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Development of New Palladium-Catalyzed Arylation Reactions

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To My Parents
Jules and Suzanne Lafrance

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List of Abbreviations

$[\alpha]_D$	specific rotation measured at 589 nm
Ac	acetyl
aq.	aqueous
Ar	aryl
Atm	atmosphere
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Bz	benzoyl
Cy	cyclohexyl
CsPiv	cesium pivalate
dba	dibenzylideneacetone
DCM	dichloromethane
DIPEA	diisopropylethylamine
DMA	*N,N*-dimethylacetamide
DMAP	4-(dimethylamino)pyridine
DME	dimethoxyethane
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
dppb	1,4-bis(diphenylphosphino)butane
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,4-bis(diphenylphosphino)ferrocene
dppm	diphenylphosphinomethane
ee	enantiomeric excess
equiv.	equivalents
Et	ethyl
Et_2O	diethyl ether
EtOAc	ethyl acetate
GC-MS	gas chromatography-mass spectrometry
HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectrum
^{i}Mes	1,3-dimesitylimidazol-2-ylidene
^{i}Pr	isopropyl
^{i}PrOAc	isopropylacetate
IPr-HCl	hydrochloride salt of 1,3-(2,6-diisopropylphenyl)-imidazol-2-ylidene
IR	infrared
KIE	kinetic isotope effect
KOPiv	potassium pivalate
L	ligand
M	generic metal
Me	methyl
MOM	Methoxy methyl ether
mp	melting point

Ms	mesyl
NMR	nuclear magnetic resonance
NMP	*N*-methylpyrrolidinone
Ph	phenyl
Piv	pivalate
py	pyridine
R	generic alkyl group
rt	room temperature
SAR	Structure Activity Relationship
T°	temperature
TBAF	tetrabutylammonium fluoride
^{t}Bu	*tert*-butyl
Tf	triflate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
Ts	tosyl
X	generic halide

Abstract

Penta-, tetra-, tri- and difluorobenzenes undergo intermolecular direct arylation with a wide range of arylhalides in high yield. Inverse reactivity is observed compared to the common electrophilic aromatic substitution pathway since electron-deficient, C-H acidic arenes react preferentially. Computational studies indicate that C-H bond cleavage occurs *via* a concerted carbon-palladium and carbon-hydrogen bond cleaving event involving a carbonate or a bromide ligand. The reactions are rapid, require only a slight excess of the perfluoroarene reagent, and utilize commercially available, air-stable catalyst precursors.

A second generation catalyst was developed that enables the direct arylation of pentafluorobenzene with sterically encumbered aryl bromides and aryl chlorides. These reactions occur in high yield and under mild conditions. Notably, the reactions can be performed at 80 °C in isopropyl acetate with a catalyst generated by the *in situ* mixing of $Pd(OAc)_2$ and S-Phos. The enhanced scope of these transformations should further reduce the need to use pentafluorophenylboronic acid in the construction of perfluoroarenes.

From our mechanistic analysis of the direct arylation of perfluoroarenes, a palladium-pivalic acid co-catalyst system has been developed that exhibits unprecedented reactivity in direct arylations. This reactivity is illustrated with the first examples of high yielding direct metallation-arylation reactions of a completely unactivated arene, benzene, milder reaction conditions for the intramolecular direct arylation of simple arenes as well as the development of a novel direct alkylation reaction. Experimental and computational evidence indicates that the pivalate anion is a key component in the palladation / C-H bond breaking event, that it lowers the energy of C-H bond cleavage and acts as a catalytic proton shuttle from benzene to the stoichiometric carbonate base.

In addition, the palladium-catalyzed direct arylation of aryl chlorides, bromides and iodides has been applied to the preparation of new aporphine analogues including C2 substituted aporphines by reaction with benzodioxole, pyridine *N*-oxide and pyrazine *N*-oxide. Successful application of direct arylation in these diversification reactions highlights its utility not only in convergent, but also in divergent synthesis. We also

describe enantioselective syntheses of (*R*)-nornuciferine and (*R*)-nuciferine employing a catalytic asymmetric transfer hydrogenation in high yield and excellent enantiomeric excess.

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Thanks to my partners in crime Mathieu Parisien and L-C Campeau. These guys have always been there to keep me as sane as possible throughout our undergraduate and graduate studies. Mathieu you have been an amazing friend, roommate and co-worker. Unlike Keith, I would completely trust you with a can of whipped cream. My good cop/bad cop partner LC is a highly knowledgeable and passionate chemist. We definitely had a good time "training" the future chemists together.

Although she might go to bed early, you can always count on Meli Leblanc for help and support. As for JP Leclerc, I will always remember the moment we shared with the ice cream cone in Halifax. I must also give a special thanks to the two highly gifted students who have survived my good and bad temper while working with me. Nicole Blaquiere, column queen and lab mom, you never ceased to be an amazing friend throughout the years, I wish you all the best. Dan Shore, a man whose ability in the laboratory at the time was only beaten by his ability to quote TV shows. Even though you shave your legs, I still have a lot of respect for you.

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train Caron, thanks for life's discussion as well as listening when I needed someone to vent off when I was upset. If you ever need anything; I will be there for you. Sophie Rousseaux, you're a exceptionally bright and talent chemist, good luck with taking over my projects; I know they are in good hands. Thanks to Elisia Villemure and David Lapointe. I had a good time in your company during our hikes and camping expeditions. As for Derek Schipper, thanks for showing me how to solve the Rubik's cube and how to appreciate mom' joke. Kayode Akinnusi, thanks for the company during our late nights at the lab (or technically early morning). Good luck on your graduate studies Chris Whipp, remember that reactions love to rock with the loud music. As for my Asian friends: "Yo-Han" Sun and D-Lee, keep it up, I know you will both succeed. Megaaan, the only person with 3 consecutive a's in her name, thanks for everything. Remember Praew Thansandote we only tease and argue with those we like, and we can always resolve our issues over maple cookies. I want to acknowledge all the other Fagnou members (Catherine Lebel, Sarah Diallo-Garcias, Julien Dugal-Tessier, Damien Valette, Annie Jean, Mélanie Lecavalier, Sandrine Lacelle, Mathieu André, Irena Denissova, Malcolm Huestis and Valérie Charbonneau).

I would also like to thank my department friends Natalie Nagougen and Unkle Joe Jebreen for always being there for me, no matter what, I am honored to call you friends. I also want to acknowledge Joe #2 Moran, Jenny Scott, *ti*-Pat Beaulieu, Pat Crewdson, Joffrey, Louis "LUMO" Morency, Rochy Lavigne (thanks for the Survivor experience), Max Rioux, Alex Bush, Mathieu Frenette and Matt Lemay. Thanks for always being there to discuss chemistry as well as entertain me when I needed it the most.

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PS. You are all invited and welcome to visit me in Zürich.

It ain't what you don't know that gets you into trouble.

It's what you know for sure that just isn't so.

- Mark Twain

Chapter 1

General Introduction

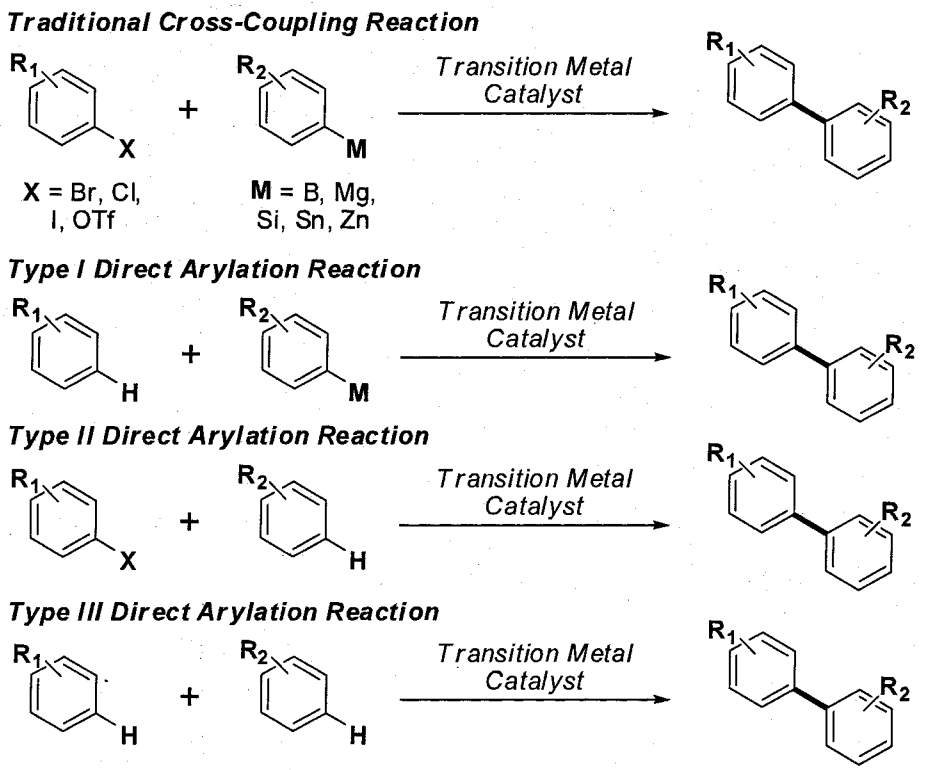
The biaryl core constitutes a "privileged" structural motif that is found in approximately 4.3% of all medicinally active compounds.[1] Consequently, the development of simple and broad methods for the formation of this structural element is still required.[1] While many different approaches have been developed, the use of transition metal-catalyzed cross-coupling reactions is commonplace. Initial work was achieved in the early 1900's with the appearance of the Ullmann coupling reaction.[2] The development of modern palladium-catalyzed cross-coupling reactions constituted a significant advance allowing for the first time, the formation of unsymmetrical biaryl moeties in high yield, with a broad functional group tolerance.[3] Since their development, significant effort has been focused on simplifying the reaction conditions such that these reactions can now be performed in high yield, using low catalyst loading, under mild conditions, with many different organometallics (tin, silicon, boron, magnesium). A

[1] Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359.
[2] Ullmann, F.; Bielecki, J. *Chem. Ber.* **1901**, *34*, 2174.
[3] For reviews on this topic, see: *Metal-catalyzed Cross-coupling Reactions*, ed. F. Diederich and J. Stang, Wiley-VCH, New York, 1998.

particularly important recent advance has been the use of the less activated aryl chlorides as the coupling partner.

When evaluating the efficiency of a given transformation, many factors must be taken into account. Ideally, the starting materials should be commercially available or easily synthesized from simpler precursors. In most palladium-catalyzed cross-coupling reactions, the organometallic component (when commercially available) can frequently be expensive. Furthermore, the need for a stoichiometric organometallic reagent can pose a risk of toxicity to the researcher and the environment. The sensitivity to air and/or moisture of these reagents makes it difficult to carry them over several steps in a synthesis. Finally, this pre-activation (as an organometallic and haloarene) is inherently wasteful since they require several steps to be installed and are then discarded as waste once the cross-coupling has been performed.

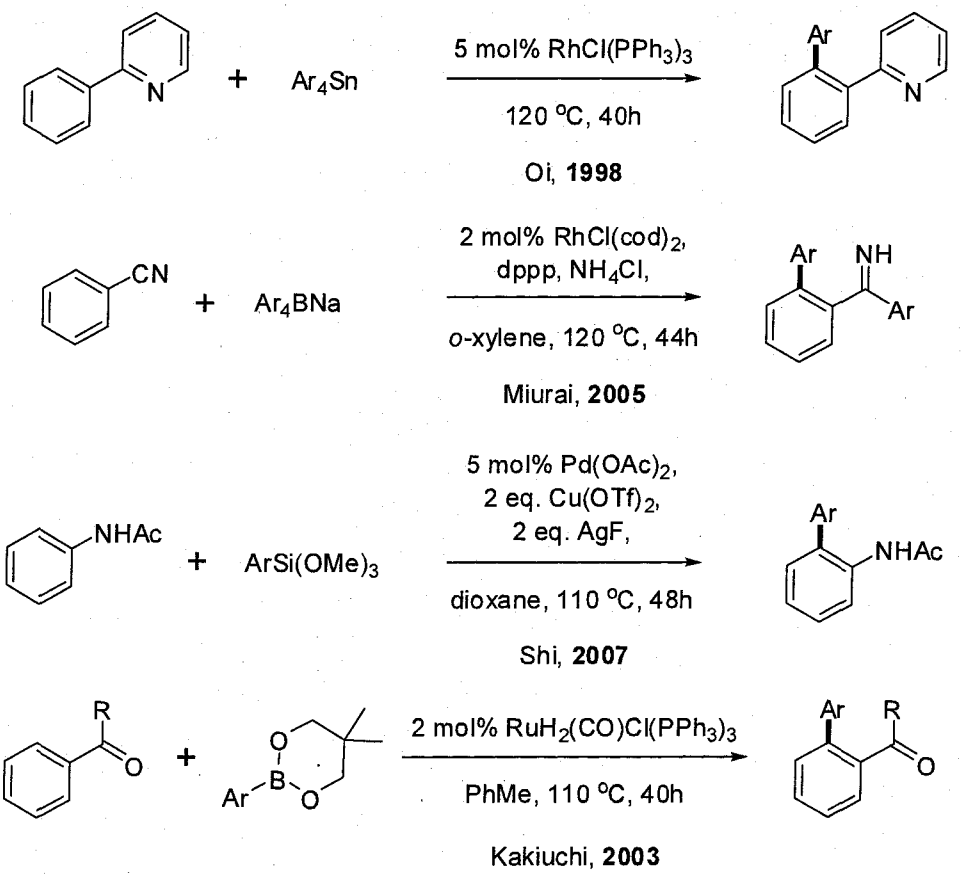
Scheme 1. 1. Different Types of Direct Arylation Reactions.



These issues have prompted a re-evaluation of cross-coupling reactions in order to limit the requirements for pre-activation to only one (Type I and II direct arylation) or

ideally to neither of the coupling partners (Type III) (Scheme 1.1).[4] While significant advances have been made with these types of transformations, more research is required to expand the scope of compatible arenes and to control the regioselectivity in reactions with arenes bearing different C-H bonds. While some attention has been focused on replacing the haloarene component with a simple arene (Scheme 1.2),[5] most efforts have been directed towards the replacement of the more problematic organometallic species instead.

Scheme 1. 2. Established Type 1 Direct Arylation Reactions.



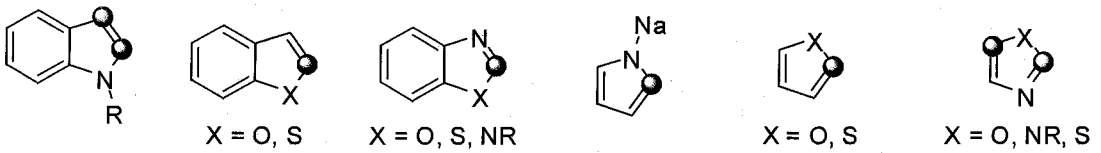
[4] For recent reviews, see: (*a*) Campeau, L.-C.; Fagnou, K., *Chem. Comm.* **2006**, 1253. (*b*) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.*, **2007**, *107*, 174. (*c*) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.*, **2002**, *35*, 826; (*d*) Ritleng, C.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731; (*e*) Miura, M.; Nomura, M. *Top. Curr. Chem.* **2002**, *219*, 211; (*f*) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077.

[5] (*a*) Kakiuchi, F.; Kan, S.; Igi, Chatani, N. ; Murai, S. *J. Am. Chem. Soc.* **2003**, *125*, 1698; (*b*) Kakiuchi, F.; Matsuura, Y.; Kan, S.; Chatani, N. *J. Am. Chem. Soc.* **2005**, *127*, 5936; (*c*) Oi, S.; Fukita, S.; Inoue, Y. *Chem. Commun.* **1998**, 2439; (*d*) Ueura, K. ; Satoh, T. ; Miura, M. *Org. Lett.* **2005**, 2229. (*e*) Yang, S.; Li, B.; Wan, X.; Shi, Z. *J. Am. Chem. Soc.* **2007**, *129*, 6066.

Prior to our contributions in the field of direct arylation, different heteroarenes and simple arenes with directing groups had been shown to be efficient cross-coupling partners (Figure 1.1) and these systems have recently been reviewed.[4] In order to limit the present discussion, only relevant type II and type III processes that have been developed over the last five years will be discussed. This chapter will be divided as follows: the use of heteroarenes will be followed by a description of the use of electron deficient arenes and will conclude with the use of directing groups in intermolecular direct arylation reactions of haloarenes.

Figure 1. 1. Examples of Direct Arylation Prior to Our Contribution.

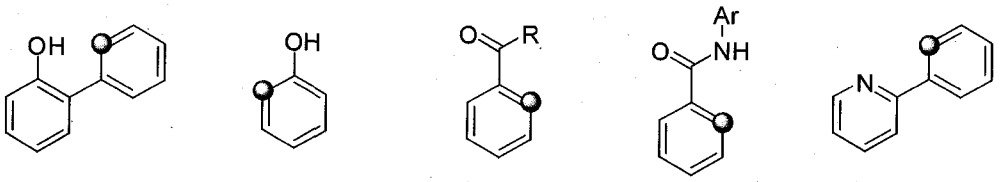
Heteroarenes



Ohta, **1989** | Ohta, **1992** | Ohta, **1992** Miura, **1998** | Filippini, **1992** | Ohta, **1992** Lemaire, **1999** McClure, **2001** Miura, **2002** | Ohta, **1992** Miura, **1998**

Note: *The blue balls indicate the primary position for arylation while the red balls represent alternative positions for arylation*

Directing Groups



Miura, **1997** | Miura, **1999** | Miura, **1999** | Miura, **2000** | Oi, **2001**

Note: *The red balls indicate the position of arylation*

1.1 – Alternative Approaches to Modern Cross-Coupling Reactions

Electron rich heteroarenes, have often been examined in direct arylation reactions because they are believed to mimic the nucleophilicity of the organometallic species in a cross-coupling reaction. Although it is often postulated that the enhanced nucleophilicity is responsible for the reactivity, it is also possible that the heteroatoms have a directing

effect as well. While this strategy is efficient for electron rich arenes, the use of an *ortho*-directing group is often required to achieve reactivity with simpler arenes due to weak arene-transition metal interactions. The directing group holds the metal in close proximity to a neighboring site within its coordination sphere, allowing the required transition metal aryl complex to be formed.

The mechanism for a Type II reaction generally begins with an oxidative addition of the metal into the carbon-halide bond and then may follow at least five possible mechanistic pathways (Figure 1.2). One possibility involves an electrophilic aromatic substitution at the metal center (S_EAr), in which the electron rich arene will attack the metal center to generate a Wheland arenium, which upon deprotonation, generates a metal diaryl complex (pathway I).[6-14] σ-Bond metathesis is also posible, in which the metal interacts with the arene allowing partial hybridization prior to a concerted intramolecular deprotonation/metallation step with a basic ligand (pathway 2).[10,15-20] A concerted S_E3 process may occur, which is similar to the previous mechanism but employs an outer sphere base (pathway 3).[15] A Heck-type (or carbometalation) process followed by either a *trans* β-hydride elimination or through an isomerization followed by *syn* β-hydride elimination may also occur (pathway 4).[21] Finally, an oxidative addition to this C-H bond may occur, forming a metal hydride which then undergoes two consecutive reductive eliminations to generate the biaryl product (pathway 5). It should be noted that the exact mechanism for any system will be affected by the substrate, the transition metal, solvent, additives, base and/or the ligand involved in the reaction.

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[7] González, J.J.; García, N.; Gómez-Lor, B.; Echavarren, A.M. *J. Org. Chem.* **1997**, *62*, 1286.
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[13] Gómez-Lor, B.; Echavarren, A.M. *Org. Lett.* **2004**, *6*, 2993.
[14] Lanes, B.S.; Brown, M.A.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 8050.
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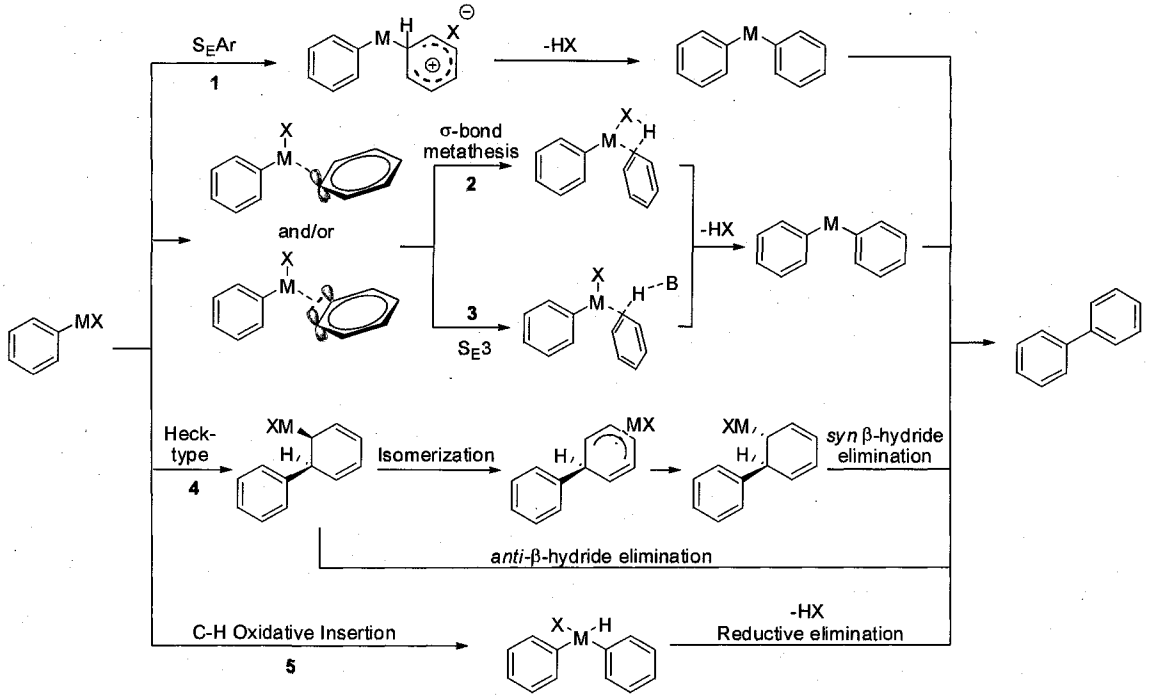
[18] (*a*) Garcias-Cuadrado, D.; Braga, A.A.C.; Maseras, F.; Echavarren, A.M. *J. Am. Chem. Soc.* **2006**, *128*, 1066. (*b*) Garcias-Cuadrado, D.; Braga, A.A.C.; Maseras, F.; Echavarren, A.M. *J. Am. Chem. Soc.* **2007**, *129*, 6880.
[19] Lafrance, M.; Rowley, C.N.; Woo, T.K.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 8754.

Figure 1. 2. Different Mechanistic Pathways for Direct Arylation.



1.1.1 – Direct Arylation of π-Electron Rich Heteroarenes

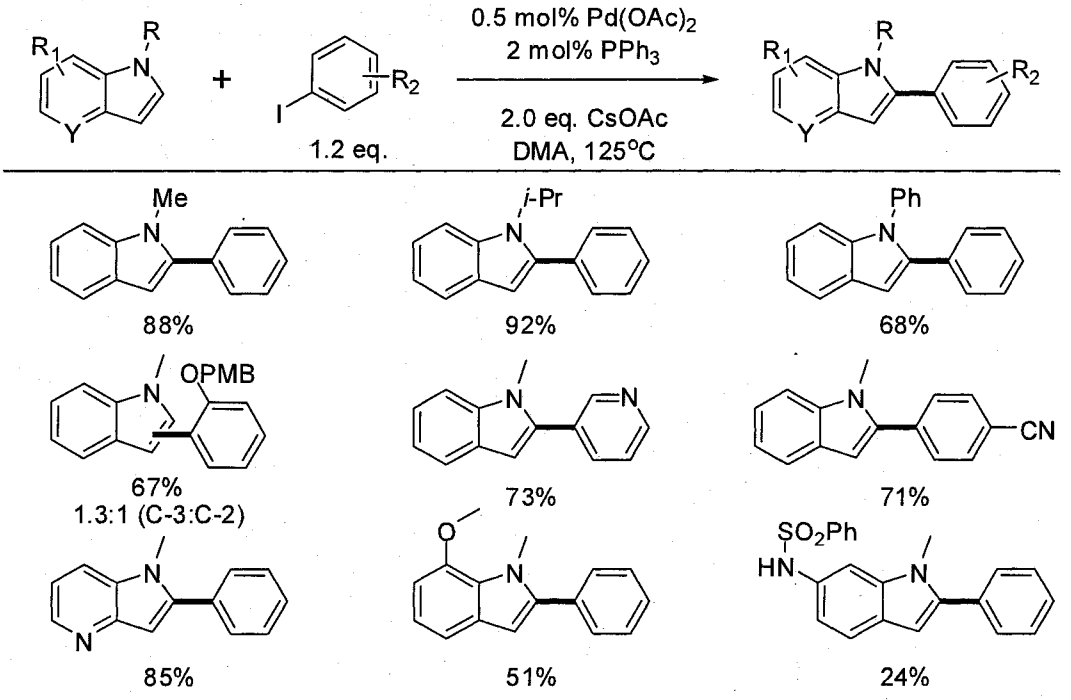
The control of the regioselectivity in both intra- and intermolecular systems remains a significant challenge in direct arylation. While the intramolecular variant takes advantage of steric hinderance and strategic positioning of the tether, the intermolecular variant is more complicated. Fortunately, the inherent electronic bias of many heteroarenes simplifies this task resulting in reaction at one site predominantly. This selectivity can be fine tuned through several factors such as the proper choice of solvent, additives (e.g., Cu(I) salts) as well as the nature of the catalyst employed (metal, size and electronic properties of the ligands). This section will focus largely on the developments of direct arylation through the use of heterocycles in the last five years with their associated mechanistic investigations.

[20] Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 16496.
[21] Zollinger, H. *Adv. Phys. Org. Chem.* **1964**, *2*, 162.

1.1.1.1 –Indoles and Azaindoles.

The first report dealing with the use of indoles as a coupling partner in direct arylation was described by Ohta involving different *N*-substituted indoles with a variety of chloropyrazines.[22] In 2004, the group of Prof. Sames reinvestigated the use of indoles as coupling partners in direct arylation and reported a protocol for the highly C2-selective arylation of *N*-substituted indoles using iodoarenes.[23] Through meticulous catalyst screening they noticed base and catalyst loading effects on reactivity. As the catalyst loading was increased, the yield of the product decreased significantly due to an increase in iodoarene homocoupling. Using 0.5 mol% palladium acetate in conjunction with 2 mol% triphenylphosphine and cesium acetate as the base they could isolate moderate to good yields of a wide array of indoles (including 7-azaindole) and electron poor aryl iodides (Table 1.1). As previously observed by Ohta,[22] sterically hindered iodoarenes gave the C-3 arylation product predominantly.

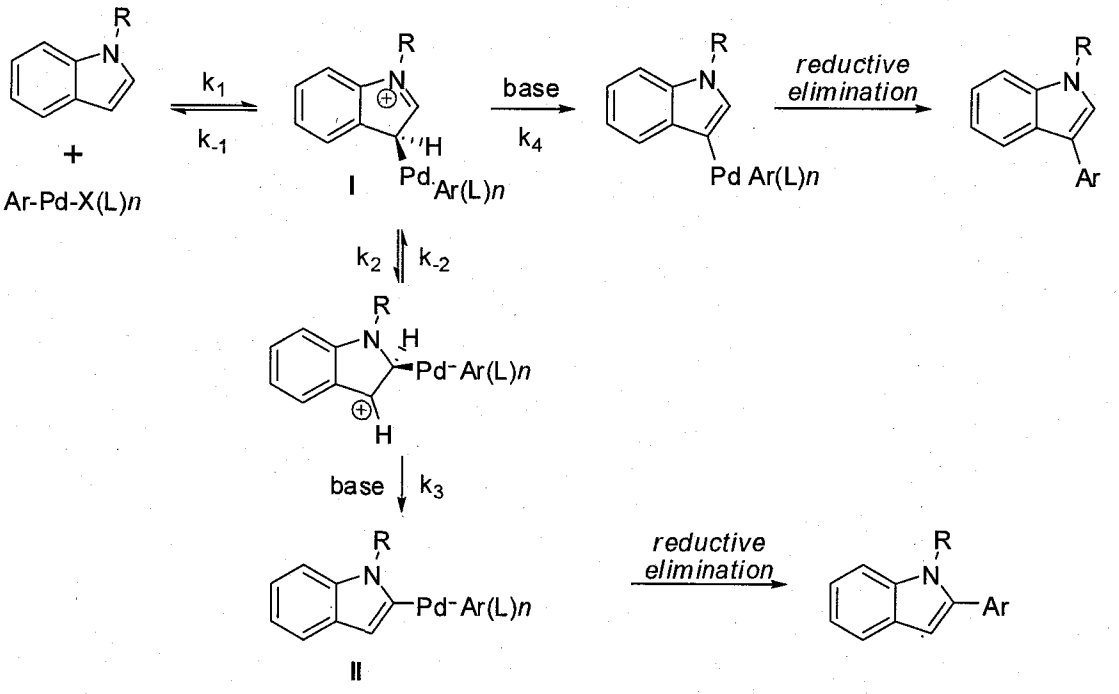
Table 1. 1. Scope for Direct Arylation Using *N*-Methylindole by the Group of Sames.



[22] Akita, Y.; Itagaki, Y.; Takizawa, S.; Ohta, A. *Chem Pharm. Bull.* **1989**, *37*, 1477.
[23] Lane, B.S.; Sames, D. *Org. Lett.* **2004**, *6*, 2897.

Based on mechanistic investigations, a rationale was proposed to explain the regioselectivity (Scheme 1.3).[14] Although C-2 arylation was found to be the major product, they proposed the reaction occurs initially *via* an electrophilic metalation at the C-3 position giving intermediate **I**. A 1,2-palladium migration would then occur to yield **II**, which upon subsequent reductive elimination would give the C-2 arylation product. When poor regioselectivity is observed (sterically encumbered iodoarene), the rate for the 1,2-palladium migration step would be slower, allowing time for deprotonation/reductive elimination at the 3-metalloindole **I** to occur, giving the C-3 arylation predominantly.

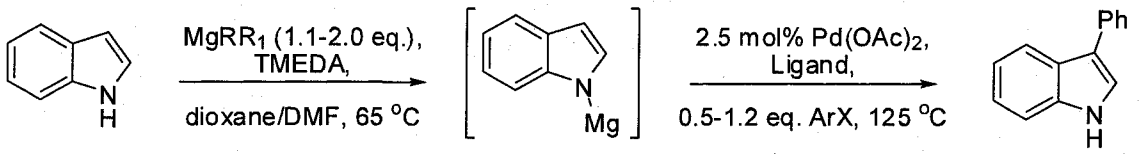
Scheme 1. 3. Mechanistic Rational for the Regioselectivity Proposed by Sames.

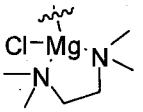
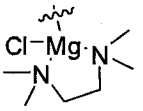


From these results, they developed a different protocol employing bulky magnesium indole salts. These new reaction conditions gave the C-3 arylated indoles in low to excellent yields (Table 1.2). The magnesium indole salts were generated *in situ* prior to the addition of the catalyst. Furthermore, the nature of the magnesium coordination sphere has a significant impact on the regioselectivity. For instance, when employing a more bulky (1,3-bis-mesitylimidazolyl carbene) ligand as well as adding

TMEDA (tetramethylethylenediamine) as an additive, they isolated the product in 96% yield in a 67:1 regioselectivity in favor of the C-3 adduct (Table 1.2).

Table 1. 2. Selective C-3 Arylation of Indoles.

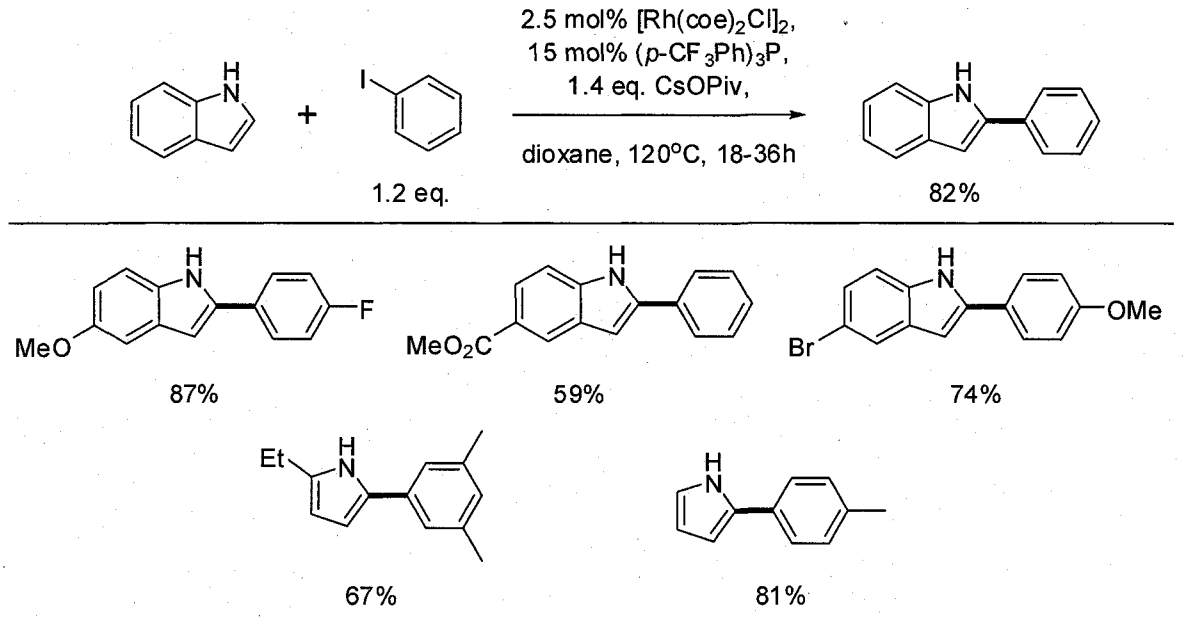


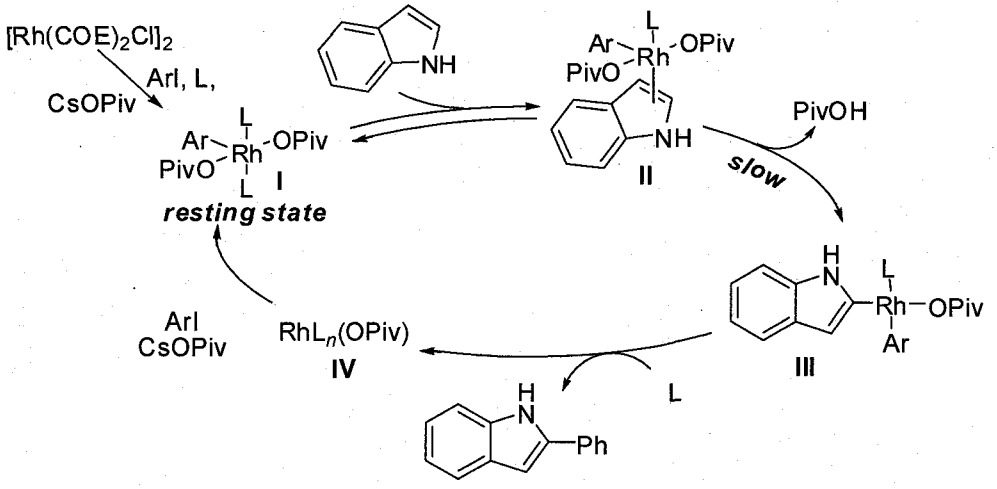
Mg	Ligand	ArX	Yield	C-3:C-2
$\frac{s}{s}$MgCl	PPh_3	PhI	24%	7:1
$\frac{s}{s}$MgN(TMS)$_2$	PPh_3	PhI	77%	26:1
	PPh_3	PhI	61%	14:1
	IMes	PhBr	96%	67:1

Sames has also described a rhodium catalyst capable of arylating free (NH)-indole and pyrrole at the C-2 position.[24] The proposed catalytic cycle and selected examples are shown in Scheme 1.4. The catalyst could be either generated *in situ* or isolated prior to the reaction by combining the indole, $[Rh(COE)_2Cl]_2$, (p-$CF_3Ph)_3P$, CsOPiv and the appropriate iodoarene in dioxane at 120°C. After oxidative insertion of the $[Rh(COE)_2Cl]_2$ complex into carbon-iodine bond, a Rh(III) complex **I** is generated as a resting state, which has been isolated and characterized. This complex can then metalate the indole in a slow step giving the intermediate **III**. Upon reductive elimination of the coupled indole a Rh(I) catalyst is regenerated which can re-enter the catalytic cycle. Mechanistic studies revealed that both the CsOPiv and the iodoarene serve as trapping agents,[25] stabilizing the rhodium intermediates from decomposition.

[24] Wang, X.; Lane, B.S.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 4996.
[25] Baranano, D.; Hartwig, J.F. *J. Am. Chem. Soc.* **1995**, *117*, 2937.

Scheme 1. 4. Rhodium Catalyzed Arylation of Indole and the Proposed Mechanism.



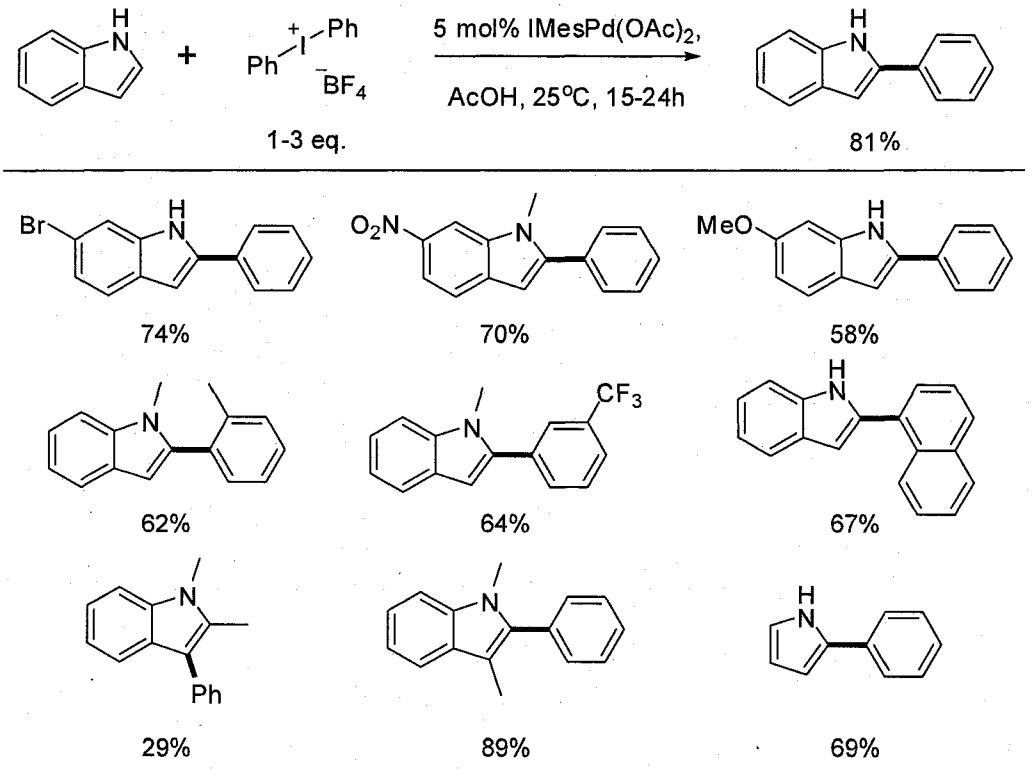


Under an oxidative $Pd^{II/IV}$ manifold, the group of Prof. Sanford achieved C-2 arylation of indoles and pyrroles under very mild conditions.[26] They reasoned that the electrophilic palladation, which is rate limiting in the $Pd^{0/II}$ cycle, could proceed faster using an electron-deficient palladium species such as palladium acetate rather than an electron rich palladium complex such as $PdPh(PPh_3)_2I$. A second oxidation using hypervalent iodide complex such as $[Ar\text{-}I\text{-}Ar]BF_4$ would give a palladium (IV) biaryl complex capable of reductively eliminating the product while regenerating the palladium

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

(II) catalyst. As expected, the formation of 2-arylindoles in good to excellent yield were obtained. Unlike their predecessors, the protocol is air and moisture compatible, reacts at room temperature to give high conversion to the C-2 adduct in 24h using acetic acid as the solvent. A number of different diaryliodonium salts and indole are shown in Table 1.3. When the C-2 position is blocked, the C-3 product could be isolated albeit in lower yield. These diaryliodonium salts can be easily prepared from cheap commercially available starting materials.[27]

Table 1. 3. Scope for the Direct Arylation of Indoles and Pyrrole Using Diaryliodonium salts.

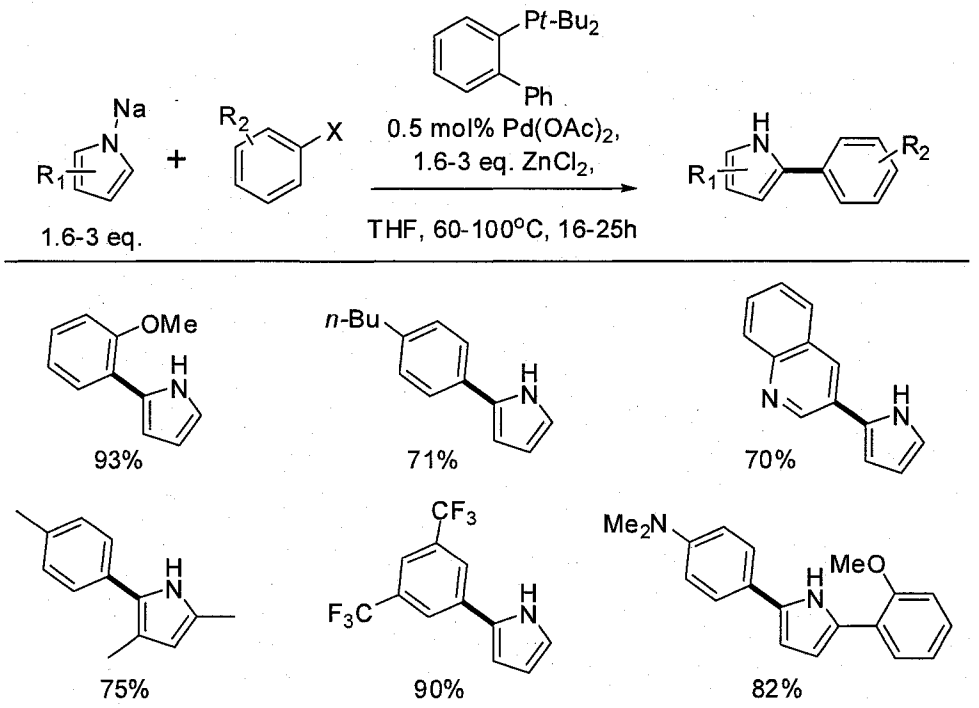


[27] (*a*) Chen, D. W.; Ochiai, M. *J. Org. Chem.* **1999**, *64*, 6804. (*b*) for the synthesis of $ArI(OAc)_2$: McKillop, A.; Kemp, D. *Tetrahedron.* **1989**, *45*, 3299.

1.1.1.2 – Azoles

By changing Filippini's protocol,[28] Sadighi and coworkers were able to improve the efficacy of pyrrole direct arylation while reducing the catalyst loading (Table 1.4).[29] Using Buchwald's bulky and electron rich biphenyl ligands, the modified protocol allowed the arylation of many different aryl iodides, bromides as well as chlorides in good to excellent yields. Furthermore, sterically encumbered 2,4-dimethylpyrrole reacted in similar yields.

Table 1. 4. Selected Example of Direct Arylation Using Pyrrole.

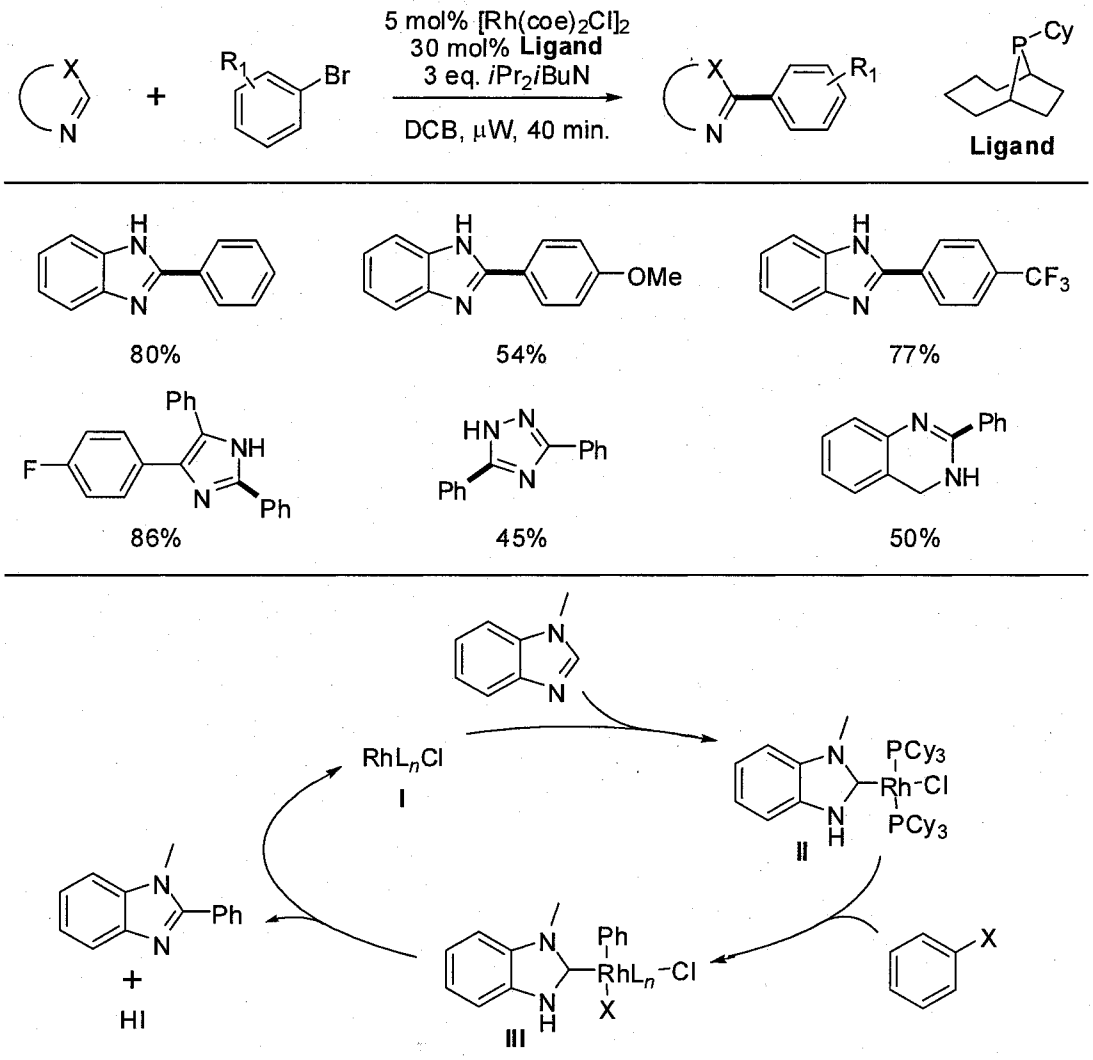


In 2006, the groups of Bergman and Ellman reported new conditions allowing their previously described rhodium catalyst to be extended to include less reactive aryl bromides.[30] Through a careful ligand evaluation, a wide array of azoles could be reacted with many different aryl bromides under microwave irradiation in good to excellent yields

[28] Filippini, L.; Gusmeroli, M.; Riva, R. *Tetrahedron Lett.* **1992**, *33*, 1755.
[29] Rieth, R.D.; Mankad, N.P.; Calimano, E.; Sadighi, J.P. *Org Lett.* **2004**, *6*, 3981.
[30] Lewis, J.C.; Wiedemann, S.H.; Bergman, R.G.; Ellman, J.A. *Org. Lett.* **2004**, *6*, 35.

(Scheme 1.5).[31] They also demonstrated the formation of the rhodium carbene **II**, which was postulated to be an essential intermediate in their catalytic cycle as depicted in Scheme 1.10. Once the carbene intermediate **II** is generated, oxidative insertion into the aryl halide bond gives the diarylrhodium species **III**, from which subsequent reductive elimination gives the arylazole.[30]

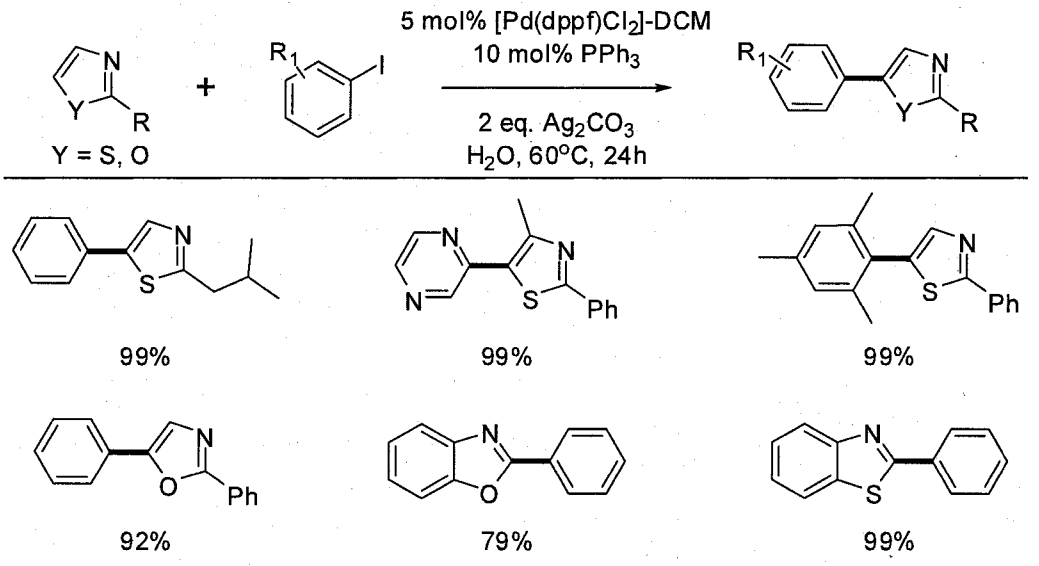
Scheme 1. 5. Catalytic Cycle and Substrate Tolerance by Bergman and Ellman.



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

A re-evaluation of the direct arylation of thiazoles by Greaney and co-workers has also been recently reported.[32] Under these new conditions, the C-5 arylation of C-2 substituted thiazoles were realized under milder reaction conditions than previously described (Table 1.5). The explanation for such mild conditions is attributed to the use of silver additives, which are known to sequester iodide anions which have inhibitory effects in these types of transformations.[33] The beneficial effect of water was accredited to a substantial increase in the concentration of the catalyst and reagents. While the scope is restricted to iodoarenes, these conditions were found to be compatible with different heterocycles including benzimidazoles, benzoxazole, benzothiazole, oxazole and thiophenes.

Table 1. 5. High Yielding Arylation of Heterocycles on Water.

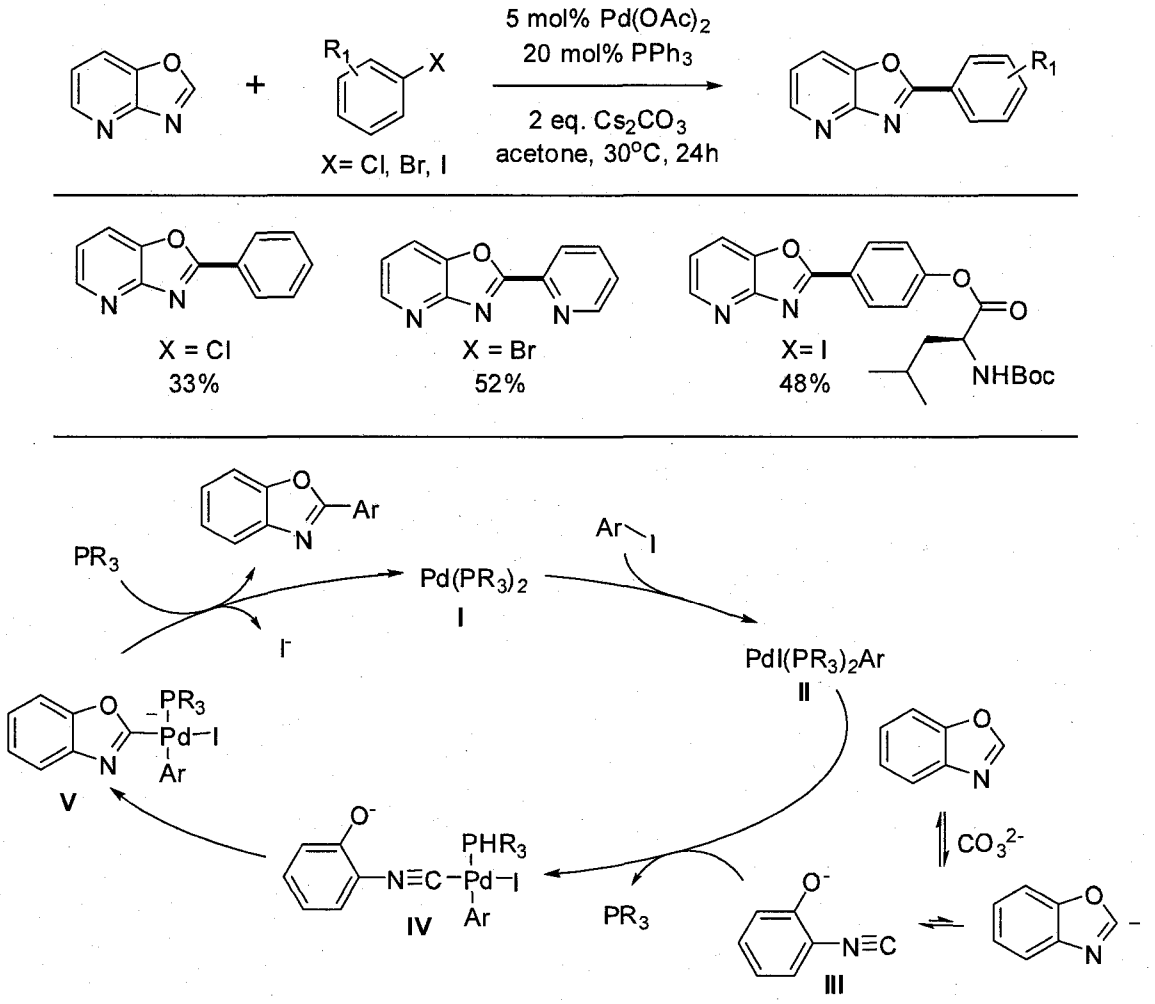


In 2006, Zhuravlev reported the mild arylation of oxazolo[4,5-*b*]pyridine with aryl halides using a palladium-triphenylphosphine catalyst in acetone at 30°C. Several representative examples are shown in Scheme 1.6.[34] The increased reactivity of these heterocycles was associated with the facile deprotonation of the highly acidic C-2 protons under the reaction conditions. In 2007, they reported mechanistic evidence for a

[32] Turner, G.L.; Morris, J.A.; Greaney, M.F. *Angew. Chem. Int. Ed.* **2007**, *46*, 7996.
[33] (*a*) Masui, K.; Mori, A.; Okano, K.; Takamura, K.; Kinoshita, M.; Ikeda, T. *Org. Lett.* **2004**, *6*, 2011 (*b*) Campeau, L.-C., Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 581.
[34] Zhuravlev, F.A. *Tetrahedron Lett.* **2006**, *47*, 2929.

ring-opening mechanism.[35] The cycle begins with reversible deprotonation of the benzoxazole, followed by a ring opening to the more stable 2-isocyanophenolate **III** which are known to be excellent ligands for palladium.[36] Association of **III** with the palladium (II) intermediate **II**, generated from oxidative addition onto the aryl iodide followed by ring closure, generates the required anionic diarylpalladium intermediate **V**. Reductive elimination of the product regenerates of the active catalyst (Scheme 1.6).

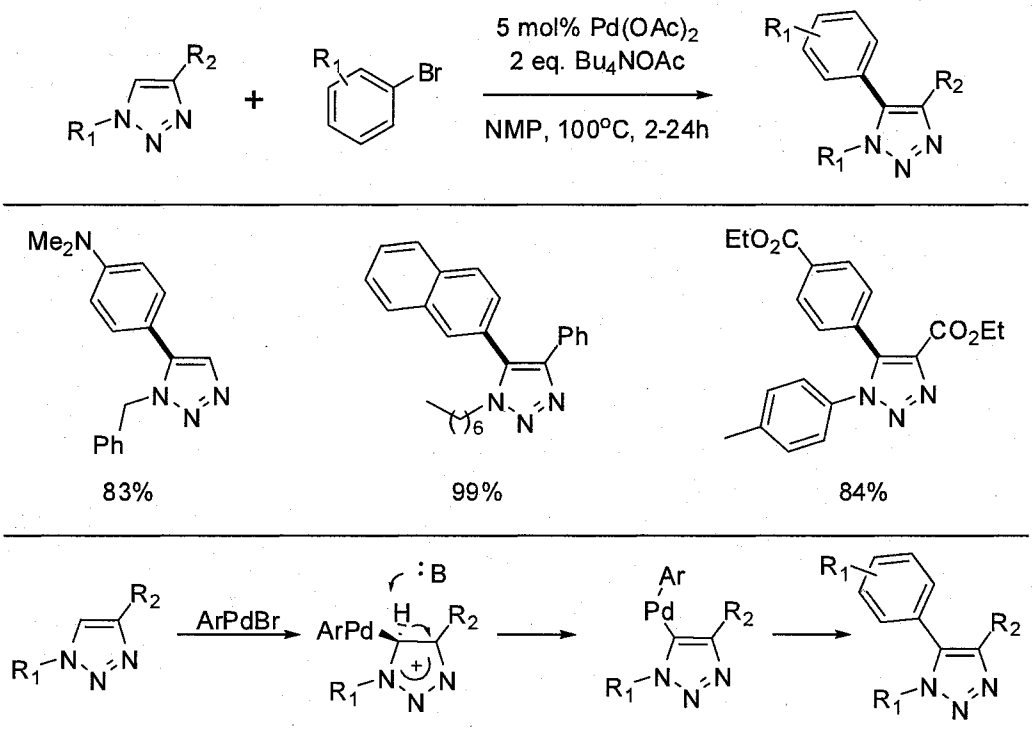
Scheme 1. 6. Proposed Catalytic Cycle for the Arylation of Benzoxazoles.



[35] Sánchez, R.S.; Zhuravlev, F.A. *J. Am. Chem. Soc.* **2007**, *129*, 5824.
[36] Kernbach, U.; Lugger, T.; Hahn, F.E.; Fehlhammer, W.P. *J. Organomet. Chem.* **1997**, *541*, 51.

The direct arylation of 1,2,3-triazole at the C-5 position was first accomplished by the group of Gevorgyan.[37] Using 5 mol% of palladium acetate with 2 equivalents of tetrabutylammonium acetate in NMP at 100°C, various 1,2,3-triazoles were coupled with different aryl bromides in good to excellent yield (Scheme 1.7). Kinetic isotope effect studies and DFT calculations of the electrostatic potential charge at C-4 and C-5 strongly suggest an electrophilic palladation mechanism as the most probable pathway as shown in Figure 1.2.

Scheme 1. 7. Direct Arylation and Proposed Mechanism of 1,2,3-Triazoles.

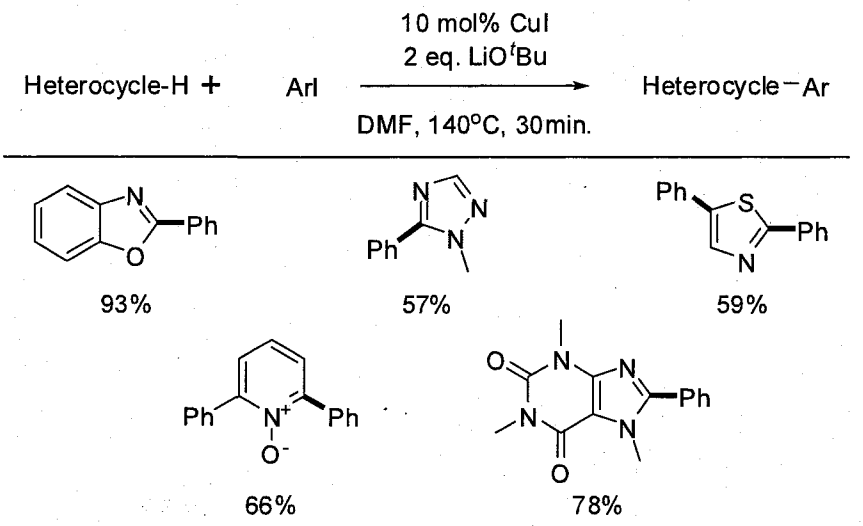


Daugulis and Do have developed a new protocol using inexpensive copper iodide (I) as the catalyst in conjunction with lithium *tert*-butoxide.[38] These conditions are compatible with many different heterocycles including benzoxazoles, oxazoles, thiazoles, benzothiazoles, benzimidazoles, 1,2,4-triazoles, caffeine as well as electron poor pyridine *N*-oxides. When potassium *tert*-butoxide was employed as the base, the mechanism was demonstrated to proceed through a benzyne intermediate while use of

[37] Chuprakov, S.; Chernyak, N.; Dudnik, A.S.; Gevorgyan, V. *Org. Lett.* **2007**, *9*, 2333.
[38] Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 12404.

lithium *tert*-butoxide proceeds through a copper assisted deprotonation of the heteroarene. Illustrative examples are shown in Table 1.6.

Table 1. 6. Copper Catalyzed Direct Arylation of Heterocycles.

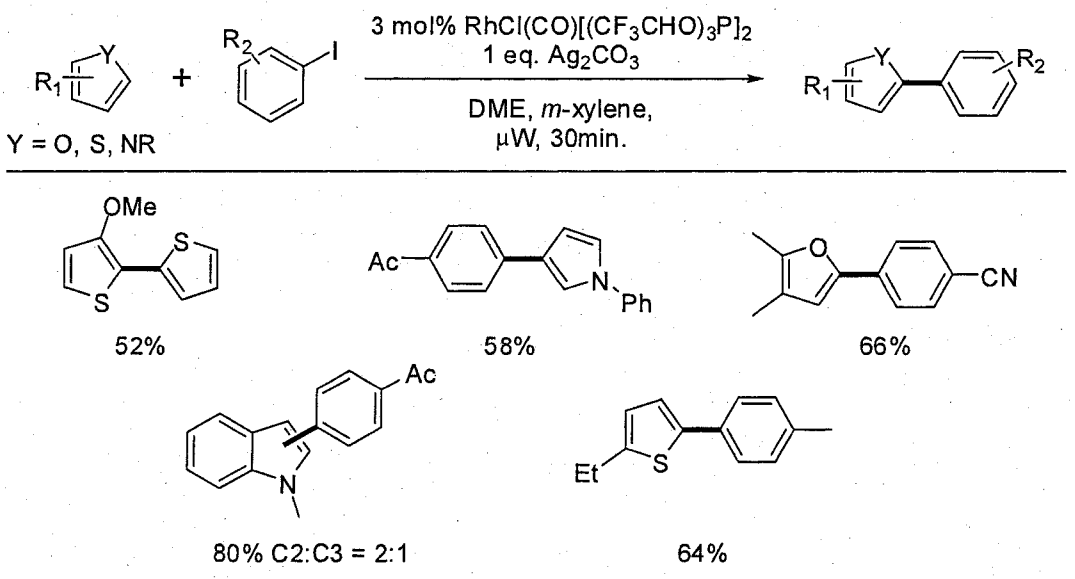


1.1.1.3 – Thiophenes and Furans

In 2006, Itami and coworkers developed an alternative rhodium catalyst for the arylation of thiophene, furans, pyrroles and indoles (Table 1.7).[39] Contrary to the previous systems, their rhodium catalyst included strong π-accepting perfluoroalkylphosphite ligands which were suggested to facilitate the electrophilic rhodation step of the catalytic cycle. The reaction was compatible with different aryl iodides while aryl bromides and triflates reacted with difficulty. Arylation at the C-2 position was favored with thiophenes and furans while *N*-phenylpyrrole gave exclusive C-3 arylation.

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

Table 1. 7. Direct Arylation of Aryl Iodide by Heteroarenes.



1.1.2 – Direct Arylation of π-Electron Poor Arenes.

As opposed to the wealth of examples involving π-electron rich heteroarenes in direct arylation, π-electron deficient heteroarenes such as pyridines have rarely been examined. Their low nucleophilicity makes them unsuitable substrates for an electrophilic metallation mechanism. Furthermore, pyridine is often employed as a ligand for transition metals which may poison the catalyst. Aside from one report for the synthesis of 2-phenylpyridine in low yield (through a free-radicals process),[40] no examples of direct arylation of pyridine or its derivatives were reported prior to 2005.

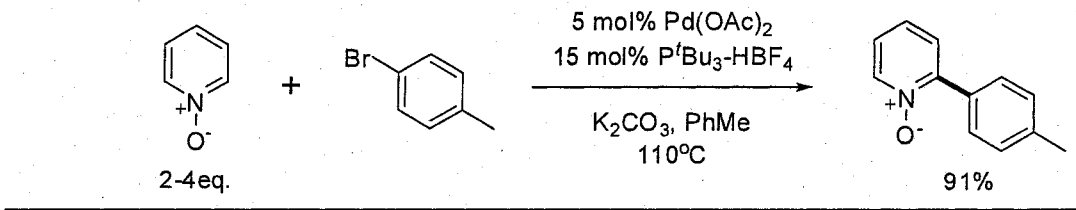
1.1.2.1 – Pyridine *N*-Oxides and Diazines *N*-Oxides

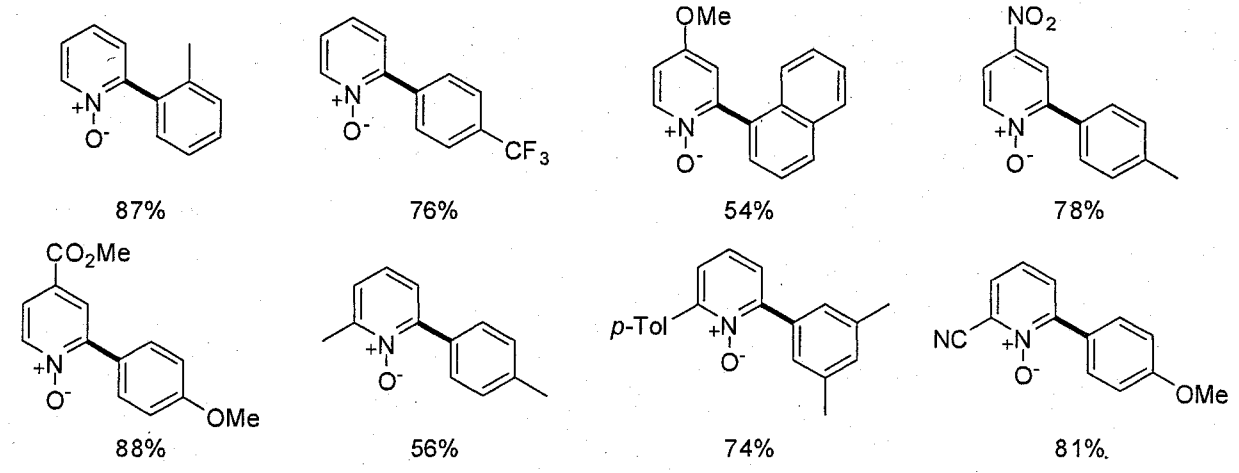
In an attempt to overcome the challenges associated with the use of pyridines in direct arylation, our group investigated the use of pyridine *N*-oxides as masked pyridine analogues. These species are commercially available, cheap and bench stable. Furthermore, the C-2 position is more nucleophillic and posses more acidic protons than

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

their pyridine counterparts.[41] Using an excess of pyridine *N*-oxide (4 eq.), 5 mol% $Pd(OAc)_2$, 15 mol% $P^tBu_3{\cdot}HBF_4$, 4-bromotoluene and K_2CO_3 in refluxing toluene, the cross-coupling product could be isolated in 91% yield.[42] It is worth noting that these reactions are not sensitive to water and the excess of pyridine *N*-oxide can be recuperated after the reaction in high yields. Illustrative examples of the reaction scope are shown in Table 1.8. This methodology was also optimized for its application on multi-gram scale.[43] Pyridine *N*-oxides have been shown to exothermically decompose at elevated temperature, therefore careful controlling of the reaction temperature is recommended.[44]

Table 1. 8. Selected Examples of Direct Arylation Using Pyridine *N*-Oxides.



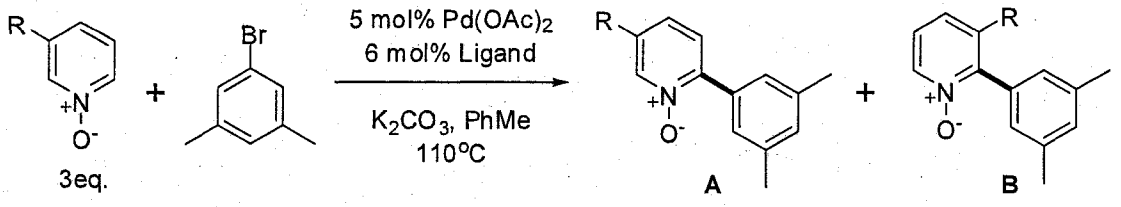


When using C-3 substituted pyridine *N*-oxides, the regioselectivity was governed by both the electronics and the sterics of the substituent. The product distribution could

[41] For a review on oxidation of pyridine, see: Ochiai, E. *Aromatic Amine Oxides*; Elsevier: Amsterdam, 1967; Albini, A.; Pietra, S. *Heterocyclic N-Oxides*; CRC Press: Boca Raton, FL, 1991.
[42] (*a*) Campeau, L.-C.; Rousseaux, S.; Fagnou, K. *J. Am.Chem. Soc.* **2005**, *127*, 18020. (*b*) Campeau, L.-C.; Stuart, D.R.; Sun H.-Y. ; Fagnou, K. *Unpublisehd Results*.
[43] Campeau, L.-C.; Fagnou, K. *Unpublished Results*.
[44] Ando, T.; Fujimoto, Y.; Morisaki, S. *J. Haz. Mat.* **1991**, *28*, 251.

be modulated by replacing the bulky $P^tBu_3 \cdot HBF_4$ with a slightly smaller $P^tBu_2Me \cdot HBF_4$. Different examples are shown in Table 1.9.

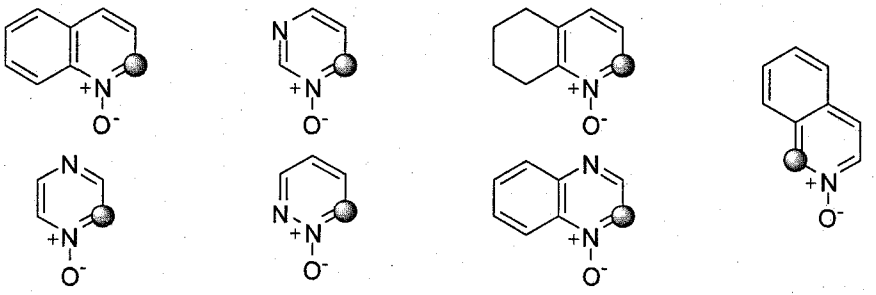
Table 1. 9. Effects of C-3 Substituents on Selectivity.



Entry	R	Ligand	Yield (%)	Ratio **A**:**B**
1	Ph	P^tBu_3-HBF_4	94	10:1
2	OMe	P^tBu_3-HBF_4	88	1.1:1
		P^tBu_2Me-HBF_4	96	1:5.2
3	NO_2	P^tBu_3-HBF_4	89	1:3.7
		P^tBu_2Me-HBF_4	86	1:6.3
4	CN	P^tBu_3-HBF_4	98	1:9.5
		P^tBu_2Me-HBF_4	88	1:15
5	F	P^tBu_3-HBF_4	83	1:25

This methodology was extended to the quinoline,[42b] isoquinoline,[42b] pyrimidine,[45] pyrazine,[45] pyridazine,[45] quinoxaline[45] and the phtalazine[45] *N*-oxide families, all of which react adjacent to the *N*-oxide moiety in moderate to excellent yield. The preferred position of arylation is demonstrated in Figure 1.3.

Figure 1. 3. Preferred Position of Direct Arylation of Azines *N*-Oxides.

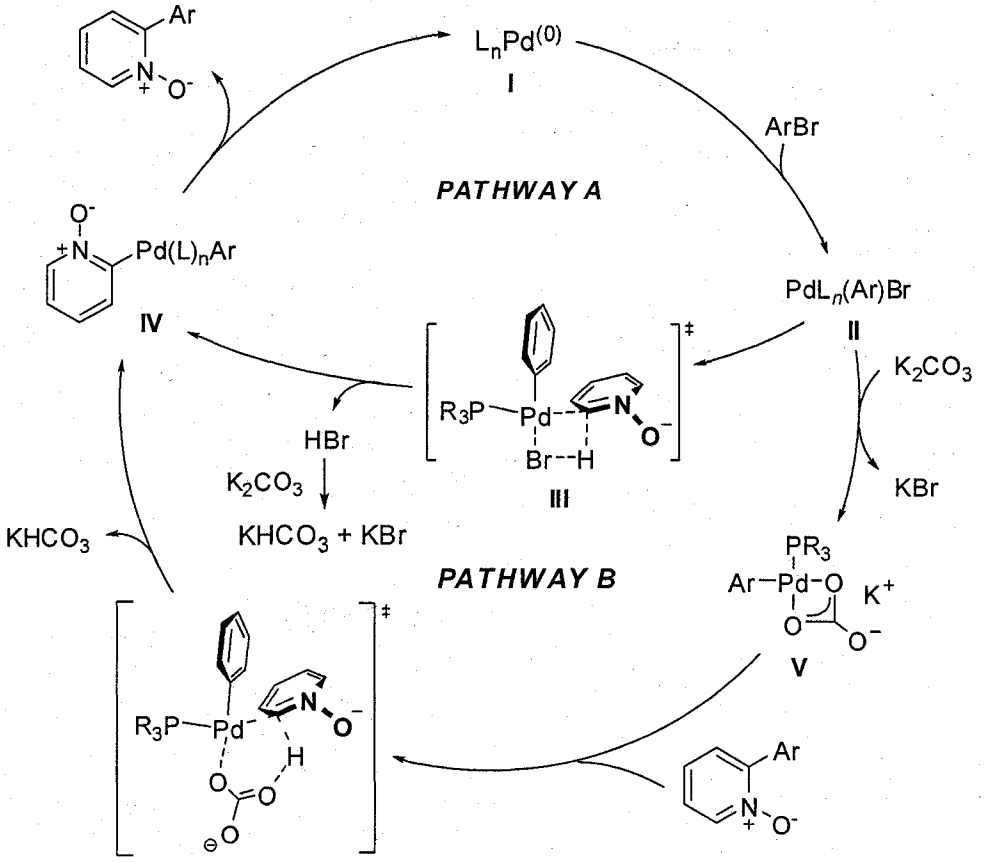


● = denotes the preferred position of arylation

[45] Leclerc, J,-P.; Fagnou, K. *Angew.Chem., Int. Ed,* **2006**, *45*, 7781.

Mechanistic and DFT studies support a concerted intramolecular deprotonation/metallation mechanism as illustrated in Scheme 1.8. Oxidative addition of a palladium (0) species into the aryl halide bond generates intermediate **II** from which two viable pathways were found. In pathway A, a concerted deprotonation/metallation sequence occurs to generate the palladium complex **IV**. Alternatively (pathway B), ligand exchange of the halide with a carbonate generates a palladium carbonate **V** which undergoes a similar six membered ring deprotonation/metallation to give the same species **III**. Reductive elimination of **III** produces the product as well as regenerating the palladium (0) catalyst.

Scheme 1. 8. Proposed Mechanism for Arylation of Pyridine *N*-Oxides.



1.1.3. – Directing Groups as a Mean to Direct Arylation

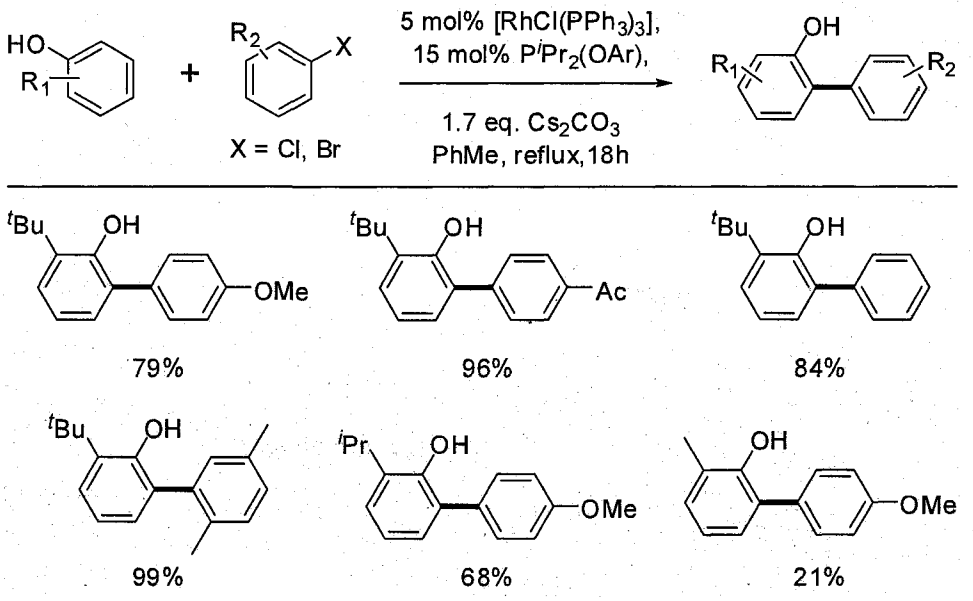
Simple arenes have been the most challenging substrate class to employ in direct arylation due to the attennuated nucleophilicity. A solution to this problem involves the use of Lewis basic moieties as directing groups. By creating a temporary tether between the arene and the metal catalyst, the process is rendered more facile by minimizing the large entropy factor. The group of Kleinman and Dubeck were the first to use this concept in C-H bond activation over 40 years ago.[46] Since this first application, many examples have appeared. Phenols, imines, pyridines, ketones, amides, aldehydes, oxazolines, imidazolines and pyrazoles have all been demonstrated to serve this purpose.

1.1.3.1 – Phenols

Bedford and coworkers have capitalized on the enhanced reactivity of phenolic substrate through the addition of catalytic amounts of phosphorus donors such as phosphites.[47] Good to excellent yields of 2-arylated phenols were obtained under optimal conditions using Wilkinson's catalyst regardless of the nature of the aryl bromides. Selected examples are shown in Table 1.10.

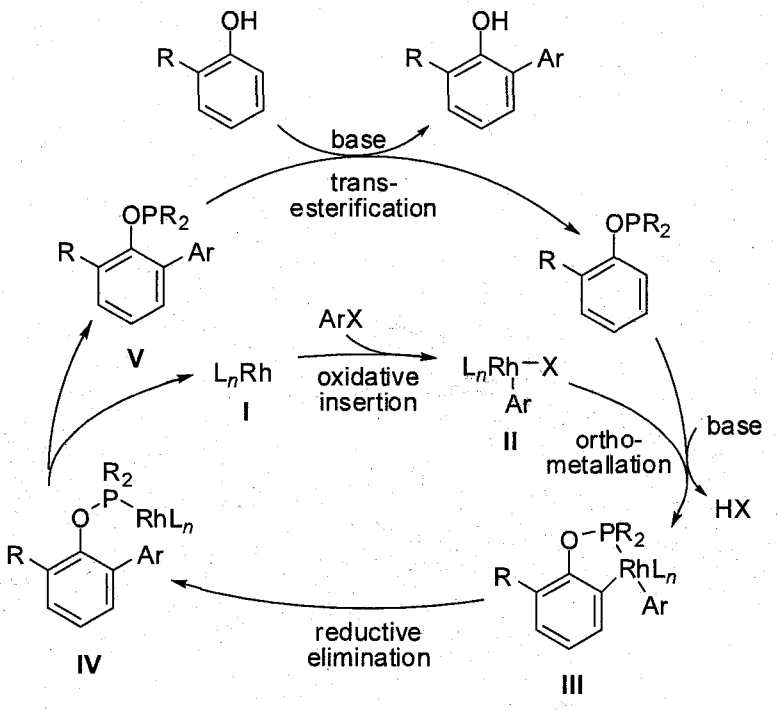
[46] Kleinman, J. P.; Dubeck, M., *J. Am. Chem. Soc.*, **1963**, *85*, 1544.
[47] (*a*) Bedford, R.B.; Coles, S.J.; Hursthouse, M.B.; Limmert, M.E. *Angew.Chem., Int. Ed.* **2003**, *42*, 112. (*b*) Bedford, R.B.; Limmert, M.E. *J. Org. Chem.* **2003**, *68*, 8669.

Table 1. 10. *Ortho* Direct Arylation of Phenols.



The mechanism, as depicted in Scheme 1.9, commences with the coordination and orthometallation of the phosphinite co-catalyst phenolate adduct with the rhodium **II** center. Reductive elimination of the diarylrhodium intermediate **III** regenerates the active catalyst. Transesterification of the product with new phenol substrates gives the desired 2-arylphenol as well as the regeneration of the phosphinite co-catalyst.

Scheme 1. 9. Proposed Mechanism for *Ortho* Direct Arylation of Phenols.



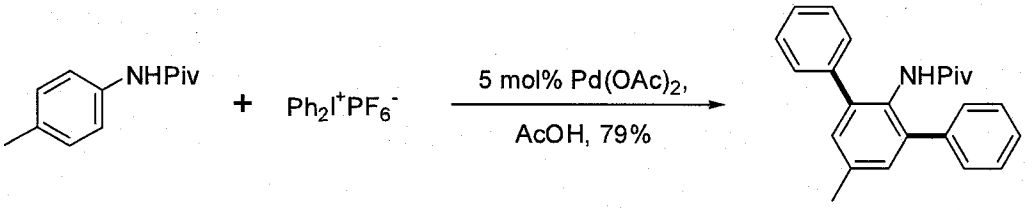
Oi and Inoue have also reported a similar rhodium system for the same transformation. Using 2.5 mol% of $[RhCl(cod)_2]$ in conjunction with hexamethylphosphorous triamide as a cocatalyst, different phenols were arylated in the C-2 position in low to good yields. [48]

1.1.3.2 – Amides and Benzylamines

Xia and Chen have reported the synthesis of 1,6-diphenylanilines by *ortho* direct arylation of 4-methyl-pivalanilide with diphenyliodonium salts in 79% yield (Scheme 1.10).[49] This motif is useful for the synthesis of many ligands for the Brookhart-type metal-catalyzed polymerizations reactions.[50]

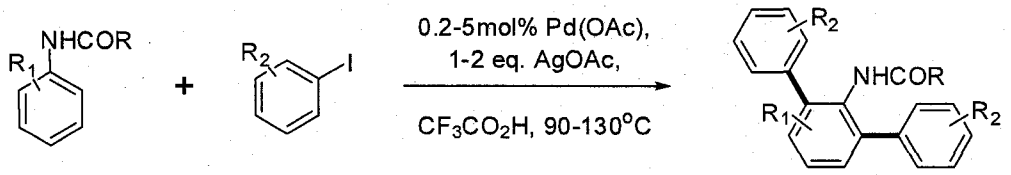
[48] Oi, S. ; Watanabe, S.-I. ; Fukita, S.; Inoue, Y. *Tetrahedron Lett.* **2003**, *44*, 8665.
[49] Xia, M.; Chen, Z. *Synth. Commun.* **2000**, *30*, 531.
[50] Schmid, M.; Eberhardt, R.; Klinga, M.; Leskelae, M.; Rieger, B. *Organometallics,* **2001**, *20*, 2321.

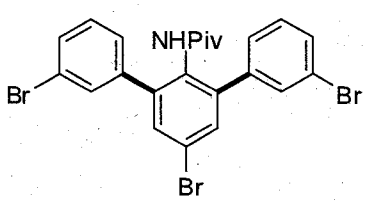
Scheme 1. 10. Amide Arylation with Iodonium Salts.



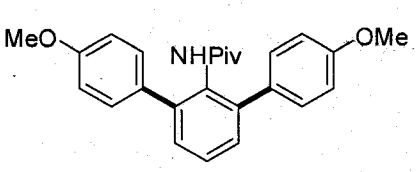
Due to the high cost and low availability of these diaryliodonium salts, Daugulis improved the protocol by making use of the commercially and widely available iodoarenes. This was achieved by employing stochiometric amounts of silver acetate in trifluoroacetic acid (Table 1.11).[51] The reaction conditions were compatible with different pivalanilides and acetanilides with different aryl iodides affording 2,6-diarylanilines in good to excellent yield.

Table 1. 11. Amide Arylation with Iodoarenes.

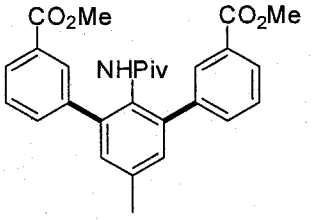




79%



96%



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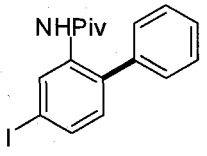

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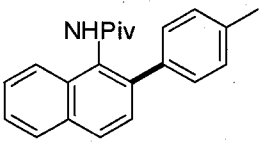
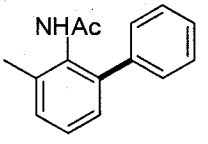


68%



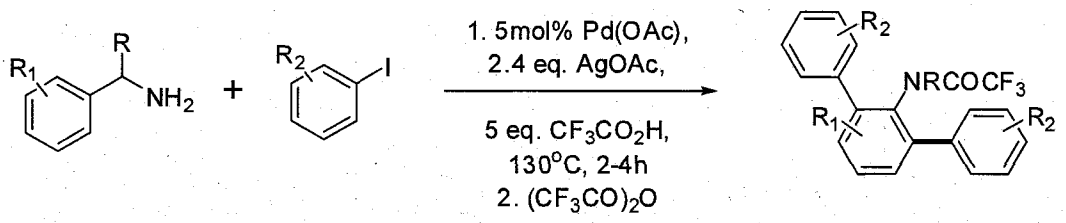
21%

Subsequently, Daugulis investigated the use of benzylamines and benzamides as potential directing groups. Using similar reaction conditions, double *ortho*-arylation of *N*-

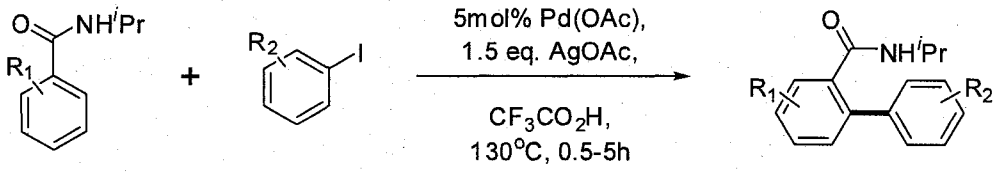
[51] Daugulis, O.; Zaitsev, V.G. *Angew.Chem., Int. Ed.* **2005**, *44*, 4046.

acetyl protected benzylamines was obtained in moderate to good yields,[52] while unprotected benzylamines gave the mono addition product in similar yields.[53] Different examples from these two reactions are shown in Table 1.12.

Table 1. 12. Benzylamine and Benzamide *ortho*-Arylation with Iodoarenes.



R	R_1	R_2	Yield
Me	H	4-Me	83%
H	4-Me	4-F	67%
Me	4-Br	H	61%



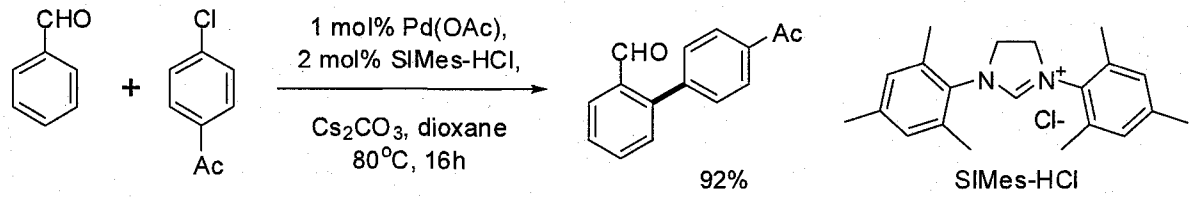
R_1	R_2	Yield
3,4-dimethyl	3-OCF_3	96%
3-Br	4-Cl	79%
2-Cl	4-Br	59%

1.1.3.3 – Aldehydes

In 2005, Çetinkaya reported the direct *ortho*-arylation of benzaldehyde derivatives with chloro- and bromoarenes in good yields.[54] Using small amounts of palladium acetate with imidazolium salts as carbene ligand precursors and chloroarenes, they isolated the mono addition product in good to excellent yield. With aryl bromides, they isolated the 2,6-diarylatedbenzaldehyde products instead. An example of the reaction with an aryl chloride is shown in Scheme 1.11.

[52] Lazareva, A.; Daugulis, O. *Org. Lett.* **2006**, *8*, 5211.
[53] Shabashov, D.; Daugulis, O. *Org. Lett.* **2006**, *8*, 4947.
[54] Gürbüz, N.; Özdemir, I.; Çetinkaya, B. *Tetrahedron Lett.* **2005**, *46*, 2273.

Scheme 1. 11. *ortho*-Arylation of Benzaldehyde with Chloroarenes.

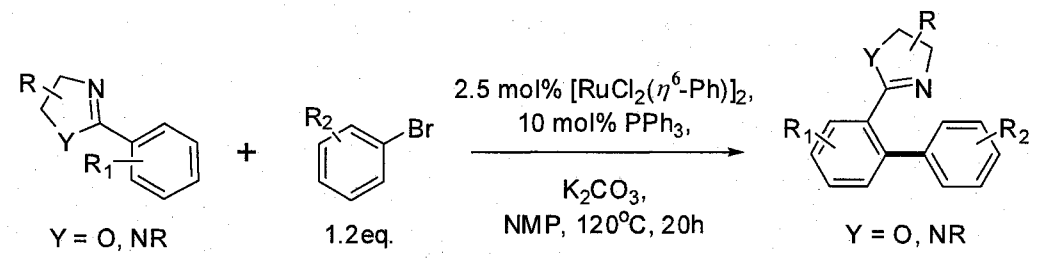


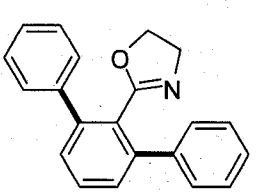
1.1.3.4 – Oxazolines and Imidazolines

Oxazolines and imidazolines, when attached to an aromatic ring, are known to undergo direct *ortho*-ruthenation.[55] Further, these functional groups can easily be converted to other functional groups such as carboxylic acids.[56] Oi and Inoue took advantage of this by designing a direct arylation reaction using these directing groups.[57] Different oxazolines and imidazolines were compatible as well as sterically and electronically different aryl bromides (Table 1.13). They propose that the mechanism proceeds through an *ortho*-ruthenation to form a stable five-membered ring intermediate before or after oxidative insertion into the carbon bromide bond.

[55] (*a*) Ie, Y.; Chatani, N.; Ogo, T.; Marshall, D.R.; Fukuyama, T.; Kakiuchi, F.; Murai, S. *J. Org. Chem.* **2000**, *65*, 1475. (*b*) Kakiuchi, F.; Matsumoto, M.; Tsuchiya, K.; Igi, K.; Hayamizu, T.; Chatani, N.; Murai, S. *J. Organomet. Chem.* **2003**, *686*, 134.
[56] For a review, see: Gant, T.G.; Meyers, A.I. *Tetrahedron.* **1994**, *50*, 2297.
[57] Oi, S.; Aizawa, E.; Ogino, Y.; Inoue, Y. *J. Org. Chem.* **2005**, *70*, 3113.

Table 1. 13. *ortho*-Arylation of Oxazolines and Imidazolines with Bromoarenes.





2.5 eq.
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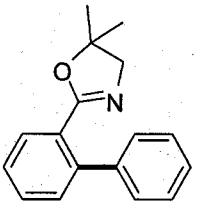
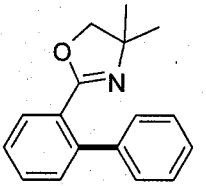
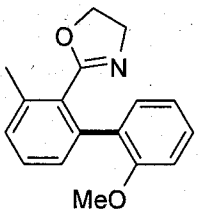


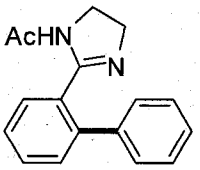
62%
mono:di = 3:7



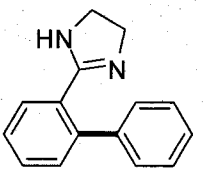
11%



71%



76%
mono:di = 9:1



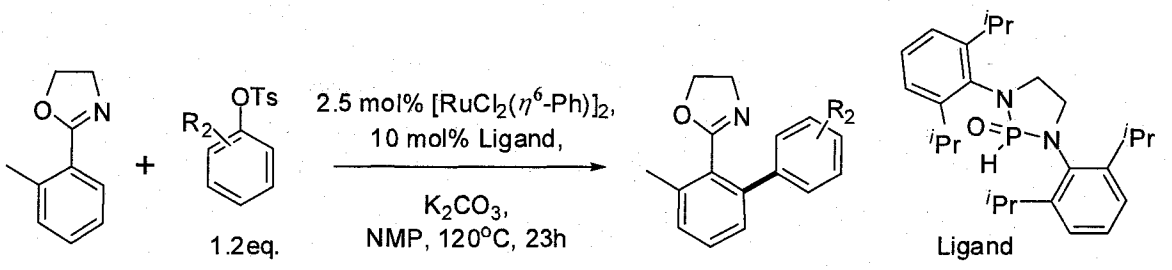
64%
mono:di = 3:7

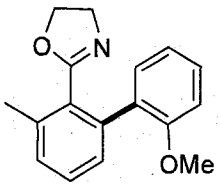
Aryl tosylates are an attractive electrophile in cross-coupling reactions. Unlike triflates, they are highly stable, crystalline and can be prepared from simple and inexpensive starting material. Unfortunately, their increased stability and hence diminished reactivity has limited their utility in traditional cross-coupling reactions until recently.[58] Using the same catalyst as Oi and Inoue, but replacing the ligand with a more bulky, air- and moisture-stable diaminophosphine oxide, Ackermann and coworkers could achieve the direct arylation of 2-aryloxazolines using different aryl tosylates in good to excellent yields.[59] This constitutes the first example of direct arylation using the less reactive aryl tosylate. A small sample of arylated products is shown in Table 1.14.

[58] For recent examples, see: (*a*) Tang, Z.-Y. Hu, Q.-S. *J. Am.Chem. Soc.* **2004**, *126*, 3058. (*b*) Zhou, J.; Fu, G.C. *J. Am.Chem. Soc.* **2003**, *125*, 12527. (*c*) Roy, A.H.; Hartwig, J.F. *J. Am.Chem. Soc.* **2003**, *125*, 8704. (*d*) Limmert, M.E.; Roy, A.H.; Hartwig, J.F. *J. Org. Chem.* **2005**, *70*, 9364. (*e*) Percec, V.; Golding, G.M.; Smidrkal, J.; Weichold, O.. *J. Org. Chem.* **2004**, *69*, 3447.

[59] Ackermann, L.; Althammer, A.; Born, R. *Angew.Chem., Int. Ed,* **2006**, *45*, 2619.

Table 1. 14. *ortho*-Arylation of Oxazolines with Tosylates.





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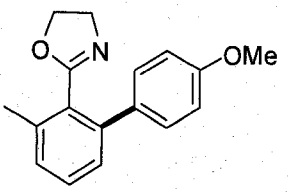

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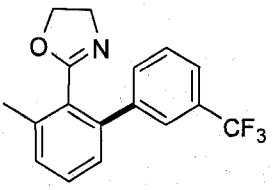

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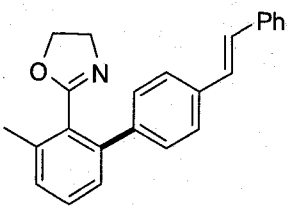
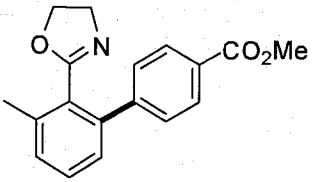


85%



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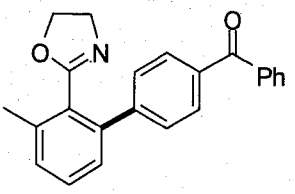


94%

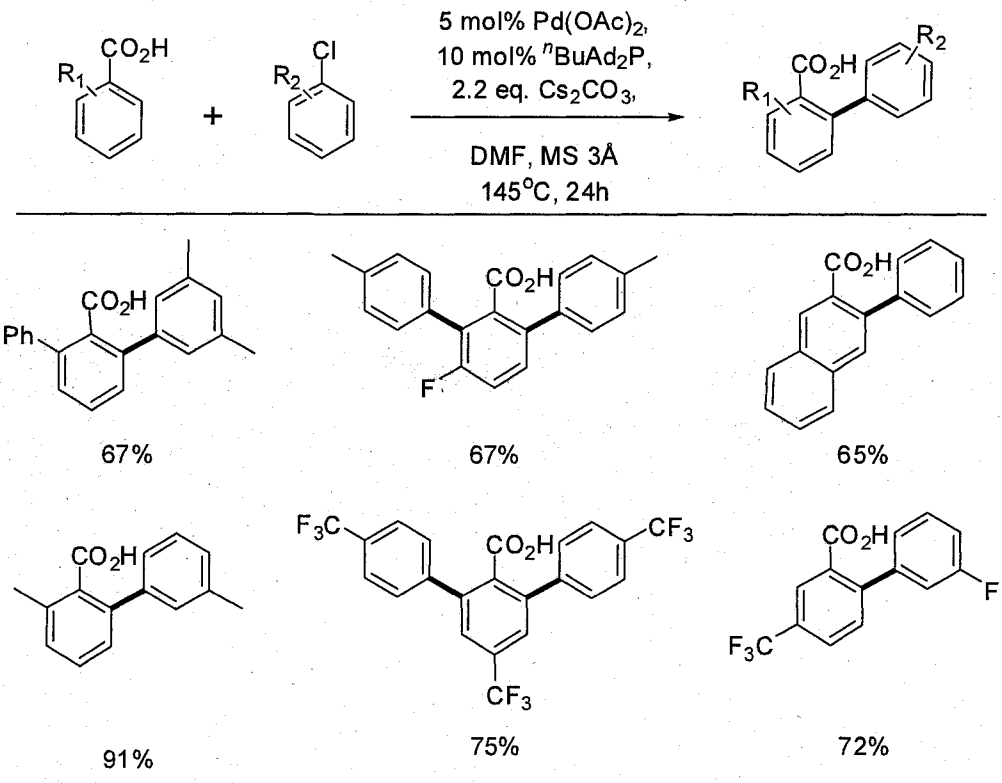
1.1.3.5 – Benzoic Acids

While many carbonyl derivatives are known to be good directing groups for direct arylation, it was not until recently that unprotected carboxylic acids were investigated. Daugulis and coworkers reported two different reaction conditions, one using aryl iodides and one using aryl chlorides.[60] With iodoarenes, the reaction was performed using 5 mol % of palladium acetate, 1.3 equivalents of silver acetate and 3.5 equivalents of acetic acid at 130°C, giving moderate yields of the biaryl. On the other hand, the arylation of chloroarenes was performed with 5 mol% of palladium acetate, 10 mol% *n*-butyl-di-1-adamantylphosphines, 3Å molecular sieves and cesium carbonate at 145°C. In both cases, good functional group tolerance was observed with respect to the benzoic acid

[60] Chiong, H.A.; Pham, Q.-N.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 9879.

component (Table 1.15). Using the protocol of Gooβen and coworkers, the carboxylic moiety can be decarboxylated, making it a traceless activator.[61]

Table 1. 15. *ortho*-Arylation of Benzoic Acids with Aryl Chlorides.



