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Catalyst Development for the Direct Arylation of Aryl Chlorides, Bromides and Iodides

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Catalyst Development for the Direct Arylation of Aryl Chlorides, Bromides and Iodides

By

Mathieu Parisien

B.Sc. (Honours), University of Ottawa, 2003

A Thesis Submitted to the School of Graduate Studies and Research in Partial Fulfillment of the Requirements for the Degree of Master of Science

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List of Abbreviations

Ac	acetyl
Acac	acetylacetonate
Aq.	aqueous
Ar	aryl
Atm	atmosphere
Bn	benzyl
Bz	benzoyl
CDI	carbonyldiimiadazole
Cod	cyclooctadiene
Coe	cyclooctene
Cy	cyclohexyl
Dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.3.0]undec-7-ene
DCM	dichloromethane
DIAD	disopropylazodicarboxylate
DIPEA	diisopropylethylamine
DMA	*N,N*-dimethylacetamide
DMAP	4-(dimethylamino)pyridine
DME	dimethoxyethane
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
Dppm	diphenylphosphinomethane
Equiv.	equivalents
Et_2O	diethyl ether

EtOAc	ethyl acetate
Et_3N	triethylamine
GC-MS	gas chromatography-mass spectrometry
HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectrum
iMes	1,3-dimesitylimidazol-2-ylidene
iPr	isopropyl
IPr-HCl	hydrochloride salt of 1,3-(2,6-diisopropylphenyl)-imidazol-2-ylidene
IR	infrared
KIE	kinetic isotope effect
L	ligand
Me	methyl
MOM	methoxymethyl
Mp	melting point
Ms	mesyl
NMR	nuclear magnetic resonance
NMP	*N*-methylpyrrolidinone
Ph	phenyl
Piv	pivalate
PPTS	Pyridinium p-toluenesulfonate
R	generic alkyl group
Rt	room temperature
T°	temperature
TBAF	tetrabutylammonium fluoride
tBu	*tert*butyl
Tf	triflate

TFA	trifluoroacetic acid
THF	tetrahydrofuran
Ts	tosyl
X	generic halide

Abstract

Tricyclic biaryls were formed by a direct arylation reaction conducted in the presence of catalytic amounts of $Pd(OAc)_2$ and tricyclohexylphosphine. Aryl chlorides, bromides and iodides could all be used and the methodology was applied to the synthesis of 6*H*-benzo[c]chomenes; 9, 10-dihydrophenanthenes; 5, 6-dihydrophenanthridines (if the nitrogen atom was protected) with yields ranging between 79% - >99%. Fluorene, dibenzofurans and carbazoles (unprotected NH) could also be formed in high yields (81% – 99%) using this technique.

It has been found that both electronic and steric factors influence the regioselectivity of the reaction. Furthermore, mechanistic investigations have been conducted to establish which one of four possible pathways is taking place. The results of these experiments point towards either a σ-bond metathesis or an S_E3 palladation.

The methodology described above was applied to the synthesis of natural products. An efficient synthesis of mukonine, a carbazole with cytotoxic and anti-platelet aggregation activity, was completed in three steps with an overall yield of 75%. A two step synthesis of Paullone, a family of compounds active against Alzheimer's disease, was achieved as well.

In addition, a heterogeneous catalyst system was developed for the formation of tricyclic biaryls. Pearlman's catalyst ($Pd(OH)_2/C$) was shown to provide an active palladium species that led to the formation of five and six membered rings from a wide range of aryl bromides and iodides. Intermolecular coupling of aryl bromides and iodides with heteroaromatic rings could also be achieved with this catalyst. Studies aimed at determining the nature of the active catalyst demonstrated that an active homogeneous palladium species produced under the reaction conditions was the only active catalyst on the time scale studied.

ACKNOWLEDGEMENTS

I would like to begin by thanking my supervisor, Keith Fagnou, for the two great years I have spent in his lab. Keith has been a wonderful mentor, and even though I have recently learned at the groups summer BBQ that I should not always trust him (he sprayed whipped cream in my face, twice!), I have tremendous respect for him. He took a chance starting his group with Marc and I (the other professors in the department thought he was crazy), I just hope that he does not regret it too much today. I expect an annual invitation to the Mathieu Parisien Invitational golf tournament so I can return the taunting that I endured at the first edition.

I would also like to thank the members of the Fagnou group. Marc Lafrance, an old friend, a roommate and a co-worker, some might say that he is a little rough around the edges but I assure you that he is a fantastic friend to have; Louis-Charles Campeau, my golf partner, who worked in conjunction with me on the homogeneous catalysis project. Without his help, I would never have gotten this far; Mélissa Leblanc for her friendship and support since the first day she joined the lab. I can not help but have tremendous respect for someone who managed to survive four months alone in the lab with Marc, Louis-Charles and myself; Valérie Charbonneau for her time and suggestions while I was practicing oral presentations and for many discussions on hot topics; Jea*N*-Philippe Leclerc for his help, especially while I was preparing for interviews and most of all for taking over the GC-MS just in time for it to start breaking. I would not forget the undergraduate students and our post-graduate fellow. Julien Dugal-Tessier who founded the lab with Marc and I; Irina Denissova whom I had the pleasure of sharing the small lab with for eight months and who's knowledge always impressed me; Nicole Blaquiere who still enjoys chemistry after two interesting summer projects; Praew Thansadote, the Negishi queen, I wish her all the best in the Lautens group; Annie Jean, the crazy athlete that walked to school in -30°C weather! I am sure she will be as good at podiatry as she was at organic chemistry; and last but not

least, Sophie Rousseaux, her thirst for knowledge seems insatiable. Remember Sophie, we have confidence in your ability to solve the problem.

Finally, I would like to thank my family and most importantly my fiancée Sabrina for their support over the past two years. My parents have always been there for me when I needed their help with anything and everything. Sabrina was also always there for me when chemistry was being as chemistry is and insisted on not working. Although she does not share my passion for chemistry, she accepted to date a chemist and will now be sharing her life with me.

"Why do something today if it can be done tomorrow."

I guess this saying usually goes the other way around
but this always worked pretty good for me.

"The early bird gets the worm, but the second mouse gets the cheese."

1 – General Introduction

The biaryl core has occupied a very important place in organic chemistry over the past century. Novel transition metal catalyzed processes for the formation of biaryls, such as the Suzuki, Stille, Hiyama, Negishi and Kumada-Corriu reactions, have been developed.[1] Even though these methods have become very efficient in the past few years, they still require the pre-activation of both coupling partners, one as a haloarene and the other as an organometallic species. The organometallic coupling partner is usually the more problematic of the two since it often needs to be prepared because it is not commercially available. The majority of organometallic species also suffer from the fact that they are air and/or moisture sensitive and difficult to carry through many synthetic steps. There are many areas of traditional cross-coupling reactions still under investigation today, but efficient novel processes requiring the pre-activation of only one of the two coupling partners are making their apparition. Replacing the organometallic species by a simple arene is clearly advantageous and even though the direct arylation of arenes was discovered more than 20 years ago[2], it was not until the late 1990s that it truly became a valid alternative to conventional cross-coupling.[3] Since the development of novel catalyst systems for the direct arylation of arenes is discussed in this thesis, recent advances in the field will be reviewed.

1.1 – Biaryl Formation via Direct Arylation

The field of direct arylation can be divided into two main categories: intermolecular direct arylation and intramolecular direct arylation. Clearly, intermolecular processes are more challenging than their intramolecular equivalent and this is why the properties of the substrates that undergo the two types of reaction are quite different. In order to undergo an intermolecular direct arylation, the substrates must either be highly nucleophilic (electron

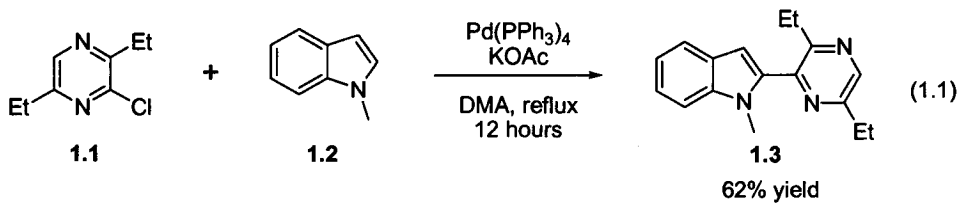
rich heteroaromatic rings), or in the case of simple arenes, bare a directing group that can bind to the metal center rendering the reaction more intramolecular. Very recently, an example of direct arylation of π-deficient arenes was reported but a considerable amount of work is still required before these substrates can be commonly used. The range of substrates for intramolecular processes includes heteroaromatic rings and simple arenes without directing groups.

1.1.1 – Intermolecular Direct Arylation of Arenes

1.1.1.1 – Direct Arylation of Electron Rich Heteroaromatic Rings

1.1.1.1.1 – Early Examples of Direct Arylation of Heteroaromatic Rings

One of the first examples of direct arylation of heteroaromatic rings was developed by the group of Dr. Akihiro Ohta at the Tokyo College of Pharmacy in 1989.[4] The reaction involved the coupling of *N*-methylindole **1.2** with 2-chloro-3,6-diethylpyrazine **1.1** (Equation 1.1). After heating a mixture of the substrate, palladium tetrakistriphenylphosphine and potassium acetate to reflux in *N,N*-dimethylacetamide for twelve hours, the 2-arylated indole **1.3** was obtained in 62% yield. Various mixtures of 2- and 3-arylated indoles could be obtained by changing the nature of the *N*-substituted indole.



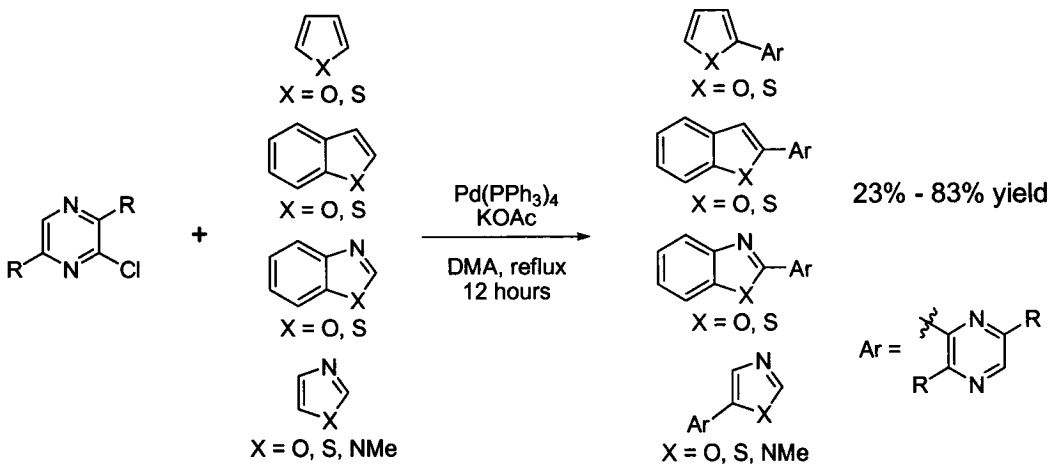
1.1 **1.2** **1.3**

62% yield

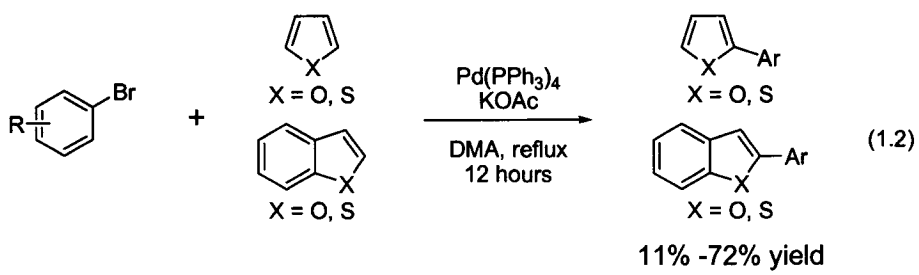
(1.1)

After further investigation, the arylation procedure was expanded to include thiazole, oxazole, benzothiazole, benzoxazole and *N*-methylimidazole as substrates (Scheme 1.1). [5] The yields were sometimes quite modest, as low as 23%, but the reactivity pattern had been established.

Scheme 1.1. Direct Arylation of Azoles with 2-chloro-3,6-dialkylpyrazine.

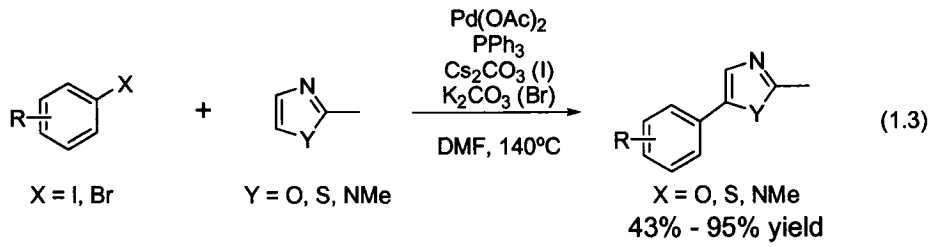


Simple aryl halides could also be coupled with different heteroaromatic rings.[6] The yields ranged from 11% to 72% and in most cases good selectivity was achieved (Equation 1.2). It was noted that the sulfur based arenes gave better results than their oxygen counterpart.



(1.2)

Miura *et al.* reported, nearly 10 years after Ohta's first report, that a catalyst based on palladium acetate and triphenylphosphine catalyzed the arylation of 2-methyl-*N*-methylimidazole, 2-methyloxazole and 2-methylthizaole at the 5-position (Equation 1.3).[7] Moreover, it was noted that the nature of the base used in the reaction had a significant impact on the results of the reaction. When an aryl iodide is used, it was established that the more soluble cesium carbonate was required, but if the coupling reaction involves an aryl bromide, the reaction reaches completion faster with potassium carbonate than it does with cesium carbonate.



(1.3)

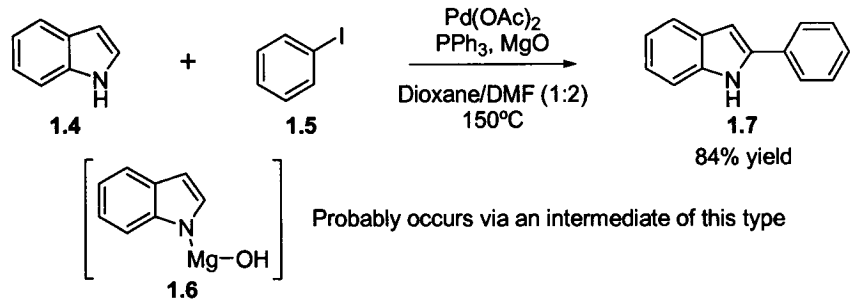
The examples mentioned above are some of the key precedents to the major developments that have occurred in the direct arylation of heteroarenes in the past five years.

1.1.1.1.2 – Recent Developments in the Direct Arylation of Heteroaromatic Rings

1.1.1.1.2.1 – Direct Arylation of Indole and Pyrrole

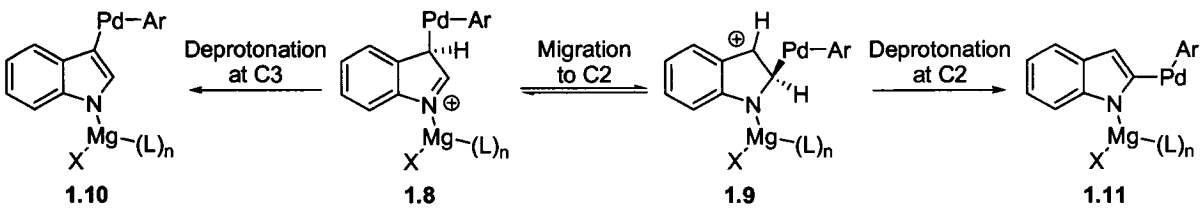
The group of professor Sames has made major contributions in the development of novel processes for the arylation of indoles. In 2003, they reported the first example of arylation of free (NH)-indoles.[8] The catalyst based on palladium acetate and triphenylphosphine was only compatible with aryl iodides as aryl bromides led to an important decrease in yield. Once again, the choice of base was crucial as the indole must be deprotonated in order to get the desired reactivity. Magnesium oxide proved to be the ideal base for the reaction as it allows the formation of an indolyl Grignard intermediate **1.6**, with the magnesium salt acting as a protecting group for the acidic nitrogen. Selective formation of 2-phenylindole **1.7** is achieved under the reaction conditions (Scheme 1.2). The methodology could also be applied to a variety of other azoles. Indeed, 2-phenylpyrrole, 3-phenylpyrazole and 4-phenylimidazole can be formed selectively demonstrating the generality of the method.

Scheme 1.2. Direct Arylation of Indolyl Magnesium Hydroxide.



If the arylating agent is switched from iodobenzene to 2-iodotoluene, the selectivity drops considerably giving a 3.2:1 mixture of 2- and 3-(o-tolyl)indole respectively. Since it is believed that the reaction occurs via electrophilic attack of the aryl palladium on the 3-position of indole (**1.8**), followed by migration to the thermodynamically more stable 2-position (**1.9**), it can be reasoned that more sterically demanding substrates will migrate more slowly due to the presence of the magnesium salt and that deprotonation at C3 (**1.10**) could compete with migration and deprotonation at C2 (**1.11**) (Scheme 1.3). This would lead to greater amounts of 3-arylindole. This hypothesis is supported in a report on the mechanism of the reaction published in 2005, in which they show that larger ligands on the magnesium such as hexamethyldisalazide lead to selective arylation of the 3-position.[9]

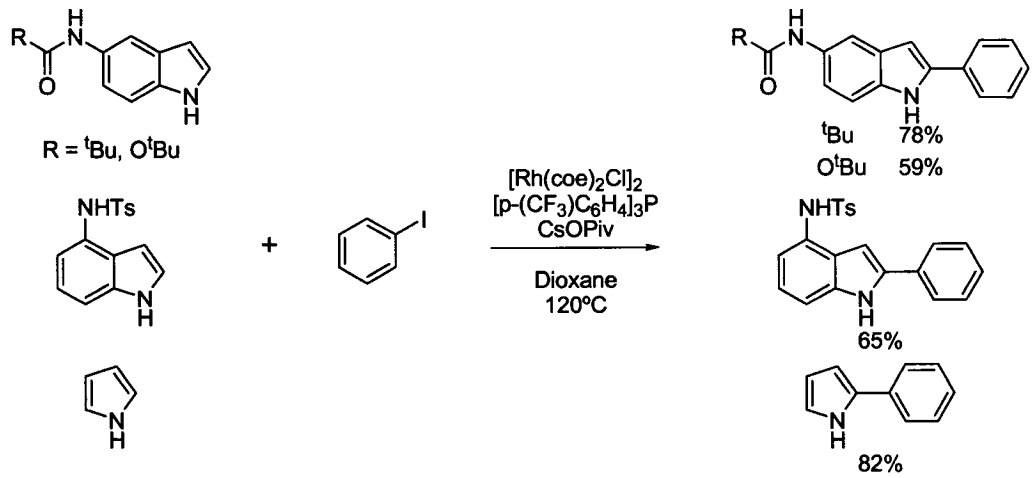
Scheme 1.3. Mechanism of the Arylation Step.



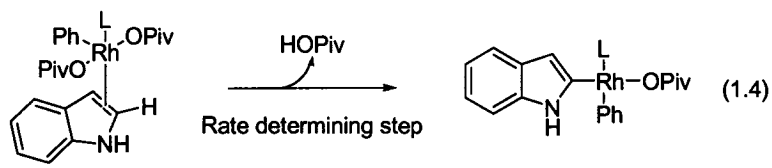
In 2005, Sames *et al.* reported another procedure for the arylation of unprotected indoles using an electron deficient rhodium catalyst.[10] This is the first true example of arylation in the presence of free (NH)-indole, since in the previous case, the indole was protected as a magnesium salt (Scheme 1.4). A weak carboxylate base, cesium pivalate, is

used in the reaction; the indole therefore, probably remains protonated throughout the course of the reaction. This also allows the presence of more than one (NH) group, thus, secondary amides, carbamates and sulfonamides are all compatible with the rhodium catalyst and once more, pyrrole can also be arylated under these conditions.

Scheme 1.4. Arylation in the Presence of free (NH) groups.



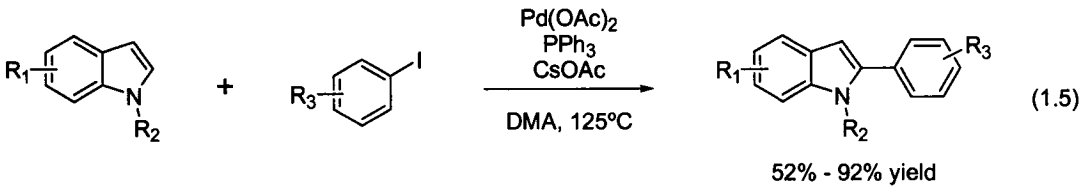
A more electron deficient phosphine improved the results, but a primary kinetic isotope effect (KIE) at the 2-position is observed which is contrary to the analogous palladium catalyzed process. Sames therefore proposed an intramolecular deprotonation at C-2 of **1.12** by a pivalate ligand on the rhodium, after displacement of a phosphine ligand by indole to generate **1.13** (Equation 1.4).



1.12 **1.13**

The arylation of *N*-alkylindoles as also been studied by the group of professor Sames. In 2004, it was demonstrated that the arylation of these substrates with a variety of iodoarenes can be achieved in the presence of a palladium catalyst (Equation 1.5).[11] Electron rich and deficient indoles can be arylated in good yields. Secondary sulfonamides

can be present without interfering with the reaction. While *N*-methyl, *N*-isopropyl, *N*-benzyl and various *N*-arylindoles could be used, *N*-acetyl and *N*-sulfonylindole remained inert demonstrating that the arene needs to maintain a certain electron density in order to react. The scope was explored using *N*-methylindoles.



(1.5)

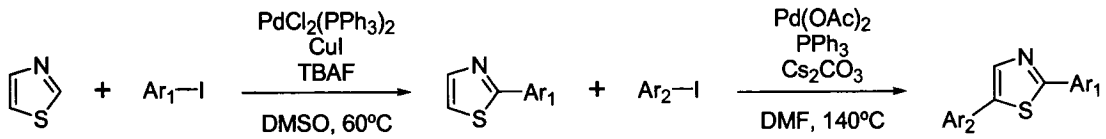
52% - 92% yield

Once again, the reaction is quite selective for the 2-position when para substituted aryl halides are used, however when ortho substituted haloarenes are employed a mixture of products is obtained favoring arylation of the 3-position. The mechanistic reasoning described in the arylation of indolyl magnesium salts applies once again to explain this change in selectivity.

1.1.1.1.2.2 – Direct Arylation of Thiazole, Oxazole, Imidazole and their Derivatives

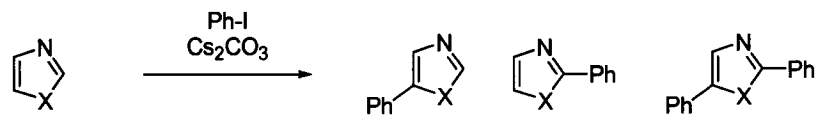
Mori *et al.* reported in 2003 that thiazole could be arylated at the 2-position in high yields and with good regioselectivity.[12] The substitution pattern observed in the reaction is complementary to the work of Miura *et al.*, reported in 1998, where a mixture of products favoring arylation at C5 is obtained.[7] A palladium catalyst is used but copper iodide and tetrabutyl ammonium fluoride are added to the reaction mixture to afford the product in 82% yield. In the presence of the copper co-catalyst, the most acidic position of the thiazole is arylated. Even though the reaction is usually done at 60°C, the temperature can be lowered to room temperature if longer reaction times are allowed. The authors report the use of this reaction in tandem with the process developed by Miura to generate a library of 2,5-diarylated thiazole which demonstrate liquid crystalline and light emitting properties (Scheme 1.5).

Scheme1.5. Tandem bis-arylation of Thiazole.



A process for the selective arylation of thiazole at either the 2- or 5-position, using a cobalt catalyst has been developed by Sezen and Sames.[13] In a report published in 2003, complete selectivity for the 5-position is obtained with a cobalt catalyst based on $Co(OAc)_2$ and the *N*-heterocyclic carbene ligand IMes. Once more, addition of copper iodide to the reaction mixture reverses the selectivity to give arylation of the 2-position exclusively.

Scheme 1.6. Comparison of Cobalt and Palladium Mediated Arylation of Azoles.



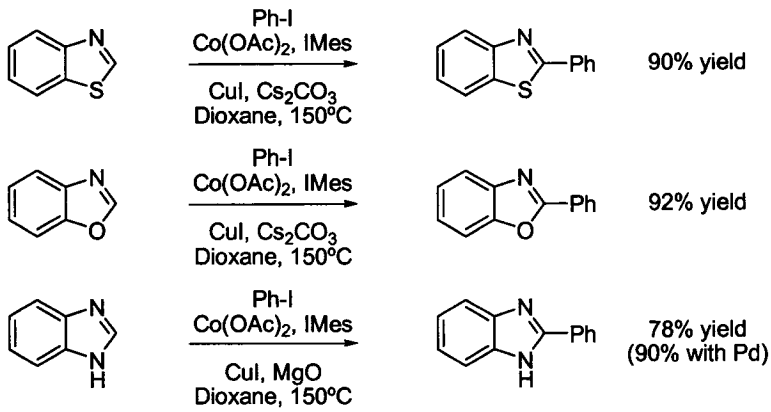
Thiazole		Oxazole	
Conditions	**Yield (%)**	**Conditions**	**Yield (%)**
$Co(OAc)_2$, IMes DMF, 150°C	64 / 0 / 0	$Co(OAc)_2$, IMes DMF, 150°C	34 / 6 / 0
$Co(OAc)_2$, IMes Dioxane, 120°C, CuI	0 / 84 / 0	$Co(OAc)_2$, IMes DMF, 100°C, CuI	0 / 73 / 0
$Pd(OAc)_2$, PPh_3 DMF, 150°C	42 / 0 / 17	$Pd(OAc)_2$, PPh_3 DMF, 150°C	24 / 5 / 31
$Pd(OAc)_2$, PPh_3 DMF, 150°C, CuI	0 / 18 / 37	$Pd(OAc)_2$, PPh_3 DMF, 150°C, CuI	0 / 13 / 42

The methodology can be applied to oxazoles as well. Arylation of the 5-position is less selective with oxazole (6:1) than with thiazole (complete selectivity), but is still higher than what has been observed in previous reports, where bis-arylation of C2 and C5 of the oxazole is the major product (Scheme 1.6). On the other hand, C2 arylation of oxazole is completely selective in the presence of copper iodide.

Even though the arylation of imidazole with $Co(OAc)_2$ is not as high yielding (41%) as the palladium catalyzed coupling of imidazole magnesium salt with aryl halides (72%),

the use of zinc oxide as the base instead of magnesium oxide gave selective arylation at C5. Addition of copper led to arylation of the 2-position in 78% yield (83% with palladium). Benzothiazole, benzoxazole and benzimidazole were all compatible with the cobalt catalyzed arylation in the presence of copper iodide (Scheme 1.7). Once again the yield with benzimidazole was lower using the cobalt catalyst than with the palladium based procedure.

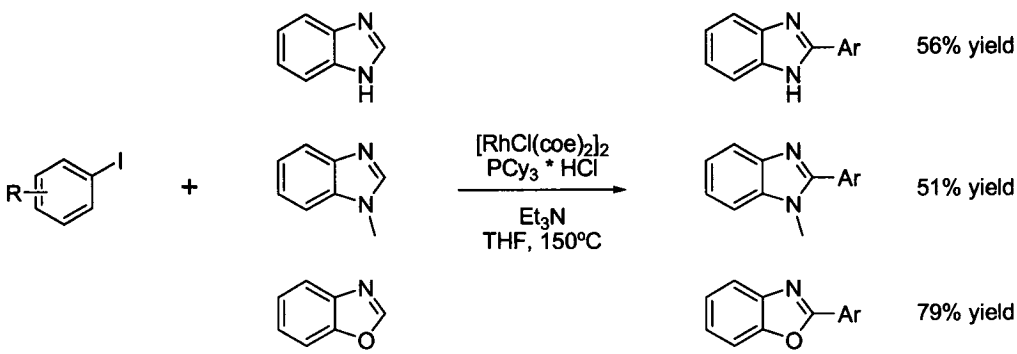
Scheme 1.7. Cobalt Catalyzed Direct Arylation of Benzazoles.



Ellman *et al.* have developed an alternative to the use of copper salts in the presence of a palladium or cobalt catalyst. After having reported a procedure for the coupling of various azoles with alkenes, they reported, in 2004, the use of a rhodium based catalyst consisting of bis-cyclooctaene rhodium chloride dimer and tricyclohexylphosphine for the arylation of azoles at C2.[14] The optimal base proved to be triethylamine, inorganic bases leading to considerably poorer results. This is in contrast with the vast majority of reactions that have been shown thus far in which the use of organic bases does not lead to the formation of the desired product. Mechanistic studies have shown evidence for the formation of a rhodium carbenoid intermediate. Once the carbenoid is formed, it is proposed that dissociation of a phosphine from the rhodium complex precedes insertion into the aryl halide. The yields are moderate with benzimidazole (56%) and *N*-

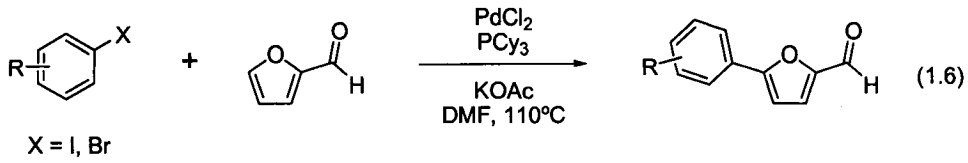
methylbenzimidazole (51%), but they become quite good when the substrate is benzoxazole (79%). Electron rich and deficient aryl halides can be coupled, but the yields are considerably better when electron rich arenes are used.

Scheme 1.8. Rhodium Catalyzed Arylation of Benzazoles.



1.1.1.1.2.3 – Direct Arylation of Other Heteroarenes

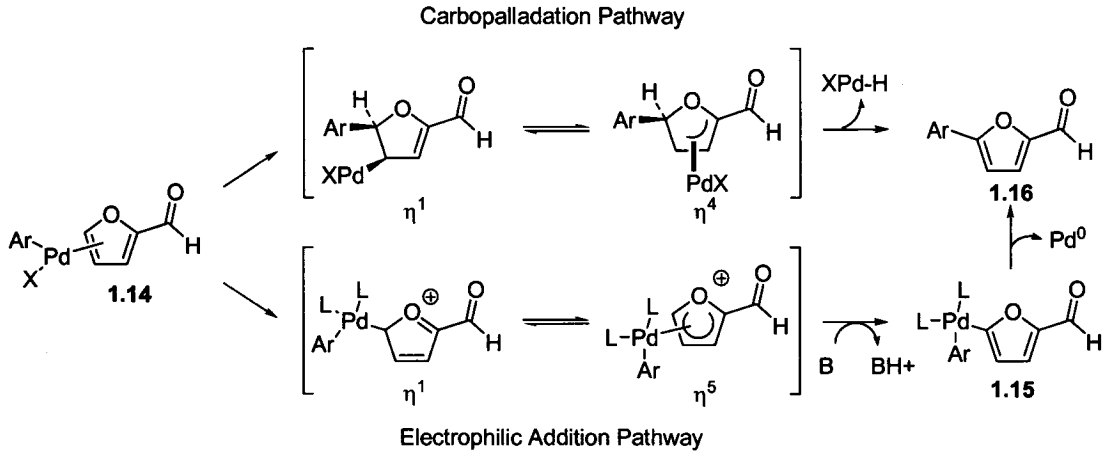
In 2001, the palladium catalyzed arylation of 2-furaldehyde was reported by McClure *et al* (Equation 1.6).[15] A factorial screen of palladium sources, ligands, solvents and additives demonstrated that palladium chloride was the optimal catalyst although palladium on carbon could also catalyze the reaction. Tricyclohexylphosphine was the optimal ligand, potassium acetate the base of choice and DMF the best solvent. If potassium acetate is replaced by Hunig's base, an 8-fold increase of homocoupling of the aryl halide is observed. The reaction could be accomplished under Jeffrey condition's (no phosphine, added Bu_4NBr) but adding tricyclohexylphosphine generated a more general catalyst. In the examination of the scope, ten equivalents of 2-furaldehyde is used to minimize the amount of homocoupling of the aryl halide. The substitution pattern of the aryl halide does not seem to impact the result of the reaction, as similar yields are obtained when para-, meta-, and ortho-iodotoluene are coupled. Electron rich and deficient aryl bromides and iodides are compatible with this methodology.



(1.6)

The arylation of 2-furaldehyde occurs in the 5-position. Greater conjugation resonance stabilization most likely explains the arylation at C5 rather than C3. The reaction can proceed via two possible mechanisms (Scheme 1.9). **1.14** can undergo a carbopalladation (traditional Heck type reaction), but formal anti β-hydride elimination has to occur to regenerate aromaticity. The authors mention that although this is possible, the carbopalladation pathway is unlikely. The reaction thus most likely proceeds via an electrophilic palladation of **1.14**. Although arylation at the 3-position and the 5-position seem as plausible in this case, an equilibrium favoring the longest conjugated system can arise from a shift in the binding of palladium to the furan ring from η^1 to η^5 to give **1.15**. Reductive elimination gives the desired product **1.16**.

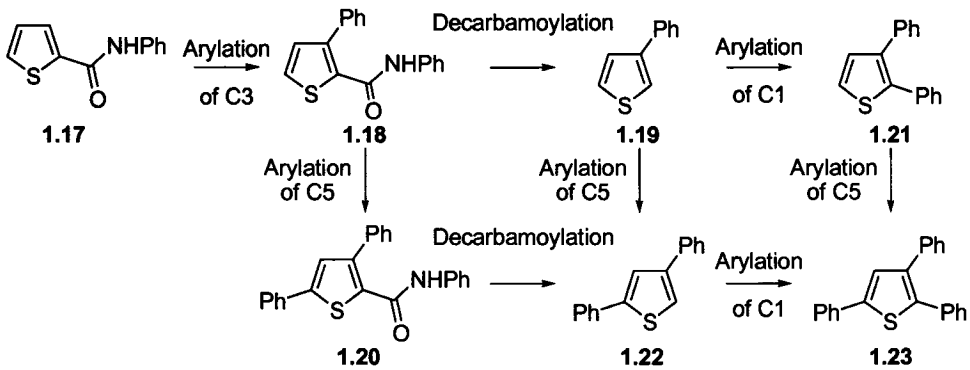
Scheme 1.9. Possible Pathways in the Arylation of 2-Furaldehyde.



Similarly to the reaction above, the triarylation of 2-thiophenecarboxamides and of 3-cyanothiophene under palladium catalysis was reported in 2002 by Miura *et al.*[16] In the first case, the reaction involves the decarbamoylation of the thiophene unit **1.17** (Scheme 1.10). The reactions catalyzed by palladium acetate and tri-*tert*butylphosphine in the presence of

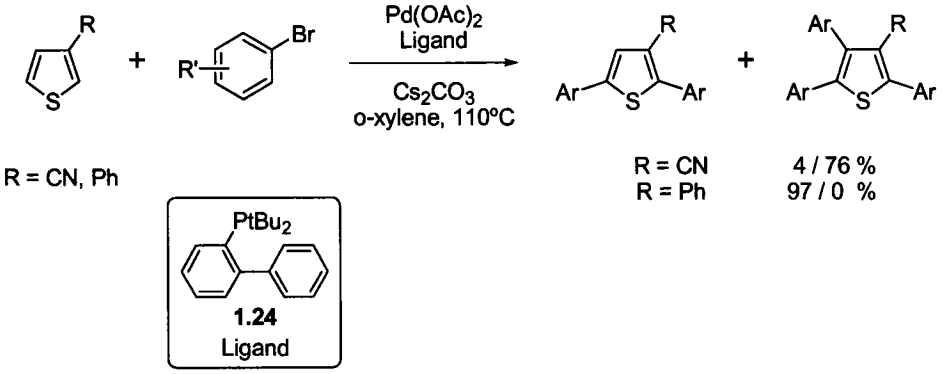
cesium carbonate seem to occur in the following order. First, directed arylation of the 3-position of thiophene occurs and forms **1.18**. This is followed by either decarbamoylation to **1.19** or arylation of the 5-position to **1.20**. The bis-arylated thiophene undergoes decarbamoylation (**1.22**) and finally mono- or bis-arylation occurs to generate the 2,3,5-triarylated thiophene **1.23**. The bis-arylated amine is also usually isolated as a by-product. Switching from palladium acetate to palladium dibenzylideneacetone or removing the base does not allow the decarbamoylation to occur indicating that the catalyst and base play an important role in this step.

Scheme 1.10. Triarylation of Thiophene via Decarbamoylation.

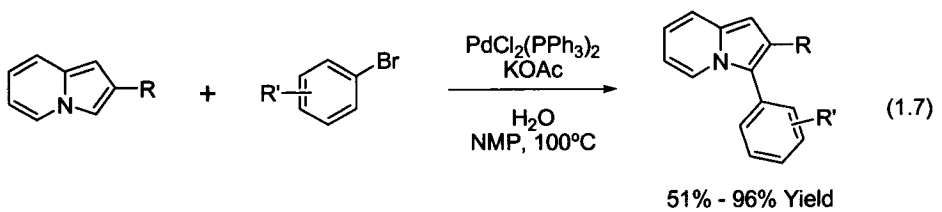


The triarylation of 3-cyanothiophene on the other hand starts with electrophilic arylation of the 2- and 5-positions. This is to be expected since these are the most nucleophilic positions of the thiophene ring. The authors propose that the electron withdrawing group in the 3-position makes the C4 proton more acidic. Deprotonation by cesium carbonate facilitates the final arylation (Scheme 1.11). This is further supported by the fact that the presence of a weakly electron donating group in the 3-position blocks the arylation of C4.

Scheme 1.11. Impact of the Cyano Group on the Triarylation of 3-Substituted Thiophenes.



Indolizines and the reduced equivalent indolizidines have demonstrated important biological properties. In 2004, an account of the first procedure for the direct arylation of indolizines was published by Gevorgyan *et al.*[17] The catalyst used in this reaction is palladium dichloride di-triphenylphosphine. The optimal conditions require the use of potassium acetate and the addition of two equivalents of water to NMP. Heating the reaction mixture to 100°C gives the products in moderate to excellent yields (51% - 96%) (Equation 1.7). Under the optimal conditions, a number of indolizines and aryl bromides can be coupled.

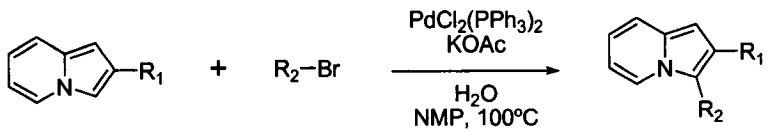


(1.7)

Mechanistic investigations have demonstrated that electrophilic substitution is the most likely of the four possible pathways (Heck, C-H activation, cross-coupling of an indolizine anion and electrophilic substitution). The authors attempted to conduct intramolecular Heck reactions but were unsuccessful. Addition of copper salts to the reaction led to longer reaction times and poorer yields. This is contrary to what is expected to happen if an anion was formed. It was also reported that no kinetic isotope effect was observed. This would be expected in the rapid deprotonation of the arenium cation, but one

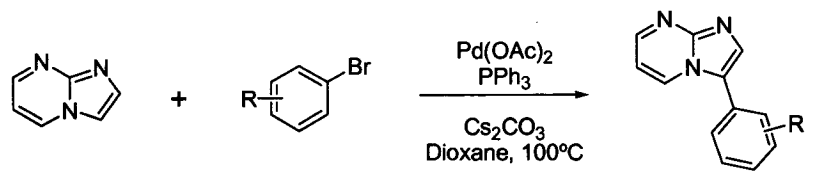
would expect to see a primary kinetic isotope effect if C-H activation was occurring. In order to further ascertain the electrophilic substitution pathway, the electronic properties of the indolizines were tested. It was discovered that electron deficient indolizines were arylated more slowly than their activated equal (Scheme 1.12). Similar trends were observed in the Friedel-Crafts acylation of indolizines.

Scheme 1.12. Relative Rates of Direct Arylation and Friedel-Crafts Acylation of Indolizines.



	Relative Rate	
R_1	**Direct Arylation**	**Friedel-Crafts Acylation**
H	1	1
Me	0.96	0.67
CO_2Et	0.66	0.33

While preparing 3-substituted imidazo[1,2-a]pyrimidines Li *et al.* proposed that arylation of these substrates should occur in the 2- or 3-position since the imidazole ring is more electron rich than the pyrimidine ring.[18] This represents an alternative to the cross-coupling of halogenated pyrimidine derivatives with aryl boronic acids.



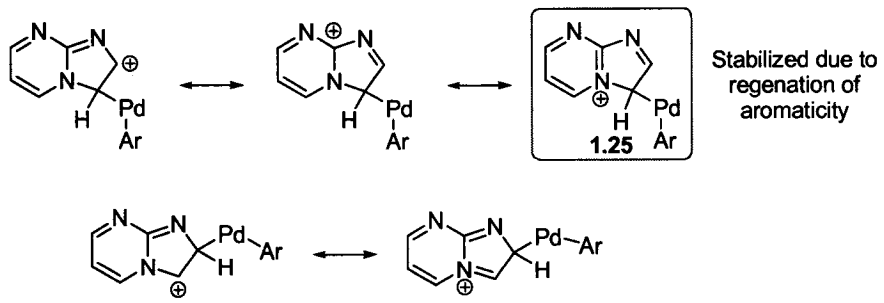
(1.8)

39% - 96% Yield

Testing of common arylating conditions showed that palladium acetate, triphenylphosphine and either cesium or potassium carbonate were optimal for the coupling of aryl bromides in refluxing dioxane or in DMF at 100°C. A multitude of aryl halides were added to the 3-position exclusively with yields ranging between 39% and 96% (Equation

1.8). The formation of the more stable arenium ion **1.25** when arylation of the 3-position occurs is invoked to explain the high regioselectivity (Scheme 1.13).

Scheme 1.13. Rationalization of the Increased Stability of the Intermediate in C3 Arylation.



1.1.1.2 – Intermolecular Direct Arylation of Simple Arenes

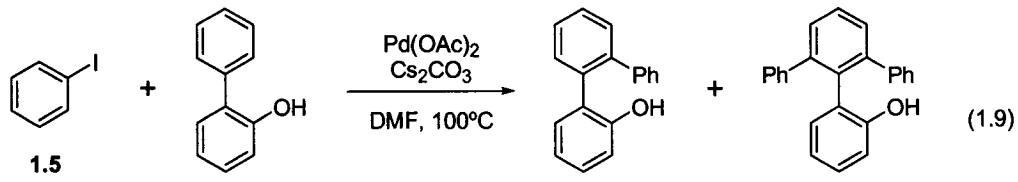
The intermolecular direct arylation of simple arenes is a challenging task. Unlike their heteroarene complement, they are not very good nucleophiles. For the vast majority of substrates in the previous section, electrophilic palladation was believed to be the mechanism through which the arylation occurred. In order for simple arenes to undergo this type of process, a directing group must be present to hold the arene in close proximity to the aryl palladium(II) intermediate. Heteroatoms can act as temporary tethers, bringing the two coupling partners together.

1.1.1.2.1 – Directing Groups in the Arylation of Simple Arenes

1.1.1.2.1.1 – Direct Arylation of Phenols

In 1997, Miura *et al.* reported that 2-phenylphenol **1.26** could be arylated in the 2'-position to generate 1,1': 2', 1"-terphenyl-2-ol **1.27** in 76% yield (Equation 1.9).[19] It is mentioned that cesium carbonate must be used as the base in order to obtain good yields, as other alkali carbonates lead to poor results (possibly due to solubility issues).[20] Palladium acetate or palladium chloride can be used and in certain more challenging cases,

triphenylphosphine is added to the reaction mixture. The authors propose that the reaction occurs via the formation of an aryl(aryloxy)palladium species which allows the functionalization of the adjacent aromatic ring in an intramolecular fashion. Bis-arylation of the 2'- and 6'-position becomes the major product (**1.28**) of the reaction if four equivalents of aryl halide are used, but if the biphe*N*-2-ol bears a substituent in the 3'-position, the mono-arylated product is obtained exclusively even in the presence of an excess of aryl halide.



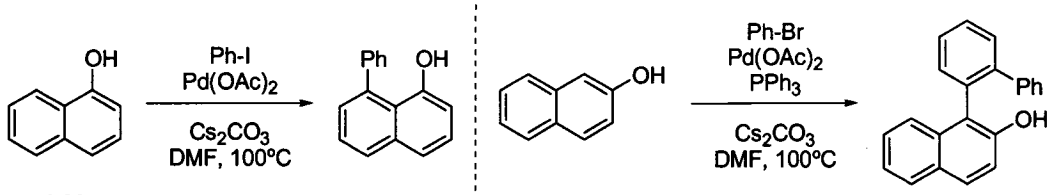
(1.9)

1.5 **1.26** **1.27** **1.28**

1.2 equiv. 76% N/A
4 equiv. 25% 62%

This methodology can also be applied to the arylation of 1- and 2-naphthol **1.29** and **1.31** (Scheme 1.14). Arylation of 1-naphthol occurs in the 8-position to produce **1.30** in 70% yield. In the presence of two equivalents of aryl bromide and four equivalents of triphenylphosphine to palladium, 2-naphthol generated a formally bis-arylated product **1.32** in 55% yield. In this case, arylation at the more nucleophilic 1-position is followed by a 2-phenylphenol type arylation at the 2'-position.

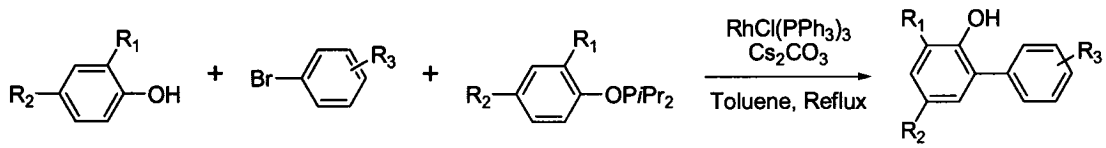
Scheme 1.14. Direct Arylation of Naphthol Derivatives.



1.29 **1.30** 70% yield **1.31** **1.32** 55% yield

Based on the fact that when aryloxides are incorporated into phosphites, $P(OAr)_3$, or phosphinites, $PR_2(OAr)$, they can undergo facile orthometalation to generate a stable five membered ring metallacycle, Bedford *et al.* developed in 2003, a co-catalytic system based

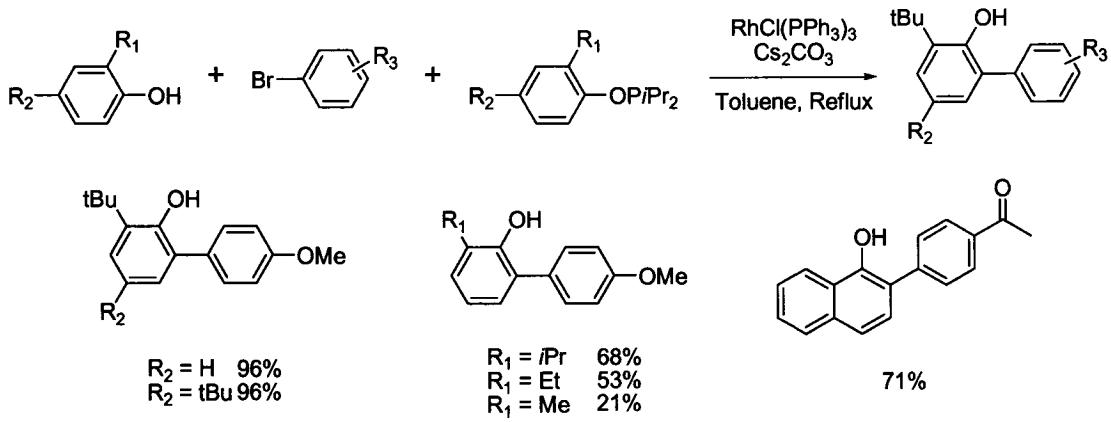
on a phosphinite ligand and rhodium catalyst.[21] The reaction is catalytic in phosphinite ligand because transesterification can occur, replacing a more substituted aryloxide group by a less hindered one. Therefore, after arylation of the 2-position of the phenol has occurred, the group is displaced from the phosphinite ligand by a smaller no*N*-arylated phenol. After screening different metals and phosphinite ligands, it was established that the optimal conditions required the use of Wilkinson's catalyst, aryl-diisopropylphosphinite and cesium carbonate in refluxing toluene (Equation 1.10). The reaction works best when the phenol bears a bulky group in the 2-position at which point arylation can occur at C6.



