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GRADE / DEGREE

Department of Science

FACULTÉ, ÉCOLE, DÉPARTEMENT / FACULTY, SCHOOL, DEPARTMENT

Transition Metal-Catalyzed Preparation and Functionalization of Nitrogen-Containing Heterocycles

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Transition Metal-Catalyzed Preparation and Functionalization of Nitrogen-Containing Heterocycles

By

Malcolm P. Huestis

B.Sc., Dalhousie University, 2006

A thesis submitted to the Faculty of Graduate and Postdoctoral Studies
In partial fulfillment of the requirements for the Master's degree (M.Sc.) in Chemistry

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ISBN: 978-0-494-69101-4
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ISBN: 978-0-494-69101-4

"The concept of the tetrahedral carbon atom and its corollaries the trigonal and digonal carbon atoms comprise the greatest single idea in science. This simple concept has satisfied the many rigorous demands of organic chemical structure and configuration, and biochemistry and molecular biology derive inherently from this one idea."

-Professor K. Barry Sharpless quoting Professor Orville L. Chapman,
Nobel Prize Lecture 2001

Abstract

The formation of carbon-carbon bonds is the single most fundamentally important operation in synthetic organic chemistry. Arguably, the aldol and Diels-Alder reactions stand as the most significant advances in forging linkages between carbons of an sp^3-hybridized nature.

Beginning in the early 1970s, seminal advances were made with respect to formation of carbon-carbon bonds between sp^2 centers. These transformations, termed "cross-coupling" reactions, have undoubtedly changed the way synthetic organic chemistry is carried out, rendering the synthesis of carbon-carbon sp^2 linkages a relatively trivial task. New synthetic technologies that utilize catalytic quantities of transition metals continue to be developed, and have paved the way to enable rapid increases in molecular complexity with far less effort than previously required.

The active ingredient in traditional cross-coupling reactions is a catalytic quantity of palladium. Provided that the two reactants to be cross-coupled have the appropriate functional groups for cross-coupling, they bind to the palladium and eliminate together, bound by a covalent Csp^2-Csp^2 bond. These functional groups include halides, boronic acids and esters, and organometallic fragments.

Direct arylation is a recent advance in cross-coupling between aryl groups whereby one cross-coupling partner (usually the one bearing an organometallic fragment) is replaced by the simple arene (C-H bond).

In the first section, we describe our efforts in extending the direct arylation technique to azaindole compounds. Ultimately, this research led to two different palladium-based catalyst systems - one that performed the cross-coupling event on the azine ring of azaindole, and one that arylated the azole ring.

In the second section, we extend our work on a cross-coupling technique catalyzed by rhodium, wherein a five-membered azole ring is constructed oxidatively by reaction between an anilide and an alkyne. This reaction finds its precedent in the Larock indole synthesis, a reaction catalyzed by palladium that features the anilide possessing an *ortho*-iodo function.

In the final section, we demonstrate the direct coupling of two unactivated C-H bonds in an intramolecular sense. This methodology was particularly useful for synthesizing carbazoles, and the synthesis of several highly oxygenated, naturally-occurring carbazoles is described.

Acknowledgments

It's pretty mainstream to thank your parents. But they really are responsible for me getting this far. The other day, my mom played me a tape of us talking when I was 2 years old. Besides the minor detail that I couldn't pronounce my name, our conversations were pretty normal. I believe that teaching as much as possible as early as possible aids good cognitive development. My Dad is about as far from the science world as possible. And while I was never interested in learning about politics or the world and I didn't like reading books, he let me do my own thing. He spent countless hours teaching me how to write, and I only realized how valuable it was when I started to write chemistry manuscripts.

To this day, I have never even had marks good enough to *apply* for an NSERC scholarship. I am eternally grateful to Dr. T. Bruce Grindley of Dalhousie University because he didn't care. He saw how I felt about chemistry and put his own grant money down so that I could work in his lab. I'll never forget the year when I had a small lab to myself. Weeks sometimes went by; he didn't bother me and he didn't really have time to be bothered. It was perfect. I didn't know any named reactions, I had no idea what chemicals to mix together, and I don't know how I didn't get hurt. No publications, no surprise. But my passion grew fast – there were so many possibilities in organic chemistry. Dr. Grindley treated me like a close friend, not like his student (except I still don't know what his first name is!). He gave me the freedom to try my terrible ideas and didn't worry about the results or the fact that I didn't keep a lab book or get a yield. If I fished out the compound, it was enough.

When I took a year off of school, I was about ready to give up trying to find a job in chemistry when Dr. David L. Jakeman (Dalhousie Pharmacy) took me in. What a year. He knew I wanted to get serious about publishing something, and he made it happen. I think we were an unlikely combination, so I am so happy that we got along and never had any big disagreements. I suppose it was slightly inappropriate when my summer student and I became involved. Dr. Jakeman didn't interfere, which was *super* cool (or maybe he didn't know...ha). After my departure, he has offered continuous and unwavering support. I really don't think the work I did warranted the generosity he has shown.

I am not get into how Dr. Keith Fagnou has changed my life because everyone who has ever been a part of this lab knows what I am talking about. I am just glad he let me in. As I write this, it's mid-January and I'm wearing shorts and T-shirt in the sun near some palm trees, eating free food at my free hotel that I got to in my free rental car. Oh yeah, and the flight was free too. Keith is responsible for all of it and I'm just happy I got to thank him before he died. It was a bit awkward being the only unqualified guy with no NSERC, OGS or fancy co-op work terms from big pharma. I don't know what made him take a chance on me, but I'm happy he didn't regret it.

I shouldn't say that though without bringing up Mégan Bertrand-Laperle and David Stuart. Mégan and Dave were really the only people who made me feel truly welcome when I joined the Fagnou Factory. As I hinted above, it wasn't easy trying to get "in". I also want to thank Dave again and Derek Schipper for their unrelenting chemistry advice. I will never forget how they dropped everything to help me out again and again and again. Those guys filled in all the blanks. I also have to thank Dan Shore for helping me waste the evenings on endless conversations and for truly believing in me.

Lastly, I want to thank Olivier René. When he joined the lab and became my drinking partner, I finally had someone to do some serious partying with.

List of Abbreviations

Ac, Acetyl
acac, Acetylacetonate
Ar, aryl
BINAP, (*2R*,3*S)*,2,2-Bis-(diphenylphosphino)-1,1-binapthyl
Bn, Benzyl
Bz, Benzoyl
Bu, Butyl
BQ, 1,4-Benzoquinone
cod, Cyclooctadiene
Cp, Cyclopentadienyl
Cp*, 1,2,3,4,5-Pentamethylcyclopentadienyl
Cy, Cyclohexyl
DCE, Dichloroethane
DDQ, 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL, DIBAL-H, Diisobutylaluminum hydride
DMA, *N,N*–Dimethylacetamide
DMAP, 4-Dimethylaminopyridine
DME, Dimethoxyethane
DMF, Dimethylformamide
DMSO, Dimethylsulfoxide
DPPE (dppe), 1,2-Bis(diphenylphosphino)ethane
DPPF (dppf), Bis-(diphenylphosphino)ferrocene
Et, Ethyl
EWG, Electron–withdrawing group
Hex, Hexyl
HMDS, Hexamethyldisilazane
HMPV, 5-(4-Hydroxymethyl-3-methoxyphenoxy)valeric acid
L, Ligand
LAH, Lithium aluminum hydride, LiAlH4
LDA, Lithium diisopropylamide
m-CPBA, *m*-Chloroperoxybenzoic acid
Me, Methyl
MEM, Methoxyethoxymethyl
Mes, Mesityl
Ms, Mesyl, Methanesulfonyl
MOM, Methoxymethyl
Naph, Naphthyl
NBS, *N*-Bromosuccinimide
NCS, *N*-Chlorosuccinimide
NIS, *N*-Iodosuccinimide
NMP, *N*–Methylpyrrolidone
NMR, Nuclear magnetic resonance
NOE, Nuclear Overhauser effect.

Oct, Octyl
Pent, Pentyl
Ph, Phenyl
Phen, 1,10-Phenanthroline
Pr, *n*-Propyl
Py, Pyridine
PTSA, *p*-Toluenesulfonic acid
R, An organic group
SEM, 2-(Trimethylsilyl)ethoxymethyl
*t*AmOH, *tert*-amylalcohol
TBAF, Tetrabutylammonium fluoride
TBS, *tert*–Butyldimethylsilyl
t-Bu, *t*Bu, *tert*-Bu, Tertiary butyl
Tf, Trifluoromethanesulfonyl, triflyl
TFA, Trifluoroacetic acid
TFE, 2,2,2-Trifluoroethanol
THF, Tetrahydrofuran
THP, Tetrahydropyran(yl)
TMEDA, Tetramethylethylenediamine
TMS, Trimethylsilyl
Tol, Tolyl
Tr, Trityl
Ts, Tosyl, *p*-Toluenesulfonyl

Table of Contents

List of Figures

List of Schemes

List of Tables

1

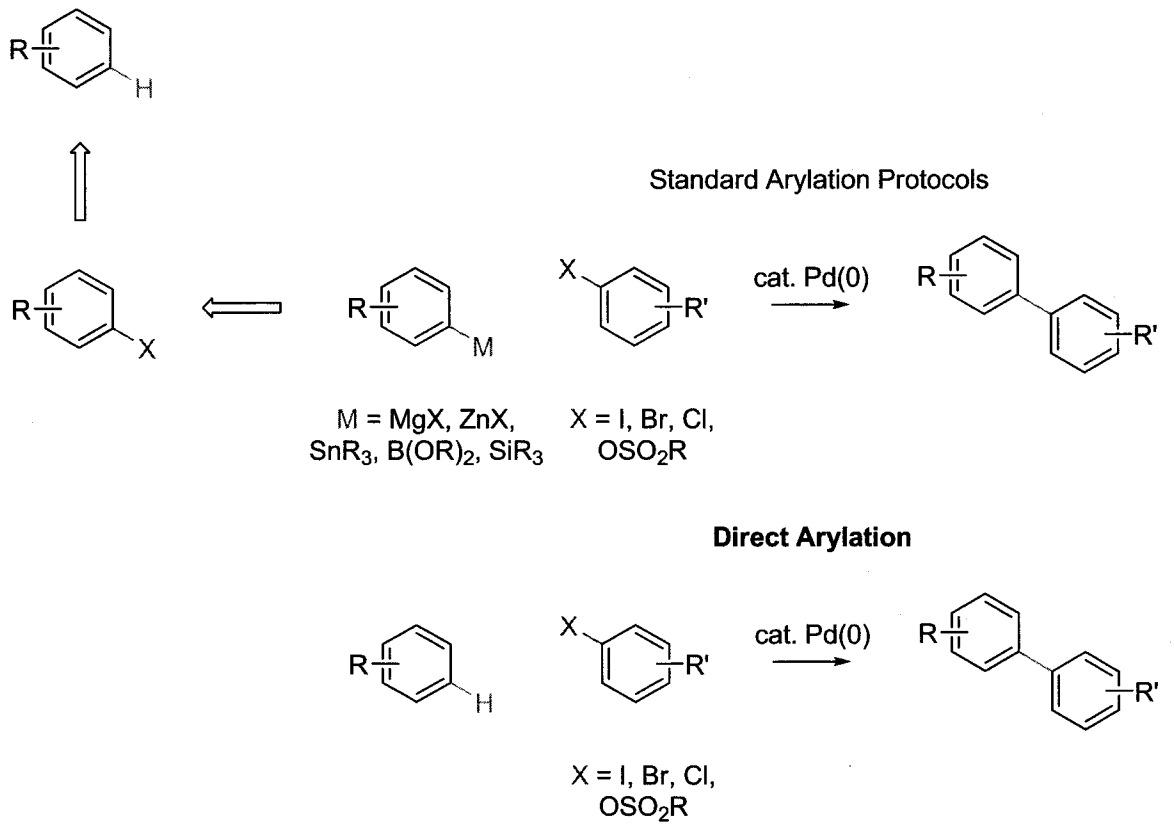
Biaryl Synthesis by Direct Arylation

Introduction

A recent survey of frequently used chemical reactions in the pharmaceutical industry highlight both the reoccurrence of the biaryl scaffold in biologically active compounds and the value of palladium catalysis in drug synthesis.[1] The emergence of palladium-catalyzed cross-coupling reactions in the 1970s and 80s constituted an important advance in the ability to prepare biaryl molecules from aryl halide and arylorganometallic (i.e. Ar-MgX, Ar-ZnX, Ar-SnR_3, Ar-

[1] (a) Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006,** *4,* 2337-2347. (b) Dugger, R. W.; Radan, J. A.; Ripin, D. H. B. *Org. Proc. Res. Rev.* **2005,** *9,* 253-258.

$B(OR)_3$, Ar-SiR_3) coupling partners (Scheme 1.1).[2] Successful application of this method relies on the availability of the arene components with halides and the organometallic activating groups installed with the necessary regiochemistry. These may not always be commercially available, and in non-ideal cases, may be very challenging to prepare. Thus, in addition to the loss in overall efficiency that arises during the pre-activation steps, there are compelling chemical reasons to pursue the development of new cross-coupling methods.



Scheme 1.1 - Summary of palladium-catalyzed cross-coupling techniques

In the past decade, direct arylation has emerged as an increasingly viable alternative to traditional cross-coupling techniques (Scheme 1.1).[3] In these reactions, the organometallic

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[2] (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995,** *95,* 2457-2483. (b) Stille, J. K. *Angew. Chem. Int. Ed. Engl.* **1986,** *25,* 508-524. (c) Kiso, Y.; Yamamoto, K.; Tamao, K.; Kumada M. *J. Am. Chem. Soc.* **1972,** *94,* 4373-4374. (d) Hiyama, T.; Shirakawa, E. *Top. Curr. Chem.* **2002,** *219,* 61-85. (e) Negishi, E. *Acc. Chem. Res.* **1982,** *15,* 340-348.

[3] Recent reviews on direct arylation: (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007,** *107,* 174-238. (b) Campeau, L.-C.; Stuart, D. R.; Fagnou, K. *Aldrichimica Acta* **2007,** *40,* 35-41. (c) Campeau, L.-C.; Fagnou, K. *Chem. Commun.* **2006,** 1253-1264. (d) Satoh, T.; Miura, M. *Chem. Lett.* **2007,** *36,* 200-205. (e) Lewis, J. C.; Bergman, R. C.; Ellman, J. A. *Acc. Chem. Res.* **2008,** *41,* 1013-1025. (f) Li, B.-J.; Yang, S.-D.; Shi, Z.-J. *Synlett* **2008,** 949-957. (g) Daugulis, O.; Zaitsev, V. G.; Shabashov, D.; Pham, Q.-N.; Lazareva, A. *Synlett* **2006,** 3382-3388.

reagent of traditional cross-coupling reactions is replaced by a simple arene (Ar-H), thus minimizing the number of synthetic manipulations prior to cross-coupling.

Since the first reports of direct arylation, which were intramolecular, a number of arenes have been shown to participate in intermolecular transformations. Achieving useful levels of regioselectivity with intermolecular direct arylation can pose a significant challenge due to the presence of several competing C-H bond sites. This is in stark contrast to the intramolecular variant, wherein the degrees of freedom are severely limited owing to the tethered coupling partners. The founding work on intra-[4] and intermolecular[5] direct arylation of simple arenes has been extensively reviewed[3] and will not be discussed here. Given the studies at hand, it is most pertinent to examine the role of intermolecular direct arylation in the functionalization unsaturated heterocyclic compounds.

Direct Arylation of Heterocycles

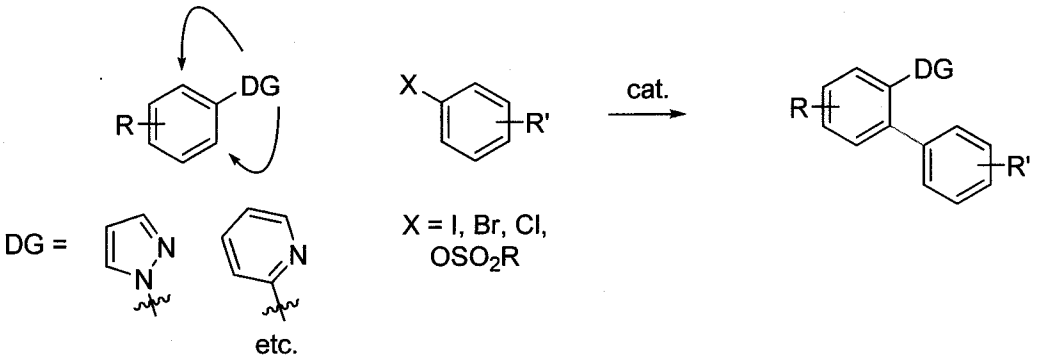
One of the main challenges associated with intermolecular direct arylation is the presence of multiple competing C-H bond sites on the arene. Achieving regioselectivity in such a scenario is no doubt why so few examples exist that employ simple arenes not possessing directing groups (Scheme 1.2).[6] Fortunately, embedding heteroatoms within a cyclic aromatic structure significantly alters the electronic characteristics of the arene. These inherent differences in the reactivity of C-H bonds on heterocycles is often enough to provide high levels of regioselectivity in direct arylation reactions.

(h) Pascual, S.; de Mendoza, P.; Echavarren, A. M. *Org. Biomol. Chem.* **2007,** *5,* 2727-2734. (i) Catellani, M.; Motti, E.; Della Ca', N.; Ferraccioli, R. *Eur. J. Org. Chem.* **2007,** 4153-4165. (j) McGlacken, G. P.; Bateman, L. M. *Chem. Soc. Rev.* **2009,** *38,* 2447-2464. (k) Ackermann, L.; Vincente, R.; Kapdi, A. R. *Angew. Chem. Int. Ed.* **2009,** *48,* 9792-9826.

[4] (a) Ames, D. E.; Bull, D. *Tetrahedron* **1982,** *38,* 383-387. (b) Ames, D. E.; Opalko, A. *Synthesis* **1983,** 234-235. (c) Ames, D. E.; Opalko, A. *Tetrahedron* **1984,** *40,* 1919-1925.

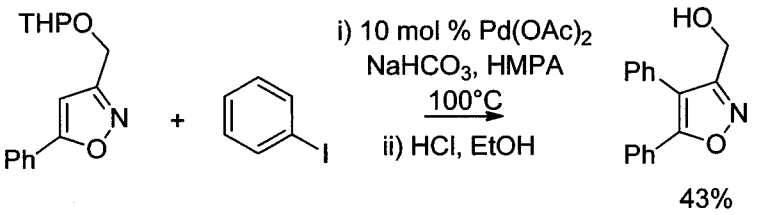
[5] Catellani, M.; Chiusoli, G. P. *J. Organomet. Chem.* **1985,** *286,* C13-C16.

[6] (a) Qin, C.; Lu, W. *J. Org. Chem.* **2008,** *73,* 7424. (b) Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006,** *128,* 16496-16497. (c) Wen, J.; Zhang, J.; Chen, S.-Y.; Li, J.; Yu, X.-Q. *Angew. Chem. Int. Ed.* **2008,** *47,* 8897-8900. (d) Fujita, K.-i.; Nonogawa, M.; Yamaguchi, R. *Chem. Commun.* **2004,** 1926-1927.



Scheme 1.2 - Use of directing groups to achieve regioselective direct arylation

The first example of intermolecular direct arylation of a heterocycle employing catalytic palladium was reported by Nakamura in 1982.[7] In the event, an isoxazole was reacted with iodobenzene in the presence of palladium(II) acetate to yield the coupled product in 43% yield after a protecting group removal (Scheme 1.3).

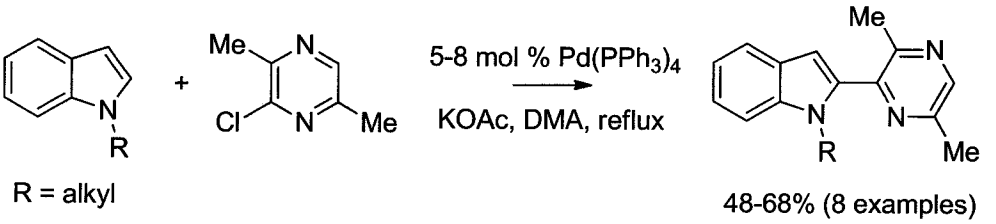


Scheme 1.3 - First catalytic, intermolecular direct arylation of a heterocycle

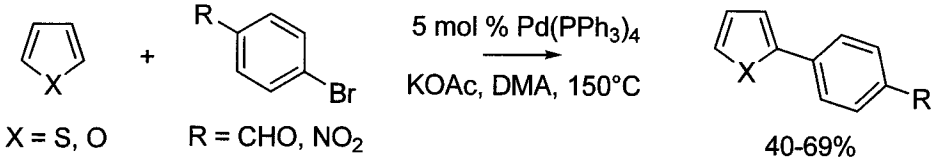
A second example did not appear until 1989, when Ohta reported the regioselective cross-coupling of indoles and chloropyrazines (Scheme 1.4).[8] The following year, Ohta published his seminal report that described the direct arylation of thiophenes and furans in synthetically useful yields, as well as preliminary results with benzothiophenes and benzofurans (Scheme 1.5).[9]

---

[7] Nakamura, N.; Tajima, Y.; Sakai, K. *Heterocycles* **1982,** *17,* 235-245.
[8] Akita, Y.; Itagaki, Y.; Takizawa, S.; Ohta, A. *Chem. Pharm. Bull.* **1989,** *37,* 1477-1480.
[9] Ohta, A.; Akita, Y.; Ohkuwa, T.; Chiba, M.; Fukunaga, R.; Miyafuji, A.; Nakata, T.; Tani, N.; Aoyagi, Y. *Heterocycles* **1990,** *31,* 1951-1958.



Scheme 1.4 - First direct arylation of indoles



Scheme 1.5 - Direct arylations of thiophenes and furans

Direct Arylation of Electron-Rich Heterocycles

In subsequent years, direct arylation methods has been extended to various other π - excessive heterocycles (Figure 1.1).[10] Interestingly, the major advances in this area have used indoles as the heteroarene substrate (*vide infra*). Of particular importance, examples of direct arylation that employ catalytic metals other than palladium have been developed. Examples that use rhodium[11] have been followed by instances with iridium,[12] as well as more economic catalysts such as copper,[13] nickel,[14] and iron.[6c]

---

[10] For recent examples, see: (a) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007,** *36,* 1173-1193. (b) Ackermann, L.; Vicente, R.; Born, R. *Adv. Synth. Catal.* **2008,** *350,* 741-748. (c) Bellina, F.; Cauteruccio, S.; Rossi, R. *Eur. J. Org. Chem.* **2006,** 1379-1382. (d) Bellina, F.; Benelli, F.; Rossi, R. *J. Org. Chem.* **2008,** *73,* 5529-5535. (e) Flegeau, E. F.; Popkin, M. E.; Greaney, M. F. *Org. Lett.* **2008,** *10,* 2717-2720. (f) Martin, T.; Verrier, C.; Hoarau, C.; Marsais, F. *Org. Lett.* **2008,** *10,* 2909-2912. (g) Ban, I.; Sudo, T.; Taniguchi, T.; Itami, K. *Org. Lett.* **2008,** *10,* 3607-3609. (h) Wang, X.; Gribkov, D. V.; Sames, D. *J. Org. Chem.* **2007,** *72,* 1476-1479. (i) Wang, J. X.; McCubbin, J. A.; Jin, M.; Laufer, R. S.; Mao, Y.; Crew, A. P.; Mulvihilland, M. J.; Snieckus, V. *Org. Lett.* **2008,** *10,* 2923-2926. (j) Yang, S.-D.; Sun, C.-L.; Fang, Z.; Li, B.-J.; Li, Y.-Z.; Shi, Z.-J. *Angew. Chem. Int. Ed.* **2008,** *47,* 1473-1476. (k) Ackermann, L.; Althammer, A.; Fenner, S. *Angew. Chem. Int. Ed.* **2009,** *48,* 201-204. (l) Goikhman, R.; Jacques, T. L.; Sames, D. *J. Am. Chem. Soc.* **2009,** *131,* 3042-3048. (m) Liégault, B.; Lapointe, D.; Caron, L.; Vlassova, A.; Fagnou, K. *J. Org. Chem.* **2009,** *74,* 1826-1834. (n) René, O.; Lapointe, D.; Fagnou, K. *Org. Lett.* **2009,** *11,* 4560-4563.

[11] (a) Lewis, J. C.; Wiedemann, S. H.; Bergman, R. H.; Ellman, J. A. *Org. Lett.* **2004,** *6,* 35-38. (b) Wang, X.; Lane, B. S.; Sames, D. *J. Am. Chem. Soc.* **2005,** *127,* 4996-4997. (c) Yanagisawa, S.; Sudo, T.; Noyori, R.; Itami, K. *J. Am. Chem. Soc.* **2006,** *128,* 11748-11749. (d) Yanagisawa, S.; Sudo, T.; Noyori, R.; Itami, K. *Tetrahedron* **2008,** *64,* 6073-6081. (e) Yanagisawa, S.; Ueda, K.; Sekizawa, H.; Itami, K. *J. Am. Chem. Soc.* **2009,** *131,* 14622-14623.

[12] Join, B.; Yamamoto, T.; Itami, K. *Angew. Chem. Int. Ed.* **2009,** *48,* 3644-3647.

[13] (a) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2007,** *129,* 12404-12405. (b) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2008,** *130,* 1128-1129. (c) Do, H.-Q.; Khan, R. M. K.; Daugulis, O. *J. Am. Chem. Soc.* **2008,** *130,* 15185-15192. (d) Phipps, R. J.; Grimster, N. P.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008,** *130,* 8172. (e) Phipps, R. J.; Gaunt, M. J. *Science* **2009,** *323,* 1593-1597. (f) see ref 10g. (g) Kawano, T.; Yoshizumi, T.; Hirano, K.; Satoh, T.; Miura, M. *Org.*

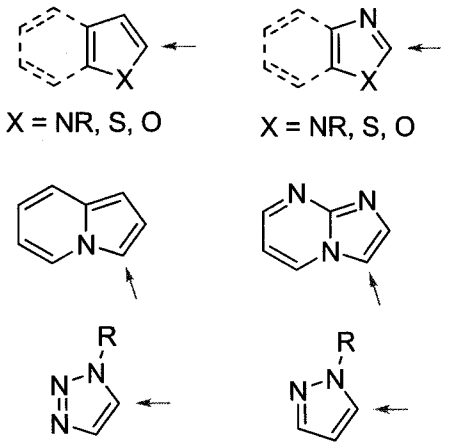


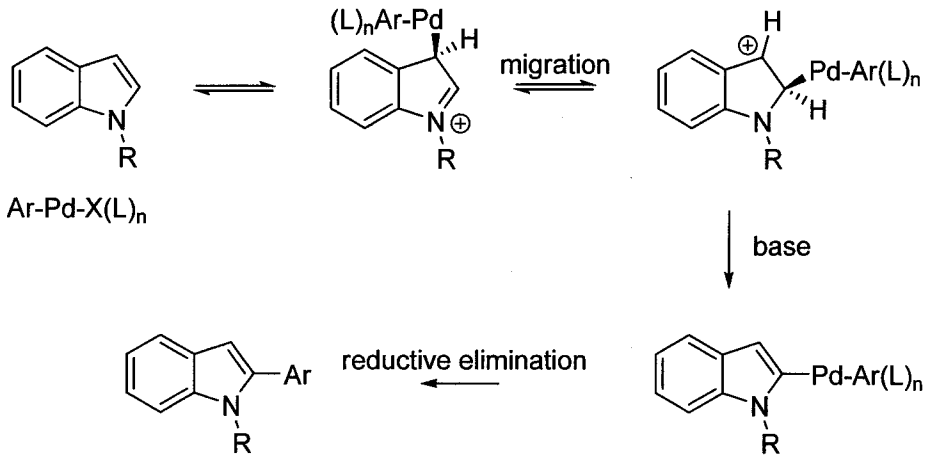
Figure 1.1 - Common positional selectivities for direct arylation

Several mechanistic proposals have been put forth for direct arylation of electron-rich heterocycles. That the regioselectivity was often consistent with electrophilic aromatic substitutions led to the suggestion that direct arylation proceeded through an electrophilic aromatic palladate. Although a C3 direct arylation (C2 is observed experimentally) would be consistent with electrophilic aromatic palladation of indole, a significant stride in gaining support was made by Sames (Scheme 1.6), whose mechanistic studies[15] accounted for the C2 regioselective outcome of indole direct arylation. Sames rationalized a migration from C3 to C2, followed by reductive elimination of the C2 arylated product.

Lett. **2009,** *11,* 3072-3075. (h) Zhao, D.; Wang, W.; Yang, F.; Lan, J.; Yang, L.; Gao, G.; You, J. *Angew. Chem. Int. Ed.* **2009,** *48,* 3296-3300.

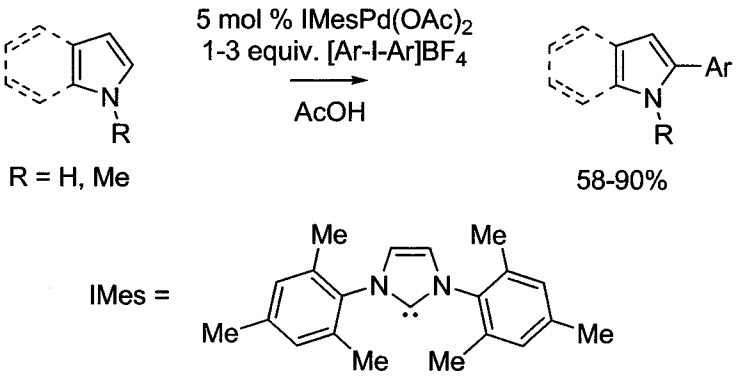
[14] (a) Canivet, J.; Yamaguchi, J.; Ban, I.; Itami, K. *Org. Lett.* **2009,** *11,* 1733-1736. (b) Hachiya, H.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2009,** *11,* 1737-1740.

[15] Lane, B. S.; Brown, M. A.; Sames, D. *J. Am. Chem. Soc.* **2005,** *127,* 8050-8057.



Scheme 1.6 - Mechanistic proposal for direct arylation (Sames)

The next breakthrough in this area of research was made by Sanford, who disclosed C2 direct arylation of indoles and pyrroles at room temperature by replacing aryl iodides with diaryl iodonium salts (Scheme 1.7).[16]

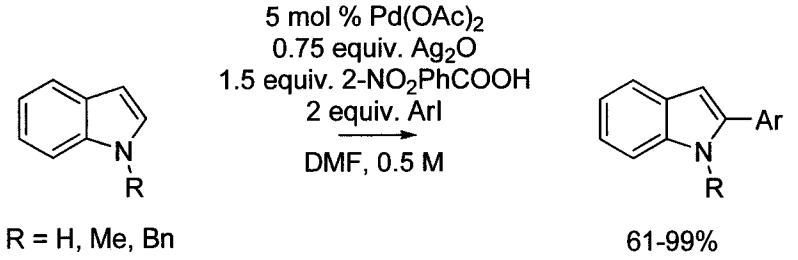


Scheme 1.7 - Direct arylation at room temperature (Sanford)

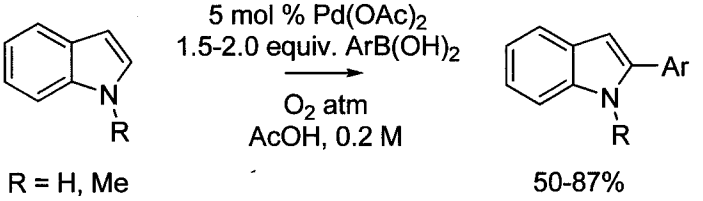
Two years later, in 2008, three other examples of room temperature protocols for indole direct arylation appeared in the literature. Further to Sanford's work, Larrosa revealed that aryl iodides could be used for ambient indole arylation in the presence of stoichiometric silver(I) oxide and *ortho*-nitrobenzoic acid (Scheme 1.8).[17] Meanwhile, Shi demonstrated a wide scope for palladium(II)-catalyzed couplings of heteroarenes with aryl boronic acids (Scheme 1.9).[10j] Finally, in a seminal advance in the field, Gaunt disclosed C3 indole arylation using inexpensive

[16] Deprez, N. R.; Kalyani, D.; Krause, A.; Sanford, M. S. *J. Am. Chem. Soc.* **2006,** *128,* 4972-4973.
[17] Lebrasseur, N.; Larrosa, I. *J. Am. Chem. Soc.* **2008,** *130,* 2926-2927.

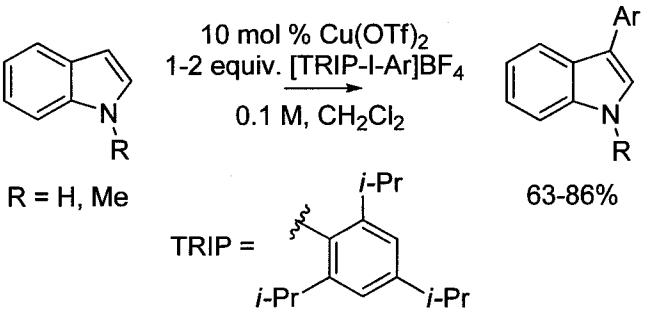
copper catalysis (Scheme 1.10).[13d] Of particular note is Gaunt's use of unsymmetrical diaryliodonium salts to minimize unproductive chemical waste.



Scheme 1.8 - Larrosa's direct arylation of indole



Scheme 1.9 - Direct arylation with aryl boronic acids (Shi)



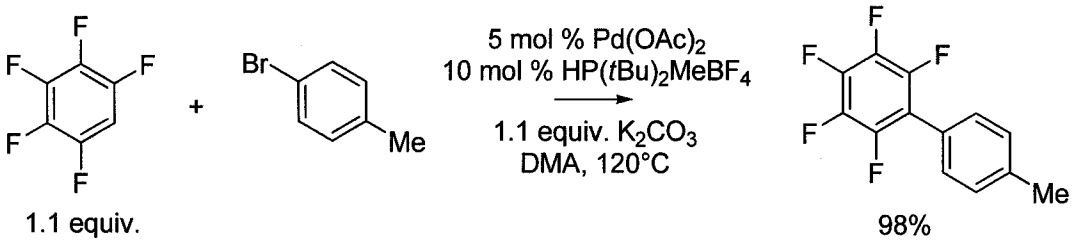
Scheme 1.10 - Copper-catalyzed direct arylation of indoles (Gaunt)

Direct Arylation of Electron-Poor Heterocycles

With the increasing acceptance of the electrophilic aromatic palladation mechanistic hypothesis for direct arylation (*vide supra*), came the assumption that electron deficient arenes were not compatible substrates. In 2006, our research group reported on the direct arylation of highly electron-deficient fluoroarenes (Scheme 1.11),[18] prompting studies into an apparent

[18] (a) Lafrance, M.; Rowley, C. N.; Woo, T. K.; Fagnou, K. *J. Am. Chem. Soc.* **2006,** *128,* 8754-8756. (b) Lafrance, M.; Shore, D.; Fagnou, K. *Org. Lett.* **2006,** *8,* 5097-5100.

mechanistic dichotomy. Our research was independently related to an earlier observation by Maseras and Echavarren that electron-deficient arenes underwent intramolecular direct arylation faster than electron neutral arenes.[19]



Scheme 1.11 - Direct arylation of electron-deficient pentafluoroarenes

The experimental and computational evidence in their group and ours led to a mechanistic proposal (Figure 1.2) featuring a concerted proton abstraction/palladation pathway which we termed concerted metalation-deprotonation (CMD).[20] As seen in Figure 1.2, the stoichiometric carbonate base employed removes the arene proton at the same time that the arene arrives on the metal. Later, it was shown that using a more soluble base (potassium pivalate) significantly increase the catalyst system's reactivity.[6b]

[19] (a) García-Cuadrado, D.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006,** *128,* 1066-1067. (b) García-Cuadrado, D.; de Mendoza, P.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2007,** *129,* 6880-6886. (c) Pascual, S.; de Mendoza, P.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *Tetrahedron* **2008,** *64,* 6021-6029.

[20] A similar process had already been proposed with mercury: Fung, C.; Khorramdel-Vahed, M.; Ranson, R. J.; Roberts, R. M. G. *J. Chem. Soc., Perkin Trans. 2* **1980,** 267-272.

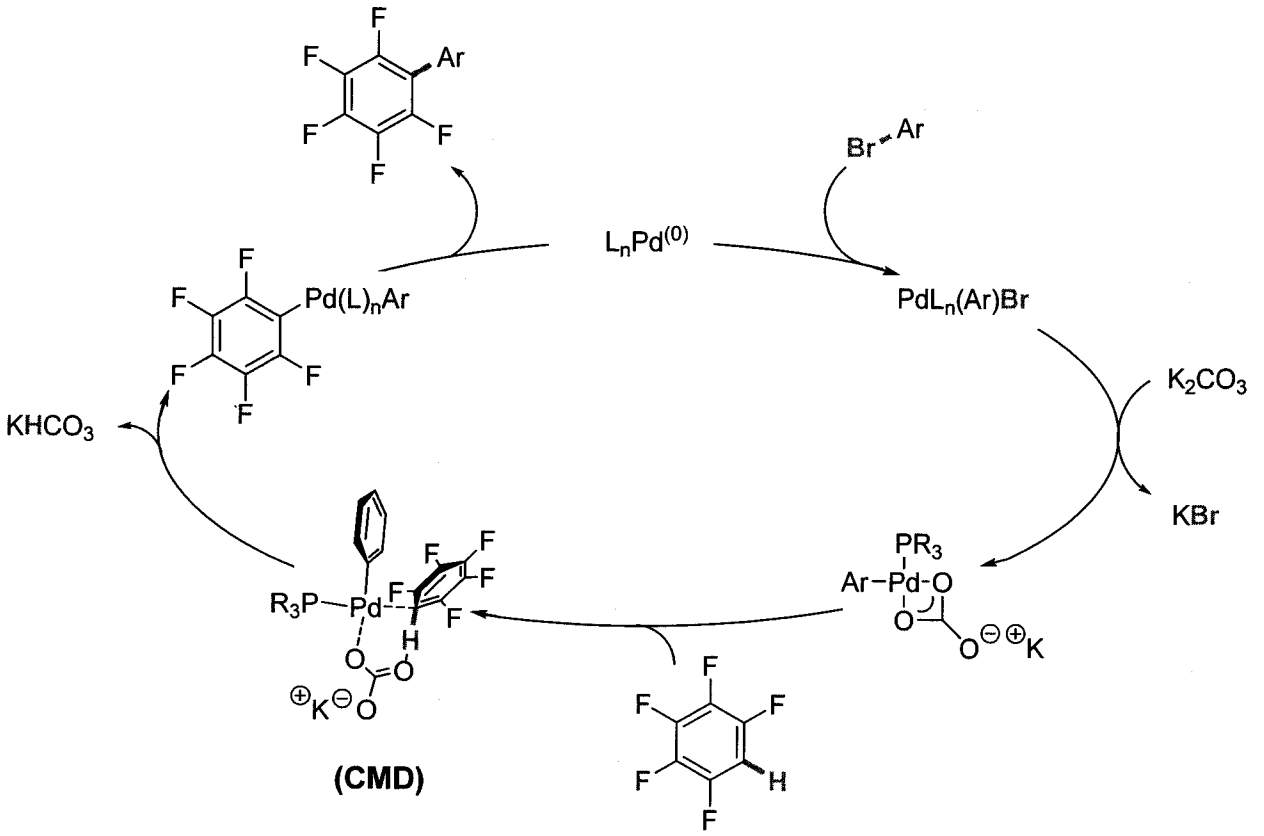


Figure 1.2 - Concerted metalation-deprotonation (CMD) mechanism

Considerable evidence has now surmounted for the involvement of the CMD mechanism in direct arylation of electron-rich heterocycles as well, partially eclipsing the originally proposed Friedel-Crafts type pathway (*vide supra*).[21]

Importantly, fluoroarenes have recently been shown undergo direct arylation under copper catalysis[13b,c] and direct alkenylation under nickel catalysis.[22] The compatibility of electron-poor arenes with direct arylation protocols also sparked the development of conditions for regioselective arylation of nitrobenzenes.[23]

A very important class of electron-deficient aromatics that had not yet succumb to direct arylation were those containing different types of azine rings, such as quinolines, isoquinolines, diazines and pyridines.[24] Although examples utilizing 2-pyridyl stannanes[25] and zinc species[26]

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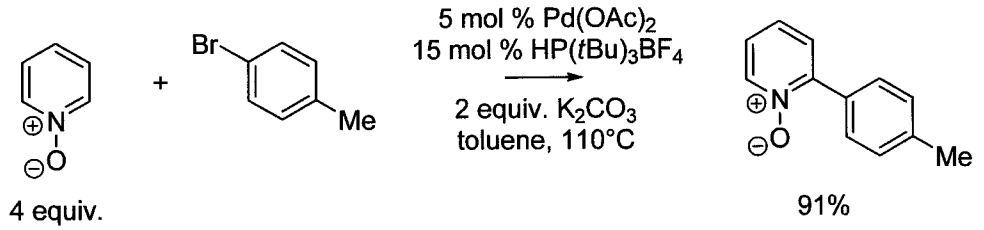
[21] Gorelsky, S. I.; Lapointe, D.; Fagnou, K. *J. Am. Chem. Soc.* **2008,** *130,* 10848-10849.
[22] Nakao, Y.; Kashihara, N.; Kanyiva, K. S.; Hiyama, T. *J. Am. Chem. Soc.* **2008,** *130,* 16170-16171.
[23] Caron, L.; Campeau, L.-C.; Fagnou, K. *Org. Lett.* **2008,** *10,* 4533-4536.
[24] A direct arylation of pyridine was reported, but was plagued by side reactions: Mukhopadhyay, S.; Rothenberg, G.; Gitis, D.; Baidossi, M.; Ponde, D. E.; Sasson, Y. *J. Chem. Soc., Perkin Trans. 2* **2000,** 1809-1812.

have shown considerable precedent, boron based reagents[27] for Suzuki-Miyaura cross-coupling are inherently unstable. Only recently has a reasonably stable (1 month under argon) 2-pyridyl boronate salt been prepared.[28] Regardless, numerous steps are still required to prepare the cross-coupling partners.

In 2005, our group reported that pyridine *N*-oxides undergo direct arylation with a variety of aryl bromides in high yield (Scheme 1.12).[29] Notably, *N*-oxidized pyridines are stable indefinitely under ambient atmosphere. Following arylation, the *N*-oxide was cleaved reductively by ammonium formate in the presence of catalytic Pd/C to afford the cross-coupled pyridines. A competition experiment between an electron-rich and an electron-deficient pyridine *N*-oxide provided preliminary evidence that the CMD pathway was operative (Scheme 1.13).[30]



Scheme 1.12 - Direct arylation of pyridine *N*-oxides

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[25] (a) Darabantu, M.; Boully, L.; Turck, A.; Plé, N. *Tetrahedron* **2005,** *61,* 2897-2905. (b) Littke, A. F.; Schwarz, L.; Fu, G. C. *J. Am. Chem. Soc.* **2002,** *124,* 6343-6348. (c) Gronowitz, S.; Björk, P.; Malm, J.; Hörnfeldt, A.-B. *J. Organomet. Chem.* **1993,** *460,* 127-129.

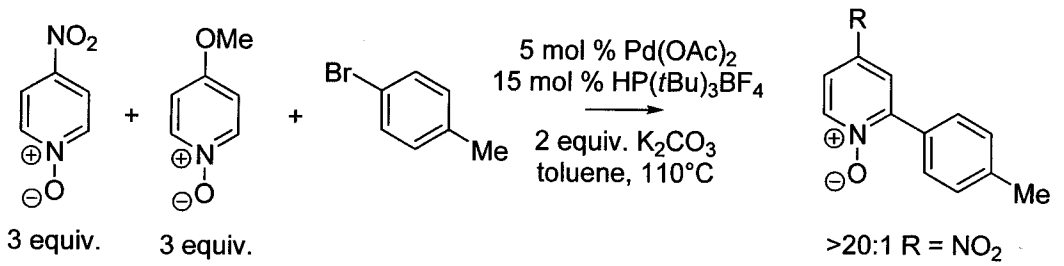
[26] (a) Deshayes, K.; Broene, R. D.; Chao, I.; Knobler, C. B.; Diederich, F. *J. Org. Chem.* **1991,** *56,* 6787-6795. (b) Trécourt, F.; Gervais, B.; Mallet, M.; Quéguiner, G. *J. Org. Chem.* **1996,** *61,* 1673-1676. (c) Fang, Y.-Q.; Hanan, G. S. *Synlett* **2003,** *6,* 852-854. (d) Walla, P.; Kappe, C. O. *Chem. Commun.* **2004,** 564-565.

[27] (a) Bouillon, A.; Lancelot, J.-C.; de Oliveira Santos, J. S.; Collot, V.; Bovy, P. R.; Rault, S. *Tetrahedron* **2003,** *59,* 10043-10049. (b) Bouillon, A.; Lancelot, J.-C.; Collot, V.; Bovy, P. R.; Rault, S. *Tetrahedron* **2002,** *58,* 2885-2890. (c) Bouillon, A.; Lancelot, J.-C.; Collot, V.; Bovy, P. R.; Rault, S. *Tetrahedron* **2002,** *58,* 3323-3328. (d) Bouillon, A.; Lancelot, J.-C.; Collot, V.; Bovy, P. R.; Rault, S. *Tetrahedron* **2002,** *58,* 4369-4373. (e) Hodgson, P. B.; Salingue, F. H. *Tetrahedron Lett.* **2004,** *45,* 685-687.

[28] Billingsley, K. L.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2008,** *47,* 4695-4698.

[29] Campeau, L.-C.; Rousseaux, S.; Fagnou, K. *J. Am. Chem. Soc.* **2005,** *127,* 18020-18021.

[30] Ongoing experimental and computational evidence has confirmed this surmise: Sun, H.-Y.; Gorelsky, S. I.; Campeau, L.-C.; Stuart, D. R.; Fagnou, K. *Unpublished results.*



Scheme 1.13 - Evidence for a CMD pathway in pyridine *N*-oxide direct arylation

The use of *N*-oxides as activating groups for direct arylation of a variety of heterocycles has continued to be the focus of our research group's studies.[31] Figure 1.3 displays examples of that have been validated for *N*-oxide arylations.

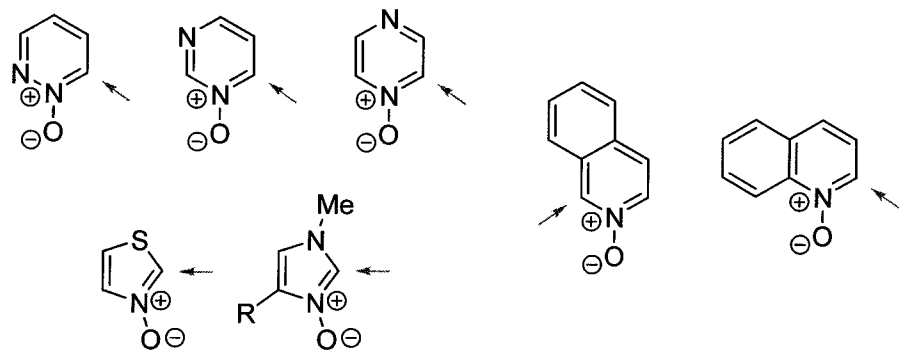


Figure 1.3 - Positional selectivity for direct arylation of *N*-oxidized heterocycles

Other research groups have since made important contributions to this area. For example, Charette has shown that *N*-iminopyridinium ylides demonstrate kinetically faster direct arylation reactivity than pyridine *N*-oxides (Scheme 1.14).[32]

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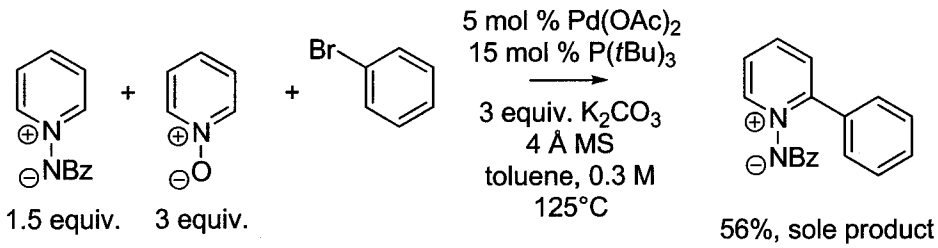
[31] (a) Campeau, L.-C.; Stuart, D. R.; Leclerc, J.-P.; Bertrand-Laperle, M.; Villemure, E.; Sun, H.-Y.; Lasserre, S.; Guimond, N.; Lecavallier, M.; Fagnou, K. *J. Am. Chem. Soc.* **2009,** *131,* 3291-3306. (b) Schipper, D. J.; Campeau, L.-C.; Fagnou, K. *Tetrahedron* **2009,** *65,* 3155-3164. (c) Schipper, D. J.; El-Salfiti, M.; Whipp, C. J.; Fagnou, K. *Tetrahedron* **2009,** *65,* 4977-4983. (d) Campeau, L.-C.; Schipper, D. J.; Fagnou, K. *J. Am. Chem. Soc.* **2008,** *130,* 3266-3267. (e) Campeau, L.-C.; Bertrand-Laperle, M.; Leclerc, J.-P.; Villemure, E.; Gorelsky, S.; Fagnou, K. *J. Am. Chem. Soc.* **2008,** *130,* 3276-3277. (f) Leclerc, J.-P.; Fagnou, K. *Angew. Chem. Int. Ed.* **2006,** *45,* 7781-7786.