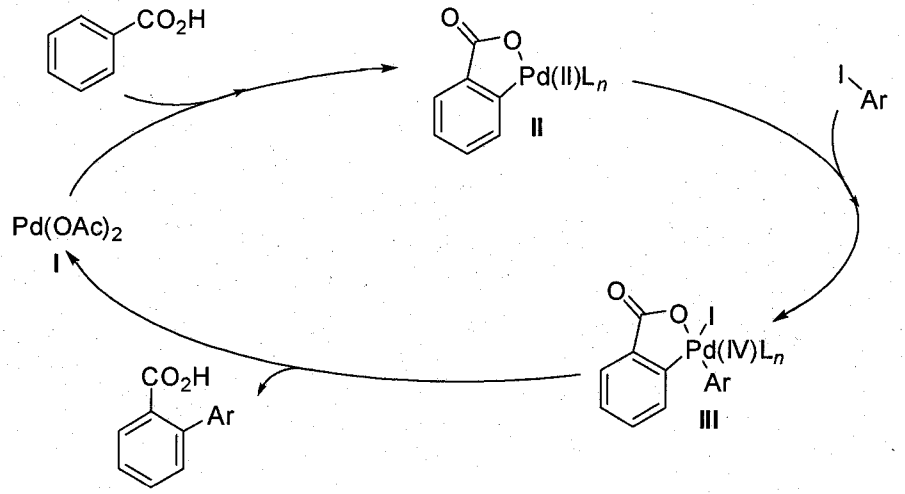
The mechanism that best suits the experimental data for the direct arylation with an iodoarene involves a palladium II/IV cycle as shown in Scheme 1.12. Palladation into the *ortho*-position of the benzoic acid generates a stable five-membered ring intermediate **II**. This intermediate reacts with the aryl iodide to give the palladium (IV) species. Reductive elimination regenerates the palladium (II) catalyst **I** and liberates the product. The mechanism for the arylation using an aryl chloride is proposed to operate under a palladium 0/II manifold. The palladium (0) species undergoes oxidative insertion into the aryl chloride bond to give the palladium (II) complex. Association of the deprotonated benzoate with this intermediate leads to a concerted deprotonation/palladation sequence to give the intermediate **IV**. Reductive elimination

[61] Gooβen, L.J.; Deng, G.; Levy, L.M. *Science,* **2006**, *313*, 662.

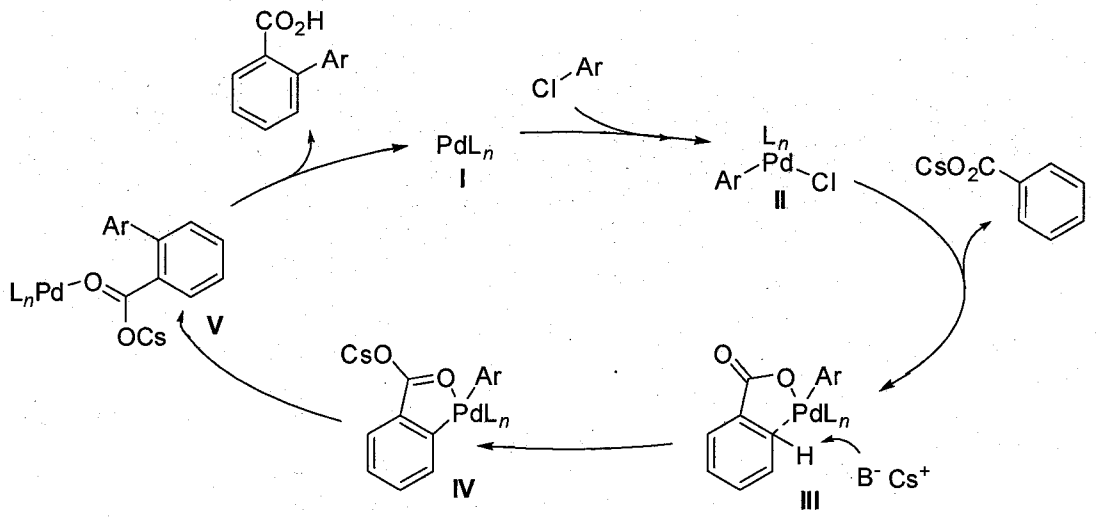
followed by dissociation of the catalyst gives the product and regenerates the palladium (0) catalyst.

Scheme 1. 12. Catalytic Cycle for the *ortho*-Arylation of Benzoic Acids.

Iodoarene Catalytic Cycle



Chloroarene Catalytic Cycle

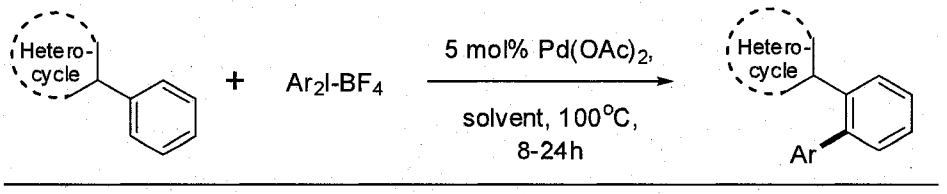


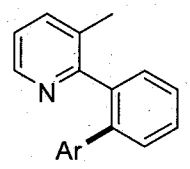
1.1.3.6 – Pyridines, Pyrazoles, Imines and Other Heterocycles.

One of the most commonly employed directing groups in direct arylation is the pyridine moiety. Sanford has shown that the coupling of different 2-arylpyridines can be

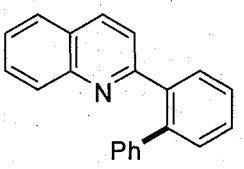
achieved with aryl iodine (III) reagents using palladium acetate in acetic acid.[62] In addition to pyridine directing groups, quinolines, pyrrolidinones, oxazolidinones as well as acetanilides can be employed (Table 1.16). The lack of strong base, the good functional group tolerance as well as the ease of reaction setup in the open air is noteworthy.

Table 1. 16. Direct Arylation Using Pyridines as Directing Group by Sanford.

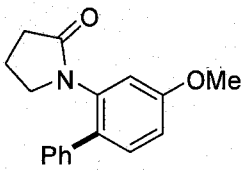




Ar	Yield
Ph	85%
p-CF_3Ph	87%
p-FPh	88%
p-ClPh	83%
p-MePh	84%
o-MePh	72%
p-OMePh	81%



58%



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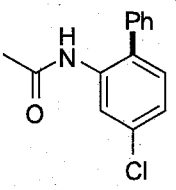

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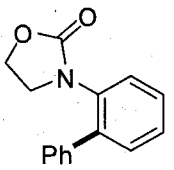
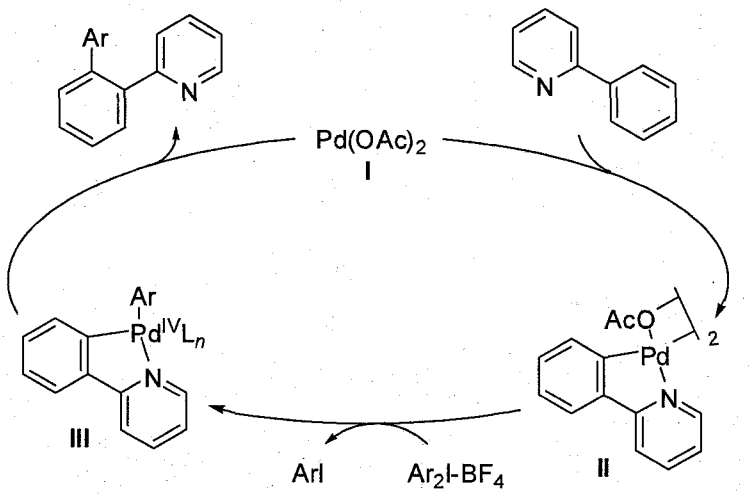


83%

An investigation of the mechanism suggests the reaction proceeds through a palladium II/IV manifold. The catalytic cycle begins with the formation of a metallacyclic dimer **II**. Oxidation of the palladium (II) dimer **II** to palladium (IV) **III** aryl adduct with subsequent C-C bond reductive elimination forms the product and regenerates the palladium (II) acetate catalyst as seen in Scheme 1.13.

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

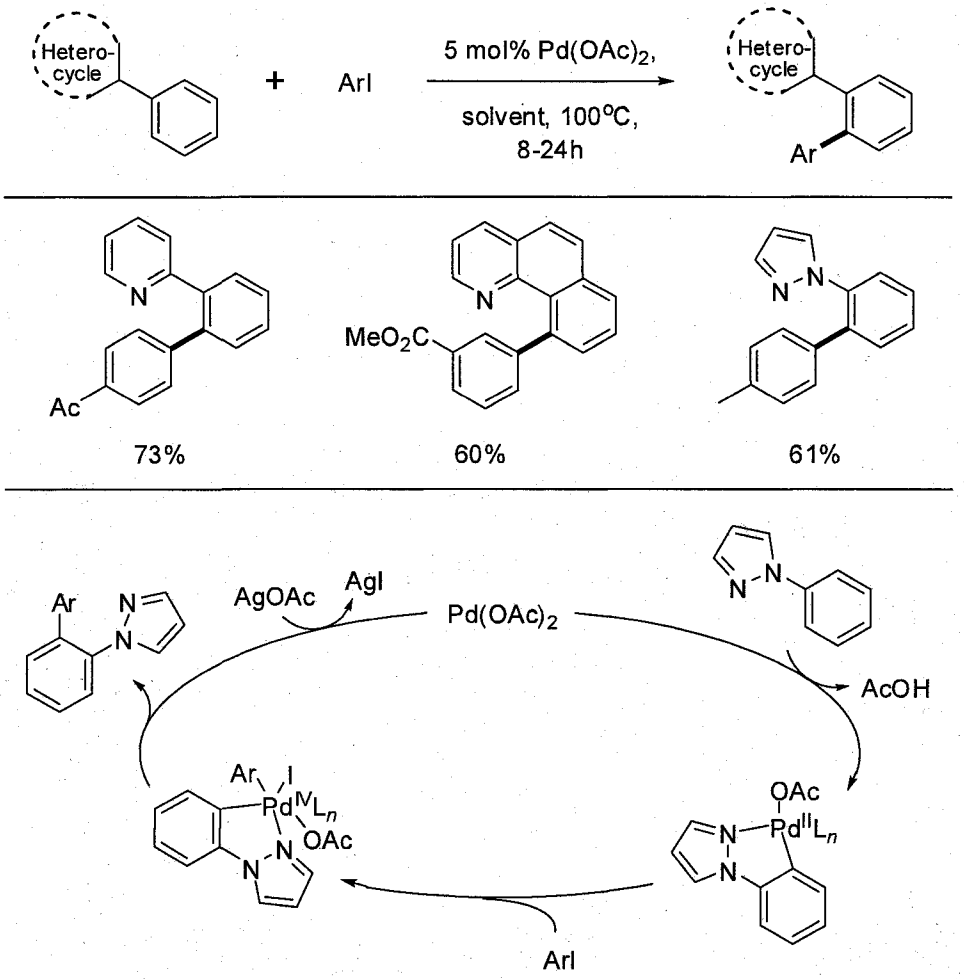
Scheme 1. 13. Catalytic Cycle for Oxidative Direct Arylation with Diaryliodonium Salts.



Using previously established conditions,[51,52,53] Daugulis and Shabashov were also able to employ pyridines, benzoquinolines as well as the first example of pyrazoles as directing groups for direct arylation with iodoarenes.[63] Although few examples were demonstrated, reactions using electron rich iodoaryls underwent faster reaction, which is atypical of a palladium 0/II processes. They propose that the reaction operates through a palladium II/IV manifold. Electrophilic C-H addition of the palladium center followed by oxidative addition of the haloarene forms a palladium (IV) intermediate. Reductive elimination of this intermediate followed by anion exchange of iodide with silver acetate completes the catalytic cycle and generates the desired product. Selected examples as well as the proposed mechanism are portrayed in Scheme 1.14.

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

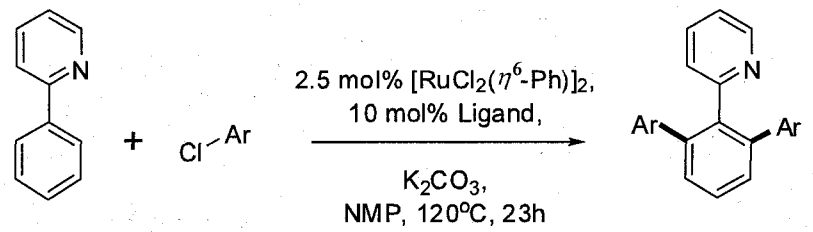
Scheme 1. 14. Catalytic Cycle for Oxidative Direct Arylation with Aryl Iodide.

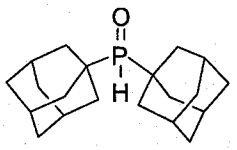


Ackermann reported the direct arylation of aryl chlorides using 2-arylpyridines as well as aromatic imines using a ruthenium catalyst equipped with a bulky electron-rich phosphine oxide ligand.[64] The advantage of this protocol lies in the use of air- and moisture-stable ligands while employing the commercially available and cheap aryl chlorides. Using reaction conditions previously described,[59] they were able to isolate the di-arylated product using the 2-phenylpyridine system in good to excellent yields while the aryl imines afforded the mono-arylated product selectively in moderate to good yields (Table 1.17). Only 4-nitrochlorobenzene was found to be unreactive. No details regarding the mechanism were given.

[64] Ackermann, L. *Org Lett.* **2005**, *7*, 3123.

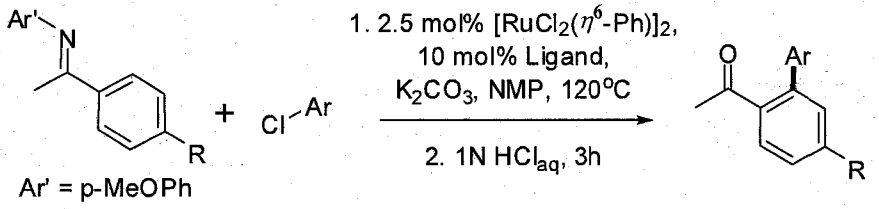
Table 1. 17. Direct Arylation of 2-Arylpyridine and Imines using Aryl Chlorides.



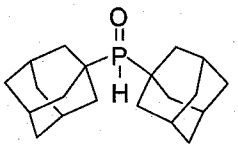


Ligand

Ar	Yield
Ph	95%
p-OMePh	87%
p-CO_2EtPh	85%



Ar' = p-MeOPh



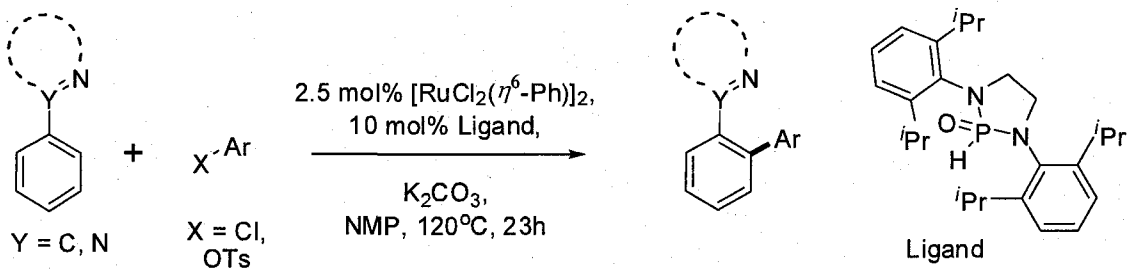
Ligand

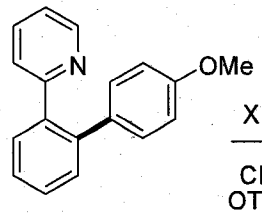
R	Ar	Yield
H	*p*-CO_2EtPh	72%
Me	*p*-CF_3Ph	75%
OMe	*o*-MePh	65%

In 2006, Ackermann's group reported a catalyst which could this time make use of aryl chlorides as well as aryl tosylates in the direct arylation of 2-arylpyridines.[65] Unlike the use of aryl chlorides, tosylates gave clean conversions to the mono-arylated product when using unsubstituted 2-arylpyridines as shown in Table 1.18. The reaction was found to be highly functional group tolerant and allowed the use of pyrazoles as the directing group. Again, no reaction mechanism was described.

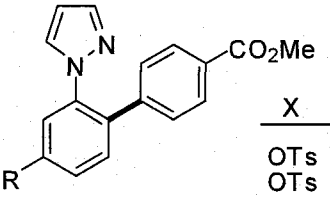
[65] Ackermann, L; Althammer, A. *Angew. Chem.; Int. Ed.* **2006**, *45*, 2619.

Table 1. 18. Direct Arylation of 2-Arylpyridine and *N*-Arylpyrazoles using Aryl Tosylates.





X	Yield mono : di
Cl	9% : 91%
OTs	78% : <1%

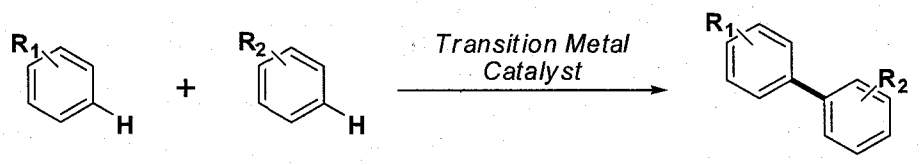


X	R	Yield
OTs	H	61%
OTs	Me	55%

1.2 – Type III Direct Arylation Reactions

An attractive and efficient alternative to traditional cross-coupling reactions are Type III direct arylation reactions (Scheme 1.15). In these types of transformation, two different arenes are directly cross-coupled without substrate pre-activation. While oxidative dimerization of arenes has been known,[66] oxidative cross-coupling has not surfaced until recently.

Scheme 1. 15. Type III Direct Arylation Reaction.

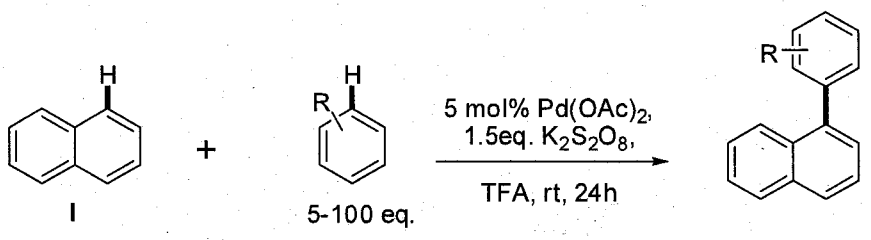


[66] For recent examples, see: (*a*) Burton, H.A.; Kozhevnikov, I.V. *J. Mol. Catal. A,* **2002**, *185*, 285. (*b*) Takahashi, M.; Masui, K.; Sekiguchi, H.; Kobayashi, N.; Mori, A.; Funahashi, M.; Tamaoki, N. *J. Am. Chem. Soc.* **2006**, *128*, 10930. (*b*) Hull, K.L.; Lanni, E.L.; Sanford, M.S. *J. Am. Chem. Soc.* **2006**, *128*, 14047.

1.2.1 – Oxidative Cross-Coupling between π-Electron Rich Arenes and Simple Arenes

The first report of a Type III cross-coupling appeared in 2006.[67] While low yields were isolated, it nonetheless demonstrated the feasibility of the reaction. Different arenes such as benzene, anisole, chlorobenzene, mesitylene and *para*-xylene were coupled with naphthalene at the most nucleophilic C-1 position in yields ranging from 15 to 50% using 5 mol% of palladium acetate and 3 equivalent of potassium persulfate as the oxidant (Table 1.19). With substituted benzenes, which result in the formation of regioisomers, product distribution was affected by both electronic and the steric factors. No homocoupling product could be detected and a kinetic isotope effect was observed on the benzene component, but not on the naphthalene. Insufficient evidence was obtained to validate the mechanism.

Table 1. 19. Oxidative Cross-Coupling of Napthalene with Simple Arenes.



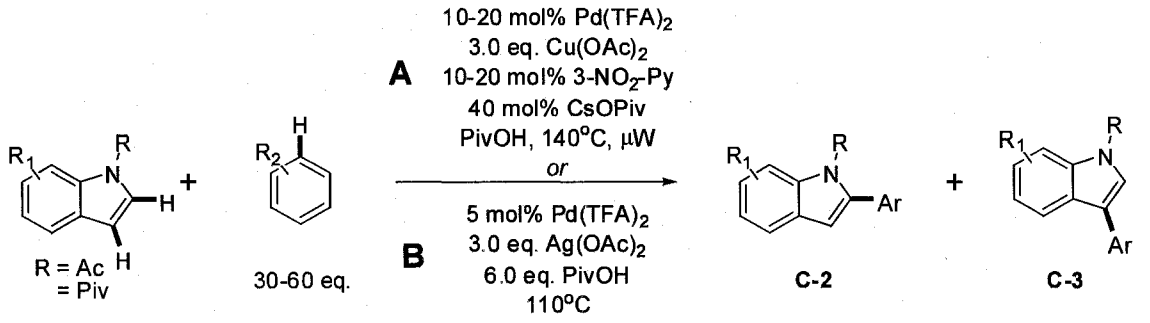
R	ArH/I	Ratio *o:m:p*	Yield
H	100	n/a	32%
1,4-diMe	25	n/a	50%
1,3,5-triMe	15	n/a	25%
OMe	5	29:0:79	15%
Cl	60	47:8:45	16%

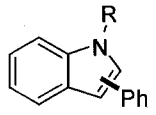
In 2007, our group reported the first high yielding example of Type III direct arylation (Scheme 1.28) using *N*-acetylindoles and simple arenes.[68] Under optimal conditions, $Pd(TFA)_2$ (10-20 mol%), $Cu(OAc)_2$ (3.0 eq.), 3-nitropyridine (1eq. to Pd) and CsOPiv (40 mol%) in a 4:1 solvent mixture of benzene to pivalic acid under microwave irradiation gave predominantly the C-3 arylated product. Surprisingly, using a bulkier

[67] Lang, R.L.; Lu, W. *Organometallics.* **2006**, *25*, 5973.
[68] Stuart, D.R.; Fagnou, K. *Science*, **2007**, *316*, 1172.

N-pivalylindole in conjunction with a silver oxidant inverted the regioselectivity to the C-2 position.[69] Comparative results from these two complimentary reaction conditions are displayed in Table 1.20. These conditions were also found to be compatible with *N*-substituted pyrroles.

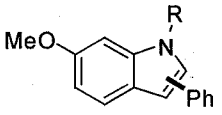
Table 1. 20. Oxidative Cross-Coupling of *N*-Protected Indoles with Simple Arenes.





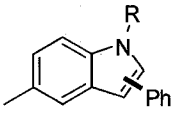
R = Ac; 87%
C2:C3 = 1:8.9

R = Piv; 84%
C2:C3 = 25:1



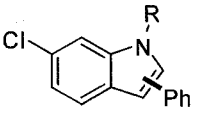
R = Ac; 84%
C2:C3 = 1:11

R = Piv; 90%
C2:C3 = 46:1



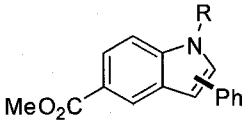
R = Ac; 81%
C2:C3 = 1:10

R = Piv; 88%
C2:C3 = 31:1



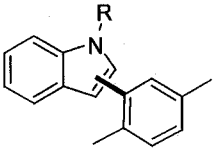
R = Ac; 63%
C2:C3 = 1:6.5

R = Piv; 86%
C2:C3 = 31:1



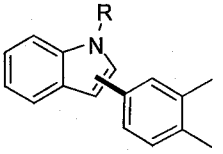
R = Ac; 54%
C2:C3 = 1:2.8

R = Piv; 86%
C2:C3 = 31:1



R = Ac; 45%
C2:C3 = 1:10

R = Piv; 58%
C2:C3 = 31:1



R = Ac; 61%
C2:C3 = 19:1

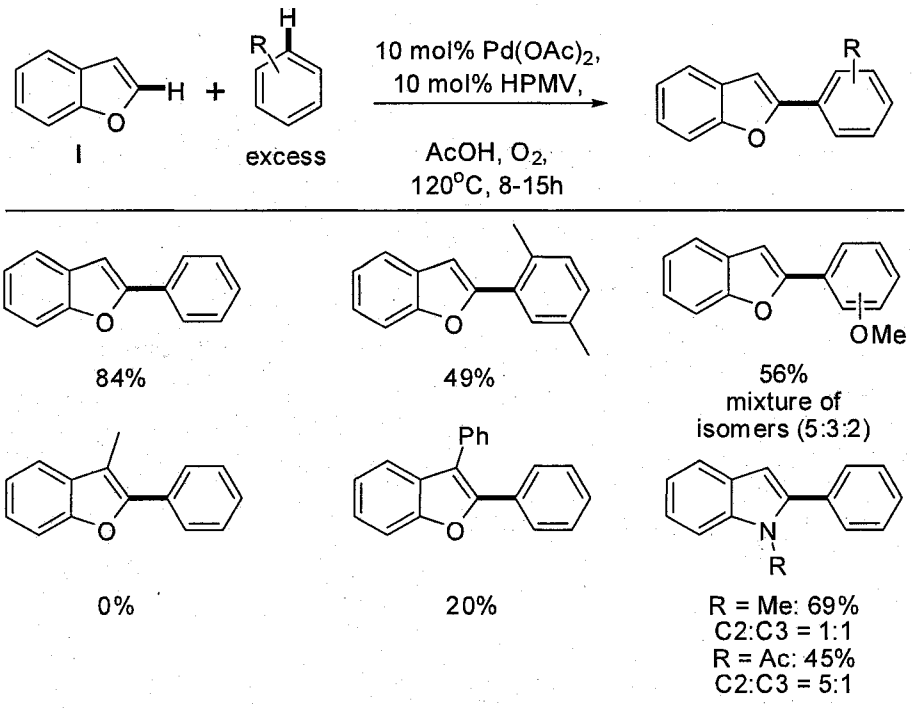
R = Piv; 75%
C2:C3 = 30:1

Shortly afterward, DeBoef and coworkers reported a different catalyst system for the oxidative cross-coupling of benzofuran derivatives and *N*-protected indoles with simple arenes.[70] C-2 Cross-coupling between benzofuran and benzene was achieved using 10 mol% of palladium acetate and 10 mol% of heteropolymolybdovanadic acid

[69] Stuart, D.R.; Villemure, E. ; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 12072.
[70] Dwight, T.A.; Rue, N.R.; Charyk, D.; Josselyn, R.; DeBoef, B. *Org. Lett.* **2007**, *9*, 3137.

(HPMV) in conjunction with molecular oxygen in acetic acid at 120°C in 84% yield (Table 1.21).

Table 1. 21. Oxidative Cross-Coupling of Benzofuran and Indoles with Simple Arenes.

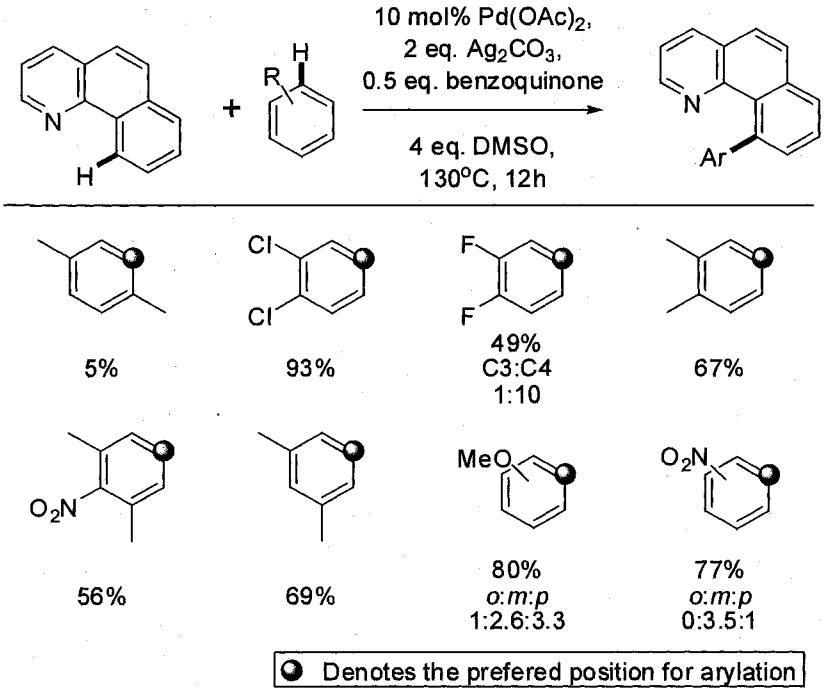


1.2.2 – Oxidative Cross-Coupling with Directing Groups

A different approach to oxidative cross-coupling reaction, relying on the use of a directing group, appeared recently.[71] Sanford explored the use of benzo[*h*]quinoline with palladium acetate to control the regioselectivity by holding the palladium catalyst in close proximity to a single reactive site. A second nondirected benzene metallation would generate a diaryl palladium complex which upon reductive elimination would generate the product. Using 10 mol% palladium acetate, 2 equivalents silver carbonate, 4 equivalents DMSO and 0.5 equivalent benzoquinone with a large excess of the simple arene (65-100eq.), they isolated in low to good yield the nonsymmetrical biaryl products. Under these conditions, no homocoupling of either arene was observed. The scope is tolerant to many functional groups with sterics governing the regioselectivity (Table 1.22). In this respect, 1,4-disubstituted arenes were found to be difficult substrates.

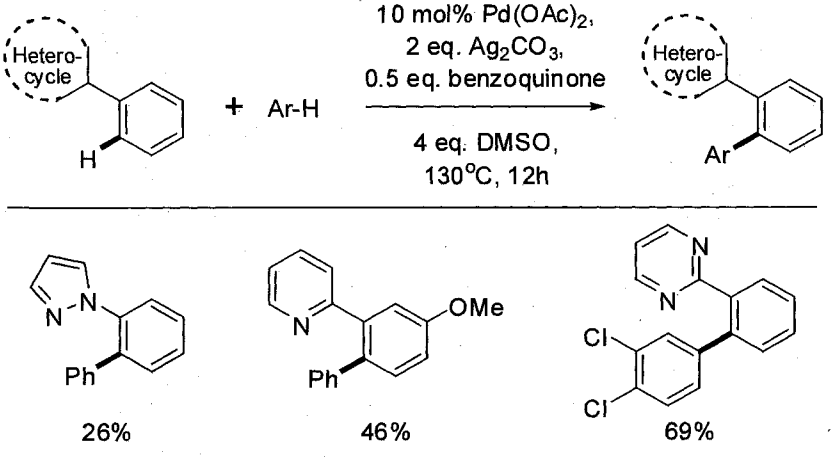
[71] Hull, K.L.; Sanford, M.S. *J. Am.Chem. Soc.* **2007**, *129*, 11904.

Table 1. 22. Oxidative Cross-Coupling of Benzo[*h*]quinoline with Simple Arenes.



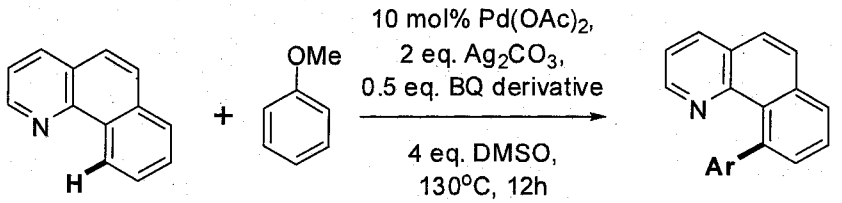
Sanford also investigated the use of other heterocycles as potential directing groups. When Benzo[*h*]quinoline was replaced by a 2-arylpyridine or a 1-arylpyrazole, a significant decrease in yield was observed with the product being isolated in 46% and 26% yield, respectively. 2-Phenylpyrimidine was found to be as efficient giving the product in 69% isolated yield (Table 1.23).

Table 1. 23. Compatible Heterocycles as Directing Group.

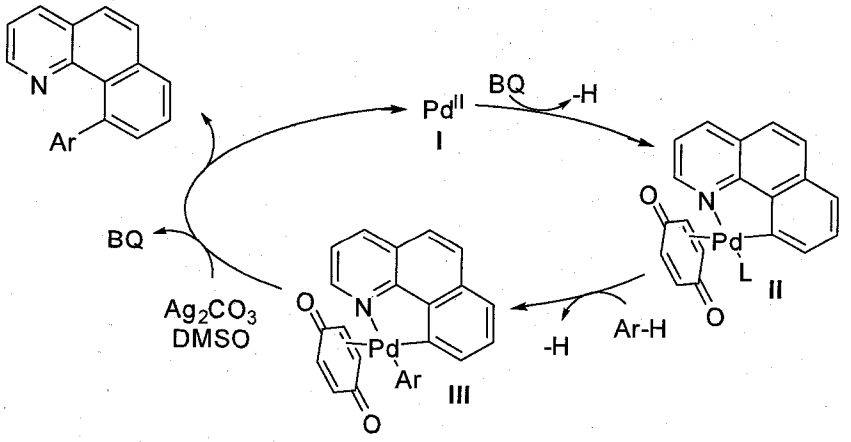


Different mechanistic investigations were performed to give insights on the mechanism for the transformation. Sanford hypothesized that the benzoquinone (BQ) acts as a ligand on the palladium and contributes to the regioselectivity in the C-H bond cleaving step of the simple arene. In order to validate this theory, the reaction was performed with different benzoquinone derivatives and the effect on regioselectivity in the arylation of anisole was compared. With a more sterically hindered benzoquinone the regioselectivity for the *meta*-position was increased albeit in reduced yield (Table 1.24). They therefore proposed the following mechanism: Initial ligand-directed C-H activation affords the *cyclopalladated intermediate* **II** *followed by a benzoquinone-assisted C-H bond activation* onto the arene to give **III**. Reductive elimination of the product generates a palladium (0) intermediate, which is re-oxidized back to palladium (II) by the silver acetate. The DMSO would help in preventing catalyst decomposition and/or Pd^0 aggregation.

Table 1. 24. Benzoquinone Effect and Proposed Catalytic Cycle.



BQ derivative	*o*:*m*:*p* ratio	Yield (GC)
BQ	1:2:3.3	88%
2-MeBQ	1:5:4.4	81%
2,5-diMeBQ	1:15:6.7	51%
2,3,5,6-tetraMeBQ	1:18.1:6.5	35%



Chapter 2

Intermolecular Direct Arylation of Perfluoroarenes

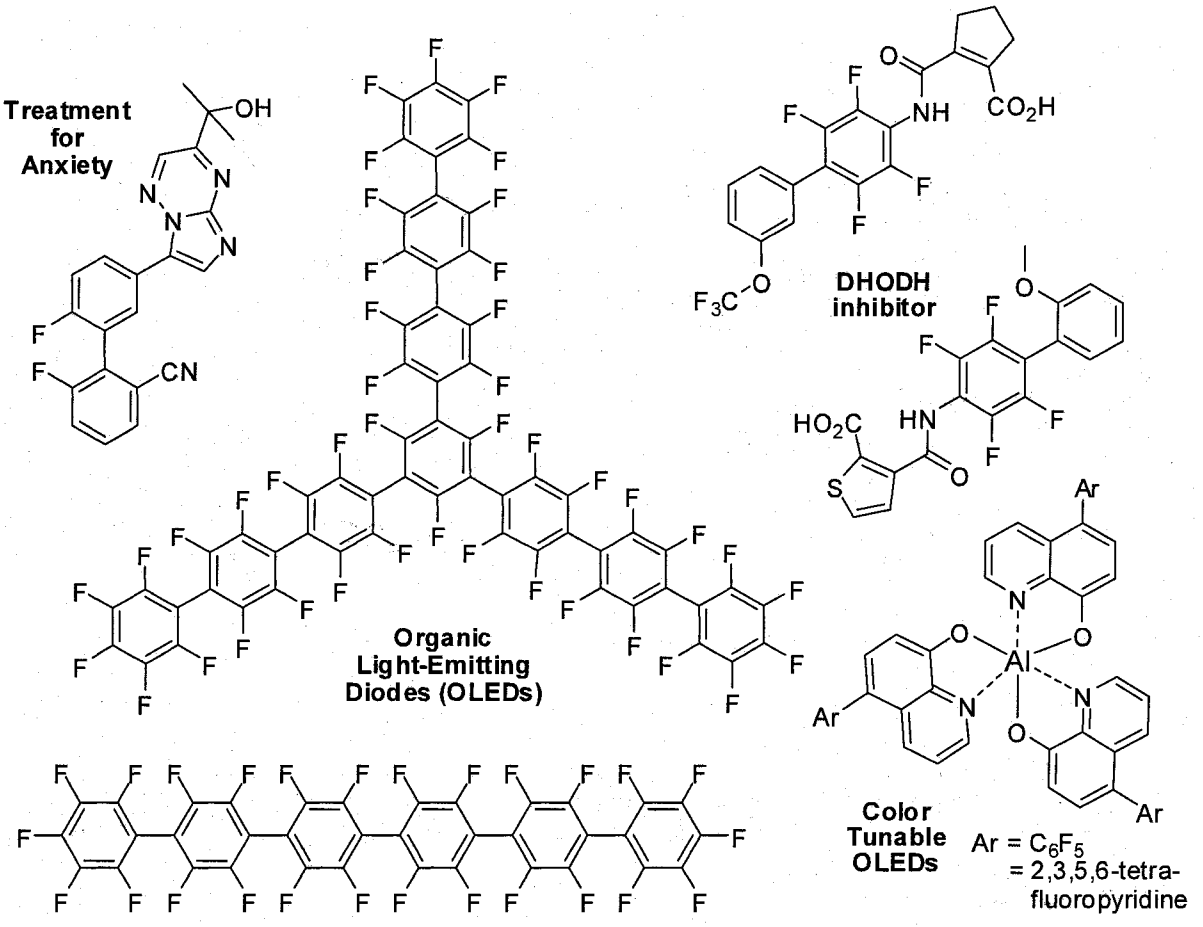
Recently, increased attention is being given to fluorinated arenes due their unique characteristics in the fields of agricultural and medicinal science.[72] They are also important in materials chemistry where applications as organic light-emitting diodes or as field-effect transistors have emerged (Scheme 2.1).[73] Despite the importance of these

[72] For representative examples see: (*a*) Banks, R.E. Organo Fluorine Compounds and Their Applications. Ellis Horwood. Chinchester. 1979. (*b*) Leban, J.; Kralik, M.; Mies, J.; Gassen, M.; Tentschert, K.; Baumgartner, R. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 267. (*c*) Leban, J.; Kralik, M.; Mies, J.; Baumgartner, R.; Gassen, M.; Tasler, S. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 267. (*d*) Russell, M. G. N.; Carling, R.W.; Street, L.J.; Hallet, D.J.; Goodacre, S.; Mezzogori, E.; Reader, M.; Cook, S.M.; Bromidge, F.A.; Newman, R.; Smith, A.J.; Wafford, K.A.; Marshall, G.R.; Reynold, D.S.; Dias, R.; Ferris, P.; Stanley, J.; Lincoln, R.; Tye, S.J.; Sheppard, W.F.A.; Sohal, B.; Pike, A.; Dominguez, M.; Atack, J.R.; Castro, J.L. *J. Med. Chem.* **2006**, *49*, 1235.

[73] For representative examples, see: (*a*) Sakamoto, Y.; Suzuki, T.; Miura, A.; Fujikawa, H.; Tokito, S.; Taga, Y. *J. Am. Chem. Soc.* **2000**, *122*, 1832. (*b*) Heidenhain, S.; Sakamoto, Y.; Suzuki, T.; Miura, A.; Fujikawa, H.; Mori, T.; Tokito, S.; Taga, Y. *J. Am. Chem. Soc.* **2000**, *122*, 10240. (*c*) Hwang, D. H.; Song, S. Y.; Ahn, T.; Chu, H. Y.; Do, L. M.; Kim, S. H.; Shim, H. K.; Zyung, T. *Synth. Met.* **2000**, *111*, 485. (*d*) Montes, V. A.; Li, G.; Pohl, R.; Shinar, J.; Anzenbacher, P. *Adv. Mat.* **2004**, *16*, 2001. (*e*) Tsuzuki, T.; Shirasawa, N.; Suzuki, T.; Tokito, S. *Adv. Mat.* **2003**, *15*, 1455. (*f*) Kitamura, T.; Wada, Y.; Yanagida, S., *J. Fluorine Chem.* **2000**, *105*, 305. (*g*) Weck, M.; Dunn, A. R.; Matsumoto, K.; Coates, G. W.; Lobkovsky, E. B.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **1999**, *38*, 2741. (*h*) Nitschke, J. R.; Tilley, T. D., *J. Am. Chem. Soc.* **2001**, *123*, 10183. (*i*) Chen, W.; Wang, L.; Huang, C.; Lin, T.T.; Gao, X.Y.; Loh, K.P.; Chen, Z.K.; Wee, A.T.S. *J. Am. Chem. Soc.* **2006**, *128*, 935.

building blocks, their synthesis remains challenging *via* traditional cross-coupling methods.

Figure 2. 1. Perfluorobiaryls Applications in Medicinal and Material Chemistry.



2.1 – Synthesis of Perfluorobiaryls by Modern Cross-Coupling Reactions

The palladium-catalyzed cross-coupling of aryl boronic acids with aryl halides, known as the Suzuki-Miyaura reaction, is one of the most powerful methods for the synthesis of biaryl compounds. Nonetheless, electron-deficient aryl (heteroaryl) organometallic reagents constitute a challenging substrate class in cross-coupling

reactions and the use of pentafluorophenyl organometallics is illustrative.[74] This can be rationalized by a difficult transmetallation to the palladium center due to the highly electron-deficient C_6F_5 group.[75] Furthermore, Frohn and coworkers demonstrated the susceptibility of these perfluorophenylboronic acids to undergo hydrodeboration in basic media, making typical conditions for Suzuki cross-coupling reactions incompatible with these substrates.[76]

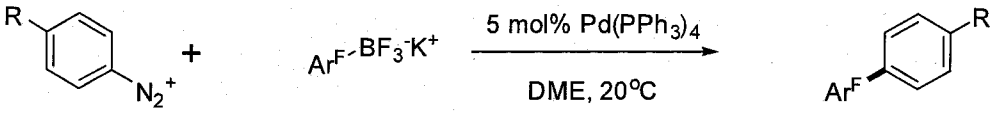
In this chapter, a novel synthesis of perfluorobiaryls that constitutes the first non-directed intermolecular direct arylation of electron-deficient arenes will be discussed.

2.1.1 – Perfluorophenyltrifluoroborate Salts.

In order to circumvent the hydrodeboration decomposition pathway, Frohn and coworkers explored the coupling of trifluoroborate salts with highly electrophilic arenediazonium tetrafluoroborates.[77] These trifluoroborate salts display higher thermal and protolytic stability compared to their analogous boronic acids or esters. Using 5 mol% tetrakis(triphenylphosphine)palladium(0) in DME, they achieved the coupling between 4-fluorobenzenediazonium tetrafluoroborate with potassium pentafluorophenyltrifluoroborate in 40% isolated yield. Different functional groups on the benzenediazonium tetrafluoroborates as well as different levels of fluorinated trifluoroborates salts were evaluated and representative results can be seen in Table 2.1.

[74] (*a*) Havelková, M.; Dvořák, D.; Hocek, M. *Synthesis,* **2001**, 1704. (*b*) Havelková, M.; Hocek, M.; Česnek, M.; Dvořák, D. *Synlett,* **1999**, 1145. (*c*) Thiemann, T.; Umeno, K.; Ohira, D.; Inohae, E.; Sawada, T.; Mataka, S. *New J. Chem.* **1999**, *23*, 1067.
[75] Korenaga, T.; Kosaki, T.; Fukumura, R.; Ema, T. ; Sakai, T. *Org. Lett.* **2005**, *7*, 4915.
[76] Frohn, H.-J.; Adonin, N.Y.; Bardin, V.V.; Starichenko, V.F. *Z. Anorg. Allg. Chem.* **2002**, *628*, 2834.
[77] Frohn, H.-J.; Adonin, N.Y.; Bardin, V.V.; Starichenko, V.F. *J. Fluorine Chem.* **2002**, *117*, 115.

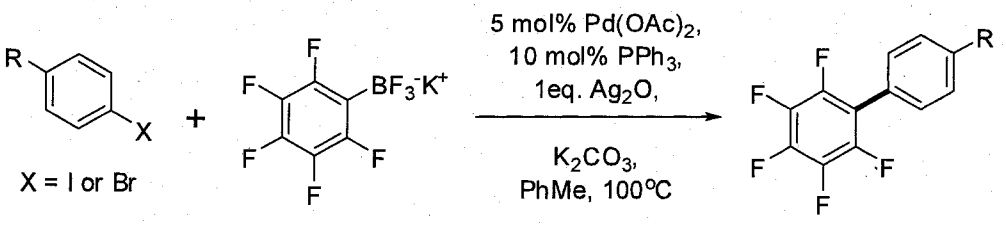
Table 2. 1. Coupling of Polyfluorotrifluoroborates with Arenediazoniums.

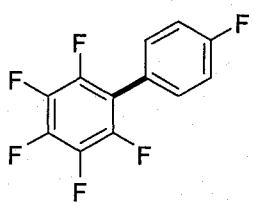


R	Ar^F	Yield
F	C_6F_5	40%
F	2,3,4,5-C_6HF_4	45%
F	3,4,5-$C_6H_2F_3$	27%
NO_2	C_6F_5	13%
CO_2Et	C_6F_5	46%
Me	C_6F_5	10%

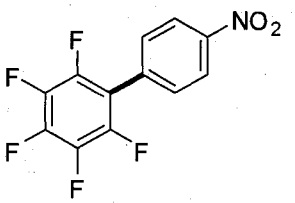
With the goal of simplifying the reaction conditions, Frohn and coworkers replaced the benzenediazonium salt coupling partner with a simpler aryl iodide.[78] Coupling between potassium pentafluorophenyltrifluoroborate with different aryl iodides was achieved using 5 mol% of palladium acetate, 10 mol% triphenylphosphine, 1.4 equivalents of potassium carbonate and 1 equivalent of silver oxide in toluene at 100°C (Table 2.2). This approach was advantageous, as not only are the starting materials commercially available but an increase in yields was also observed. It should be noted that the stochiometric use of silver oxide is crucial, since no reaction was observed in its absence. Furthermore, activated aryl bromides could also be employed, although lower yields were observed.

Table 2. 2. Coupling of Polyfluorotrifluoroborate with Aryl Halides.

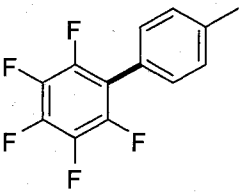




X = I: 76%
= Br: 28%



X = I: 81%
= Br: 62%



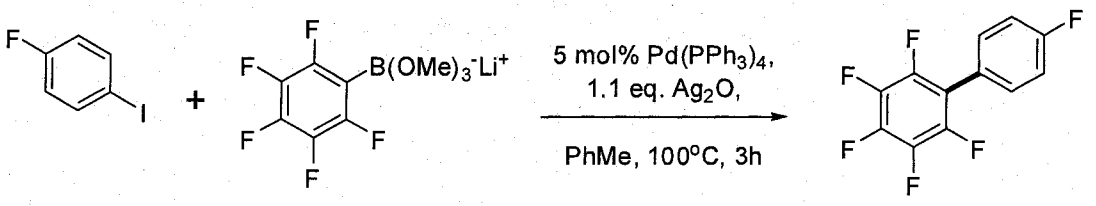
X = I: 93%

[78] Frohn, H.-J.; Adonin, N.Y.; Bardin, V.V.; Starichenko, V.F. *Tetrahedron Lett.* **2002**, *43*, 8111.

2.1.2 – Lithium Perfluorophenyltrimethoxyborates.

Frohn and coworkers also investigated cross-coupling between lithium perfluorophenyltrimethoxyborates and iodoarenes as an alternative solution to the hydrodeboration problem associated with boronic acids.[79] These closely related hygroscopic salts displayed similar reactivity to the trifluoroborate analogues. Under optimal conditions, 4-bromofluorobenzene was coupled with pentafluorophenyltrimethoxyborate in 60% isolated yield (Scheme 2.1).

Scheme 2. 1. Coupling of Pentafluorophenyltrimethoxyborate with 4-bromofluorobenzene.



90%

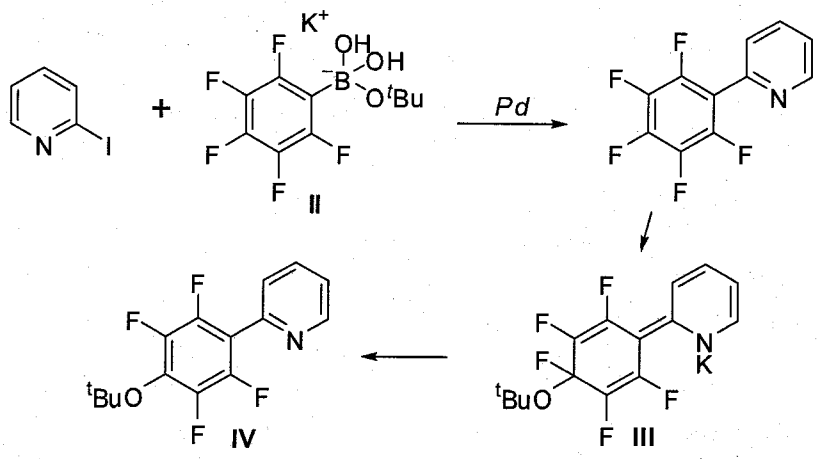
2.1.3 – Arylboronic Acid.

With the goal of generating 2-(fluoroaryl)pyridine derivatives, Cammers-Goodwin studied the cross-coupling of perfluorophenyl boronic acids with 2-iodopyridine.[80] The specific challenge associated with this coupling is the susceptibility of 2-polyfluoroarenepyridines of undergoing *ipso*-substitution[81] by the alkoxide base, which is commonly employed to activate the boron to a borate intermediate **II** through a pathway shown in Scheme 2.2. As expected the product isolated from the standard reaction conditions was the *ipso*-substituted product **IV** in 60% yield.

---

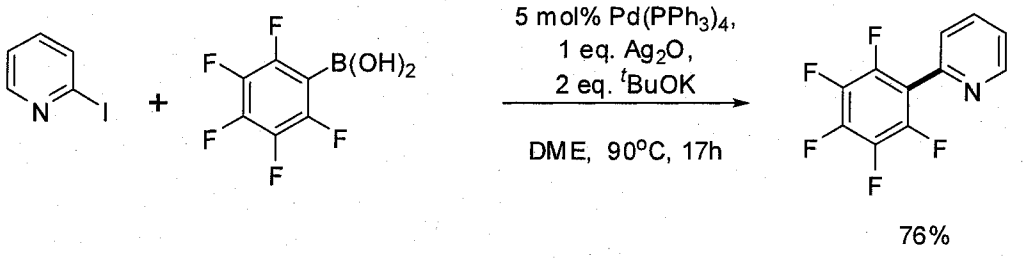
[79] Frohn, H.-J.; Adonin, N.Y.; Bardin, V.V.; Starichenko, V.F. *J. Fluorine Chem.* **2003**, *122*, 195.
[80] Chen, J.; Cammers-Goodwin, A. *Tetrahedron Lett.* **2003**, *44*, 1503.
[81] For selected examples, see : (*a*) Strekowski, L.; Janda, L.; Patterson, S.E.; Nguyen, J. *Tetrahedron,* **1996**, *52*, 3273. (*b*) Banks, R.E.; Jondi, W.; Tipping, A.E. *Chem. Commun.* **1989**, 1268. (*c*) Aksenov, V.V.; Vlasov, V.M.; Yakobson, G.G. *J. Fluorine Chem.* **1982**, *20*, 439.

Scheme 2. 2. *Ipso* Substitution Pathway.



In order to attenuate the *ipso*-substitution side reaction, two different approaches were considered: i) the use of fluoride as a nucleophile to generate the required borate, and ii) a re-optimization of the reaction conditions to increase the rate of the coupling reaction. The first approach was unsuccessful; therefore a re-optimization of the reaction conditions was performed. The authors proposed an acceleration of the transmetallation step by the addition of stochiometric amounts of silver oxide. Under their optimal conditions, the coupled product was isolated in 76% yield as shown in Scheme 2.3.

Scheme 2. 3. Coupling of Polyfluoroboronic acids with 2-Iodopyridine.



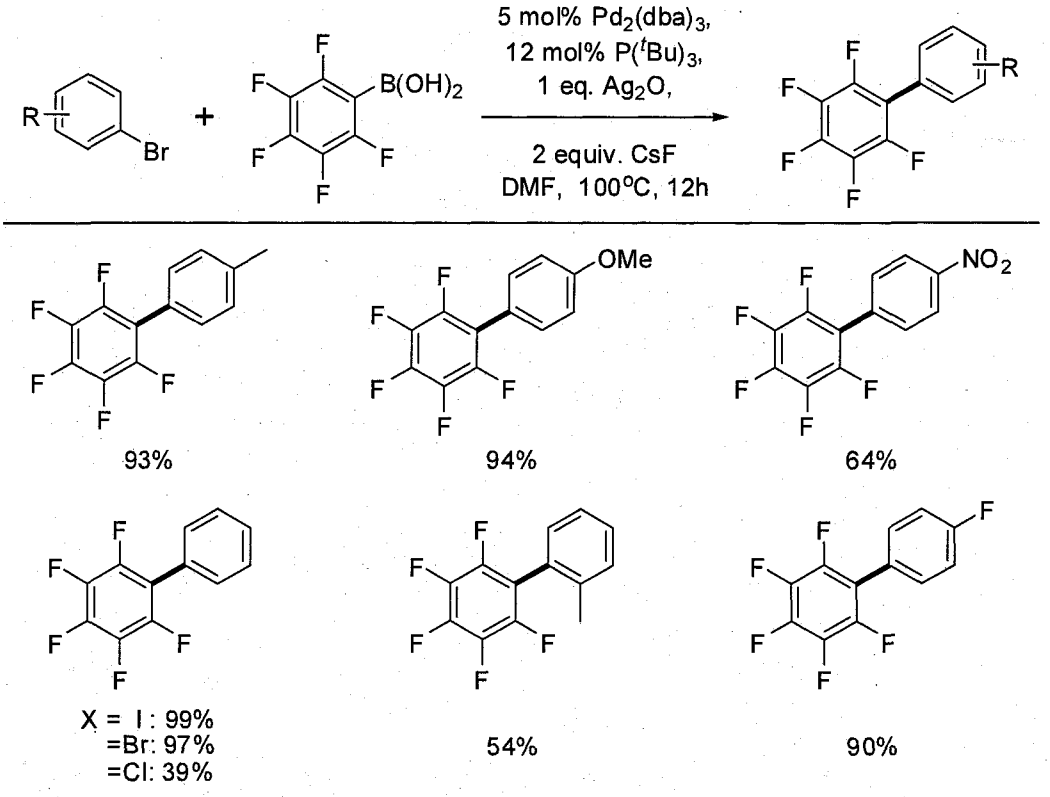
76%

A re-optimization of Cammers-Goodwin's protocol by Korenaga and Sakai provided a broad and improved protocol for the coupling of boronic acids with aryl bromides.[82] High functional group tolerance was observed, including the use of aryl chlorides as coupling partners, albeit in lower yield (Table 2.3). This methodology was

[82] Korenaga, T.; Kosaki, T.; Fukumura, R.; Ema, T. ; Sakai, T. *Org. Lett.* **2005**, *7*, 4915.

then applied to the synthesis of molecular tweezers bearing pentafluorophenyl substituents.[83]

Table 2. 3. Coupling of Polyfluoroboronic acids with Aryl Halides.

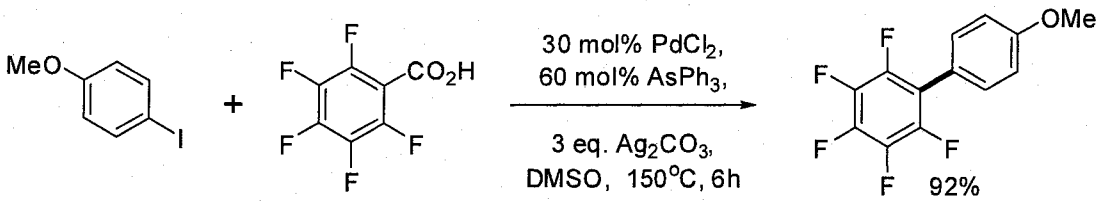


2.1.4 – Decarboxylative Palladium-Catalyzed Cross-Coupling Reaction.

Recently, the group of Becht and Wagner reported a palladium-catalyzed decarboxylative cross-coupling reaction in which iodoarenes and benzoic acid analogues were coupled in good to excellent yields.[84] Different carboxylic acids were found to undergo conversion to the biaryl, including pentafluorobenzoic acid (Scheme 2.4).

[83] Korenaga, T.; Kosaki, T.; Kawauchi, Y.; Ema, T. ; Sakai, T. *J. Fluorine Chem.* **2006**, *127*, 604.
[84] Becht, J.-M.; Catala, C.; Le Drian, C.; Wagner, A. *Org. Lett.* **2007**, *9*, 1781.

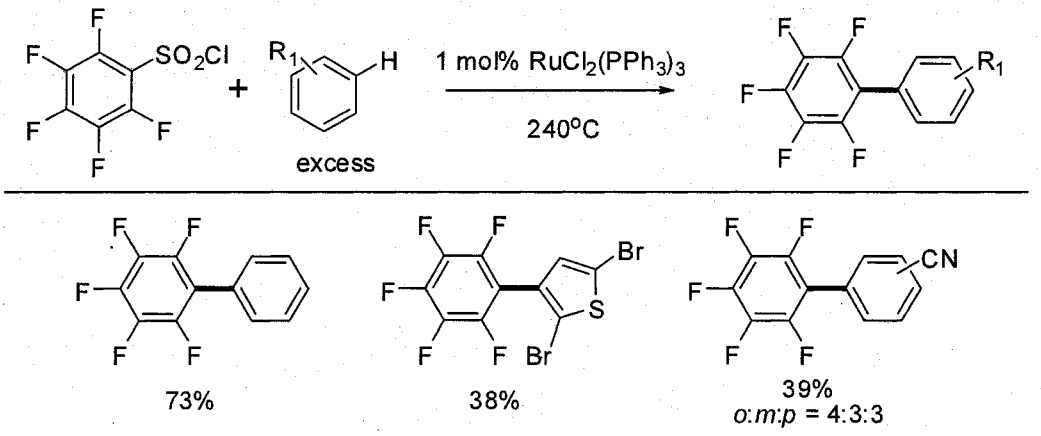
Scheme 2. 4. Decarboxylative Cross-Coupling Reaction in the Synthesis of Perfluoroarenes.



2.1.4 – Pentafluorobenzenesulfonyl Chlorides and Simple Arenes.

In 1998, Kamigata and coworkers discovered a new route to the formation of perfluorobiaryls through a ruthenium-catalyzed cross-coupling of pentafluorobenzenesulfonyl chlorides with different simple arenes.[85] When 1 mol% of dichlorotris(triphenylphosphine)-ruthenium was sealed in the presence of 1 equivalent of pentafluorobenzenesulfonyl chloride with an excess of benzene at 240°C, 73% yield of 2,3,4,5,6-pentafluorobiphenyl was isolated. Unfortunately, due to the required elevated temperature, some reactions suffered from lower yields from decomposition (Table 2.4).

Table 2. 4. Coupling of Pentafluorobenzenesulfonyl Chlorides with Simple Arenes.

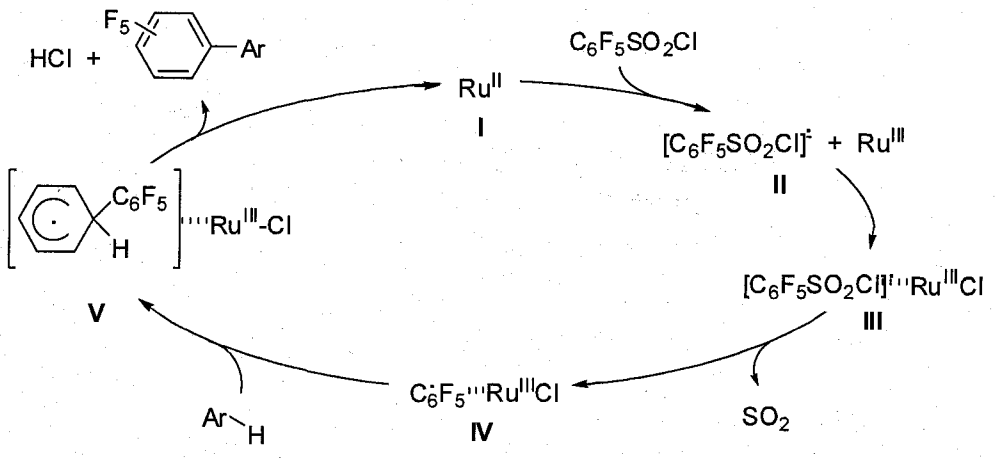


The proposed catalytic cycle is shown in Scheme 2.5. A redox-transfer reaction between the pentafluorophenylsulfonyl chloride and the ruthenium (II) species **I** leads to

[85] Kamigata, N.; Yshikawa, M.; Shimizu. *J. Fluorine Chem.* **1998**, *87*, 91.

the radical anion **II**. Subsequent homolytic cleavage of this species generates a pentafluorobenzenesulfonyl radical **III** intermediate. Extrusion of sulfur dioxide generates the pentafluorophenyl radical **IV** which can then react with the simple arene to give the cyclohexadienyl radical **V**. Proton abstraction from the ruthenium chloride (III) gives the product, hydrochloric acid and regenerates the ruthenium (II) catalyst.

Scheme 2. 5. Catalytic Cycle for the Cross-Coupling Reaction Between Pentafluorobenzenesulfonyl Chlorides with Simple Arenes.



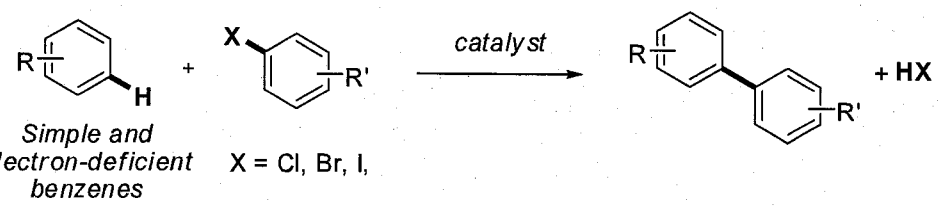
2.2 – Direct Arylation in the Construction of Highly Fluorinated Biaryls.

For reasons discussed in chapter 1 as well as the limitations of the traditional cross-coupling approach for the synthesis of perfluorobiaryls, the development of a new catalytic direct arylation for the synthesis of this important class of molecules would be of great utility to the chemical community. While important advances have been made in direct arylation, many aromatic compounds do not possess sufficient nucleophilicity to participate in the S_EAr-like mechanism.[86] For example, simple and electron-deficient arenes (Scheme 2.6) have never been successfully employed in direct arylation, with the

[86] Electron-rich heterocyclic arenes have been successfully employed. For example, see: (*a*) Lane, B. S.; Sames, D. *Org. Lett.* **2004**, *6*, 2897. (*b*) Li, W. J.; Nelson, D. P.; Jensen, M. S.; Hoerrner, R. S.; Javadi, G. J.; Cai, D.; Larsen, R. D. *Org. Lett.* **2003**, *5*, 4835. (*c*) Mori, A.; Sekiguchi, A.; Masui, K.; Shimada, T.; Horie, M.; Osakada, K.; Kawamoto, M.; Ikeda, T. *J. Am. Chem. Soc.* **2003**, *125*, 1700. (*d*) Wang, X.; Lane, B. S.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 4996.

exception of the use of a directing group which can help form a metallacycle.[87,88] New mechanistic insights that can overcome these constraints, would not only be of tremendous importance in biaryl synthesis, but would also be transformative in the rational design of other types of catalytic arene functionalization.

Scheme 2. 6. Direct Arylation of Simple and Electron-Deficient Arenes.



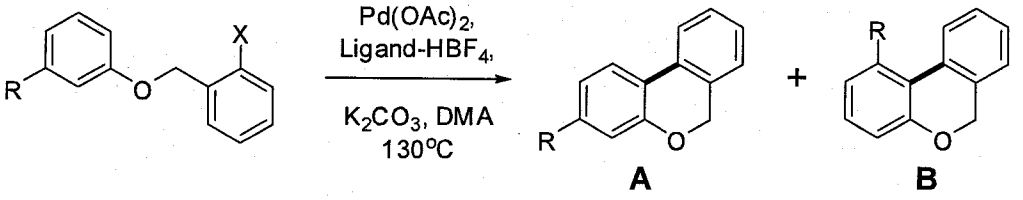
2.2.1 – Precedent Reactivity from Intramolecular Systems.

As part of our analysis of the intramolecular direct arylation of simple arenes, Louis-Charles Campeau investigated different *meta* substitution patterns on simple arenes and observed their effects on the regioselectivity.[17b] Various electronically and sterically different functional groups were tested. In general, arylation occurred at the most sterically accessible site giving **A** predominantly. Strangely, a reversal of regioselectivity was observed when the substituent was a fluorine atom, giving the isomer **B** preferentially (Table 2.5). The product distribution was also found to be affected by the choice of the ligand as well as the choice of the aryl halide, indicating that both the ligand and the halide must be interacting with the metal during the arylation step of the catalytic cycle.

[87] For example, see: (*a*) Daugulis, O.; Zaitsev, V. G. *Angew. Chem.; Int. Ed.* **2005**, *44*, 4046. (*b*) Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 7330. (*c*) Kakiuchi, F.; Kan, S.; Igi, K.; Chatani, N.; Murai, S. *J. Am. Chem. Soc.* **2003**, *125*, 1698. (*d*) Bedford, R. B.; Coles, S. J.; Hursthouse, M. B.; Limmert, M. E., *Angew. Chem. Int. Ed.* **2003**, *42*, 112.

[88] Intramolecular direct arylation reactions have also been reported. For example, see: : (*a*) Campeau, L.-C.; Parisien, M.; Leblanc, M.; Fagnou, K. ; *J. Am. Chem. Soc.*, **2004**, *126*, 9186. (*b*) Campeau, L.-C.; Parisien, M.; Jean, A.; Fagnou, K. ; *J. Am. Chem. Soc.*, **2006**, *128*, 581. (*c*) Huang, Q.; Fazio, A.; Dai, G.; Campo, M. A.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 7460. (*d*) Garcia-Cuadrado, D.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006**, *128*, 1066.

Table 2. 5. Catalyst Regioselectivity in Direct Arylation.

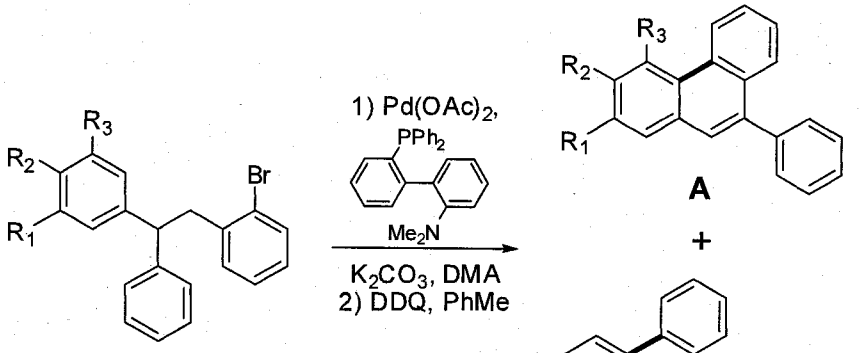


R	X	Ligand-HBF_4	ratio **A**:**B**
OMe	Br	PCy_3-HBF_4	10:1
Me	Br	PCy_3-HBF_4	15:1
^{i}Pr	Br	PCy_3-HBF_4	>30:1
^{t}Bu	Br	PCy_3-HBF_4	>30:1
CF_3	Br	PCy_3-HBF_4	>30:1
NO_2	Br	PCy_3-HBF_4	>30:1
CO_2Me	Br	PCy_3-HBF_4	>30:1
Cl	Br	PCy_3-HBF_4	3.2:1
F	Br	PCy_3-HBF_4	1:4.3
F	Cl	PCy_3-HBF_4	1:8.3
F	Br	P^tBu_3-HBF_4	1:1.3
F	Br	P^tBu_2Me-HBF_4	1:6.9

A similar effect was observed by Echavarren and coworkers in their work on the elucidation of the mechanism of this transformation.[17d,89] The authors performed a series of intramolecular competition experiments between two sterically and electronically different arenes tethered to an aryl bromide. While most systems gave poor discrimination between the 2 arenes, when R_1 and R_3 were substituted by fluorines, high selectivity was observed, favoring ring closure onto the arene containing the fluorines (Table 2.6). Similarly, the nature of the ligand had an impact on the observed regioselectivity.

[89] Garcia-Cuadrado, D.; de Mendoza, P.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2007**, *129*, 6880.

Table 2. 6. Catalyst Regioselectivity in Direct Arylation.



R_1	R_2	R_3	ratio **A**:**B**
H	OMe	H	1.1:1
H	CF_3	H	1.3:1
H	Cl	H	1.5:1
H	F	H	1.6:1
F	F	F	25:1
F	H	F	19:1

Both these results seemed to indicate that arenes containing electron-withdrawing fluorine substituents could undergo intermolecular direct arylation through a mechanism which would differ from the most commonly proposed electrophilic metallation.

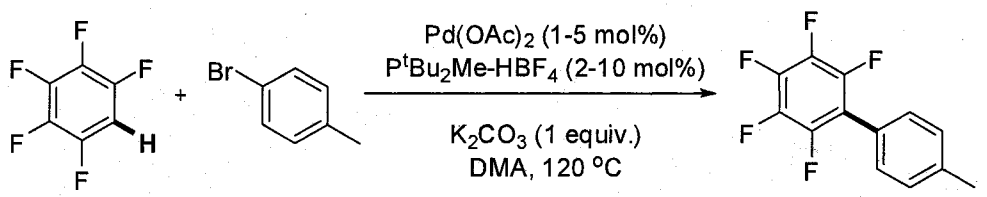
2.2.2 – Development of a Direct Arylation Reaction of Electron-Deficient Arenes. Reaction Development and Reaction Scope

As a starting point, we decided to examine the intermolecular direct arylation of pentafluorobenzene. [90] This substrate can only react at one site and should not be able to participate in an S_EAr-type process. Reaction screens were performed with 4-bromotoluene as the second coupling partner, and efforts were made to achieve conditions that were operationally simple starting from reaction conditions for the intramolecular arylation of simple arenes.[88b] We were pleased to find that reacting a nearly equimolar ratio of 4-bromotoluene and pentafluorobenzene (1: 1.1) in conjunction with one equivalent of potassium carbonate in *N,N*-dimethylacetamide (DMA, 3.0 to 6.0 M) at 120 °C with a 5 mol% catalyst generated *in situ* from $Pd(OAc)_2$ and the HBF_4 salt

[90] Lafrance, M.; Rowley, C.N.; Woo, T.K.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 8754.

of di-*tert*-butylmethylphosphine[91] provided a 98% isolated yield of the cross-coupled product in less than three hours (Scheme 2.7). These reactions are rapid, since more than 50% conversion is achieved within 5 minutes. This high turnover freqency prompted the investigation of lower catalyst loading. In fact, 1 mol% palladium is sufficient to induce complete conversion if the reaction is allowed to proceed overnight.

Scheme 2. 7. Direct Arylation using Pentafluorobenzene.



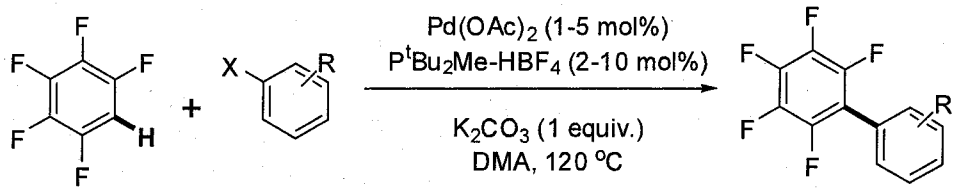
1.1 to 1.5 equiv.

98% isolated yield

This reaction exhibits broad scope with respect to the aryl halide (Table 2.7). In addition to aryl bromides, aryl chlorides and iodides can also be used (entries 1 to 4). When using aryl iodides, the addition of 0.5 equiv of AgOTf can improve the yield as illustrated by entries 3 and 4, but its use is not imperative. Electron-withdrawing (entries 5 and 10) and donating groups (entries 6 and 7) are compatible on the aryl halide, and heterocyclic aryl halides may also be used (entry 8). When the aryl halide contains both chlorine and bromine functionalities, high selectivity can be achieved for reaction at the aryl bromide (entry 11). If two bromine atoms are present, double direct arylation can be performed to produce valuable perfluoroterarylbenzenes in high yield (entry 12).

[91] Use of the HBF_4 salt renders the phosphine ligand air and bench stable until it becomes deprotonated by the action of base under the reaction conditions. Netherton, M. R.; Fu, G. C. *Org. Lett.* **2001**, *3*, 4295.

Table 2. 7. Scope of Haloarenes for the Direct Arylation using Pentafluorobenzene.



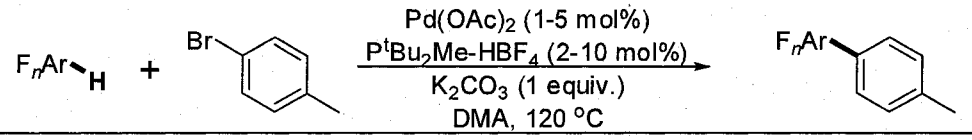
Entry	Aryl Halide	Product	Fluoroarene Equiv.	Yield (%)[a]
1	X = Cl	**1**	1.5	57
2	X = Br	**1**	1.1	98
3	X = I	**1**	1.5	83
4	X = I[b]	**1**	1.5	95
5	F_3C–Br	**2**	1.5	89
6	MeO–Br	**3**	1.5	85
7	MeO–Br	**4**	1.5	76
8	N, Br	**5**	1.5	78
9	Br	**6**	1.5	91
10	EtO_2C–Br	**7**	1.5	83
11	Cl, Br	**8**	1.5	96
12	Br, Br	**9**	3	76[c]

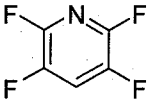
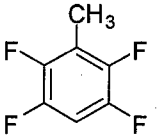
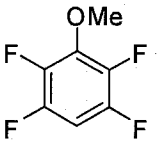
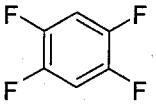
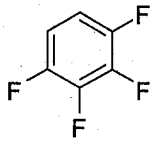
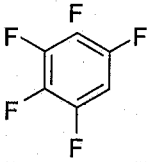
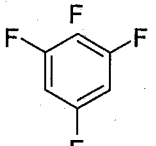
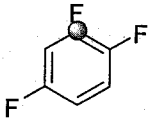
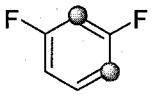
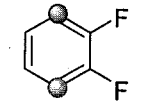
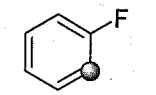
[a] Isolated yield.[b] AgOTf added (0.5 equiv.). [c] Yield of the product of double direct arylation.

Tetrafluoro-, trifluro and even some difluorobenzenes can be selectively cross-arylated (Table 2.9). For example, 2,3,5,6-tetrafluoropyridine, 2,3,5,6-tetrafluorotoluene and 2,3,5,6-tetrafluoroanisole all react in excellent yield and require only a slight excess of the fluoroarene to be employed (entries 1, 2 and 3).

In reactions with perfluorobenzenes having more than one potential site for reaction, mixtures of mono, di and tri-arlyation can occur which can be minimized by using a slight excess of the fluoroarene (Table 2.8, entries 4 to 10). In all cases, arylation occurs only ortho to the fluorine substituant. When 1,2,3,4-tetrafluorobenzene is employed, steric encumbrance disfavors double arylation providing synthetically useful selectivity for mono-arylation with 1.1 equivalents of the fluorobenzene (entry 5). When reacting 1,4-difluorobenzene, two different diarylation product were isolated in a 1:1 ratio as an inseperable mixture (entry 8). It was therefore impossible to assign the position of the second arylation but since the steric factor seems to be important, we believe the second arylation to occure 2,5 and 2,6. With 1,3-difluorobenzene, arylation occurs selectively at the C-H bond between the two fluorine atoms in 85% yield (entry 9). Pushing the limits of these reactions, we were surprised to find that even fluorobenzene itself could be arylated, albeit in substantially lower yield (entry 11). This last result bodes well for the development of direct arylation reactions with other arenes as catalyst design improves.

Table 2. 8. Scope of Perfluoroarenes for the Direct Arylation of Aryl Bromides.



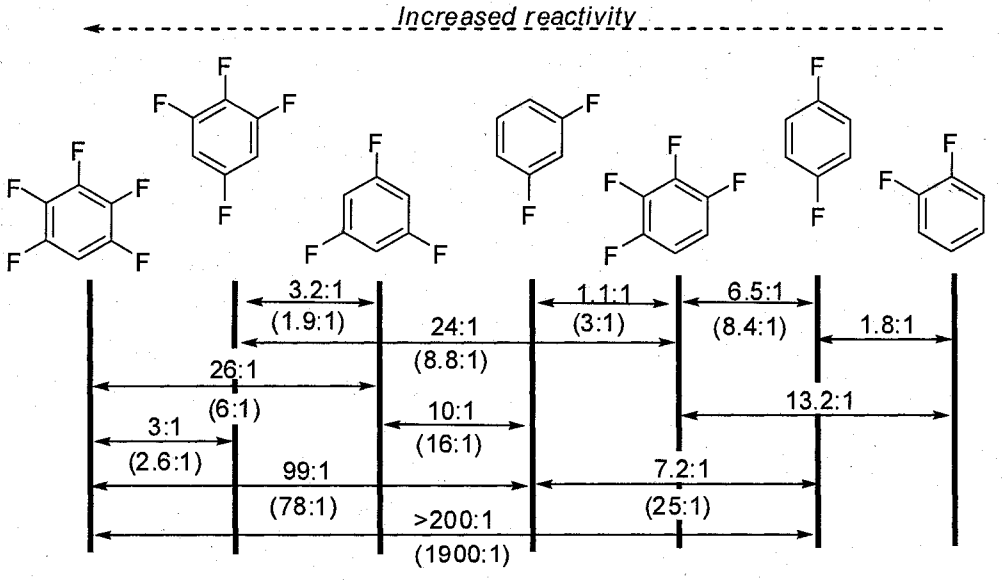
Entry	Fluoroarene	Product	Fluoroarene Equiv.	Yield (%)[a]
1		**10**	1.5	86
2		**11**	1.1	86
3		**12**	1.1	92
4		**13** **14**	3	79 (mono) 20 (bis)
5		**15** **16**	1.1	68 (mono) 10 (bis)
6		**17** **18**	3	75 (mono) 24 (bis)
7		**19** **20** **21**	3	69 (mono) 24 (bis) 2 (tris)
8[c,d]		**22** **23**	3	42 (mono) 13 (bis)[b]
9[d]		**24** **25**	3	85 (mono) 9 (bis)
10[c,d]		**26** **27**	3	29 (mono) 9 (bis)
11[c,d]		**28**	3	8

[a] Isolated yield [b] Isolated as an inseperable mixture of regioisomers. [c] 10 mol% catalyst was employed. [d] The blue ball represent the position for the mono addition while the red one represent the position for the second arylation.

2.2.3 – Mechanistic Investigation and Computational Studies

Competition experiments were performed to establish the relative reactivity of different perfluoroarenes. Equimolar quantities of two different levels of fluorinated arenes were reacted with 4-bromotoluene. We then compared the product distribution at 10-15% conversion by GCMS. As depicted in Figure 2.2, two trends emerge. First, this relative reactivity parallels their relative acidities as the most reactive arene was found to be pentafluorobenzene.[92] Thus, the introduction of fluorine substituent at positions remote to the C-H bond being cleaved increases the reactivity. In many cases it is the more electron-deficient arene that reacts preferentially, which is a complete reversal in reactivity compared to other direct arylations occurring *via* the S_EAr mechanism. Second, direct arylation of substrates having two chemically distinct C-H bonds occurs preferentially at the most acidic C-H bond which, with perfluoroarenes, is *ortho* to a fluorine atom.[21] These trends were also observed for the product resulting from a double arylation as the arylation always occurred next to the carbon which contained a fluorine substituent.

Figure 2. 2. Competition experiments performed to determine relative reactivity.

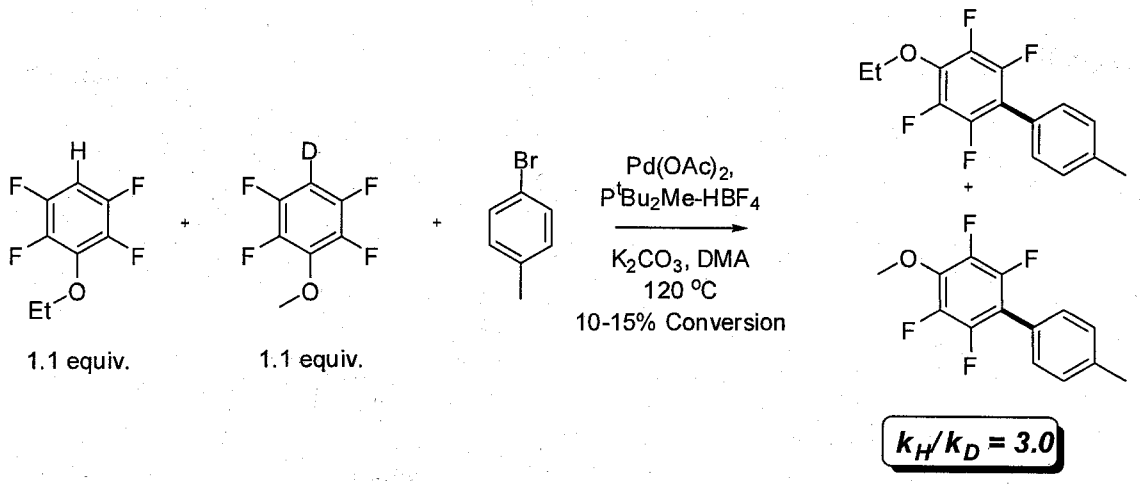


Two perfluoroarenes were reacted simultaneously in the presence of 4-bromotoluene under the standard reaction conditions, stopped at 5 to 10% conversion and analyzed by ^{1}H NMR and GCMS. Values in parenthesis are determined from calculated reaction barrier differences at 120 °C by comparing the energy of the two transition states using the mechanism C-4 in Scheme 2.13.

[92] (*a*) Schlosser, M.; Marzi, E. *Chem. Eur. J.* **2005**, *11*, 3449. (*b*) Shen, K.; Fu, Y.; Li, J.-N.; Liu, L.; Guo, Q.-X. *Tetrahedron*, **2007**, *63*, 1568.

Computational studies indicate that this selectivity is a result of the C-H acidity and not due to a stabilizing interaction between the palladium and a fluorine substituent (vide infra). This selectivity is clearly illustrated by the reaction of 1,3-difluorobenzene which undergoes selective arylation at the 2-position. A kinetic isotope effect of 3.0 is also observed, indicating that C-H bond-cleavage is a kinetically significant catalytic event (Scheme 2.8). A control experiment of 2,3,5,6-tetrafluoroanisole with 3-ethoxy-1,2,4,5-tetrafluorobenzene in a 1:1 ratio resulted in a 1:1 ratio of product distribution at approximately 10 to 15% conversion.

Scheme 2. 8. Kinetic Isotope Effect Experiment.



In collaboration with Christopher Rowley from Prof. Tom Woo's research group, the mechanism of C-H bond cleavage was examined by density functional theory calculations using the B3LYP[93] exchange-correlation functional. While all of the following computational work was performed by Christopher Rowley, due to its pertinence towards understanding the reaction mechanism, it will be discussed in detail. To decrease the computational time required for the calculations, PH_3 was used as a ligand instead of P^tBu_2Me.[94] Several distinct reaction mechanisms were explored, including oxidative addition of the arene C-H bond to the Pd center (**A**), electrophillic

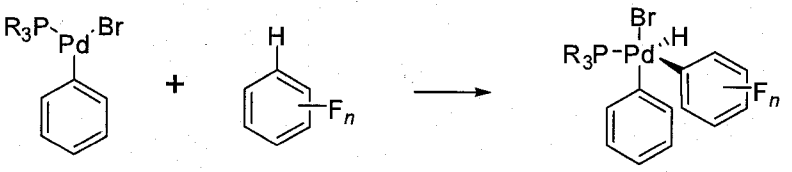
[93] (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. (b) Lee, C. T.; Yang, W. T.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.

[94] B3LYP17 density functional theory calculations were performed with the Jaguar 6.0 package with the LACV2P* basis set and pseudopotential combination of Jaguar.

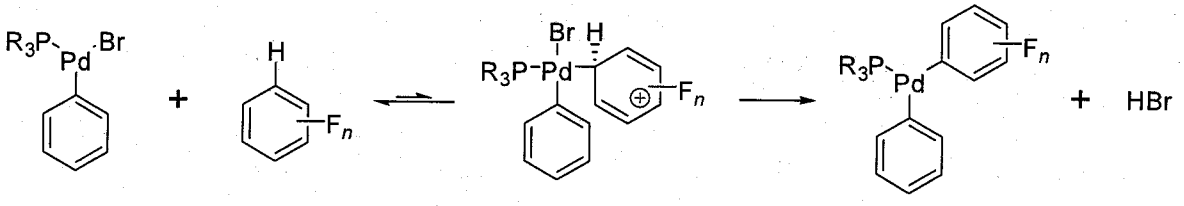
aromatic substitution (**B**) (Scheme 2.9), as well as a concerted metalation/proton abstraction to a base (**C**) (Scheme 2.10).

Scheme 2. 9. Proposed Mechanisms **A** and **B**.

Oxidative Insertion of the Arene C-H Bond to the Pd Catalyst - Mechanism A.



Electrophillic Aromatic Substitution - Mechanism B.



For the oxidative addition of the arene C-H bond through mechanism **A**, all attempts to locate a stable palladium hydride intermediate were unsuccessful. All failed attempts resulted in reformation of the starting material or the products of mechanism **C**. Similar results were obtained when attempting to locate any appropriate intermediates corresponding to an electrophilic aromatic substitution reaction (mechanism **B**). This result is not surprising, considering that the reactivity trends of the perfluoroarenes are inversed to experimentally determined trends for these types of reaction pathway.

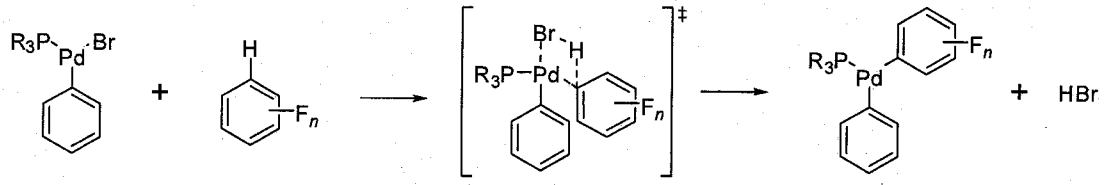
Since all attempts to locate relevant stationary points for mechanisms **A** or **B** failed or resulted in stationary points characteristic of other mechanisms, these mechanisms were deemed unlikely and were not considered further.

Mechanisms **C1-C4** are closely related concerted deprotonation/palladation reactions as first proposed by Echavarren and coworkers.[88d,89] They differ from one another through the nature of the active catalytic species as well as the base employed in the proton abstraction sequence. In the **C1** pathway, the active catalytic species is a (PH_3)ArPd-Br complex with an intramolecular deprotonation from the Br ligand. Through a ligand exchange of the bromide with a more basic bicarbonate anion prior to the

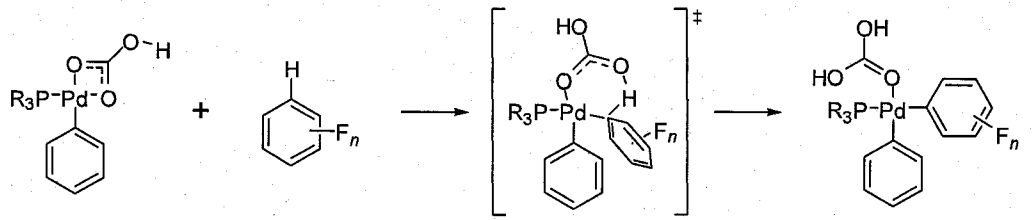
deprotonation step, we obtain a $(PH_3)ArPd\text{-}HCO_3$ catalytic species which can perform a similar intramolecular deprotonation through mechanism **C2**. It is also possible that the $(PH_3)ArPd\text{-}Br$ complex would bind weakly with the perfluoroarene followed by an external deprotonation from a "free" carbonate ion (mechanism **C3**). Since the bicarbonate anion was found to bind with such ease with the palladium species, a 4 coordinate palladium species with both the bromide and the bicarbonate anion bound to it, could undergo similar intramolecular deprotonation through a mechanism **C4** (Scheme 2.10).

Scheme 2. 10. Proposed Mechanism **C1-C4**.

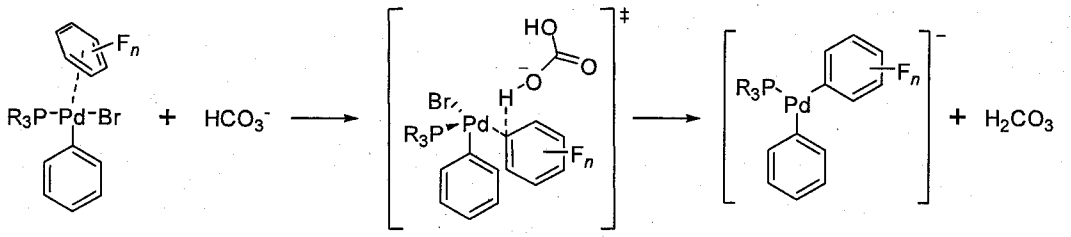
Concerted Palladation/Deprotonation by Bromide Ligand - Mechanism C1.



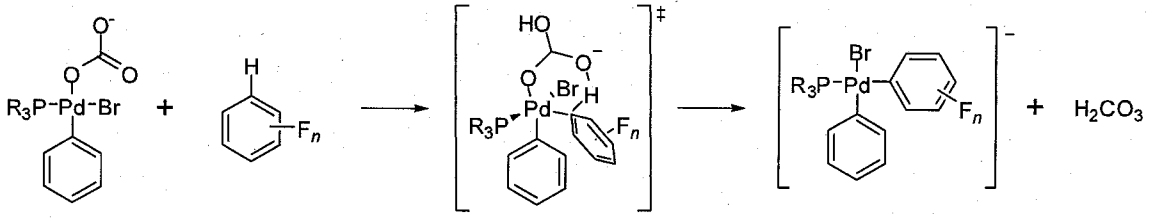
Concerted Palladation/Deprotonation by Bicarbonate Anion Ligand - Mechanism C2.



Concerted Palladation/Deprotonation by "Free" Bicarbonate - Mechanism C3.



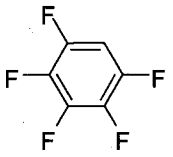
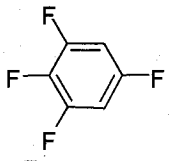
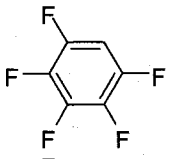
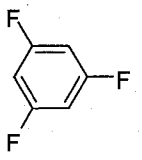
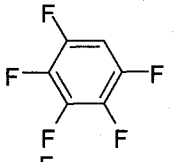
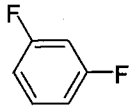
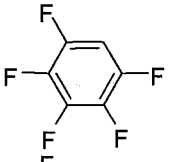
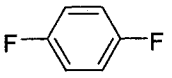
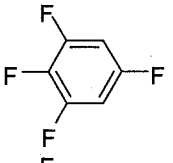
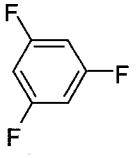
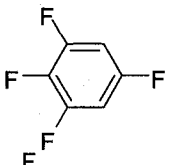
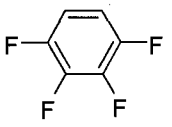
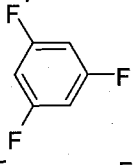
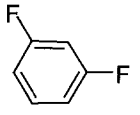
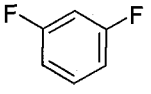
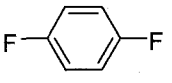
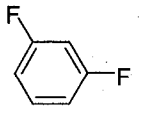
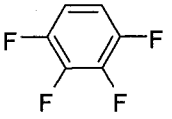
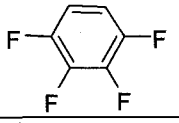
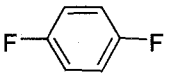
Concerted Palladation/Deprotonation by Bicarbonate Anion Ligand (4 Coordinate Pd) - Mechanism C4.



No transition state could be located for mechanism **C1**. However, a forward and reverse coordinate scan where the C-H bond distance was altered revealed that the energetic barrier is thermodynamic in nature with an associated value of 23.7 kcal/mol. In other words, the reverse reaction is essentially barrierless. For mechanism **C2**, a reaction barrier of 9.9 kcal/mol was calculated while mechanism **C4** was found to possess a reaction barrier of 13.3 kcal/mol. No pathway could be located for mechanism **C3** involving intermolecular proton transfer. Instead, the bicarbonate ion was always found to first bind the Pd center and give $(PR_3)ArPd(Br)HCO_3$, which would then abstract the proton *via* mechanism **C4**. At this point we could not rule out any of the remaining mechanism (**C1**, **C2** or **C4**). We therefore performed a comparison of the calculated results of the competition studies with the experimental data.

For comparison, the reaction barriers for mechanisms **C1**, **C2** and **C4** were calculated for the series of perfluoroarenes used in the competition experiments. Since the competition experiments are performed under kinetic conditions, the relative product ratios obtained from these experiments can be qualitatively compared to the calculated relative reaction barriers. Using approximate transition state theory, with the assumption that the prefactors are identical for all perfluoroarenes, we can calculate the product ratio at a given temperature from the calculated relative barriers. The calculated product ratios are compared to those from the competition experiments in Table 2.9 for mechanisms **C1**, **C2** and **C4**. It should be noted that the calculated product ratios are very sensitive to small differences in the calculated barrier differences due to the exponential dependence. For example, a 100:1 product ratio corresponds to a 3.6 kcal/mol difference in reaction barriers at 120 °C whereas a 20:1 ratio corresponds to a 2.33 kcal/mol barrier difference. Thus, inconsistency in the absolute product ratios can be expected.

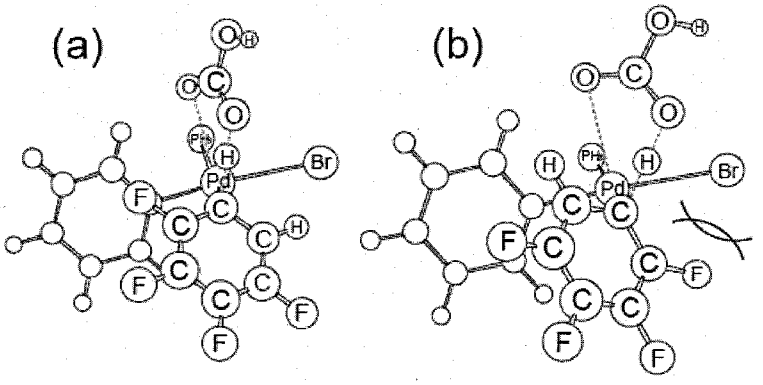
Table 2. 9. Calculated Product Ratios for Mechanisms **C1**, **C2** and **C4** Compared to the Experimental Ratios from Competition Experiments.

Entry	Arene A	Arene B	C1	C2	C4	Experimental
1			0.95:1	2.6:1	26:1	3:1
2			33:1	4.9:1	1543:1	26:1
3			147:1	1900:1	90:1	>200:1
4			794:1	1.9:1	29:1	3.2:1
5			35:1	88:1	1:244	24:1
6			130:1	88:1	1:244	24:1
7			4.4:1	16:1	72:1	10:1
8			5.4:1	25:1	1:1264	7.2:1
9			0.83:1	3:1	1:10	1.1:1
10			6.5:1	8.4:1	830:1	6.5:1

The numbers in blue correlates with the experimental value while the numbers in red are displaying opposite reactivity.

The calculated results for mechanism **C4** correlate poorly with the experimental reactivity trends. In general, the calculated reaction barriers increase as the perfluoroarene becomes less acidic, with some exceptions. Calculated barrier heights for mechanism **C4** predict the opposite preference for entries 6, 8 and 9. The calculated barrier differences for these pairs of reactants not only have the wrong sign, but the magnitude of the difference is significant, resulting in predicted product ratios that are large for the wrong reactant. The cause of this inversion is associated with a steric repulsion between an *o*-fluoride substituent and the Br of the catalyst. This interaction is highlighted in Figure 2.3. When a perfluoroarene possessing two *ortho* fluoride substituents is used, this unfavorable interaction cannot be avoided. However, when the perfluoroarene has only one *ortho* fluororine substituent, there are two possible transition state geometries. Therefore with mechanism **C4**, the calculated barriers for the perfluoroarenes with one *ortho* fluororine substituent are lower than those bearing two fluorines. These results are not consistent with the experimental data, leading us to conclude that mechanism **C4** is not operating in a significant way.

Figure 2. 3. Two Calculated Transition State Geometries for Mechanism **C4** for 1,2,3,4-Tetrafluorobenzene.



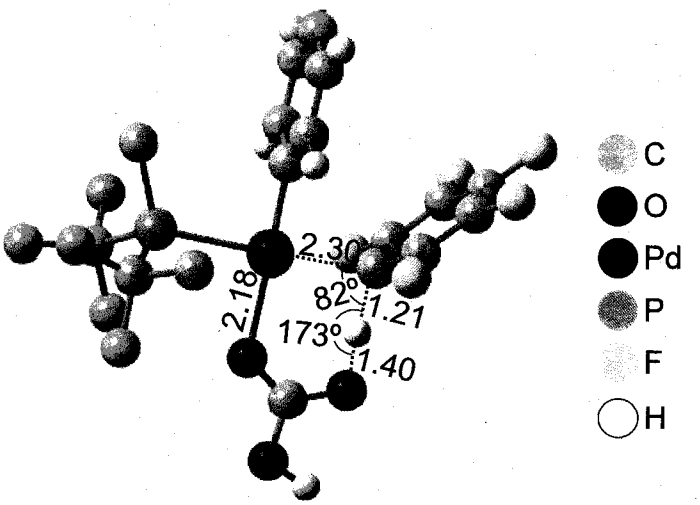
Geometry (b) posses a repulsive interaction between the *ortho* fluorine substituent and the bromide ligand

Both mechanisms **C1** and **C2** not only predict the correct reactivity trends, they also predict the regiochemistry of the reaction. With several perfluoroarenes, there is more than one position in which the direct arylation can occur. For example, for 1,3-

difluorobenzene arylation occurs between the two fluorine atoms, whereas with fluorobenzene arylation is observed at the *ortho* position preferentially. These results were examined computationally, and for both fluoroarenes the lowest energy barrier matches the site of arylation observed experimentally under both **C1** and **C2** mechanisms.

Using a continual solvation model to approximately account for the solvent using a dielectric constant equal to that of bulk DMA, an increase in the thermodynamic barrier was observed for mechanism **C1** to 36.2 kcal/mol and to 19.8 kcal/mol for mechanism **C2**. Of the remaining mechanisms, proton abstraction with the bicarbonate ion *via* mechanism **C2** was found to have the lowest reaction barrier and gave results most consistent with available experimental data. Furthermore, the computed value of k_H/k_D was found to be 3.25 at 120°C, correlating strongly with the experimental value of 3.0. When taking into account the exponential dependence between product ratio and the calculated barrier differences, the experimental and calculated ratios are in excellent agreement, lending strong support to the plausibility of this pathway. The transition state structure with C_6F_5H and P^tBu_2Me as the ancillary ligand is shown in Figure 2.4. Importantly, there is no indication of catalyst-fluorine interactions in any of the transition states for all the different perfluoroarenes indicating that these reactions constitute the first example of non-directed catalytic benzene functionalization.

Figure 2. 4. Calculated Transition State Structure for Mechanism **C2**.



