Direct transition metal-catalyzed functionalization of heteroaromatic compounds

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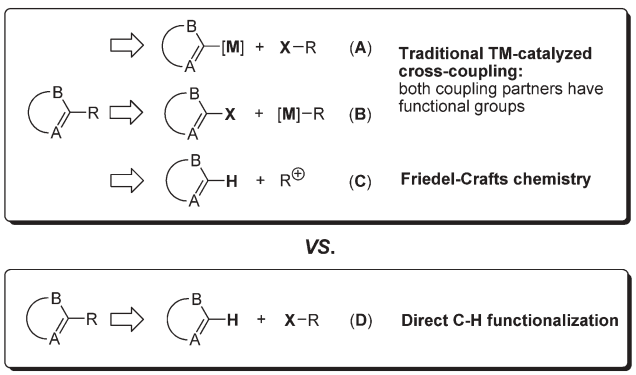
During the last two decades there has been considerable growth in the development of catalytic reactions capable of activating unreactive C–H bonds. These methods allow for the synthesis of complex molecules from easily available and cheaper precursors in a fewer number of steps. Naturally, the development of C–H activation methods for direct functionalization of heterocyclic molecules, invaluable building blocks for pharmaceutical and synthetic chemistry and material science, has received substantial attention as well. This *critical review* summarizes the progress made in this field until November 2006 (117 references).

Introduction

The traditional methods for functionalization of heterocyclic compounds usually employ different types of cross-coupling reactions, where the heterocyclic partner bears either a metal-containing functionality (nucleophilic component) or a halogen atom (electrophilic component) (**A** and **B**, Scheme 1). Friedel–Crafts-type alkylation (**C**) is also well-established, however it is limited to electron-rich substrates only and often is not regioselective. Alternatively, direct functionalization of heterocycles *via* the activation of unreactive C–H bonds (**D**) constitutes a much more attractive approach.[1]

Pd-catalyzed arylation of heteroaromatics with aryl halides is the most developed type of C–H functionalization of heterocyclic compounds. The earliest report containing an example of a very low yielding intramolecular arylation of pyridine appeared in 1984.[2] Since then, this chemistry has been



Scheme 1

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Ilya Seregin was born in Moscow, Russia, in 1979. He received his BSc from Moscow State University in 2001. In 2001–2003 he was a graduate student at Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences. He is currently a PhD student in Professor Gevorgyan's group at the University of Illinois at Chicago.

Vladimir Gevorgyan

Vladimir Gevorgyan was born in Krasnodar, Russia, in 1956. He received his BSc from Kuban State University in 1978 and his PhD from the Latvian Institute of Organic Synthesis in 1984, where he was promoted to Group Leader in 1986. He spent two years (1992–1994) in Tohoku University in Sendai, Japan, the first as a JSPS Postdoctoral Fellow and the second as a Ciba-Geigy International Postdoctoral Fellow. In the following year (1995) he worked as a Visiting Professor at CNR, Bologna, Italy. He returned to Tohoku University in 1996 as an Assistant Professor and was promoted to Associate Professor in 1997. In 1999 he moved to The University of Illinois at Chicago as an Associate Professor. He was promoted to the rank of Full Professor in 2003. Prof. Gevorgyan's current research interests cover four main areas. The first is concerned with development of highly selective Pd-catalyzed benzannulation reactions. The second area of interest focuses on development of novel transition metal-catalyzed methods for the synthesis of heterocyclic and naturally occurring compounds. The third area of interest covers the development of selective Lewis acid-catalyzed bond formation and cleavage reactions. The fourth deals with the chemistry of strained ring systems.

rapidly growing and new types of direct intra- and intermolecular reactions, as well as cascade transformations of heterocycles, such as C–H arylation, heteroarylation, vinylation, and formal alkylation, have been developed. Palladium complexes are among the most frequently used catalysts; however, there are some reports on efficient rhodium-catalyzed transformations.

This review provides mechanistic discussions on transition metal-catalyzed direct C–H functionalization of electron-rich and electron-deficient heterocycles, discusses different sets of conditions used for functionalization of both types of heterocycles, and covers the most essential synthetic applications.

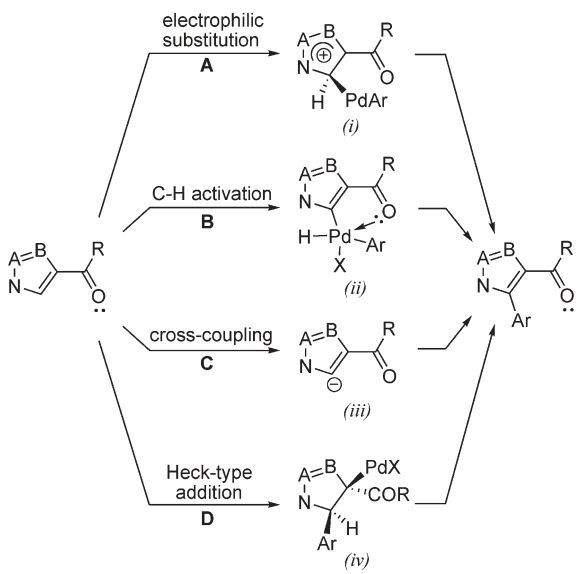
1. C–H arylation of electron-rich heterocyclic systems

1.1. Reactions involving Pd^0/Pd^{II} manifold: mechanistic studies

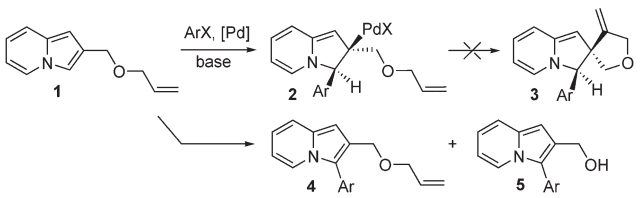
One of the most abundant protocols for transition metal-catalyzed functionalization of heteroaromatic compounds involves a Pd^0/Pd^{II} catalytic cycle. For C–H arylation of heterocyclic substrates, four distinct mechanisms have been proposed to date: electrophilic aromatic substitution (**A**),[3] C–H activation (**B**),[4] cross-coupling (**C**),[3] and Heck-type arylation (**D**)[5] (Scheme 2).

The first systematic mechanistic studies on the palladium-catalyzed arylation of heterocycles were reported by Gevorgyan.[6] Indolizine, one of the most electron-rich heterocycles known,[7] was chosen for these studies. Experimental and theoretical studies were performed to evaluate possible involvement of any of the four mechanisms depicted in Scheme 3.

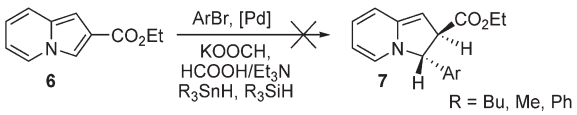
First, to evaluate the possible involvement of a Heck-type process **D**, a cascade Heck reaction[8] of **1** (Scheme 3) was tested, aiming at spirocyclic compound **3**. The latter would form *via* the second carbopalladation of the first Heck reaction product **2**. However, trials on this cascade transformation with



Scheme 2 Proposed mechanisms for Pd-catalyzed arylation of electron-rich hetroaromatic compounds.



Scheme 3 Attempts to perform cascade Heck reaction on indolizine.

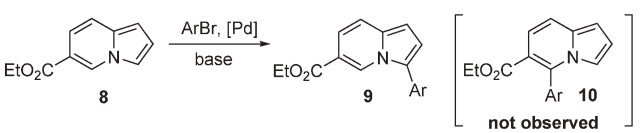


Scheme 4 Attempts to perform reductive Heck reaction.

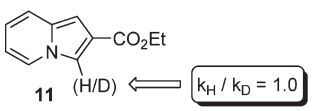
allyl ether **1** were unsuccessful, producing a mixture of C-3 arylated indolizines **4** and **5** instead. In another set of experiments, indolizine **6** was subjected to reductive Heck reaction conditions,[9] aiming at dihydroindolizine derivative **7** (Scheme 4). However, numerous efforts to perform this transformation under a variety of reduction conditions failed. It was rationalized that if this reaction does operate *via* a Heck-type mechanism,[5] the arylation of 6-carboethoxyindolizine **8** should lead to 7-arylindolizine **10** (Scheme 5). However, **8** was selectively arylated at C-3 instead, producing **9** as a sole regioisomer.

Next, the possibility of C–H activation pathway (**B**), proposed by Miura for the "coordination-assisted" C-3 arylation of 2-carbamoyl-substituted thiophenes,[10] was tested. Normally reactions proceeding *via* C–H activation motif experience a substantial isotope effect.[11] However, studies performed by the Gevorgyan group on indolizine **11** (Scheme 6) indicated no isotope effect ($k_{H/D}$ = 1.0), thus disfavoring involvement of C–H activation (Path **B**, Scheme 3) in this transformation.[6]

Furthermore, the absence of KIE at position C-3 of indolizine **11** contradicts another possible mechanism: a cross-coupling type process (Path **C**, Scheme 2), as it is known that reactions proceeding *via* proton–metal exchange should also exhibit a substantial KIE.[12] The possibility of involvement of this mechanism was originally proposed by Miura for the copper-assisted C-2 arylation of azoles, where arylation of "acidic" sites of the heterocycles was promoted by the addition of Cu salts.[3] However, addition of copper salts during the

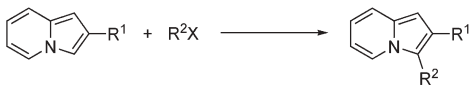


Scheme 5 Arylation of 6-carboethoxyindolizine.



Scheme 6 Possible C–H activation mechanism: isotope effect study.

Table 1 Relative rates of Pd-catalyzed arylation (**Method I**) and Lewis acid-mediated acylation (**Method II**) of selected indolizines



12 13 14

	Relative rates	
R^1	**Method I**	**Method II**
H	1.00	1.00
Me	0.97	0.67
CO_2Et	0.66	0.33

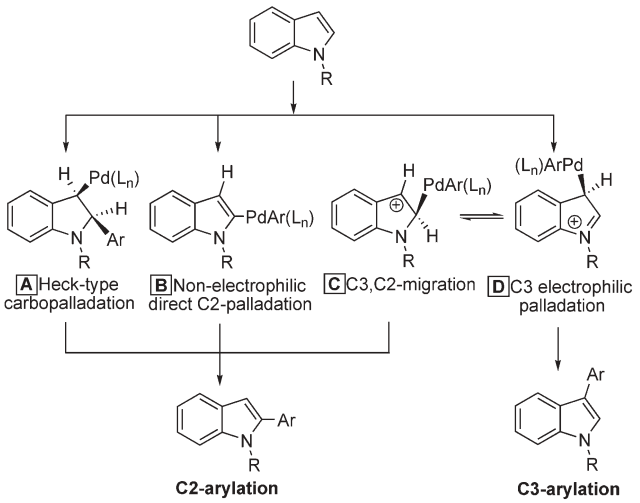
arylation of indolizine **6** resulted in greatly prolonged reaction times and reduced yields, thus, not supporting Path **C**.[6]

Next, experimental and theoretical studies were performed to elucidate the possible involvement of the electrophilic aromatic substitution process (**A**). This mechanism has often been considered as the most probable mechanism for arylation of heterocycles.[3,5,13,14] Naturally, the absence of an isotope effect in the arylation of **11** (Scheme 6) does not contradict pathway **A**, as the deprotonation event in the electrophilic mechanisms is not a rate-limiting step.[15] Additionally, it is well known that the pyrrole ring of an indolizine is electron-rich and easily undergoes electrophilic substitution reactions.[7] DFT calculations perfectly confirmed this point, revealing that the pyrrole ring has an extended HOMO density, whereas the LUMO mostly resides at the pyridine ring.[6] To gather further support for electrophilic mechanism **A**, kinetic studies were performed (Table 1).[6] As expected for an electrophilic path, the EWG-substituted indolizine underwent the slowest arylation among tested substrates (**Method I**, Table 1). A similar trend of reactivity was observed in the Lewis acid-mediated Friedel–Crafts acylation of the same indolizines (**Method II**, Table 1), thus strongly supporting electrophilic nature of the arylation (Path **A**, Scheme 2).[6]

Shortly thereafter, Sames reported detailed mechanistic studies on C-2 and C-3 arylation of indoles.[16] Three mechanisms that rationalize strong preference for the palladium-catalyzed C-2 arylation of indole were considered (Scheme 7): Heck-type reaction (**A**), non-electrophilic metalation of the C-2 position (**B**), and the electrophilic metalation at C-3 with or without subsequent migration to C-2 (**C** or **D**, respectively). While pathways **A** and **B** were briefly commented on, electrophilic mechanisms **C** and **D** received the most attention in this work.

First, it was mentioned that a Heck-type mechanism (Path **A**) might be operational in this process.[5,17,18] In this case, the process would involve a carbopalladation step, followed by *anti*-dehydropalladation or by isomerization and *syn*-elimination.[19] However, the isomerization step requires a reversible α-hydride elimination to form a carbene intermediate, a process unknown for palladium (unlike for Pt or Ru).[20]

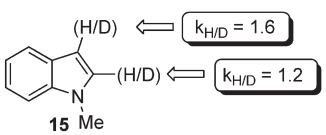
The next possible pathway is a non-electrophilic C-2-palladation of indole (Path **B**), which has been proposed by Tollari[21] and Nonoyama.[22] However, it was concluded that involvement of this scenario for non-functionalized indoles is unlikely, as the presence of a strong directing group is a strict requirement.[21,22]



Scheme 7 Possible pathways for C-2 and C-3 arylation of indoles.

Sames further evaluated the feasibility of pathways **C** and **D**, which involve an electrophilic palladation of indole.[16] It is well known that electrophilic substitution at indole has a strong preference for the C-3 position.[23] On the other hand, multiple examples of palladium-catalyzed arylation demonstrate predominant or exclusive C-2 selectivity. Thus, an interesting suggestion was made: the initial metalation does occur at the more nucleophilic C-3 carbon, followed by the C-3 to C-2 migration of an aryl palladium moiety, resulting in the apparent C-2 arylation (Path **C**). Better stabilization of the C-2–Pd bond by the adjacent nitrogen was proposed to be the driving force for this migration.[24] Kinetic isotope effect studies performed by Sames revealed an unexpectedly large kinetic isotope effect of 1.6 at C-3, a position in **15** where no substitution occurs (Scheme 8), which was rationalized in terms of secondary KIE. However, it was pointed out, an unusual value of 1.6 may be the sum of several rate-contributing steps. At the same time, the KIE at C-2 was ~1.2, evidently too small for the cleavage of C-2–H bond at the rate-limiting step. Sames concluded, that these results, if not clearly in support migratory pathway **C**, seem to be somewhat contradictory with the mechanism wherein a direct palladation at position C-2 takes place.

