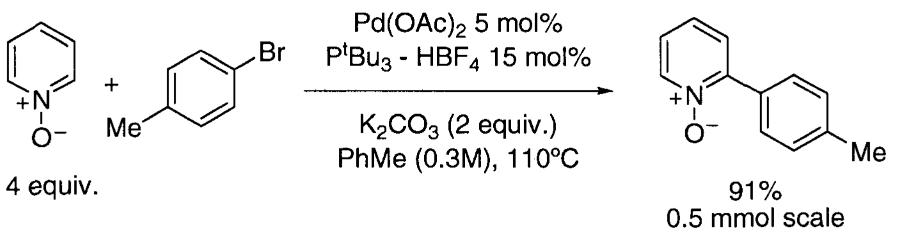
**Table 4.7** - Selecitve Oxidation of Diazine *N*-Oxide.$^a$

| Entry | Azine | % MTO | Product | Yield (%) | Entry | Azine | % MTO | Product | Yield (%) |
|---|---|---|---|---|---|---|---|---|---|
| 1 |  | 1 |  | 77<br>(79) | 6 |  | 1 |  | 93$^b$ |
| 2 |  | 1 |  | 63<br>(66) | 7 |  | 1 |  | 94<br>(89) |
| 3 |  | 1 |  | 84<br>(76) | 8 |  | 2 |  | 93 |
| 4 |  | 1 |  | 85 | 9 |  | 1 |  | 94<br>(78) |
| 5 |  | 1 |  | 85<br>(75) | 10 |  | 3 |  | 73 |

$^a$Conditions: diazine (1 equiv.), MTO (indicated amount), 1.0-1.2 equiv. 50% aqueous $H_2O_2$ in DCM (2-3M) >99% conversion, isolated yields. Yield in parenthesees resulting from mCPBA oxidation performed by Jean-Philippe Leclerc, conditions: diazine (1 equiv.), mCPBA (1.1 equiv.) in DCM (0.5M) >99% conversion. $^b$Isolated as a 1:1 mixture of isomers

## Optimization for a multi-gram scale process

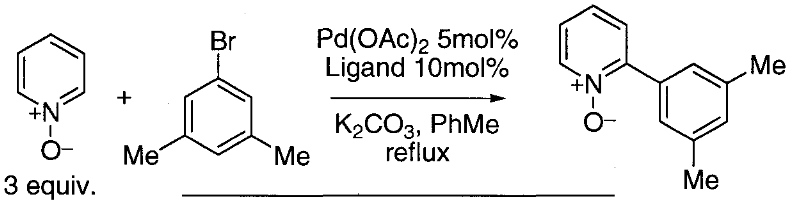
In the context of an *Organic Synthesis* preparation, we were faced with the challenge of developing a reliable and scalable process (5-10 g) for the arylation of pyridine *N*-oxide. Given that the current reaction conditions were meant to be as broad in scope as possible, we decided to perform an in-depth optimization of the reaction, including the isolation protocol, for one substrate in the context of this large scale procedure.



(4.4)

This optimization was geared towards confirming the most active palladium and ligand combination as well as the need for any excess reagents, the ideal reaction solvent and concentration. A larger scale purification protocol would also have to be developed. All reaction optimization was carried out in a Radley's Greenhouse reactor on 0.5 mmol scale. Once optimized, the reaction was attempted on 5 mmol scale using conventional glassware. When reproducible results were obtained, scale up to 50 mmol was attempted.

Our optimization began with the choice of ligand, including Pd:L ratio. Initially triaryl, trialkyl as well as biaryl type phosphines were screened using 3 equivalents of pyridine *N*-oxide and a ligand to palladium ratio of 2:1 (Figure 4.1). From this screen, it became evident that trialky and biaryl phosphines generated superior catalysts.

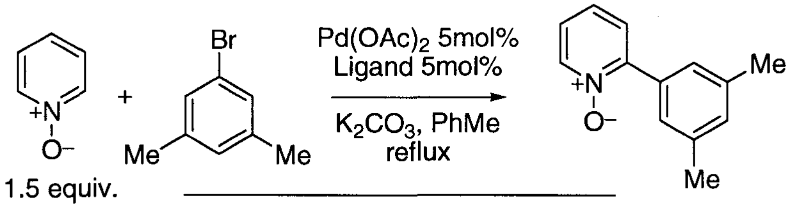


| Entry | Ligand | Yield |
|---|---|---|
| 1 | $P^tBu_3$ | 87 |
| 2 | $\mathrm{P}t\mathrm{Bu_2Me}$ | 71 |
| 3 | $PCy_3$ | 38 |
| 4 | DavePhos | 41 |
| 5 | $PPh_3$ | 19 |
| 6 | $(p\text{-}CF_3C_6H_4)_3P$ | 19 |
| 7 | $(p\text{-}OMeC_6H_4)_3P$ | 18 |

[a]Yields determined by NMR using 1,3,5-trimethoxybenzene as internal standard.

**Figure 4.1** – Screen of Trialkyl-, Triaryl- and Biaryl-phosphines

We next turned our attention to bidentate phosphines, this time under more demanding conditions, using 1.5 equivalents of pyridine *N*-oxide (Figure 4.2). Again, the results of the screen illustrated the superiority of $PtBu_3$ for this transformation. It should be noted that the use of a ligand to palladium ratio of 1:1 with $PtBu_3$ led to superior results. However, it was observed that certain reactions afforded much lower yields at this Pd:L ratio, instead leading to rapid palladium black formation. Assuming this to be a problem with irreproducible catalyst initiation, a slight excess of the phosphine was used in the optimal protocol (Pd:L = 1:1.2) which led to high reproducibility.



| Entry | Ligand | Yield[a] |
|---|---|---|
| 1 | P$^t$Bu$_3$* | 73 |
| 2 | P$^t$Bu$_3$ | 80 |
| 3 | dppm | 30 |
| 4 | dppe | 17 |
| 5 | dppp | 27 |
| 6 | dppb | 34 |
| 7 | dppf | 10 |
| 8 | XantPhos | 22 |
| 9 | JosiPhos | 27 |

[a]Yields determined by NMR using 1,3,5-trimethoxybenzene as internal standard.

**Figure 4.2** – Screen of Trialkyl- versus Bidentate-phosphines

A number of different bases were screened using 2 equivalents of base in relation to aryl bromide. $K_2CO_3$, KOAc, $Cs_2CO_3$ and CsOPiv all gave identical conversions. Only $K_3PO_4$ resulted in lower yields. It was also observed that the use of a large excess of base is not necessary. Although as little as 1.1 equivalents can be employed to give similar yields, typically 1.3 equivalents are used. A re-investigation of the concentration of the reaction media revealed that diluting by a factor of two is beneficial (Figure 4.3).

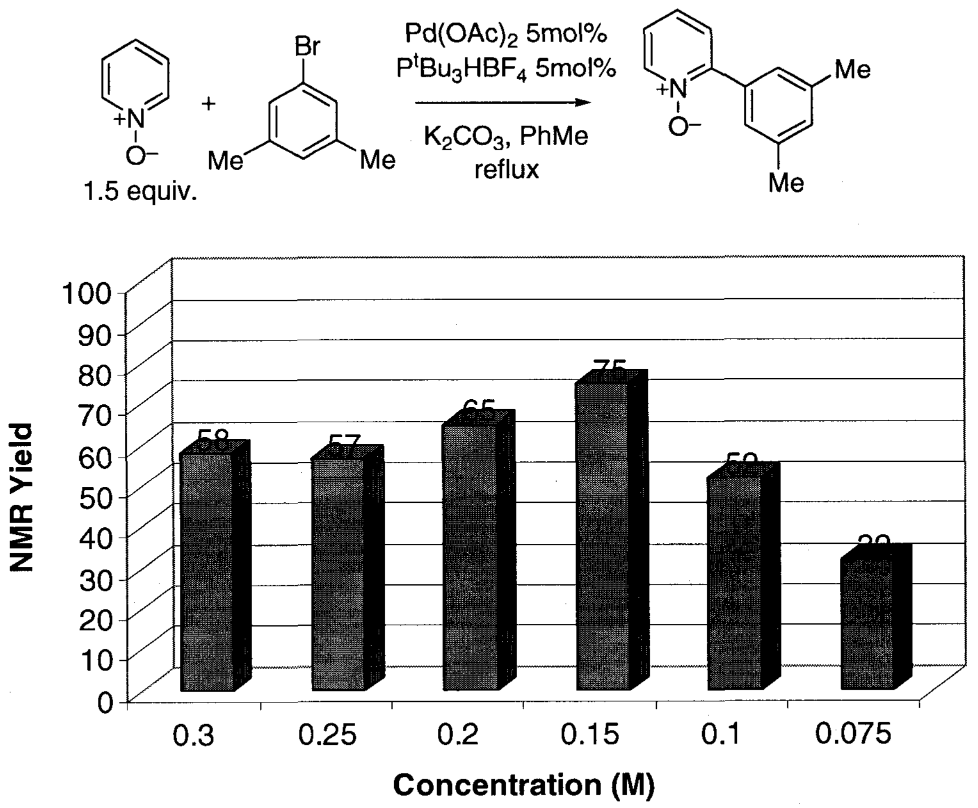


**Figure 4.3** – Effect of Concentration on the Direct Arylation of Pyridine N-oxide

Finally, screening various palladium sources revealed that a number of these were compatible with reaction conditions although $PdCl_2$ was found to lead to irreproducible results, perhaps due to its low solubility in toluene (Figure 4.4).

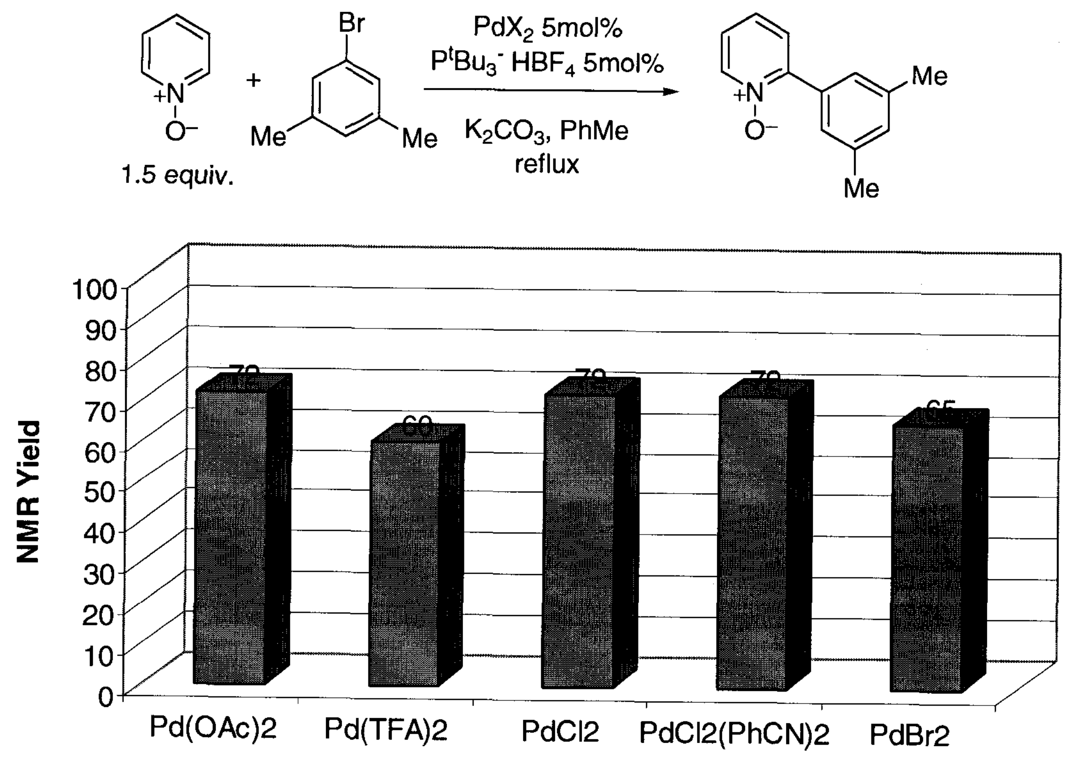


**Figure 4.4** – Effect of the Source of Palladium on the Direct Arylation of Pyridine N-oxide

The new re-optimized reaction conditions were then set as follows: pyridine *N*-oxide (1.5 equiv.), aryl bromide (1 equiv.), $Pd(OAc)_2$ (5 mol %), $P^tBu_3$ – $HBF_4$ (6 mol %) with $K_2CO_3$ (1.3 equiv.) in refluxing toluene (0.15M) for 16 hours (overnight). While isolated yields ranging from 65-75% could be obtained on 0.5 mmol scale in the Greenhouse reactor, scaling up the reaction using conventional glassware even to 5-6 mmol resulted in reduced yields ranging from 60-69%. It was hypothesized that the reduced turnover numbers were due to oxygen poisoning of the catalyst over the course of the reaction. In an effort to accelerate the reaction, equivalents of *N*-oxides were raised. With 2 equivalents, yields ranging from 70-72% were obtained. However, with 4 equivalents, it was possible to achieve 78-83% yields even on 50 mmol scale. We found that unreacted pyridine *N*-oxide could be recovered in >90% yield from the reaction mixture during the extraction.[181]

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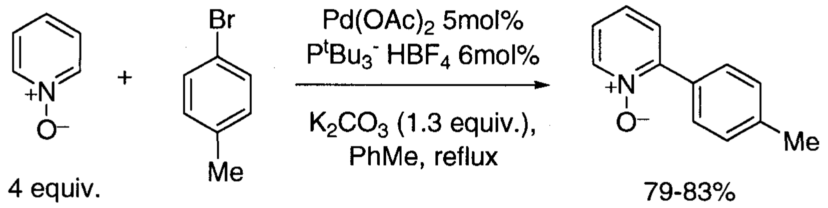
[181] Campeau, L.-C.; Fagnou, K.; *Org. Synth. submitted.* A copy of the protocol is presented in the supporting information (chp 7)

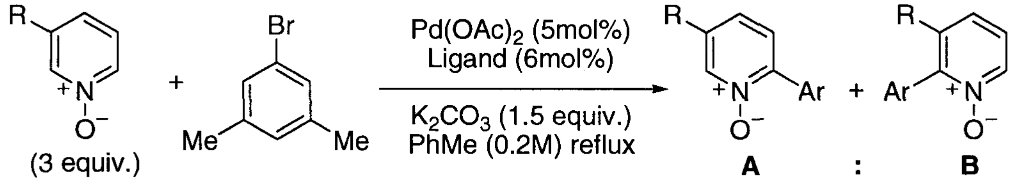


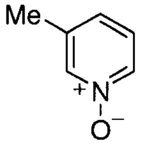
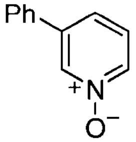
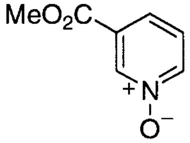
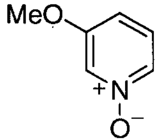
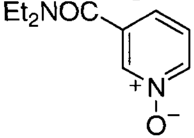
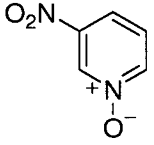
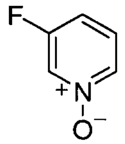
**Scheme 4.2** – Re-optimized Protocol for the Direct Arylation of Pyridine N-oxide

### Regioselectivity in the direct arylation of pyridine *N*-oxides

The use of 3-substituted pyridine *N*-oxides as substrates can provide useful information about catalyst selectivity as well as the mechanism of the reaction. Substituents tested range from electron donating to withdrawing groups as well as alkyl and aryl groups. Table 4.8 provides illustrative examples of the selectivity and yield of these reactions. In the case of an alkyl or aryl substitution, the more sterically available C-6 position is arylated (Entries 1 and 2). 3-Picolinic ester derived substrates also follow this trend and favor arylation of the C-6 position (Entry 3). In contrast, 3-picolinamide *N*-oxide affords very poor selectivity (Entry 6). Likewise, methyl ether substituted pyridine *N*-oxide undergoes arylation without bias resulting in a 1.1:1 ratio (Entry 4). Based on our previous work with intramolecular arylation (see chapter 2), we attempted substituting $P^tBu_3$ with $P^tBu_2Me$ to observe any resulting change in selectivity. We were gratified to see that this modification led to increased selectivity with 3-methoxypyridine *N*-oxide leading to opposite isomer **B** as the major isomer in a 5.2:1 ratio. However when a similar experiment was carried out with *N,N*-diethyl 3-picolinamide *N*-oxide, a more modest reversal in selectivity was observed leading to 1.4:1 ratio favoring isomer **B**. On the other hand, we consistently observed a strong bias for isomer **B** with less sterically demanding electron withdrawing groups such as CN, $NO_2$ and F (Entries 8, 10 and 12), with 3-fluoropyridine *N*-oxide exclusively providing isomer **B**. Selectivity for isomer **B** can also be enhanced for the 3-CN and 3-$NO_2$ substrates by using $P^tBu_2Me$ (Entries 9 and 11). In all cases, it was possible to separate the isomers by flash chromatography to afford the major products in good to excellent yield.

**Table 4.8** – Regioselectivity in Pyridine N-oxide Direct Arylation[a]

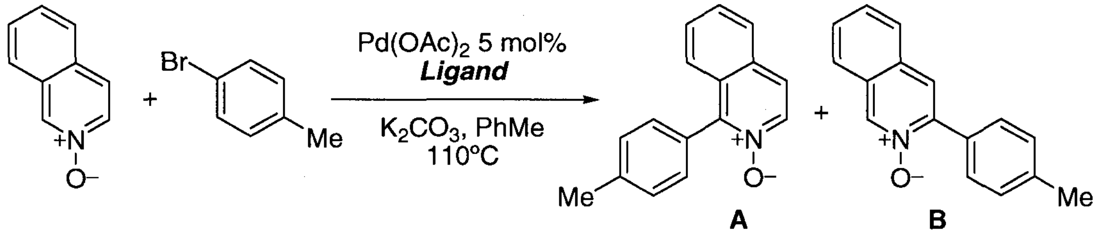


| Entry | Pyridine *N*-Oxide | Ligand | Yield (%)[b] | Ratio **A**:**B**[c] |
|---|---|---|---|---|
| 1 |  | $P^{t}Bu_{3}$-$HBF_{4}$ | 78 (59) | 3.3 : 1 |
| 2 |  | $P^{t}Bu_{3}$-$HBF_{4}$ | 94 (80) | 10 : 1 |
| 3 |  | $P^{t}Bu_{3}$-$HBF_{4}$ | 86 (74) | 6.7 : 1 |
| 4 |  | $P^{t}Bu_{3}$-$HBF_{4}$ | 88 | 1.1 : 1 |
| 5 | | $P^{t}Bu_{2}Me$-$HBF_{4}$ | 96 (79) | 1 : 5.2 |
| 6 |  | $P^{t}Bu_{3}$-$HBF_{4}$ | 99 (55) | 1.1 : 1 |
| 7 | | $P^{t}Bu_{2}Me$-$HBF_{4}$ | 83 | 1 : 1.4 |
| 8 |  | $P^{t}Bu_{3}$-$HBF_{4}$ | 89 (67) | 1 : 3.7 |
| 9 | | $P^{t}Bu_{2}Me$-$HBF_{4}$ | 86 | 1 : 6.3 |
| 10 |  | $P^{t}Bu_{3}$-$HBF_{4}$ | 98 (88) | 1 : 9.5 |
| 11 | | $P^{t}Bu_{2}Me$-$HBF_{4}$ | 88 | 1 : 15 |
| 12 |  | $P^{t}Bu_{3}$-$HBF_{4}$ | 83 (78)[d] | 1 : 25 |

[a]Conditions: Aryl halide (1 equiv.), pyridine *N*-oxide (3 equiv.), $K_2CO_3$ (1.5 equiv.), $Pd(OAc)_2$ (0.05 equiv.) and $P^tBu_3$ – $HBF_4$ (0.06 equiv.) in toluene (0.15M) at 110 °C overnight. [b]Yield determined by NMR using 1,3,5-trimethoxybenzene as standard. Yield in parentheses are isolated yield of major isomer. [c]Determined by NMR. [d]Using 1.1 equiv. of *N*-oxide.

**Isoquinoline as substrates in direct arylation**

Early reaction screening revealed that isoquinoline *N*-oxides could be suitable substrates for the chemistry previously described (Scheme 4.3). Using the reaction conditions developed for pyridine *N*-oxide, we found that a modest ratio of 1.5:1 was obtained in favor of arylation of the C-1 position on isoquinoline. Following this lead result, David R. Stuart developed a high yielding and site selective protocol for the arylation of isoquinoline *N*-oxide. Using $\mathrm{P^tBu_2Me}$ as the ligand affords the product in high yield with a 13.5:1 ratio in favor of the C-1 isomer.



| Ligand | Yield | Ratio **A**:**B** |
|---|---|---|
| $PtBu_3$-$HBF_4$ | 92% | 1.5:1 |
| $PtBu_2Me$-$HBF_4$ | 98% | 13.5:1 |

**Scheme 4.3** – Direct Arylation of Isoquinoline Derivatives

## Mechanistic Studies

In hopes of gaining insight into catalyst and substrate requirements, as well as understanding the results presented in the previous section, we were interested in investigating the reaction mechanisms. A number of different mechanisms have been proposed for direct arylation. Evidence of electrophilic palladation pathways ($S_EAr$) with electron-rich arenes has been demonstrated.[182] More recently, concerted metallation/deprotonation processes have been proposed for simple and electron deficient benzenes.[183] Among other possibilities, C-H activation[184] and carbo-palladation

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[182] (a) Yanagisawa, S.; Sudo, T.; Noyori, R.; Itami, K.; *J. Am. Chem. Soc.* **2006**, *128*, 11748; (b) Lane, B. S.; Brown, M. A.; Sames, D.; *J. Am. Chem. Soc.* **2005**, *127*, 8050 and references therein

[183] (a) Lafrance, M.; Rowley, C. N.; Woo, T. K.; Fagnou, K.; *J. Am. Chem. Soc.* **2006**, *127*, 8754; (b) Lafrance, M.; Fagnou, K; *J. Am. Chem. Soc.* **2006**, *128*, 16496 (c) Garcia-Cuadrado, D.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M.; *J. Am. Chem. Soc.* **2006**; *128*, 1066; (d) Garcia-Cuadrado, D.; de Mendoza, P.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M.; *J. Am. Chem. Soc.*; **2007**, *129*, 6880.

[184] Campo, M. A.; Huang, Q.; Yao, T.; Tian, Q.; Larock, R. C. *J. Am. Chem. Soc.* **2003**, *125*, 11506.

(aromatic Heck reactions) have also been proposed as possible pathways.[185] In addition, this investigation is complicated by the fact that the *N*-oxide moiety provides additional possibilities when considering the reaction mechanism. Pyridine *N*-oxides can not only react as electrophiles in the presence of strong nucleophiles, such as Grignard reagents,[186] but also as nucleophiles in electrophilic aromatic substutition (Figure 4.5).[187] Additionally, the *N*-oxide moiety might participate in the formation of palladacycles or act as a basic directing group to bring both metal and arene in close proximity.[188] Given recent reports dealing with direct metallation of azines[189], as well as our interest in developing better catalysts for direct arylations, we sought to identify the mode of pyridine metallation in this reaction. In order to ascertain the true mechanism operating in the case of azine *N*-oxides, we decided to match both experimental results and a theoretical DFT study.

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[185] This pathway has been proposed as a possibility before: (a) Toyata, M.; Ilangovan, A.; Okamoto, R.; Masaki, T.; Arakawa, M.; Ihara, M.; *Org. Lett.* **2002**, *4*, 4293 Proposed but dismissed: (b) Trauner, D.; Hughes, C.C.; *Angew. Chem. Int. Ed.* **2002**, *41*,1569

[186] Andersson, H.; Almqvist, F.; Olsson, R. *Org. Lett.* **2007**, *9*, 1335

[187] Taylor Jr., E. C. Crovetti, A. J. *Organic Syntheses, Coll. Vol. 4*, p.654 (**1963**); *Vol. 36*, p.53 (**1956**).

[188] Palladium complexes of azine *N*-oxides are known : (a) López, G.; García, G.; Cutillas, N.; Ruiz, J.; *J. Organomet. Chem.* **1983**, *241*, 269; (b) Mikulski, C. M. ; Gelfand, L. S.; Pytlewski, L. L. ; Skryantz, J. S.; Karayannis, N. M.; *Inorganica Chem. Acta,* **1977**, *21*, 9

[189] (a) Esteruelas, M. A.; Fernandez-Alvarez, F. J.; Onate, E.; *J. Am. Chem. Soc.* **2006**, *26*, 5239**.** (b) Pool, J. A.; Scott, B. L.; Kiplinger, J. L.; *J. Am. Chem. Soc.* **2005**, *127*, 1338. (c) Alvares, E.; Conejero, S. Paneque, M.; Petronilho, A.; Poveda, M. L. Serrano, O.; Carmona, E.; *J. Am. Chem. Soc.* **2006**, *128*, 13060.

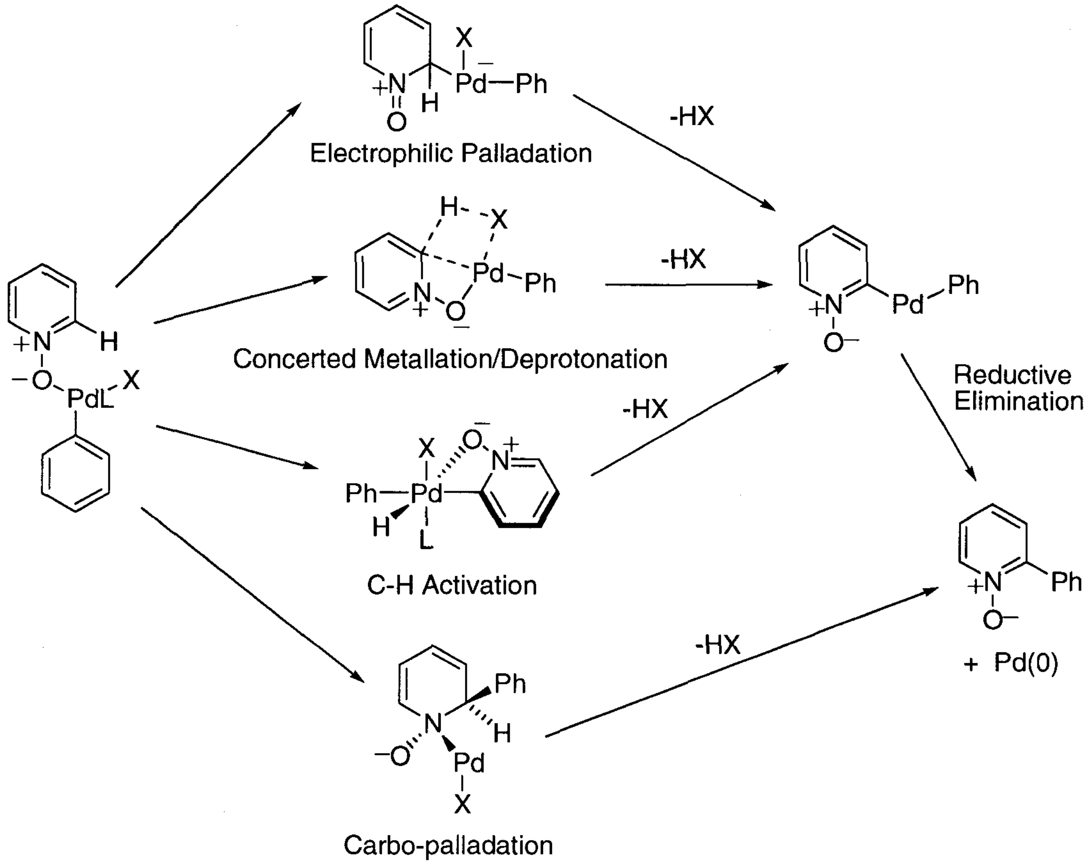
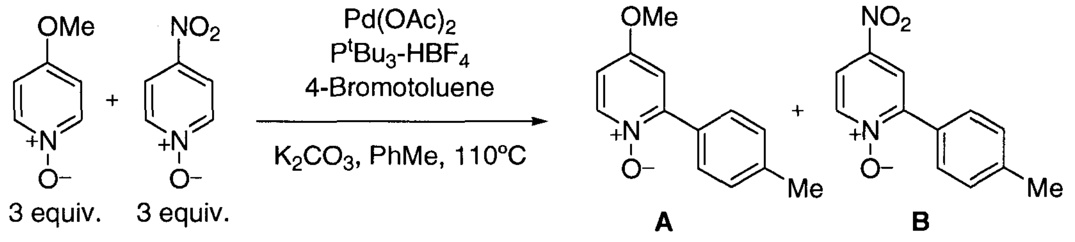


**Figure 4.5** - Possible Mechanisms for the Direct Arylation of Pyridine N-Oxide

To probe the presence of any electronic bias in these direct arylation reactions, a number of competition experiments were performed to determine whether the catalyst would have a preference for electron-rich or electron-poor azine *N*-oxides. In the first case we examined the reaction of 4-bromotoluene (1 equiv.) with a mixture of 4-methoxypyridine *N*-oxide (3 equiv.) and 4-nitropyridine *N*-oxide (3 equiv.) (Equation 4.5).

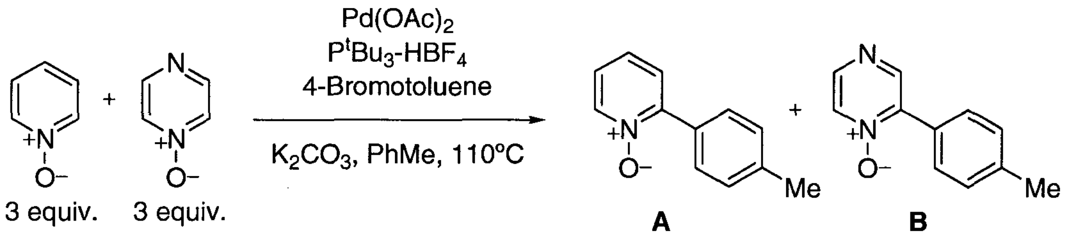


(4.5)

**A**:**B** = >1:25

The preferential reaction of the electron-poor pyridine indicates that an $S_EAr$ pathway is unlikely. To confirm this result, a second experiement was performed using pyrazine *N*-

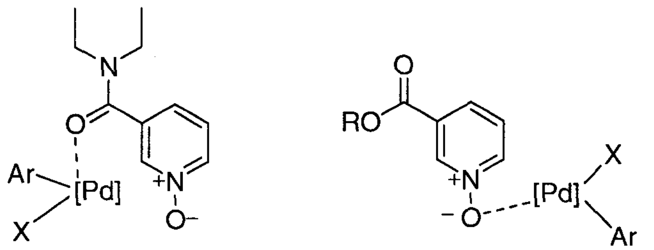
oxide and pyridine *N*-oxide (Equation 4.6). Once again, the preferential reaction of the more π-deficient pyrazine *N*-oxide was observed, supporting our previous observation.



(4.6)

**A**:**B** = >1:25

Another informative experiment is the reactivity of 3-substituted pyridine *N*-oxides. The regioselectivity obtained could provide clues as to the reaction mechanism. Many factors can play a role in determining selectivity. Certainly, steric bulk will play an important role. We might also expect to see trends in selectivity paralleling the electronic properties of the ring as well as C-H acidity. We found that in the absence of any electronic effects, sterics was a major factor in reaction selectivity. This can be clearly seen as the methyl substituted pyridine *N*-oxide led to a more modest selectivity than phenyl which would occupy a larger space when considering free rotation about the biaryl bond. Contrasting results were obtained when comparing the selectivity of ester functionality versus amide functional groups. While the ester groups directed reactions at the sterically accessible C-6 position, amides were unselective and when used with the smaller $P^tBu_2Me$-based catalyst, these substrates even slightly favored C-2 arylation. This dramatic effect could be the result of a directing effect of the amide carbonyl on the catalyst (Scheme 4.4), a key feature in many directed arylation reactions.[190]



**Scheme 4.4** - Possible Directing Effect of an Amide Substituent in the Direct Arylation of Pyridine *N*-Oxides

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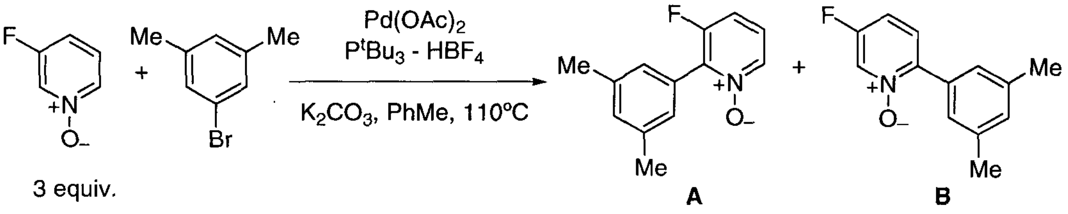
[190] Daugulis, O.; Zaitsev, V. G.; Shabashov, D.; Pham, Q.-N.; Lazareva, A. *Synlett*, **2006**, *20*, 3382

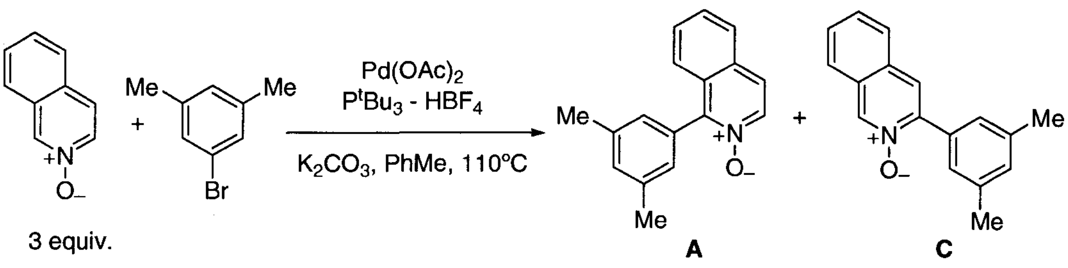
Similar results were observed with 3-methoxy pyridine *N*-oxide which afforded a 5.2:1 ratio in favor of C-2 arylation with the $P^tBu_2Me$ based catalyst compared to no selectivity when $P^tBu_3$ was used as a ligand. Whether this is the result of a binding effect, or increased C-H acidity at the C-2 position due to the σ-withdrawing nature of the electronegative oxygen atom, still remains to be determined. The strong bias for arylation of the C-2 position with small electron withdrawing groups is a trend evident with the reactions of 3-$NO_2$-, 3-CN- and 3-fluoro-pyridine *N*-oxide. In fact when 3-fluoro-pyridine *N*-oxide is reacted with 3,5-bromoxylene, a single product resulting from reaction at C-2 is observed (Equation 4.7). The strong σ-withdrawing nature of these substitutents would certainly affect kinetic acidity in the *ortho*-position. The increased selectivity for 3-CN and 3-$NO_2$ substrates with the use of a smaller ligand ($P^tBu_2Me$) demonstrates the catalyst's sensitivity to sterics.



(4.7)

**A**:**B** > 25:1

Similar arguments can be used to explain the reactions of isoquinoline *N*-oxide, which slightly favor arylation at the 1-position over the more sterically accessible 3-positions (Equation 4.8). While it is unclear whether this is due to C-H acidity, one must also consider the nucleophilic nature of the carbon, which is simultaneously forming a bond with the palladium center as deprotonation occurs. Electrophilic aromatic substitution on isoquinoline *N*-oxide tends to occur at the C-1 position. This effect might be an important contributing factor in these concerted processes. More interestingly, changing the phosphine in this reaction for the less sterically demanding $P^tBu_2Me$, increases regioselectivity for the C-1 position leading to a ratio of 13:1. Overall, the proposed mechanistic model should be able to accurately predict the trends observed in these important selectivity studies.



(4.8)

$P^tBu_3$-$HBF_4$ **A**:**B** = 1.5:1
$P^tBu_2Me$-$HBF_4$ **A**:**B** = 13 :1

Kinetic isotope effects are also useful mechanistic probes. With pyridine *N*-oxide, a primary kinetic isotope effect of 4.7 is observed, indicating a kinetically significant C-H bond cleavage during the arylation step. This observation, along with preferential reactions of electron deficient azine *N*-oxides, indicates that an electrophilic palladation mechanism is unlikely. Unfortunately, none of the experimental observations could definitively distinguish between the remaining possible reaction pathways. We therefore turned to DFT analysis to collect additional information about the relative energetics of these possibilities and develop a working mechanistic hypothesis.

## Theoretical Results

### *Computational Details*

Quantum chemical[191] density functional theory[192] (DFT) calculations were performed with Becke's three parameter hybrid gradient-corrected exchange functional[193] and the gradient-corrected correlation functional of Lee, Yang and Parr,[194] commonly abbreviated as B3LYP. All calculations were performed with the Jaguar 6.0 software package.[195] The triple-zeta basis set, LACV3P**, that includes polarization functions was used. Frequency calculations were performed on all stationary points and the energies reported include unscaled zero-point vibrational energy corrections. A slightly smaller model system was used for the catalyst by replacing the bulky phosphine ligand used experimentally with a $PH_3$ ligand. This is a typical approach used in quantum chemical

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[191] Ziegler, T.; Autschbach, *Chem. Rev.* **2005**, *105*, 2695.

[192] (a) Hohenburg, P.; Kohn, W. *Phys. Rev. B* **1964**, *136*, 864. b) Kohn, W.; Sham, L. J. *Phys. Rev. A* **1965**, *140*, 1133.

[193] Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.

[194] Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B.* **1988**, *37*, 785.

[195] *Jaguar 6.0*; Schrodinger, LLC: Portland, Oregon, 2004

calculations to reduce computation times. The effect of the phosphine ligand is not expected to change the qualitative nature of these calculations.[196]

### C-H Activation

Although C-H activation is often proposed as a mechanism for direct arylation, there is growing evidence that these processes are much higher in energy in relation to other pathways. For example, recent computational work on a 1,5-palladium vinyl to aryl shift has shown that concerted pathways involving only the palladium (II) oxidation state is more favorable to the high energy palladium (IV) intermediate generation required for C-H activation.[197] In our system, this pathway would involve insertion of the palladium (II) species **4.4** to give the octahedral species **4.5**. Reductive elimination would give **4.6** which is a common intermediate in the catalytic cycle. Ground state structures were found for all three intermediates and their relative energies were evaluated (Figure 4.8).

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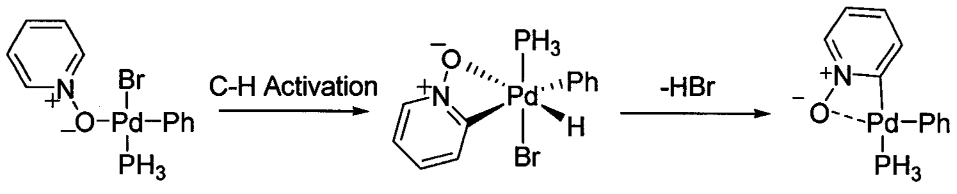
[196] This approach was recently used in similar systems : (a) Garcia-Cuadrado, D.; de Mendoza, P.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2007,** *129,* 6880 (b) Garcia-Cuadrado, D.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006,** *128,* 1066. (c) Lafrance, M.; Rowley, C. N.; Woo, T. K.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128,* 8754.

[197] Mota, A.J.; Dedieu, A.; Bour, C.; Suffert, J.; *J. Am. Chem. Soc.* **2005**, *127,* 7171



**4.4** **4.5** **4.6**

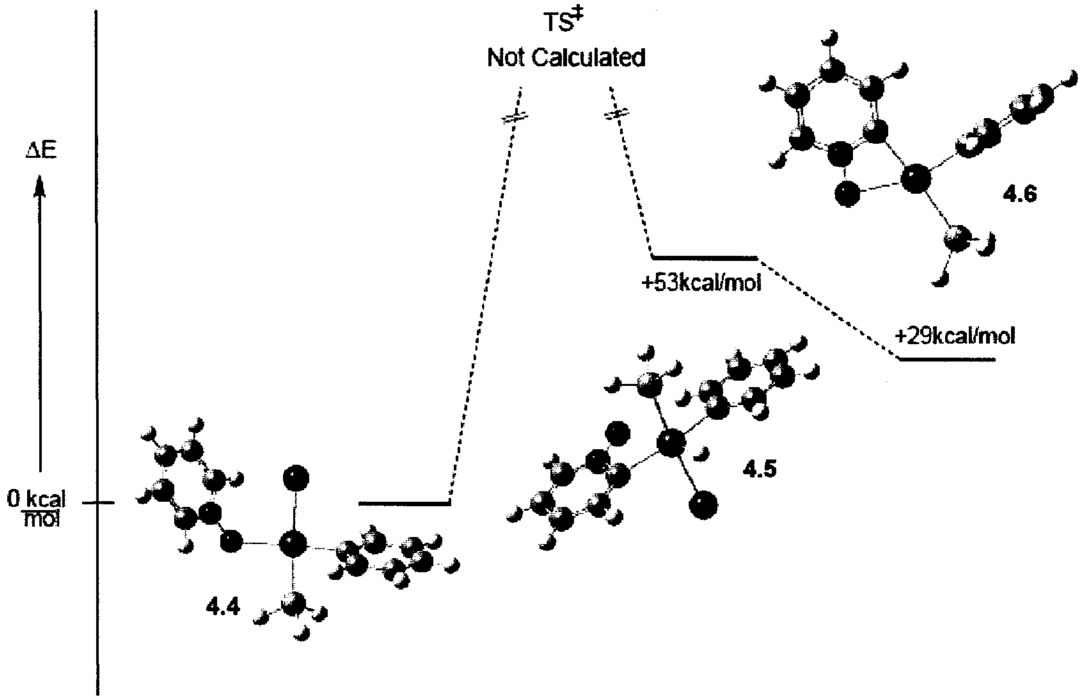


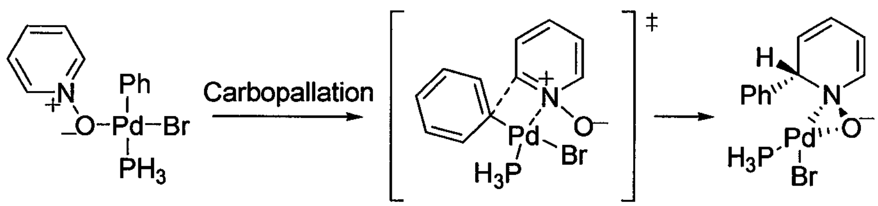
**Figure 4.6** - Energetics for the C-H Activation of Pyridine N-Oxide

An energy difference of 53 kcal/mol was calculated between the starting complex **4.4** and the intermediate palladium IV species (**4.5**). This high energy barrier makes this pathway unlikely since the relative transition state energy would exceed this value. This would represent an unreasonable energetic barrier for the reaction conditions that are used.

### *Carbo-palladation*

Direct arylation reactions have been classified as aromatic Heck reactions is some cases, and the iminium character of pyridine *N*-oxides might facilitate such a pathway. In this system it would imply *syn* carbo-palladtion via transition state **4.7** of the Pd (II) aryl halide intermediate **4.4** onto the pyridine *N*-oxide which would lead to a 1,2-dihydro-

1-hydroxypyridyl palladium (II) intermediate **4.8** followed by a formal *anti*-β-hydride elimination. We first examined the thermochemistry of the carbopalladation with respect to the first step of this process (Figure 4.9).



**4.4** **4.7** **4.8**

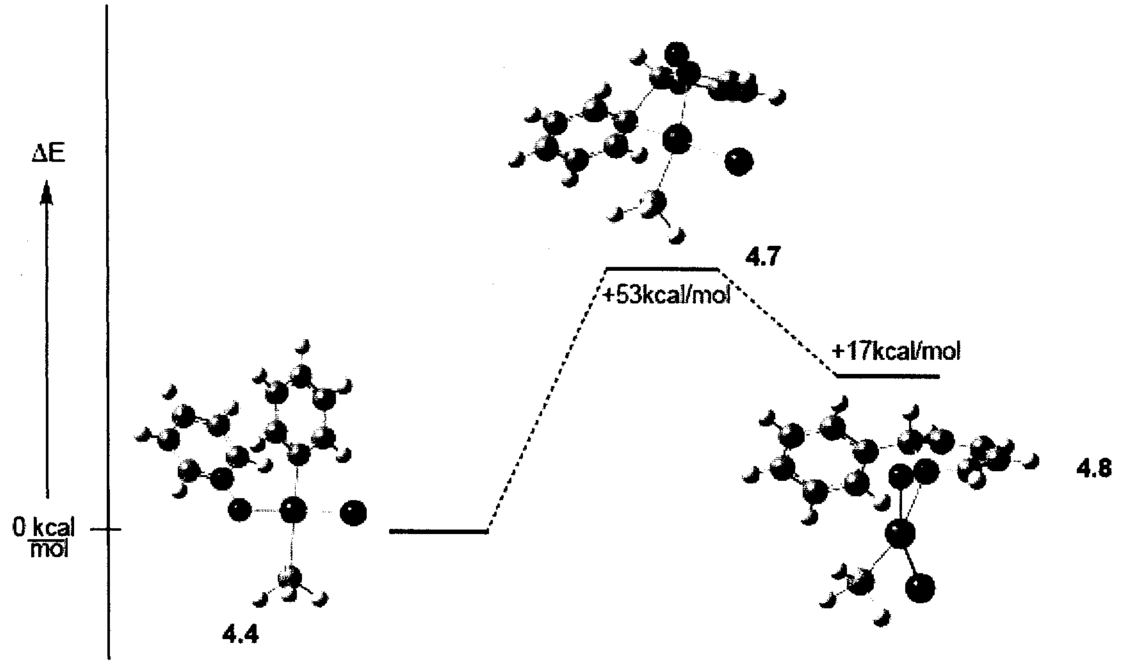
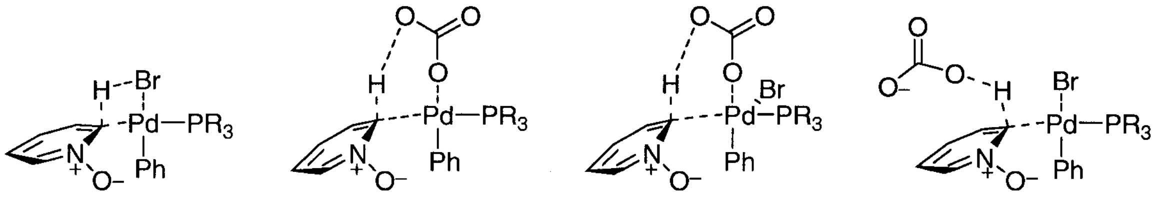


**Figure 4.7** - Energetics for Carbopalladation of pyridine N-oxide

The energy difference between the two ground state structures (**4.4** and **4.8**) was 17 kcal/mol. Given this result, we located the transition state structure for the carbopalladation and *anti*-β-hydride elimination. The carbopalladation transition state (**4.7**) has a relative energy of 53 kcal/mol when compared to the ground state **4.4**.

*Concerted metallation/deprotonation*

This mechanism can occur via different pathways. First a concerted loss of H-Br with concomitant formation of the C-Pd bond is possible (Figure 4.8, **4.9**). If carbonate can exchange with the Br anion, a concerted intramolecular deprotonation via carbonate could occur (Figure 4.8, **4.10**). A pentavalent transition state could also arise if the carbonate and Br are present on the metal during deprotonation/metallation (Figure 4.8, **4.11**). Finally, an intermolecular $S_E3$-like scenario could occur with carbonate acting as an intermolecular base (Figure 4.8, **4.12**).



**4.9** **4.10** **4.11** **4.12**

**Figure 4.8** - Possible Transition States for a Concerted Metallation/Deprotonation Pathway

The relative energy between the starting complex **4.4** and palladium pyridine *N*-oxide complex **4.6** was previously calculated in the context of the C-H activation pathway and was found to be 29 kcal/mol. Attempts to locate a transition state were unsuccessful, but further investigation of stationary points along the reaction coordinate revealed that the energetic barrier is thermodynamic in nature. In fact, a study of the reverse process (protonation of **4.6** with HBr) revealed it to be a barrierless exothermic process through intermediates like **4.13** (Figure 4.9).

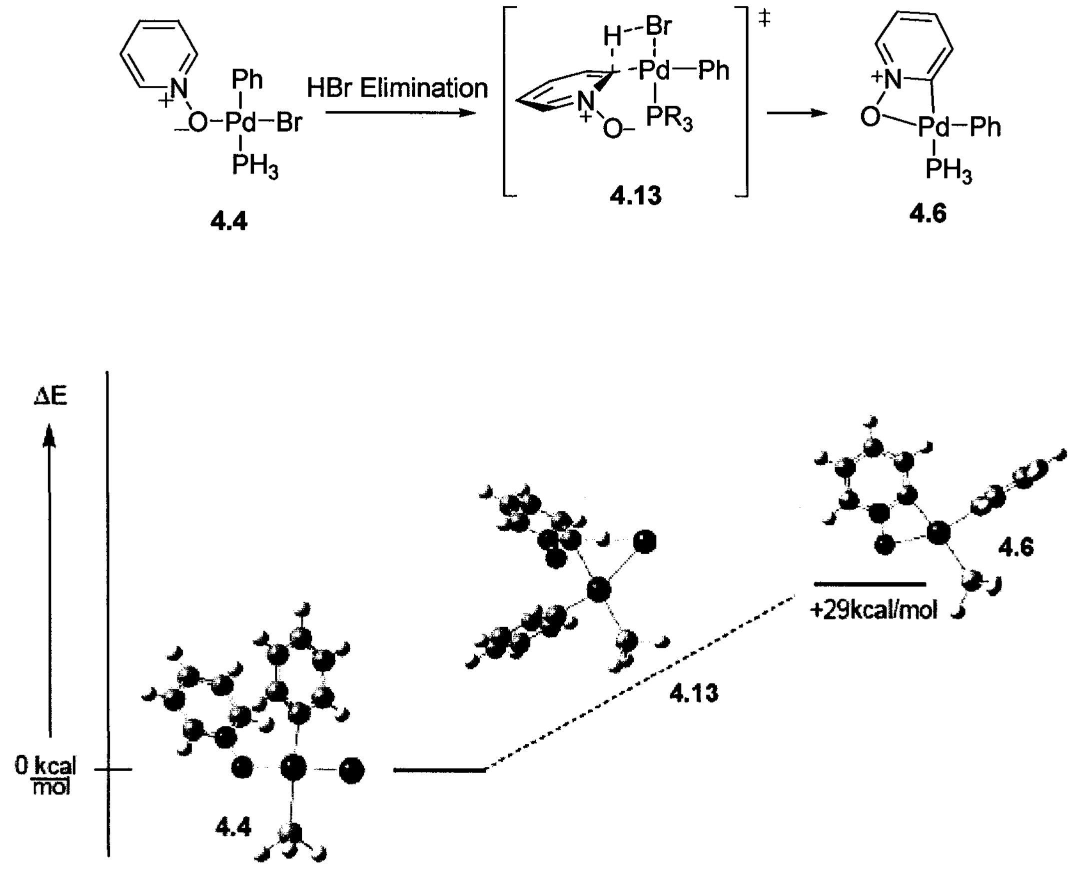


**Figure 4.9** - Concerted Metallation-Deprotonation with H-Br Elimination

Transition state **4.10** would arise if the bromide ion underwent exchange with the potassium carbonate base resulting in a palladium carbonate intermediate. We were able to locate transition state **4.10** which is 24 kcal/mol higher than the resting state when bicarbonate is used as a base. Attempts at modeling $KCO_3^-$ ions in place of bicarbonate afforded structures related to **4.10**. However, dubious η-6 coordination of the $K^+$ ion unlikely in a real system led us to exclude this data. All attempts to locate transition state **4.11** were unsuccessful leading to dissociation of the pyridine *N*-oxide and formation of a arylpalladium (II) bearing both bromide and carbonate. Likewise, no pathway could be located for a mechanism involving **4.12**, consisting in intermolecular proton transfer instead leading to substrate separation. It is also worth noting that during these studies we identified a η-2 C2/C3-bound Pd-complex of intermediate energy (+16 kcal/mol) between the O-bound **4.14** and transition state **4.10**. This intermediate was deemed on the reaction path indicating that isomerization from O- to C-bound palladium might be an important step in the catalytic cycle. Based on these findings as well as the other computational and experimental evidence presented previously, we propose transition state **4.10** as our working mechanistic model. To verify our hypothesis we tested various observed results with **4.10** in order to establish its accordance with experimental observations.

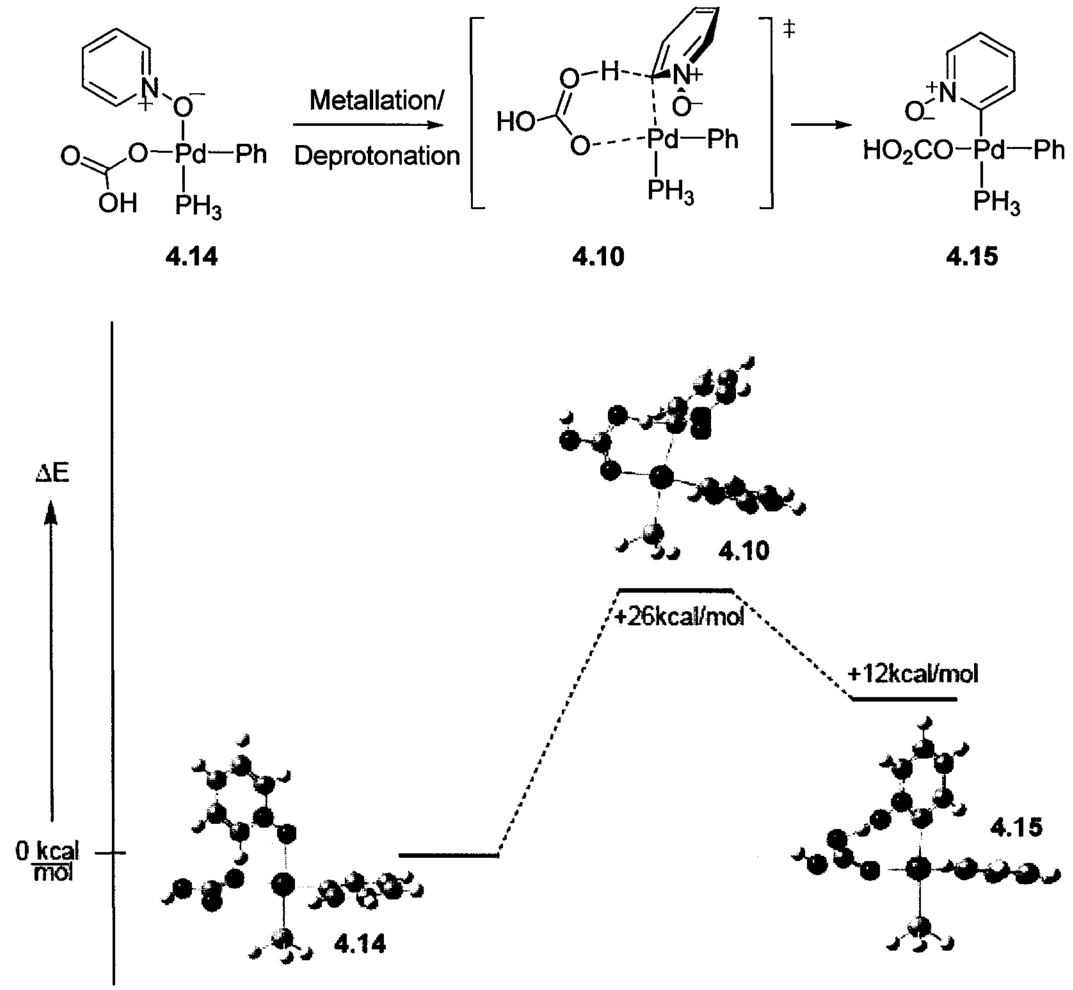
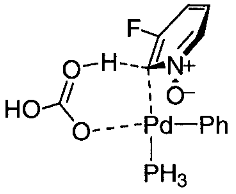
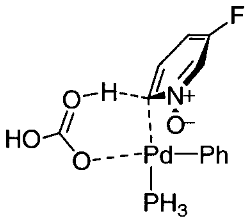
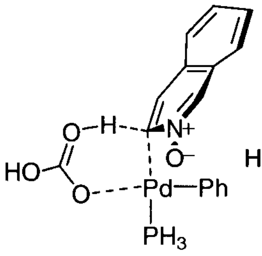
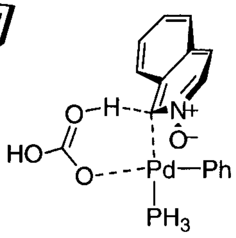


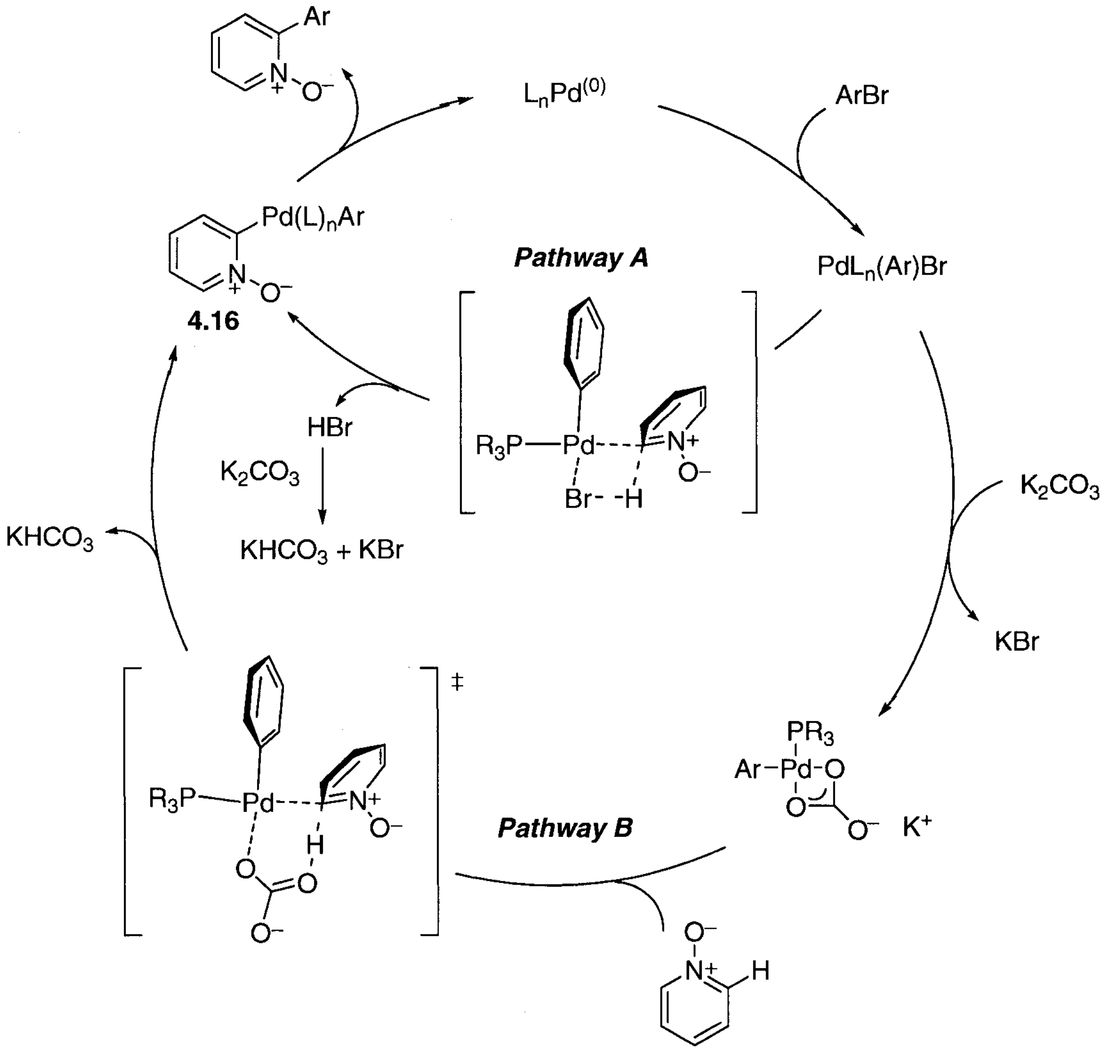
**Figure 4.10** - Concerted Metallation-Deprotonation with Bicarbonate

The two reactions selected for further computational investigation were the reactions of 3-fluoropyridine *N*-oxide as well as isoquinoline *N*-oxide. Using **4.10** as a starting point, transition state energies were calculated for both possible regioisomeric transition states of 3-fluoropyridine *N*-oxide. The two structures were found to be 2.7 kcal/mol apart (experimentally observed, 2.5 kcal/mol), with reaction at the 2-position being lower in energy. One might expect the increased C-H acidity to be responsible for this significant energy difference. The same exercise was applied to isoquinoline *N*-oxide and again, the DFT model predicted accurately the formation of the major isomer with an energy difference of 1.95 kcal/mol (experimentally observed, 1.8 kcal/mol). Rationale for the selectivity observed in isoquinoline *N*-oxide can be explained using different physical properties of the substrate. First, substrate binding might favor regiochemistry. Although the lowest energy binding mode is clearly the O-bound *N*-oxide, this complex probably undergoes isomerization to an η-2 C-bound isomer similar as in the pyridine case. Perhaps the resonance stabilization of the C1-C9 (through a δ+ C-9) bond favors palladium binding rather than the C3-C4. As mentioned before, C-H acidity may play an important role, although it is not clear as to why C-1 would bear a more acidic C-H bond. Finally, given the concerted nature of the mechanism, the nucleophilic character of C1 might play an important role in favoring attack of the Pd at this position, analogous to electrophilic additions to naphthalene systems. In either case, the predicted values and experimental values are in good accord showing only <0.2 kcal/mol difference.

**Table 4.9** – Correlation of Working Mechanistic Model vs Experimental Results

|  |  |  |  |  |
|---|---|---|---|---|
| Experimental | 25 : 1 |  | 1 : 13 |  |
| Calculated | 34.7 : 1 |  | 1 : 10.6 |  |

Given these results, we propose the working mechanistic model in Scheme 4.5 for this transformation. The oxidative addition of the aryl halide by a Pd(0) species results in a palladium aryl halide (II) intermediate which can undergo two different modes of concerted metallation deprotonation. The first consisting of a concerted loss of HBr to generate the diaryl palladium (II) intermediate **4.16**. Alternatively, the palladium (II) intermediate can undergo metathesis with the $K_2CO_3$ in solution to generate a palladium carbonate species which can, in turn, undergo a similar concerted deprotontation event to generate **4.16**. Reductive elimination regenerates the catalyst and provides the product. At this point it is difficult to discriminate between the two pathways which both accurately predict the reaction outcome. Our group has shown that pivalic acid can act as a soluble proton shuttle favoring pathway B in these types of reactions with other substrates, although no beneficial effect of pivalic acid additive was observed for these reactions. Although this may point to pathway A as the major pathway in these reactions, the high polarity of pyridine *N*-oxide may increase the solubility of $K_2CO_3$ favoring pathway B. Another possibility is that excess pyridine *N*-oxide itself is acting as a soluble proton shuttle, although no experimental or computational evidence of such a pathway was identified. While a single viable mechanism cannot be singled out, the current working model can serve as an important tool in reaction and catalyst design and was in fact used to develop a novel azole *N*-oxide arylation, presented in the following section.



**Scheme 4.5** – Working Mechanistic Model for Pyridine *N*-oxide Direct Arylation

## Direct Arylation of Azoles[198]

Given that azoles, such as thiazoles and imidazoles, are prevalent structural motifs in pharmaceutical compounds and in materials science,[199] methods that enable their functionalization and incorporation into organic molecules are in high demand.[200,201] We decided to undertake a study of the physical properties that could be used to facilitate their direct arylation reactions. Increasingly, these processes, which replace the organometallic coupling partner with the simple arene, are being investigated with these substrates.[202]

Understanding and exploiting the inherent reactivity/selectivity of an organic molecule is a fundamental aspect of reaction development. Simultaneously, however, the intrinsic physical properties of a molecule can delimit the possibilities. For example, known azole direct arylation reactions capitalize on π-nucleophilicity.[203] The electrophilic aromatic substitution pathway ($S_EAr$) of these processes induces preferential reactivity at C5 followed by reaction at C2.[204] To our knowledge no reactions at C4 with thiazoles or *N*-substituted imidazole have been reported. In some cases, the addition of copper salts results in preferential reaction at C2, but selectivity remains a continued challenge.[205] To induce azole metallation, forcing conditions are commonplace (often with heating >150 °C).[204,206] To meet these challenges, particularly the void of C4 arylation processes, reactivity based on other physical parameters must be accessed.

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[198] Part of this section was published as a communication: Campeau, L.-C.; Bertrand-Lapèrle, M.; Leclerc, J.-P.; Villemure, E.; Gorelsky, S.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 3276

[199] D. J. Hlasta, C. A. Zificsak, *Tetrahedron* **2004**, *60*, 8991 – 9016.

[200] For cross-coupling reactions involving these building blocks, see: (a) M. Schnürch, R. Flasik, A. F. Khan, M. Spina, M. D. Mihovilovic, P. Stanetty, *Eur. J. Org. Chem.* **2006**, 3283. (b) C. A. Zificsak, D. J. Hlasta, *Tetrahedron,* **2004**, *60*, 8991

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[204] (a) S. Pivsa-Art, T. Satoh, Y. Kawamura, M. Miura and M. Nomura, *Bull. Chem. Soc. Jpn.*, **1998**, *71*, 467. (b) A. Yokooji, T. Okazawa, T. Satoh, M. Miura and M. Nomura, *Tetrahedron*, **2003**, *59*, 5685. (c) Y. Aoyagi, A. Inoue, I. Koizumi, R. Hashimoto, K. Tokunaga, K. Gohma, J. Komatsu, K. Sekine, A. Miyafuji, J. Kunoh, R. Honma, Y. Akita and A. Ohta, *Heterocycles*, **1992**, *33*, 257. (d) Y. Kondo, T. Komine and T. Sakamoto, *Org. Lett.*, **2000**, *2*, 3111. (e) F. Bellina, S. Cauteruccio, L. Mannina, R. Rossi and S. Viel, *J. Org. Chem.*, **2005**, *70*, 3997. (f) B. B. Toure, B. S. Lane and D. Sames, *Org. Lett.*, **2006**, *8*, 1979.