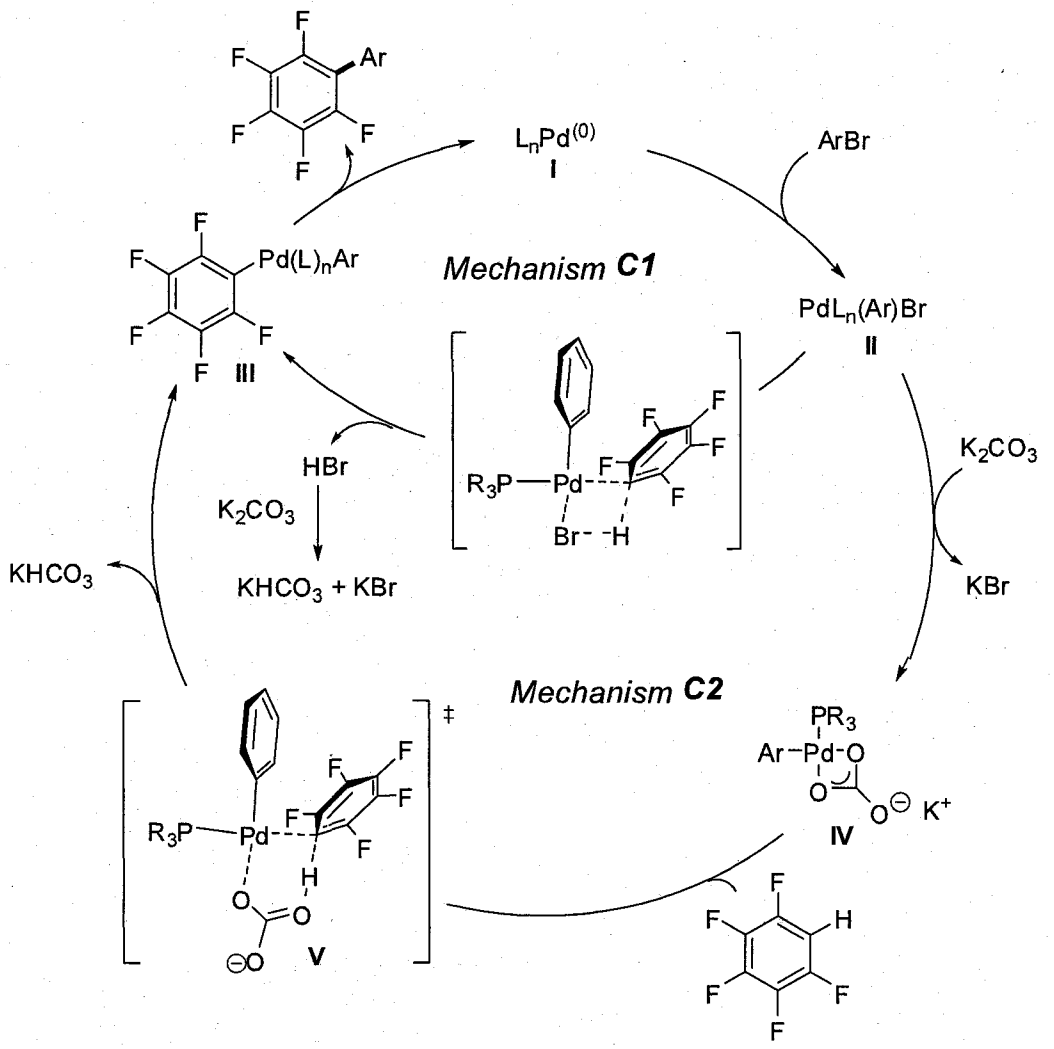
Calculated transition state structure for mechanism **C2** with C_6F_5H as the perfluoroarene and P^tBu_2Me as the ancillary ligand. Selected H atoms have been removed for clarity.

While computationally the exchange of the bromide for a carbonate or bicarbonate ligand was a viable process, the quantity of bicarbonate dissolved in solution is unknown. It is therefore difficult to estimate the actual amount of $(PR_3)ArPd\text{-}X$ species formed in solution. Although the reaction occurs in the presence of excess potassium bicarbonate, only a very small amount (~1 to 2%) is actually dissolved in the DMA.[95] It is therefore very difficult to validate that such an anion exchange occurs on the palladium catalyst prior to C-H bond cleavage. Moreover, approximate continuum solvent calculations suggest that the brominated species, $(PR_3)ArPd\text{-}Br$, is 6.0 kcal/mol more stable in DMA than $(PR_3)ArPd\text{-}CO_3H$. It is important to note that precedent exists for palladium-catalyzed arene functionalizations in the absence of a carbonate or acetate base.[96] This may indicate that multiple reactions pathways may be operative depending on the reaction conditions. The excellent agreement between experimental reactivity trends and regioselectivity with the computed results for both mechanisms **C1** and **C2** supports that one or both of the mechanisms are operative as shown in Scheme 2.15.

Based on these findings, a plausible catalytic cycle can be described as outlined in Scheme 2.11. The catalytic cycle begins with oxidative addition of the palladium (0) species with the aryl halide to generate the palladium (II) intermediate **II**. This intermediate can undergo two different pathways **C1** or **C2**. In the **C1** pathway, a concerted deprotonation/palladation sequence occurs to generate the palladium diaryl **III** with concomitant hydrogen bromide formation. Alternatively, a ligand exchange of the bromide for a carbonate generates **IV**. A similar six-membered ring deprotonation/palladation sequence takes place through an intermediate **V** to generate the same palladium diaryl **III** which can reductively eliminate the perfluorobiaryl product and regenerate the palladium (0) catalyst **I**.

[95] The solubility of K_2CO_3 was evaluated by heating it in DMA at 120°C for 30 minutes followed by rapid filtration of the hot solution. Less than 1% of the K_2CO_3 had dissolved.
[96] For example see: Hennessy, E.J.; Buchwald, S.L. *J. Am. Chem. Soc.* **2003**, *125*, 12084.

Scheme 2. 11. Proposed catalytic cycle of perfluorobenzene direct arylation.



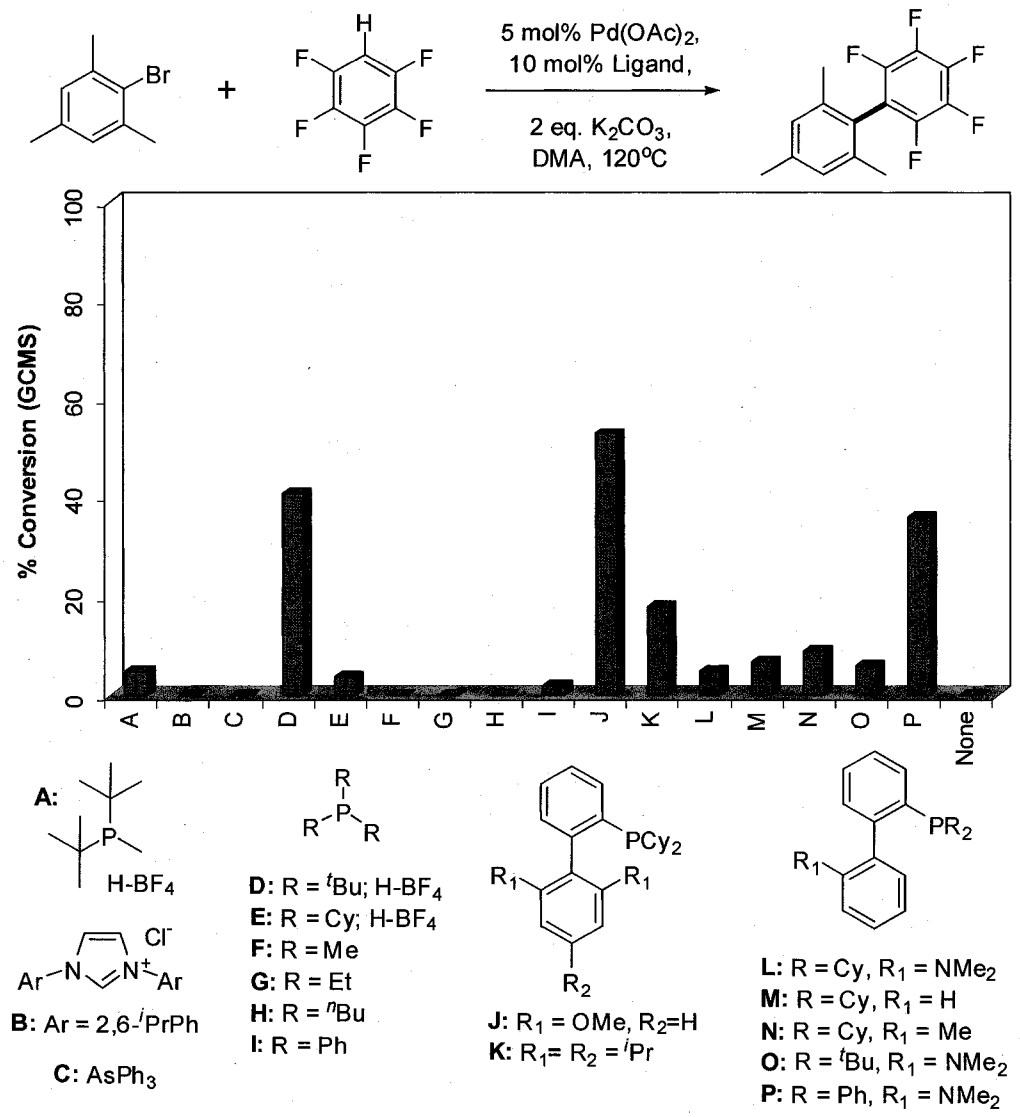
For the C-H bond cleavage step, two possible mechanisms (**C1**, **C2**) are depicted involving concerted metalation of the fluoroarene and H-transfer to either a carbonate ligand or Br ligand on the catalyst.

2.2.4 – Optimization of the Reaction for Use of Aryl Chlorides and Sterically Hindered Aryl Halides.

While exploring the reaction scope, these reactions were found to occur in high yield with several aryl bromides, but suffered from lower yields when aryl chlorides or *ortho*-substituted aryl bromides were employed. These limitations prompted a re-evaluation of the catalyst and reaction conditions, focusing on these more challenging

substrates.[97] Catalyst and reaction condition screens were performed with bromomesitylene as the model substrate in a reaction with pentafluorobenzene. A variety of phosphine ligands were evaluated for the transformation and the conversions were analyzed by GCMS (Table 2.10). For technical simplicity, the trialkylphosphines were used as the tetrafluoroborate salts.[91]

Table 2. 10. Ligand Optimization for Sterically Hindered Aryl Halides.



[97] Lafrance, M.; Shore, D.; Fagnou, K. *Org. Lett.* **2006**, *8*, 5097.

Trialkylphosphines **A** and **E** through **H** gave either no or poor conversions to the desired product with the exception of the highly sterically hindered tri-*tert*-butylphosphine tetrafluoroborate salt **D** which gave the product in 41% yield. Similarly, *N*-heterocyclic carbene ligand (**B**), triphenyl arsene (**C**) and triphenyl phosphine (**I**) also gave essentially none of the desired product. The Buchwald biaryl ligands proved to be the best ligand class for this process. Of particular interest is S-Phos[98] (**J**) as well as ligand **P** which gave the product in 53% and 36% yield. We therefore continued our optimization with ligands **D** and **J**.

2.2.4.1 – Reaction Optimization

Different reaction parameters were optimized with ligands **D** and **J** including reaction concentration, ligand equivalents, palladium source, perfluoroarene equivalents and reaction temperature. A series of inorganic and organic bases (K_2CO_3, KOPiv, CsOPiv, Cs_2CO_3, CsF, Et_3N, DBU, Na_2CO_3, K_3PO_4 and MgO) were also evaluated.

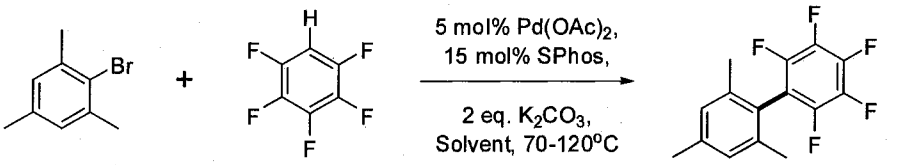
The use of 2 equivalents of potassium carbonate was found to be optimal. Amine bases were found to be highly incompatible with the reaction. A significant counter ion effect was observed, for example, potassium carbonate giving the product in 74% yield while cesium carbonate provides only 15% yield using S-Phos (**J**) as the ligand.

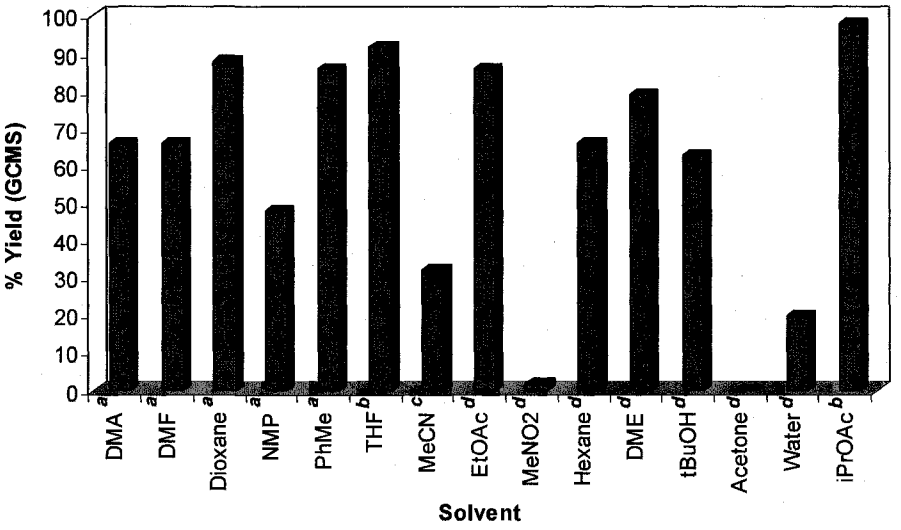
Different solvents were found to be suitable for this transformation (Table 2.11). Polar aprotic solvents such as *N*,*N*-dimethylacetamide (DMA), *N*,*N*-dimethylformamide (DMF) and *N*-methylpyrrolidin-2-one (NMP) were found to give the product in poor to good yields with increased amounts of concomitant dehalogenated product (4-7%). Polar ether solvents such as dioxane, 1,2-dimethoxyethane (DME) and tetrahydrofuran were good solvents, giving the product in 88%, 79% and 92% yield respectively. Non polar solvents were also effective, including toluene and hexane which give the product in 86% and 66% yield. Nitromethane and acetonitrile were completely incompatible with the reaction, leading to the rapid formation of palladium black within seconds. Polar protic solvents such as *tert*-butanol and water were also non ideal for the reaction, giving the product in 63% and 20% yield respectively. The optimal solvent was found to be

[98] Walker, S.D.; Barder, T.E.; Martinelli, J.R.; Buchwald, S.L. *Angew. Chem. Int. Ed.* **2004**, *43*, 1871.

isopropylacetate which gave clean conversion to the biaryl in 98% isolated yield with little to no reduced byproduct.

Table 2. 11. Solvent Effect on Direct Arylation of Sterically Hindered Aryl Halides.





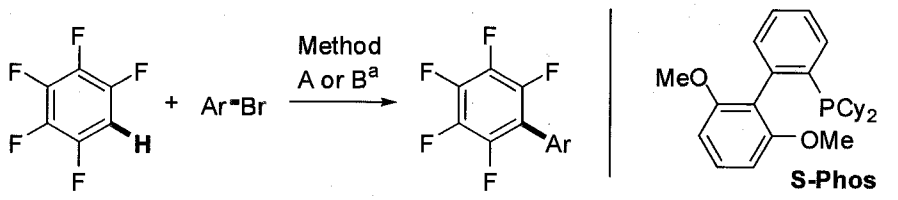
[a] Reaction performed at 120°C. [b] Reaction performed at 80°C. [c] Reaction performed at 100°C. [d] Reaction performed at 70°C.

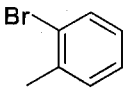
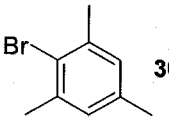
2.2.4.2 – Reaction Scope

A comparaison of the initial and the second generation conditions is outlined in Table 2.12. Under first generation conditions (method A),[90] very poor conversion was obtained with **29** (entry 1) and no reaction was observed with **30** (entry 3). Using our new catalyst conditions (method B) generated by mixing $Pd(OAc)_2$ with 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (S-Phos) in isopropyl acetate at 80 °C with K_2CO_3 as the base, complete conversion was achieved with both aryl bromides **29** and **30**, resulting in 99% and 98% isolated yields, respectively. The combination of the

$Pd(OAc)_2$/S-Phos catalyst and the ^{i}PrOAc[99] solvent appears to be an excellent combination for these reactions. Notably, use of our previously reported $Pd(OAc)_2/P^tBu_2Me{\cdot}HBF_4$ catalyst in ^{i}PrOAc or use of $Pd(OAc)_2$/S-Phos in DMA leads to significantly diminished outcomes. We also note that the reaction temperature can be lowered to 70 °C, but occasionally incomplete conversion is obtained; thus, we chose 80 °C as the standard reaction temperature for subsequent studies.

Table 2. 12. Solvent Effect on Direct Arylation Sterically Hindered Aryl Halides.[a]



entry	aryl bromide	method	convn. (%)[b]	yield (%)[c]
1	 **29**	A	12	nd
2		B	100	99
3	 **30**	A	0	0
4		B	100	98

[a] Method A: $Pd(OAc)_2$ (5 mol %), $P^tBu_2Me{\cdot}HBF_4$ (10 mol %), K_2CO_3, DMA, 120 °C; Method B: $Pd(OAc)_2$ (5 mol %), S-Phos (10 mol %), K_2CO_3, ^{i}PrOAc, 80 °C. [b] Determined by GCMS analysis. [c] Isolated Yield.

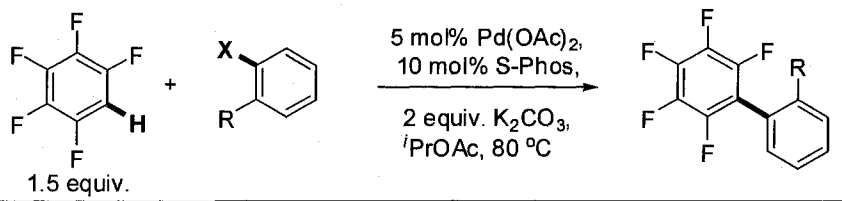
The scope of the reaction between pentafluorobenzene and a range of aryl halides was investigated and is outlined in Table 2.13. In addition to *ortho*-substituted aryl bromides (entry 2), aryl iodides may also be employed (entry 3). With aryl iodides, 0.5 equivalents of Ag_2CO_3 must be employed as an additive in order to achieve reaction completion. An inhibitory effect of iodide salts on direct arylation has previously been observed[17b,100] and we postulate that the silver salts are serving to remove the iodide salts from the mixture as they are generated by the catalytic cycle. The silver carbonate may also be facilitating a iodide-carbonate ligand exchange, which may facilitate C-H

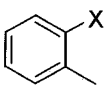
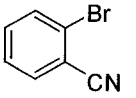
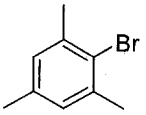
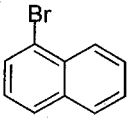
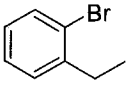
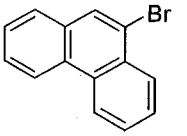
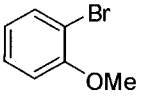
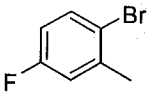
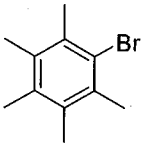
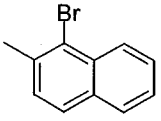
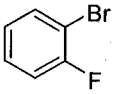
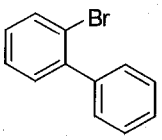
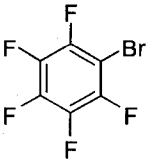
[99] EtOAc can also be employed. However the lower volatility and slightly higher boiling point of ^{i}PrOAc results in greater reproducibility and greater ease in performing the reactions. Notably, it allows the reactions to be run below the solvent boiling point (85-91 °C).

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

bond cleavage.[17d] A variety of *ortho*-substituents can be present including methyl (entries 1 to 3 and 7), ethyl (entry 5), methoxy (entry 6), nitrile (entry 10) and fluoro groups (entries 14 and 15). Sp^2 hybridized carbones were also compatible such as 1-bromonaphthalene (entries 8 and 11), 2-bromobyphenyl (entry 9) as well as phenanthrene (entry 12). Even more sterically encumbered bis-*ortho*-substituted aryl bromides can be arylated in high yield (entries 4 and 13).

Table 2. 13. Scope for Sterically Hindered Aryl Halides.[a]

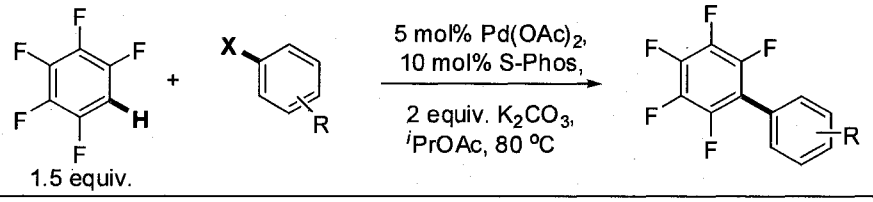


entry	aryl halide	product	yield[a]	entry	aryl halide	product	yield[a]
1	 X = Cl	**31**	97				
2	X = Br	**31**	99				
3	X = I	**31**	82				
				10		**38**	73[c]
4		**32**	98	11		**39**	99
5		**33**	82				
				12		**40**	97
6		**34**	99				
7		**35**	96	13		**41**	85[c]
8		**36**	96	14		**42**	99
9		**37**	92[b]	15		**43**	83[c]

[a] Isolated yield. [b] Performed using $Pd(OAc)_2$ with $P^tBu_3.HBF_4$ in DMA at 120°C. [c] Three equivalents of pentrafluorobenzene used.

Given the low yields associated with aryl chlorides in Suzuki cross-coupling reactions of pentafluorophenylboronic acid and in direct arylation of pentafluorobenzene in our previous report,[20] we were pleased to find that a wide range of aryl chlorides can now be employed with these new conditions (Table 2.14). Chlorobenzene was found to react and give the product in 99% isolated yield (entry 16). An aryl triflate may also be employed as illustrated by entry 17. Electron donating groups are also compatible with the reaction (entry 18 and 19). Activated arenes were found to react smoothly affording the product in high yields (entries 20 to 23). Sterically encumbered aryl chlorides reacted without any dramatic decrease in yield (entry 24). More complex aryl chlorides can also be employed as illustrated by the high yielding reaction of the C2 chlorinated aporphine to generate **49** in 99% yield (entry 25). We also evaluated the compatibility of these new reaction conditions with heterocyclic aryl halides. For example, 3-chloropyridine can be cross-coupled in good yield (entry 26) as can 3-bromoquinoline (entry 27). Additionally, 3- and 2-bromothiophene (entries 28 and 29) and 3-bromofuran (entry 30) may be arylated in 70, 63 and 55% yields, respectively.

Table 2. 14. Scope for Aryl chlorides– and Heterocycles–Pentafluorobenzene Cross-Coupling.



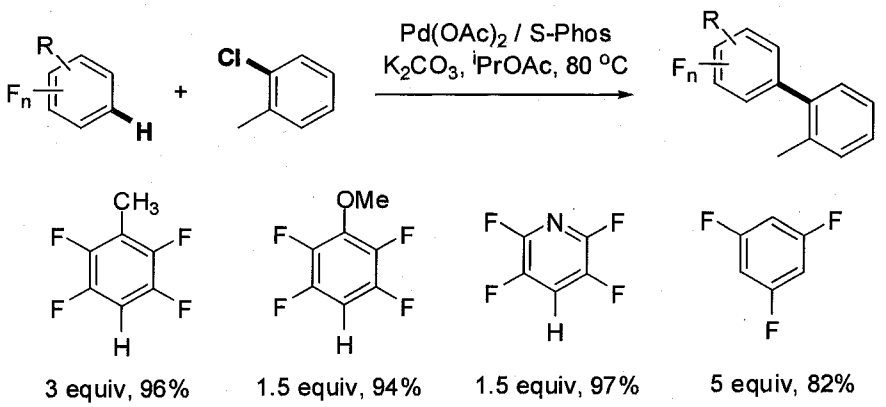
entry	aryl halide	product	yield[a]	entry	aryl halide	product	yield[a]
16 17	X= Cl X= OTf	**44** **44**	99 98	24	Cl	**48**	90
18	Cl	**1**	99	25	Cl, N, Boc	**49**	99
19	MeO, Cl	**3**	89				
20	Cl, NC	**45**	97	26	Cl, N	**5**	79
21	Cl, F_3C	**2**	97	27	Br, N	**50**	92
22	Cl, O	**46**	62	28	Br, S	**51**	70
				29	Br, S	**52**	63[b]
23	Cl, MeO_2C	**47**	99	30	Br, O	**53**	55[b]

[a] Isolated yield. [b] Three equivalents of pentrafluorobenzene used.

Other perfluoroaromatic compounds can also be arylated in high yield. To evaluate the applicability of these conditions to other aromatic compounds, 2-chlorotoluene was employed as a model aryl halide (Table 2.15). Under the second generation conditions, 2,3,5,6-tetrafluoroanisole and 2,3,5,6-tetrafluoropyridine both reacted to give 94 and 97% isolated yields, respectively. With 2,3,5,6-tetrafluorotoluene, three equivalents were found to give a better yield, allowing the isolation of the arylated

product in 96%. 1,3,5-Trifluorobenzene can also be employed. In this case, five equivalents of the arene were employed to give 82% isolated yield.

Table 2. 15. Arylation of Substituted Perfluoroaromatics.



In conclusion, we have established two complimentary sets of conditions for the direct cross-coupling of perfluoroaromatics with a wide range of sterically encumbered bromides and chlorides, as well as, aryl iodides, triflates and heterocyclic aryl halides. Strikingly, the latest reaction conditions allow the reaction to occur at 80°C, which is milder than our initially disclosed conditions (120°C) and are among the mildest conditions reported for this type of transformation. The successful identification of these reaction conditions should, in most cases, replace the use of pentafluorophenyl organometallics in the synthesis of these biaryl molecules.

Chapter 3

Development of a Palladium-Pivalic Acid Co-Catalyst System for the Direct Arylation of Simple Benzenes

While there have been many reports of direct arylation in the synthesis of biaryl molecules over the past decade, little progress has been achieved with simple unsubstituted arenes such as benzene. Electron rich arenes are thought to rely on nucleophilicity that may mimic the organometallic moiety, while electron poor arenes can react through a concerted deprotonation/metallation.[101] Consequently, simple arenes such as benzene are some of the most challenging substrates in these processes since

[101] For a more detailed discussion, see Chapter 1 and 2.

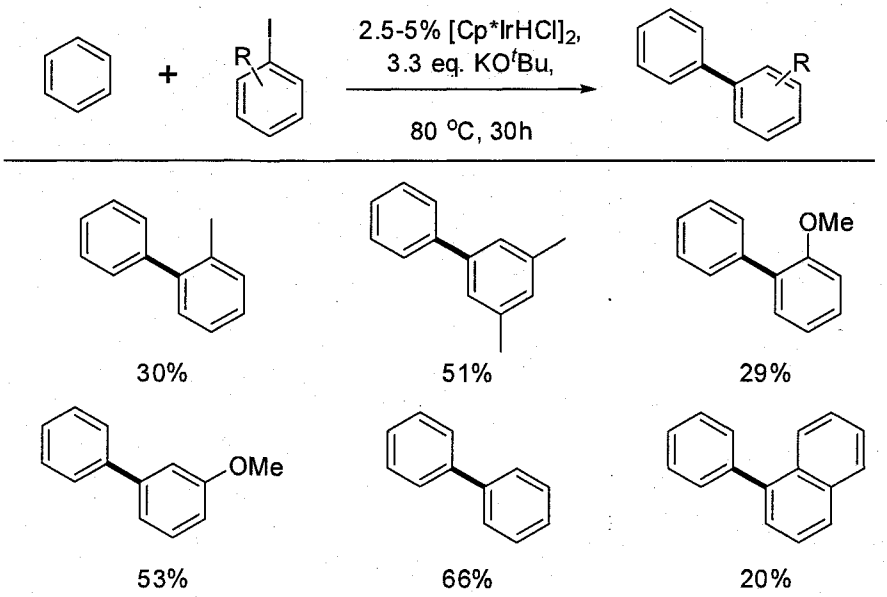
they benefit from poorly of these properties. As a result, the application of traditional processes, such as the use of phenylboronic acid as an activated arene reagent in Suzuki couplings, remains the most common method to perform the cross-coupling of simple arenes such as benzene.

3.1 – Direct Arylation of Simple Arenes

3.1.1 – Cross-Coupling of Benzene through Aryl Radical.

In 2004, the group of Fujita and Tamaguchi reported the first example of direct arylation of benzene through the use of a pentamethylcyclopentadienyliridium complex.[102] With the use of 2.5-5 mol% of $[Cp^*IrHCl]_2$ and 3.3 equivalent of potassium *tert*-butoxide in benzene as their solvent, different iodoarenes were coupled with benzenes as shown in Table 3.1. Electron rich and neutral iodoarenes reacted smoothly while electron deficient iodoarenes were found to be more challenging substrates. Sterically hindered aryl iodides were also coupled successfully albeit in lower yields.

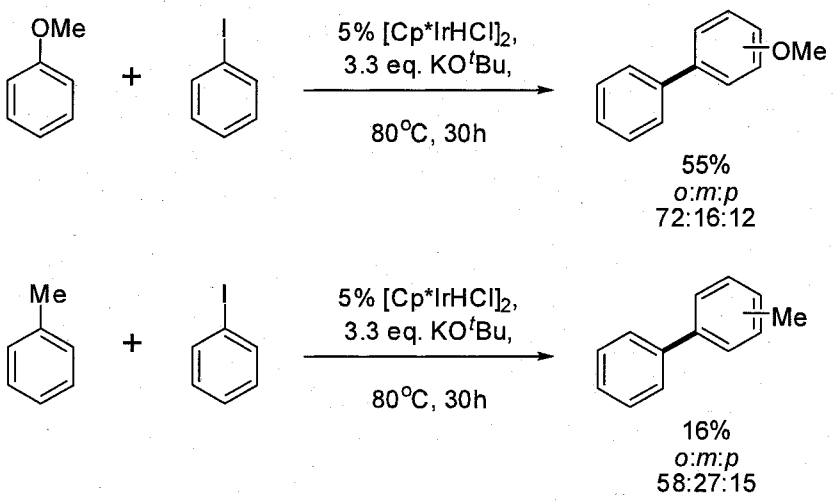
Table 3. 1. Direct Arylation of Benzene.



[102] Fujita, K.-i.; Nonogawa, M.; Yamaguchi, R. *Chem. Commun.* **2004**, 1926.

In an effort to elucidate the reaction mechanism by which this transformation occurs, different mechanistic investigations were performed. When benzene was replaced by anisole or toluene (Scheme 3.1), all 3 regioisomers were formed in ratios consistent with the presence of a radical intermediate.[103] Furthermore, when the reaction was performed in the presence of 2,6-di-*tert*-butylphenol, a radical scavenger, the yield for the reaction using 3-iodotoluene dropped from 70% to 10% by gas chromatography. They therefore attributed the reactivity to a metal induced phenyl radical formation.

Scheme 3. 1. Direct Arylation of Anisole and Toluene.



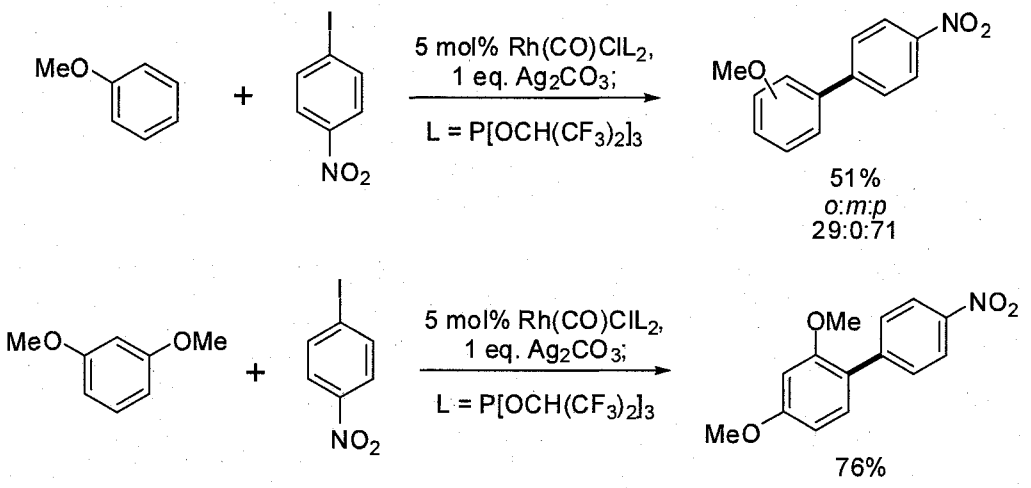
3.1.2 – Cross-Coupling of Anisole and 1,3-Dimethoxybenzene.

Using the same catalyst developed for the direct arylation of thiophenes, furans, pyrroles and indoles, Itami and coworkers were able to also achieve the direct arylation of some simple arenes.[104] Using a highly electrophilic rhodium catalyst, they were able to arylate anisole as well as 1,3-dimethoxybenzene in 51% and 76% yield (Scheme 3.2). The regioselectivity observed is consistent with an S_EAr pathway, in which anisole gives the *para* isomer preferentially along with *ortho* arylation as a minor product. Arylation at

[103] (*a*) Davies, D. I.; Hey, D. H.; Summers, B. *J. Chem. Soc. (C)*, **1970**, 2653. (*b*) Davies, D. I.; Hey, D. H.; Summers, B. *J. Chem. Soc. (C)*, **1971**, 2681.
[104] Yanagisawa, S.; Sudo, T.; Noyori, R.; Itami, K. *J. Am. Chem. Soc.* **2006**, *128*, 11748.

the C-4 position was the sole product observed from a reaction with 1,3-dimethoxybenzene.

Scheme 3. 2. Direct Arylation of Anisole and 1,3-Dimethoxybenzene.

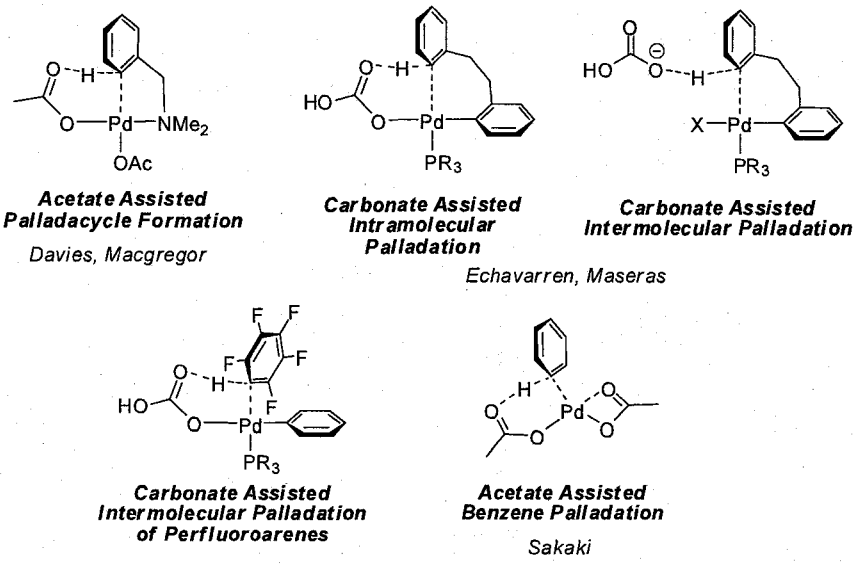


3.2 – Internal Base Carboxylate Derivatives Ligand.

In the previous chapter, a new palladium-catalyzed direct arylation of electron deficient arenes was described. The reactivity was rationalized by a concerted metallation-deprotonation pathway, in which the acidity of the C-H bond influenced both the site selectivity as well as the reactivity.[105] While the inner sphere proton abstraction by a carbonate ligand was shown to be the lowest energy pathway, the exchange of the bromide ligand by a carbonate anion remained uncertain due to the low solubility of potassium carbonate in DMA. Such pathways have been proposed and evaluated by others, including Davies and Macgregor[106], Echavarran and Maseras[107] and Sakaki[108] (Figure 3.1).

[105] Lafrance, M.; Rowley, C.N.; Woo, T.K.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 8754.
[106] Davies, D.L.; Donald, S.M.A. ; Macgregor, S.A. *J. Am. Chem. Soc.* **2005**, *127*, 13754.
[107] (*a*) Garcia-Cuadrado, D.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006**, *128*, 1066. (*b*) Garcia-Cuadrado, D.; de Mendoza, P.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2007**, *129*, 6880.
[108] Biswas, B.; Sugimoto, M.; Sakaki, S. *Organometallics*. **2000**, *19*, 3895.

Figure 3. 1. Mechanistic Possibilities for Arene Palladation for Biaryl Synthesis.



Several important implications can be drawn from these studies: (1) The anionic ligand (base) is directly involved in C-H bond cleavage; (2) The anion must bind to the catalyst, but not impede the catalytic cycle by competitive occupation of vacant coordination sites.[109,110] And, (3) the arene (benzene), which interacts with the catalyst very weakly, must compete for binding to the arylpalladium(II) intermediate with the excess anion (base).

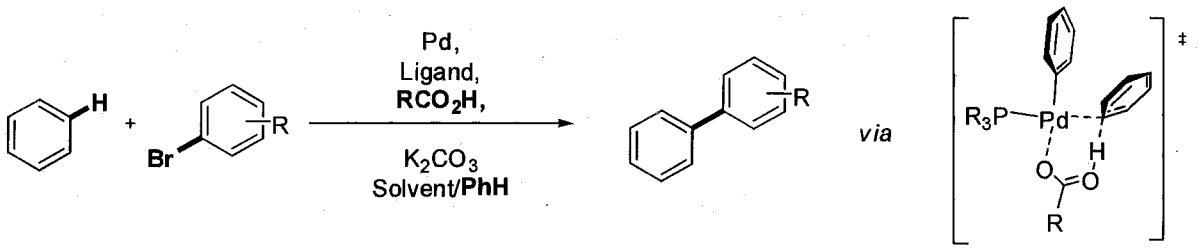
In this chapter, a novel palladium-pivalic acid co-catalyst system that constitutes the first non-directed intermolecular direct arylation of simple arenes such as benzene will be discussed (see Scheme 3.3). [111]

[109] We have previously observed a poisoning effect on direct arylation by the presence of iodide salts. See: Campeau, L.-C.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.*, **2006**, *128*, 581.

[110] In polar media, an excess of anionic ligands could result in the formation of palladate species which may prevent the arene from binding and achieving C-H bond cleavage. For a discussion of palladates in cross-coupling reactions, see: Amatore, C.; Jutand, A. *Acc. Chem. Res.* **2000**, *33*, 314.

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

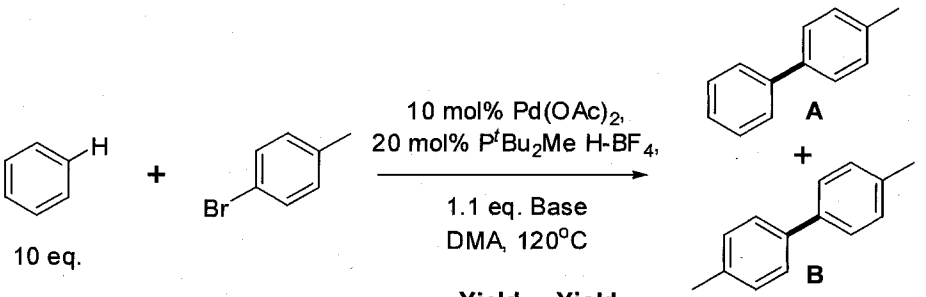
Scheme 3. 3. Proposed Solution for Direct Arylation of Benzene.



3.3 – Development of a New Palladium-Carboxylic Acid Co-Catalyst System for the Direct Arylation of Benzene.

Reaction development began with a focus on more soluble bases (Table 3.2). When cesium carbonate was employed, the yield rose from 6 to 9% by GCMS analysis.[112] Potassium pivalate gave 15% yield while cesium pivalate gave a 22% yield. Unfortunately, while the overall yield increased, the amount of dehalogenation by-product increased from 5% to 17% and a significant amount of aryl bromide dimerisation was produced. We then investigated the addition of tetrabutylammonium bromide salts, which could help increase the solubility of the carbonate base. Unfortunately, this led to complete conversion to the homocoupling and reduced by-products.

Table 3. 2. Evaluation of Some More DMA Soluble Carboxylic Derivative Bases.

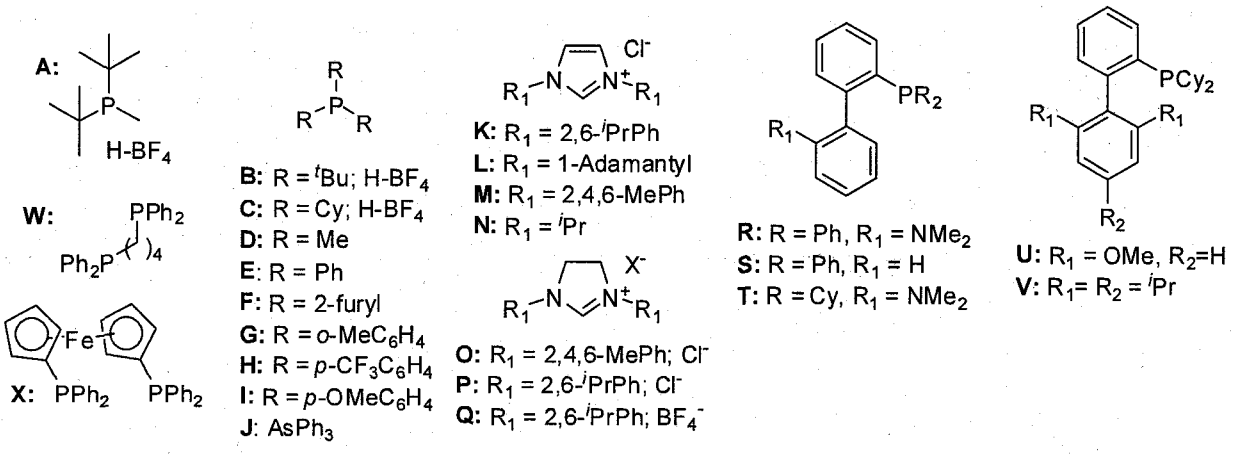


Base	Conv.	Toluene	Yield A	Yield B
K_2CO_3	70%	4%	6%	30%
Cs_2CO_3	74%	7%	9%	29%
KOPiv	72%	15%	15%	21%
CsOPiv	76%	17%	22%	16%

[112] The conversions as well as the yields were established using GCMS analysis with trimethoxybenzene as an internal standard.

With the goal of decreasing the amounts of homocoupling by-product we decided to re-evaluate our choice of ligand and employ a larger excess of benzene. Different ligands were evaluated as shown in Figure 3.2 (both phosphines and *N*-heterocyclic carbenes). We increased the amount of benzene to 50 equivalents with a ligand to metal ratio of 2:1.

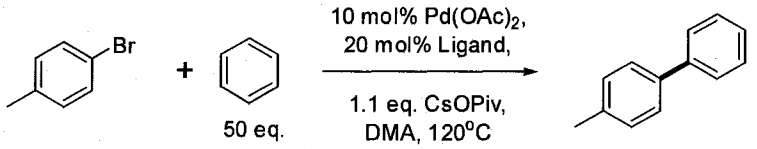
Figure 3. 2. Different Ligand Evaluated for the Direct Arylation using Benzene.

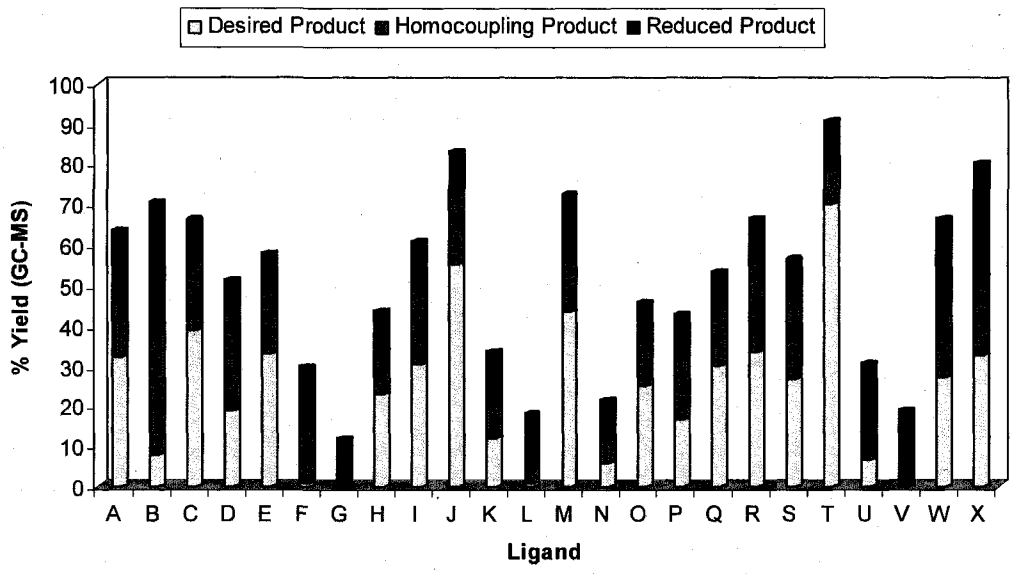


Ligands with large steric encumbrance were inappropriate (**B** and **G**) giving low conversions to the desired product. Trialkylphosphines, triarylphosphines and *N*-heterocyclic carbenes gave poor to moderate quantities of the desired product. Bidentate ligands were also unsuitable, giving large quantities of the reduced by-product. The best result was obtained using DavePhos[113] (ligand **T**), which gave the desired product in 71% yield with 8% of the homocoupled by-product. Further reaction development was therefore performed using this ligand (Table 3.3).

[113] Harris, M. C.; Geis, O.; Buchwald, S. L. *J. Org. Chem.* **1999**, *64*, 6019.

Table 3. 3. Ligand Screen for Direct Arylation using Benzene.





Subsequent tuning of the reaction conditions established that a metal to ligand ratio of 1:1 was optimal. High dilution to 0.05M as well as a large excess of benzene was deemed necessary in order to suppress the formation of the homocoupling by-product. Interestingly, reduction of the catalyst loading, led to an increased yield by suppressing the formation of the homocoupling; a similar result had been reported by Sames.[114] Treatment of 4-bromotoluene with $Pd(OAc)_2$ (3 mol%), DavePhos (3 mol%), potassium carbonate (2.5 equiv.) in a 1.2:1 mixture of *N,N*-dimethyacetamide (DMA) and benzene at 120 °C (conditions similar to those employed for perfluorobenzene arylation) gave no detectable benzene arylation (Table 3.4, entry 1). When we replaced the palladium acetate by a $Pd(OPiv)_2$,[115] a 10% yield by GCMS was observed (entry 2). Use of KOPiv[116] or KOAc as the stoichiometric bases in conjunction with $Pd(OAc)_2$ revealed the superior reactivity of pivalate which provided benzene arylation in 41% yield (entry 3

[114] Lanes, B.S.; Brown, M.A.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 8050.
[115] Bancroft, D.P.; Cotton, F.A.; Falvello, L.R.; Schwotzer, W. *Polyhedron* **1988**, *7*, 615.
[116] Larock has employed CsOPiv as a stoichiometric base for migratory processes, see: Huang, Q.; Fazio, A.; Dai, G.; Campo, M. A.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 7460. Here, the use of Cs salts results in inferior outcomes as we have observed elsewhere (ref. 7)

vs. 4) with high levels of hydrodebromination and homocoupling of the aryl bromide.[117] The beneficial effect of a soluble carboxylate base is again exemplified in Table 3.4 (entries 5 to 9) with pivalic acid being the most favourable additive.

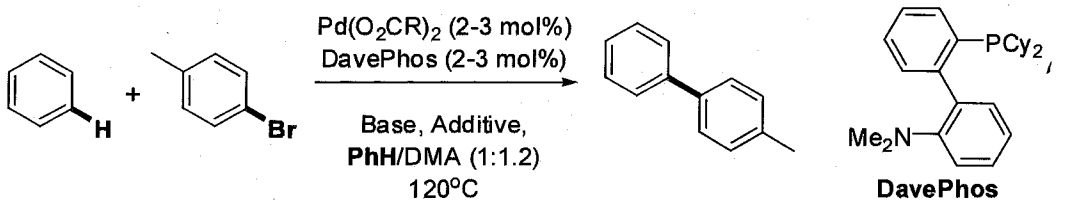
Reasoning that the excess carboxylate base was interfering with the catalytic activity, we sought to use soluble acid co-catalysts in conjunction with a stoichiometric and insoluble[118] potassium carbonate base. We tested several carboxylic acids possessing different structural and electronic properties. It became evident from these studies that both the strength as well as the steric component of the base is critical for the reactivity. Our best results are shown in Table 3.4.

For example, use of 30 mol% acetic acid provides no benefit compared to the use of stoichiometric amount of potassium acetate (Entries 5 *vs.* 3). Increasing the steric bulk through the use of propionic acid and 2-methylpropionic acid did not positively influence the outcome (Entries 6 and 7). Gratifyingly, however, the addition of 30 mol% pivalic acid resulted in 100% conversion and 81% isolated yield (entry 8). Increasing the steric bulk further, as with 1-adamantylcarboxylic acid, gave inferior results (entry 9).

[117] These by-products account for the remainder of the converted mass balance in approximately equal measure. The % conversion is based on the amount of aryl bromide consumed during the reaction.

[118] The solubility of K_2CO_3 was evaluated by heating it in DMA at 120°C for 30 minutes followed by rapid filtration of the hot solution. Less than 1% of the K_2CO_3 had dissolved.

Table 3. 4. Selected Examples from our Optimization.[a]

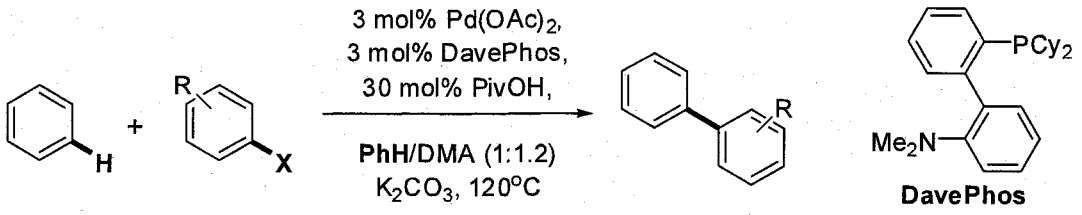


Entry	Pd Source	Base	Additive	Conversion[b]	Yield[b]
1	$Pd(OAc)_2$	K_2CO_3	none	<5	0
2	$Pd(OPiv)_2$	K_2CO_3	none	13	10
3	$Pd(OAc)_2$	AcOK	none	21	8
4	$Pd(OAc)_2$	PivOK	none	65	41
5	$Pd(OAc)_2$	K_2CO_3	AcOH (30 mol%)	20	11
6	$Pd(OAc)_2$	K_2CO_3	$EtCO_2H$ (30 mol%)	14	6
7	$Pd(OAc)_2$	K_2CO_3	$^{i}PrCO_2H$ (30 mol%)	32	13
8	$Pd(OAc)_2$	K_2CO_3	$^{t}BuCO_2H$ (30 mol%)	100	82
9	$Pd(OAc)_2$	K_2CO_3	1-$AdCO_2H$ (30 mol%)	60	36

[a] Conditions: $Pd(OAc)_2$ or $Pd(OPiv)_2$ (2-3 mol%), DavePhos (2-3 mol%), K_2CO_3 (2.5 equiv.), the additive and the aryl halide were heated to 120 °C in benzene/DMA (1.2:1) for 10 to 15 hours (overnight). [b] Determined by GCMS.

These reaction conditions were found to react with a wide array of substituted aryl bromides. The aryl chlorides and iodides appear to be incompatible under the present reaction conditions and can be recovered unreacted after the typical reaction time for aryl bromides (Table 3.5, entry 1 to 3). Substitutions in *para*, *meta* and the sterically encumbered *ortho* are all compatible with these reactions conditions (entry 1, 4, 5). Sterically hindered aryl bromides were found to be excellent substrates giving the product in higher yield due to the suppression of homocoupling as demonstrated by the increased yield of entry 6 vs. 7. Electron rich aryl bromides (entry 8) as well as electron deficient (entry 9) were both found to be viable substrate. Reaction with 1-bromo-3-chlorobenzene gave the coupling product, while leaving the chlorine atom untouched, in 63% isolated yield (entry 10).

Table 3. 5. Scope for Direct Arylation of Aryl Bromide using Benzene.



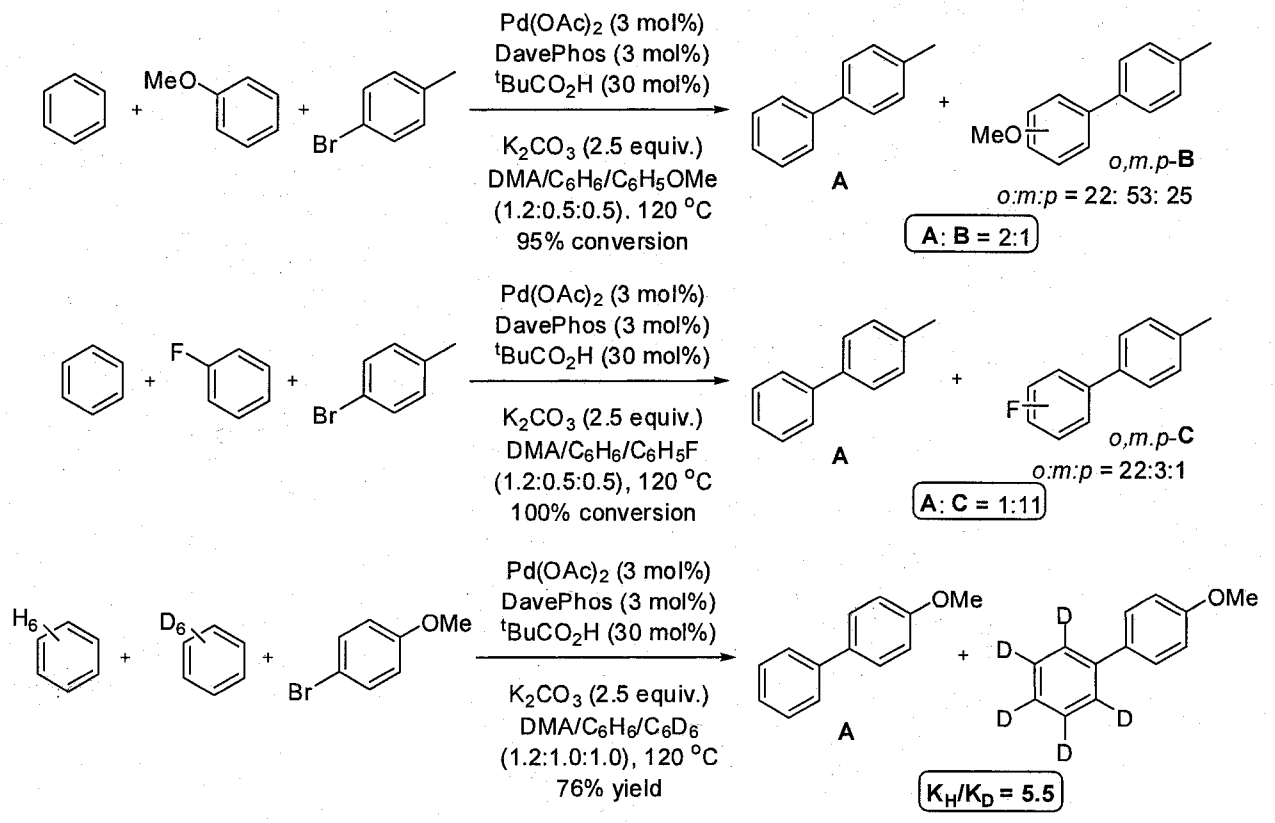
Entry	Aryl Halide	Product	Yield
1	X = Br	Ph	81%
2	= Cl		< 5%[a]
3	= I		< 10%[a]
4	Br	Ph	84%
5	Br	Ph	85%
6	Br	Ph	80%
7	Br	Ph	55%
8	MeO, Br	MeO, Ph	69%
9	O_2N, Br	O_2N, Ph	81%
10	Br, Cl	Ph, Cl	63%

[a] Determined by GCMS.

Substituted arenes were also found to be compatible, but resulted in regioisomeric mixtures. For example, anisole gave a 22:53:25 mixture of *ortho*:*meta*:*para* regioisomers in 62% yield, while fluorobenzene gave a 22:3:1 *o*:*m*:*p* ratio in 91% yield. Competition studies were then performed to elucidate the mechanism. Benzene was found to react preferentially over more electron-rich anisole in a ratio of 2:1 (Scheme 3.4; equation 1) while fluorobenzene reacted preferentially over benzene in a ratio of 11:1 (Scheme 3.4; equation 2). The regioisomeric distribution in

the reaction with anisole suggests no directing effect from the methoxy substituent, as the *ortho* position was disfavoured. Furthermore, arene chemoselectivity as well as the site selectivity are not consistent with an electrophilic aromatic substitution mechanism. The reaction using fluorobenzene as the simple arene clearly demonstrates the importance of the C-H bond acidity for both the regioselectivity and reactivity.

Scheme 3. 4. Competition Studies and Kinetic Isotope Effect.



We also noted the presence of a large intermolecular kinetic isotope effect of 5.5 (Table 3.4, equation 3). These results are incompatible with the reactivity profiles of electrophilic aromatic substitution[104] and radical processes,[102,119] but correlate very well with a proton-transfer pathway.[107] The influence of the pivalate anion on the C-H bond-cleaving transition state has been probed by DFT analysis.[120] Use of a pivalate anion

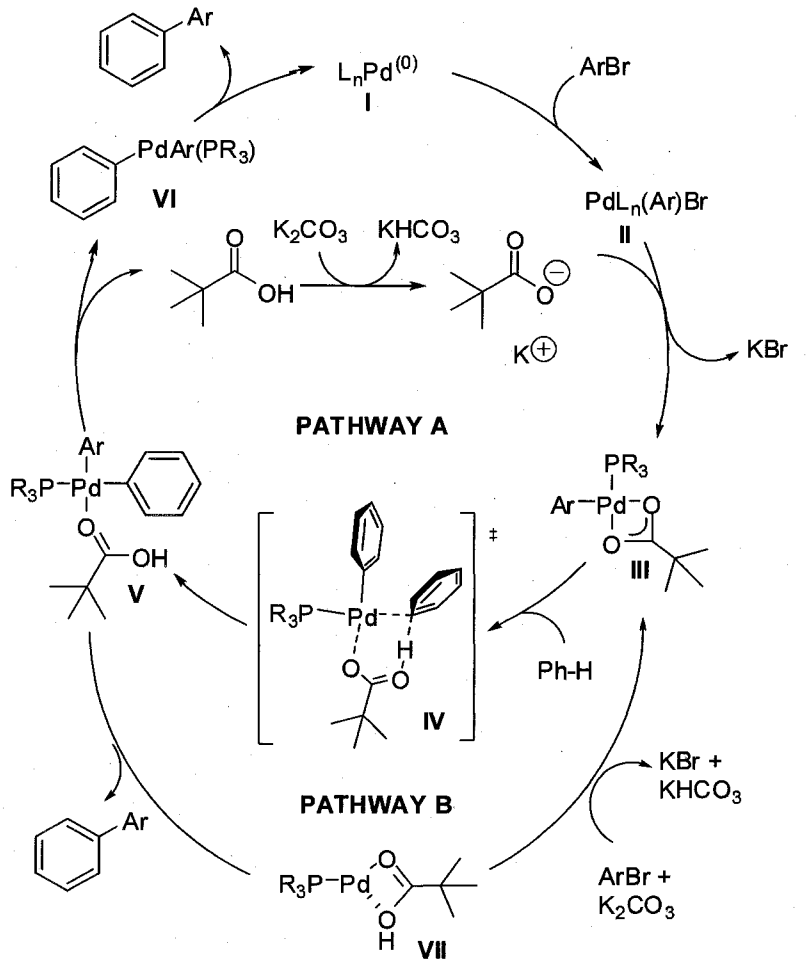
[119] Mukhopadhyay, S.; Rothenberg, G.; Gitis, D.; Baidossi, M.; Ponde, D.E.; Sasson, Y. *J. Chem. Soc., Perkin. Trans. 2* **2000**, 1809.

[120] B3LYP density functional theory calculations were performed with the Jaguar 6.0 package with the LACV3P+** basis set and pseudopotential combination of Jaguar.

results in a decrease in transition state energy of 1.3 kcal/mol compared to a bicarbonate anion (24.9 *vs.* 26.2 kcal/mol). Thus, the enhanced reactivity of this co-catalyst system may result not only from the controlled concentration of pivalate anion but also from favourable energetics.

These studies support the involvement of a catalytic cycle similar to that illustrated in Scheme 3.5. After the oxidative addition step, the palladium (II) intermediate undergoes a rapid exchange of the bromide ligand for pivalate to generate species **III**. Concerted deprotonation-palladation through the intermediate **IV** gives the palladium diaryl **V**. Subsequent loss of pivalic acid and reductive elimination regenerates the palladium (0) species and the desired cross-coupled product. The pivalic acid undergoes deprotonation to regenerate the potassium pivalate co-catalyst. Alternatively, reductive elimination of the product from the palladium diaryl **V** followed by oxidative addition and concomitant deprotonation of the pivalic acid would regenerate the complex **III**.

Scheme 3. 5. Proposed Catalytic Cycle.

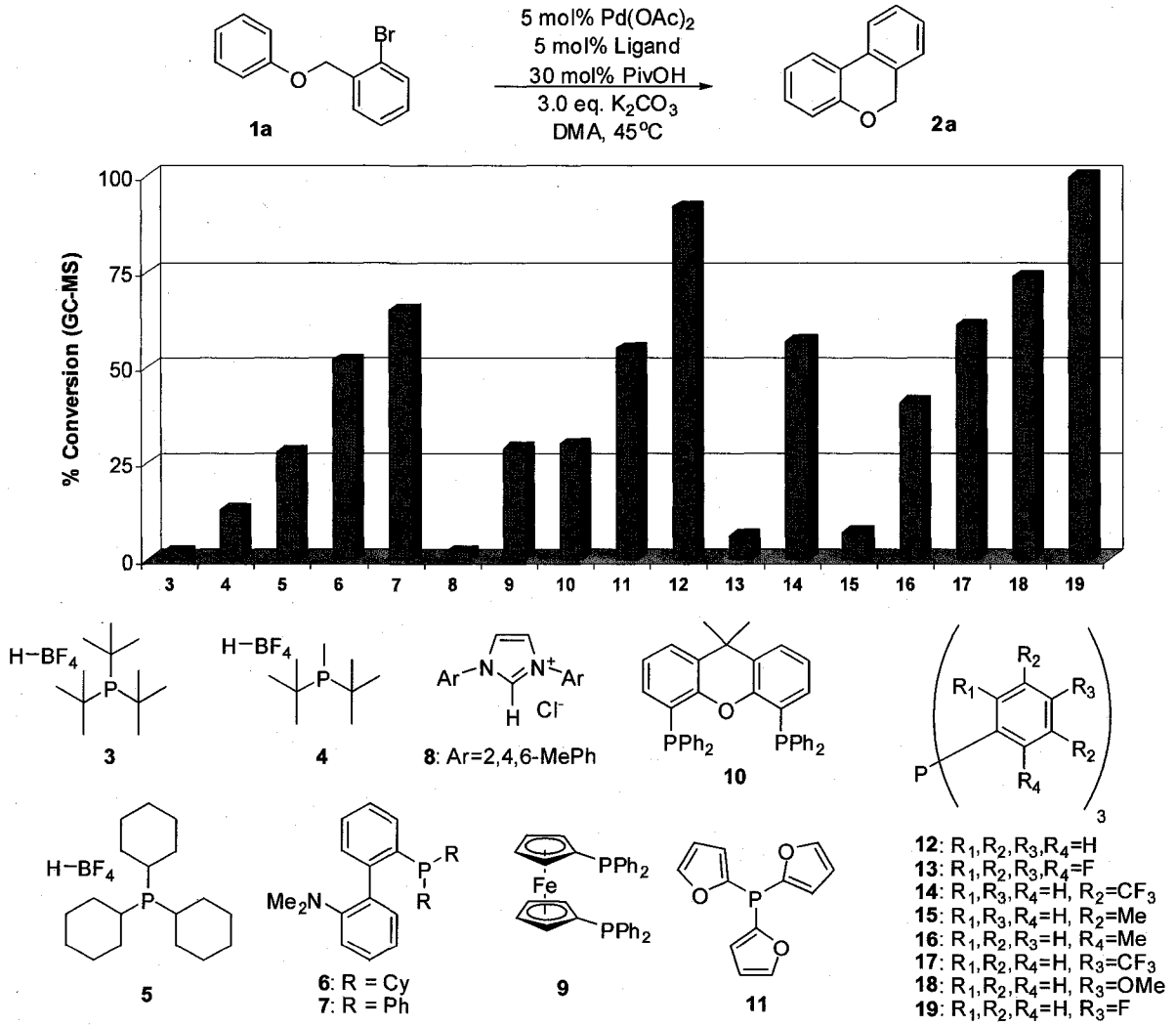


3.4 – Application to the Intramolecular Direct Arylation of Simple Arenes.

As described, the combined use of a catalytic amount of pivalic acid (30 mol%) in conjunction with an excess of K_2CO_3 was found to provide superior outcomes when compared to the use of K_2CO_3 alone. These observations prompted us to re-evaluate intramolecular direct arylation processes[109] to determine if any of these benefits could be transferred. Reaction development focused on the appropriate choice of ligand in the reaction of **1a** to give the biaryl **2a**. A variety of ligands were screened using 5 mol% $Pd(OAc)_2$, 30 mol% pivalic acid, 3 equivalents of potassium carbonate in DMA at 45 °C (Table 3.6). From these experiments, two ligands were found to give the highest conversion, triphenylphosphine **12** and tri(4-fluorophenyl)phosphine **19**. Since **19** gave

slightly superior yield, it was chosen for further optimization. The observation that electron-deficient phosphines can provide the optimal outcomes in direct arylation has previously been noted by Beaudoin[121] and by us.[122] It is plausible that the use of such ligands may facilitate arene binding by creating a more electron-deficient palladium metal atom or by providing for a vacant site for arene binding by undergoing more facile displacement from the metal center.

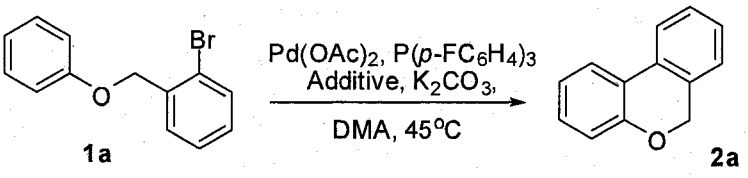
Table 3. 6. Ligand Evaluation in Intramolecular Direct Arylation.

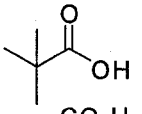
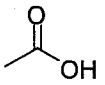
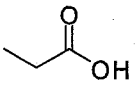
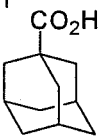
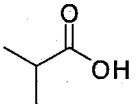
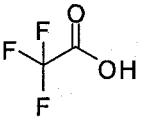


[121] Hitce, J.; Retailleau, P.; Baudoin, O. *Chem. Eur. J.* **2007**, *13*, 792.
[122] Campeau, L.-C.; Parisien, M.; Leblanc, M.; Fagnou, K. *J. Am. Chem. Soc.* **2004**, *126*, 9186.

Employing $Pd(OAc)_2$ with ligand **19,** a variety of carboxylic acid additives were evaluated in conjunction with K_2CO_3 as the stoichiometric insoluble base (Table 3.7). There is a marked increase in conversion as the steric encumbrance of the acid increases from acetic acid to pivalic acid (entries 2 to 5). In contrast the use of adamantylcarboxylic acid results in an inferior conversion (entry 6). The use of more acidic additives, such as with trifluoroacetic acid does not influence the reaction outcome compared to a control when no additive is employed (entry 7 *vs.* entry 1).

Table 3. 7. Effect of Carboxylic Acid Additives on Direct Arylation



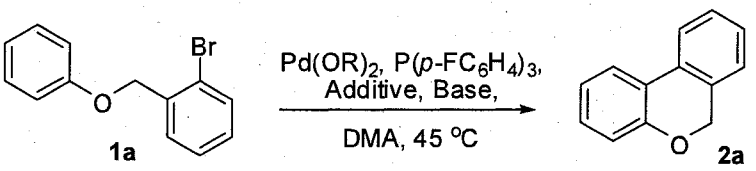
Entry	Additive	Conv. (%)[a]	Entry	Additive	Conv. (%)[a]
1	none	31	5		100
2		32			
3		36	6		56
4		63	7		28

[a] Determined by GC-MS.

The selection of stoichiometric base also has a profound effect on the transformation. For example, use of sodium carbonate provides slightly lower conversions than the potassium salt while use of cesium carbonate results in very low conversions after the same reaction time (Table 3.8, entries 1 to 3). The use of a catalytic quantity of pivalic acid (which generates potassium pivalate *in situ* when treated with potassium carbonate) is also superior to simply employing potassium pivalate as the terminal stoichiometric base as illustrated by entries 4 and 5. The enhanced reactivity associated with the presence of 30 mol% potassium pivalate in the reaction mixture can be partially gained through the use of a palladium pivalate catalyst precursor. With

$Pd(OPiv)_2$ and potassium carbonate as the base, a 71% conversion is observed after 12 hours compared to the use of $Pd(OAc)_2$ which provides only 32% (entry 7 *vs.* entry 2).

Table 3. 8. Influence of Stoichiometric Base on Direct Arylation

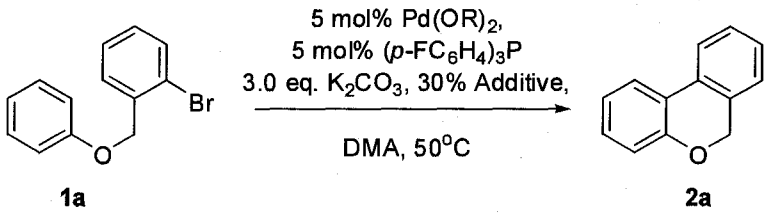


Entry	Pd Source	Additive	Base	Conv. (%)[a]
1	$Pd(OAc)_2$	None	Na_2CO_3	22
2	$Pd(OAc)_2$	None	K_2CO_3	32
3	$Pd(OAc)_2$	None	Cs_2CO_3	5
4	$Pd(OAc)_2$	None	KOPiv	22
5	$Pd(OAc)_2$	PivOH	K_2CO_3	100
6	$Pd(OPiv)_2$	None	K_2CO_3	71
7	$Pd(OPiv)_2$	PivOH	K_2CO_3	100

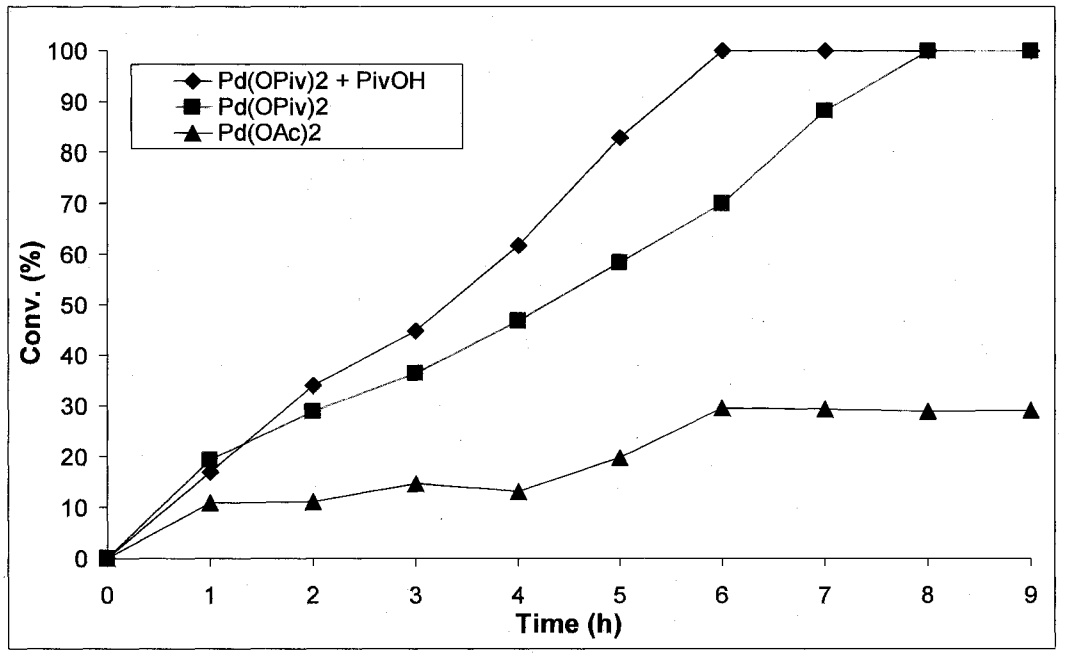
[a] Determined by GC-MS.

The acceleration in product formation over time resulting from the addition of pivalic acid is illustrated in Scheme 3.6. After 6 hours, a reaction performed under the standard conditions in the absence of pivalic acid provides approximately 30% conversion while an identical reaction performed with 30 mol% pivalic acid reached 100% conversion. A similar, albeit less pronounced, acceleration is also observed using palladium pivalate as the catalyst precursor in place of palladium acetate.

Scheme 3. 6. Acceleration of Carboxylic Acid Co-Catalyst on the Direct Arylation.

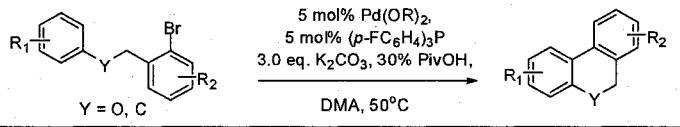


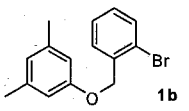
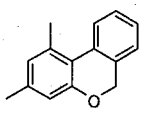
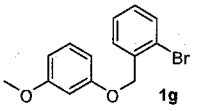
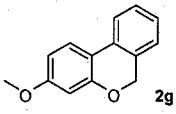
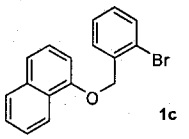
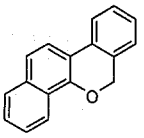
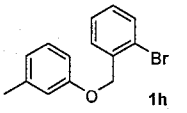
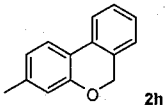
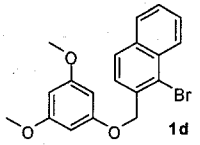
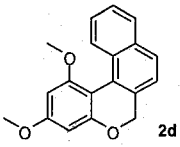
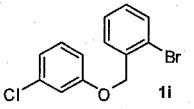
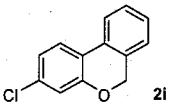
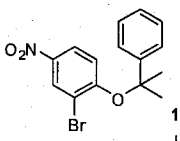
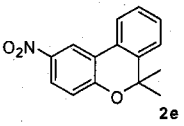
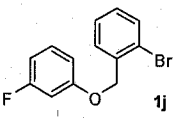
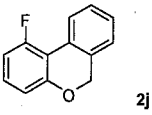
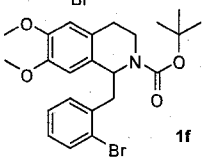
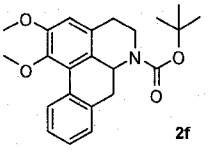
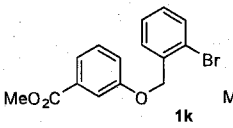
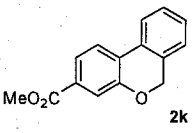
1a **2a**



Application of these optimized reaction conditions is illustrated in Table 3.9. A variety of activated and deactivated aryl bromides are compatible, including those that form sterically encumbered biaryls. Arylation of a broad range of simple arenes can be achieved under mild conditions. A range of substitution patterns are compatible including electron-donating (entries 3, 5 and 6) and withdrawing groups (entries 4, 9 and 10). Reaction at more sterically encumbered positions can also occur in high yield (entries 1, 3 and 5). More highly functionalized substrates can also be employed as illustrated by the use of a precursor for aporphine synthesis in entry 5.

Table 3. 9. Substrate Scope in Intramolecular Direct Arylation



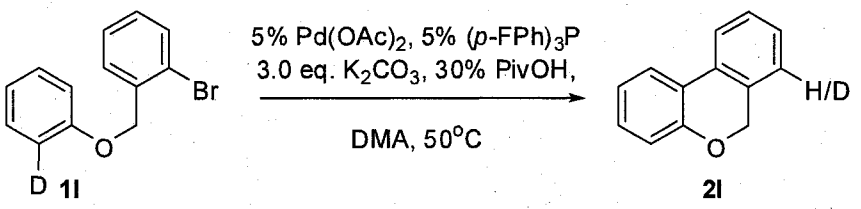
Entry	Substrate	Product	Yield[a]	Entry	Substrate	Product	Ratio[b]	Yield[a]
1	 1b	 2b	96%[c]	6	 1g	 2g	>30:1	99%
2	 1c	 2c	97%	7	 1h	 2h	>30:1	98%
3	 1d	 2d	95%	8	 1i	 2i	15:1	96%
4	 1e	 2e	94%	9	 1j	 2j	1.4:1	93%
5	 1f	 2f	70%[d]	10	 1k	 2k	>30:1	92%

[a] Isolated yield. [c] Ratio of regioisomers formed at the unequivalent ortho positions. [d] Reaction performed at 60°C. [e] Reaction performed at 70°C.

The presence of primary kinetic isotope effects is strong evidence for a mechanism where the C-H bond cleavage is a kinetically significant step in the catalytic cycle – a feature which is inconsistent with electrophilic aromatic substitution pathways. Under the current reactions conditions, reaction of **1l** reveals the presence of a pronounced primary intramolecular hydrogen/deuterium kinetic isotope effect of 5.4 (see Scheme 3.7). This magnitude of KIE is in line with our previously observed KIE of 3.5[122] for similar reactions performed in the absence of pivalic acid and of 3.0[105] and 5.5[111] for intermolecular direct arylation reactions with perfluorobenzenes and benzene respectively. It is also consistent with KIEs reported by Echavarren and Maseras with similar substrates for intramolecular reactions.[107] Pronounced KIEs are compatible with,

and characteristic of, mechanisms where C-H bond cleavage is occurring simultaneously with carbon-palladium bond formation.[123]

Scheme 3. 7. Kinetic Isotope Effect Experiment.



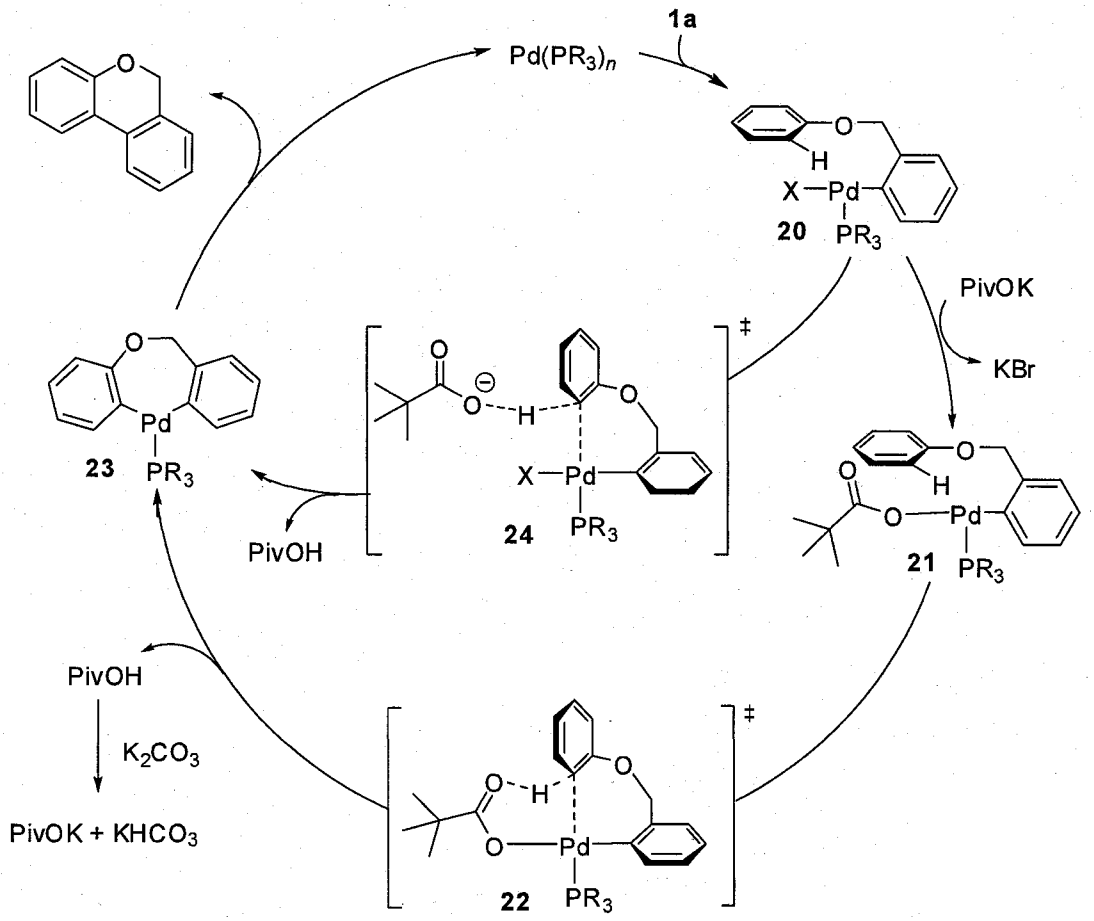
1l **2l**

99% yield
K_H/K_D = 5.4

In line with Echavarren's and Maseras' proposed mechanism for intramolecular direct arylation[107] and our own work in intermolecular processes,[109] we favour the involvement of a catalytic cycle similar to that illustrated in Scheme 3.8 Subsequent to oxidative insertion into the carbon-halide bond, two pathways may be followed. The first involves an anion exchange of a pivalate for the bromide ligand to give **21**. This species can then undergo a concerted deprotonation-palladation to give the biarylpalladium(II) intermediate **23** which will reductively eliminate to give the observed product and regenerate the catalyst. Alternatively, the pivalate may be acting as an external base at the C-H bond cleaving transition state via **24** to intercept intermediate **23** of the other pathway. The reason for the superior reactivity of pivalic acid as an additive in these reactions compared to other carboxylic acids may be related to both its steric bulk and the increased basicity of its conjugate base. The ability to control the amount of pivalate present is crucial to achieving maximal reactivity.

[123] Zollinger, H. *Adv. Phys. Org. Chem.* **1964**, *2*, 162.

Scheme 3. 8. Proposed Catalytic Cycle.



While evidence points to the involvement of concerted palladation-deprotonation pathways in the present reactions, insufficient data exists to state whether one, the other, or both of these pathways are responsible for the observed reactivity. Indeed, as previously pointed out,[107] the intimate reaction mechanism may change from reaction to reaction as the substrate, solvent, base and additives are changed. If accurate, such a flat thermodynamic landscape can make a detailed understanding of the exact mechanism for any precise reaction elusive. Nonetheless, we have, and are continuing to use these transition states and reaction pathways as an enabling technology in the development of other, novel carbon-carbon bond forming processes.

These reactions, and more importantly, the reaction conditions that enable them should be of use in the synthetic community for the preparation of biaryl molecules. The particular mildness of these conditions with respect to the base and temperature should

enable an application to more complex molecules that may be prone to decomposition under more forcing reaction conditions and the commonly employed elevated reaction temperatures that are commonly associated with direct arylation protocols.

Chapter 4

Intramolecular Alkane Arylation

While new reactions have appeared over the past decade for catalytic hydrocarbon functionalization, in the context of C-C bond formation reactions occurring at sp^2 C-H bonds are far more prevalent and widespread[124] than those at sp^3 C-H bonds.[125] Transformations at sp^2 C-H bonds benefit from catalyst interactions with the aromatic π-electrons, facilitating the C-H bond cleaving event. Since this type of interaction cannot occur with unactivated sp^3 centers, they must rely on other, less clearly defined, substrate catalyst interactions. Furthermore, growing mechanistic understanding of reactions at sp^2 bonds has inspired methodological development. This lack of insight at aliphatic C-H bonds, on the other hand, makes a rational approach to this class of reaction more challenging. Three different strategies have typically been employed to allow reactivity. The first consists of reacting at a sites possessing acidic

[124] See chapters 1, 2 and 3.
[125] For a recent highlight, see: Tobisu, M.; Chatani, N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1683.

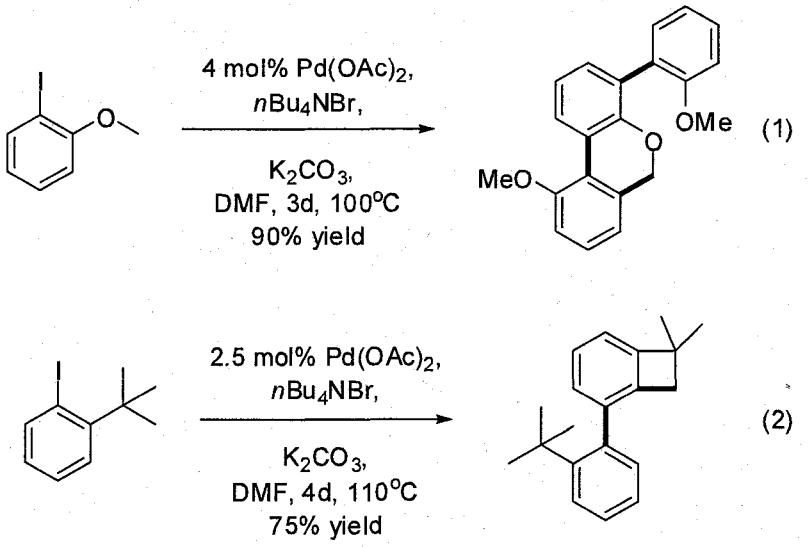
protons[126] (i.e. benzylic, an α-position to carbonyls derivatives). The second employs basic direct groups to hold the metal in close proximity to the reacting site. The last approach relies on a geometric bias in which the alkyl moiety is held adjacent to the reacting site, allowing a cyclometallation. A discussion of the latter two approaches will be given due to their pertinence with this work.

4.1.1 - Arylation of Simple Unactivated Alkyls.

Dyker reported in 1992 a catalytic direct alkylation reaction, where 2-iodoanisole derivatives were submitted to Jeffery's conditions (4 mol% palladium acetate, potassium carbonate and tetrabutylammonium bromide in DMF) to give excellent yields to different bi- and triaryls through a domino-coupling sequence (Scheme 4.1, example 1).[127] Based on the observed regioselectivity for different 2-iodoanisoles, Dyker proposed that the mechanism operates under a palladium II/IV manifold. The same author later reported an extension of this methodology for the rapid formation of 1,2-dihydrocyclobutabenzene derivatives using 2-iodo-^{t}butylbenzene as a precursor (Scheme 4.1, example 2).[128] In this case, the coupling was limited to a dimerization-arylation sequence.

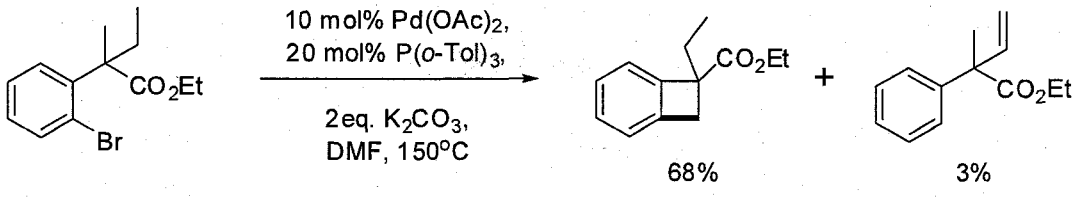
[126] For a recent review, see: Culkin, D.A.; Hartwig, J.F. *Acc. Chem. Res.* **2003**, *36*, 234.
[127] Dyker, G. *Angew. Chem., Int. Ed.* **1992**, *31*, 1023.
[128] Dyker, G. *Angew. Chem., Int. Ed.* **1994**, *33*, 103.

Scheme 4. 1. Domino Coupling Reaction.



In 2003, Baudoin and coworkers reported a palladium-catalyzed olefination of ethyl 2-(2-bromophenyl)-2-ethylbutanoate derivatives through a direct aliphatic C-H functionalization pathway.[129] When one of the ethyl groups was replaced by a methyl, formation of benzocyclobutenes was then observed as the major product through a proposed direct alkylation mechanism (Scheme 4.2).

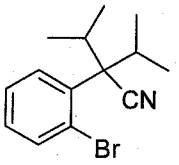
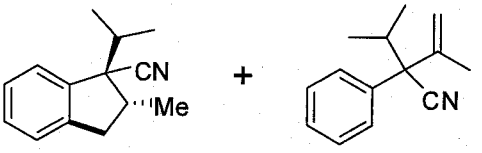
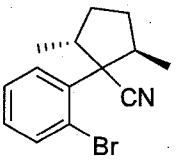
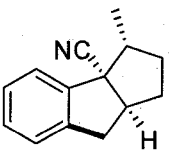
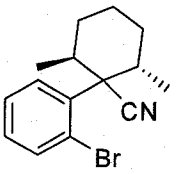
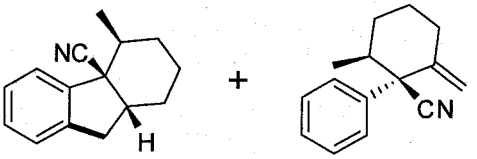
Scheme 4. 2. Synthesis of Benzocyclobutenes.



Through a fine tuning of the electronic properties of their ligand, from tri-*o*-tolylphosphine to a more labile tri-(5-fluoro-2-methylphenyl)-phosphine, the authors were able to generate different bi- and tricyclic molecules in good yields (Table 4.1).[130] The substrate required the presence of a tertiary center containing one electron-deficient group for reactivity. They proposed the mechanism to operate through a palladium 0/II catalytic cycle involving a cyclopalladation step.

[129] Baudoin, O.; Herrbach, A.; Guéritte, F. *Angew. Chem., Int. Ed.* **2003**, *42*, 5736.
[130] Hitce, J.; Retailleau, P.; Baudoin, O. *Chem. Eur. J.* **2007**, *13*, 792.

Table 4. 1. Synthesis of Bi- and Tricyclic Structures.[a]

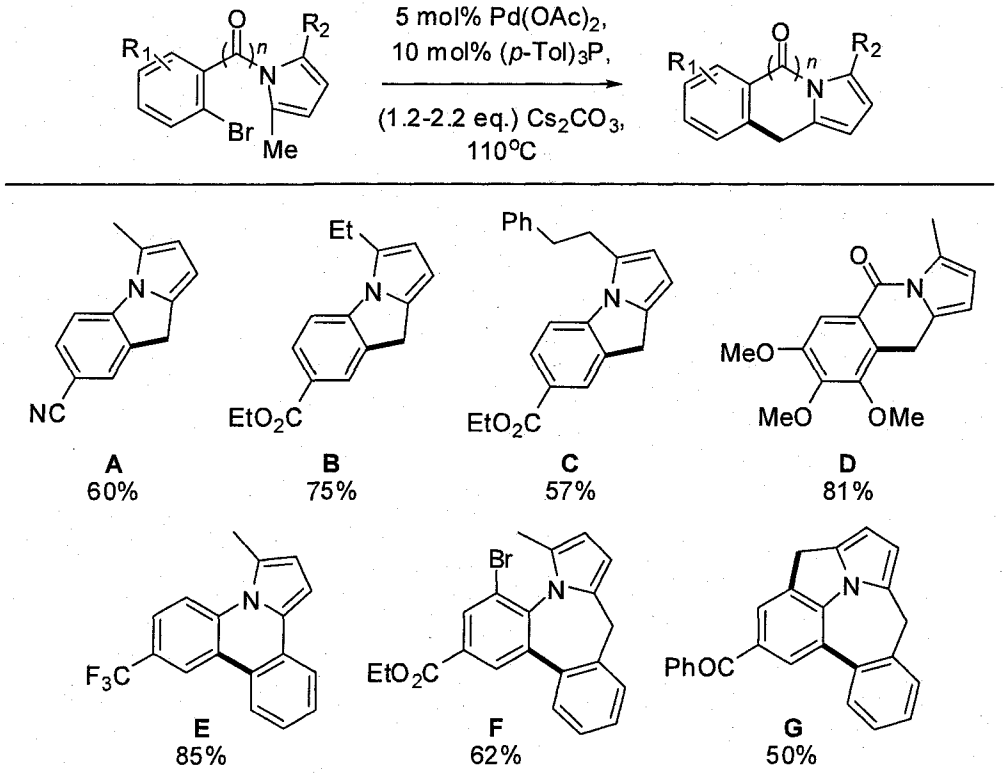
Entry	Substrate	Product(s)	Yield (ratio)
1			62% (4:1)
2			62%
3			70% (7:3)

[a] 5 mol% $Pd(OAc)_2$, 20 mol% tri-(5-fluoro-2-methylphenyl)-phosphane, 2eq. K_2CO_3, DMF, 100°C.

A synthesis of a variety of condensed *N*-heterocycles through a alkane arylation reaction of bromoarenes was reported by Knochel.[131] Several *N*-(2-bromo-phenyl)-2,5-dimethylpyrrole derivatives were cyclized onto a methyl group center using 5 mol% palladium acetate, 10 mol% tris-*p*-tolylphosphine with cesium carbonate at 110°C in good to excellent yields (Table 4.2) . Broad functional group tolerance was observed as both electron rich and deficient arenes were employed. The more facile arylation of sp^2 center over sp^3 center is exemplified by the cyclization of substrates E and F where preferential cyclization of a six- and seven-membered ring onto the aromatic C-H bond over the formation of a five-membered ring onto the methyl C-H bond was observed.

[131] (*a*) Ren, H.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 3462. (*b*) Ren, H.; Li, Z.; Knochel, P. *Chem. Asian J.* **2007**, *2*, 416.

Table 4. 2. Synthesis of Condensed *N*-Heterocycles.

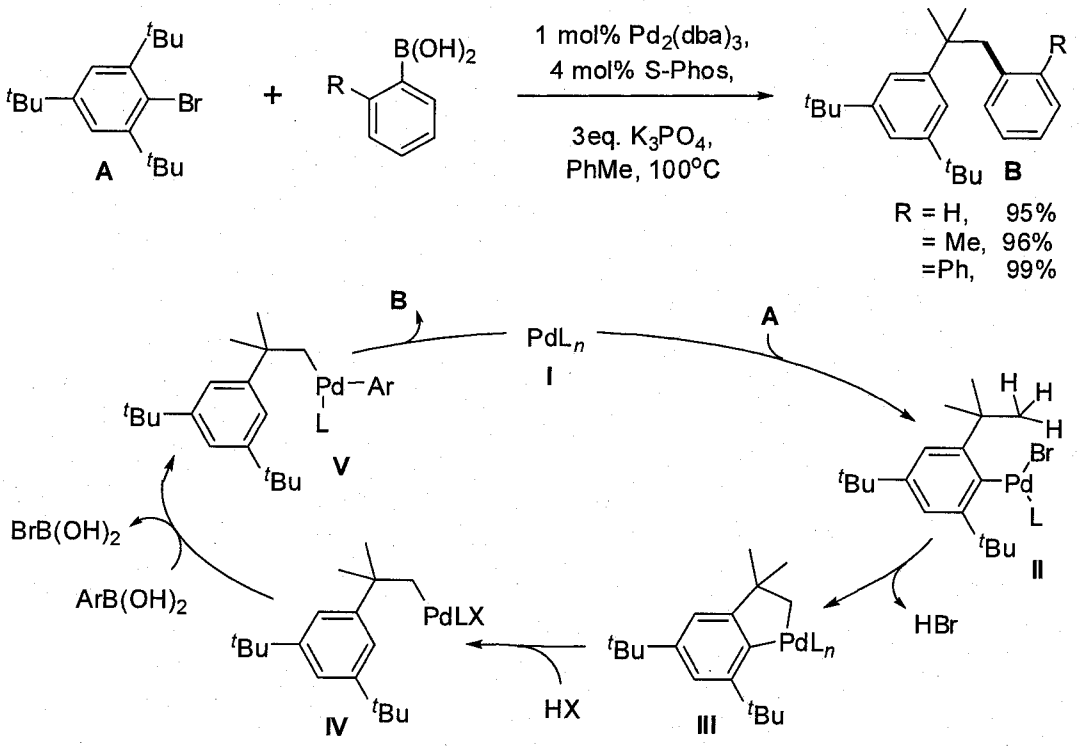


4.1.2 – Tandem C-H Functionalization–Cross-Coupling Reaction.

During the course of a study of the Suzuki-Miyaura reaction, Buchwald and coworkers noticed an unusual arylation at a sp^3 center from the cross-coupling reaction of 2,4,6-tri-tertbutylbromobenzene with different arylboronic acids (Scheme 4.3).[132] They rationalized the process using the catalytic cycle shown in Scheme 4.4. Oxidative addition of a palladium (0) species **I** to the bromoarene followed by a palladium migration to one of the neighboring *tert*-butyl group would generate the alkyl palladium intermediate **IV**. This species undergoes a standard transmetallation-reductive elimination sequence to generate the product and regenerate the palladium (0) catalyst.

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

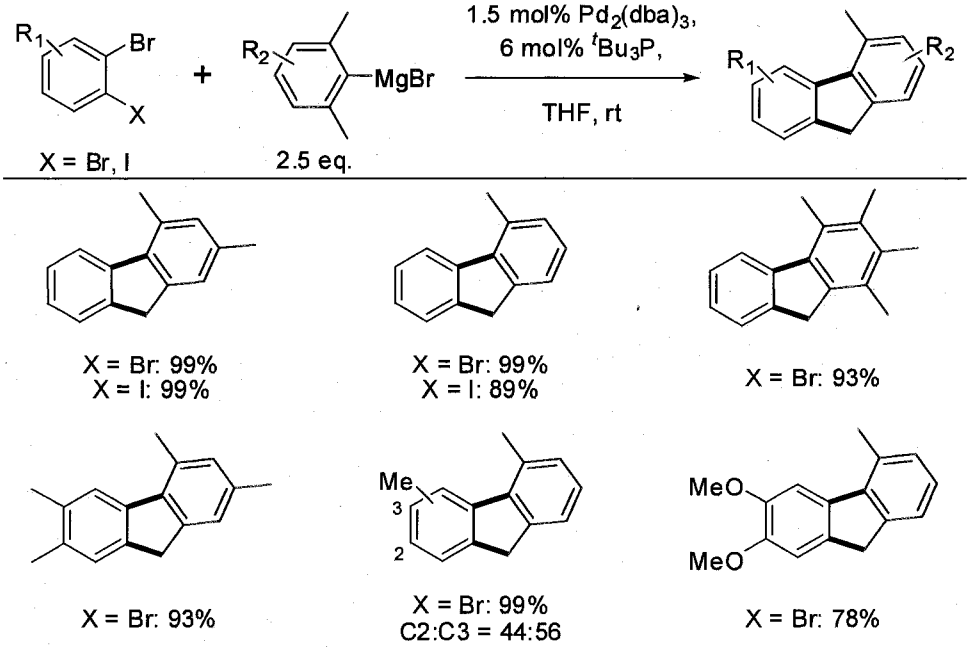
Scheme 4. 3. Tandem C-H Functionalization–Suzuki-Miyaura Process.



Through a tandem annulative Kumada cross-coupling/direct alkylation reaction between different 1,2-dihaloarenes and hindered Grignard reagents, Hu and coworker synthesized different substituted fluorenes.[133] The reaction was found to be compatible with diverse 1,2-dibromoarenes as well as 1-bromo-2-iodobenzene. However, substitution of one of the halogens for a chlorine atom led to the exclusive formation of 2-chlorobiaryls (Table 4.3). Due in part to the harsh reaction conditions from the required excess of Grignard reagents, functional groups are limited to non electrophilic and base stable groups. Preliminary studies using an excess of the 1,2-dihaloarene suggested that reaction sequence consists of the Kumada-Corriu cross-coupling reaction followed by the annulation through a direct alkylation reaction.

[133] Dong, C.-G.; Hu, Q.-S. *Angew. Chem., Int. Ed.* **2006**, *45*, 2289.

Table 4. 3. Annulative Tandem Reactions for the Synthesis of Fluorenes.

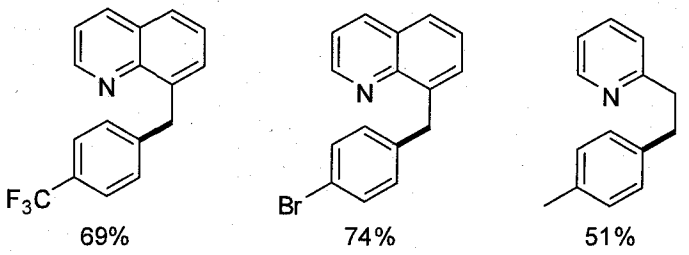


4.1.3 – Directing Groups as a Synthetic Tool in Alkane Arylation Reactions.

