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Part 2: The Site-Selective Direct Arylation of Substituted Indoles
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Part 1: The Direct Arylation of Azine *N*-Oxides with Aryl Triflates

Part 2: The Site-Selective Direct Arylation of Substituted Indoles

Christopher J. Whipp

Thesis submitted to the Faculty of Graduate & Postdoctoral Studies
in partial fulfilment of the requirements for the M.Sc. degree

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List of Abbreviations

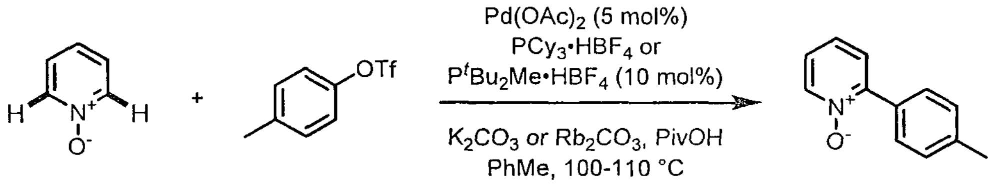
Ac	acetyl
acac	acetylacetonate
Ad	adamantyl
Alk	alkyl
Ar	aryl
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
br	broad
Bu	butyl
COD	cyclooctadiene
COE	cyclooctene
Cy	cyclohexyl
d	doublet
dba	dibenzylideneacetone
DBU	1,8-diazabicyloundec-7-ene
DCE	dichloroethane
DDQ	2,3-dichloro-5,6-dicyanoquinone
DG	directing group
DMA	*N,N*-dimethylacetamide
DME	dimethoxyethane
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide
dppp	1,3-bis(diphenylphosphino)propane
Et	ethyl
GC-MS	gas chromatograph mass spectrometer
Het	heteroaromatic
HMDS	hexamethyldisilazide
IMes	1,3-dimesitylimidazol-2-ylidene
*i*Pr	isopropyl
L	generic ligand

M	generic metal
Me	methyl
Ms	mesylate
MS	molecular sieves
NMP	*N*-methylpyrrolidinone
NMR	nuclear magnetic resonance
Piv	pivalyl
Ph	phenyl
Py	pyridyl
q	quadruplet
R	generic group
rt	room temperature
s	singlet
SEM	[2-(trimethylsilyl)ethoxy]methyl
t	triplet
*t*Bu	*tert*-butyl
Tf	triflate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMEDA	*N,N,N',N'*-tetramethylethylenediamine
Ts	tosylate
X	generic halide

Abstract

Part 1: The Direct Arylation of Azine *N*-Oxides with Aryl Triflates

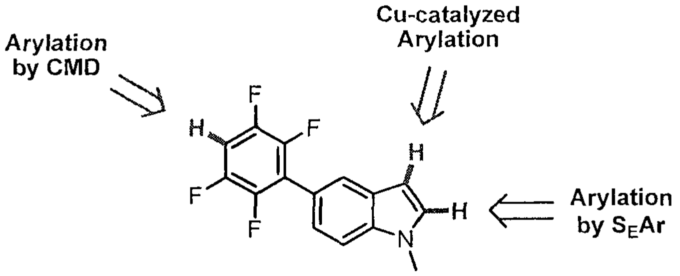
Two sets of conditions for the palladium-catalyzed direct arylation of azine *N*-oxides with aryl triflates have been developed. Using palladium(II) acetate, a trialkylphosphine ligand, a carbonate base and pivalic acid, both mono- and diarylated azine *N*-oxides could be synthesized in good to excellent yields.



The reaction regioselectivity was examined for 3-substituted pyridine *N*-oxides, with arylation at C2 being favoured. The methodology was applied to the efficient formal synthesis of a biologically active diaryl pyridine.

Part 2: The Site-Selective Direct Arylation of Substituted Indoles

Initial studies into the site selectivity of the direct arylation reaction were conducted. Several competition studies were performed using various methodologies to determine the selectivity, if any, between two arenes capable of undergoing direct arylation. It was found that selectivity was greatest when competition was between one electron-rich and one electron-poor arene.



From these results a substituted indole was synthesized and subsequently derivatized at three different positions. It was demonstrated that site selectivity on a complex molecule could be achieved through careful selection of reaction conditions.

Acknowledgements

First, I would like to thank my supervisor, Keith Fagnou. Of all the things I've learned from you, the most important lessons have had very little to do with chemistry; the importance of maintaining a proper balance between work and fun, taking the proper time to enjoy some of the finer (and scotchier) moments in life, and most of all, to do what you love and what makes you happy, not just what you're good at. Thank you for encouraging me to pursue a career path where I could both succeed and truly love the work, it was a hard decision but your advice eventually sunk in. I wish you could have read this. Though you are no longer with us, you will never be forgotten.

I would also like to thank Bill Ogilvie for acting as my co-supervisor and proofreading this thesis. I really appreciate you taking on the extra responsibility and helping polish it up, thank you.

To all the Fagnou group members, past and present, thanks for always being there with advice when chemistry decided to misbehave, to fix incomprehensible slides for seminar or just listen to me vent my frustrations. But especially thank you for the almost neverending stream of jokes, laughs and nerdy chemistry Youtube videos, your ability to degenerate any serious conversation or group meeting into something about someone's mom, and the Friday evening drinks in the upstairs lab. I wish every one of you the best of luck wherever you may end up, and I hope that you bring the amazing spirit of the Fagnou Factory to your new labs.

A special thank you to David Lapointe, who shared tiny DRO 329 with me; thanks for all your help in preparing this thesis and my seminar, for putting up with that stuff I call music, and the countless chats discussing chemistry, bikes, beer and scotch. I couldn't have asked for a better person to share that tiny lab with, it was a pleasure and made my two years there that much better, thank you.

Finally, thank you to all my friends and family for being understanding when I could not make it out due to school work and would disappear for weeks or months at a time, and for making sure to drag me out to remind me that life still went on outside my fumehood. I'm lucky to have you around.

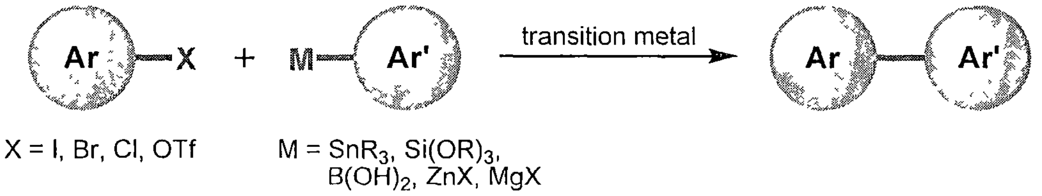
Chapter 1

Introduction

1.1 Biaryl Formation via Cross Coupling Reactions

The biaryl core has become an increasingly important motif in both material science and pharmaceutical development. Recently, there has been a surge in the development of methodologies that facilitate the fabrication of this highly desired structure, with the majority of the efforts focused around transition-metal-catalyzed cross couplings.[1] Traditionally, these reactions involve the coupling of two pre-activated species; an aryl halide (Ar-X) and an organometallic (Ar-M); catalyzed by a transition metal complex (Scheme 1.1). Most of the recent innovation in cross coupling has focused on the modification[1] or elimination[2] of the organometallic species, due to the associated difficulty in their preparation or lack of availability from commercial sources. Conversely, replacing or modifying the aryl halide has seen considerably less attention.

Scheme 1.1 **Traditional biaryl cross coupling reaction involving two pre-activated species.**



1.1.1 Aryl Halides and Triflates as Cross Coupling Partners

The vast majority of reactions prominently feature aryl bromides and iodides as coupling partners, and to a lesser extent, aryl chlorides. For the most part, aryl triflates have received relatively little focus. This can be attributed to the fact that triflates are not

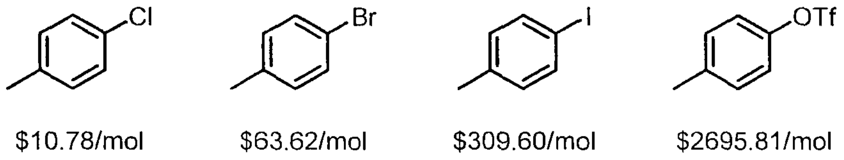
---

[1] (a) *Modern Arylation Methods*; Ackermann, L., Ed.; Wiley-VCH: Weinheim, 2009 (b) *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F.; Stang, P. J., Eds.; Wiley-VCH: New York, 2004. (c) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem Rev.* **2002**, *102*, 1359.

[2] For reviews on direct arylation see: (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (b) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173. (c) Yu, J.-Q.; Shi, Z., Eds.; *Topics in Current Chemistry*; *C-H Activation*; Springer: Berlin; 2010; Vol. 292.

as available commercially, and cost significantly more than other aryl halides. When comparing the cost per mole of various *p*-tolyl halides from Sigma Aldrich, *p*-tolyl triflate is almost 9 times the cost of *p*-tolyl iodide and 250 times the cost of *p*-tolyl chloride (Scheme 1.2).[3] Furthermore trifluoromethanesulfonyl anhydride, the reagent most commonly used to install triflates, is prohibitively expensive, making synthesis in the laboratory unappealing economically.

Scheme 1.2 **Cost per mole of *p*-tolyl halides and triflates from Sigma-Aldrich.**



While aryl triflates do have disadvantages, they also present unique benefits. They are most commonly synthesized from phenols, presenting an attractive alternative to the sometimes frustrating synthesis of aryl halides. The stability of phenols, as well as the numerous methods for their protection, allows chemists to carry a synthetic handle through to the late stages of a synthesis. The mild conditions for used to create triflates also provide an excellent alternative to circumventing the regioselective problems and harsh conditions that can be problematic for the late-stage installation of a halide on a large, complex molecule. Since the application of aryl triflates in palladium-catalyzed direct arylation is discussed in this thesis, recent advances specific to triflates will be reviewed.

1.2 Aryl Triflates in Direct Arylation

Direct arylation can be separated into two general areas: intramolecular reactions and intermolecular reactions. Intramolecular reactions are generally considered the easier of the two as there is no significant decrease in entropy of the system during coupling. The reaction can also affected by the size of the ring being formed, with 5- and 6-membered rings being most facile.[4] Intermolecular reactions must overcome entropy for

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[3] Prices quoted from Sigma-Aldrich on November 23, 2009.

[4] Beletskaya, I. P.; Cheprakov, A. V. *J. Organomet. Chem.* **2004**, *689*, 4055.

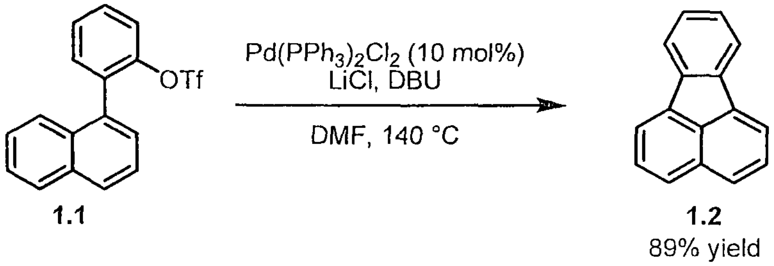
arylation to occur. As well, the electronic effects present on the coupling partner have greater effect on regioselectivity due to the increased degrees of freedom freedom available compared to their intramolecular counterparts.

1.2.1 Intramolecular Direct Arylation with Aryl Triflates

1.2.1.1 Synthesis of Polycyclic Aromatic Hydrocarbons

The first example of direct arylation involving triflates was published by the Rice group at Rutgers University in 1992.[5] Upon heating aryl triflate **1.1** in the presence of catalytic bis(triphenylphosphine)palladium(II) dichloride, excess lithium chloride and DBU, fluoranthene **1.2** could be isolated in 89% yield (Scheme 1.3). The synthesis of benzo[*ab*]fluoranthenes and substituted fluoranthenes could also be achieved under these conditions in excellent yields, though derivatives with electron-rich substituents required the addition of triphenylphosphine in order to achieve respectable yields. The synthesis of benzo[*ghi*]fluoranthenes has been reported by Shevlin using identical conditions.[6]

Scheme 1.3 **Fluoranthene synthesis via intramolecular direct arylation.**

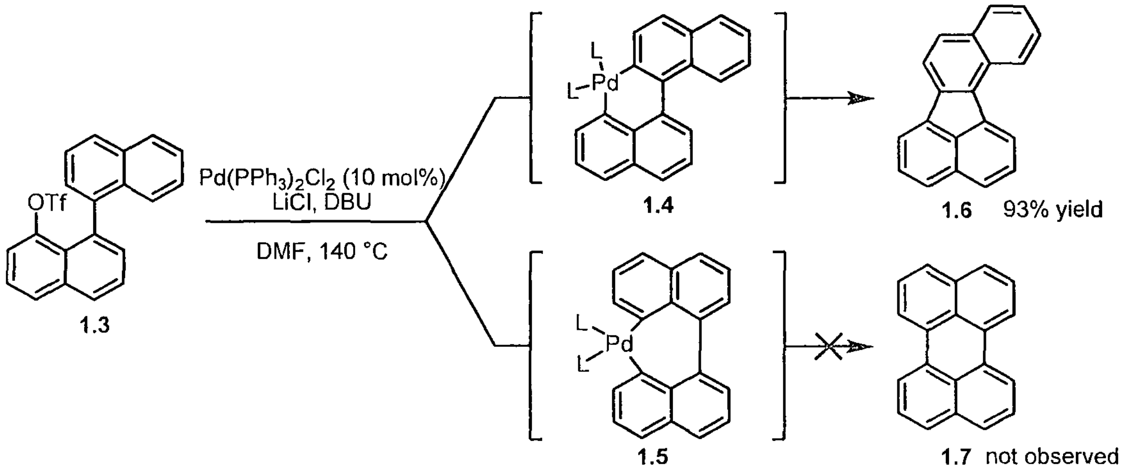


In subsequent research, Rice examined factors controlling regioselectivity when competition between the formation of 5- and 6-membered rings was possible.[7] When binaphthyl triflate **1.3** was subjected to the previously reported conditions, benzo[*j*]fluoranthene **1.6** was observed in 93% yield (Scheme 1.4). The presence of perylene **1.7** could not be detected. It was reasoned that the formation of the 6-membered palladacycle **1.4** was thermodynamically favoured over the formation of the 7-membered palladacycle **1.5**, resulting in the production of the observed product.

---

[5] Rice, J. E.; Cai, Z.-W. *Tetrahedron Lett.* **1992**, *33*, 1675.
[6] Wang, L.: Shevlin, P. B. *Tetrahedron Lett.* **2000**, *41*, 285.
[7] Rice, J. E.; Cai, Z.-W. *J. Org. Chem.* **1993**, *58*, 1415.

Scheme 1.4 **Possible pathways for the intramolecular arylation of a binaphthyl triflate.**

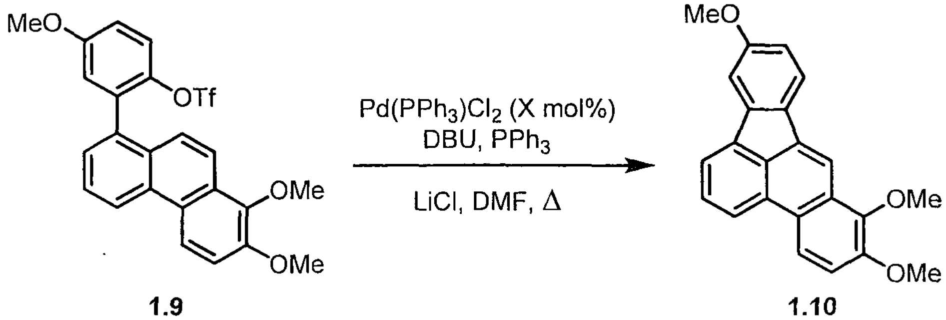


Several years later, the Rice group examined the synthesis of polyoxygenated benzofluoranthenes via this methodology.[8] When triflate **1.9** was subjected to the previously reported conditions, the desired benzofluoranthene **1.10** could only be isolated in 10% yield (Table 1.1, Entry 1). Increasing both the reaction temperature and catalyst loading resulted in only marginal improvement (Table 1.1, Entry 2). When lithium chloride was omitted from the reaction conditions, a substantial increase in yield resulted (Table 1.1, Entry 3). This was surprising, as lithium chloride was generally considered to be a necessary additive in cross coupling reactions involving triflates. It was suggested that lithium chloride was demethylating triflate **1.9** *via* a Krapcho-type process, which would result in the degradation of the starting material under the reaction conditions and the poor isolated yields.

---

[8] Rice, J. E.; Cai, Z.-W.; He, Z.-M.; LaVoie, E. J. *J. Org. Chem.* **1995**, *60*, 8101.

Table 1.1 **Reaction conditions for the cyclization of polyoxygenated benzofluoranthenes.**



1.9 **1.10**

Entry	Pd(PPh$_3$)Cl$_2$ (mol%)	Temp. (°C)	LiCl (equiv.)	Yield (%)
1	10	140	3.0	10
2	30	155	3.0	34
3	30	155	0	55

^{a}All reactions were performed in DMF (0.155M) with 1.4 equiv. DBU and 1.2 equiv. PPh$_3$.

Echavarren and co-workers completed the synthesis of "crushed fullerene" $C_{60}H_{30}$ via a tandem direct arylation-dehydrogenation as their key step.[9] Tris(triflate) **1.11** was subjected to 150 mol% of Pd(PPh$_3$)Cl$_2$ and excess sodium pivalate, then heated for an extended period to provide a triarylated intermediate (Scheme 1.5). Aromatization by concomitant dehydration afforded the desired product **1.12** in 11% isolated yield, or roughly 69% yield per transformation. The synthesis was also performed from a tribromide precursor under slightly different conditions to give the identical product in a more synthetically useful 42% yield. From **1.12**, it was proposed that fullerene C_{60} could be accessible through a series of cyclodehydrogenations. While Echavarren did eventually confirm the successful detection of the radical cation $C_{60}^{\cdot +}$ by MALDI-TOF MS after cyclodehydrogenation from **1.12**,[10] the result was independently documented by Scott *et al.* only a few months prior.[11] To date, there have been no reports of the isolation of C_{60} via this methodology.

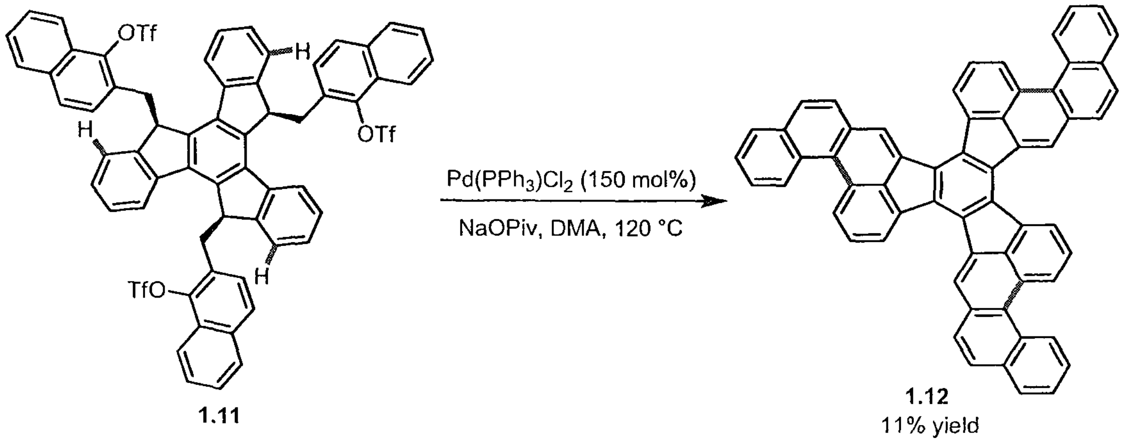
---

[9] Gómez-Lor, B.; de Frutos, Ó.; Echavarren, A. M. *Chem. Commun.* **1999**, 2431.

[10] Gómez-Lor, B.; Koper, C.; Fokkens. R. H.; Vlietstra, E. J.; Cleij, T. J.; Jenneskens, L. W.; Nibbering, N. M. M.; Echavarren, A. M. *Chem. Commun.* **2002**, 370.

[11] Boorum, M. M.; Vasil'ev, Y. V.; Drewello, T.; Scott, L. T. *Science* **2001**, *294*, 828.

Scheme 1.5 **Synthesis of "crushed fullerene" $C_{60}H_{30}$ via intramolecular direct arylation.**



1.2.1.2 Alkenyl Triflates as Coupling Partners

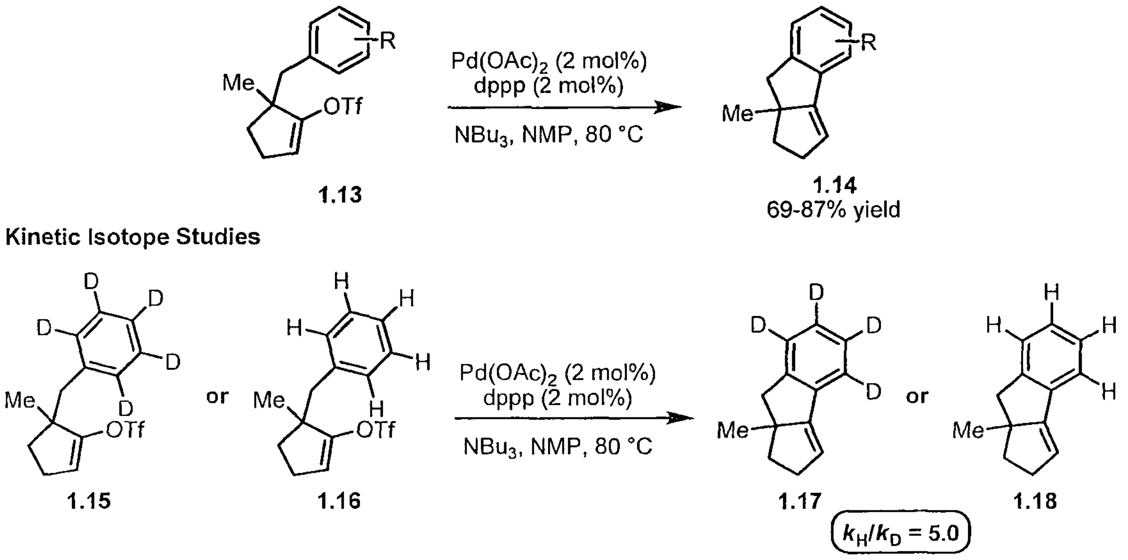
The use of activated alkenes in direct arylation is still a relatively undeveloped area. In 2007, the Willis group reported a methodology for an intramolecular direct arylation involving alkenyl triflates.[12] Using a palladium catalyst and a bidentate ligand, triflate **1.13** could be cyclised under mild conditions to afford **1.14** in excellent yield (Scheme 1.6). The scope of the reaction included both electron-rich and electron-poor arenes, as well as simple electron-rich heteroaromatics. The methyl group could be substituted with another alkyl chain or even removed with no adverse effects to the reaction. Kinetic isotope experiments were also performed to help understand the mechanism. When the rate of reaction of **1.16** was compared to the rate of reaction of pentadeuterated derivative **1.15**, a kinetic isotope effect $k_H/k_D = 5.0$ was observed. This result, combined with the observed increase in reaction rate in the presence of electron-withdrawing substituents, suggested a concerted metallation-deprotonation pathway.[13]

---

[12] Cruz, A. C. F.; Miller, N. D.; Willis, M. C. *Org. Lett.* **2007**, *9*, 4391.

[13] (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. (c) Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 16496.

Scheme 1.6 **Direct arylation of alkenyl triflates.**



1.2.1.3 Synthesis of Lactams and Lactones via Ring Closure

The Harayama group has published several reports on the development of an intramolecular direct arylation reaction for the formation of phenanthridones.[14,15,16] Initially, it was found that triflate-amide **1.19** could be cyclised using stoichiometric palladium to afford phenanthridone **1.20** in excellent yield (Table 1.2, Entry 1). Unfortunately, catalyst turnover was not observed when palladium and ligand amounts were dropped below stoichiometric quantities (Table 1.2, Entry 2), though this problem could be overcome when increased amounts of PBu_3 were added to the reaction medium (Table 1.2, Entries 3 and 4). The reaction was found to be tolerant of both carbonate and amine bases and catalyst loadings as low as 20 mol% were found to be effective when a 3:1 ligand to metal ratio was used. Interestingly, it appeared that the removal of dppp from the reaction conditions had no deleterious consequences on the results (Table 1.2, Entry 7).

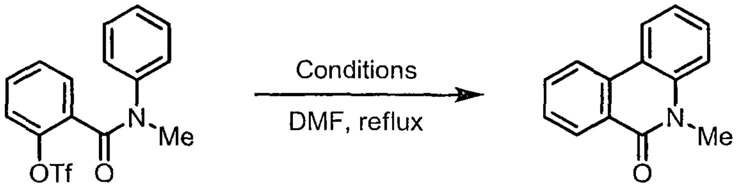
---

[14] Harayama, T.; Akiyama, T.; Nakano, Y. *Chem. Pharm. Bull.* **1997**, *45*, 1723.

[15] Harayama, T.; Akiyama, T.; Nakano, Y.; Nishioka, H.; Abe, H.; Takeuchi, Y. *Chem. Pharm. Bull.* **2002**, *50*, 519.

[16] Harayama, T.; Hori, A.; Nakano, Y.; Akiyama, T.; Abe, H.; Takeuchi, Y. *Heterocycles* **2002**, *58*, 159.

Table 1.2 **Reaction conditions for the synthesis of *N*-methylphenanthridones.**



1.19 **1.20**

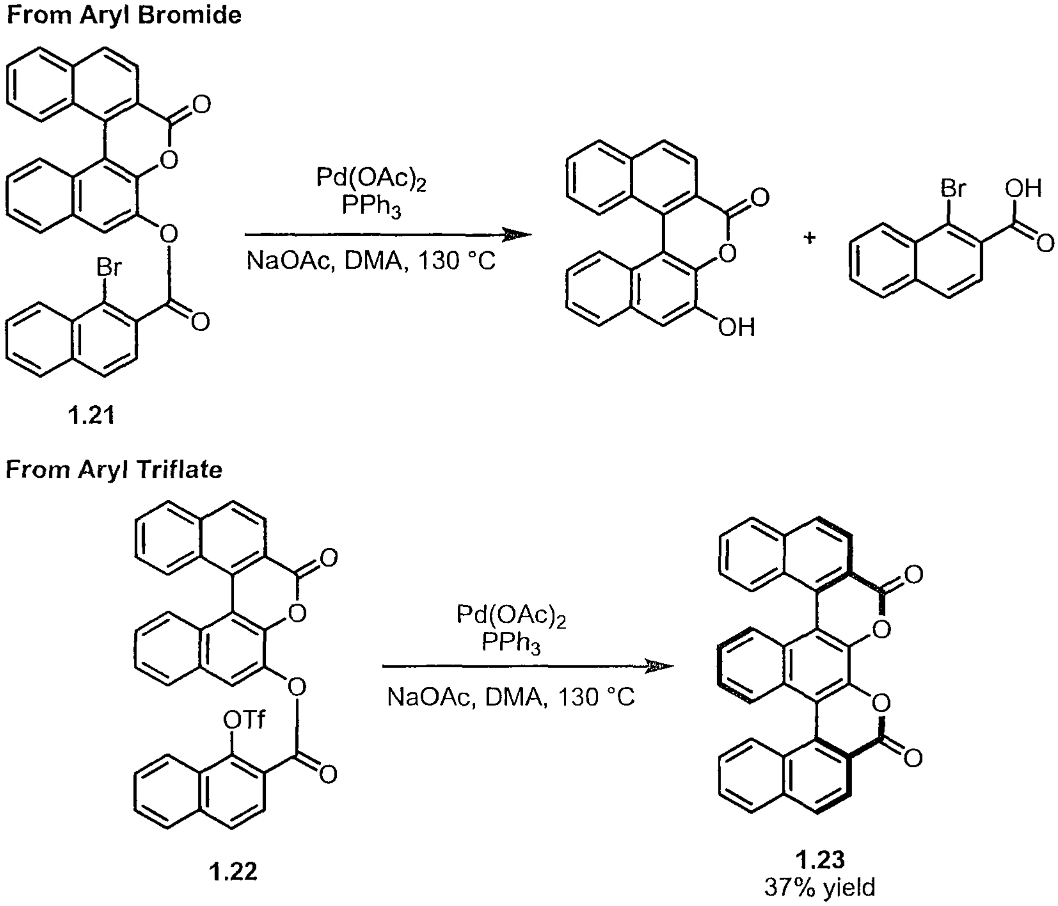
Entry	$Pd(OAc)_2$ (mol %)	dppp (equiv.)	PBu_3 (equiv.)	Base	Yield (%)
1	100	1.0	1.0	Ag_2CO_3	93
2	30	0.3	0.3	Ag_2CO_3	26
3	30	0.3	1.0	Ag_2CO_3	58
4	30	0.3	3.0	Ag_2CO_3	71
5	100	1.0	1.0	$i Pr_2NEt$	92
6	30	0.3	0.3	$i Pr_2NEt$	17
7	20	0	0.6	$i Pr_2NEt$	84

In 1998 the Bringmann group reported the first synthesis of an extended biaryl lactone system.[17] Their initial route involved the use of aryl bromide **1.21** as a precursor to the desired product. Unfortunately only cleavage of the ester was observed when **1.21** was submitted to the reaction conditions (Scheme 1.7). When the transformation was performed under identical conditions but instead using aryl triflate **1.22** as the precursor, the desired bislactone **1.23** could be isolated in 37% yield. An X-ray diffraction of the crystalline product revealed that the molecule adopted a *meso*-conformation. Computational studies confirmed that this conformation is favoured almost exclusively to the other two stereoisomeric conformers.

---

[17] Bringmann, G.; Wuzik, A.; Kraus, J.; Peters, K. Peters, E.-M. *Tetrahedron Lett.* **1998**, *39*, 1545

Scheme 1.7 **Synthesis of a lactone-bridged ternapthyl.**



1.21

1.22

1.23
37% yield

1.2.1.4 Intramolecular Reactions in Total Synthesis

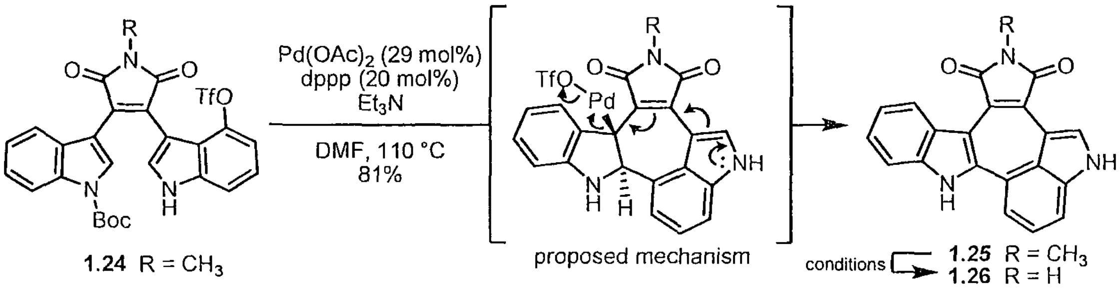
The application of direct arylation involving triflates in total synthesis is surprisingly rare. One example was published by Steglich *et al.* as the key step in a total synthesis of arcyriacyanin A, an alkaloid isolated from the sporangia of the slime mold *Arcyria obvelata.*[18] In the key step, the precursor indolyl triflate **1.24** was cyclised onto the C-2 position of the second Boc-protected indole to close the 7-membered ring and afford *N*-methylarcyriacyanin A **1.25** in 81% isolated yield (Scheme 1.8). It is of noted interest that the Boc group was cleaved in this transformation. Standard conditions could then be used to convert **1.25** into the natural product **1.26**. The authors suggested that this reaction was an example of an intramolecular Heck-type reaction. As *syn*-beta

---

[18] Brenner, M., Mayer, G ; Terpin. A.; Steglich, W. *Chem Eur J.* **1997**, *3*, 70.

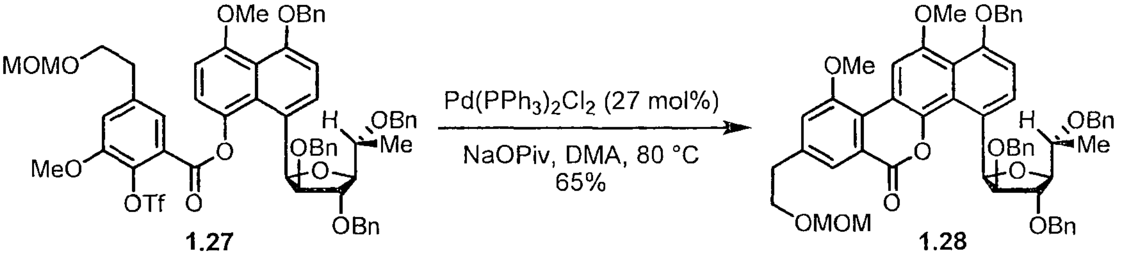
elimination would not be possible, they proposed that reductive elimination would instead occur through a base-catalyzed fragmentation (Scheme 1.8). Whether or not this reaction proceeded through a Heck-type mechanism is debatable, and recent reports by the Trauner group suggest the possibility of alternate pathways (*vide infra*).

Scheme 1.8 **Total synthesis of the slime mold alkaloid arcyriacyanin A.**



A total synthesis of gilvocarcin V was reported by the Suzuki group in 1994.[19] This antibiotic, noted for excellent antitumor activity and exceptionally low toxicity, is a metabolite of certain *Streptomyces* strains. A palladium-catalyzed direct arylation of triflate **1.27** was used in the key step to construct the fully formed tetracyclic core **1.28** in 65% yield (Scheme 1.9). Surprisingly, this reaction proceeded rapidly under mild conditions despite the sterically encumbered nature of the triflate. Manipulation of the MOM-protected primary alcohol into a vinyl group and deprotection of the benzylated oxygens then converted **1.28** into gilvocarcin V in six steps.

Scheme 1.9 **Total synthesis of the antibiotic gilvocarcin V.**



The Trauner group recently published an elegant synthesis of (–)-frondosin B, a marine terpenoid isolated from the sponge *Dysidea frondosa*, which exhibits both anti-

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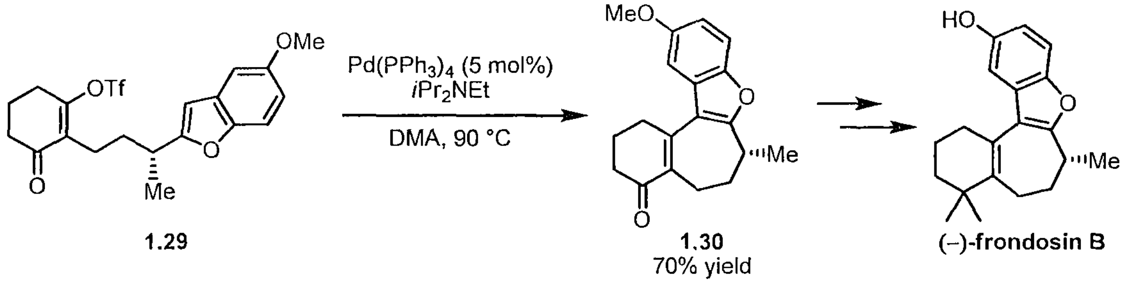
[19] Hosoya, T.; Takashiro, E.; Matsumoto, T.; Suzuki, K. *J. Am. Chem. Soc.* **1994**, *116*, 1004.

inflammatory and HIV-inhibitory properties.[20,21] The synthesis centers around an intramolecular direct vinylation reaction at the C-3 position of a substituted benzofuran (Scheme 1.10). Vinyl triflate **1.29** was reacted in the presence of a palladium catalyst and an amine base for an extended period of time to provide the 7-membered ring and complete the molecular core in 70% yield. Conversion of **1.30** into the natural product was achieved in three steps. Surprisingly, the optical rotation of the synthesized molecule was opposite to that of the natural product, even though the absolute stereochemistry of frondosin B had recently been confirmed by Danishefsky.[22] Upon further examination, an unnoticed inversion of the stereocenter occurred early in the Danishefsky synthesis, resulting in the misassignment of stereochemistry of the natural product.

Scheme 1.10 **Total synthesis of marine terpenoid (–)-frondosin B.**



Trauner originally considered that the ring-closing step in the synthesis of frondosin B could be an example of a heteroaryl Heck reaction, though upon further examination this pathway seemed unlikely (Scheme 1.11, Mechanism 1). Following oxidative and migratory insertion (Mechanism 1, **1.31** and **1.32**), palladium must undergo *syn* β-hydride elimination. In this particular case, elimination involving the only hydrogen *syn* to the palladium would result in the destruction of the stereocenter (Mechanism 1, **1.33**), and afford racemic **1.30** upon rearomatization. As no loss in enantiomeric excess was observed, it was likely that this transformation occurred via another mechanism. Alternately, the electron-rich benzofuran could attack the palladium species in a manner similar to an electrophilic aromatic substitution (Mechanism 2, **1.34**).

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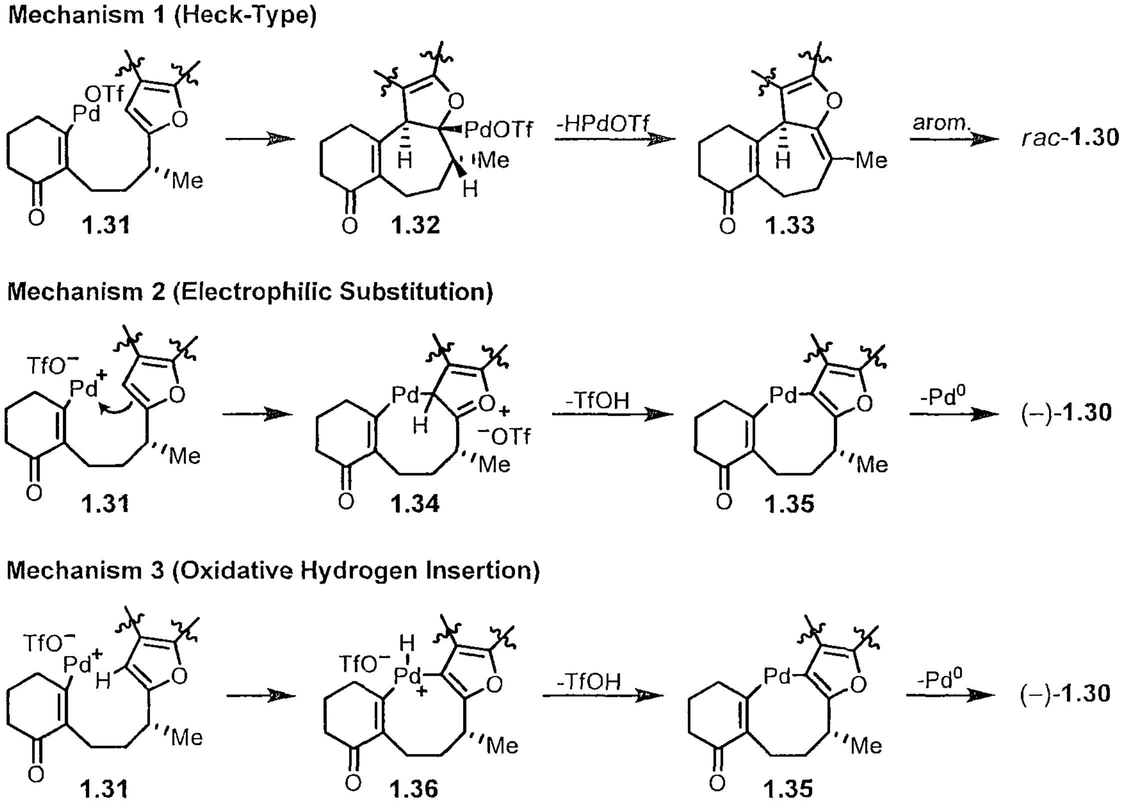
[20] Hughes, C. C.; Trauner, D. *Angew. Chem. Int. Ed.* **2002**, *41*, 1569.

[21] Hughes, C. C.; Trauner, D. *Tetrahedron* **2004**, *60*, 9675.

[22] Inoue, M.; Carson, M. W.; Frontier, A. J.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 1878.

Following rearomatization, reductive elimination of the palladium(II) species **1.35** would afford (–)-**1.30**. A third possibility would involve a second oxidative insertion into the C-H bond at C-3 of the benzofuran to give a palladium(IV) intermediate (Mechanism 3, **1.36**). Subsequent reductive eliminations of triflic acid and the product would regenerate the catalyst and afford the desired chiral product. It should be noted that this transformation is reminiscent of the key step in the synthesis of arcyriacyanin A by Stegleich, and brings into question whether a Heck-like mechanism was indeed occurring (Scheme 1.8).

Scheme 1.11 **Possible mechanisms for the key step in the synthesis of (–)-frondosin B.**

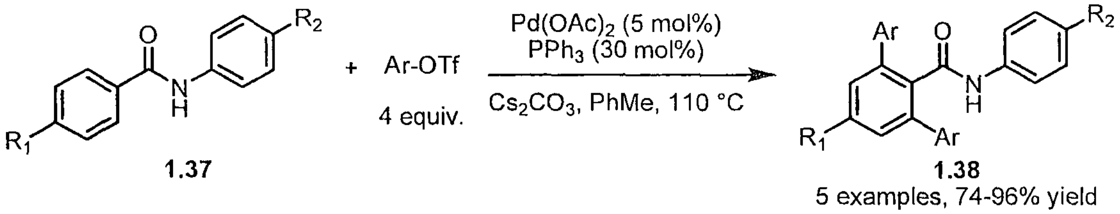


1.2.2 Intermolecular Direct Arylation with Aryl Triflates

1.2.2.1 Intermolecular Reactions Involving Directing Groups

The use of directing groups in the intermolecular direct arylation of aryl triflates is largely unreported. One example was disclosed by Miura involving the direct arylation of benzanilides **1.37** via a palladium catalyst (Scheme 1.12).[23] The reaction was directed by the amide group and occured at both the C2- and C6-positions to afford a series of *N*-(2,6-diarylbenzoyl)anilides **1.38** in excellent yields. Mono arylation could also be achieved when one of the *ortho* positions was blocked. The scope of aryl triflates was not examined, as examples involving only phenyl and *p*-tolyl triflate were reported.

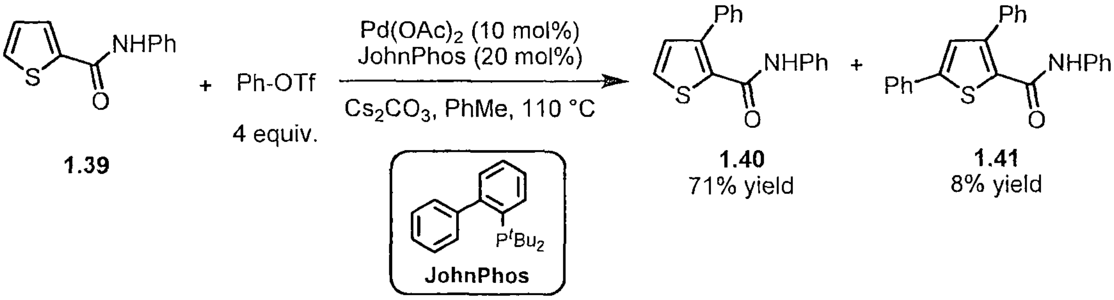
Scheme 1.12 **Arylation of benzanilides with an amide acting as a directing group.**



1.2.2.2 Intermolecular Direct Arylation of Heterocycles

In 2002, Miura also reported the multiple arylation of a thiophene.[24] When thiophene **1.39** and phenyl triflate were subjected to palladium acetate and JohnPhos in the presence of a carbonate base, both monoarylated thiophene **1.40** and diarylated thiophene **1.41** were isolated from the reaction mixture (Scheme 1.13). Miura concluded from the distribution of products that the C3-position was the favoured site of arylation, followed by reaction at the C5-position.

Scheme 1.13 **Multiple step-wise arylations of a thiophene.**



The Doucet group recently disclosed a methodology for the direct arylation of a broad range of electron-rich heterocycles (Scheme 1.14).[25] Thiazoles **1.42**, with

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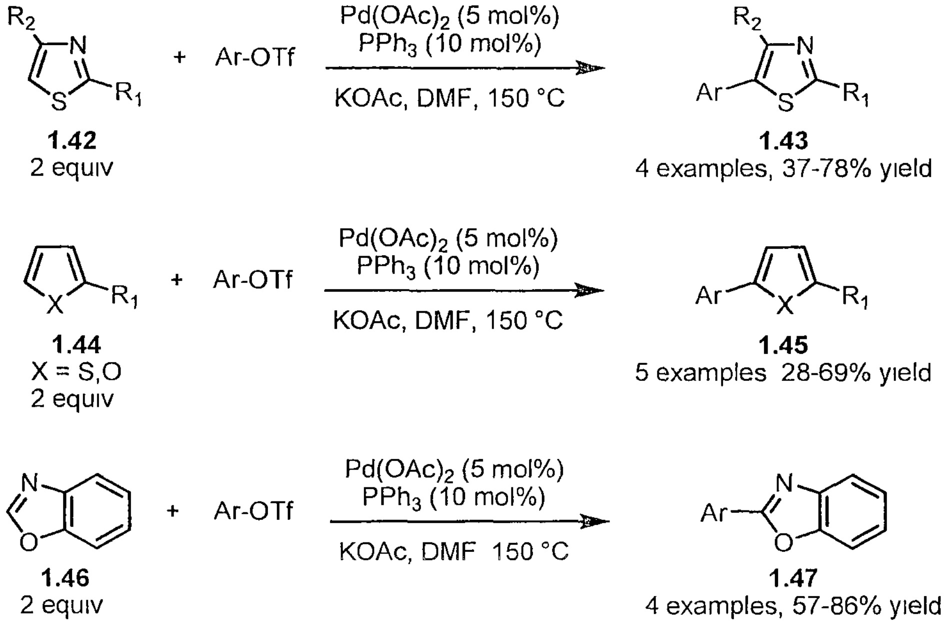
[23] Kametani, Y.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **2000**, *41*, 2655.

[24] Okazawa, T.; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc.* **2002**, *124*, 5286.

[25] Roger, J.; Doucet, H. *Org. Biomol. Chem.* **2008**, *6*, 169.

substitution at the C2- and C4-positions, underwent arylation at the C5-postion to afford di- and trisubstituted thiazoles **1.43** in acceptable yields Arylation could also be accomplished at the 2-position when the 5-position was blocked Substituted thiophenes and furans **1.44** could also be arylated under identical conditions to afford the corresponding 2,5-disubstituted products. With the substitution of a carbonate base for potassium acetate, benzoxazole **1.46** could be arylated by a variety of triflates The reaction was found to be highly dependent on the electronic nature of the triflate, with electron rich triflates providing excellent yields No reaction was observed when electron deficient triflates were used

Scheme 1.14 **Direct arylation of electron-rich heterocycles.**



There are few examples of intermolecular direct arylation involving triflates being applied to synthesis One example involves the preparation of an analog of an HIV-1 reverse transcriptase inhibitor as described by a group at Boehinger Ingelheim (Scheme 1 15)[26] Oxazole **1.48** and pyridyl triflate **1.49** were coupled in the presence of a palladium catalyst to afford the desired analog **1.50** in moderate yield In biological

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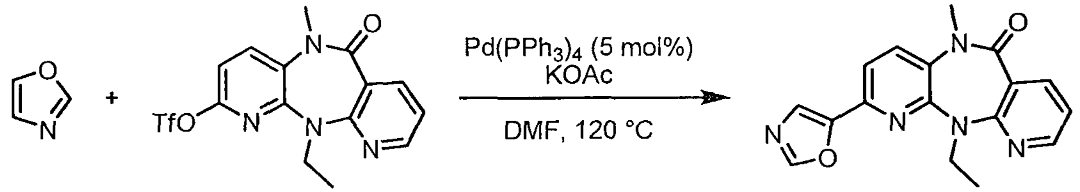
[26] Proudfoot, J R , Hargrave, K D , Kapadia, S R , Patel, U R , Grozinger, K G , McNeil, D W , Cullen, E , Cardozo, M , Tong, L , Kelly, T A , Rose, J , David, E , Mauldin, S C , Fuchs, V U , Vitous, J , Hoermann, M , Klunder, J M , Raghavan, P , Skiles, J W , Mui, P , Richman, D D , Sullivan, J L , Shih, C -K , Grob, P M , Adams, J *J Med Chem* **1995**, *38*, 4830

assays, this analog displayed IC_{50} values of less than 1 μM for both wild-type and drug-resistant variants of HIV-1 reverse transcriptase.

Scheme 1.15 **Synthesis of an HIV-1 reverse transcriptase inhibitor.**



1.48 **1.49** **1.50** 34% yield

1.2.2.3 Tosylates and Mesylates in Intermolecular Direct Arylation

While triflates have seen some use in direct arylation, the use of other sulfonates, specifically tosylates and mesylates, is extremely rare. While these sulfonates exhibit greater stability than triflates, they suffer from decreased reactivity in transition metal catalyzed reactions. The first report of a direct arylation reaction involving tosylates and mesylates was recently disclosed by the Ackermann group.[27] Using palladium acetate and the sterically bulky X-Phos ligand, a variety of heterocycles could be coupled to aryl tosylates **1.51** (Scheme 1.16). Specifically oxazole **1.52**, caffeine **1.53** and triazoles **1.54** all afforded excellent yields without modification to the reported conditions. Furthermore, the reaction was unaffected by the electronic nature of they aryl tosylate, showing tolerance for both electron-rich and electron-poor aryl groups.

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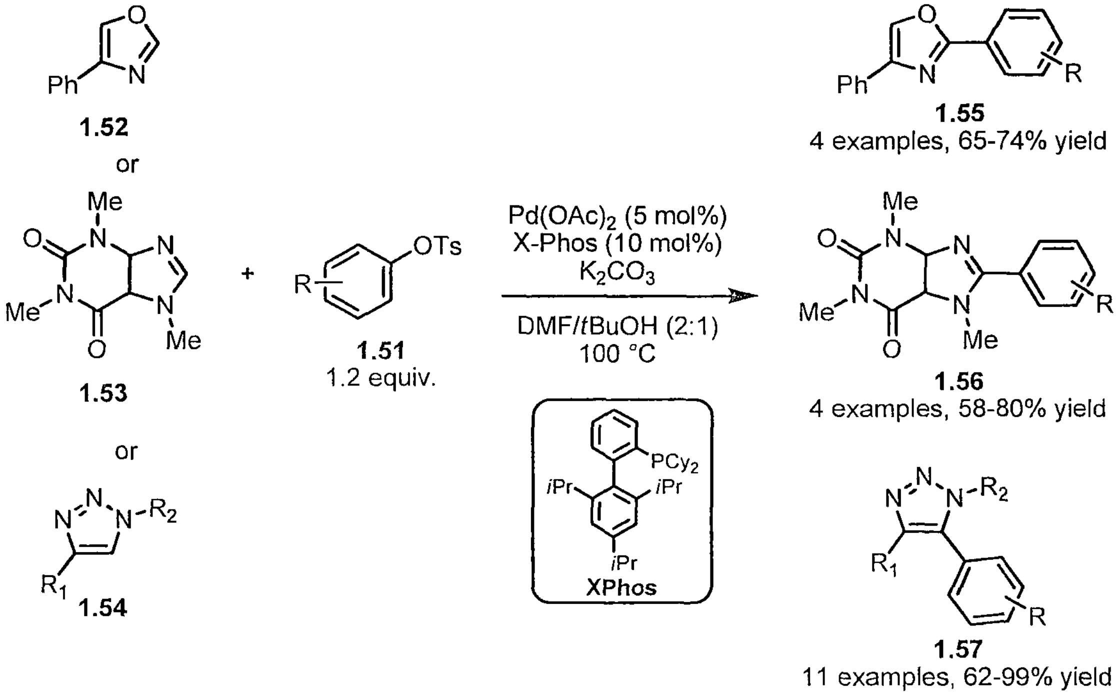
[27] Ackermann, L.; Althammer, A.; Fenner, S. *Angew. Chem. Int. Ed.* **2009**, *48*, 201.

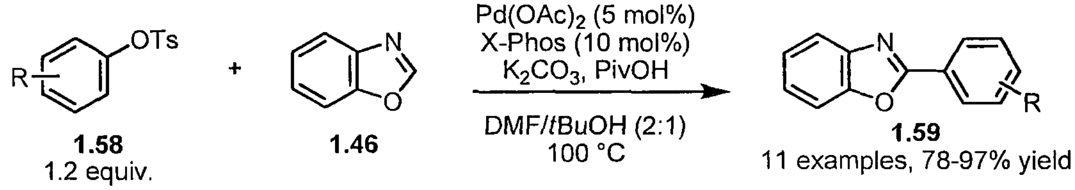
Scheme 1.16 **Arylation of various heterocycles with aryl tosylates.**



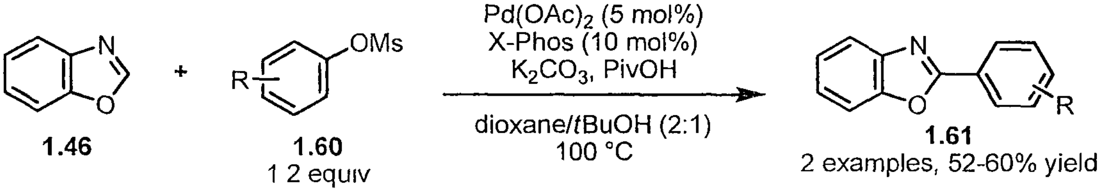
In the same report, Ackermann reported the arylation of benzoxazole **1.46** using slightly modified conditions (Scheme 1.17). With the addition of catalytic amounts of pivalic acid, the arylation with tosylates **1.58** proceeded smoothly to afford 2-arylbenzoxazoles in excellent yields. Surprisingly, arylation could also be achieved using aryl mesylates **1.60** when 1,4-dioxane was used in place of DMF. While product yields were moderate, this was the first reported example of aryl mesylates being used in direct arylation.

Scheme 1.17 **Arylation of benzoxazole with aryl tosylates and mesylates.**

Coupling of Aryl Tosylates



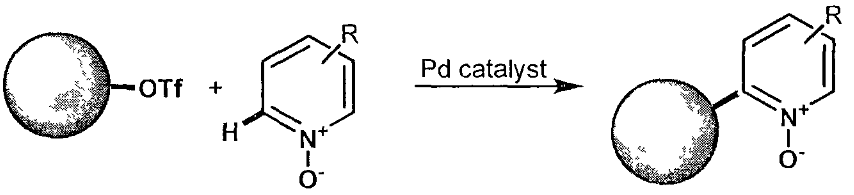
Coupling of Aryl Mesylates



1.3 Project Goals

The goal of this research project was to develop a general set of conditions for the arylation of pyridine *N*-oxides with aryl triflates using a palladium catalyst. More specifically, the scope of both the *N*-oxide and triflate were to be explored with respect to their steric and electronic properties. Finally, the methodology was to be applied toward the synthesis of a biologically active molecule.

Scheme 1.18 **General synthetic plan.**



Chapter 2

Results and Discussion – Arylation of Azine N-Oxides with Aryl Triflates

2.1 Background

2.1.1 Previous Group Work in Azine N-Oxide Arylation

Our group has been interested in the direct arylation of electron-deficient arenes and hetero-arenes for some time. One of the earliest results disclosed involved the coupling of pyridine *N*-oxides **2.1** with aryl bromides **2.2**.[28] Using palladium acetate, tri-*t*-butylphosphine (in the form of an air-stable HBF_4 salt)[29] and potassium carbonate, arylation proceeded smoothly to afford the desired *ortho*-arylated *N*-oxides **2.3** in 74-97% yield (Scheme 2.1). Unfortunately, up to 4 equivalents of the *N*-oxide was required to achieve these excellent results, and when this number was reduced the reaction suffered from diminished yields. The scope of substituted pyridine *N*-oxides was further elaborated in a subsequent manuscript, adding another 31 examples, with yields ranging from 34-98%.[30] Mechanistic insight was also gained through a competition study involving the electron-rich 4-methoxypyridine *N*-oxide **2.4** and electron-deficient 4-nitropyridine *N*-oxide **2.5**.[28] When the distribution of the two products formed in the reaction was analysed by ^{1}H NMR, it was found that **2.7** was greatly when compared to **2.8**. This result is inconsistent with an S_EAr mechanism, which predicts that the electron-rich **2.4** would be more reactive.

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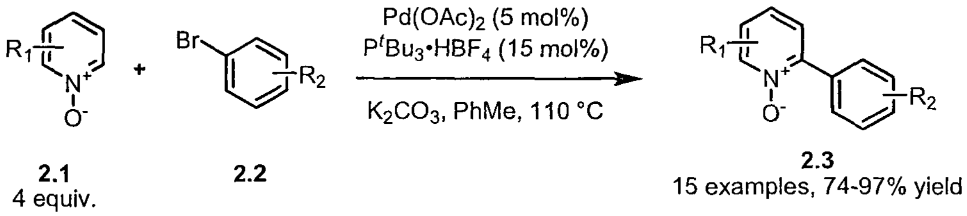
[28] Campeau, L.-C.; Rousseaux, S.; Fagnou, K. *J. Am. Chem. Soc.* **2005**, *127*, 18020.

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

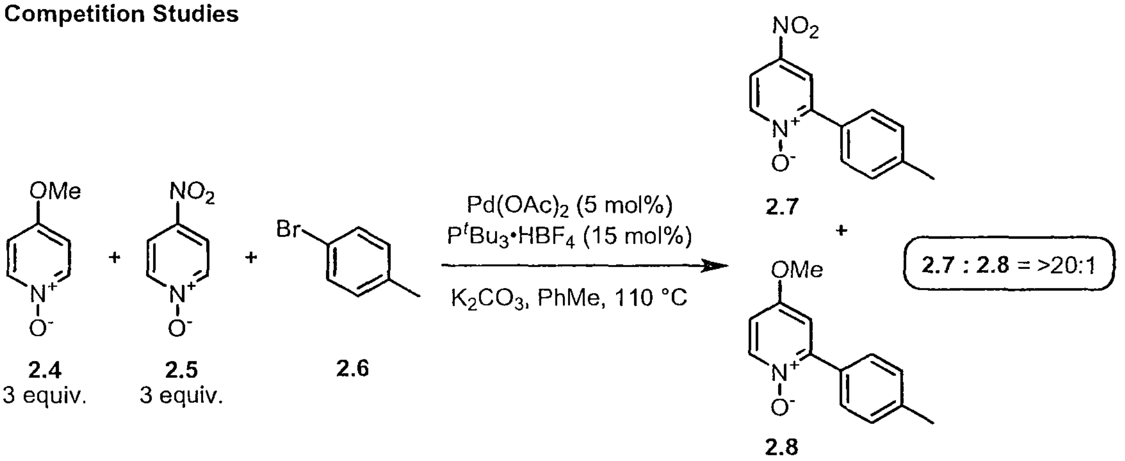
[30] Campeau, L.-C.; Stuart, D. R.; Leclerc, J.-P.; Bertrand-Laperle, M.; Villemure, E.; Sun, H.-Y.; Lasserre, S.; Guimond, N.; Lecavallier, M.; Fagnou, K. *J. Am. Chem. Soc.* **2009**, *131*, 3291.