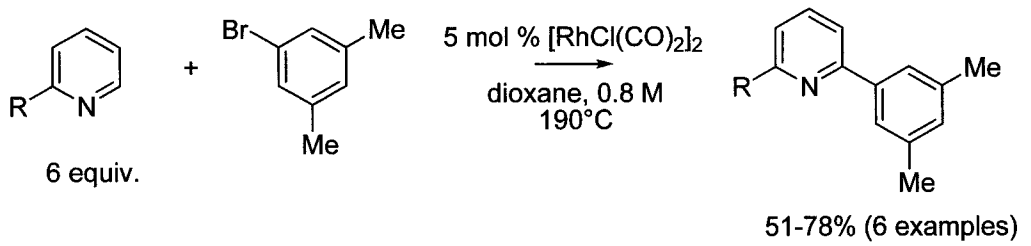
[32] Larivée, A.; Mousseau, J. J.; Charette, A. B. *J. Am. Chem. Soc.* **2008,** *130,* 52-54. For copper-catalyzed direct alkenylation of these arenes, see: Mousseau, J. J.; Bull, J. A.; Charette, A. B. *Angew. Chem. Int. Ed.* **2010,** DOI: 10.1002/anie.200906020.



Scheme 1.14 - Charette's direct arylation of *N*-iminopyridinium ylides

Furthermore, Nakao and Hiyama have demonstrated C2 alkenylation of pyridine *N*-oxides with alkynes under nickel catalysis[33] and have extended their method to include free-base pyridines by using catalytic Lewis acid activation.[34] Finally, in an elegant report by Chang,[35] pyridine, diazine, quinoline and isoquinoline *N*-oxides were arylated and alkenylated oxidatively with no pre-activation.

Very recently, two examples featuring free-base nitrogen atoms have appeared. Bergman and Ellman have reported a rhodium catalyst that permits direct arylation of pyridines with aryl bromides, provided that the pyridyl nitrogen is sterically encumbered (Scheme 1.15).[36] Also, a new approach to pyridine, quinoline, and isoquinoline direct arylation has been demonstrated by Tobisu and Chatani (Scheme 1.16).[37] Under nickel catalysis and in the presence of an aryl-delivering zinc species, the ensuing biaryl linkage is proposed to install via S_NAr. A non-aromatic S_NAr adduct was able to be isolated directly from a reaction between the Ar_2Zn reagent and the heteroaromatic compound in the absence of the catalyst.



Scheme 1.15 - Rhodium-catalyzed direct arylation of free-base pyridines

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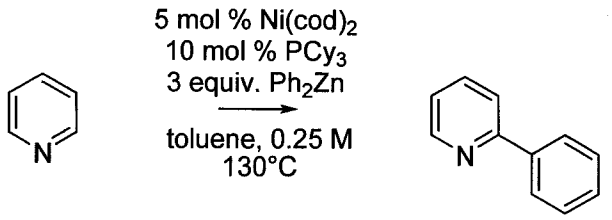
[33] Kanyiva, K. S.; Nakao, Y.; Hiyama, T. *Angew. Chem. Int. Ed.* **2007,** *46,* 8872-8874.
[34] Nakao, Y.; Kanyiva, K. S.; Hiyama, T. *J. Am. Chem. Soc.* **2008,** *130,* 2448-2449.
[35] Cho, S. H.; Hwang, S. J.; Chang, S. *J. Am. Chem. Soc.* **2008,** *130,* 9254-9256.
[36] Lewis, J. C.; Berman, A. M.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008,** *130,* 2493-2494.
[37] Tobisu, M.; Hyodo, I.; Chatani, N. *J. Am. Chem. Soc.* **2009,** *131,* 12070-12071.



55%

Scheme 1.16 - Nickel-catalyzed direct arylation of pyridine

2

Site-Selective Azaindole Arylation at the Azine and Azole Rings via *N*-Oxide Activation[38]

Introduction

As part of a program dedicated to the development of novel direct arylation reactions, we became interested in the use of azaindole compounds. Azaindoles, which possess the same [4.3]-bicyclic indene architecture as indoles but with a second nitrogen in the azine ring (Figure 2.1), have demonstrated importance in medicinal chemistry.[39] Compared to indoles, however, they are

[38] A significant portion of the work described in this chapter has been published in the form of a communication: Huestis, M. P.; Fagnou, K. *Org. Lett.* **2009,** *11,* 1357-1360.

[39] (a) Rodriguez, J.; Feraud, M. *Spec. Chem. Mag.* **2005,** *25,* 16-17. (b) Fernandez, D.; Ahaidar, A.; Danelon, G.; Cironi, P.; Marfil, M.; Perez, O.; Cuevas, C.; Albericio, F.; Joule J. A.; Alvarez, M. *Monatsh. Chem.* **2004,** *135,* 615-627. (c) Fresneda, P. M.; Delgado, S.; Francesch, A.; Manzanares, I.; Cuevas, C.; Molina, P. *J. Med. Chem.* **2006,** *49,* 1217-1221. (d) Beswick, P.; Gleave, R.; Swarbrick, M. Patent WO 0169241, 2005. (e) Tang, P. C.; Sun, L.; McMahon, G. Patent US 6849641, 2005. (f) David, L.; Hansen, P. Patent WO 099205, 2004. (g) Wang, T.; Wallace, O. B.; Zhang, Z.; Meanwell, N. A.; Bender, J. A. Patent WO 0622551, 2001. (h) Benoit, S.; Gingras, S.; Soundararajan, N. Patent WO 0822891, 2003.

far more challenging to prepare, especially in highly functionalized form.[40] In the context of direct arylation, two C2 arylations of 7-azaindole have been described by Sames (Scheme 2.1),[41] but methods for the direct functionalization of the azine ring have not been forthcoming.

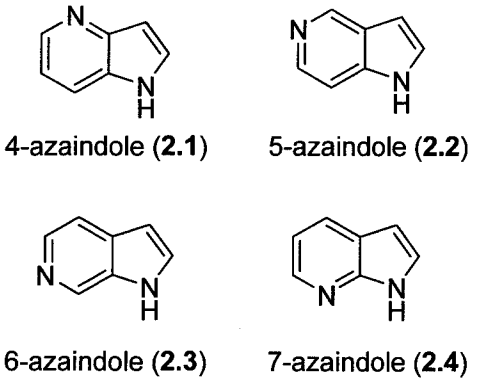
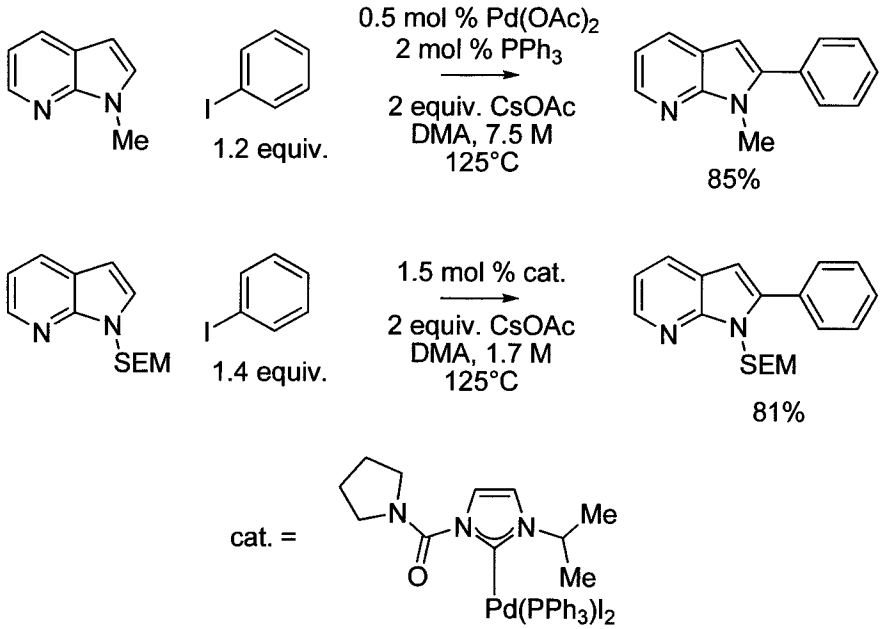


Figure 2.1 - Azaindoles (pyrrolo[2,3]pyridines)



Scheme 2.1 - Direct arylation of 7-azaindoles (Sames)

Since azaindoles have electron-rich azole and electron-deficient azine ring systems, we wondered if it might be possible to capitalize on recent advances in direct arylation methods to

[40] Reviews on azaindoles: (a) Prokopov, A. A.; Yakhontov, L. N. *Pharm. Chem. J.* **1994,** *28,* 471-506. (b) Song, J. J.; Reeves, J. T.; Gallou, F.; Tan, Z.; Yee, N. K.; Senanayake, C. H. *Chem. Soc. Rev.* **2007,** *36,* 1120-1132. (c) Yakhontov, L. N. *Russ. Chem. Rev.* **1968,** *37,* 551-565.

[41] (a) Lane, B. S.; Sames, D. *Org. Lett.* **2004,** *6,* 2897-2900. (b) Touré, B. B.; Lane, B. S.; Sames, D. *Org. Lett.* **2006,** *8,* 1979-1982.

selectively functionalize both rings in a controlled fashion. Such advances are of particular value since they can enable a rapid increase in molecular complexity with a minimal amount of synthetic expenditure. As new catalysts systems continue to be developed, a greater emphasis on understanding and controlling site-selectivity will become possible.

In this chapter, following the preparation of the azaindole cross-coupling partners, we describe that by employing *N*-oxide azine activation, both 7- and 6-azaindoles undergo regioselective direct arylation at the azine ring. We also report that, by modifying the Larrosa arylation protocol[17] slightly (heating to 80 °C), highly selective C2 arylation can be induced, offering a divergent method for the preparation of polyaromatic compounds based on an azaindole core. These studies point to new opportunities for the site-selective functionalization of useful organic building blocks and may find application in the preparation of novel medicinal compounds.

Synthesis of Azaindole Coupling Partners

Of the four azaindole isomers, 7-azaindole is commercially available from TCI ($16/g) or Aldrich ($19/g). According to a Scifinder database commercial chemical search, the three other azaindole isomers were not available at costs less than $80/g. Therefore, after gathering intelligence from literature sources, we initiated a plan to synthesis all four isomers on gram-scale.

The origin of 7-azaindole's commercial affordability was immediately apparent, stemming from its rapid and high-yielding synthesis from cheaply available materials. Hands described the synthesis of >100 g of 7-azaindole in 79% overall yield over 2 steps without the use of chromatography, crystallization, or distillation.[42] Accordingly, 2-amino-3-picoline was first Boc-protected in 80% yield (Scheme 2.2). After being deprotonated twice (*n*-BuLi, 2 equiv.), the Boc-protected adduct was condensed unto DMF and treatment with 5.5 M HCl in the same reaction vessel resulted in a quantitative yield of 7-azaindole.

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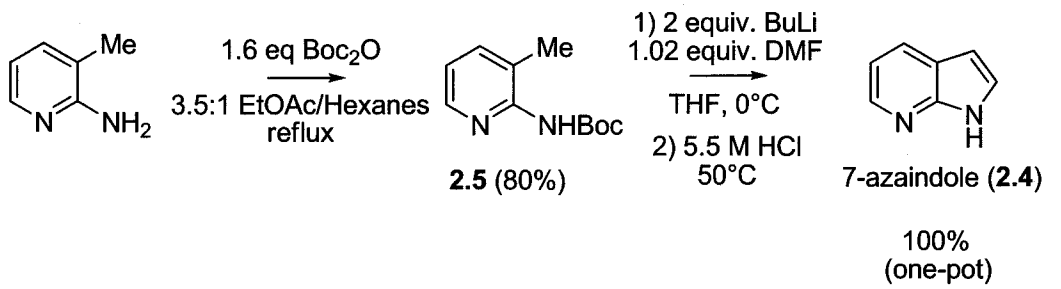
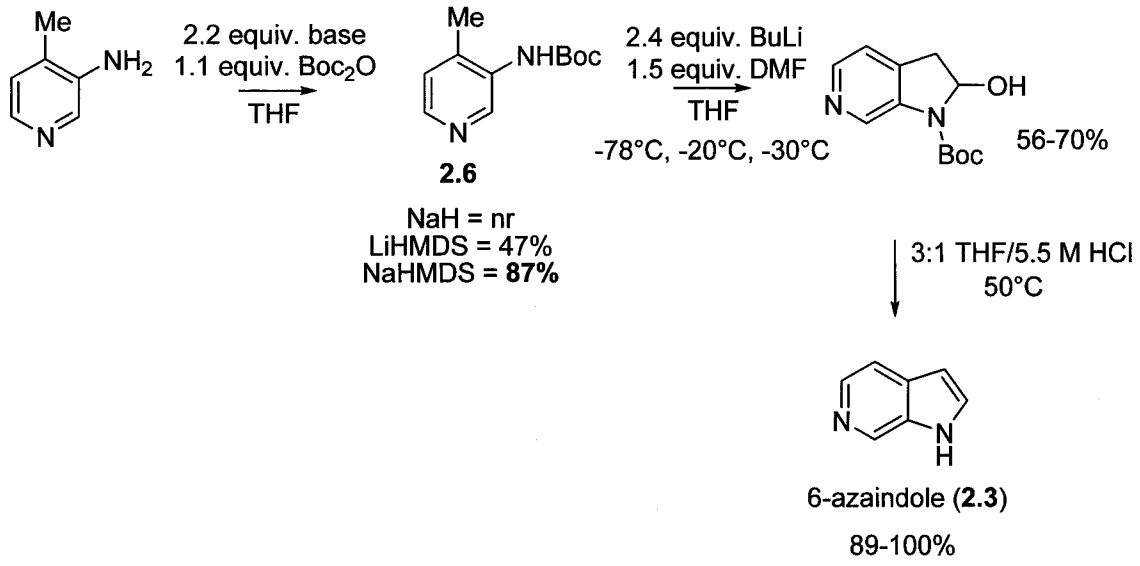
[42] (a) Hands, D.; Bishop, B.; Cameron, M.; Edwards, J. S.; Cottrell, I. F.; Wright, S. H. B. *Synthesis* **1996,** 877-882. (b) Bishop, B. C.; Cottrell, I. F.; Cameron, M.; Hands, D. Patent US 5681959, 1997.



Scheme 2.2 - Synthesis of 7-azaindole following the method of Hands

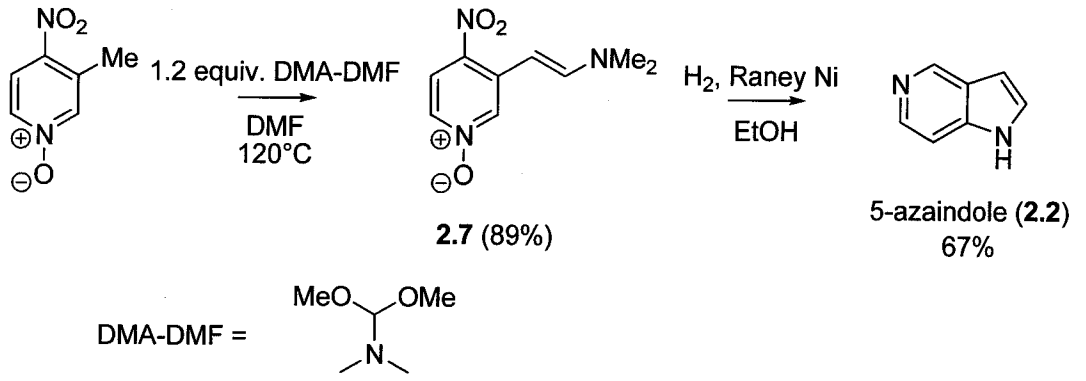
6-Azaindole was constructed by a similar overall strategy. Hands had described the preparation of the requisite Boc-protected picoline beginning from 3-aminopyridine. We were only able to effect lower yields (18-23%) for the installation of the 4-methyl substituent, and chromatographic separation from unreacted starting material was also an issue. We therefore elected to purchase 3-amino-4-picoline ($148/25g, TCI) in order to intercept the Hands intermediate in a single step (Scheme 2.3).

Thus, Boc-protection of 3-amino-4-picoline, which proceeded best with NaHMDS as base (87%) was followed by cyclization with DMF (56-70%) and deprotection/aromatization with 5.5 M HCl (89-100%).



Scheme 2.3 - Synthesis of 6-azaindole

The synthesis of 5-azaindole was carried out exactly as described by Dormoy (Scheme 2.4).[43] Beginning from 3-methyl-4-nitropyridine *N*-oxide, the dimethyl acetal of dimethylformamide reacted efficiently to provide an enamine (89%). Hydrogenation conditions with Raney Nickel resulted in clean conversion to 5-azaindole (67%).



Scheme 2.4 - Preparation of 5-azaindole according to the method of Dormoy

Literature precedent existed for accessing 4-azaindole by following a similar strategy,[44] however no experimental details, compound characterization or yields were reported. The starting material, 3-nitro-2-picoline, was able to be synthesized by S_NAr with sodium diethylmalonate followed by saponification/decarboxylation (Scheme 2.5).[45] This process was also able to be carried out in a single reaction vessel in a yield of 78%.[46]

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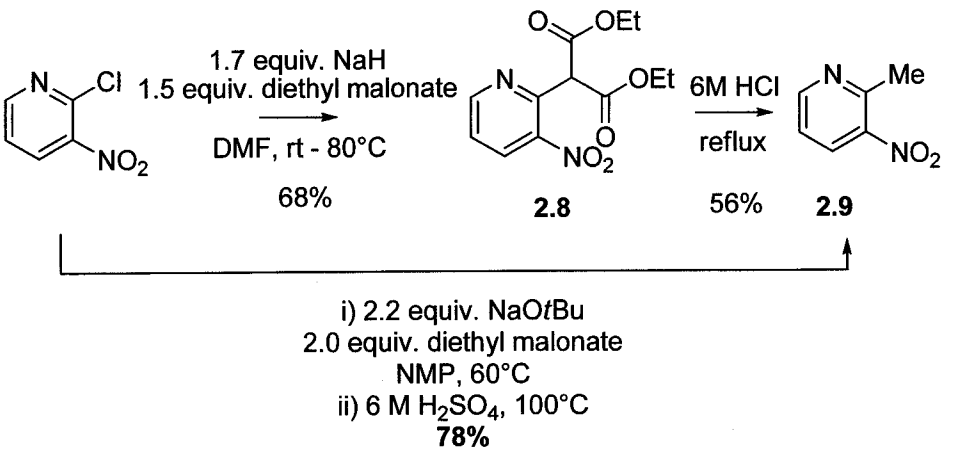
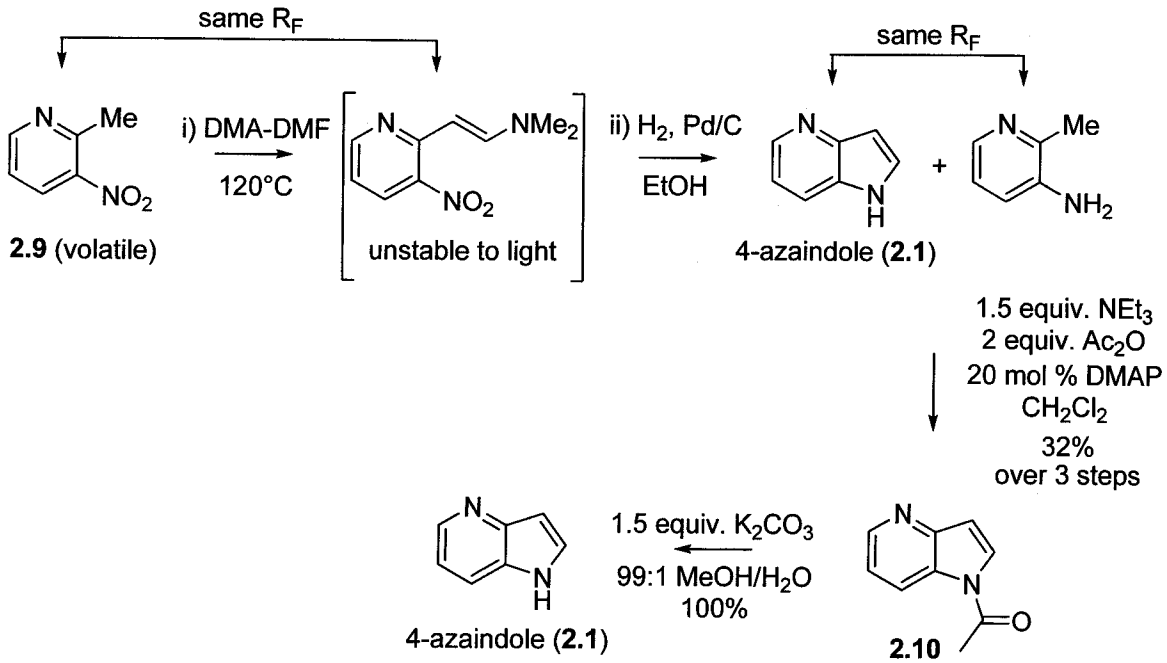
[43] Dormoy, J.-R.; Heymes, A. Patent FR 2564836, 1984.
[44] Sloan, M. J.; Phillips, R. S. *Bioorg. Med. Chem. Lett.* **1992,** *2,* 1053-1056.
[45] Cash, M. T.; Schreiner, P. R.; Phillips, R. S. *Org. Biomol. Chem.* **2005,** *3,* 3701-3706.
[46] Metz, W. A.; Halley, F.; Dutruc-Rosset, G.; Choi-Sledeski, Y. M.; Poli, G. B.; Fink, D. M.; Doerflinger, G.; Huang, B.-G.; Gelormini, A. M.; Gamboa, J. A.; Giovanni, A.; Roehr, J. E.; Tsay, J. T.; Camacho, F.; Hurst, W. J.; Harnish, S. W.; Chiang, Y. Patent WO 061498, 2005.



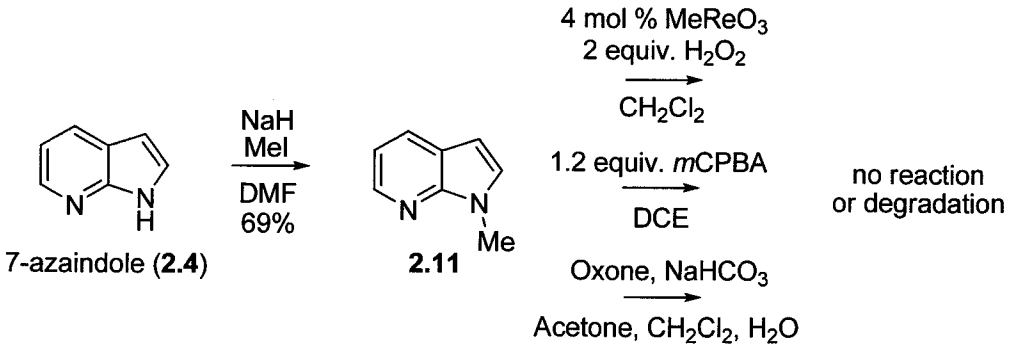
Scheme 2.5 - Synthesis of 3-nitro-2-picoline

The conversion of this material into 4-azaindole was complicated by several problems (Scheme 2.6). The picoline's condensation with DMA-DMF (*N*,*N*-dimethylformamide dimethyl acetal), whose reaction progress is driven by the release of gaseous methanol, was not able to be seen to completion. This came as a result of having to perform the reaction in a closed vessel to prevent loss of the starting material, which was volatile. Unfortunately, the enamine product, which was not stable to light, could not be separated chromatographically from the starting picoline. Therefore, the impure mixture was reductively cyclized to the azaindole with the hopes of effecting separation afterwards. Regrettably, the target azaindole coincided chromatographically with 2-methylpyridin-3-amine, whose origin lay in nitro reduction of unreacted 3-nitro-2-picoline. Acetylation of 4-azaindole permitted its separation from the mixture, and quantitative removal of the acetamide led to the target azaindole.

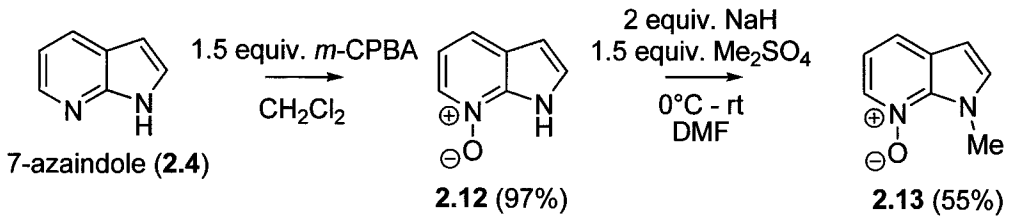


Scheme 2.6 - Problems encountered and eventual synthesis of 4-azaindole

The next task was to synthesize the azole-*N*-protected, azine-*N*-oxidized azaindoles to evaluate their direct arylation compatibility (Scheme 2.7). *N*-Methyl-7-azaindole, whose methylation had been previously described,[41] proved resistant to oxidation under several protocols, presumably due to steric hindrance at the azine nitrogen. As delineated in Scheme 2.8, this hurdle was bypassed by first oxidizing 7-azaindole (97%), and then alkylating with dimethylsulfate (55%), which provided more consistent results than methyl iodide (15-51%).

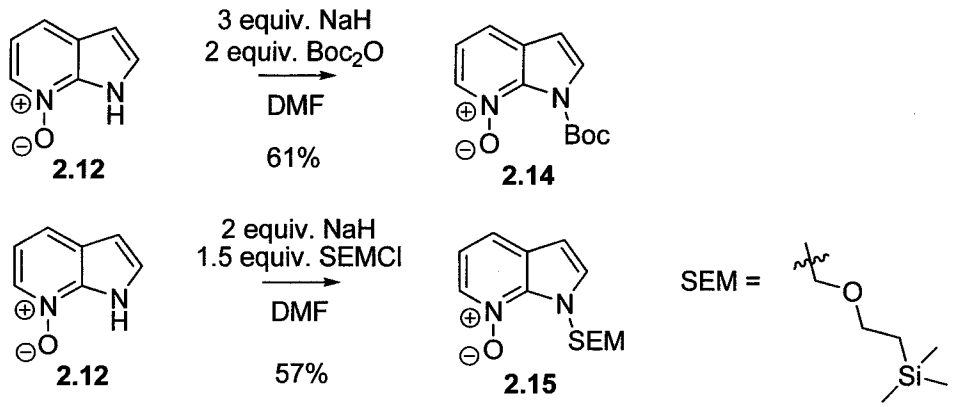


Scheme 2.7 - Preliminary attempts at securing a suitable azaindole *N*-oxide for azine arylation



Scheme 2.8 - Synthesis of *N*-methyl-7-azaindole *N*-oxide

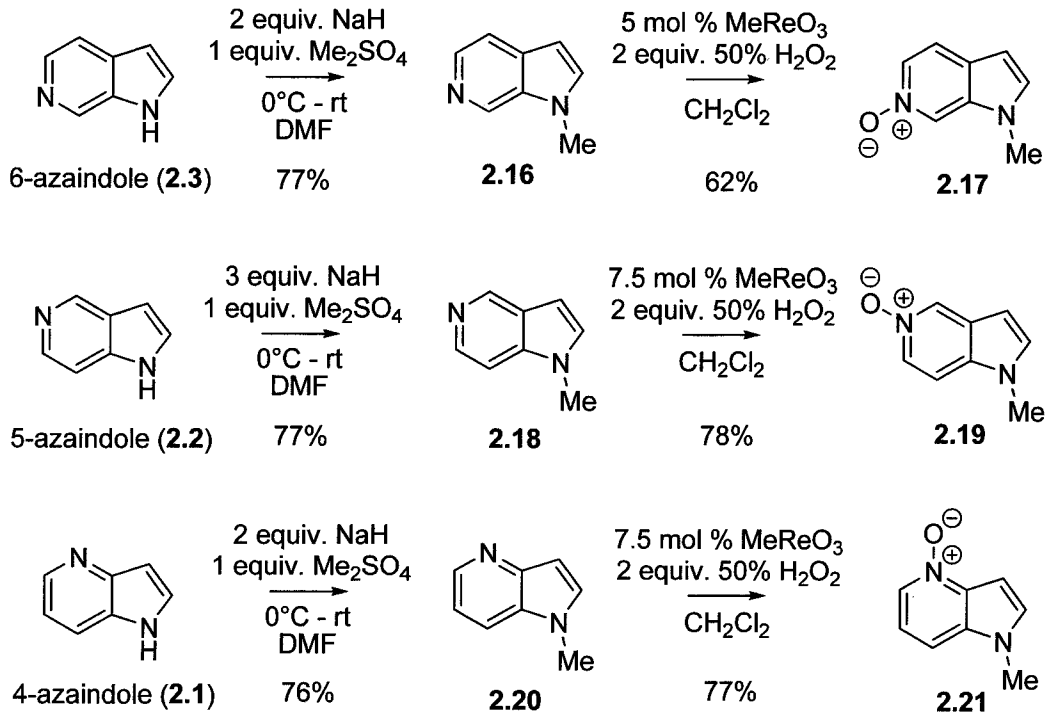
We also investigated the use of several other azole protecting groups (Scheme 2.9). Employing a Boc protecting group would ultimately fail due to its lability and *N*-SEM-7-azaindole *N*-oxide would prove unreactive to direct arylation reaction conditions.



Scheme 2.9 - Other possible azaindole cross-coupling partners

The three remaining *N*-methyl-azaindole *N*-oxides were constructed in good yield by methylation followed by oxidation using the Sharpless protocol (Scheme 2.10).[47]

[47] Copéret, C.; Adolfsson, H.; Khuong, T.-A. V.; Yudin, A. K.; Sharpless, K. B. *J. Org. Chem.* **1998,** *63,* 1740-1741.



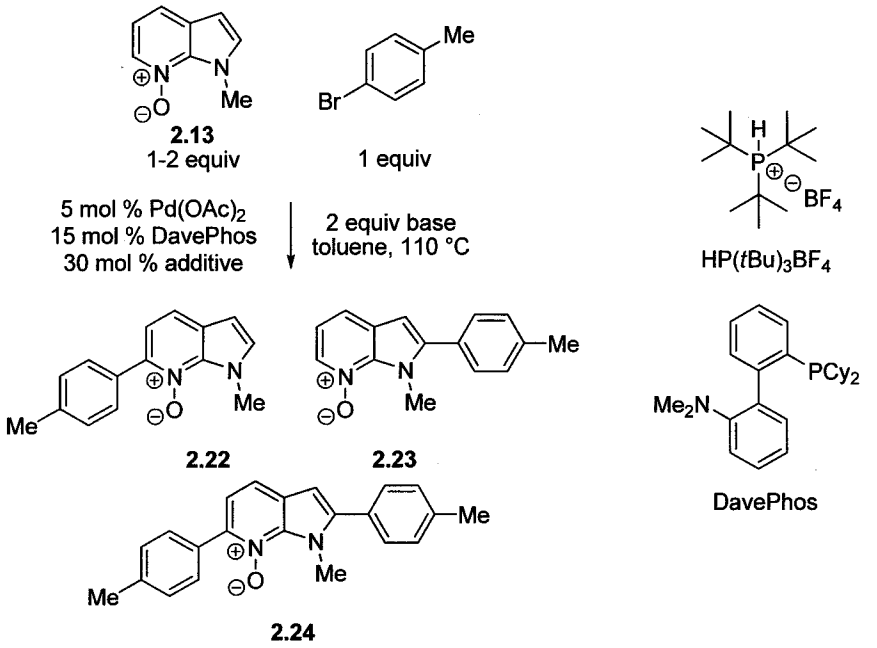
Scheme 2.10 - Preparation of 4,5, and 6-azaindole cross-coupling partners

Direct Arylation at the Azine Ring of Azaindoles

Initial optimization studies were performed with *N*-methyl-7-azaindole *N*-oxide **2.13** and 4-bromotoluene as cross-coupling partners. Under previously reported conditions for azine *N*-oxides,[29] only 5% NMR yield was obtained favoring the formation of regioisomer **2.22** (Table 2.1, entry 1). The structure of this C6 isomer was differentiated from the C2 (**2.23**) by ^{1}H NMR coupling constants and NOESY correlations. In subsequent work, particularly promising results were obtained when utilizing palladium(II) acetate, Buchwald phosphine ligands,[48] and carbonate bases. For example, by employing DavePhos[49] in a 3:1 ligand-to-metal ratio, the NMR yield of **2.22** could be increased to 24% (entry 2). The use of cesium carbonate instead of potassium carbonate as base was found to further increase the yield to 37% (entry 3). Increasing the concentration from 0.3 M to 0.5 M also provided an improvement to 52% NMR yield (entry

[48] For a review of these ligands in Pd-catalyzed amination see: Surry, D. S.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2008,** *47,* 6338-6361.
[49] Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998,** *120,* 9722-9723.

4), and a 57% yield could be reached by the addition of 30 mol % pivalic acid[50] (entry 5). With these conditions in hand, the influence of reagent stoichiometry was evaluated. These studies revealed that through the use of two equivalents of *N*-oxide **2.13** a 65% NMR yield could be obtained (entry 6). Finally, if 30 mol % pivalic acid is added to the reaction mixture, **2.22** can be obtained in 87% isolated yield (entry 7).



entry	base	additive	equiv **2.13**	molarity	NMR yield (**2.22**:**2.23**:**2.24**)[b]
1	K_2CO_3	none	1	0.3	5:1:0[c]
2	K_2CO_3	none	1	0.3	24:2:1
3	Cs_2CO_3	none	1	0.3	37:4:6
4	Cs_2CO_3	none	1	0.5	52:4:5
5	Cs_2CO_3	PivOH	1	0.5	57:1:4
6	Cs_2CO_3	none	2	0.5	65:6:4
7	Cs_2CO_3	PivOH	2	0.5	87:7:0[d]

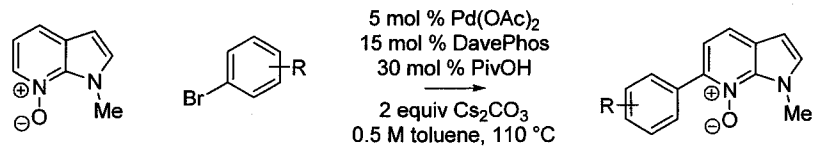
Table 2.1 - Optimization of azine arylation[a]

[a] Conditions: aryl halide (1 equiv), *N*-oxide (1 or 2 equiv), base (2 equiv), $Pd(OAc)_2$ (5 mol %), ligand (15 mol %), PivOH (0 or 30 mol %) were weighed into a vial, purged with argon, charged with toluene (0.3 or 0.5 M), and stirred at 110 °C overnight. [b] Determined by NMR analysis relative to 1,3,5-trimethoxybenzene as an internal standard. [c] $HP(tBu)_3BF_4$ used as ligand. [d] isolated yield, 35% recovered **2.13**.

[50] (a) see ref 6b. (b) Lafrance, M.; Lapointe, D.; Fagnou, K. *Tetrahedron* **2008,** *64,* 6015-6020. (c) see ref 21. (d) Watanabe, T.; Oishi, S.; Fujii, N; Ohno, H. *Org. Lett.* **2008,** *10,* 1759-1762. (e) see ref 10k. (f) see ref 10l. (g) see ref 10m. (h) see ref 31c.

Illustrative examples of the scope for C6 arylation of *N*-methyl-7-azaindole *N*-oxide **2.13** under standard reaction conditions are included in Table 2.2. The transformation is equally compatible with electron-donating and electron-withdrawing substituents (entries 2 and 4-7). 4-Bromoanisole can be cross-coupled in 54%, while methyl 4-bromobenzoate results in 53% yield (entries 2 and 4). Entries 5 and 7 demonstrate that the reaction works well with fluorinated aryl bromides (65% for *p*-CF_3 and 62% for *p*-F). Sterically encumbered aryl halides are compatible, albeit in lower yield (46%, entry 8). A bis-indole compound could also be assembled in 68% yield (entry 3), providing access to polycyclic heteroaromatic compounds. However, it is important to note several heterocyclic aryl bromides that were not compatible (Figure 2.2).

The remaining three isomeric *N*-methyl azaindole *N*-oxide coupling partners were also synthesized and evaluated under the conditions established for the 7-azaindole substrate. Although those derived from 4- and 5-azaindole displayed minimal reactivity, *N*-methyl-6-azaindole *N*-oxide **2.17** and *p*-tolyl bromide reacted to give the C7 cross-coupled product in 62% yield (Table 2.3, entry 1). As with the 7-azaindole analogue, electron-donating (entries 2-3) and inductively withdrawing substituents (entries 4-6) are compatible. Aryl halides possessing methoxy substituents were particularly reactive, giving yields of 68% and 70% for 4-methoxy and 3,5-dimethoxy aryl bromides, respectively (entries 2 and 3). As exemplified by entries 4 and 5, fluorinated aryl halides readily participate in direct arylation, furnishing 57% yield for *p*-CF_3 and 60% yield for *p*-F (entries 4 and 5). Again, a 5-bromoindole could be cross-coupled in acceptable yield (55%, entry 6).



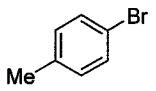
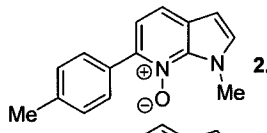
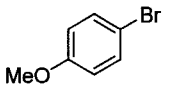
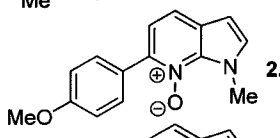
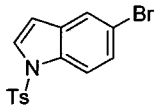
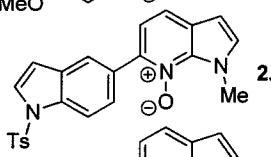
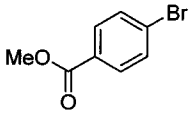
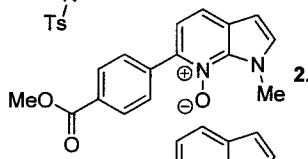
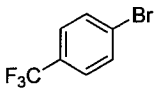
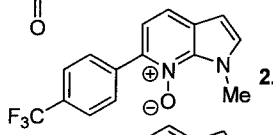
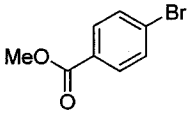
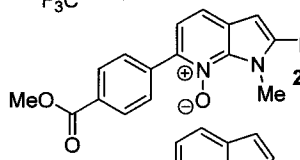
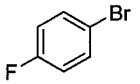
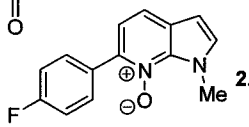
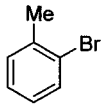
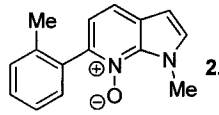
entry	aryl bromide	product		% yield
1			**2.22**	87%
2			**2.25**	54%[b]
3			**2.26**	68%
4			**2.27**	53%[b]
5			**2.28**	65%
6			**2.29**	56%[c]
7			**2.30**	62%
8			**2.31**	46%

Table 2.2 - Scope of *N*-methyl-7-azaindole *N*-oxide azine arylation[a]

[a] Conditions: aryl halide (1 equiv), *N*-oxide (2 equiv), Cs_2CO_3 (2 equiv), $Pd(OAc)_2$ (5 mol %), DavePhos (15 mol %), and PivOH (30 mol %) were weighed into a vial, purged with argon, charged with toluene (0.5 M), and stirred at 110 °C overnight. [b] 3 equivalents of *N*-oxide used. [c] *N*-Oxide reactant was compound **2.23**.

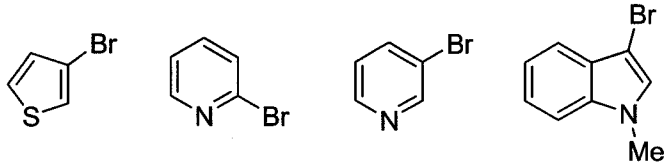
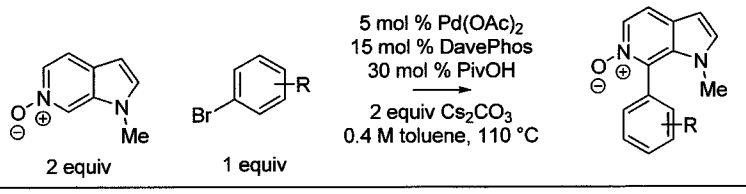


Figure 2.2 - Incompatible aryl bromides



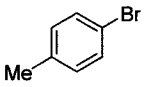
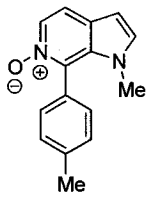
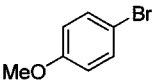
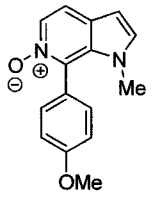
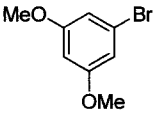
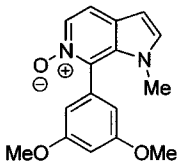
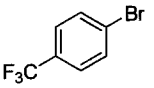
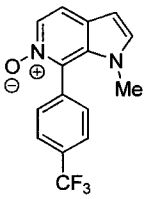
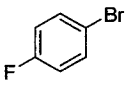
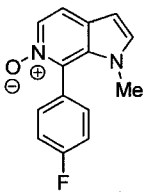
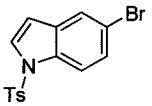
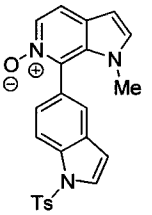
entry	aryl bromide	product		% yield
1			**2.32**	62%[b]
2			**2.33**	68%
3			**2.34**	70%
4			**2.35**	57%
5			**2.36**	60%
6			**2.37**	55%

Table 2.3 - Scope of *N*-methyl-6-azaindole *N*-oxide azine arylation[a]

[a] Conditions: aryl halide (1 equiv), *N*-oxide (2 equiv), Cs_2CO_3 (2 equiv), $Pd(OAc)_2$ (5 mol %), DavePhos (15 mol %), and PivOH (30 mol %) were weighed into a vial, purged with argon, charged with toluene (0.4 M), and stirred at 110 °C overnight. [b] No PivOH added.

It is important to note that in addition to other modes of reactivity that the *N*-oxide moiety enables, it may also be easily reduced by phosphorus trichloride[51] or zinc dust[52] to afford the arylated azaindoles in high yield (Table 2.4).

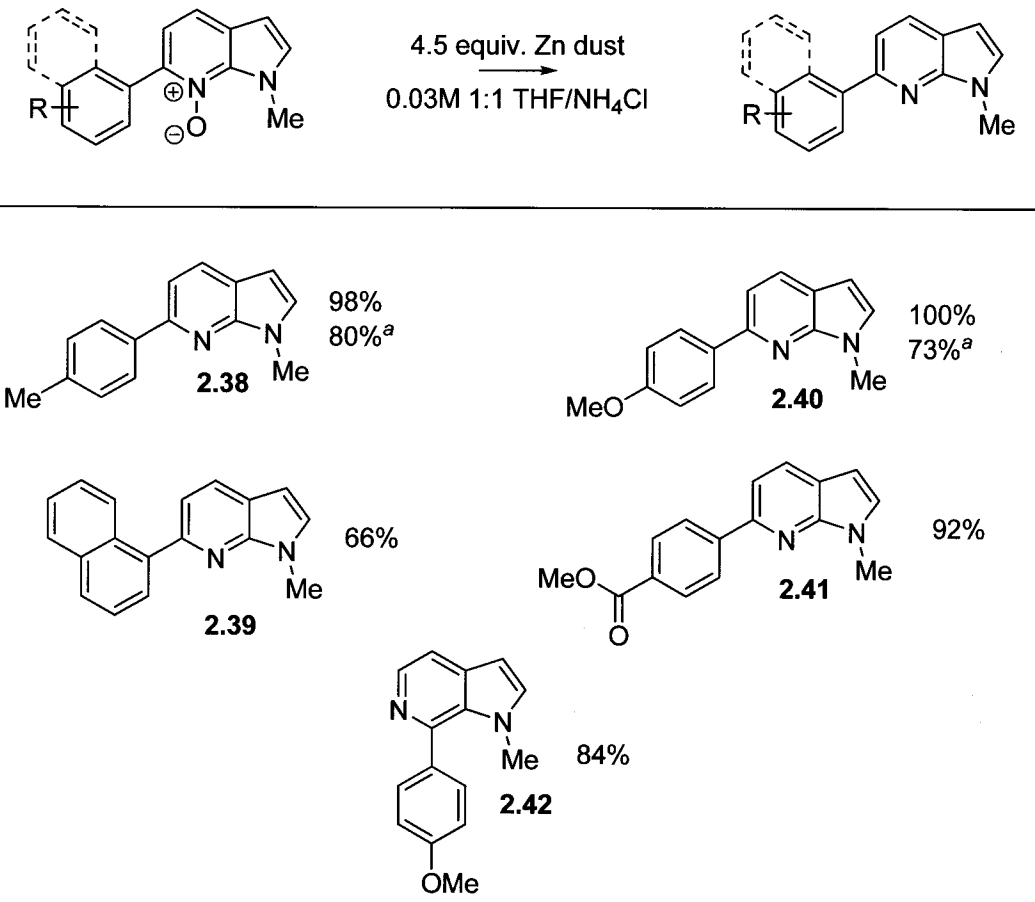


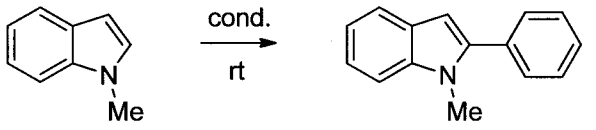
Table 2.4 - Deoxygenation of azaindole *N*-oxides[a]

[a] Phosphorus trichloride (1.5-2.0 equiv.) in toluene at room temperature.

[51] (a) Fang, Y.-Q.; Yuen, J.; Lautens, M. *J. Org. Chem.* **2007,** *72,* 5152-5160. (b) Kanyiva, K. S.; Nakao, Y.; Hiyama, T. *Angew. Chem. Int. Ed.* **2007,** *46,* 8872-8874.
[52] Aoyagi, Y.; Abe, T.; Ohta, A. *Synthesis* **1997,** 891-894.

Direct Arylation at the Azole Ring of Azaindoles

Drawing inspiration from direct arylation reaction conditions (Table 2.5) that have been shown to functionalize the conventional indole nucleus (Chapter 1), we then explored arylation of the azole ring of azaindoles. In preliminary screens, unsatisfactory outcomes were obtained with *N*-oxidized substrates.



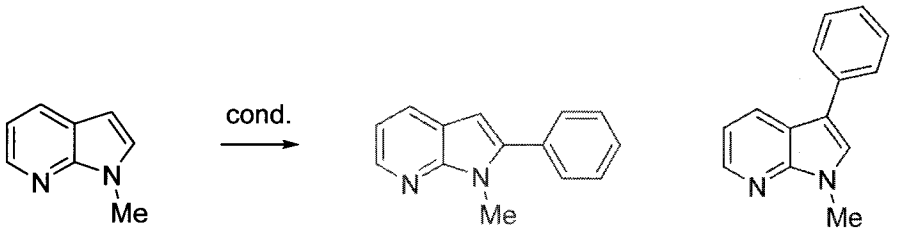
entry	catalyst system	coupling partner/equiv.	yield	
1	$Pd(OAc)_2$, PPh_3	Ph-I (1.2 equiv.)	88%	**Sames, 2004 (ref. 45a)**
2	$IMesPd(OAc)_2$	Ph-I-$Ph^+BF_4^-$ (2 equiv.)	86%	**Sanford, 2006 (ref. 17)**
3	$Pd(OAc)_2$, O_2	Ph-$B(OH)_2$ (1.5 equiv.)	77%	**Shi, 2008 (ref. 10j)**
4	$Pd(OAc)_2$, Ag_2O, 2-NO_2-PhCOOH	Ph-I (2 equiv.)	92%	**Larrosa, 2008 (ref. 18)**
5	$Cu(OTf)_2$	Ph-I-Ph^+OTf^- (2 equiv.)	72%	**Gaunt, 2008 (ref. 13d)**

Table 2.5 - Direct arylation of indole as seen in Chapter 1

Consequently, *N*-methyl-7-azaindole **2.11** was investigated as the coupling partner, in conjunction with the use of palladium(II) catalysts and boronic acids,[10j] palladium(0) catalysts with aryl iodides,[53] and palladium(II)[16] or copper(II) catalysts[13d] with iodine(III) reagents. In no case was arylation detected at the azine ring, with varying reactivity being observed at C2/C3 of the azole moiety. For example, reactions using copper gave no conversion to product,[54] while those with Pd(0) and boronic acids gave low conversions upon heating (~30% by GCMS). On the other hand, good conversion was seen with no modification to the originally reported conditions for reaction with Pd(0) and aryl iodides[53] (75% by GCMS), but an inseparable (10:1) mixture of C2:C3 isomers was obtained. Similarly, at 110 °C, Pd(II) and iodine(III) reagents provided exclusively the C2 arylated product, using 10 mol % Pd catalyst and 3 equivalents of iodine(III) reagent (64% isolated yield). While the conditions described by Larrosa initially provided only 6% conversion by GCMS, a survey of the reaction components revealed that by simply heating the reaction mixture to 80 °C with no other modifications, arylation of *N*-methyl-

[53] (a) see ref 41a. (b) see ref 17.
[54] We postulate that catalyst inhibition may be occurring via substrate binding through the azine nitrogen atom.

