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Recent advances in the synthesis of (hetero)aryl-substituted heteroarenes via transition metal-catalysed direct (hetero)arylation of heteroarene C–H bonds with aryl halides or pseudohalides, diaryliodonium salts, and potassium aryltrifluoroborates

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Abbreviations: Ac, acetyl; Ad, 1-adamantyl; Ar, aryl; Biph, 2-biphenyl; Bn, benzyl; Boc, *tert*-butoxycarbonyl; *i*-Bu, *iso*-butyl; *n*-Bu, *n*-butyl; *t*-Bu, *tert*-butyl; coe, cyclooctene; COX, cyclooxygenase; Cy, cyclohexyl; dba, *trans*,*trans*-dibenzylideneacetone; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DCB, 1,2-dichlorobenzene; DCE, 1,2-dichloroethane; DCH-18-C6, dicyclohexano-18-crown-6; DCM, dichloromethane; DFT, density functional theory; DMA, *N*,*N*-dimetylacetamide; DMF, *N*,*N*-dimethylformamide; DME, dimethoxyethane; DMEDA, *N*,*N*′-dimethylethylene diamine; DMPU, 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidone; DMSO, dimethylsulfoxide; dppb, 1,4-bis(diphenylphosphino)butane; dtbpy, 2,6-di-*tert*-butylpyridine; Et, ethyl; (Het)Ar, (hetero)aryl; IMes, *N*,*N*-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene; KIE, kinetic isotope effect; Me, methyl; MOM, methoxymethyl; NBS, *N*-bromosuccinimide; NHC, *N*-heterocyclic carbene; NMP, *N*-methylpyrrolidinone; Ph, phenyl; PivOH, pivalic acid; *i*-Pr, *iso*-propyl; Py, pyridil; SEM, 2-(trimethylsilyl)ethoxymethyl; TBAF, tetrabutylammonium fluoride; TBS, *tert*-butyldimethylsilyl; Tf, trifluoromethanesulfonyl; TFA, trifluoroacetic acid; TIPS, triisopropylsilyl; TMHD, 2,2,6,6-tetramethyl-3,5-heptadienoate; Ts, *p*-toluenesulfonyl.

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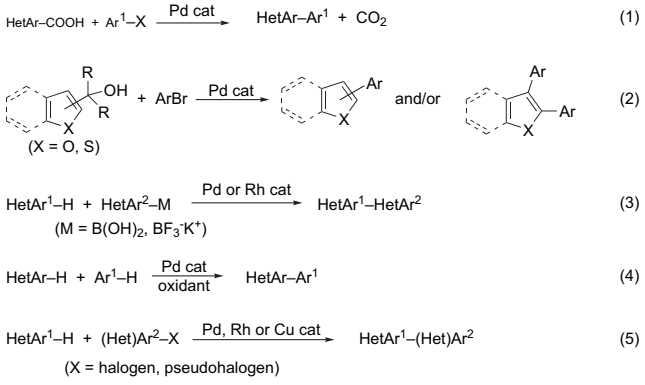
1. Introduction

(Hetero)aryl groups directly connected by single Csp^2–Csp^2 bonds to heteroaryl moieties are present as core structures in many biologically active compounds,[1] naturally-occurring substances,[2] agrochemicals,[3] and optical and photochromic materials in polymer science.[4] As a consequence, particular interest has been paid to devise highly efficient, regio- and chemoselective methods to form (hetero)aryl–heteroaryl C–C bonds.

Until the late 1980s, the transition metal-catalysed cross-coupling reactions between (hetero)aryl halides or pseudohalides and (hetero)arylmetal derivatives, including (hetero)arylboronic acids, (hetero)arylzinc reagents, (hetero)aryltin derivatives, (hetero)arylsilicon compounds, and (hetero)aryl Grignard reagents represented the most effective methodology for the synthesis of arylheteroarenes and unsymmetrical biheteroaryls and these reactions still represent a versatile, very useful tool for the preparation of these compounds.[5] Nevertheless, they are unfavourable from the point of view of the cost and atom-economy since they require that activating groups must be present on both coupling partners. Thus, in the past few decades some new, more eco-friendly and economic methodologies have been designed and investigated (Scheme 1). In most of them, the preparation and use of stoichiometric amounts of organometallic reagents are avoided and so the number of the reaction steps is reduced.



Scheme 1. New methodologies for the synthesis of (hetero)aryl-substituted heteroarenes.

A recently introduced interesting approach consists of a decarboxylative cross-coupling between a heteroaryl carboxylic acid and an aryl halide (Eq. 1, Scheme 1).[6] The regioselectivity of this reaction, which produces carbon dioxide as waste, is ensured by the carboxylic acid functionality. On the other hand, arylfuran and aryl(benzo)thiophene derivatives have recently been synthesised by palladium-catalysed cleavage of C–H and C–C bonds of α,α-disubstituted furyl- and (benzo)thienylmethanol derivatives, respectively, with aryl halides (Eq. 2, Scheme 1).[7] Very recently, it has also been reported that heteroarene C–H bonds can be transformed into heteroaryl–aryl C–C bonds via palladium- or rhodium-catalysed reaction with arylboronic acids or (hetero)aryl trifluoroborates (Eq. 3, Scheme 1).[8] An appealing and highly advantageous alternative to all these approaches, which enables the simultaneous functionalisation of Csp^2–H bonds of heteroarenes and arenes, involves the palladium-catalysed cross-dehydrogenative coupling of five-membered heteroarenes and some of their benzocondensed derivatives with benzene, monosubstituted, and 1,4-disubstituted benzene derivatives (Eq. 4, Scheme 1).[9] However, despite this approach can providing arylheteroarenes in satisfactory yields, with no products arising from arene or heteroarene homocoupling, its utility for the efficient and highly regioselective preparation of a wide range of classes of arylheteroarenes has yet to be explored.

In the last two decades, much more attention has been paid to the synthesis of arylheteroarenes and unsymmetrical biheteroaryls via transition metal-catalysed non-chelation assisted direct (hetero)arylation of heteroarene C–H bonds with (hetero)aryl halides or pseudohalides (Eq. 5, Scheme 1) and, at present, this approach has emerged as the most developed type of C–H bond functionalisation of heteroarenes. One of the first examples demonstrating the feasibility of this approach was published by Nakamura, Tajima and Sakai in 1982.[10] Since then, the field of transition metal-catalysed direct inter- and intramolecular arylation of electron-rich and electron-deficient heteroarenes has undergone rapid growth. Interestingly, much of this chemistry has been developed with the use of palladium catalysts.

Some reviews published in the early 2000s summarise the progress achieved in this field in the 1990s[11] and the increasing frequency with which transition metal-catalysed direct (hetero)arylation reactions with (hetero)aryl halides or pseudohalides, involving the use of new catalyst systems and new substrates, have been developed and applied in a wide array of settings has been documented in the excellent reviews published in 2006 by Fagnou,[12a] in 2007 by Miura,[13] Fagnou,[12b] Gevorgyan,[13c] and Lautens,[14a] and more recently in three chapters of a book on the modern arylation methods edited by Ackermann,[14b] in which, however, literature data on the direct (hetero)arylation of heteroarenes published until 2007 have been partly reported. These reviews include synthetic aspects and mechanistic considerations of these catalytic reactions capable of activating unreactive Csp^2–H bonds of heteroarenes.

This critical review aims to complete the picture of the studies in this hot area of research, also outlining the contribution of our research group in devising new and convenient protocols for the direct inter- and intramolecular (hetero)arylation of a broad spectrum of five-membered heteroarenes with (hetero)aryl halides. Significant results that have been considered partly or have not been summarised and discussed in the above mentioned reviews[11–14] have also been highlighted in this article, which covers developments appeared from January 2006 until the end of February 2009. A major emphasis has been put on the synthetic aspects of the various direct inter- and intramolecular arylation protocols, but significant mechanistic proposals have also been shortly reported and discussed.

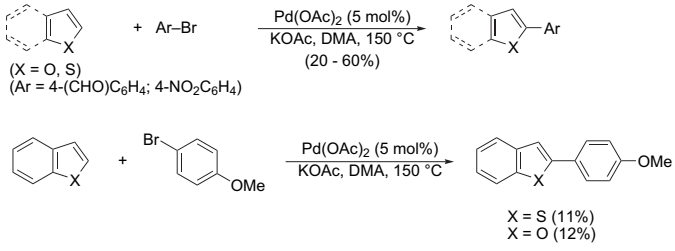
For the sake of clarity, the scientific literature of this review with 475 references has been subdivided into four sections: i) intermolecular direct (hetero)arylation of five-membered heteroarenes with one heteroatom; ii) intermolecular direct (hetero)arylation of five-membered heteroarenes with two and three heteroatoms; iii) intermolecular direct (hetero)arylation of six-membered heteroarenes; and iv) synthesis of fused-ring heteroarenes via intramolecular direct (hetero)arylation of heteroarenes containing a (hetero)aryl halide tether. It is also worth noting that the Conclusions section includes literature references concerning the major developments in the area of this review, which appeared from March to June 2009. However, the patent literature has been mentioned only occasionally.

2. Intermolecular direct (hetero)arylation of five-membered heteroarenes with one heteroatom

2.1. (Hetero)arylation of thiophene, benzothiophene, thieno[2,3-*b*]thiophene, furan, and benzofuran ring systems

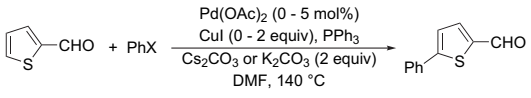
(Hetero)arylthiophenes have attracted remarkable attention as important structural elements in biologically active compounds and in materials showing conductive, semiconductive, non-linear, and liquid crystalline characteristics.[15] On the other hand, 2-arylbenzothiophene derivatives have proven to be promising agents for the treatment of diseases such as hypolipemia and estrogen-dependent diseases.[16]

The palladium-catalysed direct arylation of thiophene, benzothiophene, furan, and benzofuran with aryl bromides under ligandless conditions was first reported by Ohta and co-workers in 1990.[17] Electron-deficient aryl bromides were found to give C-2 arylated compounds in low to moderate yields and 4-bromoanisole, a deactivated aryl bromide, was shown to undergo reactions with benzofuran and benzothiophene to provide the corresponding C-2 arylated products in 12 and 11% yield, respectively (Scheme 2).[17] In 1992, the same authors investigated the palladium-catalyed C-2 arylation of furan, benzofuran, thiophene, benzothiophene, and 1,4-dimethyl-1*H*-imidazole with pyrazinyl chlorides and found that the required C-2 aryl-substituted heterocycles could be obtained in moderate-to-good yields using $Pd(PPh_3)_4$ as the catalyst precursor, AcOK as the base, and DMA as the solvent.[18] In subsequent years, significant contributions to the development of efficient protocols for the regioselective palladium-catalysed direct arylation of sulfur- and oxygen-containing five-membered heterocycles and their benzocondensed derivatives with aryl halides were given by the research groups of Miura,[19] Lemaire,[20] and Mori.[21]



Scheme 2. $Pd(OAc)_2$-catalysed C-2 arylation of thiophene, benzothiophene, furan, and benzofuran with aryl bromides under ligandless conditions.

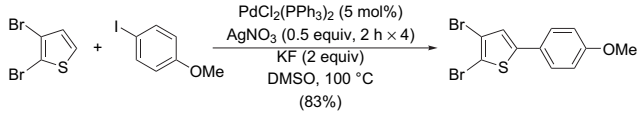
Especially noteworthy is the discovery by Miura's group that the addition of CuI to the palladium catalyst precursor increases the yield of the arylated derivatives obtained by treatment of iodo- or bromobenzene with 2-thiophene carbaldehyde (Scheme 3) and azoles including 1-methyl-1*H*-benzimidazole, benzothiazole, and benzoxazole.[19]



X	$Pd(OAc)_2$ (mol%)	CuI (mol%)	Base	Yield (%)
I	5	–	Cs_2CO_3	12
I	5	2	Cs_2CO_3	82
Br	5	2	K_2CO_3	57
I	–	2	Cs_2CO_3	0

Scheme 3. Pd-catalysed C-5 arylation of 2-thiophene carbaldehyde.

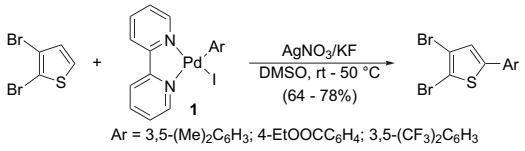
Mori and co-workers also found that C–H arylation reactions of 2-thiophene carbaldehyde, thiophene and benzothiophene with aryl iodides are efficiently catalysed by a Pd(II) complex in the presence of an $AgNO_3$/KF system or AgF.[21] Moreover, these authors observed that fractional addition of the additives remarkably improved the yield of the arylation reactions.[21c] Although the yield of the C-5 palladium-catalysed arylation of 2,3-dibromothiophene with 4-iodoanisole was only 41% by the addition of $AgNO_3$ (1 equiv) in one portion, the addition of $AgNO_3$ in four portions (0.5 equiv×4), namely one portion every 2 h improved the yield to 83% (Scheme 4).[21c]



Scheme 4. Pd-catalysed C-5 arylation of 2,3-dibromothiophene with 4-iodoanisole.

Remarkably, the C–H arylation proceeded smoothly and occurred without affecting the bromo groups of the substrate. A high yield (79%) was also obtained when the reaction of 2,3-dibromothiophene with 4-iodoanisole was performed in the presence of 5 mol % $PdCl_2(PPh_3)_2$, 1.0 equiv of $AgNO_3$ and 1.5 equiv of TBAF in DMSO at 100 °C for 5 h.[21c] Analogously, the C–H arylation of 2-bromothiophene with aryl iodides took place in the presence of a palladium catalyst and $AgNO_3$/KF or AgF to give 2-bromo-5-arylthiophenes.[21b]

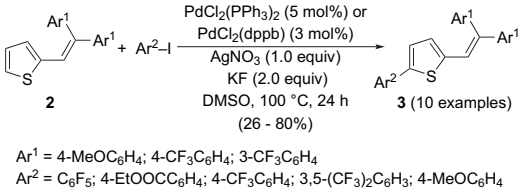
In 2006, Mori and co-workers reported that the $AgNO_3$/KF system also induces the C–H arylation of 2,3-dibromothiophene with aryl(iodo)palladium(II)(2,2′-bipyridine)complex **1** in 64–78% yield (Scheme 5).[22]



Scheme 5. C-5 arylation of 2,3-dibromothiophene with complex **1**.

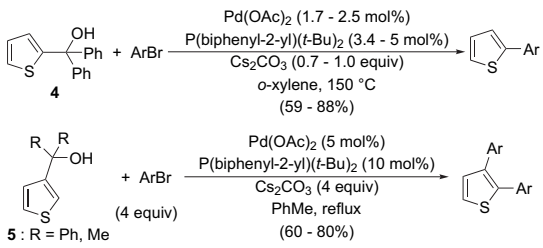
They interpreted this result by supposing that the palladium-catalysed C-5 arylation of bromothiophene derivatives proceeds through electrophilic substitution of complex **1** triggered by the $AgNO_3$/KF system to give an aryl(thienyl)palladium(II) complex, which undergoes reductive elimination to provide the C–H arylation product.[22]

More recently, the palladium-catalysed C–H arylation in the presence of the $AgNO_3$/KF system as an activator has been utilised to prepare a variety of 2,5-disubstituted thiophene derivatives **3** in moderate-to-good yields from trisubstituted ethenes **2** and aryl iodides (Scheme 6).[23] Interestingly, the reactions with aryl iodides bearing an electron-withdrawing substituent were found to proceed in a relatively higher yield than the reactions involving aryl iodides bearing an electron-donating group.



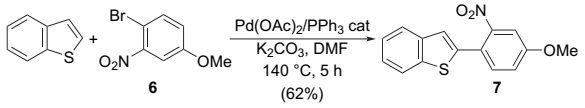
Scheme 6. Pd-catalysed synthesis of 2,5-disubstituted thiophenes **3**.

In 2006, Miura and co-workers established that, in contrast to the reaction between diphenyl(thiophen-2-yl)methanol (**4**) with aryl bromides in *o*-xylene at 150 °C in the presence of Cs_2CO_3 as the base and catalytic amounts of $Pd(OAc)_2$ and the sterically hindered electron-rich P(biphen-2-yl)(*t*-Bu)$_2$ ligand, which produces 2-arylthiophenes in high yields,[19c] treatment of α,α-disubstituted 3-thiophenemethanols **5** with a molar excess of aryl bromides under similar experimental conditions gives 2,3-diarylthiophenes in good yields via cleavage of the C–H and C–C bonds of the 2- and 3- position of compounds **5**, respectively (Scheme 7). Thus, the tertiary alcohol at C-2 in compound **4** and at C-5 in compounds **5** served as a masked group of the corresponding C–H bonds.



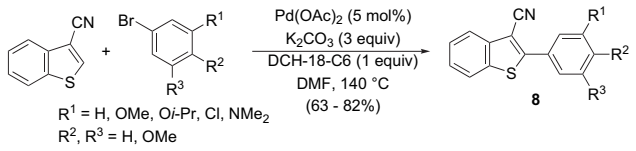
Scheme 7. Synthesis of 2-aryl- and 2,3-diarylthiophenes from compounds **4** and **5**, respectively.

In the same year, Lemaire and co-workers synthesised 2-(4-methoxy-2-nitrophenyl)benzothiophene (**7**) in 62% yield by direct C-2 arylation of benzothiophene with bromide **6** in the presence of a $Pd(OAc)_2/PPh_3$ catalyst system and K_2CO_3 as the base (Scheme 8).[24]



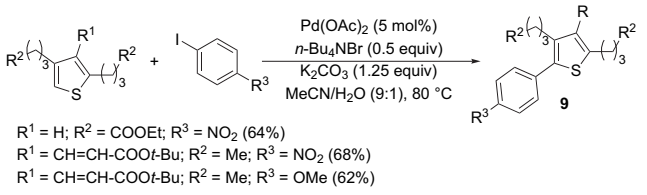
Scheme 8. C-2 Arylation of benzothiophene with bromide **6**.

Lemaire also prepared a variety of 2-aryl-3-cyanobenzothiophenes **8** by the reaction of 3-cyanobenzothiophene with a slight molar excess of aryl bromides in the presence of catalytic amounts of $Pd(OAc)_2$, a molar excess of K_2CO_3, and the crown ether DCH-18-C6 in DMF at 110 °C (Scheme 9).[25] Compounds **8** were then used as precursors to new benzo[*c*]thiophene[2,3-*e*]azepine derivatives possessing potential biological properties.[25] A variety of compounds **8** had previously been synthesised in satisfactory yields via C-2 arylation of 3-cyanobenzothiophene with aryl bromides and iodides in the presence of *n*-Bu$_4$NBr, a catalytic quantity of $Pd(OAc)_2$, and a molar excess of K_2CO_3 as the base in DMF at 90 °C under ligandless conditions.[20f]



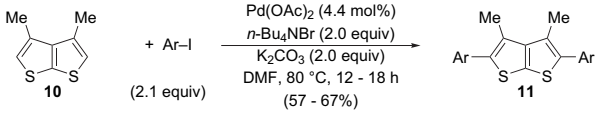
Scheme 9. Synthesis of 2-aryl-3-cyanobenzothiophenes **8**.

A small modification of this protocol involving the use of a mixture of MeCN and water as the reaction solvent in place of DMF was subsequently employed by Lautens and co-workers for the direct C-2 arylation of selectively substituted thiophenes with aryl iodides (Scheme 10).[26] Tri- and tetrasubstituted thiophenes **9** were so prepared in satisfactory yields.



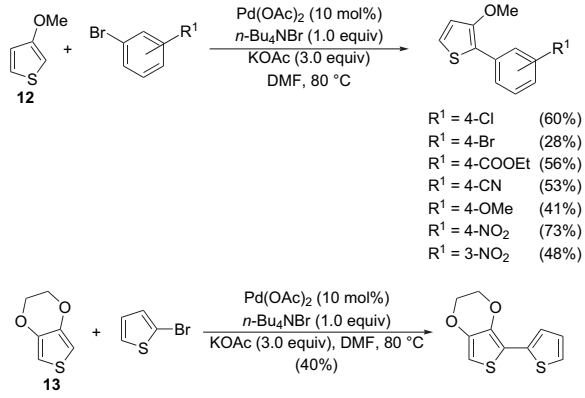
Scheme 10. Synthesis of tri- and tetrasubstituted thiophenes **9**.

$Pd(OAc)_2$-catalysed direct C–H arylation reactions in the presence of *n*-Bu$_4$NBr were also employed by Mashraqui and co-workers to prepare the first examples of 2,5-diaryl-3,4-dimethoxythieno[2,3-*b*]thiophenes **11** from 3,4-dimethoxythieno[2,3-*b*]thiophene **10** and both electron-deficient and electron-rich aryl iodides (Scheme 11).[27]



Scheme 11. Synthesis of 2,5-diaryl-3,4-dimethoxythieno[2,3-*b*]thiophenes **11**.

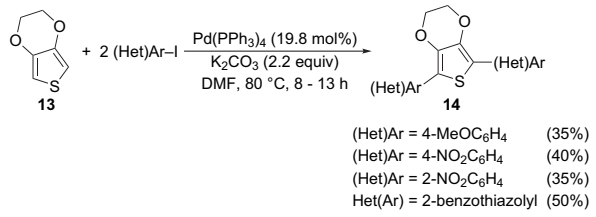
Similar reaction conditions, in which, however, KOAc was used instead of K_2CO_3 as the base, were employed by Borghese and co-workers for the direct C-2 arylation of 3-methoxythiophene (**12**) and 3,4-ethylenedioxythiophene (**13**) (EDOT) with aryl halides in moderate to satisfactory yields (Scheme 12).[28] Noteworthy, the arylation reactions of **12** with functionalised aryl bromides were found to be highly regioselective.



Scheme 12. C-2 arylation of compounds **12** and **13**.

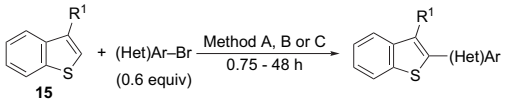
The palladium-catalysed direct C–H arylation of EDOT, which is a building block frequently used in the field of new organic materials,[29] was also investigated by Mohanakrishnan and co-workers.[30] They prepared C-2 monoarylated EDOT derivatives in moderate yields by the treatment of **13** with equimolar amounts of electron-deficient (hetero)aryl iodides or bromides in DMF at 80 °C in the presence of a slight molar excess of K_2CO_3 and a catalytic amount of $Pd(PPh_3)_4$.[30b]

On the other hand, 2,5-di(hetero)arylated EDOT derivatives **14** were obtained in 35–50% yield by reaction of **13** with 2 equiv of (hetero)aryl iodides in DMF at 80 °C in the presence 2.2 equiv of K_2CO_3 and 19.8 mol % $Pd(PPh_3)_4$ (Scheme 13).[30b]

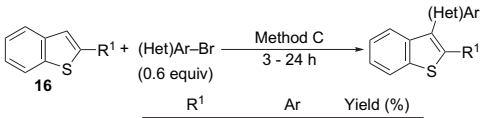


Scheme 13. Synthesis of 2,5-di(hetero)arylated EDOT derivatives **14**.

In 2007, Pellet-Rostaing and co-workers investigated the palladium-catalysed C–H arylation of both 2- and 3-functionalised benzothiophenes with (hetero)aryl bromides in the presence of different additives: 1 equiv of *n*-Bu_4NBr (Method A), 1 equiv of DHC-18-C6 (Method B) or a catalytic quantitity of PPh_3 (Method C).[31] Representative examples of C-2 arylations of 3-functionalised benzothiophenes **15** and C-3 arylations of 2-functionalised benzothiophenes **16** with (hetero)aryl bromides according to Methods A–C are illustrated in Scheme 14. In general, arylations at position 3 of benzothiophenes **16** gave the required products in higher reaction times and lower yields than arylations at position 2 of compounds **15**. Interestingly, Methods A and B were also employed for the synthesis of 3-functionalised 2-arylthiophenes **18** by C-2 arylation of 3-functionalised thiophenes **17** (Fig. 1).[31] On the other hand, 3-functionalised 2,5-diarylthiophenes **19** (Fig. 1) were prepared from compounds **17** via a one-pot process involving the use of Method B or C-5 arylation of compounds **18** according to Method C.[31]



Method	R^1	Ar	Yield (%)
A	CHO	Ph	47
A	CHO	4-$MeOC_6H_4$	64
A	CHO	4-$CF_3C_6H_4$	70
C	CHO	3-Py	51
B	CN	4-ClC_6H_4	68
C	OMe	2-Py	18
B	OCH_2CF_3	2-(CN)C_6H_4	76



R^1	Ar	Yield (%)
CN	3-Py	17
CN	4-$CF_3C_6H_4$	67
OCH_2CF_3	3-Py	34
OCH_2CF_3	2-(CN)C_6H_4	69

Scheme 14. Pd-catalysed C-2 and C-3 arylation of compounds **15** and **16**, respectively, according to methods described in the text.

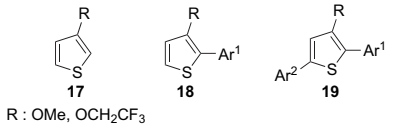
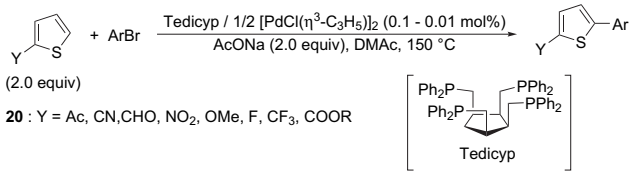


Figure 1. Structures of compounds **17**–**19**.

The arylated benzothiophenes and thiophenes synthesised in this study were then evaluated on bacteria strains. Most of them did not exhibit any antibiotic activity, but were found to selectively inhibit the NorA multidrug transporter of *Staphylococcus aureus*.[31]

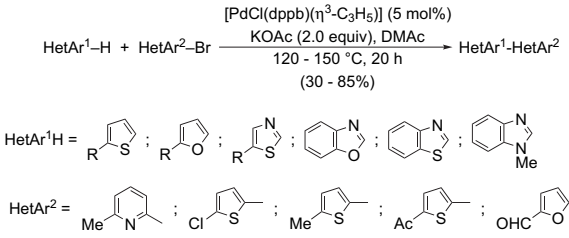
In 2008, palladium bis(2,2,6,6-tetramethyl-3,5-heptadienoate) was employed as the catalyst precursor for the C-2 arylation of benzothiophene with aryl iodides in modest yields.[32] This complex also proved to be active for the regioselective C-2 arylation of other electron-rich heteroarenes, including 1-methyl-1*H*-imidazole, 1-methyl-1,2,4-triazole, and caffeine.[32]

Doucet, Santelli and co-workers[33] had previously found that the catalyst system composed of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ and the unusual ligand, *cis*,*cis*,*cis*-1,2,3,4-tetrakis(diphenylphosphinomethyl)cyclopentane (Tedicyp) is able to promote the direct C-5 arylation of a variety of 2-substituted thiophene derivatives **20** with electron-deficient, electron-rich or sterically congested aryl bromides in good yields also using very low catalyst loadings (Scheme 15). The most reactive aryl bromides were coupled with thiophene derivatives using as little as 0.1–0.001 mol% catalyst.[33] Interestingly, very low loadings of the $[PdCl(\eta^3\text{-}C_3H_5)]_2$/Tedicyp catalyst system also enabled the direct C-5 arylation of 2-substituted furans with aryl bromides.[34] NMR studies revealed that the transition metal circulates around the four phosphorus atoms of Tedicyp and this might account for an easy reductive elimination step in the catalytic cycle and thus a high turnover.[34]



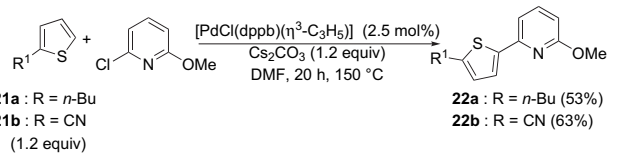
Scheme 15. $[PdCl(\eta^3\text{-}C_3H_5)]_2$/Tedicyp-catalysed C-5 arylation of 2-substituted thiophenes with aryl bromides.

Since the use of a phosphine ligand such as Tedicyp seemed to increase the longevity and stability of the palladium catalyst system, Doucet and co-workers thought it is right to examine the use of a bidentate phosphine ligand for the palladium-catalysed heteroarylation of heteroaromatics including 2-substituted furan, thiazole and thiophene derivatives, benzoxazole, benzothiazole, and 1-methyl-1*H*-benzimidazole with heteroaryl halides. Recently, these authors reported that the use of the air-stable complex $[PdCl(dppb)(C_3H_5)]$ as a catalyst precursor allows the heteroarylation of the above mentioned heteroarenes with heteroaryl bromides in moderate-to-good yields (Scheme 16).[35]



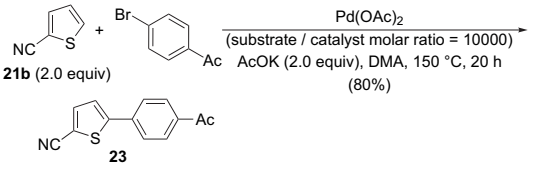
Scheme 16. $[PdCl(dppb)(C_3H_5)]$-catalysed heteroarylation of five-membered heteroarenes with heteroaryl bromides.

Moreover, very recently, this complex has been used as the catalyst for the regioselective heteroarylation of a range of heteroaryl derivatives, including 2-cyano- and 2-butylthiophene, 2-propylthiazole, 2-methyl-4-methylthiazole, benzoxazole, and benzothiazole both with chloropyridines and chloroquinolines in low to high yields.[36] The reaction conditions used for the C-5 arylation of 2-butyl- and 2-cyanothiophene, **21a** and **21b**, respectively, with 2-chloro-6-methoxypyridine are reported in Scheme 17. Compounds **22a** and **22b** were so obtained in 53 and 63% yield, respectively.



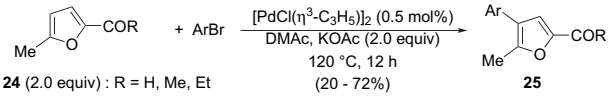
Scheme 17. Pd-aatalysed C-5 arylation of compounds **21a**,**b** with 2-chloro-6-methoxypyridine.

It is also worth noting that investigations recently carried out by Doucet and co-workers have revealed that also $Pd(OAc)_2$ is a suitable catalyst precursor for the direct C-5 arylation of 2-butylfuran, 2-butylthiophene, 2-methyl-3-methoxycarbonylfuran, and 2-*n*-propylthiazole under ligandless conditions.[37] However, the efficiency of this system has been found to be limited to reactions with activated aryl bromides and does not seem to be appropriate for reactions involving heteroaryl bromides. Nevertheless, the successful reactions can be performed with as little as 0.01 mol% catalyst.[38] The high-yielding synthesis of compound **23** by C-5 arylation of 2-cyanothiophene (**21b**) with 4-bromoacetophenone is illustrated in Scheme 18. This synthesis occurred with a TON of 8000.[37]



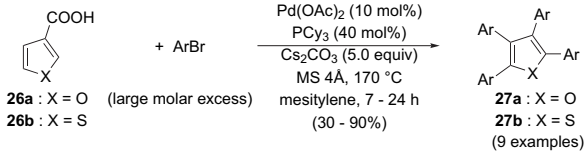
Scheme 18. $Pd(OAc)_2$-catalysed synthesis of compound **23** under ligandless conditions.