(1.10)

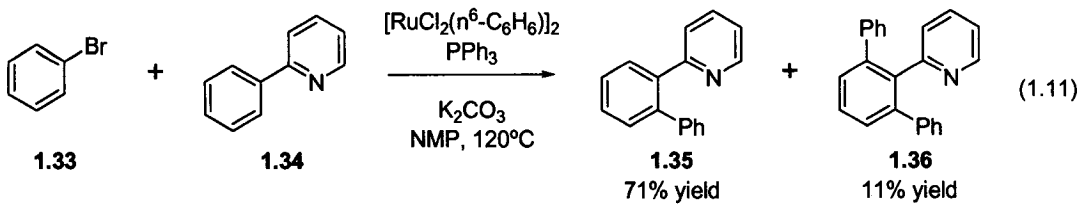
Under these conditions, 2-*tert*-butylphenol is arylated with a variety of aryl halides in 79% to 100% yield (Scheme 1.15). If bromobenzene is the arylating agent, multiple arylations can occur in the 2'- and 6'-position of the biphenyl formed in situ as reported by Miura *et al.* Decreasing the size of the substituent in the 2-position of the phenol leads to a decrease in yield all the way down to 21% for a methyl group. Naphthol can also be arylated in the 2-position under the reaction conditions. A second arylation at the 8-position can also occur, but, the authors propose that the second arylation occurs via a different mechanism.

Scheme 1.15. Scope of the Direct Arylation of Phenols.



1.1.1.2.1.2 – Direct Arylation of 2-Arylpyridines and Aryl imines

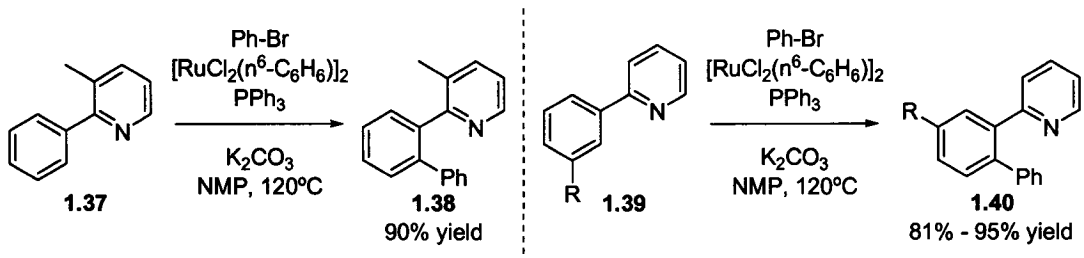
After having reported a procedure for the arylation of 2-arylpyridines with aryl stannanes using a rhodium catalyst, Oi *et al.* looked at a similar arylation process using aryl halides instead of aryl stannanes and the results appeared in the literature in 2001.[22] The rhodium(I) catalyst used with stannanes is changed to a ruthenium(II) catalyst and when 2-phenylpyrridine **1.34** is treated with one equivalent of phenyl bromide **1.33**, triphenylphosphine and potassium carbonate in NMP, the desired o-biphenyl-2-pyrridine **1.35** is obtained in 71% yield along with the diphenylated product **1.36** in 11% yield (Equation 1.11). While three different ruthenium sources, $[RuCl_2(\eta^6\text{-}C_6H_6)]_2$, $RuCl_2(PPh_3)_3$ and $[RuCl_2(cod)_2]$-$4PPh_3$, gave similar results indicating that analogous active catalysts are generated *in situ*, other metal complexes led to little or no conversion. Aryl iodides and aryl triflates could be used but lower ratios of mono- to diphenylated product were obtained. Aryl chlorides were considerably less reactive giving the desired product in only 32% yield. Increasing the amount of aryl halide allows for the selective formation of diphenylated product **1.36**. The scope of the reaction was explored under the optimal conditions described above and it was established that most aryl halides give between 40% and 64% of monoarylated and 14% to 18% of diarylated product.



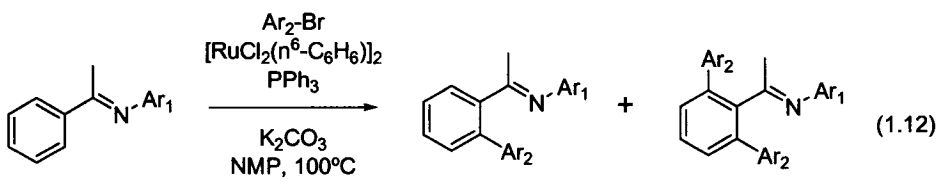
1.33 1.34 1.35 71% yield 1.36 11% yield (1.11)

The monoarylated product **1.38** can be obtained selectively if 3-methyl-2-phenylpyridine **1.37** is used or if meta-substituted phenylpyridines **1.39** are used, giving the desired product **1.40** in 81% to 95% yield (Scheme 1.16). The reaction is believed to occur via the formation of a five membered ring aryl ruthena(IV)cycle formed by electrophilic attack of ruthenium on the phenyl ring of 2-phenylpyrridine.

Scheme 1.16. Monoarylation of Selected Substrates.



This methodology was also applied in 2002 to the arylation of *N*-(4-methoxyphenyl)-arylimines.[23] The reaction conditions were nearly identical to those described above and the results were very similar as well (Equation 1.12).

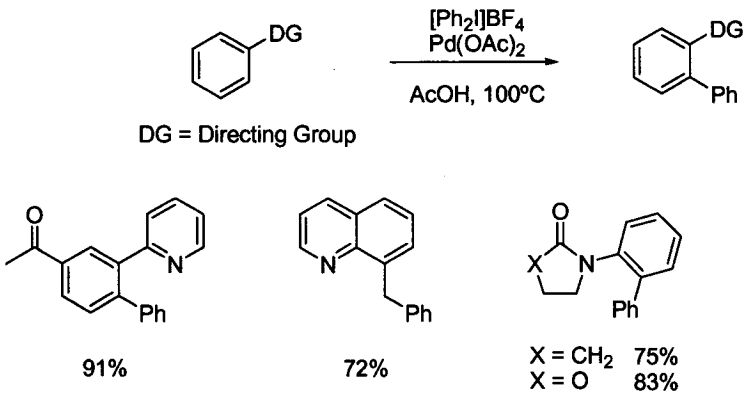


Ar_1 = 4-methoxyphenyl 73% - 95% yield (1.12)

Recently the Sanford group at the University of Michigan reported a palladium catalyzed oxidation of aromatic C-H bonds.[24] This process is believed to go through a palladium(II)/palladium(IV) catalytic cycle as opposed to the usual palladium(0)/palladium(II) cycle.[25] In 2005, Sanford *et al.* used the knowledge gained in these studies to develop a

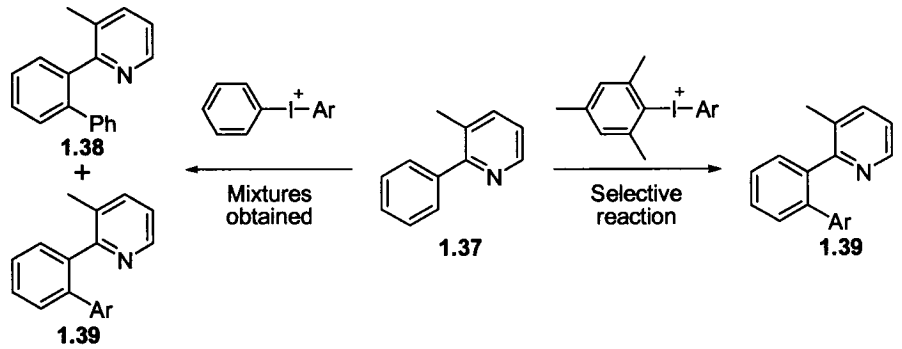
new process for the arylation of 2-arylpyridines and other aromatic compounds bearing a directing group.[26] Iodine(III) arylating agents were selected instead of the usual aryl halides. The mechanism once again most likely goes through a Pd(II)/Pd(IV) cycle rendering it air and moisture stable. The optimal conditions involve the use of palladium acetate and diphenyliodonium tetrafluoroborate in acetic acid at 100°C. Ligands for palladium are not required, lowering the overall cost of the reaction. Diverse heterocycles, such as pyridines, quinolines, pyrrolidinones, and oxazolidinones, can act as directing groups and the products are obtained in 49% to 91% yield (Scheme 1.17).

Scheme 1.17. Iodonium Salts as Substrates for Direct Arylation.



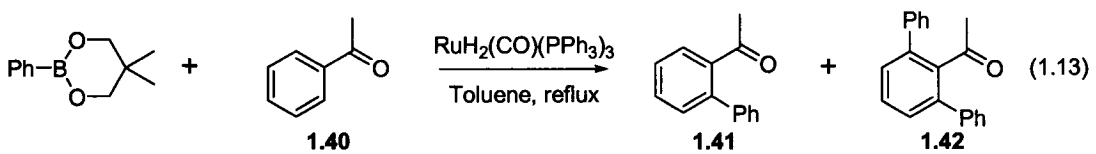
Having established a good procedure for the transfer of phenyl groups, a method for the transfer of substituted aromatic rings not requiring symmetrical diaryliodonium salts was sought. When aryl-phenyliodonium salts are employed, varying mixtures of aryl (**1.39**) and phenyl (**1.38**) transfer occurs. The procedure is particularly problematic with hindered substrates for which the phenyl is transferred preferentially. Taking advantage of this fact, highly hindered mesityl-aryliodonium salts allow a very selective transfer of a less hindered aryl (Scheme 1.18). Even an o-tolyl group can be transferred selectively.

Scheme 1.18. Selective Arene Transfer.



If the diaryliodonium salts are replaced by aryl iodides or aryl triflates, the reaction shuts down completely indicating that oxidative insertion into the aryliodonium is unlikely. Further investigation also demonstrated that neither palladium nanoparticles nor free radicals are participating in the reaction. The authors therefore propose that either the aryliodonium salt oxidizes Pd(II) to Pd(IV) or that direct electrophilic cleavage of the Pd(II)-carbon bond by the iodonium occurs without a change of the oxidation state at the metal.

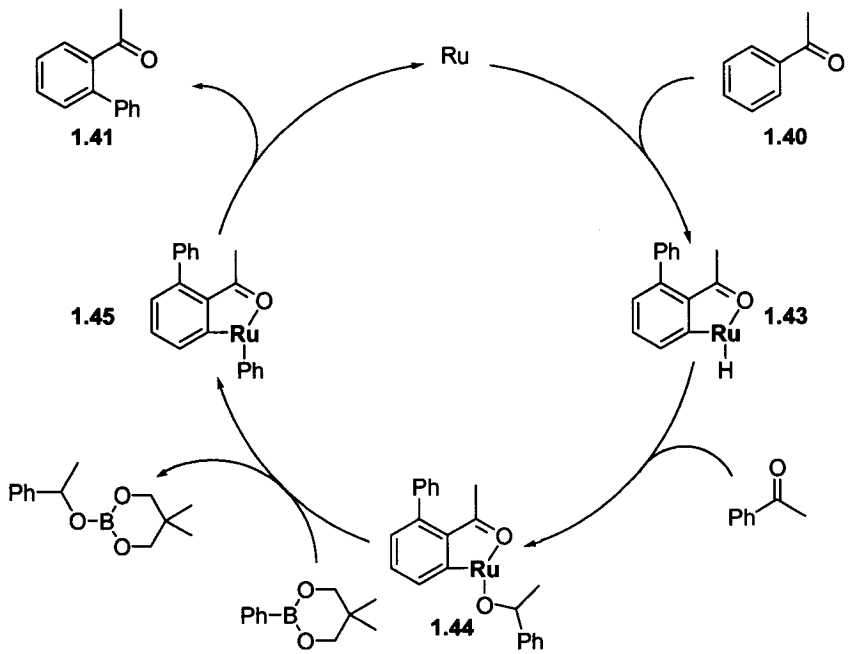
1.1.1.2.1.3 – Direct Arylation of α-Ketones



In 2003, Kakiuchi *et al.* reported that aromatic ketones (**1.40**) could be arylated with arylboronates in the presence of a ruthenium catalyst (Equation 1.13).[27] Contrary to the majority of direct arylation reactions present in the literature in which insertion into an aryl halide is followed by electrophilic metalation, this process is believed to begin with binding of the ketone **1.40** to ruthenium followed by insertion of ruthenium(0) into the aromatic C-H bond to generate a five membered ring ruthenacycle **1.43** (Scheme 1.19). Reduction of a stoichiometric amount of a second molecule of ketone with the hydride generated in the insertion forms the (alkoxy)-ruthenium complex **1.44**. The alkoxide participates in the

transmetalation with the aryl boronate generating a trialkoxyborane and a diarylruthenium **1.45**. Reductive elimination finally gives the desired product (**1.41** or **1.42** if two cycles). The reduction of a full equivalent of the aromatic ketone greatly diminishes the usefulness of this reaction.

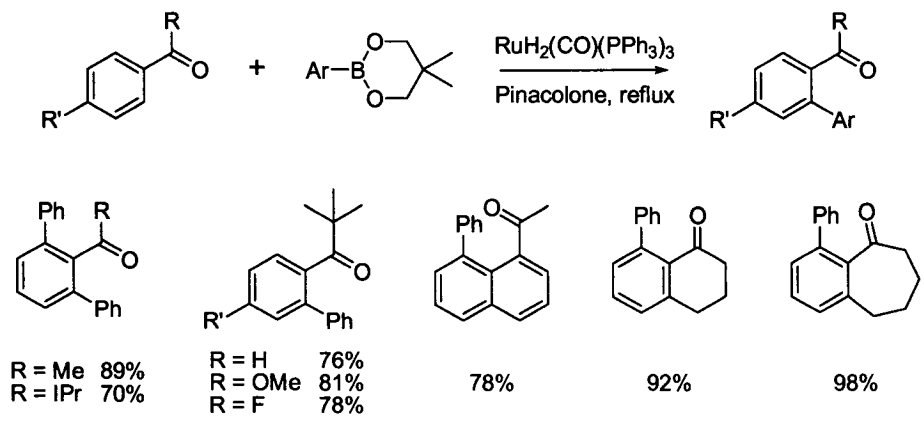
Scheme 1.19. Mechanism of the Ruthenium Catalyzed Arylation of α-Ketones.



Changing the reaction solvent from toluene to pinacolone (methyl-*tert*-butylketone) solved this problem.[28] The solvent acts as a hydride acceptor eliminating the need for the second equivalent of aromatic ketone. In the case of methyl or *iso*-propyl ketones, a mixture of mono- and diarylated product is obtained if 1.1 equivalent of arylboronate is added, but if 2.2 equivalents of aryl boronate are added, the diarylated product is obtained predominantly in 89% and 70% yield respectively (Scheme 1.20). On the other hand, if a *tert*-butyl ketone is arylated in the presence of 2.2 equivalents of aryl boronate, the mono-arylated product is obtained exclusively in 76% yield. It is proposed that important steric interactions between the *tert*-butyl group and the ortho-phenyl would block the second arylation. The electronic properties of the aromatic ketone do not seem to impact the yield

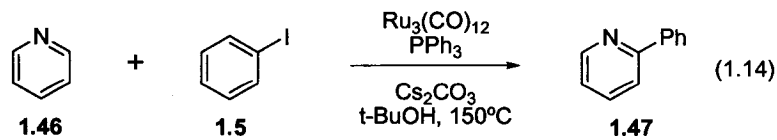
of the reaction since methoxy, hydrogen and fluoride groups all give similar results. Bicyclic structures are also compatible with the methodology, leading to the formation of monoarylated product in excellent yield (92% and 98%).

Scheme 1.20. Scope of the Arylation of α-Ketones.



1.1.1.3 – Intermolecular Direct Arylation of Electron Deficient Arenes - Pyridines

The direct arylation of heteroaromatic rings and simple arenes has been known for approximately 20 years, but, the arylation of electron deficient aromatic rings is nearly unprecedented.[29] In 2005, Sames *et al.* reported a protocol for the arylation of pyridine **1.46** in the 2-position (Equation 1.14).[30] The catalyst consists of $Ru_3(CO)_{12}$ and triphenylphosphine. When pyridine **1.46**, iodobenzene **1.5**, ruthenium, phosphine and cesium carbonate are heated to 150°C in *tert*-butanol, the product (**1.47**) is obtained in 36% yield.

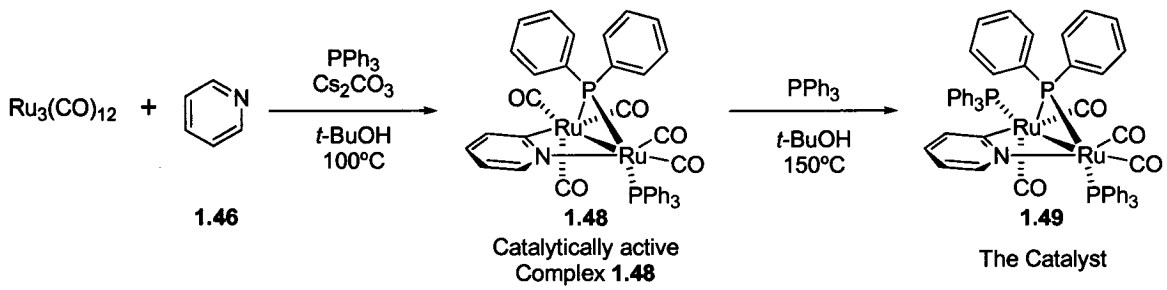


1.46 **1.5** **1.47** (1.14)

Studies to determine the nature of the active catalyst were undertaken in an effort to increase the yield of the reaction. Addition of triphenylphosphine and cesium carbonate to a

mixture of ruthenium and pyridine generates a very surprising catalyst **1.48** in which a phosphine bearing only two phenyl rings is bridging two ruthenium centers (Scheme 1.21). This catalyst has already inserted into the C-H bond at the 2-position of the pyridine and eliminated the hydride. This represents a formal loss of benzene from complex **1.48**. The catalyst undergoes a few more changes to become the true catalyst **1.49** before inserting into the aryl iodide. Reductive elimination of 2-arylpyridine, followed by insertion into the C-H bond of another pyridine and elimination of HI regenerates the active species. When the true catalyst is pre-generated instead of formed *in situ*, the yield of the reaction goes up to 55% and can be brought up to nearly 70% after longer reaction times.

Scheme 1.21. Identification of the Active Catalyst in Direct Arylation of Pyridine.

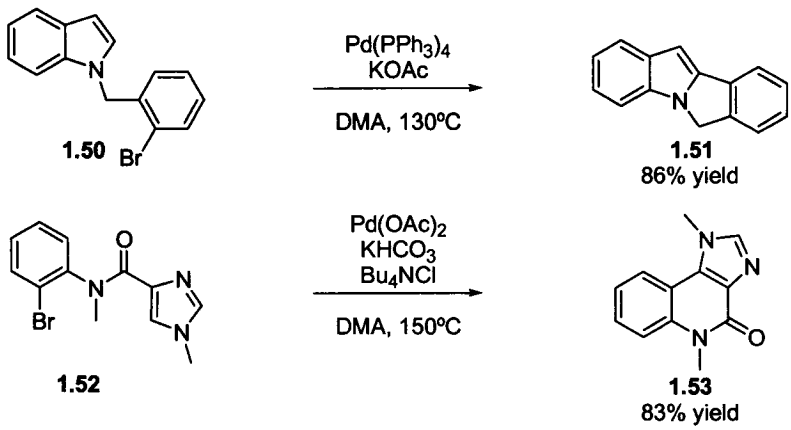


1.1.2 – Intramolecular Direct Arylation of Arenes

1.1.2.1 – Intramolecular Direct Arylation of Heteroaromatic Rings

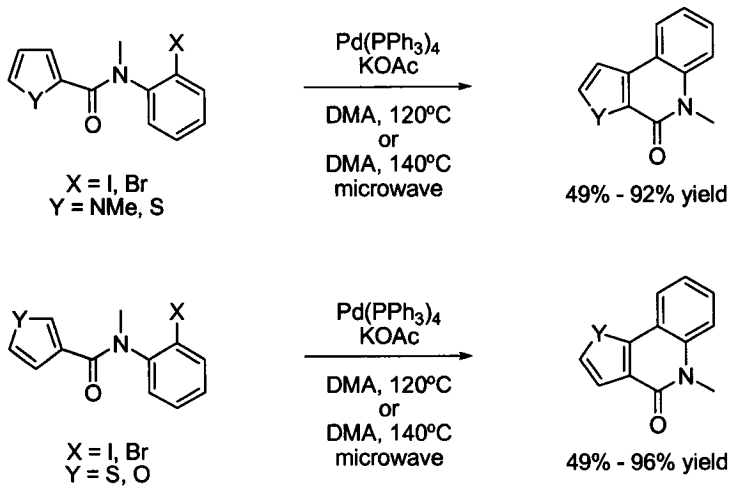
Following the pioneering work of Dr. Ohta in 1989, protocols for the intramolecular arylation of indole **1.50** and *N*-methylimidazole **1.52** were developed by Kozikowski *et al.* and Suzuki *et al.* in 1991 (Scheme 1.22).[31] The reaction conditions are similar to the ones used in the Ohta protocol mentioned earlier, but the yields of products **1.51** and **1.53** are now over 80%.

Scheme 1.22. Intramolecular Direct Arylation of Indoles and Imidazoles.



Becalli *et al.* found that thiophene, furan and *N*-methylpyrrole could be arylated in an intramolecular fashion to form six membered rings (Scheme 1.23).[32] The microwave assisted palladium catalyzed process is very rapid reaching completion in less than 45 minutes affording the product in high yield (greater than 90%). If the reaction is simply heated for 24 hours at 120°C, the yields are considerably lower (~ 50%). The authors use palladium tetrakistriphenylphosphine as the catalyst and potassium acetate as the base in DMA. Aryl iodides and bromides can be used in the presence of an aryl chloride and the chloride remains untouched. The mechanism is proposed to go through a Heck reaction but no mechanistic investigations were reported.

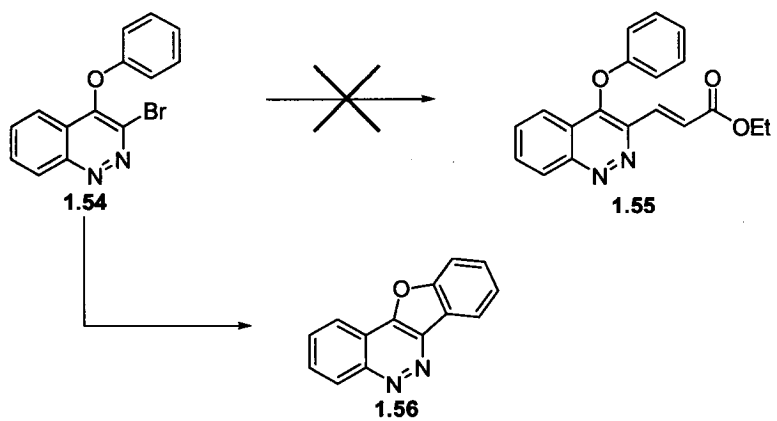
Scheme 1.23. Intramolecular Arylation of Azoles.



1.1.2.2 – Intramolecular Direct Arylation of Simple Arenes

One of the earliest examples of direct arylation of simple arenes was reported in 1982 by Ames and Bull.[33] While exploring the reactivity of 3-halogeno-4-substituted cinnolines towards palladium catalyzed processes such as the Heck reaction, they stumbled across the intramolecular cyclization of 3-bromo-4-phenoxycinnoline **1.54** to generate benzofurocinnoline **1.56** (Scheme 1.24). This result seemed rather surprising and experiments

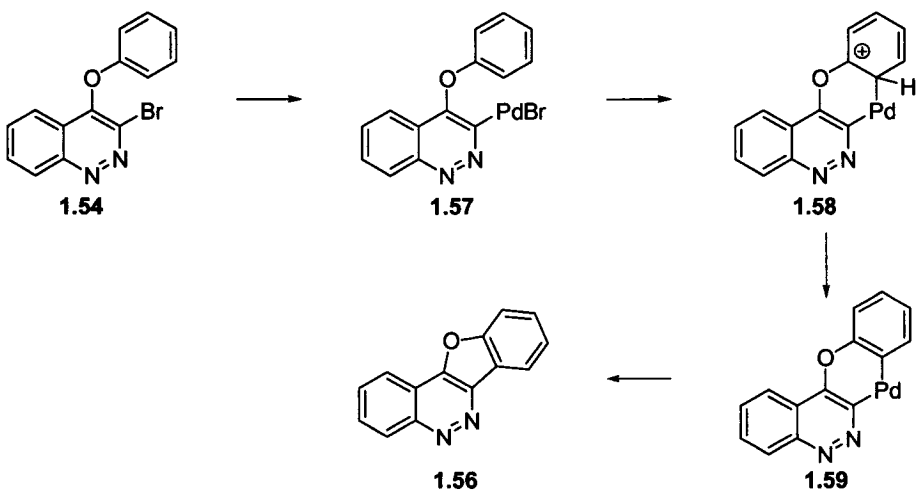
Scheme 1.24. Early Example of Intramolecular Direct Arylation of Simple Arenes.



Conditions: Ethyl Acrylate, $PdOAc_2$, PPh_3, Et_3N, MeCN, 150°C

were conducted to see whether the product was generated by oxidative coupling of the two aryl groups after dehalogenation would have occurred. Dibenzofuran had been previously generated from diphenyl ether using stoichiometric amounts of palladium in acetic acid or a catalytic amount of palladium in an atmosphere of oxygen to re-oxidize the catalyst, but benzofurocinnoline could not be obtained under these conditions. It was therefore proposed that the reaction proceeded through the oxidative addition of palladium to aryl bromide **1.54**, followed by nucleophilic attack of the phenoxy onto palladium (**1.57**) to generate a six membered ring palladacycle **1.58** and an arenium cation (Scheme 1.25). The arenium could be deprotonated by triethylamine to regenerate aromaticity (**1.59**) and reductive elimination would form the desired product (**1.56**).

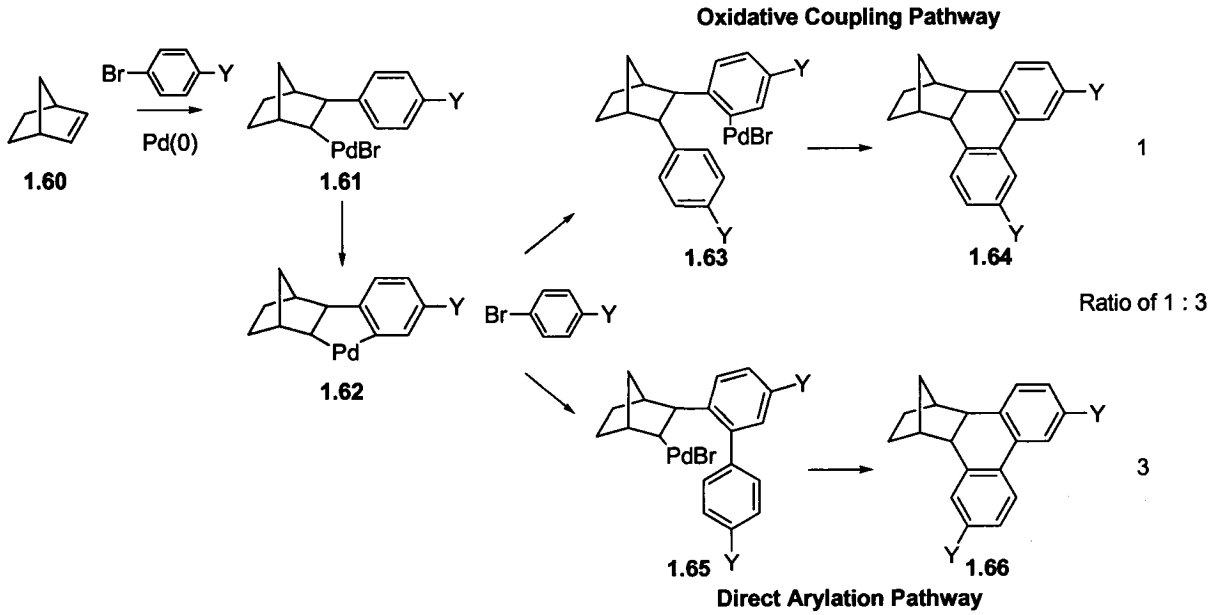
Scheme 1.25. Proposed Mechanism of the Direct Arylation Step.



The intramolecular reaction described above can be extended to the cross-annulation of aryl halides with unsaturated compounds. Phenanthrenes can be generated by the coupling of norbornene **1.60** with two equivalents of aryl halide.[34] An account published in 1985 by Catellani and Chiusoli describes how palladium tetrakistriphenylphosphine catalyzes the formation of two different products, in a 3 to 1 mixture, when potassium *tert*-butoxide is added to a mixture of norbornene **1.60** and p-

substitutedbromobenzene (Scheme 1.26). One product can arise from the bis-arylation of norbornene (**1.63**) followed by an oxidative coupling between the aryl groups to yield **1.64**.

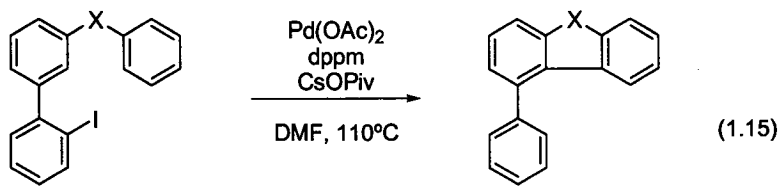
Scheme 1.26. Rationalization of the Product Formation in Arylation of 4-Substituted Haloarenes.



The second product most likely goes through a five membered ring palladacycle intermediate **1.62**. Oxidative insertion into a second aryl halide forms a palladium(IV) complex that reductively eliminates to generate the biaryl **1.65**. Intramolecular functionalization of a second aromatic C-H bond gives the final product **1.66**.

In 2003, a tandem 1,4 aryl to aryl palladium migration followed by direct arylation to generate fused polycyclic compounds was reported by Larock *et al.*[35] After inserting into the carbon iodide bond of 3'-benzyl-2-iodobiphenyl, palladium migrates to the 2'-position, possibly through a hydridopallada(IV)cycle that would arise from insertion into the C-H bond.[36] Once at the 2'-position, palladium arylates the benzyl ring attached in the 3'-position to form a five membered ring. After extended reaction times at 110°C, the product was obtained in 40% yield. Switching from a 3'-benzyl to a 3'-phenoxy group increased the

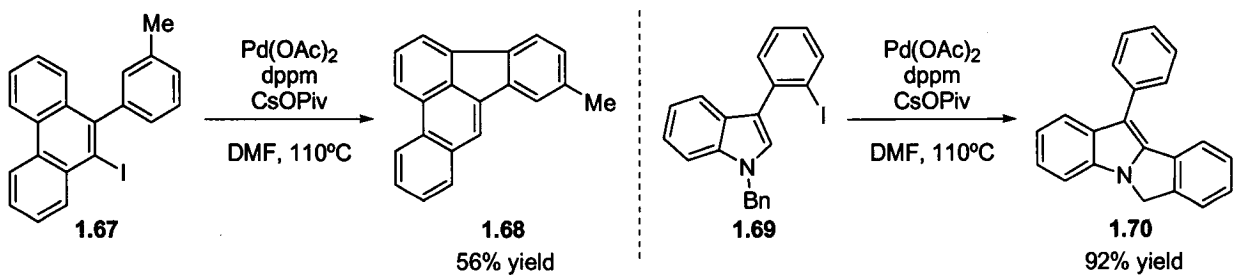
yield to 89% after 24 hours. This is in concordance with previous literature reports that state that arylation rates parallel electrophilic aromatic substitution rates.



(1.15)

The regioselectivity of the migration step was explored with the use of 10-m-tolyl-9-iodophenanthrene **1.67** (Scheme 1.27). Benz[e]acephenanthrylene **1.68** was formed as a single product indicating that either the migration occurs solely at the less hindered position or that ring closure is completely inhibited in hindered settings.

Scheme 1.27. Palladium Migration in Direct Arylation.



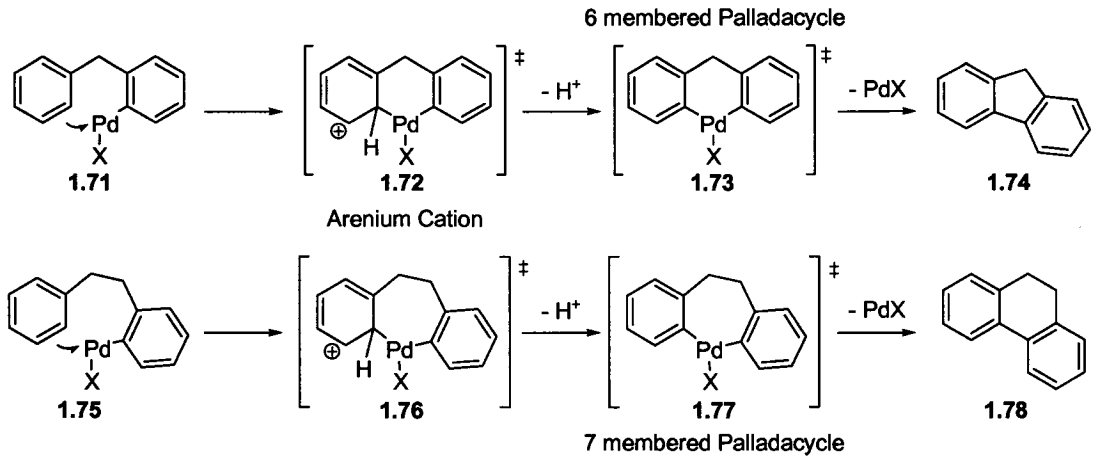
The authors suspected that migration to a more electro*N*-rich position would be favored. This hypothesis was tested using 3-(2'-iodophenyl)-*N*-benzylindole **1.69** (Scheme 1.27). Migration of palladium to the indole carbon is rapid and arylation of the benzyl protecting group (**1.70**) occurs in 92% yield. Multiple migrations are also possible and lead to yields that are as high (88%) as single migration (89%). Addition to an alkyne is possible and the insertion into alkenes followed by 1,4-alkyl to aryl migration was later reported.[37]

1.2 – Project Goals

1.2.1 – Synthetic Precedent

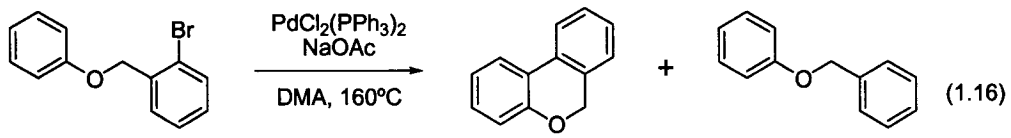
The majority of the examples of intramolecular direct arylation reactions described above generate five membered rings (**1.74**) through the intermediacy of a six membered ring palladacycle (**1.73**). The examples that will follow go one step further and generate six membered rings (**1.78**) via a seven membered ring palladacycle (**1.77**) (Scheme 1.28). This is considerably more challenging as we move away from the strain free six membered ring transition state and increase the entropy factor therefore increasing the overall energy required for the reaction to occur. Since the binding of the arene to the metal center is likely part of the rate equation, moving to a longer tether should lower the turnover frequency of the catalyst. The reports of Ames *et al.*[2] and Rawal *et al.*[38] open the door to the generation of larger rings via direct arylation. Increasing the scope of the reaction to include six membered rings renders the reaction significantly more useful.

Scheme 1.28. Formation of Larger Ring Systems by Direct Arylation.



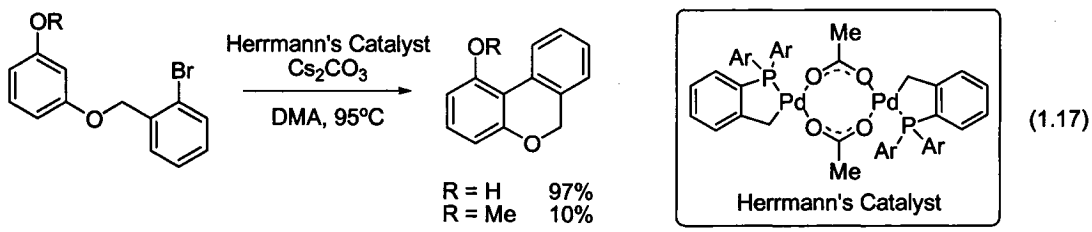
In 1984, Ames & Opalko reported the palladium catalyzed intramolecular direct arylation of 2-bromobenzyl phenyl ether **1.79** to generate 6H-dibenzo[*b, d*]pyran **1.80**.[2] Although, this was one of the first examples of direct arylation using a simple aryl halide and arene, the reaction suffered from the formation of a side product, benzyl phenyl ether **1.81**,

resulting from the dehalogenation of the starting material. The cyclized and dehalogenated products were generated in nearly equivalent ratios (40% cyclized and 35% dehalogenated) and were very difficult to separate (Equation 1.16). Ames therefore never pursued further developments with this type of substrates.



1.79 **1.80** 40% yield **1.81** 35% yield (1.16)

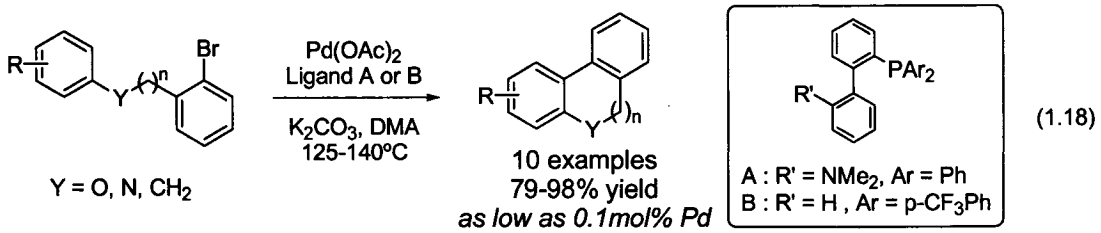
Nearly fifteen years later, Rawal et al. discovered that if rescorcinols rather than phenols were coupled with a 2-bromobenzyl bromide, the cyclization products could be obtained in good yield under considerably milder conditions.[38] Under basic conditions, the hydroxyl group left after the coupling is deprotonated, forming a much better nucleophile. Attack of the enolate onto an electrophilic palladium species occurs at the ortho position yielding 97% of the tri-substituted biaryl (Equation 1.17). The optimal conditions require the use of Herrmann's catalyst[39] (1:1 of $PdOAc_2$ and tri-o-tolylphosphine) and cesium carbonate with DMA as the solvent. Unfortunately, if the hydroxyl group is removed or even just capped as a methoxy group, only 10% conversion to the desired product is obtained.



(1.17)

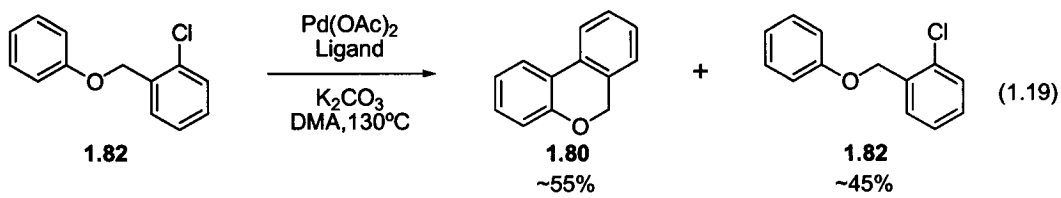
In the summer of 2004, our group reported a new catalyst for the intramolecular direct arylation of unactivated aryl ethers to generate six membered rings.[40] As opposed to the Ames procedure which gives a 1:1 mixture of cyclized to dehalogenated product, the conditions developed in our laboratories are very selective providing the cyclized product in a 160:1 ratio. The catalyst developed for this process by Louis-Charles Campeau based on

palladium acetate and 2-(diphenylphosphino)-2'-(*N*,*N*-dimethylamino)biphenyl is robust and highly active. A variety of aryl bromides can be cyclized to give the desired tricyclic products in good to excellent yields (78% - 98%) with catalyst loadings as low as 0.1 mol% (Equation 1.18). The methodology can be expanded to generate a seven membered ring if the ligand is switched to the electron deficient 2-(di-(4-trifluoromethyl)phenylphosphino)biphenyl.[41]



(1.18)

Attempts to catalyze the direct arylation of aryl chlorides (**1.82**) were unsuccessful as only 55% conversion to the desired product **1.80** was observed under optimal conditions, while 45% of starting material remained untouched after catalyst deactivation had occurred (Equation 1.19). Attempts to increase the conversion were unsuccessful using this catalyst system.



(1.19)

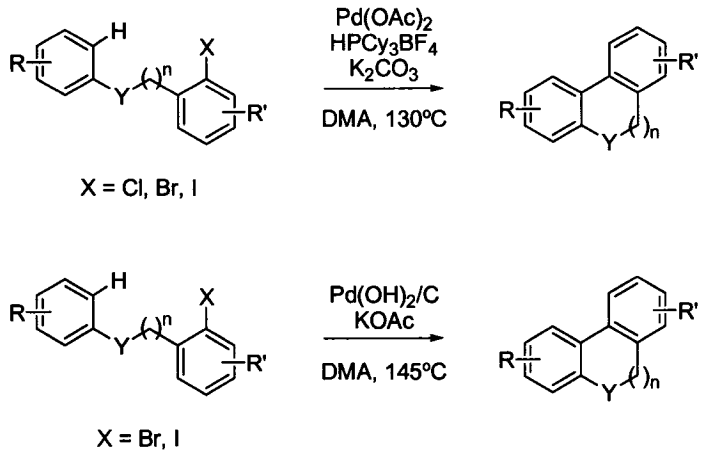
1.2.2 – The Development of a General Method for the Direct Arylation of Aryl Chlorides, Bromides and Iodides

The studies depicted herein describe the development of a general method for the intramolecular direct arylation of aryl chlorides, bromides and iodides (Scheme 1.28). A ligand screen allowed the identification of a catalyst able to cyclize a wide range of aryl chlorides and bromides in excellent yields. Minor changes to the reaction conditions

expanded the scope to include aryl iodides. Further studies to understand the regioselectivity and mechanism of the reaction, as well as, the applicability of the methodology to the synthesis of natural products complete the main chapter.

Also described is the use of Pearlman's catalyst in the intra- and intermolecular direct arylation of aryl iodides and bromides.[42] Mechanistic investigations have demonstrated that a soluble palladium species is responsible for the catalysis observed in these reactions.

Scheme 1.28. New Catalysts for the Intramolecular Direct Arylation of Aryl Halides.



2 – Catalytic Intramolecular Direct Arylation with Aryl Chlorides, Bromides and Iodides

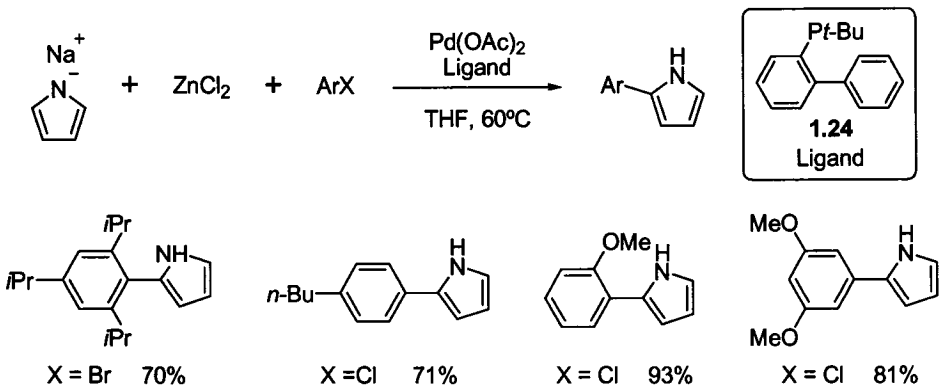
2.1 – Aryl Chlorides

2.1.1 – Background

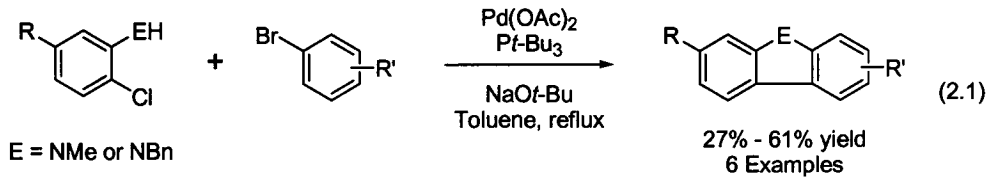
The development of novel catalyst systems during the past decade has broadened the scope of cross-coupling methodologies to include the more readily available and less expensive aryl chlorides. This has not transpired in direct arylation where aryl iodides and bromides are nearly exclusively used.[10, 38] Thus far, there have only been a few isolated examples of aryl chlorides used successfully as substrates in direct arylation reactions.

One account by Sadighi *et al.* describes the coupling of pyrrole anions with aryl chlorides and bromides.[43] Deprotonation of pyrrole with sodium hydride and transmetalation with zinc chloride prevents the amination side reaction. In the presence of palladium acetate, dialkylphosphinobiphenyl ligands (**1.24**) developed by Buchwald and the desired aryl halide, pyrrolylzinc chloride can be arylated selectively at the 2-position in good to excellent yield (70% - 93%) (Scheme 2.1). The reaction works quite well for most electron rich and deficient aryl chlorides and bromides. Even the highly hindered 2,4,6-triisopropylbromobenzene can be coupled in high yields (70%) under these conditions. The only substrate that leads to a lower yield is the very electron rich 4-bromo-*N,N*-dimethylaniline (48%). Surprisingly, aryl chlorides require lower reaction temperatures than aryl bromides.

Scheme 2.1. Direct Arylation of Pyrrolyl Zinc Anions with Aryl Chlorides.



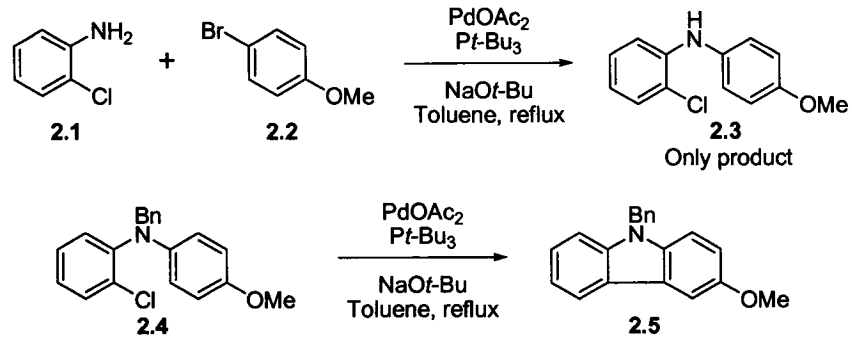
If one can utilize aryl chlorides in direct arylation processes, the possibility of running tandem reactions with aryl bromides or iodides becomes available. Bedford & Cazin reported in 2002 a tandem aminatio*N*-direct arylation process to generate *N*-substituted carbazoles.[44] 2-Chloro-*N*-methyl- or *N*-benzylanilines could be coupled with various aryl bromides to generate the cyclized product (Equation 2.1). The optimal conditions require the use of palladium acetate, tri-*tert*-butylphosphine and sodium *tert*-butoxide in toluene and generate the products in modest isolated yields (27% - 61%).



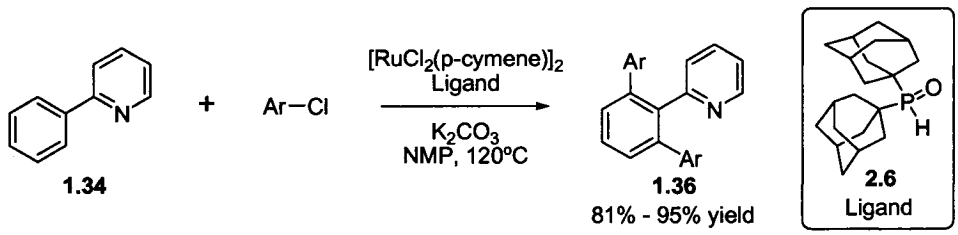
(2.1)

The direct arylation step is completely inhibited in the presence of a free (NH) group (Scheme 2.2). However, protecting the nitrogen atom of intermediate **2.3** with a benzyl group (**2.4**) allows the cyclization step to occur (**2.5**). The authors propose that the amination reaction occurs first with *N*-substitutedanilines and is followed by the direct arylation step.

Scheme 2.2. Effect of free (NH) group on the Formation of Carbazoles.