[205] (a) A. Mori, A. Sekiguchi, K. Masui, T. Shimada, M. Horie, K. Osakada, M. Kawamoto and T. Ikeda, *J. Am. Chem. Soc.*, **2003**, *125*, 1700. (b) F. Bellina, S. Cauteruccio and R. Rossi, *Eur. J. Org. Chem.*, **2006**, 1379. (c) F. Bellina, S. Cauteruccio, L. Mannina, R. Rossi and S. Viel, *Eur. J. Org. Chem.*, **2006**, 693. (d) J. C. Lewis, S. H. Wiedemann, R. G. Bergman and J. A. Ellman, *Org. Lett.*, **2004**, *6*, 35.

[206] For reactions at lower temperatures, see: (a) with indole and iodonium salts at 25 °C: N. R. Deprez, D. Kalyani, A. Krause, M. S. Sanford, *J. Am. Chem. Soc.* **2006**, *128*, 4972. (b) with oxazo[4,5*b*]pyridine at 30 °C: F. A. Zhuravlev,

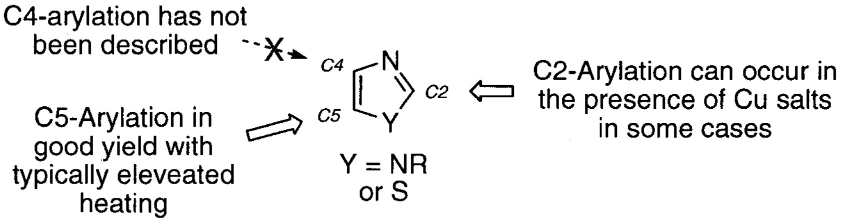

**Figure 4.11** – Capabilities and Limitations of Azole Arylation

Recent findings correlating C-H acidity and enhanced reactivity in direct arylation, as well as the viability of *N*-oxide aromatics in these reactions, drew our attention to the use of azole *N*-oxides as substrates. We were pleased to find that treatment of thiazole *N*-oxide with KOH in $D_2O$ lead to rapid H/D exchange first at the C2 position. Encouragingly, we also found a slower exchange at C5 and C4. We surmised that this property could not only enable the development of mild C2 direct arylation processes, but might also fill the C4 reactivity void. Additionally, DFT modeling of thiazole *N*-oxide arylation predicted that these substrates should be reactive in this type of reaction manifold.[207]

Using thiazole *N*-oxide under the reaction conditions developed for pyridine *N*-oxide, resulted in a 79% isolated yield of a single isomer that was at C2. The promising physical properties of thiazole *N*-oxides and the facile H/D exchange that could be induced at C2 prompted method development efforts targeting reactions at 25°C. Evaluation of a variety of ligands, with a range of ligand to palladium catalyst ratios, in a variety of solvents, with different bases, in conjunction and in the absence of pivalic acid as a catalytic additive, lead to the development of high yielding, highly selective C2-arylation reactions. For example, treatment of **4.17** and 1-bromo-3,5-dimethylbenzene with $Pd(OAc)_2$ (5 mol %), ligand **4.18** (10 mol %), PivOH (20 mol %) and $K_2CO_3$ (1.5 equiv.) in PhMe at 25 °C provides the C2-arylated product in 84% isolated yield (Table 4.10, entry 1). Notably, and in contrast to our observations with pyridine and several diazine *N*-oxides, the thiazole *N*-oxide can be used in near equimolar quantities relative to the aryl halide. In the majority of cases, use of 1.1 equivalents of the thiazole *N*-oxide results in high yields and complete conversion of the aryl halide. It should also be noted that many solvents are compatible with the arylation protocol.

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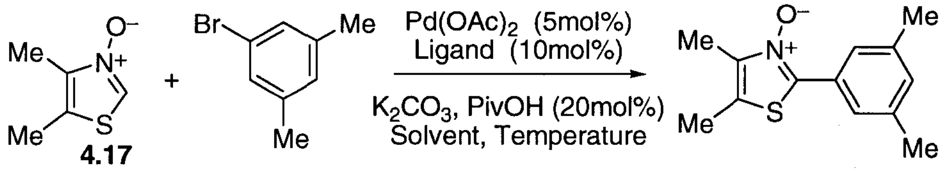
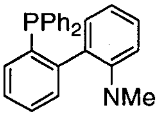
*Tetrahedron Lett.* **2006**, *47*, 2929. (c) with thiazole and aryl iodides at 60 °C: ref 204a (d) For a recent mild arylation in water see, Turner, G. M.; Morris, J. A.; Greaney, M. F.; *Angew. Chem. Int. Ed.* **2007**,*46*, 1.

[207] Preliminary results obtained are being studied in-depth and will be reported in due course.

**Table 4.10** – Optimization of Reaction Conditions with Thiazole *N*-Oxides[a]

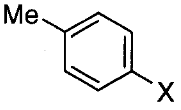
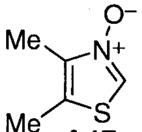
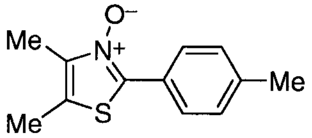
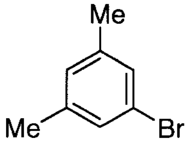
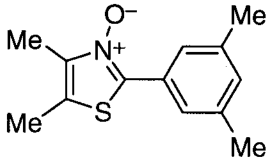
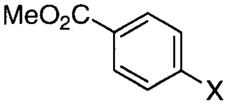
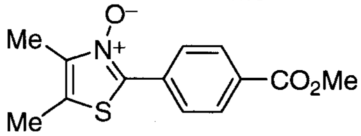
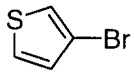
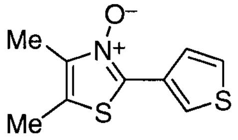
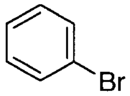
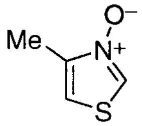
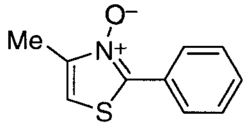
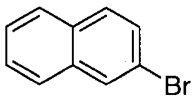
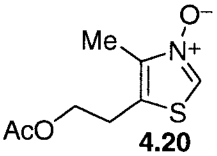
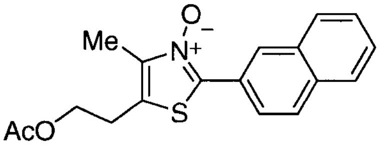
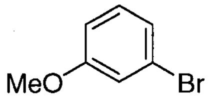
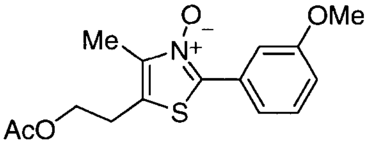
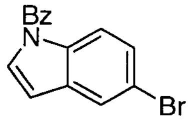
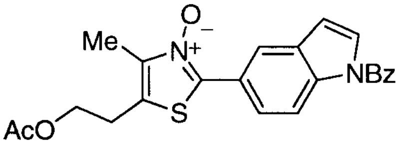
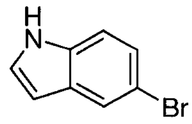
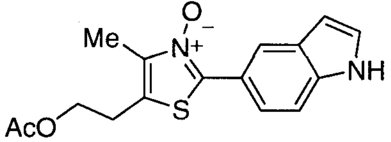


| Entry | Ligand | Solvent | Temperature | Yield[b] |
|---|---|---|---|---|
| 1 | $P^tBu_3$-$HBF_4$ | Toluene | 110°C | 79%[c] |
| 2 | $P^tBu_3$-$HBF_4$ | Toluene | 25°C | 5% |
| 3 | $PPh_3$ | MeCN | 25°C | 2.5% |
| 4 | dppf | MeCN | 25°C | 3.5%[d] |
| 5 |  **4.18** | MeCN | 25°C | 40% |
| 6 | **4.18** | Dioxane | 25°C | 89% |
| 7 | **4.18** | DMSO | 25°C | 88% |
| 8 | **4.18** | $^i$PrOAc | 25°C | 91% |
| 9 | **4.18** | Toluene | 25°C | 98% |
| 10 | Dave-Phos | Toluene | 25°C | 97% |

[a]All reactions carried out at a concentration of 0.2M for 24h. [b] Yields determined by NMR using 1,3,5-trimethoxybenzene as an internal standard. [c]Isolated yield without pivalic acid. [d]5 mol % of dppf was added.

Under optimal conditions ($Pd(OAc)_2$ (5 mol %), ligand **4.18** or Dave-Phos (10 mol %), PivOH (20 mol %) and $K_2CO_3$ (1.5 equiv.) in PhMe at 25 °C) the 2-aryl thiazoles are obtained in good yield as a single regioisomer. Illustrative examples of direct arylation with thiazole *N*-oxides are shown in Table 4.11. A variety of aryl bromides can be coupled in good to excellent yields with functionalized thiazoles. Both electon-poor (Entry 4) and electron-rich (Entry 9) substrates can be used. The use of heteroaryl bromides is tolerated as illustrated by reactions of bromothiophene and bromoindole (Entries 5 & 11). It is also possible to achieve good yields with unprotected bromoindole (Entries 10). Aryl iodides (Entry 2) can be coupled in excellent yields if $Cs_2CO_3$ is used. With aryl chlorides, Dave-Phos was found to be the optimal ligand and the reaction must be heated to 70 °C (Entry 5).

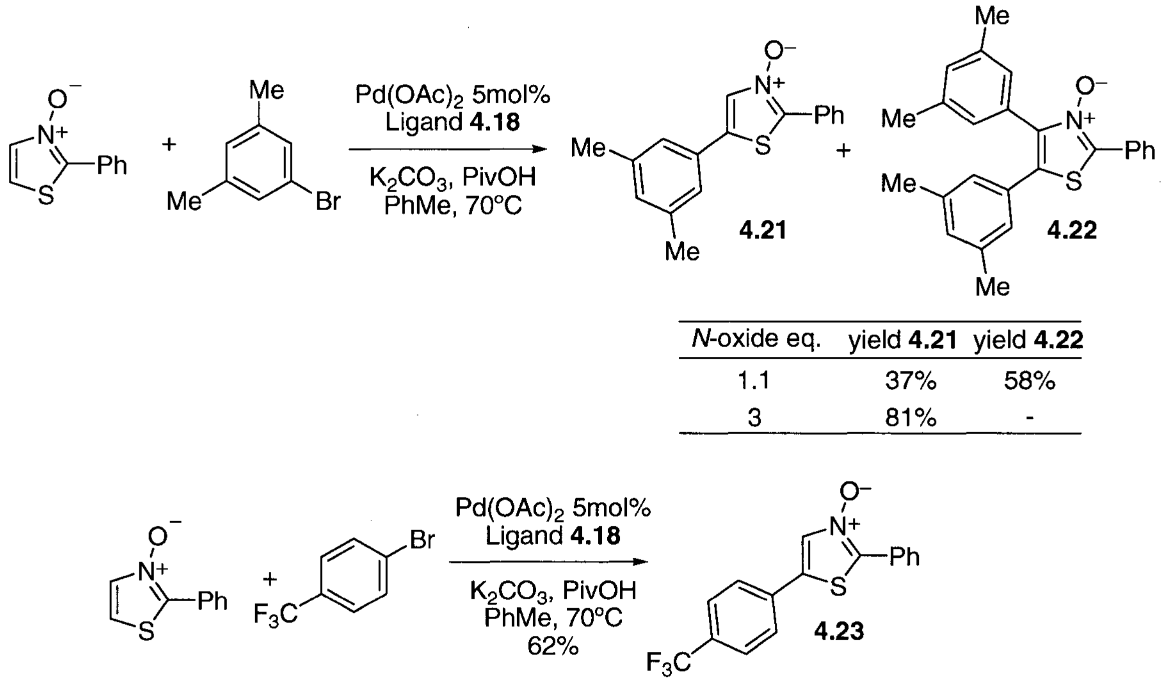
**Table 4.11** – Site-Selective Direct Arylation with Thiazole *N*-Oxides[a]

| Entry | Aryl Halide | Thiazole *N*-oxide | Product | Yield[b] |
|---|---|---|---|---|
| 1<br>2 |  X = Br<br>X = I |  **4.17** |  | 88<br>79[c] |
| 3 |  | **4.17** |  | 84 |
| 4<br>5 |  X = Br<br>X = Cl | **4.17**<br>**4.17** |  | 80<br>79[e] |
| 6 |  | **4.17** |  | 83 |
| 7 |  |  **4.19** |  | 63 |
| 8 |  |  **4.20** |  | 86 |
| 9 |  | **4.20** |  | 85[d] |
| 10 |  | **4.20** |  | 77[d] |
| 11 |  | **4.20** |  | 64[d] |

[a]Conditions: Aryl halide (1 equiv.), thiazole *N*-oxide (1.1 equiv.), $K_2CO_3$ (1.5 equiv.), $Pd(OAc)_2$ (0.05 equiv.) and ligand **4.18** (0.1 equiv.) in PhMe (0.2M) at 25 °C overnight. [b]Isolated Yields. [c]Using $Cs_2CO_3$ ( 1.5 equiv.) as base. [d]Using Dave-Phos (0.1 equiv.) as ligand. [e]Using Dave-Phos (0.1 equiv.) as ligand and heated to 70°C for 48 hours.

The adaptability of these reaction conditions to include imidazole *N*-oxides was undertaken by other graduate students and led to the discovery of two different sets of conditions for this arylation.[208]

Given the good precedent that thiazoles and imidazoles could undergo selective direct arylation at C-5 using palladium catalysts at 140 °C,[205a] we were curious to examine whether the presence of the *N*-oxide functionality in these 2-aryl azoles would increase the reactivity of these substrates. Gratifyingly, when 2-phenylthiazole *N*-oxide (1 equiv.) is reacted with5-bromo-*m*-xylene (1 equiv.) under optimized conditions at 70 °C, the diaryl thiazole N-oxide is obtained in 37% yield (Scheme 4.6). However, further studies revealed that the remainder of the material recovered was in fact tri-arylated product resulting from arylation occuring at C-4. This unexpected side reaction, which to our knowledge has never been observed before, could therefore allow us to develop a protocol allowing for the synthesis of tri-aryl thiazoles with complete regioselectivity. An optimization of reaction conditions for C5 arylation of 2-aryl thiazole revealed that diarylation could be suppressed via the use of an excess of the starting *N*-oxide.



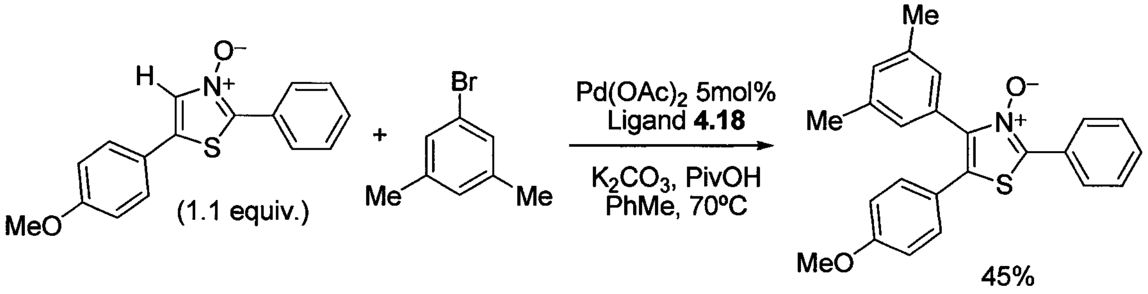
| *N*-oxide eq. | yield **4.21** | yield **4.22** |
|---|---|---|
| 1.1 | 37% | 58% |
| 3 | 81% | - |

**Scheme 4.6** – C-5 Arylation of 2-arylthiazole *N*-oxide

---

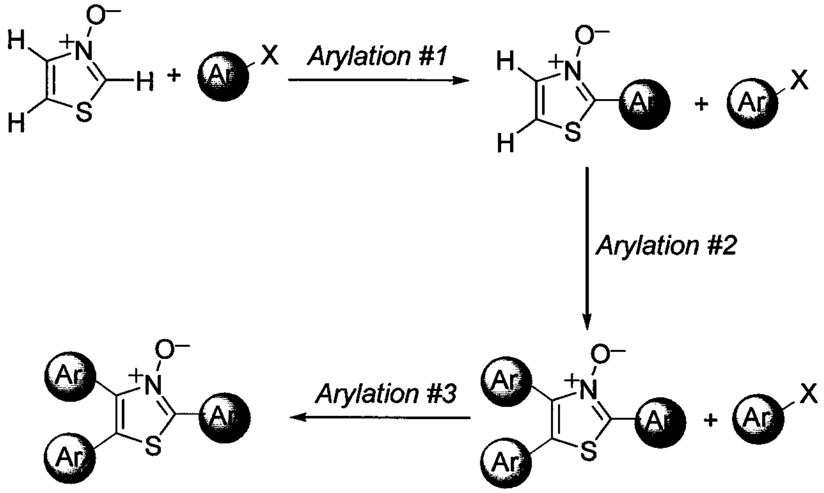
[208] Campeau, L.-C.; Bertrand-Lapèrle, M.; Leclerc, J.-P.; Villemure, E.; Fagnou, K.; *Unpublished results.*

We then investigated if C-4 arylation could be achieved using the same catalyst and near equimolar amounts of aryl bromide and *N*-oxide (Scheme 4.6). Gratifyingly, this led to arylation of the 2,5-diarylthiazole *N*-oxide in modest yield. It is our hope that using these lead results, we will be able to improve on the yield of these reactions.[209]



**Scheme 4.7** – C-4 Arylation of 2,5-diarylthiazole *N*-oxide

This methodology could allow for a completely programmable synthesis of triarylthiazoles using direct arylation methodology (Scheme 4.7). Changing the sequence of the arylation reactions would allow us to have access to every possible isomer of any given triarylthiazole using a single method in only 4 steps including three C-C bond forming reactions. Efforts towards this goal are ongoing.[209] The preactivation of the substrate as an *N*-oxide serves for all three coupling reactions and allows for high regiocontrol over each arylation reaction. This type of strategy using conventional cross-coupling methods would be difficult.



**Scheme 4.8** – Programmable Synthesis of Triarylthiazoles

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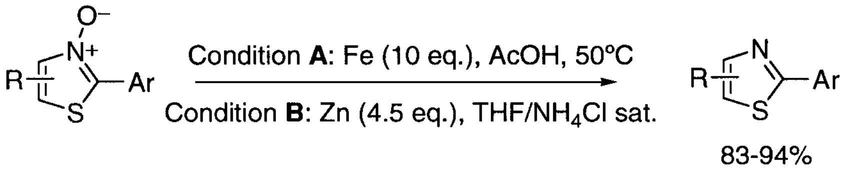
[209] This work was passed on to another graduate student; Mégan Bertrand-Lapèrle, July 2007

Conditions for the swift deoxygenation of the *N*-oxide products were achieved by Elisia Villemure via two different methods.[198] For thiazole *N*-oxide, it is possible to perform the transformation at room temperature using zinc mediated reduction. However, iron reductions are also compatible (Equation 4.8).



(4.8)

Direct arylation of thiazole *N*-oxides occur in high yields with excellent site-selectivity for a wide range of aryl halides. This process allows for the use of equimolar amounts of each coupling partner and represents the first examples of room temperature direct arylations of azoles. Additionally, a second direct arylation can be performed to afford the 2,5-diarylthiazoles under mild reaction conditions than most described direct arylation methods. Finally, the *N*-oxidation of the azole allows for reactions at C4 of azoles which had previously not been observed in direct arylation reactions. These reactions can then be sequentially used for a programmable synthesis of triarylthiazoles. The mild reaction conditions, high site-selectivity and complimentary regiochemistry that are obtainable make this a powerful method for the synthesis of substituted thiazoles which should find use in the preparation of these important building blocks.

# 5

# Direct Arylation at $sp^3$ Centers

## *Introduction*

The development of methods for the direct functionalization of hydrocarbons is of high value. As described in Chapters 1 & 3, the recent rapid growth in direct *$sp^2$*-carbon arylation has improved both catalyst efficiency and substrate scope. Direct functionalization of *$sp^3$*-carbons is still particularly difficult. While often associated with the strength of the *$sp^3$* C-H bond is also in part due to the inability of metals to establish coordination to most typical *$sp^3$* C-H bonds. Initial direct arylation reactions at *$sp^3$* centers were performed using activated substrates such as carbonyl compounds, which can be stoichiometrically deprotonated. Recently, functionalizations at relatively unreactive *$sp^3$* centers have appeared.[210] This chapter will briefly discuss recent

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[210] For a recent highlight, see : Tobisu, M.; Chatani, N.; *Angew. Chem. Int. Ed.* **2006**, *45*, 1683

progress in these two areas of direct arylation with a strong emphasis on palladium-catalyzed systems.

## Arylation of Carbonyl Compounds

While the addition of enolate nucleophiles to alkyl halide electrophiles is a reaction commonly used to demonstrate basic principles of organic chemistry, the analogous reaction of enolates with aryl halides is rarely presented. In fact, although stabilized enolates can add to certain aromatic systems via nucleophilic aromatic substitution ($S_NAr$),[211] these reactions present severe limitations in terms of substrate scope as one or more electron-withdrawing groups are required on the aromatic partner for successful reactions to occur.[212] As a solution to this limitation, the groups of Buchwald,[213] Hartwig[214] and Miura[215] concurrently reported palladium-catalyzed direct arylation reactions of ketones with aryl bromides. Further studies in this area have lead to improved methods for the arylation of ketones,[216] diketones,[216c] amides,[217] esters,[218] aldehydes,[219] nitriles,[220] malonates,[216,221] cyanoesters,[222] nitroalkanes,[223] sulfones[224] and lactones.[225] Asymmetric arylation reactions have also been developped.[217(b),225,226]

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[211] Heckmann, J. *Ann.* **1883**, *220*, 128

[212] Bunnett, J. F.; Zahler, R. E.; *Chem. Rev.* **1951**, *49*, 273

[213] Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 11108

[214] Hamann, B. C.; Hartwig, J. F.; *J. Am. Chem. Soc.* **1997**, *119*, 12382

[215] Satoh, T.; Kawamura, T.; Miura, M.; Nomura, M.; *Agnew. Chem. Int. Ed.* **1997**, *36*, 1740

[216] (a) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 1473. (b) Satoh, T.; Kametani, Y.; Terao, Y.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **1999**, *40*, 5345. (c) Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L.; *J. Am. Chem. Soc.* **2000**, *122*, 1360. (d) Terao, Y.; Kametani, Y.; Wakui, H.; Satoh, T.; Miura, M.; Nomura, M.; *Tetrahedron* **2001**, *57*, 5967-5974. (e) Ehrentraut, A.; Zapf, A.; Beller, M.; *Adv. Synth. Catal.* **2002**, *344*, 209. (f) Satoh, T.; Jones, W. D.; *Organometallics* **2001**, *20*, 2916.

[217] (a) Shaughnessy, K. H.; Hamann, B. C.; Hartwig, J. F.; *J. Org. Chem.* **1998**, *63*, 6546. (b) Lee, S.; Hartwig, J. F.; *J. Org. Chem.* **2001**, *66*, 3402.

[218] (a) Moradi, W. A.; Buchwald, S. L.; *J. Am. Chem. Soc.* **2001**, *123*, 7996. (b) Gaertzen, O.; Buchwald, S. L.; *J. Org. Chem.* **2002**, *67*, 465. (c) Jørgensen, M.; Lee, S.; Liu, X.; Wolkowski, J. P.; Hartwig, J. F.; *J. Am. Chem. Soc.* **2002**, *124*, 12557.

[219] Terao, Y.; Fukuoka, Y.; Satoh, T.; Miura, M.; Nomura, M.; *Tetrahedron Lett.* **2002**, *43*, 101.

[220] (a) Satoh, T.; Inoh, J.-i.; Kawamura, Y.; Kawamura, Y.; Miura, M.; Nomura, M.; *Bull. Chem. Soc. Jpn.* **1998**, *71*, 2239. (b) Culkin, D. A.; Hartwig, J. F.; *J. Am Chem. Soc.* **2002**, *124*, 9330.

[221] (a) Djakovitch, L.; Köhler, K. *J. Organomet. Chem.* **2000**, 606, 101. (b) Beare, N. A.; Hartwig, J. F.; *J. Org. Chem.* **2002**, *67*, 541.

[222] Stauffer, S. R.; Beare, N. A.; Stambuli, J. P.; Hartwig, J. F.; *J. Am. Chem. Soc.* **2001**, *123*, 4641.

[223] (a) Muratake, H.; Nakai, H.; *Tetrahedron Lett.* **1999**, *40*, 2355. (b) Vogl, E. M.; Buchwald, S. L.; *J. Org. Chem.* **2002**, *67*, 106.

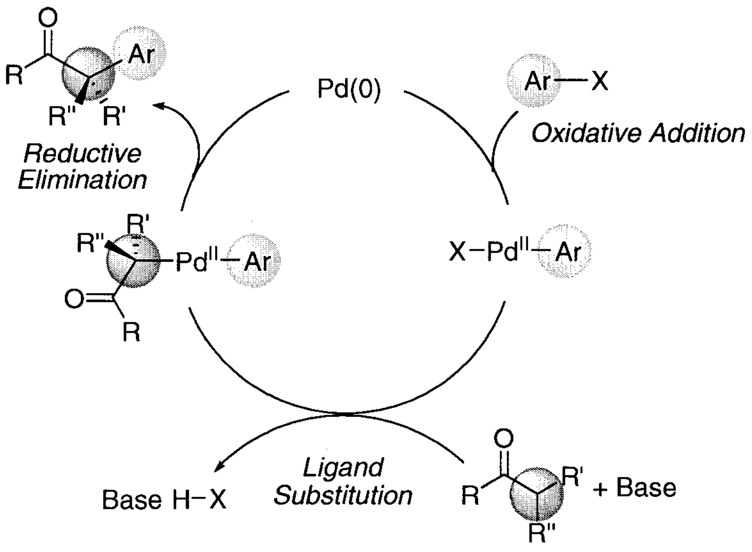
[224] Kashin, A. N.; Mitin, A. V.; Beletskaya, I. P.; Wife, R.; *Tetrahedron Lett.* **2002**, *43*, 2539.

[225] Spielvogel, D. J.; Buchwald, S. L.; *J. Am. Chem. Soc.* **2002**, *124*, 3500.

[226] (a) Ahman, J.; Wolfe, J. P.; Troutman, M. V.; Palucki, M.; Buchwald, S. L.; *J. Am. Chem. Soc.* **1998**, *120*, 1918. (b) Hamada, T.; Chieffi, A.; A¡ hman, J.; Buchwald, S. L.; *J. Am. Chem. Soc.* **2002**, *124*, 1261-1268.

Since these methods were recently reviewed, only a brief discussion of the reaction mechanism will follow.[227]

The proposed mechanism for arylation of carbonyl compounds is presented in Scheme 5.1. Oxidative addition of the aryl halide to palladium(0) is followed by ligand substitution by the enolate, which is generated *in situ* using a strong base. Most reactions are carried out using KHMDS or NaHMDS. However, in the case of more acidic substrates, $NaO^tBu$ can be used. This step is followed by reductive elimination to afford the product and regenerate the catalyst. A key feature of this reaction mechanism is the requirement for increased acidity of the C-H bond being functionalized. This allows for deprotonation and favours nucleophilic attack on the palladium. In most cases, reactions are selective for mono arylation, with less selective reactions leading to ratios of 6:1 in favor of monoarylation over diarylation.



**Scheme 5.1** – Catalytic Cycles for the α-Arylation of Carbonyl Compounds

Recently, Oshima and co-workers have reported an arylation of aryl(azaaryl)methanes (Equation 5.1).[228] The basis for the observed reactivity is attributed to the structural similarity between imines and azines as well as the increased acidity conferred by the neighbouring phenyl ring.

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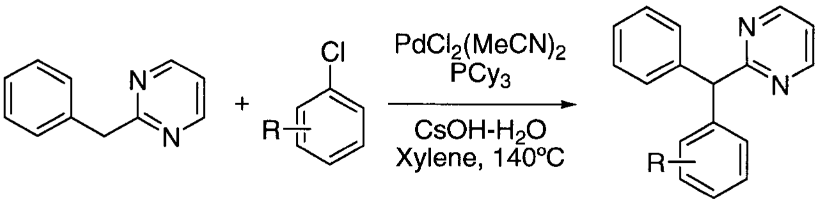
[227] Culkin, D. A.; Hartwig, J. F.; *Acc. Chem. Res.* **2003**, *36*, 234.
[228] Niwa, T.; Yorimitsu, H.; Oshima, K. *Org. Lett.*; **2007**, *9*, 2373.



(5.1)

The reactions proceed at 140 °C with as low as 2.5 mol % [Pd] with yields typically ranging from 60-90%.

Recent interest in the arylation of unactivated hydrocarbons has stimulated interest in developing methods to achieve functionalization where C-H bonds are not acidic enough to allow for full deprotonation. The next section will discuss recent advances in this type of reactivity.

## *Arylation of Unactivated sp$^3$-Centers*

Many obstacles must be overcome for reactions of transition metals at unactivated centers. Bringing the metal in close proximity to the wanted reactive site poses a significant challenge. Once this can be achieved, metallation of the carbon can take place via a number of mechanisms. In certain cases, the metal only serves as a dehydrogenating catalyst, allowing for nucleophilic additions to take place on the newly activated carbon. In other cases, metallation can be followed by reductive elimination of a ligand to afford the new carbon-carbon bond. Examples of both of these pathways will be discussed further.

In 2005, Li and co-workers achieved the arylation of tetrahydroisoquinolines with indoles via their cross-dehydrogenative coupling reaction.[229] The reaction is catalyzed by copper and requires the use of tert-butyl hydroperoxide as a stoichiometric oxidant. A number of indoles were shown to be compatible with *N*-aryltetrahydroisoquinoline (Table 5.1)

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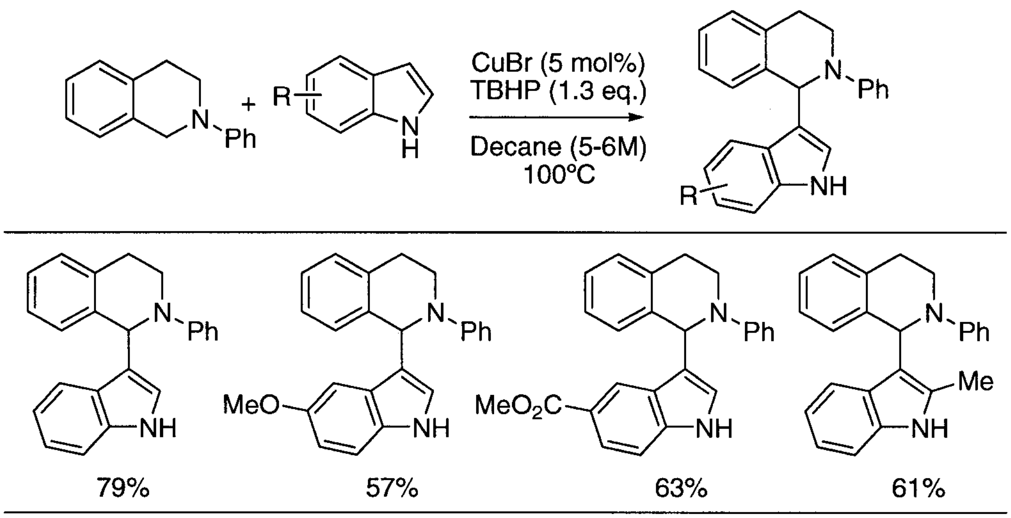
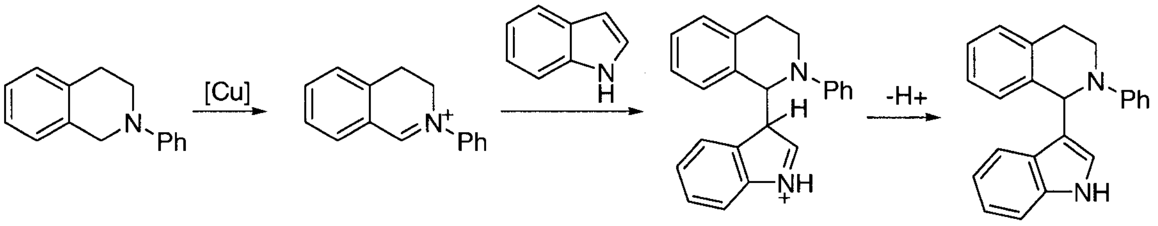
[229] Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2005**, *127*, 6968.

**Table 5.1** – Cross-dehydrogenative Coupling with Indole Nucleophiles[a]



[a] Isolated yield reported

The proposed mechanism for this transformation is outlined in Scheme 5.2. Copper catalyzes the formation of an iminium type intermediate, which may or may not be coordinated to the catalyst. This potent electrophile is then attacked by the nucleophilic indole.



**Scheme 5.2** – Mechanism of Cross-Dehydrogenative Coupling with Indole Nucleophiles

Sames and co-workers observed similar reactivity when exploring the arylation of cyclic amines.[230] Their reported protocol couples pyrrolidinone-derived amidines with arylboronic esters as arylating agents. The amidine function is essential as less basic directing groups such as carbamates and ketones were unreactive. The reaction is catalyzed by $Ru_3(CO)_{12}$ to afford the arylated products in yields ranging from 45-76% (Equation 5.2).

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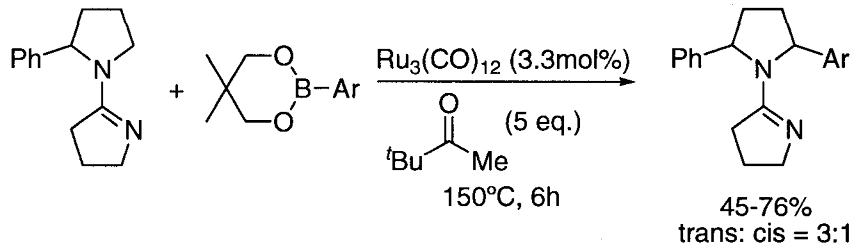
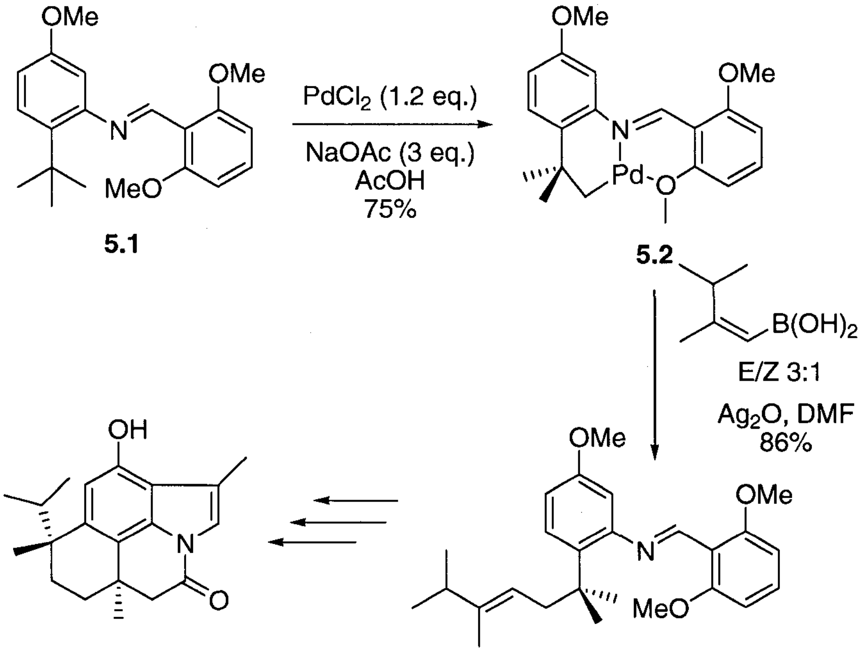
[230] Pastine, S. J.; Gribkov, D. V.; Sames, D. *J. Am. Chem. Soc.* **2006,** *128,* 14220.



(5.2)

The authors also report that the parent piperidine derived substrates react in lower yields than the pyrrolidine substrates. While the use of 1-pyrroline is convenient since it may be removed using hydrazine, the directing group can be a pyridine or pyrimidine. While no mechanistic investigations were performed, the authors suggest that the ruthenium catalyst activates the C-H bond via oxidative addition. The ketone additive can then be reduced by this ruthenium hydride intermediate resulting in a ruthenium alkoxide intermediate which can transmetallate the boronic ester.

Sames and co-workers also reported the stoichiometric arylation of an *sp*$^3$-center in the synthesis of the carbocyclic core of Teleocidin B-4.[231] They observed that imine **5.1** could be metallated with stoichiometric $PdCl_2$ to afford palladacycle **5.2**. This intermediate could then be treated with the corresponding boronic acid to complete the synthesis (Scheme 5.3).



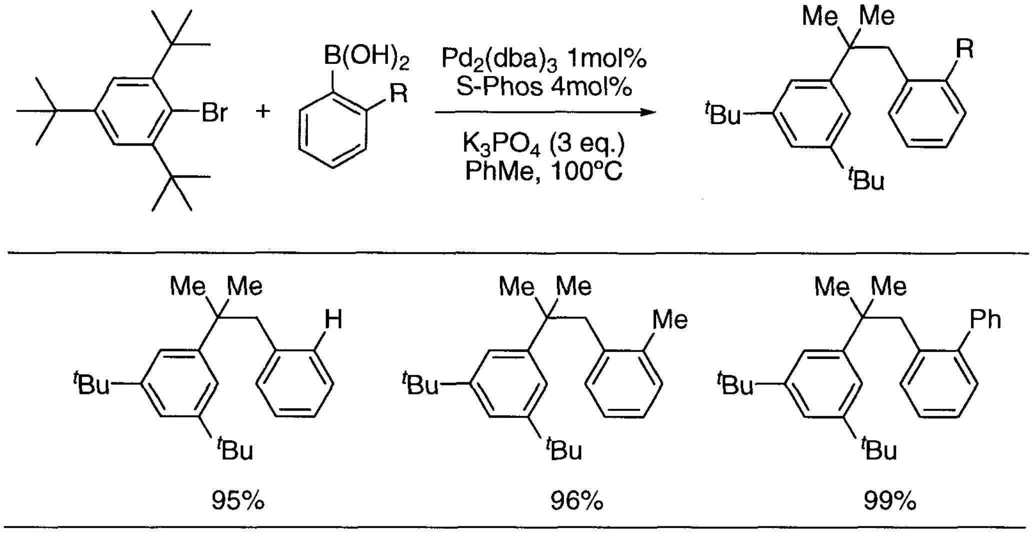
**Scheme 5.3** – Key Palladacycle Formation in the Synthesis of the Teleocidin B-4 Core

---

[231] Dangel, B. D.; Gadula, K.; Youn, S. W.; Sezen, B.; Sames, D.; *J. Am. Chem. Soc.* **2002**, *124*, 11856.

Buchwald and co-workers also observed the arylation of *tert*-butyl groups in their study of Suzuki-Miyaura coupling processes.[232] When attempting to couple 2,4,6-tri-*tert*-butylbromobenzene with aryl boronic acids, they observed *tert*-butyl group functionalization instead of the expected biaryl product. Unlike the Sames result, these reactions were catalytic in palladium and were shown to be compatible with three different boronic acids (Table 5.2).

**Table 5.2** – Arylation of *tert*-Butyl Groups with Arylboronic Acids[a]



[a]Isolated yield reported

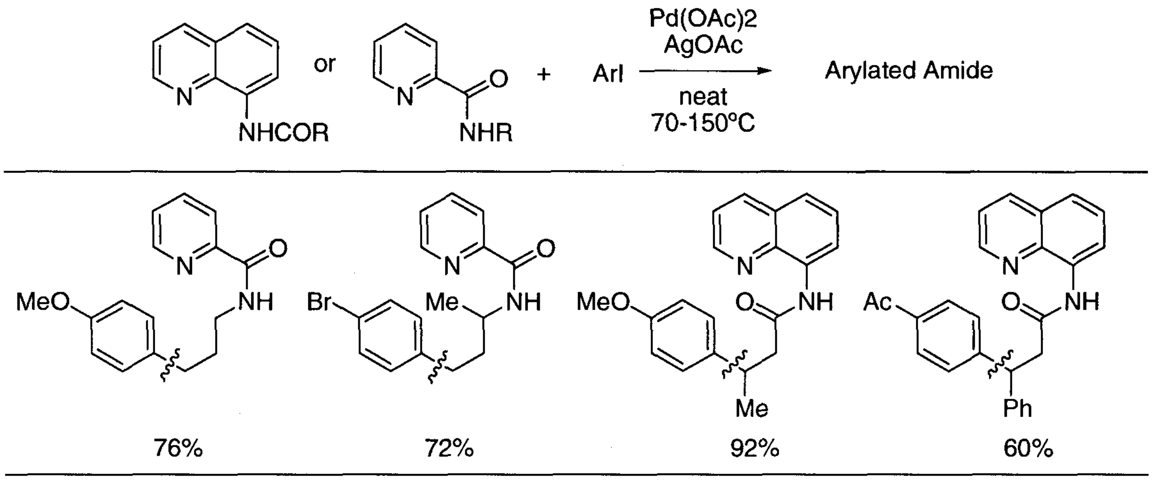
In an effort to develop a broadly applicable auxiliary for such reactions, Daugulis and co-workers have also reported the arylation of unactivated $sp^3$-carbons. The directing group used in these reactions may vary but usually includes the basic nitrogen of a pyridyl or quinoline moiety. In a 2005 report, they achieve the arylation of $sp^3$-carbons found in a *beta* relationship with amides.[233] Their protocol affords the arylated amides in good yields. Secondary carbons rather than primary react at higher rates, allowing for diarylation to be achieved. Using a similar strategy, the arylation of picolinamides was achieved, allowing for arylation *gamma* to amine functional groups via the installation of the auxiliary. Representative results are found in Table 5.3.

---

[232] Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L.; *J. Am. Chem. Soc.* **2005,** *127,* 4685.

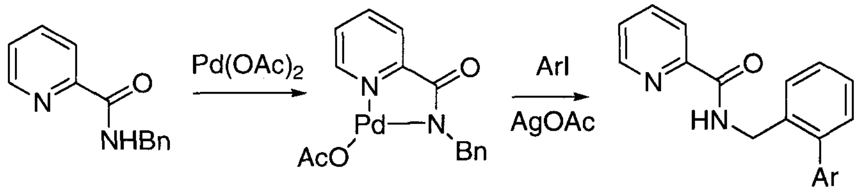
[233] Zaitsev, V. G.; Shabashov, D.; Daugulis, O.; *J. Am. Chem. Soc.* **2005**, *127*, 13154.

**Table 5.3** – Arylation of Picolinamides and 8-Aminoquinoline Amides[a]



[a]Isolated yield reported

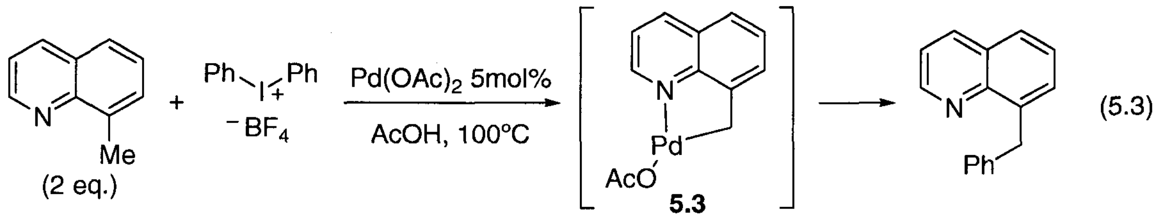
Reactions are typically carried out with 4-6 equivalents of aryl iodide and 1.1-1.4 equivalents of AgOAc. Catalyst loadings are substrate dependant and can vary from 0.1 mol % to 5 mol % palladium acetate. These auxiliaries are also compatible for direct arylation of $sp^2$-centers affording 81% and 64% yield with the picolinamide and 8-aminoquinoline auxiliaries respectively. Although the authors offer only a speculative discussion about the reaction mechanism, the requirement for a secondary amide function suggests that its binding to palladium is important. In fact, when benzyl picolinamide is reacted with $Pd(OAc)_2$, a crystalline complex is formed which has been characterized by X-ray diffraction (Scheme 5.4). Also, the increased reactivity of electron-rich aryl iodides points towards a Pd(II)/Pd(IV) catalytic cycle rather than the typical Pd(0)/Pd(II) pathway.



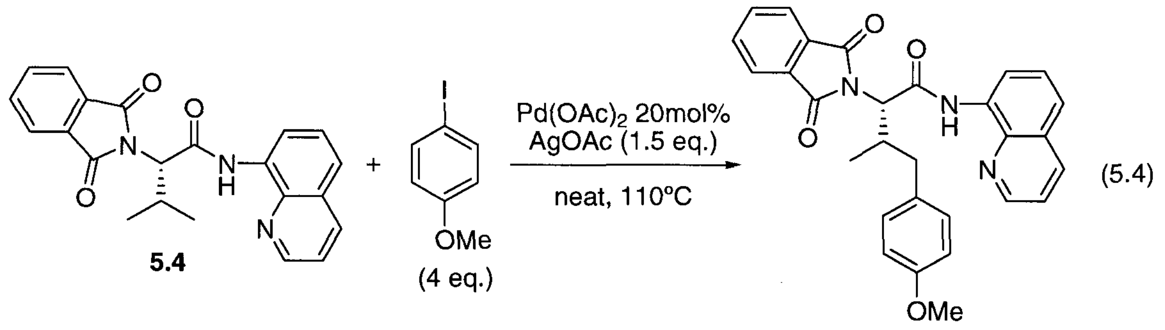
**Scheme 5.4** – Mechanistic Considerations for Picolinamide Arylation

Similar reaction conditions can also be applied to the arylation of 2-ethylpyridine and 8-methylquinoline. The reactions are carried out in acetic acid or *tert*-butyl alcohol and yield products in 51%, 69% and 74% yield in the three reported examples.[234]

The pyridyl directing group is one of the privileged motifs in this type of chemistry and has been exploited by other researchers. In 2005, Sanford and co-workers reported that 8-methylquinoline could be arylated using diphenyliodonium tetrafluoroborate under palladium catalysis.[235] The iodine (III) species is used as a limiting reagent and is thought to oxydize the alkyl-Pd(II) intermediate **5.3** leading to a Pd(IV) species which reductively eliminates the product (Equation 5.3).



Amino acid amides of 8-aminoquinoline have been used for arylation reaction by Corey and co-workers.[236] In a 2006 report, they show that these amides can undergo arylation at the γ-carbon to afford functionalized amino acid derivatives. For example valine derivative **5.4** can be arylated with *p*-iodoanisole in 85% yield (Equation 5.4).



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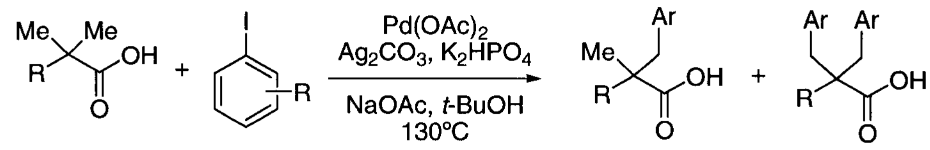
[234] Shabashov, D.; Daugulis, O.; *Org. Lett.* **2005**, *7*, 3657.

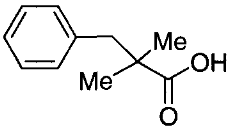
[235] Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S.; *J. Am. Chem. Soc.* **2005**, *127*, 7330

[236] Reddy, B. V. S.; Reddy, L. R.; Corey, E. J.; *Org. Lett.* **2006**, *8*, 3391

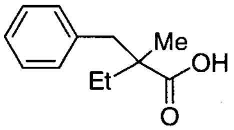
In 2005, Yu and co-workers reported the directed arylation of neopentyl carboxylates using $Pd(OAc)_2$ and aryl iodides.[237] This reaction was an extenstion of their work on the arylation of benzoic acid derivatives. The reaction is amendable to a variety of neopentyl carboxylic acids giving yields ranging from 42-72%. Optimal reaction conditions call for the use of 10 mol % $Pd(OAc)_2$, 2 equivalents of aryl iodide, 2 equivalents of $Ag_2CO_3$ and NaOAc and 1 equivalent of $K_2HPO_4$. Representative examples are found in Table 5.4.

**Table 5.4** – Arylation of Aliphatic Acids With Aryl Iodides[a]

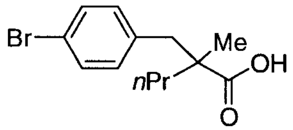




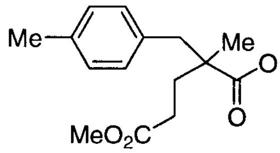
70% 2.5:1



72% 4:1



63% 3:1



43% 5:1

[a]Isolated yield of methyl ester reported

Reactions afford a mixture of mono- and diarylated products with ratios ranging from 2.5:1 to 5:1 in favour of mono-arylated products. The authors propose that the carboxylate generated under the reaction conditions may act as a directing group. They also suggest that this reaction follows a Pd(II)/Pd(IV) catalytic cycle, although no mechanistic evidence is presented to this effect.

Clearly, the number of recent reports on direct arylation reactions at $sp^2$-centers is greater than those of $sp^3$-centers. Additionally, the number of reaction partners that have been shown to undergo these processes are limited. For example, most arylations require either an organometallic or an aryl iodide coupling partner. A more desirable reactivity profile where aryl bromides and chlorides could be used with simple arenes would find immediate use because of its low cost and ready availablility.

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[237] Giri, R.; Maugel, N.; Li, J.-J.; Wang, D.-H.; Breazzano, S. P.; Saunders, L. B.; Li, J.-Q.; *J. Am. Chem. Soc.* **2007**, *129*, 3510

# 6

# Site-Selective Aliphatic Direct Arylation using Picoline *N*-Oxide Derivatives

## *Introduction*

While rare even just a decade ago, direct arylation of heterocycles has become a valuable tool in the transformation of otherwise chemically inert C-H bonds into a number of functional groups.[238] A particularly appealing and frequently discussed aspect of this chemistry involves the ubiquity of the C-H bond as a functional group and the potential to strategically introduce multiple functional groups on a given molecule with high site selectivity. In practice however, the challenge associated with achieving a high yielding reaction at even just one position makes the pursuit of controlled multi-site

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[238] Seregin, I. V.; Gevorgyan, V.; *Chem. Soc. Rev.* **2007**, *36*, 1173

selectivity a daunting task. Toward this goal, important advances have been made with some classes of electron-rich heteroaromatics (Figure 6.1). For example, the inherent bias of azoles to undergo C5 direct arylation can be overridden through the use of copper additives which induce reaction at C2.[239] Sames has also reported examples of C2/C3 site selectivity in indole arylations.[240] In some cases, modification to the substrate can cause a shift in site selectivity. Gaunt has demonstrated that regiocontrol can be achieved in indole and pyrrole alkenylation reactions through the choice of the solvent and the azole *N*-substituent.[241] Our group has recently demonstrated that the choice of oxidant as well the nature of the *N*-acyl substituent can completely reverse the site selectivity of the oxidative coupling of benzene with indole.[242] Significantly, these reactions all involve selectivity at aromatic $sp^2$ C-H bonds with a plausibly similar mechanism of C-H bond cleavage. Furthermore, only site selective direct arylation of thiazoles has been demonstrated to occur in high yield when performed serially on the same substrate.[239a]

As a greater appreciation of the possible mechanisms of C-H bond cleavage/functionalization is gained, and particularly as transformations and mechanisms which exhibit complimentary and orthogonal reactivity are discovered, this long-term goal of chemo- and site-selective direct functionalization should become increasingly achievable. In this section, we describe reactions where both $sp^2$ and $sp^3$ positions of heterocycles can be arylated in high yield with complete control of site selectivity. While both arylations may be facilitated by p$K_a$, it is the subtle combination of catalyst-substrate interactions and a change in C-H bond cleavage mechanism that enables the site selectivity to be achieved.

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[239] (a) Mori, A.; Sekiguchi, A.; Masui, K. ; Shimada, T. ; Horie, M. ; Osakada, K.; Kawamoto, M.; Ikeda, T. *J. Am. Chem. Soc.*, **2003**, *125*, 1700. (b) Bellina, F.; Cauteruccio S.; Rossi, R. *Eur. J. Org. Chem.*, **2006**, 1379. (c) Bellina, F.; Cauteruccio, S.; Mannina, L.; Rossi, R.; Viel, S. *Eur. J. Org. Chem.*, **2006**, 693. (d) Yokooji, A.; Okazawa, T.; Satoh, T. Miura, M.; Nomura, M. *Tetrahedron*, **2003**, *59*, 5685. (d) With rhodium catalysts, see: Lewis, J. C.; Wiedemann, S. H.; Bergman, R. G.; Ellman, J. A.; *Org. Lett.*, **2004**, *6*, 35.

[240] Lane, B. S. ; Brown, M. A.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 8050 and references therein.

[241] Beck, E. M.; Grimster, N. P.; Hatley, R.; Gaunt, M. J. *J. Am. Chem. Soc.*; **2006**, *128*, 2528

[242] Stuart, D. R.; Villemure, E.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 12072

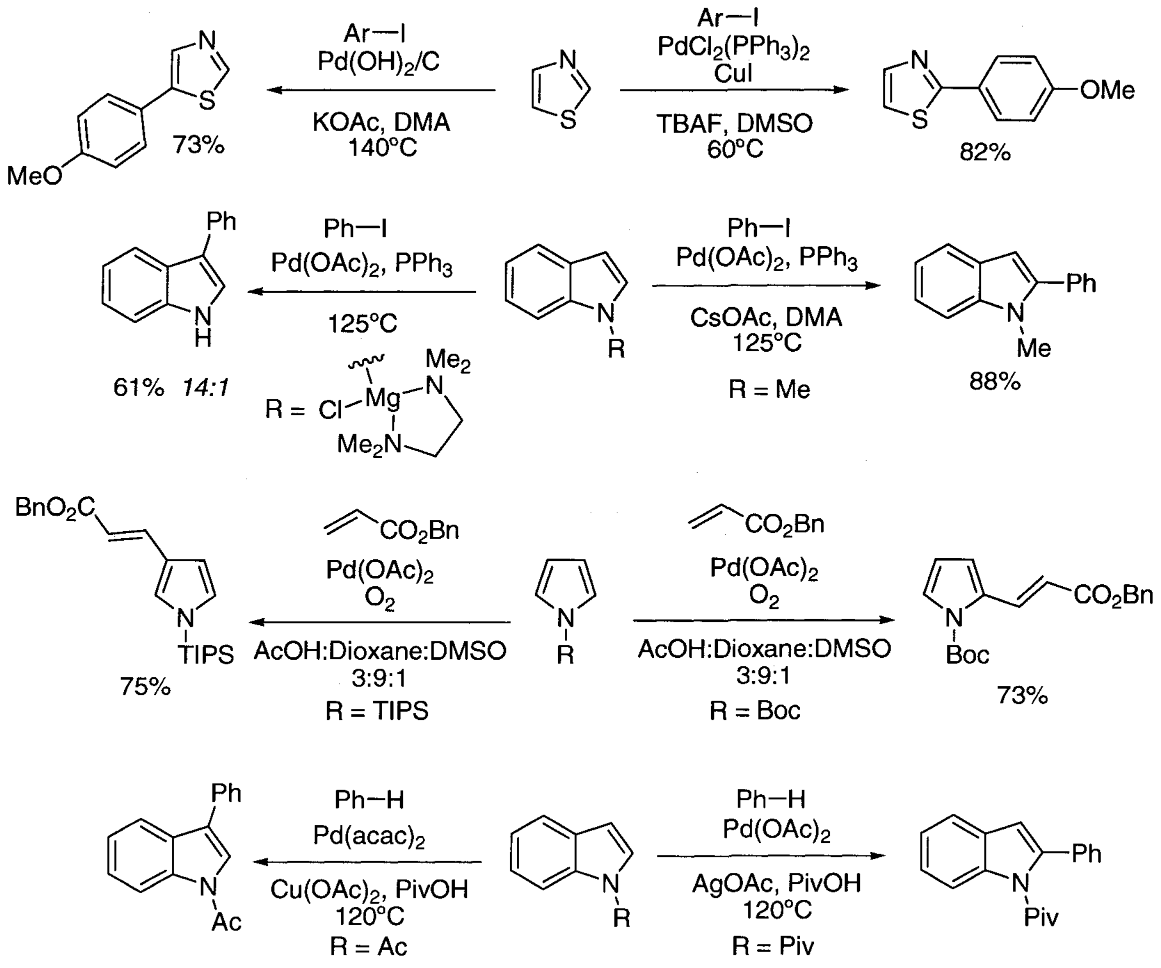
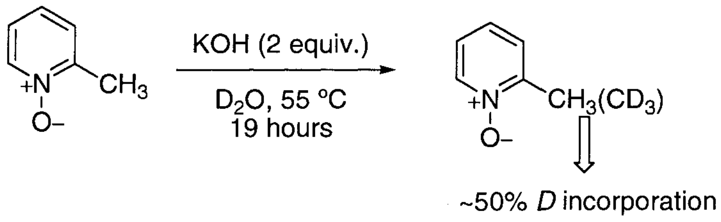


**Figure 6.1** – Examples of Site Selectivity in Direct Functionalization Reactions

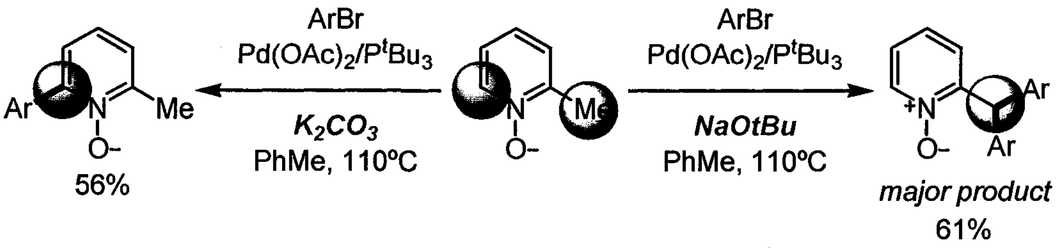
## *Initial Discovery*

During the investigation of pyridine *N*-oxide arylation (see chapter 4) we attempted H/D exchange experiments on various picoline *N*-oxides. Our arylation protocol was effective in providing the C-6 arylated picoline. However, the $sp^3$ C-H bonds of the methyl group on picoline actually exchange much faster than the C-6 $sp^2$ C-H bond which is functionalized (Equation 6.1).



(6.1)

We therefore set out to probe whether we could take advantage of this physical property to develop novel *sp*$^3$-arylation of picoline *N*-oxide derivatives. Screening of bases revealed that NaO$^t$Bu affected arylation at the *sp*$^3$-carbon giving the diarylated product in 61% yield (Equation 6.2). In view of the limited number of substrates capable of catalyst controlled *sp*$^2$- and *sp*$^3$- carbon arylation, we decided to pursue the development of this side reaction into a versatile route to functionalized picoline derivative.

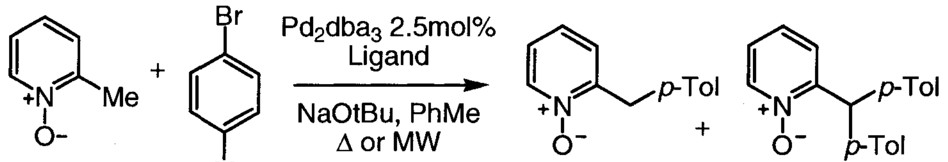


(6.2)

## Catalyst Development and Catalyst Scope

Reaction development was carried out with picoline *N*-oxide and 4-bromotoluene. From these studies, $Pd_2(dba)_3$ in combination with S-Phos emerged as the optimal metal-ligand combination. The use of alkoxide bases is critical to achieve high site selectivity and NaO$^t$Bu was found to be the optimal base. Toluene was a suitable solvent. Although increasing the equivalents of *N*-oxide resulted in an improved ratio of mono- to diarylation, the use of 2 equivalents of base with only a slight excess of the substrate led to synthetically useful selectivities albeit in modest yield (table 6.1, entry 3). Finally the optimal stoichiometry was judged to be 2 equivalents of *N*-oxide with 3 equivalents of base which afforded 77% isolated yield of the monoarylated adduct. Substituting S-Phos for the recently reported Ru-Phos led to modest increase in selectivity while maintaining similar conversion. On the other hand the use of X-Phos led to greatly improved selectivity, essentially giving a single product by $^1$H NMR. The low conversions led us to consider alternative methods of heating to increase conversion using this catalyst. We were gratified to find that microwave heating at 110 °C for 30 minutes resulted in a 89% isolated yield of **6.1** while the presence of **6.2** could not be detected by $^1$H NMR. These conditions also allow for 1.5 equivalents of *N*-oxide to be used and the catalyst loading to be reduced to 1 mol % palladium (Entry 9).

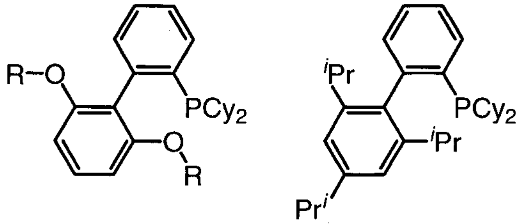
**Table 6.1** – Optimization of Picoline *N*-Oxide Arylation



**6.1** **6.2**

| Entry | Ligand | *N*-oxide eq. | Base eq. | Heating | Yield of **6.1**[a] | Ratio **6.1**:**6.2** |
|---|---|---|---|---|---|---|
| 1 | S-Phos | 1.5 | 1.05 | 70°C | 31% | 4.3:1 |
| 2 | S-Phos | 4 | 1.05 | 70°C | 48% | >20:1 |
| 3 | S-Phos | 1.5 | 2 | 70°C | 51% | 9:1 |
| 4 | S-Phos | 2 | 3 | 70°C | 77% | 6.7:1 |
| 5 | X-Phos | 2 | 3 | 70°C | 41% | >20:1 |
| 6 | Ru-Phos | 2 | 3 | 70°C | 78% | 8:1 |
| 7 | S-Phos | 1.5 | 2 | MW[d] | 61% | 1.5:1 |
| 8 | X-Phos | 1.5 | 3 | MW[d] | 90% | >20:1 |

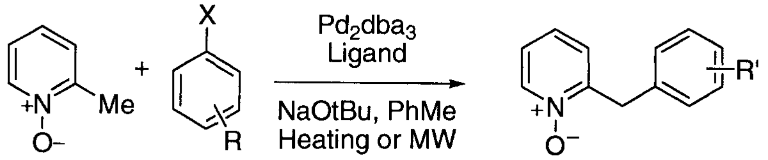
[a]NMR yield using 1,3,5-trimethoxybenzene as standard. [b]Isolated yield. [c]Using 1 mol % palladium. [d]Heating to 110 °C

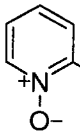
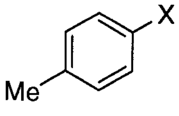
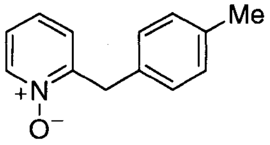
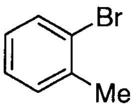
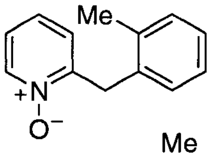
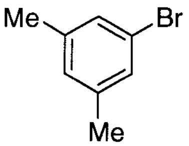
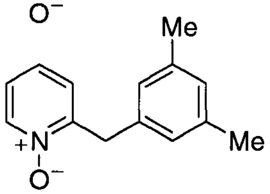
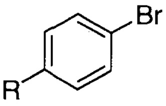
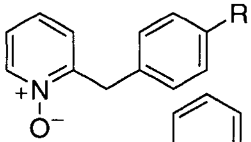
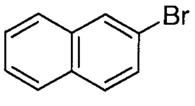
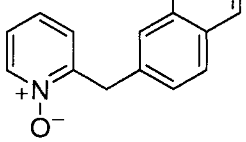
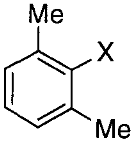
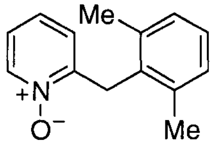
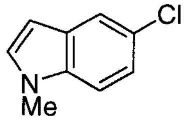
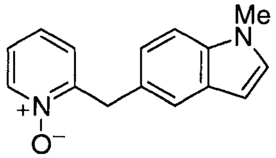


R = Me S-Phos
R = iPr Ru-Phos
X-Phos

Illustrative examples of the reaction scope are included in Table 6.2. A variety of substitution patterns, including *ortho*, *meta* and *para* can be employed in these transformations. The reaction is compatible with aryl bromides, iodides and chlorides. Although *ortho* substitution is well tolerated, we found that the use of *di-ortho* substituted aryl bromides led to almost no reaction and the reaction parameters needed to be re-evaluated for these substrates. We found that simply replacing X-Phos with S-Phos in these reactions led to excellent yields, as these substrates are predisposed to selective monoarylation due to the increased steric bulk around the reactive center once one arylation has occurred. Heterocycles can also be used, as exemplified by reaction of the chloroindole derivative.