In conclusion, the mechanisic pathway for Pd^0/Pd^{II}-catalyzed arylation of electron-rich heterocycles, proposed by Miura[3] (Path **A**, Scheme 2), has received the most unambiguous experimental support so far. The key step of the process involves an electrophilic attack of arylpalladium species at the heterocycle. The regioselectivity of this step is governed by the distribution of electron density in the



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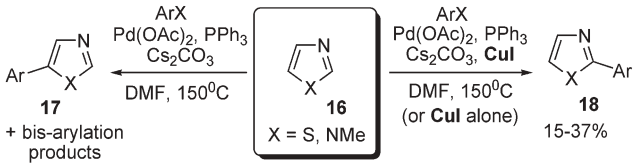
Scheme 8 Kinetic isotope effect in the phenylation of C-2 and C-3 positions of indole.



Scheme 9

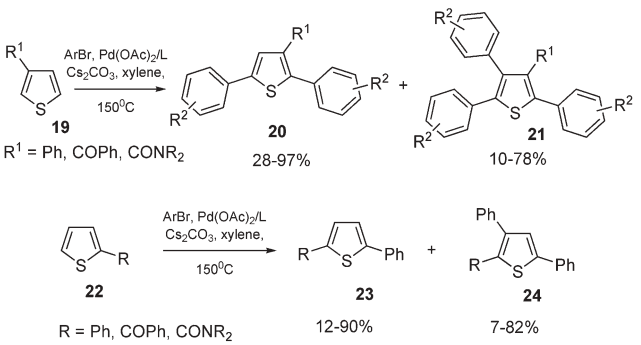
substrate. In indoles, however, the altering regiochemical outcome may be a result of palladium migration (Path **C**, Scheme 7). Nevertheless, the potential involvement of other aforementioned pathways or mixed mechanisms can not, at this point, be completely ruled out.

1.2. Reactions involving Pd^0/Pd^{II} manifold: synthetic applications

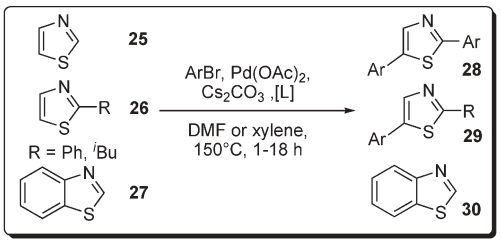
Miura investigated reactions of bromo- and iodobenzene with imidazoles, oxazoles, and thiazoles **16** (Scheme 9).[3] It was found that in the presence of catalytic amounts of $Pd(OAc)_2$ and PPh_3 in DMF, the coupling products, 5-arylated azoles **17**, can be synthesized selectively in good yields.[3] Interestingly, it was shown that the addition of stoichiometric Cu(I) salt significantly increases reactivity of the C-2 position of azoles leading to 2-arylated products **18**. Although the trend of reactivity in the electrophilic reactions of the azole ring is known to be C-5>C-4>C-2, in the presence of CuI alone (no Pd catalysis), a substantial amount of C-2 substituted product formed, which was attributed to an alternative operating mechanism. It was proposed that exchange of the most acidic proton at C-2 with Cu results in an organocopper intermediate, which is enabled to undergo cross-coupling with aryl halide to form C-2 arylated product **18** (Scheme 9).[3]

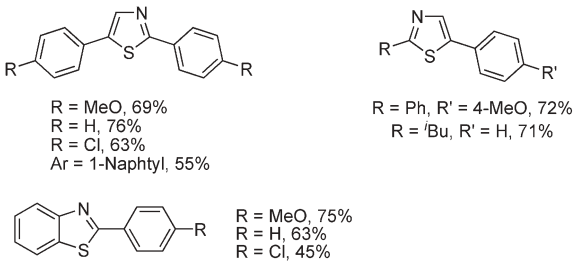
Furthermore, Miura reported a method for palladium-catalyzed multiple arylation of thiophenes **19** and **22** (Scheme 10).[25] Thiophene carboxamides were shown to undergo triarylation, accompanied by formal decarbamoylation in the presence of $Pd(OAc)_2$, Buchwald's ligand ($P(o\text{-biphenyl})(^tBu)_2$) or $P(^tBu)_3$, and Cs_2CO_3 in refluxing xylene.[25] 3-Substituted thiophenes **19**, bearing EWGs, can also be converted to triarylated products **21** in high yields. At the same time, selective diarylation can also be achieved in the presence of an excess of ArBr (Scheme 10).

Later, Miura disclosed a similar protocol for palladium-catalyzed C-2 and C-5 arylation of thiazoles **25**, **26** and

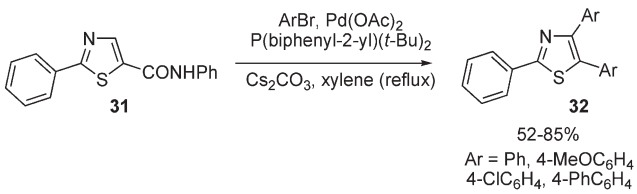


Scheme 10





Scheme 11

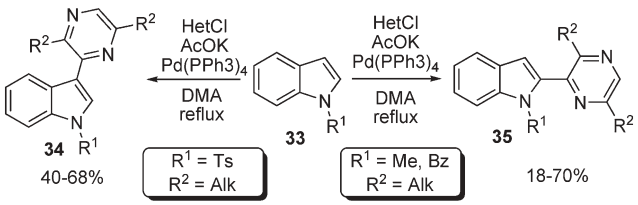


Scheme 12

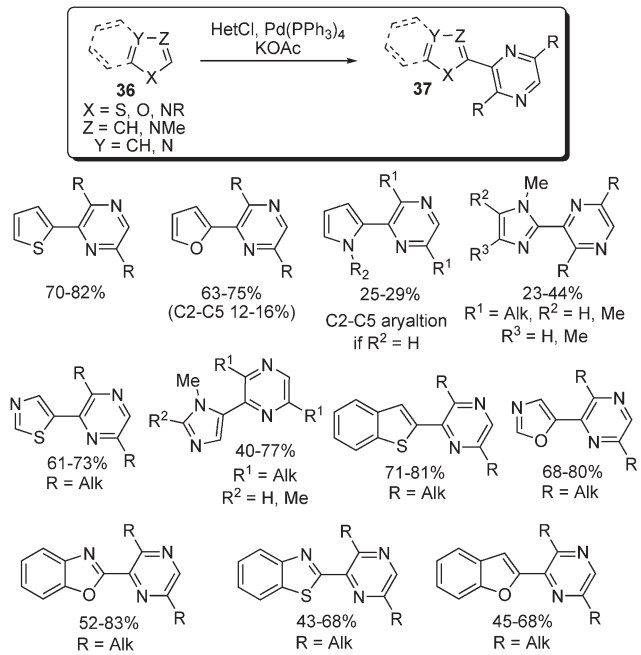
benzothiazoles **27** with aryl bromides (Scheme 11).[26] The best yields of diarylated products were obtained by employment of bulky phosphine ligands ($P(o\text{-biphenyl})(^tBu)_2$) or $P(^tBu)_3$ in DMF at 150 °C. At the same time, arylation of thiazole **31** bearing a carboxanilide function as sacrificial group in less polar *o*-xylene afforded 4,5-diarylated thiazole **32** exclusively, (Scheme 12).[26]

One of the first direct heteroarylations of heterocycles was reported in 1989 by Ohta who investigated palladium-catalyzed coupling of 2-chloro-3,6-dialkylpyrazines with protected indoles **33** (Scheme 13).[27,28] Reactions of 1-tosylindole with chloropyrazine in the presence of catalytic $Pd(PPh_3)_4$ led predominately to 3-heteroaryl indoles **34** in moderate to good yields. Alternatively, under the same conditions, 1-alkyl- and benzylindoles were shown to undergo substitution at C-2, affording the corresponding 2-heteroarylated products **35** in good yields (Scheme 13).[27,28]

Later, Ohta demonstrated palladium-catalyzed heteroarylation of other electron-rich heterocycles **36** (Scheme 14).[28] Coupling of chloropyrazines with pyrroles, furans, thiophenes,



Scheme 13

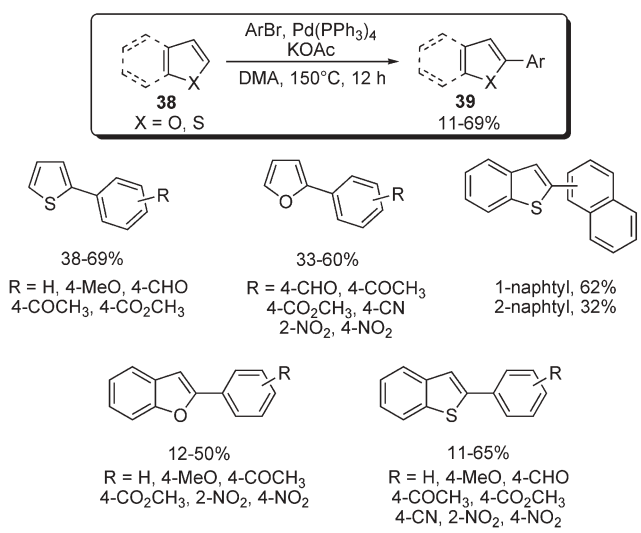


Scheme 14

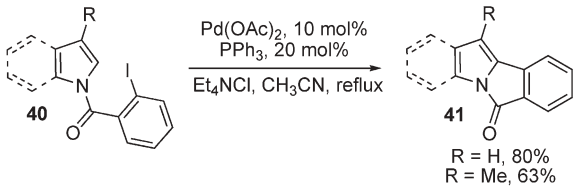
and a number of azoles in the presence of $Pd(PPh_3)_4$ gave the corresponding pyrazine-substituted products **37** in moderate to very good yields.[28]

Furthermore, this methodology was extended by Ohta for the arylation of furan, thiophene, and their benzo-analogues **38** (Scheme 15).[29] The developed protocol allowed for the synthesis of a variety of compounds arylated selectively at the C-2 position (**39**). It was noted that electron-deficient aryl components generally result in lower yields, while aryl bromides bearing EWGs react very smoothly.[29]

In 1990, Grigg reported an intramolecular arylation of iodo-1-aroylpyrroles and indoles **40** (Scheme 16).[30,31] It was demonstrated that in the presence of $Pd(OAc)_2$, $PhPh_3$ and tetraethylammonium chloride the reaction affords good yields of tri- and tetracyclic products **41**.[30,31]



Scheme 15



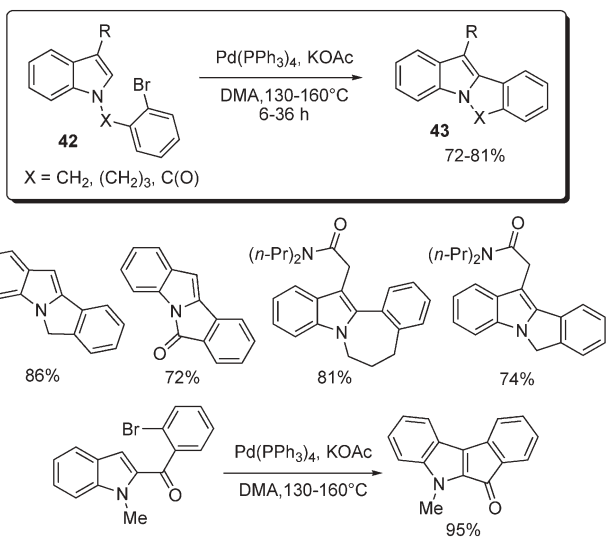
Scheme 16

Later, Kozikowski disclosed a methodology towards polycyclic indoles **43** featuring intramolecular cyclization of bromoaryl-bearing indoles **42** (Scheme 17).[32] It was demonstrated that intramolecular C–H arylation proceeded readily in the presence of $Pd(PPh_3)_4$ and KOAc in DMA, affording polycyclic products **43** in very good yields.

