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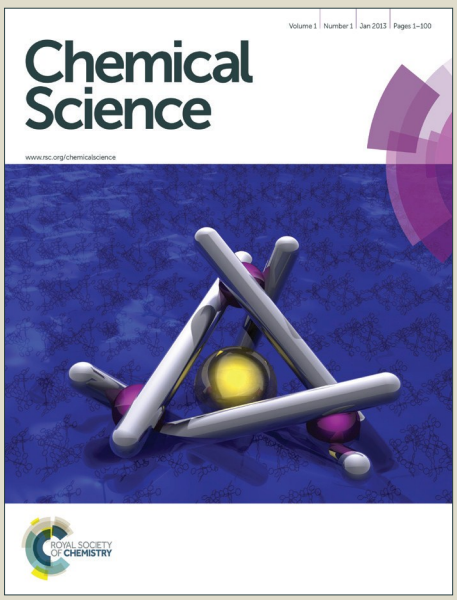

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PERSPECTIVE

Site-selective Suzuki-Miyaura Coupling of Heteroaryl halides – Understanding the Trends for Pharmaceutically Important Classes

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Suzuki-Miyaura cross-coupling reactions of heteroaryl polyhalides with aryl boronates are surveyed. Drawing on data from literature sources as well as bespoke searches of Pfizer's global chemistry RKB and CAS Scifinder® databases, the factors that determine the site-selectivity of these reactions are discussed with a view to rationalising the trends observed.

1. Introduction

Substituted heteroarenes form the core of numerous pharmacologically active agents and drug substances,[1] as well as agrochemical products, ligands, secondary metabolites, polymers and electronic materials.[2] Notwithstanding widespread recent advances in transition metal-catalysed C-H bond activation processes,[3] Pd-catalysed Suzuki-Miyaura coupling (SMC)[4] of (pseudo)halogenated[5] heteroarenes with (hetero)aryl boronic acids/esters constitutes the most widely used approach to heteroarene elaboration with C-C bond formation particularly in a pharmaceutical discovery chemistry setting.[6] This reflects the wide palette of methods available for preparation of both reaction partners, the versatility and functional group compatibility of these methods, the general stability, low toxicity, ease of handling and commercial availability of the reaction partners, the relatively environmentally benign conditions of the SMC reactions themselves (*e.g.* high efficiencies, low catalyst loadings *etc.*), as well as the opportunities the SMC disconnection affords for rapid parallel exploration of structural diversity and chemical space.[4b, 6]

When multiple SMC reactions are to be choreographed to occur sequentially, this can sometimes be achieved by judicious site-selective introduction of *different types* of halogen into a substrate. However, particularly for heteroaryl substrates, the intrinsic polarities of the ring carbons also strongly influence site-selectivity and this factor is critical when coupling substrates containing two or more of the *same type* of halogen. These latter substrates are often the preferred precursors on cost and availability grounds and are the main focus of this review. Underscoring not only the importance of site-selective cross-coupling reactions of heteroaryl halides from a synthesis perspective, but also highlighting the challenges associated with predicting the outcome of such reactions, there have been several excellent reviews compiling and classifying published examples of these reactions including notable contributions by Bach (heteroarenes),[7] Stanetty (azoles),[8] Handy (heteroarenes),[9] Fairlamb (heteroarenes),[10] Manabe (polyhalides),[11] Rossi (heteroarenes)[12] and Langer (*bis*-triflates).[13]

Notwithstanding these previous compilations, we considered that systematic interrogation of reaction databases would reveal patterns of selectivity that could reinforce and extend our understanding of the factors that affect site-selectivity in SMC reactions of heteroarenes and improve our ability to predict outcomes for new substrates. In particular, we envisioned that the in-house Pfizer global chemistry Reaction Knowledge Base (RKB)[14] would constitute a rich source of reaction data that would extend and compliment data mined from the CAS Scifinder®[15] database. To this end, in this review we provide a concise overview of the factors determining the site-selectivity of SMC reactions of heteroaryl halides (Section 3) and then a summary of the results of some database searches of structures of potential medicinal interest (Section 4). The overview draws on data both from the literature and from the structure-by-structure database searches.

2. Data Gathering and Analysis

Based on our perception of their relevance as scaffolds and/or intermediates in drug discovery programs,[6] the heteroarene ring systems that were selected for investigation were: pyridines, pyrimidines, pyrazines, pyridazines, pyrroles, furans, thiophenes, imidazoles, pyrazoles, (is)oxazoles, (iso)thiazoles, (iso)quinolines, benzodiazines, indoles, benzoxazoles, benzothiazoles, benzodiazoles, benz(is)oxazoles, benz(is)othiazoles and aza(iso)quinolones (naphthyridines). Parallel searches were carried

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out on the CAS Scifinder® and RKB reaction databases using as similar search queries as their respective interfaces would allow (see Supporting Information). Only reactions with (hetero)aromatic boronic acid and ester coupling partners were retrieved;[16, 17] alkenyl and alkynyl congeners were excluded since these motifs occur much less frequently in pharmaceuticals. Alkyl coupling partners,[18] stereoselective processes,[19] and non-Pd-mediated processes[20] were also excluded.[4c] Reactions involving substrates having two (or more) of the same halide substituents were systematically retrieved; specifically, di-chlorides, di-bromides and di-iodides although selected examples containing two different halides were also noted where these enable complementary site-selectivities to be achieved.

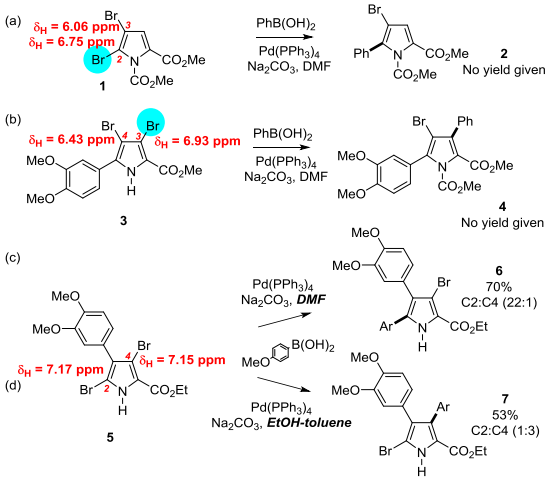
3. Factors Affecting the Site-selectivity of SMC Reactions of Heteroryl Halides

As indicated above, we have divided our analysis into two sections. In this section factors that determine site-selectivity in SMC reactions based both on published studies and our database searches are presented. In Section 4, the data from the CAS Scifinder® and RKB database searches are summarised by class of heterocycle. Hopefully, this structure will help readers both to predict the outcome of reactions on new heterocyclic systems *per se* and also to quickly locate relevant prior-art on key heterocyclic systems of interest. In the Schemes and Figures, the halide highlighted with a blue disk is the preferred site of reaction.

When discussing SMC reactions, it is generally accepted that the oxidative addition (OA) step is rate-determining and irreversible, and that the rate of OA is largely controlled by the bond dissociation energies (BDEs) of the C-Hal bond such that usually Ar-I>Ar-Br>Ar-Cl>Ar-F.[21] Although cases where OA is not rate limiting in SMC reactions have been proposed,[22] and OA can be reversible under high steric stress,[23] this assumption is probably accurate for most catalytic reaction situations. The BDE is however by no means the exclusive arbiter of ease of OA because other structural features and the reaction conditions (particularly: solvent, pre-catalyst, ligand, base, additive *etc*.) are also influential. When *different* halides are present in a substrate, the site-selectivity of SMC reactions is strongly influenced by the intrinsic propensity of each halide to undergo OA (Section 3d). However, we will start by discussing the key factors that influence site-selectivity in heteroarenes containing two or more of the *same* type of halogen. We will see that for these cases the 'molecular environment/electrophilicity' of the carbon atom to which the halide is bound is a key factor and that this is reasonably predictable for a given heteroarene core (Sections 3a-c).

3a. Influence of the Intrinsic Relative Electrophilicities of Different Ring Carbons

For heteroarenes containing two or more of the same type of halogen (*e.g.* di-chlorides, tri-bromides *etc*.), several indicators based on experimental data have been identified to help predict the intrinsically most reactive positions for OA. Since the OA step in SMC reactions and the addition step in S_NAr reactions have mechanistic similarities, both are generally favoured at the more electrophilic carbon when two identical halogen substituents are in competition. Consequently, experimental S_NAr site-selectivity data has been used to predict SMC reactivity.[7, 24] Others have drawn the analogy with propensity to undergo lithium-halogen exchange, which generally favours the position that results in the most stable resulting aryl lithium derivative.[25] ^{13}C NMR chemical shift values (δ_C) can similarly provide insight into the relative electrophilicities of carbons bearing halogens.[26] Most notably, Handy and Zhang have advocated analysis of the ^1H NMR chemical shift values (δ_H) of the parent *non*-halogenated heteroarenes as a guide for predicting the site of cross-coupling reactions;[9] with the position of the most deshielded proton being the favoured site for SMC. Although this has the appeal of simplicity, it is not fail-safe, particularly in cases where $\Delta\delta_H$ <0.3 ppm.[25, 27] For example, although the method was accurate for several polysubstituted pyrroles, for the case of 3-arylpyrrole **5**, where $\Delta\delta_H$ was just 0.02 ppm, the site of SMC could be switched from C4 to C4 simply by changing the solvent from DMF to ethanol-toluene (Scheme 1).[9, 28]



***Scheme 1**. The Handy and Zhang method for site-selectivity prediction based on the ^1H NMR δ_H values for the corresponding non-halogenated heteroarenes – as applied to (a) 2,3-, (b) 3,4-, and (c) 2,4-dibromopyrroles, the last of which displays solvent dependent selectivity.*[9, 28]

