Aryl−Aryl Bond Formation by Transition-Metal-Catalyzed Direct Arylation

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Contents

1. Introduction

The biaryl structural motif is a predominant feature in many pharmaceutically relevant and biologically active compounds. As a result, for over a century[1] organic chemists have sought to develop new and more efficient aryl−aryl bond-forming methods. Although there exist a variety of routes for the construction of aryl−aryl bonds, arguably the most common method is through the use of transition-metal-mediated reactions.[2−4] While earlier reports focused on the use of stoichiometric quantities of a transition metal to carry out the desired transformation, modern methods of transition-metal-catalyzed aryl−aryl coupling have focused on the development of high-yielding reactions achieved with excellent selectivity and high functional group tolerance under

mild reaction conditions. Typically, these reactions involve either the coupling of an aryl halide or pseudohalide with an organometallic reagent (Scheme 1), or the homocoupling of two aryl halides or two organometallic reagents. Although a number of improvements have developed the former process into an industrially very useful and attractive method for the construction of aryl−aryl bonds, the need still exists for more efficient routes whereby the same outcome is accomplished, but with reduced waste and in fewer steps. In particular, the obligation to use coupling partners that are both activated is wasteful since it necessitates the installation and then subsequent disposal of stoichiometric activating agents. Furthermore, preparation of preactivated aryl substrates often requires several steps, which in itself can be a time-consuming and economically inefficient process.

An attractive alternative to this approach is to treat the aryl C−H bond as a functional group, in analogy to a carbon−metal or carbon−halogen bond. The simplest approach would involve the coupling of two aryl C−H bonds to give the corresponding biaryl product (Scheme 2), although this process is unfavorable from a thermodynamic perspective due to the high bond strength of an aryl C−H bond (e.g., the homocoupling of benzene to give biphenyl and hydrogen is thermodynamically disfavored by 13.8 kJ/mol).[5] Furthermore, while such an approach is alluring, the ubiquitous and diverse nature of C−H bonds in complex organic compounds makes a regioselective oxidative coupling of this type a formidable challenge.

One solution which addresses the thermodynamic issue as well as the need for stoichiometric activating agents on both coupling partners is to use a preactivated aryl substrate as one coupling partner and a simple unactivated aryl substrate as the other (Scheme 3). Although the advantages of this strategy for aryl−aryl coupling have made it a popular topic of research since the first reports over 20 years ago, the more subtle issue of C−H bond regioselectivity remains unsolved in some systems.

While the coupling of an aryl halide or pseudohalide with an organometallic reagent is commonly referred to as a cross-coupling reaction, several terms such as C−H (bond) activation, C−H (bond) functionalization, cross-dehalogenative coupling, and catalytic direct arylation have been used to describe the corresponding coupling of an aryl halide or pseudohalide with a simple arene (Scheme 3).[6−8] Although the former two terms are more prevalent in the literature, we have elected to use the term direct arylation, which we define as the direct coupling of a nonactivated aryl C−H bond with an activated arene. This term best describes the overall process illustrated in Scheme 3, while additionally preventing any erroneous implications regarding the mechanistic pathway by which the process occurs.

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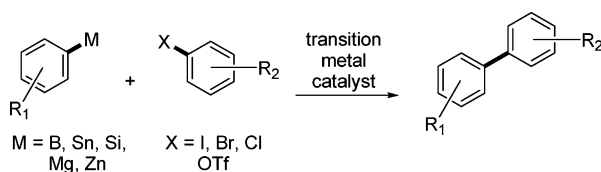
Dino Alberico was born in Hamilton, Ontario, Canada, in 1976. He received his B.Sc. degree from McMaster University in 1999. In 2001 he received his M.Sc. degree from the University of Guelph under the supervision of Adrian L. Schwan, where he studied Diels–Alder reactions of α,β-unsaturated sulfinate esters. He then joined the research group of Mark Lautens at the University of Toronto and received his Ph.D. degree in 2005. His research focused on norbornene-mediated palladium-catalyzed annulation reactions. He is currently pursuing postdoctoral work at the Université de Montréal with André B. Charette.

Mark E. Scott was born in Simcoe, Ontario, Canada, in 1977. He received his bachelor degree (honors) in engineering chemistry at Queen's University in 2000. In 2002, he received his M.Sc.Eng. in chemical engineering from Queen's University under the supervision of Profs. Scott Parent and Ralph Whitney. He is currently a Ph.D. candidate in Mark Lautens' research group at the University of Toronto, where he is studying the Lewis acid-mediated ring expansion of methylenecyclopropanes. He has been the recipient of an NSERC Postgraduate (M.Sc.Eng.) Scholarship and an NSERC Postgraduate (Ph.D.) Scholarship. He will be pursuing his postdoctoral studies at Harvard University under the supervision of Prof. David A. Evans following the completion of his Ph.D.
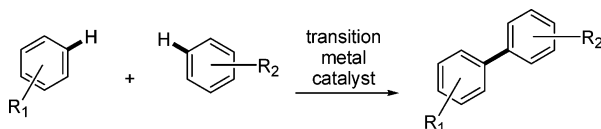
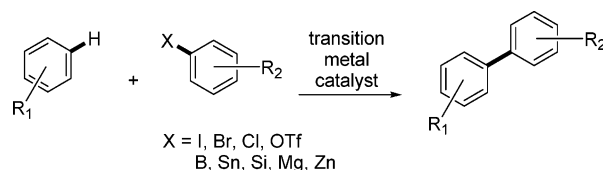Mark Lautens was born in Hamilton, Ontario, Canada, on July 9, 1959. He obtained his undergraduate degree in chemistry at the University of Guelph, where he graduated with distinction in 1981. He attended the University of Wisconsin–Madison, where he was awarded a Ph.D. in 1985 under the supervision of Barry M. Trost while supported by an NSERC Postgraduate Scholarship. From 1985 to 1987 he was an NSERC Postdoctoral Fellow working in the laboratories of David A. Evans at Harvard University. In 1987 he was appointed as an Assistant Professor and University Research Fellow at the University of Toronto. In 1992 he was promoted to Associate Professor, and in 1995 he became Professor of Chemistry. Since 1998 he has held the AstraZeneca Chair in Organic Synthesis, and in 2003 he became an Industrial Research Chair supported by Merck Frosst and NSERC. He has received a number of awards including an Eli Lilly Granteeship, an A.P. Sloan Fellowship, and an E.W.R. Steacie Fellowship. He was awarded the Rutherford Medal in Chemistry from the Royal Society of Canada, the Alfred Bader Award, and the R.W. Lemieux Award from the Canadian Society for Chemistry. In 2001 he was elected as a Fellow of the Royal Society of Canada, and in 2006 he was selected as an A.C. Cope Scholar from the American Chemical Society. Throughout his career he has been interested in metal-catalyzed transformations that make carbon–carbon and carbon–heteroatom bonds as well as asymmetric catalysis. His work has appeared in nearly 200 publications, reviews, and book chapters. He edited Volume 1 of *Science of Synthesis* and is an Editor of *Synthesis and Synfacts*.

Scheme 1

M = B, Sn, Si,   X = I, Br, Cl
    Mg, Zn   OTf

Scheme 2

Scheme 3

X = I, Br, Cl, OTf
B, Sn, Si, Mg, Zn

Despite the fact that several reviews on this topic have appeared as sections of other reviews[3,8–18] and books,[19–22] in most cases only a general overview was given, or the review was limited in that it emphasized the author's own work. In this review we will outline the development and advances in transition-metal-catalyzed aryl–aryl bond formation by direct arylation, as well as its application to the synthesis of important compounds including natural products, pharmaceuticals, catalyst ligands, and materials. Additionally, this review is organized into the direct arylation of aryl and heteroaryl C–H bonds (Scheme 4), and does not include examples using stoichiometric amounts of transition metals. Furthermore, this review will not discuss aryl–aryl bond formation via oxidative coupling reactions of the type outlined in Scheme 2. Instead, the reader is directed elsewhere[23,24] for references on this topic.

2. Direct Arylation of Aryl C–H Bonds

Reaction Conditions. Although a variety of transition metals have been used for the formation of aryl–aryl bonds, second-row transition metals in low oxidation states (Rh, Ru, Pd) have emerged as the preferred catalysts in catalytic direct

Scheme 4

Direct Arylation of Aryl C-H Bonds

Direct Arylation of Heteroaryl C-H Bonds
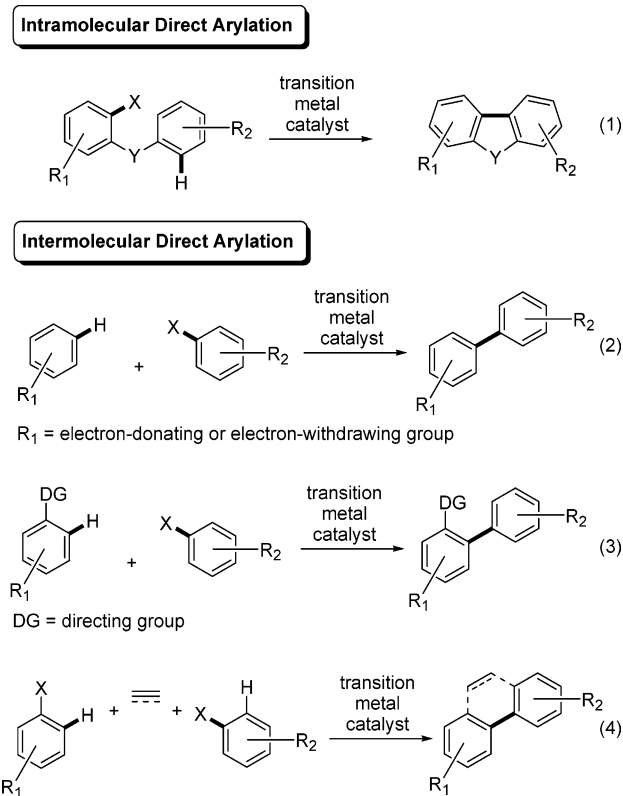
X = I, Br, Cl, OR, B, Sn
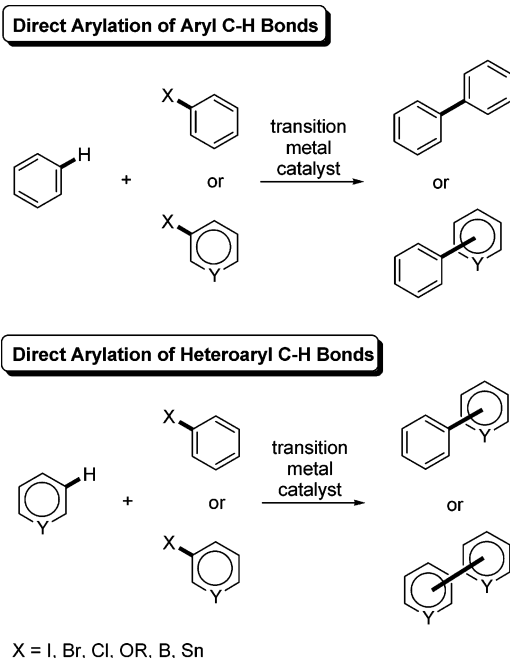
arylation reactions. In some cases, the high reactivity of the transition-metal complexes employed in direct arylation reactions has allowed for the use of extremely low catalyst loadings (as low as 0.1 mol %), making them industrially attractive.

The ligands used in direct arylation depend on the nature of the aryl halide being used. For more reactive aryl iodides, moderately electron-rich monodentate phosphines such as PPh$_3$ are typically used. These same phosphines have also been successfully utilized for aryl bromides, although in some systems far superior yields have been obtained using palladium and more sterically bulky and electron-rich trialkyl-phosphine or Buchwald's biphenylphosphines.[25] Recently, the use of aryl chlorides in a palladium-catalyzed direct arylation reaction has also been reported. However, as in other cross-coupling reactions,[26] the low reactivity of the C—Cl bond to oxidative addition necessitated the use of electron-rich and sterically-hindered trialkylphosphines, Buch-wald's biphenylphosphines, or N-heterocyclic carbene ligands to achieve synthetically useful yields of the direct arylation product. It should also be noted that ligand-free conditions (Jeffery's conditions) have also been successfully used in palladium-catalyzed direct arylation reactions for a variety of aryl halides.

While base is generally required in direct arylation reactions,[27] in most cases the exact role of the base remains unclear. Some recent evidence, however, suggests that in some systems the base may be intimately involved in the formation of the diarylpalladium(II) species (and not simply as a bystander whose role is to regenerate the active catalyst).[7,28,29] Typically, inorganic bases such as K$_2$CO$_3$, Cs$_2$CO$_3$, KOAc, t-BuOK, and CsOPiv are used. In particular, cesium carbonate and CsOPiv have proven to be very effective in many cases due to increased solubility in organic solvents. While polar, aprotic solvents such as DMF, DMA, CH$_3$CN, NMP, and DMSO are commonly used, nonpolar solvents such as toluene and xylene have also been employed successfully. In addition, temperatures >100 °C are typically used, and in most cases heating for several hours to days is necessary.

Regioselectivity. Direct arylation reactions can take place in either an intermolecular or an intramolecular fashion (Scheme 5). While intramolecular direct arylation reactions
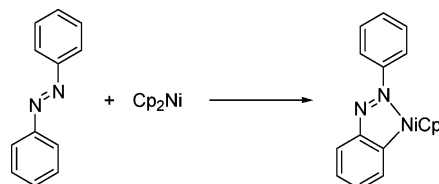
Scheme 5

Intramolecular Direct Arylation

(1)

Intermolecular Direct Arylation

(2)

R$_1$ = electron-donating or electron-withdrawing group

(3)

DG = directing group

(4)

employ tethers to limit the degree of freedom in a system, thereby controlling the regioselectivity of the reaction (eq 1, Scheme 5), intermolecular direct arylation reactions present a more formidable task since the catalyst has a greater degree of freedom when reacting at the C—H bond. Two factors that influence the regioselectivity of the intermolecular direct arylation are the electronics of the arene being functionalized (eq 2, e.g., the reaction occurs *ortho* or *para* to the electron-donating group via an electrophilic aromatic substitution process), and more commonly the directing group. Typically, directing group-assisted reactions employ nitrogen- and oxygen-coordinating functional groups to direct the arylation (eq 3), although in some cases external alkenes or alkynes in a cascade process have been used to create a "directing" alkyl- or alkenylmetal species in situ (eq 4).

This concept of using a directing group to control the regioselectivity of the subsequent transition-metal insertion into a C—H bond was first reported by Kleinman and Dubeck over 40 years ago (Scheme 6).[30]

Scheme 6

Since this initial report, the preparation and use of metallacycles not only as mechanistic tools but also as highly active precatalysts has been extensively reported.[31-33] Gener-

Scheme 7
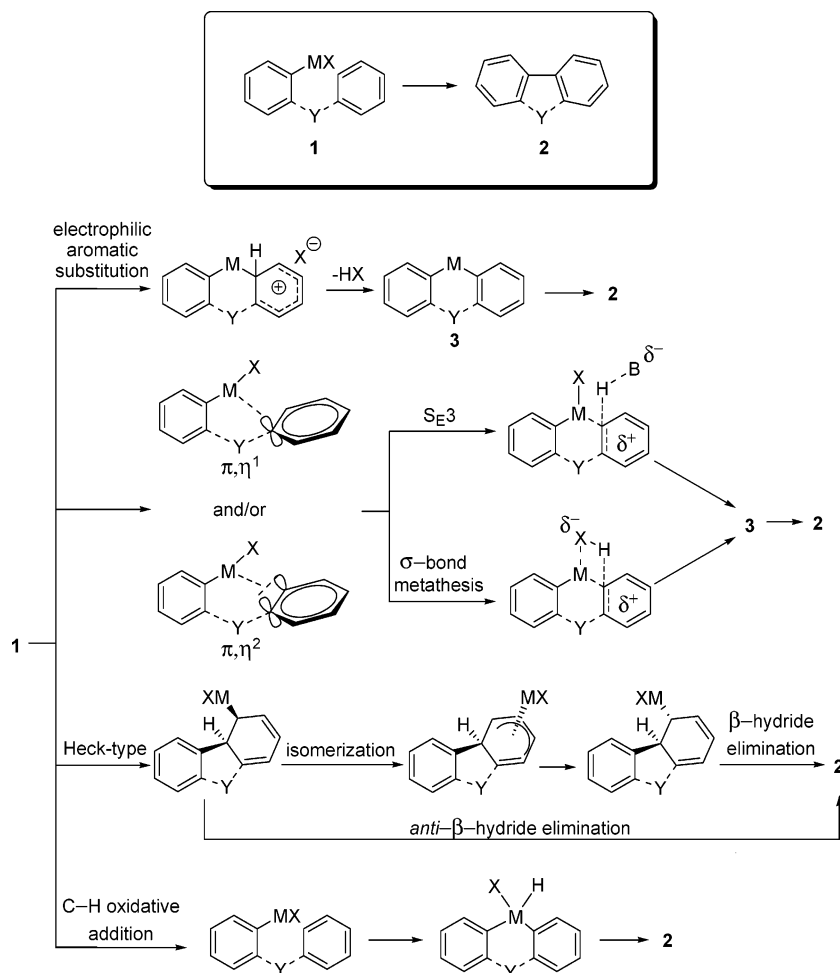
ally, these metallacycles are obtained through the use of a coordinating group that aids in directing the subsequent transition-metal C−H bond insertion, usually resulting in the formation of either the kinetically or thermodynamically favored five- or six-membered metallacycle. It is this same approach that is often employed in direct arylation chemistry to control the regioselectivity of the requisite C−H bond transformation. In symmetrical substrates, mono- or bis-direct arylation typically proceeds *ortho* to the directing group via formation of a five- or six-membered metallacycle. In unsymmetrical substrates, sterics become the controlling factor, resulting in direct arylation occurring predominately at the less hindered *ortho* position.

Mechanism of C−H Insertion. Mechanistically, the intramolecular and intermolecular direct arylation of arenes is proposed to occur via oxidative addition of the transition metal into the aryl halide, followed by one of a number of possible key carbon−carbon bond-forming steps (Scheme 7): (1) electrophilic aromatic substitution at the metal (S$_E$Ar),[34−42] (2) a concerted S$_E$3 process,[43] (3) a σ-bond metathesis,[38,44,45] (4) a Heck-type (or carbometalation) process either through a formal *anti* β-hydride elimination or via isomerization followed by a *syn* β-hydride elimination,[37−40,42,46,47] or (5) a C−H bond oxidative addition.[44,48−50] While the exact nature of this step has been investigated for some systems, it should be noted that *the exact mechanism for any given example depends heavily on the substrate, transition metal, solvent, base, and ligand used.*

Accordingly, this portion of the review will highlight developments in both the intramolecular and intermolecular direct arylation reactions. Where appropriate, additional mechanistic discussion will be presented.

2.1. Intermolecular Aryl–Aryl Bond Formation

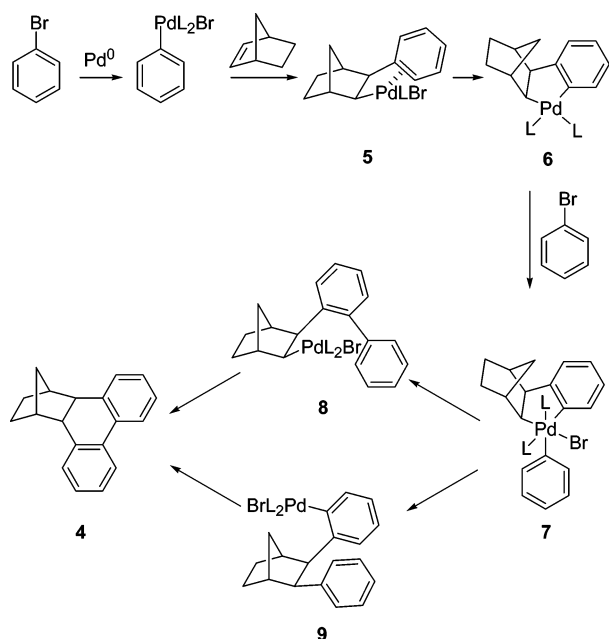### 2.1.1. Direct Arylation via Transition-Metal Cascade Reactions Involving Alkenes and Alkynes

2.1.1.1. Alkenes. The direct arylation of aryl halides via a palladium-catalyzed, norbornene-mediated cascade reaction has been described by Catellani and co-workers in various reviews.[51−55] In earlier work by Catellani, reaction of bromobenzene with norbornene in the presence of Pd(PPh$_3$)$_4$ and *t*-BuOK in anisole at 105 °C afforded the hexahydromethanotriphenylene (**4**) in 65% yield (Scheme 8).[56]

Scheme 8
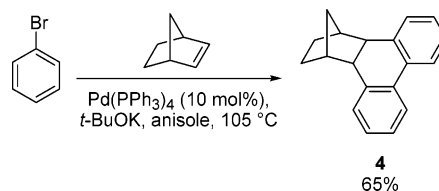
The unusual product was proposed to be a direct consequence of the different reactivities of the palladium(0), palladium(II), and palladium(IV) intermediates (Scheme
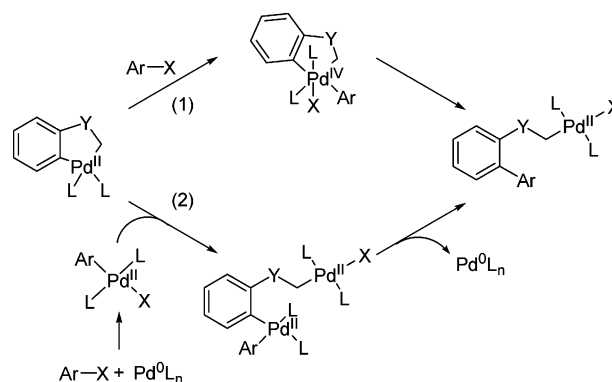
Scheme 9

Scheme 10

Catellani has also demonstrated that a terminating Heck coupling step was possible for her norbornene-mediated, palladium-catalyzed cascade reactions in the presence of excess methyl acrylate (Scheme 11).[60] Applying these

Scheme 11

9).[52,54] The catalytic cycle is initiated by oxidative addition of palladium(0) into bromobenzene to afford the phenylpalladium bromide. *Syn* insertion of norbornene affords the *cis,exo*-complex **5**, which in the absence of a *syn* β-hydrogen undergoes insertion into an aryl C−H bond to afford palladacycle **6**, presumably via electrophilic substitution at the *ortho* aromatic carbon. In the presence of an additional equivalent of bromobenzene, **6** undergoes an oxidative addition/reductive elimination sequence to afford either intermediate **8** or **9**, likely via a palladium(IV) intermediate, **7**.[54] Finally, cyclization of **8** or **9** occurs to give the desired cyclized product **4**. The authors have also reported the use of this methodology in the synthesis of other related polycyclic compounds.[57,58]

Although palladium(IV) species are often presumed to be an intermediate in the aforementioned reaction, there is no experimental evidence for the oxidative addition of aryl halides to palladium(II) complexes.[59] Recently, Echavarren and co-workers have found that this process may in fact proceed without the intermediacy of palladium(IV) complexes.[59] The authors conducted a computational study to determine how palladacycles such as **6** (Scheme 9) (and **28**, Scheme 71) react with C(sp^2)−X electrophiles to form the C(sp^2)−C(sp^2) bond that is present in the final compound. DFT calculations were conducted on model complexes to explore two possible mechanisms (Scheme 10): (1) the oxidative addition of aryl halides to palladacycles to give palladium(IV) intermediates and (2) a transmetalation-type reaction of arene ligands between a palladacycle and a palladium(II) complex formed by oxidative addition of an aryl halide to palladium(0). Calculations conducted by Echavarren and co-workers indicated that aryl electrophiles react more easily with unsaturated palladium(0) complexes than with palladium(II) metallacycles, suggesting that the formation of C(sp^2)−C(sp^2) bonds in palladium-catalyzed reactions of this type occurs without the intermediacy of palladium(IV) complexes. While these results may apply to this and related processes discussed in this section, the proposed mechanism put forth by the original authors will be discussed where appropriate.
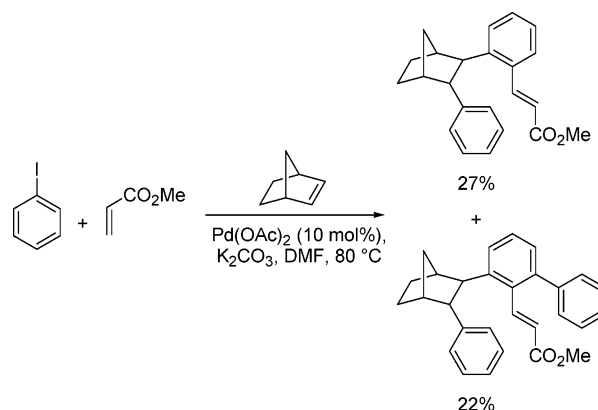
conditions to 2-iodotoluene in the absence of an additional coupling partner afforded an unusual C(sp^2)−C(sp^3) coupling product via an intramolecular benzylic C−H activation (Scheme 12).[61]
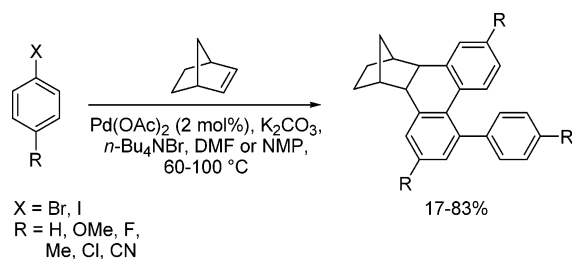
Scheme 12
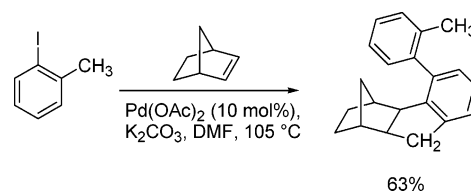
de Meijere reported a similar coupling in which a number of norbornene-annulated 4-phenyl-9,10-dihydrophenanthrene derivatives could be prepared from a variety of unsubstituted and *para*-substituted bromo- and iodobenzenes using Jeffery's conditions in the presence of 3 equiv of aryl halide (Scheme 13).[62,63] In addition, this methodology could be extended to include other strained norbornene-type alkenes such as dicyclopentadiene, norbornenol, and norbornenone.[64]

This palladium-catalyzed, norbornene-mediated coupling has also been carried out using aryl halides containing an *ortho* substituent in the presence of a coupling partner to generate norbornene-free biaryl products (Scheme 14).[65] While the mechanism is similar to that illustrated in Scheme 9, one noteworthy difference is that, in this case, the presence of an *ortho* substituent results in the faster reductive elimination of the palladium(IV) intermedate **10** to form an

Scheme 13

X = Br, I
R = H, OMe, F,
    Me, Cl, CN

17-83%

Scheme 14

R = CO₂Me
93%
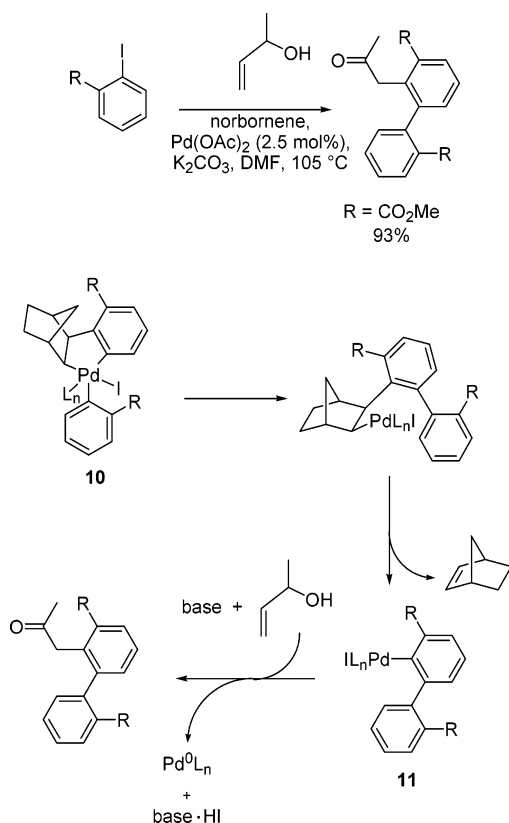
aryl−aryl bond instead of the corresponding aryl−norbornyl bond. The resulting sterically-hindered complex then expels norbornene via retrocarbopalladation to afford the biphenylyl complex **11**, which then reacts with the final coupling partner. The authors have subsequently extended the scope of this reaction to include a large variety of coupling partners such as olefins,[66,67] allylic alcohols,[65] diphenyl- and alkylphenylacetylenes,[68] arylboronic acids,[69] hydrogen donors,[70] and amides[71] (Scheme 15).

de Meijere also demonstrated that indene reacts analogously to norbornene-type alkenes (Scheme 16).[10,62] Subsequent studies by Thiemann described a similar triple arylation process using a dihydronaphthalene tricarbonylchromium(0) complex under Jeffery's conditions (Scheme 17).[72]

Other highly strained double-bond-containing systems have been successfully utilized in palladium-catalyzed domino processes.[73,74] Treatment of the strained hexacyclic hydrocarbon **12** with iodobenzene and iodobenzene derivatives afforded the corresponding propellanes in modest to good yields (Scheme 18). Interestingly, reactions carried out with 4-iodotoluene were observed to afford products bearing a regiochemical outcome similar to that of products previously reported using norbornene-type systems.
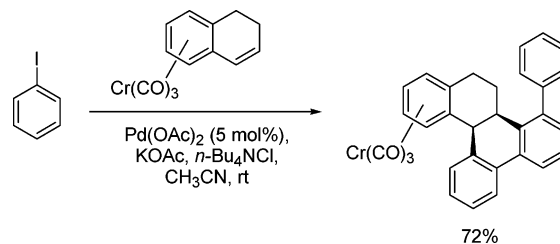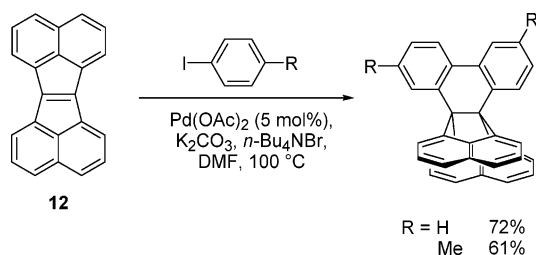
Scheme 15

83%

82%

88%


86%

86%

Scheme 16

35%

Scheme 17

72%
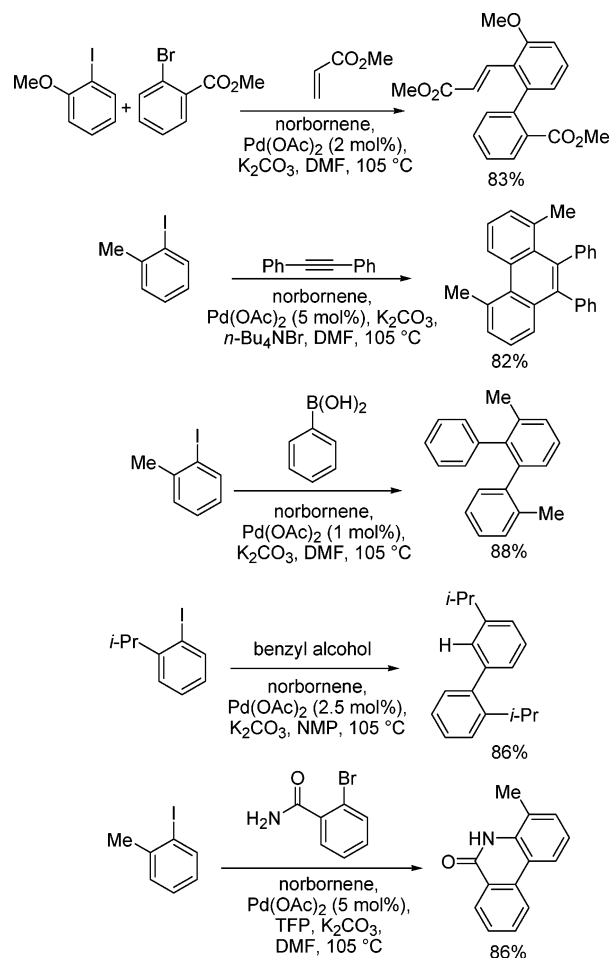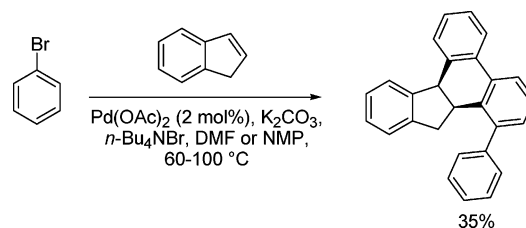
Acyclic alkenes have also been reported in similar palladium-catalyzed cascade arylations.[75,76] Reaction of α,β-unsaturated phenyl sulfones with aryl iodides using Pd(OAc)₂ and Ag₂CO₃ gave 9-(phenylsulfonly)-9,10-dihydrophenanthrenes as the major product along with small amounts of the Heck product (Scheme 19). A variety of β-substituents on the α,β-unsaturated sulfone were tolerated including alkyl, aryl, and alkenyl substituents. In addition, other electron-poor olefins including α,β-unsaturated alkyl sulfones, sulfonamides, phosphine oxides, and phosphonate esters gave substantial amounts of the corresponding dihydrophenan-

Scheme 18

R = H   72%
     Me   61%

Scheme 19

69%
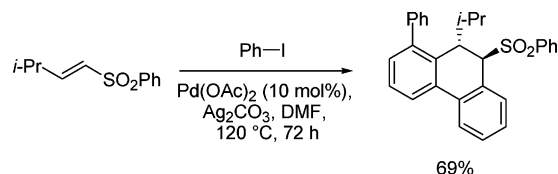
threnes. In contrast, typical π-conjugated olefins such as α,β-unsaturated esters and enones almost exclusively afforded the Heck-type products.

The proposed mechanistic pathway for this palladium-catalyzed cascade arylation reaction is illustrated in Scheme 20. Oxidative addition of palladium(0) to iodobenzene in the

Scheme 20
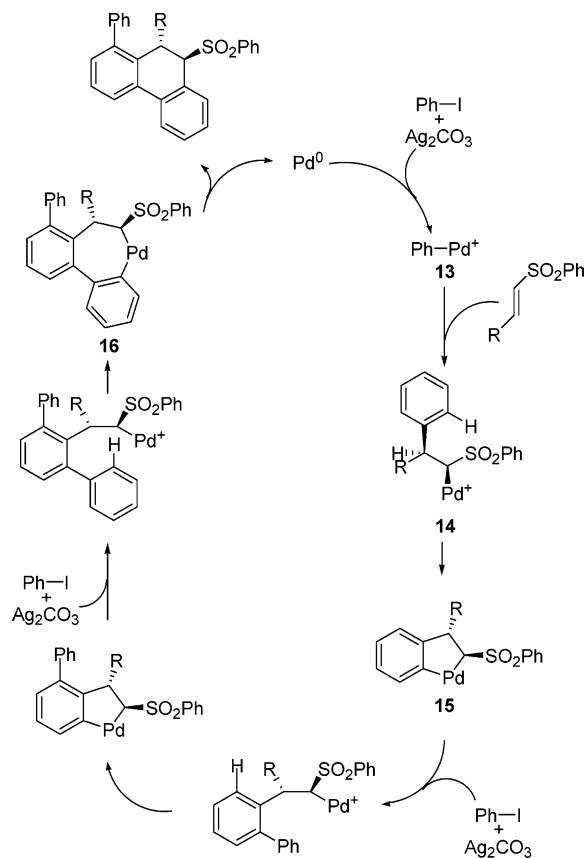
presence of Ag$_2$CO$_3$ affords the cationic phenylpalladium intermediate **13**. Regioselective *syn* insertion of the alkene then generates a highly electrophilic sulfonylalkylpalladium intermediate, **14**. Unlike the usual behavior of other types of acyclic alkenes, which afford Heck-type products (via *syn* β-hydride elimination), complex **14** would evolve faster through an aromatic C–H bond insertion to furnish the five-membered palladacycle **15**. Support for this process was

recently put forth in a computational study on the mechanism of this domino arylation reaction. The results showed that vinyl sulfones, unlike enones, are more able to reach the transition state that leads to the formation of the key five-membered palladacycle.[77] The next step then occurs via two possible mechanisms: (1) an oxidative addition/reductive elimination pathway via a palladium(IV) palladacycle intermediate or (2) a ligand exchange reaction between two palladium(II) centers. The same sequence of steps results in arylation of the second *ortho* position, which subsequently undergoes aromatic C–H bond activation to afford the seven-membered palladacycle **16**. Finally, reductive elimination generates the observed dihydrophenanthrene product.

2.1.1.2. Alkynes. The use of alkynes in a tandem, palladium-catalyzed annulation reaction has also been reported by Dyker as a new route to substituted phenanthrenes (Scheme 21).[78] Various aryl iodides bearing a variety of
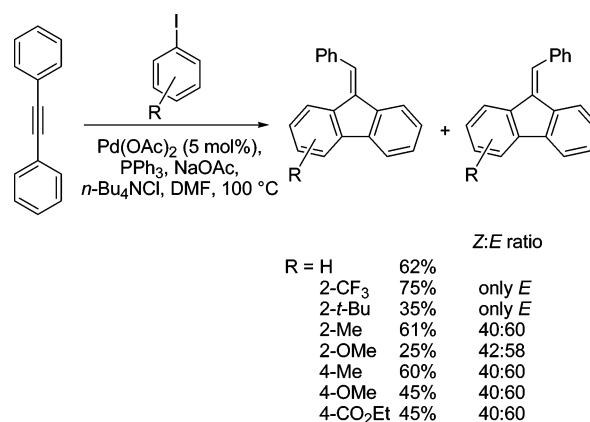
Scheme 21
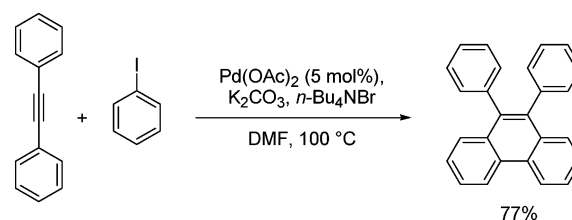
77%

electron-withdrawing and electron-donating substituents were compatible under the reaction conditions, giving mixtures of regioisomeric products.

This reaction was later found by Larock to be highly dependent on the nature of the base used in the reaction. In fact, the product distribution could be drastically altered simply by using NaOAc, which selectively afforded 9-alkyli-dene-9*H*-fluorenes in 25–75% yield (Scheme 22).[79,80] Vari-

Scheme 22

		Z:E ratio
R = H	62%	
2-CF$_3$	75%	only *E*
2-*t*-Bu	35%	only *E*
2-Me	61%	40:60
2-OMe	25%	42:58
4-Me	60%	40:60
4-OMe	45%	40:60
4-CO$_2$Et	45%	40:60

ous electron-withdrawing and electron-donating aryl substituents worked well under the reaction conditions, often affording mixtures of *E/Z* products depending on the nature of the aromatic substituents. In addition, suitable alkyne partners for this reaction included those with an aryl group at one end of the alkyne and another sterically large group such as an aryl or *tert*-butyl group at the other.

The proposed mechanism for this transformation is illustrated in Scheme 23. Oxidative addition of palladium(0) to the aryl iodide followed by alkyne insertion affords a vinylic palladium(II) species. 1,4-Palladium migration furnishes the arylpalladium(II) intermediate **17**. Cyclization of **17** either via an oxidative addition/reductive elimination pathway or

Scheme 23
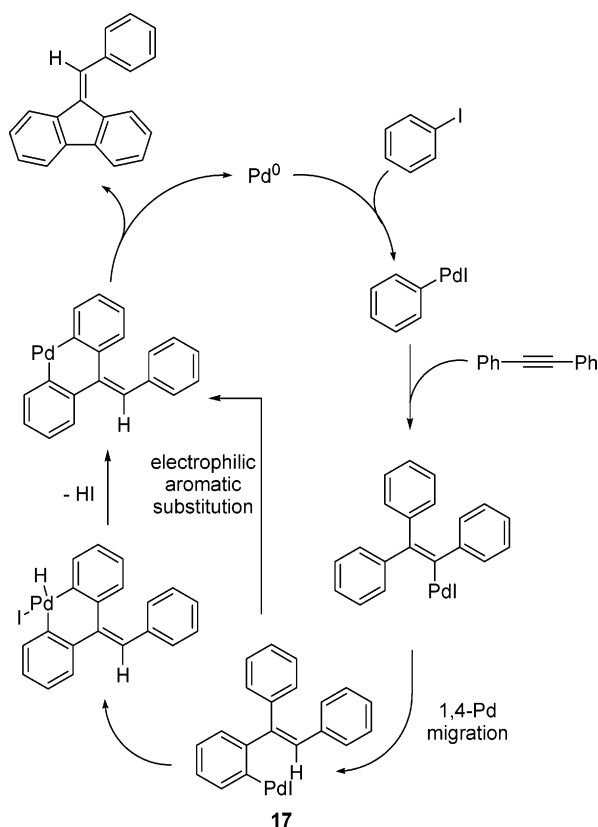
by an electrophilic aromatic substitution/reductive elimination route then affords the fluorene product.
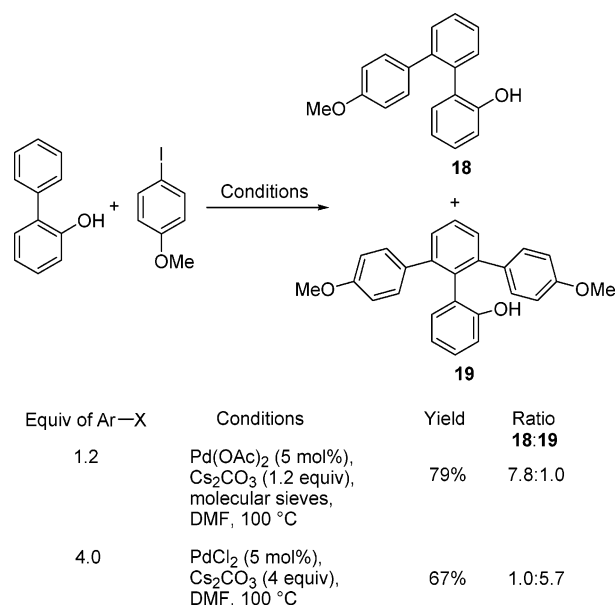
2.1.2. Directing Group-Assisted Arylation of Functionalized Aromatic Hydrocarbons

One method by which the regioselectivity of arene arylation can be controlled is through the use of directing groups. Common directing groups employed for this reaction typically bear a lone pair of electrons that can coordinate to the transition-metal catalyst to direct arylation via a five- or six-membered metallacycle. This section will highlight the contributions in this area of direct arylation according to the nature of the directing group employed.
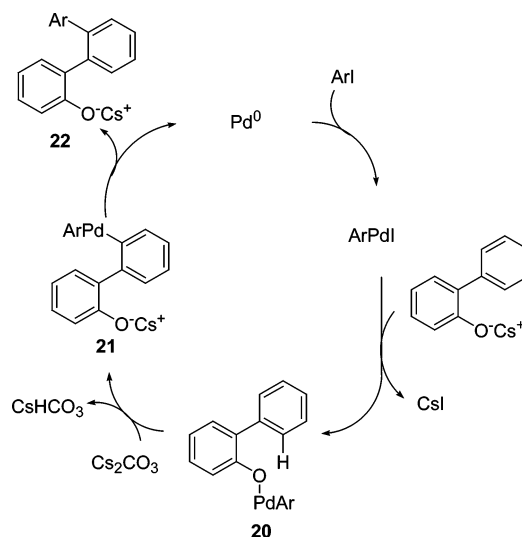
2.1.2.1. Phenols. Following Rawal's report on the intramolecular arylation of phenols (Scheme 82), Miura disclosed a selective intermolecular arylation of 2-phenylphenols and naphthols. Using a variety of substituted aryl halides in the presence of Pd(OAc)$_2$ or PdCl$_2$, and Cs$_2$CO$_3$ in DMF at 100 °C, the desired mono- or diarylated product could be selectively obtained by varying the amount of aryl iodide and Cs$_2$CO$_3$ used (Scheme 24).[81,82]

The authors propose that the reaction proceeds via initial oxidative addition of palladium(0) to the aryl iodide, followed by transmetalation of the cesium phenolate to form an aryl-(aryloxido)palladium intermediate, **20** (Scheme 25). Coordination of the phenolic oxygen to the palladium center in **20** is proposed to control the regioselectivity of the resulting C−H bond activation to form intermediate **21**. Reductive elimination of **21** then furnishes the desired monoarylated product **22**. The authors note that use of cesium carbonate as a base was crucial to the success of the reaction since its relatively high solubility in DMF is expected to enhance the rate of deprotonation, thereby facilitating the transformation of **20** to **21**.
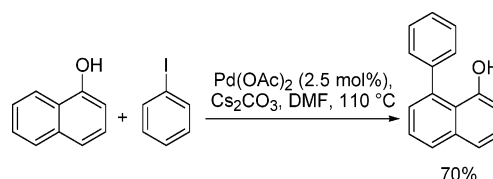
Scheme 24

| Equiv of Ar—X	Conditions	Yield	Ratio **18**:**19**
1.2	Pd(OAc)$_2$ (5 mol%), Cs$_2$CO$_3$ (1.2 equiv), molecular sieves, DMF, 100 °C	79%	7.8:1.0
4.0	PdCl$_2$ (5 mol%), Cs$_2$CO$_3$ (4 equiv), DMF, 100 °C	67%	1.0:5.7

Scheme 25

Scheme 26

These studies have also been extended to the arylation of naphthols, phenol, and 2,6-disubstituted phenols. While monoarylation of 1-naphthol occurred selectively to give 8-phenyl-1-naphthol (Scheme 26),[81,82] use of unsubstituted phenol was reported to undergo pentaarylation around the oxygen when treated with an excess of aryl bromide (Scheme 27).[83] Interestingly, 2,6-disubstituted phenols were found to undergo arylation exclusively at the *para* position. For example, sterically hindered 2,6-di-*tert*-butylphenol resulted in a number of 1,1′-biphenyl-4-ols when reacted with various substituted aryl bromides (Scheme 28).[84] These compounds were believed to arise through electrophilic attack at the *para* position.