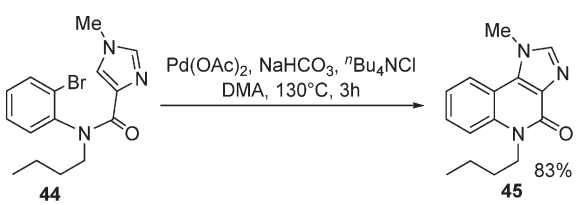
Suzuki reported synthesis of imidazo[4,5-*c*]quinolin-4(5*H*)-one ring systems **45** *via* an intramolecular palladium-catalyzed cyclization of **44** (Scheme 18).[33] The effect of solvent and type of base used in the C–H arylation of imidazole ring were thoroughly investigated.[33]

In 1995, Merour reported a protocol for the intramolecular annulation of **46**, leading to polycyclic indole- and pyrrolo[2,3-*b*]pyridine-containing structures **47** (Scheme 19).[34] The employment of $Pd(PPh_3)_4$–KOAc catalytic system allowed for obtaining annulated products **47** in moderate to very high yields. Notably, it was demonstrated that this method perfectly tolerates sensitive functional groups, such as aldehyde and halogen (Scheme 19).[34]

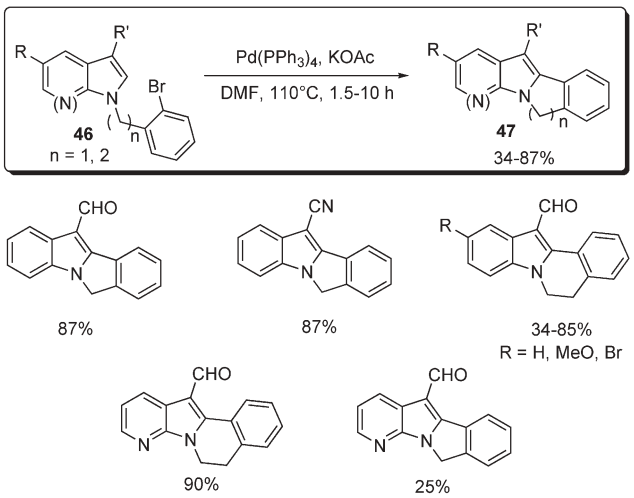
In 1997, Lemaire reported a method for the arylation of thiophenes **48** under Jeffery's conditions[35] (Scheme 20).[36,37] It



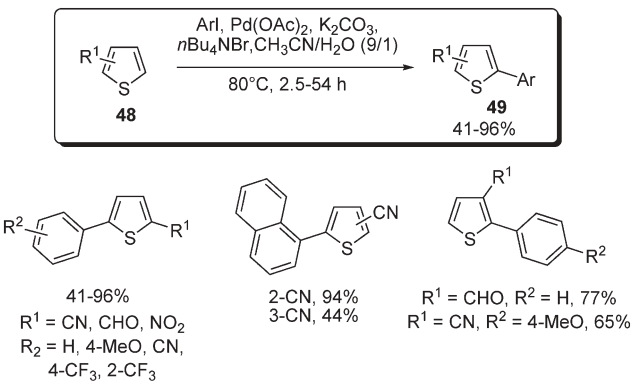
Scheme 17



Scheme 18



Scheme 19

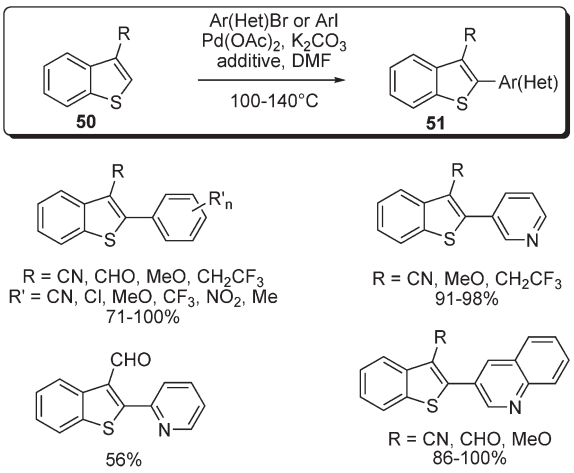


Scheme 20

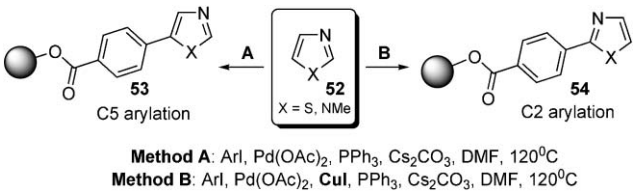
was found that in thiophenes bearing an EWG at C-2, arylation occurred at C-5 regiospecifically. In the case of 3-substituted substrates **48**, the reaction was not regiospecific, leading to the formation of C-2–C-5 disubstituted products. The arylation of 2-carboxaldehyde thiophene proceeded in rather moderate yields; however, the reaction of 2-cyanothiophene gave arylated products in excellent yields (Scheme 20).[36,37]

Later, Lemaire disclosed an approach towards 2-aryl- and 2-heteroaryl-benzothiophenes **51** (Scheme 21).[38] It utilized a phosphine-free system: $Pd(OAc)_2$, K_2CO_3, and crown ether. In particular, good results were obtained in the presence of dicyclohexyl-18-crown-6. In the case of sensitive functional groups, such as aldehyde, a quaternary ammonium salt was used as an additive instead of a crown ether. Importantly, this protocol allowed for obtaining high yields of arylated products **51** from benzothiazoles **50** bearing both electron-donating and electron-withdrawing groups (Scheme 21).[38]

A method for regiodivergent palladium-catalyzed monoarylation of azoles **52** with aryl iodides, immobilized on a solid polymer support, was developed by Kondo (Scheme 22).[39] The switch of regioselectivity (C-2 *vs* C-5) was primarily achieved by the employment of CuI, which led to the exclusive formation of C-2-functionalized product **54**, while only C-5



Scheme 21

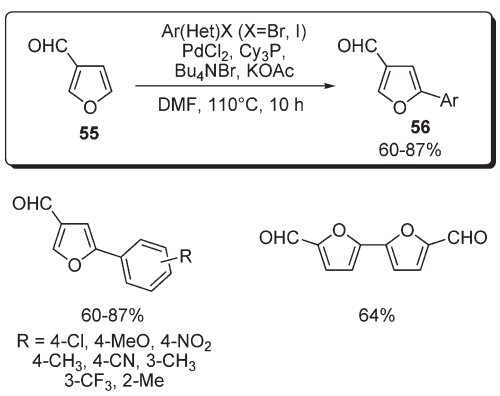


Scheme 22

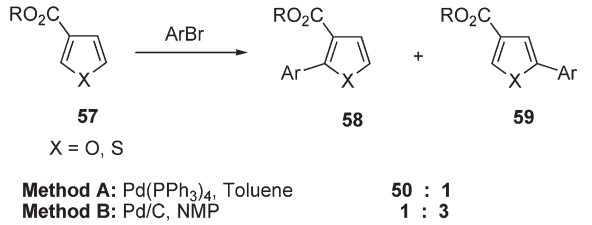
arylation occurred in the absence of copper additive. Remarkably, unsymmetrical diarylation was demonstrated in the sequential derivatization mode (Scheme 22).[39]

McClure reported a regioselective method for the C-5 arylation of furaldehyde **55** (Scheme 23).[40] In the presence of $PdCl_2$, PCy_3, Bu_4NBr, and KOAc, a variety of 5-arylfurfurals **56** were obtained in high yields. The mechanistic rationale proposed included both Heck-type carbopalladation and electrophilic metalation pathways. However, no experimental support for these mechanisms was provided (Scheme 23).[40]

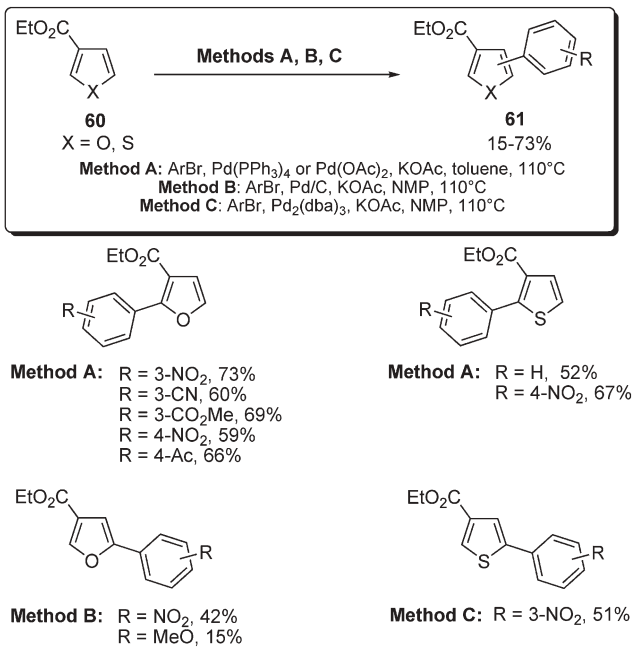
Sharp developed a method for the regioselective Heck-type arylation of 3-ester-substituted furans and thiophenes (Schemes 24 and 25).[5] Notably, it was suggested that a change in the reaction mechanism can occur depending on the reaction conditions (Scheme 24). Particularly, a nonpolar solvent and phosphine ligands used in Method **A** stabilize the σ-bonded



Scheme 23



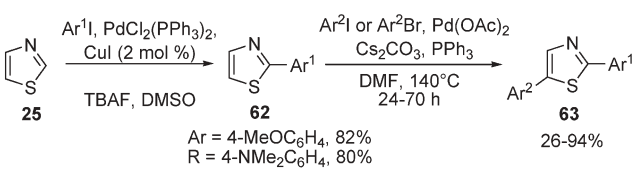
Scheme 24 Condition-dependent Heck *vs* electrophilic arylation.



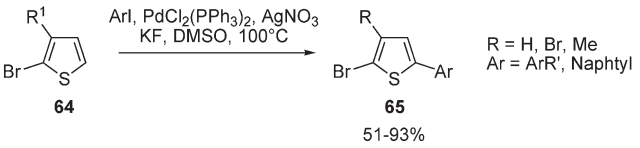
Scheme 25

Pd(II) species, favoring the Heck-type carbopalladation and affording intermediate *i* (see above, Scheme 2), which leads to the C-2-arylated product **58**. Alternatively, in Method **B**, a polar solvent and an absence of stabilizing phosphine ligands are likely to promote the ionization of the Pd–X to form an electrophilic Pd(II) species. These species would be expected to react preferentially at the more electron-rich C-5 position of the heterocycle, resulting in the regioisomer **59**. Application of these methods (**A**, **B**, **C**) for arylation of furans and thiophenes **60** led to selectively functionalized heterocycles **61** in moderate to good yields (Scheme 25).[5]

Mori reported a mild and regioselective C-2 arylation of thiazole **25** employing a palladium/copper(I) catalytic system in the presence of tetrabutylammonium fluoride (Scheme 26).[41] A variety of 2,5-diarylthiazoles **63** bearing two different aryl groups were synthesized in a subsequent second-fold arylation of **62** under standard Cu-free conditions (Scheme 26).[41]



Scheme 26



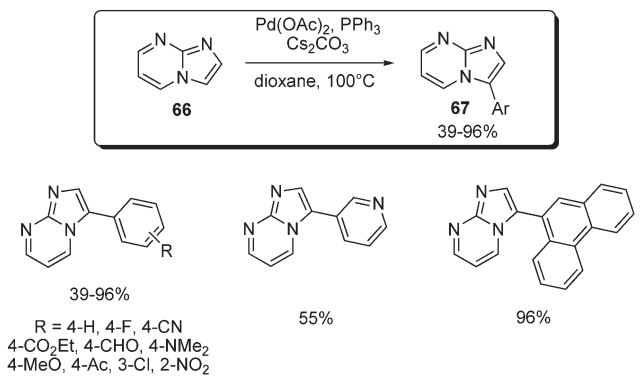
Scheme 27

Later, Mori investigated Pd-catalyzed arylation reactions of thiophenes **64** possessing Br-substituent at C-2 with aryl iodides, while preserving the carbon–bromine bond (Scheme 27).[42] The arylation with ArI was shown to proceed selectively at C-5 in the presence of $PdCl_2(PPh_3)_2$, $AgNO_3$, and KF in DMSO, affording high to excellent yields of arylated bromothiophenes **65**, building blocks for further derivatization *via* standard cross-coupling techniques. Remarkably, no homocoupling reaction of bromothiophenes **64** occurred under these conditions.

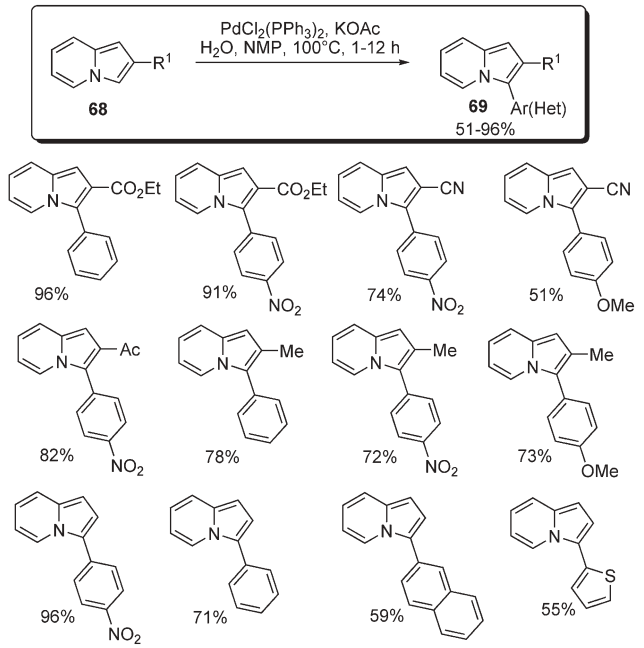
A method for direct arylation and heteroarylation of imidazopyrimidine **66** was reported by Li (Scheme 28).[43] The protocol involved employment of the $Pd(OAc)_2/PPh_3$ catalytic system in the presence of Cs_2CO_3 in dioxane, affording the corresponding aryl derivatives **67** with good to excellent yields (Scheme 28).[43] It was suggested that this arylation proceeds *via* Miura's electrophilic mechanism.[3]

Gevorgyan reported an efficient and regioselective method for C-3 arylation and heteroarylation of indolizines **68** (Scheme 29).[6] It was demonstrated that a variety of substituents on both the indolizine and aryl bromide are tolerated, providing easy access to substituted indolizines **69** in yields ranging from good to very high. Detailed mechanistic studies (Schemes 3–6, Table 1) strongly supported an electrophilic mechanism for this transformation.[6]

Sames reported a method for the selective C-2-arylation of *N*-substituted indoles **70** (Scheme 30).[44] Optimization of the reaction conditions and catalyst loads has identified an optimal protocol which allowed for up to good yields of arylated derivatives **71**. This method exhibited good functional group tolerance. Interestingly, it was demonstrated that employment of haloarenes possessing bulky *ortho*-substituents afforded mixtures of C-2 and C-3 substituted indoles **72** and **73** (Scheme 30).[16,44] A selective C-3 arylation of *N*-unprotected indole (**74**) was achieved by the employment of magnesium bases (Table 2).[16] Interestingly, arylation of **75**, in which



