# Regioselective (site-selective) functionalisation of unsaturated halogenated nitrogen, oxygen and sulfur heterocycles by Pd-catalysed cross-couplings and direct arylation processes

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***Received 14th February 2007***
***First published as an Advance Article on the web 27th April 2007***
**DOI: 10.1039/b611177g**

This *tutorial review* focuses on several practical synthetic transformations utilising palladium catalysis that facilitate the synthesis of functionalised unsaturated heterocycles in a regioselective (site-selective) manner. Cross-couplings of electron-deficient, electron-neutral and electron-rich unsaturated halogenated heterocycles with various organometallic reagents, and other types of nucleophiles, are detailed. Direct arylation of electron-rich unsaturated heterocyclic compounds by C–H functionalisation is also presented.

## Introduction

Unsaturated heterocycles, including heteroaromatics, containing nitrogen, oxygen and sulfur, hereafter *heterocycles*, are found in abundance in natural products and bioprobes, materials, and pharmaceutical agents, leading many researchers to develop efficient synthetic routes[1] to these ubiquitous structures. An eclectic array of parent heterocyclic compounds can be easily prepared by classical synthetic routes. However, the incorporation of substituents onto the parent heterocycle can sometimes prove problematic, *e.g.* due to competing side-reactions or low reactivity toward common organic reagents. To diversify the structural identity of heterocyclic compounds it is often desirable to take a suitably reactive and functional parent compound, *e.g.* a halogenated heterocycle that can be reacted with a suitable nucleophilic reagent. The methods of choice for the introduction of C, N, O and S-substituents on to heterocyclic compounds are palladium(0) catalysed cross-couplings, hereafter coupling processes.[2] Reactions such as Hartwig–Buchwald, Heck, Negishi, Sonogashira, Stille and Suzuki couplings are commonplace in synthetic laboratories. One can easily introduce various substituents on to electron-rich and electron-deficient halogenated heterocyclic compounds. A heterocycle can also be used as the nucleophilic component.

The general purpose of this tutorial review is to highlight some of the regioselective (site-selective) couplings that are possible on poly-halogenated or poly-functionalised heterocycles. For selected examples the equivalent reaction of the mono-halogenated heterocycle is discussed, particularly in relation to side reactions, as will the formation of unusual $Pd^{II}$ complexes in the coupling reactions. An emphasis will be placed upon the origin of regioselective processes, providing details of new developments. It should be noted that in early 2005 an excellent comprehensive review was reported by Bach and co-workers,[3] describing regioselective couplings of various heterocyclic compounds from a synthetic perspective. This review will complement this, highlighting efficient couplings of electron-deficient, electron-neutral and electron-rich heterocyclic compounds, and provide coverage for other substrates. The review is split into the following subsections: origin of regioselectivity in heterocyclic couplings; electron-deficient/neutral heterocyclic couplings; electron-rich heterocyclic couplings, including direct arylation.

Given the nature of this review a simple discussion concerning coupling reactions is provided below. This is by

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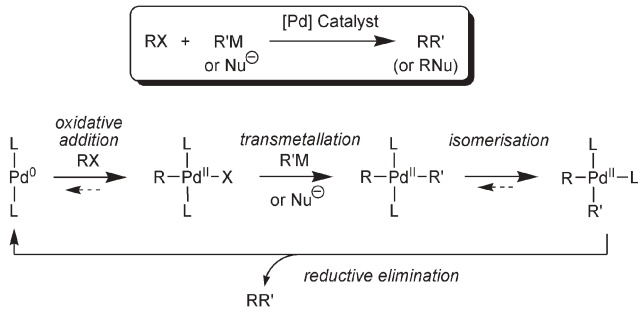



**Scheme 1** A generic catalytic cycle for coupling processes.[2]

no means thorough—it merely serves as a guide to an area which is vast and continues to expand at a staggering rate.

### Coupling processes: a general guide

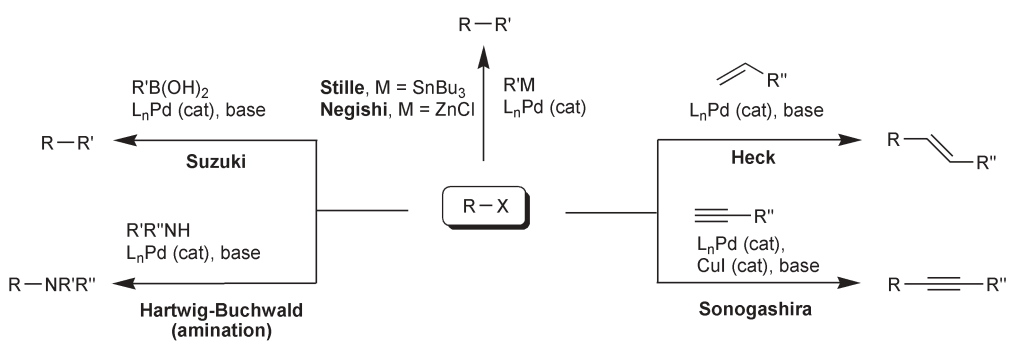
There are three steps in the catalytic cycles of most coupling processes mediated by $Pd^0$, which is usually ligated and sometimes specified as "$L_nPd^0$" ($n$ = 1 or 2; usually solvated) (Scheme 1). Oxidative addition of the organohalide to $Pd^0$ to afford a $Pd^{II}$ intermediate is the first step of the catalytic cycle. This intermediate can undergo transmetallation with an organometallic reagent (or other type of nucleophile) to give another $Pd^{II}$ species, with loss of a by-product (salt or other metal halogen species) from the reaction. Isomerisation (*trans* to *cis*) serves to orientate the organic groups for favourable reductive elimination, affording the coupled product and regenerating the $Pd^0$ catalyst. The rate-limiting step for the catalytic cycle depends on a number of factors, *e.g.* the strength of the C–X bond in the organohalide or reactivity of the organometallic reagent in transmetallation.

The steric and electronic effects of the selected ligands can dramatically affect individual steps of the catalytic cycle. The named transformations given above involve reaction of a certain type of nucleophilic component with an organohalide (Scheme 2). For example, in Hartwig–Buchwald amination a deprotonated amine is the nucleophile (strong base required; etherification and thioetherification are possible using either an alcohol or thiol); Heck coupling employs an alkene as the nucleophile (base required); Negishi couplings employ organozinc, organozirconium or organoaluminium reagents; Sonogashira couplings employ organocuprate reagents which are generated *in situ* by the presence of co-catalytic CuI (Cu-free Sonogashira coupling is historically known as Heck alkynylation; base required); Stille couplings involve an organostannyl reagent; and Suzuki couplings involve an organoborane reagent, most commonly a boronic acid (base required).