Computation has also been used to predict the order of susceptibility to OA in heteroaryl polyhalides on a case-by-case basis.[26] Computation can in principle not only dissect out the heteroaryl electronic components but also account for steric factors and directing effects from adjacent functional groups during the OA process. Studies that draw out trends rather than focus on isolated examples are of particular interest. Houk *et al*. have noted that computed BDEs cannot account for all observed reaction selectivities and have used a DFT-based 'distortion–interaction' model (sometime referred to as an 'activation-strain' model) to better understand the origins of selectivity in Pd(0)-catalysed cross-coupling reactions of heteroaryl polychlorides and polybromides including isoquinolines, pyridines, benzofurans and furans.[27a, 29] Using $Pd(PH_3)_2$ as a model di-ligated complex, the energies required to distort isolated reactants to the OA transition state geometries (the distortion energy, ΔE_{dist}) were computed along with the energy of interaction between these distorted reactants (the interaction energy, ΔE_{int}). It was concluded that ΔE_{dist} closely tracks the BDE and that ΔE_{int} is dominated by a favourable back-bonding ($d_{xy}\rightarrow\pi^*$) secondary frontier molecular orbital (FMO) interaction as the bent PdL_2 moiety approaches the C-Hal bond η^2-fashion (*i.e*. side-on).[27a] The ΔE_{dist} contribution is therefore relatively invariant when one type of halogen is involved although they note that in general BDE values are i) lower in 6-membered compared to 5-membered rings,[30] and ii) lowered by the presence of a sulfur atom in the ring

or when the halogen is an iminoyl halide.[29] The stabilising ΔE_{int} term is dependent on the π^* LUMO coefficient[31] which is generally increased for positions adjacent to ring heteroatoms (Figure 1).[32, 29]

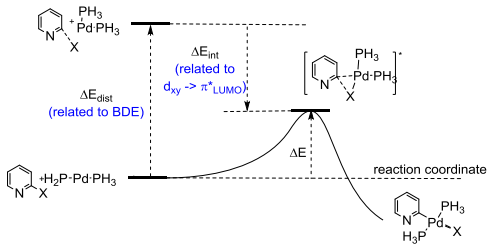


***Figure 1**. Houk's 'distortion-interaction' DFT approach to computationally predicting the most favourable position for OA by bis-ligated Pd-catalysts in heteroaryl polyhalides.*[24]

Thus for each of the three systems **8-10** shown below, the experimentally observed site for SMC reaction is not the one predicted on the basis of having the lowest calculated BDE value but the one with the lowest activation barrier (ΔE). The larger the δΔE value, the more selective a reaction can be expected to be (Figure 2).[25]

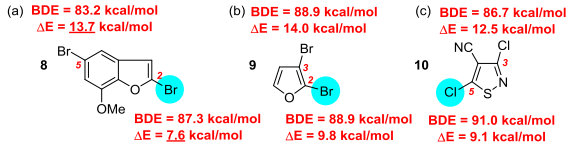


***Figure 2**. The Houk 'distortion-interaction' DFT approach to site-selectivity prediction – as applied to (a) benzofuran **8**, (b) furan **9** and (c) isothiazole **10**.*[9]

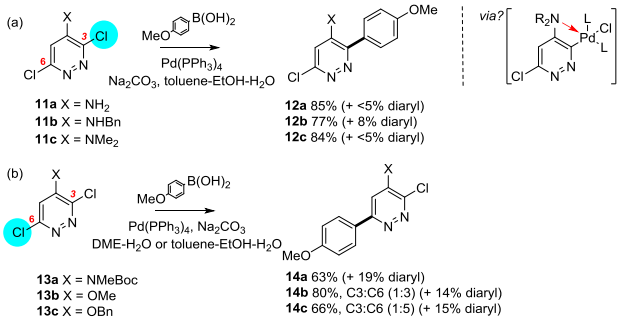
Computational studies have also thrown significant light on how the nature of the phosphine ligands, the ligation state of the Pd and complexation of a pre-catalyst with the substrate[33] can all influence OA activation energies, but this will be discussed later in the context of the influence of reaction conditions (Section 3c).

In general, for heteroaryl polyhalides containing a single type of halogen, the intrinsic relative electrophilicities of different ring carbons is a critical factor controlling SMC site-selectivity. In the case of otherwise unsubstituted substrates, the electronic distribution is controlled by the position of the halides in the ring-system relative to the ring heteroatoms. In cases where the heteroaryl polyhalide contains other substituents, these substituents provide additional electronic and steric perturbations but it appears that the intrinsic heterocycle polarity is usually dominant (Section 3b). These generalisations are strongly supported by the data from our database searches which show that the position at which SMC reactions occur are characteristic of the particular heterocycle and largely independent of substituents and the nature of the boronic acid/ester coupling partner (Section 4).

3b. Influence of Ring Substituents

The influence of substituents on site-selectivities in heteroarene SMC reactions appears to be surprisingly limited, with significant perturbations to the intrinsic directing influence of the ring-system generally being restricted to situations where the heterocycle itself is not strongly polarised and/or where substituents are strongly electron withdrawing and/or are sufficiently Lewis basic to coordinate to the catalyst and promote reaction *via* a palladacycle. Steric factors can sometimes be decisive but these generally appear to be of secondary importance.

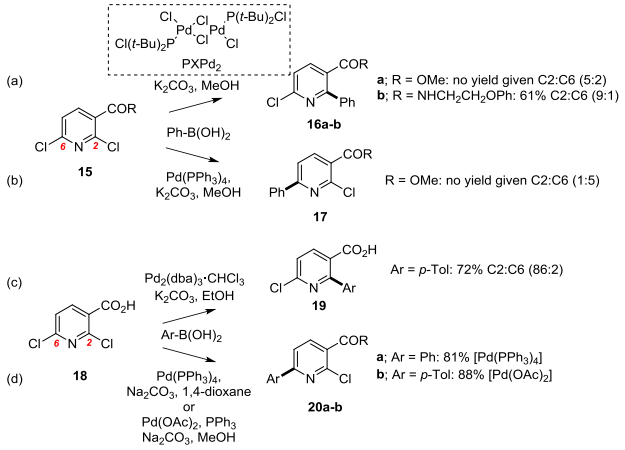
To illustrate this, consider first the case of 4-substituted 3,6-dichloropyridazines **11a-c** and **13a-c** (Scheme 2).



***Scheme 2**. The site-selectivity of SMC reactions can be determined by substituents: e.g. (a) 3,6-dichloropyrimidines containing 1º, 2º or 3º amine substituents at C4 (**11a-c**) generally react at C3, but (b) when the C4 substituent is non-basic (**13a-c**) reaction is at C6 presumably for steric reasons.*[34]

Blaise *et al.*[34a] have investigated a range of heteroatom-based substituents at the 4-position of 3,6-dichloropyridazines and found that 1°, 2° and 3° amines (**11a-c**) promote SMC reaction at C3 (*i.e.* proximal to the amine) using $Pd(PPh_3)_4/Na_2CO_3$/toluene/EtOH/H_2O but that the reactivity and selectivity of these substrates decreases with increasing bulk of the amine substituents. An *N*-MeBoc group at C4 (**13a**) however promotes SMC reaction at C6 (*i.e.* distal to the amine); similarly, OMe and OBn groups at C4 (**13b** and **13c**) promote SMC reactions at C6 in 60% and 50% yields respectively, implicating coordination of the Pd to a Lewis basic amine group as facilitating reaction at C3 (Scheme 2, above).[34a]

The reactivity of 2,6-dichloro nicotinic acid **15** and its derivatives is also instructive and demonstrates the role that catalyst coordination to Lewis basic functional groups can have on the site-selectivity of SMC reactions (Scheme 3).[35]

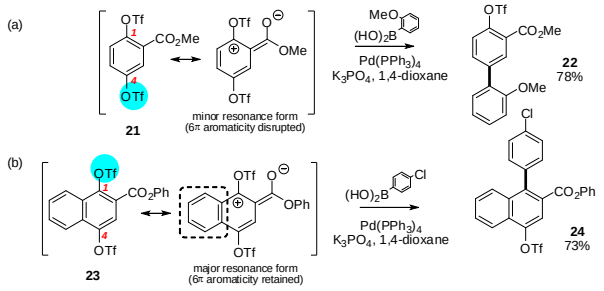


***Scheme 3**. Carboxylic ester, -amide and -acid modulation of site-selectivity: e.g. 2,6-dichloro nicotinic acid (**18**) and its derivatives can undergo SMC reactions at C2 or C6 selectively depending on the conditions (a-d).*[35]

With the methyl ester derivative (**15**, R = OMe), Yang *et al.*[35a] found that $Pd(PPh_3)_4$ promoted SMC reactions at C6 (⟶**17**), but that Li's $PXPd_2$ pre-catalyst $[Pd(t\text{-}Bu_2Cl)_2Cl_2]_2$[36] promoted SMC

reactions at C2 (⟶**16a**). Yang *et al.* hypothesised that the latter, more electron rich and coordinatively unsaturated complex was able to coordinate to the ester carbonyl thereby overcoming the inherent steric bias of the substrate. To corroborate this, they showed that a more Lewis basic amide congener gave even greater selectivity for SMC reaction at C2 (⟶**16b**, Scheme 3, above). This notion was extended to the case of the free acid **18** by Ma *et al*[35b]. and by Houpis *et al*.[35c] who found that $Pd(PPh_3)_4$ and $Pd(OAc)_2/PPh_3$ promoted SMC reactions at C6 (⟶**20**), but that phosphine-free Pd [*i.e.* $Pd_2(dba)_3{\cdot}CHCl_3$] resulted in high levels of selectivity for SMC reaction at C2 (⟶**19**), presumably by virtue of its ability to coordinate to the carboxylate.

The divergent behaviour of methyl 1,4-ditrifloxy phenyl-2-carboxylate (**21**)[37] and phenyl 1,4-ditrifloxynaphthalene-2-carboxylate (**23**)[38] with respect to their SMC site-selectivity is also revealing. Although not heteroarenes, a comparison of their behaviour demonstrates how the subtle interplay between steric and electronic effects imparted by a substituent can be critical in controlling SMC reactions when intrinsic ring polarity effects are weak (Scheme 4).