Compared to the vast amount of research on the palladium-catalysed direct arylation reactions of sulfur-containing five-membered heteroarenes, there are fewer studies dealing with furans, which have been published in the period January 2006–February 2009. In 2008, Guttumukkala and Doucet reported that, despite the fact that palladium-catalysed (hetero)arylation of five-membered heteroarenes with one heteroatom usually occurs at the α-position to the heteroatom, 2-methyl-5-acylfurans **24** undergo C-4 arylation with activated aryl bromides in DMA at 120 °C in the presence of KOAc as the base and a catalytic amount of commercially available $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (Scheme 19).[38] The procedure, which is tolerant to a wide variety of functional groups on the aryl bromide [e.g., 4-CN, 4-F, 4-EtCO, 3-CN, 3,5-$(CF_3)_2$, and 4-Ac], furnished C-4 arylated furans **25** in modest to satisfactory yields.[38]



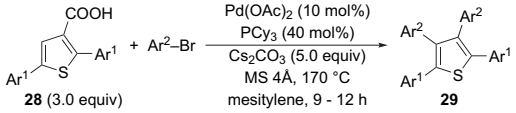
Scheme 19. Pd-catalysed C-4 arylation of 2-methyl-5-acylfurans.

In continuation of his studies on the multiple arylation of five-membered heteroarenes with one heteroatom,[19] Miura in 2008 demonstrated that 3-furancarboxylic acid (**26a**) and its thiophene analogue **26b** undergo a unique perarylation reaction, involving cleavage of three C–H bonds and decarboxylation, upon treatment with 5–8 equiv of aryl bromides in the presence of a $Pd(OAc)_2/PCy_3$ catalyst system and Cs_2CO_3 as the base to give the corresponding tetraarylated products **27a** and **27b**, respectively, in modest to good yields (Scheme 20).[39]



Scheme 20. Perarylation of compounds **26a** and **26b**.

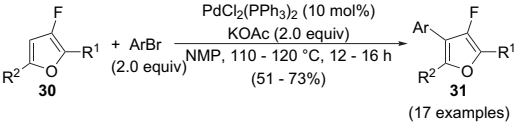
The synthesis of tetraarylthiophenes **29** by palladium-catalysed diarylation of 2,5-diaryl-3-thiophenecarboxylic acids **28** with aryl bromides was also described (Scheme 21).[39]



Ar^1	Ar^2	Yield (%)
Ph	4-$MeOC_6H_4$	47
4-$MeOC_6H_4$	Ph	48
Ph	4-$CF_3C_6H_4$	57
4-$MeOC_6H_4$	4-$CF_3C_6H_4$	69

Scheme 21. Pd-catalysed reaction of 2,5-diaryl-3-thiophenecarboxylic acids with aryl bromides.

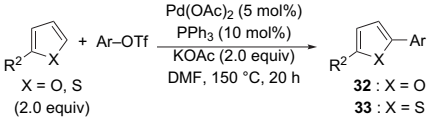
Very recently, Zhu and co-workers have described that the direct C-4 arylation of 2,5-disubstituted 3-fluorofurans **30** with a variety of aryl bromides in NMP at 110–120 °C in the presence of KOAc as the base and a catalytic quantity of $PdCl_2(PPh_3)_2$ is facilitated by the neighboring effect of the fluorine atom and provides tetrasubstituted monofluorofurans **31** in moderate-to-good yields (Scheme 22).[40]



Scheme 22. C-4 Arylation of 2,5-disubstituted 3-fluorofurans **30** with aryl bromides.

It has also been shown that 2-substituted heteroarenes, including 2-substituted furan, thiophene, thiazole, benzoxazole, and benzothiazole derivatives, are able to undergo palladium-catalysed direct C-5 arylation with aryl triflates,[19,41] an important class of electrophiles, which can be easily synthesised from the corresponding phenols. The arylation reactions using these electrophiles, which were carried out in the presence of KOAc as the base, DMF as the solvent and a $Pd(OAc)_2/PPh_3$ catalyst system, occurred in modest-to-satisfactory yields.[41a] Interestingly, the electronic properties of the aryl triflates proved to have a decisive influence on the yields of the arylation reactions. In fact, electron-rich aryl triflates gave satisfactory yields, but the electron-poor counterparts led to the formation of phenols.[41a]

The synthesis of 2-substituted furans and thiophenes, **32** and **33**, respectively, by palladium-catalysed C-5 arylation with aryl triflates is illustrated in Scheme 23.

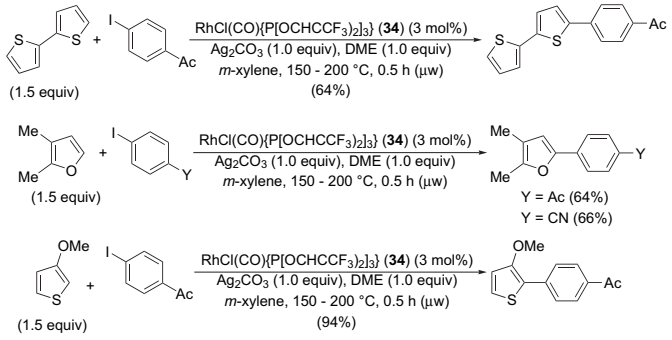


X	R^1	Ar	Yield (%)
O	$MeCOCH_2$	Ph	28
O	*n*-Bu	Ph	51
O	*n*-Bu	2-Naphthyl	53
S	*n*-Bu	Ph	69
S	CN	Ph	64
S	CN	4-*t*-BuC_6H_4	64

Scheme 23. C-5 arylation of 2-substituted furans and thiophenes with aryl triflates.

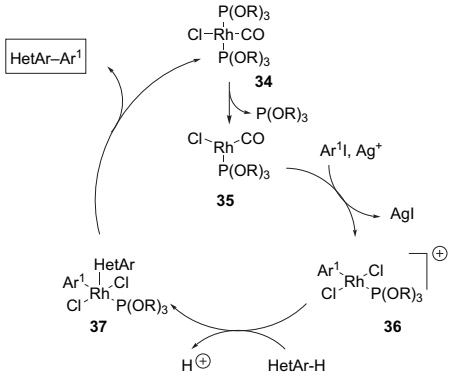
The regioselective direct arylations of five-membered heteroarenes with one heteroatom has also been achieved by the use of rhodium catalysts. In 2006, Itami and co-workers reported in a short communication that thiophene, furan and *N*-substituted pyrrole and indole derivatives can be arylated with aryl iodides in

m-xylene under microwave irradiation with the in the presence of $AgNO_3$ and DME and a catalytic amount of RhCl(CO)-{P[OCH(CF$_3$)$_2$]$_3$}$_2$ (**34**) to furnish the required α-arylated derivatives in good to excellent yields and with complete regioselectivity.[42] The use of the π-accepting phosphite ligand P[OCH(CF$_3$)$_2$]$_3$ was found to be critical for obtaining high yields of α-arylated derivatives. Representative examples of these reactions are reported in Scheme 24.



Scheme 24. Direct C–H arylation of furan and thiophene derivatives catalysed by complex **34**.

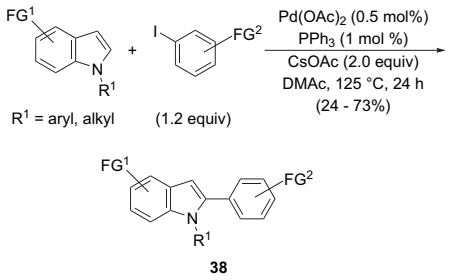
In a subsequent full paper,[43] in which a possible mechanism of these arylation reactions was reported, it was surmised that ligand dissociation from complex **34** is an initial step generating a coordinatively unsaturated Rh(I) species **35**, which thereafter initiates an Rh(I)/Rh(III) redox cycle (Scheme 25). The proposed catalytic cycle specifically involves: (i) oxidative addition of aryl iodide to **35** and generation of the cationic arylRh(III) species **36**; (ii) electrophilic rhodation of the heteroarene with **36** to give the heteroarylRh(III) species **37**; and (iii) reductive elimination of the arylheteroarene with regeneration of complex **34**.[43]



Scheme 25. Possible mechanism of the Rh-catalysed arylation of five-membered heteroarenes with one heteroatom.

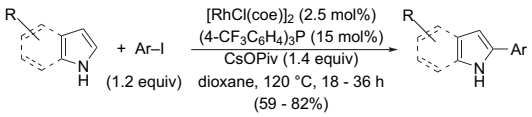
2.2. (Hetero)arylation of pyrrole, indole, and indolizine ring systems

In the last few years, significant attention has been paid particularly by the Sames research group to the direct arylation of pyrroles and indoles with aryl halides.[44–47] In 2004, this group reported that *N*-aryl- and *N*-alkyl-substituted indoles undergo C-2 arylation by treatment with aryl iodides in DMA at 125 °C in the presence of CsOAc as the base and a Pd(OAc)$_2$/PPh$_3$ catalyst system.[44] The reactions (Scheme 26) that occurred with low catalyst loadings demonstrated a high degree of functional-group tolerance and provided the C-2 arylated derivatives **38** in modest to good yields.



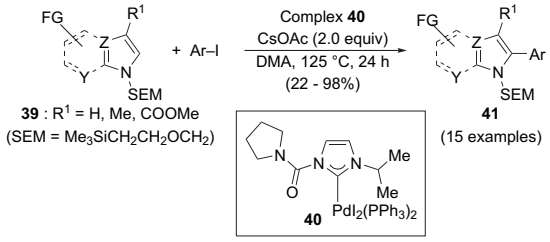
Scheme 26. Pd(OAc)$_2$/PPh$_3$-catalysed C-2 arylation of *N*-aryl and *N*-alkyl-substituted indoles.

In 2005, Sames disclosed an efficient and reliable method for the C-2 arylation of free (NH)-pyrrole and -indoles.[45] The reactions were carried out by the use of a catalyst system consisting of a mixture of [RhCl(coe)]$_2$ in the presence of cesium pivalate as the base (Scheme 27). Unfortunately, this method was not applicable to the arylation of 7-azaindole.



Scheme 27. Rh-catalysed C-2 arylation of free (NH)-pyrrole and -indoles.

Sames found later that palladium complexes containing an imidazolyl carbene ligand catalyse the efficient C-2 arylation of *N*-2-(trimethylsilyl)ethoxymethyl (SEM) protected pyrroles, indoles and other azoles, including imidazoles and imidazo[1,2-*a*]pyridines with aryl iodides.[47a] Scheme 28 illustrates the C-2 arylation reactions of heteroarenes **39** including derivatives bearing basic nitrogens with aryl iodides, which are catalysed by the palladium complex **40** containing an imidazolyl carbene ligand. Simple removal of the SEM protecting group from the resulting C-2 arylated heteroarenes **41** in the presence of a fluoride ion source provided a convenient access to 2-arylated free (NH)-azoles.[47a]

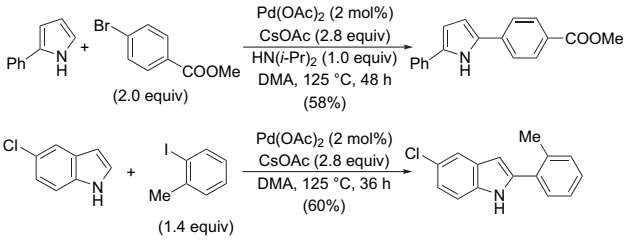


Scheme 28. C-2 arylation of SEM-protected azoles.

In 2007, Sames and co-workers proposed a phosphine-free palladium-catalysed method for the direct C-2 arylation of free (NH)-pyrroles and -indoles with aryl bromides and iodides.[47b] The reactions were carried out in DMA at 125 °C in the presence of CsOAc as the base and a catalytic quantity of Pd(OAc)$_2$ and provided the required C-2-arylated heteroarenes, including tryptamine derivatives, in low to satisfactory yields. Remarkably, aryl bromides proved to be arylating reagents less efficient than the corrisponding aryl iodides, giving low conversions and poor C-2/C-3 selectivity. However, it was possible to significantly increase the conversion of the reactions of aryl bromides by the addition of stoichiometric amounts of (*i*-Pr)$_2$NH.[47b]

Two representative examples of reactions involving the use of an aryl bromide and an aryl iodide, respectively, are reported in Scheme 29. Noteworthy, this phosphine-free palladium-catalysed method proved to be tolerant to a wide range of functional groups,

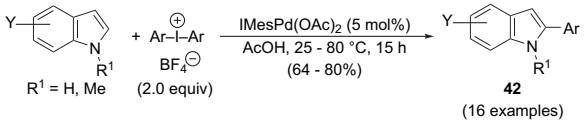
including esters, ketones and carboxamides, but suffered from sensitivity to the basic sp^2 nitrogen of imidazole and pyridine.[47b]



Scheme 29. Phosphine-free Pd-catalysed direct C-2 arylation of a free (NH)-pyrrole and -indole derivatives.

On the other hand, in 2009, Fall, Doucet and Santelli have demonstrated that, by using $Pd(OAc)_2$ as catalyst precursor, 1,2,5-trisubstituted pyrrole derivatives undergo direct C-3 or C-4 arylation with functionalised aryl bromides in DMA at 130 °C in the presence of KOAc as the base to give arylated derivatives in moderate-to-good yields.[48] Unfortunately, this procedure is limited to activated aryl bromides; aryl chlorides have been found to be unreactive. On the contrary, a high-yielding $Pd(OAc)_2$/DavePhos [2-dicyclohexylphosphino-2'-(*N*,*N*-dimethylamino)biphenyl]-catalysed intramolecular C-4 arylation of a 1,2,5-trisubstituted pyrrole derivative with an *o*-substituted aryl iodide had previously been used by Trauner and co-workers to prepare racemic rhazinilam, a compound able to interfere with tubulin polymerisation.

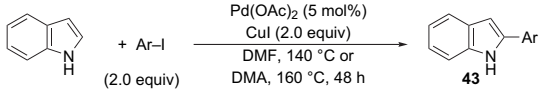
In recent years, other research groups have investigated the direct C-2 arylation of *N*-protected and free (NH)-indoles.[49–54] In 2006, Sanford and co-workers utilised catalytic amounts of $IMesPd(OAc)_2$ for promoting the C-2 arylation reaction of 1-methyl- and free (NH)-indole with diaryliodonium tetrafluoroborates in acetic acid.[49] The reactions proceeded under remarkably mild conditions (often at room temperature), were highly selective and gave the required arylated derivatives **42** in good isolated yields (Scheme 30).[49]



Scheme 30. Pd-catalysed C-2 arylation of indoles with diaryliodonium tetrafluoroborates.

Appreciable amounts of arylation at the more electrophilic position of indoles were only observed when the 2-position was blocked. It was also found that conditions similar to those reported in Scheme 30 were suitable for the arylation of 1-methyl- and free (NH)-pyrrole.[49]

In 2006, studies on the transition metal-catalysed arylation of indoles also commenced from our research group and we described the first examples of palladium-catalysed and copper-mediated highly selective C-2 arylation reactions of free (NH)-indole with aryl iodides under ligandless and base-free conditions (Scheme 31).[50,51]

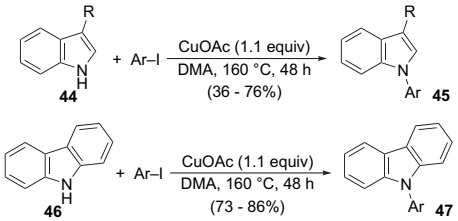


Solvent	Reaction temperature	Ar	Yield (%)
DMF	140 °C	4-$MeOC_6H_4$	35
DMA	160 °C	4-$MeOC_6H_4$	53
DMA	160 °C	Ph	29
DMA	160 °C	4-$CF_3C_6H_4$	33

Scheme 31. Pd-catalysed and Cu-mediated C-2 arylation of free (NH)-indole with aryl iodides under base-free and ligandless conditions.

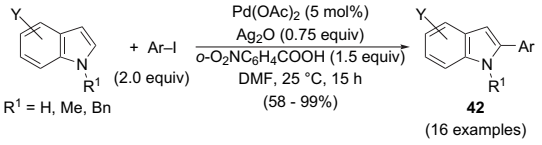
DMA proved to be the solvent of choice for these reactions, which were performed using a molar excess of aryl iodide.[51] However, the required 2-aryl-1*H*-indoles **43** were so obtained in modest yields.

An attempt to improve these results by examining the role of $Pd(OAc)_2$ and the Cu(I) salt in the arylation reaction was unsuccessful. Nevertheless, in the course of this investigation, it was found that 1*H*-indoles **44** and 9*H*-carbazole (**46**) undergo reaction with aryl iodides in the presence of 1.1 equiv of CuOAc under base-free and ligandless conditions to give the corresponding *N*-arylazoles **45** and **47**, respectively, with complete *N*-selectivity and in modest-to-good yields (Scheme 32).[55]



Scheme 32. CuOAc-mediated N-arylation of 1*H*-indoles **44** and 9*H*-carbazole (**46**).

In 2008, Larrosa developed a methodology, which, for the first time, enabled the direct palladium-catalysed C-2 arylation of *N*-protected and free (NH)-indoles with aryl iodides at room temperature without the presence of phosphines or other ligands.[52] As shown in Scheme 33, functionalised indoles were reacted with a molar excess of aryl iodides in DMF at 25 °C in the presence of 5 mol% $Pd(OAc)_2$, 0.75 equiv of Ag_2O and 1.5 equiv of *o*-nitrobenzoic acid to give the corresponding 2-arylindoles **42** in good to excellent yields.



Scheme 33. Room temperature C-2 arylation of indoles with aryl iodides.

o-Nitrobenzoic acid and Ag_2O were used in order to generate silver *o*-nitrobenzoate in situ. This salt, which is characterised by a relatively poorly coordinating carboxylate, is presumably able to remove the iodide anion from the oxidative complex **48** to give a cationic palladium species **49** (Fig. 2), which would be more electrophilic towards the indole unit.[52]

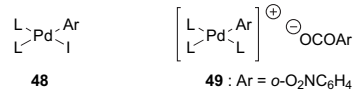
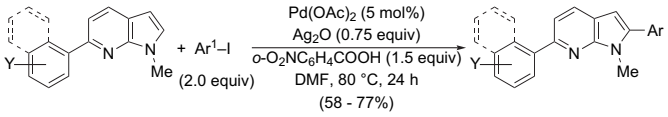


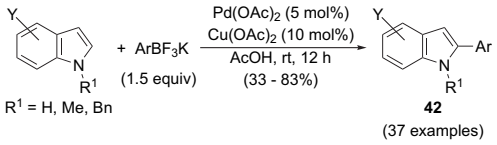
Figure 2. Structures of complexes **48** and **49**.

Very recently, the Larrosa conditions have been utilised by Huestis and Fagnou for the efficient C-2 arylation of *N*-methyl-7-azaindoles with aryl iodides, including electron-neutral derivatives and compounds, which bear a cyano or a phenolic functional group (Scheme 34).[53]



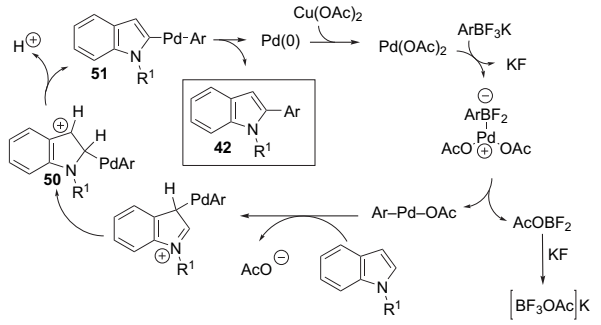
Scheme 34. Pd-catalysed C-2 arylation of *N*-methyl-7-azaindoles with aryl iodides.

In 2008, Zhang and co-workers discovered that the direct C-2 arylation of *N*-protected and free (NH)-indoles can be achieved with potassium aryltrifluoroborates in acetic acid at room temperature in the presence of catalytic amounts of $Pd(OAc)_2$ and $Cu(OAc)_2$ (Scheme 35).[54]



Scheme 35. Pd/Cu-catalysed direct arylation of indoles with potassium aryltrifluoroborates.

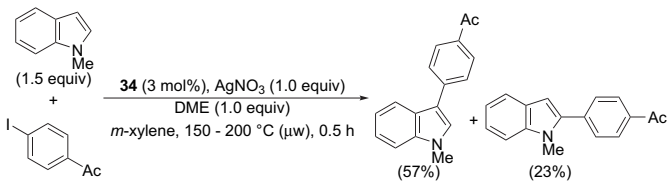
The formation of an ArPdOAc species from $Pd(OAc)_2$ and the $ArBF_3K$ salt, followed by electrophilic palladation of the indoles at the C-3 position, was proposed for the mechanism of this reaction (Scheme 36).[54] The subsequent C-3→C-2 migration with formation of intermediates **50** and deprotonation should give the intermediates **51**, which should undergo reductive elimination with generation of Pd(0) and the 2-arylated indoles **42**. The final step of this process should involve oxidation of Pd(0) to Pd(II) by $Cu(OAc)_2$.[54]



Scheme 36. Proposed mechanism for direct C-2 arylation of indoles with potassium aryltrifluoroborates.

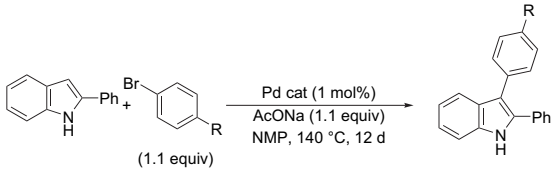
It should be noted that a mechanism for the palladium-catalysed C-2 arylation of the indole ring with aryl halides, based on an electrophilic attack at the C-3 position of the heteroarene scaffold followed by a C-3→C-2 migration, had been previously proposed by Sames and co-workers.[46]

In the last few years, significant attention has also been focused on the design and development of highly regioselective protocols for the efficient synthesis of 3-arylated indoles derivatives via transition metal-catalysed direct arylation reactions.[42,56–62] Unsatisfactory results were obtained by Itami and co-workers, who found that the microwave-mediated arylation of 1-methyl-1*H*-indole with 4-iodoacetophenone in *m*-xylene in the presence of $AgNO_3$ and a catalytic amount of $RhCl(CO)\{P[OCH(CF_3)_2]_3\}_2$ (**34**) furnishes a mixture of the C-3 and C-2 arylated derivatives (Scheme 37).[42]



Scheme 37. Rh(I)-catalysed arylation of 1-methyl-1*H*-indole with 4-iodoacetophenone.

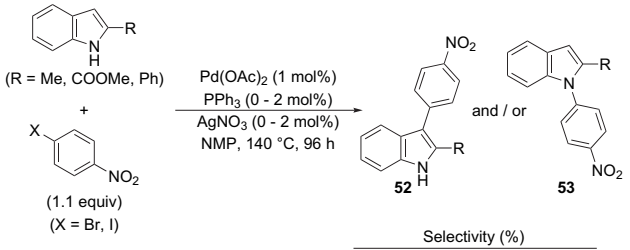
On the other hand, in 2006, Djakovitch and co-workers investigated the application of heterogeneous palladium catalysts to the arylation of 2-phenyl-1*H*-indole[56] and found that C-3 arylated derivatives can be obtained in low to moderate yields by treatment of this heteroarene both with 1-bromo-4-fluoro- and 1-bromo-4-nitrobenzene in NMP at 140 °C in the presence of AcONa as the base and a catalytic quantity of the heterogeneous [Pd]/SBA-15, $[Pd(NH_3)_4]$/NaY or $Pd(OAc)_2$ (Scheme 38).[56]



R	Catalyst	GLC yield (%)
F	$Pd(OAc)_2$	48
F	[Pd] / SBA-15	35
F	$[Pd(NH_3)_4]$ / NaY	7
NO_2	$Pd(OAc)_2$	55
NO_2	[Pd] / SBA-15	36
NO_2	$[Pd(NH_3)_4]$ / NaY	7

Scheme 38. Pd-catalysed C-3 arylation of 2-phenyl-1*H*-indole.

Subsequently, Djakovitch and co-workers investigated the influence of the PPh_3 ligand and the $AgBF_4$ additive on the selectivity of the $Pd(OAc)_2$-catalysed arylation of 2-substituted indoles, including 2-methyl-, 2-methoxycarbonyl- and 2-phenyl-1*H*-indole, with 4-bromo- or 4-iodonitrobenzene in NMP at 140 °C in the presence of AcONa as a base and observed that C-3 or N-1 arylated indole derivatives, **52** and **53**, respectively, could be obtained by fine tuning of the reaction conditions for each substrate (Scheme 39).[57] Specifically, compounds **52** were selectively obtained in quantitative conversion when 2-methyl-, 2-methoxycarbonyl- and 2-phenyl-1*H*-indole were reacted with 4-bromonitrobenzene in the presence of 2 mol % $AgBF_4$. Interestingly, a 3-arylated derivative **52** was also obtained from the reaction of 2-methoxycarbonyl-1*H*-indole with 4-iodonitrobenzene in the presence of 2 mol % PPh_3, but formation of the N-1 arylated derivatives **53** was observed when the reactions of 2-methyl- and 2-phenyl-1*H*-indole with 4-iodonitrobenzene were performed in the presence of 2 mol % PPh_3.



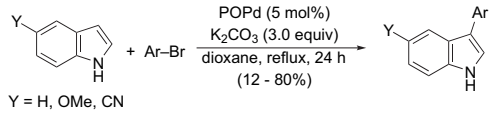
				Selectivity (%)	
R	X	Ligand	Additive	N-1 Arylation	C-3 Arylation
Me	Br	–	$AgBF_4$	0	100
COOMe	Br	–	$AgBF_4$	0	100
Ph	Br	–	$AgBF_4$	0	100
Ph	Br	PPh_3	–	22	78
Me	I	PPh_3	–	100	0
COOMe	I	PPh_3	–	0	100
Ph	I	PPh_3	–	100	0
Me	I	–	–	85	15
Ph	I	–	–	100	0

Scheme 39. Influence of reaction conditions on selectivity of the arylation of 2-substituted indoles with activated aryl halides.

Remarkably, 1-(4-nitrophenyl)-2-phenyl-1*H*-indole could also be selectively obtained by a $Pd(OAc)_2$–catalysed reaction of 2-phenyl-1*H*-indole with 4-iodonitrobenzene in the absence of ligands and additives.[57]

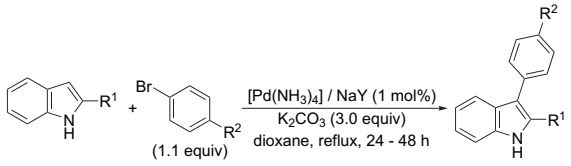
In 2007, Zhang and co-workers[58] reported that free (NH)-indoles are able to undergo regioselective C-3 arylation when treated with aryl bromides and K_2CO_3 in refluxing dioxane in the presence of catalytic amounts of $Pd(OAc)_2(PPh_3)_2$ or $[(t\text{-}Bu)_2P(OH)]_2PdCl_2$

(POPd), a commercially available but expensive palladium complex (Scheme 40). Unfortunately, the use of POPd, which was the catalyst precursor of choice, proved to be unsuitable for the C-3 arylation of electron-withdrawing-group-substituted free (NH)-indoles, which were found to depress the reaction.[58]



Scheme 40. POPd-catalysed C-3 arylation of free (NH)-indoles with aryl bromides.

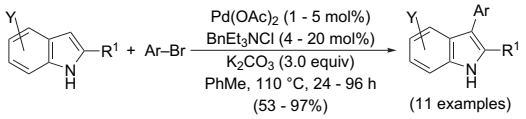
One year later, Djakovitch found that free (NH)-indoles substituted or unsubstituted at position 2 are able to react with activated aryl bromides in refluxing dioxane in the presence of K_2CO_3 as the base and $[Pd(NH_3)_4]$/NaY as the catalyst to give C-3 arylated indoles with complete selectivity (Scheme 41).[59]



Scheme 41. $[Pd(NH_3)_4]$/NaY-catalysed C-3 arylation of free (NH)-indoles.

Unfortunately, this procedure was either unsatisfactory or did not furnish the required arylated indoles when free (NH)-indole, 2-methyl- and 2-phenyl-1*H*-indole were reacted with deactivated or unactivated aryl bromides.[59]

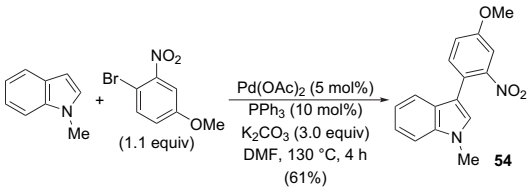
Within the same year, we established that a combination of $Pd(OAc)_2$ and PCy_3 can be used as catalyst precursor for highly regioselective C-3 arylation reactions of free (NH)-indole with 4-bromobenzene and 4-bromoanisole in refluxing toluene in the presence of K_2CO_3.[60] We also found that, when bulky and electron-rich phosphines such as P(*t*-Bu)$_2$(Biph), PBu(1-Ad)$_2$ and P(*t*-Bu)$_3$ were used in place of PCy_3, arylation of free (NH)-indole with 4-bromoanisole takes place at the 1-position with complete regioselectivity. We additionally observed that the $Pd(OAc)_2/PCy_3$ catalyst system was unexpectedly unsuitable for the efficient C-3 arylation of free (NH)-indoles with aryl bromides different from bromobenzene and 4-bromoanisole.[60] Thus, this catalyst system was significantly modified and, after an in-depth study, it was found that clean and high yielding C-3 arylation reactions of free (NH)-indole and its electron-rich 1-unsubstituted derivatives could be performed with activated, unactivated and deactivated aryl bromides in refluxing toluene in the presence of K_2CO_3 as the base and a catalyst system consisting of a combination of $Pd(OAc)_2$ and $BnEt_3NCl$ under ligandless conditions (Scheme 42).[60]



Scheme 42. $Pd(OAc)_2/BnEt_3NCl$-catalysed C-3 arylation of free (NH)-indoles under ligandless conditions.

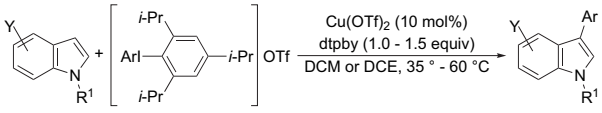
It should be noted that a catalyst comprising $Pd(OAc)_2$ and a tetraalkylammonium salt had been previously used by Jeffery for a Heck-type reaction of methyl acrylate with iodobenzene in polar solvents in the presence of K_2CO_3 as base.[61] Moreover, Jeffery's conditions have also been used for the direct arylation of 2- and 3-substituted thiophenes in a mixture of acetonitrile and water,[20a] as well as benzothiophenes[20f] and 3-methoxythiophene[28] in DMF.