Scheme 2.1 **Arylation of pyridine *N*-oxides with aryl bromides.**

General Conditions



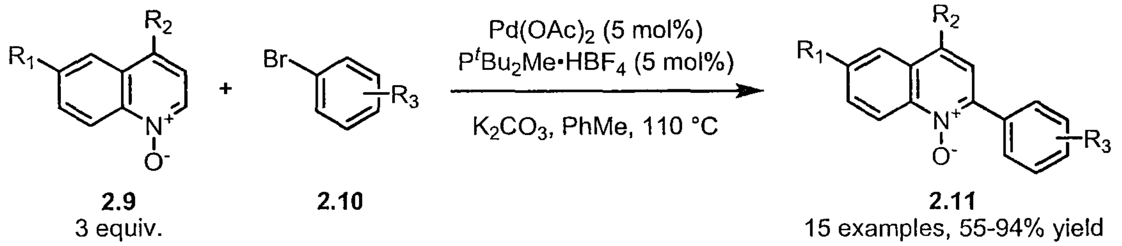
Competition Studies



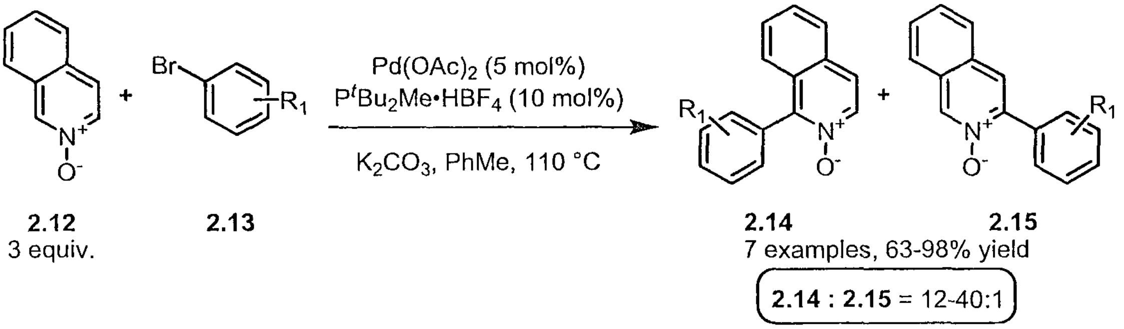
The reaction was also examined using other azine *N*-oxides as coupling partners.[30] Optimization of reaction conditions with quinoline and isoquinoline *N*-oxides found that di-*t*-butylmethylphosphine provided both the greatest reactivity and yield. Using these new conditions, substituted quinolines **2.9** were reacted with various aryl bromides **2.10**, affording 15 examples with yields ranging from 55-94% (Scheme 2.2). The use of isoquinoline *N*-oxide **2.12** provided an additional challenge as the unsymmetrical nature of this substrate gave rise to two regioisometrical products. It was found that the C2-postion, leading to arylated isoquinoline *N*-oxide **2.14**, was much more reactive under the experimental conditions, with ^{1}H NMR regioselectivites of **2.14**:**2.15** ranging from 12:1 to almost 40:1 (Scheme 2.2). Overall reaction yields were also very high, with the majority of examples providing yields greater than 90%. Isolation by chromatography of the individual regioisomers could only be achieved following deoxygenation, as the two products proved to be inseparable by silica gel chromatography when the *N*-oxide motif was present.

Scheme 2.2 **Direct arylation of other azine *N*-oxides with aryl bromides.**

Quinoline Scope



Isoquinoline Scope



2.1.2 Azine and Azole N*-Oxide Arylation with Other Aryl Halides*

An investigation of the use of aryl chlorides and iodides in place of aryl bromides in the reaction was also performed.[31] Various diazine *N*-oxides were used as coupling partners as they have been proven to be more reactive than pyridine *N*-oxide, which helped to compensate for the decreased reactivity that is commonly associated with aryl chlorides in cross-coupling reactions. As azine *N*-oxides have previously been shown to be only sparingly soluble in toluene, a switch to the more polar dioxane provided superior results to the previously reported conditions. Both substituted pyrazine *N*-oxides **2.16** and pyridazine *N*-oxide **2.17** were shown to afford excellent yields when reacted with various aryl halides **2.18** (Scheme 2.3). Aryl chlorides proved to be highly reactive under the reported conditions, though when aryl iodides were employed half an equivalent of Ag_2CO_3 was required for the reaction to proceed efficiently.

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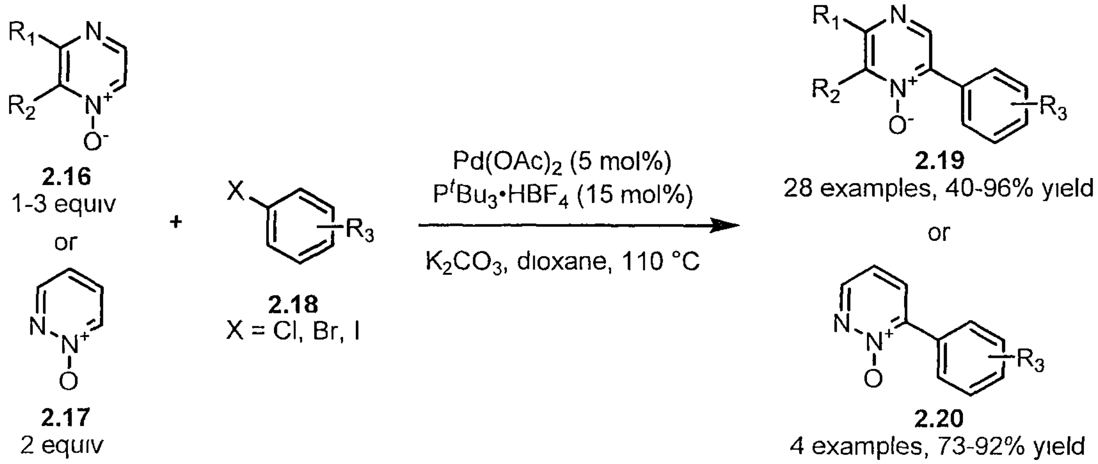
[31] Leclerc, J.-P.; Fagnou, K. *Angew. Chem. Int. Ed.* **2006**, *45*, 7781.

Scheme 2.3 **Arylation of diazine *N*-oxides with aryl halides.**



The coupling of aryl triflates with thiazole *N*-oxides was also briefly examined.[30] Using slightly modified conditions involving the DavePhos ligand and pivalic acid[32] as an additive, 4-methylthiazole *N*-oxide **2.21** reacted selectively with aryl triflates **2.22** to provide C2-arylated thiazoles **2.23** (Scheme 2.4). While this reaction usually proceeded at room temperature with aryl bromides, elevated temperatures were required to obtain good yields when triflates were employed. With the C2 position blocked, arylation of *N*-oxide **2.24** proceeded at C5 to give 2,5-disubstituted thiazole *N*-oxide **2.26** in an acceptable 55% yield (Scheme 2.4). Higher conversions could be obtained when the reactions were performed with bromobenzene, though reaction conditions were never fully optimized for the use of triflates in this transformation as it was not the primary focus of the research.

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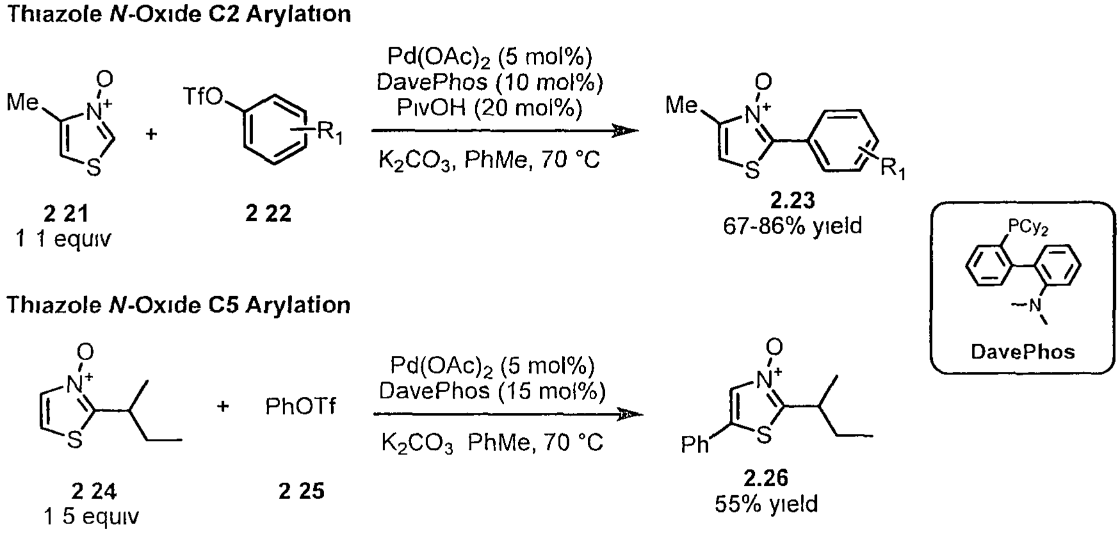
[32] Lafrance, M., Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 16496

Scheme 2.4 **Direct arylation of thiazole *N*-oxides at various sites with aryl triflates.**



2.2 Reaction Development

2.2.1 Initial Results

We began our initial examination of the azine *N*-oxide direct arylation[33] using pyridine *N*-oxide **2.28**, *p*-tolyl triflate **2.27** and conditions previously developed for use in coupling aryl bromides with azine *N*-oxides [28] Unfortunately only a 14% yield was noted when the reaction was analysed by gas chromatography (Scheme 2 5) This was a surprising result, and indicated that this reaction was more difficult than comparable reactions using aryl bromides Gratifyingly, when the reaction was repeated with the addition of a small amount of pivalic acid, a three-fold increase in yield was observed This was the first time our group had observed that pivalic acid contributed a significant effect to the yield in azine *N*-oxide direct arylations [34] These results indicated that a thorough optimization of the conditions would be required in order to achieve acceptable yields

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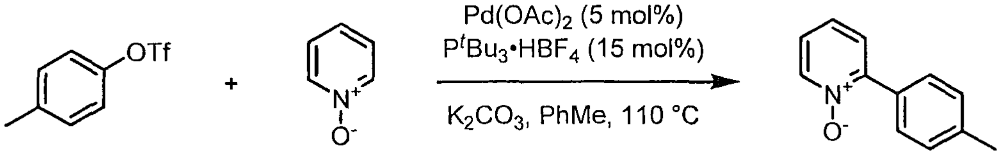
[33] This work was done in collaboration with Derek J Schipper and Mohamed El-Salfiti

[34] For examples of PivOH in azole *N*-oxide arylation, see Campeau, L -C , Bertrand-Laperle, M , Leclerc, J P , Villemure, E , Gorelsky, S , Fagnou, K *J Am Chem Soc* **2008**, *130*, 3276

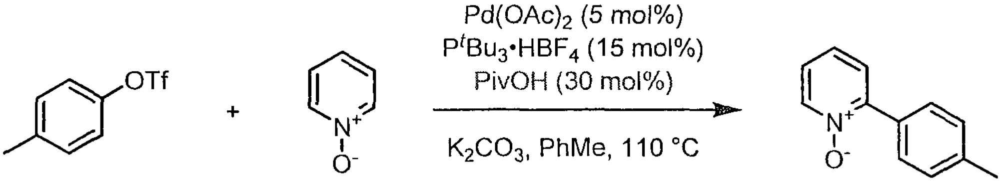
Scheme 2.5 **Initial hits using previous *N*-oxide direct arylation conditions.**

Original *N*-oxide conditions



2.27 **2.28** 2 equiv. **2.29** 14% GC yield

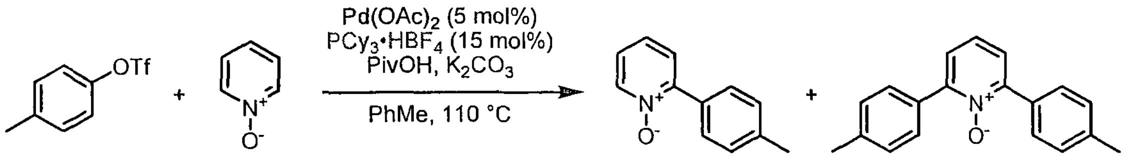
Addition of pivalic acid



2.27 **2.28** 2 equiv. **2.29** 43% GC yield

Another interesting result was obtained when the tri-*t*-butylphosphine ligand was substituted for tricyclohexylphosphine. When the reaction mixture was analysed, it was discovered that *N*-oxide **2.28** had been converted not only to the mono-arylated *N*-oxide **2.29**, but to the diarylated *N*-oxide **2.30** as well (Scheme 2.6). This was unexpected, as diarylation had never been a problem in the previous work with aryl bromides, and had never been observed in large quantities. In fact, only one example of diarylation had been reported previously, and the conditions required the use of the more reactive pyrazine *N*-oxide and a three-fold excess of aryl bromide.[31] The large amount of diarylation observed when aryl triflate **2.27** was employed, even with an excess of pyridine *N*-oxide, meant that selectivity would also be a major concern in optimizing this reaction. A further complication was that NMR analysis of the reaction mixture would now be impossible, due to the disappearance of the diagnostic hydrogens *ortho* to the *N*-oxide moiety on the diarylated products. Instead, reactions were analysed using GC-FID (with a calibrated curve), though it was found that diarylated *N*-oxide **2.30** provided broad, misshapen peaks which did not always give reproducible results. As a consequence, some yields for the diarylated product were inflated, resulting in total yields sometimes greater than 100%. While this was not ideal, GC-FID analysis would allow for the faster development of reaction conditions than isolating the products from each trial.

Scheme 2.6 **Initial appearance of diarylation under reaction conditions.**



2.27

2.28
2 equiv.

2.29
62% GC yield

2.30
38% GC yield

2.2.2 Reaction Optimization

With a starting set of reaction conditions in place, a broad range of electron-rich phosphine ligands were screened (Table 2.1).[35] Examining the simple phosphines, both di-*t*-butylmethylphosphine and tricyclohexylphosphine displayed the highest yields for mono-arylation, with di-*t*-butylmethylphosphine exhibiting higher reactivity as illustrated by the presence of more product **2.30** (Table 2.1, Entries 1 and 2). Triphenylphosphine showed a significant decrease in reactivity and provided the lowest yields, however no diarylation (Entry 8). Several 2'-biphenyl phosphine ligands were also screened, with the bulkier S-Phos and X-Phos providing better yields than the two Dave-Phos type ligands (Entries 3-6). The bidentate BINAP ligand was also tried and this ligand gave excellent results but was not further pursued as simpler ligands provided comparable results (Entry 7). It was decided that tricyclohexylphosphine would be used for further optimization as it showed a greater selectivity for the monoarylated product **2.29**, though di-*t*-butylmethylphosphine would also be examined as a substitute ligand when increased reactivity was required.

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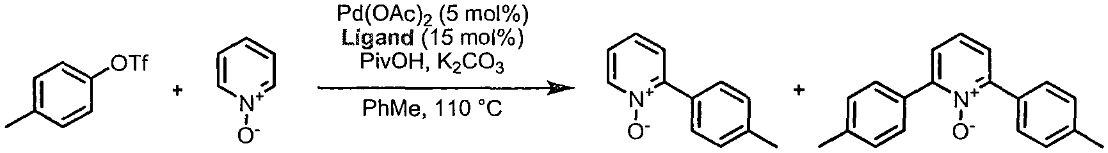
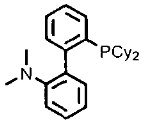
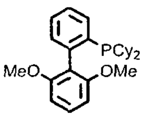
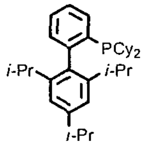
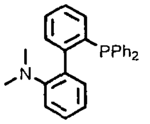
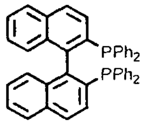
[35] Reaction optimization performed by Derek J. Schipper and Mohamed El-Salfiti; unpublished results.

Table 2.1 **Ligand screen for the triflate *N*-oxide reaction.**



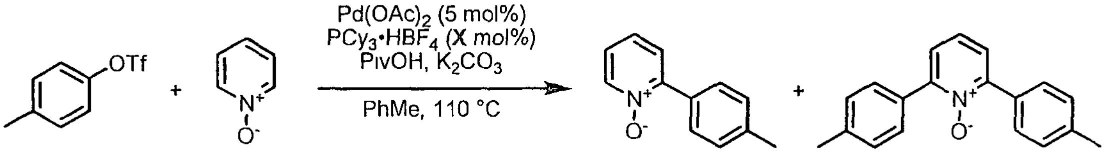
2.27 **2.28** **2.29** **2.30**

Entry	Ligand		Yield **2.29** (%)[b]	Yield **2.30** (%)[b]
1	$P(^tBu)_2Me{\bullet}HBF_4$		65	34
2	$PCy_3{\bullet}HBF_4$		65	26
3	Dave-Phos		50	8
4	S-Phos		58	16
5	X-Phos		60	24
6	PhDave-Phos		42	12
7	BINAP		62	24
8	PPh_3		30	0

[a] Conditions: Triflate (1 equiv.), *N*-oxide (2 equiv.), $Pd(OAc)_2$ (5 mol%), Ligand (15 mol%), PivOH (0.3 equiv.), K_2CO_3 (2 equiv.), PhMe (0.3 M), 110 °C, overnight. [b] GC yields determined using calibrated curve based on amount of reacted triflate.

Next, the ligand-to-metal ratio was examined using tricyclohexylphosphine (Table 2.2). A ratio of 2:1 was found to provide optimal reactivity, and afforded the highest yields for both monoarylated *N*-oxide **2.29** and diarylated *N*-oxide **2.30** (Table 2.2, Entry 2). It should be noted that the results for the 3:1 ratio trial (Entry 1) were somewhat lower than previous trials with identical conditions (Table 2.1, Entry 2). Despite this discrepancy, the ligand-to-metal ratio of 2:1 still gave comparable results to previous 3:1 ratio trials (Table 2.1, Entry 2), and offered the added benefit of lower amounts of ligand. Further screenings were performed using a ligand-to-metal ratio of 2:1.

Table 2.2 **Optimization of the ligand to metal ratio.**



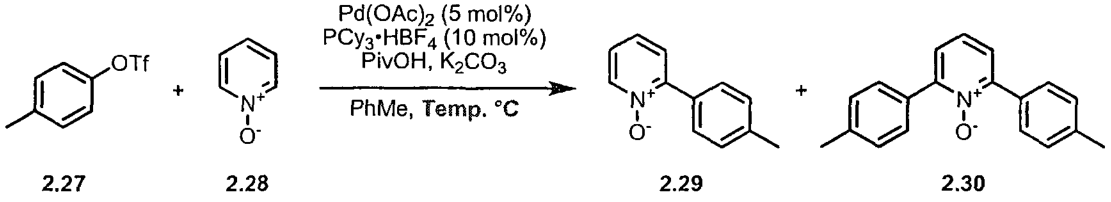
2.27 **2.28** **2.29** **2.30**

Entry	Ligand Ratio (mol%)	Yield **2.29** (%)[b]	Yield **2.30** (%)[b]
1	3:1 (15 mol%)	56	30
2	2:1 (10 mol%)	67	40
3	1.2:1 (6 mol%)	56	31

[a] Conditions: Triflate (1 equiv.), *N*-oxide (2 equiv.), $Pd(OAc)_2$ (5 mol%), PCy_3•HBF_4 (X mol%), PivOH (0.3 equiv.), K_2CO_3 (2 equiv.), PhMe (0.3 M), 110 °C, overnight. [b] GC yields determined using calibrated curve based on amount of reacted triflate.

The effect of temperature on the triflate *N*-oxide coupling reaction was also examined (Table 2.3). Very little reactivity was observed at low temperatures and no diarylation was noted (Table 2.3, Entry 1). Reactions performed at both 90 °C and 100 °C gave comparable amounts of the monoarylated *N*-oxide **2.29**, though the amount of diarylation was higher at 100 °C (Entries 2, 3). When temperatures were elevated to 110 °C and beyond, a decrease in the yield of monoarylation was observed (Entries 4, 5). Upon analysis of the results, it was decided that 100 °C would be the ideal temperature. While the reaction performed at 90 °C gave less of the diarylated product **2.30**, which would indicate better selectivity, more difficult substrates would suffer from a decrease in yield. It was decided that 100 °C would provide the optimum balance of reactivity and selectivity for the monoarylated product.

Table 2.3 **Temperature scan of the triflate *N*-oxide reaction.**

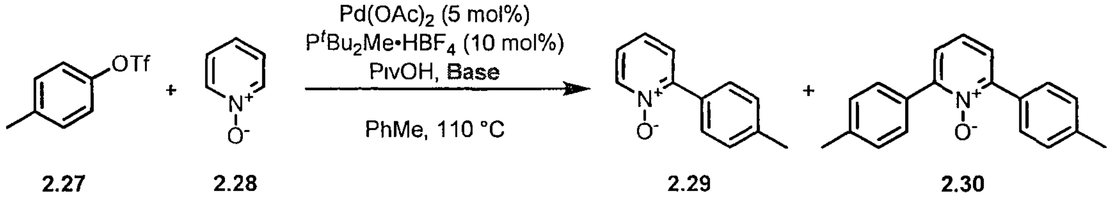


Entry	Temperature (°C)	Yield **2.29** (%)[b]	Yield **2.30** (%)[b]
1	70	20	0
2	90	71	36
3	100	70	42
4	110	60	46
5	120	58	36

[a] Conditions: Triflate (1 equiv.), *N*-oxide (2 equiv.), $Pd(OAc)_2$ (5 mol%), $PCy_3 \cdot HBF_4$ (10 mol%), PivOH (0.3 equiv.), K_2CO_3 (2 equiv.), PhMe (0.3 M), overnight. [b] GC yields determined using calibrated curve based on amount of reacted triflate.

The effect of the base on the reaction was also examined, this time using di-*t*-butylmethylphosphine as the ligand (Table 2.4). Several carbonate bases were screened, with the best results being obtained with potassium and rubidium carbonates (Table 2.4, Entries 1-4). Potassium carbonate offered the highest overall yield, but also produced a large amount of diarylation (Entry 2). Rubidium carbonate was more selective towards monoarylated product **2.29** yet still gave high overall yields (Entry 3). Potassium phosphate was also examined and displayed similar reactivity to potassium carbonate (Entry 5). Two strong *tert*-butoxide bases were also tried but these provided poor results (Entries 6, 7). From these results, rubidium carbonate was selected as the base of choice due to the greater selectivity for a single arylation. Potassium carbonate was also retained for further experiments when more reactivity would be required for difficult substrates.

Table 2.4 **Screening of various bases.**



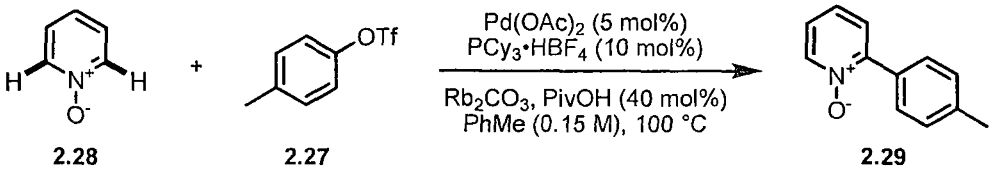
Entry	Base	Yield **2.29** (%)[b]	Yield **2.30** (%)[b]
1	Na_2CO_3	48	48
2	K_2CO_3	69	40
3	Rb_2CO_3	71	32
4	Cs_2CO_3	47	10
5	K_3PO_4	68	28
4	KO^{t}Bu	8	0
5	NaO^{t}Bu	13	0

[a] Conditions Triflate (1 equiv), *N*-oxide (2 equiv), $Pd(OAc)_2$ (5 mol%), $P^tBu_2Me{\cdot}HBF_4$ (10 mol%), PivOH (0 3 equiv), K_2CO_3 (2 equiv), PhMe (0 3 M), 110 °C, overnight [b] GC yields determined using calibrated curve based on amount of reacted triflate

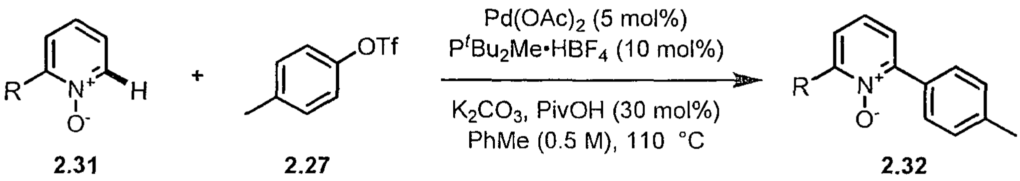
With optimizations complete, it was decided that two sets of conditions would be required for this transformation (Scheme 2.7). Conditions A were designed to provide the optimum amount of monoarylation and minimize the formation of diarylated side products. This would apply most to substrates containing two free sites that can undergo reaction, such as *N*-oxide **2.28**. These conditions run the risk of decreased overall yields as selectivity for monoarylation is favoured at the cost of reactivity. Conditions B were also developed to help compensate for the weakness in the first set of conditions. The goal was to provide the most reactive catalyst without concern for selectivity. Conditions B would be most appropriately used for substrates such as 2-substituted *N*-oxides **2.31** where there was no concern for diarylation, or other difficult, less reactive substrates.

Scheme 2.7 **Final optimized conditions for the triflate *N*-oxide arylation reaction.**

Conditions A: Optimized to be selective for mono-arylation



Conditions B: Optimized for reactivity using difficult substrates



2.3 Scope and Application

2.3.1 Scope of 3-Substituted Pyridine N*-Oxides*

With two sets of conditions developed, the reaction scope involving 3-substituted pyridine *N*-oxides was examined.[36] These substrates pose an additional challenge due to their asymmetry, allowing for the formation of up to three different products. Various meta-substituted pyridine *N*-oxides **2.33** were reacted with 3,5-dimethylphenyl triflate **2.34** under one, or both sets of general conditions to generate monoarylated, 6-substituted **2.35A** and 2-substituted **2.35B** products, as well as the diarylated product **2.35C** (Table 2.5). Using the highly reactive Conditions B, alkyl groups afforded a modest 2:1 ratio of isolated yields for the 2-substituted product, though diarylation proved to be the major product (Entry 2). Diarylation could be controlled by turning to the more selective Conditions A, and employing 4 equivalents of the *N*-oxide, though selectivity between the two monoarylated products did not show improvement (Entry 1). Electron-donating groups proved to be more selective, with the 2-substituted product **2.35B** being favoured approximately 6:1 over **2.35A** (Entries 3 and 4). Surprisingly this substrate afforded similar yields and selectivities regardless of which set of conditions were used. Electron-

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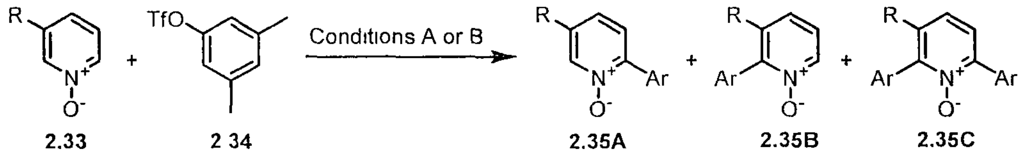
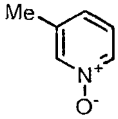
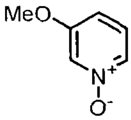
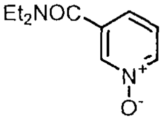
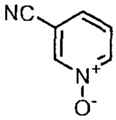
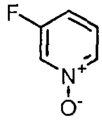
[36] For examples of other substrates that underwent arylation using these conditions, see: Schipper, D. J.; El-Salfiti, M.; Whipp, C. J.; Fagnou, K. *Tetrahedron* **2009**, *65*, 4977.

withdrawing groups generally continued the trend of favouring reactivity at the 2-position preferentially, and showed the most regioselectivity (Entries 6 and 7). Yields were unexpectedly low when 3-cyanopyridine *N*-oxide was employed, even using the more reactive Conditions B (Entry 6). Preferential arylation at the 6-position was only possible with the diethylamide substituent, providing a 5:1 selectivity in favour of **2.35A** when 4 equivalents of *N*-oxide were present (Entry 5). It is possible that the C2-position was less accessible due to the steric bulk of this group, allowing the catalyst preferential access to the C6-position.

Table 2.5 **Scope of the arylation of 3-substituted *N*-oxides.**



Entry	*N*-Oxide	Conditions[a]	Yield (A B C)[b]
1 2		Conditions A[c] Conditions B	94 (28 55 11) 92 (16 32 44)
3 4		Conditions A Conditions B	85 (11 67 7) 81 (9 64 8)
5		Conditions A[c]	97 (73 14 10)
6		Conditions B	68 (0 61 7)
7		Conditions A	90 (0 90 0)

[a] Conditions A *N*-oxide (2 equiv), triflate (1 equiv), $Pd(OAc)_2$ (0 05 equiv), $PCy_3{\cdot}HBF_4$ (0 10 equiv), Rb_2CO_3 (2 equiv), PivOH (0 4 equiv), PhMe (0 15 M), 100 °C, 15 h Conditions B *N*-oxide (2 equiv), triflate (1 equiv), $Pd(OAc)_2$ (0 05 equiv), $P^tBu_2Me{\cdot}HBF_4$ (0 10 equiv), K_2CO_3 (2 equiv), PivOH (0 3 equiv), PhMe (0 5 M), 110 °C, 15 h [b] Isolated yields, isolated yield for each isomer in brackets [c] Using 4 equiv of *N*-oxide

2.3.2 Synthesis of a Biologically Active Diarylpyridine

The developed methodology was applied to the formal synthesis of diarylpyridine **2.42**, a biologically active molecule that has been shown to exhibit both antibiotic[37] and antimalarial[38] activity. A previous synthesis published by Markovac[39] relied on the assembly of the pyridine ring as a key intermediate, which required the synthesis of two precursor components (Scheme 2.8). Component A **2.38** was synthesized via an aldol condensation, and subsequent dehydration, starting from acetophenone **2.36** and 2-oxoacetic acid. Component B **2.40** was formed by the α-bromination of acetophenone **2.36**, followed by treatment with pyridine in ethanol to afford the desired pyridinium bromide salt. These components were reacted with ammonium acetate to form diarylpyridine **2.41**, by way of a Krohnke pyridine synthesis in 50% yield over the 3 linear steps.[40] From this intermediate, two additional steps were required to isolate the desired molecule **2.42**, resulting in a route of 5 linear steps, or 7 steps overall.

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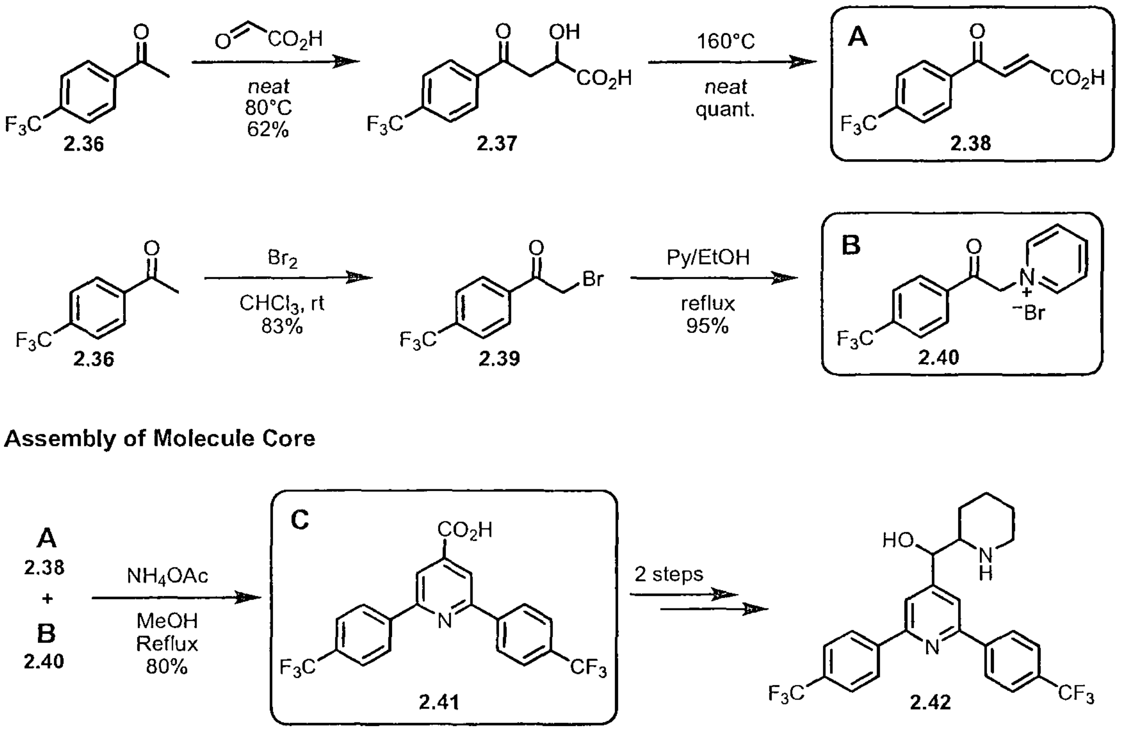
[37] (a) Martin-Galiano, A. J.; Gorgojo, B.; Kunin, C. M.; De la Campa, A. G. *Antimicrob. Agents Chemother.* **2002**, *46*, 1680 (b) Kunin, C. M.; Ellis, W. Y. *Antimicrob. Agents Chemother.* **2000**, *44*, 848.

[38] (a) Kim, K. H.; Hansch, C.; Fukunaga, J. Y.; Steller, E. E.; Jow, P. Y. C.; Craig, P. N.; Page, J. *J. Med. Chem.* **1979**, *22*, 366. (b) Schmidt, L. H.; Crosby, R.; Rasco, J.; Vaughan, D. *Antimicrob. Agents Chemother.* **1978**, *14*, 420. (c) LaMontagne, M. P.; Markovac, A.; Blumbergs, P. *J. Med. Chem.* **1974**, *17*, 519.

[39] Markovac, A.; LaMontagne, M. P.; Blumbergs, P.; Ash, A. B.; Stevens, C. L. *J. Med. Chem.* **1972**, *15*, 918.

[40] Zecher, W.; Krohnke, F. *Angew. Chem. Int. Ed.* **1963**, *2*, 380.

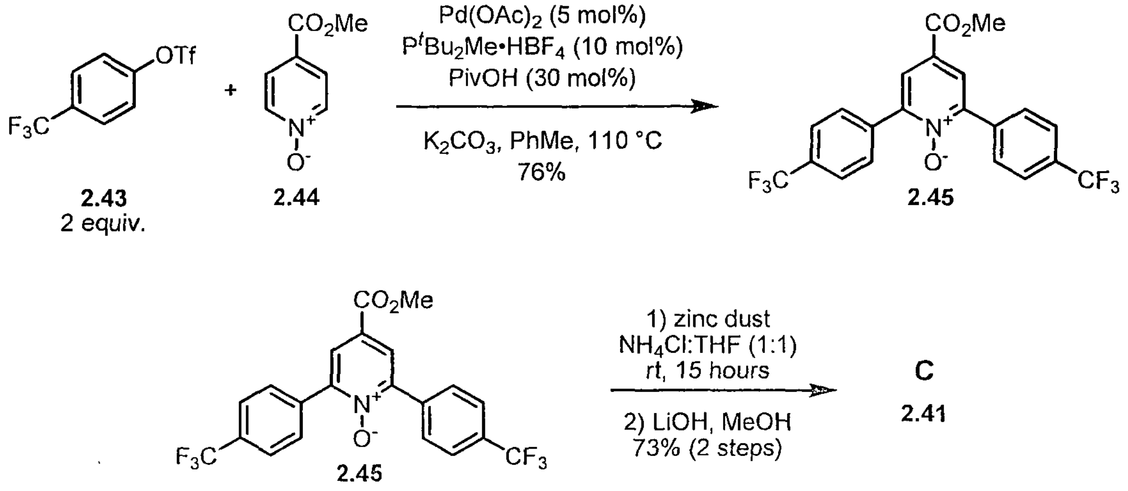
Scheme 2.8 **Previous synthesis of a diarylpyridine antimalarial.**


Synthesis of Components

Assembly of Molecule Core

Upon analysis, we decided that diarylpyridine C **2.41** was an appropriate target to intercept and would allow us to test our triflate direct arylation methodology (Scheme 2.9). Using our more reactive Conditions B, and two equivalents of aryl triflate **2.43** we were pleased to see that pyridine *N*-oxide **2.44** underwent double arylation to give the bis-arylated *N*-oxide **2.45** in 76% isolated yield. This result was somewhat surprising as double arylation was never observed when reactions were carried out using the previous *N*-oxide arylation methodology developed by our group.[28,30] The product was then reacted with zinc dust in ammonium chloride and THF to reduce the *N*-oxide moiety, followed by saponification of the methyl ester by treatment with lithium hydroxide in methanol to generate diarylpyridine C **2.41** in 55% yield over 3 steps. While both syntheses require 3 linear steps to reach diarylpyridine C **2.41** and have similar overall yields of 55% compared to 50%, the previous synthesis required 5 steps overall. In addition to our approach providing a more direct route to the target compound, the ability to substitute various aryl triflates in the reaction allows for the facile synthesis of various derivatives, a synthetic advantage for medicinal chemists.

Scheme 2.9 **Formal synthesis *via* triflate *N*-oxide direct arylation.**



2.4 Conclusion

In conclusion, we have developed two sets of conditions for the direct arylation of azine *N*-oxides with aryl triflates. Various C3-substituted pyridine *N*-oxides were shown to undergo arylation, including those possessing either electron-rich or electron-poor functional groups. In most cases, the C2-position was the favoured site of arylation unless steric crowding was a factor.

A formal synthesis of a biologically active molecule was conducted using the developed conditions. The target molecule could be made in 3 steps in 55% overall yield, an improvement over the previous route of 5 total steps and 50% overall yield. The conditions used in the direct arylation step display the power of this transformation, which would have been difficult to achieve using other direct arylation methodology previously developed by our group.

Chapter 3

Introduction

3.1 Site-Selectivity in Direct Arylation

The construction of biaryl molecules via metal-catalyzed processes has become of significant interest to chemists as of late, due in part to their prevalence in pharmaceutical compounds. While the issue of regioselectivity in biaryl cross coupling has traditionally been addressed by pre-activating both coupling partners, direct arylation has begun to emerge as an efficient alternative. Unfortunately regioselective control has yet to be fully mastered due in part to the presence of multiple C-H bonds that can serve as potential reaction sites. As well, the traditional reactive properties of a molecule do not always correlate to the site of reactivity, compounding the difficulty of predicting reaction regioselectivity. For example, Sames and co-workers reported that the palladium-catalyzed arylation of SEM-protected pyrazole **3.1** occurred predominantly at C-5, the most acidic C-H bond (Scheme 3.1).[41] On the other hand, Zhang *et al.* reported that the arylation of indole **3.5** occurred exclusively at the more nucleophilic C-3 position when the POPd pre-catalyst **3.7** was employed (Scheme 3.1).[42] As these two reports demonstrate, selectivity is not always directly related to the reactive properties of a substrate. Thus a more comprehensive understanding of all the factors that govern a direct arylation reaction will improve our ability to reliably predict regioselectivity. In this chapter, an examination of recent advances in site selective direct arylation will be presented.

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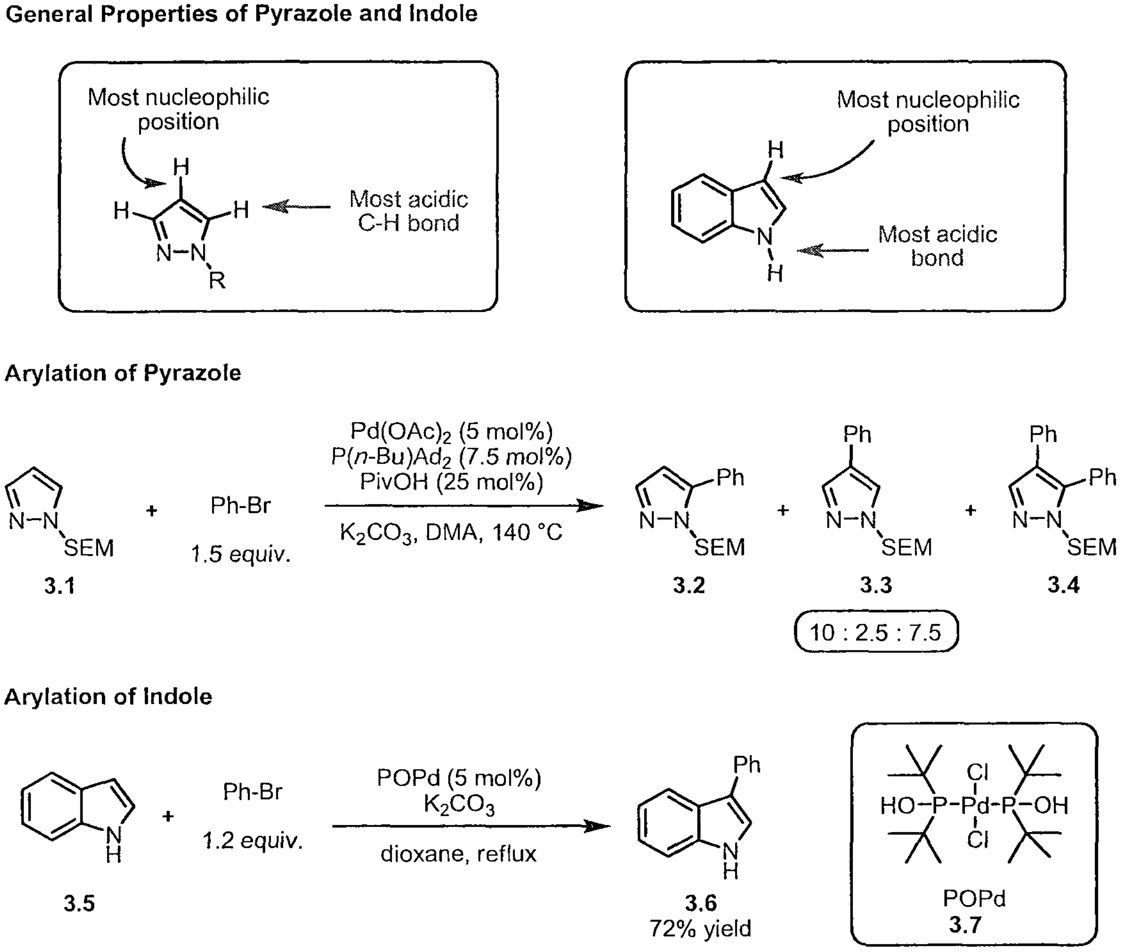
[41] Goikhman, R.; Jacques, T. L.; Sames, D. *J. Am. Chem. Soc.* **2009**, *131*, 3042.

[42] Zhang, Z.; Hu, Z.; Yu, Z.; Lei, P.; Chi, H.; Wang, Y.; He, R. *Tetrahedron Lett.* **2007**, *48*, 2415.

Scheme 3.1 **Direct arylation of pyrazole and indole.**



3.2 Directing Group-Controlled Arylation

The first type of site selective arylation that will be examined involves reactions directed by a functional group present on the substrate.[43] These directing groups rely on the lone pairs of heteroatoms to chelate the catalyst, allowing it to react at a specific C-H bond (Scheme 3.2). An examination of the various directing groups that influence the regioselectivity of metal-catalyzed arylation reactions will be presented. Currently, a large majority of directed reactions involve the use of palladium or ruthenium as the catalyst, with sporadic reports of success using rhodium and iron. While non-chelating

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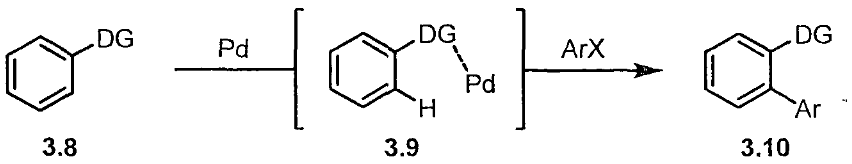
[43] For recent reviews on directing group-controlled arene arylation see: (a) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (b) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074.

functional groups, such as alkyls,[44] have also been reported to influence selectivity, they will not be addressed in this review.

Scheme 3.2 **Overview of a directed arylation reaction showing catalyst complexation.**



3.2.1 Palladium-Catalyzed Directed Arylation

Palladium is the most studied of any metal in direct arylation and has been shown to catalyze a large variety of reactions. Due to the privileged nature of this metal, there has been an overwhelming number of publications and reviews that highlight its synthetic usefulness.[2,43,45] The following section will therefore outline selected recent work involving the use palladium in directing group-controlled arylation and is not meant to be a comprehensive review of the field.

3.2.1.1 Amine-Directed Reactions

Palladium-catalyzed arylations can be directed by primary amines. The Daugulis group reported a procedure in which substituted benzamines **3.11** could be arylated with aryl iodides in both *ortho* positions (Scheme 3.3).[46] A large excess (10 equivalents) of aryl iodide was required for the reaction to proceed smoothly, and only alkyl and halide substitutions on the arene were examined. As the arylated products were found to be a mixture of amines and amides, trifluoroacetic anhydride was added to facilitate isolation with arylated benzamides **3.12** being isolated in good yield. A control reaction with benzamide **3.13** provided no product, confirming that the reaction was not directed by the amide.

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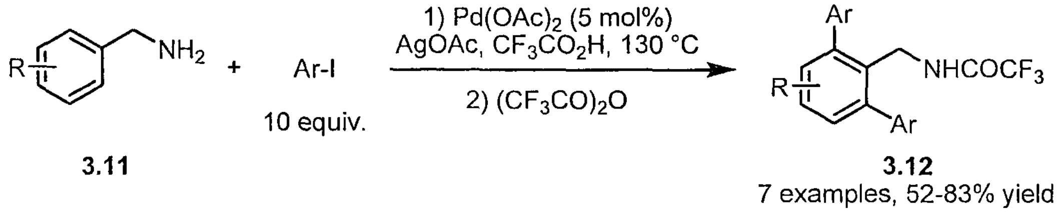
[44] (a) Dyker, G. *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 1023. (b) Dyker, G. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 103.

[45] For more recent reviews on direct arylation see: (a) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem. Int. Ed.* **2009**, *48*, 9792. (b) McGlacken, G. P.; Bateman, L. M. *Chem. Soc. Rev.* **2009**, *38*, 2447. (c) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2009**, *48*, 5094.

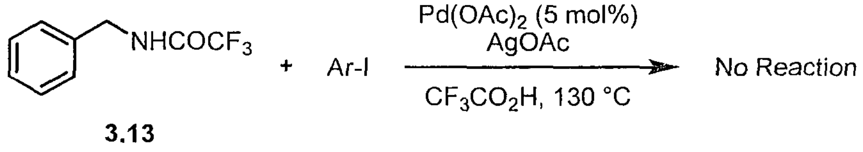
[46] Lazareva, A.; Daugulis, O. *Org. Lett.* **2006**, *8*, 5211.

Scheme 3.3 **Arylation of benzamines with aryl iodides.**

Reaction Conditions



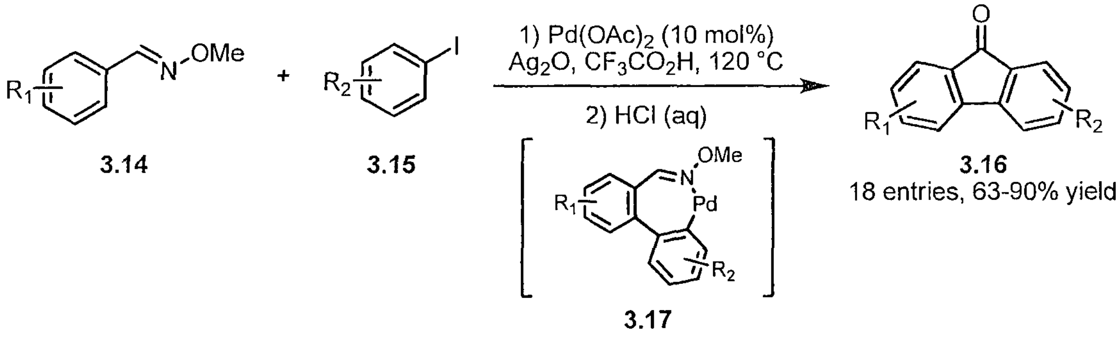
Control Reaction



3.2.1.2 Imine-Directed Reactions

Oxime ethers have also been shown to direct palladium-catalyzed direct arylations. Cheng and co-workers have developed a novel synthesis of substituted fluorenones **3.16** *via* a tandem intermolecular-intramolecular coupling process (Scheme 3.4).[47] Substituted oxime ethers **3.14** could direct the *ortho* arylation of aryl iodides **3.15**, followed by a second directed intramolecular C-H insertion via palladacycle **3.17**. The desired fluorenone could be obtained in good yield upon hydrolysis. The reaction was compatible with electron-neutral and electron-deficient substituents, though compatibility with electron-rich groups is unknown.

Scheme 3.4 **Synthesis of fluorenones from oxime ethers.**



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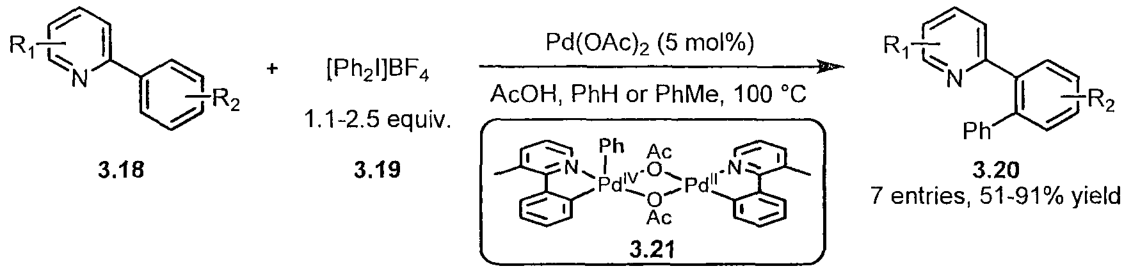
[47] Thirunavukkarasu, V. S.; Parthasarathy, K.; Cheng, C.-H. *Angew. Chem. Int. Ed.* **2008**, *47*, 9462.

3.2.1.3 Heterocycle-Directed Reactions

3.2.1.3.1 Reactions Directed by Pyridine

The use of pyridines in directed oxidative arylations has become prominent recently. The Sanford group has used 2-arylpyridines such as **3.18** extensively, and have found that they can be coupled with aryl iodonium reagents such as **3.19**, in the presence of palladium acetate (Scheme 3.5).[48] Exclusive monoarylation was observed, including reactions with *meta-* and *para*-substituted substrates. Lactams and amides could also direct the reaction. An extensive mechanistic study was conducted[48b] and bimetallic Pd(II)/Pd(IV) species **3.21** was discovered as a key intermediate.

Scheme 3.5 **Oxidative arylation of 2-arylpyridines with idodine(III) salts.**



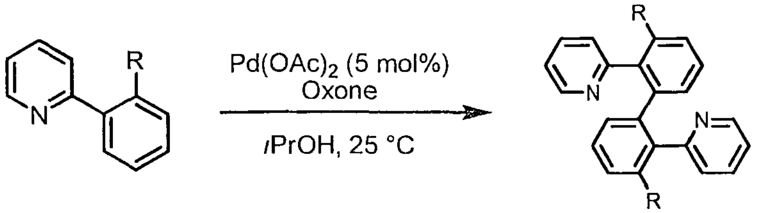
The oxidative *ortho*-directed homocoupling of 2-arylpyridines **3.22** has also been reported by Sanford *et al.* (Scheme 3.6).[49] Oxone was selected as the oxidizing agent. While the reaction scope was small, homocoupled products **3.23** could be isolated in good to excellent yields. Additionally, this reaction occurred readily at room temperature, which is unusual for direct arylation.

---

[48] (a) Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 7330. (b) Deprez, N. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 11234.

[49] Hull, K. L.; Lanni, E. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 14047.

Scheme 3.6 **Oxidative homocoupling of 2-arylpyridines.**

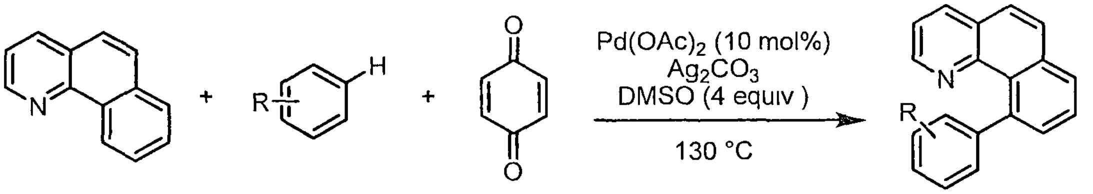


3.22

3.23
5 examples, 41-86% yield

Sanford has also reported the oxidative coupling of benzo[*h*]quinoline **3.24** with simple arenes **3.25**, relying on benzoquinone **3.26** as an oxidizing agent (Scheme 3 7).[50] The addition of DMSO to the reaction mixture was thought to help slow catalyst decomposition[51] The reaction scope focused primarily on disubstituted arenes and generally provided only one regioisomer in high yield When arylation was forced to occur *ortho* to another group, yields were severely affected due to steric hindrance

Scheme 3.7 **Oxidative coupling of benzo[*h*]quinoline and simple arenes.**



3.24

3.25
65-100 equiv

3.26
0 5 equiv

3.27
12 entries, 5-93% yield

Acyl peroxides have also been shown to be effective coupling partners by Yu and co-workers[52] Various 2-arypyridines **3.28** could be connected to with aryl acylperoxides **3.29** in satisfactory yields when in the presence of catalytic amount of palladium acetate (Scheme 3 8) Only electron deficient aryl acylperoxides were compatible with the reaction A radical mechanism was presumed to be at work, and was supported by the observation of decreased yields when a radical scavenger is present

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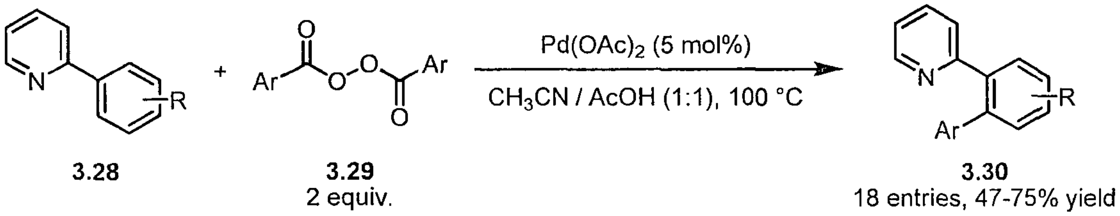
[50] Hull, K L , Sanford, M S *J Am Chem Soc* **2007,** *129,* 11904
[51] Steinhoff, B A , Stahl, S S *J Am Chem Soc* **2006,** *128,* 4348
[52] Yu, W -Y , Sit, W N , Zhou, Chan, A S -C *Org Lett* **2009,** *11,* 3174

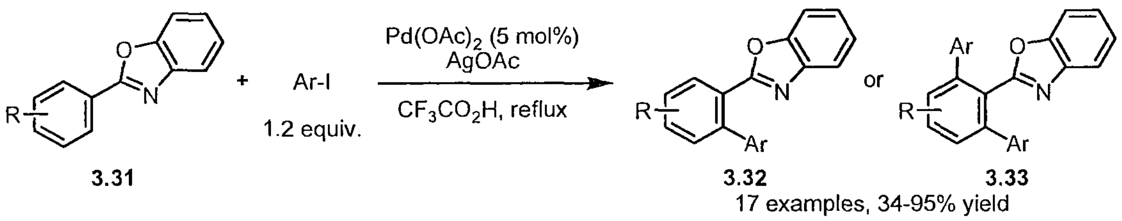
Scheme 3.8 **Decarboxylative arylation using aryl acylperoxides.**



3.2.1.3.2 Reactions Directed by Other Heterocycles

The use of benzoxazoles as directing groups has been demonstrated by Wu and co-workers.[53] Several 2-arylbenzoxazoles **3.31** were found to direct the coupling of aryl iodides to afford mono- and diarylated products **3.32** and **3.33** respectively (Scheme 3.9). Yields were generally lower when electron-deficient iodides were employed. A large excess of iodide was required for the reaction to proceed efficiently and consequently, almost 5 equivalents of silver acetate were required to achieve synthetically useful yields.

Scheme 3.9 **Directed arylation of 2-arylbenzoxazoles.**



3.2.1.4 Carbonyl-Directed Reactions

3.2.1.4.1 Aldehyde-Directed Reactions

The efficiency of N-heterocyclic carbene ligands in palladium catalysis has been demonstrated by Doğan *et al.* in the coupling of aryl chlorides and substituted benzaldehydes **3.34** (Scheme 3.10).[54] Three different 1,3-dialkylbenzimidazolium chlorides **3.35** could be used in conjunction with low catalyst loadings of palladium acetate to facilitate the synthesis of arylated benzaldehydes **3.36** in excellent yields.

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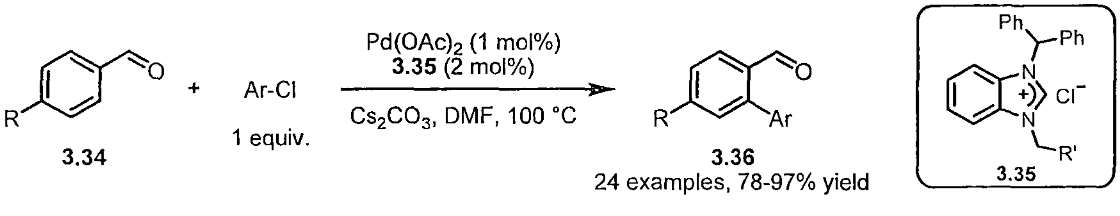
[53] Yang, F.; Wu, Y.; Zhu, Z.; Zhang, J.; Li, Y. *Tetrahedron* **2008**, *64*, 6782.

[54] Doğan, Ö.; Gürüz, N.; Özdemir, İ.; Çetinkaya, B. *Heteroatom Chem.* **2008**, *19*, 569.

Reaction scope focused primarily on alkyl-substituted benzaldehydes and the scope of aryl chlorides was also limited.