While investigating the scope of their direct arylation reaction using pyridine as a directing group, Daugulis observed the arylation of 2-ethylpyridine as well as 8-methylquinoline at the sp^3 position using 5 mol% of palladium acetate, 1-3 equivalents of silver acetate in acetic acid or *tert*-butanol at 130°C.[134] The reported scope was limited to the 3 examples shown in Figure 4.1.

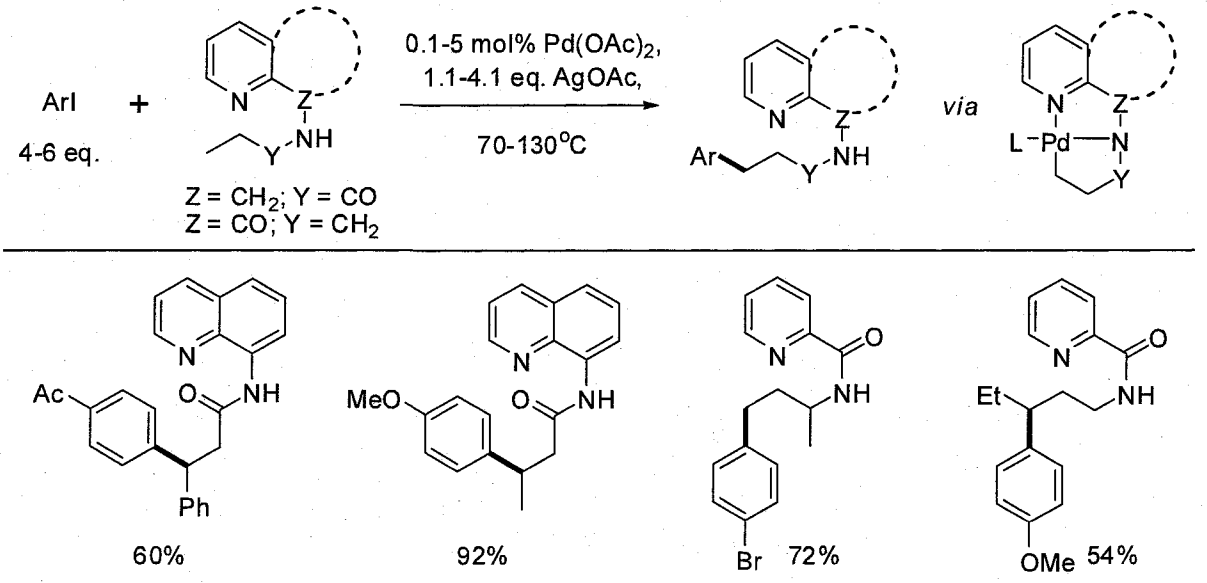
[134] Shabashov, D.; Daugulis, O. *Org. Lett.* **2005**, *7*, 3657.

Figure 4. 1. Pyridine as a Directing Group.



Daugulis investigated the use of 8-aminoquinoline amides as well as picolinamides as detachable directing groups for the arylation of sp^3 C-H bond.[135] Using conditions similar to their previous work,[134] arylation at the *beta-* position of the 8-aminoquinoline amides was achieved in good to excellent yields. Similarly, picolinamides could be arylated at the *gamma-* position. Interestingly, secondary carbons reacted at a faster rate than primary carbons when 8-aminoquinoline amide was employed while the opposite was true for the picolinamide auxiliaries. Representative examples as well as the speculated intermediate are shown in Table 4.4.

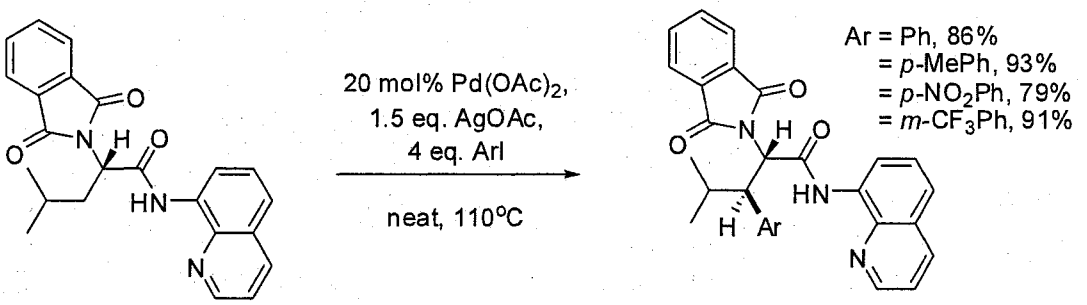
Table 4. 4. Picolinamides and 8-Aminoquinoline Amides as Directing Auxiliaries.



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

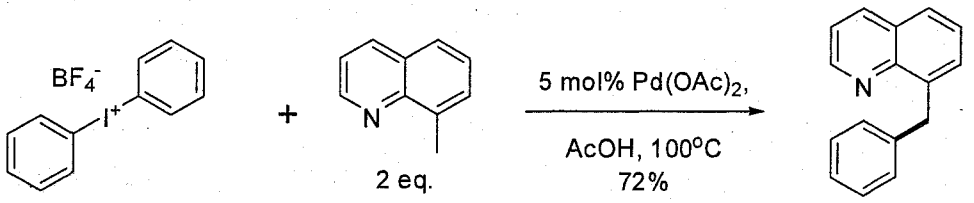
Inspired from this work, Corey took advantage of this reaction for the derivatization of amino acids at their *beta-* position.[136] As predicted, the authors were able to arylate different *N*-protected valine derivatives in good to excellent yield from different aryl iodides (Scheme 4.4).

Scheme 4. 4. β-Arylation of Valine Derivatives.



A similar system was developed by Sanford and coworkers in which 8-methylquinoline was arylated using a diphenyliodonium salt through a proposed palladium II/IV manifold.[137] Using 2 equivalents of the starting material, 1 equivalent of $[Ph_2I]BF_4$ and 5 mol% of palladium acetate in acetic acid at 100°C gave the monoarylated product in 72% isolated yield (Scheme 4.5).

Scheme 4. 5. Direct Alkylation of Diaryliodonium Salts.

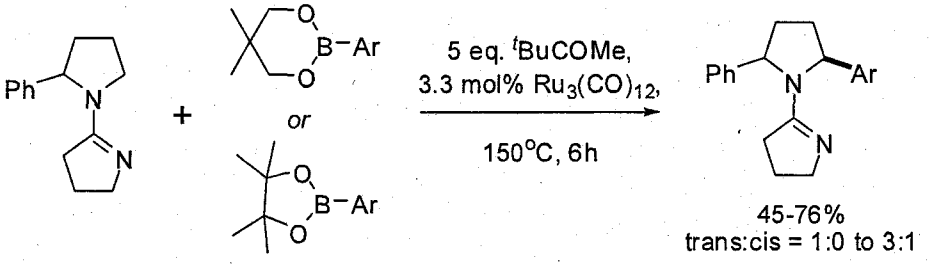


Inspired from the work of Kakiuchi and Chatani on the ruthenium catalyzed *ortho*-arylation of ketones,[138] Sames and coworkers reported an amidine directed aliphatic arylation.[139] Under their optimal conditions, 3.3 mol% $Ru_3(CO)_{12}$ and 5 equivalents of pinacolone at 150°C, the authors were able to isolate the α-arylated product of pyrrolidines and piperidines with different arylboronate esters in yields ranging from 38-

[136] Reddy, B.V.S.; Reddy, L.R.; Corey, E.J. *Org. Lett.* **2006**, *8*, 3391.
[137] Kalyani, D.; Deprez, N.R.; Desai, L.V.; Sanford, M.S. *J. Am. Chem. Soc.* **2005**, *127*, 7330.
[138] Kakiuchi, F.; Ohtaki, H.; Sonoda, M.; Chatani, N.; Murai, S. *Chem. Lett.* **2001**, 918.
[139] Pastine, S.J. ; Gribkov, D.V. Sames, D. *J. Am. Chem. Soc.* **2006**, *128*, 14220.

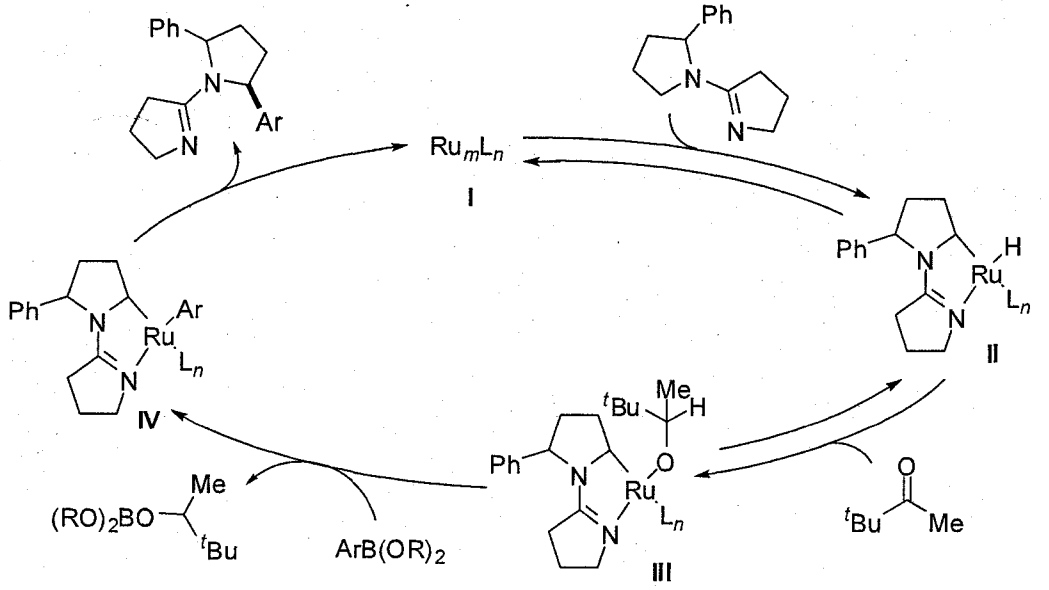
76% (Scheme 4.6). The 1-pyrroline moiety is extremely important as less basic groups such as carbonates and ketones were inactive. Furthermore, these groups can be easily cleaved with hydrazine to release the 2-arylated pyrrolidine. Pyridine and pyrimidine can also be employed but as a permanently attached directing group.

Scheme 4. 6. α-Arylation of Pyrrolidines.



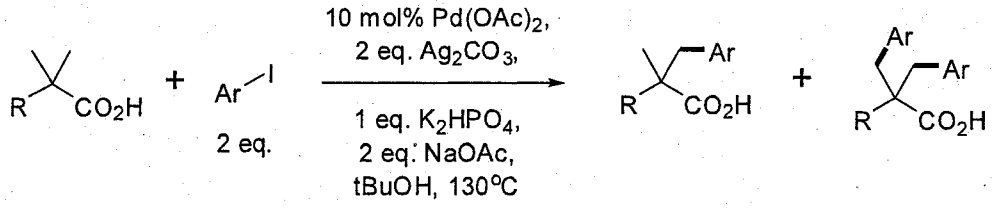
The reaction was proposed to occur *via* the catalytic cycle shown in Scheme 4.7. Reversible oxidative addition of the ruthenium complex **I** onto the C-H bond generates the ruthenium hydride complex **II**. Hydrogenation of the ketone additive forms the ruthenium alkoxyde which undergoes a transmetallation with the boronic ester to give **IV**. Reductive elimination of this complex regenerates the catalyst and liberates the product.

Scheme 4. 7. Proposed Catalytic Cycle for the α-Arylation of Pyrrolidines.



In 2007, Yu and coworkers extended their work on the direct arylation of benzoic acid derivatives to include the direct arylation of neopentyl carboxylates.[140] A variety of dimethylneopentyl carboxylic acids were mono- and diarylated (ratios ranging from 2.5:1 to 5:1 respectively) on the methyl group in yields ranging from 42-72%. The reaction conditions as well as some representative examples are illustrated in Table 4.5. Without any experimental evidence, the authors proposed the carboxylate acts as a directing group to the palladium through a palladium II/IV cycle.

Table 4. 5. β-Arylation of Aliphatic Acids using Iodoarenes.

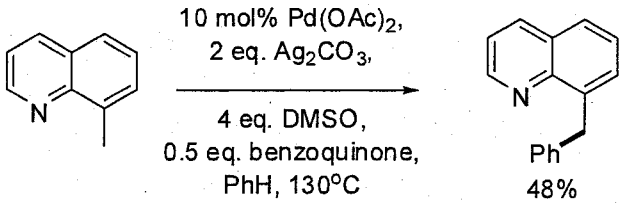


70%	43%	63%	72%
mono:di	mono:di	mono:di	mono:di
5:2	5:1	3:1	4:1

As previously discussed in Chapter 1, a more direct approach would avoid relying on pre-activation altogether, by reacting directly at the C-H bonds of both coupling partners. In 2007, Sanford reported one example of direct arylation of an aliphatic group through an oxidative cross-coupling reaction between the methyl group of 8-methylquinoline and benzene (Scheme 4.12).[141]

[140] Giri, R.; Maugel, N.; Li, J.-J.; Wang, D.-H. ; Breazzano, S.P. ; Saunders, L.B. ; Yu, J.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 3510.
[141] Hull, K.L.; Sanford, M.S. *J. Am. Chem. Soc.* **2007**, *129*, 11904.

Scheme 4. 8. Direct Arylation at the Aliphatic Position of 8-Methylquinoline.

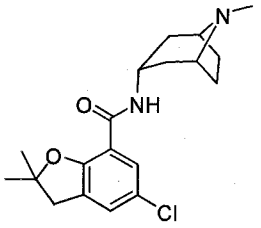


In this chapter, a discussion of the development of a palladium-catalyzed aliphatic arylation of aryl bromides and chlorides which occurs in excellent yield will be described.[142] These reactions provide a novel route to medicinally important 2,2-dialkyldihydrobenzofurans. Several examples of these biologically active molecules are shown in Figure 4.2.[143] Mechanistic studies point to the involvement of a concerted, inner sphere palladation-deprotonation pathway enabled by the presence of 3-center agostic interactions at the transition state. This mechanism accurately predicts the preference for reaction at a methyl group over other secondary sp^3 C-H bonds at the same proximity, a feature which has also been observed in other classes of alkane functionalization.[131,135]

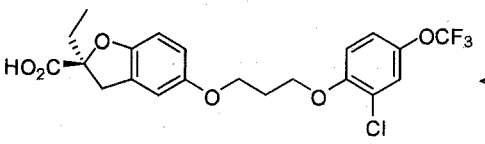
[142] Lafrance, M.; Gorelsky, S. I.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 14570.

[143] For example, see: (*a*) Gidda, J.S.; Evans, D.C.; Cohen, M.L.; Wong, D.T.; Robertson, D.W.; Parli, C.J. *J. Phamacol. Exp. Ther.***1995**, *273*, 695. (*b*) O'Brien, E.T.; Asai, D.J.; Jacobs, R.S.; Wilson, L. *Mol. Phamacol.***1989**, *35*, 635. (*c*) Villarroel, L.; Torres, R.; Urzúa, A. ; Reina, M. ; Cabrera, R. ; González-Colona, A. *J. Nat. Prod.* **2001**, *64*, 1123. (*d*) Ohkawa, S.; Fukatsu, K.; Miki, S.; Hashimoto, T.; Sakamoto, J.; Doi, T.; Nagai, Y.; Aono, T. *J. Med. Chem.* **1997**, *40*, 559. (*e*) Shi, G.Q.; Dropinski, J.F.; Zhang, Y.; Santini, C.; Sahoo, S.P. ; Berger, J.P. ; MacNaul, K.L. ; Zhou, G. ; Agrawal, A.; Alvaro, R.; Cai, T.-Q.; Hernandez, M.; Wright, S.D.; Moller, D.E.; Heck, J.V.; Meinke, P.T. *J. Med. Chem.* **2005**, *48*, 5589. (*f*) Tamura, K.; Kato, Y.; Ishikawa, A.; Kato, Y.; Himori, M.; Yoshida, M.; Takashima, Y.; Suzuki, T.; Kawabe, Y.; Cynshi, O.; Kodama, T.; Niki, E.; Shimizu, M. *J. Med. Chem.* **2003**, *46*, 3083.

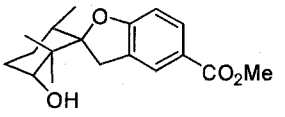
Figure 4. 2. Medicinally Active 2,2-Dialkyldihydrobenzofurans.



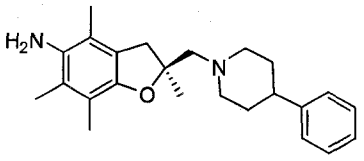
Zatosetron, *Eli Lilly*
Serotonin$_3$ (5-HT$_3$) Antagonist



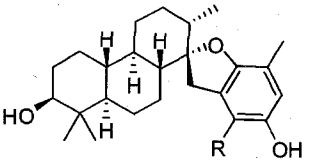
Merck Frosst
Hypolipidemic Activity



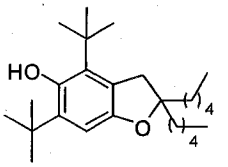
Filifolinol
Insecticidal; Antifungal



TAK-218
CNS Trauma and Ischemia



R=H, **Stypodiol**;
R=OH, **Stypotriol**
Inhibit Cell Division



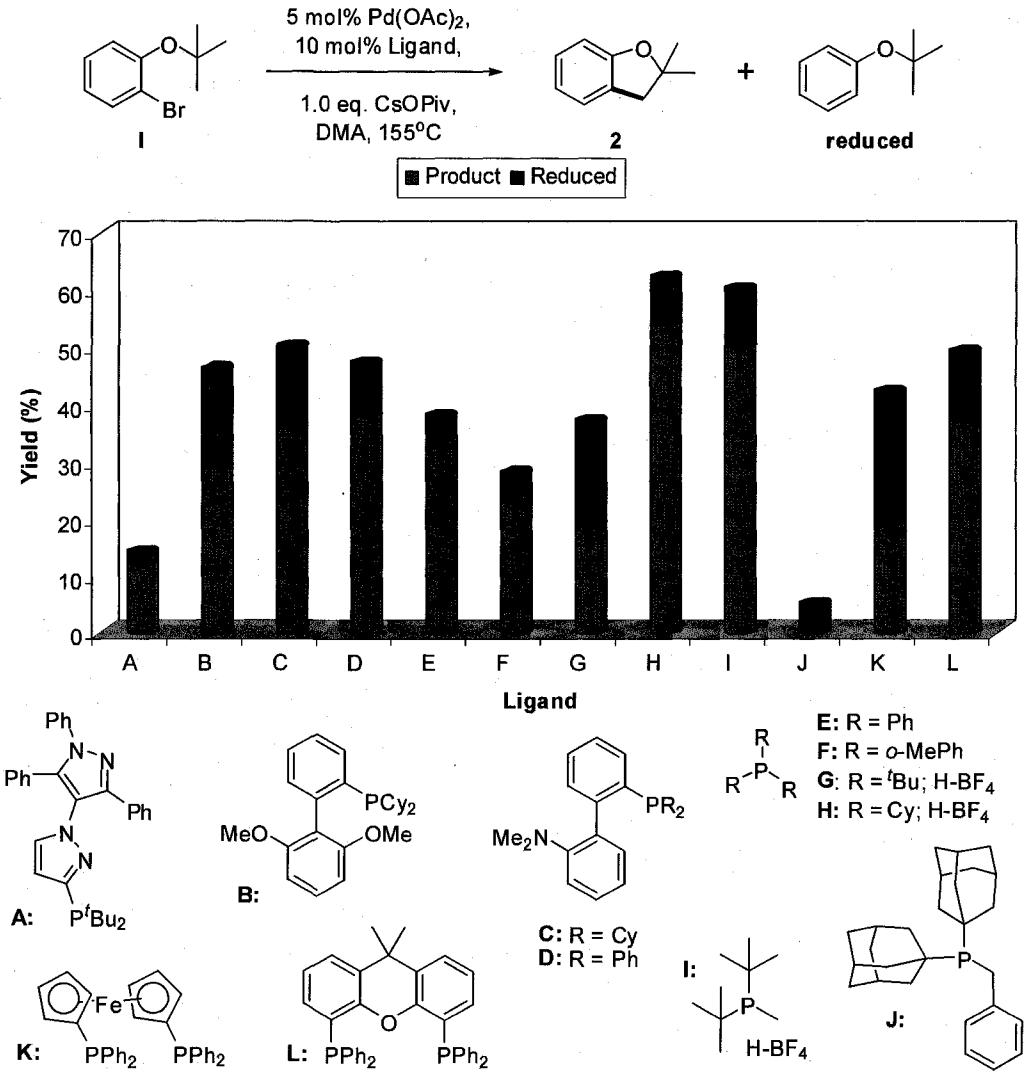
Chugai Pharmaceutical
Antiatherogenic Agent

4.2 – Intramolecular Alkane Arylation of Aryl Halides for the Synthesis of 2,2-Dialkyldihydrobenzofuran Derivatives.

Following a similar strategy to that previously employed in the development of our direct benzene arylation reactions,[144] a variety of ligands were evaluated using the highly soluble cesium pivalate base. Representative examples are shown in Table 4.6. Ligand **A** gave complete consumption of the starting material but gave many by-products resulting from the loss of the *tert*-butyl group. Buchwald type biphenyl ligands (**B-D**) gave moderate conversion to the desired product but were accompanied by a significant amount of the reduced by-product. Triarylphosphines gave better product to reduced ratios but their conversions were much lower (**E-F**). Bidentate ligands (**K-L**) gave unsatisfying amounts of reduced byproduct. Sterically hindered trialkylphosphines **G** and **J** gave poor conversion. Fortunately, slightly less hindered trialkylphosphine **I** but more importantly **H** gave the best results, giving the product in 50% (10% reduced) and 54% (7% reduced) yield. Subsequent optimization was therefore performed using tricyclohexylphosphonium tetrafluoroborate salt as the ligand.

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

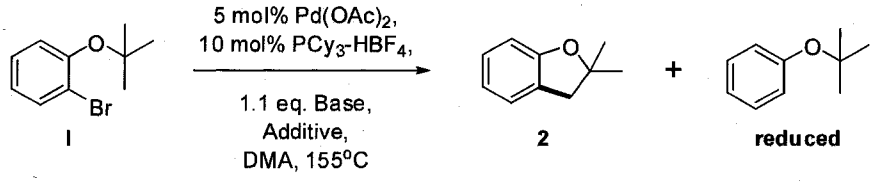
Table 4. 6. Ligand Evaluation of Direct Sp^3 Arylation.

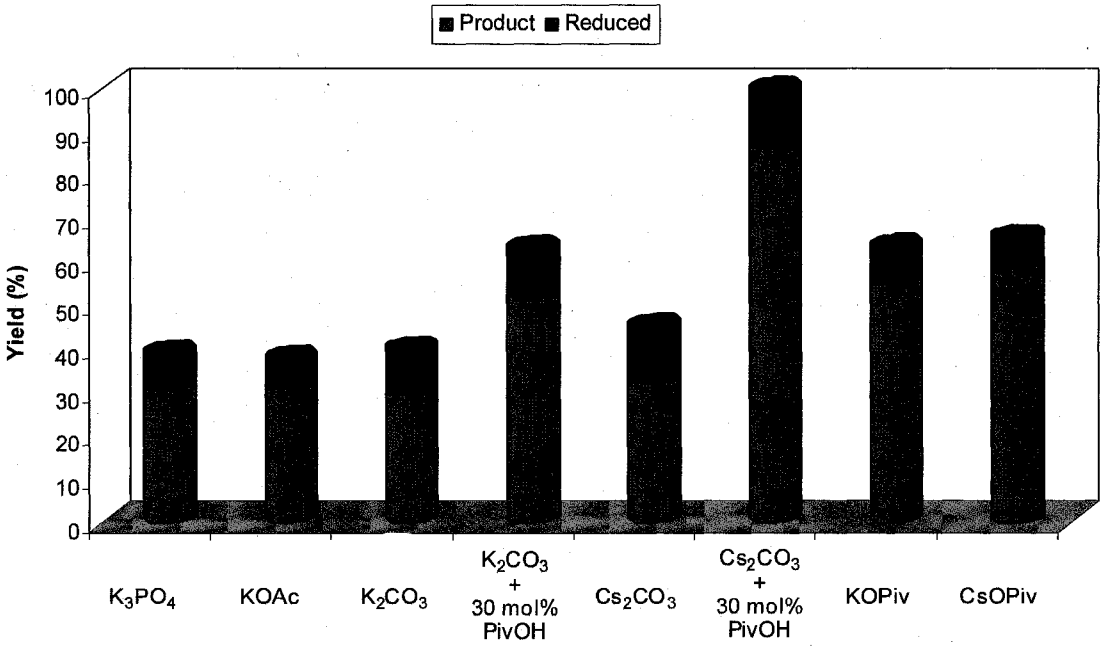


Having found the optimal ligand, we turned our attention on the role of the pivalate base. We therefore screened different bases in the presence and absence of catalytic amounts of pivalic acid (Table 4.7). From these results it became clear that a similar beneficial effect to that observed in the direct arylation of benzene was present.[144] Again, a combination of catalytic amounts of carboxylic acids in conjunction with stochiometric amounts of a less soluble inorganic base gave superior results. As illustrated in Figure 4.4, when the pivalate anion is omitted, the yield remained constant at 32% for many different inorganic bases. The yield increases drastically to 83% when

stoichiometric amounts of cesium carbonate were employed with catalytic amounts of pivalic acid. The use of potassium carbonate was less efficient giving the product in only 55% yield.

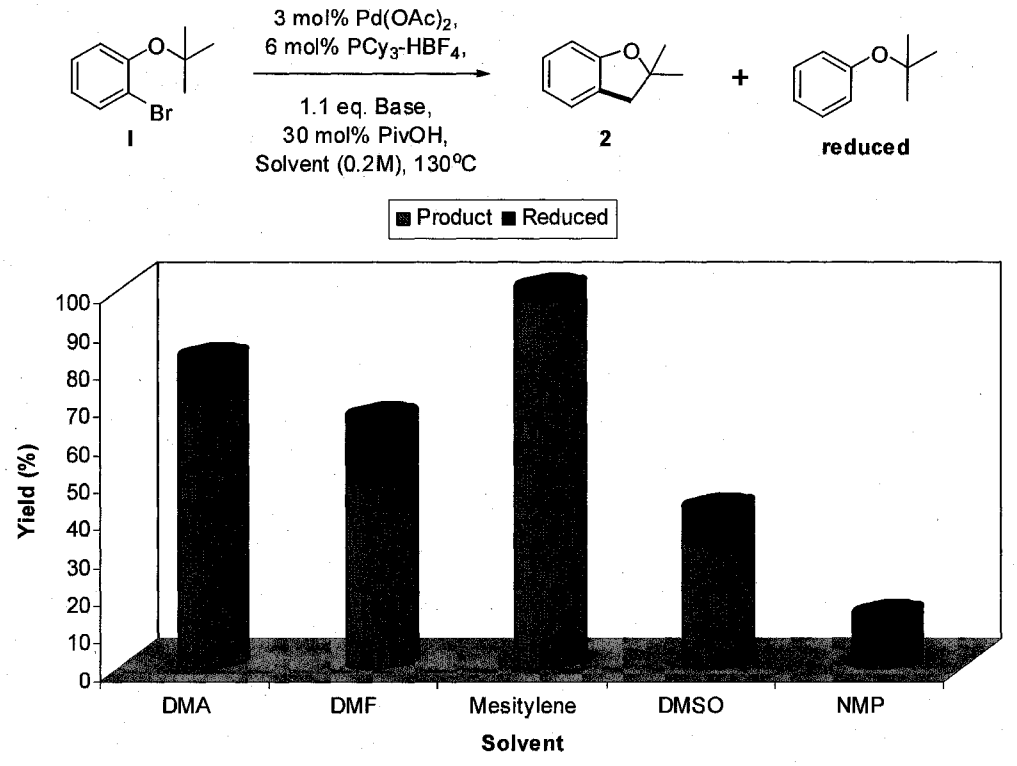
Table 4. 7. Effect of Pivalate Anion on the Reaction.





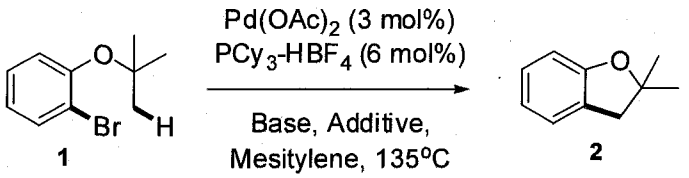
Different reaction parameters were then optimized including the palladium source, solvent concentration, catalyst loading, equivalents of base and pivalic acid, temperature as well as ligand to metal ratios. Polar solvents such as DMSO and NMP led to quick catalyst decomposition to palladium black with little product formation. DMA and DMF were found to be good solvents giving the product in 71% and 49% yield but with unsatisfactory amounts of the reduced by-product (14-20%)(Table 4.8). Gratifyingly, when the reaction was performed in mesitylene as the solvent, 97% conversions to the desired cyclized product with 3% formation of the reduced by-product.

Table 4. 8. Solvent Effect on the Reaction.



These studies lead to the finding that reaction of **1** in the presence of $Pd(OAc)_2$ (3 mol%) and $PCy_3 \cdot HBF_4$ (6 mol%) in conjunction with Cs_2CO_3 (1.1 equiv.) and 2,2-dimethylpropionic acid (30 mol%) in mesitylene at 130 °C results in complete and clean conversion to **2** which can be isolated in 97% yield. The superior reactivity associated with the combined use of an insoluble carbonate base and a catalytic quantity of soluble carboxylate base (in this case via deprotonation of the pivalic acid *in situ*) is exemplified by the lower conversions and yields that are obtained when either component is used as the stoichiometric base alone under optimal reaction condition (Table 4.9; entry 6 *vs.* entries 1 and 2). The same effect as in the direct arylation of benzene is observed,[144] where the yield increases as the carboxylate becomes more basic and hindered. Again, pivalic acid was found to be ideal in terms of sterics over the slightly bulkier 1-adamantylcarboxylic acid.

Table 4. 9. Effects of the Carboxylic Acid on the Reaction.



1 2

Entry	Base	Additive	Conversion (%)[a]	Yield (%)[a]
1	Cs_2CO_3	none	22	15
2	CsOPiv	none	23	14
3	Cs_2CO_3	$MeCO_2H$ (30 mol%)	23	16
4	Cs_2CO_3	$EtCO_2H$ (30 mol %)	26	18
5	Cs_2CO_3	$^iPrCO_2H$ (30 mol %)	43	37
6	Cs_2CO_3	$^tBuCO_2H$ (30 mol%)	100	97[b]
7	Cs_2CO_3	1-AdCO_2H (30 mol%)	72	67

[a] Determined by GCMS. [b] Isolated yield.

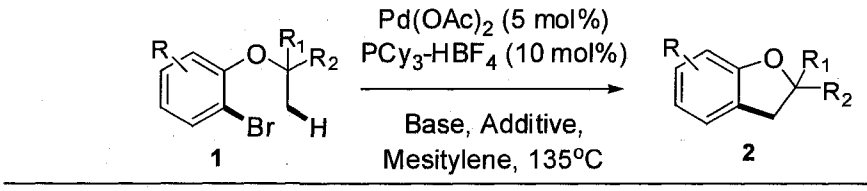
Additional examples of this reaction are included in Table 4.10. Broad functional group tolerance is observed including electron deficient, electron rich as well as sterically encumbered aryl bromides. Aryl chlorides were also found to be suitable substrates, although an increased amount of the dehalogenation byproduct was observed. In contrast, the aryl iodide gave incomplete conversion, most probably due to poisoning of the catalyst from the iodide.[145] When different aliphatic groups are present that may undergo arylation, high selectivity is observed for reaction at a methyl center over a secondary carbon atom as illustrated by the formation of **9**, **10**, **11** and **13**. Trifluoromethyl substituents are inert under the reaction conditions enabling the preparation of CF_3 substituted dihydrobenzofuran compounds such as **12** which would be difficult to prepare *via* the more commonly employed cationic cyclization routes to this class of molecules.[146] Aromatic substituents are also tolerated so long as a six

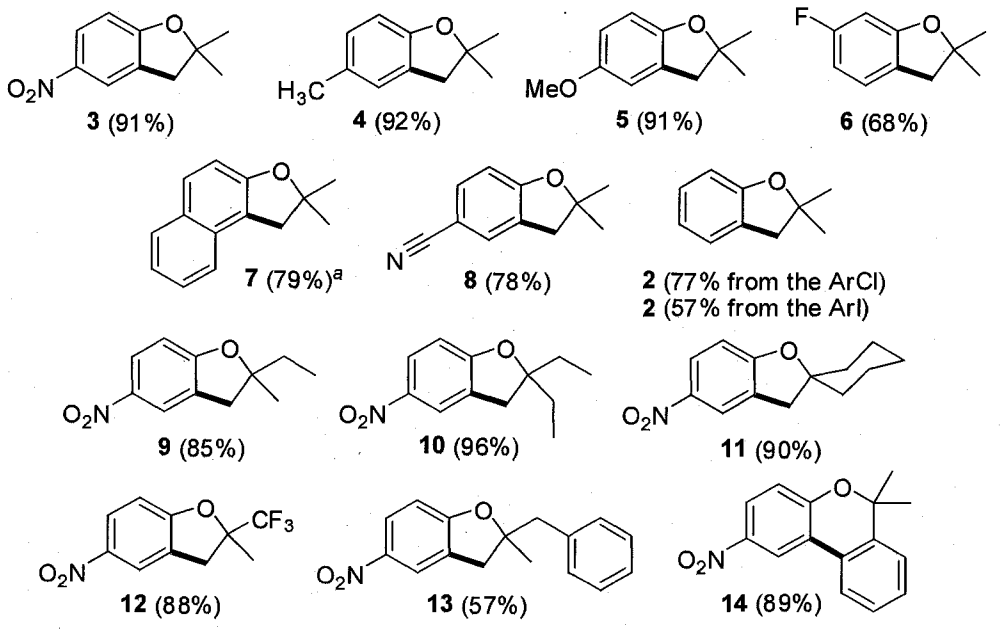
[145] We have previously observed a poisoning effect on direct arylation by the presence of iodide salts. See: Campeau, L.-C.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 581.

[146] The most common route to simple analogues involves phenol alkylation with an appropriately substituted allyl fragment followed by a Claisen rearrangement and subsequent cationic ring closure. For example, see: Kataoka, K.-I.; Shiota, T.; Takeyasu, T.; Minoshima, T.; Watanabe, K.; Tanaka, H.; Mochizuki, T.; Taneda, K.; Ota, M.; Tanabe, H.; Yamaguchi, H. *J. Med. Chem.* **1996**, *39*, 1262.. This approach relies on sufficient substituent stabilization of the carbocation which cannot occur when electron-withdrawing groups are present.

membered ring closure is not accessible as illustrated in the formation of **13** and **14**.[147] The preferential reactivity at the aromatic C-H bond over the aliphatic one is exemplified by the exclusive formation of **14**.

Table 4. 10. Synthesis of Different 2,2-Dialkyldihydrobenzofuran.





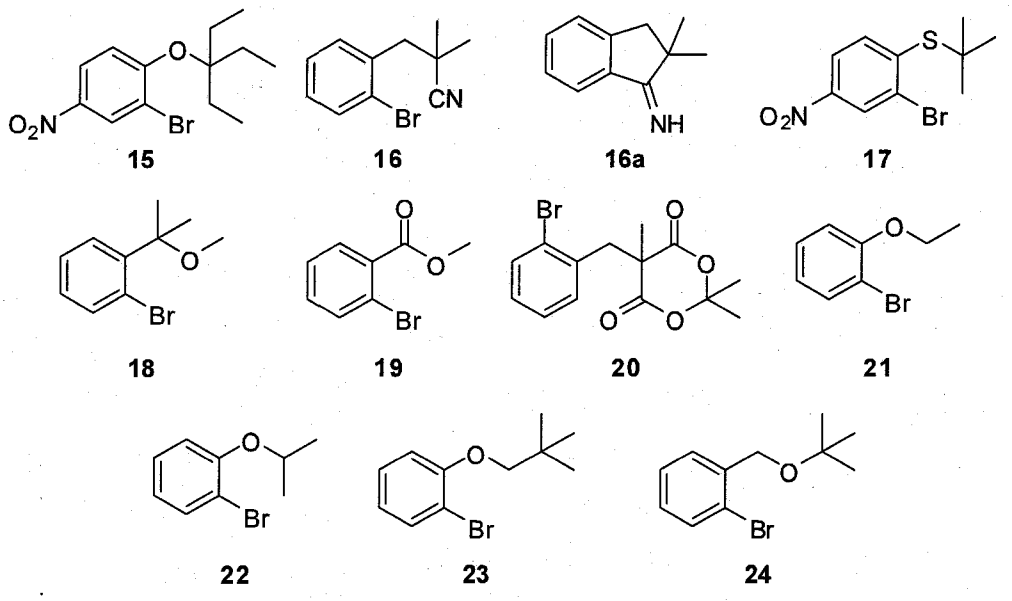
[a] Performed at 150 °C

The reaction does possess certain limitations, however (Figure 4.3). For instance, the substrate must contain a primary carbon, as exemplified by the isolation of the starting material from reacting **15**. Also, substitution of one alkyl group for a cyanide group resulted in the cyclization onto the cyanide as the major product (**16** to **16a**). These types of additions using palladium have precedent.[148] Synthesis of 2,2-dialkyldihydrobenzothiophene through this methodology also failed, probably due to the

[147] Reaction of **13** was accompanied by the formation of the seven-membered ring by-product in 34% yield.
[148] (*a*) Deng, J.H; Tai, H.-M; Yang, C.-C. *J. Chin. Chem. Soc.* **2000**, *47*, 327. (*b*) Pletnev, A.A.; Larock, R.C. *Tetrahedron Lett.* **2002**, *43*, 2133. (*c*) Pletnev, A.A.; Larock, R.C. *J. Org. Chem.* **2002**, *67*, 9428.

poisoning of the catalyst by the sulfur atom (**17**).[149] Cyclization onto a methoxy (**18**), methyl ester (**19**) or the methyl of **20** also failed resulting in recovery of the starting material. These results can be rationalized by the formation of stable five-membered ring palladacycles. The requirement for a quaternary center is critical as tertiary or secondary center gave <5% and <30% to the desired product respectively (**21-22**). This result is also in correlation with our computational analysis which shows a higher transition state energy for these transformations (Table 4.2). Finally, all attempts at generating 3,3-dimethylchroman or 3,3-dimethylisochroman failed (**23-24**), perhaps in part to the higher degree of flexibility of the alkyl chain and/or the harder formation of the seven-membered ring palladacycle intermediate.

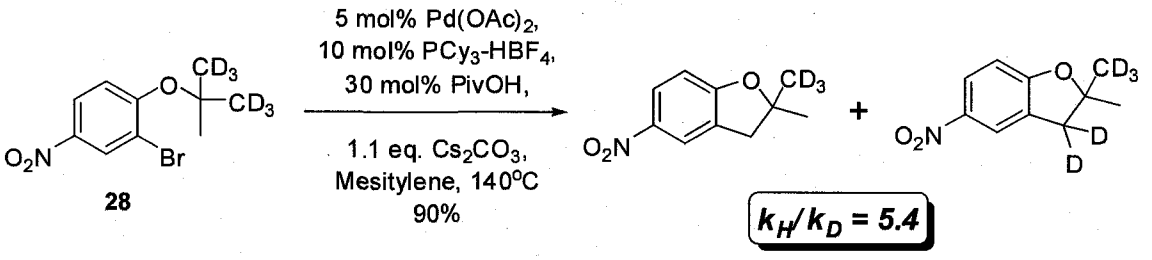
Figure 4. 3. Incompatible Cyclization Precursors and Products.



Understanding the reaction mechanism is important since it may facilitate the future development of these types of reaction. We began our mechanistic investigation by finding the kinetic isotope effect of the reaction using the hexadeuterated substrate **28** (Scheme 4.9). We observed a large primary kinetic isotope effect of 5.4, indicating that C-H bond-cleavage is a kinetically significant catalytic event.

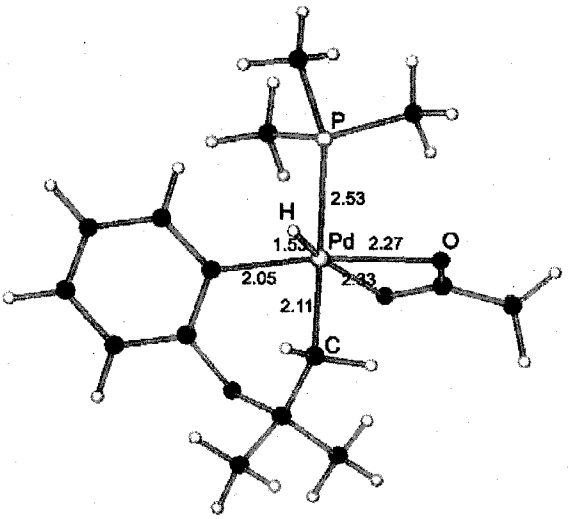
[149] A similar effect was observed in the intramolecular direct arylation of tethered arenes; unpublished results.

Scheme 4. 9. Kinetic Isotope Effect Evaluation.



The reaction was then examined by density functional theory (DFT) calculations.[150] All of the following computational calculations were performed by Serge Gorelski. Due to its pertinence toward the understanding of the reaction mechanism, it will be discussed in detail. Both Pd^{II} and Pd^{IV} pathways were explored. The Pd^{IV} pathway which involves an oxidative insertion into the methyl C-H bond was ruled out based on the high energy of the Pd^{IV} alkyl-hydride intermediate (Figure 4.4, ΔG_{298K}= 47.7 kcal/mol) calculated at the B3LYP/DZVP level of theory, and by the fact that re-optimization of this intermediate at the B3LYP/TZVP level failed to locate the corresponding energy minimum.

Figure 4. 4. Structure of the Pd^{IV} intermediate.

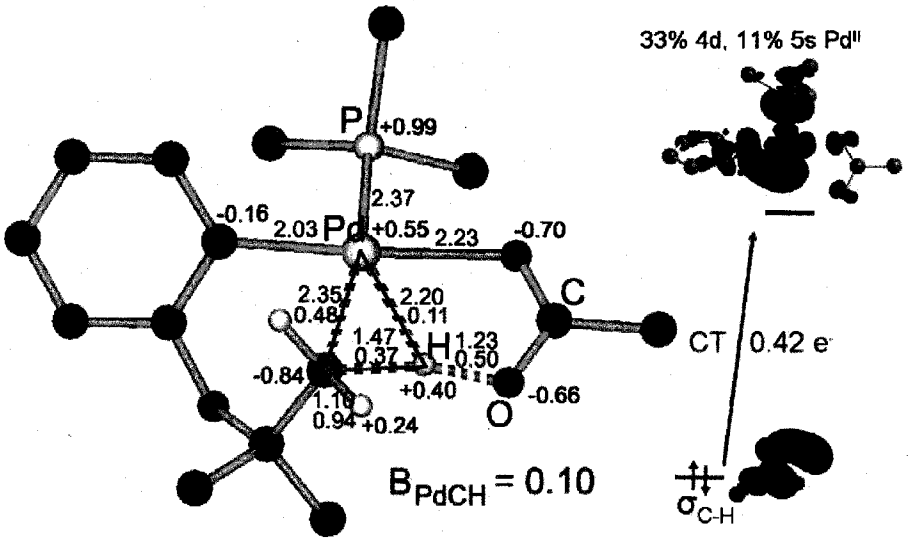


Structure of the Pd^{IV} intermediate (a local energy minimum) for the direct alkylation reaction of the $Pd(C_6H_4\text{-}O\text{-}C(CH_3)_3)(P(CH_3)_3)(O_2CCH_3)$ complex (at the B3LYP/DZVP level). Relevant bond distances (Å) are shown.

[150] For computational details, see supporting information of ref. 20.

On the other hand, a transition state (TS) corresponding to a concerted palladation-deprotonation pathway (Figure 4.5) was found to have a $\Delta G^{\ddagger}_{298K}$ of 29.4 kcal/mol in the gas phase and 27.7 kcal/mol in benzene (Table 4.11). At the TS, agostic, 3-center 2-electron interactions occur[151] between the C-H σ bond and the Pd^{II} atom (the 3-center bond order B_{PdCH} is 0.10)[152] resulting in a significant weakening of the C-H bond (the Mayer bond order[153] for the C-H bond is 0.37 *vs.* 0.94 for the non-broken C-H bond). Thus, the energetic cost of C-H bond cleavage is compensated for by the Pd-C and Pd-H interactions that involve electron donation (~0.42 e^-) from both the C-H bond to the Pd^{II} atom, and the simultaneous formation of the O-H bond (Figure 4.8).

Figure 4. 5. Transition State for a Concerted Palladation-Deprotonation Pathway.



Selected H atoms have been removed for clarity. Relevant 2- and 3-center bond orders (red), distances (Å) (black) and NPA-derived atomic charges (blue) are shown. The 3-center covalent interaction and charge transferred (CT) between from the C-H bond to the metal-based acceptor orbital are shown at right.

The computed value of the deuterium kinetic isotope effect (k_H/k_D) *via* this pathway was found to be 3.6 at 115 °C (Table 4.11). Considering that this calculation

[151] Brookhart, M.; Green, M. L. H.; Parkin, G. *Proc. Nat. Acad. Sci. USA* **2007,** 104, 6908-6914.
[152] (a) Sannigrahi, A. B.; Kar, T. *Chem. Phys. Lett.* **1990,** 173, 569-572. (b) Giambiagi, M.; Giambiagi, M. S.; Mundim, K. C. *Struct. Chem.* **1990,** 1, 123.
[153] Mayer, I. *Chem. Phys. Lett.* **1983,** 97, 270-274.

does not include any rate enhancement due to quantum mechanical tunneling,[154] the calculated k_H/k_D is consistent with the experimentally determined value of 5.4±0.3. Furthermore, the reaction barrier at a secondary carbon to give intermediate **30** (-$\underline{\mathbf{CH_2}}CH_3$) was found to be 5.5 kcal mol^{-1} higher than the $\Delta G^{\ddagger}$ for reaction at the -CH_3 group to give **29**, correlating very well with the experimentally observed reactivity and selectivity for reaction at methyl groups (Scheme 4.10, Table 4.11). Similarly, the reaction at more remote positions, as in the formation of **31**, is also less kinetically and thermodynamically favored (Table 4.11).

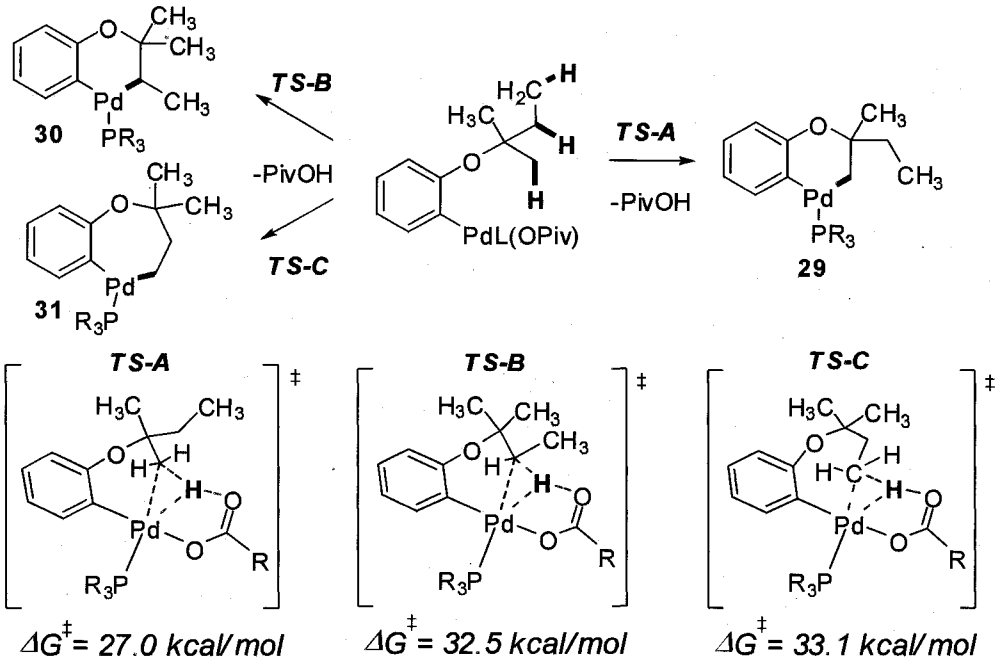
Table 4. 11. Calculated Activation Barriers, Gibbs Free Energy, 3-Center Pd-C-H Bond Order Indices and Reaction Energy Change.[a]

RH [b]	$\Delta E^{\ddagger}$	$\Delta G_{298K}^{\ddagger}$	B_{PdCH}	$\Delta G_{r,298K}$
	kcal/mol	kcal/mol		kcal/mol
$CH_2\mathbf{C}H_3$	31.5	32.6 (33.8)	0.116	20.6 (19.1)
$C(\mathbf{C}H_3)_3$	30.5	29.4[c] (27.7)	0.102	16.3 (13.1)
$C(\mathbf{C}H_3)_2(CH_2CH_3)$	30.3	28.8 (27.0)	0.100	15.6 (11.3)
$C(\mathbf{C}H_3)_2(CH_2CH_3)$[d]	30.4	29.4 (27.5)	0.102	16.5 (12.0)
$C(CH_3)_2(\mathbf{C}H_2CH_3)$	35.0	34.2 (32.5)	0.102	15.5 (10.8)
$C(CH_3)_2(\mathbf{C}H_2CH_3)$[d]	37.4	35.7 (34.5)	0.106	16.4 (11.9)
$C(CH_3)_2(CH_2\mathbf{C}H_3)$	36.0	34.9 (33.1)	0.112	21.9 (17.8)

[a] Activation barriers (electronic energy difference ($\Delta E^{\ddagger}$) and Gibbs free energy at 298K ($\Delta G_{298K}^{\ddagger}$)), 3-center Pd-C-H bond order indices (BPdCH) for the transition states and the reaction free energy change ($\Delta Gr_{,298K}$) for the PdII palladation-deprotonation reaction step in the $Pd(P(CH_3)_3)(C_6H_4\text{-}O\text{-}R)(O_2CCH_3)$ complexes $Pd(P(CH_3)_3)(C_6H_4\text{-}O\text{-}RH)(O_2CCH_3)$ = $Pd(P(CH_3)_3)(C_6H_4\text{-}O\text{-}R)$ + HO_2CCH_3. The free energies in the C_6H_6 solvent are shown in parenthesis. [b] H indicates the abstracted H atom. [c] $\Delta G_{413K}^{\ddagger}$ is 30.4 kcal/mol and 31.5 kcal/mol for $Pd(P(CH_3)_3)(C_6H_4\text{-}O\text{-}C(\mathbf{C}H_3)(CD_3)_2)(O_2CCH_3)$ and $Pd(P(CH_3)_3)(C_6H_4\text{-}O\text{-}C(CH_3)(\mathbf{C}D_3)_2)(O_2CCH_3)$, respectively. [d] Using the second isomer.

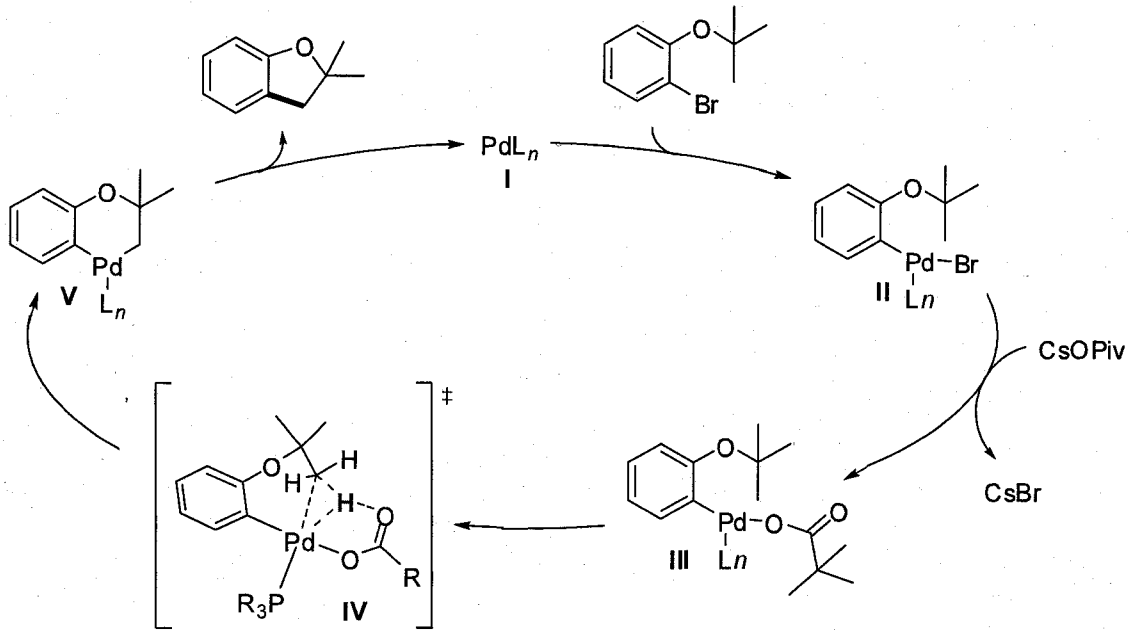
[154] Garrett, B. C.; Truhlar, D. G. *J. Chem. Phys.* **1980,** 72, 3460.

Scheme 4. 10. Mechanistic Rationale for Site Selectivity.



From this data, we propose the following catalytic cycle as depicted in Scheme 4.11. Oxidative addition of the palladium (0) into the aryl halide bond generates the palladium (II) intermediate **II**. Halogen exchange for the more basic pivalate anion, followed by a concerted deprotonation-palladation step enabled by the presence of 3-center agostic interactions at the transition state **IV** gives the alkylarylpalladium **V**. Subsequent reductive elimination regenerates the palladium (0) catalyst and liberates the desired product.

Scheme 4. 11. Proposed Catalytic Cycle for the Direct Alkylation of Aryl Halides.



These results point to new opportunities in the catalytic formation of C-C bonds that are less reliant on stoichiometric and wasteful substrate pre-activation, particularly with palladium 0/II catalysis. The mechanistic insights regarding the intimate role of the base and the 3-center agostic interactions at the sp^3 C-H bond cleaving TS should also facilitate the development of new catalysts and transformations.

Chapter 5

Aporphine Alkaloid Synthesis and Diversification via Direct Arylation

The aporphines are a diverse group of alkaloids predominantly found in the poppy plant family.[155] All 300 plus members share the following characteristics: a tetracyclic skeleton made in part by an isoquinoline motif as part of a biaryl subunit, a stereogenic center at the C6a position, as well as different oxidation on both aromatic rings (Figure 5.1). A diverse array of biological properties have been documented including dopaminergic and serotonergic effects,[156] antiparkinson's,[157] antifibrillogenesis

[155] (*a*) Ríos, J.L.; Máñez, S.; Giner, R. M.; Recio, M. C. *The Alkaloids*, G. A. Cordell, Ed., Academic: New York, **2000**, Vol. *53*, p 57. (*b*) Guinaudeau, H.; Leboeuf, M. ; Cavé, A. *J. Nat. Prod.*, **1994**, *57*, 1033, and references cited therein.

[156] (*a*) Hedberg, M.H.; Johansson, A.M.; Nordvall, G.; Yliniemela, A.; Li, H.B.; Martin, A.R.; Hjorth, S.; Unelius, L.; Sundell, S.; Hacksell. U. *J. Med. Chem.*, **1995**, *38*, 647. (*b*) Shin, J.S.; Kim, K.T.; Lee, M.K. *Neuroscience Letters*, **1998**, *244*, 161. (*c*) Asencio, M. ; Delaquerrière, B. ; Cassels, B.K. ; Speisky, H. ; Comoy, E. ; Protais, P. *Pharmacology Biochemistry and Behavior*, **1999**, *62*, 7. (*d*) Dajas-Bailador, F.A.; Asencio, M.; Bonilla, C.; Scorza, C.; Echeverry, C.; Reyes-Parada, M.; Silveira, R.; Protais, P.; Russell, G.; Cassels, B.K.; Dajas, F. *Gen. Pharma.*, **1999**, *32*, 373. (*e*) Linnanen, T.; Brisander, M.; Mohell, N.; Johansson, A. M. *Bioorg. Med. Chem. Lett.*, **2001**, *11*, 367.

[157] (*a*) Lees, A.J.; *Fundam. Clin, Pharmacol.*, **1993**, *7*, 121. (*b*) Muguet, D.; Broussolle, E.; Chazot, G. *Biomed. Pharmacother.*, **1995**, *49*, 197. (*c*) Sit, S.Y., *Curr. Pharm.Des.*, **2000**, *6*, 1211. (*d*) Poewe, W.; Wenning, G.K., *Mov. Disorders,* **2000**, *15*, 789. (*e*) Tyne, H.L.; Parson, J.; Sinott, A ; Fox, S.H. ; Steiger, M.J. *J. Neurol.*, **2004**, *251*, 1370.

(Alzheimer's disease),[158] antiplatelet,[159] anticancer,[160] treatment for erectile dysfunction,[161] cadiotonic agent,[162] antipoliovirus,[163] anti-acetylcholinesterase,[164] antimalarial,[165] antipsychotics,[166] antibacterial[167] and adrenergic effects.[168] In fact, naturally occurring aporphines have been extracted from plants and used for many years as antitussive agents for the suppression of cough.[169] These pharmacological properties have prompted different structure activity relationship (SAR) studies over the past three decades.[170] These studies revealed that the biphenyl subunits, as well as the benzylic C6a hydrogen with its associated absolute configuration, were found responsible for the aporphines' activity.[171] Further, a recent study of the effects of C2 substitution on the binding of aporphines to the dopamine D_2 receptor supported the notion that it contains a lipophilic cavity in the vicinity of that position.[170a]

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[158] Lashuel, H.A.; Hartley, D.M.; Balakhaneh, D.; Aggarwal, A.; Teichberg, S.; Callaway, D.J.E. *J. Bio. Chem.,* **2002**, *277*, 42881.

[159] (*a*) Wu, Y.-C; Chang, F.-R.; Chao, Y.-C.; Teng, C.-M. *Phytotherapy Res.,* **1998**, *12*, S39. (*b*) Chia, Y.-C.; Chen, K.-S.; Chang, Y.-L.; Teng, C.-M.; Wu, Y.-C. *Bioorg. Med. Chem. Lett.*, **1999**, *9*, 3295. (*c*) Kuo, R.-Y.; Chang, F.-R.; Chen, C.-Y.; Teng, C.-M.; Yen, H.-Y.; Wu, Y.-C. *Phytochemistry*, **2001**, *57*, 421.

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[161] (*a*) Altwein, J.E.; Keuler, F.U.; *Urol. Int.*, **2001**, *67*, 257. (*b*) Morales, A. Clin.*Geriatr. Med.*, **2003**, *19*, 529. (*c*) Martinez, R. ; Puigvert, A. ; Pomerol, J.M. ; Rodriguez-Villalba, R. *J. Urol.*, **2003**, *170*, 2352. (*d*) Hsieh, G.C. ; Hollingsworth, P.R. ; Martino, B. ; Chang, R.J. ; Terranova, M.A. ; O'Neil, A.B. ; Lynch, J.J. ; Moreland, D.L. ; Donnelly-Roberts, D.L. ; Kolasa, T. ; Mikusa , J.P. ; Mcvey, J.M. ; Marsh, K.C. ; Sullivan, J.P. ; Brioni, J.D. *J. Pharmacol. Exp. Ther.*, **2004**, *308*, 330. (*e*) Perimenis, P. ; Gyftoppoulos, K. ; Giannitsas, S.A. ; Markou, I.; Totsa, A.; Chrysanthopoulou, A.; Athanasopoulos, A. ; Barbalias, G. Int. *J. Impotence Res.*, **2004**, *16*, 2.

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[164] Chiou, C.-M.; Kang, J.-J.; Lee, S.-S. *J. Nat. Prod.*, **1998**, *61*, 46.

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[167] Zhang, Z.; ElSohly, H. N.; Jacob, M.R.; Pasco, D.S.; Walker, L.A.; Clark, A. M. *J. Nat. Prod,.* **2002**, *65*, 856.

[168] (*a*) Martinez, S.; Madrero, Y.; Elorriaga, M.; Noguera, M.-A. ; Cassels, B. ; Sobarzo, E. ; D'Ocon, P.; Ivorra, M.-D. *Life Sciences*, **1999**, *64*, 1205. (*b*) Bremmer, J.B. ; Coban, B. ; Giffith, R. ; Groenewoud, K.M. ; Yates, B.F. *Bioorg. Med. Chem.*, **2000**, *8*, 201. (*c*) Indra, B.; Matsunaga, K.; Hoshino, O.; Suzuki, M.; Ogasawara, H.; Ohizumi, Y.; *Eur. J. Pharmacol.* **2002**, *437*, 173.

[169] Shoji, N.; Umeyama, A.; Takemoto, T.; Ohizumi, Y. *J. Pharmacol. Sci.*, **1984**, *73*, 568.

[170] (*a*) Sondergaard, K.; Kristensen, J. L.; Palner, M.; Gillings, N.; Knudsen, G. M.; Roth, B. L.; Begtrup, M. *Org. Biomol. Chem.*, **2005**, *3*, 4077. (*b*) Zhang, A.; Csutoras, C.; Zong, R.; Neumeyer, J. L. *Org. Lett.*, **2005**, *7*, 3239, and references cited therein.

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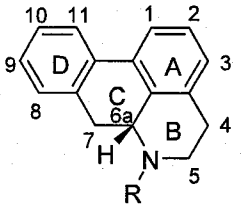
Figure 5. 1. The Aporphine Skeleton.



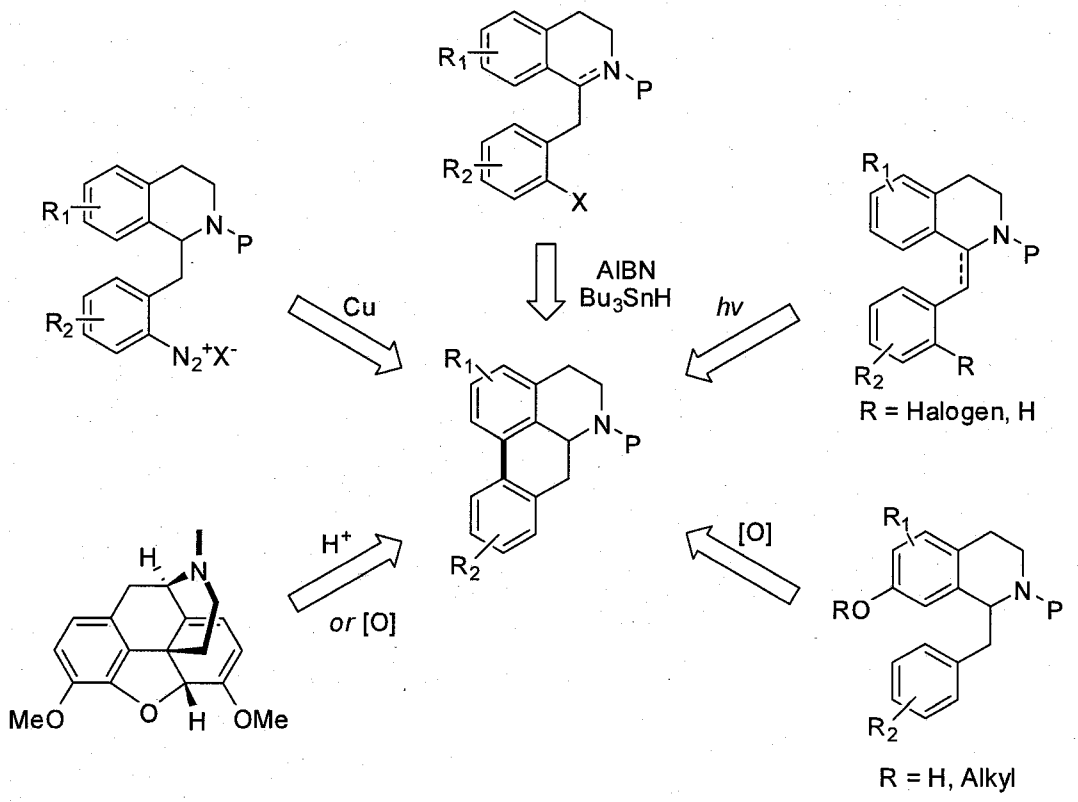
This section describes the development of new convergent and divergent stereoselective synthetic routes to the aporphine alkaloids using direct arylation to generate the key biaryl bond.[172] In order to demonstrate the advantages of the chemistry described herein, a general discussion of the alternative approach *via* a late biaryl bond formation will be discussed.

5.1 – Previous Synthesis of Aporphines *via* a Late Biaryl Formation.

The most commonly employed strategy for the synthesis of aporphines involves a late biaryl bond formation. A resume of the different bond forming reactions reported to date is illustrated in Figure 5.2. These include the Pschorr reaction, radical and photochemical cyclization, degradation/rearrangement of natural products (ie. morphine analogues) as well as phenolic and non-phenolic oxidative couplings by a variety of oxidants.

[172] (*a*) Lafrance, M.; Blaquiere, N.; Fagnou, K. *Eur. J. Org. Chem.* **2007**, *5*, 811. (*b*) Lafrance, M.; Blaquiere, N.; Fagnou, K. *Chem. Comm.* **2004**, *24*, 2874.

Figure 5. 2. Retrosynthesis of Aporphines through the Formation of the Biaryl Bond.

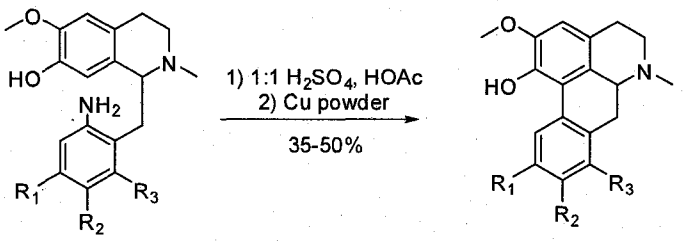


5.1.1.1 – Pschorr Cyclization Approach.

Nearly a century ago, Gadamer's synthesis of glaucine became the first preperation of an aporphine.[173] For the next 50 years, the Pschorr cyclization would remain the only viable pathway for the generation of the aporphine scaffold.[174] In general, as the oxygenation level of the D ring increased, the cyclization yield decreased. In order to improve the yield of the reaction, the group of Kupchan employed a free hydroxyl at the C1 position. [175] This structural change doubled the yields from a previously reported synthesis of a Thalicarpine precursor from 15% to a moderate 35% yield (Scheme 5.1).

[173] Gadamer, J. *Arch. Pharm.* **1911**, *249*, 680.
[174] For a brief review of the synthesis of aporphines up to 1960, see: (*a*) Pinder, A.R., *Chemistry of Carbon Compounds*, Vol. IV, Elsevier Publishing Co., New York, **1960**, chapter 25. (*b*) Taylor, W.I., *Tetrahedron*, **1961**, *14*, 42.
[175] Kupchan, M.S.; Kameswaran, V.; Findlay, J.W. *J. Org. Chem.*, **1972**, *37*, 405.

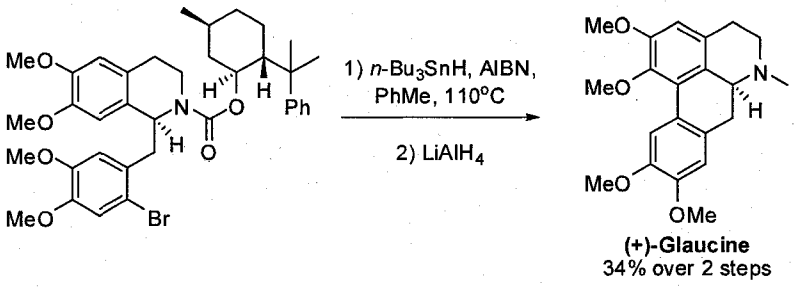
Scheme 5. 1. Improved Synthesis of Natural Aporphine Alkaloids *via* Pschorr Reaction.



5.1.1.2 – Tin-Mediated Radical Cyclization.

The first example of a tin-mediated radical cyclization for the formation of the biaryl bond of aporphines was demonstrated by Comins and coworkers.[176] Using a slow syringe pump addition of a solution containing 2 equivalents of tributyltin hydride and azobisisobutylonitrile in toluene, the authors were able to isolate 48% yield of the cyclized aporphine, with concomittant 46% yield of the hydrodebrominated by-product (Scheme 5.2).

Scheme 5. 2. Asymmetric Synthesis of (+)-Glaucine by Tin-Mediated Radical Cyclization.

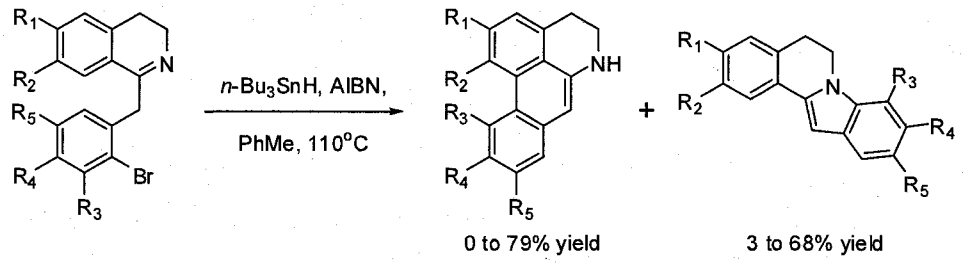


With the goal of circumventing the nitrogen protection step, Orito and coworkers explored the cyclization from the imine bromide precursor. The challenge involved preventing the addition of the phenyl radical onto the C=N group in a 5-*endo* cyclization mode.[177] Higher yields were obtained when R_3 was unsubstituted while mixtures of the

[176] Comins, D.L.; Thakker, P.M.; Baevsky, M.F.; Badawi, M.M. *Tetrahedron,* **1997**, *53*, 16327.
[177] Orito, K.; Uchiito, S.; Satoh, Y.; Tatsuzawa, T.; Harada, R.; Tokuda, M. *Org. Lett.*, **2000**, *2*, 307.

6a,7-dehydroaporphine and 5,6-dihydroindolo[2,1-*a*]-isoquinoline were obtained when R3 was substituted (Scheme 5.3).

Scheme 5. 3. Synthesis of 6a,7-dehydroaporphines.

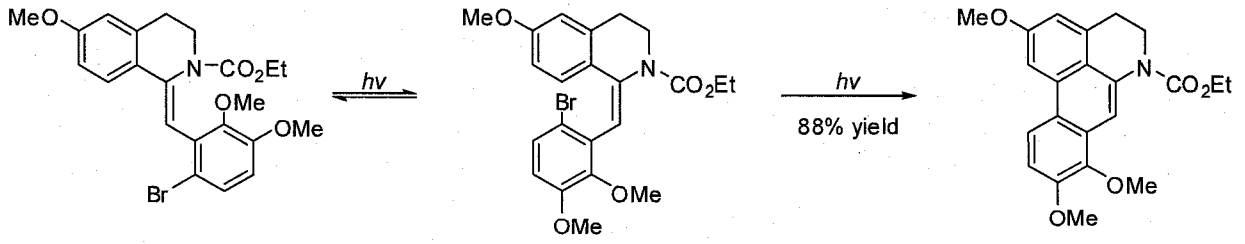


5.1.1.3 – Photolytic Cyclization.

Two different types of photocyclization were explored for the construction of aporphines. The first consists of a rapid iodide assisted *cis/trans* isomerisation/photocyclization of stilbene derivatives.[178] While simplicity in the synthesis of the starting material was of great advantage, the reaction gave greater than 55% yields for the cyclization step.

Through the installment of a halide at the C-2 position on the bottom arene, a more facile photocyclization was observed. Further, greater control of the regioselectivity was demonstrated by the strategic positioning of the halogen.[179] Yields as high as 88% were reported using this more controlled route (Scheme 5.4).[179d]

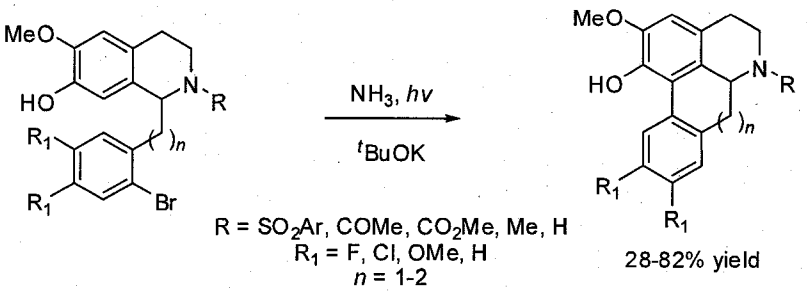
Scheme 5. 4. Photocyclization of the Aporphine Core.



[178] (*a*) Cava, M.P.; Havlicek, S.C.; Lindert, A.; Spangler, R.J. *Tet. Lett.*, **1966**, *26*, 2937. (*b*) Yang, N.C.; Lenz, G.R.; Shani, A. *Tet. Lett.*, **1966**, *26*, 2941. (*c*) Atanes, N.; Guitián, E.; Castedo, L.; Saá, J.M. *Tetrahedron,* **1994**, *50*, 11257.
[179] (*a*) Cava, M.P.; Mitchell, M.J.; Havlicek, S.C.; Lindert, A.; Spangler, R.J. *J. Org. Chem.* **1970**, *35*, 175. (*b*) Cava, M. P.; Stern, P.; Wakisaka, K. *Tetrahedron*, **1973**, *29*, 2245. (*c*) Nimgirawath, S.; Taylor, W.C. *Aust. J. Chem.* **1983**, *36*, 1061. (*d*) Zhou, D.-M.; Yue, B.-Z.; Cui, J.-Q.; Cai, M.-S. ; Zhang, L.-H. *Heterocycles*, **1997**, *45*, 439.

Alternatively, cyclization of different 1-(2-halobenzyl)-1,2,3,4-tetrahydroisoquinolines can be also employed.[180] Removal of the isomerization step led to significant increase in yield. Recently, Cuny and Rossi reported an intramolecular *ortho*-arylation of phenols with different aryl halides *via* $S_{RN}1$ reactions.[181] This time, different synthetic *N*-substituted aporphine analogues were synthesized in moderate to good yields (Scheme 5.5).

Scheme 5. 5. Photoinduced $S_{RN}1$ reactions for the Synthesis of Aporphines.



5.1.1.4 – Thebaine, Codeine and Morphine Degradation/Rearrangement.

Several groups have turned their attention to the degradation and/or rearrangement of natural products to the aporphine core.[170,182] Due to the need for strong acids or oxidants for these rearrangements/degradations, low to moderate yields are often observed due to decomposition by-products. While this route did access the required material for different SAR studies, the need for highly advanced natural product precursors is disadvantageous since limited precursors are commercially available. Also, several group manipulations are often required to achieve the desired target.

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[180] (*a*) Kupchan, M.S.; Kanojia, R.M. *Tetrahedron Lett.* **1966**, *44*, 5353. (*b*) Spangler, R.J.; Boop, D.C. *Tetrahedron Lett.* **1971**, *50*, 4851. (*c*) Kupchan, S.M.; Moniot, J.L.; Kanojia, R.M.; O'Brien, J.B. *J. Org. Chem.* **1971**, *36*, 2413. (*d*) Kametani, T.; Shibuya, S.; Sugi, H.; Kusama, O.; Fukumoto, K. *J. Chem. Soc.* **1971**, 2446. (*e*) Shama, M.; Hwang, D.-Y. *Tetrahedron,* **1974**, 2279.

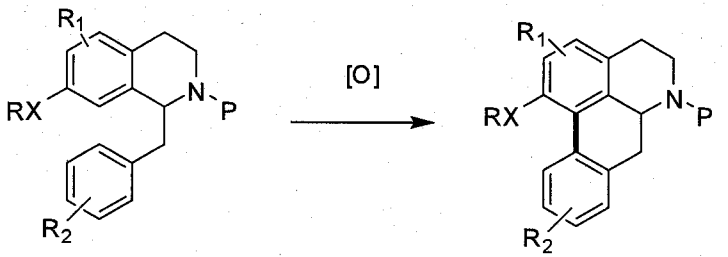
[181] Barolo, S.M.; Teng, X.; Cuny, G.D.; Rossi, R.A. *J. Org. Chem.* **2006**, *71*, 8493.

[182] (*a*) Granchelli, F.E.; Filer, C.N.; Soloway, A.H.; Neumeyer, J.L. *J. Org. Chem.* **1980**, *45*, 2275. (*b*) Cannon, J.G.; Mohan, P.; Bojarski, J.; Long, J.P.; Bhatnagar, R.K.; Leonard, P.A.; Flynn, J.R.; Chatterjee, T.K. *J. Med. Chem.* **1988**, *31*, 313. (*c*) Hedberg, M.H.; Johansson, A.M.; Hacksell, U. *Chem. Commun.* **1992**, 845. (*d*) Berényi, S.; Csutorás, C.; Gyulai, S.; Rusznyák, G. *Synth. Commun.* **2001**, *31*, 1987.

5.1.1.5 – Oxidative Phenolic and Nonphenolic Biaryl Coupling Approach.

Oxidative phenolic and nonphenolic biaryl coupling is an efficient alternative for the construction of the biaryl bond (Scheme 5.6). Different oxidants have been employed throughout the years. Amongst them are $FeCl_3$,[183] $MoOCl_4$,[184] Ph_2SeO,[185] enzymes,[186] $Pb(OAc)_4$,[187] VOF_3,[188] $Tl(TFA)_3$,[189] RuO_2,[190] Cr_2O_3[191] as well as $PhI(TFA)_2$.[192] This approach is most efficient for the synthesis of aporphines containing highly oxidized precursors generating the biaryl bonds in moderate to excellent yield. Good functional groups tolerance is observed with the exceptions of groups which are sensitive to strong oxidants.

Scheme 5. 6. Phenolic and Non-Phenolic Oxidative Coupling for the Synthesis of Aporphine.



X = O or C
R = H, Alkyl
P = H, Ac, Ts, CO_2Me

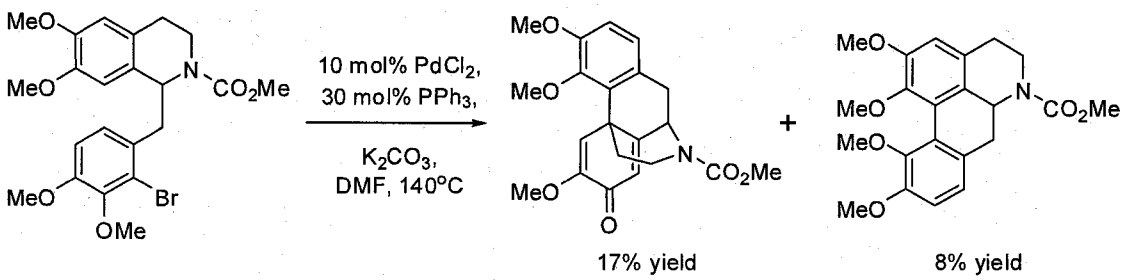
[183] (*a*) Franck, B.; Tietze, L.-F. *Angew. Chem., Int. Ed.* **1967**, *6*, 799. (*b*) Goralski, C.T.; Hasha, D.L.; Henton, D.R.; Krauss, R.C.; Pfeiffer, C.D.; Williams, B.M. *Org. Proc. Res. Dev.* **1997**, *1*, 273.
[184] Kupchan, M.S.; Liepa, A.J. *J. Am. Chem. Soc.* **1973**, *95*, 4062.
[185] Marino, J.P.; Schwartz, A. *Tet. Lett.* **1979**, *35*, 3253.
[186] Coutts, I.G.C.; Hamblin, M.R.; Tinley, E.J.; Bobbitt, J.M. *J. Chem. Soc., Perkin 1,* **1979**, 2744.
[187] Ogasawara, H.; Suzuki, M.; Shiohara, T.; Hoshino, O. *Heterocycles,* **1998**, *47*, 911.
[188] Kupchan, M.S.; Liepa, A.J.; Kameswaran, V.; Bryan, R.F. *J. Am. Chem. Soc.* **1973**, *95*, 6861.
[189] (*a*) Taylor, E.C.; Andrade, J.G.; Rall, G.J.H.; McKillop, A. *J. Am. Chem. Soc.* **1980**, *102*, 6513. (*b*) Meyers, A.I.; Dickman, D.A.; Boes, M. *Tetrahedron,* **1987**, *43*, 5095. (*c*) Gottlieb, L.; Meyers, A.I. *J. Org. Chem.* **1990**, *55*, 5659.
[190] Planchenault, D.; Dhal, R.; Robin, J.-P. *Tetrahedron,* **1993**, *49*, 5823.
[191] Czarnocki, Z.; Mieczkowski, J.B.; Ziólkowski, M. *Tetrahedron: Asymm.* **1996**, *7*, 2711.
[192] Anakabe, E.; Carrillo, L.; Badia, D.; Vicario, J.L.; Villegas, M. *Synthesis,* **2004**, *7*, 1093.

5.2 – Direct Arylation in the Synthesis of Aporphines.

5.2.1 – Literature Precedents.

In 1995, Schäfer and coworkers explored the use of palladium (0) catalyzed intramolecular direct arylation of highly oxygenated arenes.[193] Using 10 mol % palladium dichloride, 30 mol % triphenylphosphine and potassium carbonate in DMF at 140°C, gave the desired product in 8% yield. Instead, demethylation and formation of a quaternary center in 17% yield with concomitant formation of the reduced by-products were observed as the major products (Scheme 5.7).

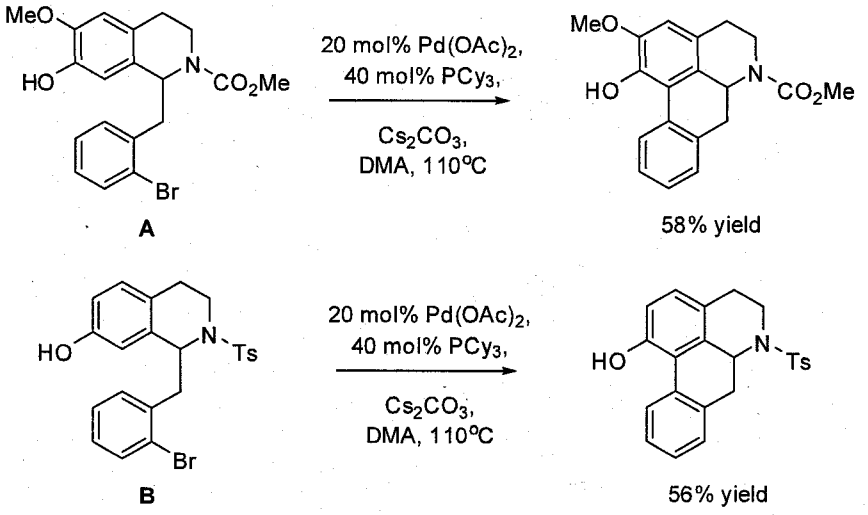
Scheme 5. 7. Synthesis of Aporphine Through a Palladium (0) Catalyzed Cyclization.



Inspired by the work of Rawal on the direct *ortho*-arylation reaction,[194] Cuny designed a racemic synthesis of Nuciferine and Lirinidine.[195] Optimization was performed with substrate **A**. Using 20 mol% palladium acetate, 40 mol% tricyclohexylphosphine and 3.2 equivalents of cesium carbonate in DMA at 110°C, he was able to isolate a 58% yield of the Nuciferine precursor (Scheme 5.8). In a subsequent report, the author reported the synthesis of a C2-phenol aporphine **B** using the same methodology in 56% isolated yield (Scheme 5.8).[196]

[193] Wiegand, S.; Schäfer, H.J. *Tetrahedron,* **1995**, *51*, 5341.
[194] Hennings, D.D.; Iwasa, S.; Rawal, V. *J. Org. Chem.* **1997**, *62*, 2.
[195] Cuny, G.D. *Tetrahedron Lett.* **2003**, *44*, 8149.
[196] Cuny, G.D. *Tetrahedron Lett.* **2004**, *45*, 5167.

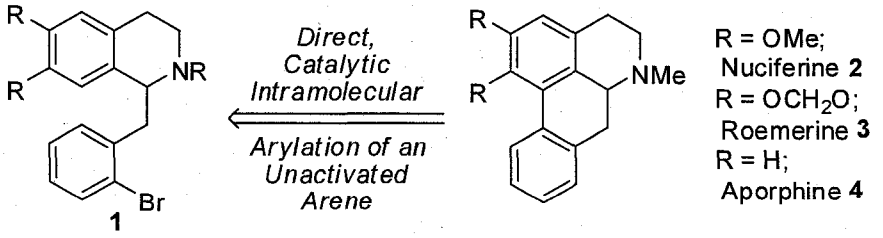
Scheme 5. 8. Direct Arylation as a Synthetic Tool for the Synthesis of Aporphines.



5.2.2 – Direct Arylation as a Strategic Tool for the Synthesis and Diversification of Aporphines.

Although numerous reports have been published throughout the last century, these methodologies always suffered from low yields and/or poor substrate compatibility. Consequently, the need for a general, efficient yet simple approach was still required. After reporting a catalyst system that enables direct intramolecular arylation reactions to be performed with unactivated substrates[197] in high yields and low catalyst loadings, we devised a retrosynthesis to the aporphines alkaloids as depicted in Figure 5.3.

Figure 5. 3. Direct Arylation of Unactivated Arenes in Aporphine Synthesis.

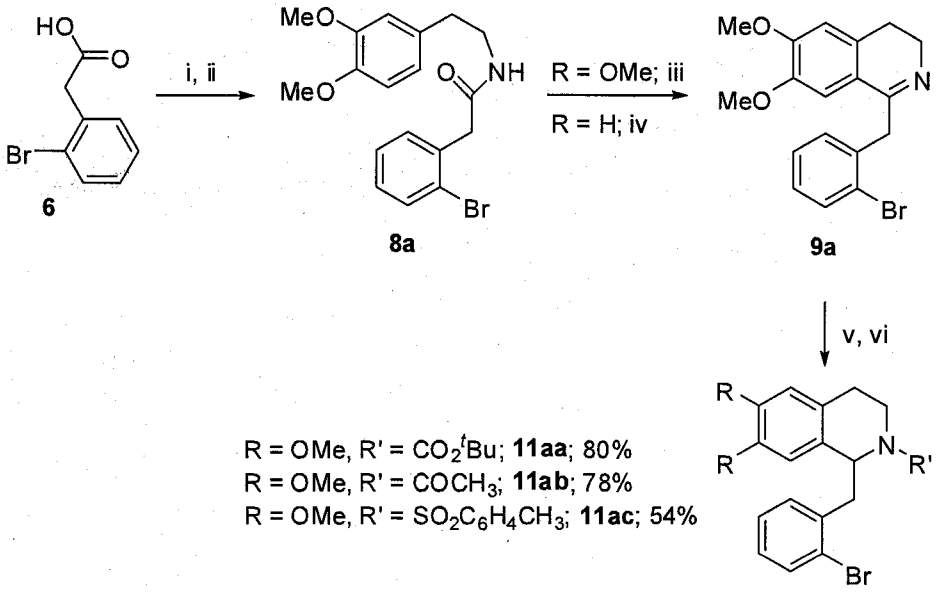


[197] (*a*) Campeau, L.-C. ; Parisien, M. ; Leblanc, M. ; Fagnou, K. *J. Am. Chem. Soc.* **2004**, *126*, 9186. (*b*) Campeau, L.-C. ; Parisien, M. ; Jean, A. ; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 581.

Three structural aspects of the aporphine core, and their potential impact on the arylation chemistry, needed to be addressed. First, the aliphatic tether of **1** was found to be the most challenging case in our methodological studies.[197] Additionally, the nitrogen functionality on the tether (and its associated protecting group) as well as the rigidifying effect of the isoquinoline ring differentiates these substrates from those we had previously examined.

To assess the compatibility of these features, isoquinoline **11a** was selected as our test substrate and prepared with various *N*-protecting groups as outlined in Scheme 5.9. Reaction of carboxylic acid **6** with oxalyl chloride followed by treatment with the corresponding benzylamine gave amides **8a** in >95% yield. Bischler-Napieralski cyclization of **8a** occurred upon treatment with phosphorous oxychloride in refluxing dichloromethane to give dihydroisoquinoline **9a** in 99% yield. Imine reduction with sodium borohydride followed by protection as the *tert*-butylcarbamate (Boc), acetate (Ac) and *para*-toluenesulfonate (Ts) gave isoquinolines **11aa-ac** in good yields.

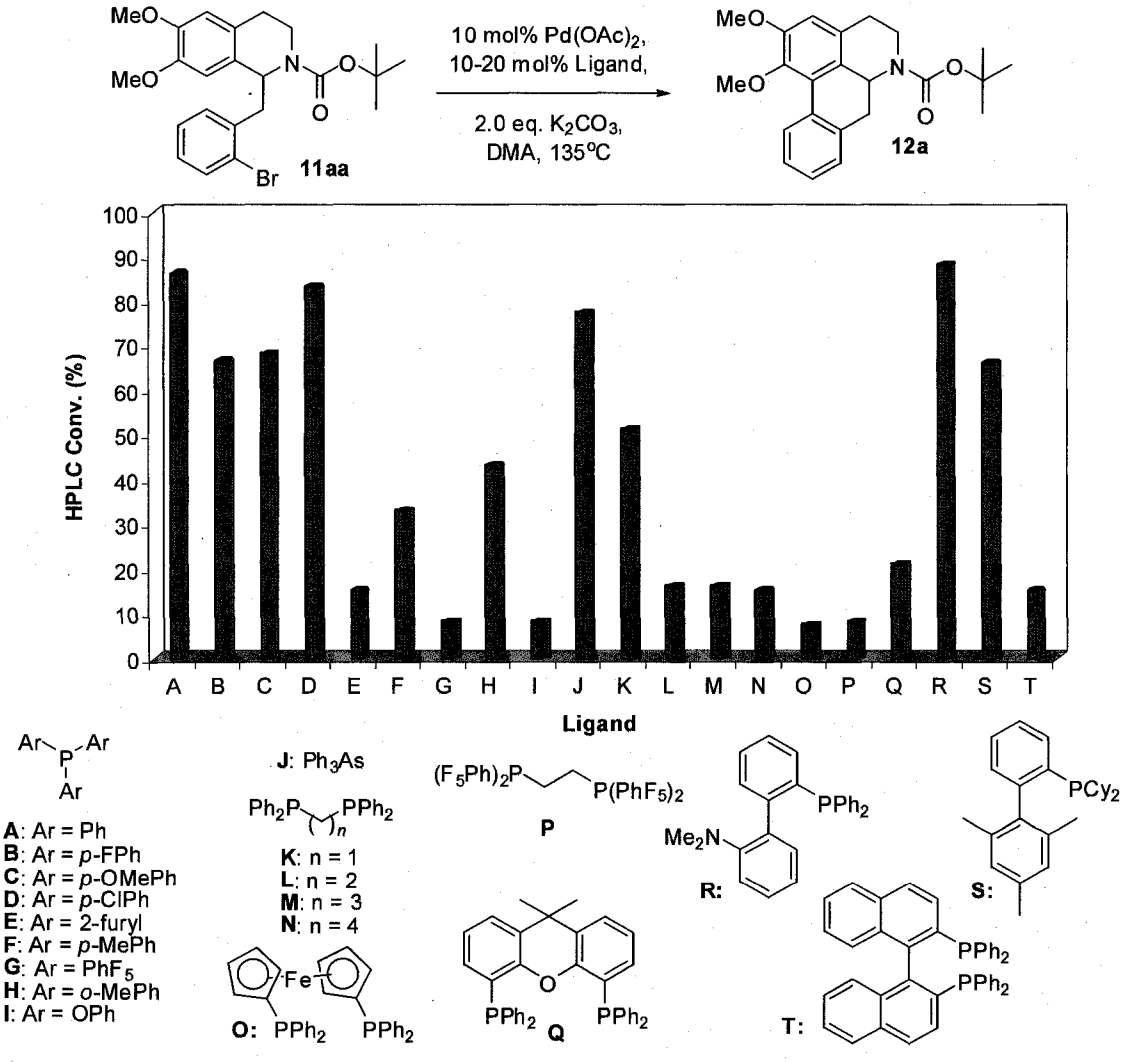
Scheme 5. 9. Preparation of the Starting Material.



Reagents and Conditions. (i) $(COCl)_2$, CH_2Cl_2; (ii) $ArCH_2CH_2NH_2$, Et_3N, CH_2Cl_2, two steps >95%; (iii) $POCl_3$, CH_2Cl_2, reflux, 99%; (iv) polyphosphoric acid, 150°C, 90%; (v) $NaBH_4$, MeOH, 99%; (vi) $(ROC)_2O$, DMAP (cat.), $^iPr_2EtN$, yield indicated.

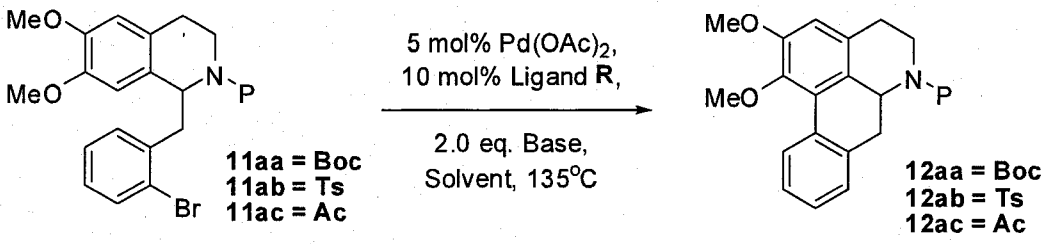
Initial screening began from our previously reported conditions.[197a] Using isoquinoline **11aa**, the influence of the ligand was investigated (Table 5.1). 20 Mol% of monodentate triarylphosphines (**A-H**) were found to be suitable ligands for this transformation giving the product in good to excellent yield. When employing 10 mol% of different bidentate ligands (**J-Q, T**), poor conversion to the cyclic product was observed. Buchwald biaryl type ligand **R** was found to be a superior ligand giving the product in 88% conversion. We therefore decided to continue our optimization using **R** as the optimal ligand.

Table 5. 1. Ligand Screening.



With the optimal ligand in hand, the influences of the solvent as well as the base were investigated (Table 5.2). The optimal solvent was found to be *N,N*-dimethylacetamide (DMA). Less polar solvents including mesitylene, acetonitrile and dioxane gave poor outcomes. A variety of bases were also screened. Optimal results were obtained with K_2CO_3, KOAc and Cs_2CO_3. Organic bases such as diisopropylethylamine and DBU were incompatible.

Table 5. 2. Solvent and Base Effects on the Direct Arylation Reaction.



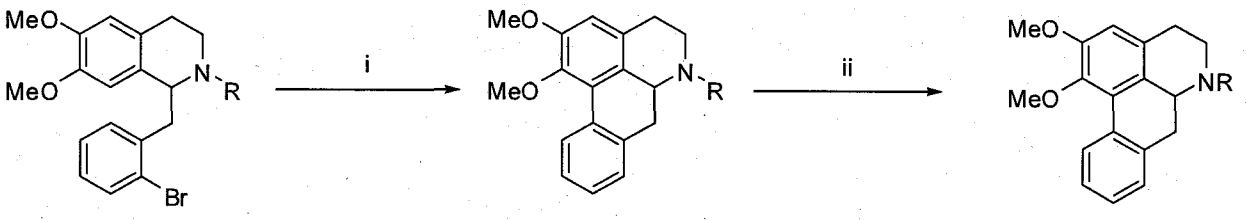
Entry	Protecting Group	Solvent	Base	% Conv.[a] (Yield)[b]
1	Boc	DMA	K_2CO_3	>95% (87%)
2	Boc	DMA	KOAc	>95% (90%)
3	Boc	DMA	Na_2CO_3	17
4	Boc	DMA	Cs_2CO_3	>95
5	Boc	DMA	$^iPr_2NEt$	<5
6	Boc	DMA	DBU	<5
7	Boc	DMF	KOAc	54
8	Boc	DMSO	KOAc	51
9	Boc	Mesitylene	KOAc	5
10	Boc	MeCN[c]	KOAc	<5
11	Boc	Dioxane[c]	KOAc	<5
12	Ts	DMA	KOAc	(97)
13	Ac	DMA	KOAc	(99)

[a] As determined by crude ^{1}H NMR. [b] Isolated yield. [c] Heated to reflux.

Under optimal conditions, reaction of **11aa** with only 3 mol % $Pd(OAc)_2$, 6 mol % 2-(diphenylphosphino)-2'-(*N,N*-dimethylamino)-biphenyl **R**, 2 equivalents KOAc in *N,N*-dimethylacetamide (DMA) at 130°C gives aporphine **12aa** in greater than 90% isolated yield (Scheme 5.10). Importantly, no dehalogenated byproduct is observed which is a common side reaction associated with these processes. The *N*-protecting group of **11** can be varied without any appreciable difference in reaction outcome. For example, *N*-

acetyl **11ab** reacts to give the natural product *N*-acetylnuciferine in quantitative yield. The *N*-toluenesulfonyl substrate **11ac** also reacts well, giving **12ac** in 99% isolated yield. Aporphine **12ab** can be easily deprotected and transformed to Nuciferine **2** according to known literature procedures.[180c]

Scheme 5. 10. Synthesis of Aporphine Alkaloids.



R = CO_2tBu, **11aa**
R = $COCH_3$, **11ab**
R = $SO_2C_6H_4CH_3$, **11ac**

R = CO_2tBu, **12aa**
R = $COCH_3$, **12ab** (*N*-acetylnornuciferine)
R = $SO_2C_6H_4CH_3$, **12ac**

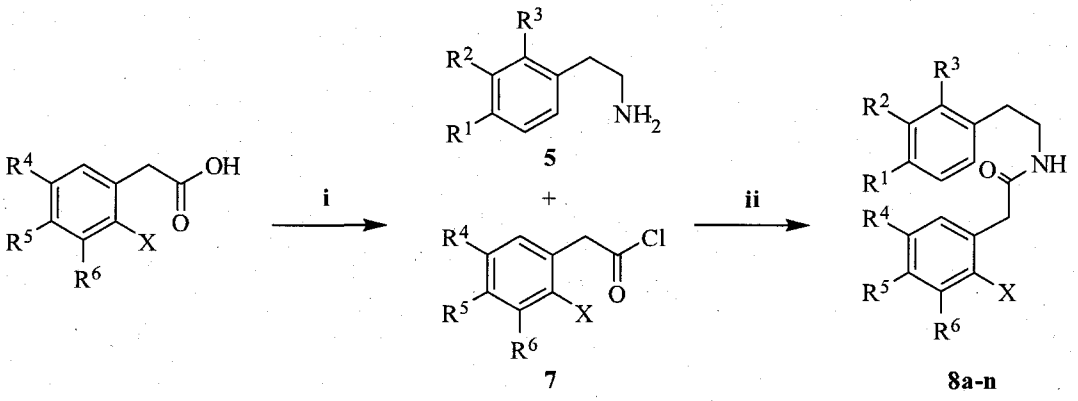
R = H; nornuciferine
R = Me; nuciferine **2**

Reagents and Conditions. (i) See Table 5.1; **11aa-ac**, $Pd(OAc)_2$ (2-5mol%), ligand **R** (4-10 mol%), base (2 equiv.) dissolved in DMA and heated to 135°C; (ii) R = $COCH_3$: (reference 44)

5.2.3 – Reaction Scope and Development of a Second Generation Catalyst.

These results indicate that this approach should be useful in the preparation of a wide range of aporphines, possessing a diverse range of arene substituents. Using the same synthetic route, a total of 15 different amides (**8a–o**) were prepared by initial conversion of the carboxylic acids to the acyl chloride (**7**) by reaction with oxalyl chloride followed by treatment with the desired 2-phenylethylamine (**5**). These reactions occur in good to excellent yields, typically ranging from 72–99% yield (Table 5.3).