A more conventional $Pd(OAc)_2/PPh_3$ catalyst system was used by Lemaire and co-workers to prepare 3-(4-methoxy-2-nitrophenyl)-1-methyl-1*H*-indole (**54**) by C-3 arylation of 1-methyl-1*H*-indole with 4-bromo-3-nitroanisole in DMF in the presence of K_2CO_3 as a base (Scheme 43).[62] Compound **54** was then employed as a building block for the synthesis of an indole-containing rhodamine dye.[62]



Scheme 43. Synthesis of 3-(4-methoxy-2-nitrophenyl)-1-methyl-1*H*-indole (**54**).

The interesting results of an in-depth investigation of copper-catalysed direct arylation of indoles with diaryliodonium salts have been published recently by Gaunt and co-workers.[63] They found that free (NH)-indole and 1-methyl-1*H*-indole undergo high-yielding C-3 arylation reactions with (aryl)(2,4,6-triisopropylphenyl)iodonium triflates in DCM or DCE at 35 °C in the presence of 1–1.5 equiv of 2,6-di-*t*-butylpyridine (dtbpy) and 10 mol % $Cu(OTf)_2$ (Scheme 44).[63] In many cases, the C-3/C-2 selectivity of these reactions was higher than 20:1.

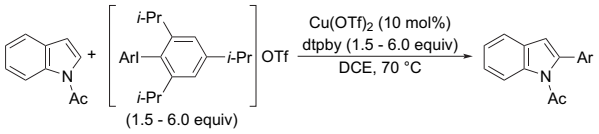


Y	R^1	Ar	Yield (%)	C3 : C2 selectivity
H	Me	Ph	72	n.d.
H	Me	4-MeC_6H_4	74	> 20 : 1
H	Me	4-FC_6H_4	74	> 20 : 1
H	Me	4-$MeOC_6H_4$	73	11 : 1
H	H	4-FC_6H_4	71	10 : 1
H	Me	4-BrC_6H_4	82	> 20 : 1
H	Me	4-IC_6H_4	65	> 20 : 1
H	Me	4-$(NO_2)C_6H_4$	86	> 20 : 1
H	Me	3-$CF_3C_6H_4$	77	> 20 : 1
H	Me	2-MeC_6H_4	86	> 20 : 1
H	Me	2-$(AcNH)C_6H_4$	72	> 20 : 1
H	Me	3-thienyl	57	8 : 1
H	Me	2-Br-4 pyridyl	38	> 20 : 1
H	H	Ph	74	n.d.
6-COOMe	H	Ph	85	n.d.
5-NO_2	H	Ph	73	n.d.
5-Br	H	Ph	75	n.d.

Scheme 44. Cu(II)-catalysed C-3 arylation of indoles.

Gaunt and co-workers speculated that a Cu(I) catalytic species is oxidized to a highly electrophilic Cu(III)-aryl intermediate ,which undergoes Friedel–Crafts-type metalation and arylation at position C-3 of the indole.[63] However, the C-3/C-2 selectivity proved to be highly dependent on the electronic nature of the *N*-protecting group of the indole derivatives.

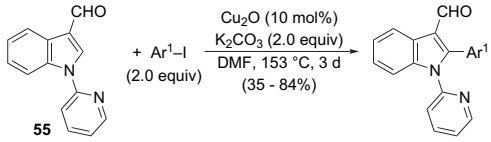
In fact, 1-acetyl-1*H*-indole was found to undergo preferential C-2 arylation by treatment with a molar excess of diaryliodonium triflates in DCE at 70 °C in the presence of 1.5–6 equiv of dtbpy and 10 mol % $Cu(OTf)_2$ (Scheme 45).[63]



Ar	Yield (%)	C3 : C2 selectivity
4-MeC_6H_4	69	6.5 : 1
4-$MeOC_6H_4$	49	2.6 : 1
4-FC_6H_4	72	6 : 1
4-ClC_6H_4	83	5 : 1
4-BrC_6H_4	82	6 : 1
4-IC_6H_4	56	5.5 : 1
3-BrC_6H_4	80	7 : 1
3-$CF_3C_6H_4$	78	6.5 : 1
4-$EtOOCC_6H_4$	73	4 : 1
4-$O_2NC_6H_4$	54	3 : 1

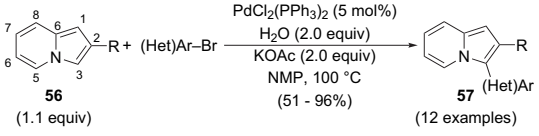
Scheme 45. Cu(II)-catalysed C-2 arylation of 1-acetyl-1*H*-indole.

Many of the latter reactions were shown to occur with C-2/C-3 selectivity higher than 4:1. Very recently, it has also been found that 1-(pyridinyn-2-yl)indole-3-carboxaldehyde (**55**) undergoes C-2 arylation by reaction with a molar excess of aryl iodides in the presence of K_2CO_3 as the base and a catalytic quantity of Cu_2O in DMF at 153 °C (Scheme 46).[64] The reaction requires a very long reaction time and gives the C-2 arylated derivatives in satisfactory yields when aryl iodides bearing an electron-donating group on the *ortho*-, *meta*-, or *para*-position are used as the electrophiles. On the contrary, a modest yield (35%) is obtained by the reaction of **55** with 4-iodonitrobenzene under these experimental conditions.[64]



Scheme 46. Cu(I)-catalysed C-2 arylation of 1-(pyridinin-2-yl)indole-3-carboxaldehyde (**55**).

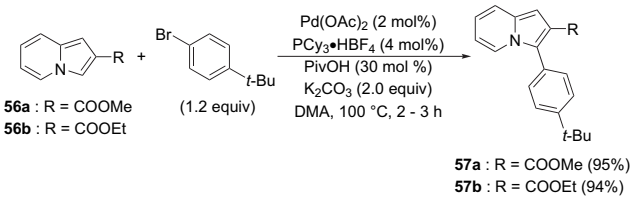
On concluding this section, we should mention that indolizines have also been used as substrates for palladium-catalysed direct arylation reactions.[65,66] In 2004, Gevorgyan and co-workers reported that indolizines **56** undergo (hetero)arylation with (hetero)aryl bromides in NMP at 100 °C in the presence of water, AcOK, and catalytic quantities of $PdCl_2(PPh_3)_2$ to give 3-(hetero)arylindolizines **57** in good to excellent yields (Scheme 47).[65]



Scheme 47. $PdCl_2(PPh_3)_2$-catalysed C-3 arylation of indolizines **56**.

Mechanistic studies supported an electrophilic substitution pathway for these arylation reactions.[65]

More recently, Fagnou and co-workers[66] have synthesised 3-arylindolizines **57a** and **57b** in excellent yields by treatment of the corresponding indolizines, **56a** and **56b**, respectively, with 4-*t*-butylbromobenzene in DMA in the presence of K_2CO_3 as the base and catalytic amounts of pivalic acid, $Pd(OAc)_2$ and $PCy_3 \cdot HBF_4$ (Scheme 48).

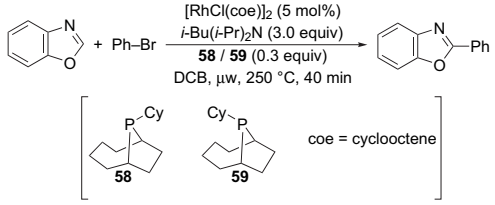


Scheme 48. $Pd(OAc)_2/PCy_3$-catalysed C-3 arylation of indolizines **56a**,**b** in the presence of pivalic acid.

3. Intermolecular direct (hetero)arylation of five-membered heteroarenes with two or three heteroatoms

3.1. (Hetero)arylation of oxazole, benzoxazole, and oxazolo[4,5-*b*]pyridine ring systems

Benzoxazole derivatives include compounds of particular interest for their known pharmacological properties.[67] In 2006, Bergman, Ellman and co-workers reported a method for the rhodium-catalysed microwave-assisted C-2 arylation of benzoxazole and other azoles, including free (NH)-benzimidazole, 1-methyl-1*H*-benzimidazole, a 4,5-disubstituted free (NH)-imidazole, and 3-phenyl-1,2,4-triazole with bromobenzene.[68] A mixture of *exo*- and *endo*-9-cyclohexylbicyclo[4.2.1]-9-phosphanonane (Cy-Phob), (**58**) and (**59**), respectively, served as a highly active supporting ligand in these rhodium(I)-catalysed reactions. As illustrated in Scheme 49 where the reaction conditions of the 2-arylation of benzoxazole with bromobenzene are illustrated, the highly hindered amine *i*-Bu(*i*-Pr)$_2$N was employed as the base.



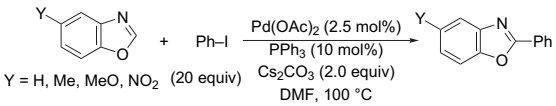
Scheme 49. Rh(I)-catalysed C-2 arylation of benzoxazole.

It is notable that both electron-rich and electron-deficient aryl bromides coupled with benzimidazole in good yields and that reactive functionalities such as carboxamide, ketone and nitrile were well tolerated under the optimised conditions of these $[RhCl(coe)_2]_2$/Cy-Phob-catalysed reactions performed utilising microwave heating and *i*-Bu(*i*-Pr)$_2$N as the base.[68a]

However, palladium catalyst systems have often allowed the C-2 arylation of benzoxazoles, oxazole and oxazolo[4,5-*b*]pyridine to be performed under experimental conditions milder than those employed by Bergman and Ellman for the above-mentioned rhodium-catalysed reactions.

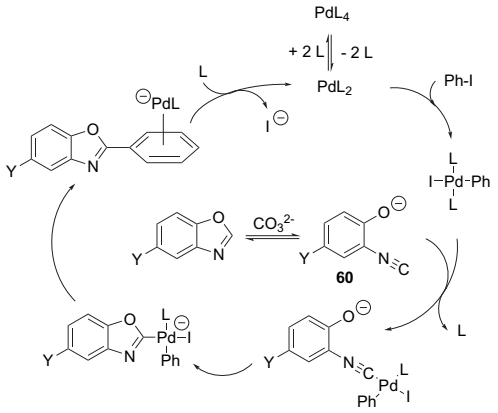
In 1992, Ohta and co-workers published the first report concerning a palladium-catalysed protocol for the arylation of benzoxazole.[18] The researchers employed $Pd(PPh_3)_4$ as the catalyst precursor for the C-2 arylation of this heteroarene with 2-chloro-3,6-dimethylpyrazine, an activated heteroaryl halide, in refluxing DMA in the presence of AcOK as the base.

In 2007, Sánchez and Zhuravlev investigated the reaction of iodobenzene with benzoxazoles in DMF at 100 °C in the presence of Cs_2CO_3 as the base and a $Pd(OAc)_2/PPh_3$ catalyst system (Scheme 50).[69]



Scheme 50. $Pd(OAc)_2/PPh_3$-catalysed C-2 arylation of benzoxazoles.

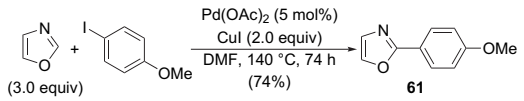
A mechanistic investigation enabled the authors to establish that these arylation reactions could not be rationalised on the basis of the electrophilic mechanism, which is presumably implicated in palladium-catalysed direct arylation of other electron-rich heteroarenes,[19a,46] and a new mechanism (Scheme 51), which includes generation of 2-isocyanophenolate derivatives **60** by ring-opening of benzoxazoles as a key step, was proposed on the basis of experimental and computational studies.[69]



Scheme 51. Proposed reaction mechanism for Pd-catalysed C-2 phenylation of benzoxazoles.

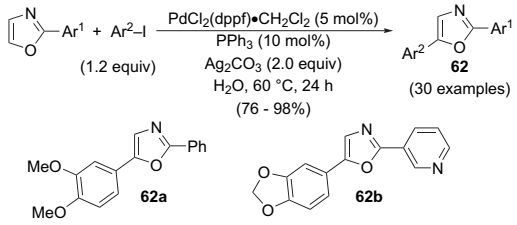
However, in our opinion, this mechanism should not operate in the $Pd(OAc)_2$-catalysed and CuI-mediated C-2 arylation reactions of oxazole and other azoles, including 1-aryl-, 1-benzyl- and 1-methyl-1*H*-imidazole, free (NH)-imidazole, -benzimidazole and -indole, thiazole, and benzothiazole, with aryl iodides in DMF at 140 °C under base-free and ligandless conditions, which we recently developed.[50,51,70] We proposed that, under these experimental conditions, very different from those previously employed for performing transition metal-catalysed arylation reactions of π-excessive and π-sufficient heteroarenes, which invariably involve the use of a base,[11b,46,71] the reaction mechanism is based on the formation of 2-azolylcopper(I) derivatives, followed by a transmetallation reaction with arylpalladium(II) species and reductive elimination.[70] On the other hand, coordination of the azole to CuI to form π-complexes might significantly lower the pK_a value of their C–H bond at position 2 and facilitate their conversion into C–Cu bonds via reaction with CuI in the presence of DMF, a solvent with mildly basic characteristics.[72]

The experimental conditions used for the synthesis of 2-(4-methoxyphenyl)oxazole (**61**) by palladium-catalysed and CuI-mediated arylation of oxazole with 4-iodoanisole under base-free and ligandless conditions are reported in Scheme 52.[51]



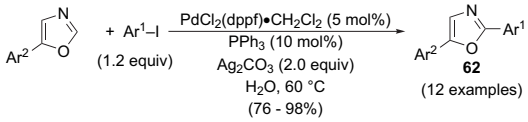
Scheme 52. Synthesis of 2-(4-methoxyphenyl)oxazole (**61**).

A significant contribution to the development of new and highly efficient general methods for the direct arylation of five-membered heteroarenes with two heteroatoms, by Greaney and co-workers, who described the high-yielding, on-water direct C-5 arylation of 2-aryloxazoles with electron-poor, electron-rich, and sterically hindered aryl iodides containing additional functional handles for further chemical elaboration, in the presence of suprastoichiometric amounts of Ag_2CO_3 and catalytic quantities of $PdCl_2$(dppf) and PPh_3 (Scheme 53).[73] In this system whereby the organic components react in a heterogeneous aqueous solution, Ag_2CO_3 was employed as both base and source of silver. 2,5-Diaryloxazoles **62**, which were prepared according to this protocol, included balsoxin (**62a**) and texaline (**62b**), two compounds isolated from *Amyris* species of plants in the Caribbean.[74]



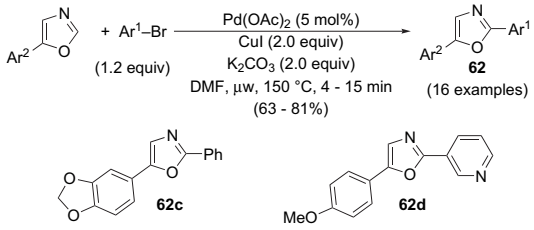
Scheme 53. On-water direct C-5 arylation of 2-aryloxazoles.

Remarkably, these reaction conditions proved also to be suitable for the synthesis of 2,5-diaryloxazoles **62** via direct C-2 arylation of 5-aryloxazoles with aryl iodides (Scheme 54).[75]



Scheme 54. On-water direct C-2 arylation of 5-aryloxazoles.

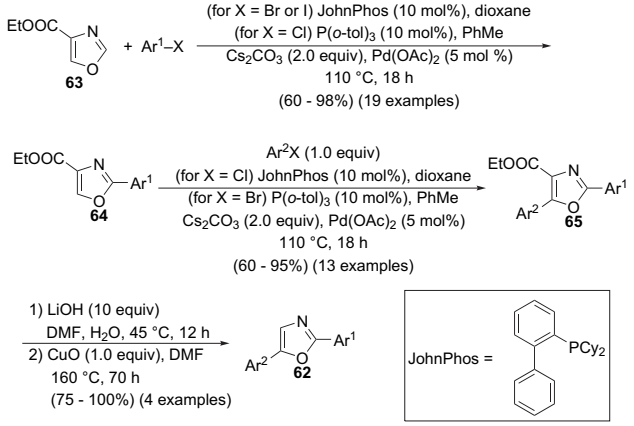
Two additional reliable methods for the preparation of 2,5-diaryloxazoles via direct palladium-catalysed arylation reactions have been recently described.[76,77] Piguel and co-workers[76] synthesised a large variety of these heteroarene derivatives, including the four alkaloids **62a**, **62b**, texamine (**62c**), and *O*-methylhalfordinol (**62d**) (Scheme 55) by the use of a modification of our previously reported procedure for the palladium-catalysed and copper-mediated C-2 arylation of 1-aryl-1*H*-imidazoles with aryl halides under ligandless conditions.[78]



Scheme 55. Microwave-assisted Pd-catalysed and Cu-mediated C-2 arylation of 5-aryloxazoles under ligandless conditions.

The modification, involving the microwave-assisted $Pd(OAc)_2$-catalysed and CuI-mediated C-2 arylation of 5-aryloxazoles with aryl bromides in DMF in the presence of K_2CO_3 as the base, allowed the synthesis of 2,5-diaryloxazoles **62** in short reaction times and high yields.

On the other hand, 2,5-di(hetero)arylated oxazoles were synthesised by Hoarau and co-workers through a palladium-catalysed C-2 and subsequent C-5 direct (hetero)arylation process of ethyl oxazole-4-carboxylate (**63**) with iodo-, bromo- and chloro(hetero)arenes.[77] A two-step hydrolysis/decarboxylation sequence involving the so-prepared ethyl 2,5-di(hetero)arylated oxazole-4-carboxylates (**65**) enabled the synthesis of a variety of compounds **63**, including **62a** and **62b**, in high overall yields (Scheme 56).[77]

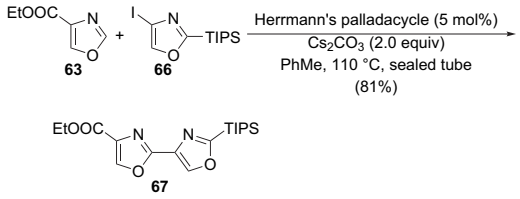


Scheme 56. Synthesis of compounds **62** from ethyl oxazole-4-carboxylate (**63**).

As illustrated in this scheme, Buchwald's JohnPhos ligand was used both for the C-2 arylation of **63** with (hetero)aryl bromides and iodides and the C-5 arylation of the resulting ethyl 2-(hetero)aryloxazole-4-carboxylates **64** with (hetero)aryl chlorides. On the other hand, P(*o*-tolyl)$_3$ was the ligand of choice both for the C-2 arylation of **63** with (hetero)aryl chlorides and the C-5 arylation of compounds **64** with (hetero)aryl bromides.

It was also found that the C-2 direct arylation conditions on water, successfully used for the synthesis of **62a** and **62b**, were ineffective for the arylation of **63** with 4-iodo-2-triisopropylsilyloxazole (**66**).[76]

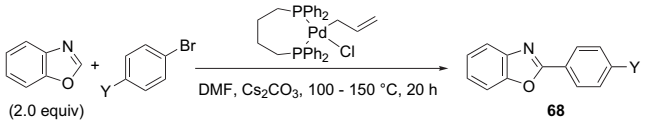
Nevertheless, the use of Herrmann's palladacycle[79] allowed the preparation of triisopropylsilyl-[2,4′]-bisoxazolyl-4-carboxylic acid ethyl ester (**67**) from **63** and **66** in 81% yield (Scheme 57).[76]



Scheme 57. Direct C-2 arylation of oxazole **63** with iodide **66**.

In 2008, Doucet and co-workers accomplished the direct C-2 arylation of oxazole and benzoxazole with either a range of electron-rich and electron-poor aryl bromides or electron-poor aryl chlorides in DMF at 100–150 °C in the presence of Cs_2CO_3 as the base and PdCl(dppb)(allyl) as the catalyst precursor.[80]

Interestingly, the results were generally better in reactions involving electron-rich aryl bromides compared to those of their electron-poor counterparts. Scheme 58 illustrates the results obtained in the synthesis of compounds **68** from benzoxazole and 4-substituted aryl bromides.[80]

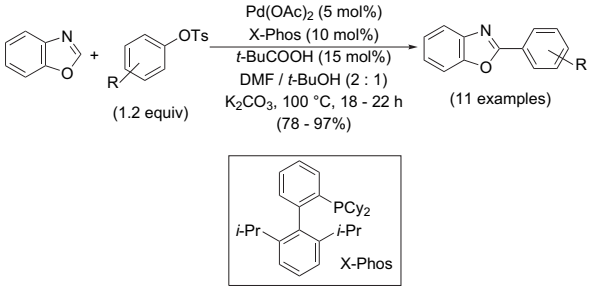


Substrate / catalyst ratio	Temp (°C)	Y	Isolated yield (%)
80	100	Ac	78
100	150	ArCO	61
100	150	CF_3	84
20	100	CN	79
100	150	F	traces
20	120	F	78
100	150	*t*-Bu	80
100	150	Me	61
100	150	MeO	85
100	150	Me_2N	87

Scheme 58. PdCl(dppb)(allyl)-catalysed C-2 arylation of benzoxazole with 4-substituted aryl bromides.

Most recently, Ackermann and co-workers have investigated the challenging use of aryl tosylates and mesylates in palladium-catalysed direct arylations of benzoxazole, 5-phenyloxazole and caffeine.[81]

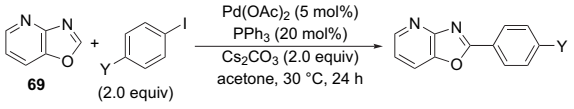
Aryl tosylates and mesylates are easily accessible from phenols and would thus be highly advantageous alternatives to aryl halides from both ecological and economical standpoints. Ackermann and co-workers discovered that a catalyst system composed of $Pd(OAc)_2$ and X-Phos enables high-yielding reactions of benzoxazole with electron-rich aryl tosylates in a mixture of DMF and *t*-BuOH in the presence of K_2CO_3 and a catalytic amount of pivalic acid (Scheme 59). Notably, addition of pivalic acid[82] proved to be beneficial for the direct arylation of benzoxazole with aryl tosylates and mesylates, but did not affect the catalytic performance of the arylation of 5-phenyloxazole and caffeine.[81]



Scheme 59. Pd-catalysed direct arylation of benzoxazole with aryl tosylates.

In this regard, it must be mentioned that, very recently, You and co-workers have developed a new palladium-catalysed methodology which, for the first time, enables the direct C-arylation of azoles, including benzoxazole, caffeine and thiazoles, with a broad spectrum of aryl bromides without the presence of phosphines, the aid of CuI, or metal additives by using pivalic acid as the cocatalyst.[82b]

An additional heteroarene containing two heteroatoms, which has been used as a substrate in direct arylation reactions, is oxazolo[4,5-*b*]pyridine (**69**). In 2006, Zhuravlev described that **69**, a compound with an electron-rich ring fused to an electron-deficient system, undergoes C-2 arylation in modest to satisfactory yields by treatment with a molar excess of aryl iodides in acetone at 30 °C in the presence of a $Pd(OAc)_2/PPh_3$ catalyst system and Cs_2CO_3 as the base (Scheme 60).[83]

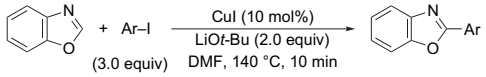


Y	Yield (%)
Me	52
Ac	67
NH_2	74
Cl	39
CN	61
$CH_2OLeu(L)NBoc$	41
$CH_2OLeu(D)NBoc$	48

Scheme 60. C-2 arylation of oxazolo[4,5-*b*]pyridine (**69**).

Finally, we think it right to point out that, in recent years, attention has also been turned to the replacement of expensive palladium catalysts with cheaper copper compounds in many types of reactions[84–86] including the direct arylation of heteroarene C–H bonds. In 2007, Do and Daugulis developed a method for the CuI-catalysed C-2 arylation of benzoxazole and other azoles, including oxazole, thiazole, 1-methyl-1*H*-benzimidazole, 1-methyl-1,2,4-triazole, and caffeine, with aryl iodides.[87]

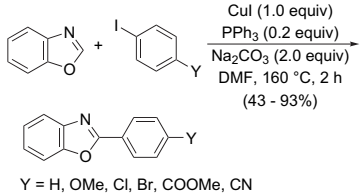
As shown in Scheme 61, where the results of representative arylations of benzoxazole are summarised, the method entails the use of a molar excess of aryl iodides, DMF as solvent, and LiO*t*-Bu as the base under ligandless conditions. Notably, this protocol also enabled the efficient C-6 arylation of 2-phenylpyridine-*N*-oxide with iodobenzene,[87] but suffers from a limitation due to the fact that it requires the use of a large excess of aryl iodides and the strongly basic LiO*t*-Bu.



Ar	Yield (%)
4-$CF_3C_6H_4$	91
4-FC_6H_4	90
4-$MeOC_6H_4$	80
3,5-$(Me)_2C_6H_3$	85
2-MeC_6H_4	91
2,4,6-$(Me)_3C_6H_2$	55
1-naphthyl	90
2-pyridyl	89

Scheme 61. CuI-catalysed C-2 arylation of benzoxazole.

More recently, Miura and co-workers have performed C-2 arylation reactions of 1,3-benzoazole compounds, including benzoxazole, 1-methyl-1*H*-benzimidazole, and benzothiazole, with a molar excess of aryl iodides in the presence of a stoichiometric amount of CuI, a catalytic quantity of PPh_3 as the supporting ligand, and a molar excess of Na_2CO_3 or K_3PO_4 as the base in DMF or DMSO.[88] Remarkably, the use of these mild bases made various functional groups tolerant in these copper-mediated reactions. Scheme 62 illustrates the CuI-mediated C-2 arylation of benzoxazole with aryl iodides.

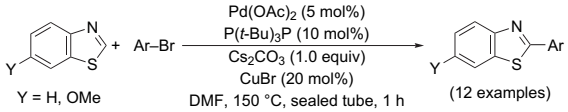


Scheme 62. CuI-mediated C-2 arylation of benzoxazole with aryl iodides.

3.2. (Hetero)arylation of thiazole and benzothiazole ring systems

Several protocols for the palladium-catalysed direct arylation of thiazole[24,32,35,37,41,51,87] and benzothiazole ring systems[20a,33,36,42,52] with aryl halides have been described in the previous sections of this article. However, in recent years, a number of additional procedures for the palladium-catalysed direct C-2 arylation of thiazole, its derivatives, and benzothiazole have been developed.[89–102]

In 2005, the efficient C-2 arylation of thiazole and other electron-sufficient five-membered heteroarenes with aryl halides was performed by Fagnou and co-workers by the use of $Pd(OH)_2$ on carbon as the catalyst under ligandless conditions.[89] Within the same year, Tamagnan and co-workers reported the high yielding synthesis of a variety of 2-arylbenzothiazoles by direct coupling of benzothiazoles with aryl bromides in DMF at 150 °C in a sealed tube in the presence of Cs_2CO_3 as the base and catalytic amounts of $Pd(OAc)_2$, P(*t*-Bu)$_3$ and CuBr (Scheme 63).[90] Interestingly, 2-arylbenzoxazoles could be analogously synthesised in good yields from benzoxazole and aryl bromides.[90]

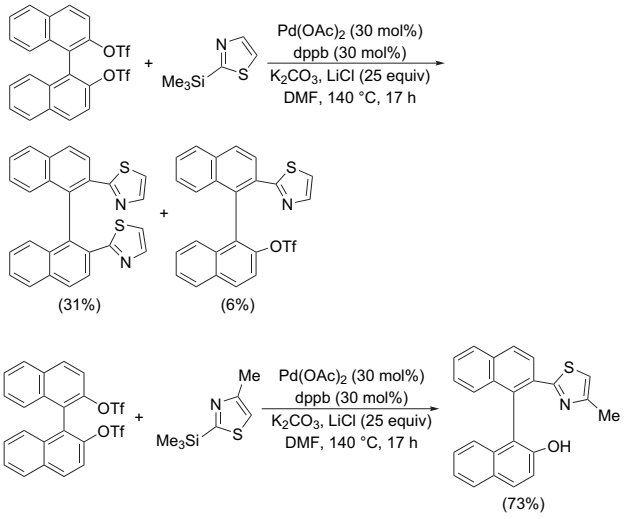


Scheme 63. $Pd(OAc)_2$/P(*t*-Bu)$_3$/CuBr-catalysed C-2 arylation of benzothiazoles with aryl bromides.

It should be noted that a catalyst system composed of $Pd(OAc)_2$ and P(*t*-Bu)$_3$, but lacking in CuBr, had been previously employed by Miura and co-workers for the C-2 arylation of benzothiazole and the C-5 arylation of 2-substituted thiazoles with aryl bromides in DMF at 150 °C.[102]

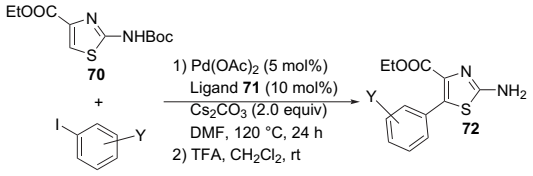
This research group had also discovered that the use of a less polar solvent such as *o*-xylene and P(bipheny-2-yl)(*t*-Bu)$_2$ as the ancillary ligand was essential for the successive 4,5-diarylation of a thiazole substrate having a 5-carboxyanilide as a sacrificial group.[102]

In 2006, Hamada and co-workers showed that 2-trimethylsilylthiazoles serve as efficient substrates for the synthesis of 2-arylthiazoles by a direct palladium-catalysed cross-coupling reaction with biaryl triflates without the use of any fluoride source.[91] Two representative examples of these reactions, which were performed in DMF at 140 °C in the presence of K_2CO_3, LiCl and a $Pd(OAc)_2$/dppb catalyst system, are shown in Scheme 64.



Scheme 64. Pd-catalysed reaction of 2-trimethylsilylthiazoles with biaryl triflates.

One year later, Priego and co-workers published a new synthetic route to afford 2-amino-5-arylthiazoles **72** in high yields via direct C-5 arylation of *N*-protected 2-aminothiazole **70** with aryl iodides in DMF at 140 °C in the presence of of Cs_2CO_3 as the base and a catalyst system composed of $Pd(OAc)_2$ and DavePhos (**71**), followed by treatment with trifluoroacetic acid in CH_2Cl_2 (Scheme 65).[92]



Y	Yield (%)
H	80
3-Me	76
4-*i*-Pr	90
3-NO_2	45
3-Cl	79
4-Cl	85
3,4-Cl_2	75
4-NO_2	48

Scheme 65. Synthesis of 2-amino-5-arylthiazoles **72**.