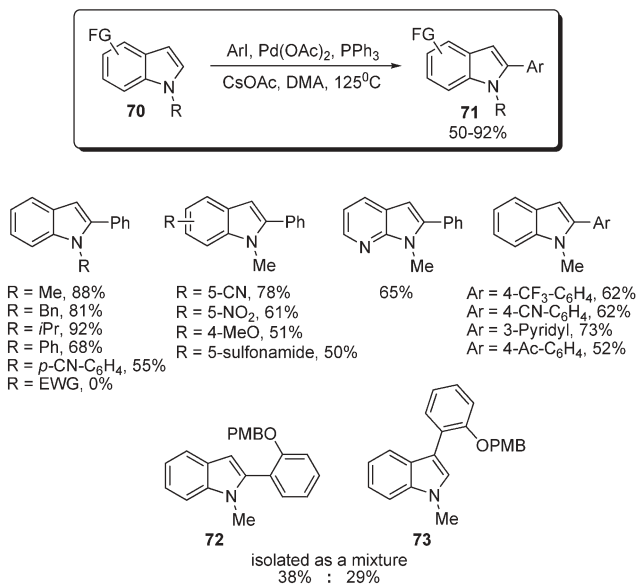
Scheme 28



Scheme 29

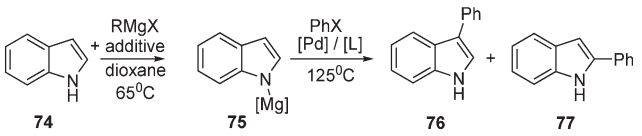
nitrogen is protected *via* treatment of **74** with a combination of MeMgCl with TMEDA (tetramethylethylenediamine) or $Mg(HMDS)_2$, selectively led to 3-phenylindole **76**. This result was explained in terms of the formation of a sterically demanding magnesium which, in combination with bulky phosphine ligand at the arylpalladium (see above: Path **C**, Scheme 7), governed the regioselectivity of arylation. Systematic mechanistic studies on this transformation were discussed above (Schemes 7 and 8).[16]

Sames also disclosed an efficient method of C–H arylation of 2-(trimethylsilyl)ethoxymethyl (SEM) protected azoles **78**, including pyrroles, indoles, imidazoles, and imidazopyridines (Scheme 31).[45] The reaction was catalyzed by employment of



Scheme 30

Table 2 Control of regioselectivity by the choice of magnesium salt



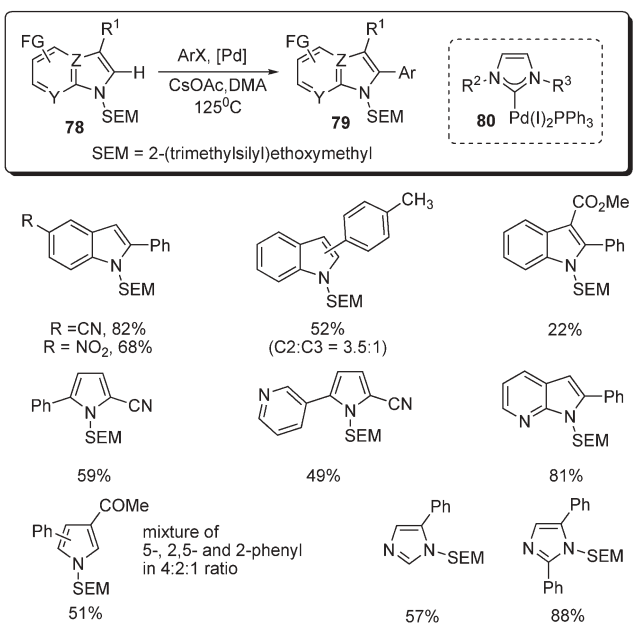
X	[Mg]	Yield	75:76
I	MgCl	24%	7 : 1
I	MgCl–TMEDA	61%	14 : 1
Br	MgCl–TMEDA	96%	67 : 1
I	$MgN(TMS)_2$	77%	26 : 1

[a] Conditions: $Pd(OAc)_2$ (2.5 mol%), Ph_3P (10 mol%), IMes (2.5 mol%)

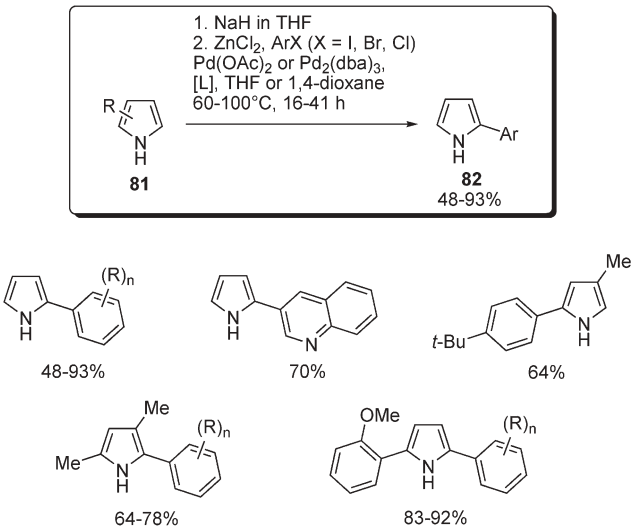
palladium imidazolyl carbene complexes **80**. Remarkably, simple deprotection of the SEM group allowed for convenient access to aryl-substituted azoles, not available by direct arylation (Scheme 31).[45]

A general method for the conversion of pyrrole *N*-anions to 2-aryl derivatives **82** was proposed by Sadighi (Scheme 32).[46] It was shown that in the presence of $Pd(OAc)_2$ or $Pd_2(dba)_3$, along with sterically-demanding 2-(dialkylphosphino)biphenyl ligands, the Zn salt of pyrrole **81** smoothly undergoes cross-coupling with chloro- and bromoarenes and heteroarenes to afford arylated products **82** in moderate to very high yields (Scheme 32).[46]

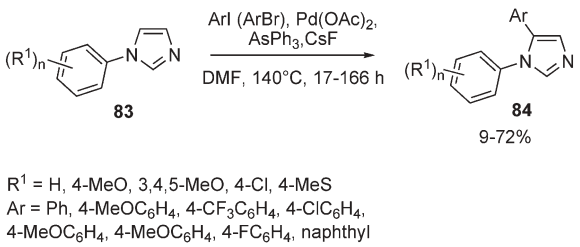
Rossi demonstrated that a variety of 1,5-diarylimidazoles **84** can be synthesized *via* a direct palladium-catalyzed C–H arylation of 1-arylimidazoles **83** (Scheme 33).[47] The protocol involves a $Pd(OAc)_2/AsPh_3$ catalyst system. Although the yields are often moderate, very high degrees of regioselectivity were achieved. It was demonstrated that experimental data on the reaction selectivity supports the electrophilic mechanism proposed by Miura[3] for arylation of azoles and are in



Scheme 31



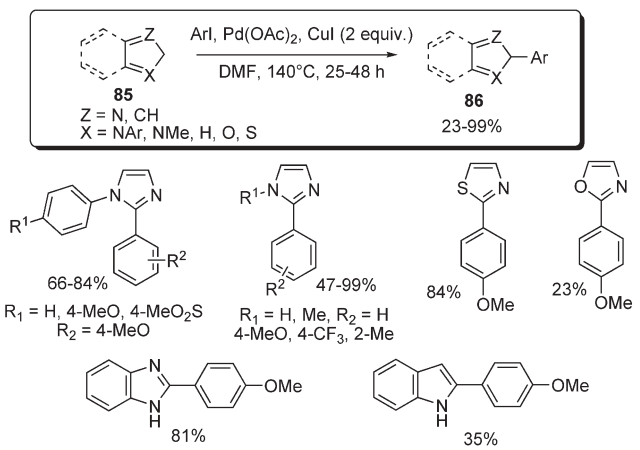
Scheme 32



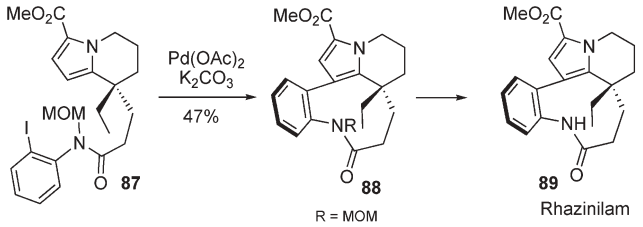
Scheme 33

accordance with the trend of nucleophilicity in azole ring C-5>C-4>C-2.

Very recently, Rossi reported developments on C-2-regioselective arylation of a number of different heterocyclic systems including thiazoles, oxazoles, free and *N*-substituted imidazoles, benzoimidazoles and indoles **85** (Scheme 34).[48,49] Under the unprecedented base- and ligand-free conditions, complete regioselectivity has been achieved. The protocol involved catalytic $Pd(OAc)_2$ and stoichiometric CuI in DMF. Remarkably, no products of *N*-arylation of *N*-unprotected heterocycles were observed under these conditions. The



Scheme 34



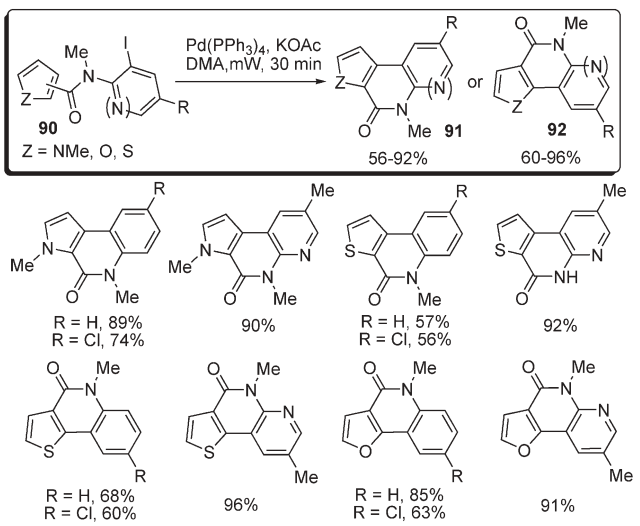
Scheme 35

regioselectivity of arylation was rationalized by a mechanism involving the formation of a 2-copper derivative, followed by transmetalation with aryl palladium(II) halide species with subsequent reductive elimination (Scheme 34),[49] analogously to the protocol reported by Mori for C-2 arylation of thiazoles (Scheme 26).[41]

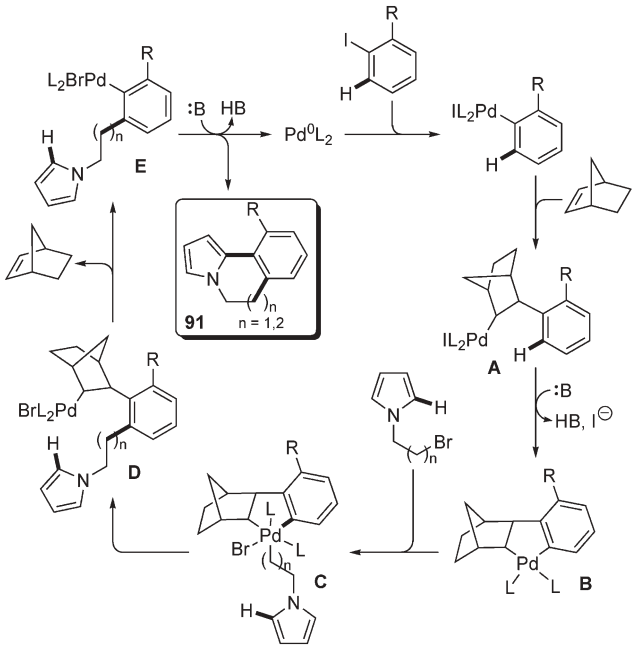
An example of palladium-catalyzed intramolecular cross-coupling of a heterocyclic C–H bond with aryl iodide was reported by Trauner in the context of his efforts in the total synthesis of (±)-Rhazinilam **89** (Scheme 35).[50] The key step, C–H derivatization of an unactivated pyrrole ring in **87** afforded a 9-membered ring in **88** with 47% yield. Importantly, the presence of an unprotected amide functionality was shown to be incompatible with this protocol (Scheme 35).[50]

Recently, Beccalli reported a strategy for the preparation of tricyclic fused quinolones **91** and naphthyridones **92** *via* the palladium-catalyzed intramolecular arylation of **90** (Scheme 36).[51] Microwave irradiation was shown to be advantageous over conventional heating, as it accelerates the coupling reactions and leads to better yields.

Lautens demonstrated an elegant approach for the formation of six- and seven-membered rings, which allowed for the efficient assembly of polycyclic frameworks. The method involved a norbornene-mediated tandem *ortho*-alkylation/C–H functionalization between an aryl iodide and a bromoalkyl heterocycle (Scheme 37).[56] The key alkylation step of this cascade transformation proceeds *via* a Catellani reaction.[52] Among possible mechanisms for the C–H functionalization step, Lautens names a Heck reaction, a direct nonelectrophilic



Scheme 36

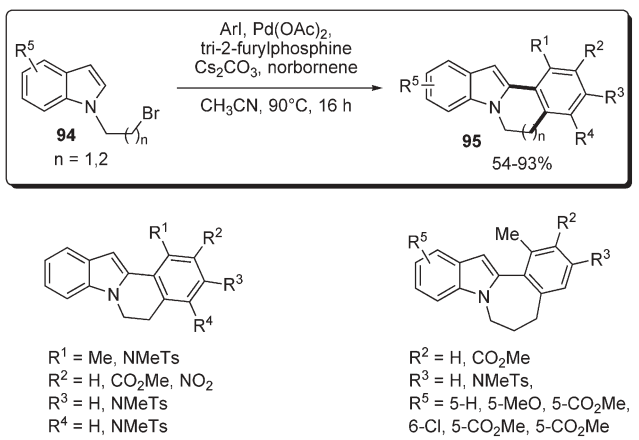


Scheme 37

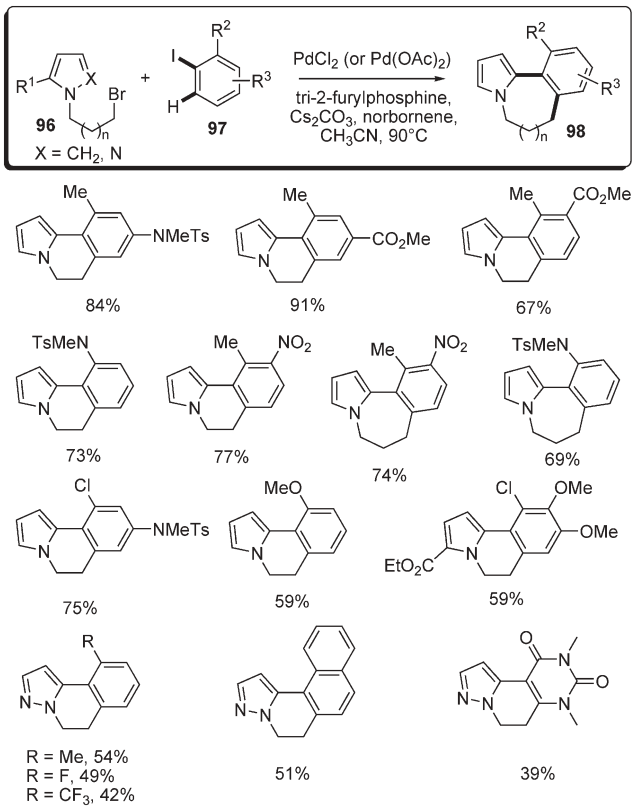
palladation at C-2 (although requiring a directing group[53–55]), and electrophilic substitution at C-3 followed by migration of palladium to C-2.[16] Thus, a variety of substituted annulated indoles **95** containing six- and seven-membered rings were synthesized in good to excellent yields from bromoalkyl indoles **94** and aryl iodides in the presence of catalytic amounts of $Pd(OAc)_2$, tri-2-furylphosphine, Cs_2CO_3 and a stoichiometric amount of norbornene (Scheme 38).[56]