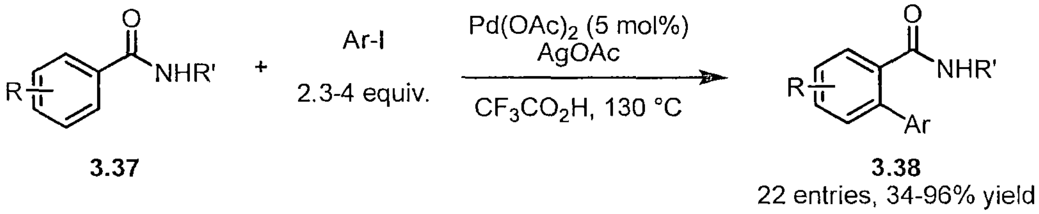
Scheme 3.10 **Palladium-NHC-catalyzed arylation of aryl aldehydes with aryl chlorides.**



3.2.1.4.2 Reactions Directed by Amides

The Daugulis group has studied benzamides extensively as substrates in directed arylation.[55] In one publication, substituted anilides **3.37** could be *ortho* coupled with various aryl iodides (Scheme 3.11).[56] No ligand was required and exclusive monoarylated **3.38** was observed. Arylated products could also be isolated and resubmitted to the reaction conditions in the presence of a different aryl iodide to afford unsymmetrical 2,6-diarylated benzamides as well.

Scheme 3.11 Ortho-**arylation of benzamides with aryl iodides.**



Organometallic reagents are also capable of participating in the directed arylation of anilides. Shi and co-workers have developed procedures for the arylation of alkylated acetanilides **3.39** with aryl boronic acids,[57] and free N-H acetanilides **3.41** with aryl silyl ethers[58] (Scheme 3.12). The electronic nature of the organometallic did not have a deleterious effect on reaction outcome. In both cases copper(II) was used to reoxidize the

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[55] For a review of the recent work published by the Daugulis group see: Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074.

[56] (a) Shabashov, D.; Daugulis, O. *Org. Lett.* **2006**, *8*, 4947. (b) Shabashov, D.; Daugulis, O. *J. Org. Chem.* **2007**, *72*, 7720.

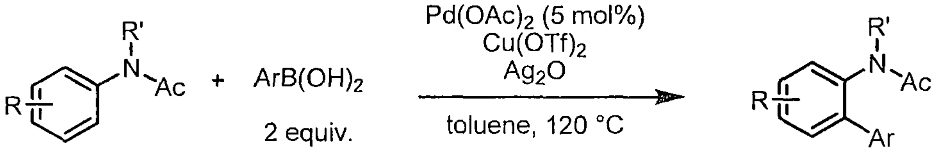
[57] Shi, Z.; Li, B.; Wan, X.; Cheng, J.; Fang, Z.; Cao, B.; Qin, C.; Wang, Y. *Angew. Chem. Int. Ed.* **2007**, *46*, 5554.

[58] Yang, S.; Li, B.; Wan, X.; Shi, Z. *J. Am. Chem. Soc.* **2007**, *129*, 6066.

catalyst after a turnover. The addition of a silver additive was also required in order for acceptable yields to be achieved.

Scheme 3.12 **Arylation of acetanilides with boron and silicon reagents.**

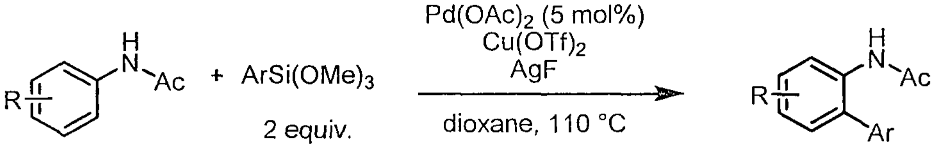
Arylation with Boronic Acids



3.39 **3.40**

22 entries, 20-92% yield

Arylation with Silyl Ethers

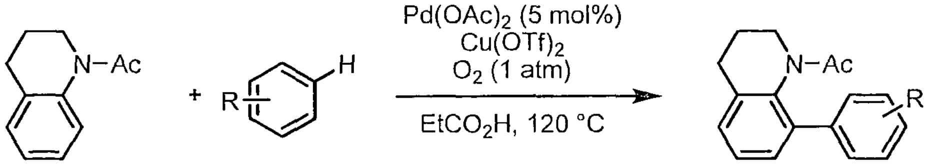


3.41 **3.42**

18 entries, 33-80% yield

The Shi group later improved their methodology, dispatching the need for organometallic reagents and instead replacing them with simple arenes.[59] *N*-Acetyl tetrahydroquinoline **3.43** was capable of being coupled with various substituted arenes **3.44** (Scheme 3.13). There was no need for silver additives and molecular oxygen could be used as the terminal oxidant. Arene scope was mostly limited to alkyl substitutions, and 6 to 37 equivalents were required.

Scheme 3.13 **Oxidative arylation of acetanilides with simple arenes.**



3.43 **3.44** **3.45**

large excess

8 examples, 43-78% yield

Further contribution to the oxidative coupling of anilides **3.46** was made by Buchwald and co-workers (Scheme 3.14).[60] Electron-neutral and electron rich arenes **3.47** could be used as coupling partners to provide *ortho*-arylated anilides **3.48** in good to

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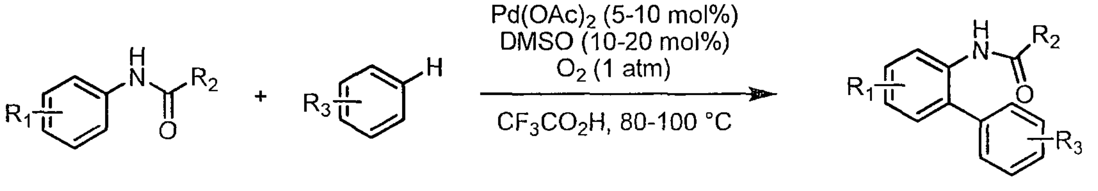
[59] Li, B.-J.; Tian, S.-L.; Fang, Z.; Shi, Z. *Angew. Chem. Int. Ed.* **2008**, *47*, 1115.

[60] Brasche, G.; García-Fortanet, J.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 2207.

excellent yields. One distinct advantage of this methodology was the use of molecular oxygen without the presence of metal co-oxidants. The addition of small amounts of DMSO to the reaction helped prevent catalyst degradation.

***Scheme 3.14 Ortho*-arylation of anilides with simple arenes.**



3.46

3.47
4-11 equiv.

3.48
18 examples, 59-94% yield

3.2.1.4.3 Reactions Directed by Carboxylic Acids

The Daugulis group has also described the directed arylation of benzoic acids **3.49** with aryl iodides and aryl chlorides using two distinct methodologies (Scheme 3.15).[61] Aryl iodides required only the presence of the palladium catalyst and a silver additive for reactivity to occur, though isolated yields were disappointing and did not enter the 70% range. Reactivity with aryl chlorides relied on the presence of a bulky, electron-rich phosphine ligand and a carbonate base and isolated yields were much higher when compared to aryl iodides. In both cases only electron-deficient and electron-neutral aryl halides were examined as coupling partners.

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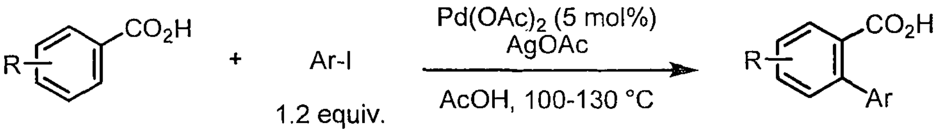
[61] Chiong, H. A.; Pham, Q.-N.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 9879.

Scheme 3.15 ***Ortho*** **arylation of benzoic acids with aryl iodides and chlorides.**

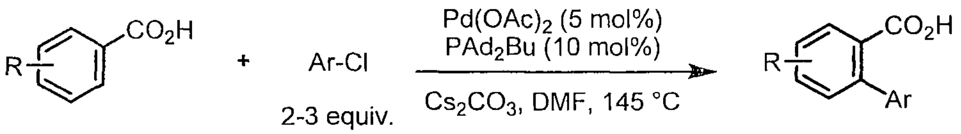
Arylation with Aryl Iodides



3.49

3.50
6 entries, 55-69% yield

Arylation with Aryl Chlorides

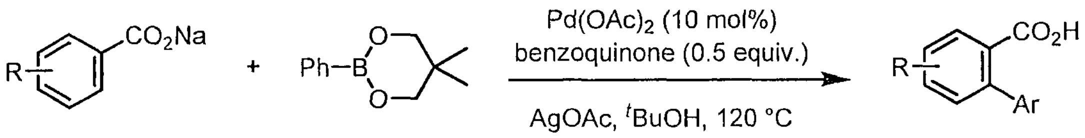


3.49

3.51
14 entries, 65-91% yield

Aryl boron reagents have also found a use in benzoic acid arylation. Yu *et al.* reported a sequence for the arylation of sodium benzoates **3.52** with phenylboronate **3.53** in the presence of catalytic palladium and an oxidant (Scheme 3.16).[62] While yields were unspectacular and the scope limited, methylboronic acid was also compatible with the conditions allowing for the *ortho* methylation of benzoates.

Scheme 3.16 **Directed oxidative arylation of sodium benzoates.**



3.52 **3.53** **3.54**
4 entries, 40-63% yield

Expanding on their previous methodology, the Yu group published an improved benzoic acid arylation procedure.[63] Aryltrifluoroborates **3.56** and benzoic acids **3.55** or arylacetic acids **3.58** could be coupled using palladium acetate and molecular oxygen as the oxidant (Scheme 3.17). It was noted that 20 atmospheres were required to reduce reaction times, but reactions could still proceed at one atmosphere. Both electron-rich

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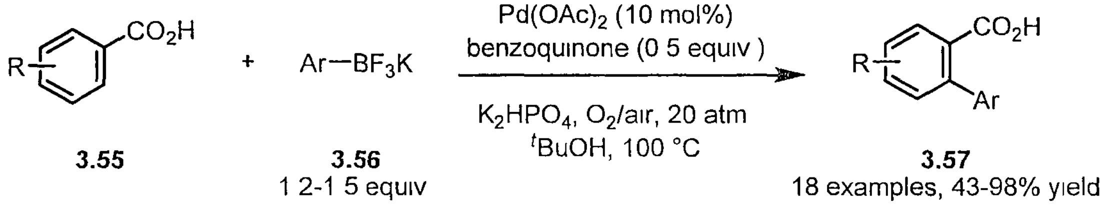
[62] Giri, R.; Maugel, N.; Li, J.-J.; Wang, D.-H.; Breazzano, S. P.; Saunders, L. B.; Yu, J.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 3510.

[63] Wang, D.-H.; Mei, T.-S.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 17676.

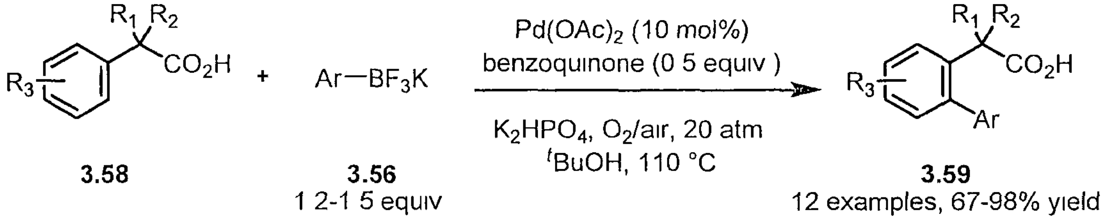
and electron-deficient acids were compatible with the conditions and only monoarylated products were isolated.

Scheme 3.17 **Oxidative arylation of benzoic and arylacetic acids.**

Arylation of Benzoic Acids



Arylation of Arylacetic Acids



3.2.2 Ruthenium-Catalyzed Directed Arylation

3.2.2.1 Imine-Directed Reactions

Ruthenium has become a popular alternative to palladium for directed cross coupling reactions.[64] Imines, though not as prevalent as other functional groups, have been the primary focus in a handful of directed ruthenium-catalyzed arylation procedures. Oi and co-workers have developed conditions for the *ortho* arylation and diarylation of aryl imines **3.60** with aryl bromides (Scheme 3.18).[65] During optimization, it was found that triphenylphosphine provided ideal results when compared to other alkyl phosphines. Generally, excellent yields could be achieved on most substrates, though mixtures of mono- and diarylated products were seen with *para* or mono substituted arenes *Meta*

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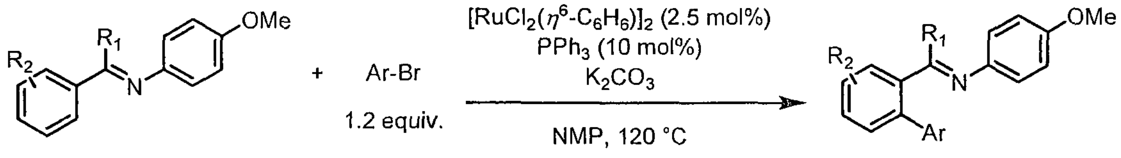
[64] For a recent review on ruthenium in C-H bond arylation see Ackermann, L , Vicente R Ruthenium-Catalyzed Direct Arylations Through C-H Bond Cleavages In *Topics in Current Chemistry, C-H Activation*, Yu, J -Q , Shi, Z , Eds , Springer· Berlin, 2010, Vol 292

[65] Oi, S , Ogino, Y , Fukita, S , Inoue, Y *Org Lett* **2002**, *4*, 1783

substituted arenes showed exclusive monoarylation, but substrates that already contained one *ortho* substitution suffered from poor overall reactivity.

Scheme 3.18 **Ruthenium-catalyzed *ortho* arylation of aryl imines.**

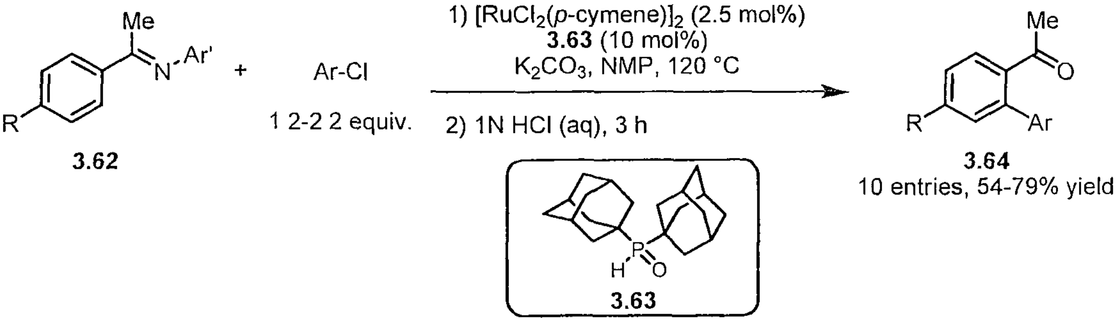


3.60

3.61
15 entries, 17-95% yield

Ackermann has also spent considerable effort examining directed reactions using ruthenium catalysts. Recently, he reported the *ortho* coupling of aryl ketimines **3.62** with aryl chlorides promoted by a ruthenium-phosphine oxide catalyst system (Scheme 3.19).[66] A ligand screen produced adamantyl phosphine oxide derivative **3.63** as the optimal ligand. Mono arylation was seen exclusively, and the reaction was tolerant of both electron-rich and electron-poor aryl chlorides. Substituted aryl ketones **3.64** were isolated as final products in good yields after the arylated ketimines were subjected to hydrolysis. In addition, several 2-arylpyridines were exposed to these conditions and provided excellent yields.

Scheme 3.19 **Synthesis of 2-substituted acetophenones from aryl ketimines.**



10 entries, 54-79% yield

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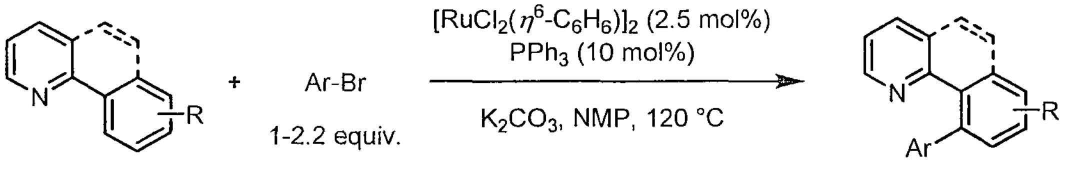
[66] Ackermann, L. *Org. Lett.* **2005**, *7*, 3123.

3.2.2.2 Heterocycle-Directed Reactions

3.2.2.2.1 Reactions Directed by Pyridine

There is widespread use of the pyridyl group to direct ruthenium-catalyzed arylations. One of the first reports was disclosed by Oi *et al.* in 2001.[67,68] Using conditions identical to those that were later used for the arylation of aryl imines (*vide supra*), substituted 2-arylpyridines **3.65** and their derivatives were coupled with an assortment of aryl bromides (Scheme 3.20). While yields were almost always above 65%, the use of 2-bromothiazole and 2-bromopyrimidine resulted in dismal yields of 10% and 17% respectively.

Scheme 3.20 **Ruthenium-catalyzed arylation of 2-arylpyridines.**



3.65

3.66
23 examples, 10-99% yield

The Ackermann group has also studied the application of simple ruthenium compounds for use in directed arylation reactions. Specifically, ruthenium(III) chloride hydrate complexes in the presence of only a carbonate base could catalyze the coupling of 2-phenylpyridine **3.67** with aryl and heteroaryl halides in excellent yields (Scheme 3.21).[69] Electron-deficient aryl bromides generally afforded higher yields than electron-rich coupling partners, with *para* substituted arenes usually providing the best results. The reaction also proceeded efficiently when a 2-oxazolyl group was substituted for the 2-pyridyl group, with 15 examples ranging from 51-80% yield being reported.

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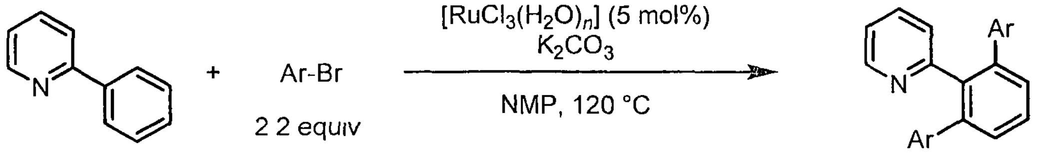
[67] Oi, S.; Fukita, S.; Hirata, N.; Watanuki N.; Miyano, S.; Inoue, Y. *Org. Lett.* **2001**, *3*, 2579.

[68] Oi, S.; Funayama, R.; Hattori, T.; Inoue, Y. *Tetrahedron* **2008**, *64*, 6051.

[69] (a) Ackermann, L.; Althammer, A.; Born, R. *Synlett.* **2007**, 2833. (b) Ackermann, L.; Althammer, A.; Born, R. *Tetrahedron* **2008**, *64*, 6115.

Scheme 3.21 **Ligand-free arylation of 2-arylpyridines with aryl bromides.**



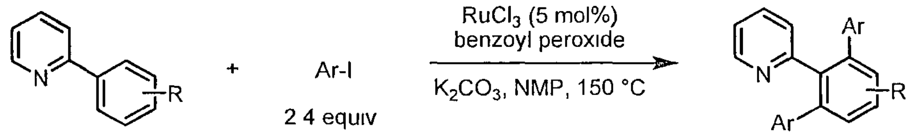
3.67

3.68
12 examples, 45-95% yield

The use of iodides as coupling partners in ruthenium-catalyzed arylations has been problematic. Initially, poor yields were observed when Zhang *et al.* attempted to apply conditions for the coupling 2-arylpyridines with aryl bromides, developed by Ackermann, for use with aryl iodides.[70] Surprisingly, the addition of benzoyl peroxide to the reaction conditions allowed for the transformation to proceed smoothly (Scheme 3.22). Yields were generally above 80%, though substitutions on the aryl iodides were limited to only other halides. Aryl iodonium **3.71** was also compatible with the reaction conditions and only required catalytic amounts of peroxide to achieve excellent yields (Scheme 3.22). It was noted that the omission of peroxide had a deleterious effect, with only 48% yield being observed.

Scheme 3.22 **Peroxide-promoted arylation using aryl iodides.**

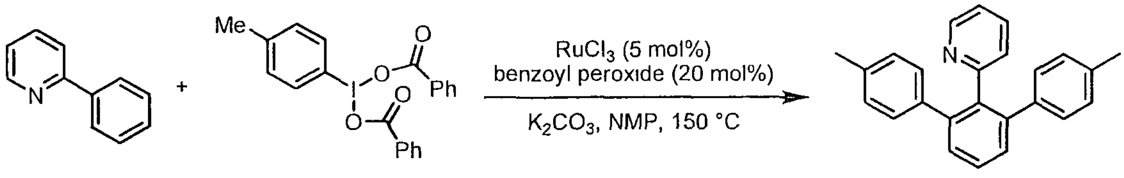
Reaction with aryl iodides



3.69

3.70
11 examples, 43-96% yield

Reaction with an aryliodonium dibenzoate



3.67

3.71

3.72
91% yield

Dixneuf and Požgan performed an extensive examination of the use of 2-halopyridines **3.73** and 2- and 3-halothiophenes **3.76** as coupling partners with 2-

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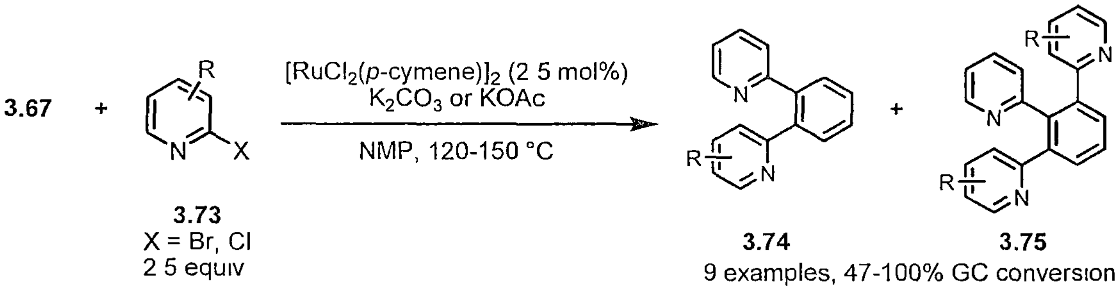
[70] Cheng, K., Zhang, Y., Zhao, J., Xie, C. *Synlett* **2008**, 1325.

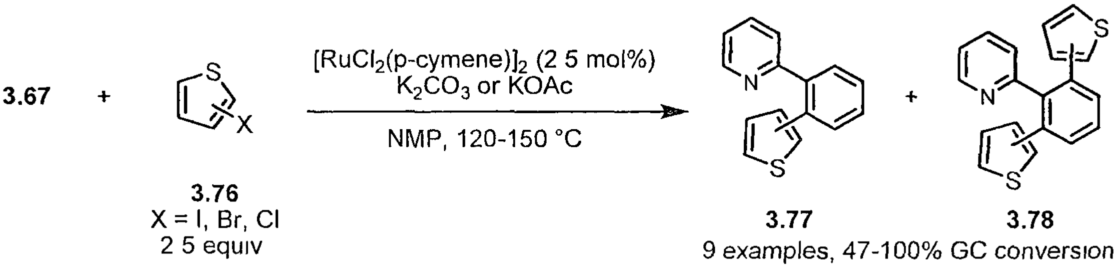
phenylpyridine **3.67** (Scheme 3.23).[71] Bromides usually provided greater yields, though chlorides displayed comparable results. While the choice of base seemed specific to individual substrates for use with 2-halopyridines **3.73**, potassium acetate clearly gave superior results when halothiophenes **3.77** and **3.78** were employed as coupling partners. Only reactions displaying complete conversion were isolated, with the average yield being around 85%.

Scheme 3.23 **Arylation of 2-phenylpyridine with halopyridines and halothiophenes.**

Arylation with 2-halopyridines



Arylation with 2- or 3-halothiophenes



3.2.2.2.2 Reactions Directed By Other Heterocycles

In addition to their work on with 2-arylpyridines, the Oi group has examined the use of 2-arylazoles as potential substrates for ruthenium-catalyzed directed arylations.[68,72] Their previously developed methodology was found to be extendable to 2-arylazoles **3.79** (Scheme 3.24). Both 2-aryloxazolines and 2-arylimidazolines showed proficiency in the ability to direct the *ortho* coupling with various aryl bromides, affording mixtures of both mono- and diarylated products. There was no bias towards the electronic nature of the

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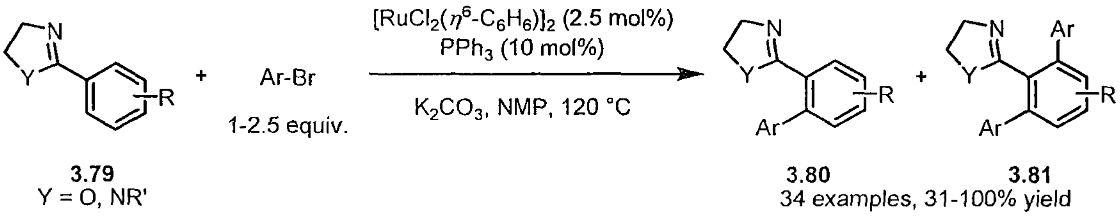
[71] Požgan, F , Dixneuf, P H ; *Adv Synth Catal* **2009**, *351*, 1737

[72] Oi, S , Aizawa, E , Ogino, Y , Inoue, Y *J Org Chem* **2005**, *70*, 3113

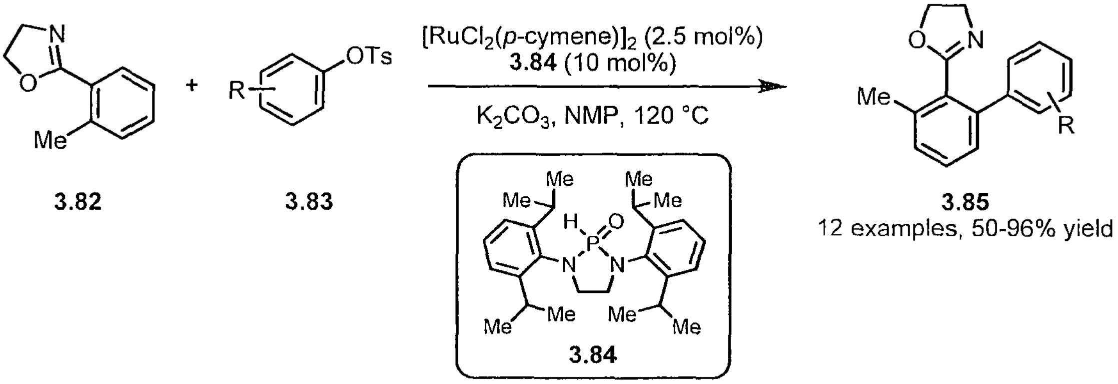
aryl bromide, though steric crowding near the site of coupling resulted in lower yields. Alkenyl bromides were also functional, albeit less reactive coupling partners.

***Scheme 3.24 Ortho* arylation of 2-aryloxazolines and 2-arylimidazolines.**



The use of aryl tosylates in direct arylation is less prominent than traditional halide coupling partners. Ackermann and co-workers have developed an elegant procedure for the arylation of 2-*o*-tolyl-oxazoline **3.82** with aryl tosylates **3.83** (Scheme 3.25).[73] Diamino phosphine oxide **3.84** provided the highest yields during a ligand screen of several phosphine oxides. Electron-deficient tosylates afforded higher yields than their electron-rich counterparts. 2-Arylpyridines also proved to be viable substrates under these conditions.

***Scheme 3.25* Arylation of a 2-aryloxazoline with aryl tosylates.**



Ackermann soon reported an improvement to his earlier procedure with aryl tosylates.[74] With the addition of *p*-tolyl chloride to the reaction conditions, it was found that substituted phenols **3.86** could now participate in the reaction via generation of an aryl tosylate *in situ* (Scheme 3.26). The reaction still showed a preference for electron-

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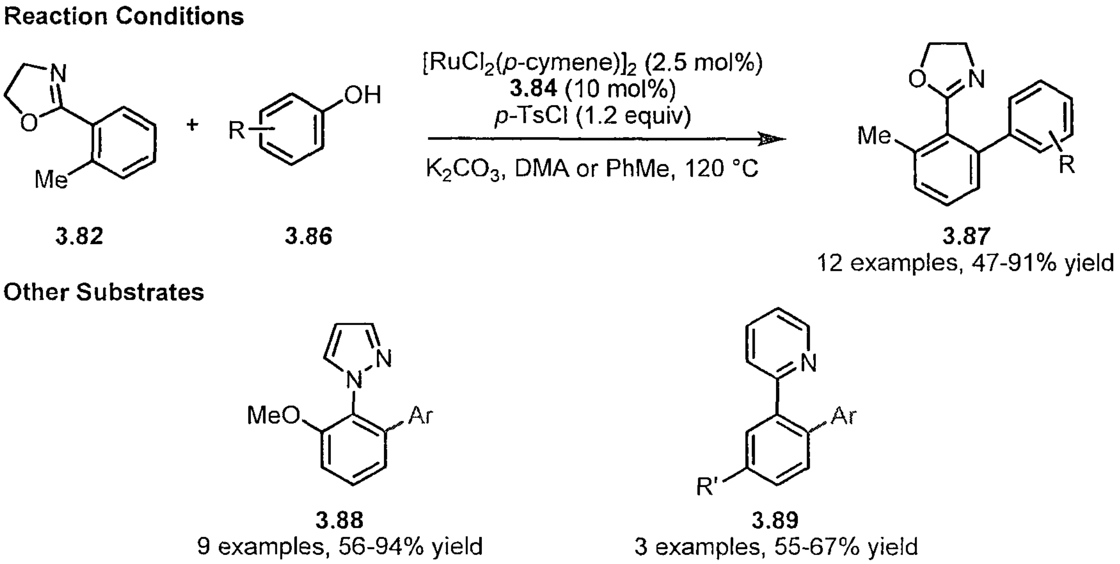
[73] Ackermann, L.; Althammer, A.; Born, R. *Angew. Chem. Int. Ed.* **2006**, *45*, 2619.
[74] Ackermann, L.; Mulzer, M. *Org. Lett.* **2008**, *10*, 5043.

deficient phenols and several groups, including 2-oxanolinyl **3.82**, 1-pyrazolyl **3.88** and 2-pyridyl **3.89** displayed the ability to direct the reaction exclusively at the *ortho* position.

Scheme 3.26 **Ruthenium-catalyzed dehydrative arylation.**



3.82 **3.86** **3.87**
12 examples, 47-91% yield

3.88
9 examples, 56-94% yield

3.89
3 examples, 55-67% yield

Aryl bromides could also be used as coupling partners by replacing diamino phosphine oxide **3.84** with mesitylenecarboxylic acid as a co-catalyst (Scheme 3.27).[75] It has been proposed that the addition of the carboxylic acid helps facilitate hydrogen abstraction by way of 6-membered transition state **3.92**. Aryl triazoles **3.90** underwent coupling and provided excellent yields. Several other heterocycles were also compatible with the reaction conditions.

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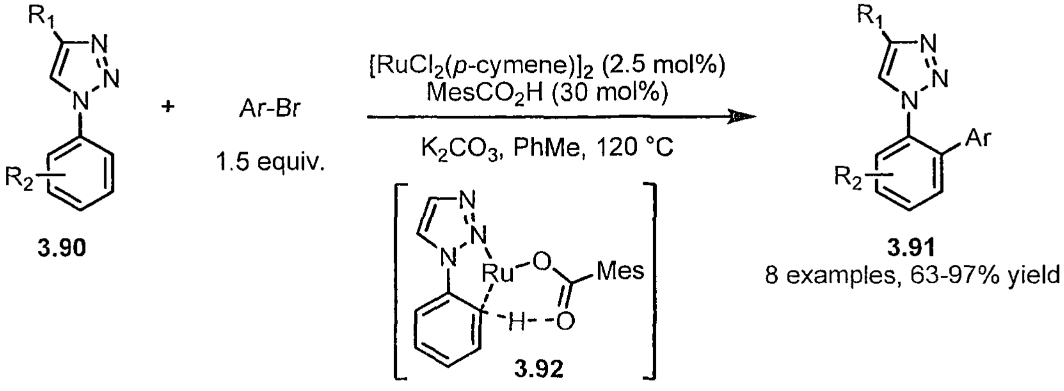
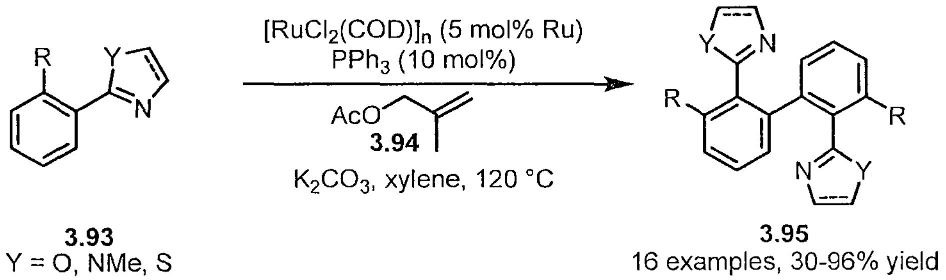
[75] Ackermann, L.; Vicente, R.; Althammer, A. *Org. Lett.* **2008**, *10*, 2299.

Scheme 3.27 **Ruthenium-catalyzed directed arylation using a carboxylic co-catalyst.**



Oi *et al.* have found that the homocoupling 2-arylazoles **3.93** can be mediated by the addition of methallyl acetate **3.94** to their previously developed reaction conditions (Scheme 3.28).[76] In mechanistic studies, it was found that allyl acetates undergo oxidative addition with the catalytically active ruthenium species and help facilitate the transfer of the second unit of 2-arylazole **3.93** onto the catalyst. Though specifics are still unclear, deuterium-labelling studies showed that the hydrogen abstracted from the second molecule of **3.93** ends up on the isobutene by-product.

Scheme 3.28 **Heterocycle-directed homocoupling.**



The Sames group has also published an elegant procedure for the *sp*^{3} arylation of substituted pyrrolidine derivatives **3.96** with aryl boronates **3.97** (Scheme 3.29).[77] Using a ruthenium catalyst and pinacolone as solvent and hydrogen scavenger, arylated pyrrolidine derivatives **3.98** were isolated in good yield, albeit in a mixture of *cis* and *trans* isomers. The *trans* products were preferred by at least a 3:1 ratio. The mechanism of the reaction is presumed to be similar to the one proposed by Kakiuchi (*vide infra*).

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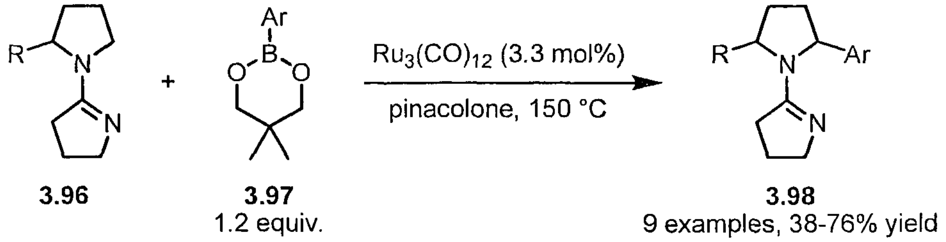
[76] Oi, S.; Sato, H.; Sugawara, S. Inoue, Y. *Org. Lett.* **2008**, *10*, 1823.

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

Scheme 3.29 sp^3 **arylation of substituted pyrrolidines.**



3.2.2.3 Carbonyl-Directed Reactions

The Kakiuchi group reported the use of a ruthenium hydride catalyst for the coupling of aromatic ketones **3.99** with aryl boronates **3.100** (Scheme 3.30).[78,79] Several types of aryl ketones showed reactivity when coupled with phenyl boronate, including acyclic **3.102-3.104** and cyclic **3.105** ketones, and displayed exclusive monoarylation. One exception was acetophenone, which afforded a diarylated product. The reaction also displayed excellent tolerance to both electron-rich and electron–poor aryl boronates, with high yields observed regardless of electronic nature.

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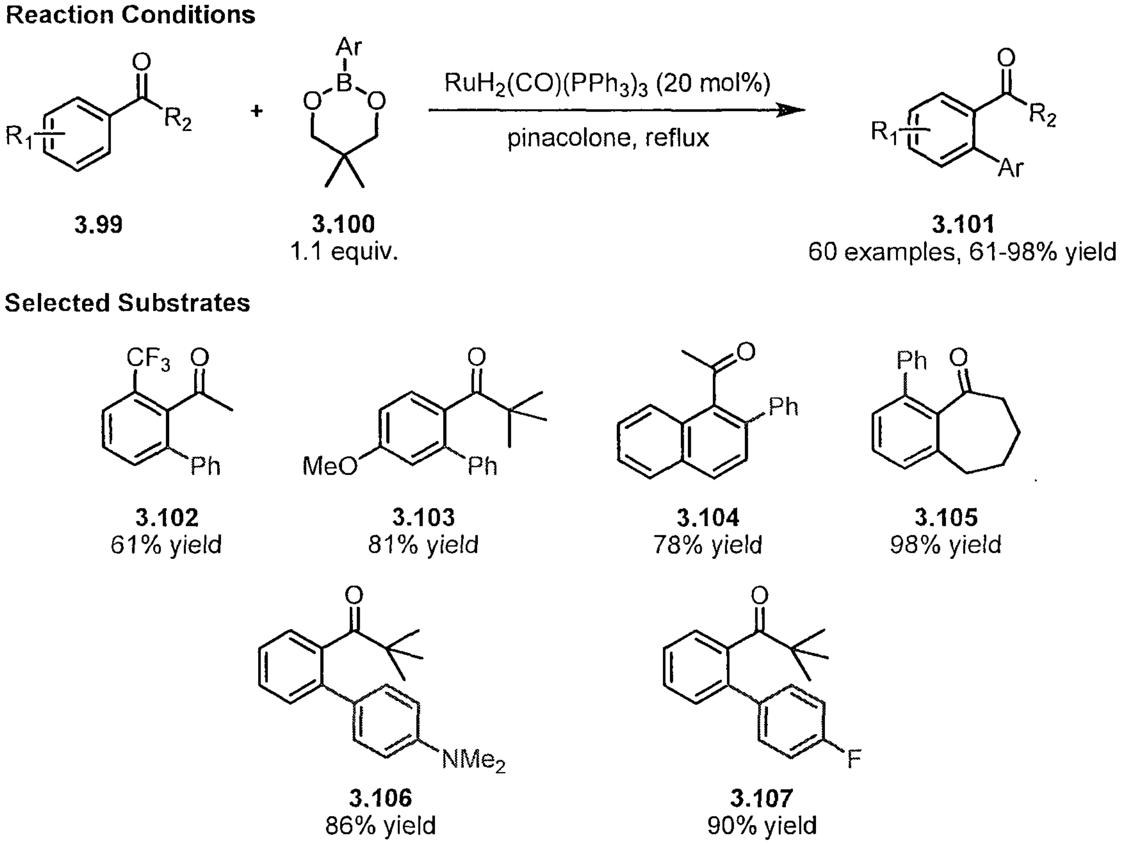
[78] Kakiuchi, F.; Kan, S.; Igi, K.; Chatani, N.; Murai, S. *J. Am. Chem. Soc.* **2003**, *125*, 1698.

[79] Kakiuchi, F.; Matsuura, Y.; Kan, S.; Chatani, N. *J. Am. Chem. Soc.* **2005**, *127*, 5936.

Scheme 3.30 **Ruthenium-catalyzed arylation of aromatic ketones with aryl boronates.**



3.99

3.100
1.1 equiv.

3.101
60 examples, 61-98% yield

3.102
61% yield

3.103
81% yield

3.104
78% yield

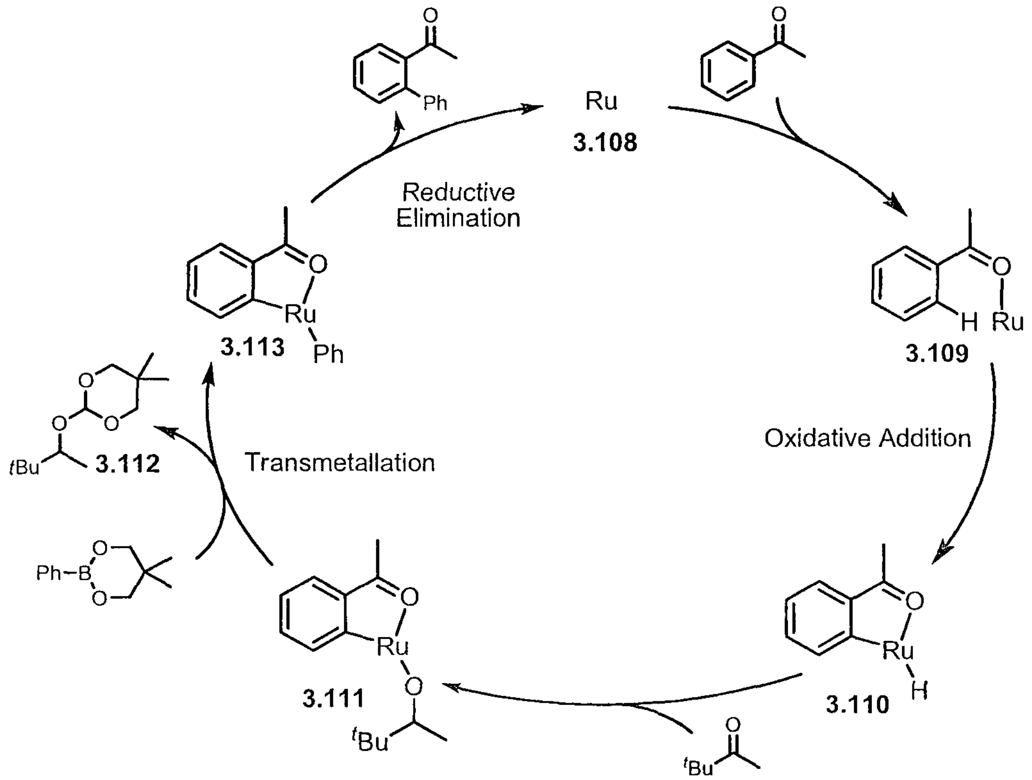
3.105
98% yield

3.106
86% yield

3.107
90% yield

Several mechanistic studies were also performed and a possible mechanism for the transformation was proposed (Scheme 3.31).[79] Ruthenium species **3.108** first undergoes coordination with the ketone carbonyl, followed by insertion into the *ortho* C-H bond to form ruthenacycle **3.110**. Formation of alkoxy-ruthenium complex **3.111** follows by way of transfer of the ruthenium hydrogen to the carbonyl of pinacolone. This intermediate undergoes transmetallation with the aryl boronate to provide ruthenium intermediate **3.113** and trialkoxyborane by-product **3.112**. Reductive elimination provides the *ortho* arylated product and regenerates the active ruthenium catalyst.

Scheme 3.31 **Proposed mechanism for the arylation of aromatic ketones.**



Kakiuchi and co-workers have also applied their methodology to the synthesis of tetraarylanthraquinones **3.115**.[80] Anthraquinone **3.113** could be arylated using various aryl boronates **3.114** in generally good yields when in the presence of a ruthenium catalyst (Scheme 3.32). Surprisingly, the worst reported yield was when simple phenyl boronate was used as a coupling partner. Hexaaylanthracenes were accessible in three steps from the tetraaryl products.

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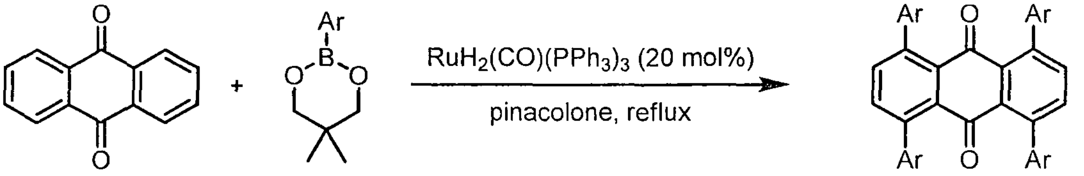
[80] Kitazawa, K.; Kochi, T.; Sato, M.; Kakiuchi, F. *Org. Lett.* **2009**, *11*, 1951.

Scheme 3.32 **Arylation of anthraquinone with aryl boronates.**



3.113

3.114
10 equiv.

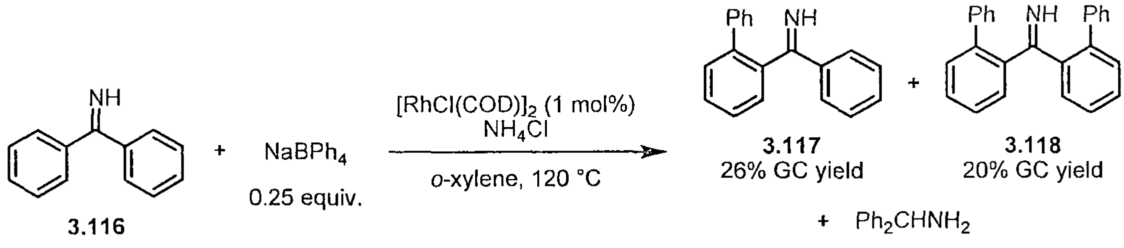
3.115
8 examples, 28-89% yield

3.2.3 Rhodium-Catalyzed Directed Arylation

3.2.3.1 Imine-Directed Reactions

Though there have been fewer publications involving rhodium in direct arylation than with palladium or ruthenium, there have been several recent advances.[81] Miura and co-workers accidentally discovered the use of imines as directing groups while examining the rhodium-catalyzed cross coupling of arylboron reagents with aryl halides.[82] When arylation of 4-chlorobenzonitrile was attempted, a mixture of multiply arylated products was observed. Similar results were obtained when the same reaction was performed on diphenylmethanimine **3.116**, suggesting a common intermediate (Scheme 3.33). While both monoarylated **3.117** and diarylated **3.118** products were obtained, a large amount of imine was reduced to the corresponding amine **3.119**, limiting the synthetic utility of the transformation.

Scheme 3.33 **Rhodium-catalyzed arylation of diphenylmethanimine.**



3.116

3.117
26% GC yield

3.118
20% GC yield

3.119
51% GC yield

---

[81] For recent reviews on rhodium in C-H bond arylation see: (a) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (b) Bouffard, J.; Itami, K. Rhodium-Catalyzed C-H Bond Arylation of Arenes. In *Topics in Current Chemistry; C-H Activation*; Yu, J.-Q.; Shi, Z., Eds.; Springer: Berlin, 2010; Vol. 292.

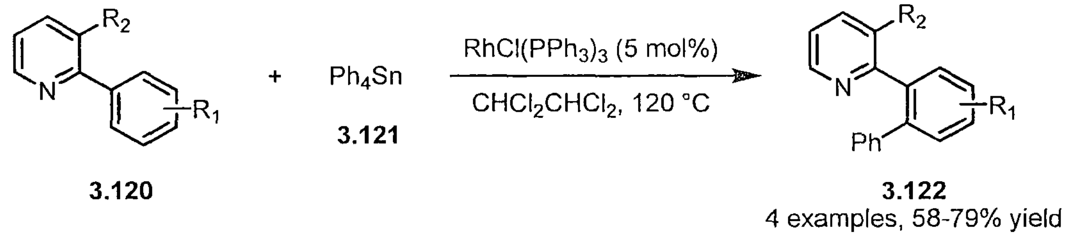
[82] Ueura, K.; Satoh, T.; Miura, M. *Org. Lett.* **2005**, *7*, 2229.

3.2.3.2 Heterocycle-Directed Reactions

3.2.3.2.1 Reactions of 2-Aylpyridines

In 1998, Oi *et al.* reported a methodology for the arylation of substituted pyridylbenzenes **3.120** with tetraphenylstannane **3.121** (Scheme 3.34).[83] Several metals were screened for catalytic activity, including palladium, platinum, iridium and ruthenium, though only rhodium afforded any turnover. Good yields were observed for substrates with various alkyl and aryl substitutions, though functional group tolerance involving heteroatoms was not examined. The lack of a base in the reaction conditions is surprising, and indicates a different mechanistic pathway could be at work when compared to other rhodium-catalyzed arylations of 2-arylpyridines (*vide infra*).

Scheme 3.34 ***Ortho*-arylation of pyridylbenzenes with tetraarylstannanes.**



Several azoles have been shown to act as directing groups in rhodium-catalyzed arylation reactions, with one such report being published by Miura.[84] Various phenylazoles could be mono- or diarylated with sodium tetraphenylborate to give the corresponding products **3.126-3.129** in the presence of a rhodium catalyst, potassium fluoride and ethyl α-chloroacetate (Scheme 3.35). The chloroacetate acts as a hydrogen donor, protecting the imine functionality.[85] In addition to the phenylazoles, azobenzene and 2-phenylpyridine were also compatible substrates under slightly modified conditions.

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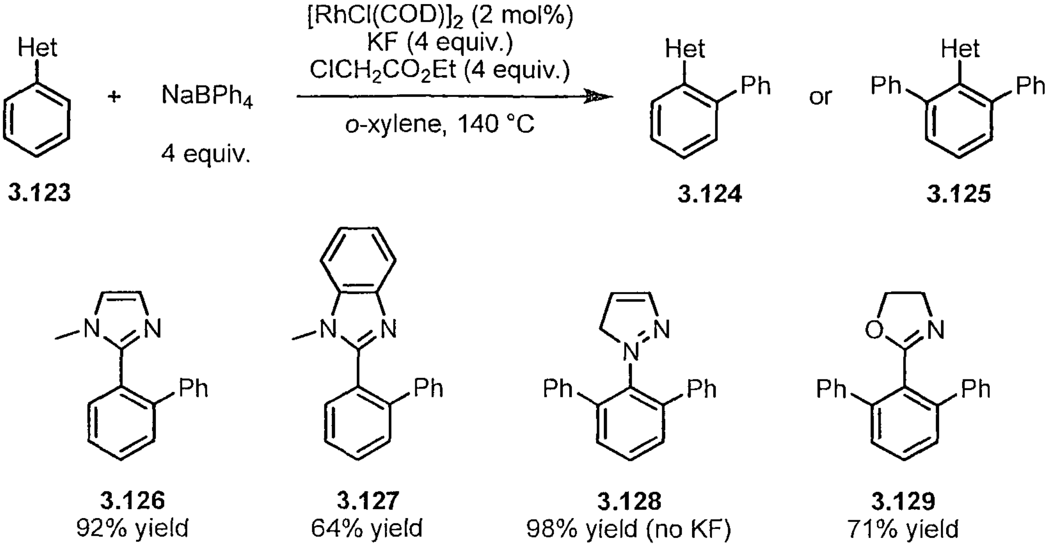
[83] Oi, S.; Fukita, S.; Inoue, Y. *Chem. Commun.* **1998**, 2439.

[84] Miyamura, S.; Tsurugi, H.; Satoh, T.; Miura, M. *J. Organomet. Chem.* **2008**, *693*, 2438.

[85] Du, X.; Suguro, M.; Hirabayashi, K.; Mori, A.; Nishikata, T.; Hagiwara, N.; Kawata, K.; Okeda, T.; Wang, H. F.; Fugami, K.; Kosugi, M. *Org. Lett.* **2001**, *3*, 3313.

Scheme 3.35 **Rhodium-catalyzed arylation of phenylazoles with arylboron reagents.**



3.123 **3.124** **3.125**

3.126 92% yield

3.127 64% yield

3.128 98% yield (no KF)

3.129 71% yield

A unique procedure involving acid chlorides as coupling partners was reported by Zhao and Yu.[86] Benzo[*h*]quinoline **3.24** and other related substrates could be arylated with aroyl chlorides **3.130** using a rhodium catalyst and sodium carbonate in xylene heated to 140 °C (Scheme 3.36). This reaction does not require the presence of a ligand in the conditions. In the case of phenyl(pyridin-2-yl)methanone **3.134**, it is unclear whether the ketone or pyridine functional group is directing the reaction, as the option to form either a 5-membered or 6-membered metallacycle is available. Yu also found that 3-aryl-2-propenoyl chlorides **3.135** could also be used as coupling partners with minor modifications to the reaction conditions (Scheme 3.36).[87] Though yields were somewhat lower on average when compared to aroyl chlorides, the transformation is still synthetically useful.

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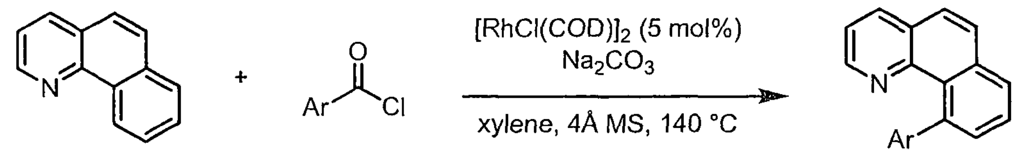
[86] Zhao, X.; Yu, Z. *J. Am. Chem. Soc.* **2008**, *130*, 8136.

[87] Ye, W.; Luo, N.; Yu, Z. *Organometallics* **2010**, *29*, 1049.

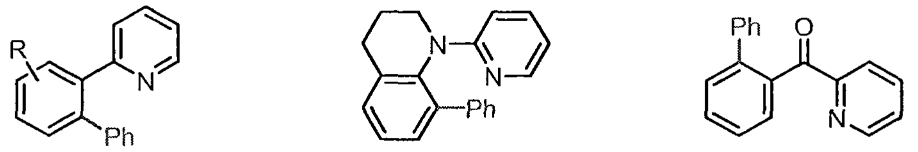
Scheme 3.36 **Directed arylation and alkenylation with acid chlorides.**

Arylation of benzo[*h*]quinoline



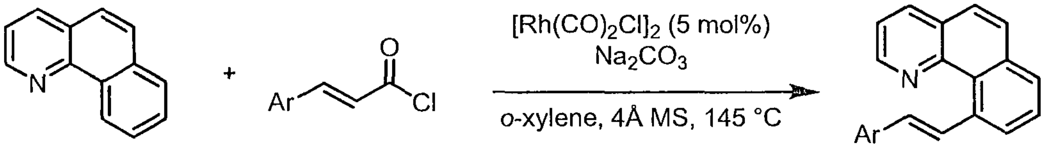
3.24 **3.130** 3 equiv. **3.131** 10 entries, 37-95% yield

Other Substrates



3.132 6 entries, 60-76% yield **3.133** 33% yield **3.134** 54% yield (10% cat.)

Alkenylation of benzo[*h*]quinoline



3.24 **3.135** 3 equiv. **3.136** 14 entries, 30-77% yield

The Chang group has also published their own methodology for the rhodium-catalyzed arylation of benzo[*h*]quinoline **3.24** (Scheme 3.37).[88] The conditions required the presence of both tricyclohexylphosphine and IMes·HCl **3.137** to achieve the greatest yields. Reactions performed during optimization with only one of the two ligands provided poor results. Though the performed reaction scope was small, alkyl and electron-deficient aryl bromides were well tolerated, though lower yields were observed with the electron-rich 1-bromo-4-methoxybenzene. Stoichiometric ^{1}H NMR studies of benzo[*h*]quinoline **3.24** showed almost complete deuterium incorporation at the C10 position (Scheme 3.37). No exchange was observed when either base or catalyst was omitted from the reaction, suggesting that base-assisted proton abstraction is aided by metal coordination similar to rhodium complex **3.139**.

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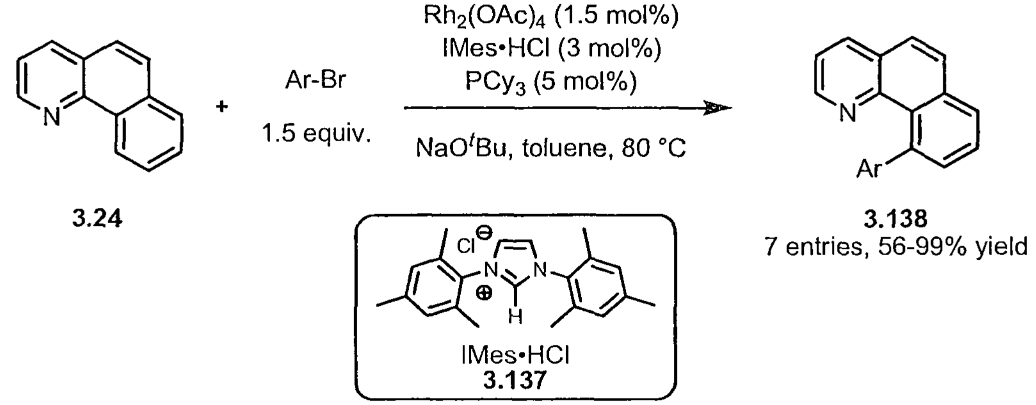
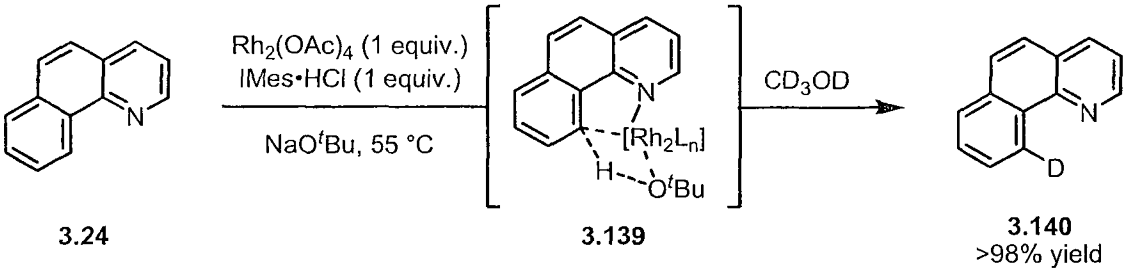
[88] Kim, M.; Kwak, J.; Chang, S. *Angew. Chem. Int. Ed.* **2009**, *48*, 8935.

Scheme 3.37 **Rhodium-NHC-catalyzed arylation of benzo[*h*]quinoline.**

Arylation of benzo[*h*]quinoline



Mechanistic Insight



3.2.3.2.2 Reactions directed by other heterocycles

The first rhodium-catalyzed direct arylation that employed arylboronic acids was developed by Studer and Vogler in 2008.[89] Several 2-aryl pyridines could be coupled with various arylboronic acids in good to excellent yields in the presence of a rhodium complex, a triarylphosphine and an oxidant (Scheme 3.38). For the arylation of 2-(thiophen-2-yl)pyridine **3.143**, it is interesting to note that reaction occurs at the C3 position and not the traditionally more reactive C5 position. One example of arylation directed by an imine was also presented.

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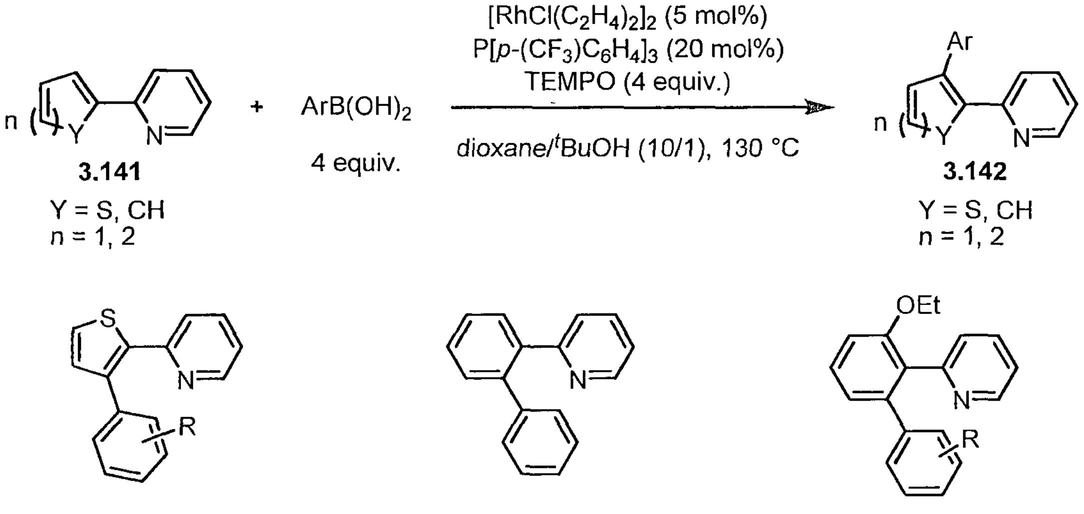
[89] Vogler, T.; Studer, A. *Org. Lett.* **2008**, *10*, 129.