Mechanistic studies of the palladium-catalysed reaction suggested a proton-abstraction pathway involving a transition state **73** (Fig. 3).[92] This pathway was similar to that proposed by Echavarren, Maseras and co-workers for a related intramolecular direct arylation reaction.[103]

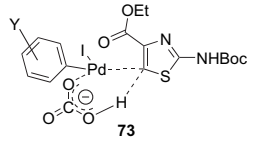
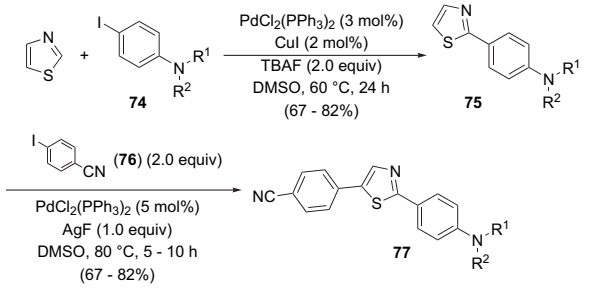


Figure 3. Transition state for Pd-catalysed C-5 arylation of compound **70**.

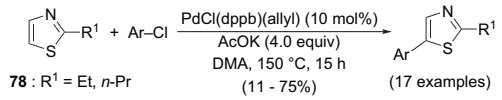
In 2007, a two-step process involving direct arylation reactions was used by Mori and co-workers for the synthesis of 2,5-diarylthiazoles **77** bearing electron-withdrawing cyano and electron-donating *N*,*N*-dialkylamino groups at the 5- and 2- position, respectively (Scheme 66).[93] Thus, C-2 arylation of thiazole with 4-(*N*,*N*-dialkylamino)iodobenzenes **74** in the presence of TBAF as the activator and a $PdCl_2(PPh_3)_2$/CuI catalyst system gave the compounds **75** in good yields. A further C–H arylation of these heteroarenes at the 5-position with 4-iodobenzonitrile (**76**) was carried out in DMSO at 80 °C in the presence of AgF and a catalytic amount of $PdCl_2(PPh_3)_2$ to afford the donor–acceptor type 2,5-diarylthiazoles **77**, showing strong light emission,[23b] in 32–57% overall yields.[93]



Scheme 66. Synthesis of donor–acceptor-type 2,5-diarylthiazoles **77**.

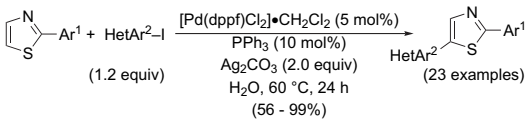
It should be noted that Mori and co-workers had previously found that AgF is transformed into AgI when the palladium-catalysed C–H arylation of thiazole or thiophene is performed with aryl iodides.[15c]

Again in 2007, Gottumukkala and Doucet reported that the 2-substituted thiazoles **78** undergo C-5 arylation with activated aryl chlorides containing a range of functionalities such as acetyl, formyl, ester, nitro, nitrile or trifluoromethyl when reacted in DMA at 150 °C in the presence of AcOK as the base and catalytic amounts of the air-stable PdCl(dppb)(allyl) complex (Scheme 67).[94]



Scheme 67. Direct C-5 arylation of 2-substituted thiazoles with aryl chlorides.

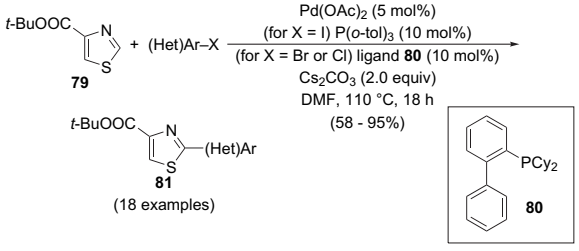
Within the same year, Greaney and co-workers developed the first methodology for the direct C-5 arylation of 2-arylthiazoles with aryl iodides on water.[96] In this method, which compares favourably with existing thiazole arylations[50,89,90,102] working in higher yields for a greater substrate range and being significantly milder, the reactions are performed at 60 °C in the presence of Ag_2CO_3 and a $[Pd(dppf)Cl_2]\cdot CH_2Cl_2$/$PPh_3$ catalyst system (Scheme 68). Remarkably, the on-water reactions proved to be entirely unsuccessful when they were carried out in the absence of Ag_2CO_3.[96]



Scheme 68. Direct C-5 arylation of 2-arylthiazoles on-water.

It is also worth noting that, as far as we know, this C-5 arylation method on water as well as all those reported in this section of the review have never been tested for the direct C-5 arylation of thiazole with an unblocked C-2 position.

More recently, a large variety of *t*-butyl 2-(hetero)aryl-4-thiazolecarboxylates **81** have been synthesised by direct palladium-catalysed C-2 arylation of *t*-butyl 4-thiazolecarboxylate (**79**) with (hetero)aryl iodides, bromides and chlorides (Scheme 69).[95] The reactions involving (hetero)aryl iodides were performed using P(*o*-tol)$_3$ as the ancillary ligand, but those with (hetero)aryl bromides and chlorides were found to require the use of 2-dicyclohexylphosphinobiphenyl (**80**) as the ligand.[95]

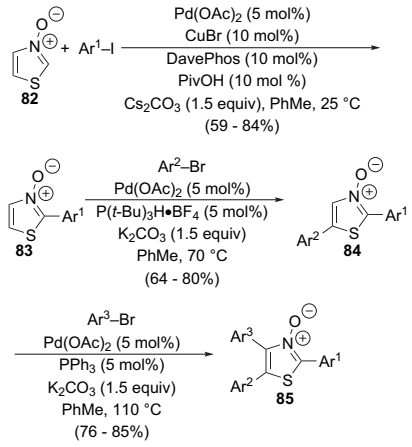


Scheme 69. Direct C-2 arylation of *t*-butyl 4-thiazolecarboxylate (**79**).

In 2008, Fagnou and co-workers made the highly important discovery that the *N*-oxide group imparts a dramatic increase in reactivity in direct palladium-catalysed arylation at all positions of the azole ring.[97] It was found that this group permits regioselective, high yielding, and room temperature arylation at C-2 of thiazole-*N*-oxide (**82**), high yielding arylation at C-5 of the resulting

2-arylthiazole-*N*-oxides **83**, and also C-4 arylation of the so obtained 2,5-diaryl-thiazole-*N*-oxides **84**, thus providing a very useful entry into exhaustively arylated thiazole derivatives **85**.

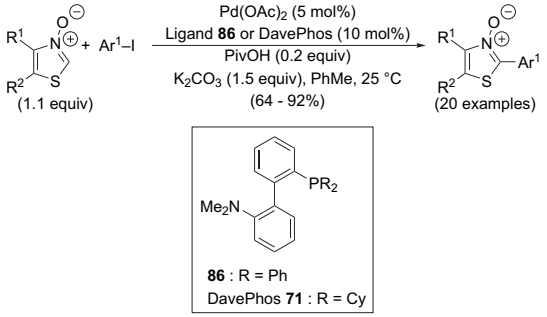
As illustrated in Scheme 70, the synthesis of compounds **83** was performed in toluene at room temperature in the presence of Cs_2CO_3, a $Pd(OAc)_2$/CuBr/DavePhos/pivalic acid catalyst system and by the use of aryl iodides as electrophiles.



Scheme 70. Synthesis of 2,4,5-triarylthiazole-*N*-oxides **85** by sequential arylation of thiazole-*N*-oxide (**82**).

On the other hand, a $Pd(OAc)_2/P(t\text{-}Bu)_3\cdot HBF_4$ catalyst system was used for the C-5 arylation of compounds **83** with aryl bromides in toluene at 70 °C in the presence of K_2CO_3 as the base, but more forcing conditions proved to be necessary to convert the resulting compounds **84** into **85**. In fact, the compounds **84** were reacted with aryl bromides in refluxing toluene in the presence of K_2CO_3 as the base and a $Pd(OAc)_2/PPh_3$ catalyst system. Interestingly, the compounds **85** could be easily deoxygenated by treatment with zinc powder and aqueous NH_4Cl in THF.[97]

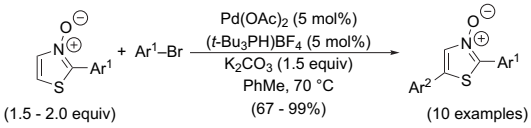
In 2009, in continuation of these studies Fagnou and co-workers have found that thiazole-*N*-oxides undergo C-2 direct arylation by treatment with activated and unactivated aryl bromides in toluene at room temperature in the presence of K_2CO_3 as the base, pivalic acid as the additive and a catalyst system consisting of a mixture of $Pd(OAc)_2$ and 2-diphenylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl (**86**) as the optimal ligand (Scheme 71).[98]



Scheme 71. C-2 direct arylation of thiazole-*N*-oxides.

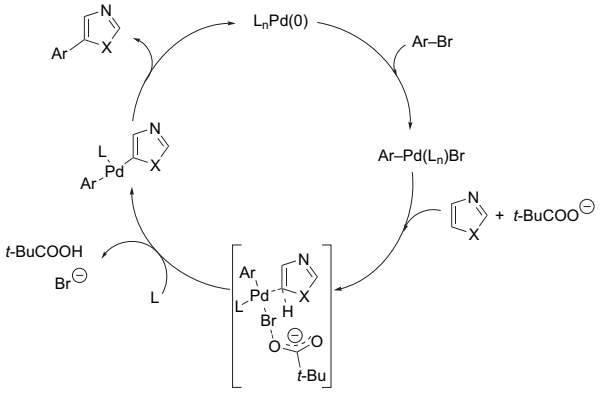
Interestingly, superior yields have been obtained by switching the ligand from **86** to DavePhos (**71**) when sterically congested aryl bromides were used as electrophiles.[98]

It has also been found that C-2 arylated thiazole-*N*-oxides can undergo highly selective C-5 arylation by treatment, as previously reported,[97] with aryl bromides in toluene at 70 °C in the presence of K_2CO_3 and a $Pd(OAc)_2/P(t\text{-}Bu)_3\cdot HBF_4$ catalyst system (Scheme 72). Under these conditions good yields of 2,5 diarylated thiazole-*N*-oxides have been obtained also using sterically encumbered aryl bromides.[98]



Scheme 72. C-5 direct arylation of 2-arylthiazole-*N*-oxides.

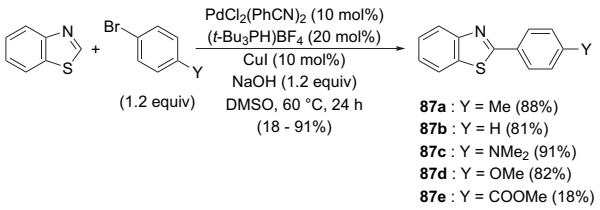
Recently, Fagnou's research group has also established that the regioselectivity and reactivity observed in the $Pd(OAc)_2/PCy_3$-catalysed direct arylation reactions of thiazole-*N*-oxides and other heteroarenes, including thiophene, benzothiophene, furan, indolizine, imidazo[1,2-*a*]pyridine and pyridine-*N*-oxide, with aryl bromides in DMA in the presence of pivalic acid can be predicted by a concerted-metalation–deprotonation (CMD) mechanism (Scheme 73), which involves concerted metalation of the heteroarene and H-transfer to the pivalate ligand.[66] DFT and B3LYP exchange correlation functional experiments supported this mechanism.[66] On the other hand, it was observed that 3-fluorobenzothiophene reacts preferentially over the more nucleophilic benzothiophene with several aryl bromides. Thus, this reactivity was not consistent with an S_EAr mechanism, but was compatible with a CMD pathway.[66]



Scheme 73. CMD-pathway for Pd-catalysed arylation of 1,3-azoles with aryl bromides.

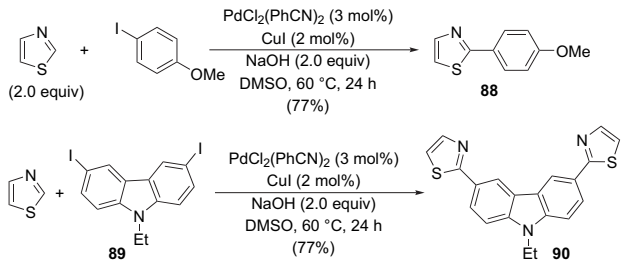
Again in 2009, a new protocol for the regioselective arylation of thiazole and benzothiazole has been developed by Miyaoku and Mori.[99]

They used NaOH as a new activator for the reaction of benzothiazole with aryl bromides in DMSO at 60 °C in the presence of a $PdCl_2(PhCN)_2/P(t\text{-}Bu)_3\cdot HBF_4$/CuI catalyst system ,which generally provides 2-arylthiazoles **87a**–**e** in excellent yields (Scheme 74). A low yield, probably due to a concurrent saponification reaction, was obtained only in the preparation of compound **87e**.



Scheme 74. Use of NaOH as activator for the Pd/Cu-catalysed C-2 arylation of benzothiazole with aryl bromides.

Miyaoku and Mori also found that the reaction of a molar excess of thiazole with 4-iodoanisole in DMSO at 60 °C in the presence of NaOH as the base and catalytic amounts of $PdCl_2(PPh_3)_2$ and CuI provides compound **88** in 77% yield (Scheme 75).



Scheme 75. Use of NaOH as activator for the Pd/Cu-catalysed synthesis of compounds **88** and **90.**

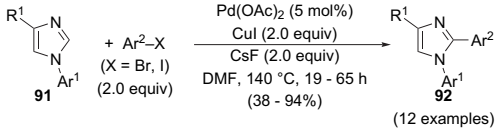
Furthermore, these authors showed that similar reaction conditions can be used for the preparation of compound **90**, which is potentially useful for the preparation of photoluminescent materials, from the bifunctional aryl iodide **89** and thiazole (Scheme 75).[99]

Very recently it has also been shown that ligand-free $Pd(OAc)_2$ is capable of catalysing very efficiently the direct arylation of thiazole derivatives at very low catalyst loadings.[100] By using activated aryl bromides, the reaction can be performed employing as little as 0.1–0.01 mol % catalyst, but disappointing results are obtained when sterically congested aryl bromides or strongly deactivated aryl bromides are used as arylating reagents.[100]

On the other hand, differently substituted 2,5-diarylthiazole derivatives have been very recently synthesised by Mori and coworkers in modest-to-low overall yields via $PdCl_2(PPh_3)_2$-catalysed, $AgNO_3$-mediated C–H arylation at the 5-position and C–C bond activation at the 2-position of a thiazole derivative masked at C-2 by a (hydroxy)diphenylmethyl group.[101] The C-5 arylation reactions were carried out using aryl iodides as electrophiles in DMSO at 100 °C in the presence of KF as the base, and the resulting arylated derivatives were found to undergo $Pd(OAc)_2$/P(biphenylene-2-yl)(t-Bu)$_2$-catalysed arylation at the 2-position with aryl iodides in xylenes at 150 °C in the presence of Cs_2CO_3 as the base through the C–C bond activation.[101]

3.3. (Hetero)arylation of imidazole and benzimidazole ring systems

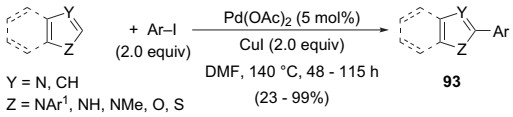
In 2006, our research group disclosed an efficient procedure for the highly regioselective synthesis of 1,2-diaryl-1*H*-imidazoles **92** via ligandless $Pd(OAc)_2$-catalysed and CuI-mediated C-2 arylation of 1-aryl-1*H*-imidazoles **91** with aryl iodides and bromides in DMF at 140 °C in the presence of CsF (Scheme 76).[104]



Scheme 76. Pd-catalysed and Cu-mediated C-2 arylation of 1-aryl-1*H*-imidazoles.

This simple and practical method, which compares favourably with those previously reported in the literature that are based on the construction of the imidazole ring,[105] allowed us to prepare 1,2-diaryl-1*H*-imidazoles **92** containing electron-donating and/or electron-withdrawing substituents on the aryl groups linked at their N-1 and C-2-substituted positions.[104] Compounds **92** included a selective COX-2 inhibitor and derivatives able to exhibit significant cytotoxic activity against some human tumor cell lines.

Shortly afterwards, we found that a number of different 1,3-azoles, including *N*-imidazoles, free (NH)-imidazole, -benzimidazole and -indole, thiazole and oxazole, undergo highly regioselective arylation by treatment with aryl iodides in DMF at 140 °C in the presence of a suprastoichiometric amount of CuI and a catalytic quantity of ligandless $Pd(OAc)_2$ under base-free conditions to give the corresponding 2-arylated derivatives **93** in moderate to excellent yields (Scheme 77).[50,55] Remarkably, no product of N-arylation of *N*-unprotected heteroarenes were observed under these experimental conditions.



Scheme 77. Pd-catalysed and Cu-mediated C-2 arylation of 1,3-azoles with aryl iodides under base-free and ligandless conditions.

Some so-prepared novel compounds **93** and 1,5-diaryl-1*H*-imidazoles **94** were evaluated for their in vitro antitumor activity against the NCI 60 human tumor cell line panel[106] and it was established that compounds **94a** and **94b** were more cytotoxic than combretastatin A-4 (**95**) (Fig. 4), a potent antimitotic agent isolated from the stem of *Combretum caffrum*,[107] of which they are structural analogues.

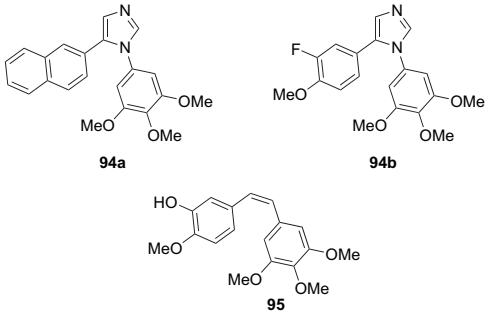
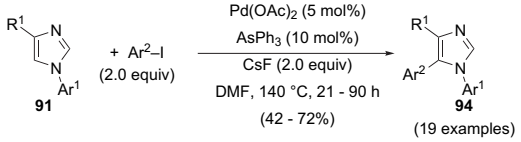


Figure 4. Structures of compounds **94a**, **94b** and **95**.

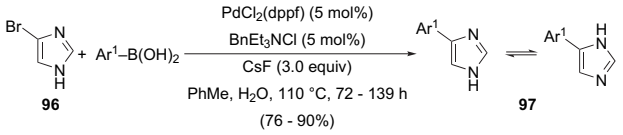
The compounds **94** were regioselectively synthesised in satisfactory to good yields by coupling of 1-aryl-1*H*-imidazoles **91** with aryl iodides in DMF at 140 °C in the presence of CsF as the base and a catalyst precursor composed of $Pd(OAc)_2$ and $AsPh_3$ (Scheme 78).[108]



Scheme 78. Regioselective synthesis of 1,5-diaryl-1*H*-imidazoles **94**.

In 2007, we focused our attention on the development of efficient and practical methods to access 4(5)-aryl-1*H*-imidazoles **97**. In fact, many of these compounds elicit important biological and pharmacological properties.[109] Our initial investigations were turned to the preparation of **97** by direct C-5 arylation of free (NH)-imidazole with aryl iodides, but, to our disappointment no expected arylation product was obtained when the reaction was carried out in DMF at 140 °C in the presence of 2 equiv of a base such as Cs_2CO_3 or AcOK and a catalyst system such as $Pd(OAc)_2$/P(2-furyl)$_3$ or $Pd(OAc)_2$/PPh_3.[110] We then searched for an alternative synthetic route and

found that a large variety of compounds **97** could be efficiently and selectively prepared by a $PdCl_2$(dppf)-catalysed Suzuki–Miyaura reaction of the commercially available, 4(5)-bromo-1*H*-imidazole (**96**), with arylboronic acids in a refluxing mixture of toluene and water in the presence of a suprastoichiometric quantity of CsF and 5 mol % $BnEt_3NCl$ (Scheme 79).[110]



Scheme 79. Synthesis of 4(5)-aryl-1*H*-imidazoles **97** from 4(5)-bromo-1*H*-imidazole (**96**).

We also speculated that heteroarenes **97** might be conveniently prepared via a two-step reaction sequence involving the regioselective C-5 arylation of an *N*-protected imidazole such as 1-benzyl-1*H*-imidazole (**98**), followed by N-deprotection of the resulting arylated derivatives **99** (Fig. 5).

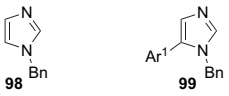
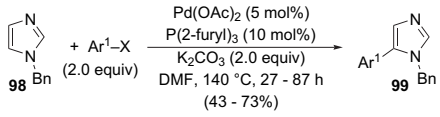


Figure 5. Structures of compounds **98** and **99**.

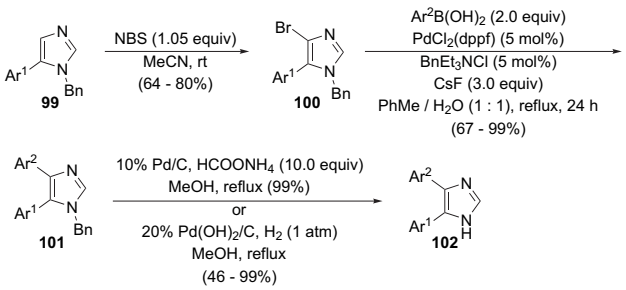
In a study on this subject we found that the commercially available **98** undergoes $Pd(OAc)_2$/P(2-furyl)$_3$-catalysed arylation both with electron-neutral and electron-deficient aryl bromides in DMF in the presence of K_2CO_3 as the base to give 5-aryl-1-benzyl-1*H*-imidazoles **99** in good yields and 94–100% C-5 regioselectivity (Scheme 80).[111]



Scheme 80. Direct C-5 arylation of 1-benzyl-1*H*-imidazole (**98**).

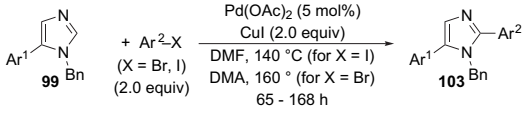
Compounds **99** could be converted into 4(5)-aryl-1*H*-imidazoles **97** in high yields by treatment with a large molar excess of ammonium formate in refluxing methanol in the presence of Pd/C or Pearlman's reagent.[111]

The application of 5-aryl-1-benzyl-1*H*-imidazoles **99** in the synthesis of 4,5-diaryl- and 2,4(5)-diaryl-1*H*-imidazoles **102** and **104**, respectively, was also investigated.[111] It was found that the compounds **102** could be regioselectively prepared via a three-step reaction sequence involving the regioselective C-4 bromination of **99** and a palladium-catalysed Suzuki-type reaction of the resulting bromoimidazoles **100** with arylboronic acids, followed by catalytic N-debenzylation of the so-obtained 1-benzyl-4,5-diaryl-1*H*-imidazoles **101** (Scheme 81).[111]



Scheme 81. Synthesis of 4,5-diaryl-1*H*-imidazoles **102**.

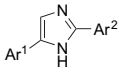
On the other hand, some representative 2,4(5)-diaryl-1*H*-imidazoles **104** were regioselectively synthesised via palladium-catalysed and copper-mediated C-2 arylation of the compounds **99** with aryl bromides and iodides under base-free and ligandless conditions, followed by catalytic N-debenzylation of the resulting 2,5-diaryl-1-benzyl-1*H*-imidazoles **103**.[111] As illustrated in Scheme 82, compounds **103a**, **103b**, **103d** and **103e** were so obtained in satisfactory yields, but unexpectedly, **103c** and **103f** were both isolated in 21% yield.



			Product	
Ar^1	Ar^2	X	**103**	Yield (%)
4-$MeOC_6H_4$	Ph	I	**103a**	56
Ph	4-$MeOC_6H_4$	I	**103b**	88
4-$MeOC_6H_4$	4-$MeOC_6H_4$	I	**103c**	21
Ph	2-naphthyl	Br	**103d**	59
4-MeC_6H_4	4-(EtOOC)C_6H_4	Br	**103e**	65
5-pyrimidyl	4-$MeOC_6H_4$	Br	**103f**	21

Scheme 82. Pd-catalysed and Cu-mediated C-2 arylation of compounds **99**.

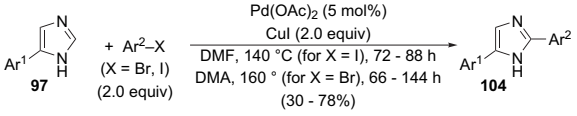
Compounds **103a** and **103b** were then converted into the corresponding 2,4(5)-diaryl-1*H*-imidazoles, **104a** and **104b** (Fig. 6), by a clean and efficient N-debenzylation reaction with a molar excess of ammonium formate in refluxing methanol in the presence of 10% Pd/C. On the other hand, compound **104c** was prepared from **103c** by the use of Pearlman's reagent and ammonium formate as the hydrogen source in refluxing methanol.



104a : Ar^1 = 4-$MeOC_6H_4$; Ar^2 = Ph
104b : Ar^1 = Ph; Ar^2 = 4-$MeOC_6H_4$
104c : Ar^1 = Ar^2 = 4-$MeOC_6H_4$
104d : Ar^1 = Ph; Ar^2 = 2-naphthyl

Figure 6. Structures of compounds **104a–d**.

This protocol, however, proved to be unsuitable to convert **103d** into **104d** (Fig. 6), but this imidazole derivative could be obtained in high GLC yield by debenzylation of **103d** with H_2 at atmospheric pressure in the presence of $Pd(OH)_2$/C in refluxing methanol.[111] Notably, this protocol for the three-step synthesis of compounds **104** from 1-benzyl-1*H*-imidazole (**98**) proved to give overall yields similar to those obtained by the procedure involving their two-step preparation via a Suzuki-type reaction of **96** with arylboronic acids, followed by highly regioselective palladium-catalysed and copper-mediated C-2 arylation of the resulting 4(5)-aryl-1*H*-imidazoles **97**, both with activated and deactivated aryl bromides and iodides under base-free and ligandless conditions (Scheme 83).[110]

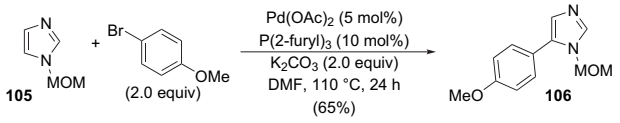


Scheme 83. C-2 arylation of 4(5)-aryl-1*H*-imidazoles **97**.

Nevertheless, the difficulties occasionally encountered in the N-debenzylation of 1-benzyl protected imidazole derivatives prompted us to investigate the corresponding 1-MOM protected derivatives in direct palladium-catalysed arylation reactions. In

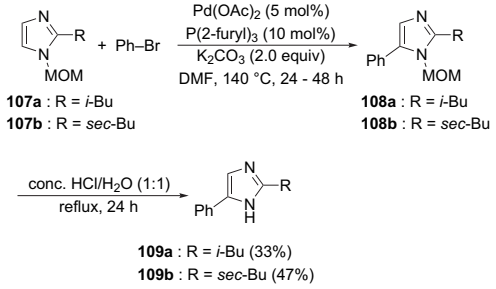
fact, we hoped that the deprotection of 1-MOM-1*H*-imidazoles might be easily performed under acidic conditions.

In a preliminary study, we found that 1-MOM-1*H*-imidazole (**105**) undergoes arylation with 4-bromoanisole in DMF at 110 °C in the presence of K_2CO_3 as the base and a $Pd(OAc)_2$/P(2-furyl)$_3$ catalyst system to give 5-(4-methoxyphenyl)-1-MOM-1*H*-imidazole (**106**) with complete C-5 selectivity and in 65% yield (Scheme 84).[112] As expected, compound **106** underwent complete N-deprotection by treatment with dilute HCl at 90 °C.



Scheme 84. Direct C-5 arylation of 1-MOM-1*H*-imidazole (**106**) with 4-bromoanisole.

In the light of this finding, we next synthesised catharsitoxins D and E, **109a** and **109b**, respectively, which are two naturally occurring 2-alkyl-4(5)-phenyl-1*H*-imidazoles isolated from the Chinese remedy, quing laug,[113] via a reaction sequence involving the direct palladium-catalysed C-5 arylation of 2-substituted 1-MOM-protected 1*H*-imidazoles **107a** and **107b** with bromobenzene, followed by N-deprotection of the resulting heteroarenes **108a** and **108b**, respectively (Scheme 85).[112] Investigations to improve the unsatisfactory overall yields of this protocol are under way.



Scheme 85. Synthesis of catharsitoxin D (**109a**) and catharsitoxin E (**109b**).

Recently, our continuing interest in the regioselective synthesis of biologically active vicinal diaryl-substituted five-membered heteroarenes,[70,105,114] has led us to turn our attention also to the synthesis and evaluation of the cytotoxic activity against human tumor cell lines of 4,5-diaryl-1-methyl-1*H*-imidazoles **110**. On the other hand, Wang and co-workers had previously reported that compounds **110a** and **110b** (Fig. 7) exhibit significant cytotoxic and antitubulin activities and are characterised by excellent bioavailability and pharmacokinetic properties.[115]

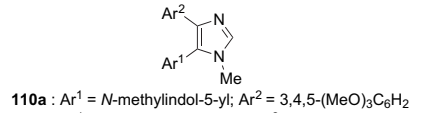
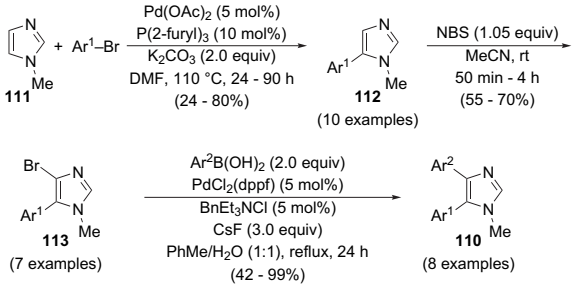


Figure 7. Structures of compounds **110a** and **110b**.

It was our goal to prepare compounds **110** possessing cytotoxic activity much higher than that of the previously described imidazole derivatives using an environmentally friendly and inexpensive procedure suitable to be scaled up for synthesising amounts of these heteroarenes suitable for biological testing.

The results of a preliminary study concerning such a method were briefly mentioned in a review on the synthesis and biological properties of vicinal diaryl-substituted 1*H*-imidazoles[104] but, more recently, we developed an improved, general and efficient three-step procedure for the synthesis of compounds **110** bearing electron-rich, electron-neutral and/or electron-deficient aryl moieties at their 4- and 5-positions (Scheme 86).[115]



Scheme 86. Synthesis of imidazoles **110** via direct C-5 arylation of 1-methyl-1*H*-imidazole (**111**).