A complementary, rhodium-catalyzed *ortho*-selective intermolecular arylation of phenols has also been reported by
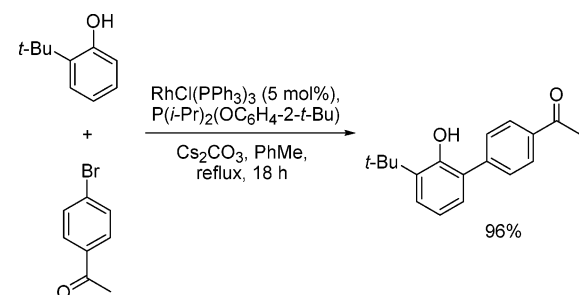
Scheme 27
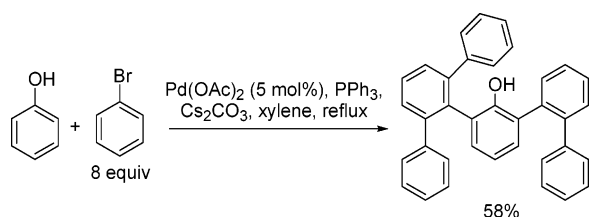
Scheme 28
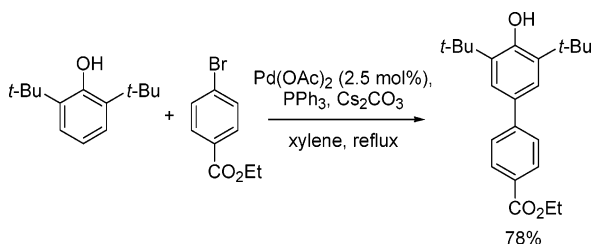
Scheme 29

Bedford (Scheme 29).[85,86] Using RhCl(PPh₃)₃ (5 mol %) as the catalyst and P(*i*-Pr)₂(OAr) (15 mol %) as the cocatalyst, a variety of 2-substituted phenols could be selectively *ortho* arylated in good yield. The proposed mechanism involves initial oxidative addition of Rh(I) to the aryl bromide, followed by coordination of phosphinite and *ortho* metalation of the phenolic moiety of the ligand to provide intermediate **22** (Scheme 30). Reductive elimination of the *ortho*-

Scheme 30
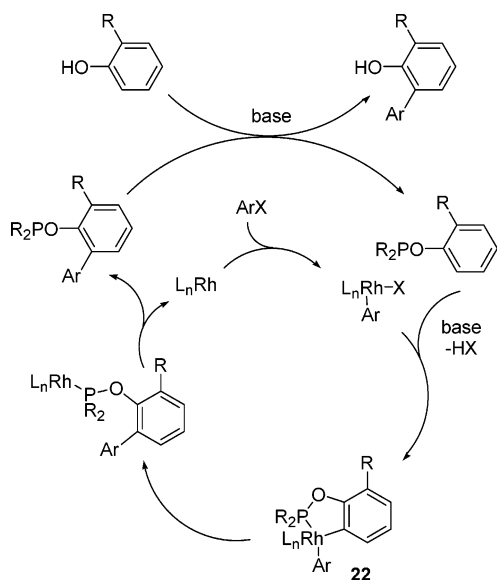
metalated ligand and the aryl group regenerates the active catalyst and forms a 2-arylated aryl dialkylphosphinite intermediate. Transesterification of this intermediate with the starting phenol then regenerates the cocatalyst and furnishes the 2-arylated phenol product.

Although these original conditions using RhCl(PPh₃)₃/P(*i*-Pr)₂(OAr) worked well for 2-substituted phenols, use of catalytic [RhCl(cod)]₂/P(NMe₂)₃ was found to give better results for phenols lacking an *ortho* substituent. For example, treatment of phenol and 4-bromoanisole with [RhCl(cod)]₂/P(NMe₂)₃ afforded a 50:3 ratio of di- to triarylated products in 62% yield (Scheme 31).[86]

Scheme 31
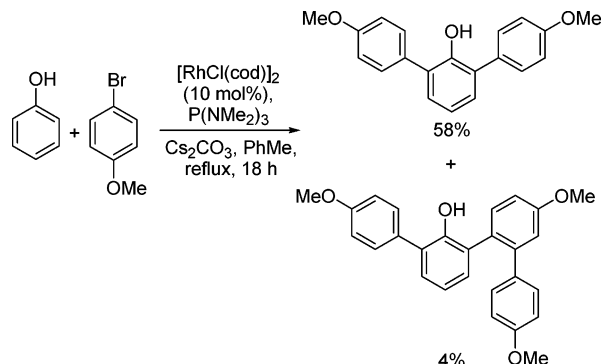
At the same time, Oi and co-workers independently reported a rhodium-catalyzed *ortho* arylation of phenols with aryl bromides.[87] Arylation of a number of substituted phenols with aryl bromides could be carried out in the presence of [RhCl(cod)]₂, HMPT, K₂CO₃, and Cs₂CO₃ in toluene at 100 °C. In all cases, a mixture of mono- and diarylated products were obtained in moderate yields (Scheme 32). The authors
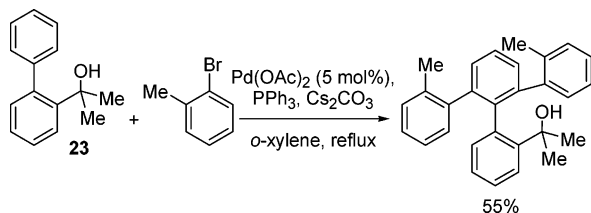
Scheme 32
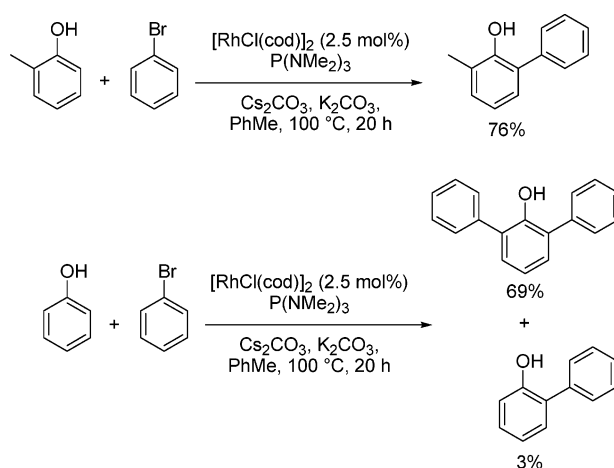
suggest a mechanism similar to that proposed by Bedford, in which the reaction proceeds via in situ generation of an arylphosphite intermediate, followed by phosphorus-directed *ortho* metalation and transesterification of the arylated arylphosphites with the phenol substrate.

2.1.2.2. Arylmethanols. Miura recently demonstrated the utility of an alcohol directing group for the direct arylation of α,α-disubstituted arylmethanols with aryl halides (Scheme 33).[88,89] During the course of their studies, a competing side reaction was discovered in which tandem palladium-catalyzed C−H and C−C bond cleavage occurred. The sp²−sp³ C−C bond was cleaved to eject acetone, followed by aryl−aryl coupling.[90,91] One particularly interesting example is the reaction of alcohol **23** with 1,2-dibromo-4,5-dimethylbenzene to afford triphenylene in 60% yield (Scheme 34).[89]

Scheme 33

55%

Scheme 34

60%
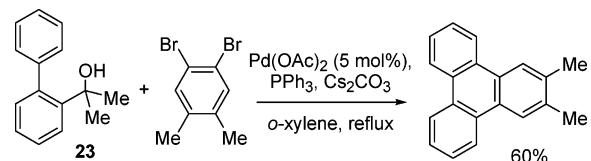
2.1.2.3. Ketones. Miura and co-workers[92,93] have also investigated the keto-directed arylation of aryl ketones.[94] Reaction of benzyl phenyl ketones with substituted aryl bromides in the presence of Pd(PPh$_3$)$_4$ and Cs$_2$CO$_3$ in refluxing *o*-xylene afforded various triarylated products in moderate yields (Scheme 35). This reaction was found to

Scheme 35

| R^1 = H | R^2 = H | 61% |
| R^1 = Cl | R^2 = H | 59% |
| R^1 = H | R^2 = 3-CF$_3$ | 41% |
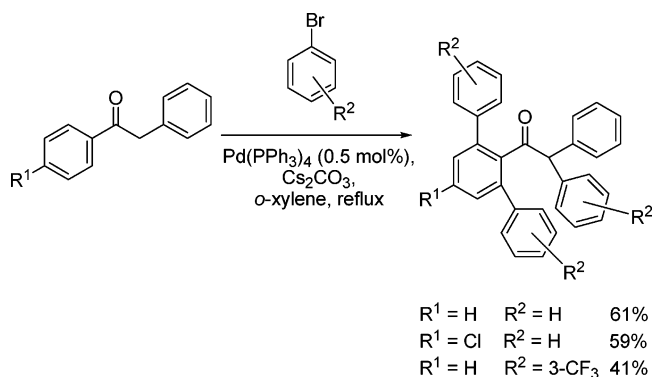
be highly sensitive to the electronics of both the aryl bromide and phenyl ketone. In particular, use of electron-donating substituents on the aryl bromide were found to slow the rate of arylation. Conversely, electron-withdrawing substituents on the phenyl ketone enhanced the rate of *ortho* arylation, presumably by the promotion of enolate formation of the α-arylated intermediate **24** (Scheme 36). In addition, the use of acetophenone and propyl and butyl phenyl ketone led to a mixture of both *ortho* arylation and alkyl arylation products, while ethyl phenyl ketone was reported to undergo arylation exclusively on the alkyl moiety.[95]

Mechanistically, the authors propose that deprotonation of the α-arylated intermediate **24**[96] occurs to afford the cesium enolate **25** (Scheme 36). Subsequent coordination of the enolate oxygen to the arylpalladium halide, followed by *ortho* palladation gives the diarylpalladium intermediate **26**. Reductive elimination of **26** and enolate protonation then generate the biaryl product **27**, which undergoes the same sequence of steps for the second *ortho* arylation.[92]

While the majority of transition-metal-catalyzed direct arylation reactions of arenes involve the use of aryl halides or pseudohalides as the coupling partner, several groups have recently reported the direct arylation of arene C–H bonds using aryl organometallic compounds. An interesting example of this was reported by Kakiuchi, who described a

Scheme 36

Scheme 37

| 1 mmol | 1 mmol | 47% | 40% |
| 2 mmol | 1 mmol | 82% | 71% |
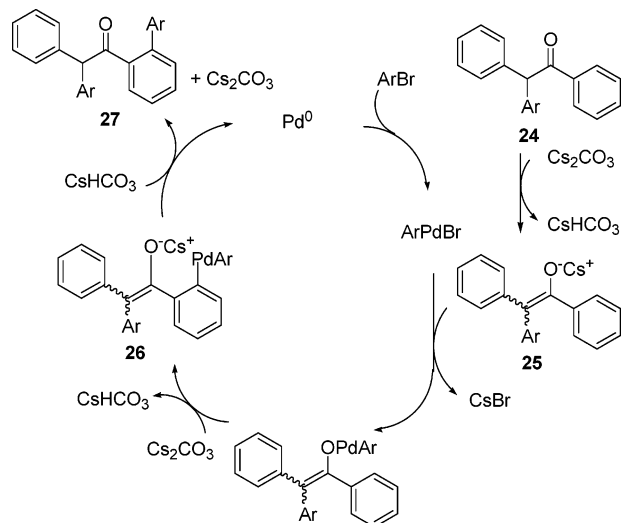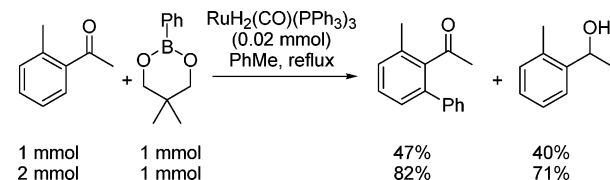
ruthenium-catalyzed arylation of aromatic ketones using arylboronic esters (Scheme 37).[97,98] The reaction of 1 equiv of 2′-methylacetophenone with 1 equiv of the phenylboronic ester using RuH$_2$(CO)(PPh$_3$)$_3$ as the catalyst in refluxing toluene gave the *ortho*-phenylated product in 47% yield. In addition, a nearly equivalent amount of alcohol derived from the reduction of the starting ketone was obtained as a byproduct. When a 2-fold excess of the ketone was employed, the phenylated product was obtained in 82% yield (based on the phenylboronic ester) (Scheme 37).[98] Based on these observations, the authors propose that the mechanism likely proceeds via a ruthenium-catalyzed *ortho*-hydride abstraction, followed by reduction of the ketone carbonyl. The authors later found that this undesired reduction of the aromatic ketone could be suppressed by the addition of a hydride scavenger such as pinacolone.

The scope of the reaction was next examined using the optimized reaction conditions. While acetophenone and isopropyl phenyl ketone furnished the corresponding diarylated ketone as the major product, use of the bulkier *tert*-butyl phenyl ketone afforded the *ortho*-monoarylated ketone exclusively in 76% yield (Scheme 38). It is suggested that the large steric repulsion between the *tert*-butyl group and the phenyl group introduced at the *ortho* position inhibits the second C–H bond cleavage.

Scheme 38

R = Me	1.0 mmol	17%	39%
Me	2.2 mmol	3%	89%
i-Pr	2.0 mmol	0	70%
t-Bu	1.1 mmol	76%	0
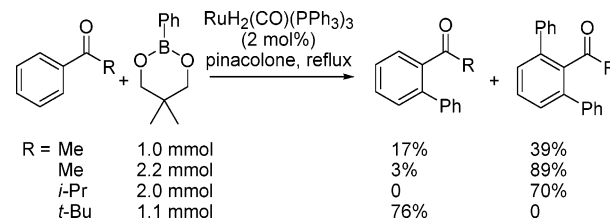
The reaction can be applied to various electron-rich and electron-poor aromatic ketones, including functionalized acetophenones and acetonaphthones. High yields of products were obtained, and the electronic nature of the substituent on the aromatic ring did not greatly affect the reactivity of the reaction.

Fused aromatic ketones showed significant reactivity in this reaction. Excellent yields of products were obtained for α-tetralone, 2,2-dimethyl-α-tetralone, and 1-benzosuberone (Scheme 39). Various electron-rich, electron-poor, and

Scheme 39
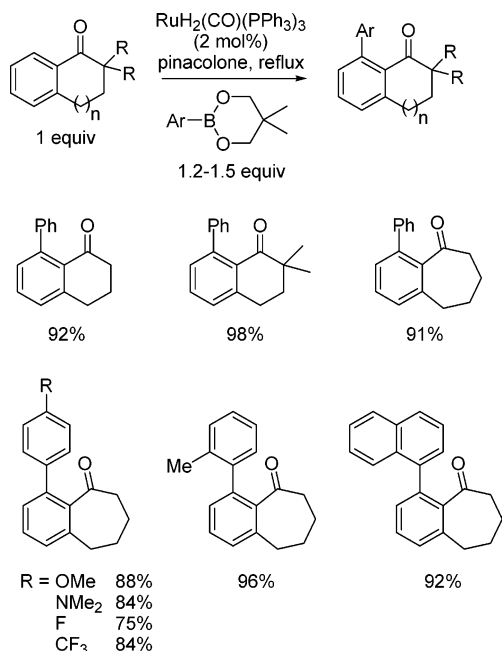
sterically-hindered arylboronic esters were reacted with 1-benzosuberone to give the corresponding products in excellent yields.

The authors conducted several labeling experiments to gain insight into the reaction mechanism. Intermolecular and intramolecular competition reactions were conducted as shown in Schemes 40 and 41, respectively. The authors

Scheme 40
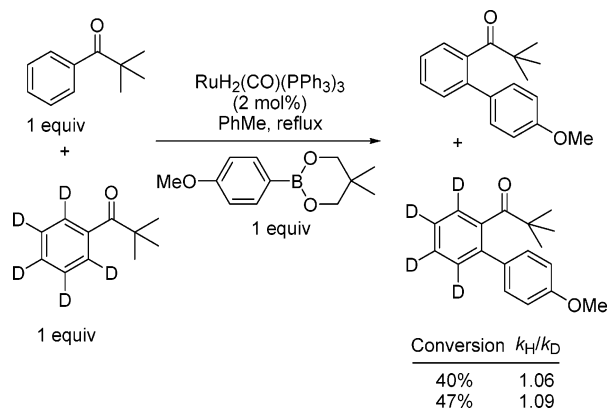
suggest that if the C−H bond cleavage proceeds without coordination of the ketone carbonyl group, the k_H/k_D values for both the intra- and intermolecular competitive reactions should be nearly the same. On the other hand, if the ketone carbonyl coordinates to the ruthenium prior to C−H bond cleavage, the k_H/k_D values should be different. The kinetic

Scheme 41
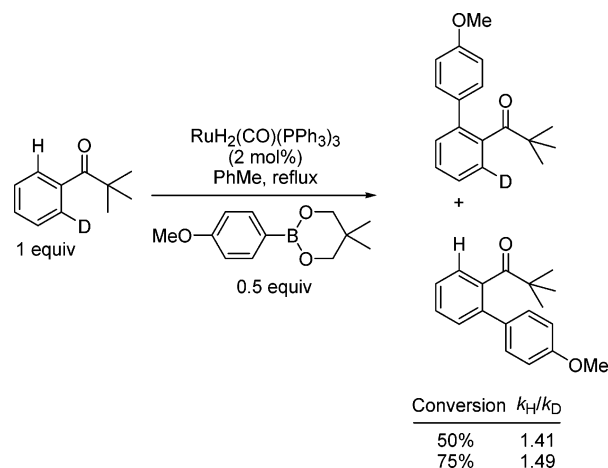
isotope effects for the intermolecular competitive reactions ($k_H/k_D = 1.06$ and 1.09) were different from those for the intramolecular competition ($k_H/k_D = 1.41$ and 1.49), supporting the proposal that the ketone carbonyl group coordinates to the ruthenium prior to C−H bond cleavage.

The proposed mechanism begins with coordination of the ketone to ruthenium, followed by cleavage of the C−H bond to afford a five-membered ruthenacycle (Scheme 42). Ad-
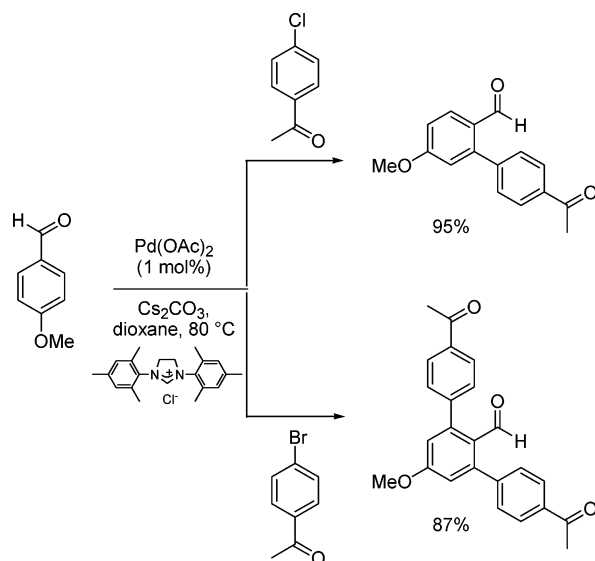
Scheme 42
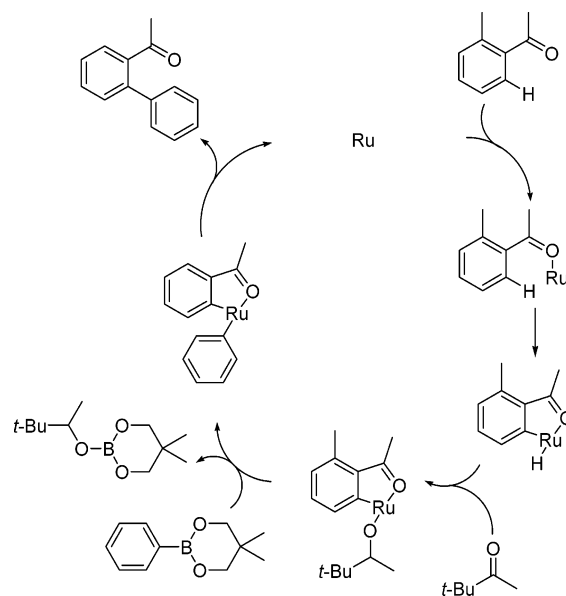
dition of Ru−H to the pinacolone carbonyl results in an alkoxyruthenium intermediate. Transmetalation between the alkoxyruthenium intermediate and the arylboranate then affords the diarylruthenium intermediate and a trialkoxyborane, which was detected by ^{1}H and ^{11}B NMR and GC/MS spectrometry. Reductive elimination furnishes the biaryl product and regenerates the active catalyst.

2.1.2.4. Benzaldehyde and Phenylacetaldehydes. More recently, the use of aldehydes as directing groups for the palladium-catalyzed arylation of arenes has also been reported. Using Pd(OAc)$_2$ and a bulky electron-rich N-heterocyclic carbene ligand, arylation of a variety of benzaldehyde derivatives could be carried out with a large range of electron-rich and electron-poor aryl halides in good to excellent yields.[99] In addition, the authors showed that aryl chlorides can also be used to achieve selective monoarylation
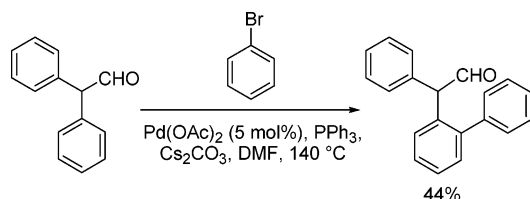
Scheme 43

in contrast to the diarylated products typically obtained with aryl bromides (Scheme 43).

The palladium-catalyzed arylation of a phenylacetaldehyde with bromobenzene has also been studied by Miura (Scheme 44).[95] In this case, only the *ortho*-monoarylated compound was obtained in a modest 44% yield.

Scheme 44

2.1.2.5. Amides. Following the successful arylation of aromatic ketones and phenols, Miura utilized this methodology for the palladium-catalyzed arylation of benzanilides.[100] In this investigation, benzanilides were found to efficiently undergo diarylation with aryl triflates and bromides in good to excellent yields (Scheme 45). Importantly, neither the
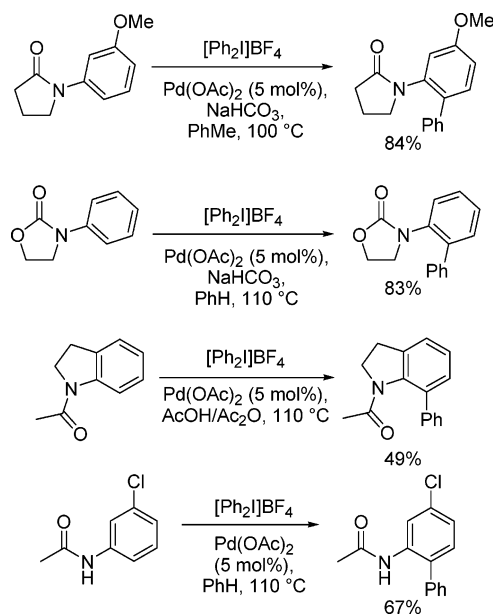
Scheme 45

X = Br, OTf
R₁ = H, OMe, Cl
R₂ = H, Me
R₃ = H, Me, Cl
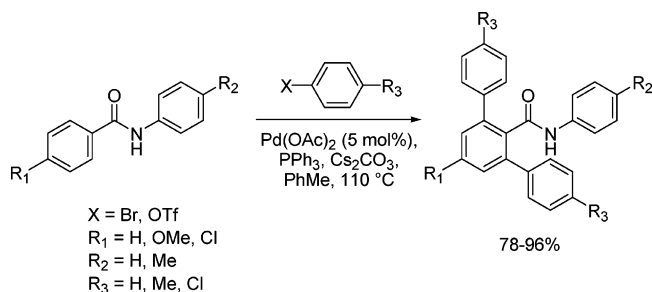
N-arylated product nor the arylated *N*-phenyl-substituted regioisomer was observed. The authors propose a mechanism similar to that reported for the corresponding phenolic and ketone systems (see sections 2.1.2.1 and 2.1.2.3, respectively), whereby in this instance, coordination of the amidate ion to the intermediary arylpalladium species would occur as the key step.

Sanford and co-workers[101] recently reported a palladium-catalyzed oxidative C−H activation/arylation of amide

Scheme 46

derivatives using hypervalent iodine compounds as the oxidizing arylation reagent (Scheme 46). One advantage of this highly practical reaction is that it does not require the use of strong bases or expensive ligands, and can be conducted without any precautions with regard to the exclusion of air and moisture. The mechanism is believed to involve a Pd(II)/Pd(IV) catalytic cycle and is described in more detail in section 2.1.2.7.

An interesting direct arylation side reaction was observed during the palladium-catalyzed synthesis of pyridones from *o*-bromoarylcarboxamides.[102] While the desired product was obtained in only 23% yield, the competing direct arylation side product was isolated in 34% yield. The final arylation is believed to be directed by the amide functionality via a five-membered palladacycle intermediate (Scheme 47).

Scheme 47
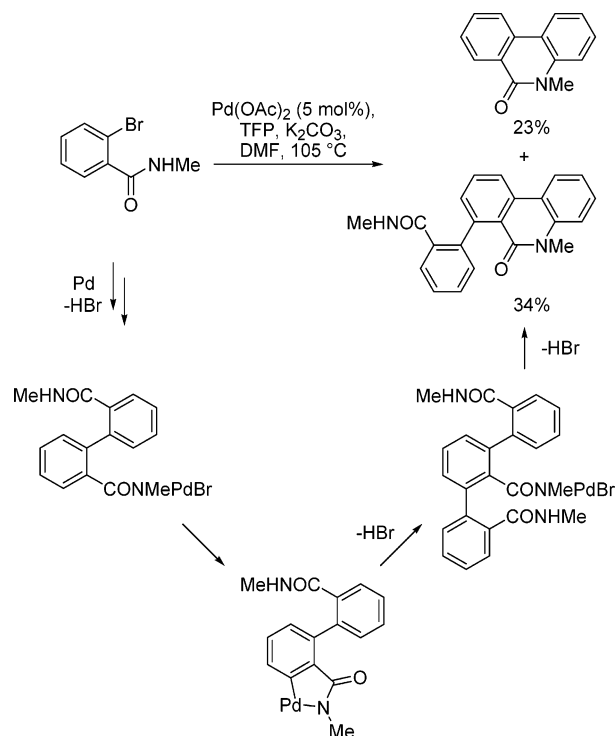
2.1.2.6. Imines. Imines have also been successfully utilized as directing groups for the ruthenium-catalyzed direct *ortho* arylation of aromatic imines with a variety of aryl and 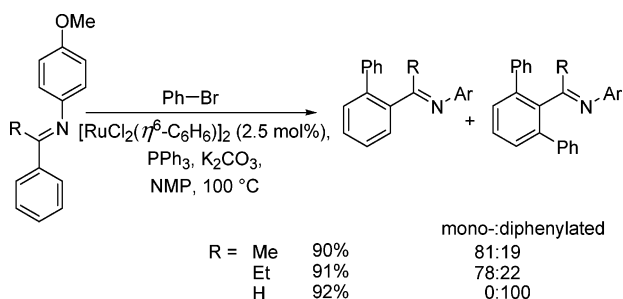alkenyl halides.[103] Interestingly, the size of the alkyl group on the imino moiety was found to affect the ratio of mono- to diphenylated product (Scheme 48). The authors propose that

Scheme 48

this phenomenon is due to steric interactions between the alkyl group on the imine moiety and the newly introduced phenyl group, thereby preventing imine rotation and subsequent arylation. Support for this proposal was obtained through scope investigations in which an ethyl group on the imino moiety was also observed to give a similar ratio of mono- to diphenylated products compared to the methyl analogue, while use of hydrogen on the imino moiety was found to undergo diphenylation exclusively. Additional scope studies also revealed that *meta*-substituted imines underwent selective monoarylation at the less hindered *ortho* position (Scheme 49).
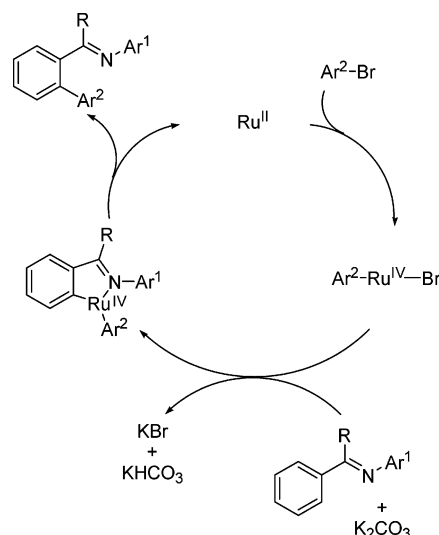
Scheme 49
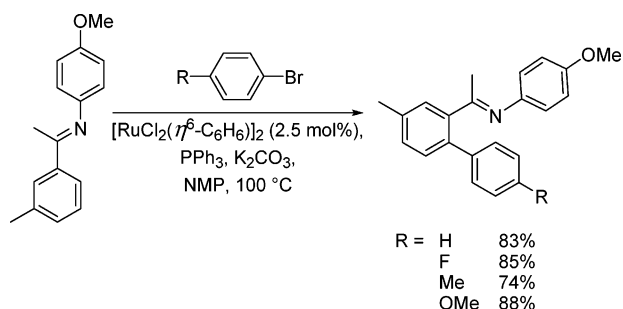
Mechanistically, the reaction is proposed to occur via initial oxidative addition of Ru(II) to the aryl bromide (Scheme 50). The resulting arylruthenium(IV) complex coordinates to the imino group to afford an arylated ruthenacycle intermediate, which undergoes subsequent reductive elimination to furnish the *ortho*-arylated product.

A ruthenium-catalyzed arylation using aryl chlorides has also been achieved using phosphine oxides as preligands.[104] Reaction of an imine with an aryl chloride in the presence of [RuCl$_2$(*p*-cymene)]$_2$ and an adamantyl-substituted secondary phosphine oxide afforded the desired aryl imine, which upon hydrolysis afforded the monoarylated ketone in good yield (Scheme 51). Both electron-rich and electron-poor aryl chlorides were tolerated in this reaction, and a wide variety of functional groups were compatible including enolizable ketones, nitriles, and esters.

Miura and co-workers[105] have also demonstrated the utility of imines as directing groups for the rhodium-catalyzed *ortho* arylation of benzophenone imine with sodium tetraphenylborate (Scheme 52). In this example, a mixture of mono- and diphenylated products were obtained in addition to the

Scheme 50

Scheme 51
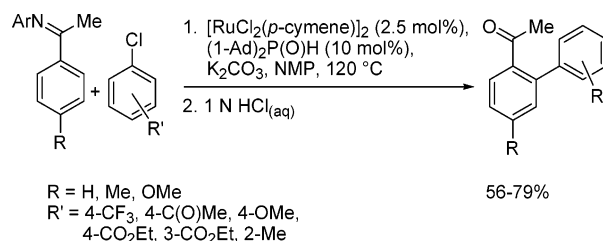
Scheme 52
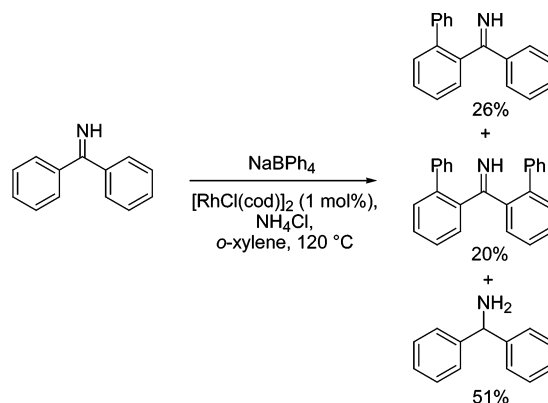
reduced aminodiphenylmethane byproduct. The formation of significant amounts of this byproduct suggests that the benzophenone imine acts as a hydride scavenger in the reaction. The authors propose that this most likely occurs via initial coordination of the benzophenone imine nitrogen to the phenylrhodium intermediate, followed by *ortho* rhodation to afford a five-membered rhodacycle intermediate (Scheme 53). Subsequent reductive elimination generates the monophenylated product and a rhodium hydride species, which then reduces the benzophenone imine in the presence of a proton donor to regenerate the active catalyst.

2.1.2.7. Pyridines and Quinolines. In addition to the direct arylation of aromatic pyrrolidinones and oxazolidinones described in section 2.1.2.5, Sanford has demonstrated that pyridines and quinolines are effective directing groups for palladium-catalyzed arene arylation using hypervalent iodine arylating agents.[101] Under these conditions, a number of functionalized pyridines could be used to direct monoarylation onto a variety of both electron-rich and electron-poor

Scheme 53

Scheme 54

Scheme 55

R = H   85%
     CF$_3$ 87%
     F   88%
     Cl   83%
     CH$_3$ 84%
     OCH$_3$ 81%

agents such as PhI or PhOTf resulted in less than 1% of the desired phenylated product.

On the basis of experimental evidence, the authors proposed a mechanism in which initial C–H activation occurs to form a cyclometalated palladium(II) intermediate, followed by either: (1) oxidation of palladium(II) to palladium(IV) by [Ph$_2$I]BF$_4$ followed by subsequent C–C bond formation via reductive elimination (Scheme 56), or (2) direct
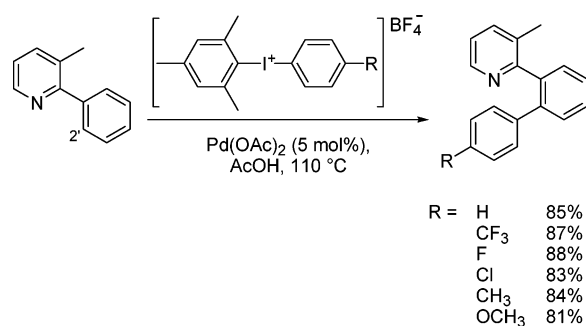
Scheme 56

electrophilic cleavage of the palladium(II)–carbon bond by [Ph$_2$I]BF$_4$ (without changing the oxidation state of the metal).

Daugulis also reported a palladium-catalyzed direct arylation using a pyridine moiety as a directing group (Scheme 57).[106] In the presence of excess aryl iodide, 2-phenylpyri-

Scheme 57

73%   74%
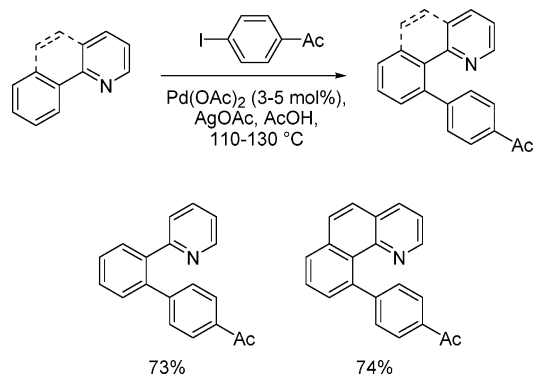
dine and 7,8-benzoquinoline could be selectively monoarylated in good yield. It was also shown that the diarylated product could be obtained after prolonged reaction times. The authors speculate that a Pd(0)–Pd(II)–Pd(IV) catalytic cycle is likely involved in the reaction.

Recently, the same group disclosed a highly regioselective direct arylation of carboxylic amides possessing a directing aminoquinoline group (Scheme 58).[107] The reaction was carried out using only 0.1 mol % palladium. Remarkably, the iodide on the benzamide was compatible under the reaction conditions. In addition, similar substrates wherein the position of the carbonyl is inverted afforded the monoarylated product in 81% yield (Scheme 58).

An analogous ruthenium-catalyzed 2′-arylation of 2-aryl-pyridines has also been reported by Oi (Scheme 59).[108] Although a mixture of mono- and diarylated products were obtained when 2-phenylpyridine was treated with 1 equiv of bromobenzene in the presence of [RuCl$_2$(η^6-C$_6$H$_6$)]$_2$, PPh$_3$,

arenes (Scheme 54). Interestingly, arenes bearing a coordinating group at the 3′-position (e.g., 3′-acetyl) exclusively afforded a single regioisomeric product in which arylation occurred at the less sterically-hindered 6′-position. These findings suggest that the regioselectivity of C–H activation in this system is predominantly controlled by steric effects.

Selective transfer of an aryl group from a mixed hypervalent iodine reagent has also been achieved using [MesIAr]-BF$_4$. In this case, the bulky Mes group acts as a dummy ligand, resulting in selective transfer of the potentially more precious arene component (Scheme 55). Use of hypervalent iodine arylating agents proved crucial to the success of the reaction since all attempts to employ alternative arylating
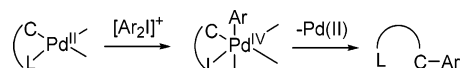
Scheme 58

65%

81%

Scheme 59

71%   11%

95%

76%

and K_2CO_3 in NMP at 120 °C, use of 3 equiv of bromobenzene could be used to exclusively afford the diarylated product in 77% yield. As observed in Sanford's system, monoarylated products at the less sterically hindered position were exclusively obtained for 2'- or 3'-substituted arylpyridines. A variety of substituted aryl bromides were tolerated under these conditions to give the desired products in good yields. Mechanistically, the authors propose that the reaction proceeds via a pathway analogous to the *ortho* arylation of aryl imines (Scheme 50).

Ackermann subsequently reported a similar ruthenium-catalyzed coupling to include aryl chlorides and aryl tosylates.[104,109] In this system the reaction was found to be compatible with a wide variety of electron-rich and electron-poor functional groups. Notably, aryl chlorides gave rise to doubly arylated products, while aryl tosylates selectively generated monoarylated products (Scheme 60).

While most methods of direct arylation employ the use of aryl halides, Oi and co-workers have reported a rhodium-catalyzed direct arylation of pyridylarenes using arylstannanes (Scheme 61).[110] Under these conditions, a variety of arylpyridines could be selectively arylated in good yield at the 2'-position. The mechanism of this transformation is believed to occur via nitrogen-directed oxidative addition of a low-valent rhodium complex to the *ortho* C–H bond of the phenyl ring, followed by phenylation with tetraphenyl-stannane.

Scheme 60

R = H   99%
R = OMe   91%
R = C(O)Me 87%

R = C(O)Me 87%
R = C(O)Ph 54%

Scheme 61

79%
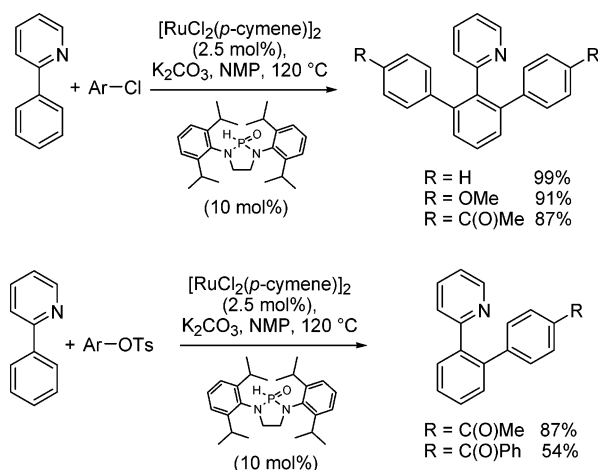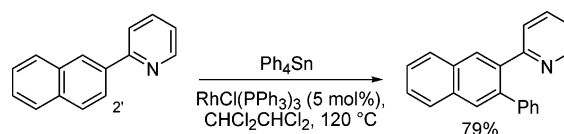
2.1.2.8. Oxazolines, Imidazolines, and Pyrazoles. Various nitrogen-containing five-membered heterocycles have been employed as directing groups in intermolecular direct arylation reactions. Oi and Inoue reported a selective *ortho* arylation of 2-arylimidazolines with aryl halides in the presence of a ruthenium(II)–phosphine complex (Scheme 62).[111] While the reaction of 2-phenylimidazoline with 1.2

Scheme 62

		Combined yield	mono-:diphenylated
R =	H	64%	31:69
	H (2.5 equiv)	90%	0:100
	C(O)Me	76%	89:11
	C(O)t-Bu	84%	86:14
	C(O)Ph	88%	77:23
	Ts	0%	
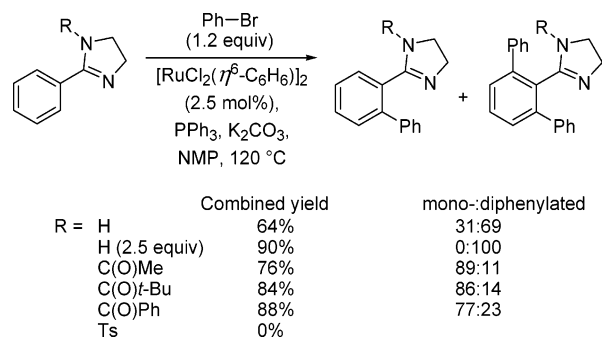
equiv of bromobenzene using $[RuCl_2(\eta^6\text{-}C_6H_6)]_2$ gave the mono- and diarylated products in a 64% yield and in a 31:69 ratio, exclusive formation of the diarylated product could be achieved in 90% yield using 2.5 equiv of bromobenzene. Furthermore, the reaction of various *N*-substituted derivatives, which are expected to block the second coupling reaction, were found to preferentially give the monoarylated products. In addition, an *N*-tosyl derivative failed to give any product, presumably due to the effects of the strong electron-withdrawing tosyl group, which is thought to decrease the ability of the imidazoline nitrogen to coordinate to the ruthenium complex.

The authors have also applied this method to the direct arylation of 2-aryloxazolines (Scheme 63).[111] The reaction of 2-phenyl-2-oxazoline with a slight excess of bromobenzene afforded a mixture of mono- and diarylated products in 60% yield. The preferential formation of the diarylated product was further enhanced when 2.5 equiv of bromobenzene was used, affording the product in quantitive yield. The

Scheme 63

Ph–Br
[RuCl$_2$(η_6-C$_6$H$_6$)]$_2$
(2.5 mol%),
PPh$_3$, K$_2$CO$_3$,
NMP, 120 °C

	Yield	mono-:diphenylated
1.2 equiv PhBr	60%	25:75
2.5 equiv PhBr	100%	0:100

Ph–Br
(1.2 equiv)
[RuCl$_2$(η_6-C$_6$H$_6$)]$_2$
(2.5 mol%),
PPh$_3$, K$_2$CO$_3$,
NMP, 120 °C

62%
(31:69)

Ph–Br
(1.2 equiv)
[RuCl$_2$(η_6-C$_6$H$_6$)]$_2$
(2.5 mol%),
PPh$_3$, K$_2$CO$_3$,
NMP, 120 °C

11%

Scheme 65

Me + Ar–OTs
[RuCl$_2$(p-cymene)]$_2$
(2.5 mol%),
K$_2$CO$_3$, NMP, 120 °C

(10 mol%)

4-OMe 71%	4-CO$_2$Me 93%	4-C(O)Ph 94%	81%
3,5-OMe 51%	3-CO$_2$Et 73%	4-C(O)Me 93%	
2-OMe 50%			

85% 59% 96%

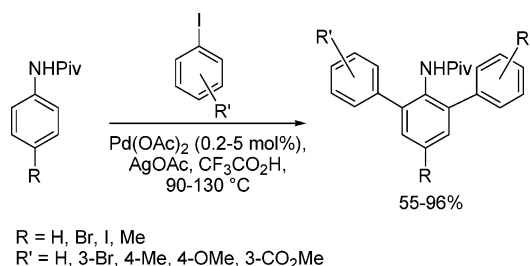influence of the oxazoline ring substitutents on the mono- and diarylated product distribution was examined using 5,5-dimethyl-2-phenyl-2-oxazoline and 4,4-dimethyl-2-phenyl-2-oxazoline. While *gem*-dimethyl substitution at the 5-position had no effect on the product yield or distribution, the same substituents at the 4-position exclusively afforded the monoarylated product, albeit in a low 11% yield. The authors propose that the low yield for this example is due to the inability of the sterically-encumbered nitrogen to coordinate to the ruthenium complex.

The following two steps are believed to play some part in the catalytic cycle: (1) oxidative addition of the aryl halide to the ruthenium complex to furnish an arylruthenium intermediate, and (2) oxazoline- or imidazoline-directed *ortho* ruthenation of the aromatic ring. Two possible mechanisms are depicted in Scheme 64. In pathway A, oxidative addition of the aryl halide to a ruthenium(II) complex generates an

Scheme 64

+ K$_2$CO$_3$

Ar–RuX$_2$–Br

KBr + KHCO$_3$

Pathway A

Ar–Br

RuX$_2$

K$_2$CO$_3$

KX + KHCO$_3$

Ar–Br

Pathway B

arylruthenium intermediate. *Ortho* ruthenation of the aryl-oxazoline or arylimidazoline with the arylruthenium inter-mediate then furnishes a ruthenacycle which undergoes reductive elimination to afford the desired product and to regenerate the active catalyst. In pathway B, the ruthena-cycle is formed from the reaction of the aryloxazoline or arylimidazoline with a ruthenium(II) complex. Oxidative addition of the aryl halide affords a second ruthena-cycle which undergoes reductive elimination to furnish the desired product. On the basis of previous literature precedent, the authors propose that this reaction likely proceeds via pathway B.

Oxazoline and pyrazole have also been efficiently used as directing groups in direct arylation reactions with aryl chlorides and tosylates. In these examples, a highly active ruthenium catalyst derived from an air-stable secondary diaminophosphine oxide was used.[109] Various electron-rich and electron-poor aryl tosylates with a diverse range of functional groups including alkenes, esters, nitriles, and ketones were compatible under the reaction conditions, affording high yields of the expected products (Scheme 65).

Both aryl chlorides and aryl tosylates were used in the direct arylation of a pyrazole derivative. Interestingly, aryl chlorides gave rise to a doubly arylated product, while aryl tosylates formed the monoarylated product selectively (Scheme 66).

In addition, pyrazole has also been reported as an effec-tive directing group in the palladium-catalyzed direct ary-lation of 1-phenylpyrazole using aryl iodides (Scheme 67).[106]

2.1.2.9. Anilides. The preparation of *ortho*-substituted anilides via a palladium-catalyzed direct arylation has recently been reported by Daugulis (Scheme 68).[112] This method demonstrated a wide functional group tolerance on both the anilide and aryl iodide moieties. Again, monoary-lated products were exclusively obtained when *ortho*- or *meta*-substituted anilides were used in the reaction.

2.1.2.10. Ethers. Fagnou recently reported the direct arylation of an aryl ether (Scheme 69).[28] A broad range of electron-rich and electron-poor aryl bromides and chlorides

Scheme 66

81%

55%

Scheme 67

61%   59%

Scheme 68


55-96%

R = H, Br, I, Me
R' = H, 3-Br, 4-Me, 4-OMe, 3-CO₂Me

could be used in the presence of 10 equiv of benzodioxole to give high yields of the coupled products. Sterically-encumbered aryl bromides could also be used to afford the desired product in good yield. Unexpectedly, the use of aryl iodides under the reaction conditions was found to instead give homocoupled products.