**Table 6.2** – Scope of Picoline *N*-Oxide Arylation[a]

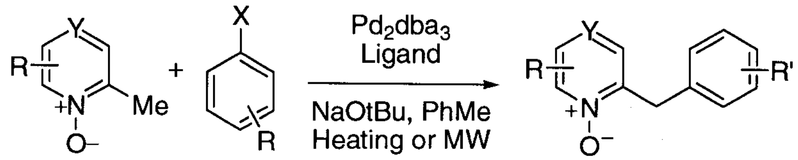


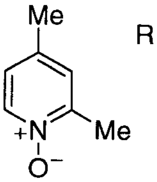
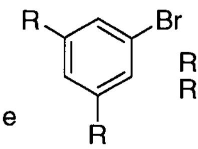
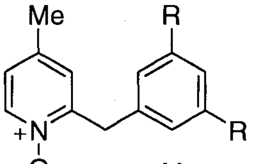
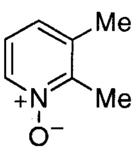
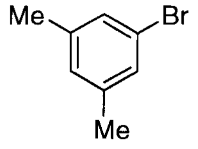
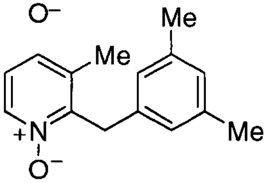
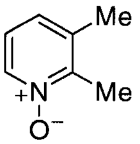
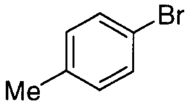
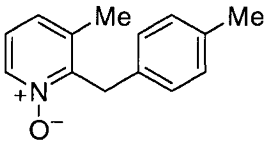
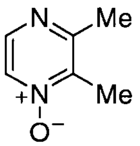
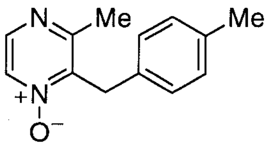
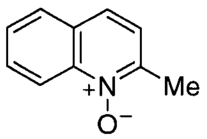
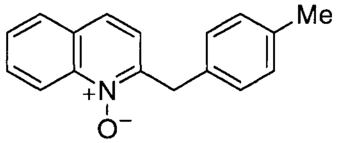
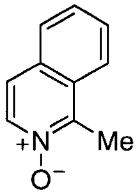
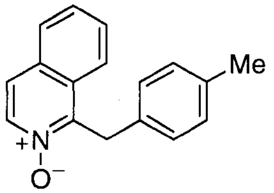
| Entry | *N*-Oxide | Aryl Halide | Product | Yield[b] |
|---|---|---|---|---|
| 1<br>2<br>3<br>4 |  **6.3** |  X=Br<br>X=Br<br>X=Cl<br>X=I |  | $77^{c}$<br>89<br>$91^{f}$<br>85 |
| 5 | **6.3** |  |  | 92 |
| 6 | **6.3** |  |  | 93 |
| 7<br>8 | **6.3**<br>**6.3** |  R=OMe<br>R=F |  | $72^{f}$<br>$72^{f}$ |
| 9 | **6.3** |  |  | 72 |
| 10<br>11<br>11<br>12 | **6.3**<br>**6.3**<br>**6.3**<br>**6.3** |  X=Br<br>X=Br<br>X=Br<br>X=Cl |  | $7^{d}$<br>$90^{c}$<br>$90^{e}$<br>$84^{e,f}$ |
| 13 | **6.3** |  |  | 90 |

[a]Conditions: Picoline *N*-oxide (1.5 equiv.), Aryl Halide (1 equiv.), Pd$_2$dba$_3$ (0.025 equiv.), X-Phos (0.05 equiv.) and NaO$^t$Bu (3 equiv.) in PhMe (0.5-1M), MW, 110 °C for 45min. [b]Isolated yield. [c]Conditions: Picoline *N*-oxide (2 equiv.), Aryl Halide (1 equiv.), Pd$_2$dba$_3$ (0.025 equiv.), Ru-Phos (0.1 equiv.) and NaO$^t$Bu (3 equiv.) in PhMe (0.3M), 70°C overnight. [d]NMR yield. [e]Using microwave conditions with S-Phos. [f]Reaction performed by Dereck Schipper

Other alpha methyl azines and diazines can also be used in the current protocol, providing the arylated heterocycles in good yield. Selective reactions are also possible when more than one methyl group is present on the heterocycle. 2,3- and 2,4-lutidine react exclusively at the 2-position to afford the products in good to excellent yields. .

**Table 6.2** – Scope of 2-Methyl Azine and Diazine *N*-Oxide Arylation[a]



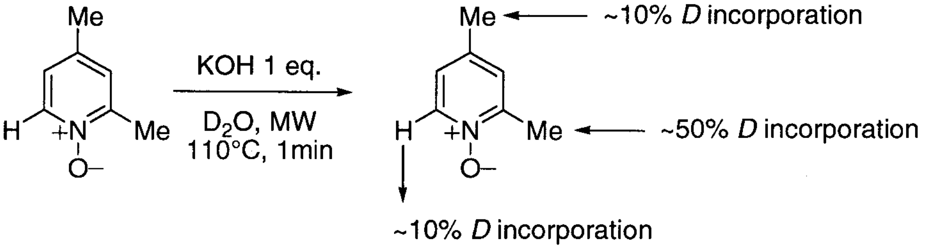
| Entry | *N*-Oxide | Aryl Halide | Product | Yield[b] |
|---|---|---|---|---|
| 1<br>2 |  | <br>R=Me<br>R=OMe |  | 64<br>70 |
| 3 |  |  |  | 90 |
| 4 |  | <br>**6.4** |  | $76^{c}$ |
| 5 |  | **6.4** |  | $79^{d}$ |
| 6 |  | **6.4** |  | $73^{d,e}$ |
| 7 |  | **6.4** |  | 60 |

[a]Conditions: Picoline *N*-oxide (1.5 equiv.), Aryl Halide (1 equiv.), $Pd_2dba_3$ (0.025 equiv.), X-Phos (0.05 equiv.) and NaO$^t$Bu (3 equiv.) in PhMe (0.5-1M), MW, 110 °C for 45min. [b]Isolated yield. [c]Conditions: Picoline *N*-oxide (2 equiv.), Aryl Halide (1 equiv.), $Pd_2dba_3$ (0.025 equiv.), Ru-Phos (0.1 equiv.) and NaO$^t$Bu (3 equiv.) in PhMe (0.3M), 70°C overnight. [d]Using 3 equiv. of *N*-oxide. [e]Reaction performed by Dereck Schipper

However, while 1-methyl isoquinoline *N*-oxide was a suitable substrate for the benzylic activation, reaction of 3-methyl isoquinoline *N*-oxide led to a mixture of *sp*$^3$ and *sp*$^2$ arylated products. Nonetheless this is the only substrate where we have observed a problem in selectivity for the benzylic arylations.

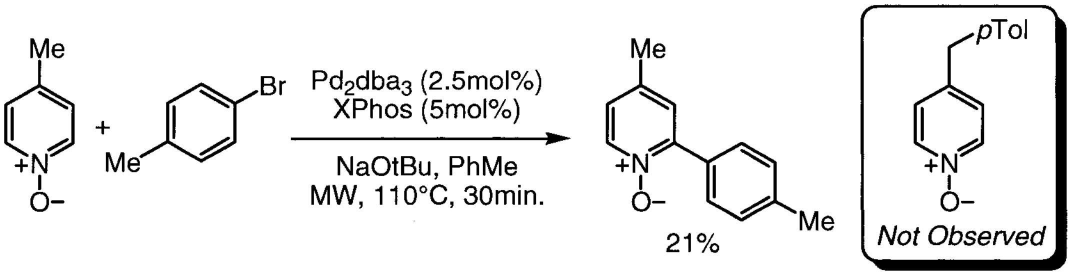
## Mechanistic Insights and Site-Selectivity

The reactions of lutidine *N*-oxides provide information regarding the reaction mechanism. Although H/D exchange experiments indicate that many sites show increased acidity in 2,4-lutidine (Equation 6.3), we exclusively see direct arylation at the C-2 methyl group.



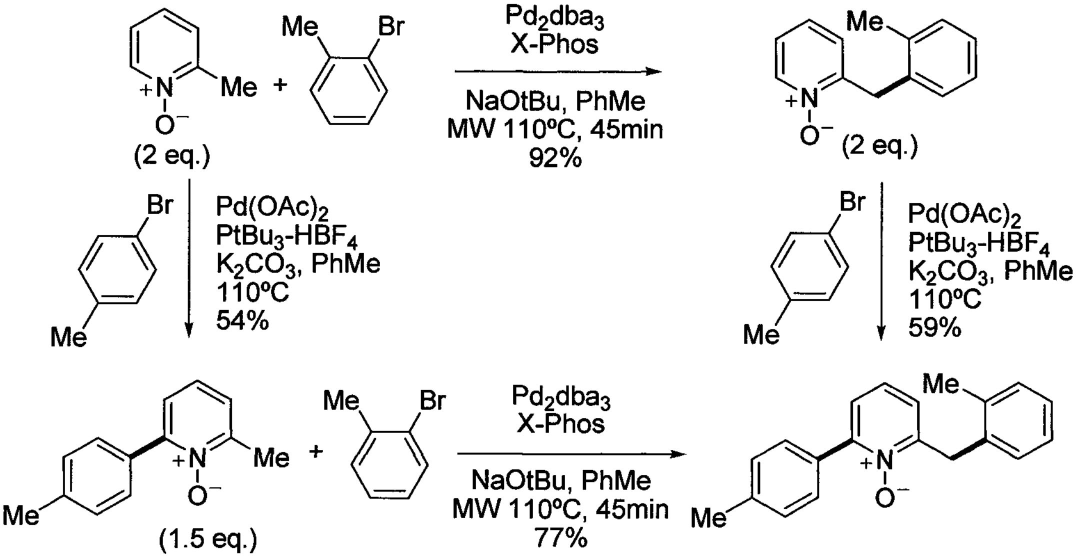
(6.3)

This result indicates that the *N*-oxide functionality has a directing influence that promotes arylation at the C-2 position. In fact, reaction of 4-picoline under the conditions developed for *sp*$^3$-arylation afforded none of the expected *sp*$^3$-arylation product, but rather a low yield of the *sp*$^2$ arylated product (Equation 6.4).



(6.4)

The high site selectivity of this transformation allows it to be performed in conjunction with the previously presented arylation of *sp*$^2$-centers on pyridine *N*-oxide for the synthesis of diarylated compounds in which it is possible to install different aryl groups at the C-2 methyl group and C-6 position of picoline *N*-oxide as presented in Scheme 6.1. The structural motifs attainable using this methodology represent an important class of ligands used in Hf and Zr catalyzed olefin polymerization.[243] To our knowledge, this represents the first examples of multiple site selective direct arylations of a *sp*$^2$ and *sp*$^3$ center on the same molecule which is completely controlled by the catalytic conditions.



**Scheme 6.1** – Site Selective Synthesis of Diarylpicoline *N*-Oxide Derivatives

The differing site selectivity can be attributed to diverging mechanisms for both reactivities. While previously described work has demonstrated evidence for a concerted metallation/deprotonation pathway for the *sp*$^2$ arylation, the 6-membered ring transition state for this transformation is not accessible when using alkoxide bases. On the other hand, the *sp*$^3$ arylation may occur via a deprotonation of the methyl group under the reaction conditions which would allow it to act as a nucleophile on the palladium (II) center. Such a process would be related to *alpha* arylation reactions of carbonyl compounds, except that the *N*-oxide plays a dramatic directing effect. The proposed catalytic cycle is presented in Scheme 6.2. After oxidative addition, the newly formed palladium (II) center can interact with the *N*-oxide functionality of the substrate bringing it in close proximity with the methyl. Deprotonation to form the metallacycle, followed by reductive elimination would afford the product.

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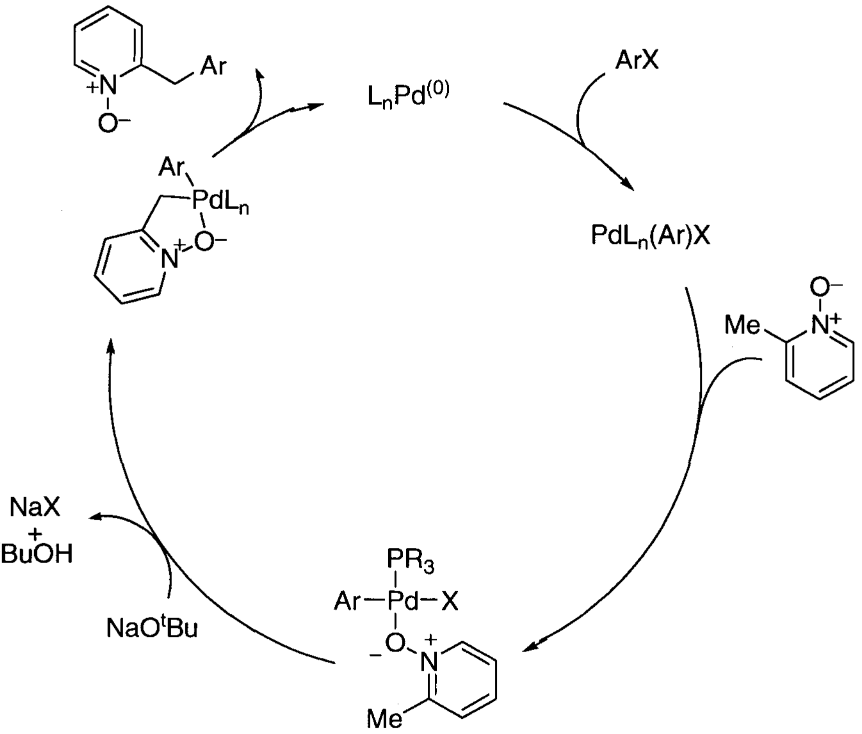
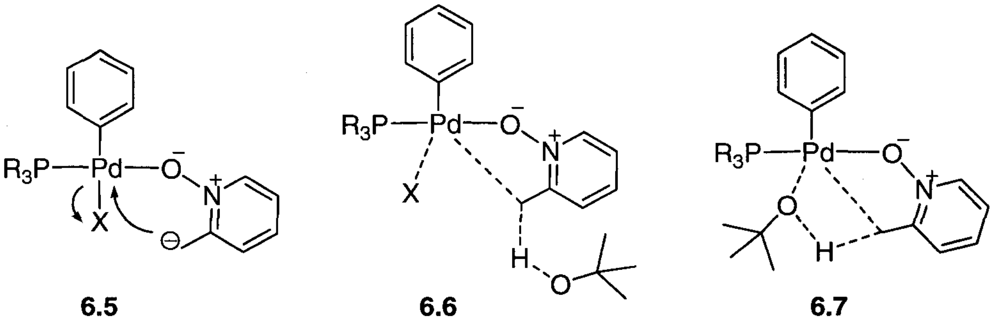
[243] Boussie, T. R.; Diamond, G. M.; Goh, C.; Hall, K. A.; LaPointe, A. M.; Leclerc, M. K.; Murphy, V.; Shoemaker, J. A. W.; Turner, H.; Rosen, R. K.; Stevens, J. C.; Alfano, F.; Busico, V.; Cipullo, R.; Talarico, G.; *Angew. Chem. Int. Ed.* **2006**, *45*, 3278



**Scheme 6.2** – Proposed Mechanism for Picoline *N*-Oxide *sp*$^3$ Arylation

Though the exact mechanism of metallation of the methyl group still remains to be ascertained, many possibilities exist (Scheme 6.3). Given the high selectivity for the C-2 methyl groups we believe that *N*-oxide binding to the metal center is fundamental. Whether deprotonation occurs before or after binding takes place is yet undertermined. If the former takes place, metallation via anion **6.5** could be a primary pathway. However, if the binding occurs first, deprotonation could occur via two pathways. An external base could deprotonate the methyl group, allowing the formation of the Pd-C bond such as illustrated in **6.6**. On the other hand, salt metathesis between NaO$^t$Bu and Pd-X could occur, generating a palladium alkoxide intermediate which could undergo internal deprotonation such as **6.7**.



**6.5** **6.6** **6.7**

**Scheme 6.3** – Possible Mechanism of Metallation of *sp*$^3$-carbon

Given the low cost and ready availability of *N*-oxides, these reactions should find significant use in the preparation of benzyl azines. Preliminary experiments suggest that this type of reactivity could also be applied to 2-alkyl pyridine *N*-oxides.[244]

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[244] This work was passed on to another graduate student; Derek Schipper, July 2007. Results were obtained by Derek.

# 7

# Supporting Information

## Introduction

All reagents, unless otherwise indicated, were purchased from commercial sources and used without further purification. Reagent grade dichloromethane and HPLC grade toluene were used without further purification. Dry HPLC Grade THF, $Et_2O$, benzene, toluene and $CH_2Cl_2$ are dried and purified via MBraun SP Series solvent purification system. Triethylamine was freshly distilled over NaOH before every use. Acetonitrile was freshly distilled over $CaH_2$ before every use. Dioxane was freshly distilled over $LiAlH_4$ before everyuse. Dimethylacetamide was degassed with Argon before every use. Palladium sources and ligands were purchased from Strem and stored in a dessicator and were weighed out to air unless otherwise specified. Phosphonium salts were synthesized according to literature procedures[245] or purchased from Strem, stored in a dessicator and used without further purification. $Pd(PCy_3)_2$ were stored in a glove-box but were weighed to air. Imidazolium salts were either synthesized according to literature procedures, as described in the supporting information, or purchased from Strem and used without further purification and stored in a dessicator and were weighed out to air unless otherwise specified. All other reagents and solvents were used as is from commercial sources. Unless noted below, all other compounds have been reported in the literature or are commercially available.

All reactions were performed in air-dried glassware. Coupling reactions were performed with regard for exclusion of ambient air. Microwave heating was performed using a *CEM* Discover Microwave (specific reaction conditions are described below). Analysis of crude reaction mixture was done using TLC or NMR. Reactions were purified by flash chromatography on silica gel. $^1H$, $^{13}C$, and DEPT-135 spectra were typically recorded in $CDCl_3$ or $(CD_3)_2CO$ solutions on a Bruker AVANCE 300 MHz or 400 MHz or a Varian INOVA 500 MHz spectrometer at ambient temperature and chemical shifts are reported relative to tetramethylsilane (TMS). Fourier-transform infra-red (FTIR) spectra were obtained as thin films on sodium chloride plates. High resolution mass spectra were obtained with a Kratos Concept IIH mass spectrometer. Melting points were recorded using a Gallenkamp Melting Point Apparatus and are reported uncorrected.

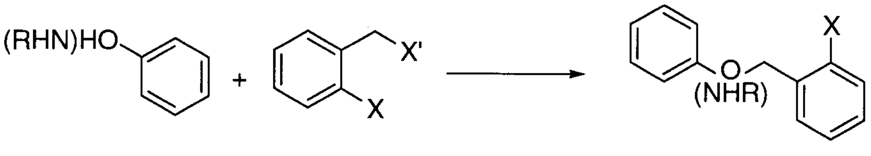
## Procedures and Characterization of New Compounds

## Chapter 2

### Starting Materials:

All starting material synthesis was preformed on 0.5-2g scale. The following procedures were not optimized for each individual substrate.

### General procedure A:



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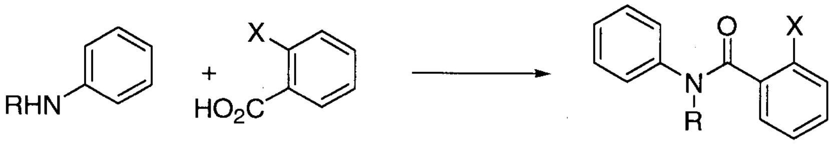
[245] Netherton, M. R.; Fu, G. C.; *Org. Lett.*, **2001**; *3*; 4295-4298

The appropriate phenol or methansulfonaniline (2 equiv.), $K_2CO_3$ (3 equiv.) and NaI (0.1 equiv.) were placed in a round bottom flask equipped with a magnetic stir bar. Reagent grade acetone was added (0.5M) and the flask was fitted with a reflux condenser. Addition of the appropriate 2-halobenzylchloride (or 2-halobenzylbromide) (1 equiv.) was followed by heating (50°C) of the reaction overnight. The reaction was allowed to cool and was extracted using $Et_2O$/Brine. The organics were dried using $MgSO_4$, filtered and the volatiles were evaporated under reduced pressure. The residues were then purified via silica gel column chromatography using ethyl acetate/hexanes mixtures.

**General procedure B:**

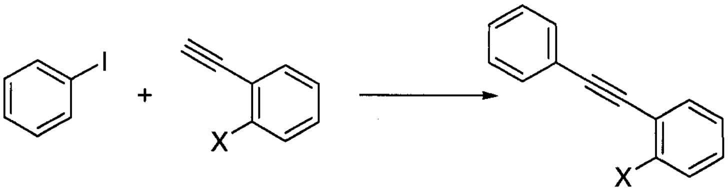
In a 50mL round-bottom flask equipped with a magnetic stirrer were added 2-halobenzaldehyde (1.0 equiv.) and $MgSO_4$ (0.5g/mmol), dissolved in dichloromethane (0.9M). The addition of the appropriate aniline (1.0 equiv.) was done dropwise, and the reaction was stirred overnight at room temperature. $MgSO_4$ salt was filtered and the volatiles were evaporated under reduced pressure. This crude mixture was then dissolved in anhydrous ether, and the reaction was brought to 0°C using an ice bath. $LiAlH_4$ (2.0 equiv.) was added dropwise to the mixture, and the reaction was stirred overnight at room temperature. The mixture was then quenched using tartrate salts, followed by the addition of water and ether, vigorously stirring for 1 hour. The mixture was extracted using $Et_2O$/Brine. The organics were dried using $MgSO_4$, filtered and the volatiles were evaporated under reduced pressure. The residues were then purified via column chromatography using ethyl acetate/hexanes mixtures.

**General Procedure C:**



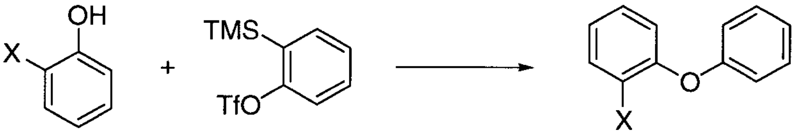
The appropriate carboxylic acid (1 equiv.) was dissolved in $CH_2Cl_2$ (0.25-0.5M). The flask was purged with argon and placed in an ice bath. To this stirring solution was added oxalyl chloride (1.2 equiv.) followed by 1 drop of DMF. The reaction was allowed to stir and warm to room temperature. Once reaction was complete, the solvent was evaporated under reduced pressure. The crude mixture was then re-dissolved in dry $CH_2Cl_2$ (0.5M). The mixture was cooled to 0°C and DIPEA or $NEt_3$ (1.5 equiv.), DMAP (cat.) and appropriate aniline (0.9 equiv.) was then added. The reaction was allowed to stir under argon at room temperature overnight. The reaction mixture was then extracted with Brine/DCM and evaporated under reduced pressure. The crude product was purified via silica gel column chromatography with ethyl acetate/hexane mixtures.

**General Procedure D:**



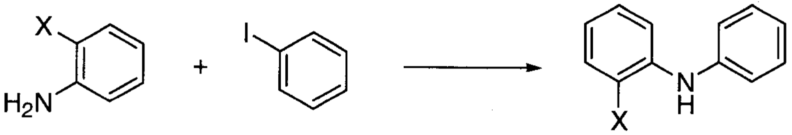
The appropriate iodoarene (1.05 equiv.), CuI (0.02 equiv.) and $Pd(PPh_3)_2Cl_2$ (0.02 equiv.) were weighed to open air and placed in a round bottom flask equipped with a magnetic stir bar. The flask was purged with nitrogen and THF (0.2M) and $NEt_3$ (5% volume to THF) were added. To this stirring mixture was added 2-halophenylacetylene dropwise and the reaction was allowed to stir overnight under positive nitrogen pressure. The volatiles were then evaporated under reduced pressure and the residue was extrated using $EtOAc/Et_2O$/Brine. The organics were dried using $MgSO_4$, filtered and the volatiles were evaporated under reduced pressure. The residue was then purified via silica gel column chromatography using hexane to afford the diarylacetylene.

**General Procedure E:**



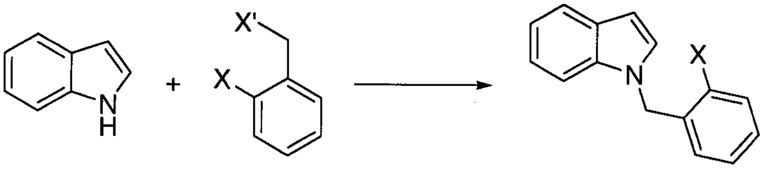
The appropriate 2-halophenol (1 equiv.) and silylaryl triflate (1.4 equiv.) were dissolved in dry MeCN. To this stirring solution was added cesium fluoride (3 equiv.) at room temperature. The flask was then purged with argon and the reaction was allowed to stir at room temperature for 48 hours. After evaporation of the solvent under reduced pressure, the residue was extracted with $Et_2O$/Brine, dried with $MgSO_4$, filtered and the volatiles were evaporated under reduced pressure. The products were purified via silica gel column chromatography using hexane/ether mixtures to afford the aryl ethers.

**General Procedure F:**



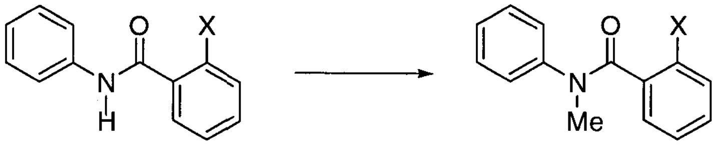
$Pd_2dba_3$ (0.01 equiv.), Ligand[246] (0.04 equiv.) and $NaO^tBu$ (1.4 equiv.) were weighed to air and transferred to a resealable Schlenk tube. Amine (1.2 equiv.) and aryl iodide (1 equiv.) were added at this point if solid. The tube was then evacuated and backfilled with argon. The flask was capped with a rubber septum under an argon purge, and the liquid reagents (amine and/or aryl iodide) added. Dioxane (0.3M) is then added; the tube is sealed and stirred at 45°C overnight. The mixture is then diluted with ether, filtered through a plug of Celite and evaporated under reduced pressure. The crude product was purified via silica gel column chromatography using hexane/ether mixtures to afford the aryl amines.

**General Procedure G:**



Indole (1 equiv.) and crushed KOH (4 equiv.) were placed in a round bottom flask equipped with a magnetic stir bar. DMSO was added (0.5M) and the reaction was left stirring at room temperature for 30 minutes. The appropriate benzyl chloride was then added in one portion and the reaction was left stirring at room temperature for 2 hours. The reaction mixture was then extracted with $H_2O$ and $Et_2O$. The organics were washed with $NH_4Cl$ and re-extrated with $Et_2O$ and the organic residue was dried over $MgSO_4$ and evaporated under reduced pressure. The product was purified by silica gel column chromatography using hexanes as the eluent.

**General Procedure H:**



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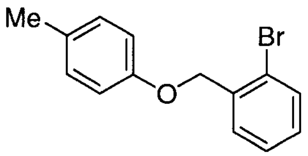
[246] For choice of ligand see : Ali, M.H.; Buchwald, S.L.; *J. Org. Chem.* **2001**, *66*, 2560

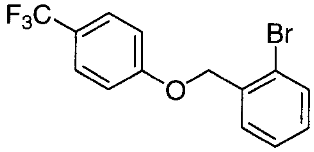
Sodium hydride (1.2 equiv.) was triturated with pentane under argon and then was suspended in dry THF (0.9M). The appropriate amide (1 equiv.), dissolved in THF (0.7M) was added dropwise to the suspension of sodium hydride at 0°C. After 30 minutes of stirring, MeI (1.05 equiv.) is added. The reaction was allowed to warm to room temperature and stirred for 6 hours. $NH_4Cl$ (aq.) was added and the volatiles are removed under reduced pressure. The residue is then extracted with ethyl acetate/brine and the organic layer was dried with $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was then purified via silica gel column chromatography using hexanes/ethyl acetate mixtures.

Table 2.2, Entry 3



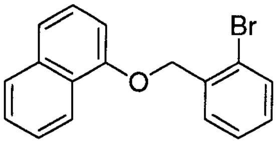
Synthesized according to general procedure **A**.
**$^1$H NMR (300MHz, $CDCl_3$, 293K, TMS):** 2.26 (3H, s), 5.06 (2H, s), 6.85 (2H, m), 7.10 (3H, m), 7.27 (1H, td, $J$=8Hz & $J$=1Hz ), 7.52 (2H, m);
**$^{13}$C NMR (75MHz, $CDCl_3$, 293K, TMS)**: 20.5, 69.4, 114.7, 122.2, 127.5, 128.8, 129.0, 129.9, 130.3, 132.5, 136.5, 156.3;
**IR ($\nu_{max}$/cm$^{-1}$)** 3029 (weak), 1510, 1237, 1024, 816, 745;
**HRMS** calculated for $C_{14}H_{13}BrO$ (M+) 276.0163; Found : 276.0150
**R$_f$**: 0.64 on silica gel (5% EtOAc:Hexanes);

Table 2.2, Entry 7



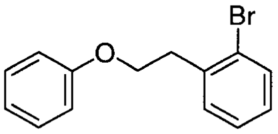
Synthesized according to general procedure **A**.
**$^1$H NMR (300MHz, $CDCl_3$, 293K, TMS):** 5.14 (2H, s), 7.02 (2H, d, $J$=9Hz), 7.17 (1H, t, $J$=8Hz), 7.31 (1H, d, $J$=7Hz), 7.52 (4H, m);
**$^{13}$C NMR (75MHz, $CDCl_3$, 293K, TMS):** 69.5, 114.9, 122.4, 123.3 (q, $J$=33Hz), 124.3 (q, $J$=271Hz), 127.0 (q, $J$=3Hz), 127.7, 128.9, 129.6, 132.8, 135.5. 160.8;
**IR** ($\nu_{max}$/cm$^{-1}$) 2925 (weak), 1320, 1248, 1108, 841, 750 ;
**HRMS** calculated for $C_{14}H_{11}BrF_3O$ (M+) 329.9853; Found: 329.9867
**R$_f$**: 0.62 on silica gel (5% EtOAc:Hexanes);

Table 2.2, Entry 11



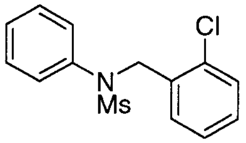
Synthesized according to general procedure **A**.
**$^1$H NMR (300MHz, CDCl$_3$, 293K, TMS):** 5.33 (2H, s), 6.89 (1H, d, *J*=8Hz), 7.24 (1H, d, *J*=3Hz), 7.38 (2H, m), 7.49 (3H, m), 7.62 (1H, d, *J*=8Hz), 7.69 (1H, d, *J*=8Hz), 7.82 (1H, m), 8.38 (1H, m); **$^{13}$C NMR (75MHz, CDCl$_3$, 293K, TMS)**: 69.5, 105.4, 120.8, 122.3, 125.3, 125.7, 125.8, 126.5, 127.5, 127.6, 128.7, 129.5, 132.6, 134.6, 136.4, 154.0;
**IR** ($\nu_{max}$/cm$^{-1}$) 3053 (weak), 1364, 1246, 1096, 758 ;
**HRMS** calculated for $C_{17}H_{13}BrO$ (M+) 312.0046; Found: 312.0150
**R$_f$:** 0.55 on silica gel (5% EtOAc:Hexanes);

Scheme 2.1



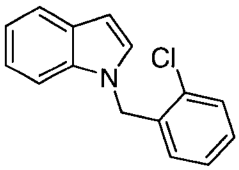
Synthesized according to general procedure **A**.
**$^1$H NMR (300MHz, CDCl$_3$, 293K, TMS):** 3.22 (2H, t, J=7Hz), 4.17 (2H, t, *J*=7Hz), 6.91 (3H, m), 7.08 (1H, m), 7.26 (4H, m), 7.53 (1H, dd, *J*=9Hz & 1Hz);
**$^{13}$C NMR (75MHz, CDCl$_3$, 293K, TMS)** : 36.0, 66.6, 114.5, 120.7, 124.6, 127.5, 128.3, 129.4, 131.3, 123.8, 137.5, 158.6;
**IR ($\nu_{max}$/cm$^{-1}$)**: 2938 (weak), 1240, 1036, 747 ;
**HRMS** calculated for $C_{14}H_{13}BrO$ (M+) 276.0135; Found: 276.0150;
**R$_f$** : 0.50 on silica gel (5% EtOAc:Hexanes);

Table 2.3, Entry 3



Synthesized according to general procedure **A**.
**$^1$H NMR (300MHz, CDCl$_3$, 293K, TMS):** 2.99 (3H, s), 5.03 (2H, s), 7.26 (8H, m), 7.49 (1H, m,);
**$^{13}$C NMR (75MHz, CDCl$_3$, 293K, TMS):** 37.9, 51.8, 127.0, 128.1, 128.3, 129.0, 129.4, 130.3, 133.3, 133.7, 139.1;
**IR ($\nu_{max}$/cm$^{-1}$)**: 3065(w), 1595(w), 1492(m), 1342(s), 1154(s), 1048(m), 873(m);
**HRMS** calculated for $C_{14}H_{14}ClNO_2S$ (M+) 295.0403; Found: 295.0415
**m.p.** = 98-99°C (EtOAc/Hex)
**R$_f$:** 0.35 on silica gel (5% EtOAc:Hexanes);

Table 2.1, Entry 6



Indole (1 equiv.) and crushed KOH (4 equiv.) were placed in a round bottom flask equipped with a magnetic stir bar. DMSO was added (0.5M) and the reaction was left stirring at room temperature for 30 minutes. The appropriate benzyl chloride was then added in one portion and the reaction was left stirring at room temperature for 2 hours. The reaction mixture was then extracted with $H_2O$ and $Et_2O$. The organics were washed with $NH_4Cl$ and re-extrated with $Et_2O$ and the organic residue was dried over $MgSO_4$ and evaporated under reduced pressure. The product was purified by silica gel column chromatography using hexanes as the eluent.

**$^1$H NMR (300MHz, CDCl$_3$, 293K, TMS):** 5.34 (2H, s), 6.52 (1H, dd, *J*=7.7 & 0.5Hz), 6.56, (1H, dd, *J*=3.2 & 0.7Hz), 7.00 (1H, td, *J*=7.5 & 1.2Hz), 7.15 (5H, m), 7.36, (1H, dd, *J*=7.9 & 1.2Hz);

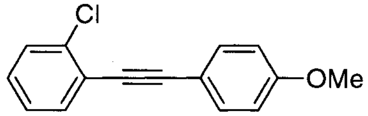
**$^{13}$C NMR (75MHz, CDCl$_3$, 293K, TMS):** 48.1, 105.5, 110.1, 120.2, 121.6, 122.4, 127.7, 128.4, 128.9, 129.1, 129.3, 129.4, 132.8, 135.6, 136.7;

**IR ($\nu_{max}$/cm$^{-1}$)**: 3057(s), 2925(m), 1574(m), 1462(s), 1319(s), 1050(s), 740(s)

**HRMS** calculated for $C_{15}H_{12}ClN$ (M+) 241.0658; Found: 241.0652

**R$_f$:** 0.2 on silica gel (Hexanes);

Table 2.3, Entry 5



Synthesized according to general procedure **D**.

**$^1$H NMR (300MHz, CDCl$_3$, 293K, TMS):** 3.84 (s, 3H), 6.87-6.92 (m, 2H), 7.22-7.25 (m, 2H), 7.41-7.44 (m, 1H), 7.49-7.51 (m, 1H), 7.53-7.56 (m, 2H);

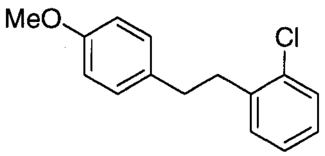
**$^{13}$C NMR (75MHz, CDCl$_3$, 293K, TMS):** 55.3, 94.7, 114.0, 115.0, 123.5, 126.4, 128.9, 129.2, 133.0, 133.2, 135.7;

**IR ($\nu_{max}$/cm$^{-1}$):** ): 2954(s), 2925(s), 2854(s), 1458(m);

**HRMS** calculated for $C_{15}H_{11}ClO$ (M$^+$): 242.0498; Found: 242.0488;

**m.p.** = 65–66°C (ether)

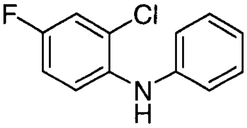
**R$_f$:** 0.75 on silica gel (1% EtOAc:Hexanes);



The 1-(2-(2-chlorophenyl)ethynyl-4-methoxybenzene (1 equiv.) and *p*-toluenesulfonylhydrazine (20 equiv.) were then dissolved in DME (0.1M) and heated to 85°C. To this stirring mixture was added a solution of NaOAc (20 equiv.) in water over 8 hours via syringe pump. The reaction was stirred for an additional 4 hours and the heat source was removed. The reaction mixture was then extracted with hexane/ethyl acetate and brine. The organic extracts were dried using $MgSO_4$, and concentrated under reduced pressure. Purification was done by flash chromatography using hexanes.

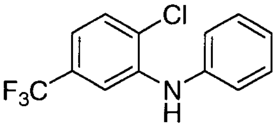
**$^1$H NMR (300MHz, $CDCl_3$, 293K, TMS):** 2.82-2.88 (m, 2H), 2.96-3.02 (m, 2H), 3.79 (s, 3H), 6.81-6.86 (m, 2H), 7.11-7.17 (m, 5H), 7.34-7.37 (m, 1H);
**$^{13}$C NMR (75MHz, $CDCl_3$, 293K, TMS):** 35.1, 36.1, 55.2, 113.7, 126.7, 127.4, 129.4, 129.4, 130.5, 133.6, 133.9, 139.3, 157.8;
**IR ($\nu_{max}$/$cm^{-1}$):** 2933 (w), 2834 (w), 1512 (s), 1246 (s), 1037 (m);
**HRMS** calculated for $C_{15}H_{15}ClO$ ($M^+$): 246.0811; Found: 246.0811
**$R_f$:** 0.55 on silica gel (1% EtOAc:Hexanes);

Table 2.3, Entry 9



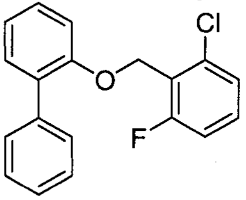
Synthesized according to general procedure **F**.
**$^1$H NMR (300MHz, $CDCl_3$, 293K, TMS):** 5.87 (s, 1H), 6.89 (td, J = 8.6 Hz & 2.7 Hz, 1H), 7.01 (t, 1H), 7.08 (d, 2H), 7.14 (dd, *J*=8.1 Hz & 2.7 Hz, 1H), 7.21-7.33 (m, 3H);
**$^{13}$C NMR (75MHz, $CDCl_3$, 293K, TMS):** 114.2, 114.5, 116.7, 117.0, 117.3, 117.5, 119.1, 122.2, 129.5, 129.5;
**IR ($\nu_{max}$/$cm^{-1}$):** 3412 (m), 1599 (s), 1516 (s), 1478 (s), 860 (m);
**HRMS** calculated for $C_{12}H_9ClFN$ ($M^+$): 221.0408; Found: 221.0389
**$R_f$:** 0.32 on silica gel (10% EtOAc:Hexanes);

Table 2.3, Entry 10



Synthesized according to general procedure **F**.
**$^1$H NMR (300MHz, $CDCl_3$, 293K, TMS):** 6.25 (s, 1H), 7.00-7.03 (m, 1H), 7.11-7.21 (m, 3H), 7.35-7.46 (m, 4H);
**$^{13}$C NMR (75MHz, $CDCl_3$, 293K, TMS):** 110.9 (q, *J*=3.9 Hz), 116.2 (q, *J*=3.9 Hz), 121.3, 123.8 (q, *J*=273.1 Hz), 124.0, 129.8, 130.0 (q, *J*=32.5 Hz), 130.1, 140.1, 141.1;
**IR ($\nu_{max}$/$cm^{-1}$):** 2855 (s), 1454 (s), 1065 (m);
**HRMS** calculated for $C_{13}H_9ClF_3N$ ($M^+$): 271.0376; Found: 271.0377
**$R_f$:** 0.35 on silica gel (10% EtOAc:Hexanes);

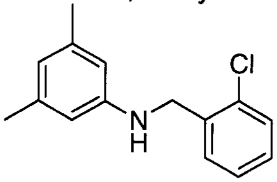
Table 2.5, Entry 2



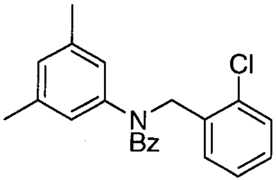
Synthesized according to general procedure **A**:
**$^1$H NMR (300MHz, $CDCl_3$, 293K, TMS):** 5.11 (2H, d, J=1.2Hz), 6.91 (1H, td, J=3.6Hz & 6.3Hz), 7.06 (1H, t, J=7.5Hz), 7.14 (3H, m), 7.24 (1H, d, J=7.5Hz), 7.27-7.36 (4H, m), 7.53 (2H, m);
**$^{13}$C NMR (75MHz, $CDCl_3$, 293K, TMS):** 62.0 (d, J=4.35Hz), 114.1 (d, J=13.1Hz), 114.3, 121.9, 122.5 (d, J=17.5Hz), 125.3 (d, J=3.3Hz), 126.7, 127.8, 128.5, 129.5, 130.5 (d, J=9.8Hz), 131.8, 136.4, 136.4, 138.3, 155.5, 161.9 (J=251.0Hz);

**IR** (*$\nu_{max}$* **/cm$^{-1}$**): 3064, 3029, 2939, 1609, 1482, 1221, 1003, 851, 778;
**HRMS** calculated for $C_{19}H_{14}FClO$ (M+): 312.0717; Found: 312.0727;
**m.p.** = 115-117°C ($CHCl_3$)
**R$_f$**: 0.55 on silica gel (5% EtOAc:Hexanes);

Table 2.5, Entry 3

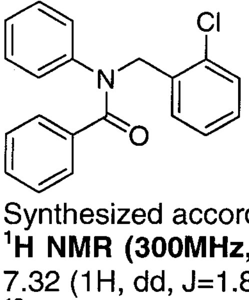


Synthesized according to general procedure **B**:
**$^1$H NMR (300MHz, CDCl$_3$, 293K, TMS):**, 2.17 (6H, s), 4.02 (1H, b), 4.31 (2H, s), 6.18 (2H, s), 6.34 (1H, s), 7.15-7.10 (2H, m), 7.35-7.29 (2H, m);
**$^{13}$C NMR (75MHz, CDCl$_3$, 293K, TMS):** 21.5, 45.7, 110.7, 119.6, 126.2, 128.8, 128.9, 129.3, 133.0, 136.9, 138.8, 147.9;
**IR ($\nu_{max}$ /cm$^{-1}$)**: 3410, 2916, 1603, 1335, 751;
**HRMS**: calculated for $C_{15}H_{16}NCl$ (M$^+$): 245.0971; Found: 245.0960
**R$_f$**: 0.35 on silica gel (5% EtOAc:Hexanes);



**$^1$H NMR (300MHz, CDCl$_3$, 293K, TMS):** 2.12 (6H, s), 5.29 (2H, s), 6.58 (2H, s), 6.72 (1H, b), 7.26-7.17 (5H, m), 7.34 (1H, dd, 1.2Hz & 9Hz), 7.41-7.38 (2H, m), 7.48 (1H, dd, 1.5Hz & 6Hz);
**$^{13}$C NMR (75MHz, CDCl$_3$, 293K, TMS):** 21.5, 51.9, 125.3, 127.3, 128.1, 128.7, 128.8, 129.1, 129.2, 129.9, 130.2, 133.6, 135.4, 136.3, 139.1, 143.7, 171.1;
**IR ($\nu_{max}$ /cm$^{-1}$)**: 3061, 1650, 1595, 703;
**HRMS**: calculated for $C_{22}H_{20}NOCl$ (M$^+$): 349.1233; Found: 349.1221
**m.p.** = 145-146°C ($CHCl_3$)
**R$_f$**: 0.35 on silica gel (10% EtOAc:Hexanes);

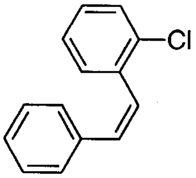
Table 2.5, Entry 5



Synthesized according to general procedure **C**:
**$^1$H NMR (300MHz, CDCl$_3$, 293K, TMS):** 5.28 (2H, s), 6.95 (2H, m), 7.03-7.28 (8H, m), 7.32 (1H, dd, J=1.8Hz & 7.5Hz), 7.37 (2H, m), 7.49 (1H, dd, J=1.2Hz & 7.5Hz);
**$^{13}$C NMR (75MHz, CDCl$_3$, 293K, TMS):** 51.2, 126.7, 126.9, 127.4, 127.8, 128.5, 128.8, 129.0, 129.2, 129.5, 129.8, 133.3, 134.8, 135.7, 143.3, 170.6;
**IR** (*$\nu_{max}$* **/cm$^{-1}$**): 3063, 2933, 1649, 1493, 1381, 1033, 697;
**HRMS** calculated for $C_{20}H_{16}ClNO$ (M+): 321.0920; Found: 321.0903;
**m.p.** = 97-99°C ($CHCl_3$)

**R$_f$:** 0.35 on silica gel (10% EtOAc:Hexanes);

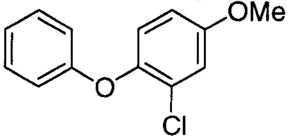
Table 2.5, Entry 6



The known diarylacetylene (1 equiv.) is dissolved in a mixture of ethanol/ethyl acetate (3:1, 0.025M). The flask is purged with argon and Lindlar's catalyst was added (0.1 equiv.). The flask and solution are then purged with hydrogen gas (2L) and the mixture is kept under 1 atm (balloon) for the duration of the reaction. Conversion is monitored by GC-MS. After 1.5 hours the reaction is filtered through celite, evaporated under reduced pressure and purified via silica gel column chromatography using hexane to afford diarylethene which exhibited spectral data identical to previous reports.

Kabalka, G. W.; Li, N.-S.; Tejedor, D.; Malladi, R. R.; Trotman, S.; *J. Org. Chem.* **1999**, *64*, 3157.

Table 2.5, Entry 7



Synthesized according to general procedure **E**:

**$^1$H NMR (300MHz, CDCl$_3$, 293K, TMS):** 3.78 (3H, s), 6.78 (1H, dd, J=3.1Hz & 9.2Hz), 6.88 (2H, d, J=8.5Hz), 7.02 (3H, m), 7.27 (2H, m);

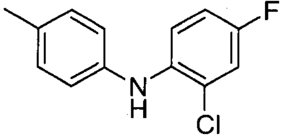
**$^{13}$C NMR (75MHz, CDCl$_3$, 293K, TMS):** 55.7, 113.7, 115.6, 116.5, 122.5, 122.8, 127.1, 129.6, 145.2, 156.5, 157.9;

**IR** ***($\nu_{max}$/cm$^{-1}$)***: 2960, 2941, 1605, 1217, 844, 749;

**HRMS** calculated for $C_{13}H_{11}ClO_2$ (M+): 234.0448; Found: 234.0464;

**R$_f$:** 0.55 on silica gel (5% EtOAc:Hexanes);

Table 2.5, Entry 8



Synthesized according to general procedure **F**:

**$^1$H NMR (300MHz, CDCl$_3$, 293K, TMS):** 2.31 (3H, s), 5.78 (1H, s), 6.83 (1H, td, J=3.2Hz & 9.2Hz), 6.98 (2H, d, J=8.5Hz), 7.10 (4H, m);

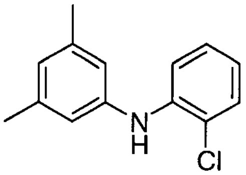
**$^{13}$C NMR (75MHz, CDCl$_3$, 293K, TMS):** 20.7, 114.2 (d, J=21.9Hz), 116.2 (d, J=7.5Hz), 116.7 (d, J=25.1Hz), 120.3, 121.5 (d, J=9.9Hz), 130.0, 132.3, 137.4 (d, J=3.4Hz), 139.2, 155.8 (d, J=240.6Hz);

**IR** ***($\nu_{max}$/cm$^{-1}$)***: 3413, 1607, 1516, 1316, 1246, 1040, 857, 805;

**HRMS** calculated for $C_{13}H_{11}ClNF$ (M+): 235.0564; Found: 235.0541;

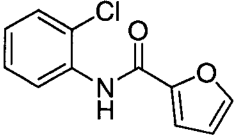
**R$_f$:** 0.35 on silica gel (10% EtOAc:Hexanes);

Table 2.5, Entry 10

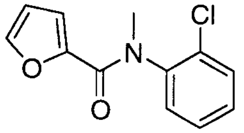


Synthesized according to general procedure **F**:
**$^1$H NMR (300MHz, CDCl$_3$, 293K, TMS):** 2.29 (6H, s), 6.02 (1H, s), 6.69 (1H, s), 6.75-6.81 (2H, m), 6.02 (1H, m), 7.10-7.15 (1H, m), 7.27 (1H, dd, J=1.2Hz & 9Hz), 7.33 (1H, dd, J= 1.2Hz & 9Hz);
**$^{13}$C NMR (75MHz, CDCl$_3$, 293K, TMS):** 21.4, 115.7, 117.9, 120.0, 121.3, 124.4, 127.4, 129.6, 139.1, 140.4, 141.3;
**IR ($v_{max}$ /cm$^{-1}$):** 3409, 3026, 2917, 1587, 1330, 1051;
**HRMS**: calculated for $C_{14}H_{14}NCl$ ($M^+$): 231.0815; Found: 231.0789
**R$_f$**: 0.29 on silica gel (10% EtOAc:Hexanes);

Table 2.5, Entry 13

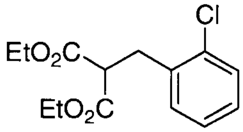


Synthesized according to general procedure **C**:
**$^1$H NMR (300MHz, CDCl$_3$, 293K, TMS):** 6.57 (1H, dd, J=1.8Hz & 3.8Hz), 7.06 (1H, t, J=8.3Hz), 7.29 (2H, m), 7.40 (1H, d, J=8.1Hz), 7.55 (1H, s). 8.52 (1H, d, J=8.0Hz), 8.70 (1H, s);
**$^{13}$C NMR (75MHz, CDCl$_3$, 293K, TMS):** 112.6, 115.6, 121.2, 122.7, 124.6, 127.7, 129.0, 134.2, 144.5, 147.5, 155.8;
**IR ($v_{max}$ /cm$^{-1}$)**: 3399, 3123, 1682, 1599, 1316, 935, 864, 745;
**HRMS** calculated for $C_{11}H_8ClNO_2$ (M+) 221.0244; Found: 221.0226;
**m.p.** = 90-92°C ($CHCl_3$)
**R$_f$**: 0.25 on silica gel (DCM);



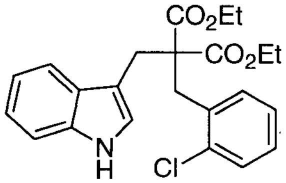
Synthesized according to general procedure **H**:
**$^1$H NMR (300MHz, CDCl$_3$, 293K, TMS):** 3.37 (3H, s), 5.92 (1H, s), 6.21 (1H, s), 7.32 (4H, m), 7.51 (1H, m);
**$^{13}$C NMR (75MHz, CDCl$_3$, 293K, TMS):** 36.9, 111.1, 115.8, 128.1, 129.6, 130.0, 130.6, 133.1, 141.3, 144.5, 146.9, 159.3;
**IR ($v_{max}$ /cm$^{-1}$)**: 3118, 3030, 1646, 1482, 1007, 884, 769, 751;
**HRMS** calculated for $C_{12}H_{10}ClNO_2$ (M+, $C_{12}H_{10}NO_2$): 200.0712; Found: 200.0696;
**m.p.** = 84-86°C ($CHCl_3$)
**R$_f$**: 0.35 on silica gel (DCM);

Table 2.5, Entry 14



Sodium hydride (0.95 equiv.) was triturated with pentane under argon and then suspended in dry THF (0.3M). Diethylmalonate (1 equiv.), dissolved in THF (1.8M), was added dropwise to the suspension of sodium hydride at 0°C. After 30 minutes of stirring, 2-chlorobenzyl chloride (1.1 equiv.), dissolved in THF (3.0M), is added dropwise. The reaction is allowed to warm to room temperature and stirred for 8 hours. $NH_4Cl$ (aq.) is added and the volatiles are removed under reduced pressure. The residue is then extracted with ethyl acetate/brine and the organic layer is dried with $MgSO_4$, filtered and evaporated under reduced pressure. The crude product is then purified via silica gel column chromatography using 15% ethyl acetate in hexanes mixtures.

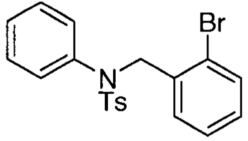
**$^1$H NMR (300MHz, $CDCl_3$, 293K, TMS):** 1.21 (6H, t, J=7.5H), 3.34 (2H, d, J=8.1Hz), 3.83 (2H, t, J= 8.1), 4.15 (2H, q, J=7.5H), 4.16 (2H, q, J=7.5H), 7.17 (2H, m), 7.25 (1H, m), 7.35 (1H, m);
**$^{13}$C NMR (75MHz, $CDCl_3$, 293K, TMS):** 14.0, 32.7, 51.4, 61.5, 126.8, 128.4, 129.6, 131.5, 134.2, 135.4, 168.7;
**IR ($v_{max}$/cm$^{-1}$):** 2982, 1749, 1732, 1476, 1227, 1039, 755;
**HRMS** calculated for $C_{15}H_{20}ClO_4$ (M+): 284.0815; Found: 284.0809;
**R$_f$:** 0.35 on silica gel (10% EtOAc:Hexanes);



Sodium hydride (1.1 equiv.) was triturated with pentane under argon and then suspended in dry THF (0.1M). 2-(2-chlorobenzyl)diethylmalonate (1 equiv.), dissolved in THF (1.8M), was added dropwise to the suspension of sodium hydride at 0°C. After 30 minutes of stirring, 1H-indole-3-ethanaminium, N,N,N-trimethyl ammonium iodide (quaternized gramine) (1 equiv.), dissolved in DMF (0.1M), is added dropwise. The reaction is allowed to warm to room temperature and stirred for 8 hours. $NH_4Cl$ (aq.) is added and the volatiles are removed under reduced pressure. The residue is then extracted with ethyl acetate/brine and the organic layer is dried with $MgSO_4$, filtered and evaporated under reduced pressure. The crude product is then purified via silica gel column chromatography using ethyl acetate/hexanes mixtures.

**$^1$H NMR (300MHz, $CDCl_3$, 293K, TMS):** 1.05 (6H, t, J=7.2Hz), 3.49 (2H, s), 3.57 (2H, s), 4.01 (2H, d, J=7.2Hz), 4.02 (2H, d, J=7.2Hz), 7.11 (5H, m), 7.30 (3H, m), 7.54 (1H, d, J=7.5Hz), 8.21 (1H, s);
**$^{13}$C NMR (75MHz, $CDCl_3$, 293K, TMS):** 13.7, 29.6, 36.0, 56.2, 61.4, 110.1, 111.0, 118.8, 119.3, 121.9, 123.1, 126.5, 128.0, 128.2, 129.4, 131.8, 134.9, 135.2, 135.7, 171.3;
**IR ($v_{max}$/cm$^{-1}$):** 3404, 2981, 1723, 1368, 1252, 1198, 910, 742;
**HRMS** calculated for $C_{23}H_{24}ClNO_4$ (M+): 413.1394; Found: 413.1398;
**R$_f$:** 0.19 on silica gel (10% EtOAc:Hexanes);

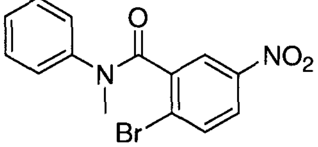
Table 2.6, Entry 5



Synthesized according to general procedure **A**:
**$^1$H NMR (300MHz, $CDCl_3$, 293K, TMS):** 2.43 (3H, s), 4.87 (2H, s), 7.00-7.12 (3H, m), 7.18-7.30 (6H, m), 7.40 (1H, dd, J=1.2Hz & 8.1Hz), 7.53 (2H, d, J=8.4Hz), 7.61 (1H, dd, J=1.2Hz & 7.5Hz);

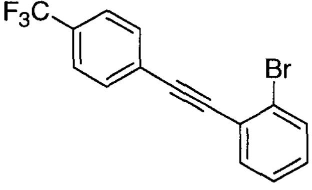
**$^{13}C$ NMR (75MHz, $CDCl_3$, 293K, TMS):** 21.6, 54.1, 123.1, 127.5, 127.7, 127.8, 128.6, 128.9, 129.0, 129.5, 130.3, 132.6, 135.1, 135.3, 139.1, 143.7;
**IR ($\nu_{max}$/cm$^{-1}$):** 3381, 3066, 2933, 1596, 1350, 1164, 1092, 814, 695;
**HRMS** calculated for $C_{20}H_{18}BrNO_2S$ (M+) 415.0242; Found: 415.0268;
**m.p.** = 107-109°C ($CHCl_3$)
**$R_f$:** 0.31 on silica gel (10% EtOAc:Hexanes);

Table 2.6, Entry 6

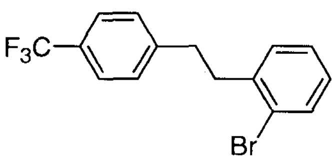


Synthesized according to general procedure **C**:
**$^1H$ NMR (300MHz, $CDCl_3$, 293K, TMS):** (Major rotamer) 3.53 (3H, s), 7.10-7.27 (mixture) (5H, m), 7.58 (1H, d, J=9.3Hz), 7.87 (1H, dd, J=3.0Hz & 8.7Hz), 7.98 (1H, d, J=2.7Hz); (Minor rotamer) 3.24 (3H, s), 7.10-7.27 (mixture) (2H, m)7.46 (4H, m), 8.15 (1H, dd, J=2.7Hz & 8.7Hz), 8.32 (1H, d, J=2.7Hz);
**$^{13}C$ NMR (75MHz, $CDCl_3$, 293K, TMS):** (mixture of rotamers) 37.1, 122.7, 123.5, 124.0, 124.7, 125.6, 126.6, 127.0, 127.2, 127.7, 129.2, 133.7, 134.0, 139.7, 142.1, 146.0, 166.2, 170.9;
**IR ($\nu_{max}$/cm$^{-1}$):** 3097, 3075, 1655, 1527, 1351, 1112, 849, 739;
**HRMS** calculated for $C_{14}H_{11}BrN_2O_3$ (M+): 333.9953; Found: 333.9946;
**m.p.** = 130-132°C ($CHCl_3$)
**$R_f$:** 0.12 on silica gel (10% EtOAc:Hexanes);

Table 2.6, Entry 7



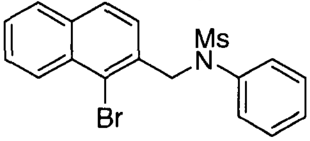
Synthesized according to general procedure **D**:
**$^1H$ NMR (300MHz, $CDCl_3$, 293K, TMS):** 7.22 (1H, td, J=1.8Hz & 7.8Hz), 7.32 (1H, td, J=1.2Hz & 7.5Hz), 7.56-7.70 (6H, m);
**$^{13}C$ NMR (75MHz, $CDCl_3$, 293K, TMS):** 90.3, 92.3, 123.9 (q, J=270.6Hz), 124.7, 125.3 (q, J=4.4Hz), 125.8, 126.7, 127.1, 130.0, 130.2 (q, J=32.7Hz), 131.9, 132.6, 133.4;
**IR ($\nu_{max}$/cm$^{-1}$):** 2925, 2855, 1466, 1324, 1171, 1130, 1104, 1067, 842;
**HRMS** calculated for $C_{15}H_8F_3Br$ (M+): 323.9762; Found: 323.9785;
**m.p.** = 76-77°C (Ether)



The diarylacetylene (1 equiv.) and *p*-toluenesulfonylhydrazine (20 equiv.) were then dissolved in DME (0.1M) and heated to 85°C. To this stirring mixture was added a solution of NaOAc (20 equiv.) in water over 8 hours via syringe pump. The reaction was stirred for an additional 4 hours and the heat source was removed. The reaction mixture was then extracted with hexane/ethyl acetate and brine. The organic extracts were dried using $MgSO_4$, and concentrated under reduced pressure. The crude product was purified via silica gel chromatography using hexanes.