The first step of this procedure consists of the palladiun-catalysed C-5 arylation of the commercially available 1-methyl-1*H*-imidazole (**111**) with aryl bromides. In the second and the third step of the sequence, the resulting 5-aryl-1-methyl-1*H*-imidazoles **112** undergo selective C-4 bromination with NBS, followed by a $PdCl_2$(dppf)-catalysed Suzuki-type reaction between the so-obtained bromo derivatives **113** and arylboronic acids under phase-transfer conditions.[116]

As regards the first step of this process, it should be noted that the protocol used to prepare compounds **112** proved to offer advantages in terms of yields, selectivity and/or electronic nature of the aryl halides used as electrophiles over the previously reported procedures for the direct palladium-catalysed C-5 arylation of **111**.[18,19a,117,118]

It is also worth mentioning that some compounds, including **110c a**nd **110d** (Fig. 8), which were prepared according to the above reported three-step process, are structural analogues of combretastin A-4 (**95**) found to be highly cytotoxic against the panel of 60 human tumor cell lines of the NCI. In particular, **110d** proved to be more cytotoxic than **95** and all of the other imidazole tested at that time.[116]

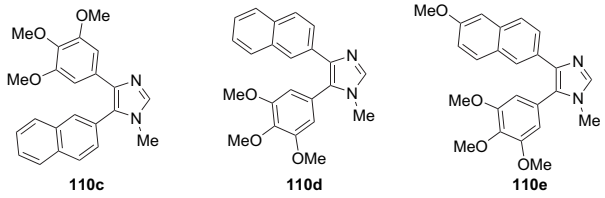
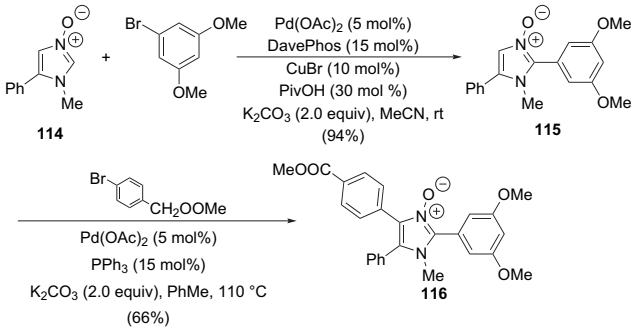


Figure 8. Structures of compounds **110c–e**.

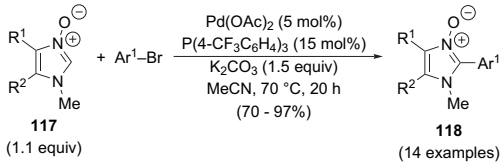
More recently, we have also found that compound **110e** (Fig. 8), which we prepared using the reaction sequence illustrated in Scheme 86, is more cytotoxic than **95**, but to a less extent than **110d**.[119]

In 2008, the stepwise, exhaustive transition metal-catalysed arylation of imidazole-*N*-oxide **114** was investigated by Fagnou and co-workers,[97] who found that **114** undergoes C-2 arylation by treatment with 1-bromo-3,5-dimethoxybenzene in acetonitrile at room temperature in the presence of K_2CO_3 and catalytic amounts of pivalic acid, DavePhos, $Pd(OAc)_2$ and CuBr (Scheme 87). The resulting arylated heteroarene-*N*-oxide **115** was then reacted with 4-bromoanisole in refluxing toluene in the presence of K_2CO_3 and a $Pd(OAc)_2/PPh_3$ catalyst system to give compound **116** in 62% overall yield (Scheme 87).[97]



Scheme 87. Stepwise C-2 and C-4 direct arylation of imidazole-*N*-oxide **114**.

Very recently, the experimental conditions to achieve the C-2 arylation of imidazole-*N*-oxides have been optimised and it has been found that 1-methylimidazole-3-oxides **117** bearing an alkyl or aryl group at the C-4 or C-5 position, when treated with aryl bromides in acetonitrile at 70 °C for 20 h in the presence of K_2CO_3 and a $Pd(OAc)_2/P(4\text{-}FC_6H_4)_3$ catalyst system, provide the corresponding C-2 arylated imidazole derivatives **118** in excellent yields (Scheme 88).[98]



Scheme 88. C-2 direct arylation of 1-methylimidazole-3-oxides **117**.

The compounds **118** have been synthesised alternatively by treatment of **117** with aryl bromides in acetonitrile at room temperature in the presence of K_2CO_3 and catalytic quantities of pivalic acid, CuBr, $Pd(OAc)_2$, and ligand **86**.[98]

It has also been found that, as determined with the thiazole-*N*-oxide substrates, when both the C-2 and C-5 positions of 1-methylimidazole-*N*-oxides are substituted, arylation can be achieved at C-4 under identical conditions used for thiazole-*N*-oxide compounds.[98] The potential utility of this methodology has been illustrated in a five-step synthesis of a Tie tyrosine kinase inhibitor **119** (Fig. 9).[98]

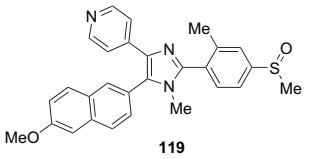
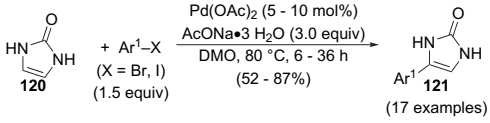


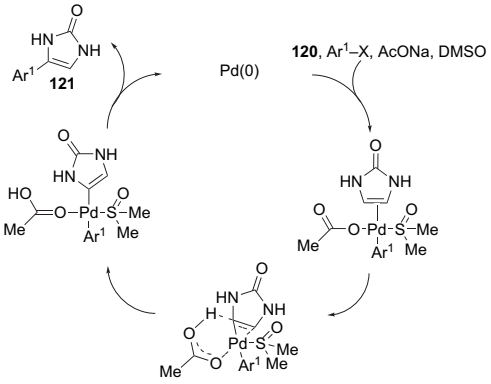
Figure 9. Structure of compound **119**.

Two years before this study, Chen and co-workers had demonstrated that the reaction of 2-imidazolinone (**120**) both with electron-deficient or electron-rich aryl iodides and electron-deficient aryl bromides in DMSO at 80 °C in the presence of $AcONa\cdot 3H_2O$ as the base and a catalytic quantity of ligandless $Pd(OAc)_2$ produces 5-aryl-2-imidazolinones **121** in high yields (Scheme 89).[120]



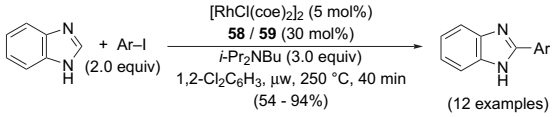
Scheme 89. Direct C-5 arylation of 2-imidazolinone (**120**).

On the basis of an observed primary kinetic isotope effect (KIE) in the competing experiment of **120** with 4,5-dideuterated **120**, the authors ruled out the possibility of an electrophilic palladation mechanism and claimed the support of their DFT calculations for the acetate ligand-assisted C–H bond insertion pathway illustrated in Scheme 90.[120]



Scheme 90. Proposed mechanism for Pd-catalysed arylation of 2-imidazolinone (**121**).

Remarkably, direct C-arylation reactions of benzimidazole and imidazole derivatives have also been carried out by using rhodium-based catalysts.[68,121] In 2006, Bergman, Ellman and co-workers used a catalyst system composed of $[RhCl(coe)_2]_2$ and a mixture of phosphines (phobans) **58** and **59** in the microwave-promoted arylation of free (NH)-benzimidazole with aryl bromides (Scheme 91).[68a] In 2008, it was found that the *P*-olefin complex, which was prepared from $[RhCl(coe)_2]_2$ and **58** in THF at 125 °C and characterised by single-crystal X-ray analysis, allowed the arylation of benzimidazole to be performed with a rate and a yield similar to those obtained with the use of $[RhCl(coe)_2]_2$ and a mixture of phobans **58** and **59**.[68b]



Scheme 91. Rh(I)/Ligand **58**/**59**-catalysed C-2 arylation of benzimidazole.

Within the same year, the structure of the [4.2.1] phoban isomers **58** and **59** was simplified and (*Z*)-1-*t*-butyl-2,3,6,7-tetrahydrophosphepine (**122**) (Fig. 10) was used as the ancillary ligand in the microwave-promoted $[RhCl(coe)_2]_2$-catalysed direct arylation of free (NH)-benzimidazole and other azoles, including 4,5-diaryl-1*H*-imidazoles, benzoxazole and benzothiazole, with aryl bromides in THF at 200 °C for 2 h in the presence of $i\text{-}Pr_2(i\text{-}Bu)N$.[121] By using the tetrafluoroborate of the phosphonium salt of **122**, the reactions could be assembled outside a glovebox without purification of the reagents or solvent to obtain excellent product yields. Functional groups such as acetamide, formamide, sulfoxide, free hydroxyl, and free amine were all tolerated.

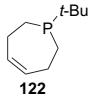
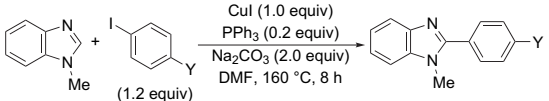


Figure 10. Structure of ligand **122**.

It should be noted that ligand **122** coordinates to rhodium in a bidentate *P*-olefin fashion to provide a highly active, yet thermally stable, arylation catalyst, which is essential to the success of this

method. Moreover, the unique reactivity of this ligand, compared with that of the ligands previously investigated, suggests that the *P*-olefin coordination modulates the reactivity of the rhodium center to enable the required heteroarene arylation, while reducing off-cycle hydrodehalogenation of the aryl bromides.[121]

In concluding this section, it should be mentioned that the direct C-arylation of benzimidazole derivatives has also been achieved using copper(I) derivatives as catalyst components. In fact, in 2008, Miura and co-workers found that 1-methyl-1*H*-benzimidazole undergoes C-2 arylation in fair to good yields by treatment with aryl iodides in DMF at 160 °C in the presence of Na_2CO_3 as the base, a stoichiometric amount of CuI and a catalytic amount of PPh_3 (Scheme 92).[88]

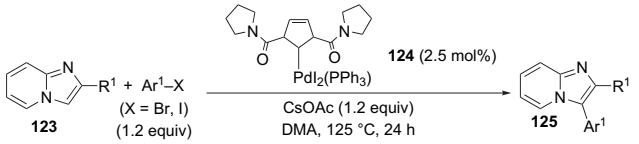


Y	Yield (%)
H	75
Cl	89
Br	60
COOMe	52
CN	69

Scheme 92. Cu-mediated C-2 arylation of 1-methyl-1*H*-benzimidazole.

3.4. (Hetero)arylation of imidazo[1,2-*a*]pyridine, imidazo[1,2-*a*]pyrimidine, purine (imidazo[4,5-*d*]pyrimidine), imidazo[1,5-*a*]pyrazine, imidazo[1,2-*b*]pyridazine, imidazo[1,2-*b*][1,2,4]triazine, and imidazo[2,1-*f*][1,2,4]triazine ring systems

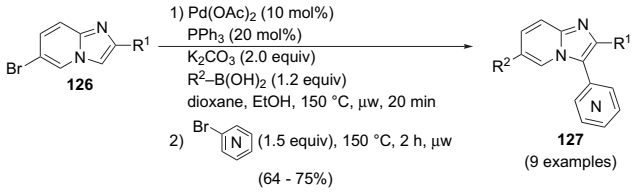
Imidazo[1,2-*a*]pyridines are a potentially useful class of heterocycles that include PI3 kinase p110α inhibitors,[122] potential agents for imaging β-amyloid in Alzheimer's disease,[123] HIF-1α prolyl hydroxylase inhibitors,[124] and inhibitors of THF-α expression in T cells.[125] These properties have stimulated the development of a number of useful methods for the synthesis of this class of heteroarenes.[126] In 2005, Sames prepared three 3-arylimidazo[1,2-*a*]pyridines **125** in good-to-excellent yields by direct C-3 arylation of imidazo[1,2-*a*]pyridines **123** with aryl halides in DMA at 125 °C in the presence of CsOAc as the base and a catalytic amount of the NHC–palladium(II) complex **124** (Scheme 93).[46]



R^1	Ar^1	X	Yield (%)
H	Ph	I	93
COOEt	Ph	I	98
COOEt	4-MeOOCC$_6$H$_4$	Br	51

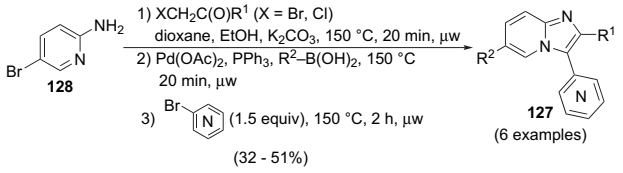
Scheme 93. Direct C-3 arylation of imidazo[1,2-*a*]pyridines **123**.

Shortly afterwards, Berteina-Raboin and co-workers[127] reported that imidazo[1,2-*a*]pyridines undergo high yielding direct C-3 arylation with aryl bromides in the presence of K_2CO_3 as the base and a $Pd(OAc)_2/PPh_3$ catalyst system under microwave irradiation or by conventional heating. Interestingly, the reactions proved to be compatible with the presence of a bromo or chloro substituent in the 6-position of the heteroarene. Subsequently, these authors developed two efficient methods for the synthesis of 2,3,6-trisubstituted imidazo[1,2-*a*]pyridine derivatives **127**.[128] The first method furnished these compounds in good yields via a microwave-assisted one-pot, two-step Suzuki/heteroarylation of 6-bromoimidazo[1,2-*a*]pyridines **126** (Scheme 94).



Scheme 94. Synthesis of 2,3,6-trisubstituted Imidazo[1,2-*a*]pyridines **127** via one-pot, two-step Suzuki/heteroarylation sequence.

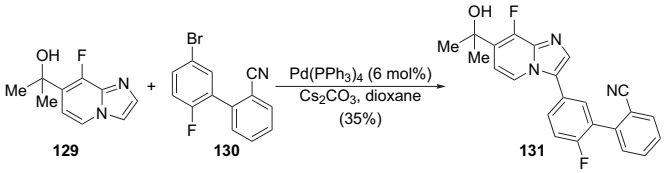
In the second method, the compounds **127** were synthesised via a one-pot, three step cyclisation/Suzuki/heteroarylation starting from 2-amino-5-bromopyridine (**128**) (Scheme 95).



Scheme 95. Synthesis of compounds **127** via one-pot, three-step cyclisation/Suzuki/heteroarylation sequence.

Interestingly, the $Pd(OAc)_2/PPh_3$ system proved to be the optimal catalyst system both for the Suzuki couplings and for the direct heteroarylation reactions.[128]

One year before the publication of these results, 8-fluoroimidazo[1,2-*a*]pyridine **131** was synthesised in 35% yield by C-3 arylation of compound **129** with 5′-bromo-2′-fluorobiphenylcarbonitrile (**130**) in dioxane in the presence of Cs_2CO_3 and 6 mol % $Pd(PPh_3)_4$ (Scheme 96).[129]



Scheme 96. Synthesis of compound **131**.

It should be noted that the 8-fluoroimidazo[1,2-*a*]pyridine moiety of **131** acts as a bioisostere of the imidazo[1,2-*a*]pyrimidine ring system in the $GABA_A$ receptor modulator **132** (Fig. 11).[129,130]

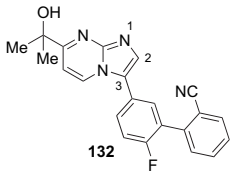
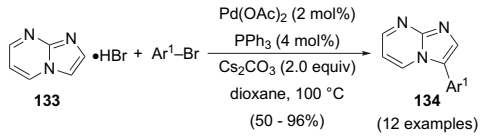


Figure 11. Structure of compound **132**.

The first synthesis of 3-arylimidazo[1,2-*a*]pyrimidines **134** by the palladium-catalysed direct arylation of imidazo[1,2-*a*]pyrimidine (**133**) was first reported by Li and co-workers in 2003.[131] The reaction, which was performed in dioxane at 100 °C in the presence of Cs_2CO_3 as the base and a $Pd(OAc)_2/PPh_3$ catalyst system, produced the compounds **134** in good-to-excellent yields (Scheme 97).



Scheme 97. C-3 arylation of imidazo[1,2-*a*]pyrimidine (**133**).

A very similar procedure was subsequently used for the synthesis of 2-[3-(3-chloro-4-fluorophenyl)imidazo[1,2-a]pyrimidin-7-yl]-propan-2-ol (**137**) from 2-imidazo[1,2-a]pyrimidin-7-yl-propan-2-ol (**135**) and the bromide **136** (Fig. 12),[132] as well as for the C-3 arylation of various imidazo[1,2-*a*]pyrimidines **138** (Fig. 12) bearing an aryl, carboxamide, or carboxylate function at the 2-position.[133] Compound **137** was used as a precursor to a $GABA_A$ $\alpha_{2,3}$-selective allosteric modulator.[132] On the other hand, C-3 arylation of compounds **138** provided access to a 45-membered library of 2,3-substituted imidazo[1,2-*a*]pyrimidines, including substances that possess interesting therapeutic properties.

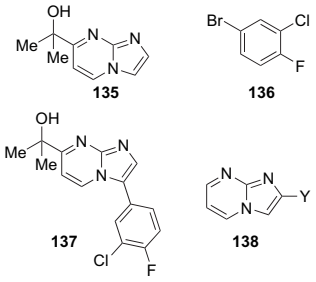
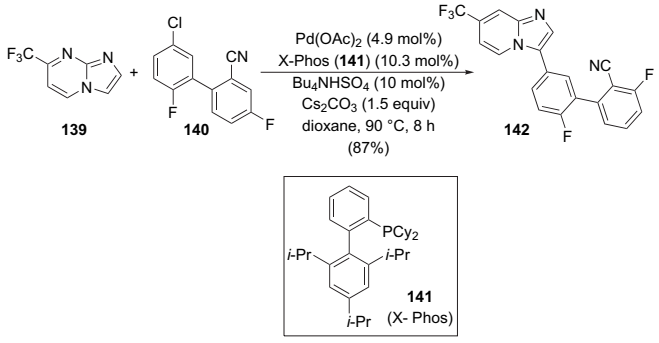


Figure 12. Structures of compounds **135**–**138**.

In fact, some 2,3-diarylimidazo[1,2-*a*]pyrimidines are selective COX-2 inhibitors[134] and 3-aryl-2-carboxamido-imidazo[1,2-*a*]pyrimidines include derivatives that display analgesic, antipyretic, and antiinflammatory activity.[135]

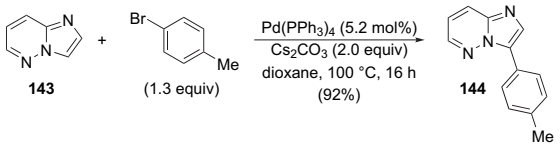
In 2006, 4,2′-difluoro-5′-(7-trifluoromethylimidazo[1,2-*a*]pyrimidin-3-yl)biphenyl-2-carbonitrile (**142**), a GABA $\alpha_{2,3}$ agonist, was synthesised in 87% yield by C-3 arylation of 7-trifluoromethylimidazo[1,2-*a*]pyrimidine (**139**) with the aryl chloride **140** in dioxane at 90 °C in the presence of Cs_2CO_3 and catalytic amounts of $Pd(OAc)_2$, 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (X-Phos) (**141**) and n-Bu_4NHSO_4 (Scheme 98).[136]



Scheme 98. Synthesis of imidazo[1,2-*a*]pyrimidine **142**.

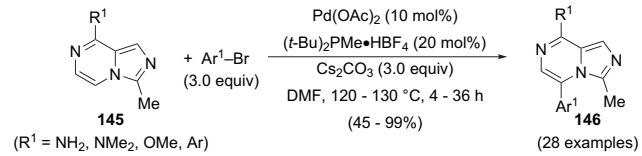
Even though a wide spectrum of biological and therapeutic properties is also shown by imidazo[1,2-*b*]pyridazine derivatives,[137] as far as we know, only one method has been reported in the literature to date for the synthesis of a 3-arylimidazo[1,2-*b*]pyridazine derivative via palladium-catalysed regioselective arylation of imidazo[1,2-*b*]pyridazine (**143**).[138]

In fact, Wang has recently described that treatment of **143** with 4-bromotoluene in dioxane at 100 °C in the presence of Cs_2CO_3 and a catalytic quantity of $Pd(PPh_3)_4$ gives 3-(4-tolyl)imidazo[1,2-*b*]pyridazine (**144**) in 92% yield (Scheme 99).[138]



Scheme 99. Direct C-3 arylation of imidazo[1,2-*b*]pyridazine (**144**).

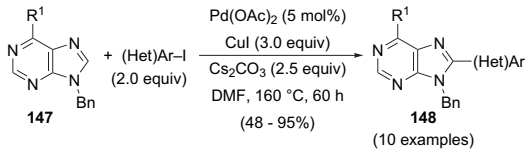
Numerous bioactive natural products, drugs, and drug candidates also contain imidazo[1,5-*a*]pyrazine structural units. These compounds include substances acting on a number of targets such as the CFR receptor,[139] $GABA_A$ receptor,[140] and melanocortin receptor.[141] However, until recently, the synthesis of arylated derivatives of imidazo[1,5-*a*]pyrazine by the transition metal-catalysed direct arylation of imidazo[1,5-*a*]pyrazines has received little attention. Only in 2008 it was reported that 3-methylimidazo[1,5-*a*]pyrazines **145** are able to react with aryl bromides in DMF at 120–130 °C in the presence of Cs_2CO_3 and catalytic amounts of $Pd(OAc)_2$ and $P(t\text{-}Bu)_2Me\cdot HBF_4$ to give the C-5 arylated derivatives **146** in good to excellent yields (Scheme 100).[142]



Scheme 100. Direct C-5 arylation of 3-methylimidazo[1,5-*a*]pyrazines **145**.

It should be noted that, in contrast to direct arylation of the imidazo[1,2-*a*]pyrimidines, arylation of compounds **145** proved to take place in the electron-deficient albeit electron-donor group-containing ring. Moreover, results of reactivity and KIE studies were found to be consistent with a Heck-type mechanism for the arylation of these heteroarenes.[142]

Within the past few years, greater attention has been directed to the development of efficient procedures for the regioselective direct C-arylation of purine (imidazo[4,5-*d*]pyrimidine) derivatives with aryl halides.[143–148] In 2006, Hocek and co-workers described that direct C-8 arylation of 9-benzyl-9*H*-purines **147** with (hetero)-aryl iodides can be achieved by a $Pd(OAc)_2$-catalysed and CuI-mediated reaction in DMSO at 160 °C in the presence of Cs_2CO_3 under ligandless conditions (Scheme 101).[143] The compounds **148** were so obtained in good to excellent yields.



Scheme 101. C-8 arylation of purines **147**.

This protocol was next applied, in combination with regioselective cross-coupling reactions of 2,6-dichloro-9*H*- purines **149a**, in the synthesis of 9-benzyl-9*H*-purines 9*H*-purines **150** bearing three different substituents at the 2, 6 and 8 positions

(Fig. 13).[143,148] Furthermore, this protocol was used in stepwise syntheses of 6,8,9-trisubstituted 9*H*-purines **151** and 8,9-diaryl-6-methyl-9*H*-purines **152**, in which compounds **149b** and **149c**, respectively (Fig. 13), were the starting heteroarenes.[148]

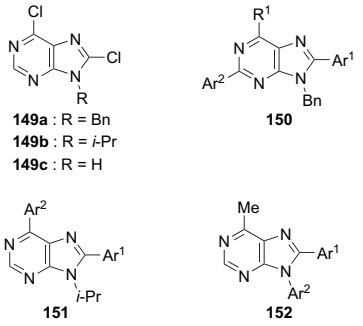
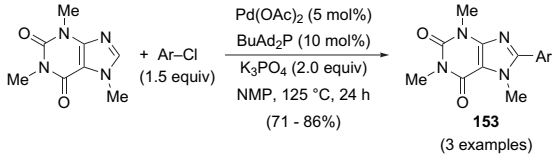


Figure 13. Structures of compounds **149a–c** and **150–152**.

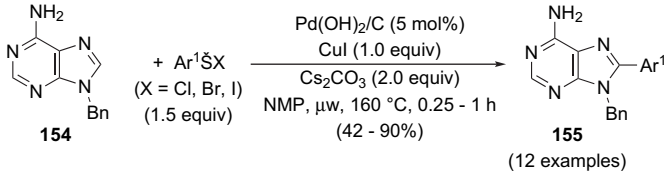
In this connection, it should be noted that 6,8,9-trisubstituted and 2,6,8,9-tetrasubstituted purines include compounds that display a wide range of biological properties.[149]

The arylation of caffeine at the C-8 position with aryl chlorides was described by Chiong and Daugulis in 2007.[144] The reaction, which was carried out in NMP at 125 °C in the presence of K_3PO_4 as the base and a catalyst system consisting of $Pd(OAc)_2$ and *n*-$BuAd_2P$, a bulky electron-rich phosphine, allowed the preparation of the compounds **153** in high yields (Scheme 102). Remarkably, this protocol was also useful for high-yielding arylations of a variety of electron-rich heteroarenes including thiophene, benzothiophene, 2-substituted thiazoles, 1-butyl-1*H*-imidazole, and 1-methyl-1,2,4-triazole.[144]



Scheme 102. Direct C-8 arylation of caffeine with aryl chlorides.

An efficient microwave-promoted C-8 regio- and chemoselective arylation of free-(NH_2) 6-amino-9-benzyladenine (**154**) with aryl iodides, bromides and chlorides involving the use of Pearlman's catalyst and a stoichiometric amount of CuI under ligandless conditions (Scheme 103) was described by Alami and co-workers in 2008.[147] This method enabled the rapid preparation of a variety of 6-amino-8-aryl-9-benzylpurines **155** in good-to-excellent yields without prior protection of the amino group of **154**.

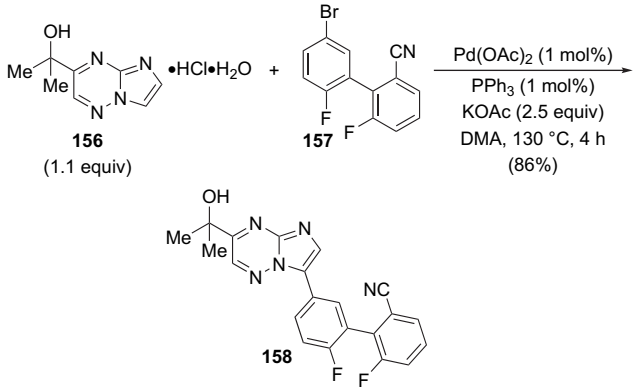


Scheme 103. C-8 arylation of 9-benzyladenine (**154**).

Within the same year, the synthesis of C-8 arylated free-(NH_2) adenine nucleosides in moderate-to-good yields by direct aryl functionalisation of free-(NH_2) adenine nucleosides was reported by Hocek[145] and Fairlamb.[146] The optimal conditions employed by these authors involve the use of $Pd(OAc)_2$ as the catalyst precursor in association with CuI, Cs_2CO_3 or piperidine as the base, and conventional heating in DMF.

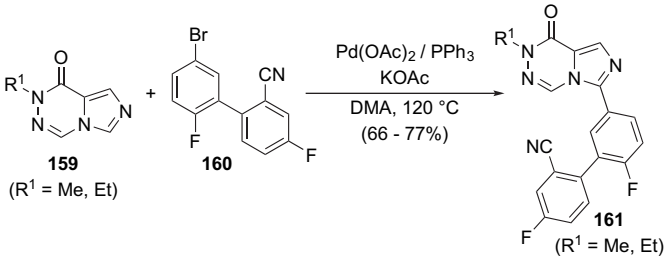
An important paper on this subject described the direct arylation of an imidazo[1,2-*b*][1,2,4]triazine.[150] In fact, aryl derivatives of these imidazotriazines, which are isosteres of purines, have been identified as $GABA_A$ $\alpha_{2,3}$ subtype selective agonists for the treatment of anxiety.[151]

In 2005, one of these compounds, 2′,6-difluoro-5′-[3-(1-hydroxy-1-methylethyl)imidazo[1,2-*b*][1,2,4]triazin-7-yl]biphenyl-2-carbonitrile (**158**), which is an orally active $GABA_A$ $\alpha_{2,3}$ selective agonist, was efficiently prepared on a multigram scale by a seven-step, chromatography-free, synthesis in which the final step was the highly regioselective $Pd(OAc)_2/PPh_3$-catalysed C-7 arylation of 2-imidazo[1,2-*b*][1,2,4]triazin-3-ylpropan-2-ol hydrochloride hydrate (**156**) with the bromide **157** in DMA at 120 °C in the presence of AcOK as a base (Scheme 104).[150]



Scheme 104. Pd-catalysed synthesis of compound **158**.

Finally, in 2006, the synthesis of two 3-arylimidazo[2,1-*f*][1,2,4]triazin-8-ones **161** was investigated.[152] These compounds, which are $\alpha_{2,3}$ subtype selective $GABA_A$ antagonists for the treatment of anxiety, were prepared in 66–77% yield by the reaction of imidazo[2,1-*f*][1,2,4]triazin-8-ones **159** with the bromide **160** in DMA at 120 °C in the presence of a $Pd(OAc)_2/PPh_3$ catalyst system (Scheme 105).[152]



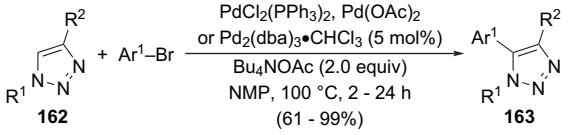
Scheme 105. Pd-catalysed synthesis of 3-arylimidazo[2,1-*f*][1,2,4]triazin-8-ones **161**.

3.5. (Hetero)arylation of 1,2,3- and 1,2,4-triazole ring systems

Several members of the 1,2,3-triazole family are known to possess intriguing biological properties.[153] Consequently, various strategies have been developed for the synthesis of these heterocycles.[154] In recent years, it has been reported that fully substituted 1,2,3-triazoles **163** can be conveniently prepared via transition metal-catalysed C-5 arylation of 1,4-disubstituted 1,2,3-triazoles **162** with aryl halides.[81,155–159] On the other hand, the compounds **162** are readily accessible via *click chemistry*.[160]

In 2007, Gevorgyan and co-workers synthesised a variety of multisubstituted 1,2,3-triazoles **163** by the reaction of aryl bromides with 1,4-disubstituted 1,2,3-triazoles **162**, containing electron-withdrawing aryl or carbethoxy groups, electron-donating

aryl groups as well as a secondary aliphatic alcohol at position C-4 and benzyl, aryl and alkyl groups at nitrogen, in NMP at 100 °C in the presence of *n*-Bu_4NOAc and catalytic quantities of $PdCl_2(PPh_3)_2$, $Pd(OAc)_2$ or $Pd_2(dba)_3{\cdot}CHCl_3$ (Scheme 106).[155]



Scheme 106. C-5 arylation of 1,2,3-triazoles **162** with aryl bromides.

Similar reaction conditions were then used to prepare 5-aryl-1-benzyl-1,2,3-triazoles **165** in good yields from 1-benzyl-1,2,3-triazole (**164**) (Fig. 14).[155]

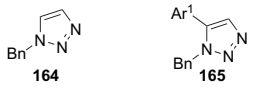
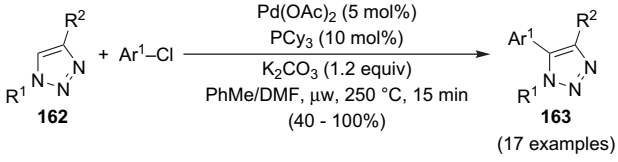


Figure 14. Structures of compounds **164** and **165**.