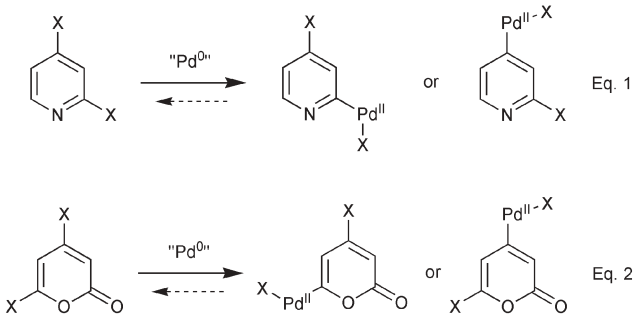
In terms of the types of catalysts/ligands that should be used for efficient couplings, an area that is arguably saturated but where much still needs to be done in terms of catalyst development for heterocyclic coupling components, it is quite evident from a large body of literature that standard catalyst systems work well for many types of couplings. For example, $PdCl_2(PPh_3)_2$ is commonly used as a precatalyst, as is $Pd(OAc)_2$ in the presence or absence of an activating ligand (*e.g.* phosphine). Such complexes are reduced *in situ* by the organometallic reagent or base, *e.g.* $Et_3N$, or even phosphine, to give a catalytically active $Pd^0$ species. The main advantage in using a precatalyst stems from their general stability to air and moisture. The most common $Pd^0$ sources are $Pd(PPh_3)_4$ and $Pd_2(dba)_3$ (dba = (*E*,*E*)-dibenzylideneacetone). For the latter complex, phosphines or other activating ligands are commonly added to $Pd_2(dba)_3$.[4] It ought to be borne in mind that dba often plays a non-innocent role[5] in such coupling processes (sometimes for better or worse).[6] Other electron-deficient alkenes, *e.g.* maleic anhydride or fumarates, can also influence coupling. The dba ligand actually meters out/lowers the concentration of the reactive $L_nPd^0$ species in oxidative addition with the organohalide.[7] Halides and pseudohalides can also play active roles in catalysis, altering the rate of oxidative addition and transmetallation steps in the coupling catalytic cycles. Finally, catalyst loading, better referred to as [Pd] concentration,[8] can have a dramatic effect on whether coupling occurs or not—higher turnovers are usually seen at lower [Pd] concentrations.[9] The inverse correlation of catalytic activity and [Pd] concentration is rationalised by agglomeration of Pd and precipitation of Pd black—this explains why some couplings appear to turnover slowly, if at all. Moreover, the addition of further Pd catalyst/precatalyst likely hinders further turnover of substrate. These points will be elaborated at appropriate junctures in the review.

## Origin of regioselectivity in heterocyclic couplings

The majority of regioselective coupling processes have been executed on poly-halogenated compounds. There is no doubt that the origin of the regioselectivity derives from the oxidative addition step, which can be a reversible process; two examples are presented in Scheme 3.




**Scheme 2** Common $Pd^0$-mediated cross-coupling processes.[2]




**Scheme 3** Regioselective oxidative addition reactions.

The reactivity of $Pd^0$ towards each C–X bond is likely to parallel the rate of nucleophilic aromatic substitution (NAS) in the same poly-haloaromatic compounds.[10,11] Generally, the rates of NAS will be dependent on the strength of the C–X bond, with higher rates seen for more electron-deficient sites.

NMR spectroscopy is a useful technique for predicting the preferred position of coupling. The $^{13}C$ chemical shifts of halogenated heterocycles have been used as a general means to differentiate two or more C–X positions in coupling. A more useful and reliable method has been developed by Handy and Zhang,[11] which utilises the $^1H$ NMR chemical shift data of the parent heterocyclic compound, prior to halogenation, to predict the most likely oxidative addition reaction and hence the preferred site for coupling. For example, in five-membered heterocyclic compounds regioselective coupling is observed at the more electron-deficient carbon centres, as indicated by the $^1H$ NMR chemical shift of the parent compound (Fig. 1). The six-membered ring heterocycles follow a similar trend (Fig. 2). In some cases, where the halogens are different, or in the case where a pseudohalogen is used, it is evident that the chemical shift method, and the electronic preference of the heterocyclic ring, can be overcome by halogens/pseudohalogens of different intrinsic reactivity. For example, 4-iodo-2-bromopyridine undergoes regioselective Kumada coupling at the 4-position, the site possessing the weaker C–X bond.

Theoretical calculations may also be used to predict the origin of regioselectivity (Fig. 3). For example, Fairlamb and co-workers have demonstrated that 4,6-dichloro-2-pyrone should undergo regioselective coupling at the 6-position.[12] Here, electron-rich $PMe_3$ was employed as a model phosphine ligand. The oxidative addition leading to $Pd^{II}$ intermediate **I** is more favourable than **II**, both kinetically and thermodynamically. Crucially, however the α-oxygen appears to act like a π-donor ligand, stabilising the developing positive charge on the carbon in TS-I. The TS-II structure does not bear this additional stabilisation. This type of electron delocalisation also influences the reactivity of the carbon–palladium bond in **I**. Theoretical calculations can thus be a useful tool in predicting the regioselectivity outcome, moreover the reactivity of the subsequent Pd–C and Pd–X bonds. The degree of electronic character on the heterocycle is expected to alter subsequent steps in the catalytic cycle(s).

With the scene now set, some specific examples of regioselective couplings will be described.

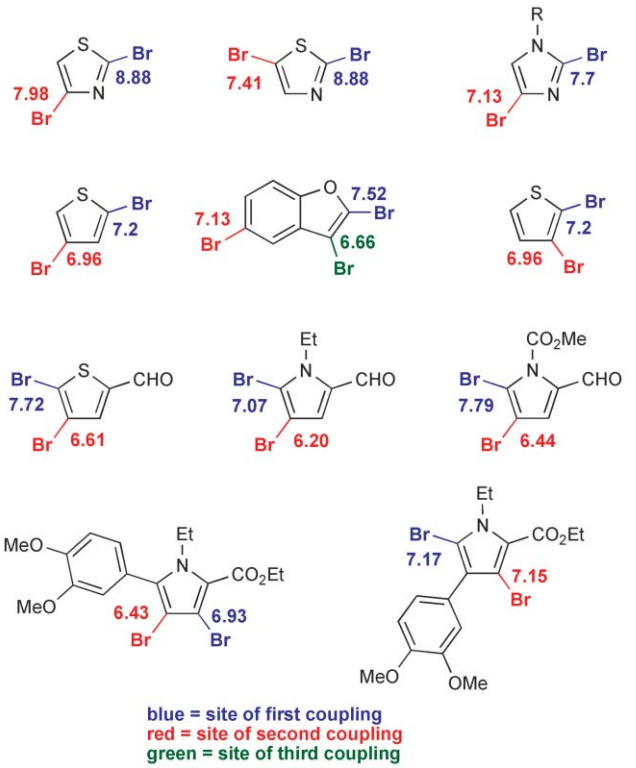



**Fig. 1** Prediction of cross-coupling regioselectivity based on Handy and Zhang's NMR method.[11] The $^1H$ NMR chemical shifts refer to the respective non-halogenated, five-membered ring parent heterocycle. The most deshielded proton (highest chemical shift) indicates the preferred site for coupling in the halogenated compound.