Scheme 4. *A subtle interplay of steric and electronic factors can control SMC reaction site-selectivity: e.g. (a) methyl 1,4-ditrifloxy phenyl-2-carboxylate (**21**) and (b) phenyl 1,4-ditrifloxynaphthalene-2-carboxylate (**23**) undergo SMC at C4 and C1 respectively*.[37-38]

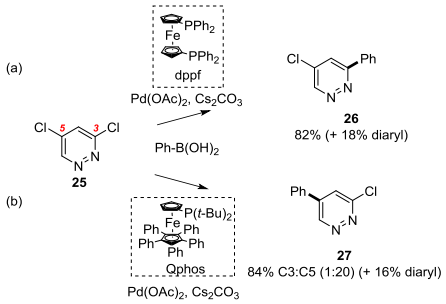
Phenyl ditriflate **21** undergoes SMC reactions at C4 (→**22**) whereas napthyl ditriflate **23** undergoes SMC reactions at C1 (→**24**). In both cases, the steric crowding at C1 is essentially equivalent and so the divergent behaviour is presumably electronic in origin: *i.e*. C1 is sufficiently electrophilic in naphthyl derivative **23** to override the steric crowding due to the ester but insufficiently electrophilic in phenyl derivative **21** to do likewise. Langer *et al.* have proposed that this is consistent with the naphthalene having significant diene character and being relatively easily polarised in its substituted ring thus allowing the ester substituent to impart greater electrophilicity to the proximal C1 position than is possible for the phenyl system without incurring a concomitant energetic penalty from loss of aromaticity.[38] Langer has studied several additional ditriflate-containing substrates in a systematic fashion and similar conclusions regarding the delicate balance of steric *vs*. electronic factors emerge.[13]

Notwithstanding the above studies, it is perhaps surprising how limited the influence of ring substituents is in controlling site-selectivity in SMC coupling reactions. As emphasised previously, this allows the outcome of most reactions to be predicted simply on the basis of the position of the halides in a given heteroarene. A contributory factor towards this situation is that a large proportion of the available data both in the CAS Scifinder® and the Pfizer RKB databases relates to reactions using using 'standard conditions' (*e.g.* $Pd(dppf)Cl_2$ or $Pd(PPh_3)_4$ with Na_2CO_3 or $NaHCO_3$ or K_2CO_3 in DME-H_2O or THF-H_2O or 1,4-dioxane-H_2O)[†]. The predominance of these conditions reflect the low cost and high convenience of these conditions and also their wide substrate scope. However, there are of course SMC reactions of heteroaryl polyhalides where the choice of reaction conditions, particularly the choice of ligand and solvent, can be decisive in dictating site-selectivity (Section 3c). This is the case for substrates containing a single type of halogen and even more so for those containing mixed halides.

3c. Influence of the reaction conditions – particularly the Pd pre-catalyst/ligand

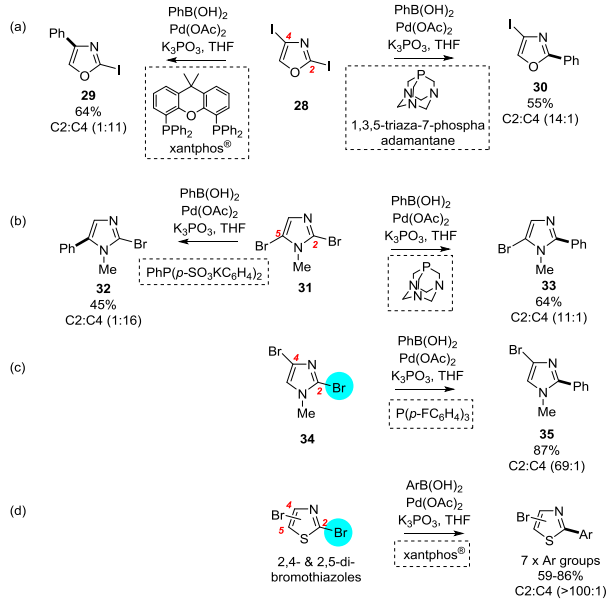
The specific reaction conditions used for a SMC reaction on a heteroaryl polyhalide can sometimes strongly influence the outcome in terms of site-selectivity of coupling. Due to the mechanistic complexity of these reactions, interpretation let alone prediction of these effects is difficult, but a number of studies which have documented such reactions and sought to rationalise them have been published.

An investigation by Dai *et al.* examined the effect of different phosphines on the site-selectivity of SMC reactions of 3,5-dichloropyridazine **25**.[39] They found that chelation and electron density played key roles and specifically that electron deficient bidentate ligands (such as dppf) favoured SMC reactions at C3 over C5 (*i.e*. →**26**) whereas electron rich monodentate ligands (such as Qphos) favoured C5 over C3 (*i.e*. →**27**). Electron rich bidentate ligand dtbpf also promoted reactions at C5 over C3, although this was interpreted as indicating that steric effects as well as electronic effects play a role in determining site-selectivity (Scheme 5).[39]



Scheme 5. *Ligand-dependent site-selectivity: e.g. 3,5-dichloropyridazine **25** undergoes SMC (a) at C3 with $Pd(OAc)_2$/dppf, (→**26**) and (b) at C5 with $Pd(OAc)_2$/Qphos (→**27**).*[39]

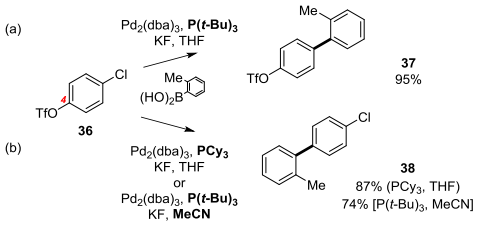
The effect of different phosphines on the site-selectivity of SMC reactions of various diiodo- and dibromo-oxazoles, -imidazoles and -thiazoles has been studies by Strotman *et al*.[25] and their findings are summarised below (Scheme 6).



***Scheme 6**. Ligand-dependent site-selectivity: (a) 2,4-diiodooxazole, (b) 2,5-dibromoimidazole, (c) 2,4-dibromoimidazole, and (d) 2,4- and 2,5-dibromothiazoles.*[25]

Handy and Zhang's ^{1}H NMR analysis on the parent non-halogenated heteroaryls predicts SMC reactions should occur at C2 for oxazole **28** and *N*-methylimidazoles **31** and **34** (*cf.* Scheme 1). It was found experimentally however that under most conditions 2,4-diiodooxazole (**28**) underwent SMC at C4 but often with poor selectivity over C2 and with high levels of bis-arylation. After screening ~200 achiral phosphines, xantphos® was found to be uniquely capable of mediating highly selective mono-SMC reactions at C4 (→**29**) and 1,3,5-triaza-7-phospha-adamantane in MeCN gave high selectivity for mono-SMC reactions at C2 (→**30**). *N*-Methyl-2,5-dibromoimidazole (**31**, and its diiodo- congener) behaved very similarly: all phosphines except the phospha-adamantane in MeCN gave C5 selectivity (→**32**). Intriguingly however, *N*-methyl-2,4-diiodoimidazole (**34**) showed no appreciable reactivity at C4 for any of the ligands screened and the most selective conditions in terms of minimising bis-arylation involved the use of tri-(*p*-fluorophenyl)phosphine to give the C2 product **35**. Similarly, both 2,4- and 2,5-dibromothiazoles gave almost exclusive mono-SMC reactions at C2 irrespective of the conditions employed. As for the case of the dichloropyridazines, it appears that the electron density, ability to chelate and steric demand of the ligand system play key roles in determining selectivity with particularly electron rich and/or sterically demanding ligands being prevalent among ligands which promote unusual selectivities.

Our understanding of the basis of some of these ligand effects has been significantly enhanced by observations made on mixed halide-containing, non-heteroaryl substrates and associated computational studies. Hayashi made the seminal observations on ligand-dependent regiodivergent Pd-catalysed Kumada couplings of 4-trifloxybromobenzene in 1997,[40] which Brown in 2007 showed to be replicated for Stille and Negishi type couplings but interestingly not for SMC reactions.[41] In 2000, Fu *et al*. reported that the site-selective SMC reaction of 4-trifloxychlorobenzene (**36**) occurred selectively at the chloride (*i.e*. C1, →**37**) when using $Pd_2(dba)_3$/P(*t*-Bu)$_3$ in THF (as expected on the basis of BDE), but selectively at the triflate (*i.e*. C4, →**38**) when using $Pd_2(dba)_3$/PCy_3 in THF.[42] (Scheme 7).



***Scheme 7**. Control of site-selectivity in the SMC reaction of 4-trifloxychlorobenzene (**36**) according to the conditions: (a) ligand,*[42-43] *and (b) solvent*[44] *control.*

Subsequent theoretical and experimental studies concluded that the steric bulk of P(*t*-Bu)$_3$ generally favours formation of mono-ligated, 12 electron Pd complexes (*i.e*. PdL) whereas the less sterically demanding PCy_3 generally stabilises di-ligated, 14 electron complexes (*i.e.* PdL_2),[45] and that this difference accounts for their divergent behaviour. This hypothesis was tested computationally by Houk and Schoenbeck using the aforementioned 'distortion-interaction' DFT analysis (see Figure 1, above).[43] Unsurprisingly, the computed activation energies (**Δ**E) were found to be highly sensitive to the ligation state of the Pd: *e.g.* PdL_2 *vs*. $[PdL_2X]^-$ *vs*. PdL *vs*. $[PdLX]^-$.[46, 47, 43] Specifically, it was shown that for PdL complexes, the computed activation energies (**Δ**Es) were dominated by the ΔE_{dist}(substrate) term whereas for PdL_2 complexes the ΔE values were dominated by the interaction energy (ΔE_{int}). This situation, combined with the aforementioned expectation that the highly bulky ligand P(*t*-Bu)$_3$ would favour a mono-ligated PdP(*t*-Bu)$_3$ complex in THF whereas the less bulky PCy_3 would favour a di-ligated $Pd(PCy_3)_2$ complex, explained the observed site-divergent behaviour. Decisively, the lower BDE of the chloride *cf*. the triflate minimised ΔE for insertion of the mono-ligated PdP(*t*-Bu)$_3$ complex into the C-Cl bond whereas the strong $d_{xy}\rightarrow\pi^*$ interaction between the highly nucleophilic di-ligated $PdPCy_3$ and the distorted vinyl triflate group minimised ΔE for insertion into the C-OTf bond.[43] Subsequent higher level DFT computational studies have corroborated these conclusions and furnish reaction energy profiles for PdL and PdL_2 pathways that mirror experiment provided dispersion terms are incorporated in the calculations.[48]