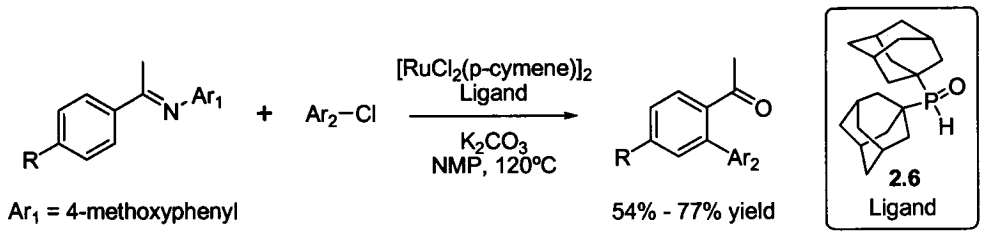
Ackermann reported in 2005 a modification of the Oi procedure for the direct arylation of 2-arylpyridines and arylimines. The combination of dialkylphosphine oxide ligands and a ruthenium catalyst allows the use of aryl chlorides as substrates.[45] Sames has demonstrated that anionic phosphine ligands generated in the presence of ruthenium can be good catalysts for direct arylation reactions.[30] The author proposes that the dialkylphosphine oxides likely react as anionic phosphorus ligands. Even though many different phosphine oxides catalyze the arylation in modest yields (8% to 61%), diadamanthylphosphine oxide **2.6** proved to be the best giving the 2',6'-diarylated product **1.36** in excellent yield (98%). The reaction can be applied to a number of electron rich and deficient aryl chlorides. Many reactive functional groups such as esters, nitriles and enolizable ketones are well tolerated (Equation 2.2).



(2.2)

The reaction can also be expanded to the arylation of aromatic imines. Diadamanthylphosphine oxide **2.6** once again proved to be a good pre-ligand for this reaction. Monoarylation at the 2-position is achieved with electron rich and deficient aryl

chlorides (Equation 2.3). Ortho-substituted aryl chlorides are compatible with the methodology.



(2.3)

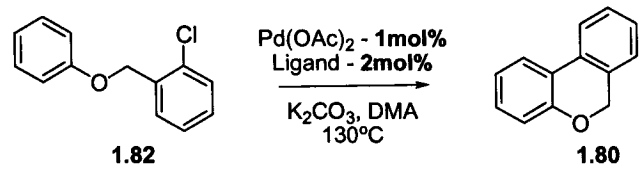
2.1.2 – Developing a Highly Active Catalyst for the Intramolecular Direct Arylation of Aryl Chlorides

2.1.2.1 – Ligand Screen

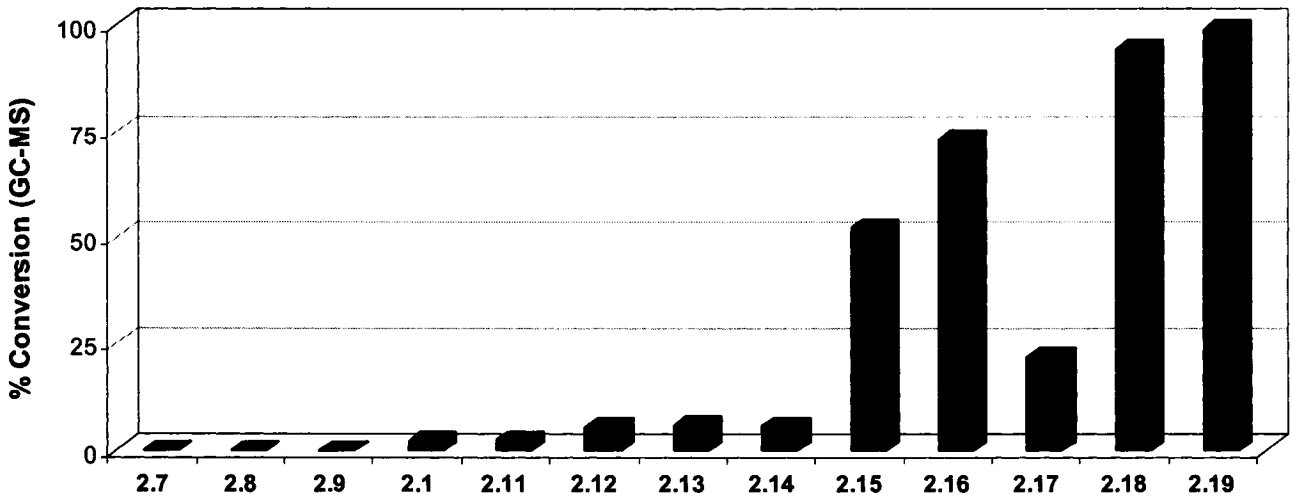
In order to claim that a general catalyst had been developed, it was important that it reacts with aryl chlorides, bromides and iodides. Since the first generation catalyst gave unsatisfactory results with aryl chlorides, it was clear that a ligand screen was needed if a more general catalyst system was to be identified.

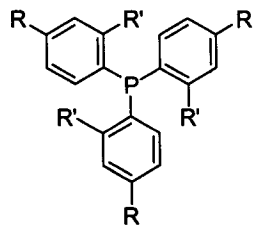
A variety of phosphine ligands were screened under the optimal conditions (Scheme 2.3). The conversions were established by GC-MS analysis. Triarylphosphines give modest conversions to the desired product (Entries **2.7-2.10**). Even electron deficient phosphines, which have shown promising results with aryl bromides, are not catalytically active with aryl chlorides. Biaryl based ligands bearing two electron rich alkyl groups on the phosphine also give less than 10% conversion (Entries **2.11-2.14**). Interesting results are obtained with *N*-heterocyclic carbenes (70%) (Entry **2.16**)[46], but trialkylphosphines proved to be the best ligands for this process (Entries **2.17-2.19**). Tricyclohexylphosphine and di-*tert*-butylmethylphosphine both give greater than 90% conversions. The more hindered tri-*tert*-butylphosphine forms less than 25% of the desired product demonstrating that a very fine balance between the electronic properties and the size of the ligand needs to be reached in order to achieve maximum catalyst efficiency.

Scheme 2.3. Ligand Screen for the Direct Arylation of Aryl Chlorides.[a]

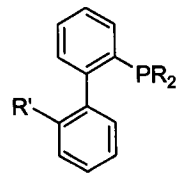


1.82 **1.80**

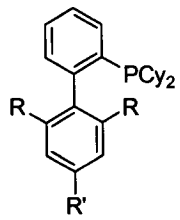




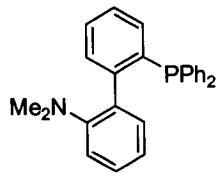
2.7: R=R'=H
2.8: R=CF_3, R'=H
2.9: R=OMe, R'=H
2.10: R=H, R'=Me



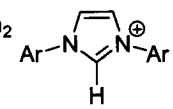
2.11: R=Cy, R'=Me
2.12: R=^{t}Bu, R'=Me



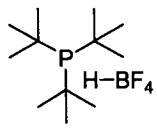
2.13: R=OMe, R'=H
2.14: R=R'=^{i}Pr



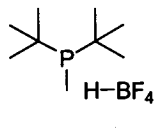
2.15



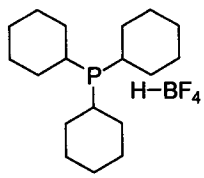
2.16: Ar=2,6^{i}PrPh



2.17



2.18



2.19

[a]Conditions: Substrate **1.82**, $Pd(OAc)_2$ (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.

For technical simplicity, the trialkylphosphines are used as the tetrafluoroborate salts.[47] This renders the otherwise air sensitive phosphine ligands completely bench stable.

Tricyclohexylphosphonium tetrafluoroborate was the ligand selected for the second generation catalyst.

2.1.2.2 – Optimization of the Reaction Conditions

Having established a catalyst, we needed to establish the optimal conditions. Palladium sources, ligand equivalents, as well as the choice of base, were considered for the optimization process.

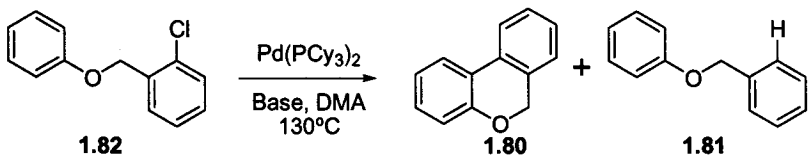
A number of palladium sources with various oxidation states are available when searching for a catalyst. Five sources of palladium(II) ($Pd(OAc)_2$, $PdBr_2$, $PdCl_2$, $Pd(acac)_2$ and $Pd(tfa)_2$) and two sources of palladium(0) ($Pd_2(dba)_3$ and $Pd(PCy_3)_2$) were scanned utilizing two equivalents of phosphine ligand per palladium (except in the case if $Pd(PCy_3)_2$ since the phosphine is already present). Although many palladium sources ($Pd(OAc)_2$, $PdBr_2$, $Pd(tfa)_2$ and $Pd(PCy_3)_2$) give similar results, palladium acetate was chosen as the optimal catalyst due to its high reactivity and ease of use.

The number of equivalents of ligand to palladium was verified. A ligand to metal ratio of 1:1 leads to decreased reactivity compared to a ratio of 2:1, while a 4:1 ratio gives similar results to a 2:1 ratio. Two equivalents of ligand were, therefore, chosen as the optimal ligand to metal ratio.

Next, the effect of many organic and inorganic bases was tested (Table 2.1). The choice of counterion proved to be a crucial factor in the establishment of optimal reaction conditions, potassium bases consistently giving better results than their sodium or cesium counterparts. Potassium carbonate, the optimal base, gives full conversion to the desired product **1.80**, while sodium carbonate and cesium carbonate only give 11% and 25% conversion respectively. Both bases also furnish lower ratios of cyclized to dehalogenated product (20:1 for Na_2CO_3 and 15:1 for Cs_2CO_3 compared to >99:1 for K_2CO_3). Potassium acetate also allows the reactions to proceed quite well, giving 81% conversion with an

excellent ratio of cyclized over dehalogenated product of >99:1. Once again, sodium acetate is far less effective, with only 41% conversion. Potassium *tert*-butoxide leads to good conversion, but a much greater amount of dehalogenated product **1.81** is formed (ratio of 2.3:1). Organic bases, such as triethylamine, Hunig's base and dicyclohexylmethylamine, on the other hand, are ineffective for this transformation and also favor the formation of dehalogenated product **1.81**.

Table 2.1. Effect of Base on the Direct Arylation Reaction.[a]



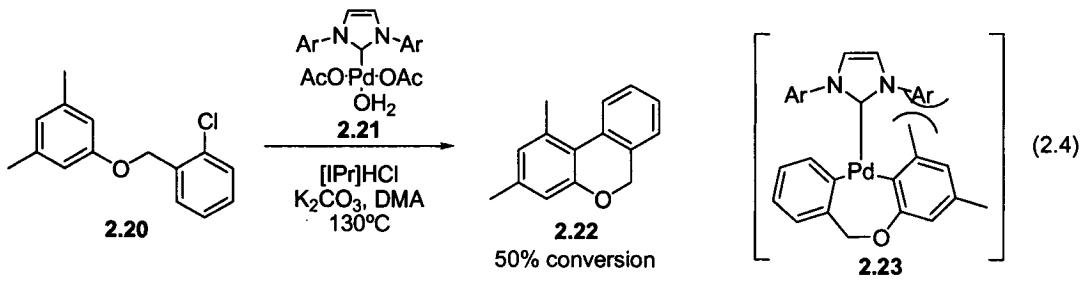
1.82 **1.80** **1.81**

Entry	Base	Conversion (%)[b]	Ratio 1.80:1.81[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: Substrate, $Pd(PCy_3)_2$ 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.

2.1.3 – Scope of the Reaction with Aryl Chlorides

The optimal conditions were applied in scope studies and satisfyingly, the catalyst system seems very general (Table 2.2). Carbon linkers, oxygen linkers, as well as nitrogen linkers, can be used for the reaction. Five, six and seven membered rings can be formed under these conditions. Electron deficient aromatic rings can be arylated in high yields (Entry 1). When a nitrogen atom is present in the tether, amides and sulfonamides can be used as protecting groups for the formation of six membered rings (Entries 4, 5). When carbazoles are formed, the nitrogen atom can be left unprotected (Entries 8-10). Substitution on the ring bearing the halide is also well tolerated with the presence of fluoride and trifluoromethyl groups (Entries 2, 8, 9), although higher catalyst loadings are required when deactivated aryl chlorides are used (Entry 7). Cis alkenes can be arylated in good yield without the apparition of byproducts arising from the competing intermolecular Heck reaction (Entry 6). This catalyst also allows the formation of hindered tri-substituted biaryls **2.22** which had been problematic in previous direct arylation reports (Equation 2.4) (Entries 3, 10).[46]

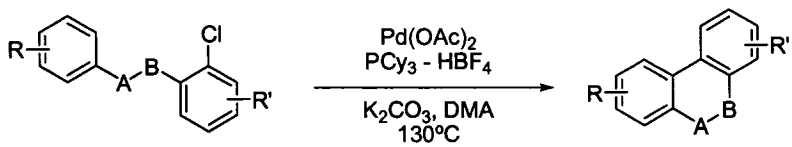


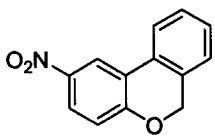
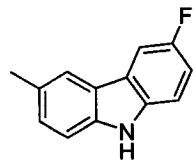
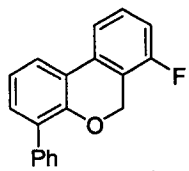
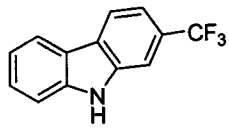
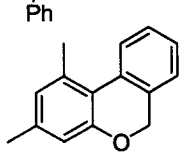
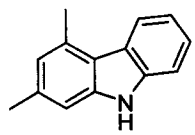
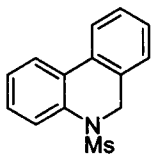
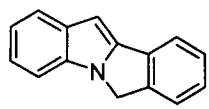
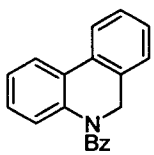
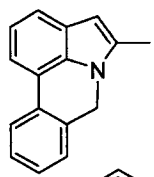
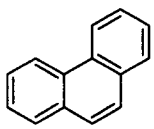
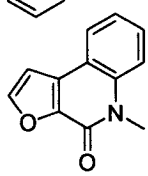
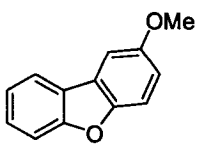
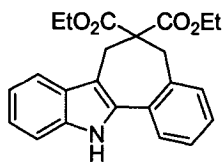
(2.4)

Heteroaromatic rings are compatible with the second generation catalyst. When indoles are linked through the nitrogen, cyclization occurs in the 2-position, giving a five membered ring (Entry 11). If the 2-position is blocked, cyclization occurs at the 7-position and six membered ring formation occurs to give the phenanthridine-type product (Entry 12). Indoles bearing a free *N*-H group can also be used in the preparation of seven membered

rings (Entry 14).[48] Finally, furans can be arylated in good yields to afford the furoquinolinone (Entry 13).

Table 2.2. Scope of the Intramolecular Direct Arylation of Aryl Chlorides.[a]



Entry	Substrate	mol% Pd	Yield[b]	Entry	Substrate	mol% Pd	Yield[b]
1		1	97	8		3	88
2		1	92	9		3	87
3		5	86	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, $Pd(OAc)_2$, Ligand (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. Ms=CH_3SO_2-, Bz=PhC(O)-

2.2 – Aryl Bromides

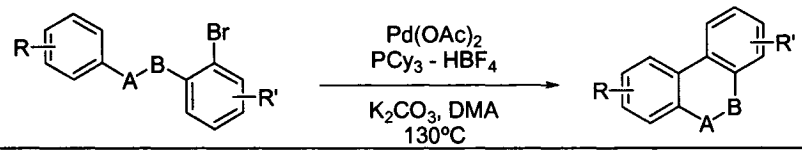
2.2.1 – Reaction with Aryl Bromides

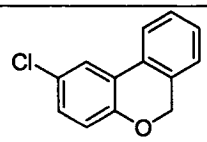
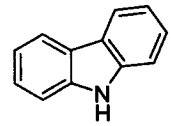
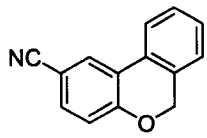
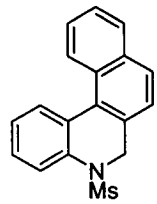
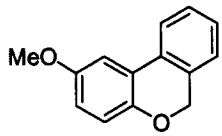
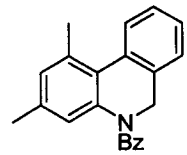
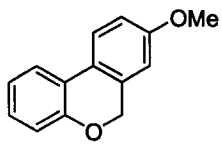
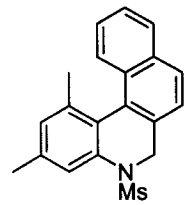
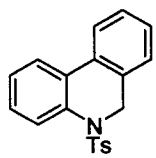
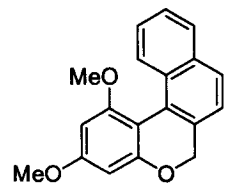
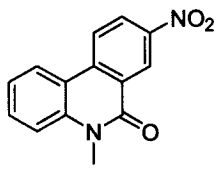
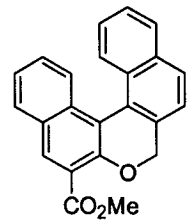
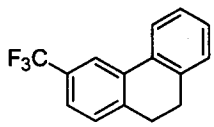
Following the success obtained with aryl chlorides, the applicability of the second generation catalyst to bromide and iodide substrates was tested. Since the first generation catalyst reacted with aryl bromides to afford the tricyclic products in good yields with low catalyst loadings, it was crucial that the second generation catalyst be shown to react with a broader range of functional groups.

Reactions with aryl bromides can be performed under identical reaction conditions as with aryl chlorides (Table 2.3). A variety of aryl bromides bearing oxygen, nitrogen or carbon tethers could be cyclized under the reaction conditions. Electron rich and deficient arenes can be arylated in excellent yields (Entries 2, 3). Deactivated aryl chlorides remain intact providing a handle for further functionalization (Entry 1). Deactivated aryl bromides can be used, but require increased catalyst loadings (Entry 4). If a nitrogen atom is part of the tether and a six membered ring is formed, various protecting groups, such as mesylate, tosylate and benzoate can be used to give the appropriate phenanthridine or *N*-methylated phenanthridinones (Entries 5, 6, 9, 10).

The yields of these reactions are comparable to those obtained with the first generation catalyst. We did not explore thoroughly the possibility of using extremely low catalyst loadings in these reactions.

Table 2.3. Scope of the Intramolecular Direct Arylation of Aryl Bromides.[a]



Entry	Substrate	mol% Pd	Yield[b]	Entry	Substrate	mol% Pd	Yield[b]
1		1	90(97)	8		3	94
2		1	99	9		5	98
3		1	92	10		5	89
4		5	75	11		5	97
5		3	97	12		5	90
6		3	84	13		5	85
7		5	87[c]				

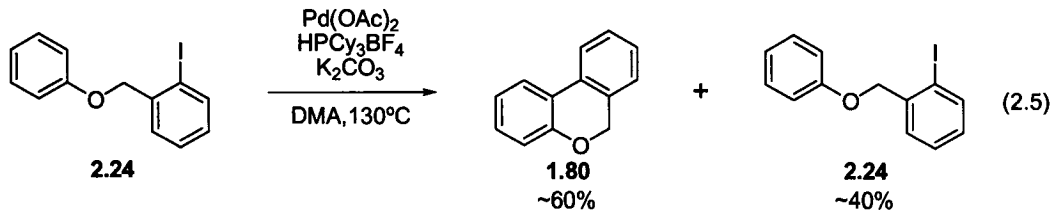
[a]Conditions: Substrate, $Pd(OAc)_2$, Ligand (2 equiv. per Pd) and K_2CO_3 (2 equiv.) are dissolved in DMA (0.2M) and heated to 130°C for 8-16hrs. [b]Isolated Yields. Value in brackets is the yield obtained with the first generation catalyst. [c]Heated to 145°C. Ts=4-$MePhSO_2$-, Ms=CH_3SO_2-, Bz=PhC(O)-

The formation of tri and tetra ortho-substituted biaryls remains an important area of study in cross-coupling methodology.[49] The formation of these very hindered substrates usually requires high catalyst loadings when compared to their less hindered counterparts. We were pleased to see that both tri and tetra ortho-substituted biaryls can be formed in high yields (Entries 9 - 13). The hindered biaryls were prepared by Annie Jean[50].

2.3 – Aryl Iodides

2.3.1 – Low Conversion and Reaction Kinetics

Aryl iodides had posed a problem during the development of the first generation catalyst and when ether **2.24** was treated under optimal conditions, GC-MS analysis showed that only a disappointing 60% conversion to **1.80** had been achieved after 20 hours (Equation 2.5).

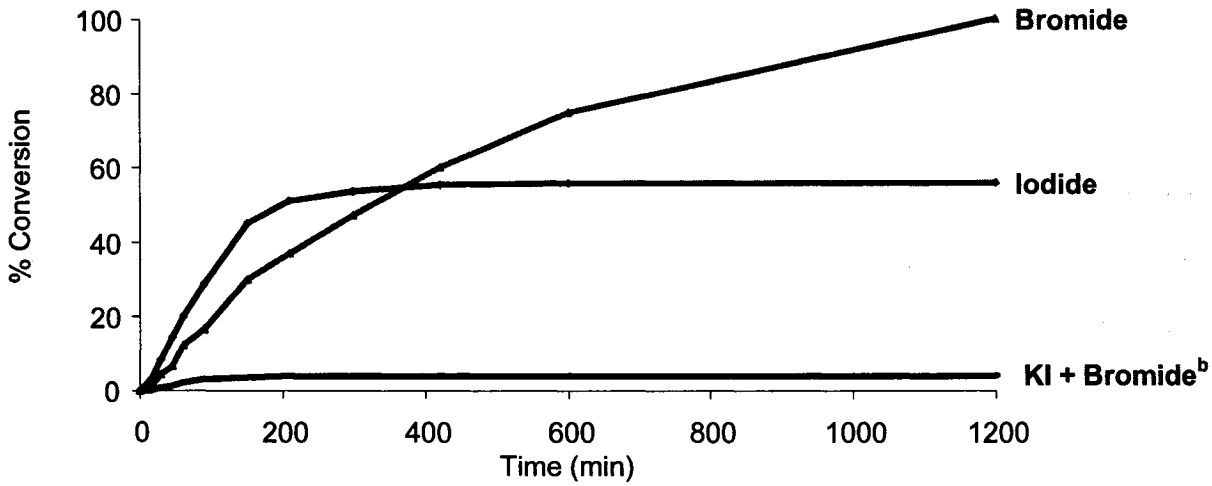


(2.5)

Early attempts to adjust the conditions did not lead to any improvements, so the reaction kinetics of aryl bromides and aryl iodides were compared (Scheme 2.4). Aliquots were taken at regular intervals to establish the rates of each reaction. We were surprised to see that the initial rate of reaction of the aryl iodide and bromide are comparable. It is not until the reaction has reached nearly 50% conversion that a drastic decrease in the rate of the reaction of the aryl iodide occurs. Accumulation of iodide ions in the reaction mixture might therefore be the problem. Addition of one equivalent of potassium iodide to a reaction containing a bromide substrate confirmed this hypothesis. Less than 10% conversion was observed after 24 hours of reaction time. Similar results have been observed by Miura *et al.*[20] They proposed that the high solubility of potassium iodide is the cause of the problem.

This was verified when switching from potassium carbonate to cesium carbonate solved the problem. Changing from potassium carbonate to cesium carbonate is not an acceptable option in this case, as, increased amounts of dehalogenated product are obtained in the presence of cesium carbonate.

Scheme 2.4. Effect of Iodide Ions on the Reaction Kinetics.[a]

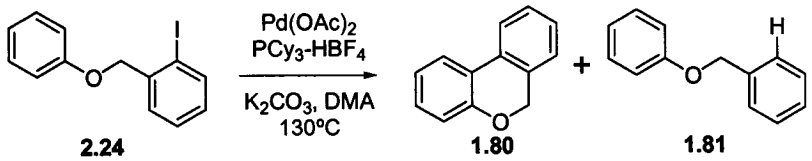


[a]Conditions: Substrate **2.24**, $Pd(OAc)_2$ (1 mol%), Ligand (2 mol%) and K_2CO_3 (2 equiv.) are dissolved in DMA (0.2 M) and heated to 130°C. [b]KI (1 equiv.) is added. [c]Determined by GC-MS.

2.3.2 – Silver Salts, the Solution to Low Reactivity Concerns

Silver salts are very effective at removing halides from solution, it was consequently suggested that the active catalyst would be regenerated if silver salts were added to the reaction mixture. This was tested with a range of silver salts to establish the ideal source.

Table 2.4. Silver Salt Screen.[a]

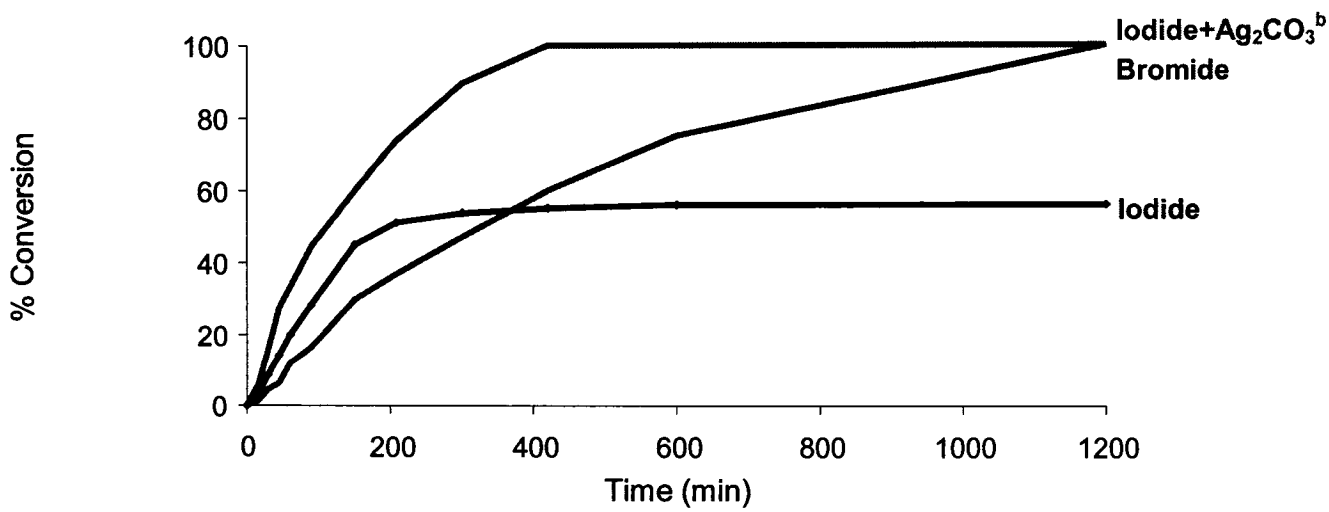


Entry	Silver Additive	Conversion (%)[b]	Ratio 1.80:1.81[b]
1	Ag_2CO_3	100	>99:1
2	$AgNO_3$	91	30:1
3	AgF	95	>99:1
4	AgOTf	87	43:1
5	$AgClO_4$	84	38:1

[a]Conditions: Substrate, $Pd(OAc)_2$, Ligand (2 equiv. per Pd) and K_2CO_3 (2 equiv.) are dissolved in DMA (0.2M) and heated to 130°C. [b]Determined by GC-MS.

The majority of sources give good results with conversions ranging between 84% and 100% and ratios of cyclized to dehalogenated product between 30:1 and >99:1 (Table 2.4). Silver carbonate proved to be the ideal source because of its low cost and less hygroscopic nature compared to the majority of silver salts.[51]

Scheme 2.5. Effect of Addition of Silver on the Reaction Kinetics.[ac]

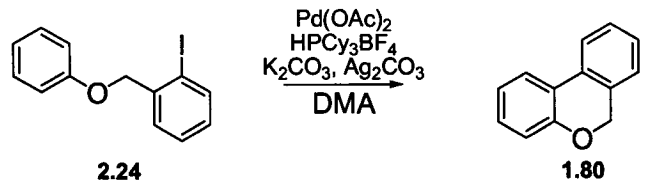


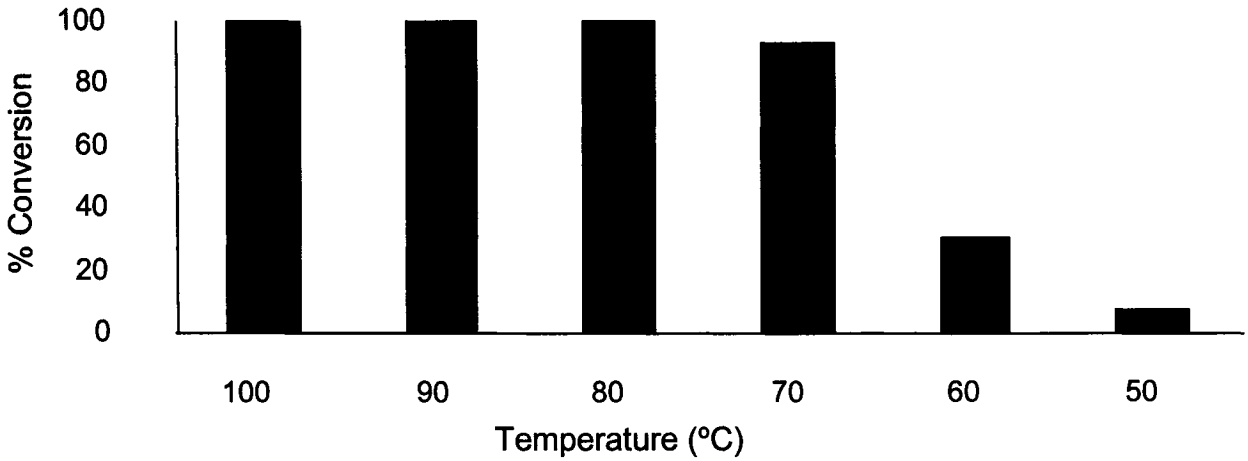
[a]Conditions: Substrate, $Pd(OAc)_2$, Ligand (2 equiv. per Pd) and K_2CO_3 (2 equiv.) are dissolved in DMA (0.2M) and heated to 130°C. [b]Ag_2CO_3 (0.5 equiv.) added. [c]Determined by GC-MS.

These observations should warn against the presumption that aryl iodides will always give better reactivity than their bromide or chloride counterpart. It might therefore be better to screen aryl bromides if low reactivity is observed with iodides. The remainder of the reaction conditions remained the same as for aryl chlorides and bromides. The addition of silver leads to the formation of an even more active catalyst (Scheme 2.5). Removal of the halide from the reaction mixture likely causes the formation of a cationic catalyst with an open coordination site on palladium. The catalyst, consequently binds more willingly with other groups in its surroundings, accelerating the rate of the arylation process. This rate increase is observed regardless of the aryl halide used.

Taking advantage of the increased reactivity, we explored the possibility of varying the temperature at which the reaction is performed (Scheme 2.6). Using 5 mol% catalyst, the lower limits of the catalyst were established. It was found that at temperatures as low as 80 °C, the reaction goes to completion. It is only when the temperature is brought down to 70 °C that starting material remains after catalyst deactivation has occurred.

Scheme 2.6. Lowering the Reaction Temperature.[ab]





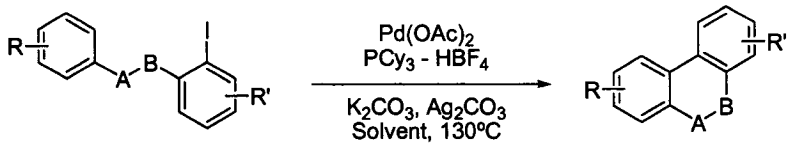
Lowering the reaction temperature opens the possibility of using lower boiling polar solvents (Figure 2.1). Under optimal conditions, it is now possible to obtain complete conversion of aryl iodide **2.24** to the desired product (**1.80**) in refluxing dioxanes. Furthermore, it is also possible to obtain good conversions to **1.80** (86%) in refluxing THF when 3 equivalents of HMPA are added to the reaction.

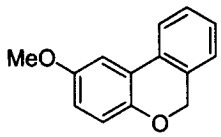
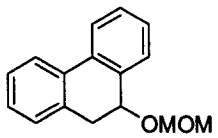
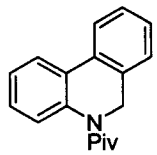
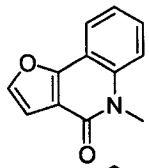
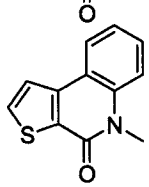
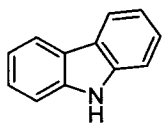
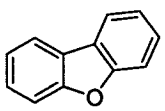
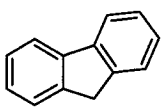
Figure 2.1. Direct arylation in Dioxane and THF.

2.3.3 – Scope with Aryl Iodides

The conditions described above were applied to a selection of substrates (Table 2.5). Electron rich aromatics can be cyclized in high yields both in THF and dioxane (Entries 1, 2). If a hydroxyl group is present on the tether, it can be protected as a methoxymethyl ether without interfering with the catalyst (Entry 2). The pivaloyl group can be used to protect nitrogen linkers in excellent yields in DMA and good yields when the reaction is conducted in dioxanes (Entries 4, 5). Thiophenes and furans can also be used as substrates in good yields (Entries 6, 7). Finally, carbazoles, benzopyranes, as well as fullerenes can be prepared using this methodology (Entries 8-10).

Table 2.5. Scope of the Direct Arylation Reaction of Aryl Iodides.[a]



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

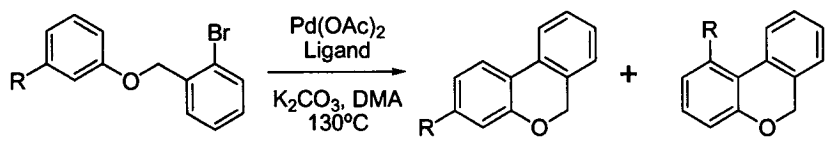
[a]Conditions: Substrate, $Pd(OAc)_2$, Ligand (2 equiv. per Pd), Ag_2CO_3 (0.5 equiv.) and K_2CO_3 (2 equiv.) are dissolved in solvent (0.2M) and heated (DMA - 130°C;Dioxane – 100°C;THF – 70°C) for 8-16hrs. [b]Isolated Yields. [c]3 equivalents HMPA added. MOM= $MeOCH_2$- Piv=^{t}BuC(O)-

2.4 – Catalyst Selectivity

2.4.1 – Establishing the Selectivity for Various Functionalities

Many factors can influence the regioselectivity of this reaction. Electronic factors can play an important role on the distribution of the observed products. For example, strongly electron withdrawing groups such as nitro and ester may undergo cyclization in a Heck type fashion leading to the formation of the ortho-substituted product rather than the para-substituted product. The para substituted product on the other hand should be favored when large substituents such as iso-propyl, *tert*-butyl and trifluoromethyl groups are present on the arene. In these cases, the steric bulk created by substituents with large A values should dominate and the palladium should functionalize the position opposite these large groups.

Table 2.6. Effect of Substituents on the Regiochemistry of the Reaction.[a]



A **B**

Entry	Substituent	Ligand	Ratio A:B[b]
1	OMe	PCy_3 - HBF_4	10:1
2	Me	PCy_3 - HBF_4	15:1
3	iPr	PCy_3 - HBF_4	>30:1
4	tBu	PCy_3 - HBF_4	>30:1
5	CF_3	PCy_3 - HBF_4	>30:1
6	NO_2	PCy_3 - HBF_4	>30:1
7	CO_2Me	PCy_3 - HBF_4	>30:1
8	Cl	PCy_3 - HBF_4	3.2:1
9	F	PCy_3 - HBF_4	1:4.3

[a]Conditions: Aryl halide, $Pd(OAc)_2$ (2 mol%), Ligand (4 mol%) and K_2CO_3 (2 equiv.) are dissolved in DMA (0.2 M) and heated to130°C for 8-16hrs. [b]Ratio determined by NMR.

Nine aryl bromides bearing different functional groups were tested and the results are separated in three categories (Table 2.6). The sterically demanding groups all give very selective reactions generating product **A** almost exclusively (Entries 3-5). Strongly electron withdrawing groups also lead to the formation of product **A** in >30:1 ratio (Entries 6, 7). This indicates that both sterics and electronics play an important role in the cyclization process. Methyl, methoxy and chloride substituents give modest selectivity with ratios varying from 3.2:1 to 15:1 (Entries 1, 2, 8). The 3-fluoroaryl group is the only one that favors the ortho-product **B** with a 1:4.3 ratio (Entry 9).[52] This work was done in conjunction with Louis-Charles Campeau.

2.5 – Mechanistic Studies

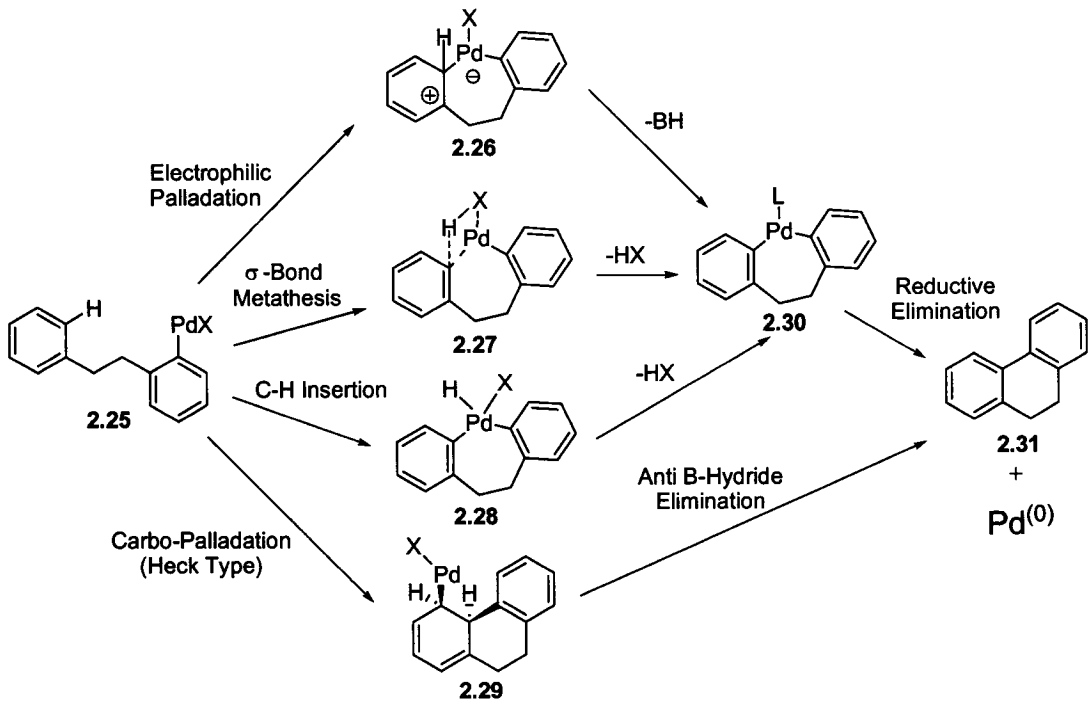
2.5.1 – Possible Mechanistic Pathways

Although the studies related to the mechanism of the reaction conducted by Louis-Charles Campeau were not part of my contributions to this project, it is important that they be discussed to give a complete overview of the development of the intramolecular direct arylation methodology.

The mechanism of the direct arylation of inactivated arenes has not yet been clearly identified. One or more different pathways could be operating in these reactions (Scheme 2.7). After palladium(0) inserts into the aryl halide (**2.25**), it could undergo electrophilic palladation onto the arene.[53, 54] This would produce a Wieland intermediate **2.26** with a positive charge on the aromatic ring. Deprotonation would regenerate aromaticity (**2.30**) and reductive elimination would give the desired product (**2.31**). The second possibility is a more concerted pathway. Sigma bond metathesis between the carbon hydrogen bond and palladium halide bond (**2.27**) would lead to the palladacycle (**2.30**).[55] The third option is a true C-H insertion in which, a palladium(IV) intermediate **2.28** is generated by insertion into the carbon hydrogen bond.[35] The final alternative is a carbo-palladation.[56] This is a Heck

type process in which carbon and palladium add across the same face of the aromatic ring (**2.29**). Formal anti β-hydride elimination would afford the final product.

Scheme 2.7. Possible Mechanistic Pathways.

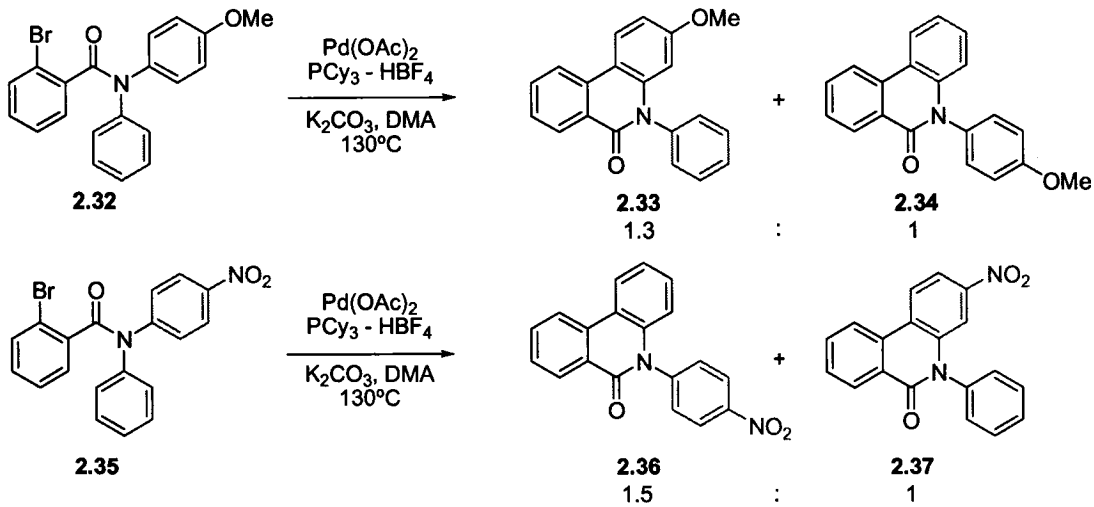


The electrophilic palladation and C-H insertion pathways are the two pathways most commonly proposed in direct arylation processes.

2.5.2 – Experiments Aimed at Establishing the Mechanism of the Reaction

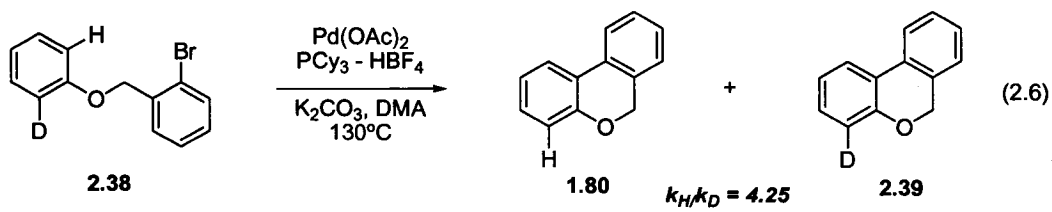
In order to establish which one of the above mentioned mechanisms is taking place under our reaction conditions, competition experiments were designed to ascertain the electronic preferences of the catalyst (Scheme 2.8). If an electrophilic palladation is taking place, it is expected that a strong preference for the most electron rich arene will be observed since the arenium cation will be stabilized by resonance. The modest selectivity observed does not support this mechanism but does not prove that it is not taking place.

Scheme 2.8. Electronic Preferences in Direct Arylation.



Establishing the kinetic isotope effect (KIE) for a reaction can give valuable information about its mechanism. For example, it would not be expected to observe a kinetic isotope effect in an electrophilic palladation pathway since deprotonation of the arenium cation should be very rapid. Conversely, one would expect to see a kinetic isotope effect if the mechanism involves C-H insertion.

During the studies done on the first generation catalyst, we established that the reaction had a first order intramolecular KIE of 3.5.[40] This indicates that there is breaking of the carbon hydrogen bond during the rate limiting step of the arylation process. When we repeated this experiment with the new catalyst, a primary KIE of 4.25 was found (Equation 2.6). This value did not change when silver salts were added to the reaction mixture.



$k_H/k_D = 4.25$

Once again, this result does not support an electrophilic palladation pathway. It could, on the other hand, support either a more concerted pathway or a C-H insertion pathway.

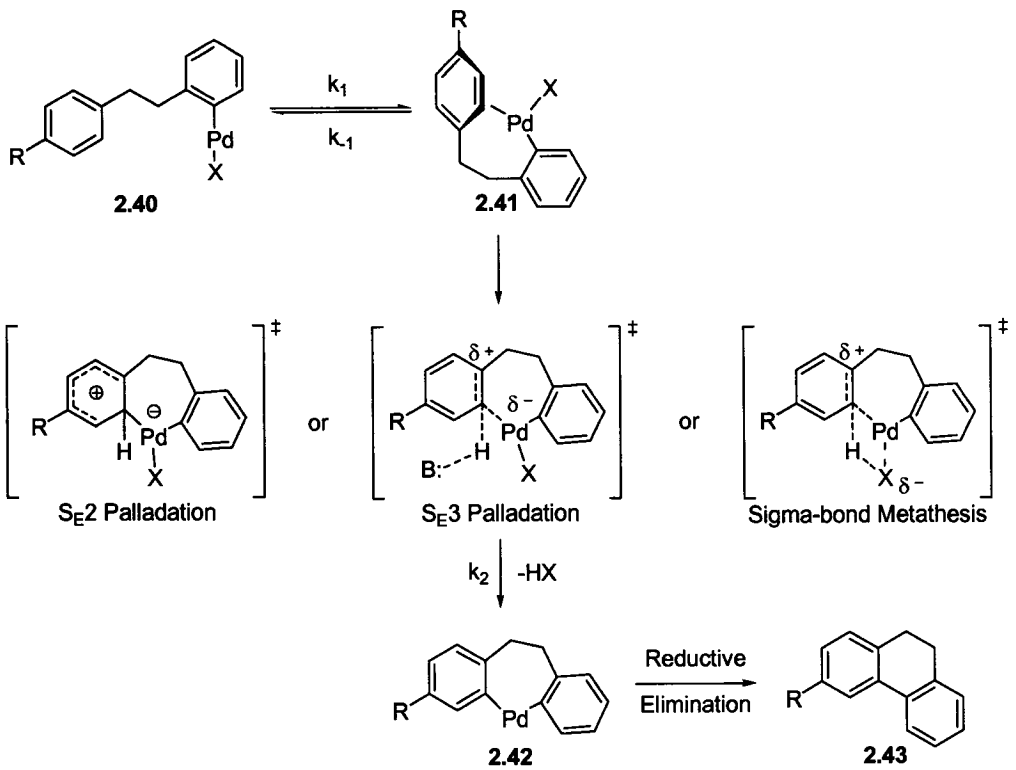
While it cannot be definitively ruled out, the carbopalladation or Heck-type route is unlikely. It is reasonable that the mechanism of these processes should parallel that involved in the preparation of palladacycles. [57] These processes often exhibit large kinetic isotope effects, but deuterium NMR studies have shown that no hydrogen shifts occur during the reaction. The carbo-palladation pathway is, therefore, disfavored even though anti β-hydride eliminations have been observed.

2.5.3 – Favored Pathway

If an electrophilic palladation or S_E2 palladation is taking place, reversible binding of arene **2.40** to the metal center (**2.41**) is expected to be much slower than deprotonation of the Wieland intermediate (k_1 and $k_{-1} >> k_2$) (Scheme 2.9).[58] The rate of deprotonation of the hydrogen or deuterium atom (k_2) should not impact the distribution of the product since the catalyst is already committed by this point and no kinetic isotope effect should be observed. The fact that we do observe a kinetic isotope effect, combined with the facility with which electron deficient arenes undergo cyclization and the low selectivity observed in the electronic preference experiments strongly indicate that the reaction does not undergo an electrophilic palladation.

In contrast, if a more concerted S_E3 palladation or σ-bond metathesis is occurring, it would be expected that reversible binding of arene **2.40** to the metal center would be rapid compared to the removal of the hydrogen or deuterium atom. This reaction would, therefore, be under Curti*N*-Hammett conditions.[59] If such is the case, then the difference in energy between the transition state in which the hydrogen is removed and the one in which the deuterium is removed should control the distribution of products. Since the carbon deuterium bond is stronger than the carbon hydrogen bond, we would expect to see a kinetic isotope effect.

Scheme 2.9. Favored Pathways.