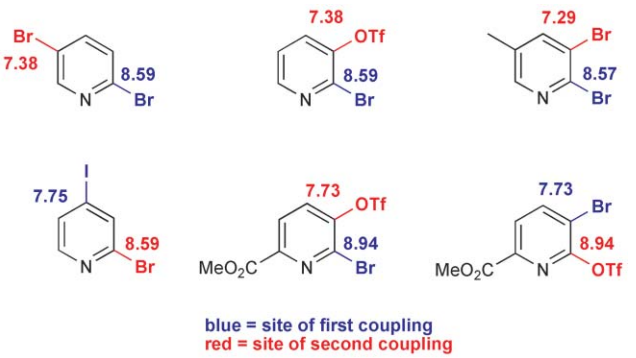



**Fig. 2** Six-membered ring heterocyclic compounds. Other details as for Fig. 1.[11]

## Couplings of electron-deficient and electron-neutral heterocycles

### 2-Pyrones

Several research groups have published reports on couplings of halogenated 2-pyrones.[13] Fewer reactions have been carried out on poly-halogenated 2-pyrones. Cho and co-workers have led the way in terms of couplings on 3,5-dibromo-2-pyrone, reporting a range of regioselective processes.[14] For example, this compound undergoes regioselective Stille coupling at the 3-position with organostannanes to give 3-substituted-5-bromo-2-pyrones (Scheme 4).

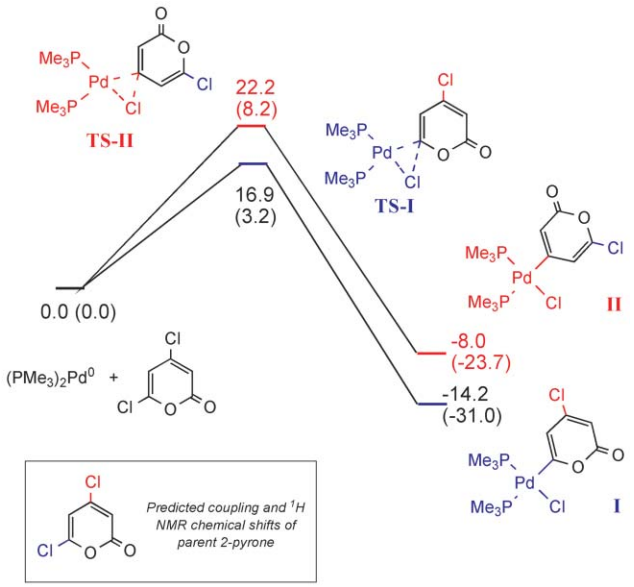
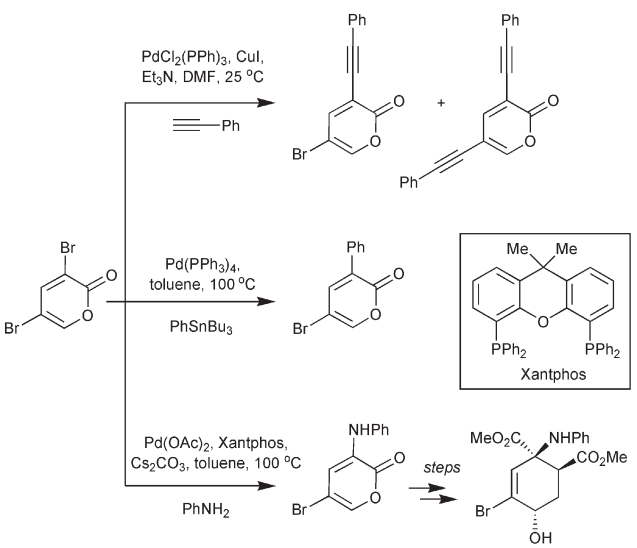
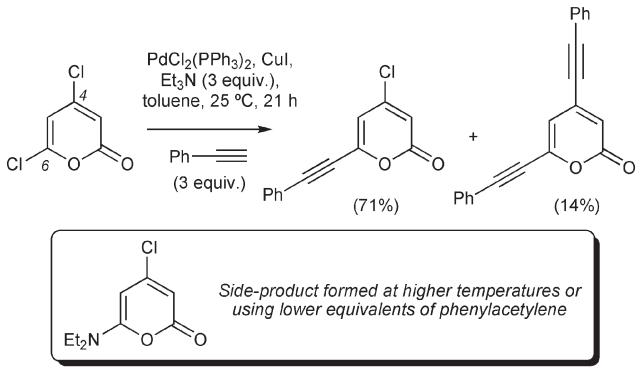



**Fig. 3** Energy profiles for the two possible pathways in the oxidative addition of 4,6-dichloro-2-pyrone with $(PMe_3)_2Pd^0$.[12] The relative free energies and reaction energies (in parentheses) are given in kcal $mol^{-1}$.

Remarkable $Cu^I$ effects are observed, resulting in a switch in regioselectivity for the 5-position in the presence of stoichiometric amounts of $Cu^I$.[15] It is presumed, but not proven, that a more reactive organocuprate is formed in the presence of stoichiometric copper(I) iodide, a reasonable assumption in a polar solvent like DMF. More generally, coupling occurs at the 3-position for Sonogashira coupling,[16] Suzuki coupling[17] and amination reactions.[18] The type of bidentate ligand is important for amination, with Xantphos effective for aromatic amines and BINAP for alkyl amines. The formation of 2-pyridone by-products formed by direct reaction of the 2-pyrone and primary amine were not reported. The amination products interestingly undergo facile Diels–Alder cycloadditions with electron-deficient dienophiles to afford stereochemically defined cycloadducts, which on subsequent




**Scheme 4** Regioselective couplings of 3,5-dibromo-2-pyrone.[14–19]




**Scheme 5** Regioselective Sonogashira alkynylation of 4,6-dichloro-2-pyrone.[12]

ring-opening with NaOMe provide constrained α-amino acid derivatives.[19]

The example of 4,6-dichloro-2-pyrone, *vide supra*, involved Sonogashira couplings.[12] This compound is highly reactive and amine bases such as $Et_3N$, react directly with it. The 6-position is activated, indeed similar reactions have been reported for 6-chloro-2-pyrone;[20] reaction at the 4-position is more sluggish at 25 °C (Scheme 5). Interestingly, the dba ligand from $Pd(dba)_2$, also known as $Pd_2(dba)_3{\cdot}dba$, appears to slow down the rate of oxidative addition with $Pd^0(PPh_3)_n$, leading to a higher proportion of the side-product, in addition to a small amount of hydrodechlorination, suggesting a role for dba on the oxidative addition intermediate [{σ-6-(2-pyrone)}$PdCl(PPh_3)_2$] complex to give [σ-{6-(2-pyrone)}$PdH(PPh_3)_2$]; reductive elimination revealing the hydrodechlorinated product, 4-chloro-2-pyrone. Hydrodehalogenation is a common side-reaction in heterocyclic couplings and is usually the result of an inefficient transmetallation step.