2.1.2.11. Alkyls. Dyker reported a procedure for the synthesis of annulated pyrans and furans via a palladium-catalyzed domino coupling of *o*-iodoanisoles.[113−116] In this unusual domino coupling, three molecules of 2-iodoanisole combine to selectively form the substituted dibenzopyran in 90% yield (Scheme 70). The proposed mechanism involves an initial oxidative addition/cyclometalation sequence that results in the formation of a five-membered oxapalladacycle, **28**, which subsequently undergoes oxidative addition with a

Scheme 69

62%   78% (X = Cl)   86%
(X = Cl)   83% (X = Br)   (X = Br)

81%   80%
(X = Br)   (X = Br)
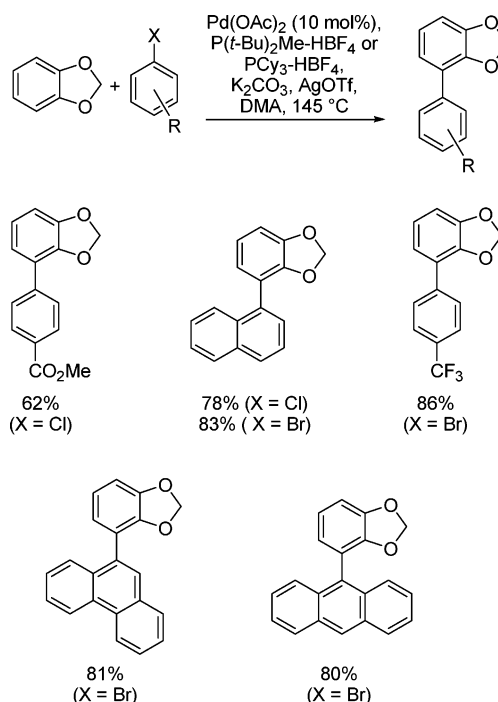
Scheme 70

90%
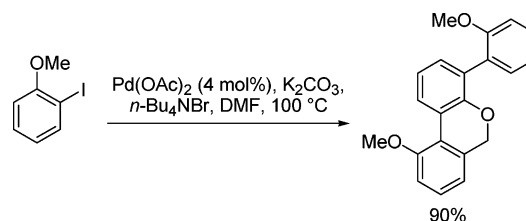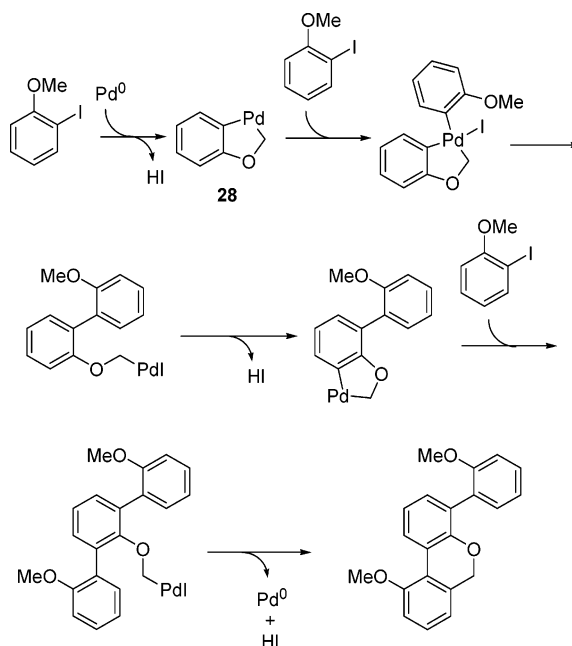
Scheme 71

second equivalent of 2-iodoanisole to afford a palladium-(IV) intermediate (Scheme 71). Reductive elimination of this palladium(IV) intermediate to generate the first aryl−aryl bond, followed by a second *ortho* cyclometalation and oxidative addition of a third equivalent of 2-iodoanisole then forms a second palladium(IV) intermediate. Finally, reductive

elimination and subsequent cyclometalation/reductive elimination result in the dibenzopyran product. Alternatively, a transmetalation-type exchange of aryl ligands between different palladium(II) centers is possible (Scheme 10).[59]

The same authors have also demonstrated that *tert*-butyl-substituted arenes undergo C−H activation at the sp^3-hybridized center followed by direct arylation to afford the benzocyclobutyl product (Scheme 72).[117] Although this

Scheme 72
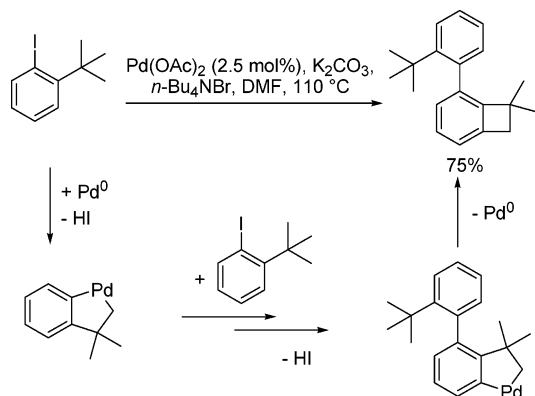
pathway involves formation of a strained four-membered ring, the authors propose that carbocycle formation may be driven in this case by the steric interaction between the aryl substituent and the *gem*-dimethyl group.[118]

2.1.2.12. Phosphines. More recently, Hartwig and co-workers developed conditions for the preparation of an air-stable, sterically-hindered ferrocenyldialkylphosphine used for palladium-catalyzed C−C, C−N, and C−O cross-coupling reactions.[119] Treatment of (di-*tert*-butylphosphino)-ferrocene with Pd(OAc)$_2$ and sodium *tert*-butoxide in neat phenyl chloride at 95−110 °C afforded the pentaphenylferrocenyl ligand in 90% yield by NMR spectroscopy (Scheme 73).

Scheme 73
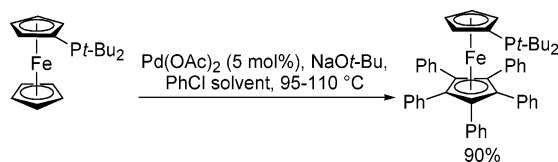
2.1.3. Direct Arylation of Aromatic Hydrocarbons in the Absence of a Directing Group

While reports of direct arylation of unfunctionalized aromatics are uncommon, Dyker reported the arylation of azulene, an aromatic hydrocarbon that exhibits an increased reactivity due to its dipolar nature (Scheme 74).[120] Under

Scheme 74

X	R	Equiv of ArX	Pd(OAc)$_2$	Yield
I	H	5	5 mol%	5%
I	H	30	5 mol%	13%
Cl	NO$_2$	5	5 mol%	16%
Cl	NO$_2$	5	15 mol%	28%
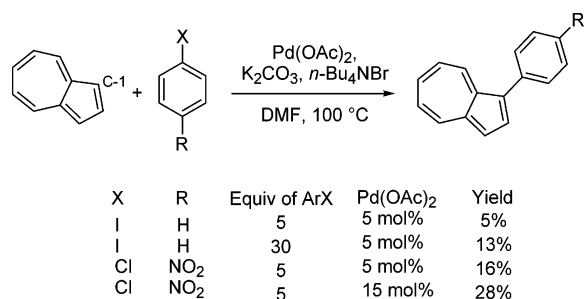
palladium-catalyzed conditions, azulene is arylated regioselectively at the electron-rich C-1 position. Several mechanistic experiments suggest a process involving electrophilic aromatic substitution of azulene with the in situ generated arylpalladium halide. Typical yields for this process were low, exemplifying the difficulty associated with palladium-catalyzed nondirected intermolecular arylation. Extension of this arylation protocol to the arylation of other polycyclic aromatic hydrocarbons including anthracene, phenanthrene, and pyrene were not successful.

Iridium has also been used for the direct arylation of arene C−H bonds in the absence of a directing group.[121] In this study, various aryl iodides were reacted with benzene in the presence of [Cp*IrHCl]$_2$ (5−10 mol %) at 80 °C to afford the corresponding biaryl products in moderate yields (Scheme 75).

Scheme 75

|	R =	2-OMe	29%
		3-OMe	53%
		4-OMe	66%
		2-Me	30%
		3-Me	52%
		4-Me	30%
		3,5-Me	51%
		H	66%
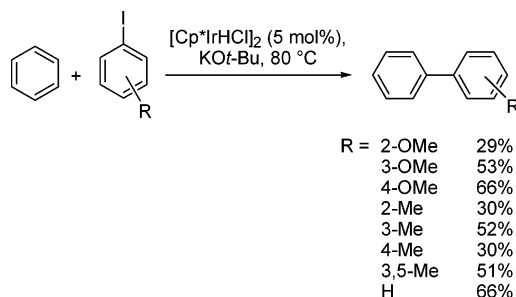
The authors propose that the reaction proceeds via initial base-mediated reduction of Cp*Ir(III) to Cp*Ir(II), followed by electron transfer from Cp*Ir(II) to the aryl iodide to afford an aryl iodide radical anion and the starting Cp*Ir(III) catalyst. Subsequent elimination of I$^-$ from the radical anion furnishes an aryl radical which can then react with benzene to give the biaryl product.

Miura and Dyker have developed a procedure for the synthesis of pentaarylated cyclopentadienes via arylation of five-membered aromatic-containing metallocenes.[122−124] Reaction of zirconocene dichloride with bromobenzene in the presence of Pd(OAc)$_2$, PPh$_3$, and Cs$_2$CO$_3$ in DMF at 130 °C afforded the 1,2,3,4,5-pentaphenyl-1,3-cyclopentadiene in 70% yield (Scheme 76). While titanocene dichloride and

Scheme 76
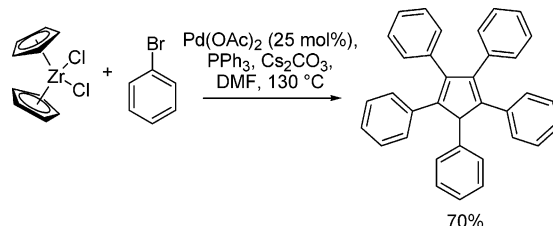
nickelocene afforded >60% yields of product, cobaltocene and ferrocene gave low yields (23% and <1%, respectively) of the desired product. Both electron-rich and electron-poor aryl bromides were found to be compatible under the reaction conditions. In addition, use of tri-*tert*-butylphosphine was shown to enhance the efficiency of the reaction with certain aryl bromides. Mechanistically, the authors propose that while the first arylation is considered to involve transmetalation between the metallocene and the phenylpalladium halide intermediate, subsequent arylations likely occur with the corresponding monoarylated cyclopentadiene moiety via

a base-mediated process that resembles arylation reactions of other soft nucleophiles.[125] This method was also extended to the palladium-catalyzed arylation of cyclopentadiene with aryl bromides. In this case, deprotonation of cyclopentadiene in the presence of base affords a relatively stable cyclopentadienyl anion, which can then undergo transmetalation and subsequent arylation.

A direct arylation of electron-deficient perfluorobenzenes with various aryl halides using Pd(OAc)$_2$ and P(t-Bu)$_2$Me$-$HBF$_4$ was recently reported (Scheme 77).[126] Aryl chlorides,

Scheme 77
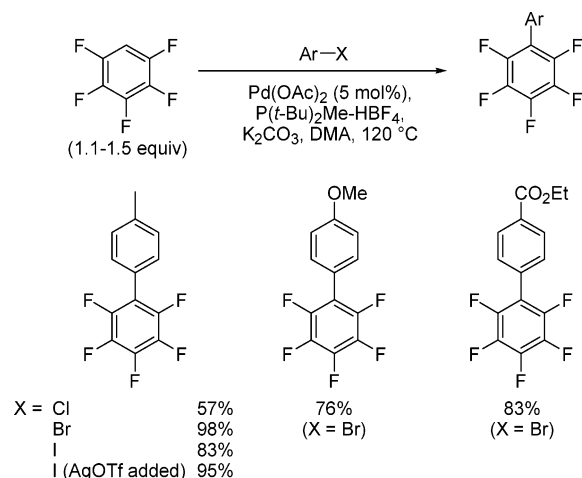
bromides, and iodides all afforded the desired biaryl products, with aryl bromides being the most effective. Higher yields of products were obtained with aryl iodides when AgOTf was added. Arylation of pentafluorobenzene with a number of arylbromides with varying electron-donating and electron-withdrawing substituents afforded the desired biaryl products in good to excellent yields.

In addition, these conditions could be used for the selective monoarylation of mono-, di-, tri-, and tetrafluorobenzenes using 4-bromotoluene (Scheme 78). Interestingly, arylation

Scheme 78
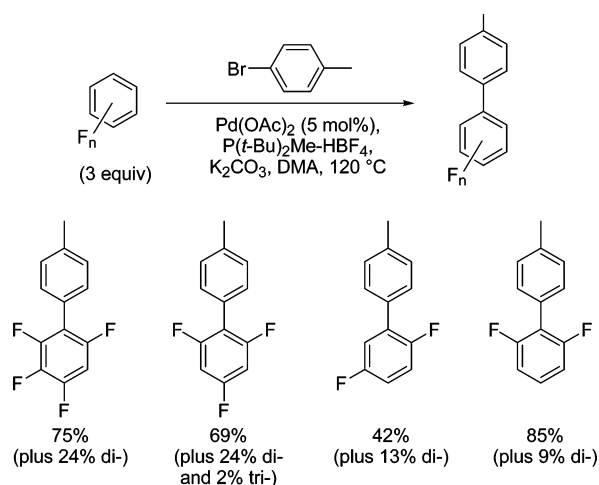
of 1,3-difluorobenzene occurred selectively at the C$-$H bond between the two fluorine atoms in 85% yield.

This reaction exhibits reactivity opposite that of S$_E$Ar reactions. Further computational and experimental studies determined that the key C$-$H bond functionalization step occurs via a concerted arene metalation and proton abstraction. The proposed mechanism is illustrated in Scheme 79

Scheme 79
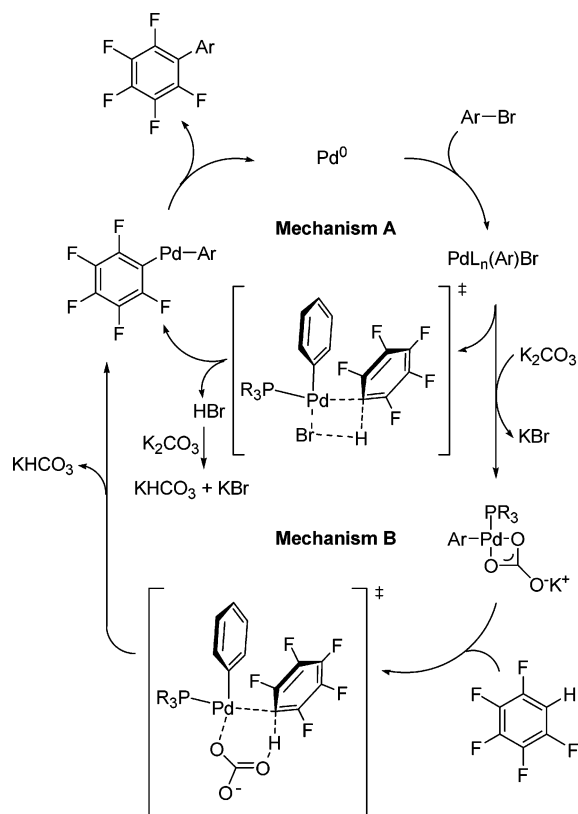
and is believed to occur via proton abstraction by a ligated bicarbonate ion (mechanism B). Alternatively, it is also possible that proton abstraction could occur with a ligated Br ion as well (mechanism A).

2.2. Intramolecular Aryl–Aryl Bond Formation

Intramolecular direct arylation reactions have been extensively utilized in organic synthesis as a route to numerous complex polycyclic ring systems. This section of the review will focus on the developments of this important reaction with regard to recent mechanistic studies and the application of this methodology toward a variety of natural products and synthetically interesting materials.
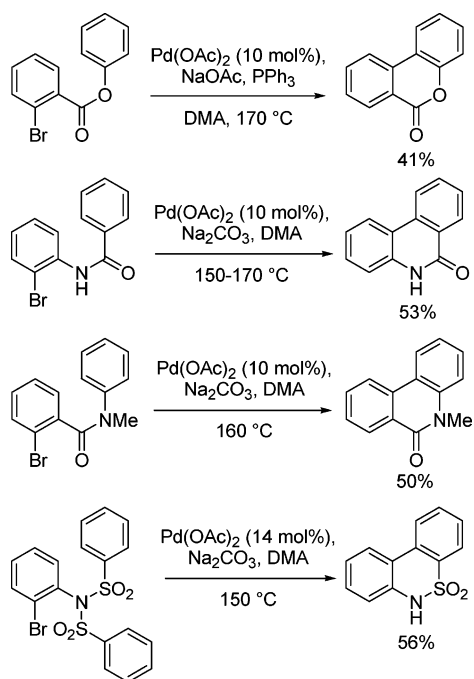
2.2.1. Scope and Limitations

One of the earliest examples of intramolecular direct arylation was reported by Ames in the early 1980s.[127] In this seminal study, a variety of functionalized dibenzofurans were prepared by treating the corresponding 2-bromophenyl phenyl ethers in DMA at 170 °C in the presence of Pd(OAc)$_2$ and Na$_2$CO$_3$ (Scheme 80). Electron-donating and electron-withdrawing substituents were tolerated under the reaction conditions to afford the desired products in good yields. In addition, reactions using (iodophenyl)phenylamine and iodobenzophenone were found to yield the corresponding carbazole and fluorenone products in high yields.[128]

The authors extended this method to the synthesis of other cyclic compounds by preparing substrates with varying linkages between the two aryl groups (CH$_2$O, NRCO, SO$_2$NR) and subjecting these compounds to their palladium-catalyzed direct arylation conditions (Scheme 81).[128] In these cases however, preparation of the desired fused six-membered ring products occurred in low yields.
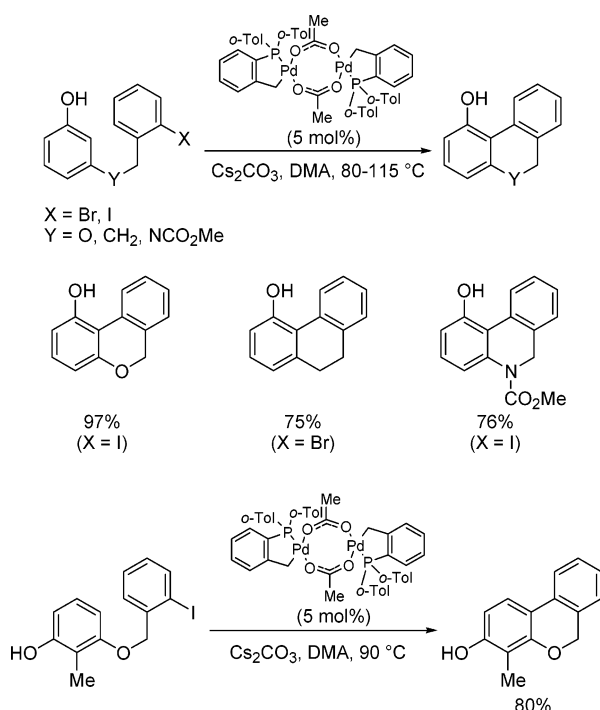
Scheme 80

Pd(OAc)$_2$ (10 mol%),
Na$_2$CO$_3$, DMA
170 °C

R = 4-NO$_2$ 78%
2-NO$_2$ 76%
2-CN   80%
H   74%
2-HOCH$_2$ 56%
2-CO$_2$H   66%

Pd(OAc)$_2$ (3 mol%),
NEt$_3$, CH$_3$CN
150 °C

73%

Pd(OAc)$_2$ (10 mol%),
PPh$_3$, 190 °C
N-methylimidazole

100%

Scheme 81

Pd(OAc)$_2$ (10 mol%),
NaOAc, PPh$_3$
DMA, 170 °C

41%

Pd(OAc)$_2$ (10 mol%),
Na$_2$CO$_3$, DMA
150-170 °C

53%

Pd(OAc)$_2$ (10 mol%),
Na$_2$CO$_3$, DMA
160 °C

50%

Pd(OAc)$_2$ (14 mol%),
Na$_2$CO$_3$, DMA
150 °C

56%

Scheme 82

(5 mol%)
Cs$_2$CO$_3$, DMA, 80-115 °C

X = Br, I
Y = O, CH$_2$, NCO$_2$Me

97%
(X = I)

75%
(X = Br)

76%
(X = I)

CO$_2$Me

(5 mol%)
Cs$_2$CO$_3$, DMA, 90 °C

80%

Scheme 83

(5 mol%)
Cs$_2$CO$_3$, DMA, 115 °C

29

+

30

96%
1:2 = **29**:**30**

Scheme 84

base·HX   base

The intramolecular arylation of phenolates using Herrmann's catalyst and Cs$_2$CO$_3$ in DMA has been reported by Rawal (Scheme 82).[129] Under these conditions, a variety of biaryl compounds containing various linkages between the two aryl groups were obtained in good to excellent yields.

Selective direct arylation for this system was observed to occur *ortho* to the phenol functionality. For substrates bearing an *ortho* blocking group, cyclization also occurred, although in this instance cyclization occurred *para* to the phenol functionality. The reaction was also found to be sensitive to steric effects, since bulky aryl iodides underwent cyclization preferentially at the less hindered 4-position (Scheme 83).

The proposed mechanism for this reaction begins with the oxidative addition of palladium to the aryl halide to afford an arylpalladium halide intermediate (Scheme 84). *Ortho* nucleophilic attack of the palladium(II) species by the phenolate, followed by tautomerization, generates a dia-

rylpalladium species which undergoes reductive elimination to afford the desired product. The authors suggest that the improved yields in this system are due to the increased electron density on the aromatic ring in the phenolate, thereby making it more reactive in the coupling reaction. In fact, the importance of the free hydroxyl group to the success of
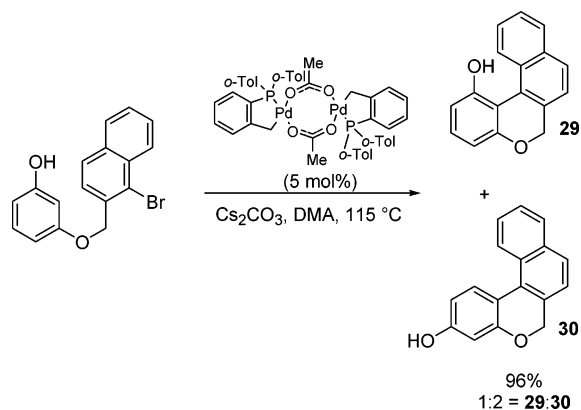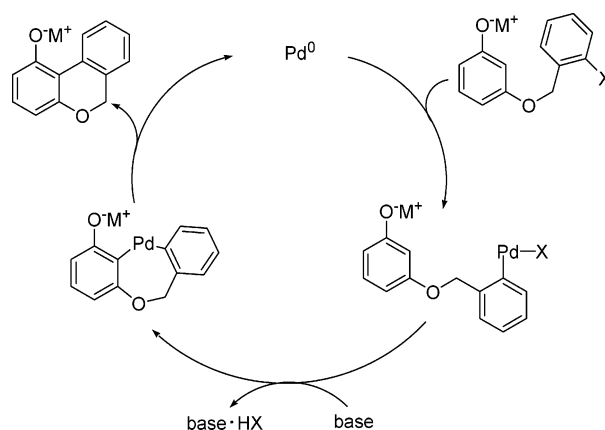
Scheme 85
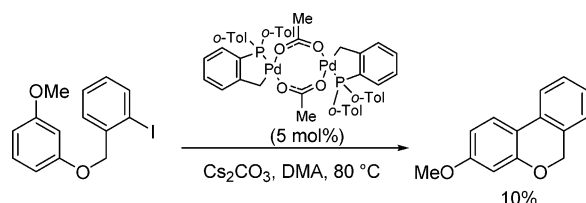
the reaction was demonstrated by a comparison study in which a substrate containing a methyl ether instead of a phenol was found to afford only a 10% yield of the desired 4-cyclized product along with recovered starting material (Scheme 85).

Recently, Fagnou reported extensive investigations into the scope and limitations of the intramolecular direct arylation reaction of arenes.[130] Their improved reaction conditions resulted in enhanced catalytic activity using very low catalyst loadings for previously reported unreactive and poorly reactive substrates. Formation of the desired biaryl was achieved in 96% yield using 0.1 mol % Pd(OAc)$_2$, ligand **31**, and K$_2$CO$_3$ in DMA at 145 °C (Scheme 86). In addition

Scheme 86
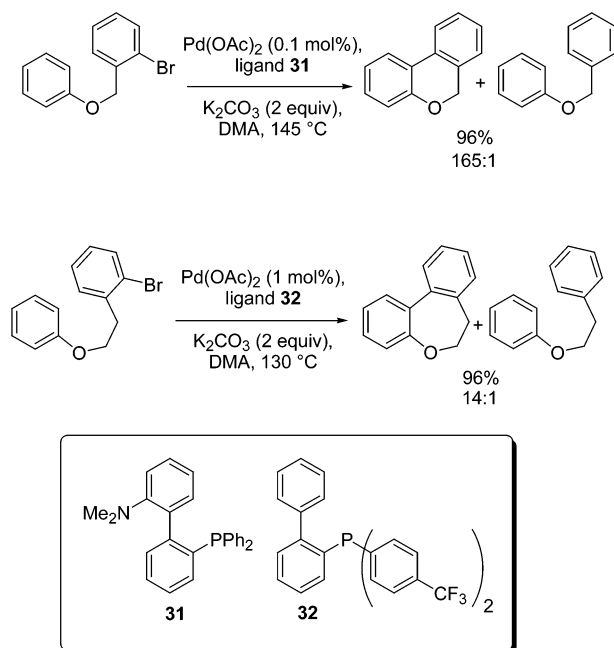
to the expected biaryl product, a small amount of hydrodebromination byproduct was also observed. This method was also effective for the preparation of more challenging seven-membered ring products. In this particular example, use of the electron-deficient ligand **32** significantly enhanced the reaction, affording the biaryl product in 96% yield. The authors suggest the enhanced activity might be due to the facile dissociation of the bulky, electron-poor ligand from the palladium metal, thereby allowing for facile coordination of the arene.

A variety of six-membered ring biaryl compounds were prepared bearing both electron-donating and electron-withdrawing substituents in excellent yields (Scheme 87). Furthermore, alkyl- and nitrogen-containing tethers were tolerated, but required higher catalyst loadings to ensure complete conversion.

While the aforementioned catalytic system proved extremely effective for the direct arylation of aryl bromides,

Scheme 87
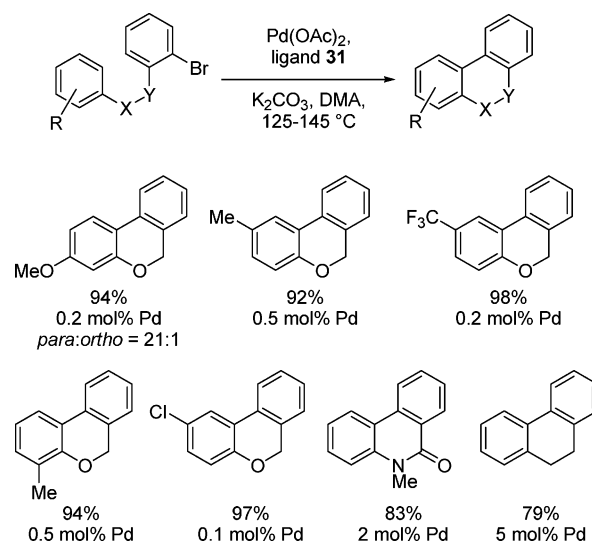
poor yields of the cyclized products or no reaction at all was observed for aryl chlorides. To address this issue, Fagnou[131] developed new conditions employing electron-rich N-heterocyclic carbene (NHC) ligands.[132] Using 1−3 mol % catalyst **33** and K$_2$CO$_3$ in DMA at 130 °C, a variety of functionalized five- and six-membered rings could be prepared in excellent yields with varying tethers that included ether, amine, amide, and alkyl functionalities (Scheme 88).
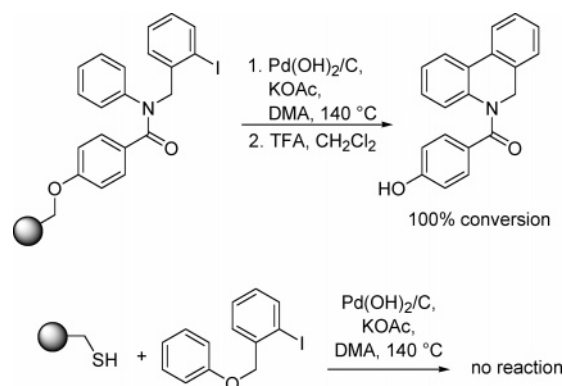
Scheme 88
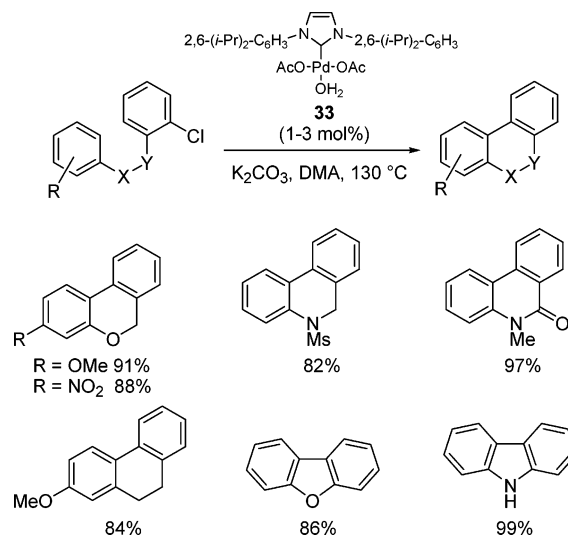
The same authors subsequently demonstrated that Pd(OH)$_2$/C is also very effective for the intramolecular direct arylation of aryl iodides and aryl bromides to form five- and six-membered hetero- and carbocyclic ring systems (Scheme 89).[28,133]

Investigations were also conducted to ascertain the nature of the active catalyst. Treatment of a solid support substrate with Pd(OH)$_2$/C, followed by cleavage with TFA, gave the desired product in 100% conversion (Scheme 90). This result indicates that a soluble catalyst species had leached into solution, since it is not possible for two solid phases to interact. In a second test, a homogeneous aryl iodide was treated with Pd(OH)$_2$/C in the presence of a solid-phase thiol scavenger resin. In this case, no reaction occurred, suggesting a homogeneous active catalyst was operative since this
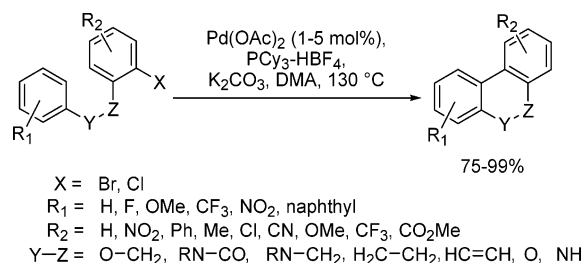
Scheme 89

| 100% (X = I)	98% (X = I)	80% (X = Br)	86% (X = I)

92% (X = I)	84% (X = I)	84% (X = I)

Scheme 90

100% conversion

no reaction

Scheme 91

75-99%

X =   Br, Cl
R_1 =   H, F, OMe, CF_3, NO_2, naphthyl
R_2 =   H, NO_2, Ph, Me, Cl, CN, OMe, CF_3, CO_2Me
Y−Z =   O−CH_2, RN−CO,   RN−CH_2, H_2C−CH_2, HC=CH, O, NH
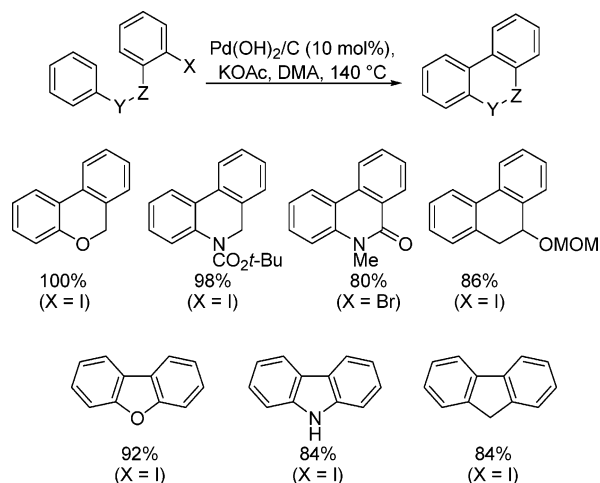
scavenger resin would be expected to only remove the homogeneous catalyst present in the reaction.

More recently, Fagnou developed an efficient general catalyst system for the intramolecular direct aryation of a broad scope for aryl chlorides, bromides, and iodides (Scheme 91) to generate numerous five- and six-membered carbo- and heterocyclic biaryl compounds.[28] A variety of ether-, amine-, amide-, alkyl-, and alkenyl-based tethers were also tolerated. In addition, a variety of electron-withdrawing and electron-donating substituents were compatible on both aryl moieties, affording the desired products in excellent yields and high regioselectivity. Furthermore, this catalyst system also allowed for the direct arylation of more sterically-demanding substrates (Scheme 92).

Although these conditions worked well for aryl bromides and chlorides, aryl iodides were found to react poorly (Scheme 93). Subsequent studies in which the addition of 1 equiv of KI retarded the direct arylation of an aryl bromide led the authors to suggest that the iodide anions generated during the course of the reaction act as catalyst inhibitors.

Scheme 92

97%	90%	85%

Scheme 93

X	Additive	Yield
Br	none	99%
Br	KI	< 5%
I	none	64%
I	Ag_2CO_3	99%
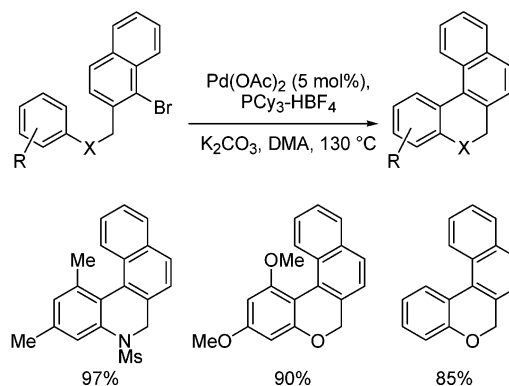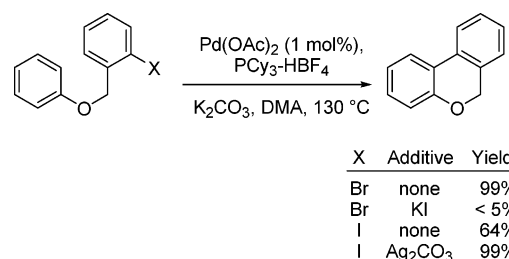
This problem was overcome by the addition of Ag_2CO_3 to the catalyst system. Using these slightly modified conditions, a diverse range of biaryl compounds were prepared from the corresponding aryl iodides in high yield.

Since the use of aryl iodides is common in cross-coupling reactions, it is unlikely that the accumulation of iodide in the reaction mixture inhibits the oxidative addition or reductive elimination steps. Instead, the authors suggest that iodide inhibition occurs during the arylation step by binding to the palladium, forming a coordinatively saturated and therefore unreactive palladium species (Scheme 94).

Scheme 94

catalyst sequestration via palladate formation
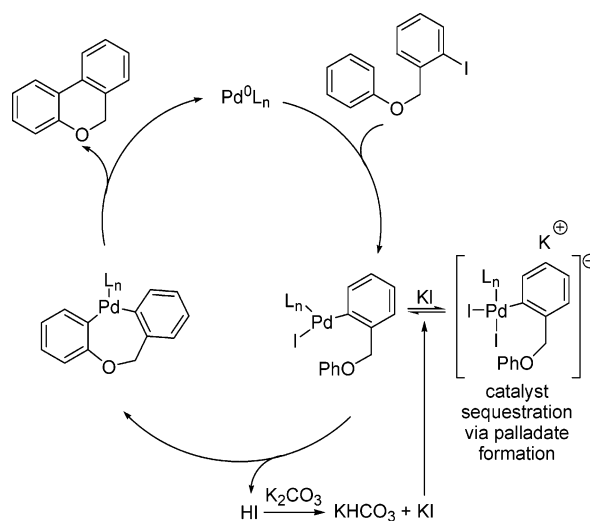
This methodology was further extended to a tandem Heck/direct arylation reaction sequence.[134] Substrates containing both a bromide and a chloride functionality were reacted with a Heck acceptor using $Pd(OAc)_2$ (10 mol %), Pt-Bu_3−HBF_4 (20 mol %), and K_2CO_3 in DMA at 130 °C. Under these conditions, a variety of substituted biaryl products could be prepared in good yields (Scheme 95). In addition, the reaction

Scheme 95

71%

67%

72%

Scheme 96

69%
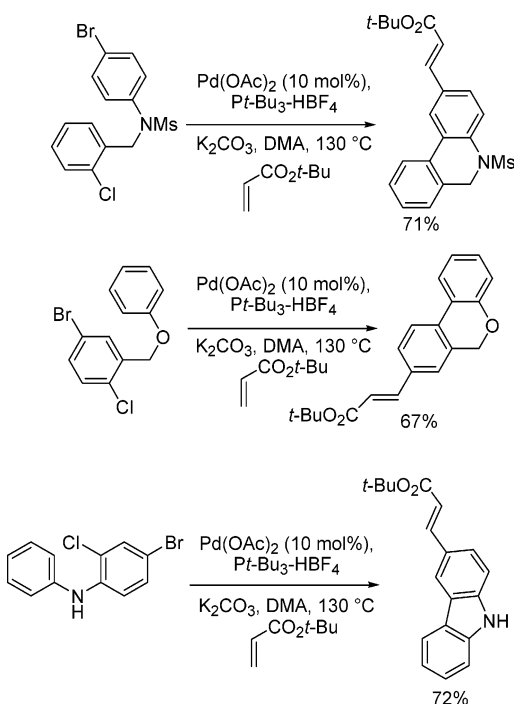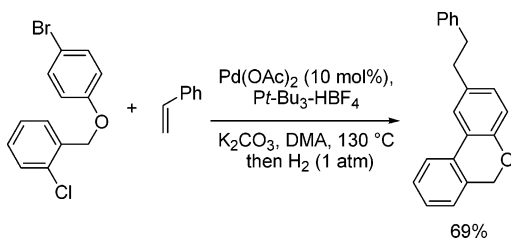
was compatible with a number of acrylates and other alkenes. Further extension of these conditions allowed for an interesting tandem-sequential Heck/direct arylation/hydrogenation sequence by replacing the nitrogen atmosphere of the completed reaction with hydrogen (Scheme 96).

Fagnou subsequently conducted a series of experiments aimed at providing insight into palladium-catalyzed direct arylation reactions.[28] Competition experiments depicted in Scheme 97 were carried out to determine whether the catalyst would react preferentially with a more electron-poor or

Scheme 97

1.3:1

2:1
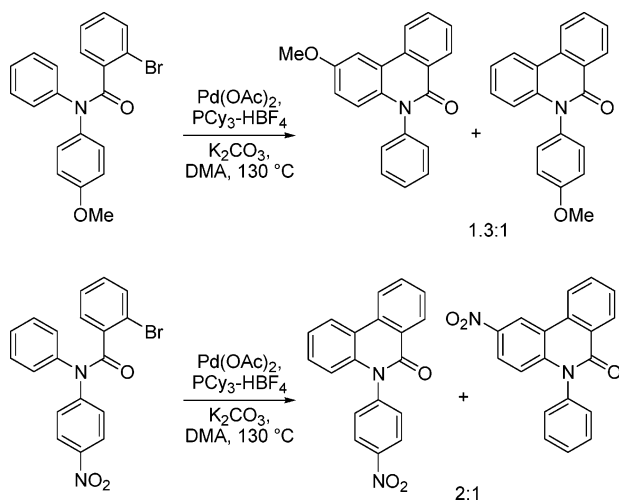
electron-rich arene. In both cases, a small selectivity was observed with preference for the more electron-rich arene, although this argument assumes that the reaction occurs under Curtin−Hammett conditions (i.e., that amide rotation is fast compared to the rate of direct arylation).

In addition, while a primary kinetic isotope effect of 3.5 was reported under the conditions described in Scheme 87, direct arylation of a simple unsubstituted aryl bromide resulted in a primary kinetic isotope effect of 4.25 (Scheme 98).

Scheme 98

$k_H/k_D = 4.25$
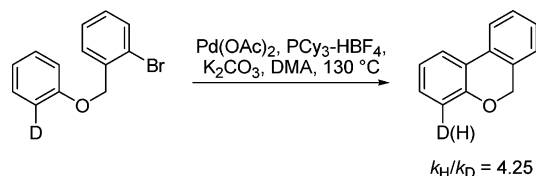
These results exclude an electrophilic aromatic substitution pathway since this type of reaction usually does not exhibit a kinetic isotope effect. The authors rationalize the observed primary kinetic isotope effect by comparing the relative rates of coordination of the arene to give π,η^1 and/or π,η^2 species from the corresponding palladium(II) arene intermediate (k_1 and k_{-1}) to the rate of deprotonation (k_2) (Scheme 99). A fast and reversible k_1 and k_{-1} compared to k_2 would make k_2 kinetically significant, thereby resulting in a primary kinetic isotope effect. Two possible pathways may exist under these circumstances: (1) a concerted S_E3 process in which an external base deprotonates the arene at the same time as Pd−C bond formation, or (2) a σ-bond metathesis pathway where an anionic ligand on the palladium removes the proton. As well, the small electronic bias observed for the competion reaction may suggest the absence of a cationic arenium intermediate in the rate-determining step, which further supports the aforementioned concerted Pd−C bond formation/C−H bond cleavage processes.

At the same time, Echavarren independently conducted experiments and carried out computational studies to gain insight into the mechanism of this direct arylation reaction.[29] Competition experiments were preformed on substrates whereby the aryl bromide could react with either a substituted or an unsubstituted arene (Scheme 100). In this study, the substrates used contained an alkyl tether between the two aryl groups to minimize steric and/or electronic bias in the reaction. Since small amounts of phenanthrenes were observed in the reaction, the crude mixtures were treated with DDQ to fully convert the remainder of the cyclized products to the corresponding phenanthrenes to facilitate the measurement of the ratio of regioisomers.
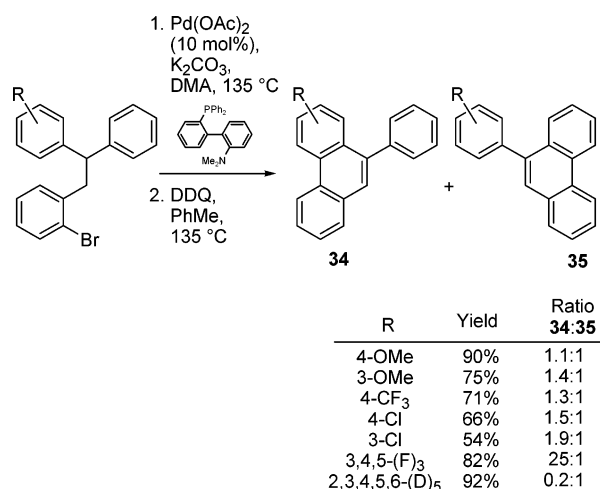
These studies by Echavarren found a trend different from that of Fagnou's experiment, in that electron-deficient aromatics were slightly favored over electron-rich ones, although this electronic bias was very small regardless of the electronic nature of the substituent (for example, R = OMe, CF$_3$, and Cl). Additional studies found that reaction with R = 3,4,5-F$_3$ resulted in almost exclusive coupling at the trifluorophenyl ring (25:1), which is not consistent with an electrophilic aromatic substitution reaction. Furthermore, studies using a deuterated substrate gave an isotope effect (k_H/k_D) of 5 under the reaction conditions, and $k_H/k_D = 6.7$ when run in DMF at 100 °C.

On the basis of these experimental studies along with corroborating computational findings, the authors concluded
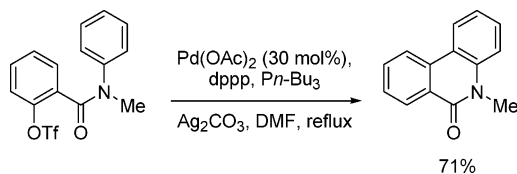
Scheme 99

S_E3

π,η^1

and/or

π,η^2

σ−bond metathesis

k_1 / k_{-1}

k_2

+ HX

Scheme 100

1. Pd(OAc)$_2$ (10 mol%), K$_2$CO$_3$, DMA, 135 °C

2. DDQ, PhMe, 135 °C

34 + **35**

R	Yield	Ratio 34:35
4-OMe	90%	1.1:1
3-OMe	75%	1.4:1
4-CF$_3$	71%	1.3:1
4-Cl	66%	1.5:1
3-Cl	54%	1.9:1
3,4,5-(F)$_3$	82%	25:1
2,3,4,5,6-(D)$_5$	92%	0.2:1
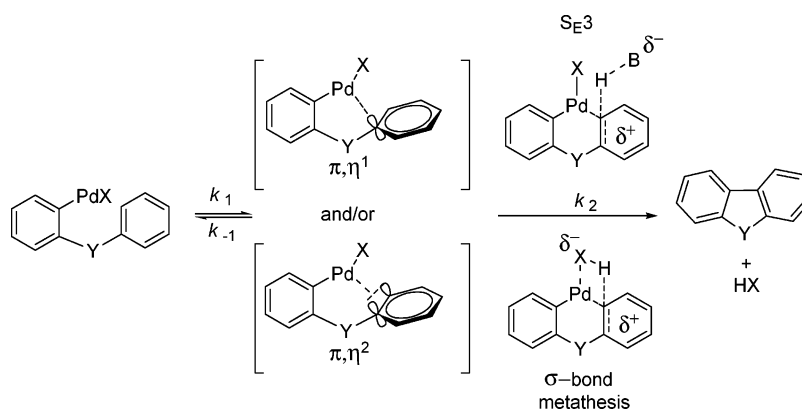
that the palladium-catalyzed arylation does not involve an electrophilic aromatic substitution. Instead, the authors proposed a mechanism whereby proton abstraction by carbonate or a related ligand (but not bromide according to computational studies) more likely occurs.