Further, Lautens applied this methodology for annulation of pyrroles and pyrazoles **96** (Scheme 39).[57] Similar to the previous example,[56] this one-pot protocol was proven to be very effective towards formation of a number of fused six- and seven-membered ring systems.[57]

Very recently, Lautens disclosed the synthesis of polycyclic furans and thiophenes **101** *via* an analogous one-pot alkylation–intramolecular heteroarylation sequence (Scheme 40).[58] It was found that the reaction provides good to excellent yields of oxygen and sulfur-containing polycyclic products **101** only



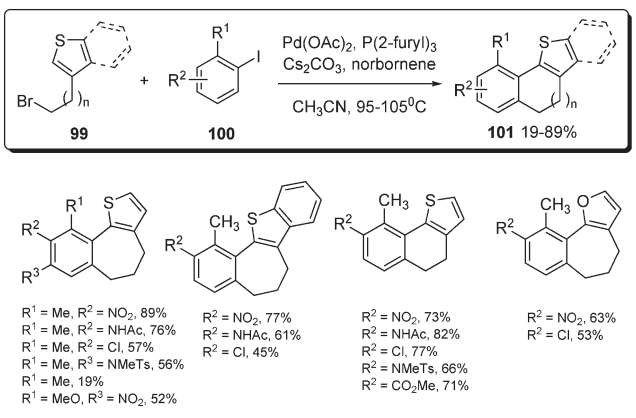
Scheme 38



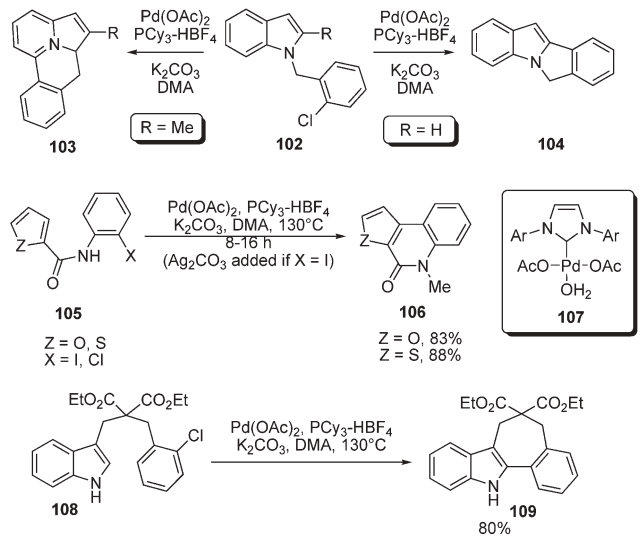
Scheme 39

when electron-deficient aryl iodides are used. The fact that electron-rich aryl iodides do not work equally well provided additional insight into the mechanistic aspect of this process. Since the arylation step involves an attack at the electron-deficient arylpalladium(II) halide, it was concluded that electron-rich aryl component **100** stabilizes Pd(II) species, reducing its electrophilicity and, consequently, making it less reactive in the arylation step.[58]

A method for intramolecular arylation of simple arenes and heteroarenes **102** was developed by Fagnou (Scheme 41).[59,60,61] The catalytic system consisting of $Pd(OAc)_2$ and PCy_3–HBF_4 (or palladium complex **107**) enabled formation of polycyclic ring systems with indole (**103**, **104** and **109**), furan, and



Scheme 40

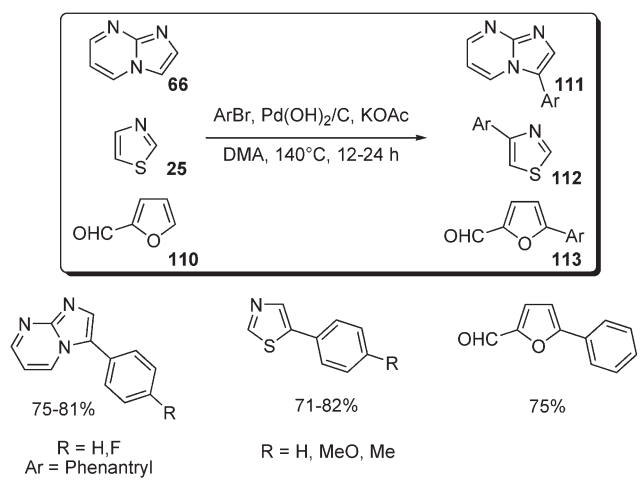


Scheme 41

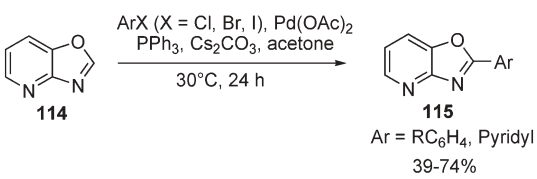
thiophene **106** fragments. Catalyst poisoning during this reaction was observed. It was shown to be associated with the accumulation of KI in the reaction media when aryl iodides are used. Consequently, addition of a stoichiometric amount of silver salts allowed this problem to be overcome. Mechanistic studies revealed a "kinetic importance" of the C–H bond cleavage step, which allowed the mechanism to be rationalized as proceeding *via* metalation involving either σ-bond methathesis or an S_E3 C–H functionalization step.[59–61]

Further, Fagnou demonstrated that $Pd(OH)_2$/C (Pearlman's catalyst)–KOAc catalytic system effectively works in direct C–H arylation reactions affording high yields of aryl-substituted thiazoles **112**, imidazopyrimidines **111** and furans **113** (Scheme 42).[62]

Very recently, Zhuravlev reported a method for Pd-catalyzed arylation of oxazolo[4,5-*b*]pyridine **114** (Scheme 43).[63] Remarkably, the reaction proceeded efficiently at temperatures as low as 30 °C and exhibited good functional group tolerance at the aryl coupling partner, including derivatized amino acids. It was suggested that the combination



Scheme 42



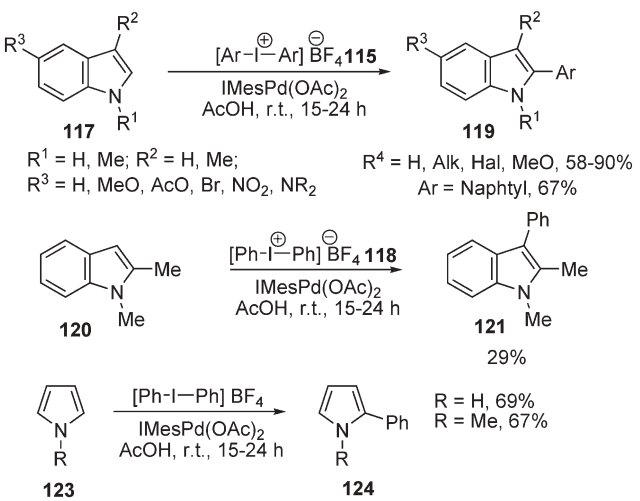
Scheme 43

of the electron-deficiency of the oxazolopyridine system and its high reactivity might indicate that arylation in this ring system proceeds *via* a non-electrophilic pathway. Additional studies provided certain support for this suggestion: a substantial proton–deuterium exchange was observed in acetone-d_6 in the presence of Cs_2CO_3, supporting the possible involvement of an anionic intermediate, analogous to that proposed by Miura.[3]

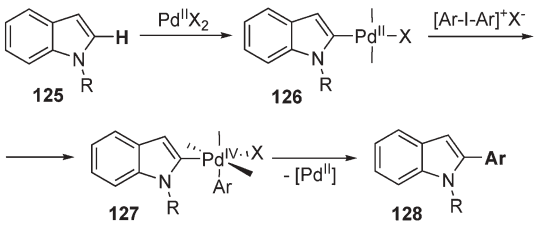
1.3. Arylation reactions involving Pd^{II}/Pd^{IV} manifold

In the last few years an impressive array of publications came from the groups of Sanford,[64,65] Yu,[66,67] and Daugulis[68–72] on oxidative C–H functionalization of arenes. The methods, operating *via* Pd^{II}/Pd^{IV} couple, were proposed to be advantageous over those employing Pd^0/Pd^{II} manifold as they exhibit higher functional group tolerance, and often operate under milder conditions.

In 2006, Sanford reported an efficient protocol for the regioselective arylation of free and *N*-substituted indoles and pyrroles (Scheme 44).[73] In this method, iodonium salts [Ar–I–Ar]BF_4 (**115** and **118**) were used as arylating agents. Remarkably this mild room temperature method allowed for the efficient synthesis of a variety of C-2-arylated indoles and pyrroles with very good functional group tolerance and high yields (Scheme 44). Interestingly, arylation of *N*-unprotected and *N*-methyl indoles was similarly effective. Moreover, as a consequence of a Pd^{II}/Pd^{IV} mechanism (Scheme 45), this methodology demonstrated not only high functional group tolerance, but appeared to be completely air/moisture insensitive, in contrast to the traditionally used methodology, involving a Pd^0/Pd^{II} pair.



Scheme 44

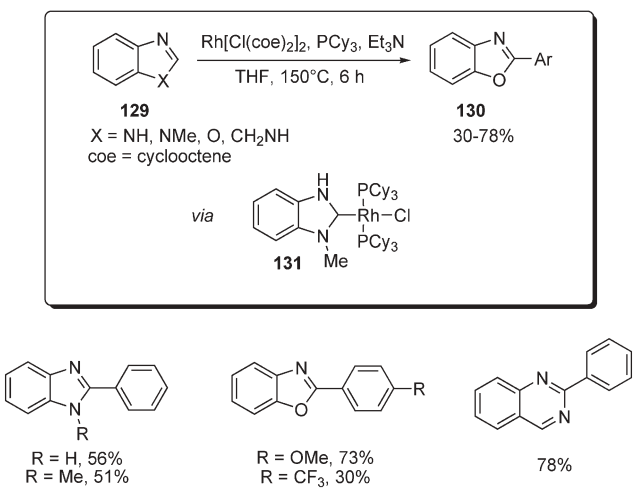


Scheme 45

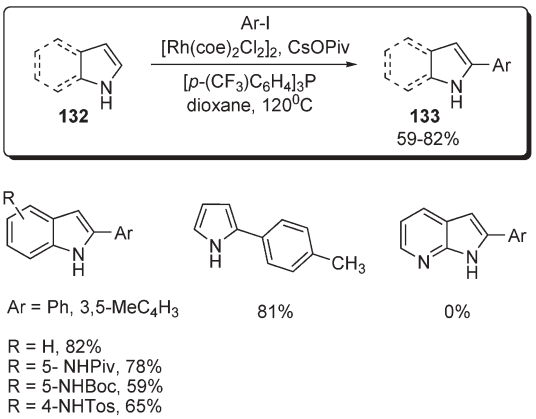
1.4. Arylation reactions involving Rh catalysis

In 2004, Bergman and Ellman reported a method for the rhodium-catalyzed arylation of various heterocyclic systems **129**: benzimidazoles, benzothiazoles, quinazolines, dihydroquinazolines, and oxazolines (Scheme 46).[74] The protocol utilizes $[RhCl(coe)_2]_2$ complex in a combination with PCy_3 and Et_3N, affording the arylated products **130** in moderate to very good yields. Remarkably, *N*-unprotected heterocycles were tolerated in this method. Preliminary mechanistic studies revealed the involvement of rhodium *N*-heterocyclic carbene complex **131**, which was isolated and characterized by X-ray analysis (Scheme 46).[74,75]

Later, a similar methodology was applied by Sames for arylation of indoles and pyrroles **132** (Scheme 47).[76] Application of a modified catalytic system, consisting of $[Rh(coe)_2Cl_2]_2$, $[p\text{-}(CF_3)C_6H_4]_3P$, and CsOPiv, allowed the arylation of free indoles and pyrroles in high yields to be performed (Scheme 47). It was shown that, analogously to the previous example (Scheme 46),[74] this catalytic system targets specifically C–H bonds in the presence of more acidic N–H bonds. This selectivity was explained in terms of a greater electrophilicity of the Ar–Rh(III) species (compared to Ar–Pd(II)) which, in conjunction with the electron- deficient phosphine- and pivalate ligands, gain additional reactivity. It was observed that this arylation method is incompatible with pyridine-containing substrates possessing nucleophilic nitrogen, which is a well-known limitation in the chemistry involving rhodium catalysis.[77]



Scheme 46

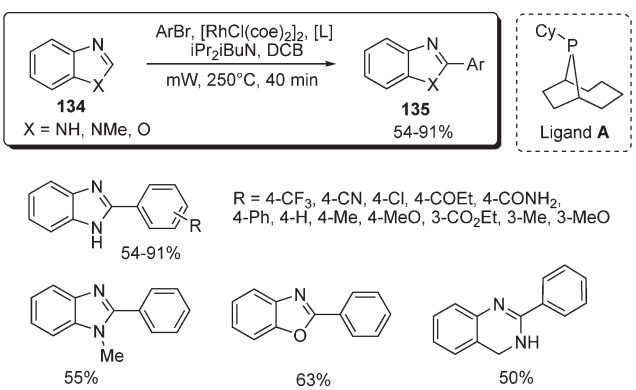


Scheme 47

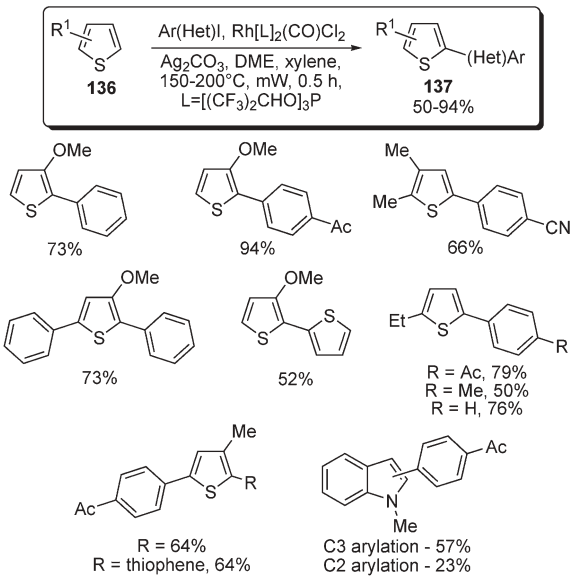
Shortly thereafter, Bergman and Ellman reported a method for Rh-catalyzed microwave-assisted coupling of various azoles **134** with aryl bromides (Scheme 48).[78] Employment of the slightly modified procedure ($[RhCl(coe)_2]_2$ with trialkylphosphine ligand **A**, bulkier than PCy_3) in combination with microwave irradiation allowed for a dramatic shortening of reaction times (40 minutes *vs* 6 hours reported earlier,[74] Scheme 46).