A σ-bond metathesis pathway has been proposed in other palladium based processes such has [1,5] alkyl to aryl shifts and [1,4] aryl to aryl shifts. These mechanisms are preferred to the C-H insertion pathway because it has been shown computationally that these processes are lower in energy than the corresponding C-H insertion going through a palladium (IV) intermediate.[60]

2.6 – Application in Synthesis

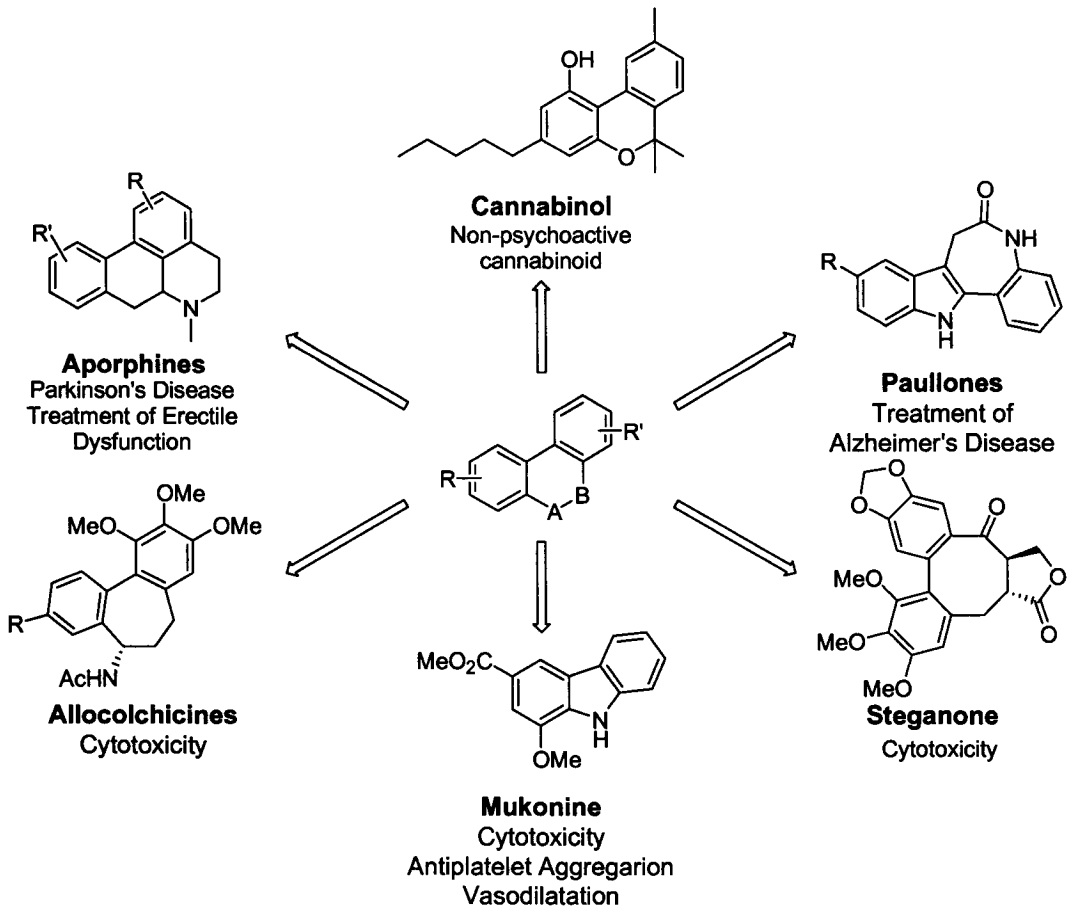
2.6.1 – The Biaryl Core, a Privileged Structural Motif in Medicinal Chemistry

It is estimated that the biaryl core is present in 4.3% of all drugs on the market.[61] The development of new methods of forming biaryls can open the door to shorter and more efficient syntheses of both natural and synthetic products. Up to now, biaryls have normally

been formed by traditional cross-coupling methods.[1] Direct arylation is an efficient alternative to these processes.

When searching the literature, one can find many biologically active targets containing tricyclic biaryls (Scheme 2.10). The scheme below shows just a few examples of available targets, some of which have already been synthesized in our laboratories.

Scheme 2.10. Biaryl Containing Natural Products.



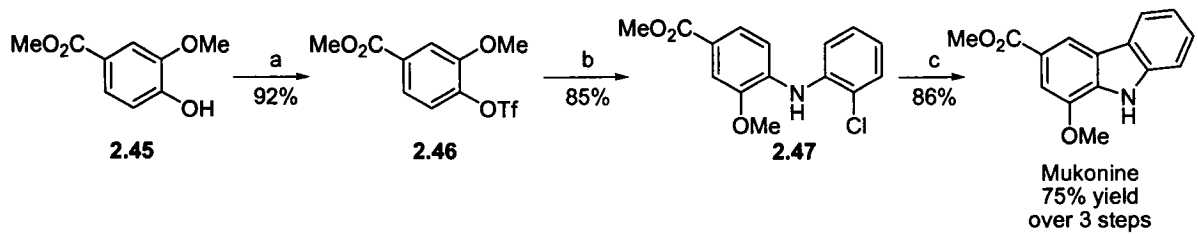
The synthesis of Aporphines and Aporphine analogs was reported by Lafrance, Blaquiere and Fagnou in 2004.[62] In 2005, Leblanc and Fagnou also reported an enantioselective formal synthesis of Allocolchicinoids, a family of natural products identified by the National Cancer Institute (US) as an important lead structure for the development of

new anti-tumor agents.[63, 64] Highly efficient syntheses of Mukonine and of the Paullones were also devised and will be described next.

2.6.2 – Synthesis of Mukonine

Carbazoles have interested the pharmaceutical industry for a long time because of the variety of biological activity related with their structure.[65] The methodology developed in our group is ideally suited for the synthesis of this class of compounds (Scheme 2.11). Starting from methyl vanilate **2.45**, triflation of the phenol leads to **2.46** which can be coupled with 2-chloroaniline in a Buchwald-Hartwig amination reaction.[66] The product **2.47** is ready for the direct arylation step and under typical cyclization conditions the final step occurs in high yield with 3 mol% catalyst to afford mukonine in 75% overall yield over three steps starting from methyl vanilate **2.45**.

Scheme 2.11. Synthesis of Mukonine.



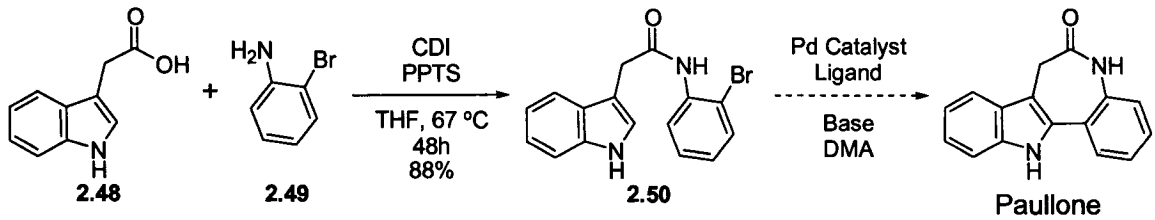
[a]Conditions: a) Tf_2O (1.1 equiv.), DIPEA (2 equiv.), THF -78°C-0°C. b) Pd_2dba_3 (0.025 equiv.), %.), 2-(di-t-butylphosphino)-2'-methylbiphenyl (0.1 equiv.), K_3PO_4 (1.4 equiv.), 2-chloroaniline (1.2 equiv.) DME 80°C. c) $Pd(OAc)_2$ (0.03 equiv.), PCy_3-HBF_4 (0.06 equiv.), K_2CO_3 (2 equiv.), DMA 130°C.

2.6.3 – Synthesis of Paullones

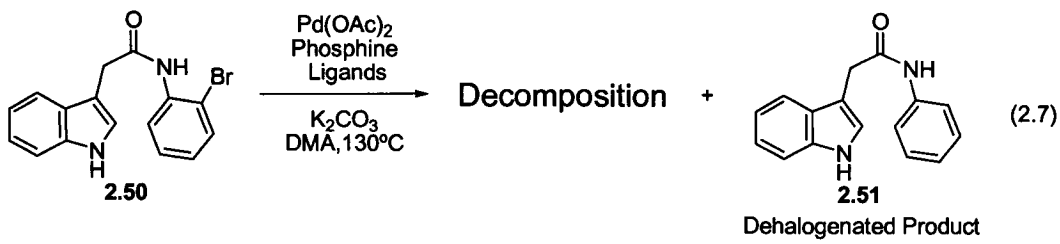
The Paullones are a family of indole based natural products to which a seven membered ring, comprised of an amide, is attached. Developing a synthesis of these compounds that have shown biological activity against Alzheimer's disease[67], represented a nice challenge, as seven membered rings have been scarcely explored in direct arylation

reactions.[68] Using the methodology we have developed, the simplest member of the Paullone family could be synthesized in two steps from commercially available indole-3-acetic acid **2.48** and 2-bromoaniline **2.49** (Scheme 2.12). Using the coupling agent carbonyl diiimidazole (CDI) and pyridinium para-toluene sulfonate (PPTS) as a source of acid, the two partners could be coupled in 88% yield to form **2.50**. We were hopeful that cyclization would occur without protecting the (NH) groups present on the molecule.

Scheme 2.12. Preparation of the Paullones Class of Natural Products



Efforts to cyclize the precursor **2.50** using the conditions described in our initial report ($Pd(OAc)_2$, 2-(diphenylphosphino)-2'-*N,N*-dimethylaminobiphenyl, K_2CO_3 in DMA at 130 °C) led to decomposition (Equation 2.7).[40] Trace amounts of dehalogenated product **2.51** were isolated, but no product was formed. Other aromatic phosphines also led to decomposition.

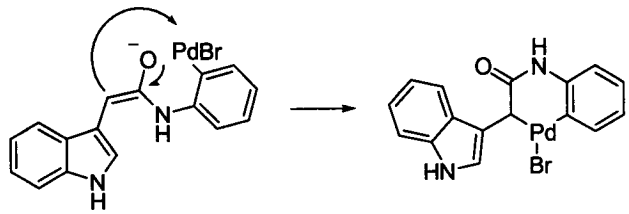


(2.7)

At this point, other members of the group were obtaining definite success in direct arylation of aryl chlorides using *N*-heterocyclic carbenes (NHC), so the hydrochloride salt of 1,3-bis(2,6-diisopropylbenzene) imidazole (IPr-HCl) was tested under the reaction conditions.[46] The reaction was considerably cleaner, but once again only reduced product could be isolated. The formation of enolate **2.52** in the tether which could form a six

membered ring palladacycle (**2.53**) might lead to the formation of bi-products (Scheme 2.13).

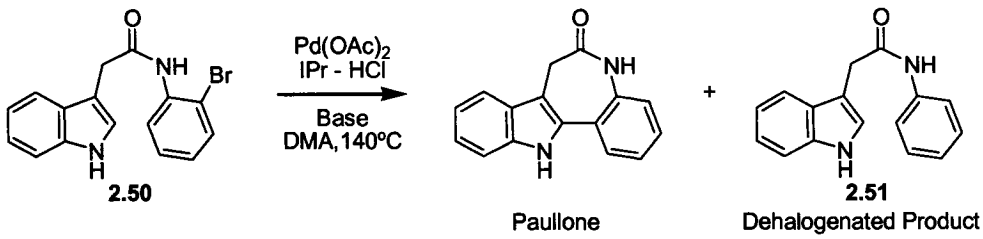
Scheme 2.13. Possible Side Reaction in the Cyclization of Paullones.

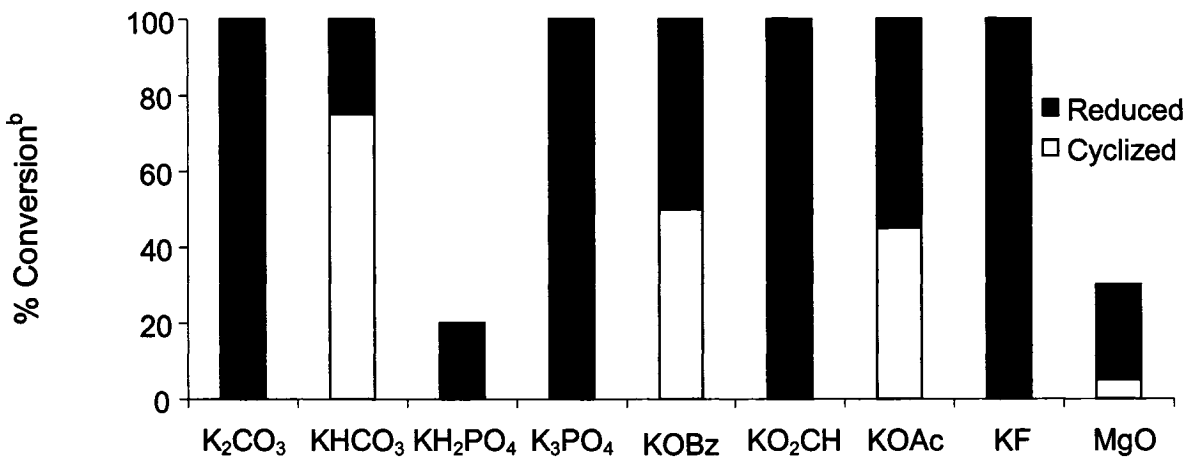


2.52 **2.53**

A base screen was conducted using three equivalents of IPr-HCl per palladium and we quickly realized that the pKa of the base used had an enormous impact on the distribution of products formed (Scheme 2.14). Stronger bases like potassium carbonate, potassium phosphate and potassium fluoride gave only dehalogenated product **2.51**. Conversely, weaker bases such as potassium bicarbonate, potassium acetate and potassium benzoate led to the formation of various mixtures of cyclized and dehalogenated products. Potassium bicarbonate proved to be the optimal base for the reaction as it gave a 3.5:1 mixture favoring the desired product.

Scheme 2.14. Base Screen for the Cyclization of Paullone.[a]





[a]Conditions: Substrate, $Pd(OAc)_2$ (10 mol%), Ligand (3 equiv. per Pd) and Base (2 equiv.) are dissolved in solvent (0.2 M) and heated for 8-16hrs. [b]Determined by GC-MS.

The ligand to metal ratio and reaction temperature were varied in attempts to increase the amount of cyclized product formed, but this did not lead to improved results. Isolation of the product was also problematic. When the reaction is conducted under ideal conditions, a maximum of 40% of the desired product is isolated. Further optimization might allow us to increase the ratio and isolated yield of the reaction. Another option available is the protection of the nitrogen atoms, but this doubles the number of steps to the synthesis.

2.7 – Conclusion

In conclusion, we have developed a new catalyst system for the intramolecular direct arylation of aryl chlorides, bromides and iodides. Under optimal conditions, the presence of a wide range of functional groups is very well tolerated. Oxygen, nitrogen and carbon atoms can be part of the tether without hindering the reaction.

It was established that the accumulation of iodide ions in the reaction mixture led to catalyst poisoning after approximately 50% conversion. Silver salts, more particularly silver carbonate, proved to be an excellent solution to the reactivity problems we had encountered, forming an even more active catalyst. The use of this catalyst has allowed us to lower the reaction temperature to 80 °C, if 5 mol% catalyst is used. It has also opened the door to lower boiling solvents such as dioxanes and even THF if three equivalents of HMPA are added to the reaction.

We have established the regioselectivities associated with a wide range of functional groups. We have also demonstrated that both steric and electronic factors influence the distribution of products.

The mechanistic studies conducted have shown that the reaction likely proceeds through a σ-bond metathesis or S_E3 palladation. Deuterium NMR studies have demonstrated that there is no deuterium migration during the course of the reaction disfavoring the carbo-palladation pathway, even though anti β-hydride elimination has been reported.

A very efficient three step synthesis of Mukonine, a natural product with cytotoxic activity, with an overall yield of 75% was described. A two step synthesis of the Paullone

class of natural product was also reported. *N*-heterocyclic carbene ligands proved to be the most efficient in the synthesis of this natural product with activity against Alzheimer's disease.

3 – Heterogeneous Catalysis

3.1 – Introduction

3.1.1 – Advantages and Disadvantages of Heterogeneous Catalysts

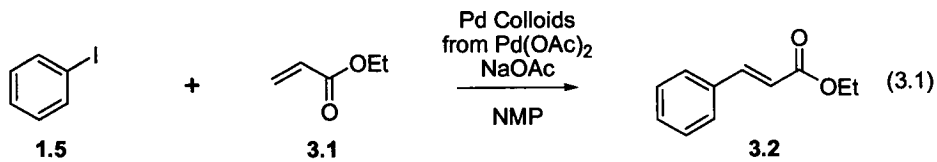
Heterogeneous catalysts hold a crucial role in industrial processes such as hydrogenation, skeletal isomerization and hydroformylation reactions, but, they are now making their way into other organic reactions in which homogeneous catalysts are generally used. Whether they are bound to a carbon matrix or attached to beads, these catalysts offer many advantages.

Since they are insoluble, heterogeneous catalysts can be easily removed from a reaction mixture by simple filtration. The majority of systems do not require the use of ligands which can be challenging to remove. Minimizing the amount of transition metals left in a product for animal or human consumption is a matter that many industries have to deal with on regular basis. Heterogeneous catalyst can help in this matter, since they usually diminish the amount of transition metal contaminants in the product after isolation.[69]

Unfortunately, heterogeneous catalysts also have their drawbacks. The nature of the active species is often difficult to ascertain.[70] Leaching of metal from the matrix can occur and these soluble species are sometimes catalytically active.[71] This can become problematic if the leaching is permanent, but release and capture mechanisms of action are often in play, which reduce transition metal contamination of the products.[71c, 72] Finally, heterogeneous catalysts are often found to be less active than their homogeneous counterpart, requiring increased loadings.

3.1.2 – The Different Types of Heterogeneous Catalysts

As opposed to homogeneous catalysis, where the active species is always soluble, heterogeneous catalysis incorporates a multitude of different types of catalysts. The metal itself can act as an insoluble catalyst or it can be bound to many different forms of matrixes.



1.5 + 3.1 → 3.2 (3.1)

Metal colloids, nanoparticles, blacks or powders can be used in various processes ranging from hydrogenation reactions to cross-coupling reactions (Equation 3.1). They are insoluble metal particles not bound to any type of matrix and can be formed by reduction of metal salts with reducing agents, such as phosphorus, carbon monoxide, or hydride sources.[73] The conditions under which the reduction takes place establishes the type of atomic metal generated. Skeletal metals are also part of this family. They are formed by the leaching of one metal out of an alloy of two or more metals. Raney nickel for example is generated from a 1:1 alloy of nickel and aluminum.[74] When the alloy is placed in a solution of sodium hydroxide, the aluminum is etched away leaving a network of pores for the substrate to fill before undergoing the desired reaction. Metal particles can also be deposited on a matrix, such as activated carbon to generate active catalysts.

Another method of generating heterogeneous catalysts involves the immobilization of a homogeneous species to an insoluble material. Polystyrene beeds are commonly used as supports because they are easy to functionalize and they can swell considerably when

placed in an appropriate solvents to allow the substrate to get inside the pores and react with the catalyst.

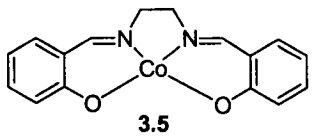
3.3 **3.4** (3.2)

A phosphine attached to a polymer **3.3** can act as a ligand to anchor palladium or rhodium catalysts for example (**3.4**) (Equation 3.2). Soluble iron, manganese and copper species can also be attached to pyridine or imidazole groups on solid supports.[75] The systems generated this way have good activity and can be removed very easily. One problem that arises from polymer supported metals is aggregation of metal atoms because they are not covalently bound to the ligands. The catalyst therefore becomes less active as the reaction progresses or after multiple uses.

One way of preventing this problem, is to use inorganic solids that bind covalently with the metal. In the ideal situation, the metal adopts the same geometry when it is bound to the inorganic solid as when it is homogeneous, but, this is very rarely the case.[76] Most often, the coordination geometry changes because the bond to the support is too strong. On the other hand, if the bond is too weak leaching of the metal into solution can occur. Although silica is the most commonly used support, any other inorganic oxides can be used.[77] Zeolites and clays can also be used and offer nice advantages since they have well-defined structures and pores. One of the reasons why solid supported complexes can sometimes perform reactions that homogeneous catalysts can not is that the concentration of the substrates within the pores of the solid structure is increased considerably compared to a reaction done in solution. This is particularly important in hydrogenation reactions, where inactive homogeneous complexes have been shown to become active when bound to zeolites.[78]

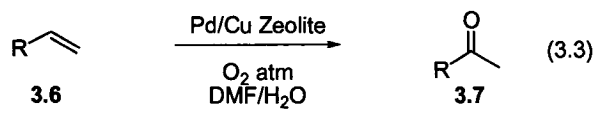
Another good method of supporting homogeneous catalysts is encapsulating macrocyclic metal complexes in zeolites. The main advantage of this method is that the

metal complex is now trapped in the zeolite cage without being covalently bound to it. This is often referred to as the "Ship in a bottle" method.[79] Systems of this type can be prepared by letting the ligand diffuse through the zeolite in which the metal is already present, once the ligand binds to the metal, the complex becomes too big to come out of the pore where it is situated.[80] It is also possible to crystallize the zeolite around the metal complex, building the bottle around the ship.[80] This method has been used to encapsulate metal-Salen complexes (**3.5**) that act as oxygen transporters for the oxidation of various groups.



3.5
Cobalt Salen complex

Inorganic ion exchanger supports offer an attractive way of forming heterogeneous metal salts. Zirconium phosphate and zirconium molybdate materials are commonly used ion exchange resins. Rhodium(III) complexes have been incorporated in these supports to generate stable catalysts for the oxidation of CO and the conversion of anilines to carbamates.[81] Palladium(II)/copper(II) zeolite has been shown to be active for the Wacker oxidation (Equation 3.3).[82]



3.6 **3.7** (3.3)

Finally, zeolite encapsulated catalyst have been embedded into hydrophobic polymers to generate membranes that catalyze the oxidation of alkanes.[83] The membranes were mounted as an interface between the apolar alkanes and the polar oxidants (peroxides) in a reactor and the reaction did not require the addition of other reaction solvents.

3.1.3 – Identifying the Active Catalyst

In transition metal catalysis, the metal complex that is added to the reaction is usually not the active species. The true catalyst is frequently formed *in situ* under the reaction conditions. More and more groups have started reporting that the homogeneous catalyst that they were using, generates an active heterogeneous species under the reaction conditions. Heterogeneous catalysts can also form soluble palladium species that can be considered homogeneous catalysts. These issues have been known for more than 30 years and many different tests have been designed to establish the true nature of a catalyst.[84]

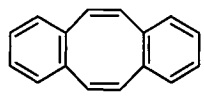
Since catalytic processes are usually kinetic in nature, a good method of determining the character of a catalyst is to look at the kinetics of the reaction. It is generally accepted that sigmoidal and irreproducible kinetic curves indicate that a heterogeneous species is responsible for the catalysis.[85] This is due to the fact that the active catalyst needs to be generated or modified before the reaction begins. This is particularly well established in hydrogenation reactions but can be applied to many other complex processes.[86] No*N*-sigmoidal and/or reproducible kinetic curves however do not mean that the active catalyst is homogeneous. Sigmoidal kinetic curves would not be expected if the catalyst is completely formed before the reaction is at an advanced stage or if the catalyst is premixed with its activator before the substrate is added. It has been shown that certain heterogeneous catalysts have ±15% kinetic reproducibility.[86]

Transmission electron microscopy can be used to detect the presence of metal colloids or nanoclusters as small as 1nm.[86] This technique can establish the presence of metal colloids at concentrations as low as 10^{-12} M. The problem is that it can not tell whether the colloids or nanoparticles are active or not, therefore, this technique is not sufficient on its own to establish the nature of the catalyst.

Poisoning experiments offer a different approach to this problem. Selective poisons have been identified for both heterogeneous and homogeneous species. Mercury(0) is

known for its ability to deactivate heterogeneous catalysts by amalgamating the metal or adsorbing on the metal surface.[87] Suppression of catalytic activity is evidence for heterogeneous catalysis. Mercury can cause the apparition of various side reactions though, so once again, this test on its own does not constitute proof of heterogeneous catalysis. In order to ensure a close contact between the poison and the catalyst, a large excess of mercury (100 to 500 equivalents) is required and the mixture must be stirred vigorously.

Crabtree *et al.* discovered in the early eighties that dibenzo[*a,e*]cyclooctatetraene (DCT) **3.8** binds very strongly to many homogeneous catalysts, deactivating them in the process.[88] In opposition, DCT has no effect on the majority of heterogeneous catalysts such as palladium or rhodium colloids or palladium on carbon.[88] This test can be run in conjunction with the mercury poisoning test to establish the validity of the results. Sadly, this experiment still poses certain problems as DCT does not bind to all homogeneous catalysts. DCT also binds slowly to metal complexes, requiring a few hours to completely inhibit the catalyst.



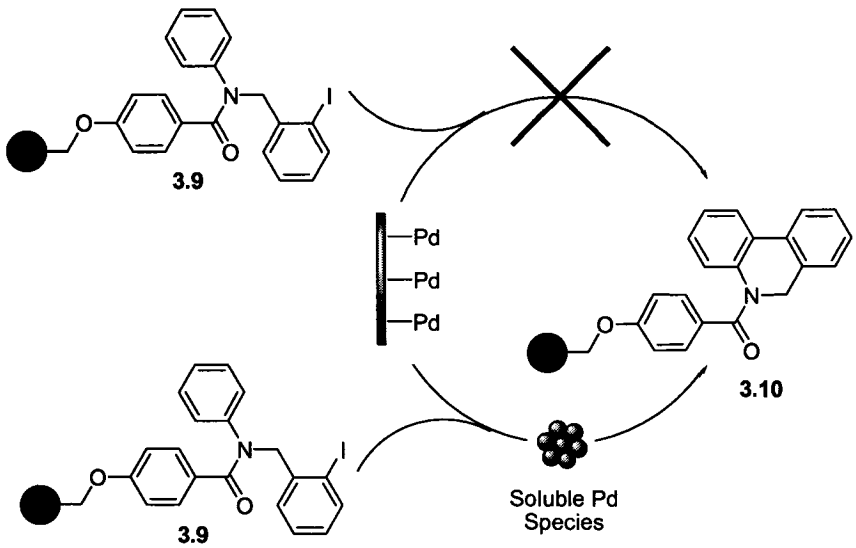
3.8
Dibenzo[*a,e*]cyclooctatetraene

A filtration test can also reveal a lot of information on the nature of the catalysts in a reaction. To conduct this test, cellulose, Celite or powdered graphite is added to a reaction where the catalyst is still active.[88, 89] The mixture is filtered through a glass frit and the solids are washed with solvent. After rinsing the flask to remove any remaining metal particles, the solids are placed back into the flask and new substrate and solvent are added. If the reaction keeps going the catalyst is heterogeneous since it remained on the filter aid but if no reaction occurs, then the active catalyst is probably homogeneous. The same thing should be done with the filtrate to see if any catalytic activity arises from soluble species.

This can be particularly important if both homogeneous and heterogeneous species are acting simultaneously.

Finally, a three phase test using a polymer bound substrate can help distinguish between soluble and insoluble active species (Scheme 3.1).[90] Interaction between a solid supported substrate **3.9** and a solid supported catalyst is nearly impossible. Therefore, if catalytic activity is observed and product **3.10** is generated, it must be caused by soluble metal species that have the ability to get into the pores of the polymer, but, if the starting material remains untouched, the active catalyst is most likely heterogeneous. A problem observed with this test, is that the substrate can fall off of the polymer and react with the insoluble catalyst, dragging it into solution. This catalyst can then react with the resin bound substrate misrepresenting the results of the test.

Scheme 3.1. The Three Phase Test Concept.

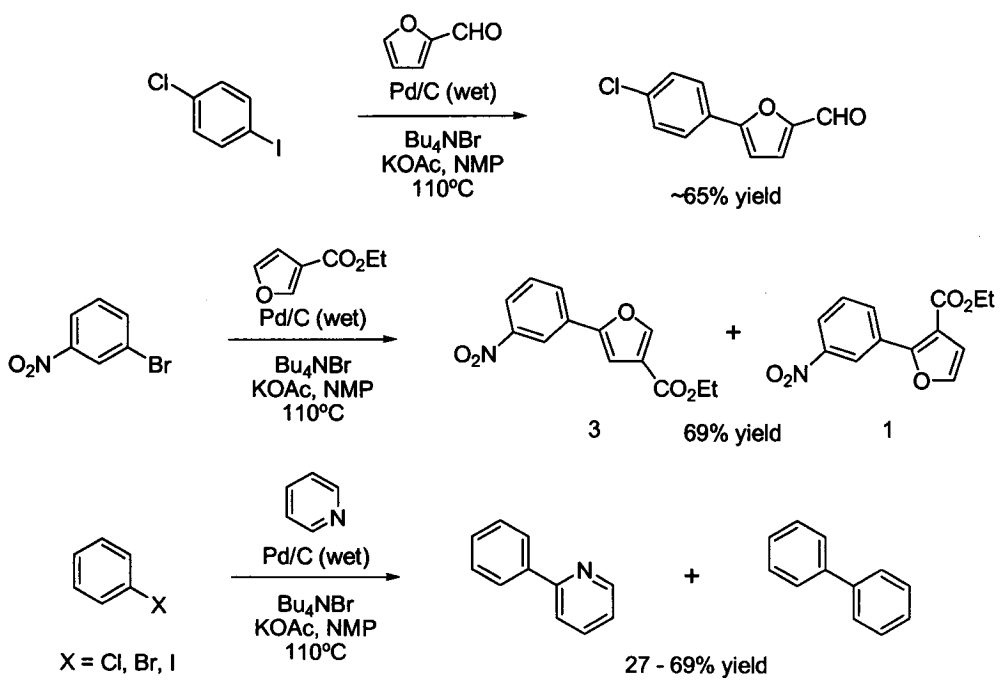


3.1.4 – Heterogeneous Catalysis in Cross-Coupling Reactions and Direct Arylation Reactions

Heterogeneous catalysts started appearing in cross-coupling methodologies over thirty years ago. In his initial report (1972), Heck reported that palladium on carbon catalyzed the reaction, but it was not until the 1990s that heterogeneous catalysts became more popular for the Heck reaction.[91, 92] Many groups have reported catalyst systems employing palladium on carbon or even palladium colloids generated from the thermolysis of palladium acetate or palladium chloride in the presence of sodium acetate for various Heck reactions.[93] Palladium colloids, as well as, palladium perovskites have also been shown to catalyze the Suzuki-Miyaura reaction demonstrating that heterogeneous catalysis can be used in a variety of cross-coupling reactions.[94]

More recently, heterogeneous catalysts have made their way into the field of direct arylation (Scheme 3.2). For example, palladium on carbon has been used in the direct arylation of 2-furaldehydes and 3-carboalkoxy furans.[15, 95] Palladium on carbon has also been used for the coupling of aryl halides with pyridines.[96]

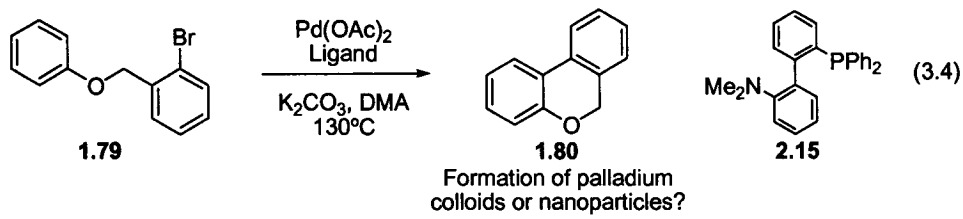
Scheme 3.2. Heterogeneous Catalysts in Direct Arylation Reactions.



3.2 – Development of a Heterogeneous Catalyst for Direct Arylation

3.2.1 – Catalyst Screen

The formation of heterogenous palladium black sometimes occurred during the early stages of the development of the first generation catalyst.[40] It was observed that these reactions were as successful as the ones that remained homogeneous (Equation 3.4). We consequently became interested in probing whether soluble palladium species generated in the reaction media could catalyze the formation of the desired product.

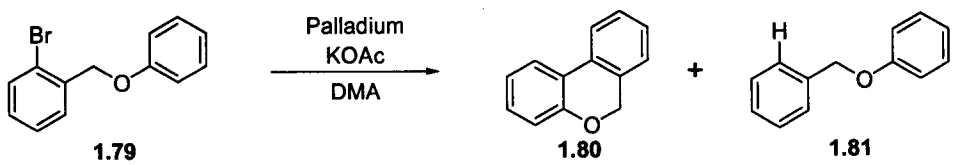


1.79 **1.80** **2.15** (3.4)

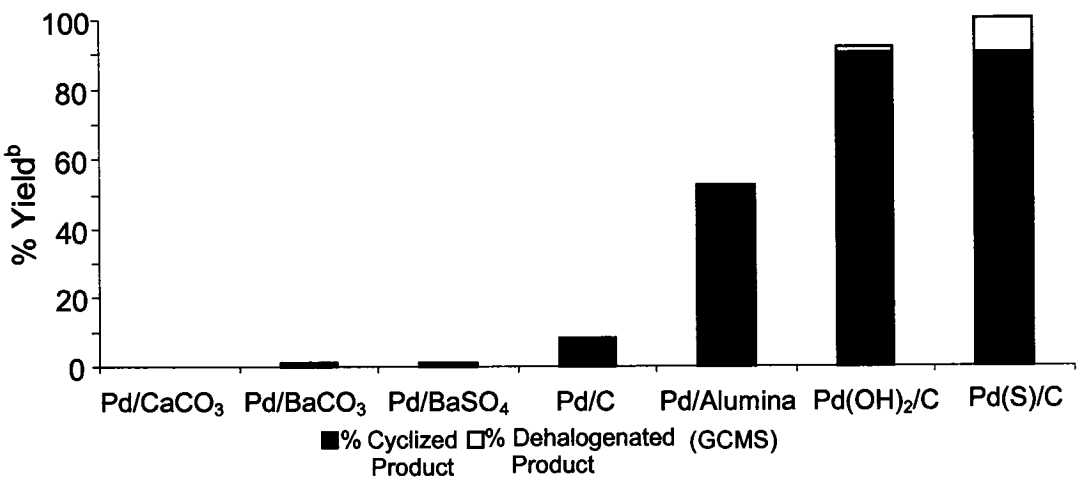
Formation of palladium colloids or nanoparticles?

In view of the fact that heterogeneous catalysts can generate catalytically active soluble species via leaching, they might represent a good source of active colloids for the current transformation. Various solid supported palladium catalysts were screened for the direct arylation of **1.79** (Scheme 3.3). Palladium on calcium carbonate, palladium on barium carbonate and palladium on barium sulfate all lead to the formation of trace amounts of the desired product. Palladium on carbon, also gives less than 10% conversion. A considerable increase in yield is observed when employing palladium on alumina, but palladium hydroxide on carbon and palladium sulfided on carbon proved to be more active, giving the product in >90% yield. Since palladium sulfided on carbon causes increased dehalogenation, palladium hydroxide on carbon, Pearlman's catalyst, was chosen for further optimization.

Scheme 3.3. Evaluation of Various Solid-Supported Palladium Catalysts.[a]



1.79 1.80 1.81



[a]Conditions: Substrate, Palladium (10 mol%) and KOAc (2 equiv.) are added in solvent (0.2M) and heated for 8-16hrs. [b]Determined by GC-MS.

3.2.2 – Optimization of the Reaction Parameters

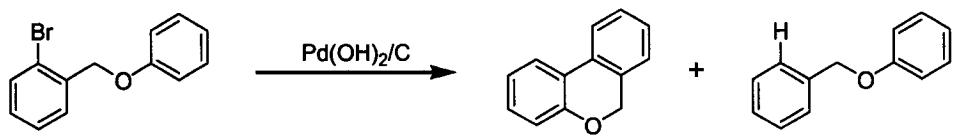
Subsequent to a screen of both organic and inorganic bases, it was noticed that the majority of bases (CsOAc, NaOAc, Cs_2CO_3, K_3PO_4, DIPEA and DBU) lead to irreproducible results. Contrarily, potassium acetate does not suffer from this problem and was thus selected as the optimal base. Potassium acetate also brings an increase in yield when

compared to potassium carbonate, which is the preferred base in the homogeneous catalysis. Organic bases lead to dehalogenation as the main product.

Changing the solvent from DMA to DMF increases the amount of dehalogenated product formed. Other solvents, such as dioxane, acetonitrile and toluene, were also tested, but did not allow the transformation to occur. This is most likely due to the elevated reaction temperature required in order to achieve good conversion (Scheme 3.4).

The optimal conditions require the use of DMA, two equivalents of potassium acetate and 10 mol% catalyst, since lower catalyst loadings lead to irreproducible results. In order to ensure that the reaction goes to completion, the reaction temperature is brought up to 145°C.

Scheme 3.4. Optimization.



1.79 **1.80** **1.81**

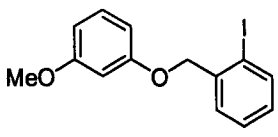
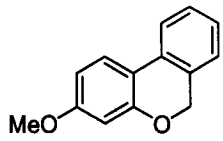
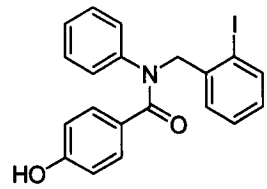
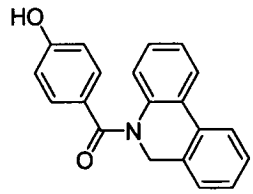
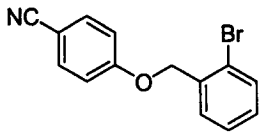
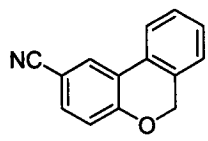
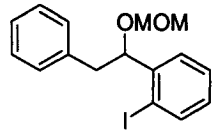
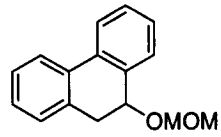
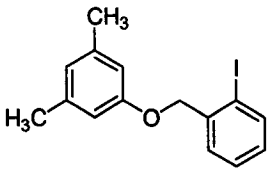
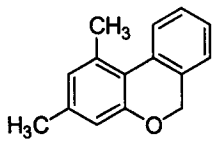
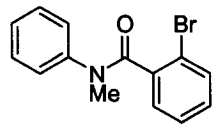
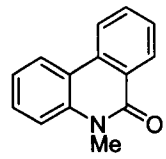
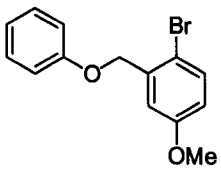
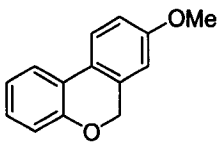
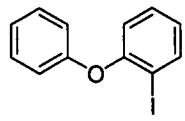
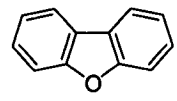
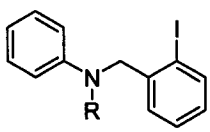
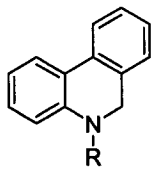
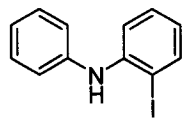
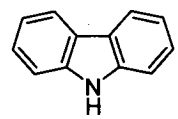
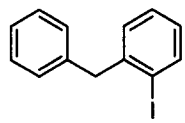
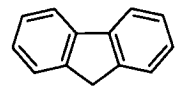
Solvent	Base	T°	% Yield GC (Ratio 1.80/1.81)
DMA	KOAc	130°C	92% (45/1)
DMF	KOAc	130°C	98% (19/1)
DMA	K_2CO_3	130°C	62% (30/1)
DMA	KOAc	145°C	99% (45/1)

3.3 – Scope of Intramolecular Direct Arylation Reaction

Palladium hydroxide on carbon catalyzes the intramolecular direct arylation of aryl iodides and bromides (Table 3.1). Electron rich and deficient arenes can be cyclized in high yields (Entries 1, 2). Trisubstituted aryl ethers can be generated efficiently (Entry 3), but when deactivated aryl bromides are used, the reaction is sluggish giving the desired product

in 69% yield, while forming 20% of the dehalogenated product (Entry 4). Benzoate and pivalate can be used to protect the nitrogen atom when dihydro-phenanthredines are formed (Entries 5, 6). The amide group can also be part of the ring system if the nitrogen is methylated (Entry 9). An unprotected phenol away from the reaction site does not poison the catalyst (Entry 7). Alternatively, if the alcohol is on the tether, it can be protected as its methoxymethyl ether without hindering the reaction (Entry 8). Finally, five membered rings with oxygen, nitrogen or carbon tethers are compatible with this methodology (Entries 10-12).

Table 3.1. Scope of the Intramolecular Direct Arylation Reaction.

Entry	Substrate	Product	Yield	Entry	Substrate	Product	Yield
1			95	7			83
2			92	8			86
3			92	9			80
4			69	10			92
5	 R = COPh	 R = COPh	81	11			84
6	R = CO^{t}Bu	R = CO^{t}Bu	98	12			84

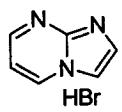
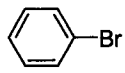
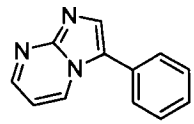
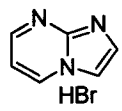
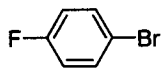
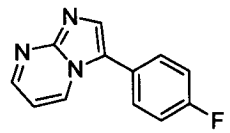
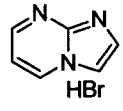
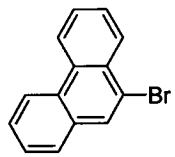
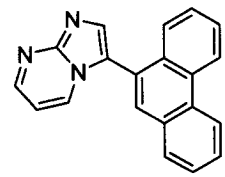
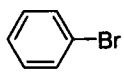
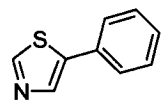
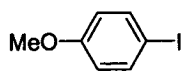
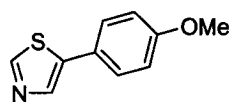
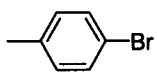
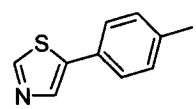
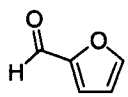
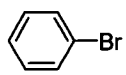
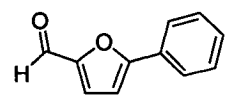
[a]Conditions: Substrate, Palladium (10 mol%) and KOAc (2 equiv.) are added in solvent (0.2 M) and heated for 8-16hrs.

3.4 – Scope of Intermolecular Direct Arylation Reaction

Pearlman's catalyst can also achieve the intermolecular direct arylation reaction of aryl iodides and bromides with a variety of heteroaromatic rings (Table 3.2). Imidazo-[1,2-a]pyrimidines can be arylated selectively at the 3-position in good yields (Entries 1-3).[18] This catalyst is also compatible with thiazole, arylating the five membered ring at the 5-position (Entries 4-6).[97] It has been previously reported that the arylation of thiazole occurs at the more acidic 2-position in the presence of copper salts, but, adding 20 mol% copper

bromide to a reaction of phenyl bromide and thiazole did not affect the regioselectivity of the reaction.[12] 2-furaldehydes can also be arylated in good yields (Entry 7).[15] A 12:1 mixture of products favoring arylation at the 5-position over the 3-position is obtained under the reaction conditions. Other heterocycles such as imidazole, *N*-methylimidazole and benzothiazole were considerably less reactive, giving the desired arylation product in less than 10% yield.

Table 3.2. Scope of the Intermolecular Direct Arylation Reaction.[a]

Entry	Arene	Aryl halide	Product	Yield
1				75
2				76
3				81
4				82
5				73
6				71
7				75

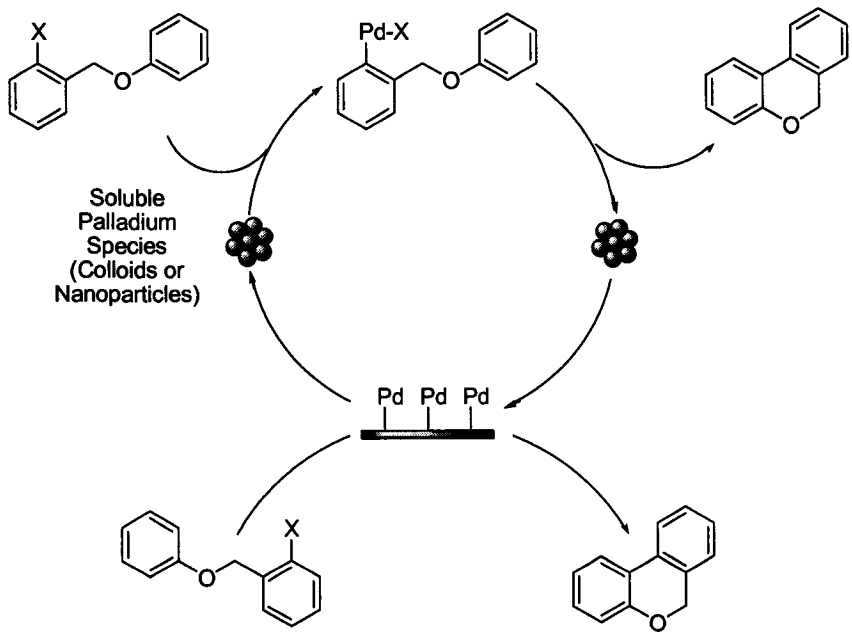
[a]Conditions: Substrate, Palladium (10 mol%) and KOAc (2 equiv.) are added in solvent (0.2 M) and heated for 8-16hrs.

3.5 – Determining the True Nature of the Catalyst

3.5.1 – Modes of Action of Heterogeneous Catalysts

Heterogeneous catalysts can be active while still bound to the matrix (Scheme 3.5). This is the case for most hydrogenation reactions and it explains the stereospecificity of the process. Soluble palladium species, colloids or nanoparticles, can also be active and catalyze the formation of the desired product. These particles can then either remain in solution, or return to the matrix in a release and capture mechanism.[71c, 72]

Scheme 3.5. Possible Modes of Action of Heterogeneous Catalysts.

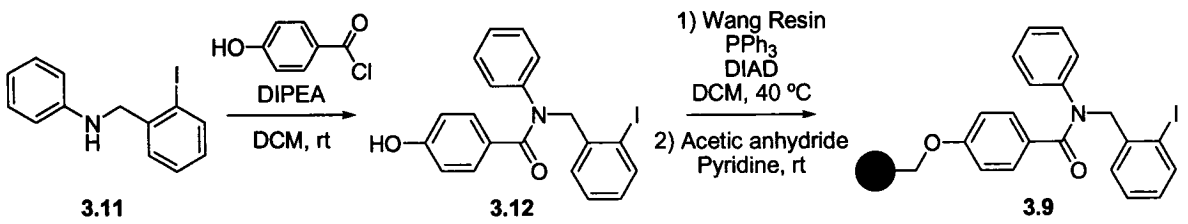


A series of three phase tests were carried out to establish the nature of the catalyst.[98]

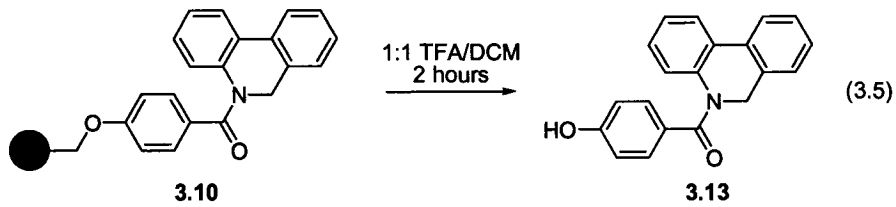
3.5.2 – Loading the Substrate onto Solid Support

Substrate and resin selection is crucial for the success of the test. The link between the substrate and the matrix must survive the reaction conditions, but be cleaved without inducing product decomposition. Since the cyclization conditions are relatively harsh, an ether linkage was employed. It was also established that a Wang resin prepared with 2% divinylbenzene rather than the usual 1% divinylbenzene would be robust enough to withstand the high reaction temperature.

Scheme 3.6. Loading the Substrate on Resin.