Whilst compiling this tutorial review it was interesting to use the Handy–Zhang $^1$H NMR chemical shift method to compare the regioselectivity observed in the coupling reactions of dihalogenated 2-pyrones (Fig. 4). Based on the $^1$H NMR chemical shifts of 2-pyrone,[21] one would predict coupling in the following order: C6 ⩾ C4 > C5 ⩾ C3. C6 is much more reactive than C4 experimentally in the coupling reactions of 4,6-dichloro-2-pyrone. The preferred regioselectivity for the 3-position in 3,5-dibromo-2-pyrone could not be predicted using this method, although the $^1$H NMR chemical shifts for

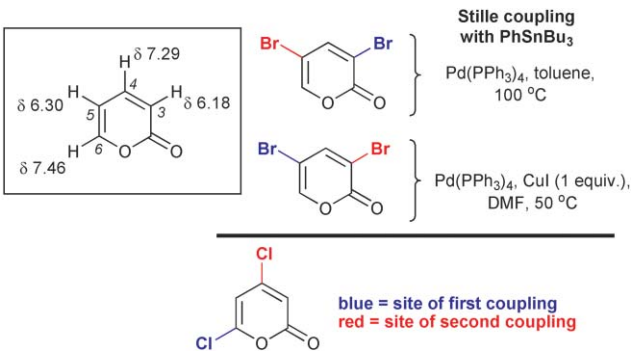



**Fig. 4** Comparison of the $^1$H NMR chemical shifts of 2-pyrone and the regioselectivity outcome for coupling poly-halogenated 2-pyrones.

both positions are similar ($\Delta\delta$ = 0.12 ppm). It is evident where the $^1$H NMR chemical shifts of any two positions are within $\delta$ 0.2–0.3 that a reversal of regioselectivity could be observed depending on the reaction conditions used for coupling.

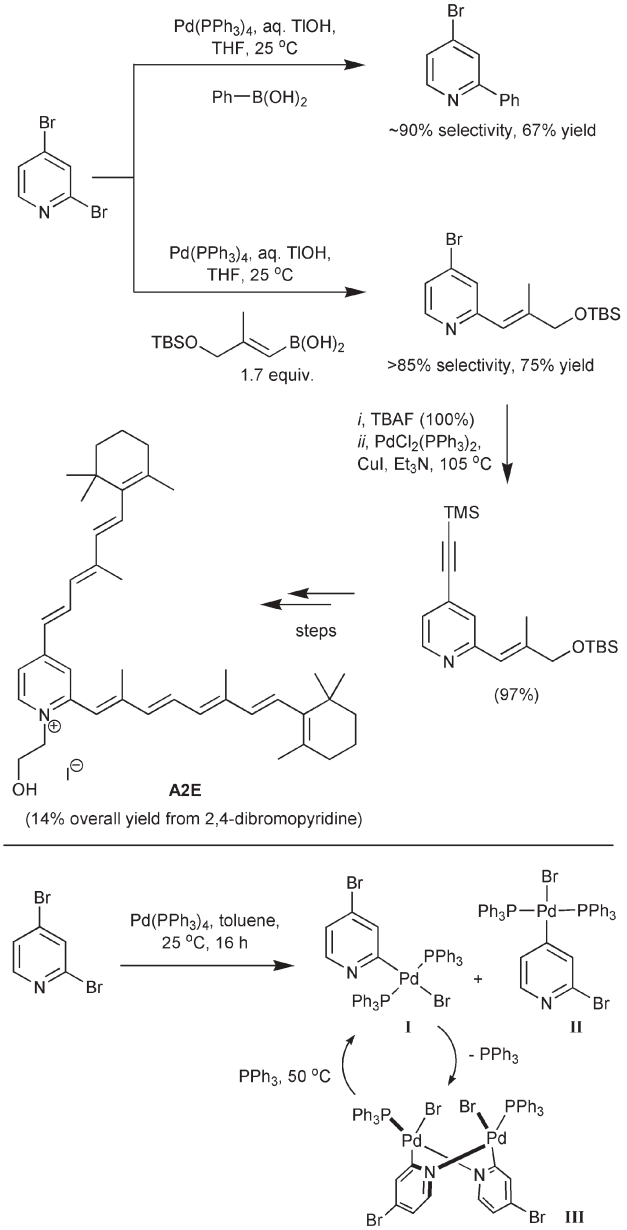
It being clear that electronic effects likely dominate the regioselectivity outcome, here a chelating role for the carbonyl moiety of the 2-pyrone could be important, something which could be probed with a 2-pyridone.

### Pyridines

The 2,4-substituted pyridyl moiety is a common structural motif in pharmaceutical agents and natural products.[22] This led Cid and co-workers to explore the regioselectivity in Suzuki couplings of 2,4-dibromopyridine.[23] Treatment of 2,4-dibromopyridine with alkenylboronic acids in the presence of $Pd(PPh_3)_4$–TlOH in THF at 25 °C affords 2-alkenyl- and 2-aryl-4-bromopyridines in good yields with predominant selectivity for the 2-position. Despite their high toxicity, thallium type bases may be employed in coupling reactions for more awkward Suzuki couplings.[24] The activated organoboronic acid intermediate $[R'B(OH)_3^-]Tl^+$ is likely more reactive in the transmetallation step, where rate-limiting, also forming water-insoluble salts. 2-Alkenylated-4-bromopyridine underwent Sonogashira coupling to give a key intermediate in the synthesis of the visual pigment A2E.[25] It should be noted that TlOEt is as reactive as TlOH[26] and more readily available commercially.

In a stoichiometric reaction of $Pd(PPh_3)_4$ with 2,4-dibromopyridine, to test for the origin of the regioselectivity, two mono-nuclear oxidative addition intermediates **I** and **II** (Scheme 6), derived from the reaction of $Pd(PPh_3)_2$ at the 2- and 4-positions, respectively, were formed in a ratio of roughly 17 : 1 (determined by $^1$H NMR), as well as a trace amount of $Pd^{II}$ dimer complex **III**, formed by loss of phosphine from **I**, which becomes the major product if the reaction is conducted in the presence of air ($OPPh_3$ driving its formation and a favourable *N*-coordination to $Pd^{II}$). The equivalent dimer complexes of **III** derived from 2-bromopyridine have been reported previously,[27a] and shown to be of central importance in the catalytic cycle of Suzuki coupling.[27b] In the examples reported by Cid dimer **III** does not react with arylboronic acid at 25 °C. Similar dimer complexes to **III** can be expected for other organohalides possessing a α-nitrogen moiety, *e.g.* pyrrole, indole, quinoline, benzo[*f*]quinoline or benzo[*g*]quinoline *etc*. A similar preference for the 2-position of 2,4-dichloro-3-amino-6-methylpyridine has been recorded in Sonogashira coupling (Scheme 7).[28]

Perhaps one of the most remarkable switches in regioselectivity was observed in the couplings of 2,6-dichloro-3-substituted pyridines with phenylboronic acid (Scheme 8).[29] Where the 3-substituent was an ester, preferential reaction was observed at the 6-position in THF, whereas in MeOH the regioselectivity switched to the 2-position. Altering the 3-substituent to an amide resulted in preferential reaction at the 2-position, again in MeOH. Although chelation of the amide is proposed to account for the regioselectivity outcome, likely through a coordinatively unsaturated $Pd^0$ intermediate, the switch in solvent is also important. Note: the reaction of the ester compound mediated by $Pd(PPh_3)_4$ in MeOH was not reported, which could confirm such a proposal.