7-azaindole was achieved in 71% isolated yield with complete C2 regioselectivity (Table 2.6, entry 5).

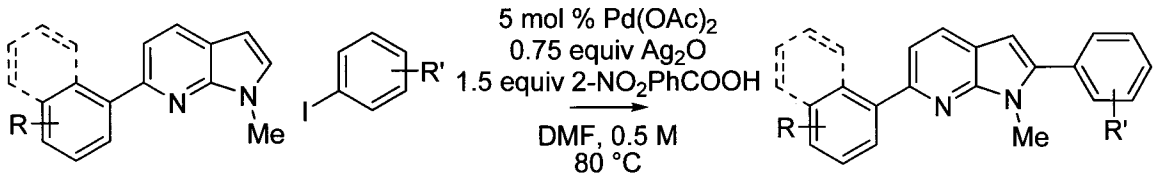


entry	catalyst system	coupling partner	temp	isolated yield (C2 : C3)	
1	$Pd(OAc)_2$, PPh_3	Ph-I	125°C	58% : 6% inseparable	**Sames, 2004**
2	$Pd(OAc)_2$	Ph-I-$Ph^+PF_6^-$	110°C	64% C2	**Sanford, 2006**
3	$Pd(OAc)_2$, O_2	Ph-$B(OH)_2$	100°C	30% GCMS conversion	**Shi, 2008**
4	$Pd(OAc)_2$, Ag_2O, 2-NO_2-PhCOOH	Ph-I	rt	6% GCMS conversion	**Larrosa, 2008**
5	$Pd(OAc)_2$, Ag_2O, 2-NO_2-PhCOOH	Ph-I	80°C	*71% C2*	
6	$Cu(OTf)_2$	Ph-I-$Ph^+PF_6^-$	80°C	nr	**Gaunt, 2008**

Table 2.6 - Optimization of C2-direct arylation of 7-azaindole

The Larrosa arylation conditions are robust and exhibit broad scope as illustrated in Table 2.7. Yields of up to 77% were obtained with electron neutral aryl iodides (entries 4 and 5). Arenes possessing cyano (58%) and phenolic (64%) functional groups (entries 3 and 6, respectively) were also able to be employed. Furthermore, 1-bromo-4-iodobenzene was selective for reaction at the iodo functional group, preserving the aryl bromide handle intact in the product (entry 2).

In conclusion, the regioselective direct arylation of the azaindole core can be achieved by making use of both the *N*-oxide activation strategy and the Larrosa arylation protocol. Validation of this reactivity should prompt a consideration of the direct arylation method with other substrate classes, where multiple reaction sites may be available for diversification.



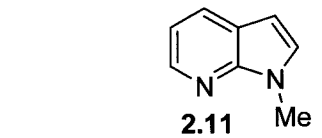
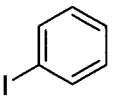
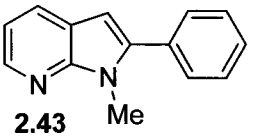
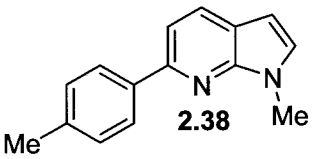
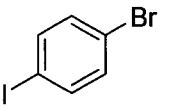
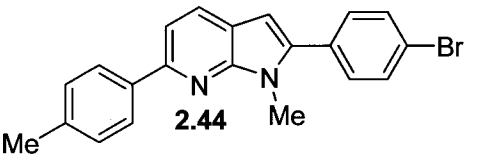
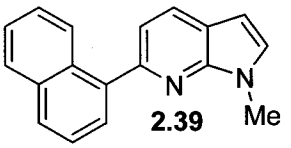
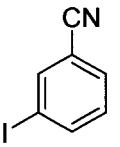
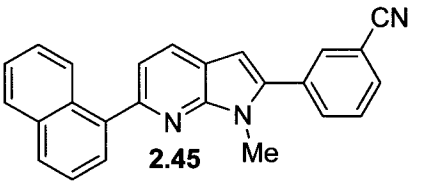
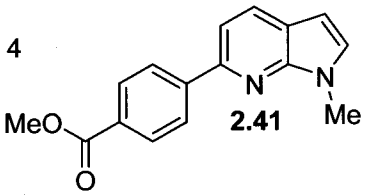
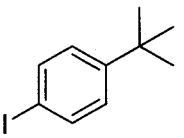
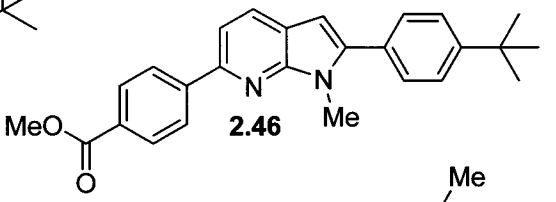
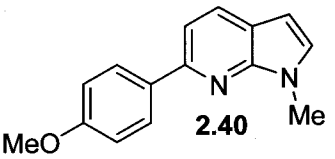
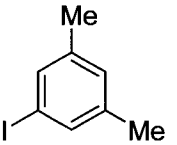
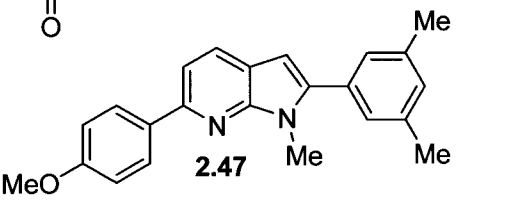
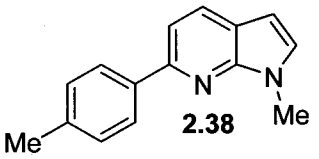
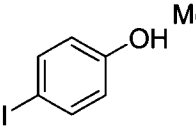
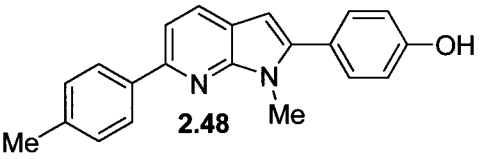
entry	reactant	aryl iodide	product	% yield
1				71%
2				75%
3				58%
4				64%
5				77%
6				64%

Table 2.7 - Azole arylation of 7-azaindoles[a]

[a] Conditions: Azaindole (1 equiv), aryl iodide (2 equiv), $Pd(OAc)_2$ (5 mol %), silver(I) oxide (0.75 equiv), and 2-nitrobenzoic acid (1.5 equiv) were weighed into a vial, purged with argon, charged with DMF (0.5 M), and stirred at 80°C overnight.

3

Advances in the Synthesis of Unsaturated Heterocycles via Transition-Metal Catalysis: Development of a Regioselective Rh-Catalyzed Synthesis of C2/C3-Substituted Indoles and Pyrroles

Introduction

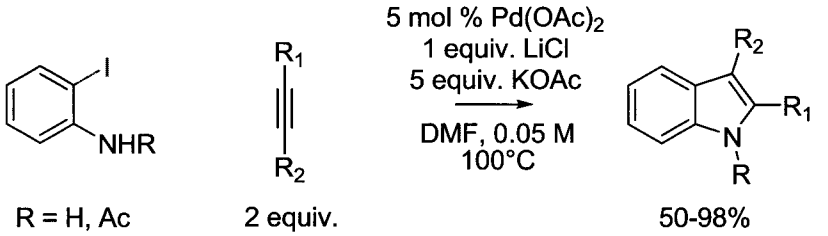
Since their introduction in the 1880s, the Paal-Knorr pyrrole synthesis[55] and the Fischer indole synthesis[56] have ranked among the most reliable and scaleable reactions in heterocyclic chemistry. The unwavering industrial and medicinal importance of these heterocycles have driven chemists to continue to develop novel methods to access differentially substituted pyrroles[57] and indoles.[58] In recent years, transition metal-catalyzed approaches for the synthesis

[55] (a) Knorr, L. *Ber.* **1884,** *17,* 2863-2870. (b) Paal, C. *Ber.* **1884,** *17,* 2756-2767. (c) Knorr, L. *Ber.* **1885,** *18,* 299-311. (d) Paal, C. *Ber.* **1885,** *18,* 367-371.
[56] (a) Fischer, E.; Jourdan, F. *Ber.* **1883,** *16,* 2241-2245. (b) Fischer, E.; Hess, O. *Ber.* **1884,** *17,* 559-568.
[57] Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1* **1999,** 2849-2866.

of unsaturated heterocycles[59] have introduced new possibilities, with palladium[60] playing a central role. This section will present a survey of the most recent developments in this broad area of research with an emphasis on methods involving alkynes as one of the coupling partners, a strategy that provides obvious advantages in terms of starting material accessibility. Later, we describe the development of a regioselective rhodium-catalyzed synthesis of C2/C3-substituted indoles and pyrroles.

Palladium-Catalyzed Methods with Pd(0)

In 1991, Larock introduced an efficient and regioselective route to C2/C3 substituted indoles catalyzed by palladium (Scheme 3.1).[61] In the event, a palladium(0) catalyst generated from a palladium(II) acetate pre-catalyst unites an *ortho*-iodo analine with an internal alkyne in the presence of base and a chloride source to yield an indole with the bulkiest substituent installed at C2.



Scheme 3.1 - The Larock indole synthesis

Similarly, pyridines and isoquinolines were able to be made from iodo-vinylic amines and *ortho*-iodo-*tert*-butylbenzyl imines, respectively (Scheme 3.2).[62] Terminal alkynes were compatible.[63]

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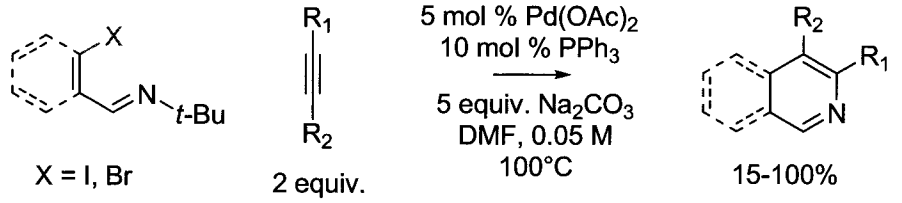
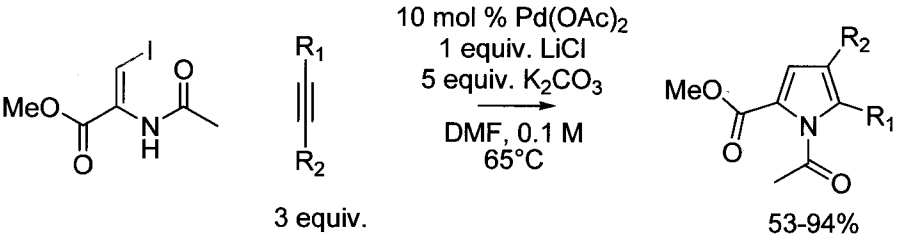
[58] Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006,** *106,* 2875-2911.
[59] (a) Nakamura, I.; Yamamoto; Y. *Chem. Rev.* **2004,** *104,* 2127-2198. (b) Hegedus, L. S. *Angew. Chem. Int. Ed. Engl.* **1988,** *27,* 1113-1126.
[60] (a) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004,** *104,* 2285-2309. (b) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005,** *105,* 2873-2920. (c) Sakamoto, T.; Kondo, Y.; Yamanaka, H. *Heterocycles* **1988,** *27,* 2225-2249.
[61] (a) Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991,** *113,* 6689-6690. (b) Larock, R. C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem.* **1998,** *63,* 7652-7662.
[62] (a) Roesch, K. R.; Larock, R. C. *J. Org. Chem.* **1998,** *63,* 5306-5307. (b) Roesch, K. R.; Zhang, H.; Larock, R. C. *J. Org. Chem.* **2001,** *66,* 8042-8051.
[63] Roesch, K. R.; Larock, R. C. *Org. Lett.* **1999,** *1,* 553-556.



Scheme 3.2 - The Larock isoquinoline synthesis

A related strategy for the construction of pyrroles was introduced by Crawley in 2006 (Scheme 3.3).[64] It was shown that under conditions adapted from the Larock indole protocol that an *N*-acetyl vinyl iodide and internal alkynes are competent in affording trisubstituted pyrroles in moderate to good yields.



Scheme 3.3 - Crawley's synthesis of pyrroles

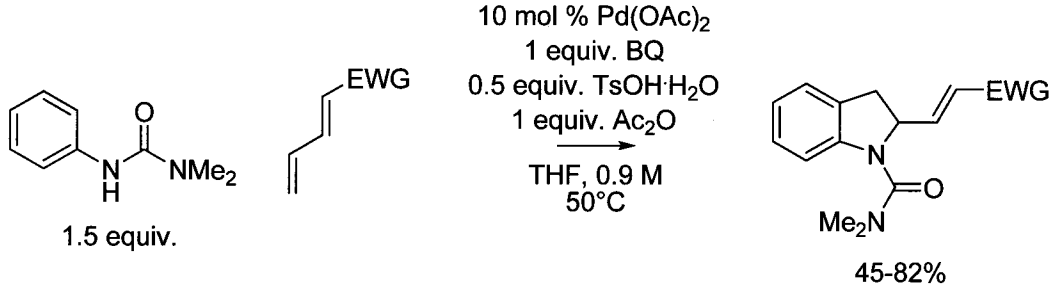
Palladium-Catalyzed Methods with Pd(II) or Cu(I)

Several examples have recently appeared that rely on oxidative C-H functionalization to form the heterocycle. This mode of reactivity is particularly desirable since the cost to install pre-activated functionality such as halides is obviated. Lloyd-Jones and Booker-Milburn demonstrated that a tosyl palladium species generated *in-situ* from $Pd(OAc)_2$ and $TsOH{\cdot}H_2O$ catalyzes the oxidative coupling of *N*-aryl ureas with electron-deficient dienes to afford 2-alkenylindolines (Scheme 3.4).[65] Further studies on this type of catalyst have shown that

[64] Crawley, M. L.; Goljer, I.; Jenkins, D. J.; Mehlmann, J. F.; Nogle, L.; Dooley, R.; Mahaney, P. E. *Org. Lett.* **2006,** *8,* 5837-5840.

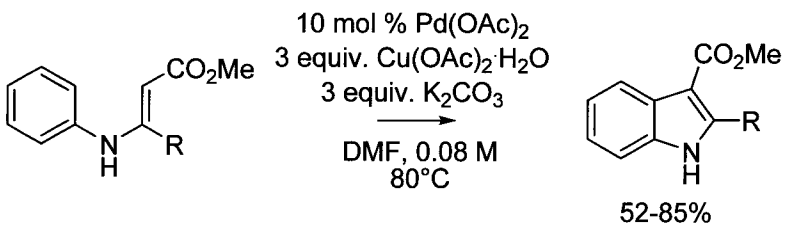
[65] Houlden, C. E.; Bailey, C. D.; Ford, J. G.; Gagné, M. R.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *J. Am. Chem. Soc.* **2008,** *130,* 10066-10067.

$(MeCN)_2Pd(OTs)_2$ enables a multitude of other C-H functionalizations *ortho* to the urea directing group.[66]



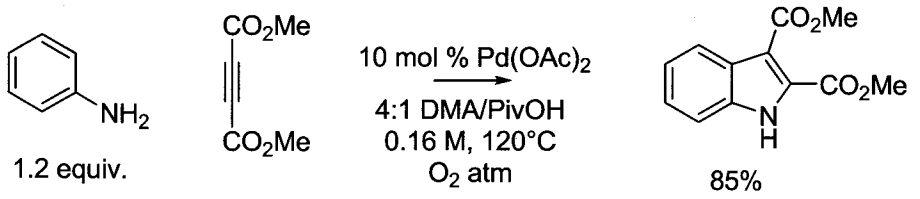
Scheme 3.4 - Lloyd-Jones and Booker-Milburn's indoline synthesis

Shortly thereafter, Glorius reported a palladium(II)-catalyzed synthesis of indoles by oxidative ring closure of *N*-aryl enamines (Scheme 3.5).[67] An important feature of this transformation is that the products possess no blocking group at the indolyl nitrogen. Although the resulting products all possess an ester at C3, the scope with respect to the functionality on the phenyl ring is impressive. An improvement on this reaction was made by Jiao, who disclosed that the *N*-aryl enamine could be formed *in-situ* by reaction between a free aniline and an internal alkyne (Scheme 3.6).[68] Furthermore, the terminal re-oxidant employed was atmospheric oxygen, a significant stride beyond stoichiometric copper metal. However, a major limitation was that dimethyl acetylenedicarboxylate appeared to be the only compatible alkyne. Lastly, Cacchi has demonstrated that the reaction will proceed under copper catalysis (Scheme 3.7).

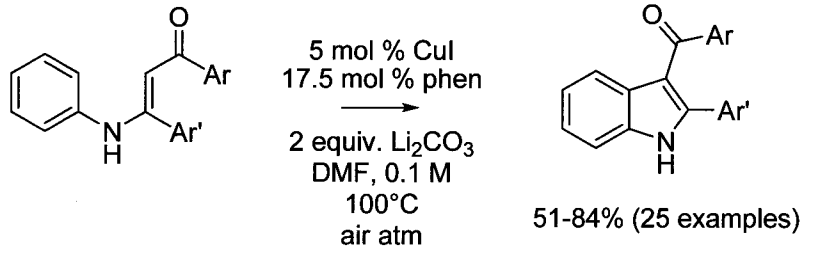


Scheme 3.5 - Glorius' indole synthesis

[66] Houlden, C. E.; Hutchby, M.; Bailey, C. D.; Ford, J. G.; Tyler, S. N. G.; Gagné, M. R.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *Angew. Chem. Int. Ed.* **2009,** *48,* 1830-1833.
[67] Würtz, S.; Rakshit, S.; Neumann, J. J.; Dröge, T.; Glorius, F. *Angew. Chem. Int. Ed.* **2008,** *47,* 7230-7233.
[68] Shi, Z.; Zhang, C.; Li, S; Pan, D.; Ding, S.; Cui, Y.; Jiao, N. *Angew. Chem. Int. Ed.* **2009,** *48,* 4572-4576.



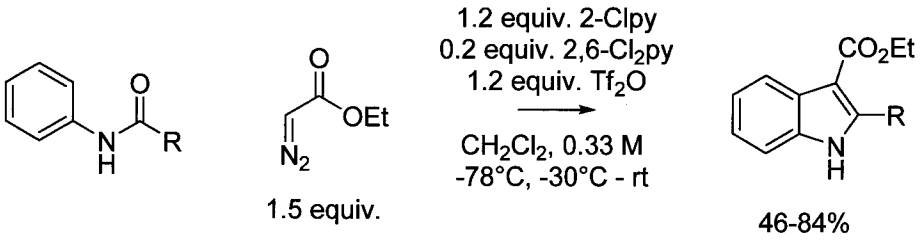
Scheme 3.6 - Jiao's indole synthesis



Scheme 3.7 - Cacchi's indole synthesis

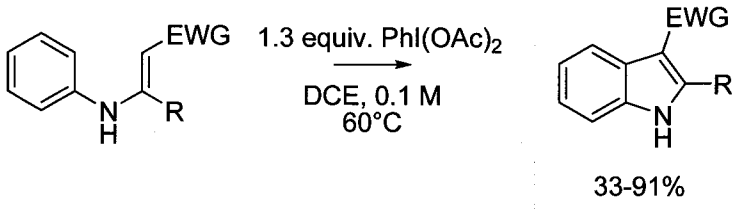
Non-Metal Catalyzed Methods

Two other indole syntheses have also appeared that do not require the use of transition-metals, but they are also limited because all products bear electron-withdrawing functionality. Wang reported the reaction between anilides and ethyl diazoacetate under the influence of triflic anhydride and chloropyridines (Scheme 3.8).[69] Zhao's method[70] is similar to that of Glorius, relying on oxidative ring closure of *N*-aryl enamines, but using hypervalent iodine instead of transition-metals (Scheme 3.9).



Scheme 3.8 - Wang's indole synthesis

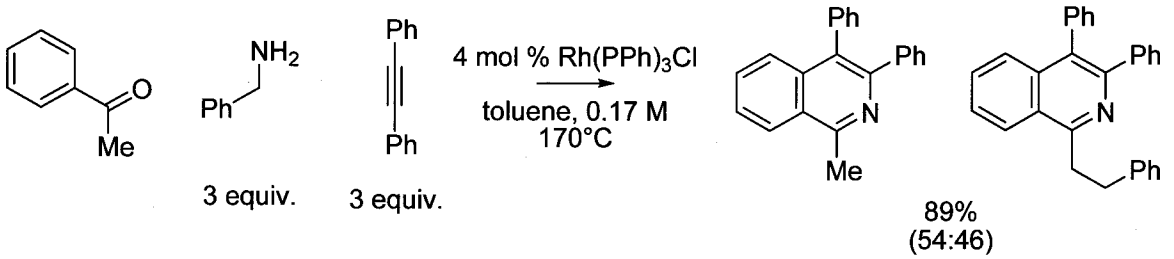
[69] Cui, S.-L.; Wang, J.; Wang, Y.-G. *J. Am. Chem. Soc.* **2008,** *130,* 13526-13527.
[70] Yu, W.; Du, Y.; Zhao, K. *Org. Lett.* **2009,** *11,* 2417-2420.



Scheme 3.9 - Zhao's indole synthesis

Rhodium-Catalyzed Methods

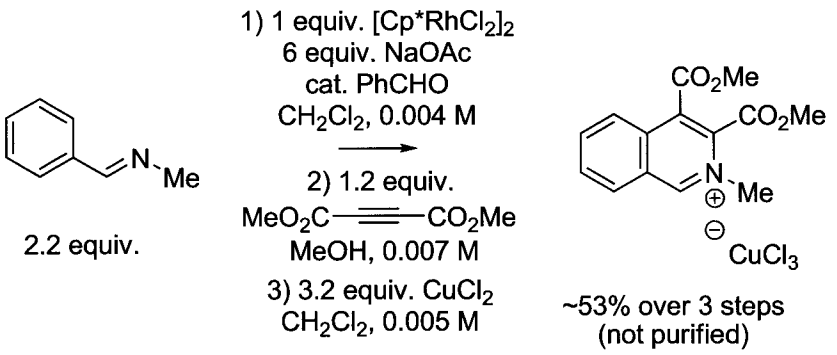
Several methods that construct heterocycles by rhodium catalysis have been reported. The most relevant examples to this discussion couple acetylenes oxidatively onto other staring materials via C-H functionalization. Following the initial reports of the Larock isoquinoline synthesis, Jun reported preliminary results that a mixture of isoquinolines could be synthesized directly by the coupling of diphenylethylene with a benzyl imine that was generated *in situ* (Scheme 3.10).[71]



Scheme 3.10 - Jun's isoquinoline synthesis

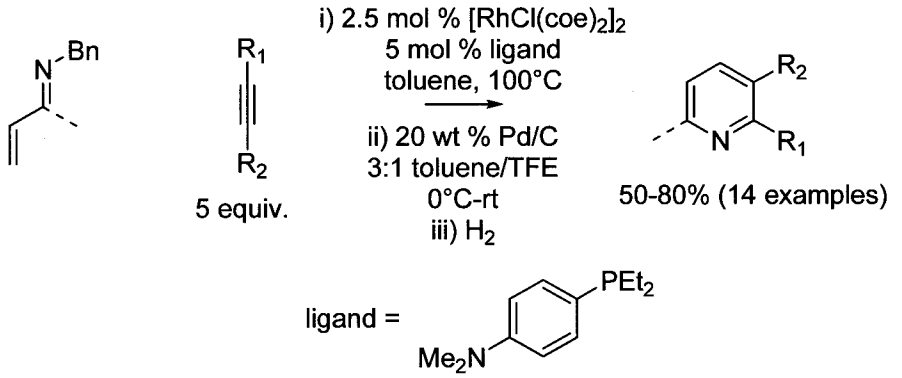
A much more recent report by Jones that gave an isoquinoline product featured crystallographically characterized rhodium intermediates (Scheme 3.11).[72]

[71] Lim, S.-G.; Lee, J. H.; Moon, C. W.; Hong, J.-B.; Jun, C.-H. *Org. Lett.* **2003,** *5,* 2759-2761.
[72] Li, L.; Brennessel, W. W.; Jones, W. D. *J. Am. Chem. Soc.* **2008,** *130,* 12414-12419.



Scheme 3.11 - Jones' isoquinoline synthesis

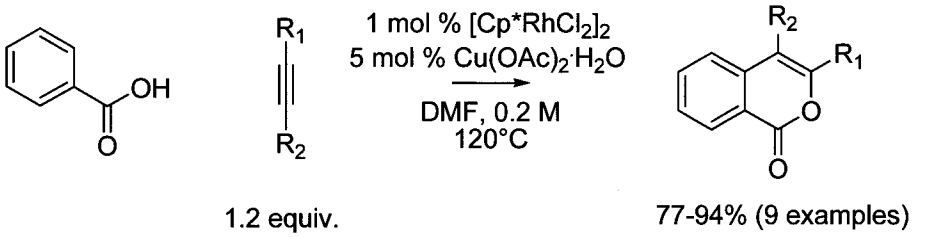
Bergman and Ellman described an approach to pyridines that is of significant synthetic utility (Scheme 3.12).[73] The coupling of alkynes and α,β-unsaturated *N*-benzyl aldimines and ketimines to form a *N*-benzyldihydropyridine is followed by hydrogenation/oxidation in one-pot to afford the free-base pyridines.



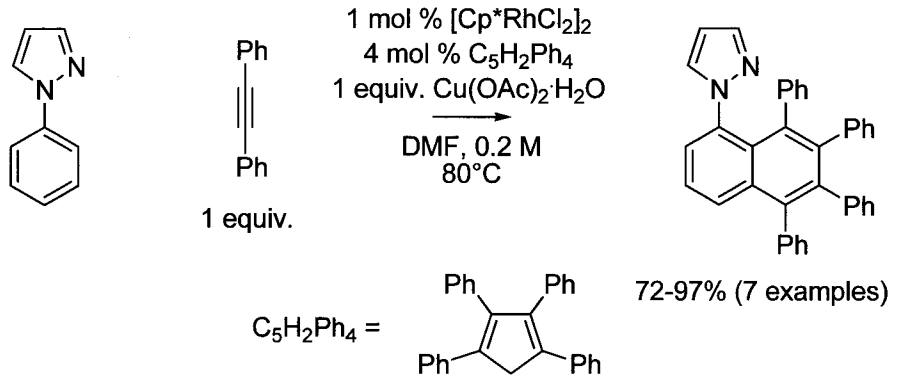
Scheme 3.12 - Bergman and Ellman's pyridine synthesis

Satoh and Miura have made several important contributions to this area. In 2007, they reported the synthesis of isocoumarins from the coupling of alkynes with benzoic acids (Scheme 3.13).[74] Following a similar precedent, highly fluorescent compounds were generated by double insertion products of phenylacetylene directed by a pyrazolyl nitrogen (Scheme 3.14).[75]

[73] Colby, D. A.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008,** *130,* 3645-3651.
[74] Ueura, K.; Satoh, T.; Miura, M. *Org. Lett.* **2007,** *9,* 1407-1409.
[75] Umeda, N.; Tsurugi, H.; Satoh, T.; Miura, M. *Angew. Chem. Int. Ed.* **2008,** *47,* 4019-4022.

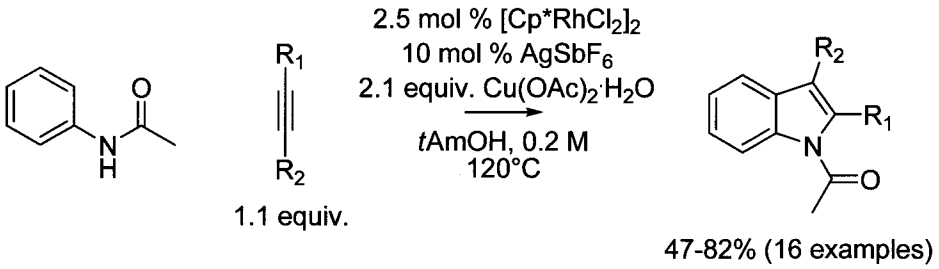


Scheme 3.13 - Synthesis of isocoumarins (Satoh and Miura)



Scheme 3.14 - Synthesis of highly fluorescent compounds (Satoh and Miura)

With this literature precedent, our research group uncovered an expedient rhodium-catalyzed indole synthesis based on the Larock concept (Scheme 3.15).[76] Without installation of an *ortho*-halide, acetanilide undergoes regioselective coupling with an internal alkyne in the presence of $[Cp^*RhCl_2]_2$, silver hexafluoroantimony and copper(II) acetate.

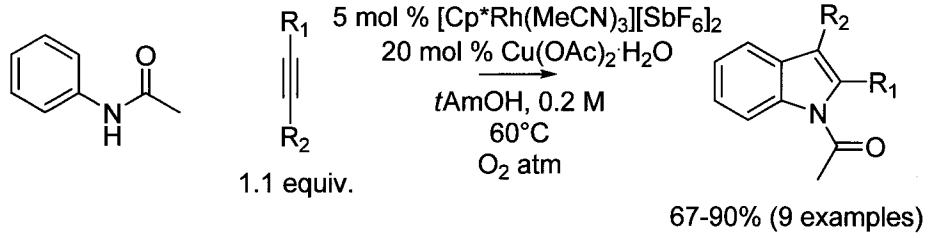


Scheme 3.15 - The Fagnou indole synthesis

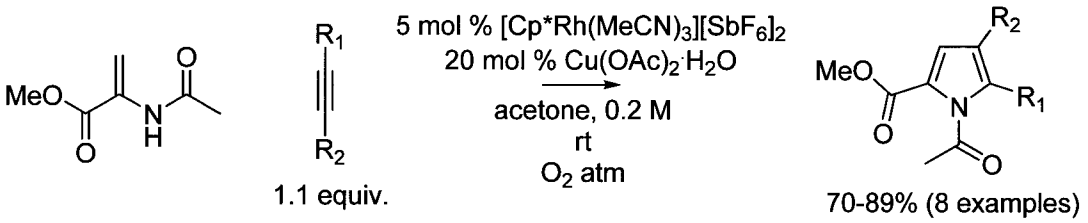
Milder reaction conditions have since been developed[77] which allow for easier reaction set up (a single, non-hygroscopic catalyst), and oxygen as terminal re-oxidant (Scheme 3.16). In

[76] Stuart, D. R.; Bertrand-Laperle, M.; Burgess, K. M. N.; Fagnou, K. *J. Am. Chem. Soc.* **2008,** *130,* 16474-16475.
[77] Stuart, D. R.; Alsabeh, P.; Kuhn, M.; Fagnou, K. *Unpublished results.*

addition, it was found that pyrroles may be efficiently synthesized at ambient temperature (Scheme 3.17).[78]

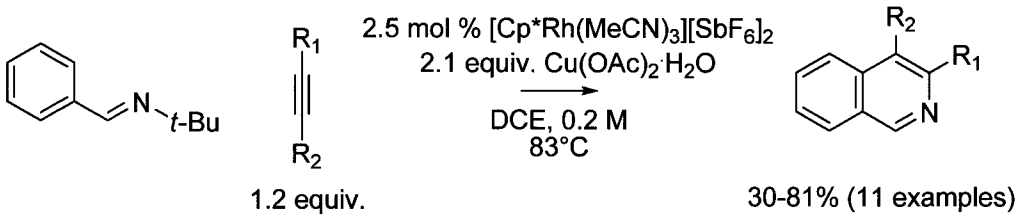


Scheme 3.16 - Second generation conditions for the Fagnou indole synthesis



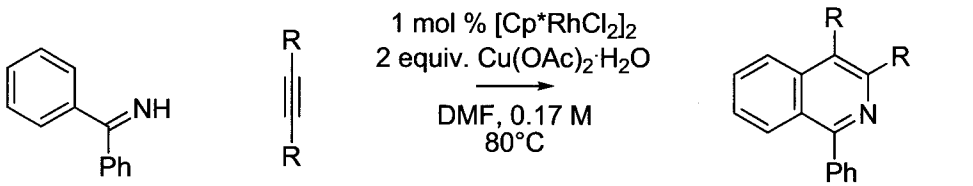
Scheme 3.17 - The Fagnou pyrrole synthesis

This method was recently extended to *N-tert*-butylbenzaldimines to form isoquinolines (Scheme 3.18).[79] Miura independently reported a similar transformation limited by symmetrical alkynes but using lower catalyst loadings (Scheme 3.19).[80]



Scheme 3.18 - The Fagnou isoquinoline synthesis

[78] Stuart, D. R. Ph.D. Thesis, University of Ottawa, **2009**.
[79] Guimond, N.; Fagnou, K. *J. Am. Chem. Soc.* **2009,** *131,* 12050-12051.
[80] Fukutani, T.; Umeda, N.; Hirano, K.; Satoh, T.; Miura, M. *Chem. Commun.* **2009,** 5141-5143.

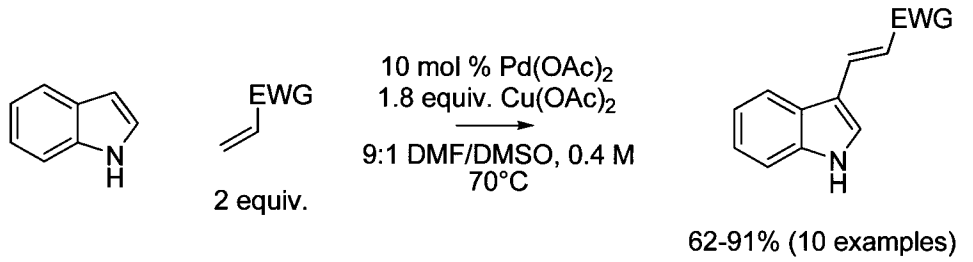


Scheme 3.19 - Miura's isoquinoline synthesis

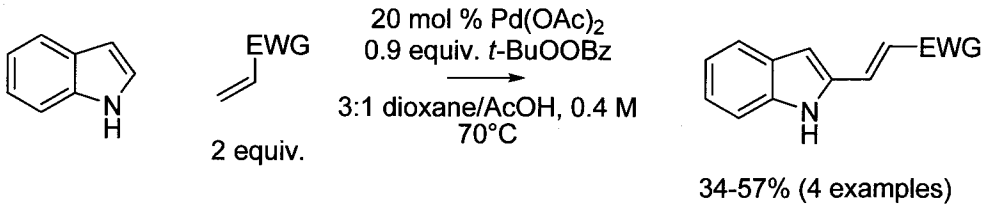
Direct Azole Alkenylation Methods

It is relevant at this junction to discuss briefly the recent advances in direct alkenylation of azole rings. The alkene functionality is a versatile functional-group, enabling a variety of elaborations on a molecule not limited to epoxidation, hydroboration, oxidative cleavage, and the Heck reaction.

In 2005, Gaunt demonstrated Pd(II)-catalyzed oxidative Heck (Fujiwara-Moritani) reactions on indoles possessing no protecting groups (Scheme 3.20).[81] By employing a different solvent and terminal re-oxidant, the regioselectivity could be strayed from C3 to C2, albeit in lower yields (Scheme 3.21).



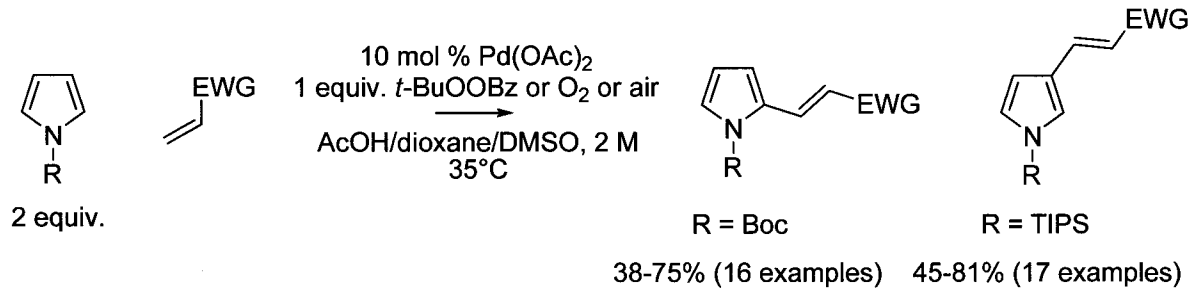
Scheme 3.20 - Gaunt's direct C3-alkenylation of indoles



Scheme 3.21 - Gaunt's direct C2-alkenylation of indoles

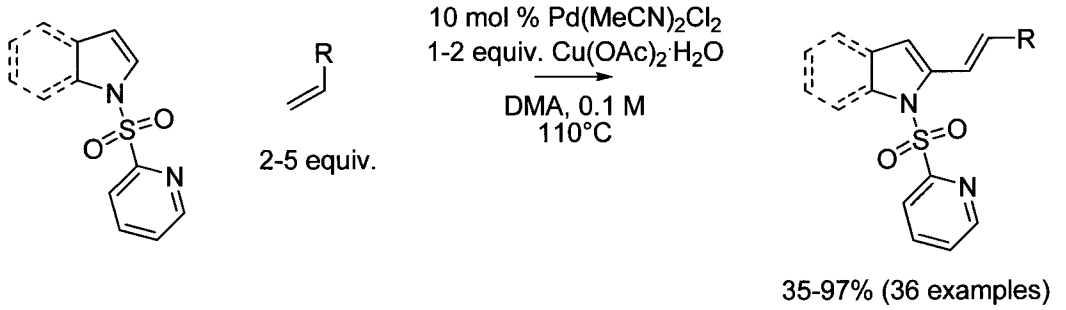
[81] Grimster, N. P.; Gauntlett, C.; Godfrey, C. R. A.; Gaunt, M. J. *Angew. Chem. Int. Ed.* **2005,** *44,* 3125-3129.

Gaunt elaborated on this advance by extending the direct alkenylation method to pyrroles (Scheme 3.22).[82] Compatible terminal oxidants included peroxides, oxygen or air. The regioselectivity was controlled by the steric bulk of the protecting group at nitrogen and the mild nature of the reaction permitted its use as the key step in a total synthesis of (±)-Rhazinocine.[83]



Scheme 3.22 - Gaunt's direct alkenylation of pyrroles

More recently, Gaunt's indole and pyrrole C2 alkenylation strategy was significantly improved by Arrayás and Carretero (Scheme 3.23).[84] They showed that a 2-pyridylsulfone protecting group was able to direct the alkenylation event to C2 with a scope that was not limited to conjugated alkenes.



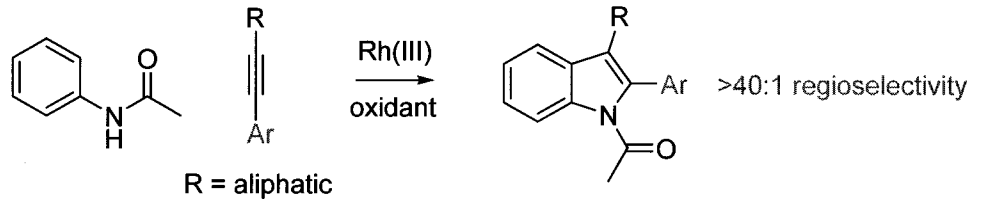
Scheme 3.23 - The direct alkenylation of Arrayás and Carretero

[82] Beck, E. M.; Grimster, N. P.; Hatley, R.; Gaunt, M. J. *J. Am. Chem. Soc.* **2006,** *128,* 2528-2529.
[83] Beck, E. M.; Hatley, R.; Gaunt, M. J. *Angew. Chem. Int. Ed.* **2008,** *47,* 3004-3007.
[84] García-Rubia, A.; Arrayás, R. G.; Carretero, J. C. *Angew. Chem. Int. Ed.* **2009,** *48,* 6511-6515.

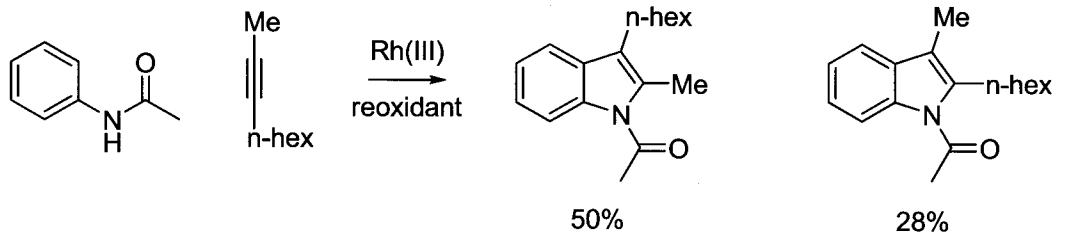
The Alkenyl Handle as a Director for Regioselectivity

In terms of transition metal-catalyzed heterocycle synthesis involving alkynes as coupling partners, the latest direct oxidative C-H functionalizations are still part of a relatively new field. However, high levels of regioselectivity for the coupling of *unsymmetrical* alkynes have only been achieved in the dihydropyridine synthesis of Bergman and Ellman[73] and our rhodium-catalyzed indole[76] and isoquinoline[79] methodologies (*vide supra*).

The regioselective outcomes seen in our synthesis of indoles was consistent with the Larock method, wherein aryl functionality installs at C2 (Scheme 3.24). Rationalization of the aryl group's high propensity for regioselective outcomes is an ongoing investigation. Nevertheless, the undesirable levels of regioselectivity obtained with alkynes possessing solely aliphatic decoration provided an opportunity for further development of the reaction (Scheme 3.25).

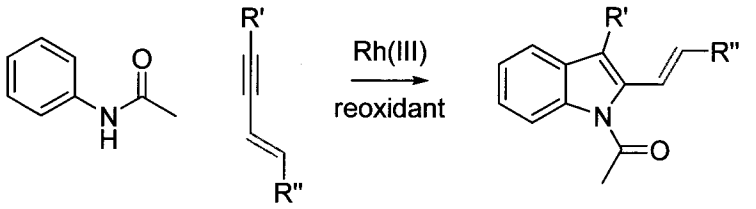


Scheme 3.24 - Regioselectivity of the Fagnou indole synthesis



Scheme 3.25 - Shortcoming seen when employing all-aliphatic alkynes

To this end, a working hypothesis was conceived which would potentially side-step the aliphatic conundrum. We had hoped that the alkenyl bond would function in an electronic manner analogous to the aryl moiety and impart regioselective triple bond migratory insertions, leading to the production of indoles as single regioisomers (Scheme 3.26). Described herein are the studies that led to the successful realization of such an approach.

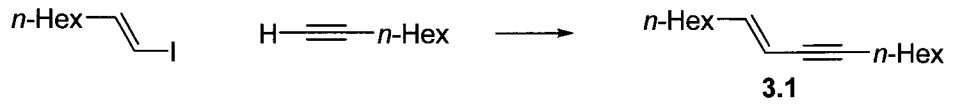


Scheme 3.26 - The enyne hypothesis

Synthesis of the Enyne Coupling Partners

The enyne used for method development was (*E*)-hexadec-7-en-9-yne **3.1** since it was readily prepared on gram-scale. Initially, we used a Sonogashira cross-coupling approach with (*E*)-1-iodooct-1-ene, obtained by reductive iodination of 1-octyne.[85] Thus, following the copper-catalyzed Sonogashira protocol of Li,[86] the target enyne was obtained in 46% yield (Table 3.1, entry 1). Although more traditional Sonogashira conditions[87] provided little improvement (entry 2), we found that an 86% yield could be obtained if the triphenylphosphine-palladium catalyst was generated *in-situ* (entry 3). Ultimately, we settled on a palladium-catalyzed dimerization of 1-octyne,[88] which provided the material in a single step, free of a colored impurity that was present in previous material (Scheme 3.27).

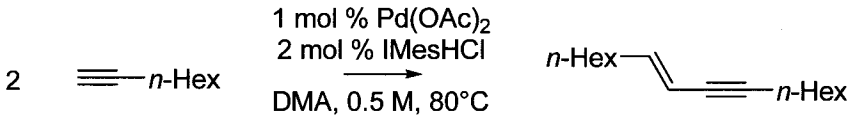
[85] Trost, B. M.; Rudd, M. T. *Org. Lett.* **2003,** *5,* 4599-4602.
[86] Li, J.-H.; Li, J.-L.; Wang, D.-P.; Pi, S.-F.; Xie, Y.-X.; Zhang, M.-B.; Hu, X.-C. *J. Org. Chem.* **2007,** *72,* 2053-2057.
[87] Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975,** *16,* 4467-4470.
[88] Yang, C.; Nolan, S. P. *J. Org. Chem.* **2002,** *67,* 591-593.



3.1

entry	conditions	isolated yield
1	10 mol % CuI 20 mol % DABCO 1 equiv. NBu_4Br 2 equiv. Cs_2CO_3 DMF, 0.2 M, 140°C	46%
2	5 mol % $PdCl_2(PPh_3)_2$ 10 mol % CuI 3 equiv. NEt_3 DMF, 0.2 M, rt	48%
3	5 mol % $Pd(OAc)_2$ 10 mol % PPh_3 10 mol % CuI NEt_3, 0.5 M, rt	86%

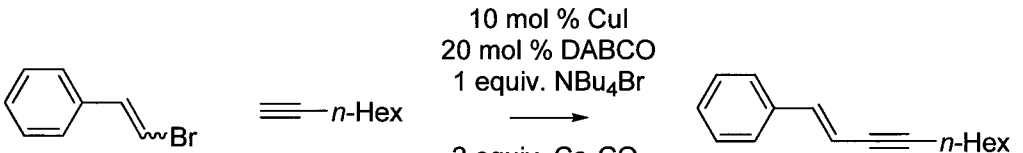
Table 3.1 - Synthesis of (*E*)-hexadec-7-en-9-yne



3.1 (46%)

Scheme 3.27 - Efficient synthesis of (*E*)-hexadec-7-en-9-yne

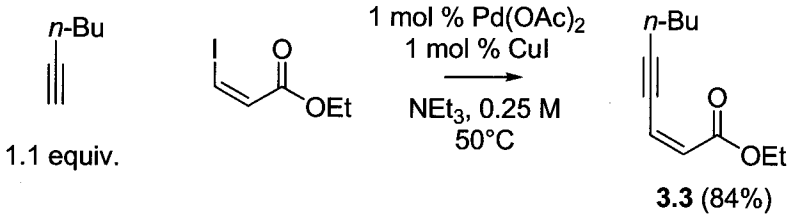
The copper-catalyzed Sonogashira method of Li[86] was also used to synthesize an enyne bearing an aromatic function (Scheme 3.28). A more standard Sonogashira reaction provided a (*Z*)-enyne that included an ester (Scheme 3.29).[89]



3.2 (58%)
20:1 (E)/(Z)

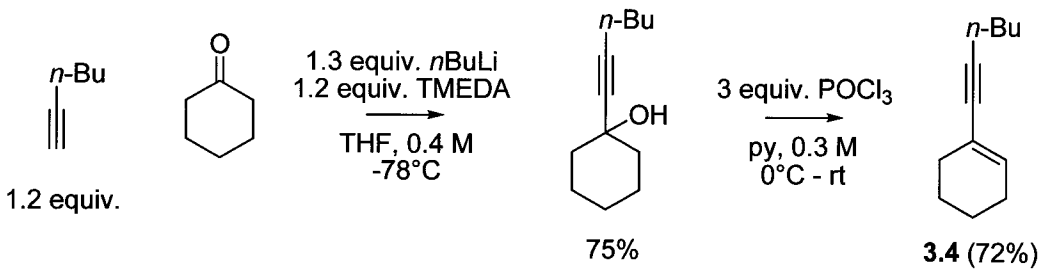
Scheme 3.28 - Synthesis of an enyne possessing an aryl function

[89] Takeuchi, R.; Tanabe, K.; Tanaka, S. *J. Org. Chem.* **2000,** *65,* 1558-1561.

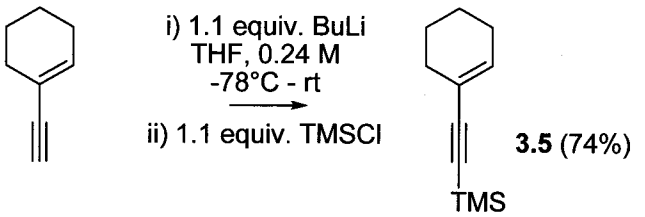


Scheme 3.29 - An enyne possessing an ester

Following a procedure reported by Yoshida,[90] an enyne that bore the ene portion within a cyclic moiety was also synthesized in two steps (Scheme 3.30). By attack of the lithium acetylide of commercially available 1-ethynylcyclohexene upon chlorotrimethylsilane, we prepared an enyne that possessed a silyl protecting group (Scheme 3.31).