The phenol moiety of substrate **3.12** is coupled to the Wang resin via a Mitsunobu reaction in refluxing dichloromethane to give **3.9** (Scheme 3.6).[99] The remaining hydroxyl groups of the resin are capped with acetic anhydride to prevent interference with the catalyst. Cleavage of **3.10** from the resin is achieved with a one to one mixture of trifluoroacetic acid and dichloromethane to obtain **3.13** (Equation 3.5).[100]

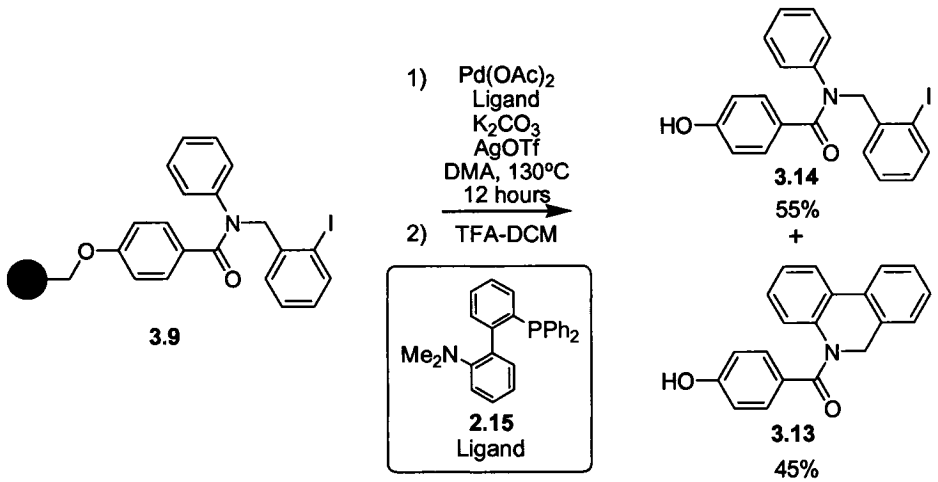


(3.5)

3.5.3 – Conducting the Three Phase Tests

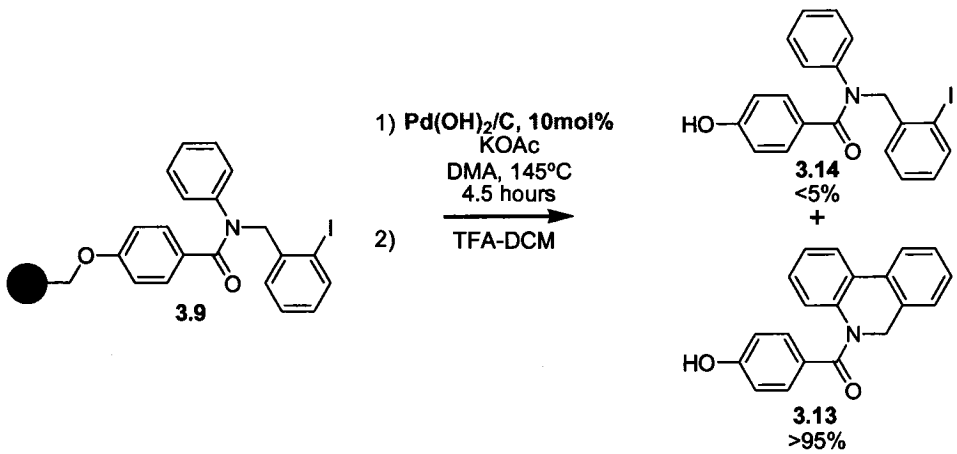
In order to ensure that the resin does not prevent the substrate from undergoing the transformation (Scheme 3.7), substrate **3.9** is placed in the presence of 5 mol% palladium acetate and 10 mol% 2-(diphenylphosphino)-2'-*N,N*-dimethylaminobiphenyl **2.15** at 130°C for twelve hours. After cleavage, 45% conversion to the cyclized product **3.13** is observed; demonstrating that the resin bound substrate can react.

Scheme 3.7. Testing the Reactivity of the Resin Bound Substrate.



The substrate is then reacted with 10 mol% of the heterogeneous palladium hydroxide on carbon for four and a half hours at 145°C (Scheme 3.8). Cleavage from the resin established that more than 95% conversion to the desired product **3.13** has occurred. This strongly supports the notion that catalytically active soluble palladium species are being formed under the reaction conditions.

Scheme 3.8. Reaction with both Heterogeneous Catalyst and Substrate.

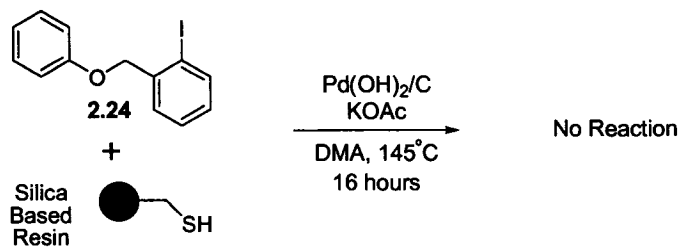


To determine if an active heterogeneous catalyst species is also contributing to the direct arylation reaction, a second three phase test was conducted.

Homogeneous substrate **2.24** is reacted under standard conditions in the presence of a silica-supported thiol-based scavenger resin (Scheme 3.9). Since thiols have a high

affinity for metals, soluble palladium species should be sequestered by the scavenger resin as they are produced. However, catalytically active heterogeneous species should not be poisoned by the silica-supported scavenger. After sixteen hours at 145°C in the presence of 10 mol% catalyst, no product had been formed, clearly indicating that the soluble catalyst formed *in situ* is the only active species, on the time scale examined.

Scheme 3.9. Heterogeneous Catalyst and Scavenger Resin.



The fact that the active catalyst is formed via leaching from the solid support under the reaction conditions may explain why high catalyst loadings are required in these reactions when compared to the homogeneous first and second generation catalysts.[40] The quantity of active catalyst formed under the reaction conditions might also be dependant on the heterogeneous catalyst used. Lower levels of leaching may explain the low reactivity observed with certain catalysts ($Pd/CaCO_3$, $Pd/BaCO_3$, Pd/C).

3.6 – Conclusion

In conclusion, we have developed a process for the intramolecular direct arylation of aryl bromides and iodides catalyzed by palladium hydroxide on carbon. Pearlman's catalyst was also active for the intermolecular direct arylation of aryl bromides and iodides with a range of heteroaromatic rings. Using the three phase test technique, it was established that homogeneous soluble palladium species, colloids or nanoparticles, were responsible for the

catalytic activity. It was also determined that the heterogeneous catalyst itself was not active on the time frame studied.

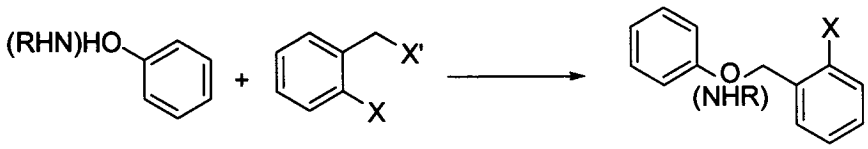
4 – Supporting Information

General Methods:

^{1}H and ^{13}C NMR were recorded in $CDCl_3$, $(CD_3)_2O$ or $(CD_3)_2SO$ solutions using a Bruker AVANCE 300 or 500 spectrometer or Varian INOVA 500 spectrometer with Me_4Si as an internal standard for $CDCl_3$ solutions. High-resolution mass spectra were obtained on a Kratos Concept IIH. Infra-Red analysis was performed with a Bruker EQUINOX 55. 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 every use. Dimethylacetamide was degassed with Argon before every use. Phosphonium salts **2.17-2.19** were synthesized according to literature procedures[47] or purchased from Strem, stored in a dessicator and used without further purification. Palladium, copper and ligands **2.7-2.10** and **2.15-2.16** were stored in a dessicator and were weighed out to air unless otherwise specified. Ligands **2.11-2.14** and $Pd(PCy_3)_2$ are stored in a glove-box but where weighed to air. All other reagents and solvents were used as is from commercial sources unless noted below.

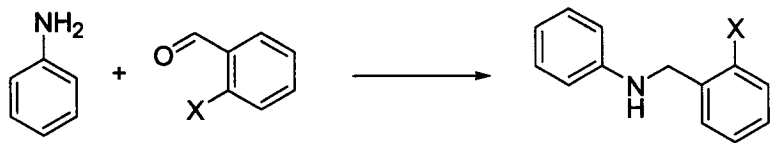
Starting Materials

General Procedure A:



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 (0.5 M) 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. The reactions were conducted on scales ranging from 1 to 25 mmol.

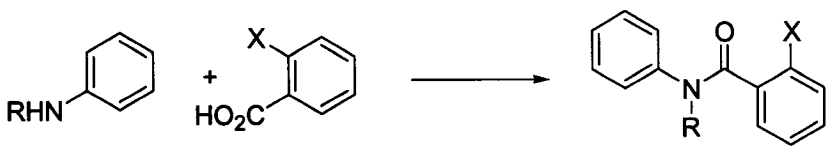
General procedure B:



In a 50 mL round-bottom flask equipped with a magnetic stirrer are added 2-halobenzaldehyde (1.0 equiv.) and $MgSO_4$ (0.5 g/mmol), dissolved in dichloromethane (0.9 M). The addition of the appropriate aniline (1.0 equiv.) is done dropwise, and the reaction is stirred overnight at room temperature. $MgSO_4$ salt is filtered and the volatiles are evaporated under reduced pressure. This crude mixture is then dissolved in anhydrous ether, and the reaction is brought to 0 °C using an ice bath. $LiAlH_4$ (2.0 equiv.) is added slowly to the mixture, and the reaction is stirred overnight at room temperature. The mixture

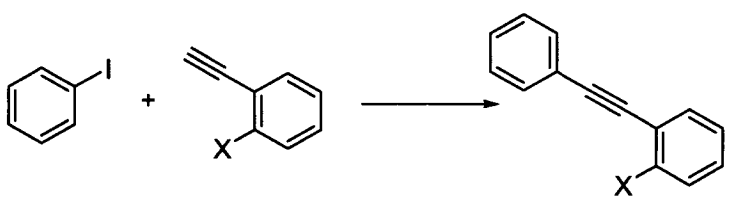
is then quenched using tartrate salts, followed by the addition of water and ether, vigorously stirring for 1 hour. The mixture is extracted using Et_2O/Brine. The organics are dried using $MgSO_4$, filtered and the volatiles are evaporated under reduced pressure. The residues are then purified via column chromatography using ethyl acetate/hexanes mixtures. The reactions were conducted on scales ranging from 3 to 12 mmol.

General Procedure C:



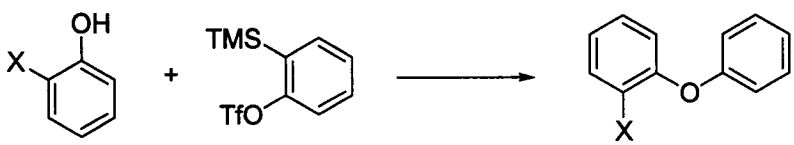
The appropriate carboxylic acid (1 equiv.) is dissolved in CH_2Cl_2 (0.25-0.5 M). The flask is purged with argon and placed in an ice bath. To this stirring solution is added oxalyl chloride (1.2 equiv.) followed by 1 drop of DMF. The reaction is allowed to stir and warm to room temperature. Once reaction is complete, the solvent is evaporated under reduced pressure. The crude mixture is then re-dissolved in dry CH_2Cl_2 (0.5 M). The mixture is cooled to 0 °C and DIPEA or NEt_3 (1.5 equiv.), DMAP (cat.) and the appropriate aniline (0.9 equiv.) are added. The reaction is allowed to stir under argon at room temperature overnight. The reaction mixture is then extracted with Brine/DCM and evaporated under reduced pressure. The crude product is purified via silica gel column chromatography with ethyl acetate/hexane mixtures. The reactions were conducted on scales ranging from 1 to 10 mmol.

General Procedure D:



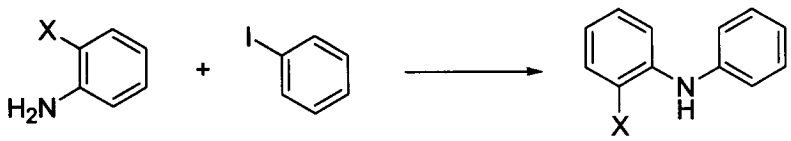
The appropriate iodoarene (1.05 equiv.), CuI (0.02 equiv.) and $Pd(PPh_3)_2Cl_2$ (0.02 equiv.) were weighed to open air and placed in a round bottom flask equipped with a magnetic stir bar. The flask was purged with nitrogen and THF (0.2 M) and NEt_3 (5% volume to THF) were added. To this stirring mixture 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. The reactions were conducted on scales ranging from 2 to 10 mmol.

General Procedure E:



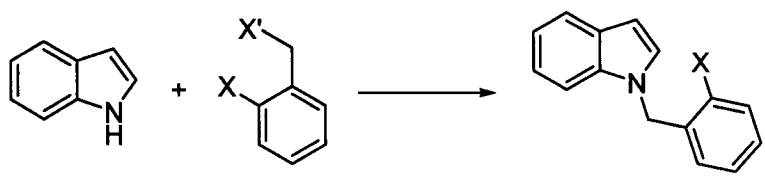
The appropriate 2-halophenol (1 equiv.) and silylaryl triflate (1.4 equiv.) are dissolved in dry MeCN. To this stirring solution is added cesium fluoride (3 equiv.) at room temperature. The flask is then purged with argon and the reaction is allowed to stir at room temperature for 48 hours. After evaporation of the solvent under reduced pressure the residue is extracted with Et_2O/Brine, dried with $MgSO_4$, filtered and the volatiles were evaporated under reduced pressure. The products are purified via silica gel column chromatography using hexane/ether mixtures to afford the aryl ethers. The reactions were conducted on scales ranging from 1.5 to 6 mmol.

General Procedure F:



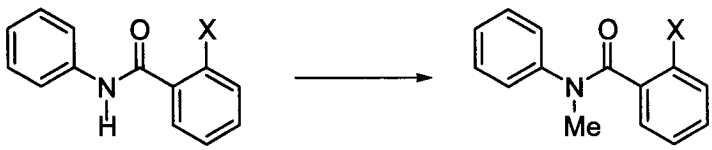
Pd_2dba_3 (0.01 equiv.), Ligand[101] (0.04 equiv.) and NaO^tBu (1.4 equiv.) were weighed to air and transferred to a resealable Schlenk tube. Amine (1.2 equiv.) and aryl iodide (1 equiv.) were added at this point if solid. The tube was then evacuated and backfilled with argon. The flask was capped with a rubber septum under an argon purge, and the liquid reagents (amine and/or aryl iodide) added. Dioxane (0.3 M) 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. The reactions were conducted on scales ranging from 2 to 7 mmol.

General Procedure G:



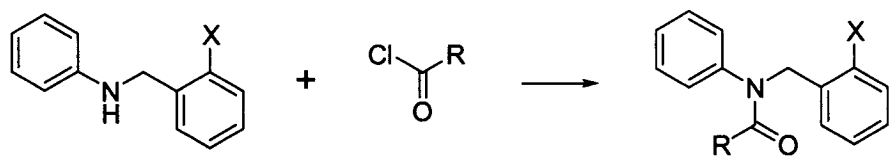
Indole (1 equiv.) and crushed KOH (4 equiv.) were placed in a round bottom flask equipped with a magnetic stir bar. DMSO was added (0.5 M) and the reaction was left stirring at room temperature for 30 minutes. The appropriate benzyl chloride was then added in one portion and the reaction was left stirring 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. The reactions were conducted on scales ranging from 3 to 5 mmol.

General Procedure H:



Sodium hydride (1.2 equiv.) is triturated with pentane under argon and then is suspended in dry THF (0.9 M). The appropriate amide (1 equiv.), dissolved in THF (0.7 M) 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 is allowed to warm to room temperature and stirred for 6 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 hexanes/ethyl acetate mixtures. The reactions were conducted on scales ranging from 1 to 4 mmol.

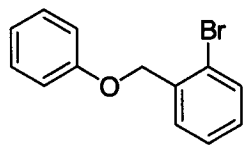
General Procedure I:



To a solution of acid chloride (1 equiv.) in dichloromethane (0.25 M) at 0 °C was first added triethylamine (2 equiv.) dropwise followed by the appropriate amine (0.9 equiv.) in one portion. The mixture is allowed to warm to room temperature and stirred overnight. An aqueous $NaHCO_3$ solution was then added and the mixture was extracted with dichloromethane. The organic phase is dried using $MgSO_4$, filtered and the volatiles were evaporated under reduced pressure. The crude product is then purified via silica gel column

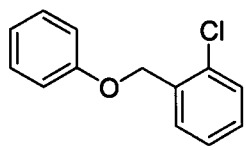
chromatography using hexanes/ethyl acetate mixtures. The reactions were conducted on scales ranging from 1 to 10 mmol.

Equation 1.16



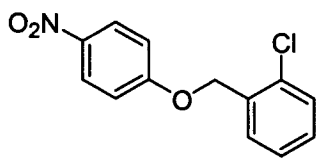
1-bromo-2-(phenoxymethyl)benzene (**1.79**): Synthesized according to general procedure A and exhibited spectral data identical to previous reports (93%).[2]

Equation 1.19



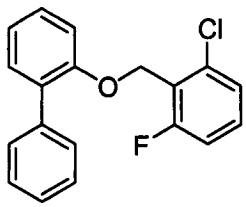
1-chloro-2-(phenoxymethyl)benzene (**1.82**): Synthesized according to general procedure A and exhibited spectral data identical to previous reports (91%).[102]

Table 2.2, entry 1



1-((4-nitrophenoxy)methyl)-2-chlorobenzene: Synthesized according to general procedure A and exhibited spectral data identical to previous reports (94%).[46]

Table 2.2, entry 2



1-chloro-6-fluoro-2-((2-phenyl-phenoxy)methyl)benzene: Synthesized according to general procedure A (87%).

^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): 5.11 (2H, d, *J*= 1.2 Hz), 6.91 (1H, td, *J*= 3.6 Hz & 6.3 Hz), 7.06 (1H, t, *J*= 7.5 Hz), 7.14 (3H, m), 7.24 (1H, d, *J*= 7.5 Hz), 7.27-7.36 (4H, m), 7.53 (2H, m);

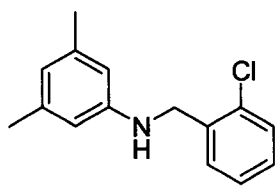
^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): 62.0 (d, *J*= 4.35 Hz), 114.1 (d, *J*= 13.1 Hz), 114.3, 121.9, 122.5 (d, *J*= 17.5 Hz), 125.3 (d, *J*= 3.3 Hz), 126.7, 127.8, 128.5, 129.5, 130.5 (d, *J*= 9.8 Hz), 131.8, 136.4, 136.4, 138.3, 155.5, 161.9 (*J*= 251.0 Hz);

IR (ν_{max} /cm^{-1}): 3064, 3029, 2939, 1609, 1482, 1221, 1003, 851, 778;

HRMS calculated for $C_{19}H_{14}FClO$ (M+): 328.0074; Found: 327.9891;

mp 115-117 °C ($CHCl_3$)

Table 2.2, entry 3



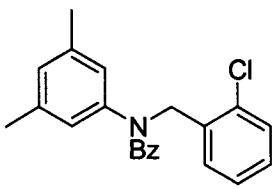
N-(2-chlorobenzyl)-3,5-dimethylbenzenamine: Synthesized according to general procedure B (91%).

^{1}H NMR (300 MHz, $CDCl_3$, 293 K, 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 (75 MHz, $CDCl_3$, 293 K, 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 (ν_{max} /cm^{-1}): 3410, 2916, 1603, 1335, 751;

HRMS: calculated for $C_{15}H_{16}NCl$ (M^+): 245.0971; Found: 245.0960



N-(2-chlorobenzyl)-*N*-(3,5-dimethylphenyl)benzamide: Synthesized according to general procedure I (71%).

^1H NMR (300 MHz, $CDCl_3$, 293 K, 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, 1.2 Hz & 9 Hz), 7.41-7.38 (2H, m), 7.48 (1H, dd, 1.5 Hz & 6 Hz);

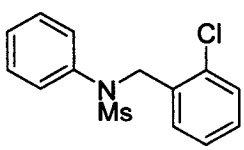
^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): 21.5, 51.9, 125.3, 127.3, 128.1, 128.7, 128.8, 129.1, 129.2, 129.9, 130.2, 133.6, 135.4, 136.3, 139.1, 143.7, 171.1;

IR (ν_{max} /cm^{-1}): 3061, 1650, 1595, 703;

HRMS: calculated for $C_{22}H_{20}NOCl$ (M^+): 349.1233; Found: 349.1221

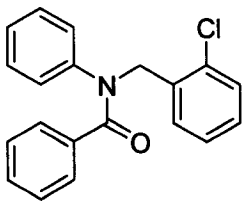
mp 145-146 °C ($CHCl_3$)

Table 2.2, entry 4



N-(2-chlorobenzyl)-*N*-mesylbenzenamine: Synthesized according to general procedure A and exhibited spectral data identical to previous reports (83%).[46]

Table 2.2, entry 5



N-(2-chlorobenzyl)-*N*-phenylbenzamide: Synthesized according to general procedure I (88%).

^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): 5.28 (2H, s), 6.95 (2H, m), 7.03-7.28 (8H, m), 7.32 (1H, dd, *J*= 1.8 Hz & 7.5 Hz), 7.37 (2H, m), 7.49 (1H, dd, *J*= 1.2 Hz & 7.5 Hz);

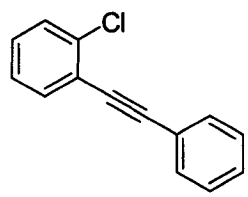
^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): 51.2, 126.7, 126.9, 127.4, 127.8, 128.5, 128.8, 129.0, 129.2, 129.5, 129.8, 133.3, 134.8, 135.7, 143.3, 170.6;

IR (ν_{max} /cm^{-1}): 3063, 2933, 1649, 1493, 1381, 1033, 697;

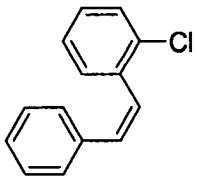
HRMS calculated for $C_{20}H_{16}ClNO$ (M+): 321.0920; Found: 321.0903;

mp 97-99 °C ($CHCl_3$)

Table 2.2, entry 6

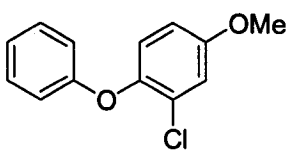


1-(2-(2-chlorophenyl)ethynyl)benzene: Synthesized according to general procedure D and exhibited spectral data identical to previous reports (86%).[103]



1-chloro-2-styrylbenzene: The diarylacetylene (1 equiv.) is then dissolved in a mixture of ethanol/ethyl acetate (3:1, 0.025 M). 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 (91%).[104]

Table 2.2, entry 7



1-(2-chloro-4-methoxyphenoxy)benzene: Synthesized according to general procedure E (77%).

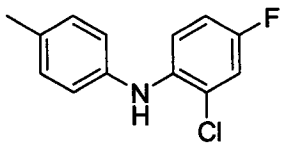
^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): 3.78 (3H, s), 6.78 (1H, dd, *J*= 3.1 Hz & 9.2 Hz), 6.88 (2H, d, *J*= 8.5 Hz), 7.02 (3H, m), 7.27 (2H, m);

^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): 55.7, 113.7, 115.6, 116.5, 122.5, 122.8, 127.1, 129.6, 145.2, 156.5, 157.9;

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

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

Table 2.2, entry 8



2-chloro-4-fluoro-*N*-p-tolylbenzenamine: Synthesized according to general procedure F (83%).

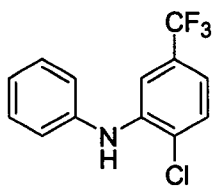
^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): 2.31 (3H, s), 5.78 (1H, s), 6.83 (1H, td, *J*= 3.2 Hz & 9.2 Hz), 6.98 (2H, d, *J*= 8.5 Hz), 7.10 (4H, m);

^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): 20.7, 114.2 (d, *J*= 21.9 Hz), 116.2 (d, *J*= 7.5 Hz), 116.7 (d, *J*= 25.1 Hz), 120.3, 121.5 (d, *J*= 9.9 Hz), 130.0, 132.3, 137.4 (d, *J*= 3.4 Hz), 139.2, 155.8 (d, *J*= 240.6 Hz);

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

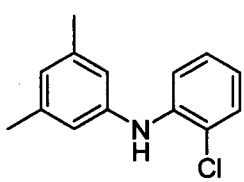
HRMS calculated for $C_{13}H_{11}ClNF$ (M+): 235.0564; Found: 235.0541;

Table 2.2, entry 9



2-chloro-5-(trifluoromethyl)-*N*-phenylbenzenamine: Synthesized according to general procedure F and exhibited spectral data identical to previous reports (82%).[46]

Table 2.2, entry 10



2-chloro-*N*-(3,5-dimethylphenyl)benzenamine: Synthesized according to general procedure F (82%).

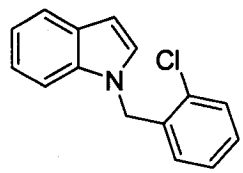
^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): 2.29 (6H, s), 6.02 (1H, s), 6.69 (1H, s), 6.75-6.81 (2H, m), 6.02 (1H, m), 7.10-7.15 (1H, m), 7.27 (1H, dd, *J*= 1.2 Hz & 9 Hz), 7.33 (1H, dd, *J*= 1.2 Hz & 9 Hz);

^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): 21.4, 115.7, 117.9, 120.0, 121.3, 124.4, 127.4, 129.6, 139.1, 140.4, 141.3;

IR (ν_{max} /cm^{-1}): 3409, 3026, 2917, 1587, 1330, 1051;

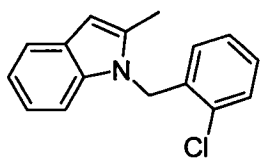
HRMS: calculated for $C_{14}H_{14}NCl$ (M^+): 231.0815; Found: 231.0789

Table 2.2, entry 11



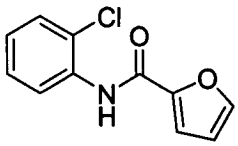
1-(2-chlorobenzyl)-1H-indole: Synthesized according to general procedure G and exhibited spectral data identical to previous reports (89%).[46]

Table 2.2, entry 12



1-(2-chlorobenzyl)-2-methyl-1H-indole: Synthesized according to general procedure G and exhibited spectral data identical to previous reports (86%).[105]

Table 2.2, entry 13



N-(2-chlorophenyl)fura*N*-2-carboxamide: Synthesized according to general procedure C (88%).

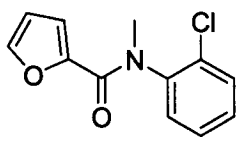
^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): 6.57 (1H, dd, *J*= 1.8 Hz & 3.8 Hz), 7.06 (1H, t, *J*= 8.3 Hz), 7.29 (2H, m), 7.40 (1H, d, *J*= 8.1 Hz), 7.55 (1H, s). 8.52 (1H, d, *J*= 8.0 Hz), 8.70 (1H, s);

^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): 112.6, 115.6, 121.2, 122.7, 124.6, 127.7, 129.0, 134.2, 144.5, 147.5, 155.8;

IR (ν_{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;

mp 90-92 °C ($CHCl_3$)



N-(2-chlorophenyl)-*N*-methylfura*N*-2-carboxamide: Synthesized according to general procedure H (94%).

^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): 3.37 (3H, s), 5.92 (1H, s), 6.21 (1H, s), 7.32 (4H, m), 7.51 (1H, m);

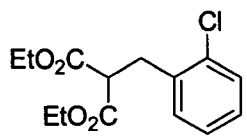
^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): 36.9, 111.1, 115.8, 128.1, 129.6, 130.0, 130.6, 133.1, 141.3, 144.5, 146.9, 159.3;

IR (ν_{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;

mp 84-86 °C ($CHCl_3$)

Table 2.2, entry 14



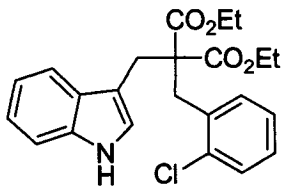
Diethyl 2-(2-chlorobenzyl)malonate: Sodium hydride (0.95 equiv.) was triturated with pentane under argon and then suspended in dry THF (0.3 M). Diethylmalonate (1 equiv.), dissolved in THF (1.8 M), was added dropwise to the suspension of sodium hydride at 0 °C. After 30 minutes of stirring, 2-chlorobenzyl chloride (1.1 equiv.), dissolved in THF (3.0 M), 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 (91%).

^1H NMR (300 MHz, $CDCl_3$, 293 K, TMS): 1.21 (6H, t, *J*= 7.5H), 3.34 (2H, d, *J*= 8.1 Hz), 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 (75 MHz, $CDCl_3$, 293 K, TMS): 14.0, 32.7, 51.4, 61.5, 126.8, 128.4, 129.6, 131.5, 134.2, 135.4, 168.7;

IR (ν_{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;



Diethyl 2-((1H-indol-3-yl)methyl)-2-(2-chlorobenzyl)malonate: Sodium hydride (1.1 equiv.) was triturated with pentane under argon and then suspended in dry THF (0.1 M). 2-(2-chlorobenzyl)diethylmalonate (1 equiv.), dissolved in THF (1.8 M), 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 (0.1 M), 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 (80%).

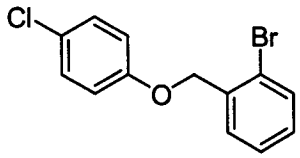
^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): 1.05 (6H, t, *J*= 7.2 Hz), 3.49 (2H, s), 3.57 (2H, s), 4.01 (2H, d, *J*= 7.2 Hz), 4.02 (2H, d, *J*= 7.2 Hz), 7.11 (5H, m), 7.30 (3H, m), 7.54 (1H, d, *J*= 7.5 Hz), 8.21 (1H, s);

^{13}C NMR (75 MHz, $CDCl_3$, 293 K, 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 (ν_{max} /cm^{-1}): 3404, 2981, 1723, 1368, 1252, 1198, 910, 742;

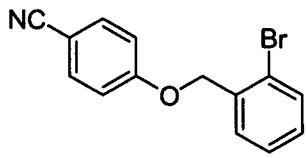
HRMS calculated for $C_{23}H_{24}ClNO_4$ (M+): 413.1394; Found: 413.1398;

Table 2.3, entry 1



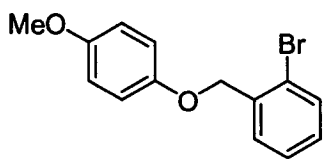
1-(2-bromobenzyloxy)-4-chlorobenzene: Synthesized according to general procedure A and exhibited spectral data identical to previous reports (93%).[106]

Table 2.3 , entry 2 & Table 3.1, entry 2



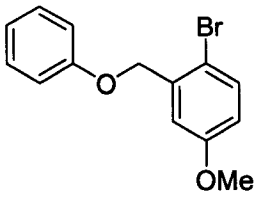
4-(2-bromobenzyloxy)benzonitrile: Synthesized according to general procedure A and exhibited spectral data identical to previous reports (96%).[107]

Table 2.3, entry 3



1-(2-bromobenzyloxy)-4-methoxybenzene: Synthesized according to general procedure A and exhibited spectral data identical to previous reports (94%).[106]

Table 2.3, entry 4 & Table 3.1, entry 4



1-(2-bromo-5-methoxybenzyloxy)benzene: Synthesized according to general procedure A and exhibited spectral data identical to previous reports (91%).

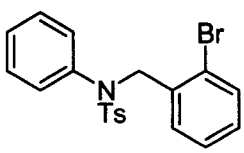
^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): 3.78 (3H, s), 5.09 (2H, s), 6.74 (1H, dd, *J*= 3.1 Hz & 8.7 Hz), 6.98 (3H, m), 7.13 (1H, d, *J*= 2.4 Hz), 7.29 (1H, d, *J*= 6.7 Hz), 7.32 (1H, d, *J*= 7.6 Hz), 7.46 (1H, d, *J*= 8.7 Hz);

^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): 55.4, 69.2, 112.2, 114.3, 114.8, 114.8, 121.2, 129.5, 133.1, 137.3, 158.3, 159.1;

IR (ν_{max} /cm^{-1}) 3062, 3006, 2935, 1585, 1472, 1295, 1230, 1054, 753;

HRMS calculated for $C_{14}H_{14}INO$ (M^+) 292.0099; Found: 292.0088

Table 2.3, entry 5



N-(2-bromobenzyl)-*N*-tosylbenzenamine: Synthesized according to general procedure A (83%).

^{1}H NMR (300 MHz, $CDCl_3$, 293 K, 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*= 1.2 Hz & 8.1 Hz), 7.53 (2H, d, *J*= 8.4 Hz), 7.61 (1H, dd, *J*= 1.2 Hz & 7.5 Hz);

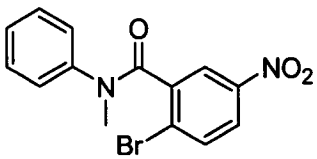
^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): 21.6, 54.1, 123.1, 127.5, 127.7, 127.8, 128.6, 128.9, 129.0, 129.5, 130.3, 132.6, 135.1, 135.3, 139.1, 143.7;

IR (ν_{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;

mp 107-109 °C ($CHCl_3$)

Table 2.3, entry 6



2-bromo-*N*-methyl-5-nitro-*N*-phenylbenzamide: Synthesized according to general procedure C (76%).

^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): (Major rotamer) 3.53 (3H, s), 7.10-7.27 (mixture) (5H, m), 7.58 (1H, d, *J*= 9.3 Hz), 7.87 (1H, dd, *J*= 3.0 Hz & 8.7 Hz), 7.98 (1H, d, *J*= 2.7 Hz); (Minor rotamer) 3.24 (3H, s), 7.10-7.27 (mixture) (2H, m), 7.46 (4H, m), 8.15 (1H, dd, *J*= 2.7 Hz & 8.7 Hz), 8.32 (1H, d, *J*= 2.7 Hz);

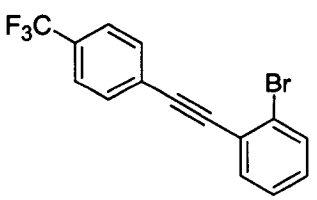
^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): (mixture of rotamers) 37.1, 122.7, 123.5, 124.0, 124.7, 125.6, 126.6, 127.0, 127.2, 127.7, 129.2, 133.7, 134.0, 139.7, 142.1, 146.0, 166.2, 170.9;

IR (ν_{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;

mp 130-132 °C ($CHCl_3$)

Table 2.3, entry 7



1-(2-(2-bromophenyl)ethynyl)-4-(trifluoromethyl)benzene: Synthesized according to general procedure D (84%).

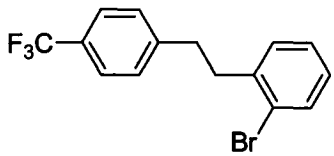
^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): 7.22 (1H, td, *J*= 1.8 Hz & 7.8 Hz), 7.32 (1H, td, *J*= 1.2 Hz & 7.5 Hz), 7.56-7.70 (6H, m);

^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): 90.3, 92.3, 123.9 (q, *J*= 270.6 Hz), 124.7, 125.3 (q, *J*= 4.4 Hz), 125.8, 126.7, 127.1, 130.0, 130.2 (q, *J*= 32.7 Hz), 131.9, 132.6, 133.4;

IR (ν_{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;

mp 76-77 °C (Ether)



1-(4-(trifluoromethyl)phenethyl)-2-bromobenzene: The diarylacetylene (1 equiv.) and *p*-toluenesulfonyl-hydrazine (20 equiv.) were then dissolved in DME (0.1 M) 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 (93%).

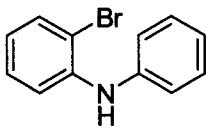
^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): 2.90-3.07 (4H, m), 7.03-7.14 (2H, m), 7.20 (1H, td, *J*= 1.2 Hz & 6.9 Hz), 7.29 (2H, d, *J*= 8.1 Hz), 7.53 (3H, m);

^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): 35.9, 38.0, 124.4 (q, *J*= 270.6 Hz), 124.4, 125.3, 125.3 (q, *J*= 4.4 Hz), 127.5, 128.0, 128.4 (q, *J*= 32.7 Hz), 128.8, 130.5, 132.9, 140.3;

IR (ν_{max} /cm^{-1}): 3058, 2933, 1326, 1164, 1120, 1067, 825, 749;

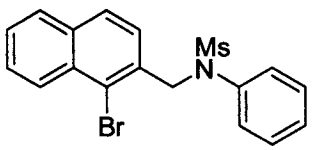
HRMS calculated for $C_{15}H_{12}F_3Br$ (M+): 328.0074; Found: 327.9891;

Table 2.3, entry 8



N-(2-bromophenyl)benzenamine: Synthesized according to general procedure F and exhibited spectral data identical to previous reports (86%).[108]

Table 2.3, entry 9



N-((1-bromonaphthale*N*-2-yl)methyl)-*N*-mesylbenzenamine: Synthesized according to general procedure A (64%).

^{1}H NMR (300 MHz, $CDCl_3$, 293 K, 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*= 8.4 Hz);

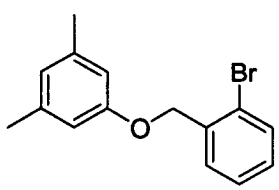
^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): 37.7, 54.9, 123.5, 126.7, 126.8, 126.9, 127.3, 127.5, 127.9, 128.1, 128.2, 129.4, 132.0, 133.3, 133.9, 138.8;

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: 389.00615

mp 137-138 °C

Table 2.3, entry 10



1-((3,5-dimethylphenoxy)methyl)-2-bromobenzene: Synthesized according to general procedure A (97%).

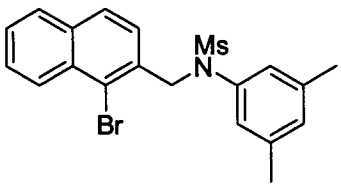
^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): 2.29 (6H, s), 5.08 (2H, s), 6.62 (3H, s), 7.16 (1H, td, *J*= 1.8 Hz & 7.5 Hz), 7.32 (1H, td, *J*= 1.2 Hz & 7.5 Hz), 7.58-7.53 (2H, m);

^{13}C NMR (75 MHz, $CDCl_3$, 293 K, 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 (ν_{max} /cm^{-1}): 2917, 1595, 1322, 1154, 1029, 749, 644;

HRMS: calculated for $C_{15}H_{15}OBr$ (M^+): 290.0306, Found: 290.0324

Table 2.3, entry 11



N-((1-bromonaphthale*N*-2-yl)methyl)-3,5-dimethyl-*N*-mesylbenzenamine: Synthesized according to general procedure A (71%).

^{1}H NMR (300 MHz, $CDCl_3$, 293 K, 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*= 8.4 Hz);

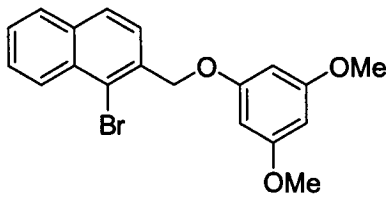
^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): 21.2, 37.5, 54.9, 123.2, 125.7, 126.5, 126.7, 127.2, 127.4, 127.8, 128.1, 129.8, 131.9, 133.6, 133.9, 138.7, 138.9;

IR (ν_{max} /cm^{-1}): 3012, 2920, 1339, 1156, 1088;

HRMS: calculated for $C_{20}H_{20}NO_2SBr$ (M^+): 417.0398; Found: 417.0410

mp 161-162 °C

Table 2.3, entry 12



2-((3,5-dimethoxyphenoxy)methyl)-1-bromonaphthalene: Synthesized according to general procedure A (89%).

^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): 3.77 (6H, s), 5.35 (2H, s), 6.12 (1H, t, *J*= 2.4 Hz), 6.21 (2H, d, *J*= 2.1 Hz), 7.51-7.67 (3H, m), 7.83 (2H, d, *J*= 8.4 Hz), 8.34 (1H, d, *J*= 7.8 Hz);

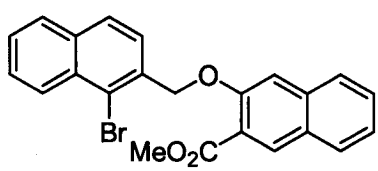
^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): 55.3, 70.1, 93.3, 93.7, 122.2, 125.5, 126.6, 126.9, 127.5, 127.9, 128.1, 132.0, 134.0, 134.3, 160.3, 161.5;

IR (ν_{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

mp 97-98 °C

Table 2.3, entry 13



Methyl 3-((1-bromonaphthale*N*-2-yl)methoxy)naphthalene-2-carboxylate: Synthesized according to general procedure A (88%).

^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): 4.02 (3H, s), 5.55 (2H,s), 7.32 (1H, s), 7.39 (1H, t, *J*= 9 Hz), 7.49-7.65 (3H, m), 7.74 (1H, d, *J*= 8.1 Hz), 7.83-7.90 (3H, m), 7.99 (1H, d, *J*= 8.7 Hz), 8.35 (1H, d, *J*= 8.1 Hz), 8.40 (1H, s);

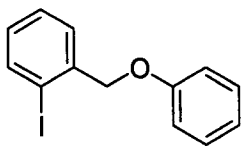
^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): 52.7, 70.9, 108.9, 121.7, 122.1, 125.1, 125.6, 126.9, 127.0, 127.1, 127.9, 128.2, 128.5, 128.7, 128.9, 129.1, 129.2, 133.7, 134.4, 134.8, 136.4, 154.7, 167.0;

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

mp 141-142 °C

Equation 2.5



1-Iodo-2-phenoxymethyl-benzene (**2.24**): The substrate was prepared following the general procedure for the synthesis of haloarenes (92%).

^1H NMR (300 MHz, $CDCl_3$, 293 K, TMS): 5.04 (2H, s), 6.99 (4H, m), 7.33 (3H, m), 7.51 (1H, dd, *J*= 0.75 Hz & 7.8 Hz), 7.86 (1H, dd, *J*= 1.2 Hz & 7.8 Hz);

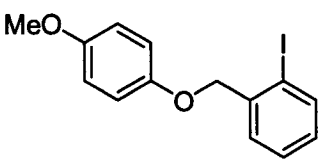
^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): 73.5, 97.1, 112.5, 122.9, 128.2, 128.5, 129.2, 139.0, 139.0, 139.2, 158.4;

IR (v_{max} /cm^{-1}) 3064, 2945, 2884, 1373, 1232, 759, 751;

HRMS calculated for $C_{13}H_{11}IO$ (M^+) 309.9855; Found: 309.9847;

mp 50-52 °C

Table 2.5, entry 1, 2



1-(2-iodobenzyloxy)-4-methoxybenzene: Synthesized according to general procedure A and exhibited spectral data identical to previous reports (94%).

^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): 3.65 (3H, s), 4.89 (2H, s), 6.78 (2H, m), 6.88 (3H, m), 7.25 (1H, td, *J*= 0.9 Hz & 7.5 Hz), 7.44 (1H, dd, *J*= 0.9Hz & 7.8 Hz), 7.76 (1H, dd, *J*= 0.9 Hz & 7.8 Hz);

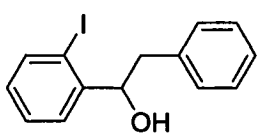
^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): 55.7, 74.6, 97.1, 114.6, 115.9, 128.3, 128.6, 129.4, 139.2, 139.4, 152.5, 154.1;

IR (ν_{max} /cm^{-1}) 3061, 2997, 2949, 1505, 1231, 823, 749;

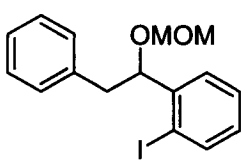
HRMS calculated for $C_{14}H_{13}IO_2$ (M^+) 339.9960; Found: 339.9976;

mp 54-56°C

Table 2.5, entry 3 & Table 3.1, entry 8



1-(2-iodophenyl)-2-phenylethanol: Prepared according to literature procedure and exhibited spectral data identical to literature values (81%).[109]



1-(2-(2-iodophenyl)-2-(methoxymethoxy)ethyl)benzene: Sodium hydride (1.2 equiv.) was triturated with pentane in a flask equipped with a mechanical stir bar. After leftover pentane was removed using a flow of nitrogen, THF (0.1 M) was added. The reaction vessel was placed in an ice bath and 1-(2-iodophenyl)-2-phenylethanol (1 equiv.) was added. The reaction mixture was stirred for 2 hours. Chloromethyl methyl ether (1.2 equiv.) was then added at 0 °C. The reaction was allowed to warm up to room temperature and stirred overnight. The reaction was quenched with a saturated solution of ammonium chloride and

extracted with ether. The organic phase was dried with $MgSO_4$, filtered and the volatiles were evaporated under reduced pressure. The residue was then purified via silica gel column chromatography using 5% ethyl acetate/hexanes (83%).

^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): 2.75 (1H, dd, *J*= 9.9 Hz & 14.1 Hz), 2.88 (3H, s), 3.07 (1H, dd, *J*= 3.0 Hz & 14.1 Hz), 4.37 (2H, s), 5.04 (1H, dd, *J*= 3.0 Hz & 9.9 Hz), 6.99 (1H, t, *J*= 7.5 Hz), 7.25 (6H, m), 7.49 (1H, d, *J*= 7.8 Hz), 7.82 (1H, d, *J*= 8.0 Hz);

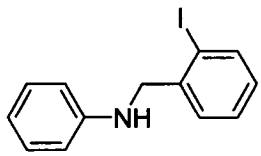
^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): 43.8, 55.7, 82.5, 94.8, 98.8, 126.7, 127.8, 128.5, 128.9, 129.7, 130.0, 139.0, 139.7, 144.5;

IR (ν_{max} /cm^{-1}) 3061, 2944, 2886, 1150, 1098, 1052, 1020, 756;

HRMS calculated for $C_{16}H_{17}IO_2$ (M^+ $C_{14}H_{12}I$) 306.9984; Found: 307.0012;

mp 44-46 °C

Table 2.5, entry 4, 5 & Table 3.1, entry 6



N-(2-iodobenzyl)aniline: Synthesized according to general procedure B (82%).

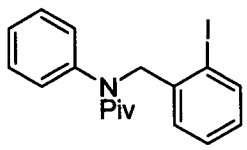
^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): 4.18 (1H, s), 4.31 (2H, s), 6.59 (2H, m), 6.71 (1H, t, *J*= 7.5 Hz), 6.96 (1H, td, *J*= 1.8 Hz & 7.5 Hz), 7.16 (2H, m), 7.28 (1H, td, *J*= 1.3 Hz & 7.5 Hz), 7.37 (1H, dd, *J*= 2.1 Hz & 7.3 Hz), 7.84 (1H, dd, *J*= 1.3 Hz & 8.0 Hz);

^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): 53.2, 98.5, 112.9, 117.7, 128.4, 128.7, 128.9, 129.2, 139.4, 140.9, 147.6;

IR (ν_{max} /cm^{-1}) 3419, 3051, 3017, 1602, 1506, 1324, 1011, 747;

HRMS calculated for $C_{13}H_{12}IN$ (M^+) 309.0014; Found: 309.0032

mp 66-68 °C



N-(2-iodobenzyl)-*N*-phenylpivalamide: Synthesized according to general procedure I (89%).

^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): 1.06 (9H, s), 4.92 (2H, s), 6.88 (1H, m), 7.04 (2H, m), 7.26 (5H, m), 7.72 (1H, d, *J*= 7.8 Hz);

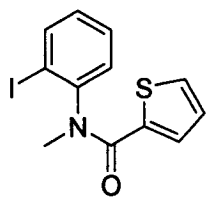
^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): 29.5, 41.1, 60.2, 99.5, 128.0, 128.1, 128.7, 129.3, 129.7, 139.2, 139.6, 142.7, 177.7;

IR (ν_{max} /cm^{-1}) 3062, 2958, 2873, 1638, 1493, 1290, 1187, 748;

HRMS calculated for $C_{18}H_{20}INO$ (M^+ $C_{18}H_{20}NO$) 266.1545; Found: 266.1564

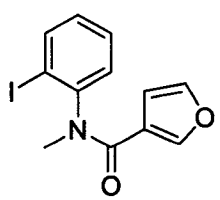
mp 118-121 °C

Table 2.5, entry 6



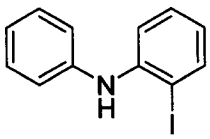
N-(2-iodophenyl)-*N*-methylthiophene-2-carboxamide: Synthesized according to general procedure H and exhibited spectral data identical to previous reports (86%).[32]

Table 2.5, entry 7



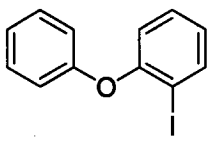
N-(2-iodophenyl)-*N*-methylfura*N*-3-carboxamide: Synthesized according to general procedure H and exhibited spectral data identical to previous reports (84%).[32]

Table 2.5, entry 8 & Table 3.1, entry 11



2-iodo-*N*-phenylbenzenamine: Prepared according to literature procedure and exhibited data identical to previous reports (89%).[110]

Table 2.5, entry 9 & Table 3.1, entry 10



1-iodo-2-phenoxybenzene: Prepared according to literature procedure (87%).