Schoenebeck *et al.* showed experimentally that if a polar solvent like MeCN was used in place of THF for the SMC reaction of 4-trifloxychlorobenzene (**36**) then the $Pd_2(dba)_3$/P(*t*-Bu)$_3$ conditions promote selective SMC coupling at the C4 triflate (→**38** in 74% yield) like Fu's $Pd_2(dba)_3$/PCy_3 conditions (see Scheme 7, above).[49] Schoenebeck also performed calculations to demonstrate that this experimental outcome was consistent with the formation of an anionic $[PdLX]^-$ complex under these conditions (where X was either F or $ArBO_2H$).[44] Subsequent studies demonstrated that the Pd(I) dimer complex $[BrPdP(t\text{-}Bu)_3]_2$, also promotes these reactions and favours reaction at C1 (→**37**) in THF and at C4 (→**38**) in MeCN.[50] The behaviour of the dimer in these reactions was attributed to its *in situ* conversion to PdP(*t*-Bu)$_3$ induced by the base acting as a nucleophile;[51] the bromine-bridged Pd(I) dimer is more labile in this respect than corresponding iodide-bridged one, although with an appropriately nucleophilic base both can act as precursors to catalytically active Pd(0) species.[52]

Schoenebeck has also introduced the P(*i*-Pr)(*t*-Bu)$_2$ ligand, which has a Tolman cone angle[53] (175°) intermediate between that of P(*t*-

$Bu)_3$ (182°) and PCy_3 (170°), and which imparts P(*t*-Bu)$_3$-like behaviour (OA at C1 →**37**) when added 1:1 relative to Pd [*i.e*. favouring monoligated PdP(*i*-Pr)(*t*-Bu)$_2$], but PCy_3-like behaviour (OA at C4 →**38**) when added in excess (*e.g.*10:1 relative to Pd).[54] Sigman has also recorded concentration-dependent selectivity for other phosphines in this reaction.[55]

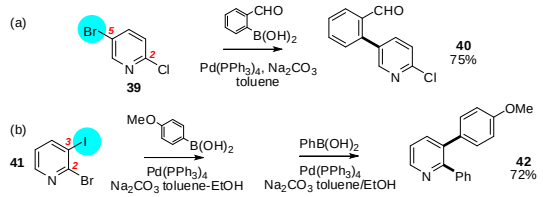
More generally, there is increasing evidence for phosphine-free Pd (nanoparticles) being active catalytic species in SMC reactions (*i.e*. heterogeneous catalysis).[56] The likleyhood of nanoparticulate Pd being the catalytically active species is minimal for SMC reactions carried out at ambient temperature using chlorides, but significant for high temperature reactions using *e.g.* bromides.[57] Given that adventitious Pd(0) contaminants can be active at levels as low as 50 ppb,[58] caution must be applied when trying to rationalise switches in site-selectivities as a function of changes of conditions as the observed products may not arise from the ligated species expected.

Notwithstanding these caveats when interpreting changes in site-selectivity in SMC reactions, the aforementioned studies highlight how the steric and electronic characteristics of phosphines affect the ligation state of the Pd and consequently reaction outcomes. Although this has been most intensively studied for 4-trifloxychlorobenzene (**36**, Scheme 7), this applies in all SMC reactions and particularly those of substrates containing *mixed* halides (Section 3d). These compounds are frequently investigated with a view to overriding the 'intrinsic' site-selectivity of the parent heterocycle.

3d. Influence of the nature of the halide

Arguably the most conceptually straightforward method to ensure that site-selective sequential SMC reactions take place in a required order is to anticipate the relative reactivity of different types of carbon-halogen bonds towards the initial OA step, by varying the halides present in the substrate. As noted previously, this prediction is based on the generalisation that OA in SMC reactions is usually rate-determining, irreversible, and strongly affected by the relative BDEs which in turn vary predictably as a function of the halide: Ar-I>Ar-Br>Ar-Cl>Ar-F.[24, 59] Although this is certainly the case for relatively unpolarised carboaromatic ring systems, how well does it hold for more intrinsically polarised systems of pharmaceutical interest? Often this can be a successful tactic, but for strongly polarised positions in heteroarenes it can be difficult to overturn the intrinsic site-selectivity trends discussed above (Sections 3a-c). The reactivity of mixed halide- triflates in particular are rather difficult to predict in this context - a discussion of these is provided in the Supporting Information.

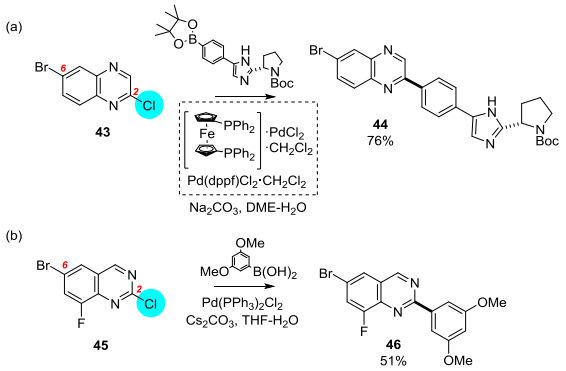
5-Bromo-2-chloropyridine (**39**) and 2-bromo-3-iodopyridine (**41**) are illustrative of heteroarenes that undergo SMC reactions with aryl boronic acids at C5 and C3 respectively despite the fact that the C2 position is intrinsically 'activated' in both cases *vide infra* (Scheme 8).[60]



Scheme 8. *The BDE of the C-Hal bond clearly influences the site of SMC reaction for pyridine derivatives: e.g. (a) 5-bromo-2-chloropyridine (**39**), and (b) 2-bromo-3-iodopyridine (**41**) undergo SMC at C5 (→**40**) and C3 (→**42**) respectively*.[60]

In both cases, OA takes place at the position bearing the more reactive halide as predicted on the basis of average C-Hal BDEs. Additional examples where judicious use of mixed halides can successfully allow the intrinsic electronic bias of a particular ring-system to be overturned are highlighted in Section 4 (*i.e*. Schemes 16, 19, 20 and 25).

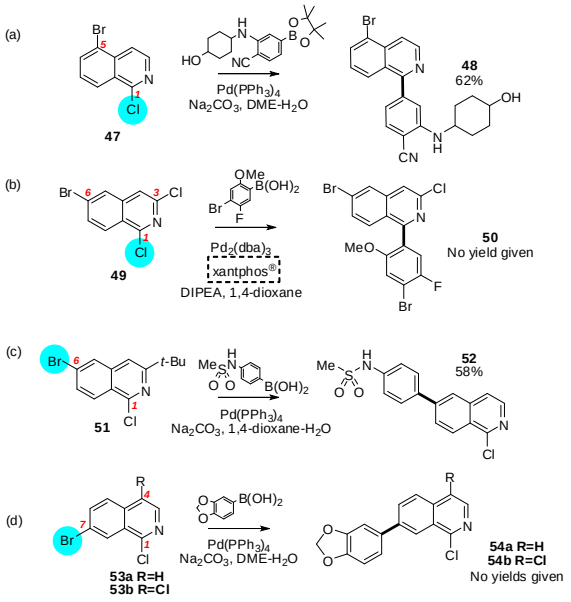
By contrast, 6-bromo-2-chloroquinoxaline (**43**)[61] and 6-bromo-2-chloro-8-fluoroquinazoline (**45**)[62] both react in SMC reactions first at the chlorides at C2 in preference to the bromides at C6 (Scheme 9).



Scheme 9. *The high intrinsic electrophilicity of certain ring positions (e.g. C2 in quinoxalines and quinazolines) can perturb the BDE sufficiently to override the usual ArBr>ArCl order of reactivity: e.g. (a) 6-bromo-2-chloroquinoxaline (**43**), and (b) 6-bromo-2-chloro-8-fluoroquinazoline (**45**) undergo SMC at C2*.[61-62]

Apparently, for these ring systems the intrinsic, strong electrophilicity at C2 (Section 4c) can facilitate OA to a greater extent than can be 'compensated for' by the normally lower BDE of C-Br relative to C-Cl.

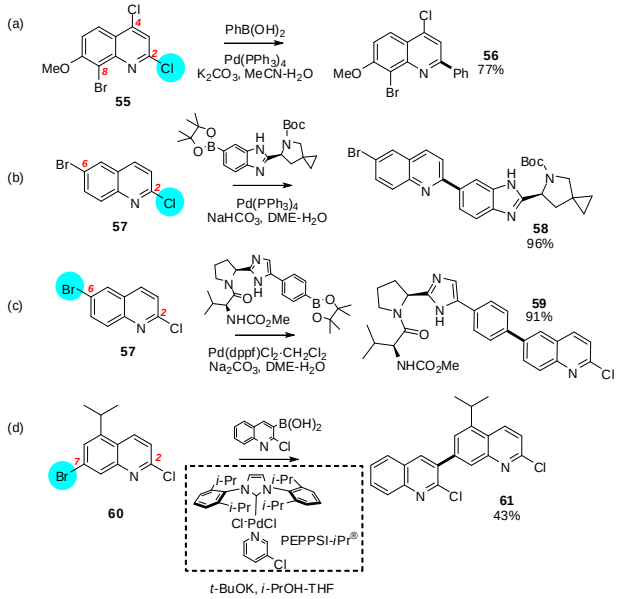
Reactions involving isoquinolines and quinolones (Section 4c), containing halides at C1 and C2 respectively, constitute an intermediate situation between these contrasting pyridine and quinoxaline/quinazoline cases. For these substrates, a chloride substituent at these intrinsically electrophilic positions sometimes reacts in preference to a bromide elsewhere in the heteroarene but not always (Schemes 10 and 11). For example, 1-chloro-5-bromoisoquinoline reacts at C1 (**47**→**48**),[63] as does a 1,3-dichloro-6-bromoisoquinoline (**49**→**50**),[64] but 1-chloro-3-*tert*-butyl-6-bromoisoquinoline reacts at C6 (**51**→**52**)[65] and 1-chloro-7-bromoisoquinoline and 1,4-dichloro-7-bromoisoquinoline react at C7 (**53a/b**→**54a/b**[66] (Scheme 10).