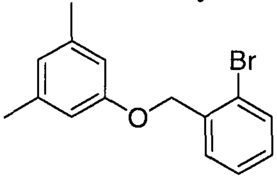
**$^1$H NMR (300MHz, CDCl$_3$, 293K, TMS):** 2.90-3.07 (4H, m), 7.03-7.14 (2H, m), 7.20 (1H, td, J=1.2Hz & 6.9Hz), 7.29 (2H, d, J=8.1Hz), 7.53 (3H, m);
**$^{13}$C NMR (75MHz, CDCl$_3$, 293K, TMS):** 35.9, 38.0, 124.4 (q, J=270.6Hz), 124.4, 125.3, 125.3 (q, J=4.4Hz), 127.5, 128.0, 128.4 (q, J=32.7Hz), 128.8, 130.5, 132.9, 140.3;
**IR ($v_{max}$ /cm$^{-1}$):** 3058, 2933, 1326, 1164, 1120, 1067, 825, 749;
**HRMS** calculated for $C_{15}H_{12}F_3Br$ (M+): 328.0074; Found: 328.0044;
**R$_f$:** 0.55 on silica gel (Hexanes);

Table 2.6, Entry 9



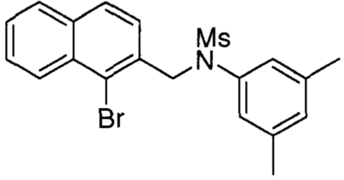
Synthesized according to general procedure **A**:
**$^1$H NMR (300MHz, CDCl$_3$, 293K, TMS):** 3.01 (3H, s), 5.27 (2H, s), 7.20-7.36 (5H, m), 7.44-7.65 (2H, m), 7.67-7.76 (3H, m), 8.20 (1H, d, J=8.4Hz);
**$^{13}$C NMR (75MHz, CDCl$_3$, 293K, TMS):** 37.7, 54.9, 123.5, 126.7, 126.8, 126.9, 127.3, 127.5, 127.9, 128.1, 128.2, 129.4, 132.0, 133.3, 133.9, 138.8;
**IR ($v_{max}$ /cm$^{-1}$):** 1596, 1491, 1341, 1154, 753, 519;
**HRMS**: calculated for $C_{18}H_{16}N_1O_2Br_1S_1$ (M$^+$); 389.0085; Found: 389.0062
**m.p.** = 137-138°C
**R$_f$:** 0.31 on silica gel (10% EtOAc:Hexanes);

Table 2.6, Entry 10



Synthesized according to general procedure **A**:
**$^1$H NMR (300MHz, CDCl$_3$, 293K, TMS):** 2.29 (6H, s), 5.08 (2H, s), 6.62 (3H, s), 7.16 (1H, td, J=1.8Hz & 7.5Hz), 7.32 (1H, td, J=1.2Hz & 7.5Hz), 7.58-7.53 (2H, m);
**$^{13}$C NMR (75MHz, CDCl$_3$, 293K, TMS):** 21.5, 69.1, 112.5, 122.2, 123.0, 127.5, 128.8, 129.1, 132.5, 136.5, 139.3, 158.0;
**IR ($v_{max}$ /cm$^{-1}$):** 2917, 1595, 1322, 1154, 1029, 749, 644;
**HRMS**: calculated for $C_{15}H_{15}OBr$ (M$^+$): 290.0306, Found: 290.0324
**R$_f$:** 0.55 on silica gel (10% EtOAc:Hexanes);

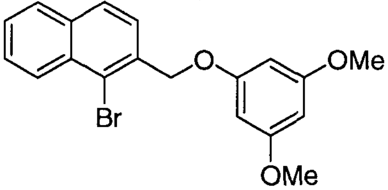
Table 2.6, Entry 11



Synthesized according to general procedure **A**:
**$^1$H NMR (300MHz, CDCl$_3$, 293K, TMS):** 2.22 (6H, s), 3.01 (3H, s), 6.84 (1H, s), 6.99 (2H, s), 7.44-7.56 (2H, m), 7.70-7.77 (3H, m), 8.23 (1H, d, J=8.4Hz);
**$^{13}$C NMR (75MHz, CDCl$_3$, 293K, TMS):** 21.2, 37.5, 54.9, 123.2, 125.7, 126.5, 126.7, 127.2, 127.4, 127.8, 128.1, 129.8, 131.9, 133.6, 133.9, 138.7, 138.9;
**IR ($v_{max}$ /cm$^{-1}$):** 3012, 2920, 1339, 1156, 1088;

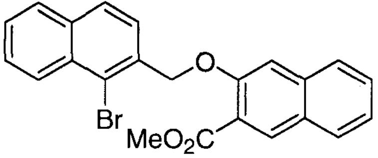
**HRMS**: calculated for $C_{20}H_{20}NO_2SBr$ ($M^+$): 417.0398; Found: 417.0410
**m.p.** = 161-162°C ($CHCl_3$)
**R$_f$:** 0.30 on silica gel (10% EtOAc:Hexanes);

Table 2.6, Entry 12



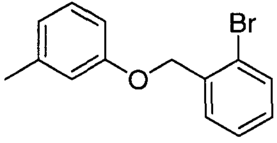
Synthesized according to general procedure **A**:
**$^1$H NMR (300MHz, $CDCl_3$, 293K, TMS):** 3.77 (6H, s), 5.35 (2H, s), 6.12 (1H, t, J=2.4Hz), 6.21 (2H, d, J=2.1Hz), 7.51-7.67 (3H, m), 7.83 (2H, d, J=8.4Hz), 8.34 (1H, d, J=7.8Hz);
**$^{13}$C NMR (75MHz, $CDCl_3$, 293K, TMS):** 55.3, 70.1, 93.3, 93.7, 122.2, 125.5, 126.6, 126.9, 127.5, 127.9, 128.1, 132.0, 134.0, 134.3, 160.3, 161.5;
**IR ($v_{max}$ /cm$^{-1}$):** 1537, 1038, 813;
**HRMS**: calculated for $C_{19}H_{17}O_3Br$ ($M^+$, $C_{19}H_{17}O_3$): 293.1178; Found: 293.1171
**m.p.** = 97-98°C ($CHCl_3$)
**R$_f$:** 0.20 on silica gel (Hexanes);

Table 2.6, Entry 13



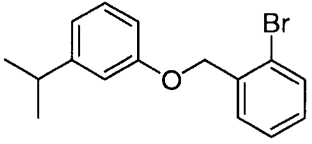
Synthesized according to general procedure **A**:
**$^1$H NMR (300MHz, $CDCl_3$, 293K, TMS):** 4.02 (3H, s), 5.55 (2H,s), 7.32 (1H, s), 7.39 (1H, t, J=9Hz), 7.49-7.65 (3H, m), 7.74 (1H, d, J=8.1Hz), 7.83-7.90 (3H, m), 7.99 (1H, d, J=8.7Hz), 8.35 (1H, d, J=8.1Hz), 8.40 (1H, s);
**$^{13}$C NMR (75MHz, $CDCl_3$, 293K, TMS):** 52.7, 70.9, 108.9, 121.7, 122.1, 125.1, 125.6, 126.9, 127.0, 127.1, 127.9, 128.2, 128.5, 128.7, 128.9, 129.1, 129.2, 133.7, 134.4, 134.8, 136.4, 154.7, 167.0;
**IR ($v_{max}$ /cm$^{-1}$):** 1736, 1270, 1204, 1076, 734;
**HRMS**: calculated for $C_{23}H_{14}O_3Br$ ($M^+$): 420.0381; Found: 420.0338
**m.p.** = 141-142°C ($CHCl_3$)
**R$_f$:** 0.18 on silica gel (Hexanes);

Table 2.8, Entry 2



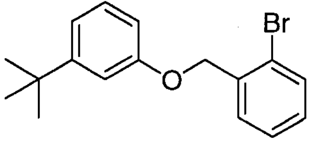
Synthesized according to general procedure **A**:
**$^1$H NMR (300MHz, $CDCl_3$, 293K, TMS):** 2.34 (3H, s), 5.11 (2H, s), 6.80 (3H, m), 7.18 (2H, m), 7.32 (1H, t, J=8.1Hz), 7.56 (2H, m);
**$^{13}$C NMR (75MHz, $CDCl_3$, 293K, TMS):** 21.5, 69.2, 111.6, 115.7, 122.0, 122.2, 127.5, 128.8, 129.1, 129.3, 132.6, 136.5, 139.6, 158.5;
**IR ($v_{max}$/cm$^{-1}$):** 9057, 2919, 1603, 1440, 1258, 1027, 747;
**HRMS** calculated for $C_{14}H_{13}BrO$ (M+) 276.0150; Found: 276.0163;
**R$_f$:** 0.52 on silica gel (10% EtOAc:Hexanes);

Table 2.8, Entry 3



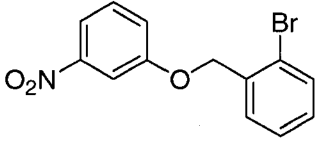
Synthesized according to general procedure **A**:
**$^1$H NMR (300MHz, CDCl$_3$, 293K, TMS):** 1.24 (6H, d, J=6.6Hz), 2.88 (1H, sept, J=6.9Hz), 5.19 (2H, s), 6.78 (1H, dd, J=8.1Hz & 1.8Hz), 6.86 (2H, m), 7.19 (2H, m), 7.32 (1H, td, J=7.5Hz & 1.2Hz), 7.57 (2H, m);
**$^{13}$C NMR (75MHz, (CDCl$_3$, 293K, TMS):** 23.9, 34.1, 69.3, 111.6, 113.5, 119.4, 122.3, 127.5, 129.0, 129.2, 129.3, 132.5, 136.5, 150.7, 158.5;
**IR** ***(v$_{max}$* /cm$^{-1}$)**: 3059, 2960, 1584, 1445, 1026, 749;
**HRMS** calculated for $C_{16}H_{17}BrO$ (M+) 304.0463; Found: 304.0468;
**R$_f$:** 0.54 on silica gel (10% EtOAc:Hexanes);

Table 2.8, Entry 4



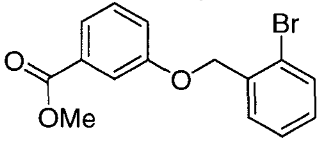
Synthesized according to general procedure **A**:
**$^1$H NMR (300MHz, CDCl$_3$, 293K, TMS):** 1.31 (9H, s), 5.12 (2H, s), 6.78 (1H, dd, J=8.1Hz & 2.4Hz), 7.02 (2H, m), 7.20 (2H, m), 7.31 (1H, t, J=8.1Hz), 7.56 (2H, d, J=8.1Hz);
**$^{13}$C NMR (75MHz, CDCl$_3$, 293K, TMS):** 31.3, 34.7, 69.3, 110.9, 113.0, 118.3, 122.3, 127.5, 129.0, 129.0, 129.2, 132.5, 136.5, 153.0, 158.3;
**IR** ***(v$_{max}$* /cm$^{-1}$)**: 3071, 2963, 1607, 1582, 1274, 1027, 749;
**HRMS** calculated for $C_{17}H_{19}BrO$ (M+) 318.0619; Found: 318.0597;
**R$_f$:** 0.49 on silica gel (10% EtOAc:Hexanes);

Table 2.8, Entry 6



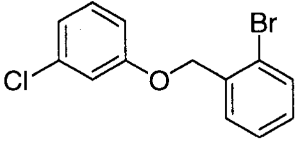
Synthesized according to general procedure **A**:
**$^1$H NMR (300MHz, CDCl$_3$, 293K, TMS):** 5.19 (2H, s), 7.31 (3H, m), 7.45 (1H, t, J=8.4Hz), 7.53 (1H, d, J=8.7Hz), 7.61 (1H, d, J=8.7Hz), 7.85 (2H, m);
**$^{13}$C NMR (75MHz, CDCl$_3$, 293K, TMS):** 70.0, 109.5, 116.2, 121.7, 122.6, 127.7, 129.1, 129.8, 130.1, 132.8, 135.0, 149.2, 158.9;
**IR** ***(v$_{max}$* /cm$^{-1}$)**:1610, 1594, 1490, 1263, 1136, 1026, 748;
**HRMS** calculated for $C_{13}H_{10}BrNO_3$ (M+) 306.9844; Found: 306.9866;
**m.p.** = 80-82°C (CHCl$_3$)
**R$_f$:** 0.45 on silica gel (10% EtOAc:Hexanes);

Table 2.8, Entry 7



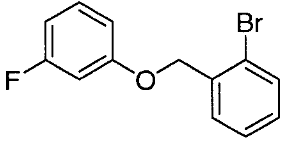
Synthesized according to general procedure **A**:
**$^1$H NMR (300MHz, $CDCl_3$, 293K, TMS):** 3.92 (3H, s), 5.17 (2H, s), 7.20 (2H, m), 7.35 (2H, m), 7.55 (1H, dd, J=7.5Hz & 1.8Hz), 7.60 (1H, dd, J=8.1Hz & 1.8Hz), 7.67 (2H, m);
**$^{13}$C NMR (75MHz, $CDCl_3$, 293K, TMS):** 52.2, 69.5, 115.3, 120.0, 122.5, 127.6, 129.0, 129.4, 129.5, 131.6, 132.7, 135.8, 152.4, 158.4, 166.9;
**IR *($v_{max}$/cm$^{-1}$)*:**2946, 1721, 1586, 1278, 1026, 751;
**HRMS** calculated for $C_{15}H_{13}BrO_3$ (M+) 320.0048; Found: 320.0025;
**R$_f$:** 0.51 on silica gel (10% EtOAc:Hexanes);

Table 2.8, Entry 8



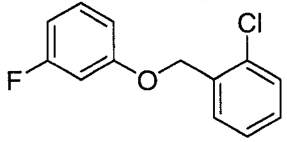
Synthesized according to general procedure **A**:
**$^1$H NMR (300MHz, $CDCl_3$, 293K, TMS):** 5.09 (2H, s), 6.85 (1H, dd, J=8.1Hz & 1.8Hz), 6.97 (2H, m), 7.19 (2H, m), 7.32 (1H, d, J=7.5Hz), 7.50 (1H, d, J=7.5Hz), 7.57 (1H, d, J=8.1Hz);
**$^{13}$C NMR (75MHz, $CDCl_3$, 293K, TMS):** 69.5, 113.2, 115.4, 121.4, 122.3, 127.6, 128.8, 129.4, 130.3, 132.7, 134.9, 135.7, 159.1;
**IR *($v_{max}$/cm$^{-1}$)*:** 3069, 2934, 1594, 1477, 1244, 1026, 749;
**HRMS** calculated for $C_{13}H_{10}BrClO$ (M+) 295.9604; Found: 295.9631;
**R$_f$:** 0.52 on silica gel (10% EtOAc:Hexanes);

Table 2.8, Entry 9



Synthesized according to general procedure **A**:
**$^1$H NMR (300MHz, $CDCl_3$, 293K, TMS):** 5.11 (2H, s), 6.71 (3H, m), 7.21 (2H, m), 7.33 (1H, t, J=7.5Hz), 7.52 (1H, d, J=7.8Hz), 7.83 (1H, d, J=7.8Hz)
**$^{13}$C NMR (75MHz, $CDCl_3$, 293K, TMS):** 69.6, 102.7 (d, J=30.0Hz), 108.0 (d, J=20.7Hz), 110.5 (d, J=3.3Hz), 122.3, 127.6, 129.1 (d, J=45Hz), 130.2, 130.4, 132.7, 135.7, 159.7 (d, J=11.0Hz), 165.2;
**IR *($v_{max}$/cm$^{-1}$)*:**1530, 1348, 1246, 1025, 732;
**HRMS** calculated for $C_{13}H_{10}BrFO$ (M+) 279.9899; Found: 279.9897;
**R$_f$:** 0.52 on silica gel (10% EtOAc:Hexanes);

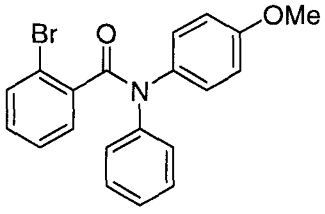
Table 2.8, Entry 10



Synthesized according to general procedure **A**:
**$^1$H NMR (300MHz, $CDCl_3$, 293K, TMS):** 5.13 (2H, s), 6.72 (3H, m), 7.25 (3H, m), 7.38 (1H, m), 7.52 (1H, m);
**$^{13}$C NMR (75MHz, $CDCl_3$, 293K, TMS):** 67.3, 102.7 (d, J=22.5Hz), 107.9, 108.2, 110.5 (d, J=2.2Hz), 127.0, 128.7, 129.1, 129.4, 130.3 (d, J=15.0Hz), 133.4 (d, J= 120Hz), 159.8 (d, 15.0Hz), 162.0;

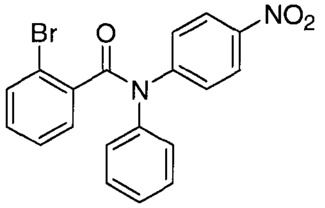
**IR ($\nu_{max}$/cm$^{-1}$)**: 3073, 2883, 1920, 1610, 1490, 1281, 1135, 749;
**HRMS** calculated for $C_{13}H_{10}ClFO$ (M+) 236.0404; Found: 236.0377;
**R$_f$**: 0.52 on silica gel (10% EtOAc:Hexanes);

Scheme 2.6



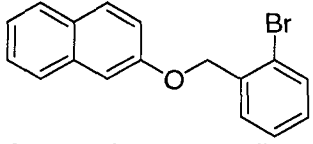
Synthesized according to general procedure **C**:
**$^1$H NMR (300MHz, $(CD_3)_2SO$, *373K*)**: 3.72 (3H, s), 6.86 (2H, d, J=7.5Hz), 7.10-7.40 (9H, m), 7.47 (2H, d, J=7.2Hz);
**$^{13}$C NMR (75MHz, $(CD_3)_2SO$, *373K*)**: 54.8, 113.8, 118.2, 126.0, 126.3, 126.5, 128.2, 128.3, 128.7, 129.5, 131.6, 134.6, 138.2, 142.1, 157.6, 167.0;
**IR ($\nu_{max}$/cm$^{-1}$)**: 2835, 1959, 1509, 1350, 1246, 1028, 758;
**HRMS** calculated for $C_{20}H_{16}BrO_2N$ (M+) 381.0364; Found: 381.0410;
**R$_f$**: 0.25 on silica gel (10% EtOAc:Hexanes);

Scheme 2.6



Synthesized according to general procedure **C**:
**$^1$H NMR (300MHz, $(CD_3)_2SO$, *373K*)**: 7.13-7.43 (7H, m), 7.44-7.63 (4H, m), 8.19 (2H, d, J=8.1Hz);
**$^{13}$C NMR (75MHz, $(CD_3)_2SO$, *373K*)**: 118.2, 123.6, 126.5, 126.7, 127.3, 127.7, 128.7, 129.0, 130.2, 131.8, 137.2, 140.6, 144.7, 147.3, 167.1;
**IR ($\nu_{max}$/cm$^{-1}$)**:1673, 1588, 1491, 1345, 1113, 698;
**HRMS** calculated for $C_{19}H_{13}N_2BrO_3$ (M+) 396.0110; Found: 396.0090;
**R$_f$**: 0.29 on silica gel (10% EtOAc:Hexanes);

Equation 2.6



Synthesized according to general procedure **A**:
**$^1$H NMR (300MHz, $CDCl_3$, 293K, TMS)**: 5.27 (2H, s), 7.36 (6H, m), 7.67 (2H, dd, J=8.1Hz & J=1.2Hz), 7.82 (3H, m);
**$^{13}$C NMR (75MHz, $CDCl_3$, 293K, TMS)**: 71.1, 109.0, 120.6, 124.5, 125.6, 128.2, 128.7, 129.4, 129.6, 130.1, 131.1, 131.3, 131.5, 134.5, 136.5, 138.1, 158.3;
**IR ($\nu_{max}$/cm$^{-1}$)**: 3056, 1629, 1256, 1218, 1177, 1025, 741;
**HRMS** calculated for $C_{17}H_{13}BrO$ (M+): 312.0150; Found: 312.0157;

**m.p.** = 80-82°C ($Me_2CO$)
**R$_f$:** 0.55 on silica gel (10% EtOAc:Hexanes);

### Procedures for Intramolecular Direct Arylation Reactions

#### *First Generation Catalyst:*

Reactions typically carried out on 0.6mmol although one attempt at 3.5mmol was successful: To a mixture of *crushed* $K_2CO_3$ (2 equiv.) and bromo ether (1 equiv.) under nitrogen atmosphere was added 3mL of *N,N*-Dimethylacetamide (DMA) in a 10mL round bottom flask equipped with a mechanical stir bar. To the stirring reaction mixture was added 50μL of a $Pd(OAc)_2$ and Ligand[247] stock solution containing 7mg/mL $Pd(OAc)_2$ and 36mg/mL Ligand. (Similar results are obtained if the palladium and ligand are weighed out exactly and placed in the reaction mixture prior to addition the solvent). The reaction mixture is then heated overnight at 125°C. After the reaction was judged complete by TLC or GC/MS analysis, the heat source was removed and the reaction mixture was allowed to cool. The crude mixture was then loaded directly onto a silica gel flash chromatography column 10% ethyl acetate in hexanes as the eluent to afford the biaryl.

#### *Second Generation Catalyst:*

Reactions typically performed as outlined in the following procedure: Crushed $K_2CO_3$ (0.72mmol), substrate (0.36mmol), iPr-HCl (0.0036mmol) and complex **2.14-iPr** (0.0036mmol) were placed in a 2mL screw-cap vial equipped with a magnetic stir. The vial was purged with nitrogen and 1.8mL of *N,N*-dimethylacetamide (DMA) was added. The reaction was heated to 130°C overnight. After the reaction was judged complete by TLC or GC/MS analysis, the heat source was removed and the reaction mixture was allowed to cool. The crude mixture was then loaded directly onto silica and purified by flash chromatography using ethyl acetate/hexanes mixtures as the eluent.

#### *Third Generation Catalyst:*

Reactions typically performed on 0.36mmol scale although isolated attempts at scaling up to 4 mmol were successful: Crushed $K_2CO_3$ (2 equiv.), substrate (1 equiv.), $Pd(OAc)_2$ (appropriate amount) and $PCy_3 - HBF_4$ (2 equiv. per Pd) were placed in a 2mL screw-cap vial equipped with a magnetic stir. The vial was purged with argon and 1.8mL of

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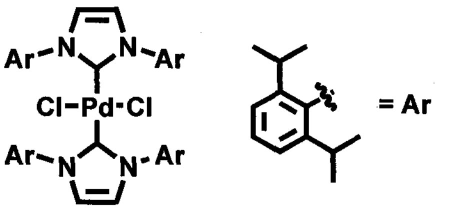
[247] 2-(Diphenylphosphino)-2'-(N,N-dimethyl-amino)byphenyl is the ligand used for all cyclization reactions and is available from Strem Chemicals.

degassed *N,N*-dimethylacetamide (DMA) was added. The reaction was heated to 130°C overnight. After the reaction was judged complete by TLC or GC/MS analysis, the heat source was removed and the reaction mixture was allowed to cool. The crude mixture was then loaded directly onto silica and purified by flash chromatography using ethyl acetate/hexanes mixtures as the eluent.

***Catalyst Synthesis:***

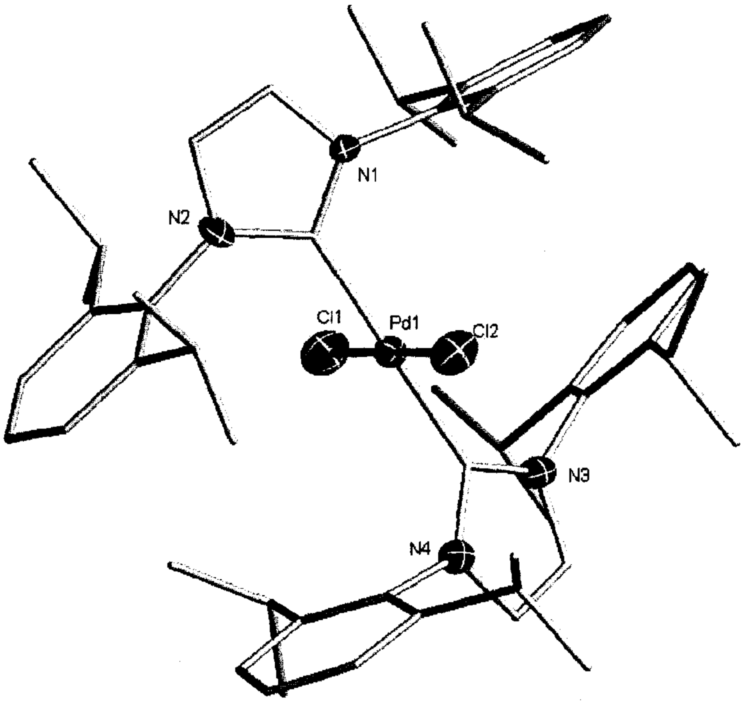


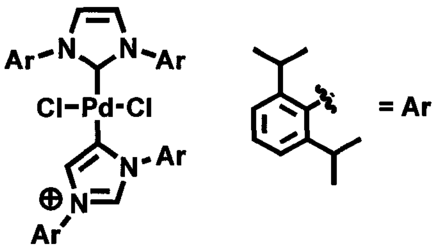
**2.15**

$PdCl_2$ (0.25mmol), iPrHCl (0.505mmol) and $Cs_2CO_3$ (2.5mmol) were weighed out to air and placed in a 50mL round bottom flask. The flask was fitted with a condenser and then purged with nitrogen. THF (25mL) was then added via syringe and the reaction was refluxed overnight. Heating was discontinued and volatiles were evaporated under reduced pressure. The residue was then purified by silica gel chromatography using 1:1 $CH_2Cl_2$:hexane affording an off-white solid in 51% yield. Single crystals of the complex were then grown from slow evaporation of a saturated ether solution. Crystal structure deposited to the Cambridge Crystallographic Data Center – CCDC 261497

**$^1$H NMR (300MHz, $CDCl_3$, 293K, TMS):** 0.87 (24H, d, *J*=7Hz), 0.93 (24H, d, *J*=7Hz), 2.90 (8H, sept, *J*=7Hz), 6.71 (4H, s), 7.78 (8H, d, *J*=8Hz), 7.33 (2H, s), 7.36 (4H, t, *J*=8Hz);

**$^{13}$C NMR (75MHz, $CDCl_3$, 293K, TMS):** 22.9, 26.0, 28.1, 123.7, 129.1, 136.3, 146.4, 172.5;



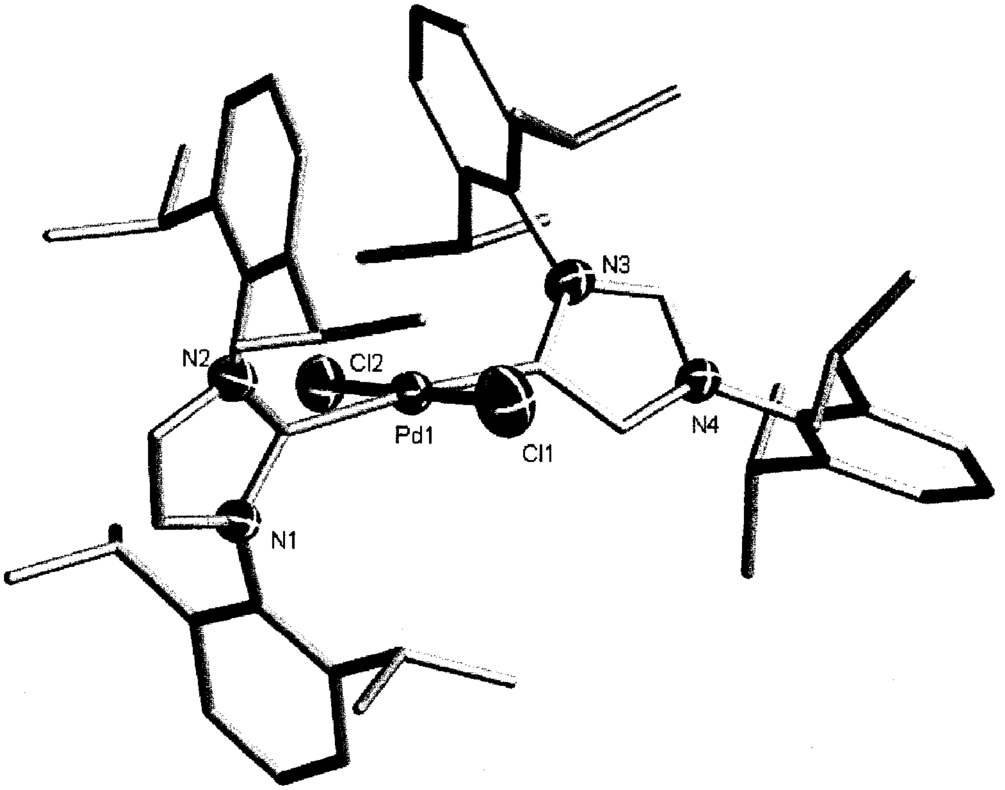


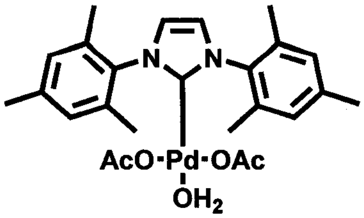
**2.17**

Pd(OAc)$_2$ (0.25mmol), iPrHCl (0.505mmol) and were weighed out open to air and placed in a 50mL round bottom flask. The flask was fitted with a condenser and purged with nitrogen. THF (25mL) was then added via syringe and the reaction was refluxed overnight. Heating was discontinued and the volatiles were evaporated under reduced pressure. The residue was then purified by silica gel chromoatography using 1:1 CH$_2$Cl$_2$:hexane affording an pale yellow solid in 71% yield. Single crystals of the complex were then grown from slow evaporation of a saturated DCM/Hexane solution. Crystal structure deposited to the Cambridge Crystallographic Data Center – CCDC 261499

**$^1$H NMR (300MHz, CDCl$_3$, 293K, TMS):** 0.83 (6H, d, *J*=6.9Hz), 0.91 (6H, d, *J*=6.6Hz), 1.01 (18H, m), 1.22(18H, m), 2.43 (2H, sept, *J*=6.8Hz), 2.73 (2H, sept, *J*=6.8Hz), 3.14 (4H, sept, *J*=6.8Hz), 6.52 (1H, d, *J*=1.4), 6.89 (2H, s), 7.08 (2H, d, *J*=7.7Hz), 7.22 (6H, t, *J*=7.7Hz), 7.38 (4H, m), 7.53 (1H, d, *J*=1.4Hz);

**$^{13}$C NMR (75MHz, CDCl$_3$, 293K, TMS):** 22.8, 23.2, 24.7, 24.8, 26.0 ,26.5, 28.0, 28.1, 28.3, 123.4, 123.6, 123.6, 124.0, 124.1, 126.1, 129.2, 129.4, 130.5, 131.4, 133.0, 134.8, 136.2, 145.9, 146.3, 146.5, 152.3, 178.0;

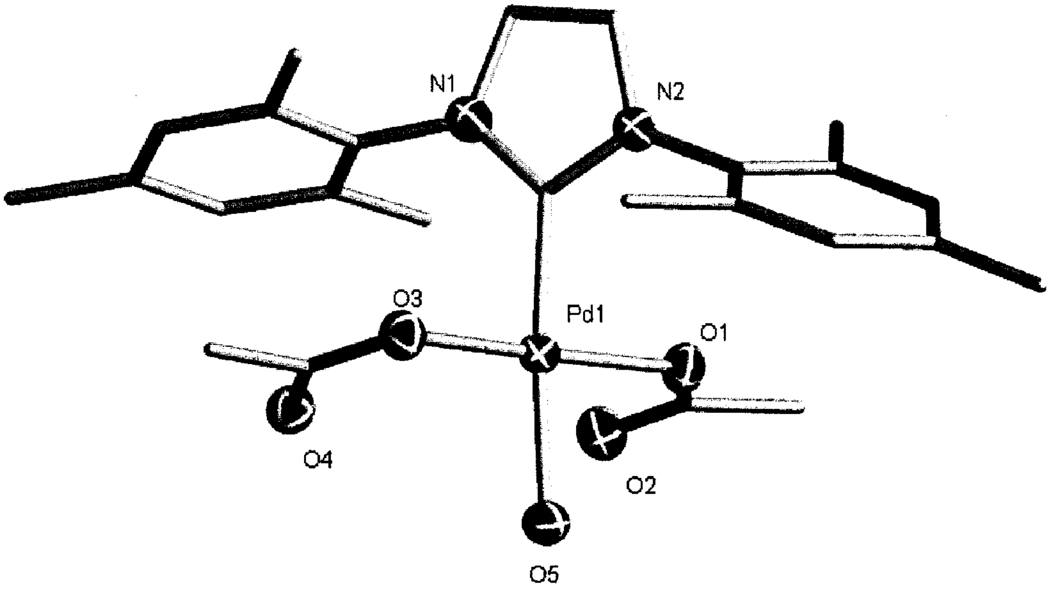




**2.14-IMes**

Prepared from corresponding iMes chloride dimer[248] using a method adapted from the Sigman protocol using AgOAc in reagent grade $CH_2Cl_2$.[249] Single crystals were grown by slow evaporation of a saturated hexanes/dichloromethane solution. Crystal structure deposited to the Cambridge Crystallographic Data Center – CCDC 261498

**$^1$H NMR (300MHz, $CDCl_3$, 293K, TMS):** 1.69 (6H, s), 2.16 (12H, s), 2.42 (6H, s), 7.05 (2H, s), 7.08 (4H, s);
**$^{13}$C NMR (75MHz, $CDCl_3$, 293K, TMS):** 17.6, 21.2, 23.3, 123.5, 129.4, 134.4, 135.6, 139.7, 149.6, 181.5;



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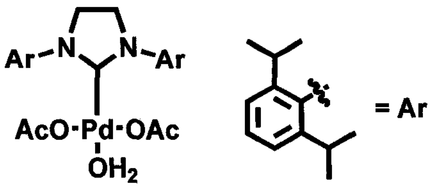
[248] D.R. Jensen, M.S. Sigman, *Org. Lett.* **2003**, *5*, 63

[249] D.R. Jensen, M.J. Schultz, J.A. Mueller, M.S. Sigman, *Angew. Chem. Int. Ed.* **2003**, *42*, 3810

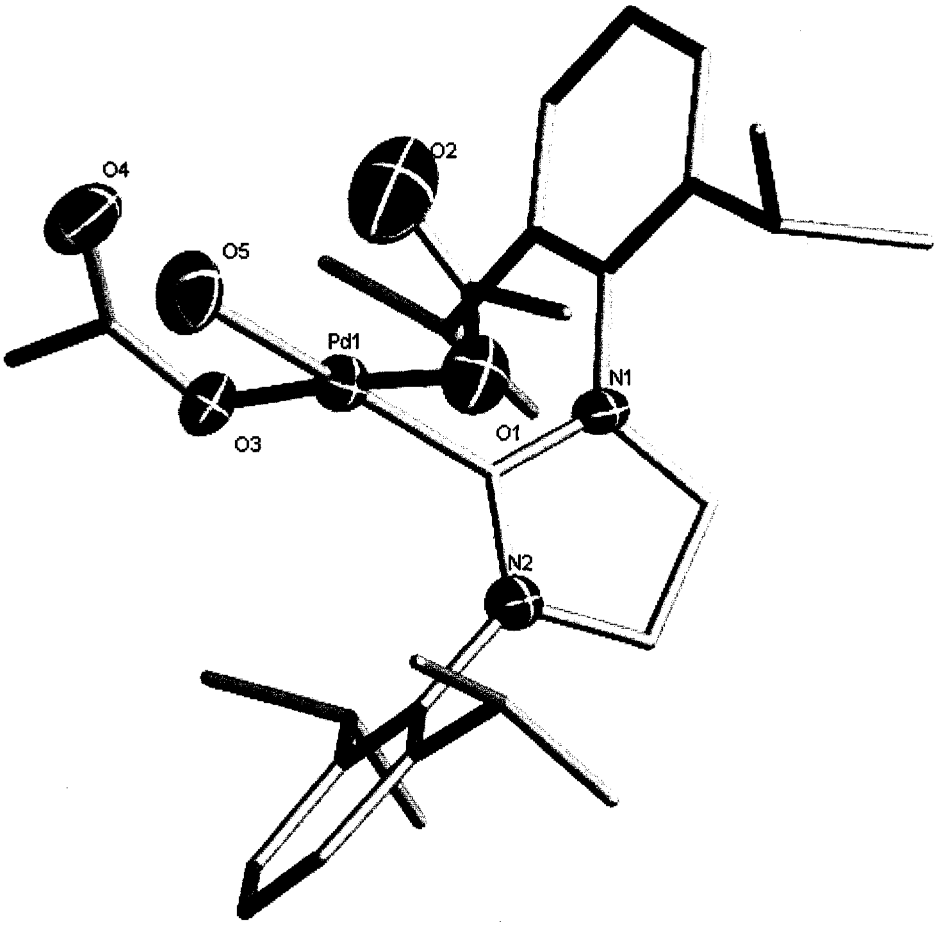


**2.14-SiPr**

Prepared from corresponding the SiPr chloride dimer[250] using a method adapted from the Sigman protocol using AgOAc in reagent grade $CH_2Cl_2$.[249] Single crystals were grown by slow evaporation of a saturated hexanes/dichloromethane solution. Crystal structure deposited to the Cambridge Crystallographic Data Center – CCDC 261500

**$^1$H NMR (300MHz, $CDCl_3$, 293K, TMS):** 1.26 (12H, d, *J*=6.7Hz), 1.43 (12H, d, *J*=6.7Hz), 1.75 (6H, s), 3.25 (4H, sept, *J*=6.7Hz), 4.05 (4H, s), 7.36 (4H, d, *J*=7.7Hz), 7.49 (2H, t, *J*=7.7Hz);

**$^{13}$C NMR (75MHz, $CDCl_3$, 293K, TMS):** 23.9, 24.6, 26.4, 28.5, 53.6, 124.8, 129.8, 134.4, 147.0, 182.0, 183.0



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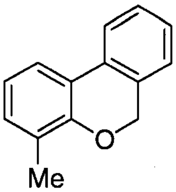
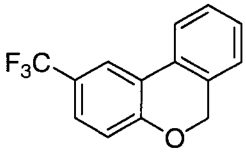
[250] Y. Ma, C. Song, W. Jiang, G. Xue, J.F. Cannon, X. Wang, M.B. Andrus, *Org. Lett.* **2003**, *5*, 4635

Table 2.2, Entry 5



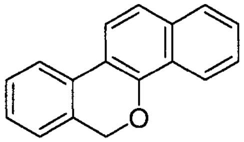
**$^1$H NMR (300MHz, CDCl$_3$, 293K, TMS):** 2.26 (3H, s), 5.08 (2H, s), 6.93 (1H, t, *J*=7Hz), 7.09 (2H, t, *J*=7Hz), 7.23 (1H, t, *J*=7Hz), 7.32 (1H, t, *J*=3Hz), 7.55 (1H, d, *J*=8Hz), 7.64 (1H, d, *J*=8Hz);
**$^{13}$C NMR (75MHz, CDCl$_3$, 293K, TMS):** 15.9, 68.3, 120.9, 121.4, 122.2, 122.4, 124.5, 126.6, 127.4, 128.3, 130.5, 130.8, 131.4, 152.9;
**IR (*v$_{max}$*/cm$^{-1}$)** 2921 (weak), 1421, 1249, 1195, 1020, 752;
**HRMS** calculated for $C_{14}H_{12}O$ (M+) 196.0869; Found: 196.0888
**R$_f$** = 0.43 on silica gel (5% EtOAc:Hexanes);

Table 2.2, Entry 7



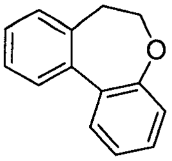
**$^1$H NMR (300MHz, CDCl$_3$, 293K, TMS):** 5.12 (2H, s), 7.01 (1H, d, *J*=8Hz), 7.11 (1H, m), 7.33 (2H, m), 7.44 (1H, m), 7.66 (1H, d, *J*=7Hz), 7.93 (1H, s);
**$^{13}$C NMR (75MHz, CDCl$_3$, 293K, TMS):** 68.5, 117.8, 120.6 (q, *J*=4Hz), 122.2, 123.1, 124.3 (q, *J*=33Hz), 124.5 (q, *J*=272Hz), 124.8, 126.3 (q, *J*=4Hz), 128.6, 128.7, 131.0, 157.2;
**IR (*v$_{max}$*/cm$^{-1}$)** 2850 (weak), 1315, 1250, 1112, 752 ;
**HRMS** calculated for $C_{14}H_9F_3O$ (M+) 250.0601; Found: 250.0605
**R$_f$** = 0.43 on silica gel (5% EtOAc:Hexanes);

Table 2.2, Entry 11



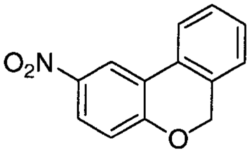
**$^1$H NMR (300MHz, CDCl$_3$, 293K, TMS):** 5.23 (2H, s), 7.11 (1H, d, *J*=7Hz), 7.22 (1H, t, *J*=2Hz), 7.33 (1H, t, *J*=3Hz), 7.45 (3H, m), 7.65 (1H, d, *J*=3Hz), 7.75 (2H, m), 8.25 (1H, m);
**$^{13}$C NMR (75MHz, CDCl$_3$, 293K, TMS):** 68.7, 117.1, 120.9, 121.5, 121.9, 122.2, 124.5, 125.3, 125.7, 126.6, 127.3, 127.6, 128.5, 130.6, 130.6, 134.3, 150.2;
**IR (*v$_{max}$*/cm$^{-1}$)** 2870 (weak), 1395, 1351, 1096, 758;
**HRMS** calculated for $C_{17}H_{12}O$ (M+) 232.0871; Found: 232.0888
**R$_f$** = 0.47 on silica gel (5% EtOAc:Hexanes);

Scheme 2.1



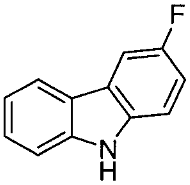
**$^1$H NMR (300MHz, CDCl$_3$, 293K, TMS):** 2.82 (2H, t, *J*=6Hz), 4.57 (2H, t, *J*=6Hz), 7.14 (1H, d, *J*=8Hz), 7.29 (4H, m), 7.41 (3H, m);
**$^{13}$C NMR (75MHz, CDCl$_3$, 293K, TMS):** 33.4, 78.4, 122.3, 124.6, 127.4, 127.7, 128.0, 128.1, 129.0, 129.2, 135.2, 137.4, 138.9, 154.3;
**IR** ***(v$_{max}$*** **/cm$^{-1}$)** 2870 (weak), 1309, 1252, 1030, 758;
**HRMS** calculated for $C_{14}H_{12}O$ (M+) 196.0893; Found: 196.0888
**R$_f$** = 0.36 on silica gel (5% EtOAc:Hexanes);

Table 2.3, Entry 2



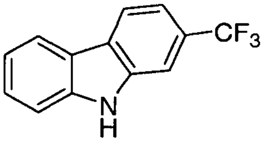
**$^1$H NMR (300MHz, CDCl$_3$, 293K, TMS):** 5.27 (s, 2H), 7.06 (d, *J*=9 Hz, 1H), 7.20 (d, *J*=7.5 Hz, 1H), 7.42 (m, 2H), 7.80 (d, *J*=7.8 Hz, 1H), 8.13 (dd, *J*=9.0 Hz & 2.7 Hz, 1H), 8.65 (d, *J*=2.7 Hz, 1H);
**$^{13}$C NMR (75MHz, CDCl$_3$, 293K, TMS):** 68.8, 118.0, 119.3, 122.4, 123.0, 124.8, 125.0, 127.9, 129.0, 129.1, 130.3, 142.6, 142.6, 159.8;
**IR** ***(v$_{max}$*** **/cm$^{-1}$):** 2954 (s), 2924 (s), 2854 (s), 1339 (m);
**HRMS** calculated for $C_{13}H_9NO_3$ (M$^+$): 227.0580; Found: 227.0582
**m.p.** = 158-159°C (EtOAc/Hex)
**R$_f$** = 0.43 on silica gel (5% EtOAc:Hexanes);

Table 2.3, Entry 9



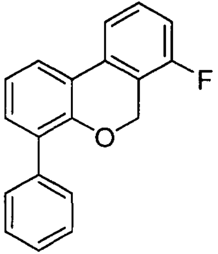
**$^1$H NMR (300MHz, CDCl$_3$, 293K, TMS):** 7.12-7.25 (m, 2H), 7.35 (dd, *J*=8.7 Hz & 4.5 Hz, 1H), 7.44 (d, *J*=3.6 Hz, 2H), 7.73 (dd, *J*=9.0 Hz & 2.7 Hz, 1H), 8.03 (d, *J*=7.8 Hz, 2H);
**$^{13}$C NMR (75MHz, CDCl$_3$, 293K, TMS):** 105.8, 106.1, 109.3, 110.8, 111.0, 111.1, 113.4, 113.8, 119.4, 120.5, 126.4;
**IR** ***(v$_{max}$*** **/cm$^{-1}$):** 3418 (m), 2925 (s), 2854 (s), 1457 (s), 1168 (m);
**HRMS** calculated for $C_{12}H_8FN$ (M$^+$): 185.0641; Found: 185.0632
**m.p.** = 211-212°C (EtOAc/Hex)
**R$_f$** = 0.25 on silica gel (5% EtOAc:Hexanes);

Table 2.3, Entry 10



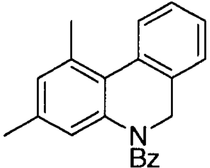
**$^1$H NMR (300MHz, $(CD_3)O$, 293K, TMS):** 7.26 (1H, t, *J*=7.4Hz), 7.50 (2H, m), 7.60 (1H, m), 7.89 (1H, s), 8.21 (1H, d, *J*=7.8Hz), 8.30 (1H, d, *J*=8.1Hz), 10.57 (1H, s, broad)
**$^{13}$C NMR (75MHz, $(CD_3)O$, 293K, TMS):** 109.9 (q, *J*=4.3Hz), 113.2, 117.0 (q, *J*=3.7Hz), 121.4, 122.6, 122.7, 123.9, 127.2 (q, *J*=271.1Hz), 127.7, 128.5 (q, 31.6Hz), 128.9, 141.0, 143.0;
**IR (*$v_{max}$*/cm$^{-1}$):** 3418 (m), 2925 (s), 2854 (s), 1457 (s), 1168 (m);
**HRMS** calculated for $C_{13}H_8F_3N$ ($M^+$): 235.0609; Found: 235.0589
**m.p.** = 210-211°C (EtOAc/Hex)
**$R_f$** = 0.26 on silica gel (5% EtOAc:Hexanes);

Table 2.5, Entry 2



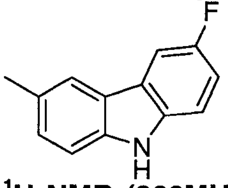
**$^1$H NMR (300MHz, $CDCl_3$, 293K, TMS):** 5.16 (2H, s), 6.98 (1H, t, J=8.7Hz), 7.10 (1H, t, J=8.1Hz), 7.28-7.37 (3H, m), 7.38-7.51 (3H, m), 7.54 (2H, m), 7.68 (1H, dd, J=2.1Hz & 8.1Hz);
**$^{13}$C NMR (75MHz, $CDCl_3$, 293K, TMS):** 61.9 (d, J=4.4Hz), 114.3 (d, J=20.7Hz), 118.0 (d, J=3.2Hz), 122.1, 122.7 (d, J=3.3Hz), 123.0, 127.2, 128.1, 129.2, 129.3, 129.4, 131.1, 131.2, 132.7 (d, J=4.4Hz), 137.7, 151.5, 157.9 (d, J=243.2Hz);
**IR (*$v_{max}$*/cm$^{-1}$):** 3061, 3030, 2853, 1418, 1240, 1019, 909, 757, 698;
**HRMS** calculated for $C_{19}H_{13}FO$ (M+): 276.0950; Found: 276.0967;
**$R_f$** = 0.43 on silica gel (5% EtOAc:Hexanes);

Table 2.5, Entry 3



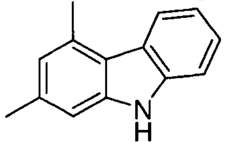
**$^1$H NMR (300MHz, $CDCl_3$, 293K, TMS):** 2.16 (6H, s), 4.86 (2H, s), 7.40-7.60 (6H, m), 7.79 (1H, m), 7.84 (1H, d, J=8.4Hz), 7.91 (1H, dd, J=2.4Hz & 7.2Hz), 8.06 (1H, m), 8.54 (1H, d, J=7.8Hz);
**$^{13}$C NMR (75MHz, $CDCl_3$, 293K, TMS):** 30.9, 38.0, 50.7, 123.5, 124.9, 126.0, 127.3, 128.4, 128.9, 129.1, 129.1, 129.3, 130.1, 133.3, 134.4, 137.4, 169.1;
There is also three overlapping carbon signals as 3 peak are missing even with prolonged scans.
**IR ($v_{max}$/cm$^{-1}$):** 3380, 2946, 1646, 753, 691;
**HRMS**: calculated for $C_{22}H_{19}NO$ ($M^+$): 313.1467; Found: 313.1438
**$R_f$** = 0.35 on silica gel (5% EtOAc:Hexanes);

Table 2.5, Entry 8



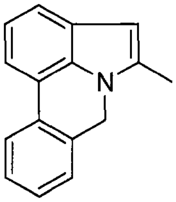
**$^1$H NMR (300MHz, CDCl$_3$, 293K, TMS):** 2.50 (3H, s), 7.10 (1H, td, J=2.2Hz & 8.8Hz), 7.23 (3H, m), 7.66 (1H, dd, J=2.7Hz & 8.4Hz), 7.77 (2H, m);
**$^{13}$C NMR (75MHz, CDCl$_3$, 293K, TMS):** 21.8, 106.3 (d, J=23.2Hz), 111.0, 111.5 (d, J=8.7Hz), 113.8 (d, J=25.3Hz), 120.8, 123.6 (d, J=4.4Hz), 124.0 (d, J=9.8Hz), 128.2, 129.2, 136.4, 139.1, 157.8 (d, J=234.9Hz);
**IR *($\nu_{max}$* /cm$^{-1}$):** 3401, 1578, 1463, 1142, 869, 808;
**HRMS** calculated for $C_{13}H_{10}NF$ (M+): 199.0797; Found: 199.0792;
**m.p.** = 175-177°C (CHCl$_3$)
**R$_f$** = 0.30 on silica gel (5% EtOAc:Hexanes);

Table 2.5, Entry 10



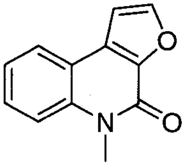
**$^1$H NMR (300MHz, CDCl$_3$, 293K, TMS):** 2.50 (3H, s), 2.86 (3H, s), 6.90 (2H, d, J=6.3Hz), 7.24-7.42 (3H, m), 7.70 (1H, s), 8.16 (1H, d, J=7.8Hz);
**$^{13}$C NMR (75MHz, CDCl$_3$, 293K, TMS):** 20.7, 21.8, 108.3, 110.3, 119.2, 122.1, 122.2, 122.5, 123.9, 124.6, 132.9, 135.8, 139.4, 139.9;
**IR ($\nu_{max}$ /cm$^{-1}$):** 3406, 1457, 834, 726;
**HRMS**: calculated for $C_{14}H_3N$ (M$^+$): 195.1048; Found: 195.1040
**m.p.** = 148-149°C (CHCl$_3$)
**R$_f$** = 0.28 on silica gel (5% EtOAc:Hexanes);

Table 2.5, Entry 12



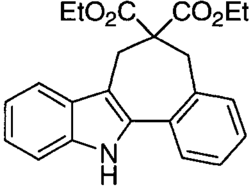
Caution! – This compound must be kept under nitrogen as it decomposes to air.
**$^1$H NMR (500MHz, CDCl$_3$, 293K, TMS):** 2.34 (3H, s), 5.26 (2H, s), 6.20 (1H, s), 7.01 (1H, t, J=8.0Hz), 7.09 (1H, d, J=8.0Hz), 7.18 (1H, td, J=7.0Hz & 1.0Hz), 7.27 (1H, t, J=8.0Hz), 7.37 (2H, m), 7.85 (1H, d, J=8.0Hz);
**$^{13}$C NMR (125MHz, CDCl$_3$, 293K, TMS):** 11.9, 45.7, 99.7, 112.3, 117.6, 119.4, 120.0, 122.5, 126.2, 127.2, 127.4, 127.7, 129.9, 130.1, 133.6, 135.9;
**IR *($\nu_{max}$* /cm$^{-1}$):**3060, 1548, 1395, 1349, 753;
**HRMS** calculated for $C_{16}H_{13}N$ (M+): 219.1048; Found: 219.1030;
**R$_f$** = 0.43 on silica gel (5% EtOAc:Hexanes);

Table 2.5, Entry 13



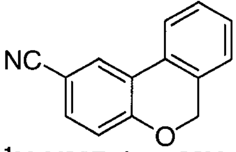
**$^1$H NMR (300MHz, CDCl$_3$, 293K, TMS):** 3.76 (3H, s), 7.01 (1H, d, J=1.9Hz), 7.30 (1H, t, J=7.0Hz), 7.39 (1H, d, J=8.7Hz), 7.51 (1H, td, J=1.4Hz & 7.3Hz), 7.80 (2H, m);
**$^{13}$C NMR (75MHz, CDCl$_3$, 293K, TMS):** 29.1, 105.6, 115.0, 116.2, 122.3, 124.2, 128.5, 129.1, 137.6, 142.0, 153.5, 175.8;
**IR ($v_{max}$/cm$^{-1}$):** 3095, 1662, 1584, 1233, 895, 805;
**HRMS** calculated for $C_{12}H_9NO_2$ (M+) 199.0633; Found: 199.0633;
**m.p.** = 140-142°C ($CHCl_3$)
**R$_f$** = 0.30 on silica gel (10% EtOAc:Hexanes);

Table 2.5, Entry 14



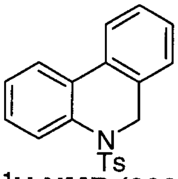
**$^1$H NMR (300MHz, CDCl$_3$, 293K, TMS):** 1.21 (6H, t, J=7.2Hz), 3.29 (2H, s), 3.38 (2H, s), 4.14 (4H, q, J=7.2Hz), 7.09-7.29 (3H, m), 7.33 (2H, t, J=7.5Hz), 7.42 (2H, d, J=7.5Hz), 7.65 (1H, d, J=7.5Hz), 8.28 (1H, s);
**$^{13}$C NMR (75MHz, CDCl$_3$, 293K, TMS):** 14.0, 29.0, 38.9, 61.5, 63.3, 110.9, 111.2, 118.6, 119.7, 122.5, 125.2, 127.1, 127.4, 129.0, 132.2, 132.7, 133.6, 137.9, 136.0, 171.3;
**IR ($v_{max}$/cm$^{-1}$):** 2980, 2934, 1715, 1445, 1253, 1219, 1104, 909, 738;
**HRMS** calculated for $C_{23}H_{23}NO_4$ (M+): 377.1627; Found: 377.1617;
**R$_f$** = 0.19 on silica gel (5% EtOAc:Hexanes);

Table 2.6, Entry 2



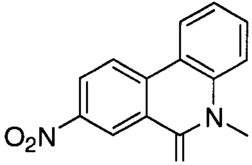
**$^1$H NMR (300MHz, CDCl$_3$, 293K, TMS):** 5.16 (2H, s), 6.98 (1H, d, *J*=7.8Hz), 7.13 (1H, d, J=7.3Hz), 7.35 (2H, m), 7.45 (1H, dd, J=8.2Hz & 1.9Hz), 7.61 (1H, d, J=7.3Hz), 7.94 (1H, d, J=2.1Hz);
**$^{13}$C NMR (75MHz, CDCl$_3$, 293K, TMS):** 68.6, 105.5, 118.5, 119.1, 122.1, 123.7, 124.9, 127.6, 127.8, 128.9, 129.0, 130.6, 133.1, 158.1;
**IR ($v_{max}$/cm$^{-1}$):** 2224, 1609, 1493, 1248, 1011, 824;
**HRMS** calculated for $C_{14}H_9NO$ (M+) 207.0684; Found: 207.0697;
**m.p.** = 85-87°C ($CHCl_3$)
**R$_f$** = 0.42 on silica gel (5% EtOAc:Hexanes);

Table 2.6, Entry 5



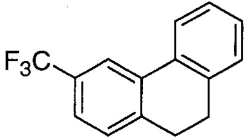
**$^1$H NMR (300MHz, $CDCl_3$, 293K, TMS):** 2.13 (3H, s), 4.84 (2H, s), 6.68 (2H, d, J=8.1Hz), 6.93 (2H, d, J=8.1Hz), 7.08 (3H,m), 7.20 (1H, m), 7.35 (2H,m), 7.57 (1H, dd, J=8.4Hz & J=1.5Hz), 7.79 (1H, dd, J=8.4Hz & 1.5Hz);
**$^{13}$C NMR (75MHz, $CDCl_3$, 293K, TMS):** 21.2, 49.8, 122.9, 123.7, 126.0, 127.0, 127.4, 127.5, 127.8, 128.1, 128.3, 130.6, 130.9, 131.3, 134.4, 135.9, 142.8; There is also an overlapping carbon signal as 1 peak is missing even with prolonged scans.
**IR** *($\nu_{max}$* **/cm$^{-1}$):**3402, 3065, 1645, 1439, 1353, 1165, 1069, 666;
**HRMS** calculated for $C_{20}H_{17}NO_2S$ (M+) 335.0980; Found: 335.0964;
**m.p.** = 83-85°C ($CHCl_3$)
**R$_f$** = 0.30 on silica gel (5% EtOAc:Hexanes);

Table 2.6, Entry 6



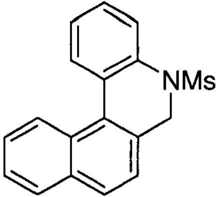
**$^1$H NMR (300MHz, $(CD_3)_2SO$, *373K*):** 3.76 (3H, s), 7.42 (1H, t, J=7.0Hz), 7.63 (1H, d, J=8.0Hz), 7.73 (1H, t, J=7.0Hz), 8.51 (2H, m), 8.71 (1H, d, J=9.0Hz), 9.06 (1H, d, J=3.0Hz),;
**$^{13}$C NMR (75MHz, $(CD_3)_2SO$, *373K*):** 29.3, 98.8, 115.1, 116.6, 122.3, 122.7, 123.9, 124.2, 125.5, 131.2, 137.8, 138.3, 146.3, 158.8;
**IR** *($\nu_{max}$* **/cm$^{-1}$):** 2921, 2857, 1648, 1533, 1340, 1142, 831, 762;
**HRMS** calculated for $C_{14}H_{10}N_2O_3$ (M+): 254.0691; Found: 254.0680;
**m.p.** = 290-293°C ($CHCl_3$)
**R$_f$** = 0.30 on silica gel (15% EtOAc:Hexanes);

Table 2.6, Entry 7



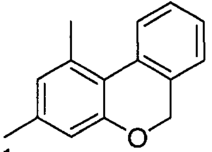
**$^1$H NMR (300MHz, $CDCl_3$, 293K, TMS):** 2.88 (4H, m), 7.21-7.36 (4H, m), 7.45 (1H, d, 7.5Hz), 7.76 (1H, d, J=7.2Hz), 7.96 (1H, s);
**$^{13}$C NMR (75MHz, $CDCl_3$, 293K, TMS):** 28.6, 29.0, 120.5 (q, J=4.4Hz), 120.5, 123.8 (q, J=4.4Hz), 123.8, 124.6 (q, J=270.6Hz), 127.3, 128.4, 128.5, 129.4 (1, J=32.7Hz), 133.2, 135.2, 137.3, 141.2;
**IR** *($\nu_{max}$* **/cm$^{-1}$):** 3064, 2942, 1701, 1417, 1335, 1167, 1122, 1077, 830, 767;
**HRMS** calculated for $C_{15}H_{11}F_3$ (M+): 248.0813; Found: 248.0795;
**R$_f$** = 0.7 on silica gel (Hexanes);

Table 2.6, Entry 9



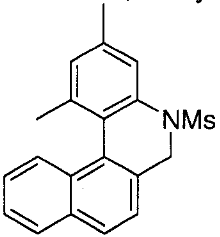
**$^1$H NMR (300MHz, CDCl$_3$, 293K, TMS):** 2.06 (2H, s), 2.63 (3H, s), 6.86 (1H, s), 7.20-7.42, (8H, m), 7.80 (1H, d, J=7.8Hz);
**$^{13}$C NMR (75MHz, CDCl$_3$, 293K, TMS):** 20.9, 22.8, 124.0, 125.7, 125.9, 126.0, 126.9, 127.1, 127.3, 127.9, 128.9, 129.0, 129.9, 130.3, 132.1, 135.1, 135.3, 136.6;
**IR ($v_{max}$ /cm$^{-1}$)**: 1646, 1373, 1233, 741;
**HRMS**: calculated for $C_{18}H_{15}NO_2S(M^+)$: 309.0823; Found: 309.0817
**m.p.** = 161-162°C (CHCl$_3$)
**R$_f$** = 0.30 on silica gel (5% EtOAc:Hexanes);

Table 2.6, Entry 10



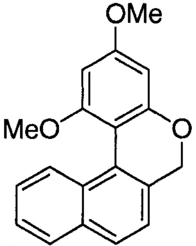
**$^1$H NMR (300MHz, CDCl$_3$, 293K, TMS):** 2.31 (3H, s), 2.64 (3H, s), 4.92 (2H, s), 6.75 (2H, d, J=9.3Hz), 7.20-7.29 (2H, m), 7.36 (1H, td, J=1.2Hz & 7.5Hz), 7.73 (1H, d, J=7.8Hz);
**$^{13}$C NMR (75MHz, CDCl$_3$, 293K, TMS):** 21.6, 23.0, 69.5, 115.8, 120.9, 125.2, 126.4, 126.8, 126.9, 128.2, 131.2, 133.8, 135.6, 139.1, 156.8;
**IR ($v_{max}$ /cm$^{-1}$)**: 1615, 1284, 1151, 1064, 735
**HRMS**: calculated for $C_{15}H_{14}O$ (M$^+$): 210.1045; Found: 210.1056
**m.p.** = 82-83°C (CHCl$_3$)
**R$_f$** = 0.45 on silica gel (5% EtOAc:Hexanes);

Table 2.6, Entry 11



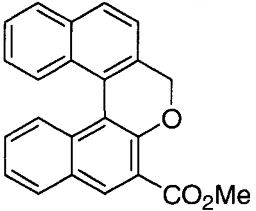
**$^1$H NMR (300MHz, CDCl$_3$, 293K, TMS):** 1.86 (3H, s), 2.19 (3H, s), 2.45 (3H, s), 4.45 (1H, d, J=16.2Hz), 5.11 (1H, dd, J=1.2Hz & 16.8Hz), 7.17 (1H, s), 7.50 (4H, m), 7.70 (1H, m), 7.84 (2H, m);
**$^{13}$C NMR (75MHz, CDCl$_3$, 293K, TMS):** 21.3, 22.6, 37.9, 51.5, 123.6, 125.4, 125.8, 126.1, 126.4, 127.4, 128.4, 128.6, 128.8, 129.3, 131.1, 133.7, 134.4, 136.3, 138.4, 138.6;
**IR ($v_{max}$ /cm$^{-1}$)**: 1345, 1157, 1061, 756;
**HRMS**: calculated for $C_{20}H_{19}NO_2S$ (M$^+$): 337.1136; Found: 337.1135
**m.p.** = 150-151°C (CHCl$_3$)
**R$_f$** = 0.31 on silica gel (5% EtOAc:Hexanes);

Table 2.6, Entry 12



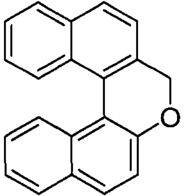
**$^1$H NMR (300MHz, CDCl$_3$, 293K, TMS):** 3.80 (3H, s), 3.86 (3H, s), 5.03 (2H, s), 6.39 (2H, dd, J=2.4Hz & 12.3Hz), 7.31 (1H, d, J=8.4Hz), 7.38-7.47 (2H, m), 7.78 (3H, m);
**$^{13}$C NMR (75MHz, CDCl$_3$, 293K, TMS):** 54.9, 55.5, 70.7, 93.9, 94.6, 107.2, 122.4, 124.5, 125.2, 125.9, 127.2, 127.7, 128.1, 128.6, 132.1, 134.2, 157.3, 159.5, 161.2;
**IR ($v_{max}$ /cm$^{-1}$)**: 2840, 1609, 1150, 1098, 812, 756;
**HRMS**: calculated for $C_{19}H_{16}O_3$ (M$^+$): 292.1099; Found: 292.1086
**R$_f$** = 0.45 on silica gel (5% EtOAc:Hexanes);

Table 2.6, Entry 13



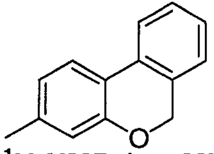
**$^1$H NMR (300MHz, CDCl$_3$, 293K, TMS):** 4.00 (3H, s), 4.98 (1H, d, J=12.6Hz), 5.37 (1H, d, J=12.6Hz), 7.24-7.48 (5H, m), 7.62 (2H, m), 7.88-7.97 (3H, m), 8.45 (1H, s);
**$^{13}$C NMR (75MHz, CDCl$_3$, 293K, TMS):** 52.4, 71.1, 119.9, 121.2, 122.7, 125.4, 125.5, 125.9, 126.8, 126.9, 127.4, 128.5, 128.6, 128.7, 128.9, 129.3, 132.1, 132.9, 133.7, 134.3, 154.3, 166.2;
There is also one overlapping carbon signal as 1 peak is missing even with prolonged scans.
**IR ($v_{max}$ /cm$^{-1}$)**: 1728, 1447, 1204, 1084, 750;
**HRMS**: calculated for $C_{23}H_{16}O_3$ (M$^+$): 340.1099; Found: 340.1095
**R$_f$** = 0.40 on silica gel (5% EtOAc:Hexanes);

Equation 2.6



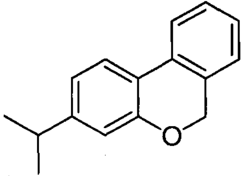
**$^1$H NMR (300MHz, CDCl$_3$, 293K, TMS):** 4.98 (1H, d, J=12.6Hz), 5.23 (1H, d, J=12.6Hz), 7.27-7.48 (6H, m), 7.71 (2H, dd, J=3.0Hz & 7.8Hz), 7.91-7.82 (4H, m);
**$^{13}$C NMR (75MHz, CDCl$_3$, 293K, TMS):** 71.7, 118.1, 118.4, 122.9, 123.9, 125.2, 125.4, 125.5, 126.6, 126.9, 127.3, 128.1, 128.3, 128.5, 128.9, 129.9, 130.3, 130.6, 133.6, 134.4, 156.1;
**IR ($v_{max}$ /cm$^{-1}$)**: 1592, 1508, 1238, 1049, 813, 749;
**HRMS**: calculated for $C_{21}H_{14}O$ (M$^+$): 282.1045; Found: 282.1050
**R$_f$** = 0.40 on silica gel (5% EtOAc:Hexanes);

Table 2.8, Entry 2



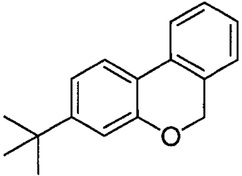
$^{1}$**H NMR (500MHz, $(CD_3)_2CO$, 293K):** 2.31 (3H, s), 5.09 (2H, s), 6.79 (1H, s), 6.88 (1H, d, J= 7.5Hz), 7.22 (1H, d, J=7.5Hz), 7.27 (1H, t, J=7.5Hz), 7.37 (1H, t, J=7.5Hz), 7.69 (1H, d, J=8.0Hz), 7.73 (1H, d, J=8.0Hz);
$^{13}$**C NMR (125MHz, $(CD_3)_2CO$, 293K):** 20.7, 68.2, 117.8, 120.4, 121.8, 123.2, 123.4, 124.9, 127.5, 128.6, 130.4, 131.5, 139.9, 155.1;
**IR** ($\nu_{max}$ **/cm$^{-1}$**): 2963, 2844, 1618, 1484, 1151, 1031, 766;
**HRMS** calculated for $C_{14}H_{12}O$ (M+) 196.0888; Found: 196.0876;
**R$_f$** = 0.40 on silica gel (5% EtOAc:Hexanes);

Table 2.8, Entry 3



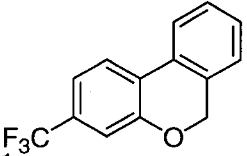
$^{1}$**H NMR (500MHz, $(CD_3)_2CO$, 293K):** 1.24 (6H, d, J=7.0Hz), 2.89 (1H, sept, J=7.0Hz), 5.10 (2H, s), 6.85 (1H, d, J=1.5Hz), 6.96 (1H, dd, J=7.5Hz & 1.5Hz), 7.23 (1H, d, J=7.5Hz), 7.28 (1H, td, J= 7.5Hz & 1.0Hz), 7.37 (1H, td, J= 7.0Hz & 1.0Hz), 7.75 (2H, m);
$^{13}$**C NMR (125MHz, $(CD_3)_2CO$, 293K):** 25.1, 35.6, 69.8, 116.7, 122.2, 122.3, 123.4, 125.1, 126.5, 129.2, 130.2, 132.0, 133.2, 152.7, 156.8;
**IR** ($\nu_{max}$ **/cm$^{-1}$**): 2958, 1590, 1482, 1026, 730;
**HRMS** calculated for $C_{16}H_{16}O$ (M+) 224.1201; Found: 224.1212;
**R$_f$** = 0.39 on silica gel (5% EtOAc:Hexanes);

Table 2.8, Entry 4



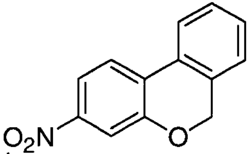
$^{1}$**H NMR (500MHz, $(CD_3)_2CO$, 293K):** 1.32 (9H, s), 5.11 (2H, s), 6.99 (1H, d, J=2.0Hz), 7.12 (1H, dd, J=8.0Hz & 2.0Hz), 7.23 (1H, d, J=7.0Hz), 7.28 (1H, td, J=7.5Hz & 1.0Hz), 7.37 (1H, td, J=7.5Hz & 1.0Hz), 7.75 (2H, m);
$^{13}$**C NMR (125MHz, $(CD_3)_2CO$, 293K):** 32.4, 36.2, 69.8, 115.8, 121.1, 121.9, 123.4, 124.8, 126.5, 129.2, 130.2, 131.9, 133.2, 154.9, 156.5;
**IR** ($\nu_{max}$ **/cm$^{-1}$**): 3037, 2963, 1589, 1782, 1275, 1031, 733;
**HRMS** calculated for $C_{17}H_{18}O$ (M+) 238.1358; Found: 238.1361;
**m.p.** = 58-59°C (Acetone)
**R$_f$** = 0.41 on silica gel (5% EtOAc:Hexanes);

Table 2.8, Entry 5



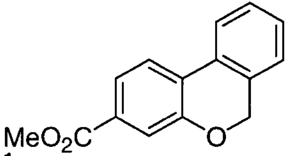
**$^1$H NMR (500MHz, $(CD_3)_2CO$, 293K):** 5.23 (2H, s), 7.24 (1H, s), 7.31 (1H, d, J=7.5Hz), 7.39 (2H, m), 7.45 (1H, t, J=6.5Hz), 7.88 (1H, d, J=8Hz), 8.05 (1H, d, J=8Hz);
**$^{13}$C NMR (125MHz, $(CD_3)_2CO$, 293K):** 70.0, 116.0 (q, J=3.8Hz), 120.4 (q, J=3.9Hz), 124.5, 125.9 (q, J=269.9Hz), 126.2, 126.9, 128.4, 130.3, 130.6, 131.0, 132.3 (q, J=32.4), 133.8, 156.8;
**IR ($v_{max}$/cm$^{-1}$):** 1422, 1337, 1170, 1118, 883, 772;
**HRMS** calculated for $C_{15}H_{12}O_3$ (M+) 250.0605; Found: 250.0582;
**m.p.** = 67-69°C (Acetone)
**$R_f$** = 0.40 on silica gel (5% EtOAc:Hexanes);

Table 2.8, Entry 6



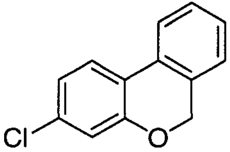
**$^1$H NMR (500MHz, $(CD_3)_2CO$, 293K):** 5.30 (2H, s), 7.37 (1H, d, J=8.0Hz), 7.45 (2H, m), 7.76 (1H, d, 2.5Hz), 7.94 (1H, dd, J=9Hz & 2.5Hz), 7.97, (1H, m), 8.14 (1H, d, J=9Hz);
**$^{13}$C NMR (125MHz, $(CD_3)_2CO$, 293K):** 70.2, 114.1, 118.9, 125.1, 126.2, 127.0, 129, 8, 130.8, 131.1, 131.8, 133.9, 134.0, 156.9;
**IR ($v_{max}$/cm$^{-1}$):** 2954, 2924, 2854, 1339, 847;
**HRMS** calculated for $C_{13}H_9NO_3$ (M+) 227.0582; Found: 227.0592;
**$R_f$** = 0.38 on silica gel (5% EtOAc:Hexanes);

Table 2.8, Entry 7



**$^1$H NMR (500MHz, $(CD_3)_2CO$, 293K):** 3.88 (3H, s), 5.19 (2H, s), 7.29 (1H, d, J=7.8Hz), 7.39 (1H, td, J=7.5Hz & J=1Hz), 7.43 (1H, t, J=7.5Hz), 7.53 (1H, d, J=1.5Hz), 7.68 (1H, dd, J=8.5Hz & 2Hz), 7.86 (1H, d, J=8Hz), 7.94 (1H, d, J=8.5Hz);
**$^{13}$C NMR (125MHz, $(CD_3)_2CO$, 293K):** 53.4, 65.1, 69.9, 119.7, 119.8, 124.6, 127.9, 125.4, 126.8, 130.5, 130.7, 130.8, 134.0, 156.5, 167.6;
**IR ($v_{max}$/cm$^{-1}$):**1707, 1412, 1308, 1233, 1197, 760;
**HRMS** calculated for $C_{15}H_{12}O_3$ (M+) 240.0786; Found: 240.07887;
**m.p.** = 93-94°C (Acetone)
**$R_f$** = 0.37 on silica gel (5% EtOAc:Hexanes);

Table 2.8, Entry 8



**Characterized as an 3.2:1 mixture**

**$^1$H NMR (500MHz, $(CD_3)_2CO$, 293K):** Major: 5.16 (2H, s), 6.99 (1H, d, J=2.0Hz), 7.08 (1H, dd, J=8.0Hz & 2.0Hz), 7.26 (1H, d, J=7.5Hz), 7.34 (1H, td, J=7.5Hz & 1.0Hz), 7.40 (1H, t, J=7.5Hz), 7.79 (1H, d, J=7.5Hz), 7.84 (1H, d, J=8.0Hz);

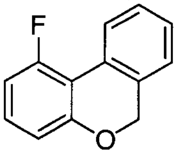
**$^{13}$C NMR (125MHz, $(CD_3)_2CO$, 293K):** Mixture: 70.0, 70.6, 119.0, 123.7, 123.8, 124.0, 126.6, 126.7, 126.8, 126.9, 127.9, 129.7, 130.0, 130.0, 130.5, 130.8, 131.2, 133.0, 135.7, 157.4, 159.5;

**IR (*$v_{max}$* /cm$^{-1}$):** 2850, 1479, 1198, 1017, 855;

**HRMS** calculated for $C_{15}H_{12}O_3$ (M+) 240.0786; Found: 240.0789;

**R$_f$** = 0.40 on silica gel (5% EtOAc:Hexanes);

Table 2.8, Entry 9



**Characterized as an 8.03:1 mixture**

**$^1$H NMR (500MHz, $(CD_3)_2CO$, 293K):** Major: 5.11 (2H, s), 6.84-6.91 (2H, m), 7.26 (1H, m), 7.32 (1H, d, J= 7.5Hz), 7.36 (1H, td, J=7.0Hz & 1.0Hz), 7.43 (1H, t, J=8.0Hz), 8.00 (1H, d, J=8.0Hz), Minor: 5.16 (2H, s), 6.75 (1H, dd, J=10.0Hz & 2,5Hz), 6.84 (1H, m, overlapping with major), 7.76 (1H, d, J=7.5Hz), 7.87 (1H, d, J=9.0Hz & 6.5Hz), 3H complete overlap with major isomer;

**$^{19}$F NMR (500MHz, $(CD_3)_2CO$, 293K):** No standard used relative shift given. Major : (8.03F, q, J=7.5Hz), Minor +3.48 (1F, m);

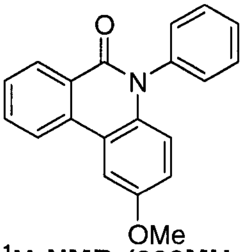
**$^{13}$C NMR (125MHz, $(CD_3)_2CO$, 293K):** Major only: 70.2, 111.3 (d, J=22.9Hz), 113.9 (d, J=13.3), 115.1 (d, J=3.9Hz), 127.6, 127.7, 128.5, 130.0, 130.4, 131.3 (d, J=11.5Hz), 133.8, 158.7 (d, J=7.6Hz), 162.4 (d, 247.9);

**IR (*$v_{max}$* /cm$^{-1}$):** 3063, 2839, 1619, 1294, 1228, 762;

**HRMS** calculated for $C_{13}H_9OF$ (M+) 200.0637; Found: 200.0650;

**R$_f$** = 0.42 on silica gel (5% EtOAc:Hexanes);

Scheme 2.6



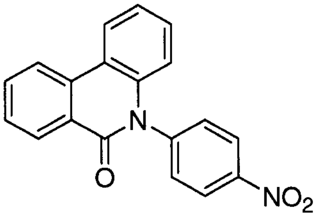
**$^1$H NMR (300MHz, $CDCl_3$, 293K, TMS):** 3.91 (3H, s), 6.76 (1H, dd, J=7.5Hz), 1.8Hz), 7.12 (2H, d, J=8.7), 7.21-7.36 (4H, m), 7.62 (1H, td, J=7.5Hz & 1.2Hz), 7.82 (1H, td, J=7.5Hz & 1.2Hz), 8.33 (2H, m), 8.56 (1H, dd, J=8.1Hz & 1.2Hz);

**$^{13}$C NMR (75MHz, $CDCl_3$, 293K, TMS):** 55.6, 115.5, 117.1, 119.1, 121.8, 121.8, 122.6, 123.0, 125.9, 128.1, 129.1, 130.0, 130.8, 132.8, 134.0, 139.5, 159.6, 162.0;

**IR (*$v_{max}$* /cm$^{-1}$):** 2999, 1655, 1607, 1511, 1245, 753;

**HRMS** calculated for $C_{20}H_{15}O_2N$ (M+) 301.1103; Found: 301.1104;
**$R_f$** = 0.30 on silica gel (15% EtOAc:Hexanes);

Scheme 2.6

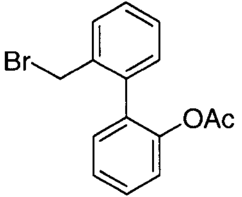


**Characterized as a 1:2 mixture of isomers.**

**$^1$H NMR (500MHz, $(CD_3)_2CO$, 293K):** Major: 6.62 (1H, m), 7.57 (2H, d, J=9.0Hz), 7.60 (1H, m), 7.86 (1H, td, J=8.0Hz & 1.5Hz), 8.49 (2H, d, J=8.5Hz), 8.53 (1H, dd, J=8.0Hz & 1.0Hz); Minor: 6.81 (1H, d, J=9.5Hz), 7.73 (1H, t, J=8.0Hz), 7.93 (1H, td, J=8.0Hz & 1.5Hz), 8.14 (1H, dd, J=9.5Hz & 2.5Hz), 8.42 (1H, d, J=8.0Hz), 8.57 (1H, dd, J=8.0Hz & 1.5Hz), 9.21 (1H, d, J=2.0Hz); Unassigned mixtures: 7.34 (m), 7.65 (m), 8.35 (m);
**$^{13}$C NMR (125MHz, $(CD_3)_2CO$, 293K):** mixture of isomers: 116.6, 117.6, 119.2, 119.3, 122.0, 122.2, 123.3, 123.4, 123.8, 125.4, 125.6, 125.9, 128.5, 128.7, 129.3, 129.4, 129.5, 129.6, 130.6, 130.7, 132.6, 133.4, 133.7, 137.4, 138.2, 143.3, 144.2, 147.8, 161.5;
**IR ($\nu_{max}$/cm$^{-1}$):** 2929, 1661, 1607, 1522, 1345, 751;
**HRMS** calculated for $C_{19}H_{12}O_3N_2$ (M+) 316.0848; Found: 316.0840;
**$R_f$** = 0.30 on silica gel (15% EtOAc:Hexanes);

**General Procedure for Ring Opening of *6H*-Benzo[*c*]chromenes:**
The corresponding *6H*-Benzo[*c*]chromenes is placed in a dry round bottom flask, and dissolved in DCM (0.3M). The flask is purged with argon, and $BBr_3$ (1.1 equiv) are added dropwise to the mixture. The reaction is allowed to stir at room temperature for 4 hours. The reaction is quenched with 10% HCl solution, and is extracted using DCM. The organics are dried using $MgSO_4$, filtered and the volatiles are evaporated under reduced pressure. Crude is then placed in a 10ml round bottom flask, and 3mL $Ac_2O$ and 3ml benzene are added to the flask. The reaction temperature is brought to 0°C for the addition of 2,6-dimethylpyridine (1mL), dropwise. The reaction is allowed to stir at room temperature for 16 hours. The mixture is extracted using $Et_2O$/Brine/$NH_4Cl$, and the organics are dried using $MgSO_4$, filtered and the volatiles are evaporated under reduced pressure. The residues are then purified via column chromatography using ethyl acetate/hexanes mixtures.