^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): 6.87 (2H, m), 6.94 (2H, m), 7.11 (1H, td, *J*= 0.9 Hz & 7.5 Hz), 7.30 (3H, m), 7.86 (1H, dd, *J*= 1.5 Hz & 7.8 Hz);

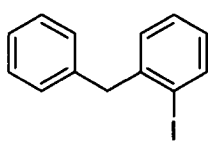
^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): 88.9, 118.4, 119.4, 123.4, 125.3, 129.6, 129.7, 139.8, 156.4, 156.8;

IR (ν_{max} /cm^{-1}) 3062, 2923, 1573, 1234, 748;

HRMS calculated for $C_{12}H_9IO$ (M^+) 295.9698; Found: 295.9690;

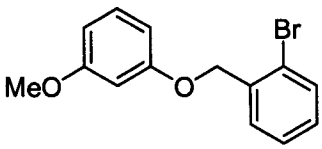
mp 53-54 °C

Table 2.5, entry 10 & Table 3.1, entry 12



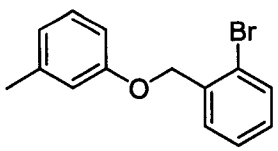
1-benzyl-2-iodobenzene: Prepared according to literature procedure and exhibited data identical to previous reports (78%).[35]

Table 2.6, entry 1



1-(2-bromobenzyloxy)-3-methoxybenzene: Synthesized according to general procedure A and exhibited spectral data identical to previous reports (92%).[40]

Table 2.6, entry 2



1-((m-tolyloxy)methyl)-2-bromobenzene: Synthesized according to general procedure A (94%).

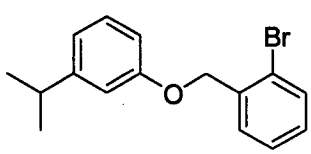
^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): 2.34 (3H, s), 5.11 (2H, s), 6.80 (3H, m), 7.18 (2H, m), 7.32 (1H, t, *J*= 8.1 Hz), 7.56 (2H, m);

^{13}C NMR (75 MHz, $CDCl_3$, 293 K, 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 (ν_{max} /cm^{-1}): 9057, 2919, 1603, 1440, 1258, 1027, 747;

HRMS calculated for $C_{14}H_{13}BrO$ (M+) 276.0150; Found: 276.0163;

Table 2.6, entry 3



1-((3-isopropylphenoxy)methyl)-2-bromobenzene: Synthesized according to general procedure A (95%).

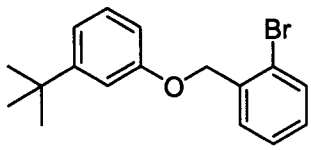
^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): 1.24 (6H, d, *J*= 6.6 Hz), 2.88 (1H, sept, *J*= 6.9 Hz), 5.19 (2H, s), 6.78 (1H, dd, *J*= 8.1 Hz & 1.8 Hz), 6.86 (2H, m), 7.19 (2H, m), 7.32 (1H, td, *J*= 7.5 Hz & 1.2 Hz), 7.57 (2H, m);

^{13}C NMR (75 MHz, ($CDCl_3$, 293 K, 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 (ν_{max} /cm^{-1}): 3059, 2960, 1584, 1445, 1026, 749;

HRMS calculated for $C_{16}H_{17}BrO$ (M+) 304.0463; Found: 304.0468;

Table 2.6, entry 4



1-((3-*tert*-butylphenoxy)methyl)-2-bromobenzene: Synthesized according to general procedure A (90%).

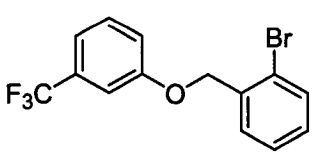
^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): 1.31 (9H, s), 5.12 (2H, s), 6.78 (1H, dd, *J*= 8.1 Hz & 2.4 Hz), 7.02 (2H, m), 7.20 (2H, m), 7.31 (1H, t, *J*= 8.1 Hz), 7.56 (2H, d, *J*= 8.1 Hz);

^{13}C NMR (75 MHz, $CDCl_3$, 293 K, 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 (ν_{max} /cm^{-1}): 3071, 2963, 1607, 1582, 1274, 1027, 749;

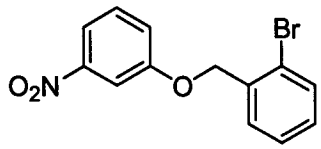
HRMS calculated for $C_{17}H_{19}BrO$ (M+) 318.0619; Found: 318.0597;

Table 2.6, entry 5



1-((3-(trifluoromethyl)phenoxy)methyl)-2-bromobenzene: Synthesized according to general procedure A and exhibited spectral data identical to previous reports (91%).[111]

Table 2.6, entry 6



1-((3-nitrophenoxy)methyl)-2-bromobenzene: Synthesized according to general procedure A (94%).

^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): 5.19 (2H, s), 7.31 (3H, m), 7.45 (1H, t, *J*= 8.4 Hz), 7.53 (1H, d, *J*= 8.7 Hz), 7.61 (1H, d, *J*= 8.7 Hz), 7.85 (2H, m);

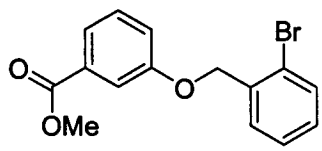
^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): 70.0, 109.5, 116.2, 121.7, 122.6, 127.7, 129.1, 129.8, 130.1, 132.8, 135.0, 149.2, 158.9;

IR (ν_{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;

mp 80-82 °C ($CHCl_3$)

Table 2.6, entry 7



Methyl 3-(2-bromobenzyloxy)benzoate: Synthesized according to general procedure A (93%).

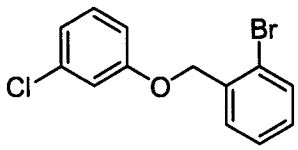
^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): 3.92 (3H, s), 5.17 (2H, s), 7.20 (2H, m), 7.35 (2H, m), 7.55 (1H, dd, *J*= 7.5 Hz & 1.8 Hz), 7.60 (1H, dd, *J*= 8.1 Hz & 1.8 Hz), 7.67 (2H, m);

^{13}C NMR (75 MHz, $CDCl_3$, 293 K, 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 (ν_{max} /cm^{-1}):2946, 1721, 1586, 1278, 1026, 751;

HRMS calculated for $C_{15}H_{13}BrO_3$ (M+) 320.0048; Found: 320.0025;

Table 2.6, entry 8



1-((3-chlorophenoxy)methyl)-2-bromobenzene: Synthesized according to general procedure A (95%).

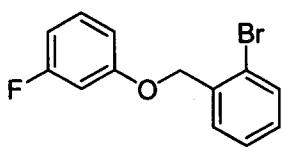
^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): 5.09 (2H, s), 6.85 (1H, dd, *J*= 8.1 Hz & 1.8 Hz), 6.97 (2H, m), 7.19 (2H, m), 7.32 (1H, d, *J*= 7.5 Hz), 7.50 (1H, d, *J*= 7.5 Hz), 7.57 (1H, d, *J*= 8.1 Hz);

^{13}C NMR (75 MHz, $CDCl_3$, 293 K, 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 (ν_{max} /cm^{-1}): 3069, 2934, 1594, 1477, 1244, 1026, 749;

HRMS calculated for $C_{13}H_{10}BrClO$ (M+) 295.9604; Found: 295.9631;

Table 2.6, entry 9



1-((3-fluorophenoxy)methyl)-2-bromobenzene: Synthesized according to general procedure A (90%).

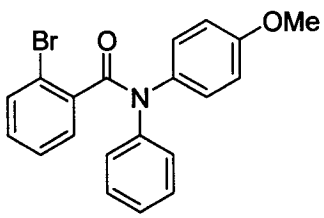
^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): 5.11 (2H, s), 6.71 (3H, m), 7.21 (2H, m), 7.33 (1H, t, *J*= 7.5 Hz), 7.52 (1H, d, *J*= 7.8 Hz), 7.83 (1H, d, *J*= 7.8 Hz)

^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): 69.6, 102.7 (d, *J*= 30.0 Hz), 108.0 (d, *J*= 20.7 Hz), 110.5 (d, *J*= 3.3 Hz), 122.3, 127.6, 129.1 (d, *J*= 45 Hz), 130.2, 130.4, 132.7, 135.7, 159.7 (d, *J*= 11.0 Hz), 165.2;

IR (ν_{max} /cm^{-1}):1530, 1348, 1246, 1025, 732;

HRMS calculated for $C_{13}H_{10}BrFO$ (M+) 279.9899; Found: 279.9897;

Scheme 2.8



2-bromo-*N*-(4-methoxyphenyl)-*N*-phenylbenzamide: Synthesized according to general procedure C (70%).

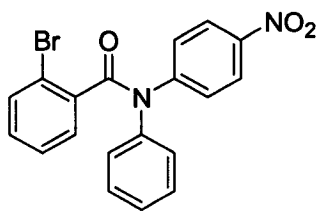
^{1}H NMR (300 MHz, $(CD_3)_2SO$, 373 K): 3.72 (3H, s), 6.86 (2H, d, *J*= 7.5 Hz), 7.10-7.40 (9H, m), 7.47 (2H, d, *J*= 7.2 Hz);

^{13}C NMR (75 MHz, $(CD_3)_2SO$, 373 K): 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 (ν_{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;

Scheme 2.8



2-bromo-*N*-(4-nitrophenyl)-*N*-phenylbenzamide: Synthesized according to general procedure C (68%).

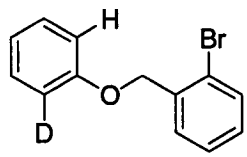
^{1}H NMR (300 MHz, $(CD_3)_2SO$, 373 K): 7.13-7.43 (7H, m), 7.44-7.63 (4H, m), 8.19 (2H, d, *J*= 8.1 Hz);

^{13}C NMR (75 MHz, $(CD_3)_2SO$, 373 K): 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 (ν_{max} /cm^{-1}):1673, 1588, 1491, 1345, 1113, 698;

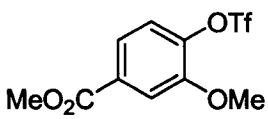
HRMS calculated for $C_{19}H_{13}N_2BrO_3$ (M+) 396.0110; Found: 396.0090

Equation 2.6



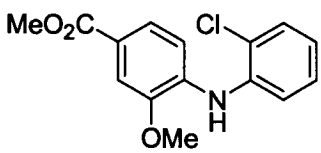
(2-bromobenzyloxy)-2-*d*-benzene (**2.38**): Synthesized according to a previous report and exhibited spectral data (92%).[40]

Scheme 2.11



4-(methoxycarbonyl)-2-methoxyphenyl trifluoromethanesulfonate (**2.46**): Synthesized according to a previous report and exhibited spectral data (92%).[112]

Scheme 2.11



Methyl 4-(2-chlorophenylamino)-3-methoxybenzoate (**2.47**): Synthesized according to general procedure F but with aryl triflate instead of iodide (85%).

^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): 3.89 (3H, s), 3.98 (3H, s), 6.80 (1H, s), 6.95 (1H, t, *J*= 7.5 Hz), 7.23 (2H, m), 7.41 (1H, d, *J*= 7.5 Hz), 7.50 (1H, d, *J*= 7.8 Hz), 7.56 (1H, s), 7.62 (1H, d, *J*= 7.8 Hz)

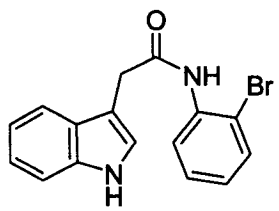
^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): 51.9, 55.9, 111.2, 112.2, 119.3, 121.3, 122.8, 123.5, 124.7, 127.4, 130.1, 136.6, 137.7, 147.4, 167.0

IR (ν_{max} /cm^{-1}): 3401, 2950, 1711, 1585, 1530, 1354, 1275, 1231, 1125, 747;

HRMS calculated for $C_{15}H_{14}ClNO_3$ (M+) 291.0662; Found: 291.0636;

mp 106-108 °C ($CHCl_3$)

Scheme 2.12



N-(2-bromophenyl)-2-(1H-indol-3-yl)acetamide (**2.50**): Synthesized according to general procedure C (88%).

^1H NMR (300 MHz, $CDCl_3$, 293 K, TMS): 3.95 (2H, s), 6.88 (1H, td, *J*= 1.8 Hz & 7.5 Hz), 7.16 (1H, td, *J*= 1.2 Hz & 8.1 Hz), 7.21-7.30 (3H, m), 7.33-7.45 (2H, m), 7.63 (1H, d, *J*= 8.1 Hz), 8.03 (1H, s), 8.38 (1H, dd, *J*= 1.2 Hz & 8.7 Hz), 8.46 (1H, s)HH;

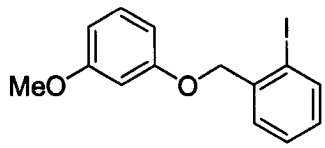
^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): 34.7, 108.2, 111.4, 113.2, 118.8, 120.3, 121.4, 122.9, 124.1, 125.0, 126.9, 128.2, 132.1, 135.6, 136.5, 169.9;

IR (ν_{max} /cm^{-1}): 3407, 3340, 1673, 1595, 1521, 1435, 1301, 743;

HRMS calculated for $C_{16}H_{13}BrN_2O$ (M+) 328.0211; Found: 328.0224;

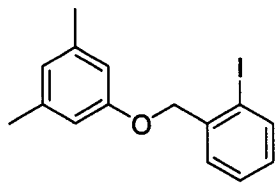
mp 133-135 °C ($CHCl_3$)

Table 3.1, entry 1



1-((3-methoxyphenoxy)methyl)-2-iodobenzene: Synthesized according to general procedure A and exhibited spectral data identical to previous reports (95%).[106]

Table 3.1, entry 3



1-((3,5-dimethylphenoxy)methyl)-2-iodobenzene: Synthesized according to general procedure A (94%).

^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): 2.30 (6H, s), 5.00 (2H, s), 6.62 (3H, m), 7.01 (1H, td, *J*= 1.5 Hz & 7.8 Hz), 7.36 (1H, td, *J*= 1.2 Hz & 7.8 Hz), 7.51 (1H, dd, *J*= 0.75 Hz & 7.8 Hz), 7.85 (1H, dd, *J*= 0.9 Hz & 7.8 Hz);

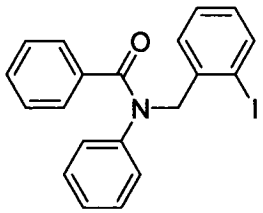
^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): 21.5, 73.7, 97.2, 112.6, 123.0, 128.3, 128.6, 129.4, 139.2, 139.3, 139.4, 158.4;

IR (ν_{max} /cm^{-1}) 2917, 2865, 1295, 828, 748;

HRMS calculated for $C_{15}H_{15}IO$ (M^+) 338.0168; Found: 338.0172;

mp 42-43 °C

Table 3.1, entry 5



N-(2-iodobenzyl)-*N*-phenylbenzamide: Synthesized according to general procedure I (87%).

^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): 5.19 (2H, s), 6.92 (3H, m), 7.06-7.45 (10H, m), 7.79 (1H, d, *J*= 8.1 Hz);

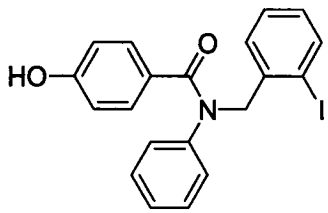
^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): 58.4, 98.6, 126.7, 127.3, 127.8, 128.4, 128.5, 128.8, 128.9, 129.0, 129.8, 135.6, 139.2, 139.5, 143.2, 170.6;

IR (ν_{max} /cm^{-1}) 3064, 3031, 2851, 1648, 1376, 1247, 759, 736;

HRMS calculated for $C_{20}H_{16}INO$ (M^+ $C_{20}H_{16}NO$) 286.1232; Found: 286.1229;

mp 122-125 °C

Table 3.1, entry 7



N-(2-iodobenzyl)-4-hydroxy-*N*-phenylbenzamide: Synthesized according to general procedure H (78%).

^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): 5.14 (s, 2H), 6.49 (2H, d, *J*= 8.2 Hz), 6.92 (3H, m), 7.08-7.20 (5H, m), 7.27 (1H, t, *J*= 7.3 Hz), 7.37 (1H, d, *J*= 7.3 Hz), 7.77 (1H, d, *J*= 7.3 Hz), 8.40 (1H, s);

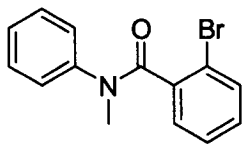
^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): 59.1, 98.5, 114.9, 125.8, 126.8, 127.1, 128.2, 128.4, 129.0, 131.0, 138.9, 139.5, 143.4, 158.6, 171.4;

IR (ν_{max} /cm^{-1}) 3261, 1607, 1579, 1388, 1280, 1013, 759;

HRMS calculated for $C_{20}H_{16}INO_2$ (M^+) 429.0226; Found: 429.0210;

mp 155-158 °C

Table 3.1, entry 9



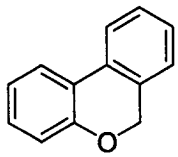
2-bromo-*N*-methyl-*N*-phenylbenzamide: Synthesized according to general procedure H and exhibited spectral data identical to previous reports (94%).[113]

Products

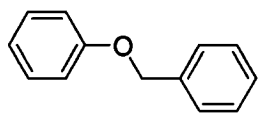
General procedure for intramolecular direct arylation:

Crushed K_2CO_3 (2 equiv.), substrate (1 equiv.) (unless otherwise noted 0.36 mmol), $Pd(OAc)_2$ (appropriate amount) and $PCy_3 - HBF_4$ (2 equiv. per Pd) were placed in a 2 mL screw-cap vial equipped with a magnetic stir. The vial was purged with argon and 1.8 mL of 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.

Scheme 1.19

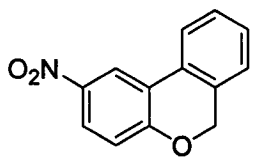


6H-benzo[c]chromene (**1.80**): Synthesized according to the general procedure for direct arylation and exhibited spectral data identical to previous reports (94%).[2]



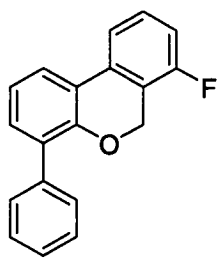
1-(phenoxymethyl)benzene (**1.81**): Exhibited spectral data identical to previous reports.[114]

Table 2.2, entry 1



2-nitro-6H-benzo[c]chromene: Synthesized according to the general procedure for direct arylation and exhibited spectral data identical to previous reports (97%).[46]

Table 2.2, entry 2



7-fluoro-4-phenyl-6H-benzo[c]chromene: Synthesized according to the general procedure for direct arylation (92%).

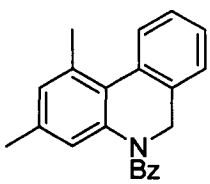
^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): 5.16 (2H, s), 6.98 (1H, t, *J*= 8.7 Hz), 7.10 (1H, t, *J*= 8.1 Hz), 7.28-7.37 (3H, m), 7.38-7.51 (3H, m), 7.54 (2H, m), 7.68 (1H, dd, *J*= 2.1 Hz & 8.1 Hz);

^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): 61.9 (d, *J*= 4.4 Hz), 114.3 (d, *J*= 20.7 Hz), 118.0 (d, *J*= 3.2 Hz), 122.1, 122.7 (d, *J*= 3.3 Hz), 123.0, 127.2, 128.1, 129.2, 129.3, 129.4, 131.1, 131.2, 132.7 (d, *J*= 4.4 Hz), 137.7, 151.5, 157.9 (d, *J*= 243.2 Hz);

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;

Table 2.2, entry 3



N-benzoyl-1,3-dimethyl-(6H)phenanthridine: Synthesized according to the general procedure for direct arylation (89%).

^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): 2.16 (6H, s), 4.86 (2H, s), 7.40-7.60 (6H, m), 7.79 (1H, m), 7.84 (1H, d, *J*= 8.4 Hz), 7.91 (1H, dd, *J*= 2.4 Hz & 7.2 Hz), 8.06 (1H, m), 8.54 (1H, d, *J*= 7.8 Hz);

^{13}C NMR (75 MHz, $CDCl_3$, 293 K, 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.

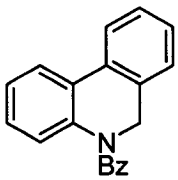
IR (v_{max} /cm^{-1}): 3380, 2946, 1646, 753, 691;

HRMS: calculated for $C_{22}H_{19}NO$ (M^+): 313.1467; Found: 313.1438

Table 2.2, entry 4

5,6-dihydro-5-mesylphenanthridine: Synthesized according to the general procedure for direct arylation and exhibited spectral data identical to previous reports (94%).[115]

Table 2.2, entry 5 & Table 3.1, entry 5



N-benzoyl-(6H)phenanthridine: Synthesized according to the general procedure for direct arylation (97%).

^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): 5.02 (2H, s), 6.72 (1H, s), 6.97 (1H, t, *J*= 8.2 Hz), 7.11-7.48 (9H, m), 7.78 (1H, d, *J*= 7.5 Hz), 7.84 (1H, d, *J*= 8.2 Hz);

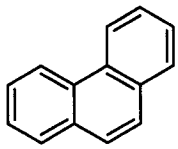
^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): 46.8, 123.3, 124.2, 125.5, 126.4, 127.3, 128.0, 128.1, 128.2, 128.5, 129.0, 130.1, 131.7, 134.3, 135.1, 138.2, 169.1;

IR (ν_{max} /cm^{-1}) 3064, 2851, 1650, 1374, 1350, 761, 736;

HRMS calculated for $C_{20}H_{15}NO$ (M^+) 285.1154; Found: 285.1162;

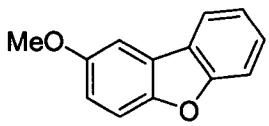
mp 115-117 °C

Table 2.2, entry 6



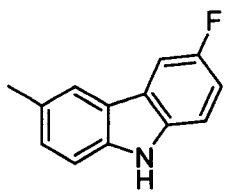
Phenanthrene: Synthesized according to the general procedure for direct arylation and exhibited spectral data identical to previous reports (87%).[116]

Table 2.2, entry 7



2-methoxydibenzofuran: Synthesized according to the general procedure for direct arylation and exhibited spectral data identical to previous reports (81%).[117]

Table 2.2, entry 8



3-fluoro-6-methyl-9H-carbazole: Synthesized according to the general procedure for direct arylation (88%).

^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): 2.50 (3H, s), 7.10 (1H, td, *J*= 2.2 Hz & 8.8 Hz), 7.23 (3H, m), 7.66 (1H, dd, *J*= 2.7 Hz & 8.4 Hz), 7.77 (2H, m);

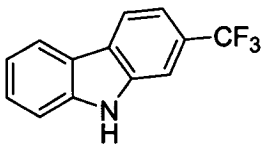
^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): 21.8, 106.3 (d, *J*= 23.2 Hz), 111.0, 111.5 (d, *J*= 8.7 Hz), 113.8 (d, *J*= 25.3 Hz), 120.8, 123.6 (d, *J*= 4.4 Hz), 124.0 (d, *J*= 9.8 Hz), 128.2, 129.2, 136.4, 139.1, 157.8 (d, *J*= 234.9 Hz);

IR (ν_{max} /cm^{-1}): 3401, 1578, 1463, 1142, 869, 808;

HRMS calculated for $C_{13}H_{10}NF$ (M+): 199.0797; Found: 199.0792;

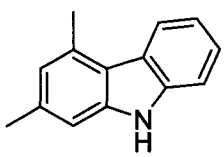
mp 175-177 °C ($CHCl_3$)

Table 2.2, entry 9



2-(trifluoromethyl)-9H-carbazole: Synthesized according to the general procedure for direct arylation and exhibited spectral data identical to previous reports (87%).[46]

Table 2.2, entry 10



2,4-dimethyl-9H-carbazole: Synthesized according to the general procedure for direct arylation (78%).

^1H NMR (300 MHz, $CDCl_3$, 293 K, TMS): 2.50 (3H, s), 2.86 (3H, s), 6.90 (2H, d, *J*= 6.3 Hz), 7.24-7.42 (3H, m), 7.70 (1H, s), 8.16 (1H, d, *J*= 7.8 Hz);

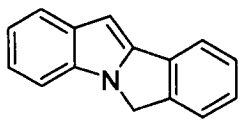
^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): 20.7, 21.8, 108.3, 110.3, 119.2, 122.1, 122.2, 122.5, 123.9, 124.6, 132.9, 135.8, 139.4, 139.9;

IR (ν_{max} /cm^{-1}): 3406, 1457, 834, 726;

HRMS: calculated for $C_{14}H_3N$ (M^+): 195.1048; Found: 195.1040

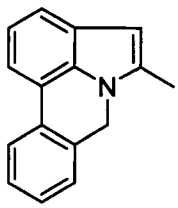
mp 148-149 °C

Table 2.2, entry 11



6H-isoindolo[2,1-a]indole: Synthesized according to the general procedure for direct arylation and exhibited spectral data identical to previous reports (91%).[46]

Table 2.2, entry 12



5-methyl-7H-pyrrolo[3,2,1-de]phenanthridine: Synthesized according to the general procedure for direct arylation (82%).

Caution! – This compound must be kept under nitrogen as it decomposes to air.

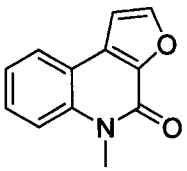
^{1}H NMR (500 MHz, $CDCl_3$, 293 K, TMS): 2.34 (3H, s), 5.26 (2H, s), 6.20 (1H, s), 7.01 (1H, t, *J*= 8.0 Hz), 7.09 (1H, d, *J*= 8.0 Hz), 7.18 (1H, td, *J*= 7.0 Hz & 1.0 Hz), 7.27 (1H, t, *J*= 8.0 Hz), 7.37 (2H, m), 7.85 (1H, d, *J*= 8.0 Hz);

^{13}C NMR (125 MHz, $CDCl_3$, 293 K, 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 (ν_{max} /cm^{-1}):3060, 1548, 1395, 1349, 753;

HRMS calculated for $C_{16}H_{13}N$ (M+): 219.1048; Found: 219.1030;

Table 2.2, entry 13



5-methylfuro[2,3-c]quinoli*N*-4(5H)-one: Synthesized according to the general procedure for direct arylation (83%).

^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): 3.76 (3H, s), 7.01 (1H, d, *J*= 1.9 Hz), 7.30 (1H, t, *J*= 7.0 Hz), 7.39 (1H, d, *J*= 8.7 Hz), 7.51 (1H, td, *J*= 1.4 Hz & 7.3 Hz), 7.80 (2H, m);

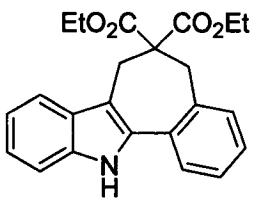
^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): 29.1, 105.6, 115.0, 116.2, 122.3, 124.2, 128.5, 129.1, 137.6, 142.0, 153.5, 175.8;

IR (ν_{max} /cm^{-1}): 3095, 1662, 1584, 1233, 895, 805;

HRMS calculated for $C_{12}H_9NO_2$ (M+) 199.0633; Found: 199.0633;

mp 140-142 °C ($CHCl_3$)

Table 2.2, entry 14



5,12-Dihydro-7H-benzo[6,7]cyclohepta[1,2-b]indole-6,6-dicarboxylic acid diethyl ester: Synthesized according to the general procedure for direct arylation (80%).

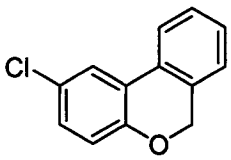
^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): 1.21 (6H, t, *J*= 7.2 Hz), 3.29 (2H, s), 3.38 (2H, s), 4.14 (4H, q, *J*= 7.2 Hz), 7.09-7.29 (3H, m), 7.33 (2H, t, *J*= 7.5 Hz), 7.42 (2H, d, *J*= 7.5 Hz), 7.65 (1H, d, *J*= 7.5 Hz), 8.28 (1H, s);

^{13}C NMR (75 MHz, $CDCl_3$, 293 K, 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 (ν_{max} /cm^{-1}): 2980, 2934, 1715, 1445, 1253, 1219, 1104, 909, 738;

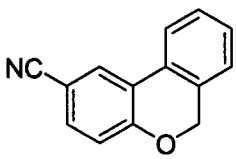
HRMS calculated for $C_{23}H_{23}NO_4$ (M+): 377.1627; Found: 377.1617;

Table 2.3, entry 1



2-chloro-6H-benzo[c]chromene: Synthesized according to the general procedure for direct arylation and exhibited spectral data identical to previous reports (90%).[40]

Table 2.3, entry 2 & Table 3.1, entry 2



6H-benzo[c]chromene-2-carbonitrile: Synthesized according to the general procedure for direct arylation (99%).

^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): 5.16 (2H, s), 6.98 (1H, d, *J*= 7.8 Hz), 7.13 (1H, d, *J*= 7.3 Hz), 7.35 (2H, m), 7.45 (1H, dd, *J*= 8.2 Hz & 1.9 Hz), 7.61 (1H, d, *J*= 7.3 Hz), 7.94 (1H, d, *J*= 2.1 Hz);

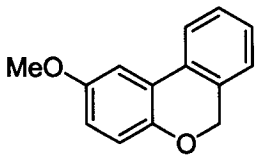
^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): 68.6, 105.5, 118.5, 119.1, 122.1, 123.7, 124.9, 127.6, 127.8, 128.9, 129.0, 130.6, 133.1, 158.1;

IR (ν_{max} /cm^{-1}): 2224, 1609, 1493, 1248, 1011, 824;

HRMS calculated for $C_{14}H_9NO$ (M+) 207.0684; Found: 207.0697;

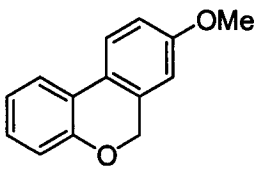
mp 85-87 °C ($CHCl_3$)

Table 2.3, entry 3 and Table 2.6, entry 1



2-methoxy-6H-benzo[c]chromene: Synthesized according to the general procedure for direct arylation and exhibited spectral data identical to previous reports (92%).[106]

Table 2.3, entry 3 & Table 3.1, entry 4



8-methoxy-6H-benzo[*c*]chromene: Synthesized according to the general procedure for direct arylation (75%).

^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): 3.81 (3H, s), 5.07 (2H, s), 6.66 (1H, d, *J*= 2.5 Hz), 6.88 (1H, dd, *J*= 2.6 Hz & 8.5 Hz), 6.99 (2H, m), 7.17 (1H, td, *J*= 1.5 Hz & 7.7 Hz), 7.63 (2H, m);

^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): 55.3, 68.4, 110.0, 113.9, 117.2, 122.1, 122.6, 122.9, 122.9, 123.4, 128.4, 133.0, 153.9, 159.3;

IR (ν_{max} /cm^{-1}) 3066, 2936, 2836, 1605, 1408, 1321, 1277, 1168, 846, 748;

HRMS calculated for $C_{14}H_{12}O_2$ (M^+) 212.0837; Found: 212.0842;

mp 71-73 °C

Table 2.3, entry 5

5,6-dihydro-5-tosylphenanthridine: Synthesized according to the general procedure for direct arylation (97%).

^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): 2.13 (3H, s), 4.84 (2H, s), 6.68 (2H, d, *J*= 8.1 Hz), 6.93 (2H, d, *J*= 8.1 Hz), 7.08 (3H,m), 7.20 (1H, m), 7.35 (2H,m), 7.57 (1H, dd, *J*= 8.4 Hz & *J*= 1.5 Hz), 7.79 (1H, dd, *J*= 8.4 Hz & 1.5 Hz);

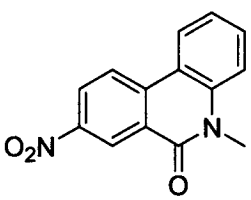
^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): 21.2, 49.8, 122.9, 123.7, 126.0, 127.0, 127.4, 127.5, 127.8, 128.1, 128.3, 130.6, 130.9, 131.3, 134.4, 135.9, 142.8; There is also an overlapping carbon signal as 1 peak is missing even with prolonged scans.

IR (ν_{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;

mp 83-85 °C ($CHCl_3$)

Table 2.3, entry 6



5-methyl-8-nitrophenanthridi*N*-6(5H)-one: Synthesized according to the general procedure for direct arylation (84%).

^{1}H NMR (300 MHz, $(CD_3)_2SO$, 373 K): 3.76 (3H, s), 7.42 (1H, t, *J*= 7.0 Hz), 7.63 (1H, d, *J*= 8.0 Hz), 7.73 (1H, t, *J*= 7.0 Hz), 8.51 (2H, m), 8.71 (1H, d, *J*= 9.0 Hz), 9.06 (1H, d, *J*= 3.0 Hz);

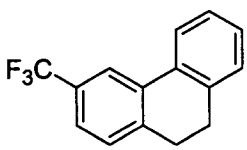
^{13}C NMR (75 MHz, $(CD_3)_2SO$, 373 K): 29.3, 98.8, 115.1, 116.6, 122.3, 122.7, 123.9, 124.2, 125.5, 131.2, 137.8, 138.3, 146.3, 158.8;

IR (ν_{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;

mp 290-293 °C ($CHCl_3$)

Table 2.3, entry 7



3-(trifluoromethyl)-9,10-dihydrophenanthrene: Synthesized according to the general procedure for direct arylation (87%).

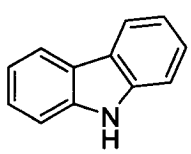
^1H NMR (300 MHz, $CDCl_3$, 293 K, TMS): 2.88 (4H, m), 7.21-7.36 (4H, m), 7.45 (1H, d, 7.5 Hz), 7.76 (1H, d, *J*= 7.2 Hz), 7.96 (1H, s);

^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): 28.6, 29.0, 120.5 (q, *J*= 4.4 Hz), 120.5, 123.8 (q, *J*= 4.4 Hz), 123.8, 124.6 (q, *J*= 270.6 Hz), 127.3, 128.4, 128.5, 129.4 (1, *J*= 32.7 Hz), 133.2, 135.2, 137.3, 141.2;

IR (ν_{max} /cm^{-1}): 3064, 2942, 1701, 1417, 1335, 1167, 1122, 1077, 830, 767;

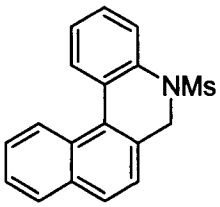
HRMS calculated for $C_{15}H_{11}F_3$ (M+): 248.0813; Found: 248.0795;

Table 2.3, entry 8 & Table 3.1, entry 11



9H-Carbazole: Synthesized according to the general procedure for direct arylation and exhibited spectral data identical to previous reports (94%).[118]

Table 2.3, entry 9



5,6-dihydro-5-mesylbenzo[k]phenanthridine: Synthesized according to the general procedure for direct arylation (98%).

^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): 2.06 (2H, s), 2.63 (3H, s), 6.86 (1H, s), 7.20-7.42, (8H, m), 7.80 (1H, d, *J*= 7.8 Hz);

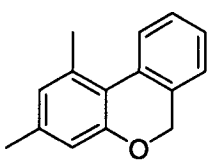
^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): 20.9, 22.8, 124.0, 125.7, 125.9, 126.0, 126.9, 127.1, 127.3, 127.9, 128.9, 129.0, 129.9, 130.3, 132.1, 135.1, 135.3, 136.6;

IR (v_{max} /cm^{-1}): 1646, 1373, 1233, 741;

HRMS: calculated for $C_{18}H_{15}NO_2S(M^+)$: 309.0823; Found: 309.0817

mp 161-162 °C

Table 2.3, entry 10 & Table 3.1, entry 3



1,3-dimethyl-6H-benzo[c]chromene (**2.22**): Synthesized according to the general procedure for direct arylation (86%).

^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): 2.31 (3H, s), 2.64 (3H, s), 4.92 (2H, s), 6.75 (2H, d, *J*= 9.3 Hz), 7.20-7.29 (2H, m), 7.36 (1H, td, *J*= 1.2 Hz & 7.5 Hz), 7.73 (1H, d, *J*= 7.8 Hz);

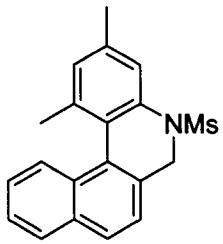
^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): 21.6, 23.0, 69.5, 115.8, 120.9, 125.2, 126.4, 126.8, 126.9, 128.2, 131.2, 133.8, 135.6, 139.1, 156.8;

IR (v_{max} /cm^{-1}): 1615, 1284, 1151, 1064, 735

HRMS: calculated for $C_{15}H_{14}O$ (M^+): 210.1045; Found: 210.1056

mp 82-83 °C

Table 2.3, entry 11



5,6-dihydro-1,3-dimethyl-5-mesylbenzo[k]phenanthridine: Synthesized according to the general procedure for direct arylation (97%).

^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): 1.86 (3H, s), 2.19 (3H, s), 2.45 (3H, s), 4.45 (1H, d, *J*= 16.2 Hz), 5.11 (1H, dd, *J*= 1.2 Hz & 16.8 Hz), 7.17 (1H, s), 7.50 (4H, m), 7.70 (1H, m), 7.84 (2H, m);

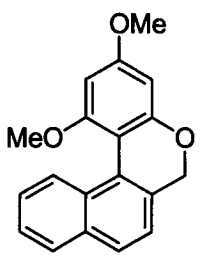
^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): 21.3, 22.6, 37.9, 51.5, 123.6, 125.4, 125.8, 126.1, 126.4, 127.4, 128.4, 128.6, 128.8, 129.3, 131.1, 133.7, 134.4, 136.3, 138.4, 138.6;

IR (ν_{max} /cm^{-1}): 1345, 1157, 1061, 756;

HRMS: calculated for $C_{20}H_{19}NO_2S$ (M^+): 337.1136; Found: 337.1135

mp 150-151 °C

Table 2.3, entry 12



1,3-dimethoxy-6H-naphtho[2,1-c]chromene: Synthesized according to the general procedure for direct arylation (90%).

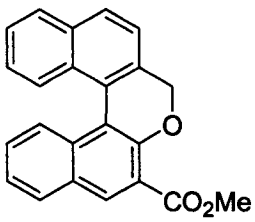
^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): 3.80 (3H, s), 3.86 (3H, s), 5.03 (2H, s), 6.39 (2H, dd, *J*= 2.4 Hz & 12.3 Hz), 7.31 (1H, d, *J*= 8.4 Hz), 7.38-7.47 (2H, m), 7.78 (3H, m);

^{13}C NMR (75 MHz, $CDCl_3$, 293 K, 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

Table 2.3, entry 13



4H-3-Oxa-dibenzo[c,g]phenanthrene-2-carboxylic acid methyl ester: Synthesized according to the general procedure for direct arylation (85%).

^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): 4.00 (3H, s), 4.98 (1H, d, *J*= 12.6 Hz), 5.37 (1H, d, *J*= 12.6 Hz), 7.24-7.48 (5H, m), 7.62 (2H, m), 7.88-7.97 (3H, m), 8.45 (1H, s);

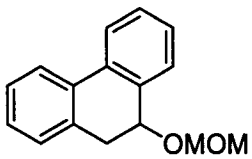
^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): 52.4, 71.1, 119.9, 121.2, 122.7, 125.4, 125.5, 125.9, 126.8, 126.9, 127.4, 128.5, 128.6, 128.7, 128.9, 129.3, 132.1, 132.9, 133.7, 134.3, 154.3, 166.2;

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

Table 2.5, entry 3 & Table 3.1, entry 8



9,10-dihydro-9-(methoxymethoxy)phenanthrene: Synthesized according to the general procedure for direct arylation and exhibited spectral data identical to previous reports (85%).

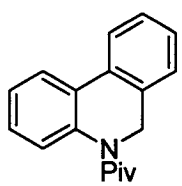
^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): 3.15 (2H, dd, *J*= 3.5 Hz & 4.6 Hz), 3.36 (3H, s), 4.65 (2H, dd, *J*= 7.0 Hz & 11.8 Hz), 4.82 (1H, t, *J*= 4.8 Hz), 7.22-7.33 (4H, m), 7.41 (2H, m), 7.80 (2H, t, *J*= 7.0 Hz);

^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): 35.2, 55.3, 71.7, 94.1, 123.5, 124.1, 127.2, 127.4, 127.9, 128.3, 128.9, 129.2, 133.7, 133.7, 133.9, 134.9;

IR (ν_{max} /cm^{-1}) 3067, 3033, 2941, 2887, 1327, 1147, 1096, 1041, 755, 740;

HRMS calculated for $C_{16}H_{16}O_2$ (M^+) 240.1150; Found: 240.1150

Table 2.5, entry 4, 5 & Table 3.1, entry 6



N-(2,2-dimethylpropanoyl)-(6H)phenanthridine: Synthesized according to the general procedure for direct arylation and exhibited spectral data identical to previous reports (94%, 86%).

^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): 1.34 (9H, s), 4.82 (2H, s), 7.28 (4H, m), 7.39 (1H, t, *J*= 7.4 Hz), 7.55 (1H, d, *J*= 7.5 Hz), 7.76 (2H, m);

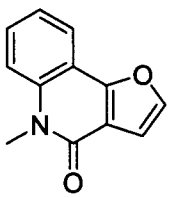
^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS): 28.9, 39.8, 49.1, 123.5, 124.0, 125.3, 125.8, 126.3, 127.3, 127.7, 128.3, 132.5, 134.4, 138.9, 177.4;

IR (ν_{max} /cm^{-1}) 3068, 2973, 1650, 1358, 1168, 764, 738;

HRMS calculated for $C_{18}H_{19}NO$ (M^+) 265.1467; Found: 265.1451;

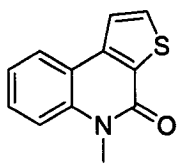
mp 114-116 °C

Table 2.5, entry 6



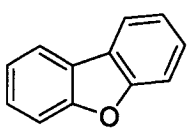
5-methylfuro[3,2-c]quinoli*N*-4(5H)-one: Synthesized according to the general procedure for direct arylation and exhibited spectral data identical to previous reports (81%).[32]

Table 2.5, entry 7



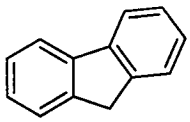
5-methylthieno[2,3-c]quinoli*N*-4(5H)-one: Synthesized according to the general procedure for direct arylation and exhibited spectral data identical to previous reports (88%).[32]

Table 2.5, entry 8 & Table 3.1, entry 10



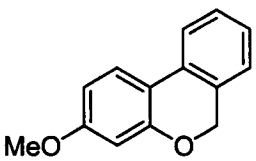
Dibenzofuran: Synthesized according to the general procedure for direct arylation and exhibited spectral data identical to previous reports (99%).[119]

Table 2.5, entry 9 & Table 3.1, entry 12



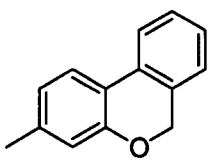
Fluorene: Synthesized according to the general procedure for direct arylation and exhibited spectral data identical to previous reports (81%).[120]

Table 2.6, entry 1 & Table 3.1, entry 1



3-methoxy-6H-benzo[c]chromene: Synthesized according to the general procedure for direct arylation and exhibited spectral data identical to previous reports.[106]

Table 2.6, entry 2



3-methyl-6H-benzo[c]chromene: Synthesized according to the general procedure for direct arylation and exhibited spectral data identical to previous reports.

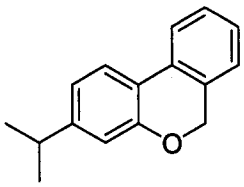
^{1}H NMR (500 MHz, $(CD_3)_2CO$, 293 K): 2.31 (3H, s), 5.09 (2H, s), 6.79 (1H, s), 6.88 (1H, d, *J*= 7.5 Hz), 7.22 (1H, d, *J*= 7.5 Hz), 7.27 (1H, t, *J*= 7.5 Hz), 7.37 (1H, t, *J*= 7.5 Hz), 7.69 (1H, d, *J*= 8.0 Hz), 7.73 (1H, d, *J*= 8.0 Hz);

^{13}C NMR (125 MHz, $(CD_3)_2CO$, 293 K): 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 (ν_{max} /cm^{-1}): 2963, 2844, 1618, 1484, 1151, 1031, 766;

HRMS calculated for $C_{14}H_{12}O$ (M+) 196.0888; Found: 196.0876;

Table 2.6, entry 3



3-isopropyl-6H-benzo[c]chromene: Synthesized according to the general procedure for direct arylation and exhibited spectral data identical to previous reports.

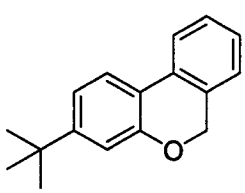
^{1}H NMR (500 MHz, $(CD_3)_2CO$, 293 K): 1.24 (6H, d, *J*= 7.0 Hz), 2.89 (1H, sept, *J*= 7.0 Hz), 5.10 (2H, s), 6.85 (1H, d, *J*= 1.5 Hz), 6.96 (1H, dd, *J*= 7.5 Hz & 1.5 Hz), 7.23 (1H, d, *J*= 7.5 Hz), 7.28 (1H, td, *J*= 7.5 Hz & 1.0 Hz), 7.37 (1H, td, *J*= 7.0 Hz & 1.0 Hz), 7.75 (2H, m);

^{13}C NMR (125 MHz, $(CD_3)_2CO$, 293 K): 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 (ν_{max} /cm^{-1}): 2958, 1590, 1482, 1026, 730;

HRMS calculated for $C_{16}H_{16}O$ (M+) 224.1201; Found: 224.1212;

Table 2.6, entry 4



3-*tert*-butyl-6H-benzo[c]chromene: Synthesized according to the general procedure for direct arylation and exhibited spectral data identical to previous reports.

^{1}H NMR (500 MHz, $(CD_3)_2CO$, 293 K): 1.32 (9H, s), 5.11 (2H, s), 6.99 (1H, d, *J*= 2.0 Hz), 7.12 (1H, dd, *J*= 8.0 Hz & 2.0 Hz), 7.23 (1H, d, *J*= 7.0 Hz), 7.28 (1H, td, *J*= 7.5 Hz & 1.0 Hz), 7.37 (1H, td, *J*= 7.5 Hz & 1.0 Hz), 7.75 (2H, m);

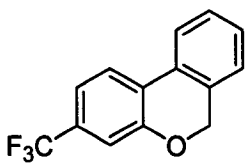
^{13}C NMR (125 MHz, $(CD_3)_2CO$, 293 K): 32.4, 36.2, 69.8, 115.8, 121.1, 121.9, 123.4, 124.8, 126.5, 129.2, 130.2, 131.9, 133.2, 154.9, 156.5;

IR (ν_{max} /cm^{-1}): 3037, 2963, 1589, 1782, 1275, 1031, 733;

HRMS calculated for $C_{17}H_{18}O$ (M+) 238.1358; Found: 238.1361;

mp 58-59 °C (Acetone)

Table 2.6, entry 5



3-(trifluoromethyl)-6H-benzo[c]chromene: Synthesized according to the general procedure for direct arylation and exhibited spectral data identical to previous reports.

^1H NMR (500 MHz, $(CD_3)_2CO$, 293 K): 5.23 (2H, s), 7.24 (1H, s), 7.31 (1H, d, *J*= 7.5 Hz), 7.39 (2H, m), 7.45 (1H, t, *J*= 6.5 Hz), 7.88 (1H, d, *J*= 8 Hz), 8.05 (1H, d, *J*= 8 Hz);

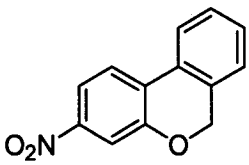
^{13}C NMR (125 MHz, $(CD_3)_2CO$, 293 K): 70.0, 116.0 (q, *J*= 3.8 Hz), 120.4 (q, *J*= 3.9 Hz), 124.5, 125.9 (q, *J*= 269.9 Hz), 126.2, 126.9, 128.4, 130.3, 130.6, 131.0, 132.3 (q, *J*= 32.4), 133.8, 156.8;

IR (ν_{max} /cm^{-1}): 1422, 1337, 1170, 1118, 883, 772;

HRMS calculated for $C_{15}H_{12}O_3$ (M+) 250.0605; Found: 250.0582;

mp 67-69 °C (Acetone)

Table 2.6, entry 6



3-nitro-6H-benzo[c]chromene: Synthesized according to the general procedure for direct arylation and exhibited spectral data identical to previous reports.

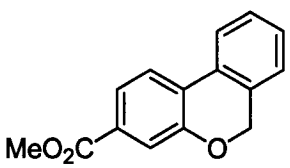
^{1}H NMR (500 MHz, $(CD_3)_2CO$, 293 K): 5.30 (2H, s), 7.37 (1H, d, *J*= 8.0 Hz), 7.45 (2H, m), 7.76 (1H, d, 2.5 Hz), 7.94 (1H, dd, *J*= 9 Hz & 2.5 Hz), 7.97, (1H, m), 8.14 (1H, d, *J*= 9 Hz);

^{13}C NMR (125 MHz, $(CD_3)_2CO$, 293 K): 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 (ν_{max} /cm^{-1}): 2954, 2924, 2854, 1339, 847;

HRMS calculated for $C_{13}H_9NO_3$ (M+) 227.0582; Found: 227.0592

Table 2.6, entry 7



Methyl 6H-benzo[c]chromene-3-carboxylate: Synthesized according to the general procedure for direct arylation and exhibited spectral data identical to previous reports.