Itami reported studies on rhodium-catalyzed C–H arylation of indoles and thiophenes **136** (Scheme 49).[79] The protocol employed $RhCl(CO)\{P[OCH(CF_3)_2]_3\}_2$ complex, bearing π-accepting ligands, in combination with Ag_2CO_3. An electrophilic metalation of heterocycles with the aryl–Rh(III) species was proposed as a key step for this transformation. This methodology was also efficient for the arylation of moderately electron-rich arenes: such as anisole and 1,3-dimethoxybenzene. The *ortho–para* selectivity of arylation in this process was entirely consistent with an electrophilic mechanism.[79]

In summary, the employment of Pd^0 or Pd^{II} catalysts with excess base at elevated temperatures with slight variations in techniques can be considered as a general method for the arylation of electron-rich heteroaromatics. Generally, arylation of pyrroles, furans, thiophenes, indoles, and other substrates with one heteroatom shows strong preference to the position adjacent to the heteroatom. However, arylation of indoles can be redirected to the C-3 position by employing anionic *N*-magnesium derivatives.[16] Additionally, it was



Scheme 48



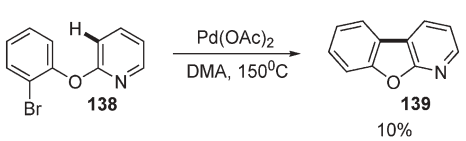
Scheme 49

demonstrated that arylation of furans and thiophenes bearing an EWG at C-3 can be achieved selectively at C-2 or C-5 by switching reaction conditions to favor either electrophilic or Heck-type mechanisms, leading to different products.[5] Arylation of azoles, in most cases, is not selective and leads to the mixtures of C-2 and C-5 arylated products or results in bis-arylation. Nevertheless, excellent C-2 selectivity can be achieved in the presence of stoichiometric amounts of Cu salts.[3,41,48]

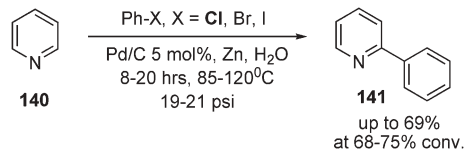
2. C–H arylation of electron-deficient heterocyclic systems

The first example of direct C–H functionalization of an electron-deficient heterocycle was reported by Ames in 1984 (Scheme 50).[80] In the context of their studies on intramolecular palladium-catalyzed cyclizations of haloarenes, it was found, that pyridine ring in **138** undergoes intramolecular C–H arylation at the C-3 position by an aryl bromide. However, the reaction was reported to be sluggish and very low yielding, producing **139** in 10% only (Scheme 50).

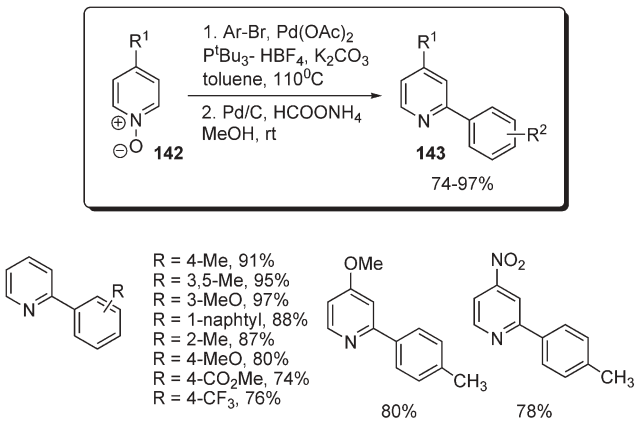
Later, an interesting method for C–H cross-coupling of pyridine **140** with phenylhalides, catalyzed by heterogeneous palladium on carbon in the presence of Zn dust, was reported by Sasson (Scheme 51).[81] The mechanism was rationalized as a radical process or, alternatively, as a heterogeneous Heck-type reaction. This method allowed for the regioselective preparation of 2-arylpyridine **141**, though it was accompanied by comparable amounts of biaryl side-products.[81]



Scheme 50

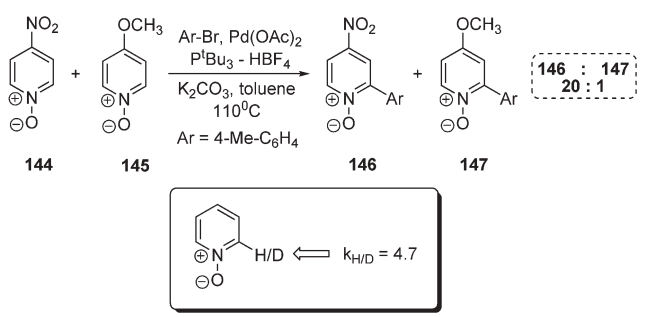


Scheme 51

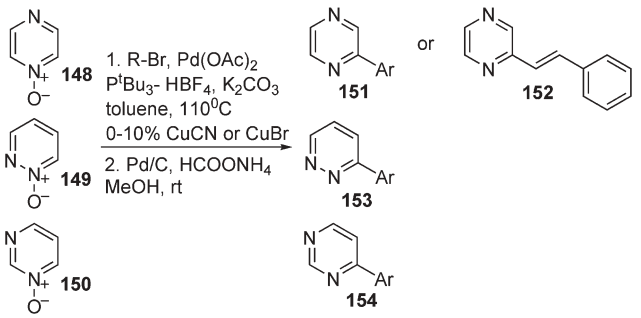


Scheme 52

Recently, Fagnou reported an elegant solution to the arylation of pyridines (Scheme 52).[82] He demonstrated that, unlike the pyridine, a pyridine *N*-oxide **142** can undergo smooth, selective and high-yielding C-2-arylation with a variety of aryl bromides in the presence of $Pd(OAc)_2/P^tBu_3$–HBF_4 catalytic system (Scheme 52). After completion of arylation, pyridine oxide can be efficiently reduced to pyridine derivative **143** in very good overall yield. Importantly, the mechanistic studies pointed out that electrophilic S_EAr is not operating in this case. A competition reaction between electron-deficient and electron-rich pyridine oxides (**144** *vs* **145**, Scheme 53) was performed. It was suggested, that if an S_EAr mechanism operates, then electron-rich substrate **145** would react preferentially. However, electron-deficient pyridine **144** reacted faster, yielding product **146**, accompanied by negligible amounts of arylpyridine **147**. The kinetic isotope effect studies further disproved the involvement of S_EAr mechanism: in the one-pot arylation reaction of pyridine oxide and pyridine oxide-d_5, a primary KIE of 4.7 was observed, a value incompatible with the electrophilic mechanism, for



Scheme 53 Competitive experiment and kinetic studies of pyridine oxide arylation.



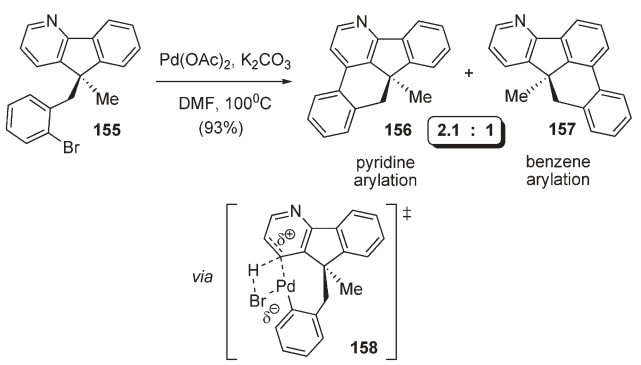
Scheme 54

which loss of proton is not a rate-limiting step (Scheme 53).[15] Although the S_EAr mechanism was disproved, no mechanistic rationale to account for the observed transformation has been proposed.[82]

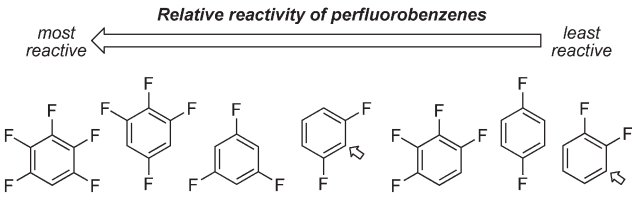
Later, Fagnou extended this methodology for functionalization of diazine *N*-oxides series (Scheme 54).[83] Direct arylation of pyrazine- **148**, pyridazine- **149**, and pyrimidine-containing **150** substrates was performed with a wide range of both electron-rich and electron-deficient aryl-iodides, -bromides and -chlorides. It was also found that addition of catalytic amounts of Cu(I) salts enhances reactivity of low-reactive substrates like pyrimidine *N*-oxides **150**.

Recently, Echavarren also confirmed, that the Pd-catalyzed arylation of pyridine does not operate *via* an electrophilic aromatic substitution mechanism.[84] In this work, an ambident substrate **155** (Scheme 55), which can be intramolecularly arylated at both pyridine and benzene rings, was tested in the arylation reaction conditions. Notably, the reaction yielded regioisomer **156**, resulting from arylation of the pyridine ring as the major product. In other words, substitution mostly occurred at the more electron-deficient pyridine ring, rather than at the more electron-rich benzene. To account for the observed regioselectivity, a concerted proton abstraction mechanism operating *via* a four-membered transition state (**158**, Scheme 55) was proposed.[84,85]

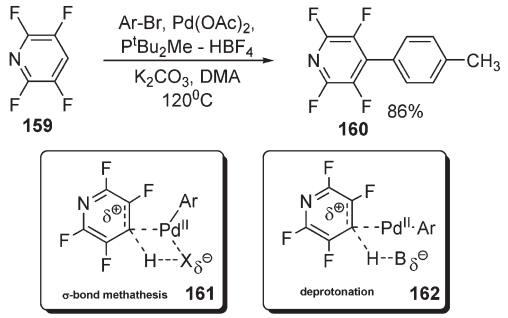
Almost simultaneously, Fagnou disclosed his computational and experimental studies on the arylation of perfluorobenzenes (Schemes 56, 57).[86,87] The computational studies indicated that C–H bond cleavage occurs *via* a concerted mechanism. A complete inversion of the reactivity trend to that expected for the S_EAr mechanism was observed in the arylation of a series



Scheme 55



Scheme 56



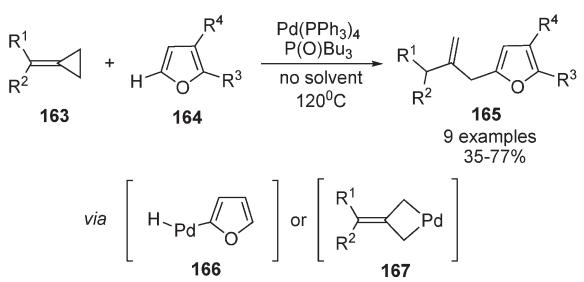
Scheme 57

of perfluorinated aromatics, where more electron-deficient substrates reacted faster (Scheme 56). In addition, in the cases of substrates with more than one C–H bond available, arylation occurred at the most acidic site, which in fluorobenzenes is *ortho* to a fluorine atom.[88] Notably, under these conditions, 2,3,5,6-tetrafluoropyridine **159** was arylated in a very good yield (Scheme 57). Computational studies supported that this selectivity originates not from palladium–fluorine stabilizing interactions, but from the increased C–H acidity. Additionally, primary KIE of 3.0 at C–H bond was observed, indicating the ''kinetic significance'' of the C–H bond cleavage event. It was suggested that this reaction may proceed *via* a concerted palladation and proton abstraction by the halogen anion (intermediate **161**, Scheme 57) at palladium or by an external base (intermediate **162**), analogously to the mechanism proposed by Echavarren[84] (intermediate **158**, Scheme 55).