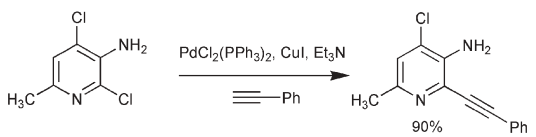






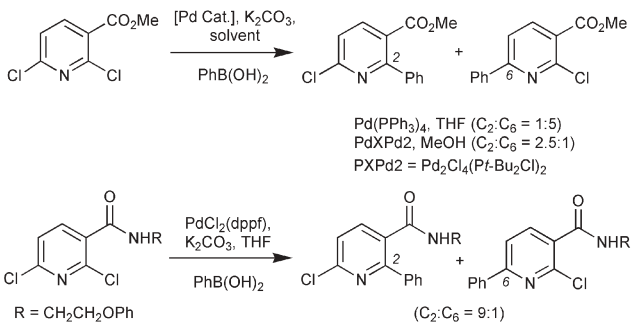
**Scheme 6** Regioselective Suzuki coupling of 2,4-dibromopyridine.[23]

Coupling of 2,5-dihalopyridines in the majority of cases results in regioselectivity for the 2-position.[30] The same reactivity sequence is mirrored in Pd-catalysed carbonylation reactions, where lower [Pd] concentrations lead to higher turnover frequencies.[31] The $Pd^0$-catalysed carbonylative

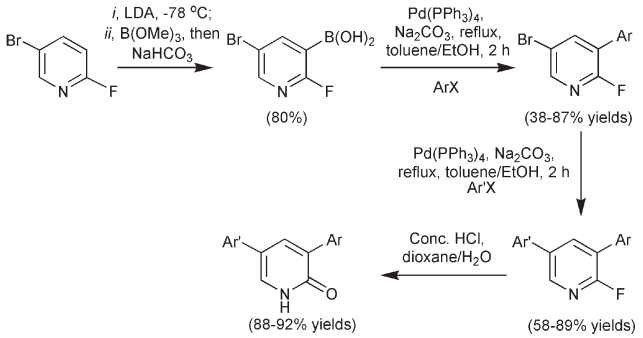



**Scheme 7** Regioselective Sonogashira coupling on a 2,4-dichloropyridine.[28]

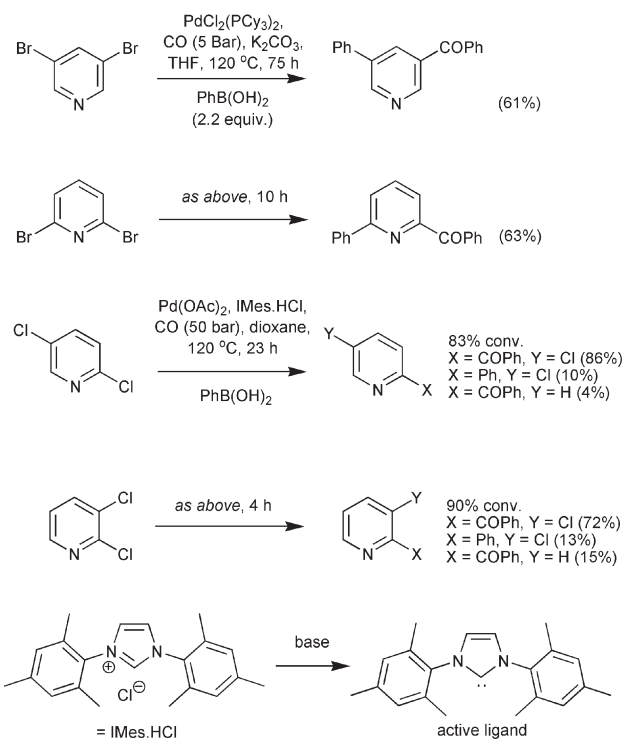
 




**Scheme 8** Participation of a neighbouring group in regioselective Suzuki coupling.[29]




**Scheme 10** Suzuki couplings of 2-fluoro-5-bromopyridine.[34]

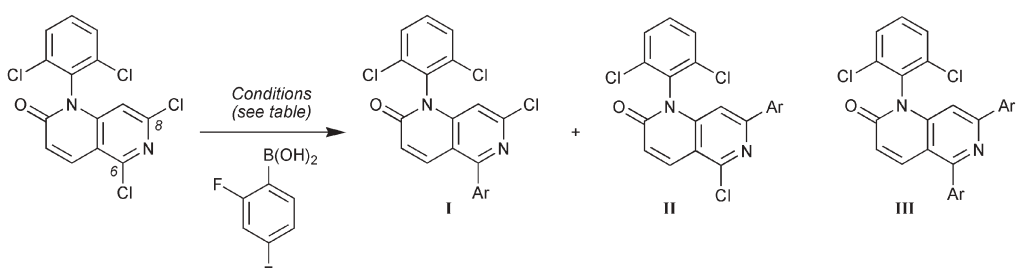



**Scheme 9** Carbonylative Suzuki couplings of dibromopyridines.[32]

Suzuki coupling of 3,5-dibromo- and 2,6-dibromopyridines gave unsymmetrical arylated carbonylation products (Scheme 9).[32] Use of the more electron-rich σ-donor *N*-heterocyclic carbene ligands, commonly generated *in situ* from the imidazolium salt and base, allows various dichloropyridines to be coupled under similar conditions.[33] Here, hydrodechlorination is observed, albeit to a minor extent.

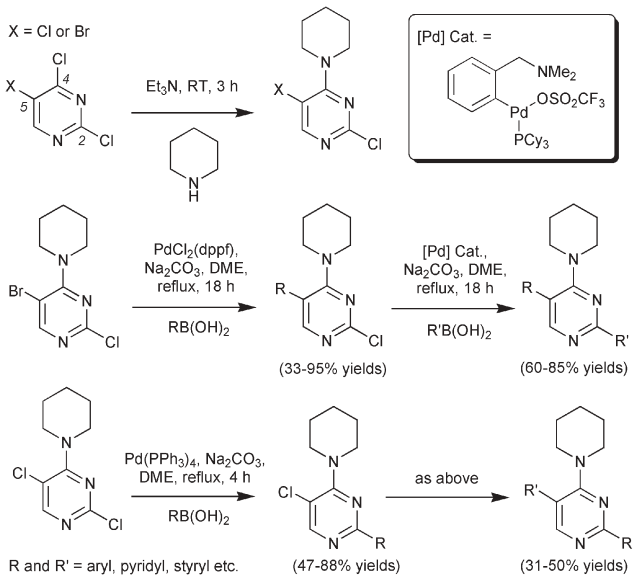
Sutherland and Gallagher have reported that 2-fluoro-5-bromopyridine is readily converted to 2-fluoro-3,5-diarylpyridines in generally good yields (Scheme 10).[34] Initial *ortho*-lithiation of 2-fluoro-5-bromopyridine, followed by trimethyl borate trapping and hydrolytic work-up, provides a versatile, thermally stable, non-hygroscopic and easily purified organoboronic acid which undergoes two successive Suzuki couplings. Important points emerge from the development of suitable conditions, namely a relatively short reaction time of 2 h is essential in thwarting hydrodebromination on the first coupling product. Interestingly, the presence of the boronic acid moiety is proposed to deactivate the 5-bromo substituent. A second coupling reaction, or hydrodebromination side-reaction, thus occurs once the first coupling has taken place. Treatment of the diarylated products with conc. HCl affords 2-pyridones, not easily accessible by other synthetic means.