Scheme 3.38 **Oxidative coupling of 2-arylpyridines with arylboronic acids.**



3.141
Y = S, CH
n = 1, 2

3.142
Y = S, CH
n = 1, 2

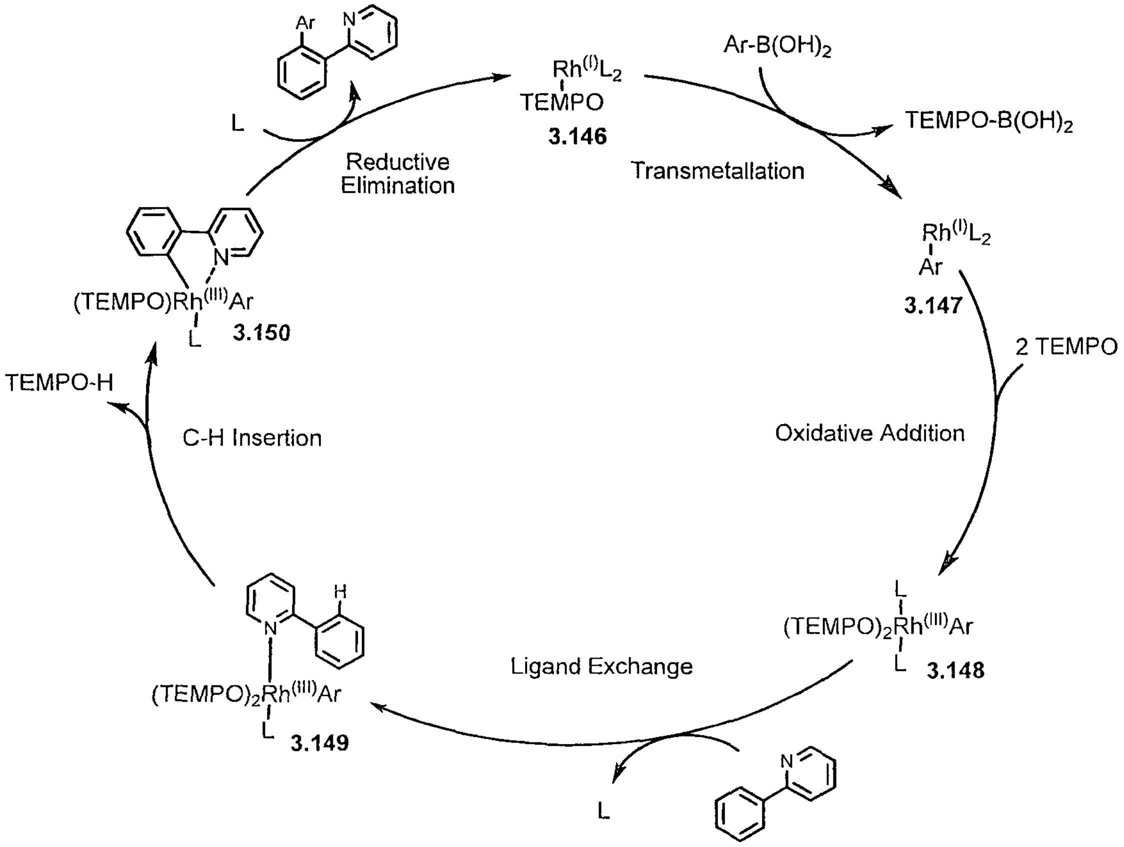
3.143
7 examples, 76-92% yield

3.144
50% mono + 18% di

3.145
7 examples, 57-75% yield

The proposed mechanism first begins with transmetallation of the boronic acid and rhodium(I)TEMPO complex **3.146** to afford the rhodium(I) complex **3.147** (Scheme 3.39). Oxidative addition of two TEMPO molecules provides rhodium(III) species **3.148** which then exchanges a ligand for the 2-arylpyridine. From here, rhodium(III) species **3.149** inserts into an *ortho* C-H bond while generating a molecule of TEMPO-H. Reductive elimination and a ligand exchange regenerates the original rhodium(I) complex **3.146** and affords the arylated product.

Scheme 3.39 **Proposed mechanism for the oxidative directed arylation reaction.**



3.2.3.3 Directed Arylation of Phenols

In 2003, Bedford *et al.* published a procedure for the *ortho* arylation of 2-substituted phenols **3.151** (Scheme 3.40).[90,91] Using Wilkinson's catalyst, both aryl bromides and aryl chlorides could be used as coupling partners, though chlorides suffered from reduced yields. Phosphinite co-catalysts **3.153** were employed, though they have the disadvantage of limiting the reaction scope. Transesterification between the co-catalyst and phenol **3.151** is required for the reaction to proceed, and this results in a mixture of products if the co-catalyst and substrate differ in structure.

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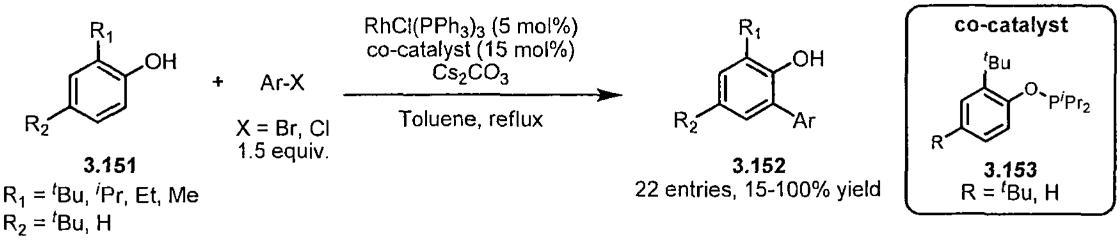
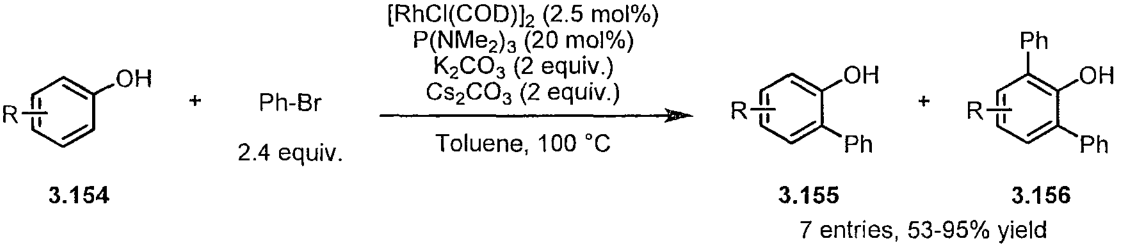
[90] Bedford, R. B.; Coles, S. J.; Hursthouse, M. B.; Limmert, M. E. *Angew. Chem. Int. Ed.* **2003**, *42*, 112.
[91] Bedford, R. B.; Limmert, M. E. *J. Org. Chem.* **2003**, *68*, 8669.

Scheme 3.40 **Intermolecular *ortho* arylation of phenols.**



Soon after, Oi and co-workers reported another methodology for the directed *ortho* arylation of phenols using a rhodium catalyst (Scheme 3.41).[92] Various substituted phenols **3.154** could be arylated in moderate to excellent yield using the optimized conditions, though both mono-arylated **3.155** and diarylated **3.156** products were isolated from the reaction mixture. Surprisingly, optimal conditions required the presence of both potassium and cesium carbonate bases to achieve the highest yields. An almost identical report was published simultaneously by Bedford, with modifications being higher catalyst loadings and the omission of potassium carbonate in the reaction conditions.[91]

Scheme 3.41 **Rhodium-catalyzed arylation of phenols using HMPT as a ligand.**



Bedford and co-workers also contributed to the rhodium-catalyzed arylation of phenols in 2008 with the development of a new catalyst system.[93] To overcome the limitations of their previous work, a chlorophosphine ligand was used instead of their co-catalyst **3.153**. The arylation of 2-*tert*-butylphenol **3.157** with various aryl bromides **3.159-3.163** provided excellent yields and the reaction displayed tolerance for various functional groups (Scheme 3.42). Stoichiometric studies were also performed to help gain insight into the reaction mechanism. When rhodium-chlorophosphine species **3.164** and 2,4-di-*tert*-butylphenol **3.165** were heated in the presence of potassium *tert*-butoxide,

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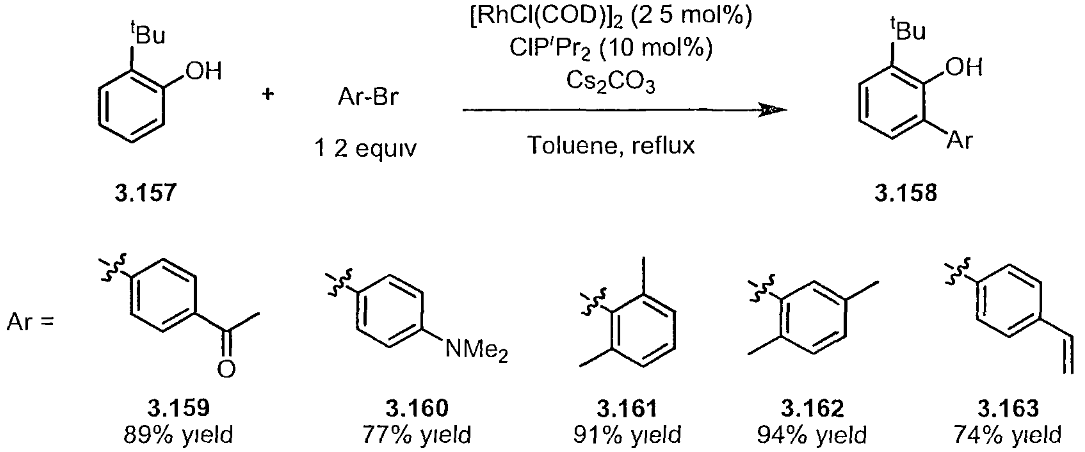
[92] Oi, S.; Watanabe, S.-I.; Fukita, S.; Inoue, Y. *Tetrahedron Lett.* **2003**, *44*, 8665.

[93] Bedford, R. B.; Betham, M.; Caffyn, A. J. M.; Charmant, J. P. H.; Lewis-Alleyne, L. C.; Long, P. D.; Polo-Céron, D.; Prashar, S. *Chem. Commun.* **2008**, *44*, 990.

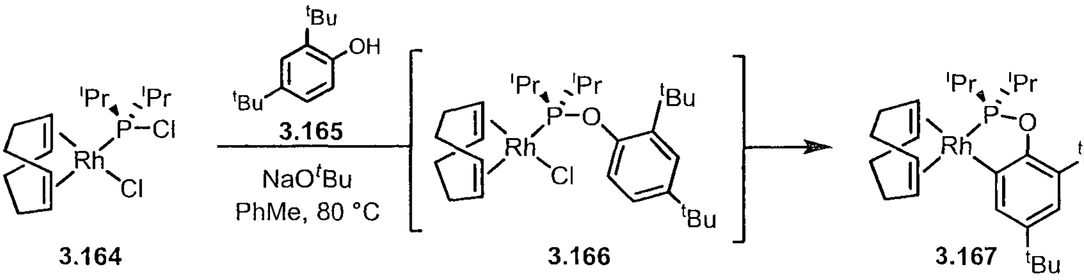
phosphinite complex **3.167** is generated *in situ*. A second equivalent of base was found to be required for C-H insertion to occur, suggesting a base-assisted deprotonation mechanism is at work.

Scheme 3.42 **Arylation of phenols using a rhodium-chlorophosphine catalyst system.**

Reaction Scope



Mechanistic Insight



3.2.4 *Iron-Catalyzed Directed Arylation*

3.2.4.1 *Heterocycle-Directed Reactions*

Very few direct arylation reactions involving iron catalysts have been reported.[94] One example was recently disclosed by Nakamura and co-workers involving the directed arylation of 2-arylazines **3.168** using arylzinc reagents (Scheme 3.43).[95] The presence of

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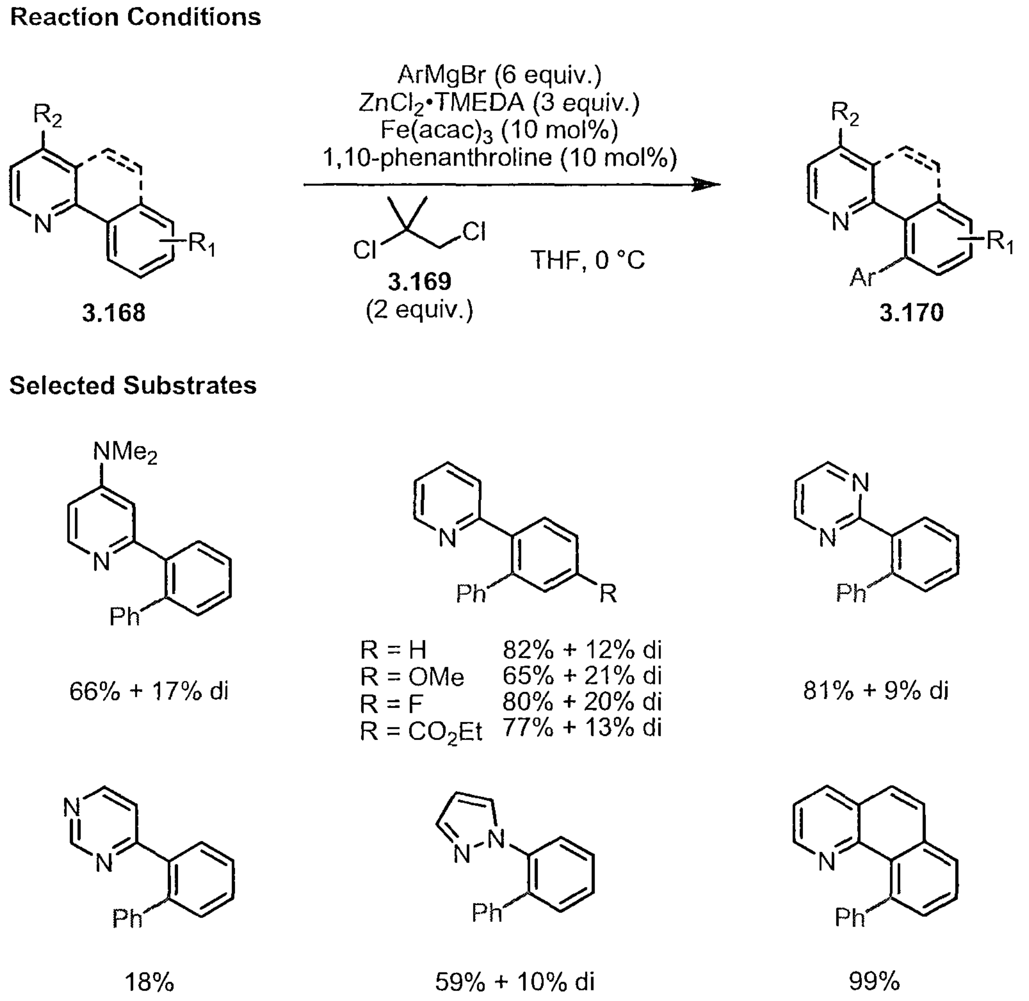
[94] For a review on iron-catalyzed reactions see. Bolm, C ; Legros, J , Le Paih, J , Zani, L *Chem Rev* **2004**, *104*, 6217

[95] Norinder, J , Matsumoto, A , Yoshikai, N , Nakamura, E *J Am Chem Soc* **2008**, *130*, 5858

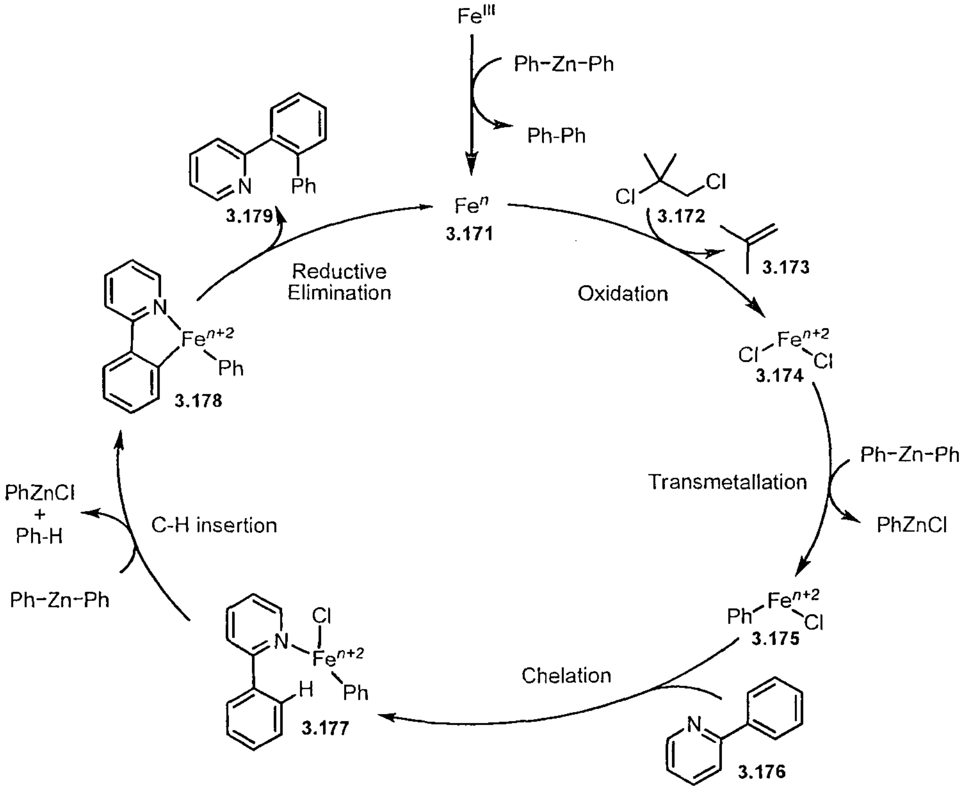
1,2-dichloro-2-methylpropane **3.169**, or similar 1,2-dichloroalkanes, and *N,N,N',N'*-tetramethylethylenediamine (TMEDA) were required as additives. In terms of scope, the reaction was tolerant of both electron-rich and electron-deficient functional groups present on the substrate and showed compatibility with various azines and azoles. Diarylation was observed in most substrates when both *ortho* positions were accessible. Arylmagnesium bromides with electron-rich or electron-poor functional groups were well tolerated, though 2-substituted aryls showed no reactivity, presumably due to steric bulk. Imines were also able to direct the catalyst. The temperature of this reaction should be noted. While most arylation reactions require temperatures in elevation of 100 °C, this methodology proceeds smoothly at 0 °C.

Scheme 3.43 **Iron-catalyzed arylation of 2-arylazines with diarylzinc reagents.**



Mechanistic insight into the reaction was also acquired by Nakamura,[95] and from those studies a plausible catalytic cycle can be proposed (Scheme 3.44). The actual oxidation state of the catalytically-active iron species **3.171** is unknown, but the reaction proceeds with through a similar path to other directed reactions. It was also found that 1,2-dichloro-2-methylpropane **3.172** was readily converted to isobutene **3.173**, most likely oxidizing the catalyst. Similar reactions have also used 1,2-dichloroalkanes as an oxidant.[96] As the initial oxidation state of the iron catalyst was found to have little impact on the reaction, it is possible that the diarylzinc reagent was reducing the iron to the catalytically-active species **3.171**, explaining the observation of a small amount of biphenyl side product. Two equivalents of the arylzinc reagent were found to be required for the reaction to proceed. While one equivalent was required for arylation, deuterium-labelling studies showed that the second equivalent was used to abstract the hydrogen from complex **3.177** during C-H insertion.

Scheme 3.44 **Proposed catalytic cycle for the iron-catalyzed direct arylation reaction.**



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[96] Cahiez, G.; Chaboche, C.; Mahuteau-Betzer, F.; Ahr, M. *Org. Lett.* **2005**, *7*, 1943.

3.3 Catalyst-Controlled Site Selective Arylation

The second type of site selective arylation relies on regioselective control that does not involve physical direction of the catalyst by chelation. In this case, no directing groups are present on the substrate and site selectivity is determined by specific reaction conditions. The focus of this section will be on substrates where multiple individual sites can be arylated selectively through use of the proper reaction conditions. Substrates that only display reactivity at one site will not be covered.

3.3.1 Site-Selective Arylation of Indole

Arylated indoles are a common motif in both natural and pharmaceutical products,[97] and the selective arylation of the indole core presents an interesting academic challenge. As transition-metal-catalyzed reactions have the potential to occur at the N1-, C2-, or C3-positions, indole has become a popular target for developing regioselective reactions.[98] Beyond the academic interest of these transformations, their medicinal uses and subsequent need for chemists to synthesize derivatives of these molecules has helped drive the large amount of research involving the selective arylation of indole. While metal-catalyzed methodologies for the arylation at the N1-position have been developed, such as those by the Buchwald and Hartwig groups, focus will be limited to C-C bond-forming processes occurring at the C2- and C3-positions.

3.3.1.1 Copper-Catalyzed Arylation of Indole

3.3.1.1.1 C2-Selective Reactions

There are very few successful reports on the use of copper in the arylation of indole. One elegant procedure was developed by Gaunt *et al.* in which *N*-acetylindoles could be selectively arylated using diaryl-iodine(III) reagents (Scheme 3.45).[99] Substituted *N*-acetylindoles **3.180** could be arylated with diphenyliodonium triflate in moderate to excellent yields. While most functional groups were well tolerated, the 5-

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[97] Newger, M. *Organic Drugs and Their Synonyms: An International Survey*, 7th ed.; Akademie Verlag: Berlin, 1994.

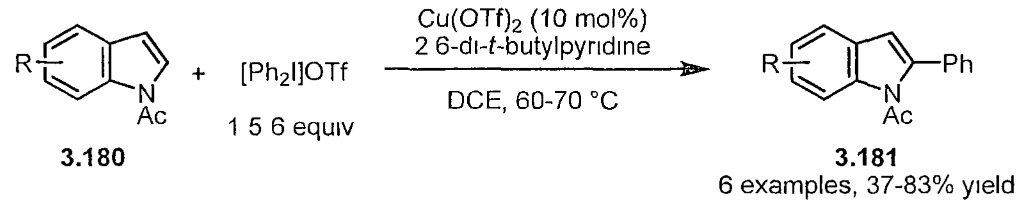
[98] For a recent review on the arylation of indole see: Joucla, L.; Djakovitch, L. *Adv. Synth. Catal.* **2009**, *351*, 673.

[99] Phipps, R. J.; Grimster, N. P.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 8172.

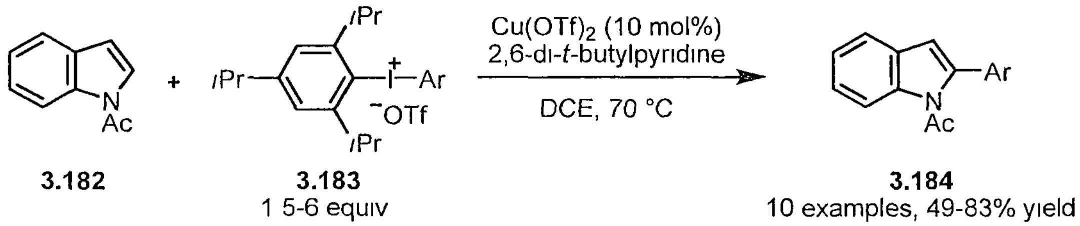
nitro substitution provided disappointing yields The reaction was not completely selective for C2, with C2 C3 ratios ranging from 6 1 to 9 1 *N*-Acetylindole **3.182** was also arylated with various diaryl-iodine(III) reagents **3.183** (Scheme 3 45) The use of the 2,4,6-tri-*iso*propylphenyl group as a large spectator group in **3.183** allowed for the selective transfer of the other attached aryl group The reaction was compatible with many electron-deficient and electron-rich groups, though C2 C3 selectivity, which ranged from 2 6 1 to 7 1, did not appear to be affected by the electronic nature of the aryl group being transferred

Scheme 3.45 **C2 arylation of *N*-acetylindoles with diaryliodonium salts.**

C2-phenylation of substituted *N*-acetylindoles



Cu(II)-catalyzed C2 arylation

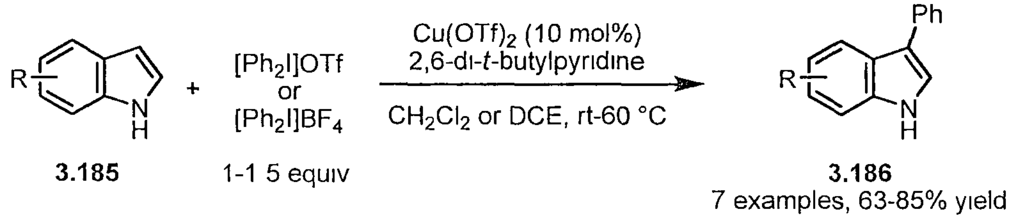


3.3.1.1.2 C3-Selective Reactions

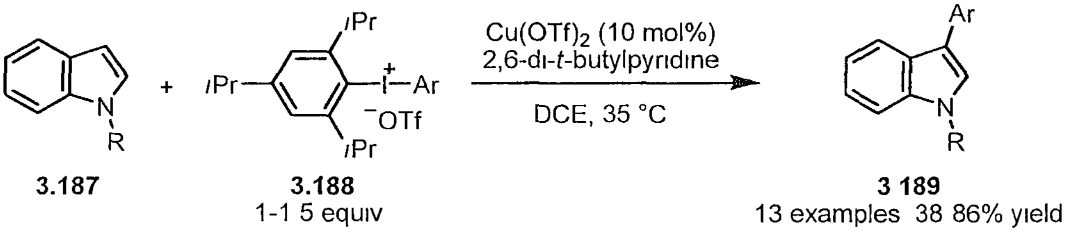
In the same communication, Gaunt also disclosed a procedure for the selective C3 arylation of indoles by changing or simply removing the *N*-acetyl protecting group [99] Substituted free (NH)-indoles **3.185** could be arylated with excellent selectivity for the C3-position (Scheme 3 46) Surprisingly, reactivity could be maintained even at room temperature When diaryl-iodine(III) reagents **3.188** were reacted with free (NH)-indole or *N*-methylindole **3.187**, C3 regioselectivities were substantially higher than for the C2 selective procedures The nature of the group attached to N1 had a significant effect on selectivity, with free (NH)-indole showing C3 C2 selectivities of 10 1 When *N*-methylindole was used, C3 C2 selectivity increased to greater than 20 1 The electronic nature of the aryl group had no deleterious effect on yield and even heteroaryl groups could be used

Scheme 3.46 **C3-arylation of indoles with diaryl-iodine(III) reagents.**

C3-phenylation of substituted indoles



Cu(II)-catalyzed C3 arylation



3.3.1.2 Palladium-Catalyzed Arylation of Indole

Palladium has received by far the most interest of all metals in regards to the arylation of indoles [100] Due to the volume of work published, the following section will attempt to give a general overview of the recent use of palladium in the arylation of the indole core and is not intended to be a comprehensive review

3.3.1.2.1 C2-Selective Reactions

In 2006, Sanford *et al* published a procedure for the selective C2 arylation of free (NH)- and *N*-methylindoles **3.190** with diaryliodonium reagents **3.191** (Scheme 3 47) [101] Using only a palladium-IMes complex in acetic acid, C2-arylated indoles **3.192** could be synthesized in good to excellent yields Most reactions could be carried out at room temperature, though the insolubility of some diaryliodonium salts required the use of higher temperatures C2 C3 selectivities were consistently greater than 20 1

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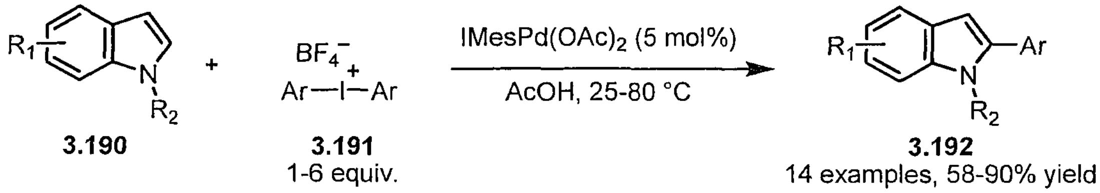
[100] For a recent review on palladium in the arylation of indole see Beck, E M , Gaunt, M J Pd-Catalyzed C-H Bond Functionalization on the Indole and Pyrrole Nucleus In *Topics in Current Chemistry, C-H Activation*, Yu, J -Q , Shi, Z , Eds , Springer Berlin, 2010, Vol 292

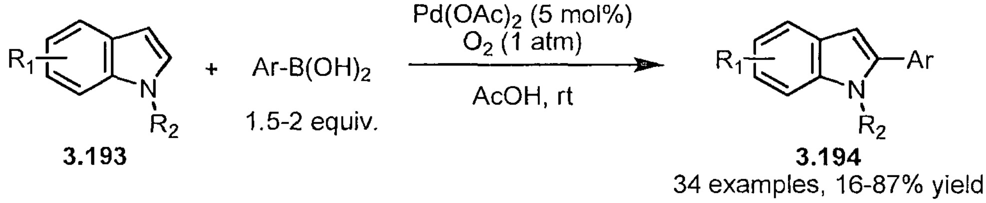
[101] Deprez, N R , Kalyani, D , Krause, A , Sanford, M S *J Am Chem Soc* **2006**, *128*, 4972

Scheme 3.47 **C2-selective arylation of indoles using a Pd-NHC catalyst.**



Aryl boronic acids have been shown to be competent coupling partners. Shi and co-workers recently reported a simple, yet elegant procedure for the C2-arylation of substituted indoles **3.193** (Scheme 3.48).[102] Surprisingly, only palladium acetate under an oxygen atmosphere at room temperature was required to achieve excellent results of C2-arylated indoles **3.194**. While free (NH)- and *N*-methylindoles proved to be competent substrates, *N*-acetylindole provided disappointing yields. The use of electron-rich boronic acids resulted in increased yields though there was also an observed increase in homocoupled arene. Free indoles were also more sensitive to the steric bulk of the aryl boronic acid. Several other electron-rich heterocycles proved to be compatible with the reaction conditions, expanding the scope of this transformation.

Scheme 3.48 **Oxidative C2 arylation of substituted indoles.**



Potassium aryltrifluoroborate salts have also been used as coupling partners in the oxidative arylation of indoles. Zhang and co-workers have developed a procedure, similar to that of the Shi group,[102] that results in the synthesis of C2-arylated indoles **3.196** (Scheme 3.49).[103] Aryl boronic acids could also be used though yields were consistently lower when compared to the trifluoroborate salts. Both free (NH)- and *N*-methylindoles were reactive under the conditions and generally afforded comparable results. Indoles containing electron-deficient functional groups displayed poor reactivity and *N*-acetylindole was unreactive.

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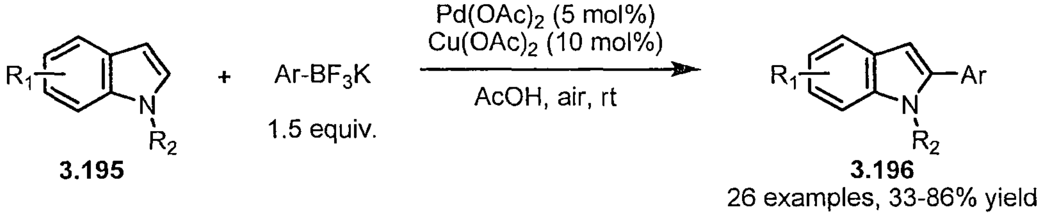
[102] Yang, S.-D.; Sun, C.-L.; Fang, Z.; Li, B.-J.; Li, Y.-Z.; Shi, Z.-J. *Angew. Chem. Int. Ed.* **2008**, *47*, 1473.
[103] Zhao, J.; Zhang, Y.; Cheng, K. *J. Org. Chem.* **2008**, *73*, 7428.

Scheme 3.49 **Arylation of substituted indoles with potassium aryltrifluoroborate salts.**



Another C2 arylation methodology that can be performed at room temperature has been developed by Lebrasseur and Larrosa.[104] Substituted *N*-methylindoles **3.197** were shown to react with aryl iodides through the use of an electron-deficient palladium catalyst (Scheme 3.50). While the electronic nature of the aryl iodide did not have a large impact on yields, sterically hindered *ortho*-substituted aryl iodides were problematic. A plausible explanation for the reactivity observed at room temperature is provided. Following oxidative addition, aryl-palladium(II) complex **3.199** undergoes ligand exchange to generate carboxylate-palladium(II) complex **3.200**. The carboxylate ligand can then dissociate, generating highly electrophilic cationic palladium species **3.201** which can rapidly react with the nucleophilic indole. If no ligand exchange occurs, the more electron-rich palladium species **3.199** should be less reactive, resulting in a slower palladation step.

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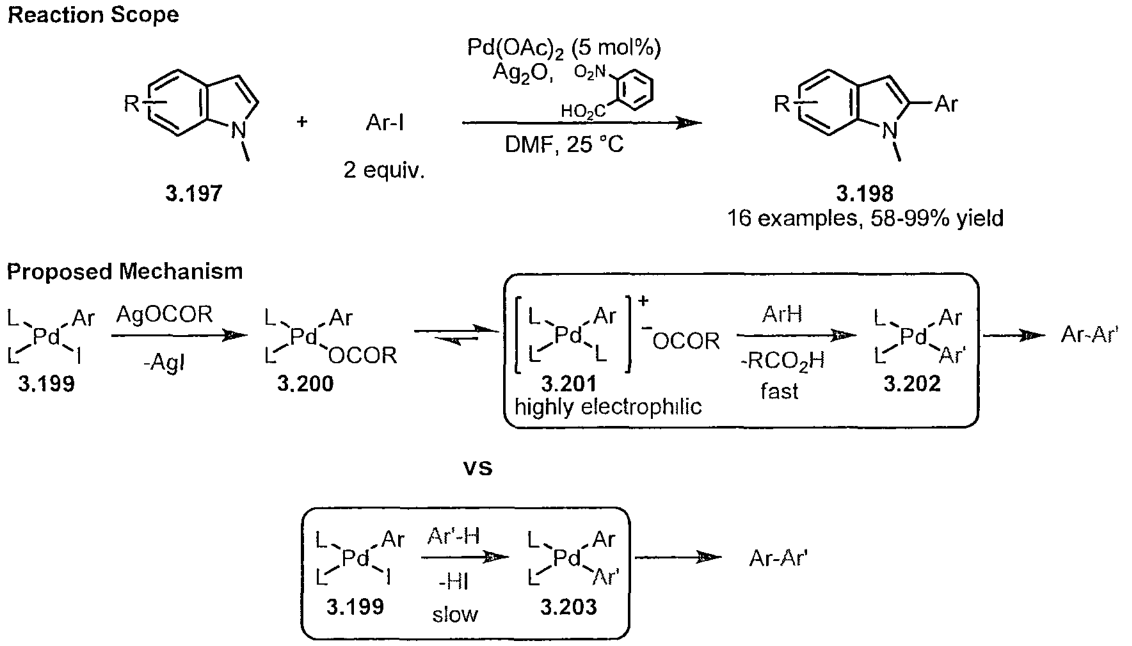
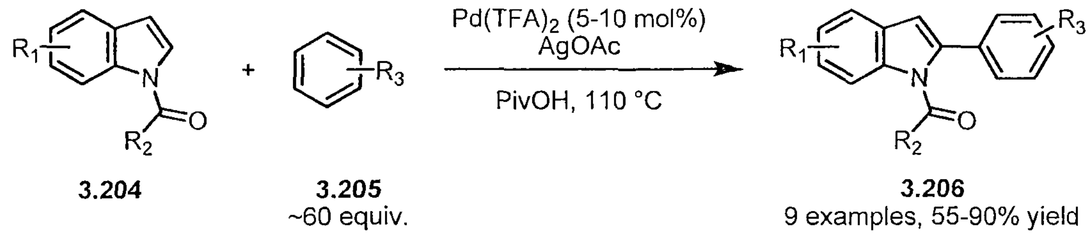
[104] Lebrasseur, N.; Larrosa, I. *J. Am. Chem. Soc.* **2008**, *130*, 2926.

Scheme 3.50 **Room temperature coupling of *N*-methylindoles with aryl iodides.**



Fagnou and co-workers have developed an oxidative procedure for the arylation of *N*-protected indoles **3.204** with simple arenes (Scheme 3.51).[105] During their studies, it was found that specific additives had a dramatic effect on selectivity. Reactivity favoured C2 when silver acetate was present, though selectivity could be inverted to favour C3 through the use of a copper additive. Substituted arenes proved to be more difficult substrates than simple benzene, and C2:C3 selectivities ranged from 9:1 to 46:1. A similar methodology was reported by DeBoef, though reaction yields were poor and ranged between 22% and 56%.[106]

Scheme 3.51 **Oxidative C2 arylation of indoles with simple arenes.**



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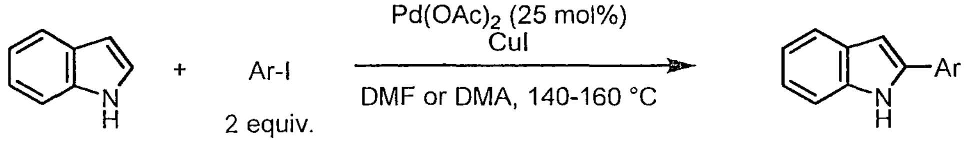
[105] Stuart, D. R.; Villemure, E.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 12072.

[106] (a) Dwight, T. A.; Rue, N. R.; Charyk, D.; Josselyn, R.; DeBoef, B. *Org. Lett.* **2007**, *9*, 3137. (b) Potavathri, S.; Dumas, A. S.; Dwight, T. A.; Naumiec, G. R.; Hammann, J. M.; DeBoef, B. *Tetrahedron Lett.* **2008**, *49*, 4050.

Rossi and co-workers have developed a procedure for the C2 arylation of several azoles, including free (NH)-indole **3.207**, with aryl iodides (Scheme 3.52).[107] While the reported yields for indole were poor, the conditions performed better for other azoles.

Scheme 3.52 **Arylation of free (NH)-indole with aryl iodides.**



3.207

3.208
4 examples, 29-53% yield

The Sames group has also developed a procedure for the C2-selective arylation of indoles using low loadings of a palladium catalyst (Scheme 3.53).[108] Substituted *N*-methylindoles **3.209** could be arylated in good yields using only 0.5 mol% of palladium acetate. Surprisingly, yields for difficult substrates could be improved by reducing catalyst loadings and extending the reaction time. It was later found that phosphine ligands were not required to achieve reactivity and were subsequently omitted from the conditions for the arylation of free (NH)-indoles **3.211**.[108c] While selectivity was generally in favour of C2 over C3, it could be inverted when large, bulky *ortho*-groups were present on the aryl iodide.

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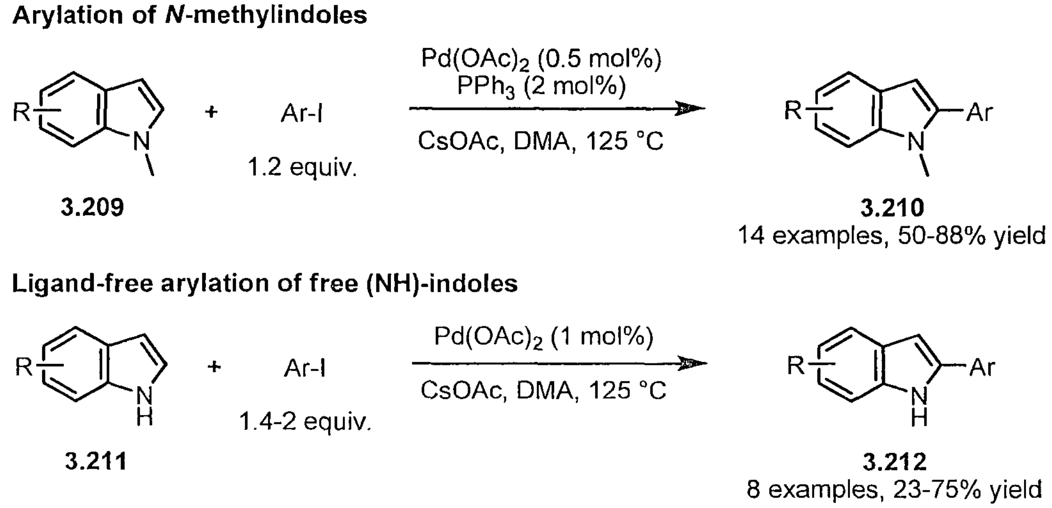
[107] (a) Bellina, F.; Cauteruccio, S.; Rossi, R. *Eur. J. Org. Chem.* **2006**, *2006*, 1379. (b) Bellina, F.; Calandri, C.; Cauteruccio, S.; Rossi, R. *Tetrahedron*, **2007**, *63*, 1970.

[108] (a) Lane, B. S.; Sames, D. *Org. Lett.* **2004**, *6*, 2897. (b) Lane, B.S.; Brown, M. A.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 8050. (c) Wang, X.; Gribkov, D. V.; Sames, D. *J. Org. Chem.* **2007**, *72*, 1476.

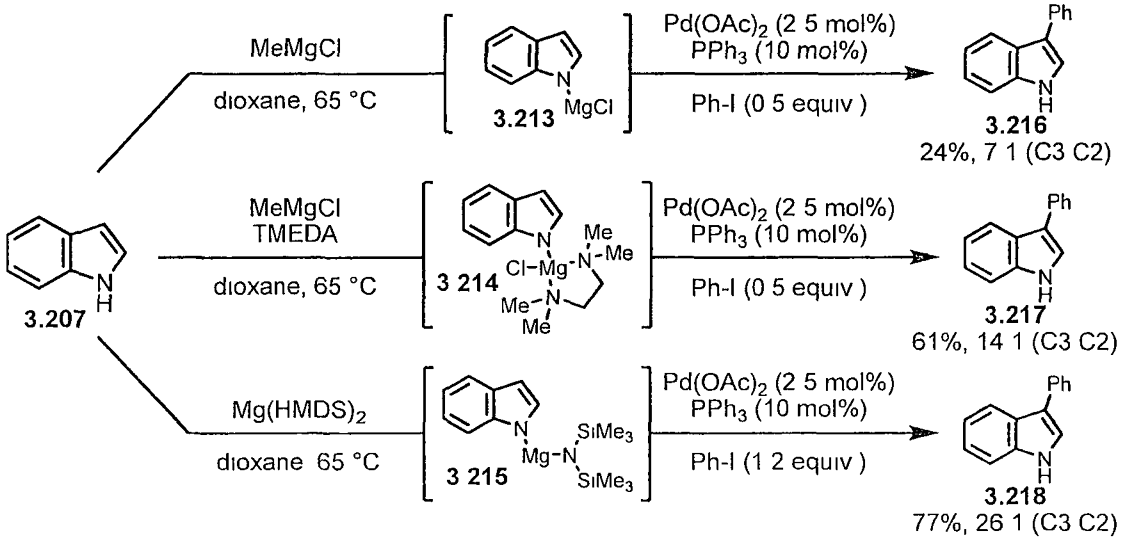
Scheme 3.53 **Selective C2 arylation of indoles with aryl iodides.**



3.3.1.2.2 C3-Selective Reactions

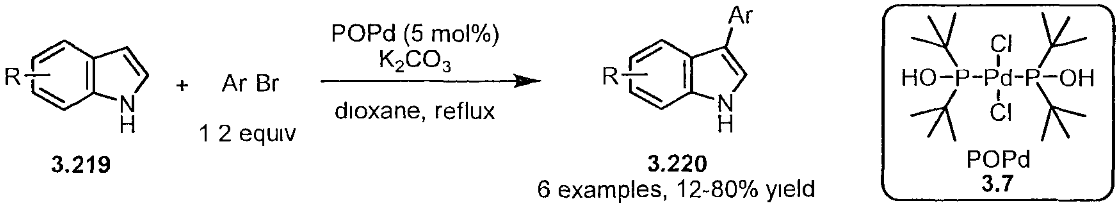
Sames and co-workers discovered that regioselectivity in the arylation of indoles could be controlled by altering the steric bulk around the catalyst.[108b] By preparing indole Grignard salts **3.13-3.215** *in situ,* free (NH)-indole **3.207** could be preferentially arylated at C3 with varying selectivity (Scheme 3.54). Indolylmagnesium chloride **3.213** provided low yields and only moderate selectivity, but when the large magnesium reagent $Mg(HMDS)_2$ was used as a controlling group, yields and selectivities became synthetically useful. The selection of ligand and aryl halide also had an impact on selectivity. It was noted that bromobenzene and palladium-IMes were also used to arylate indolylmagnesium chloride-TMEDA complex **3.214** resulted in almost quantitative yields and a C3:C2 selectivity of 67:1.

Scheme 3.54 **C3-selective arylation of free (NH)-indole using magnesium salts.**



Aryl bromides have also been studied extensively as coupling partners for the C3-arylation of indoles. Zhang *et al.* disclosed a procedure for selectively arylating free (NH)-indoles **3.219** using the air-stable POPd catalyst **3.7** (Scheme 3.55).[109] The conditions displayed several shortcomings, as only electron-deficient and electron-neutral aryl bromides were reported to react under the reaction conditions and electron-withdrawing groups on the indole resulted in poor yields or no reaction at all.

Scheme 3.55 **C3-selective arylation of free (NH)-indoles.**



In an attempt to improve the procedure published by Zhang, Rossi and co-workers developed a set of ligand-free conditions for the palladium-catalyzed arylation of free (NH)-indoles.[110] It was found that the presence of a quaternary ammonium salt helped prevent premature catalyst death and allowed for the successful synthesis of C3-arylated

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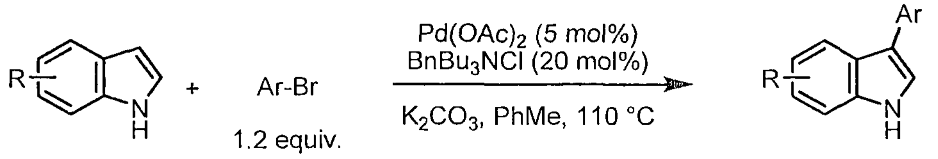
[109] Zhang, Z., Hu, Z., Yu, Z., Lei, P., Chi, H., Wang, Y., He, R. *Tetrahedron Lett.* **2007**, *48*, 2415.
[110] Bellina, F., Benelli, F., Rossi, R. *J. Org. Chem.* **2008**, *73*, 5529.

indoles **3.222** in good to near-quantitative yields (Scheme 3.56). Electron-rich aryl bromides were now compatible with these conditions but electron-deficient indoles still displayed no reactivity. The C3-arylation of 2-substituted indoles was also possible with these conditions.[111]

Scheme 3.56 **Ligand-free palladium catalyzed C3-arylation of free (NH)-indoles.**

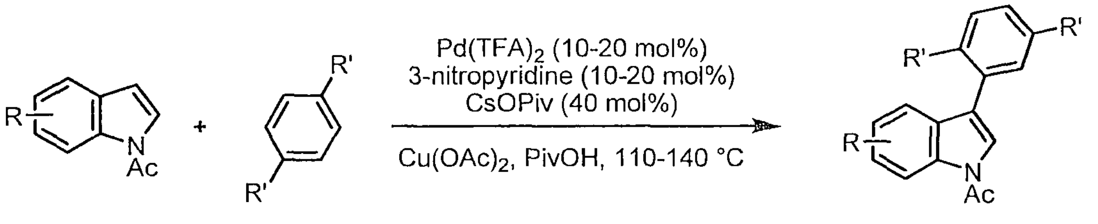


3.221

3.222
10 examples, 53-97% yield

An elegant and highly selective procedure for the oxidative arylation of *N*-acetylindoles was recently reported by Stuart and Fagnou.[112] Using a palladium catalyst in conjunction with a copper oxidant, *N*-acetylindoles **3.223** could be arylated with simple arenes **3.224** at the C3-position, without traces of homocoupled products (Scheme 3.57). Mechanistically, this requires the catalyst to invert the initial substrate selectivity in order to provide C3-arylated indoles **3.225**. While reaction scope was small, electron-deficient indoles provided much lower C3:C2 selectivities than those containing electron-rich groups, with the range lying from 2.8:1 to 11.2:1. The use of 3-nitropyridine and cesium pivalate as additives was not essential for catalyst turnover, though reactivity was significantly hindered when they are omitted from the reaction conditions.

Scheme 3.57 **Oxidative coupling of *N*-acetylindoles and simple arenes.**



3.223

3.224
~30 equiv.

3.225
9 examples, 42-84% yield

---

[111] For other reports of C3-arylation of 2-substituted indoles see: (a) Djakovitch, L.; Dufaud, V.; Zaidi, R. *Adv. Synth. Catal.* **2006**, *348*, 715. (b) Djakovitch, L.; Rouge, P.; Zaidi, R. *Catal. Commun.* **2007**, *8*, 1561. (c) Cusati, G.; Djakovitch, L. *Tetrahedron Lett.* **2008**, *49*, 2499.

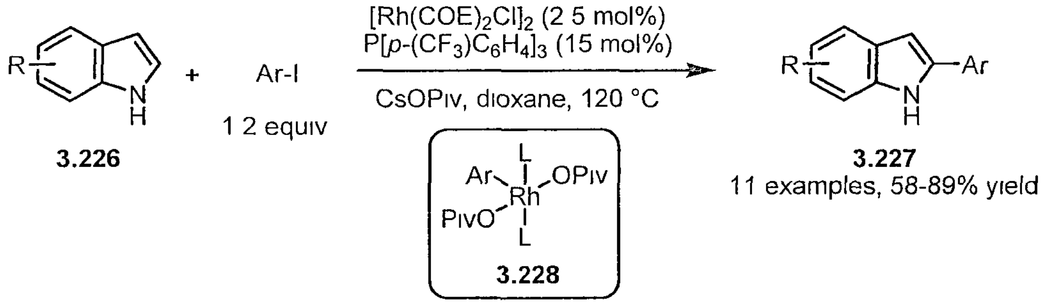
[112] Stuart, D. R.; Fagnou, K. *Science* **2007**, *316*, 1172.

3.3.1.3 Rhodium-Catalyzed Arylation of Indole

3.3.1.3.1 C2-Selective Reactions

In 2005, the Sames group reported one of the first procedures for the arylation of free (NH)-indoles.[113] By employing a rhodium catalyst and an electron-deficient triarylphosphine ligand in the presence of a pivalate base, substituted indoles **3.226** could be coupled with aryl iodides in good to excellent yields (Scheme 3.58). The active catalyst was found to be a penta-coordinate, square pyramidal rhodium(III) species **3.228** containing two phosphine and two pivalate ligands. In terms of scope related to the aryl iodide, both electron-rich and electron-poor functional groups were well tolerated.

Scheme 3.58 **Rhodium-catalyzed C2 arylation of free (NH)-indoles.**



3.226

3.228

3.227

11 examples, 58-89% yield

3.3.1.3.2 C3-Selective Reactions

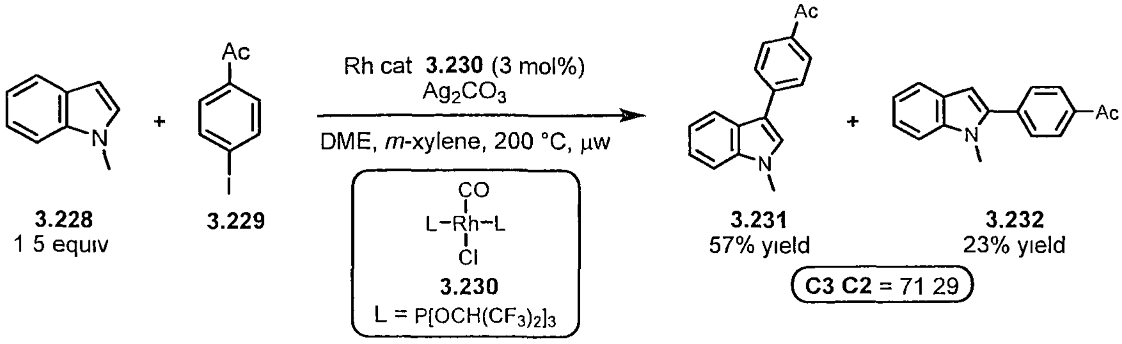
The Itami group has also reported the successful arylation of *N*-methylindole using their own rhodium-catalyzed methodology.[114] While only one example involving an indole was reported, *N*-methylindole **3.228** could be coupled with 4-iodoacetophenone **3.229** by way of rhodium complex **3.230** and silver acetate using microwave heating (Scheme 3.59). While selectivity for C3-arylated indole **3.231** is favoured, the ratio of C3 to C2 products leaves much to be desired. Nevertheless, this is the only reported rhodium-catalyzed arylation procedure that favours the C3 arylation of indole.

---

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

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

Scheme 3.59 **Microwave-promoted C3 Arylation of *N*-methylindole.**



3.3.2 Other Catalyst-Controlled Site Selective Arylations

3.3.2.1 Selective Arylation and Alkylation of Perylene Bisimides

Two complimentary procedures for the *ortho* arylation and *meta* alkylation of perylene bisimides **3.233** and **3.236** have been published by the Osuka and Wang groups respectively Tetraarylated perylene bisimides **3.235** could be synthesized through the use of aryl boronate reagent **3.234** and the use of a ruthenium hydride catalyst (Scheme 3 60)[115] While both electron-rich and mildly electron-deficient boronates were compatible, *p*-bromophenyl boronate provided disappointing yields and *p*-nitrophenyl boronate was unreactive Reaction conditions were adopted from the methodology developed by Kakiuchi[79] A complementary, palladium-catalyzed *meta*-selective alkylation procedure developed by Wang and co-workers allows for the synthesis of alkylated perylene bisimides **3.238** (Scheme 3 60)[116] Both alkyl bromides and iodides were compatible, with yields being slightly higher for the iodides While hydrocarbon chains were ideal, fluorocarbons and other substituted chains underwent reaction, albeit with lower isolated yields The use of aryl halides was unfortunately not examined

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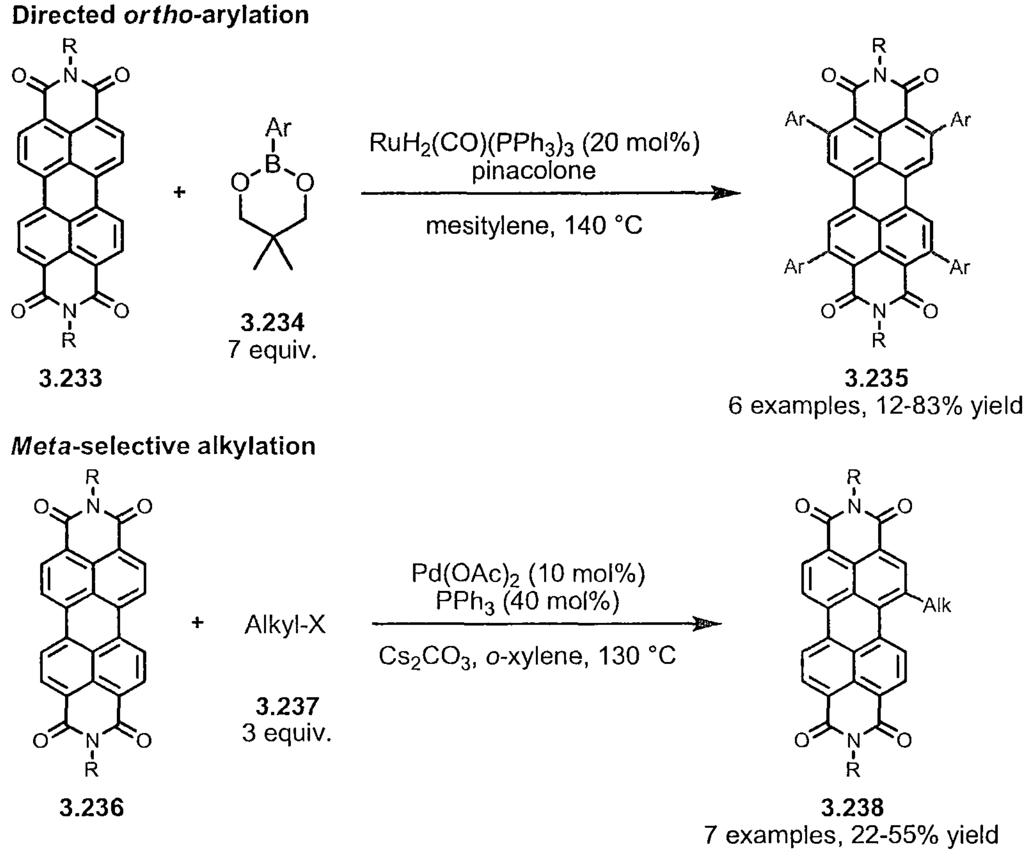
[115] Nakazono, S , Easwaramoorthi, S , Kim, D , Shinokubo, H , Osuka, A *Org Lett* **2009**, *11*, 5426
[116] Yue, W , Li, Y , Jiang, W , Zhen, Y , Wang, Z *Org Lett* **2009**, *11*, 5430

Scheme 3.60 **Regioselective arylation and alkylation of perylene bisimides.**



3.3.2.2 Site Selective Arylation of Peptides

Willis and co-workers have elegantly demonstrated the ability to chemoselectively arylate a complex molecule through judicious selection of reaction conditions.[117] Using rhodium or palladium catalysts, tripeptide **3.239** could be selectively arylated at one of three different positions (Scheme 3.61). The rhodium-catalyzed conjugate addition of *p*-fluorophenyl boronic acid and tripeptide **3.239** proceeded smoothly in 54% yield with no side reactions. Palladium-catalyzed *O*-arylation of the free phenol proved more difficult, with only 48% of the desired product being isolated. Furthermore, the reaction was not completely selective, with 13% of the *N*-arylated product was also isolated. By simply changing the ligand and counterion attached to the

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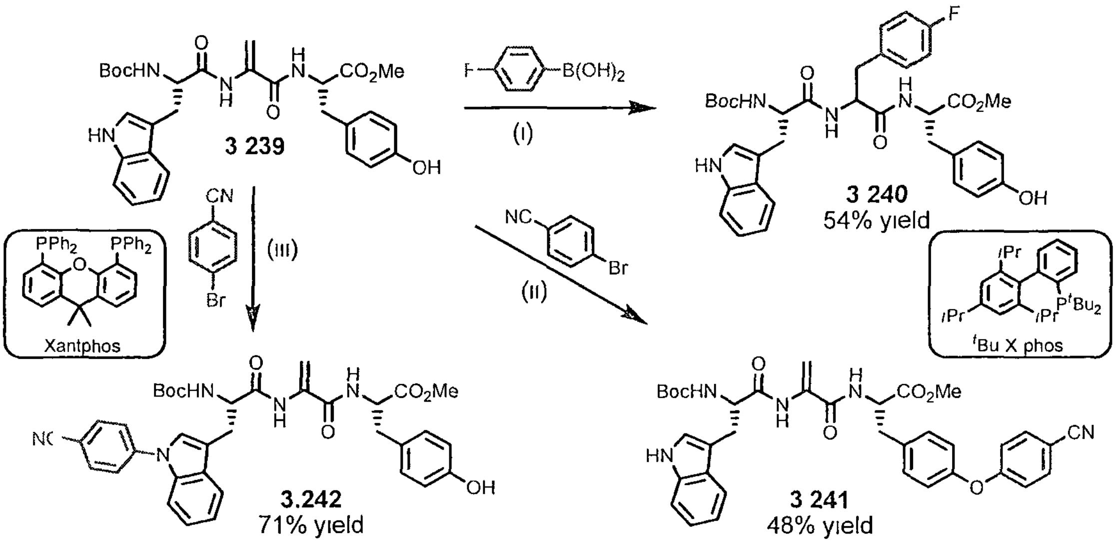
[117] Chapman, C. J.; Matsuno, A ; Frost, C. G.; Willis, M. C. *Chem. Commun.* **2007**, *38*, 3903.

palladium catalyst, *N*-arylation of the tryptophan residue could be exclusively arylated in 71% yield

Scheme 3.61 **Chemoselective arylation of a tripeptide.**



Conditions (i) Rh(acac)(C_2H_4) (6 mol%), *rac*-BINAP (6 6 mol%), dioxane H_2O (10 1), 100 °C, (ii) $Pd_2(dba)_3$ (5 mol%) ^{t}Bu-X-phos (10 mol%), K_3PO_4 (2 equiv), dioxane, 80 °C, (iii) $Pd(OAc)_2$ (5 mol%), Xantphos (7 5 mol%), K_3PO_4 (1 4 equiv) dioxane, 80 °C

3.3.2.3 Site Selective Arylation of Oxindoles

Buchwald and co-workers have recently reported the selective arylation of oxindoles [118] Due to the identical proton acidity of 18 5 at N1 and C3, metal catalyzed transformations should be able to afford either *N*-arylated or C3-arylated products (Scheme 3 62) Aryl chlorides and oxindoles **3.243** could be coupled at the C3-position through the use of a palladium catalyst and a sterically bulky ligand Though m*eta* and *para* substituted aryl chlorides showed excellent reactivity, *ortho* substitutions proved to be poor substrates Reactions were carried out in a variety of polar solvents, with THF and dioxane being the most common Selective N1 arylation could be achieved through the use of copper(I) iodide and the *trans-N,N'*-dimethylcyclohexane-1,2-diamine ligand **3.245** Both aryl iodides and bromides could be used in the reaction, though better yields

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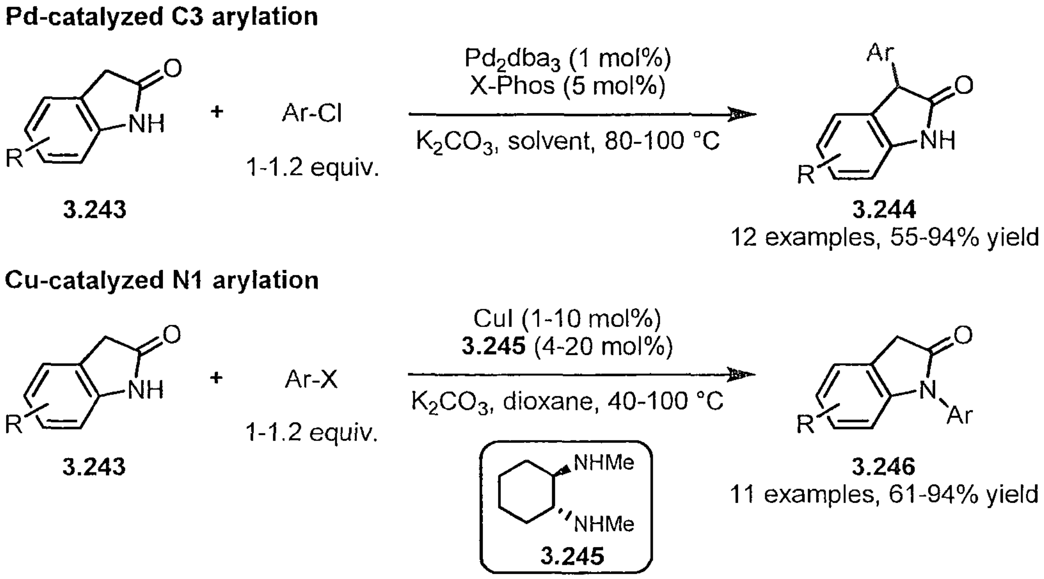
[118] Altman, R A , Hyde, A M , Huang, X , Buchwald, S L *J Am Chem Soc* **2008**, *130*, 9613

were generally achieved through the use of aryl iodides. Again, *ortho*-substituted aryl halides proved to be unreactive.