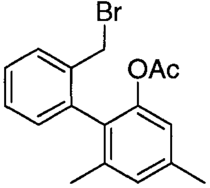
Table 2.7, Entry 1



**$^1$H NMR (300MHz, $CDCl_3$, 293K, TMS):** 1.89 (3H, s), 4.28 (1H, d, J=10.0Hz), 4.38 (1H, d, J=10.0Hz), 7.15 (2H, d, J=7.5Hz), 7.26-7.46 (5H, m), 7.52 (1H, d, J=7.5Hz);
**$^{13}$C NMR (75MHz, $CDCl_3$, 293K, TMS):** 20.5, 31.8, 122.5, 126.0, 128.1, 128.4, 129.2, 130.4, 130.5, 131.0, 133.0, 136.1, 136.8, 148.1, 169.2;

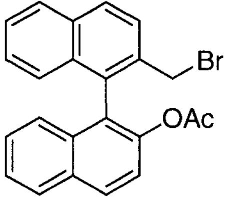
**IR ($v_{max}$ /cm$^{-1}$)**: 3061, 1762, 1476, 1368, 1213, 1186, 755;
**HRMS** calculated for $C_{15}H_{13}BrO_2$ (M+): 304.0099; Found: 304.0119;
**R$_f$** = 0.25 on silica gel (5% EtOAc:Hexanes);

Table 2.7, Entry 2



**$^1$H NMR (300MHz, CDCl$_3$, 293K, TMS):** 1.79 (3H, s) , 2.06 (3H, s), 2.37 (3H, s), 4.25 (2H, s), 6.80 (1H, s), 7.07-7.03 (2H, m), 7.38-7.27 (2H, m), 7.53 (1H, dd, 7.2Hz & 1.5Hz);
**$^{13}$C NMR (75MHz, CDCl$_3$, 293K, TMS):** 20.3, 20.4, 21.2, 31.6, 119.1, 128.4, 128.9, 129.4, 130.3, 130.5, 135.9, 136.2, 138.2, 138.8, 128.2, 169.4;
**IR ($v_{max}$ /cm$^{-1}$)**: 1760, 1621, 1367, 1206, 1044, 752, 610;
**HRMS**: calculated for $C_{17}H_{17}O_2Br$ (M$^+$): 332.0412; Found: 332.0418
**R$_f$** = 0.25 on silica gel (5% EtOAc:Hexanes);

Table 2.7, Entry 3

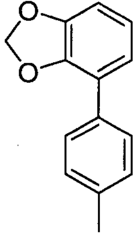


**$^1$H NMR (300MHz, CDCl$_3$, 293K, TMS):** 1.75 (3H, s), 4.29 (2H, s), 7.10-7.15 (2H, m), 7.23-7.32 (2H, m), 7.42-7.50 (3H, m), 7.72 (1H, d, 8.7Hz), 7.88 (1H, d, 8.1Hz), 7.95 (2H, m), 8.03 (1H, d, 9.0Hz);
**$^{13}$C NMR (75MHz, CDCl$_3$, 293K, TMS):** 20.9, 32.7, 122.2, 126.3, 126.4, 126.7, 126.9, 127.1, 127.1, 127.3, 128.0, 128.3, 128.5, 129.5, 132.0, 132.1, 132.2, 132.9, 133.7, 134.8, 147.1, 169.6;
**IR ($v_{max}$ /cm$^{-1}$)**: 2360, 2340, 1829, 1684, 1558, 1457, 1362, 1197, 814;
**HRMS**: calculated for $C_{23}H_{17}O_2Br$(M$^+$): 404.0412; Found: 404.0425
**R$_f$** = 0.28 on silica gel (5% EtOAc:Hexanes);

**General Procedure for Intermolecular Arylation of Dioxole:**

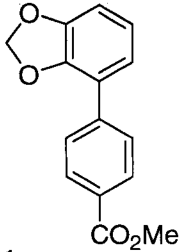
Crushed $K_2CO_3$ (2 equiv.), AgOTf (1 equiv.), $Pd(OAc)_2$ (appropriate amount) and $P^tBu_2Me$ – $HBF_4$ (3 equiv. per Pd) were placed in a 10mL reaction tube equipped with a magnetic stir. Any solid aryl halide is added at this point. The vial placed in a Radley's Parallel Synthesizer which was purged with argon. Aryl halide (1 equiv.) and dioxole (10 equiv.) are then added via syringe and 1.8mL of degassed *N,N*-dimethylacetamide (DMA) was added. The reaction was heated to 145°C overnight. After the reaction was judged complete by TLC or GC/MS analysis, the heat source was removed and the reaction mixture was allowed to cool. The crude mixture was diluted with ethyl acetate, filtered through a plug of celite and evaporated under reduced pressure. The crude product was then loaded onto silica gel chromatography column and purified using ethyl acetate/hexanes/benzene mixtures as the eluent.

Equation 2.8



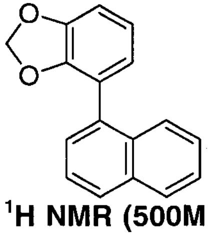
**$^1$H NMR (500MHz, CDCl$_3$, 293K, TMS):** 2.39 (3H, s), 6.00 (2H, s), 6.80 (1H, dd, J=7.5Hz & 1.5Hz), 6.90 (1H, t, J=8.0Hz), 7.04 (1H, dd, J=8.0Hz & 1.5Hz), 7.25 (2H, d, J=8.0Hz), 7.60 (2H, d, J=8.0Hz);
**$^{13}$C NMR (125MHz, CDCl$_3$, 293K, TMS):** 21.2, 100.6, 107.4, 121.1, 121.9, 127.7, 129.3, 129.4, 132.9, 137.4, 144.5, 147.8;
**IR ($\nu_{max}$/cm$^{-1}$):** 2890, 1443, 1245, 1055, 940, 766;
**HRMS** calculated for $C_{14}H_{12}O_2$ (M+): 212.0837; Found: 212.0854;
**R$_f$** = 0.21 on silica gel (5% PhH:Hexanes);

Table 2.11, Entry 1



**$^1$H NMR (500MHz, (CD$_3$)$_2$CO, 293K):** 3.90 (3H, s), 6.11 (2H, s), 6.91 (1H, dd, J=8.0Hz & 1.0Hz), 6.98 (1H, t, J=7.5Hz), 7.19 (1H, dd, J=8.0Hz & 1.5Hz), 7.91 (2H, d, J=9.0Hz), 8.08 (2H, d, J=9.0Hz);
**$^{13}$C NMR (125MHz, (CD$_3$)$_2$CO, 293K):** 50.4, 102.9, 110.2, 122.8, 123.2, 124.2, 128.4, 129.6, 131.0, 131.4, 142.3, 150.1, 167.9;
**IR ($\nu_{max}$/cm$^{-1}$):** 1717, 1635, 1453, 1252, 1058, 762;
**HRMS** calculated for $C_{21}H_{14}O_2$ (M+): 256.0736; Found: 256.0737;
**m.p.** = 125-126°C (CHCl$_3$)
**R$_f$** = 0.18 on silica gel (5% PhH:Hexanes);

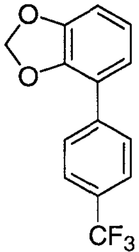
Table 2.11, Entry 2



**$^1$H NMR (500MHz, CDCl$_3$, 293K, TMS):** 5.92 (2H, s), 6.89-6.97 (3H, m), 7.43-7.54 (4H, m), 7.82 (1H, d, J=8.5Hz), 7.88 (2H, m);
**$^{13}$C NMR (125MHz, CDCl$_3$, 293K, TMS):** 100.7, 107.9, 121.6, 122.2, 124.1, 125.3, 125.9, 126.0, 126.1, 127.4, 128.3, 131.2, 133.7, 134.0, 145.3, 147.4;
There is also one overlapping carbon signal as 1 peak is missing even with prolonged scans.

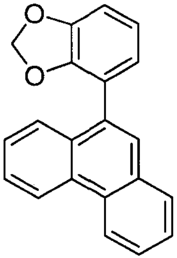
**IR** ***($v_{max}$*** **/cm$^{-1}$):** 3061, 2892, 1636, 1451, 1251, 756;
**HRMS** calculated for $C_{17}H_{12}O_2$ (M+): 248.0832; Found: 248.0822;
**m.p.** = 114-116°C ($CHCl_3$)
**R$_f$** = 0.23 on silica gel (5% PhH:Hexanes);

Table 2.11, Entry 3



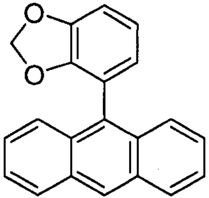
**$^1$H NMR (500MHz, CDCl$_3$, 293K, TMS):** 6.03 (2H, s), 6.86 (1H, dd, J=8.0Hz & 1.5Hz), 6.94 (1H, t, J=8.0Hz), 7.06 (1H, dd, J=8.0Hz & 1.0Hz), 7.68 (2H, d, J=8.5Hz), 7.82 (2H, d, J=8.5Hz);
**$^{13}$C NMR (125MHz, CDCl$_3$, 293K, TMS):** 100.8, 108.4, 121.0, 121.5, 122.1, 124.1 (q, J=270.8Hz), 125.4 (q, J=3.9Hz), 128.0, 129.3 (q, J=32.4Hz), 139.3, 144.8, 147.9;
**IR** ***($v_{max}$*** **/cm$^{-1}$):** 2898, 1622, 1324, 1247, 772;
**HRMS** calculated for $C_{14}H_9O_2F_3$ (M+): 266.0555; Found: 266.0551;
**m.p.** = 72-73°C ($CHCl_3$)
**R$_f$** = 0.21 on silica gel (5% PhH:Hexanes);

Table 2.11, Entry 4



**$^1$H NMR (500MHz, CDCl$_3$, 293K, TMS):** 5.91 (2H, s), 6.91-6.99 (3H, m), 7.56 (2H, m), 7.64 (2H, m), 7.76 (1H, s), 7.86 (2H, t, J=8.5Hz), 8.68 (1H, d, J=8.5Hz), 8.74 (1H, d, J=8.5Hz);
**$^{13}$C NMR (125MHz, CDCl$_3$, 293K, TMS):** 100.8, 108.0, 121.7, 122.2, 122.5, 122.9, 124.1, 126.6 (broad), 126.8 (broad), 126.8, 128.3, 128.7, 130.2, 130.3, 130.5, 131.4, 132.7, 145.4, 147.4;
There is also two overlapping carbon signal as 2 peaks are missing even with prolonged scans.
**IR** ***($v_{max}$*** **/cm$^{-1}$):** 3061, 2888, 1449, 1248, 1061, 726;
**HRMS** calculated for $C_{21}H_{14}O_2$ (M+): 298.0994; Found: 298.0997;
**m.p.** = 52-54°C ($CHCl_3$)
**R$_f$** = 0.22 on silica gel (5% PhH:Hexanes);

Table 2.11, Entry 5



**$^1$H NMR (500MHz, CDCl$_3$, 293K, TMS):** 5.88 (2H, s), 6.90 (1H, dd, J=7.0Hz & 1.5Hz), 7.02 (2H, m), 7.39 (2H, m), 7.45 (2H, m), 7.76 (2H, d, J=9.0Hz), 8.03 (2H, d, 8.5Hz), 8.50 (1H, s);
**$^{13}$C NMR (125MHz, CDCl$_3$, 293K, TMS):** 100.8, 108.1, 119.9, 121.6, 125.2, 125.2, 125.8, 126.3, 127.4, 128.5, 130.0, 130.4, 131.4, 146.1, 147.5;
**IR ($\nu_{max}$/cm$^{-1}$):** 2926, 1773, 1617, 1368, 1185, 1045, 753;
**HRMS** calculated for $C_{21}H_{14}O_2$ (M+): 298.0994; Found: 298.1014;
**m.p.** = 204-206°C (CHCl$_3$)
**R$_f$** = 0.24 on silica gel (5% PhH:Hexanes);

**Computational Analysis of Benzodioxole Arylation**

*Computational Details*

Quantum chemical[251] density functional theory[252] (DFT) calculations were performed with Becke's three parameter hybrid gradient-corrected exchange functional[253] and the gradient-corrected correlation functional of Lee, Yang and Parr,[254] commonly abbreviated as B3LYP. All calculations were performed with the Jaguar 6.0 software package.[255] The triple-zeta basis set, LACV3P**, that includes polarization functions. Frequency calculations were performed on all stationary points and the energies reported include unscaled zero-point vibrational energy corrections. A slightly smaller model system was used for the catalyst by replacing the bulky phosphine ligand used experimentally with a PH$_3$ ligand. This is a typical approach used in quantum chemical calculations to reduce computation times. The effect of the phosphine ligand is not expected to change the qualitative nature of these calculations.[256]

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[251] Ziegler, T.; Autschbach, J. Chem. Rev. **2005**, *105*, 2695.

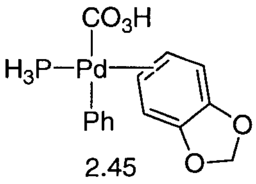
[252] (a) Hohenburg, P.; Kohn, W. *Phys. Rev. B* **1964**, *136*, 864. b) Kohn, W.; Sham, L. J. *Phys. Rev. A* **1965**, *140*, 1133.

[253] Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.

[254] Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B.* **1988**, *37*, 785.

[255] *Jaguar 6.0*; Schrodinger, LLC: Portland, Oregon, 2004

[256] This approach was recently used in similar systems : (a) Garcia-Cuadrado, D.; de Mendoza, P.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2007**, *129*, 6880 (b) Garcia-Cuadrado, D.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006**, *128*, 1066. (c) Lafrance, M.; Rowley, C. N.; Woo, T. K.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 8754.



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| P18 | -0.4107077018 | -2.8746349212 | -0.4360664281 |
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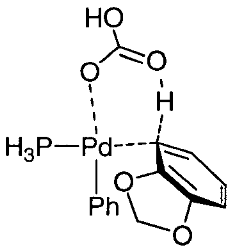

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| Pd7 | -0.5216163164 | -0.8089293587 | -0.0893038270 |
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| O11 | 0.4422943911 | 2.0560302974 | 1.7575351919 |
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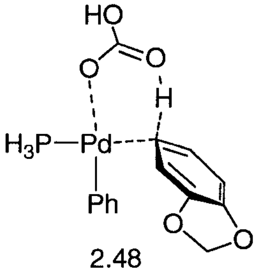

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| C4 | 2.1746392798 | -0.8050356132 | 1.1776606770 |
| C5 | 3.5669605558 | -0.7063080422 | 1.2233343994 |
| C6 | 4.2935315283 | -0.4774527598 | 0.0576880469 |
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| C14 | -0.8062793991 | 1.8321786245 | -1.4797659290 |
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| H23 | -1.3825236594 | -3.9600947029 | -0.2153770671 |
| H24 | -1.4572080378 | 1.2678256642 | -2.1396306090 |
| H25 | -0.3970862007 | 3.3569856285 | -2.9861725401 |
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| O27 | 1.5756082691 | 4.2087510128 | 0.8647409046 |
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| H31 | -1.8454058642 | 1.0559849843 | 0.4291635491 |
| H32 | -5.1036137405 | 0.3033396543 | 1.0074138872 |
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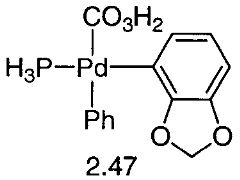

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| C4 | -0.6027794150 | -3.2775406382 | 1.2974171422 |
| C5 | -0.5911543209 | -2.5537193846 | 0.0993697407 |
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| O20 | 3.9370562064 | 0.4234751377 | 2.5468604695 |
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| O26 | 0.5903210074 | 2.7323053636 | 1.6801658864 |
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| H28 | -0.1251666629 | 4.5891228439 | 0.8294696290 |
| P29 | -2.9887838198 | -0.5574701496 | -0.0268896123 |
| H30 | -3.7483275259 | 0.6385242409 | -0.0206243186 |
| H31 | -3.5910344309 | -1.1608143790 | -1.1549807581 |
| H32 | -3.7192055746 | -1.2568669365 | 0.9614934432 |
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| H34 | 2.7007491913 | -0.4272744505 | 3.9739410986 |
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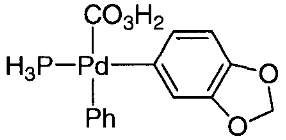

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| C4 | -0.7745645285 | -3.0967079926 | 1.3557525492 |
| C5 | -0.5625288773 | -2.4277611878 | 0.1441590781 |
| C6 | -0.3663382919 | -3.1910662526 | -1.0128650672 |
| C7 | -0.3991211460 | -4.5856616858 | -0.9618184483 |
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| H9 | -0.9731393839 | -4.9896639357 | 2.3552953244 |
| H10 | -0.9149081829 | -2.5334640291 | 2.2718854461 |
| H11 | -0.1812636256 | -2.7015894836 | -1.9624868130 |
| H12 | -0.2455847768 | -5.1582516983 | -1.8710093603 |
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| C14 | 3.2861189485 | -0.4618318219 | 1.7856517842 |
| C15 | 1.9157900415 | -0.4942422641 | 1.6458622558 |
| C16 | 1.3728672401 | -0.4569399796 | 0.3364888811 |
| C17 | 2.2581349645 | -0.4018007968 | -0.7520316319 |
| C18 | 3.6609198476 | -0.3692029140 | -0.5963907183 |
| O19 | 5.4494022012 | -0.4086317933 | 1.1220808359 |
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| P26 | -3.0540858352 | -0.5597208938 | -0.2714604225 |
| H27 | -3.8603898103 | 0.5943546806 | -0.4297024191 |
| H28 | -3.5398700759 | -1.2892458842 | -1.3812418808 |
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| H30 | 1.2837969240 | -0.5616575283 | 2.5226415284 |
| O31 | 4.0270752117 | -0.5123807574 | 2.9443901279 |
| C32 | 5.3824091078 | -0.2823446454 | 2.5469245350 |
| H33 | 5.6807259145 | 0.7335731215 | 2.8370900489 |
| H34 | 6.0276226700 | -1.0316559639 | 3.0076980116 |
| O35 | 1.2962203747 | 2.5535125318 | -0.0274935275 |
| H36 | 1.4921074195 | 1.5838465521 | -0.0198534453 |

# *Chapter 4 – Azine N-Oxide*

## Starting Materials

Many azine *N*-oxides are commercially available. In cases where it is economically favorable to purchase the azine and perform oxidation, one of the following three procedures is recommended.

**Oxidation Procedure A:** Prefered method for preparation using an adapted methyltrioxorhenium oxidation protocol first reported by Sharpless and co-workers.[257] Easily scalable with limited by products. An adapted procedure for diazine oxidation is presented lower.

The azine is dissolved in reagent grade $CH_2Cl_2$ (2.5M). This this mixture is added $MeReO_3$ (1-4mol%) which usually results in a significant color change to deep yellow. This solution is then capped with a rubber septa which is pierced with a small needle as a vent and placed in an ice bath. To the cold solution is added dropwize a 50w% aqueous solution of $H_2O_2$ (2 equiv.). Once all peroxyde has been added, the reaction is allowed to warm to room temperature where it is stirred for 12-24h. After consumption of starting material, a small amount of $MnO_2$ (5-10mg) is added to destroy unreacted peroxyde. After stirring this solution of 1-2 hours (until bubbling stops) the mixture is poured into an extraction funnel where the phases are seperated. The aqueous phase is washed with two volumes of $CH_2Cl_2$ and the organic are combined, dried with $MgSO_4$, filtered and concentrated under reduced pressure. The *N*-oxides were then purified via silica gel column chromatography using 5%MeOH/ $CH_2Cl_2$ as the eluent to afford the corresponding *N*-oxide in 60-90% yield.

**Oxidation Procedure B:** Produces large amounts of waste *m*-chlorobenzoic acid, not recommended for large scale. Compatible with diazines.

Azine (1 eq.) and *m*-chloroperoxybenzoic acid (1.2 eq.) are dissolved in reagent grade dichloroethane (0.5M). The reaction is allowed to stir at room temperature overnight from which precipitates a white solid (*m*-chlorobenzoic acid). The solvent is then evaporated under reduced pressure and the crude reaction mixture is purified by column chromatography on silica gel with EtOAc/MeOH or $CH_2Cl_2$/MeOH mixtures.

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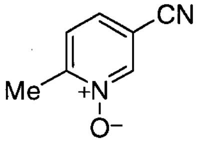
[257] Coperet, C.; Adolfsson, H.; Khuong, T.-A. V.; Yudin, A. K.; Sharpless, K. B. *J. Org. Chem.*; **1998**; *63*, 1740

**Oxidation Procedure C:** Caution, this reaction is in water. Azines with limited solubility in water showed diminished reactivity in these systems. Also, azine *N*-oxides which were highly water soluble were difficult to isolate.

Azine (1 eq.) is dissolved in acetone (2.5M) in a three neck round bottom flask and phosphate buffer is added (0.25M). One neck is fitted with an addition funnel carrying oxone (2.4 eq.) in distilled water (0.3M). A second neck is fitted with a solution of 2M NaOH. Both solutions are added dropwise simultaneously at room temperature and the pH of the reaction in monitored and kept between 7-8. Typically reactions are complete within 3 hours. The mixture is extracted twice with $CH_2Cl_2$ and once with $CHCl_3$. The organic layer is then dried over $MgSO_4$, filtered and evaporated under reduced pressure to afford the pyridine *N*-oxide, often in analytically pure form.

Table 4.3, Entry 3

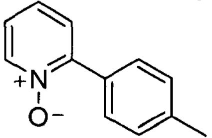


**$^1$H NMR (400MHz, $CDCl_3$, 293K, TMS):** 2.58 (3H, s), 7.42 (2H, s, br), 8.51 (1H, s);
**$^{13}$C NMR (100MHz, $CDCl_3$, 293K, TMS):** 18.2, 110.4, 114.3, 127.0, 127.1, 141.6, 154.3;
**IR** ***(*$\nu_{max}$ */cm$^{-1}$)*:** 3117, 2249, 1271, 1005, 831;;
**HRMS** calculated for $C_7H_6N_2O$ (M+) 134.0480; Found: 134.0473;
**$R_f$** = 0.18 on silica gel (3% MeOH, 10% Acetone in DCM);
**m.p.** ($CH_2Cl_2$): 136-138 °C

**General Comment:**
2-arylpyridine *N*-oxides can be very insoluble and special care should be taken when trying to purify these compounds via silica gel chromatography. In some instances the use of MeOH/Acetone/DCM mixtures was necessary to prevent the products from crashing during chromatography. We find that at least 0.5-2% volume methanol is sufficient to prevent this problem.

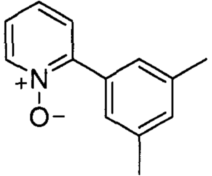
**General Procedure:**
$K_2CO_3$ (2 equiv.), $P^tBu_3$ – $HBF_4$ (0.15 equiv.), $Pd(OAc)_2$ (0.05 equiv.) and pyridine *N*-oxide (4 equiv.) are weighed to air and placed in a round bottom flask with a magnetic stir bar (if the aryl halide is a solid, it is also added). The flask is fitted with a Teflon sleeve and reflux condenser capped with rubber septa. The reaction is evacuated and backfilled with argon (x3). The aryl halide (1 equiv.) is then added via syringe as a stock solution in toluene (0.3M). The mixture is then heated to 110°C overnight (10-15 hours). The reaction mixture is filtered through celite (wash with MeOH/$Me_2CO$ and DCM) then evaporated under reduced pressure and loaded onto a short (6.5cm long x 3cm diameter for 0.6mmol scale) silica gel column for chromatography typically using DCM/Acetone/MeOH mixtures (depending on solubility of products).

Table 4.1, Entry 1



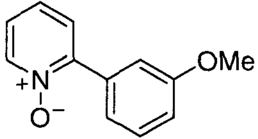
**$^1$H NMR (500MHz, $(CD_3)_2O$, 293K):** 2.38 (3H, s), 7.27 (2H, d, J=8.5Hz), 7.33 (2H, m), 7.56 (1H, m), 7.81 (2H, d, J=8.5Hz), 8.25 (1H, m);
**$^{13}$C NMR (125MHz, $(CD_3)_2O$, 293K):** 22.3, 126.1, 126.5, 128.9, 130.3, 131.0, 132.2, 140.9, 142.1;
There is an overlapping carbon signal as 1 peak is missing even with prolonged scans.
**IR ($v_{max}$ /cm$^{-1}$):** 2922, 1614, 1480, 1460, 1228, 768;
**HRMS** calculated for $C_{12}H_{11}NO$ (M+) 185.0841; Found: 185.0813;
**m.p.** : 129-131°C (Acetone)

Table 4.1, Entry 2



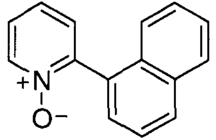
**$^1$H NMR (300MHz, $CDCl_3$, 293K, TMS):** 2.37 (6H, s), 7.08 (1H, s), 7.19 (1H, dd, J=6.9Hz & 2.0Hz), 7.27 (1H, dd, J=7.5 & 1.2Hz), 7.36-7.39 (3H, m), 8.31 (1H, dd, J=6.3Hz & 1.2Hz);
**$^{13}$C NMR (75MHz, $CDCl_3$, 293K, TMS):** 21.3, 124.3, 125.6, 126.9, 127.5, 131.2, 132.4, 137.8, 140.4, 149.7;
**IR ($v_{max}$ /cm$^{-1}$):** 2917, 1602, 1492, 1407, 1237, 1116, 769;
**HRMS** calculated for $C_{13}H_{13}NO$ (M+) 199.0997; Found: 199.0973;

Table 4.1, Entry 6



**$^1$H NMR (500MHz, $(CD_3)_2O$, 293K):** 3.83 (3H, s), 7.01 (1H, m), 7.33-7.42 (4H, m), 7.53 (1H, m), 7.58 (1H, m), 8.26 (1H, m);
**$^{13}$C NMR (75MHz, $(CD_3)_2O$, 293K):** 55.6, 115.6, 115.7, 122.3, 125.2, 125.9, 128.2, 129.8, 135.4, 141.2 (br), 160.1;
There is an overlapping carbon signal as 1 peak is missing even with prolonged scans.
**IR ($v_{max}$ /cm$^{-1}$):** 3077, 3959, 1599, 1580, 1476, 1240, 1026, 768;
**HRMS** calculated for $C_{12}H_{11}NO_2$ (M+) 201.0790; Found: 201.0765;

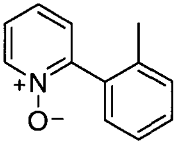
Table 4.1, Entry 9



**$^1$H NMR (500MHz, $(CD_3)_2O$, 293K):** 7.43 (1H, dt, J=8.0Hz & J=1.0Hz), 7.46 (2H, m), 7.49-7.54 (4H, m), 7.59 (1H, m), 7.97 (1H, d, J=8.0Hz), 8.02 (1H, d, J=7.5Hz), 8.33 (1H, d, J=7.0Hz)

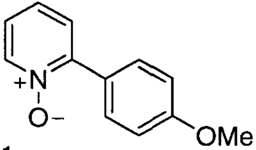
**$^{13}$C NMR (125MHz, $(CD_3)_2O$, 293K):** 124.8, 126.3, 126.8, 126.8, 126.9, 127.2, 128.6, 129.2, 129.6, 130.4, 132.1, 133.3, 134.3, 140.8, 150.0;
**IR *($\nu_{max}$* /cm$^{-1}$):** 3058, 1655, 1488, 1420, 1238, 774;
**HRMS** calculated for $C_{15}H_{11}NO$ (M+) 221.0841; Found: 221.0822;
**m.p.** : 156-159°C (Acetone)

Table 4.1, Entry 10



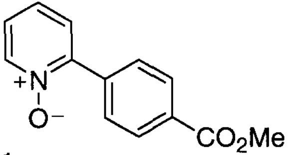
**$^1$H NMR (500MHz, $(CD_3)_2O$, 293K):** 2.20 (3H, s), 7.22 (1H, dd, J=7.0Hz & 1.5Hz), 7.25-7.29 (2H, m), 7.33-7.43 (4H, m), 8.26 (1H, d, J=6.5Hz);
**$^{13}$C NMR (75MHz, $CDCl_3$, 293K, TMS):** 20.5, 125.6, 127.3, 127.4, 129.7, 130.8, 131.3, 131.4, 135.9, 139.9, 141.5 (br);
There is an overlapping carbon signal as 1 peak is missing even with prolonged scans.
**IR *($\nu_{max}$* /cm$^{-1}$):** 3065, 1476, 1418, 1246, 1015, 764;
**HRMS** calculated for $C_{12}H_{11}NO$ (M+) 185.0841; Found: 185.0824;
**m.p.** : 108-110°C (Acetone)

Table 4.1, Entry 11



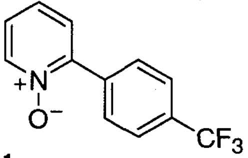
**$^1$H NMR (300MHz, $(CD_3)_2O$, 293K):** 3.85 (3H, s), 7.01 (2H, d, J=9.3Hz), 7.27-7.35 (2H, m), 7.56 (1H, dd, J=7.8Hz & J=3.3Hz), 7.92 (2H, d, J=8.7Hz), 8.24 (1H, m) ;
**$^{13}$C NMR (75MHz, $(CD_3)_2O$, 293K):** 56.6, 115.0, 126.1, 126.2, 127.2, 128.6, 132.6, 142.1 (br), 162.3;
There is an overlapping carbon signal as 1 peak is missing even with prolonged scans.
**IR *($\nu_{max}$* /cm$^{-1}$):** 2839, 1609, 1480, 1251, 1179, 833, 766;
**HRMS** calculated for $C_{12}H_{11}NO_2$ (M+) 201.0790; Found: 201.0790;
**m.p.** : 121-123°C (Acetone)

Table 4.1, Entry 12



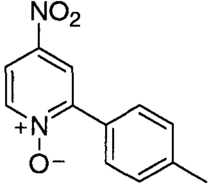
**$^1$H NMR (300MHz, $CDCl_3$, 293K, TMS):** 3.94 (3H, s), 7.25-7.37 (2H, m), 7.46 (1H, dd, J=7.5Hz & 2.4Hz), 7.92 (2H, d, J=8.4Hz), 8.14 (2H, d, J=8.1Hz), 8.35 (1H, dd, J=6.3Hz & 1.2Hz);
**$^{13}$C NMR (75MHz, $CDCl_3$, 293K, TMS):** 52.3, 125.2, 125.8, 127.5, 129.3, 129.5, 136.9, 140.6, 148.3,166.5;
There is an overlapping carbon signal as 1 peak is missing even with prolonged scans.
**IR *($\nu_{max}$* /cm$^{-1}$):** 3066, 1716, 1602, 1436, 1278, 1247, 1103, 845;
**HRMS** calculated for $C_{13}H_{11}NO_3$ (M+) 229.0739; Found: 229.0717;
**m.p.** : 200-202°C ($CHCl_3$)

Table 4.1, Entry 13



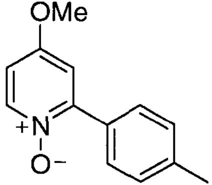
**$^1$H NMR (500MHz, CDCl$_3$, 293K, TMS):** 7.29 (1H, td, J=7.0Hz & 2.0Hz), 7.35 (1H, td, J=7.5Hz & 1.5Hz), 7.45 (1H, dd, J=8.0Hz & 2.0Hz), 7.74 (2H, d, J=8.5Hz), 7.95 (2H, d, J=8.0Hz), 8.35 (1H, dd, J=6.5Hz & 1.0Hz);
**$^{13}$C NMR (125MHz, CDCl$_3$, 293K, TMS):** 123.9 (q, J=272.1Hz), 125.3 (q, J=3.8Hz), 125.4, 125.9, 127.4, 129.8, 131.4 (q, J=27.9Hz), 136.1, 140.6, 147.9;
**IR ($\nu_{max}$/cm$^{-1}$):** 3049, 1614, 1432, 1336, 1246, 1106, 835, 758;
**HRMS** calculated for $C_{12}H_8NOF_3$ (M+) 239.0558; Found: 239.0532;
**m.p.** : 127-129°C (CHCl$_3$)

Table 4.2, Entry 11

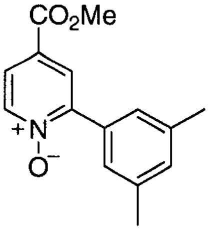


**$^1$H NMR (500MHz, (CD$_3$)$_2$O, 293K):** 2.40 (3H, s), 7.33 (2H, d, J=7.5Hz), 7.81 (2H, d, J=8.0Hz), 8.14 (1H, dd, J=7.5Hz & 3.5Hz), 8.32 (1H, d, J=3.5Hz), 8.44 (1H, d, J=7.5Hz);
**$^{13}$C NMR (500MHz, (CD$_3$)$_2$O, 293K):** 22.4, 120.6, 123.1, 130.4, 130.6, 131.0, 142.3, 143.3 (broad), 151.3;
There is an overlapping carbon signal as 1 peak is missing even with prolonged scans.
**IR ($\nu_{max}$/cm$^{-1}$):** 2950, 1711, 1585, 1530, 1354, 1275, 1231, 1125, 747;
**HRMS** calculated for $C_{12}H_{10}N_2O_3$ (M+) 230.0691; Found: 230.0688;
**m.p.** : 120-122°C (Acetone)

Table 4.1, Entry 12



**$^1$H NMR (500MHz, (CD$_3$)$_2$O, 293K):** 2.38 (3H, s), 3.93 (3H, s), 6.95 (1H, dd, J=7.0Hz & J=3.5Hz), 7.12 (1H, d, J=3.5Hz), 7.26 (2H, d, J=8.0Hz), 7.86 (2H, d, J=8.5Hz), 8.13 (1H, d, J=6.5Hz);
**$^{13}$C NMR (125MHz, (CD$_3$)$_2$O, 293K):** 22.3, 57.6, 113.1, 113.6, 128.3, 130.2, 131.2, 132.5, 141.0, 142.7, 158.2;
**IR ($\nu_{max}$/cm$^{-1}$):** 2921, 1625, 1482, 1202, 1014, 777;
**HRMS** calculated for $C_{13}H_{13}NO_2$ (M+) 215.0946; Found: 215.0931;
Table 4.2, Entry 1



Purified with 5% Acetone in DCM (Rf~0.25) – light yellow solid

**$^1$H NMR (400MHz, CDCl$_3$, 293K, TMS):** 2.38 (6H, s), 3.95 (1H, s), 7.12 (1H, br), 7.38 (2H, s), 7.78 (1H, dd, J=6.7Hz & 2.4Hz), 8.01 (1H, d, J=2.7Hz), 8.32 (1H, d, J=7.1Hz);

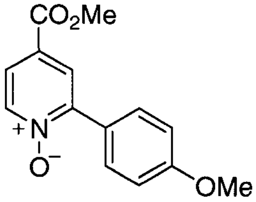
**$^{13}$C NMR (100MHz, CDCl$_3$, 293K, TMS):** 21.3, 52.7, 124.2, 126.1, 126.8, 127.7, 131.7, 138.0, 140.6, 149.9, 150.7, 164.2;

**IR (*$v_{max}$*/cm$^{-1}$):** 2951, 1721, 1269, 1238, 1113, 768;

**HRMS** calculated for $C_{15}H_{15}NO_3$ (M+) 257.1052; Found: 257.1067;

**m.p.** (CHCl$_3$): 141-143 °C

Table 4.2, Entry 2



Purified with 5% Acetone in DCM (Rf~0.25) – tan solid

**$^1$H NMR (400MHz, CDCl$_3$, 293K, TMS):** 3.87 (3H, s), 3.95 (3H, s), 7.02 (2H, d, J=9.0), 7.75 (1H, dd, J=6.7Hz & 2.4Hz), 7.82 (2H, d, J=9.0Hz), 8.04 (1H, d, J=62.4Hz), 8.31 (1H, d, J=6.7Hz);

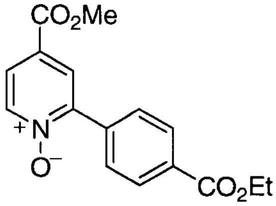
**$^{13}$C NMR (100MHz, CDCl$_3$, 293K, TMS):** 52.8, 55.4, 113.8, 123.7, 124.0, 126.2, 127.2, 130.8, 140.7, 149.1, 160.9, 164.3;

**IR (*$v_{max}$*/cm$^{-1}$):** 2953, 1722, 1305, 1256, 1113, 768;

**HRMS** calculated for $C_{14}H_{13}NO_4$ (M+) 259.0845; Found: 259.0853;

**m.p.** (CHCl$_3$): 137-139 °C

Table 4.2, Entry 7



Purified with 6% Acetone in DCM (Rf~0.25) – white solid

**$^1$H NMR (400MHz, CDCl$_3$, 293K, TMS):** 1.42 (3H, t), 3.96 (3H, s), 4.42 (2H, q, J=7.2Hz), 7.85 (1H, dd, J=6.8Hz & 2.5Hz), 7.92 (2H, d, J=8.5Hz), 8.07 (1H, d, J=2.5Hz), 8.14 (2H, d, J=8.6Hz), 8.36 (1H, d, J=6.8Hz);

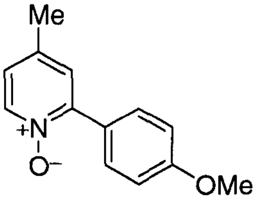
**$^{13}$C NMR (100MHz, CDCl$_3$, 293K, TMS):** 14.3, 52.8, 61.2, 125.0, 126.2, 127.7, 129.2, 129.5, 131.6, 135.9, 140.8, 148.4, 163.9, 165.8;

**IR (*$v_{max}$*/cm$^{-1}$):** 3420, 1721, 1273, 1243, 1106, 722;

**HRMS** calculated for $C_{16}H_{15}NO_5$ (M+) 301.0950; Found: 301.0930;

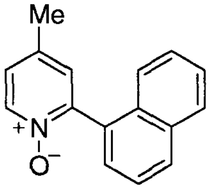
**m.p.** (CHCl$_3$): 116-118 °C

Table 4.2, Entry 3



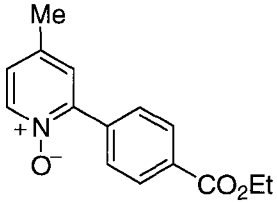
Purified with 2% Acetone, 3% MeOH in DCM (Rf~0.25) – tan oil
**$^1$H NMR (400MHz, $CDCl_3$, 293K, TMS):** 2.35 (3H, s), 3.84 (3H, s), 6.99 (3H, m), 7.22 (1H, d, J=2.3Hz), 7.80 (2H, d, J=8.9Hz), 8.19 (1H, d, J=6.6Hz);
**$^{13}$C NMR (100MHz, $CDCl_3$, 293K, TMS):** 29.0, 55.3, 113.6, 124.8, 124.9, 127.6, 130.8, 137.5, 139.8, 148.1, 160.5;
**IR (*$v_{max}$* /cm$^{-1}$):** 3384, 1607, 1476, 1251, 1180, 785;
**HRMS** calculated for $C_{13}H_{13}NO_2$ (M+) 215.0946; Found: 215.0955;

Table 4.2, Entry 4



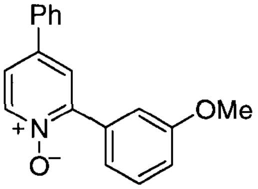
Purified with 5% MeOH in DCM (Rf~0.25) – tan solid
**$^1$H NMR (400MHz, $CDCl_3$, 293K, TMS):** 2.36 (3H, s), 7.13 (1H, dd, J=6.6Hz & 2.5Hz), 7.21 (1H, d, J=2.5Hz), 7.50 (5H, m), 7.88 (1H, d, J=8.2Hz), 7.94 (1H, d, J=8.1Hz), 8.28 (1H, d, J=6.7Hz);
**$^{13}$C NMR (100MHz, $CDCl_3$, 293K, TMS):** 29.1, 125.3, 125.4, 126.1, 126.2, 126.8, 127.7, 128.5, 129.4, 130.0, 131.0, 131.3, 133.4, 136.9, 139.6, 148.9;
**IR (*$v_{max}$* /cm$^{-1}$):** 3395, 1478, 1460, 1235, 821, 784;
**HRMS** calculated for $C_{16}H_{13}NO_1$ (M+) 235.0997; Found: 235.0984;
**m.p.** ($CHCl_3$): 135-137 °C

Table 4.2, Entry 8



Purified with 3% Acetone, 4% MeOH in DCM (Rf~0.25) – white solid
**$^1$H NMR (400MHz, $CDCl_3$, 293K, TMS):** 1.41 (3H, t), 2.39 (3H, s), 4.41 (2H, q), 7.07 (1H, dd, J=6.7Hz & 2.2Hz), 7.25 (1H, d, J=2.5Hz), 7.91 (2H, d, J=8.6Hz), 8.13 (2H, d, J=8.6), 8.22 (1H, d, J=6.7Hz);
**$^{13}$C NMR (100MHz, $CDCl_3$, 293K, TMS):** 14.3, 29.1, 61.1, 125.9, 128.0, 129.3, 129.4, 131.1, 137.0, 137.3, 139.9, 147.5, 166.1;
**IR (*$v_{max}$* /cm$^{-1}$):** 3391, 1715, 1277, 1246, 1125, 771;
**HRMS** calculated for $C_{15}H_{15}NO_3$ (M+) 257.1052; Found: 257.1045;
**m.p.** ($CHCl_3$): 155-157 °C

Table 4.2, Entry 10



Purified with 25% Acetone in DCM (Rf~0.25) – light yellow oil

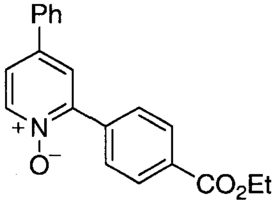
**$^1$H NMR (400MHz, $CDCl_3$, 293K, TMS):** 3.85 (3H, s), 7.00 (1H, d, J=7.5Hz), 7.43 (7H, m), 7.62 (3H, m), 8.35 (1H, d, J=6.8Hz);

**$^{13}$C NMR (100MHz, $CDCl_3$, 293K, TMS):** 27.1, 29.7, 55.4, 114.6, 115.8, 121.7, 122.2, 125.0, 126.4, 129.0, 129.3, 129.4, 134.0, 136.4, 138.4, 140.5, 149.0 159.4;

**IR *($v_{max}$/cm$^{-1}$)*:** 3060, 1470, 1251, 1212, 1035, 765;

**HRMS** calculated for $C_{18}H_{15}NO_2$ (M+) 277.1103; Found: 277.1104;

Table 4.2, Entry 9



Purified with 20% Acetone in DCM (Rf~0.25) – tan solid

**$^1$H NMR (400MHz, $CDCl_3$, 293K, TMS):** 1.41 (3H, t), 4.39 (2H, q, J=7.2Hz), 7.47 (4H, m), 7.61 (2H, d, J=7.2Hz), 7.66 (1H, d, J=2.7Hz), 7.94 (2H, d, J=8.3Hz), 8.15 (2H, d, J=8.4Hz), 8.37 (1H, d, J=6.9Hz);

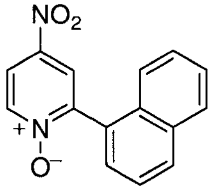
**$^{13}$C NMR (100MHz, $CDCl_3$, 293K, TMS):** 14.3, 61.2, 122.8, 125.0, 126.4, 129.2, 129.3, 129.4, 129.5, 131.3, 136.2, 136.9, 138.5, 140.5, 148.1, 166.0;

**IR *($v_{max}$/cm$^{-1}$)*:** 3396, 1713, 1470, 1276, 1106, 762;

**HRMS** calculated for $C_{20}H_{17}NO_3$ (M+) 319.1208; Found: 319.1192;

**m.p.** ($CHCl_3$): 163-165 °C

Table 4.2, Entry 5



Purified with 100% DCM (Rf~0.25) - yellow solid

**$^1$H NMR (400MHz, $CDCl_3$, 293K, TMS):** 7.40 (1H, d, J=8.2Hz), 7.54 (4H, m), 7.93 (1H, d, J=7.4Hz), 8.02 (1H, d, J=8.1Hz), 8.16 (1H, dd, J=7.2Hz & 3.2Hz), 8.31 (1H, d, J=3.1Hz), 8.42 (1H, d, J=7.3Hz);

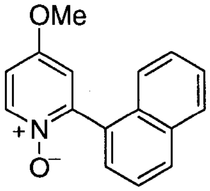
**$^{13}$C NMR (100MHz, $CDCl_3$, 293K, TMS):** 119.6, 123.1, 124.6, 125.3, 126.7 127.3, 128.2, 128.9, 129.0, 130.4, 131.2, 133.4, 141.0, 141.6, 151.0;

**IR *($v_{max}$/cm$^{-1}$)*:** 1642, 1339, 1285, 1128, 898;

**HRMS** calculated for $C_{15}H_{10}N_2O_3$ (M+) 266.0691; Found: 266.0681;

**m.p.** ($CHCl_3$): 183-185 °C

Table 4.2, Entry 6



Purified with 5% MeOH in DCM (Rf~0.25)

**$^1$H NMR (400MHz, CDCl$_3$, 293K, TMS):** 3.83 (3H, s), 6.91 (2H, m) 7.52 (5H, m), 7.90 (1H, d, J=7.1Hz), 7.95 (1H, d, J=8.0Hz), 8.30 (1H, d, J=7.2Hz);

**$^{13}$C NMR (100MHz, CDCl$_3$, 293K, TMS):** 56.1, 111.7, 113.7, 125.2, 125.4, 126.3, 126.9, 127.6, 128.5, 130.1, 130.8, 131.3, 133.4, 140.9, 150.2, 157.1;

**IR (*$\nu_{max}$*/cm$^{-1}$):** 3377, 1484, 1421, 1219, 1028, 782;

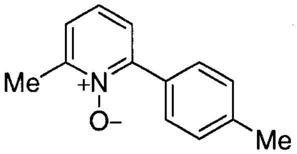
**HRMS** calculated for $C_{16}H_{13}NO_2$ (M+) 251.0946; Found: 251.0944;

**2-Substituted Pyridine *N*-Oxides**

**General Procedure:**

Pd(OAc)$_2$ (5 mol%), P$^t$Bu$_3$·HBF$_4$ (6 mol%), potassium carbonate powder (K$_2$CO$_3$, 1.5 equiv.), aryl halide (1 equiv.) and proper azine *N*-oxide (1.1-4 equiv.) are weighed to air and placed inside the flask. The flask is then fitted with a reflux condenser which is capped with a rubber septum. The whole setup is then evacuated under vacuum and refilled with Argon four times. Toluene (0.15M) is then added under a steady flow of argon. After addition, the reaction is immersed in the oil bath. Stirring is commenced and the heating source is turned on (set to 125°C). The reaction is left stirring for 12-18 hours (overnight), then allowed to cool, diluted with DCM and filtered over celite. The residues are then purified using silica gel chromatography.

Table 4.3, Entry 1



Obtained in 54% yield as a tan solid.

**$^1$H NMR (500MHz, CDCl$_3$, 293K, TMS:** 2.41 (3H, s), 2.57 (3H, s), 7.18 (1H, t, J=7.8Hz), 7.22 (1H, dd, J=7.8Hz and 1.9Hz), 7.26-7.31 (3H, m), 7.70 (2H, d, J=8.3Hz);

**$^{13}$C NMR (100MHz, CDCl$_3$, 293K, TMS):** 18.7, 21.4, 124.6, 124.8 (br), 128.8, 129.3, 130.5, 139.3, 149.5, 149.8;

1 overlaping signal as one peak is missing even with prolonged scans.

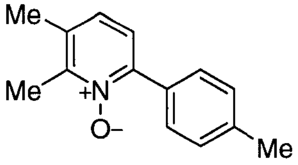
**IR (*$\nu_{max}$*/cm$^{-1}$):** 3040, 1729, 1374, 1225, 757;

**HRMS** calculated for $C_{13}H_{13}NO$ (M+) 199.0997; Found: 199.0982;

**m.p.** : 102-104 °C (CHCl$_3$)

**Rf:** 0.21 (2%MeOH, 10% Me$_2$CO, DCM)

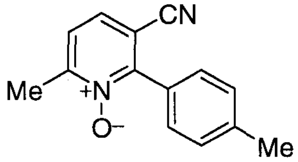
Table 4.3, Entry 2



Obtained in 34% yield as a off-white solid.

**$^1$H NMR (500MHz, CDCl$_3$, 293K, TMS:** 2.37, (3H, s), 2.40 (3H, s), 2.55 (3H, s), 7.07 (1H, d, J=8.3Hz), 7.17 (1H, d, J=8.3Hz), 7.25 (2H, d, J=8.3Hz), 7.66 (2H, d, J=8.3Hz);
**$^{13}$C NMR (100MHz, CDCl$_3$, 293K, TMS):** 14.4, 19.7, 21.4, 123.3, 126.5, 128.7, 129.3, 130.9, 133.1, 139.0, 147.0, 148.9;
**IR** ***(ν$_{max}$*** **/cm$^{-1}$):** 2925, 1490, ;
**HRMS** calculated for $C_{14}H_{15}NO$ (M+) 213.1154; Found: 213.1164;
**m.p.** : 117-119 °C (CHCl$_3$)
**Rf:** 0.19 (2%MeOH, 10% Me$_2$CO, DCM)

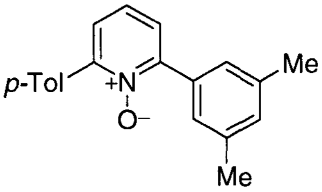
Table 4.3, Entry 3



Obtained in 74% yield as a white solid.

**$^1$H NMR (500MHz, CDCl$_3$, 293K, TMS:** 2.42 (3H, s), 2.59 (3H, s), 7.33-7.36 (3H, m), 7.47 (1H, d, J=8.1Hz), 7.53 (2H, d, J=8.2Hz);
**$^{13}$C NMR (100MHz, CDCl$_3$, 293K, TMS):** 19.0, 21.6, 110.9, 115.4, 125.1, 126.7, 127.4, 129.3, 129.6, 141.0, 152.5, 154.6, ;
**IR** ***(ν$_{max}$*** **/cm$^{-1}$):** 2919, 2231, 1348, 1269, 815;
**HRMS** calculated for $C_{14}H_{12}N_2O$ (M+) 224.0950; Found: 224.0943;
**m.p.** : 137-139 °C (CH$_2$Cl$_2$)
**Rf:** 0.20 (1%MeOH, 5% Me$_2$CO, DCM)

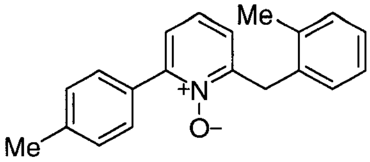
Table 4.3, Entry 5



Obtained in 74% yield as a yellow solid.

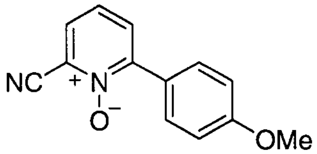
**$^1$H NMR (500MHz, CDCl$_3$, 293K, TMS:** 2.36 (6H, s), 2.40 (3H, s), 7.06 (1H, s), 7.25-7.30 (3H, m), 7.34-7.38 (2H, m), 7.24 (2H, s, br), 7.74 (2H, d, J=8.2Hz);
**$^{13}$C NMR (100MHz, CDCl$_3$, 293K, TMS):** 21.3, 21.4, 124.8, 125.8, 125.8, 127.2, 128.7, 129.5, 130.5, 130.9, 133.3, 137.6, 139.4, 150.0, 150.3;
**IR** ***(ν$_{max}$*** **/cm$^{-1}$):** 2916, 1362, 1245, 780;
**HRMS** calculated for $C_{20}H_{19}NO$ (M+) 289.1467; Found: 289.1456;
**m.p.** : 138-140 °C (CH$_2$Cl$_2$)
**Rf:** 0.27 (0.5%MeOH, 1% Me$_2$CO, DCM)

Table 4.3, Entry 4



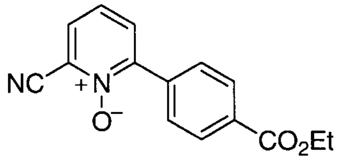
Obtained in 77% yield as a yellow solid.
**$^1$H NMR (400MHz, $CDCl_3$, 293K, TMS):** 2.23 (3H, s), 2.41 (3H, s), 4.29 (2H, s), 6.63 (1H, dd, J=7.1Hz & 2.1Hz), 7.10 (1H, t, J=7.8Hz), 7.19-7.26 (4H, m), 7.27-7.31 (3H, m), 7.73 (2H, d, J=8.2Hz);
**$^{13}$C NMR (100MHz, $CDCl_3$, 293K, TMS):** 19.4, 21.4., 35.0, 123.4, 124.6, 124.7, 126.5, 127.4, 128.8, 129.4, 130.4, 130.6, 130.7, 135.1, 137.3, 139.4, 149.4, 151.9;
**IR *($\nu_{max}$* /cm$^{-1}$):** 3019, 2921, 1479, 1378, 1254, 770;
**HRMS** calculated for $C_{20}H_{19}NO$ (M+) 289.1467; Found: 289.1445;
**m.p.** : 99-100°C ($CHCl_3$)
**Rf:** 0.2 (20% EtOAc, Petroleum Ether)

Table 4.3, Entry 7



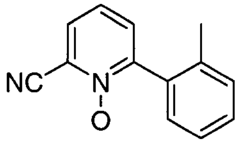
Purified with 1.5% Acetone in DCM (Rf~0.25) – light yellow solid
**$^1$H NMR (400MHz, $CDCl_3$, 293K, TMS):** 3.85 (3H, s), 6.97 (2H, d, J=8.9Hz), 7.33 (1H, dd, J=16.0Hz & 7.9Hz), 7.58 (1H, dd, J=7.8Hz & 2.0Hz), 7.62 (1H, dd, J=8.0Hz & 2.1Hz), 7.80 (2H, d, J=8.9Hz);
**$^{13}$C NMR (100MHz, $CDCl_3$, 293K, TMS):** 55.4, 112.5, 113.8, 122.9, 124.7, 126.8, 129.4, 129.8, 130.8, 149.9, 161.2;
**IR *($\nu_{max}$* /cm$^{-1}$):** 3073, 1611, 1379, 1262, 1183, 783;
**HRMS** calculated for $C_{13}H_{10}N_2O_2$ (M+) 226.0742; Found: 226.0723;
**m.p.** ($CHCl_3$): 146-148 °C

Table 4.3, Entry 6



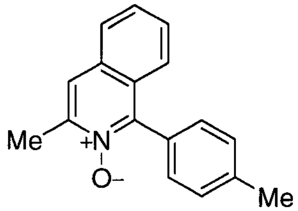
Purified with 1% Acetone in DCM (Rf~0.25) – light yellow solid
**$^1$H NMR (400MHz, $CDCl_3$, 293K, TMS):** 1.42 (3H, t, J=14.3Hz & 7.2Hz), 4.42 (2H, q, J=7.2Hz), 7.40 (1H, m), 7.68 (2H, m), 7.87 (2H, d, J=8.4Hz), 8.13 (2H, d, J=8.4Hz);
**$^{13}$C NMR (100MHz, $CDCl_3$, 293K, TMS):** 14.3, 61.4, 112.1, 124.6, 127.1, 129.2, 129.5, 130.3, 130.6, 132.1, 134.9, 149.4, 165.8;
**IR *($\nu_{max}$* /cm$^{-1}$):** 3074, 1711, 1378, 1281, 1105, 769;
**HRMS** calculated for $C_{15}H_{12}N2O_3$ (M+) 268.0848; Found: 268.0854;
**m.p.** ($CHCl_3$): 151-153 °C.

Table 4.3, Entry 8



Purified with 0.2% Acetone in DCM (Rf~0.25)
**$^1$H NMR (400MHz, $CDCl_3$, 293K, TMS):** 2.21 (3H, s), 7.21 (1H, dd, J=7.3Hz & 0.8Hz), 7.32 (4H, m), 7.49 (1H, dd, J=7.9Hz & 2.2Hz), 7.66 (1H, dd, J=7.8Hz & 2.1Hz);
**$^{13}$C NMR (100MHz, $CDCl_3$, 293K, TMS):** 19.5, 112.2, 124.0, 126.0, 126.4, 129.4, 130.1, 130.3, 130.5, 131.0, 131.1, 137.9, 152.0;
**IR ($\nu_{max}$/cm$^{-1}$):** 3067, 1470, 1380, 1270, 1246, 761;
**HRMS** calculated for $C_{13}H_{10}N_2O$ (M+) 210.0793; Found: 210.0781;
**m.p.** ($CHCl_3$): 124-126 °C

Table 4.3, Entry 10

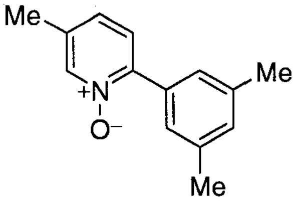


Obtained in 98% yield as a white solid. Using only 1.1 eq. of the *N*-oxide.
**$^1$H NMR (500MHz, $CDCl_3$, 293K, TMS:** 2.47 (3H, s), 2.68 (3H, s), 7.37-7.41 (5H, m), 7.44 (1H, d, J=8.3Hz), 7.50 (1H, td, J=7.3Hz & J=1.2Hz), 7.67 (1H, s), 7.72 (1H, d, J=7.8Hz);
**$^{13}$C NMR (100MHz, $CDCl_3$, 293K, TMS):** 18.3, 21.5, 122.2, 125.6, 126.0, 127.7, 127.9, 128.5, 128.7, 128.9, 129.4, 130.0, 139.0, 146.2, 146.4;
**IR ($\nu_{max}$/cm$^{-1}$):** 3050, 1329, 1292, 1212, 1109, 811;
**HRMS** calculated for $C_{17}H_{15}NO$ (M+) 249.1154; Found: 249.1146;
**m.p.** : 168-170 °C ($CHCl_3$)
**Rf:** 0.20 (1.5%MeOH, 8.5% $Me_2CO$, DCM)

### Regioselectivity with 3-Substituted Pyridine *N*-oxide

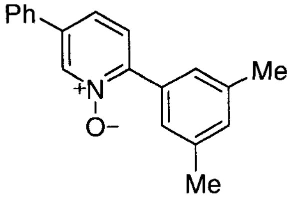
$Pd(OAc)_2$ (0.0075mmol), ligand (0.009mmol), $K_2CO_3$ (0.225mmol) and appropriate pyridine *N*-oxide (0.45mmol) are weighed to air and placed in a 10mL Radley's test-tube. A rubber septa is placed on the test-tube and the vessel is evacuated and purged with Argon. This cycle is repeated three times. 5-bromo-*m*-xylene (0.15mmol) and degassed toluene (0.15M) are then added under Argon. The reaction is then placed in a oil bath and the heat source is set to 115°C. The reaction is left stirring overnight (12-18hrs) after which it is allowed to cool. 1,3,5-trimethoxybenzene (0.05mmol) is added and the reaction is diluted with DCM (5mL). A small aliquot (1mL) is then removed for NMR analysis which provides the ratio of products and NMR yield. Column chromatography on silica gel is used to separate the major isomer.