Chung and co-workers have reported that a tetrachloro naphthyridone, possessing four potential sites for coupling, occurs preferentially at the 6-position (Scheme 11).[35] The type




| Catalyst | Base | Solvent | Temp / °C | Conversion / % | Ratio I:II:III |
|---|---|---|---|---|---|
| $PdCl_2(dppf)$ | $Cs_2CO_3$ | toluene | 110 | 97 | 1:0.1:1 |
| $Pd(OAc)_2/PPh_3$ | $K_3PO_4$ | IPA | 100 | 93 | 2:0.2:1 |
| $Pd(OAc)_2$/SPhos | $K_3PO_4$ | toluene | 35 | 88 | 7:0.5:1 |
| $Pd(OAc)_2$/IMes.HCl | $K_3PO_4$ | DMF | 50-80 | 95 | 50:0.9:1 |

**Scheme 11** Suzuki couplings of a tetrachloro naphthyridone.[35]




**Scheme 12** Suzuki couplings of halogenated pyrimidines.[37]

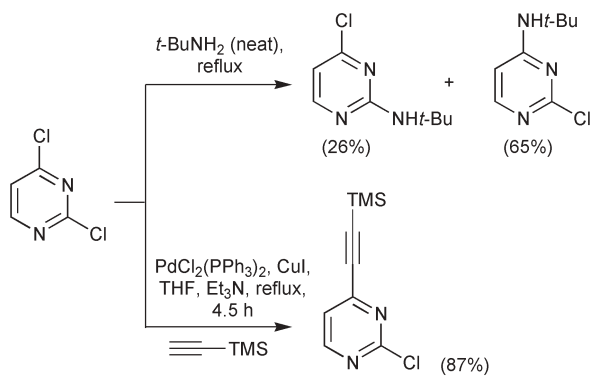
of ligand and other conditions dramatically affect the regioselectivity, with the best ligand IMes·HCl.

### Pyrimidines

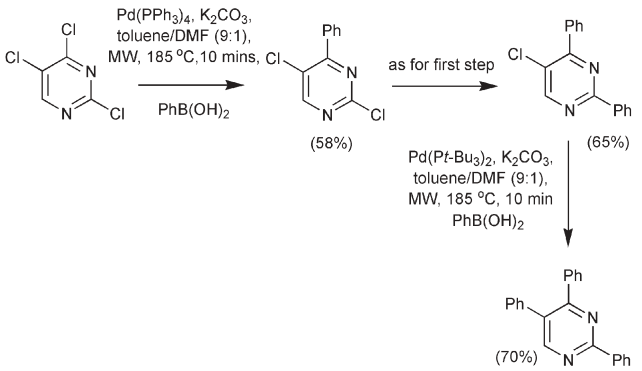
Poly-halogenated pyrimidines are known to undergo regioselective Suzuki couplings.[36] Large and co-workers have shown that trisubstituted pyrimidines can be accessed using consecutive $S_NAr$ reactions and Suzuki coupling of trihalogenated pyrimidines (Scheme 12).[37]

It is interesting to note that $S_NAr$ reaction of *tert*-butyl amine with 2,4-dichloropyrimidine affords a mixture of regioisomers.[38] In contrast, Sonogashira coupling occurs exclusively at the 4-position (Scheme 13).

Use of microwave-assisted reaction conditions is generally an effective means of accelerating coupling processes.[39] A triple sequential microwave-assisted Suzuki coupling of 2,4,5-trichloropyrimidine with phenylboronic acid reacts preferentially in the order C4 > C2 > C5 (Scheme 14).[40a] For the latter position, a more activated $Pd^0$ catalyst is required. The reactivity mirrors Stille couplings of 2,4,5-trichloropyrimidine under conventional thermal conditions.[39b]




**Scheme 13** $S_NAr$ reaction and Sonogashira coupling of 2,4-dichloropyrimidine.[38]




**Scheme 14** Sequential Suzuki coupling of 2,4,5-trichloropyrimidine.[40a]

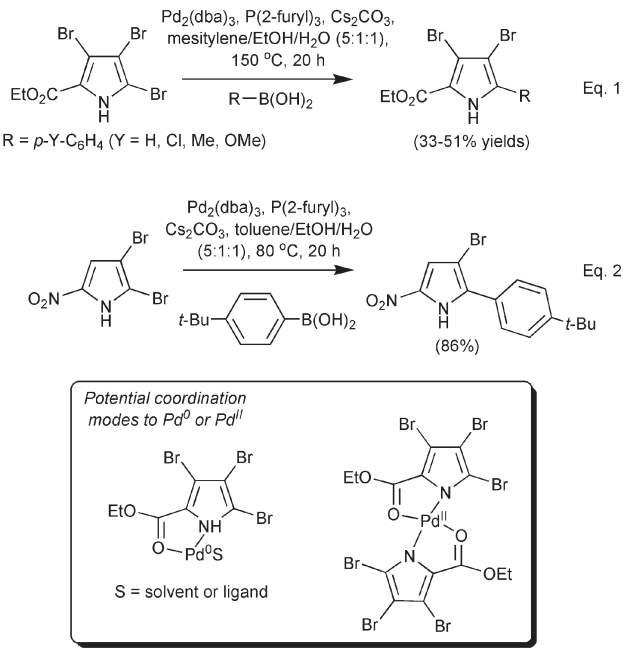
## Couplings of electron-rich heterocycles

### Classical coupling processes

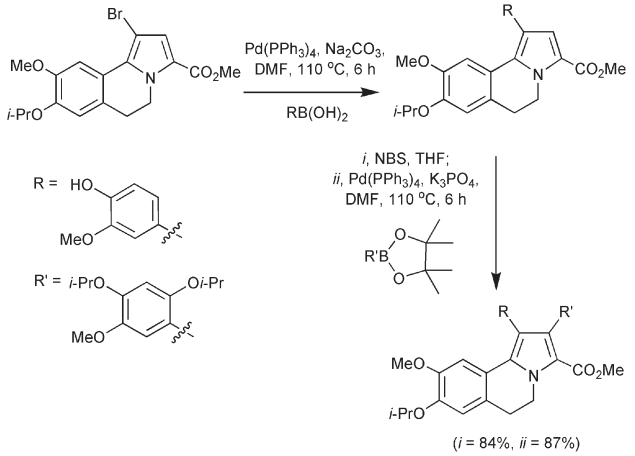
Poly-halogenated pyrroles and indoles have been extensively studied in these reactions. Recent attention has focused on more demanding substrates. For example, Schröter and Bach have reported the first coupling reactions of tribrominated pyrroles.[41] The substrate selected was a 2,3,4-tribromopyrrole carboxylate. It would appear that $Pd^0$ coordination and/or $Pd^{II}$ formation could potentially hinder the desired coupling. This point is borne out in attempted Negishi and Sonogashira couplings, proving unsuccessful.