Scheme 3.62 **Pd- and Cu-catalyzed arylation of oxindoles.**



3.3.2.4 Site Selective Arylation of Azaindoles

Huestis and Fagnou have published a procedure for the selective C2 and C6 arylation of 7-azaindoles.[119] Through the use of *N*-oxide activation, *N*-methyl-7-azaindole *N*-oxide **3.247** could by selectively coupled at the C6-postion with aryl bromides using a palladium catalyst and a bulky phosphine ligand (Scheme 3.63). The reaction was compatible with a range of aryl bromides, including heteroaryl groups. Furthermore, 6-azaindoles were also compatible with the reaction conditions and were arylated at the C7-position. When no *N*-oxide was present, C2-arylated products were accessible by applying conditions originally developed by Larrosa (Scheme 3.63).[104] Though heating was required to achieve acceptable reactivity, C2 arylation proceeded smoothly with both unsubstituted and 6-substituted *N*-methyl-7-azaindoles **3.250**. Various aryl iodides were compatible with the reaction conditions, including unprotected phenols.

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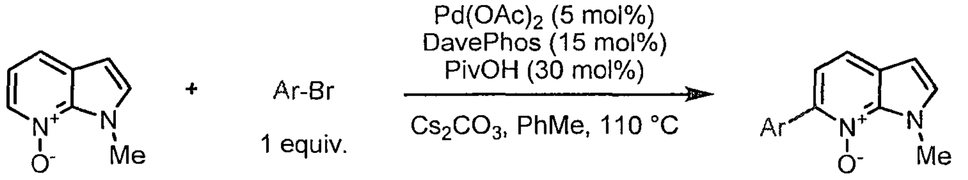
[119] Huestis, M. P.; Fagnou, K. *Org. Lett.* **2009**, *11*, 1357.

Scheme 3.63 **Selective C6 or C2 arylation of *N*-methyl-7-azaindole.**

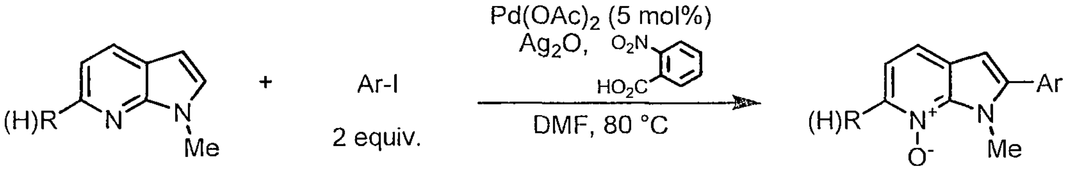
C6 arylation via *N*-oxide activation



3.247
2 equiv.

3.248
8 entries, 46-87% yield

C2 arylation



3.249

3.250
6 entries, 58-77% yield

3.3.2.5 Site Selective Arylation of Azine N*-Oxides*

The site selective arylation of azine *N*-oxides was also reported by Fagnou and co-workers.[120] By carefully selecting the catalyst and base, the coupling between 2-substituted azine *N*-oxides **3.251** and aryl bromides could be directed to either the sp^2 site at C6 or the benzylic sp^3 site (Scheme 3.64). The use of potassium carbonate resulted in the exclusive generation of 2,6-disubstituted azine *N*-oxides **3.252**. While electron-deficient aryl bromides struggled under the reaction conditions, acceptable yields could still be achieved. When the carbonate base was replaced by the stronger potassium *tert*-butoxide and the reaction was heated using a microwave, arylation of the benzylic sp^3 site was possible (Scheme 3.64). It was found that electron-poor aryl iodides were poor coupling partners, with only traces of product being detected. Mechanistic studies revealed that the nature of the base is the overwhelming factor in determining selectivity. It is proposed that only the *tert*-butoxide base is strong enough deprotonate the benzylic sp^3 hydrogens, allowing for reactivity to occur.

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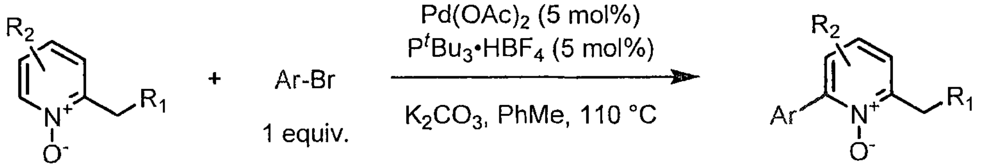
[120] (a) Campeau, L.-C.; Schipper, D. J.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 3266. (b) Schipper, D. J.; Campeau, L.-C.; Fagnou, K. *Tetrahedron* **2009**, *65*, 3155.

Scheme 3.64 **Base controlled sp^3 and sp^2 arylation of azine *N*-oxides.**

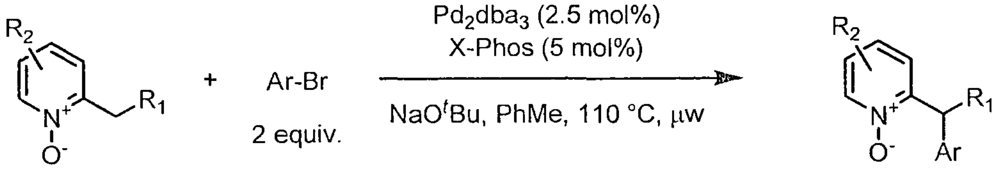
sp^2 arylation of azine *N*-oxides



3.251
2 equiv.

3.252
8 entries, 48-90% yield

sp^3 arylation of azine *N*-oxides



3.251
1.5 equiv.

3.253
21 entries, 60-93% yield

Directed arylation has received increasing amounts of focus in recent years. While reactions involving directing groups have been well examined, there has been considerably less research involving the more difficult catalyst-controlled reactions. More studies involving catalyst-controlled directed arylation are required to help expand the scope of this field.

3.4 Project Goals

Our long-term goal for this project was to develop a better understanding for predicting direct arylation selectivity. We began by examining reaction selectivity through a series of competition studies using various reported conditions and substrates. From these results, a complex molecule would then be synthesized in order to test the site selectivity of several methodologies in a setting similar to those seen by medicinal chemists.

Chapter 4

Results and Discussion – Site Selective Arylation of Substituted Indoles

4.1 Mechanistic Background

4.1.1 Proposed Mechanisms for Direct Arylation

While oxidative addition of the aryl halide to the metal catalyst is generally considered as the first step in the direct arylation reaction, several mechanisms for the following carbon-palladium bond-forming step have been proposed (Scheme 4.1). These mechanisms can be classified into one of four categories: (1) electrophilic aromatic substitution (S_EAr),[121] (2) concerted metallation-deprotonation (CMD),[122] (3) Heck-type,[123] and (4) C-H oxidative addition.[124] While it should be noted that the exact mechanism is highly dependent on the substrates and reaction conditions, the CMD and S_EAr pathways have received the most support recently. These two mechanisms, and the experimental evidence that supports them, will be examined in more detail.

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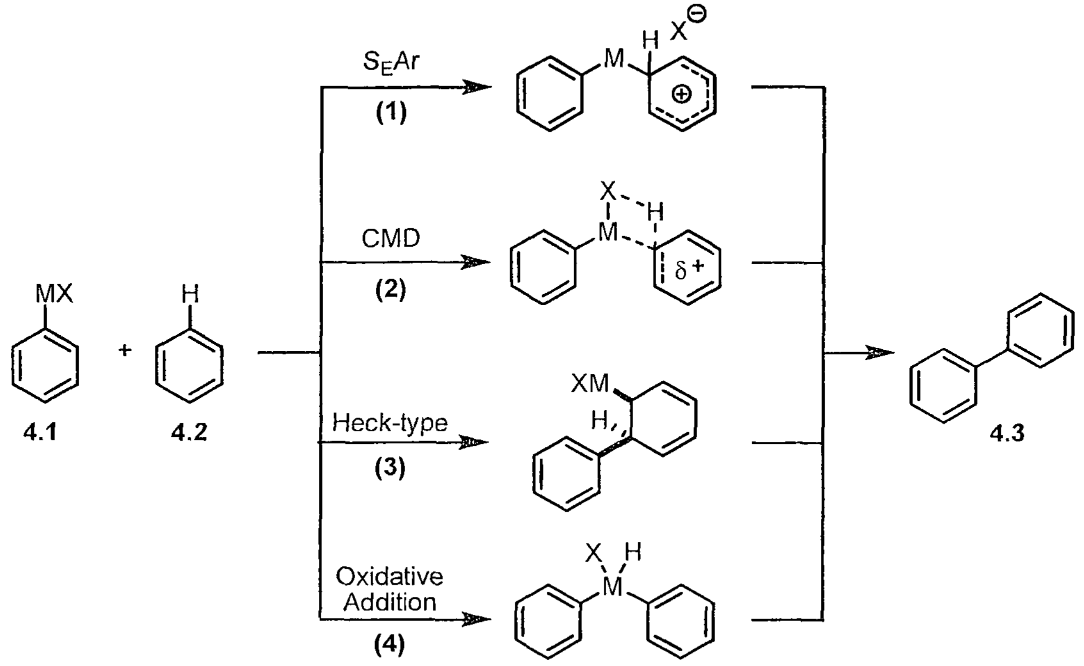
[121] (a) Park, C.-H.; Ryabova, V.; Seregin, I. V.; Sromek, A. W. Gevorgyan, V. *Org. Lett.* **2004**, *6*, 1159. (b) Lane, B. S.; Brown, M. A.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 8050.

[122] (a) García-Cuadrado, D.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006**, *128*, 1066. (b) García-Cuadrado, D.; de Mendoza, P.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2007**, *129*, 6880. (c) Lafrance, M.; Rowley, C. N.; Woo, T. K.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 8754. (d) Gorelsky, S. I.; Lapointe, D.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 10848.

[123] (a) Glover, B.; Harvey, K. A.; Liu, B.; Sharp, M. J.; Tymoshenko, M. F. *Org. Lett.* **2003**, *5*, 301. (b) Wang, J.-X.; McCubbin, J. A.; Jin, M.; Laufer, R. S.; Mao, Y.; Crew, A. P.; Mulvihill, M. J.; Snieckus, V. *Org. Lett.* **2008**, *10*, 2926.

[124] (a) Campo, M. A.; Huang, Q.; Yao, T.; Tian, Q.; Larock, R. C. *J. Am. Chem. Soc.* **2003**, *125*, 11506. (b) Capito, E.; Brown, J. M.; Ricci, A. *Chem. Commun.* **2005**, 1854.

Scheme 4.1 **Proposed mechanisms for C-H bond functionalization.**



4.1.1.2 Concerted Metallation-Deprotonation

The concerted metallation-deprotonation mechanism involving bicarbonate proton abstraction was initially proposed by Echavarren,[122a] and then elaborated by Fagnou and co-workers in their work on the arylation of perfluorobenzenes (Scheme 4.2).[122c] Following the formation of arylpalladium(II) complex **4.5** via oxidative addition, the reaction can proceed by one of two possible pathways. In Mechanism 1, formation of metallated pentafluorobenzene **4.10** proceeds through 4-membered transition state **4.6** involving the bromide ligand, similar to a mechanism proposed by Hennessy and Buchwald.[125] Ligand exchange for a bicarbonate ion allows for C-H insertion to proceed through 6-membered transition state **4.9** as shown in Mechanism 2. Computational studies also supported Mechanism 2 as the pathway with the lowest reaction barrier proceeded. Reductive elimination provided the arylated product **4.11** and regenerated the starting palladium(0) catalyst. The improved reaction performance observed with the

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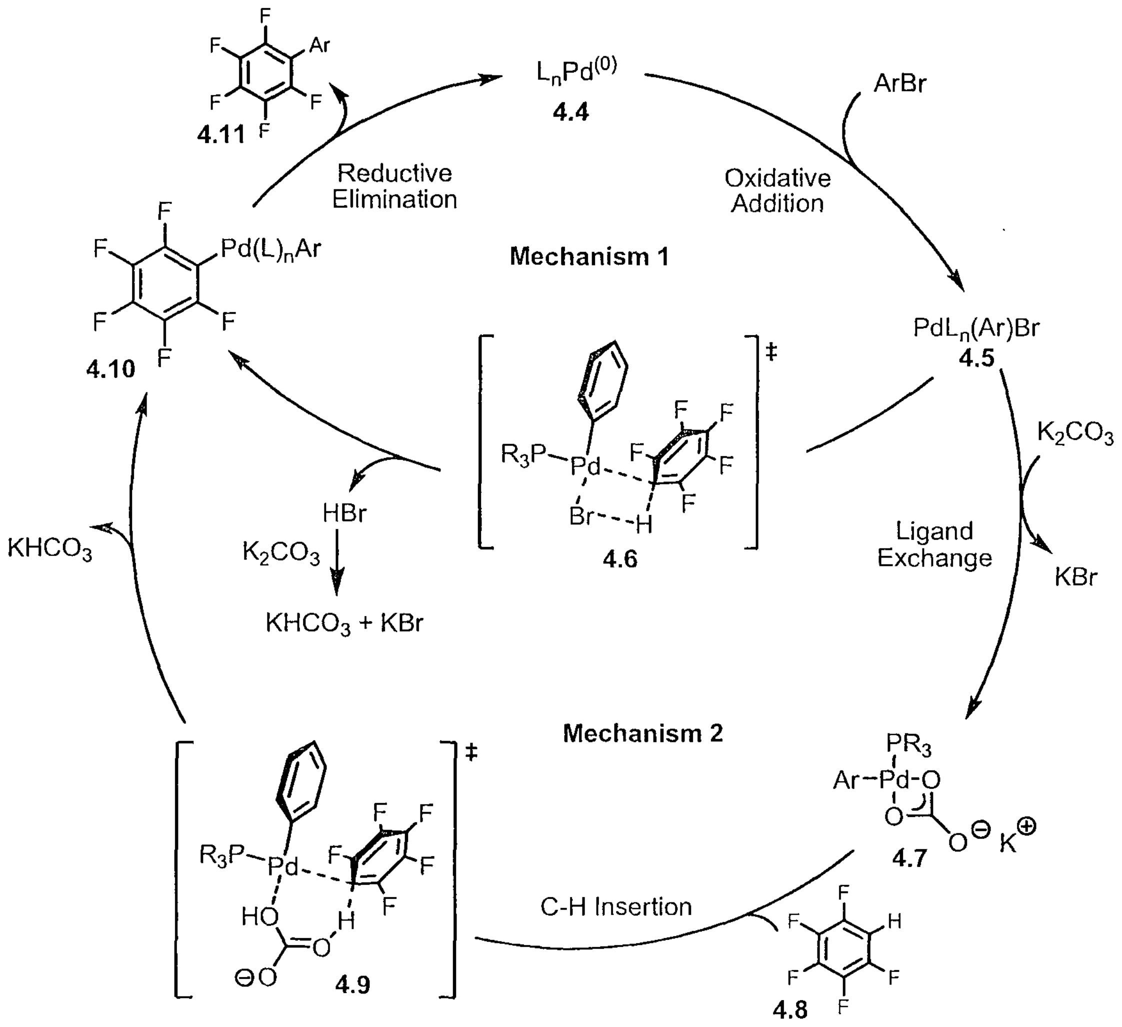
[125] Hennessy, E. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 12084.

addition of catalytic amounts of pivalic acid to the reaction conditions also supports a mechanism through 6-membered transition state **4.9**.[126]

Scheme 4.2 **Pentafluorobenzene arylation *via* CMD mechanism.**



Several studies have also been performed to help confirm experimentally the existence of the CMD mechanism. Generally, reactivity tends to parallel C-H acidity, though the two may not be directly related. An intramolecular competition study was performed by Echavarren and co-workers to examine the effect of electron-donating and electron-withdrawing groups on regioselectivity (Scheme 4.3).[122b] While methoxy-substituted **4.12** showed little selectivity, trifluoro-substituted **4.13** was highly selective

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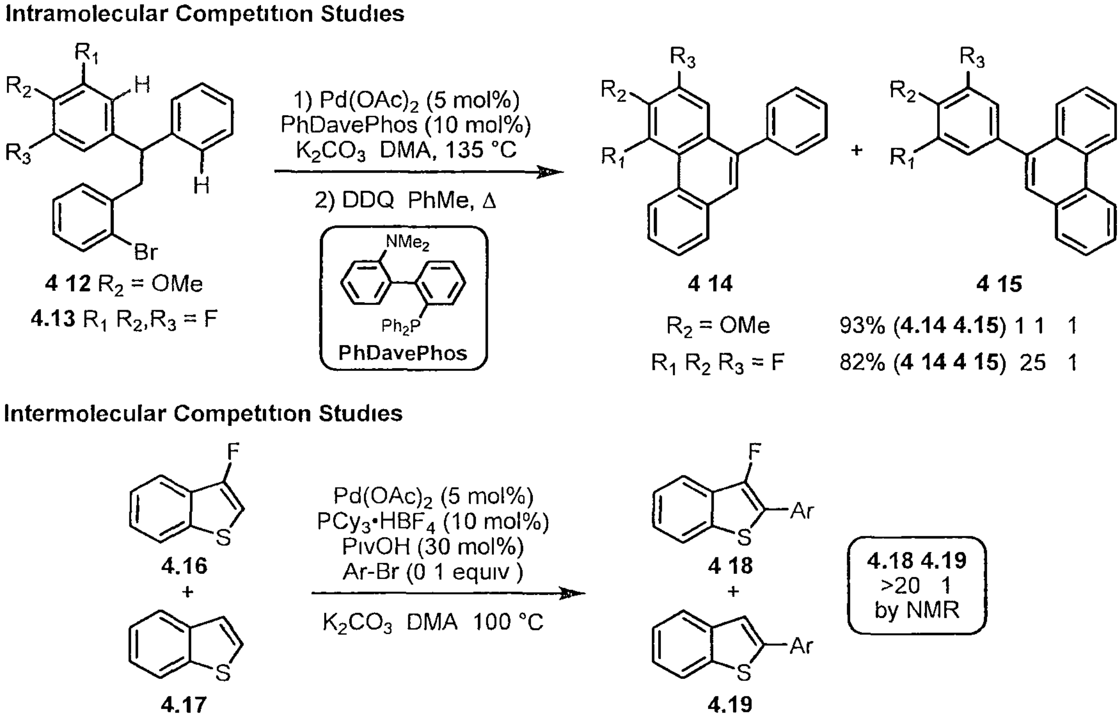
[126] Lafrance, M.; Shore, D.; Fagnou, K. *Org. Lett.* **2006**, *8*, 5097.

for the electron-deficient aryl group This result is inconsistent for an S$_E$Ar mechanism, as electron-rich arenes should react preferentially due to their ability to stabilize the Wheland intermediate that is formed Similar results have been observed in intermolecular studies When benzothiophene **4.17** and 3-fluorobenzothiophene **4.16** were placed in competition, a strong preference was seen for the more electron-deficient **4.18** (Scheme 4 3) [122d] Again, this result is not in line with an electrophilic substitution mechanism and the more reactive substrate also contains the more acidic C-H bond, lending support to a CMD pathway Computational studies also support the plausibility of this pathway,[127] including with substrates that have previously been thought to react via an S$_E$Ar mechanism [122d]

Scheme 4.3 **Experimental support for the CMD mechanism.**



4.1.1.3 Electrophilic Aromatic Substitution

Though the breadth of substrates that have been proposed to react under electrophilic aromatic substitution has recently been brought into question due to studies

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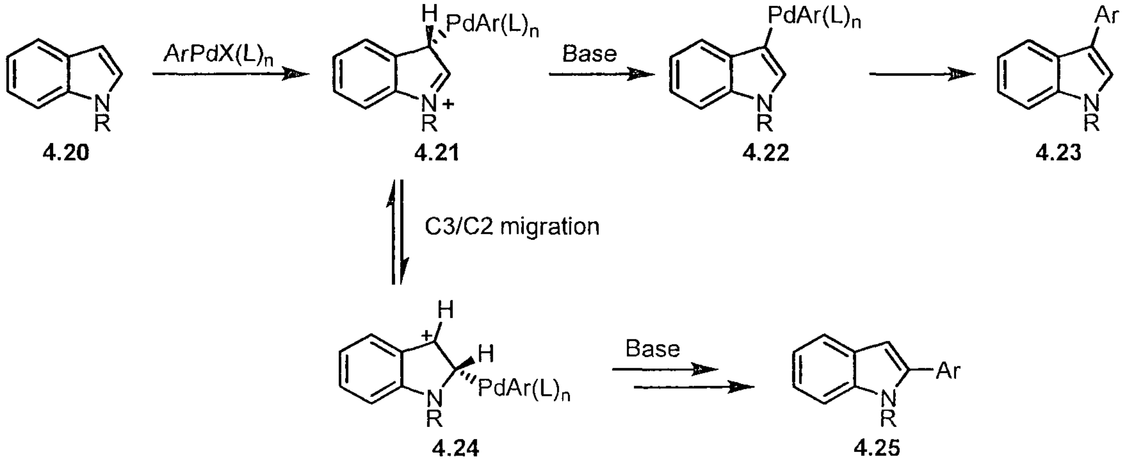
[127] (a) Davies, D L , Donald, S M A , Macgregor, S A *J Am Chem Soc* **2005**, *127*, 13754 (b) Mota, A J , Dedieu, A , Bour, C , Suffert, J *J Am Chem Soc* **2005**, *127*, 7171

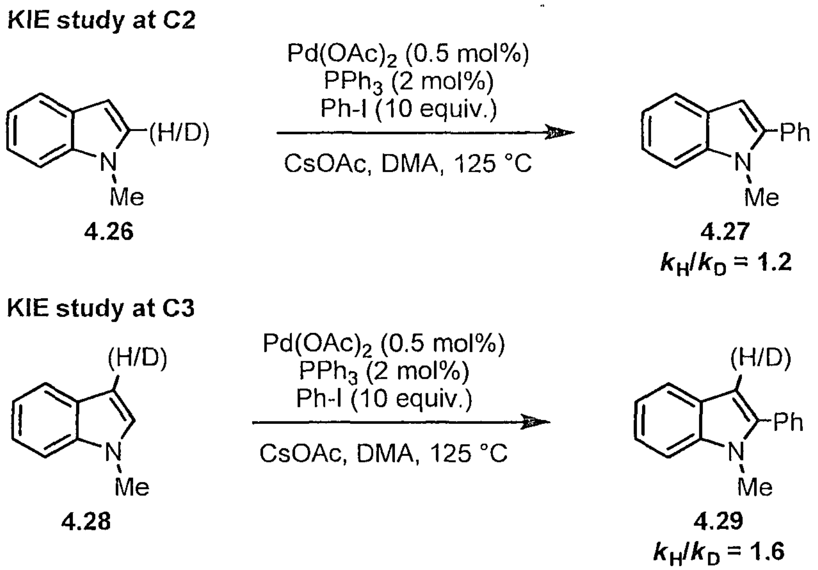
involving a concerted metallation-deprotonation, the S_EAr mechanism generally remains as the most plausible pathway for nucleophilic, electron-rich heterocycles such as indole. Again, it should be noted that the exact mechanism at work is highly dependent on both the substrate and the reaction conditions. Sames *et al.* have recently proposed an electrophilic aromatic substitution mechanism which accounts for the observation of both C2- and C3-arylated products (Scheme 4.4).[121b] Following electrophilic substitution at the nucleophilic C3-position to form C3-palladium-indole complex **4.21**, subsequent base deprotonation and reductive elimination can afford C3-arylated indole **4.23**. Alternatively, a 1,2-palladium shift can occur to provide C2-palladium-indole complex **4.24**, allowing for the formation of C2-arylated indole. Regioselectivity is proposed to be related to the competing rates of palladium-indole complex formation, palladium migration and deprotonation.

Scheme 4.4 **Indole arylation *via* an S_EAr pathway.**



Several mechanistic studies examining the C2 arylation of *N*-methylindoles were also conducted by the Sames group.[121b] When deuterium labelling studies were performed with 2-*deutero*-*N*-methylindole **4.26**, a small kinetic isotope effect (KIE) of 1.2 was observed, but deemed to be too small for this bond cleavage to be part of the rate-limiting step (Scheme 4.5). When 3-*deutero*-*N*-methylindole **4.28** was examined, a surprisingly large secondary KIE of 1.6 was found. It should be noted that this value is achieved through the contribution of several rate-contributing steps and does not represent one specific rate-determining step. Nevertheless, this result would be consistent with an S_EAr mechanism involving an initial electrophilic palladation at C3 followed by palladium migration to C2. If either of these steps are rate-determining, then a KIE would not be observed for C2 deprotonation. A Hammett plot was also conducted and the negative ρ-value that was determined indicated a build-up of positive charge at C3, providing further support for an electrophilic aromatic substitution mechanism. It should be noted that recent work published by our group has indicated that indole can also react *via* a CMD pathway, though it is likely that both mechanisms can be accessible depending on subtle changes to the reaction conditions.[128]

Scheme 4.5 **Deuterium-labelling experiments on the arylation of *N*-methylindole.**



Further evidence for 1,2 migration in electrophilic substitution reactions has been presented independently by both Jackson and Heathcock.[129] In one experiment, when tritium-labelled 3-substituted indole **4.30** was subjected to a Lewis acid, 2-alkylated indole **4.32** was observed (Scheme 4.6).[129a] Surprisingly, the labelled group could now be found at either C2 or C3, in almost a 50/50 ratio. This result requires the reaction to proceed first through C3-electrophilic substitution intermediate **4.31** followed by migration to C2 of one of the two alkyl groups.

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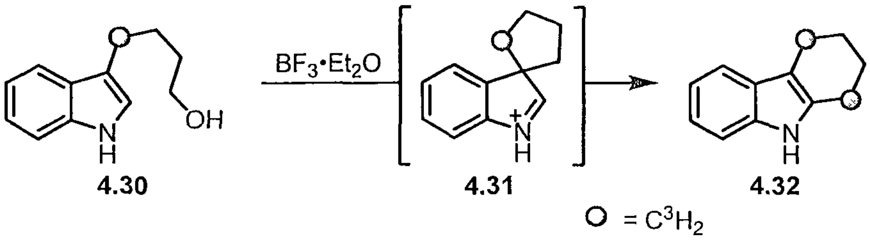
[128] Liégault, B.; Petrov, I.; Gorelsky, S. I.; Fagnou, K. *J. Org. Chem.* **2010**, *75*, 1047.

[129] (a) Jackson, A. H.; Smith, P. *Chem. Commun.* **1967**, 264. (b) Ganesan, A.; Heathcock, C. H. *Tetrahedron Lett.* **1993**, *34*, 439.

Scheme 4.6 **Experimental evidence for 1,2-migration.**



4.2 Initial Results

4.2.1 Competition Studies

Though direct arylation offers synthetic organic chemists with a more efficient route to the formation of biaryl compounds compared to traditional cross coupling methods, it is not without flaws. A chief concern is that this transformation is untested on complex molecules, such as potential drug candidates, making predicting the site selectivity of the reaction difficult. As the older, less efficient cross coupling methodologies are more established in their regioselectivity, medicinal chemists are hesitant to turn to a less predictable procedure.[130] Realising this, we set out to examine direct arylation regioselectivity in the context of larger, more complex molecules.

We began our initial studies in direct arylation site selectivity wondering if a catalyst system favouring a certain direct arylation mechanism (CMD or S_EAr) could be selective for one particular C-H bond, even in the presence of other potential reactive sites. To test this hypothesis, a series of competition studies were conducted using two substrates that have been proposed to undergo direct arylation through different mechanisms (Scheme 4.7). Pentafluorobenzene **4.32**, an electron-deficient arene, is thought to react through a concerted metallation-deprotonation mechanism,[122c] while *N*-methylindole **4.33** is thought to proceed through an electrophilic aromatic substitution pathway.[121b] When both of these substrates were placed in competition to react using our previously developed perfluorobenzene arylation conditions,[126] which involve an electron-rich palladium catalyst system, only arylated pentafluorobenzene **4.34** was observed by GC-MS. In fact, while only trace pentafluorobenzene **4.32** was detected, a

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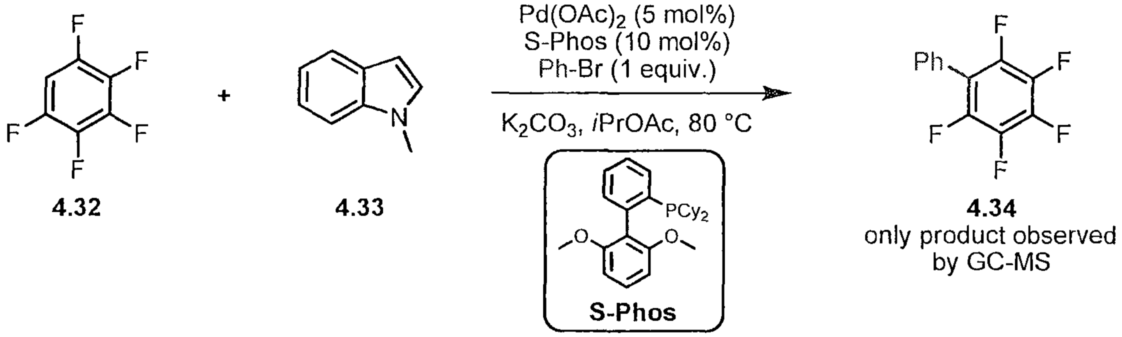
[130] *The Art of Drug Synthesis*; Johnson, D. S., Li, J. J., Eds.; Wiley-Interscience: New Jersey, 2007.

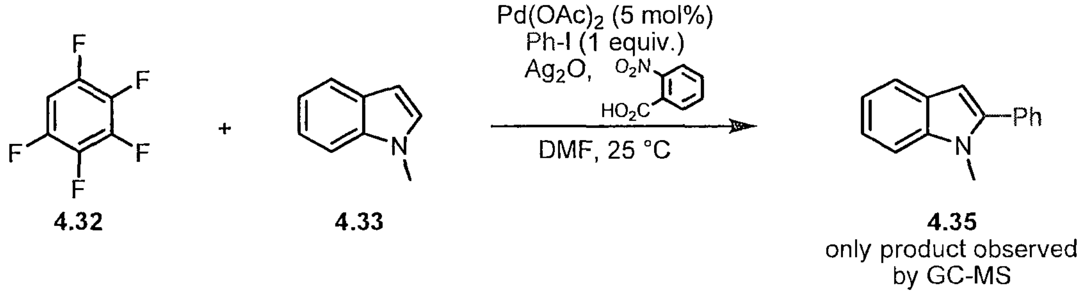
large amount of unreacted *N*-methylindole **4.33** was present. The reaction was performed again, this time using indole arylation conditions developed by Larrosa.[131] A complete inversion of selectivity was observed, with GC-MS results showing 2-phenyl-*N*-methylindole **4.35** as the only detectable product and pentafluorobenzene **4.32** remaining unreactive. This not only confirmed our initial hypothesis, but also indicated that in both cases, the presence of the non-reactive arene was not detrimental to reactivity.

Scheme 4.7 **Competition studies with *N*-methylindole and pentafluorobenzene.**

Competition study with Fagnou conditions



Competition study with Larrosa conditions



Pleased with these initial results, we decided to examine reaction selectivity when *N*-methylindole **4.33** was placed in competition with other heterocycles. We first tried a competition study with 2-methylindolizine **4.36** and *N*-methylindole **4.33** using the Larrosa indole arylation conditions (Scheme 4.8). To our surprise, no products were observed by GC-MS. While both *N*-methylindole and iodobenzene remained unreacted, there was no presence of 2-methylindolizine. Due to the sensitive and sometimes unstable nature of indolizines, we believe that the starting material degraded under the

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[131] Lebraseur, N.; Larrosa, I. *J. Am. Chem. Soc.* **2008**, *130*, 2926.

reaction conditions. The by-products from this reaction likely resulted in catalyst inhibition, explaining why no reaction took place. When the same substrates were submitted to conditions our group previously developed for the arylation of heterocycles,[132] only arylated and diarylated indolizines **4.37** and **4.38** were seen by GC-MS, while *N*-methylindole remained untouched. Encouraged, we repeated the study, this time with benzothiophene **4.39** taking the place of 2-methylindolizine. When the reaction was analyzed by GC-MS, a mixture of arylated benzothiophene **4.40** and arylated *N*-methylindole **4.35** were observed in roughly a 3:2 ratio. Under identical reaction conditions, *N*-methylindole showed reactivity in this competition, but no product formation was observed in the previous experiment. These results demonstrated that the rates of reaction of competing substrates under a specific set of conditions had a significant impact on the site selectivity of the reaction. An in-depth study examining substrate selectivity for one specific set of direct arylation conditions is currently being conducted by our group.[133]

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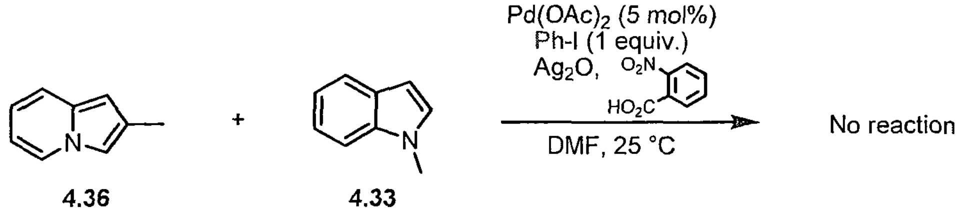
[132] Liégault, B., Lapointe, D., Caron, L., Vlassova, A., Fagnou, F. *J. Org. Chem.* **2009**, *74*, 1826.

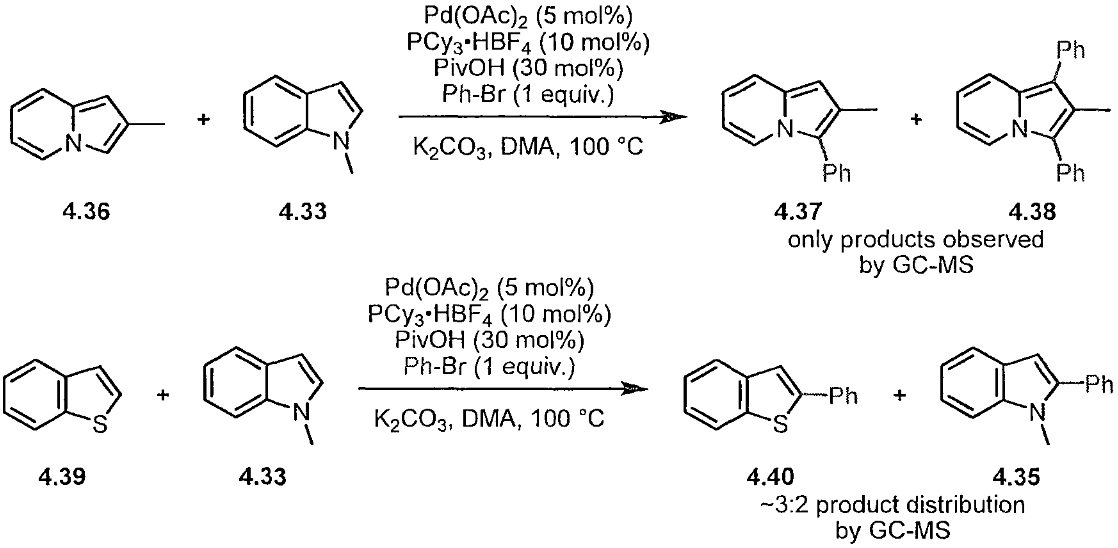
[133] Lapointe, D., Markiewicz, T., Whipp, C. J., Toderian, A., Fagnou, K. *manuscript in preparation*

Scheme 4.8 **Competition studies involving *N*-methylindole.**

Competition study with Larrosa conditions



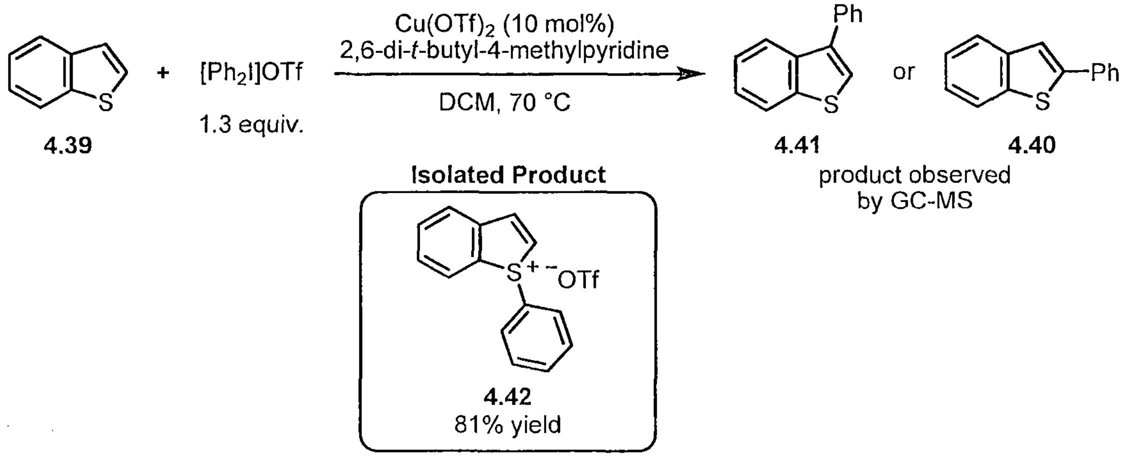
Competition studies with Fagnou conditions



4.2.2 A Misleading Hit with Benzothiophene

During the course of this project, we also examined the scope of several previously established methodologies to see if they could be extended to other classes of substrates. While this largely proved to be fruitless, one interesting result was found. When benzothiophene **4.39** was submitted to the copper-catalyzed arylation procedure developed by Gaunt and heated to 70 °C, almost complete consumption of the starting material was observed by GC-MS (Scheme 4.9). Furthermore, both the mass spectrum and retention time were consistent with either 3- or 2-arylated benzothiophene **4.41** or **4.40**. Unfortunately, attempts to isolate the observed product by silica gel chromatography were not fruitful. A product was finally isolated when the column was flushed using a solvent system of 5% methanol and 20% acetone in dichloromethane but the ^{1}H NMR spectrum was not consistent with the predicted product. Following several other NMR experiments, we discovered that benzothiophenium triflate **4.42** was the actual product being synthesized. This triflate salt proved to be quite stable and was isolated by column chromatography in an excellent 81% yield.

Scheme 4.9 **Copper-catalyzed *S*-arylation of benzothiophene.**



A literature search on benzothiophenium triflates revealed that an almost identical procedure has been previously reported by Kitamura for the synthesis of these compounds.[134] Still, we were perplexed by our initial GC-MS result that suggested the formation of a different product. A report on phenyl migration in benzothiophenium triflates by Kitamura presented a possible solution to this discrepancy.[135] It was observed that when crystalline 1-phenylbenzothiophenium triflate **4.42** was heated to 180 °C for 30 minutes, a phenyl migration was observed and 2-benzothiophene **4.40** could be isolated in 86% yield (Scheme 4.10). The authors propose this occurs through a [1,5]-phenyl migration, similar to the [1,5] sigmatropic rearrangements seen with phenyl-substituted indenes.[136] Based on this work we believe that upon injection into the hot GC-MS injection port at 280 °C, 1-phenylbenzothiophenium triflate **4.42** undergoes a [1,5]-phenyl migration to form 2-phenylbenzothiophene **4.40**, accounting for the misleading GC-MS observation.

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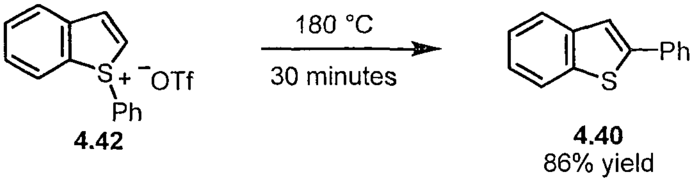
[134] (a) Kitamura, T.; Yamane, M.; Zhang, B.-X.; Fujiwara, Y.; Taniguchi, H. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 1215. (b) Kitamura, T.; Zhang, B.-X,; Fujiwara, Y. *J. Org. Chem.* **2003**, *68*, 731.

[135]) Kitamura, T.; Zhang, B.-X,; Fujiwara, Y. *Tetrahedron Lett.* **2002**, *43*, 2239.

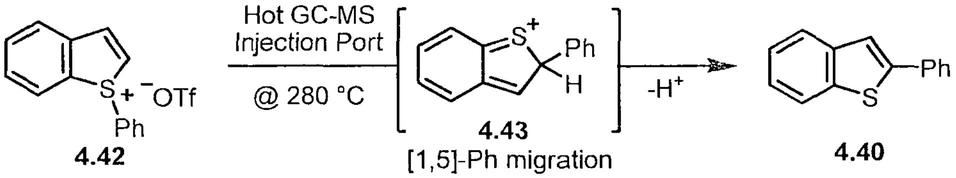
[136] (a) Miller, L. L.; Greisinger, R.; Boyer, R. F. *J. Am. Chem. Soc.* **1969**, *91*, 1578. (b) Spangler, C. W. *Chem. Rev.* **1976**, *76*, 187.

Scheme 4.10 **Phenyl migration in benzothiophenium triflates.**

Phenyl migration observed by Kitamura



Possible explanation for GC-MS result

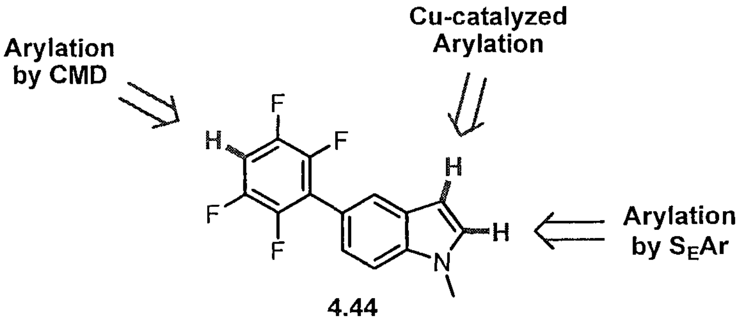


4.3 Synthesis and Arylation of Substituted Indoles

4.3.1 Synthesis of Starting Materials

With the positive outcome of the competition studies involving pentafluorobenzene **4.32** and *N*-methylindole **4.33** (Scheme 4.7), we set out to validate this reactivity on a complex molecule. We selected 5-arylated indole **4.44** as a suitable scaffold to test this reactivity, as it contains three different sites that can undergo arylation (Scheme 4.11). Site 1 (red) would be accessible by a CMD mechanism using conditions for our perfluorobenzene arylation conditions. Site 2 (green) could be arylated using the copper-catalyzed procedure developed by Gaunt, and arylation at Site 3 (red) would be accessible through the use of Larrosa conditions.

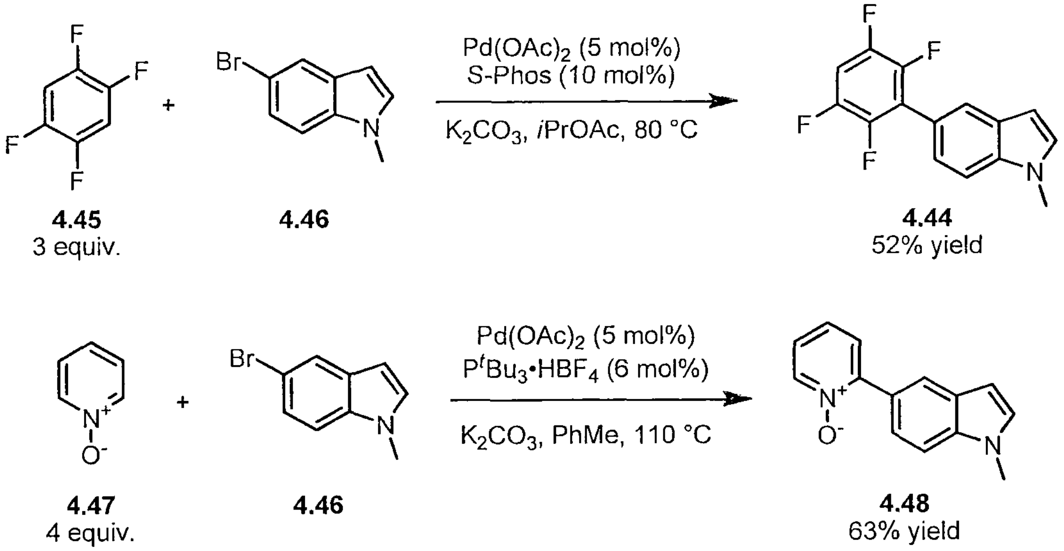
Scheme 4.11 **Synthetic plan for arylation of a substituted indole.**



4.44

Several possible synthetic routes were considered for the construction of 5-arylated indole **4.44**, including a traditional Suzuki cross-coupling and assembly of the indole core through various procedures. Unfortunately, all of these routes required several synthetic steps. The most direct route to **4.44** involved the direct coupling of 1,2,4,5-tetrafluorobenzene **4.45** and 5-bromo-*N*-methylindole **4.46** and gratifyingly, 5-arylated indole **4.44** was isolated in 52% yield when our standard perfluorobenzene conditions were used (Scheme 4.12). While this route did theoretically present a concern for reaction selectivity, as homocoupling of the indole could be possible, no such product was observed. Coupling between pyridine *N*-oxide **4.47** and 5-bromo-*N*-methylindole **4.46** also proceeded smoothly using our standard pyridine *N*-oxide arylation conditions to afford 2-arylated pyridine *N*-oxide **4.48** in 63% yield.

Scheme 4.12 **Synthesis of substituted** ***N*****-methylindoles.**

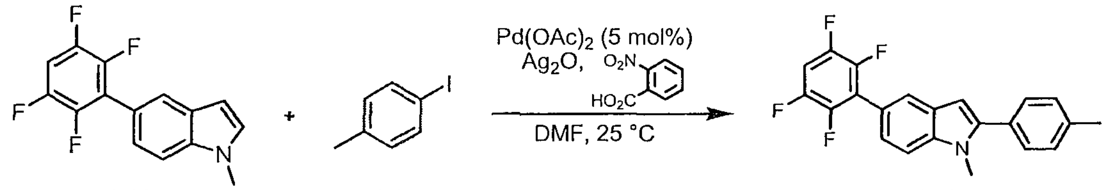


4.3.2 Examination of Site Selective Arylation

The selective arylation of 5-arylated indole **4.44** was then attempted. Using the conditions developed by Larrosa, 2,5-diarylated indole **4.50** could be selectively synthesized in 64% isolated yield (Scheme 4.13). By changing conditions to use an electron-rich phosphine ligand and pivalic acid, arylation selectivity could be switched to favour reaction at the fluorinated arene, affording 1,4-diarylated tetrafluorobenzene **4.52** in 54% yield. Selective C3 arylation could also be achieved using the Gaunt copper-catalyzed conditions and diphenyliodonium triflate **4.53**, though mild heating was required. Throughout these studies we were pleased to find that arylation was specific for only the desired site, with no side reactions being observed.

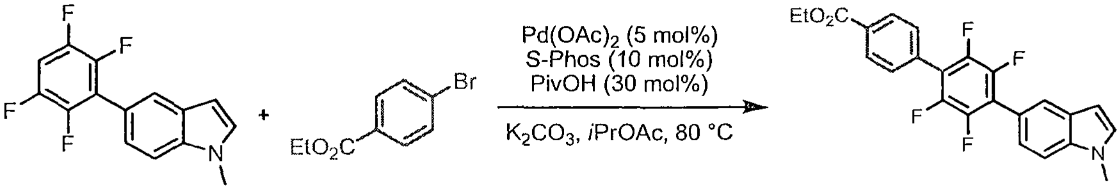
Scheme 4.13 **Site-selective arylation of a substituted indole.**

Indole C2 Arylation



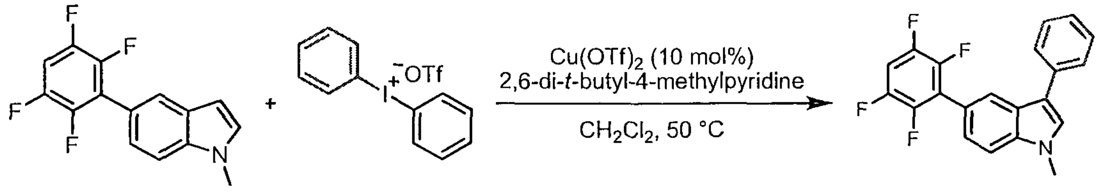
4.44 **4.49** 1.5 equiv. **4.50** 64% yield

Fluorobenzene Arylation



4.44 **4.51** 1.5 equiv. **4.52** 54% yield

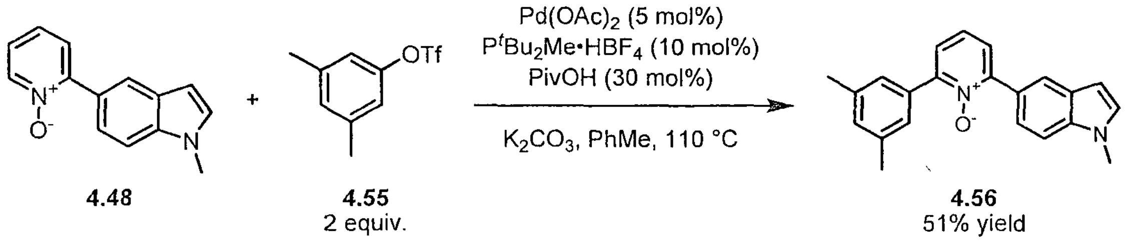
Indole C3 Arylation



4.44 **4.53** 1.3 equiv. **4.54** 64% yield

Based on these excellent results, we decided to test the selectivity of our pyridine *N*-oxide triflate coupling conditions on 2-arylated pyridine *N*-oxide **4.48**. We had previously noted that these conditions were highly reactive, with diarylation of the *N*-oxide being problematic. Even so, when *N*-oxide **4.48** and aryl triflate **4.55** were coupled using the more reactive conditions, only the formation of 2,6-diarylated pyridine *N*-oxide **4.56** was observed (Scheme 4.14). While the arylation of other locations was not examined with this substrate, competition studies performed earlier indicate that the selective C2 arylation of the indole moiety would be possible.

Scheme 4.14 **Selective arylation of a substituted pyridine *N*-oxide.**



4.4 Conclusion

To conclude, we have begun an examination into the site selectivity of the direct arylation reaction. Competition studies indicated that both the reaction conditions and the nature of the competing substrates affected regioselectivity. These results were applied to the synthesis and subsequent selective arylation of a substituted indole containing three possible reactive sites. This work has initiated a more comprehensive study on direct arylation site selectivity currently underway in our lab.

Furthermore, we have found a possible explanation for the discrepancy between the GC-MS and ^{1}H NMR analysis of 1-phenylbenzothiophenium triflate. A [1,5]-phenyl migration likely occurs in the hot GC-MS injection port, resulting in the detection of 2-phenylbenzothiophene.

Chapter 5

Supporting Information – Arylation of Azine N-Oxides with Aryl Triflates

5.1 General Methods

^{1}H and ^{13}C NMR were recorded in $CDCl_3$ solutions using a Bruker AVANCE 300 or 400 spectrometer or Varian INOVA 500 spectrometer with Me_4Si as an internal standard. 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 were dried and purified via MBraun SP Series solvent purification system. Unless otherwise specified, all reagents and solvents were used as-is from commercial sources.

5.2 Synthesis of Starting Materials

5.2.1 Synthesis of Aryl Triflates

General Procedure: following a previously published procedure.[137]

To a solution of the appropriate phenol (1 equiv.) in pyridine (2 M) cooled to 0 °C was slowly added trifluoromethanesulfonic anhydride (1.1 equiv.). The reaction was slowly warmed to room temperature and stirred for 48 hours. The reaction was quenched with water and extracted with DCM (5 x 20 ml). The organic extracts were washed sequentially with 10% HCl, water, and brine. The organic layer was dried with magnesium sulfate, filtered and concentrated. The crude product was purified by column chromatography using ether/petroleum ether as the eluent.

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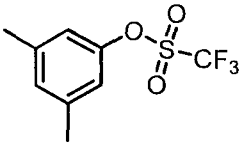
[137] Gill, D.; Hester, A. J.; Lloyd-Jones, G. C. *Org. Biomol. Chem.* **2004**, *2*, 2547.

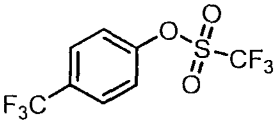


3,5-dimethylphenyl trifluoromethanesulfonate

Obtained in 83% yield.

^{1}H NMR (400MHz, $CDCl_3$, 297K, TMS): δ ppm 2.34 (s, 3H), 2.34 (s, 3H), 6.88 (s, 2H), 7.00 (s, 1H).

Exhibited spectral data identical to previous reports: Arnold, J.; Artis, D. R.; Hunt, C. R.; Ibrahim, P. N.; Krupka, H.; Lin, J.; Milburn, M. V.; Wang, W.; Zhang, C. PPAR Active Compounds. U.S. Patent 7202266, April 10, 2007.



4-(trifluoromethyl)phenyl trifluoromethanesulfonate

Obtained in 86% yield.

^{1}H NMR (400MHz, $CDCl_3$, 297K, TMS): δ ppm 7.42 (d, *J* = 8.5 Hz, 2H), 7.75 (d, *J* = 8.5 Hz, 2H).

Exhibited spectral data identical to previous reports: Gill, D.; Hester, A. J.; Lloyd-Jones, G. C. *Org. Biomol. Chem.* **2004**, *2*, 2547.