Table 4.8, Entry 1



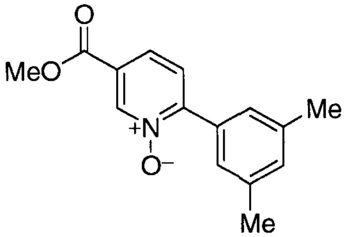
Chromatography using 2% MeOH, 10% Acetone in DCM; Isolated in 58% yield
**$^1$H NMR (400MHz, CDCl$_3$, 293K, TMS):** 2.33 (3H, s), 2.37 (6H, s), 7.07 (1H, s), 7.11 (1H, d, J=7.8Hz), 7.28 (1H, d, J=7.8Hz), 7.37 (2H, s), 8.19 (1H, s);
**$^{13}$C NMR (400MHz, CDCl$_3$, 293K, TMS):** 21.4, 27.1, 126.8, 126.9, 127.1, 131.1, 132.6, 134.9, 137.8, 140.2, 147.0, ;
**IR (*$v_{max}$* /cm$^{-1}$):** 2920, 1508, 1372, 1268, 816;
**HRMS** calculated for $C_{14}H_{15}NO$ (M+) 213.1154; Found: 213.1137;

Table 4.8, Entry 2



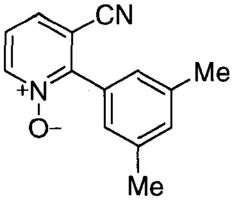
Chromatography using 1% MeOH, 10% Acetone in DCM; Isolated in xx% yield
**$^1$H NMR (400MHz, CDCl$_3$, 293K, TMS):** 2.39 (6H, s), 7.09 (1H, s), 7.43-7.52 (7H, m), 7.57-7.60 (2H, m), 8.59 (1H, d, J=1.5Hz);
**$^{13}$C NMR (400MHz, CDCl$_3$, 293K, TMS):** 21.4, 124.3, 126.8, 126.9, 127.2, 129.1, 129.3, 131.3, 132.3, 135.2, 137.9, 138.3, 138.5, 148.0, ;
**IR (*$v_{max}$* /cm$^{-1}$):** 3058, 2917, 1367, 1204, 760;
**HRMS** calculated for $C_{19}H_{17}NO$ (M+) 275.1310; Found:275.1319;
**m. p.** (CHCl$_3$): 137-139°C

Table 4.8, Entry 3



Chromatography using 10% Acetone in DCM; Isolated in 74% yield
**$^1$H NMR (400MHz, CDCl$_3$, 293K, TMS):** 2.37 (6H, s), 3.97 (3H, s), 7.11 (1H, s) 7.44 (2H, s), 7.47 (1H, d, J=8.2Hz), 7.83 (1H, dd, J=8.2Hz & 1.7Hz), 8.89 (1H, d, J=1.4Hz);
**$^{13}$C NMR (400MHz, CDCl$_3$, 293K, TMS):** 21.3, 52.9, 125.7, 126.9, 127.1, 127.7, 131.7, 132.0, 138.0, 141.5, 152.9, 163.6;
**IR (*$v_{max}$* /cm$^{-1}$):** 2954, 1729, 1297, 1106, 758;
**HRMS** calculated for $C_{15}H_{15}NO_3$ (M+) 257.1052; Found: 257.1063;
**m. p.** (CHCl$_3$): 108-110°C

Table 4.8, Entry 10



Chromatography using 1% MeOH, 10% Acetone in DCM ; Isolated in 88% yield

**$^1$H NMR (500MHz, CDCl$_3$, 293K, TMS):** 2.39 (6H, s), 7.17 (s, 1H), 7.21 (s, 2H), 7.32 (1H, t, J=7.8Hz), 7.56 (1H, d, J=8.3Hz), 8.46 (1H, d, J=6.4Hz);

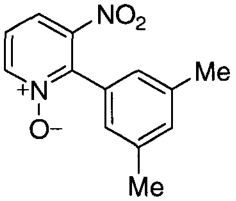
**$^{13}$C NMR (500MHz, CDCl$_3$, 293K, TMS):** 152.9, 143.7, 138.5, 132.8, 128.7, 127.0, 124.7, 114.9, 113.7, 21.3 ;

**IR** ***($\nu_{max}$/cm$^{-1}$)***: 2921, 2242, 1603, 1414, 1275, 732;

**HRMS** calculated for $C_{14}H_{12}N_2O$ (M+) 224.0950; Found: 224.0943;

**m. p.** ($CHCl_3$): 134-136°C

Table 4.8, Entry 8



Chromatography using 4% MeOH, 30% Ethyl Acetate in PhH ; Isolated in 67% yield

**$^1$H NMR (500MHz, CDCl$_3$, 293K, TMS):** 2.36 (6H, s), 7.03 (2H, s), 7.13 (1H, s), 7.37 (1H, dd, J=8.3Hz and 6.4Hz), 7.62 (1H, d, J=8.3Hz), 8.47 (1H, d, J=6.4Hz);

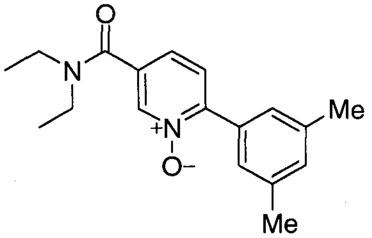
**$^{13}$C NMR (400MHz, CDCl$_3$, 293K, TMS):** 21.3, 119.2, 124.0, 126.4, 127.3, 132.5, 138.6, 142.8, 145.8, 149.5;

**IR** ***($\nu_{max}$/cm$^{-1}$)***: 2921, 1539, 1371, 1272, 811;

**HRMS** calculated for $C_{13}H_{12}N_2O_3$ (M+) 244.0848; Found: 244.0855;

**m. p.** ($CHCl_3$): 178-180°C

Table 4.8, Entry 6



Chromatography using 2% MeOH, 10% Acetone in DCM ; Isolated in 55% yield

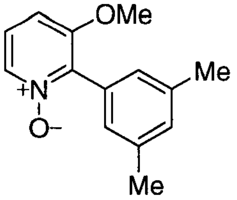
**$^1$H NMR (300MHz, (CD$_3$)$_2$CO, 293K):** 1.20 (6H, t, J=7.0Hz), 2.35 (6H, s), 3.47 (4H, br), 7.10 (1H, s), 7.31 (1H, dd, J=8.1Hz & 1.9Hz), 7.51 (2H, s), 7.59 (1H, d, 8.1Hz), 8.25 (1H, d, J=1.9Hz);

**$^{13}$C NMR (400MHz, CDCl$_3$, 293K, TMS):** 14.0 (15.5 rotamer), 22.3, 41.0 (45.0 rotamer), 123.8, 128.8, 129.0, 132.7 (br), 134.6, 137.0, 139.2, 139.9 (br), 150.6, 167.3;

**IR** ***($\nu_{max}$/cm$^{-1}$)***: 2974, 1634, 1436, 1293, 753;

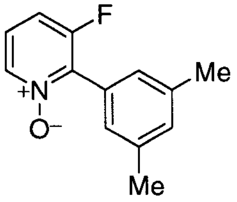
**HRMS** calculated for $C_{18}H_{22}N_2O_2$ (M+) 298.1681; Found: 298.1696;

Table 4.8, Entry 4



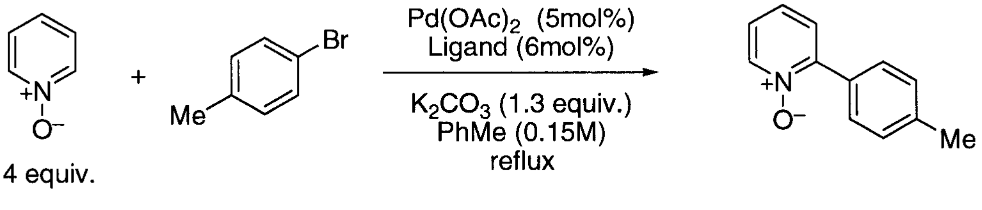
Chromatography using 2% MeOH, 15% Acetone in DCM ; Isolated in 79% yield
**$^1$H NMR (300MHz, $CDCl_3$, 293K, TMS):** 2.36 (6H, s), 3.78 (3H, s), 6.89 (1H, d, J=8.7Hz), 7.07 (3H, s), 7.15 (1H, dd, J=8.7Hz & 6.2Hz), 8.03 (1H, dd, J=6.8Hz & J=1.2Hz);
**$^{13}$C NMR (400MHz, $CDCl_3$, 293K, TMS):** 21.4, 56.5, 108.5, 123.4, 127.5, 128.9, 131.1, 133.3, 137.8, 141.5, 156.0;
**IR ($\nu_{max}$/cm$^{-1}$):** 2938, 1561, 1414, 1221, 1080, 849;
**HRMS** calculated for $C_{14}H_{15}NO_2$ (M+) 229.1103; Found: 229.1077;
**m. p.** ($CHCl_3$): 161-162°C

Table 4.8, Entry 12



Using only 1.1 eq. of *N*-Oxide. Chromatography using 2% MeOH, 10% Acetone in DCM; Isolated in 78% yield
**$^1$H NMR (400MHz, $CDCl_3$, 293K, TMS):** 2.38 (6H, s), 7.09-7.21 (5H, m), 8.20 (1H, dt, J=6.5Hz & J=1.2Hz);
**$^{13}$C NMR (400MHz, $CDCl_3$, 293K, TMS):** 21.3, 113.3 (d, J=22.7Hz), 123.4 (d, J=10.3Hz), 126.2 (d, J=1.8Hz), 127.5, 127.5, 131.9, 136.7 (d, J=3.7Hz), 138.1, 159.4 (d, J=250.9Hz);
**IR ($\nu_{max}$/cm$^{-1}$):** 1602, 1416, 1238, 1205, 1033, 789;
**HRMS** calculated for $C_{13}H_{12}NOF$ (M+) 217.0903; Found: 217.0898;
**m. p.** ($CHCl_3$): 85-87°C

**Procedure for gram scale synthesis:**



A 1L pear-shaped flask is fitted with a Teflon sleeve and a cylindrical (4cm x 1cm) stir bar is placed inside. $Pd(OAc)_2$ (0.560 g, 2.5 mmol, 5 mol%), $P^tBu_3{\cdot}HBF_4$ (0.870 g, 3 mmol, 6 mol%) (Note 1), potassium carbonate powder ($K_2CO_3$, 8.97 g, 65 mmol, 1.3 equiv.) (Note 2), 4-bromotoluene (8.55 g, 50 mmol, 1 equiv.) (Note 3,4) and pyridine *N*-oxide (19 g, 200 mmol, 4 equiv.) (Note 5) are weighed to air and placed inside the flask. The flask is then fitted with a reflux condenser which is capped with a rubber septum. The whole setup is then evacuated under vacuum and refilled with Argon four times (Note 6). Toluene (Note 7) (330mL) is then added in 50mL portions under a steady flow of argon. After addition of the first 50mL, the reaction is immersed in the oil bath. Stirring (400rpm) is commenced and the heating source is turned on (set to 125°C). The remaining toluene is then added (Note 8) after which the reaction is kept under an argon atmosphere (Note 9). The mixture starts to reflux after approximately 20 minutes and the color of the mixture pales to off-white after 30-40 minutes.

Heating and stirring is maintained for 16 hours (overnight), after which the now black reaction is allowed to cool to room temperature and the toluene evaporated under reduced pressure on a rotary evaporator equipped with a Büchi V-500 membrane pump. To the dark slurry is added 150mL of saturated aqueous $NH_4Cl$ and 200mL of $CH_2Cl_2$. The mixture is filtered on 9-10g of packed Celite and 15-20g of sand (Note 10). 50 mL of $H_2O$ and 50 mL of $CH_2Cl_2$ are added to the flask and filtered. The filter cake is washed with an additional 50 mL of $CH_2Cl_2$. The resulting yellow biphasic solution is poured into a (1L) separatory funnel and the organic layer is separated from the aqueous layer. 50mL of $H_2O$ is added to the aqueous phase and is re-extracted twice with $CH_2Cl_2$ (100 mL x 2). $MgSO_4$ (15g) is added to the combined organic layers. This pale yellow solution is filtered (Note 11) and evaporated under reduced pressure using a rotary evaporator. The resulting yellow solid (Note 12) is then dissolved in 20-35 mL of eluent (Note 13) loaded onto silica gel chromatography (Note 14). The product is obtained as a very pale off-white yellow solid in 79-83% yield which can be contaminated with <1% of tri-*t*-butylphosphine oxide (Note 15). This material is usually carried through to further transformations, although analytically pure material can be obtained if a second chromatography is performed (Note 14, 15).

## Waste Disposal Information

All hazardous materials should be handeled and siposed of in accordance with "Prudent Practicies in the Laboratory"; National Academy Press; Washington, DC, 1995

## Notes:

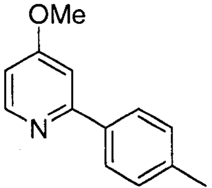
1. Palladium (II) acetate (46-1780) and phosphonium salt (15-6000) were purchased from *Strem* and used as is.
2. Purchased from *Aldrich* (347825) and used as is.
3. Purchased from *Aldrich* (B82200) and used as is.
4. 4-Bromotoluene is a low melting solid (m.p. 30°C), we therefore find it convenient to store it in the freezer before use to facilitate its weighing as a solid. Alternatively, one could add it as a stock solution in toluene or as a liquid if heated. If it is added as a stock solution or a liquid is should be added with the solvent.
5. Purchased from *Aldrich* (131652), particles greater than $1cm^3$ were crushed. An excess of this reagent is used to increase the yield of the reaction. The identical procedure can be performed with 1.5 equivalents of pyridine *N*-oxide resulting in yields ranging from 65-70%. During the extraction protocol the excess *N*-oxide can be recuperated from the aqueous phase by evaporation of the water and chromatography of the residu with 10% MeOH in DCM.
6. The vacuum line is connected to the apparatus via the septum with a needle and the atmosphere is refilled with an Argon balloon.
7. Certified A.C.S. Grade purchased from *Fisher Scientific* (T324) and degassed with argon (10 minutes) before use.
8. The total volume of toluene was added within 10 minutes and stirring speed is raised to 700rpm.

9. An argon filled balloon is place at the top of the reflux condenser. Reaction should be an orange/yellow color
10. The Celite is weighed dry and packed using acetone in a 60mL coarse fritted Büchner funnel. 15-20g of sand is added to the top of the Celite column.
11. The flask is rinsed with 50mL of $CH_2Cl_2$ and the filter cake is also rinsed with 50 mL $CH_2Cl_2$.
12. In some cases a yellow oil is obtained which can be reduced to a yellow solid under high vacuum.
13. The eluent used is made up of 2% MeOH, 8% Acetone in $CH_2Cl_2$. Sonication or heating with heat gun was used to fully dissolve the solid.
14. Using 175 g of Silicycle (R10030B) silica gel on a 8.5cm diameter column. 200mL is collected in an Erlenmeyer flask followed by 15mL fractions. The majority of the compound is obtained from fractions 20-48 but tends to tail off past fraction 55 but resulted only in a 2% increase in yield when collected.
15. The second chromatography affords lower yields 71-75% given the high affinity of the substrate for silica gel and therefore should be avoided if not necessary

**General Procedure for Reduction of *N*-oxides[258]:**

Ammonium formate (~10 equiv.) is added to a stirring solution of *N*-oxide (1 equiv.), Pd/C (0.1 equiv.) in MeOH (0.3M) in a round bottom flask. The flask is then capped with a rubber septa and purged with Argon. The mixture is then stirred under an atmosphere of Argon at room temperature. When the reaction is deemed complete by TLC analysis, the reaction is filtered on celite and evaporated under reduced pressure. The residue is then purified via silica gel chromatography using DCM/Acetone mixutres.

Table 4.4



**$^1$H NMR (300MHz, $(CD_3)_2O$, 293K):** 2.37 (3H, s), 3.94 (3H, s), 6.85 (1H, dd, J=5.7Hz & 2.4Hz), 7.27 (2H, d, J=8.1), 7.40 (1H, d, J=2.5Hz), 8.01 (2H, d, J=8.7Hz), 8.45 (1H, d, J=5.7Hz);
**$^{13}$C NMR (300MHz, $(CD_3)_2O$, 293K):** 22.2, 56.6, 107.4, 110.0, 128.5, 131.0, 138.5, 140.6, 152.6, 160.3, 168.4;
**IR ($\nu_{max}$/cm$^{-1}$):** 2921, 1593, 1561, 1473, 1316, 1220, 1034, 819;
**HRMS** calculated for $C_{13}H_{13}NO$ (M+) 199.0997; Found: 199.0991;

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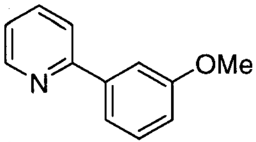
[258] Balicki, R.; *Synthesis*, **1989**, *8*, 645; Similar yield were also obtained using zinc mediated reduction, see: Aoyagi, Y.; Abe, T.; Ohta, A.; *Synthesis*, **1997**, *8*, 891

Table 4.4



**$^1$H NMR (500MHz, CDCl$_3$, 293K, TMS):** 3.88 (3H, s), 6.96 (1H , dd, J=8.0Hz & 2.0Hz), 7.19-7.22 (1H, m), 7.37 (1H, t, J=8.0Hz), 7.54 (1H, d, J=7.0Hz), 7.59 (1H, m), 7.69-7.72 (2H, m), 8.68 (1H, d, J=5.0Hz);
**$^{13}$C NMR (125MHz, CDCl$_3$, 293K, TMS):** 55.3, 112.0, 115.0, 119.3, 120.7, 122.2, 129.7, 136.7, 140.8, 149.6, 157.2, 160.0, ;
**IR ($\nu_{max}$/cm$^{-1}$):** 3005, 2835, 1584, 1463, 1291, 1220, 1033, 770;
**HRMS** calculated for $C_{11}H_{11}NO$ (M+) 185.0841; Found: 185.0826;

## Computational Analysis of Pyridine *N*-Oxide Arylation

### *Computational Details*

Quantum chemical[259] density functional theory[260] (DFT) calculations were performed with Becke's three parameter hybrid gradient-corrected exchange functional[261] and the gradient-corrected correlation functional of Lee, Yang and Parr,[262] commonly abbreviated as B3LYP. All calculations were performed with the Jaguar 6.0 software package.[263] The triple-zeta basis set, LACV3P**, that includes polarization functions. Frequency calculations were performed on all stationary points and the energies reported include unscaled zero-point vibrational energy corrections. A slightly smaller model system was used for the catalyst by replacing the bulky phosphine ligand used experimentally with a $PH_3$ ligand. This is a typical approach used in quantum chemical calculations to reduce computation times. The effect of the phosphine ligand is not expected to change the qualitative nature of these calculations.[264]

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[259] Ziegler, T.; Autschbach, J. Chem. Rev. **2005**, *105*, 2695.

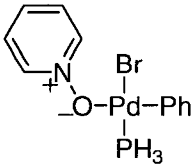
[260] (a) Hohenburg, P.; Kohn, W. *Phys. Rev. B* **1964**, *136*, 864. b) Kohn, W.; Sham, L. J. *Phys. Rev. A* **1965**, *140*, 1133.

[261] Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.

[262] Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B.* **1988**, *37*, 785.

[263] *Jaguar 6.0*; Schrodinger, LLC: Portland, Oregon, 2004

[264] This approach was recently used in similar systems : (a) Garcia-Cuadrado, D.; de Mendoza, P.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2007**, *129*, 6880 (b) Garcia-Cuadrado, D.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006**, *128*, 1066. (c) Lafrance, M.; Rowley, C. N.; Woo, T. K.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 8754.



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| H4 | 5.9385011870 | 1.8793966295 | 4.5719772900 |
| H5 | 7.3544944665 | 3.2743528395 | 3.7424883161 |
| H6 | 5.2378446593 | 3.5651772818 | 3.4658153562 |
| C7 | 1.7389602152 | 0.0347582313 | 2.2293890210 |
| C8 | 2.0248450087 | 1.1804858514 | 1.4814739117 |
| C9 | 3.3528230455 | 1.5605229339 | 1.2469204410 |
| C10 | 4.4021090183 | 0.7900708158 | 1.7602672497 |
| C11 | 4.1185163396 | -0.3585981798 | 2.5083097141 |
| C12 | 2.7887076192 | -0.7342640279 | 2.7395358131 |
| H13 | 0.7082355246 | -0.2595858951 | 2.4072570340 |
| H14 | 1.2161430903 | 1.7805249979 | 1.0710545317 |
| H15 | 3.5598678390 | 2.4429984791 | 0.6482526824 |
| H16 | 4.9242255817 | -0.9758586715 | 2.8955656119 |
| H17 | 2.5783707204 | -1.6331819086 | 3.3141943827 |
| O18 | 8.4761055148 | 1.9747477139 | 1.2258268189 |
| C19 | 10.9825903415 | 0.2953499073 | -1.5380773534 |
| C20 | 11.0855845311 | -0.0330292979 | -0.1831832598 |
| C21 | 10.2173863833 | 0.5389040984 | 0.7316344102 |
| N22 | 9.2683397115 | 1.4233832904 | 0.3269117227 |
| C23 | 9.1315461155 | 1.7365250783 | -0.9867348268 |
| C24 | 9.9888256785 | 1.1904884325 | -1.9317104216 |
| H25 | 11.6542941098 | -0.1446261416 | -2.2672090756 |
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| H27 | 10.2206689557 | 0.3413196551 | 1.7951102899 |
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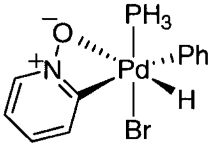

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| P4 | -16.3688140129 | 21.7219361727 | -6.1631350542 |
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| C11 | -16.6158289227 | 19.3849173611 | -8.0159316495 |
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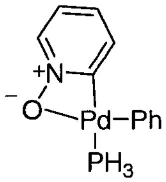

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| O17 | 9.0777654795 | 1.3571175694 | 1.5074052051 |
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| C20 | 10.9292313555 | 1.8737088522 | 0.1550700472 |
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| C22 | 9.0245469281 | 0.6514399617 | -0.6353068874 |
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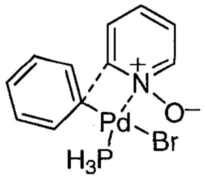

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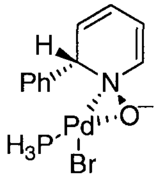

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| H20 | 13.9590824662 | 20.7503455648 | -10.2163066377 |
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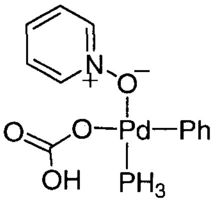

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| P3 | 6.2722094135 | 2.2194120211 | 3.5819036674 |
| H4 | 5.8587305462 | 1.3789291196 | 4.6346295035 |
| H5 | 7.4534100823 | 2.7548741083 | 4.1336514880 |
| H6 | 5.3885211305 | 3.2996665463 | 3.7895123449 |
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| C12 | 2.6126071823 | -0.5224421823 | 2.2592250569 |
| H13 | 0.6627044628 | 0.0711450282 | 1.5640480364 |
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| O18 | 6.4236049269 | 0.3519499912 | -0.4040202116 |
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| C23 | 8.1291592540 | -1.1457083023 | 0.1711808932 |
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| H25 | 9.9297133992 | -3.1261093146 | -1.9153862734 |
| H26 | 8.4478531840 | -1.9418204494 | -3.5653587300 |
| H27 | 6.7947643665 | -0.2512965439 | -2.7028891956 |
| H28 | 8.0058213032 | -0.8449368677 | 1.2045798070 |
| H29 | 9.6775286341 | -2.5456499650 | 0.5193088332 |
| C30 | 9.3279102833 | 1.1618348954 | 2.1194676350 |
| O31 | 9.0722650762 | 0.2309031516 | 2.8963473141 |
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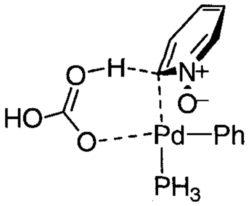

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| C9 | -3.4256652313 | -0.1301423662 | 0.2881033775 |
| O10 | -4.7230483904 | -0.3880287279 | 0.5458975760 |
| O11 | -0.0617933809 | 1.6497336689 | 1.8715195755 |
| N12 | 0.0462580708 | 2.0787575994 | 0.6804578524 |
| C13 | -0.5760813277 | 1.4079837554 | -0.3718741225 |
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| H25 | 0.5137396345 | 3.4145313548 | -2.9330315803 |
| H26 | 1.5827593928 | 4.5701460718 | -0.9703202882 |
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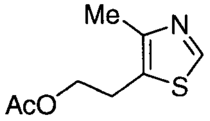
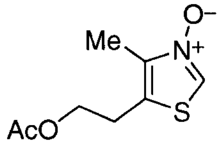
| H32 | -5.1681166393 | 0.4663410006 | 0.6167622703 |
| H33 | 1.7886383082 | 0.0082965476 | 1.7326534702 |

under reduced pressure at 28°C to afford 1.27g of a white powder (74% yield). The compound was analytically pure as judged by $^1$H NMR which matched literature reports (*J. Med. Chem.* **2005**, *48*, 1367)

Table 4.11, Entry 8

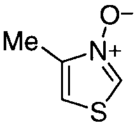


1.43g of 4-methyl-5-thiazole-ethanol (1 equiv.) is dissolved in 10mL of reagent grade dichloromethane (DCM, 0.1M). 0.11g of triethylamine (1.1 equiv.) and 0.06g (0.05 equiv.) of DMAP are added. The reaction is cooled to 0°C (ice bath) and 1.02g of acetic anhydride is added (1.1 equiv.) dropwise. After addition the reaction is allowed to warm room temperature. After 3 hours the reaction was deemed complete by TLC analysis. The reaction mixture is diluted with 10mL of $NH_4Cl$ (aq.) and poured into an extraction funnel. Another 25mL of DCM and $NH_4Cl$ (aq.) is added and the layers are separated. The aqueous layer is washed twice with DCM (15mL x 2). The organic layer is then dryed with $MgSO_4$, filtered and evaporated under reduced pressure at 35°C. The crude residue is then filtered over a plug of silica with 5% acetone in DCM. The product obtained was then used directly in the next step without further purification.



To a dichloroethane (DCE) solution (0.05M) of the crude acetylated 4-methyl-5-thiazole-ethanol is added 2.86g of mCPBA (~75%). After 18 hours another 1.5g of mCPBA is added and the reaction is allowed to stir overnight. The next day, a white suspension is formed. The reaction is cooled to 0°C (ice bath) and the white solid is filtered off. The filter cake is washed with cold dichloromethane (DCM, 10-20mL) and the yellow filtrate is concentrated under reduced pressure at 30°C. To afford a yellow oil which is purified via silica gel column chromatography first with 250mL EtOAc/MeOH (9:1) as eluent followed by DCM/MeOH (9:1). The fractions containing pure material were collected and evaporated under reduced pressure at 30°C to afford 1.21g of a yellow oil (61% yield over the two steps). The compound was analytically pure as judged by $^1$H NMR which matched literature reports (*Chem. Commun.* **2006**, 2262)

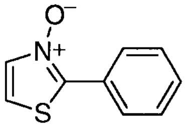
Table 4.11, Entry 7



To a solution of 4-methylthiazole (1g, 10.1mmol) in DCM (25mL) is added 3g of mCPBA (~70%, 1,2 equiv.). The reaction is left to stir at room temperature over a weekend (~72hours). The yellow solution was then concentrated under reduced pressure at 28°C. The resulting light yellow solid is then dissolved in 10mL of EtOAc/MeOH (9:1) and purified by silica gel column chromatography, first with 300mL EtOAc/MeOH (9:1) as eluent followed by DCM/MeOH (9:1). The fractions containing pure material were collected and evaporated under reduced pressure at 28°C to afford 830mg of a light yellow liquid which became a solid in a refrigerator (4°C) (72% yield).

**$^1$H NMR (300MHz, $CDCl_3$, 293K, TMS):** 2.40 (3H, s), 7.07 (1H, d, J=2.2Hz), 8.22 (1H, d, J=3.1Hz);
**$^{13}$C NMR (100MHz, $CDCl_3$, 293K, TMS):** 12.6, 113.2, 129.8, 145.9;
**IR ($\nu_{max}$/cm$^{-1}$):** 3133, 1659, 1536, 1351, 1197, 1013, 763;
**HRMS** calculated for $C_4H_5NOS$ (M+) 115.0092; Found: 115.0091;
**Melting Point ($CHCl_3$):** 75-77°C

Scheme 4.5

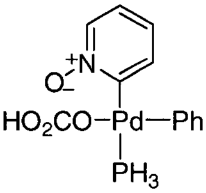


527mg of mCPBA (~75%) is added to a stirring solution of 2-phenylthiazole (400mg) in dichloroethane (DCE, 6mL). The reaction was left to stir over a weekend after which a white suspension is formed. The reaction is cooled to 0°C (ice bath) and the white solid is filtered off. The filter cake is washed with cold dichloromethane (DCM, 10-20mL) and the filtrate is concentrated under reduced pressure. The residue is then dissolved in EtOAc/MeOH (9:1) and purified by silica gel column chromatography, with EtOAc/MeOH (9:1) as eluent followed by DCM/MeOH (9:1). The white solid is obtained in 56% yield.

**$^1$H NMR (300MHz, $CDCl_3$, 293K, TMS):** 7.24 (1H, d, J=4.0Hz), 7.40-7.48 (3H, m), 7.70 (1H, d, J=4.0Hz), 8.27-8.31 (2H, m);
**$^{13}$C NMR (100MHz, $CDCl_3$, 293K, TMS):** 115.0, 127.0, 127.7, 128.9, 130.6, 139.6, 143.8;
**IR ($\nu_{max}$/cm$^{-1}$):** 3118, 1663, 1422, 1178, 801;
**HRMS** calculated for $C_9H_7NOS$ (M+) 177.0248; Found: 177.0261;

**Products**

**General Procedure:**
All reactions were performed on 0.2 to 0.4mmol scale: $Pd(OAc)_2$ (0.05 equiv.), Ligand **1a** or Dave-Phos (0.1 equiv.), PivOH (0.2 equiv.) $K_2CO_3$ (1.5 equiv.), and thiazole *N*-oxide (1.1 equiv.) are weighed to air and placed in a test tube with a magne tic stir bar (if the aryl halide is a solid, it is also added). The flask is placed in a Radley's parallel greenhouse reactor. The reactor is then sealed and the head space is purged with argon (10 min.). The aryl halide (1 equiv.) is then added via syringe as a degassed (with Argon) stock solution in ACS grade toluene (0.2M). (Similar yields are obtained using a rubber septa in an oil bath set to 25°C.) The mixture is then stirred at 25°C overnight (10-15 hours – reaction times were not optimized). The reaction is then diluted with 50mL of DCM/MeOH (9:1) and filtered through celite then evaporated under reduced pressure (30°C). The residu is then loaded onto a silica gel column for chromatography typically using DCM/Acetone/MeOH mixtures.



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| H5 | -20.3246816707 | 1.0979507179 | 2.5454553174 |
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| H23 | -29.2987617758 | 1.1761586585 | 1.5818820367 |
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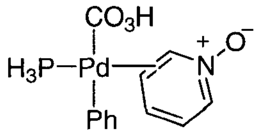

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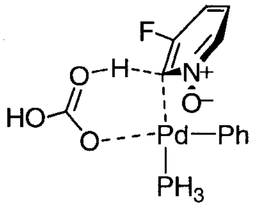

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| N12 | 0.0536901772 | 2.0991034169 | 0.6831441275 |
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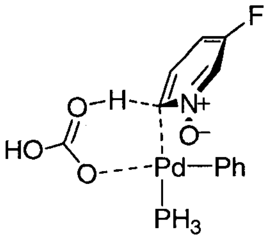

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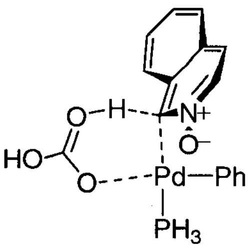
| H21 | 1.5475171041 | -1.2418455857 | -2.3533180720 |
| H22 | 0.4675957074 | -3.8027086609 | -0.8120525700 |
| H23 | -1.3565422576 | -3.8627837728 | 0.3491226192 |
| H24 | -0.9482034124 | 1.3990608026 | -2.4497890686 |
| H25 | 0.4997667090 | 3.3916042341 | -2.9582459156 |
| F26 | 1.7514860120 | 4.7122722529 | -1.0757985051 |
| H27 | 1.2921671525 | 3.6556378968 | 1.2740341311 |
| H28 | 4.2368935600 | 0.1018736578 | 1.5820425131 |
| H29 | 5.3603391562 | -0.4024224591 | -0.5752638960 |
| H30 | 3.9962353866 | -1.0677183179 | -2.5415914920 |
| H31 | -1.8707723855 | 1.1668052927 | -0.0196806212 |
| H32 | -5.1735953472 | 0.4575933097 | 0.6549893094 |
| H33 | 1.7794712508 | -0.0394930457 | 1.7701709296 |



UTot = -1443.028478

Coordinates

| | | | |
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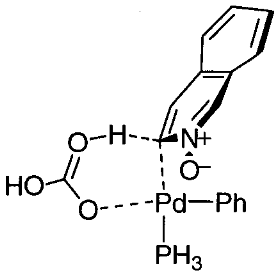
| C1 | 3.5389092060 | -0.8731898159 | -1.5748401043 |
| C2 | 2.1475125370 | -0.9527259929 | -1.4820158633 |
| C3 | 1.5022787927 | -0.6644219562 | -0.2752499391 |
| C4 | 2.2670145860 | -0.3005848190 | 0.8374048883 |
| C5 | 3.6577944395 | -0.2240972995 | 0.7393230386 |
| C6 | 4.2978643960 | -0.5122450186 | -0.4642776267 |
| Pd7 | -0.5049095678 | -0.7870332707 | -0.1054215537 |
| O8 | -2.6764866822 | -1.0557773004 | 0.1271365069 |
| C9 | -3.4132194804 | -0.0578482041 | 0.2398544177 |
| O10 | -4.7140540605 | -0.2910234802 | 0.5048507103 |
| O11 | -0.0518124218 | 1.6660810997 | 1.8176136806 |
| N12 | 0.0606459310 | 2.0759694075 | 0.6206471879 |
| C13 | -0.5343503923 | 1.4109141405 | -0.4243004161 |
| C14 | -0.3435731982 | 1.9325428555 | -1.7478990602 |
| C15 | 0.4446686573 | 3.0952569135 | -1.9791933152 |
| C16 | 1.0180588199 | 3.7209435536 | -0.8399557923 |
| C17 | 0.8155035368 | 3.2260889905 | 0.4077214288 |
| P18 | -0.2187759358 | -3.0538548848 | 0.2299845184 |
| O19 | -3.0685847365 | 1.1624813519 | 0.1222910949 |
| H20 | 0.5310876054 | -3.4677183388 | 1.3512478326 |
| H21 | 1.5718609444 | -1.2291704311 | -2.3585893447 |
| H22 | 0.4291600829 | -3.8254981910 | -0.7579246205 |
| H23 | -1.3827286967 | -3.8306403339 | 0.4198120702 |
| H24 | 4.2387803536 | 0.0654365059 | 1.6089641423 |
| H25 | 5.3781786686 | -0.4535534944 | -0.5366041768 |
| H26 | 4.0257664918 | -1.0936216621 | -2.5192268175 |
| H27 | -1.8186652657 | 1.1953970280 | -0.1169083024 |
| H28 | -5.1437978792 | 0.5715379117 | 0.5707762664 |
| H29 | 1.7762003453 | -0.0423959018 | 1.7692124969 |
| H30 | 1.2163241451 | 3.6468841123 | 1.3175145908 |
| C31 | 0.6171443523 | 3.5845043184 | -3.2934160258 |
| C32 | -0.9611420977 | 1.3103247460 | -2.8603505483 |
| C33 | 0.0137228103 | 2.9505630506 | -4.3552703158 |
| C34 | -0.7851874185 | 1.8087708910 | -4.1315389430 |
| H35 | -1.5715565094 | 0.4303069149 | -2.6935909958 |
| H36 | -1.2651945435 | 1.3198786106 | -4.9717011867 |
| H37 | 0.1453214078 | 3.3269617040 | -5.3628590317 |
| H38 | 1.2279491038 | 4.4670056238 | -3.4515119820 |
| H39 | 1.6263570783 | 4.6107802065 | -0.9557421935 |



UTot = -1443.025605

Coordinates

| | | | |
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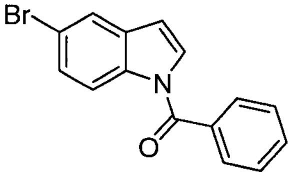
| C2 | 2.1286135326 | -1.0053407072 | -1.5053724848 |
| C3 | 1.4973903833 | -0.6574885229 | -0.3066789704 |
| C4 | 2.2740752597 | -0.2363526015 | 0.7772791686 |
| C5 | 3.6630293743 | -0.1604123331 | 0.6563430579 |
| C6 | 4.2891163208 | -0.5050579148 | -0.5396726020 |
| Pd7 | -0.5077662048 | -0.7742604251 | -0.1085908184 |
| O8 | -2.6678343697 | -1.0754246854 | 0.1481178282 |
| C9 | -3.4254156438 | -0.0893866609 | 0.2259432129 |
| O10 | -4.7241659713 | -0.3420212438 | 0.4809233963 |
| O11 | -0.1070222312 | 1.6458746929 | 1.8549979584 |
| N12 | 0.0563526560 | 2.1140167955 | 0.6802414631 |
| C13 | -0.5636359348 | 1.4472062737 | -0.4084292782 |
| C14 | -0.3448699809 | 1.9489084955 | -1.6752144967 |
| C15 | 0.4602392645 | 3.0802184779 | -1.9375854988 |
| C16 | 1.0478113814 | 3.7273242071 | -0.8092707592 |
| C17 | 0.8081203348 | 3.2095758346 | 0.4765578674 |
| P18 | -0.1991615240 | -3.0299169979 | 0.2356811713 |
| O19 | -3.1015759433 | 1.1330973614 | 0.0815061107 |
| H20 | 0.5699176531 | -3.4292920646 | 1.3484559024 |
| H21 | 1.5440090505 | -1.3339026592 | -2.3580371611 |
| H22 | 0.4364274749 | -3.8042034148 | -0.7578475666 |
| H23 | -1.3593707946 | -3.8053879919 | 0.4487148814 |
| H24 | -0.8412467133 | 1.4518087617 | -2.5025159841 |
| H25 | 4.2537404377 | 0.1736958999 | 1.5030575009 |
| H26 | 5.3680148849 | -0.4451646612 | -0.6290194303 |
| H27 | 3.9939573297 | -1.1912850487 | -2.5588929298 |
| H28 | -1.8508808541 | 1.1860341790 | -0.1284247864 |
| H29 | -5.1710774509 | 0.5132288118 | 0.5223270024 |
| H30 | 1.7929146272 | 0.0632860738 | 1.7018542271 |
| C31 | 1.8573335220 | 4.8731209277 | -1.0195225498 |
| H32 | 1.2241463960 | 3.6427419272 | 1.3755037863 |
| C33 | 1.4859234342 | 4.7043522681 | -3.4120053941 |
| C34 | 2.0684537200 | 5.3453950401 | -2.2929674954 |
| H35 | 1.6657568579 | 5.0946620602 | -4.4066731389 |
| H36 | 2.6889794229 | 6.2211506667 | -2.4453589136 |
| C37 | 0.6956811513 | 3.5934675115 | -3.2354326559 |
| H38 | 0.2440266921 | 3.0950070325 | -4.0863451631 |
| H39 | 2.3066237256 | 5.3685150935 | -0.1661396229 |

# Chapter 4 – Azole N-Oxides

## Starting Materials

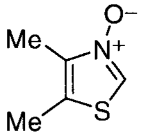
### *N*-Benzoyl-5-bromoindole:



The title compound was prepared according to the referenced procedure[265] and was subjected to column chromatography on silica gel with 10% diethyl ether in hexanes as the solvent to afford the title compound in 91% yield.
**$^1$H NMR (400 MHz, CDCl$_3$, 293 K):** 8.27 (1H , d, J=8.8Hz), 7.72 – 7.69 (3H, m), 7.60 (1H, m), 7.51 (2H, m,), 7.45 (1H, dd, J=8.7Hz & J=2.0Hz), 7.29 (1H, d, J=3.7Hz), 6.53 (1H, d, J=3.8Hz).
$^{13}$C NMR (100 MHz, CDCl$_3$, 293 K): 168.5, 134.7, 134.1, 132.5, 132.2, 129.2, 128.7, 128.7, 127.8, 123.6, 117.8, 117.2, 107.7.
**IR (*$v_{max}$*/cm$^{-1}$):** 1688, 1445, 876, 708.
**HRMS** calculated $C_{15}H_{10}BrNO$ ($M^+$) 298.9946; Found: 298.9967.
**Melting Point (Et$_2$O/hexane)**: 89-90°C.
**R$_f$**: (10% diethyl ether/hexanes)0.35

**General Comment:**
*2-Unsubstituted Thiazole N-oxides are sensitive to heat. All N-oxides for this study were stored in a freezer under $N_2$ or Ar. Evaporation under reduced pressure was always carried out with mild heating to 28-30°C.*

Table 4.11, Entry 1



3.8g of mCPBA (~75%) is added to a stirring solution of 4,5-dimethylthiazole (1.5g) in dichloroethane (DCE, 25mL). The reaction was left to stir for 12h after which an additional 2.0g of mCPBA (~75%) is added and the reaction is allowed to stir overnight. The next day, a white suspension is formed. The reaction is cooled to 0°C (ice bath) and the white solid is filtered off. The filter cake is washed with cold dichloromethane (DCM, 10-20mL) and the yellow filtrate is concentrated under reduced pressure at 28°C. *!! Heating to 45°C during concentration of filtrate led to diminished yields !!* The resulting yellow concentrate is cooled to 0°C (ice bath) which causes crystallization into a yellow solid. This solid is then dissolved in 10mL of EtOAc/MeOH (9:1) and purified by silica gel column chromatography, first with 500mL EtOAc/MeOH (9:1) as eluent followed by DCM/MeOH (9:1). The fractions containing pure material were collected and evaporated

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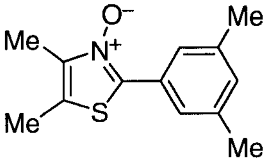
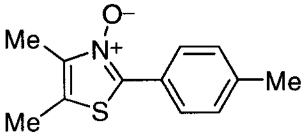
[265] Campeau, L.-C.; Parisien, M.; Jean, A.; Fagnou, K. ; *J. Am. Chem. Soc.*; **2006,** *128,* 581.

Table 4.11, Entry 2



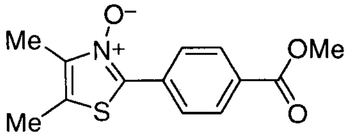
**$^1$H NMR (400MHz, CDCl$_3$, 293K, TMS):** 2.31 (3H, s), 2.36 (6H, s), 2.37 (3H, s), 7.04 (1H, s), 7.96 (2H, s);
**$^{13}$C NMR (100MHz, CDCl$_3$, 293K, TMS):** 11.2, 13.0, 21.4, 121.6, 124.4, 128.3, 131.7, 138.3, 141.5, 142.9;
**IR (*$v_{max}$*/cm$^{-1}$)**: 2922, 1603, 1332, 1108, 830;
**HRMS** calculated for $C_{13}H_{15}FNOS$ (M+) 233.0874; Found: 233.0873;
**Melting Point (CHCl$_3$):** 118-119°C
**Rf:** 0.24 on silica gel (1% MeOH, 7.5% Acetone in DCM)

Table 4.11, Entry 1



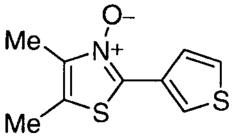
**$^1$H NMR (400MHz, CDCl$_3$, 293K, TMS):** 2.33 (3H, d, J=0.7Hz), 2.39 (6H, br), 7.26 (2H, d, J=8.3Hz), 8.23 (2H, d, J=8.3Hz);
**$^{13}$C NMR (100MHz, CDCl$_3$, 293K, TMS):** 11.2, 13.0, 21.5, 121.2, 125.9, 126.6, 129.4, 140.2, 142.8;
**IR (*$v_{max}$*/cm$^{-1}$)**: 2922, 1623, 1505, 1331, 1097, 822;
**HRMS** calculated for $C_{12}H_{13}NOS$ (M+) 219.0718; Found: 219.0725;
**Melting Point (CHCl$_3$):** 132-134°C
**Rf:** 0.22 on silica gel (1% MeOH, 10% Acetone in DCM)

Table 4.11, Entry 4



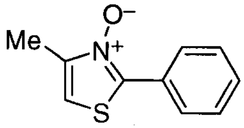
**$^1$H NMR (400MHz, CDCl$_3$, 293K, TMS):** 2.35 (3H, s), 2.44 (6H, s), 3.94 (3H, s), 8.11 (2H, d, J=8.9Hz), 8.44 (2H, d, J=8.9Hz);
**$^{13}$C NMR (100MHz, CDCl$_3$, 293K, TMS):** 11.2, 13.2, 52.3, 123.2, 126.2, 126.3, 130.0, 130.7, 132.5, 143.6, 166.4;
**IR (*$v_{max}$*/cm$^{-1}$)**: 2916, 1719, 1603, 1281, 764;
**HRMS** calculated for $C_{12}H_{13}NO_3S$ (M+) 219.0718; Found: 219.0720;
**Melting Point (CHCl$_3$):** 168-170°C
**Rf:** 0.23 on silica gel (1% MeOH, 10% Acetone in DCM)

Table 4.11, Entry 6



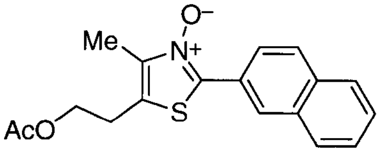
**$^1$H NMR (400MHz, CDCl$_3$, 293K, TMS):** 2.34 (3H, d, J=0.8Hz), 2.40 (3H, d, J=0.8Hz), 7.37 (1H, dd, J=5.2Hz & 3.0Hz), 7.41 (1H, dd, J=5.1Hz & 1.3Hz), 9.05 (1H, dd, J=3.0Hz & 1.3Hz);
**$^{13}$C NMR (100MHz, CDCl$_3$, 293K, TMS):** 11.0, 13.0, 120.6, 125.5, 125.8, 125.9, 128.3, 137.5, 142.0;
**IR ($\nu_{max}$/cm$^{-1}$):** 3069, 1615, 1407, 1102, 795;
**HRMS** calculated for $C_9H_9NOS_2$ (M+) 211.0126; Found: 211.0129;
**Melting Point (CHCl$_3$):** 137-139°C
**Rf:** 0.24 on silica gel (1% MeOH, 10% Acetone in DCM)

Table 4.11, Entry 7



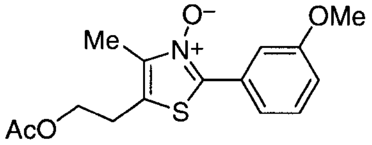
**$^1$H NMR (400MHz, CDCl$_3$, 293K, TMS):** 2.42 (3H, d, J=1.0Hz), 6.99 (1H, d, J=1.0Hz), 7.41-7.51 (3H, m), 8.35-8.39 (2H, m);
**$^{13}$C NMR (100MHz, CDCl$_3$, 293K, TMS):** 13.4, 109.6, 126.7, 128.5, 128.8, 130.3, 143.5, 147.3;
**IR ($\nu_{max}$/cm$^{-1}$):** 3069, 1497, 1345, 1127, 760;
**HRMS** calculated for $C_{10}H_9NOS$ (M+) 191.0405; Found: 191.0410;
**Melting Point (CHCl$_3$):** 121-123°C
**Rf:** 0.20 on silica gel (3% MeOH, 10% Acetone in DCM)

Table 4.11, Entry 8



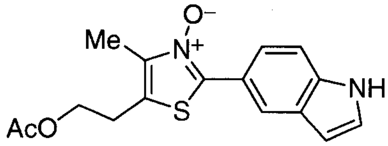
**$^1$H NMR (400MHz, CDCl$_3$, 293K, TMS):** 2.10 (3H, s), 2.42 (3H, s), 3.13 (2H, t, J=6.3Hz), 4.32 (3H, t, J=6.3Hz), 7.51-7.56 (2H, m), 7.82-7.86 (1H, m), 7.89 (1H, d, J=8.7Hz), 7.94-7.98 (1H, m), 8.00 (1H, dd, J=8.7Hz & 1.8Hz);
**$^{13}$C NMR (75MHz, CDCl$_3$, 293K, TMS):** 11.5, 20.9, 27.1, 63.0, 122.9, 123.8, 125.4, 126.6, 126.8, 127.3, 127.6, 128.4, 129.2, 130.1, 133.8, 142.2, 144.3, 170.6;
**IR ($\nu_{max}$/cm$^{-1}$):** 3056, 1740, 1238, 1047, 750;
**HRMS** calculated for $C_{18}H_{17}NO_3S$ (M+) 327.0929; Found: 327.0938;
**Rf:** 0.21 on silica gel (1% MeOH, 15% Acetone in DCM)

Table 4.11, Entry 9



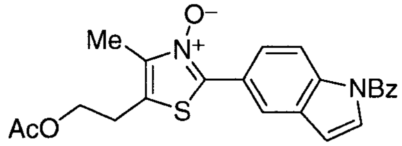
**$^1$H NMR (400MHz, CDCl$_3$, 293K, TMS):** 2.08 (3H, s), 2.38 (3H, s), 3.10 (2H, t, J=6.37Hz), 3.89 (3H, s), 4.29 (2H, t, J=6.27Hz), 6.99 (1H, dd, J=8.13Hz & 2.45Hz), 7.35 (1H, t, J=8.13Hz), 7.65 (1H, d, J=7.84Hz), 8.32 (1H, dd, J=2.06Hz & 2.06Hz);
**$^{13}$C NMR (75MHz, CDCl$_3$, 293K, TMS):** 11.5, 20.9, 27.2, 55.4, 63.0, 111.1, 116.9, 119.2, 122.9, 129.5, 129.7, 142.0, 144.3, 159.8, 170.6;
**IR ($\nu_{max}$/cm$^{-1}$):** 2957, 1740, 1239, 1047, 781;
**HRMS** calculated for $C_{15}H_{17}NO_4S$ (M+) 307.0878; Found: 307.0877;
**Rf:** 0.28 on silica gel (2% MeOH, 10% Acetone in DCM)

Table 4.11, Entry 11



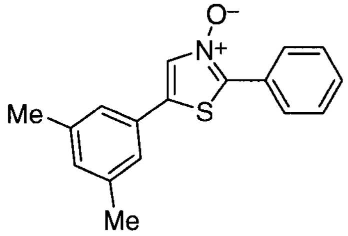
**$^1$H NMR (400MHz, CDCl$_3$, 293K, TMS):** 2.07 (3H, s), 2.40 (3H, s), 3.06 (2H, t, J=6.3Hz), 4.27 (2H, t, J=6.4Hz), 6.53 (1H, br), 7.11 (1H, t, J=2.7Hz), 7.30 (1H, d, J=8.6Hz), 7.94 (1H, dd, J=8.6Hz & 1.7Hz), 8.80 (1H, d, J=1.5Hz), 9.88 (1H, br);
**$^{13}$C NMR (75MHz, CDCl$_3$, 293K, TMS):** 11.6, 20.9, 27.0, 63.1, 103.1, 111.7, 119.5, 120.7, 121.0, 121.6, 126.0, 127.8, 137.0, 143.5, 145.1, 170.7;
**IR ($\nu_{max}$/cm$^{-1}$):** 3125, 1740, 1239, 1094, 730;
**HRMS** calculated for $C_{16}H_{16}N_2O_3S$ (M+) 316.0082; Found: 316.0909;
**Melting Point (CHCl$_3$):** 172-174 °C
**Rf:** 0.21 on silica gel (2% MeOH, 10% Acetone in DCM)

Table 4.11, Entry 12

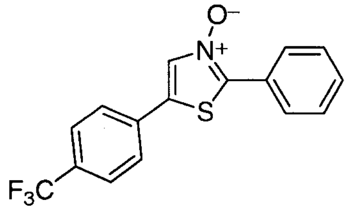


**$^1$H NMR (400MHz, CDCl$_3$, 293K, TMS):** 2.10 (3H, s), 2.40 (3H, s), 3.11 (2H, t, J=6.4Hz), 4.31 (2H, t, J=6.3Hz), 6.69 (1H, dd, J=3.8Hz & 0.6Hz), 7.36 (1H, d, J=3.7Hz), 7.52-7.57 (2H, m), 7.60-7.65 (1H, m), 7.74-7.77 (2H, m), 8.00 (1H, dd, J=8.8Hz &1.8Hz), 8.43 (1H, d, J=8.7Hz), 9.11 (1H, 1.4Hz);
**$^{13}$C NMR (75MHz, CDCl$_3$, 293K, TMS):** 11.5, 20.9, 27.2, 63.1, 109.1, 116.6, 119.8, 122.3, 123.8, 124.2, 128.6, 128.7, 129.2, 130.9, 132.2, 134.1, 136.6, 142.5, 144.1, 168.6, 170.6;
**IR ($\nu_{max}$/cm$^{-1}$):** 3023, 1359, 1115, 681;
**CI-MS** calculated for $C_{23}H_{20}N_2O_4S$ (M+1) 421; Found: 421 (M+1), 420 (M+);
**Melting Point (CHCl$_3$):** 147-149 °C
**Rf:** 0.21 on silica gel (1% MeOH, 10% Acetone in DCM)

Scheme 4.5

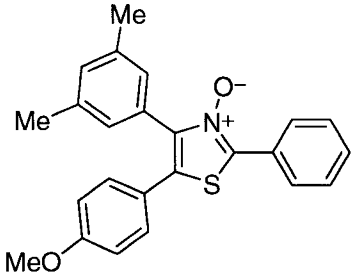


**$^1$H NMR (400MHz, CDCl$_3$, 293K, TMS):** 2.38 (6H, s), 7.07 (1H, s), 7.15 (2H, d), 7.43-7.53 (3H, m), 7.89 (1H, s), 8.35-8.38 (2H, m);
**$^{13}$C NMR (75MHz, CDCl$_3$, 293K, TMS):** 21.3, 123.7, 126.9, 128.0, 128.8, 128.9, 130.4, 131.7, 133.4, 134.3, 139.2, 142.6;
**IR *($\nu_{max}$/cm$^{-1}$)*:** 3044, 1360, 1207, 1035;
**HRMS** calculated for $C_{17}H_{15}NOS$ (M+) 281.0874; Found:281.0877;
**Melting Point (CHCl$_3$):** 179-181 °C
**Rf:** 0.22 on silica gel (25% Acetone in DCM)



**$^1$H NMR (400MHz, CDCl$_3$, 293K, TMS)**: 7.47-7.54 (3H, m), 7.66 (2H, d, J=8.2Hz), 7.74 (2H, d, J=8.2Hz), 8.02 (1H, s), 8.35-8.39 (2H, m);
**$^{13}$C NMR (75MHz, CDCl$_3$, 293K, TMS):** 123.6 (q, J=272.5Hz), 126.2, 126.5 (q, J=3.7Hz), 126.9, 127.7, 129.0, 130.9, 131.2, 131.7 (q, J=33.0Hz), 132.4 (q, J=1.1Hz), 135.8, 143.8;
**IR *($\nu_{max}$/cm$^{-1}$)*:** 3135, 1653, 1538, 1351, 1197, 1012;
**HRMS** calculated for $C_{16}H_{10}F_3NOS$ (M+) 321.0435; Found: 321.0443;
**Melting Point (CHCl$_3$):** 213-215 °C
**Rf:** 0.22 on silica gel (20% Acetone in DCM)

Scheme 4.6



**$^1$H NMR (400MHz, CDCl$_3$, 293K, TMS)**: 2.31 (6H, s), 3.79 (3H, s), 6.82 (2H, d, J=8.9Hz), 7.07 (1H, s), 7.11 (2H, s), 7.22 (2H, d, J=9.0Hz), 7.41-7.50 (3H, m), 8.43-8.45 (2H, m);
**$^{13}$C NMR (75MHz, CDCl$_3$, 293K, TMS):** 21.3, 55.3, 114.4, 122.8, 127.0, 128.5, 128.6, 128.8, 129.1, 129.6, 130.2, 131.2, 138.1, 141.5, 144.0, 160.3;
**IR *($\nu_{max}$/cm$^{-1}$)*:** 2919, 1607, 1506, 1250, 827;
**HRMS** calculated for $C_{24}H_{21}NO_2S$ (M+) 387.1293; Found: 387.1274;
**Melting Point (CHCl$_3$):** 192-193 °C
**Rf:** 0.22 on silica gel (20% EtOAc in Hexanes)

# Chapter 6

## $sp^3$ Direct Arylation of Picoline *N*-Oxides Procedures:

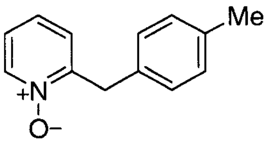
**Procedure A :** Using Microwave Irradiation

All reactions were performed on 0.6 mmol scale: $Pd_2dba_3$ (0.025 equiv.), X-Phos (0.05 equiv.), $NaO^tBu$ (3 equiv.), and Azine *N*-oxide (1.5 equiv.) are weighed to air and placed in a microwave tube with a magnetic stir bar (if the aryl halide is a solid, it is also added). The flask is capped with a rubber septa and purged with argon. The aryl halide (1 equiv.) is then added via syringe followed by degassed (with Argon) ACS grade toluene (0.5-1.0M). The rubber septa is then replace by a microwave tube cap and the mixture is then placed in the a CEM Discover microwave reactor at 110°C for 30-45 minutes (conditions: max. power: 200W; T°: 110°C; max. pressure: 250 psi). The reaction is then diluted with 50mL of DCM and filtered through celite then evaporated under reduced pressure. The residue is then loaded onto a silica gel column for chromatography typically using DCM/Acetone/MeOH mixtures.

**Procedure B:** Using Conventional Heating

All reactions were performed on 0.6 mmol scale: $Pd_2dba_3$ (0.025 equiv.), S-Phos or Ru-Phos (0.1 equiv.), $NaO^tBu$ (3 equiv.), and Azine *N*-oxide (2 equiv.) are weighed to air and placed in a test-tube with a magnetic stir bar (if the aryl halide is a solid, it is also added). The flask is capped with a rubber septa and purged with argon. The aryl halide (1 equiv.) is then added via syringe followed by degassed (with Argon) ACS grade toluene (0.3M). The mixture is then placed in an oil bath and the heat source is set to 69°C. Reactions were left stirring at this temprature for 12-15hours (overnight, reaction times were not optimized). The reaction is then diluted with 50mL of DCM and filtered through celite then evaporated under reduced pressure. The residu is then loaded onto a silica gel column for chromatography typically using DCM/Acetone/MeOH mixtures.

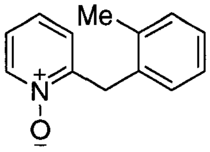
Table 6.2, Entry 1



Obtained in 89% yield as a yellow oil.

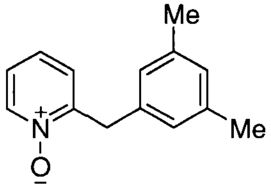
**$^1$H NMR (400MHz, $CDCl_3$, 293K, TMS):** 2.35 (3H, s), 4.22 (2H, s), 6.92-6.95 (1H, m), 7.10-7.17 (6H, m), 8.28-8.30 (1H, m);
**$^{13}$C NMR (100MHz, $CDCl_3$, 293K, TMS):** 21.1, 36.1, 123.4, 125.5, 125.7, 129.6, 129.6, 133.1, 136.7, 139.4, 152.3.
**IR ($\nu_{max}$/cm$^{-1}$):** 2922, 1436, 1245, 766
**HRMS** calculated for $C_{13}H_{13}NO$ (M+) 199.0997; Found: 199.1010;
**M.P.**: 47-49 °C (Chloroform)
**Rf:** 0.18 (1%MeOH, 15% $Me_2CO$, DCM)

Table 6.2, Entry 5



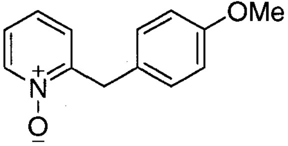
Obtained in 92% yield as a yellow oil.
**$^1$H NMR (300MHz, CDCl$_3$, 293K, TMS):** 2.20 (3H, s), 4.25 (2H, s), 6.71 (1H,d, J=7.5Hz), 7.10-7.25 (6H, m), 8.33 (1H, d, J=6.0Hz)
**$^{13}$C NMR (75MHz, CDCl$_3$, 293K, TMS):** 19.3, 34.4, 123.4, 125.0, 125.6, 126.5, 127.5, 130.6, 134.4, 137.2, 139.4, 151.3. There is an overlapping peak.
**IR (*$v_{max}$* /cm$^{-1}$):** 3019, 1489, 1435, 1244, 745
**HRMS** calculated for $C_{13}H_{13}NO$ (M+) 199.0997; Found: 199.0987;
**Rf:** 0.22 (1%MeOH, 20% Me$_2$CO, DCM)

Table 6.2, Entry 6



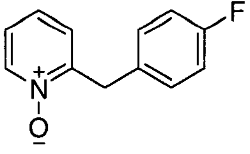
Obtained in 93% yield as a yellow oil.
**$^1$H NMR (400MHz, CDCl$_3$, 293K, TMS):** 2.30 (6H, s), 4.20 (2H, s), 6.88-7.14 (6H, m), 8.28 (1H, s)
**$^{13}$C NMR (100MHz, CDCl$_3$, 293K, TMS):** 21.3, 36.3, 123.4, 125.8, 127.5, 128.7, 136.1, 138.4, 139.5, 152.4 There is an overlapping peak
**IR (*$v_{max}$* /cm$^{-1}$):**2923, 1604, 1487, 1435, 1239, 848
**HRMS** calculated for $C_{14}H_{15}NO$ (M+) 213.1154; Found: 213.1175;
**Rf:** 0.17 (1%MeOH, 20% Me$_2$CO, DCM)

Table 6.2, Entry 7



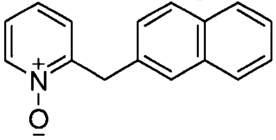
Obtained in 72% yield as a white solid.
**$^1$H NMR (400MHz, CDCl$_3$, 293K, TMS):** 3.81 (3H, s), 4.20 (2H, s), 6.88-6.91 (2H, m), 6.93-6.96 (1H, m), 7.10-7.16 (2H, m), 7.18-7.22 (2H, m), 8.28 (1H, s)
**$^{13}$C NMR (100MHz, CDCl$_3$, 293K, TMS):** 35.7, 55.3, 114.3, 123.4, 125.5, 125.7, 128.2, 130.8, 139.4, 152.4, 158.7
**IR (*$v_{max}$* /cm$^{-1}$):**2931, 1512, 1436, 1247, 1031
**HRMS** calculated for $C_{13}H_{13}NO_2$ (M+) 215.0946 Found: 215.0948;
**M.P.**: 94-96 °C (Chloroform)
**Rf:** 0.16 (1%MeOH, 20% Me$_2$CO, DCM)

Table 6.2, Entry 8



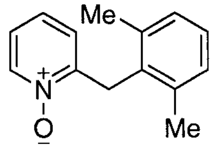
Obtained in 72% yield as a yellow solid.
**$^1$H NMR (400MHz, $CDCl_3$, 293K, TMS):** 4.24 (2H, s), 6.95-7.00 (1H,m), 7.01-7.06 (2H, m), 7.14-7.19 (2H, m), 7.23-7.28 (2H, m), 8.27-8.31 (1H, m)
**$^{13}$C NMR (100MHz, $CDCl_3$, 293K, TMS):** 35.8, 115.7 (d, J=21.3Hz), 123.8, 125.5, 125.7, 131.2 (d, J=8.1Hz), 132.0 (d, J=3.3Hz), 139.5, 151.7, 162.0 (d, J=245.4Hz);
**IR (*$v_{max}$* /cm$^{-1}$)**:3075, 2928, 1508, 1222, 770
**HRMS** calculated for $C_{12}H_{10}FNO$(M+) 203.0746 Found: 203.0753;
**M.P.**: 79-81 °C (Chloroform)
**Rf:** 0.17 (1%MeOH, 20% $Me_2CO$, DCM)

Table 6.2, Entry 9



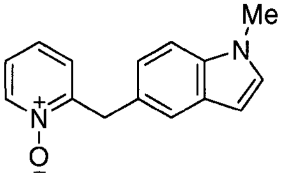
Obtained in 72% yield as a yellow oil.
**$^1$H NMR (400MHz, $CDCl_3$, 293K, TMS):** 4.44 (2H, s), 6.95 (1H, d, J=7.1Hz), 7.05-7.17 (2H, m), 7.38 (1H, d, J=8.4Hz), 7.44-7.50 (2H, m), 7.74 (1H, s), 7.79-7.84 (3H, m), 8.30 (1H, s)
**$^{13}$C NMR (100MHz, $CDCl_3$, 293K, TMS):** 123.5, 125.6, 125.9, 126.3, 127.6, 127.7, 127.8, 128.4, 128.6, 128.8, 132.5, 133.6, 133.8, 139.5,
**IR (*$v_{max}$* /cm$^{-1}$)**:3054, 2927, 1487, 1434, 1241
**HRMS** calculated for $C_{16}H_{13}NO$ (M+) 235.0997 Found: 235.0987;
**Rf:** 0.18 (1%MeOH, 20% $Me_2CO$, DCM)

Table 6.2, Entry 10



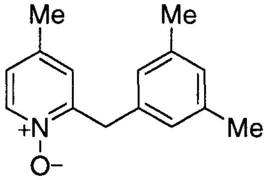
Obtained in 90% yield as a yellow oil.
**$^1$H NMR (400MHz, $CDCl_3$, 293K, TMS):** 2.18 (6H, s), 4.26 (2H, s), 6.56 (1H, d, J=7.7 Hz), 7.07-7.18 (5H, m), 8.36 (1H, d, J=6.3Hz)
**$^{13}$C NMR (100MHz, $CDCl_3$, 293K, TMS):**20.0, 30.6, 123.3, 123.9, 125.7, 127.2, 128.4, 133.0, 137.5, 139.4, 150.5
**IR (*$v_{max}$* /cm$^{-1}$)**:3072, 2921, 1488, 1433, 1242
**HRMS** calculated for $C_{14}H_{15}NO$ (M+) 213.1154 Found: 213.1155;
**Rf:** 0.21 (1%MeOH, 20% $Me_2CO$, DCM)

Table 6.2, Entry 13



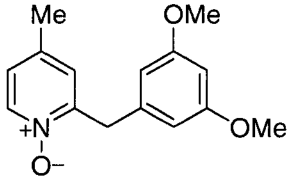
Obtained in 90% yield as a yellow oil.
**$^1$H NMR (400MHz, CDCl$_3$, 293K, TMS):** 3.79 (3H, s), 4.36 (2H, s), 6.45 (1H, d, J=2.9Hz), 6.88 (1H, d, J=7.4Hz), 7.04-7.12 (4H, m), 7.31 (1H, d, J=8.3Hz), 7.52 (1H, s), 8.28 (1H, s)
**$^{13}$C NMR (100MHz, CDCl$_3$, 293K, TMS):** 32.9, 36.5, 100.7, 109.6, 121.9, 123.1, 123.4, 125.6, 125.8, 126.8, 128.9, 129.4, 135.9, 139.2, 153.4
**IR (*ν$_{max}$*/cm$^{-1}$):** 3091, 1488, 1435, 1245, 763;
**HRMS** calculated for $C_{15}H_{14}N_2O$ (M+) 238.1106; Found: 238.1116;
**Rf:** 0.17 (1%MeOH, 20% Me$_2$CO, DCM)

Table 6.3, Entry 1



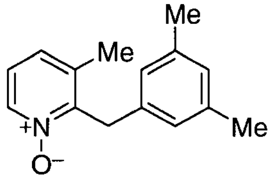
Obtained in 64% yield as a yellow oil.
**$^1$H NMR (500MHz, CDCl$_3$, 293K, TMS:** 2.25 (3H, s), 2.31 (6H, s), 4.17 (2H, s), 6.74 (1H, s, br), 6.89 (2H, s), 6.92-6.95 (2H, m), 8.17 (1H, d, J=6.4Hz)
**$^{13}$C NMR (125MHz, CDCl$_3$, 293K, TMS):** 20.4, 21.3, 36.2, 124.2, 126.3, 127.4, 128.6, 137.1, 138.3, 138.6, 151.2;
**IR (*ν$_{max}$*/cm$^{-1}$):** 2918, 1605, 1477, 1234, 852;
**HRMS** calculated for $C_{15}H_{17}NO$ (M+) 227.1310; Found: 227.1298;
**Rf:** 0.20 (4%MeOH, 20% Me$_2$CO, DCM)

Table 6.3, Entry 2



Obtained in 70% yield as a yellow solid.
**$^1$H NMR (400MHz, CDCl$_3$, 293K, TMS:** 2.24 (3H, s), 3.75 (6H, s), 4.10 (2H, s), 6.38 (1H, t, J=2.3Hz), 6.55 (2H, d, J=2.3Hz), 7.02-7.09 (2H, m), 8.09 (1H, d, J=6.7);
**$^{13}$C NMR (100MHz, CDCl$_3$, 293K, TMS):** 20.1, 36.7, 55.5, 99.2, 108.3, 125.6, 127.4, 136.3, 139.2, 140.7, 150.9, 162.0;
**IR (*ν$_{max}$*/cm$^{-1}$):** 2938, 1595. 1495, 1205, 1064;
**HRMS** calculated for $C_{15}H_{17}NO_3$ (M+) 259.1208; Found: 259.1195;
**m.p.** : 109-111 °C (CHCl$_3$)
**Rf:** 0.21 (3%MeOH, 15% Me$_2$CO, DCM)

Table 6.3, Entry 3



Obtained in 90% yield as a orange solid.