Suzuki coupling was however possible, under optimised conditions, which proceeded regioselectively for the 2-position (Eq. 1, Scheme 15). Similar regioselectivity was observed for the 2-position in Suzuki coupling of 2,3-dibromo-5-nitropyrrole (Eq. 2, Scheme 15).

Several research groups have been engaged in utilising Suzuki couplings in total syntheses to the lamellarins and synthetic analogues, compounds that exhibit promising




**Scheme 15** Suzuki coupling of halogenated pyrroles.[41]




**Scheme 16** Sequential Suzuki couplings in a synthesis to lamellarin D.[42]

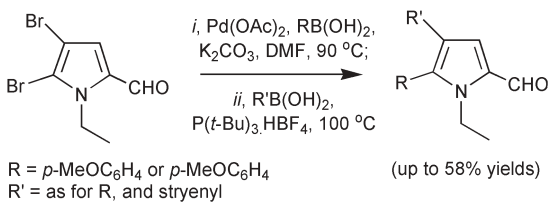
cytotoxic properties toward various tumour cells, where pyrrole represents the core skeleton. Álvarez and co-workers have developed a sequential protocol for the arylation of halogenated 5,6-dihydropyrrolo[2,1-*a*]isoquinoline-2-carboxylate substrates (Scheme 16).[42]

Handy and co-workers developed a similar route to lamellarin G trimethyl ether.[43] In an effort to develop a more concise synthetic route to differentially substituted pyrroles, relevant to the lamellarin general structure, a regioselective one-pot double Suzuki coupling on 4,5-dibromopyrroles has recently been reported.[44] The first coupling occurs at the 5-position, but the trick is to utilise *ligand-free* conditions at this stage, *e.g.* using a Pd catalyst without intentionally added phosphine or related ligand (Scheme 17).

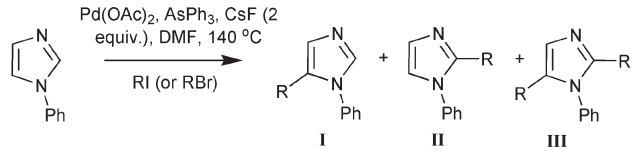
An activating electron-rich σ-donor ligand, P(*t*-Bu)$_3$, used here in its protected form as P(*t*-Bu)$_3$·HBF$_4$ due to the inherent air sensitivity in the free ligand, is required to activate the 4-position towards coupling. The protocol thus circumvents the need to halogenate a second time as in routes developed previously (*e.g.* to that shown in Scheme 16).

### Direct arylation/C–H functionalisation processes

This type of process has attracted significant attention over the last several years,[45] mainly as a more efficient atom economic method complementary to classical cross-coupling processes. Direct arylation by functionalisation of a C–H bond in both aromatic and heterocyclic compounds can be accomplished using various transition metal catalysts, *e.g.* Rh, Ru, or Pd, with aryl halides in the presence of a base. Heterocyclic compounds that are π-excessive, *e.g.* furans, thiophenes,




**Scheme 17** One-pot double Suzuki coupling.[44]




| R | time / h | ratio I:II:III | yield / % |
|---|---|---|---|
| *p*-MeOPh | 42 | 95:5:0 | 49 |
| Ph | 23 | 86:3:11 | 41 |

**Scheme 18** Direct arylation of 1-aryl-imidazoles.[46]

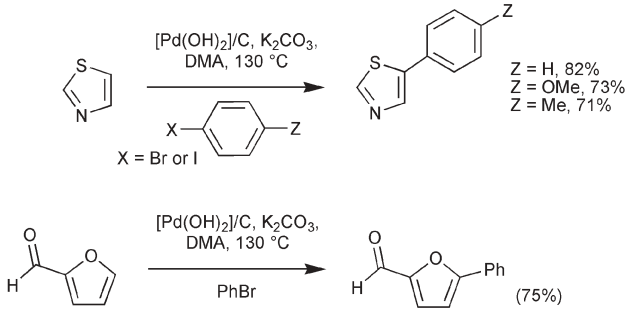
oxazoles, thiazoles, imidazoles, indoles, indolizines and imidazo[1,2-*a*]pyrimidines, can be considered as nucleophiles in these reactions, which circumvents the requirement to use an organometallic reagent. Some examples are detailed below.

Many 1,5-diaryl-1*H*-imidazoles can be prepared in moderate yields by Pd-catalysed direct arylation of 1-aryl-1*H*-imidazoles with a variety of aryl iodides or bromides (Scheme 18).[46] Such substrates possess two potential C–H functionalisation sites at the 2- and 5-positions; a selective reaction is seen at the latter position.

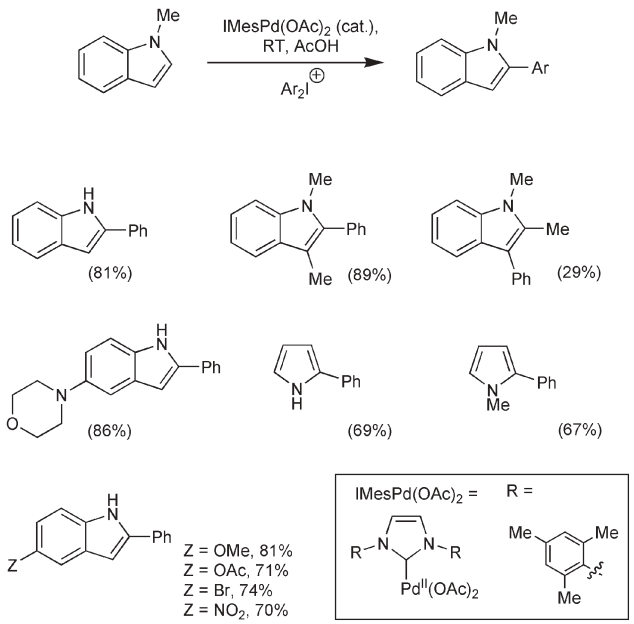
Fagnou and co-workers have demonstrated that palladium hydroxide on carbon, better known as Pearlman's catalyst, [Pd(OH)$_2$]/C, effectively catalyses direct arylation of thiazoles at the 5-position (Scheme 19).[47] Substitution also occurs regioselectively at the 5-position on a 2-substituted furan.