Table 5. 3. Synthesis of the Different Amide Precursors.[a]



Entry	R^1	R^2	R^3	R^4	R^5	R^6	X	Amide	Yield [%][b]
1	OMe	OMe	H	H	H	H	Br	**8a**	99%
2	OMe	OMe	H	OMe	H	H	Br	**8b**	99%
3	OMe	OMe	H	F	H	H	Br	**8c**	72%
4	OMe	OMe	H	-O-CH_2-O-		H	Br	**8d**	99%
5	OMe	OMe	H	H	-CH=CH-CH=CH-		Br	**8e**	76%
6	-O-CH_2-O-		H	H	H	H	Br	**8f**	91%
7	OMe	H	H	H	H	H	Br	**8g**	91%
8	H	OMe	H	H	H	H	Br	**8h**	80%
9	H	H	H	H	H	H	Br	**8i**	99%
10	H	H	H	H	H	H	I	**8j**	93%
11	H	H	H	H	H	H	Cl	**8k**	98%
12	H	-CH=CH-CH=CH-		H	H	H	Br	**8l**	79%
13	H	Me	H	H	H	H	Br	**8m**	82%
14	Cl	H	H	H	H	H	Br	**8n**	79%
15	H	F	H	H	H	H	Br	**8o**	56%

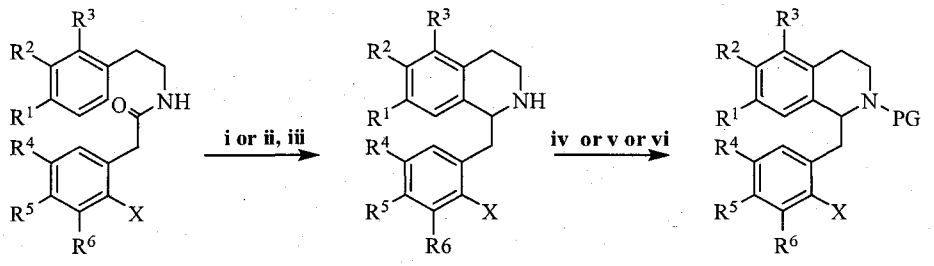
[a] Reagents and conditions: (i) $(COCl)_2$, CH_2Cl_2, 25°C, 1h; (ii) **7**, Et_3N, CH_2Cl_2 then **5**, 25°C, 12h. [b] Isolated yield.

With the necessary amides synthesized, reaction conditions for the Bischler-Napieralski cyclization were investigated (Table 5.4). The optimal conditions for the different amides (**8a–o**) were found to be substrate dependant. Treatment of the electron-rich substrates (**8a–f**), bearing two electron-donating groups on the aromatic ring, with phosphorous oxychloride in refluxing methylene chloride gave the corresponding Bischler-Napieralski products (**8a–f**) in good yields (entries 1 to 9). Amides (**8g–h**), which possess one electron-donating group on the aromatic ring could

be cyclized under similar conditions but required more elevated temperatures such as refluxing toluene and acetonitrile respectively (entries 10, 11). Unactivated amides (**8i–o**) did not react under either of these conditions. The difficulty of reacting unactivated arenes *via* Bischler-Napieralski cyclization has been previously reported.[196,198] Fortunately, we found that more forcing conditions, such as treatment with polyphosphoric acid at 150°C for 4 to 48 hours, gave the desired isoquinoline products (**8i–n**) in moderate to good yields (entries 12 to 18). Longer reaction time (48h) was required for **8n**. Unfortunately, all our attempts (150-200 °C) in reacting amide **8o** resulted in recovery of the starting material or decomposition of the starting material. The dihydroisoquinoline compounds (**9a–n**) proved to be unstable and were therefore reduced immediately using $NaBH_4$ in methanol to give the tetrahydroisoquinolines (**10a–n**) in 54–98% yields over two chemical steps. The amines were then protected as *tert*-butylcarbamates (Boc), methylcarbamates as well as acetates (Ac) in 57–88% yields (Table 5.4). Due to the presence of reliable high yields and the greater ease of deprotecting the *N*-Boc group subsequent to direct arylation, it was employed as the standard nitrogen protecting group in scope investigation.

[198] Martin, N. H.; Jefford, C.W. *Helv. Chim. Acta.* **1982**, *65*, 762.

Table 5. 4. Synthesis of Different Isoquinoline Cyclization Precursors.[a]



8a–n **10a–n** **11a–n**

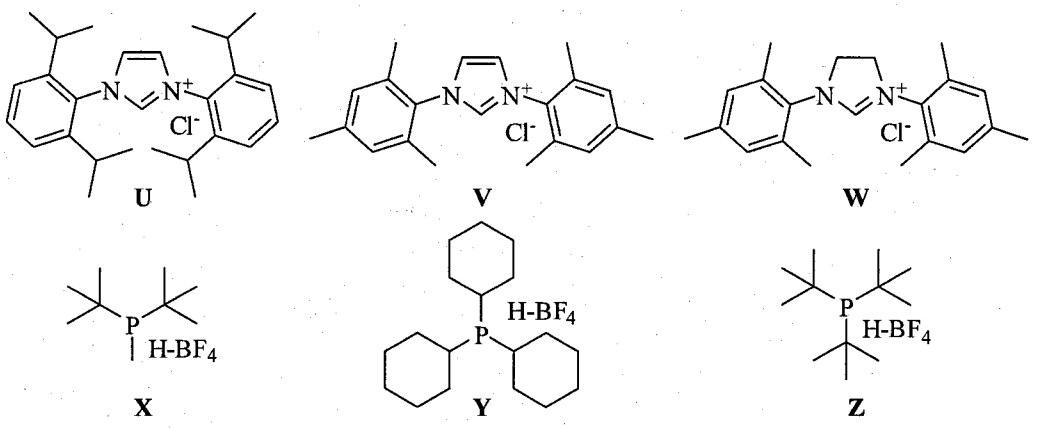
Entry	R¹	R²	R³	R⁴	R⁵	R⁶	X	Method	Product	Yield [%][b] 10a–n	PG	Product	Yield [%][c] 11a–n
1	OMe	OMe	H	H	H	H	Br	A	10a	99%	Boc	11aa	80%
2											CO_2Me	11ad	84%
3	OMe	OMe	H	OMe	H	H	Br	A	10b	68%	Boc	11b	77%
4	OMe	OMe	H	F	H	H	Br	A	10c	75%	Boc	11c	65%
5	OMe	OMe	H	-O-CH_2-O-		H	Br	A	10d	90%	Boc	11d	71%
6	OMe	OMe	H	H	-CH=CH-CH=CH-		Br	A	10e	79%	Boc	11e	87%
7	-O-CH_2-O-		H	H	H	H	Br	A	10f	54%	Boc	11f	70%
8	OMe	H		H	H	H	Br	A[d]	10g	88%	Boc	11g	86%
9	H	OMe	H	H	H	H	Br	A[e]	10h	73%	Boc	11h	57%
10	H	H	H	H	H	H	Br	B	10i	89%	Boc	11ia	88%
11											Ac	11ib	81%
12	H	H	H	H	H	H	I	B	10j	83%	Boc	11j	82%
13	H	H	H	H	H	H	Cl	B	10k	77%	Boc	11k	75%
14	H	-CH=CH-CH=CH-		H	H	H	Br	B	10l	68%	Boc	11l	67%
15	H	Me	H	H	H	H	Br	B	10m	85%	Boc	11m	82%
16	H	Cl	H	H	H	H	Br	B[f]	10n	98%	Boc	11n	69%

[a] Reagents and conditions: (i) Method A: $POCl_3$, CH_2Cl_2, reflux, 12h; (ii) Method B: Polyphosphoric acid, 150°C, 12h; (iii) $NaBH_4$, MeOH, 25°C, 3h; (iv) $(ROC)_2O$, DMAP (cat.), $^iPr_2EtN$, CH_2Cl_2; (v) pyridine, TsCl, CH_2Cl_2; (vi) Acetic anhydride, DMAP (cat.), $^iPr_2EtN$, CH_2Cl_2. [b] Isolated yield over 2 chemical steps. [c] Isolated yield. [d] Reaction performed in refluxing toluene. [e] Reaction performed in acetonitrile. [f] Reaction was heated for 48h. PG = protecting group.

With 18 cyclization precursors in hand (**11aa-11n**), we turned to the key direct arylation carbon-carbon bond forming step. In our initial report, we described the use of 2-(diphenylphosphino)-2'-(*N*,*N*-dimethylamino)-biphenyl ligand **R** for the synthesis of the aporphine core. Using our previous conditions, we discovered that this particular catalyst system was unable to achieve completion when employing less than 3 mol% catalyst loading with aryl bromides (entry 2) and failed to induce arylation using aryl chlorides. These limitations prompted us to search for a more reactive catalyst. In 2005, our group reported a new catalyst system for the intramolecular direct arylation using

aryl chlorides.[199] All attempts of cyclizing **11aa** using these carbene base catalysts led to incomplete conversions. The failure of this system is probably due to the large size of these ligands (Figure 5.3, **U-W**). Trialkylphosphines were also shown to generate highly active catalysts for these types of transformation with aryl chlorides.[197b] Different trialkylphosphines were therefore tested (Figure 5.3, **X-Z**). Gratifyingly, when **11aa** was reacted with 1 mol% $Pd(OAc)_2$, 2 mol% di-*tert*-butylmethylphosphine (added as the air-stable HBF_4 salt),[200] 2 equivalents of K_2CO_3 in DMA (0.2M) at 130°C gave the aporphine **12aa** in 88% yield (entry 3). Under both our initial and new conditions, no dehalogenated by-product is observed, being a common side reaction associated to these processes. During the assessment of substrate scope, 5 mol% catalyst loading was typically employed for convenience of scale.

Figure 5. 4. Ligands Re-Evaluation for Direct Arylation.

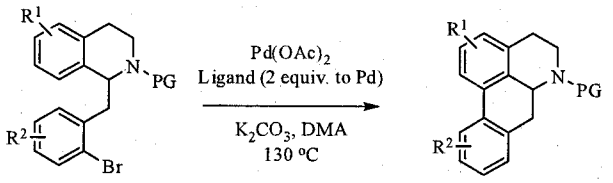


The different *N*-protecting groups were again found to be variably compatible with the reaction conditions (Table 5.5). The *N*-acetyl isoquinolines **11ab** and **11ib** both reacted to give the aporphines in high yields (entries 5 and 16). Conversely, use of the slightly more labile *N*-Boc and *N*-methylcarbamate isoquinolines **11aa**, and **11ad** resulted in yields of 80% and 58% respectively (entries 1-4, 7). In addition to arylbromides, arylchlorides and aryliodides are also compatible (entries 17 and 18). In accord with our previous studies,[197] the use of silver carbonate as an additive was required for the reaction using an aryl iodide (entry 18). Deactivated aryl bromides can

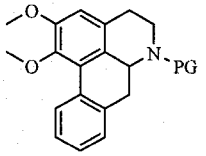
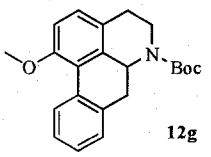
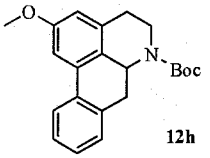
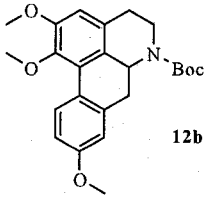
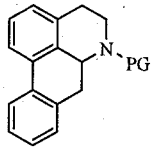
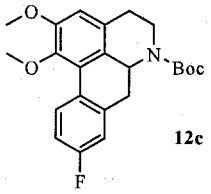
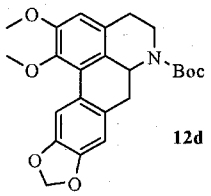
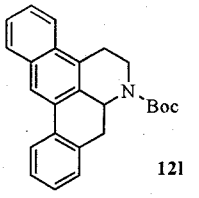
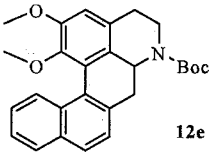
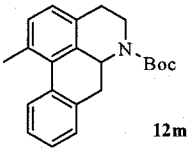
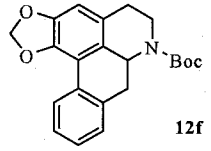
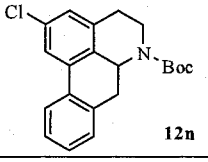
[199] Campeau, L.-C.; Thansandote, P.; Fagnou, K. *Org. Lett.* **2005**, *7*, 1857.
[200] Netherton, M. R.; Fu, G. C. *Org. Lett,* **2001**, *3*, 4295.

be used without any negative impact (entries 8 and 10) as can electron deficient aryl bromides (entry 9). Sterically hindered bromides can also be employed to generate a tetra-substituted aporphine in 86% yield (entry 11). Ring A can be an electron rich (entries 12–14) or electron neutral arene (entries 19 and 20) to give the aporphine in excellent yield. Direct arylation of an isoquinoline bearing both chloride and bromide functionalities was also achieved in 86% yield using 2-(diphenylphosphino)-2'-(*N*,*N*-dimethylamino)-biphenyl as the ligand (entry 21). This ligand does not interact with the aryl chloride functionality under the reaction conditions leaving it untouched for subsequent elaboration.

Table 5. 5. Formation of the Aporphine Core *via* Direct Arylation.[a]



11a–n **12a–l**

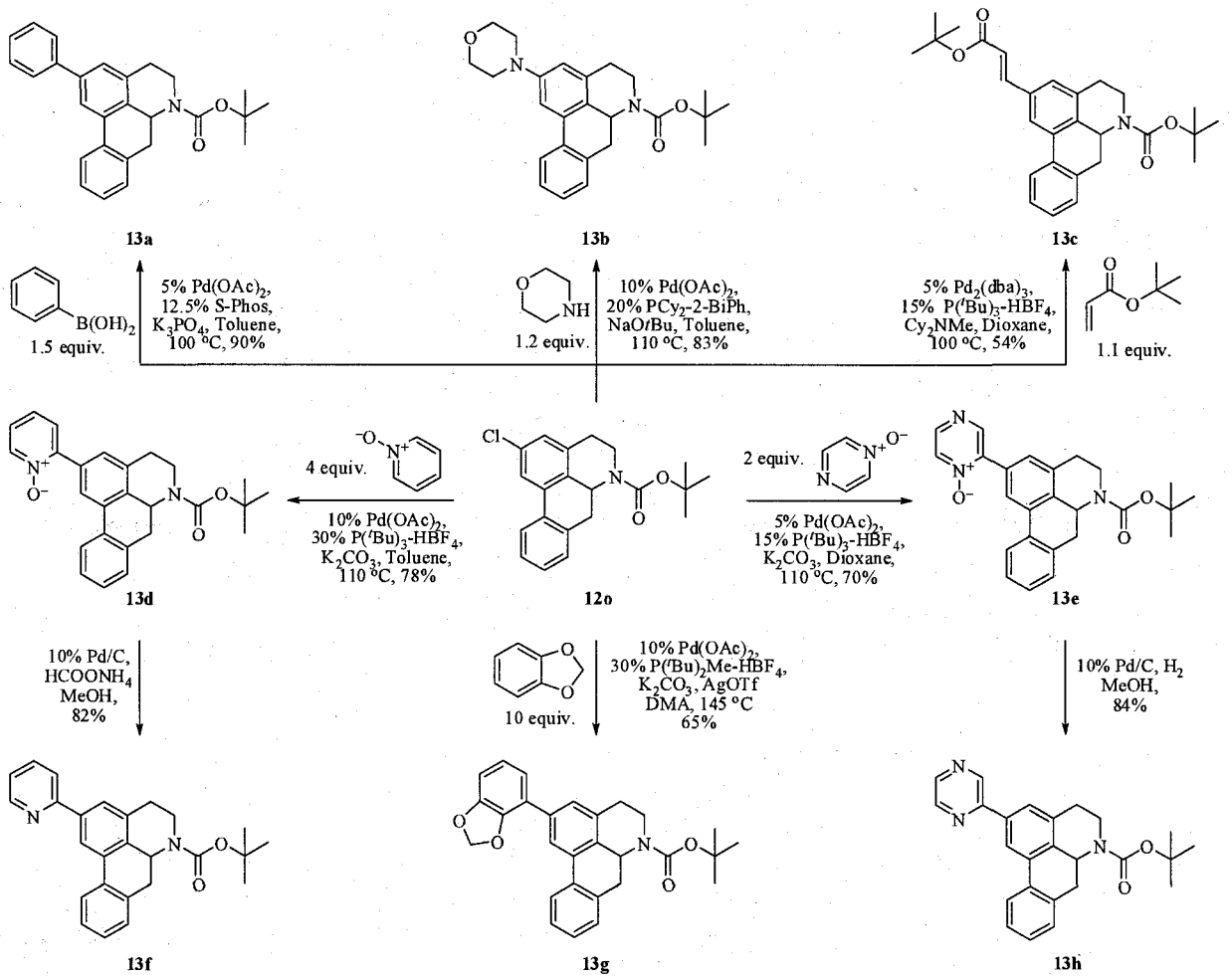
Entry	Product	Ligand	mol% Pd	Yield[b]	Entry	Product	Ligand	mol% Pd	Yield[b]
					13	 **12g**	R	5	99
1	PG = Boc	R	5	87					
2	PG = Boc	R	1	80					
3	PG = Boc	X	1	88					
4	PG = Boc **12aa**	Z	1	79	14	 **12h**	R	5	99
5	PG = Ac **12ab**	R	5	99					
6	PG = Ts **12ac**	R	5	99					
7	PG = CO_2Me **12ad**	R	5	58					
8	 **12b**	X	5	99					
9	 **12c**	R	5	99	15	PG = Boc **12ia**	R	5	88
					16	PG = Ac **12ib**	R	5	81
					17[c]	PG = Boc **12ia**	X	5	98
					18[d]	PG = Boc **12ia**	X	5	78
10	 **12d**	R	5	99	19	 **12l**	X	5	92
11	 **12e**	R	5	86	20	 **12m**	R	5	99
12	 **12f**	X	5	99	21	 **12n**	R	5	86

[a] Reaction Conditions: isoquinoline **11a-n**, $Pd(OAc)_2$, ligand (2 equiv. to Pd), K_2CO_3 (2 equiv.), DMA (0.2 M). [b] Isolated yield. [c] Using aryl chloride as a substrate. [d] Using aryl iodide as a substrate and 0.5 equiv. of Ag_2CO_3 was added as an additive. PG = protecting group.

Inspired by the SAR studies that pointed to the importance of C2 substituents,[170] aryl chloride **12o** was derivatized *via* different cross-coupling reactions (Scheme 5.11). Introduction of a phenyl substituent via Suzuki-Miyaura coupling gave **13a** in 90% yield.[201] Buchwald-Hartwig amination was also achieved with morpholine to give analogue **13b** in 83% yield.[202] A vinyl group could also be installed using conditions developed by Fu for aryl chlorides to give **13c** in 54% yield.[203] In addition to the established cross-coupling process, we also evaluated the use of direct arylation as a means of enabling divergent synthesis. For example, direct arylation of pyridine and pyrazine *N*-oxides at C2 was achieved using conditions developed in our laboratories[204] followed by subsequent reduction of the *N*-oxides to give **13f** and **13h** in 64% and 59% over the 2 steps. Direct intermolecular arylation of benzodioxole can also be achieved to give rise to **13g** in 65% yield. These results validate the role of direct arylation for the preparation of analogues in medicinal chemistry.

[201] Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem. Int. Ed.*, **2004**, *43*, 1871.
[202] Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.*, **2000**, *65*, 1158.
[203] Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.*, **2001**, *123*, 6989.
[204] (*a*) Campeau, L.-C.; Rousseaux, S.; Fagnou, K. *J. Am. Chem. Soc.* **2005**, *127*, 18020. (*b*) Leclerc, J.-P.; Fagnou, K. *Angew. Chem. Int. Ed.*, **2006**, *45*, 7781.

Scheme 5. 11. Formation of C2 Aporphine Analogues Through Various Cross-Coupling Reactions.

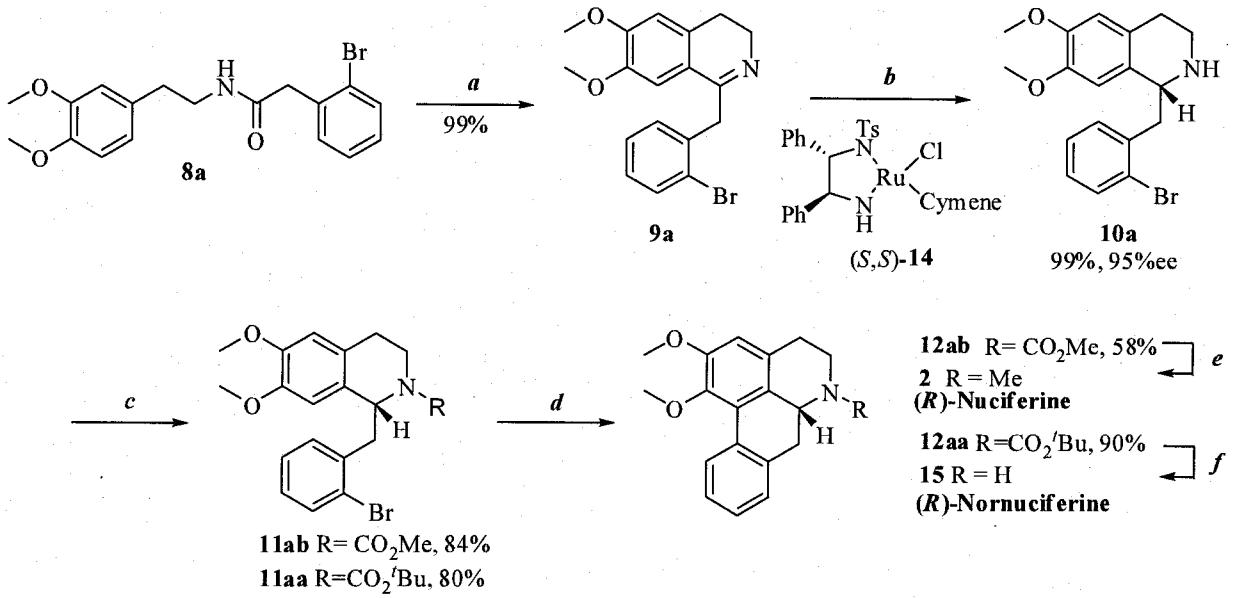


The direct arylation methodology was also employed in the enantioselective syntheses of (*R*)-Nornuciferine and (*R*)-Nuciferine alkaloids (Scheme 5.12). We were gratified to find that Bischler-Napieralski cyclization of the amide **8a** followed by a catalytic asymmetric transfer hydrogenation of the newly generated imine **9a** using Noyori's ruthenium based catalyst provides **10a** in 99% yield and 95% ee.[205] Immediate protection as the methyl and *tert*-butyl carbamates to give **11ab** and **11aa** was achieved by treatment with the corresponding carbamate anhydrides and direct arylation using standard conditions gave **12ab** in 58% and **12aa** in 90% yields. Reduction of the methyl carbamate of **12ab** with lithium aluminum hydride gave the natural product (*R*)-

[205] Tietze, L. F.; Rackelmann, N.; Sekar, G. *Angew. Chem. Int. Ed.*, **2003**, *42*, 4254.

Nuciferine in 42% overall yield and 95% ee. Finally, deprotection of the *tert*-butyl carbamate group of **12aa** under acidic conditions gave (*R*)-Nornuciferine in 37% overall yield and 95% ee. The low yield of 53% for the last step is probably due to the instability of the aporphine core to strongly acidic conditions resulting in some decomposition.[195,206]

Scheme 5. 12. Enantioselective Synthesis of (*R*)-Nornuciferine and (*R*)-Nuciferine.



[a] Reaction Conditions: (a) $POCl_3$, DCM, reflux; (b) (*S,S*)-**14** (5 mol%), HCO_2H/NEt_3, DMF, rt, 60min, 99% over 2 steps, 95% ee; (c) $(ROC)_2O$, DMAP (cat.), $^iPr_2EtN$, yield indicated; (d) $Pd(OAc)_2$ (5 mol%), 2-(diphenylphosphino)-2'-(*N,N*-dimethylamino)-biphenyl (10 mol%), KOAc (2.0 equiv.), DMA, 130°C, 4h, yield indicated; (e) LAH, THF, 0°C to rt, 24h, 88%; (f) trifluoroacetic acid (13 equiv.), DCM, rt, 1h, 53%.

In conclusion, a wide range of aporphine compounds, including C2 analogues, can be efficiently prepared by making use of direct arylation for both the key carbon-carbon biaryl bond forming and C2 diversification steps. These reactions can be performed with aryl chlorides, bromides and iodides with 1 to 5 mol% catalyst. These syntheses highlight the utility of the direct arylation methodology both in target oriented synthesis as well as a tool for the introduction of diversity in medicinal compounds. We have also achieved an enantioselective synthesis of the (*R*)-Nornuciferine in 37% overall yield and (*R*)-Nuciferine in 42% yield.

[206] *a*) C.-M. Chiou, J.-J. Kang, S.-S. Lee, *J. Nat. Prod.*, **1998**, *61*, 46. (*b*) L. Castedo, A. R. de Lera, J. M. Saa, R. Suau, C. Villaverde, *Heterocycles*, **1980**, *14*, 1135.

Chapter 6

Experimental Information

6.1 Organization:

The experimental section has been organized to coincide with the body of this thesis. Experimental procedure for all new compounds, as well as those for which were modified from literature are included. All spectral data (^{1}H, ^{13}C, ^{19}F NMR, IR, Rf, HRMS, MP and $[\alpha]^{25}_{D}$) are included for all newly reported compounds. References and CAS number for all known compounds for which their synthesis were done from literature precedents are found within this section where the chemistry is described and are not repeated herein.

6.2 General Experimental

All experiments were carried out under an atmosphere of argon. ^{1}H, ^{19}F and ^{13}C NMR were recorded in $CDCl_3$, $(CD_3)_2O$ or $(CD_3)_2SO$ solutions using a Bruker AVANCE 300, 400 or 500 spectrometer or Varian INOVA 500 spectrometer with Me_4Si as an internal standard for $CDCl_3$ solutions. Trifluorotoluene (δ = -67.73 ppm) was employed as an external standard in ^{19}F NMR spectra (D1 = 20 seconds). 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 and isopropyl acetate were degassed with Argon before every use. Phosphonium salts were synthesized according to literature procedures[207] or purchased from Strem, stored in a dessicator and used without further purification. Palladium was stored in a dessicator and was weighed out to air unless otherwise specified. Ligands are stored in a glove-box but were weighed to air. All other reagents and solvents were used as is from commercial sources unless noted below. Unless otherwise stated, reactions were performed on 100-200mg scale.

6.3 Experimental Data for Section 2: Intermolecular Direct Arylation of Perfluoroarenes

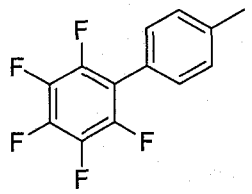
6.3.1 Direct Arylation of Perfluoroarenes: First Generation Catalyst

6.3.1.1 General Procedure for the Direct Arylation of Perfluoroarenes

General Procedure: K_2CO_3 (1.1 equiv.), $P^tBu_2Me{\cdot}HBF_4$ (0.10 equiv.), $Pd(OAc)_2$ (0.05 equiv.) were weighed to air and placed in a Schlenk tube (15 ml) or screw capped vial (2mL) with a magnetic stir bar (if the aryl halide is a solid, it is also added). The reaction vessel was evacuated and backfilled with argon (x3). The aryl halide (1 equiv.), the fluoroarene (1.5 eq.) and DMA (an equal volume to the amount of added fluoroarene) were then added via syringe and the reaction was heated to 120 °C for 4-12 hours. Upon completion, the reaction was then cooled to room temperature and purified by loading the crude reaction mixture directly onto a silica gel packed flash chromatography column typically using hexane or pentane/ether mixtures as the eluent.

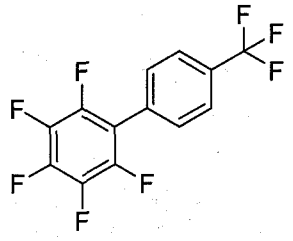
[207] Netherton, M.R.; Fu, G.C. *Org. Lett.* **2001**, *3*, 4295.

4'-Methyl-2,3,4,5,6-pentafluoro-1,1'-biphenyl



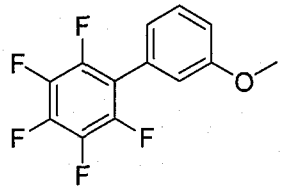
The compound was prepared following the general procedure and exhibited the same spectral data as previously reported[208] (98%). ^{1}H NMR (400MHz, $CDCl_3$, 293K, TMS): 2.42 (3H, s), 7.31 (4H, s).

4'-Trifluoromethyl-2,3,4,5,6-pentafluoro-1,1'-biphenyl



The compound was prepared following the general procedure and exhibited the same spectral data as previously reported[208] (89%). ^{1}H NMR (400MHz, $CDCl_3$, 293K, TMS): 7.54-7.57 (2H, m), 7.74-7.77 (2H, m).

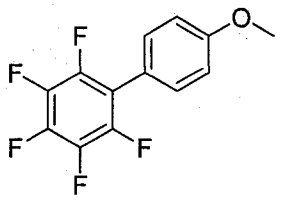
3'-Methoxy-2,3,4,5,6-pentafluoro-1,1'-biphenyl



The compound was prepared following the general procedure and exhibited the same spectral data as previously reported[208] (85%). ^{1}H NMR (400MHz, $CDCl_3$, 293K, TMS): 3.84 (3H, s), 6.93 (1H, m), 6.96-7.01 (2H, m), 7.40 (1H, m).

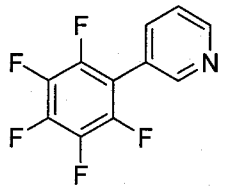
[208] Korenaga, T.; Kosaki, T.; Fukumura, R.; Ema, T.; Sakai, T. *Org. Lett.*, **2005**, *7*, 4915.

4'-Methoxy-2,3,4,5,6-pentafluoro-1,1'-biphenyl



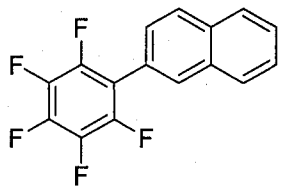
The compound was prepared following the general procedure and exhibited the same spectral data as previously reported[208] (76%). ^{1}H NMR (400MHz, $CDCl_3$, 293K, TMS): 3.86 (3H, s), 6.99-7.03 (2H, m), 7.33-7.37 (2H, m).

3-Pentafluorophenyl-pyridine



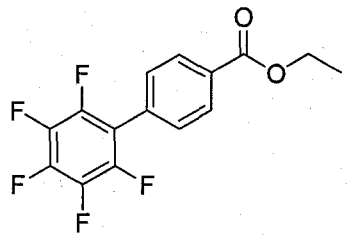
The compound was prepared following the general procedure (78%): mp = 59-60 °C ($CHCl_3$); R_f = 0.17 (SiO_2, 30% Et_2O/hexane); IR (ν_{max} /cm^{-1}): 2929, 1490, 1485, 984; ^{1}H NMR (400MHz, $CDCl_3$, 293K, TMS): 7.38-7.41 (1H, m), 7.71-7.73 (1H, m), 8.63-65 (2H, m); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 112.6-113.0 (m), 123.2, 123.7, 137.6, 138.1 (dm, J_F = 253.5Hz), 141.1 (dm, J_F = 255.5Hz), 144.4 (dm, J_F = 249.0Hz), 150.5, 150.6; ^{19}F NMR (377MHz, $CDCl_3$, 293K, TMS): -148.0 (2F, dd, J_F = 22.6, 8.6Hz), -158.7 (1F, t, J_F = 20.6Hz), -166.4 (2F, ddd, J_F = 21.8, 21.8, 7.7Hz); HRMS calcd for $C_{11}H_4F_5N$ (M+) 245.0264; found: 245.0278.

2-Perfluoronaphtalene



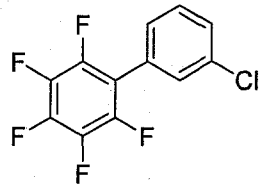
The compound was prepared following the general procedure and exhibited the same spectral data as previously reported[208] (91%). ^{1}H NMR (400MHz, $CDCl_3$, 293K, TMS): 7.47-7.59 (3H, m), 7.87-7.96 (4H, m).

4'-Ethylester-2,3,4,5,6-pentafluoro-1,1'-biphenyl



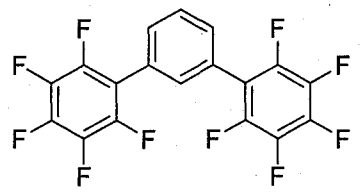
The compound was prepared following the general procedure and exhibited the same spectral data as previously reported[208] (83%). ^{1}H NMR (400MHz, $CDCl_3$, 293K, TMS): 1.42 (3H, t, *J*= 7.2 Hz), 4.42 (2H, q, *J*= 7.2 Hz), 7.50-7.53 (2H, m), 8.15-8.18 (2H, m).

3'-Chloro-2,3,4,5,6-pentafluoro-1,1'-biphenyl



The compound was prepared following the general procedure and exhibited the same spectral data as previously reported[209] (96%). ^{1}H NMR (400MHz, $CDCl_3$, 293K, TMS): 7.31 (1H, d, *J*= 6.7 Hz), 7.43 (1H, d, *J*= 6.7 Hz), 7.44 (1H, t, *J*= 6.7 Hz), 7.47 (1H, s).

1,3-Dipentafluorophenylbenzene

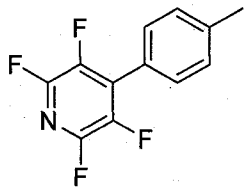


The compound was prepared following the general procedure using 3 eq. of fluoroarene and 2.2 eq. of K_2CO_3 (76%): mp = 99-100 °C ($CHCl_3$); R_f = 0.30 (SiO_2, pentane); IR (ν_{max} /cm^{-1}): 2929, 1528, 1500, 988; ^{1}H NMR (400MHz, $CDCl_3$, 293K, TMS): 7.53-7.56 (3H, m), 7.62-7.66 (1H, m); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 115.0-115.4 (m), 127.3, 129.4, 131.2, 132.1, 138.2 (dm, J_F = 253.8Hz), 141.1 (dm, J_F = 256.3Hz), 144.4 (dm, J_F =

[209] Kamigata, N.; Yoshikawa, M.; Shimizu, T. *J. Fluorine Chem.*, **1998**, *87*, 91.

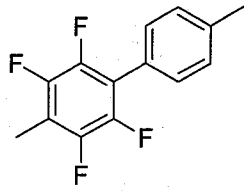
247.8Hz); ^{19}F NMR (377MHz, $CDCl_3$, 293K, TMS): -148.2 (2F, dd, J_F = 22.7, 8.2Hz), -159.8 (1F, t, J_F = 21.2Hz), -167.0 (2F, ddd, J_F = 21.7, 21.7, 8.2Hz); HRMS calcd for $C_{18}H_4F_{10}$ (M+) 410.0153; found: 410.0138.

2,3,5,6-Tetrafluoro-4-p-tolyl-pyridine



The compound was prepared following the general procedure (86%): mp = 97-98 °C ($CHCl_3$); R_f = 0.30 (SiO_2, hexane); IR (ν_{max} /cm^{-1}): 2927, 1644, 1457, 1405, 1152, 963, 947, 820; ^1H NMR (400MHz, $CDCl_3$, 293K, TMS): 2.43 (3H, s), 7.33 (2H, d, *J*=8.0Hz), 7.42 (2H, d, *J*=8.0Hz); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 21.5, 123.0, 129.6, 129.7, 133.4-133.8 (m), 139.3 (dm, J_F = 257.4Hz), 141.1, 144.1 (dm, J_F = 244.8Hz); ^{19}F NMR (377MHz, $CDCl_3$, 293K, TMS): -96.1--96.3 (2F, m), -150.3--150.5 (2F, m); HRMS calcd for $C_{12}H_7F_4N$ (M+) 241.0515; found: 241.0523.

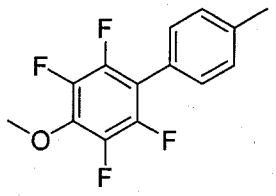
2,3,5,6-Tetrafluoro-4,4'-dimethyl-biphenyl



The compound was prepared following the general procedure using 1.1 eq. of fluoroarene (86%): mp = 67-68 °C ($CHCl_3$); R_f = 0.39 (SiO_2, hexane); IR (ν_{max} /cm^{-1}): 2926, 1475, 1064, 923, 817; ^1H NMR (400MHz, $CDCl_3$, 293K, TMS): 2.28 (3H, s), 2.39 (3H, s), 7.26 (2H, d, *J*=8.3Hz), 7.30 (2H, d, *J*=8.3Hz); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 7.4, 21.2, 114.5-114.9 (m), 117.8-118.1 (m), 124.7, 129.2, 130.0, 138.9, 143.6 (dm, J_F = 240.6Hz), 145.3 (dm, J_F = 240.6Hz); ^{19}F NMR (377MHz, $CDCl_3$, 293K, TMS): -

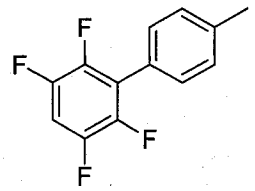
149.3 (2F, dd, J_F = 22.5, 12.8Hz), -150.7 (2F, dd, J_F = 22.5, 12.9Hz); HRMS calcd for $C_{14}H_{10}F_4$ (M+) 254.0719; found: 254.0723.

2,3,5,6-Tetrafluoro-4-methoxy-4'-methyl-biphenyl



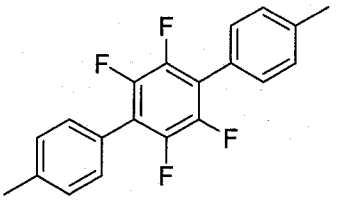
The compound was prepared following the general procedure using 1.1 eq. of fluoroarene in 92% yield: mp = 49-51 °C ($CHCl_3$); R_f = 0.18 (SiO_2, hexane); IR (ν_{max} /cm^{-1}): 2953, 1485, 1090, 981, 826; ^{1}H NMR (400MHz, $CDCl_3$, 293K, TMS): 2.39 (3H, m), 4.07 (3H, s), 7.25 (2H, d, *J*=8.2Hz), 7.30 (2H, d, *J*=8.2Hz); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 21.3, 62.1-62.2 (m), 114.2-114.6 (m), 124.4, 129.4, 130.1-130.2 (m), 137.2-137.5 (m), 139.0, 141.3 (dm, J_F = 247.3Hz), 144.4 (dm, J_F = 245.8Hz); ^{19}F NMR (377MHz, $CDCl_3$, 293K, TMS): -150.3 (2F, dd, J_F = 22.3, 8.7Hz), -163.4 (2F, dd, J_F = 22.3, 9.0Hz); HRMS calcd for $C_{14}H_{10}F_4O$ (M+) 270.0668; found: 270.0693.

2,3,5,6-Tetrafluoro-4'-methyl-biphenyl



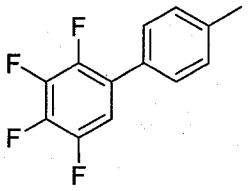
The compound was prepared following the general procedure using 3 eq. of 1,2,4,5-tetrafluorobenzene (79%): mp = 88-89 °C ($CHCl_3$); R_f = 0.26 (SiO_2, hexane); IR (ν_{max} /cm^{-1}): 2921, 1488, 1171, 927, 812, 770; ^{1}H NMR (400MHz, $CDCl_3$, 293K, TMS): 2.41 (3H, s), 6.98-7.07 (1H, m), 7.29 (2H, d, *J*=8.4Hz), 7.35 (2H, d, *J*= 8.4Hz); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 21.4, 104.3-104.8 (m), 121.4-121.7 (m), 124.5, 129.4, 130.0 (m), 139.3, 143.9 (dm, J_F = 251.5Hz), 146.2 (dm, J_F = 258.2Hz); ^{19}F NMR (377MHz, $CDCl_3$, 293K, TMS): -139.4 (2F, dd, J_F = 22.5, 13.0Hz), -144.0 (2F, dd, J_F = 22.2, 12.7Hz); HRMS calcd for $C_{13}H_8F_4$ (M+) 240.0562; found: 240.0541.

1,4-Di-(p-tolyl)-2,3,5,6-tetrafluorobenzene



The compound was obtained as the minor product in the 1,2,4,5-tetrafluorobenzene reaction (20%): mp = 210-212 °C ($CHCl_3$); R_f = 0.17 (SiO_2, hexane); IR (ν_{max} /cm^{-1}): 2961, 1454, 1159, 889; ^1H NMR (400MHz, $CDCl_3$, 293K, TMS): 2.43 (6H, s), 7.32 (4H, d, *J*=8.0Hz), 7.41 (4H, d, *J*= 8.0Hz); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 21.4, 124.6, 129.3, 130.0, 139.2. Since this was isolated as a minor product, insufficient sample was available to locate the C-F carbons in the ^{13}C NMR; ^{19}F NMR (377MHz, $CDCl_3$, 293K, TMS): -149.7 (4F, s); HRMS calcd for $C_{20}H_{14}F_4$ (M+) 330.1032; found: 330.1033.

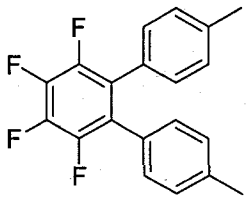
2,3,4,5-Tetrafluoro-4'-methyl-biphenyl



The compound was prepared following the general procedure using 1.1 eq. of 1,2,3,4-tetrafluorobenzene (68%): mp = 71-73 °C ($CHCl_3$); R_f = 0.36 (SiO_2, hexane); IR (ν_{max} /cm^{-1}): 2926, 1624, 1510, 1478, 1077, 988, 908; ^1H NMR (400MHz, $CDCl_3$, 293K, TMS): 2.38 (3H, s), 6.90-7.02 (1H, m), 7.23 (2H, d, *J*= 8.4Hz), 7.33 (2H, d, *J*=8.4Hz); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 21.2, 111.1-111.4 (m), 125.4-125.7 (m), 128.6-128.7 (m), 129.7, 130.3, 139.0, 139.6 (dm, J_F = 253.8Hz), 141.3 (dm, J_F = 252.3Hz), 145.0 (dm, J_F = 249.5Hz), 147.1 (dm, J_F = 245.0Hz); ^{19}F NMR (377MHz, $CDCl_3$, 293K, TMS): -144.9 (1F, ddd, J_F = 21.9, 13.6, 2.6Hz), -148.8--148.9 (1F, m), -160.5 (1F, ddd, J_F = 19.6, 19.6,

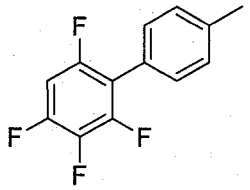
2.4Hz), -162.8 (1F, ddd, J_F = 20.0, 20.0, 3.0Hz); HRMS calcd for $C_{13}H_8F_4$ (M+) 240.0562; found: 240.0571.

1,2-Di-(p-tolyl)-3,4,5,6-tetrafluorobenzene



The compound was obtained as the minor product in the 1,2,3,4-tetrafluorobenzene reaction (10%): R_f = 0.21 (SiO_2, hexane); IR (ν_{max} /cm^{-1}): 2926, 1501, 1466, 1080, 1028, 820; ^1H NMR (400MHz, $CDCl_3$, 293K, TMS): 2.29 (6H, s), 6.92 (4H, d, J= 8.2Hz), 7.03 (4H, d, J=8.2Hz); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 21.2, 125.3-125.5 (m), 126.8, 128.8, 130.5, 137.7, 139.8 (dm, J_F = 250.7Hz), 144.9 (dm, J_F = 246.7Hz); ^{19}F NMR (377MHz, $CDCl_3$, 293K, TMS): -146.2--146.3 (2F, m), -162.5--162.7 (2F, m); HRMS calcd for $C_{20}H_{14}F_4$ (M+) 330.1032; found: 330.1028.

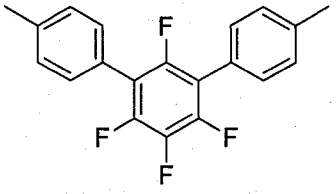
2,3,4,6-Tetrafluoro-4'-methyl-biphenyl



The compound was prepared following the general procedure using 3 eq. of 1,2,3,5-tetrafluorobenzene (75%): mp = 69-71 °C ($CHCl_3$); R_f = 0.44 (SiO_2, hexane); IR (ν_{max} /cm^{-1}): 2929, 1505, 1460, 1195, 1051, 1030, 817; ^1H NMR (400MHz, $CDCl_3$, 293K, TMS): 2.35 (3H, s), 6.70-6.78 (1H, m), 7.22 (2H, d, J= 8.4Hz), 7.27 (2H, d, J=8.4Hz); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 21.3, 100.7-101.3 (m), 116.1-116.5 (m), 124.7, 129.5, 130.2, 137.8 (dm, J_F = 247.9Hz), 139.1, 149.2 (dm, J_F = 247.9Hz), 149.9 (dm, J_F =

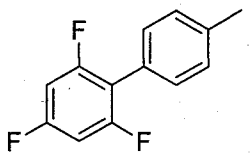
252.1Hz), 154.6 (dm, J_F = 246.7Hz); ^{19}F NMR (377MHz, $CDCl_3$, 293K, TMS): -123.1 (1F, d, J_F = 11.3Hz), -139.0 (1F, dd, J_F = 21.1, 5.2Hz), -140.6 (1F, ddd, J_F = 21.9, 5.5, 2.6Hz), -170.1 (1F, ddd, J_F = 21.1, 21.1, 11.0Hz); HRMS calcd for $C_{13}H_8F_4$ (M+) 240.0562; found: 240.0572.

1,3-Di-(p-tolyl)-2,4,5,6-tetrafluorobenzene



The compound was obtained as the minor product in the 1,2,3,5-tetrafluorobenzene reaction (24%): mp = 115-116°C ($CHCl_3$); R_f = 0.22 (SiO_2, hexane); IR (ν_{max} /cm^{-1}): 2927, 1477, 1055, 1038, 908, 815; ^{1}H NMR (400MHz, $CDCl_3$, 293K, TMS): 2.39 (6H, s), 7.26 (4H, d, J= 7.9Hz), 7.34 (4H, d, J=7.9Hz); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 21.3, 115.6-116.0 (m), 124.8, 129.3, 130.1, 137.8 (dm, J_F = 253.7Hz), 138.8, 147.5 (dm, J_F = 252.6Hz), 151.7 (dm, J_F = 245.0Hz); ^{19}F NMR (377MHz, $CDCl_3$, 293K, TMS): -127.5 (1F, d, J_F = 11.2Hz), -142.8 (1F, dd, J_F = 20.5, 2.7Hz), -169.7 (1F, ddd, J_F = 21.9, 23.2, 10.9Hz); HRMS calcd for $C_{20}H_{14}F_4$ (M+) 330.1032; found: 330.1043.

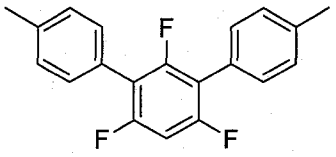
2,4,6-Trifluoro-4'-methyl-biphenyl



The compound was prepared following the general procedure using 3 eq. of 1,3,5-trifluorobenzene (69%): mp = 74-75°C ($CHCl_3$); R_f = 0.40 (SiO_2, hexane); IR (ν_{max} /cm^{-1}): 3036, 1636, 1596, 1439, 1027; ^{1}H NMR (400MHz, $CDCl_3$, 293K, TMS): 2.33 (3H, s), 6.60-6.69 (2H, m), 7.19 (2H, d, J= 8.1Hz), 7.28 (2H, d, J=8.1Hz); ^{13}C NMR (100MHz,

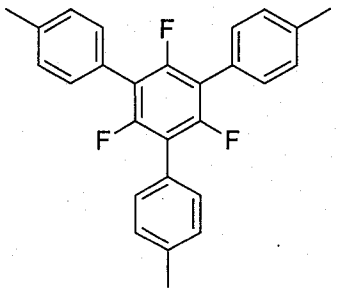
$CDCl_3$, 293K, TMS): 21.2, 100.2-100.7 (m), 115.0-115.4 (m), 125.5, 129.3, 130.2, 138.4, 160.5 (ddd, J_F = 249.4, 14.7, 10.3Hz), 161.8 (ddm, J_F = 248.0, 14.7Hz); ^{19}F NMR (377MHz, $CDCl_3$, 293K, TMS): -114.3 (1F, t, J_F = 6.1Hz), -116.1 (2F, d, J_F = 5.5Hz); HRMS calcd for $C_{13}H_9F_3$ (M+) 222.0656; found: 222.0650.

1,3-Di-(p-tolyl)-2,4,6-trifluorobenzene



The compound was obtained as the minor product in the 1,3,5-trifluorobenzene reaction (24%): mp = 84-85°C ($CHCl_3$); R_f = 0.16 (SiO_2, hexane); IR (ν_{max} /cm^{-1}): 2922, 1598, 1480, 1140, 1039; ^1H NMR (400MHz, $CDCl_3$, 293K, TMS): 2.38 (6H, s), 6.79-6.85 (1H, m), 7.25 (4H, d, J= 7.4Hz), 7.34 (4H, d, J=7.4Hz); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 21.3, 100.1-100.6 (m), 114.9-115.3, 125.6, 129.1, 131.2, 138.2, 157.3 (ddm, J_F = 247.9, 10.1Hz), 158.8 (ddd, J_F = 248.3, 16.0, 10.0Hz); ^{19}F NMR (377MHz, $CDCl_3$, 293K, TMS): -118.2 (2F, d, J_F = 6.9Hz), -120.0 (1F, d, J_F = 6.3Hz); HRMS calcd for $C_{20}H_{15}F_3$ (M+) 312.1126; found: 312.1102.

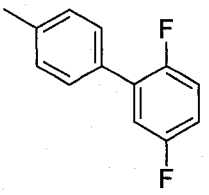
1,3,5-Tri-(p-tolyl)-2,4,6-trifluorobenzene



The compound was obtained as the minor product in the 1,3,5-trifluorobenzene reaction (2%): mp = 186-187°C ($CHCl_3$); R_f = 0.07 (SiO_2, hexane); IR (ν_{max} /cm^{-1}): 2930, 1607,

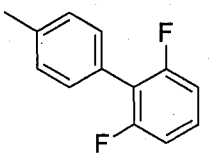
1435, 1039, 913; ^{1}H NMR (400MHz, $CDCl_3$, 293K, TMS): 2.41 (9H, s), 7.27 (6H, d, *J*= 7.8Hz), 7.39 (6H, d, *J*=7.8Hz); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 21.3, 125.9, 129.1, 130.3, 138.2. Since this was isolated as a minor product, insufficient sample was available to locate the C-F carbons in the ^{13}C NMR; ^{19}F NMR (377MHz, $CDCl_3$, 293K, TMS): -122.0 (3F, s); HRMS calcd for $C_{27}H_{21}F_3$ (M+) 402.1595; found: 402.1601.

2,5-Difluoro-4'-methyl-biphenyl



The compound was prepared following the general procedure using 10% $Pd(OAc)_2$, 20% $PtBu_2Me{\cdot}HBF_4$ and 3.0 eq. of fluoroarene (42%): R_f = 0.30 (SiO_2, hexane); IR (ν_{max} /cm^{-1}): 2917, 1490, 1241, 1180, 821, 763; ^{1}H NMR (400MHz, $CDCl_3$, 293K, TMS): 2.37 (3H, s), 6.90-6.96 (1H, m), 7.04-7.12 (2H, m), 7.24 (2H, d, *J*= 7.5Hz), 7.42 (2H, d, *J*=7.5Hz); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 21.2, 114.7-117.2 (m), 126.8, 128.7 (d, J_F = 2.9Hz), 129.3, 130.3-130.5 (m), 131.9, 138.1, 155.8 (dd, J_F = 243.5, 2.9Hz), 158.8 (dd, J_F = 242.1, 2.9Hz); ^{19}F NMR (377MHz, $CDCl_3$, 293K, TMS): -124.2 (1F, d, J_F = 18.1Hz), -129.1 (1F, d, J_F = 17.7Hz); HRMS calcd for $C_{13}H_{10}F_2$ (M+) 204.0751; found: 204.0741

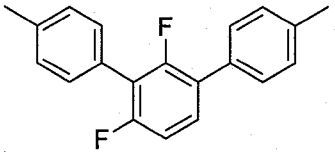
2,6-Difluoro-4'-methyl-biphenyl



The compound was prepared following the general procedure using 3.0 eq. of 1,3-difluorobenzene (85%): mp = 39-40°C ($CHCl_3$); R_f = 0.26 (SiO_2, hexane); IR (ν_{max} /cm^{-1}): 3036, 1591, 1459, 990; ^{1}H NMR (400MHz, $CDCl_3$, 293K, TMS): 2.37 (3H, s), 6.90-6.94

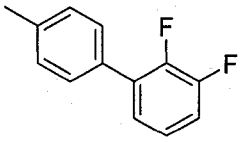
(2H, m), 7.15-7.21 (1H, m), 7.24 (2H, d, *J*= 7.7Hz), 7.35 (2H, d, *J*=8.2Hz); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 21.3, 111.4-111.7 (m), 118.6 (d, J_F = 19.1Hz), 126.2, 128.5 (t, J_F = 10.3Hz), 129.0, 130.2, 138.1, 160.2 (dd, J_F = 247.9, 7.3Hz); ^{19}F NMR (377MHz, $CDCl_3$, 293K, TMS): -119.4 (2F, s); HRMS calcd for $C_{13}H_{10}F_2$ (M+) 204.0751; found: 204.0728.

2,4-Di-(p-tolyl)-1,3-difluorobenzene



The compound was obtained as the minor product in the 1,3-difluorobenzene reaction (9%): R_f = 0.11 (SiO_2, hexane); IR (ν_{max} /cm^{-1}): 2923, 1589, 1478, 1087, 1001, 806; ^1H NMR (400MHz, $CDCl_3$, 293K, TMS): 2.40 (3H, s), 2.41 (3H, s), 7.03 (1H, ddd, *J*= 8.8, 8.8, 1.6Hz), 7.24-7.44 (9H, m); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 21.2, 21.3, 111.4-111.9 (m), 118.6-118.7 (m), 126.4, 128.9, 128.9, 129.0, 129.2, 129.4-129.5 (m), 130.2, 132.5, 137.5, 138.1. Since this was isolated as a minor product, insufficient sample was available to locate the C-F carbons in the ^{13}C NMR; ^{19}F NMR (377MHz, $CDCl_3$, 293K, TMS): -120.8 (1F, d, J_F = 7.6Hz), -123.0 (1F, d, J_F = 8.0Hz); HRMS calcd for $C_{20}H_{16}F_2$ (M+) 294.1220; found: 294.1248.

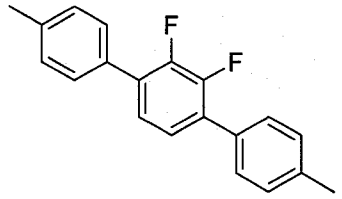
2,3-Difluoro-4'-methyl-biphenyl



The compound was prepared following the general procedure using 10% $Pd(OAc)_2$, 20% $PtBu_2Me{\cdot}HBF_4$ and 3.0 eq. of 1,2-difluorobenzene (29%): R_f = 0.20 (SiO_2, hexane); IR (ν_{max} /cm^{-1}): 2929, 1482, 1261, 1097, 894, 778; ^1H NMR (400MHz, $CDCl_3$, 293K, TMS):

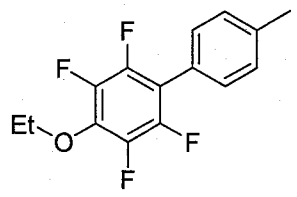
2.40 (3H, s), 7.08-7.19 (3H, m), 7.26 (2H, d, J= 8.3Hz), 7.43 (2H, dd, J=8.3, 1.5Hz); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 21.2, 115.7 (d, J_F = 17.6Hz), 125.2-125.3 (m), 126.8, 128.8 (d, J_F = 2.9Hz), 129.3, 131.3 (d, J_F = 10.3Hz), 131.8 (d, J_F = 3.2Hz), 138.1, 147.5 (dd, J_F = 247.9, 13.2Hz), 151.1 (dd, J_F = 247.9, 13.2Hz); ^{19}F NMR (377MHz, $CDCl_3$, 293K, TMS): -143.1 (1F, d, J_F = 20.4Hz), -148.8 (1F, d, J_F = 20.5Hz); HRMS calcd for $C_{13}H_{10}F_2$ (M+) 204.0751; found: 204.0763.

3,6-Di-(p-tolyl)-1,2-difluorobenzene



The compound was obtained as the minor product in the 1,2-difluorobenzene reaction (9%): R_f = 0.12 (SiO_2, hexane); IR (ν_{max} /cm^{-1}): 2918, 1483, 1455, 1398, 805; ^1H NMR (400MHz, $CDCl_3$, 293K, TMS): 2.42 (6H, s), 7.22-7.24 (2H, m), 7.28 (4H, d, J= 8.1Hz), 7.48 (4H, d, J=8.1Hz); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 21.3, 124.5, 126.8, 128.7, 129.3, 131.8, 138.1, 148.4 (d, J_F = 250.9Hz); ^{19}F NMR (377MHz, $CDCl_3$, 293K, TMS): -148.3 (1F, s); HRMS calcd for $C_{20}H_{16}F_2$ (M+) 294.1220; found: 294.1220.

2,3,5,6-Tetrafluoro-4-ethoxy-4'-methyl-biphenyl

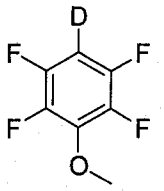


The compound was prepared following the general procedure using 1.1 eq. of fluoroarene (89%): mp = 77-78 °C ($CHCl_3$); R_f = 0.22 (SiO_2, hexane); IR (ν_{max} /cm^{-1}): 2986, 1483, 1403, 1083, 975, 824; ^1H NMR (400MHz, $CDCl_3$, 293K, TMS): 1.44 (3H, t,

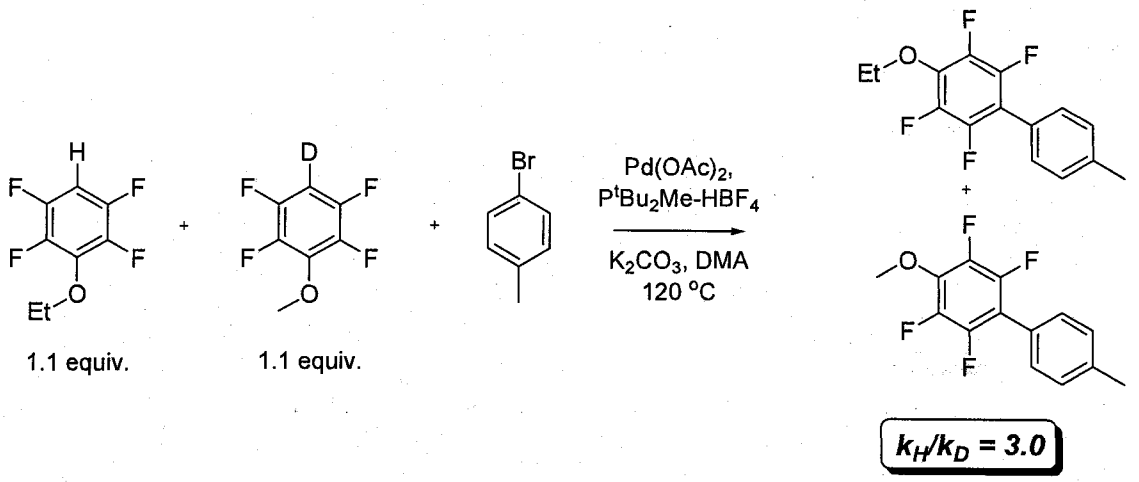
J=7.1Hz), 2.39 (3H, m), 4.31 (2H, d, *J*=7.1Hz), 7.26 (2H, d, *J*=7.9Hz), 7.31 (2H, d, *J*=7.9Hz); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 15.5, 21.2, 71.0-71.1 (m), 114.3-114.6 (m), 124.4, 129.4, 130.0-130.1 (m), 136.2-136.4 (m), 139.0, 140.4 (dm, J_F = 246.4Hz), 144.4 (dm, J_F = 244.9Hz); ^{19}F NMR (377MHz, $CDCl_3$, 293K, TMS): -150.4 (2F, dd, J_F = 22.1, 8.8Hz), -162.7 (2F, dd, J_F = 22.1, 8.5Hz); HRMS calcd for $C_{15}H_{12}F_4O$ (M+) 284.0824; found: 284.0833.

6.3.1.2 Procedure for Kinetic Isotope Effect Experiments

4-Deutero-2,3,5,6-tetrafluoroanisole



To a flame dried flask containing 2,3,5,6-tetrafluoroanisole (1g, 5.6 mmol, 1.0 eq.) was added dropwise *tert*-butyl lithium (1.4M in pentane, 5.8mmol, 1.05eq.) at -78°C. The solution was stirred for 5 mins and then quenched by addition of acetic acid-OD (0.7mL, 8.3 mmol, 1.5eq.). The resulting mixture was stirred for 5 mins and extracted using 5M NaOH solution and dried over magnesium sulfate to give the product in 99% yield. The product was then used without further purification. ^1H NMR (400MHz, $CDCl_3$, 293K, TMS): 4.09 (3H, s).



p-Bromotoluene (0.125g, 0.7 mmol, 1 eq.), K_2CO_3 (0.112g, 0.8 mmol, 1.1eq.), $P^tBu_2Me{\cdot}HBF_4$ (0.009g, 0.04 mmol, 0.05eq.), $Pd(OAc)_2$ (0.004g, 0.02 mmol, 0.025eq.) were weighed to air and placed in a screw capped vial (2mL) with a magnetic stir bar. The reaction vessel was evacuated and backfilled with argon (x3). The 4-deutero-2,3,5,6-tetrafluoroanisole (0.146g, 0.8 mmol, 1.1eq.), 3-ethoxy-1,2,4,5-tetrafluorobenzene (0.156g, 0.8 mmol, 1.1eq.) were then added via syringe as a stock solution in DMA (0.24mL). The mixture was then heated to 120°C for 2 minutes. The solution was then extracted and analyzed by GCMS.

Note: A control experiment of 2,3,5,6-tetrafluoroanisole with 3-ethoxy-1,2,4,5-tetrafluorobenzene in a 1:1 ratio resulted in a 1:1 ratio of product distribution at approximately 10 to 15% conversion.

6.3.1.3 General Procedure for the Competition Studies

General Procedure: *p*-Bromotoluene (1 eq.), K_2CO_3 (1.1eq.), $P^tBu_2Me{\cdot}HBF_4$ (0.1eq.), $Pd(OAc)_2$ (0.05eq.) were weighed to air and placed in a screw capped vial (2mL) with a magnetic stir bar. The reaction vessel was evacuated and backfilled with argon (x3). The perfluoroarenes (3.0eq. of each) were then added via syringe as a stock solution in DMA (0.24mL). The mixture was then heated to 120°C for 3 to 30 minutes. Reactions were allowed to reach 5 to 15% conversion and were then stopped. The solution was

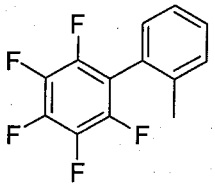
then extracted and analyzed by GCMS and ^{19}F NMR as a crude mixture to determine the product distribution.

6.3.2 Direct Arylation of Perfluoroarenes: Second Generation Catalyst

6.3.2.1 General Procedure for the Direct Arylation of Perfluoroarenes

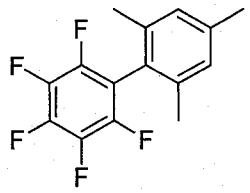
General Procedure: K_2CO_3 (2.0 equiv.), 2-cyclohexylphosphino-2',6'-dimethoxy-1,1'-biphenyl (0.10 equiv.), $Pd(OAc)_2$ (0.05 equiv.) were weighed to air and placed in a screw capped vial (2mL) with a magnetic stir bar. The reaction vessel was evacuated and backfilled with argon (x3). The fluoroarene (1.5 eq.) and isopropylacetate (1M) were then added via syringe and the reaction was stirred for one minute. The aryl halide (1 equiv.) was then added and the reaction was heated to 80°C for 12 hours (If the aryl halide is a solid, it is added as a solution in *i*-PrOAc). Upon completion, the reaction was then cooled to room temperature and purified by loading the crude reaction mixture directly onto a short silica gel packed flash chromatography column typically using hexane or pentane/ether mixtures as the eluant.

2'-Methyl-2,3,4,5,6-pentafluoro-1,1'-biphenyl



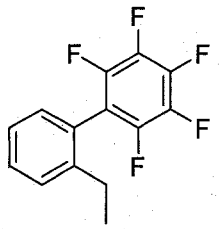
The compound was prepared following the general procedure and exhibited the same spectral data as previously reported[208] (99%). ^1H NMR (400MHz, $CDCl_3$, 293K, TMS): 2.19 (3H, s), 7.18-7.41 (4H, m).

2',4',6'-Trimethyl-2,3,4,5,6-pentafluoro-1,1'-biphenyl



The compound was prepared following the general procedure and exhibited the same spectral data as previously reported[210] (98%). ^{1}H NMR (400MHz, CD_6O, 293K, TMS): 2.10 (6H, s), 2.36 (3H, s), 7.10 (2H, s).

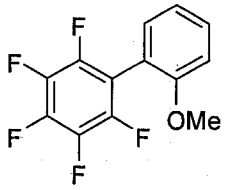
3'-Ethyl-2,3,4,5,6-pentafluoro-1,1'-biphenyl



The compound was prepared following the general procedure (82%): R_f = 0.46 (SiO_2, 100% Hexane); IR (ν_{max} /cm^{-1}): 2973, 1522, 1494, 1062, 989; ^{1}H NMR (400MHz, $CDCl_3$, 293K, TMS): 1.10 (3H, t, *J*= 7.6Hz), 2.45 (2H, q, *J*= 7.6Hz), 7.15 (1H, dd, *J*= 7.5, 1.0Hz), 7.30 (1H, ddd, *J*= 7.5, 7.5, 1.3Hz), 7.40 (1H, dd, *J*= 7.5, 1.1Hz), 7.42 (1H, ddd, *J*= 7.4, 7.4, 1.3Hz); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 15.0, 26.6, 115.7 (td, J_F = 20.3, 4.0Hz), 125.4, 125.4, 126.3, 129.0, 130.0, 130.9, 137.8 (dm, J_F = 253.2Hz), 140.8 (dm, J_F = 253.4Hz), 143.6, 144.4 (dm, J_F = 245.8Hz); ^{19}F NMR (377MHz, $CDCl_3$, 293K, TMS): -145.2 (2F, dd, J_F = 23.2, 8.2Hz), -160.4 (1F, t, J_F = 21.3Hz), -167.5 (2F, ddd, J_F = 23.1, 21.6, 8.3Hz); HRMS calcd for $C_{14}H_9F_5$ (M+) 272.0624; found: 272.0628.

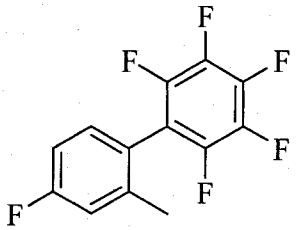
[210] Chen, Q.-Y. and Li, Z.-T. *J. Org. Chem.* **1993**, *58*, 2599.

2'-Methoxy-2,3,4,5,6-pentafluoro-1,1'-biphenyl



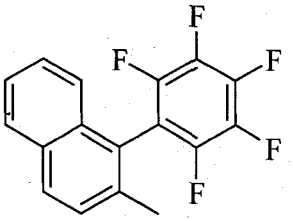
The compound was prepared following the general procedure and exhibited the same spectral data as previously reported[210] (99%). ^{1}H NMR (400MHz, $CDCl_3$, 293K, TMS): 3.80 (3H, s), 7.03 (1H, t, *J* = 8.2Hz), 7.06 (1H, d, *J* = 8.2Hz), 7.23 (1H, d. *J* = 8.2Hz), 7.45 (1H, t, *J* = 8.2Hz).

2'-Methyl-4'fluoro-2,3,4,5,6-pentafluoro-1,1'-biphenyl



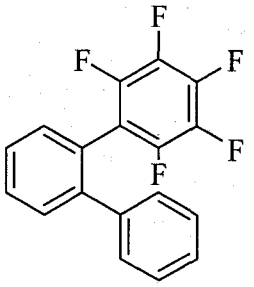
The compound was prepared following the general procedure (96%): R_f = 0.46 (SiO_2, 100% Hexane); IR (ν_{max} /cm^{-1}): 2931, 1521, 1493, 1057, 835; ^{1}H NMR (400MHz, $CDCl_3$, 293K, TMS): 2.18, (3H, s), 7.0 (1H, ddd, *J*=8.3, 8.3, 2.7Hz), 7.07 (1H, dd, *J*= 9.5, 2.5Hz), 7.16(1H, dd, *J*= 8.5, 5.7Hz); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 19.8 (d, J_F = 1.1Hz), 113.3 (d, J_F = 21.6Hz), 114.4-114.8 (m), 117.5 (d, J_F = 21.6Hz), 121.8 (d, J_F = 1.5Hz), 132.4, (d, J_F = 8.8Hz), 137.8, (dm, J_F = 253.5Hz), 140.9 (dm, J_F = 253.8Hz), 140.2 (d, J_F = 8.4Hz), 144.4 (dm, J_F = 249.0Hz), 150.5, 150.6; ^{19}F NMR (377MHz, $CDCl_3$, 293K, TMS): -117.3 (1F, s), -145.4 (2F, dd, J_F = 23.4, 8.7Hz), -159.8 (1F, t, J_F = 20.7Hz), -166.9 (2F, ddd, J_F = 22.9, 21.4, 8.6Hz); HRMS calcd for $C_{13}H_6F_6$ (M+) 276.0374; found: 276.0383.

2-Methyl-1-(perfluorophenyl)naphthalene



The compound was prepared following the general procedure (96%): mp 82-85 °C ($CHCl_3$); R_f = 0.34 (SiO_2, 100% Hexane); IR (ν_{max} /cm^{-1}): 3057, 1521, 1494, 1108, 987; ^1H NMR (400MHz, $CDCl_3$, 293K, TMS): 2.28, (3H, s), 7.29 (1H, d, *J*= 7.8Hz), 7.40-7.47 (3H, m), 7.85-7.89 (2H, m); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 20.4, 113.3 (td, J_F = 20.6, 3.9Hz), 121.9 (d, J_F = 1.2Hz), 124.1, 125.5, 127.1, 128.4, 128.4, 129.8, 132.1, 132.2, 136.0, 137.9 (dm, J_F = 253.9Hz), 141.0, (dm, J_F = 253.9Hz), 144.4 (dm, J_F = 246.8Hz); ^{19}F NMR (377MHz, $CDCl_3$, 293K, TMS): -144.0 (2F, dd, J_F = 23.6, 9.1Hz), -159.4 (1F, t, J_F = 21.2Hz), -166.6 (2F, ddd, J_F = 24.2, 21.9, 9.3Hz); HRMS calcd for $C_{17}H_9F_5$ (M+) 308.0624; found: 308.0607.

2-(Perfluorophenyl)biphenyl[211]

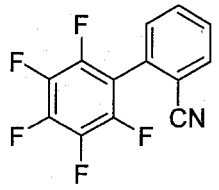


The compound was prepared following the general procedure but employing *t*-Bu_3-HBF_4 as the ligand as well as DMA as the solvent and heating the reaction to 120°C (92%): mp 89-91 °C ($CHCl_3$); R_f = 0.33 (SiO_2, 100% Hexane); IR (ν_{max} /cm^{-1}): 3068, 1522, 1495, 988; ^1H NMR (400MHz, $CDCl_3$, 293K, TMS): 7.12-7.14 (2H, m), 7.24-7.28 (3H, m), 7.32-7.34 (1H, m), 7.44-7.50 (2H, m), 7.53-7.57 (1H, m); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 116.0 (td, J_F = 19.4, 4.0Hz), 125.0, 127.5, 127.5, 128.2, 128.5, 129.8, 130.4,

[211] Birchall, J. M.; Evans, L. R.; Haszeldine, R.N.; *J. Chem. Soc. Perkin Trans. 1*; **1974**, 1715.

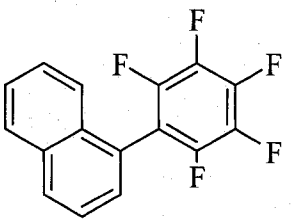
131.1, 137.4 (dm, J_F = 252.9Hz), 140.4, 140.6 (dm, J_F = 253.4Hz), 143.1, 144.1 (dm, J_F = 246.5Hz); ^{19}F NMR (377MHz, $CDCl_3$, 293K, TMS): -145.1 (2F, dd, J_F = 24.5, 9.5Hz), -160.4 (1F, t, J_F = 20.8Hz), -167.5 (2F, ddd, J_F = 23.3, 20.6, 8.5Hz); HRMS calcd for $C_{18}H_9F_5$ (M+) 320.0624; found: 320.0613.

2'-Cyano-2,3,4,5,6-pentafluoro-1,1'-biphenyl



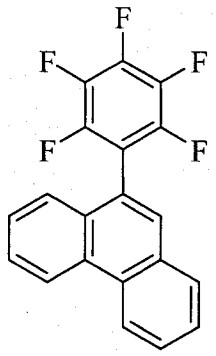
The compound was prepared following the general procedure but using 3.0 equiv. of pentafluorobenzene and exhibited the same spectral data as previously reported[209] (73%). ^{1}H NMR (400MHz, $CDCl_3$, 293K, TMS): 7.40 (1H, d, *J*= 7.8Hz), 7.54 (1H, t, *J*= 7.8Hz), 7.66 (1H, t, *J*= 7.8Hz), 7.76 (1H, d, *J*= 7.8Hz).

1-(Perfluorophenyl)naphthalene



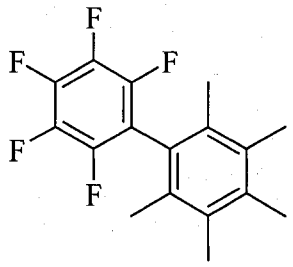
The compound was prepared following the general procedure (99%): mp 92-93 °C ($CHCl_3$); R_f = 0.34 (SiO_2, 100% Hexane); IR (ν_{max} /cm^{-1}): 3066, 1516, 1493, 992; ^{1}H NMR (400MHz, $CDCl_3$, 293K, TMS): 7.44-7.60 (5H, m), 7.94-8.01 (2H, m); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 114.4 (td, J_F = 19.6, 3.9Hz), 123.8, 124.6, 125.2, 126.4, 127.1, 128.7, 129.0, 130.2, 131.6, 133.7, 137.8 (dm, J_F = 253.5Hz), 141.0 (dm, J_F = 254.0Hz), 144.6 (dm, J_F = 247.4Hz), 150.5, 150.6; ^{19}F NMR (377MHz, $CDCl_3$, 293K, TMS): -144.5 (2F, dd, J_F = 25.4, 9.9Hz), -159.6 (1F, t, J_F = 21.2Hz), -166.9 (2F, ddd, J_F = 22.3, 20.5, 8.7Hz); HRMS calcd for $C_{16}H_7F_5$ (M+) 294.2188; found: 294.2132.

9-(Perfluorophenyl)phenanthrene



The compound was prepared following the general procedure (97%): mp 151-153 °C ($CHCl_3$); R_f = 0.30 (SiO_2, 100% Hexane); IR (ν_{max} /cm^{-1}): 3067, 1520, 1499, 1490, 988; ^1H NMR (400MHz, $CDCl_3$, 293K, TMS): 7.51 (1H, d, *J*= 7.5Hz), 7.58 (1H, d, *J*= 7.6Hz), 7.65 (1H, d, *J*= 7.3Hz), 7.69-7.75 (3H, m), 7.90 (1H, d, *J*= 7.8Hz) 8.74 (1H, d, *J*= 8.3Hz), 8.78(1H, d, *J*= 8.3Hz); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 114.4 (td, J_F = 19.5, 4.0Hz), 122.7, 122.7, 123.2, 125.3, 127.2, 127.2, 127.2, 127.9, 129.0, 130.0, 130.5, 130.7, 130.9, 130.9, 137.8 (dm, J_F = 253.7Hz), 141.0 (dm, J_F = 254.4Hz), 144.9 (dm, J_F = 247.5Hz); ^{19}F NMR (377MHz, $CDCl_3$, 293K, TMS): -144.1 (2F, dd, J_F = 24.5, 9.3Hz), -159.4 (1F, t, J_F = 20.3Hz), -166.7 (2F, ddd, J_F = 23.4, 20.8, 8.6Hz); HRMS calcd for $C_{20}H_9F_5$ (M+) 344.0624; found: 344.0635.

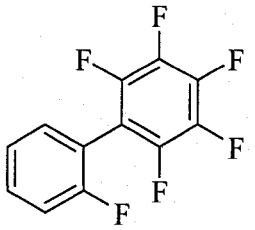
2',3',4',5',6'-Pentamethyl-2,3,4,5,6-pentafluoro-1,1'-biphenyl



The compound was prepared following the general procedure but using 3.0 eq. of pentafluorobenzene (85%): mp 157-160 °C ($CHCl_3$); R_f = 0.42 (SiO_2, 100% pentane); IR (ν_{max} /cm^{-1}): 2950, 1492, 1120, 978; ^1H NMR (400MHz, $CDCl_3$, 293K, TMS): 1.99 (6H, s), 2.26 (6H, s), 2.29 (3H, s); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 16.7, 17.0, 17.9,

116.5 (td, J_F = 21.2, 3.8Hz), 123.2 (d, J_F = 1.1Hz), 132.6, 133.2, 136.8, 137.8 (dm, J_F = 253.3Hz), 140.5 (dm, J_F = 252.6Hz), 144.0 (dm, J_F = 244.4Hz); ^{19}F NMR (377MHz, $CDCl_3$, 293K, TMS): -144.9 (2F, dd, J_F = 23.9, 8.7Hz), -161.0 (1F, t, J_F = 20.8Hz), -167.4 (2F, ddd, J_F = 23.7, 20.7, 8.5Hz); HRMS calcd for $C_{17}H_{15}F_5$ (M+) 314.1094; found: 314.1114.

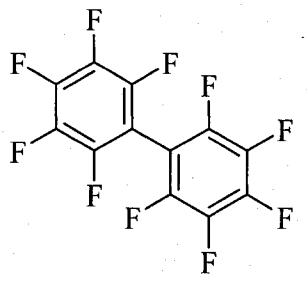
2'-Fluoro-2,3,4,5,6-pentafluoro-1,1'-biphenyl[212]



The compound was prepared following the general procedure (99%): mp 57-59 °C ($CHCl_3$); R_f = 0.44 (SiO_2, 100% Hexane); IR (ν_{max} /cm^{-1}): 2939, 1488, 1445, 1231, 1064, 987; ^{1}H NMR (400MHz, $CDCl_3$, 293K, TMS): 7.22 (1H, ddd, *J*=8.5, 8.5, 1.0Hz), 7.26 (1H, td, *J*=7.6, 1.1Hz), 7.35 (1H, td, *J*=6.9, 0.6Hz), 7.45-7.51 (1H, dddd, *J*=15.7, 7.3, 5.3, 1.8Hz); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 110.3 (td, J_F = 18.6, 4.0Hz), 114.4 (dd, J_F = 16.0, 1.5Hz), 116.3 (d, J_F = 21.6Hz), 124.5 (d, J_F = 3.7Hz), 131.8 (d, J_F = 8.3Hz) 132.1 (d, J_F = 0.8Hz), 137.9 (dm, J_F = 252.7Hz), 141.3 (dm, J_F = 254.6Hz), 144.5 (dm, J_F = 160.1Hz), 160.1 (d, J_F = 250.7Hz); ^{19}F NMR (377MHz, $CDCl_3$, 293K, TMS): -117.9 (1F, t, J_F = 10.9Hz), -145.4 (2F, ddd, J_F = 24.8, 10.6, 7.7Hz), -159.3 (1F, t, J_F = 21.0Hz), -167.2 (2F, ddd, J_F = 22.9, 20.5, 7.8Hz); HRMS calcd for $C_{12}H_4F_6$ (M+) 262.0217; found: 262.0218.

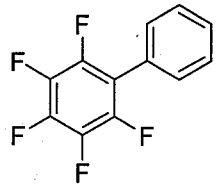
[212] Frohn, H.J.; Klose, A.; Bardin, V.V. *J. Fluorine Chem.* **1993**, 201.

Decafluorobiphenyl[213]



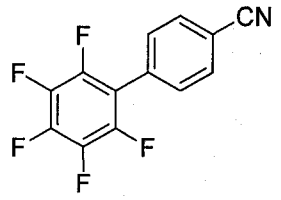
The compound was prepared following the general procedure but using 3.0 eq. of pentafluorobenzene (83%): mp 68-70 °C ($CHCl_3$); R_f = 0.55 (SiO_2, 100% pentane); IR (ν_{max} /cm^{-1}): 2929, 1507, 976; ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 101.5-102.0 (m), 138.2 (dm, J_F = 253.8Hz), 142.8 (dm, J_F = 258.1Hz), 144.8 (dm, J_F = 252.3Hz); ^{19}F NMR (377MHz, $CDCl_3$, 293K, TMS): -142.6--142.7 (2F, m), -155.0 (1F, t, J_F = 20.7Hz), -165.5--165.7 (2F, m); HRMS calcd for $C_{12}F_{10}$ (M+) 333.9840; found: 333.9826.

2,3,4,5,6-Pentafluoro-1,1'-biphenyl



The compound was prepared following the general procedure and exhibited the same spectral data as previously reported[208] (99%). ^1H NMR (400MHz, $CDCl_3$, 293K, TMS): 7.39-7.43 (2H, m), 7.45-7.49 (3H, m).

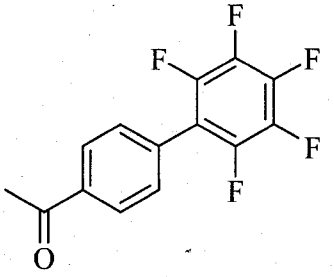
4'-Cyano-2,3,4,5,6-pentafluoro-1,1'-biphenyl



The compound was prepared following the general procedure and exhibited the same spectral data as previously reported[208] (97%).^1H NMR (400MHz, $CDCl_3$, 293K, TMS): 7.56 (2H, d, *J*= 8.4Hz), 7.80 (2H, d, *J*= 8.4Hz).

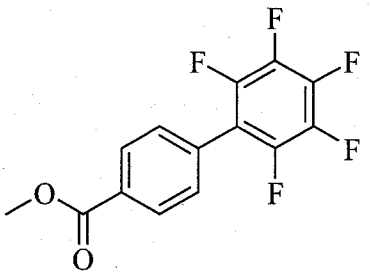
[213] Von Fircks, G.; Hausmann, H.; Francke, V.; Gunther, H. *J. Org. Chem.* **1997**, 5074.

4-(Perfluorophenyl)acetophenone



The compound was prepared following the general procedure (62%): mp 78-81 °C ($CHCl_3$); R_f = 0.29 (SiO_2, 15% Ether/Hexane); IR (ν_{max} /cm^{-1}): 2933, 1688, 1486, 1264, 1062, 982; ^1H NMR (400MHz, $CDCl_3$, 293K, TMS): 2.63, (3H, s), 7.52 (2H, d, J= 8.3Hz), 8.05 (2H, d, J= 8.4Hz); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 26.7, 115.0 (td, J_F = 16.8, 4.1Hz), 128.6, 130.6, 131.1, 137.6, 138.0 (dm, J_F = 253.3Hz), 140.9 (dm, J_F = 255.1Hz), 144.1 (dm, J_F = 248.7Hz), 197.4; ^{19}F NMR (377MHz, $CDCl_3$, 293K, TMS): -148.3 (2F, dd, J_F = 22.9, 8.2Hz), -161.2 (1F, t, J_F = 20.9Hz), -167.5 (2F, ddd, J_F = 22.2, 20.4, 9.0Hz); HRMS calcd for $C_{14}H_7F_5O$ (M+) 286.0417; found: 286.0428.

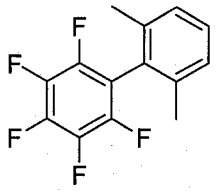
4-(Perfluorophenyl)methylbenzoate



The compound was prepared following the general procedure (99%): R_f = 0.26 (SiO_2, 5% Ether/Hexane); IR (ν_{max} /cm^{-1}): 2967, 1730, 1485, 1281, 1117, 983; ^1H NMR (400MHz, $CDCl_3$, 293K, TMS): 3.96, (3H, s), 7.52 (2H, d, J= 8.6Hz), 8.16 (2H, d, J= 8.6Hz); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 52.4, 115.0 (td, J_F = 17.0, 4.0Hz), 129.9, 130.3, 131.0, 138.0 (dm, J_F = 253.3Hz), 140.9 (dm, J_F = 255.1Hz), 144.2 (dm, J_F = 248.8Hz), 166.4; ^{19}F NMR (377MHz, $CDCl_3$, 293K, TMS): -147.8 (2F, dd, J_F = 23.1,

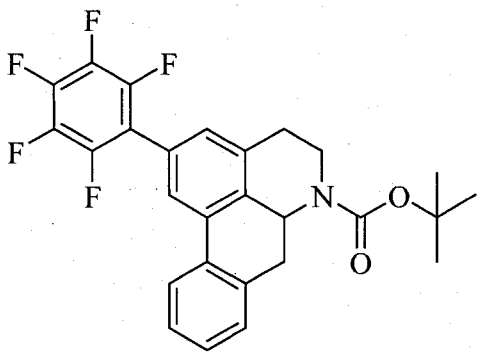
8.4Hz), -159.1 (1F, t, J_F = 20.8Hz), -166.6 (2F, ddd, J_F = 23.4, 21.8, 8.3Hz); HRMS calcd for $C_{14}H_7F_5O_2$ (M+) 302.0366; found: 302.0366.

2',6'-Dimethyl-2,3,4,5,6-pentafluoro-1,1'-biphenyl



The compound was prepared following the general procedure and exhibited the same spectral data as previously reported[214] (90%). ^{1}H NMR (400MHz, $CDCl_3$, 293K, TMS): 2.08 (6H, s), 7.13-7.17 (2H, m), 7.29-7.30 (1H, m).

2-(Perfluorophenyl)-4,5,6a,7-tetrahydro-dibenzo[de,g]quinoline-6-carboxylic acid tert-butyl ester

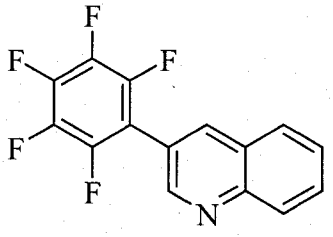


The compound was prepared following the general procedure (99%): mp 176-178 °C ($CHCl_3$); R_f = 0.16 (SiO_2, 10% Ether/Hexane); IR (ν_{max} /cm^{-1}): 2976, 1693, 1522, 1498, 1411, 1170, 990; ^{1}H NMR (400MHz, $CDCl_3$, 293K, TMS): 1.52 (9H, s), 2.76-3.06 (4H, m), 3.14 (1H, dd, J= 14.1, 3.3Hz), 4.49 (1H, d, J= 6.7Hz), 4.95 (1H, d, J= 11.8Hz), 7.16 (1H, s), 7.24-7.34 (3H, m), 7.64 (1H, s), 7.74 (1H, d, J= 7.5Hz); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 28.6, 30.5, 34.2, 38.7, 51.6, 80.2, 115.8 (td, J_F = 17.3, 3.8Hz), 123.8, 124.0, 124.9, 127.5, 128.5, 128.8, 129.2, 133.2, 134.1, 135.1, 135.8, 135.9, 137.9 (dm, J_F = 253.4Hz), 140.5 (dm, J_F = 249.4Hz), 144.3 (dm, J_F = 247.4Hz), 154.6; ^{19}F NMR

[214] Altenhoff, G.; Goddard, R.; Lehmann, C. W.; Glorius, F. *J. Am. Chem. Soc.* **2004**, *126*, 15195.

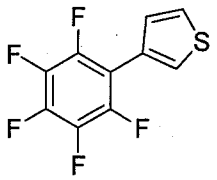
(377MHz, $CDCl_3$, 293K, TMS): -147.8 (2F, dd, J_F = 22.9, 8.1Hz), -160.5 (1F, t, J_F = 21.0Hz), -167.0 (2F, ddd, J_F = 22.7, 21.6, 7.8Hz); HRMS calcd for $C_{23}H_{13}F_5NO_2$ (M+-C_4H_9) 430.0866; found: 430.0858.

3-(Perfluorophenyl)quinoline



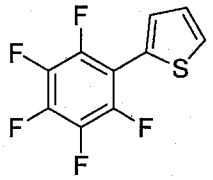
The compound was prepared following the general procedure (92%): mp 135-137 °C ($CHCl_3$); R_f = 0.17 (SiO_2, 10% Ether/Hexane); IR (ν_{max} /cm^{-1}): 2933, 1500, 1365, 1064, 990; ^1H NMR (400MHz, $CDCl_3$, 293K, TMS): 7.63 (1H, t, *J*= 7.4Hz), 7.82 (1H, td, *J*= 7.2, 0.9Hz), 7.89 (1H, d, *J*= 8.1Hz), 8.18 (1H, d, *J*= 8.5Hz), 8.28 (1H, s), 8.95 (1H, s); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 112.8 (dt, J_F = 17.2, 4.0Hz), 120.1, 127.4, 127.6, 128.2, 129.5, 130.9, 137.8, 138.1 (dm, J_F = 253.8Hz), 141.1 (dm, J_F = 255.6Hz), 144.5 (dm, J_F = 248.9Hz), 147.9; ^{19}F NMR (377MHz, $CDCl_3$, 293K, TMS): -147.8 (2F, dd, J_F = 22.7, 8.3Hz), -158.4 (1F, t, J_F = 20.7Hz), -166.1 (2F, ddd, J_F = 22.9, 20.5, 7.1Hz); HRMS calcd for $C_{15}H_6NF_5$ (M+) 295.0420; found: 295.0428.

3-(Perfluorophenyl)thiophene



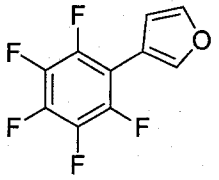
The compound was prepared following the general procedure and exhibited the same spectral data as previously reported[209] (70%). ^1H NMR (400MHz, $CDCl_3$, 293K, TMS): 7.19 (1H, t, *J*= 4.9Hz), 7.53 (1H, m), 7.55 (1H, d, *J*= 4.9Hz).

2-(Perfluorophenyl)thiophene



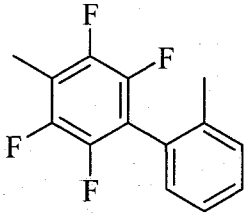
The compound was prepared following the general procedure but employing 3.0 equiv. of pentafluorobenzene and exhibited the same spectral data as previously reported[209] (63%). ^{1}H NMR (400MHz, $CDCl_3$, 293K, TMS): 7.36 (1H, m), 7.46 (1H, m), 7.65 (1H, m).

3-(Perfluorophenyl)furan



The compound was prepared following the general procedure but employing 3.0 equiv. of pentafluorobenzene and exhibited the same spectral data as previously reported[215] (55%). ^{1}H NMR (400MHz, $CDCl_3$, 293K, TMS): 6.87 (1H, m), 6.56 (1H, dd, J= 3.4, 1.8Hz), 7.60 (1H, m).

2,3,5,6-Tetrafluoro-4,2'-dimethyl-biphenyl

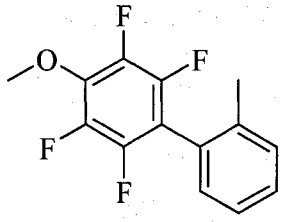


The compound was prepared following the general procedure but using 3.0 eq. of pentafluorobenzene (96%): R_f = 0.43 (SiO_2, 100% Hexane); IR (ν_{max} /cm^{-1}): 2932, 1481, 1303, 1065, 923; ^{1}H NMR (400MHz, $CDCl_3$, 293K, TMS): 2.19 (3H, s), 2.3 (3H, t, J= 2.1Hz), 7.20 (1H, d, J= 7.4Hz), 7.27 (1H, tdd, J= 6.5, 2.2, 0.6Hz), 7.31-7.38 (2H, m); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 7.6-7.7 (m), 19.7 (t, J_F = 1.2Hz), 115.3 (t, J_F =

[215] Kasemann, R.; Naumann, D. *J. Fluorine Chem.* **1990,** 207.

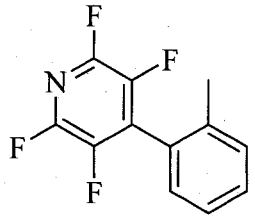
19.2Hz), 117.6 (t, J_F = 19.5Hz), 125.8, 127.2 (t, J_F = 2.1Hz), 129.3, 130.4, 130.6, 137.4, 143.6 (dddd, J_F = 244.2, 14.3, 5.9, 3.8Hz), 145.1 (dddd, J_F = 244.3, 14.5, 7.3, 4.0Hz); ^{19}F NMR (377MHz, $CDCl_3$, 293K, TMS): -143.0 (2F, dd, J_F = 23.1, 13.4Hz), -144.2 (2F, dd, J_F = 23.1, 12.4Hz); HRMS calcd for $C_{14}H_{10}F_4$ (M+) 254.0719; found: 254.0707.

2,3,5,6-Tetrafluoro-4-methoxy-4'-methyl-biphenyl



The compound was prepared following the general procedure (94%): R_f = 0.33 (SiO_2, 100% Hexane); IR (ν_{max} /cm^{-1}): 2959, 1485, 1123, 1082, 990; ^{1}H NMR (400MHz, $CDCl_3$, 293K, TMS): 2.19 (3H, s), 4.13 (3H, t, *J*= 1.3Hz), 7.19 (1H, d, *J*= 7.7Hz), 7.27 (1H, tdd, *J*= 6.8, 2.1, 0.6Hz), 7.32-7.38 (2H, m); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 19.7, 62.2, 113.8 (t, J_F = 19.9Hz), 125.9, 126.7, 129.3, 130.4, 130.8, 137.6, 137.7 (dt, J_F = 12.0, 3.6Hz), 141.1 (ddt, J_F = 247.4, 15.8, 4.3Hz), 144.2 (dddd, J_F = 244.7, 12.1, 7.9, 3.8Hz); ^{19}F NMR (377MHz, $CDCl_3$, 293K, TMS): -163.5 (2F, dd, J_F = 22.4, 8.9Hz), -147.7 (2F, dd, J_F = 22.4, 8.8Hz); HRMS calcd for $C_{14}H_{10}OF_4$ (M+) 270.0668; found: 270.0689.

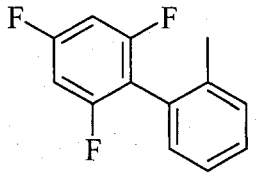
2,3,5,6-Tetrafluoro-4-*o*-tolyl-pyridine



The compound was prepared following the general procedure (97%): mp 55-57 °C ($CHCl_3$); R_f = 0.36 (SiO_2, 100% Hexane); IR (ν_{max} /cm^{-1}): 2967, 1448, 1278, 967; ^{1}H NMR (400MHz, $CDCl_3$, 293K, TMS): 2.23 (3H, s), 7.22 (1H, d, *J*= 7.6Hz), 7.27 (1H, dt, *J*= 7.7, 0.4Hz), 7.38 (1H, dd, *J*= 7.0, 0.6Hz), 7.44 (1H, dt, *J*= 7.5, 1.1Hz); ^{13}C NMR (100MHz,

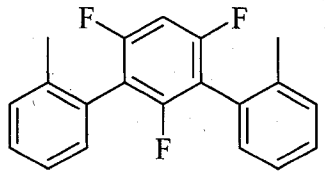
$CDCl_3$, 293K, TMS): 19.6, 125.4 (t, J_F = 1.9Hz), 126.2, 129.7, 130.5, 130.8, 134.0 (tt, J_F = 17.6, 2.9Hz), 136.8, 139.4 (ddt, J_F = 257.6, 21.1, 6.2Hz), 143.7 (dddd, J_F = 245.7, 17.6, 13.2, 2.6Hz); ^{19}F NMR (377MHz, $CDCl_3$, 293K, TMS): -95.9—96.1 (2F, m), -147.2—147.4 (2F, m); HRMS calcd for $C_{12}H_7NF_4$ (M+) 241.0515; found: 241.0493.

2,4,6-Trifluoro-2'-methyl-biphenyl



The compound was prepared following the general procedure but using 5.0 eq. of pentafluorobenzene (82%): R_f = 0.42 (SiO_2, 100% pentane); mp 37-38 °C ($CHCl_3$); IR (ν_{max} /cm^{-1}): 3066, 1597, 1475, 1119, 998; ^1H NMR (400MHz, $CDCl_3$, 293K, TMS): 6.71-6.76 (2H, m), 7.18 (1H, d, J= 7.3Hz), 7.26 (1H, td, J= 7.9, 2.6Hz), 7.30-7.32 (2H, m); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 19.7, 99.9-100.5 (m), 114.3-114.8 (m), 125.7, 128.0, 128.9, 130.2, 130.8, 137.5, 160.3 (dt, J_F = 248.4, 12.6Hz), 162.1 (dt, J_F = 249.1, 15.5Hz); ^{19}F NMR (377MHz, $CDCl_3$, 293K, TMS): -114.1 (3F, broad s); HRMS calcd for $C_{13}H_9F_3$ (M+) 222.0656; found: 222.0650.

1,3-Di-(*o*-tolyl)-2,4,6-trifluorobenzene



The compound was obtained as the minor product in the 1,3,5-trifluorobenzene reaction (15%): R_f = 0.25 (SiO_2, 100% pentane); IR (ν_{max} /cm^{-1}): 2924, 1636, 1416, 1141, 1042; ^1H NMR (400MHz, $CDCl_3$, 293K, TMS): 2.21 (3H, s), 2.22 (3H, s), 6.87 (1H, tt, J= 9.0,

2.3Hz), 7.25-7.27 (4H, m), 7.31-7.34 (4H, m); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 19.7, 19.8, 100.1 (tt, J_F = 27.0, 4.5Hz), 114.0-114.7 (m), 125.6, 125.7, 128.2, 128.8, 128.8, 130.1, 130.2, 130.8, 130.8, 137.4, 137.5, 157.2 (dm, J_F = 246.6Hz), 159.1 (dm, J_F = 242.8Hz); ^{19}F NMR (377MHz, $CDCl_3$, 293K, TMS): -147.8 (2F, dd, J_F = 22.7, 8.3Hz), -158.4 (1F, t, J_F = 20.7Hz), -166.1 (2F, ddd, J_F = 22.9, 20.5, 7.1Hz); HRMS calcd for $C_{20}H_{15}F_3$ (M+) 312.1126; found: 312.1120.

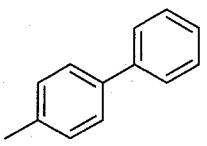
6.4 Experimental Data for Section 3: Development of an Highly Active Palladium-Pivalic Acid Co-Catalyst System

6.4.1 Direct Arylation of Simple Arenes

6.4.1.1 General Procedure for the Direct Arylation of Benzene

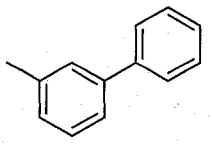
General Procedure: K_2CO_3 (2.5 equiv.) was weighed to air and placed in a Schlenk tube (15ml) or screw capped vial (2mL) with a magnetic stir bar. The reaction vessel was evacuated and backfilled with argon (x3). The aryl halide (1 equiv.) was then added to the Schlenk tube as a solution in benzene (0.21M). $Pd(OAc)_2$ (3mol %), DavePhos (3mol %) and pivalic acid (0.3 eq.) were then added as a solution in DMA (1.16 times the volume of benzene) and the reaction was heated to 120°C for 12 hours. Upon completion, the reaction was cooled to room temperature. If possible the solvents were removed by distillation and the resulting mixture was purified by a silica gel packed flash chromatography column typically using hexane or pentane/ether mixtures as the eluent. If the product is too volatile for removal of the DMA by distillation, it was loaded directly onto a silica gel packed flash chromatography column.

4-Phenyltoluene



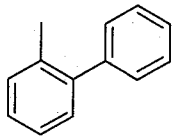
The compound was prepared following the general procedure using 110mg of 4-bromotoluene and exhibited the same spectral data as previously reported[216] (81%). The reaction was loaded onto a silica pad and was eluted using hexane in order to remove the DMA which does not elute. The resulting mixture was then purified by preparative TLC using pentane as the eluent. ^{1}H NMR (400MHz, $CDCl_3$, 293K, TMS): 2.42 (3H,m), 7.26-7.62 (9H, m).

3-Phenyltoluene



The compound was prepared following the general procedure using 110mg of 3-bromotoluene and exhibited the same spectral data as previously reported[216] (83%). The reaction was loaded onto a silica pad and was eluted using hexane in order to remove the DMA which does not elute. The resulting mixture was then purified by preparative TLC using pentane as the eluent. ^{1}H NMR (400MHz, $CDCl_3$, 293K, TMS): 2.43 (3H, s), 7.16-7.74 (9H, m).

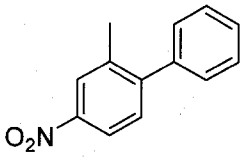
2-Phenyltoluene



The compound was prepared following the general procedure using 110mg of 2-bromotoluene and exhibited the same spectral data as previously reported[216] (85%). The reaction was loaded onto a silica pad and was eluted using hexane in order to remove the DMA which does not elute. The resulting mixture was then purified by preparative TLC using pentane as the eluent. ^{1}H NMR (400MHz, $CDCl_3$, 293K, TMS): 2.24 (3H, s), 7.20-7.41 (9H, m);

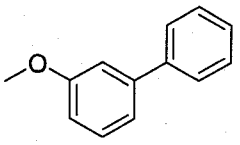
[216] Zim, D.; Lando, V.R.; Dupont, J.; Monteiro, A.L. *Org. Lett.* **2001**, *3*, 3049.