**$^1$H NMR (400MHz, CDCl$_3$, 293K, TMS:** 2.24 (6H, s), 2.32 (3H, s), 4.36 (2H, s), 6.82 (1H, s, br), 6.86 (2H, s, br), 7.05 (2H, d, J=4.1Hz), 8.19 (1H, d, J=3.9Hz)

**$^{13}$C NMR (100MHz, CDCl$_3$, 293K, TMS):** 19.3, 21.3, 32.5, 122.8, 126.1, 127.4, 128.2, 135.9, 136.6, 137.5, 138.0, 150.4;

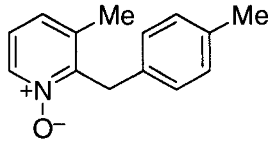
**IR (*$v_{max}$* /cm$^{-1}$)**: 2915, 1603, 1422, 1248, 822;

**HRMS** calculated for $C_{15}H_{17}NO$ (M+) 227.1310; Found: 227.1297;

**m.p.** : 108-110 °C (CHCl$_3$)

**Rf:** 0.16 (1.5%MeOH, 15% Me$_2$CO, DCM)

Table 6.3, Entry 4



Obtained in 90% yield as a yellow solid.

**$^1$H NMR (400MHz, CDCl$_3$, 293K, TMS:** 2.28 (3H, s), 2.32 (3H, s), 4.38 (2H, s), 7.04-7.07 (4H, m), 7.17 (2H, d, J=7.84Hz), 8.18 (1H, s);

**$^{13}$C NMR (100MHz, CDCl$_3$, 293K, TMS):** 19.3, 21.0, 32.3, 122.8, 127.7, 128.3, 129.2, 133.7, 135.7, 136.0, 137.5, 150.6;

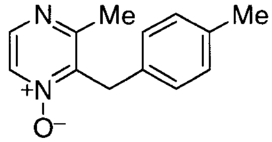
**IR (*$v_{max}$* /cm$^{-1}$)**: 3049, 1429, 1250, 809;

**HRMS** calculated for $C_{14}H_{15}NO$ (M+) 213.1154; Found: 213.1143;

**m.p.** : 100-102 °C (CHCl$_3$)

**Rf:** 0.18 (1.5%MeOH, 15% Me$_2$CO, DCM)

Table 6.3, Entry 5



Obtained in 79% yield as a yellow oil.

**$^1$H NMR (300MHz, CDCl$_3$, 293K, TMS:** 2.30 (3H, s), 2.60 (3H, s), 4.31 (2H,s), 7.08 (2H, d, J=8..1Hz), 7.14 (2H, d, J=8.1Hz), 8.04 (1H, d, J=4.3Hz), 8.21 (1H, d, J=4.3Hz);

**$^{13}$C NMR (75MHz, CDCl$_3$, 293K, TMS):** 21.0, 22.4, 31.4, 128.2, 129.4, 132.0, 132.6, 136.6, 143.6, 145.2, 157.0;

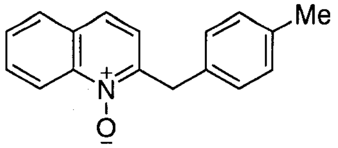
**IR (*$v_{max}$* /cm$^{-1}$)**: 2923, 1513, 1423, 1251, 791;

**HRMS** calculated for $C_{15}H_{17}NO$ (M+) 214.1166; Found: 214.1166;

**m.p.** : 95-97 °C (CHCl$_3$)

**Rf:** 0.20 (2%MeOH, 10% Me$_2$CO, DCM)

Table 6.3, Entry 6



Obtained in 73% yield as a yellow oil.

**$^1$H NMR (400MHz, CDCl$_3$, 293K, TMS):** 2.35 (3H, s), 4.44, (2H, s), 7.06 (1H, d, J=8.7Hz), 7.16 (2H, d, J=7.9Hz), 7.22 (2H, d, J=8.0Hz), 7.57-7.61 (2H, m), 7.75 (1H, ddd, J=7.2Hz & 7.0Hz & 1.18Hz), 7.80 (1H, d, J=8.1Hz), 8.81 (1H, d, J=8.8Hz)

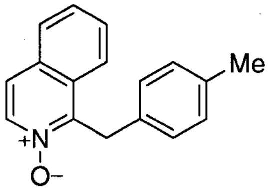
**$^{13}$C NMR (100MHz, CDCl$_3$, 293K, TMS):** 21.1, 37.0, 119.8, 121.9, 125.1, 127.9, 128.0, 129.1, 129.6, 129.6, 130.4, 133.4, 136.6, 141.6;

**IR** ***($v_{max}$* /cm$^{-1}$):** 2922, 1513, 1349, 1240, 807

**HRMS** calculated for $C_{17}H_{15}NO$ (M+) 249.1154; Found: 249.1151;

**Rf:** 0.19 (1%MeOH, 1% Me$_2$CO, DCM)

Table 6.3, Entry 7



Obtained in 60% yield as a light yellow solid.

**$^1$H NMR (400MHz, CDCl$_3$, 293K, TMS):** 2.26 (3H, s), 4.77, (2H, s), 7.05 (2H, d, J=7.8Hz), 7.24 (2H, d, J=8.0Hz), 7.51-7.56 (2H, m), 7.59 (1H, ddd, J=7.0Hz & 7.0Hz & 1.3Hz), 7.75 (1H, d, J=7.9Hz), 8.00 (1H, d, J=8.0Hz), 8.22 (1H, d, J=7.0Hz)

**$^{13}$C NMR (100MHz, CDCl$_3$, 293K, TMS):** 21.0, 31.3, 122.5, 124.0, 127.4, 128.1, 128.5, 128.9, 128.9, 129.3, 133.9, 136.1, 136.9 (br), 147.1;

1 overlaping signal as one peak is missing even with prolonged scans.

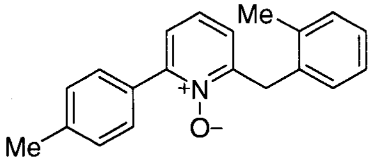
**IR** ***($v_{max}$* /cm$^{-1}$):** 3051, 1513, 1336, 1219, 749

**HRMS** calculated for $C_{17}H_{15}NO$ (M+) 249.1154; Found: 249.1133;

**m.p.** : 170-172°C (CHCl$_3$)

**Rf:** 0.20 (1%MeOH, 15% Me$_2$CO, DCM)

Scheme 6.1



Obtained in 77% yield as a yellow solid.

**$^1$H NMR (400MHz, CDCl$_3$, 293K, TMS):** 2.23 (3H, s), 2.41 (3H, s), 4.29 (2H, s), 6.63 (1H, dd, J=7.1Hz & 2.1Hz), 7.10 (1H, t, J=7.8Hz), 7.19-7.26 (4H, m), 7.27-7.31 (3H, m), 7.73 (2H, d, J=8.2Hz);

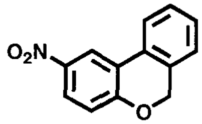
**$^{13}$C NMR (100MHz, CDCl$_3$, 293K, TMS):** 19.4, 21.4., 35.0, 123.4, 124.6, 124.7, 126.5, 127.4, 128.8, 129.4, 130.4, 130.6, 130.7, 135.1, 137.3, 139.4, 149.4, 151.9;

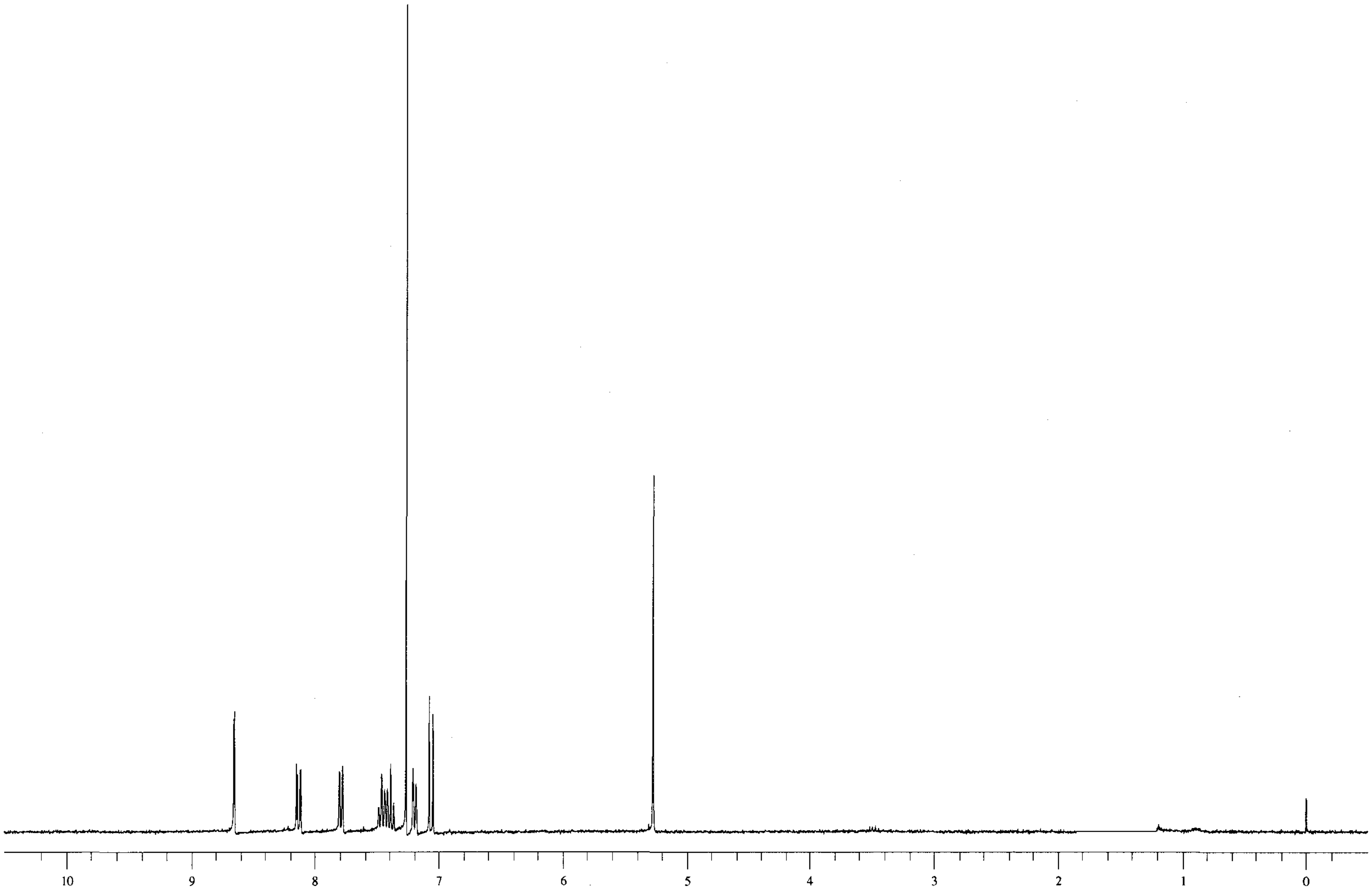
**IR** ***($v_{max}$* /cm$^{-1}$):** 3019, 2921, 1479, 1378, 1254, 770;

**HRMS** calculated for $C_{20}H_{19}NO$ (M+) 289.1467; Found: 289.1445;

**m.p.** : 99-100°C (CHCl$_3$)

**Rf: 0.2** (20% EtOAc, Petroleum Ether)


O2N
O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9
8
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4
3
2
1
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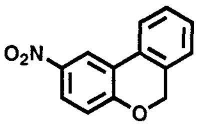
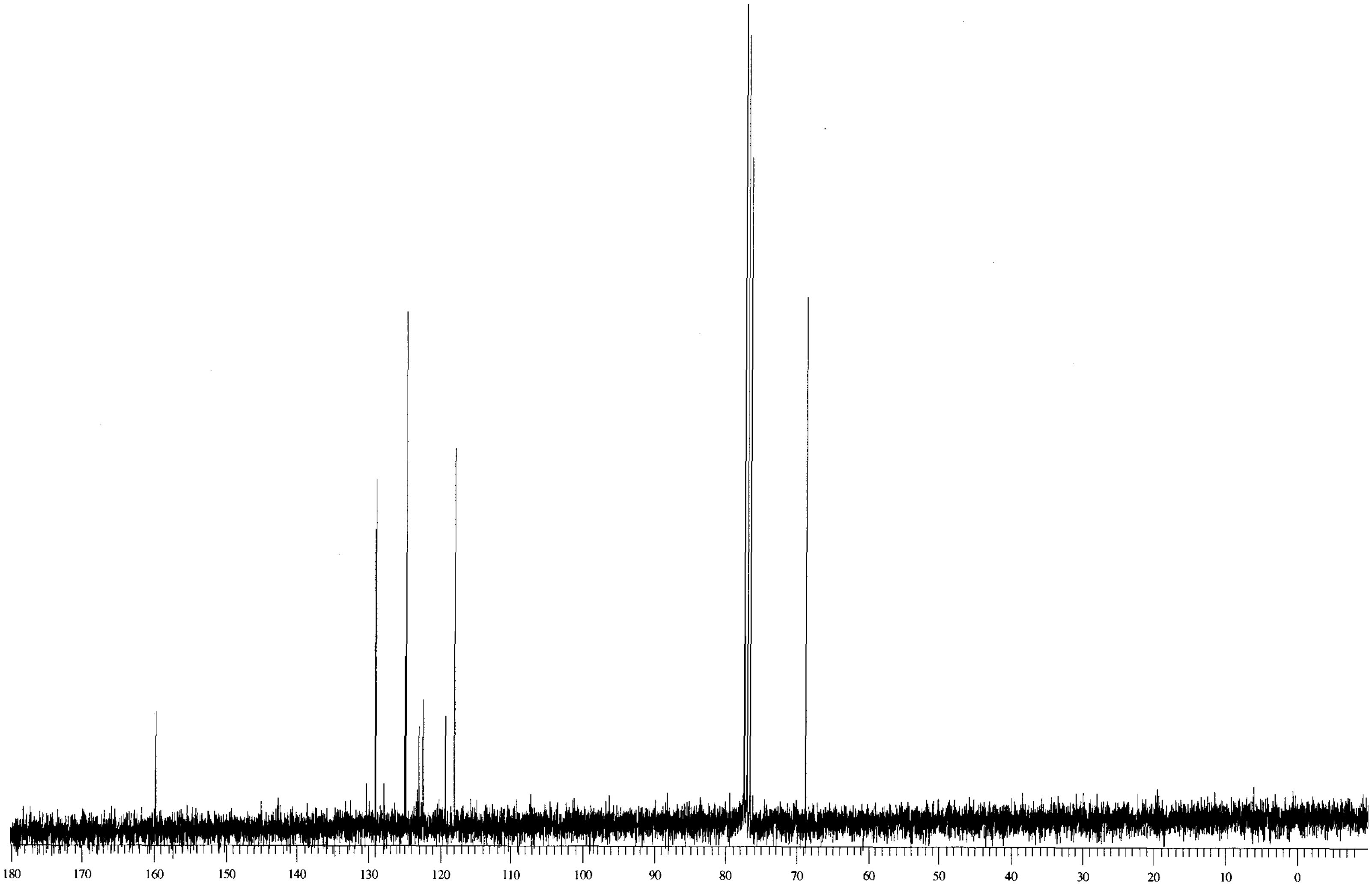

O2N
O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130
120
110
100
90
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70
60
50
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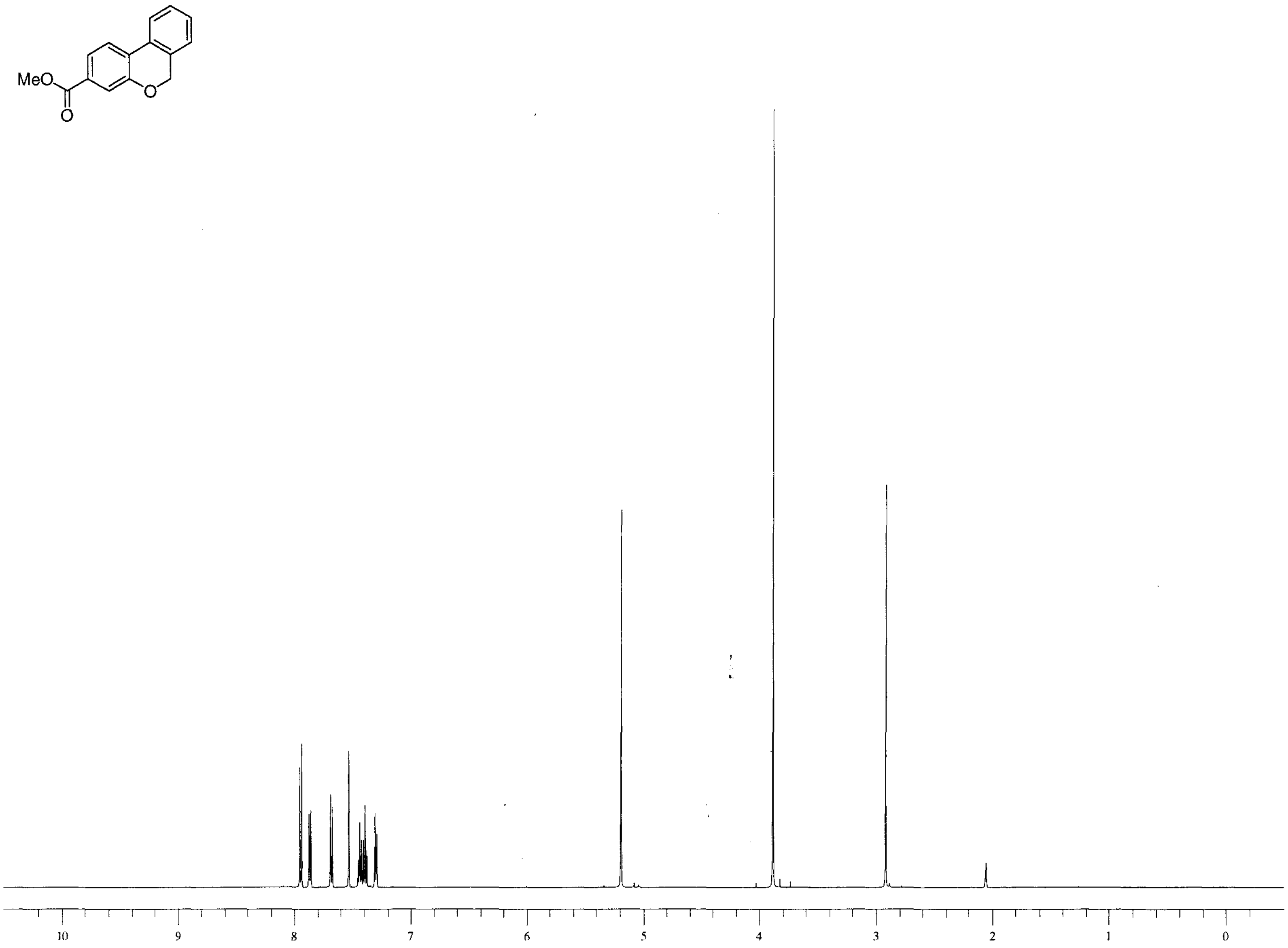
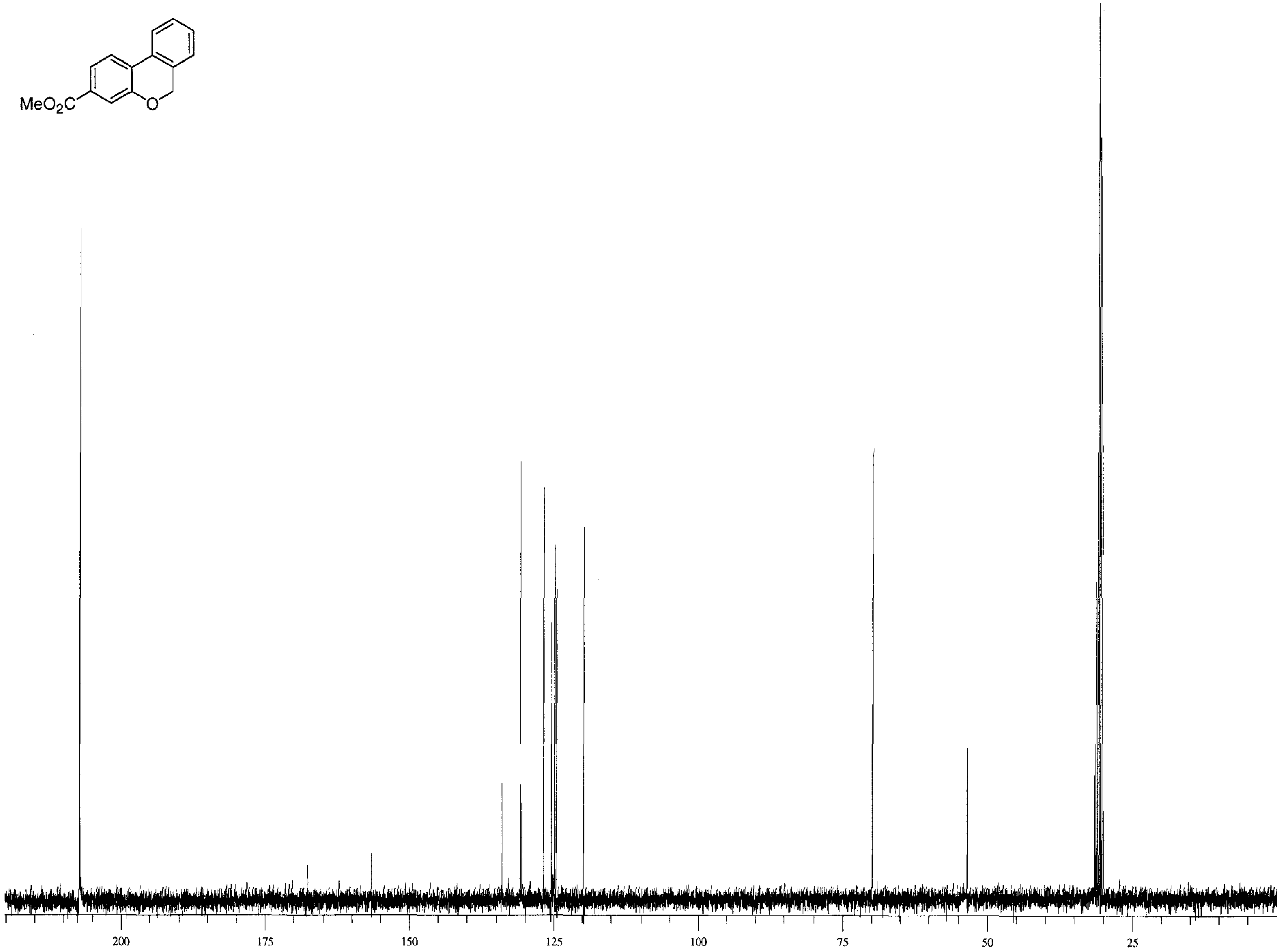
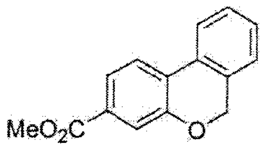
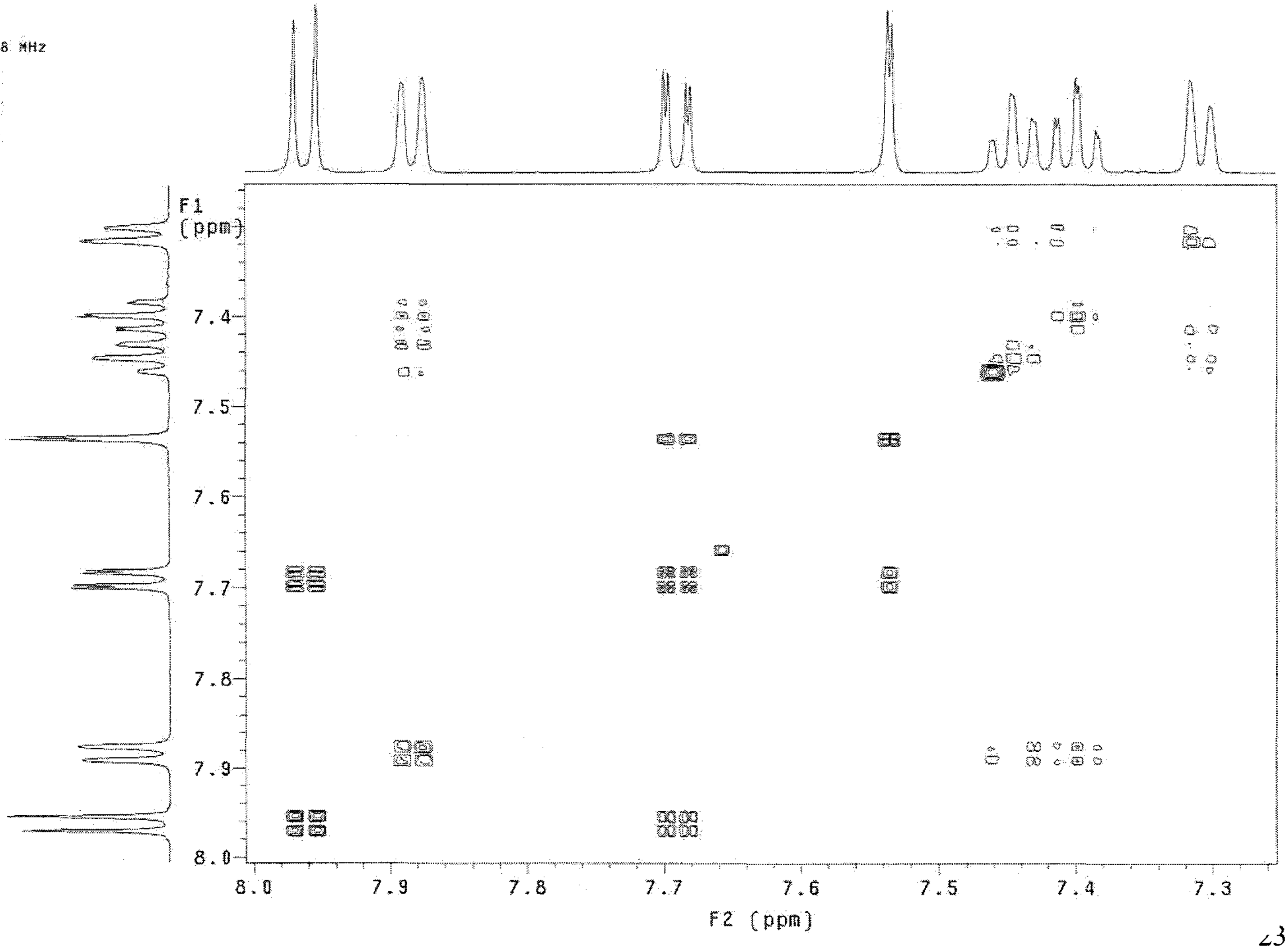
20
10
0

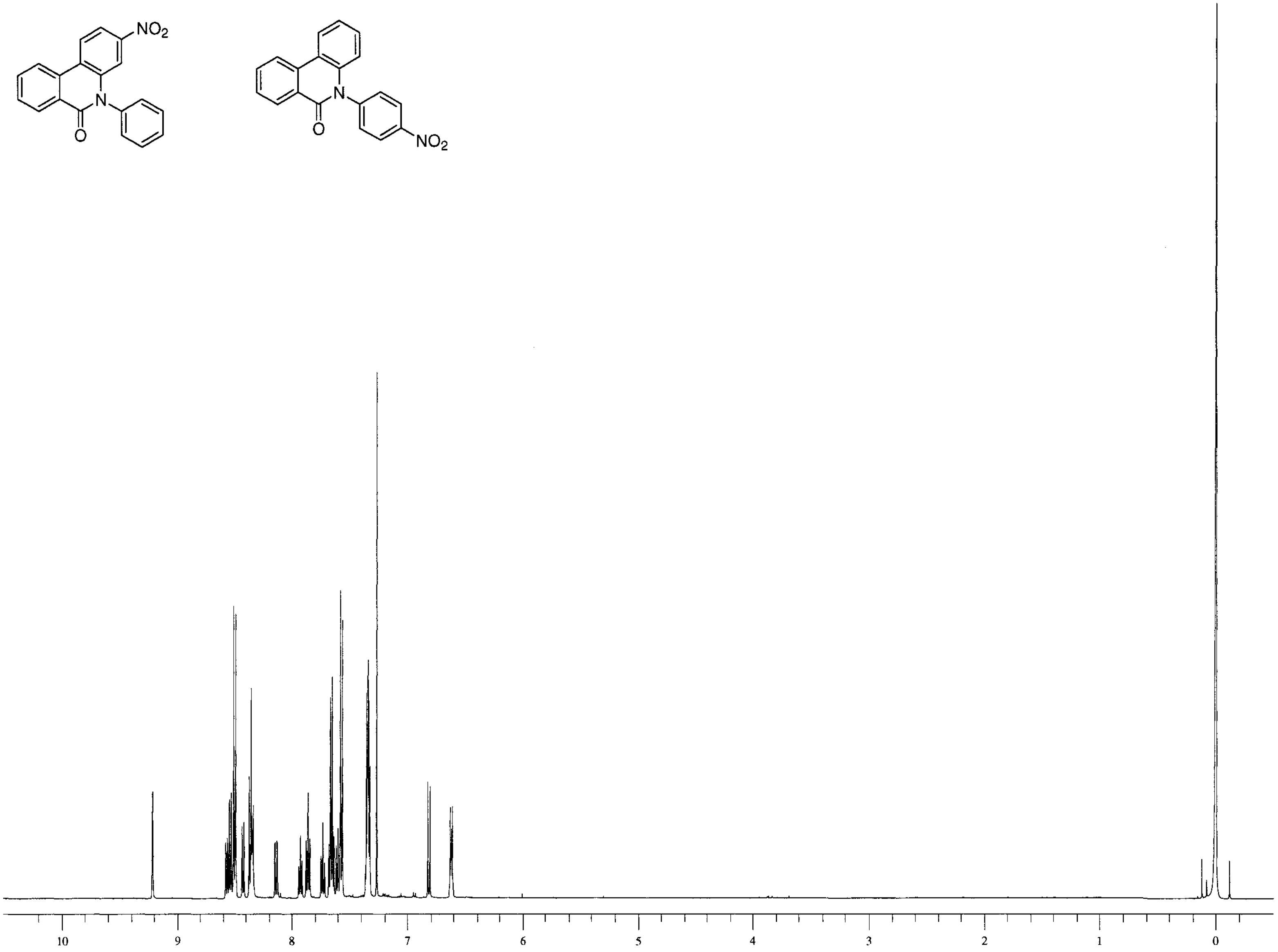

MeO
O
O
10
9
8
7
6
5
4
3
2
1
0

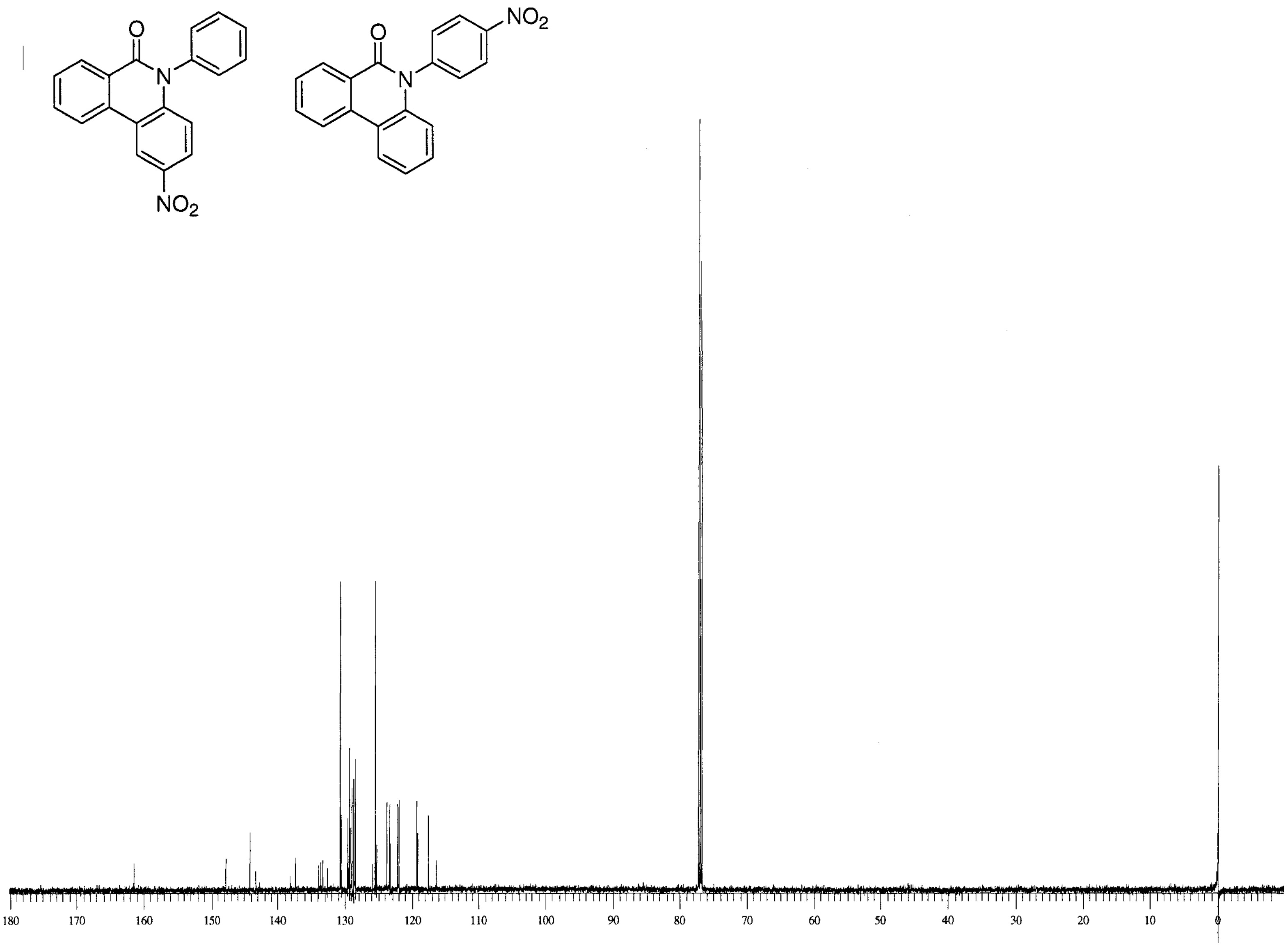

MeO2C
O
200
175
150
125
100
75
50
25

```
STANDARD PROTON PARAMETERS

 Archive directory: /export/home/vnmr1/vnmrsys/data
 Sample directory:
 File: PROTON

Pulse Sequence: gCOSY
 Solvent: Acetone
 Temp. 20.0 C / 293.1 K
INOVA-500  "inova500"

 Relax. delay 1.000 sec
 Acq. time 0.170 sec
 Width    377.1 Hz
 2D Width 377.1 Hz
 Single scan
 350 increments
OBSERVE   H1, 500.1765438 MHz
DATA PROCESSING
 Sq. sine bell 0.085 sec
F1 DATA PROCESSING
 Sq. sine bell 0.339 sec
FT size 1024 x 1024
Total time 9 min, 54 sec
```






NO2
N
O
N
O
NO2
10
9
8
7
6
5
4
3
2
1
0


O
N
NO2
O
N
NO2
180
170
160
150
140
130
120
110
100
90
80
70
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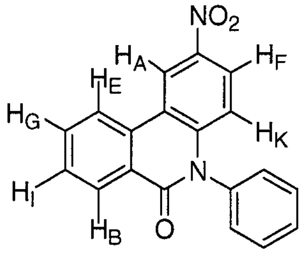
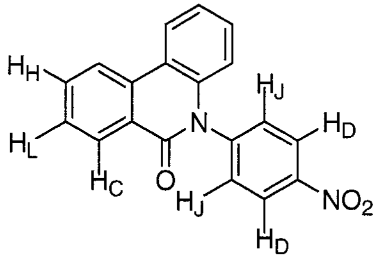
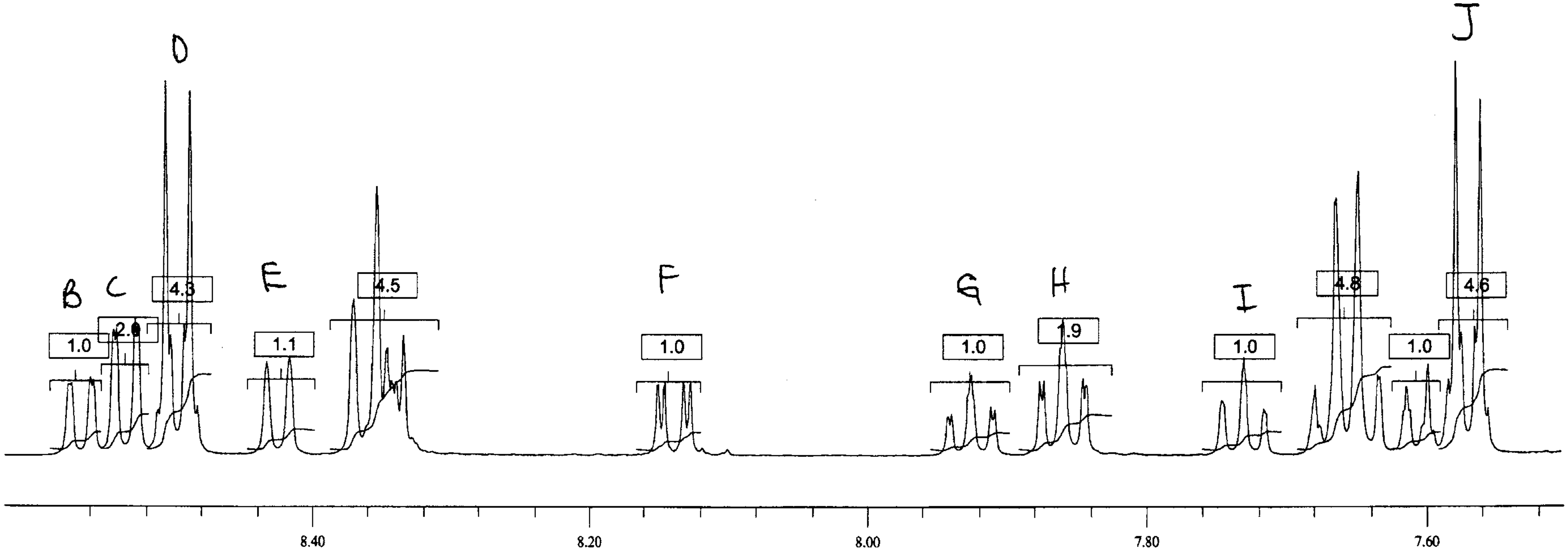
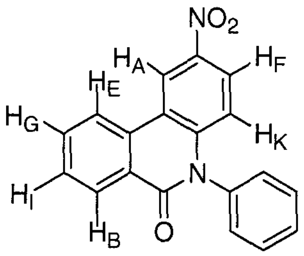
50
40
30
20
10
0

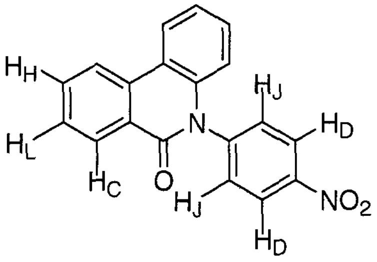

NO2
HA
HF
HE
HG
HK
HI
N
HB
O


HH
HJ
HD
HL
N
HC
O
HJ
NO2
HD

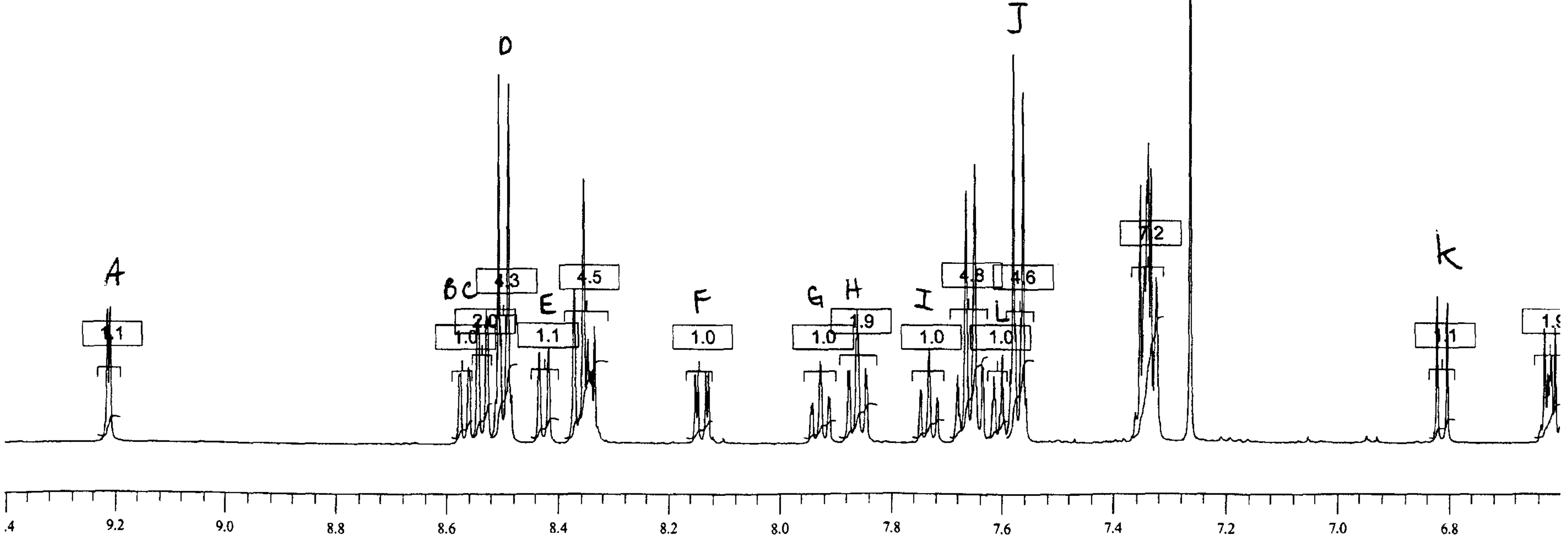

B
C
D
E
F
G
H
I
J
1.0
2.0
4.3
1.1
4.5
1.0
1.0
1.9
1.0
4.8
1.0
4.6
8.40
8.20
8.00
7.80
7.60



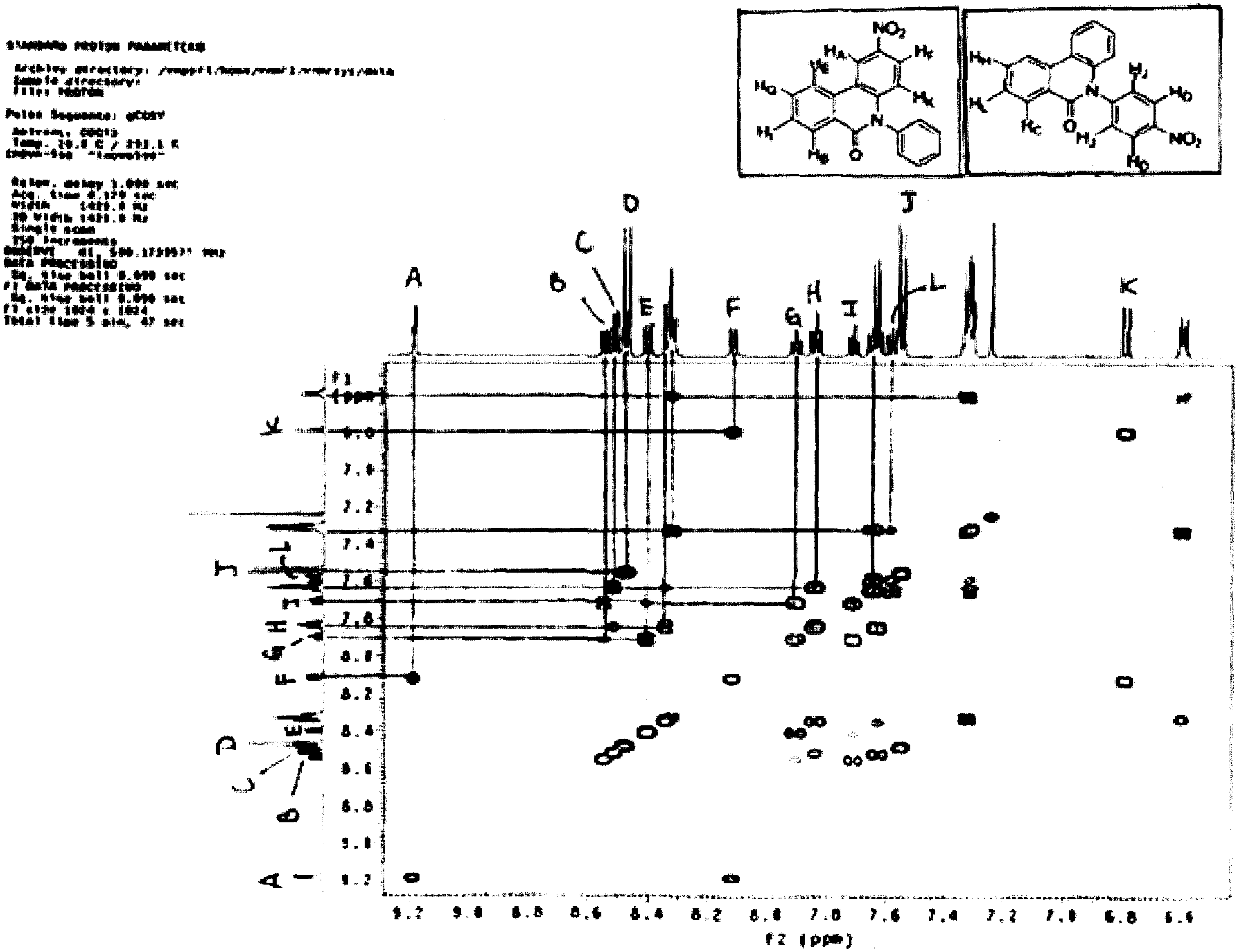
NO$_2$
H$_A$
H$_E$
H$_F$
H$_G$
H$_K$
H$_I$
N
H$_B$
O

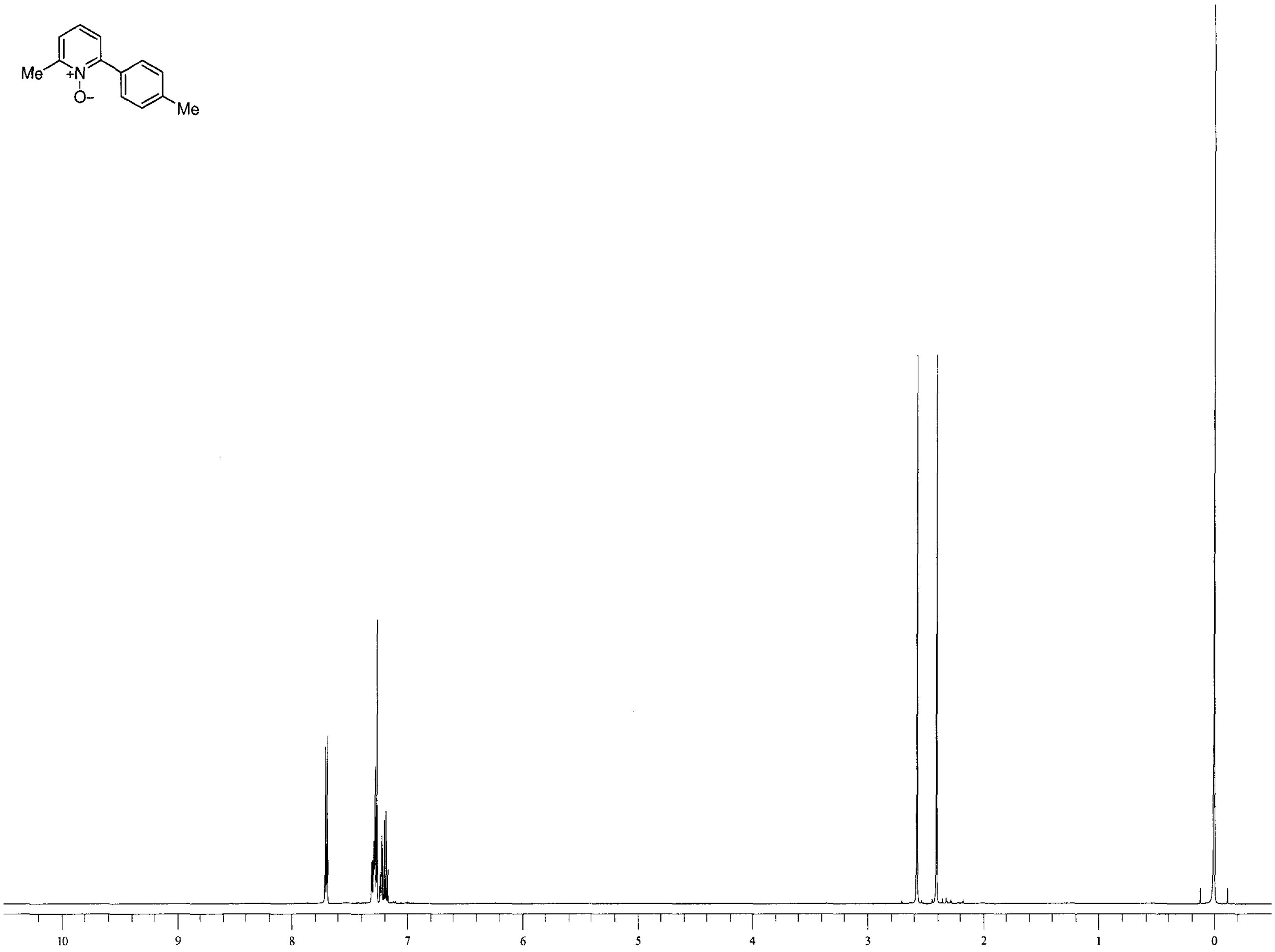


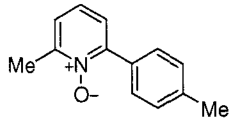
H$_H$
H$_J$
H$_D$
H$_L$
N
H$_C$
O
H$_J$
NO$_2$
H$_D$

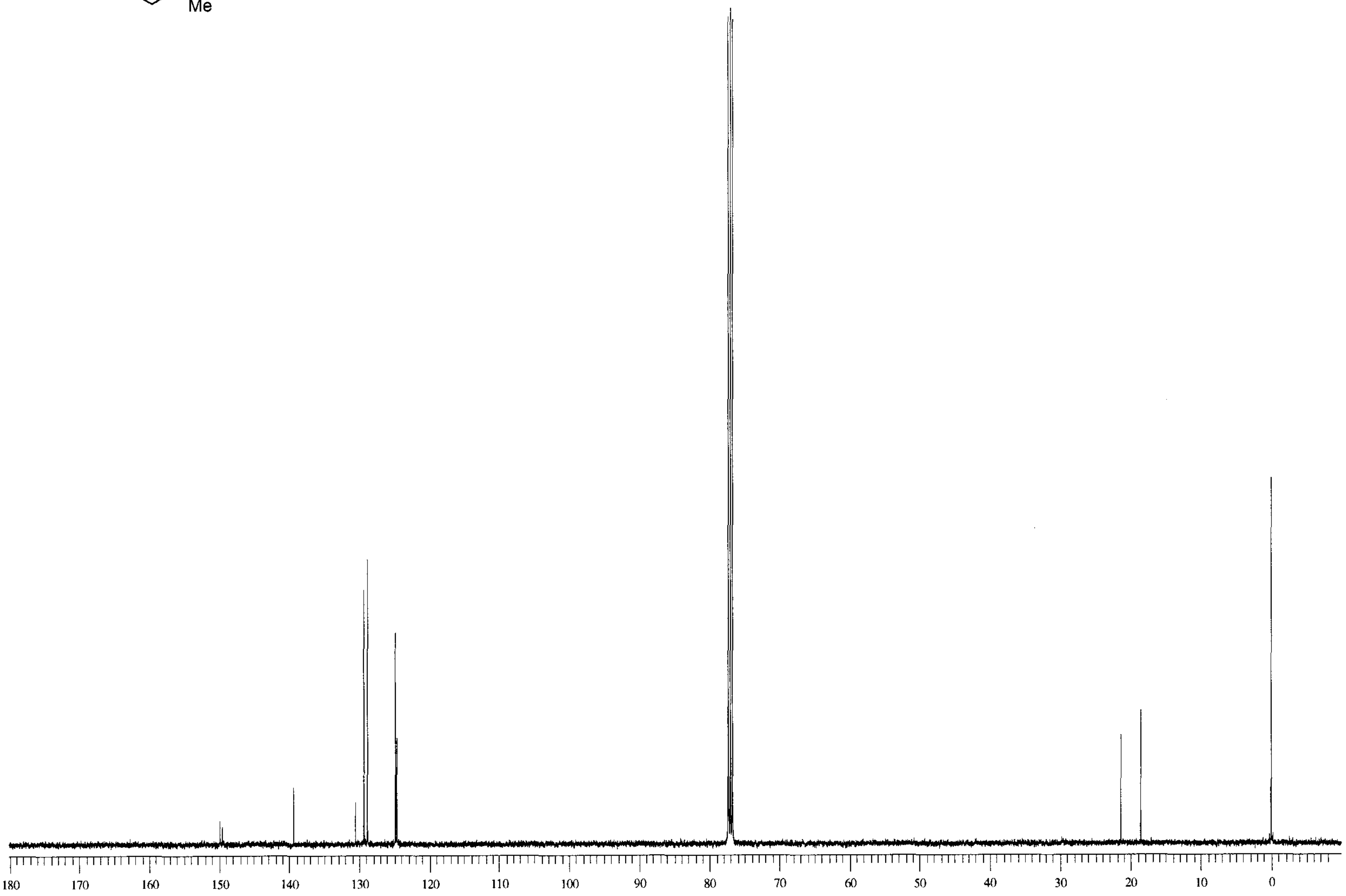


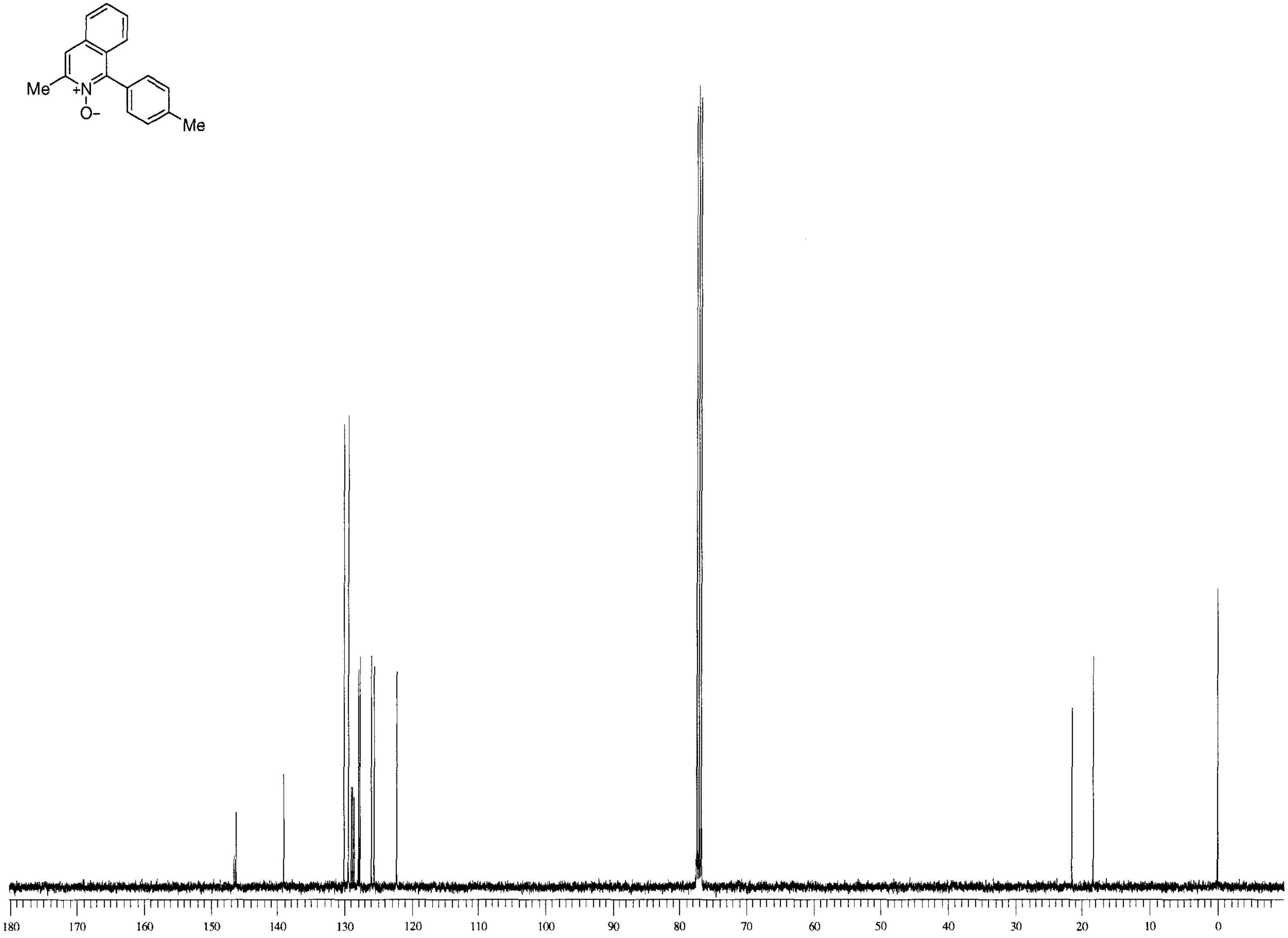
A
1.1
BC
1.0
2.0
4.3
D
E
1.1
4.5
F
1.0
G
1.0
H
1.9
I
1.0
4.8
L
1.0
J
4.6
7.2
K
1.1
1.9
.4
9.2
9.0
8.8
8.6
8.4
8.2
8.0
7.8
7.6
7.4
7.2
7.0
6.8


NO₂
H_A
H_F
H_E
H_K
H_G
H_I
H_B
N
O
H_H
H_C
H_J
H_D
A
B
C
D
E
F
G
H
I
J
K
L
F1
(ppm)
F2 (ppm)
9.2
9.0
8.8
8.6
8.4
8.2
8.0
7.8
7.6
7.4
7.2
7.0
6.8
6.6