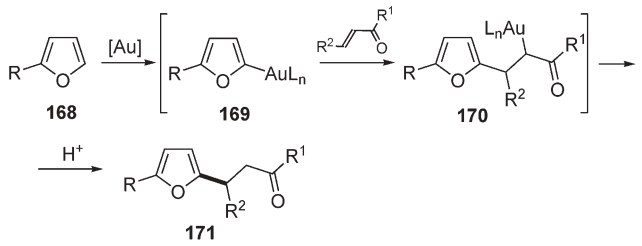
3. Other types of C–H functionalization

3.1 Reactions involving C–C bond formation

Yamamoto reported a mild and regioselective method for Pd-catalyzed hydrofurylation of alkylidenecyclopropanes, which provides access to 2-allyl furans and benzofurans **165** (Scheme 58).[89] It was proposed that this process may operate



Scheme 58



Scheme 59

via two alternative key intermediates; first involving a hydride–palladium intermedíate **166**, and second, a palladocyclobutane **167**, resulting from the insertion of Pd^0 into a distal bond of methylenecyclopropane **163** (Scheme 58).[89]

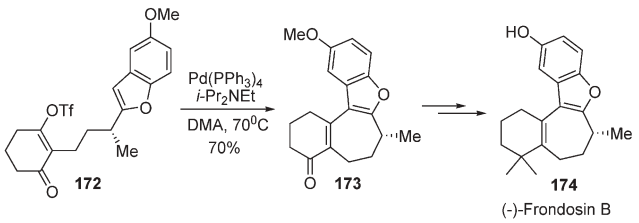
Hashmi found that furans **168** undergo a formal C–H alkylation with α,β-unsaturated ketones in the presence of gold catalyst (Scheme 59).[90] It was suggested that the mechanism might involve activation of the enone by gold followed by an electrophilic aromatic substitution at C-5 position of furan to form a new C–C bond. Alternatively, the process might start with a direct electrophilic metalation of furan to form furyl gold intermediate **169** which, subsequently, undergoes a 1,4-addition to the unsaturated system and protonolysis to give the substituted product **171** (Scheme 59).[90]

Within studies towards the total synthesis of (−)-Frondosin B **174**, Trauner disclosed an intramolecular C–H cross-coupling of a triflate with the benzofuran fragment as a key macrocyclization step. (Scheme 60).[91,92]

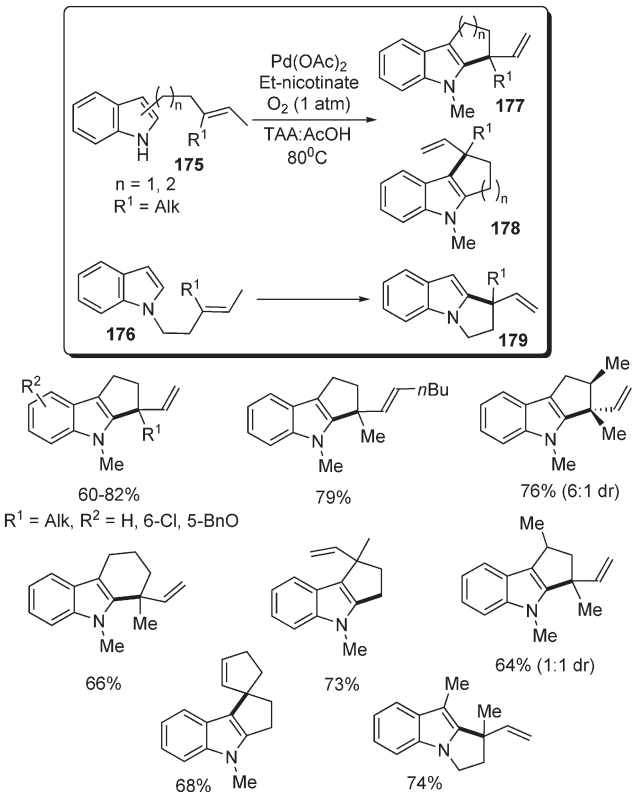
The first method for an oxidative palladium-catalyzed intramolecular formal C–H alkylation of indoles **175** and **176** was reported by Stoltz (Scheme 61).[93] Remarkably, the method allowed the annulation to be performed with good yields in three possible directions: C-2 to C-3 **178**, C-3 to C-2 **177**, and *N* to C-2 **179**. This method allows the construction of 5/5 or 5/6 fused, as well as 5/5-*spiro* skeletons (Scheme 61).[83]

Further, Beccalli developed a protocol for the intramolecular regioselective cyclization of indole carboxamide derivatives **180** into β-carbolinones **182** or pyrazino[1,2-*a*]indoles **181** (Scheme 62).[94,95] It was found that the regiochemistry can be completely controlled by the reaction conditions to allow for either C–H or N–H functionalization selectively or exclusively.

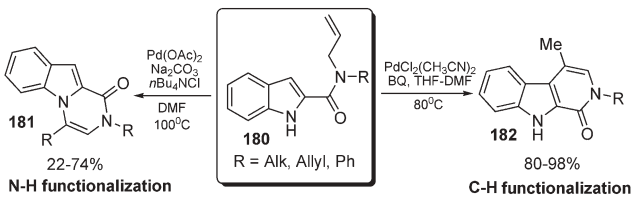
In the course of the investigations of gold- and silver-catalyzed hydroarylation of alkynes **184**, Reetz disclosed examples of an alkyne addition to the furan ring of **183** (Scheme 63).[96] Under mild conditions furan and methylfuran underwent formal C–H vinylation to afford C-2-functionalized products **185** with good selectivity and high yield.



Scheme 60



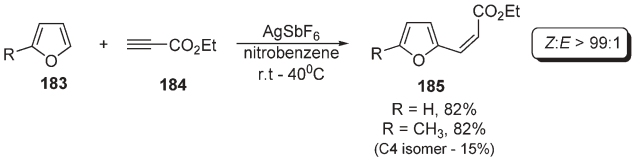
Scheme 61



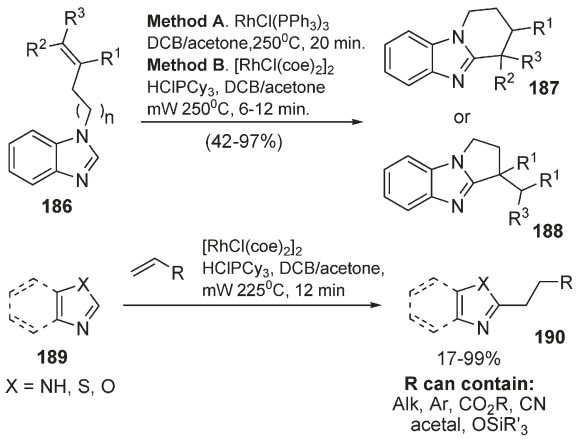
Scheme 62

Bergman and Ellman developed a method for Rh-catalyzed intra- and intermolecular alkylation of azoles and their benzo-analogues (Scheme 64).[97–99] It was demonstrated that the employment of microwave irradiation for intramolecular cyclizations of **186** allows reaction times of less than 20 minutes and for the tricyclic products **187** and **188** to be obtained in good yields. The intramolecular version of this reaction was shown to have excellent functional group tolerance: silyl ethers, acetals, esters, and nitriles were all compatible with this protocol (Scheme 64).[97–99]

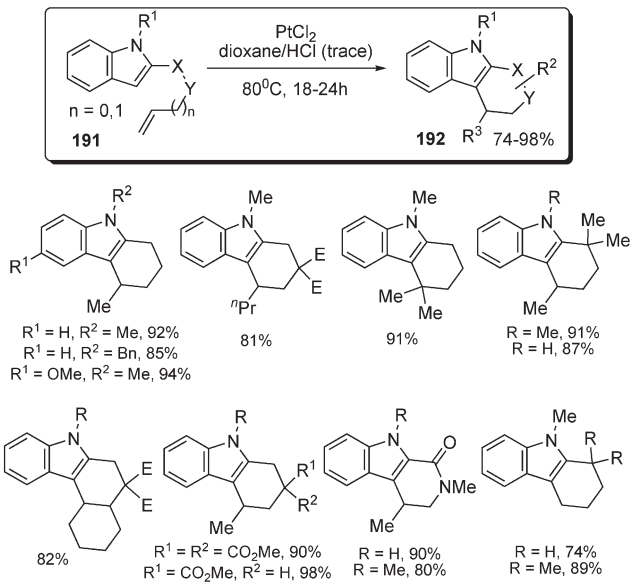
Widenhoefer developed a method for platinum-catalyzed intramolecular alkylation of indoles with tethered unactivated olefins **191** which allowed for construction of tri- and



Scheme 63



Scheme 64

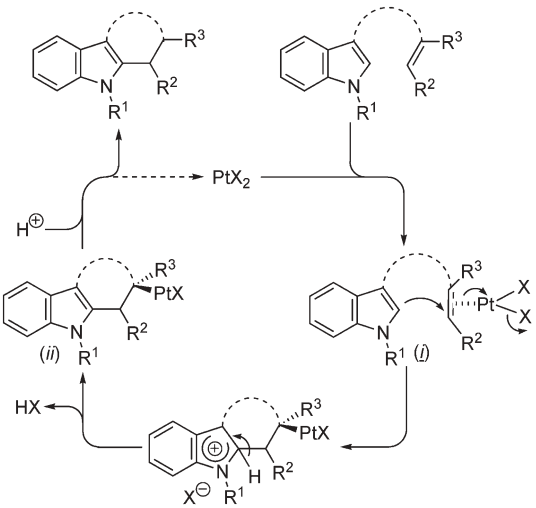


Scheme 65

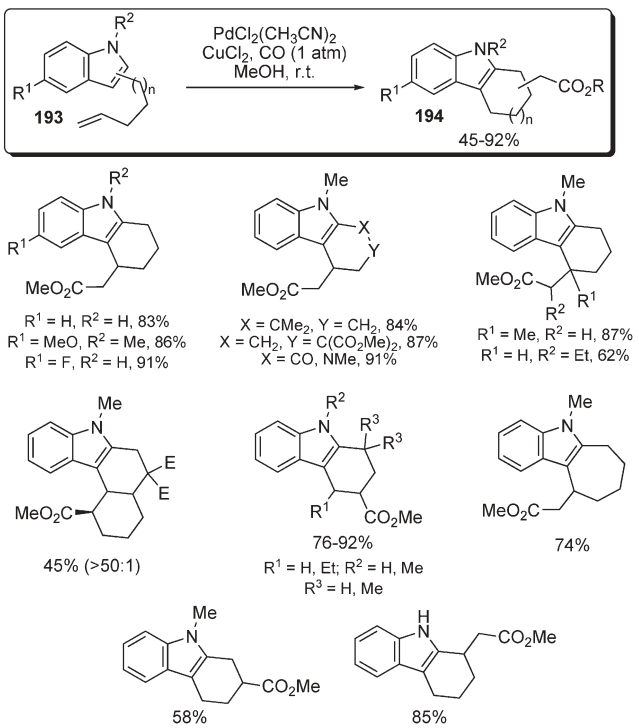
tetracyclic indole-containing structures **192** in excellent yields (Scheme 65).[100] The mechanistic rationale (Scheme 66) involved a nucleophilic attack on a platinum-complexed olefin (*i*) with subsequent protonolysis of the intermediate (*ii*).[100]

Further, Widenhoefer disclosed a palladium-catalyzed protocol for the alkylation/carboalkoxylation of alkenyl-indoles **193** (Scheme 67).[101] The method utilizes a $PdCl_2(CH_3CN)_2$–$CuCl_2$ catalytic system and allows for very mild, selective and high-yielding syntheses of functionalized policyclic indoles **194**. Remarkably, this method represents the first example of transition metal-catalyzed addition of carbonyl group and carbon nucleophile across the double bond of an olefin (Scheme 67).[101]

A method for selective and switchable intramolecular alkenylation of indoles **195** was developed by Gaunt (Scheme 68).[102] It was found that the choice of solvent governs the regioselectivity of this transformation directing it selectively to C-2 or C-3 positions to produce **196** or **197**, respectively. It was rationalized that the mechanism involves an initial electrophilic palladation step at C-3 center with a



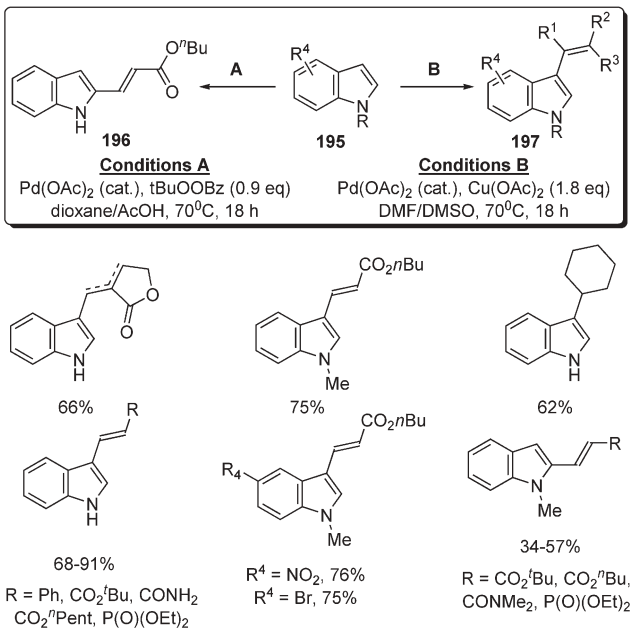
Scheme 66 Generalized mechanistic rationale for intramolecular alkylation of indole with olefins.



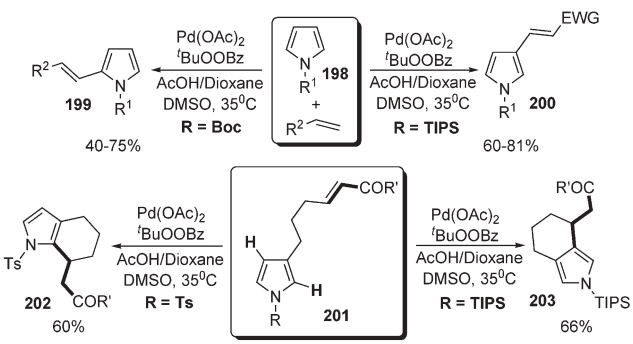
Scheme 67

subsequent solvent-controlled C-3–C-2 migration of the PdX moiety. It was speculated that strongly coordinating solvents such as DMSO or acetonitrile disfavor the migration, thus leading to C-3-regioselectivity, while weakly coordinating solvents, such as 1,4-dioxane, in conjunction with AcOH, facilitate the migration affording the products of C-2 substitution.[102]

Further, Gaunt disclosed a method for C-2 and C-3 regioselective intermolecular C–H alkenylation and annulation of pyrroles **198** and **199** (Scheme 69).[103] Notably, the regiochemistry in this mild and high-yielding aerobic protocol can be completely controlled *via* sterically and electronically