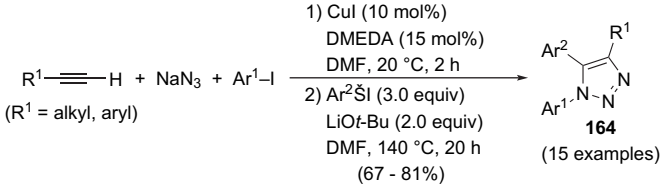
On the other hand, a catalyst system consisting of a mixture of $Pd(OAc)_2$ and PCy_3 was used by Yorimitsu and Oshima for the arylation of 1,4-disubstituted 1,2,3-triazoles **162** with electron-neutral aryl chlorides in the presence of K_2CO_3 under microwave irradiation at 250 °C for 15 min (Scheme 107).[156] Notably, aryl chlorides proved to be superior to aryl bromides and iodides as electrophiles under these experimental conditions.



Scheme 107. C-5 arylation of 1,2,3-triazoles **162** with aryl chlorides.

A $Pd(OAc)_2/PCy_3$ catalyst system was also used by Ackermann and co-workers in 2008 for the direct arylation of *N*-alkyl- and *N*-benzyl-1,4-disubstituted 1,2,3-triazoles with aryl chlorides through conventional heating at reaction temperatures of 105–120 °C.[157] These reactions, which were performed in toluene in the presence of K_2CO_3, furnished the required trisubstituted 1,2,3-triazoles **163** in high yields.

Ackermann and co-workers also reported that diversely substituted 1,2,3-triazoles **164** can efficiently be prepared by a modular one-pot multi-component approach involving a CuI-catalysed click reaction/direct arylation sequence.[158] In detail, 1-alkynes were reacted with NaN_3 and aryl iodides, Ar^1-I, in the presence of a catalytic amount of CuI and DMEDA at room temperature. Aryl iodides, Ar^2-I, LiO-*t*-Bu and DMF were then added and the resulting mixtures were stirred at 140 °C for 20 min to give the compounds **164** in high yields (Scheme 108).[158]

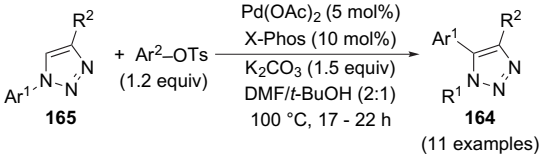


Scheme 108. Synthesis of compounds **164** via Cu-catalysed click reaction/direct arylation sequence.

These authors also synthesised a variety of trisubstituted 1,2,3-triazoles of general formula **163** in excellent yields by the CuI-catalysed arylation of the corresponding compounds **162** with aryl iodides in DMF at 140 °C in the presence of LiO-*t*-Bu as the base.[158]

A modification of this procedure, involving the use of CuCl in place of CuI as the catalyst precursor, was used by Fukuzawa and co-workers in 2008.[159]

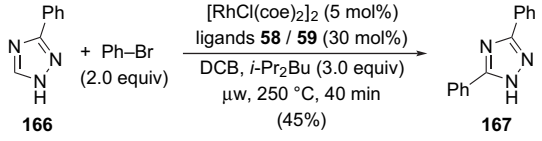
Finally, very recently, Ackermann and co-workers have reported that triazoles **165** can be arylated at position C-5 with activated and deactivated aryl tosylates in a mixture of DMF and *t*-BuOH at 100 °C in the presence of K_2CO_3 and a catalyst system composed of $Pd(OAc)_2$ and X-Phos (Scheme 109).[81]



Scheme 109. Direct C-5 arylation of triazoles **165** with aryl tosylates.

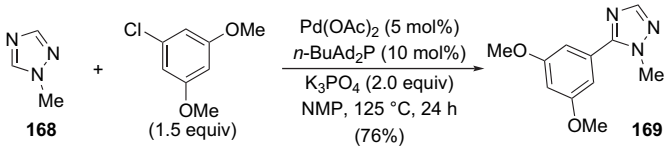
In the last few years, the synthesis of *C*-arylated 1,2,4-triazoles by direct transition metal-catalysed arylation reactions has also been investigated.[32,68a,144,161] In fact, some 3,5-disubstituted 3-aryl-1*H*-1,2,4-triazoles have been shown to possess potent antibacterial and antifungal activities[162] and some 1,3,5-trisubstituted 1,2,4-triazole compounds have proved to be useful for treatment of circulatory diseases[163] or have been used in the treatment of asthma, the symptoms of allergy and, in some instances, in gout and hyperuricemia.[164]

In 2006, Bergman and Ellman synthesised 3,5-diphenyl-1*H*-1,2,4-triazole (**167**) in 45% yield by treatment of free-(NH) 3-phenyl-1,2,4-triazole (**166**) with a molar excess of bromobenzene in DCB at 250 °C for 40 min under microwave irradiation in the presence of *n*-Bu(*i*-Pr_2)N and catalytic quantities of $[RhCl(coe)_2]_2$ and a mixture of the bulky trialkylphosphines **58** and **59** (Scheme 110).[68a]



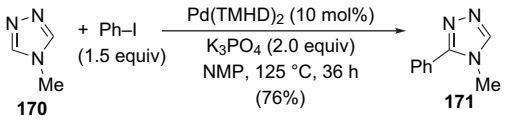
Scheme 110. Rh(I)-catalysed synthesis of 1,2,4-triazole **167**.

One year later, Chiong and Daugulis used a $Pd(OAc)_2$/*n*-$BuAd_2P$ catalyst system for the synthesis of 1,2,4-triazole **169** via C-5 arylation of 1-methyl-1,2,4-triazole (**168**) with 3,5-dimethoxychlorobenzene in NMP at 125 °C in the presence of K_3PO_4 as the base (Scheme 111).[144]



Scheme 111. Pd-catalysed synthesis of 1,2,4-triazole **169**.

On the other hand, in 2008, 1-methyl-5-phenyl-1,2,4-triazole (**171**) was prepared in 76% yield by the reaction of **170** with iodobenzene in NMP at 125 °C in the presence of K_3PO_4 and 10 mol% $Pd(TMHD)_2$ (Scheme 112).[32]



170 171

Scheme 112. $Pd(TMHD)_2$-catalysed arylation of 1,2,4-triazole **170**.

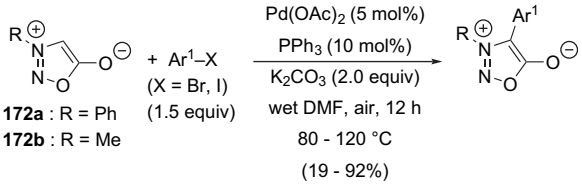
It should be noted that K_3PO_4 is a weak base, which can be used in the arylation of heterocycles possessing DMSO pK_a values lower than 27 and allows regioselective arylation reactions to be performed, which involve less acidic electron-rich heterocycles such as 1,2,4-triazole and caffeine derivatives, hunting down a benzyne-type mechanism.[87]

Compound **171** was also prepared in 88% yield by the arylation of **170** with 2 equiv of iodobenzene in DMF at 100 °C for 5 h in the presence of 1.7 equiv of LiO*t*-Bu, 10 mol % CuI, and 10 mol % 1,10-phenanthroline, a bidentate ligand.[161]

Interestingly, similar reaction conditions enabled high yielding regioselective arylation reactions of other heteroarenes, including caffeine, thiophenes, benzothiophene, benzofuran, 1-methyl-1*H*-imidazole, pyridine *N*-oxides, pyridazine and pyrimidine to be performed, employing aryl iodides or bromides as the coupling partners.[161] It was also found that the use of K_3PO_4 as a base was required for arylations involving heteroarenes, which possess pK_a values below 35, but the reaction of less acidic heteroarenes (pK_a 27–35) had to be performed using a stronger lithium alkoxide base.[161]

3.6. Arylation of sydnones

Sydnones are mesoionic heteroaromatic compounds having the 1,2,3-oxadiazole skeleton bearing an oxygen attached to the 5-position.[165] Very recently, Rodriguez and Moran have reported that 3-phenylsydnone (**172a**) and 3-methylsydnone (**172b**) undergo $Pd(OAc)_2/PPh_3$-catalysed C-4 arylation by treatment with a molar excess of aryl bromides or iodides in wet DMF in the presence of K_2CO_3 as a base (Scheme 113).[166]



172a : R = Ph
172b : R = Me

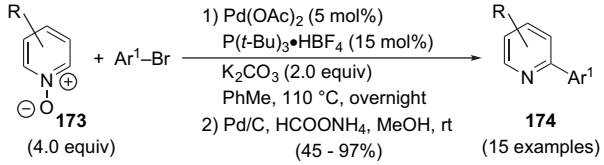
Scheme 113. $Pd(OAc)_2/PPh_3$-catalysed C-4 arylation of 3-substituted sydnones.

The reactions involving **172a** were carried out at 120 °C, but those of **172b** needed lowering of the reaction temperature to 80 °C and gave the required 4-aryl derivatives in slightly diminished yields, compared to those of **172a**.[166]

4. Intermolecular direct (hetero)arylation of six-membered heteroarenes

Until few years ago, the direct arylation reactions of π-electron-deficient heteroarenes remained a challenging goal. Nevertheless, at the present time, due to the significant achievements by Fagnou's research group and by Bergman, Ellman and co-workers, several protocols are available for performing efficient and regioselective direct C-arylations of six-membered heteroarenes, including pyridines,[167,168] quinolines,[167] pyrazine[168], pyridazine and pyrimidine,[161] pyridine-*N*-oxides,[98,161,169–171,172] quinoline- and isoquinoline-*N*-oxides,[98,171] *N*-iminopyridinium ylides,[173] diazine-*N*-oxides,[172] and *N*-methyl 6- and 7-azaindole oxides,[54] through the use of a variety of transition metal catalyst systems.

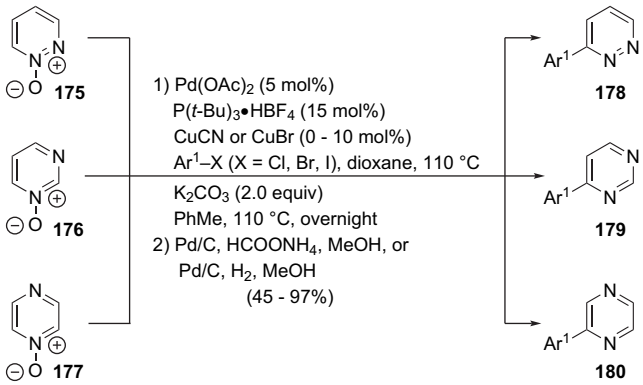
The first data in this field were published in 2005 by Fagnou and co-workers, who reported that bench-stable pyridine-*N*-oxides **173** undergo C-2 arylation with a wide variety of aryl bromides in refluxing toluene in the presence of K_2CO_3 as a base and catalytic quantities of $Pd(OAc)_2$ and P(*t*-Bu)$_3$.[169] The resulting arylated derivatives were then converted into 2-arylpyridines **174** by palladium-catalysed hydrogenolysis (Scheme 114).



173 (4.0 equiv) **174** (15 examples)

Scheme 114. Synthesis of 2-arylpyridines **174** via direct arylation of pyridine-*N*-oxides **173**.

One year later, Leclerc and Fagnou established that reaction conditions similar to those employed for the arylation of compounds **173** allowed high-yielding arylations of the pyridazine-, pyrimidine- and pyrazine-*N*-oxide, (**175**), (**176**) and (**177**), respectively, both with electron-deficient and electron-rich aryl iodides, bromides and chlorides (Scheme 115).[173]

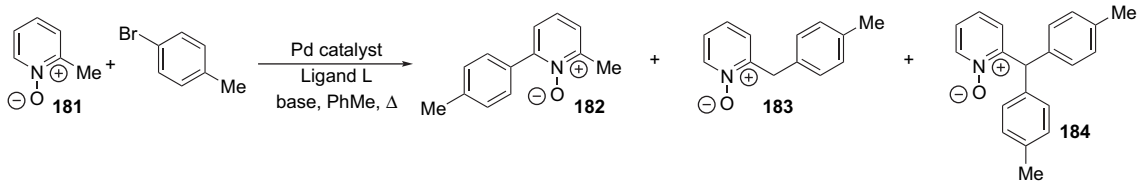


175 **176** **177** **178** **179** **180**

Scheme 115. Synthesis of 5-aryldiazines **178**–**180** via direct arylation reactions.

However, it was observed that, in the case of pyrimidine-*N*-oxide (**176**), a catalytic amount of CuCN or CuBr had to be added to increase the reactivity of this heteroarene derivative. On the other hand, 0.5 equiv of Ag_2CO_3 had to be added when aryl iodides were used as the electrophiles.[173] As shown in Scheme 115, the arylated derivatives of compounds **175**–**177** were then converted into the corresponding 5-aryldiazines **178**–**180** by palladium-catalysed hydrogenolysis.

In 2008, Fagnou and co-workers found that the selectivity of the palladium-catalysed reaction of 2-methylpyridine-*N*-oxide (**181**) with 4-bromotoluene is strongly dependent either on the nature of the phosphine used as the ancillary ligand or the base and the **181**/4-bromotoluene molar ratio used in the reaction.[170] Thus, treatment of 2 equiv of **181** with 4-bromotoluene in toluene at 110 °C in the presence of 1.05 equiv of K_2CO_3 and a catalyst system consisting of a 3:1 mixture of P(*t*-Bu)$_3$·HBF$_4$ and $Pd(OAc)_2$ gave compound **182** in 21% yield (Scheme 116). However, the use of 3 equiv of NaO-*t*-Bu and a catalyst system consisting of 1:1 mixture of $Pd_2(dba)_3$ and *S*-Phos in toluene at 70 °C gave in 41% yield a mixture of **183** and **184** in a 6.7:1 M ratio, respectively. Representative data illustrating the influence of the experimental conditions on the site-selectivity of the palladium-catalysed reaction between 4-bromoluene and **181** are reported in Scheme 116.

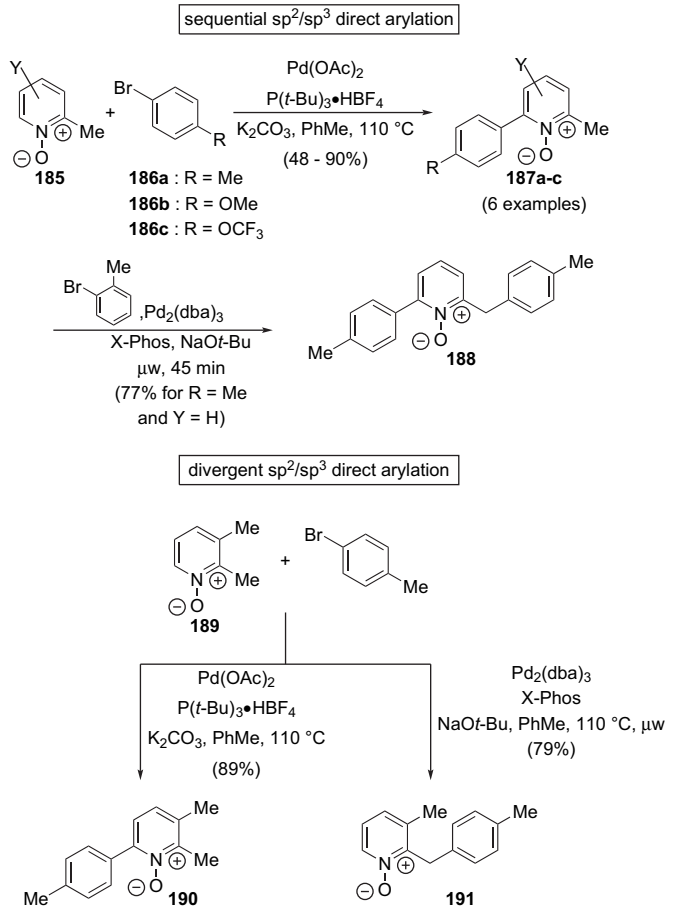


Pd source	Ligand L	L / Pd molar ratio	Temp (°C)	Equiv of **181**	Base (equiv)	**182** : **183** : **184** molar ratio	Yield (%)
$Pd(OAc)_2$	$P(t\text{-}Bu)_3{\bullet}HBF_4$	3 : 1	110	2	K_2CO_3 (2.0)	1 : 0 : 0	21
$Pd_2(dba)_3$	S-Phos	1 : 1	70	4	NaO*t*-Bu (3.0)	0 : 6.7 : 1	77
$Pd_2(dba)_3$	X-Phos	1 : 1	70	2	NaO*t*-Bu (3.0)	0 : 20 : 1	41

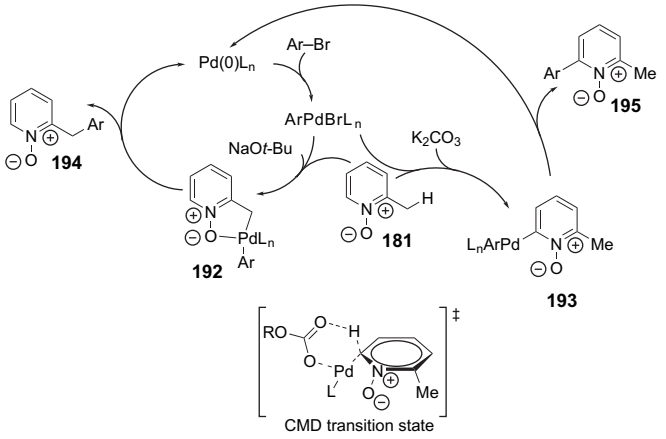
Scheme 116. Pd-catalysed arylation of 2-methylpyridine-*N*-oxide (**181**) with 4-bromotoluene.

Remarkably, this methodology was validated in both sequential sp^2/sp^3 arylation of 2-methylpyridine-*N*-oxides **185** with aryl bromides and in divergent sp^2/sp^3 arylation of 2,3-dimethylpyridine-*N*-oxide (**189**) (Scheme 117).[170,171]

The sequential sp^2/sp^3 arylation of **185** with **186a–c** enabled the authors to prepare compounds **187a–c** in 48–90% yield and compound **188** in 41.6% overall yield. On the other hand, the divergent sp^2/sp^3 arylation of **189** furnished compounds **190** and **191** in 89 and 79% yield, respectively. Mechanistic investigations pointed towards the intimate involvement of the base in the mechanism of these reactions[171] and it was proposed that, with the strong base NaO-*t*-Bu. the most acidic sp^3 2-methyl position of **181** can be deprotonated and the reaction (Schemes 117 and 118) proceeds via a pathway similar to the α-arylation of carbonyl compounds[174] to yield **192**. On the other hand, K_2CO_3 is not a strong base to deprotonate the methyl group at position 2, but it does allow the transition state of a concerted metalation–deprotonation (CMD) pathway to activate the C-5, which gives rise to **193** (Scheme 118). Both intermediates **192** and **193** might then undergo reductive elimination to form products **194** and **195**, respectively.[171]

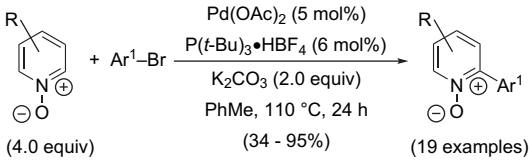


Scheme 117. Site-selective sp^2 and benzylic sp^3 direct arylation of compounds **185** and **189**.



Scheme 118. Proposed catalytic cycle for sp^2/sp^3 arylation of **181**.

Very recently, Fagnou and co-workers have published improved protocols for the direct arylation of a variety of azine derivatives, including substituted pyridine-, quinoline- and isoquinoline-*N*-oxides.[98] In the case of 2- and 4-substituted pyridine-*N*-oxides the optimised reaction conditions require treatment of a large molar excess of these substrates with aryl bromides in refluxing toluene in the presence of K_2CO_3 and a catalyst system composed of a mixture of $Pd(OAc)_2$ and $P(t\text{-}Bu)_3$ (Scheme 119).[98] Similar reaction conditions have been used for the arylation of quinoline-*N*-oxides, but it has been found the the yields are significantly improved by the use of $P(t\text{-}Bu)_2Me{\cdot}HBF_4$ in place of $P(t\text{-}Bu)_3{\cdot}HBF_4$.[98]

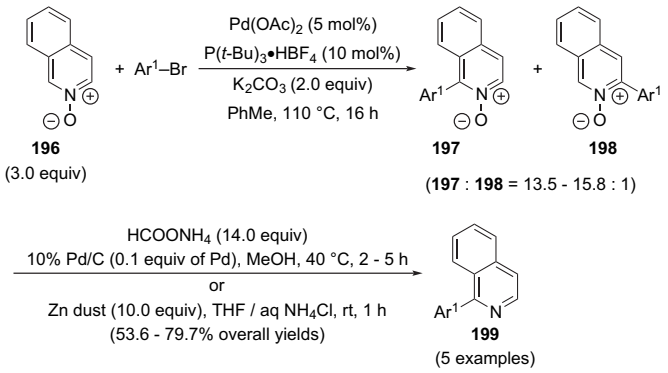


Scheme 119. Direct arylation of 2- and 4-substituted pyridine-*N*-oxides.

Fagnou's research group has also studied aspects of regioselectivity in the direct arylation of unsymmetrical azine-*N*-oxides, including isoquinoline-*N*-oxide (**196**) and 3-substituted pyridine-*N*-oxides. The reactions involving **196** with aryl bromides were carried out using a $Pd(OAc)_2/P(t\text{-}Bu)_2Me{\cdot}HBF_4$ catalyst system and

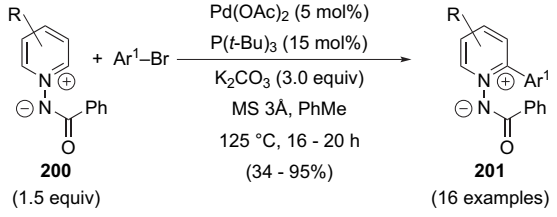
were found to provide regioisomeric products **197** and **198**, which were often inseparable by silica gel flash chromatography.

For this reason, the mixtures of these products were subjected to deoxygenation reaction conditions, since the resulting free bases could be easily chromatographically separated. In this way, the compounds **199** were obtained in good overall yields (Scheme 120).[98]



Scheme 120. Regioselectivity in direct arylation of isoquinoline-*N*-oxide (**196**).

On the contrary, less satisfactory results have been obtained in the direct arylation of 3-substituted pyridine-*N*-oxides. In fact, with these substrates, the regioselectivity has been shown to be significantly lower than that observed with **196** and dramatically influenced by the nature of the azine substituents and the ligand.[98] In 2008, the group of Charette investigated the direct C–H arylation of *N*-benzoyliminopyridinium ylides **200** with aryl halides[172] and found that treatment of **200** with activated or deactivated aryl bromides in dry toluene in the presence of K_2CO_3 and a $Pd(OAc)_2/P(t\text{-}Bu)_3$ catalyst system provides the C-2 arylated derivatives **201** in high yields (Scheme 121). An aryl chloride was also used as electrophile in one example but with a lower yield.



Scheme 121. Pd-catalysed arylation of *N*-iminopyridinium ylides **200**.

In addition, it was shown that it was possible to reductively cleave the N–N bond of compounds **201** to afford 2-aryl-substituted pyridines **174**, including a precursor to the TFA salt of racemic anabasine, a pyridine alkaloid.[170]

Interestingly, experimental conditions similar to those used to prepare compounds **201** could successfully be employed for the arylation of *N*-benzoyliminoquinolinium and *N*-benzoyliminoisoquinolinium ylides **202** and **203**, respectively (Fig. 15).[172]

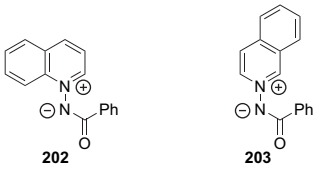
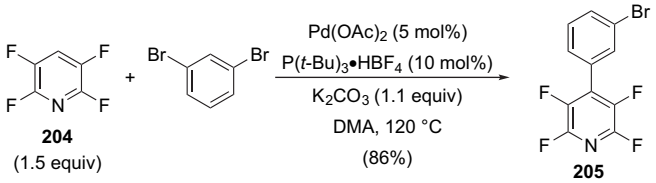


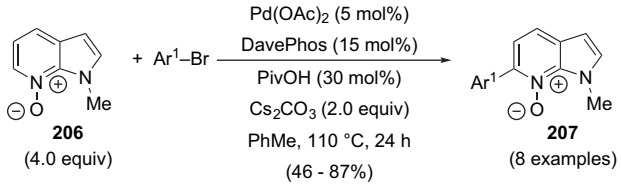
Figure 15. Structures of compounds **202** and **203**.

Two years before this study, Fagnou and co-workers had shown that a catalyst system consisting of a combination of $Pd(OAc)_2$ and $P(t\text{-}Bu)_2Me$ allows the synthesis of compound **205** in 86% yield by C-4-arylation of 2,3,5,6-tetrafluoropyridine (**204**), a strongly deactivated heteroarene, with 1,3-dibromobenzene (Scheme 122).[175]



Scheme 122. Pd-catalysed arylation of 2,3,5,6-tetrafluoropyridine (**204**).

Very recently, Fagnou's group has investigated the site-selective azaindole arylation at the azine ring via *N*-oxide activation[53] and has reported that subjecting 1-methyl-1*H*-pyrrolo[2,3-*b*]pyridine-*N*-oxide (**206**) to a $Pd(OAc)_2$/DavePhos catalyst system enables the regioselective direct arylation of the azine ring with aryl bromides, which provides compounds **207** in satisfactory to good yields (Scheme 123).



Scheme 123. Direct arylation of *N*-methyl-7-azaindole-*N*-oxide (**206**).

Interestingly, the reaction conditions used to prepare the compounds **207** have also proved to be suitable for the preparation of 7-aryl-1-methyl-1*H*-pyrrolo[2,3-*c*]pyridine-*N*-oxides **209** in synthetically useful yields by direct arylation of *N*-methyl-6-azaindole-*N*-oxide [1-methyl-1*H*-pyrrolo[2,3-*c*]pyridine-*N*-oxide] (**208**) (Fig. 16).[53]

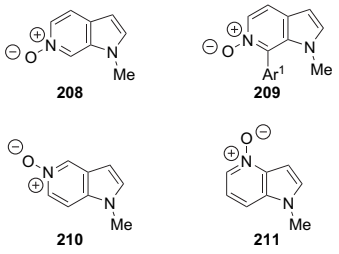


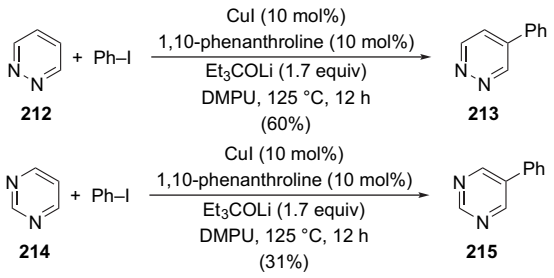
Figure 16. Structures of compounds **208**–**211**.

On the contrary, 1-methyl-1*H*-pyrrolo[3,2-*c*]pyridine-5-oxide (**210**) and 1-methyl-1*H*-pyrrolo[3,2-*b*]pyridine-4-oxide (**211**) (Fig. 16) have been found to exhibit minimal reactivity under these conditions.[53]

In the last few years it has also been discovered that the direct arylation of azines and diazines with aryl halides can be achieved using copper-, rhodium- or gold-based catalyst systems without the need for an N-functionalisation of these π-electron-deficient heteroarenes.

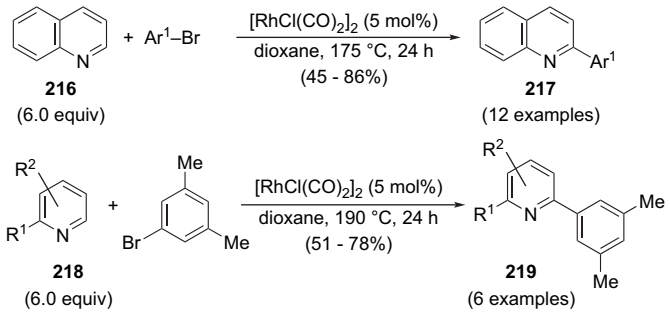
A CuI/1,10-phenanthroline catalyst system was used by Daugulis and co-workers in 2008 for the direct arylation of pyridazine (**212**), pyrimidine (**214**) and pyridine-*N*-oxides **173** with aryl iodides.[161] 4-Phenylpyridazine (**213**) and 5-phenylpyrimidine (**215**) were prepared in 60 and 31% yield by the reaction of **212** and **214**, respectively, with iodobenzene (Scheme 124). Unfortunately, these

arylation reactions required the use of the commercially unavailable, hindered Et_3COLi as the base.



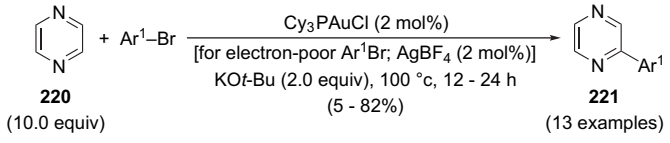
Scheme 124. Direct Cu-catalysed arylation of compounds **212** and **214**.

In the same year, Bergman and co-workers reported that $[RhCl(CO)_2]_2$ is a suitable catalyst precursor for the direct C-2 arylation of quinoline (**216**) and pyridines **218**, except unsubstituted pyridine, with aryl bromides in dioxane at 175–190 °C in a sealed Schlenk tube under ligandless conditions.[167] The reactions (Scheme 125), which unfortunately required the use of a large molar excess of the heteroarene substrate, gave the arylated derivatives **217** and **219** in moderate to high yields.



Scheme 125. Rh(I)-catalysed C-2 arylation of quinoline (**216**) and pyridines **218**.

Finally, the first example of a gold-catalysed direct C–H arylation of heteroarenes with aryl halides has been reported very recently by Li and Hua.[168] They have found that, in the presence of a catalytic amount of $AuCl(PCy_3)$ and with the use of KO-*t*-Bu as a base, pyrazine (**220**) undergoes C-2 arylation with aryl bromides at 100 °C to give the arylated products **221** in high yields in the case of electron-rich aryl bromides. However, for electron-poor aryl bromides, the addition of a catalytic quantity of $AgBF_4$ was crucial to obtain the arylated products in moderate yields (Scheme 126).



Scheme 126. Au(I)-catalysed direct C-2 arylation of pyrazine (**220**).