Me
+N
O–
Me
10
9
8
7
6
5
4
3
2
1
0


Me
+N
O–
Me


180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


Me
+N
O-
Me
180
170
160
150
140
130
120
110
100
90
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70
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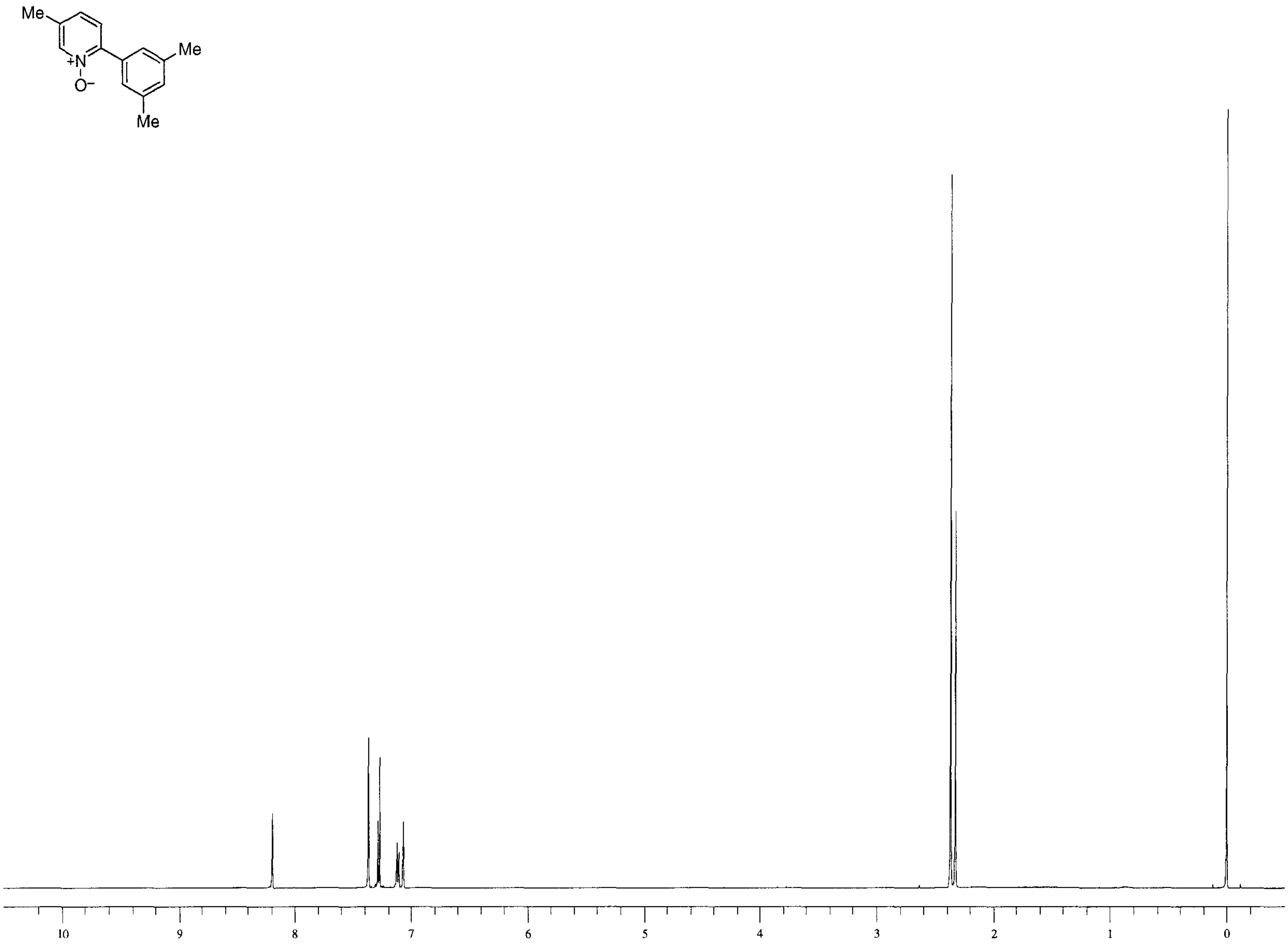
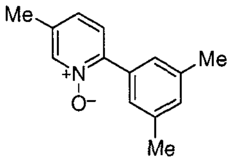
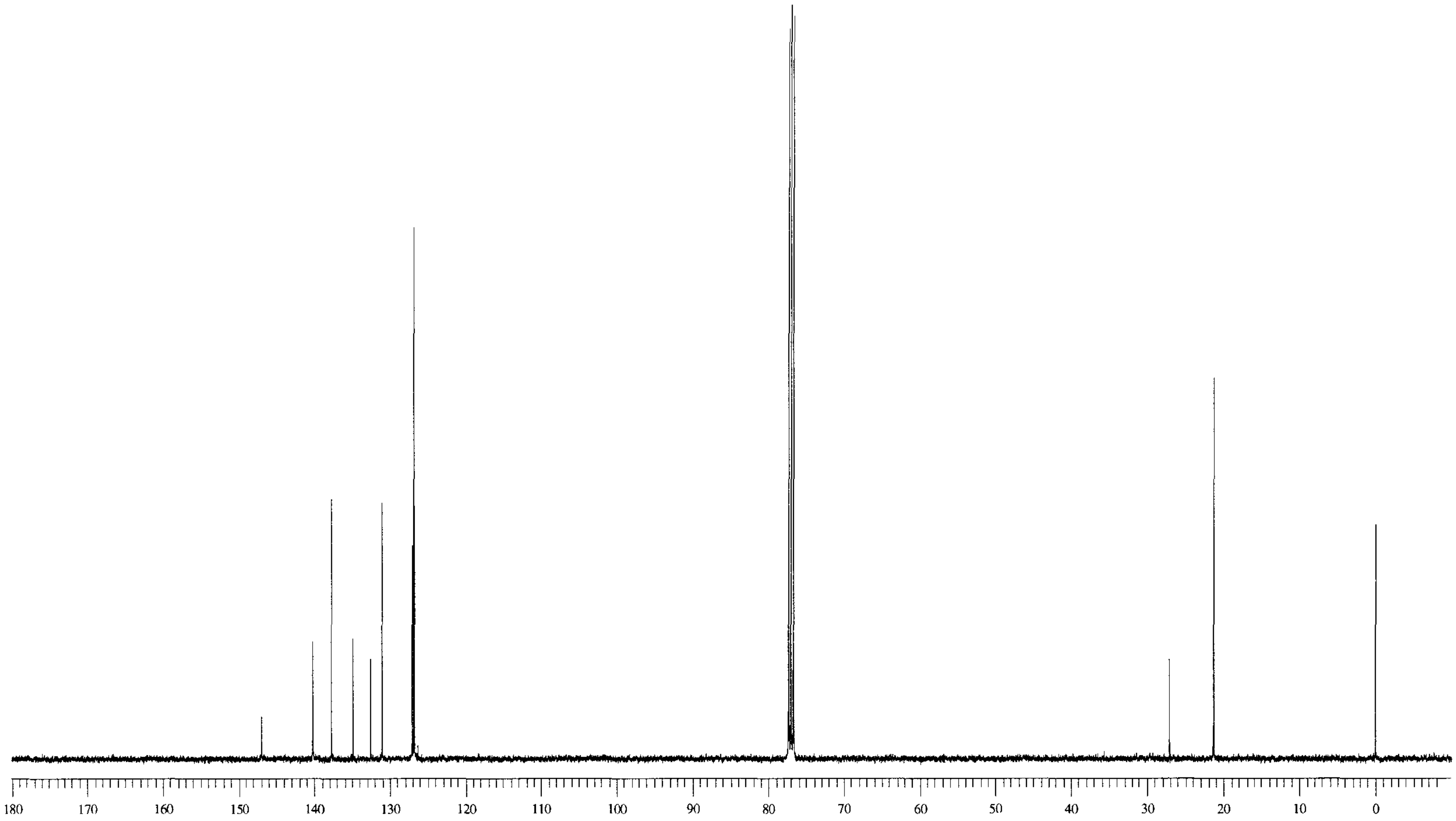
30
20
10
0


Me
+N
O−
Me
Me
10
9
8
7
6
5
4
3
2
1
0


Me
Me
Me
+N
O−


180
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150
140
130
120
110
100
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70
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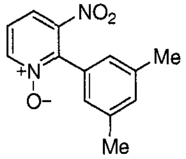
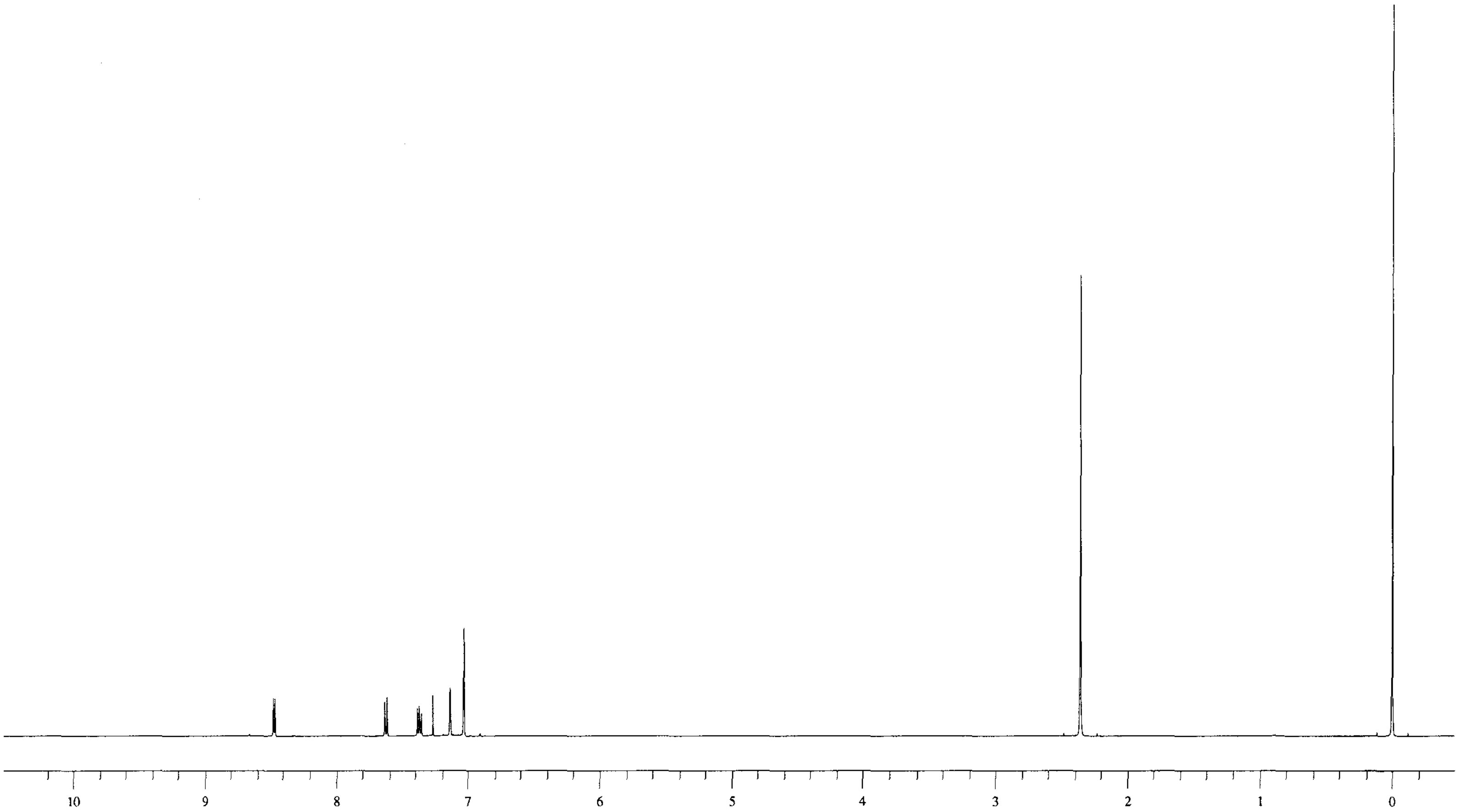
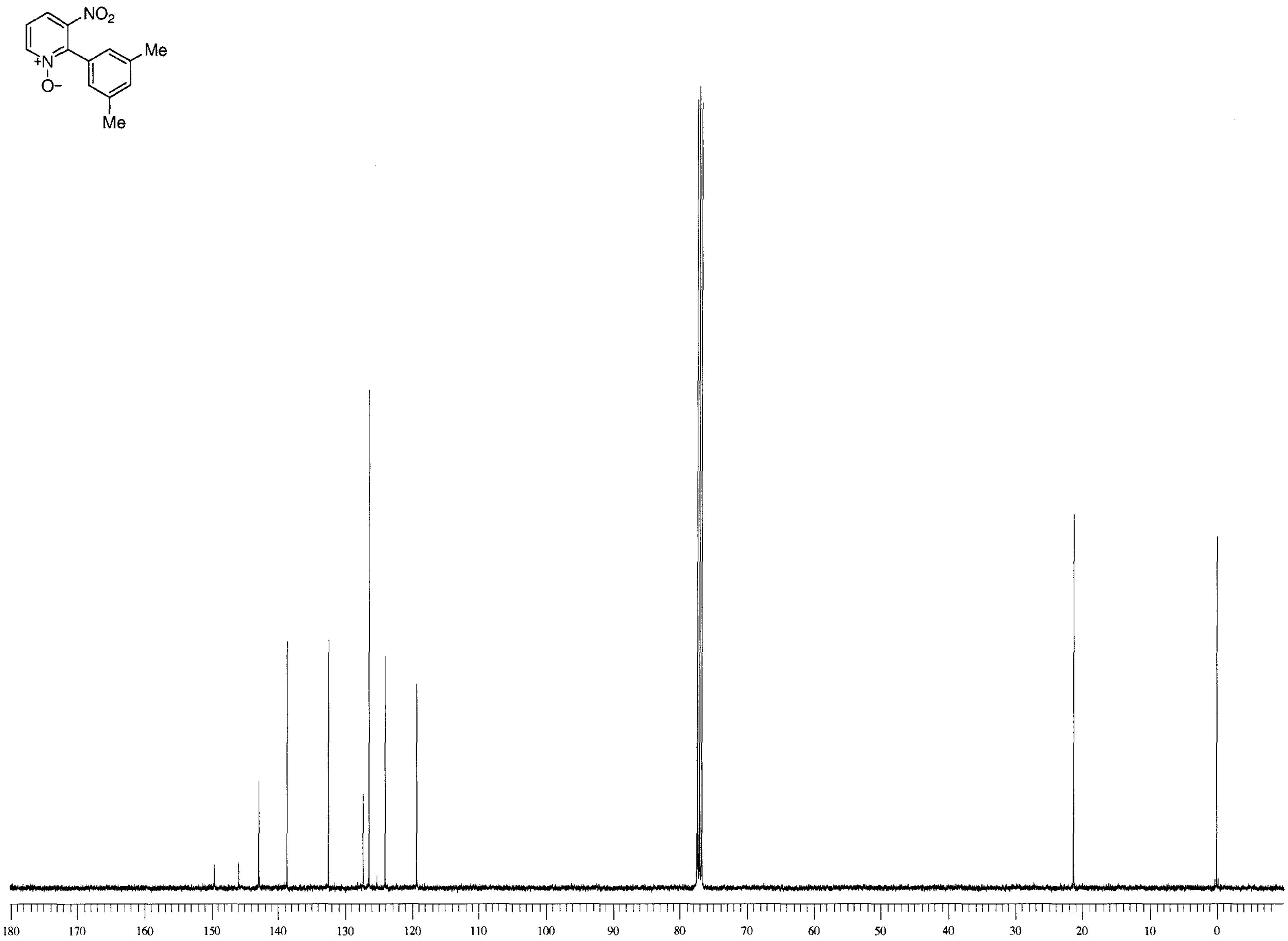
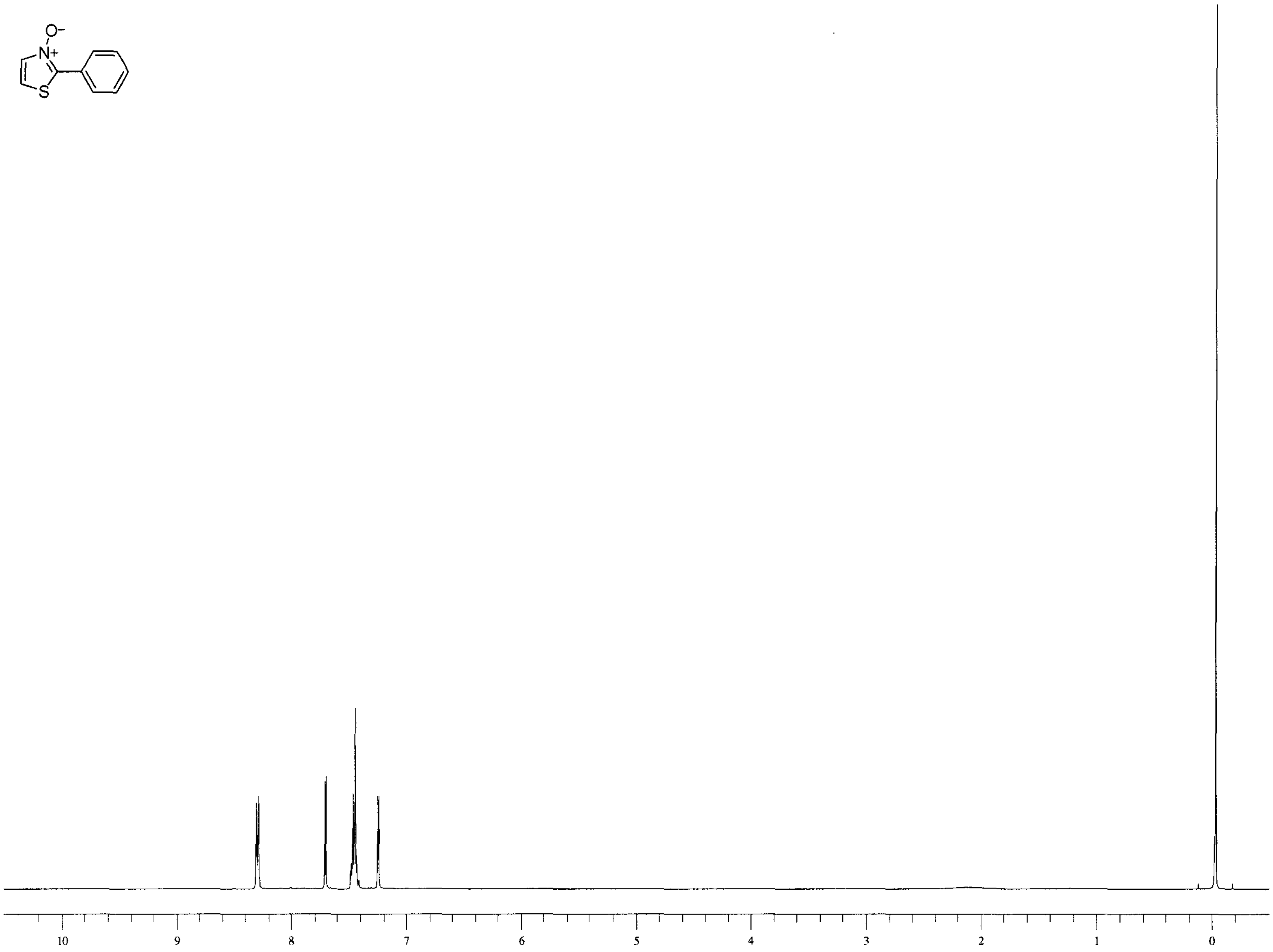
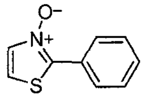
10
0

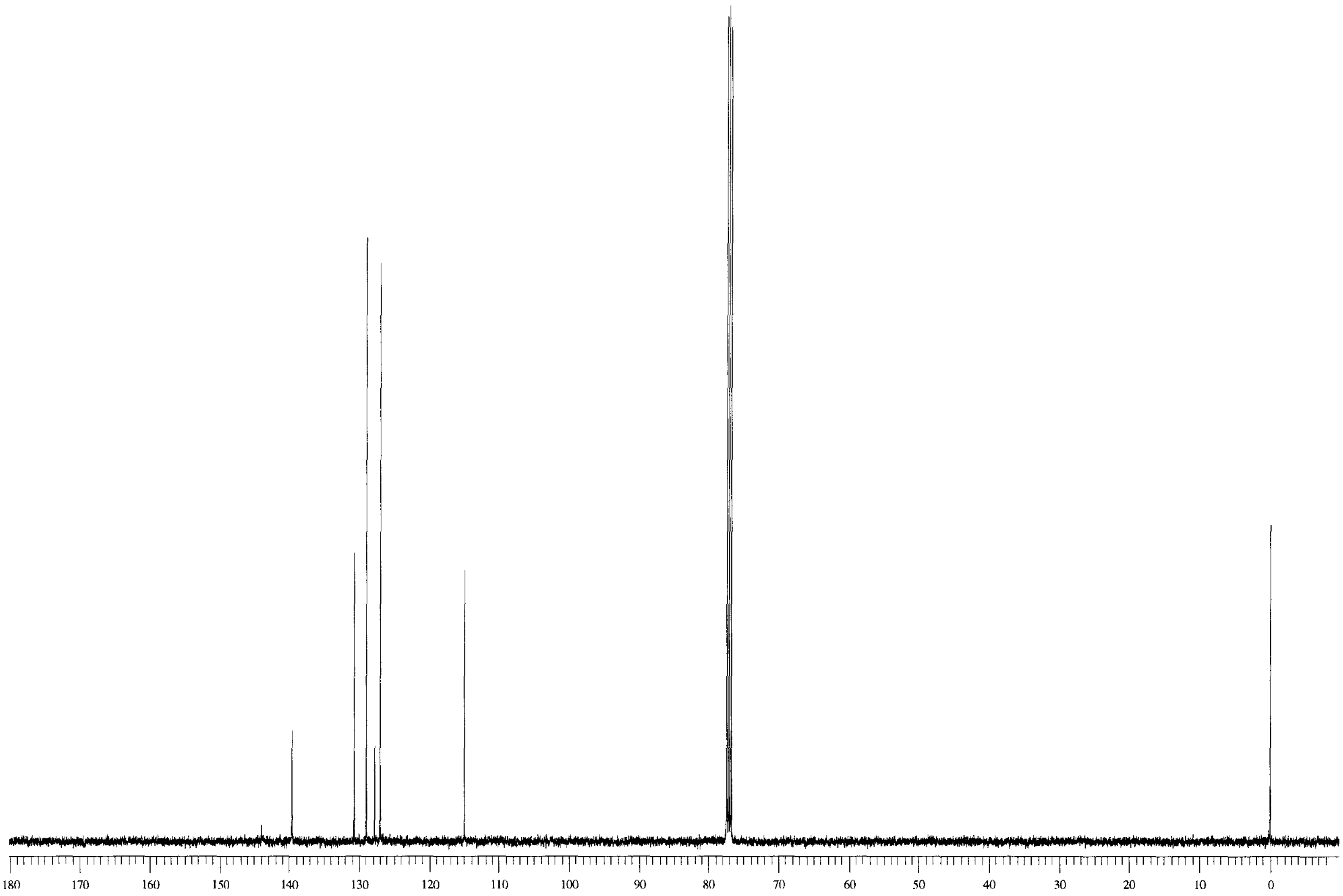

NO2
Me
+N
O−
Me


10
9
8
7
6
5
4
3
2
1
0


NO2
Me
+N
O-
Me
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


O−
N+
S
10
9
8
7
6
5
4
3
2
1
0


O–
N+
S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110
100
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80
70
60
50
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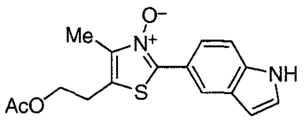
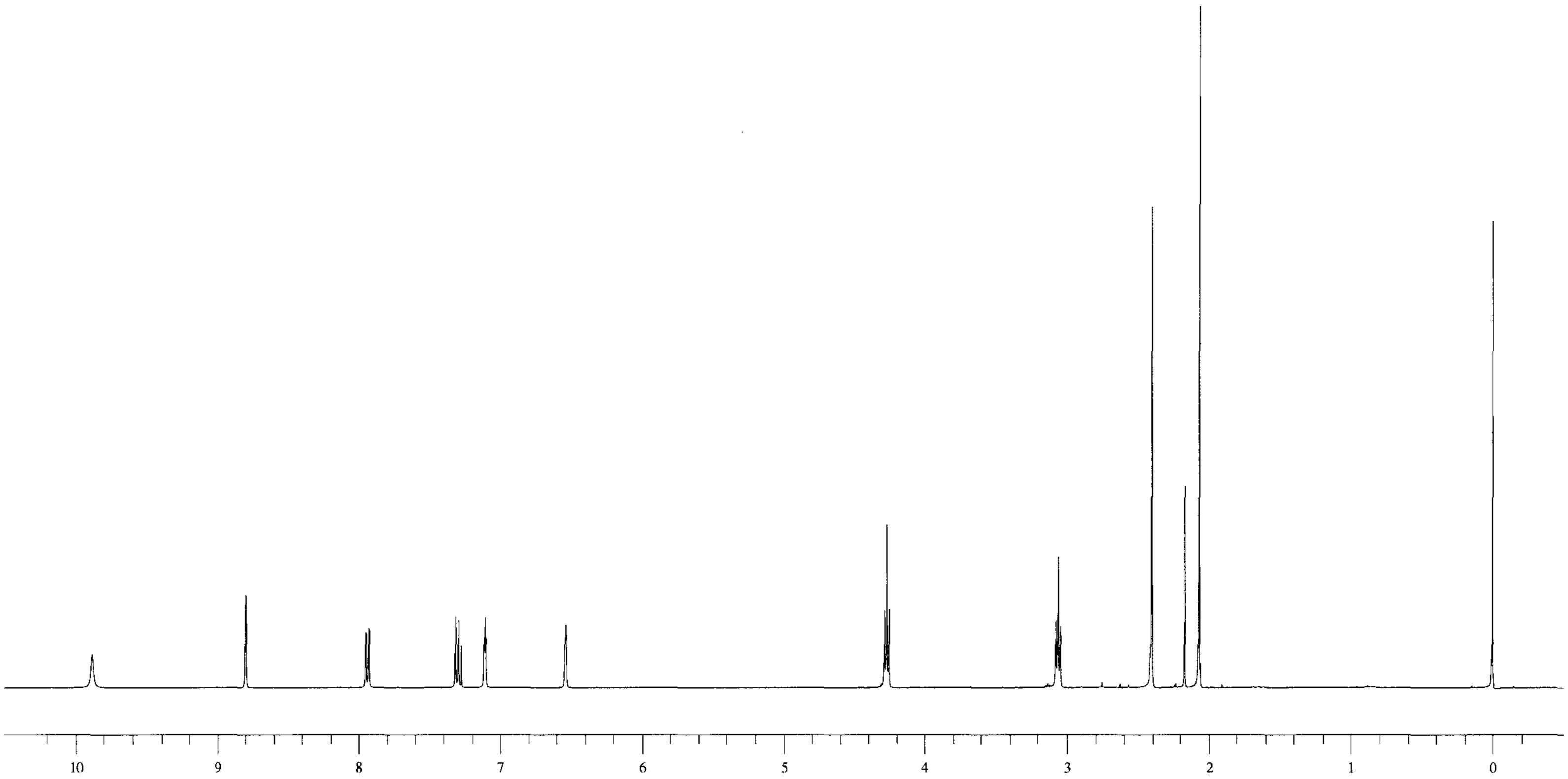
20
10
0


Me
O⁻
N+
S
NH
AcO


10
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6
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4
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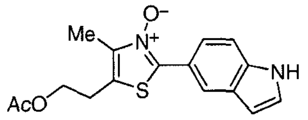
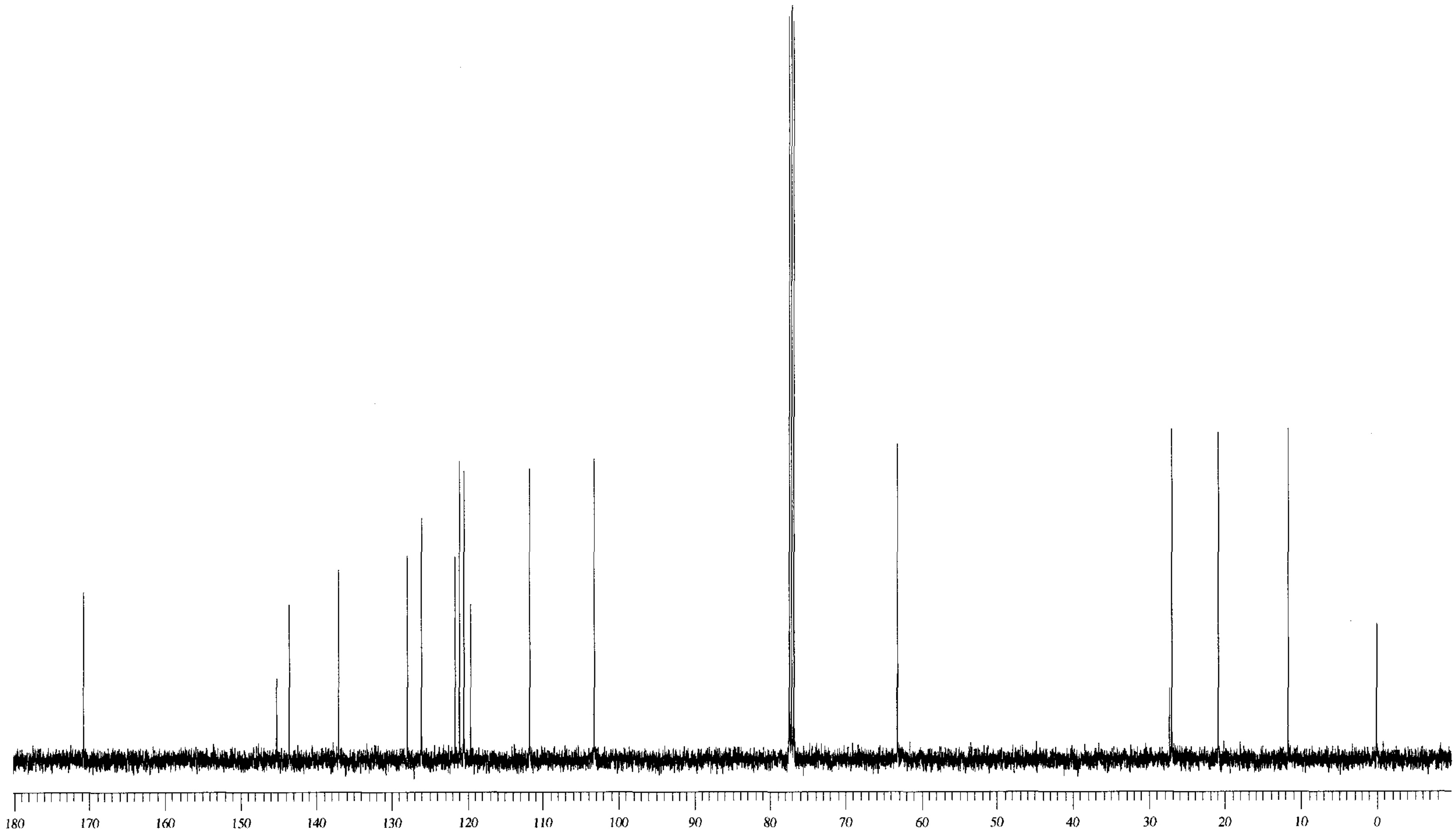

O⁻
Me
N+
S
NH
AcO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100
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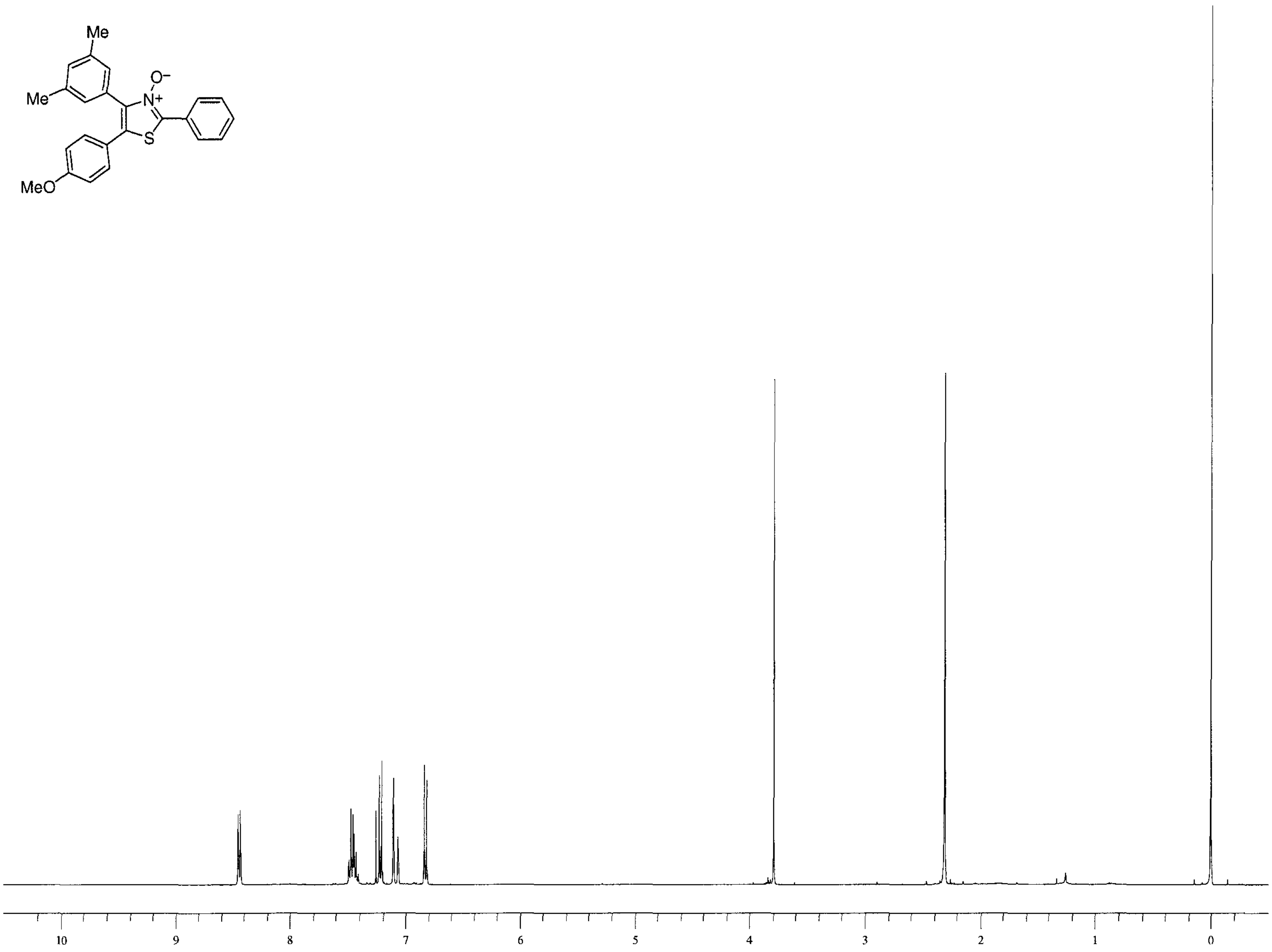
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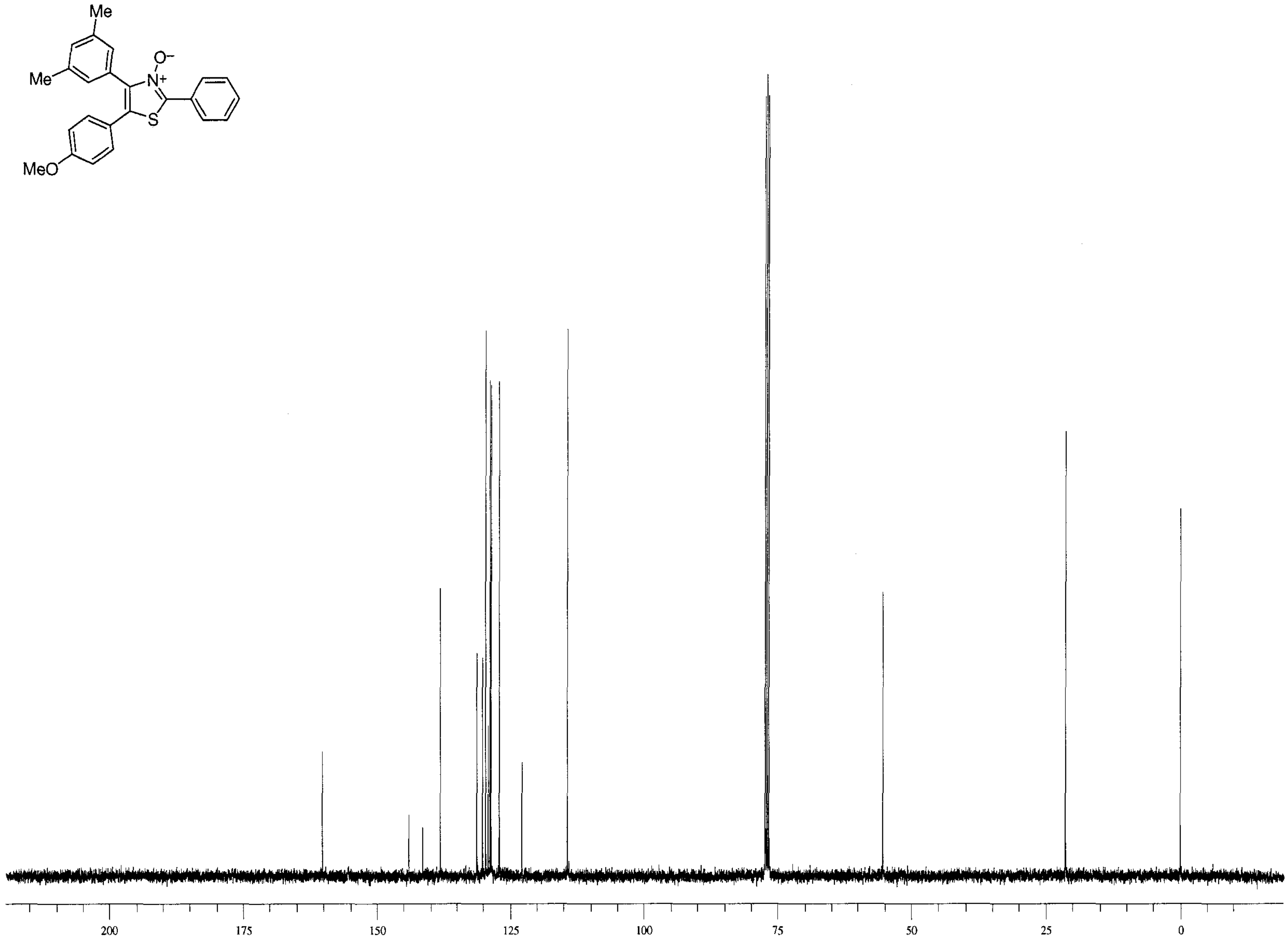
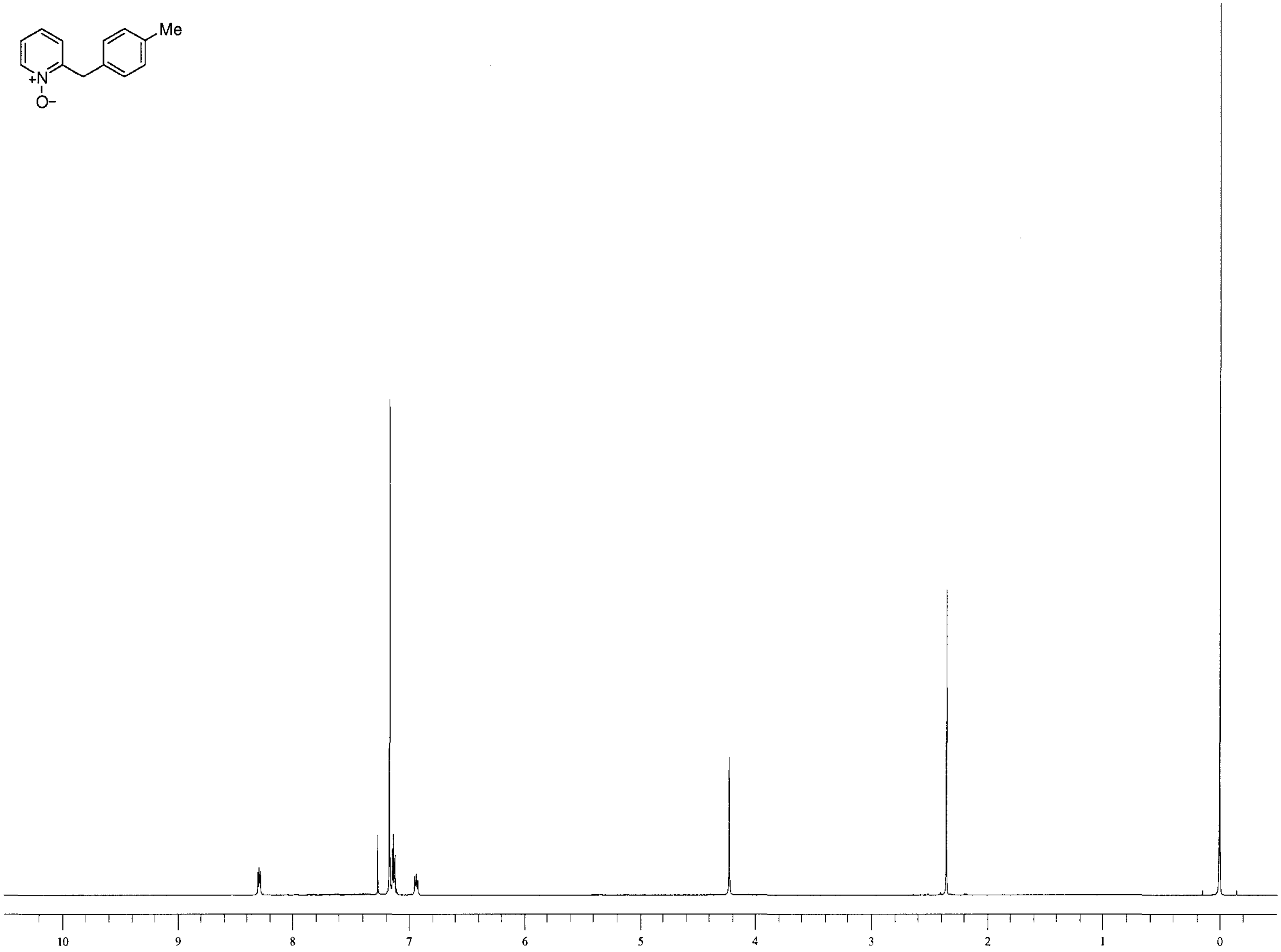
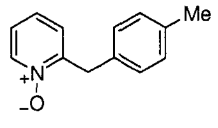
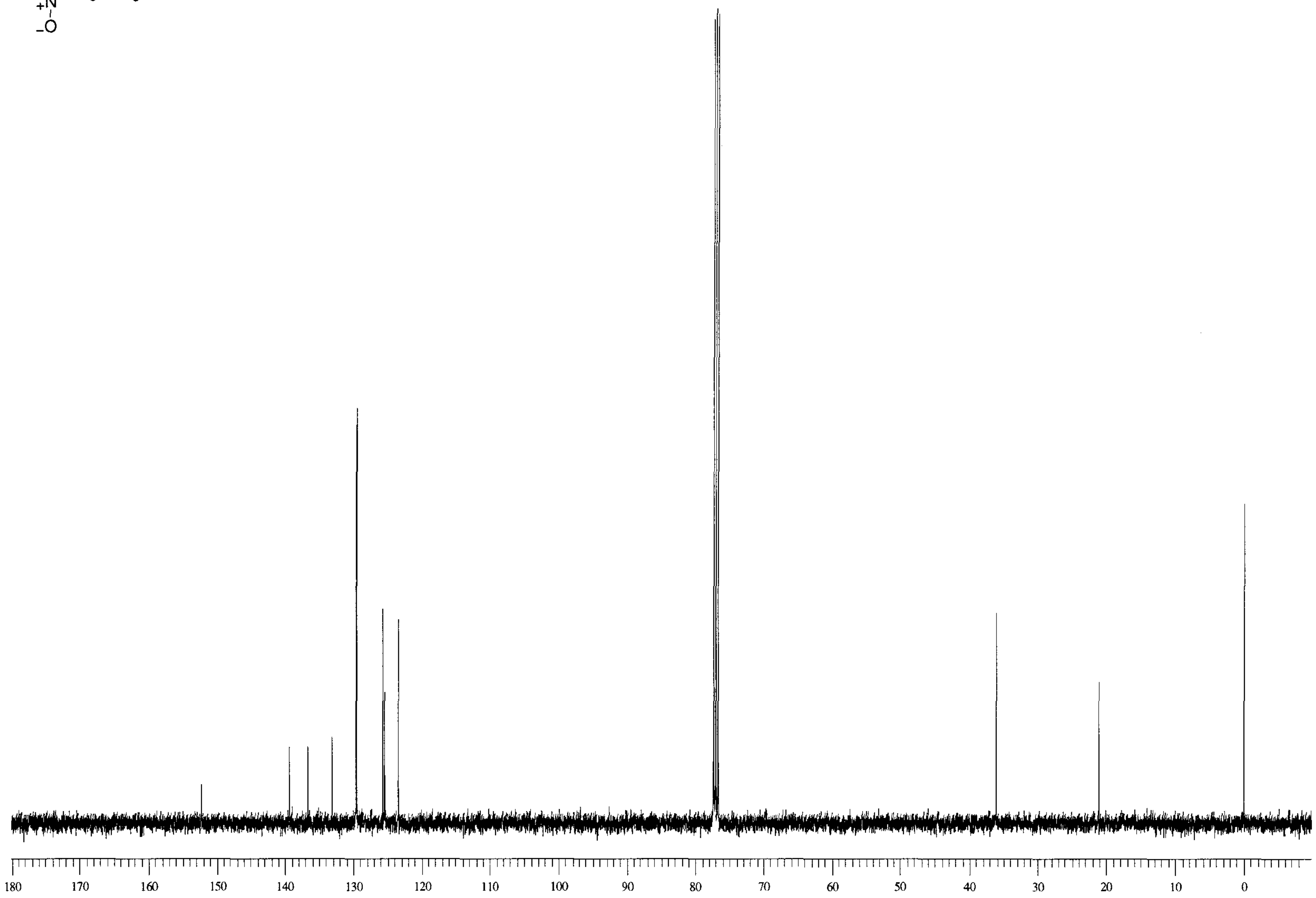
Me
O−
N+
S
MeO
10
9
8
7
6
5
4
3
2
1
0


Me
Me
MeO
O−
N+
S
200
175
150
125
100
75
50
25
0


Me
+N
O–
10
9
8
7
6
5
4
3
2
1
0


Me
+N
-O


180
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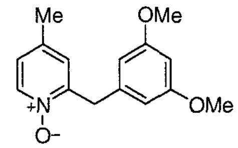
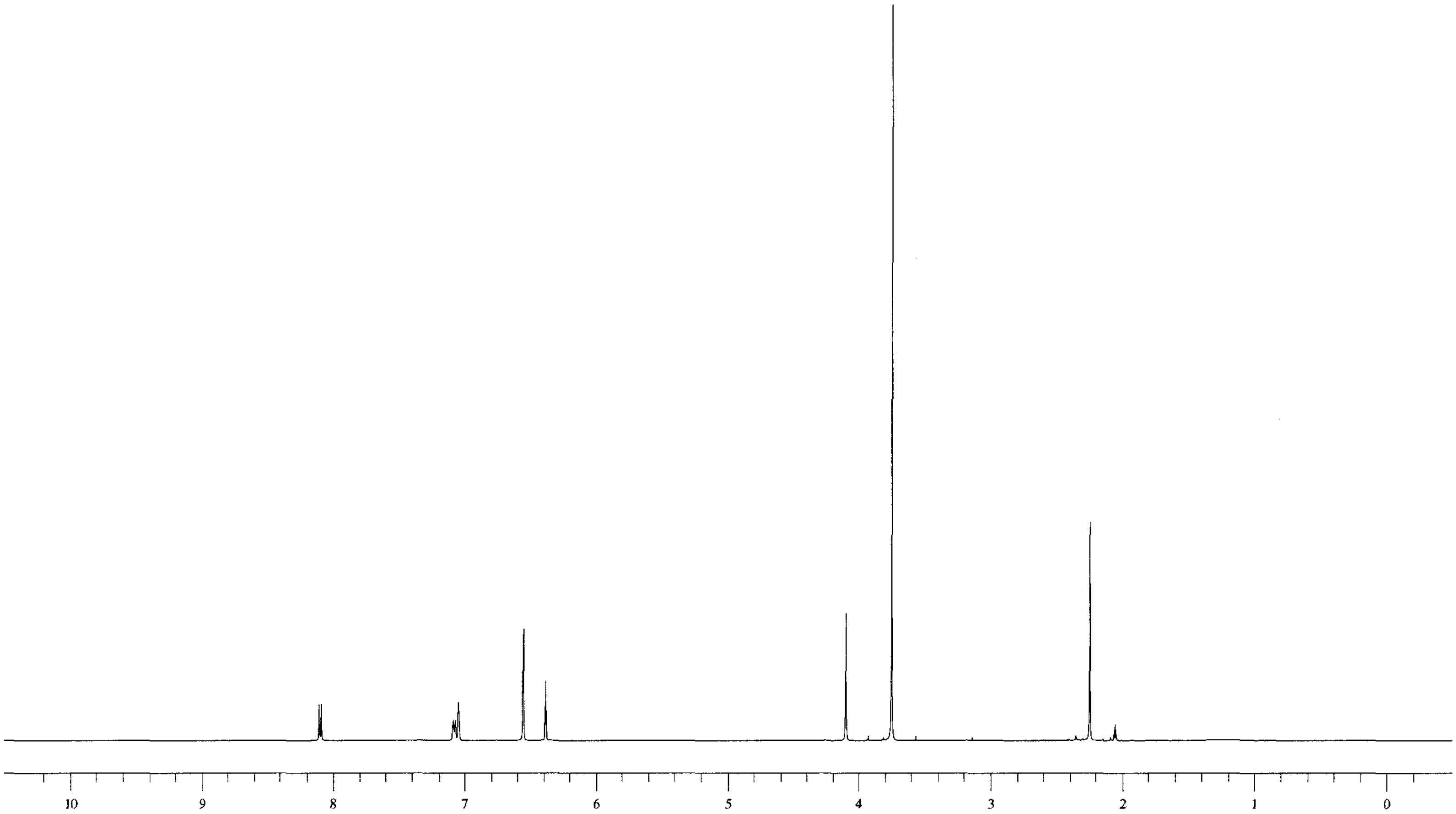
20
10
0


Me
OMe
OMe
+N
O–


10
9
8
7
6
5
4
3
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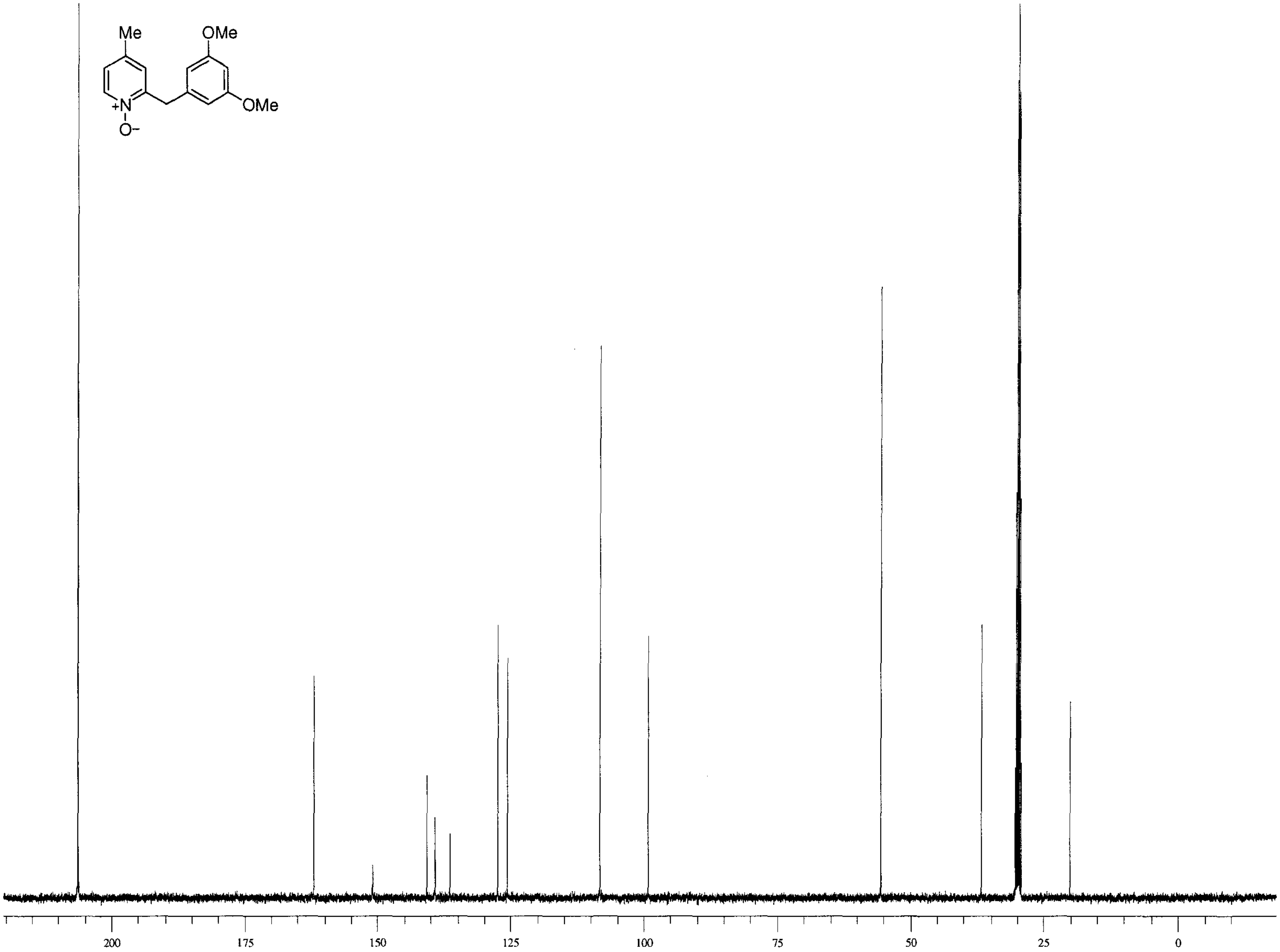
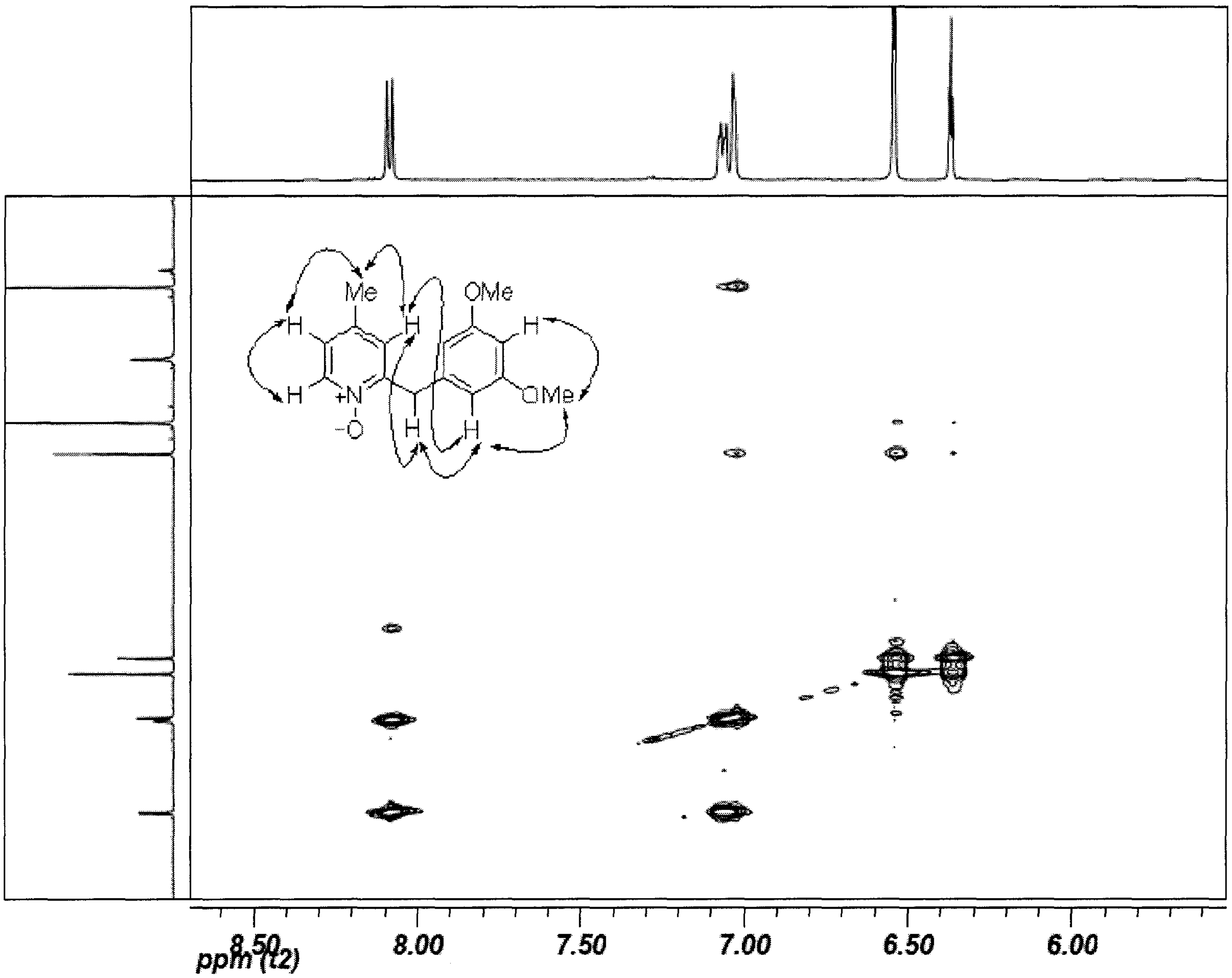
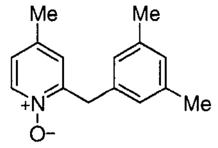
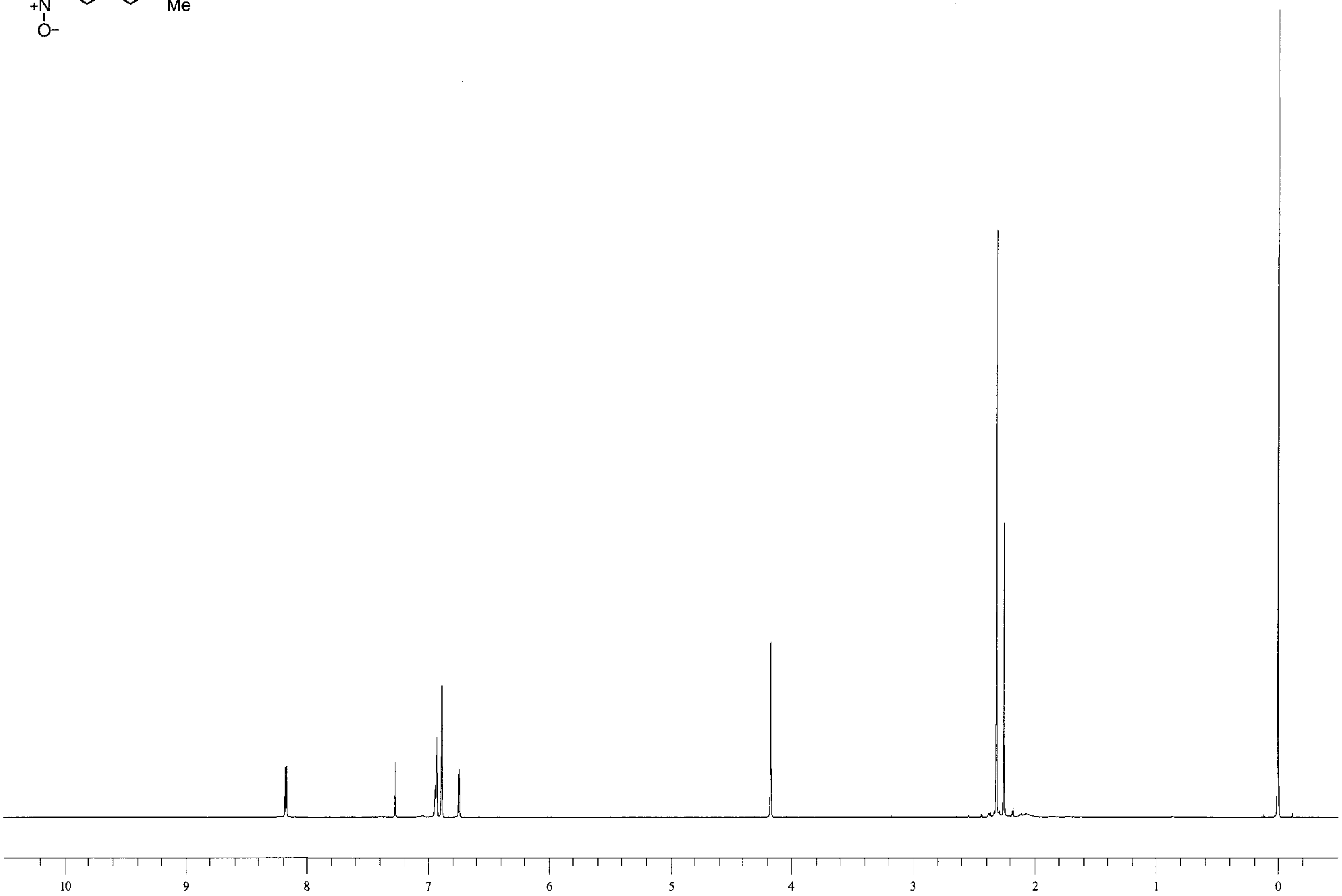
1
0


Me
OMe
OMe
+N
O–
200
175
150
125
100
75
50
25
0


Me
OMe
H
H
H
+N
-O
H
H
OMe
H
8.50
8.00
7.50
7.00
6.50
6.00
ppm (t2)


Me
Me
+N
Me
O–


10
9
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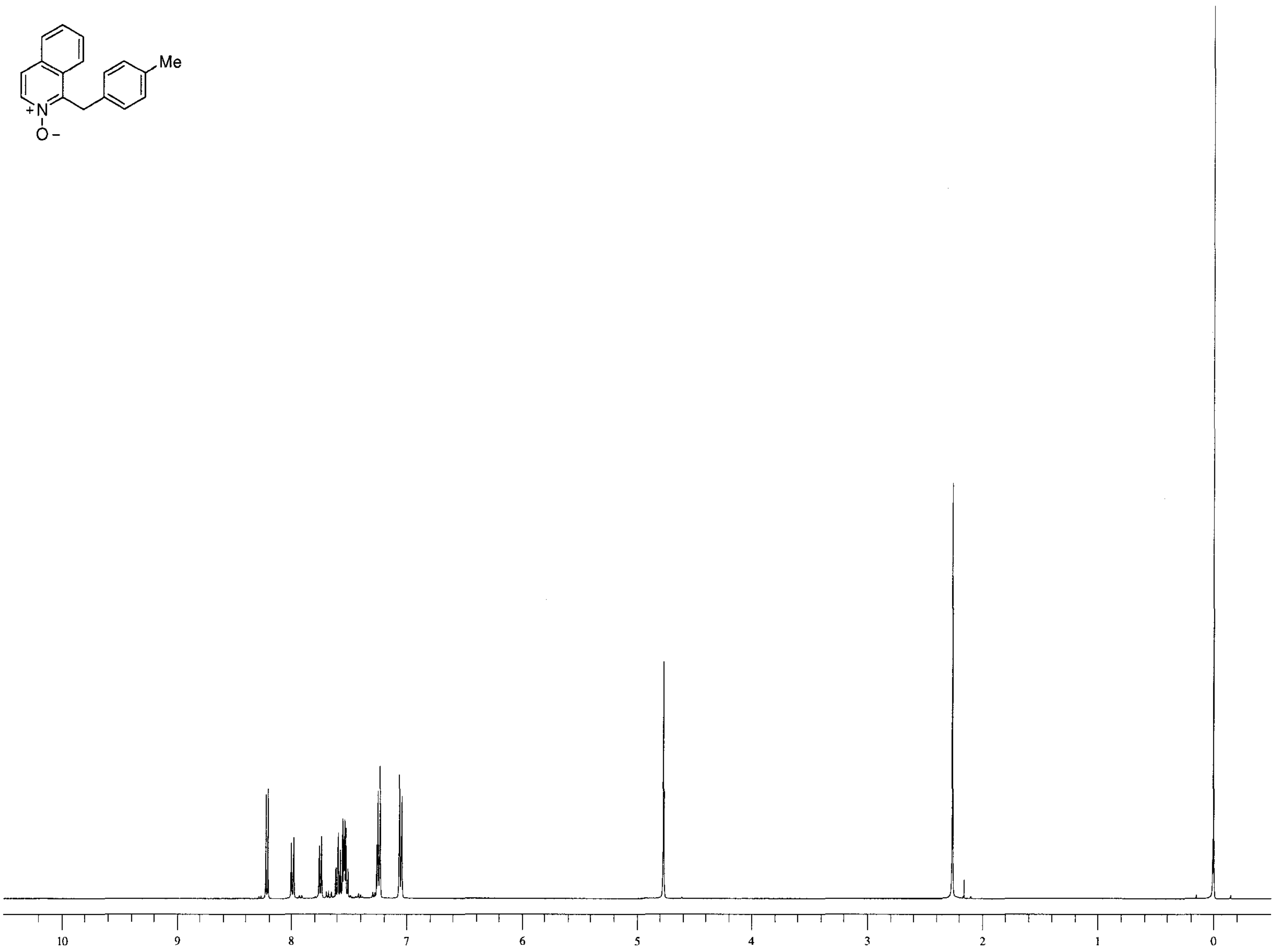
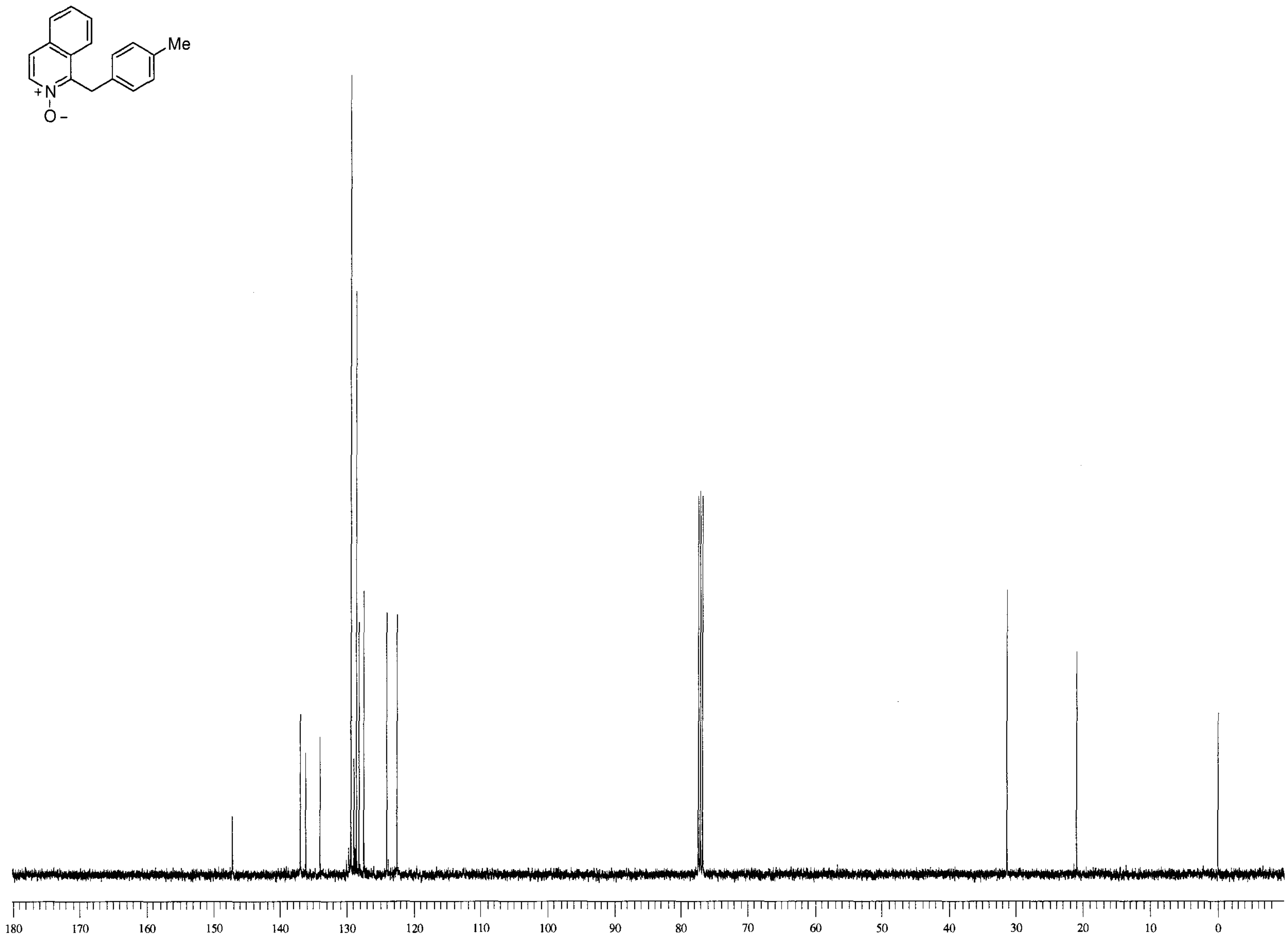

Me
+N
O–
10
9
8
7
6
5
4
3
2
1
0


Me
+N
O-
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0