Harayama has also reported extensive studies on palladium-catalyzed intramolecular direct arylation reactions and their application toward the synthesis of numerous natural products (see section 2.2.2.1).[135] In the early stage of development, stoichiometric Pd(OAc)$_2$ was typically required in this intramolecular reaction for the coupling of aryl iodides, bromides, and triflates. However, the authors found that in several cases, only 30 mol % Pd(OAc)$_2$ was required to afford the cyclized product in good yield (Scheme 101).[136,137]

Scheme 101

Pd(OAc)$_2$ (30 mol%), dppp, Pn-Bu$_3$

Ag$_2$CO$_3$, DMF, reflux

71%

Subsequent studies led to the development of improved conditions that allowed for the coupling of aryl iodides, bromides, and triflates using catalytic palladium (eq 1, Scheme 102).[138−140] While these conditions worked well for oxy-substituted haloarenes (eq 2, Scheme 102), extension to oxy-substituted aryl triflates afforded poor yields of the desired product. Further studies by the authors have since

Scheme 102

Pd(OAc)$_2$ (20 mol%), Pn-Bu$_3$, base, DMF, reflux (1)

X	Base	Yield
OTf	i-Pr$_2$NEt	84%
I	Ag$_2$CO$_3$	90%
Br	Ag$_2$CO$_3$	64%

Pd(OAc)$_2$ (20 mol%), Pn-Bu$_3$, base, DMF, reflux (2)

X	R$_1$	R$_2$	Base	Yield
OTf	H	OMe	i-Pr$_2$NEt	11%
OTf	OMe	H	i-Pr$_2$NEt	6%
I	H	OMe	Ag$_2$CO$_3$	83%
I	OMe	H	Ag$_2$CO$_3$	59%
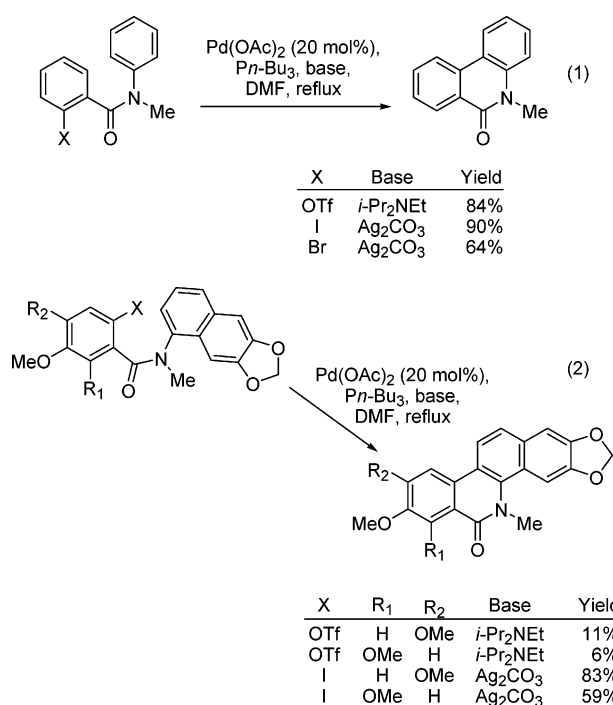
found that use of similar conditions with DBU as the base proved effective for these oxy-substituted aryl triflates.[141]

The cyclization of substrates containing nitrogen in a ring was also reported.[142−144] Six-membered tetrahydroquinoline gave an excellent yield of the desired tetracyclic product (Scheme 103), while use of the five-membered dihydroindole gave a low yield of the desired product under similar conditions. An alternative and higher yielding route to the same product was achieved using the corresponding substrate containing the iodide on the dihydroindole moiety.

This methodology has also been utilized for the regioselective synthesis of benzonaphthazepines (Scheme 104).[145,146] Substrates containing an unsubstituted naphthyl moiety underwent selective cyclization at the 8-, rather than the 2-position. The authors propose a mechanism involving oxidative addition of palladium(0) to the aryl bromide, followed by amine coordination to palladium(II) and regioselective electrophilic substitution of palladium(II) at the 8-position. Subsequent reductive elimination then affords the observed product. Other substituted naphthyl rings also showed the same regioselectivity except when bulky substituents such as a 7-isopropoxynaphthalene was used.
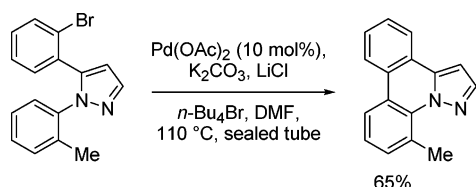
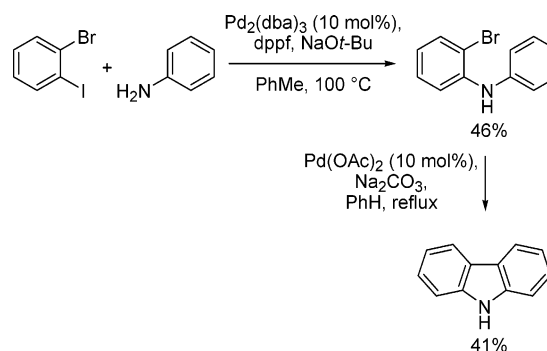**Scheme 103**
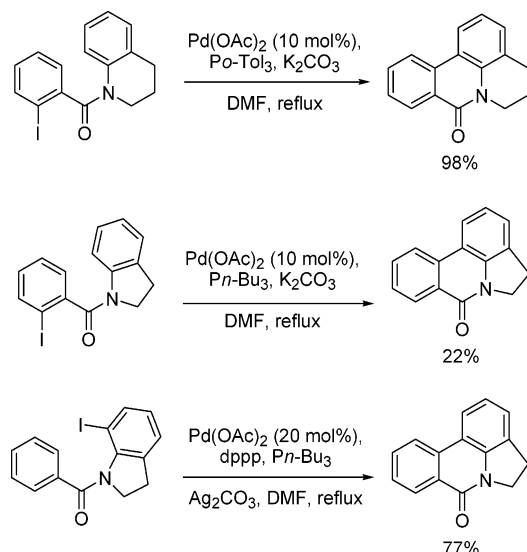
Scheme 104
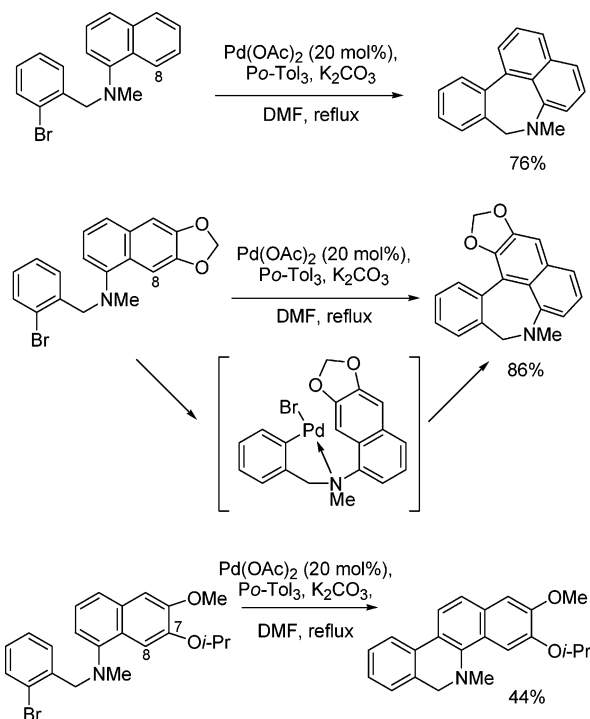
Scheme 105

Cyclization in this latter case afforded the 2-cyclized product exclusively.

Domínguez has described the synthesis of pyrazolophenanthridines via a palladium-catalyzed direct arylation of aryl-substituted pyrazoles (Scheme 105).[147] The resulting cyclization using Pd(OAc)$_2$, K$_2$CO$_3$, LiCl, and n-Bu$_4$Br in DMF at 110 °C in a sealed tube generated a number of pyrazolophenanthridines in 42−65% yields.
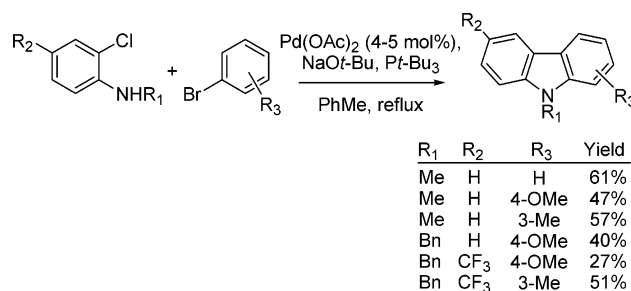
Scheme 106

A synthesis of carbazoles via a two-step process involving a palladium-catalyzed amination/intramolecular direct arylation reaction sequence has also been reported (Scheme 106).[148] The reaction of 2-bromoiodobenzene with aniline in the presence of Pd$_2$(dba)$_3$, dppf, and NaOt-Bu in toluene at 100 °C afforded (2-bromophenyl)aniline in 46% yield. This compound was then treated with Pd(OAc)$_2$ and Na$_2$CO$_3$ in refluxing benzene to afford the desired carbazole in 41% yield.

Bedford subsequently reported a similar one-pot carbazole synthesis.[149] Various N-substituted 2-chloroanilines were reacted with aryl bromides using Pd(OAc)$_2$, NaOt-Bu, and Pt-Bu$_3$ in refluxing toluene (Scheme 107). Experimental

Scheme 107

R$_1$	R$_2$	R$_3$	Yield
Me	H	H	61%
Me	H	4-OMe	47%
Me	H	3-Me	57%
Bn	H	4-OMe	40%
Bn	CF$_3$	4-OMe	27%
Bn	CF$_3$	3-Me	51%

evidence suggests that the palladium-catalyzed amination occurs first, followed by direct arylation of the aryl chloride. Unsubstituted 2-chloroanilines afford only the amination product, and none of the desired carbazole scaffold.

Larock has also reported a convenient one-pot two-step synthesis of carbazoles.[150] The first step of the process involves addition of o-iodoaniline to a benzyne intermediate generated in situ from silylaryl triflates using CsF. The resulting N-arylated o-iodoaniline then undergoes a palladium-catalyzed intramolecular direct arylation to afford the desired carbazole. Using this methodology, a variety of NH- and N-substituted carbazoles could be prepared in good yields (Scheme 108). In addition, nitrogen-containing six-membered rings and dibenzofurans could be prepared from the corresponding benzylamines and phenol derivatives, respectively.

An interesting coupling between an intermediate palladacycle derived from a bromopyridine and biphenylene has recently been reported by Gallagher and co-workers (Scheme 109).[151] Mechanistic studies suggest that the reaction proceeds via initial oxidative addition followed by C−H insertion to form a palladacycle intermediate. Reaction with biphenylene then affords the desired product. Additional mechanistic studies found that the presence of an o-aryl group adjacent to the bromide functionality was required for the
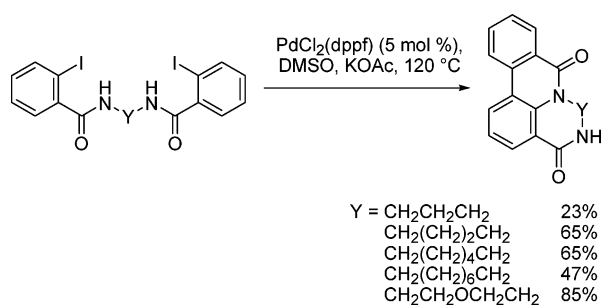
Scheme 108
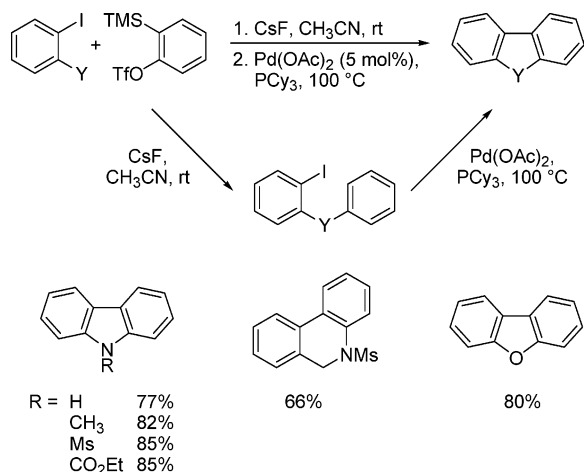
Scheme 109
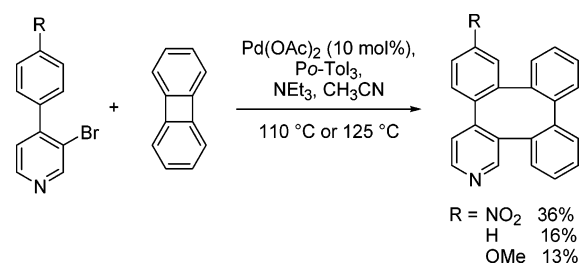
reaction to proceed, further suggesting the role of an intermediate palladacycle species.

Zhu recently reported a palladium-catalyzed domino process involving intramolecular *N*-arylation/direct arylation.[152,153] Various fused macrocyclic dihydroazaphenanthrenes and other medium-ring heterocycles were prepared by subjecting the corresponding bisaryl diiodide to PdCl$_2$-(dppf) (5 mol %) and KOAc in DMSO (0.001 or 0.02 M) at 120 °C (Scheme 110).
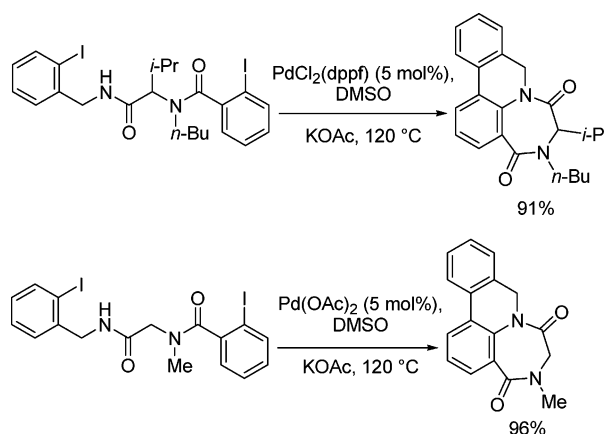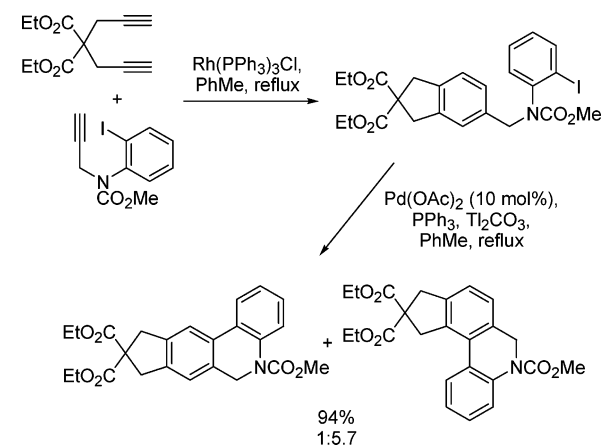
Scheme 110

This method was later extended to the synthesis of 1,4-benzodiazepine-2,5-dione derivatives (Scheme 111). The reaction was also found to work efficiently with "ligandless" palladium acetate as the catalyst, furnishing the desired polyheterocycle from the corresponding bisaryl diiodide.

Grigg described a procedure for the synthesis of phenanthrene-type heterocycles via a Rh(I)-catalyzed [2+2+2]-cycloaddition followed by a palladium-catalyzed direct arylation of the newly formed aromatic functionality (Scheme 112).[154] Analogous substrates containing an oxygen atom in the tether also underwent cyclization to afford a 1:1 regioisomeric mixture of biaryl products in 82% yield (Scheme 113).

Scheme 111

Scheme 112

Scheme 113
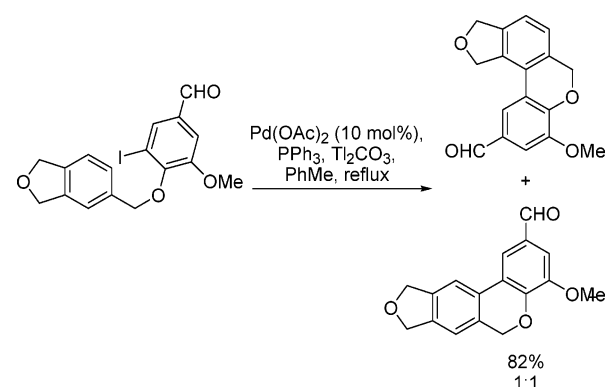
A similar cyclization using iodoindoles bearing a tethered arene has also been reported (Scheme 114).[154] This approach afforded a single dihydroazaphenanthrene derivative in 62% yield, despite the possibility of regioselectivity issues.

Scheme 114
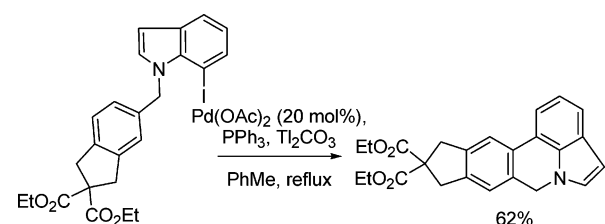
Bringmann has extensively reported on the use of direct arylation as part of an efficient strategy toward the asym-

Scheme 115

Scheme 117
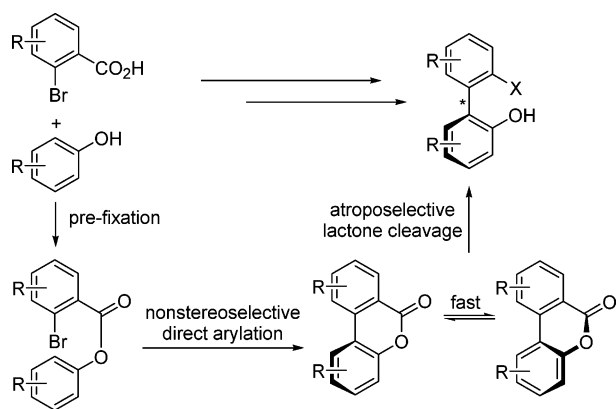
Scheme 118

metric synthesis of biaryl compounds. The principle of this method, referred to as the "lactone method," is illustrated in Scheme 115.[24,155−161] In this procedure, bromoesters are prepared by esterification of *o*-bromobenzoic acids with phenols, followed by a palladium-catalyzed direct arylation to afford configurationally unstable biaryl lactones. Atropoenantio- or atropodiastereoselective cleavage of the lactone moiety results in an axially chiral and configurationally stable acyclic biaryl product.

The direct arylation step was initially examined for a series of model compounds with varying steric bulk at the axis (Scheme 116).[162,163] While biaryl bond formation using

Scheme 116

Conditions:

A Pd(OAc)$_2$ (10 mol%), PPh$_3$, NaOAc, DMA, 130 °C

B (1 mol%)
NaOAc, DMA, 130 °C

| R | Yields | |
	Conditions A	Conditions B
H	80%	91%
OMe	77%	90%
Me	75%	87%
Et	71%	83%
i-Pr	72%	82%
t-Bu	44%	81%
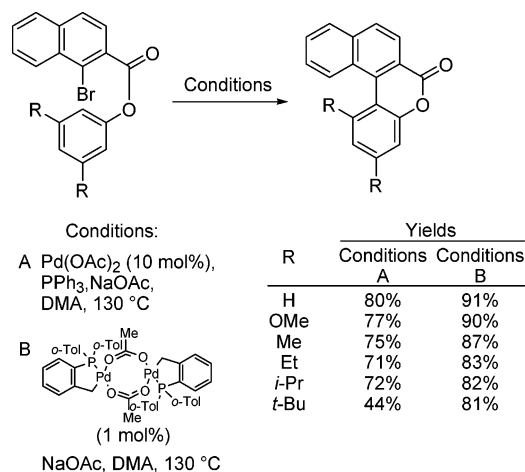
Pd(OAc)$_2$/PPh$_3$ occurred in good yields, improved yields using Herrmann's catalyst[164−166] could be achieved for more sterically-hindered substituents.

Attempts to extend this strategy toward the synthesis of the bislactone ternaphthyl resulted in only the mono direct arylation bromoacid (Scheme 117).[167]

An alternative route toward the bislactone ternaphthyl was then carried out via an intramolecular direct arylation, followed by deprotection of the benzyl ether and esterification of the resulting phenol and carboxylic acid (Scheme 118). Conversion of the benzyl ether to the aryl triflate followed by intramolecular direct arylation then afforded the desired bislactone.

Four different methods have been developed for the stereoselective lactone cleavage step (Figure 1): (1) nucleophilic ring-opening using chiral anionic nucleophiles such as amines, alcohols, and hydride transfer reagents, (2) activation of the lactone using a chiral Lewis acid followed
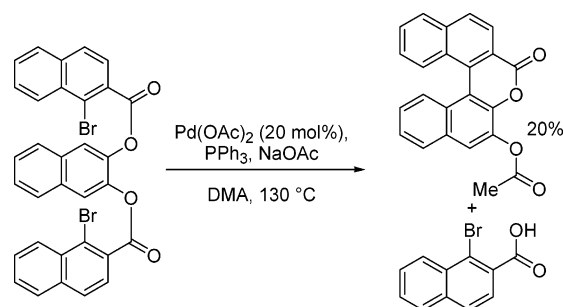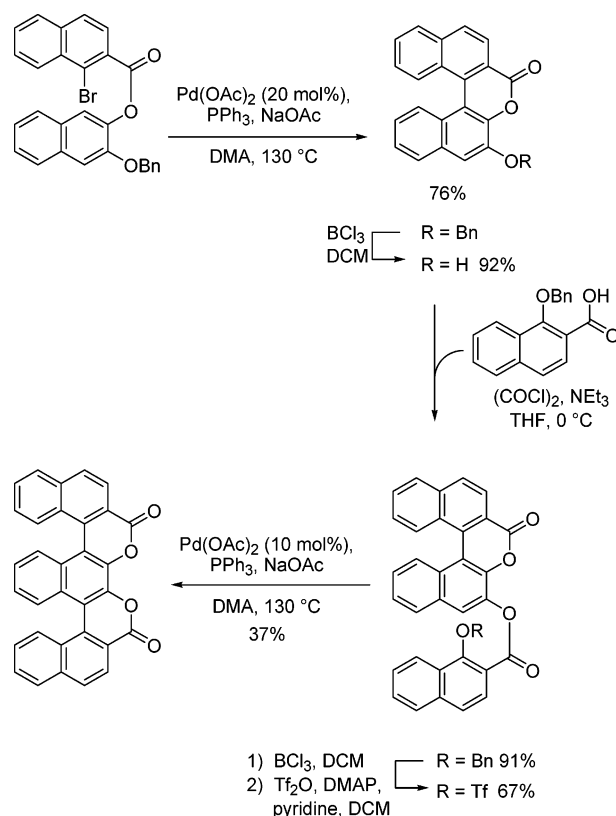
by ring-opening with a charged or uncharged achiral nucleophile, (3) activation of the lactone using an achiral Lewis acid followed by ring-opening with a charged or uncharged chiral nucleophile, and (4) selective chiral transition-metal η^6-coordination to one of the aromatic rings followed by cleavage with an achiral nucleophile.

Method I
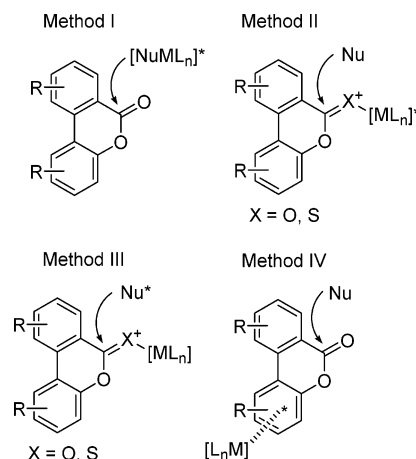
Method II

Method III

Method IV

Figure 1.

The authors have subsequently applied this methodology toward the synthesis of numerous axially chiral ligands, reagents, catalysts, and more than 30 natural products. Select examples are described in section 2.2.2.1, and more extensive reviews have also been reported.[24,155−161]

Recently, Larock developed a palladium migration/arylation method for the synthesis of fused polycycles.[48,168] The process involved a palladium-catalyzed C−H activation/1,4-palladium migration to generate a key arylpalladium intermediate that subsequently undergoes C−C bond formation by intramolecular direct arylation (Scheme 119).

Scheme 119
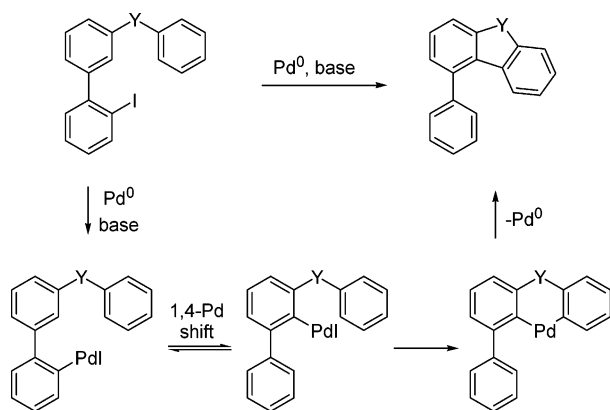
Optimal reaction conditions utilized Pd(OAc)$_2$ (5 mol %), dppm (5 mol %), and CsOPiv in DMF at 100 °C. The choice of a highly soluble cesium pivalate base proved crucial to the success of the reaction. Excellent yields of the desired phenyldibenzofurans were obtained when phenoxybiphenyls were employed, while benzylbiphenyls gave poor yields of the corresponding product (Scheme 120). The low yields of

Scheme 120

40%   89%   75%
(60:40)
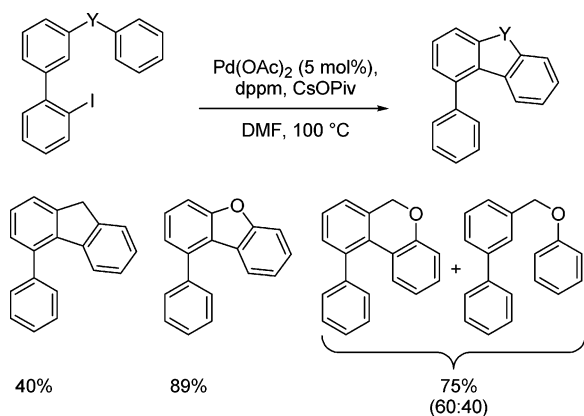
the latter substrates might be explained by the poor reactivity (as an intramolecular trap) of the benzyl moiety compared to the electron-rich oxygen-substituted phenyl ring of a phenoxybiphenyl system. In addition, six-membered ring formation is not as favorable as for the five-membered ring analogue. For six-membered ring formation, a 60:40 mixture of the desired compound to reduced product was obtained from the corresponding benzyl phenyl ether. This poor result might be due to the difficulty in forming a seven-membered ring palladacycle prior to the reductive elimination step.

This process also works with phenylnaphthalenes and arylphenanthrenes to generate the corresponding polycyclic

Scheme 121

X = I, Y = H   81%   X = I, Y = H   81%
X = Br, Y = H   70%   X = I, Y = OMe 71%
                       X = I, Y = CO$_2$Et 50%
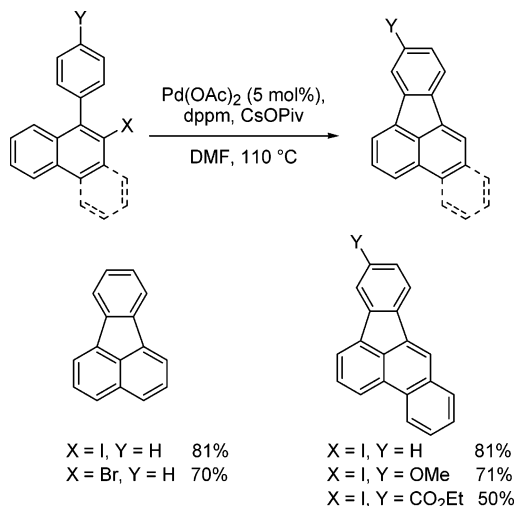
aromatic hydrocarbons in good yields (Scheme 121).[168] Iodophenylnaphthalene gave a higher yield of fluoranthene compared to the bromide starting material. In addition, the electronics of the phenanthrene were found to be important since electron-rich substrates typically gave higher yields versus electron-deficient ones. Moreover, the typical byproduct in all reactions was the reduced product, which accounted for approximately 20% of the mole balance.

This methodology was further extended to an impressive double palladium migration/direction arylation sequence. Treatment of 2-iodo-5-phenoxybiphenyl to the reaction conditions afforded the phenyldibenzofuran product in 88% yield (Scheme 122).[168] The proposed mechanism involves
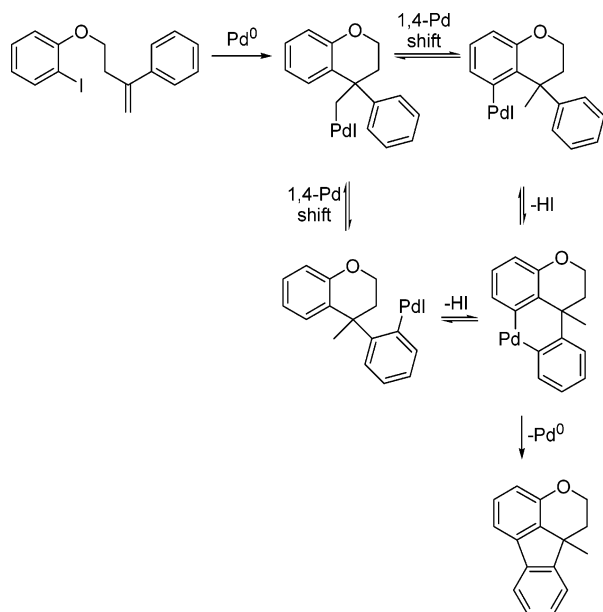
Scheme 122

88%
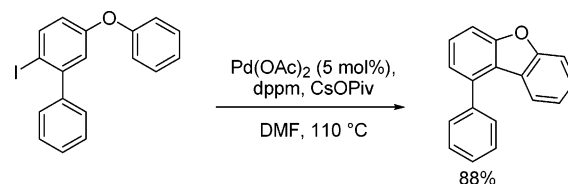
oxidative insertion of palladium into the aryl iodide, followed by 1,4-migration of palladium to the phenyl moiety by C−H activation. Bond rotation followed by 1,4-migration then affords an *o*-phenoxy palladium species, which undergoes direct arylation to form the desired phenyldibenzofuran product (Scheme 123).
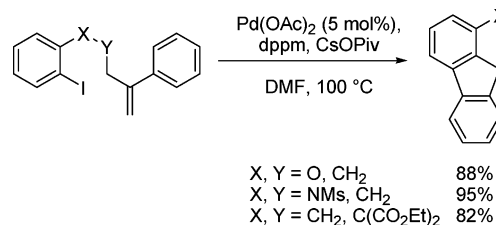
Scheme 123

Scheme 124

Scheme 125

|	
X, Y = O, CH₂	88%
X, Y = NMs, CH₂	95%
X, Y = CH₂, C(CO₂Et)₂	82%
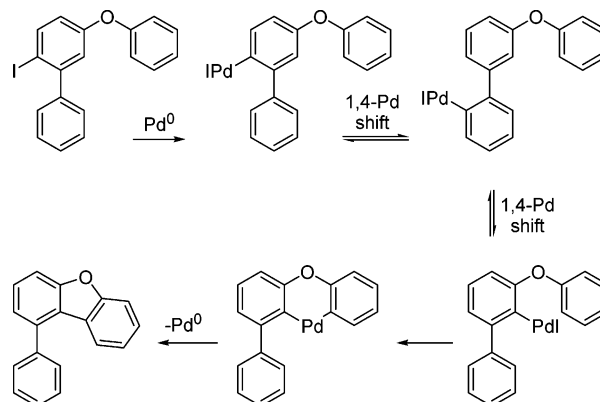
These conditions were also applied to a tandem palladium-catalyzed alkyl to aryl migration/direct arylation reaction.[169] Mechanistically, the authors propose that this process occurs via a carbopalladation followed by a forced 1,4-migration/intramolecular direct arylation (Scheme 124).

Various oxygen, nitrogen, and carbon linkages between the alkene and aryl iodide were tolerated, affording the tetracyclic products in good to excellent yields (Scheme 125). In addition, studies indicate that electron-rich aryl iodides were superior to electron-deficient ones.[169]

Another interesting example of this tandem migratory coupling is the preparation of dibenzofuran from the corresponding diaryl ether (Scheme 126).[169] Mechanistically, the

Scheme 126

Scheme 127

R₁ = H	69%	48%	73%
Me	61%		(R₂=Et, R₃=Ph):(R₂=Ph, R₃=Et)
OMe	75%		10:1
CO₂Me	71%		
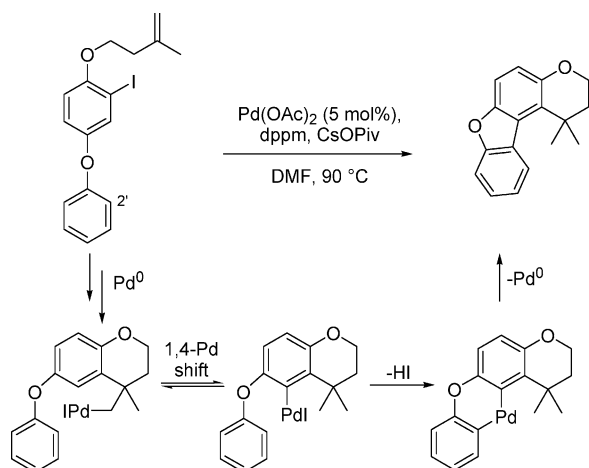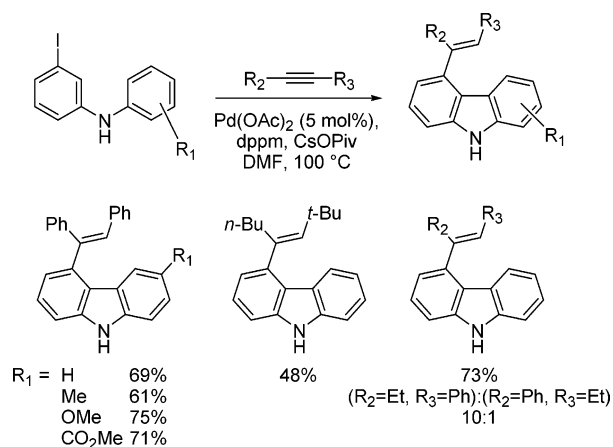
reaction is proposed to proceed via carbopalladation followed by a 1,4-palladium migration. Direct arylation at the 2′-position of the diaryl ether then affords the observed product.

Various carbazoles could also be prepared using a related palladium-catalyzed reaction of alkynes and N-(3-iodophenyl)anilines.[170,171] Reaction of various N-phenyl-3-iodo-anilines with internal alkynes using Larock's standard palladium-migration conditions afforded the corresponding carbazoles in moderate to excellent yields (Scheme 127). A number of internal alkynes were tolerated including aryl-, alkyl-, diaryl-, and dialkyl-substituted alkynes. In addition, the reaction tolerates both electron-withdrawing and electron-donating substituents on the aromatic ring undergoing direct arylation. The absence of a substituent on the aniline nitrogen is crucial since the corresponding methyl- and phenyl-substituted amines produced none of the anticipated carbazole products. The process is proposed to proceed by carbopalladation of the alkyne, followed by nitrogen-directed vinyl to aryl palladium migration and direct arylation.

This method was also applied to the synthesis of dibenzofurans (Scheme 128).[171] The reaction of 3-iodophenyl
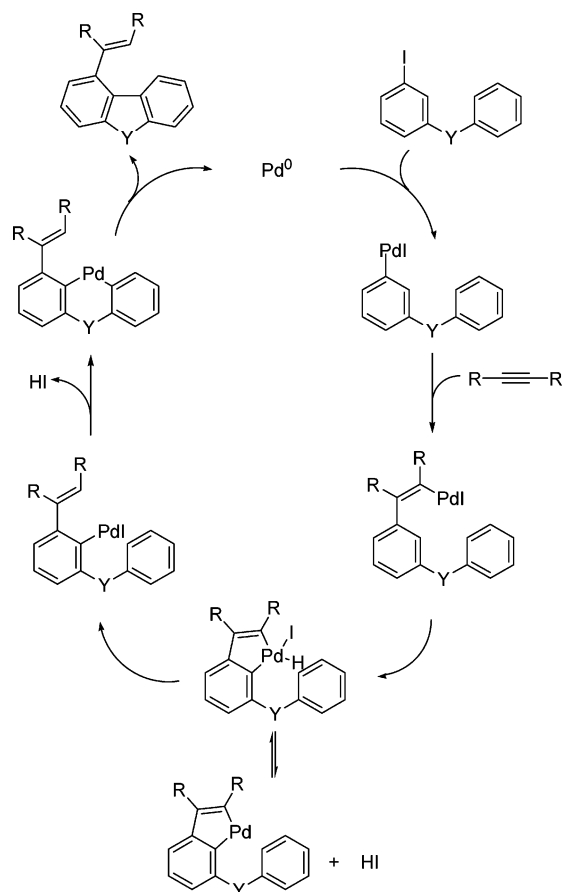
Scheme 128

R = H	30% (8:1)
OMe	80% (9:1)
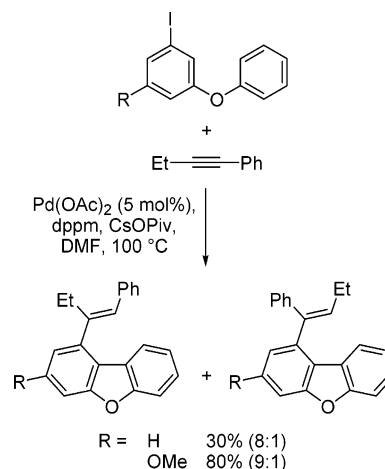
phenyl ether with 1-phenyl-1-butyne gave the corresponding isomeric dibenzofurans in a low 30% yield. A more electron-rich substrate containing a methoxy substituent on the iodoarene moiety resulted in a significant increase in yield (80%), presumably due to the arene's increased ability to facilitate the vinyl to aryl palladium migration.

On the basis of deuterium labeling studies, the authors propose that the mechanism proceeds via oxidative addition

Scheme 129

Scheme 130

X = O 19%
N 23%

of the aryl iodide to palladium(0), followed by subsequent intermolecular carbopalladation to generate a vinylic palladium intermediate (Scheme 129). Palladium migration to the arene via a possible organopalladium(IV) hydride intermediate then occurs. The arylpalladium species then undergoes either palladium insertion into the C−H bond of the neighboring arene or electrophilic aromatic substitution to afford the six-membered ring palladacycle. Reductive elimination furnishes the product and regenerates the active catalyst.

While there are many examples of intramolecular direct arylations of arene C−H bonds with aryl halides, few examples exist for direct arylation reactions with heteroaryl halides. As part of their pioneering work in this field, Ames and co-workers reported a palladium-catalyzed intramolecular direct arylation reaction for the synthesis of benzofuro[3,2-*c*]cinnoline and indolo[3,2-*c*]cinnolines (Scheme 130).[172]
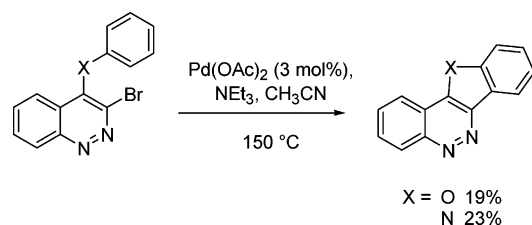
More recently, the palladium-catalyzed intramolecular arylation of pyrimidine was reported in which 4-anilino-5-iodopyrimidines or 4-(aryloxy)-5-iodopyrimidines could be prepared in good yields and in one step from the corresponding aniline or phenol and 4-chloro-5-iodopyrimidine.[173]

Scheme 131

R = 4-CO$_2$Me 58%
3,4,5-OMe 64%
4-Et 74%

R = 4-CO$_2$Me 60%
4-OMe 68%
4-Me 37%
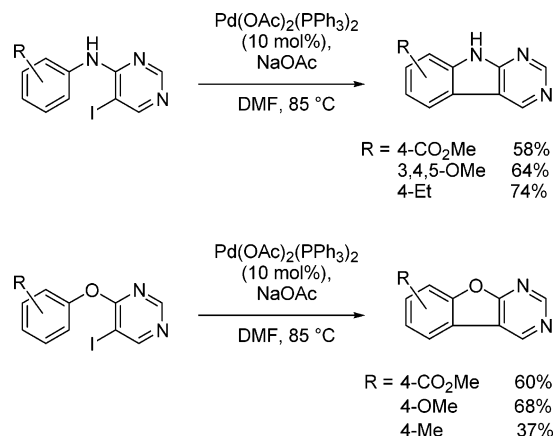
Coupling of the iodopyrimidine to the tethered aryl group was then carried out to generate either the pyrimido[4,5-*b*]indole or benzo[4,5]furo[2,3-*d*]pyrimidine in moderate to good yields (Scheme 131). Several limitations to this method were noted by the authors; first, strong electron-withdrawing groups (i.e., nitro) on the phenoxy ring gave no cyclized adduct, and second, six-membered ring formation from 4-(benzyloxy)-5-iodopyrimidine failed to give the cyclized product.

2.2.2. Applications

The value of intramolecular direct arylation reactions is evident from their application to the synthesis of many chemically important compounds. In this section we will describe the utilization of this method toward the synthesis of natural products, ligands, chiral auxiliaries, and polycyclic aromatic hydrocarbons (PAHs).

2.2.2.1. Natural Products. The lactone method described in section 2.2.1 has been efficiently employed for the atropoenantioselective synthesis of antimalarial knipholone and related phenylanthraquinones.[174,175] Initial studies conducted on a model bromoester using Pd(OAc)$_2$, PPh$_3$, and NaOAc in DMA at 120 °C furnished the desired lactone in good yield (Scheme 132).

Scheme 132

89%
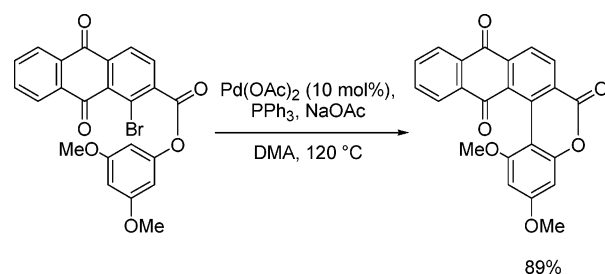
Extension and slight modification of these preliminary conditions toward the direct arylation of the dibromoester **36** gave the desired knipholone lactone precursor **37** in a respectable 68% yield (Scheme 133). Shorter reaction times and the use of sodium pivalate as a sterically-hindered base compared to sodium acetate led to improved yields.

The authors have also reported the stereoselective total synthesis of axially chiral[176] sesquiterpenes mastigophorene A and B (Figure 2),[177] which are natural products that exhibit nerve-growth-stimulating activity.[178] The key steps included a palladium-catalyzed direct arylation and a subsequent dynamic kinetic resolution using Corey's oxazaborolidine–
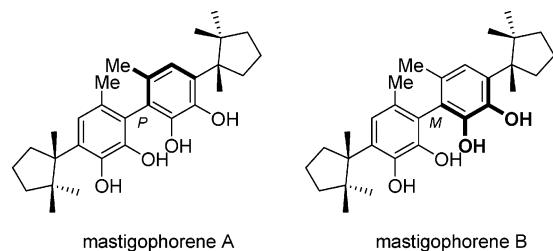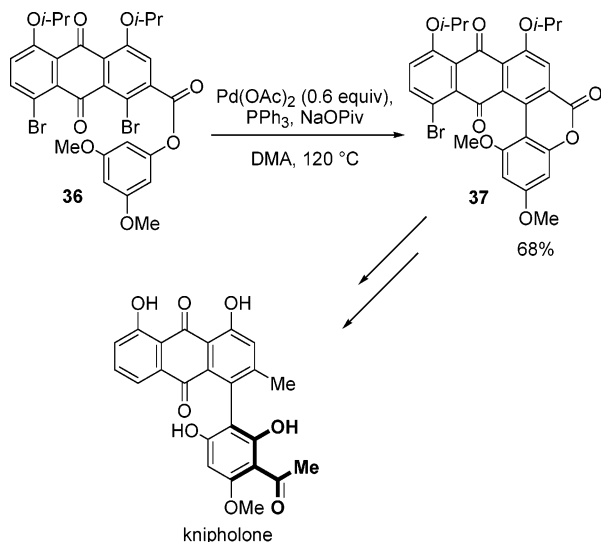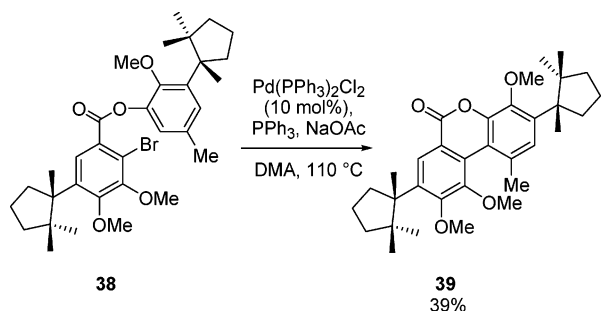
mastigophorene A   mastigophorene B

Figure 2.

Scheme 133

knipholone

borane catalyst. The optimized palladium-catalyzed intramolecular biaryl coupling reaction of **38** resulted in the desired biaryl lactone **39** in 39% yield together with 41% recovered starting material (Scheme 134). This yield was unexpected
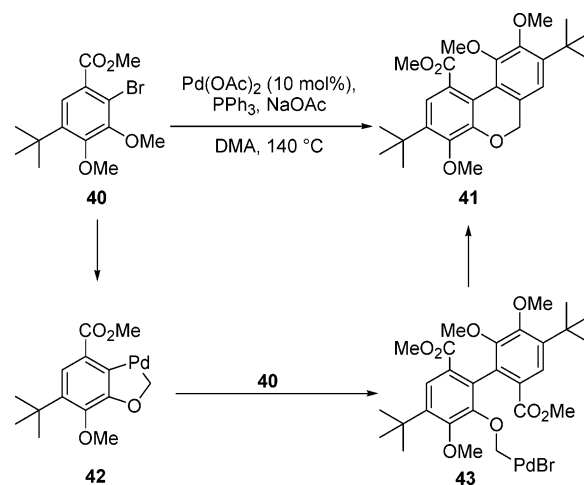
Scheme 134

given that model studies with similar coupling partners gave excellent yields.

To determine the reason for the low reactivity of **38**, the model bromoester **40** was subjected to the palladium-catalyzed conditions to possibly detect any relevant C−H activation byproducts (Scheme 135). Analysis of the reaction mixture found the presence of the cyclic biaryl ether **41** in 10% yield, indicating that the methoxy group in **38** may be responsible for the low yield of **39**. The authors propose that **42** is formed by initial oxidative addition of palladium(0) and subsequent cyclometalation by C−H activation at the neighboring methoxy group. Addition of a second molecule of **40** and reductive elimination generates **43**, which undergoes ring closure with decarboxylation to furnish **41**.

To overcome this problem, the authors modified the bromoester such that the *o*-methoxy group was replaced by

Scheme 135

Scheme 136
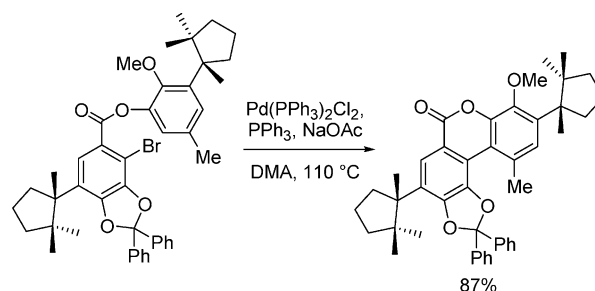
a diphenylmethylene acetal (Scheme 136). Intramolecular palladium-catalyzed cyclization of this substrate now afforded the desired lactone in 87% yield.