Catalytic quantities of $AuCl(PCy_3)$ can also allow the direct arylation of pyridine with aryl bromides, but the reactions give mixtures of arylated regioisomers in moderate yields.[168]

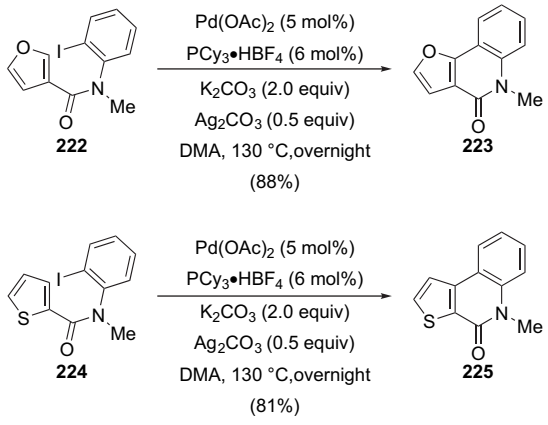
5. Synthesis of fused-ring heteroarenes via intramolecular direct (hetero)arylation of heteroarenes containing a (hetero)aryl tether

Heteroarenes fused with (hetero)aromatic rings have attracted the attention of organic chemists for several years, since compounds containing these scaffolds demonstrate diverse and interesting biological properties. In the last two decades, there has been a growing interest in the design and development of efficient and versatile procedures for the synthesis of fused-ring heteroarenes, which do not involve the use of stoichiometric amounts of preformed organometallic reagents. These procedures include transition metal-catalysed cycloisomerisation reactions,[176] annulation reactions of arynes and 1-halo-2-heteroarylbenzenes or 1-halo-2-arylheteroarenes,[177] and protocols based on the activation of heteroarene C–H bonds such as rhodium-[178] platinum-,[179] and palladium-catalysed intramolecular C–H alkylation of azoles,[180] palladium-catalysed intramolecular alkenylation of five-membered heteroarenes,[181] gold-catalysed intramolecular C–H alkenylation of indoles,[182] and palladium-catalysed oxidative cyclisations.[183] In addition, great emphasis has been placed on the development of efficient protocols for the synthesis of heteroarenes by palladium-catalysed intramolecular (hetero)arylation reactions of electron-rich and electron-poor heteroarenes containing a (hetero)aryl halide tether.[184–191]

This section of the review is aimed at summarising and commenting the studies performed during the period, January 2006–February 2009, on the synthesis of polycyclic heteroarenes by the use of the latter synthetic methodology. In fact, it is our goal to complete the description of this type of reactions, which, for the first time, was reviewed by Lautens and co-workers in 2007.[15] The reactions will be described on the basis of the type of annulated heteroarenes synthesised via intramolecular arylation.

5.1. Synthesis of annulated furan, benzofuran, thiophene, and benzothiophene derivatives

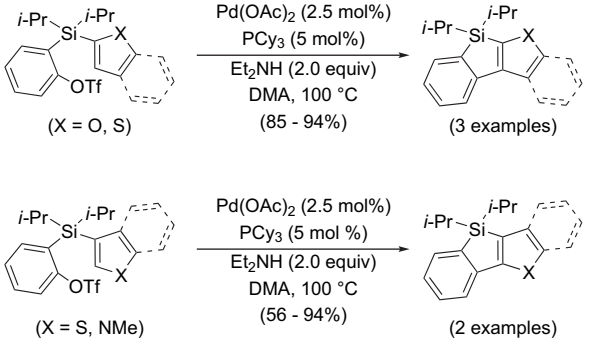
In 2006, Fagnou and co-workers performed the intramolecular direct arylation of the 3-substituted furan and the 2-substituted thiophene derivatives **222** and **224**, respectively, in the presence of K_2CO_3 as the base, Ag_2CO_3 as an additive, and a $Pd(OAc)_2/PCy_3\cdot HBF_4$ catalyst system (Scheme 127).[193] The polycyclic compounds **223** and **225** were obtained in 88 and 81% yield, respectively. Addition of the silver salt was found to accelerate the reactions, which could be performed at temperatures as low as 130 °C.[192]



Scheme 127. Pd-catalysed intramolecular arylation of compounds **222** and **224**.

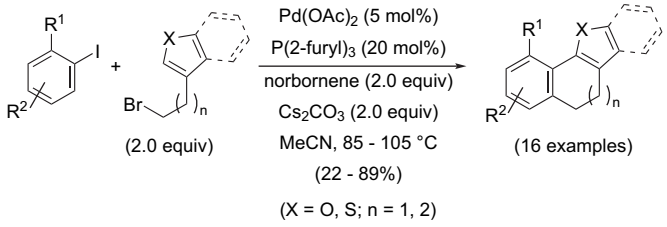
More recently, some polycyclic silicon-bridged benzofuran, thiophene, benzothiophene, and indole derivatives have been synthesised by intramolecular direct arylation of the corresponding heteroarene-containing triflates using Et_2NH as the base and a $Pd(OAc)_2/PCy_3$ catalyst system in DMA at 100 °C.[193] Remarkably, this new approach allowed the synthesis of a silicon-bridged 2-phenylindole that exhibits a blue photoluminescence in the solid state with very high quantum yields.[193] Scheme 128 illustrates the

preparation of some polycyclic silicon-bridged heteroarenes according to this protocol.



Scheme 128. Intramolecular coupling of 2-(heteroarylsilyl)aryl triflates.

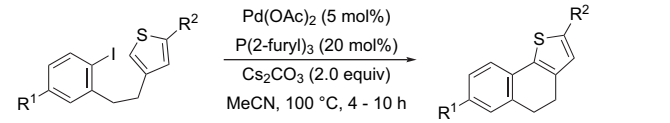
Recently, the synthesis of polycyclic furans,[194] thiophenes[194,195] and benzothiophenes[195] has been accomplished by Lautens and co-workers via a $Pd(OAc)_2/P(2\text{-furyl})_3$-catalysed domino norbornene-mediated *ortho*-alkylation/direct arylation reaction involving aryl iodides and 3-(bromoalkyl)heteroarenes (Scheme 129). This interesting and synthetically very useful approach was based on a combination of the strategies of palladium-catalysed aromatic *ortho*-alkylation derived from the Catellani reaction[196] with the direct arylation of thiophene-based heterocycles.[18,20a,21,197]



Scheme 129. Synthesis of polycyclic heterocycles via a Pd-catalysed domino *ortho*-alkylation/direct arylation reaction.

The Catellani reaction is a remarkable one-pot, norbornene-mediated, Pd-catalysed three component reaction whereby three C–C bonds are formed, palladacycles in oxidation states (II) and (IV) are involved, and norbornene, which acts as a scaffold implicated in the assembly of the reaction product, is not incorporated in the final product.[196]

Remarkably, when experimental conditions similar to those represented in Scheme 130, but omitting the use of norbornene, were employed for the intramolecular direct arylation of 3-[2(2-iodoaryl)ethyl]thiophenes **226a** and **226b**, 4,5-dihydronaphtho[1,2-*b*]thiophenes **227a** and **227b** were obtained in 87 and 81% yield, respectively (Scheme 129).[195] However, compound **226c**, containing an electron-deficient thiophene ring, proved to be a poor substrate for this cyclisation and compound **227c** was obtained in only 32% yield (Scheme 130).[195] This result provided support for an electrophilic mechanism of the intramolecular arylation reaction.[195]

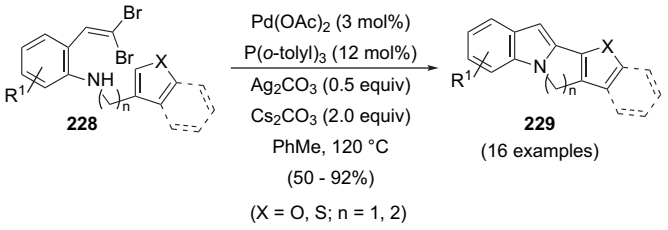


226a : $R^1 = NO_2$; $R^2 = H$
226b : $R^1 = R^2 = H$
226c : $R^1 = H$; $R^2 = NO_2$

227a : $R^1 = NO_2$; $R^2 = H$ (87%)
227b : $R^1 = R^2 = H$ (81%)
227c : $R^1 = H$; $R^2 = NO_2$ (32%)

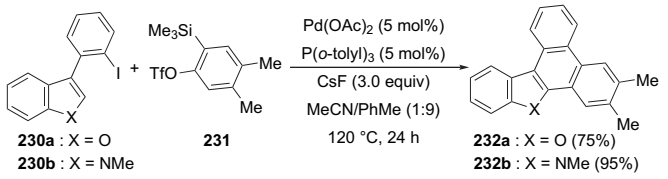
Scheme 130. Synthesis of 4,5-dihydronaphtho[1,2-*b*]-thiophenes **227a–c**.

Novel tetracyclic and pentacyclic indole derivatives **229** have recently been prepared by Bryan and Lautens via an efficient silver-promoted domino $Pd_2(dba)_3/P(o\text{-tolyl})_3$-catalysed amination/direct arylation of readily available *gem*-dibromoalkenes **228** (Scheme 131).[198] The authors found that the use of Ag_2CO_3 as the additive to sequester bromide ions improved the reaction rate and selectivity of the domino process, which furnished the required fused indole derivatives **229** generally in high yields.



Scheme 131. Synthesis of fused indole derivatives **229**.

Liu and Larock prepared in high yields 6,7-dimethylbenzo[*b*]-phenanthro[9,10-*d*]furan (**232a**) and 6,7,9-trimethyldibenzo[*a*,*c*]carbazole (**232b**) by palladium-catalysed reaction of silylaryl triflate **231** with 3-(2-iodophenyl)benzofuran (**230a**) and 3-(2-iodophenyl)-1-methylindole (**230b**), respectively (Scheme 132).[199]



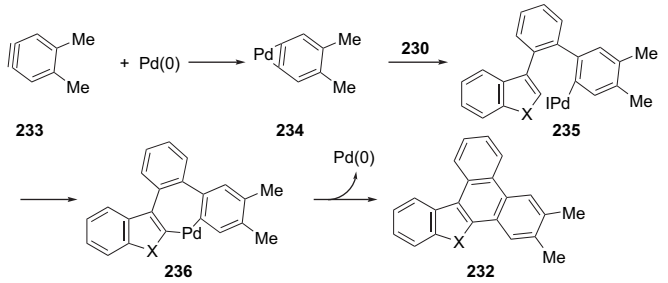
230a : X = O
230b : X = NMe

232a : X = O (75%)
232b : X = NMe (95%)

Scheme 132. Synthesis of compounds **232a**,**b**.

A supposed catalytic cycle for the reaction entails the in situ generation of aryne **233** from **231** and oxidative addition of Pd(0) to **233** to generate the palladacycle **234** (Scheme 133). Subsequent reaction with compounds **230** would afford the intermediates **235**, which would undergo intramolecular C–H activation to give the palladacycles **236**. These complexes, in turn, would yield the annulation products **232** by reductive elimination (Scheme 133).[200]

The authors also proposed a second reaction mechanism, which involves an intramolecular heteroarene C–H activation and produces the palladacycles **236** from aryne **233** and the complex initially formed by oxidative addition of **231** to a Pd(0) species.[199]

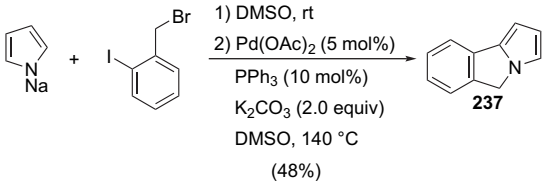


Scheme 133. Plausible mechanism for Pd-catalysed synthesis of compounds **232**.

5.2. Synthesis of annulated pyrrole, indole, azaindole, and pyrazole derivatives

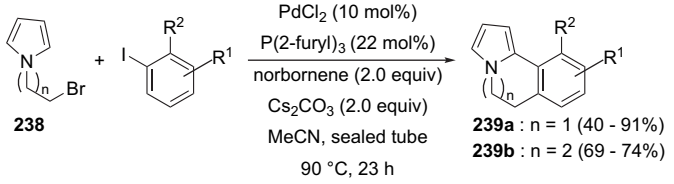
In 2006, Mori and co-workers synthesised 5*H*-pyrrolo[2,1-*g*]isoindole-*d* (**237**) by the reaction of pyrrolylsodium with

2-iodobenzyl bromide, followed by $Pd(OAc)_2/PPh_3$-catalysed intramolecular C–H arylation of the resulting *N*-benzylated product (Scheme 134).[200]



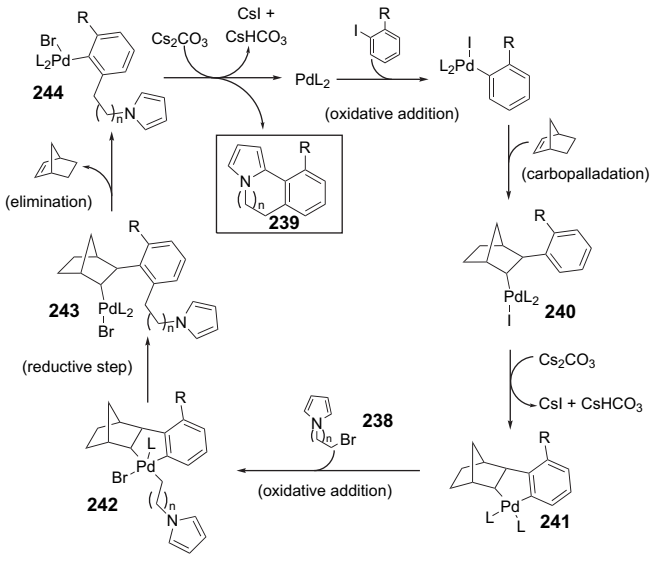
Scheme 134. Synthesis of 5*H*-pyrrolo[2,1-*g*]isoindole (**237**).

In the same year, several other annulated pyrrole derivatives, including 5,6-dihydropyrrolo[2,1-*a*]isoquinolines **239a**, and 6,7-dihydro-5*H*-benzo[*c*]pyrrolo[1,2-*a*]azepines **239b** were efficiently synthesised from *N*-bromoalkylpyrroles **238** and aryl iodides via a one-pot procedure involving an sp^2 C–H functionalisation as the key step, which was based on a palladium-catalysed, norbornene-mediated sequential aromatic alkylation/aryl-heteroaryl coupling reaction (Scheme 135).[201]



Scheme 135. Synthesis of annulated pyrroles **239a**,**b**.

The proposed mechanism for the synthesis of compounds **239** (Scheme 136) entails an aromatic sp^2 C–H activation (**240**→**241**).

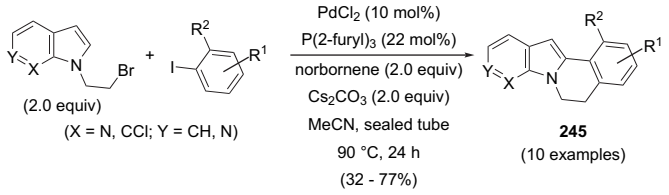


Scheme 136. Proposed mechanism for synthesis of compounds **239**.

The intermediate **244** would arise from reductive elimination of the Pd(IV) complex **242** followed by elimination of norbornene (**243**→**244**). Finally, aryl-heteroaryl intramolecular coupling of **244** via C-2 functionalisation of the pyrrole ring would provide the annulated pyrroles **239**.[201]

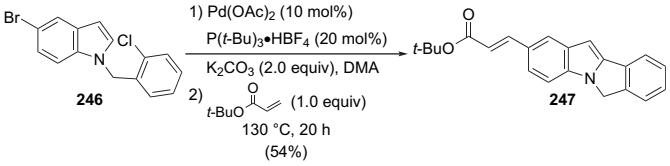
It should be noted that, despite the fact that norbornene could theoretically be used in catalytic quantities according to this mechanism, in the annulation process two equivalents of this strained cycloalkene were employed, probably to force the formation of intermediate **240** via carbopalladation.

More recently, Blaszykowski, Lautens and co-workers have used tandem norbornene-mediated palladium-catalysed alkylation/direct arylation reactions for the synthesis of a number of six-, seven- and eight-membered ring-annulated indoles, pyrroles, pyrazoles, and azaindoles.[202] The synthesis of annulated azaindoles **245** is illustrated in Scheme 137.



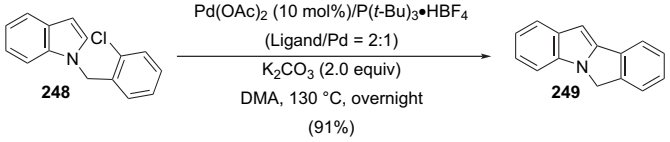
Scheme 137. Synthesis of annulated azaindoles **245**.

In 2006, Fagnou and co-workers prepared (*E*)-*tert*-butyl 3-(6*H*-isoindolo[2,1-*a*]indol-2-yl)acrylate (**247**) in 54% yield by a $Pd(OAc)_2/P(t\text{-}Bu)_3$-catalysed a tandem Heck/direct arylation reaction involving 1-(2-chlorobenzyl)-5-bromo-1*H*-indole (**246**) and *tert*-butyl acrylate (Scheme 138).[203]



Scheme 138. Synthesis of compound **247** via tandem Heck/direct arylation.

On the other hand, 6*H*-isoindolo[2,1-*a*]indole (**249**) was prepared in 91% yield by $Pd(OAc)_2/P(t\text{-}Bu)_3$-catalysed direct intramolecular arylation of 1-[(2-chlorophenyl)methyl]-1*H*-indole (**248**) (Scheme 139).[192]



Scheme 139. Synthesis of 6*H*-isoindolo[2,1-*a*]indole (**249**).

A similar procedure was used to prepare compound **251** from **250** (Fig. 17).[192]

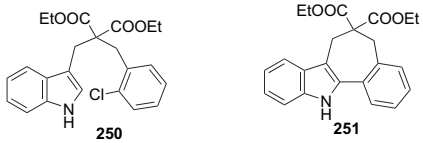


Figure 17. Structures of compounds **250** and **251**.

Compound **249** had been formerly synthesised in 89% yield by intramolecular arylation of **248** in DMA at 130 °C in the presence of K_2CO_3 as the base and an *N*-heterocyclic carbene palladium catalyst system.[184p]

On the other hand, in 2009, Barbero, SanMartin and Domínguez have prepared **249** in 88% yield by stirring **248** along with Cu powder (10 mol %) in polyethylene glycol-400 (PEG-400) at 180 °C in the presence of 2 equiv of K_2CO_3.[204] This reaction represents the first reported example of a copper-catalysed intramolecular C–H functionalisation of an indole.

Barbero, SanMartin and Domínguez have also prepared indolo[1,2-*a*]indole (**253**) in 88% yield by the reaction of 2-(2-bromobenzyl)indole (**252**) (Fig. 18) with 10 mol% CuI in toluene at 110 °C in the presence of 2 equiv of K_3PO_4 and 10 mol% *trans*-1,2-diaminocyclohexane.[204]

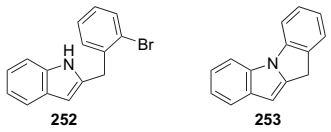
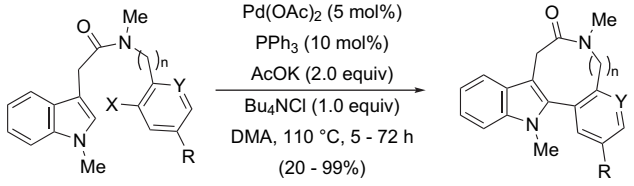


Figure 18. Structures of compounds **252** and **253**.

In 2006, Beccali and co-workers employed AcOK as the base, Bu_4NCl as an additive and catalytic quantities of $Pd(OAc)_2$ and PPh_3 for the synthesis of a variety of indolo-fused nitrogenated heterocycles of various sizes, including 7,12-dihydroindolo-benzazepine (**255a**), 5,7,8,13-tetrahydroindolo-benzazocine (**255b**) and 6,8,914-tetrahydroindolo-benzazonine (**255c**) by intramolecular direct arylation of the readily accessible carboxamides **254a**, **254b** and **254c**, respectively, in DMA at 110 °C (Scheme 140).[205]



Scheme 140. Pd-catalysed synthesis of compounds **255a–c**.

Interestingly, microwave irradiation was found to increase the yields of the reactions involving the less reactive substrates.[205]

On the other hand, 7,12-dihydroindolo[3,2-*d*][1]benzazepin-6(5*H*)-one (paullone) (**257**), a compound, which belongs to a class of cyclin-dependent kinase inhibitors,[206] was synthesised in 70% yield by $Pd(OAc)_2$-catalysed intramolecular arylation of the *N*-unsubstituted indole derivative **256** (Fig. 19) in DMF at 130 °C in the presence of MgO as the base under ligandless conditions.[207] Likewise, compound **259**, which is a dimethyl derivative of paullone, was obtained in 86% yield by intramolecular arylation of **258** (Fig. 19) in DMF at 130 °C, but by using Cs_2CO_3 as a base.[207]

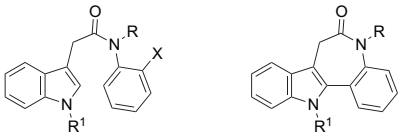
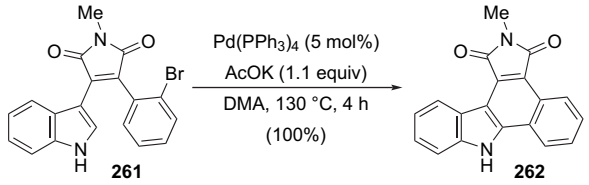


Figure 19. Structures of compounds **256–260**.

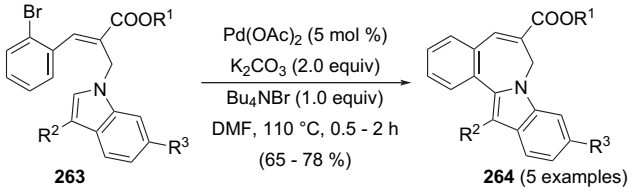
Compound **259** had been formerly prepared in 89% yield by intramolecular arylation at position 2 of the indole derivative **260** (Fig. 19) using a $Pd(OAc)_2/PPh_3$ catalyst system and Ag_2CO_3 as the base.[184q]

In 2006, 2-methylbenzo[*a*]pyrrolo[3,4-*c*]carbazole-1,3(2*H*,8*H*)-dione (**262**) was synthesised in quantitative yield by intramolecular arylation of 3-(2-bromophenyl)-4-(1*H*-indol-3-yl)-1-methylpyrrole-2,5-dione (**261**) in DMA at 130 °C in the presence of AcOK as the base and a catalytic quantity of $Pd(PPh_3)_4$ (Scheme 141).[208]



Scheme 141. Synthesis of 2-methylbenzo[*a*]pyrrolo[3,4-*c*]carbazole-1,3(2*H*,8*H*)-dione (**262**).

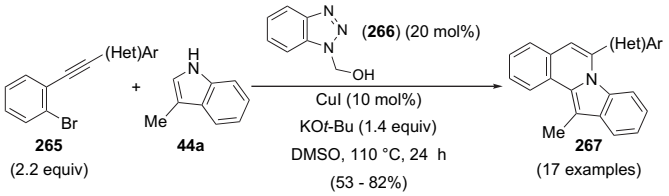
More recently, 7*H*-benzo[3,4]azepino[1,2-*a*]indole-6-carboxylic acid derivatives **264** have been prepared in good yields by $Pd(OAc)_2$-catalysed C-2 intramolecular arylation of indole moiety-containing Baylis–Hillman adducts **263** in DMF at 100 °C in the presence of K_2CO_3 and Bu_4NBr under ligandless conditions (Scheme 142).[209]



Scheme 142. Synthesis of 7*H*-benzo[3,4]azepino[1,2-*a*]indole-6-carboxylic acid derivatives **264**.

Interestingly, a similar procedure was used for the synthesis of poly-fused heterocyclic compounds from Baylis–Hillman adducts modified with imidazole, benzimidazole and isatin.[209]

Finally, diversely substituted, medicinally useful indolo[2,1-*a*]isoquinolines **268** have been very recently synthesised by Verma and Larock via tandem reaction of 2-unsubstituted 1*H*-indole **44a** with 2-[(hetero)arylethynyl]bromobenzenes **265** in DMSO at 110 °C in the presence of catalytic amounts of benzotriazol-1-ylmethanol (**266**) as a novel and inexpensive ligand and CuI (Scheme 143).[210] The compounds **267** were obtained in good yields and with excellent regioselectivity.



Scheme 143. Tandem synthesis of substituted indolo[2,1-*a*]isoquinolines **267** catalysed by CuI/benzotriazol-1-ylmethanol.

It should be noted that analogous reaction conditions enabled the tandem synthesis of some substituted pyrrolo[2,1-*a*]isoquinolines **268** (Fig. 20) from free (NH)-pyrrole and bromides **265** in moderate-to-good yields.[210]

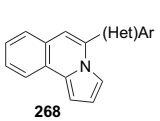
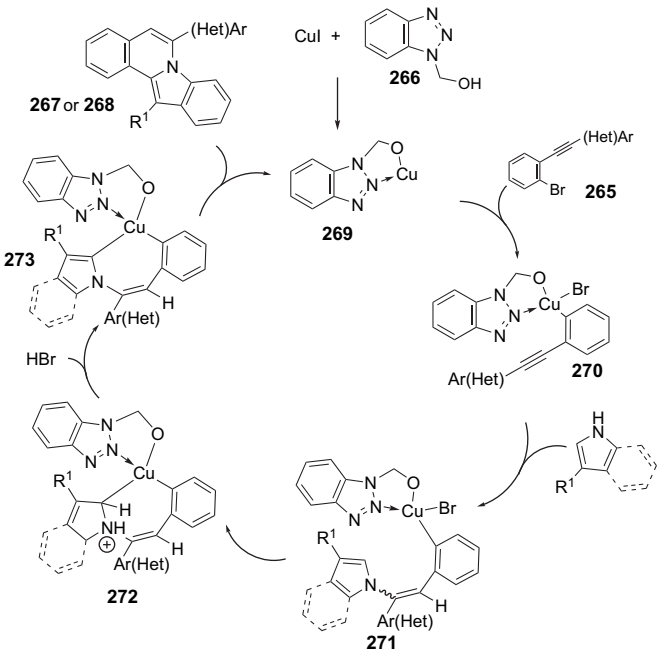


Figure 20. Structure of pyrrolo[2,1-*a*]isoquinolines **268**.

A plausible catalytic cycle (Scheme 144) for these tandem reactions involves the formation of complex **269** from CuI and ligand **266**. Oxidative addition of bromides **265** to **269** and subsequent π-complexation of the alkyne moiety to copper, which generates complex **270**, enables the nucleophilic addition of indoles and pyrrole onto the 2-bromoarylalkynes and the resulting complex

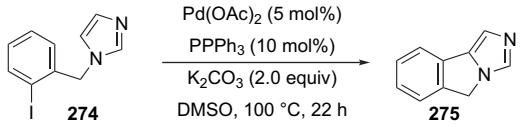
271 undergoes intramolecular attack onto the 2-position of the hetereoarenes followed by elimination of HBr from complex **272**, which results in the formation of intermediate **273**. Finally, reductive elimination of **273** provides the products **267** or **268** and regenerates complex **269**.[210]



Scheme 144. Plausible mechanism for the Cu-catalysed tandem synthesis of indolo- and pyrrolo[2,1-*a*]isoquinolines.

5.3. Synthesis of annulated imidazole and benzimidazole derivatives

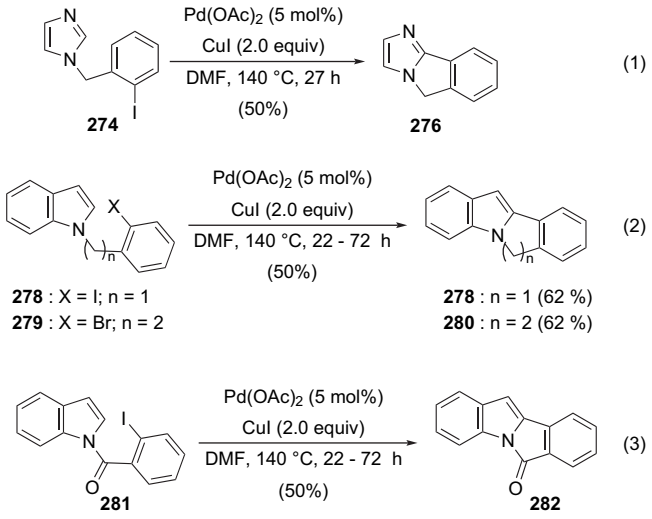
In recent years, some different protocols dealing with the synthesis of 5*H*-imidazo[5,1-*a*]isoindole (**275**) have been described in the literature.[200,211,212] In 2006, this compound was synthesised in 55% yield by $Pd(OAc)_2/PPh_3$-catalysed intramolecular C-5 arylation of 1-(2-iodobenzyl)-1*H*-imidazole (**274**) in DMSO at 100 °C in the presence of K_2CO_3 as the base (Scheme 145).[200]



Scheme 145. $Pd(OAc)_2/PPh_3$-catalysed intramolecular C-5 arylation of compound **274**.

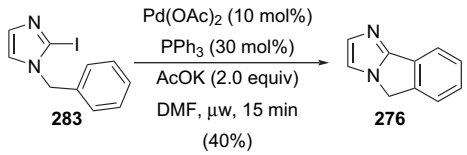
More recently, we prepared compound **275** in 63% yield by ligandless $Pd(OAc)_2$-catalysed reaction of **274** in DMF at 140 °C in the presence of CsF as the base.[211] On the other hand, Majumdar and co-workers synthesised **275** in 81% yield by cyclisation of **274** in DMF at 100 °C in the presence of an equimolar amount of Bu_4NBr as an additive, a large molar excess of AcOK as the base and a catalytic quantity of $Pd(OAc)_2$.[212]

We also found that the palladium-catalysed and copper-mediated intramolecular C-2 arylation of **274** under base-free and ligandless conditions affords 5*H*-imidazo[2,1-*a*]isoindole (**276**) in 50% yield (Eq. 1, Scheme 146) and that similar reaction conditions enable the preparation of 1*H*-benzo[4,5]imidazo[1,2-*a*]isoindole (**278**) from **277**, 5,6-dihydrobenzo[4,5]imidazo[2,1-*a*]isoquinoline (**280**) from **279**, and 11*H*-isoindolo[2,1-*a*]benzimidazol-11-one (**282**) from **281** in 62, 62 and 31% yield, respectively (Eqs. 2 and 3, Scheme 146).[211]



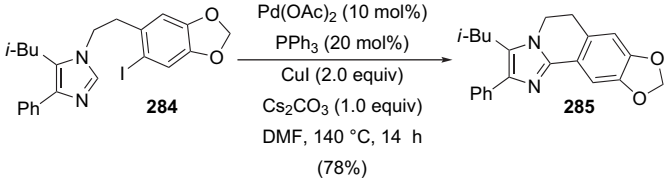
Scheme 146. Pd-catalysed and Cu-mediated intramolecular C-2 arylation of compounds **274**, **277**, **279**, and **281**.

Compound **276** had been previously synthesised in 40% yield by microwave-assisted intramolecular arylation of 1-benzyl-2-iodo-1*H*-imidazole (**283**) in DMF in the presence of AcOK as the base and a $Pd(OAc)_2/PPh_3$ catalyst system (Scheme 147).[213]



Scheme 147. Pd-catalysed intramolecular arylation of compound **283**.