Scheme 3.30 - Yoshida's enyne

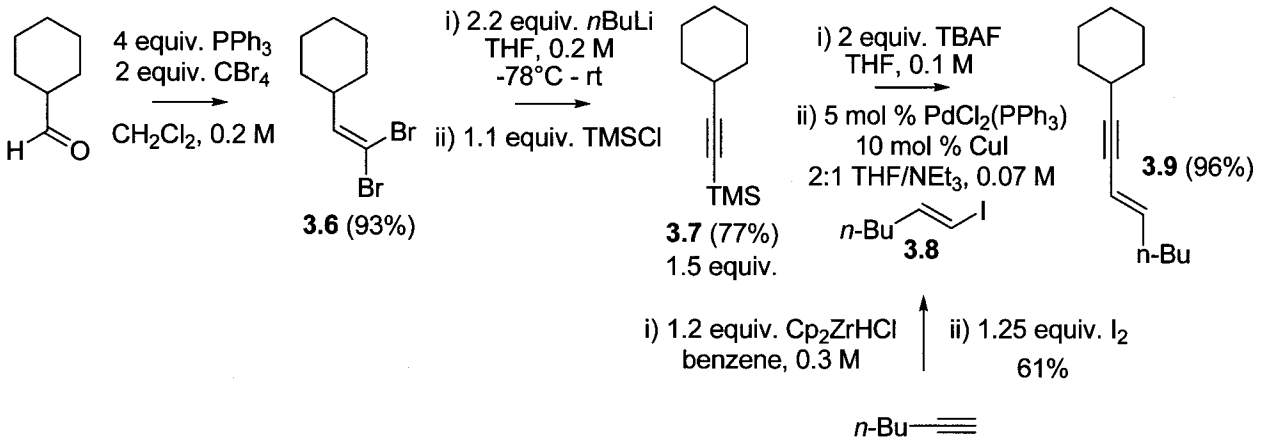


Scheme 3.31 - Silyl-protected enyne

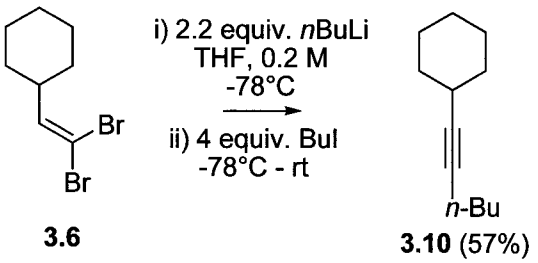
Finally, we submitted cyclohexylcarboxaldehyde to a Ramirez Olefination[91]/Corey-Fuchs Alkynylation[92] sequence with one-pot trimethylsilane capture in order to prepare a non-volatile surrogate for cyclohexylacetylene (Scheme 3.32). Thus, desilylation was followed by Sonogashira reaction with *trans*-iodo-1-hexene (prepared by Schwartz hydrozirconation[93] with iodine) to deliver the alkyl-alkyl enyne in 96% yield. For our studies, we also required the

[90] Yoshida, M.; Hayashi, M.; Shishido, K. *Org. Lett.* **2007,** *9,* 1643-1646.
[91] Ramirez, F.; Desai, N. B.; McKelvie, N. *J. Am. Chem. Soc.* **1962,** *88,* 1745-1747.
[92] Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972,** *13,* 3769-3772.
[93] Hart, D. W.; Blackburn, T. F.; Schwartz, J. *J. Am. Chem. Soc.* **1975,** *97,* 679-680.

internal alkyne **3.10** which was prepared by alkylation of the lithium acetylide derived from **3.6** (Scheme 3.33).



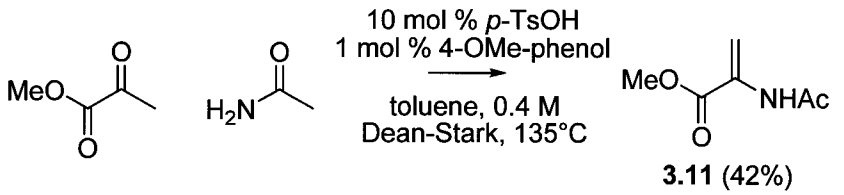
Scheme 3.32 - Desilylative Sonogashira protocol



Scheme 3.33 - Cyclohexyl-bearing alkyne

Synthesis of the Anilides

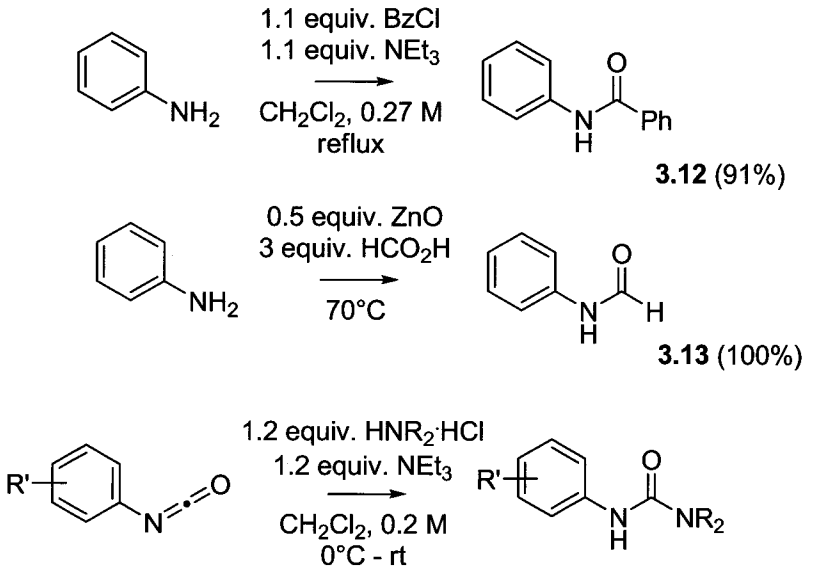
The enamide used in the synthesis of pyrroles was synthesized by a literature method in 42% yield (Scheme 3.34).[94]



Scheme 3.34 - Synthesis of enamide cross-coupling partner

[94] Crestey, F.; Collot, V.; Stiebing, S.; Rault, S. *Synthesis* **2006,** 3506-3514.

The various anilides investigated for use in the impending indole synthesis, if not purchased or borrowed,[95] were synthesized as depicted below (Table 3.2).



entry	R'	R_2	product (isolated yield)
1	H	H, Me	**3.14** (36%)
2	H	Et, Et	**3.15** (92%)
3	H	Me, Me	**3.16** (89%)
4	1-naph	Me, Me	**3.17** (87%)
5	4-OMe	Me, Me	**3.18** (86%)
6	2-Me	Me, Me	**3.19** (81%)

Table 3.2 - Synthesis of anilide coupling partners

Rh-catalyzed 2-Alkenyl-Pyrrole Synthesis

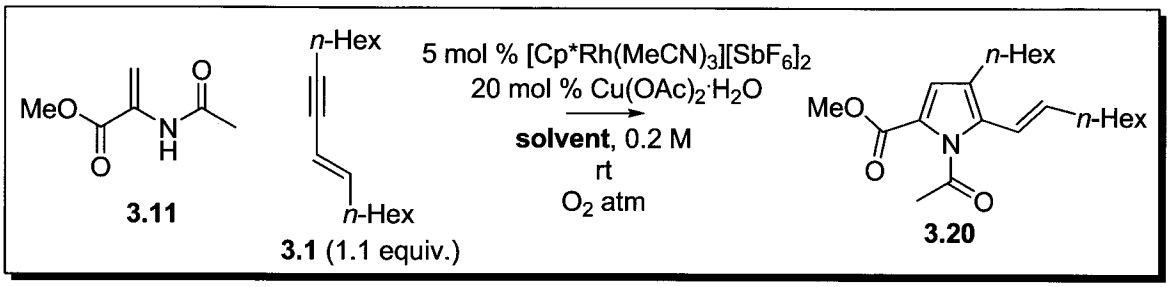
Optimization studies were conducted with methyl 2-acetamidoacrylate **3.11** and (*E*)-hexadec-7-en-9-yne **3.1**. The results of a solvent screen are summarized in Table 3.3. An isolated

[95] Thanks to Kevin M. N. Burgess, David R. Stuart and Daniel G. Shore.

yield of 46% was obtained for the desired 2-alkenylpyrrole under the previously reported conditions for the synthesis of 2-arylpyrroles. The regioisomeric outcome of the reaction was established by NOESY correlations. This yield was increased to 55% when the copper(II) acetate was powdered (entry 24). Finally, cyclohexanone delivered the target product in 77% isolated yield (entry 25).

With the optimal conditions in hand, we proceeded to evaluate the scope of the reaction with a variety of enynes (Table 3.4). Different aliphatic substitution patterns about the double bond are compatible as seen in compounds **3.20** (77%), **3.21** (37%) and **3.22** (84%). Furthermore, compounds **3.27** (53%) and **3.28** (70%)[96] demonstrate the ability to make both regioisomers. Compounds **3.24** (59%)[96] and **3.23** (73%)[96] demonstrate that not only esters are able to be installed, but also a Boc-protected nitrogen possessing a free NH, as well as trityl ethers. Another masked alcohol, in the form of a TBS-ether is also installable in conjunction with an indole, albeit in lower yield (compound **3.25**, 36%).[96] Styryl groups are able to be fused onto the pyrroles (compound **3.26**, 79%), and the ester at C5 is not required (compound **3.31**, 48%). Access to pyrroles not possessing functionality at C3 is possible through the use of TMS-enynes (Compound **3.29**, 69% and compound **3.30**, 69%).

[96] This compound and its parent enyne were synthesized by Lina Chan and the pertaining characterization data will be reported in her thesis.



entry	solvent	GC yield (isolated)
1	MeOAc	37%
2	EtOAc	38%
3	iPrOAc	42%
4	DME	10%
5	dioxane	18%
6	THF	31%
7	tAmOH	nr
8	tBuOH	1%
9	EtOH	5
10	NMP	58%
11	MeCN	nr
12	trifluorotoluene	17%
13	trifluoroethanol	23%
14	trifluoroacetic acid	nr
15	ethyltrifluoroacetate	nr
16	CCl_4	nr
17	$CHCl_3$	nr
18	CH_2Cl_2	30%
19	chlorobenzene	0%
20	toluene	(4%)
21	DCE	58% (60%)
22	MEK	58%
23	acetone[a]	(46%)
24	acetone	57% (55%)
25	cyclohexanone	81% (**77%**)

[a] $Cu(OAc)_2 \cdot H_2O$ had not been powdered

Table 3.3 - Solvent optimization for pyrrole synthesis

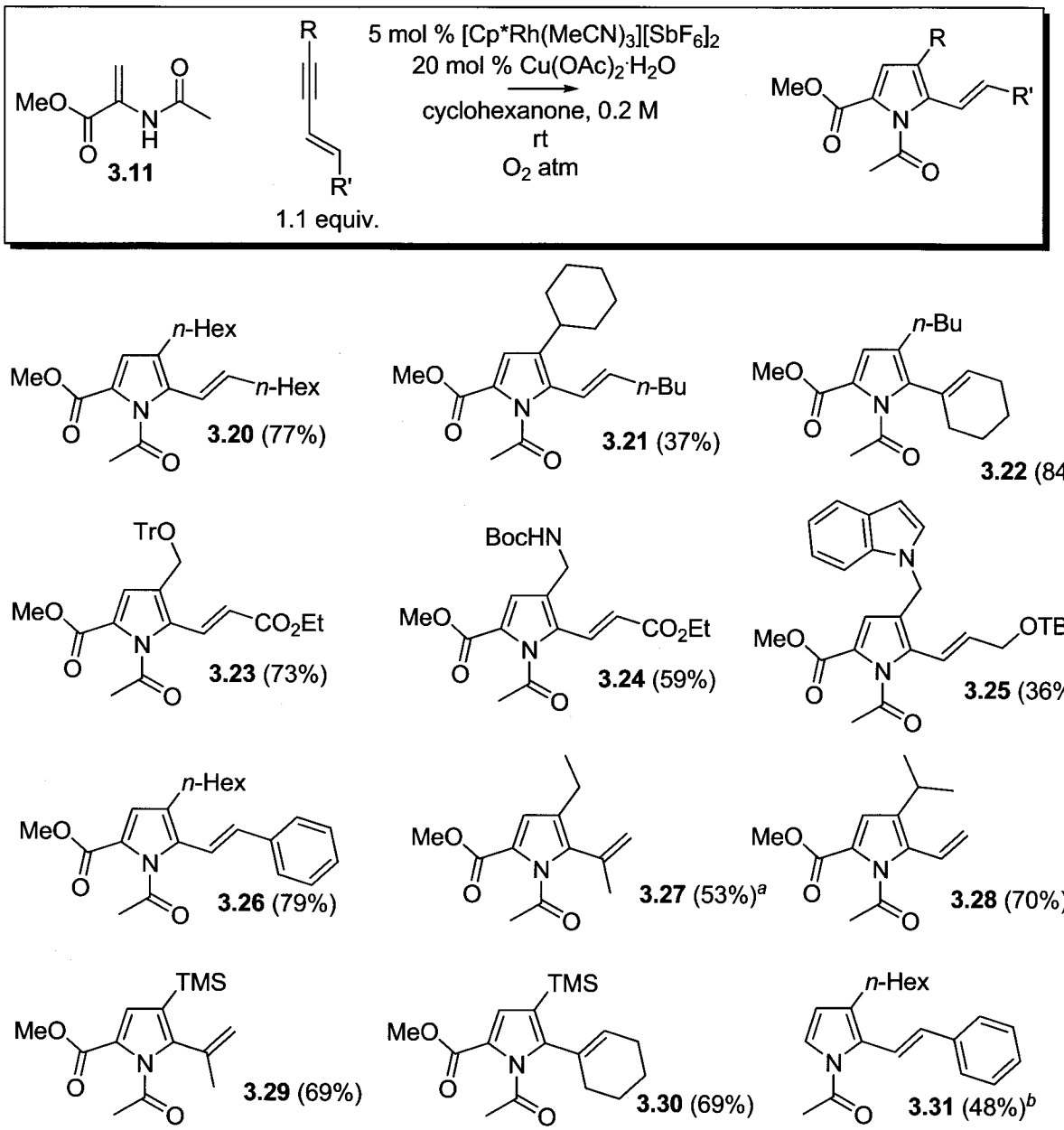
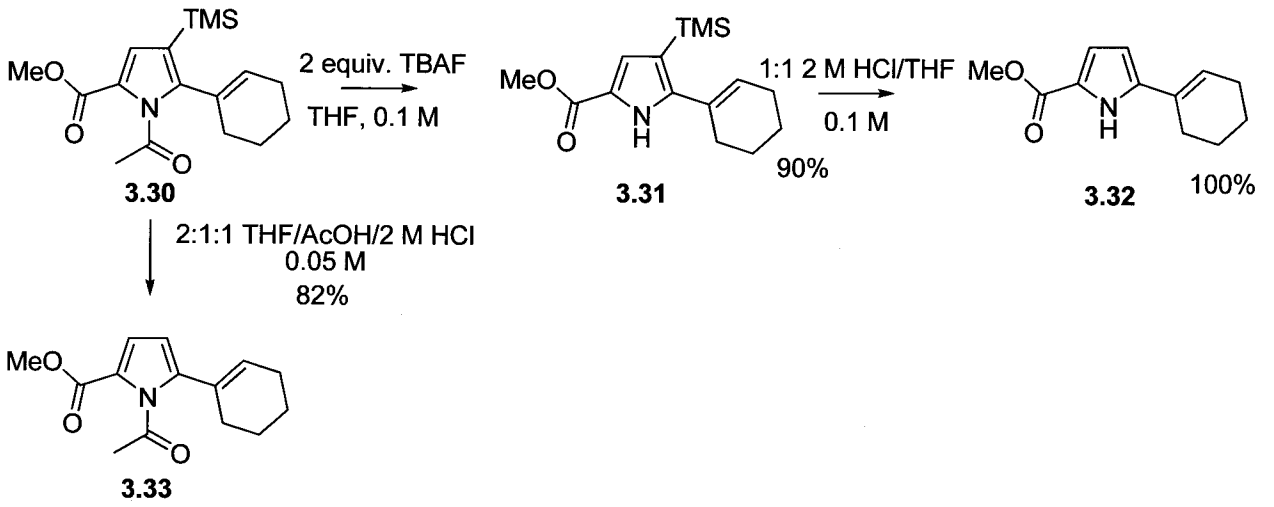


Table 3.4 - Scope of 2-alkenyl pyrrole synthesis

[a] Conditions: methyl 2-acetamidoacrylate (1 equiv.), $[Cp^*Rh(MeCN)_3][SbF6]_2$ (5 mol %), and $Cu(OAc)_2.H_2O$ (20 mol %), were weighed into a test tube and a solution of enyne (1.1 equiv.) in cyclohexanone (0.2 M) was added. The reaction vessel was purged with oxygen and stirred overnight. [b] 2 equiv. of methyl 2-acetamidoacrylate was used instead. [c] *N*-Vinylacetamide (3 equiv.) was used as coupling partner.

Removal of the C3-trimethylsilyl functionality from pyrrole **3.30** was non-trivial. Tetrabutylammonium fluoride only brought about cleavage of the acetyl blocking group

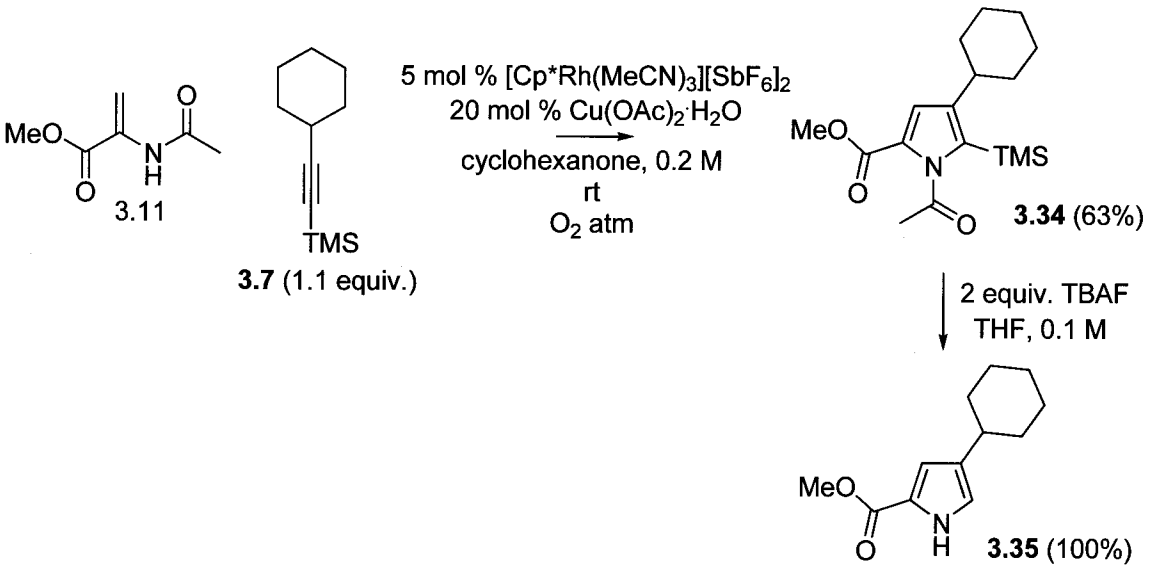
(Scheme 3.35). When the product was subjected to HCl the TMS group could be cleaved (90%), but it could not be done directly from **3.30** without obtaining inseparable mixtures of **3.31**[96] and **3.32**. However, acetic acid and HCl selectively cleaved the TMS unit (82%).[96]



Scheme 3.35 - Rupture of aryl-TMS linkage

As an added bonus, we noted that when the reaction was conducted with a simple TMS-alkyne, the silyl group was directed to C2, providing entry into 3-aliphatic pyrroles (Scheme 3.36).[97] Reports of these molecules are exceedingly rare since they cannot be accessed by traditional methods such as the Paal-Knorr pyrrole synthesis.

[97] A similar outcome was seen with reaction of 1-trimethylsilyloct-1-yne, observed previously in our lab: Stuart, D. R. Ph.D. Thesis, University of Ottawa, **2009**.

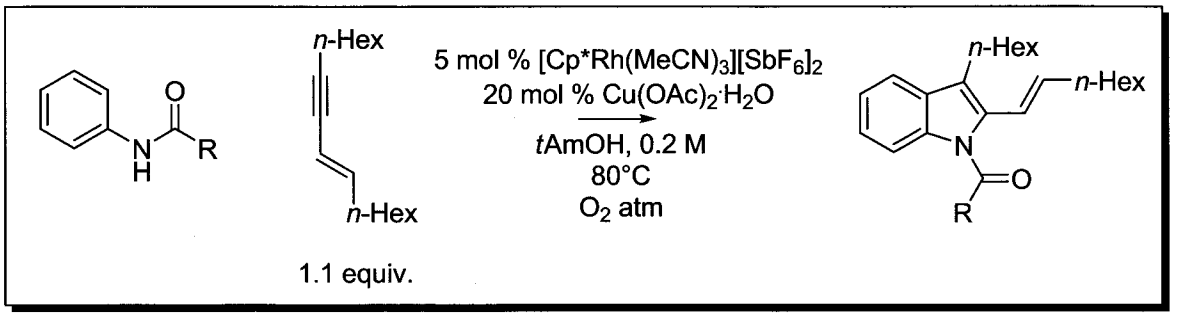


Scheme 3.36 - Synthesis of a C3-aliphatic pyrrole

Rh-catalyzed 2-Alkenyl-Indole Synthesis

Extension of the enyne chemistry to the synthesis of 2-alkenyl indoles proved more challenging. The incompatibility of acetanilide[98] (Table 3.5, entry 2) led us to examine a wide variety of anilides, eventually revealing *N*-aryl ureas as competent substrates for the desired coupling (entries 9-13).[65] Thus, reaction of *N,N*-dimethyl-*N'*-phenylurea under the second generation conditions of the Fagnou indole synthesis afforded the target indole in 15% isolated yield as a single regioisomer (entry 10).

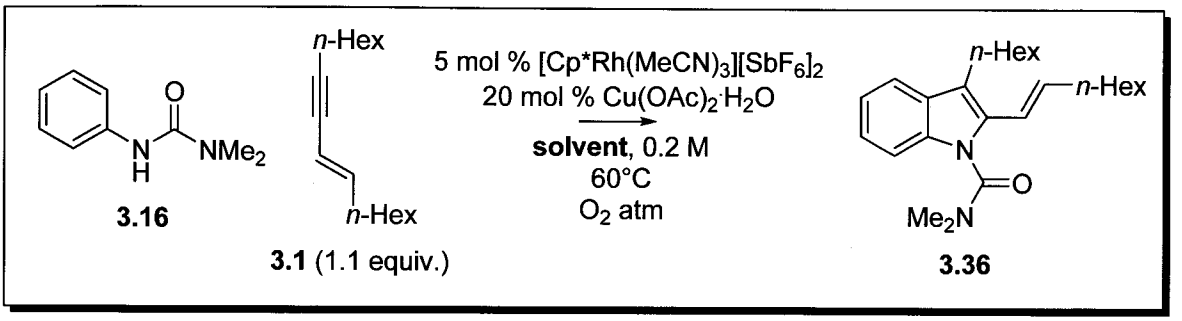
[98] Under the first generation conditions (ref 86), an 11% percent yield of the target product was able to be obtained: Stuart, D. R. Ph.D. Thesis, University of Ottawa, **2009**.



entry	R	NMR yield (isolated)
1	H	nr
2	Me	nr
3	CF_3	nr
4	*t*Bu	nr
5	Ph	nr
6	OMe	nr
7	OEt	nr
8	OtBu	nr
9	NHMe	nr
10	NMe_2	16% (15%)
11	NEt_2	7%
12	N*i*Pr	4%
13	morpholine	1%

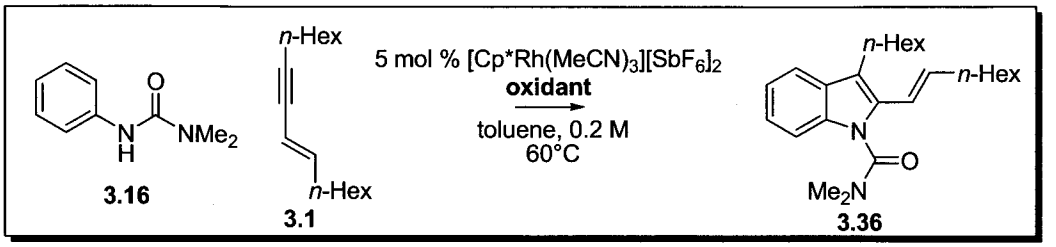
Table 3.5 - Optimization of anilide

The reaction outcome was significantly influenced by changes in solvent, guiding us to a 48% yield with toluene (Table 3.6, entries 7-15). We also experimented with other terminal re-oxidants (Table 3.7). The most notable results included aqueous hydrogen peroxide with copper(II) acetate (55%, entry 8) and *tert*-butylhydroperoxide (70%, entry 10). Ultimately, we revisited copper(II) acetate and oxygen (48%, entry 11), which afforded 57% with finely powered copper(II) acetate (entry 12). Although 10 mol % rhodium catalyst gave 77% (entry 13), we deemed this unpractical and instead resorted to stoichiometric copper(II) acetate, which secured the final conditions (entry 14, 74% isolated yield).



entry	solvent	GC yield (isolated)
1	EtOAc	29%
2	*i*PrOAc	35%
3	acetone	14%
4	cyclohexanone	20%
5	*t*AmOH	29%
6	*t*BuOH	25%
7	H_2O	nr
8	dioxane	33%
9	MTBE	25%
10	DMSO	nr
11	DMA	28%
12	benzene	43%
13	toluene	46% (48%)
14	xylenes	42%
15	mesitylene	47%

Table 3.6 - Solvent optimization for indole synthesis



entry	oxidant	equiv. urea	equiv. enyne	GC yield (isolated)
1	BQ	1	1.1	trace
2	BzOOBz (1.2 equiv.)	1	1.1	22%
3	*t*BuOOBz (1.2 equiv.)	1	1.1	34%
4	*m*CPBA (1.2 equiv.)	1	1.1	nr
5	AcOOH (1.2 equiv.)	1	1.1	nr
6	H_2O_2·urea (1.2 equiv.)	1	1.1	nr
7	H_2O_2 (1.2 equiv.)	1	1.1	nr
8	H_2O_2 (1.2 equiv.) + $Cu(OAc)_2·H_2O$ (20 mol %)[a]	2	1	55%
9	*t*BuOOH (1.2 equiv.) + $Cu(OAc)_2·H_2O$ (20 mol %)[a]	2	1	62%
10	*t*BuOOH (1.2 equiv.)	2	1	68% (70%)
11	O_2 atm + $Cu(OAc)_2·H_2O$ (20 mol %)	1	1.1	46% (48%)
12	O_2 atm + $Cu(OAc)_2·H_2O$ (20 mol %)[a]	1	1.1	57%
13	O_2 atm + $Cu(OAc)_2·H_2O$ (20 mol %)[a,b]	1	1.1	77%
14	$Cu(OAc)_2·H_2O$ (2.1 equiv.)[a]	1	1.1	76% (**74%**)

[a] $Cu(OAc)_2·H_2O$ was powdered with mortar and pestle
[b] 10 mol % $[Cp^*Rh(MeCN)_3][SbF_6]_2$

Table 3.7 - Final optimization outcome for indole synthesis

A number of functional groups are compatible on the benzo ring (compounds **3.37-3.40**, 53-62%), even when used in combination with different enynes (Table 3.8). For example, the styrene-containing indole **3.41**[96] was isolated in 63% yield while esters could be installed *cis* (compound **3.44**, 77%) or *trans* (compound **3.43**, 54%)[96] at C2, or directly on C3 (compound **3.42**, 57%). A 66% yield was obtained for an indole with a 1,1-substituted alkene (compound **3.46**).[96] A Boc-protected nitrogen was tolerated with exceptional efficiency, affording 80% yield for compound **3.45**.[96] Finally, a 58% yield was obtained for the -OTBS, heterocycle-bearing indole **3.47**.[96]

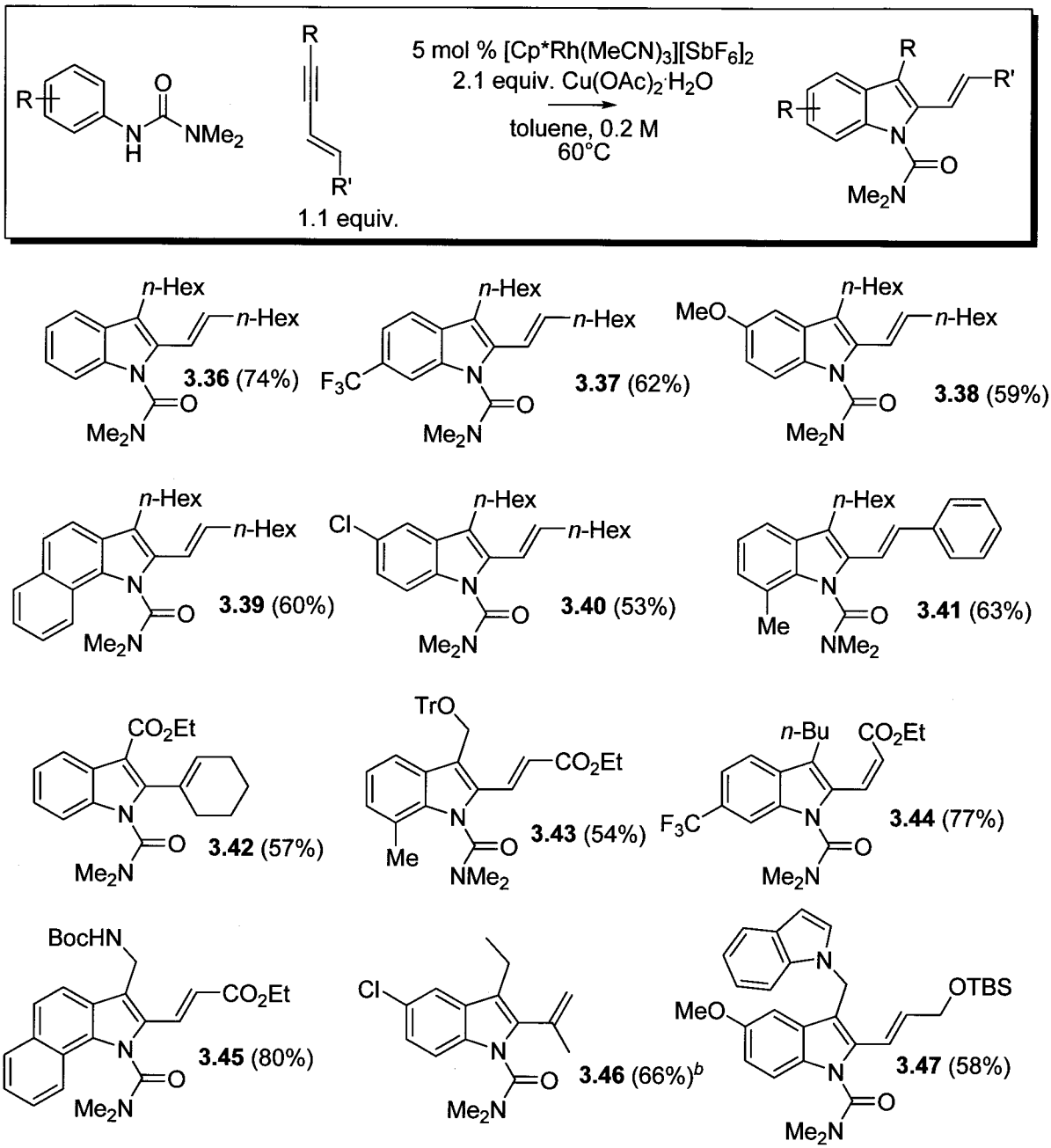
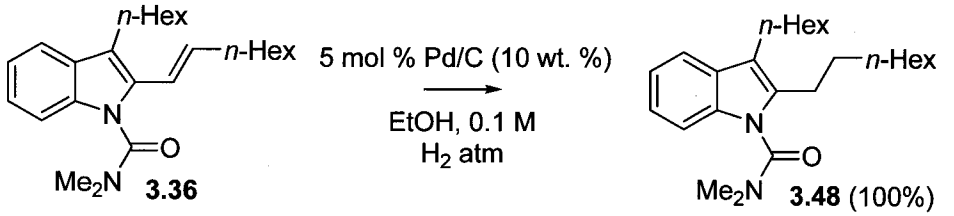


Table 3.8 - Scope of 2-alkenyl indole synthesis

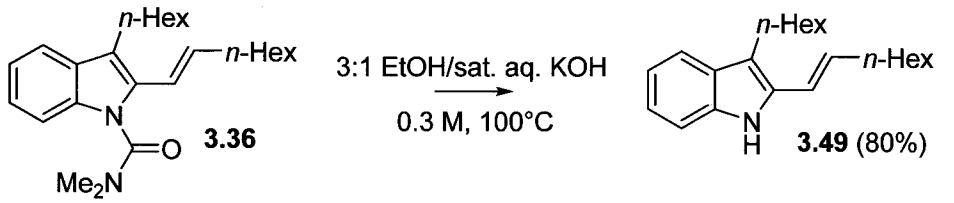
[a] Conditions: *N*-aryl urea (1 equiv.), $[Cp^*Rh(MeCN)_3][SbF6]_2$ (5 mol %), and $Cu(OAc)_2.H_2O$ (2.1 equiv.), were weighed into a test tube and a solution of enyne (1.1 equiv.) in toluene (0.2 M) was added, and the mixture was stirred at 60°C overnight. [b] 2 equiv. of enyne were employed.

Again, the double bond on the indoles may be reduced with quantitative transfer of material (Scheme 3.37), providing a single regioisomer of a C2/C3 alkyl-substituted indole.



Scheme 3.37 - Saturation of 2-alkenyl bond

Finally, we sought to establish conditions for removal of the robust dimethylurea protecting group since conditions that were found in the literature did not preserve the integrity of the C2 double bond.[99] Our extensive forays in this regard finally led to the conditions delineated in Scheme 3.38, which freed the 2-alkenyl indole in 80% yield.



Scheme 3.38 - Deprotection of 2-alkenyl indole

In conclusion, C2/C3-aliphatic-substituted pyrroles and indoles may be accessed under mild conditions by the rhodium-catalyzed union of enynes with simple nitrogen-containing starting materials.

[99] Hartung, C. G.; Fecher, A.; Chapell, B.; Snieckus, V. *Org. Lett.* **2003,** *5,* 1899-1902.

4

Pd(II)-Catalyzed Oxidative Aryl-Aryl Bond Formation: Application to the Synthesis of Carbazole Alkaloids[100]

Introduction

Palladium(II)-catalyzed oxidative C-H arylation is an atom-efficient means for forging aryl linkages.[101] While direct arylation (Chapters 1 and 2) still makes use of one element of arene pre-activation (halide or sulfonate), oxidative arylation unites two inert C-H bonds in direct C-C bond formation. The value of such a direct approach to biaryl linkages has led it to become an increasingly competitive area of research.

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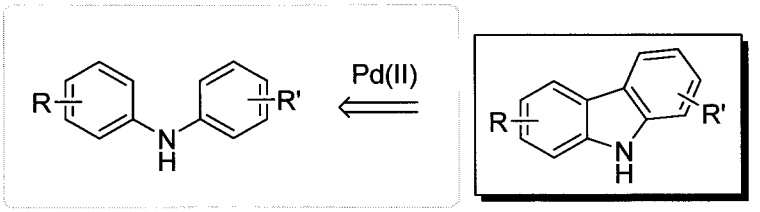
[100] A significant portion of the work described in this chapter has been published in the form of a full article: Liégault, B.; Lee, D.; Huestis, M. P.; Stuart, D. R.; Fagnou, K. *J. Org. Chem.* **2008,** *73,* 5022–5028.
[101] A recent review: Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2009,** *48,* 5094-5115.

In the realm of palladium(II)-catalyzed processes, there are several important challenges that must be overcome in order to achieve oxidative C-H arylation: 1) The high strength of a typical C-H bond (113 kcal/mol)[102] when compared to that of a C-Cl (79 kcal/mol) or C-Br (69 kcal/mol) bond establishes the C-H functional group as inert to the reaction conditions of most known transition metal-catalyzed transformations. 2) In contrast to Pd(0) catalytic cycles that return the active catalyst after each turnover, Pd(II) catalysts require a stoichiometric amount of re-oxidant. 3) In intermolecular couplings, achieving high levels of regioselectivity when *both* of the arenes have multiple C-H bonds is difficult, combined with the fact that the catalyst must *differentiate* between the two arenes in order to disfavor homocoupling.

Heretofore, we recount the most seminal advances in palladium(II)-catalyzed oxidative C-H arylation with an emphasis on approaches to carbazoles (Scheme 4.1), a motif for which the intramolecular oxidative C-H arylation reactions are particularly useful for. We also report new conditions that can be used to assemble electron-rich carbazole alkaloids.



Scheme 4.1 - Ring closing strategy for carbazole synthesis

Intramolecular Oxidative Arylation

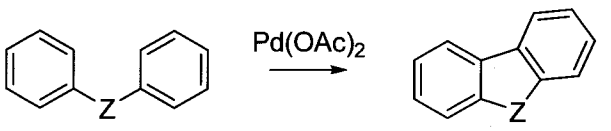
In examining intramolecular oxidative arylation, the issue of regioselectivity is largely overcome due to the inherent restrictions exerted by degrees of freedom. In other words, the most favorable ring size that would result will dictate which C-H bonds participate.

The first observation of the union of two C-H bonds to form a C-C bond under the action of palladium(II) was presented by Itatani (Table 4.1, entry 1).[103] In the event, diphenyl ether was

[102] Blanksby, S. J.; Ellison, G. B. *Acc. Chem. Res.* **2003,** *36,* 255-263.
[103] (a) Yoshimoto, H.; Itatani, H. *Bull. Chem. Soc. Jpn.* **1974,** *46,* 2490-2492. (b) Shiotani, A.; Itatani, H. *Angew. Chem. Int. Ed. Engl.* **1974,** *13,* 471-472

converted to dibenzofuran in variable yields, along with competing dimerization arising from intermolecular reactivity.

In his landmark paper (1975), Åkermark demonstrated that a variety of tricyclic heterocycles could be accessed through intramolecular cyclizations initiated by submission of tethered aryl rings to stoichiometric palladium(II) acetate in acetic acid (entry 2).[104] In the years that followed, Åkermark particularly secured this reaction as a reliable approach to carbazoles by developing conditions that utilize catalytic quantities of palladium (entries 3,4).[105] A notable example by Fujii and Ohno in 2007 featured the use of ambient air as re-oxidant (entry 5).[106]



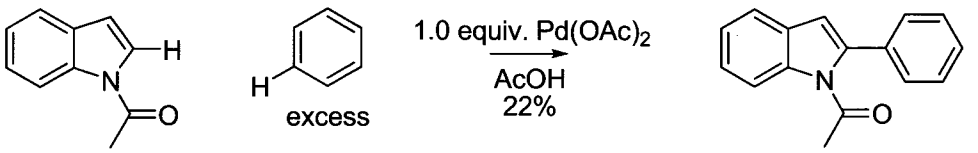
entry	Z	re-oxidant	equiv. $Pd(OAc)_2$	solvent/temp	Yield	
1	O	O_2	1	none/150°C	variable + dimers	**Itatani, 1974**
2	O, NH, CO	none	1-2	AcOH/120°C	45%, 70%, 65%	**Åkermark, 1975**
3	NH	TBHP	0.05	AcOH/90°C	31%	**Åkermark, 1995**
4	NH	O_2	0.05	AcOH/90°C	64%	**Åkermark, 1999**
5	NH	air	0.10	AcOH/80°C	90%	**Fujii; Ohno, 2007**

Table 4.1 - Developments in intramolecular oxidative arylation

Intermolecular Oxidative Arylation

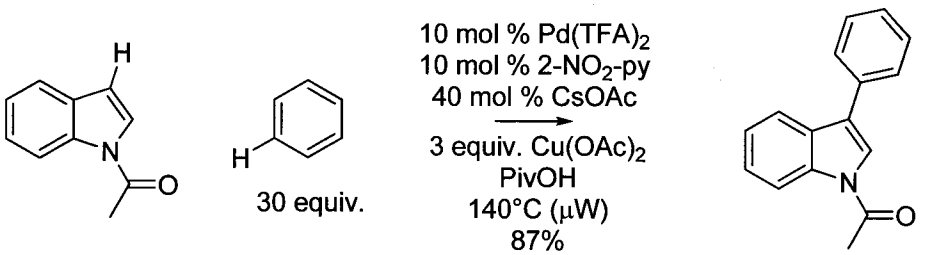
For quite some time, the great challenges posed by intermolecular C-H cross-couplings (outlined above) prevented their practical realization. For example, only a C2 arylation of indole had been reported in low yield in the year 1981 (Scheme 4.2).[107]

[104] Åkermark, B.; Eberson, L.; Jonsson, E.; Pettersson, E. *J. Org. Chem.* **1975,** *40,* 1365-1367.
[105] (a) Åkermark, B.; Oslob, J. D.; Heuschert, U. *Tetrahedron Lett.* **1995,** *36,* 1325-1326. (b) Hagelin, H.; Oslob, J. D.; Åkermark, B. *Chem. Eur. J.* **1999,** *5,* 2413-2416.
[106] (a) Watanabe, T.; Ueda, S.; Inuki, S.; Oishi, S.; Fujii, N.; Ohno, H. *Chem. Commun.* **2007,** 4516-4518. (b) Watanabe, T.; Oishi, S.; Fujii, N.; Ohno, H. *J. Org. Chem.* **2009,** *74,* 4720-4726.
[107] Itahara, T. *J. Chem. Soc., Chem. Commun.* **1981,** 254-255.

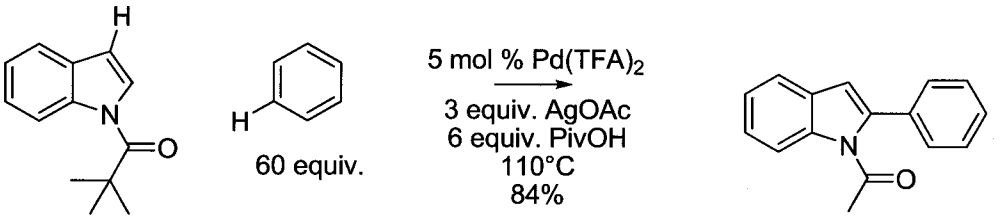


Scheme 4.2 - Intermolecular oxidative arylation

Finally, in 2007, our group reported a palladium(II) catalyst system that would oxidatively install an aryl handle at the C3 position of indoles (Scheme 4.3).[108] Later that year, this method was extended to include C2 arylations of indoles and pyrroles by using silver re-oxidants instead of copper (Scheme 4.4).[109]



Scheme 4.3 - Fagnou oxidative arylation (C3)



Scheme 4.4 - Fagnou oxidative arylation (C2)

Later, other groups reported examples of similar reactions. DeBoef reported C2 arylation of benzofuran (Scheme 4.5),[110] while Sanford used an azine directing group to arylate benzo[*h*]quinoline (Scheme 4.6).[111]

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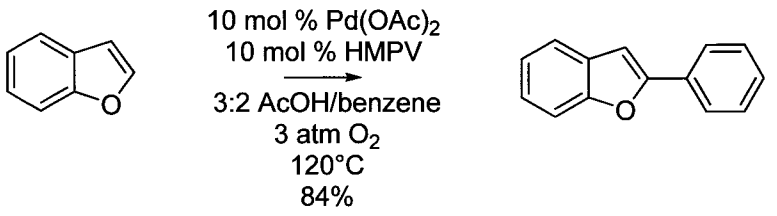
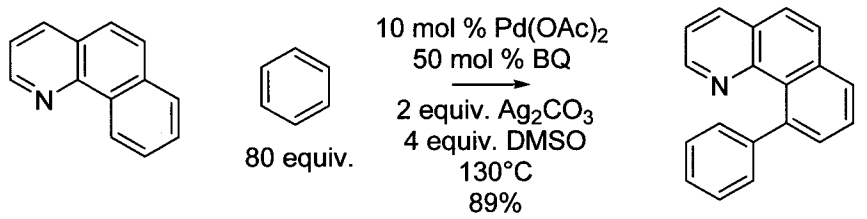
[108] Stuart, D. R.; Fagnou, K. *Science* **2007,** *316,* 1172-1175.
[109] Stuart, D. R.; Villemure, E.; Fagnou, K. *J. Am. Chem. Soc.* **2007,** *129,* 12072-12073.
[110] Dwight, T. A.; Rue, N. R.; Charyk, D.; Josselyn, R.; DeBoef, B. *Org. Lett.* **2007,** *9,* 3137-3139.
[111] Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2007,** *129,* 11904-11905.

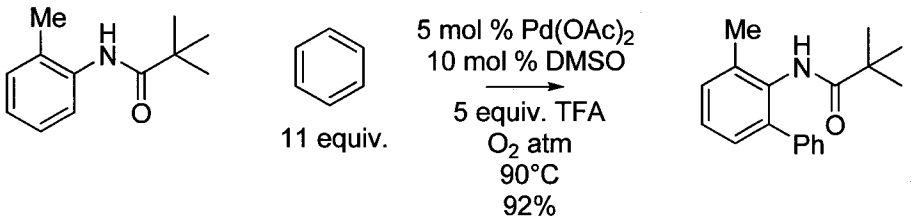


Scheme 4.5 - DeBoef's intermolecular oxidative arylation



Scheme 4.6 - Sanford's intermolecular oxidative arylation

Another interesting example by Buchwald that arylated a simple aromatic used a pivaloyl group to direct arylation *ortho* (Scheme 4.7).[112]



Scheme 4.7 - Buchwald's intermolecular oxidative arylation of simple benzenes

Reaction Development and Extension of Scope[113]

Following our investigations in the intermolecular realm of palladium(II)-catalyzed oxidative C-H arylations, we revisited the intramolecular research program with the intent to expand the substrate scope significantly. Extensive investigations by other members of our laboratory resulted in the discovery of reaction conditions suitable for the synthesis of several different unsaturated heterocyclic cores. In contrast to reaction parameters that were present in the literature, the new conditions displayed remarkable compatibility towards the construction of

[112] Brasche, G.; García-Fortanet, J.; Buchwald, S. L. *Org. Lett.* **2008,** *10,* 2207-2210.
[113] This work was performed by Dr. Benoît Liégault, Doris Lee and David R. Stuart.

electron-rich carbazoles. This new trait was capitalized upon in the synthesis of the natural products murrayafoline A, clausenine and mukonine (Figure 4.1).

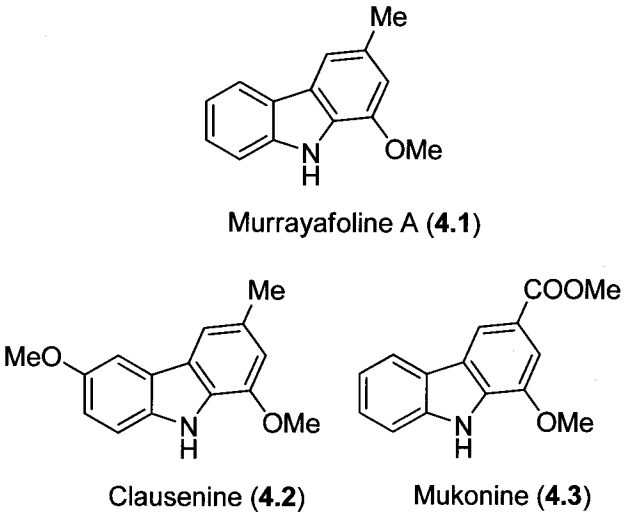
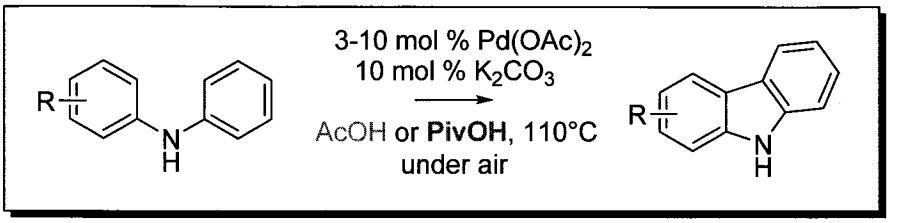
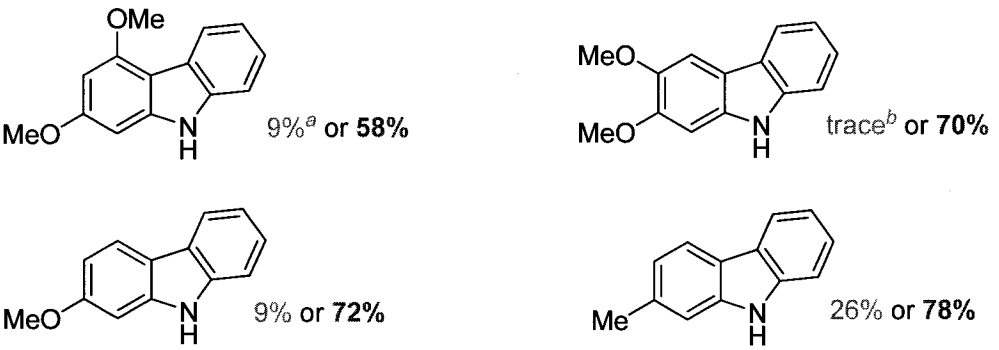


Figure 4.1 - Targeted naturally-occuring carbazoles

When typical reaction conditions employing palladium(II) acetate in acetic acid are brought upon electron-rich diarylamines, the target carbazoles are isolated in low yields. Not only does decomposition occur, but other unusual side products arise as well (Table 4.2). It was found that by using pivalic acid as solvent, consistently high yields were obtained.