3-Methyl-4-phenylnitrobenzene



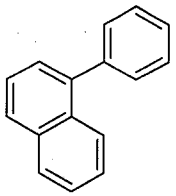
The compound was prepared following the general procedure using 139mg of 2-bromo-5-nitrotoluene and exhibited the same spectral data as previously reported[217] (81%). The reaction was purified by removal of DMA by distillation followed by a silica chromatography column using a 2% ether/hexane eluent. ^{1}H NMR (400MHz, $CDCl_3$, 293K, TMS): 2.36 (3H, s), 7.25-7.50 (6H, m), 8.08 (1H, dd, *J*= 8.3, 2.2Hz), 8.14 (1H, d, *J*= 2.2Hz).

3-Phenylanisole



The compound was prepared following the general procedure using 119mg of 3-bromoanisole and exhibited the same spectral data as previously reported[218] (69%). The product was purified by removal of DMA by distillation followed by a silica chromatography column using 2% ether/hexane eluent. ^{1}H NMR (400MHz, $CDCl_3$, 293K, TMS): 3.77 (3H, s), 6.85 (1H, ddd, *J*= 8.2, 2.5, 0.9Hz), 7.06-7.18 (2H, m), 7.24-7.34 (2H, m), 7.34-7.44 (2H,m), 7.51-7.59 (2H,m).

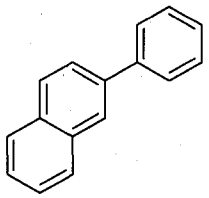
1-Phenylnaphthalene



[217] Iihama, T.; Fu J.-M.; Bourguignon, M. ; Snieckus, V. *Synthesis*, **1989**, *3*, 184.
[218] Mino, T.; Shirae, Y.; Sakamoto, M.; Fujita, T. *J. Org. Chem.* **2005**, *70*, 2191.

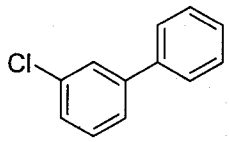
The compound was prepared following the general procedure using 133mg of 1-bromonaphtalene and exhibited the same spectral data as previously reported[216] (80%). The reaction was loaded onto a silica pad and was eluted using hexane in order to remove the DMA which does not elute. The resulting mixture was then purified by preparative TLC using pentane as the eluent. ^{1}H NMR (400MHz, $CDCl_3$, 293K, TMS): 7.43-7.57 (9H, m), 7.86-7.93 (3H, m);

2-Phenylnaphthalene



The compound was prepared following the general procedure using 133mg of 2-bromonaphtalene and exhibited the same spectral data as previously reported[216] (55%). The resulting mixture was then purified by preparative TLC using pentane as the eluent. ^{1}H NMR (400MHz, $CDCl_3$, 293K, TMS): 7.44-7.47 (1H, m), 7.52-7.59 (4H, m), 7.78-7.83 (3H,m), 7.91-7.99 (3H,m), 8.11-8.12 (1H, m).

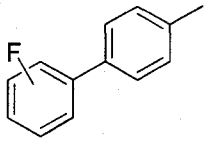
3-Phenylchlorobenzene



The compound was prepared following the general procedure using 123mg of 3-bromochlorobenzene and exhibited the same spectral data as previously reported[219] (63%). The reaction was loaded onto a silica pad and was eluted using hexane in order to remove the DMA which does not elute. The resulting mixture was then purified by preparative TLC using pentane as the eluent. ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 124.7, 126.5, 126.5, 126.7, 126.7, 127.3, 128.3, 128.3, 129.4, 133.9, 138.8, 142.2.

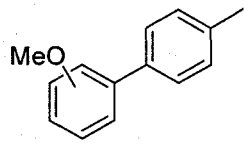
[219] Wilson, N. *J. Am. Chem. Soc.* **1975**, *97*, 3573.

Fluoro-4-methylbiphenyl



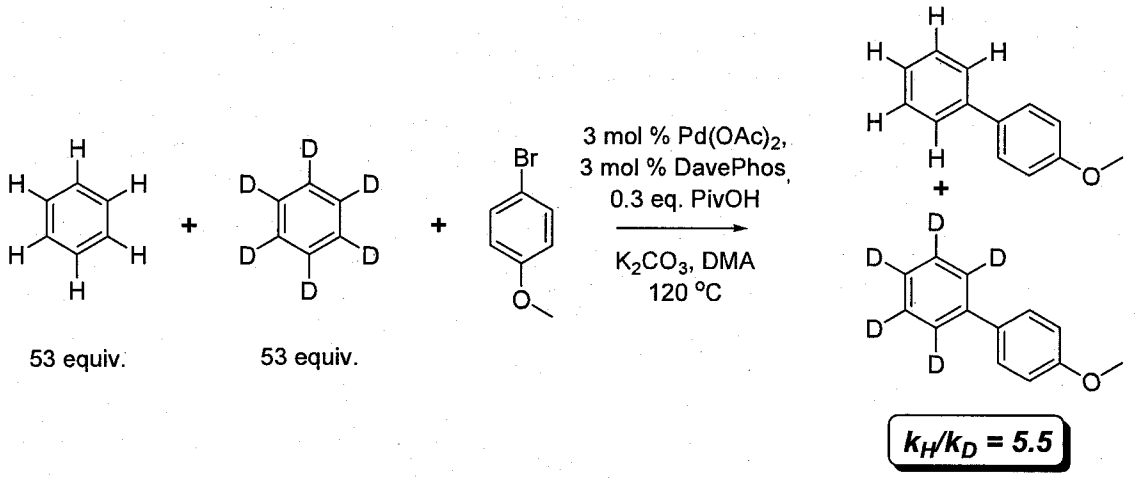
The compound were prepared following the general procedure using 110mg of 4-bromotoluene as well as using fluorobenzene instead of benzene in 91% yield as a o:m:p regiomeric distribution of 22:3:1 as determined by ^{19}F NMR[220]. The reaction was loaded onto a silica pad and was eluted using hexane in order to remove the DMA which does not elute. The resulting mixture was then purified by a silica chromatography column using 100% hexane eluent.

Methoxy-4-methylbiphenyl



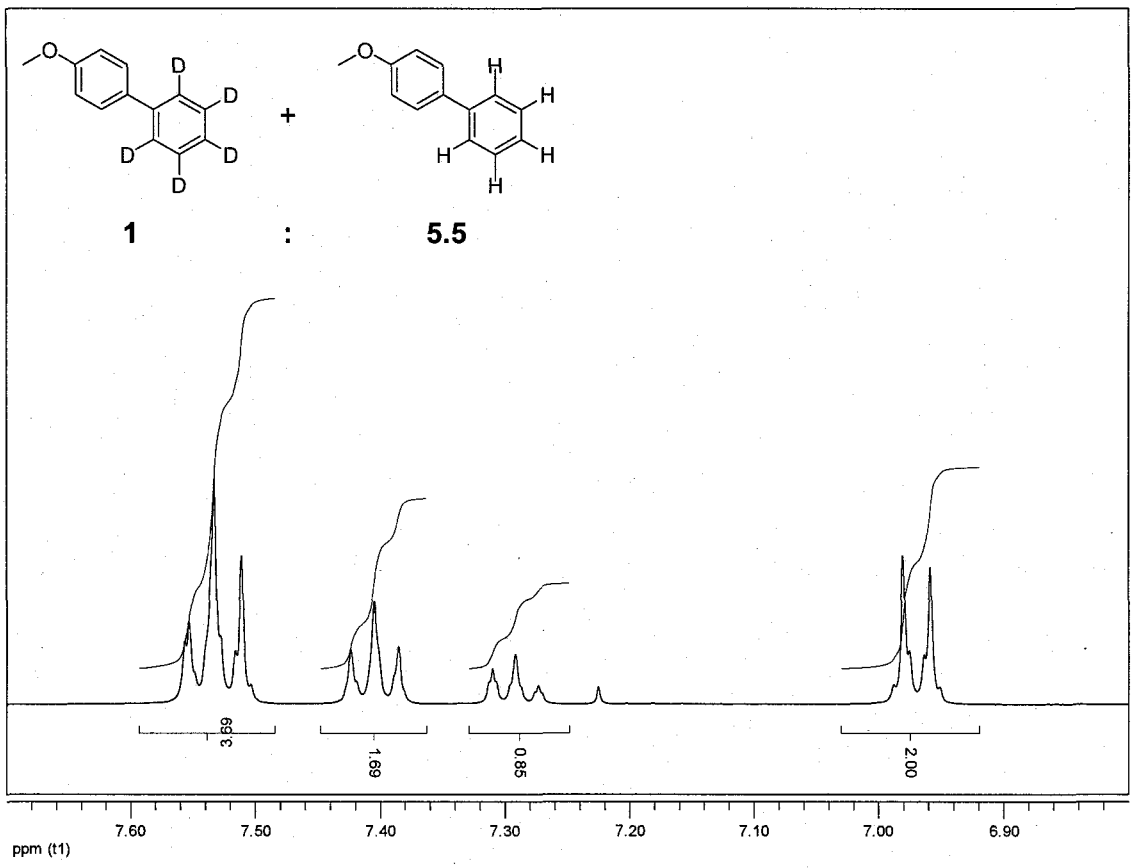
The compound were prepared following the general procedure using 110mg of 4-bromotoluene as well as using anisole instead of benzene in 62% yield as a o:m:p regiomeric distribution of 1:2:1 by GCMS and comparison to authentic samples. The reaction was loaded onto a silica pad and was eluted using 2% ether/hexane mixture in order to remove the DMA which does not elute. The resulting mixture was then purified by preparative TLC using 2% ether/hexane as the eluent.

6.4.1.2 Procedure for the Kinetic Isotope Effect Experiment

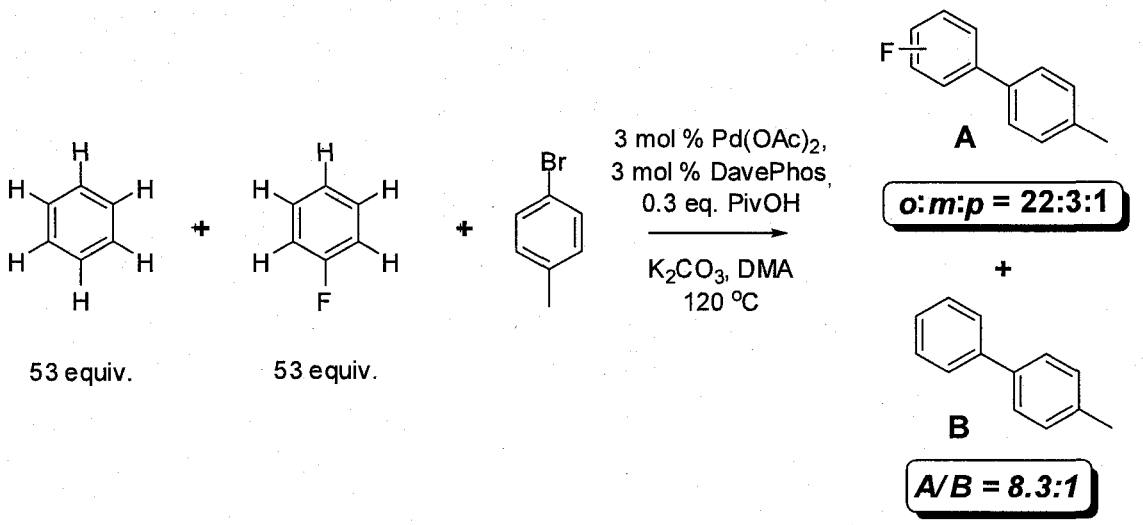


k_H/k_D = 5.5

K_2CO_3 (0.225g, 2.5 equiv.) was weighed to air and placed in a Schlenk tube (15ml) with a magnetic stir bar. The reaction vessel was evacuated and backfilled with argon (x3). 4-bromoanisole (0.122g, 1 equiv.) was then added to the Schlenk tube as a solution in Benzene-H_6 (3mL) and Benzene-D_6 (3mL). $Pd(OAc)_2$ (0.004g, 0.03equiv.), DavePhos (0.008g, 0.03 equiv.) and pivalic acid (0.02g, 0.3 equiv.) were then added as a stock solution in DMA (7mL) and the reaction was heated to 120°C for 12 hours. Upon completion, the reaction was cooled to room temperature. The resulting mixture was then loaded directly onto a silica gel packed flash chromatography column and eluted with 1% ether/hexane mixture. The product distribution was then analyzed by ^{1}HNMR and MS.

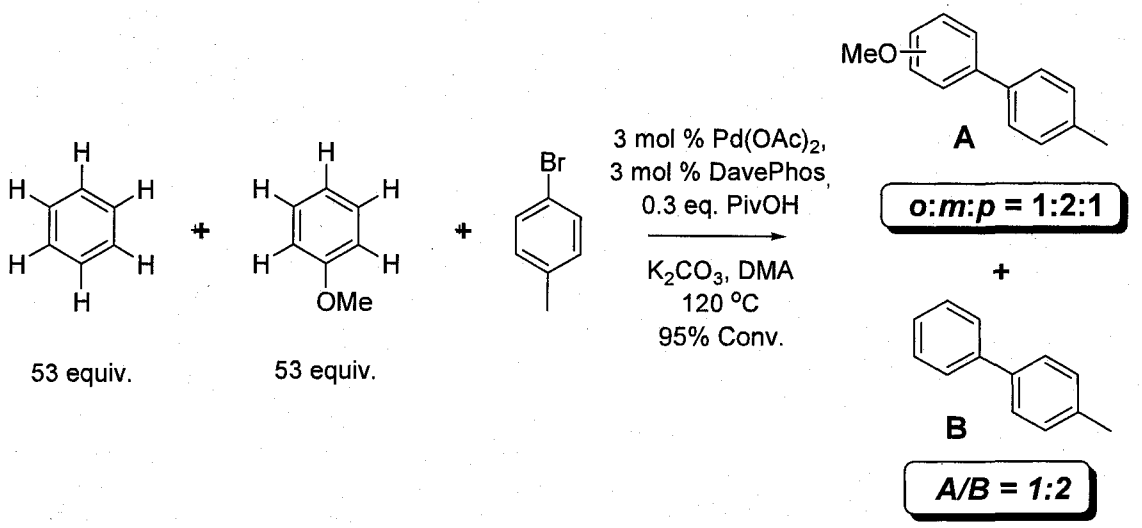


6.4.1.3 Procedures for the Competition Studies



K_2CO_3 (0.225g, 2.5 equiv.) was weighed to air and placed in a Schlenk tube (15ml) with a magnetic stir bar. The reaction vessel was evacuated and backfilled with argon (x3). 4-bromotoluene (0.110g, 1 equiv.) was then added to the Schlenk tube as a solution in

benzene (3mL) and fluorobenzene (3mL). $Pd(OAc)_2$ (0.004g, 0.03equiv.), DavePhos (0.008g, 0.03 equiv.) and pivalic acid (0.02g, 0.3 equiv.) were then added as a stock solution in DMA (7mL) and the reaction was heated to 120°C for 12 hours. Upon completion, the reaction was cooled to room temperature. The resulting mixture was analyzed by GCMS and then filtered through a small silica pad (5cm) using hexane as the eluent. The product distribution was then assigned by GCMS. The regioisomeric distribution was establish by ^{19}F NMR and compared with literature values[220].



K_2CO_3 (0.225g, 2.5 equiv.) was weighed to air and placed in a Schlenk tube (15ml) with a magnetic stir bar. The reaction vessel was evacuated and backfilled with argon (x3). 4-Bromotoluene (0.110g, 1 equiv.) was then added to the Schlenk tube as a solution in benzene (3mL) and anisole (3mL). $Pd(OAc)_2$ (0.004g, 0.03equiv.), DavePhos (0.008g, 0.03 equiv.) and pivalic acid (0.02g, 0.3 equiv.) were then added as a stock solution in DMA (7mL) and the reaction was heated to 120°C for 12 hours. Upon completion, the reaction was then cooled to room temperature. The resulting mixture was analyzed by GCMS against authentic samples in order to assign the product distribution.

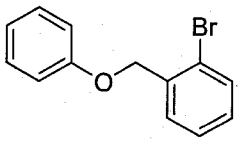
[220] Kelm, J. and Strauss, K. *Spectrochimica Acta*, **1981**, *37A*, 689.

6.4.2 Re-Evaluation of the Intramolecular Direct Arylation of Simple Arenes

6.4.2.1 Synthesis of the Cyclization Precursors

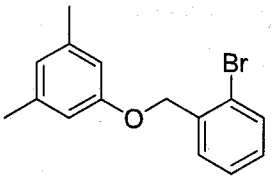
General Procedure: The appropriate phenol, K_2CO_3 (3 equiv.), NaI (0.10 equiv.) and 2-halobenzylbromide (or 2-halobenzylchloride) were placed in a round bottom flask equipped with a refluxed condenser. Reagent grade acetone (0.5M) was added and the reaction was refluxed overnight. The reaction was allowed to cool and was extracted using Et_2O/H_2O. 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 diethyl ether/hexanes mixtures.

1-Bromo-2-(phenoxymethyl)benzene



The compound was prepared according to the general procedure and exhibited spectral data identical to previous reports (93%).[221]

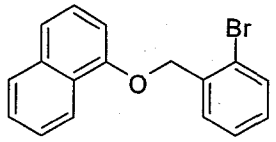
1-((3,5-Dimethylphenoxy)methyl)-2-bromobenzene



The compound was prepared according to the general procedure (97%). R_f = 0.31 (SiO_2, 4% ether/hexane); IR (ν_{max} /cm^{-1}): 2917, 1595, 1322, 1154; ^{1}H NMR (400MHz, $CDCl_3$, 293K, TMS): 2.29 (6H, s), 5.08 (2H, s), 6.62 (3H, s), 7.16 (1H, td, *J*= 1.8, 7.5 Hz), 7.32 (1H, td, *J*= 1.2, 7.5 Hz), 7.58-7.53 (2H, m); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 21.5, 69.1, 112.5, 122.2, 123.0, 127.5, 128.8, 129.1, 132.5, 136.5, 139.3, 158.0; HRMS calcd for $C_{15}H_{15}OBr$ (M^+): 290.0306, Found: 290.0324.

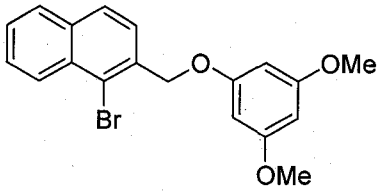
1-(2-Bromo-benzyloxy)-naphthalene

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



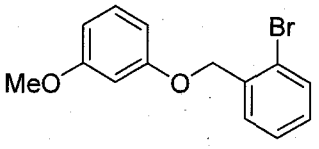
The compound was prepared according to the general procedure (91%). R_f = 0.55 (SiO_2, 5% EtOAc/hexane); IR (ν_{max} /cm^{-1}): 2924, 1364, 1246, 1096; ^1H NMR (400MHz, $CDCl_3$, 293K, TMS): 5.33 (2H, s), 6.89 (1H, d, *J*= 8.0Hz), 7.24 (1H, d, *J*= 3.0Hz), 7.38 (2H, m), 7.49 (3H, m), 7.62 (1H, d, *J*= 8.0Hz), 7.69 (1H, d, *J*= 8.0Hz), 7.82 (1H, m), 8.38 (2H, m); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 69.5, 105.4, 120.8, 122.3, 125.3, 125.7, 125.8, 126.5, 127.5, 127.6, 128.7, 129.2, 129.2, 132.6, 134.6, 136.4, 154.0; HRMS calcd for $C_{17}H_{13}OBr$ (M^+): 312.0046, Found: 312.0150.

2-((3,5-Dimethoxyphenoxy)methyl)-1-bromonaphthalene



The compound was prepared according to the general procedure (89%). mp: 97-98°C ($CHCl_3$); R_f = 0.28 (SiO_2, 6% ether/hexane); IR (ν_{max} /cm^{-1}): 2917, 1537, 1038; ^1H NMR (400MHz, $CDCl_3$, 293K, 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 (100MHz, $CDCl_3$, 293K, TMS): 55.3, 70.1, 93.3, 93.7, 122.2, 125.5, 126.6, 126.9, 127.5, 127.9, 128.1, 132.0, 134.0, 134.3, 160.3, 161.5; HRMS calcd for $C_{19}H_{17}O_3$ (M^+-Br): 293.1178; Found: 293.1171.

1-(2-Bromobenzyloxy)-3-methoxybenzene

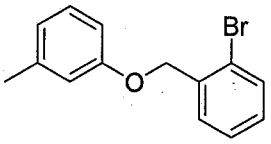


The compound was prepared according to the general procedure and exhibited spectral data identical to previous reports (92%).[222] ^1H NMR (400MHz, $CDCl_3$, 293K, TMS): 3.74

[222] Bowman, R.; Mann, E.; Parr, J. *J. Chem. Soc., Perkin Trans. 1*, **2000**, 2991.

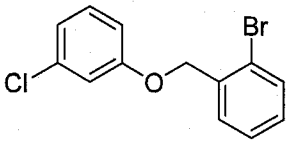
(3 H, s), 5.10 (2 H, s), 6.50-6.60 (3 H, m), 7.12-7.22 (2 H, m), 7.31 (1 H, ddd, *J*= 7.5, 7.5, 1.3 Hz), 7.51-7.58 (2 H, m).

1-((*m*-Tolyloxy)methyl)-2-bromobenzene



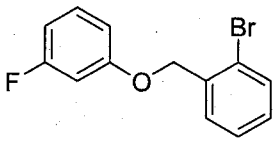
The compound was prepared according to the general procedure (94%). R_f = 0.32 (SiO_2, 4% ether/hexane); IR (ν_{max} /cm^{-1}): 2919, 1603, 1440, 1258, 1027; ^1H NMR (400MHz, $CDCl_3$, 293K, TMS): 2.34 (3H, s), 5.11 (2H, s), 6.80 (3H, m), 7.18 (2H, m), 7.32 (1H, t, *J*= 8.1 Hz), 7.56 (2H, m); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 21.5, 69.2, 111.6, 115.7, 122.0, 122.2, 127.5, 128.8, 129.1, 129.3, 132.6, 136.5, 139.6, 158.5; HRMS calcd for $C_{14}H_{13}BrO$ (M+) 276.0150; Found: 276.0163.

1-((3-Chlorophenoxy)methyl)-2-bromobenzene



The compound was prepared according to the general procedure (95%). R_f = 0.33 (SiO_2, 5% ether/hexane); IR (ν_{max} /cm^{-1}): 3069, 1594, 1477, 1244, 1026; ^1H NMR (400MHz, $CDCl_3$, 293K, 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 (100MHz, $CDCl_3$, 293K, TMS): 69.5, 113.2, 115.4, 121.4, 122.3, 127.6, 128.8, 129.4, 130.3, 132.7, 134.9, 135.7, 159.1; HRMS calcd for $C_{13}H_{10}BrClO$ (M+) 295.9604; Found: 295.9631.

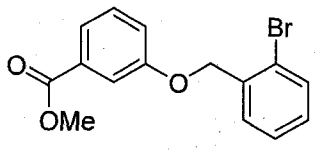
1-((3-Fluorophenoxy)methyl)-2-bromobenzene



The compound was prepared according to the general procedure (90%). R_f = 0.35 (SiO_2, 5% ether/hexane); IR (ν_{max} /cm^{-1}): 3024, 1530, 1348, 1246, 1025; ^1H NMR (400MHz, $CDCl_3$, 293K, TMS): 5.11 (2H, s), 6.71 (3H, m), 7.21 (2H, m), 7.33 (1H, t, *J*= 7.5 Hz), 7.52 (1H,

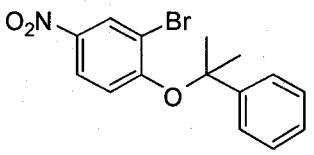
d, *J*= 7.8 Hz), 7.83 (1H, d, *J*= 7.8 Hz); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 69.6, 102.7 (d, *J*= 30.0 Hz), 108.0 (d, *J*= 20.7 Hz), 110.5 (d, *J*= 3.3 Hz), 122.3, 127.6, 129.1 (d, *J*= 45 Hz), 130.2, 130.4, 132.7, 135.7, 159.7 (d, *J*= 11.0 Hz), 165.2; HRMS calcd for $C_{13}H_{10}BrFO$ (M+) 279.9899; Found: 279.9897.

Methyl 3-(2-bromobenzyloxy)benzoate



The compound was prepared according to the general procedure (93%). R_f = 0.35 (SiO_2, 5% ether/hexane); IR (ν_{max} /cm^{-1}): 2946, 1721, 1586, 1278, 1026; ^1H NMR (400MHz, $CDCl_3$, 293K, TMS): 3.92 (3H, s), 5.17 (2H, s), 7.20 (2H, m), 7.35 (2H, m), 7.55 (1H, dd, *J*= 1.8, 7.5 Hz), 7.60 (1H, dd, *J*= 1.8, 8.1 Hz), 7.67 (2H, m); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 52.2, 69.5, 115.3, 120.0, 122.5, 127.6, 129.0, 129.4, 129.5, 131.6, 132.7, 135.8, 152.4, 158.4, 166.9; HRMS calcd for $C_{15}H_{13}BrO_3$ (M+) 320.0048; Found: 320.0025.

1-(2-(2-Bromo-5-nitrophenoxy)propan-2-yl)benzene



To a flask containing a suspension of potassium hydride (0.27g, 2.0mmol, 1.1eq.) in THF (3mL) at 0°C was added slowly the 2-phenylpropan-2-ol (0.4g, 2.0mmol, 1.1eq.) and the solution was stirred for 10mins. This solution was then added slowly to a solution of 2-bromo-1-fluoro-4-nitrobenzene (0.4g, 1.8mmol, 1.0eq.) in THF (9mL) at 0°C. The solution was then allowed to warm to room temperature and was stirred for an additional 2h. Saturated aqueous ammonium chloride was then added and the solution was extracted with DCM and dried over magnesium sulfate. The product was then purified by column chromatography on silica gel using 3%ether/hexanes as the eluant. (83%): R_f = 0.30 (SiO_2, 5% ether/hexane); IR (ν_{max} /cm^{-1}): 2984, 1516, 1473, 1341, 1275, 1138; ^1H NMR (400MHz, $CDCl_3$, 293K, TMS): 1.85 (6H, s), 6.36 (1H, d, *J*=9.2Hz), 7.28-7.41 (5H,

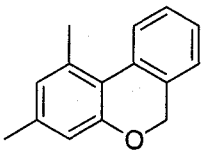
m), 7.80 (1H, dd, *J*=9.2, 2.8Hz), 8.42 (1H, d, *J*=2.8Hz); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 29.3, 83.9, 114.5, 116.8, 123.4, 124.9, 127.8, 128.9, 128.9, 141.0, 144.1, 158.4; HRMS calcd for $C_{15}H_{14}O_3NBr$ (M+) 335.0157; found: 335.0105.

6.4.2.2 Cyclization Products

General Cyclization Procedure

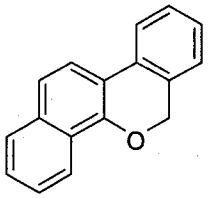
K_2CO_3 (1.7mmol, 3.0eq.), $Pd(OPiv)_2$ (0.03, 0.05eq.), P(*p*-FPh)$_3$ (0.03, 0.05eq.) and pivalic acid (0.17mmol, 0.3eq.) were weighed to air and placed in a screw capped vial (4mL) with a magnetic stir bar. The reaction vessel was evacuated and backfilled with argon 3 times. The cyclization precursor (0.57mmol, 1.0eq.) was then added to the reaction vessel as a solution in *N,N*-dimethylacetamide (3mL). The reaction was heated to 50-60°C for 12 hours. Upon completion, the reaction was cooled to room temperature. The products were loaded directly onto a silica gel packed column and eluted using ether/hexane mixtures.

1,3-Dimethyl-6H-benzo[c]chromene



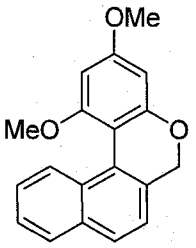
The compound was prepared according to the general cyclization procedure but the reaction was performed at 60°C (96%). mp= 82-83°C ($CHCl_3$); R_f = 0.29 (SiO_2, 3% ether/hexane); IR (ν_{max} /cm^{-1}): 2924, 1615, 1284, 1151, 1064; ^{1}H NMR (400MHz, $CDCl_3$, 293K, TMS): 2.31 (3H, s), 2.64 (3H, s), 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, 7.5 Hz), 7.73 (1H, d, *J*= 7.8 Hz); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 21.6, 23.0, 69.5, 115.8, 120.9, 125.2, 126.4, 126.8, 126.9, 128.2, 131.2, 133.8, 135.6, 139.1, 156.8; HRMS calcd for $C_{15}H_{14}O$ (M^+): 210.1045; Found: 210.1056.

6H-Dibenzo[c,*h*]chromene



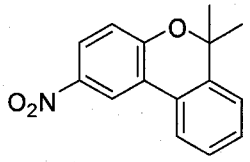
The compound was prepared according to the general cyclization procedure (97%). R_f = 0.47 (SiO_2, 5% EtOAc/hexane); IR (ν_{max} /cm^{-1}): 2870, 1395, 1351, 1096; ^1H NMR (400MHz, $CDCl_3$, 293K, TMS): 5.23 (2H, s), 7.11 (1H, d, *J*=7Hz), 7.22 (1H, t, *J*=2Hz), 7.33 (1H, t, *J*=3Hz), 7.45 (3H, m), 7.65 (1H, d, *J*=3Hz), 7.75 (2H, m), 8.25 (1H, m); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 68.7, 117.1, 120.9, 121.5, 121.9, 122.2, 124.5, 125.3, 125.7, 126.6, 127.3, 127.6, 128.5, 130.6, 130.6, 134.3, 150.2; HRMS calcd for $C_{17}H_{12}O$ (M^+): 232.0871; Found: 232.0888.

1,3-Dimethoxy-6H-naphtho[2,1-c]chromene



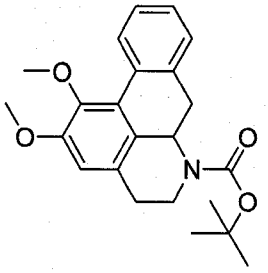
The compound was prepared according to the general cyclization procedure (95%). R_f = 0.31 (SiO_2, 6% Et_2O/hexane); IR (ν_{max} /cm^{-1}): 2840, 1609, 1150, 1098; ^1H NMR (400MHz, $CDCl_3$, 293K, TMS): 3.80 (3H, s), 3.86 (3H, s), 5.03 (2H, s), 6.39 (2H, dd, *J*= 2.4, 12.3 Hz), 7.31 (1H, d, *J*= 8.4 Hz), 7.38-7.47 (2H, m), 7.78 (3H, m); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 54.9, 55.5, 70.7, 93.9, 94.6, 107.2, 122.4, 124.5, 125.2, 125.9, 127.2, 127.7, 128.1, 128.6, 132.1, 134.2, 157.3, 159.5, 161.2; HRMS calcd for $C_{19}H_{16}O_3$ (M^+): 292.1099; Found: 292.1086.

6,6-Dimethyl-2-nitro-6H-benzo[c]chromene



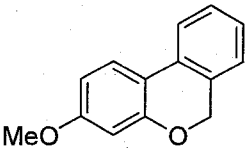
The compound was prepared following the general cyclization procedure at 50°C (94%): mp = 92-95°C(ether); R_f = 0.23 (SiO_2, 3% ether/hexane); IR (ν_{max} /cm^{-1}): 2982, 1518, 1339, 1266, 1106; ^1H NMR (400MHz, $CDCl_3$, 293K, TMS): 1.67 (6H, s), 7.00 (1H, d, *J*=8.9Hz), 7.25-7.27 (1H, m), 7.36-7.43 (2H, m), 7.76-7.79 (1H, s), 8.10 (1H, dd, *J*=8.9, 2.7Hz), 8.64 (1H, d, *J*=2.7Hz); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 27.9, 79.5, 118.4, 118.9, 122.4, 122.5, 123.4, 124.9, 126.3, 128.2, 129.4, 138.7, 142.2, 158.2; HRMS calcd for $C_{15}H_{13}O_3N$ (M+) 255.0895; found: 255.0873.

1-(1,2-Dimethoxy-4,5,6a,7-tetrahydro-dibenzoquinoline-6-carboxylic acid tert-butyl ester



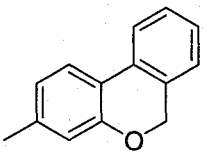
The compound was prepared according to the general cyclization procedure but the reaction was performed at 70°C (70%). R_f = 0.57 (100% EtOAc); mp = 149-151 °C ($CHCl_3$); IR (ν_{max} /cm^{-1}): 3070, 2930, 1687, 1406, 1249, 1163, 1106 cm^{-1}. ^1H NMR (300MHz, $CDCl_3$, 293K, TMS): 1.49 (9H, s), 2.63-3.00 (5H, m), 3.66 (3H, s), 3.89 (3H, s), 4.41-4.44 (1H, m), 4.64-4.69 (1H, m), 6.67 (1H, s), 7.21-7.34 (3H, m), 8.44 (1H, d, *J*=7.8 Hz); ^{13}C NMR (75MHz, $CDCl_3$, 293K, TMS) : 28.8, 30.7, 35.7, 38.7, 51.9, 56.2, 60.3, 80.2, 111.7, 126.8, 127.3, 127.9, 128.0, 128.4, 128.7, 130.1, 132.0, 137.3, 145.8, 152.2, 155.0; HRMS calculated for $C_{23}H_{27}NO_4$ (M+) 381.1940; found: 381.1943.

3-Methoxy-6H-benzo[c]chromene



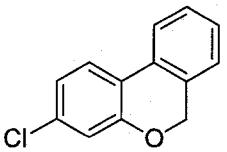
The compound was prepared according to the general cyclization procedure and isolated with 1-methoxy-6H-benzo[c]chromene as a minor contaminant in a >30:1 ratio and and exhibited spectral data identical to previous reports[223] (99%).

3-Methyl-6H-benzo[c]chromene



The compound was prepared according to the general cyclization procedure and isolated with 1-methyl-6H-benzo[c]chromene as a minor contaminant in a >30:1 ratio (98%). R_f = 0.27 (SiO_2, 3% ether/hexane); IR (ν_{max} /cm^{-1}): 2963, 1618, 1484, 1151, 1031; ^1H NMR (400MHz, $CDCl_3$, 293K, TMS): 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 (100MHz, $CDCl_3$, 293K, TMS): 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; HRMS calcd for $C_{14}H_{12}O$ (M+) 196.0888; Found: 196.0876.

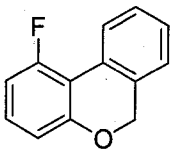
3-Chloro-6H-benzo[c]chromene



The compound was prepared according to the general cyclization procedure and isolated with 1-chloro-6H-benzo[c]chromene as a minor contaminant in a 15:1 ratio (96%). R_f = 0.28 (SiO_2, 3% ether/hexane); IR (ν_{max} /cm^{-1}): 2850, 1479, 1198, 1017; ^1H NMR (400MHz, $CDCl_3$, 293K, TMS): 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 (100MHz, $CDCl_3$, 293K, TMS, 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; HRMS calcd for $C_{15}H_{12}O_3$ (M+) 240.0786; Found: 240.0789.

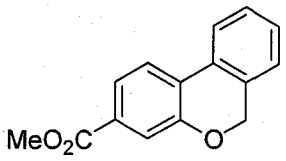
[223] Commercially Available – CAS#: 679810-63-0

1-Fluoro-6H-benzo[c]chromene[224]



The compound was prepared according to the general cyclization procedure and isolated with 3-fluoro-6H-benzo[c]chromene as a minor contaminant in a 1.2:1 ratio (93%). R_f = 0.28 (SiO_2, 3% ether/hexane); IR (ν_{max} /cm^{-1}): 3063, 2839, 1619, 1294, 1228; ^1H NMR (400MHz, $CDCl_3$, 293K, TMS): 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*= 1.0, 7.0 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*= 2,5, 10.0 Hz), 6.84 (1H, m, overlapping with major), 7.76 (1H, d, *J*= 7.5 Hz), 7.87 (1H, d, *J*= 6.5, 9.0 Hz), 3H complete overlap with major isomer; ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 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); HRMS calcd for $C_{13}H_9OF$ (M+) 200.0637; Found: 200.0650.

Methyl 6H-benzo[c]chromene-3-carboxylate

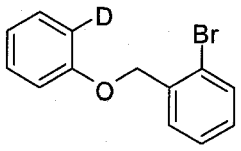


The compound was prepared according to the general cyclization procedure and isolated with 1-methyl-6H-benzo[c]chromene as a minor contaminant in a >30:1 ratio (92%). mp 93-94 °C (acetone); R_f = 0.36 (SiO_2, 5% ether/hexane); IR (ν_{max} /cm^{-1}): 2947, 1707, 1412, 1308, 1233, 1197; ^1H NMR (400MHz, $CDCl_3$, 293K, TMS): 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 (100MHz, $CDCl_3$, 293K, TMS): 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; HRMS calcd for $C_{15}H_{12}O_3$ (M+) 240.0786; Found: 240.0788.

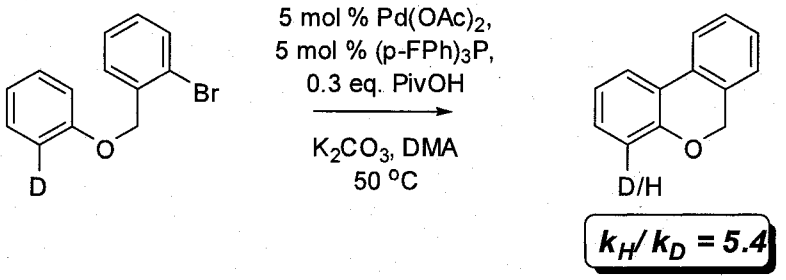
[224] Campeau, L.-C; Parisien, M.; Jean, A.; Fagnou, F. *J. Am. Chem. Soc.* **2006**, *128*, 581.

6.4.2.3 Kinetic Isotope Effect Experiment

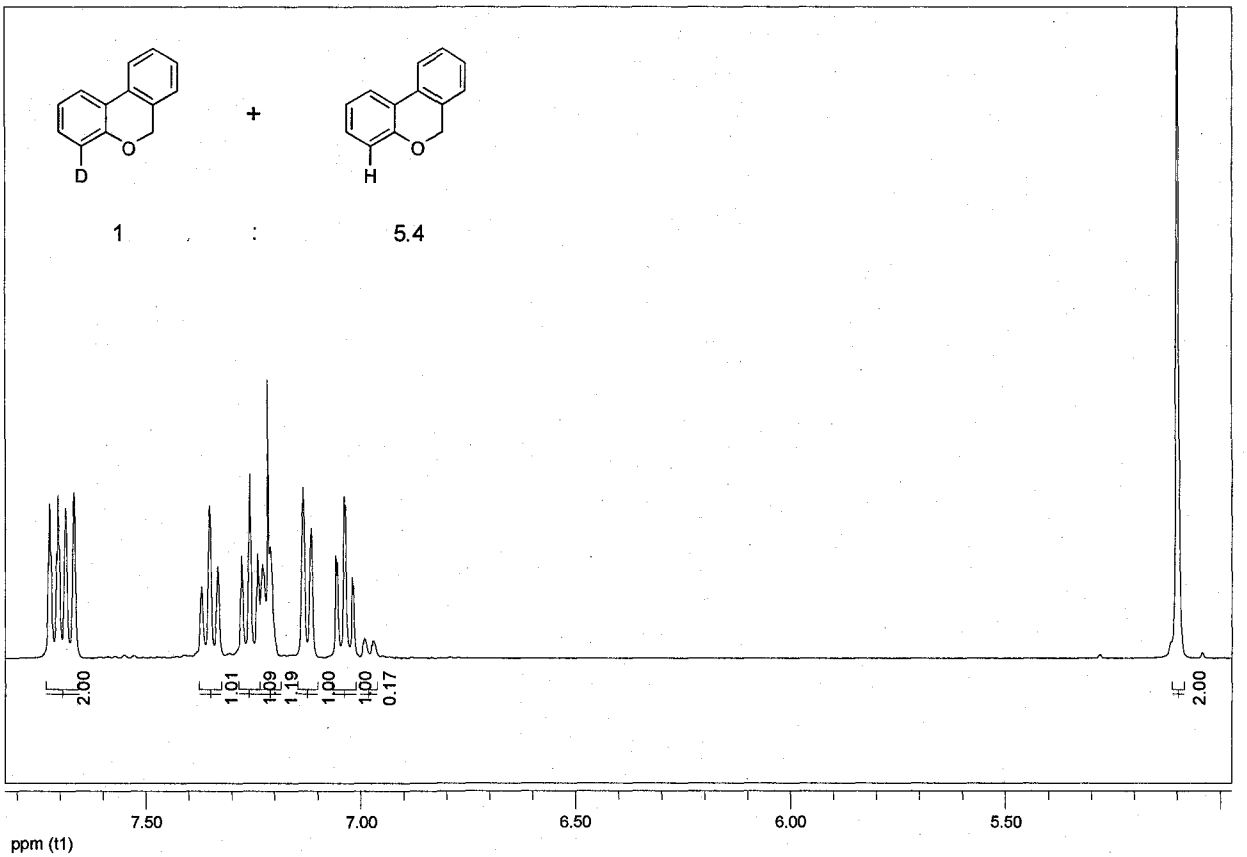
(2-Bromobenzyloxy)-2-*d*-benzene



The compound was prepared according to the general procedure and exhibited spectral data identical to previous reports (93%). Rf = 0.64 on silica gel (5% EtOAc:Hexanes); IR *(vmax* /cm-1) 3030 (weak), 1515, 1240, 1028, 819, 735 ; 1H NMR (300MHz, CDCl3, 293K, TMS): 5.14 (2H, s), 6.98 (2H, m), 7.18 (1H, td, *J*=7.6 et *J*=1.6), 7.31 (3H, m), 7.57 (2H, m); 13C NMR (75MHz, CDCl3, 293K, TMS): 69.27, 114.87, 121.16, 122.23, 127.56, 128.84, 129.18, 129.43, 129.53, 132.59, 136.33, 158.36; HRMS calculated for $C_{10}H_{13}DBrO$ (M+) 263.0055; Found 263.0066;



K_2CO_3 (1.7mmol, 3.0eq.), $Pd(OPiv)_2$ (0.03, 0.05eq.), P(*p*-FPh)$_3$ (0.03, 0.05eq.) and pivalic acid (0.17mmol, 0.3eq.) were weighed to air and placed in a screw capped vial (4mL) with a magnetic stir bar. The reaction vessel was evacuated and backfilled with argon 3 times. The cyclization precursor (0.57mmol, 1.0eq.) was then added to the reaction vessel as a solution in *N,N*-dimethylacetamide (3mL). The reaction was heated to 50°C for 12 hours. Upon completion, the reaction was cooled to room temperature. Upon completion, the reaction was cooled to room temperature. The resulting mixture was then loaded directly onto a silica gel packed flash chromatography column and eluted with 3% ether/hexane mixture. The product distribution was then analyzed by ^{1}HNMR.

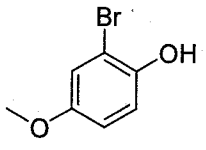


6.5 Experimental Data for Section 4: Intramolecular Direct Alkylation of Aryl Halides

6.6.1 Synthesis of 2,2-dialkyldihydrobenzofurans

6.6.1.1 Synthesis of the Cyclization Precursors

3-Bromo-4-hydroxyanisole



The 2-bromophenol was prepared following literature preparation[225] and exhibited the same spectral data as previously reported (99%). ^{1}H NMR (400MHz, $CDCl_3$, 293K,

[225] Zaja, M.; Connon, S.J.; Dunne, A.M.; Rivard, M.; Buschmann, N.; Jiricek, J.; Blechert, S. *Org. Lett.*, **2004**, *6*, 457.

TMS): 3.75 (3H, s), 5.17 (1H, s), 6.80 (1H, dd, *J* = 9.0, 2.9 Hz), 6.94 (1H, d, *J* = 9.0 Hz), 7.01 (1H, d, *J* = 2.9 Hz).

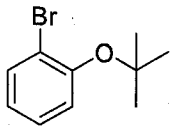
General Procedure A:

To a solution of phenol (5.8mmol) in dichloromethane (6.5mL) at -78°C was added liquefied isobutylene (5mL). To this vigorously stirred solution was added slowly trifluoromethanesulfonic acid (0.46mmol) and the resulting mixture was stirred for an additional 4h at -78°C. Triethylamine was then added (0.46mmol) and the solution was allowed to warm to room temperature. The solvents were then evaporated and the products were purified using chromatography on column using ether/hexanes mixtures.

General Procedure B:

To a flask containing a suspension of potassium hydride (2.5mmol) in THF (3mL) at 0°C was added slowly the corresponding tertiary alcohol (2.5mmol) and the solution was stirred for 10mins. The newly generated tertiary alkoxy was then added slowly to a solution of 2-bromo-1-fluoro-4-nitrobenzene (2.3mmol) in tetrahydrofuran (11mL) at 0°C. The solution was then allowed to warm to room temperature and was stirred for 2h. Saturated aqueous ammonium chloride was then added and the solution was extracted with DCM and dried over magnesium sulfate. The products were then purified using chromatography on column using ether/hexanes mixtures.

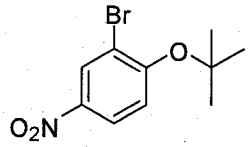
2-*Tert*-butoxybromobenzene



The compound was prepared following the general procedure A (99%): R_f = 0.51 (SiO_2, 6% ether/hexane); IR (ν_{max} /cm^{-1}): 2979, 1470, 1165; ^1H NMR (400MHz, $CDCl_3$, 293K, TMS): 1.43 (9H, s), 6.91 (1H, td, *J*=7.9, 1.6Hz), 7.11 (1H, dd, *J*= 8.2, 1.6Hz), 7.19 (1H,

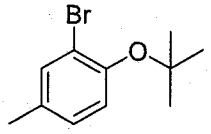
td, *J*=8.2, 1.6Hz), 7.55 (1H, dd, *J*=7.9, 1.6Hz); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 29.0, 81.3, 119.2, 123.9, 124.2, 127.8, 133.4, 153.3; HRMS calcd for $C_{10}H_{13}OBr$ (M+) 228.0150; found: 228.0132.

2-Bromo-1-tert-butoxy-4-nitrobenzene



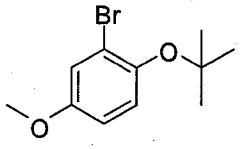
The compound was prepared following the general procedure B but employing potassium *tert*-butoxide (8xs4%): R_f = 0.35 (SiO_2, 10% ether/hexane); IR (ν_{max} /cm^{-1}): 2982, 1580, 1518, 1474, 1344, 1283, 1155; ^{1}H NMR (400MHz, $CDCl_3$, 293K, TMS): 1.54 (9H, s), 7.20 (1H, d, *J*=9.1Hz), 8.12 (1H, dd, *J*=9.1, 2.8Hz), 8.44 (1H, d, *J*=2.8Hz); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 28.9, 83.4, 117.5, 119.9, 123.7, 129.0, 142.2, 159.3; HRMS calcd for $C_{10}H_{12}O_3NBr$ (M+) 273.0001; found: 273.0017.

1-*Tert*-butoxy-2-bromo-4-methylbenzene



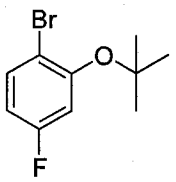
The compound was prepared following the general procedure A (99%): R_f = 0.25 (SiO_2, 2% ether/hexane); IR (ν_{max} /cm^{-1}): 2978, 1485, 1161; ^{1}H NMR (400MHz, $CDCl_3$, 293K, TMS): 1.41 (9H, s), 2.27 (3H, s), 6.98-6.99 (2H, m), 7.36 (1H, s); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 20.4, 29.0, 80.9, 118.9, 123.8, 128.4, 133.6, 134.1, 150.8; HRMS calcd for $C_{11}H_{15}OBr$ (M+) 242.0306; found: 242.0290.

2-Bromo-1-tert-butoxy-4-methoxybenzene



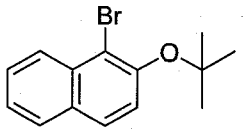
The compound was prepared following the general procedure A (99%): R_f = 0.25 (SiO_2, 3% ether/hexane); IR (ν_{max} /cm^{-1}): 2977, 1599, 1487, 1366, 1264, 1217, 1163, 1038; ^1H NMR (400MHz, $CDCl_3$, 293K, TMS): 1.39 (9H, s), 3.76 (3H, d, *J*=1.2Hz), 6.75 (1H, dd, *J*=8.9, 3.1Hz), 7.02 (1H, d, *J*=8.9Hz), 7.09 (1H, d, *J*=3.1Hz); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 28.9, 55.6, 80.9, 113.6, 118.0, 119.5, 124.6, 146.8, 155.6; HRMS calcd for $C_{11}H_{15}O_2Br$ (M+) 258.0255; found: 258.0221.

1-*Tert*-butoxy-2-bromo-5-fluorobenzene



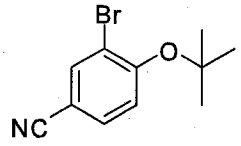
The compound was prepared following the general procedure A (93%): mp = 52-53°C(ether); R_f = 0.29 (SiO_2, 2% ether/hexane); IR (ν_{max} /cm^{-1}): 2974, 1600, 1475, 1151; ^1H NMR (400MHz, $CDCl_3$, 293K, TMS): 1.45 (9H, s), 6.68 (1H, ddd, *J*=8.8, 7.8, 2.9Hz), 6.86 (1H, dd, *J*=10.2, 2.9Hz), 7.48 (1H, dd, *J*=8.8, 6.4Hz); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 28.9, 82.1, 110.9 (d, *J*=17.6Hz), 111.2 (d, *J*=16.6Hz), 113.3 (d, *J*=3.9Hz), 133.4 (d, *J*=9.6Hz), 154.3 (d, *J*=10.5Hz), 161.9 (d, *J*=246.7Hz); ^{19}F NMR (377MHz, $CDCl_3$, 293K, TMS): -118.16; HRMS calcd for $C_{10}H_{12}OBrF$ (M+) 246.0056; found: 246.0060.

2-*Tert*-butoxy-1-bromonaphthalene



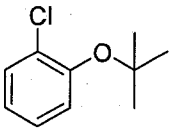
The compound was prepared following the general procedure A using 30 mL of DCM instead (98%): R_f = 0.27 (SiO_2, 2% ether/hexane); IR (ν_{max} /cm^{-1}): 2980, 1474, 1165; ^1H NMR (400MHz, $CDCl_3$, 293K, TMS): 1.49 (9H, s), 7.32 (1H, d, *J*=8.9Hz), 7.41 (1H, ddd, *J*= 8.1, 6.9, 1.1Hz), 7.54 (1H, ddd, *J*=8.3, 6.9, 1.1Hz), 7.69 (1H, d, *J*=8.9Hz), 7.77 (1H, d, *J*=8.1Hz), 8.26 (1H, d, *J*=8.3Hz); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 29.4, 81.8, 117.1, 123.6, 125.0, 127.1, 127.3, 127.9, 127.9, 131.1, 133.2, 151.5; HRMS calcd for $C_{14}H_{15}OBr$ (M+-C_2H_6) 247.9837; found: 247.9810.

3-Bromo-4-*tert*-butoxybenzonitrile



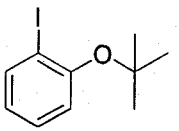
To a solution of 3-bromo-4-fluorobenzonitrile (0.5g, 2.5mmol, 1.0 eq.) in DMF (8mL) was added potassium *tert*-butoxide (0.42g, 3.8mmol, 1.5eq.) and the solution was heated to 135°C overnight. The reaction was then quenched with water and the solution was extracted with Et_2O and dried over magnesium sulfate. The product was then purified using chromatography on column using 3% ether/hexane as the eluent. (81%): R_f = 0.21 (SiO_2, 3% ether/hexane); IR (ν_{max} /cm^{-1}): 2981, 2228, 1594, 1484, 1370, 1271, 1160; ^1H NMR (400MHz, $CDCl_3$, 293K, TMS): 1.50 (9H, s), 7.18 (1H, d, *J*=8.6Hz), 7.53 (1H, dd, *J*=8.5, 2.1Hz), 7.83 (1H, d, *J*=2.1Hz); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 28.7, 82.8, 106.4, 117.4, 118.1, 121.5, 131.8, 136.6, 157.4; HRMS calcd for $C_{11}H_{12}NOBr$ (M+) 253.0102; found: 252.9895.

2-*Tert*-butoxychlorobenzene



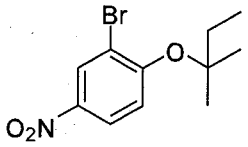
The compound was prepared following the general procedure A (98%): R_f = 0.43 (SiO_2, 3% ether/hexane); IR (ν_{max} /cm^{-1}): 2982, 1473, 1165; ^1H NMR (400MHz, $CDCl_3$, 293K, TMS): 1.41 (9H, s), 6.98 (1H, ddd, *J*=7.9, 7.1, 1.9Hz), 7.09-7.17 (1H, m), 7.36 (1H, dd, *J*=8.0, 1.6Hz); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 28.9, 81.2, 124.0, 124.7, 127.0, 129.2, 130.3, 152.1; HRMS calcd for $C_{10}H_{13}OCl$ (M+) 184.0655; found: 184.0656.

2-*Tert*-butoxyiodobenzene



The compound was prepared following the general procedure A (99%): R_f = 0.46 (SiO_2, 3% ether/hexane); IR (ν_{max} /cm^{-1}): 2978, 1466, 1165; ^1H NMR (400MHz, $CDCl_3$, 293K, TMS): 1.46 (9H, s), 6.75 (1H, td, *J*=7.6, 1.4Hz), 7.08 (1H, dd, *J*= 6.8, 1.4Hz), 7.22 (1H, td, *J*=7.1, 1.6Hz), 7.78 (1H, dd, *J*=6.3, 1.6Hz); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 29.3, 81.2, 94.8, 121.7, 124.4, 128.8, 139.4, 156.1; HRMS calcd for $C_{10}H_{13}OBr$ (M+) 276.0011; found: 276.0023.

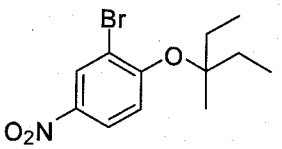
2-Bromo-4-nitro-1-(*tert*-pentyloxy)benzene



The compound was prepared following the general procedure B (73%): R_f = 0.41 (SiO_2, 10% ether/hexane); IR (ν_{max} /cm^{-1}): 2978, 1580, 1517, 1474, 1343, 1279, 1154; ^1H NMR (400MHz, $CDCl_3$, 293K, TMS): 1.04 (3H, t, *J*=7.5Hz), 1.49 (6H, s), 1.86 (2H, q, *J*=7.5Hz), 7.17 (1H, d, *J*=9.1Hz), 8.12 (1H, dd, *J*=9.1, 2.8Hz), 8.44 (1H, d, *J*=2.8Hz); ^{13}C NMR

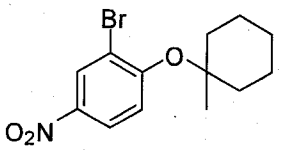
(100MHz, $CDCl_3$, 293K, TMS): 8.4, 26.0, 35.0, 85.6, 116.9, 118.9, 123.6, 129.0, 141.7, 159.1; HRMS calcd for $C_{11}H_{14}O_3NBr$ (M+) 287.0157; found: 287.0147.

2-Bromo-1-(3-methylpentan-3-yloxy)-4-nitrobenzene



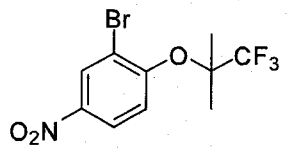
The compound was prepared following the general procedure B (76%): R_f = 0.26 (SiO_2, 3% ether/hexane); IR (ν_{max} /cm^{-1}): 2975, 1582, 1516, 1472, 1341, 1275; ^1H NMR (400MHz, $CDCl_3$, 293K, TMS): 0.98 (6H, t, *J*=7.5Hz), 1.44 (3H, s), 1.87 (4H, m), 7.13 (1H, d, *J*=9.2Hz), 8.11 (1H, dd, *J*=9.2, 2.8Hz), 8.45 (1H, d, *J*=2.8Hz); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 8.1, 23.5, 31.5, 88.2, 116.4, 118.0, 123.7, 129.1, 141.5, 159.1; HRMS calcd for $C_{12}H_{16}O_3NBr$ (M+) 301.0314; found: 301.0292.

2-Bromo-1-(1-methylcyclohexyloxy)-4-nitrobenzene



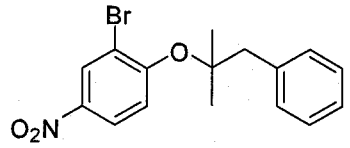
The compound was prepared following the general procedure B (69%): R_f = 0.28 (SiO_2, 3% ether/hexane); IR (ν_{max} /cm^{-1}): 2936, 1582, 1516, 1473, 1341, 1246; ^1H NMR (400MHz, $CDCl_3$, 293K, TMS): 1.30-1.39 (1H, m), 1.49 (3H, s), 1.51-1.77 (7H, m), 2.15-2.19 (2H, m), 7.16 (1H, d, *J*=9.2Hz), 8.12 (1H, dd, *J*=9.2, 2.8Hz), 8.45 (1H, d, *J*=2.8Hz); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 22.0, 25.1, 25.9, 37.6, 84.3, 116.3, 117.9, 123.7, 139.1, 141.4, 158.9; HRMS calcd for $C_{13}H_{16}O_3NBr$ (M+) 313.0314; found: 313.0295.

2-Bromo-4-nitro-1-(1,1,1-trifluoro-2-methylpropan-2-yloxy)benzene



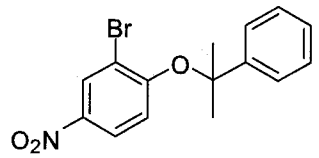
The compound was prepared following the general procedure B (79%): R_f = 0.25 (SiO_2, 3% ether/hexane); IR (ν_{max} /cm^{-1}): 3001, 1525, 1474, 1347, 1167, 1127; ^1H NMR (400MHz, $CDCl_3$, 293K, TMS): 1.61 (6H, q, *J*=1.0Hz), 7.31 (1H, d, *J*=9.0Hz), 8.16 (1H, dd, *J*=9.0, 2.8Hz), 8.47 (1H, d, *J*=2.8Hz); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 20.9 (q, *J*=1.2Hz), 82.4 (q, *J*=29.5Hz), 111.4, 119.0, 123.6, 125.1 (q, *J*=284.2Hz), 129.1, 144.1, 157.0; ^{19}F NMR (377MHz, $CDCl_3$, 293K, TMS): -86.4; HRMS calcd for $C_{10}H_9O_3NF_3Br$ (M+) 326.9718; found: 326.9698.

2-Bromo-1-(2-methyl-1-phenylpropan-2-yloxy)-4-nitrobenzene



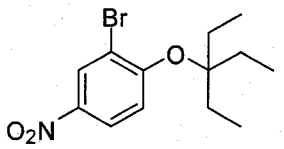
The compound was prepared following the general procedure B (82%): R_f = 0.31 (SiO_2, 5% ether/hexane); IR (ν_{max} /cm^{-1}): 2979, 1516, 1343, 1279, 1118; ^1H NMR (400MHz, $CDCl_3$, 293K, TMS): 1.46 (6H, s), 3.13 (2H, s), 7.12 (1H, d, *J*=9.1Hz), 7.24-7.31 (5H, m), 8.09 (1H, dd, *J*=9.1, 2.8Hz), 8.45 (1H, d, *J*=2.8Hz); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 26.3, 48.8, 85.4, 117.5, 120.2, 123.5, 126.6, 128.0, 129.0, 130.8, 136.6, 142.2, 159.0; HRMS calcd for $C_{16}H_{16}O_3NBr$ (M+) 349.0314; found: 349.0324.

2-Bromo-4-nitro-1-(2-phenylpropan-2-yloxy)benzene



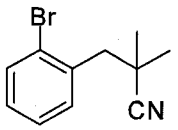
The compound was prepared following the general procedure B (83%): R_f = 0.30 (SiO_2, 5% ether/hexane); IR (ν_{max} /cm^{-1}): 2984, 1516, 1473, 1341, 1275, 1138; ^1H NMR (400MHz, $CDCl_3$, 293K, TMS): 1.85 (6H, s), 6.36 (1H, d, *J*=9.2Hz), 7.28-7.41 (5H, m), 7.80 (1H, dd, *J*=9.2, 2.8Hz), 8.42 (1H, d, *J*=2.8Hz); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 29.3, 83.9, 114.5, 116.8, 123.4, 124.9, 127.8, 128.9, 128.9, 141.0, 144.1, 158.4; HRMS calcd for $C_{15}H_{14}O_3NBr$ (M+) 335.0157; found: 335.0105.

2-Bromo-1-(3-ethylpentan-3-yloxy)-4-nitrobenzene



The compound was prepared following the general procedure B (74%): R_f = 0.39 (SiO_2, 5% ether/hexane); IR (ν_{max} /cm^{-1}): 2973, 1582, 1517, 1472, 1341, 1274; ^1H NMR (400MHz, $CDCl_3$, 293K, TMS): 0.92 (9H, t, *J*=7.5Hz), 1.87 (4H, q, *J*=7.5Hz), 7.13 (1H, d, *J*=9.2Hz), 8.10 (1H, dd, *J*=9.2, 2.8Hz), 8.44 (1H, d, *J*=2.8Hz); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 7.8, 28.1, 90.7, 115.5, 116.7, 123.8, 129.1, 141.0, 159.1; HRMS calcd for $C_{13}H_{18}O_3NBr$ (M+) 315.0470; found: 315.0451.

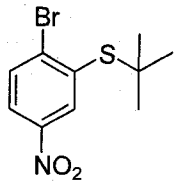
3-(2-Bromophenyl)-2,2-dimethylpropanenitrile



To a solution of isobutyronitrile (0.8mL, 9.0mmol, 1.2eq.) in THF (15mL) was added slowly fresh LDA (9.0mmol, 1.2eq.) at -78°C and the solution was stirred for 30 mins. A solution of 2-bromobenzyl bromide in THF was then added slowly and the resulting solution was allowed to warm to room temperature and stirred for 2h. The solution was then quenched with water and extracted. Purification was preformed by silica column chromatography (2% ether/hexane) to give 1.04g of a clear oil (73%): R_f = 0.27 (SiO_2, 2% ether/hexane); IR (ν_{max} /cm^{-1}): 2980, 2241, 1466, 1025; ^1H NMR (400MHz, $CDCl_3$,

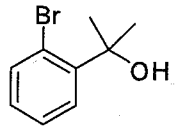
293K, TMS): 1.42 (6H, s), 3.08 (2H,s), 7.15 (1H, dt, *J*=7.5, 1.6Hz), 7.32 (1H, dt, *J*=7.6, 1.2Hz), 7.50 (1H, dd, *J*=7.8, 1.6Hz), 7.59 (1H, dd, *J*=7.9, 1.2Hz); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 26.6, 34.2, 44.4, 124.7, 125.8, 127.6, 129.0, 131.9, 133.1, 135.6; HRMS calcd for $C_{11}H_{12}NBr$ (M+) 237.0153; found: 237.0128.

Tert-butyl(2-bromo-5-nitrophenyl)sulfane



The compound was prepared following the general procedure B (77%): R_f = 0.22 (SiO_2, 3% ether/hexane); IR (ν_{max} /cm^{-1}): 2964, 1519, 1365, 1345, 1162; ^1H NMR (400MHz, $CDCl_3$, 293K, TMS): 1.45 (9H, s), 7.78 (1H, d, *J*=8.6Hz), 8.12 (1H, dd, *J*=8.6, 2.5Hz), 8.49 (1H, d, *J*=2.5Hz); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 31.0, 49.7, 121.6, 128.0, 130.0, 136.1, 144.4, 146.9; HRMS calcd for $C_{10}H_{12}O_2NSBr$ (M+) 288.9772; found: 288.9784.

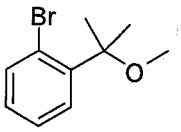
σ-Bromophenyldimethylcarbinol



A solution of 2'-bromoacetophenone (5.0g, 25.1mmol, 1.0 eq.) in ether (23 mL) was added dropwise to a magnetically stirred solution of methyl magnesium iodide (29.6mmol, 1.18 eq.) in ether (7mL) under a argon atmosphere. Upon complete addition, the reaction was stirred at room temperature for an additional 30 min. The reaction was then quenched by slow addition of a 5% HCl solution at 0°C until the ph was acidic. The layers were then separated, dried on magnesium sulfate and concentrated to give the crude product. Purification was preformed by silica column

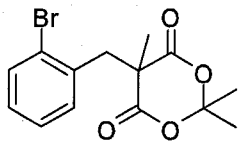
chromatography (50% ether/hexane) to give a clear oil (4.1g, 76% yield). Spectral properties exhibited data identical to that reported in the literature.[226]

1-Bromo-2-(2-methoxypropan-2-yl)benzene



A solution of σ-bromophenyldimethylcarbinol (1g, 4.6mmol, 1.0 eq.) in THF (15 mL) was added NaH (0.28g, 7.0mmol, 1.5 eq.) and the solution was stirred for 30 mins at room temperature. The reaction was then quenched by slow addition of iodomethane (0.4mL, 7.0mmol, 1.5 eq). The solution was stirred for another 3h and then extracted with water/ether. Purification was preformed by silica column chromatography (100% hexane) to give 0.92g of a clear oil. (88%): R_f = 0.29 (SiO_2, 1% ether/hexane); IR (ν_{max} /cm^{-1}): 2978, 1464, 1427, 1172, 1073; ^{1}H NMR (400MHz, $CDCl_3$, 293K, TMS): 1.68 (6H, s), 3.10 (3H, s), 7.09 (1H, dt, *J*=7.3, 1.7Hz), 7.28 (1H, dt, *J*=7.3, 1.4Hz), 7.44 (1H, dd, *J*=7.9, 1.7Hz), 7.62 (1H, dd, *J*=7.9, 1.3Hz); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 26.8, 50.6, 78.0, 121.4, 127.2, 128.6, 128.9, 135.7, 143.0; HRMS calcd for $C_{10}H_{13}OBr$ (M+) 228.0150; found: 228.0122.

5-(2-Bromobenzyl)-2,2,5-trimethyl-1,3-dioxane-4,6-dione

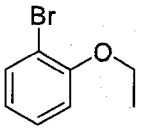


A solution of 2,2,5-trimethyl-1,3-dioxane-4,6-dione (0.72g, 4.6mmol, 1.1 eq.) in DMF (10 mL) was added NaH (0.20g, 5.0mmol, 1.2 eq.) and the solution was stirred for 30 mins at room temperature. To this solution was added 2-bromobenzyl bromide (1.04g, 4.2mmol, 1.0 eq) in DMF (5mL). Water was added and the product crystallized. The product was then triturated using Et_2O to give 0.94g of a white solid. (72%): mp = 118-119°C; R_f = 0.29 (SiO_2, 1% ether/hexane); IR (ν_{max} /cm^{-1}): 2994, 1742, 1383, 1267, 1204; ^{1}H NMR (400MHz, $CDCl_3$, 293K, TMS): 1.32 (3H, s), 1.66 (3H, s), 1.74 (3H, s),

[226] Wursthorn, K.R.; Kuivila, H. G., Smith, G. F. *J. Am. Chem. Soc.* **1978**, *100*, 2779.

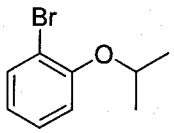
3.55 (2H, s), 7.10-7.14 (1H, m), 7.22-7.25 (2H, m), 7.56 (1H, dd, *J*=7.7, 0.8Hz), 7.62 (1H, dd, *J*=7.9, 1.3Hz); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 24.3, 28.2, 29.9, 44.2, 50.2, 105.3, 125.6, 127.5, 129.3, 131.6, 133.5, 134.6, 169.3; HRMS calcd for $C_{14}H_{15}O_4Br$ (M+) 326.0154; found: 326.0127.

1-Bromo-2-ethoxybenzene



To a solution of 2-bromophenol (1g, 5.8mmol, 1.0 equiv.) in DMF (15mL) was added at 0°C, 60% in dispersion oil NaH (0.24g, 6.4mmol, .1 equiv.). The solution was allowed to stir for 5 min. Iodoethane (0.56mL, 6.9mmol, 1.2 equiv.) was then added slowly. The solution was stirred for 3h at room temperature. The product was extracted using water and Et_2O followed by purification on chromatography on silica (2% ether/hexane). (97%): R_f = 0.43 (SiO_2, 2% ether/hexane); IR (ν_{max} /cm^{-1}): 2982, 1472, 1277, 1248; ^{1}H NMR (400MHz, $CDCl_3$, 293K, TMS): 1.44 (3H, t, *J*=7.0Hz), 4.06 (2H, q, *J*=7.0Hz), 6.79 (1H, dt, *J*= 7.7, 1.3Hz), 6.85 (1H, dd, *J*=8.2, 1.3Hz), 7.21 (1H, ddd, *J*=8.2, 7.3, 1.6Hz), 7.51 (1H, dd, *J*=7.9, 1.6Hz); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 14.7, 64.7, 112.1, 113.2, 121.6, 128.4, 133.3, 155.3; HRMS calcd for C_8H_9OBr (M+) 199.9831; found: 199.9818.

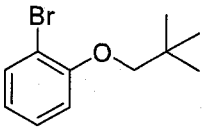
1-Bromo-2-isopropoxybenzene



To a solution of 2-bromophenol (1g, 5.8mmol, 1.0 equiv.), K_2CO_3 (1.6g, 11.6mmol, 2.0 equiv.) and potassium iodide (1.63g, 11.6mmol, 2.0 equiv.) in DMF (20mL) was added at room temperature 2-bromopropane (1.08mL, 11.6mmol, 2.0 equiv.) slowly. The solution was heated to 50°C for 10h. The product was extracted using water and Et_2O followed by purification on chromatography on silica (2% ether/hexane). (99%): R_f = 0.45 (SiO_2, 2% ether/hexane); IR (ν_{max} /cm^{-1}): 2978, 1476, 1275, 1246, 1106; ^{1}H NMR (400MHz, $CDCl_3$, 293K, TMS): 1.36 (6H, d,

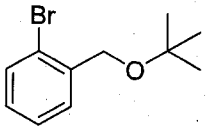
J=6.1Hz), 4.52 (1H, hept., *J*=6.1Hz), 6.79 (1H, dt, *J*= 7.7, 1.3Hz), 6.89 (1H, dd, *J*=8.3, 1.3Hz), 7.20 (1H, ddd, *J*=8.3, 7.5, 1.6Hz), 7.51 (1H, dd, *J*=7.9, 1.6Hz); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 27.6, 63.5, 122.2, 127.3, 128.3, 128.8, 132.1, 139.1; HRMS calcd for $C_9H_{11}OBr$ (M+) 213.9993; found: 214.0003.

1-Bromo-2-(neopentyloxy)benzene



To a solution of 2-bromophenol (1g, 5.8mmol, 1.0 equiv.) and Cs_2CO_3 (2.8g, 8.7mmol, 1.5 equiv.) in DMF (10mL) was added at room temperature 1-bromo-2,2-dimethylpropane (1.1mL, 8.7mmol, 1.5 equiv.) slowly. The solution was heated to 130°C for 10h. The product was extracted using water and Et_2O followed by purification on chromatography on silica (2% ether/hexane). (99%): R_f = 0.63 (SiO_2, 6% ether/hexane); IR (ν_{max} /cm^{-1}): 2957, 1474, 1248, 1054; ^{1}H NMR (400MHz, $CDCl_3$, 293K, TMS): 1.08 (9H, s), 3.61 (2H, s), 6.77 (1H, dt, *J*= 7.6, 1.3Hz), 6.82 (1H, dd, *J*=8.2, 1.3Hz), 7.20 (1H, ddd, *J*=8.2, 6.5, 1.6Hz), 7.50 (1H, dd, *J*=7.8, 6.3, 1.6Hz); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 26.6, 78.7, 112.3, 112.8, 121.4, 128.3, 133.1, 155.7; HRMS calcd for $C_{11}H_{15}OBr$ (M+) 242.0306; found: 242.0294.

1-(*Tert*-butoxymethyl)-2-bromobenzene

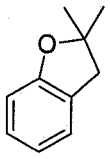


To a suspension of potassium *tert*-butoxide (3.56g, 31.7mmol, 1.5 equiv.) in THF was added 2-bromobenzylbromide (5.28g, 21.1mmol, 1.0 equiv.) slowly. The solution was stirred at room temperature for 10h. The solution was quenched by addition of water and was extracted in Et_2O followed by purification on chromatography on silica (2% ether/hexane). (88%): R_f = 0.28 (SiO_2, 2% ether/hexane); IR (ν_{max} /cm^{-1}): 2974, 1468, 1363, 1195, 1088; ^{1}H NMR (400MHz, $CDCl_3$, 293K, TMS): 1.29 (9H, s), 4.48 (2H, s), 7.07 (1H, dt, *J*= 7.9, 1.1Hz), 7.27 (1H, dt, *J*=7.6, 1.0Hz), 7.47 (1H, dd, *J*=7.9, 1.1Hz), 7.54 (1H, td, *J*=7.7, 0.8Hz); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 27.7, 63.6, 73.8, 122.3, 127.4, 128.4, 128.9, 132.2, 139.2; HRMS calcd for $C_{11}H_{15}OBr$ (M+) 242.0306; found: 242.0286.

6.6.1.2 General Procedure for the Intramolecular Direct Alkylation of Arenes

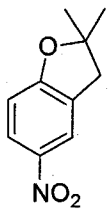
Cs_2CO_3 (0.77 mmol), $Pd(OAc)_2$ (5mol %), PCy_3-HBF_4 (10mol %) and pivalic acid (30mol %) were weighed to air and placed in a screw capped vial (4mL) with a magnetic stir bar. The reaction vessel was evacuated and backfilled with argon (x3). The cyclization precursor (0.70mmol) was then added to the reaction vessel as a solution in mesitylene (3mL). The reaction was heated to 140°C for 12 hours. Upon completion, the reaction was cooled to room temperature. The products were loaded directly onto a silica gel packed flash chromatography column and eluted using ether/hexane mixtures.

2,3-Dihydro-2,2-dimethylbenzofuran



The compound was prepared following the general cyclization procedure at 135°C and exhibited the same spectral data as previously reported[227] (97%). ^{1}H NMR (400MHz, $CDCl_3$, 293K, TMS): 1.51 (6H, s), 3.04 (2H, s), 6.77 (1H, d, *J*= 8.1Hz), 6.85 (1H, t, *J*= 7.2Hz), 7.15 (2H, m);

2,3-Dihydro-2,2-dimethyl-5-nitrobenzofuran

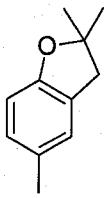


The compound was prepared following the general cyclization procedure at 140°C (91%): mp = 67-68°C(ether); R_f = 0.22 (SiO_2, 3% ether/hexane); IR (ν_{max} /cm^{-1}): 2974,

[227] Kataoka, N.; Shelby, Q.; Stambuli, J.P.; Hartwig, J.F. *J. Org. Chem.*, **2002**, *67*, 5553.

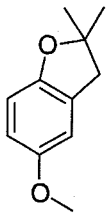
1596, 1507, 1337, 1281; ^{1}H NMR (400MHz, $CDCl_3$, 293K, TMS): 1.53 (6H, s), 3.09 (2H,s), 6.75 (1H, d, *J*=8.8Hz), 8.04-8.05 (1H, m), 8.08 (1H, dd, *J*=8.8, 2.3Hz); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 28.1, 41.9, 90.1, 109.3, 121.6, 125.8, 128.5, 141.5, 164.4; HRMS calcd for $C_{10}H_{11}O_3N$ (M+) 193.0739; found: 193.0440.

2,3-Dihydro-2,2,5-trimethylbenzofuran



The compound was prepared following the general cyclization procedure at 135°C (92%): R_f = 0.40 (SiO_2, 3% ether/hexane); IR (ν_{max} /cm^{-1}): 2973, 1490, 1257; ^{1}H NMR (400MHz, $CDCl_3$, 293K, TMS): 1.44 (6H, s), 2.26 (3H, s), 2.95 (2H,s), 6.61 (1H, d, *J*=8.1Hz), 6.88 (1H, d, *J*=8.1Hz), 6.93 (1H, s); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 20.7, 28.1, 42.9, 86.3, 109.0, 125.7, 127.0, 128.2, 19.0, 156.7; HRMS calcd for $C_{11}H_{14}O$ (M+) 162.1045; found: 162.1023

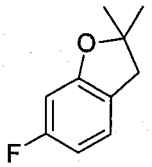
2,3-Dihydro-5-methoxy-2,2-dimethylbenzofuran



The compound was prepared following the general cyclization procedure at 140°C (91%): R_f = 0.24 (SiO_2, 3% ether/hexane); IR (ν_{max} /cm^{-1}): 2972, 1487, 1256, 1209, 1146, 1033; ^{1}H NMR (400MHz, $CDCl_3$, 293K, TMS): 1.45 (6H, s), 2.98 (2H, s), 3.74 (3H,s), 6.61-6.66 (2H, m), 6.73 (1H, dd, *J*=2.2, 1.0Hz); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS):

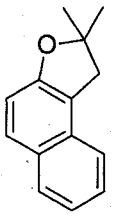
28.1, 43.3, 56.0, 86.5, 109.2, 111.5, 112.7, 128.0, 153.0, 153.7; HRMS calcd for $C_{11}H_{14}O_2$ (M+) 178.0994; found: 178.1003.

6-Fluoro-2,3-dihydro-2,2-dimethylbenzofuran



The compound was prepared following the general cyclization procedure at 135°C (68%): R_f = 0.31 (SiO_2, 2% ether/hexane); IR (ν_{max} /cm^{-1}): 2975, 1614, 1492, 1283, 1129, 1084; ^{1}H NMR (400MHz, $CDCl_3$, 293K, TMS): 1.47 (6H, s), 2.94 (2H, s), 6.45 (1H, dd, *J*=9.6, 2.4Hz), 6.50 (1H, ddd, *J*=9.6, 8.1, 2.4Hz), 7.01 (1H, td, *J*=7.0, 1.1Hz); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 28.1, 42.1, 88.4, 97.9 (d, *J*=26.2Hz), 106.3 (d, *J*=22.6Hz), 122.6 (d, *J*=2.6Hz), 125.2 (d, *J*=10.5Hz), 159.9 (d, *J*=13.0Hz), 163.2 (d, *J*=242.3Hz); ^{19}F NMR (377MHz, $CDCl_3$, 293K, TMS): -119.6; HRMS calcd for $C_{10}H_{11}FO$ (M+) 166.0794; found: 166.0803.

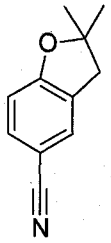
1,2-Dihydro-2,2-dimethylnaphtho[2,1-b]furan



The compound was prepared following the general cyclization procedure at 155°C (79%): R_f = 0.25 (SiO_2, 2% ether/hexane); IR (ν_{max} /cm^{-1}): 2972, 1631, 1465, 1261; ^{1}H NMR (400MHz, $CDCl_3$, 293K, TMS): 1.53 (6H, s), 3.23 (2H,s), 7.06 (1H, d, *J*=8.8Hz), 7.26 (1H, ddd, *J*=8.1, 6.8, 1.3Hz), 7.42 (1H, ddd, *J*=8.1, 6.8, 1.2Hz), 7.51 (1H, td, *J*=8.3, 0.5Hz), 7.64 (1H, d, *J*=8.8Hz), 7.76 (1H, d, *J*=8.2Hz); ^{13}C NMR (100MHz, $CDCl_3$, 293K,

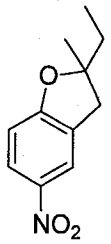
TMS): 28.5, 4.7, 87.5, 112.4, 118.2, 122.5, 122.6, 126.5, 128.7, 128.9, 129.0, 131.1, 156.2; HRMS calcd for $C_{14}H_{14}O$ (M+) 198.1045; found: 198.1040.

2,3-Dihydro-2,2-dimethylbenzofuran-5-carbonitrile



The compound was prepared following the general cyclization procedure at 140°C (78%): R_f = 0.14 (SiO_2, 5% ether/hexane); IR (ν_{max} /cm^{-1}): 2975, 2222, 1611, 1486, 1273, 1091; ^1H NMR (400MHz, $CDCl_3$, 293K, TMS): 1.50 (6H, s), 3.04 (2H, s), 6.76 (1H, d, *J*=8.2), 7.41 (1H, s), 7.42 (1H, d, *J*=8.1Hz); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 27.9, 41.8, 88.7, 102.8, 110.2, 119.6, 128.6, 129.0, 133.3, 162.3; HRMS calcd for $C_{11}H_{11}ON$ (M+) 173.0841; found: 173.0821.

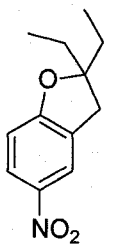
2-Ethyl-2,3-dihydro-2-methyl-5-nitrobenzofuran



The compound was prepared following the general cyclization procedure at 140°C (85%): mp = 45-46°C($CHCl_3$); R_f = 0.17 (SiO_2, 3% ether/hexane); IR (ν_{max} /cm^{-1}): 2973, 1596, 1487,1336, 1255; ^1H NMR (400MHz, $CDCl_3$, 293K, TMS): 0.98 (3H, t, *J*=6.7Hz), 1.47 (3H, s), 1.81 (2H, q, *J*=6.9Hz), 2.99 (1H, d, *J*=15.9Hz), 3.15 (1H, d, *J*=15.9Hz), 6.74 (1H, d, *J*=8.5Hz), 8.04 (1H, s), 8.07 (1H, d, *J*=8.5Hz); ^{13}C NMR (100MHz, $CDCl_3$, 293K,

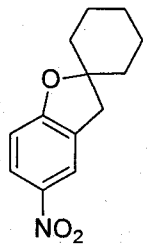
TMS): 8.1, 25.7, 33.6, 39.6, 92.6, 108.9, 121.4, 125.6, 128.4, 141.3, 164.5; HRMS calcd for $C_{11}H_{13}O_3N$ (M+) 207.0895; found: 207.0878.

2,2-Diethyl-2,3-dihydro-5-nitrobenzofuran



The compound was prepared following the general cyclization procedure at 140°C (96%): R_f = 0.21 (SiO_2, 3% ether/hexane); IR (ν_{max} /cm^{-1}): 2972, 1514, 1334, 1267; ^1H NMR (400MHz, $CDCl_3$, 293K, TMS): 0.94 (6H, t, *J*=7.5Hz), 1.77 (4H, q, *J*=7.5Hz), 3.06 (1H, s), 6.74 (1H, d, *J*=8.8Hz), 8.03 (1H, d, *J*=2.4Hz), 8.07 (1H, d, *J*=8.8, 2.4Hz); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 7.6, 31.3, 37.1, 95.0, 108.6, 121.2, 125.6, 128.5, 141.2, 165.0; HRMS calcd for $C_{12}H_{15}O_3N$ (M+) 221.1052; found: 221.1028.

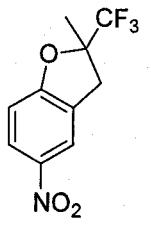
5-Nitrospiro-(benzofuran-2(3H),1'-cyclohexane)



The compound was prepared following the general cyclization procedure at 140°C (90%): mp = 104-106°C; R_f = 0.14 (SiO_2, 3% ether/hexane); IR (ν_{max} /cm^{-1}): 2931, 1593, 1504, 1339; ^1H NMR (400MHz, $CDCl_3$, 293K, TMS): 1.44-1.54 (4H, m), 1.66-1.72 (2H, m), 1.75-1.80 (2H, m), 1.83-1.87 (2H, m), 3.03 (2H, s), 6.75 (1H, d, *J*=8.8Hz), 8.02 (1H, d, *J*=2.4Hz), 8.07 (1H, dd, *J*=8.8, 2.4Hz); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 22.7,

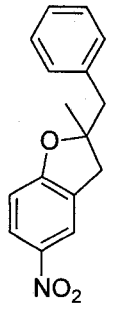
24.8, 36.9, 40.1, 91.9, 109.1, 121.5, 125.6, 128.2, 141.2, 164.3; HRMS calcd for $C_{13}H_{15}O_3N$ (M+) 233.1052; found: 233.1049.

2-(Trifluoromethyl)-2,3-dihydro-2-methyl-5-nitrobenzofuran



The compound was prepared following the general cyclization procedure at 140°C (88%): mp = 109-112°C(ether); R_f = 0.23 (SiO_2, 3% ether/hexane); IR (ν_{max} /cm^{-1}): 3097, 1514, 1348, 1177, 1146; ^{1}H NMR (400MHz, $CDCl_3$, 293K, TMS): 1.71 (3H, d, *J*=0.8Hz), 3.21 (1H, d, *J*=16.8Hz), 3.62 (1H, d, *J*=16.8Hz), 6.91 (1H, d, *J*=8.8Hz), 8.10 (1H, d, *J*=1.1Hz), 8.15 (1H, dd, *J*=8.9, 2.4Hz); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 20.9 (d, *J*=0.9Hz), 36.5 (d, *J*=1.1Hz), 87.9 (q, *J*=31.1Hz), 109.7, 121.2, 124.7 (q, *J*=282.8Hz), 126.0, 126.3, 142.7, 163.3; ^{19}F NMR (377MHz, $CDCl_3$, 293K, TMS): -88.3; HRMS calcd for $C_{10}H_8O_3NF_3$ (M+) 247.0456; found: 247.0449.

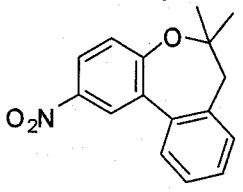
2-Benzyl-2,3-dihydro-2-methyl-5-nitrobenzofuran



The compound was prepared following the general procedure B (57%): R_f = 0.28 (SiO_2, 5% ether/hexane); IR (ν_{max} /cm^{-1}): 2928, 1514, 1335, 1273; ^{1}H NMR (400MHz, $CDCl_3$, 293K, TMS): 1.52 (3H, s), 2.99 (1H, d, *J*=16.0 Hz), 3.07 (2H, s), 3.27 (1H, d, *J*=16.0 Hz),

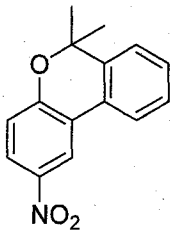
6.80 (1H, d, *J*=8.8Hz), 7.22-7.34 (5H, m), 8.09 (1H, d, *J*=2.5Hz), 8.10 (1H, dd, *J*=8.8, 2.5Hz); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 26.4, 39.7, 46.6, 91.8, 109.1, 121.4, 125.8, 126.9, 128.2, 128.3, 130.4, 135.9, 141.5, 164.3; HRMS calcd for $C_{16}H_{15}O_3N$ (M+) 269.1052; found: 269.1059.

6,6-Dimethyl-2-nitro-6,7-dihydrodibenzo[b,d]oxepine



The compound was obtained as the minor product in the 1-(2-(2-bromo-5-nitrophenoxy)-2-methylpropyl)benzene reaction in 34% yield: R_f = 0.24 (SiO_2, 5% ether/hexane); IR (ν_{max} /cm^{-1}): 2976, 1518, 1345, 1255, 1100; ^{1}H NMR (400MHz, $CDCl_3$, 293K, TMS): 1.44 (6H, s), 2.66 (2H, s), 7.15 (1H, d, *J*=8.7Hz), 7.26 (1H, dd, *J*=7.4, 1.0Hz), 7.38 (1H, dt, *J*=7.4, 1.5Hz), 7.44 (1H, dt, *J*=7.5, 1.5Hz), 7.51 (1H, dd, *J*=7.6, 1.4Hz), 8.20 (1H, dd, *J*=8.8, 2.8Hz), 8.36 (1H, d, *J*=2.8Hz); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 26.8, 44.3, 91.7, 124.0, 124.6, 124.7, 127.7, 128.2, 128.5, 129.6, 136.2, 136.3, 136.4, 144.4, 158.9; HRMS calcd for $C_{16}H_{15}O_3N$ (M+) 269.1052; found: 269.1048.

6,6-Dimethyl-2-nitro-6H-benzo[c]chromene

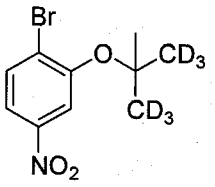


The compound was prepared following the general cyclization procedure at 140°C (89%): mp = 92-95°C(ether); R_f = 0.23 (SiO_2, 3% ether/hexane); IR (ν_{max} /cm^{-1}): 2982, 1518, 1339, 1266, 1106; ^{1}H NMR (400MHz, $CDCl_3$, 293K, TMS): 1.67 (6H, s), 7.00 (1H, d, *J*=8.9Hz), 7.25-7.27 (1H, m), 7.36-7.43 (2H, m), 7.76-7.79 (1H, s), 8.10 (1H, dd, *J*=8.9, 2.7Hz), 8.64 (1H, d, *J*=2.7Hz); ^{13}C NMR (100MHz, $CDCl_3$, 293K, TMS): 27.9,

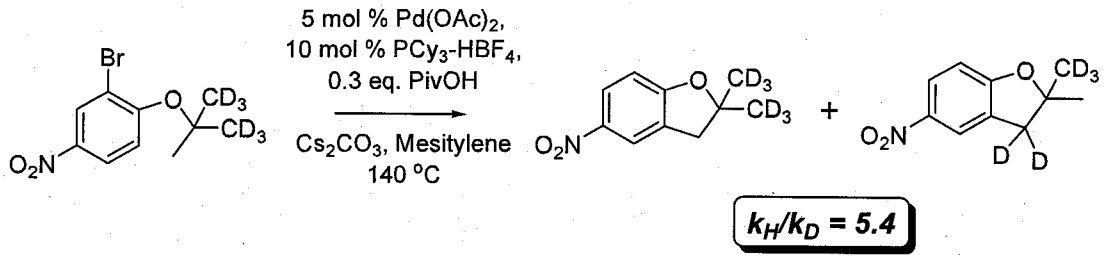
79.5, 118.4, 118.9, 122.4, 122.5, 123.4, 124.9, 126.3, 128.2, 129.4, 138.7, 142.2, 158.2; HRMS calcd for $C_{15}H_{13}O_3N$ (M+) 255.0895; found: 255.0873.

6.6.1.3 Procedure for the Kinetic Isotope Effect Experiment

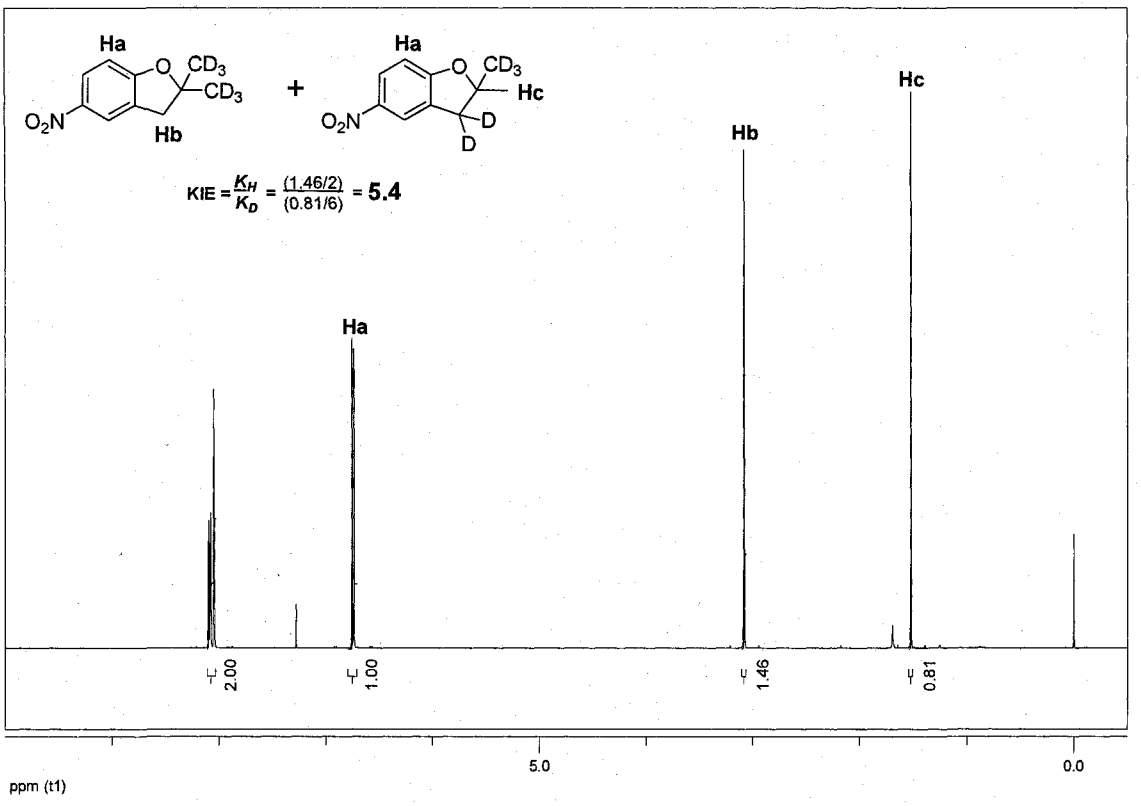
1-(1,1,1,3,3,3-Hexadeuterated-2-methylpropoxy)-2-bromo-5-nitrobenzene



The compound was prepared following the general procedure B at 140°C (86%): ^{1}H NMR (400MHz, $CDCl_3$, 293K, TMS): 1.54 (3H, s), 7.20 (1H, d, *J*=9.1Hz), 8.12 (1H, dd, *J*=9.1, 2.8Hz), 8.44 (1H, d, *J*=2.8Hz);



k_H/k_D = 5.4



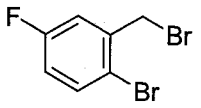
6.7 Experimental Data for Section 5: Palladium-Catalyzed Intramolecular Direct Arylation in the Synthesis of Aporphines

6.7.1 Synthesis of the Cyclization Precursors

6.7.1.1 General Procedure for the Synthesis of benzyl halides

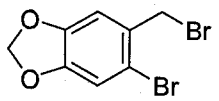
General Procedure: To a solution of toluene (1.0 equiv.) and N-bromosuccinimide (1.01 equiv.) in carbon tetrachloride (0.4M) was added benzoyl peroxide (0.008 equiv.) and the solution was refluxed overnight. The products were purified by column chromatography on silica gel eluting with EtOAc/hexane mixture.

1-Bromo-2-(bromomethyl)-4-fluorobenzene



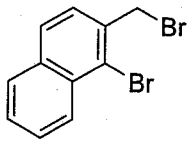
The benzyl bromide was prepared following the general procedure and exhibited the same spectral data as previously reported[228] (92%).

5-Bromo-6-(bromomethyl)benzo[d][1,3]dioxole



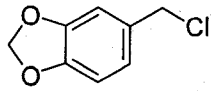
The benzyl bromide was prepared following literature preparation and exhibited the same spectral data as previously reported[229] (99%).

1-Bromo-2-(bromomethyl)naphthalene



The benzyl bromide was prepared following literature preparation and exhibited the same spectral data as previously reported[230] (82%).

5-(Chloromethyl)benzo[d][1,3]dioxole



The benzyl chloride was prepared following literature preparation[231] and exhibited the same spectral data as previously reported (99%).

6.7.1.2 General Procedure for the Synthesis of Benzocyanides

General Procedure (A): Sodium cyanide (1.25 equiv.) was dissolved in warmed water (13.7M). To this warm solution was added slowly over 15 minutes a solution of benzyl bromide (1.0 equiv.) in ethanol (1.5M). The resulting mixture was refluxed overnight.

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[228] Burguete, M. I.; Diaz, P.; Garcia-Espana, E.; Luis, S. V. ; Miravet, J. F. ; Querol, M. ; Ramirez, J. A. *Chem. Comm.* **1999**, 649. Commercially Available – CAS#: 112399-50-5.

[229] Barthel, W. F.; Alexander, B.H. *J. Org. Chem.* **1958**; *23*, 1012. Commercially Available – CAS#: 5434-47-9.

[230] Carpino, L. A. ; Lin, Y. Z. *J. Org. Chem.* **1990**; *55*, 247. Commercially Available – CAS#: 37763-43-2.

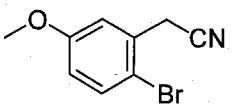
[231] Sanz, G.; Couturier, D. *J. Heterocyclic Chem.*, **2003**, 989. Commercially Available – CAS#: 20850-43-5.

The ethanol was then removed and the products were purified by column chromatography on silica gel eluting with EtOAc/hexane mixture.

General Procedure (B):

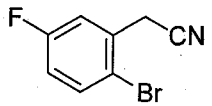
To a solution of sodium cyanide (1.2 equiv.) in DMF (1M) was added the benzyl bromide and the resulting mixture was stirred at room temperature overnight. The solution was extracted with $CHCl_3/H_2O$ and the products were purified by column chromatography on silica gel eluting with EtOAc/hexane mixture.

2-(2-Bromo-5-methoxyphenyl)acetonitrile[232]



The benzocyanide was prepared following the general procedure, method A (99%). R_f = 0.26 (30% Et_2O/hexane); mp = 53-54 °C ($CHCl_3$); IR (ν_{max} /cm^{-1}, nujol): 2252, 1514, 1034 cm^{-1}. ^1H NMR (300MHz, $CDCl_3$, 293K, TMS): 3.79 (2H, s), 3.81 (3H, s), 6.76 (1H, dd, *J*=8.8, 3.0Hz), 7.06 (1H, d, *J*=3.0Hz), 8.81 (1H, d, *J*=8.8Hz); ^{13}C NMR (75MHz, $CDCl_3$, 293K, TMS) : 25.3, 56.0, 114.0, 115.8, 115.9, 117.3, 131.1, 134.0, 159.7; HRMS calculated for C_9H_8BrNO (M+) 222.9997; found: 222.9991.

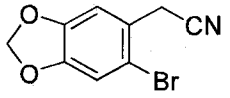
2-(2-Bromo-5-fluorophenyl)acetonitrile



The benzocyanide was prepared following the general procedure, method B and exhibited the same spectral data as previously reported[233] (96%). ^1H NMR (400MHz, $CDCl_3$, 293K, TMS): 3.82 (2H, s), 6.97 (1H, td, *J*= 9.0, 3.0Hz), 7.30 (1H, dd, *J*= 9.0, 3.0Hz), 7.57 (1H, dd, *J*= 9.0, 5.0Hz).

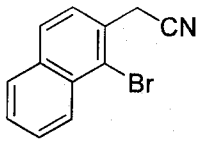
[232] Ghosh, A.K.; Mukhopadhyaya, J. K.; Ghatak, U. R. *J. Chem. Soc. Perkin Trans. 1*, **1997**, 2747.
[233] Moser, P.; Sallmann, A.; Wiesenberg; *J. Med. Chem.*, **1990**, *33*, 2358.

2-(5-Bromobenzo[d][1,3]dioxol-6-yl)acetonitrile[234]



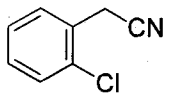
The benzocyanide was prepared following the general procedure method A (99%). R_f = 0.16 (30% Et_2O/hexane); mp = 68-71 °C ($CHCl_3$); IR (ν_{max} /cm^{-1}, nujol): 2264, 1498, 1298, 1027 cm^{-1}. ^1H NMR (300MHz, $CDCl_3$, 293K, TMS): 3.72 (2H, s), 6.00 (2H, s), 6.96 (1H, s), 7.02 (1H, s); ^{13}C NMR (75MHz, $CDCl_3$, 293K, TMS): 25.0, 102.6, 109.8, 113.4, 114.6, 117.5, 122.9, 148.3, 148.9; HRMS calculated for $C_9H_6BrNO_2$ (M+) 238.9582; found: 238.9574.

2-(1-Bromonaphthalen-2-yl)acetonitrile



The benzocyanide was prepared following the general procedure, method A (99%). R_f = 0.32 (5% Et_2O/hexane); mp = 125-127 °C ($CHCl_3$); IR (ν_{max} /cm^{-1}, nujol): 2256, 1621, 1037 cm^{-1}. ^1H NMR (300MHz, $CDCl_3$, 293K, TMS): 4.05 (2H, s), 7.52-7.64 (3H, m), 7.82 (1H, d, *J*=8.5Hz), 8.27 (1H, d, *J*=8.5Hz); ^{13}C NMR (75MHz, $CDCl_3$, 293K, TMS) : 26.3, 117.5, 124.5, 126.4, 127.6, 127.6, 128.1, 128.6, 128.7, 129.0, 132.6, 134.3; HRMS calculated for $C_{12}H_8BrN$ (M+) 244.9840; found: 244.9829.