Bringmann has also reported a stereoselective total synthesis of antimalarial korupensamines.[179,180] The key steps involved a regioselective intramolecular direct arylation (Scheme 137) to give a configurationally labile lactone-
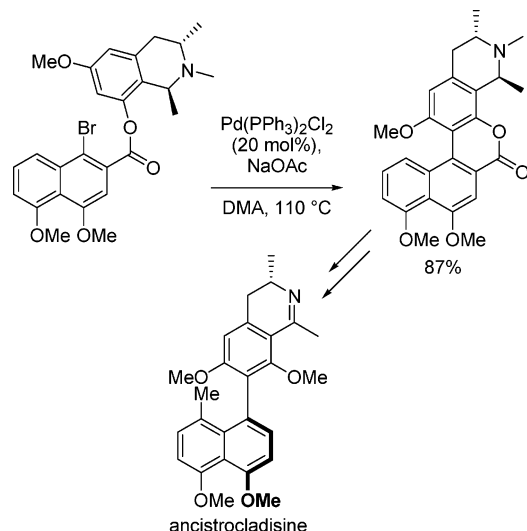
Scheme 137

korupensamine A
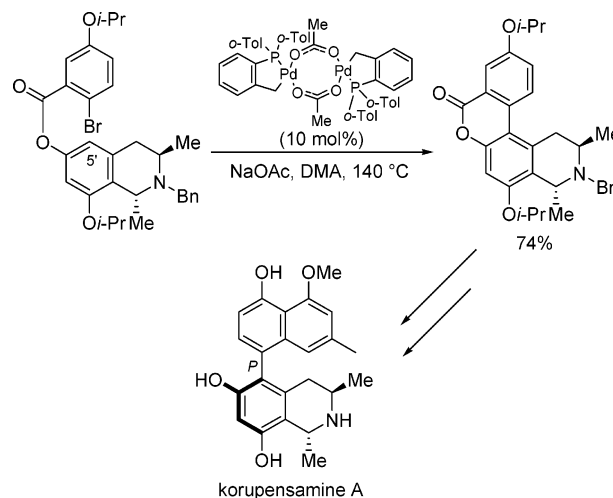
bridged biaryl, and the atropisomer-selective cleavage of the lactone with a variety of chiral and achiral hydride sources. Conditions employing Herrmann's catalyst resulted in a 74% yield of the requisite biaryl intermediate, while Pd(OAc)$_2$ and PPh$_3$ conditions afforded a much lower 26% yield. The coupling occurred exclusively at the 5′-position of the isoquinoline moiety regardless of the catalyst system used.

This lactone method was also applied to the synthesis of several other naphthylisoquinoline alkaloids including ancistrocladisine[181] (Scheme 138) and dioncophylline C[182] (Scheme 139). In both cases, the palladium-catalyzed direct arylation step afforded the desired biaryl lactone in acceptable yield.

Scheme 138

ancistrocladisine

Scheme 139

dioncophylline C
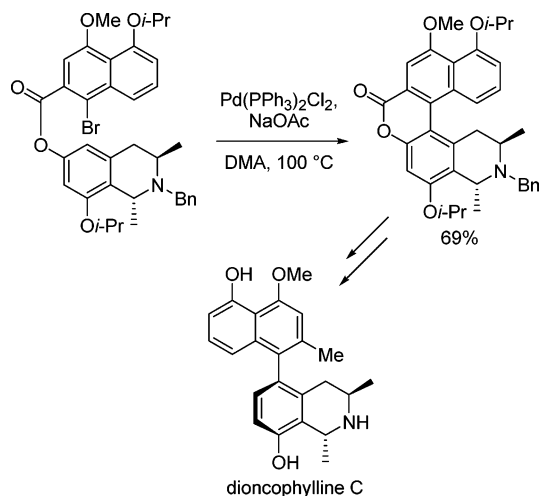
Direct arylation has also been used by Rao for the synthesis of the AB-biaryl fragment of vancomycin (Scheme 140).[183,184] Treatment of the bromoarene with Pd(PPh₃)₂Cl₂

Scheme 140
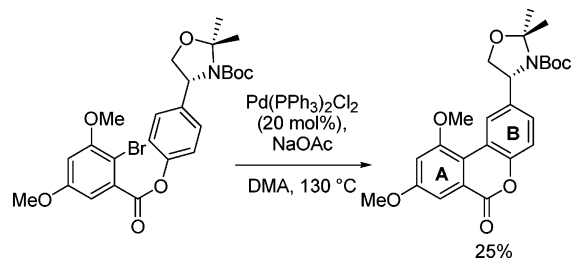
and NaOAc in DMA at 130 °C resulted in the desired biaryl lactone in a modest 25% yield along with debrominated product.

Bringmann and Lipshutz have also used this approach for the atroposelective synthesis of the AB-biaryl fragment of

Scheme 141
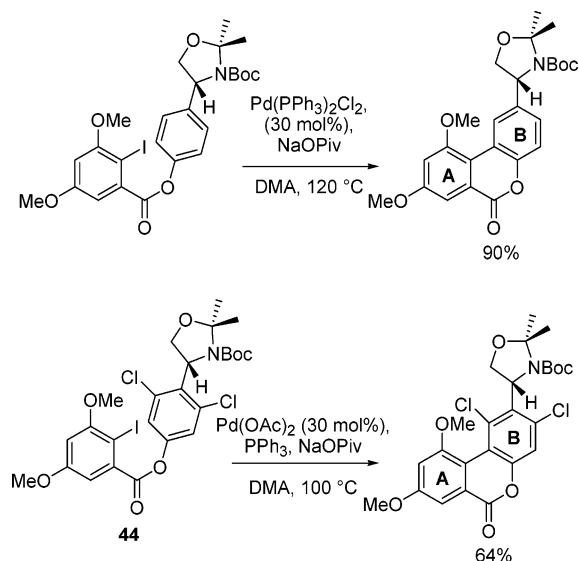
vancomycin.[185] Use of the aryl iodide along with a more sterically-hindered base allowed for greatly improved yields of the desired cyclized vancomycin precursor (Scheme 141). Unfortunately, subsequent ring-opening of the lactone occurred in good chemical yields but with low optical purity. Therefore, an alternative approach to vancomycin was used in which the 3′,5′-dichloro 2-iodophenyl ester **44** was used. In this case, the desired biaryl lactone product was obtained in 64% yield, and subsequent lactone ring-opening occurred in modest chemical yield and excellent diastereoselectivity.

Molander has also utilized the lactone method in an attempt to synthesize (+)-isoschizandrin (Scheme 142).[186]
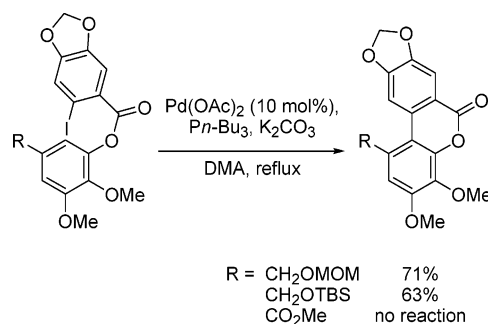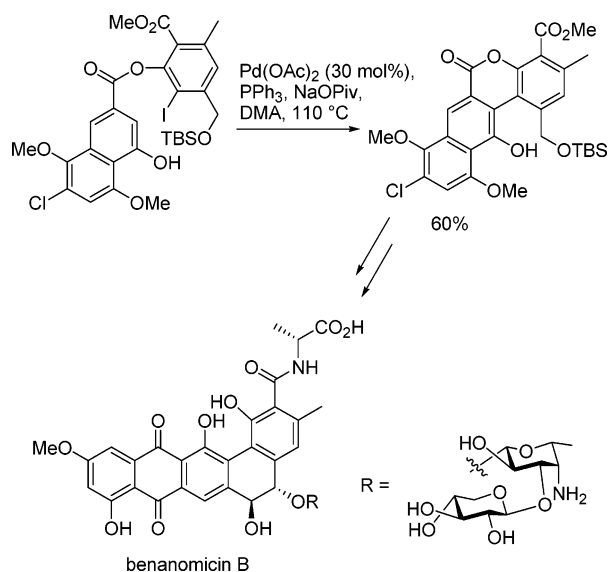
Scheme 142
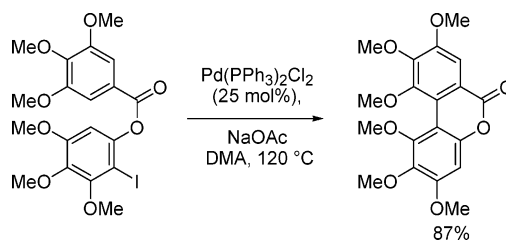
Intramolecular direct arylation of the trimethoxyiodoarene with Pd(PPh₃)₂Cl₂ and NaOAc in DMA at 120 °C afforded the biaryl lactone in 87% yield.

Abe and Harayama also employed the lactone method for the enantioselective synthesis of a key intermediate of the optically active stegane families (Scheme 143).[187] The reaction of protected alcohols gave good yields of the desired

Scheme 143

R =	CH₂OMOM	71%
	CH₂OTBS	63%
	CO₂Me	no reaction

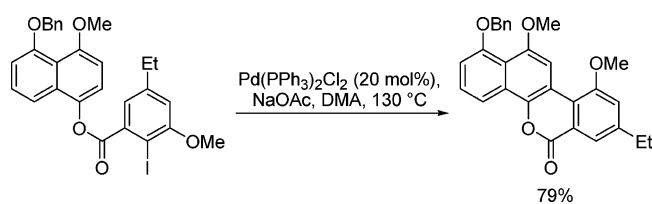**Scheme 144**

60%

benanomicin B

cyclized products, while use of the ester-substituted arene resulted in no reaction.

More recently, the lactone method was employed in the regio- and stereocontrolled total synthesis of benanomicin B (Scheme 144).[188] The direct arylation step afforded the sterically-encumbered biaryl product in 60% yield. A similar approach was employed in the total synthesis of pradimicinone.[189]

Several groups have reported the use of intramolecular direct arylation reaction for the synthesis of gilvocarcin derivatives. In 1990, Martin reported a short and convergent synthesis of the aglycon fragment of the gilvocarins.[190] The key intramolecular direct arylation step employed Pd(PPh$_3$)$_2$-Cl$_2$ (20 mol %) as the catalyst and resulted in the biaryl compound in 79% yield (Scheme 145).
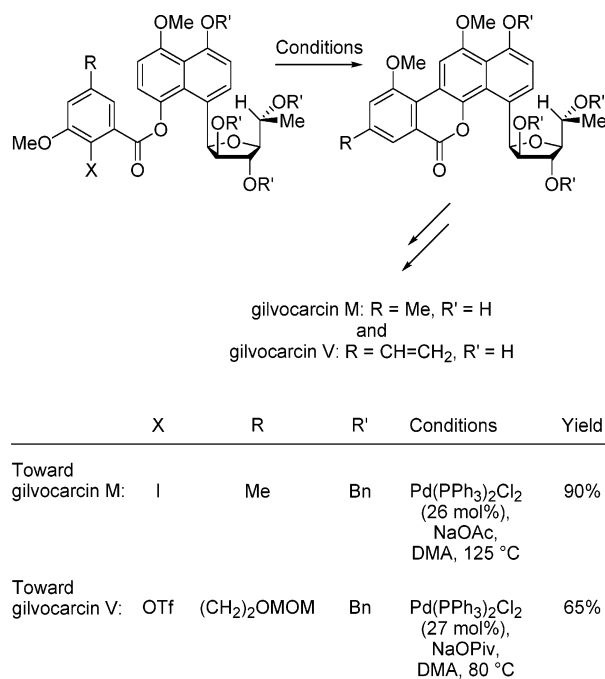
Scheme 145

79%

Shortly thereafter, Suzuki reported the total synthesis of aryl *C*-glycoside antibiotics gilvocarcin M and gilvocarcin V (Scheme 146).[191,192] The aryl−aryl bond in gilvocarcin M was easily prepared in 90% yield using Pd(PPh$_3$)$_2$Cl$_2$ (26 mol %) and NaOAc in DMA at 125 °C.

Synthesis of the aryl−aryl bond in gilvocarcin V from the corresponding aryl triflate under the same conditions used for the synthesis of gilvocarcin M proved to be problematic. A low yield of product was obtained along with several side products. It was determined in a control experiment that the observed side products were generated by attack of acetate anion at the ester carbonyl, which is highly electrophilic due to the presence of an *o*-triflate group. Use of a sterically-hindered base such as sodium pivalate was used to suppress this side reaction, affording the desired biaryl product in 65% yield (Scheme 146).

A similar approach was reported for the synthesis of the gilvocarcin-related arnottin I.[193,194] Optimization of the key direct arylation was carried out using simple model substrates

Scheme 146

gilvocarcin M: R = Me, R' = H
and
gilvocarcin V: R = CH=CH$_2$, R' = H

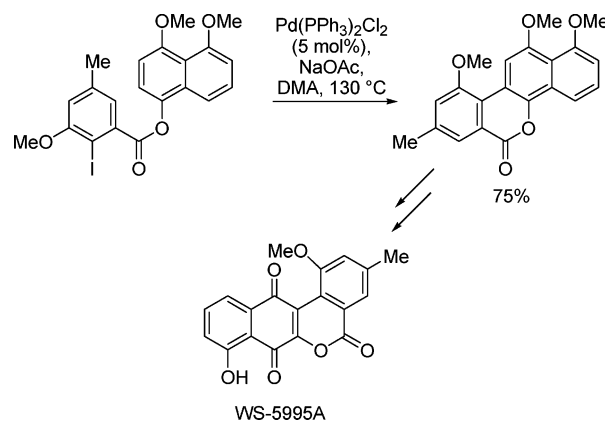|	X	R	R'	Conditions	Yield
Toward gilvocarcin M:	I	Me	Bn	Pd(PPh$_3$)$_2$Cl$_2$ (26 mol%), NaOAc, DMA, 125 °C	90%
Toward gilvocarcin V:	OTf	(CH$_2$)$_2$OMOM	Bn	Pd(PPh$_3$)$_2$Cl$_2$ (27 mol%), NaOPiv, DMA, 80 °C	65%

via the screening of a variety of direct arylation conditions. In doing so, the authors found that the best conditions for the synthesis of arnottin I were the use of Pd(acac)$_2$ (10 mol %), PPh$_3$, and NaOAc in DMF at 150 °C (Scheme 147).

Scheme 147
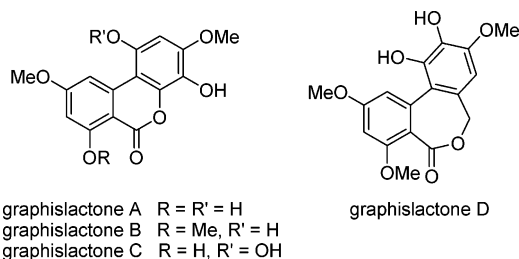

Pd(acac)$_2$ (10 mol%), NaOAc, DMF, 150 °C

arnottin I
72%
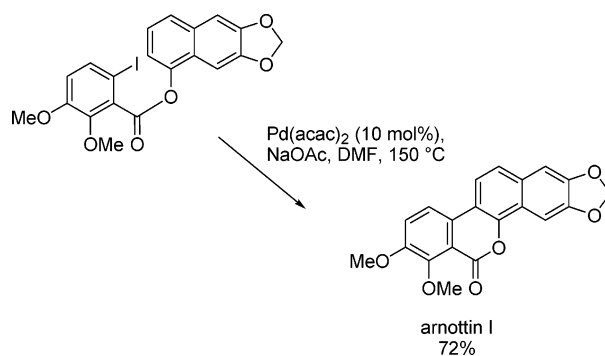
A route to the core structure of the WS-5995 family, some members of which are structurally similar to the gilvocarcin antibiotics, was reported using a palladium-catalyzed direct arylation (Scheme 148).[195] In the presence of Pd(PPh$_3$)$_2$Cl$_2$

Scheme 148

Pd(PPh$_3$)$_2$Cl$_2$ (5 mol%), NaOAc, DMA, 130 °C

75%

WS-5995A

graphislactone A   R = R' = H
graphislactone B   R = Me, R' = H
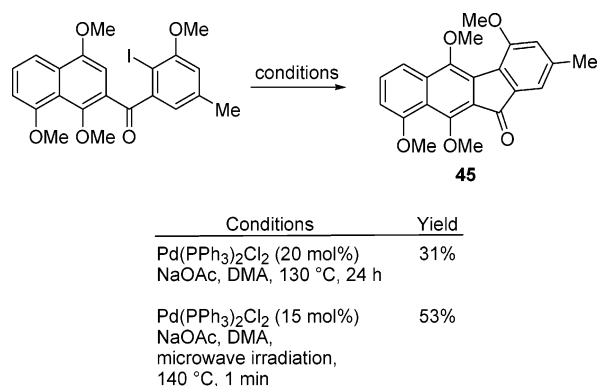graphislactone C   R = H, R' = OH

graphislactone D

Figure 3.

(5 mol %) and NaOAc, the intermediate biaryl lactone compound was furnished in 75% yield.

Various other natural products containing a biaryl compound with a lactone linkage were prepared using a direct arylation step. For example, the direct arylation step for the synthesis of the graphislactones A−D (Figure 3) was carried out using Pd(OAc)$_2$, P(*n*-Bu)$_3$, and K$_2$CO$_3$ in DMA to afford the desired lactone product in 85−93% yield.[196]

The total synthesis of cavicularin also involved the preparation of a lactone containing biaryl.[197] The reaction employed Herrmann's catalyst and resulted in a 5:2 mixture of regioisomeric products in a 38% yield (Scheme 149).
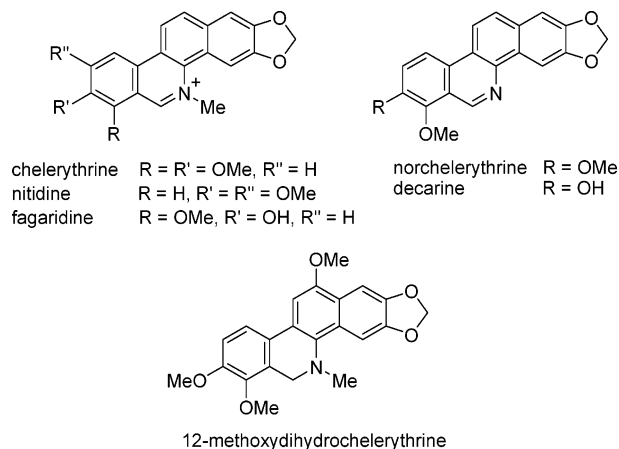
Scheme 149

cavicularin
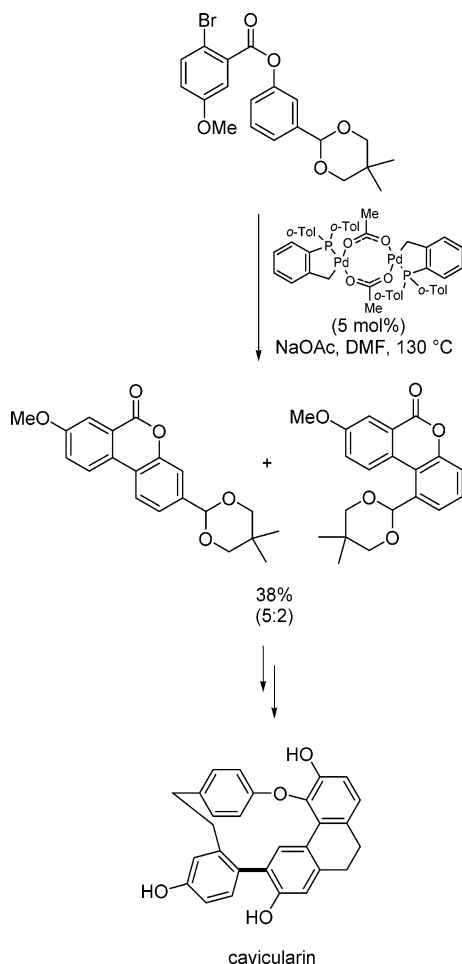
While there are many examples of natural product synthesis involving an intramolecular direct arylation step of a compound containing an ester tether, examples involving compounds with ketone tethers are scarce. One example involves the synthesis of benzo[*b*]fluorenones (Scheme 150), a class of compounds that have been used as intermediates

Scheme 150

Conditions	Yield
Pd(PPh$_3$)$_2$Cl$_2$ (20 mol%) NaOAc, DMA, 130 °C, 24 h	31%
Pd(PPh$_3$)$_2$Cl$_2$ (15 mol%) NaOAc, DMA, microwave irradiation, 140 °C, 1 min	53%

en route to the natural products stealthin C and prekinamycin.[195,198] Initial intramolecular direct arylation studies conducted on model substrates resulted in high yields of the desired products (85−92%). However, when applied to the synthesis of **45**, low yields or no reaction was observed (Scheme 150). Under microwave irradiation, yields for **45** could be improved. While microwave irradiation in transition-metal-catalyzed reactions is well-known, this study represents one of the few examples of the use of microwave heating for direct arylation reactions.

Direct arylation reactions have also been used as an efficient method of generating the biaryl bond in a number of biologically active alkaloids. Harayama and co-workers have reported the synthesis of numerous benzo[*c*]phenanthridine alkaloids using an intramolecular direct arylation reaction as the key step. Select examples are illustrated in Figure 4.[199] Their approach involves the coupling of naph-

chelerythrine	R = R' = OMe, R" = H
nitidine	R = H, R' = R" = OMe
fagaridine	R = OMe, R' = OH, R" = H

| norchelerythrine | R = OMe |
| decarine | R = OH |

12-methoxydihydrochelerythrine

Figure 4.

thylamine and a 2-halobenzoic acid to generate a *N*-napthylbenzamide. Palladium-catalyzed intramolecular direct arylation then furnishes the benzo[*c*]phenanthridone, which is subsequently converted to the benzo[*c*]phenanthridine alkaloid (Scheme 151).

Another group of interesting biologically active natural product targets that have attracted a lot of interest from the synthetic community are the *Amaryllidaceae* alkaloids.[200] Because of their biological activity,[200] many synthetic methods have been developed in an effort to generate various derivatives. As a route to this interesting scaffold, Harayama reported the palladium-catalyzed intramolecular direct arylation of *N*-(2-halobenzyl)indolines.[201,202] In most cases the reactions gave a low-yielding mixture of cyclized dihydro-

Scheme 151
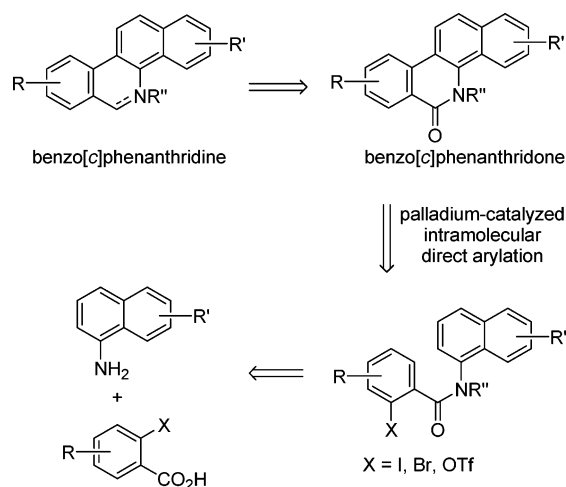
pyrrolophenanthridine and oxidized dihydropyrrolophenanthridone as well as the reduced benzylindoline and oxidized benzylindole. Using this approach, various alkaloids were prepared including anhydrolycorine, assoanine, anhydrolycorin-7-one, and oxoassoanine (Scheme 152).
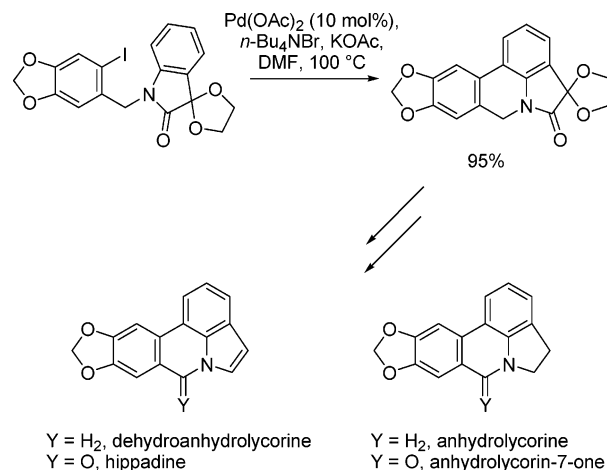
Scheme 152
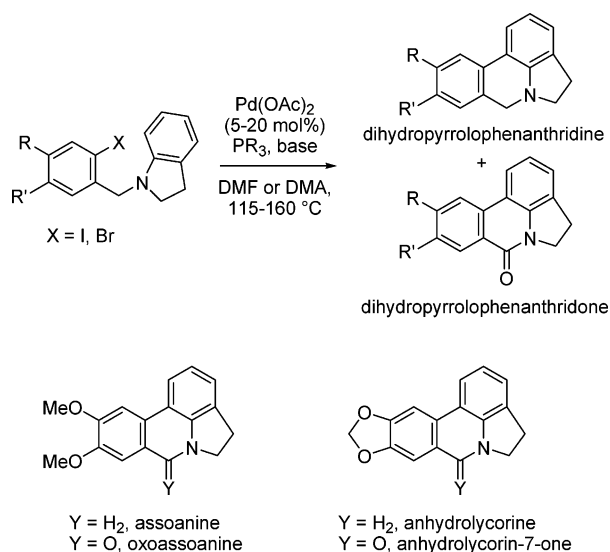
Garden reported the synthesis of a class of related *Amaryllidaceae* alkaloids using spirodioxolanes, which are formed from the corresponding *N*-benzylisatin derivatives.[203,204] These substrates were chosen to avoid the problem of regioselective cyclization at the indole C-7 position. Intramolecular direct arylation of these substrates gave the desired cyclized compounds in excellent yields using Jeffery's conditions. Subsequent manipulation of this core compound afforded a number of related alkaloid derivatives including dehydroanhydrolycorine, hippadine, anhydrolycorine, and anhydrolycorin-7-one (Scheme 153).

Cuny utilized a palladium-catalyzed intramolecular phenol *ortho* arylation for the synthesis of aporphine alkaloids such as (±)-lirinidine (Scheme 154).[205,206] Optimization of this key step in the synthesis revealed that the use of trialkylphosphines or trialkylphosphonium salts significantly increased the yield of the reaction, affording the cyclized product in 58% yield.

A related direct arylation approach has also been used for the synthesis of the aporphine alkaloid scaffold (Scheme
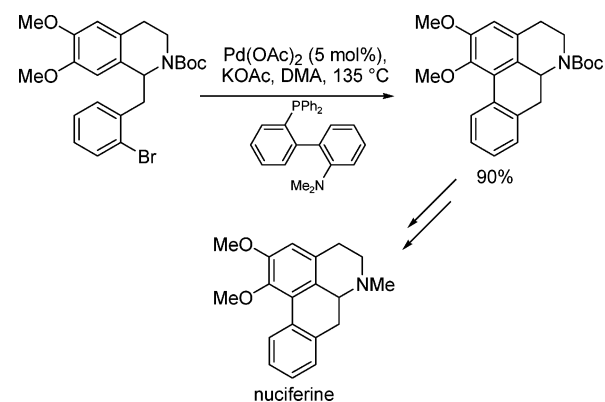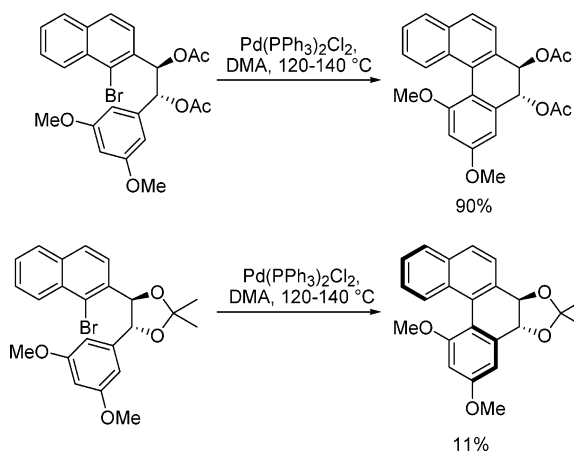
Scheme 153

Scheme 154
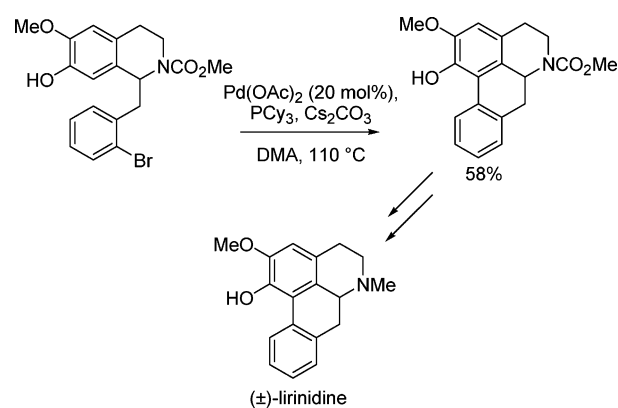
Scheme 155

155).[207] Optimization reactions for this catalyst system showed that the nature of the solvent and base drastically affected the yield of the reaction. Under the optimal conditions, the direct arylation step in the formal synthesis of nuciferine afforded a 90% yield of the cyclized product.

Bringmann has also developed an atroposelective synthesis of biaryls that utilizes a chiral 1,2-diol bridge to link the two aryl moieties prior to the direct arylation step (Scheme 156).[208] The intramolecular coupling of the diacetate gave the biaryl product in 90% yield as a 1:1 mixture of diastereomers, while the coupling of the more conformationally rigid dioxolane gave the desired product as a single diastereomer in 11% yield. This low yield is presumably due to the high conformational strain imposed by the fused 5,6-ring system in the product.

Scheme 156

90%

11%

A formal enantioselective synthesis of allocolchicine was reported employing a direct arylation using an aryl chloride to form the seven-membered ring core (Scheme 157).[209] In

Scheme 157

73%

allocolchicine
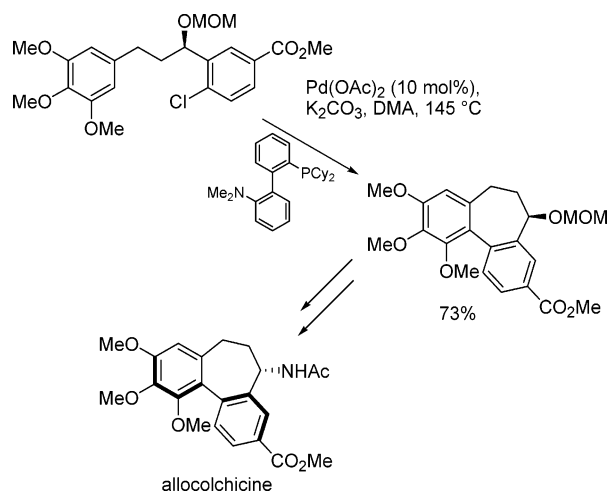
addition to the desired biaryl product, a dechlorination byproduct was also observed in the reaction. Screening various ligands found that Buchwald's 2-(dimethylamino)-2′-(dicyclohexylphosphino)biphenyl was optimal for reducing this byproduct.

2.2.2.2. Ligands and Chiral Auxiliaries. The lactone method (section 2.2.1) has also been successfully utilized for the preparation of several chiral auxiliaries and ligands. Selected examples are illustrated in Scheme 158 and include the synthesis of an axially chiral C_1-symmetric phosphine ligand, **46**, for the palladium-catalyzed stereoselective hydrosilyation of styrenes,[210] a P,N-biaryl ligand, **47**, used for asymmetric Suzuki coupling reactions,[211] a N,O-biaryl ligand, **48**, for the asymmetric addition of diethylzinc to aldehydes,[212] and an axially chiral C_3-symmetric tripodal ligand, **49**, used for the asymmetric addition of diethylzinc to aldehydes.[213]

2.2.2.3. Polycyclic Aromatic Hydrocarbons. The synthesis of fullerene fragments, also referred to as bowl-shaped PAHs, has attracted considerable attention due to their potential use as starting materials for the synthesis of fullerenes. While flash vacuum pyrolysis (FVP) is a common method of constructing fullerene fragments, it suffers from modest yields, low functional group tolerance due to harsh reaction conditions, and difficulty in scaleup. Recently, the palladium-catalyzed intramolecular direct arylation has been

Scheme 158

46

47
R = Me, OMe

48

49
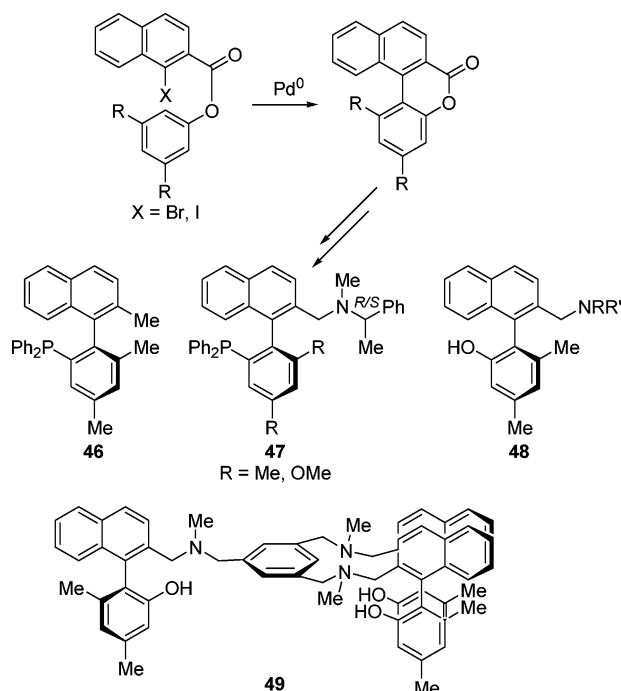
applied to the synthesis of bowl-shaped fullerene fragments and other PAHs. This mild method not only allows for a high-yielding route to this class of PAHs, but allows for construction of a wide range of PAHs due to its wide functional group tolerance.[15]

Rice reported the first example of an intramolecular direct arylation as a route to a large number of substituted and unsubstituted PAHs in 1992 (Scheme 159).[214–216]
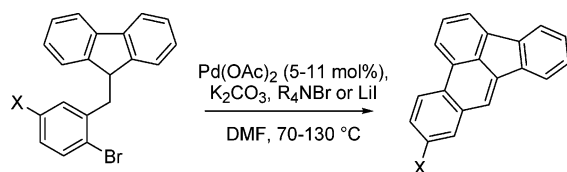
Scheme 159

89%   84%   91%   85%
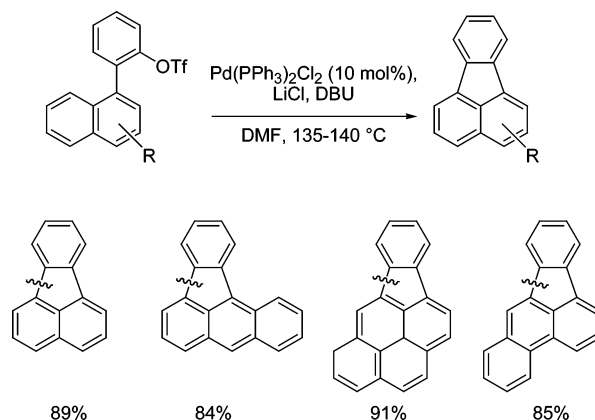
Echavarren subsequently reported the formation of a variety of fused ring systems and PAHs using a palladium-catalyzed intramolecular direct arylation.[35] The cyclization of benzylated fluorene (X = H) using Pd(OAc)$_2$, K$_2$CO$_3$, and n-Bu$_4$NBr in DMF at 130 °C for 48 h afforded the corresponding PAH in 52% yield (Scheme 160). Substrates with X = NO$_2$ and X = F afforded the corresponding products in 57% and 65% yields, respectively. While the cyclization of the methoxy derivative was sluggish, replacing R$_4$NBr with LiI allowed for the isolation of the desired product in a respectable 50% yield after four days at 130 °C.
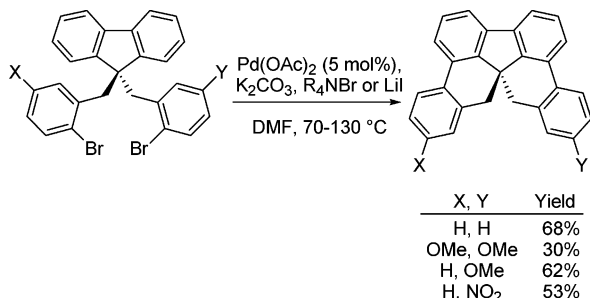
Similar trends with respect to the electronic nature of the aryl bromide were also observed for the cyclization of
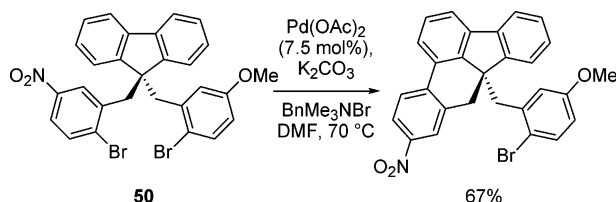
Scheme 160

X	Additive, Temperature, Time	Yield
H	*n*-Bu₄NBr, 130 °C, 48h	52%
OMe	LiI, 130°C, 4 d	50%
NO₂	*n*-Bu₄NBr, 70 °C, 48h	57%
F	BnMe₃NBr, 120 °C, 48h	65%

Scheme 161

X, Y	Yield
H, H	68%
OMe, OMe	30%
H, OMe	62%
H, NO₂	53%

dibenzylated fluorenes (Scheme 161). Higher temperatures and longer reaction times in addition to the use of LiI as an additive was required to achieve the direct arylation of methoxy-containing substrates. In addition, treatment of **50** under milder reaction conditions resulted in selective monoarylation of the *p*-nitroaryl moiety (Scheme 162).
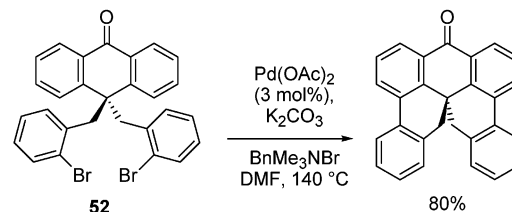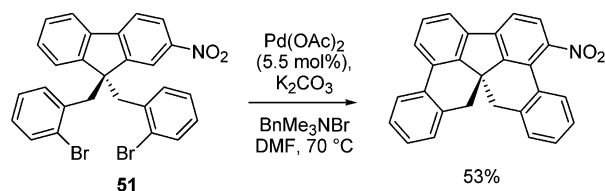
Scheme 162

The double intramolecular palladium-catalyzed direct arylation was also applied to substrates **51** and **52** to afford the corresponding products in 53% and 80% yield, respectively (Scheme 163).[35] These conditions were then applied to the synthesis of a C₄₈ polyarene via a triple direct arylation to afford **54** in 71% yield.[217−219]

The use of direct arylation for the synthesis of benzo[*ghi*]fluoranthenes from aryl triflates or bromides using Pd(PPh₃)₂Cl₂ as the catalyst has also been reported.[220] Various electron-rich and electron-poor substituents were tolerated under the reaction conditions, affording excellent yields of the desired products (Scheme 164). In addition, Pd(PCy₃)₂Cl₂ could be used for the intramolecular direct arylation of an aryl chloride in good yield. Although aryl chlorides have been reported in such reactions using Pd(OAc)₂ in the absence of a phosphine ligand, these examples suffered from low yields and significant byproduct formation.[221]
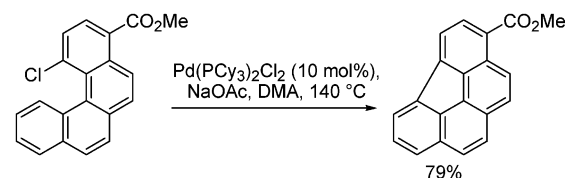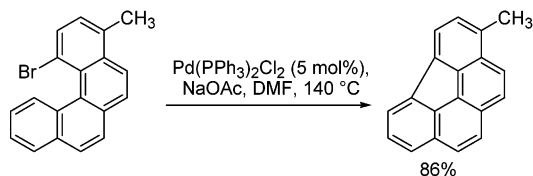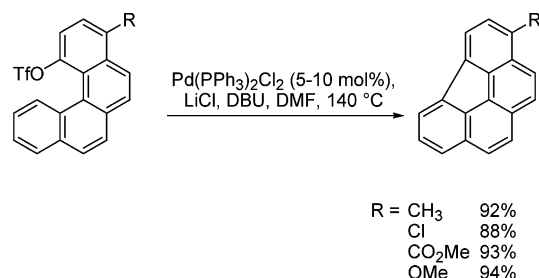
This method was also extended to the synthesis of a bowl-shaped PAH via a double palladium-catalyzed direct arylation from the corresponding dichloride in good to excellent yields (Scheme 165).[222]

Scott independently reported a similar approach for the synthesis of a bowl-shaped PAH using aryl bromides
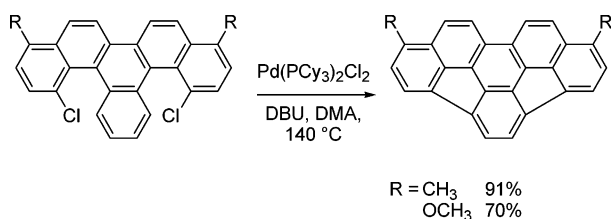
Scheme 163

Scheme 164
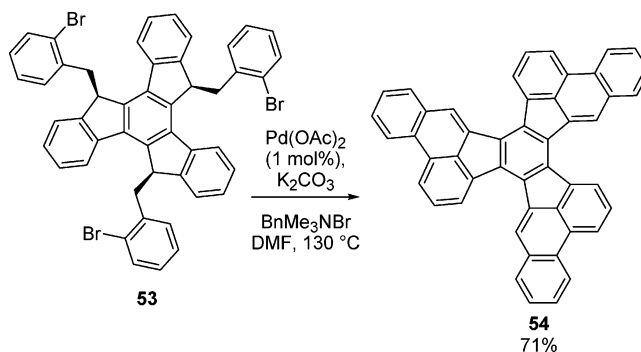
| R = CH₃	92%
Cl	88%
CO₂Me	93%
OMe	94%

(Scheme 166).[223] In the presence of Herrmann's catalyst, the desired product was obtained in 57% yield along with small quantities of monocyclized/monodebrominated and doubly debrominated products.

An almost identical approach has also been used for the synthesis of 1,2-dihydrocyclopenta[*b,c*]dibenzo[*g,m*]corannulene from the corresponding bromides in low yields (Scheme 167).[224]
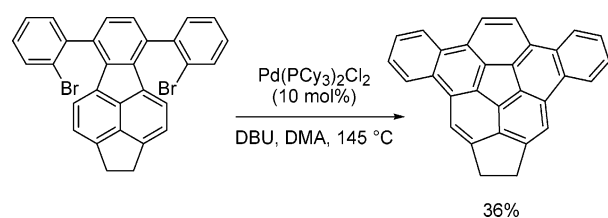
Scheme 165

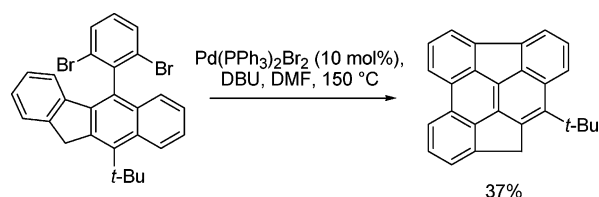R = CH₃ 91%
    OCH₃ 70%

Scheme 166

57%

Scheme 167

36%
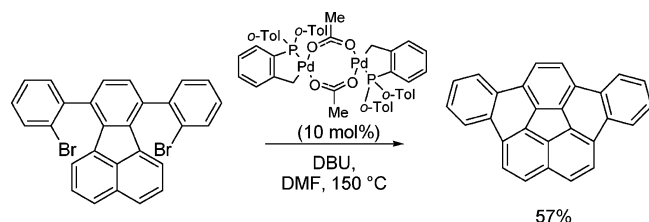
More recently, various bowl-shaped PAHs were prepared involving two subsequent palladium-catalyzed intramolecular direct arylations employing a dibromoarene substrate (Scheme 168).[225] The desired buckybowl was obtained in 37% yield,

Scheme 168

37%

along with small amounts of monocyclized/monodebrominated and didebrominated products.

Finally, the synthesis of higher oxidized metabolites of dibenz[*a,j*]anthracene, which are implicated in the mechanism of carcinogenesis, has been reported using a direct arylation reaction as one of the steps (Scheme 169).[226] Use of Pd(PPh₃)₂Cl₂ (5 mol %) and NaOAc in DMA at 140 °C afforded the desired PAH in 60% yield. The authors also reported the use of this approach for the synthesis of the K-region *trans*-9,10-dihydrodiol of benzo[*g*]chrysene.[227]

3. Direct Arylation of Heteroaryl C–H Bonds

As in the direct arylation of arenes, regioselective control for the intramolecular direct arylation often relies on a tether approach in order to limit the degree of freedom in the system. Intermolecularly, the direct arylation of heterocycles poses a challenging task with respect to the regioselectivity of the reaction. However, unlike the intermolecular direct arylation of arene systems, the inherent electronic bias of the heterocycle itself is often sufficient to control the regioselectivity of the direct arylation reaction, obviating the need for directing groups. Consequently, the regioselectivity of intermolecular direct arylation primarily depends on the

Scheme 169

60%
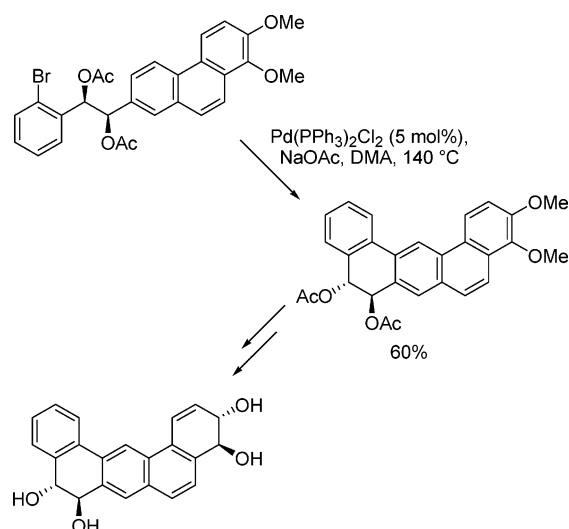
heterocycle type (Figure 5), in addition to the electronic nature of the catalyst employed. More recently, other factors

X = S, O, NH, NR¹
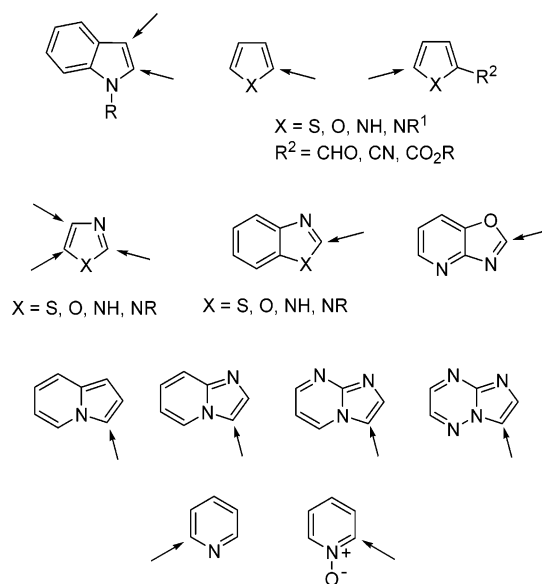R² = CHO, CN, CO₂R

X = S, O, NH, NR   X = S, O, NH, NR

Figure 5.

such as solvent, additives (i.e., Cu(I) salts), and the steric nature of the catalyst have been used to alter the regioselectivity of direct arylation for heterocyclic systems.