Sanford and co-workers have shown that indoles undergo direct arylation at the 2-position catalysed by a Pd$^{II}$ precatalyst containing an *N*-heterocyclic carbene ligand (Scheme 20).[48] The unprotected indoles exhibit comparable reactivity to *N*-methyl indoles and a variety of aryl groups can be used (including *ortho*-substitution on the phenyl ring).

Hocek and co-workers have explored the direct arylation of purine bases which facilitates the regioselective synthesis of 2,6,8-trisubstituted purine derivatives (Scheme 21).[49] Crucially, 2,6- and 6,8-dihalopurines undergo regioselective couplings with most types of organometallics.[50] In contrast, reactions of 2,6,8-trichloropurine proceed unselectively giving mixtures of products.[51] It is therefore of significance that direct C–H arylation at the 8-position of purines by several aryl iodides can be accomplished catalytically using Pd$^0$ in the presence of stoichiometric CuI with $Cs_2CO_3$ as the base. Two further consecutive couplings, with the 2- and 6-positions readily differentiated, facilitate the regioselective synthesis of




**Scheme 19** Direct C–H arylation of thiazoles and furans.[47]

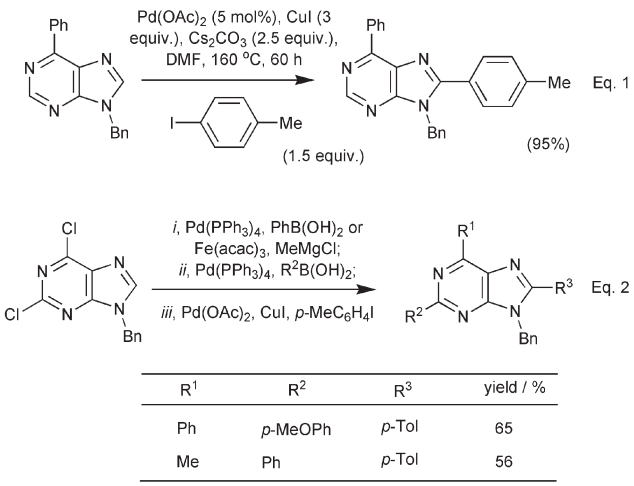



**Scheme 20** Direct arylation of indoles.[48]

2,6,8-trisubstituted purines bearing three different *C*-substituents. It remains unclear whether such reactions are possible on purines containing a ribose or deoxyribose.

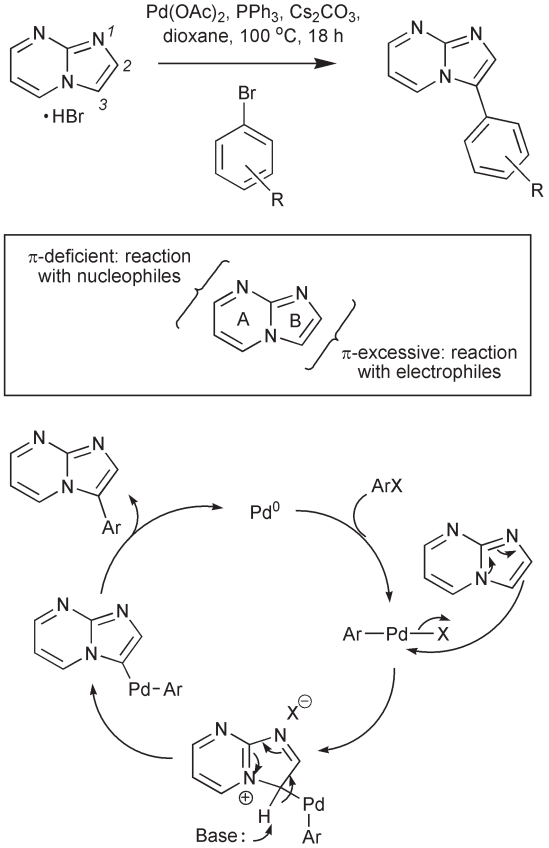
Li and co-workers have used similar conditions for regioselective arylation of imidazo[1,2-*a*]pyrimidine, which takes advantage of the electron-rich character of the imidazole ring (B-ring, Scheme 22).[52] Arylation occurs exclusively at the 3-position in all the examples reported. Similar examples have been reported by Fagnou and co-workers.[47]

The mechanism, depicted in Scheme 22, involves initial oxidative addition of the aryl halide to $Pd^0$, followed by nucleophilic attack on the electrophilic $Pd^{II}$ species. Loss of HX, assisted by base, then provides a diorgano$Pd^{II}$ species which reductively eliminates to give the coupled product, regenerating the active $Pd^0$ catalyst.




| $R^1$ | $R^2$ | $R^3$ | yield / % |
|---|---|---|---|
| Ph | *p*-MeOPh | *p*-Tol | 65 |
| Me | Ph | *p*-Tol | 56 |

**Scheme 21** Direct arylation and regioselective consecutive synthesis of 2,6,8-trisubstituted purines.[49]




**Scheme 22** Direct arylation of imidazo[1,2-*a*]pyrimidine.[52]

## Conclusions

There are many types of poly-halogenated heterocyclic substrates that undergo regioselective couplings with a variety of organometallic reagents and other nucleophiles. The coupled products are useful for a multitude of applications. On collating the literature for this area the report that stands out is the valuable NMR spectroscopic method for predicting the regioselectivity in coupling through use of $^1$H NMR chemical shifts of the parent heterocyclic compound, which appears to work in the majority of cases.[11] Whilst there are exceptions, this is likely to be very useful practically, particularly in the pharmaceutical industry.

The origin of the regioselectivity in coupling processes is undoubtedly dominated by electronic effects, but steric effects do play a role, as do functional groups neighbouring the site of reaction, *e.g.* esters, nitriles, amines *etc.*, which can assist oxidative addition by chelation to $Pd^0$, or transmetallation in stabilising a vacant coordination site on $Pd^{II}$; 3,5-dibromo-2-pyrone represents an example.

Direct arylation/C–H functionalisation of electron-rich heterocycles represents a useful alternative to classical coupling processes, and although harsher reaction conditions are generally required for this methodology, the use of organometallic reagents is not. Reactions on electron-deficient/neutral substrates are less well developed, though Fagnou and Leclerc have recently reported a protocol for the direct arylation of pyridine *N*-oxides with aryl chlorides, bromides and iodides,

occurring regioselectively at the 2-position; the products are easily reduced to 2-arylated pyridines with Pd/C and ammonium formate in MeOH.[53]

It is evident that combining classical couplings with direct arylation processes could lead to a greater diversity of polysubstituted heterocyclic products; the example given in Scheme 21 represents a guiding example. It is thus anticipated that such protocols will emerge over the coming years.

## Acknowledgements

The author thanks several members of his research group for collating some of the literature for this review (P. Ellis, A. Firth, E. Hurst, A. Kapdi and B. Moulton), and Professor M. Cid for useful discussions relating to reference 23.

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