PivOH results in dramatic increase in yield



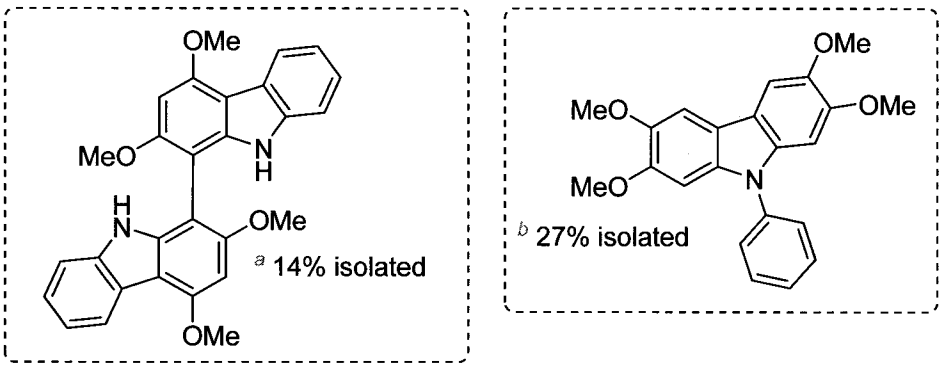


Table 4.2 - Discovery of pivalic acid as solvent for oxidative ring closure

The optimal conditions were compatible with a variety of substrates besides diarylamines (Table 4.3). Diarylethers, *N*-benzoylindoles, as well as 2-anilinonapthoquinone underwent efficient C-H ring closure to form 5-membered rings.

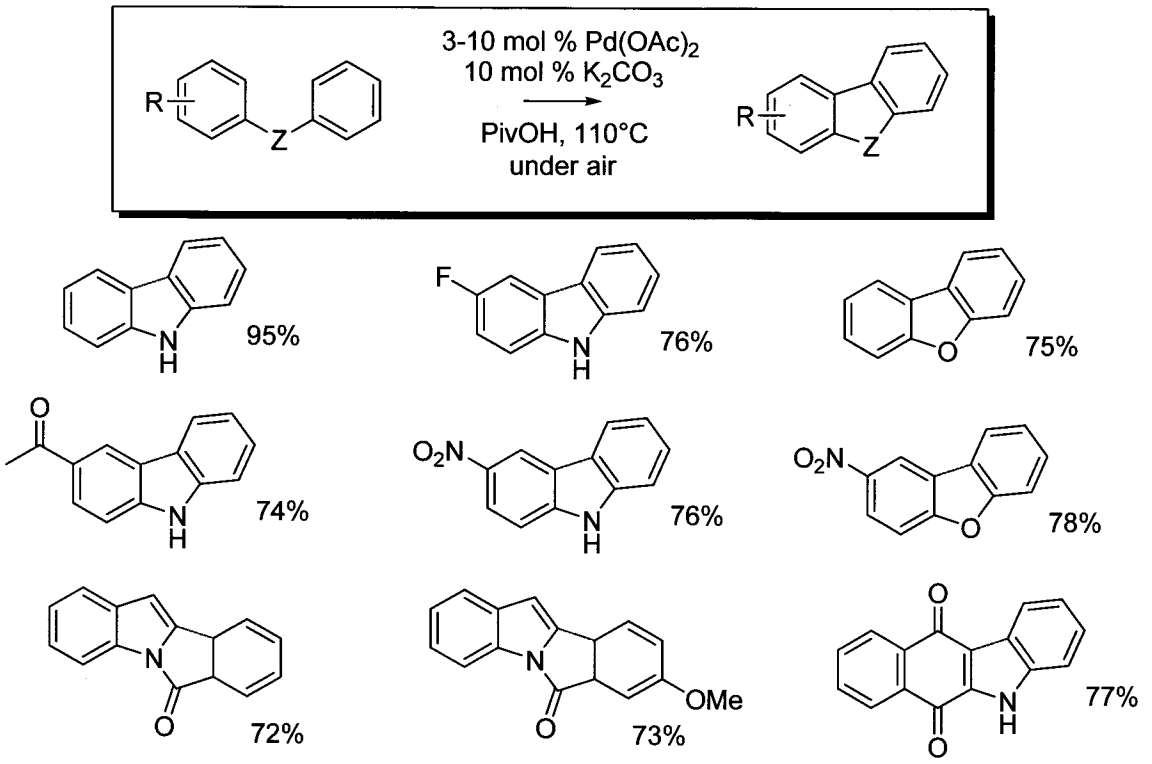
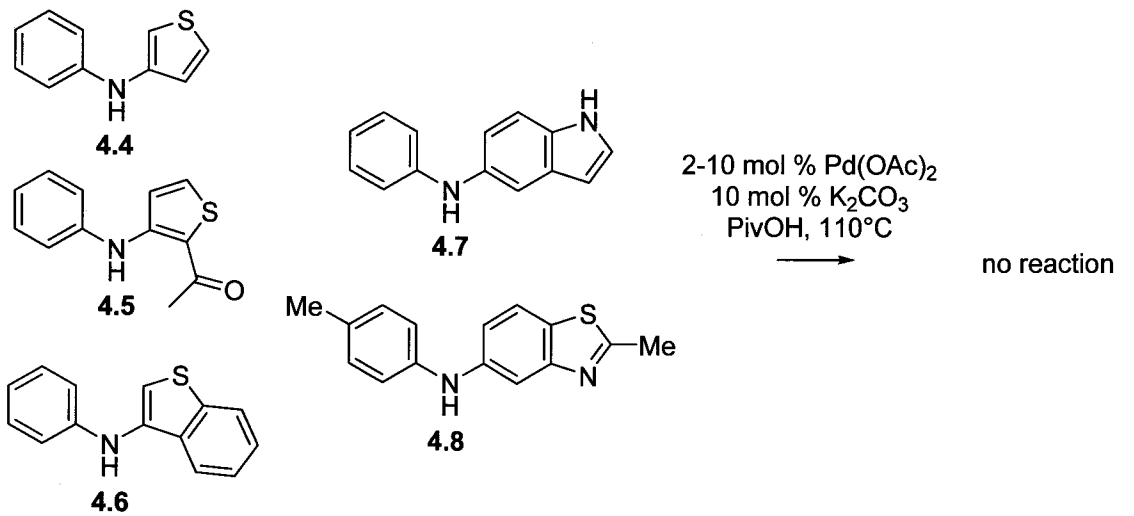


Table 4.3 - Scope of optimized reaction conditions for Pd(II)-catalyzed ring-closure

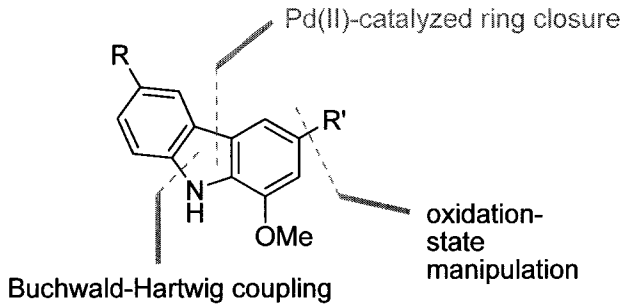
Subsequent attempts aimed at extending the reaction's compatibility to other heterocycles were thwarted (Scheme 4.8).



Scheme 4.8 - Incompatible heterocycles

Synthesis of Naturally-Occurring Carbazoles

The compatibility of electron-rich diarylamines in the intramolecular C-H ring closure reaction prompted us to demonstrate a concise synthesis of five naturally occurring 1-oxygenated tricyclic carbazole alkaloids (Figure 4.2).



Murrayafoline A	R = H	R' = Me
Mukonine	R = H	R' = COOMe
Murrayanine	R = H	R' = CHO
Mukoeic Acid	R = H	R' = COOH
Clausenine	R = OMe	R' = Me

Figure 4.2 - Retrosynthetic strategy employed in the synthesis of naturally-occurring carbazoles

Murrayanine, the first carbazole alkaloid to be isolated,[114] originates in the stem bark of the Indian tree *Murraya koenigii*, a common source of folk medicine and spices.[115] This compound has since been found in *Clausena heptaphylla*[116] and is abundant in the roots of *Murraya siamensis*.[117] Murrayanine inhibits platelet aggregation,[116] and has cytotoxic, [118] antibiotic,[119] antibacterial,[120] antifungal,[121] and antimicrobial,[119] activity. Mukonine also arises from *Murraya koenigii*,[122] and displays mild anti-cancer properties.[123] These two compounds, together with murrayfoline A from *Murraya euchrestifolia*,[124] have shown varying activity

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[114] Chakraborty, D. P.; Barman, B. K.; Bose, P. K. *Tetrahedron* **1965,** *21,* 681-685.
[115] Tachibana, Y.; Kikuzaki, H.; Lajis, N. H.; Nakatani, N. *J. Agric. Food Chem.* **2001,** *49,* 5589-5594.
[116] Bhattacharyya, P.; Chakraborty, D. P. *Phytochemistry* **1973,** *12,* 1831-1832.
[117] Fiebig, M.; Pezzuto, J. M.; Soejarto, D. D.; Kinghorn, A. D. *Phytochemistry* **1985,** *24,* 3041-3043.
[118] Cui, C.; Cai, B.; Yan, S.; Zhao, Q.; Yao, X.; Qu, G. China Pat. Appl. CN 1309964, 2001; *Chem. Abstr.* **2002,** *137,* 129827b.
[119] Das, K. C.; Chakraborty, D. P.; Bose, P. K. *Experientia* **1965,** *21,* 340-345.
[120] Wu, T.-S.; Chan, Y.-Y.; Liou, M.-J.; Lin, F.-W.; Shi, L.-S.; Chen, K. -T. *Phytother. Res.* **1998,** *12,* S80-S82.
[121] Rahman, M. M.; Gray, A. I. *Phytochemistry* **2005,** *66,* 1601-1606.
[122] Knölker, H.-J.; Reddy, K. R. *Chem. Rev.* **2002,** *102,* 4303-4427.
[123] Liger, F.; Popowycz, F.; Besson, T.; Picot, L.; Galmarinic, C. M.; Joseph, B. *Bioorg. Med. Chem.* **2007,** *15,* 5615-5619.
[124] Knölker, H.-J.; Bauermeister, M. *J. Chem. Soc., Chem. Commun.* **1990,** 664-665.

against *Mycobacterium tuberculosis*.[125] A related carbazole, clausenine (*Clausena anisata*),[126] displays action against gram-negative bacteria and fungi.[127]

Commencing from a mutual starting material, readily available 5-methyl-2-nitroanisole smoothly undergoes palladium-catalyzed nitro reduction and Buchwald-Hartwig amination[128] with a suitable aryl bromide (Scheme 4.9). Without any pre-activation, the diarylamines thus obtained (**4.10** and **4.11**) were subjected to a series of intramolecular cross-coupling experiments with varying quantities of catalytic palladium(II) acetate. A temperature of 110°C was used since it was found that increasing the reaction temperature resulted only in the evaporation of pivalic acid, leaving primarily unreacted residue. Further optimization of this oxidative arylation process was effected by varying the reaction time. In each instance, leading candidates (as determined by GCMS) were purified by flash chromatography.

Accordingly, employment of the optimal catalyst loading of 3 mol % $Pd(OAc)_2$ to compound **4.11** led to a modest conversion to murrayafoline A in 14 hours (50% isolated yield). Shorter reaction times displayed considerable unreacted starting material. Unfortunately, longer reaction times provided radically attenuated yields which might be attributed to the formation of side-products such as dimers or product degradation.

Likewise, efficient transformation of diarylamine **4.10** to clausenine was attained over 22 hours, obtaining this crystalline alkaloid in 76%, again with 3 mol % $Pd(OAc)_2$. Thereafter, facile generation of murrayanine from murrayafoline A was mediated by submission to the action of four equivalents of DDQ (77%).[129] Hence, the synthesis of naturally-occurring, 1-oxygenated tricyclic carbazoles murrayafoline A, clausenine and murrayanine were effected in 47%, 69% and 36% overall yields, respectively.

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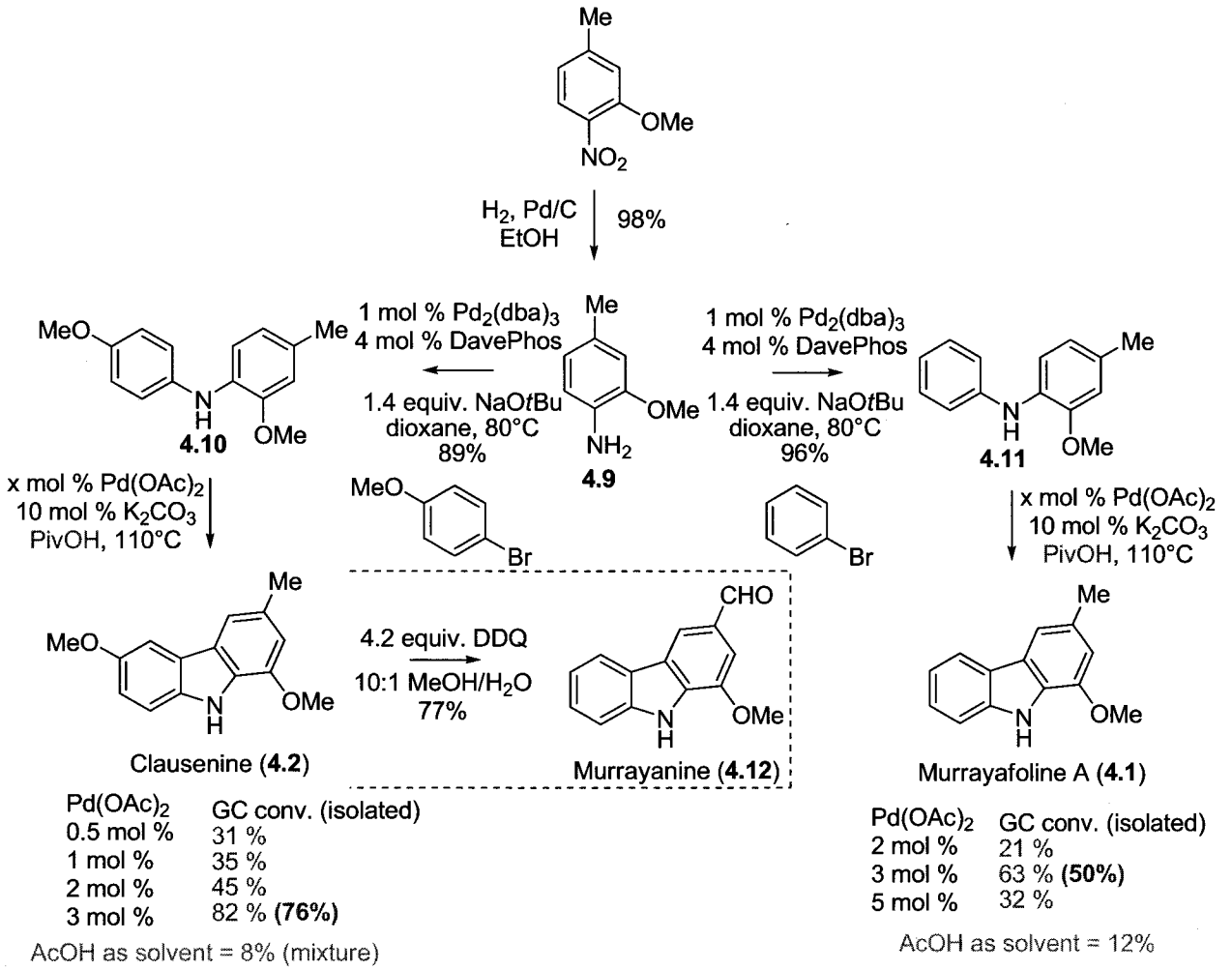
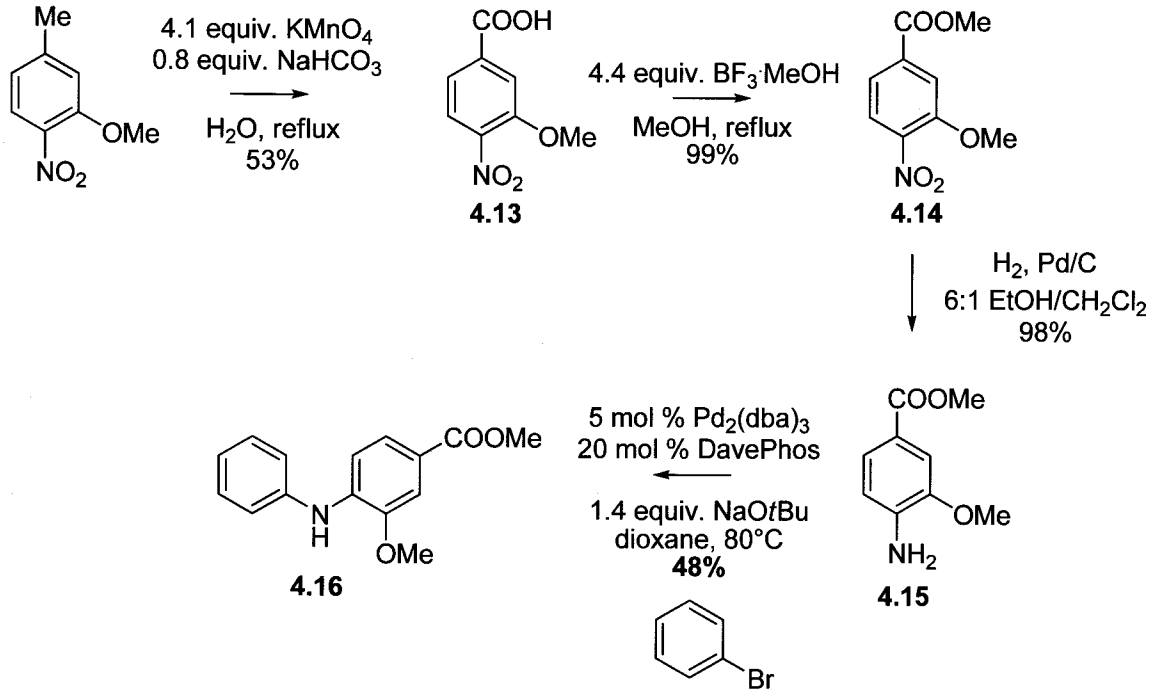
[125] Choi, T. A.; Czerwonka, R.; Fröhner, W.; Krahl, M. P.; Reddy, K. R.; Franzblau, S. G.; Knölker, H. -J. *ChemMedChem* **2006,** *1,* 812-815.
[126] Ihara, M.; Fukumoto, K. *Nat. Prod. Rep.* **1997,** *14,* 413-429.
[127] Chakraborty, A.; Chowdhury, B. K.; Bhattacharyya, P. *Phytochemistry* **1995,** *40,* 295-298.
[128] Ali, M. H.; Buchwald, S. L. *J. Org. Chem.* **2001**, *66*, 2560-2565.
[129] Krahl, M. P.; Jäger, A.; Krause, T.; Knölker, H.-J. *Org. Biomol. Chem.* **2006,** *4,* 3215-3219.



Scheme 4.9 - Synthesis of clausenine and murrayfoline A

Given the success of the aforementioned reaction sequence, the remaining tricyclic carbazole alkaloid mukonine was envisaged to arise from a similar reaction sequence with requisite manipulation of the benzylic oxidation state. To this end, the 5-methyl-2-nitroanisole scaffold was oxidized and esterified prior to the catalytic three-step reduction-amination-arylation plan (Scheme 4.10).[130]

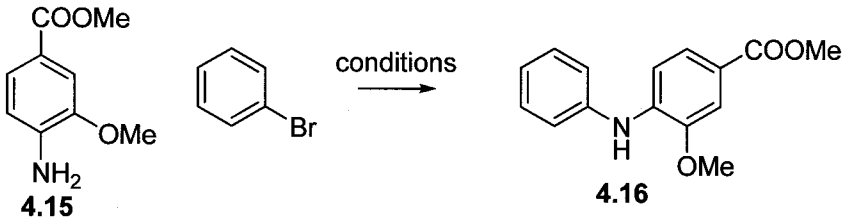
[130] Baret, P.; Beaujolais, V.; Béguin, C.; Gaude, D.; Pierre, J.-L.; Serratrice, G. *Eur. J. Inorg. Chem.* **1998,** 613-619.



Scheme 4.10 - Synthesis of requisite diarylamine for mukonine synthesis

Initially, the Buchwald-Hartwig amination step suffered from low yields (30-48%). Inspired by an elegant and extensive ligand optimization documented in the literature,[131] the reactivity of eight phosphines towards the synthesis of the target amine were ranked (Table 4.4). Unfortunately, the highest GCMS conversions still provided unreasonable isolated yields. The two best ligands (DavePhos and X-Phos) were carried onto a base screen which saw a fortuitous improvement with K_2CO_3, securing the desired phenylaminobenzoate intermediate in 76% yield with 2.5 mol % $Pd_2(dba)_3$ and 10 mol % X-Phos.

[131] Jensen, T.; Pedersen, H.; Bang-Andersen, B.; Madsen, R.; Jørgensen, M. *Angew. Chem. Int. Ed.* **2008,** *47,* 888-890.



Ligand screen:	GC conv.
10 mol % PPh_3	nr
10 mol % P(*o*-tol)$_3$	nr
10 mol % X-Phos	**72%**
7.5 mol % BINAP	44%
10 mol % Xantphos	46%
10 mol % dppf	nr
10 mol % DavePhos	26%
5 mol % P(*t*Bu)$_3$·HBF_4	nr

Ligand screen:
2.5 mol % Pd_2dba_3
x mol % ligand
2.5 equiv. NaO*t*Bu
toluene, 95°C

Base screen:	GC conv. (isolated)
NaO*t*Bu	66%
K_2CO_3	80% **(76%)**
Cs_2CO_3	40%
K_3PO_4	76%

Base screen:
2.5 mol % Pd_2dba_3
10 mol % X-Phos
1.5 equiv. base
toluene, 95°C

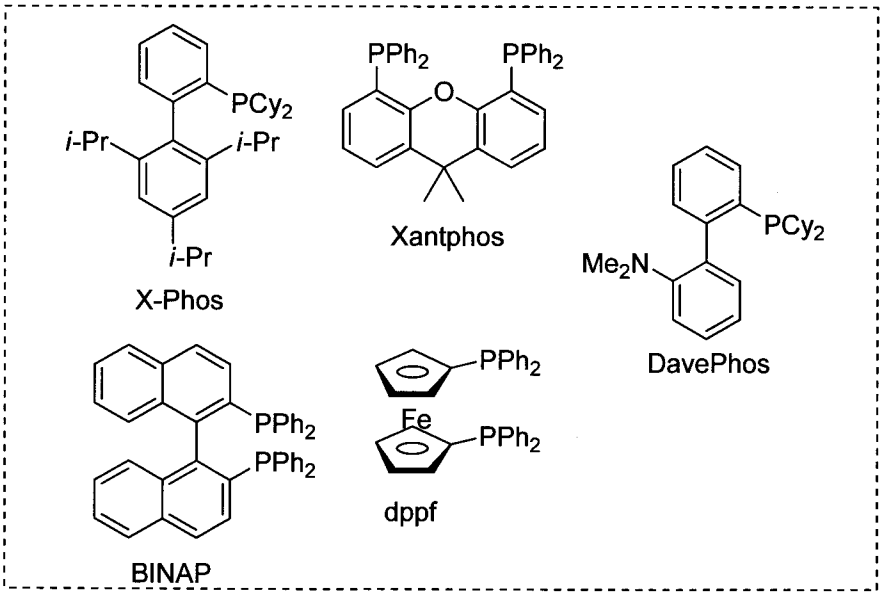
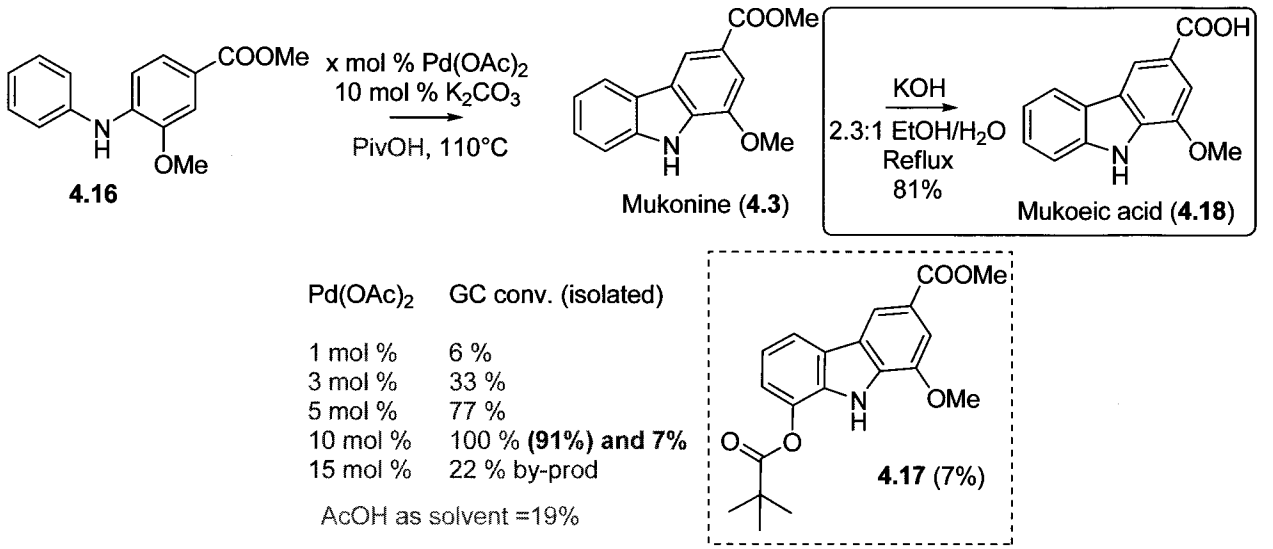


Table 4.4 - Buchwald-Hartwig optimization for mukonine

With the desired diarylamine in hand, the synthesis of mukonine (Scheme 4.11) was executed in 91% yield with a reaction time of 14 hours employing 10 mol % palladium(II)

acetate (a 35% overall yield from 5-methyl-2-nitroanisole).[132] With this, a 7% yield of compound **4.17** was also isolated, resulting from intermolecular, oxidative pivalate addition. This represents a rare example of intermolecular oxidative C-O bond formation to an sp^2 carbon and may warrant further investigation. Larger amounts were able to be accessed by charging the reaction vessel with 15 mol % of $Pd(OAc)_2$. Saponification of mukonine to mukeoic acid proceeded smoothly under standard conditions (81%).



Scheme 4.11 - Completion of the synthesis of mukonine

In conclusion, these studies not only point to the applicability of direct, oxidative C-H functionalization as a valuable method to synthesize carbazoles, but may provide succinct routes to synthetically challenging classes of aromatic compounds.

[132] This transformation was highlighted in the literature: Laird, T. *Org. Process. Rev. Dev.* **2008,** *12,* 1021-1030.

Final Conclusion

In this dissertation, described was the development of: 1) A palladium-catalyzed direct arylation protocol for azaindole compounds. 2) A rhodium-catalyzed synthesis of pyrroles and indoles possessing C2/C3 aliphatic substitution. 3) An expedient synthesis of carbazole alkaloids based on a palladium-catalyzed ring closing reaction developed in our lab.

These results constitute additional methods in the armory of the synthetic chemist, wherein the ultimate goal remains to produce organic building blocks in the most efficient and cost-effective way.

Section Claims:

Publications:

1.) Huestis, M. P.; Fagnou, K. *Org. Lett.* **2009,** *9,* 1357-1360.

2.) Liégault, B.; Lee, D.; Huestis, M. P.; Stuart, D. R.; Fagnou, K. *J. Org. Chem.* **2008,** *73,* 5022–5028.

Oral Presentations:

1.) M. P. Huestis and K. Fagnou. (2009) Site-Selective Azaindole Arylation at the Azine and Azole Rings via *N*-Oxide Activation. *Ottawa-Carleton Chemistry Institute Conference 2009 University of Ottawa, Ottawa, ON (May 15, 2009).*

Poster Presentations:

1.) M. P. Huestis and K. Fagnou. (2009) Site-Selective Azaindole Arylation at the Azine and Azole Rings via *N*-Oxide Activation. *Quebec-Ontario Mini Symposium of Bioorganic and Organic Chemistry 2009, Université Laval, Québec, QC (October 30-November 1, 2008).*

2.) M. P. Huestis and K. Fagnou. (2009) Site-Selective Azaindole Arylation at the Azine and Azole Rings via *N*-Oxide Activation. *39th Spring Organic Synthesis Symposium (Synthesis Day), University of Ottawa, Ottawa, ON (June 8, 2009).*

3.) M. P. Huestis and K. Fagnou. (2008) Pd(0)-Catalyzed Direct Arylation of Azaindole *N*-Oxides. *Quebec-Ontario Mini Symposium of Bioorganic and Organic Chemistry 2008, University of Toronto, Toronto, ON (November 7-9, 2008).*

4.) M. P. Huestis and K. Fagnou. (2008) Carbazole Alkaloids by Oxidative Pd(II)-Catalyzed Arylation Under Air and Pd(0)-Catalyzed Direct Arylation of Azaindole N-Oxides. *AstraZeneca R&D Montréal, QC (October 3, 2008).*

5.) M. P. Huestis, B. Liégault, D. Lee, D. R. Stuart and Keith Fagnou. (2008) Intramolecular Pd(II)-Catalyzed Oxidative Biaryl Synthesis Under Air: Efficient Synthesis of Carbazole Alkaloids. *38th Spring Organic Synthesis Symposium (Synthesis Day), University of Ottawa, Ottawa, ON (June 16, 2008).*

6.) M. P. Huestis, B. Liégault, D. Lee, D. R. Stuart and Keith Fagnou. (2008) Intramolecular Pd(II)-Catalyzed Oxidative Biaryl Synthesis Under Air: Efficient Synthesis of Carbazole Alkaloids. *Ottawa-Carleton Chemistry Institute Conference 2008 University of Ottawa, Ottawa, ON (May 15, 2008).*

Supporting Information

General Methods

Chemical

DMF was dried and degassed as follows:
In an oven at 111°C, a Wheaton glass bottle (100 mL, 223747) was dried overnight and filled with 3 to 4 g of 4 Å molecular sieves that had been in the oven for at least 7 days. ACS grade DMF was poured in and the container was immediately covered with a Wheaton grey butyl stopper (20 mm, 224100-181) and crimped shut with a Wheaton aluminum seal (20 mm, 224178-01). Subsequently, argon gas was then bubbled through the solvent for 2 hours.
Toluene, benzene, THF and CH_2Cl_2 were dried and degassed on an mBraun MB AUTO-SPS solvent purification system. Triethylamine was distilled from CaH_2. Unless otherwise stated, all other solvents and reagents were purchased at > 98% purity from TCI America or Sigma-Aldrich and used as is. All palladium sources, ligands and bases were purchased from Strem Chemicals and stored in a desiccator (weighing to air). All reactions were performed under an atmosphere of argon unless otherwise noted. Thin-layer chromatograms were performed on EMD TLC Silica gel 60 F_{254} aluminum-backed plates and visualized with UV light (long wave light was necessary for diarylated azaindoles) or $KMnO_4$ solution (3 g $KMnO_4$, 20 g $NaCO_3$, 5 mL 5% aqueous NaOH, 300 mL distilled water). Flash purification was performed on Silicycle SilicaFlash F60 60-63 μm (230-400 mesh) silica gel.

Analytical

Melting points were obtained on an Electrothermal MEL-TEMP fitted with a mercury thermometer and are reported uncorrected. Fourier-transform infrared information was found on undrilled NaCl using an ABB Bomem Arid-Zone. Nuclear magnetic resonance data was acquired on a Bruker AV-400 with chemical shift values reported relative to internal standards and operating frequencies shown in parentheses: ^1H (400.3 MHz) – trimethylsilane = 0.0 ppm, ^{13}C (100.1 MHz) – residual $CHCl_3$ = 77.16 ppm, ^{19}F (376.7 MHz) – α,α,α-trifluorotoluene = -62.73 ppm. In cases of uncertain assignments, structural confirmation was secured through 2D NOESY NMR experiments. High-resolution mass spectrometry was performed on a Kratos Concept IIH using electron impact in positive mode. GCMS analysis was performed on an Agilent Technologies 6890N GC System with 5973 Mass Selective Detector using an Agilent 19091S-433 HP-5MS 0.25 mm x 30 m x 0.25 μm column. For method development, the gradient performed was 130°C for 2 min, followed by a 20°C/min increase to 285°C, which was held for 6 min. The GC yields were determined relative to 1,3,5-trimethoxybenzene as internal standard (1/3 equiv.).

Preparation of $[Cp^*Rh(MeCN)_3][SbF_6]_2$ catalyst[133]

To a solution of $[Cp^*RhCl_2]_2$[134] (2.00 g, 6.47 mmol) in HPLC-grade MeCN (25 mL, 0.13 M) was added $AgSbF_6$ (4.57 g, 13.3 mmol). The mixture was stirred for 30 min and then filtered over Celite, rinsing with MeCN. The solvents were concentrated to dryness, re-dissolved in 1:1 CH_2Cl_2/MeCN, and filtered through plug

[133] White, C.; Thompson, S. J.; Maitlis, P. M. *J. Chem. Soc., Dalton Trans.* **1977,** 1654-1661.
[134] Although this compound is commercially available from Strem, it is more economical to prepare it from $RuCl_3{\cdot}3H_2O$ as described by Fujita and Yamaguchi: Fujita, K.-i.; Takahashi, Y.; Owaki, M.; Yamamoto, K.; Yamaguchi, R. *Org. Lett.* **2004,** *6,* 2785-2788.

of silica gel, eluting with 1:1 CH_2Cl_2/MeCN. After the solvents had been concentrated to a minimal volume, Et_2O was added to precipitate the target organometallic compound as light yellow powder that was collected by filtration (3.60 g, 87%).[135]

General procedure for Direct Arylation with Aryl Bromides (A)

Azaindole *N*-oxide (2 equiv.), $Pd(OAc)_2$ (5 mol %), DavePhos (15 mol %), pivalic acid (30 mol %), Cs_2CO_3 (2 equiv.), and aryl bromide (1 equiv.) were weighed into an oven-dried National Scientific 2 mL vial (4701-B4) and closed tightly with a 15 mm screw cap (C4015-1A) containing a 12 mm Teflon-Silicon Septa (C4015-60). If the aryl halide was a liquid, it was covered with base and *N*-oxide before other reactants. Through two Becton Dickinson 23G1 PrecisionGlide needles, the reaction chamber was evacuated and refilled with argon three times. Thereafter, dry, degassed toluene (0.4 or 0.5 M in aryl halide) was injected using the same gauge of needle. The septum was covered with electrical tape to prevent solvent loss, and the reaction was stirred in an oiled well of a drilled aluminum block that had been pre-heated to 110°C. After the given reaction time had passed, the vial was removed and the reaction mixture was filtered through a pad of Celite, eluting sequentially with CH_2Cl_2 and MeOH. The filtrate was evaporated and the residue was chromatographed over silica gel using the stated solvent system.

General Procedure for *N*-oxide reduction (B)[136]

Azaindole *N*-oxide (1 equiv.) was weighed into a vial, dissolved in 1:1 THF/saturated aqueous NH_4Cl (0.03 M), and submitted to the action of zinc dust (4.5 equiv.) under ambient atmosphere. Stirring vigorously for the given time period, the entire biphasic reaction mixture was filtered through Celite and diluted with dichloromethane and water. After extracting twice with dichloromethane, the organic extracts were dried with $MgSO_4$ and filtered. Unless a chromatographic system is described below, evaporation of the solvent afforded pure material.

General Procedure for C2 Direct Arylation with Aryl Iodides (C)

Azaindole (1 equiv.), $Pd(OAc)_2$ (5 mol %), silver(I) oxide (0.75 equiv.), 2-nitrobenzoic acid (1.5 equiv.), and aryl iodide (2 equiv.) were weighed into a National Scientific 2 mL vial (4701-B4) and closed tightly with a 15 mm screw cap (C4015-1A) containing a 12 mm Teflon-Silicon Septa (C4015-60). Two Becton Dickinson 23G1 PrecisionGlide needles were inserted through the septa and a balloon containing argon was attached to one. After 60 s of purging, a gastight syringe was connected to the free needle and dry, degassed DMF (0.5 M) was injected. Both needles were then removed and if the aryl halide was a liquid, it was injected at this point. The septum was then covered with electrical tape to prevent solvent loss and the vial was placed in an oiled well of a drilled aluminum block that had been pre-heated to 80°C. After the given reaction time had passed, the vial was removed and the reaction mixture was filtered through a pad of Celite, eluting sequentially with MeOH and CH_2Cl_2. The filtrate was then concentrated to dryness, taken up in CH_2Cl_2, and washed with a 50% saturated NaHCO3 solution. The aqueous layer was extracted an additional time, and the combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. The residue was subjected to flash chromatographic purification using the stated solvent system.

General Procedure for Rh(III)-catalyzed Pyrrole Synthesis (D)

Methyl 2-acetamidoacrylate (1 equiv.), $[Cp^*Rh(MeCN)_3][SbF_6]_2$ (5 mol %), and $Cu(OAc)_2{\cdot}H_2O$ (20 mol %)[137] were weighed into a microwave tube (9 x 1.2 cm). The enyne (1.1 equiv.) was weighed into a vial and rinsed into the reaction vessel with cyclohexanone (0.2 M). The reaction vessel was covered with a septum and purged

[135] This account was transcribed directly from the laboratory notebook of Derek J. Schipper.
[136] Aoyagi, Y.; Abe, T.; Ohta, A. *Synthesis* **1991,** 891-894.

with oxygen. With the oxygen balloon still on top, the mixture was stirred vigorously (750-1000 rpm). After the given reaction time had passed, the mixture was diluted with CH_2Cl_2 and filtered through Celite. After being concentrated to dryness (the use of a high-vacuum pump is necessary to remove cyclohexanone), the residue was purified by flash chromatographic methods using the stated eluent system.

General Procedure for Rh(III)-catalyzed Indole Synthesis (E)

The *N*-phenyl urea (1 equiv.), $[Cp^*Rh(MeCN)_3][SbF_6]_2$ (5 mol %), and $Cu(OAc)_2 \cdot H_2O$ (2.1 equiv.)[137] were weighed into a test tube (15 x 1.4 cm). The enyne (1.1 equiv.) was weighed into a vial and rinsed into the reaction vessel with dry, degassed toluene (0.2 M). The reaction vessel was covered with a septum and stirred vigorously (500-750 rpm). After the given reaction time had passed, the mixture was filtered through a pad of Celite, rinsing with CH_2Cl_2. After being concentrated to dryness, the residue was purified by flash chromatographic methods using the stated eluent system.

General procedure for Buchwald-Hartwig Amination (F)[138]

Pd_2dba_3 (5 mol %), BINAP (10 mol %) and Cs_2CO_3 (1.4 eq) were weighed to air and transferred to an oven-dried round-bottomed flask. The amine (1.1 eq) and aryl halide (1.0 eq) were added at this point if solid. The flask was then purged with argon and the liquid reagents (amine and/or aryl halide) were added as a solution in freshly distilled toluene (such that the resulting reaction mixture is 0.1 M in aryl halide). After stirring at 110°C overnight, the mixture was diluted with ethyl acetate, filtered through a plug of Celite, and evaporated to dryness. The residue thus obtained was purified by silica gel chromatography to afford the title compound.

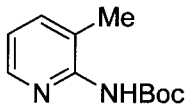
General procedure for Buchwald-Hartwig Amination (G)

Pd_2dba_3 (1 mol %), DavePhos (4 mol %) and NaO*t*Bu (1.4 eq) were weighed to air and transferred to an oven-dried round-bottomed flask. The amine (1.1 eq) and aryl halide (1.0 eq) were added at this point if solid. The flask was then purged with argon and the liquid reagents (amine and/or aryl halide) were added as a solution in freshly distilled dioxane (such that the resulting reaction mixture is 0.3 M in aryl halide). After stirring at 80°C overnight, the mixture was diluted with ethyl acetate, filtered through a plug of Celite, and evaporated to dryness. The residue thus obtained was purified by silica gel chromatography to afford the title compound.

General procedure for Intramolecular Oxidative Direct Arylation (H)

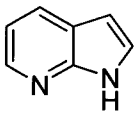
Diaryl compound (0.5 mmol), $Pd(OAc)_2$ (2-15 mol %), K_2CO_3 (10 mol%) and Pivalic acid (1 M) were weighed to air and transferred to a test tube (1.2 x 10cm). The reaction mixture was stirred under air at 110°C for 14 hr. The mixture was subsequently diluted with CH_2Cl_2 (40 mL) and washed with sat. aq. Na_2CO_3 (40 mL). The aqueous layer was back-extracted with CH_2Cl_2 (40 mL) and the organic layers were combined, dried ($MgSO_4$), and concentrated. Purification by silica gel chromatography afforded the title compound.

[137] Ground with a mortar and pestle.
[138] Luker, T. J.; Beaton, H. G.; Whiting, M; Mete, A.; Cheshire, D. R. *Tetrahedron Lett.* **2000,** *41,* 7731-7735.



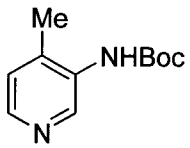
***tert*-Butyl 3-methylpyridin-2-ylcarbamate (2.5)**

Prepared following the method of Hands *et al.*[139] and exhibited an identical melting point to the literature value (80%); R_F = 0.35 (pet. ether/EtOAc, 70:30); mp 132-133°C (Lit.[140] mp 132-133°C); FTIR (ν_{max}) 3206, 2977, 1720, 1284, 1248, 1168 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.26 (dd, 1H, J = 4.8, 1.1 Hz), 7.51 (dd, 1H, J = 7.4, 1.1 Hz), 7.03 (dd, 1H, J = 7.4, 4.8 Hz), 6.97 (br s, 1H), 2.29 (s, 3H), 1.51 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.7, 149.9, 146.0, 139.7, 126.5, 120.8, 80.8, 28.4, 18.1; HRMS *m/z* calcd for $C_{11}H_{16}N_2O_2$ $[M]^+$: 208.1212. Found 208.1225.



7-Azaindole (2.4)

Prepared following the method of Hands *et al.*[139] except that the crude material was deemed pure enough by ^1H NMR (>95%) to be used in the subsequent step without tartrate resolution. The material exhibited a melting point that was comparable to the literature value (100%); R_F = 0.39 (pet. ether/EtOAc, 60:40); mp 98-99°C (Lit.[141] mp 104-105°C); FTIR (ν_{max}) 3235-2464, 1603, 1579, 1421, 1345, 1280, 901, 797, 766, 725 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.06 (br s, 1H), 8.35 (dd, 1H, J = 4.8, 1.5 Hz), 7.97 (ddd, 1H, J = 7.7, 1.5, 1.1 Hz), 7.40 (dd, 1H, J = 3.4, 1.1 Hz), 7.09 (ddd, 1H, J = 7.7, 4.8, 0.6 Hz), 6.51 (dd, 1H, J = 3.4, 0.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.0, 142.3, 129.2, 125.6, 120.7, 115.8, 100.6; HRMS *m/z* calcd for $C_7H_6N_2$ $[M]^+$: 118.0531. Found 118.0537.



***tert*-Butyl 4-methylpyridin-3-ylcarbamate (2.6)**

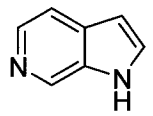
Under an argon atmosphere and at 0°C, a solution of 3-amino-4-picoline (24.32 g, 0.2249 mol) in THF (400 mL) was charged with 1.0 M sodium bis(trimethylsilyl)amide in THF (495 mL, 0.495 mol), followed by di-*tert*-butyl dicarbonate (54 g, 0.25 mol). The cold bath was removed and the viscous mixture was allowed to stir for 1 hr. The solvent was evaporated, dissolved in dichloromethane (500 mL) and washed with 0.1 M HCl (500 mL), brine (300 mL) and concentrated to dryness. Purification by column chromatography (pet. ether/EtOAc, 40:60) afforded the title compound as a yellow solid (40.64 g, 87%). Spectral data was in accordance with previous reports.[139]

^1H NMR (400 MHz, $CDCl_3$) δ 8.87 (s, 1H), 8.25 (d, 1H, J = 4.6 Hz), 7.09 (d, 1H, J = 4.6 Hz), 6.31 (br s, 1H), 2.27 (s, 3H), 1.53 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.0, 145.4, 144.1, 137.9, 133.5, 125.2, 81.2, 28.4, 17.4.

Note: We hereby intercept the synthesis of 6-azaindole published by Hands et al.139, carefully avoiding a low yielding methylation step that was accompanied by a difficult chromatographic separation. We deemed this reasonable since the starting material, 3-amino-4-picoline, was readily available from select fine chemical companies. We obtained 25 grams for $148 CDN (TCI America).

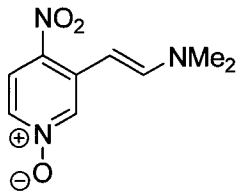
---

[139] Hands, D.; Bishop, B.; Cameron, M.; Edwards, J. S.; Cottrell, I. F.; Wright, S. H. B. *Synthesis* **1996,** 877-882.
[140] Clark, R. D.; Muchowski, J. M.; Fisher, L. E.; Flippin, L. A.; Repke, D. B.; Souchet, M. *Synthesis* **1991,** 871-878.
[141] Herbert, R.; Wibberly, D. G. *J. Chem. Soc.* **1969,** 1505-1514.



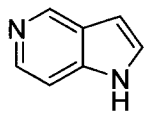
6-Azaindole (2.3)

From *tert*-butyl 4-methylpyridin-3-ylcarbamate, following the procedure of Hands *et al.*,[139] two additional steps provided the title compound and exhibited spectral data identical to previous reports (62% over 2 steps).[142] ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.71 (br s, 1H), 8.84 (s, 1H), 8.25 (d, 1H, J = 5.4 Hz), 7.60 (dd, 1H, J = 5.4, 0.9 Hz), 7.47 (d, 1H, J = 3.0 Hz), 6.57 (dd, 1H, J = 3.0, 0.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.6, 134.0, 133.8, 133.2, 129.5, 115.6, 101.5.



(E)-3-(2-(dimethylamino)vinyl)-4-nitropyridine 1-oxide (2.7)

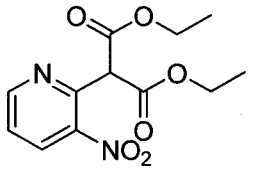
Prepared following the method of Dormoy *et al.*[143] and exhibited identical spectral data (89%).
Note: The starting material, 4-nitro-3-methylpyridine N-oxide, is available at low cost from select chemical companies. We acquired 100 grams for $150 CDN (92% pure by ^{1}H NMR, and used as received):
D-L Chiral Chemicals, LLC
118 Redbud Road
Piscataway, NJ 08854 USA



5-Azaindole (2.2)

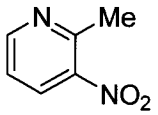
Prepared following the method of Dormoy *et al.*[143] except that the final product was purified by flash chromatography (CH_2Cl_2/MeOH, 90:10) to remove a brown contaminant that rapidly degraded the product. Spectral data was in accordance with previous reports (67%).[144]
^{1}H NMR (400 MHz, $CDCl_3$) δ 10.99 (br s, 1H), 9.00 (d, 1H, J = 0.7 Hz), 8.31 (d, 1H, J = 5.8 Hz), 7.36 (d, 1H, J = 5.8 Hz), 7.34 (d, 1H, J = 3.2 Hz), 6.68 (dd, 1H, J = 3.2, 0.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.4, 140.1, 140.1, 126.2, 125.3, 107.1, 101.6.

[142] Zhang, Z.; Yang, Z.; Meanwell, N. A.; Kadow, J. F.; Wang, T. *J. Org. Chem.* **2002,** *67,* 2345-2347.
[143] Dormoy, J.-R.; Heymes, A. French Patent 2564836, 1984.
[144] Corbally, R. P.; Mehta, L. K.; Parrick, J.; Short, E. L. *Magn. Reson. Chem.* **2000,** *38,* 1034-1036.



Diethyl 2-(3-nitropyridin-2-yl)malonate (2.8)

To an oven-dried flask containing 2-chloro-3-nitropyridine (100 mg, 0.631 mmol) and sodium hydride 60 % oil dispersion (43 mg, 1.07 mmol) under argon gas flow was added anhydrous DMF (0.5 mL) followed by diethyl malonate (144 μL, 0.947 mmol). After heating at 80°C for 2 hr, the mixture was diluted with EtOAc (15 mL) and washed with water (15 mL), brine (15 mL), dried ($MgSO_4$), and concentrated. Purification via silica gel chromatography (pet. ether/EtOAc, 75:25) yielded a colorless liquid (121 mg, 68%); R_F = 0.33 (pet. ether/EtOAc, 70:30); FTIR (ν_{max}) 2984, 2924, 1735, 1601, 1532, 1350, 1311, 1241, 1033, 863 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.82 (dd, 1H, J = 4.7, 1.6 Hz), 8.49 (dd, 1H, J = 8.3, 1.6 Hz), 7.54 (d, 1H, J = 8.3, 4.7 Hz), 5.53 (s, 1H), 4.31 (q, 2H, J = 7.2 Hz), 4.30 (q, 2H, J = 7.2 Hz), 1.30 (t, 6H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 153.1, 149.1, 144.9, 133.3, 124.0, 62.2, 59.5, 14.0; HRMS *m/z* calcd for $C_{12}H_{14}N_2O_6$ [M-HNO_2]$^+$: 236.0917. Found 236.0915.