Scheme 68

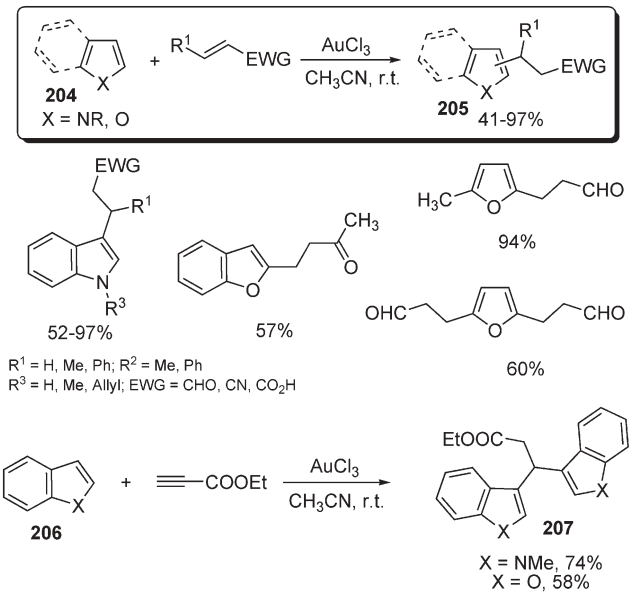


Scheme 69

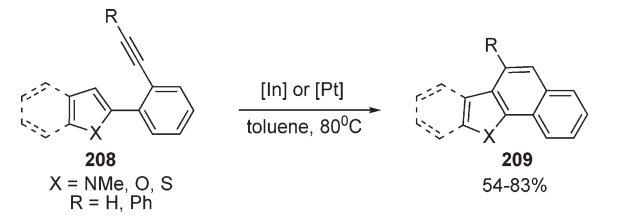
tuned *N*-protecting groups to obtain either C-2 or C-3 functionalized products **199** and **200** selectively. In intramolecular series, introduction of an electron-withdrawing protecting group at **201**, such as *N*-Ac, *N*-Boc, or *N*-Ts results in C-2-substitution to give **202** (electronic control). In contrast, *N*-TIPS pyrroles afford C-4-substituted products **203** exclusively, which was attributed to the shielding effect of sterically-demanding TIPS group, disfavoring C-2-palladation (steric control) (Scheme 69).[103]

The direct C–H addition of heterocycles to electron-deficient olefins in the presence of Au catalysts was investigated by He (Scheme 70).[104] Indoles, furans and benzofurans **204** were shown to undergo the gold(III)-catalyzed formal alkylation with functionalized alkenes and alkynes. Remarkably, this exceptionally mild and high yielding protocol demonstrated excellent functional group tolerance, allowing the production of heterocyclic structures **205** bearing sensitive functionalities, such as aldehyde, carboxylic acid, and nitrile (Scheme 70).[104]

Furstner disclosed a method for platinum- and indium-catalyzed cyclization of **208** leading to the formation of indole, furan and thiophene-containing polycyclic structures **209** in good yields (Scheme 71).[105] The mechanism of this reaction



Scheme 70

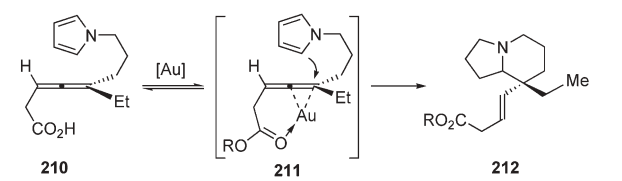


Scheme 71

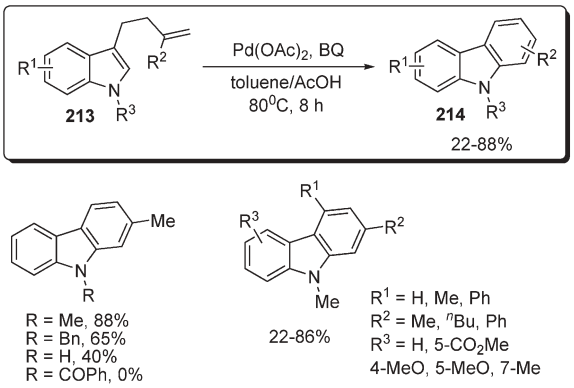
was rationalized in terms of the ability of "soft" metals to render an alkyne electrophilic, susceptible to nucleophilic attack by electron-rich heterocycle.

Nelson, in the context of his efforts towards (−)-rhazinilam, reported an asymmetric gold-catalyzed intramolecular pyrrole addition to enantioenriched allenes **210** leading to the formation of a chiral indolizidine fragment **212** (Scheme 72).[106] Activation of the π-system of the allene by a metal (intermediate **211**) with subsequent intramolecular pyrrole addition resulted in the efficient translation of allene chirality to the quaternary carbon of indolizidine unit (Scheme 72).[106]

Later, Lu reported a method for the synthesis of carbazoles *via* the palladium-catalyzed intramolecular oxidative cyclization of 3-(3′-alkenyl)indoles **213** (Scheme 73).[107] Carbazole ring system **214** formed as a result of 6-*endo*-*trig*-cyclization of the tethered terminal alkene fragment followed by benzoquinone-promoted aromatization. At the same time, substrates with internal double bond were shown to afford only



Scheme 72

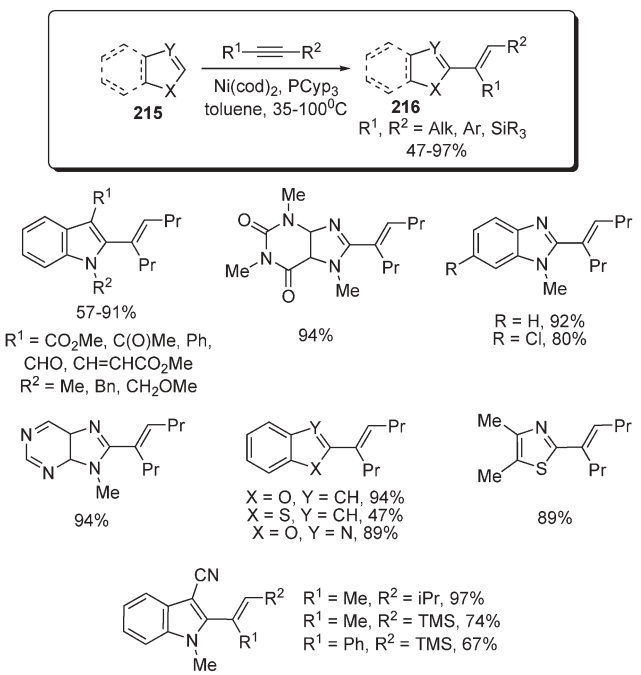


Scheme 73

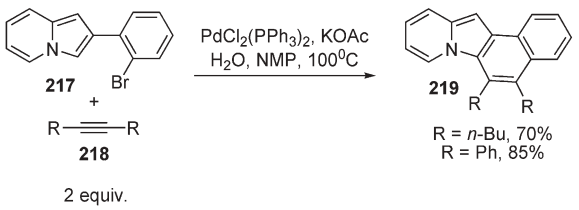
exo-cyclization products. The protocol operates under relatively mild conditions in the presence of $Pd(OAc)_2$ and stoichiometric amount of co-oxidant (Scheme 73).[107]

Very recently, Hiyama reported a versatile method for a nickel-catalyzed alkenylation of diverse heterocyclic systems **215** with alkynes (Scheme 74).[108] A wide range of hetroarenes were shown to be compatible with this remarkably mild and high-yielding protocol. Exceptional functional group tolerance and chemoselectivity were also demonstrated. For example, it was emphasized, the Ar–H bond reacted exclusively over the formyl C–H bond, which is known to undergo addition across an alkyne under Ni/PR_3 catalysis (Scheme 74).[109]

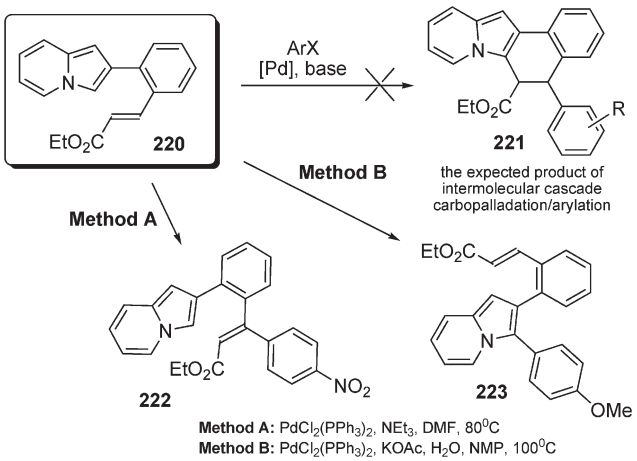
Recently, Gevorgyan developed a series of novel intra- and intermolecular cascade annulations on indole **15** and indolizine substrates **217** and **220**, involving sequential arylation and Heck carbo-palladation steps.[110] Cascade carbopalladation vinylation reaction was demonstrated on the indolizine substrate **217** (Scheme 75).[110] Palladium-catalyzed intramolecular



Scheme 74



Scheme 75



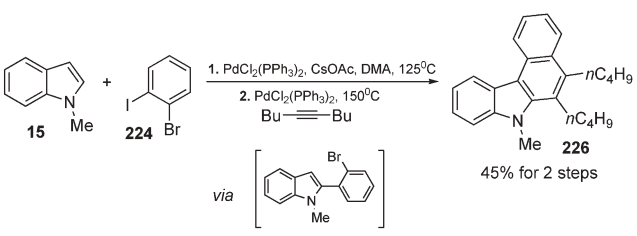
Scheme 76

reaction of 2-(2-bromophenyl)indolizine **217** with internal alkynes resulted in aromatic polycyclic indolizines **219** in high yields (Scheme 75).[110]

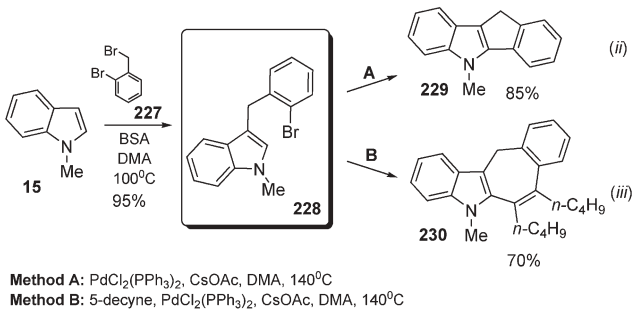
However, the attempts to perform a cascade Heck carbopalladation/formal alkylation on the indolizine substrate **220** to afford the expected tetracyclic indolizine **221** failed (Scheme 76).[110] Nonetheless, it was found that employment of different reaction conditions allowed for highly chemoselective Heck reaction at the alkene moiety (**222**), or arylation of the indolizine ring (**223**).[6]

Another novel process involved a one-pot cascade proceeding *via* a halogen-selective C-2-arylation of indole **15** with **224** to form **226** (Scheme 77), followed by an intramolecular carbopalladation/vinylation sequence to yield benzocarbazole derivative **226** in reasonable overall yield.[110]

3-Benzylindole **228**, readily available from **15** and **227** (Scheme 78), was shown to undergo an intramolecular palladium-catalyzed C-2 arylation forming a tetracyclic indole-containing heterocycle **229** (Scheme 78).[110] It was further demonstrated that, under optimized conditions: in



Scheme 77



Scheme 78

the presence of 5-decyne, a cascade carbopalladation/vinylation reaction takes place affording polycyclic indole **230** with high yield. Mechanistically, this one-pot cascade proceeds sequentially through a Heck carbopalladation of the triple bond followed by an intramolecular vinylation of indole ring to form 7-membered ring of **230** (Scheme 78).[110]

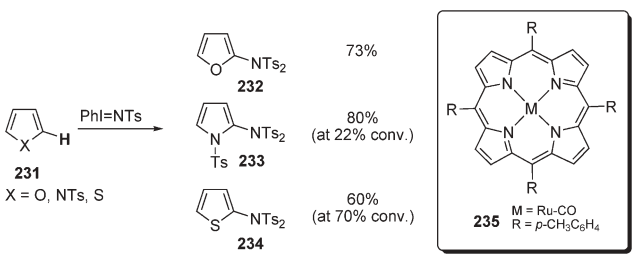
3.2 Reactions involving C–N and C–B bond formation

Che developed a method for the intermolecular amination of C–H bond of heterocycles (Scheme 79).[111,112] In the presence of ruthenium complex **235**, furan, thiophene, *N*-tosyl-pyrrole, as well as their benzo-analogues, afforded the corresponding amino-derivatives **232–234** in high yields. It was suggested, that these reactions might proceed *via* either initial direct nitrene insertion into the activated C–H bond or, alternatively, by aziridination with subsequent re-aromatization.[111,112]

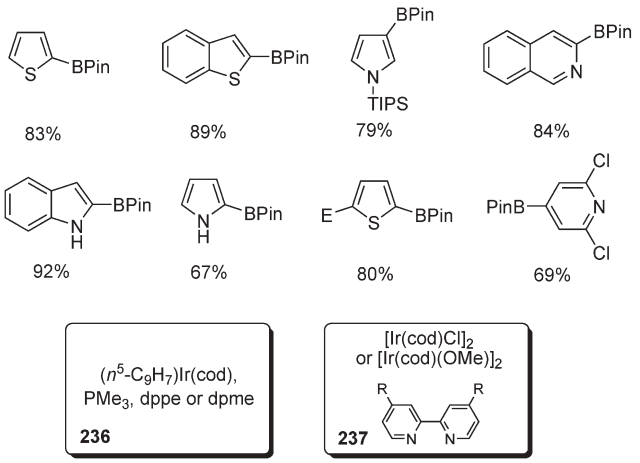
Hartwig demonstrated[115,116] that a variety of heterocycles can serve as excellent substrates for C–H activation/borylation reactions catalyzed by irridium complexes **236** and **237**[114] (Scheme 80).[113] Furans, thiophenes, pyrroles and indoles demonstrated very good C-2 selectivity, at the same time, it was shown that C–H borylation of pyrroles and indoles is not regioselective, though it can be redirected to the C-3 position by introducing a sterically demanding *N*-TIPS group (Scheme 80).[111,116,117]

4. Conclusions

In this review we have outlined the progress made in nearly two decades in the area of direct C–H functionalization of heterocyclic compounds. In spite of the enormous synthetic potential of these methods, most of them still require harsh reaction conditions and exhibit moderate functional group tolerance. In contrast to the well-elaborated methods for



Scheme 79



Scheme 80

functionalization of electron-rich heterocycles, C–H activation of electron-deficient substrates is still in its infancy. However, the latest promising results indicate that this area of chemistry will be rapidly growing. Direct C–H functionalization of heterocycles has already gained widespread acceptance within the synthetic community due to its capacity to utilize simpler and cheaper precursors for construction of complex frameworks. This methodology has already been widely employed in the synthesis of diverse heterocyclic scaffolds, and finds increasing number of applications in the synthesis of complex natural products. Future discoveries promise to add to an already solid methodology of functionalization of electron-rich heterocycles and, we believe, to promote a rapid growth of functionalization of electron-deficient systems.

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