2-(2-Chlorophenyl)acetonitrile

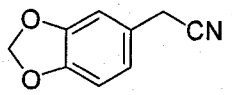


The benzocyanide was prepared following the general procedure but using the 2-chlorobenzyl chloride. The product exhibited the same spectral data as previously reported[235] (99%).

[234] Tiner-Harding, T.; Mariano, P. S. *J. Org. Chem.*, **1982**, *47*, 482.

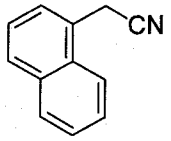
[235] Kametani, T.; Kigasawa, K.; Hiragi, M.; Aoyama, T.; Kusama, O. *J. Org. Chem.*, **1971**, *36*, 327. Commercially Available – CAS#: 2856-63-5.

2-(Benzo[d][1,3]dioxol-6-yl)acetonitrile



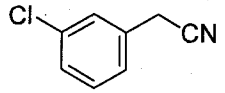
The benzocyanide was prepared following the general procedure, method B but using 5-(chloromethyl)benzo[d][1,3]dioxole. The product exhibited the same spectral data as previously reported[236] (77%).

2-(Naphthalen-4-yl)acetonitrile



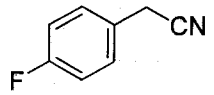
The benzocyanide was prepared following the general procedure, method B. The product exhibited the same spectral data as previously reported[237] (90%).

2-(3-Chlorophenyl)acetonitrile



The benzocyanide was prepared following the general procedure, method A. The product exhibited the same spectral data as previously reported[238] (87%).

2-(4-Fluorophenyl)acetonitrile



The benzocyanide was prepared following the general procedure, method B (91%). The product exhibited the same spectral data as previously reported[239] (99%).

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[236] Blay, G.; Cardona, L.; Garcia, B.; Lahoz, L.; Pedro, J. R. *Tetrahedron.*, **1996**, *52*, 8611. Commercially Available – CAS#: 4439-02-5.

[237] Okuro, K.; Furuune, M.; Miura, M.; Nomura, M. *J. Org. Chem.*, **1993**, *58*, 7606. Commercially Available – CAS#: 132-75-2.

[238] Tiner-Harding, T.; Mariano, P. S. *J. Org. Chem.*, **1982**, *47*, 482. Commercially Available – CAS#: 1529-41-5.

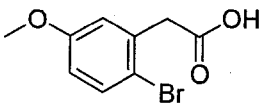
[239] Wu, L.; Hartwig, J. F. *J. Am. Chem. Soc.*, **2005**, *127*, 15824. Commercially Available – CAS#: 459-22-3.

6.7.1.3 General Procedure for the Synthesis of Phenethylacetic Acids

General Procedure (A): Benzocyanide (1.0 equiv.) was added slowly to a solution of acetic acid, sulfuric acid and water (1:1:1, 2.5M). The resulting mixture was refluxed overnight. The resulting mixture was then made basic by addition of a 10% solution of NaOH. This solution was then extracted with ether and the aqueous phase was then acidified by addition of sulfuric acid. The product was then filtered and dried.

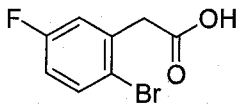
General Procedure (B): A solution of benzocyanide (1.0 equiv.) in ethanol was added slowly to a 25% sodium hydroxide in water (1.1M). The resulting mixture was refluxed overnight. This solution was then extracted with ether and the aqueous phase was then acidified by addition of sulfuric acid. The product was then filtered and dried.

2-(2-Bromo-5-methoxyphenyl)acetic acid



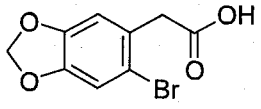
The phenethylacetic acid was prepared following the general procedure, method B (54%). The product exhibited the same spectral data as the commercial source[240].

2-(2-Bromo-5-fluorophenyl)acetic acid



The phenethylacetic acid was prepared following the general procedure, method B (56%). The product exhibited the same spectral data as the commercial source[241].

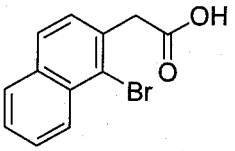
2-(5-Bromobenzo[d][1,3]dioxol-6-yl)acetic acid



[240] Commercially Available – CAS#: 66916-99-2.
[241] Commercially Available – CAS#: 61150-59-2.

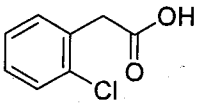
The phenethylacetic acid was prepared following the general procedure, method B (67%). The product exhibited the same spectral data as the commercial source[242].

2-(1-Bromonaphthalen-2-yl)acetic acid



The phenethylacetic acid was prepared following the general procedure, method B but the reaction was refluxed for 2 days (51%). The product exhibited the same spectral data as the commercial source[243].

2-(2-Chlorophenyl)acetic acid



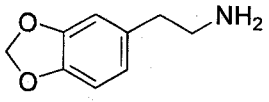
The phenethylacetic acid was prepared following the general procedure, method A (73%). The product exhibited the same spectral data as the commercial source[244].

6.7.1.4 General Procedure for the Synthesis of Phenethylamines

General Procedure: To a suspension of lithium aluminium hydride (1.6 equiv.) in tetrahydrofuran (0.7M) at 0°C was added dropwise sulfuric acid (0.8 equiv.) and the resulting mixture was stirred for 30 minutes. A solution of benzocyanide (1.0 equiv.) in tetrahydrofuran (3M) was added dropwise and the solution was stirred overnight at room temperature. The products were then purified by column chromatography on silica gel eluting with EtOAc/hexane mixture.

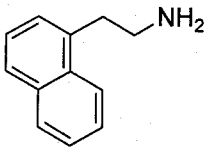
[242] Commercially Available – CAS#: 5470-14-4.
[243] Commercially Available – CAS#: 6270-01-5.
[244] Commercially Available – CAS#: 2444-36-2.

2-(Benzo[d][1,3]dioxol-6-yl)ethanamine



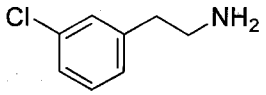
The phenethylamine was prepared following the general procedure (99%). The product exhibited the same spectral data as the commercial source[245].

2-(Naphthalen-4-yl)ethanamine



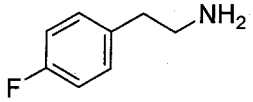
The phenethylamine was prepared following the general procedure (99%). The product exhibited the same spectral data as the commercial source[246].

2-(3-Chlorophenyl)ethanamine



The phenethylamine was prepared following the general procedure (97%). The product exhibited the same spectral data as the commercial source[247].

2-(4-Fluorophenyl)ethanamine



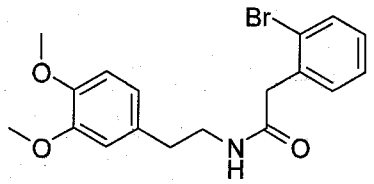
The phenethylamine was prepared following the general procedure (60%). The product exhibited the same spectral data as the commercial source[248].

[245] Commercially Available – CAS#: 1484-85-1.
[246] Commercially Available – CAS#: 4735-50-6.
[247] Commercially Available – CAS#: 13078-79-0.
[248] Commercially Available – CAS#: 1583-88-6.

6.7.1.5 General Procedure for the Synthesis of Amides

General Procedure: The acid (1 equiv.) and oxalyl chloride in dry methylene chloride (0.25M) were stirred at room temperature in a flask attached to a bubbler. To this solution is added one drop of *N,N*-dimethylformamide and the solution is stirred for 1 hour (or until no gas is formed). The solution is then concentrated and the resulting acid chloride is employed without further purification. The amine (1 equiv.) and triethylamine (1.1 equiv.) were dissolved in dry methylene chloride (0.25M). To this mixture was added the freshly prepared acid chloride dropwise (1.05 equiv.) at 0 °C. The reaction is allowed to stir at room temperature overnight. The reaction was then quenched with brine then extracted with methylene chloride followed by evaporation under reduced pressure and the crude reaction mixture was purified by column chromatography on silica gel eluting with Et_2O/hexane mixtures.

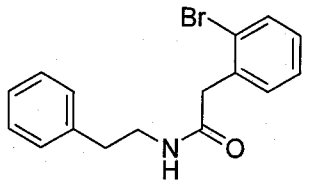
2-(2-Bromophenyl)-*N*-[2-(3,4-dimethoxy-phenyl)-ethyl]-acetamide[249]



The amide was prepared following the general procedure (99%): R_f = 0.59 (10% MeOH/DCM); mp = 127-129 °C ($CHCl_3$); IR (ν_{max} /cm^{-1}, nujol): 3313, 3062, 1647, 1551, 1235, 1141, 1027 cm^{-1}. ^1H NMR (300MHz, $CDCl_3$, 293K, TMS): 2.71 (2H, t, *J*=6.9Hz), 3.47 (2H, q, *J*=6.9Hz), 3.67 (2H, s), 3.84 (3H, s), 3.86 (3H, s), 5.42 (1H, s), 6.58-6.74 (3H, m), 7.11-7.19 (1H, m), 7.27-7.28 (2H, m), 7.55 (1H, d, *J*=7.9Hz); ^{13}C NMR (75MHz, $CDCl_3$, 293K, TMS) : 35.0, 40.8, 44.1, 55.8, 55.9, 111.2, 111.6, 120.5, 124.9, 127.9, 129.1, 131.0, 131.6, 133.1, 134.7, 147.5, 148.9, 169.4; HRMS calculated for $C_{18}H_{20}BrNO_3$ (M+) 377.0627; found: 377.0616.

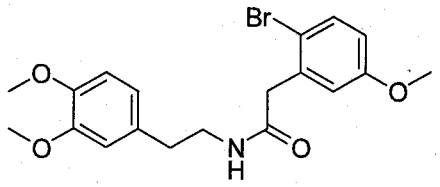
[249] Kyo, R.-Y.; Wu C.-C.; Chang, F.-R..; Yeh, J.-L. ; Chen I.-J. ; Wu, Y.-C. *Bioorg. Med. Chem. Lett.*, **2003**, *13*, 821.

2-(2-Bromophenyl)-N-phenethyl-acetamide[250]



The amide was prepared following the general procedure (95%): R_f = 0.49 (100% EtOAc with 1% TEA); mp = 111-112 °C ($CHCl_3$); IR (ν_{max} /cm^{-1}, KBr): 3269, 3084, 1643, 1562, 1026 cm^{-1}. ^1H NMR (300MHz, $CDCl_3$, 293K, TMS): 2.75 (2H, t, *J*=6.8Hz), 3.47 (2H, q, *J*=6.7Hz), 3.66 (2H, s), 5.49 (1H, s), 7.05-7.28 (8H, m), 7.55 (1H, d, *J*=7.8Hz); ^{13}C NMR (75MHz, $CDCl_3$, 293K, TMS) : 35.5, 40.7, 44.0, 125.0, 126.4, 128.0, 128.6, 128.7, 129.1, 131.7, 133.1, 134.8, 138.6, 169.4; HRMS calculated for $C_{16}H_{16}BrNO$ (M+) 317.0415; found: 317.0423.

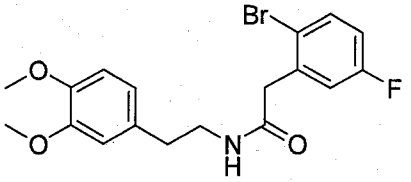
2-(2-Bromo-5-methoxyphenyl)-N-[2-(3,4-dimethoxyphenyl)-ethyl]-acetamide



The amide was prepared following the general procedure (99%): mp 135–137 °C ($CHCl_3$); IR (ν_{max} /cm^{-1}): 3302, 1635, 1517, 1236, 1141, 1026; ^1H NMR (300MHz, $CDCl_3$, 293K, TMS): 2.71 (2H, t, *J*=6.9Hz), 3.47 (2H, q, *J*=6.9Hz), 3.62 (2H, s), 3.77 (3H, s), 3.84 (3H, s), 3.85 (3H, s), 5.51 (1H, br), 6.57–6.64 (2H, m), 6.69–6.73 (2H, m), 6.82 (1H, d, *J*=3.0Hz), 7.42 (1H, d, *J*=8.8Hz); ^{13}C NMR (75MHz, $CDCl_3$, 293K, TMS): 34.9, 40.7, 44.2, 55.40, 55.7, 55.8, 111.1, 111.6, 115.0, 115.1, 116.8, 120.5, 131.0, 133.5, 135.5, 147.5, 148.9, 159.1, 169.2; HRMS calcd for $C_{19}H_{22}BrNO_4$ (M+) 407.0732; found: 407.0731.

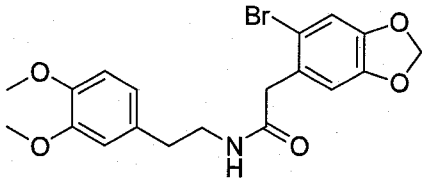
[250] Pandney, G. D.; Tiwari, Kamala, P. *Tetrahedron*, **1981**, *37*, 1213.

2-(2-Bromo-5-fluorophenyl)-N-[2-(3,4-dimethoxyphenyl)-ethyl]-acetamide



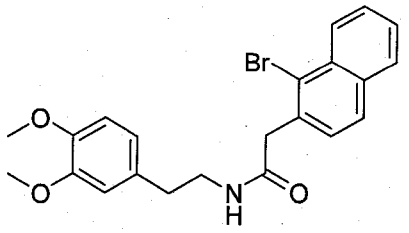
The amide was prepared following the general procedure (72%): mp 150–151 °C ($CHCl_3$); IR (ν_{max} /cm^{-1}): 3292, 1636, 1552, 1517, 1235, 1142, 1029; ^1H NMR (300MHz, $CDCl_3$, 293K, TMS): 2.73 (2H, t, *J*=6.9Hz), 3.49 (2H, q, *J*=6.8Hz), 3.62 (2H, s), 3.84 (3H, s), 3.86 (3H, s), 5.50 (1H, br), 6.62 (1H, dd, *J*=8.0, 1.9Hz), 6.64 (1H, d, *J*=1.9Hz), 6.75 (1H, d, *J*=8.0Hz), 6.89 (1H, ddd, $J_{4,F}$=8.0, $J_{3,4}$=8.0, $J_{4,6}$=3.0Hz, H-4), 7.04 (1H, dd, $J_{6,F}$=8.9, $J_{4,6}$=3.0Hz, H-6), 7.49 (1H, dd, $J_{3,4}$=8.8, $J_{3,F}$=5.3Hz, H-3); ^{13}C NMR (75MHz, $CDCl_3$, 293K, TMS): 34.9, 40.7, 43.9, 55.8, 55.8, 111.13, 111.6, 116.2 (J_F= 22.4Hz), 118.5 (J_F= 23.0Hz), 118.9 (J_F= 3.3Hz), 120.5, 130.8, 134.1 (J_F= 8.1Hz), 136.6 (J_F= 7.8Hz), 147.6, 148.9, 163.5 (J_F= 247.9Hz), 168.6; HRMS calcd for $C_{18}H_{19}BrFNO_3$ (M+) 395.0532; found: 395.0521.

2-(5-Bromo-benzo[1,3]dioxol-6-yl)-N-[2-(3,4-dimethoxyphenyl)-ethyl]-acetamide



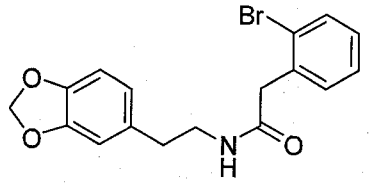
The amide was prepared following the general procedure (99%): mp 166–168 °C ($CHCl_3$); ($CHCl_3$); IR (ν_{max} /cm^{-1}): 3281, 1641, 1517, 1480, 1233, 1027; ^1H NMR (300MHz, $CDCl_3$, 293K, TMS): 2.71 (2H, t, *J*=6.9Hz), 3.47 (2H, q, *J*=6.8Hz), 3.56 (2H, s), 3.84 (3H, s), 3.85 (3H, s), 5.51 (1H, br), 5.98 (2H, s), 6.61-6.64 (2H, m), 6.73-6.76 (2H, m), 7.0 (1H, s); ^{13}C NMR (75MHz, $CDCl_3$, 293K, TMS): 34.9, 40.6, 43.7, 55.7, 55.8, 101.9, 110.8, 111.1, 111.6, 112.7, 115.2, 120.5, 127.4, 130.9, 147.5, 147.6, 147.7, 148.9, 169.5; HRMS calcd for $C_{19}H_{20}BrNO_5$ (M+) 421.0525; found: 421.0521.

2-(1-Bromo-2-naphthalen)-N-[2-(3,4-dimethoxyphenyl)-ethyl]-acetamide



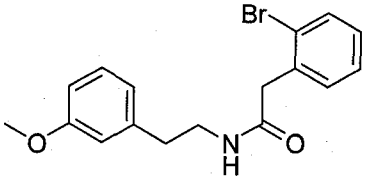
The amide was prepared following the general procedure (76%): mp 165–166 °C ($CHCl_3$); IR (ν_{max} /cm^{-1}): 3293, 1648, 1517, 1262, 1237, 1028; ^1H NMR (300MHz, $CDCl_3$, 293K, TMS): 2.73 (2H, t, *J*=6.8Hz), 3.47 (2H, q, *J*=6.7Hz), 3.68 (2H, s), 5.45 (1H, br), 6.94–6.97 (2H, m), 7.08 (1H, s), 7.13–7.18 (2H, m), 7.26–7.29 (1H, m), 7.57 (1H, d, *J*=7.8Hz); ^{13}C NMR (75MHz, $CDCl_3$, 293K, TMS): 34.9, 40.6, 45.2, 55.7, 55.7, 110.8, 111.4, 120.4, 125.0, 126.6, 127.38, 127.8, 128.1, 128.2, 128.2, 130.8, 132.4, 132.9, 133.6, 147.4, 148.8, 169.3; HRMS calcd for $C_{22}H_{22}BrNO_3$ (M+) 427.0783; found : 427.0758.

2-(2-Bromophenyl)-N-[2-benzo[1,3]dioxol-5-yl-ethyl]-acetamide



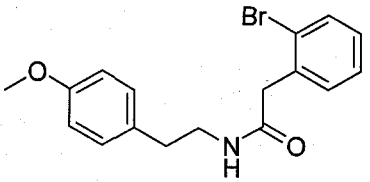
The amide was prepared following the general procedure (91%): mp 129–132 °C ($CHCl_3$); IR (ν_{max} /cm^{-1}): 3290, 2874, 1636, 1547, 1489, 1246, 1028; ^1H NMR (300MHz, $CDCl_3$, 293K, TMS): 2.65 (2H, t, *J*=6.8Hz), 3.42 (2H, q, *J*=6.7Hz), 3.66 (2H, s), 5.54 (1H, br), 5.90 (2H, s), 6.48 (1H, dd, *J*=7.9, 1.7Hz), 6.56 (1H, d, *J*=1.7Hz), 6.65 (1H, d, *J*=7.9), 7.10–7.18 (1H, m), 7.27–7.28 (2h, m), 7.56 (1H, d, *J*=7.8Hz); ^{13}C NMR (75MHz, $CDCl_3$, 293K, TMS): 35.6, 41.3, 44.4, 101.3, 108.7, 109.5, 122.0, 125.4, 128.4, 129.5, 132.1, 132.8, 133.5, 135.2, 146.5, 148.1, 169.9; HRMS calcd for $C_{17}H_{16}BrNO_3$ (M+) 361.0314; found : 361.0305.

2-(2-Bromophenyl)-N-[2-(3-methoxyphenyl)-ethyl]-acetamide



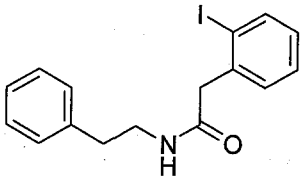
The amide was prepared following the general procedure (91%): mp 87–88 °C ($CHCl_3$); IR (ν_{max} /cm^{-1}, Nujol): 3286, 1641, 1544, 1459, 1155; ^1H NMR (300MHz, $CDCl_3$, 293K, TMS): 2.71 (2H, t, *J*=6.8Hz), 3.48 (2H, q, *J*=6.6Hz), 3.66 (2H, s), 3.77 (3H, s), 5.51 (1H, br), 6.64–6.74 (3H, m), 7.11–7.17(2H, m), 7.27 (2H, d, *J*=3.9Hz), 7.55 (1H, d, *J*=7.9Hz); ^{13}C NMR (75MHz, $CDCl_3$, 293K, TMS): 35.17, 40.47, 43.24, 54.70, 111.37, 114.04, 120.66, 124.65, 127.41, 128.49, 129.16, 131.20, 132.49, 134.75, 140.09, 159.30, 169.40; HRMS calcd for $C_{17}H_{18}BrNO_2$ (M+) 347.0521; found: 347.0516.

2-(2-Bromophenyl)-N-[2-(4-methoxyphenyl)-ethyl]-acetamide



The amide was prepared following the general procedure (80%): mp 110–111 °C ($CHCl_3$); IR (ν_{max} /cm^{-1}, Nujol): 3297, 1644, 1461, 1238, 1029; ^1H NMR (300MHz, $CDCl_3$, 293K, TMS): 2.68 (2H, t, *J*=6.9Hz), 3.44 (2H, q, *J*=6.7Hz), 3.66 (2H, s), 3.77 (3H, s), 5.50 (1H, br), 6.77 (2H, d, *J*=8.6Hz), 6.98 (2H, d, *J*=8.5Hz), 7.12–7.17 (1H, m), 7.27 (2H, d, *J*=4.5Hz), 7.56 (1H, d, *J*=7.9Hz); ^{13}C NMR (75MHz, $CDCl_3$, 293K, TMS): 34.51, 40.91, 44.00, 55.22, 113.94, 124.96, 127.94, 129.03, 129.60, 130.58, 131.67, 133.06, 134.78, 158.11, 169.42; HRMS calcd for $C_{17}H_{18}BrNO_2$ (M+) 347.0521; Found: 347.0529.

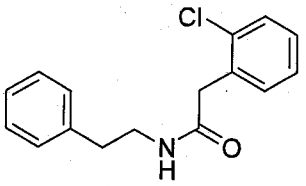
2-(2-Iodophenyl)-N-[2-phenyl-ethyl]-acetamide[251]



[251] Kupchan, S.M.; Kameswaran, V.; Findlay, J. W. A. *J. Org. Chem.*, **1973**, *38*, 405.

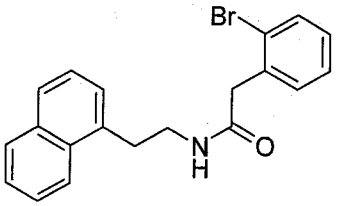
The amide was prepared following the general procedure (93%): mp 123–124 °C ($CHCl_3$); IR (ν_{max} /cm^{-1})(KBr): 3287, 3084, 1636, 1552, 1015; ^1H NMR (300MHz, $CDCl_3$, 293K, TMS): 2.76 (2H, t, *J*=6.9Hz), 3.48 (2H, q, *J*=6.8Hz), 3.67 (2H, s), 5.45 (1H, br), 6.94–6.99 (1H, m), 7.05–7.08 (2H, m), 7.15–7.33 (5H, m), 7.36–7.39 (1H, dd, *J*= 1.1, 7.9 Hz); ^{13}C NMR (75MHz, $CDCl_3$, 293K, TMS): 35.4, 40.7, 48.5, 101.2, 126.4, 128.5, 128.6, 128.8, 129.0, 130.8, 138.2, 138.5, 139.7, 169.3; HRMS calcd for $C_{16}H_{16}INO$ (M+) 365.0277; found: 365.0266.

2-(2-Chlorophenyl)-N-[2-phenyl-ethyl]-acetamide[252]



The amide was prepared following the general procedure (98%): mp 105–106 °C ($CHCl_3$); IR (ν_{max} /cm^{-1})(KBr): 3283, 3086, 1644, 1557, 1352; ^1H NMR (300MHz, $CDCl_3$, 293K, TMS): 2.74 (2H, t, *J*=6.9Hz), 3.48 (2H, q, *J*=6.8Hz), 3.64 (2H, s), 5.51 (1H, br), 7.04–7.08 (2H, m), 7.18–7.29 (6H, m), 7.36–7.39 (1H, m); ^{13}C NMR (75MHz, $CDCl_3$, 293K, TMS): 35.4, 40.7, 41.4, 126.0, 127.3, 128.5, 128.6, 128.8, 129.7, 131.6, 132.9, 134.3, 138.6, 169.4; HRMS calcd for $C_{16}H_{16}ClNO$ (M+) 273.0920; found: 273.0930.

2-(2-Bromophenyl)-N-[2-naphthalen-1-yl-ethyl]-acetamide

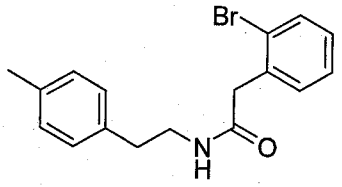


The amide was prepared following the general procedure (79%): mp 120–123 °C ($CHCl_3$); IR (ν_{max} /cm^{-1}): 3295, 3064, 1646, 1545, 1026; ^1H NMR (300MHz, $CDCl_3$, 293K, TMS): 3.23 (2H, t, *J*=6.9Hz), 3.60 (2H, q, *J*=6.8Hz), 3.67 (2H, s), 5.49 (1H, br), 7.10–7.17 (2H, m), 7.21–7.24 (2H, m), 7.28–7.33 (1H, m), 7.43–7.56 (3H, m), 7.71 (1H, d, *J*=8.2Hz), 7.82–7.85 (1H, m) 8.05 (1H, d, *J*=7.7Hz); ^{13}C NMR (75MHz, $CDCl_3$, 293K,

[252] Viel, C.; Dorme, R.; Rumpf, P. *Bull. Soc. Chim. Fr.*, **1966**, *33*, 1956.

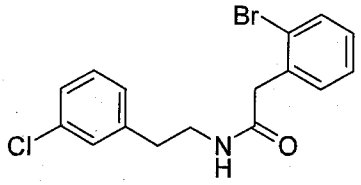
TMS): 32.5, 40.2, 44.0, 123.5, 124.9, 125.4, 125.6, 126.1, 126.7, 127.2, 127.9, 128.7, 129.0, 131.6, 131.7, 133.0, 133.8, 134.6, 134.6, 169.6; HRMS calcd for $C_{20}H_{18}BrNO$ (M+) 367.0572; found : 367.0571.

2-(2-Bromophenyl)-N-[2-(4-methylphenyl)-ethyl]-acetamide



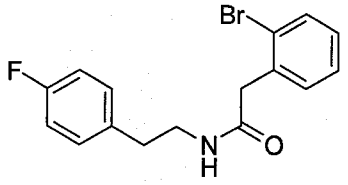
The amide was prepared following the general procedure (82%): mp 149–151 °C ($CHCl_3$); IR (ν_{max} /cm^{-1}, Nujol): 3272, 3077, 1643, 1556, 1377, 1146, 1024; ^1H NMR (300MHz, $CDCl_3$, 293K, TMS): 2.31 (3H, s), 2.71 (2H, t, *J*=6.9Hz), 3.46 (2H, q, *J*=6.6Hz), 3.67 (2H, s), 5.41 (1H, br), 6.96 (2H, d, *J*=7.9Hz), 7.04 (2H, d, *J*=7.8Hz), 7.12–7.18 (1H, m), 7.28 (2H, d, *J*=4.2Hz), 7.57 (1H, d, *J*=8.0Hz); ^{13}C NMR (75MHz, $CDCl_3$, 293K, TMS): 21.01, 35.02, 40.84, 44.09, 124.99, 127.95, 128.55, 129.03, 129.25, 131.69, 133.09, 134.79, 135.49, 135.90, 169.38; HRMS calcd for $C_{17}H_{18}BrNO$ (M+) 331.0572; found : 331.0550.

2-(2-Bromophenyl)-N-[2-(3-chlorophenyl)-ethyl]-acetamide



The amide was prepared following the general procedure (79%): mp 108–110 °C ($CHCl_3$); IR (ν_{max} /cm^{-1}): 3290, 3065, 1641, 1547, 1472, 1027; ^1H NMR (300MHz, $CDCl_3$, 293K, TMS): 2.73 (2H, t, *J*=6.8Hz), 3.47 (2H, q, *J*=6.7Hz), 3.68 (2H, s), 5.45 (1H, br), 6.94–6.97 (2H, m), 7.08 (1H, s), 7.13–7.18 (2H, m), 7.26–7.29 (1H, m), 7.57 (1H, d, *J*=7.8Hz); ^{13}C NMR (75MHz, $CDCl_3$, 293K, TMS): 35.1, 40.5, 44.0, 124.9, 126.6, 126.8, 128.0, 128.8, 129.2, 129.8, 131.6, 133.1, 134.2, 134.6, 140.7, 169.4; HRMS calcd for $C_{16}H_{15}ClBrNO$ (M+) 351.0026; found: 351.0007.

2-(2-Bromophenyl)-N-[2-(4-fluorophenyl)-ethyl]-acetamide



The amide was prepared following the general procedure (56%): mp 99-102 °C ($CHCl_3$); IR (ν_{max} /cm^{-1}, nujol): 3305, 3086, 1650, 1553, 1217, 1027; ^1H NMR (300MHz, $CDCl_3$, 293K, TMS): 2.72 (2H, t, J=6.9Hz), 3.44 (2H, q, J=6.8Hz), 3.67 (2H, s), 5.48 (1H, br), 6.89 (2H, dd, $J_{3,F}$=8.7, $J_{2,3}$=8.7, H-3), 7.01 (2H, dd, $J_{2,3}$=8.7, $J_{2,F}$=5.5Hz, H-2), 7.13-7.20 (1H, m), 7.27-7.28 (2H, m), 7.56 (1H, d, J=7.8); ^{13}C NMR (75MHz, $CDCl_3$, 293K, TMS): 34.5, 40.7, 43.9, 115.09, 111.6 (J_F= 21.2Hz), 124.8, 127.9, 129.0, 130.0 (J_F= 7.9Hz), 131.6, 133.0, 134.2 (J_F= 3.3Hz), 134.6, 161.4 (J_F= 244.4Hz), 169.5; HRMS calcd for $C_{16}H_{15}BrNOF$ (M+) 335.0321; found : 335.0321.

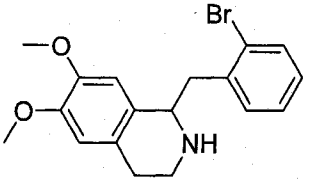
6.7.1.6 General Procedure for the Synthesis of Amines

General Procedure (A): To a solution of the amide (1.0 equiv.) in a round bottom flask equipped with a magnetic stirrer was added polyphosphoric acid (25 equiv.) and the resulting mixture was heated to 150 °C overnight. The reaction was then allowed to cool to 0 °C and the solution was neutralized with a saturated solution of Na_2CO_3. The resulting mixture was extracted with Et_2O to afford the crude dihydroisoquinoline. These compounds were found to be unstable and decompose on sitting or exposure to silica gel. They were therefore reacted without further purification immediately. To a solution of the crude dihydroisoquinoline (1.0 equiv.) in MeOH (0.2M) at 0 °C, was added slowly sodium borohydride (1.3equiv.). The resulting mixture was stirred for 3h at 23 °C. The reaction mixture was then cooled to 0 °C and a brine solution was added and then extracted with DCM. The amine was then purified by column chromatography on TEA neutralized silica gel using EtOAc/Hexane as eluant.

General Procedure (B): To a solution of the amide (1.0 equiv.) in DCM (0.2M) in a round bottom flask equipped with a magnetic stirrer and a condenser was added phosphorus oxychloride (4.0 equiv.) and the resulting mixture was refluxed overnight.

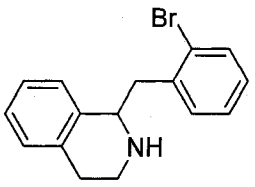
The reaction was then allowed to cool to 0 °C and the solution was neutralized with a saturated solution of Na_2CO_3. The resulting mixture was extracted with Et_2O to afford the crude dihydroisoquinoline. These compounds were found to be unstable and decompose on sitting or exposure to silica gel. They were therefore reacted without further purification immediately. To a solution of the crude dihydroisoquinoline (1.0 equiv.) in MeOH (0.2M) at 0 °C, was added slowly sodium borohydride (1.3equiv.). The resulting mixture was stirred for 3h at 23 °C. The reaction mixture was then cooled to 0 °C and a brine solution was added and then extracted with DCM. The amine was then purified by column chromatography on TEA neutralized silica gel using EtOAc/Hexane as eluant.

1-(2-Bromobenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline



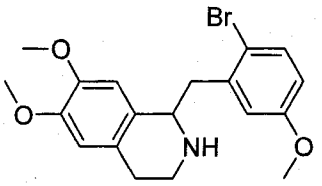
The amine was prepared following the general procedure (method B). (99%): R_f = 0.19 (100% EtOAc with 1% TEA); IR (ν_{max} /cm^{-1}): 3335, 2933, 2832, 1523, 1471, 1254, 1220, 1108, 1025 cm^{-1}. ^{1}H NMR (300MHz, $CDCl_3$, 293K, TMS): 2.67 (2H, t, *J*=7.8Hz), 3.73 (2H, t, *J*=7.7Hz), 3.79 (3H, s), 3.88 (3H, s), 4.19 (2H, s), 6.66 (1H, s), 6.91 (1H, s), 7.05 (1H, td, *J*=7.4, 1.5Hz), 7.18 (1H, td, *J*=7.4, 1.2Hz), 7.28 (1H, dd, *J*= 7.7, 1.6Hz), 7.57 (1H, dd, *J*=8.0, 1.2Hz); ^{13}C NMR (75MHz, $CDCl_3$, 293K, TMS) : 29.4, 40.0, 43.2, 54.8, 55.8, 55.9, 109.6, 111.6, 124.9, 127.1, 127.4, 128.2, 130.5, 132.0, 133.0, 138.8, 147.0, 147.4; HRMS calculated for $C_{18}H_{20}BrNO_2$ (M^+-C_7H_6Br) 192.1025; found: 192.1032. MS (CI): m/z (%) = 362 (38), 302 (21), 280 (28), 192 (100), 176 (41), 132 (90).

1-(2-Bromobenzyl)-1,2,3,4-tetrahydroisoquinoline



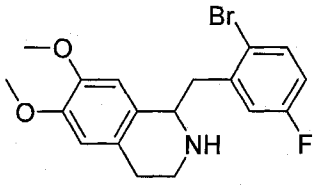
The amine was prepared following the general procedure (method A). (99%). 92%): R_f = 0.32 (30% EtOAc with 1% TEA); IR (ν_{max} /cm^{-1}): 3336, 3061, 2927, 2832, 1469, 1126, 1025 cm^{-1}. ^{1}H NMR (300MHz, $CDCl_3$, 293K, TMS): 1.44 (1H, s), 2.81-2.87 (2H, ,m), 2.94-3.02 (2H, m), 3.23-3.31 (1H, m), 3.43 (1H, dd, *J*=13.7, 3.3 Hz), 4.35 (1H, dd, *J*=10.6, 3.1 Hz), 7.10-7.20 (4H, m), 7.28-7.30 (2H, m), 7.35-7.38 (1H, m), 7.60 (1H, d, *J*= 7.8 Hz); ^{13}C NMR (75MHz, $CDCl_3$, 293K, TMS) :30.1, 40.3, 43.2, 55.4, 125.2, 126.1, 126.5, 126.8, 127.7, 128.5, 129.5, 132.2, 133.4, 135.4, 138.8, 139.0; HRMS calculated for $C_9H_{10}N$ (M^+-C_7H_6Br) 132.0813; found: 132.0800. MS (CI): m/z (%) = 302 (35), 220 (27), 132 (100).

1-(2-Bromo-5-methoxybenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline



The amine was prepared following the general procedure (method B). (68%): IR (ν_{max} /cm^{-1}): 3340, 2935, 1595, 1517, 1466, 1246, 1112, 1017; NMR (300MHz, $CDCl_3$, 293K, TMS): 1.88 (1H, br), 2.74–2.75 (2H, m), 2.88–2.99 (2H, m), 3.12–3.25 (1H, m), 3.31 (1H, dd, *J*=13.6, 3.4Hz), 3.75 (3H, s), 3.82 (3H, s), 3.84 (3H, s), 4.23 (1H, dd, *J*=9.6, 2.8Hz), 6.59 (1H, s), 6.67 (1H, dd, *J*=8.7, 2.8Hz), 6.74 (1H, s), 6.82 (1H, d, *J*=2.8Hz), 7.45 (1H, d, *J*=8.7Hz); ^{13}C NMR (75MHz, $CDCl_3$, 293K, TMS): 29.1, 39.8, 43.1, 54.7, 55.3, 55.7, 55.7, 109.4, 111.5, 113.5, 115.1, 117.5, 126.9, 130.1, 133.3, 139.5, 146.9, 147.3, 158.6; HRMS calcd for $C_{19}H_{20}NO_3$ (M+–H_2Br) 310.1443; found: 310.1433.

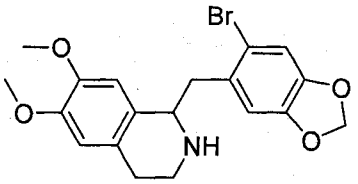
1-(2-Bromo-5-fluorobenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline



The amine was prepared following the general procedure (method B). (75%): IR (ν_{max} /cm^{-1}): 3334, 2941, 1607, 1579, 1519, 1462, 1258, 1227, 1112, 1030; NMR (300MHz, $CDCl_3$, 293K, TMS): 1.66 (1H, br), 2.68–2.73 (2H, m), 2.89–2.97 (2H, m), 3.19–3.30 (2H,

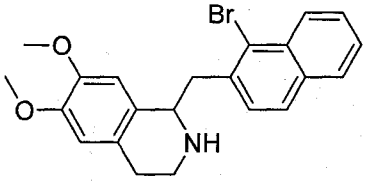
m), 3.81 (3H, s), 3.83 (3H, s), 4.21 (1H, d, *J*= 7.6Hz), 6.58 (1H, s), 6.72 (1H, s), 6.82 (1H, dd, *J*= 6.9, 5.7Hz), 7.02 (1H, d, *J*= 7.5Hz), 7.49 (1H, dd, *J*= 7.5, 5.7Hz); ^{13}C NMR (75MHz, $CDCl_3$, 293K, TMS): 28.8, 39.3, 42.6, 54.2, 55.2, 55.3, 109.0, 111.2, 114.8 (J_F= 22.2Hz), 118.2 (J_F= 19.4Hz), 118.4, 126.7, 129.7, 133.4 (J_F= 7.8Hz), 140.6 (J_F= 7.6Hz), 146.6, 147.0, 161.1 (J_F= 247.0Hz); HRMS calcd for $C_{18}H_{17}FNO_2$ (M+–H_2Br) 298.1243; found: 298.1232.

1-((5-Bromobenzo[d][1,3]dioxol-6-yl)methyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline



The amine was prepared following the general procedure (method B). (90%): IR (ν_{max} /cm^{-1}): 3334, 2925, 1610, 1515, 1476, 1261, 1112, 1038; NMR (300MHz, $CDCl_3$, 293K, TMS): 1.90 (1H, br), 2.72–2.76 (2H, m), 2.84–3.01 (2H, m), 3.19–3.27 (2H, m), 3.84 (3H, s), 3.85 (3H, s), 4.19 (1H, dd, *J*=9.9, 3.1Hz), 5.94 (2H, s), 6.59 (1H, s), 6.74 (1H, s), 6.77 (1H, s), 7.03 (1H, s); ^{13}C NMR (75MHz, $CDCl_3$, 293K, TMS): 29.1, 39.8, 42.6, 54.9, 55.6, 55.7, 101.5, 109.3, 111.1, 111.4, 112.6, 114.6, 126.9, 130.2, 131.5, 146.8, 146.9, 147.0, 147.3; HRMS calcd for $C_{19}H_{18}NO_4$ (M+–H_2Br) 324.1236; found: 324.1229.

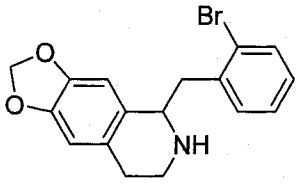
1-((1-Bromonaphthalen-2-yl)methyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline



The amine was prepared following the general procedure (method B). (79%): IR (ν_{max} /cm^{-1}): 3332, 2933, 1611, 1523, 1476, 1261, 1223, 1111, 1031; NMR (300MHz, $CDCl_3$, 293K, TMS): 1.73 (1H, br), 2.70–2.74 (2H, m), 2.91–2.99 (1H, m), 3.17–3.30 (2H, m), 3.58 (1H, dd, *J*=13.5, 3.9Hz), 3.76 (3H, s), 3.84 (3H, s), 4.36 (1H, dd, *J*=9.7, 3.8Hz), 6.58 (1H, s), 6.73 (1H, s), 7.36 (1H, d, *J*=8.3Hz), 7.46 (1H, dd, *J*=7.9, 7.9Hz), 7.53–7.58 (1H, m), 7.72 (1H, d, *J*=8.3Hz), 7.77 (1H, d, *J*=8.0Hz), 8.32 (1H, d, *J*=8.4Hz); ^{13}C NMR

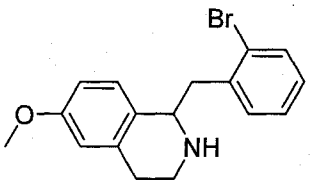
(75MHz, $CDCl_3$, 293K, TMS): 29.2, 39.9, 44.0, 55.2, 55.6, 55.6, 109.4, 111.4, 124.3, 125.9, 126.9, 127.0, 127.2, 127.8, 129.0, 129.0, 130.3, 132.3, 133.2, 136.9, 146.8, 147.2; HRMS calcd for $C_{22}H_{20}NO_2$ (M+–H_2Br) 330.1494; found: 314.0945.

5-(2-Bromobenzyl)-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinoline



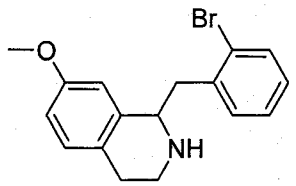
The amine was prepared following the general procedure (method B). (54%): IR (ν_{max} /cm^{-1}): 3461, 2901, 1503, 1483, 1247, 1040; NMR (300MHz, $CDCl_3$, 293K, TMS): 1.76 (1H, br), 2.73 (2H, t, *J*=5.7Hz), 2.89–2.97 (2H, m), 3.17–3.26 (1H, m), 3.33 (1H, dd, *J*=13.7, 3.1Hz), 4.22 (1H, dd, *J*=10.4, 2.6Hz), 5.90 (2H, s), 6.57 (1H, s), 6.83 (1H, s), 7.08–7.16 (1H, m), 7.25–7.28 (2H, m), 7.59 (1H, d, *J*=8.0Hz); ^{13}C NMR (75MHz, $CDCl_3$, 293K, TMS): 29.9, 39.8, 42.9, 55.1, 100.6, 106.5, 108.7, 124.8, 127.3, 128.1, 128.2, 131.6, 131.8, 133.0, 138.6, 145.7, 145.9; HRMS calcd for $C_{17}H_{15}NO_2$ (M+–H_2Br) 264.1025; found: 264.1027.

1-(2-Bromobenzyl)-6-methoxy-1,2,3,4-tetrahydro-isoquinoline



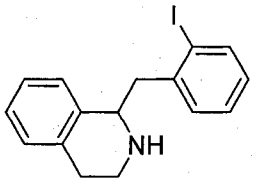
The amine was prepared following the general procedure (method B) in toluene at 100 °C for 4.5h. (88%): IR (ν_{max} /cm^{-1}): 3334, 3056, 2931, 1609, 1469, 1439, 1025; ^1H NMR (300MHz, $CDCl_3$, 293K, TMS): 1.72 (1H, br), 2.78–2.84 (2H, m), 2.89–2.98 (m, 2H), 3.20–3.28 (1H, m), 3.39 (1H, dd, *J*=13.6, 3.3Hz), 3.78 (3H, s), 4.28 (1H, dd, *J*=10.5, 3.1Hz), 6.65 (1H, d, *J*=2.6Hz), 6.74 (1H, dd, *J*=8.5, 2.7), 7.08-7.14 (1H, m), 7.24–7.27 (3H, m), 7.58 (1H, d, *J*=7.8Hz); ^{13}C NMR (75MHz, $CDCl_3$, 293K, TMS): 30.26, 40.10, 43.06, 54.68, 55.18, 112.15, 113.55, 124.87, 127.37, 127.55, 128.19, 130.94, 131.89, 133.05, 136.41, 138.76, 157.76; HRMS calcd for $C_{17}H_{17}BrNO_2$ (M+–H) 330.0494; found: 330.0466.

1-(2-Bromobenzyl)-7-methoxy-1,2,3,4-tetrahydro-isoquinoline



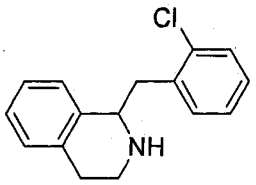
The amine was prepared following the general procedure (method B) in MeCN at 85 °C for 4.5h. (73%): IR (ν_{max} /cm^{-1}): 2931, 1611, 1503, 1248, 1040; ^{1}H NMR (300MHz, $CDCl_3$, 293K, TMS): 1.64 (1H, br), 2.74–2.77 (2H, m), 2.91–3.02 (m, 2H), 3.20-3.28 (1H, m), 3.40 (1H, dd, *J*=13.6, 3.3Hz), 3.77 (3H, s), 4.30 (1H, d, *J*=8.9Hz), 6.74 (1H, dd, *J*=8.4, 2.6), 6.87 (1H, d, *J*=2.5Hz), 7.03 (1H, d, *J*=8.4Hz), 7.09–7.14 (1H, m), 7.27 (1H, d, *J*=4.3Hz), 7.59 (1H, d, *J*=7.9Hz); ^{13}C NMR (75MHz, $CDCl_3$, 293K, TMS): 29.0, 34.3, 40.2, 43.0, 55.2, 55.2, 111.6, 112.2, 113.8, 124.8, 127.2, 127.3, 128.2, 129.5, 130.0, 131.9, 133.0, 138.7, 139.6, 157.5; HRMS calcd for $C_{17}H_{16}NO$ (M+–H_2Br) 250.1232; found: 250.1245.

1-(2-Iodobenzyl)-1,2,3,4-tetrahydro-isoquinoline



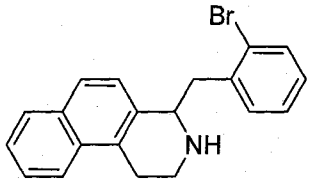
The amine was prepared following the general procedure (method A). (83%): IR (ν_{max} /cm^{-1}): 3421, 3059, 2925, 1672, 1464, 1453, 1435, 1125, 1011; ^{1}H NMR (300MHz, $CDCl_3$, 293K, TMS): 2.40 (1H, br), 2.80–3.04 (4H, m), 3.20–3.28 (1H, m), 3.34 (1H, dd, *J*=13.7, 3.2Hz), 4.33 (1H, dd, *J*=10.5, 2.7Hz), 6.90–6.95 (1H, m), 7.08–7.31 (5H, m), 7.39–7.42 (1H, m), 7.85 (1H, d, *J*=7.9Hz); ^{13}C NMR (75MHz, $CDCl_3$, 293K, TMS): 29.6, 39.9, 46.8, 54.7, 100.8, 125.5, 126.0, 126.3, 127.9, 128.1, 129.0, 130.9, 134.8, 139.5, 141.4; HRMS calcd for $C_{16}H_{14}N$ (M+–H_2I) 220.1126; found : 220.1084

1-(2-Chlorobenzyl)-1,2,3,4-tetrahydro-isoquinoline[252]



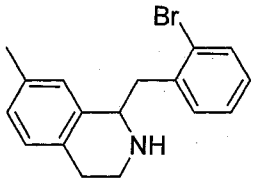
The amine was prepared following the general procedure (method A). (77%): mp 63–65 °C ($CHCl_3$); IR (ν_{max} /cm^{-1}): 3333, 3060, 2926, 1672, 1452, 1442, 1121, 1052, 1036; ^1H NMR (300MHz, $CDCl_3$, 293K, TMS): 1.69 (1H, br), 2.79–2.85 (2H, m), 2.91–2.99 (2H, m), 3.21–3.29 (1H, m), 3.42 (1H, dd, *J*= 13.7, 3.3Hz), 4.32 (1H, dd, *J*= 10.5, 3.1Hz), 7.09–7.32 (7H, m), 7.38–7.41 (1H, m); ^{13}C NMR (75MHz, $CDCl_3$, 293K, TMS): 29.8, 40.0, 40.5, 55.1, 125.7, 126.1, 126.4, 126.7, 127.9, 129.2, 129.7, 131.8, 134.3, 135.0, 137.0, 138.6; HRMS calcd for $C_{16}H_{15}ClN$ (M+–H) 256.0893; found: 256.0894.

4-(2-Bromobenzyl)-1,2,3,4-tetrahydrobenzo[f]isoquinoline



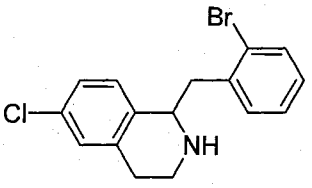
The amine was prepared following the general procedure (method A). (68%): IR (ν_{max} /cm^{-1}): 3386, 3052, 2930, 1510, 1470, 1440, 1025; NMR (300MHz, $CDCl_3$, 293K, TMS): 2.09 (1H, br), 2.97–3.14 (4H, m), 3.35–3.50 (2H, m), 4.45 (1H, d, *J*=9.7Hz), 7.09–7.14 (1H, m), 7.27–7.28 (2H, m), 7.43–7.53 (3H, m), 7.60 (1H, d, *J*=7.9Hz), 7.68 (1H, d, *J*=8.5Hz), 7.80 (1H, d, *J*=7.7Hz), 7.94 (1H, d, *J*=8.1Hz); ^{13}C NMR (75MHz, $CDCl_3$, 293K, TMS): 26.2, 39.3, 42.3, 55.5, 122.9, 124.8, 125.1, 125.2, 126.0, 126.0, 127.4, 128.2, 128.3, 130.1, 131.9, 132.1, 132.2, 133.0, 135.7, 138.7; HRMS calcd for $C_{20}H_{16}N$ (M+–H_2Br) 270.1283; found: 270.1270.

1-(2-Bromobenzyl)-7-methyl-1,2,3,4-tetrahydro-isoquinoline



The amine was prepared following the general procedure (method A). (85%): IR (ν_{max} /cm^{-1}): 3297, 1644, 1461, 1238, 1029; NMR (300MHz, $CDCl_3$, 293K, TMS): 1.63 (1H, br), 2.31 (3H, s), 2.69–2.82 (2H, m), 2.87–2.97 (2H, m), 3.16–3.24 (1H, m), 3.39 (1H, d, *J*=12.7Hz), 4.29 (1H, d, *J*=9.83Hz), 6.94–7.0 (2H, m), 7.05–7.14 (2H, m), 7.23–7.25 (2H, m), 7.55 (1H, d, *J*=7.9Hz); ^{13}C NMR (75MHz, $CDCl_3$, 293K, TMS): 21.78, 30.09, 40.74, 43.47, 55.56, 125.39, 127.50, 127.61, 127.85, 128.68, 129.65, 132.46, 132.53, 133.54, 135.59, 138.96, 139.33; HRMS calcd for $C_{17}H_{16}N$ (M+–H) 234.1283; found: 234.1298.

1-(2-Bromobenzyl)-6-chloro-1,2,3,4-tetrahydro-isoquinoline



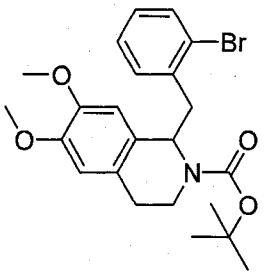
The amine was prepared following the general procedure (method A); the reaction was heated for 48h. (98%): IR (ν_{max} /cm^{-1}): 3054, 2928, 1597, 1484, 1470, 1128, 1025; ^{1}H NMR (300MHz, $CDCl_3$, 293K, TMS): 1.67 (1H, br), 2.74–2.79 (2H, m), 2.87–2.95 (m, 2H), 3.16–3.24 (1H, m), 3.33 (1H, dd, *J*=13.6, 3.4Hz), 4.27 (1H, dd, *J*=10.4, 3.2Hz), 7.08–7.13 (3H, m), 7.21–7.26 (3H, m), 7.57 (1H, dd, *J*=7.7, 0.8Hz); ^{13}C NMR (75MHz, $CDCl_3$, 293K, TMS): 29.6, 39.5, 42.7, 54.6, 124.7, 125.8, 127.3, 127.8, 128.2, 128.8, 131.5, 131.8, 132.9, 132.9, 137.0, 138.2; HRMS calcd for $C_{16}H_{13}ClBrN$ (M+) 254.0737; found: 254.0729.

6.7.1.7 General Procedure for the Protection of the Amines

6.7.1.7.1 General Procedure for the Synthesis of Carbamates

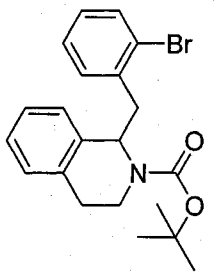
To a solution of the tetrahydro-isoquinoline (1.0 equiv.), diisopropylethylamine (2.0 equiv.) and 1-3mg of dimethylamino pyridine in DCM (0.2M) was added slowly di-*tert*-butyl dicarbonate (1.2 equiv.) and the resulting mixture was stirred overnight at 23 °C. The reaction was then quenched by adding a solution of NH_4Cl and was extracted with DCM. The crude reaction mixture was then purified by column chromatography on silica gel using Et_2O/Hexane mixtures.

Tert-butyl-1-(2-bromobenzyl)-3,4-dihydro-6,7-dimethoxyisoquinoline-2(1_H_)-carboxylate



The carbamate was prepared following the general procedure (80%). R_f = 0.51 (100% EtOAc with 1% TEA); mp = 108-109 °C ($CHCl_3$); IR (ν_{max} /cm^{-1}): 3063, 2931, 1686, 1519, 1420, 1228, 1161, 1099 cm^{-1}. ^1H NMR (300MHz, DMSO *d*-6, 383K): 1.21 (9H, s), 2.49-2.8 (2H, m), 3.07-3.23 (2H, m), 3.32-3.41 (1H, m), 3.70 (3H, s), 3.76 (3H, s), 4.00-4.07 (1H, m), 5.29-5.33 (1H, m), 6.70 (2H, d, *J*=12.9 Hz), 7.12-7.29 (3H, m), 7.56 (1H, d, *J*=7.9Hz); ^{13}C NMR (75MHz, DMSO *d*-6, 383K): 28.3, 28.7, 38.2, 42.7, 54.8, 57.1, 79.5, 112.9, 114.5, 125.6, 127.8, 128.1, 129.0, 130.1, 132.9, 133.1, 138.9, 148.8, 149.4, 154.5; HRMS calculated for $C_{23}H_{28}BrNO_4$ (M^+-C_4H_9O) 388.0548; found: 388.0559.

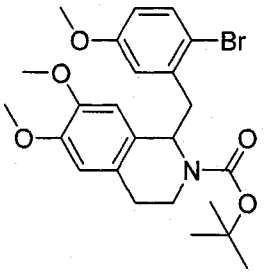
Tert-butyl 1-(2-bromobenzyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate



The carbamate was prepared following the general procedure (88%): R_f = 0.59 (30% EtOAc); mp = 108-110 °C ($CHCl_3$); IR (ν_{max} /cm^{-1}): 2977, 2930, 1690, 1451, 1158 cm^{-1}. NMR analysis revealed the presence of two amide rotamers present in a 5:1 ratio. ^1H NMR (300MHz, $CDCl_3$, 293K, TMS, Major rotamer): 1.08 (9H, s), 2.72-2.73 (1H, m), 2.78–3.13 (2H, m), 3.25-3.35 (2H, m), 4.41 (1H, dd, *J*=13.3, 5.0Hz), 5.46-5.56 (1H, m), 7.07-7.26 (6H, m), 7.40-7.43 (1H, m), 7.57 (1H, d, *J*= 7.9Hz); Minor rotamer: 1.32 (9H, s), 2.72–2.73 (1H, m), 2.78–3.13 (2H, m), 3.45 (1H, ddd, *J*=14.1, 9.8, 4.5Hz), 3.98 (1H, dt, *J*=12.9, 5.0Hz), 5.46-5.56 (1H, m), 7.07-7.26 (7H, m), 7.50 (1H, d, *J*= 7.9Hz); ^{13}C

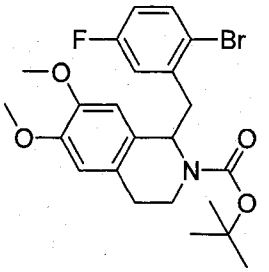
NMR (75MHz, $CDCl_3$, 293K, TMS, Major rotamer): 28.3, 29.0, 36.5, 43.2, 54.3, 79.9, 125.8, 126.6, 127.1, 127.5, 127.9, 128.7, 129.6, 132.3, 133.0, 134.9, 137.7, 138.5, 154.7; (Peaks corresponding to the minor rotamer were also detected): 28.7, 29.2, 39.1, 42.6, 54.4, 126.5, 127.0, 127.4, 127.8, 128.4, 129.0, 131.9; HRMS calculated for $C_9H_{10}N$ (M^+-C_4H_9O) 328.0337; found: 328.0345.

Tert-butyl-1-(2-bromo-5-methoxybenzyl)-3,4-dihydro-6,7-dimethoxyisoquinoline-2(1*H*)-carboxylate



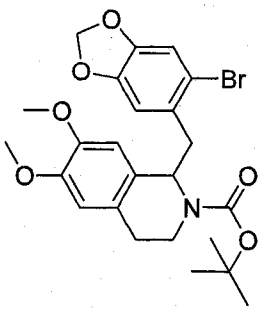
The carbamate was prepared following the general procedure (77%): mp 125–127 °C ($CHCl_3$); IR (ν_{max} /cm^{-1}): 2981, 1691, 1519, 1099; NMR analysis revealed the presence of two amide rotamers present in a 5:1 ratio. ^1H NMR (300MHz, $CDCl_3$, 293K, TMS, Major rotamer): 1.14 (9H, s), 2.62–2.67 (1H, m), 2.73–3.06 (2H, m), 3.44–3.50 (2H, m), 3.72 (3H, s), 3.85 (6H, s), 4.37 (1H, dd, *J*= 12.9, 4.7Hz), 5.34 (1H, d, *J*=7.8Hz), 6.81 (1H, s), 6.58–6.70 (3H, m), 7.43 (1H, d, *J*= 8.7Hz); Minor rotamer: 1.36 (9H, s), 2.62–2.67 (1H, m), 2.73–3.06 (2H, m), 3.44–3.50 (2H, m), 3.72 (3H, s), 3.85 (6H, s), 3.93–4.12 (1H, m), 5.42 (1H, dd, *J*= 8.3, 2.9Hz), 6.55 (1H, s), 6.58–6.70 (3H, m), 7.37 (1H, d, *J*= 8.8Hz); ^{13}C NMR (75MHz, $CDCl_3$, 293K, TMS, Major rotamer): 27.6, 27.9, 35.9, 42.5, 53.5, 55.1, 55.5, 55.6, 79.0, 109.5, 111.1, 113.5, 115.3, 117.2, 126.1, 128.5, 132.6, 138.8, 147.1, 147.5, 153.8, 158.6; (Peaks corresponding to the minor rotamer were also detected): 27.8, 38.2, 41.7, 53.1, 54.9, 109.8, 110.8, 113.3, 115.6, 116.5, 126.0, 128.4, 138.6, 146.9, 147.4, 153.9, 158.3; HRMS calcd for $C_{20}H_{21}BrNO_4$ (M+–C_4H_9O) 418.0650; found: 418.0665.

Tert-butyl-1-(2-bromo-5-fluorobenzyl)-3,4-dihydro-6,7-dimethoxyisoquinoline-2(1*H*)-carboxylate



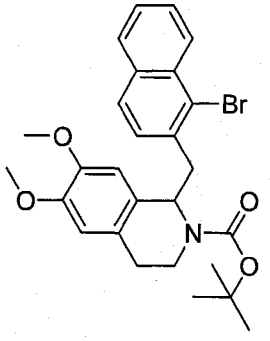
The carbamate was prepared following the general procedure (65%): mp 117–119 °C ($CHCl_3$); IR (ν_{max} /cm^{-1}): 2995, 1688, 1519, 13.64, 1166, 1125, 1098; NMR analysis revealed the presence of two amide rotamers present in a 3:1 ratio. ^1H NMR (300MHz, $CDCl_3$, 293K, TMS, Major rotamer): 1.16 (9H, s), 2.63–2.68 (1H, m), 2.78–3.06 (2H, m), 3.21–3.29 (2H, m), 3.87 (6H, s), 4.38 (1H, dd, *J*=13.2, 4.6Hz), 5.36 (1H, dd, *J*=10.7, 3.2Hz), 6.63 (1H, s), 6.80-6.92 (3H, m), 7.52 (1H, dd, *J*=8.2, 5.2Hz); Minor rotamer: 1.35 (9H, s), 2.63–2.68 (1H, m), 2.78–3.06 (2H, m), 3.21–3.29 (1H, m), 3.35–3.44 (1H, m), 3.78 (3H, s), 3.87 (3H, s), 4.03 (1H, dt, *J*=12.8, 4.8Hz), 5.40 (1H, dd, *J*=9.3, 4.6Hz), 6.60 (1H, s), 6.80–6.92 (3H, m), 7.46 (1H, dd, *J*=8.9, 5.6Hz); ^{13}C NMR (75MHz, $CDCl_3$, 293K, TMS, Major rotamer): 27.8, 28.0, 36.2, 42.6, 53.5, 55.7, 55.8, 79.4, 109.5, 111.3, 115.1 (J_F= 22.6Hz), 118.5 (J_F= 22.2Hz), 119.1(J_F= 3.1Hz), 126.4, 128.4, 133.4 (J_F= 8.0Hz), 140.2 (J_F= 7.5Hz), 147.3, 147.8, 153.9, 161.5 (J_F= 248.3Hz); (Peaks corresponding to the minor rotamer were also detected): 27.9, 38.3, 42.0, 53.2, 79.9, 109.8, 111.0, 114.7, 117.8, 118.1, 119.1, 126.2, 140.0, 147.1, 147.6, 154.1, 159.9, 163.1; HRMS calcd for $C_{19}H_{18}BrFNO_3$ (M+–C_4H_9O) 406.0454; found: 406.0404.

Tert-butyl 1-((5-bromobenzo[d][1,3]dioxol-6-yl)methyl)-3,4–dihydro-6,7-dimethoxyisoquinoline-2(1*H*)-carboxylate



The carbamate was prepared following the general procedure (71%): mp 145–146 °C ($CHCl_3$); IR (ν_{max} /cm^{-1}): 2985, 1688, 1518, 13.64, 1165, 1099, 1038; NMR analysis revealed the presence of two amide rotamers present in a 4:1 ratio. ^1H NMR (300MHz, $CDCl_3$, 293K, TMS, Major rotamer): 1.20 (9H, s), 2.61–2.66 (1H, m), 2.84–2.92 (2H, m), 3.14–3.26 (2H, m), 3.85 (6H, s), 4.36 (1H, d, *J*=12.0Hz), 5.28-5.31 (1H, m), 5.90 (1H, d, *J*=11.7Hz), 6.57 (1H, s), 6.62 (1H,s), 6.78 (1H, s), 7.02 (1H, s); Minor rotamer: 1.38 (9H, s), 2.61–2.66 (1H, m), 2.84–2.92 (2H, m), 3.14–3.26 (1H, m), 3.33–3.41 (1H, m), 3.77 (6H, s), 4.00–4.09 (1H, m), 5.28–5.31 (1H, m), 5.90 (1H, d, *J*=11.7Hz), 6.57 (1H, s), 6.62 (1H,s), 6.96 (1H, s); ^{13}C NMR (75MHz, $CDCl_3$, 293K, TMS, Major rotamer): 27.7, 27.9, 35.9, 42.1, 53.6, 55.5, 55.6, 79.0, 101.3, 109.4, 111.0, 111.1, 112.0, 114.9, 126.1, 128.4, 130.9, 146.9, 146.9, 147.0, 147.5, 153.8; (Peaks corresponding to the minor rotamer were also detected): 27.8, 28.0, 38.2, 41.6, 53.4, 79.0, 101.1, 109.8, 110.5, 110.8, 115.1, 125.9, 130.8, 146.5, 146.7, 147.3; HRMS calcd for $C_{20}H_{19}BrNO_6$ (M+–C_4H_9O) 432.0450; found: 432.0418.

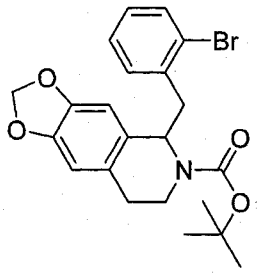
Tert-butyl-1-((1-bromonaphthalen-2-yl)methyl)-3,4-dihydro-6,7-dimethoxyisoquinoline-2(1*H*)-carboxylate



The carbamate was prepared following the general procedure (87%): mp 144–145 °C ($CHCl_3$); IR (ν_{max} /cm^{-1}): 2933, 1687, 1519, 1391, 1364, 1241, 1165, 1165; NMR analysis revealed the presence of two amide rotamers present in a 5:1 ratio. ^1H NMR (300MHz, $CDCl_3$, 293K, TMS, Major rotamer): 0.84 (9H, s), 2.66–2.71 (1H, m), 2.87–2.98 (1H, m), 3.17–3.27 (1H, m), 3.31–3.41 (1H, m), 3.53–3.59 (1H, m), 3.82 (3H, s), 3.87 (3H, s), 4.41 (1H, dd, *J*= 13.2, 4.5Hz), 5.49 (1H, dd, *J*=10.6, 4.0Hz), 6.63 (1H, s), 6.82 (1H, s), 7.20 (1H, d, *J*= 8.3Hz), 7.48 (1H, dd, *J*= 7.0, 7.0Hz), 7.59 (1H, dd, *J*= 7.0, 7.0Hz), 7.72 (1H, d, *J*= 8.3Hz), 7.80 (1H, d, *J*= 8.1Hz), 8.34 (1H, d, *J*= 8.5Hz); Minor rotamer: 1.32

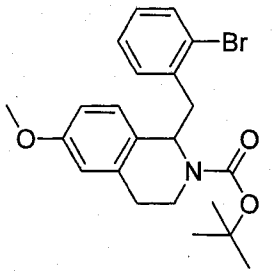
(9H, s), 2.66–2.71 (1H, m), 2.77–2.82 (1H, m), 3.17–3.27 (1H, m), 3.31–3.41 (1H, m), 3.53–3.59 (1H, m), 3.82 (3H, s), 3.83 (3H, s), 3.95 (1H, dt, *J*= 13.2, 4.8Hz), 5.49 (1H, m), 6.28 (1H, s), 6.59 (1H, s), 7.37 (1H, d, *J*= 8.3Hz), 7.42–7.81 (4H, m), 8.27 (1H, d, *J*= 8.5Hz); ^{13}C NMR (75MHz, $CDCl_3$, 293K, TMS, Major rotamer): 27.5, 28.1, 31.5, 36.3, 43.6, 53.9, 55.8, 79.1, 109.7, 111.3, 124.6, 126.0, 126.4, 126.8, 127.3, 127.3, 127.9, 128.8, 128.9, 132.2, 133.4, 136.3, 147.3, 147.8, 154.1; (Peaks corresponding to the minor rotamer were also detected): 28.8, 35.1, 43.5, 54.7, 56.0, 79.9, 110.7, 111.5, 125.6, 126.4, 126.9, 127.6, 128.0, 128.3, 129.0, 133.8, 136.7, 147.4, 148.1, 154.9; HRMS calcd for $C_{23}H_{21}BrNO_3$ (M+–C_4H_9O) 438.0700; found: 438.0656.

Tert-butyl-5-(2-bromobenzyl)-7,8-dihydro-[1,3]dioxolo[4,5-*g*]isoquinoline-6(5*H*)-carboxylate



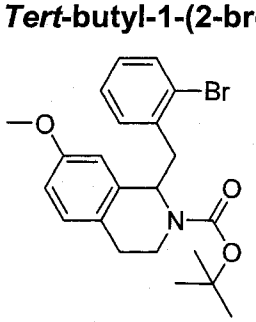
The carbamate was prepared following the general procedure (70%): mp 131–132 °C ($CHCl_3$); IR (ν_{max} /cm^{-1}): 2979, 1693, 1481, 1416, 1249, 1166, 1040; NMR analysis revealed the presence of two amide rotamers present in a 4:1 ratio. ^{1}H NMR (300MHz, $CDCl_3$, 293K, TMS, Major rotamer): 1.07 (9H, s), 2.60–2.65 (1H, m), 2.72–3.07 (2H, m), 3.22–3.30 (2H, m), 4.36 (1H, dd, *J*= 13.0, 3.9Hz), 5.36 (1H, dd, *J*=11.1, 1.7Hz), 5.91 (2H, s), 6.59 (1H, s), 6.88 (1H, s), 7.06–7.26 (3H, m), 7.56 (1H, d, *J*= 7.7Hz); Minor rotamer: 1.31 (9H, s), 2.60–2.65 (1H, m), 2.72–3.07 (2H, m), 3.22–3.30 (2H, m), 3.35–3.44 (1H, m), 3.94 (1H, dt, *J*= 13.2, 4.1Hz), 5.42 (1H, d, *J*= 4.6Hz), 5.92 (2H, s), 6.56 (1H, s), 6.62 (1H, s), 7.06–7.26 (3H, m), 7.51 (1H, d, *J*= 7.9Hz); ^{13}C NMR (75MHz, $CDCl_3$, 293K, TMS, Major rotamer): 27.7, 28.5, 35.9, 42.6, 53.8, 79.3, 100.8, 106.7, 108.5, 125.2, 127.4, 127.4, 130.1, 131.7, 132.4, 137.9, 146.0, 146.3, 154.0 (Peaks corresponding to the minor rotamer were also detected): 28.2, 28.7, 38.5, 42.0, 53.8, 79.2, 100.7, 107.1, 108.2, 126.9, 127.8, 130.0, 131.3, 137.7, 145.8, 146.1, 154.1; HRMS calcd for $C_{18}H_{15}BrNO_3$ (M+–C_4H_9O) 372.0235; found: 372.0224.

Tert-butyl-1-(2-bromobenzyl)-3,4-dihydro-6-methoxyisoquinoline-2(1_H_)-carboxylate



The carbamate was prepared following the general procedure (86%): mp 112–113 °C ($CHCl_3$); IR (ν_{max} /cm^{-1}): 2999, 1679, 1502, 1461, 1422, 1365, 1239, 1170; NMR analysis revealed the presence of two amide rotamers present in a 5:1 ratio. ^1H NMR (300MHz, $CDCl_3$, 293K, TMS, Major rotamer): 1.08 (9H, s), 2.68–2.75 (1H, m), 2.79–3.10 (2H, m), 3.23–3.33 (2H, m), 3.80 (3H, s), 4.39 (1H, dd, *J*= 13.2, 4.7Hz), 5.42 (1H, dd, *J*=10.9, 2.8Hz), 6.68 (1H, d, *J*= 2.5Hz), 6.81 (1H, dd, *J*= 8.5, 2.6Hz), 7.01–7.24 (3H, m), 7.31 (1H, d, *J*= 8.5Hz), 7.56 (1H, dd, *J*= 7.8, 1.0Hz); Minor rotamer: 1.32 (9H, s), 2.68–2.75 (1H, m), 2.79–3.10 (2H, m), 3.23–3.33 (1H, m), 3.84–3.48 (1H, m), 3.78 (3H, s), 3.96 (1H, dt, *J*= 12.9, 5.1Hz), 5.47 (1H, dd, *J*= 9.6, 5.0Hz), 6.64 (1H, m), 6.71 (1H, dd, *J*= 8.5, 2.4Hz), 7.01–7.24 (4H, m), 7.50 (1H, d, *J*= 7.8Hz); ^{13}C NMR (75MHz, $CDCl_3$, 293K, TMS, Major rotamer): 27.9, 27.9, 35.9, 42.9, 55.3, 53.5, 79.4, 112.8, 113.3, 125.3, 127.5, 128.1, 128.2, 129.5, 131.8, 132.5, 135.8, 138.2, 154.3, 158.1; (Peaks corresponding to the minor rotamer were also detected): 28.3, 29.1, 37.5, 42.5, 53.6, 55.2, 79.4, 112.2, 113.2, 127.0, 127.9, 129.3, 129.5, 130.2, 131.4; HRMS calcd for $C_{18}H_{17}BrNO_2$ (M+–C_4H_9O) 358.0443; found: 358.0393.

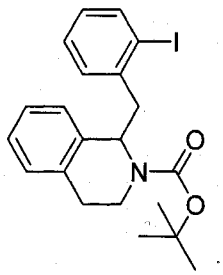
Tert-butyl-1-(2-bromobenzyl)-3,4-dihydro-7-methoxyisoquinoline-2(1_H_)-carboxylate



The carbamate was prepared following the general procedure (57%): mp 113–115 °C ($CHCl_3$); IR (ν_{max} /cm^{-1}): 2999, 1679, 1502, 1461, 1422, 1365, 1239, 1170; NMR analysis revealed the presence of two amide rotamers present in a 5:1 ratio. ^1H NMR (300MHz,

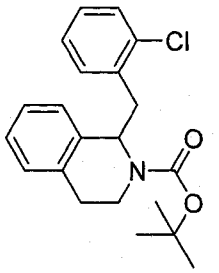
$CDCl_3$, 293K, TMS, Major rotamer): 1.08 (9H, s), 2.66–2.73 (1H, m), 2.76–3.15 (2H, m), 3.24–3.34 (2H, m), 3.82 (3H, s), 4.38 (1H, dd, *J*= 13.3, 4.8Hz), 5.44 (1H, dd, *J*=11.2, 2.9Hz), 6.78 (1H, dd, *J*= 8.4, 2.5Hz), 6.93 (1H, d, *J*= 2.5Hz), 7.00–7.23 (4H, m), 7.58 (1H, d, *J*= 7.9Hz); Minor rotamer: 1.32 (9H, s), 2.66–2.73 (1H, m), 2.76–3.15 (2H, m), 3.24–3.34 (1H, m), 3.39–3.48 (1H, m), 3.71 (3H, s), 3.97 (1H, dt, *J*= 12.6, 5.3Hz), 5.49 (1H, dd, *J*= 9.7, 5.0Hz), 6.63 (1H, d, *J*= 2.1), 6.74 (1H, dd, *J*= 8.7, 2.7Hz), 7.00–7.23 (4H, m), 7.51 (1H, d, *J*= 7.9Hz); ^{13}C NMR (75MHz, $CDCl_3$, 293K, TMS, Major rotamer): 27.7, 27.8, 36.3, 42.7, 54.0, 55.3, 79.4, 112.0, 112.8, 125.3, 126.5, 127.4, 128.2, 130.0, 131.8, 132.5, 138.0, 138.2, 154.2, 157.8; (Peaks corresponding to the minor rotamer were also detected): 27.7, 28.3, 38.9, 42.0, 54.2, 55.2, 111.8, 113.0, 127.0, 129.4, 131.4, 137.9, 154.3; HRMS calcd for $C_{18}H_{17}BrNO_2$ (M+–C_4H_9O) 358.0443; found: 358.0417.

Tert-butyl-1-(2-iodobenzyl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate



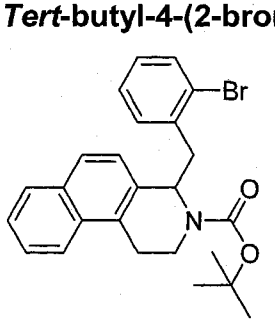
The carbamate was prepared following the general procedure (82%): mp 105–107 °C ($CHCl_3$); IR (ν_{max} /cm^{-1}): 2976, 1690, 1419, 1364, 1245, 1164, 1121; NMR analysis revealed the presence of two amide rotamers present in a 4:1 ratio. ^1H NMR (300MHz, $CDCl_3$, 293K, TMS, Major rotamer): 1.07 (9H, s), 2.75–2.80 (1H, m), 2.95–3.35 (4H, m), 4.42 (1H, dd, *J*= 13.9, 5.2Hz), 5.44 (1H, dd, *J*=10.9, 2.7Hz), 6.96 (1H, t, *J*= 7.8Hz), 7.07–7.29 (5H, m), 7.53 (1H, d, *J*= 7.4Hz), 7.86 (1H, d, *J*= 7.8Hz); Minor rotamer: 1.33 (9H, s), 2.75–2.80 (1H, m), 2.95–3.35 (4H, m), 3.98 (1H, dt, *J*= 13.1, 4.8Hz), 5.49 (1H, dd, *J*= 9.3, 5.4Hz), 6.88 (1H, t, *J*= 7.6Hz), 7.07–7.29 (5H, m), 7.53 (1H, d, *J*= 7.4Hz), 7.78 (1H, d, *J*= 7.8Hz); ^{13}C NMR (75MHz, $CDCl_3$, 293K, TMS, Major rotamer): 28.0, 28.6, 36.2, 46.9, 79.5, 101.7, 126.1, 126.8, 127.1, 128.4, 128.4, 129.2, 131.0, 134.5, 137.2, 139.2, 141.2, 154.3; (Peaks corresponding to the minor rotamer were also detected): 28.4, 28.8, 38.9, 46.5, 79.3, 101.7, 126.1, 126.7, 127.4, 128.1, 128.3, 129.7, 130.6, 136.9, 154.3; HRMS calcd for $C_{17}H_{15}INO$ (M+–C_4H_9O) 376.0198; found: 376.0231.

Tert-butyl-1-(2-chlorobenzyl)-3,4-dihydroisoquinoline-2(1_H_)-carboxylate



The carbamate was prepared following the general procedure (75%): mp 116–117 °C ($CHCl_3$); IR (ν_{max} /cm^{-1}): 2976, 1692, 1419, 1165; NMR analysis revealed the presence of two amide rotamers present in a 5:1 ratio. ^1H NMR (300MHz, $CDCl_3$, 293K, TMS, Major rotamer): 1.08 (9H, s), 2.72–2.78 (1H, m), 2.82–3.14 (2H, m), 3.14–3.35 (2H, m), 4.41 (1H, dd, *J*= 13.4, 5.3Hz), 5.49 (1H, dd, *J*=11.2, 2.8Hz), 7.07–7.26 (6H, m), 7.41 (1H, d, *J*=7.2 Hz), 7.57 (1H, d, *J*= 7.9Hz); Minor rotamer: 1.32 (9H, s), 2.72–2.78 (1H, m), 2.82–3.14 (2H, m), 3.14–3.35 (1H, m), 3.41–3.50 (1H, m), 3.98 (1H, dt, *J*= 13.2, 4.8Hz), 5.53 (1H, dd, *J*= 9.6, 5.0Hz), 7.07–7.26 (7H, m), 7.51 (1H, d, *J*= 7.8Hz); ^{13}C NMR (75MHz, $CDCl_3$, 293K, TMS, Major rotamer): 27.8, 18.6, 36.0, 42.7, 53.9, 79.4, 125.3, 126.1, 126.6, 127.0, 127.4, 128.2, 129.1, 131.8, 132.5, 134.4, 137.2, 138.1, 154.2; (Peaks corresponding to the minor rotamer were also detected): 28.3, 28.7, 38.6, 42.1, 53.9, 79.2, 126.5, 127.3, 127.9, 128.5, 131.4, 137.0, 137.9; HRMS calcd for $C_{17}H_{15}ClNO$ (M+–C_4H_9O) 284.0842; found: 284.0800.

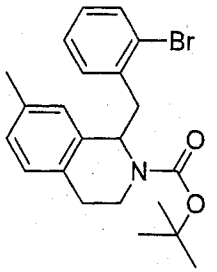
Tert-butyl-4-(2-bromobenzyl)-1,2-dihydrobenzo[_f_]isoquinoline-3(4_H_)-carboxylate



The carbamate was prepared following the general procedure (67%): mp 128–129 °C ($CHCl_3$); IR (ν_{max} /cm^{-1}): 2979, 1687, 1424, 1366, 1164, 1119, 1027; NMR analysis revealed the presence of two amide rotamers present in a 6.5:1 ratio. ^1H NMR (300MHz, $CDCl_3$, 293K, TMS, Major rotamer): 1.07 (9H, s), 2.95–3.03 (1H, m), 3.08–3.22 (2H, m), 3.31–3.48 (2H, m), 4.63 (1H, dd, *J*= 13.3, 4.8Hz), 5.56 (1H, dd, *J*=11.1, 2.0Hz), 7.03–

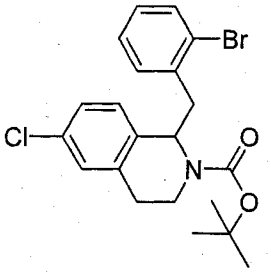
7.25 (3H, m), 7.37–7.60 (4H, m), 7.72 (1H, d, *J*= 8.5Hz), 7.81 (1H, d, *J*= 7.6Hz), 7.92 (1H, d, *J*= 8.3Hz); Minor rotamer: 1.31 (9H, s), 2.95-3.03 (1H, m), 3.08–3.22 (2H, m), 3.31–3.48 (2H, m), 3.31 (1H, dt, *J*= 13.0, 2.9Hz), 5.67 (1H, dd, *J*= 9.9, 3.4Hz), 7.03–7.25 (3H, m), 7.37–7.60 (4H, m), 7.66 (1H, d, *J*= 8.6Hz), 7.81 (1H, d, *J*= 7.6Hz), 7.88–7.91 (1H, m); ^{13}C NMR (75MHz, $CDCl_3$, 293K, TMS, Major rotamer): 25.7, 28.4, 35.9, 42.4, 54.7, 80.0, 123.4, 125.7, 125.8, 126.2, 126.9, 127.0, 128.0, 128.8, 129.0, 130.1, 132.4, 132.5, 132.8, 133.1, 134.9, 138.7, 154.6 (Peaks corresponding to the minor rotamer were also detected): 25.8, 28.8, 38.0, 41.9, 54.2, 79.8, 123.3, 126.0, 126.7, 127.6, 128.5, 129.1, 129.9, 131.8, 135.0, 138.4, 154.5; HRMS calcd for $C_{21}H_{17}BrNO$ ($M^+-C_4H_9O$) 378.0494; found: 378.0523.

Tert-butyl-1-(2-bromobenzyl)-3,4-dihydro-7-methylisoquinoline-2(1*H*)-carboxylate



The carbamate was prepared following the general procedure (82%): mp 157–158 °C ($CHCl_3$); IR (ν_{max} /cm^{-1}): 1683, 1458, 1366, 1246, 1164; NMR analysis revealed the presence of two amide rotamers present in a 6:1 ratio. ^{1}H NMR (300MHz, $CDCl_3$, 293K, TMS, Major rotamer): 1.07 (9H, s), 2.37 (3H, s), 2.66–2.75 (1H, m), 2.78–3.12 (2H, m), 3.24–3.33 (2H, m), 4.39 (1H, dd, *J*= 13.4, 5.0Hz), 5.44 (1H, dd, *J*=11.4, 2.9Hz), 6.96–7.26 (6H, m), 7.58 (1H, dd, *J*= 7.8, 1.0Hz); Minor rotamer: 1.30 (9H, s), 2.29 (3H, s), 2.66-2.75 (1H, m), 2.78–3.12 (2H, m), 3.24–3.33 (1H, m), 3.38–3.47 (1H, m), 3.99 (1H, dt, *J*= 13.5, 4.6Hz), 5.49 (1H, dd, *J*= 9.9, 4.8Hz), 6.96–7.26 (6H, m), 7.52 (1H, d, *J*= 8.2Hz); ^{13}C NMR (75MHz, $CDCl_3$, 293K, TMS, Major rotamer): 21.6, 28.3, 28.6, 36.6, 43.1, 54.2, 79.8, 125.7, 127.9, 127.9, 128.0, 128.6, 129.5, 131.8, 132.3, 132.9, 136.1, 137.5, 138.6, 154.7; (Peaks corresponding to the minor rotamer were also detected): 28.7, 39.1, 42.5, 79.6, 125.6, 127.7, 128.5, 128.8; HRMS calculated for $C_{18}H_{17}BrNO$ ($M^+-C_4H_9O$) 342.0494; Found: 342.0500;

Tert-butyl 1-(2-bromobenzyl)-3,4-dihydro-6-chloroisoquinoline-2(1*H*)-carboxylate

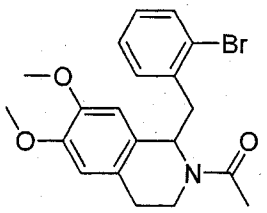


The carbamate was prepared following the general procedure (69%): mp 140-142 °C ($CHCl_3$); IR (ν_{max} /cm^{-1}): 2977, 1691, 1419, 1365, 1163, 1129; NMR analysis revealed the presence of two amide rotamers present in a 4:1 ratio. ^1H NMR (300MHz, $CDCl_3$, 293K, TMS, Major rotamer): 1.09 (9H, s), 2.69–2.75 (1H, m), 2.79–3.11 (2H, m), 3.22–3.32 (2H, m), 4.39 (1H, dd, *J*= 13.4, 4.8Hz), 5.44 (1H, dd, *J*=11.2, 3.2Hz), 7.01–7.33 (6H, m), 7.58 (1H, dd, *J*= 7.8, 1.0Hz); Minor rotamer: 1.33 (9H, s), 2.69–2.75 (1H, m), 2.79–3.11 (2H, m), 3.22–3.32 (1H, m), 3.38–3.47 (1H, m), 3.97 (1H, dt, *J*=13.3, 4.3Hz), 5.49 (1H, dd, *J*= 9.4, 5.2Hz), 7.01–7.33 (6H, m), 7.52 (1H, d, *J*= 7.9Hz); ^{13}C NMR (75MHz, $CDCl_3$, 293K, TMS, Major rotamer): 27.8, 28.5, 35.7, 42.7, 53.6, 79.7, 125.3, 126.3, 127.5, 128.4, 128.9, 131.4, 131.8, 132.2, 132.6, 135.6, 136.4, 137.7, 154.1; (Peaks corresponding to the minor rotamer were also detected): 28.3, 28.6, 125.3, 126.2, 136.4, 154.2; HRMS calcd for $C_{17}H_{14}BrClNO$ (M+) 361.9947; found: 361.9968.

6.7.1.7.2 General Procedure for the Synthesis of Acetates

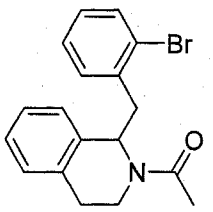
To a solution of the tetrahydro-isoquinoline (1.0 equiv.), diisopropylethylamine (2.0 equiv.) and 1-3mg of dimethylamino pyridine in DCM (0.2M) was added acetic anhydride (2.0 equiv.) and the resulting mixture was stirred overnight at 23 °C. The reaction was then quenched by adding a solution of NH_4Cl and was extracted with DCM. The crude reaction mixture was then purified by column chromatography on silica gel using Et_2O/Hexane mixtures.

1-[1-(2-Bromobenzyl)-6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl]-ethanone



The acetate was prepared following the general procedure (78%): mp = 122-123 °C ($CHCl_3$); R_f = 0.30 (100% EtOAc with 1% TEA); IR (ν_{max} /cm^{-1}): 3017, 3011, 2956, 1637, 1519, 1422, 1253, 1122 cm^{-1}. NMR analysis revealed the presence of two amide rotamers present in a 2:1 ratio. ^1H NMR (300MHz, $CDCl_3$, 293K, TMS, major rotamer): 1.49 (3H, s), 2.66-2.72 (1H, m), 2.85-2.96 (1H, m), 3.08-3.31 (2H, m), 3.38 (1H, dd *J*=13.8, 3.6Hz), 3.85 (3H, s), 3.87 (3H, s), 4.83 (1H, dd, *J*=13.0, 5.3Hz), 5.04 (1H, dd, *J*=10.2, 3.2Hz), 6.63 (1H, s), 6.76 (1H, s), 7.02-7.29 (3H, m), 7.60 (1H, d, *J*=7.9Hz); Minor rotamer: 2.09 (3H, s), 2.74-2.96 (3H, m), 3.08-3.31 (2H, m), 3.64 (3H, s), 3.67-3.80 (1H, m), 3.87 (3H, s), 5.80 (1H, t, *J*=7.2Hz), 6.29 (1H, s), 6.59 (1H, s), 7.02-7.29 (3H, m), 7.48 (1H, d, *J*=7.9Hz); ^{13}C NMR (75MHz, $CDCl_3$, 293K, TMS, major rotamer) : 20.9, 28.3, 35.3, 43.3, 56.3, 56.3, 56.9, 110.0, 111.8, 125.0, 127.5, 128.3, 128.3, 129.3, 132.6, 133.2, 138.2, 147.8, 148.5, 170.1; (Peaks corresponding to the minor rotamer were also detected): 22.3, 28.9, 41.7, 41.8, 53.1, 56.1, 56.2, 110.7, 111.2, 125.9, 126.1, 127.5, 128.4, 128.5, 132.0, 132,9, 137.5, 147.6, 148.1, 169.6; HRMS calculated for $C_{20}H_{22}BrNO_3$ (M^+-C_7H_6Br) 234.1130; found: 234.1094. MS (CI): m/z (%) = 404 (51), 302 (20), 234 (99), 220 (21), 192 (93), 176 (27), 132 (100).

1-[1-(2-Bromobenzyl)-3,4-dihydro-1H-isoquinolin-2-yl]-ethanone

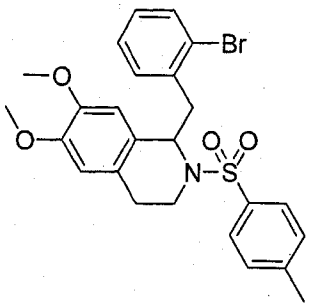


The acetate was prepared following the general procedure (81%): R_f = 0.16 (30% EtOAc/Hex with 1% TEA); IR (ν_{max} /cm^{-1}): 3063, 2932, 1636, 1421, 1026 cm^{-1}. NMR

analysis revealed the presence of two amide rotamers present in a 2:1 ratio. ^{1}H NMR (300MHz, $CDCl_3$, 293K, TMS, major rotamer): 1.41 (3H, s), 2.73-2.99 (2H, m), 3.05-3.20 (2H, m), 3.34-3.39 (1H, m), 4.82 (1H, dd, *J*=12.2, 4.0Hz), 5.12 (1H, d, *J*=9.9Hz7.01-7.25 (6H, m), 7.38 (1H, d, *J*=6.1Hz), 7.56 (1H, d, *J*=7.6Hz); Minor rotamer: 2.02 (3H, s), 2.73-2.99 (2H, m), 3.05-3.20 (1H, m), 3.27-3.33 (1H, m), 3.64-3.68 (2H, m), 5.80 (1H, t, *J*=6.4Hz), 7.01-7.25 (7H, m), 7.45 (1H, d, *J*=7.7Hz); ^{13}C NMR (75MHz, $CDCl_3$, 293K, TMS, major rotamer) : 20.0, 28.0, 34.5, 42.6, 56.4, 124.4, 126.0, 126.6, 126.8, 127.6, 128.6, 128.9, 131.8, 132.5, 134.1, 135.9, 136.7, 169.4; (Peaks corresponding to the minor rotamer were also detected): 21.5, 28.6, 41.0, 41.2, 52.6, 125.0, 126.5, 126.7, 127.1, 127.8, 128.0, 131.1, 132.2, 133.5, 136.0, 137.3, 167.0; HRMS calculated for $C_9H_{10}N$ (M^+-C_7H_6Br) 174.0919; found: 174.0936. MS (CI): m/z (%) = 344 (72), 264 (31), 174 (97), 144 (39), 132 (100).

6.7.1.7.3 General Procedure for the Synthesis of Tosylate

1-(2-Bromobenzyl)-6,7-dimethoxy-2-(toluene-4-sulfonyl)-1,2,3,4-tetrahydro-isoquinoline



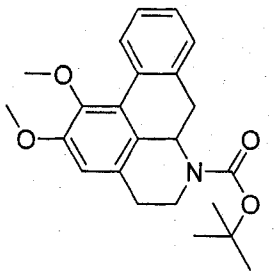
To a solution of 1-(2-Bromobenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline (1.4g, 3.9mmol, 1.0 eq.) and pyridine (0.47mL, 5.8 mmol, 1.5 eq.) in dichloromethane (DCM) was added slowly *p*-toluenesulfonyl chloride (0.81g, 4.3mmol, 1.1 eq.) and the resulting mixture was stirred overnight at 23 °C. The reaction was then quenched by adding a solution of NH_4Cl and was extracted with DCM. The product was then purified by silica chromatography (100% EtOAc) to afford the tosylate product (1.04g, 54%): R_f = 0.58 (100% EtOAc); mp = 132-133 °C ($CHCl_3$); IR (ν_{max} /cm^{-1}): 2968, 2937, 1517, 1463, 1251, 1156, 1107, 1021 cm^{-1}. ^{1}H NMR (300MHz, $CDCl_3$, 293K, TMS): 2.29 (3H, s), 2.53-2.59 (1H, m), 2.67-2.78 (1H, m), 3.16 (2H, d, *J*= 7.2Hz), 3.57 (1H, dd, *J*= 14.4, 4.4Hz), 3.64

(3H, s), 3.77 (3H, s), 3.88 (1H, dd, *J*= 13.4, 4.6Hz), 5.22 (1H, t, *J*= 7.2Hz), 6.30 (1H, s), 6.45 (1H, s), 7.05 (4H, t, *J*= 8.0Hz), 7.15 (1H, t, *J*=7.2Hz) 7.44 (3H, d, *J*=7.9Hz); ^{13}C NMR (75MHz, $CDCl_3$, 293K, TMS) : 21.1, 26.3, 38.8, 43.0, 55.4, 55.5, 109.5, 111.0, 124.8, 124.9, 126.7, 127.0, 127.1, 128.0, 129.0, 132.0, 132.3, 136.9, 137.0, 142.5, 146.6, 147.6; HRMS calculated for $C_{25}H_{26}BrSNO_4$ (M^+-C_7H_6Br) 346.1113; found: 346.1145. MS (CI): m/z (%) = 516 (31), 436 (5), 346 (100), 282 (21), 192 (63).

6.7.2 General Procedure for the Intramolecular Direct Arylation

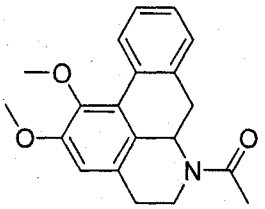
K_2CO_3 (2 equiv.), Ligand (0.1 equiv.), $Pd(OAc)_2$ (0.05 equiv.) and the aryl halide (1 equiv.) are weighed to air and placed in a round bottom flask with a magnetic stir bar. The flask is purged with argon (x3). DMA is then added (0.2M) and the resulting mixture is heated to 130 °C overnight. The reaction mixture is then concentrated and loaded onto a silica gel column for chromatography using ether/hexane mixtures.

1-(1,2-Dimethoxy-4,5,6a,7-tetrahydro-dibenzoquinoline-6-carboxylic acid tert-butyl ester



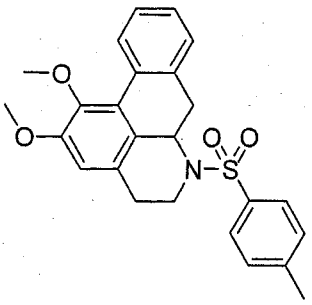
The cyclization was achieved following the general procedure (90%): R_f = 0.57 (100% EtOAc); mp = 149-151 °C ($CHCl_3$); IR (ν_{max} /cm^{-1}): 3070, 2930, 1687, 1406, 1249, 1163, 1106 cm^{-1}. ^1H NMR (300MHz, $CDCl_3$, 293K, TMS): 1.49 (9H, s), 2.63-3.00 (5H, m), 3.66 (3H, s), 3.89 (3H, s), 4.41-4.44 (1H, m), 4.64-4.69 (1H, m), 6.67 (1H, s), 7.21-7.34 (3H, m), 8.44 (1H, d, *J*=7.8 Hz); ^{13}C NMR (75MHz, $CDCl_3$, 293K, TMS) : 28.8, 30.7, 35.7, 38.7, 51.9, 56.2, 60.3, 80.2, 111.7, 126.8, 127.3, 127.9, 128.0, 128.4, 128.7, 130.1, 132.0, 137.3, 145.8, 152.2, 155.0; HRMS calculated for $C_{23}H_{27}NO_4$ (M+) 381.1940; found: 381.1943.

1-(1,2-Dimethoxy-4,5,6a,7-tetrahydro-dibenzo[de,g]quinolin-6-yl)-ethanone (N-acetyl nornuciferine)[253]



The cyclization was achieved following the general procedure (99%): R_f = 0.17 (100% EtOAc with 1% TEA); mp = 223-224 °C ($CHCl_3$); NMR analysis revealed the presence of two amide rotamers present in a 6:5 ratio. ^{1}H NMR (300MHz, $CDCl_3$, 293K, TMS, major rotamers): 2.22 (3H, s), 2.64-2.95 (3H, m), 3.03-3.15 (1H, m), 3.31 (1H, t, *J*=12.2 Hz), 3.67 (3H, s), 3.90 (3H, s), 4.01 (1H, d, *J*=12.1Hz), 5.10 (1H, d, *J*=12.6Hz), 6.67 (1H, s), 7.27-7.33 (3H, m), 8.42-8.48 (1H, m); Minor rotamer: 2.16 (3H, s), 2.64-2.95 (4H, m), 3.03-3.15 (1H, m), 3.67 (3H, s), 3.90 (3H, s), 4.57 (1H, d, *J*=12.5Hz), 4.97 (1H, d, *J*=9.1Hz), 6.70 (1H, s), 7.27-7.33 (3H, m), 8.42-8.48 (1H, m); ^{13}C NMR (75MHz, $CDCl_3$, 293K, TMS, major rotamers): 22.6, 30.7, 34.0, 41.9, 50.3, 55.9, 59.9, 111.2, 126.9, 127.4, 127.7, 127.8, 128.0, 128.3, 128.6, 131.5, 136.8, 145.7, 152.0, 169.0; (Peaks corresponding to the minor rotamer were also detected): 21.6, 39.8, 36.3, 36.5, 53.7, 111.6, 125.4, 126.4, 127.3, 127.7, 28.6, 128.9, 130.1, 131.6, 136.1, 145.5, 152.2, 169.6; IR (ν_{max} /cm^{-1}): 2935 (s), 2892 (m), 1625 (s), 1443 (m), 1423 (m), 1029 (m) cm^{-1}. HRMS calculated for $C_{20}H_{21}NO_3$ (M+) 323.1521; found: 323.1527.

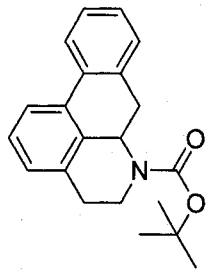
1,2-Dimethoxy-6-(toluene-4-sulfonyl)-5,6,6a,7-tetrahydro-4H-dibenzo[de,g]quinoline



[253] Kupchan, M. S.; Moniot, J. L.; Kanojia, R. M.; O'Brien, J. B.; *J. Org. Chem.*, **1971**, *36*, 2413.

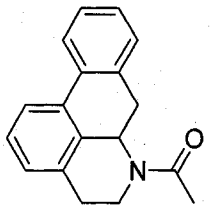
The cyclization was achieved following the general procedure (99%): R_f = 0.38 (30% EtOAc); mp = 179-181 °C ($CHCl_3$); ^1H NMR (300MHz, $CDCl_3$, 293K, TMS): 2.32-2.48 (2H, m), 2.37 (3H, s), 3.02 (1H, t, *J*=13.8Hz), 3.16 (1H, dd, *J*=13.9, 4.4Hz), 3.24-3.33 (1H, m), 3.63 (3H, s), 3.90 (3H, s), 3.84 (3H, s), 4.06-4.13 (1H, m), 4.59 (1H, dd, *J*=13.7, 4.2 Hz), 6.53 (1H, s), 7.23 (2H, d, *J*=8.1 Hz), 7.26-7.36 (3H, m), 7.69 (2H, d, *J*=8.2Hz), 8.41(1H, d, *J*=7.7Hz); ^{13}C NMR (75MHz, $CDCl_3$, 293K, TMS) : 21.8, 29.0, 38.2, 41.2, 53.4, 56.2, 60.4, 111.6, 125.6, 127.2, 127.5, 128.2, 128.2, 128.7, 128.8, 129.2, 130.2, 131.7, 136.7, 138.2, 143.6, 146.0, 152.5; IR (ν_{max} /cm^{-1}): 2928 (s), 2851 (m), 1452 (m), 1319 (m), 1149 (s), 1091 (m) cm^{-1}. HRMS calculated for $C_{25}H_{25}SNO_4$ (M+) 435.1504; found: 435.1488.