3-Nitro-2-picoline (2.9)

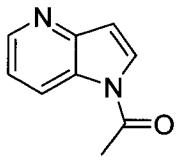
To an oven-dried flask containing 2-chloro-3-nitropyridine (26.01 g, 0.1641 mol) and sodium hydride 60 % oil dispersion (16.4 g, 0.410 mol) under argon was added anhydrous DMF (150 mL) via cannula. The solution was cooled to 0°C and under slow argon flow, diethyl malonate (37.4 mL, 0.246 mol) was added over 1 hr (*CAUTION!*). The mixture was heated to 80°C and stirred for 3 hr, and then allowed to cool to rt. The solution was then diluted with EtOAc (600 mL) and water (600 mL). The resultant dark layers were visualized by sunlight, separated, and the organic layer was washed again with water (600 mL). Following evaporation of volatiles, 6 M HCl (400 mL) was added slowly over the crude malonate and refluxed for 15 hr. Dichloromethane (300 mL) was added and after cooling in an ice bath, the aqueous portion was neutralized to pH 9 with 6 M NaOH. The organic layer was separated and the aqueous fraction was once again extracted with dichloromethane (300 mL) before being discarded. After careful solvent removal *in vacuo*, the black deposit was purified by flash chromatography on silica gel (pet. ether/EtOAc, 77:23), thus obtaining the title compound as a volatile redish oil (11.84 g, 52%). Spectral data was in accordance with previous reports.[145]

OR

Prepared following the method of Martin[146] and exhibited spectral data identical to previous reports (78%).[145]

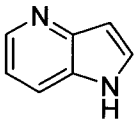
Note: Since the product is volatile, it must not be left in vacuo for extended periods of time.

[145] Niu, C.; Li, J.; Doyle, T. W.; Chen, S. -H. *Tetrahedron* **1998,** *54,* 6311-6318.
[146] Martin, L. L. World Patent 061498, 2005.



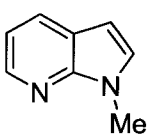
1-(1*H*-pyrrolo[3,2-*b*]pyridin-1-yl)ethanone (2.10)

Obtained as a relay compound for separation of 4-azaindole from 2-methylpyridin-3-amine (2 equiv. Ac_2O, 1.5 equiv. NEt_3, 0.2 equiv. DMAP, CH_2Cl_2). The two acetylated products were separated by chromatography (pet. ether/EtOAc, 50:50). Reverse chromatographic elution (most polar first) is observed. Deprotection is quantitatively effected with 1.5 equiv. K_2CO_3 in MeOH.
Data for acetylated compound (a white solid): R_F = 0.21 (pet. ether/EtOAc, 50:50); mp 79-80°C; FTIR (ν_{max}) 3399, 3127, 3104, 3039, 1713, 1413, 1192, 933, 777 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.66 (br d, 1H, J = 8.3 Hz), 8.56 (dd, 1H, J = 4.8, 1.6 Hz), 7.67 (d, 1H, J = 4.0 Hz), 7.26 (dd, 1H, J = 8.3, 4.8 Hz), 6.84 (dd, 1H, J = 4.0, 0.7 Hz), 2.66 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 148.9, 146.5, 129.1, 128.4, 123.8, 119.7, 110.2, 23.5; HRMS *m/z* calcd for $C_9H_8N_2O$ $[M]^+$: 160.0637. Found 160.0644.



4-Azaindole (2.1)

A round-bottomed flask containing 3-nitro-2-picoline (55 mg, 0.40 mmol) was fitted with a reflux condenser, purged with argon, and charged with freshly distilled *N*,*N*-dimethylformamide dimethyl acetal (0.75 mL). The mixture was refluxed for 17 hr before being concentrated to dryness. *Note: reflux must be performed in a closed system since the starting material is volatile. Also, reaction must be monitored by GC since the product has an identical R_f to the starting material.* The light-sensitive red solid thus obtained and 10% Pd/C (35 mg) were dissolved in 8.8% v/v formic acid in MeOH (4.5 mL) and stirred under a hydrogen atmosphere for 23 hr. The mixture was filtered through celite and concentrated to dryness. Extraction employing dichloromethane (30 mL) and sat. Na_2CO_3 (30 mL) followed by brine (30 mL) and drying ($MgSO_4$) afforded a mixture which was purified by silica gel chromatography (CH_2Cl_2/MeOH, 94:6) to forge the title compound as a brown solid (15 mg, 32%). *Note: If the preceding condensation unto 3-nitro-2-picoline does not go to completion, the residual 3-nitro-2-picoline also undergoes nitro reduction to 3-amino-2-picoline, which coincides chromatographically with the desired azaindole. In the event, separation may be effected by relay through the acetylated adduct (vide infra);* R_F = 0.20 (CH_2Cl_2/MeOH, 95:5); mp 116-117°C (Lit.[147] mp 127-128°C); FTIR (ν_{max}) 3600-2000, 1559, 1407, 1357, 1277, 888, 773 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.58 (br s, 1H), 8.49 (dd, 1H, J = 4.6, 1.1 Hz), 7.70 (ddd, 1H, J = 8.2, 1.1, 1.1 Hz), 7.47 (ddd, 1H, J = 3.1, 3.1, 1.1 Hz), 7.13 (dd, 1H, J = 8.2, 4.6 Hz), 6.77 (dddd, 1H, J = 3.1, 3.1, 1.1, 1.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.4, 143.2, 129.0, 128.3, 118.7, 116.9, 103.2; HRMS *m/z* calcd for $C_7H_6N_2$ $[M]^+$: 118.0531. Found 118.0529.



1-Methylpyrrolo[2,3-*b*]pyridine (2.11)

Prepared following the method of Lane *et al.*[148] and exhibited identical spectral data (69%). This compound could also be isolated from the reaction residue in methylation of 7-azaindole *N*-oxide (~50%).

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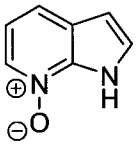
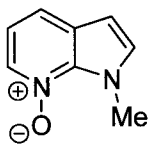
[147] Clemo, G. R.; Swan, G. A. *J. Chem. Soc.* **1948,** 198.
[148] Lane, B. S.; Sames, D. *Org. Lett.* **2004,** *6,* 2897-2900.



1*H*-Pyrrolo[2,3-*b*]pyridine 7-oxide (2.12)

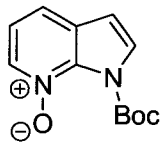
To a solution of 7-azaindole (50 mg, 0.42 mmol) in dichloromethane (2 mL) was added 77% *m*-chloroperbenzoic acid (142 mg, 0.635 mmol) and the reaction mixture was stirred for 3 days. The solvent was then removed *in vacuo* and the residue was purified by column chromatography (CH_2Cl_2/MeOH, 91:9), affording the *N*-oxide as a yellow solid (55 mg, 97%); R_F = 0.10 (CH_2Cl_2/MeOH, 95:5). The compound exhibited spectral data identical to previous reports.[149]
^{1}H NMR (400 MHz, $CDCl_3$) δ 13.77 (br s, 1H), 8.27 (dd, 1H, *J* = 6.3, 0.9 Hz), 7.69 (dd, 1H, *J* = 7.7, 0.9 Hz), 7.43 (d, 1H, *J* = 3.3 Hz), 7.05 (dd, 1H, *J* = 7.7, 6.3 Hz), 6.54 (d, 1H, *J* = 3.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.0, 131.6, 127.6, 125.6, 122.7, 115.6, 102.4.
Note: This reaction was able to be carried out on multi-gram scale in yields exceeding 75%, employing 1.2 equiv. mCPBA with a reaction time of 3 h.



1-Methyl-1*H*-pyrrolo[2,3-*b*]pyridine 7-oxide (2.13)

To an oven-dried round-bottomed flask containing 1*H*-pyrrolo[2,3-*b*]pyridine 7-oxide (3.00 g, 22.4 mmol) was added anhydrous DMF (45 mL) followed by careful addition of sodium hydride 60 % oil dispersion (1.79 g, 44.8 mmol) over 5 min. After, the flask was capped with a septum and stirring was effected for 15 min under continuous argon flow. The flask was then cooled to 0°C and dimethyl sulfate (3.19 mL, 33.6 mmol) was added dropwise over 5 min. The ice bath was removed and the reaction was stirred for 15 hr, at which time the reaction was quenched with ethanol (1 mL) and diluted with dichloromethane (500 mL). The inorganic salts were filtered off and the filtrate concentrated to dryness. The residue was purified twice by column chromatography (CH_2Cl_2/MeOH, 94:6, CH_2Cl_2/MeOH, 93:7) to afford the title compound as a brown solid (1.83 g, 55%); R_F = 0.18 (CH_2Cl_2/MeOH, 95:5); mp 61-62°C; FTIR (ν_{max}) 3228, 2924, 1690, 1451, 1235, 788, 712 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (dd, 1H, *J* = 6.2, 0.8 Hz), 7.52 (dd, 1H, *J* = 7.9, 0.8 Hz), 7.02 (d, 1H, *J* = 3.3 Hz), 6.94 (dd, 1H, *J* = 7.9, 6.2 Hz), 6.48 (d, 1H, *J* = 3.3 Hz), 4.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.7, 133.7, 131.5, 126.2, 121.3, 116.2, 101.5, 36.9; HRMS *m/z* calcd for $C_8H_8N_2O$ $[M]^+$: 148.0637. Found 148.0644.
Note: Since this workup procedure needs no aqueous workup, it offers a convenient way to isolate water-soluble organics in sodium hydride alkylation reactions.

[149] Clark, B. A. J.; Parrick, J. *J. Chem. Soc., Perkin Trans. 1* **1974,** 2270-2274.

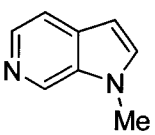


1-(*tert*-Butoxycarbonyl)-1*H*-pyrrolo[2,3-*b*]pyridine 7-oxide (2.14)

To an oven-dried round-bottomed flask containing 1*H*-pyrrolo[2,3-*b*]pyridine 7-oxide (200 mg, 1.49 mmol) was added anhydrous DMF (6.0 mL) followed by careful addition of sodium hydride 60 % oil dispersion (179 mg, 4.47 mmol). After, the flask was capped with a septum and stirring was effected for 30 min under continuous argon flow. The flask was then cooled to 0°C over 15 min and charged with a solution of di-*tert*-butyl dicarbonate (651 mg, 2.98 mmol) in anhydrous DMF (6.0 mL). Following this, the ice-bath was removed and the mixture was stirred for 40 min, heated at 60°C for 1 hr and quenched by the addition of water (1 mL). The solution was diluted with CH_2Cl_2 and extracted with sat. $NaHCO_3$ (3x) and brine. After drying ($MgSO_4$) and concentration, the residue was purified by column chromatography (CH_2Cl_2/MeOH, 95:5) to afford the title compound as a light brown solid (212 mg, 61%); R_F = 0.26 (CH_2Cl_2/MeOH, 95:5); mp 124-125°C; FTIR (ν_{max}) 1751, 1316, 1243, 1152, 856, 789, 716 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, 1H, J = 6.5 Hz), 7.48-7.46 (m, 2H), 7.11 (dd, 1H, J = 6.5 Hz), 6.55 (d, 1H, J = 3.7 Hz), 1.67 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.6, 137.8, 135.2, 129.1, 128.3, 119.5, 119.3, 104.9, 85.7, 27.8; HRMS *m/z* calcd for $C_{12}H_{14}N_2O_3$ $[M]^+$: 234.1004. Found 234.0990.

1-((2-(Trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridine 7-oxide (2.15)

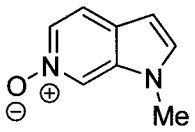
While stirring under a slow flow of argon gas, a round-bottomed flask containing 1*H*-pyrrolo[2,3-*b*]pyridine 7-oxide (100 mg, 0.745 mmol) and sodium hydride 60 % oil dispersion (60 mg, 1.5 mmol) was charged with anhydrous DMF (1 mL). After 10 minutes, the reaction vessel was cooled to 0°C and SEMCl (198 μL, 1.12 mmol) was added dropwise. Stirring was continued at rt for 14 hr, at which time the reaction was quenched with ethanol (0.5 mL) and diluted with CH_2Cl_2 (60 mL). Insoluble inorganic salts were filtered off and discarded. The mother liquor was concentrated to dryness and chromatographed over silica gel (CH_2Cl_2/MeOH, 95:5). The target SEM-protected *N*-oxide was obtained as a colorless liquid (112 mg, 57%); R_F = 0.25 (CH_2Cl_2/MeOH, 95:5); FTIR (ν_{max}) 3396, 2953, 1247, 1074, 849, 837, 713 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.10 (dd, 1H, J = 6.3, 0.6 Hz), 7.56 (dd, 1H, J = 8.0, 0.9 Hz), 7.31 (d, 1H, J = 3.5 Hz), 7.00 (dd, 1H, J = 8.0, 6.3 Hz), 6.58 (d, 1H, J = 3.5 Hz), 6.31 (s, 2H), 3.66 (ddd, 2H, J = 7.9, 7.9, 2.8 Hz), 0.90 (ddd, 2H, J = 7.9, 7.9, 2.8 Hz), -0.06 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.1, 134.2, 130.1, 126.5, 121.0, 116.8, 103.2, 77.1, 65.9, 18.0, -1.3; HRMS *m/z* calcd for $C_{13}H_{20}N_2O_2Si$ $[M]^+$: 264.1294. Found 264.1293.



1-Methyl-1*H*-pyrrolo[2,3-*c*]pyridine (2.16)

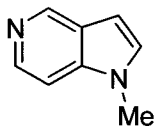
To an oven-dried round-bottomed flask containing 6-azaindole (1.00 g, 8.46 mmol) was added anhydrous DMF (10 mL) followed by careful addition of sodium hydride 60 % oil dispersion (677 mg, 16.9 mmol). After, the flask was capped with a septum and stirring was effected for 10 min under continuous argon flow. The flask was then cooled to 0°C and dimethyl sulfate (0.81 mL, 8.46 mmol) was added dropwise. The ice bath was then removed and the reaction was stirred for 19 hr, at which time the reaction was quenched with water (40 mL)

and extracted with dichloromethane (3 x 50 mL). The organic layers were washed with brine (50 mL), dried ($MgSO_4$) and concentrated. The residue was chromatographed over silica gel (CH_2Cl_2/MeOH, 94:6) to afford the title compound as a white film that darkens and decomposes over a period of days (866 mg, 77%); R_F = 0.24 (CH_2Cl_2/MeOH, 93:7); FTIR (ν_{max}) 3360, 2925, 1605, 1506, 1476, 1326, 1253, 818 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.74 (s, 1H), 8.24 (d, 1H, J = 5.5 Hz), 7.49 (dd, 1H, J = 5.5, 1.0 Hz), 7.15 (d, 1H, J = 2.9 Hz), 6.46 (dd, 1H, J = 2.9, 1.0 Hz), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 133.8, 133.2, 132.7, 132.4, 115.2, 100.5, 33.1; HRMS *m/z* calcd for $C_8H_8N_2$ $[M]^+$: 132.0687. Found 132.0705.



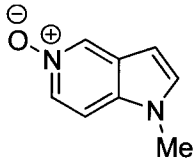
1-Methyl-1*H*-pyrrolo[2,3-*c*]pyridine 6-oxide (2.17)

To a flask containing 1-methyl-1*H*-pyrrolo[2,3-*c*]pyridine (211 mg, 1.60 mmol) was added 50 % aqueous hydrogen peroxide (217 mg, 3.20 mmol). Thereafter, the reaction vessel was charged with dichloromethane (3 mL), followed by methyltrioxorhenium (VII) (19.9 mg, 5 mol %) and the mixture was stirred for 3 hr, at which point the reaction was quenched by the addition of manganese(IV) oxide (10 mg, 0.12 mmol). After the evolution of gas had ceased (20 min), the mixture was diluted with dichloromethane (20 mL), dried ($MgSO_4$), and concentrated to dryness. Since the product was found bind to $MgSO_4$, it is not advisable to filter before concentration and concomitant purification via column chromatography (CH_2Cl_2/MeOH, 92:8), which afforded the title compound as a brown solid (147 mg, 62%); R_F = 0.29 (CH_2Cl_2/MeOH, 90:10); mp 53-55°C; FTIR (ν_{max}) 3370, 2923, 1510, 1458, 1185, 1096 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.53 (s, 1H), 8.01 (dd, 1H, J = 6.9, 1.5 Hz), 7.45 (d, 1H, J = 6.9 Hz), 7.24 (d, 1H, J = 3.0 Hz), 6.52 (dd, 1H, J = 3.0, 1.5 Hz), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.1, 133.8, 131.8, 127.0, 123.0, 117.0, 102.3, 33.5; HRMS *m/z* calcd for $C_8H_8N_2O$ $[M]^+$: 148.0637. Found 148.0599.



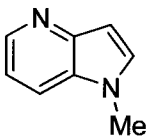
1-Methyl-1*H*-pyrrolo[3,2-*c*]pyridine (2.18)

To an open solution of 5-azaindole (1.01 g, 8.55 mmol) in anhydrous DMF (7 mL) was added sodium hydride 60 % oil dispersion (1.02 g, 25.6 mmol). The flask was fitted with an argon balloon and stirred for 10 min under argon flow. The reaction vessel was cooled to 0°C and dimethyl sulfate (814 µL, 8.55 mmol) was added dropwise. Stirring was continued at rt for 14 hr, at which time the reaction was quenched with ethanol (2 mL) and diluted with CH_2Cl_2 (300 mL). Insoluble inorganic salts were filtered off and discarded. The solution was concentrated to dryness and chromatographed over silica gel (CH_2Cl_2/MeOH, 94:6) to yield the title compound as a colorless, deliquescent solid that blackened and decomposed over time (869 mg, 77%); R_F = 0.47 (CH_2Cl_2/MeOH, 90:10); mp 41-43°C; FTIR (ν_{max}) 3399, 1608, 1326, 1242, 896, 807, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.91 (br s, 1H), 8.33 (d, 1H, J = 5.9 Hz), 7.23 (ddd, 1H, J = 5.9, 1.0, 1.0 Hz), 7.07 (d, 1H, J = 3.2 Hz), 6.59 (dd, 1H, J = 3.2, 1.0 Hz), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.0, 140.7, 140.3, 129.8, 125.5, 104.7, 101.0, 32.7; HRMS *m/z* calcd for $C_8H_8N_2$ $[M]^+$: 132.0687. Found 132.0684.



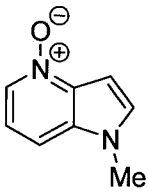
1-Methyl-1*H*-pyrrolo[3,2-*c*]pyridine 5-oxide (2.19)

To a solution of 1-methyl-1*H*-pyrrolo[3,2-*c*]pyridine (1.05 g, 7.93 mmol) in CH_2Cl_2 (14 mL) was added methyltrioxorhenium (VII) (148 mg, 7.5 mol %). Thereafter, careful treatment of the open reaction with 50 % aqueous hydrogen peroxide (1.08 g, 15.9 mmol) afforded a dark orange solution which was stirred an additional 2 hr, at which point the reaction was quenched by the addition of manganese(IV) oxide (40 mg, 0.46 mmol). After the evolution of gas had ceased (20 min), the mixture was diluted with dichloromethane (200 mL), dried ($MgSO_4$), and freed of volatiles. Including the $MgSO_4$ with the crude mixture, purification via column chromatography (CH_2Cl_2/MeOH, 91:9 - 90:10) provided the title compound as a fragrant white solid (919 mg, 78%); R_F = 0.35 (CH_2Cl_2/MeOH, 90:10); mp 77-78°C; FTIR (ν_{max}) 3401, 3171, 1479, 1229, 1134, 823, 727 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.60 (dd, 1H, J = 1.7, 0.8 Hz), 8.10 (dd, 1H, J = 7.1, 1.7 Hz), 7.22 (dd, 1H, J = 7.2, 0.9 Hz), 7.19 (d, 1H, J = 3.2 Hz), 6.50 (dd, 1H, J = 3.2, 0.8 Hz), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.9, 133.4, 133.2, 132.2, 125.8, 106.6, 100.8, 33.4; HRMS *m/z* calcd for $C_8H_8N_2O$ $[M]^+$: 148.0637. Found 148.0632.



1-Methyl-1*H*-pyrrolo[3,2-*b*]pyridine (2.20)

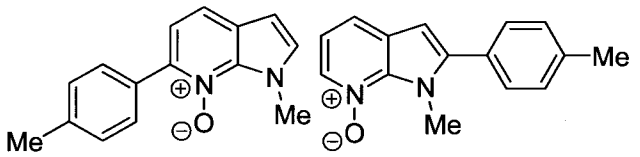
To an oven-dried round-bottomed flask containing 4-azaindole (1.18 g, 9.95 mmol) was added anhydrous DMF (10 mL) followed by careful addition of sodium hydride 60 % oil dispersion (0.80 g, 19.9 mmol). After, the flask was capped with a septum and continuous argon flow and stirring was effected for 12 min. The flask was then cooled to 0°C and dimethyl sulfate (0.95 mL, 9.95 mmol) was added dropwise. The ice bath was then removed and the reaction was stirred for 20 hr, at which time the reaction was quenched with water (40 mL) and extracted with dichloromethane (2 x 50 mL). The organic layers were washed with brine (50 mL), dried ($MgSO_4$) and concentrated. The residue was chromatographed over silica gel (pet. ether/EtOAc, 40:60 – 30:70) to afford the title compound as a colorless liquid (996 mg, 76%); R_F = 0.28 (pet. ether/EtOAc, 30:70); FTIR (ν_{max}) 2923, 2851, 1434, 1409, 1291, 768 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.45 (dd, 1H, J = 4.8, 1.4 Hz), 7.59 (ddd, 1H, J = 8.3, 1.4, 0.7 Hz), 7.25 (d, 1H, J = 3.3 Hz), 7.10 (d, 1H, J = 8.3, 4.8 Hz), 6.67 (dd, 1H, J = 3.3, 0.7 Hz), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.8, 143.1, 132.1, 129.7, 116.4, 116.3, 102.1, 33.0; HRMS *m/z* calcd for $C_8H_8N_2$ $[M]^+$: 132.0687. Found 132.0683.



1-Methyl-1*H*-pyrrolo[3,2-*b*]pyridine 4-oxide (2.21)

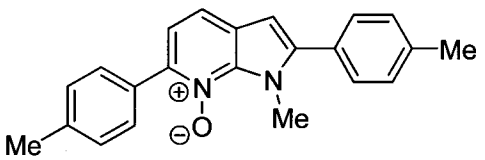
To a solution of 1-methyl-1*H*-pyrrolo[3,2-*b*]pyridine (984 mg, 7.45 mmol) in CH_2Cl_2 (14 mL) was added methyltrioxorhenium (VII) (140 mg, 7.5 mol %). Thereafter, careful treatment of the open reaction with 50 % aqueous hydrogen peroxide (1.01 g, 14.9 mmol) afforded a dark orange solution which was stirred an additional 16 hr at which point the reaction was quenched by the addition of manganese(IV) oxide (40 mg, 0.46 mmol). After the evolution of gas had ceased (20 min), the mixture was diluted with dichloromethane (200 mL), dried

($MgSO_4$), and freed of volatiles. Including the $MgSO_4$ with the crude mixture, purification via column chromatography (CH_2Cl_2/MeOH, 94:6 - 92:8) provided the title compound as a dark green solid (845 mg, 77%); R_F = 0.58 (CH_2Cl_2/MeOH, 90:10); mp 42-44°C; FTIR (ν_{max}) 3407, 1465, 1240, 985, 748 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, 1H, *J* = 6.1 Hz), 7.34 (d, 1H, *J* = 8.3 Hz), 7.23 (d, 1H, *J* = 3.2 Hz), 7.08 (dd, 1H, *J* = 8.3, 6.1 Hz), 6.92 (d, 1H, *J* = 3.2 Hz), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.1, 133.4, 131.8, 131.6, 117.4, 109.6, 96.8, 33.8; HRMS *m/z* calcd for $C_8H_8N_2O$ $[M]^+$: 148.0637. Found 148.0642.
Note: Although NMR-silent, a polar impurity noted on TLC was able to be removed by an additional chromatographic event (CH_2Cl_2/MeOH, 94:6).



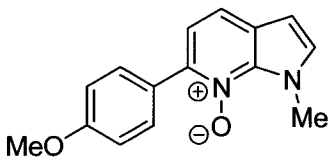
1-Methyl-6-*p*-tolyl-1*H*-pyrrolo[2,3-*b*]pyridine 7-oxide (2.22) and 1-methyl-2-*p*-tolyl-1*H*-pyrrolo[2,3-*b*]pyridine 7-oxide (2.23)

Following general procedure A, 1-methyl-1*H*-pyrrolo[2,3-*b*]pyridine 7-oxide (79.2 mg, 0.534 mmol), 4-bromotoluene (45.7 mg, 0.267 mmol), $Pd(OAc)_2$ (3.0 mg, 5 mol %), DavePhos (15.8 mg, 15 mol %), PivOH (8.2 mg, 30 mol %), and Cs_2CO_3 (174 mg, 0.534 mmol) were reacted in toluene (0.53 mL, 0.5 M) for 15 hr. Upon subjection to flash chromatographic purification (CH_2Cl_2/MeOH, 97:3), first to elute was the C6 isomer (55.7 mg, 87%), followed by the undesired C2 isomer (4.8 mg, 8%), and recovered starting material (14.5 mg, 35%), all brown solids.
Data for first; R_F = 0.42 (CH_2Cl_2/MeOH, 95:5); mp 102-103°C; FTIR (ν_{max}) 2956, 2926, 1725, 1443, 1301, 1196, 877, 805 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 (dd, 2H, *J* = 8.1, 1.7 Hz), 7.52 (d, 1H, *J* = 8.2 Hz), 7.29 (dd, 2H, *J* = 8.1, 1.7 Hz), 7.10 (d, 1H, *J* = 8.2 Hz), 7.01 (d, 1H, *J* = 3.4 Hz), 6.46 (d, 1H, *J* = 3.4 Hz), 4.44 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.7, 138.9, 137.6, 131.6, 130.6, 129.8, 128.9, 124.7, 120.8, 118.5, 101.2, 37.5, 21.5; HRMS *m/z* calcd for $C_{15}H_{14}N_2O$ $[M]^+$: 238.1106. Found 238.1087.
Data for second; R_F = 0.31 (CH_2Cl_2/MeOH, 95:5); mp 140-142°C; FTIR (ν_{max}) 3381, 2926, 2855, 1494, 1449, 1235, 791 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, 1H, *J* = 6.3 Hz), 7.52 (d, 1H, *J* = 7.9 Hz), 7.38 (d, 2H, *J* = 7.8 Hz), 7.31 (d, 2H, *J* = 7.8 Hz), 6.96 (d, 1H, *J* = 7.9, 6.3 Hz), 6.49 (s, 1H), 4.32 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.3, 139.3, 138.9 133.8, 129.6, 129.6, 128.2, 126.0, 120.6, 116.5, 101.5, 34.8, 21.5; HRMS *m/z* calcd for $C_{15}H_{14}N_2O$ $[M]^+$: 238.1106. Found 238.1117.



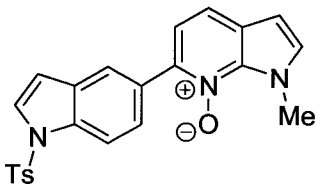
1-Methyl-2,6-di-*p*-tolyl-1*H*-pyrrolo[2,3-*b*]pyridine 7-oxide (2.24)

Isolated in small amounts from early reaction studies as a yellow solid; R_F = 0.59 (CH_2Cl_2/MeOH, 95:5); mp 204-205°C; FTIR (ν_{max}) 2925, 2851, 1440, 1203, 804 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, 2H, *J* = 8.2 Hz), 7.52 (d, 1H, *J* = 8.2 Hz), 7.39 (d, 2H, *J* = 8.1 Hz), 7.30 (d, 2H, *J* = 8.1 Hz), 7.30 (d, 2H, *J* = 8.2 Hz), 7.13 (d, 2H, *J* = 8.2 Hz), 6.48 (s, 1H), 4.33 (s, 3H), 2.44 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.3, 143.8, 139.1, 138.9, 130.9, 129.8, 129.8, 129.6, 129.5, 128.9, 128.6, 124.6, 120.1, 118.7, 101.4, 35.3, 21.6, 21.5; HRMS *m/z* calcd for $C_{22}H_{20}N_2O$ $[M]^+$: 328.1576. Found 328.1565.



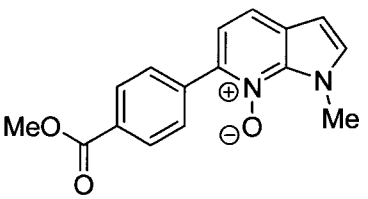
6-(4-Methoxyphenyl)-1-methyl-1*H*-pyrrolo[2,3-*b*]pyridine 7-oxide (2.25)

Following general procedure A, 1-methyl-1*H*-pyrrolo[2,3-*b*]pyridine 7-oxide (147 mg, 0.990 mmol, 3 equiv.), 4-bromoanisole (61.7 mg, 0.330 mmol), $Pd(OAc)_2$ (3.7 mg, 5 mol %), DavePhos (19.5 mg, 15 mol %), PivOH (10.1 mg, 30 mol %), and Cs_2CO_3 (215 mg, 0.660 mmol) were reacted in toluene (0.66 mL, 0.5 M) for 15 hr. Following flash chromatographic purification (CH_2Cl_2/MeOH, 98:2), the title compound was isolated as a brown solid (45.6 mg, 54%); R_F = 0.32 (CH_2Cl_2/MeOH, 95:5); mp 142-143°C; FTIR (ν_{max}) 2925, 1608, 1514, 1441, 1251 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.82 (ddd, 2H, J = 9.0, 2.9, 2.1 Hz), 7.51 (d, 1H, J = 8.2 Hz), 7.10 (d, 1H, J = 8.2 Hz), 7.02-6.99 (m, 3H), 6.45 (d, 1H, J = 3.4 Hz), 4.43 (s, 3H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 143.3, 137.7, 131.4, 131.3, 125.8, 124.5, 120.8, 118.3, 113.6, 101.2, 55.5, 37.5; HRMS *m/z* calcd for $C_{15}H_{14}N_2O_2$ $[M]^+$: 254.1055. Found 254.1041.



1-Methyl-6-(1-tosyl-1*H*-indol-5-yl)-1*H*-pyrrolo[2,3-*b*]pyridine 7-oxide (2.26)

Following general procedure A, 1-methyl-1*H*-pyrrolo[2,3-*b*]pyridine 7-oxide (33.8 mg, 0.228 mmol), 5-bromo-1-tosyl-1*H*-indole (obtained as a generous gift from Mégan Bertrand-Laperle)[150] (40 mg, 0.114 mmol), $Pd(OAc)_2$ (1.3 mg, 5 mol %), DavePhos (6.7 mg, 15 mol %), PivOH (3.5 mg, 30 mol %), and Cs_2CO_3 (74 mg, 0.228 mmol) were reacted in toluene (0.23 mL, 0.5 M) for 18 hr. Following flash chromatographic purification (CH_2Cl_2/MeOH, 98:2), the title compound was isolated as a light brown film (32.3 mg, 68%); R_F = 0.45 (CH_2Cl_2/MeOH, 95:5); FTIR (ν_{max}) 1447, 1372, 1303, 1165, 1130, 670, 583 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, 1H, J = 8.7 Hz), 8.02 (d, 1H, J = 1.7 Hz), 7.77 (d, 2H, J = 8.4 Hz), 7.73 (dd, 1H, J = 8.7, 1.7 Hz), 7.59 (d, 1H, J = 3.7 Hz), 7.54 (d, 1H, J = 8.2 Hz), 7.22 (d, 2H, J = 8.4 Hz), 7.12 (d, 1H, J = 8.2 Hz), 7.02 (d, 1H, J = 3.4 Hz), 6.71 (d, 1H, J = 3.7 Hz), 6.47 (d, 1H, J = 3.4 Hz), 4.42 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.2, 143.6, 137.6, 135.3, 134.9, 131.7, 130.7, 130.1, 128.7, 127.0, 126.9, 126.5, 124.9, 123.2, 120.9, 118.7, 113.3, 109.6, 101.3, 37.5, 21.7; HRMS *m/z* calcd for $C_{23}H_{19}N_3O_3S$ $[M]^+$: 417.1147. Found 417.1179.

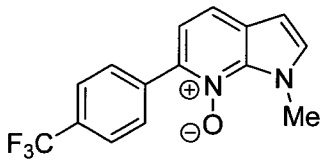


6-(4-(Methoxycarbonyl)phenyl)-1-methyl-1*H*-pyrrolo[2,3-*b*]pyridine 7-oxide (2.27)

Following general procedure A, 1-methyl-1*H*-pyrrolo[2,3-*b*]pyridine 7-oxide (165 mg, 1.12 mmol, 3 equiv.), methyl 4-bromobenzoate (80 mg, 0.372 mmol), $Pd(OAc)_2$ (4.2 mg, 5 mol %), DavePhos (22.0 mg, 15 mol %), PivOH (11.4 mg, 30 mol %), and Cs_2CO_3 (242 mg, 0.744 mmol) were reacted in toluene (0.93 mL, 0.4 M) for 15 hr. Following flash chromatographic purification (CH_2Cl_2/MeOH, 98:2), the title compound was isolated as a brown solid (56.0 mg, 53%); R_F = 0.29 (CH_2Cl_2/MeOH, 95:5); mp 124-126°C; FTIR (ν_{max}) 1719, 1438, 1284,

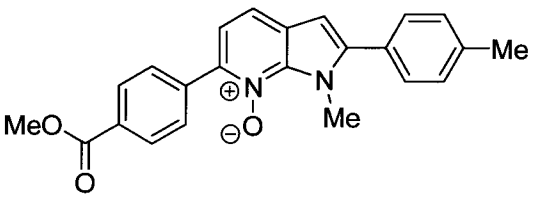
[150] Stuart, D. R.; Bertrand-Laperle, M.; Burgess, K. M. N.; Fagnou, K. *J. Am. Chem. Soc.* **2008,** *130,* 16474-16475.

1193, 1103 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.15 (ddd, 2H, J = 8.7, 1.9, 1.7 Hz), 7.94 (ddd, 2H, J = 8.7, 1.9, 1.7 Hz), 7.56 (d, 1H, J = 8.2 Hz), 7.13 (d, 1H, J = 8.2 Hz), 7.05 (d, 1H, J = 3.4 Hz), 6.49 (d, 1H, J = 3.4 Hz), 4.44 (s, 3H), 3.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 142.4, 138.0, 137.7, 132.1, 130.3, 129.9, 129.4, 125.4, 120.9, 118.4, 101.4, 52.3, 37.5; HRMS *m/z* calcd for $C_{16}H_{14}N_2O_3$ $[M]^+$: 282.1004. Found 282.0989.



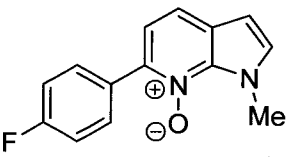
1-Methyl-6-(4-(trifluoromethyl)phenyl)-1*H*-pyrrolo[2,3-*b*]pyridine 7-oxide (2.28)

Following general procedure A, 1-methyl-1*H*-pyrrolo[2,3-*b*]pyridine 7-oxide (54.4 mg, 0.367 mmol), 4-bromobenzotrifluoride (41.3 mg, 0.184 mmol), $Pd(OAc)_2$ (2.1 mg, 5 mol %), DavePhos (10.8 mg, 15 mol %), PivOH (5.6 mg, 30 mol %), and Cs_2CO_3 (120 mg, 0.367 mmol) were reacted in toluene (0.37 mL) for 14.5 hr. Following flash chromatographic purification (CH_2Cl_2/MeOH, 100:0 - 99:1 - 98:2), the title compound was isolated as a light brown solid (34.8 mg, 65%); R_F = 0.44 (CH_2Cl_2/MeOH, 95:5); mp 88-89°C; FTIR (ν_{max}) 1325, 1306, 1165, 1121, 1109, 1061 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, 2H, J = 8.0 Hz), 7.74 (d, 2H, J = 8.0 Hz), 7.57 (d, 1H, J = 8.2 Hz), 7.12 (d, 1H, J = 8.2 Hz), 7.06 (d, 1H, J = 3.4 Hz), 6.50 (d, 1H, J = 3.4 Hz), 4.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.0, 137.6, 137.1 (q, J = 1.3 Hz), 132.2, 130.7 (q, J = 32.6 Hz), 130.3, 125.5, 125.2 (q, J = 3.8 Hz), 124.2 (q, J = 272.2 Hz), 121.0, 118.3, 101.5, 37.5; ^{19}F NMR (377 MHz, $CDCl_3$) δ -62.76 (s, 3F); HRMS *m/z* calcd for $C_{15}H_{11}N_2OF_3$ $[M]^+$: 292.0823. Found 292.0821.



6-(4-(Methoxycarbonyl)phenyl)-1-methyl-2-*p*-tolyl-1*H*-pyrrolo[2,3-*b*]pyridine 7-oxide (2.29)

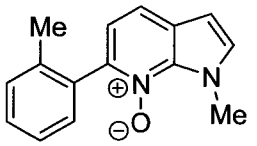
Following general procedure A, 1-methyl-2-*p*-tolyl-1*H*-pyrrolo[2,3-*b*]pyridine 7-oxide (29.1 mg, 0.122 mmol), methyl 4-bromobenzoate (26.3 mg, 0.122 mmol), $Pd(OAc)_2$ (1.4 mg, 5 mol %), DavePhos (7.2 mg, 15 mol %), PivOH (3.7 mg, 30 mol %), and Cs_2CO_3 (80 mg, 0.244 mmol) were reacted in toluene (0.24 mL, 0.5 M) for 14 hr. Following flash chromatographic purification (pet. ether/EtOAc, 60:40), the title compound was isolated as an orange solid (23.8 mg, 56%); R_F = 0.62 (CH_2Cl_2/MeOH, 95:5); mp 204-205°C; FTIR (ν_{max}) 2928, 1717, 1610, 1431, 1320, 1281, 1101, 737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, 2H, J = 8.5 Hz), 7.96 (d, 2H, J = 8.5 Hz), 7.56 (d, 1H, J = 8.2 Hz), 7.40 (d, 2H, J = 8.1 Hz), 7.31 (d, 2H, J = 8.1 Hz), 7.16 (d, 1H, J = 8.2 Hz), 6.51 (s, 1H), 4.33 (s, 3H), 3.95 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 144.8, 142.4, 139.3, 139.3, 138.3, 130.2, 130.0, 129.6, 129.6, 129.4, 128.3, 125.2, 120.1, 118.7, 101.5, 52.3, 35.3, 21.5; HRMS *m/z* calcd for $C_{23}H_{20}N_2O_3$ $[M]^+$: 372.1474. Found 372.1478.



6-(4-Fluorophenyl)-1-methyl-1*H*-pyrrolo[2,3-*b*]pyridine 7-oxide (2.30)

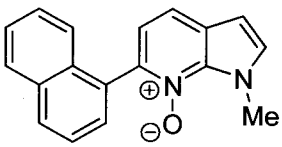
Following general procedure A, 1-methyl-1*H*-pyrrolo[2,3-*b*]pyridine 7-oxide (43.3 mg, 0.292 mmol), 1-bromo-4-fluorobenzene (25.6 mg, 0.146 mmol), $Pd(OAc)_2$ (1.6 mg, 5 mol %), DavePhos (8.6 mg, 15 mol %), PivOH

(4.5 mg, 30 mol %), and Cs_2CO_3 (95 mg, 0.292 mmol) were reacted in toluene (0.29 mL, 0.5 M) for 14.5 hr. Following flash chromatographic purification (CH_2Cl_2/MeOH, 98:2 - 97:3), the title compound was isolated as a white solid (21.8 mg, 62%); R_F = 0.35 (CH_2Cl_2/MeOH, 95:5); mp 113-115°C; FTIR (ν_{max}) 1507, 1443, 1307, 1278, 1231, 1194, 1160, 882, 807 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 (m, 2H), 7.54 (d, 1H, J = 8.2 Hz), 7.17 (m, 2H), 7.09 (d, 1H, J = 8.2 Hz), 7.03 (d, 1H, J = 3.4 Hz), 6.48 (d, 1H, J = 3.4 Hz), 4.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0 (d, J = 163.0 Hz), 142.6, 137.7, 131.9 (d, J = 8.3 Hz), 131.8, 129.5 (d, J = 3.4 Hz), 125.0, 120.9, 118.3, 115.3 (d, J = 21.7 Hz), 101.3, 37.5; ^{19}F NMR (377 MHz, $CDCl_3$) δ -112.18 (s, 1F); HRMS *m/z* calcd for $C_{14}H_{11}N_2OF$ $[M]^+$: 242.0855. Found 242.0848.



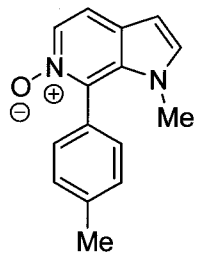
1-Methyl-6-*o*-tolyl-1*H*-pyrrolo[2,3-*b*]pyridine 7-oxide (2.31)

Following general procedure A, 1-methyl-1*H*-pyrrolo[2,3-*b*]pyridine 7-oxide (62.0 mg, 0.415 mmol), 2-bromotoluene (35.5 mg, 0.208 mmol), $Pd(OAc)_2$ (2.3 mg, 5 mol %), DavePhos (12.3 mg, 15 mol %), PivOH (6.3 mg, 30 mol %), and Cs_2CO_3 (135 mg, 0.415 mmol) were reacted in toluene (0.42 mL, 0.5 M) for 15.5 hr. Following flash chromatographic purification (CH_2Cl_2/MeOH, 97:3), the title compound was isolated as a brown solid (22.6 mg, 46%); R_F = 0.33 (CH_2Cl_2/MeOH, 95:5); mp 127-128°C; FTIR (ν_{max}) 1520, 1435, 1301, 1192, 882, 747, 724 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, 1H, J = 8.1 Hz), 7.38-7.28 (m, 4H), 7.03 (d, 1H, J = 3.4 Hz), 6.97 (d, 1H, J = 8.1 Hz), 6.50 (d, 1H, J = 3.4 Hz), 4.43 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.7, 138.0, 137.7, 133.8, 131.4, 130.1, 129.9, 129.1, 125.9, 125.0, 120.2, 118.7, 101.3, 37.3, 19.9; HRMS *m/z* calcd for $C_{15}H_{14}N_2O$ $[M]^+$: 238.1106. Found 238.1098.



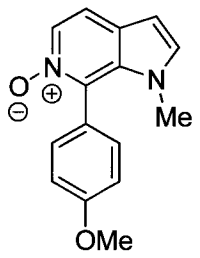
1-Methyl-6-(naphthalen-1-yl)-1*H*-pyrrolo[2,3-*b*]pyridine 7-oxide (S1)

Following general procedure A, 1-methyl-1*H*-pyrrolo[2,3-*b*]pyridine 7-oxide (134 mg, 0.908 mmol), 1-bromonaphthalene (94.0 mg, 0.454 mmol), $Pd(OAc)_2$ (5.1 mg, 5 mol %), DavePhos (26.8 mg, 15 mol %), PivOH (13.9 mg, 30 mol %), and Cs_2CO_3 (296 mg, 0.908 mmol) were reacted in toluene (0.91 mL, 0.5 M) for 15 hr. Following flash chromatographic purification (CH_2Cl_2/MeOH, 98:2), the title compound was isolated as a yellow solid (73.2 mg, 59%); R_F = 0.29 (CH_2Cl_2/MeOH, 95:5); mp 164-166°C; FTIR (ν_{max}) 1441, 1301, 1195, 1183, 886, 777, 746 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.94 (dd, 1H, J = 4.6 Hz), 7.89 (d, 1H, J = 7.6 Hz), 7.58-7.40 (m, 6H), 7.08 (d, 1H, J = 8.1 Hz), 7.05 (d, 1H, J = 3.4 Hz), 6.52 (d, 1H, J = 3.4 Hz), 4.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.5, 137.7, 133.6, 131.9, 131.8, 131.6, 129.6, 128.5, 128.2, 126.8, 126.1, 125.6, 125.4, 125.3, 120.3, 119.6, 101.4, 37.4; HRMS *m/z* calcd for $C_{18}H_{14}N_2O$ $[M]^+$: 274.1106. Found 274.1130. *Note: the material was chromatographically co-incident with small impurities (see NMR spectra). Structural identity was confirmed following N-oxide reduction.*



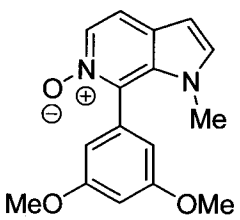
1-Methyl-7-*p*-tolyl-1*H*-pyrrolo[2,3-*c*]pyridine 6-oxide (2.32)

Following general procedure A, 1-methyl-1*H*-pyrrolo[2,3-*c*]pyridine 6-oxide (43.0 mg, 0.292 mmol), 4-bromotoluene (25 mg, 0.146 mmol), $Pd(OAc)_2$ (1.7 mg, 5 mol %), DavePhos (5.8 mg, 10 mol %), no PivOH, and Cs_2CO_3 (75 mg, 0.292 mmol) were reacted in toluene (0.29 mL, 0.5 M) for 14.5 hr (15 mol % DavePhos and 30 mol % PivOH with 0.4 M toluene likely gives a higher yield). Following flash chromatographic purification (CH_2Cl_2/MeOH, 97:3 -96:4 - 95:5), the title compound was isolated as a brown solid (22.4 mg, 62%); R_F = 0.18 (CH_2Cl_2/MeOH, 95:5); mp 66-68°C; FTIR (ν_{max}) 3365, 2926, 1441, 1211, 1196, 978, 811, 729 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, 1H, J = 6.9 Hz), 7.42-7.39 (m, 3H), 7.34 (d, 2H, J = 7.9 Hz), 7.09 (d, 1H, J = 3.1 Hz), 6.50 (d, 1H, J = 3.1 Hz), 3.16 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.6, 136.2, 135.1, 132.7, 132.2, 130.4, 129.4, 127.8, 127.2, 115.7, 101.7, 36.4, 21.7; HRMS *m/z* calcd for $C_{15}H_{14}N_2O$ $[M]^+$: 238.1106. Found 238.1112.



7-(4-Methoxyphenyl)-1-methyl-1*H*-pyrrolo[2,3-*c*]pyridine 6-oxide (2.33)

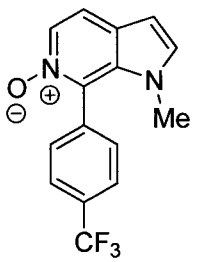
Following general procedure A, 1-methyl-1*H*-pyrrolo[2,3-*c*]pyridine 6-oxide (69.7 mg, 0.470 mmol), 4-bromoanisole (44.0 mg, 0.235 mmol), $Pd(OAc)_2$ (2.6 mg, 5 mol %), DavePhos (13.9 mg, 15 mol %), PivOH (7.2 mg, 30 mol %), and Cs_2CO_3 (153 mg, 0.470 mmol) were reacted in toluene (0.59 mL, 0.4 M) for 15 hr. Following flash chromatographic purification (CH_2Cl_2/MeOH, 94:6), the title compound was isolated as a brown solid (40.6 mg, 68%); R_F = 0.59 (CH_2Cl_2/MeOH, 90:10); mp 139-140°C; FTIR (ν_{max}) 1607, 1522, 1440, 1250, 1213, 1029, 811 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, 1H, J = 6.9 Hz), 7.44 (ddd, 2H, J = 8.8, 2.8, 2.1 Hz), 7.40 (d, 1H, J = 6.9 Hz), 7.09-7.05 (m, 3H), 6.50 (d, 1H, J = 3.1 Hz), 3.88 (s, 3H), 3.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.5, 135.9, 135.0, 132.8, 132.4, 131.9, 127.0, 122.9, 115.6, 114.2, 101.7, 55.5, 36.5; HRMS *m/z* calcd for $C_{15}H_{14}N_2O_2$ $[M]^+$: 254.1055. Found 254.1061.