5.2.2 Synthesis of Pyridine N-Oxides

General Procedure: following a procedure developed by Sharpless and co-workers.[138]

To a solution of the appropriate pyridine (1 equiv.) in CH_2Cl_2 (1 M) was added methyltrioxorhenium (1 mol%), which resulted in a colour change to deep yellow. The solution was placed in an ice bath and a 50 wt % aqueous solution of H_2O_2 (2 equiv.) was

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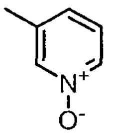
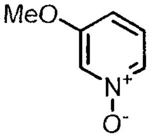
[138] Copperet, C.; Adolfsson, H.; Khuong, T.-A. V.; Yudin, A. K.; Sharpless, K. B. *J. Org. Chem.* **1998**, *63*, 1740.

added dropwise. The reaction was then warmed to room temperature and stirred for 12-24h. Excess peroxide was quenched through the addition of a small amount of MnO_2 (5-10 mg). After stirring for 1-2 hours the mixture was poured into an extraction funnel and the phases were separated. The aqueous phase was washed twice with CH_2Cl_2 and the combined organic extracts were dried with magnesium sulfate, filtered and concentrated. The crude product was purified by column chromatography using $MeOH/CH_2Cl_2$ as the eluent.



3-methylpyridine 1-oxide

Commerically available – CAS # 1003-73-2.

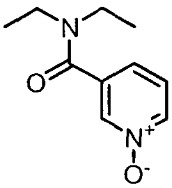


3-methoxypyridine 1-oxide

Obtained in 91% yield.

^{1}H NMR (400MHz, $CDCl_3$, 297K, TMS): δ ppm 3.85 (s, 3H), 6.89 (ddd, *J* = 8.7, 2.3, 0.7 Hz, 1H), 7.17 (dd, *J* = 8.7, 6.4 Hz, 1H), 7.91 (ddd, *J* = 6.3, 1.6, 0.8 Hz, 1H), 7.99 (dd, *J* = 1.9, 1.9 Hz, 1H).

Exhibited spectral data identical to previous reports: Sakamoto, T.; Kaneda, S.-I.; Nishimura, S.; Yamanaka, H. *Chem. Pharm. Bull.* **1985**, *33*, 565.

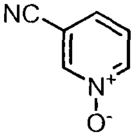


3-(diethylcarbamoyl)pyridine 1-oxide

Obtained in 95% yield.

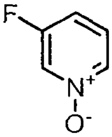
^{1}H NMR (400MHz, CDCl$_3$, 297K, TMS): δ ppm 1.17 (t, J = 6.3 Hz, 3H), 1.25 (t, J = 6.3 Hz, 3H), 3.28 (q, J = 6.3 Hz, 2H), 3.55 (q, J = 6.3 Hz, 2H), 7.27-7.23 (m, 1H), 7.35-7.30 (m, 1H), 8.22-8.21 (m, 1H), 8.24-8.22 (m, 1H).

Exhibited spectral data identical to previous reports: Sakamoto, T.; Kaneda, S.-I.; Nishimura, S.; Yamanaka, H. *Chem. Pharm. Bull.* **1985**, *33*, 565.



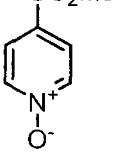
3-cyanopyridine 1-oxide

Commercially available – CAS # 14906-64-0.



3-fluoropyridine 1-oxide

Commercially available – CAS # 695-37-4.



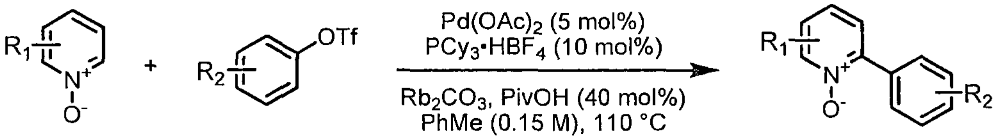
4-(methoxycarbonyl)pyridine 1-oxide

Commercially available – CAS # 3783-38-8.

5.3 Synthesis of Products

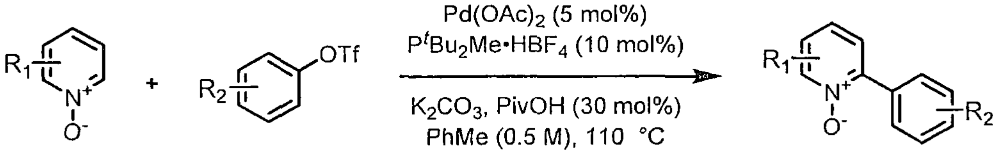
General procedure for the arylation of azine *N*-oxides with aryl triflates:

Conditions A:



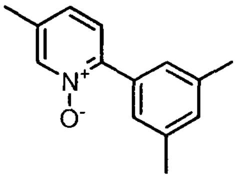
All reactions were performed on 0.5 mmol scale. To a test tube was added Rb_2CO_3 (2 equiv.), $Pd(OAc)_2$ (5 mol%), $PCy_3·HBF_4$ (10 mol%), PivOH (0.4 equiv.) and the appropriate azine *N*-oxide (2 equiv.). The tube was then sealed and purged with argon before a solution of the appropriate aryl triflate (1 equiv.) in toluene (0.15M) was added. The reaction was heated to 100 °C and stirred for 15-18 hours. Upon cooling, the reaction was diluted with dichloromethane and filtered over celite. The residues were then purified by silica gel chromatography using methanol/acetone/dichloromethane as the eluent.

Conditions B:



All reactions were performed on 0.5 mmol scale. To a test tube was added K_2CO_3 (2 equiv.), $Pd(OAc)_2$ (5 mol%), $P^tBu_2Me·HBF_4$ (10 mol%), PivOH (0.3 equiv.) and the appropriate azine *N*-oxide (2 equiv.). The tube was then sealed and purged with argon before a solution of the appropriate aryl triflate (1 equiv.) in toluene (0.5M) was added. The reaction was heated to 110 °C and stirred for 15-18 hours. Upon cooling, the reaction was diluted with dichloromethane and filtered over celite. The residues were then purified by silica gel chromatography using methanol/acetone/dichloromethane as the eluent.

Table 2.5, Entries 1A and 2A



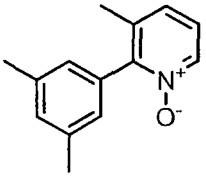
2-(3,5-dimethylphenyl)-5-methylpyridine 1-oxide

Obtained in 28% yield as a pale yellow oil by following Conditions A but using 4 equivalents of the *N*-oxide, and in 16% yield using Conditions B.

^{1}H NMR (400MHz, CDCl$_3$, 297K, TMS): δ ppm 2.32 (s, 3H), 2.37 (app d, *J* = 0.5 Hz, 6H), 7.08-7.05 (m, 1H), 7.10 (ddd, *J* = 8.1, 1.6, 0.7 Hz, 1H), 7.27 (d, *J* = 7.7 Hz, 1H), 7.39-7.36 (m, 2H), 8.20-8.18 (m, 1H).

Exhibited spectral data identical to previous reports: Campeau, L.-C.; Stuart, D. R.; Leclerc, J.-P.; Bertrand-Laperle, M.; Villemure, E.; Sun, H.-Y.; Lasserre, S.; Guimond, N.; Lecavallier, M.; Fagnou, K. *J. Am. Chem. Soc.* **2009**,*131*, 3291.

Table 2.5, Entries 1B and 2B

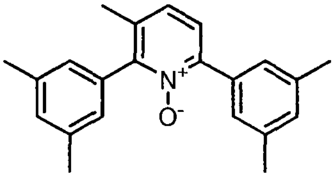


2-(3,5-dimethylphenyl)-3-methylpyridine 1-oxide

Obtained in 55% yield as an off-white solid by following Conditions A but using 4 equivalents of the *N*-oxide, and in 32% yield by following Conditions B.

^{1}H NMR (400MHz, CDCl$_3$, 297K, TMS): δ ppm 2.09 (s, 3H), 2.36 (app d, *J*=0.5 Hz, 6H), 6.96-6.92 (m, 2H), 7.09-7.05 (m, 1H), 7.15-7.10 (m, 1H), 7.18-7.14 (m, 1H), 8.22 (ddd, *J*=6.1, 1.5, 0.5 Hz, 1H); **^{13}C NMR (100MHz, CDCl$_3$, 298K, TMS):** δ ppm 19.9, 21.4, 123.6, 126.4, 127.3, 130.7, 132.2, 136.0, 137.7, 138.4, 150.2; **IR (ν_{max} /cm^{-1}):** 2911, 1601, 1413, 1268. 1237, 1196, 1076, 784; **HRMS calculated for $C_{14}H_{15}NO$ (M^+)** 213.1154; Found: 213.1151; **mp:** 149-151 °C (CHCl$_3$); **Rf:** 0.39 (2% MeOH, 10% Me$_2$CO, CHCl$_3$).

Table 2.5, Entries 1C and 2C

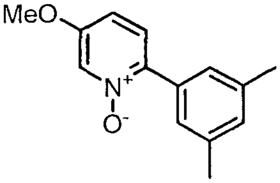


2,6-bis(3,5-dimethylphenyl)-3-methylpyridine 1-oxide

Obtained in 11% yield as a yellow oil by following Conditions A but using 4 equivalents of the *N*-oxide, and in 44% yield following Conditions B.

^{1}H NMR (400MHz, CDCl$_3$, 297K, TMS): δ ppm 2.14 (s, 3H), 2.33 (app d, J = 0.5 Hz, 6H), 2.34 (d, J = 0.5 Hz, 6H), 6.99-6.96 (m, 2H), 7.03-7.01 (m, 1H), 7.05-7.03 (m, 1H), 7.18 (dd, J = 8.1, 0.5 Hz, 1H), 7.33 (d, J = 8.1 Hz, 1H), 7.48-7.45 (m, 2H); **^{13}C NMR (100MHz, CDCl$_3$, 298K, TMS):** δ ppm 19.9, 21.3, 21.4, 124.9, 126.7, 126.8, 127.3, 130.3, 130.6, 132.9, 133.1, 134.0, 137.4, 138.2, 147.3, 150.5; **IR** ***(ν_{max}*** **/cm^{-1}):** 2920, 2863, 1603, 1346, 1275, 1219, 850, 729; **HRMS calculated for $C_{22}H_{23}NO$ (M$^+$)** 317.1780; Found: 317.1786; **Rf:** 0.92 (2% MeOH, 10% Me$_2$CO, CHCl$_3$).

Table 2.5, Entries 3A and 4A

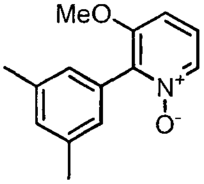


2-(3,5-dimethylphenyl)-5-methoxypyridine 1-oxide

Obtained in 11% yield as a pale yellow oil by following Conditions A, and in 9% yield by following Conditions B.

^{1}H NMR (400MHz, CDCl$_3$, 297K, TMS): δ ppm 2.36 (s, 6H), 3.87 (s, 3H), 6.91 (dd, J = 8.9, 2.4 Hz, 1H), 7.08-7.02 (m, 1H), 7.27 (d, J = 8.7 Hz, 1H), 7.36-7.31 (m, 2H), 8.08 (d, J = 2.4 Hz, 1H); **^{13}C NMR (100MHz, CDCl$_3$, 298K, TMS):** δ ppm 21.6, 56.2, 113.7, 126.87, 126.93, 127.8, 130.8, 132.5, 137.8, 143.1, 156.6; **IR** ***(ν_{max}*** **/cm^{-1}):** 2918, 2849, 1598, 1512, 1375, 1308, 1198, 1172, 1024; **HRMS calculated for $C_{14}H_{15}NO_2$ (M$^+$)** 229.1103; Found: 229.1098; **Rf:** 0.20 (1% MeOH, 10% Me$_2$CO, CHCl$_3$).

Table 2.5, Entries 3B and 4B



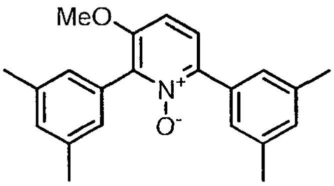
2-(3,5-dimethylphenyl)-3-methoxypyridine 1-oxide

Obtained in 67% yield as a pale yellow oil by following Conditions A, and in 64% yield using Conditions B.

^{1}H NMR (400MHz, CDCl$_3$, 297K, TMS): δ ppm 2.36 (app d J = 0.5 Hz, 6H), 3.77 (s, 3H), 6.90 (dd, J = 8.7, 0.8 Hz, 1H), 7.08-7.05 (m, 3H), 7.14 (dd, J = 8.6, 6.5 Hz, 1H), 8.03 (dd, J = 6.5, 1.0 Hz, 1H).

Exhibited spectral data identical to previous reports: Campeau, L.-C.; Stuart, D. R.; Leclerc, J.-P.; Bertrand-Laperle, M.; Villemure, E.; Sun, H.-Y.; Lasserre, S.; Guimond, N.; Lecavallier, M.; Fagnou, K. *J. Am. Chem. Soc.* **2009**,*131*, 3291.

Table 2.5, Entries 3C and 4C



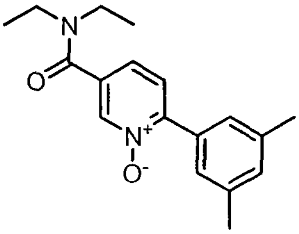
2,6-bis(3,5-dimethylphenyl)-3-methoxypyridine 1-oxide

Obtained in 7% yield as a yellow oil by following Conditions A, and in 8% yield following Conditions B.

^{1}H NMR (400MHz, CDCl$_3$, 297K, TMS): δ ppm 2.33 (app d, J = 0.5 Hz, 6H), 2.34 (d, J = 0.5 Hz, 6H), 3.82 (s, 3H), 6.98 (d, J = 9.0 Hz, 1H), 7.03-7.00 (m, 1H), 7.05-7.03 (m, 1H), 7.13-7.10 (m, 2H), 7.35 (d, J = 8.9 Hz, 1H), 7.42-7.39 (m, 2H); **^{13}C NMR (100MHz, CDCl$_3$, 298K, TMS):** δ ppm 21.3, 21.4, 56.4, 108.7, 124.7, 127.4, 127.8, 129.8, 130.4, 130.7, 133.0, 137.4, 137.6, 141.4, 143.4, 154.6; **IR *(ν_{max}* /cm^{-1}):** 3008, 2924, 1605, 1563, 1498, 1459, 1345, 1293, 1235, 1086, 852; **HRMS calculated for**

$C_{22}H_{23}NO_2$ (M^+) 333.1729; Found: 333.1734; **Rf:** 0.86 (1% MeOH, 10% Me_2CO, $CHCl_3$).

Table 2.5, Entry 5A



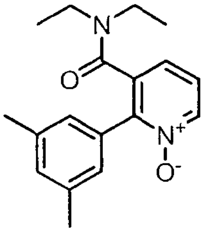
5-(diethylcarbamoyl)-2-(3,5-dimethylphenyl)pyridine 1-oxide

Obtained in 73% yield as a pale yellow oil by following Conditions A but using 4 equivalents of the *N*-oxide.

^{1}H NMR (400MHz, $CDCl_3$, 297K, TMS): δ ppm 1.32-1.14 (m, 6H), 2.38 (br s, 6H), 3.44-3.27 (m, 2H), 3.64-3.47 (m, 2H), 7.10 (s, 1H), 7.27 (dd, J = 8.0, 1.6 Hz, 1H), 7.40 (br s, 2H), 7.43 (d, J = 8.1 Hz, 1H), 8.34 (d, J = 1.2 Hz, 1H).

Exhibited spectral data identical to previous reports: Campeau, L.-C.; Stuart, D. R.; Leclerc, J.-P.; Bertrand-Laperle, M.; Villemure, E.; Sun, H.-Y.; Lasserre, S.; Guimond, N.; Lecavallier, M.; Fagnou, K. *J. Am. Chem. Soc.* **2009**,*131*, 3291.

Table 2.5, Entry 5B



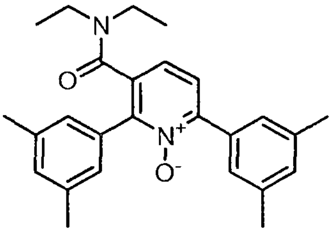
3-(diethylcarbamoyl)-2-(3,5-dimethylphenyl)pyridine 1-oxide

Obtained in 14% yield as a pale yellow oil by following Conditions A but using 4 equivalents of the *N*-oxide.

^{1}H NMR (400MHz, $CDCl_3$, 297K, TMS): δ ppm 0.73 (t, J = 7.1 Hz, 3H), 0.90 (t, J = 7.1 Hz, 3H), 2.88-2.68 (m, 2H), 3.13-3.00 (m, 1H), 3.82-3.69 (m, 1H), 7.05 (br s, 1H), 7.15 (br s, 2H), 7.21 (dd, J = 7.8, 1.3 Hz, 1H), 7.29-7.24 (m, 1H), 8.35 (dd, J = 6.3, 1.3

Hz, 1H); ^{13}C **NMR (100MHz, $CDCl_3$, 298K, TMS):** δ ppm 11.5, 13.7, 21.3, 38.5, 42.6, 123.2, 124.6, 127.2, 129.8, 131.5, 136.8, 137.8, 140.1, 146.7, 165.8; **IR** (ν_{max} **/cm^{-1}):** 2977, 2929, 1633, 1433, 1406, 1289, 1258, 1196, 859; **HRMS calculated for $C_{18}H_{22}N_2O_2$ (M^+)** 298.1681; Found: 298.1688; **Rf:** 0.15 (2% MeOH, 10% Me_2CO, $CHCl_3$).

Table 2.5, Entry 5C

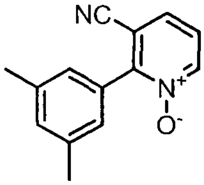


3-(diethylcarbamoyl)-2,6-bis(3,5-dimethylphenyl)pyridine 1-oxide

Obtained in 10% yield as a pale yellow oil by following Conditions A but using 4 equivalents of the *N*-oxide.

^{1}H **NMR (400MHz, $CDCl_3$, 297K, TMS):** δ ppm 0.75 (t, *J* = 7.1 Hz, 3H), 0.94 (t, *J* = 7.1 Hz, 3H), 2.30 (s, 6H), 2.35 (s, 6H), 2.92-2.72 (m, 2H), 3.25-3.10 (m, 1H), 3.85-3.72 (m, 1H), 7.02 (s, 1H), 7.06 (s, 1H), 7.20 (br s, 2H), 7.24 (d, *J* = 8.1 Hz, 1H), 7.44 (d, *J* = 8.2 Hz, 1H), 7.46 (br s, 2H); ^{13}C **NMR (100MHz, $CDCl_3$, 298K, TMS):** δ ppm 11.5, 13.7, 21.3 (two overlapping peaks), 38.5, 42.6, 122.6, 126.0, 127.2, 127.4, 130.4, 131.1, 131.2, 132.6, 134.9, 137.5, 137.6, 147.0, 149.9, 166.1; **IR** (ν_{max} **/cm^{-1}):** 2973, 2919, 1636, 1451, 1427, 1286, 846; **HRMS calculated for $C_{26}H_{30}N_2O_2$ (M^+)** 402.2307; Found: 402.2301; **Rf:** 0.80 (2% MeOH, 10% Me_2CO, $CHCl_3$).

Table 2.5, Entry 6B



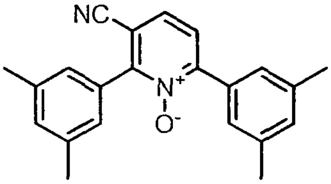
3-cyano-2-(3,5-dimethylphenyl)pyridine 1-oxide

Obtained in 61% yield as a pale yellow oil by following Conditions B.

^{1}H NMR (400MHz, CDCl$_3$, 297K, TMS): δ ppm 2.39 (s, 3H), 2.39 (s, 3H), 7.18-7.15 (m, 1H), 7.22-7.19 (m, 2H), 7.31 (dd, *J* = 7.9, 6.7 Hz, 1H), 7.56 (dd, *J* = 7.9, 1.2 Hz, 1H), 8.46 (dd, *J* = 6.6, 1.2 Hz, 1H).

Exhibited spectral data identical to previous reports: Campeau, L.-C.; Stuart, D. R.; Leclerc, J.-P.; Bertrand-Laperle, M.; Villemure, E.; Sun, H.-Y.; Lasserre, S.; Guimond, N.; Lecavallier, M.; Fagnou, K. *J. Am. Chem. Soc.* **2009**,*131*, 3291.

Table 2.5, Entry 6C

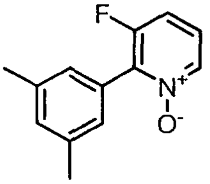


3-cyano-2,6-bis(3,5-dimethylphenyl)pyridine 1-oxide

Obtained in 7% yield as a yellow oil by following Conditions B.

^{1}H NMR (400MHz, CDCl$_3$, 297K, TMS): δ ppm 2.35 (app d, *J* = 0.5 Hz, 6H), 2.38 (d, *J* = 0.5 Hz, 6H), 7.13-7.10 (m, 1H), 7.15-7.13 (m, 1H), 7.25-7.23 (m, 2H), 7.47-7.45 (m, 2H), 7.49 (d, *J* = 8.3 Hz, 1H), 7.56 (d, *J* = 8.3 Hz, 1H); **^{13}C NMR (100MHz, CDCl$_3$, 298K, TMS):** δ ppm 21.31, 21.34, 111.5, 115.3, 125.9, 127.1, 127.2, 127.6, 129.6, 131.5, 132.2, 132.4, 138.0, 138.3, 153.8, 153.9; **IR (ν_{max} /cm^{-1}):** 2924, 2866, 2363, 2223, 1592, 1541, 1342, 848; **HRMS calculated for $C_{22}H_{20}N_2O$ (M$^+$)** 328.1576; Found: 328.1565; **Rf:** 0.89 (2% MeOH, 10% Me$_2$CO, CHCl$_3$).

Table 2.5, Entry 7B



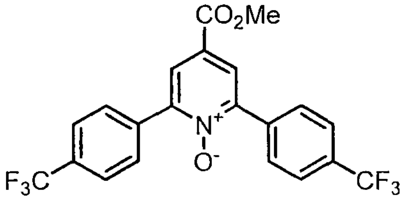
2-(3,5-dimethylphenyl)-3-fluoropyridine 1-oxide

Obtained in 90% yield as a pale yellow oil by following Conditions A.

^{1}H NMR (400MHz, CDCl$_3$, 297K, TMS): δ ppm 2.37 (s, 3H), 2.37 (s, 3H), 7.21-7.08 (m, 5H), 8.21 (ddd, *J* = 6.4, 6.4, 1.2 Hz, 1H).

Exhibited spectral data identical to previous reports: Campeau, L.-C.; Stuart, D. R.; Leclerc, J.-P.; Bertrand-Laperle, M.; Villemure, E.; Sun, H.-Y.; Lasserre, S.; Guimond, N.; Lecavallier, M.; Fagnou, K. *J. Am. Chem. Soc.* **2009**,*131*, 3291.

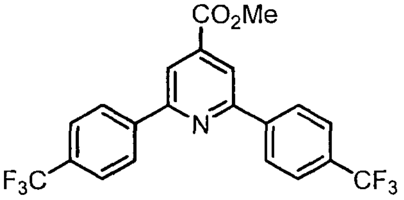
5.4 Formal Synthesis



4-(methoxycarbonyl)-2,6-bis(4-(trifluoromethyl)phenyl)pyridine 1-oxide

Obtained in 76% yield as a yellow solid by following Conditions B but using 2 equivalents of the triflate and 1 equivalent of the *N*-oxide.

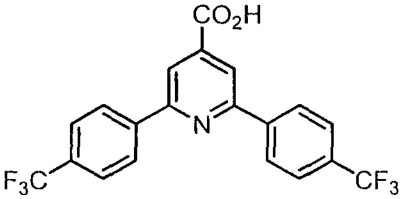
^{1}H NMR (400MHz, CDCl$_3$, 296K, TMS): δ ppm 3.98 (s, 3H), 7.76 (d, *J* = 8.2 Hz, 4H), 7.95 (d, *J* = 8.1 Hz, 4H), 8.08 (s, 2H); **^{13}C NMR (100MHz, CDCl$_3$, 298K, TMS):** δ ppm 53.0, 123.8 (q, *J* = 272.4 Hz), 125.3 (q, *J* = 3.7 Hz), 125.8, 126.6, 129.9, 131.8 (q, *J* = 32.7 Hz), 135.7, 149.1 164.0; **IR** *(ν_{max}* **/cm^{-1}):** 2957, 1726, 1620, 1562, 1325, 1251, 1169, 1125, 1067, 846, 818, 764; **HRMS calculated for $C_{21}H_{13}F_6NO_3$ (M$^+$)** 441.0800; Found: 441.0776; **mp:** 152-153 °C (CHCl$_3$); **Rf:** 0.66 (CH$_2$Cl$_2$).



methyl 2,6-bis(4-(trifluoromethyl)phenyl)isonicotinate

A solution of 4-(methoxycarbonyl)-2,6-bis(4-(trifluoromethyl)phenyl)pyridine 1-oxide (148 mg, 0.335 mmol, 1 equiv.) and zinc dust (99 mg, 1.509 mmol, 4.5 equiv.) in THF:NH_4Cl sat. 1:1 (3.5 ml) was stirred at room temperature overnight. The reaction was diluted with ether, dried over $MgSO_4$ and then filtered over celite. The crude product was purified by column chromatography (10-15% ether in petroleum ether) to give a white solid in 87% yield.

^{1}H NMR (400MHz, $CDCl_3$, 296K, TMS): δ ppm 4.05 (s, 3H), 7.79 (d, *J* = 8.2 Hz, 4H), 8.31 (d, *J* = 8.1 Hz, 4H), 8.34 (s, 2H); **^{13}C NMR (100MHz, $CDCl_3$, 297K, TMS):** δ ppm 53.0, 119.0, 124.10 (q, *J* = 272.2 Hz), 125.83 (q, *J* = 3.7 Hz), 127.4, 131.51 (q, *J* = 32.6 Hz), 139.7, 141.5, 156.6, 165.4; **IR (ν_{max} /cm^{-1}):** 2957, 1730, 1563, 1325, 1254, 1123, 1067, 847; **HRMS calculated for $C_{21}H_{13}F_6NO_2$ (M^+)** 425.0850; Found: 425.0835; **mp:** 143-145 °C ($CHCl_3$); **Rf:** 0.33 (10% ether, petroleum ether).



2,6-bis(4-(trifluoromethyl)phenyl)isonicotinic acid

A solution of methyl 2,6-bis(4-(trifluoromethyl)phenyl)isonicotinate (75 mg, 0.176 mmol, 1 equiv.) and lithium hydroxide (37 mg, 0.882 mmol, 5 equiv.) in MeOH (1 mL) was stirred at room temperature overnight. The reaction was diluted with water and the methanol was removed under reduced pressure. The solution was acidified with 10% HCl and extracted with EtOAc (3 x 20 ml). The combined organic extracts were dried over $MgSO_4$. The crude product was purified by flash chromatography (5% MeOH, 7% Acetone, $CHCl_3$) to afford a white solid in 84% yield.

^{1}**H NMR (400MHz, $(CD_3)_2CO$, 296K):** δ ppm 7.84 (d, *J* = 7.3 Hz, 4H), 8.45 (d, *J* = 7.3 Hz, 4H), 8.46 (s, 2H); ^{13}**C NMR (100MHz, $(CD_3)_2CO$, 297K):** δ ppm 119.4, 124.5 (q, *J* = 271.4 Hz), 125.7 (q, *J* = 7.3 Hz), 127.7, 130.7 (q, *J* = 32.1 Hz), 141.7, 142.0, 156.0, 165.9; **IR (ν_{max} /cm^{-1}):** 3088, 2940, 1709, 1327, 1167, 1123, 1068, 1017, 847; **HRMS calculated for $C_{20}H_{11}F_6NO_2$ (M^+)** 411.0694; Found: 411.0683; **mp:** 274-277 °C ($CHCl_3$); **Rf:** 0.53 (5% MeOH, 7% Me_2CO, $CHCl_3$).

Chapter 6

Supporting Information – Site Selective Arylation of Substituted Indoles

6.1 General Methods

^{1}H and ^{13}C NMR were recorded in $CDCl_3$ or $(CD_3)_2CO$ solutions using a Bruker AVANCE 300 or 400 spectrometer with Me_4Si or the solvent peak as an internal standard. High-resolution mass spectra were obtained on a Kratos Concept IIH. Infrared analysis was performed with a Bruker EQUINOX 55. HPLC grade THF, Et_2O, benzene, toluene and CH_2Cl_2 were dried and purified via MBraun SP Series solvent purification system. Dimethylacetamide and dimethylformamide were dried under 4Å molecular sieves, degassed with argon and stored in Wheaton bottles under an atmosphere of argon. Unless otherwise specified, all reagents and solvents were used as-is from commercial sources.

6.2 Competition Studies

General Procedure Using Fagnou Pentafluorobenzene Conditions: [139]

In a screw cap vial was added potassium carbonate (1.000 mmol, 2 equiv.), palladium(II) acetate (0.025 mmol, 5 mol%) and S-Phos (0.050 mmol, 10 mol%). The vial purged with argon before isopropyl acetate (0.5 ml, 1M) was added, followed by each of the competing substrates (0.500 mmol, 1 equiv., each substrate). The vial was stirred for one minute before bromobenzene (0.500 mmol, 1 equiv.) was added. The reaction was heated to 80 °C and stirred overnight. An aliquot was then analysed by GC-MS to determine the composition of the reaction.

General Procedure Using Fagnou Pentafluorobenzene Conditions: [140]

In a screw cap vial was added 2-nitrobenzoic acid (0.750 mmol, 1.5 equiv.), palladium(II) acetate (0.025 mmol, 5 mol%) and silver(I) oxide (0.375 mmol, 0.75 equiv.). The vial was purged with argon before DMF (1 ml, 0.5 M) was added, followed by each of the

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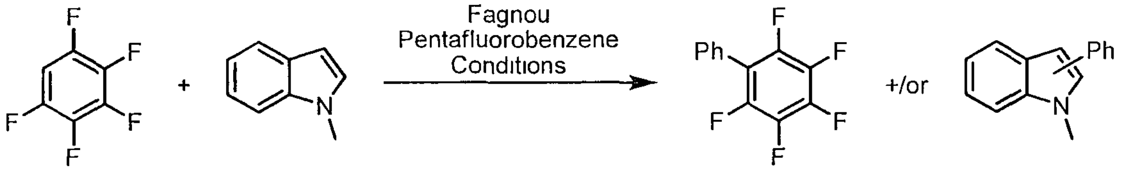
[139] Lafrance, M.; Shore, D.; Fagnou, K. *Org. Lett.* **2006**, *8*, 5097.

[140] Lebrasseur, N.; Larrosa, I. *J. Am. Chem. Soc.* **2008**, *130*, 2926.

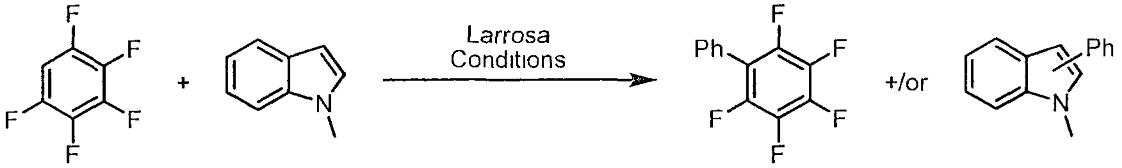
competing substrates (0 500 mmol, 1 equiv , each substrate) The vial was stirred for one minute before iodobenzene (0 500 mmol, 1 equiv) was added The reaction was stirred at room temperature overnight An aliquot was then analysed by GC-MS to determine the composition of the reaction

General Procedure Using Fagnou Heteroarene Conditions:[141]

In a screw cap vial was added potassium carbonate (0 750 mmol, 1 5 equiv), pivalic acid (0 150 mmol, 0 3 equiv) and tricyclohexylphosphonium tetrafluoroborate (0 050 mmol, 10 mol%) The vial was evacuated and backfilled with argon before DMA (1 7 mL, 0 3 M) was added, followed by each of the competing substrates (0 500 mmol, 1 equiv , each substrate) The vial was stirred for one minute before bromobenzene (0 500 mmol, 1 equiv) was added The reaction was stirred at 100 °C overnight An aliquot was then analysed by GC-MS to determine the composition of the reaction



Performed with pentafluorobenzene and 1-methyl-1*H*-indole using Fagnou pentafluorobenzene conditions [139] GC-MS detected arylated pentafluorobenzene as the only product formed



Performed with pentafluorobenzene and 1-methyl-1*H*-indole using Larrosa conditions [140] GC-MS detected 2-phenyl-1-methyl-1*H*-indole as the only product formed

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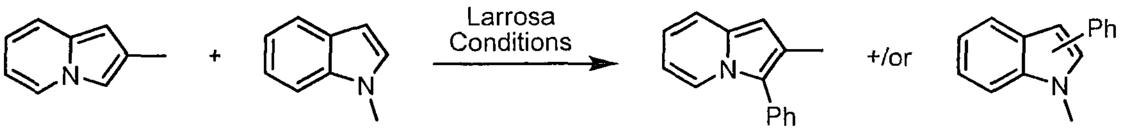
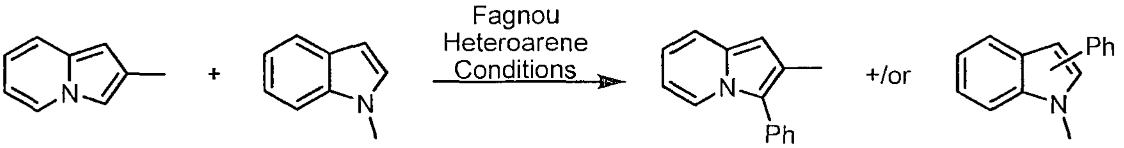
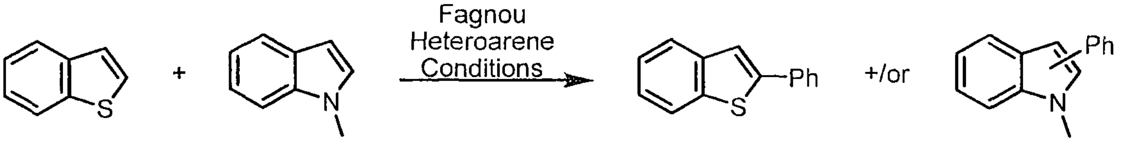
[141] Liegault, B , Lapointe, D , Caron, L , Vlassova, A , Fagnou, K *J Org Chem* **2009**, *74*, 1826



Performed with 2-methylindolizine and 1-methyl-1*H*-indole using Larrosa conditions, but 2-methylindolizine was added within a glovebox before the reaction vessel was purged with argon. GC-MS did not detect the formation of any products.

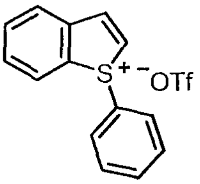


Performed with 2-methylindolizine and 1-methyl-1*H*-indole using Fagnou heteroarene conditions,[141] but 2-methylindolizine was added within a glovebox before the reaction vessel was purged with argon. GC-MS detected arylated 2-methylindolizine and a small amount of diarylated 2-methylindolizine.



Performed with benzothiophene and 1-methyl-1*H*-indole using Fagnou heteroarene conditions. GC-MS detected both arylated benzothiophene and arylated 1-methyl-1*H*-indole in roughly a 3:2 ratio.

6.2.1 Benzothiophenium Triflate Synthesis



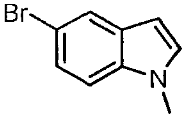
In a test tube was added benzothiophene (33.6 mg, 0.250 mmol, 1 equiv.), 2,6-di-*t*-butyl-4-methylpyridine (66.8 mg, 0.325 mmol, 1.3 equiv.), diphenyliodonium trifluoromethanesulfonate (140 mg, 0.325 mmol, 1.3 equiv.) and copper(II) trifluoromethanesulfonate (9.06 mg, 0.025 mmol, 10 mol%). The vessel was purged with argon before dichloromethane (2.5 ml, 0.1 M) was added. The reaction was stirred at 70

°C overnight. The reaction was filtered over celite and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography using 20% acetone and 5% methanol in dichloromethane. The product was isolated as a white solid in 81% yield.

^{1}H NMR (400MHz, $(CD_3)_2CO$, 295K): δ ppm 7.73-7.64 (m, 2H), 7.84-7.75 (m, 4H), 7.88 (d, J = 5.6 Hz, 1H), 7.94 (ddd, J = 7.6, 7.6, 0.8 Hz, 1H), 8.20 (d, J = 7.7 Hz, 1H), 8.32 (d, J = 8.0 Hz, 1H), 8.36 (d, J = 5.6 Hz, 1H).

Exhibited spectral data identical to previous reports: Kitamura, T.; Yamane, M.; Zhang, B.-X.; Fujiwara, Y. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 1215.

6.3 Synthesis of Starting Materials

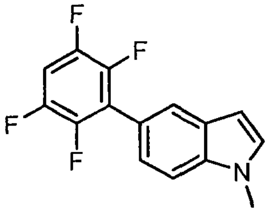


5-bromo-1-methyl-1*H*-indole

To a solution of 5-bromoindole (3.00 g, 15.30 mmol, 1 equiv.) in acetone (46.0 ml, 0.33 M) cooled to 0 °C was added freshly powdered potassium hydroxide (4.29 g, 77 mmol, 5 equiv.). After being stirred at 0 °C for 30 minutes, iodomethane (4.34 g, 30.6 mmol, 2 equiv.) was added dropwise while the solution was vigorously stirred. The reaction was slowly raised to room temperature and stirred overnight. The reaction was filtered and the solvent removed under reduced pressure. The crude product was purified by distillation on a Kugelrhor apparatus (115-125 °C) and isolated as a yellow oil in 94%.

^{1}H NMR (400MHz, $CDCl_3$, 297K, TMS): δ ppm 3.73 (s, 3H), 6.40 (dd, J = 3.1, 0.8 Hz, 1H), 7.01 (d, J = 3.1 Hz, 1H), 7.15 (d, J = 8.7 Hz, 1H), 7.27 (dd, J = 8.7, 1.9 Hz, 1H), 7.73 (dd, J = 1.9 Hz, 0.4 Hz, 1H).

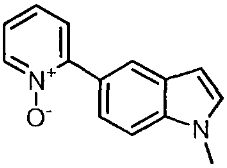
Exhibited spectral data identical to previous reports: Soll, R. M.; Parks, J. A.; Rimele, T. J.; Heaslip, R. J.; Wojdan, A.; Oshiro, G.; Grimes, D.; Asselin, A. *Eur. J. Org. Chem.* **1990**, *25*, 191.



1-methyl-5-(2,3,5,6-tetrafluorophenyl)-1H-indole

In a 4 ml screw cap vial was added potassium carbonate (658 mg, 4.76 mmol, 2 equiv.), S-Phos (98 mg, 0.238 mmol, 10 mol%) and palladium(II) acetate (26.7 mg, 0.119 mmol, 5 mol%). The vial was purged with argon before a stock solution of 5-bromo-1-methyl-1*H*-indole (500 mg, 2.380 mmol, 1 equiv.) in isopropyl acetate (2.4 ml) was added. The solution was stirred for 1 minute before 1,2,4,5-tetrafluorobenzene (1072 mg, 7.14 mmol, 3 equiv.) was added. The reaction was heated to 80 °C and stirred for 18 hours. Upon cooling, the reaction was diluted with ethyl acetate and filtered over celite. The filtrate was concentrated and the residues were purified by silica gel chromatography using 2% ether in petroleum ether as the eluent. The product was isolated as a white solid in 52% yield.

^{1}H NMR (400MHz, CDCl$_3$, 296K, TMS): δ ppm 3.84 (s, 3H), 6.56 (dd, *J* = 3.1, 0.8 Hz, 1H), 7.03 (dddd, *J* = 9.7, 9.7, 7.3, 7.3 Hz, 1H), 7.12 (d, *J* = 3.1 Hz, 1H), 7.30 (dddd, *J* = 8.5, 1.5, 1.5, 1.5 Hz, 1H), 7.43 (d, *J* = 8.5 Hz, 1H), 7.74-7.71 (m, 1H); **^{13}C NMR (100MHz, CDCl$_3$, 297K, TMS):** δ ppm, 32.9, 101.6, 103.9 (t, *J* = 22.8 Hz), 109.4, 118.2 (t, *J* = 2.3 Hz), 122.9 (t, *J* = 16.7 Hz), 123.0 (t, *J* = 1.9 Hz), 123.3 (t, *J* = 1.8 Hz), 128.5, 129.8, 136.7, 145.4-142.5 (m), 147.7-144.80 (m); **IR (ν_{max} /cm^{-1}):** 2931, 1515, 1506, 1487, 1170, 931, 887, 738, 708; **HRMS calculated for $C_{15}H_9F_4N$ (M$^+$)** 279.0671; Found: 279.0665; **mp:** 125-128 °C (CHCl$_3$); **Rf:** 0.55 (2% ether, petroleum ether).

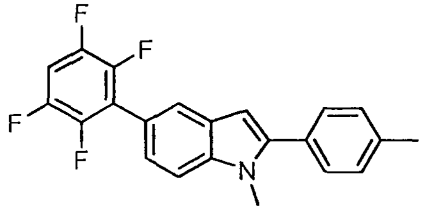


2-(1-methyl-1*H*-indol-5-yl)pyridine 1-oxide

In a test tube was added potassium carbonate (214 mg, 1.547 mmol, 1.3 equiv.), tri-*t*-butylphosphonium tetrafluoroborate (20.72 mg, 0.071 mmol, 10 mol%), palladium(II) acetate (13.36 mg, 0.060 mmol, 5 mol%) and pyridine *N*-oxide (453 mg, 4.76 mmol, 4 equiv.). The tube was fitted with a septum, purged with argon before a stock solution of 5-bromo-1-methyl-1*H*-indole (250 mg, 1.190 mmol, 1 equiv.) in Toluene (4 ml, 0.3 M) was added. The septum was covered in parafilm and the reaction was heated to 110 °C and stirred for 18 hours. Upon cooling, the reaction was diluted with dichloromethane and filtered over celite. The filtrate was concentrated and the residues were purified by silica gel chromatography using 3% methanol and 5% acetone in chloroform as the eluent. The product was isolated as an off-white solid in 63% yield.

^{1}H NMR (400MHz, CDCl$_3$, 296K, TMS): δ ppm 3.81 (s, 3H), 6.55 (d, *J* = 3.1 Hz, 1H), 7.09 (d, *J* = 3.1 Hz, 1H), 7.17 (dd, *J* = 5.7, 5.7 Hz, 1H), 7.28 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.40 (d, *J* = 8.4 Hz, 1H), 7.48 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.73 (d, *J* = 8.5 Hz, 1H), 8.05 (s, 1H), 8.35 (d, *J* = 5.6 Hz, 1H); **^{13}C NMR (100MHz, CDCl$_3$, 298K, TMS):** δ ppm 33.0, 101.9, 109.0, 122.5, 122.8, 123.6, 123.8, 125.7, 127.6, 128.2, 129.6, 137.1, 140.6, 150.7; **IR (ν_{max} /cm^{-1}):** 3102, 2948, 1606, 1513, 1476, 1421, 1339, 1245, 842, 763, 734; **HRMS calculated for $C_{14}H_{12}N_2O$ (M$^+$)** 224.0950; Found: 224.0930; **mp:** 138-142 °C (CHCl$_3$); **Rf:** 0.25 (3% MeOH, 5% Me$_2$CO, CHCl$_3$).

6.4 Synthesis of Products

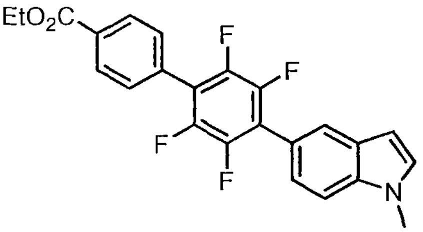


1-methyl-5-(2,3,5,6-tetrafluorophenyl)-2-p-tolyl-1*H*-indole

Following a procedure developed by Lebrasseur and Larrosa.[140]

In a 2 ml screw cap vial was added silver(I) oxide (87 mg, 0.375 mmol, 0.75 equiv.), 2-nitrobenzoic acid (125 mg, 0.750 mmol, 1.5 equiv.), 1-methyl-5-(2,3,5,6-tetrafluorophenyl)-1*H*-indole (139.7 mg, 0.500 mmol, 1 equiv.), palladium(II) acetate (5.62 mg, 0.025 mmol, 5 mol%) and 4-iodotoluene (164 mg, 0.750 mmol, 1.5 equiv.). The vial was purged with argon before DMF (1 ml) was added via syringe. The reaction was for 15 hours at room temperature. The crude product was filtered through a plug of silica gel and the solvent was removed under reduced pressure. The crude residue was purified by silica gel chromatography using 2% ether in petroleum ether. The product was isolated as a white solid in 64% yield.

^{1}H NMR (400MHz, CDCl$_3$, 296K, TMS): δ ppm 2.44 (s, 3H), 3.78 (s, 3H), 6.60 (d, *J* = 0.7 Hz, 1H), 7.03 (dddd, *J* = 9.7, 9.7, 7.3, 7.3 Hz, 1H), 7.33-7.28 (m, 3H), 7.43-7.40 (m, 2H), 7.46 (d, *J* = 8.5 Hz, 1H), 7.72 (d, *J* = 0.9 Hz, 1H); **^{13}C NMR (100MHz, CDCl$_3$, 298K, TMS):** δ ppm 21.3, 31.3, 101.7, 103.9 (dd, *J* = 22.5, 22.5 Hz), 109.7, 118.6 (dd, *J* = 2.4, 2.4 Hz), 122.5 (dd, *J* = 1.8, 1.8 Hz), 122.9 (dd, *J* = 17.3, 17.3 Hz), 123.3 (dd, *J* = 1.8, 1.8 Hz), 128.0, 129.3 (two overlapping carbon signals), 129.5, 138.2, 138.3, 142.7, 145.4-142.8 (m), 147.9-144.6 (m); **IR (ν_{max} /cm^{-1}):** 3075, 2928, 1493, 1171, 939, 801, 709; **HRMS calculated for $C_{22}H_{15}F_4N$ (M^+)** 369.1141; Found: 369.1116; **mp:** 152-155 °C (CHCl$_3$); **Rf:** 0.45 (2% ether, petroleum ether).

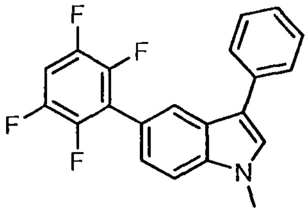


ethyl 2',3',5',6'-tetrafluoro-4'-(1-methyl-1*H*-indol-5-yl)biphenyl-4-carboxylate

Following a procedure developed by Fagnou and co-workers.[139]

In a 2 ml screw cap vial was added potassium carbonate (104 mg, 0.750 mmol, 1.5 equiv.), S-Phos (20.54 mg, 0.050 mmol, 10 mol%), 1-methyl-5-(2,3,5,6-tetrafluorophenyl)-1*H*-indole (139.7 mg, 0.500 mmol, 1 equiv.), pivalic acid (15.33 mg, 0.150 mmol, 0.3 equiv.) and palladium(II) acetate (5.62 mg, 0.025 mmol, 5 mol%). The vial was purged with argon before a stock solution of ethyl 4-bromobenzoate (172 mg, 0.750 mmol, 1.5 equiv.) in isopropyl acetate (1 ml, 0.5 M) was added via syringe. The reaction was stirred for 15 hours at 80 °C. The crude product was filtered through celite and the solvent was removed under reduced pressure. The crude residue was purified by silica gel chromatography using 5% ether in petroleum ether. The product was isolated as a white solid in 54% yield.

^{1}H NMR (400MHz, CDCl$_3$, 296K, TMS): δ ppm 1.43 (t, *J* = 7.1 Hz, 3H), 3.86 (s, 3H), 4.43 (q, *J* = 7.1 Hz, 2H), 6.58 (dd, *J* = 3.1, 0.7 Hz, 1H), 7.14 (d, *J* = 3.1 Hz, 1H), 7.36 (ddd, *J* = 8.4, 2.9, 1.4 Hz, 1H), 7.46 (d, *J* = 8.6 Hz, 1H), 7.62 (ddd, *J* = 8.6, 1.4, 1.4 Hz, 2H), 7.79 (d, *J* = 0.8 Hz, 1H), 8.19 (ddd, *J* = 8.6, 1.8 Hz, 2H); **^{13}C NMR (100MHz, CDCl$_3$, 298K, TMS):** δ ppm 14.3, 33.0, 61.2, 101.7, 109.4, 117.6 (dd, *J* = 16.5, 16.5 Hz), 118.0 (dd, *J* = 2.0, 2.0 Hz), 121.9 (dd, *J* = 16.8, 16.8 Hz), 123.1 (dd, *J* = 1.7, 1.7 Hz), 123.4 (dd, *J* = 1.6, 1.6 Hz), 128.5, 129.7, 129.9, 130.3 (dd, *J* = 2.0, 2.0 Hz), 130.9, 132.3 (dd, *J* = 2.0, 2.0 Hz), 136.8, 145.4-142.6 (m), 145.8-143.0 (m), 166.1; **IR (ν_{max} /cm^{-1}):** 2958, 2908, 1710, 1479, 1271, 1100, 979, 711; **HRMS calculated for $C_{24}H_{17}F_4NO_2$ (M$^+$)** 427.1195; Found: 427.1180; **mp:** 177-179 °C (CHCl$_3$); **Rf:** 0.21 (5% ether, petroleum ether).



1-methyl-3-phenyl-5-(2,3,5,6-tetrafluorophenyl)-1*H*-indole

Following a procedure developed by Gaunt and co-workers.[142]

In a 4 ml screw cap vial was added 1-methyl-5-(2,3,5,6-tetrafluorophenyl)-1*H*-indole (70 mg, 0.251 mmol, 1 equiv.), diphenyliodonium trifluoromethanesulfonate (140 mg, 0.326 mmol, 1.3 equiv.), copper(II) trifluoromethancsulfonate (9.07 mg, 0.025 mmol, 10 mol%) and 2,6-di-*t*-butyl-4-methylpyridine (66.9 mg, 0.326 mmol, 1.3 equiv.). The vial was purged with argon before CH_2Cl_2 (2.5 ml, 0.1 M) was added by syringe. The reaction was heated to 50 °C and stirred for 48 hr. The reaction was cooled and diluted with CH_2Cl_2 before being washed with satd. $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (15 ml) and the combined organic layers were dried with magnesium sulfate, filtered and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography using 2% ether in petroleum ether. The product was isolated as a white solid in 64% yield.

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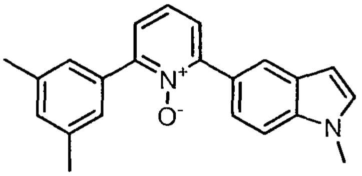
[142] Phipps, R. J,; Grimster, N. P.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 8172.

^{1}H NMR (400MHz, CDCl$_3$, 296K, TMS): δ ppm 3.89 (s, 3H), 7.04 (dddd, *J* = 9.7, 9.7, 7.3, 7.3 Hz, 1H), 7.30-7.26 (m, 1H), 7.29 (s, 1H), 7.35 (ddd, *J* = 8.5, 2.9, 1.4 Hz, 1H), 7.49-7.41 (m, 3H), 7.63 (dd, *J* = 8.3, 1.2 Hz, 2H), 8.01 (d, *J* = 0.7 Hz, 1H); **^{13}C NMR (100MHz, CDCl$_3$, 297K, TMS):** δ ppm 33.03, 104.05 (dd, *J* = 22.9, 22.9 Hz), 109.74, 117.44, 118.78 (dd, *J* = 2.2, 2.2 Hz), 122.12 (dd, *J* = 1.8, 1.8 Hz), 122.84 (dd, *J* = 17.1, 17.1 Hz), 123.77 (dd, *J* = 1.7, 1.7 Hz), 126.06, 126.23, 127.42, 127.43, 128.87, 135.04, 137.47, 145.43-142.39 (m), 147.78-144.68 (m); **IR** *(ν_{max}* **/cm^{-1}):** 3075, 2948, 1604, 1491, 1456, 1223, 1171, 939, 751, 710; **HRMS calculated for $C_{21}H_{13}F_4N$ (M^+)** 355.0984; Found: 355.0990; **mp:** 123-125 °C (CHCl$_3$); **Rf:** 0.27 (2% ether, petroleum ether).



2-(3,5-dimethylphenyl)-6-(1-methyl-1*H*-indol-5-yl)pyridine 1-oxide

In a 2 ml screw cap vial was added palladium(II) acetate (3.50 mg, 0.016 mmol, 5 mol%), pivalic acid (9.56 mg, 0.094 mmol, 0.3 equiv.), Potassium carbonate (86 mg, 0.624 mmol, 2 equiv.), di-*t*-butylmethyl phosphonium tetrafluoroborate (7.74 mg, 0.031 mmol, 10 mol%) and 2-(1-methyl-1*H*-indol-5-yl)pyridine 1-oxide (70 mg, 0.312 mmol, 1 equiv.). The vial was purged with argon before a stock solution of 3,5-dimethylphenyl trifluoromethanesulfonate (119 mg, 0.468 mmol, 1.5 equiv.) in toluene (1.1 ml, 0.3 M) was added. The reaction was heated to 110 °C and stirred overnight. Upon cooling, the reaction was diluted with dichloromethane and filtered over celite. The filtrate was concentrated and the residues were purified by silica gel chromatography using 3% acetone in chloroform as the eluent. The product was isolated as an off-white solid in 51% yield.

^{1}H NMR (400MHz, CDCl$_3$, 296K, TMS): δ ppm 2.36 (s, 6H), 3.80 (s, 3H), 6.52 (dd, *J* = 3.1, 0.8 Hz, 1H), 7.05 (m, 2H), 7.28 (dd, *J* = 7.7, 7.7 Hz, 1H), 7.33 (dd, *J* = 7.8, 2.4 Hz, 1H), 7.37 (d, *J* = 8.7 Hz, 1H), 7.47-7.42 (m, 3H), 7.78 (dd, *J* = 8.7, 1.6 Hz, 1H), 8.10 (dd, *J* = 1.6, 0.4 Hz, 1H); **^{13}C NMR (100MHz, CDCl$_3$, 298K, TMS):** δ ppm 21.33, 32.93, 101.83, 108.64, 122.76, 123.24, 124.49, 124.76, 125.27, 126.16, 127.28, 128.08, 129.37, 130.78, 133.56, 136.96, 137.52, 150.21, 151.14; **IR** *(*ν_{max} **/cm^{-1}):** 3005, 2951, 1556, 1476, 1358, 1246, 1226, 786, 721; **HRMS calculated for $C_{22}H_{20}N_2O$ (M$^+$)** 328.1576; Found 328.1556; **mp:** 195-198 °C ($CHCl_3$); **Rf:** 0.45 (3% Me_2CO, $CHCl_3$).

Claims to Original Research

1. Developed a new palladium-catalyzed methodology for the direct arylation of azine *N*-oxides with aryl triflates. The regioselectivity of the reaction was studied on C3-substituted pyridine *N*-oxides, and generally reactivity was favoured at the more hindered C2 position. The methodology was also applied to the formal synthesis of a biologically active pyridine.

2. Began studies on the site selectivity of the direct arylation reaction. It was shown in competition studies that both the reaction conditions and the competing substrates impacted the observed site selectivity. The information gathered was then applied to the selective arylation of substituted indoles.

3. Publications: i) Schipper, D. J.; El-Salfiti, M.; Whipp, C. J.; Fagnou, K. *Tetrahedron* **2009**, *65*, 4977.

4. Poster Presentations: i) Whipp, C. J.; Schipper, D. J.; El-Salfiti, M.; Fagnou, K. *Direct Arylation of Azine* N-*Oxides with Aryl Triflates* November 8th 2008, Québec-Ontario Mini-Symposium of Bio-Organic Chemistry (QOMSBOC), Toronto, Ontario.