Scheme 10 *The intrinsic electrophilicity of C1 in isoquinolines is sufficient to override the usual ArBr>ArCl order of halide reactivity for (a) 1-chloro-5-bromoisoquinoline (**47**),[63] and (b) 1,3-dichloro-6-bromoisoquinoline (**49**),[64] but not for (c) 1-chloro-3-tert-butyl-6-bromoisoquinoline (**51**), or (d) 1-chloro-7-bromoisoquinoline (**53a**) or 1,4-dichloro-7-bromoisoquinoline (**53b**).[66]*

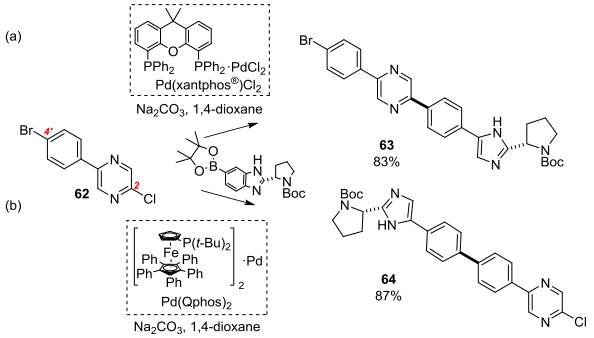
It is not clear what features of these molecules and/or the conditions employed are responsible for this site-divergent behaviour but it presumably reflects the fact that the opposing influences on the BDE elicited by the ring polarisation and the change of halogen are of similar magnitude, making both positions similarly reactive towards SMC.

Similarly, a chloride at C2 in quinolines can sometimes react in preference to a non-activated bromide elsewhere in the heterocycle but not always. For example, 2,4-dichloro-8-bromo-7-methoxyquinoline reacts at C2 (**55**→**56**),[67] but 2-chloro-6-bromoquinoline reacts at C2 (**57**→**58**)using $Pd(PPh_3)_4$[68] or at C6 (**57**→**59**) using $Pd(dppf)Cl_2$,[69] and 2-chloro-7-bromo-5-isopropylquinoline reacts at C7 (**60**→**61**)[70] (Scheme 11).



Scheme 11 *The intrinsic electrophilicity of C2 in quinolines is sufficient to override the usual ArBr>ArCl order of halide reactivity e.g. for (a) 2,4-dichloro-8-bromo-7-methoxyquinoline (**55**),[67] but 2-chloro-6-bromoquinoline (**57**) can react (b) at C2 (→**58**) using $Pd(PPh_3)_4$,[68] or (c) at C6 (→**59**) using $Pd(dppf)Cl_2$,[69] and 2-chloro-7-bromo-5-isopropylquinoline reacts at C7 (**60**→**61**).[70]*

Another particularly finely balanced case is that of 2-(4-bromophenyl)-5-chloropyrazine (**62**).[71] For this substrate, the pyrazine chloride at C2 is electronically activated but it undergoes SMC reactions in preference to the bromide only with certain pre-catalysts: $Pd(xantphos^{®})Cl_2$ gives high site-selectivity for the chloride (→**63**) but most other pre-catalysts and particularly $Pd(Qphos)_2$ favour the bromide (→**64**, Scheme 12).[71]



Scheme 12. *The site-selectivity for SMC reactions of 2-(4-bromophenyl)-5-chloropyrazine (**62**) are ligand-dependent: it undergoes SMC (a) at C2 with $Pd(xantphos^{®})Cl_2$ (→**63**) and (b) at C4' with $Pd(Qphos)_2$ (→**64**)*[61]

The authors attempted to correlate this ligand-dependent divergence of behaviour with a suite of physiochemical parameters which characterise phosphines (*e.g.* Tolman cone angle) but without success, perhaps implicating a change in ligation state as being responsible, as discussed above. However, the nature of the nucleophile, the base, additives (*e.g.* halide salts), and the solvent can also influence the energetics of OA.[21, 33, 47b, 72]

The foregoing discussion illustrates how the tactic of deploying different halogens to control site-selectivity in SMC reactions is often an effective strategy, but that the expected order of reactivity based on average C-Hal BDEs can be subverted for heteroarenes with strong intrinsic electronic bias and so allowance for this should be made in synthetic planning.

The foregoing survey of factors that control the site-selectivity of SMC reactions of heteroaryl halides can be summarised as:

- *For substrates containing two or more of the same halide*: selectivity is primarily controlled by the intrinsic relative electrophilicities of the different ring carbons but this can be tempered by the electronic (and to lesser extent steric) influence of ring substituents.
- *For substrates containing more than one kind of halide*: selectivity can be controlled by the nature of the halide but the intrinsic relative electrophilicities of different ring-carbons can subvert this order in strongly polarised systems.

In both scenarios, the influence of the reaction conditions and particularly the nature of the Pd pre-catalyst/ligand can be decisive but this is generally only observed when using significantly more sterically hindered and/or electron-rich phosphines (*e.g.* QPhos, P(*t*-Bu)$_3$, amphos, dtbpf) than the 'standard' phosphines employed for

most SMC reactions (*e.g.* PPh_3, dppf).[14] These differences likely often reflect the ligation state of the Pd as these 'non-standard' ligands are prone to adopting low-coordination complexes and ligation state is an important factor in determining the ease of OA.

These features are consistent with and reinforced by the data we retrieved from our database searches which are summarised below (Section 4).

4. Key Heteroarene Ring-systems on a Case-by-Case Basis

In this section we summarise on a heterocycle-by-heterocycle basis the results of a series of searches of the Pfizer RKB and CAS Scifinder® reaction databases as detailed in Section 2. For each ring type, a brief summary of published site-selectivity trends for the otherwise *unsubstituted* (*i.e.* unbiased 'parent') core molecule having two (or more) of the same halide substituents is presented. Preferred site-selectivity inferences based on published *substituted* cases are only mentioned if data on unsubstituted cases have not been published.[73] Subsequent discussion of substituted derivatives is restricted to cases where substituents and/or conditions apparently induce a change in the intrinsic selectivity and to cases where a single substituent dictates the site-selectivity of systems for which the parent is symmetrical.[74] Cases when the symmetry of the parent system make site-selectivity redundant (in the absence of additional substituents) are enclosed in hatched boxes; the number indicated below each of these structures indicates the number of reactions of this type found. Examples of selectivity in these reactions which arise from substituent effects are discussed as are some selected reactions which fall outside the scope of the searches but where intrinsic site-selectivities have been reversed by deploying two different halides.

As in section 3, the data is depicted in the Schemes and Figures such that the halide highlighted with a blue disk is the preferred site of reaction (or yellow if there is no actual data but the site is predicted on the basis of expected ring C electrophilicity) and, where relevant, the numbers below indicate the number of hits conforming to that selectivity and, in parenthesis, the number of exceptions. The hits from the Pfizer RKB and the CAS Scifinder® searches are separated and reported in blue and black text respectively. The figures in this section are reproduced the in Supporting Information with footnotes added giving further details of the hits retrieved (Figures 3S-11S).

4a. Pyridines, pyridazines, pyrimidines & pyrazines

Pyridines: Parent 2,3-[60b, 75], 2,4-,[39, 75e, 76] and 2,5-dihalopyridines,[60b, 75b, 75e, 76f, 77] and 2,3,5-trichloropyridine,[78] 2,3,5,6-tetrachloropyridine[79] and pentachloropyridine[79-80] are known to preferentially undergo SMC reactions at C2/C6.[7, 12] Whereas 4-aryl-2,3,5,6-tetrachloropyridine can undergo sequential SMC reactions at C2/C6 then C3/C5,[79] 3,5-dibromo-2,6-dichloropyridine undergoes sequential SMC reactions at C3/C5 then C2/C6.[81] 3,4-Dichloropyridine preferentially undergoes SMC at C4.[75c, 82]

Our data, which incorporate additionally substituted cases, corroborate these trends (Figure 3).

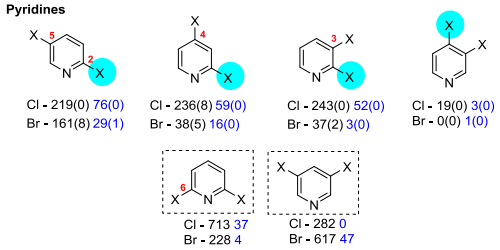
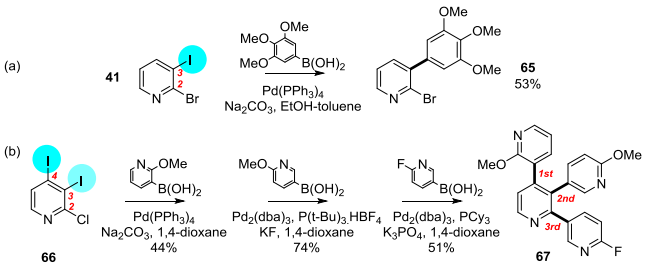


Figure 3. *Coupling outcomes for pyridines.*

The greater electrophilicities of the C2 and C4 positions relative to C3 is expected from simple resonance analysis of the intrinsic polarisation of the pyridine ring-system. The retrieved exceptions have either no yield or evidence for assignment or are minor isomers (>17% yield). Ligand dependent selectivity for coupling 2,4-dichloropyridine with phenyl boronic acid at C4 over C2 (2.4:1) can be achieved albeit with a modest yield of 36% with $Pd(OAc)_2$/Q-Phos/KF/toluene-H_2O [39] Moreover, the C4 coupled product predominates when coupling methyl-4,6-dichloropyridine-2-carboxylate with a biaryl pinnacolato boronate ester using $Pd(dppf)Cl_2$/TBAF/THF (28% yield, *cf*. 23% at C2),[83] and when coupling 3-cyano-2,4-dichloropyridine with 4-aminophenyl pinnacolato boronate using $PdCl_2(dppf)/Na_2CO_3$/DME-H_2O (no yield given but C4:C2 ratio ~2:1).[84] No useful selectivity for SMC at C4 over C3/C5 could be achieved when using symmetrical 2,6-diaryl-3,4,5-trichloropyridine substrates.[79]

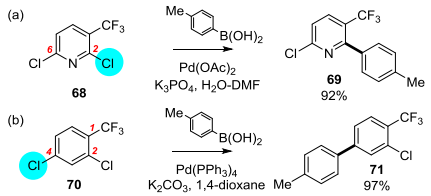
Inversion of the intrinsic selectivity trends can be engineered by deploying mixed halide substrates in which a halide more susceptible to OA is placed at the intrinsically less reactive position,[12] *e.g.* 2-bromo-3-iodopyridine reacts at C3 (**41**→**65**)[60b, 85] and 2-chloro-3,4-diiodopyridine reacts at C4 then C3 then C2 (**66**→**67**)[86] (Scheme 13).