^{1}H NMR (500 MHz, $(CD_3)_2CO$, 293 K): 3.88 (3H, s), 5.19 (2H, s), 7.29 (1H, d, *J*= 7.8 Hz), 7.39 (1H, td, *J*= 7.5 Hz & *J*= 1 Hz), 7.43 (1H, t, *J*= 7.5 Hz), 7.53 (1H, d, *J*= 1.5 Hz), 7.68 (1H, dd, *J*= 8.5 Hz & 2 Hz), 7.86 (1H, d, *J*= 8 Hz), 7.94 (1H, d, *J*= 8.5 Hz);

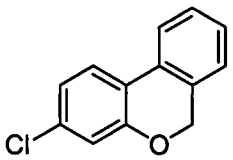
^{13}C NMR (125 MHz, $(CD_3)_2CO$, 293 K): 53.4, 65.1, 69.9, 119.7, 119.8, 124.6, 127.9, 125.4, 126.8, 130.5, 130.7, 130.8, 134.0, 156.5, 167.6;

IR (ν_{max} /cm^{-1}):1707, 1412, 1308, 1233, 1197, 760;

HRMS calculated for $C_{15}H_{12}O_3$ (M+) 240.0786; Found: 240.07887;

mp 93-94 °C (Acetone)

Table 2.6, entry 8



3-chloro-6H-benzo[c]chromene: Synthesized according to the general procedure for direct arylation and exhibited spectral data identical to previous reports.

Characterized as an 3.2:1 mixture

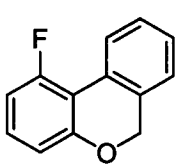
^{1}H NMR (500 MHz, $(CD_3)_2CO$, 293 K): Major: 5.16 (2H, s), 6.99 (1H, d, *J*= 2.0 Hz), 7.08 (1H, dd, *J*= 8.0 Hz & 2.0 Hz), 7.26 (1H, d, *J*= 7.5 Hz), 7.34 (1H, td, *J*= 7.5 Hz & 1.0 Hz), 7.40 (1H, t, *J*= 7.5 Hz), 7.79 (1H, d, *J*= 7.5 Hz), 7.84 (1H, d, *J*= 8.0 Hz);

^{13}C NMR (125 MHz, $(CD_3)_2CO$, 293 K): 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 (ν_{max} /cm^{-1}): 2850, 1479, 1198, 1017, 855;

HRMS calculated for $C_{15}H_{12}O_3$ (M+) 240.0786; Found: 240.0789;

Table 2.6, entry 9



1-fluoro-6H-benzo[c]chromene: Synthesized according to the general procedure for direct arylation and exhibited spectral data identical to previous reports.

Characterized as an 8.03:1 mixture

^{1}H NMR (500 MHz, $(CD_3)_2CO$, 293 K): Major: 5.11 (2H, s), 6.84-6.91 (2H, m), 7.26 (1H, m), 7.32 (1H, d, *J*= 7.5 Hz), 7.36 (1H, td, *J*= 7.0 Hz & 1.0 Hz), 7.43 (1H, t, *J*= 8.0 Hz), 8.00 (1H, d, *J*= 8.0 Hz), Minor: 5.16 (2H, s), 6.75 (1H, dd, *J*= 10.0 Hz & 2,5 Hz), 6.84 (1H, m, overlapping with major), 7.76 (1H, d, *J*= 7.5 Hz), 7.87 (1H, d, *J*= 9.0 Hz & 6.5 Hz), 3H complete overlap with major isomer;

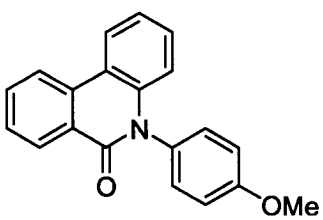
^{19}F NMR (500 MHz, $(CD_3)_2CO$, 293 K): No standard used relative shift given. Major : (8.03F, q, *J*= 7.5 Hz), Minor +3.48 (1F, m);

^{13}C NMR (125 MHz, $(CD_3)_2CO$, 293 K): Major only: 70.2, 111.3 (d, *J*= 22.9 Hz), 113.9 (d, *J*= 13.3), 115.1 (d, *J*= 3.9 Hz), 127.6, 127.7, 128.5, 130.0, 130.4, 131.3 (d, *J*= 11.5 Hz), 133.8, 158.7 (d, *J*= 7.6 Hz), 162.4 (d, 247.9);

IR (ν_{max} /cm^{-1}): 3063, 2839, 1619, 1294, 1228, 762;

HRMS calculated for $C_{13}H_9OF$ (M+) 200.0637; Found: 200.0650;

Scheme 2.8



5-(4-methoxyphenyl)phenanthridi*N*-6(5H)-one: Synthesized according to the general procedure for direct arylation and exhibited spectral data identical to previous reports.

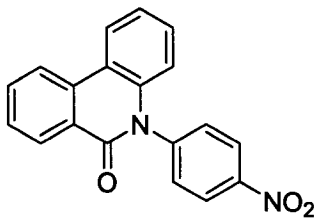
^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS): 3.91 (3H, s), 6.76 (1H, dd, *J*= 7.5 Hz), 1.8 Hz), 7.12 (2H, d, *J*= 8.7), 7.21-7.36 (4H, m), 7.62 (1H, td, *J*= 7.5 Hz & 1.2 Hz), 7.82 (1H, td, *J*= 7.5 Hz & 1.2 Hz), 8.33 (2H, m), 8.56 (1H, dd, *J*= 8.1 Hz & 1.2 Hz);

^{13}C NMR (75 MHz, $CDCl_3$, 293 K, 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 (ν_{max} /cm^{-1}): 2999, 1655, 1607, 1511, 1245, 753;

HRMS calculated for $C_{20}H_{15}O_2N$ (M+) 301.1103; Found: 301.1104;

Scheme 2.8



5-(4-nitrophenyl)phenanthridi*N*-6(5H)-one: Synthesized according to the general procedure for direct arylation and exhibited spectral data identical to previous reports.

Characterized as a 1:2 mixture of isomers.

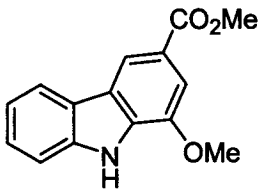
^{1}H NMR (500 MHz, $(CD_3)_2CO$, 293 K): Major: 6.62 (1H, m), 7.57 (2H, d, *J*= 9.0 Hz), 7.60 (1H, m), 7.86 (1H, td, *J*= 8.0 Hz & 1.5 Hz), 8.49 (2H, d, *J*= 8.5 Hz), 8.53 (1H, dd, *J*= 8.0 Hz & 1.0 Hz); Minor: 6.81 (1H, d, *J*= 9.5 Hz), 7.73 (1H, t, *J*= 8.0 Hz), 7.93 (1H, td, *J*= 8.0 Hz & 1.5 Hz), 8.14 (1H, dd, *J*= 9.5 Hz & 2.5 Hz), 8.42 (1H, d, *J*= 8.0 Hz), 8.57 (1H, dd, *J*= 8.0 Hz & 1.5 Hz), 9.21 (1H, d, *J*= 2.0 Hz); Unassigned mixtures: 7.34 (m), 7.65 (m), 8.35 (m);

^{13}C NMR (125 MHz, $(CD_3)_2CO$, 293 K): 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 (ν_{max} /cm^{-1}): 2929, 1661, 1607, 1522, 1345, 751;

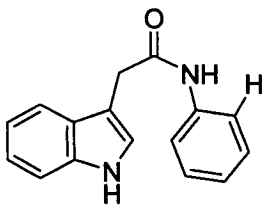
HRMS calculated for $C_{19}H_{12}O_3N_2$ (M+) 316.0848; Found: 316.0840;

Scheme 2.11, Mukonine



Mukonine: Synthesized according to the general procedure for direct arylation and exhibited spectral data identical to previous reports (86%).[121]

Equation 2.7



2-(1H-indol-3-yl)-*N*-phenylacetamide (2.51): Synthesized according to general procedure C (85%).

^{1}H NMR (300 MHz, DMSO, 293 K): 3.73, 6.94-7.12 (3H, m), 7.22-7.40 (4H, m), 7.56-7.64 (3H, m), 10.11 (1H, s), 10.93 (1H, s);

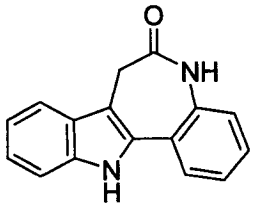
^{13}C NMR (75 MHz, DMSO, 293 K): 33.8, 108.5, 111.3, 118.3, 118.6, 119.0, 120.9, 123.0, 123.8, 127.2, 128.6, 136.0, 139.4, 169.7;

IR (ν_{max} /cm^{-1}) 3414, 3379, 3301, 1661, 1598, 1528, 1497, 1442, 743, 691;

HRMS calculated for $C_{16}H_{14}N_2O$ (M^+) 250.1106; Found: 250.1106;

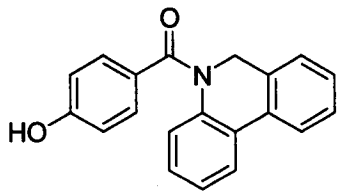
mp 152-153 °C

Scheme 2.12



Paullone: Synthesized according to a previous report and exhibited spectral data (40%).[122]

Table 3.1, entry 7



N-(4-hydroxybenzoyl)-(6H)phenanthridine: Synthesized according to the general procedure for direct arylation (83%).

^{1}H NMR (300 MHz, DMSO, 293 K): 4.90 (2H, s), 6.66 (2H, d, *J*= 8.3 Hz), 6.77 (1H, d, *J*= 8.3 Hz), 7.10 (3H, m), 7.21 (1H, t, *J*= 7.4 Hz), 7.30-7.48 (3H, m), 7.91 (1H, d, *J*= 7.7 Hz), 7.97 (1H, d, *J*= 5.4 Hz), 10.00 (1H, s);

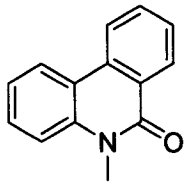
^{13}C NMR (75 MHz, DMSO, 293 K): 46.6, 114.8, 123.3, 124.3, 125.1, 125.1, 125.2, 126.1, 127.3, 127.7, 128.0, 128.2, 130.8, 131.2, 134.1, 138.4 159.5, 168.1;

IR (ν_{max} /cm^{-1}) 3259, 2926, 1608, 1495, 1390, 1230, 757;

HRMS calculated for $C_{20}H_{15}NO_2$ (M^+) 301.1103; Found: 301.1095;

mp 142-144 °C

Table 3.1, entry 9

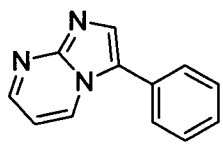


5-methylphenanthridi*N*-6(5H)-one: Synthesized according to the general procedure for direct arylation and exhibited spectral data identical to previous reports (80%).[113]

General procedure for direct arylation of Imidazo[1,2-a]pyrimidine:

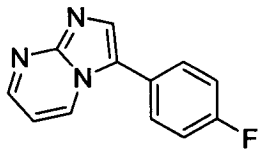
To a mixture of potassium acetate (3 equiv.), $Pd(OH)_2/C$ (0.1 equiv.), imidazo[1,2-a]pyrimidine (1 equiv.) and the appropriate aryl halide (1.1 equiv.), under nitrogen atmosphere, was added DMA (0.2 M) in a 2 mL screw cap vial equipped with a mechanical stir bar. The reaction mixture was then heated overnight at 145 °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 purified via silica gel column chromatography using ethyl acetate/hexanes mixtures.

Table 3.2, entry 1



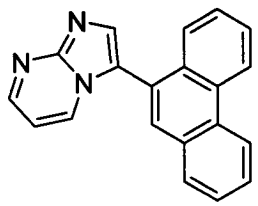
3-phenylimidazo[1,2-a]pyrimidines: Synthesized according to the general procedure for the coupling of imidazo[1,2-a]pyrimidine and exhibited spectral data identical to previous reports (75%).[123]

Table 3.2, entry 2



3-(4-fluorophenyl)imidazo[1,2-a]pyrimidines: Synthesized according to the general procedure for the coupling of imidazo[1,2-a]pyrimidine and exhibited spectral data identical to previous reports (76%).[123]

Table 3.2, entry 3

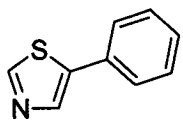


3-(phenanthre*N*-10-yl)imidazo[1,2-a]pyrimidines: Synthesized according to the general procedure for the direct arylation of imidazo[1,2-a]pyrimidine and exhibited spectral data identical to previous reports (81%).[123]

General Procedure for the direct arylation of thiazole:

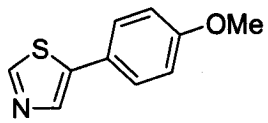
To a mixture of potassium acetate (3 equiv.), $Pd(OH)_2/C$ (0.1 equiv.), thiazole (1 equiv.) and the appropriate aryl halide (3 equiv.), under nitrogen atmosphere, was added DMA (0.2 M) in a 2 mL screw cap vial equipped with a mechanical stir bar. The reaction mixture was then heated overnight at 145 °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 purified via silica gel column chromatography using ethyl acetate/hexanes mixtures.

Table 3.2, entry 4



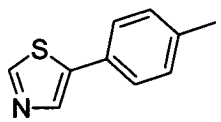
5-phenylthiazole: Synthesized according to the general procedure for the direct arylation of thiazole and exhibited spectral data identical to previous reports (82%).[124]

Table 3.2, entry 5



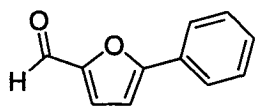
5-(4-methoxyphenyl)thiazole: Synthesized according to the general procedure for the direct arylation of thiazole and exhibited spectral data identical to previous reports (73%).[125]

Table 3.2, entry 6



5-p-tolylthiazole: Synthesized according to the general procedure for the direct arylation of thiazole and exhibited spectral data identical to previous reports (71%).[126]

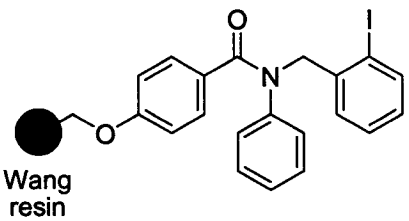
Table 3.2, entry 7



5-Phenyl-2-furaldehyde: To a mixture of potassium acetate (3 equiv.), $Pd(OH)_2/C$ (0.1 equiv.), 2-furaldehyde (3 equiv.) and phenyl bromide (1 equiv.) under nitrogen atmosphere was added DMA (0.2 M) in a 2 mL screw cap vial equipped with a mechanical stir bar. The reaction mixture was then heated overnight at 145 °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 purified via silica gel column chromatography using 2.5% ethyl acetate/hexanes (75%). The compound exhibited spectral data identical to that reported in the literature.[15]

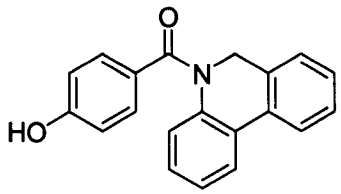
Scheme 3.6



Preparation of resin: To a suspension of Wang resin (0.3 equiv.) and triphenylphosphine (1 equiv.) in dichloromethane (0.2 M) was added a solution of compound **3.12** (1 equiv.) in dichloromethane (0.4 M). The mixture was purged with argon and cooled to 0 °C. A solution of diisopropylazodicarboxylate (1 equiv.) in dichloromethane (0.4 M) was added over one hour via syringe pump. The reaction mixture was refluxed for 48 hours. The reaction mixture was filtered and washed twice with each of the following solvents: dichloromethane, DMF, water, methanol, dichloromethane (a second time) and ether to afford compound **3.9** (0.5 mmol/g of resin).

Capping of free hydroxyls on the resin: To a suspension of the resin **3.9** (1 equiv.) in dichloromethane (0.1 M) was added acetic anhydride (5 equiv.), pyridine (6 equiv.) and 4-(*N,N*-dimethylamino)pyridine (0.01 equiv.). The reaction was stirred for 2 hours at room temperature. The reaction mixture was filtered and washed twice with each of the following solvents: dichloromethane, DMF, water, methanol, dichloromethane (a second time) and ether to afford the acetate protected resin.

Scheme 3.7



Cyclization and cleavage of compound from the resin (**3.13**): After being submitted to the general procedure for cyclization reactions, the resin (1 equiv.) was filtered and washed thoroughly before being stirred in a 1: 1 mixture of trifluoroacetic acid and dichloromethane (0.5 M) for 2 hours. The resulting mixture was filtered and washed twice with each of the following solvents: dichloromethane, DMF, water, methanol, dichloromethane (a second time) and ether. The volatiles were evaporated under reduced pressure and the resulting mixture was extracted with water and ether. The organic phase was dried with $MgSO_4$, filtered and the volatiles were evaporated under reduced pressure. The residue was then purified via silica gel column chromatography using 30% ethyl acetate/hexanes to afford compound **3.13** (see Table 3.1, entry 7).

Claims to Original Research

1. Developed a new catalyst for the intramolecular direct arylation of aryl chlorides, bromides and iodides to generate five, six and seven membered rings. The regioselectivity was studied and demonstrated that both steric and electronic factors play a role in the outcome of the reaction. The methodology was also applied to the synthesis of two natural products: Mukonine and of Paullone.

2. Applied a catalyst based on Pearlman's catalyst ($Pd(OH)_2/C$) to the intramolecular and intermolecular direct arylation of aryl bromides and iodides. Furthermore, it was demonstrated that the heterogeneous catalyst generates soluble palladium species under the reaction conditions and that it is these soluble species that are responsible for the observed catalysis.

3. Publications: i) Campeau, L.-C. ; Parisien, M.; Leblanc, M.; Fagnou, K. **Biaryl Synthesis via Direct Arylation: Establishment of an Efficient Catalyst for Intramolecular Processes**, *J. Am. Chem. Soc.*, **2004**, *126*, 9186. ii) Parisien, M.; Valette, D.; Fagnou, K. **Direct Arylation Reactions Catalyzed by $Pd(OH)_2/C$: Evidence for a Soluble Palladium Catalyst**, *J. Org. Chem.*, **2005**, *124*, 7578. iii) Campeau, L.-C.; Parisien, M.; Jean, A.; Fagnou, K. **Catalytic Direct Arylation with Aryl Chlorides, Bromides and Iodides: Intramolecular Studies Leading to New Intermolecular Reactions**, *J. Am. Chem. Soc.*, **2005**, *Accepted.*

4. Oral Presentation: Parisien, M.; Campeau, L.-C.; Fagnou, K. **Catalytic Direct Arylation with Aryl Chlorides, Bromides and Iodides**, June 3rd 2005, Ottawa-Carleton Chemistry Institute Day (OCCI), Ottawa, Ontario.

5. Poster Presentations: i) Parisien, M.; Campeau, L.-C.; Fagnou, K. **Intramolecular Catalytic Direct Arylation with Aryl Chlorides, Bromides and Iodides** June 10th 2005, Spring Synthesis Symposium, Ottawa, Ontario. ii) Parisien, M.; Fagnou, K. **Catalyst Investigation for Direct Arylation Reactions**, April 28th 2005, Symposium Internationale de Synthèse Organique de l'Université de Montréal (SISOUM), Montréal, Québec - *Winner of Outstanding Poster Award.* iii) Parisien, M.; Fagnou, K. **Catalyst Investigation for Direct Arylation Reactions**, November 6th 2004, Quebec, Ontario Mini-Symposium of Bio-Organic Chemistry (QOMSBOC), Gatineau, Québec. iv) Parisien, M.; Fagnou, K. **Rational Design of Ligands for Biaryl Synthesis via Direct Arylation**, May 5th 2004, Ottawa-Carleton Chemistry Institute Day (OCCI), Ottawa, Ontario. v) Parisien, M.; Fagnou, K. **Rational Design of Ligands for Biaryl Synthesis via Direct Arylation**, May 4th 2004, Spring Synthesis Symposium, Ottawa, Ontario.

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Spectra

Included are selected representative spectra
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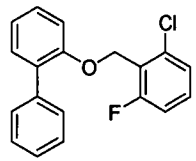

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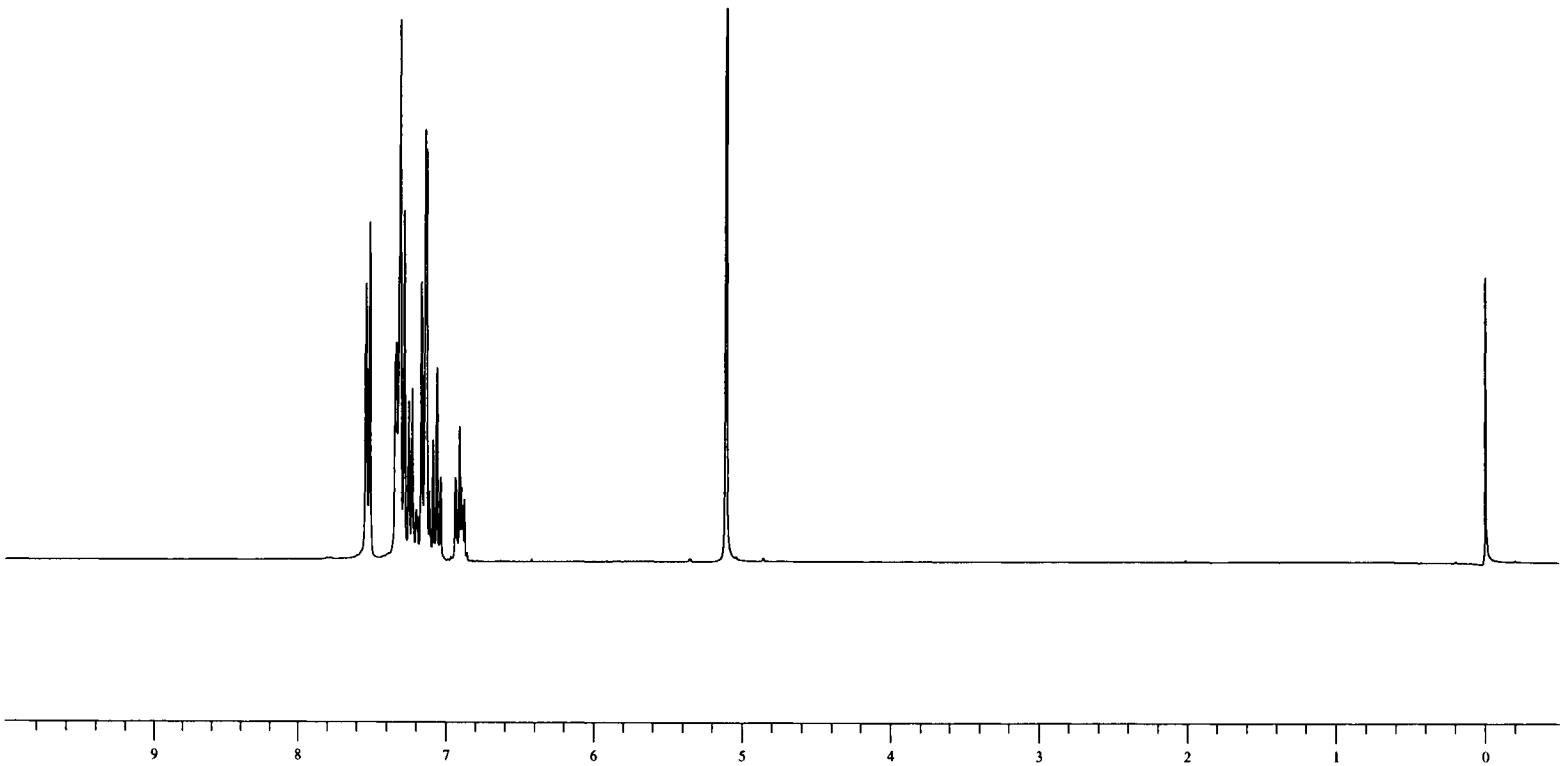

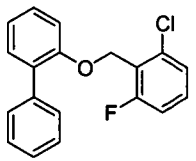

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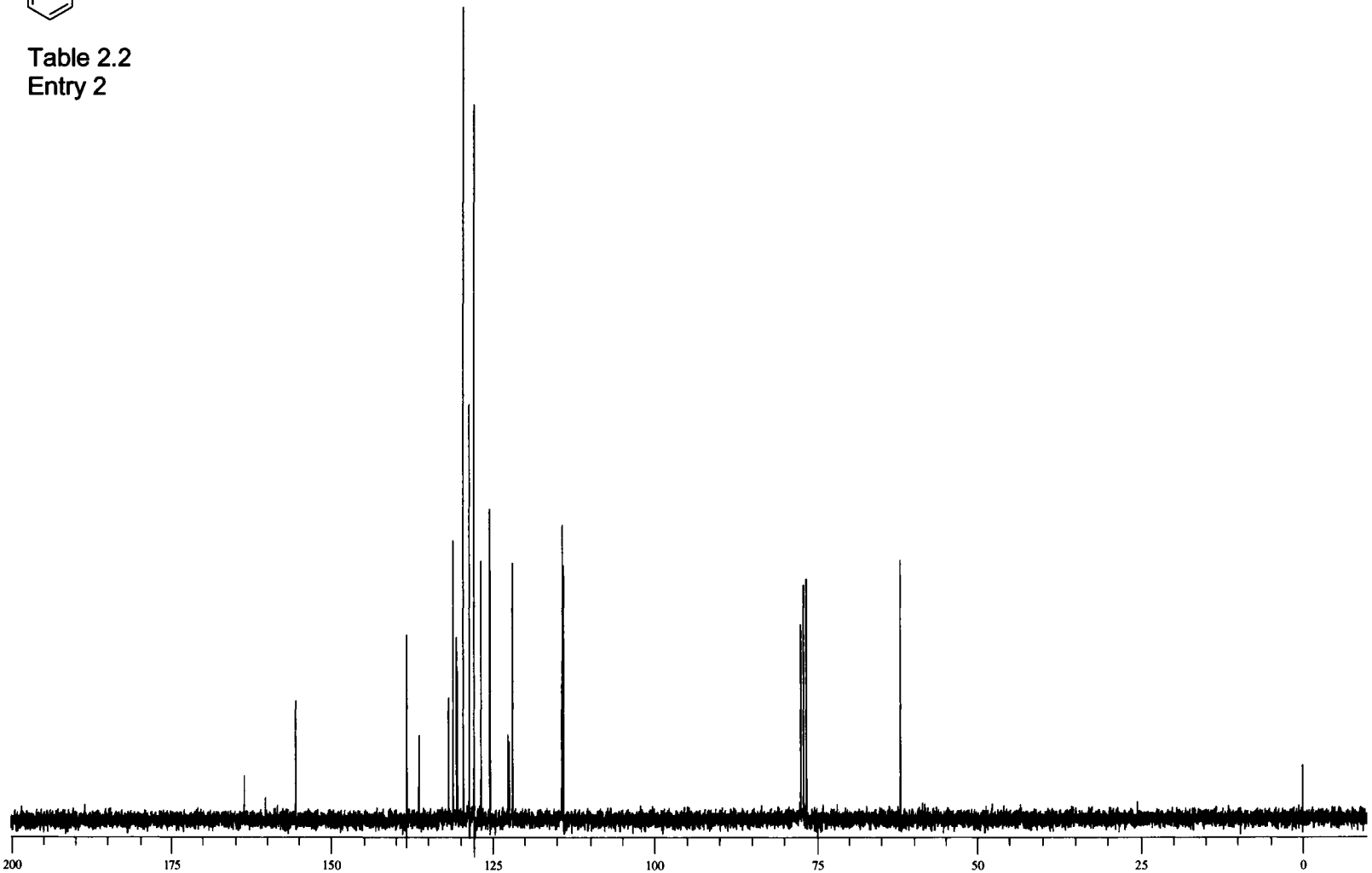

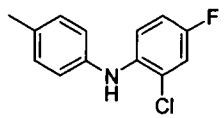

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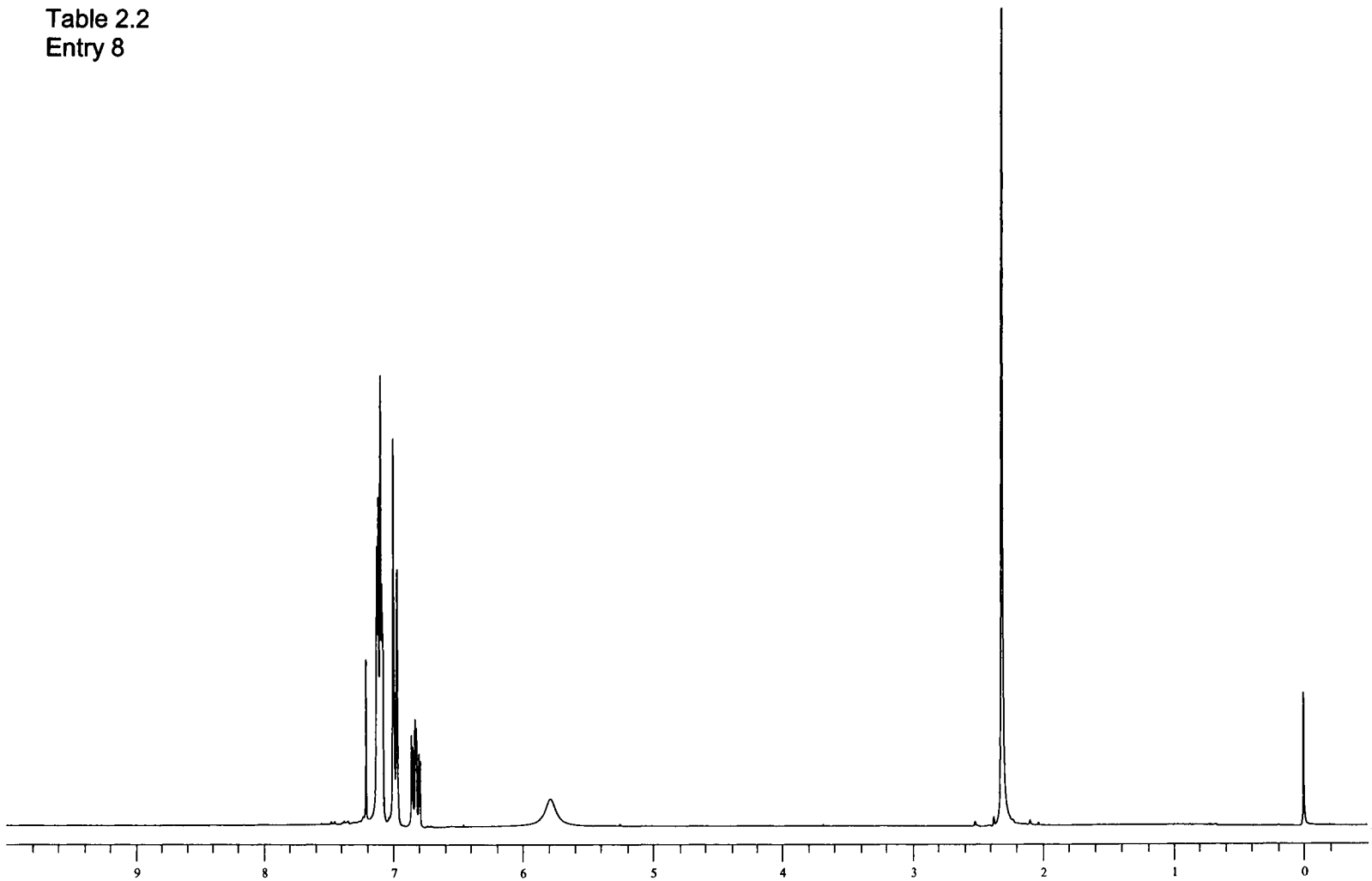

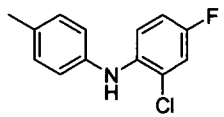

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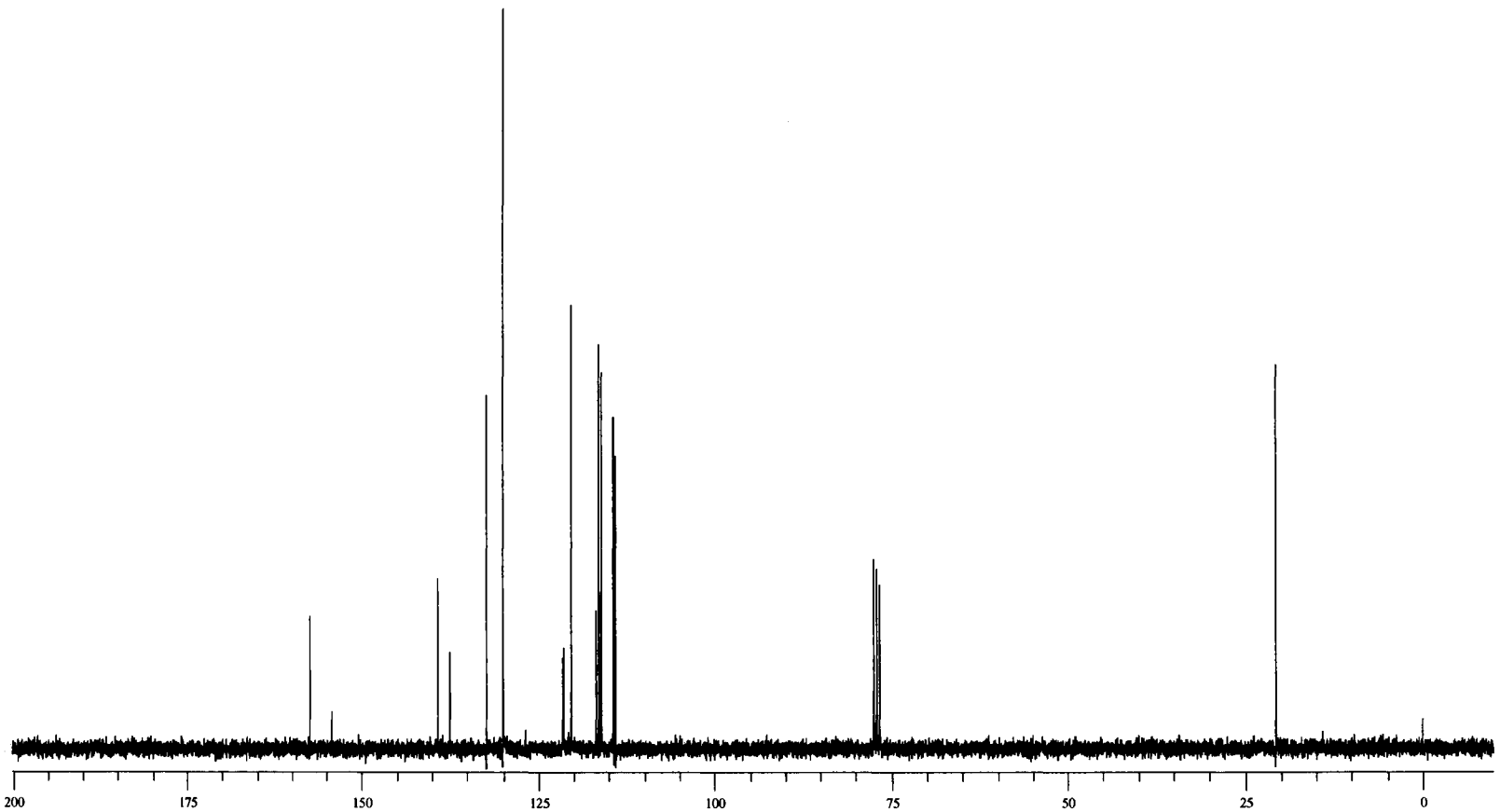

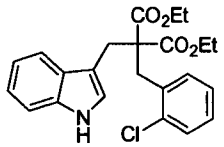

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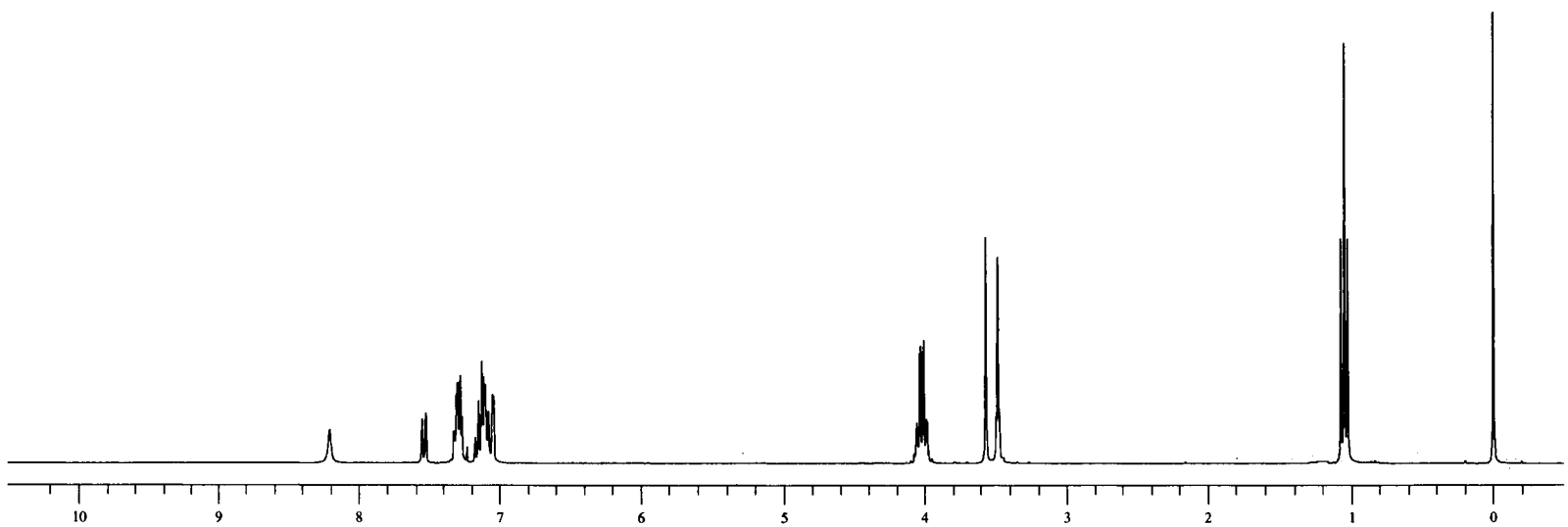

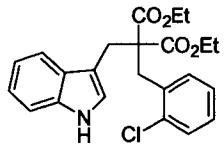

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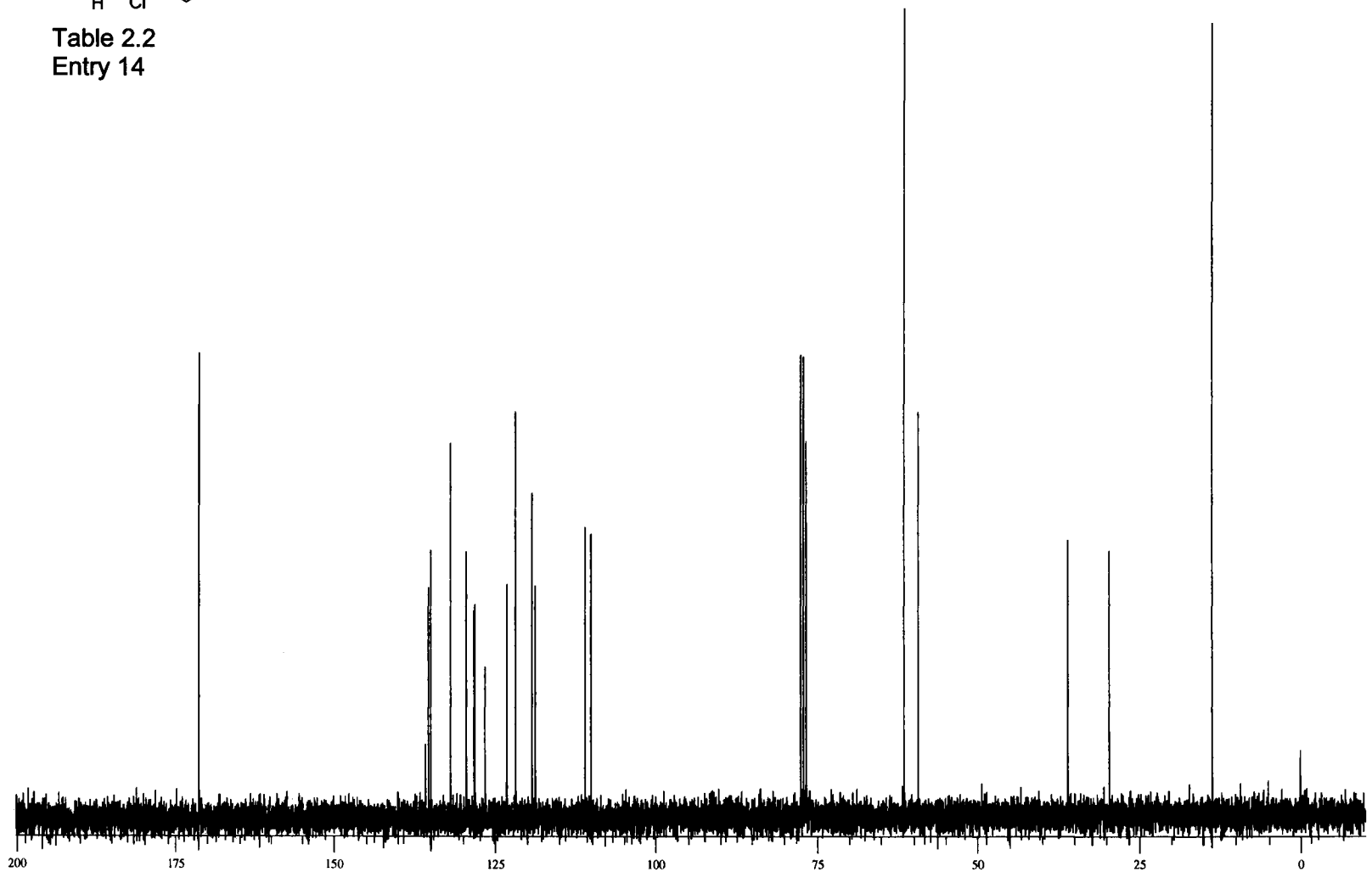

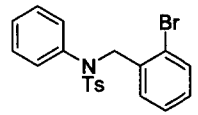

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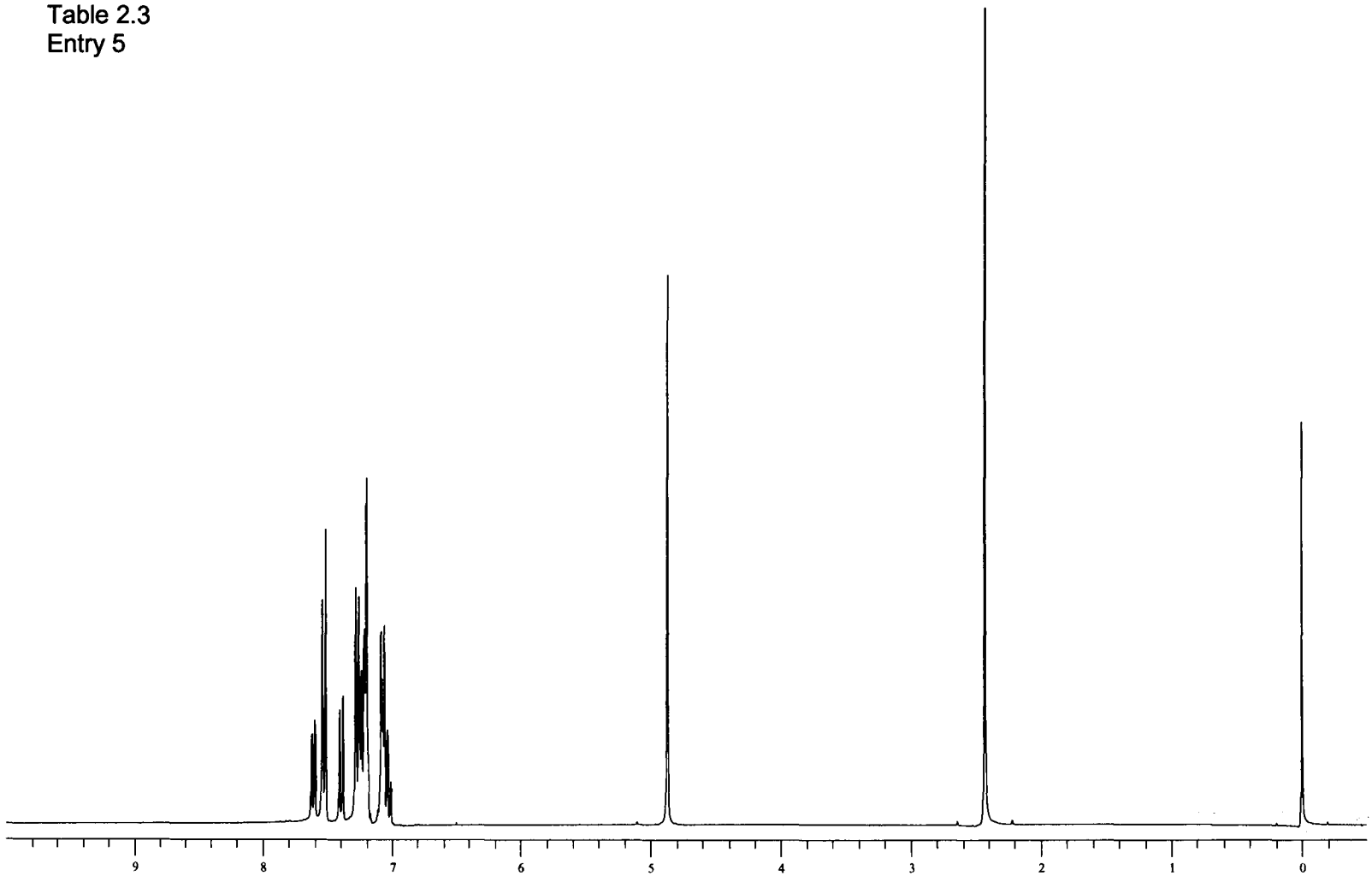

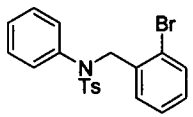

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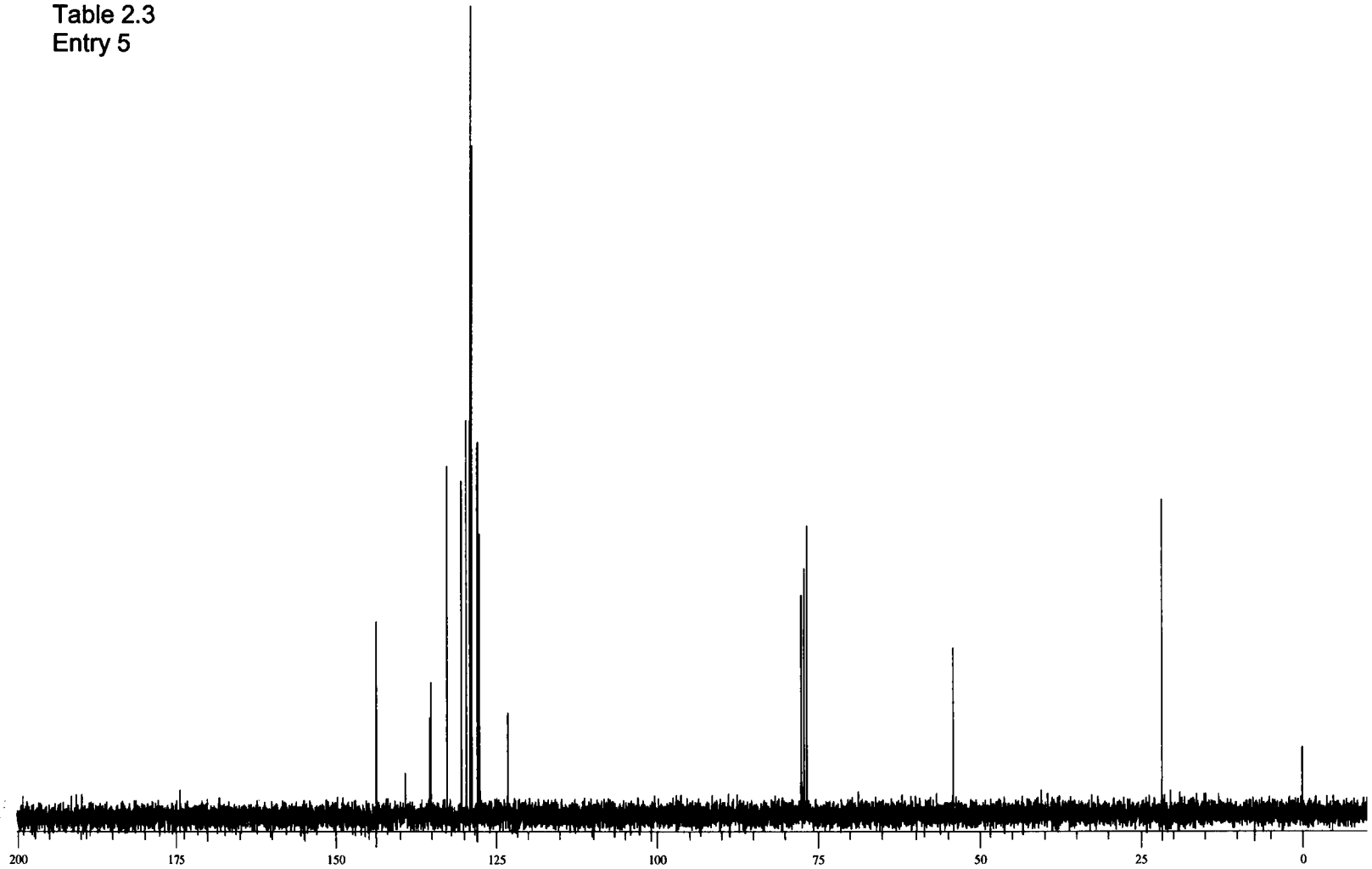