Appendix

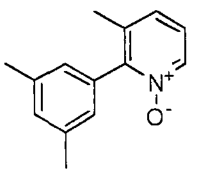
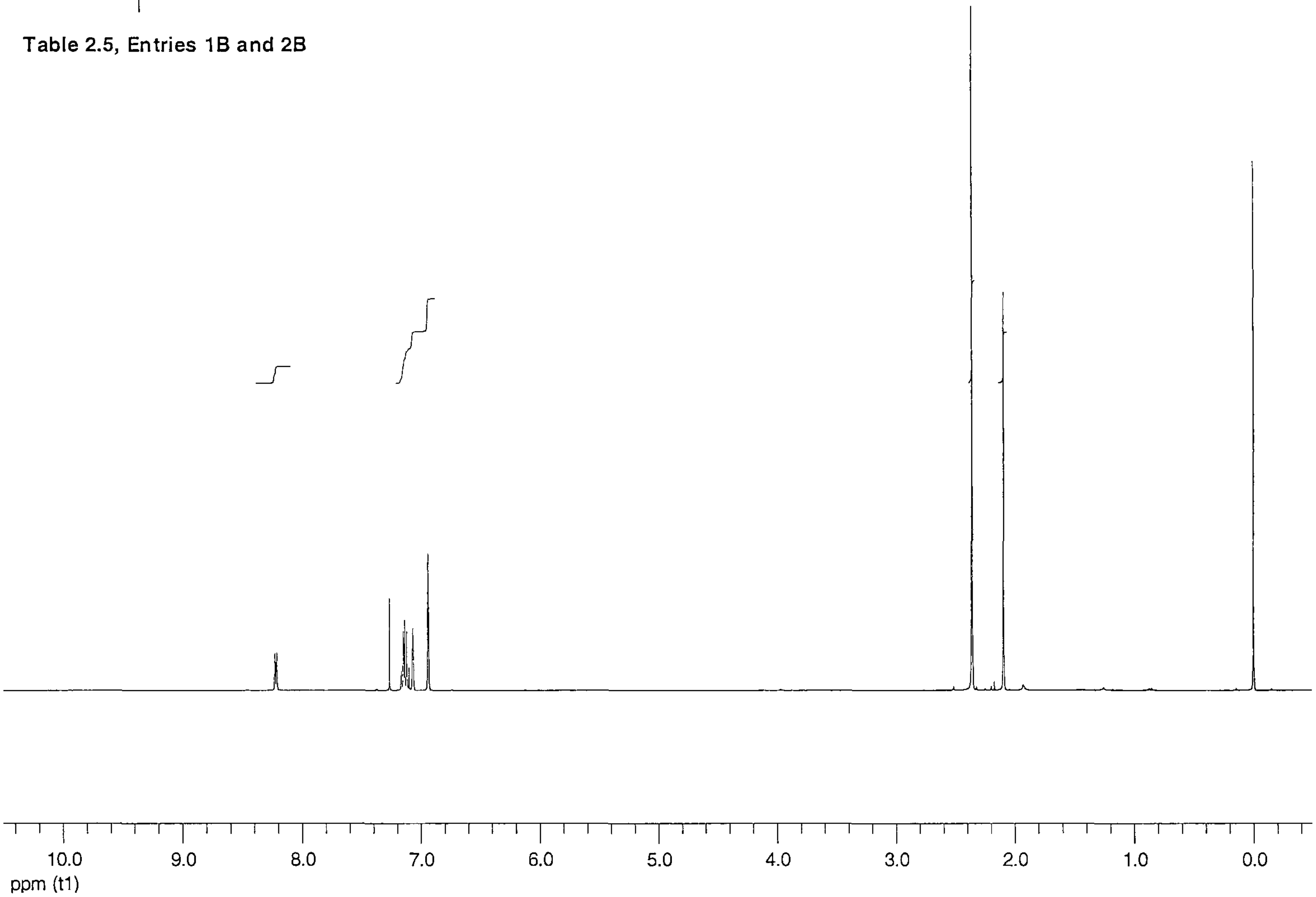
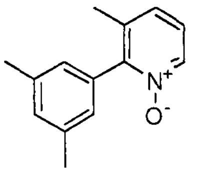


Table 2.5, Entries 1B and 2B





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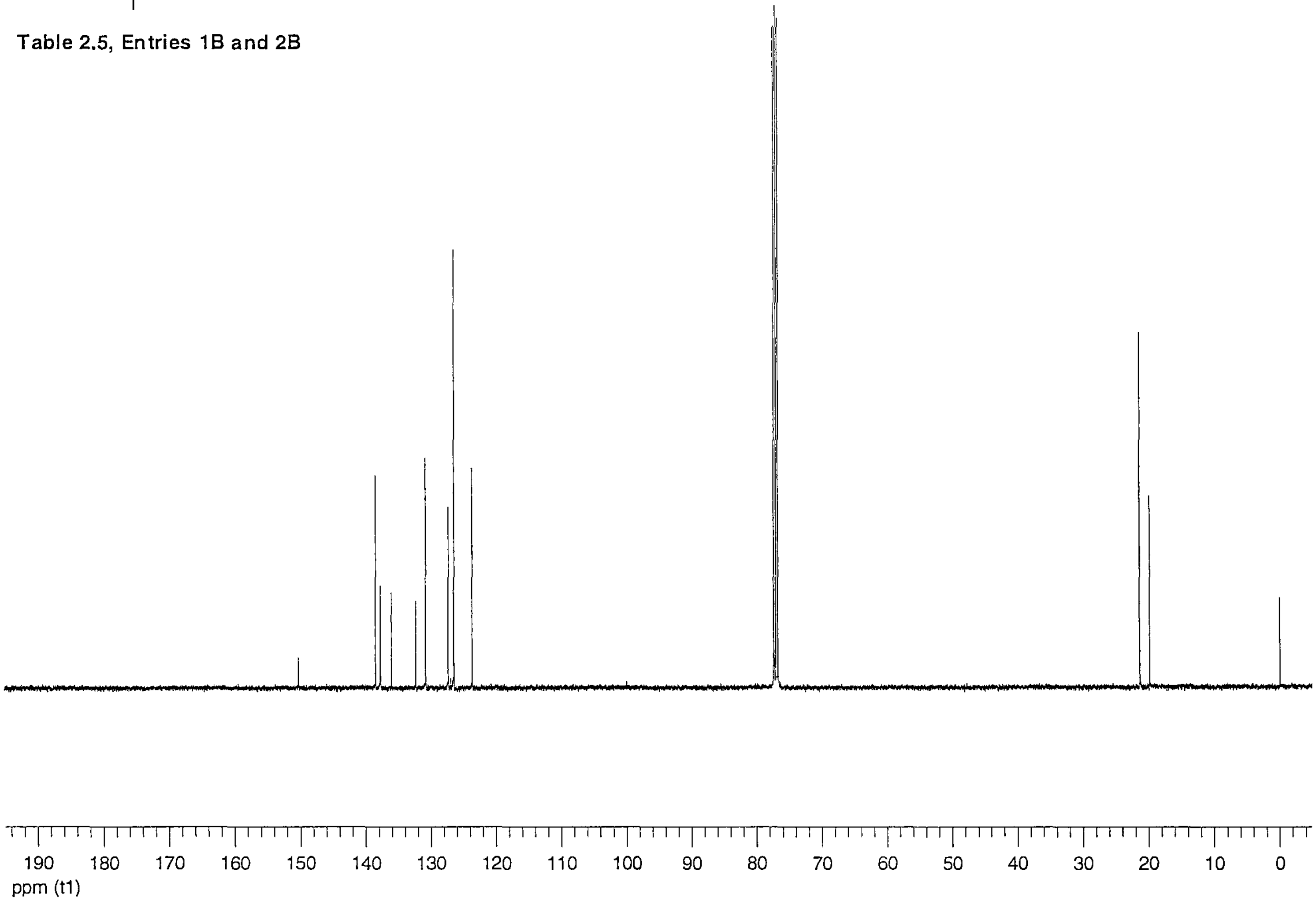

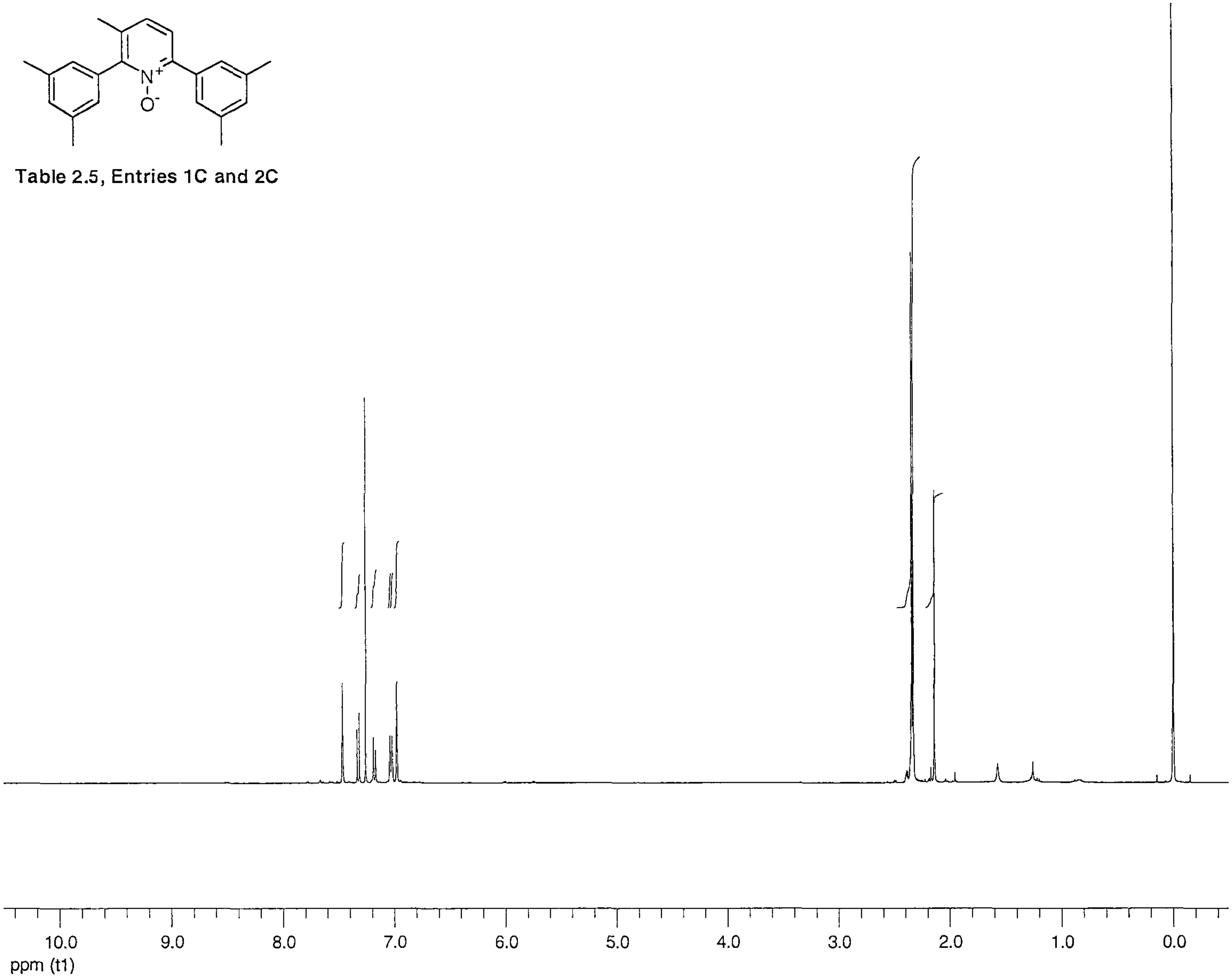

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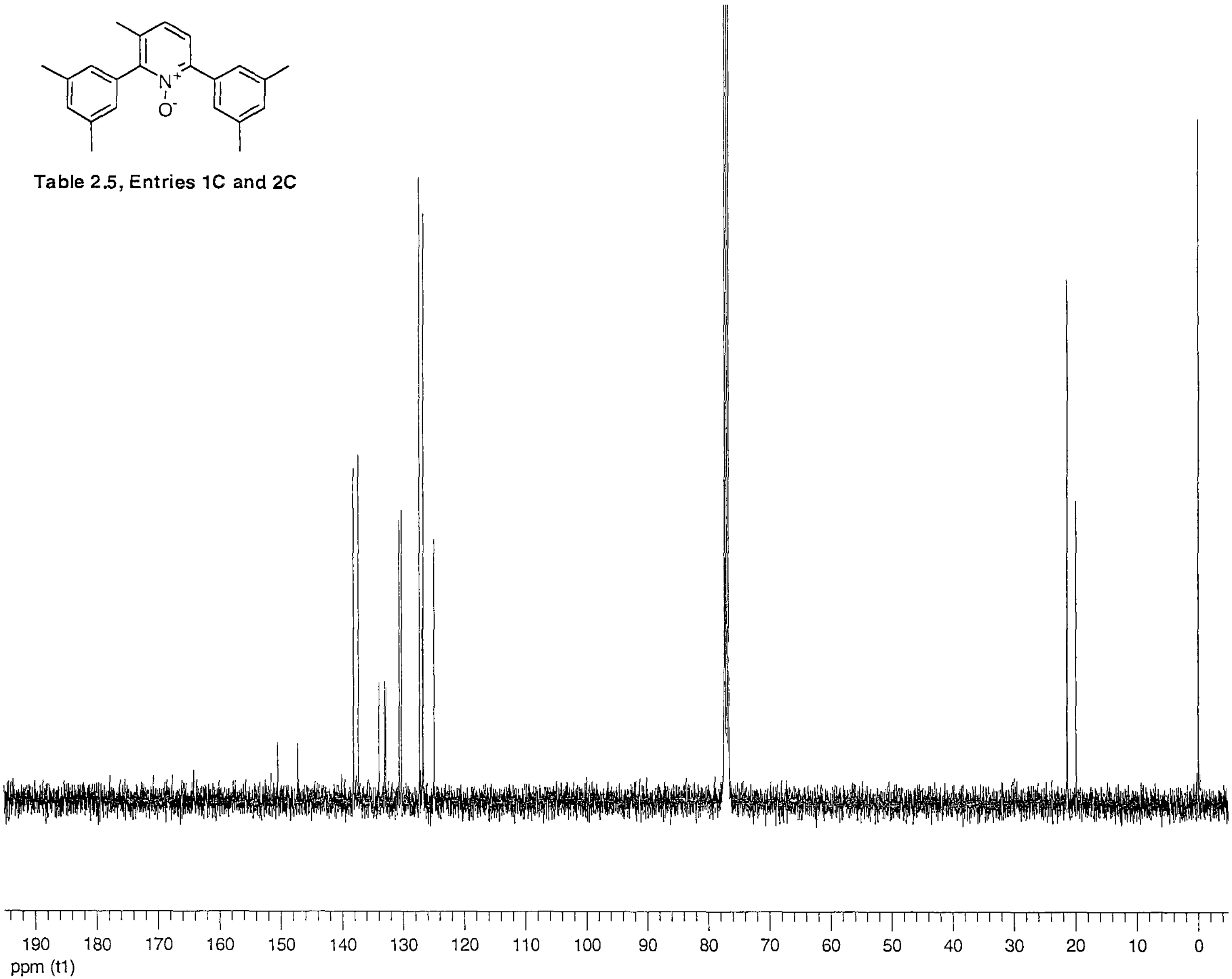

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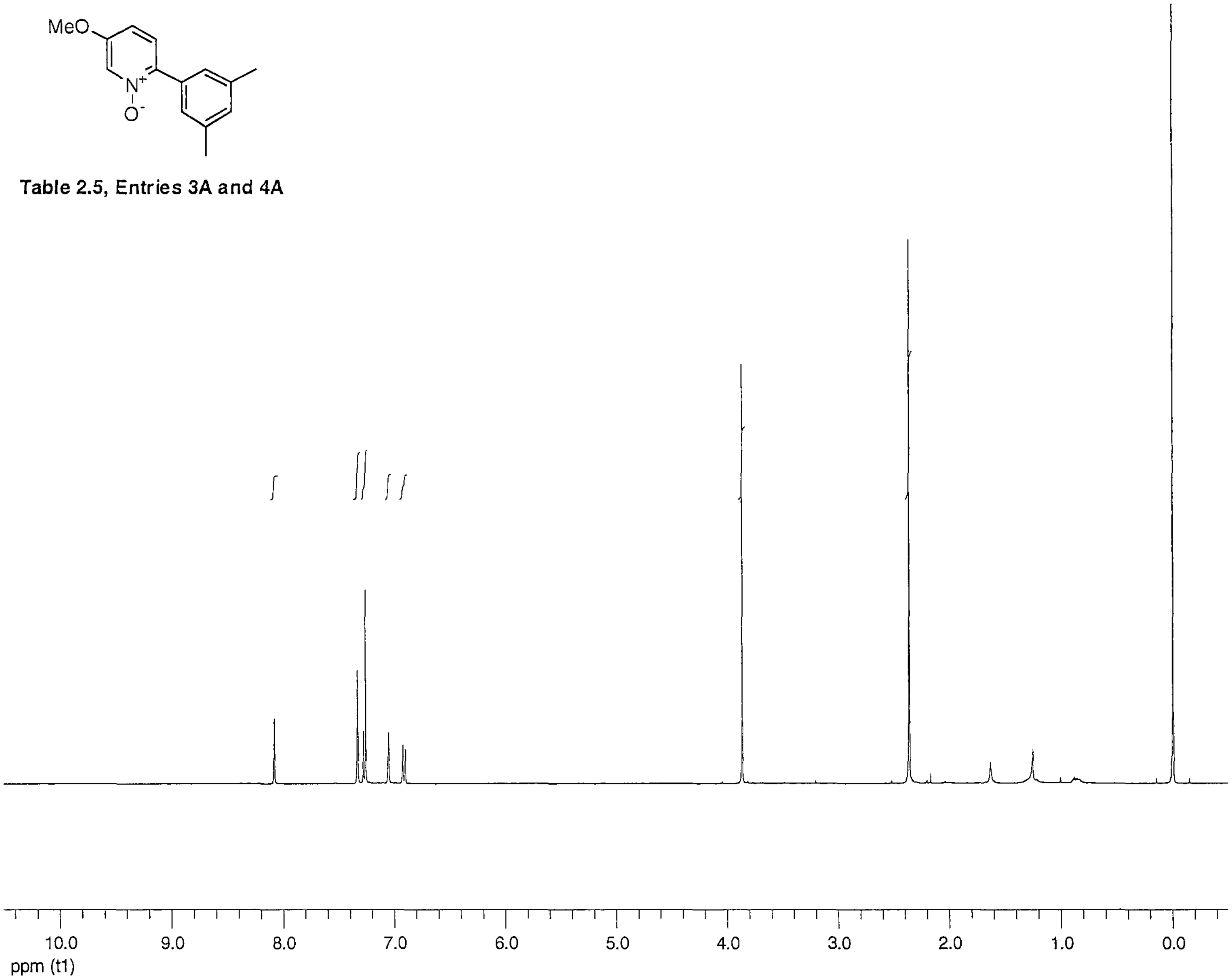

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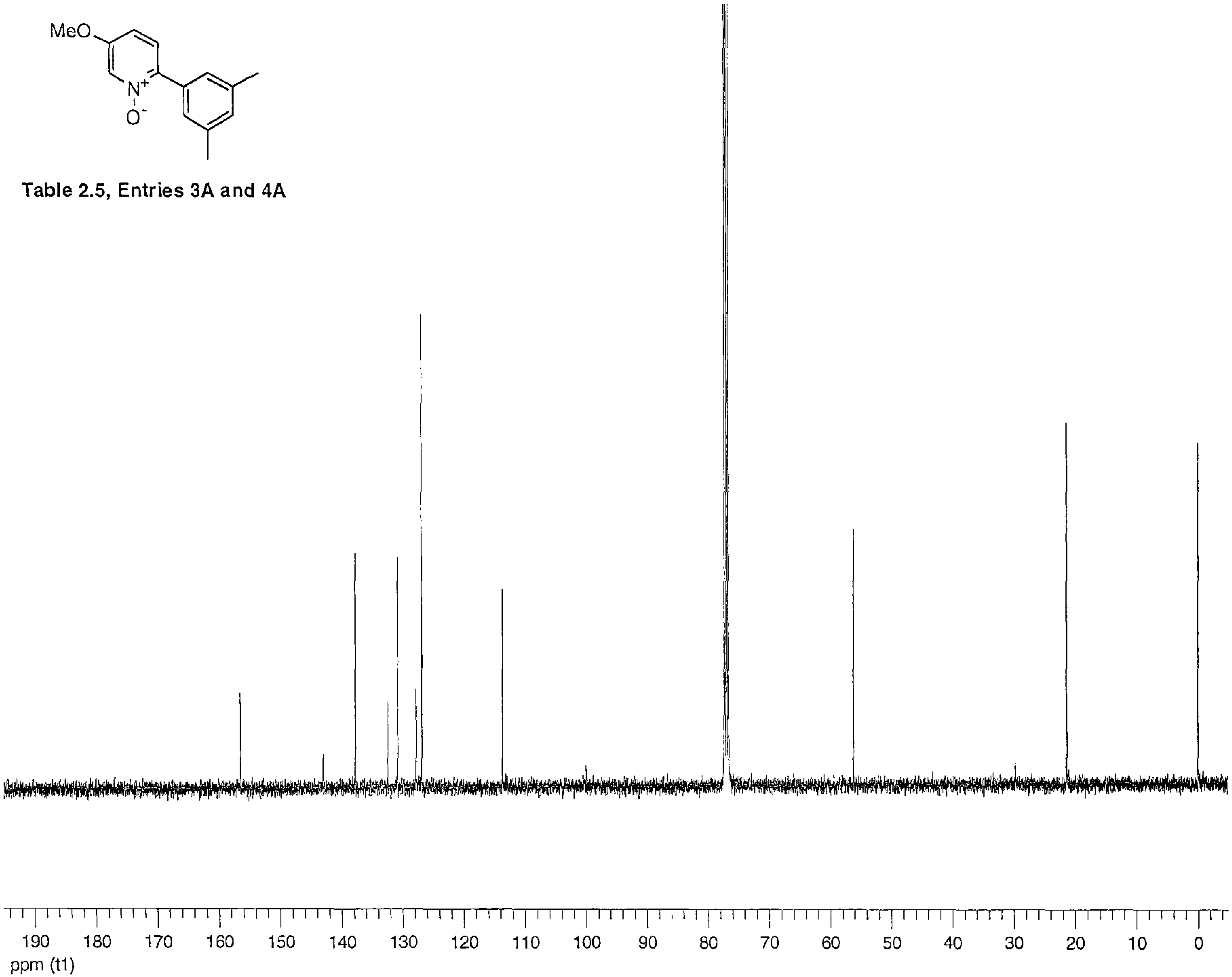

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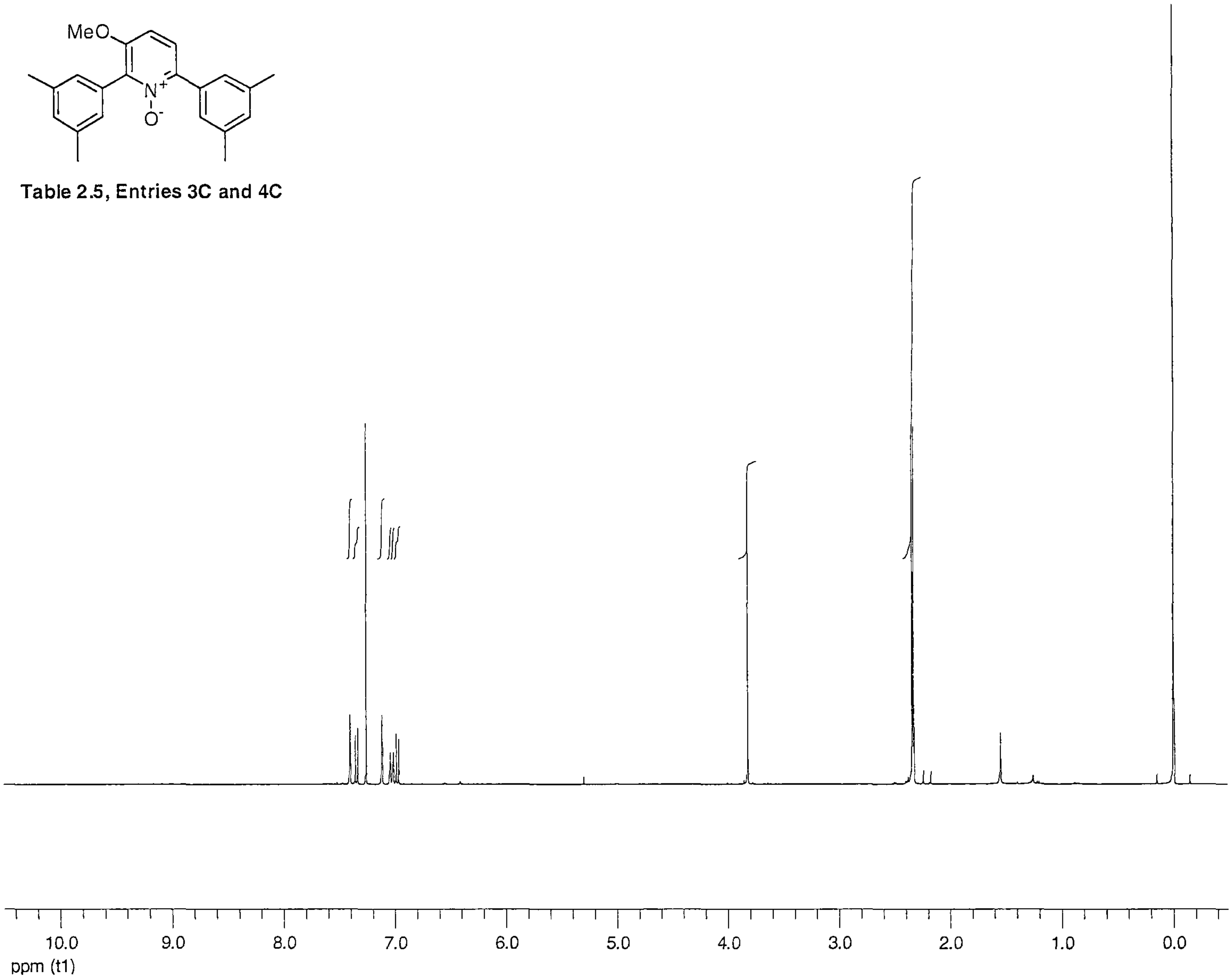

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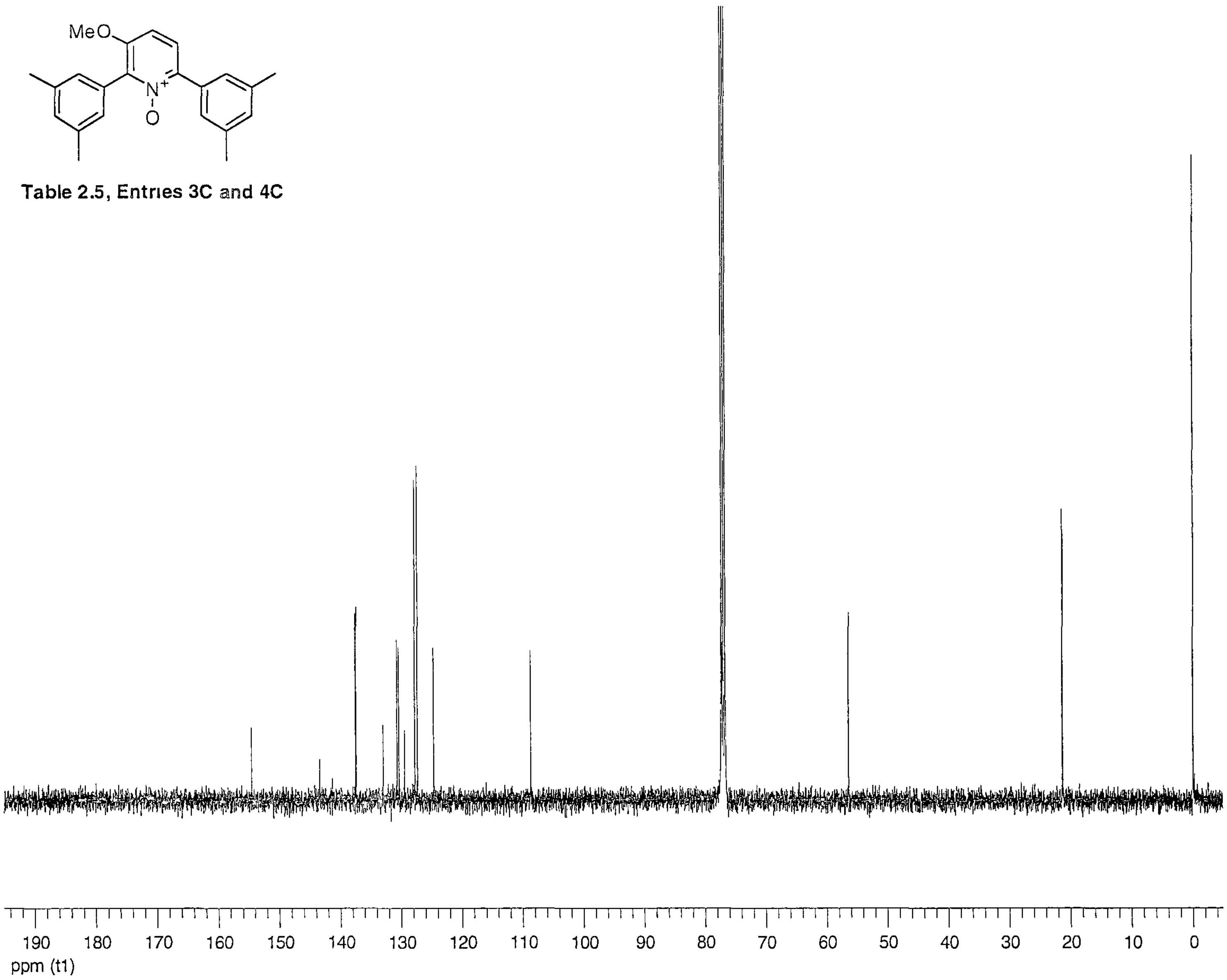

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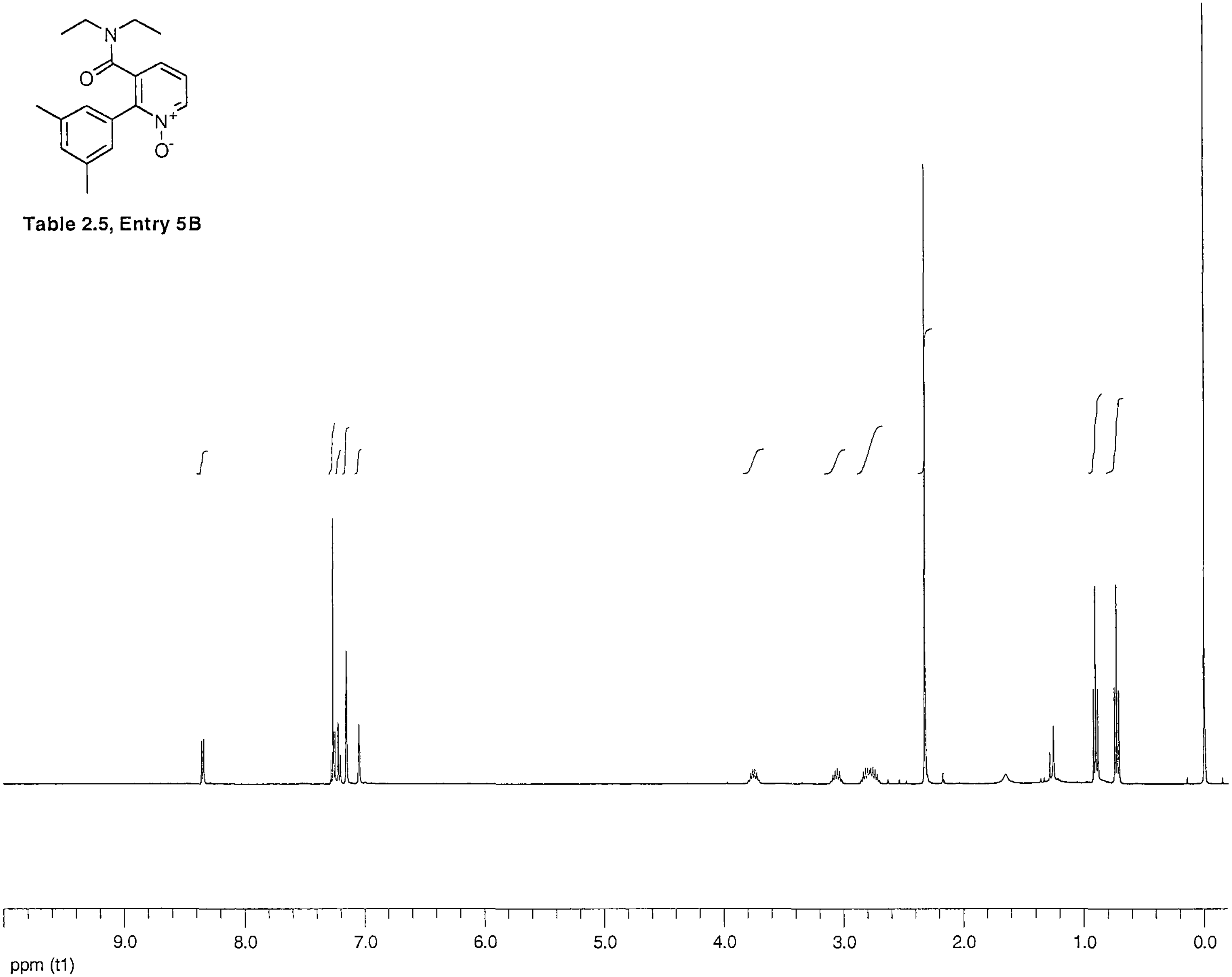

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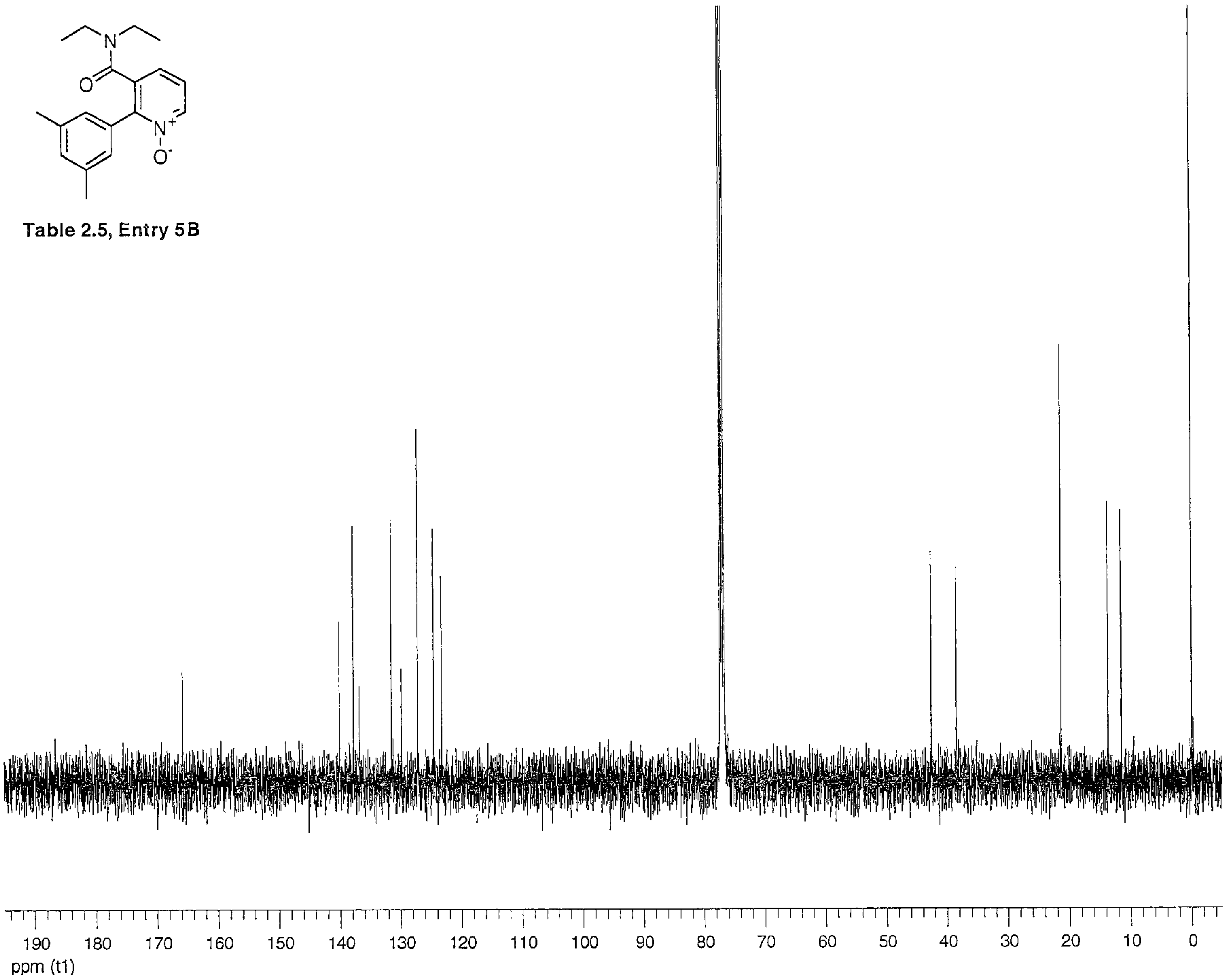

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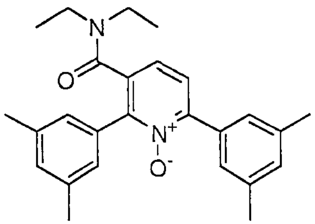

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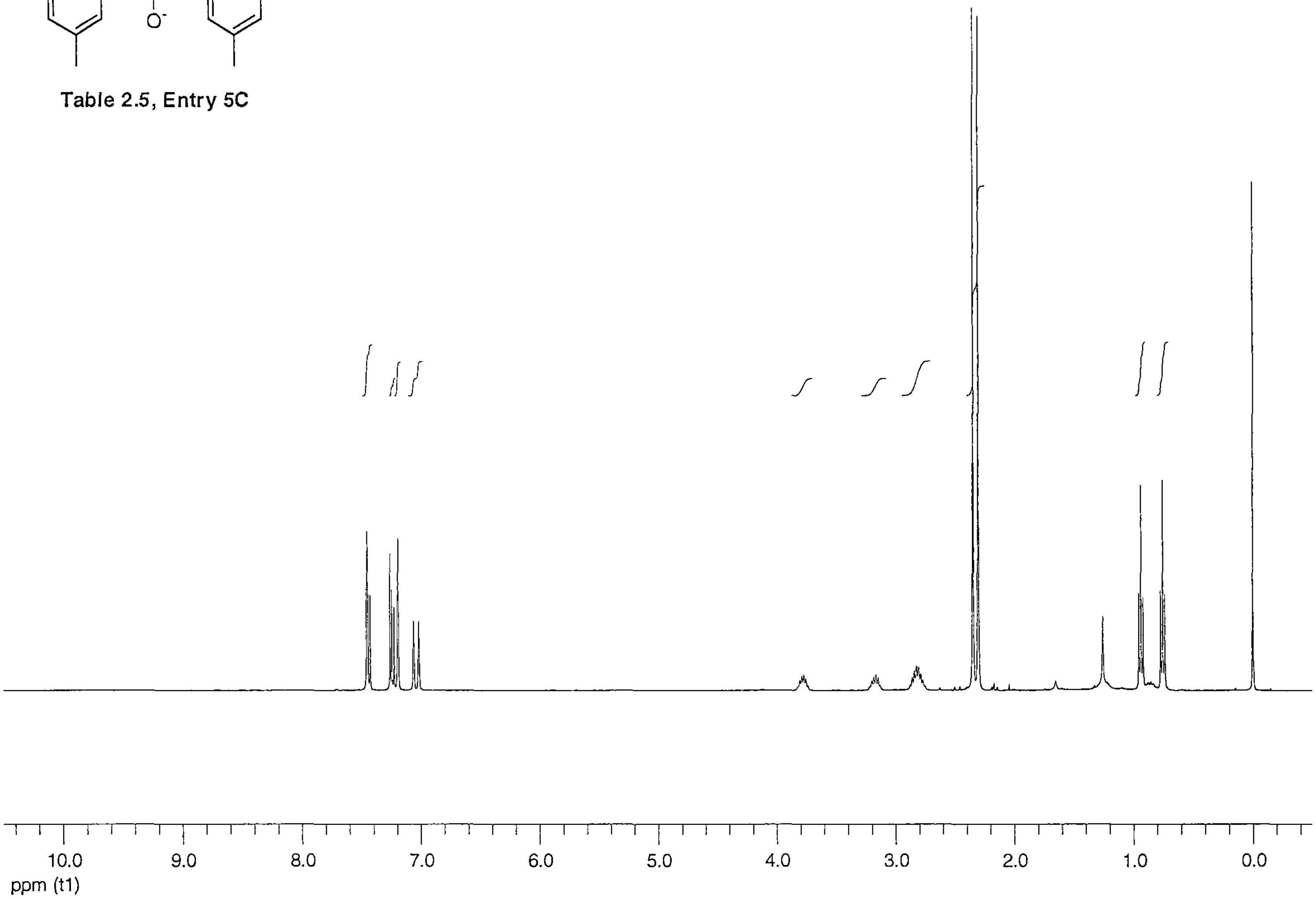

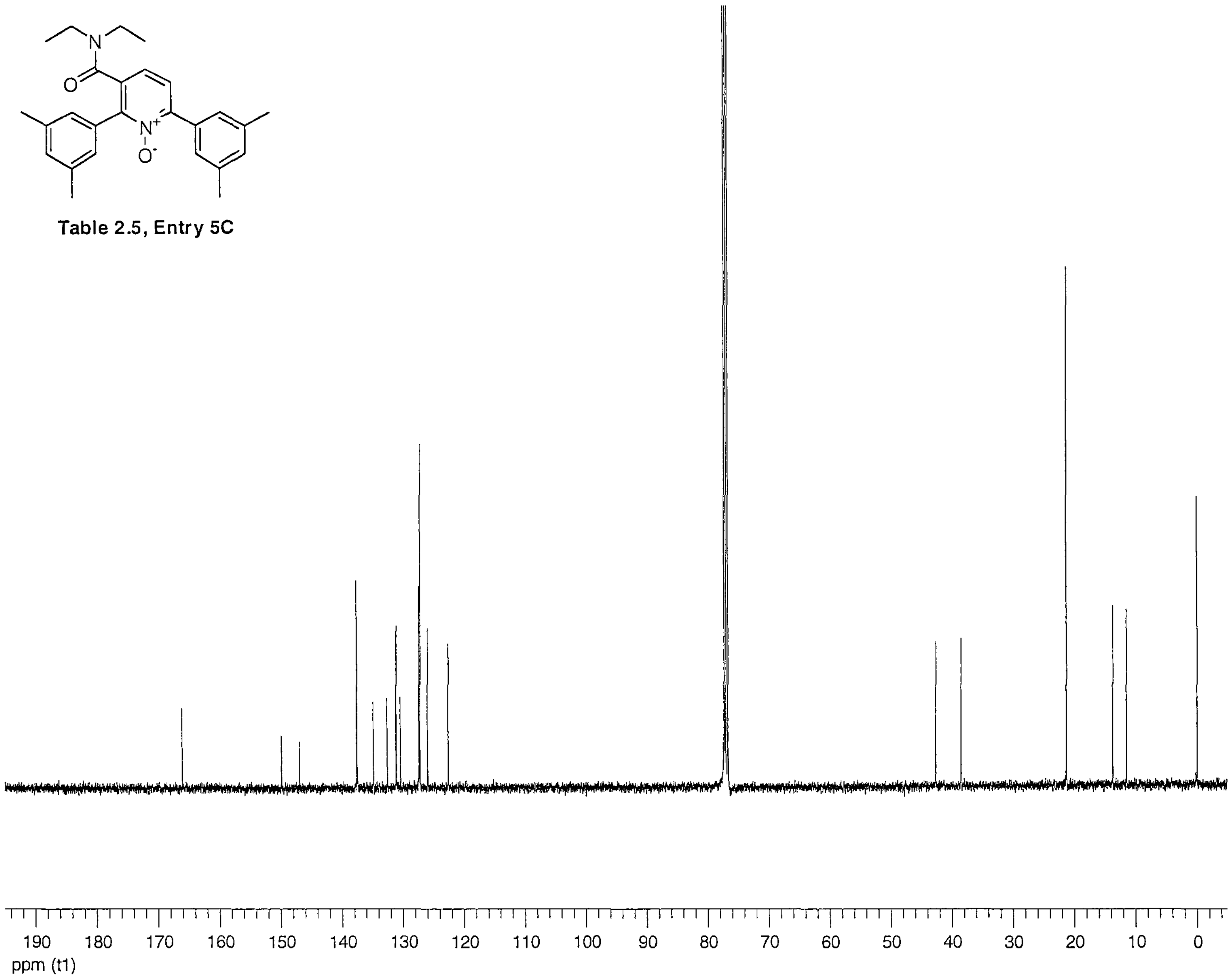

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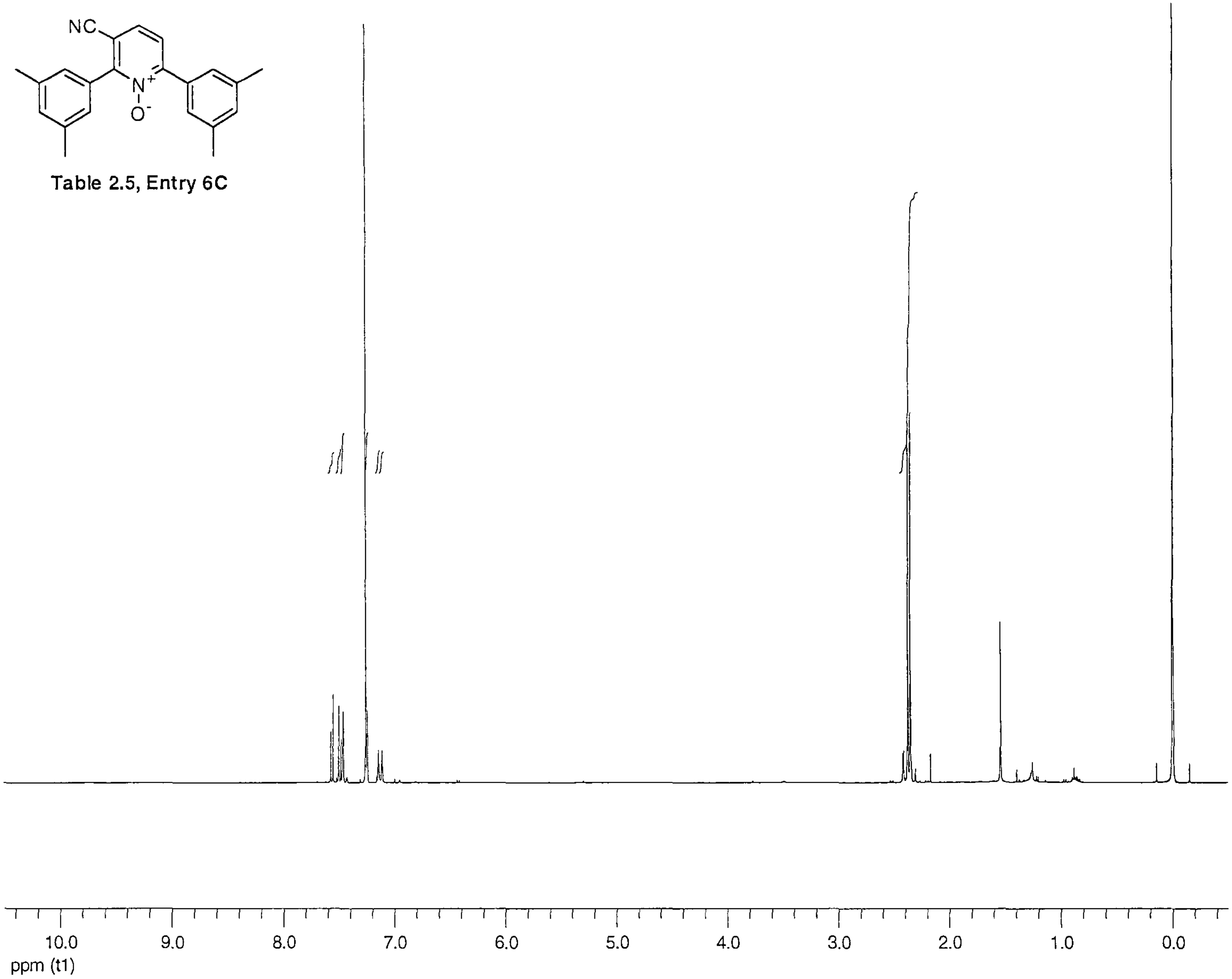
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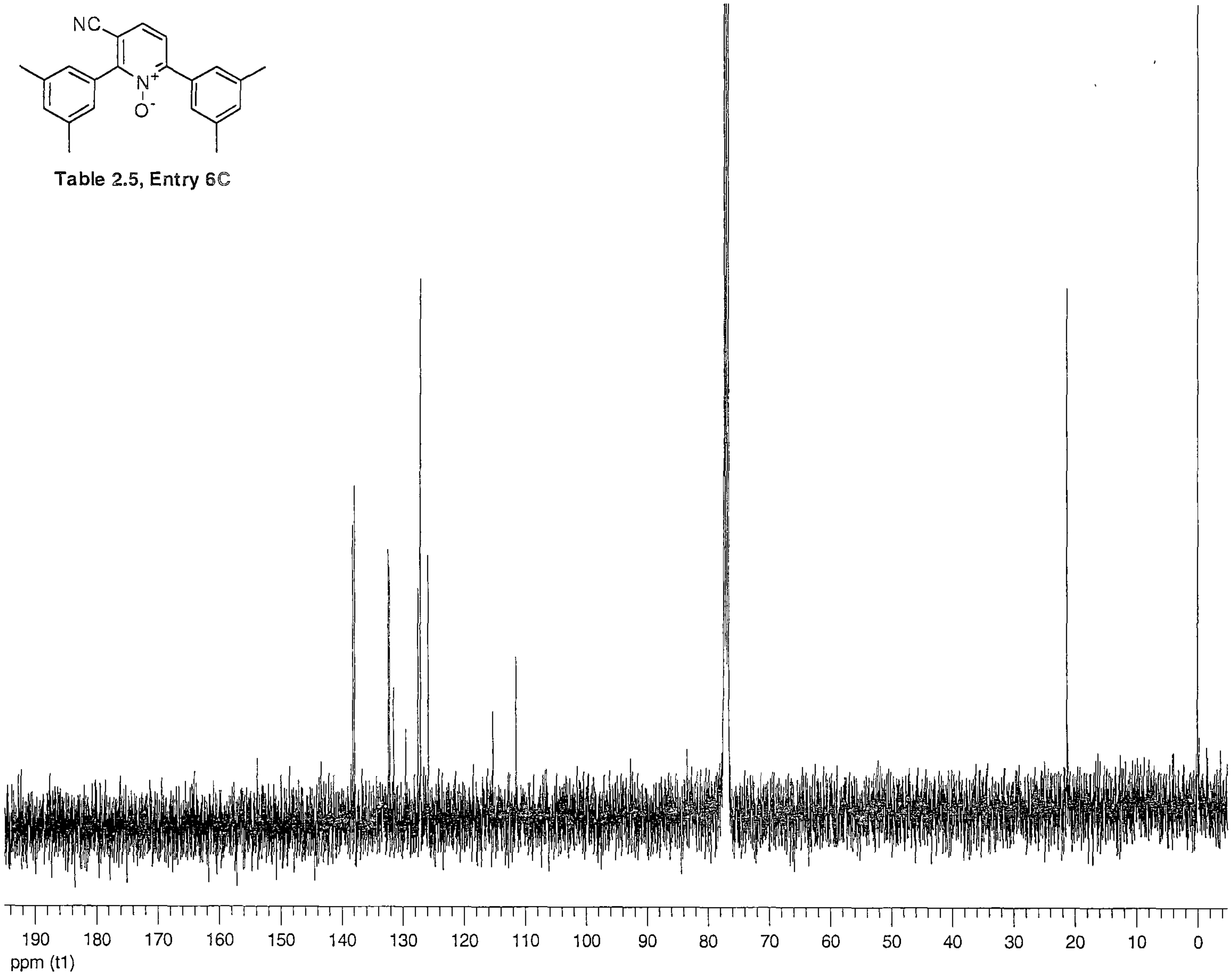

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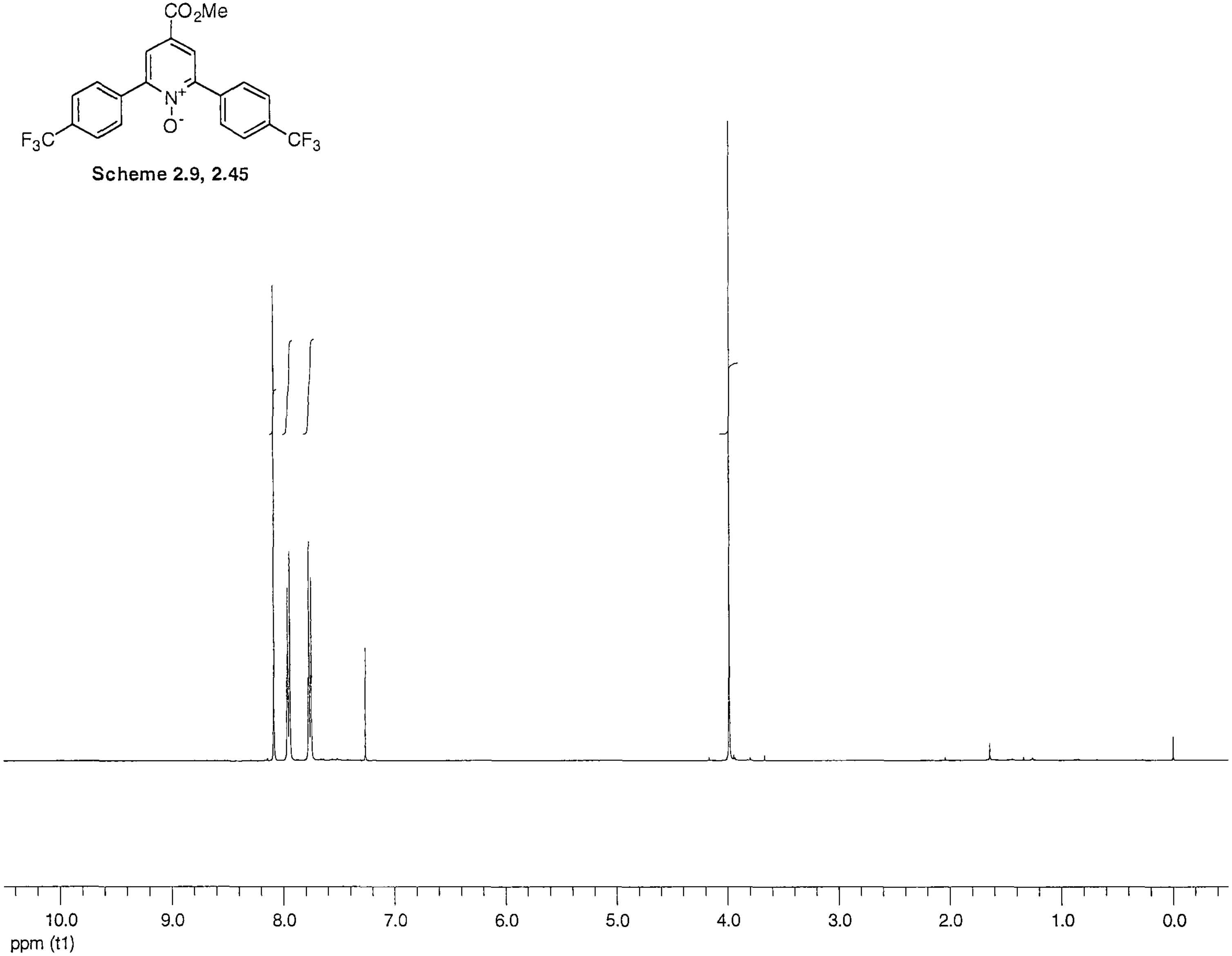
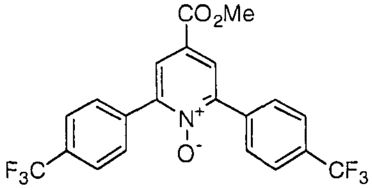
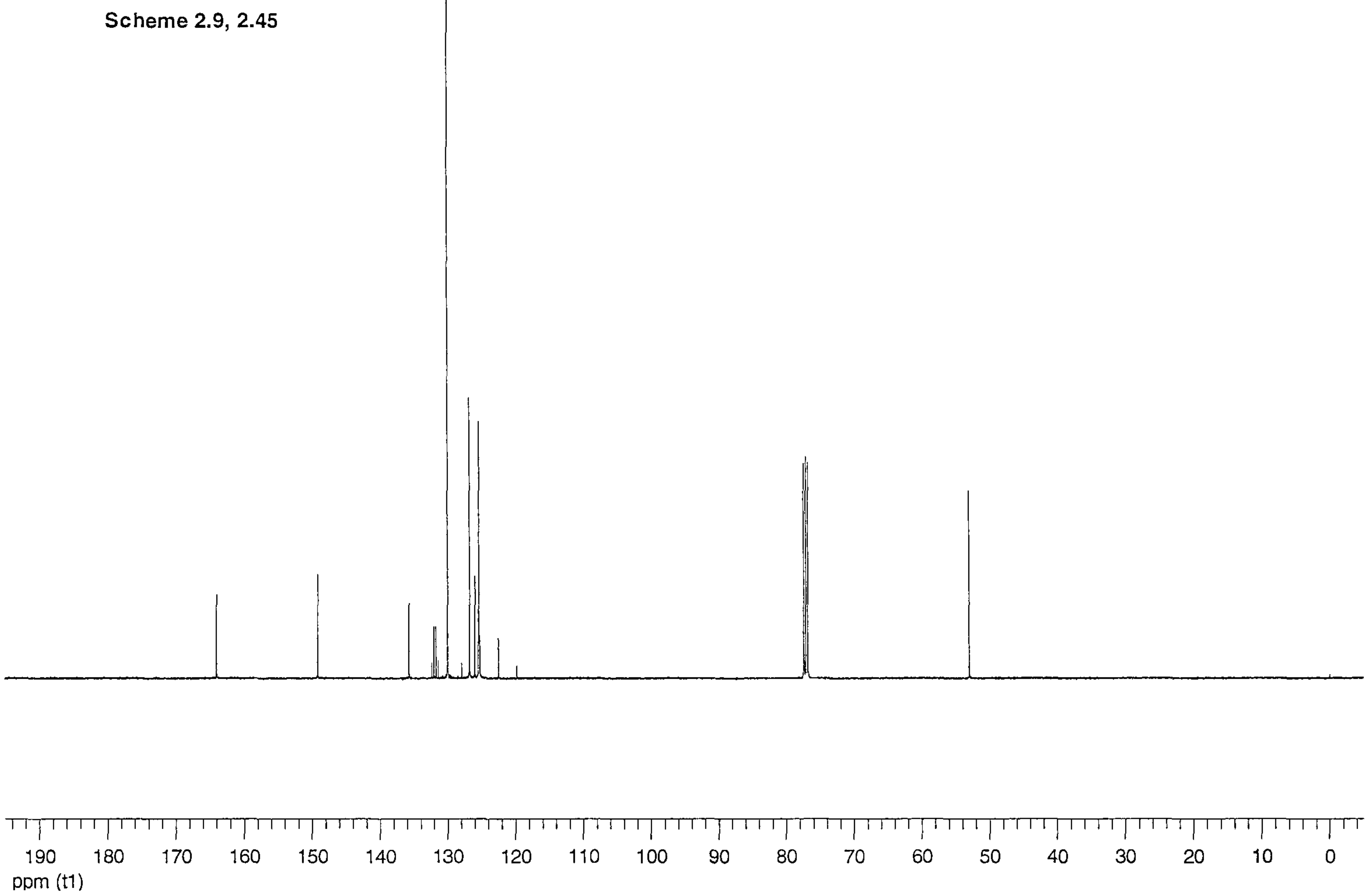
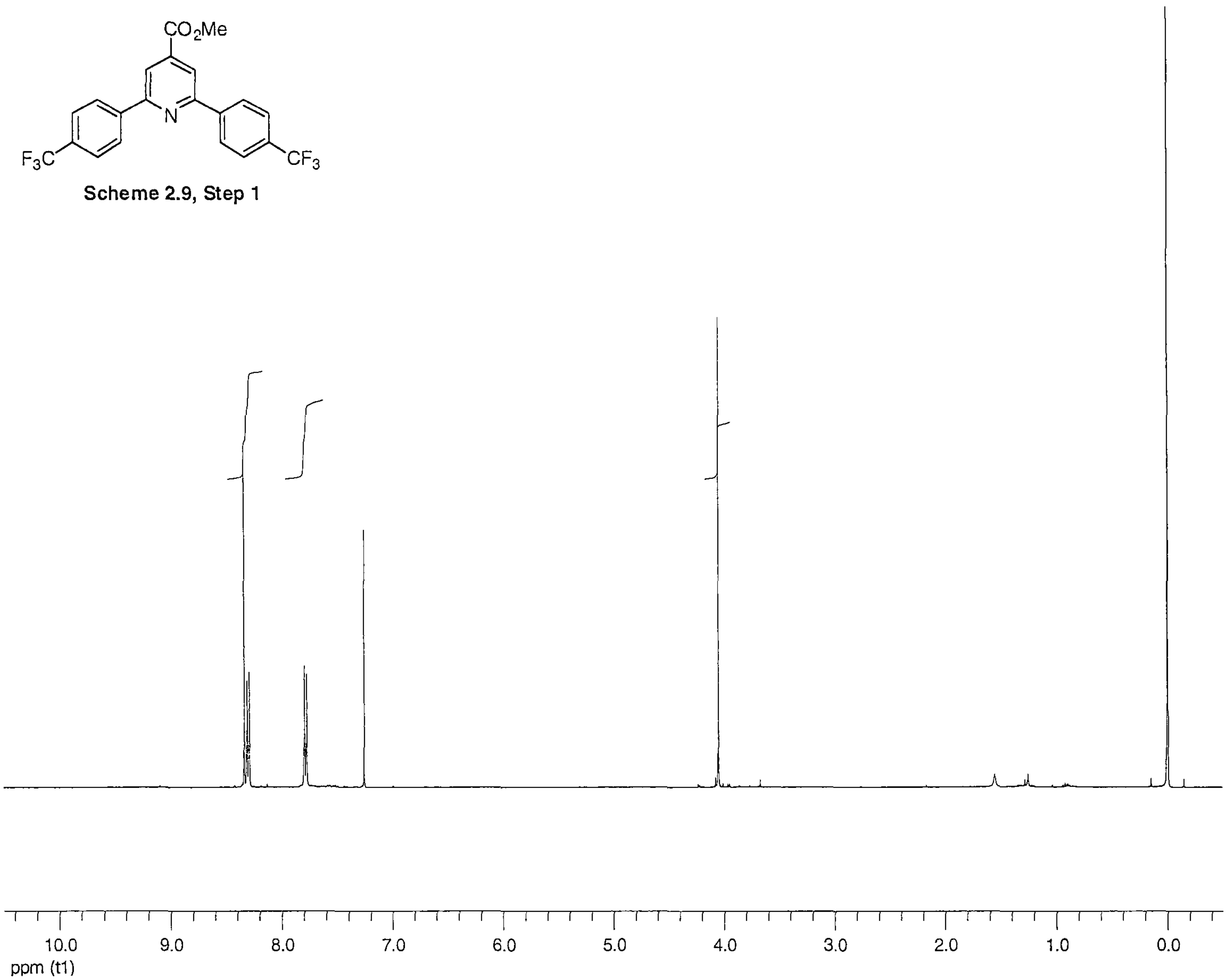