Scheme 13. *(a) 2,bromo-3-iodopyridine undergoes SMC reactions at C3 (**41**→**65**), and (b) 2-chloro-3,4-diiodopyridine reacts at C4 then C3 then C2 (**66**→**67**).*[60b, 85-86]

Symmetrical 2,6-[75e, 76f, 77t, 87] and 3,5-dibromopyridines[76f, 87d, 88] can undergo efficient sequential SMC reactions. For unsymmetrical 2,6-dichloropyridines, an ester or amide group at C3, as discussed earlier (*cf*. Scheme 3, Section 3b), promotes reaction at C6 over C2 (5:1) using $Pd(PPh_3)_4/K_2CO_3$/THF but at C2 over C6 (2.5:1) using $PdCl_2(dppf)/K_2CO_3$/MeOH. The behaviour of the $PdCl_2(dppf)$ was suggested to be as the result of chelation between the ester/amide carbonyl and the coordinatively unsaturated Pd(0).[35a] Similarly, a carboxylic acid group at C3 promotes reaction at C6 using $Pd(OAc)_2/PPh_3/Na_2CO_3$/MeOH[35c] [or $Pd(Ph_3)_4/Na_2CO_3$/1,4-dioxane-H_2O][35b] but at C2 using $Pd_2dba_3{\cdot}CHCl_3/K_2CO_3$/EtOH.[35c] A CF_3 group at C3 of 2,6-dichloropyridine promotes reaction at C2 using $Pd(OAc)_2/K_3PO_4$/DMF-H_2O) (**68**→**69**);[89] interestingly, this contrasts with the behaviour of the phenyl analogue, 2,4-dichloro-1-

trifluoromethylbenzene, which couples at C4 under identical conditions (**70**→**71**)[90] (Scheme 14).



Scheme 14. *(a) A 3-CF_3 group directs OA of 2,6-dichloropyridine to C2 (**68**→**69**),[89] whereas (b) reaction occurs at C4 in the benzene analogue (**70**→**71**)*[90]

For unsymmetrical 3,5-dibromopyridines, a pyridinium aminide (-N$^-$N$^+$C$_5$H$_5$),[91] a methylamine,[92] or a piperazine [93] substituent at C2 promotes reaction at C3, presumably by coordination to Pd(0).

Pyridazines: SMC reactions of otherwise unsubstituted 3,4-dihalopyridazine do not appear to have been reported. SMC reactions of unsubstituted 3,5-dichloro- and 3,5-dibromopyridazine are also surprisingly rare; they generally react at C3 but selectivity for C5 can be achieved by ligand tuning (see below).[39, 94] Our data suggest that substrates containing these motifs generally favour reaction at C3 in both cases (Figure 4).

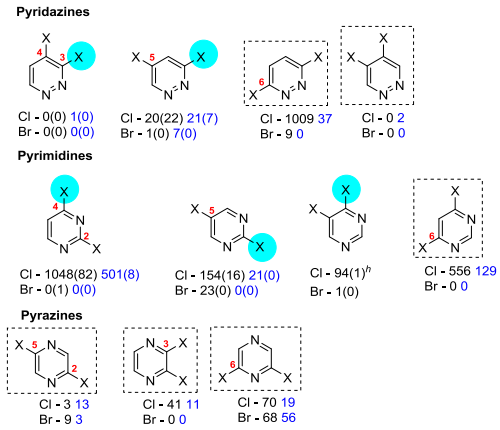
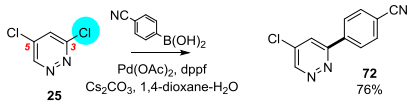


Figure 4. *Coupling outcomes for pyridazines, pyrimidines and pyrazines*.

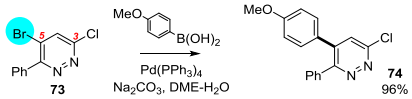
An example from the Pfizer RKB in which C3 selectivity is observed for a SMC reaction of 3,5-dichloropyridazine (**25**) is shown below[27a] (Scheme 15).[43a]



Scheme 15. *Example of SMC reaction of 3,5-dichloropyridazine at C3, (**25**→**72**) from Pfizer RKB.*[27a]

Similarly, 3,5-dichloropyridazine reacts with 2-fluoro-5-bromo-3-pyridine boronic acid using Pd(PPh$_3$)$_4$/Na$_2$CO$_3$/1,4-dioxane to give the C3 substituted product as the major isomer.[94b] Other cases for which C3 coupling has been observed include cases where *4-amino*-3,5-dichloropyridazine[95] reacts with 2-fluoro-4-trifluoromethylboronic acid using PdCl$_2$(PPh$_3$)$_2$/Na$_2$CO$_3$/1,4-dioxane-H$_2$O to give the C3 substituted product in 67% yield and where *6-methyl*-3,5-dichloropyridazine[96] reacts with a complex 4-substututed phenyl pinnacolato boronate using PdCl$_2$(PPh$_3$)$_2$/Cs$_2$CO$_3$/1,4-dioxane to give the C3 coupled product as the major isomer. However, as discussed earlier (Scheme 5, Section 3c), site selectivity for SMC reactions on 3,5-dichloropyridazine are ligand-dependent. This was highlighted by Dai *et al*.[39] who screened 20 ligands for its coupling with phenyl boronic acid: *e.g.* Pd(OAc)$_2$/dppf/Cs$_2$CO$_3$/1,4-dioxane-H$_2$O gave C3 selectivity whereas Pd(OAc)$_2$/Q-Phos/KF/toluene-H$_2$O gave C5 selectivity. The SMC reaction of 3,5-dibromopyridazine with a complex aryl boronic acid using Pd(PPh$_3$)$_2$C$_{l2}$/K$_3$PO$_4$/DMF also occurred selectively at C5,[94a] although caution should be associated with attributing these selectivity differences solely to the ligand given the concomitant changes in reaction conditions.

Mixed halide substrates can be employed to reverse the inherent bias of 3,5-dihalopyridazines for SMC reactions at C3: *e.g.* 3-chloro-5-bromo-6-phenylpyridazine, which reacts at C5 (**73**→**74**, Scheme 16).[97]



Scheme 16. *3-Chloro-5-bromo-6-phenylpyridazine undergoes SMC reaction at C5 (**73**→**74**).*[97]

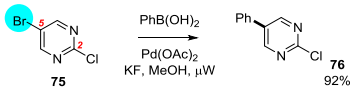
5-Amino-3,4-dichloropyridazines react preferentially at C3 over C4 (84% combined yield, C3:C4 = 8:1) using Pd(PPh$_3$)$_4$/Na$_2$CO$_3$/toluene/EtOH/H$_2$O.[34a]

Symmetrical 3,6-dibromo-[98] and 3,6-dichloropyridazines[99] can undergo efficient mono-SMC reactions; analogous reactions with symmetrical 4,5-dichloropyridazines are rare. SMC reactions of unsymmetrical 4-substituted-3,6-dichloropyridazines usually result in reaction predominantly at C6, *i.e.* distal to alkyl, aryl,[34b-f] carbamate and alkoxy groups,[34a] but for basic amine substituents at C4, reaction is promoted at C3 as discussed earlier (*cf.* Scheme 2, Section 3b).[34a]

Pyrimidines: This heteroarene core has been widely explored for sequential SMC reactions and the order of reactivity is known to generally follow the order: C4/6 over C2 over C5.[7, 12] Parent 2,4-dihalopyrimidines,[100] and 2,4,5-[27b] and 2,4,6-trihalopyrimidines,[101] react at C4/6 and 2,5-bromopyrimidine[102] reacts at C2. These trends are supported by our data which incorporate additionally substituted cases (Figure 4, above).

2,4-Dihalopyrimidines which give anomalous selectivity include a case where 2,4-dibromopyrimidine reacts with 2,4-di-*tert*-butoxypyrimidine-5-boronic acid using Pd(PPh$_3$)$_4$/NaHCO$_3$/DME to give the C2 substituted product in 58% yield.[87b] The other examples involve 2,4-dichloropyrimidines which additionally contain an amine substituent at C6.[103] An alkyl,[104] ether,[105] thioether[105] or amino[106] substituent at C5 also appears to disfavour SMC reactions at C4, resulting in reaction at C2, presumably, mainly for steric reasons.

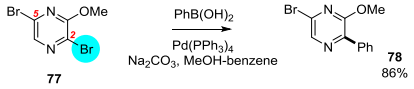
2,5-Dihalopyrimidines which give anomalous selectivity include a case where tetrachloropyrimidine reacts with 3-chloro-6-methoxyphenyl boronic acid using Pd(OAc)$_2$/PPh$_3$/K$_3$PO$_4$/MeCN-H$_2$O to give the C5 substituted product.[107] The other examples involve 2,5-dichloropyrimidines which additionally contain an amine[108] substituent at C4 which appears to promote SMC reaction at C5. Inversion of the intrinsic selectivity trends can be engineered by deploying mixed halide substrates, *e.g.* 5-bromo-2-chloropyrimidine which reacts at C5 (**75**→**76**, Scheme 17).[100g]



***Scheme 17**. 5-Bromo-2-chloropyrimidine undergoes SMC at C5 (**75**→**76**).*[100g]

All 4,6-dihalopyrimidines are symmetric and can undergo efficient mono-SMC reactions under appropriate conditions[109] and 2,4,5,6-tetrachloropyrimidines also react selectively at C4/6.[82, 110]

Pyrazines: The symmetry of the pyrazine core renders all otherwise unsubstituted dihalide derivatives symmetrical (Figure 4, above). Parent 2,5-dibromo-[111] and 2,5-dichloropyrazines[69, 112] can undergo efficient mono-SMC reactions. Alkoxy- and amino-substituents direct OA to adjacent positions, *e.g*. 2,5-dibromo-3-methoxypyrazine reacts at C2 (**77**→**78**, Scheme 18).[113]



***Scheme 18**. A 3-OMe group directs OA of 2,5-dibromopyrazine to C2 (**77**→**78**).*[113]

2,3-Dichloropyrazine itself can undergo efficient mono-SMC reactions.[114] Only two unsymmetrical variants were retrieved, one with a C5[115] amino substituent and the other with a C6[116] substituent; both gave SMC coupling at C3. Parent 2,6-dibromo-[117] and 2,6-dichloropyrazines[118] can undergo efficient mono-SMC reactions. 3-Amino-[119] and 3- pyridinium aminide (-N$^-$N$^+$C$_5$H$_5$)[91, 120] substituted 2,6-dibromopyrazines couple at C2 whereas interestingly 3-imide-substituted 2,6-dibromopyrazines couple at C6, albeit in low yields.[121] Similarly, 3-acetyl-, 3-cyano- and 3-formyl-2,6-dichloropyrazines couple at C6.[122]

4b. Pyrroles, furans, thiophenes, imidazoles, pyrazoles, (is)oxazoles & (iso)thiazoles

Pyrroles: Although SMC reactions of parent 2,3- and 2,4-dihalopyrroles do not appear to have been reported, additionally *C*-substituted derivatives in general react at C2.[12] *N*-Methyl-2,3,5-tribromopyrrole reacts at C5 then at C2 then at C3,[123] and *N*-methyl tetrabromopyrrole reacts at C2 then at C5.[124] These trends are supported by our data (Figure 5).