Mechanistically, the direct arylation of heterocycles is believed to occur primarily via three possible pathways: (1) an electrophilic aromatic substitution, (2) a Heck-type mechanism, or (3) a carbanion cross-coupling mechanism (Scheme 170). Again, the exact mechanism (and ultimately the observed regioselectivity) by which the direct arylation occurs is highly dependent upon the substrate, catalyst, reaction solvent, and additives present. Accordingly, this portion of the review will highlight all advances in this area of direct arylation according to heterocycle type. In addition, comments regarding the proposed mechanism and reaction regioselectivity will be presented where appropriate.
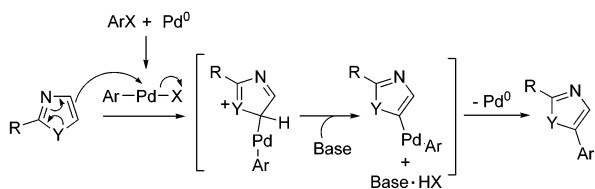
3.1. Direct Arylation of Nitrogen-Containing Heteroaryl Compounds
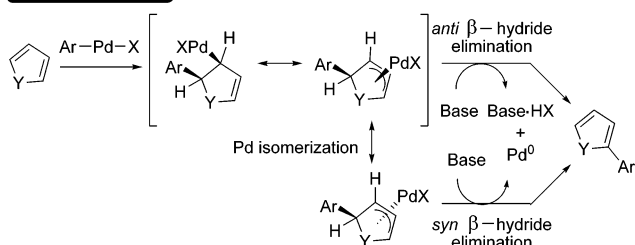
3.1.1. Indoles and Azaindoles

3.1.1.1. Intramolecular Aryl–Indolyl Bond Formation. Grigg and co-workers reported the first transition-metal-
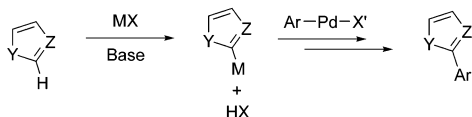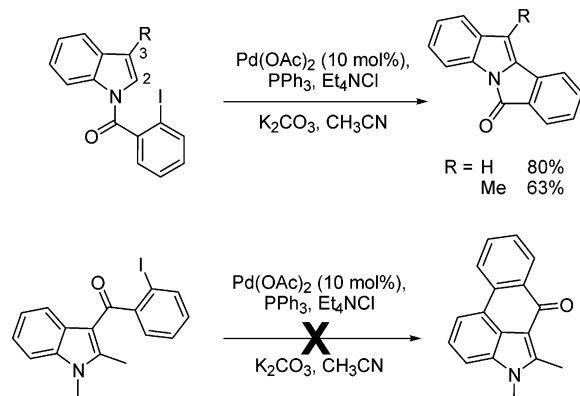
Scheme 170

Scheme 171

catalyzed direct arylation of an indole with an aryl halide in 1990.[228] They showed that an indole containing an *N*-tethered aryl iodide underwent direct arylation at the indole 2-position using Pd(OAc)$_2$, PPh$_3$, Et$_4$NCl, and K$_2$CO$_3$ in refluxing CH$_3$CN (Scheme 171). However, 2-substituted indoles bear-

ing an aryl iodide tether at the 3-position failed to give the corresponding 4-annulated product.

A similar reaction using an activated 3-formylindole containing an aryl iodide tethered at the nitrogen resulted in the cyclized product in 70% yield. The use of bromoarenes also resulted in the desired product, albeit in lower yields (Scheme 172).[229]

Higher yields for this type of cyclization were achieved using aryl bromides, Pd(PPh$_3$)$_4$, and KOAc in DMA (Scheme 173). These conditions were extended to a variety of 3-substituted five- and seven-membered annulated indoles.[230]

Kozikowski subsequently utilized this methodology for the development of a new class of ligands for the antineophobic mitochondrial diazepam binding inhibitor receptor.[231] Following Kozikowski's report, Garratt used these conditions
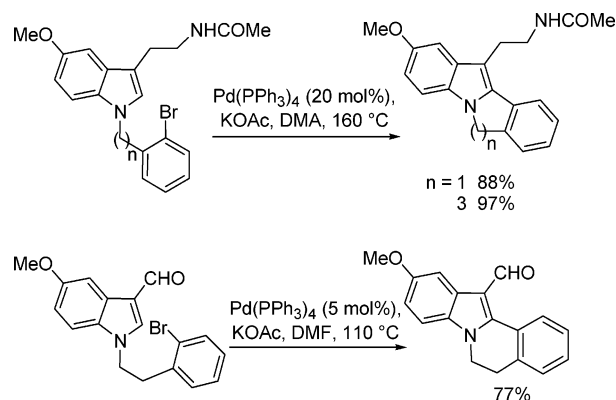
Scheme 172
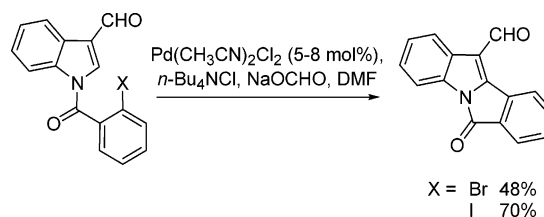
Scheme 173
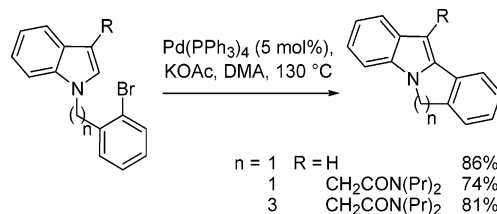
to prepare a large library of five-, six-, and seven-membered annulated indoles for probing the active site of the receptor for melatonin (Scheme 174).[232]

Scheme 174

Mérour and co-workers reported a similar intramolecular arylation as part of their study of the synthesis of novel steroid hormone receptors. A variety of activated 3-cyano- and 3-formylindoles containing an *N*-alkylated tether were used to generate a family of five- and six-membered annulated indoles (Scheme 175).[233] These conditions were

Scheme 175
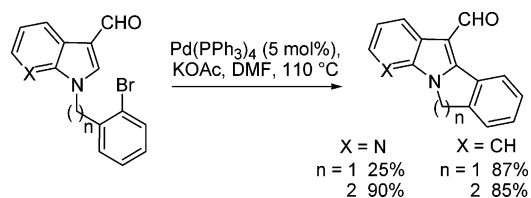
further extended to the annulation of five- and six-membered azaindoles. While excellent yields were obtained for the six-membered ring system, lower yields were observed for the five-membered ring system. This result was attributed to the formation of a kinetically more favored seven-membered versus eight-membered palladacycle that prevented subsequent annulation at the 2-position of indole. The authors have also used this methodology to prepare the 3-cyclized indole product from the corresponding C-2-tethered aryl bromide (Scheme 176).[234,235]

Scheme 176

66%
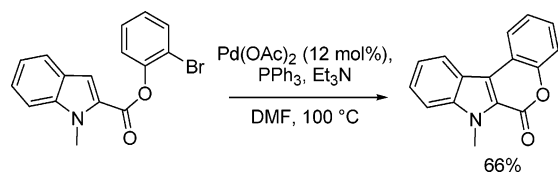
Melnyk reported a high-yielding, C-2-selective, intramolecular cyclization of an indole and a bromopyridine (Scheme 177).[236,237] Since the corresponding *NH*-containing substrate

Scheme 177

92%
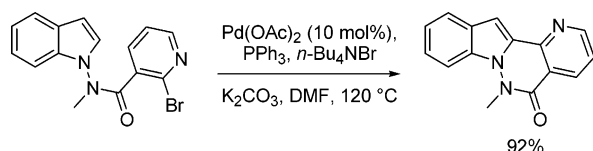
afforded a complex mixture of products, protection as the tertiary amide was necessary to achieve good yields. The authors also attempted to carry out a tandem C-2 cyclization/C-3 Heck reaction by conducting the cyclization in the presence of acrylate. Unfortunately, the use of catalytic amounts of palladium only gave the cyclized product in low yields. Use of stoichiometric amounts of catalyst along with an excess of acrylate (15 equiv) were required to achieve modest yields (63%) of the tandem cyclization/Heck reaction product.
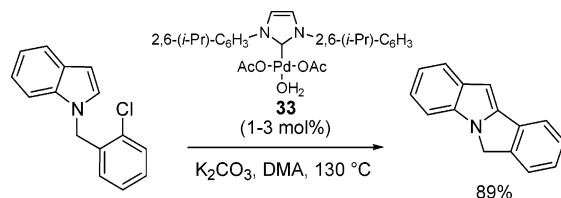
More recently, Fagnou utilized an electron-rich NHC palladium catalyst, **33**, for the intramolecular coupling of arenes and aryl chlorides. This methodology allows for the use of relatively cheap and accessible aryl chlorides instead of aryl iodides or bromides (Scheme 178). Optimization

Scheme 178

89%

studies found that the ratio of ligand to palladium was crucial in obtaining excellent yields of the desired products, with a 1.5:1 IMes:Pd ratio being more effective than a 2:1 ratio. In addition, halide effects[238] were found to play a dramatic role in obtaining reproducible results. In fact, treatment of [Pd(IMes)Cl$_2$]$_2$ with an excess of silver acetate allowed for complete removal of chloride from the catalyst, producing results that were similar to those obtained from the corresponding Pd(IMes)(OAc)$_2$(H$_2$O) (**33**) catalyst.[131] Fagnou has also reported the same intramolecular coupling of aryl chlorides and indole in excellent yield (91%) using Pd(OAc)$_2$/PCy$_3$.[28]

These same authors have subsequently reported a one-pot tandem Heck/direct arylation reaction using a bromoindole tethered to an aryl chloride (Scheme 179).[134] Given that oxidative addition is known to occur faster for aryl bromides versus aryl chlorides, the choice of halide on both the indole and aryl moieties was crucial to the success of this tandem two-step reaction. In fact, substrates in which the direct arylation step occurred prior to the Heck reaction were found to be poor substrates for this reaction, and

Scheme 179

54%
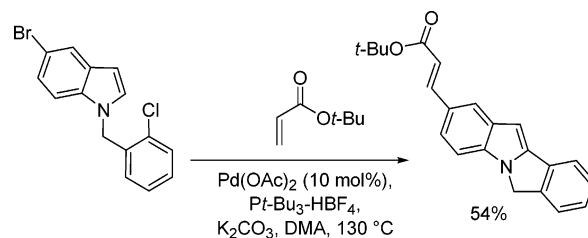
therefore, reversal of the order of steps was required to obtain good yields of the desired product.

Larock has recently reported the use of 3-arylindole in a palladium-catalyzed tandem 1,4-migration/direct arylation reaction. The reaction likely proceeds via initial oxidative addition of palladium(0) to the aryl iodide, followed by 1,4-migration of palladium to yield an indol-2-ylpalladium species. This indol-2-ylpalladium species then undergoes direct arylation with the *N*-benzyl group to give the fused tetracyclic product (Scheme 180).[48,168] The authors suggest

Scheme 180

92%
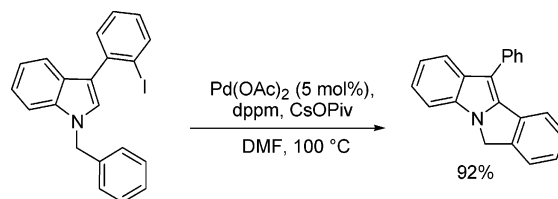
that the higher yields and shorter reaction times compared to those of other arene systems are a consequence of the relative ease of C−H activation for the electron-rich indole.

Larock also described a related example in which 3-iodo-1-*p*-tosylindole was treated with norbornene and catalytic Pd(OAc)$_2$/dppm (Scheme 181).[169] Following oxidative ad-

Scheme 181

75%
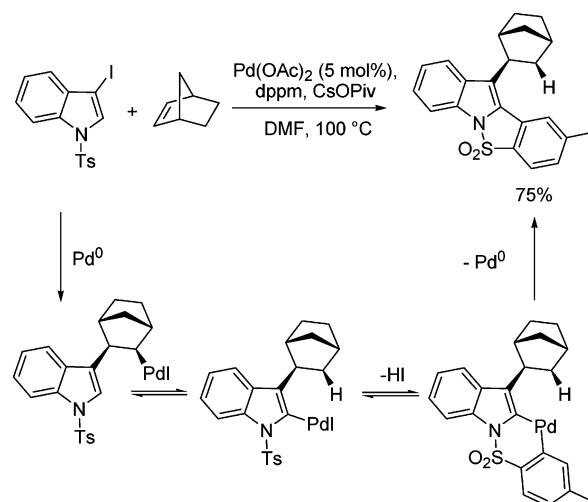
dition, the indol-3-ylpalladium intermediate undergoes *syn* addition to norbornene, affording an alkylpalladium species. Since *β*-hydride elimination in this intermediate is not favored, the palladium is forced to undergo 1,4-palladium migration to the 2-position of the indole. The resulting indol-2-ylpalladium species then undergoes intramolecular cyclization onto the tosyl group to furnish the fused ring system.

One example of the utility of intramolecular direct arylation reactions is in the rapid synthesis of a variety of

Scheme 182

96%

R¹ = Me　R² = Me　89%
R¹ = EOM　R² = EOM　92%
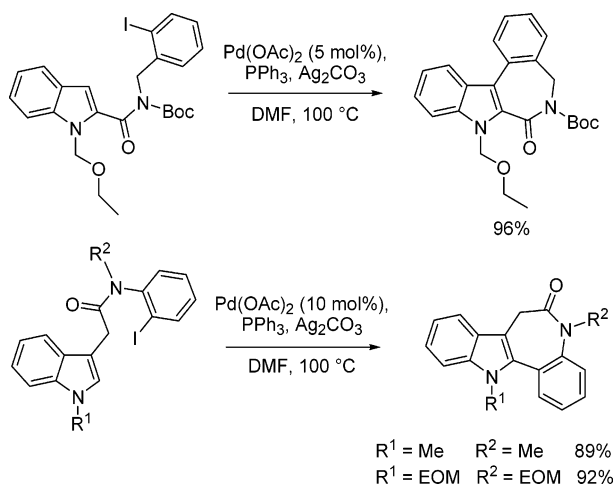
paullone derivatives from various *N*-protected indoles with aryl iodides (Scheme 182).[239] In this system, yields of the cyclized products were excellent regardless of the location of the amide tether.

This approach toward the same family of paullone derivatives has recently been reported by Beccalli and co-workers using Jeffery's conditions.[240] Use of this highly reactive catalyst system allowed for the formation of seven-, eight-, and nine-membered ring systems in modest to excellent yields (Scheme 183). Again, *N*-methylation of the amide was necessary to avoid palladium complexation.

Scheme 183

n = 0　85%
　　1　45% (μw)
　　2　51% (μw)

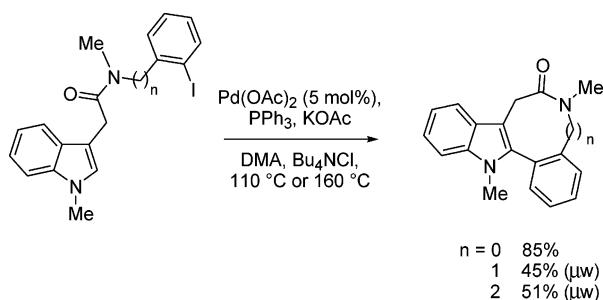A related route has also been reported for the preparation of a family of 6-substituted indolo[3,2-*c*]quinolines and 6-substituted pyrido[3′,2′:4,5][3,2-*c*]quinolines. These compounds were of interest due to their structural similarity to ellipticine, a potent antitumor compound. The authors reported that protection of the secondary amide was required to prevent deiodination of the starting material during the palladium-catalyzed cyclization (Scheme 184).[241]

Scheme 184

Y = CH　75%
　　N　72%
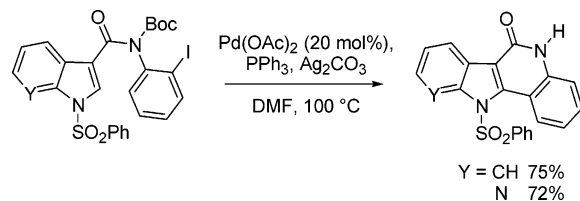
The same strategy has also been employed for the synthesis of a family of phenylcarbazole derivatives for use as potential anticancer agents.[242] Cyclization of the arene indolylmaleimide gave the desired carbazole derivatives in low to good yields depending on the protecting group and the catalyst

Scheme 185

R = H　　　100%
SO₂Ph　　15%
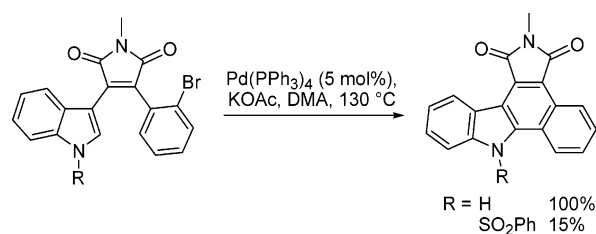
system used (Scheme 185). A group at Eli Lilly has also used this approach for the synthesis of a variety of carbazole derivatives using the corresponding *NH*-indole substrates tethered to an aryl or thienyl bromide.[243]

This method has also been utilized for the intramolecular coupling of two indole fragments as the key step in the synthesis of *N*-methylarcyriacyanin A.[244] Cyclization occurred in good yield under palladium-catalyzed conditions (Scheme 186). In this case, the authors propose that since

Scheme 186

81%
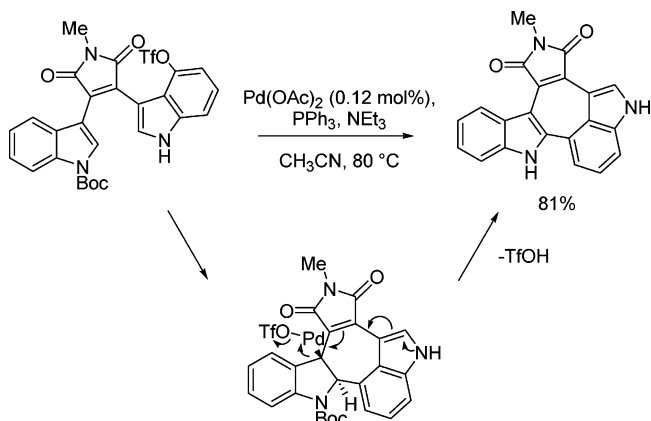
syn elimination is not possible, cyclization likely occurs via a carbopalladation/base-catalyzed fragmentation pathway. Alternatively, cyclization could also occur in this case via a Heck-type coupling followed by either *anti* β-hydride elimination[245] or palladium isomerization and *syn* β-hydride elimination.

A direct arylation has also been employed for the preparation of a triaza analogue of a "crushed-fullerene" fragment.[41] Model studies on smaller systems found that arylation of the carbazole proceeded in quantitative yields under the reaction conditions (Scheme 187). Interestingly, use of a nonsymmetrical carbazole was found to give a nearly equal mixture of products **55** and **56**, casting doubt on a proposed electrophilic aromatic substitution mechanism.

Another example of a direct arylation at the arene portion of indole was achieved by blocking the 2-position of an indole containing an aryl bromide tethered at the nitrogen (Scheme 188). This method was subsequently applied to the synthesis of the core structures of pratosine and hippadine.[246]

A similar C-7 cyclization between pyridine and indole moieties was reported as a competing side reaction in a Heck cyclization during the synthesis of a maxonine precursor (Scheme 189).[247]

A related example using 4-anilino-5-iodopyrimidine to cyclize onto the benzo portion of indole has also been reported.[173] In this example, two regioisomeric products were obtained in modest yields with preference for arylation at the 4- versus 6-position of indole (Scheme 190).

Scheme 187

100%

68%
55:**56** = 1.2:1

55: R^1 = H, R^2 = NO$_2$
56: R^1 = NO$_2$, R^2 = H

Scheme 188

95%

pratosine

Scheme 189

54%

+

16%

Scheme 190

46%

+

26%

Scheme 191

R = Me 48%
Et 62%
i-Pr 66%
H   54%

C-3:C-2
R = Me 40%   8:1
Et 58%   15:1
i-Pr 46%   50:1
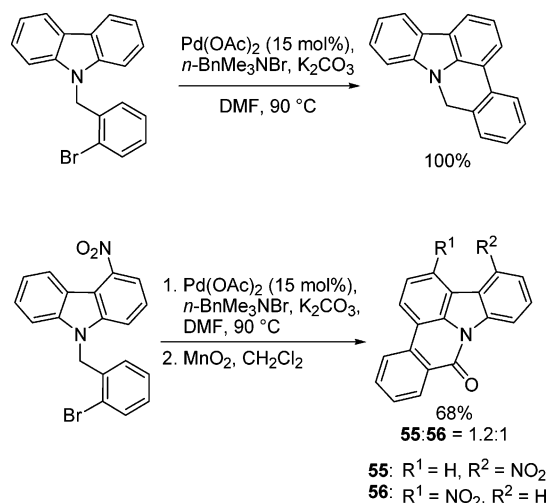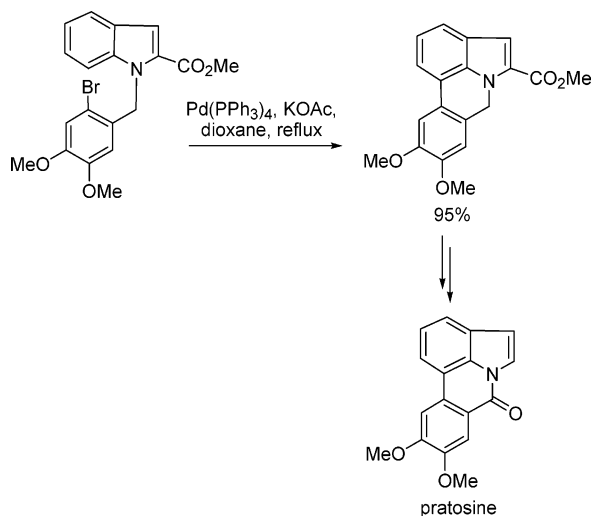
3.1.1.2. Intermolecular Aryl−Indolyl Bond Formation.

Ohta and co-workers reported the first intermolecular direct arylation of indole using chloropyrazines. Interestingly, Ohta reported that for the palladium-catalyzed coupling of chloropyrazines and indoles, the nature of the nitrogen protecting group on indole had a profound effect on the regioselectivity of the reaction (Scheme 191).[248] While use of *N*-alkyl and *NH*-indoles gave the desired 2-pyrazinylindole in modest yields, *N*-tosylindole was found to favor the 3-pyrazinylindole product. In addition, the steric bulk of the pyrazinyl chloride used for the coupling was found to have a significant effect on the regioselectivity of the arylation for *N*-tosylindole, with more sterically bulky pyrazine moieties favoring the C-3-arylated product.
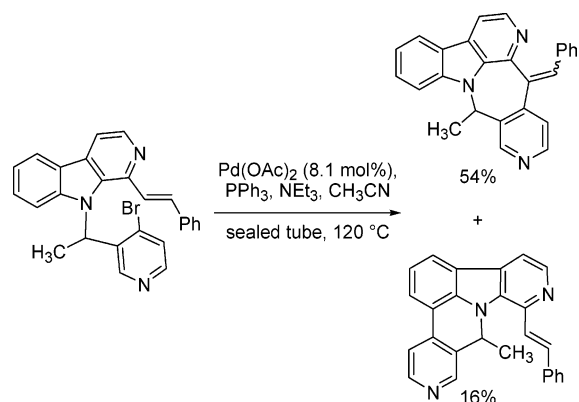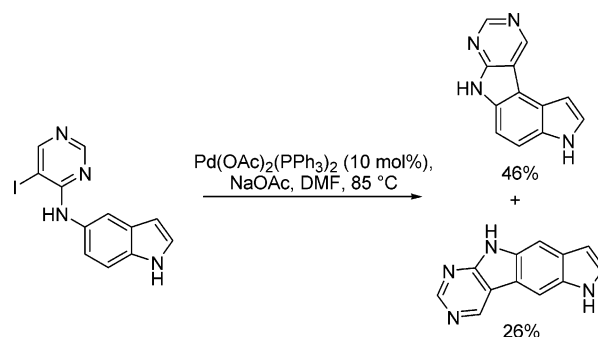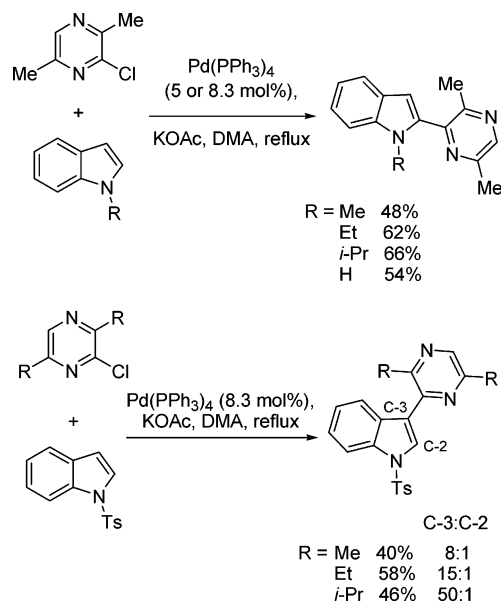
More recently, Sames reported a related palladium-catalyzed intermolecular arylation of other *N*-substituted indoles.[42,249] Judicious choice of the reaction conditions allowed for suppression of a competing palladium-catalyzed homocoupling of iodobenzene, thereby allowing for good yields of the 2-arylindole. The reaction scope allowed for a variety of alkyl substituents at the 1-position, as well as additional functional groups positioned at various other locations around the indole ring (Scheme 192). In particular, it should be noted that this method could also be extended to the arylation of 7-azaindoles to afford the desired 2-phenyl-7-azaindole in 85% yield.

This method also allowed for the selective C-2 arylation of indole using a limited variety of *para*-substituted electron-poor iodobenzenes (Scheme 193).[249] As previously observed by Ohta,[248] the use of sterically hindered aryl halides afforded a mixture of regioisomeric products under these conditions.[42] Mechanistic studies suggest that the reaction proceeds via initial electrophilic metalation at the 3-position, followed by 1,2-palladium migration, deprotonation, and reductive elimination (Scheme 194). Hence, the authors suggest that the poor regioselectivity associated with bulky iodobenzene derivatives may be due to the slow 1,2-palladium migration, thereby favoring deprotonation and subsequent formation of the 3-metalloindole intermediate. Reductive elimination of

Scheme 192

88%   68%   0%

85%   61%   51%

Scheme 193

X = CF$_3$ 62%
  = CN   71%
  = C(O)Me   52%

67%
1.3:1 C-3:C-2
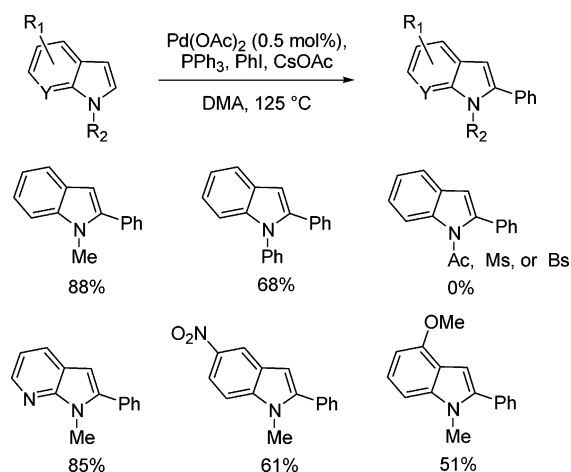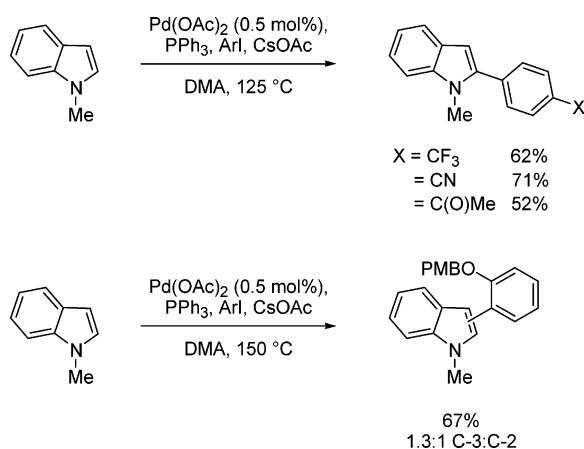
Scheme 194

the 3-metalloindole would then provide the observed 3-arylindole product.

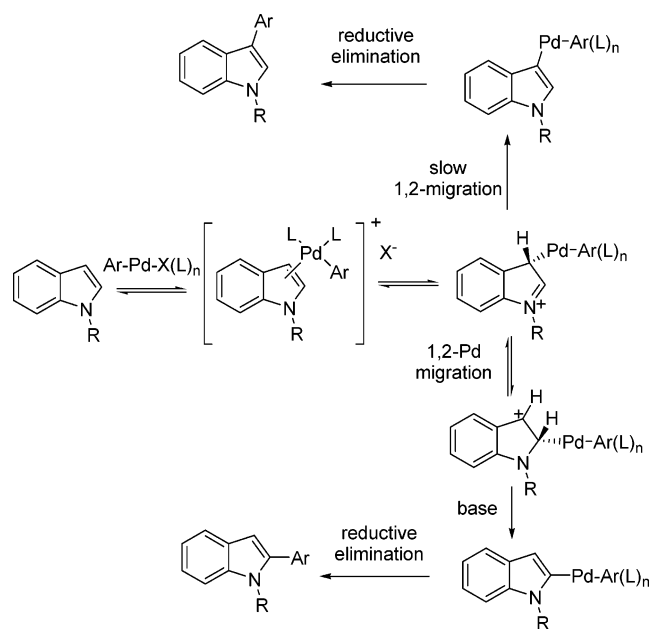The observations regarding the effect of the size of the arene group on the regioselectivity of the arylation led to the development of a method to selectively arylate the C-3 position of free indole via the in situ generation of a MgN salt. Interestingly, use of a TMEDA-ligated magnesium azole

in concert with a bulky electron-rich IMes ligand on palladium could be used to give the C-3-arylated product in excellent selectivity and yield (Scheme 195).[42]

Scheme 195

24%
7:1 C-3:C-2

61%
14:1 C-3:C-2

96%
67:1 C-3:C-2
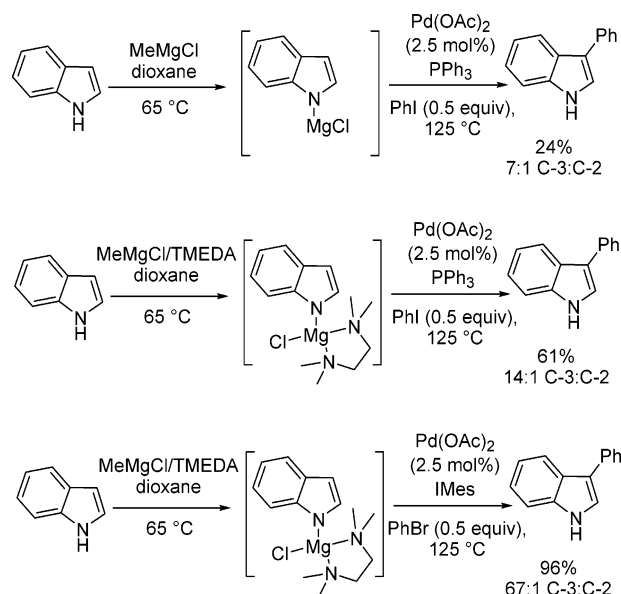
The authors later found that in situ protection of the nitrogen using MeMgCl or Mg(HMDS)$_2$ was not required when ArRh(OPiv)$_2$[P(p-CF$_3$Ph)$_3$]$_2$ was used as the catalyst. This catalyst, prepared in situ from [Rh(coe)$_2$Cl$_2$]$_2$, P(p-CF$_3$Ph)$_3$, CsOPiv, and ArI, afforded good yields of the intermolecularly coupled product with excellent selectivities (>50:1 for iodobenzene) (Scheme 196).[250] Arylation of a

Scheme 196

R$_1$ = H	R$_2$ = H	82%
NHBoc	H	59%
NHPiv	Me	78%
F	Me	76%
CO$_2$Me	H	59%
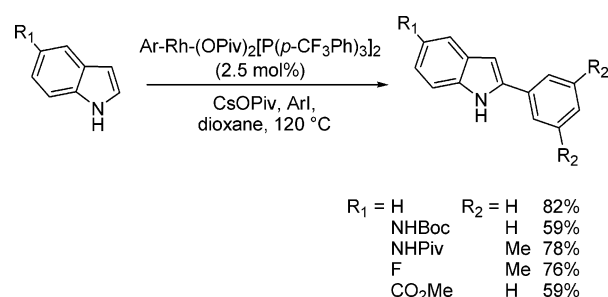
broad range of halide-, protected-amine, and ester-substituted indoles was possible.

Mechanistic studies and X-ray analysis of the active catalyst were used to provide some intriguing mechanistic details of the reaction. On the basis of these studies, the authors propose that the active Rh(III) catalyst **57** formed in situ undergoes coordination of indole and concomitant expulsion of phosphine to generate **58**. On the basis of kinetic isotope effects, the authors propose that the coordinated pivalate anion assists in C−H bond dissociation, affording complex **59**. Reductive elimination of the 2-arylindole releases the Rh(I) species, which is rapidly trapped by the iodoarene and CsOPiv to re-form the more stable resting complex **57** (Scheme 197).

Sames has subsequently reported a complementary, palladium-catalyzed C-2 arylation of *N*-SEM-protected indoles.[251] While typically less reactive, SEM-protected indoles represent an attractive class of substrates due to their relative ease of deprotection. In addition, use of these conditions

Scheme 197

Ar = *p*-CF₃Ph
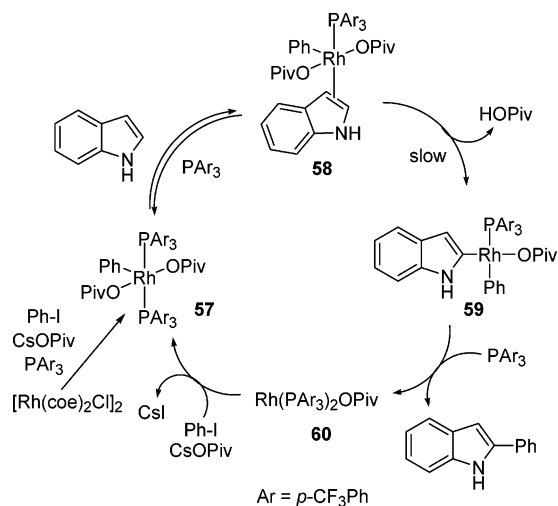
avoided the in situ generation of water-sensitive magnesium azole species used for nonprotected indoles, and allowed for a catalyst system that could be applied to the arylation of other azole derivatives in good to moderate yields (see sections 3.1.2 and 3.1.4). Treatment of *N*-SEM-protected indoles with a bulky, electron-rich NHC-bound palladium catalyst afforded the 2-arylindoles in good to modest yields (Scheme 198). As previously observed for *N*-methylindole,

Scheme 198

R = H   77%
    CN   82%
    NO₂ 68%

52%
3.5:1 = C-2:C-3

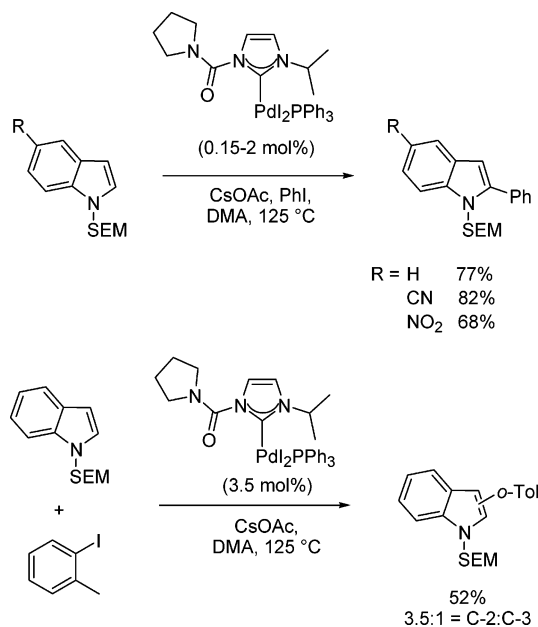use of a sterically bulky aryl iodide resulted in a mixture of 2- and 3-arylated products. In addition, C-2 arylation of more demanding 3-substituted indoles could also be carried out, albeit in lower yields.

Bellina and co-workers recently reported a palladium-catalyzed copper-mediated C-2 arylation of *NH*-indole with an aryl iodide under base-free and ligandless conditions (Scheme 199).[27] Although a low yield was observed for the direct arylation of indole, higher yields were obtained for other five-membered heterocycles using these conditions (see section 3.1.4.1).

Recently, a highly modular one-pot tandem reaction involving a direct arylation of indoles was reported by

Scheme 199

35%
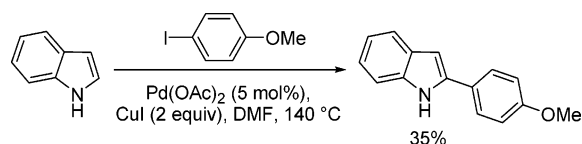
Lautens.[252] (Bromoalkyl)indoles were reacted with aryl iodides using a palladium catalyst in the presence of nor-bornene to afford a variety of fused tricyclic indole deriva-tives (Scheme 200). The reaction tolerates a wide variety of

Scheme 200


93%   83%
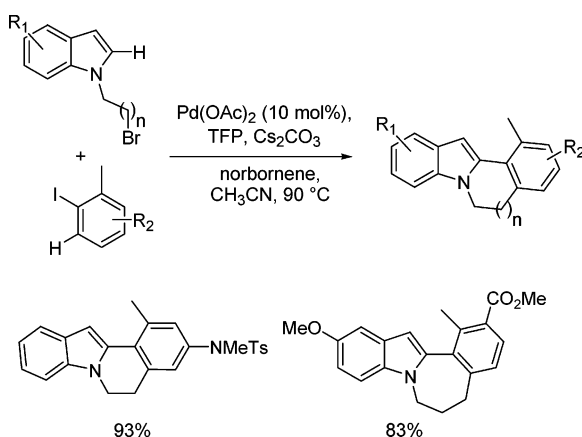
electron-donating and electron-withdrawing substituents on both the aryl iodide and the indole.

Mechanistically, the reaction is proposed to occur via initial oxidative addition of palladium(0) to the aryl iodide, followed by carbopalladation with norbornene to afford an alkylpalladium species (Scheme 201). This intermediate is incapable of β-hydride elimination and therefore oxidatively adds to the alkyl halide tether containing the indole moiety. The proposed palladium(IV) intermediate undergoes reduc-tive elimination to form an alkyl−aryl bond. Provided that the other *ortho* position is substituted, and therefore ef-fectively blocked from performing another palladium-catalyzed functionalization, the norbornylpalladium species undergoes decarbopalladative expulsion of norbornene to regenerate an arylpalladium species. The resulting arylpal-ladium species can then undergo the final intramolecular cyclization onto the indole to give a variety of six- or seven-membered annulated indoles.

More recently, there has been an emphasis on the design of direct arylation reactions that can occur under milder conditions and lower reaction temperatures. A major break-through in this area was recently reported by Sanford and co-workers in which selective C-2 arylation of indoles could be carried out at room temperature on the basis of a proposed Pd(II)/Pd(IV) catalytic cycle.[253] The authors suggest that use of a more electron-deficient Pd(OAc)₂ catalyst likely results in a faster electrophilic palladation of indole, thereby allowing for the reaction to occur quickly, even at room temperature (pathway A, Scheme 202).

Reaction yields for the room-temperature coupling were moderate to good, affording the 2-arylindoles for a broad range of electron-rich and electron-poor arenes (Scheme 203). Furthermore, sterically-hindered 1-naphthyl and *o*-methyl groups could be incorporated at the desired C-2 position in excellent (>20:1) selectivity. This extremely general protocol

Scheme 201
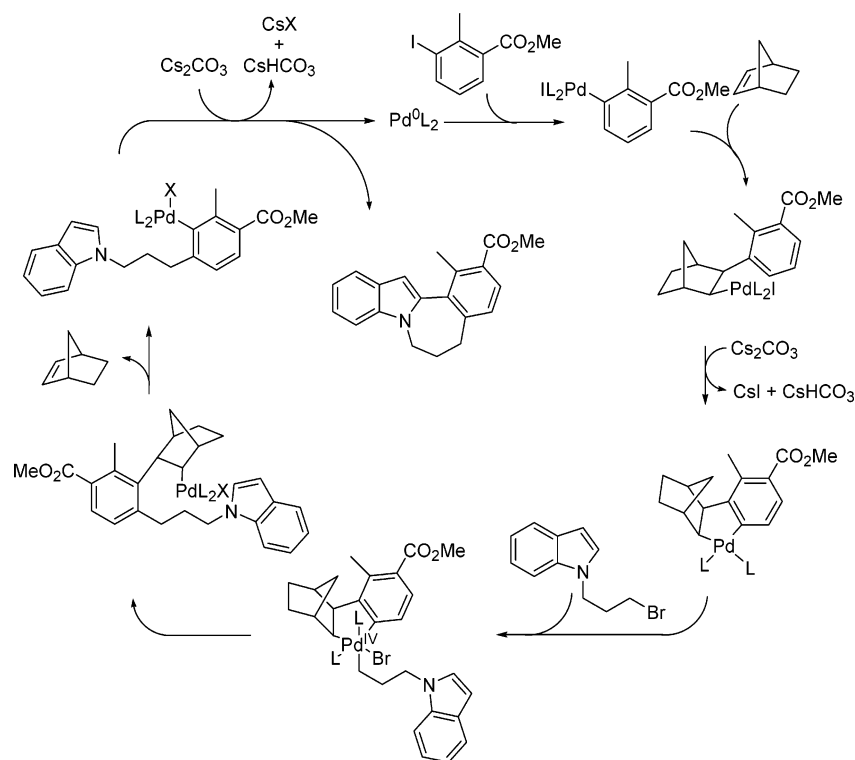
Scheme 202
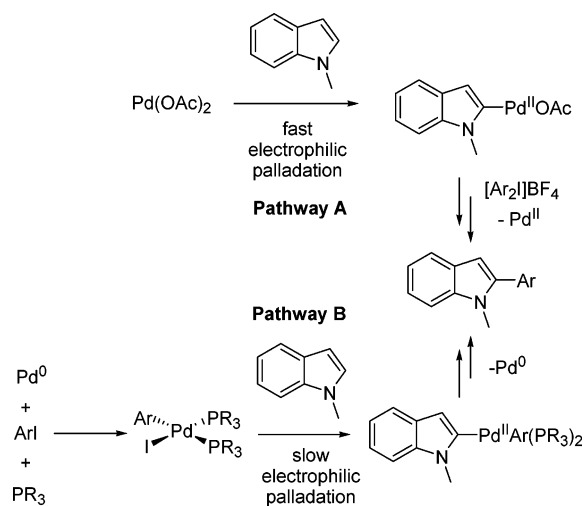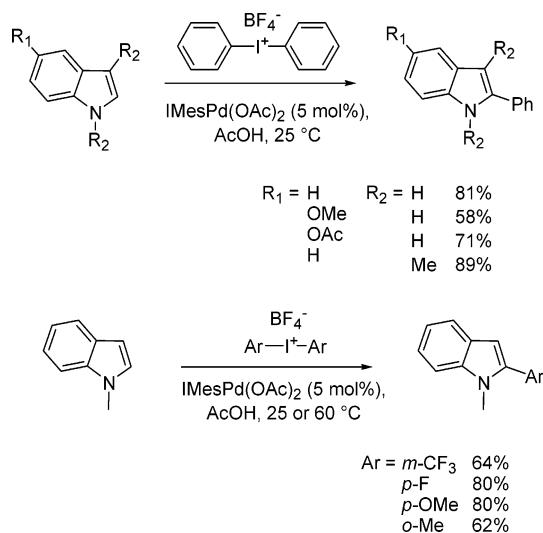
was extended to the coupling of various *N*-substituted indoles.

3.1.2. Pyrroles

3.1.2.1. Intramolecular Aryl−Pyrrolyl Bond Formation. Grigg reported the first example of the direct arylation of pyrrole using a tethered aryl iodide under palladium-catalyzed conditions (Scheme 204).[228]

The utility of this type of cyclization has since been applied to the synthesis of the core structure of lamellarin[254] as well as a library of potent cyclin-dependent kinase inhibitors (Scheme 205).[255]

An additional example of the power of this methodology was demonstrated by Trauner during the total synthesis of rhazinilam.[256] Cyclization of aryl iodide onto the pyrrole was carried out using catalytic palladium and Buchwald's Dav-ePhos ligand to give the desired rhazinilam precursor. The

Scheme 203

R₁ = H, R₂ = H: 81%
OMe, H: 58%
OAc, H: 71%
H, Me: 89%

Ar = *m*-CF₃: 64%
p-F: 80%
p-OMe: 80%
o-Me: 62%
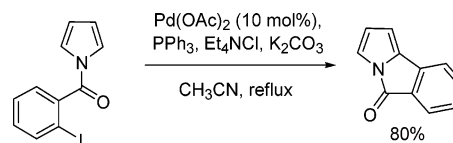
Scheme 204

authors report that introduction of a MOM protecting group proved necessary to avoid deiodination of the starting material, presumably via protonation of a stable palladacycle intermediate, **61** (Scheme 206).