Scheme 2.9, 2.45

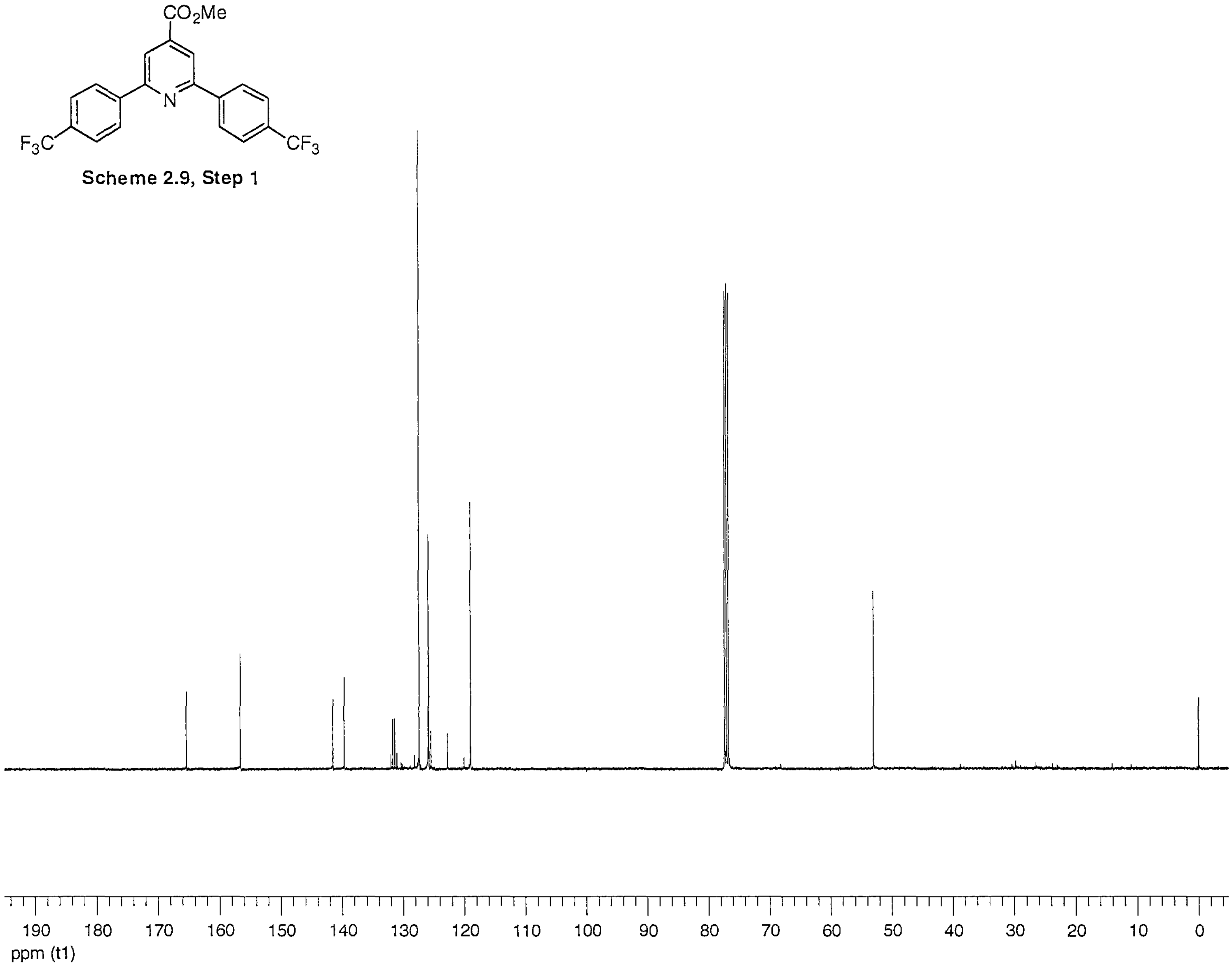


Scheme 2.9, 2.45

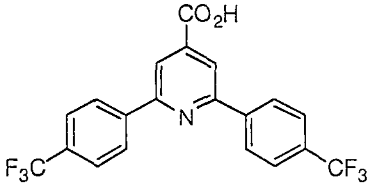




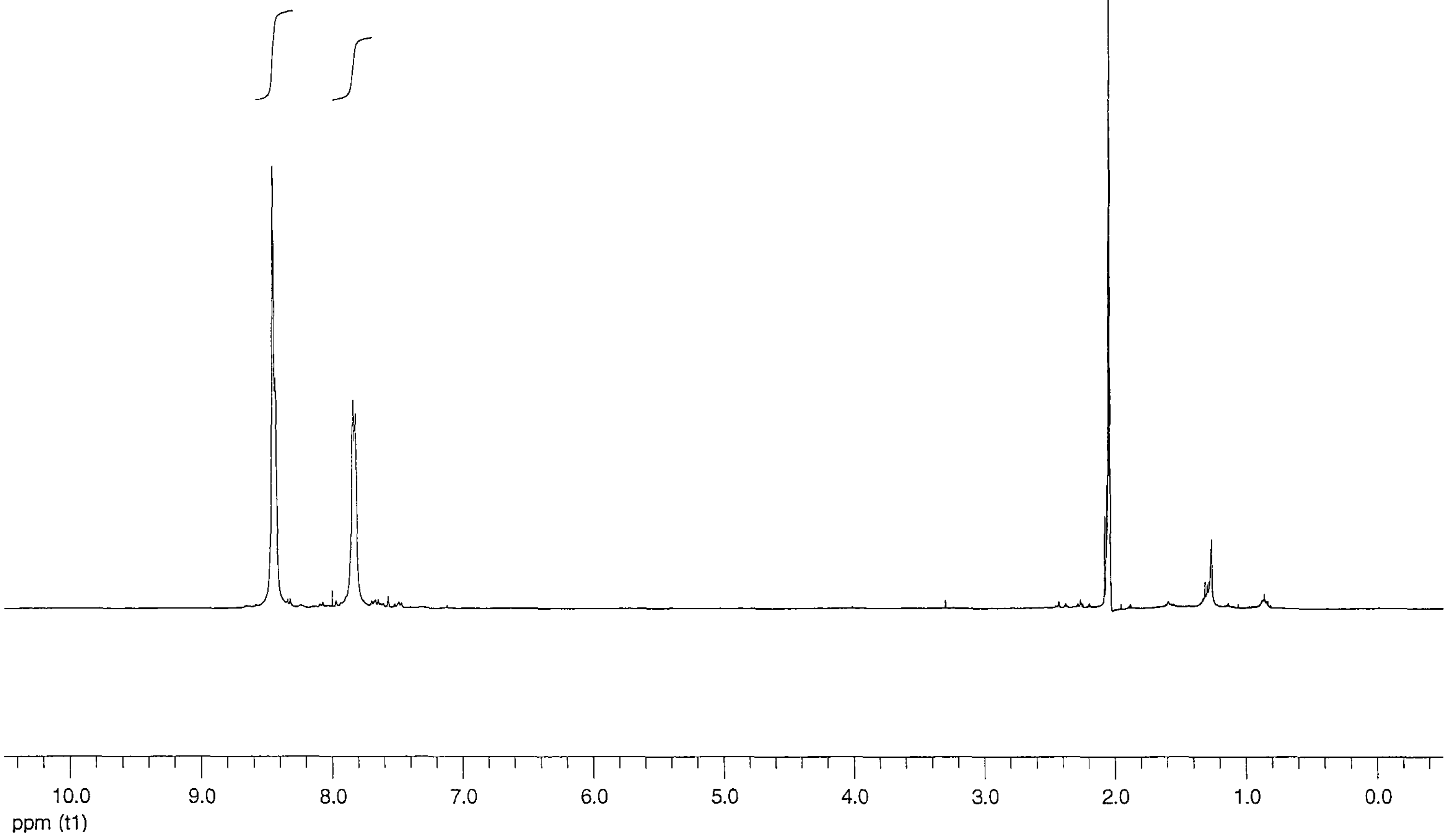
Scheme 2.9, Step 1

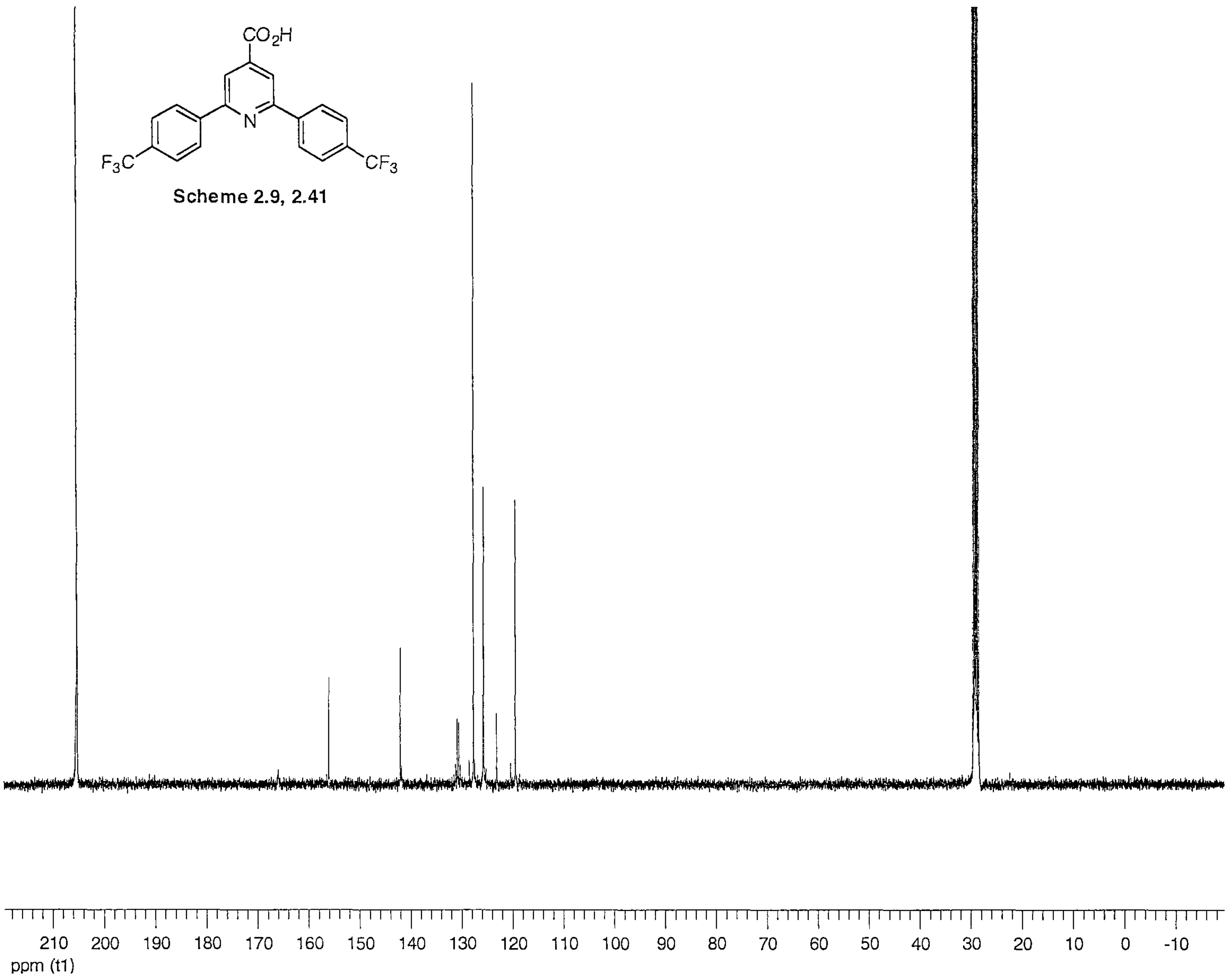


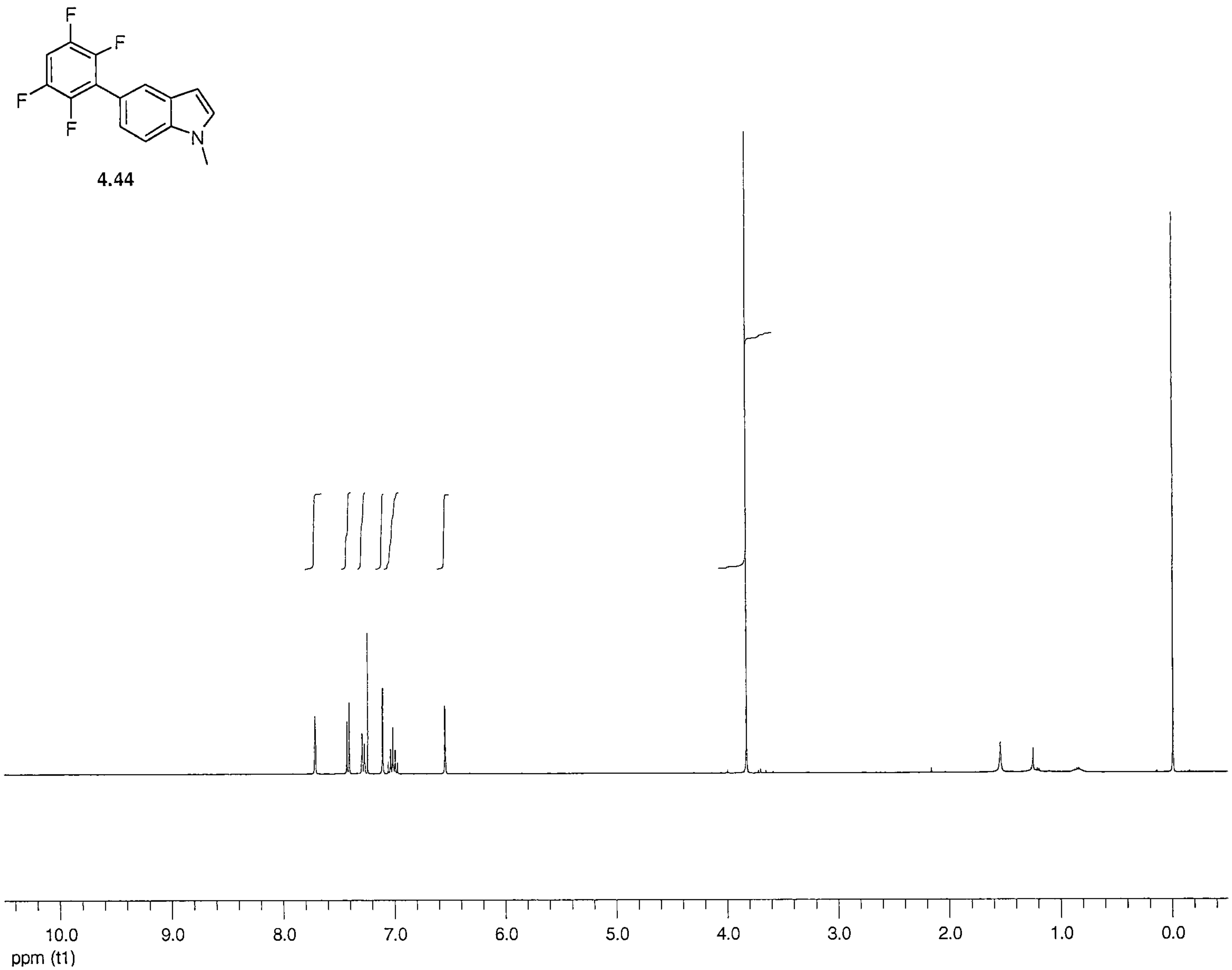
Scheme 2.9, Step 1



Scheme 2.9, 2.41




Scheme 2.9, 2.41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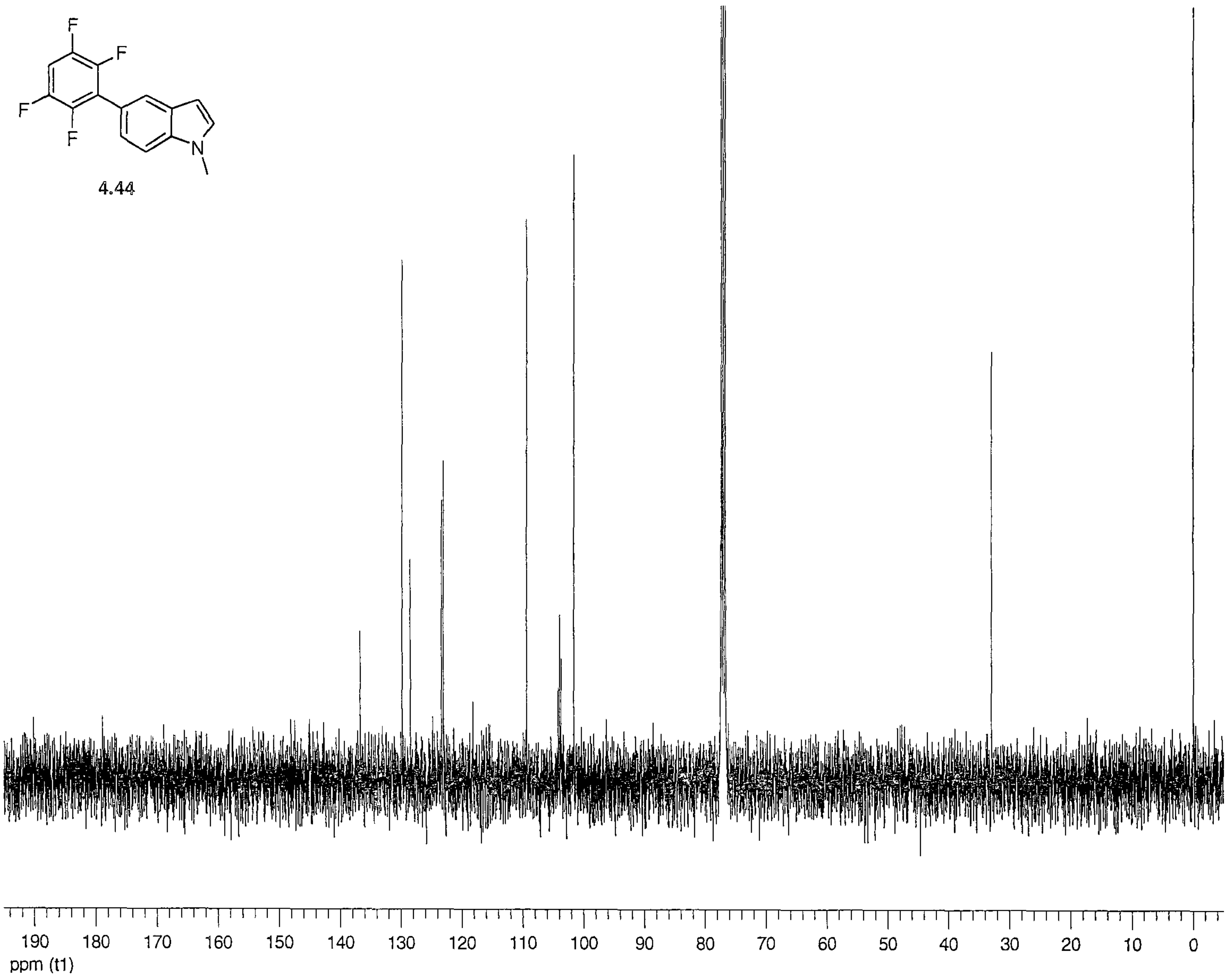
ppm (t1)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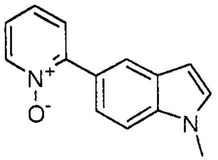

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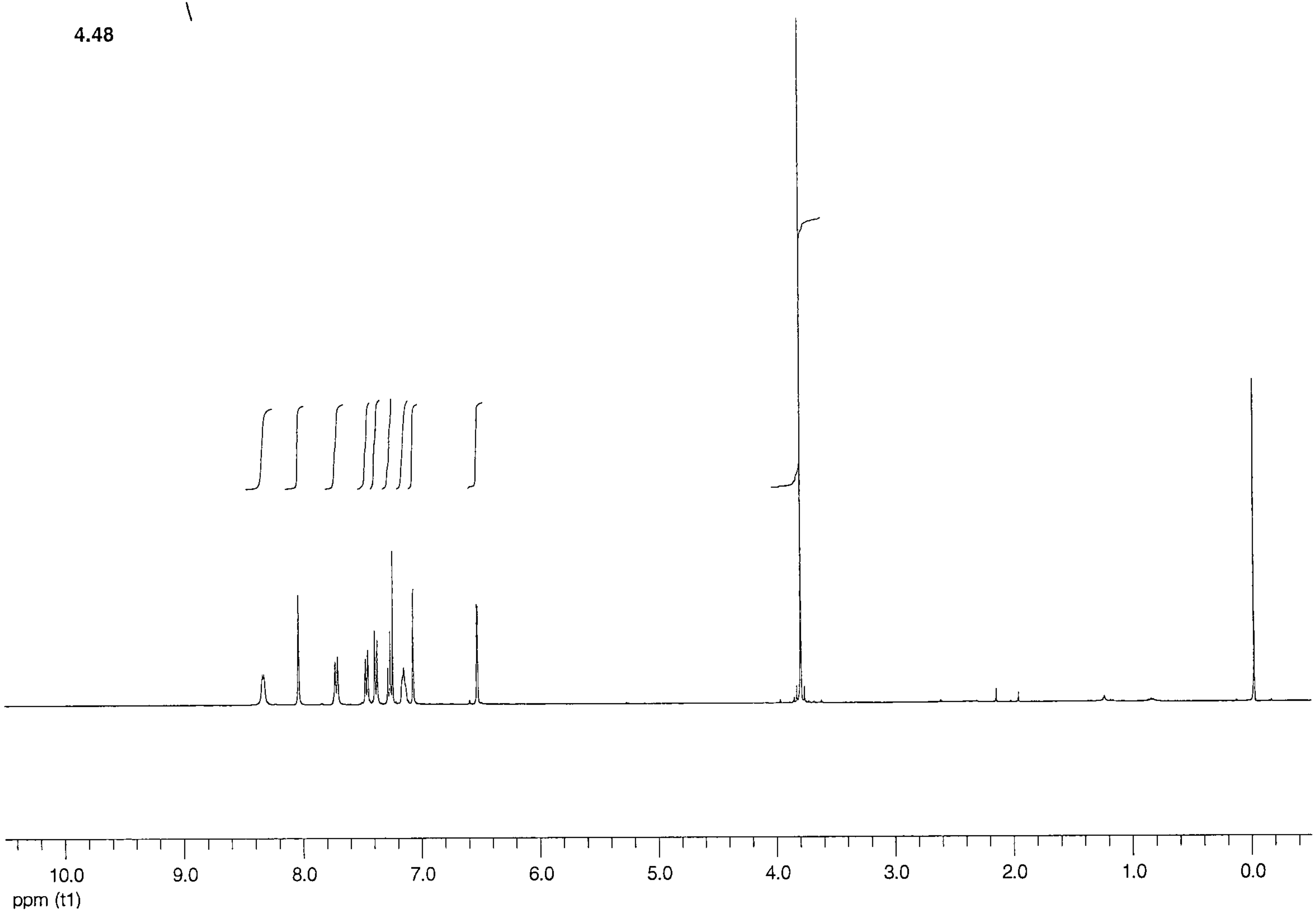

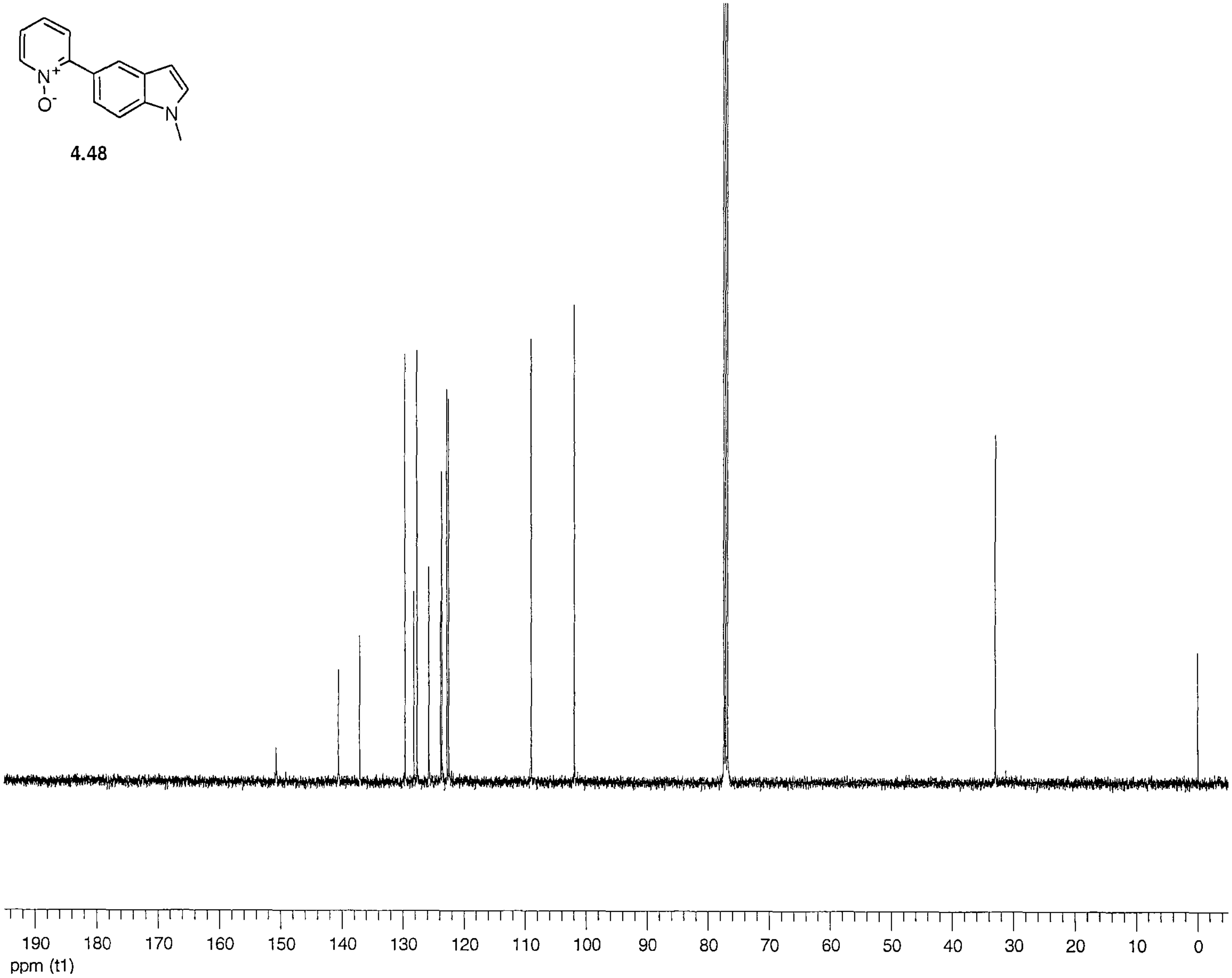
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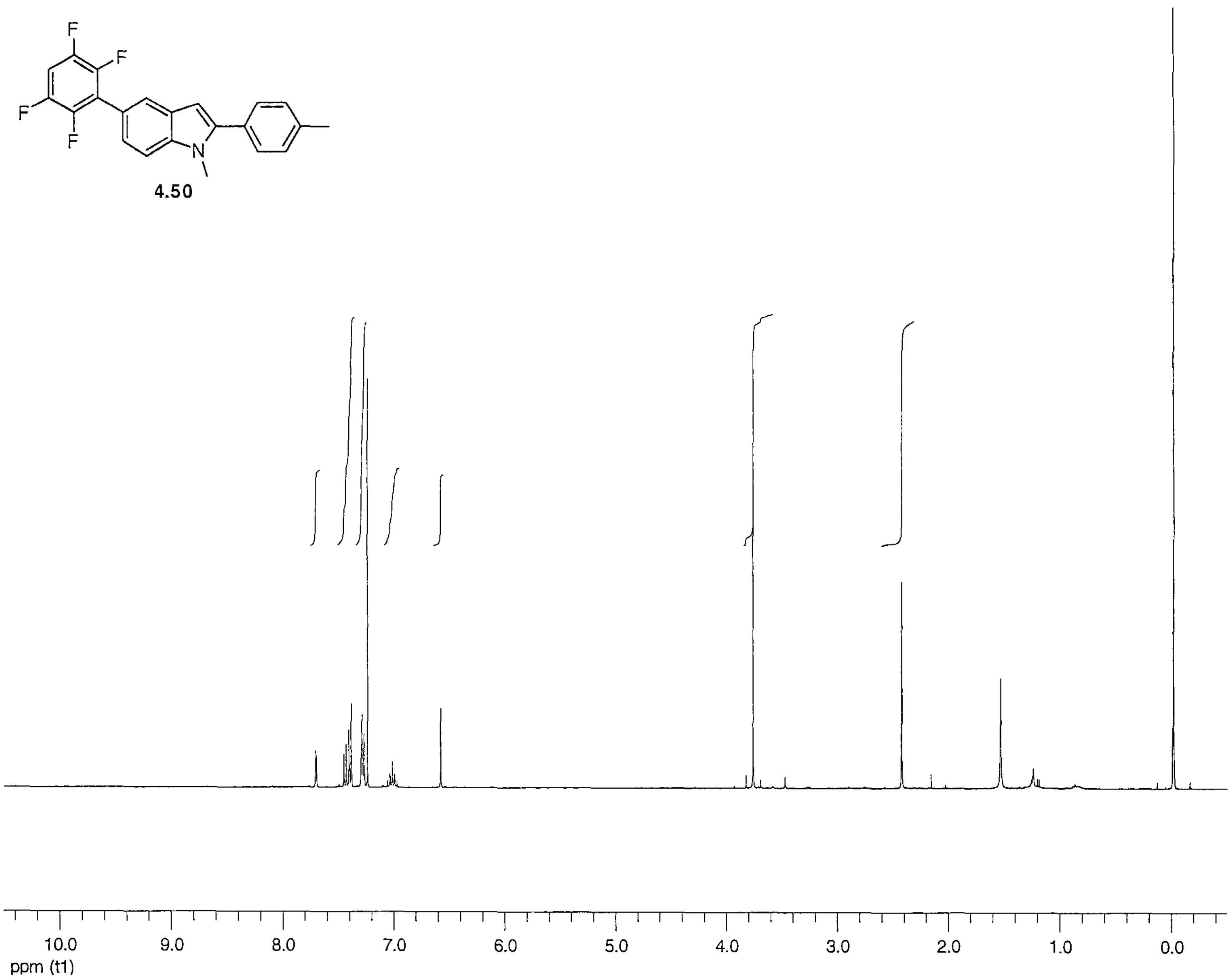

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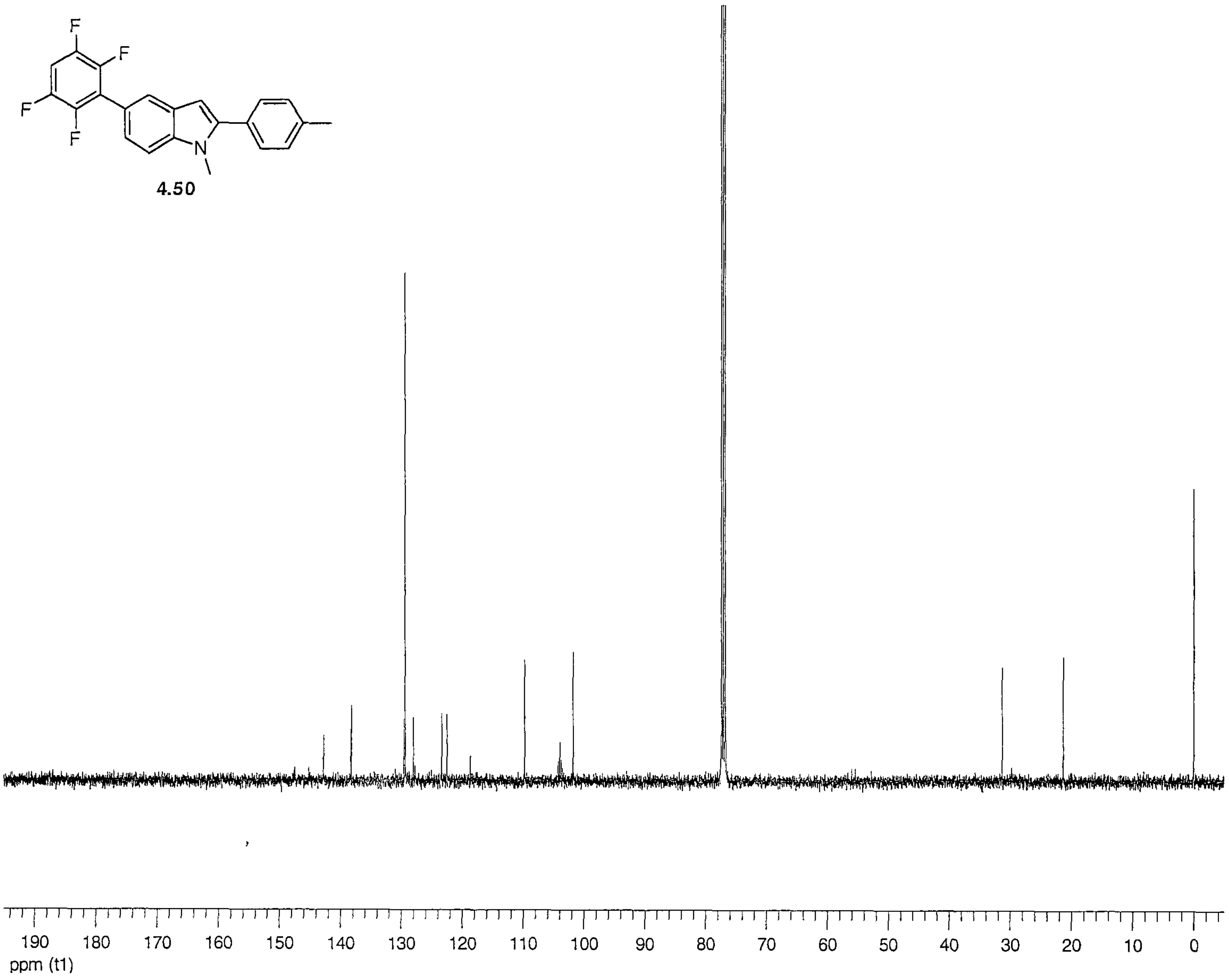

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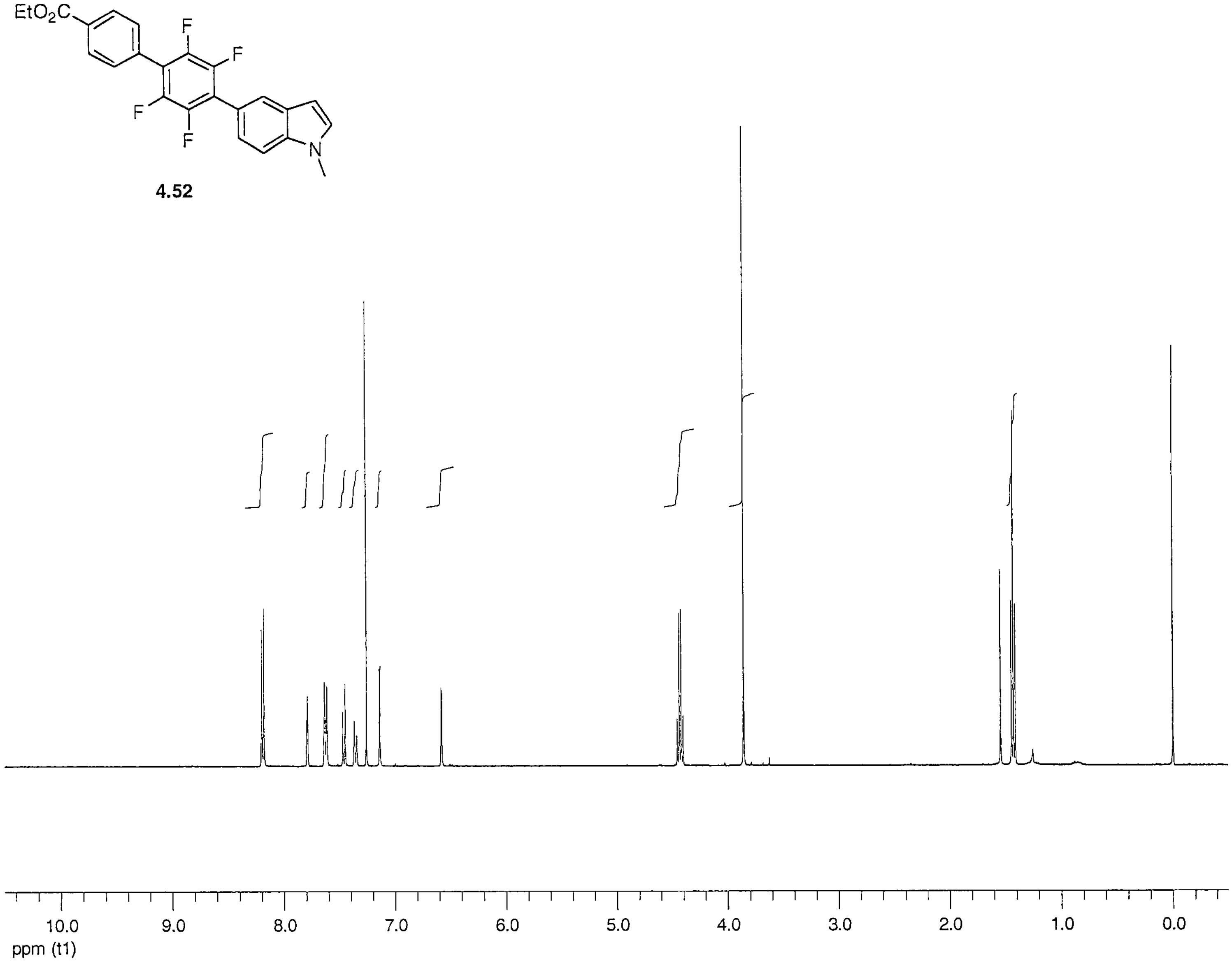

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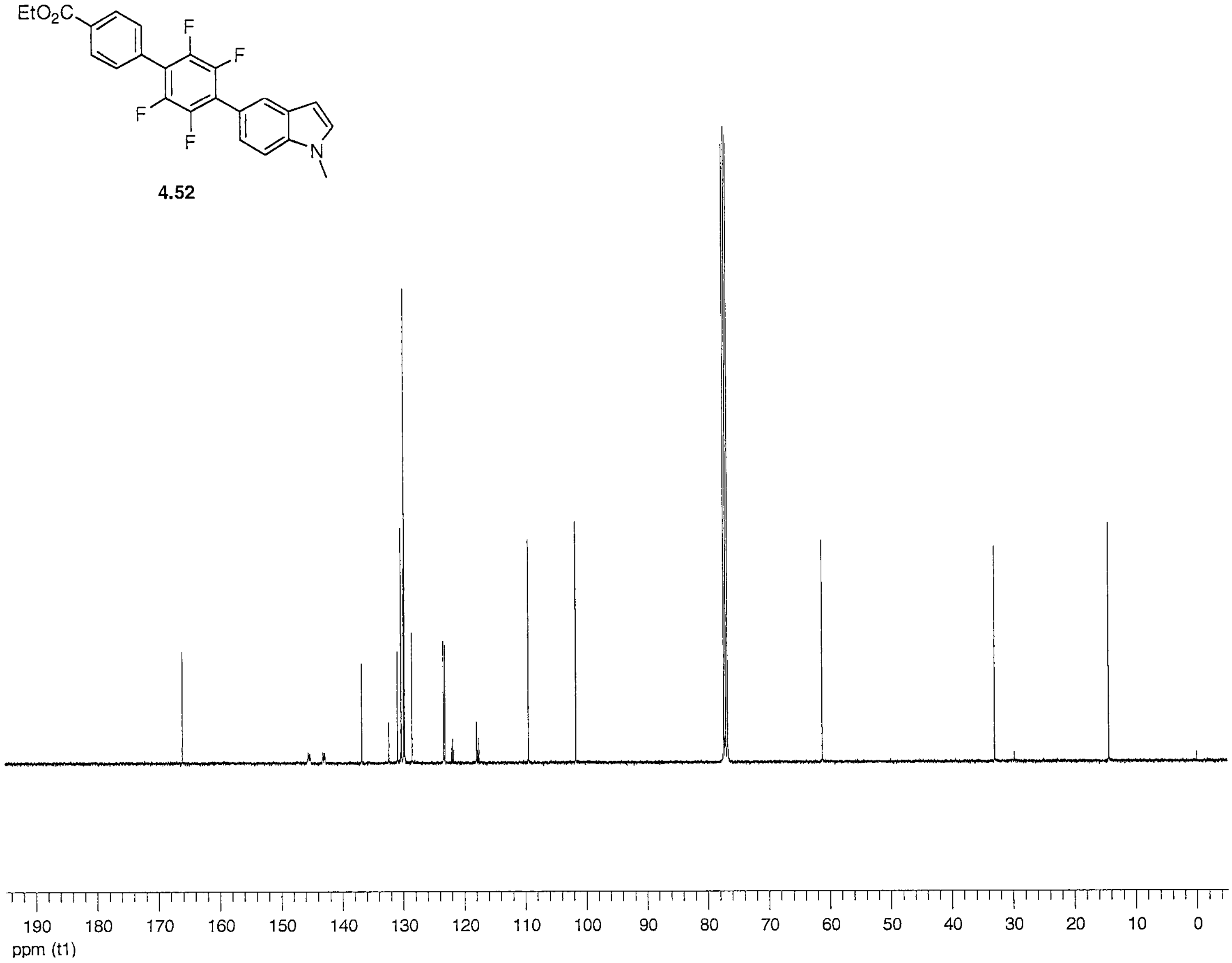
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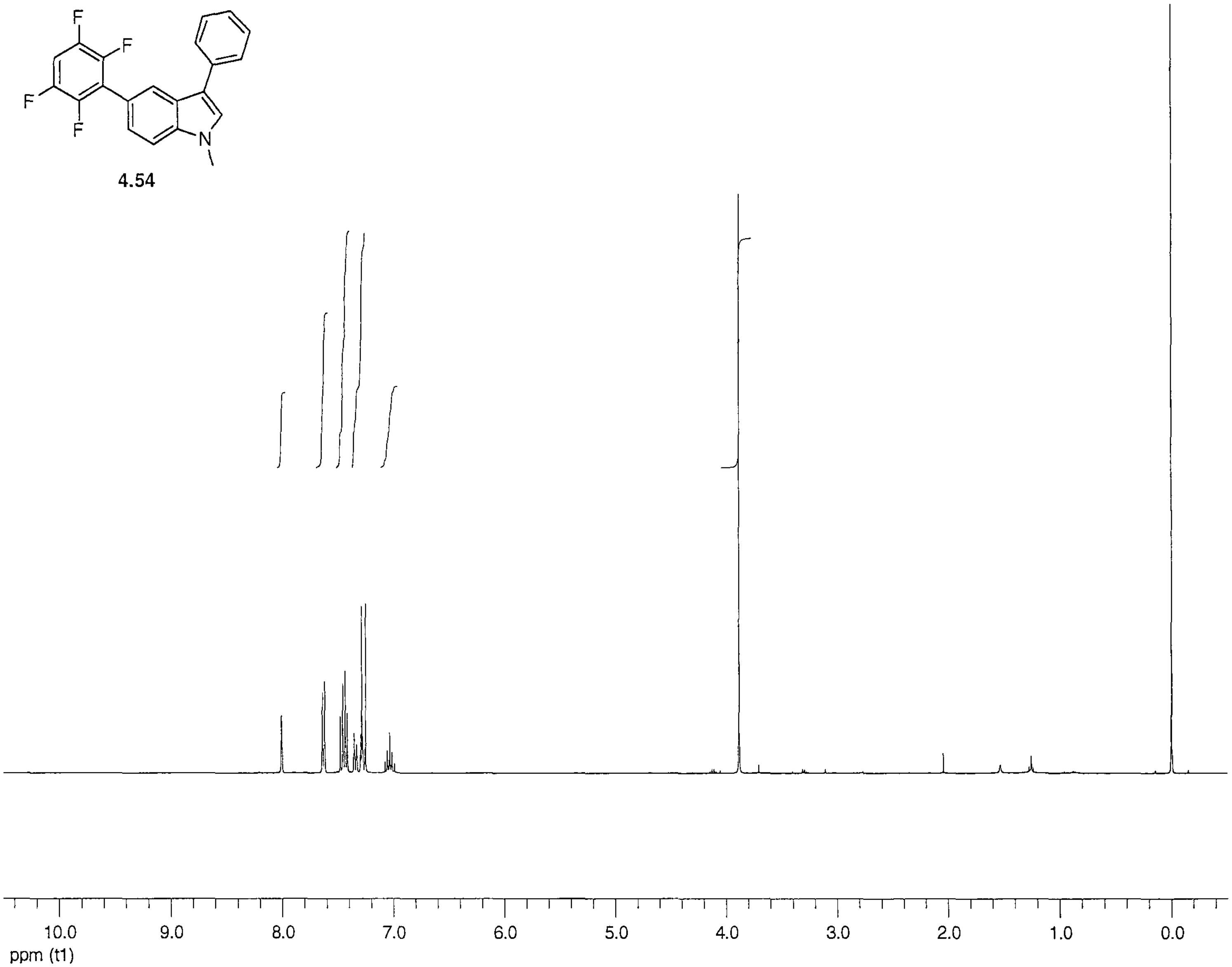

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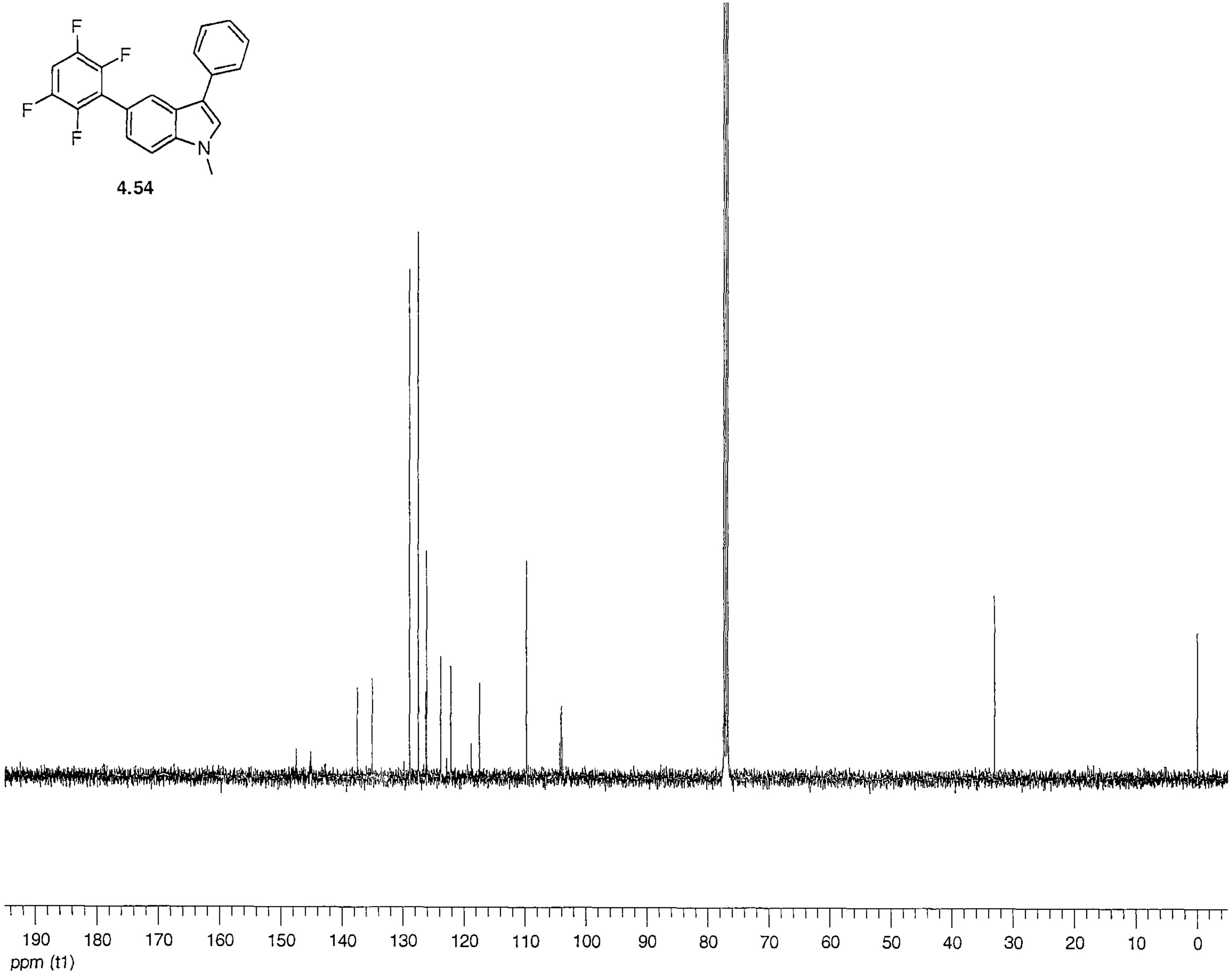
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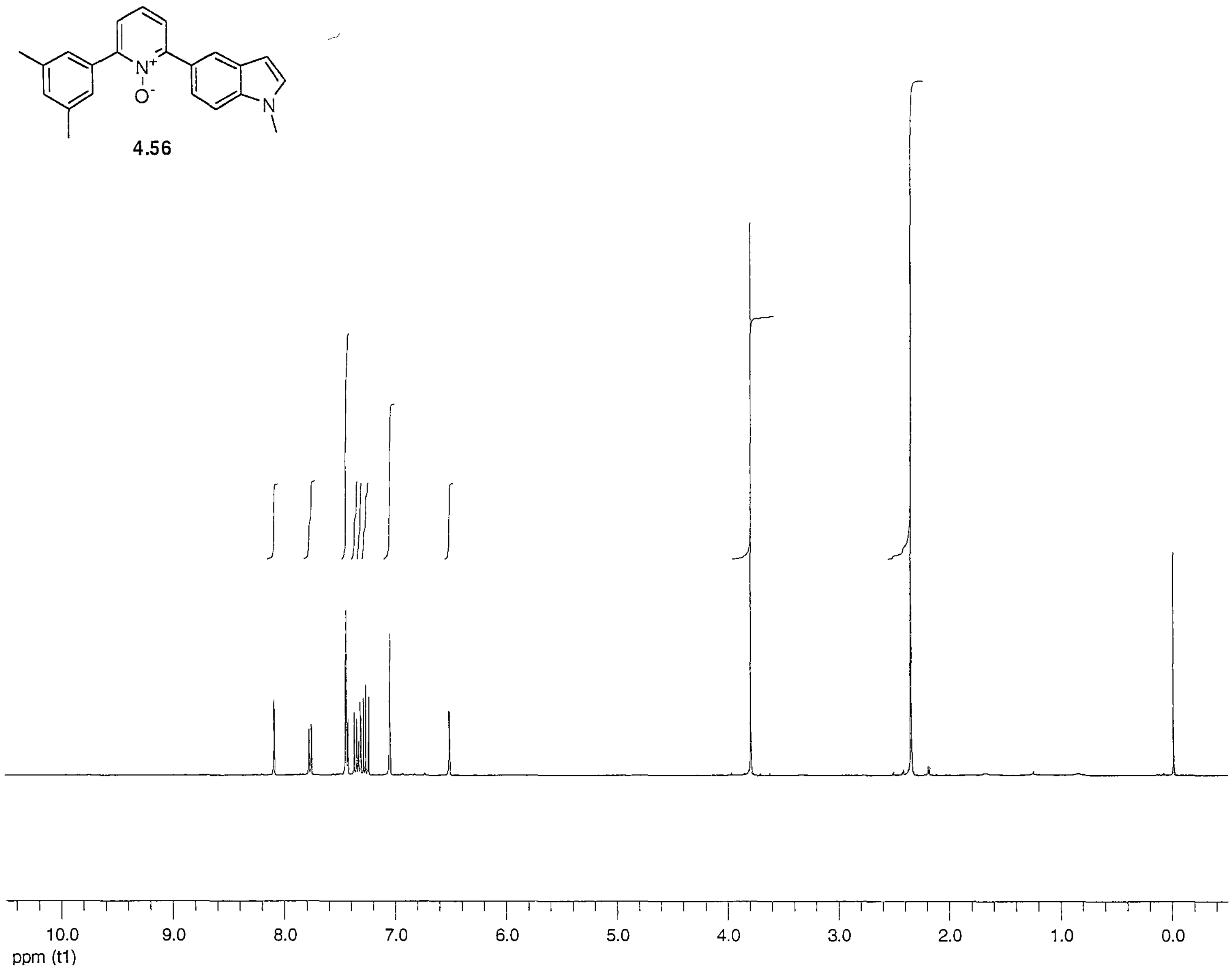

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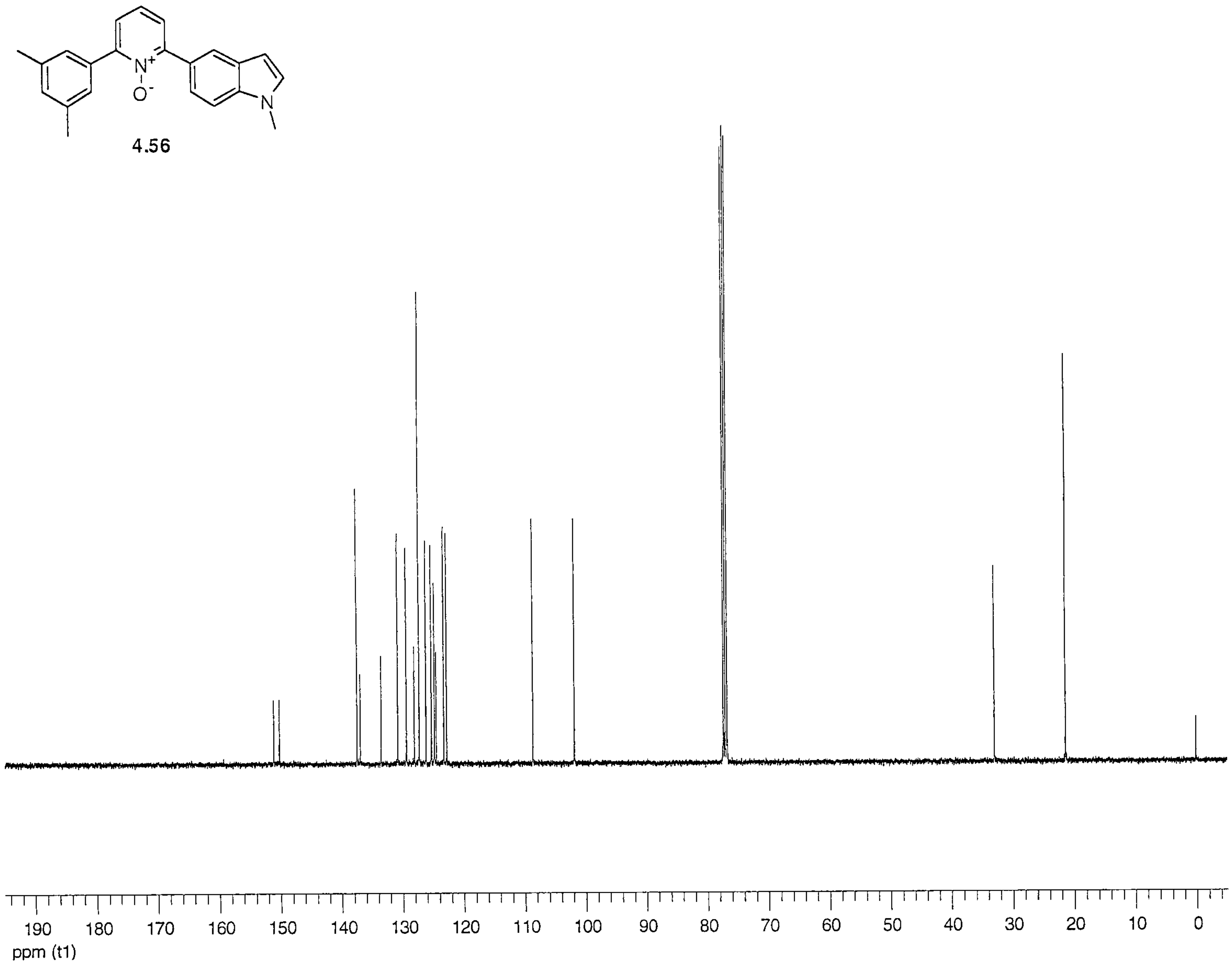
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ppm (t1)