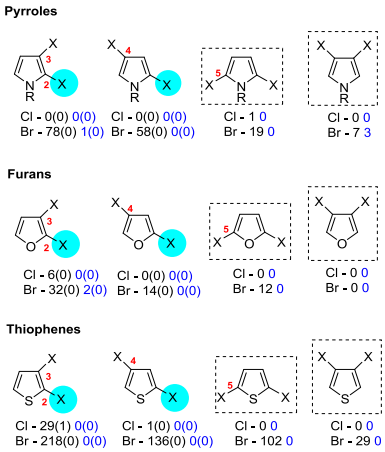
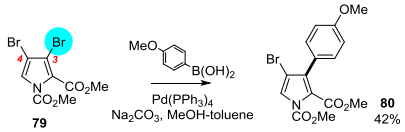


***Figure 5**. Coupling outcomes for pyrroles, furans and thiophenes.*

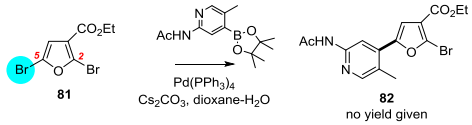
No SMC reactions displaying anomalous selectivity were retrieved; it appears that the presence of various additional substituents does not overcome the inherent bias of the pyrrole ring system. Symmetrical 3,4-dihalopyrroles,[125] 2,3,4,5-tetrabromopyrroles[124] and to a lesser extent 2,5-dihalopyrroles[126] can undergo efficient mono-SMC reactions. Unsymmetrical cases include *N*-methyl-2-cyano-,[127] 2-methoxycarbonyl-[128] and *N*-methoxycarbonyl-3,4-dibromopyrrole-2-methyl ester (**79**)[128] reacting at the proximal C3 position (→**80**, Scheme 19).[128]



***Scheme 19**. A methyl ester at C2 directs OA of 3,4-dibromopyrrole to C3 (**79**→**80**).*[128]

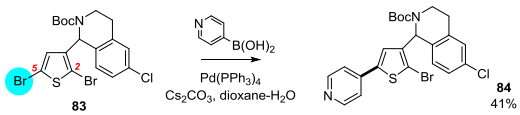
Additional unsymmetrical cases include the aforementioned *N*-methyl-2,5-dibromopyrroles with an additional bromine substituent at C3 which undergo SMC reactions at the distal C5 position,[123] and an *N*-methyl-2,5-dichloro-3-amidopyrrole which also reacts at C5.[129]

Furans: SMC reactions of 2,3-[130] and 2,4-dihalofurans,[87b] and 2,3,4,5-tetrabromofurans,[131] like pyrroles, are known to generally occur at C2. This trend is supported by our data (Figure 5, above). As for pyrroles, no SMC reactions displaying anomalous selectivity were retrieved. Symmetrical 2,5-dibromo-[87b, 100d, 132] and 2,3,4,5-tetrabromofurans[131] can undergo efficient mono-SMC reactions, but no corresponding reactions of symmetrical 3,4-dihalofurans have been reported. The only unsymmetrical 2,5-dibromofurans that have been coupled contain an ethyl ester at C3 which, in contrast to the effect in 3,4-dibromopyrroles (*cf.* Scheme 1, Section 3a), directs the coupling of a 4-pyridyl pinnacolatoboronate to the C5 position (**81**→**82**), presumably for steric reasons (Scheme 20).[133]



***Scheme 20.** A 3-ethoxycarbonyl group directs OA of 3,4-dibromofuran to C5 (**81**→**82**).*[133]

Thiophenes: SMC reactions of 2,3-[134] and 2,4-dihalothiophenes,[50, 87b, 134c, 135] like pyrroles and furans, are known to generally occur at C2. 2,3,4-Tribromothiophenes[136] react at C2 then at C4; 2,3,5-trihalothiophenes react at C5 then C2.[135b, 137] These trends are supported by our data (Figure 5, above). Again, no SMC reactions displaying anomalous selectivity were retrieved. Symmetrical 2,5-[87b, 87f, 132, 134e, 137e, 137g, 138] and 3,4-dihalothiophenes[87g, 130b, 139] can undergo efficient mono-SMC reactions. Moreover, 2,3,4,5-tetrabromothiophene is a useful precursor for 2-aryl[87f, 140] and for 2,5-diarylsubstituted products.[140c, 141] Unsymmetrical cases include 3-carboxy-,[142] and 3-keto-2,5-dibromothiophenes[143] which couple at C2 presumably due to chelation to Pd(0) and also 3-alkyl-[138e, 138p, 144] and the aforementioned 3-bromo-,[135b, 137] substituted 2,5-dibromothiophenes which couple at C5 (*e.g*. **83**→**84**) presumably due to the steric bulk of these substituents (Scheme 21).



***Scheme 21.** A 3-alkyl group directs OA of 2,5-dibromothiophene to C5 (**83**→**84**).*[138p]

Cases of unsymmetrical 3,4-dibromothiophenes undergoing selective SMC reactions include ones with 2-aryl substituents which couple at C4;[136] these substrates are often intermediates in sequential *bis*-SMC reactions of 2,3,4-tribromothiophenes. 2,5-Diaryl-3,4-dibromothiophenes appear to couple distal to most sterically demanding aryl group with good selectivity.[140a] 2-Formyl-3,4-dibromothiophenes couple at C3.[145]

Imidazoles: *N*-Protected-2,4,5-trihaloimidazoles are known to undergo sequential SMC reactions at C2 then at C5 (*i.e*. proximal to the 'pyrrole-like' nitrogen) then at C4 (*i.e*. proximal to the 'pyridine-like' nitrogen)[146] *N*-Protected-2,4- and 2,5-dibromoimidazoles generally also follow this trend (*i.e*. SMC reaction at C2 then either at C4 or at C5).[25, 147] These trends are supported by our data (Figure 6).

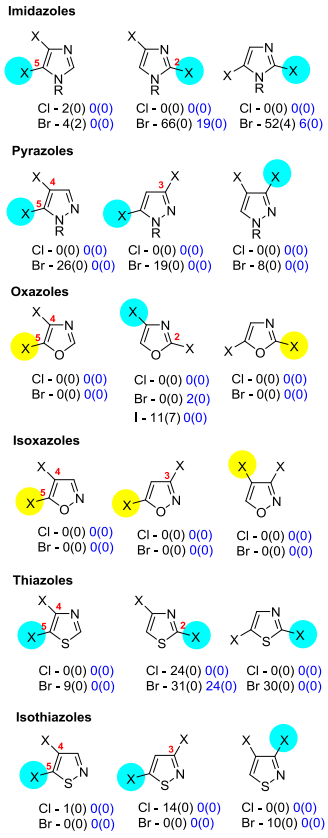


Figure 6. *Coupling outcomes for imidazoles, pyrazoles, (is)oxazoles and (iso)thiazoles.*

The retrieved exceptions include the case of *N*-methyl-2,5-dibromoimidazole for which SMC reaction at C5 was favoured when using $Pd(OAc)_2$ with either XPhos, 1,3,5-triaza-7-phospha-adamantane, dppf or tris(4-trifluoromethylphenyl)phosphine but at C2 (*i.e*. as 'normal') when using $Pd(OAc)_2$/xantphos®.[25] The reason for the anomalous behaviour with these particular ligands is not apparent. One patent also reports a 2-amino- and a 2-aryl-4,5-dibromo-*N*-SEM-imidazole undergoing SMC coupling at C4 (*i.e.* proximal to the pyridyl nitrogen) when using $Pd(PPh_3)_4/Na_2CO_3$/DME-H_2O,[148] but the SEM group is also present in two cases[149] where normal C5 selectivity is observed so this does not appear to the critical factor in the site-selectivity.

Pyrazoles: *N*-Protected-3,4,5-tribromopyrazoles are known to undergo sequential SMC reactions at C5 then at C3 then at C4.[150] This trend is supported by our data and no exceptions were retrieved, although the total number of examples was relatively small (Figure 6, above).

(Is)oxazoles: The SMC reaction of 2,5-dibromooxazole has been noted anecdotally[151] to give "a complex mixture of products", and 2,4-diiodooxazole is reported to give poor selectivity favouring reaction at C4 with most common ligand systems.[25] This report relating to 2,4-diiodooxazole and which was discussed previously (*cf.* Scheme 6, Section 3a) is also the only one retrieved by our searches (Figure 6, above). Interestingly, the highest level of C4 selectivity for 2,4-diiodooxazole was achieved using $Pd(OAc)_2$/xantphos® but SMC reaction predominantly at C2 could be achieved using $Pd(OAc)_2$/1,3,5-triaza-7-phospha-adamantane (see Scheme 6, Section 3a).[25] Reaction at C2 was also observed when coupling a 2-phenyl-4-pinacolato-2,4-diiodooxazole with 5-phenyl-2,4-diiodooxazole using $Pd_2(dba)_3/PCy_3/K_2CO_3$/DMF, likely due to the steric influence of the phenyl group at C5.[152] There were no examples of SMC reactions on any dihaloisoxazoles retrieved by our searches (Figure 6, above).