7-(3,5-Dimethoxyphenyl)-1-methyl-1*H*-pyrrolo[2,3-*c*]pyridine 6-oxide (2.34)

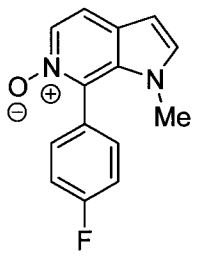
Following general procedure A, 1-methyl-1*H*-pyrrolo[2,3-*c*]pyridine 6-oxide (47.8 mg, 0.322 mmol), 1-bromo-3,5-dimethoxybenzene (35.0 mg, 0.161 mmol), $Pd(OAc)_2$ (1.8 mg, 5 mol %), DavePhos (9.5 mg, 15 mol %), PivOH (4.9 mg, 30 mol %), and Cs_2CO_3 (105 mg, 0.322 mmol) were reacted in toluene (0.40 mL, 0.4 M) for 15

hr. Following flash chromatographic purification (CH_2Cl_2/MeOH, 96:4 - 95:5), the title compound was isolated as a white film (32.2 mg, 70%); R_F = 0.56 (CH_2Cl_2/MeOH, 90:10); FTIR (ν_{max}) 1593, 1436, 1353, 1203, 1157, 1060, 971, 824, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, 1H, J = 6.9 Hz), 7.43 (d, 1H, J = 6.9 Hz), 7.10 (d, 1H, J = 3.1 Hz), 6.65 (d, 2H, J = 2.3 Hz), 6.61 (dd, 1H, J = 2.3 Hz), 6.51 (d, 1H, J = 3.1 Hz), 3.82 (s, 6H), 3.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.0, 135.8, 135.1, 132.7, 132.6, 131.9, 127.1, 115.9, 108.5, 102.2, 101.7, 55.6, 36.0; HRMS *m/z* calcd for $C_{16}H_{16}N_2O_3$ $[M]^+$: 284.1161. Found 284.1157.



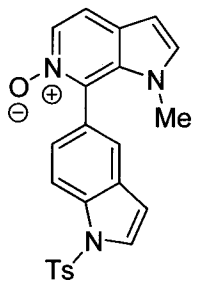
1-Methyl-7-(4-(trifluoromethyl)phenyl)-1*H*-pyrrolo[2,3-*c*]pyridine 6-oxide (2.35)

Following general procedure A, 1-methyl-1*H*-pyrrolo[2,3-*c*]pyridine 6-oxide (57.8 mg, 0.390 mmol), 4-bromobenzotrifluoride (43.9 mg, 0.195 mmol), $Pd(OAc)_2$ (2.2 mg, 5 mol %), DavePhos (11.5 mg, 15 mol %), PivOH (6.0 mg, 30 mol %), and Cs_2CO_3 (127 mg, 0.390 mmol) were reacted in toluene (0.49 mL, 0.4 M) for 15 hr. Following flash chromatographic purification (CH_2Cl_2/MeOH, 96:4), the title compound was isolated as a white solid (32.3 mg, 57%); R_F = 0.25 (CH_2Cl_2/MeOH, 95:5); mp 203-205°C; FTIR (ν_{max}) 1444, 1322, 1203, 1165, 1065 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, 1H, J = 6.9 Hz), 7.82 (d, 2H, J = 8.1 Hz), 7.68 (d, 2H, J = 8.1 Hz), 7.47 (d, 1H, J = 6.9 Hz), 7.12 (d, 1H, J = 3.1 Hz), 6.55 (d, 1H, J = 3.1 Hz), 3.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.4, 134.8 (q, J = 1.3 Hz), 134.3, 132.7, 131.9, 131.7 (q, J = 32.7 Hz), 131.3, 127.4, 125.7 (q, J = 3.7 Hz), 124.0 (q, J = 272.5 Hz), 116.4, 102.1, 36.6; ^{19}F NMR (377 MHz, $CDCl_3$) δ -62.76 (s, 3F); HRMS *m/z* calcd for $C_{15}H_{11}N_2OF_3$ $[M]^+$: 292.0823. Found 292.0814.



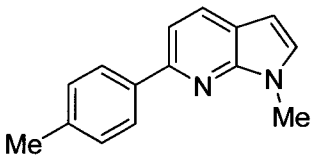
7-(4-Fluorophenyl)-1-methyl-1*H*-pyrrolo[2,3-*c*]pyridine 6-oxide (2.36)

Following general procedure A, 1-methyl-1*H*-pyrrolo[2,3-*c*]pyridine 6-oxide (50.1 mg, 0.338 mmol), 1-bromo-4-fluorobenzene (29.6 mg, 0.169 mmol), $Pd(OAc)_2$ (1.9 mg, 5 mol %), DavePhos (10.0 mg, 15 mol %), PivOH (5.2 mg, 30 mol %), and Cs_2CO_3 (110 mg, 0.338 mmol) were reacted in toluene (0.42 mL, 0.4 M) for 15 hr. Following flash chromatographic purification (CH_2Cl_2/MeOH, 93:7), the title compound was isolated as a light brown film (24.6 mg, 60%); R_F = 0.40 (CH_2Cl_2/MeOH, 90:10); FTIR (ν_{max}) 1521, 1440, 1215, 1202, 1101, 812 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, 1H, J = 6.9 Hz), 7.53-7.50 (m, 2H), 7.44 (d, 1H, J = 6.9 Hz), 7.26-7.22 (m, 2H), 7.10 (d, 1H, J = 3.1 Hz), 6.52 (d, 1H, J = 3.1 Hz), 3.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5 (d, J = 249.5 Hz), 135.3, 134.9, 132.7, 132.7 (d, J = 8.4 Hz), 132.2, 127.2, 126.8 (d, J = 3.6 Hz), 116.1, 115.9 (d, J = 21.8 Hz), 101.9, 36.5; ^{19}F NMR (377 MHz, $CDCl_3$) δ -111.12 (s, 1F); HRMS *m/z* calcd for $C_{14}H_{11}N_2OF$ $[M]^+$: 242.0855. Found 242.0861.



1-Methyl-7-(1-tosyl-1*H*-indol-5-yl)-1*H*-pyrrolo[2,3-*c*]pyridine 6-oxide (2.37)

Following general procedure A, 1-methyl-1*H*-pyrrolo[2,3-*c*]pyridine 6-oxide (33.8 mg, 0.228 mmol), 5-bromo-1-tosyl-1*H*-indole (obtained as a generous gift from Mégan Bertrand-Laperle)[150] (40.0 mg, 0.114 mmol), $Pd(OAc)_2$ (1.3 mg, 5 mol %), DavePhos (6.7 mg, 15 mol %), PivOH (3.5 mg, 30 mol %), and Cs_2CO_3 (74.0 mg, 0.228 mmol) were reacted in toluene (0.29 mL, 0.4 M) for 15 hr. Following flash chromatographic purification (CH_2Cl_2/MeOH, 95:5), the title compound was isolated as a white film (26.1 mg, 55%); R_F = 0.20 (CH_2Cl_2/MeOH, 95:5); FTIR (ν_{max}) 1438, 1370, 1165, 1131, 1090, 708, 667, 585 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.13-8.11 (m, 2H), 7.82 (d, 2H, J = 8.4 Hz), 7.70 (s, 1H), 7.66 (d, 1H, J = 3.6 Hz), 7.44-7.42 (m, 2H), 7.26 (d, 2H, J = 8.4 Hz), 7.09 (d, 1H, J = 3.1 Hz), 6.70 (d, 1H, J = 3.6 Hz), 6.52 (d, 1H, J = 3.1 Hz), 3.05 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.6, 136.0, 135.4, 135.3, 135.1, 132.7, 132.4, 130.8, 130.2, 127.3, 127.2, 127.1, 126.8, 125.6, 123.8, 115.9, 113.7, 109.0, 101.8, 36.5, 21.7; HRMS *m/z* calcd for $C_{23}H_{19}N_3O_3S$ $[M]^+$: 417.1147. Found 417.1164.

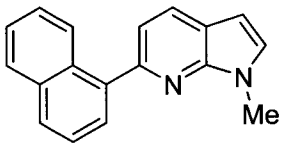


1-Methyl-6-*p*-tolyl-1*H*-pyrrolo[2,3-*b*]pyridine (2.38)

Following general procedure B, reaction of 1-methyl-6-*p*-tolyl-1*H*-pyrrolo[2,3-*b*]pyridine 7-oxide (211 mg, 0.884 mmol) and zinc dust (260 mg, 3.98 mmol) in 1:1 THF/sat. NH_4Cl (3.1 mL) for 40 min afforded the title compound as a colorless solid (197 mg, 98%);

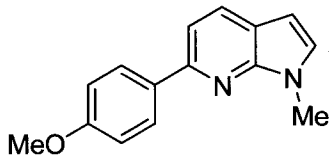
OR

1-Methyl-6-*p*-tolyl-1*H*-pyrrolo[2,3-*b*]pyridine 7-oxide (22.8 mg, 0.0957 mmol) was weighed into an oven-dried round-bottomed flask and purged with argon. Dry, degassed toluene (0.48 mL) was injected, followed by phosphorus trichloride (17 μL, 0.19 mmol), and the solution was stirred for 30 min. The septum was then removed and sat. $NaHCO_3$ (2.5 mL) was added slowly. The mixture was stirred vigorously for 10 min and then diluted with H_2O (10 mL) and CH_2Cl_2 (10 mL). The layers were partitioned, extracted an additional time with CH_2Cl_2 (10 mL), and then the organic layers were combined and washed with brine (10 mL). After drying over $MgSO_4$, the compound was afforded by column chromatography (pet. ether/EtOAc, 98:2) as a colorless solid (17 mg, 80%); R_F = 0.40 (pet. ether/EtOAc, 95:5); mp 74-75°C; FTIR (ν_{max}) 1514, 1440, 1409, 810, 713 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (ddd, 2H, J = 8.2, 1.9, 1.8 Hz), 7.92 (d, 1H, J = 8.2 Hz), 7.52 (d, 1H, J = 8.2 Hz), 7.28 (ddd, 2H, J = 8.2, 1.9, 1.8 Hz), 7.17 (d, 1H, J = 3.4 Hz), 6.44 (d, 1H, J = 3.4 Hz), 3.94 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.1, 148.2, 138.1, 138.0, 129.5, 129.3, 129.2, 127.0, 119.1, 112.9, 99.3, 31.2, 21.4; HRMS *m/z* calcd for $C_{15}H_{14}N_2$ $[M]^+$: 222.1157. Found 222.1146.



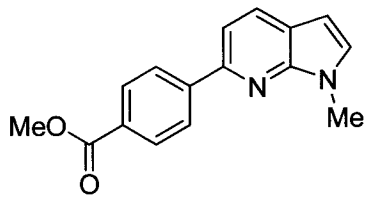
1-Methyl-6-(naphthalen-1-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (2.39)

Following general procedure B, 1-methyl-6-(naphthalen-1-yl)-1*H*-pyrrolo[2,3-*b*]pyridine 7-oxide (29.5 mg, 0.107 mmol) and zinc dust (31.6 mg, 0.484 mmol) were reacted in 1:1 THF/sat. NH_4Cl (3.6 mL) for 55 min. Following the usual workup, column chromatography on SiO_2 (pet. ether/EtOAc, 94:6) afforded the title compound as a colorless liquid (18.3 mg, 66%); R_F = 0.33 (pet. ether/EtOAc, 90:10); FTIR (ν_{max}) 3061, 1593, 1513, 1441, 1300, 910, 803, 785, 731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, 1H, J = 8.4 Hz), 8.03 (d, 1H, J = 8.0 Hz), 7.90 (d, 2H, J = 7.9 Hz), 7.70 (dd, 1H, J = 7.0, 1.5 Hz), 7.56 (dd, 1H, J = 8.4, 7.0 Hz), 7.46 (ddd, 2H, J = 7.9, 6.8, 1.5 Hz), 7.36 (d, 1H, J = 8.0 Hz), 7.24 (d, 1H, J = 3.4 Hz), 6.54 (d, 1H, J = 3.4 Hz), 3.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.2, 147.4, 139.0, 134.2, 131.8, 129.8, 129.3, 128.6, 128.4, 128.1, 126.3, 126.2, 125.8, 125.5, 119.5, 117.7, 99.6, 31.8; HRMS *m/z* calcd for $C_{18}H_{14}N_2$ $[M]^+$: 258.1157. Found 258.1132.



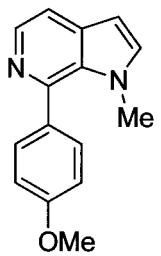
6-(4-Methoxyphenyl)-1-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (2.40)

Following general procedure B, reaction of 6-(4-methoxyphenyl)-1-methyl-1*H*-pyrrolo[2,3-*b*]pyridine 7-oxide (83.9 mg, 0.330 mmol) and zinc dust (97.0 mg, 1.49 mmol) in 1:1 THF/sat. NH_4Cl (11 mL) for 20 min afforded the title compound as a colorless solid (78.6 mg, 100%); R_F = 0.33 (pet. ether/EtOAc, 90:10); mp 68-69°C; FTIR (ν_{max}) 2937, 1608, 1512, 1436, 1249, 1030, 817 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.07 (ddd, 2H, J = 9.0, 2.9, 2.2 Hz), 7.90 (d, 1H, J = 8.2 Hz), 7.48 (d, 1H, J = 8.2 Hz), 7.14 (d, 1H, J = 3.4 Hz), 7.00 (ddd, 2H, J = 9.0, 2.9, 2.2 Hz), 6.42 (d, 1H, J = 3.4 Hz), 3.92 (s, 3H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 150.8, 148.1, 133.5, 129.2, 129.1, 128.3, 118.8, 114.2, 112.5, 99.3, 55.5, 31.1; HRMS *m/z* calcd for $C_{15}H_{14}N_2O$ $[M]^+$: 238.1106. Found 238.1105.



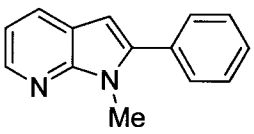
Methyl 4-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-6-yl)benzoate (2.41)

Following general procedure B, reaction of 6-(4-(methoxycarbonyl)phenyl)-1-methyl-1*H*-pyrrolo[2,3-*b*]pyridine 7-oxide (39.6 mg, 0.140 mmol) and zinc dust (41.0 mg, 0.630 mmol) in 1:1 THF/sat. NH_4Cl (4.7 mL) for 20 min afforded the title compound as a yellow solid (34.3 mg, 92%); R_F = 0.43 (pet. ether/EtOAc, 90:10); mp 131-132°C; FTIR (ν_{max}) 1711, 1608, 1437, 1300, 1280, 765 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.20 (ddd, 2H, J = 8.6, 1.9, 1.6 Hz), 8.13 (ddd, 2H, J = 8.6, 1.9, 1.6 Hz), 7.94 (d, 1H, J = 8.2 Hz), 7.58 (d, 1H, J = 8.2 Hz), 7.21 (d, 1H, J = 3.4 Hz), 6.46 (d, 1H, J = 3.4 Hz), 3.94 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 149.3, 148.1, 144.9, 130.2, 130.0, 129.5, 129.2, 126.8, 120.0, 113.3, 99.5, 52.2, 31.2; HRMS *m/z* calcd for $C_{16}H_{14}N_2O_2$ $[M]^+$: 266.1055. Found 266.1064.



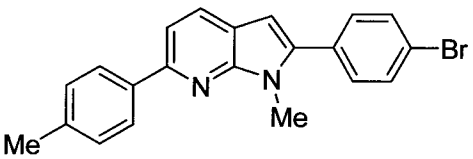
7-(4-Methoxyphenyl)-1-methyl-1*H*-pyrrolo[2,3-*c*]pyridine (2.42)

Following general procedure B, 7-(4-methoxyphenyl)-1-methyl-1*H*-pyrrolo[2,3-*c*]pyridine 6-oxide (39.3 mg, 0.154 mmol) and zinc dust (45.5 mg, 0.695 mmol) were reacted in 1:1 THF/sat. NH_4Cl (5.2 mL) for 3.5 hr (comparatively sluggish). Following the usual workup, column chromatography on SiO_2 (CH_2Cl_2/MeOH, 97:3) afforded the title compound as a white film (30.8 mg, 84%); R_F = 0.08 (CH_2Cl_2/MeOH, 98:2); FTIR (ν_{max}) 1611, 1520, 1458, 1321, 1244, 1174, 1030, 822 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, 1H, J = 5.3 Hz), 7.50-7.48 (m, 3H), 7.14 (d, 1H, J = 3.0 Hz), 7.01 (d, 2H, J = 8.7 Hz), 6.55 (d, 1H, J = 3.0 Hz), 3.88 (s, 3H), 3.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 145.0, 138.0, 135.0, 134.3, 132.3, 131.8, 130.9, 114.5, 113.5, 100.8, 55.5, 37.0; HRMS *m/z* calcd for $C_{15}H_{14}N_2O_1$ $[M]^+$: 238.1106. Found 238.1089.



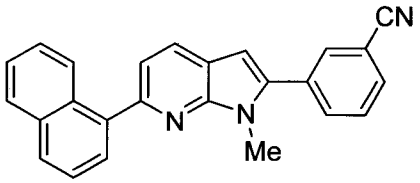
1-Methyl-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine (2.43)

Following general procedure C, 1-methylpyrrolo[2,3-*b*]pyridine (27.8 mg, 0.210 mmol), $Pd(OAc)_2$ (2.4 mg, 5 mol %), silver(I) oxide (36.6 mg, 0.158 mmol), 2-nitrobenzoic acid (53.0 mg, 0.315 mmol), and iodobenzene (47.1 μL, 0.420 mmol) were reacted in DMF (0.42 mL, 0.5 M) for 19 hr. Following flash chromatographic purification (pet. ether/EtOAc, 92:8), the title compound was isolated as a colorless liquid (31.1 mg, 71%). Exhibited spectral data identical to previous reports.[148]



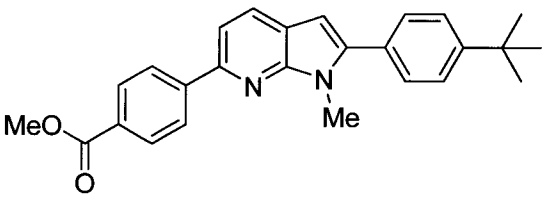
2-(4-Bromophenyl)-1-methyl-6-*p*-tolyl-1*H*-pyrrolo[2,3-*b*]pyridine (2.44)

Following general procedure C, 1-methyl-6-*p*-tolyl-1*H*-pyrrolo[2,3-*b*]pyridine (17.0 mg, 0.0765 mmol), $Pd(OAc)_2$ (0.9 mg, 5 mol %), silver(I) oxide (13.3 mg, 0.0574 mmol), 2-nitrobenzoic acid (19.2 mg, 0.115 mmol), and 1-bromo-4-iodobenzene (43.3 mg, 0.153 mmol) were reacted in DMF (0.15 mL, 0.5 M) for 17 hr. Following flash chromatographic purification (pet. ether/Et_2O, 98:2), the title compound was isolated as a colorless solid (21.6 mg, 75%); R_F = 0.25 (pet. ether/Et_2O, 96:4); mp 196-197°C; FTIR (ν_{max}) 2916, 1478, 1398, 1008, 808, 759 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, 2H, J = 8.2 Hz), 7.92 (d, 1H, J = 8.2 Hz), 7.62 (d, 2H, J = 8.5 Hz), 7.57 (d, 2H, J = 8.5 Hz), 7.29 (d, 2H, J = 8.2 Hz), 6.51 (s, 1H), 3.93 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.2, 149.7, 140.8, 138.2, 137.8, 132.0, 131.7, 130.6, 129.5, 128.8, 126.9, 122.6, 119.2, 113.6, 99.9, 30.0, 21.4; HRMS *m/z* calcd for $C_{21}H_{17}N_2Br$ $[M]^+$: 376.0575. Found 376.0569.



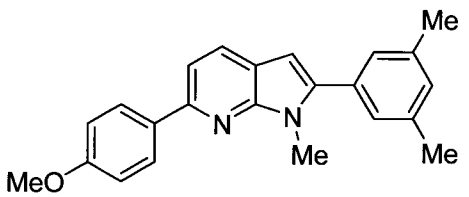
3-(1-Methyl-6-(naphthalen-1-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)benzonitrile (2.45)

Following general procedure C, 1-methyl-6-(naphthalen-1-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (32.4 mg, 0.125 mmol), $Pd(OAc)_2$ (1.4 mg, 5 mol %), silver(I) oxide (21.8 mg, 0.0938 mmol), 2-nitrobenzoic acid (31.4 mg, 0.188 mmol), and 3-iodobenzonitrile (57.4 mg, 0.250 mmol) were reacted in DMF (0.25 mL, 0.5 M) for 15 hr. Following flash chromatographic purification (hexanes/EtOAc, 92:8 - 90:10), the title compound was isolated as white crystals (23.2 mg, 58%); R_F = 0.20 (pet. ether/EtOAc, 90:10); mp 192-193°C; FTIR (ν_{max}) 2230, 1394, 802, 776, 760 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, 1H, *J* = 8.3 Hz), 8.05 (d, 1H, *J* = 8.0 Hz), 7.94-7.89 (m, 3H), 7.84 (ddd, 1H, *J* = 7.8, 1.3, 1.3 Hz), 7.74-7.70 (m, 2H), 7.63 (dd, 2H, *J* = 7.8, 7.8 Hz), 7.59 (dd, 1H, *J* = 8.3, 7.1 Hz), 7.49 (ddd, 1H, *J* = 8.0, 6.8, 1.3 Hz), 7.43 (d, 1H, *J* = 8.0 Hz), 6.66 (s, 1H), 3.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.4, 149.5, 139.6, 139.5, 134.2, 134.1, 133.3, 132.5, 131.7, 129.8, 128.9, 128.7, 128.5, 127.9, 126.3, 126.3, 125.9, 125.5, 119.0, 118.8, 118.6, 113.3, 100.9, 30.3 (one must overlap); HRMS *m/z* calcd for $C_{25}H_{17}N_3$ $[M]^+$: 359.1422. Found 359.1398.



Methyl 4-(2-(4-*tert*-butylphenyl)-1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-6-yl)benzoate (2.46)

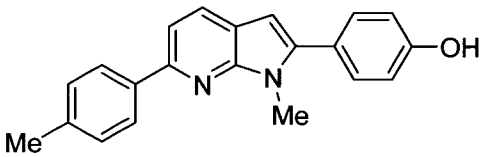
Following general procedure C, methyl 4-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-6-yl)benzoate (18.2 mg, 0.0683 mmol), $Pd(OAc)_2$ (0.8 mg, 5 mol %), silver(I) oxide (11.9 mg, 0.0512 mmol), 2-nitrobenzoic acid (17.1 mg, 0.102 mmol), and 4-*tert*-butyliodobenzene (24.2 μL, 0.137 mmol) were reacted in DMF (0.14 mL, 0.5 M) for 12 hr. Following flash chromatographic purification (hexanes/EtOAc, 95:5), the title compound was isolated as a gleaming fluorescent white solid (17.5 mg, 64%); R_F = 0.44 (pet. ether/EtOAc, 90:10); mp 178-179°C; FTIR (ν_{max}) 1718, 1609, 1491, 1276, 1110, 765 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.24 (ddd, 2H, *J* = 8.7, 1.8, 1.7 Hz), 8.14 (ddd, 2H, *J* = 8.7, 1.8, 1.7 Hz), 7.96 (d, 1H, *J* = 8.1 Hz), 7.64 (d, 1H, *J* = 8.1 Hz), 7.52 (s, 4H), 6.53 (s, 1H), 3.98 (s, 3H), 3.95 (s, 3H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 151.7, 149.6, 148.9, 145.0, 143.3, 130.1, 129.6, 129.4, 128.9, 128.5, 126.8, 125.8, 120.4, 113.9, 99.4, 52.2, 34.9, 31.5, 30.1; HRMS *m/z* calcd for $C_{26}H_{26}N_2O_2$ $[M]^+$: 398.1994. Found 398.1994.



2-(3,5-Dimethylphenyl)-6-(4-methoxyphenyl)-1-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (2.47)

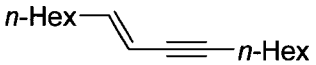
Following general procedure C, 6-(4-methoxyphenyl)-1-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (16.8 mg, 0.0705 mmol), $Pd(OAc)_2$ (0.8 mg, 5 mol %), silver(I) oxide (12.3 mg, 0.0529 mmol), 2-nitrobenzoic acid (17.7 mg, 0.106 mmol), and 1-iodo-3,5-dimethylbenzene (20 μL, 0.141 mmol) were reacted in DMF (0.14 mL, 0.5 M) for 12 hr. Following flash chromatographic purification (hexanes/EtOAc, 94:6), the title compound was isolated as a yellow solid (18.6 mg, 77%); R_F = 0.50 (pet. ether/EtOAc, 90:10); mp 129-130°C; FTIR (ν_{max}) 1515, 1246,

1173, 1031, 818 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (ddd, 2H, J = 8.9, 2.9, 2.1 Hz), 7.89 (d, 1H, J = 8.1 Hz), 7.51 (d, 1H, J = 8.1 Hz), 7.18 (br s, 2H), 7.06 (br s, 1H), 7.01 (ddd, 2H, J = 8.9, 2.9, 2.1 Hz), 6.47 (s, 1H), 3.93 (s, 3H), 3.87 (s, 3H), 2.40 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 150.4, 149.6, 142.3, 138.3, 133.6, 132.6, 130.0, 128.5, 128.2, 127.0, 119.1, 114.2, 113.0, 99.3, 55.5, 30.0, 21.5; HRMS *m/z* calcd for $C_{23}H_{22}N_2O$ $[M]^+$: 342.1732. Found 342.1708.



4-(1-Methyl-6-*p*-tolyl-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)phenol (2.48)

Following general procedure C, 1-methyl-6-*p*-tolyl-1*H*-pyrrolo[2,3-*b*]pyridine (25.5 mg, 0.115 mmol), $Pd(OAc)_2$ (1.3 mg, 5 mol %), silver(I) oxide (19.9 mg, 0.0863 mmol), 2-nitrobenzoic acid (28.8 mg, 0.173 mmol), and 4-iodophenol (50.5 mg, 0.230 mmol) were reacted in DMF (0.23 mL, 0.5 M) for 15.5 hr. Following flash chromatographic purification (pet. ether/EtOAc, 80:20), the title compound was isolated as a yellow solid (22.9 mg, 64%); R_F = 0.39 (pet. ether/EtOAc, 76:24); mp 137-139°C; FTIR (ν_{max}) 1613, 1495, 1448, 1405, 1172, 811 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, 2H, J = 8.2 Hz), 7.91 (d, 1H, J = 8.1 Hz), 7.54 (d, 1H, J = 8.1 Hz), 7.42 (ddd, 2H, J = 8.7, 2.8, 2.1 Hz), 7.28 (d, 2H, J = 8.2 Hz), 6.90 (ddd, 2H, J = 8.7, 2.8, 2.1 Hz), 6.44 (s, 1H), 5.38 (br s, 1H), 3.91 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0, 150.7, 149.5, 142.1, 138.0, 138.0, 130.7, 129.5, 128.5, 127.0, 125.2, 119.5, 115.7, 113.5, 98.9, 30.0, 21.4; HRMS *m/z* calcd for $C_{21}H_{18}N_2O$ $[M]^+$: 314.1419. Found 314.1420.



(*E*)-Hexadec-7-en-9-yne (3.1)

Into an oven-dried round-bottomed flask was weighed $Pd(OAc)_2$ (9.4 mg, 0.042 mmol), CuI (16 mg, 0.084 mmol), and triphenylphosphine (22 mg, 0.084 mmol). After the vessel had been purged with argon, it was charged with a solution of (*E*)-1-iodooct-1-ene[151] (200 mg, 0.840 mmol) in freshly distilled NEt_3 (1.68 mL, 0.5 M), followed by 1-octyne (136 μL, 0.924 mmol). The mixture was stirred vigorously for 15 hr, filtered through celite, washing with CH_2Cl_2. After evaporation of the volatiles, the crude residue was purified by column chromatography (pentane) to afford the target compound as a yellow liquid (159 mg, 86%). Spectral data was in accord with that presented in the literature.[152]

OR[153]

A round-bottomed flask containing $Pd(OAc)_2$ (81.5 mg, 0.5 mol %), 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride (247 mg, 1 mol %) and $CsCO_3$ (47.3 g, 0.145 mol) was purged under argon. To this flask was added DMA (145 mL, 0.5 M, degassed for 30 min) via cannula. The solution was stirred at 80°C for 1 min before being charged with 1-octyne (10.7 mL, 0.0726 mol). Stirring was continued at 80°C for 3 hr and then, after being cooled to rt, the mixture was diluted with Et_2O, washed with H_2O (3x), brine and dried ($MgSO_4$). Column chromatography (pet. ether) was performed three times, collecting pure fractions each time (3.56 g, 45%). The compound exhibited spectral data identical to previous reports.[152]

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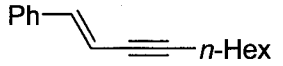
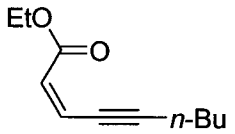
[151] David R. Stuart synthesized this compound by the action of DIBAL on 1-octyne, followed by quench with I_2.
[152] Dubbaka, S. R.; Kienle, M.; Mayr, H.; Knochel, P. *Angew. Chem. Int. Ed.* **2007,** *46,* 9093-9096.
[153] Yang, C.; Nolan, S. P. *J. Org. Chem.* **2002,** *67,* 591-593.



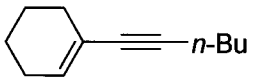
(*E*)-Dec-1-en-3-ynylbenzene (3.2)[154]

Into an oven-dried Schlenk flask was weighed CuI (19.0 mg, 0.100 mmol), DABCO (22.0 mg, 0.200 mmol), Cs_2CO_3 (652 mg, 2.00 mmol), tetrabutylammonium bromide (322 mg, 1.00 mmol) and the vessel was evacuated and refilled with argon three times. The flask was then charged sequentially with bromostyrene (128 μL, 1.00 mmol, 10:1 *E/Z* by GC), 1-octyne (197 μL, 1.33 mmol), and anhydrous DMF (10 mL) and the mixture was stirred at 140°C for 20 hr. After filtration through Celite, the mixture was diluted with ether and extracted with water (3x) and brine. After drying the organic layer over $MgSO_4$, purification via column chromatography (pet. ether) afforded the title compound as a yellow liquid (124 mg, 58%, 20:1 *E/Z* by ^{1}H NMR). Spectral data was in accord with that presented in the literature.[155]
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.25 (m, 5H), 6.86 (d, 1H, J = 16.2 Hz), 6.16 (dt, 1H, J = 16.2, 2.2 Hz), 2.36 (td, 2H, J = 7.1, 2.2 Hz), 1.56 (p, 2H, J = 7.1 Hz), 1.46-1.26 (m, 6H), 0.90 (t, 3H, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.1, 136.8, 128.8, 128.3, 126.2, 109.1, 93.2, 79.9, 31.5, 28.9, 28.8, 22.7, 19.8, 14.2.



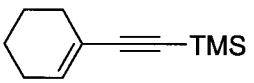
(*Z*)-Ethyl non-2-en-4-ynoate (3.3)

Reaction of *cis*-3-iodoacrylic acid ethyl ester (1.5 g, 6.64 mmol) following the method of Takeuchi *et al.*[156] afforded the target compound (1.00 g, 84%) and exhibited identical spectral data.



1-(hex-1-ynyl)cyclohex-1-ene (3.4)

Prepared following the method of Yoshida *et. al.*[157] in two steps beginning from cyclohexanone (5 mL, 0.0482 mol) and the product after the first step was used in the subsequent step without purification (4.26 g, 54% over 2 steps); R_F = 0.63 (pet. ether); FTIR (ν_{max}) 2939, 2213, 1716, 1673, 1089 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.01-5.99 (m, 1H), 2.29 (t, 2H, J = 7.0 Hz), 2.11-2.05 (m, 4H), 1.65-1.37 (m, 8H), 0.91 (t, 3H, J = 7.2; ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.2, 121.2, 87.5, 82.4, 31.2, 29.8, 25.7, 22.6, 22.1, 21.7, 19.1, 13.8; HRMS *m/z* calcd for $C_{12}H_{18}$ $[M]^+$: 162.1409. Found 162.1409.

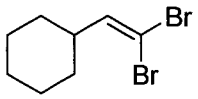


(Cyclohexenylethynyl)trimethylsilane (3.5)

To a solution of 1-ethynylcyclohexene (1.5 mL, 12.8 mmol) in THF (54 mL, 0.24 M) that was under argon and at -78°C was added *n*-BuLi (5.6 mL, 2.5 M solution in hexanes [untitrated], 14.0 mmol). The mixture was stirred for 30 min and then 30 min after the cooling bath had been removed. Chlorotrimethylsilane (1.77 mL, 14.0 mmol) was then injected and stirring was continued for 17 hr. The mixture was diluted with Et_2O and H_2O and the layers were separated. After the aqueous layer had been extracted again with Et_2O, the combined extracts were dried ($MgSO_4$) and concentrated. Purification of the residue thus obtained via flash column

[154] Li, J.-H.; Li, J.-L.; Wang, D.-P.; Pi, S.-F.; Xie, Y.-X.; Zhang, M.-B.; Hu, X.-C. *J. Org. Chem.* **2007,** *72,* 2053-2057.
[155] Miyaura, N.; Yamada, K.; Suginome, H.; Suzuki, A. *J. Am. Chem. Soc.* **1985,** *107,* 972-980.
[156] Takeuchi, R.; Tanabe, K.; Tanaka, S. *J. Org. Chem.* **2000,** *65,* 1558-1561.
[157] Yoshida, M.; Hayashi, M.; Shishido, K. *Org. Lett.* **2007,** *9,* 1643-1646.

chromatography (pet. ether) afforded the title compound as a colorless liquid (1.68 g, 74%). The compound exhibited spectral data identical to previous reports.[158]

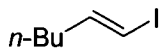


(2,2-Dibromovinyl)cyclohexane (3.6)

In an open flask, triphenylphosphine (43.45 g, 165.6 mmol) was suspended in anhydrous CH_2Cl_2 (207 mL, 0.2 M) and cooled to 0°C. While stirring, portionwise addition of tetrabromomethane (27.47 g, 82.80 mmol) afforded a dark brown solution that was then purged under argon and stirred for 1 hr at rt. The flask was then charged with cyclohexanecarboxaldehyde[159] (4.99 mL, 41.4 mmol) and stirred for 23 hr. At this point the solution was diluted with pet. ether until no more precipitate formed. Following filtration, column chromatography (pet. ether) of the concentrated residue afforded the title compound as a colorless liquid (10.34 g, 93%). The compound exhibited spectral data identical to previous reports.[160]

(Cyclohexylethynyl)trimethylsilane (3.7)

To a solution of (2,2-dibromovinyl)cyclohexane (2.00 g, 7.46 mmol) in THF (37 mL, 0.2 M) that was under argon and at -78°C was added *n*-BuLi (6.6 mL, 2.5 M solution in hexanes [untitrated], 16.4 mmol). The mixture was stirred for 1 hr and then 1 hr after the cooling bath had been removed. Chlorotrimethylsilane (1.04 mL, 8.20 mmol) was then injected and stirring was continued for 27 hr. The mixture was diluted with Et_2O and H_2O and the layers were separated. After the aqueous layer had been extracted again with Et_2O, the combined extracts were washed with brine, dried ($MgSO_4$) and concentrated. Purification of the residue thus obtained via flash column chromatography (pet. ether) afforded the title compound as a colorless liquid (1.03 g, 77%). The compound exhibited spectral data identical to previous reports.[161]



(*E*)-1-Iodohex-1-ene (3.8)

To a suspension of di(cyclopentadienyl)zirconium(IV) chloride hydride (3.77 g, 14.6 mmol) in anhydrous benzene (41 mL, 0.3 M) under argon was added 1-hexyne (1.41 mL, 12.2 mmol) and stirred for 2 hr, at which point the color of the mixture had changed from opaque white to clear red. The septum was lifted briefly in order to charge the flask with iodine (3.86 g, 15.3 mmol). After 2 min, the consumption of the metalated alkene was indicated by the persistence of a dark brown color. The reaction mixture was diluted with pet. ether (100 mL) and filtered over Celite, washing with Et_2O. The filtrate was washed with 10% aq. $Na_2S_2O_3$ and dried ($MgSO_4$). Concentration *in vacuo* afforded the compound as a red liquid (1.56 g, 61%). The compound exhibited spectral data identical to previous reports.[162]
Note: Since the product is volatile, it must not be left in vacuo for extended periods of time.

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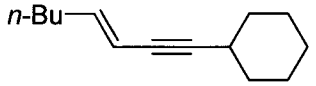
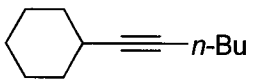
[158] Rahaim, R. J. Jr.; Shaw, J. T. *J. Org. Chem.* **2008,** *73,* 2912-2915.
[159] Freshly distilled on a Kugelrohr apparatus.
[160] Trost, B. M.; Livingston, R. C. *J. Am. Chem. Soc.* **2008,** *130,* 11970-11978.
[161] Ohmiya, H.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2006,** *8,* 3093-3096.
[162] Chen, M.-J.; Narkunan, K.; Liu, R.-S. *J. Org. Chem.* **1999,** *64,* 8311-8318.



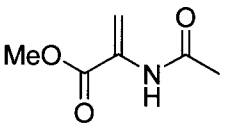
(*E*)-oct-3-en-1-ynylcyclohexane (3.9)

To a solution of (cyclohexylethynyl)trimethylsilane (386 mg, 2.14 mmol) in dry, degassed THF (14.3 mL, 0.1 M) under argon was added TBAF (2.86 mL, 1.0 M solution in THF, 2.86 mmol). The reaction was stirred until complete by TLC (1 hr) and then transferred via cannula into a flask containing $PdCl_2(PPh_3)_2$ (50.1 mg, 5 mol %) and CuI (27.2 mg, 10 mol %) under argon. Then, the flask was charged with a solution of (*E*)-1-iodohex-1-ene (300 mg, 1.43 mmol) in undistilled degassed NEt_3 (7.1 mL, 0.2 M) and stirred for 10 hr. The mixture was partitioned between CH_2Cl_2 and sat. aq. NH_4Cl and the aqueous layer was extracted a second time with CH_2Cl_2. The combined organics were dried ($MgSO_4$) and concentrated. Flash chromatographic purification (pet. ether) of the residue thus obtained afforded the target compound as a colorless liquid (260.3 mg, 96%); Spectral data was in accord with that presented in the literature.[163]



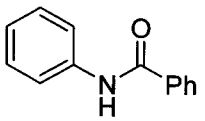
Hex-1-ynylcyclohexane (3.10)[164]

To a solution of (2,2-dibromovinyl)cyclohexane (1.06 g, 3.95 mmol) in THF (19.7 mL, 0.2 M) that was under argon and at -78°C was added *n*-BuLi (3.3 mL, 2.5 M solution in hexanes [untitrated], 8.3 mmol). The mixture was stirred for 1 hr and then the vessel was charged with 1-iodobutane (1.80 mL, 15.8 mmol). The cooling bath was removed and the solution was allowed to stir for 22 hr. The solution was then diluted with Et_2O and washed with H_2O (2x) and brine. After being dried ($MgSO_4$), the organics were concentrated to dryness. Purification of the residue thus obtained via flash column chromatography (pet. ether) afforded the title compound as a colorless liquid (373.3 mg, 57%). The compound exhibited spectral data identical to previous reports.[165]



Methyl 2-acetamidoacrylate (3.11)

Starting from pyruvic acid methyl ester (2.00 g, 0.0196 mol), prepared following the method of Collot *et al.*,[166] except that only 1 mol % 4-methoxyphenol was used and the product was purified by flash chromatography (pet. ether/EtOAc, 75:25). The compound exhibited identical spectral data.



***N*-phenylbenzamide (3.12)**

To an open round-bottomed flask was added distilled triethylamine (4.94 mL, 35.4 mmol), analine (3.00 g, 32.2 mmol) and HPLC-grade CH_2Cl_2 (60 mL). A condenser was put in place and the apparatus was purged with argon gas and slowly charged with a solution of benzoyl chloride (4.10 mL, 35.4 mmol) in HPLC-grade CH_2Cl_2 (60 mL) over a period of 45 min. Thereafter, refluxing (60°C set) was brought about for a period of 2.5 hr. After

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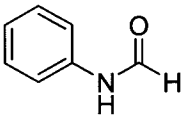
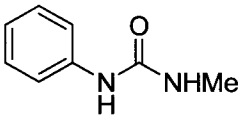
[163] Negishi, E.-i.; Yoshida, T.; Abramovitch, A.; Lew, G.; Williams, R. M. *Tetrahedron* **1991,** *47,* 343-356.
[164] Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972,** *36,* 3769-3772.
[165] Inoue, Y.; Fukunaga, T.; Hakushi, T. *J. Org. Chem.* **1983,** *48,* 1732-1737.
[166] Crestey, F.; Collot, V.; Stiebing, S.; Rault, S. *Synthesis* **2006,** 3506-3514.

being cooled to rt, the reaction mixture was diluted with CH_2Cl_2 and extracted with water (2x), sat. $NaHCO_3$, 2 M HCl. The organics were dried ($MgSO_4$), concentrated to dryness, and recrystallized from $CHCl_3$ to afford the title compound as white needles (5.76 g, 91%). Spectral data was in accord with that presented in the literature.[167]



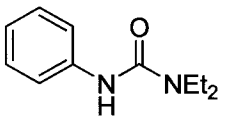
N-phenylformamide (3.13)

Reaction of analine (3.00 g, 32.2 mmol) following the method of Hosseini-Sarvarti and Sharghi[168] afforded the target compound (3.90 g, 100%) and exhibited identical spectral data.



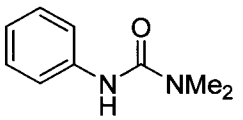
1-Methyl-3-phenylurea (3.14)

Reaction of phenyl isocyanate (2.39 mL, 22.0 mmol) following the method of Lloyd-Jones and Booker-Milburn[66] afforded the target compound (1.19 g, 36%) and exhibited identical spectral data.



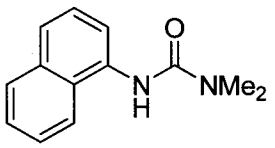
1,1-Diethyl-3-phenylurea (3.15)

Reaction of phenyl isocyanate (2.39 mL, 22.0 mmol) following the method of Lloyd-Jones and Booker-Milburn[66] afforded the target compound (3.90 g, 92%) and exhibited identical spectral data.



1,1-Dimethyl-3-phenylurea (3.16)

Reaction of phenyl isocyanate (2.39 mL, 22.0 mmol) following the method of Lloyd-Jones and Booker-Milburn[65] afforded the target compound (3.21 g, 89%) and exhibited identical spectral data.



1,1-Dimethyl-3-(naphthalen-1-yl)urea (3.17)

Reaction of 1-isocyanatonaphthalene (2.15 mL, 15.0 mmol) following the method of Lloyd-Jones and Booker-Milburn[66] afforded the target compound (2.80 g, 87%) and exhibited identical spectral data.

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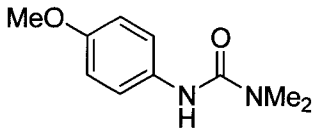
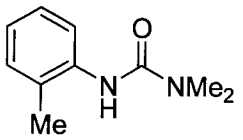
[167] Zhang, Z.; Yu, Y.; Liebeskind, L. S. *Org. Lett.* **2008,** *10,* 3005-3008.
[168] Hosseini-Sarvari, M.; Sharghi, M. *J. Org. Chem.* **2006,** *71,* 6652-6654.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85-7.81 (m, 2H), 7.70 (d, 1H, J = 7.4 Hz), 7.63 (d, 1H, J = 8.2 Hz), 7.48-7.45 (m, 2H), 7.42 (dd, 1H, J = 8.0 Hz), 6.67 (br s, 1H), 3.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6, 134.3, 134.2, 128.7, 128.1, 126.0, 125.9, 125.8, 124.9, 121.2, 120.8, 36.6.



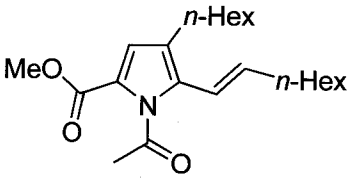
3-(4-Methoxyphenyl)-1,1-dimethylurea (3.18)

Reaction of 1-isocyanato-4-methoxybenzene (2.57 mL, 20.0 mmol) following the method of Lloyd-Jones and Booker-Milburn[65] afforded the target compound (3.35 g, 86%) and exhibited identical spectral data.



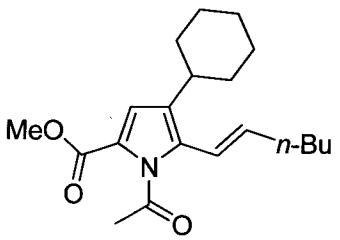
1,1-Dimethyl-3-*o*-tolylurea (3.19)

Reaction of 1-isocyanato-2-methylbenzene (1.85 mL, 15.0 mmol) following the method of Lloyd-Jones and Booker-Milburn[65] afforded the target compound (2.16 g, 81%) and exhibited identical spectral data.



(*E*)-Methyl 1-acetyl-4-hexyl-5-(oct-1-enyl)-1*H*-pyrrole-2-carboxylate (3.20)

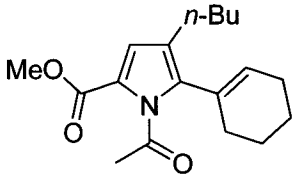
Following general procedure D, methyl 2-acetamidoacrylate (20 mg, 0.140 mmol), (*E*)-Hexadec-7-en-9-yne (33.9 mg, 0.154 mmol), $[Cp^*Rh(MeCN)_3][SbF_6]_2$ (5.8 mg, 5 mol %) and $Cu(OAc)_2{\cdot}H_2O$ (5.6 mg, 20 mol %) were reacted in cyclohexanone (0.70 mL, 0.2 M) under oxygen atmosphere for 16 hr. Following flash chromatographic purification (pet. ether/Et_2O, 93:7), the title compound was isolated as a yellow liquid (38.9 mg, 77%); R_F = 0.38 (pet. ether/Et_2O, 90:10); FTIR (ν_{max}) 1747, 1706, 1468, 1436, 1386, 1243, 1201, 1055, 761 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81 (s, 1H), 6.25 (d, 1H, J = 16.1 Hz), 5.89 (ddd, 1H, J = 16.1, 7.0, 7.0 Hz), 3.79 (s, 3H), 2.49 (s, 3H), 2.42 (t, 2H, J = 7.9 Hz), 2.17 (dt, 2H, J = 7.4, 7.0 Hz), 1.57-1.49 (m, 2H), 1.46-1.37 (m, 2H), 1.36-1.23 (m, 12H), 0.87 (t, 6H, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5, 161.3, 137.7, 134.0, 124.7, 121.6, 121.0, 118.4, 51.8, 33.7, 31.8, 31.8, 30.3, 29.3, 29.3, 28.9, 28.8, 26.6, 22.7, 22.7, 14.2, 14.2; HRMS *m/z* calcd for $C_{22}H_{35}NO_3$ $[M]^+$: 361.2617. Found 361.2626.



(*E*)-Methyl 1-acetyl-4-cyclohexyl-5-(hex-1-enyl)-1*H*-pyrrole-2-carboxylate (3.21)

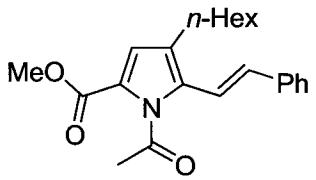
Following general procedure D, methyl 2-acetamidoacrylate (19.8 mg, 0.138 mmol), (*E*)-oct-3-en-1-ynylcyclohexane (29.0 mg, 0.152 mmol), $[Cp^*Rh(MeCN)_3][SbF_6]_2$ (5.8 mg, 5 mol %) and $Cu(OAc)_2{\cdot}H_2O$ (5.5

mg, 20 mol %) were reacted in cyclohexanone (0.69 mL, 0.2 M) under oxygen atmosphere for 20 hr. Following flash chromatographic purification (pet. ether/Et_2O, 93:7), the title compound was isolated as a white solid (17.0 mg, 37%); R_F = 0.38 (pet. ether/Et_2O, 90:10); mp 58-59°C; FTIR (ν_{max}) 2927, 2851, 1707, 1234 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.87 (s, 1H), 6.26 (d, 1H, J = 16.1 Hz), 5.87 (ddd, 1H, J = 16.1, 7.0, 7.0 Hz), 3.82 (s, 3H), 2.52 (s, 3H), 2.52 (m, 1H), 2.24-2.18 (m, 2H), 1.80-1.77 (m, 5H), 1.47-1.31 (m, 9H), 0.93 (t, 3H, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6, 161.3, 137.6, 133.3, 130.5, 121.9, 118.9, 118.4, 51.8, 35.5, 34.5, 33.4, 31.5, 28.8, 26.9, 26.3, 22.3, 14.0; HRMS *m/z* calcd for $C_{20}H_{29}NO_3$ $[M]^+$: 331.2147. Found 331.2139.