4,5,6a,7-Tetrahydro-dibenzoquinoline-6-carboxylic acid tert-butyl ester



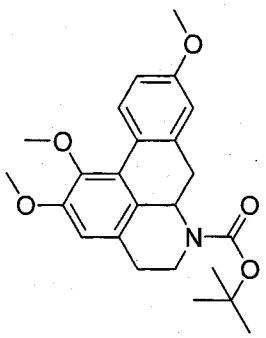
The cyclization was achieved following the general procedure (99%): R_f = 0.76 (70% EtOAc); mp = 153-155 °C ($CHCl_3$); ^1H NMR (300MHz, $CDCl_3$, 293K, TMS): 1.51 (9H, s), 2.71-2.79 (1H, m), 2.84-3.01 (3H, m), 3.1 (1H, dd, *J*=13.9, 4.1 Hz), 4.44-4.46 (1H, m), 3.89 4.86-4.91 (1H, m), 7.10 (1H, d, *J*=7.5 Hz), 7.24-7.35 (4H, m), 7.61 (1H, d, *J*=7.7 Hz), 7.77 (1H, d, *J*=7.6 Hz); ^{13}C NMR (75MHz, $CDCl_3$, 293K, TMS) : 28.8, 30.7, 34.6, 39.0, 51.8, 80.2, 122.6, 124.0, 127.1, 127.6, 128.1, 128.2, 129.0, 133.0, 134.2, 134.7, 135.3, 136.0, 155.0; IR (ν_{max} /cm^{-1}): 2963 (m), 2929 (s), 1677(s), 1414 (m), 1212 (s), 1113 (m) cm^{-1}. HRMS calculated for $C_{21}H_{23}NO_2$ (M^+-C_4H_9); 264.102 found: 5264.0968.

1-(4,5,6a,7-Tetrahydro-dibenzo[de,g]quinolin-6-yl)-ethanone[253]



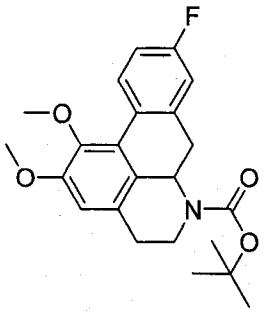
The cyclization was achieved following the general procedure (76%): R_f = 0.29 (100% EtOAc); mp = 205 -207 °C ($CHCl_3$); NMR analysis revealed the presence of two amide rotamers present in a 2:1 ratio. ^{1}H NMR (300MHz, $CDCl_3$, 293K, TMS, major rotamers): 2.22 (3H, s), 2.71-2.99 (3H, m), 3.07-3.21 (1.0H, m), 3.30 (1H, t, *J*=11.9 Hz), 4.01 (1H, d, *J*=12.8 Hz), 5.28 (1H, dd, *J*=13.8, 2.6 Hz), 7.06-7.13 (1H, m), 7.23-7.34 (4H, m), 7.59-7.61 (1H, m), 7.74-7.80 (1H, m); Minor rotamer: 2.19 (3H, s), 22.71-2.99 (3H, m), 3.07-3.21 (1.0H, m), 4.75 (1H, d, *J*=13.0 Hz), 4.98 (1H, d, *J*=10.7 Hz), 7.06-7.13 (1H, m), 7.23-7.34 (4H, m), 7.59-7.61 (1H, m), 7.74-7.80 (1H, m); ^{13}C NMR (75MHz, $CDCl_3$, 293K, TMS, major rotamers) : 22.6, 30.7, 32.8, 42.1, 50.3, 122.5, 123.5, 126.7, 127.2, 127.4, 127.9, 129.0, 132.6, 133.5, 134.0, 134.6, 135.4, 169.2; (Peaks corresponding to the minor rotamer were also detected): 21.5, 29.8, 35.5, 36.5, 53.6, 123.9, 127.8, 128.0, 128.5, 132.3, 133.8, 134.2, 134.8, 135.2, 169.7; IR (ν_{max} /cm^{-1}): 2959 (w), 2925 (s), 1730 (s), 1434 (m), 1417 (m) cm^{-1}. HRMS calculated for $C_{18}H_{17}NO$ (M+) 263.1310; found: 263.1298.

1,2,9-Trimethoxy-4,5,6a,7-tetrahydro-dibenzo[*de,g*]quinoline-6-carboxylic acid tert-butyl ester



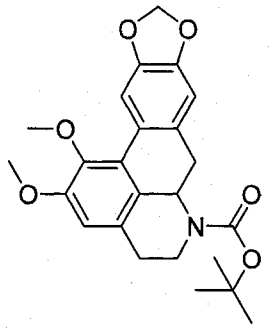
The cyclization was achieved following the general procedure (79%): mp 151–152 °C ($CHCl_3$); IR (ν_{max} /cm^{-1}): 2934, 1688, 1595, 1502, 1409, 1244, 1158, 1107; ^1H NMR (300MHz, $CDCl_3$, 293K, TMS): 1.50 (9H, s), 2.62–2.66 (1H, m), 2.78–2.97 (4H, m), 3.65 (3H, s), 3.85 (3H, s), 3.89 (3H, s), 4.41 (1H, d, *J*= 9.9Hz), 4.67 (1H, dd, *J*= 12.6, 2.1Hz), 6.63 (1H, s), 6.81 (1H, d, *J*=2.4Hz), 6.86 (1H, dd, *J*=8.8, 2.7Hz), 8.39 (1H, d, *J*=8.8Hz); ^{13}C NMR (75MHz, $CDCl_3$, 293K, TMS): 29.0, 30.8, 36.3, 39.1, 52.0, 55.6, 46.3, 60.3, 80.3, 111.0, 112.7, 113.9, 124.9126.2, 128.0, 130.2, 130.3, 139.3, 145.4, 152.4, 155.1, 159.2; HRMS calcd for $C_{24}H_{29}NO_5$ (M+) 411.2046; found: 411.2058.

9-Fluoro-1,2-dimethoxy-4,5,6a,7-tetrahydro-dibenzo[*de*,*g*]quinoline-6-carboxylic acid tert-butyl ester



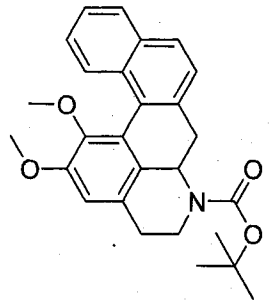
The cyclization was achieved following the general procedure (79%): mp 156–158 °C ($CHCl_3$); IR (ν_{max} /cm^{-1}): 2973, 1692, 1497, 1406, 1242, 1167, 1104; ^1H NMR (300MHz, $CDCl_3$, 293K, TMS): 1.50 (9H, s), 2.63–2.67 (1H, m), 2.77–2.97 (4H, m), 3.65 (3H, s), 3.90 (3H, s), 4.42 (1H, d, *J*= 8.5Hz), 4.67 (1H, dd, *J*= 13.1, 1.6Hz), 6.67 (1H, s), 6.96-7.04 (3H, m), 8.42 (1H, dd, *J*=8.5, 6.1Hz); ^{13}C NMR (75MHz, $CDCl_3$, 293K, TMS): 28.5, 30.3, 35.5, 38.4, 51.2, 55.8, 59.9, 79.9, 111.2, 113.7 (J_F= 20.5Hz), 114.8 (J_F= 16.1Hz), 125.8, 126.8 (J_F= 2.8Hz), 127.8, 129.9, 130.3 (J_F= 8.3Hz), 139.6 (J_F= 7.7Hz), 145.1, 151.9, 154.5, 161.7 (J_F= 248.0Hz); HRMS calcd for $C_{23}H_{26}NO_4F$ (M+) 399.1846; found: 399.1855.

1,2-Dimethoxy-4,5,6a,7-tetrahydro-9,11-dioxa-6-aza-benzo[*fg*]cyclopenta[*b*]anthracene-6-carboxylic acid tert-butyl ester



The cyclization was achieved following the general procedure (87%): mp 176–177 °C ($CHCl_3$); IR (ν_{max} /cm^{-1}): 2974, 1686, 1487, 1408, 1243, 1166, 1041; ^1H NMR (300MHz, $CDCl_3$, 293K, TMS): 1.50 (9H, s), 2.61–2.96 (5H, m), 3.66 (3H, s), 3.88 (3H, s), 4.41 (1H, d, *J*= 9.1Hz), 4.63 (1H, d, *J*= 12.6Hz), 5.97 (2H, s), 6.63 (1H, s), 6.75 (1H, s), 8.00 (1H, s); ^{13}C NMR (75MHz, $CDCl_3$, 293K, TMS): 28.4, 30.2, 35.4, 38.4, 51.6, 55.8, 59.9, 79.7, 100.8, 108.2, 108.8, 110.6, 125.0, 125.7, 127.4, 129.6, 131.4, 144.8, 146.4, 146.5, 151.8, 154.5; HRMS calcd for $C_{24}H_{27}NO_6$ (M+) 425.1838; found: 425.1847.

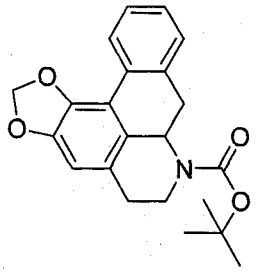
1,2-Dimethoxy-4,5,6a,7-tetrahydro-6-aza-dibenzo[*a,kl*]anthracene-6-carboxylic acid tert-butyl ester



The cyclization was achieved following the general procedure (60%): mp 189–190 °C ($CHCl_3$); IR (ν_{max} /cm^{-1}): 2973, 1690, 1408, 1252, 1162; ^1H NMR (300MHz, $CDCl_3$, 293K, TMS): 1.46 (9H, s), 2.68–2.73 (1H, m), 2.85–2.98 (4H, m), 3.02 (3H, s), 3.93 (3H, s), 4.48 (1H, d, *J*= 7.8Hz), 4.60 (1H, dd, *J*= 12.0, 2.0Hz), 6.76 (1H, s), 7.40–7.44 (3H, m), 7.78–7.82 (2H, m), 7.98–8.01 (1H, m); ^{13}C NMR (75MHz, $CDCl_3$, 293K, TMS): 28.4, 30.0, 36.6, 38.5, 51.7, 55.9, 59.9, 79.8, 111.2, 124.9, 124.9, 126.6, 127.3, 127.4, 127.6,

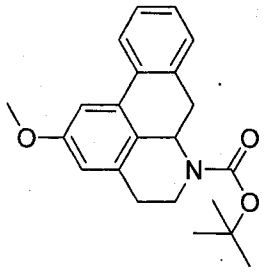
128.2, 128.4, 128.5, 129.0, 129.6, 133.1, 136.2, 144.9, 151.9, 154.7; HRMS calcd for $C_{27}H_{29}NO_4$ (M+) 431.2097; found: 431.2111.

5,6,7a,8-Tetrahydro-benzo[*g*][1,3]dioxolo[4'5':4,5]benzo[1,2,3-*de*]quinoline-7-carboxylic acid tert-butyl ester



The cyclization was achieved following the general procedure (99%): mp 186–188 °C ($CHCl_3$); IR (ν_{max} /cm^{-1}): 2974, 1690, 1410, 1226, 1160; ^1H NMR (300MHz, $CDCl_3$, 293K, TMS): 1.50 (9H, s), 2.56–2.61 (1H, m), 2.74–2.95 (3H, m), 3.06 (1H, dd, *J*= 13.9,3.8Hz), 4.39 (1H, d, *J*= 10.4Hz), 4.79 (1H, d, *J*= 11.8Hz), 5.93 (1H, d, *J*=1.0Hz), 6.06 (1H, d, *J*=1.0Hz), 6.57 (1H, s), 7.20–7.34 (3H, m), 8.09 (1H, d, *J*=7.6Hz); ^{13}C NMR (75MHz, $CDCl_3$, 293K, TMS): 28.5, 30.4, 34.9, 38.7, 51.5, 79.8, 100.8, 107.5, 117.2, 125.9, 126.9, 126.9, 127.0, 127.7, 127.8, 128.3, 130.7, 135.9, 142.8, 146.6, 154.5; HRMS calcd for $C_{22}H_{23}NO_4$ (M+) 365.1627; found: 365.1608.

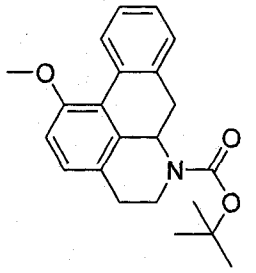
2-Methoxy-4,5,6a,7-tetrahydro-dibenzo[*de*,*g*]quinoline-6-carboxylic acid tert-butyl ester



The cyclization was achieved following the general procedure (99%): mp: 112–114 °C ($CHCl_3$); IR (ν_{max} /cm^{-1}): 2924, 1676, 1465, 1412, 1173; ^1H NMR (300MHz, $CDCl_3$, 293K, TMS): 1.51 (9H, s), 2.67–3.11 (5H, m), 3.86 (3H, s), 4.42–4.45 (1H, m), 4.80–4.84 (1H, m), 6.66 (1H, d, *J*=1.91 Hz), 7.17–7.35 (4H, m), 7.74 (1H, d, *J*=7.4 Hz); ^{13}C NMR (75MHz, $CDCl_3$, 293K, TMS): 28.58, 30.81, 51.25, 55.38, 79.87, 108.67, 112.41, 123.71,

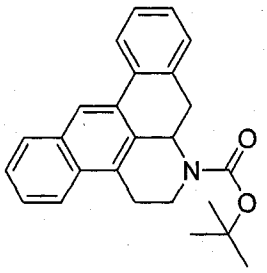
125.21, 127.28, 128.02, 128.71, 128.74, 128.77, 133.76, 136.04, 136.40, 158.47; HRMS calculated for $C_{22}H_{25}NO_3$ (M^+); 351.1834; Found: 351.1829;

1-Methoxy-4,5,6a,7-tetrahydro-dibenzo[*de,g*]quinoline-6-carboxylic acid tert-butyl ester



The cyclization was achieved following the general procedure (99%): mp = 133–135 °C ($CHCl_3$); IR (ν_{max} /cm^{-1}): 2924, 1692, 1457, 1406, 1264, 1164; ^1H NMR (300MHz, $CDCl_3$, 293K, TMS): 1.49 (9H, s), 2.66–2.7 (1H, m), 2.79–2.98 (4H, m), 3.88 (3H, s), 4.40–4.43 (1H, m), 4.71–4.77 (1H, m), 6.89 (1H, d, *J*=8.4 Hz), 7.08 (1H, d, *J*=8.4Hz), 7.18–7.33 (3H, m), 8.31 (1H, d, *J*=7.9 Hz); ^{13}C NMR (75MHz, $CDCl_3$, 293K, TMS): 28.54, 29.75, 35.09, 38.69, 52.09, 55.68, 79.81, 110.53, 122.60, 126.36, 126.52, 127.20, 127.80, 128.42, 128.82, 131.79, 135.16, 136.76, 154.61, 155.27; HRMS calculated for $C_{18}H_{16}NO_3$ (M^+); 294.1130; Found: 294.1115;

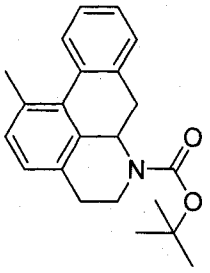
5,6,7a,8-Tetrahydro-7-aza-dibenzo[*a,de*]anthracen-7-carboxylic acid tert-butyl ester



The cyclization was achieved following the general procedure (92%): mp 200–201 °C ($CHCl_3$); IR (ν_{max} /cm^{-1}): 2974, 1690, 1414, 1168; ^1H NMR (300MHz, $CDCl_3$, 293K, TMS): 1.53 (9H, s), 2.94–3.07 (3H, m), 3.13 (1H, dd, *J*= 13.9,4.1Hz), 3.24–3.31 (1H, m), 4.57 (1H, d, *J*= 6.4Hz), 4.79 (1H, dd, *J*= 12.4, 2.6Hz), 5.93 (1H, d, *J*=1.0Hz), 7.27–7.29 (1H, m), 7.33–7.39 (1H, m), 7.43–7.53 (2H, m), 7.84–7.87 (1H, m), 7.91–7.96 (1H, m), 8.05 (1H, s); ^{13}C NMR (75MHz, $CDCl_3$, 293K, TMS): 26.0, 28.5, 34.5, 38.0, 51.9, 79.9, 121.7,

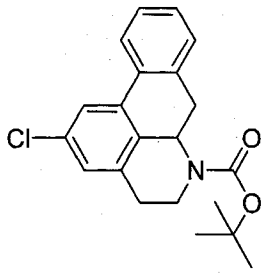
122.8, 124.1, 125.6, 126.2, 127.3, 128.0, 128.3, 128.7, 129.6, 130.1, 130.8, 131.3, 132.3, 133.8, 136.2, 154.5; HRMS calcd for $C_{21}H_{16}NO_2$ (M+–C_4H_9) 314.1181; found: 314.1211.

1-Methyl-4,5,6a,7-tetrahydro-dibenzo[*de,g*]quinoline-6-carboxylic acid tert-butyl ester



The cyclization was achieved following the general procedure (96%): mp = 138–140 °C ($CHCl_3$); IR (ν_{max} /cm^{-1}): 3001, 1678, 1465, 1364, 1248, 1177; ^1H NMR (300MHz, $CDCl_3$, 293K, TMS): 1.49 (9H, s), 2.59 (3H, s), 2.67–2.76 (1H, m), 2.85–2.96 (4H, m), 4.42–4.46 (1H, m), 4.44–4.46 (1H, m), 4.65–4.69 (1H, m), 7.03 (1H, d, *J*=7.8 Hz), 7.16 (1H, d, *J*=7.8 Hz), 7.20–7.33 (3H, m), 7.68 (1H, d, *J*=7.4Hz); ^{13}C NMR (75MHz, $CDCl_3$, 293K, TMS): 22.91, 28.54, 30.14, 35.35, 38.53, 52.36, 79.81, 126.06, 127.22, 127.51, 128.00, 128.33, 130.48, 131.68, 132.78, 133.52, 133.84, 134.51, 137.92, 154.64; HRMS calculated for $C_{18}H_{16}NO$ (M^+–C_4H_9O); 262.1298; Found: 262.1298;

2-Chloro-4,5,6a,7-tetrahydro-dibenzo[*de,g*]quinoline-6-carboxylic acid tert-butyl ester

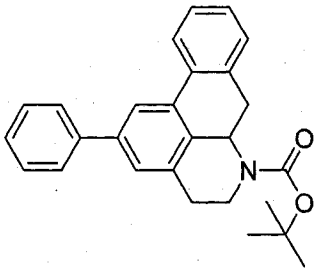


The cyclization was achieved following the general procedure (86%): mp 101–103 °C ($CHCl_3$); IR (ν_{max} /cm^{-1}): 2976, 1691, 1418, 1163; ^1H NMR (300MHz, $CDCl_3$, 293K, TMS): 1.51 (9H, s), 2.68–2.73 (1H, m), 2.80–2.98 (3H, m), 3.09 (1H, dd, *J*=14.1, 4.4Hz), 4.44 (1H, d, *J*= 8.8Hz), 4.84 (1H, dd, *J*= 13.9, 3.8Hz), 7.10 (1H, d, *J*=1.6 Hz), 7.27–7.37 (3H,

m), 7.57 (1H, d, *J*=1.9Hz), 7.71 (1H, d, *J*= 7.4Hz); ^{13}C NMR (75MHz, $CDCl_3$, 293K, TMS): 28.5, 30.4, 34.2, 38.5, 51.3, 80.1, 122.5, 123.8, 127.2, 127.5, 128.5, 128.8, 131.1, 132.6, 132.8, 134.8, 135.8, 136.1, 136.9, 154.5; HRMS calcd for $C_{17}H_{13}ClNO_3$ (M+–C_4H_9) 298.0635; found: 298.0669.

6.7.3 General Procedure for the Synthesis of C-2 Analogues

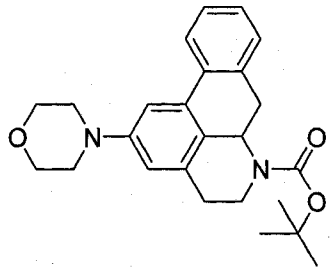
2-Phenyl-4,5,6a,7-tetrahydro-dibenzo[de,g]quinoline-6-carboxylic acid tert-butyl ester



The Suzuki-Miyaura coupling was achieved following the general procedure developed by Buchwald[254]. The aryl chloride (0.1g, 0.28mmol, 1.0 equiv.), phenyl boronic acid (0.051g, 0.42mmol, 1.5 equiv.), potassium phosphate (0.119g, 0.56mmol, 2.0 equiv.), palladium acetate (0.003g, 0.01mmol, 0.05equiv.) and S-Phos (0.014g, 0.025mmol, 0.13 equiv.) was placed in a vial and was then purged with argon. Toluene (0.6mL) was then added and the resulting mixture was heated to 100 °C overnight. The resulting reaction was then purified by chromatography on silica using benzene as the eluant. (90%): IR (ν_{max} /cm^{-1}): 2975, 1691, 1409, 1248, 1161; ^1H NMR (300MHz, $CDCl_3$, 293K, TMS): 1.50 (9H, s), 2.63–2.14 (5H, m), 4.32–4.58 (1H, m), 4.80–4.93 (1H, m), 7.06–7.30 (6H, m), 7.42–7.68 (4H, m), 7.81–7.83 (1H, m); ^{13}C NMR (75MHz, $CDCl_3$, 293K, TMS): 28.6, 30.4, 34.5, 38.6, 51.3, 80.1, 123.8, 126.5, 127.1, 127.3, 127.4, 127.5, 128.1, 128.6, 128.8, 131.9, 132.7, 132.8, 133.8, 134.8, 135.5, 135.9, 154.5; HRMS calcd for $C_{27}H_{27}NO_2$ (M+–C_4H_9O) 284.0842; found: 284.0800.

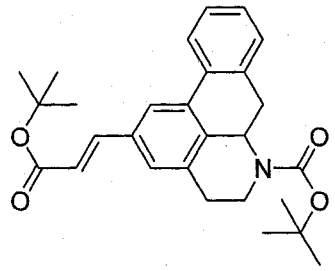
[254] Walker, S.D.; Barder, T.E.; Martinelli, J.R.; Buchwald, S.L. *Angew. Chem. Int. Ed.*, **2004**, *43*, 1871.

2-Morpholin-4-yl-4,5,6a,7-tetrahydro-dibenzo[de,g]quinoline-6-carboxylic acid tert-butyl ester



The amination coupling was achieved following the general procedure developed by Buchwald[255]. The aryl chloride (0.1g, 0.28mmol, 1.0 equiv.), (*o*-biphenyl)P(Cy)$_2$ (0.020g, 0.06mmol, 0.2 equiv.), NaO*t*Bu (0.038g, 0.39mmol, 1.4 equiv.) and Pd(OAc)$_2$ (0.006g, 0.03mmol, 0.1equiv.) was placed in a vial and was then purged with argon. A solution of morpholine (0.29ml, 0.34mmol, 1.2 equiv.) in Toluene (1.0mL) was then added and the resulting mixture was heated to 100 °C overnight. The resulting reaction was then purified by chromatography on silica (50% ether/hexane). (83%): mp 171–173 °C ($CHCl_3$); IR (ν_{max} /cm^{-1}): 2971, 1688, 1609, 1409, 1364, 1251, 1162, 1121; ^{1}H NMR (300MHz, $CDCl_3$, 293K, TMS): 1.51 (9H, s), 2.65–2.70 (1H, m), 2.78–3.12 (4H, m), 3.16–3.26 (4H, m), 3.89 (4H, t, *J*= 4.7Hz), 4.43 (1H, d, *J*= 10.2Hz), 4.32 (1H, dd, *J*= 13.3, 2.6Hz), 6.68 (1H, s), 7.21–7.34 (4H, m), 7.75 (1H, d, *J*= 7.5Hz); ^{13}C NMR (75MHz, $CDCl_3$, 293K, TMS): 28.5, 30.8, 34.6, 38.8, 49.7, 51.1, 66.8, 79.8, 110.4, 115.0, 123.5, 124.9, 127.1, 127.8, 128.7, 134.0, 135.0, 135.9, 136.0, 150.0, 154.6; HRMS calcd for $C_{25}H_{30}N_2O_3$ (M+) 406.2256; found: 406.2277.

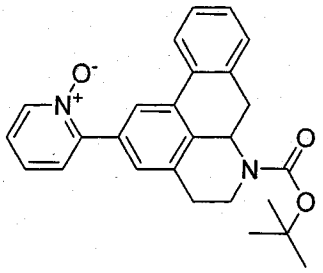
2-(2-*Tert*-butoxycarbonyl-vinyl)-4,5,6a,7-tetrahydro-dibenzo[de,g]quinoline-6-carboxylic acid tert-butyl ester



[255] Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S.L. *J. Org. Chem.*, **2000**, *65*, 1158.

The Heck coupling was achieved using the conditions developed by Fu's group[256] A vial was loaded with the aryl chloride (0.1g, 0.28mmol, 1.0 equiv.), P(*t*Bu)$_3$-HBF$_4$ (0.016g, 0.05mmol, 0.3eq) and $Pd_2(dba)_3$ (0.013g, 0.01mmol, 0.05equiv.) and was purged with argon. To this mixture was added a solution of Cy_2NMe (0.077ml, 0.36mmol, 1.3equiv.), the tert-butyl acrylate (0.045ml, 0.31mmol, 1.1 equiv.) in dioxane (0.2mL) and the resulting solution was heated to 100 °C overnight The product was then extracted and purified using chromatography on silica (10% ether/hexane). (54%): IR (ν_{max} /cm^{-1}): 2976, 1693, 1409, 1366, 1290, 1221, 1150; ^{1}H NMR (300MHz, $CDCl_3$, 293K, TMS): 1.51 (9H, s), 1.55 (9H, s), 2.72–3.00 (4H, m), 3.10 (1H, dd, *J*= 14.0, 4.0Hz), 4.45 (1H, d, *J*= 6.7Hz), 4.89 (1H, dd, *J*= 13.6, 2.8Hz), 6.43 (1H, d, *J*= 16.0Hz), 7.25–7.28 (3H, m), 7.31–7.38 (1H, m), 7.61 (1H, d, *J*= 16.0Hz), 7.74 (1H, s), 7.79 (1H, d, *J*= 7.6Hz); ^{13}C NMR (75MHz, $CDCl_3$, 293K, TMS): 28.7, 29.0, 30.9, 34.6, 39.2, 52.1, 80.5, 81.0, 120.5, 122.2, 124.2, 127.6, 127.9, 128.8, 129.1, 133.6, 133.7, 135.3, 135.4, 136.1, 136.2, 143.8, 155.0, 166.7; HRMS calcd for $C_{24}H_{24}NO_4$ (M+–C_4H_9) 390.1705; found: 390.1787.

2-(1-Oxy-pyridin-2-yl)-4,5,6a,7-tetrahydro-dibenzo[de,g]quinoline-6-carboxylic acid tert-butyl ester

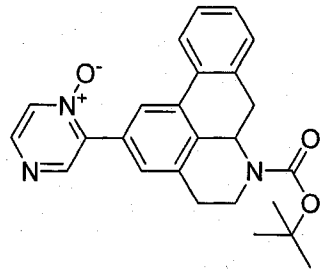


A flask was loaded with the aryl chloride (0.2g, 0.56mmol, 1.0 equiv.), P(*t*Bu)$_3$-HBF$_4$ (0.049g, 0.17mmol, 0.3eq), K_2CO_3 (0.155g, 1.12mmol, 2.0equiv.) pyridine N-oxide (0.054g, 2.25mmol, 4.0equiv.) and $Pd(OAc)_2$ (0.013g, 0.06mmol, 0.1equiv.) and was purged with argon. To the flask was introduced Toluene (1.0mL) and the resulting solution was heated to 110 °C overnight. The product was passed through a short celite pad and then purified directly on chromatography on silica (10% then 20% acetone/$CHCl_3$). (78%): mp 233–235 °C ($CHCl_3$); IR (ν_{max} /cm^{-1}): 2974, 1688, 1410, 1247, 1162; ^{1}H NMR (300MHz, $CDCl_3$, 293K, TMS): 1.52 (9H, s), 2.79–3.02 (4H, m),

[256] Littke, A.F.; Fu, G. C. *J. Am. Chem. Soc.*, **2001**, *123*, 6989.

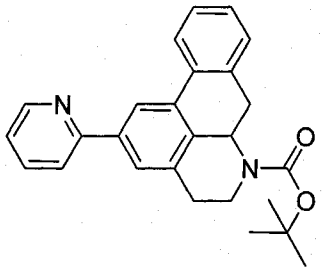
3.11–3.14 (1H, m), 4.46–4.48 (1H, m), 4.93 (1H, d, *J*= 11.7Hz), 7.24–7.33 (5H, m), 7.47 (1H, dd, *J*= 7.7, 1.2Hz), 7.58 (1H, s), 7.80 (1H, d, *J*=7.5Hz), 8.02 (1H, s), 8.34 (1H, d, *J*= 5.4Hz); ^{13}C NMR (75MHz, $CDCl_3$, 293K, TMS): 28.4, 30.3, 34.1, 38.6, 51.5, 79.9, 123.1, 123.8, 124.5, 125.7, 127.2, 128.1, 128.3, 128.5, 128.5, 131.1, 133.3, 134.2, 134.4, 135.0, 135.6, 140.4, 149.0, 154.4; HRMS calcd for $C_{26}H_{26}N_2O_2$ (M+–O) 398.1989; found: 398.1952.

2-(1-Oxy-pyrazin-2-yl)-4,5,6a,7-tetrahydro-dibenzo[de,g]quinoline-6-carboxylic acid tert-butyl ester



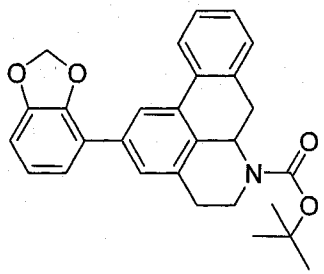
A flask was loaded with the aryl chloride (0.1g, 0.28mmol, 1.0 equiv.), P(*t*Bu)$_3$-HBF$_4$ (0.012g, 0.04mmol, 0.15eq), K_2CO_3 (0.078g, 0.56mmol, 2.0equiv.) pyrazine N-oxide (0.054g, 0.56mmol, 2.0equiv.) and $Pd(OAc)_2$ (0.003g, 0.01mmol, 0.05equiv.) and was purged with argon. To the flask was introduced dioxane (1.0mL) and the resulting solution was heated to 110 °C overnight The product was purified directly on chromatography on silica (5% acetone/$CHCl_3$). (70%): mp 210–212 °C ($CHCl_3$); IR (ν_{max} /cm^{-1}): 2979, 1688, 1410, 1306, 1161; ^{1}H NMR (300MHz, $CDCl_3$, 293K, TMS): 1.52 (9H, s), 2.80–3.04 (4H, m), 3.12–3.16 (1H, m), 4.48–4.55 (1H, m), 4.94 (1H, d, *J*= 11.0Hz), 7.29 (1H, m), 7.47–7.48 (1H, m), 7.55 (1H, s), 7.66–7.67 (1H, m), 7.79 (1H, d, *J*= 7.1Hz), 8.01 (1H, s), 8.24 (1H, s), 8.42 (1H, s), 8.69 (1H, s); ^{13}C NMR (75MHz, $CDCl_3$, 293K, TMS): 28.5, 30.4, 34.1, 38.6, 51.6, 80.1, 123.0, 123.9, 127.4, 128.1, 128.4, 128.7, 131.9, 133.0, 134.5, 135.3, 135.6, 135.6, 144.5, 145.6, 148.3, 154.5; MS (CI): m/z (%) = 416 (3), 358 (61), 342 (65), 298 (99), 240 (100).

2-Pyridin-2-yl-4,5,6a,7-tetrahydro-dibenzo[de,g]quinoline-6-carboxylic acid tert-butyl ester



Ammonium formate (0.152g, 2.4mmol, 10.0 equiv.) was added to a stirring solution of the N-oxide (0.1g, 0.24mmol, 1.0 equiv.) and Pd/C (0.026g, 0.002mmol, 0.1eq) in MeOH (1.5mL) in a round bottom flask. The resulting solution was then purged with argon and left to stir at room temperature for 1.5h. The product was purified directly on chromatography on silica (100% $CHCl_3$). (82%): mp 155–157°C ($CHCl_3$); IR (ν_{max} /cm^{-1}): 2974, 1689, 1411, 1161; ^1H NMR (300MHz, $CDCl_3$, 293K, TMS): 1.52 (9H, s), 2.84–3.03 (4H, m), 3.13 (1H, dd, *J*= 13.7, 3.0Hz), 4.48-4.49 (1H, m), 4.93 (1H, d, *J*= 11.6Hz), 7.24–7.30 (3H, m), 7.34–7.38 (1H, m), 7.75–7.81 (3H, m), 7.93 (1H, d, *J*= 7.7Hz), 8.24 (1H, s), 8.72 (1H, d, *J*= 4.7Hz); ^{13}C NMR (75MHz, $CDCl_3$, 293K, TMS): 28.6, 30.6, 34.4, 38.8, 51.6, 80.0, 120.5, 121.0, 122.2, 124.0, 126.2, 127.4, 128.1, 128.7, 133.7, 133.8, 134.9, 135.6, 135.8, 136.8, 137.9, 149.6, 154.7, 157.2, ; HRMS calcd for $C_{26}H_{26}N_2O_2$ (M+) 398.1994; found: 398.2000.

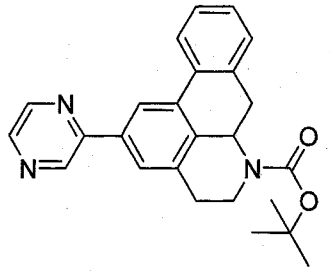
2-Benzo[1,3]dioxol-4-yl-4,5,6a,7-tetrahydro-dibenzo[de,g]quinoline-6-carboxylic acid tert-butyl ester



A flask was loaded with the aryl chloride (0.1g, 0.28mmol, 1.0 equiv.), $PMe(tBu)_2$-HBF_4 (0.021g, 0.08mmol, 0.3eq), K_2CO_3 (0.078g, 0.56mmol, 2.0equiv.) AgOTf (0.062g, 0.28mmol, 1.0equiv.) and $Pd(OAc)_2$ (0.006g, 0.02mmol, 0.1equiv.) and was purged with argon. To the flask was introduced a solution of 1,3-benzodioxole (0.3mL, 2.8mmol,

10.0 equiv.) in DMA (1.0mL) and the resulting solution was heated to 145 °C overnight. The product was purified directly on chromatography on silica (10% Ether/hexane). (65%): IR (ν_{max} /cm^{-1}): 2929, 1689, 1365, 1410, 1249, 1162; ^{1}H NMR (300MHz, $CDCl_3$, 293K, TMS): 1.52 (9H, s), 2.77–3.04 (4H, m), 3.09–3.15 (1H, m), 4.46–4.48 (1H, m), 4.92 (1H, d, *J*= 11.1Hz), 6.03 (2H, d, *J*= 6.2Hz), 6.83 (1H, d, *J*= 7.5Hz), 6.93 (1H, t, *J*= 7.8Hz), 7.09 (1H, d, *J*= 7.7Hz), 7.24–7.37 (3H, m), 7.44 (1H, s), 7.83 (1H, d, *J*=7.6Hz), 7.95 (1H, s); ^{13}C NMR (75MHz, $CDCl_3$, 293K, TMS): 28.5, 30.5, 34.3, 38.6, 51.5, 79.9, 100.7, 107.7, 121.2, 122.0, 122.0, 122.7, 123.8, 127.1, 127.3, 128.0, 128.7, 132.2, 133.8, 134.4, 134.6, 135.3, 135.8, 144.6, 147.8, 154.6; HRMS calcd for $C_{24}H_{18}NO_4$ (M+–C_4H_9) 384.1236; found: 384.1220.

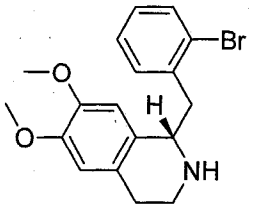
2-Pyrazin-2-yl-4,5,6a,7-tetrahydro-dibenzo[de,g]quinoline-6-carboxylic acid tert-butyl ester



A flask was loaded with the aryl chloride (0.036g, 0.09mmol, 1.0 equiv.), Pd/C (0.009g, 0.009mmol, 0.1equiv.) and MeOH (1.0mL). The flask was then bubbled with hydrogen gas and the resulting solution was stirred for 1.5h. The product was purified directly on chromatography on silica (100% $CHCl_3$). (84%): mp 137–140 °C ($CHCl_3$); IR (ν_{max} /cm^{-1}): 2974, 1689, 1409, 1160; ^{1}H NMR (300MHz, $CDCl_3$, 293K, TMS): 1.53 (9H, s), 2.83–3.04 (4H, m), 3.15 (1H, dd, *J*= 14.1, 3.8Hz), 4.50–4.52 (1H, m), 4.96 (1H, d, *J*= 12.2Hz), 7.30–7.31 (2H, m), 7.36–7.40 (1H, m), 7.76 (1H, m), 7.92 (1H, d, *J*= 7.7Hz), 8.27 (1H, d, *J*= 1.4Hz), 854 (1H, s), 8.66 (1H, s), 9.1 (1H, s); ^{13}C NMR (75MHz, $CDCl_3$, 293K, TMS): 28.6, 30.7, 34.2, 38.8, 51.7, 80.1, 120.9, 124.0, 126.0, 127.4, 128.5, 128.7, 133.5, 134.8, 135.0, 135.4, 135.8, 136.0, 142.1, 143.0, 144.2, 152.6, 154.6; HRMS calcd for $C_{25}H_{25}N_3O_2$ (M+) 399.1947; found: 399.1942.

6.7.4 Synthesis of (*R*)-Nuciferine and (*R*)-Nornuciferine

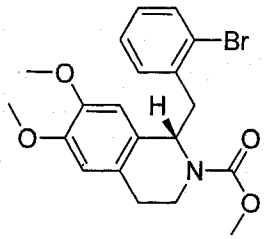
(*R*)-1-(2-Bromo-benzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline



To a solution of the 2-(2-bromophenyl)-N-[2-(3,4-dimethoxyphenyl)-ethyl]-acetamide (3.95g, 10.4mmol, 1.0 equiv.) in DCM (60mL) in a round bottom flask equipped with a magnetic stirrer and a condenser was added phosphorus oxychloride (6.38g, 41.6mmol, 4.0 equiv.) and the resulting mixture was refluxed overnight. The reaction was then allowed to cool to 0 °C and the solution was neutralized with a saturated solution of 10% NaOH. The resulting mixture was extracted with Et_2O to afford the crude dihydroisoquinoline. The product was found to be pure by NMR and was employed without further purification. The reduction was performed using Tietze[257] procedure using the 1,2-(*S*,*S*)-*N*-tosyl-1,2-diphenylethylenediamine as the ligand. (99%): IR (ν_{max} /cm^{-1}, Nujol): 3335, 2933, 2832, 1523, 1471, 1254, 1220, 1108, 1025; NMR (300MHz, $CDCl_3$, 293K, TMS): 2.67 (2H, t, *J*=7.8Hz), 3.73 (2H, t, *J*=7.7Hz), 3.79 (3H, s), 3.88 (3H, s), 4.19 (2H, s), 6.66 (1H, s), 6.91 (1H, s), 7.05 (1H, td, *J*=7.4, 1.5Hz), 7.18 (1H, td, *J*=7.4, 1.2Hz), 7.28 (1H, dd, *J*= 7.7, 1.6Hz), 7.57 (1H, dd, *J*=8.0, 1.2Hz); ^{13}C NMR (75MHz, $CDCl_3$, 293K, TMS): 29.4, 40.0, 43.2, 54.8, 55.8, 55.9, 109.6, 111.6, 124.9, 127.1, 127.4, 128.2, 130.5, 132.0, 133.0, 138.8, 147.0, 147.4; HRMS calcd for $C_{18}H_{20}BrNO_2$ (M+–H_2Br) 280.1338; Found: 280.1330. HPLC: The ee was determined to be 95% using HPLC analysis on a CHIRALCEL OJ-H column, λ=284nm. Retention times in 10% isopropanol in hexanes were 11.1 min (major) and 16.4 min. $[\alpha]_D^{22}$ = +41.5 (c = 1, CH_2Cl_2).

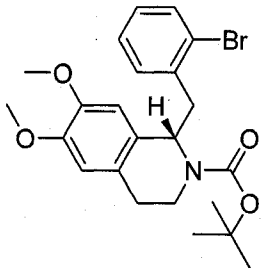
[257] Tietze, L.F.; Rackelmann, N.; Sekar, G. *Angew. Chem. Int. Ed.*, **2003**, *42*, 4254.

(*R*)-Methyl 1-(2-bromobenzyl)-3,4-dihydro-6,7-dimethoxyisoquinoline-2(1*H*)-carboxylate



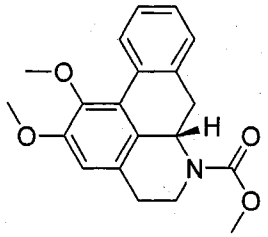
To a solution of (*R*)-1-(2-Bromo-benzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (0.86g, 23.7mmol, 1.0 equiv.), diisopropylethylamine (0.83ml, 47.5mmol, 2.0 equiv.) and 1mg of dimethylamino pyridine in DCM (15mL) was added slowly methyl chloroformate (0.22ml, 28.5mmol, 1.2 equiv.) and the resulting mixture was stirred overnight at 23 °C. The reaction was then quenched by adding a solution of NH_4Cl and was extracted with DCM. The crude reaction mixture was then purified by column chromatography on silica gel using 50% Et_2O/Hexane. (84%): mp 173-175 °C ($CHCl_3$); IR (ν_{max} /cm^{-1}): 2933, 1693, 1470, 1254, 1098; NMR analysis revealed the presence of two amide rotamers present in a 2.3:1 ratio. ^1H NMR (300MHz, $CDCl_3$, 293K, TMS): 2.66–2.72 (1H, m), 2.78–3.60 (4H, m), 3.25 (3H, s), 3.79 (3H, s), 3.86 (3H, s), 4.31 (1H, ddd, *J*= 13.2, 5.3, 2.0Hz), 5.38 (1H, dd, *J*=10.2, 4.7Hz), 6.62 (1H,s), 6.64 (1H, s), 7.04–7.23 (3H, m), 7.57 (1H, d, *J*= 7.7Hz); Minor rotamer: 2.66–2.72 (1H, m), 2.78–3.60 (4H, m), 3.62 (3H, s), 3.65 (3H, s), 3.84 (3H, s), 3.96 (1H, dt, *J*=13.1, 4.8Hz), 5.42 (1H, d, *J*= 7.1Hz), 6.31 (1H, s), 6.59 (1H, s), 7.04–7.23 (3H, m), 7.51 (1H, d, *J*= 8.9Hz); ^{13}C NMR (75MHz, $CDCl_3$, 293K, TMS, Major rotamer): 27.9, 37.2, 42.5, 51.9, 53.6, 55.7, 55.7, 109.6, 111.1, 124.9, 126.0, 127.1, 128.0, 128.0, 131.5, 132.2, 137.6, 147.1, 147.7, 155.6; (Peaks corresponding to the minor rotamer were also detected): 38.6, 41.7, 52.4, 54.5, 55.5, 110.0, 110.8, 125.3, 125.9, 126.9, 127.9, 132.4, 146.8, 147.5; HRMS calcd for $C_{13}H_{16}NO_4$ (M+–C_7H_6Br) 250.1079; found: 250.1096; MS (CI): m/z (%) = 422 (20), 420 (22), 250 (100), 205 (12); $[\alpha]_D^{22}$ = -66.8 (c = 1, CH_2Cl_2).

(*R*)-*Tert*-butyl 1-(2-bromobenzyl)-3,4-dihydro-6,7-dimethoxyisoquinoline-2(1*H*)-carboxylate



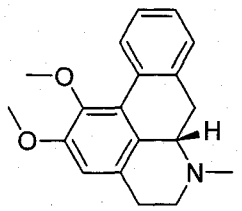
The carbamate was prepared following the general procedure (80%): mp 108–109 °C ($CHCl_3$); IR (ν_{max} /cm^{-1}): 3063, 2931, 1686, 1519, 1420, 1228, 1161, 1099; ^1H NMR (300MHz, DMSO *d*-6, 383K, TMS): 1.21 (9H, s), 2.49–2.80 (2H, m), 3.07–3.23 (2H, m), 3.32–3.41 (1H, m), 3.70 (3H, s), 3.76 (3H, s), 4.00–4.07 (1H, m), 5.29–5.33 (1H, m), 6.70 (2H, d, *J*=12.9 Hz), 7.12–7.29 (3H, m), 7.56 (1H, d, *J*=7.9Hz); ^{13}C NMR (75MHz, DMSO *d*-6, 383K): 28.3, 28.7, 38.2, 42.7, 54.8, 57.1, 79.5, 112.9, 114.5, 125.6, 127.8, 128.1, 129.0, 130.1, 132.9, 133.1, 138.9, 148.8, 149.4, 154.5; HRMS calcd for $C_{22}H_{28}BrNO_4$ (M+–C_4H_9O) 388.0548; found: 288.0559; $[\alpha]_D^{22}$ = -81.3 (c = 1, CH_2Cl_2).

(*R*)-1,2-Dimethoxy-4,5,6a,7-tetrahydro-dibenzo[*de*,*g*]quinoline-6-carboxylic acid methyl ester



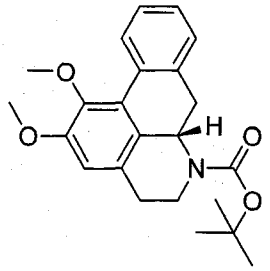
The cyclization was achieved following the general procedure (58%): mp 176–177 °C ($CHCl_3$); IR (ν_{max} /cm^{-1}): 2953, 1694, 1449, 1405, 1250, 1104; ^1H NMR (300MHz, $CDCl_3$, 293K, TMS): 2.64–2.69 (1H, m), 2.81-3.05 (4H, m), 3.66 (3H, s), 3.76 (3H, s), 3.90 (3H, s), 6.66 (1H, s), 6.91 (1H, s), 7.05 (1H, td, *J*=7.4, 1.5Hz), 7.18 (1H, td, *J*=7.4, 1.2Hz), 7.28 (1H, dd, *J*= 7.7, 1.6Hz), 7.57 (1H, dd, *J*=8.0, 1.2Hz); ^{13}C NMR (75MHz, $CDCl_3$, 293K, TMS): 30.1, 35.2, 38.8, 51.4, 52.5, 55.8, 59.8, 111.3, 125.9, 126.9, 127.4, 127.5, 128.2, 128.3, 129.5, 131.5, 136.6, 145.6, 151.9, 155.8; HRMS calcd for $C_{20}H_{21}NO_4$ (M+) 339.1471; found: 339.1467; $[\alpha]_D^{22}$ = -132.3 (c = 1, CH_2Cl_2).

(*R*)-Nuciferine



To a stirred solution of (*R*)-1,2-dimethoxy-4,5,6a,7-tetrahydro-dibenzo[*de*,*g*]quinoline-6-carboxylic acid methyl ester (0.057g, 0.17mmol, 1.0 equiv.) in dry THF (6mL) was added $LiAlH_4$ (0.0.006g, 0.17mmol, 1.0 equiv.) at 0 °C under an argon atmosphere. The temperature was allowed to rise to room temperature. The resulting mixture was stirred at room temperature for 24h. The reaction was slowly hydrolysed with water and extracted with diethyl ether, dried with $MgSO_4$, filtered, evaporated and then purified by chromatography on column using acetone as the eluant to give the product in 88% yield. The product exhibited the same spectral data as previously reported.[258] $[\alpha]_D^{22}$ = -125.4 (c = 1, EtOH). ^{1}H NMR (400MHz, $CDCl_3$, 293K, TMS): 2.56-2.60 (1H, m), 2.57 (3H, s); 2.65–2.74 (2H, m); 3.04–3.14 (3H, m); 3.16–3.25 (1H, m); 3.65 (3H, s); 3.89 (3H, s); 6.64 (1H, s); 7.20–7.34 (3H, m); 8.36 (1H, d, *J*=8.0 Hz).

(*R*)-1,2-Dimethoxy-4,5,6a,7-tetrahydro-dibenzo[*de*,*g*]quinoline-6-carboxylic acid tert-butyl ester

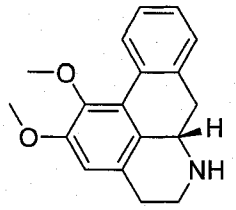


The cyclization was achieved following the general procedure (90%): mp = 149–151 °C ($CHCl_3$); IR (ν_{max} /cm^{-1}): IR: 3070, 2930, 1687, 1406, 1249, 1163, 1106 cm^{-1}; ^{1}H NMR (300MHz, $CDCl_3$, 293K, TMS): 1.49 (9H, s), 2.63–3.00 (5H, m), 3.66 (3H, s), 3.89 (3H, s), 4.41–4.44 (1H, m), 4.64–4.69 (1H, m), 6.67 (1H, s), 7.21–7.34 (3H, m), 8.44 (1H, d, *J*=7.8 Hz); ^{13}C NMR (75MHz, $CDCl_3$, 293K, TMS): 28.8, 30.7, 35.7, 38.7, 51.9, 56.2, 60.3, 80.2, 111.7, 126.8, 127.3, 127.9, 128.0, 128.4, 128.7, 130.1, 132.0, 137.3, 145.8,

[258] Cuny, G. D. *Tetrahedron Lett.*, **2003**, *44*, 8149.

152.2, 155.0; HRMS calculated for $C_{23}H_{27}NO_4$ (M+) 381.1940; Found : 381.1943; $[\alpha]_D^{22}$ = -246.8 (c = 1, CH_2Cl_2).

(*R*)-Nornuciferine



To a solution of (*R*)-1,2-dimethoxy-4,5,6a,7-tetrahydro-dibenzo[*de*,*g*]quinoline-6-carboxylic acid tert-butyl ester (0.1g, 0.26mmol, 1.0 equiv.) in methylene chloride (3mL) was added dropwise trifluoroacetic acid (0.26mL, 3.38mmol, 13.0 equiv.) and the resulting mixture was stirred at room temperature for 1h. The solution was removed under reduced pressure and 2N sodium hydroxide solution was added to the residue. The mixture was extracted with chloroform, dried with $MgSO_4$, filtered, evaporated and then purified by chromatography on column using 100% MeOH as the eluant to give the product in 53% yield. The product exhibited the same spectral data as previously reported.[259] $[\alpha]_D^{22}$ = -105.2 (c = 1, EtOH).

[259] Achenbach, H.; Renner, C.; Addae-Mensah, I., *Liebigs. Ann. Chem.*, **1982**, *9*, 1623.

Claims to Original Research

1. Developed a convergent and divergent synthesis of the aporphine alkaloids using direct arylation for the formation of biaryls.

2. Developed an enantioselective synthesis of (*R*)-nuciferine and (*R*)-nornuciferine.

3. Developed the first example of intermolecular direct arylation of an electron-deficient arene without the use of directing groups.

4. Investigated the mechanism of the intermolecular direct arylation of perfluoroarenes.

5. Developed a palladium/pivalic acid co-catalyst system for the intermolecular direct arylation of benzene.

6. Investigated the effect of the palladium/pivalic acid co-catalyst system on the intramolecular and intermolecular direct arylation of simple arenes.

7. Developed an intramolecular direct alkane arylation reaction using the palladium/pivalic acid co-catalyst system for the synthesis of 2,2-dialkyldihydrobenzofuran.

8. Investigated the mechanism of the intramolecular alkane direct arylation using a palladium/pivalic acid co-catalyst system.

Publications

1. **Lafrance M.**; Lapointe, D.; Fagnou, K. Mild and Efficient Palladium-Catalyzed Intramolecular Direct Arylation Reactions. Tetrahedron, **2008**, *in press*.

2. **Lafrance M.**; Gorelski, S.; Fagnou, K. High Yielding Palladium-Catalyzed Intramolecular Alkane Arylation: Reaction Development and Mechanistic Studies. *Journal of American Chemical Society*. **2007**, *129*, 14570-14571.

3. **Lafrance M.**; Blaquiere, N.; Fagnou, K. Aporphine Alkaloid Synthesis and Diversification *via* Direct Arylation, *European Journal of Organic Chemistry*. **2007**, *5,* 811-825.

4. **Lafrance M.**; Fagnou, K. Palladium-Catalyzed Benzene Arylation: Incorporation of Catalytic Pivalic Acid as a Proton Shuttle and a Key Element in Catalyst Design, *Journal of American Society of Chemistry*. **2006**, *128*, 16496-16497.

5. **Lafrance M.**; Shore, D.; Fagnou, K. Mild and General Conditions for the Cross-Coupling of Aryl Halides with Pentafluorobenzene and other Perfluoroaromatics, *Organic Letter*. **2006**, *8,* 5097-5100.

6. **Lafrance M.**; Rowley C. N.; Woo T. K.; Fagnou K.; Catalytic Intermolecular Direct Arylation of Perfluorobenzenes, *Journal of American Society of Chemistry*. **2006**, *128,* 8754-8756.

7. **Lafrance M.**; Blaquiere, N.; Fagnou, K. Direct Intramolecular Arylation of Unactivated Arenes: Application in the synthesis of Aporphine Alkaloids. (Communication), *Chemical Communication*. **2004**, *24*, 2874-2875.

Presentations

1. **Marc Lafrance**, Keith Fagnou (2007) Development of a Palladium-Pivalic Acid Catalyst System for Direct Reactions. 18th annual Québec Ontario Mini-Symposium in Synthetic and Organic Chemistry, Montreal, Quebec (Poster)

2. **Marc Lafrance**, Keith Fagnou (2007) Direct Transformations of Simple Arenes: An Evolution from Direct Arylation to Alkylation. 14th IUPAC Symposium on Organometallic Chemistry Directed Towards Organic Synthesis, Nara, Japan – **Winner of the OMCOS Poster Prize in Organometallic Chemistry** (Poster)

3. **Marc Lafrance**, Keith Fagnou (2007) Palladium-Catalyzed Transformation of Simple Arenes: From Direct Arylation to Direct Alkylation. Synthesis Day, University of Ottawa – **Winner of the Boehringer Ingelheim Poster Award** (Poster)

4. **Marc Lafrance**, Keith Fagnou (2007) Direct Arylation of Unactivated Arenes: From Reactivity to Catalyst Development. Ottawa-Carleton Chemistry Institute – **Winner of the CSC Prize** (Poster)

5. **Marc Lafrance**, Keith Fagnou (2006) Palladium-Catalyzed Intermolecular Arylation of Unactivated Arenes. 17th annual Québec Ontario Mini-Symposium in Synthetic and Organic Chemistry, London, Ontario (Oral)

6. **Marc Lafrance**, Christopher N. Rowley, Tom K. Woo, Keith Fagnou (2006) Catalytic Intermolecular Direct Arylation of Perfluorobenzenes. Synthesis Day, University of Ottawa – **Winner of the Boehringer Ingelheim Poster Award** (Poster)

7. **Marc Lafrance**, Christopher N. Rowley, Tom K. Woo, Keith Fagnou (2006) Catalytic Intermolecular Direct Arylation of Perfluorobenzenes. Astra-Zeneca R&D Chemistry Symposium – **Winner of the Astra Zeneca Presentation Award** (Poster)

8. **Marc Lafrance**, Christopher N. Rowley, Tom K. Woo, Keith Fagnou (2006) Catalytic Intermolecular Direct Arylation of Perfluorobenzenes. Canadian Society for Chemistry Annual Conference, Halifax, Nova Scotia (Poster) – **Winner of the Ocean Nutrition Poster Presentation Award** (Poster)

9. **Marc Lafrance**, Christopher N. Rowley, Tom K. Woo, Keith Fagnou (2006) Catalytic Intermolecular Direct Arylation of Perfluorobenzenes. Ottawa-Carleton Chemistry Institute (Poster)

10. **Marc Lafrance**, Keith Fagnou (2005) Asymmetric Synthesis of (*R*)-Nornuciferine and Analogues via Direct Arylation, 16th annual Québec Ontario Mini-Symposium in Synthetic and Organic Chemistry, Ste-Adele, Quebec (Poster)

11. **Marc Lafrance**, Keith Fagnou (2005) Aporphine Alkaloids Synthesis via Direct Arylation. Synthesis Day, University of Ottawa (Poster)

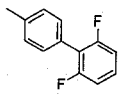
12. **Marc Lafrance**, Keith Fagnou (2005) Aporphine Alkaloids Synthesis via Direct Arylation. Ottawa Life Science Research Symposium, University of Ottawa (Poster)

13. **Marc Lafrance**, Keith Fagnou (2005) Aporphine Alkaloids Synthesis via Direct Arylation. Ottawa-Carleton Chemistry Institute (Poster)

14. **Marc Lafrance**, Nicole Blaquiere, Keith Fagnou (2004) Direct Intramolecular Arylation of Unactivated Arenes: Application in the Synthesis of Aporphine Alkaloids. 15th annual Québec Ontario Mini-Symposium in Synthetic and Organic Chemistry, Aylmer, Quebec (Poster)

15. **Marc Lafrance**, Keith Fagnou (2004) Direct Arylation as a Useful Synthetic Strategy: Application to Aporphine Alkaloids. Ottawa-Carleton Chemistry Institute (Poster)

16. **Marc Lafrance**, Keith Fagnou (2004) Direct Arylation as a Useful Synthetic Strategy: Application to Aporphine Alkaloids. Synthesis Day, University of Ottawa (Poster)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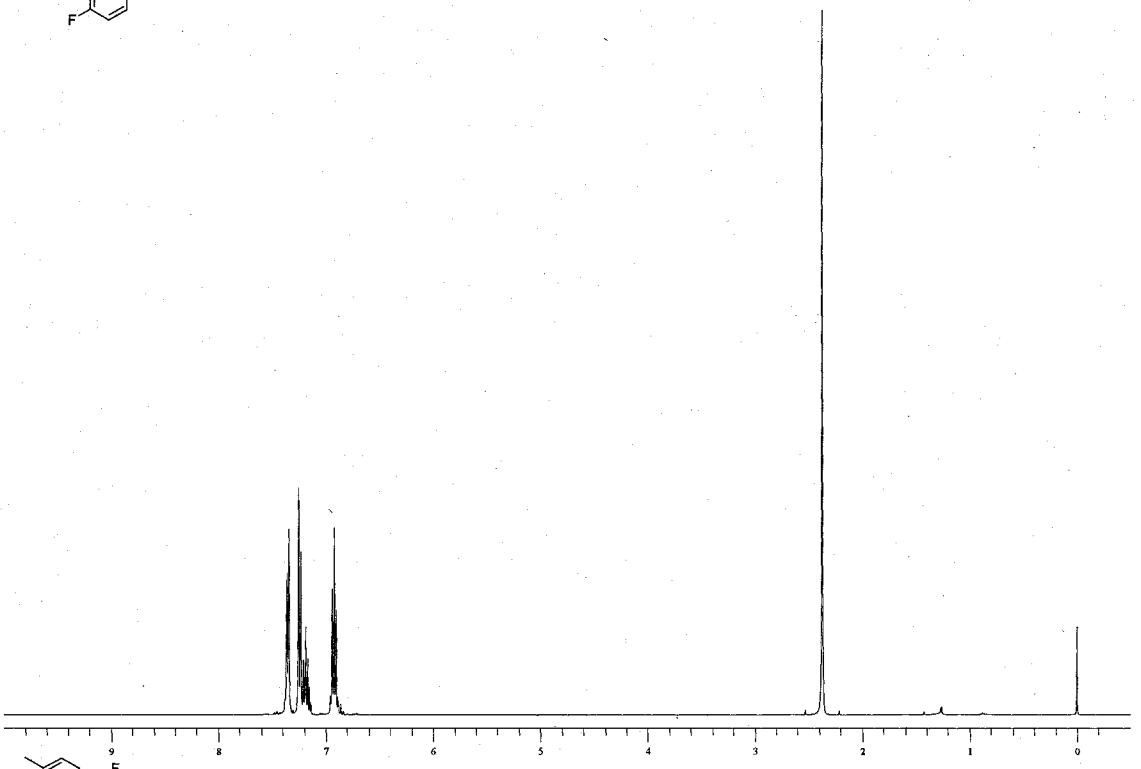
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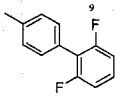
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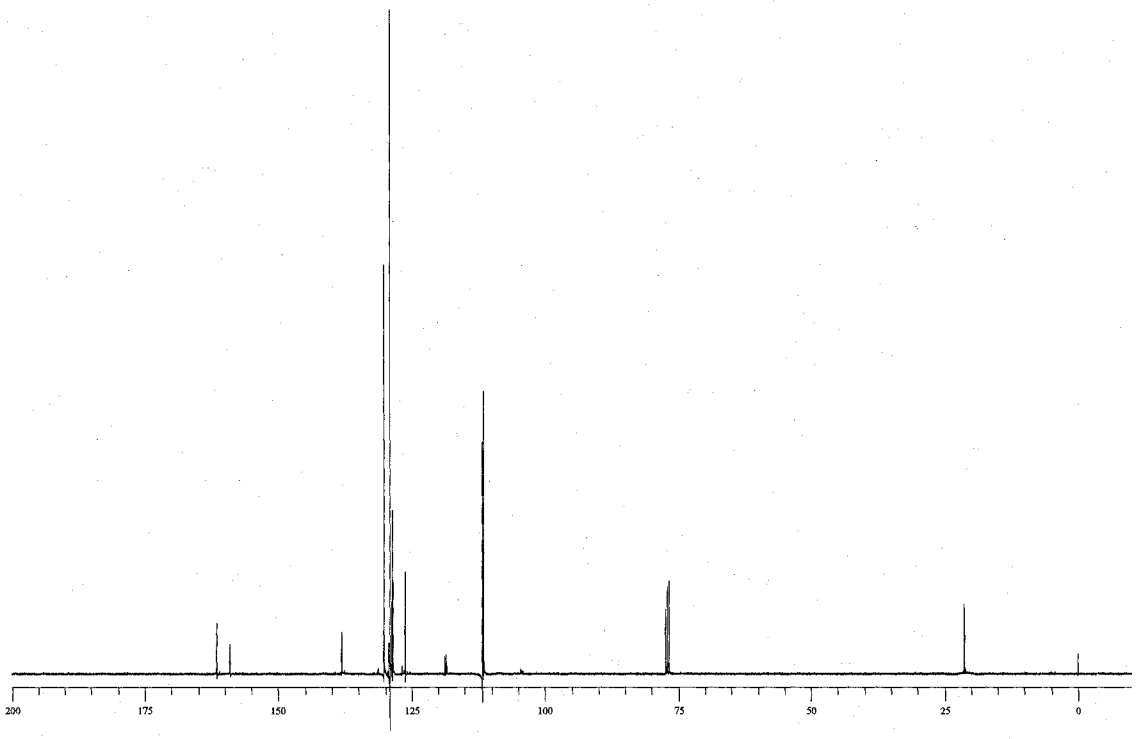
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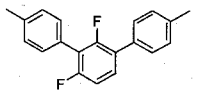
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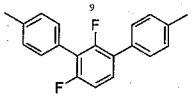
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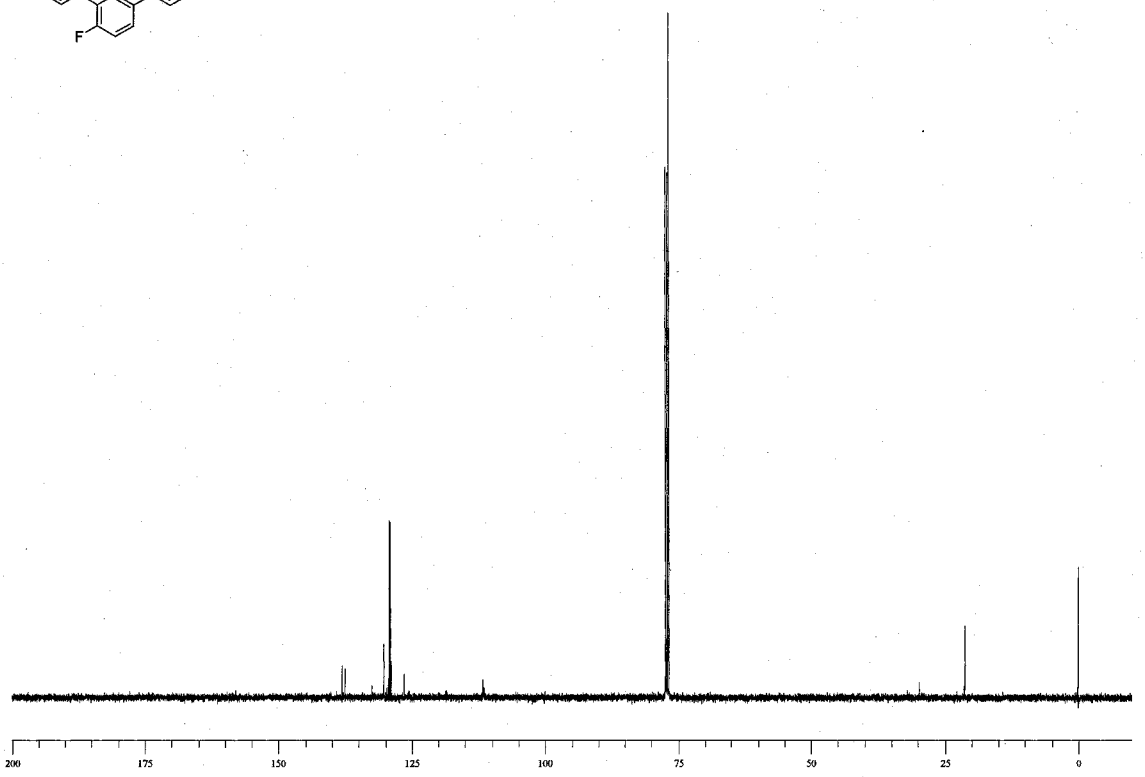
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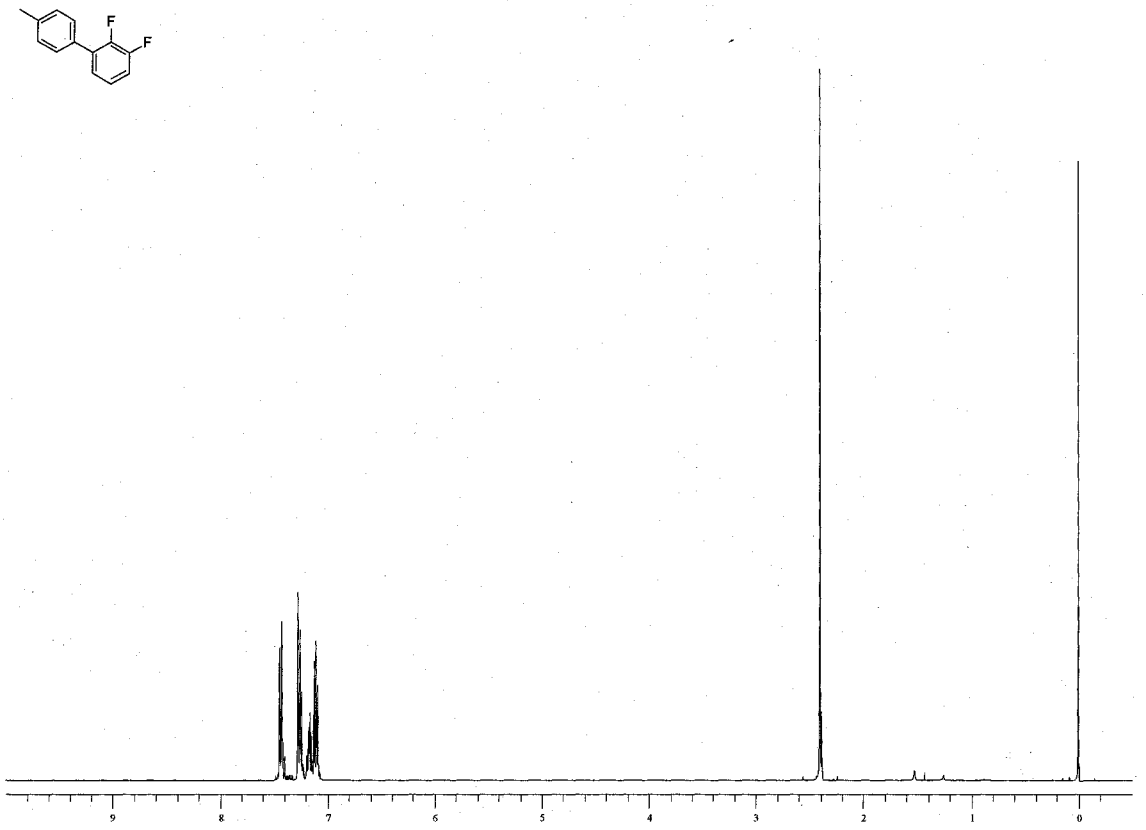
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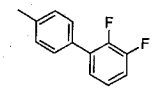
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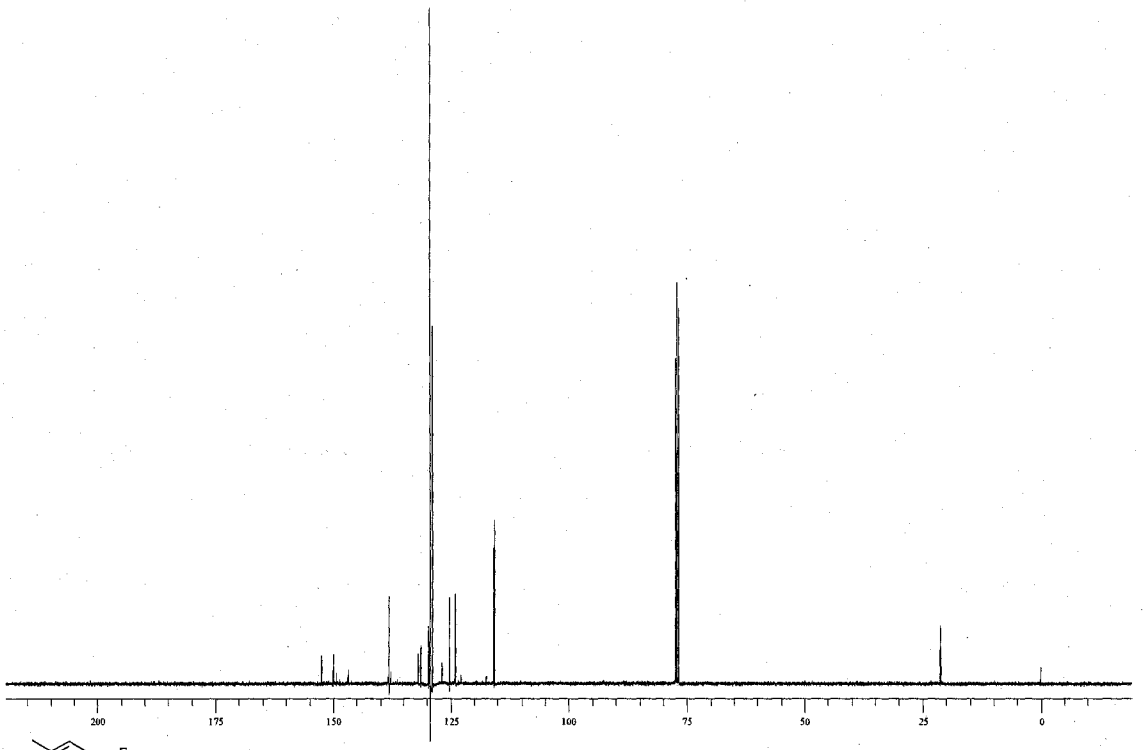
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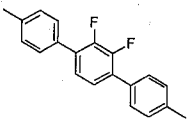
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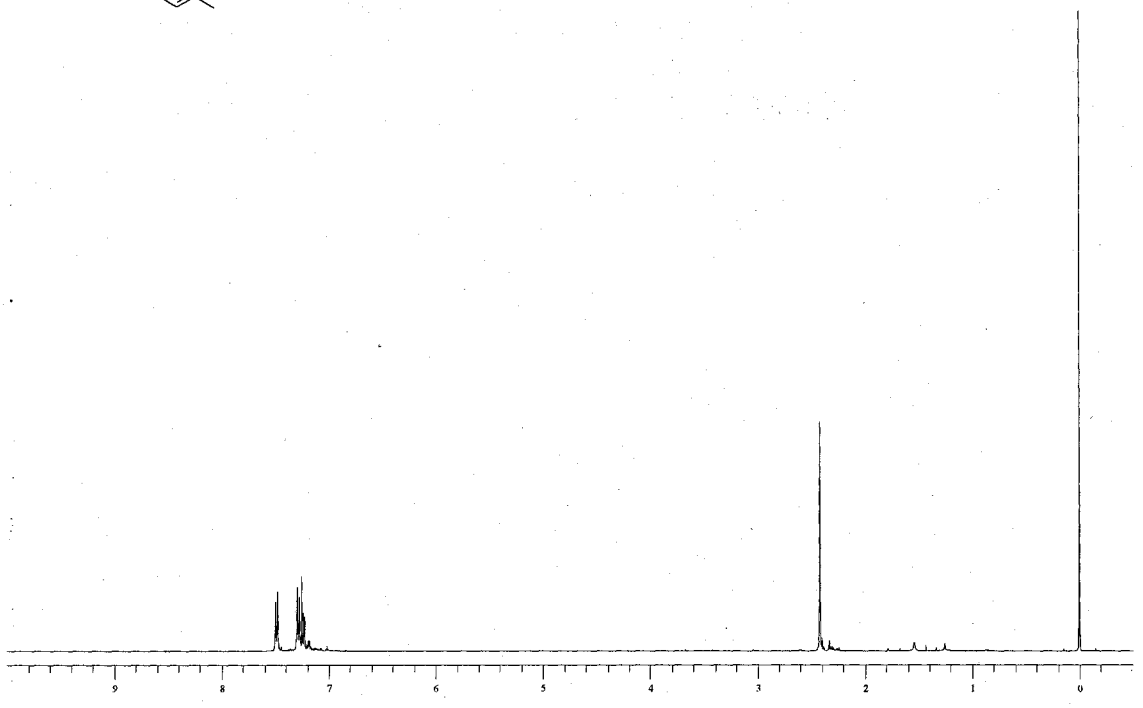
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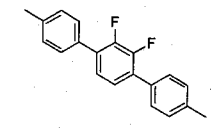
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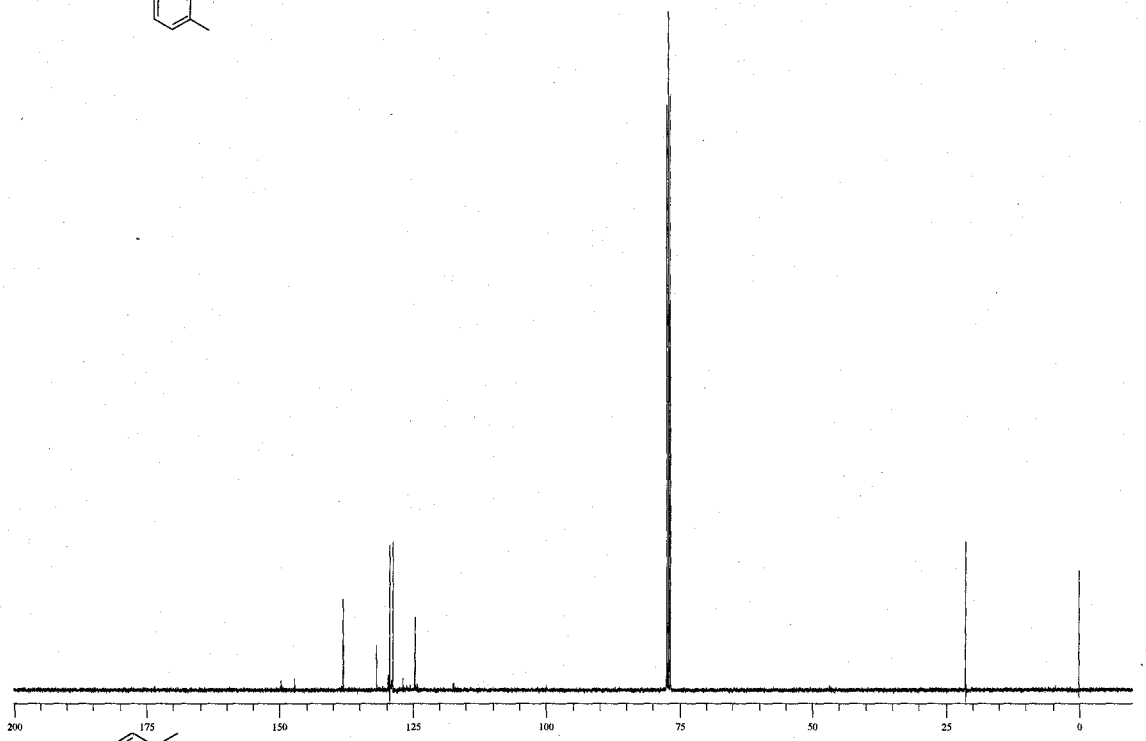
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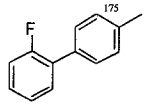
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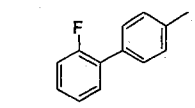
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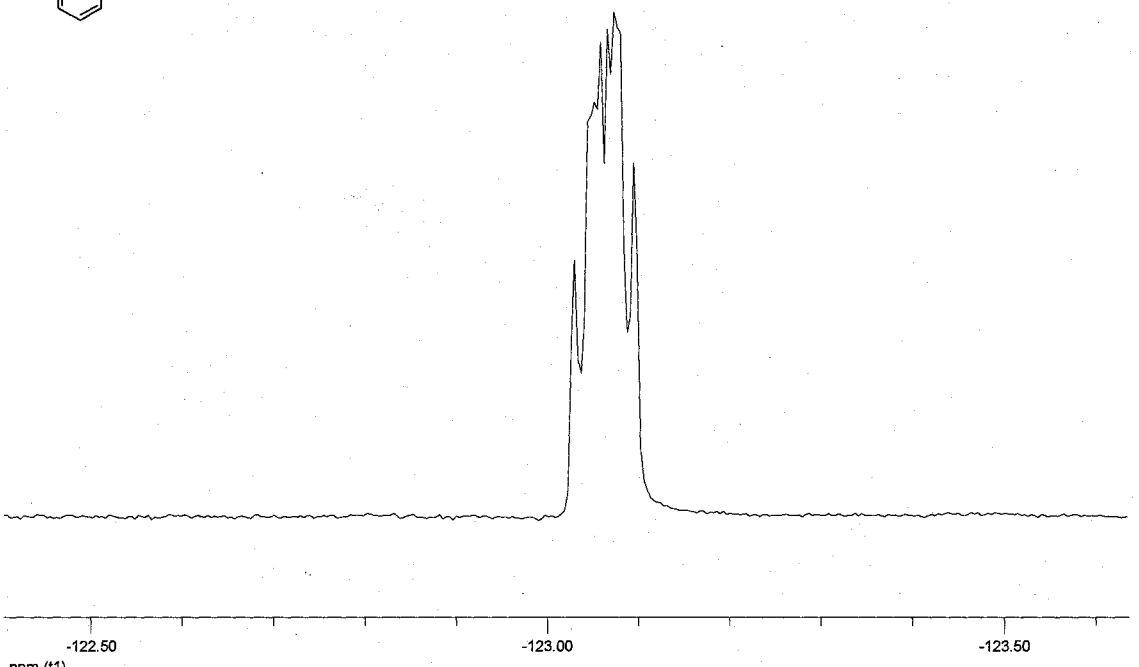
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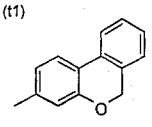
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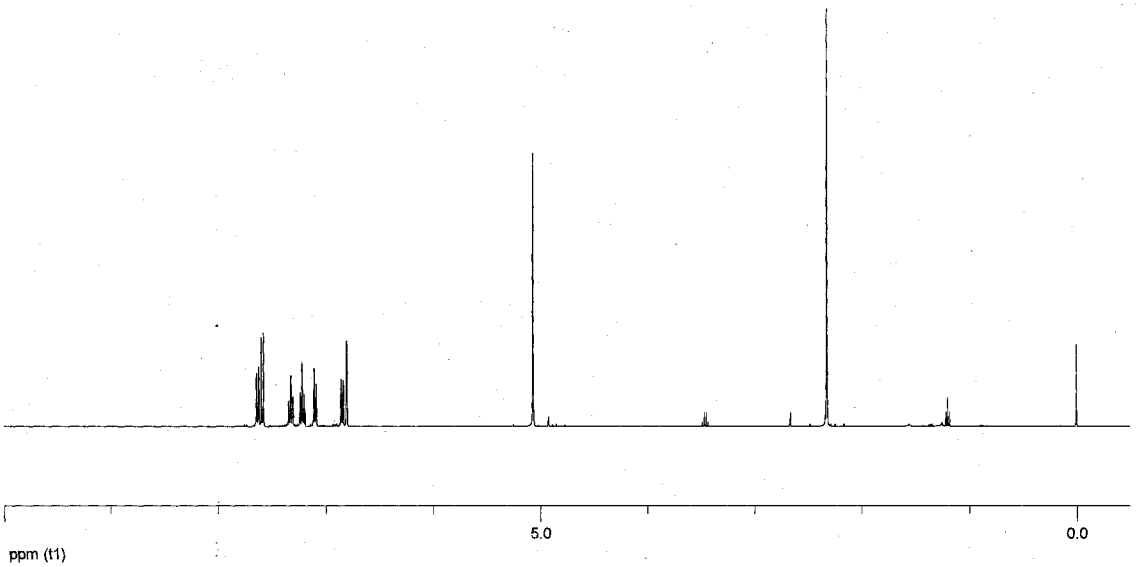
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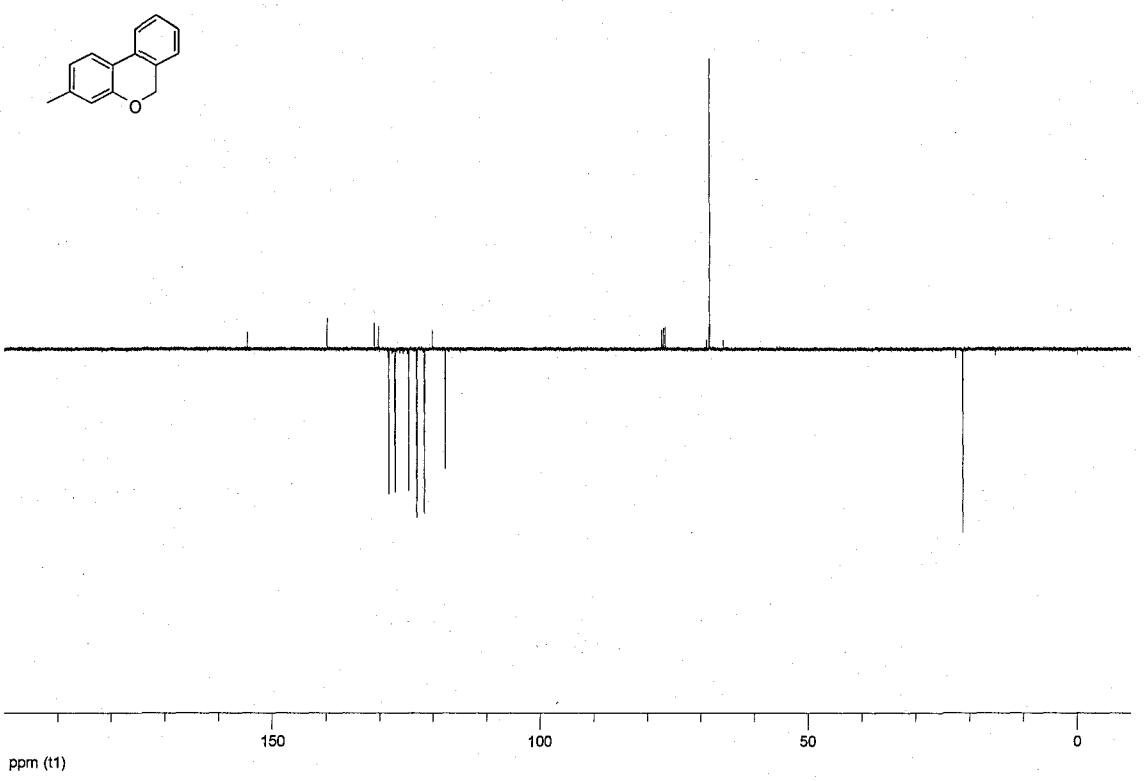
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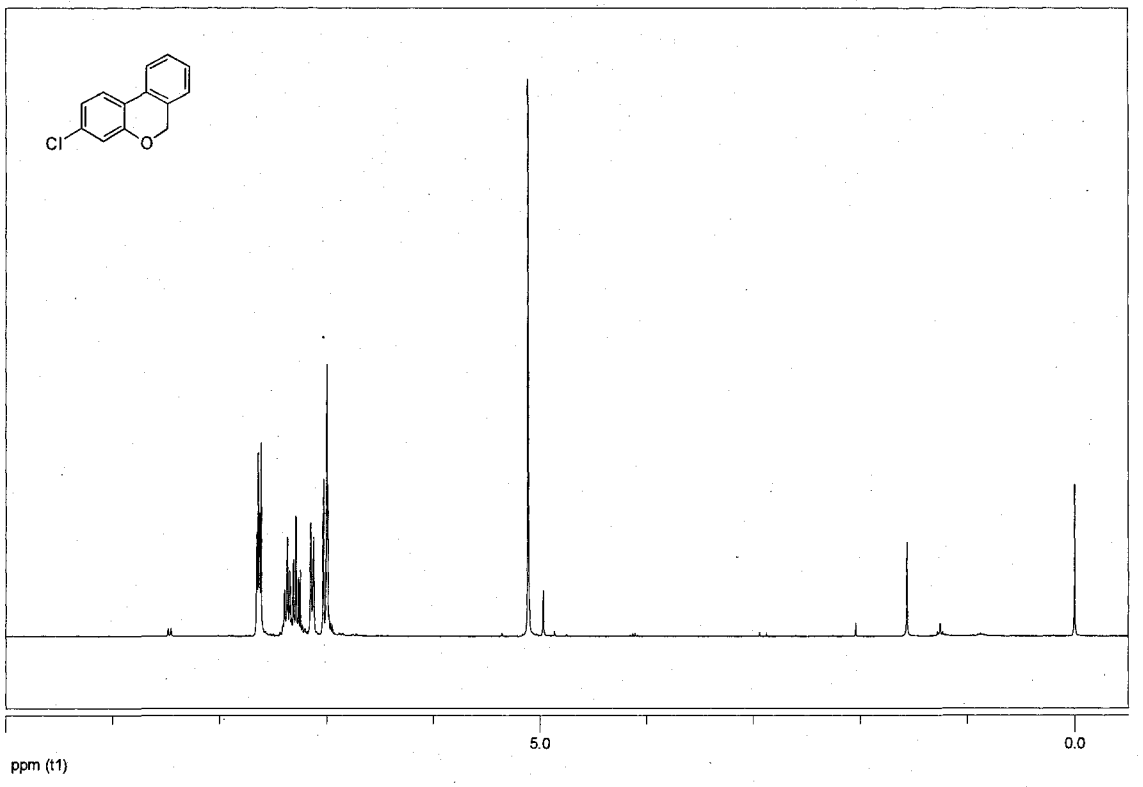
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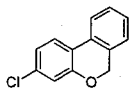
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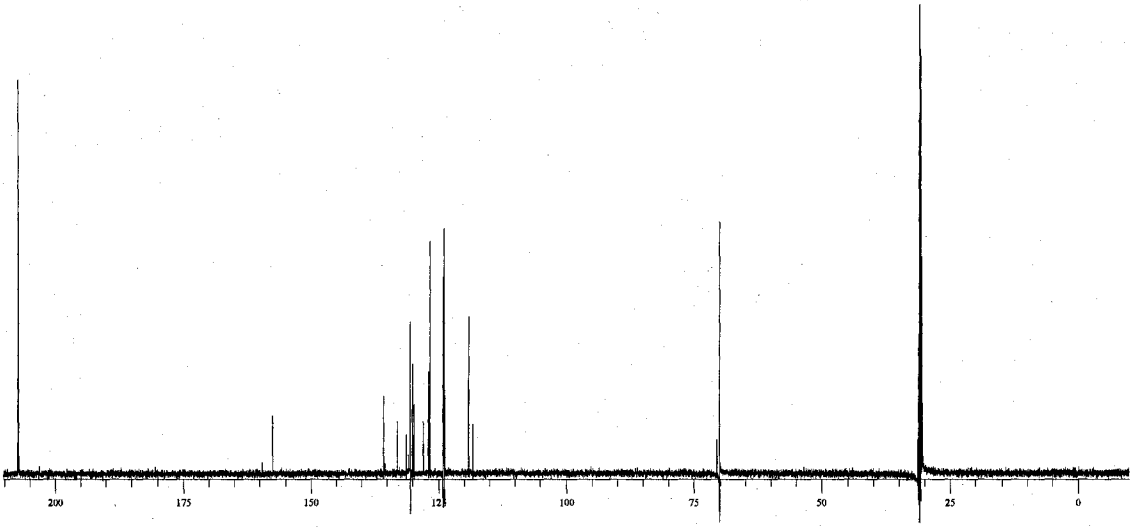
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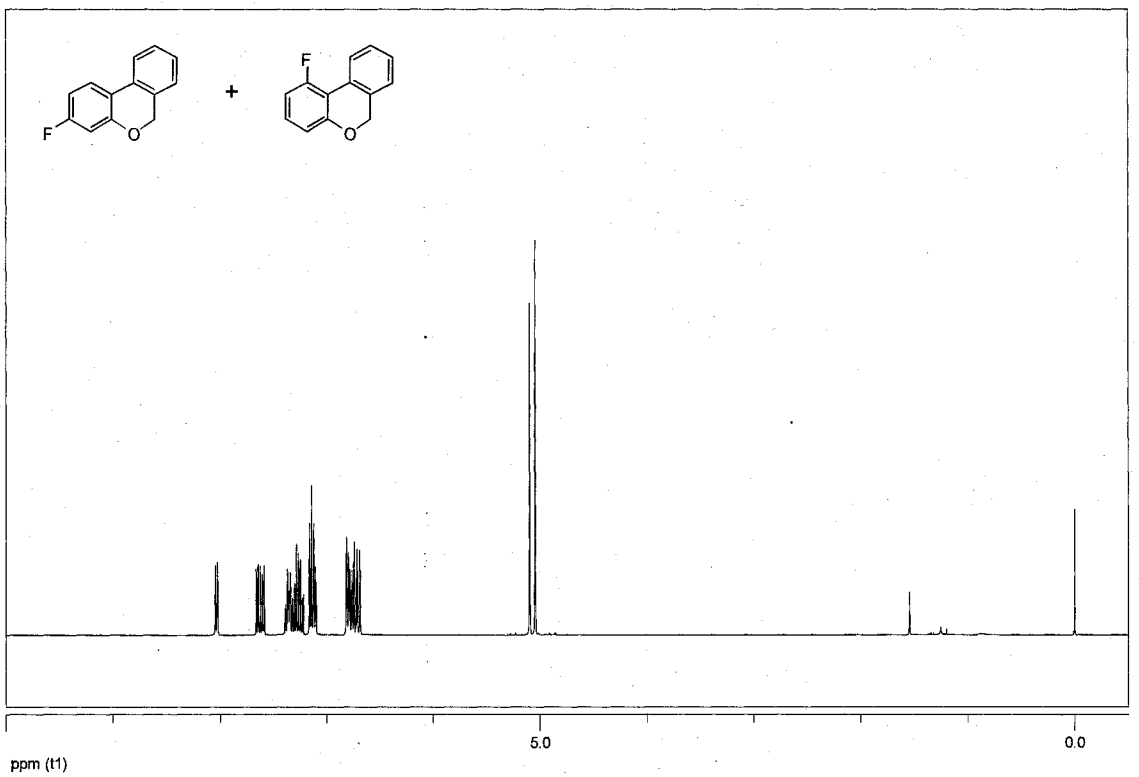
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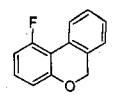
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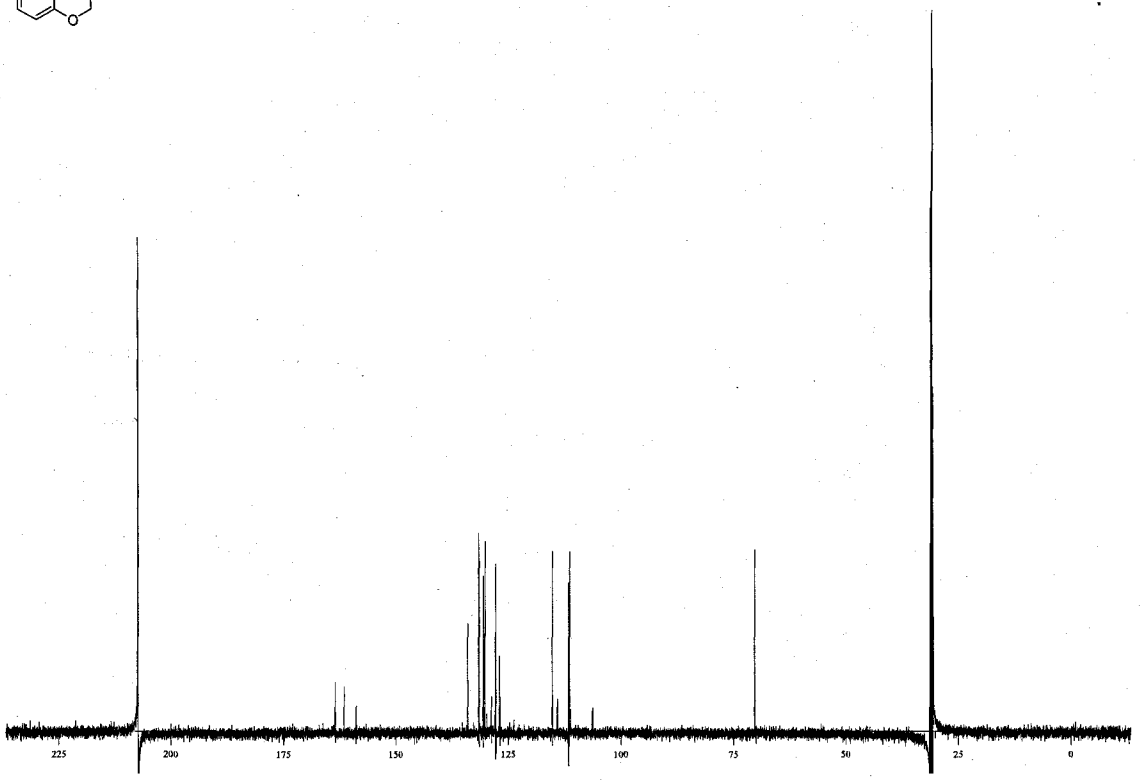
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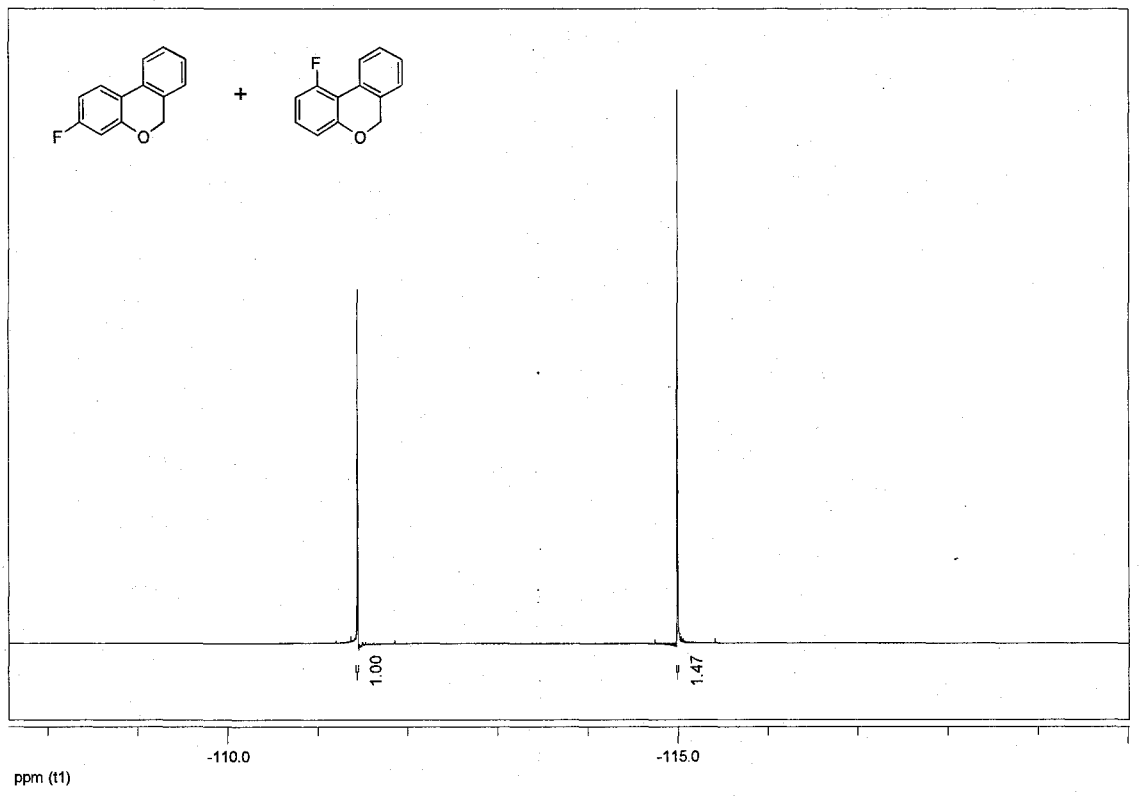
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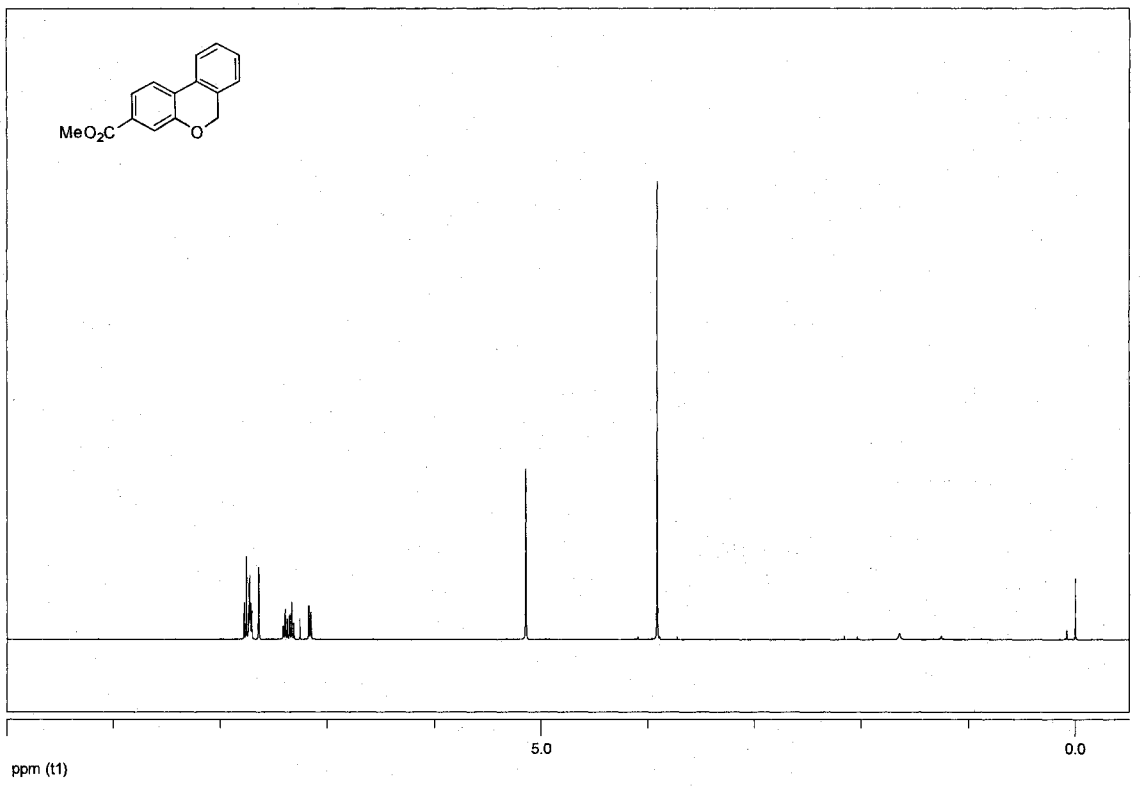
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