This methodology has also been used successfully in the synthesis of the core structure of latonduine (Scheme 207). In this study, intramolecular coupling of the aryl iodide onto the protected pyrrole was achieved in 70% yield.[239] At the same time, Beccalli and co-workers independently reported a related intramolecular cyclization of several aryl halides

Scheme 205

R = H
R = Ac

R = H   81%

R = [structure]OH   62%

Scheme 206

47%

rhazinilam

61

Scheme 207

70%

Scheme 208

89%
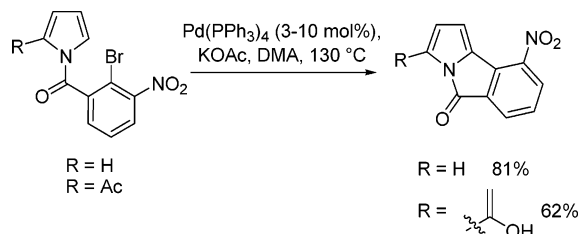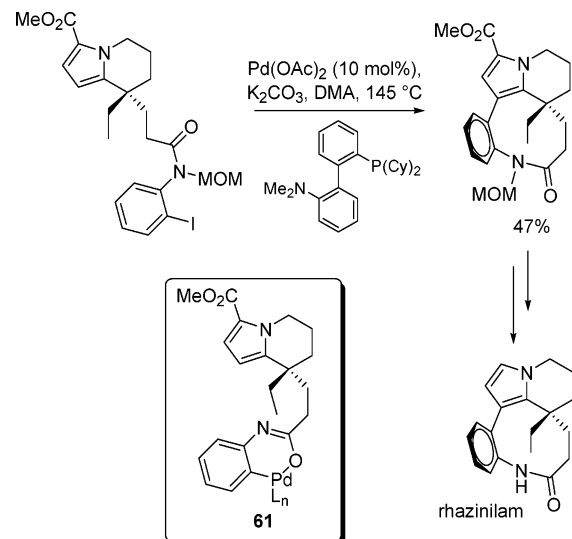
onto a tethered *N*-methylpyrrole derivative (Scheme 208).[257] In this case, the pharmaceutically interesting tricyclic heterocycles were obtained in good to excellent yields.

3.1.2.2. Intermolecular Aryl−Pyrrolyl Bond Formation. Filippini reported an interesting palladium-catalyzed direct arylation of *N*-metalated pyrrole with bromobenzene in which the nature of the cation had varying effects on product distribution.[258] While use of sodium pyrrol-1-yl gave the aryl bromide-homocoupled product in quantitative yield, trans-metalation to a more hard pyrrol-1-ylzinc bromide gave the desired 2-substituted pyrrole in 40% yield along with some of the 3-substituted pyrrole and dimerized bromobenzene product. Further improvement in reaction selectivity was possible using ZnCl₂, which afforded the desired 2-substituted pyrrole product in 75% yield with very little of the 3-substituted pyrrole and Ullman coupling byproduct (Scheme 209).

Scheme 209

M = Na	0%	0%	100%
M = ZnBr	40%	10%	50%
M = ZnCl	75%	5%	15%

Subsequent studies by Sadighi improved the aforementioned protocol such that higher yields and selectivities could be achieved while using lower catalyst loadings (Scheme 210).[259] In addition, use of the bulky, electron-rich bis(*tert*-
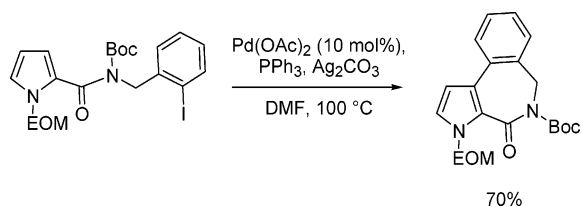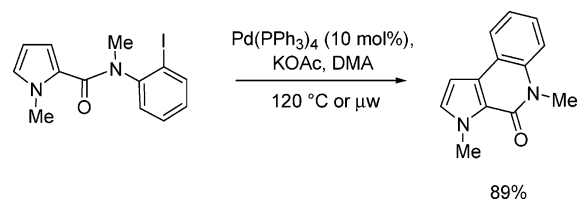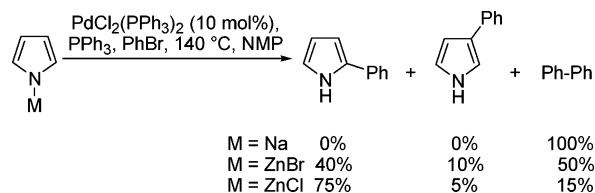
Scheme 210

ArX =	90%	48%	70%	93%
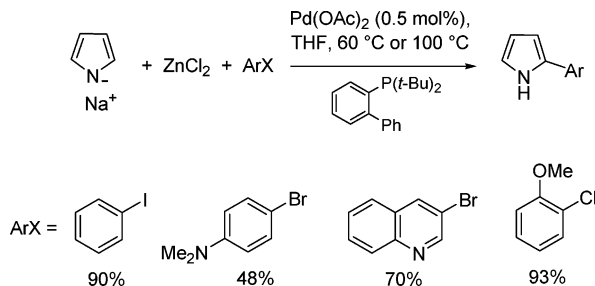
butylphosphino)biphenyl ligand allowed for the extension of this arylation procedure to include aryl chlorides as well as sterically demanding 2,4-dimethyl-substituted pyrrole substrates.

Sames has also reported several alternative procedures for the intermolecular C-2 arylation of pyrrole. The first approach uses ArRh(OPiv)₂[P(*p*-CF₃Ph)₃]₂ as the catalyst system for the C-2 arylation of *NH*-containing pyrrole (Scheme 211),[250]

Scheme 211

81%
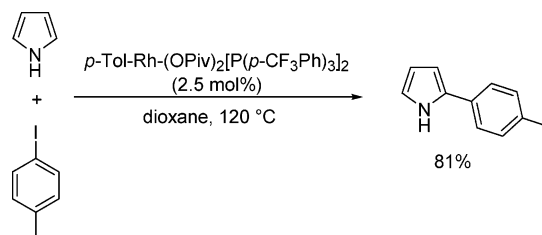
while the second relies on the use of the readily removable SEM-protected pyrrole (Scheme 212).[251] Yields for this

Scheme 212

49%
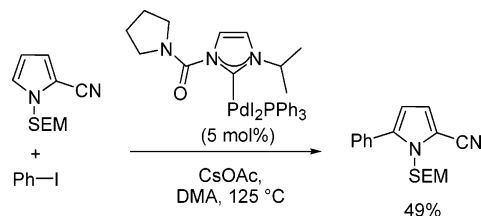
second protocol ranged from 49% to 59% for several electron-poor pyrroles.

Sanford also applied her recently disclosed room-temperature arylation procedure to both protected and nonprotected pyrroles. In these examples, C-2 arylation occurred selectively in moderate (67−69%) yields (Scheme 213).[253]

Ohta has also demonstrated the use of his methodology for the coupling of chloropyrazines and various pyrroles (Scheme 214).[260] Interestingly, while coupling of the *N*-

Scheme 213

R = H   69%
R = Me   67%

Scheme 214

R = Me 28%
    H   25% +
14% C-2/C-5 dipyrazinylated
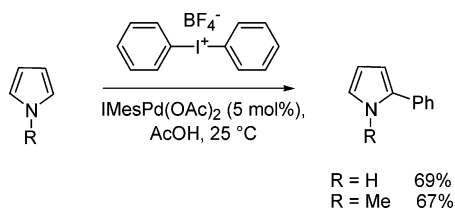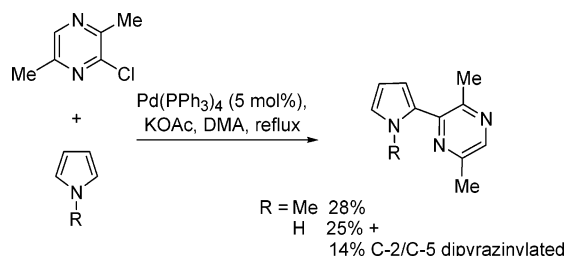
methylpyrrole occurred with no evidence of any other pyrazinylated products, the use of free pyrroles was found to afford a 2:1 mixture of mono- to diarylated products.

Lautens and co-workers have extended their palladium-catalyzed norbornene-mediated sequential coupling reaction to the annulation of pyrroles.[261] Electron-poor aromatics, which contained one blocking group *ortho* to the iodide functionality, gave good to excellent yields of the annulated pyrroles. In addition, use of electron-rich aromatics also gave the desired annulated pyrroles, although in somewhat lower yields (Scheme 215). The pyrrole coupling partner also

Scheme 215

n = 2   R = N(Me)Ts   69%
    1   N(Me)Ts   73%
    1   OMe   59%
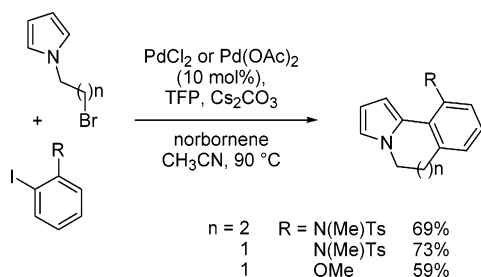
tolerated electron-withdrawing ester functionalities at the 2-position, affording the 5-annulated pyrrole in moderate yields. The use of iodouracils instead of iodoarenes in this reaction has also been reported, albeit in modest yields (Scheme 216).

Scheme 216

39%
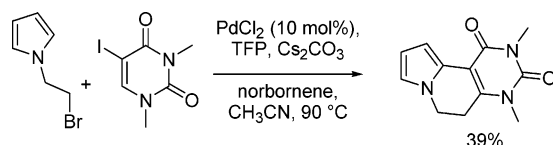
3.1.3. Pyridines and Quinolines

Ames reported the first intramolecular direct arylation reaction involving pyridine in the early 1980s. In this example, treatment of 2-(2-bromophenoxy)pyridine with Pd(OAc)$_2$ and Na$_2$CO$_3$ afforded the tricyclic compounds in a low 10% yield (Scheme 217).[128]

A related coupling in which two tethered pyridine moieties were used as a model compound for the synthesis of isocryptolepine has also been reported (Scheme 218).[262]

Scheme 217

10%

Scheme 218

52%
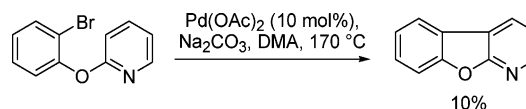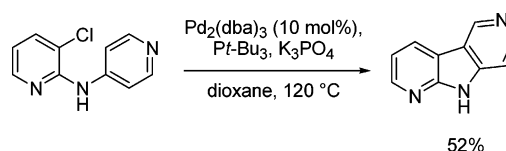
Direct arylation using the pyridyl chloride occurred in 52% yield.

de Meijere reported the use of iodopyridines in a palladium-catalyzed domino coupling using norbornene (see section 2.1.1.1 for mechanistic details) (Scheme 219).[63,64]

Scheme 219

R = H   45%
    Me   30%
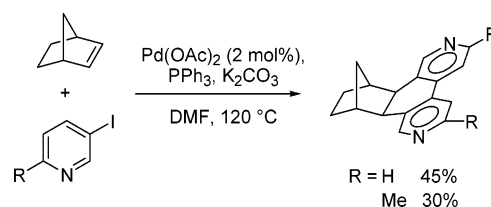
The observed norbornene-incorporated bipyridine products were obtained in low yields.

An expedient synthesis of isocryptolepine and benzo-β-carboline isoneocryptolepine was achieved via a palladium-catalyzed intramolecular direct arylation of quinoline.[262,263] Use of this direct arylation procedure allowed for the facile synthesis of D-ring analogues of isocryptolepine for subsequent SAR screening (Scheme 220).

Scheme 220

95%
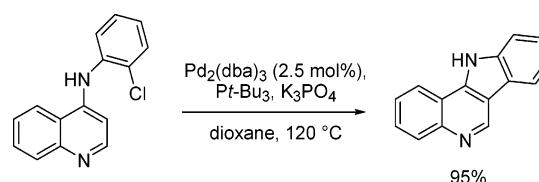
Recently, access to 2-arylpyridines via an intermolecular coupling has been achieved using palladium on charcoal in the presence of zinc metal in water (Scheme 221).[264]

Scheme 221

X = Cl 45%
    Br 15%
    I   19%
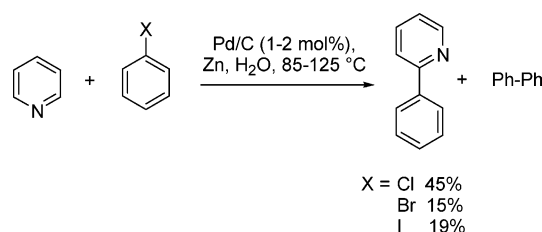
Although the authors discuss the possibility that the reaction can occur via a Heck-type or radical mechanism, they favor the latter since the aryl chloride conversion was found to decrease by 2 orders of magnitude when 5% (w/w) 2,6-di-*tert*-butyl-4-methylphenol (BHT) was added. Hence, the authors propose that adsorption of the aryl halide occurs with concomitant single-electron transfer to generate [PhX]•⁻,

which then undergoes anion expulsion to generate a phenyl radical on the catalyst surface. Reaction of the adsorbed phenyl radical is then proposed to undergo either coupling with a neighboring pyridine molecule or homocoupling with an adjacent phenyl radical. While these reaction conditions could be applied to aryl chlorides, bromides, and iodides, aryl chlorides were found to afford the best yields of the desired cross-coupled product. The authors suggest that the reason for this phenomenon is that the rate at which aryl chlorides are reduced is slower than that of aryl bromides and iodides. Therefore, in the presence of excess pyridine, the adjacent site on the palladium catalyst would most likely contain a pyridine molecule that would then be capable of a coupling reaction. However, for aryl bromides and iodides, generation of a phenyl radical would be much more facile, increasing the likelihood of radical dimerization.

Fagnou subsequently reported a more synthetically useful preparation of 2-arylpyridines through a palladium-catalyzed coupling of pyridine N-oxides and aryl bromides.[265] Both electron-rich and electron-poor pyridine N-oxides react exclusively at the 2-position. In addition, the aryl bromide partner tolerated sterically-hindering as well as electron-rich and electron-poor functionalities (Scheme 222). Deprotection

Scheme 222

R = 4-OMe	80%
4-CF$_3$	76%
2-Me	87%
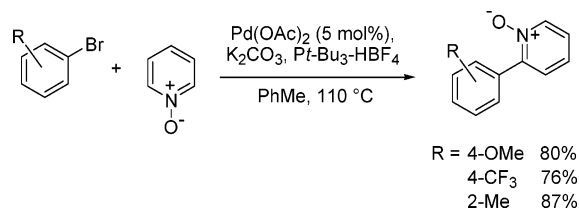
of the resulting 2-arylpyridine N-oxides was carried out using Pd/C in methanol in the presence of ammonium formate to give the expected 2-arylpyridine in good to excellent yields.

3.1.4. Other Nitrogen-Containing Heteroaromatics

The direct arylation of nitrogen-containing heterocycles is not limited to indole-, pyrrole-, and pyridine-type compounds. Numerous other nitrogen-containing five- and six-membered, as well as fused heterocyclic ring systems have been shown to undergo direct arylation (Figure 6).


Figure 6.

3.1.4.1. Five-Membered and Fused Ring Systems. In the early 1980s, Nakamura reported the coupling of an aryl

iodide to an isoxazole as a key step in the total synthesis of a lipophilic derivative of the GABA agonist muscimol.[266] While an oxidative coupling strategy was first investigated using benzene and catalytic Pd(OAc)$_2$ with Cu(OAc)$_2$/oxygen as the oxidant, the authors found that use of almost stoichiometric palladium was required to obtain synthetically useful yields. Hence, an alternative strategy using iodobenzene and base was employed, allowing for the use of catalytic amounts of palladium while still obtaining the desired coupled product in low to moderate yields (Scheme 223).

Scheme 223

R = Me	30%	
Ph	43%	
p-ClPh	37%	
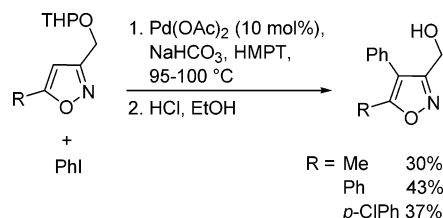
Miura and co-workers later conducted extensive studies toward the intermolecular palladium-catalyzed arylation of a variety of azoles.[267] Initial studies by the authors using 1,2-dimethylimidazole found that both the aryl halide and base played an important role in the reaction, and that arylation occurred selectively at the C-5 position (Scheme 224). The reaction scope for the transformation was fairly

Scheme 224

For X = I, M = Cs		For X = Br, M = K	
Ar = 4-OMe	80%	Ar = 4-OMe	85%
4-Cl	84%	4-Cl	85%
1-naphthyl	68%	1-naphthyl	86%
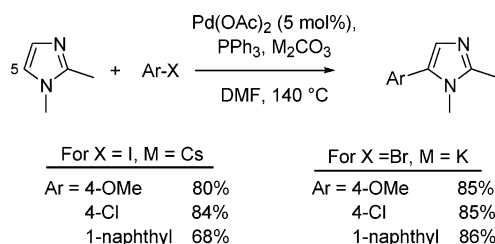
broad, affording good to excellent yields for a variety of electron-rich, electron-poor, and sterically-hindered aryl iodides and bromides. This method was also extended to other related azole systems including oxazoles and benzoxazoles (Scheme 225).

Scheme 225

Scheme 226

Scheme 227

Y = NMe	Pd(OAc)$_2$ (10 mol%)	54%	24%	0%
	Pd(OAc)$_2$ (10 mol%) / CuI (2 equiv)	0%	37%	40%
	CuI (2 equiv)	0%	0%	37%
Y = S	Pd(OAc)$_2$ (10 mol%)	17%	35%	0%
	Pd(OAc)$_2$ (10 mol%) / CuI (2 equiv)	0%	66%	0%
	CuI (2 equiv)	0%	0%	15%
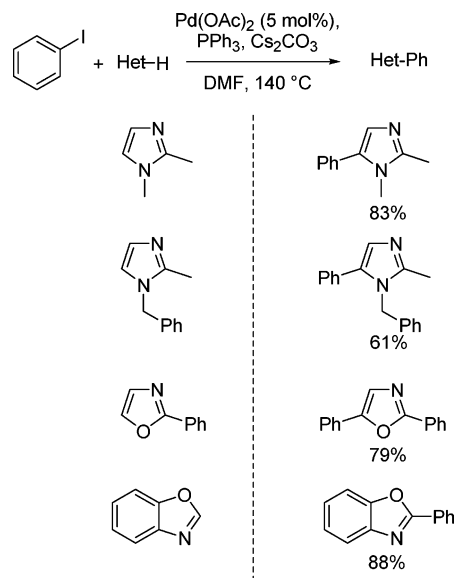
The authors also discovered that addition of CuI increased yields for the arylation of several azole compounds, with the most dramatic improvement being observed for sulfur-containing heterocycles. In fact, control reactions found that even in the absence of Pd(OAc)$_2$, CuI alone could carry out the arylation reaction in good yield for 1-methylbenzimidazole (Scheme 226).[267]

The authors also reported that for N-methylimidazole and thiazole, the C$-$H bond undergoing arylation could be somewhat controlled depending on the catalyst system used (Scheme 227).[267] Under palladium-catalyzed conditions, arylation of the azole occurred preferentially at the C-5 position, followed by subsequent arylation at C-2. Interestingly, carrying out the arylation with CuI in the absence of palladium still exclusively gave the C-2 product, albeit in low yields. The authors proposed that this copper-mediated arylation may occur via a Cu(I)/base-assisted nucleophilic substitution of the aryl iodide.[268−271]

For the palladium-catalyzed arylation process, the authors propose that the reaction likely proceeds via initial oxidative addition of palladium(0) to the aryl halide, followed by nucleophilic attack of the azole to afford a σ-azole/arylpalladium(II) adduct.[267] Reductive elimination would then afford the observed arylated product (Scheme 228).

The direct arylation of other related N-substituted imidazole systems has also been investigated. For example, Sames reported the C-5-selective direct arylation of SEM-protected imidazoles in the presence of a bulky NHC−palladium catalyst. Under these conditions, the desired arylated product was obtained in modest yields (Scheme 229).[251] In the case

Scheme 228

Scheme 229
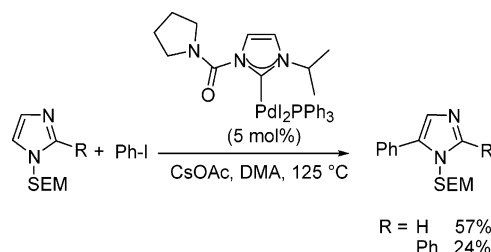
of the N-SEM-imidazole, only 3−5% of the C-2-arylated side product was isolated.

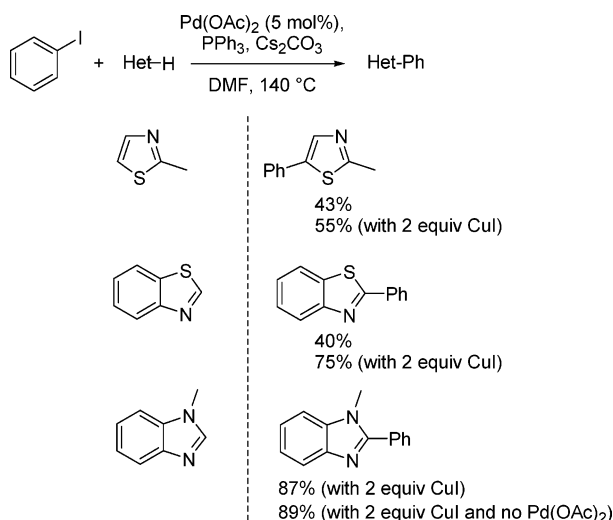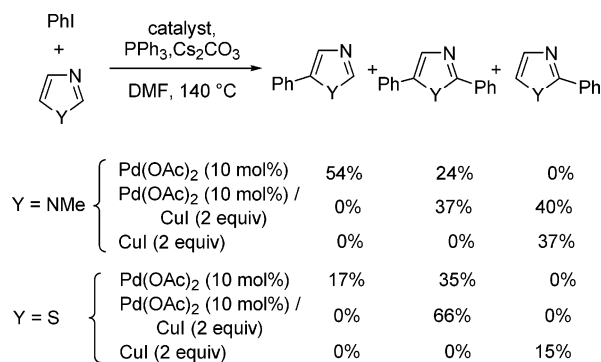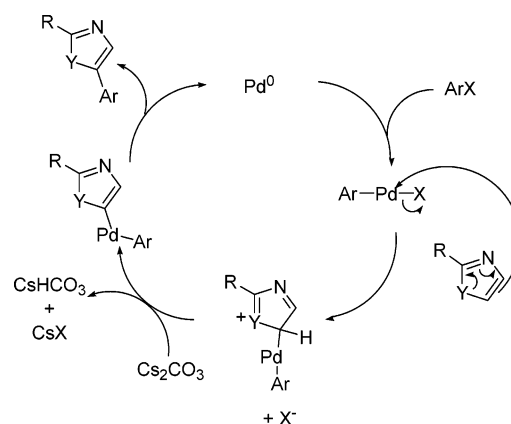Bellina described the selective C-5 arylation of N-aryl-imidazoles.[272] Following extensive optimization, C-5 arylation could be achieved while suppressing the competitive C-2 arylation and C-2/C-5 bisarylation pathways observed by Miura. These conditions provided the desired 1,5-di-arylimidazole in modest to excellent selectivity and in low to moderate yields for 1-arylimidazoles bearing an electron-rich aryl group (Scheme 230).

Scheme 230

Ar^1	Ar^{2}X	Ratio 62:63:64	Yield of **62** (%)
4-MeSO$_2$Ph	4-MeOPhI	-	0
Ph	4-MeOPhI	95:5:0	49
Ph	4-MeOPhBr	100:0:0	43
Ph	4-CF$_3$PhI	86:5:9	38
Ph	4-CF$_3$PhBr	76:0:24	59
3,4,5-(MeO)$_3$Ph	1-naphthyl-I	100:0:0	55
3,4,5-(MeO)$_3$Ph	4-MeOPhI	87:2:11	40
3,4,5-(MeO)$_3$Ph	4-MeOPhBr	100:0:0	61
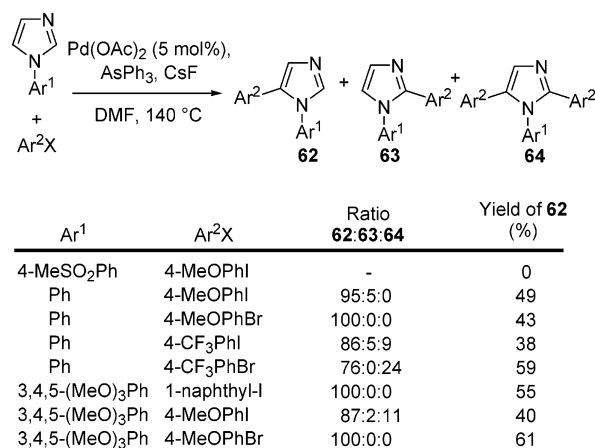
This group subsequently reported a complementary approach for the selective C-2 arylation of 1-arylimidazoles (Scheme 231).[273] Through careful optimization of the catalyst loading, amount of CuI additive, and base, the authors were able to achieve a moderate-yielding and highly selective route to 1,2-diarylimidazoles.

While most direct arylation reactions require a base, Bellina and co-workers recently reported base-free, ligandless conditions for direct arylation.[27] Various 2-arylated oxazoles,

Scheme 231
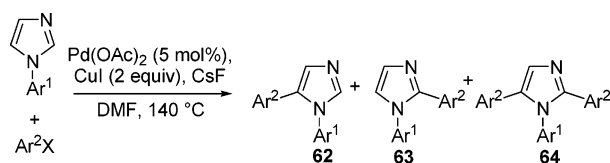
Ar^1	Ar^{2}X	Ratio 62:63:64	Yield of **63** (%)
4-MeSO$_2$Ph	3,4,5-(MeO)$_3$PhI	0:100:0	79
4-MeOPh	3,4,5-(MeO)$_3$PhI	4:94:0	59
Ph	4-MeOPhI	1:81:18	62
Ph	4-CF$_3$PhI	0:72:28	64

thiazoles, imidazoles, and benzimidazoles could be obtained in good to excellent yields using this catalyst system (Scheme 232).

Scheme 232
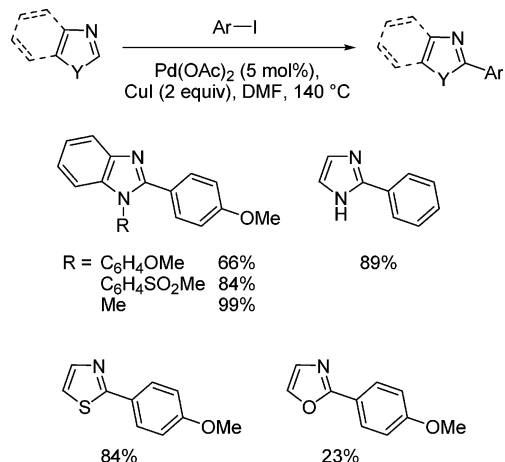
Although copper additives have been shown to significantly improve the direct arylation of various azoles, Miura subsequently developed conditions in which copper salts were not required to enhance the yield for the arylation of thiazoles.[274] In screening a variety of ligands for the bisarylation of thiazole with 4-bromoanisole, it was found that tri-*tert*-butylphosphine was optimal, affording good yields of the desired 2,5-diarylthiazole. The reaction scope using this catalyst system was broad, giving the arylthiazole in good yields for a variety of electron-rich and electron-neutral aryl bromides. In addition, unsubstituted and 2-substituted thiazoles as well as benzothiazoles could be used in the reaction to give the expected arylthiazole in moderate to good yields (Scheme 233).

Scheme 233
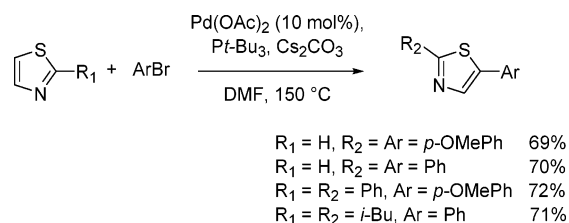
A similar method was used to prepare a large library of 2-arylbenzothiazoles with the hope of extending the results toward the synthesis of radiolabeled derivatives as biomarkers for in vivo imaging of β-amyloid plaques using positron emission tomography.[275] While attempts to prepare the desired compounds using Suzuki coupling chemistry achieved limited success, use of direct arylation allowed for the synthesis of the required 2-arylbenzothiazole or 2-arylbenzoxazole derivatives in modest to good yields for a variety of aryl bromides.

Another alternative method for the formation of 2-arylbenzothiazoles was reported by Maleczka. In this study, use of poly(methylhydrosiloxane) (PMHS) in combination with CsF was found to facilitate the arylation of benzothiazole using either an aryl iodide or aryl nonaflate at room temperature (Scheme 234).[276] The authors suggest that the

Scheme 234
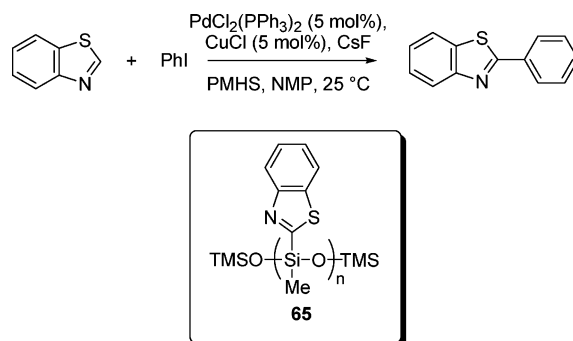
reaction takes place at room temperature due to the formation of a highly reactive benzothiazolylsilane intermediate, **65**, which subsequently undergoes rapid transmetalation and reductive elimination to form the desired 2-arylbenzothiazole products.

At the same time, Mori reported a mild, C-2-selective arylation of thiazoles for the preparation of tunable light emission and liquid crystalline compounds.[277] Use of PdCl$_2$(PPh$_3$)$_2$/CuI and TBAF in DMSO allowed for the highly regioselective arylation of thiazole at only 60 °C, well below the temperatures typically employed for this class of transformations (Scheme 235). With a selective route for the preparation of

Scheme 235
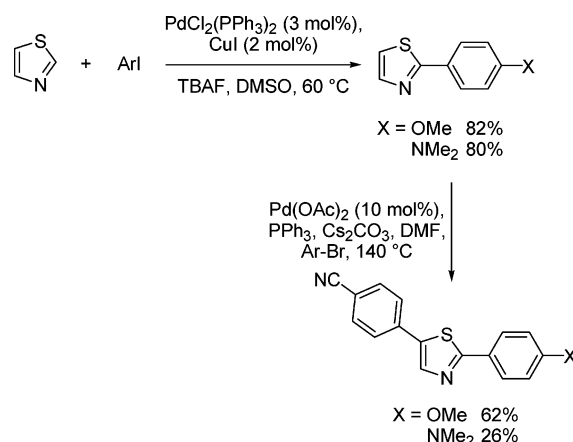
2-arylthiazoles in hand, the authors then used another direct arylation method to afford a variety of tailored liquid crystalline and light-emitting unsymmetrical 2,5-diarylthiazoles.

A complementary route for the regioselective formation of 2,5-diarylimidazoles and 2,5-diarylthiazoles using polymer-supported substrates has also been reported. The selective monoarylation of *N*-methylimidazole and thiazole was achieved using an insoluble polymer resin onto which an aryl iodide moiety was immobilized.[278] Following initial

arylation at either C-5 or C-2 (depending on the catalyst system used), subsequent diarylation could not occur since the monoarylated azole was still attached to the resin, thereby preventing any further interaction between it and another equivalent of aryl iodide. The resulting arylazole could then be hydrolyzed or further functionalized using a complementary catalyst system (Scheme 236).

Scheme 236
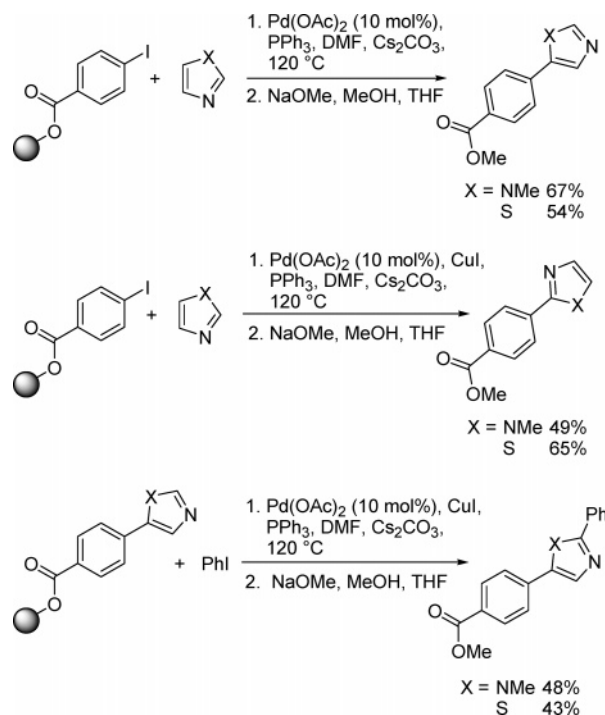
More recently, Fagnou reported a selective C-5 arylation of thiazole using Pearlman's catalyst. 5-Arylthiazoles were prepared in moderate to good yields from various iodoarenes.[133] Interestingly, no other arylation isomers were reported, and attempts to alter the regioselectivity using CuBr failed (Scheme 237).

Scheme 237
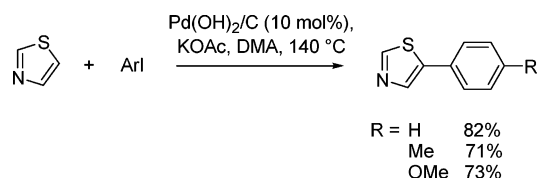
Bergman and Ellman have reported a rhodium-catalyzed intermolecular arylation of benzimidazoles and benzoxazoles using a [RhCl(coe)$_2$]$_2$/PCy$_3$ catalyst.[279] The resulting arylated products were obtained in modest to good yields (Scheme 238).

Scheme 238
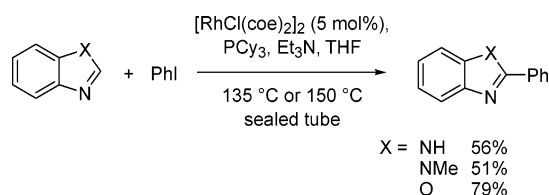
Mechanistically, the authors propose that the catalytic cycle involves addition of benzimidazole to rhodium to generate

an NHC-type intermediate, followed by phosphine dissociation and oxidative addition of the aryl iodide to give the Rh(III) complex **66**. Phosphine association to **66** along with concomitant iodide dissociation affords complex **67**, which upon reductive elimination of phenylbenzimidazole regenerates the bis(tricyclohexylphosphine)rhodium chloride catalyst (Scheme 239).

Scheme 239
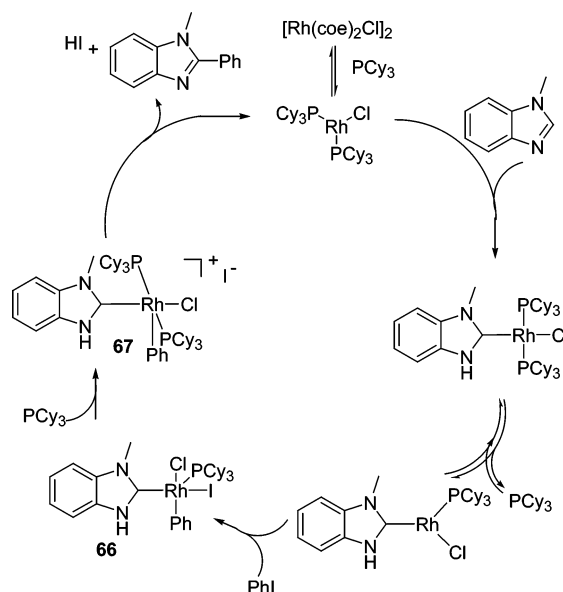
Hoarau recently disclosed a C-2-selective arylation of ethyl 4-oxazolecarboxylate using a Pd(OAc)$_2$/Po-Tol$_3$ catalyst system.[280] Selective C-2 arylation could be carried out to afford the desired product in 86% yield (Scheme 240). The

Scheme 240
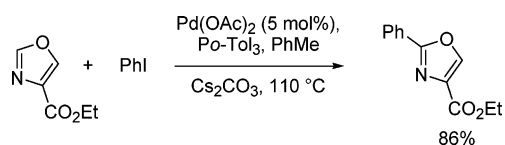
authors report that while solvent effects did play a minor role in affecting the selectivity of the reaction, a greater reduction in the amount of 5-aryloxazolecarboxylate and 2,5-diaryloxazolecarboxylate ester byproducts could be achieved using bulky, electron-rich ligands. In light of these results, the authors proposed that the reaction proceeds via either an electrophilic aromatic substitution or an alternative cross-coupling pathway. Since subsequent ab initio calculations found that the HOMO of the heteroaromatic resides on C-2 and C-5, additional experiments using CuI as a cocatalyst were carried out in an attempt to ascertain whether the reaction proceeds via a cross-coupling pathway. On the basis of this additional study, in which the use of CuI as a cocatalyst failed, the authors favored a more likely electrophilic aromatic substitution mechanism.

The intermolecular coupling of an oxazole and a pyridyl triflate has also been reported for the preparation of a derivative for the inhibition of HIV-1 reverse transcriptase (Scheme 241).[281] Coupling was carried out under standard conditions to afford the desired product in 34% yield. A similar approach was also reported for the preparation of 2,8-disubstituted dipyridodiazepinone using Boc-pro-

Scheme 241

34%
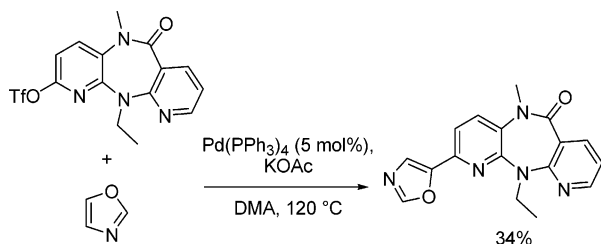
tected pyrrole and 2-chloro-8-(2-phenylethyl)dipyridodi-azepinone.[282]

A related coupling has also been used for the preparation of a potential vascular endothelial growth factor receptor-2 inhibitor (Scheme 242).[283] Coupling of the pyrazine–oxazole

Scheme 242

57%
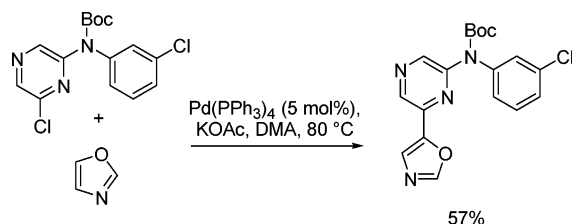
was carried out in a sealed tube to afford the desired product directly in 57% yield.

Ohta has used his conditions for the pyrazinylation of other azole systems.[260] As expected, coupling occurred selectively at the C-5 position, with no evidence of any other regio-isomeric products (Scheme 243).

Scheme 243

X = O   72%
    S   61%
    NMe 44%

X = O   52%
    S   43%
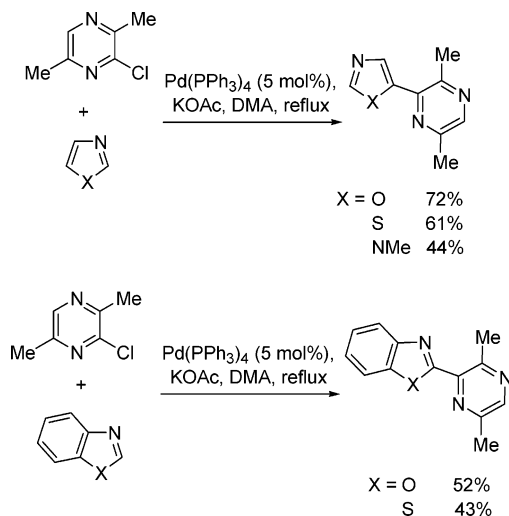
Recently, Zhuravlev reported the mild arylation of oxa-zolo[4,5-*b*]pyridines using aryl iodides.[284] Extensive opti-mization of the palladium source, ligand, and solvent found that the reaction could be carried out in modest yields for a variety of electron-rich and electron-poor aryl iodides at 30 °C by using Pd(OAc)$_2$ and PPh$_3$ in acetone (Scheme 244).

Deuterium labeling experiments carried out using the oxazolo[4,5-*b*]pyridine in acetone-d_6 and Cs$_2$CO$_3$ found that this substrate had a relatively low pK_a value, since complete deuteration of the starting material could be obtained within several hours (Scheme 245). Given the relative ease by which the anion is formed, the author proposed that the reaction likely proceeds via an anion transmetalation to ArPdI, followed by reductive elimination.

Scheme 244

R = H   52%
  = OMe 67%
  = NH$_2$ 74%
  = CN   61%
  = CH$_3$ 52%

Scheme 245

42%
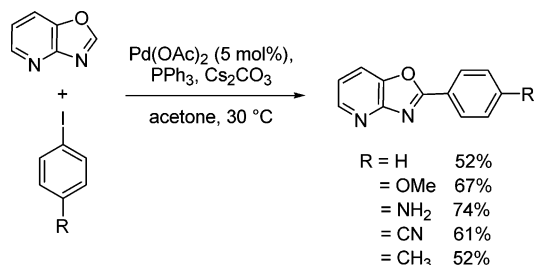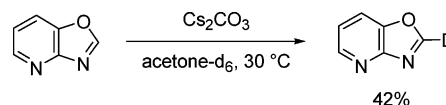
The direct arylation of a variety of other related nitrogen-containing fused aromatic ring systems has also been reported. For example, Gevorgyan reported the selective C-3 direct arylation of indolizines (Scheme 246).[40] Use of

Scheme 246

R = 4-NO$_2$ 96%
    H   71%
    2-naphthyl 59%

R = H   71%
   Me   72%
    CN   74%
    CO$_2$Et 91%
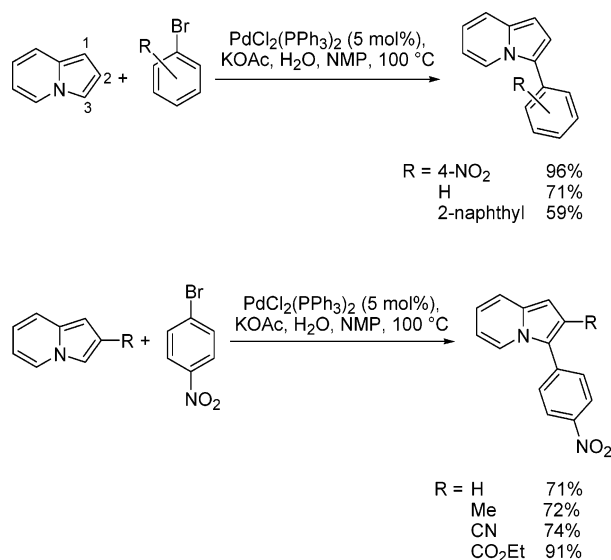
electron-rich and electron-poor aryl bromides gave the 3-arylindolizine selectively in moderate to good yields. In addition, the direct arylation of a variety of 2-substituted indolizines could also be achieved under these conditions to afford the desired 3-arylindolizine products in good to excellent yields.

The authors proposed four mechanistic possibilities for this reaction: (1) a Heck-type pathway, (2) a C–H activation pathway, (3) a cross-coupling-type pathway, or (4) an electrophilic aromatic substitution pathway (Scheme 247). Subsequent studies in which both a reductive Heck coupling and a tandem Heck cyclization with a pendent olefin at the 2-position of the indolizine failed, ruling out the possibility of a Heck-type pathway. Additional kinetic isotope effect studies carried out by the authors using a 3-deuterioindoliz-ine-2-carboxylic acid ethyl ester revealed a $k_{H/D} = 1$, thereby ruling out the possibility of a coordination-assisted C–H activation pathway. The authors next investigated the addition of CuI, since it has been reported by Miura[267] to promote the arylation of acidic C–H bonds in heterocycles. Unfor-tunately, Gevorgyan found that the addition of CuI resulted in longer reaction times and reduced yields, thereby disfavor-

Scheme 247
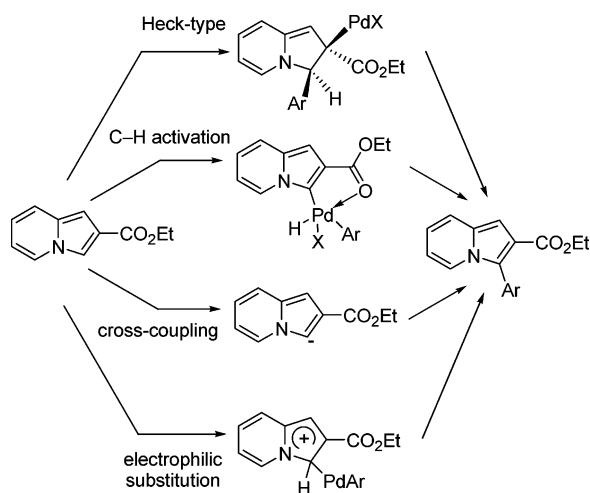
ing a cross-coupling-type pathway. The last remaining possibility was an electrophilic aromatic substitution pathway. DFT calculations found that the HOMO of the heterocycle exists on the pyrrole portion of the ring, thereby confirming that the electrophile would prefer to attack this electron-rich region of the heterocycle. In addition, the measured kinetic isotope effect of $k_{H/D} = 1$ is as expected for an electrophilic aromatic substitution since reestablishment of aromaticity is expected to be fast relative to the initial dearomatizing attack of the palladium(II) species by the heterocyclic ring. Finally, Gevorgyan carried out additional studies that investigated the effect of C-2 substitution of the indolizine for the palladium-catalyzed arylation versus Friedel−Crafts acylation. While the results were not identical, the observed trend in rates for various C-2-substituted indolizines was similar for both types of reactions, further supporting an electrophilic aromatic substitution pathway.

An intramolecular palladium-catalyzed direct arylation of an indolizine with a tethered aryl bromide was attempted for the synthesis of the benzocyclazinone derivative **68**.[285] Although the desired cyclization at C-4 failed, the C-2-cyclized adduct was instead isolated in 43% yield (Scheme 248).

Scheme 248
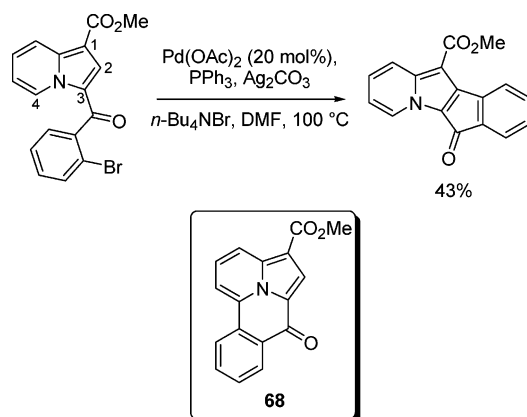
The intermolecular arylation of imidazo[1,2-*a*]pyridines has also been reported using Sames' bulky NHC−palladium catalyst system.[251] In this case, arylation occurred selectively at the more electron-rich position of the aromatic system, affording the desired arylated products in modest to excellent yields (Scheme 249).