In 2006, the 5,6-dihydrobenzo[4,5]imidazo[2,1-*a*]isoquinoline derivative **285** was prepared in 78% yield by intramolecular C-2 arylation of compound **284** in DMF at 140 °C in the presence of CuI as an additive, Cs_2CO_3 as the base, and catalytic amounts of $Pd(OAc)_2$ and PPh_3 (Scheme 148).[214]

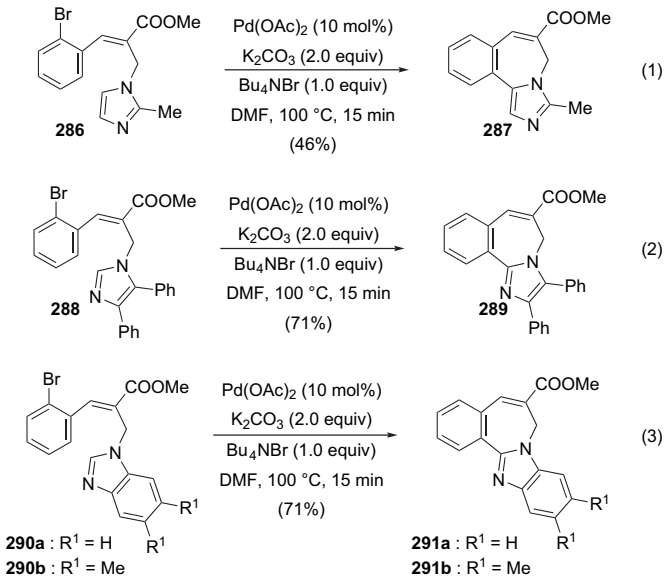


Scheme 148. Pd-catalysed and Cu-mediated synthesis of compound **285**.

However, when the reaction was carried out under base-free and ligandless conditions, **285** was obtained in only 30% yield.[214]

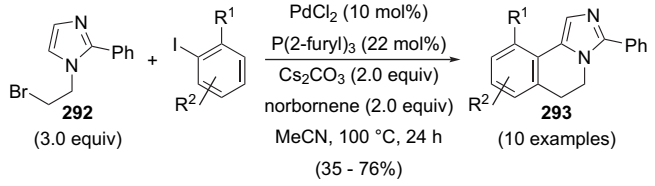
In 2008, the intramolecular arylation of the 2-substituted imidazole derivative **286** was performed in DMF at 100 °C in the presence of K_2CO_3 as the base, Bu_4NBr as an additive and a catalytic quantity of $Pd(OAc)_2$ (Eq. 1, Scheme 149).[209b] The 5*H*-imidazo[2,1-*a*][2]benzazepine derivative **287** was obtained in 46% yield. Compounds **289** (Eq. 2, Scheme 149), **291a** and **291b** (Eq. 3. Scheme 149) were similarly synthesised from the imidazole derivatives **288**, **290a** and **290b**, respectively.[209b]

Finally, a strategy consisting of palladium-catalysed norbornene-mediated sequential aromatic alkylation/direct arylation reactions, which had been formerly applied with success to the preparation of annulated indole, azaindole, pyrrole, furan and thiophene derivatives, [194,195,201,202,215,216] has been used very recently by Jafarpour and Ashtiani for the one-step synthesis of



Scheme 149. Synthesis of compounds **287**, **289**, **291a** and **291b**.

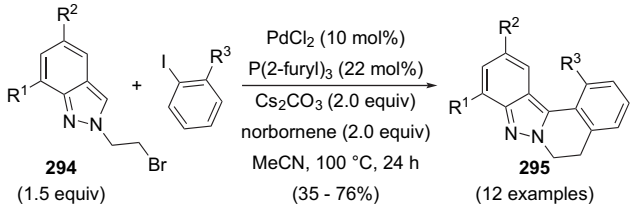
a variety of imidazo[5,1-*a*]isoquinolines **293** from 1-(1-bromoalkyl)-1*H*-imidazoles **292** and aryl iodides in modest to good yields (Scheme 150).[217]



Scheme 150. One-step synthesis of imidazo[5,1-*a*]isoquinolines **293**.

5.4. Synthesis of annulated 2*H*-indazoles and 1,2,3- and 1,2,4-triazole derivatives

In 2008, a one-pot annulation process involving a norbornene-mediated palladium-catalysed sequence, whereby an aryl–alkyl bond and a heteroaryl–aryl bond were successively formed through two C–H bond activations, was utilised by Laleu and Lautens for the synthesis of a variety of 5,6-dihydroindazolo[3,2-*a*]isoquinolines **295** in good-to-excellent yields from 2-(2-bromoethyl)indazoles **294** and aryl iodides (Scheme 151).[216] The procedure consisted of the addition of compounds **294** (1.5 equiv) via a syringe pump over 20 h to a mixture of $Pd(OAc)_2$ (10 mol %), P(2-furyl)$_3$ (22 mol %), norbornene (2 equiv), Cs_2CO_3 (2 equiv) and aryl iodides (1 equiv) in DMF heated at 90 °C.



Scheme 151. Synthesis of 5,6-dihydroindazolo[3,2-*a*]isoquinolines **295**.

Analogous reaction conditions enabled the synthesis of several 5,6-dihydro-[1,2,3]triazolo[5,1-*a*]isoquinolines **298** and 5,6-dihydro-[1,2,4]triazolo[5,1-*a*]isoquinolines **299** in high yields from aryl iodides and 1-(2-bromoethyl)-1*H*-[1,2,3]triazole (**296**) and 1-(2-bromoethyl)-1*H*-[1,2,4]triazole (**297**), respectively (Fig. 21).[216]

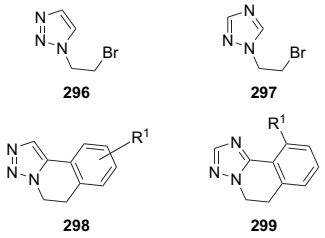
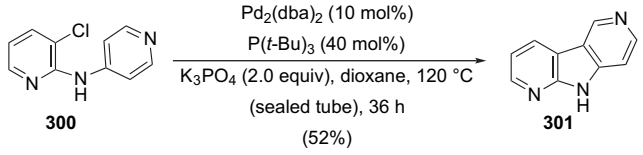


Figure 21. Structures of compounds **296**–**299**.

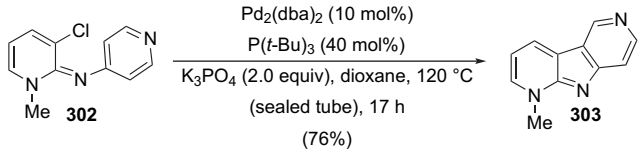
5.5. Synthesis of annulated pyridine, quinoline, isoquinoline, pyran-2-one, and coumarin derivatives

Over the past few years, several examples of direct intramolecular arylation reactions of electron-poor heteroarene derivatives have been described. In 2008, Maes and co-workers reported the synthesis of 9*H*-pyrrolo[2,3-*b*:4,5-*c*']dipyridine (6-aza-9*H*-α-carboline) (**301**) in 52% yield by $Pd_2(dba)_3$/P(*t*-Bu)$_3$-catalysed intramolecular reaction of 3-chloro-*N*-pyridin-4-ylpyridin-2-amine (**300**) in dioxane at 120 °C in the presence of K_3PO_4 as the base (Scheme 152).[218]



Scheme 152. Synthesis of 6-aza-9*H*-α-carboline (**301**).

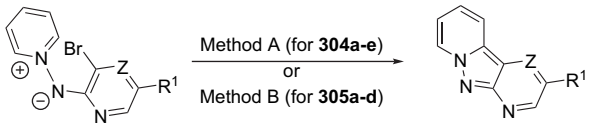
Interestingly, the yield significantly increased when the reaction was performed in dioxane at 180 °C under microwave irradiation in the presence of 2.5 mol % $Pd_2(dba)_3$, 10 mol % P(*t*-Bu)$_3$, and DBU as the base.[218] Maes also reported that the cyclisation of *N*-[3-chloro-1-methylpyridin-2(1*H*)-ylidene]pyridin-4-amine (**302**) under experimental conditions similar to those illustrated in Scheme 145, but involving a lower catalyst loading, enabled the preparation of compound **303** in 76% yield (Scheme 153).[217]



Scheme 153. Pd-catalysed cyclisation of *N*-[3-chloro-1-methylpyridin-2(1*H*)-ylidene]-pyridin-4-amine (**302**).

In the same year, the synthesis of dipyridopyrazole derivatives **306a**–**e** and pyridopyrazolopyrazines **307a**–**d** was achieved in moderate yields via microwave-assisted palladium-catalysed intramolecular arylation of *N*-azinylpiridinium *N*-aminides **304a**–**e** and **305a**–**d**, respectively (Scheme 154).[219,220]

The procedure of choice for the synthesis of the compounds **306a**–**e** from the corresponding *N*-aminides consisted of treatment of compounds **304a**–**e** with 20 mol % $Pd(OAc)_2$, 5 equiv of K_2CO_3, 1.5 equiv of LiCl, and 1 equiv of Bu_4NBr in DMF at 170 °C for 10 min under microwave irradiation (Method A). On the other hand, a similar procedure, but involving reaction at 150 °C for 80 min under microwave irradiation (Method B), was used to prepare compounds **307a**–**d** from the corresponding pyrazinyl pyridinium aminides **305a**–**d** (Scheme 153).[219] Interestingly, these methods for



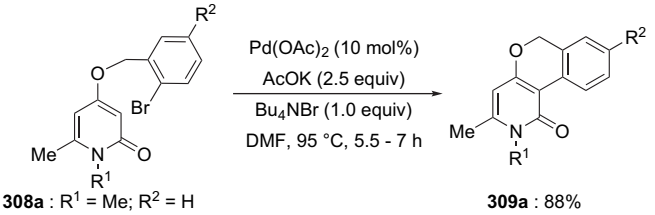
304a : Z = CH; R^1 = Cl	**306a** : 72%
304b : Z = CH; R^1 = Ph	**306b** : 73%
304c : Z = CH; R^1 = 4-MeC_6H_4	**306c** : 40%
304d : Z = CH; R^1 = 4-$MeOC_6H_4$	**306d** : 37%
304e : Z = CH; R^1 = 4-AcC_6H_4	**306e** : 53%
305a : Z = N; R^1 = Ph	**307a** : 78%
305b : Z = N; R^1 = 4-MeC_6H_4	**307b** : 41%
305c : Z = N; R^1 = 4-$MeOC_6H_4$	**307c** : 39%
305d : Z = N; R^1 = 4-AcC_6H_4	**307d** : 31%

Method A : $Pd(OAc)_2$ (20 mol%), K_2CO_3 (5.0 equiv), LiCl (1.5 equiv)
Bu_4NBr (1.0 equiv), DMF, sealed tube, μw, 170 °C, 10 min
Method B : $Pd(OAc)_2$ (20 mol%), K_2CO_3 (5.0 equiv), LiCl (1.5 equiv)
Bu_4NBr (1.0 equiv), DMF, sealed tube, 150 °C, 80 min

Scheme 154. Pd-catalysed intramolecular arylation of *N*-aminides **304a–e** and **305a–d**.

the synthesis of compounds **306** and **307** gave higher yields than the intramolecular arylations of the corresponding *N*-aminides **304** and **305**, respectively, using tris(trimethylsilyl)silane and AIBN.[219]

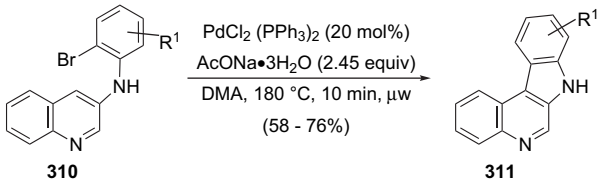
Four 2,6-dihydro-1*H*-isochromen[4,3-*c*]pyridin-1-ones, compounds **309a–d**, were synthesised in high yields by Majumdar and co-workers in 2008 by $Pd(OAc)_2$-catalysed intramolecular arylation of the corresponding 4-(2-bromobenzyloxy)-1,2-dihydropyridin-2-ones **308a–d** in DMF at 95 °C in the presence of Bu_4NBr as an additive and AcOK as the base (Scheme 155).[212]



308a : R^1 = Me; R^2 = H	**309a** : 88%
308b : R^1 = Me; R^2 = OMe	**309b** : 83%
308c : R^1 = Et; R^2 = H	**309c** : 78%
308d : R^1 = Et; R^2 = OMe	**309d** : 81%

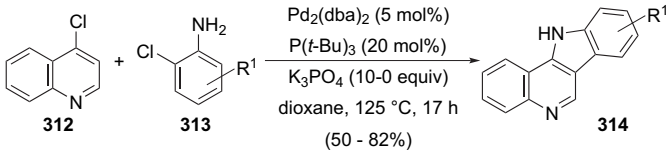
Scheme 155. Synthesis of 2,6-dihydro-1*H*-isochromen[4,3-*c*]pyridin-1-ones **309a–d**.

Maes and co-workers had previously reported that substituted 7*H*-indolo[2,3-*c*]quinolines **311** can be obtained in good yields by microwave-assisted intramolecular arylation of 3-(2-bromophenyl)quinolin-3-amines **310** in DMA at 180 °C for 10 min in the presence of AcONa·$3H_2O$ as a base (Scheme 156).[221]



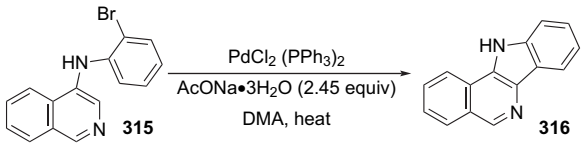
Scheme 156. Synthesis of 7*H*-indolo[2,3-c]quinolines **311**.

D-ring-substituted 11*H*-indolo[3,2-*c*]quinolines **314**, which are isomers of compounds **311**, have been more recently synthesised in good yields by Maes and co-workers[222] via auto-tandem consecutive intermolecular Buchwald–Hartwig N-arylation[223] and palladium-catalysed arylation of 4-chloroquinoline (**312**) with *N*-unsubstituted 2-chloroanilines **313** in dioxane at 125 °C (Scheme 157).



Scheme 157. Synthesis of D-ring-substituted 11*H*-indolo[3,2-*c*]quinolines **314**.

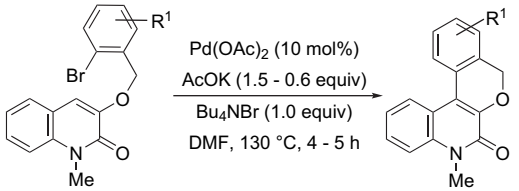
Recently, the Maes research group has also reported the synthesis of 11*H*-indolo[3,2-*c*]isoquinoline (**316**) in high yield by $PdCl_2(PPh_3)_2$-catalysed intramolecular direct arylation of *N*-(2-bromophenyl)isoquinolin-4-amine (**315**) in DMA in the presence of AcONa·$3H_2O$ as a base under conventional or microwave heating (Scheme 158).[224]



$PdCl_2(PPh_3)_2$ (mol%)	Reaction Temp. (°C)	Reaction time (h)	Yield (%) of **316**
10	130 (oil bath)	88 h	65
20	130 (oil bath)	16 h	78
1	180 (μw)	10 min	71
1	200 (μw)	10 min	79

Scheme 158. Synthesis of 11*H*-indolo[3,2-*c*]isoquinoline (**316**).

On the contrary, ligandless conditions were employed by Majumdar and co-workers for the high yielding synthesis of 5-methyl-5*H*-[2*H*]benzopyrano[3,4-*c*]quinolin-6(8*H*)-ones **318a,b** via intramolecular palladium-catalysed arylation of 1-methyl-3-(2′-bromobenzyloxy)quinolin-2(1*H*)-ones **317a,b** (Scheme 159).[225]



317a : R^1 = H — **318a** : 90 %
317b : R^1 = 4-MeO — **318b** : 88 %

Scheme 159. Synthesis of tetracyclic quinolinone annulated heterocycles **318a,b**.

Reaction conditions similar to those used for the synthesis of compounds **318a,b** were then employed to prepare 8-methylbenzopyrano[3,2-*c*]-4-methoxyquinolin-7(8*H*)-one (**323**), the tetracyclic coumarin-annulated heterocycles **324** and **325**, and the tricyclic heterocycle **326** from compounds **319**, **320**, **321** and **322**, respectively (Fig. 22).[212,225]

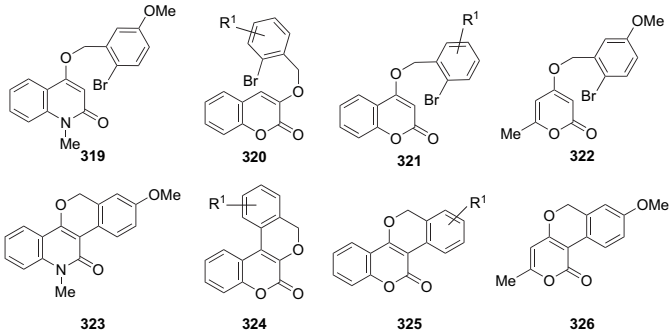
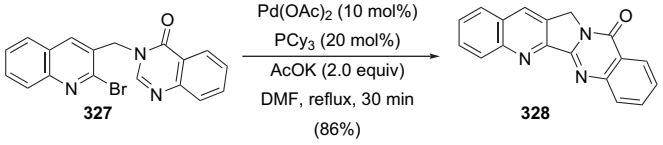


Figure 22. Structures of compounds **319–326**.

5.6. Synthesis of annulated 4(3*H*)-quinazolinone derivatives

In 2004, the total synthesis of the pyrroloquinazolinoquinoline cytotoxic alkaloid luotonin A (**328**),[226,227] was achieved in 86% yield by Harayama and co-workers via intramolecular direct arylation of 3-[(2-bromoquinol-3-yl)methyl]-4(3*H*)-quinazolinone (**327**) in DMF under reflux in the presence of AcOK as the base and a catalyst system consisting of a mixture of $Pd(OAc)_2$ and PCy_3 (Scheme 160).[228]



Scheme 160. Synthesis of luotonin A (**328**).

Analogous reaction conditions enabled the synthesis of ruteocarpine (**330**), an indolopyridoquinazoline alkaloid, from 3-[2-(*N*-acetyl-2-bromoindol-3-yl)ethyl]-4(3*H*)-quinazolinone (**329**) in excellent yield (Fig. 23).[228] Ruteocarpine has long been used to treat inflammation-related diseases.[229,230]

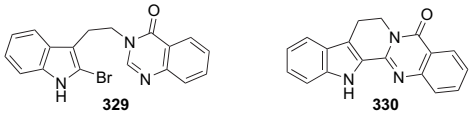
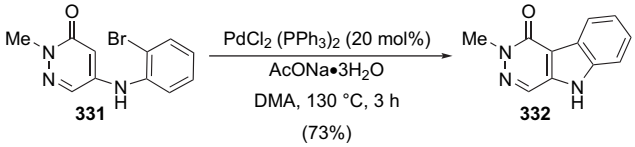


Figure 23. Structures of compounds **329** and **330**.

It is also worth noting that recent advances in the synthesis of quinazoline alkaloids, including luotonin A and ruteocarpine, via palladium-catalysed intramolecular direct heteroarylation reactions have been described by Abe and Harayama in a short review published in 2008.[231]

5.7. Synthesis of ring-fused 1,2-, 1,3- and 1,4-diazine derivatives

In the last few years, attention has also been focused on the synthesis of ring-fused pyridazin-3(2*H*)-one derivatives. In 2004, Maes and co-workers synthesised 2-methyl-2,5-dihydro-1*H*-pyridazino[4,5-*b*]indol-1-one (**332**) in 73% yield by palladium-catalysed intramolecular arylation of 5-[(2-bromophenyl)amino]-2-methylpyridazin-3(2*H*)-one (**331**) in DMA at 130 °C using $AcONa\cdot 3H_2O$ as a base and 20 mol % $PdCl_2(PPh_3)_2$ (Scheme 161).[191]



Scheme 161. Intramolecular direct arylation of compound **331**.

More recently, this procedure has been improved and compound **332** has been prepared in 85% yield by intramolecular arylation of **331** at 180 °C for 0.5 h under microwave irradiation in the presence of $AcONa\cdot 3H_2O$ as a base and 1 mol % $PdCl_2(PPh_3)_2$.[232]

This microwave-based protocol has also been used to prepare compounds **334a**,**b** from 2-benzyl-5-{[2-bromo-4-(trifluoromethoxy)-phenyl]amino}pyridazin-3(2*H*)-ones **333a**,**b** in high yields (Fig. 24).[232]

In 2009, 5-alkyl-1,3-dimethyl-5,6-dihydropyrimido[5,4-*c*]isoquinoline-2,4(1*H*,3*H*)-diones **336** and 2,4,5-trimethyl-5,6-dihydropyrimido[4,5-*c*]isoquinoline-1,3(2*H*,4*H*)-diones **338** have been

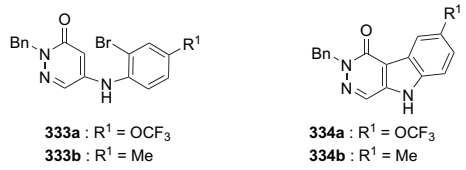
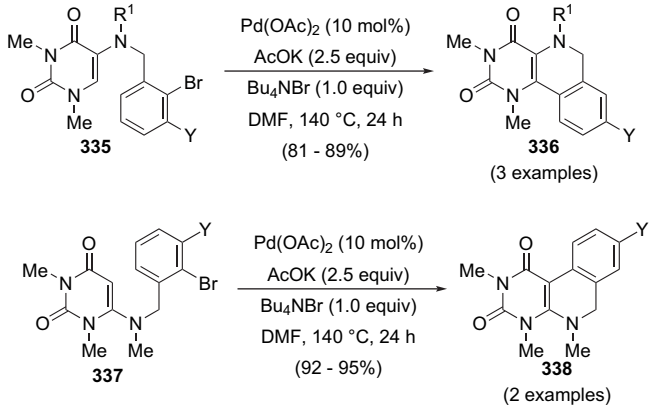


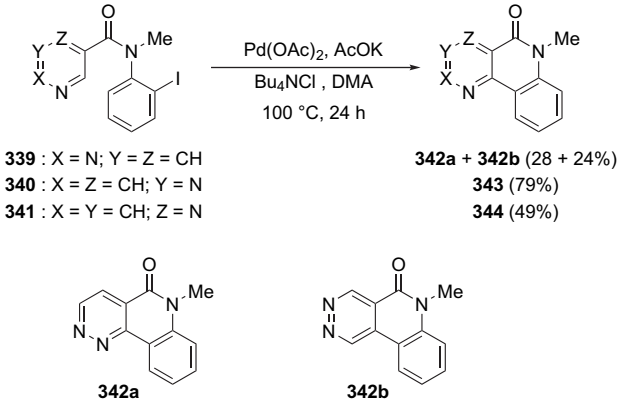
Figure 24. Structures of compounds **333a**,**b** and **334a**,**b**.

synthesised in high yields by the research group of Majumdar by palladium-catalysed intramolecular direct arylation of 5-[(2-bromobenzyl)alkylamino]-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-diones **335** and 6-[(2-bromobenzyl)methylamino]-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-diones **337**, respectively, under ligandless conditions (Scheme 162).[233]



Scheme 162. Intramolecular direct arylation of compounds **335** and **337**.

Similar conditions have been used by Beccalli and co-workers for the intramolecular arylation of the 1,2-, 1,3- and 1,4-diazine derivatives **339**, **340** and **341**, respectively (Scheme 163).[234]



Scheme 163. Intramolecular direct arylation of diazines **339**–**341**.

It should be noted that, in the case of the amide **339**, two cyclised regioisomers, **342a** and **342b**, corresponding to cyclisation on positions 3 and 5 of the pyridazyl ring, respectively, were obtained in a 1:1 ratio. However, cyclisation of compounds **340** and **341** produced selectively **343** and **344**, respectively, in high yields.[234]

6. Conclusions

This article has sought to describe and highlight the impressive developments made in the last few years in the exploding area of the transition metal-catalysed direct inter- and intramolecular

(hetero)arylation reactions of heteroarene C–H bonds and in the use of these methods for the efficient, chemo- and regioselective synthesis of several classes of heteroarene derivatives also containing many labile functional groups, often starting from rather simple materials. It has been illustrated that, at present, not only π-electron-rich, but also π-electron-deficient heteroarenes are able to undergo this type of inter- and intramolecular carbon–carbon bond forming reaction. As reported in the previous sections of this article, the activation of C–H bonds of electron-poor heteroarenes, until a few years ago considered to be unsuitable to efficiently undergo direct (hetero)arylation reactions, has been achieved through the use of effective catalyst systems and/or a suitable, and sometimes provisional, functionalisation of the heteroarene systems.

As evidenced by the very large number of publications in the field summarised and discussed in this review as well as by a very recent featured article by Fagnou's group, in which the outcomes of studies including the establishment of broadly useful direct arylation reactions that enable efficient cross-coupling between a wide variety of coupling partners with 1:1 stoichiometry have been summarised,[235] at present, the transition metal-catalysed inter- and intramolecular (hetero)arylation reactions of heteroarenes represent the most general and economically attractive methodology for forming directly, efficiently, chemo- and regioselectively (hetero)aryl–heteroaryl carbon–carbon bonds without the use of stoichiometric amounts of organometallic reagents. Our belief is supported by the fact that, after completion of this review, a large number of examples showcasing the transition metal-catalysed direct arylation of various heteroarenes have appeared in a few months.[236,237] For example, Sames and co-workers have recently developed a strategically new approach for the regioselective palladium-catalysed direct arylation of pyrazole derivatives,[236u] a class of heteroarenes never formerly used in direct arylation reactions. These authors investigated the direct arylation of SEM-protected pyrazoles due to the stability of this protecting group under the arylation conditions as well as its ability to be transposed from one nitrogen to another, enabling sequential arylations.[236u]

Moreover, a synthetically useful method for the palladium-catalysed direct arylation of azine *N*-oxides using aryl triflates have been described by Fagnou and co-workers, who has also evaluated their protocol in the synthesis of a key intermediate of a diarylpyridine, which exhibits antimalarial and antimicrobial activities.[236l]

Very interesting results have also been reported by Catellani and co-workers, who have recently described the palladium/norbornene-catalysed synthesis of heteroatom-containing *o*-teraryls from aryl iodides and heteroarenes through double C–H activation in sequence.

Another noteworthy example of an effective method for the concise functionalisation of heteroarenes is the copper-mediated direct arylation of 1,3,4-oxadiazoles and 1,2,4-triazoles in the presence suitable ligands (i.e., 1,10-phenanthroline or PPh_3) and bases (i.e., Cs_2CO_3 or Na_2CO_3), which, very recently, has been investigated by Miura and co-workers.[237c] This method enables the installation of a variety of aryl moieties bearing a functional group such as ester, nitrile, or ketone.

However, some relevant challenges concerning the direct inter- and intramolecular arylation reactions of heteroarenes must still be faced. In fact, lowering of the reaction temperature and the catalyst loading are still necessary for many specific reactions and, particularly, for those involving the use of copper salts as catalyst components. On the other hand, additional important key fields that remain underveloped include i) the use of free (NH)-pyrazoles for direct C-3(5) intermolecular arylation reactions and their application for the synthesis of pharmacologically important substances such as inhibitors of the hematopoietic form of prostaglandin D_2 synthase[238] or p38α MAP kinase inhibitors[239]; ii) the design, development and use of highly efficient, air-, moisture- and heat-resistant transition metal catalysts, which can be stored unaltered for prolonged periods of time, as well as the replacement of the expensive transition metals, usually palladium or rhodium, with cheaper ones; iii) the development of procedures for the highly regioselective and high yielding C-5 arylation of 2-unsubstituted free (NH)-imidazole, oxazole, and thiazole; and iv) effective methods for the regioselective direct arylation at the 4-position of five-membered heteroarenes with two heteroatoms and diazines as well as at C-3 of pyridines, pyridazines, and quinolines.

Nevertheless, we believe that, in the near future, due to their excellent functional-group tolerance and high chemo- and regioselectivity, the broad scope and simplicity of these valuable Csp^2–Csp^2 bond-forming reactions will increase their impact on the synthesis of biologically active natural products and pharmacologically relevant heteroaromatic substances in both the academic and industrial settings.

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Biographical sketch

Fabio Bellina was born in Catania (Italy) in 1964. He studied Chemistry at the University of Pisa and received his Laurea Degree with first-class honours in 1990. In 1992 he joined the University of Pisa as an Organic Chemistry Researcher at the Department of Chemistry and Industrial Chemistry. In October 2003 he was appointed as the Faculty of Science of the University of Pisa as an Associate Professor of Organic Chemistry. His research interests were initially mainly devoted to the total synthesis of naturally occurring compounds of biological and/or pharmacological interest and to the synthesis of structural analogues of naturally occurring fungicidal derivatives of agrochemical interest. More recently, Prof. Bellina focused his attention on new and efficient protocols for regioselective transition metal-mediated carbon–carbon and carbon–heteroatom bond forming reactions, with a particular interest towards the selective functionalisation of oxygen-containing unsaturated heterocycles such as 2(5*H*)-furanones and 2(2*H*)-pyranones. Currently, he is working on the development of novel and efficient protocols for the transition metal-catalysed direct C–H and N–H bond arylation of heteroarenes, the direct functionalisation of active C(sp^3)-H bonds, and the application of these new procedures to the selective preparation of bioactive natural and synthetic compounds.

Renzo Rossi was born in Pisa (Italy) and graduated in Organic Chemistry with first-class honours at the University of Pisa defending a thesis performed under the guidance of Professor Piero Pino. In 1969 he became Assistant Professor and in 1971 he earned the *libera docenza* in Organic Chemistry. After holding other intermediate positions at the University of Pisa and the Scuola Normale Superiore of Pisa, in 1980 he became Full Professor of Organic Chemistry at the University of Calabria. In 1982, he joined again the University of Pisa where he has held the Chair of Chemistry of Naturally Occurring Compounds. In 1999, the University of Pisa awarded him the *Ordine del Cherubino*. His current research interests include: i) the preparation of substances, which exhibit significant cytotoxicity against human tumor cell lines and antivascular properties; ii) the study of new methodologies for carbon–carbon bond formation that involve the use of organometallic reagents, transition metal-catalysed direct arylation reactions of substrates with activated sp^3-hybridized C–H bonds with aryl halides and pseudohalides; iii) the design and development of new, highly chemo- and regioselective methods for the transition metal-catalysed direct C- and N-arylation of electron-rich heteroaromatic systems, including free (NH)-azoles, with aryl halides and pseudohalides; and iv) the application of these methods to the synthesis of direct precursors to compounds with relevant biological properties. In recent years, several successful studies have also been performed by his research group in the field of the synthesis and evaluation of the biological properties of naturally-occcurring compounds of marine origin and their structural analogues, which are characterised by the 2(5*H*)-furanone ring. Professor Rossi, who has coauthored over 225 research publications and a number of highly cited review articles and patents, is a fellow of the Royal Society of Chemistry, the American Chemical Society, and the Società Chimica Italiana.