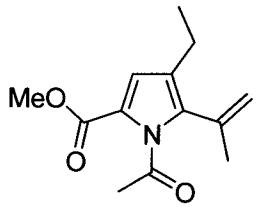
Methyl 1-acetyl-4-butyl-5-cyclohexenyl-1*H*-pyrrole-2-carboxylate (3.22)

Following general procedure D, methyl 2-acetamidoacrylate (20 mg, 0.140 mmol), 1-(hex-1-ynyl)cyclohex-1-ene (24.9 mg, 0.154 mmol), $[Cp^*Rh(MeCN)_3][SbF_6]_2$ (5.8 mg, 5 mol %) and $Cu(OAc)_2 \cdot H_2O$ (5.6 mg, 20 mol %) were reacted in cyclohexanone (0.70 mL, 0.2 M) under oxygen atmosphere for 17 hr. Following flash chromatographic purification (pet. ether/Et_2O, 95:5), the title compound was isolated as a yellow liquid (35.6 mg, 84%); R_F = 0.47 (pet. ether/Et_2O, 90:10); FTIR (ν_{max}) 2928, 1751, 1709, 1476, 1384, 1194, 1058, 763 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.80 (s, 1H), 5.72-5.70 (m, 1H), 3.81 (s, 3H), 2.51 (s, 3H), 2.31 (t, 2H, J = 7.7 Hz), 2.18 (m, 4H), 1.74-1.62 (m, 4H), 1.48 (p, 2H, J = 7.7 Hz), 1.32 (sextet, 2H, J = 7.7 Hz), 0.90 (t, 3H, J = 7.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 161.4, 139.0, 131.5, 129.7, 123.6, 121.9, 120.5, 51.7, 33.0, 30.2, 28.2, 25.6, 25.2, 22.8, 22.4, 21.8, 14.0; HRMS *m/z* calcd for $C_{18}H_{25}NO_3$ $[M]^+$: 303.1834. Found 303.1817.



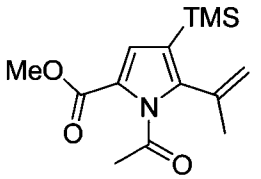
(*E*)-Methyl 1-acetyl-4-hexyl-5-styryl-1*H*-pyrrole-2-carboxylate (3.26)

Following general procedure D, methyl 2-acetamidoacrylate (20 mg, 0.140 mmol), (*E*)-dec-1-en-3-ynylbenzene (32.6 mg, 0.154 mmol), $[Cp^*Rh(MeCN)_3][SbF_6]_2$ (5.8 mg, 5 mol %) and $Cu(OAc)_2 \cdot H_2O$ (5.6 mg, 20 mol %) were reacted in cyclohexanone (0.70 mL, 0.2 M) under oxygen atmosphere for 15 hr. Following flash chromatographic purification (pet. ether/Et_2O, 94:6), the title compound was isolated as a yellow liquid (39.1 mg, 79%); R_F = 0.40 (pet. ether/Et_2O, 90:10); FTIR (ν_{max}) 2856, 1743, 1706, 1496, 1385, 1243, 1054, 959, 750, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47-7.26 (m, 5H), 7.06 (d, 1H, J = 16.5 Hz), 6.90 (s, 1H), 6.79 (d, 1H, J = 16.5 Hz), 3.84 (s, 3H), 2.58 (t, 2H, J = 7.6 Hz), 2.55 (s, 3H), 1.64 (p, 2H, J = 7.6 Hz), 1.42-1.26 (m, 6H), 0.89 (t, 3H, J = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6, 161.2, 137.0, 133.6, 133.5, 128.9, 128.3, 126.7, 126.0, 122.5, 121.3, 117.0, 51.9, 31.8, 30.2, 29.3, 28.9, 26.9, 22.7, 14.2; HRMS *m/z* calcd for $C_{22}H_{27}N_2O_3$ $[M]^+$: 353.1991. Found 353.1980.



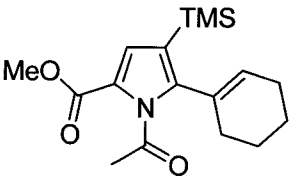
Methyl 1-acetyl-4-ethyl-5-(prop-1-en-2-yl)-1*H*-pyrrole-2-carboxylate (3.27)

Following general procedure D, methyl 2-acetamidoacrylate (20 mg, 0.140 mmol), 2-methylhex-1-en-3-yne[169] (24.9 mg, 0.154 mmol), $[Cp^*Rh(MeCN)_3][SbF_6]_2$ (5.8 mg, 5 mol %) and $Cu(OAc)_2 \cdot H_2O$ (5.6 mg, 20 mol %) were reacted in cyclohexanone (0.70 mL, 0.2 M) under oxygen atmosphere for 18 hr. Following flash chromatographic purification (pet. ether/Et_2O, 93:7), the title compound was isolated as a colorless liquid (15.7 mg, 48%); R_F = 0.40 (pet. ether/Et_2O, 90:10); FTIR (ν_{max}) 1749, 1709, 1482, 1437, 1383, 1231, 1174, 1056, 765 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.97 (s, 1H), 5.36-5-34 (m, 1H), 4.99-4.98 (m, 1H), 3.82 (s, 3H), 2.53 (s, 3H), 2.38 (q, 2H, J = 7.6 Hz), 1.99-1.98 (m, 3H), 1.14 (t, 3H, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 161.3, 137.8, 136.3, 125.2, 122.3, 120.2, 119.6, 51.8, 28.4, 23.9, 18.9, 15.4; HRMS *m/z* calcd for $C_{13}H_{17}NO_3$ $[M]^+$: 235.1208. Found 235.1194.



Methyl 1-acetyl-4-(prop-1-en-2-yl)-5-(trimethylsilyl)-1*H*-pyrrole-2-carboxylate (3.29)

Following general procedure D, methyl 2-acetamidoacrylate (20 mg, 0.140 mmol), 2-methyl-4-trimethylsilyl-1-buten-3-yne[169] (27.3 μL, 0.154 mmol), $[Cp^*Rh(MeCN)_3][SbF_6]_2$ (5.8 mg, 5 mol %) and $Cu(OAc)_2 \cdot H_2O$ (5.6 mg, 20 mol %) were reacted in cyclohexanone (0.70 mL, 0.2 M) under oxygen atmosphere for 22 hr. Upon subjection to flash chromatographic purification (pet. ether/Et_2O, 94:6), the target compound was obtained as a colorless liquid (26.8 mg, 69%); R_F = 0.36 (pet. ether/Et_2O, 90:10); FTIR (ν_{max}) 1757, 1710, 1521, 1468, 1437, 1379, 1249, 1227, 1160, 840, 759 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.87 (s, 1H), 5.34 (qd, 1H, J = 1.6, 1.3 Hz), 5.06 (d, 1H, J = 1.3 Hz), 3.83 (s, 3H), 2.58 (s, 3H), 2.01 (d, 3H, J = 1.6 Hz), 0.28 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.1, 161.3, 160.2, 140.4, 139.6, 125.9, 121.4, 116.7, 52.1, 28.4, 25.1, 0.9; HRMS *m/z* calcd for $C_{14}H_{21}N_1O_3Si$ $[M]^+$: 279.1291. Found 279.1312.

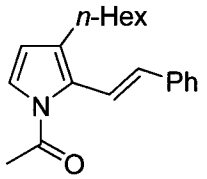


Methyl 1-acetyl-5-cyclohexenyl-4-(trimethylsilyl)-1*H*-pyrrole-2-carboxylate (3.30)

Following general procedure D, methyl 2-acetamidoacrylate (80 mg, 0.559 mmol), (Cyclohexenylethynyl)trimethylsilane (109.6 mg, 0.615 mmol), $[Cp^*Rh(MeCN)_3][SbF_6]_2$ (23.3 mg, 5 mol %) and $Cu(OAc)_2 \cdot H_2O$ (22.3 mg, 20 mol %) were reacted in cyclohexanone (2.79 mL, 0.2 M) in a test tube (15 x 1.4 cm) under oxygen atmosphere for 18 hr. Upon subjection to flash chromatographic purification (pet. ether/Et_2O, 97:3 - 96:4 - 95:5), the target C3-TMS isomer was obtained as a colorless liquid (123.7 mg, 69%); R_F = 0.36 (pet. ether/Et_2O, 95:5); FTIR (ν_{max}) 1757, 1707, 1247, 1195, 835, 758 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.96 (s, 1H), 5.78-5.77 (m, 1H), 3.82 (s, 3H), 2.51 (s, 3H), 2.16-2.14 (m, 4H), 1.72-1.64 (m, 4H), 0.19

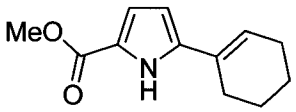
[169] Purchased from Alfa Aesar

(s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 161.2, 147.3, 131.7, 131.5, 125.8, 123.5, 118.1, 51.8, 30.7, 28.5, 25.5, 22.7, 21.6, 0.1; HRMS *m/z* calcd for $C_{17}H_{25}NO_3Si$ $[M]^+$: 319.1604. Found 319.1585.



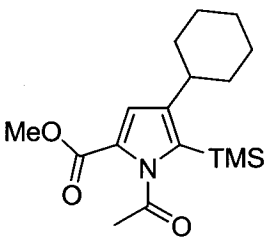
(*E*)-1-(3-hexyl-2-styryl-1*H*-pyrrol-1-yl)ethanone (3.31)

Following general procedure D, *N*-vinylacetamide[170] (53.9 mg, 0.633 mmol), (*E*)-dec-1-en-3-ynylbenzene (44.8 mg, 0.211 mmol), $[Cp^*Rh(MeCN)_3][SbF_6]_2$ (8.8 mg, 5 mol %) and $Cu(OAc)_2{\cdot}H_2O$ (8.4 mg, 20 mol %) were reacted in cyclohexanone (1.05 mL, 0.2 M) in a test tube (15 x 1.4 cm) under oxygen atmosphere for 21 hr. Following flash chromatographic purification (pet. ether/Et_2O, 93:7), the title compound was isolated as a colorless liquid (29.6 mg, 48%); R_F = 0.26 (pet. ether/Et_2O, 95:5); FTIR (ν_{max}) 1713, 1372, 1301,1282, 969, 693 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, 1H, *J* = 16.7 Hz), 7.48 (d, 1H, *J* = 7.4 Hz), 7.34 (d, 1H, *J* = 7.4 Hz), 7.33 (d, 1H, *J* = 7.4 Hz), 7.24 (d, 1H, *J* = 7.4 Hz), 7.07 (d, 1H, *J* = 3.4 Hz), 6.60 (d, 1H, J = 16.5 Hz), 6.21 (d, 1H, *J* = 3.4 Hz), 2.57 (t, 2H, J = 7.9 Hz), 2.53 (s, 3H), 1.62 (p, 2H, J = 7.9 Hz), 1.37-1.25 (m, 6H), 0.88 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 137.9, 130.5, 129.8, 128.8, 128.7, 127.4, 126.5, 120.8, 120.5, 114.3, 31.9, 30.5, 29.4, 27.0, 24.5, 22.8, 14.2; HRMS *m/z* calcd for $C_{20}H_{25}NO$ $[M]^+$: 295.1936. Found 295.1904.
Note: The product decomposed to a brown residue overnight.



Methyl 5-cyclohexenyl-1*H*-pyrrole-2-carboxylate (3.32)

A solution of methyl 5-cyclohexenyl-4-(trimethylsilyl)-1*H*-pyrrole-2-carboxylate (9.3 mg, 0.034 mmol) in 1:1 2 M aq. HCl/THF (0.34 mL, 0.1 M) was prepared in a 2 mL vial, closed tightly with a screw-cap, and stirred vigorously for 15.5 hr. The mixture was partitioned between CH_2Cl_2 and sat. aq. $NaHCO_3$ and the aqueous layer was extracted a second time with CH_2Cl_2. The combined organics were dried ($MgSO_4$) and concentrated to afford the target compound as a white solid (6.9 mg, 100%); R_F = 0.31 (pet. ether/Et_2O, 90:10); mp 84-86°C; FTIR (ν_{max}) 1680, 1252, 1237, 1147, 1051, 1004, 928, 763 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (br s, 1H), 6.86-6.85 (m, 1H), 6.20-6.19 (m, 1H), 6.15-6.12 (m, 1H), 3.84 (s, 3H), 2.35-2.31 (m, 2H), 2.22-2.18 (m, 2H), 1.77-1.74 (m, 2H), 1.67-1.64 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8, 138.8, 128.2, 123.5, 121.6, 116.4, 106.6, 51.5, 26.0, 25.5, 22.5, 22.2; HRMS *m/z* calcd for $C_{12}H_{15}NO_2$ $[M]^+$: 205.1103. Found 205.1092.

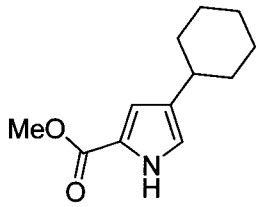


Methyl 1-acetyl-4-cyclohexyl-5-(trimethylsilyl)-1*H*-pyrrole-2-carboxylate (3.34)

Following general procedure D, methyl 2-acetamidoacrylate (40 mg, 0.279 mmol), (cyclohexylethynyl)trimethylsilane (55.4 mg, 0.307 mmol), $[Cp^*Rh(MeCN)_3][SbF_6]_2$ (11.6 mg, 5 mol %) and

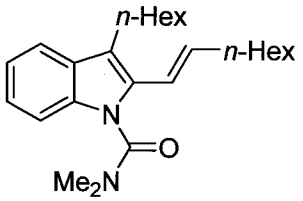
[170] Purchased from Polysciences Inc.

$Cu(OAc)_2 \cdot H_2O$ (11.2 mg, 20 mol %) were reacted in cyclohexanone (1.40 mL, 0.2 M) in a test tube (15 x 1.4 cm) under oxygen atmosphere for 20 hr. Following flash chromatographic purification (pet. ether/Et_2O, 97:3 - 96:4), the title compound was isolated as a white solid (57.0 mg, 63%); R_F = 0.45 (pet. ether/Et_2O, 95:5); mp 84-85°C; FTIR (ν_{max}) 1711, 1447, 1365, 1247, 1068, 844 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.94 (s, 1H), 3.83 (s, 1H), 2.64-2.63 (m, 1H), 2.55 (s, 3H), 1.81-1.71 (m, 5H), 1.36-1.22 (m, 5H), 0.31 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6, 161.2, 142.8, 136.3, 126.1, 119.8, 51.9, 36.3, 35.5, 28.7, 26.9, 26.2, 1.4; HRMS *m/z* calcd for $C_{17}H_{27}NO_3Si$ $[M]^+$: 321.1760. Found 321.1737.



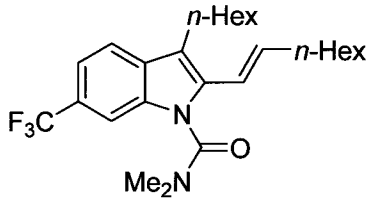
Methyl 4-cyclohexyl-1*H*-pyrrole-2-carboxylate (3.35)

To an open solution of methyl 1-acetyl-4-cyclohexyl-5-(trimethylsilyl)-1*H*-pyrrole-2-carboxylate (20.3 mg, 0.0631 mmol) in dry, degassed THF (0.63 mL, 0.1 M) was added TBAF (126 μL, 1.0 M solution in THF, 0.126 mmol). The flask was sealed and the reaction stirred for 1.5 hr. The mixture was partitioned between CH_2Cl_2 and sat. aq. NH_4Cl and the aqueous layer was extracted a second time with CH_2Cl_2. The combined organics were dried ($MgSO_4$) and concentrated. Flash chromatographic purification (pet. ether/Et_2O, 88:12 - 85:15) of the residue thus obtained afforded the target compound as a white solid (13.1 mg, 100%); R_F = 0.32 (pet. ether/Et_2O, 75:25); mp 115-117°C; FTIR (ν_{max}) 3303, 1696, 1441, 1397, 1277, 1202, 1119, 965, 770 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.96 (br s, 1H), 6.79 (dd, 1H, J = 2.1, 2.1 Hz), 6.75 (dd, 1H, J = 2.1, 2.1 Hz), 3.83 (s, 3H), 2.49-2.42 (m, 1H), 1.94-1.91 (m, 2H), 1.80-1.68 (m, 3H), 1.38-1.18 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8, 133.1, 122.1, 119.4, 113.6, 51.5, 36.1, 34.6, 26.6, 26.3; HRMS *m/z* calcd for $C_{12}H_{17}NO_2$ $[M]^+$: 207.1259. Found 207.1244.



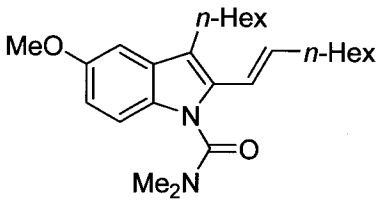
(*E*)-3-Hexyl-*N*,*N*-dimethyl-2-(oct-1-enyl)-1*H*-indole-1-carboxamide (3.36)

Following general procedure E, 1,1-dimethyl-3-phenylurea (41.0 mg, 0.250 mmol), (*E*)-hexadec-7-en-9-yne (60.6 mg, 0.275 mmol), $[Cp^*Rh(MeCN)_3][SbF_6]_2$ (10.4 mg, 5 mol %) and $Cu(OAc)_2 \cdot H_2O$ (104.8 mg, 2.1 equiv.) were reacted in toluene (1.25 mL, 0.2 M) for 19.5 hr. Following flash chromatographic purification (pet. ether/Et_2O, 80:20), the title compound was isolated as a yellow liquid (70.4 mg, 74%); R_F = 0.22 (pet. ether/Et_2O, 80:20); FTIR (ν_{max}) 1701, 1457, 1388, 1321, 1198, 1099, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 (br d, 1H, *J* = 7.6 Hz), 7.30 (br d, 1H, *J* = 8.0 Hz), 7.20 (ddd, 1H, *J* = 7.6, 7.0, 1.2 Hz), 7.13 (ddd, 1H, *J* = 8.0, 7.0, 1.1 Hz), 6.45 (ddd, 1H, *J* = 16.1, 1.4, 1.4 Hz), 5.92 (dt, 1H, *J* = 16.1, 7.0 Hz), 3.36-2.48 (br s, 6H), 2.75 (t, 2H, *J* = 7.8 Hz), 2.24 (tdd, 2H, *J* = 8.0, 7.0, 1.1 Hz), 1.66-1.27 (m, 16H), 0.90 (t, 3H, *J* = 7.0 Hz), 0.88 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0, 135.8, 133.9, 132.5, 129.1, 123.3, 120.8, 119.1, 118.5, 117.6, 110.9, 37.4 (br s), 34.0, 31.9, 31.9, 30.7, 29.6, 29.5, 29.0, 24.5, 22.8, 22.8, 14.2, 14.2; HRMS *m/z* calcd for $C_{25}H_{38}N_2O$ $[M]^+$: 382.2984. Found 382.2973.



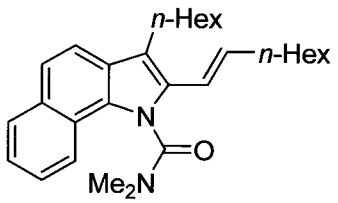
(*E*)-3-Hexyl-*N*,*N*-dimethyl-2-(oct-1-enyl)-6-(trifluoromethyl)-1*H*-indole-1-carboxamide (3.37)

Following general procedure E, 1,1-dimethyl-3-(3-(trifluoromethyl)phenyl)urea (58.1 mg, 0.250 mmol), (*E*)-hexadec-7-en-9-yne (60.6 mg, 0.275 mmol), $[Cp^*Rh(MeCN)_3][SbF_6]_2$ (10.4 mg, 5 mol %) and $Cu(OAc)_2 \cdot H_2O$ (104.8 mg, 2.1 equiv.) were reacted in toluene (1.25 mL, 0.2 M) for 19.5 hr. Following flash chromatographic purification (pet. ether/Et_2O, 93:7), the title compound was isolated as a yellow liquid (69.7 mg, 62%); R_F = 0.29 (pet. ether/Et_2O, 90:10); FTIR (ν_{max}) 2928, 2856, 1703, 1445, 1388, 1334, 1270, 1163, 1119, 1058 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.60-7.58 (m, 2H), 7.36 (d, 1H, J = 8.8 Hz), 6.45 (d, 1H, J = 16.1 Hz), 6.00 (dt, 1H, J = 16.1, 7.0 Hz), 3.51-2.45 (br s, 6H), 2.76 (t, 2H, J = 7.6 Hz), 2.71 (dt, 2H, J = 7.0, 6.9 Hz), 1.65-1.58 (m, 2H), 1.51-1.42 (m, 2H), 1.42-1.19 (m, 12H), 0.91 (t, 3H, J = 6.7 Hz), 0.88 (t, 3H, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2, 135.8, 135.0, 134.7, 131.3, 125.2 (q, J = 271.6 Hz), 125.1 (q, J = 32.0 Hz), 119.4, 118.1, 117.6 (q, J = 3.6 Hz), 117.2, 108.4 (q, J = 4.4 Hz), 37.5 (br s), 34.0, 31.8, 31.8, 30.6, 29.5, 29.4, 29.0, 24.4, 22.8, 22.8, 14.2, 14.2; ^{19}F NMR (377 MHz, $CDCl_3$) δ -60.67 (s, 3F); HRMS *m/z* calcd for $C_{26}H_{37}N_2OF_3$ $[M]^+$: 450.2858. Found 450.2837.



(*E*)-3-Hexyl-5-methoxy-*N*,*N*-dimethyl-2-(oct-1-enyl)-1*H*-indole-1-carboxamide (3.38)

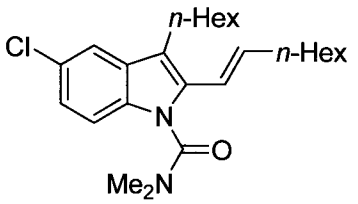
Following general procedure E, 3-(4-methoxyphenyl)-1,1-dimethylurea (48.6 mg, 0.250 mmol), (*E*)-hexadec-7-en-9-yne (60.6 mg, 0.275 mmol), $[Cp^*Rh(MeCN)_3][SbF_6]_2$ (10.4 mg, 5 mol %) and $Cu(OAc)_2 \cdot H_2O$ (104.8 mg, 2.1 equiv.) were reacted in toluene (1.25 mL, 0.2 M) for 19 hr. Following flash chromatographic purification (pet. ether/Et_2O, 75:25), the title compound was isolated as a yellow liquid (61.1 mg, 59%); R_F = 0.21 (pet. ether/Et_2O, 75:25); FTIR (ν_{max}) 2925, 2855, 1688, 1387, 1233, 1094, 1039, 802, 757 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, 1H, J = 8.8 Hz), 6.95 (d, 1H, J = 2.3 Hz), 6.84 (dd, 1H, J = 8.8, 2.3 Hz), 6.43 (d, 1H, J = 16.1 Hz), 5.89 (dt, 1H, J = 16.1, 7.0 Hz), 3.86 (s, 3H), 2.91 (br s, 6H), 2.71 (t, 2H, J = 7.7 Hz), 2.23 (dt, 2H, J = 7.0, 6.8 Hz), 1.65-1.58 (m, 2H), 1.49-1.42 (m, 2H), 1.42-1.18 (m, 12H), 0.90 (t, 3H, J = 6.6 Hz), 0.88 (t, 3H, J = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1, 154.9, 133.8, 133.4, 131.0, 129.6, 118.6, 117.4, 112.5, 111.8, 101.5, 56.0, 37.5 (br s), 33.9, 31.9, 31.9, 30.5, 29.6, 29.5, 29.0, 24.5, 22.8, 22.8, 14.2, 14.2; HRMS *m/z* calcd for $C_{26}H_{40}N_2O_2$ $[M]^+$: 412.3090. Found 412.3103.



(*E*)-3-Hexyl-*N*,*N*-dimethyl-2-(oct-1-enyl)-1*H*-benzo[*g*]indole-1-carboxamide (3.39)

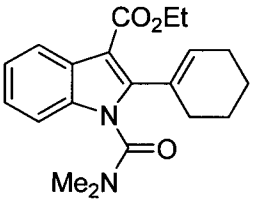
Following general procedure E, 1,1-dimethyl-3-(naphthalen-1-yl)urea (53.6 mg, 0.250 mmol), (*E*)-hexadec-7-en-9-yne (60.6 mg, 0.275 mmol), $[Cp^*Rh(MeCN)_3][SbF_6]_2$ (10.4 mg, 5 mol %) and $Cu(OAc)_2 \cdot H_2O$ (104.8 mg,

2.1 equiv.) were reacted in toluene (1.25 mL, 0.2 M) for 22 hr. Following flash chromatographic purification (pet. ether/Et_2O, 89:11 - 87:13), the title compound was isolated as a yellow liquid (64.5 mg, 60%); R_F = 0.16 (pet. ether/Et_2O, 90:10); FTIR (ν_{max}) 2926, 2855, 1696, 1460, 1388, 1263, 1140, 805, 745 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, 1H, J = 8.3 Hz), 7.89 (d, 1H, J = 7.8 Hz), 7.63 (d, 1H, J = 8.6 Hz), 7.53 (d, 1H, J = 8.6 Hz), 7.46 (ddd, 1H, J = 7.8, 7.0, 1.2 Hz), 7.39 (ddd, 1H, J = 8.3, 7.0, 1.2 Hz), 6.43 (d, 1H, J = 16.1 Hz), 6.13 (dt, 1H, J = 16.1, 7.0 Hz), 3.28 (s, 3H), 2.84 (t, 2H, J = 8.8 Hz), 2.39 (s, 3H), 2.29-2.23 (m, 2H), 1.72-1.60 (m, 2H), 1.52-1.45 (m, 2H), 1.45-1.21 (m, 12H), 0.91 (t, 3H, J = 6.7 Hz), 0.88 (t, 3H, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5, 134.0, 131.5, 130.9, 129.2, 128.5, 126.1, 125.2, 124.0, 122.0, 121.9, 119.8, 118.8, 118.2, 117.6, 37.4, 37.1, 34.1, 31.9, 31.9, 31.1, 29.7, 29.5, 29.0, 24.5, 22.8, 14.3, 14.2; HRMS *m/z* calcd for $C_{29}H_{40}N_2O$ $[M]^+$: 432.3141. Found 432.3128.



(*E*)-5-Chloro-3-hexyl-*N*,*N*-dimethyl-2-(oct-1-enyl)-1*H*-indole-1-carboxamide (3.40)

Following general procedure E, 3-(4-chlorophenyl)-1,1-dimethylurea (55.1 mg, 0.250 mmol), (*E*)-hexadec-7-en-9-yne (60.6 mg, 0.275 mmol), $[Cp^*Rh(MeCN)_3][SbF_6]_2$ (10.4 mg, 5 mol %) and $Cu(OAc)_2 \cdot H_2O$ (104.8 mg, 2.1 equiv.) were reacted in toluene (1.25 mL, 0.2 M) for 20 hr. Following flash chromatographic purification (pet. ether/Et_2O, 80:20), the title compound was isolated as a yellow liquid (55.4 mg, 53%); R_F = 0.31 (pet. ether/Et_2O, 75:25); FTIR (ν_{max}) 2928, 2856, 1695, 1456, 1387, 1323, 1198, 1063, 798 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, 1H, J = 1.7 Hz), 7.22 (d, 1H, J = 8.6 Hz), 7.14 (dd, 1H, J = 8.6, 1.7 Hz), 6.42 (d, 1H, J = 16.1 Hz), 5.94 (dt, 1H, J = 16.1, 7.0 Hz), 3.51-2.43 (br s, 6H), 2.70 (t, 2H, J = 7.6 Hz), 2.71 (dt, 2H, J = 7.0, 6.9 Hz), 1.64-1.56 (m, 2H), 1.49-1.42 (m, 2H), 1.42-1.18 (m, 12H), 0.90 (t, 3H, J = 6.5 Hz), 0.89 (t, 3H, J = 6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 134.9, 134.1, 133.8, 130.1, 126.5, 123.4, 118.6, 118.2, 116.9, 112.0, 37.5 (br s), 33.9, 31.8, 31.8, 30.6, 29.5, 29.5, 29.0, 24.4, 22.8, 22.8, 14.2, 14.2; HRMS *m/z* calcd for $C_{25}H_{37}N_2OCl$ $[M]^+$: 416.2594. Found 416.2588.

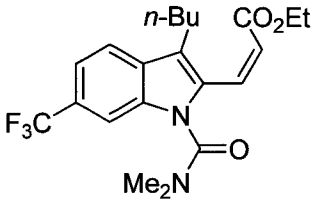


Ethyl 2-cyclohexenyl-1-(dimethylcarbamoyl)-1*H*-indole-3-carboxylate (3.42)

Following general procedure E, 1,1-dimethyl-3-phenylurea (41.1 mg, 0.250 mmol), ethyl 3-cyclohexenylpropiolate[171] (49.0 mg, 0.275 mmol), $[Cp^*Rh(MeCN)_3][SbF_6]_2$ (10.4 mg, 5 mol %) and $Cu(OAc)_2 \cdot H_2O$ (104.8 mg, 2.1 equiv.) were reacted in toluene (1.25 mL, 0.2 M) for 20 hr. Following flash chromatographic purification (pet. ether/Et_2O, 74:26 - 70:30), the title compound was isolated as a colorless paste (48.1 mg, 57%); R_F = 0.20 (pet. ether/Et_2O, 75:25); FTIR (ν_{max}) 1701, 1454, 1383, 1262, 1163, 1114, 790, 751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.19-8.15 (m, 1H), 7.28-7.24 (m, 3H), 5.88-5.86 (m, 1H), 4.38 (q, J = 7.1 Hz), 3.20 (br s, 3H), 2.79 (br s, 3H), 2.46 (br m, 2H), 2.21 (br m, 2H), 1.80-1.70 (m, 4H), 1.43 (t, 3H, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0, 152.8, 147.2, 134.2, 130.7, 126.8, 123.7, 122.9, 122.2, 110.8,

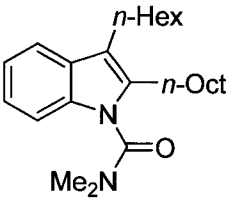
[171] Obtained as a generous gift from Kevin M. N. Burgess, who prepared it by the action of *n*-BuLi upon 1-ethynylcyclohex-1-ene, followed by treatment with ethyl chloroformate.

106.3, 60.0, 38.4, 36.8, 28.8, 25.7, 22.8, 21.8, 14.6; HRMS *m/z* calcd for $C_{20}H_{24}N_2O_3$ $[M]^+$: 340.1787. Found 340.1782.



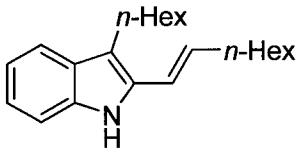
(*Z*)-Ethyl 3-(3-butyl-1-(dimethylcarbamoyl)-6-(trifluoromethyl)-1*H*-indol-2-yl)acrylate (3.44)

Following general procedure E, 1,1-dimethyl-3-(3-(trifluoromethyl)phenyl)urea (58.1 mg, 0.250 mmol), (*Z*)-ethyl non-2-en-4-ynoate yne (49.6 mg, 0.275 mmol), $[Cp^*Rh(MeCN)_3][SbF_6]_2$ (10.4 mg, 5 mol %) and $Cu(OAc)_2{\cdot}H_2O$ (104.8 mg, 2.1 equiv.) were reacted in toluene (1.25 mL, 0.2 M) for 20 hr. Following flash chromatographic purification (pet. ether/Et_2O, 75:25 - 70:30), the title compound was isolated as a yellow liquid (79.2 mg, 77%, >95:5 by NMR). The minor impurity was removed by Semi-Preparatory HPLC on a Waters 600 with 2487 Dual λ Absorbance Detector with using a Waters XTerra Prep RP_{18} Column (5 μm, 10 x 150 mm). The product t_r was 10.0 min running MeCN/H_2O, 50:50 - 90:10 over 30 min. Rotary evaporation of the solvents was conducted with added toluene for azeotropic removal of residual H_2O; R_F = 0.27 (pet. ether/Et_2O, 75:25); FTIR (ν_{max}) 1722, 1695, 1445, 1389, 1334, 1271, 1180, 1119, 1059 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, 1H, *J* = 8.3 Hz), 7.60 (s, 1H), 7.40 (d, 1H, *J* = 8.3 Hz), 7.04 (d, 1H, *J* = 12.3 Hz), 6.13 (d, 1H, *J* = 12.3 Hz), 4.12 (q, 2H, *J* = 7.1 Hz), 3.04 (s, 6H), 2.70 (t, 2H, *J* = 7.7 Hz), 1.63-1.56 (m, 2H), 1.34 (sextet, 2H, *J* = 7.6 Hz), 1.22 (t, 3H, *J* = 7.1 Hz), 0.90 (t, 3H, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 154.0, 135.2, 132.8, 131.7, 130.9, 126.2 (q, *J* = 32.0 Hz), 125.0 (q, *J* = 271.9 Hz), 123.1, 122.0, 120.3, 117.9 (q, *J* = 3.6 Hz), 109.6 (q, *J* = 4.4 Hz), 60.6, 38.5 (br s), 32.3, 24.5, 22.8, 14.3, 14.0; ^{19}F NMR (377 MHz, $CDCl_3$) δ -60.89 (s, 3F); HRMS *m/z* calcd for $C_{21}H_{25}N_2O_3F_3$ $[M]^+$: 410.1817. Found 410.1791.



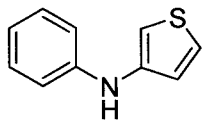
3-Hexyl-*N*,*N*-dimethyl-2-octyl-1*H*-indole-1-carboxamide (3.48)

To a flask containing (*E*)-3-Hexyl-*N*,*N*-dimethyl-2-(oct-1-enyl)-1*H*-indole-1-carboxamide (45.1 mg, 0.118 mmol) and palladium 10% on activated carbon (6.3 mg, 5 mol %) under argon was charged 99% ethanol (1.18 mL, 0.1 M). The flask was purged with hydrogen gas and stirred vigorously under a hydrogen balloon for 25 hr. The reaction mixture was filtered over celite and rinsed with EtOAc. Following concentration to dryness, the residue was dissolved in $CHCl_3$ and filtered through silica to afford, after concentration, the title compound as a yellow liquid (45.3 mg, 100%); R_F = 0.52 (pet. ether/Et_2O, 75:25); FTIR (ν_{max}) 2926, 2855, 1689, 1459, 1390, 1199, 1098, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (ddd, 1H, *J* = 7.4, 1.2, 1.2 Hz), 7.19-7.10 (m, 3H), 3.03 (br s, 6H), 2.83 (br s, 2H), 2.66 (t, 2H, *J* = 7.6 Hz), 1.65-1.58 (m, 2H), 1.55-1.47 (m, 2H), 1.42-1.25 (m, 16H), 1.66-1.27 (m, 16H), 0.89 (t, 3H, *J* = 7.0 Hz), 0.87 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 136.6, 135.1, 129.1, 122.1, 120.5, 118.9, 116.2, 110.8, 37.6 (br s), 32.0, 31.9, 30.8, 30.2, 29.6, 29.5, 29.4, 24.8, 24.8, 24.4, 22.8, 22.8, 14.2, 14.2; HRMS *m/z* calcd for $C_{25}H_{40}N_2O$ $[M]^+$: 384.3141. Found 384.3147.



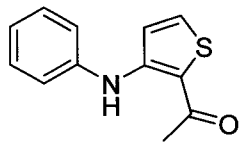
(*E*)-3-Hexyl-2-(oct-1-enyl)-1*H*-indole (3.49)

A solution of (*E*)-3-Hexyl-*N,N*-dimethyl-2-(oct-1-enyl)-1*H*-indole-1-carboxamide (49.3 mg, 0.129 mmol) in 3:1 EtOH/sat. aq. KOH (0.43 mL, 0.3 M) was prepared in a 2 mL vial, closed tightly with a screw-cap, and stirred at 100°C for 18.5 hr. The mixture was partitioned between CH_2Cl_2 and sat. aq. NH_4Cl and the aqueous layer was extracted a second time with CH_2Cl_2. The combined organics were dried ($MgSO_4$) and concentrated. Flash chromatographic purification (pet. ether/Et_2O/NEt_3, 96:5:1) of the residue thus obtained afforded the target compound as a yellow liquid (32.0 mg, 80%); R_F = 0.80 (pet. ether/Et_2O/NEt_3, 96:5:1); FTIR (ν_{max}) 2924, 1525, 1464, 1448, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (br s, 1H), 7.52 (d, 1H, *J* = 7.9 Hz), 7.26 (d, 1H, *J* = 7.8 Hz), 7.13 (ddd, 1H, *J* = 7.8, 7.1, 1.1 Hz), 7.05 (ddd, 1H, *J* = 7.9, 7.1, 1.0 Hz), 6.49 (d, 1H, *J* = 16.1 Hz), 5.93 (dt, 1H, *J* = 16.1, 7.0 Hz), 2.74 (t, 2H, *J* = 7.5 Hz), 2.26 (td, 2H, *J* = 7.0, 6.5 Hz), 1.66-1.58 (m, 2H), 1.52-1.45 (m, 2H), 1.40-1.13 (m, 16H), 0.90 (t, 3H, *J* = 7.0 Hz), 0.88 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.3, 132.3, 129.3, 128.8, 122.3, 119.3, 119.2, 119.0, 115.2, 110.4, 33.4, 31.9, 31.9, 31.2, 29.6, 29.5, 29.0, 24.1, 22.8, 22.8, 14.3, 14.3; HRMS *m/z* calcd for $C_{22}H_{33}N$ $[M]^+$: 311.2613. Found 311.2627.
Note: The product's instability on silica gel also requires that TLC plates be soaked down with NEt_3 prior to use.



Phenyl-thiophen-3-yl-amine (4.4)

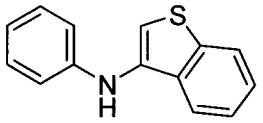
Prepared following the method of Hooper *et al.*[172] and exhibited spectral data identical to previous reports[173] (60%).



1-(3-(Phenylamino)thiophen-2-yl)ethanone (4.5)

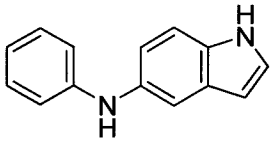
Following general procedure F, reaction of analine (227 mg, 2.44 mmol), 2-acetyl-3-bromothiophene (500 mg, 2.44 mmol), Cs_2CO_3 (1.11 g, 3.42 mmol), Pd_2dba_3 (112 mg, 5 mol %), and BINAP (152 mg, 10 mol %) in toluene (25 mL) afforded after flash column chromatography (pet. ether/EtOAc, 97:3), the coupled product as a yellow oil (125 mg, 24%); R_F = 0.26 (pet. ether/EtOAc, 95:5); FTIR (ν_{max}) 3268, 1614, 1591, 1558, 1380, 1245 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.10 (br s, 1H), 7.36 (d, 1H, *J* = 5.5 Hz), 7.33 (ddd, 2H, *J* = 7.4, 7.4, 1.1 Hz), 7.19 (dd, 2H, *J* = 7.4, 1.1 Hz), 7.11 (d, 1H, *J* = 5.5 Hz), 7.08 (ddd, 2H, *J* = 7.4, 7.4, 1.1 Hz), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.5, 151.9, 141.1, 132.4, 129.5, 123.7, 121.1, 118.0, 113.5, 28.7; HRMS *m/z* calcd for $C_{12}H_{11}NOS$ $[M]^+$: 217.0561. Found 217.0569.

[172] Hooper, M. W.; Utsunomiya, M.; Hartwig, J. F. *J. Org. Chem.* **2003,** *68,* 2861-2873.
[173] Charles, M. D.; Schultz, P.; Buchwald, S. L. *Org. Lett.* **2005,** *7,* 3965-3968.



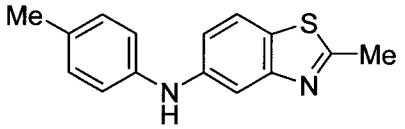
4-Benzo[*b*]thiophen-3-yl-phenyl-amine (4.6)

Following general procedure F, reaction of analine (18 mg, 0.188 mmol), 3-bromothianaphthene (40 mg, 0.188 mmol), Cs_2CO_3 (86 mg, 0.26 mmol), Pd_2dba_3 (8.6 mg, 5 mol %), and BINAP (12 mg, 10 mol %) in toluene (2 mL) furnished the title compound (13 mg, 31%). Spectral data was identical to previous reports[173]



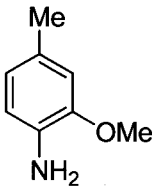
(1*H*-Indol-5-yl)-phenyl-amine (4.7)

Prepared following the method of Charles *et al.*[173] and exhibited identical spectral data (86%).



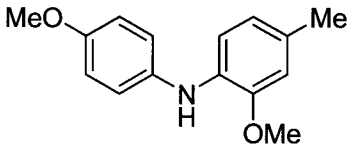
(2-Methyl-benzothiazol-5-yl)-*p*-tolyl-amine (4.8)

Prepared following the method of Charles *et al.*[173] and exhibited identical spectral data (74%).



2-Methoxy-4-methylaniline (4.9)

Prepared following the method of Knölker *et al.*[174] and exhibited spectral data identical to previous reports[175] (98%).



***N*-(4-Methoxyphenyl)-*N*-(2-methoxy-4-methylphenyl)amine (4.10)**

Following general procedure G, reaction of 2-methoxy-4-methylaniline (700 mg, 5.10 mmol), 4-bromoanisole (954 mg, 5.10 mmol), NaO*t*Bu (687 mg, 7.14 mmol), Pd_2dba_3 (47 mg, 1 mol %), and DavePhos (81 mg, 4 mol %) in dioxane (17 mL) furnished the title compound (1.10 g, 89%). Spectral data was identical to previous reports.[176]

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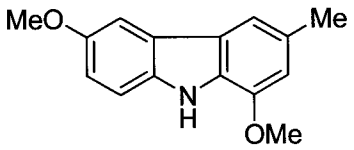
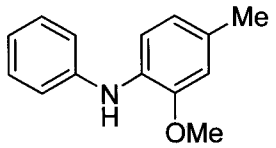
[174] Knölker, H. -J.; Bauermeister, M. *J. Chem. Soc., Chem. Commun.* **1990,** 664-665.
[175] Okuyama, M.; Laman, H.; Kingsbury, S. R.; Visintin, C.; Leo, E.; Eward, K. L.; Stoeber, K.; Boshoff, C.; Williams, G. H.; Selwood, D. L. *Nat. Methods* **2007,** *4,* 153-159.
[176] Bernal, P.; Benavides, A.; Bautista, R.; Tamariz, J. *Synthesis* **2007,** 1943-1948.



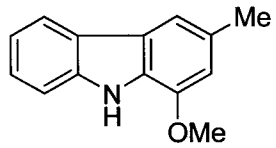
Clausenine (4.2)

Following general procedure H, reaction of *N*-(4-methoxyphenyl)-*N*-(2-methoxy-4-methylphenyl)amine (150 mg, 0.617 mmol), $Pd(OAc)_2$ (2.8 mg, 2 mol %), and K_2CO_3 (8.5 mg, 10 mol %) in Pivalic acid (0.55 g) furnished the title compound (118 mg, 79%). Spectral data was identical to previous reports.[177]



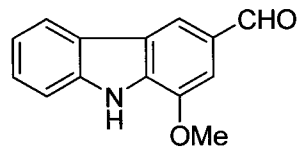
(2-Methoxy-4-methylphenyl)phenylamine (4.11)

Following general procedure G, reaction of 2-methoxy-4-methylaniline (700 mg, 5.10 mmol), bromobenzene (801 mg, 5.10 mmol), NaO*t*Bu (687 mg, 7.14 mmol), Pd_2dba_3 (47 mg, 1 mol %), and DavePhos (81 mg, 4 mol %) in dioxane (17 mL) furnished the title compound (1.05 g, 96%). Spectral data was identical to previous reports.[177]



Murrayafoline A (4.1)

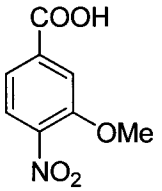
Following general procedure H, reaction of (2-Methoxy-4-methylphenyl)phenylamine (107 mg, 0.500 mmol), $Pd(OAc)_2$ (3.4 mg, 3 mol %), and K_2CO_3 (6.9 mg, 10 mol %) in Pivalic acid (0.44 g) furnished the title compound (53 mg, 50%). Spectral data was identical to previous reports.[176]



Murrayanine (4.12)

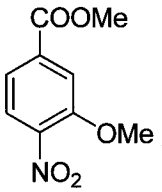
Synthesized following the procedure of Krahl *et al.*[178] for the preparation of Clauszoline-K and exhibited spectral data identical to previous reports (77%).[176]

[177] Benavides, A.; Peralta J.; Delgado, F.; Tamariz, J. *Synthesis* **2004,** 2499-2504.
[178] Krahl, M. P.; Jäger, A.; Krause, T.; Knölker, H. -J. *Org. Biomol. Chem.* **2006,** *4,* 3215-3219.



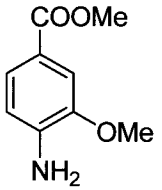
3-Methoxy-4-nitrobenzoic acid (4.13)

Prepared following the method of Baret *et al.* [179] and exhibited identical spectral data (53%).



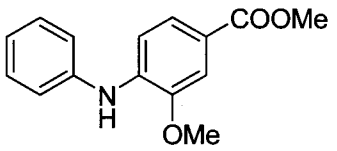
Methyl 3-methoxy-4-nitrobenzoate (4.14)

Prepared following the method of Baret *et al.*[179] and exhibited identical spectral data (98%).



Methyl 4-amino-3-methoxybenzoate (4.15)

Prepared following the method of Baret *et al.*[179] except that the product was obtained as a pure white solid without purification by recrystallization. The compound exhibited identical spectral data (99%).



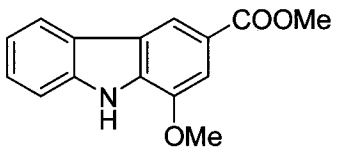
Methyl 3-methoxy-4-(phenylamino)benzoate (4.16)

Following general procedure G, reaction of methyl 4-amino-3-methoxybenzoate (50 mg, 0.276 mmol), bromobenzene (43 mg, 0.276 mmol), NaO*t*Bu (37 mg, 0.39 mmol), Pd_2dba_3 (13 mg, 1 mol %), and DavePhos (22 mg, 4 mol %) in dioxane (1.2 mL) furnished the title compound (34 mg, 48%). Spectral data was identical to previous reports.[180]

OR

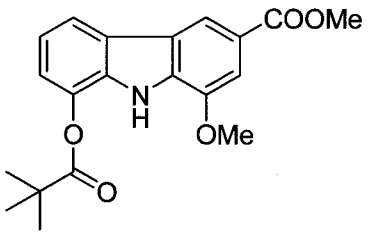
Following general procedure G, reaction of methyl 4-amino-3-methoxybenzoate (30 mg, 0.17 mmol), bromobenzene (23 mg, 0.15 mmol), K_2CO_3 (31 mg, 0.23 mmol), Pd_2dba_3 (3.4 mg, 2.5 mol %), and X-Phos (7.2 mg, 10 mol %) in toluene (0.9 mL) furnished the title compound (29 mg, 76%).

[179] Baret, P.; Beaujolais, V.; Béguin, C.; Gaude, D.; Pierre, J.-L.; Serratrice, G. *Eur. J. Inorg. Chem.* **1998,** 613-619.
[180] Zempoalteca, A.; Tamariz, J *Heterocycles* **2003,** *57,* 259-267.



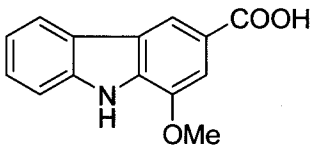
Mukonine (4.3)

Following general procedure C, reaction of methyl 3-methoxy-4-(phenylamino)benzoate (30 mg, 0.117 mmol), $Pd(OAc)_2$ (2.6 mg, 10 mol %), and K_2CO_3 (1.6 mg, 10 mol %) in Pivalic acid (0.10 g) furnished the title compound (27 mg, 91%). Spectral data was identical to previous reports.[181]



Methyl 1-methoxy-8-(pivaloyloxy)-9*H*-carbazole-3-carboxylate (4.17)

Following general procedure C, reaction of methyl 3-methoxy-4-(phenylamino)benzoate (30 mg, 0.12 mmol), $Pd(OAc)_2$ (4 mg, 15 mol %), and K_2CO_3 (1.6 mg, 10 mol %) in Pivalic acid (0.10 g) afforded after flash column chromatography (pet. ether/EtOAc, 85:15), the coupled, pivalated product as a colorless liquid (3 mg, 7%); R_F = 0.38 (pet. ether/EtOAc, 80:20); FTIR (ν_{max}) 3325, 2962, 2932, 1749, 1709, 1346, 1242, 1215, 1118, 758 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.45 (dd, 1H, J = 1.2, 0.6 Hz), 8.23 (br s, 1H), 7.95 (ddd, 1H, J = 7.3, 1.3, 0.6 Hz), 7.61 (d, 1H, J = 1.2 Hz), 7.28-7.21 (m, 2H), 4.07 (s, 3H), 3.98 (s, 3H), 1.49 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.7, 167.9, 145.4, 136.6, 133.1, 131.9, 126.7, 124.0, 122.7, 120.7, 118.6, 118.3, 116.4, 107.3, 55.9, 52.2, 39.7, 27.5; HRMS *m/z* calcd for $C_{20}H_{21}NO_5$ $[M]^+$: 355.1420. Found 355.1416.



Mukoeic acid (4.18)

Synthesized following the procedure of Krahl *et al.*[178] for the preparation of Clausine N and exhibited spectral data identical to previous reports (81%).[182]

[181] Kuwahara, A.; Nakano, K.; Nozaki K. *J. Org. Chem.* **2005,** *70,* 413-419.
[182] Bringmann, G.; Tasler, S.; Endress, H.; Peters, K.; Peters, E. -M. *Synthesis* **1998,** 1501-1505.