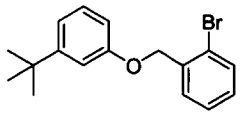

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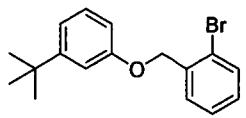

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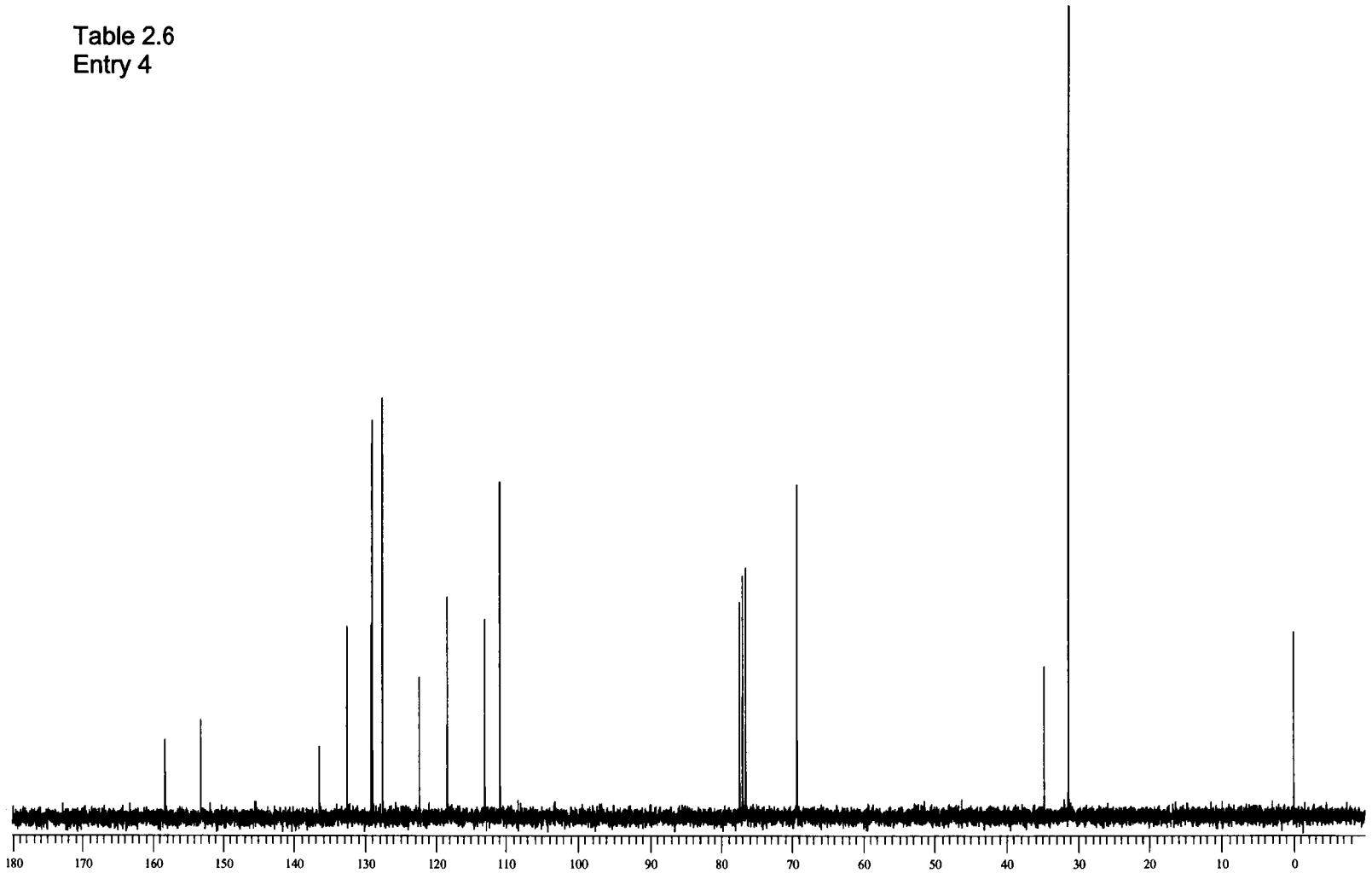

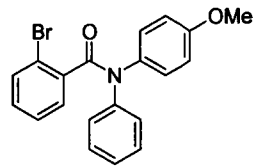

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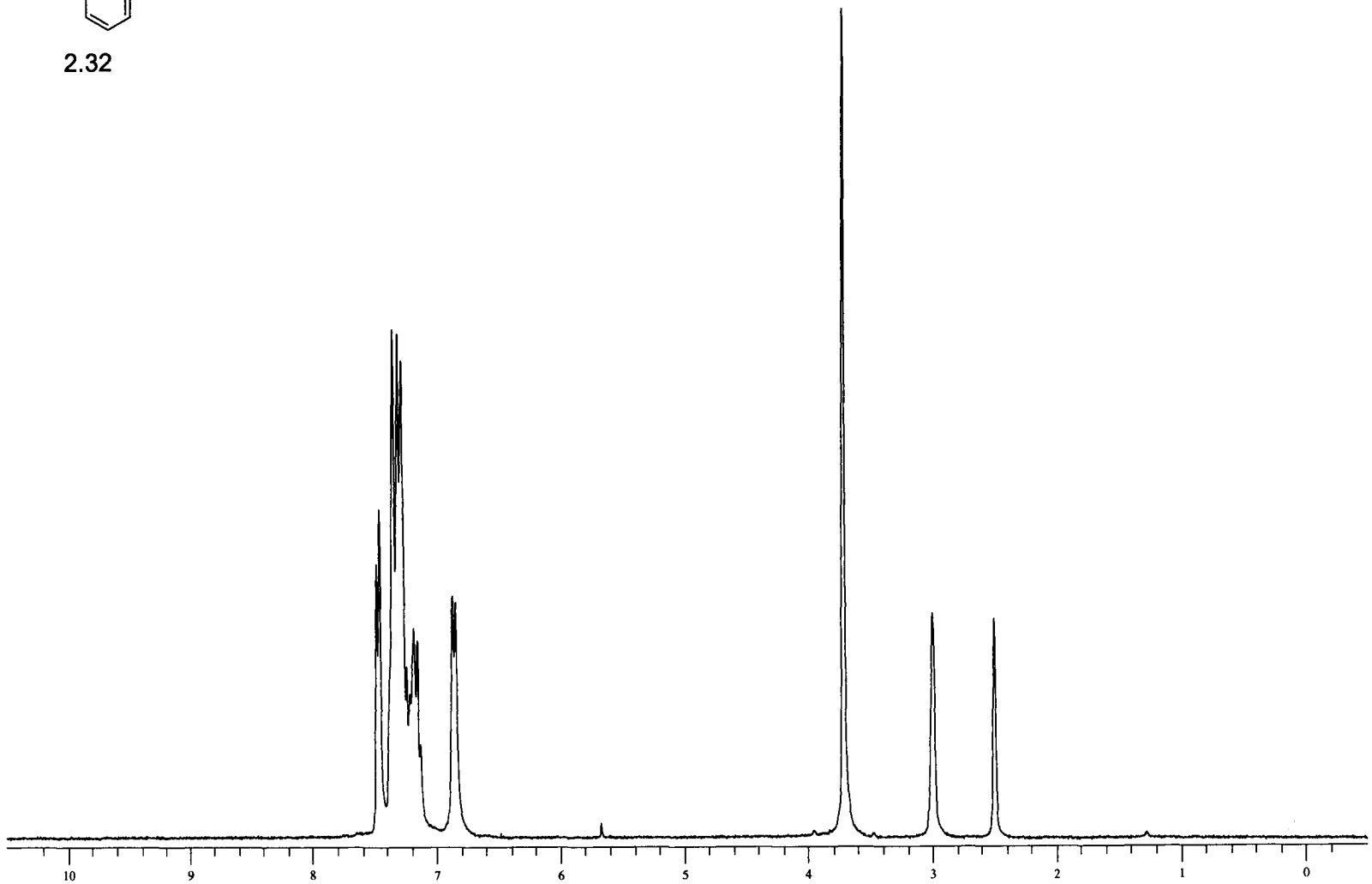

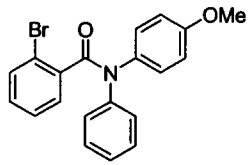
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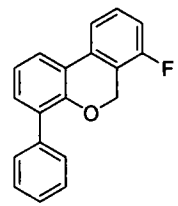

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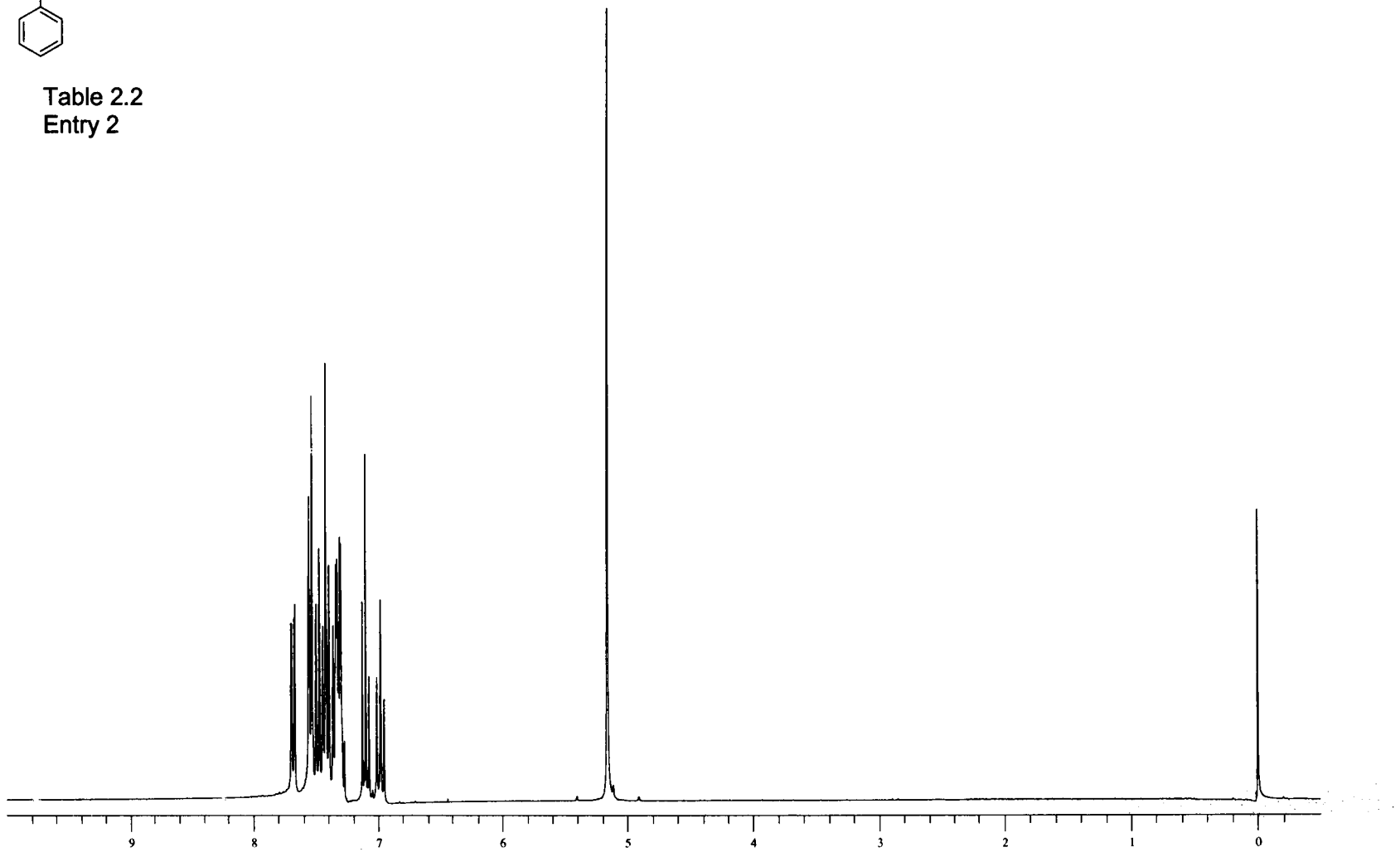

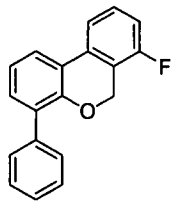

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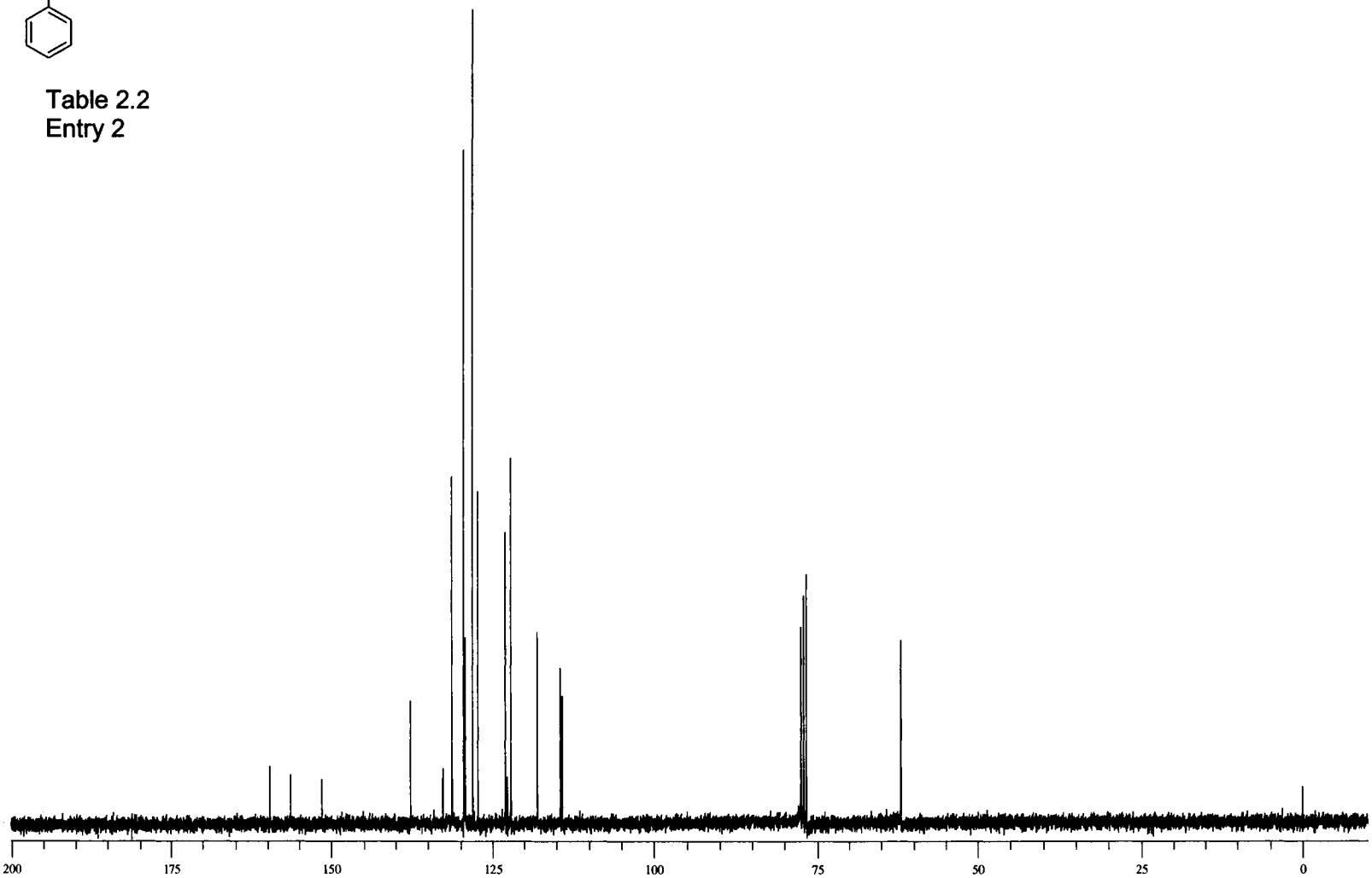

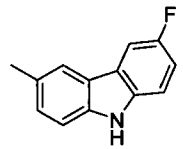

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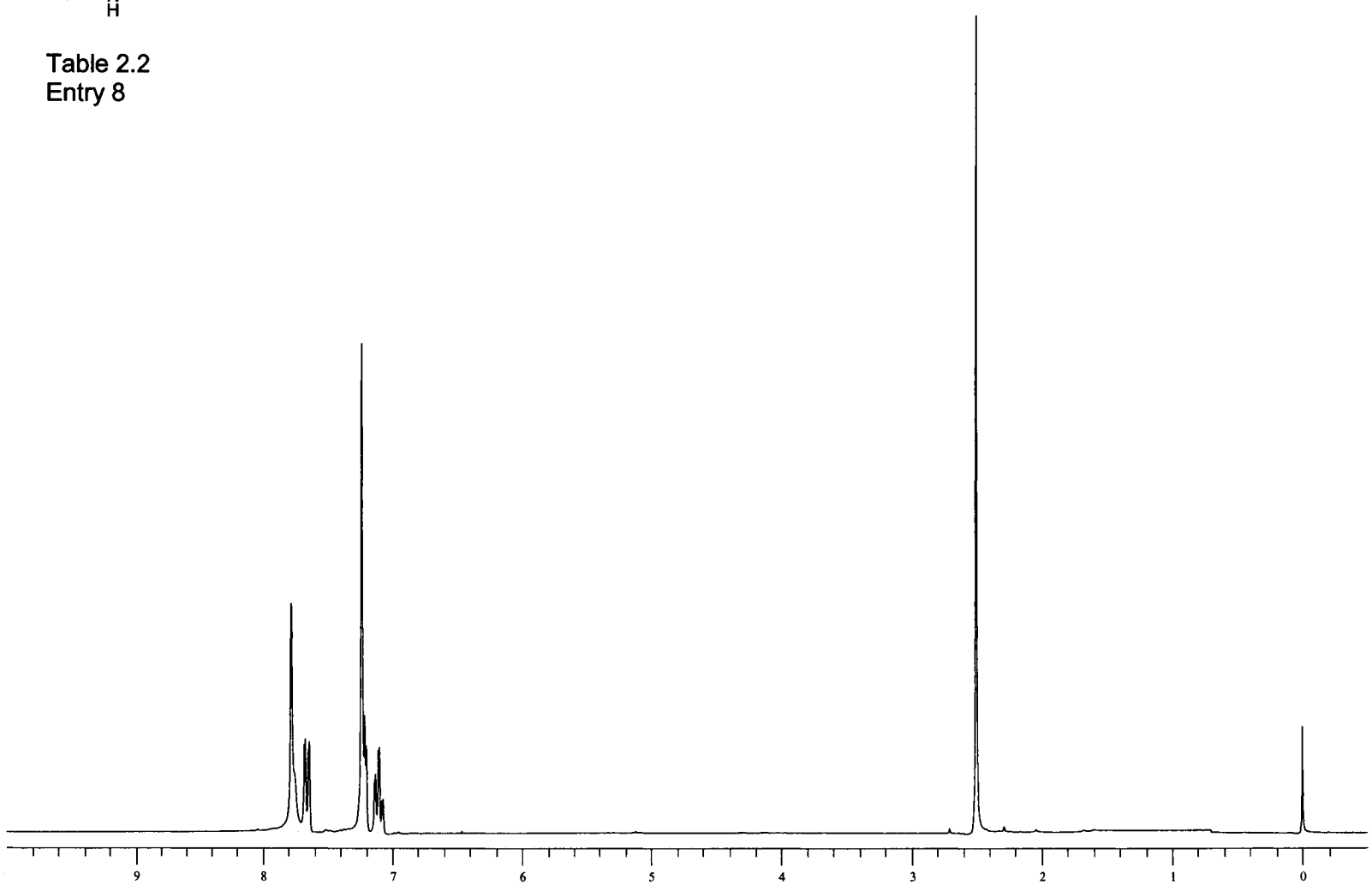

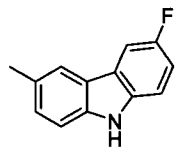

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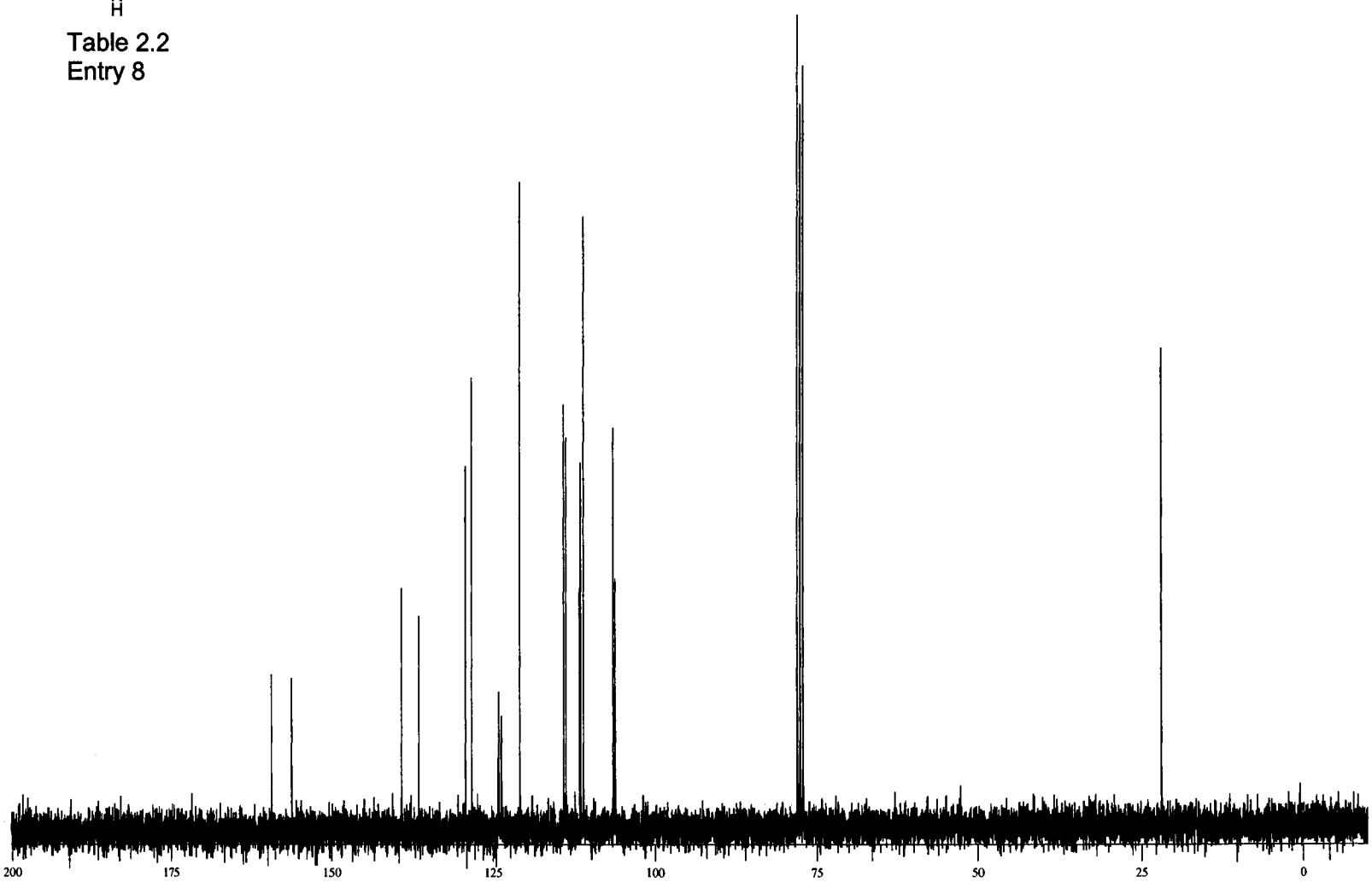

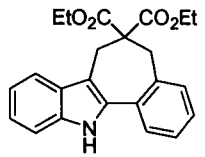

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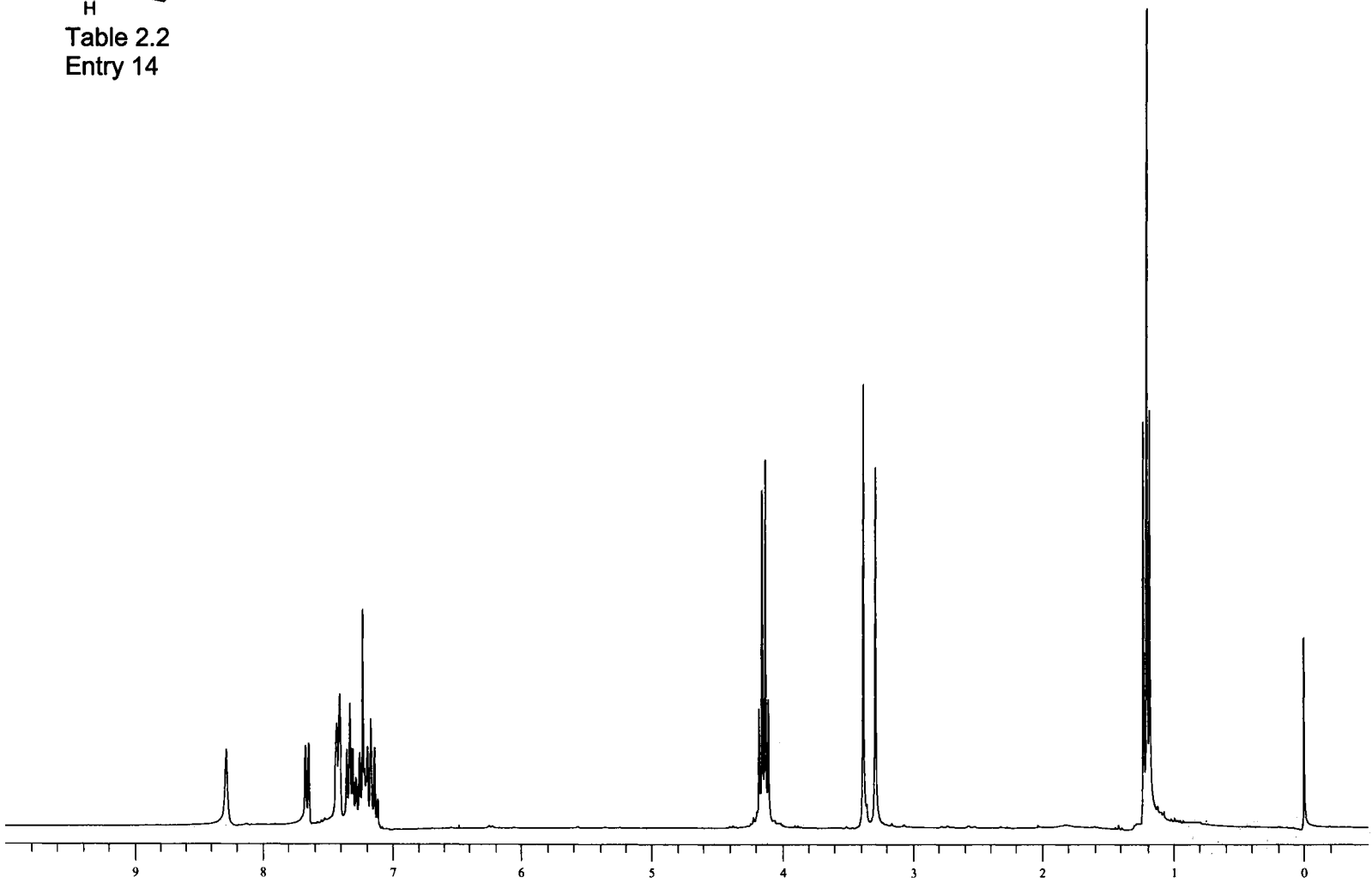

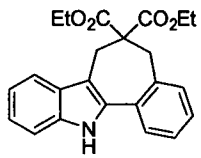

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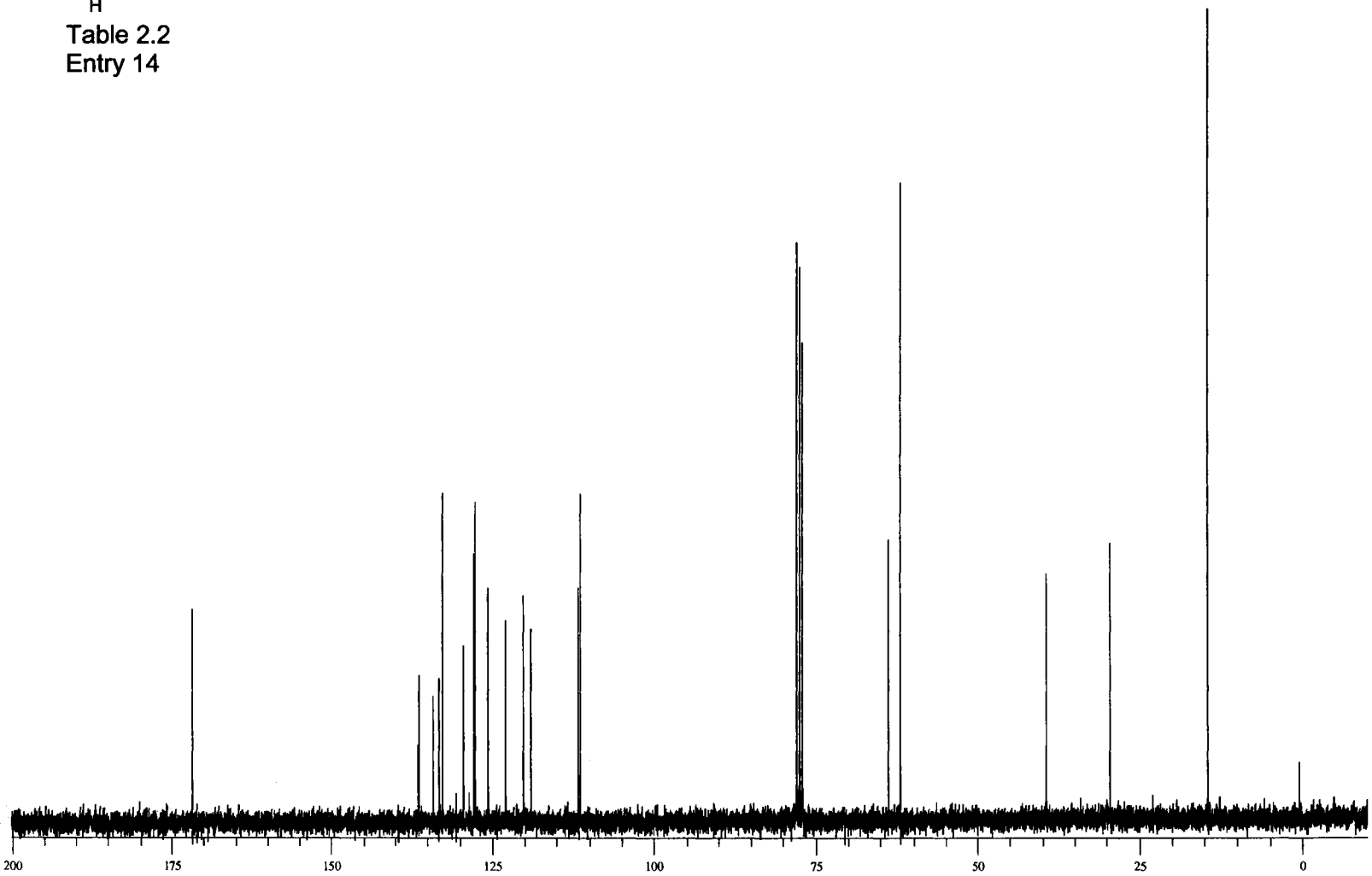


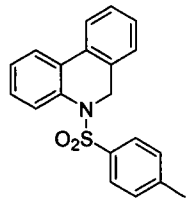


Table 2.3
Entry 5

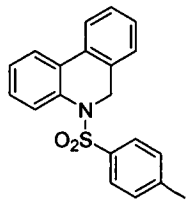


Table 2.3
Entry 5

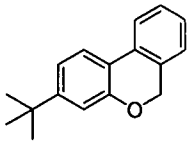
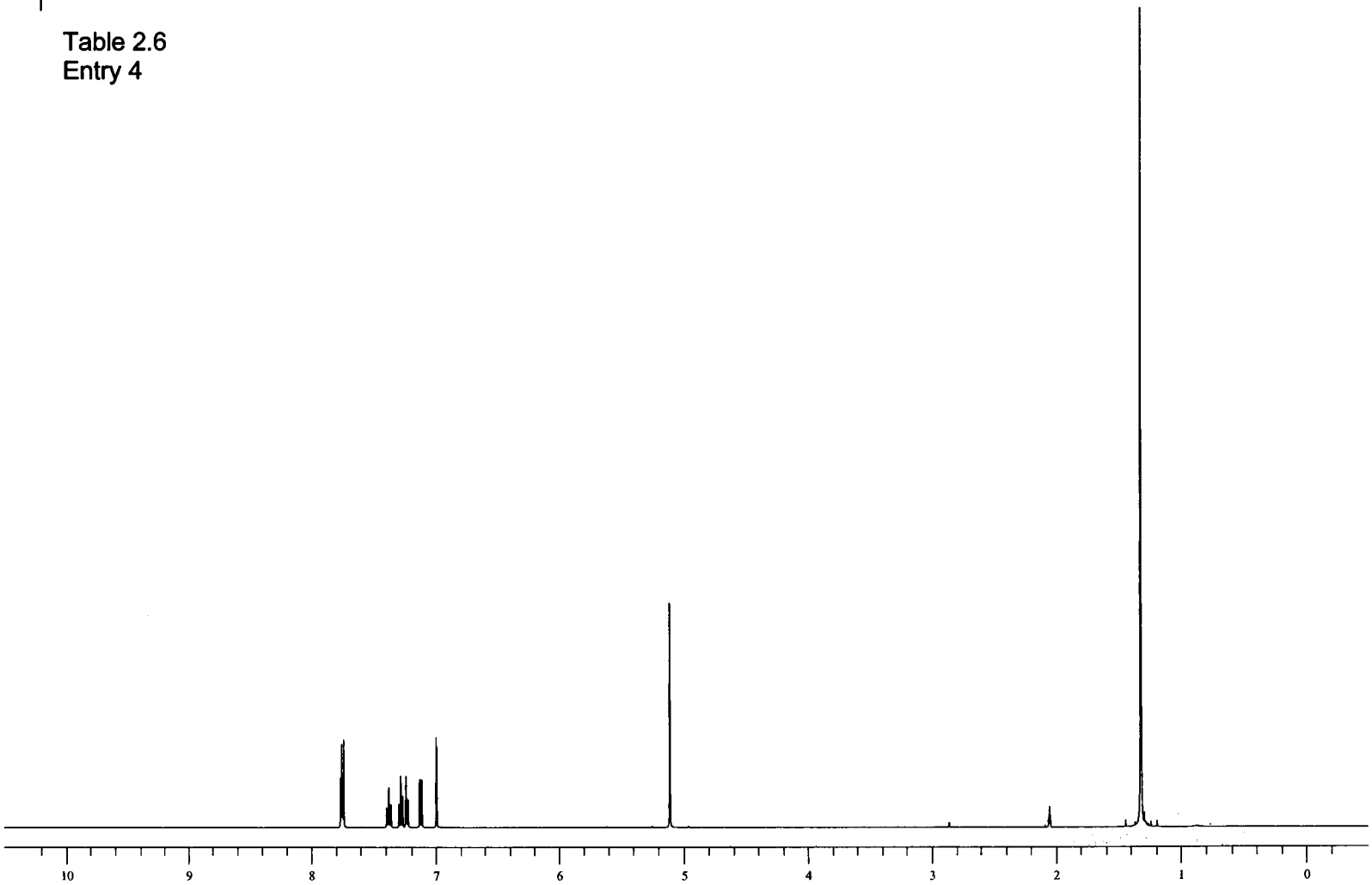


Table 2.6
Entry 4



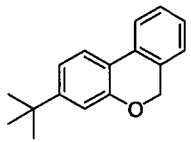
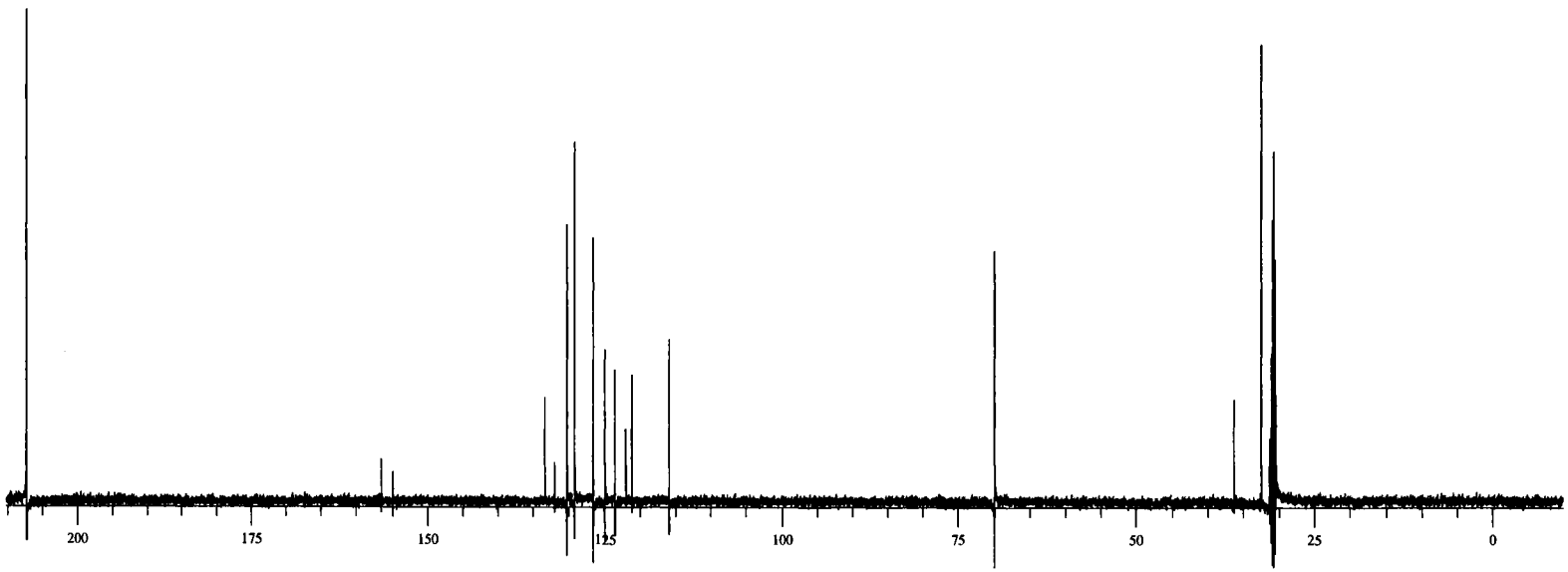


Table 2.6
Entry 4



LCC-XIII-83

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 0.141 sec
Width 455.0 Hz
2D Width 455.0 Hz
16 repetitions
256 increments
OBSERVE H1, 500.1765458 MHz
DATA PROCESSING
Sq. sine bell 0.070 sec
F1 DATA PROCESSING
Sq. sine bell 0.281 sec
FT size 1024 x 1024
Total time 1 hr, 38 min, 11 sec

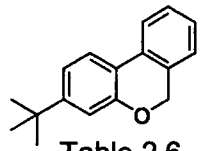
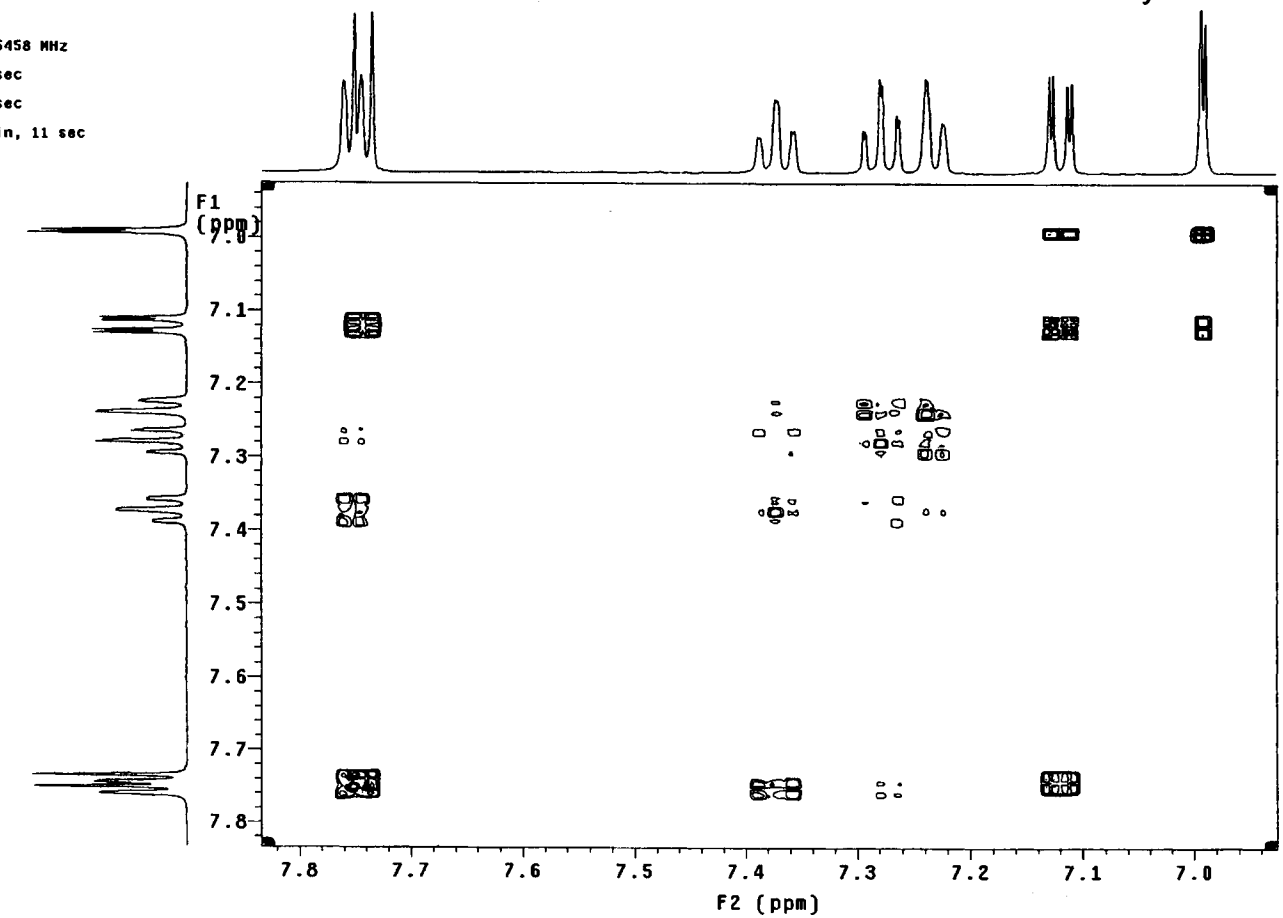
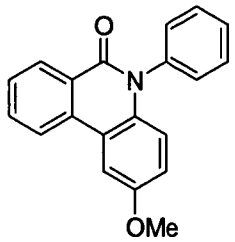
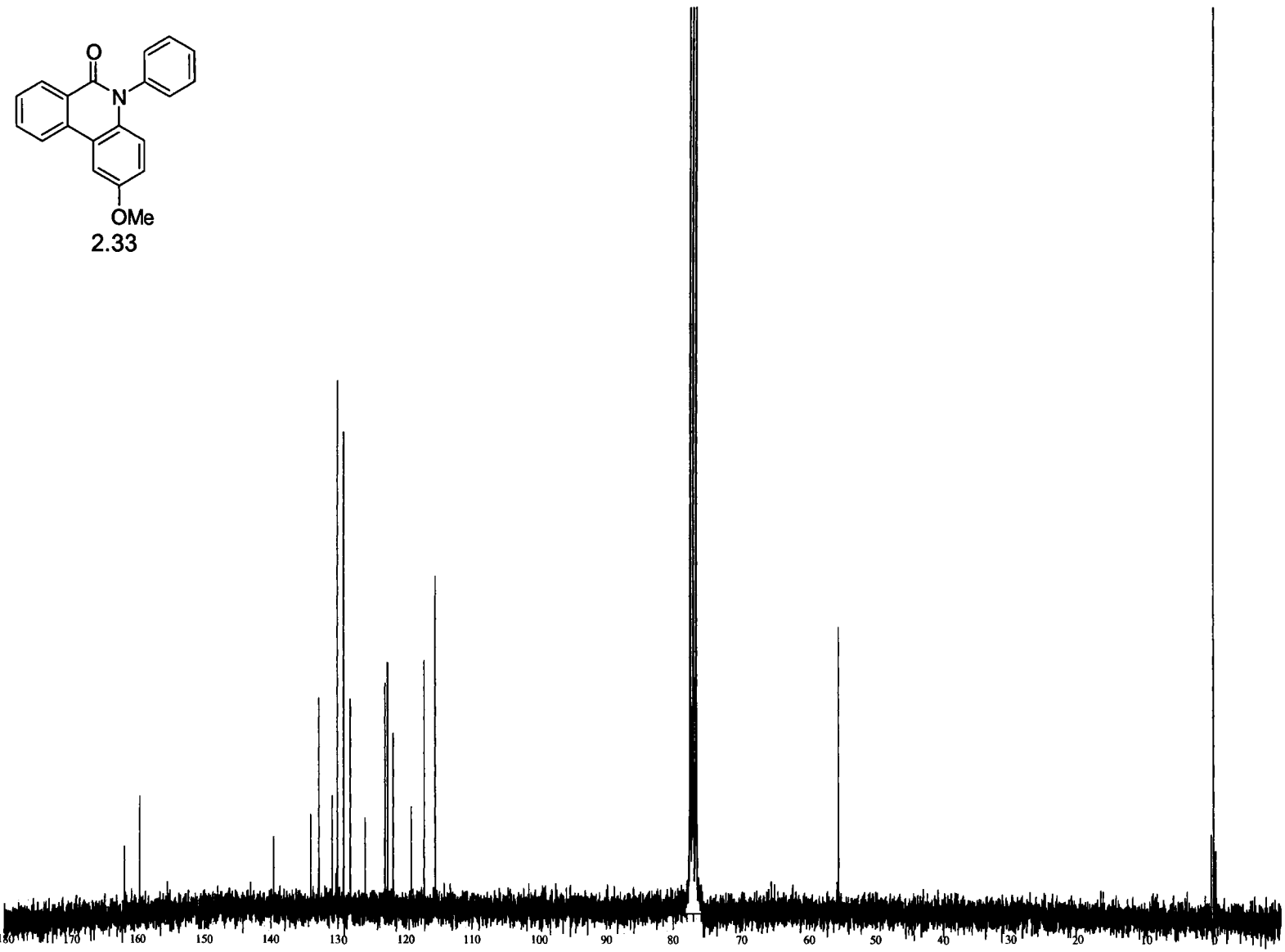


Table 2.6
Entry 4





2.33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