Scheme 249

Ar-X	R	Yield
Ph-I	H	93%
Ph-I	CO$_2$Et	98%
Br—⟨⟩—CO$_2$Me	CO$_2$Et	51%
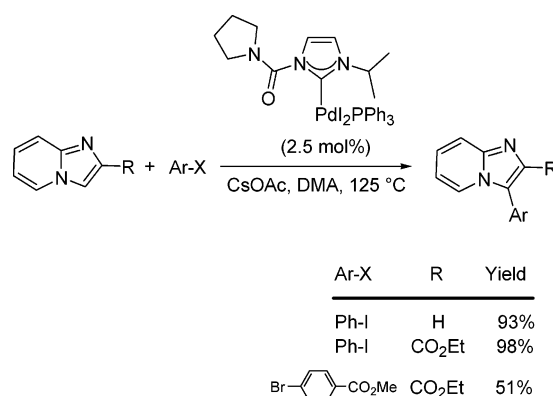
Li described an intermolecular palladium-catalyzed direct arylation of imidazo[1,2-*a*]pyrimidines with aryl bromides (Scheme 250).[286] Product yields were typically high for most

Scheme 250

R = 4-CO$_2$Et	84%
4-OMe	50%
9-phenanthrene	96%
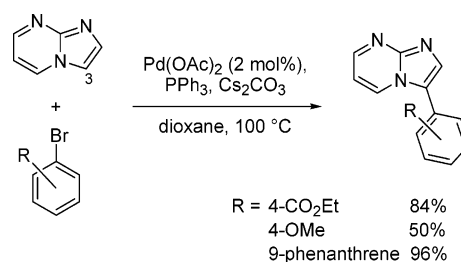
types of aryl bromides. In particular, coupling with electron-deficient aryl bromides led to good yields, while coupling with electron-rich aryl bromides was less efficient. In either case, coupling occurred exclusively at the π-rich 3-position of the heteroaromatic system.

In light of these electronic effects, the authors suggest that an electrophilic aromatic substitution mechanism is occurring. Hence, following oxidative addition of the aryl bromide by palladium(0), electrophilic attack by the π-rich imidazole portion of the imidazopyrimidine occurs, followed by base-mediated deprotonation to give an aryl(imidazopyrimidyl)-palladium(II) intermediate which subsequently undergoes reductive elimination to afford the desired 3-arylimidazo-[1,2-*a*]pyrimidine (Scheme 251).

Scheme 251
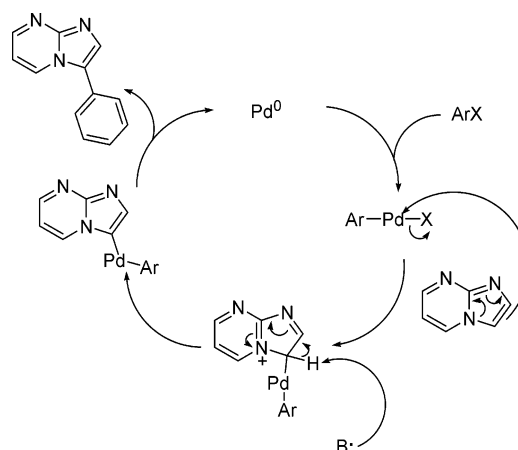
A similar palladium-catalyzed direct arylation of imidazopyrimidines using Pearlman's catalyst and KOAc in DMA

at 140 °C has also been reported. In this case, the coupled products were obtained in high yields.[133]

Recently, a Merck process group reported the direct arylation of an imidazo[1,2-*a*]pyrimidine as the key step in a short seven-step synthesis of an $\alpha_{2/3}$-selective GABA$_A$ agonist.[287] Extensive optimization revealed that use of the aryl bromide gave far superior results compared to that of the chloride, and that some water (<5% (w/w) with respect to the imidazotriazine) was required to achieve good conversion. Further studies found that direct arylation of the imidazotriazine using only 1 mol % Pd(OAc)$_2$ could be carried out on several kilograms of material to afford the desired product in 86% yield (Scheme 252). Use of this

Scheme 252
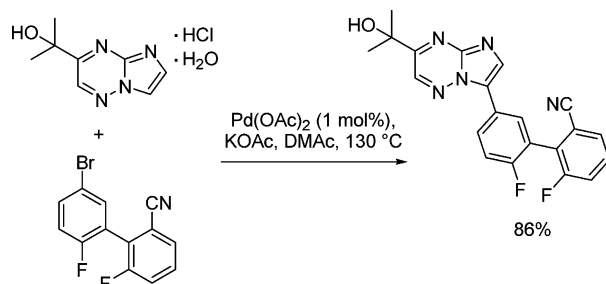
approach also allowed for the synthesis of other related potential GABA$_A$ agonist candidates[288,289] as well as a diverse library of compounds during the drug discovery phase that included imidazo[1,2-*a*]pyridines, imidazo[1,2-*d*][1,2,4]-triazin-8-ones, and imidazo[2,1-*f*][1,2,4]triazin-8-ones as coupling partners.[290,291]

Although the use of pyrazoles for direct arylation reactions is uncommon, Lautens reported the arylation of a pyrazole via a tandem *ortho* alkylation/intramolecular direct arylation reaction in which fused tricyclic pyrazole derivatives could be produced in modest yields (Scheme 253).[261] While yields

Scheme 253
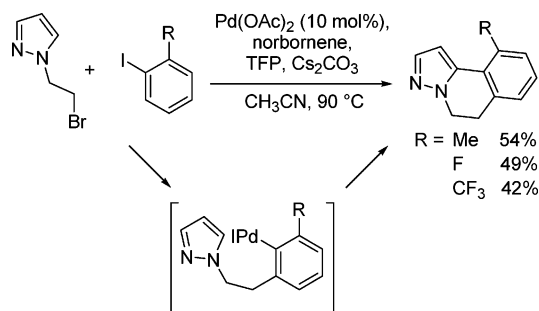
were lower than those of the analogous pyrrole systems (see section 3.1.2.2), pyrazoles represent a challenging class of heterocycle, since the pyrazole nitrogen functionality may tightly bind to the catalyst, thereby acting as a catalyst poison. Unfortunately, all attempts to carry out the reaction in the presence of MgO or any other Lewis acids in an attempt to limit the coordination ability of the pyrazole failed to improve reaction yields.

An intramolecular direct arylation was used as the key step in the synthesis of a potent antiasthmatic compound.[292] While attempts to cyclize the free amide failed, alkylation of the amide *NH* followed by treatment with Pd(OAc)$_2$ under Jeffery's conditions allowed for smooth cyclization to the desired target compound (Scheme 254).

Scheme 254

R = H   0%
     C$_4$H$_9$ 83%
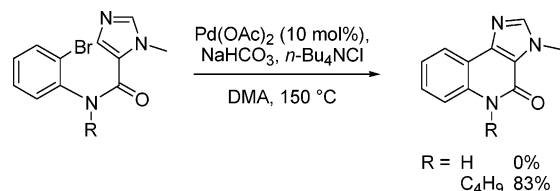
The intramolecular annulation of imidazoles and benzimidazoles containing an aryl iodide tethered to the nitrogen atom has also been reported.[293] Cyclization occurred in good yield for the imidazole, but in somewhat lower yields for the benzimidazole (Scheme 255). The authors suggest that

Scheme 255
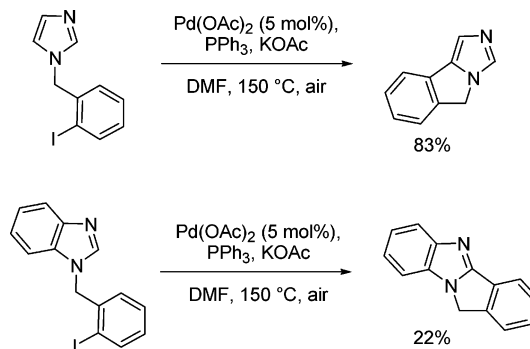
the reason for this is that the C-5 position of the imidazole is more reactive.

A similar intramolecular direct arylation was applied to the synthesis of the GABA receptor ligand 2-aryloxazolo-[4,5-*c*]quinolin-4(5*H*)-one.[294] Coupling of an aryl iodide and an isoxazole was efficiently carried out, furnishing the fused tricyclic product in an unoptimized 63% yield (Scheme 256).

Scheme 256
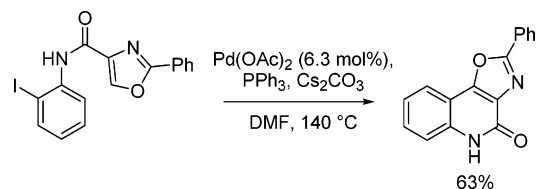
3.1.4.2. Six-Membered Rings. Comins has reported the use of an intramolecular palladium-catalyzed cyclization as the final step in the synthesis of camptothecin (Scheme 257).[295−297] This approach has subsequently been used for

Scheme 257
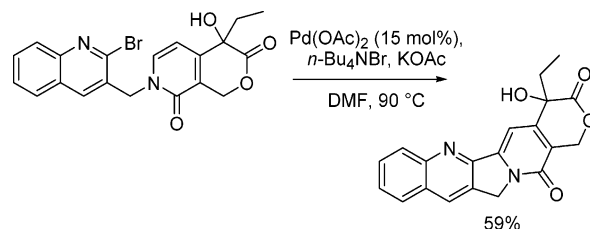
the synthesis of the camptothecin analogue GI147211C,[298] and also for the assembly of ring C in the synthesis of several homocamptothecin analogues.[299,300]

Comins' elegant approach toward the synthesis of camptothecin has also been utilized by others for the synthesis of various natural products, including mappicine, luotonin A

Scheme 258
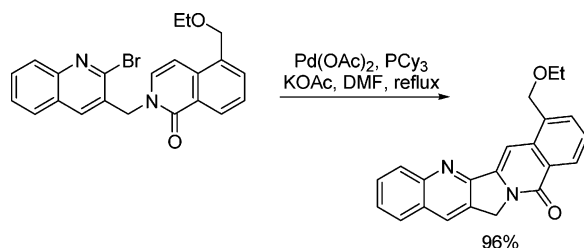
and B, and rutaecarpine.[301−304] A similar strategy was also utilized for the synthesis of a camptothecin-like alkaloid, 22-hydroxyacuminatine. Cyclization in this case led to the desired 22-hydroxyacuminatine precursor in 96% yield (Scheme 258).[305]

A related cyclization has also been reported by Grigg as a convenient route to a family of pharmaceutically interesting isoindoles (Scheme 259).[228]

Scheme 259
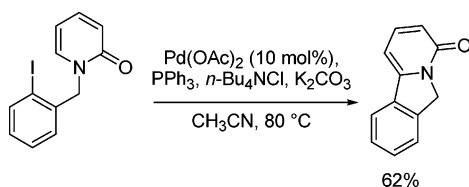
The intramolecular direct arylation reaction of related pyridazinone systems has also been reported (Scheme 260).[306]

Scheme 260
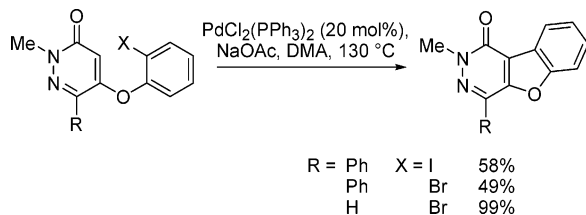
Good yields of the cyclized product could be obtained with substrates containing the halogen on either the arene or pyridazinone moiety. In addition, this method was compatible with substrates containing a nitrogen or oxygen tether.

3.2. Direct Arylation of Furans and Thiophenes

3.2.1. Intramolecular Aryl–Furyl and Aryl–Thiophenyl Bond Formation

The first intramolecular arylation of furan and thiophene was reported by Grigg for the preparation of a variety of interesting polycyclic β-lactams (Scheme 261).[307] Subsequent studies by the same authors later utilized the same approach for the synthesis of a large number of interesting fused six- to eight-membered heterocycles in good yields (Scheme 262).[308]

The intramolecular direct arylation of furans, thiophenes, and pyrroles onto an anthracene core was carried out with the corresponding dichloroanthracene derivative using Jeffery's conditions, providing a variety of strained polycyclic aromatic hydrocarbons in low yields (Scheme 263).[309]

An intramolecular direct arylation of benzothiophenes with a tethered aryl bromide was also reported using palladium-catalyzed conditions (Scheme 264).[310,311] Attempts using an *ortho* blocking group to favor direct arylation to occur at

Scheme 261
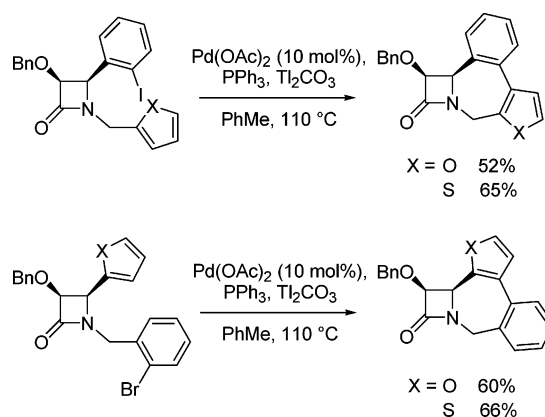
Scheme 262
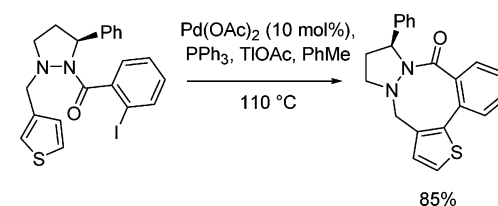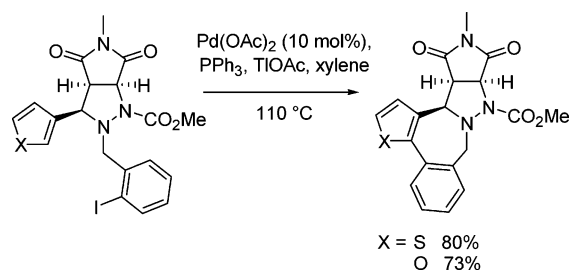
Scheme 263
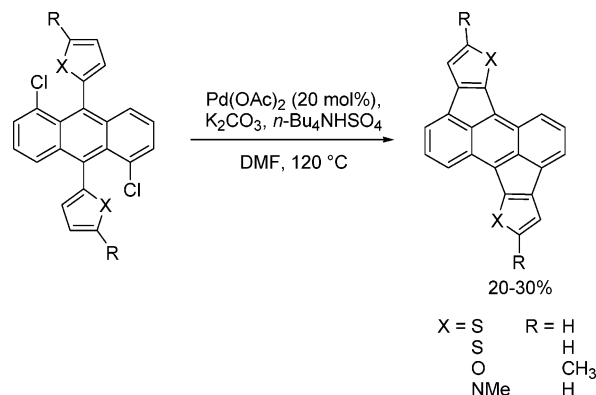
the benzo core of the benzothiophene resulted in lower yields even after prolonged reaction times and high catalyst loadings.

Cyclization onto the C-3 position of benzothiophene as a route to seven-membered benzazepinone ring systems has also been reported (Scheme 265).[239] A similar cyclization has also been utilized for the preparation of a variety of six-membered ring thiophene analogues (Scheme 266).[257]

More recently, general conditions were developed for the intramolecular direct arylation of furans using aryl chlorides and iodides (Scheme 267).[28] Interestingly, aryl iodides were found to give lower yields of the desired product versus aryl chlorides. This limitation could be overcome by addition of silver salts to the reaction to sequester the inhibitory iodide

Scheme 264

R₁ = OMe R₂ = H   60%
R₁ = R₂ = OMe   60%
R₁ = R₂ = H   100%

Pd(OAc)₂ (10 mol%),
Na₂CO₃, DMF, reflux

Pd(OAc)₂ (50 mol%),
K₂CO₃, n-Bu₄NBr
DMF, 75 °C

30%

Scheme 265

Pd(OAc)₂ (5 mol%),
PPh₃, Ag₂CO₃
DMF, 100 °C

82%

Scheme 266

Pd(PPh₃)₄ (10 mol%),
KOAc, DMA, 120 °C

57%

Scheme 267

Pd(OAc)₂ (3 or 5 mol%),
PCy₃-HBF₄,
K₂CO₃, DMA, 130 °C

X = Cl   83%
X = I (with Ag₂CO₃)   81%
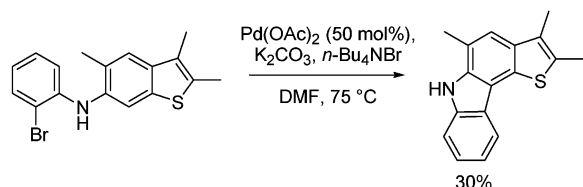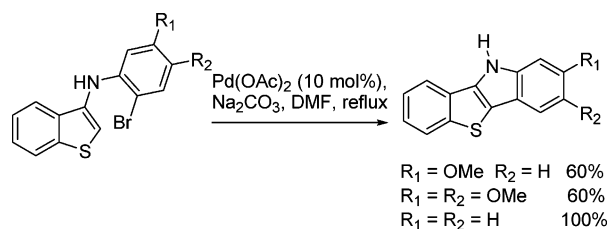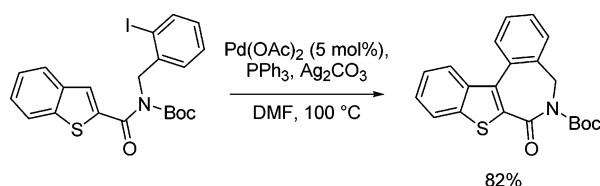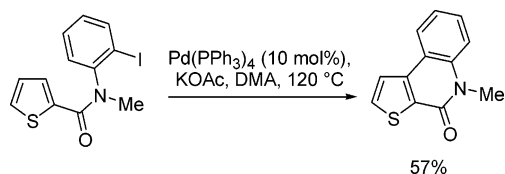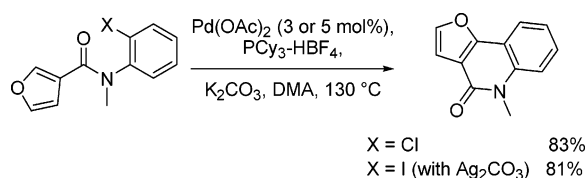
released from the catalytic cycle. Under these new conditions, yields of the cyclized products obtained from the aryl iodide were found to be comparable to those obtained using the aryl chloride. An intramolecular cyclization of aryl iodide onto thiophene was also reported in good yield.

The application of an intramolecular direct arylation of furan with an aryl iodide was also reported as a failed route toward (±)-γ-lycorane.[312] Although the cyclization occurred in 57% yield (Scheme 268), all attempts to convert the

Scheme 268

Pd(OAc)₂ (33 mol%),
n-Bu₄NCl, KOAc
DMF, 100 °C

57%
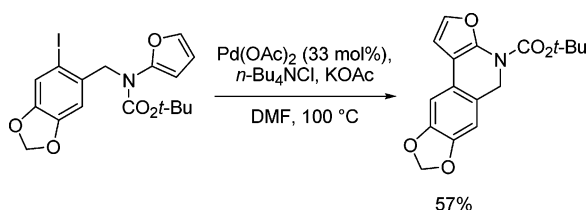
cyclized product into the required (±)-γ-lycorane precursor failed, forcing the exploration of an alternate route.

3.2.2. Intermolecular Aryl–Furyl and Aryl–Thiophenyl Bond Formation

While the direct aryl−benzofuran coupling using stoichiometric palladium has been known for over 30 years,[313] the first catalytic studies on the direct arylation of furan, thiophene, benzothiophene, and benzofuran were reported by Ohta and co-workers almost 20 years later.[314] Use of catalytic Pd(PPh₃)₄ allowed for the direct and selective C-2 coupling of these heteroaromatic compounds (Scheme 269).

Scheme 269

Pd(PPh₃)₄ (5 mol%),
KOAc, DMA, 150 °C
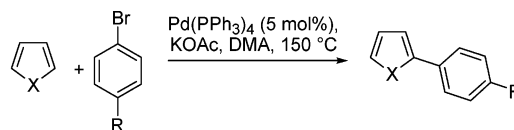
X = O R = H   0% | X = S R = H   69%
X = O R = CHO   40% | X = S R = CHO   63%
X = O R = NO₂   59% | X = S R = NO₂   66%

Pd(PPh₃)₄ (5 mol%),
KOAc, DMA, 150 °C
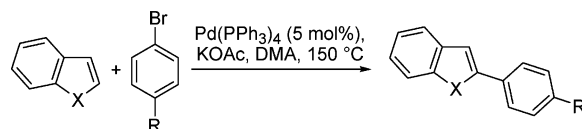
X = O R = H   23% | X = S R = H   35%
X = O R = OCH₃ 12% | X = S R = OCH₃ 11%
X = O R = NO₂   20% | X = S R = NO₂   55%

Aryl bromides lacking an electron-withdrawing group were found to give little or no arylated products for all four heteroaromatic systems, with the exception of bromobenzene and thiophene, which gave a moderate yield of the expected product. Conversely, almost all electron-poor aryl bromides used in the study afforded the desired product in modest yields for all four heteroaromatic compounds.

These conditions have also been reported by the same authors for the selective pyrazinylation of unactivated thiophenes and furan systems.[260] In all cases, coupling occurred regioselectively at the C-2 position in good yields using a variety of chloropyrazoles (Scheme 270).

Scheme 270

Pd(PPh₃)₄ (5 mol%),
KOAc, DMA, reflux

X = O   75%
    S   77%

Pd(PPh₃)₄ (5 mol%),
KOAc, DMA, reflux

X = O 54%
    S 81%
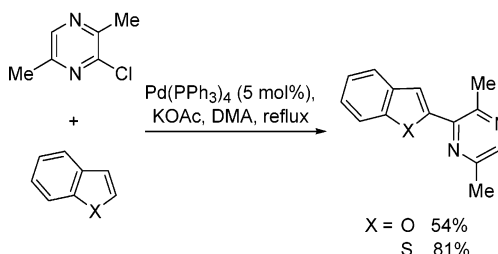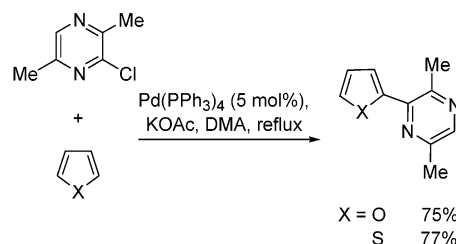
Walker subsequently reported a related direct arylation of thiophene using iodopyrimidine (Scheme 271).[315] Under

Scheme 271
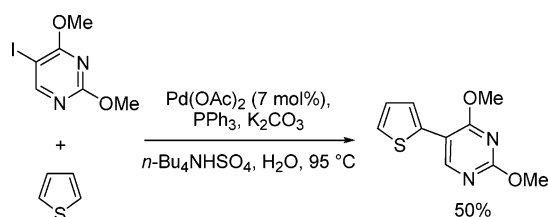
these conditions, the desired heterocyclic products were obtained in modest yields. A similar approach was later utilized for the palladium-catalyzed coupling of a substituted imidazole and 5-bromopyrimidine en route toward the preparation of a novel pyrroloquinolone PDE5 inhibitors for the treatment of erectile dysfunction.[316]

The selective C-2 direct arylation of activated thiophene systems was subsequently reported by Miura.[267] Particularly noteworthy is the discovery that as in azole systems (see section 3.1.4.1), addition of CuI significantly increased the yield of the arylated product. However, unlike the direct arylation of 1-methylbenzimidazole, which can occur with copper salts in the absence of a palladium catalyst, Pd(OAc)$_2$ was required for the direct arylation in this system (Scheme 272).

Scheme 272
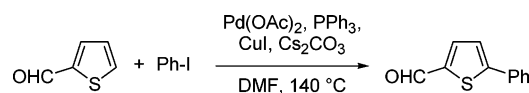
The authors also reported the triarylation of *N*-(2-thienoyl)-aniline using Pd(OAc)$_2$, Cs$_2$CO$_3$, and Buchwald's JohnPhos ligand in refluxing toluene (Scheme 273).[317] In these

Scheme 273
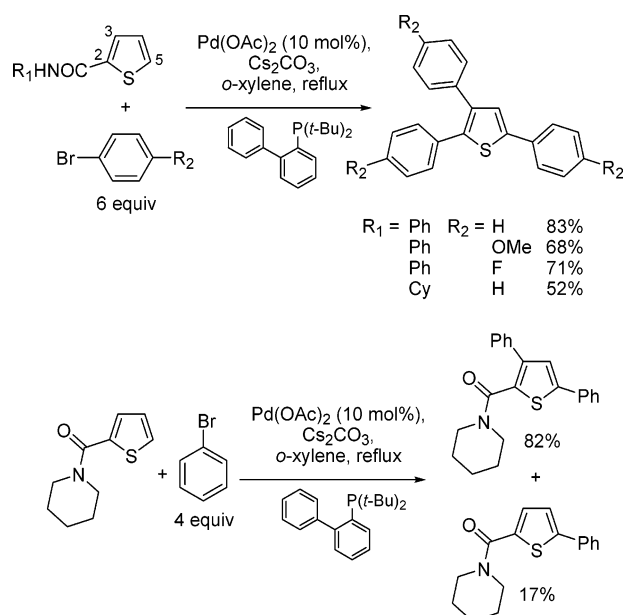
examples, the reaction is believed to occur via two direct arylations followed by decarbamoylation and subsequent

coupling at the position containing the amide moiety. On the basis of mechanistic studies, the authors propose that arylation likely occurs first at the C-3 position, followed by C-5 arylation. Regardless of the order of arylation, the authors found that the resulting mixture of C-3- and C-3/C-5-arylated products both undergo decarbamoylation and subsequent C-2/C-5 or C-2 arylation, respectively, to afford the final observed triarylated products. Interestingly, use of a C-2 tertiary amide showed no evidence of any decarbamoylation product, instead affording the usual C-5- and C-3/C-5-diarylated products (Scheme 273). The authors propose that while the free *NH* allows for arylation via a coordination-assisted mechanism, use of a tertiary amide system lead to arylation via an electrophilic addition or carbopalladation mechanism. This decarbamoylative arylation procedure has also been extended to the bisarylation of 2-phenyl-5-thiazolecarbox-anilide and 2-phenyl-5-oxazolecarboxanilide, affording the expected 4,5-diaryl-2-phenylthiazole or 4,5-diaryl-2-phenyl-oxazole in modest to good yields.[274]

Similar conditions were also applied for the bisarylation of various 2,2′-bithiophenes and 3,4-disubstituted thiophenes (Scheme 274).[318] The reaction afforded good to excellent yields for a variety of aryl bromides.

Scheme 274
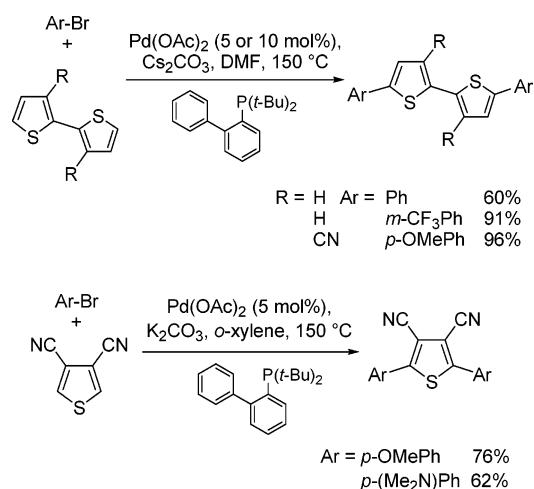
While the method described above was limited to symmetrical thiophene derivatives, unsymmetrical arylated thiophenes could be obtained from *tert*-benzyl alcohols (Scheme 275). The first aryl substituent is introduced by

Scheme 275

Scheme 276

	R^1 =	H	R^2 =	OMe	60%
		H		CO$_2$Et	93%
		Br		OMe	87%
		Me		OMe	61%
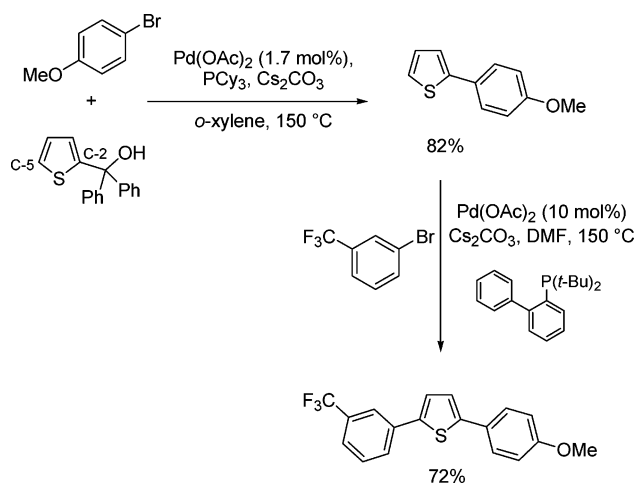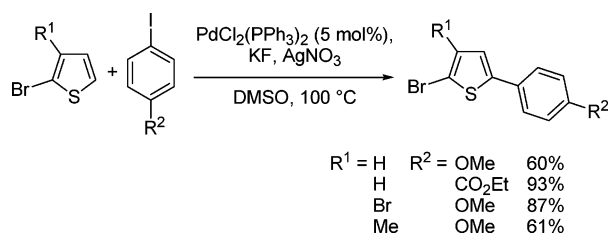
arylation at the C-2 position, followed by direct arylation at the C-5 position to furnish the unsymmetrical 2,5-diaryl-thiophene product (Scheme 275). This approach has also been applied to the preparation of unsymmetrical 2,2′-bithiophenes.

A complementary method of preparing unsymmetrical 2,5-disubstituted thiophene products was achieved via a selective arylation of bromothiophenes using fluoride base and silver nitrate.[319] Portionwise addition of AgNO$_3$ was required to ensure good yields of the desired C-5-arylated bromothiophenes. The reaction scope was broad, affording good yields for electron-rich, electron-poor, and sterically-demanding aryl iodides (Scheme 276). No side reactions of the C−Br bond were observed during the course of the studies, allowing for the subsequent derivitization of the products via a variety of metal-catalyzed cross-coupling reactions. These conditions have also been extended to the arylation of non-bromine-containing thiophenes.[320]

Additional approaches toward the direct arylation of activated thiophenes have also been reported by Lemaire and co-workers using Jeffery's conditions.[321−324] Again, direct arylation was found to occur exclusively at the C-5 position for a range of sterically-demanding as well as electron-rich and electron-poor aryl iodides (Scheme 277). 2-Formyl- and

Scheme 277

	R^1 =	CHO	R^2 =	H	30%
		NO$_2$		p-OMe	37%
		CN		H	63%
		CN		p-OMe	77%
		CN		p-CF$_3$	79%
		CN		o-CF$_3$	81%
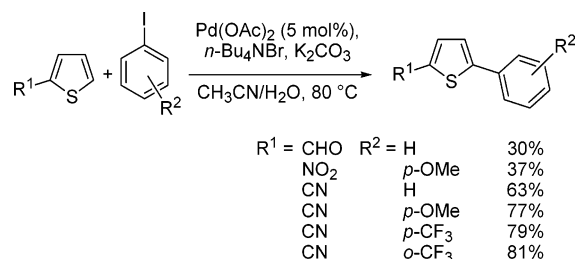
2-nitrothiophene were found to give poor yields of the 5-arylated thiophene, most likely due to product instability.

In a series of papers, Lemaire subsequently described a related palladium-catalyzed thiophene−thiophene coupling for the polymerization of alkylthiophenes (Scheme 278).[324−326]

Scheme 278
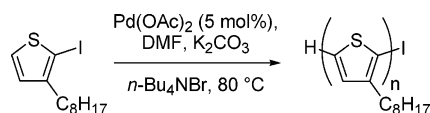
Use of typical Heck type conditions allowed for a highly regiocontrolled polymerization of iodothiophene to afford polythiophenes with weight average molecular weights of approximately 6400 g/mol with moderate polydispersities. The application of this method toward the preparation of well-defined thiophene tetramers has also been subsequently reported by the same group.[327]

Similar conditions have also been applied to the arylation of benzo[b]thiophene systems (Scheme 279).[328−330] Good

Scheme 279

	R^1 =	CN	R^2 =	o-CH$_3$	66%
		CN		m-Cl	72%
		CHO		p-OCH$_3$	64%
		CHO		p-CF$_3$	70%
		CHO		o-CN	54%
		OMe		o-CN	69%
		OMe		o-CH$_3$	42%
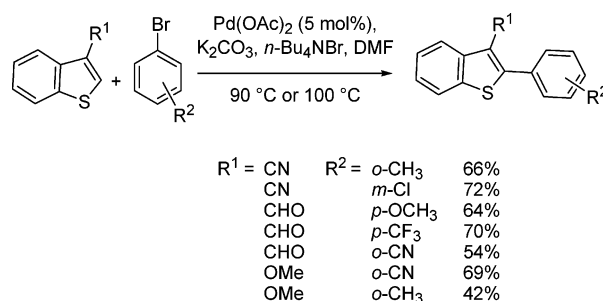
yields of the arylated products were obtained with both electron-rich and electron-poor benzo[b]thiophenes. Interestingly, nonactivated benzo[b]thiophenes such as benzo[b]-thiophene and 3-(cyanomethyl)benzo[b]thiophene were found to give little or no product. Aryl bromides were better than aryl iodides since they gave higher yields and selectivities for direct arylation versus Ullman-type coupling.

In addition, replacing tetrabutylammonium bromide with dicyclohexyl-18-crown-6 (DCH-18-6) was found to afford better yields of the arylated product in shorter reaction times, as well as higher selectivity over the Ullman-type coupling (Scheme 280). These improved conditions have since been

Scheme 280
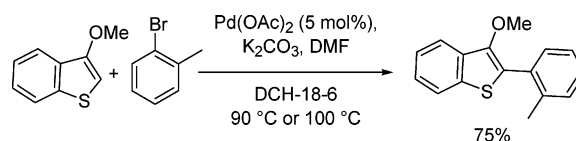
employed for the arylation of 3-phenoxybenzo[b]thiophene and 3-aminobenzo[b]thiophene derivatives in good yields and in short reaction times.[331]

An unusual ruthenium-catalyzed pentafluorophenylation of thiophene has also been reported using pentafluoroben-zenesulfonyl chloride.[332] Yields for this reaction were low, typically affording a mixture of pentafluorophenylthiophene regioisomers (Scheme 281). Mechanistically, the authors

Scheme 281
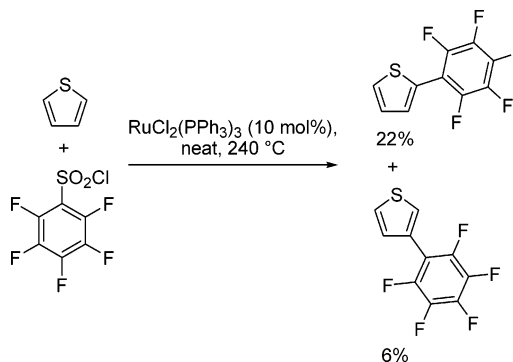
propose that initial electron transfer from Ru(II) affords a Ru(III) intermediate and a sulfonyl chloride radical anion, which then undergoes cleavage and subsequent extrusion of SO$_2$ to generate a pentafluorophenyl radical/Ru(III)Cl species. Radical addition to thiophene, followed by hydrogen radical abstraction by Ru(III)Cl affords the arylated product and regenerates the catalyst (Scheme 282).

Scheme 282
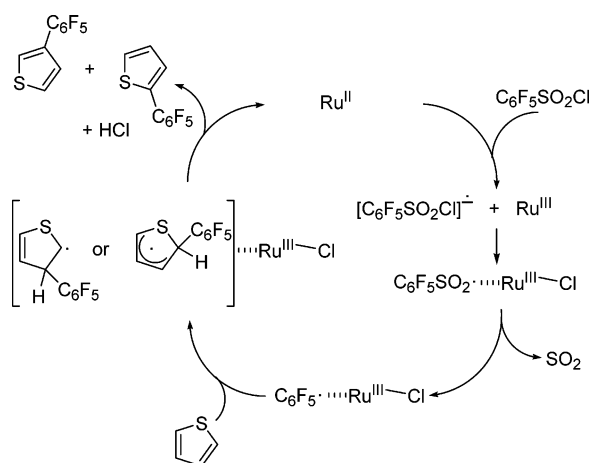
de Meijere has also extended his palladium-catalyzed domino coupling to 2-bromothiophenes (see section 2.1.1.1 for mechanistic details) (Scheme 283).[64] The observed

Scheme 283
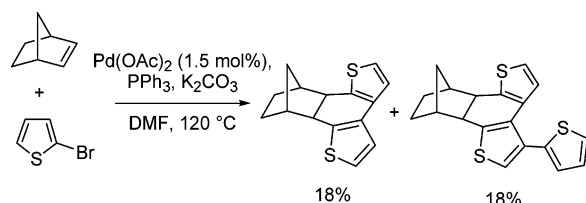
norbornene-containing products were obtained in low yields as a 1:1 mixture of di- and trithiophene products.

Recently, Sharp investigated the issue of selectivity for activated 3-(methoxycarbonyl)thiophenes[39] by carrying out a full set of factorially designed experiments in which the solvent, base, and catalyst were screened. These studies found that the most important factors influencing regiochemistry were a combination of solvent and catalyst type. In fact, use of a nonpolar solvent such as toluene in the presence of a phosphine-ligated palladium catalyst was found to selectively afford the C-2-arylated product, while use of a polar aprotic solvent such as NMP in the presence of a phosphine-free palladium catalyst drastically changed the selectivity to favor arylation at the C-5 position (Scheme 284). The authors

Scheme 284
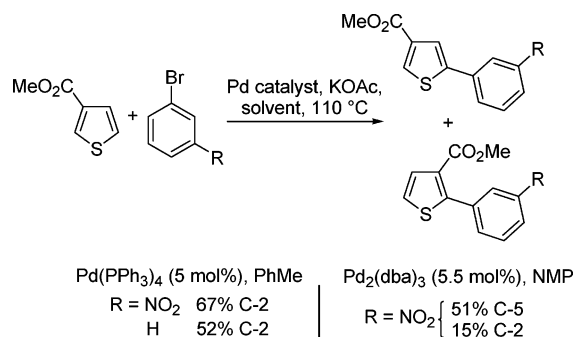
propose that in the presence of a nonpolar solvent and a phosphine-ligated palladium catalyst, a σ-bonded palladium-(II) species is favored, thereby promoting a Heck-type reaction. Conversely, use of a polar aprotic solvent such as NMP in concert with a phosphine-free palladium catalyst likely promotes ionization of Pd$-$X to give a cationic

palladium species that undergoes an electrophilic reaction at the more electron-rich C-5 position of thiophene. Base-promoted deprotonation and reductive elimination of the palladium(II) species would furnish the C-5-arylated product (Scheme 285).

Scheme 285
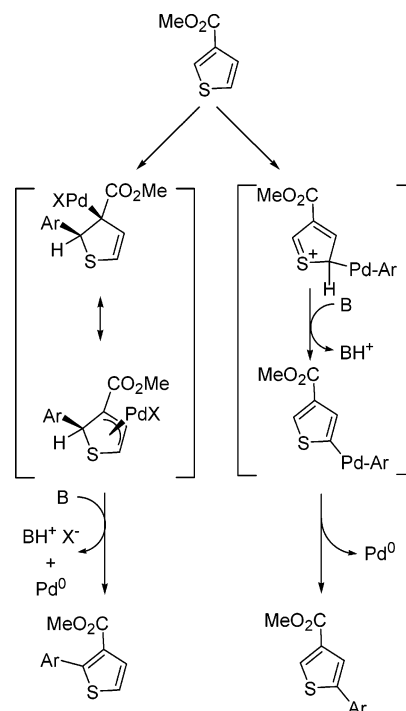
The regioselective arylation of 3-(alkoxycarbonyl)furans has also been reported since the regioselectivity of aryla-tion in these systems is typically poor.[39] As with the corresponding thiophene system, use of a nonpolar sol-vent and phosphine-ligated palladium catalyst favored the C-2-arylated product, while use of a polar aprotic sol-vent such as NMP and Pd/C favored the formation of the C-5-arylated product. Although electron-rich aryl bromides failed to give any of the arylated furan, use of electron-poor aryl bromides typically afforded moderate to good yields of the desired product. As observed for the thio-phene systems, arylation using the C-2-selective conditions occurred with more regiocontrol than arylation carried out under the corresponding C-5-selective conditions (Scheme 286).

The intermolecular palladium-catalyzed C-5 arylation of 2-arylfurans has also been reported for the preparation and

Scheme 286
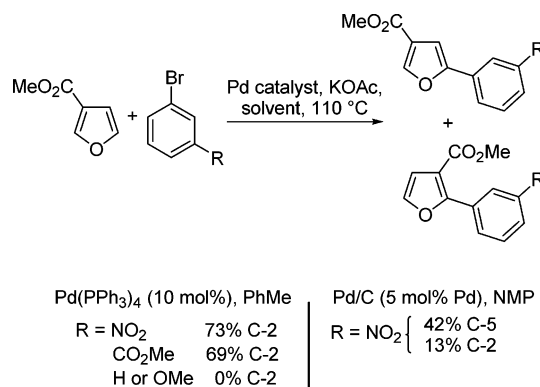
study of metabolites of the prodrug 2,5-bis[4-(*O*-methoxy-amidino)phenyl]furan (Scheme 287).[333]

Scheme 287
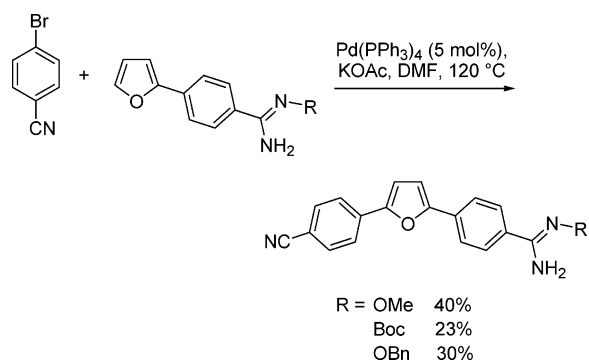
A regioselective arylation of activated furans with aryl iodides or bromides was reported using PdCl$_2$, PCy$_3$, KOAc, and *n*-Bu$_4$NBr in DMF at 110 °C (Scheme 288).[334] As

Scheme 288
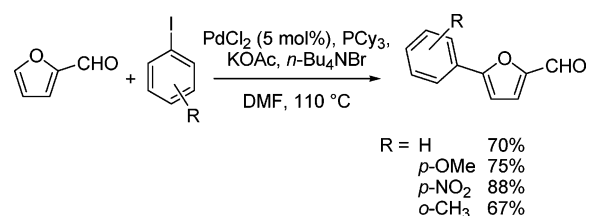
observed for the corresponding thiophene systems (Scheme 271), arylation of activated furans occurred selectively at the C-5 position to give the desired products in good yields. A comparable yield has also been reported for the arylation of furfural using bromobenzene and Pearlman's catalyst.[133]

Finally, a palladium-catalyzed bisarylation of benzofuran was attempted using 1,8-diiodonaphthalene (Scheme 289).[335]

Scheme 289
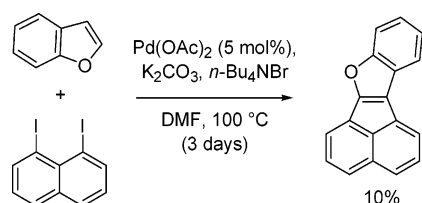
In this example, the poor reactivity of benzofuran resulted in a low yield of the desired pentacyclic product even after prolonged reaction times.

4. Conclusions

The use of direct arylation as a route toward the formation of a specific aryl–aryl bond has been an ongoing challenge in synthetic organic chemistry over the last 20 years. In particular, the exploration of new catalyst systems for direct arylation has grown considerably to encompass the formation of a wide range of aryl–aryl, aryl–heteroaryl, and heteroaryl–heteroaryl bonds. More recently, studies have focused on developing milder, lower temperature direct arylation reactions. In addition, some recent studies have also focused on the fine-tuning of catalyst systems to allow for the use of more inexpensive and industrially attractive aryl

chlorides. Undoubtedly, these developments will help both synthetic and material chemists a great deal, making direct arylation a valuable tool for diverse academic and industrial applications.

5. Notations and Abbreviations

acac	acetylacetonate
Ac$_2$O	acetic anhydride
AcOH	acetic acid
Ad	adamantyl
Ar	aryl
B	base
BHT	2,6-di-*tert*-butyl-4-methylphenol
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Bs	benzenesulfonyl
Bu	butyl
cod	cyclooctadiene
coe	cyclooctene
Cp	cyclopentadienyl
Cp*	η^6-pentamethylcyclopentadienyl
Cy	cyclohexyl
dba	dibenzylideneacetone
DCH-18-6	dicyclohexyl-18-crown-6
DCM	dichloromethane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DDQ	dichlorodicyanoquinone
DFT	density functional theory
DG	directing group
DMA	dimethylacetamide
DMAP	4-(dimethylamino)pyridine
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
dppf	1,1′-bis(diphenylphosphino)ferrocene
dppm	bis(diphenylphosphino)methane
dppp	bis(diphenylphosphino)propane
EOM	ethoxymethyl
Et	ethyl
equiv	equivalents
FVP	flash vacuum pyrolysis
GABA	γ-aminobutyric
GC/MS	gas chromatography/mass spectrometry
Het	heterocycle
HIV	human immunodeficiency virus
HMDS	hexamethyldisilazide
HMPT	hexamethylphosphorous triamide
HOMO	highest occupied molecular orbital
IMes	1,3-bis(mesitylimidazolyl)carbene
i-Pr	isopropyl
L	ligand
M	metal
Me	methyl
MeOH	methanol
Mes	mesityl
MOM	methoxymethyl
Ms	methanesulfonyl
NHC	*N*-heterocyclic carbene
NMP	*N*-methylpyrrolidine
NMR	nuclear magnetic resonance
Nu	nucleophile
OAc	acetate
OPiv	pivalate
OTf	triflate
o-Tol	*ortho*-tolyl
PAH	polycyclic aromatic hydrocarbon
PDE	phosphodiesterase
Ph	phenyl
PhH	benzene
PhMe	toluene

Piv	pivyl
PMHS	poly(methylhydrosiloxane)
rt	room temperature
SAR	structure—activity relationship
S_E3	trimolecular electrophilic substitution
S_EAr	electrophilic aromatic substitution
SEM	[2-(trimethylsilyl)ethoxy]methyl
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
t-Bu	*tert*-butyl
TFA	trifluoroacetic acid
Tf_2O	triflic anhydride
TFP	tri(2-furyl)phosphine
THF	tetrahydrofuran
TMEDA	tetramethylethyldiamine
TMS	trimethylsilyl
Ts	tosyl
X	halide
μw	microwave irradiation

6. Acknowledgments

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