(Iso)thiazoles: SMC reactions of 2,4-[25, 50, 87b, 134e, 153] and 2,5-dihalothiazoles[25, 87b, 134e, 137e, 153a, 154] are known to occur selectively at C2. This trend is corroborated by our data and no exceptions were retrieved (Figure 6, above). In stark contrast to 2,4-diiodooxazole (see above), 2,4-dibromothiazole (and its 2,5-congener) couple exclusively at C2 using not only the $Pd(OAc)_2$/xantphos® conditions but under all conditions evaluated by Strotman *et al*. (see Scheme 6, Section 3a).[25] The data also demonstrate that SMC reactions of 4,5-dihalothiazoles occur selectively at C5 (*i.e*. proximal to the S).[155] Although SMC reactions of parent 4,5-,[156] 3,5-[157] or 3,4-dihaloisothiazoles[158] do not appear to have been reported, the additionally *C*-substituted derivatives in our data conform to a trend whereby reaction occurs at C5 (*i.e*. proximal to the S) then at C3 (*i.e.* proximal to the N) then at C4 (Figure 6).

4c. (Iso)quinolines & benzodiazines

Quinolines: 2,3-[159] and 2,4-dihaloquinolines[160] are known to preferentially undergo SMC reactions at C2; 3,4-dihaloquinolines preferentially undergo coupling at C4.[161] 2,6-,[162] -2,8-,[163] 3,8-,[164] 3,6-,[161a] 3,7-,[165] 4,6-,[166] 4,7-,[75b, 161a, 167] 4,8-[168] dihaloquinolines all react preferentially in the pyridyl ring. These trends are confirmed by our data which show that SMC reactions occur at C2 then at C4 then at C3 in the pyridyl ring and that all these positions are more reactive than any positions in the annelated benzo-ring (Figure 7).

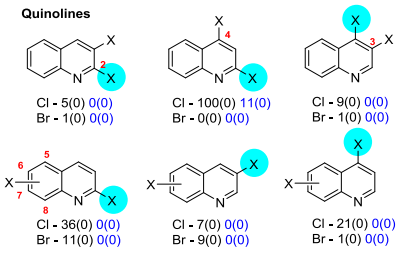
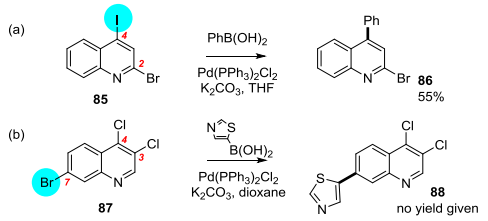


Figure 7. *Coupling outcomes for quinolines*.

No exceptions were retrieved although inversion of the intrinsic selectivity trends can be engineered by deploying mixed halide substrates, *e.g*. 2-bromo-4-iodoquinoline which reacts at C4 (**85**→**86**)[169] and 3,4-dichloro-7-bromoquinoline which reacts at C7 (**87**→**88**)[170] (Scheme 22).



***Scheme 22**. (a) 2-Bromo-4-iodoquinoline undergoes SMC at C4 (**85**→**86**),[169] and (b) 3,4-dichloro-7-bromoquinoline reacts at C7 (**87**→**88**).*[170]

<u>*Isoquinolines*</u>: 1,3-Dihalo-[171] and 1,6-dichloroisoquinolines[172] are known to undergo selective SMC reactions at C1 and interestingly 4,7-dibromoisoquinoline reacts at C7.[173] Our data support these trends and reveal that surprisingly few additional examples of selective SMC reactions of dihaloisoquinolines have been reported (Figure 8).

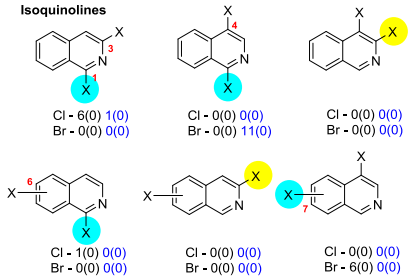
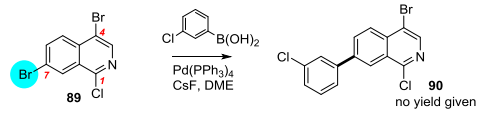


***Figure 8**. Coupling outcomes for isoquinolines.*

That SMC reactions are favoured in the annelated benzo-ring over the pyridyl ring holds also for 4,7-dibromo-1-chloroisoquinoline (**89**→**90**, Scheme 23).[173b]



***Scheme 23**. 4,7-Dibromo-1-chloroisoquinolines undergoes SMC at C7 (**89**→**90**).*[173b]

<u>*Benzopyridazines (Cinnolines & Phthalazines)*</u>: 4,6-Dichlorocinnoline[174] and 1,6-dichlorophthalazine[175] are known to undergo selective SMC reactions at C4 and C1 respectively. Our data confirm this and reveal that no additional substituted examples of these or any other dihalocinnolines have been investigated (Figure 9).

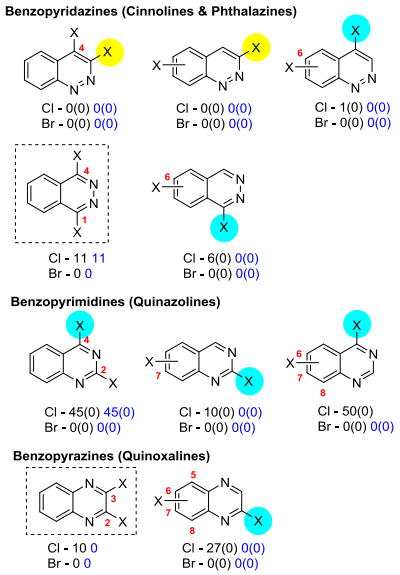
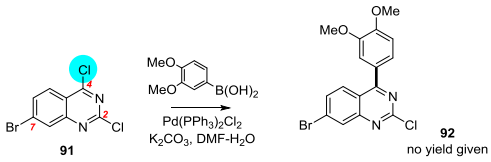


***Figure 9**. Coupling outcomes for benzodiazines.*

Symmetrical 1,4-dichlorophthalazines can undergo mono-SMC reactions[176] but unsymmetrical derivatives do not appear to have been investigated.

<u>*Benzopyrimidines (Quinazolines)*</u>: 2,4-Dichloroquinazoline is known to undergo SMC reactions selectively at C4[177] but other parent dihaloquinazolines do not appear to have been investigated. Our data support this trend and moreover reveals that both the C4 and C2 positions in the pyrimidyl ring are favoured over the C6,[178] C7[179] and C8[180] positions in the annelated benzo-ring (Figure 9; also see Scheme 9, Section 3d). Interestingly, even 6-bromo-2,4-dichloroquinazoline reacts selectively at C4 using $Pd(PPh_3)_2Cl_2/K_2CO_3$/DMF-H_2O conditions (**91**→**92**, Scheme 24).[181]



***Scheme 24**. 6-Bromo-2,4-dichloroquinazoline undergoes SMC at C4 (**91**→**92**).*[181]

<u>*Benzopyrazines (Quinoxalines)*</u>: 2,6-Dichloroiquinoxaline is known to undergo SMC reactions selectively at C2.[182] Our data support this and additionally indicate that substituted 2,5-[183] and 2,8-dichloroquinoxalines[184] undergo SMC reactions at C2 (Figure 9, above). Symmetrical 2,3-dichloroquinoxalines can undergo efficient mono-SMC reactions.[82, 99b, 185] Unsymmetrical derivatives do not appear to have been investigated except the mixed halide case discussed earlier (Scheme 9, Section 3d).

4d. Indoles, benzofurans, benzothiophenes, benzodiazoles, benz(is)oxazoles & benz(is)othiazoles

<u>*Indoles*</u>: SMC reactions of *N*-Me-[186] and to a lesser extent *N*-$PhSO_2$-2,3-dibromoindoles[187] occur preferentially at C2. Moreover, *N*-Me-2,3,6-tribromoindole reacts at C2 then C6 then C3.[186b] *N*-H-2,5-Dibromoindole[188] also undergoes SMC reactions at C2 but *N*-TBS-3,6-Dibromoindole[146a] reacts at C6. These trends are supported by our data which show that C2 in the pyrrole-like ring is the most

reactive followed by the C5 and C6 positions in the benzo-fused ring and that C3 in the pyrrole-like ring is the least reactive (Figure 10).

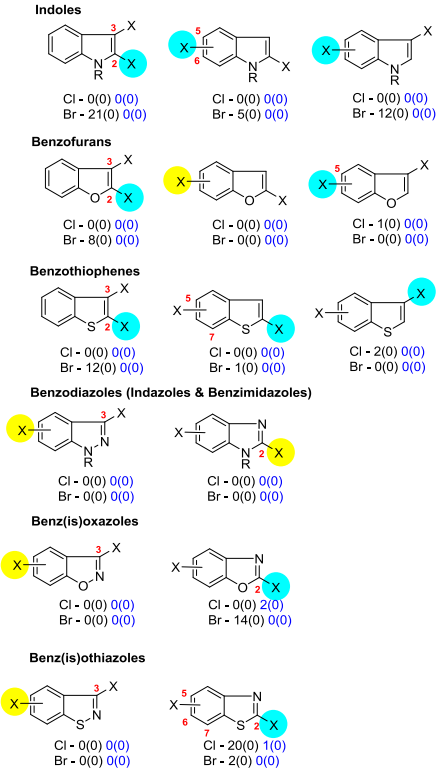
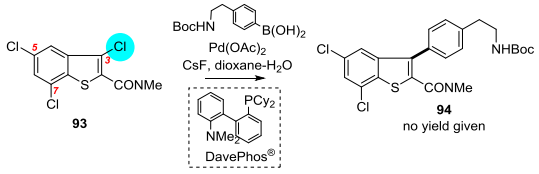


Figure 10. *Coupling outcomes for indoles, benzoxazoles, benzothiazoles and benzodiazoles*.

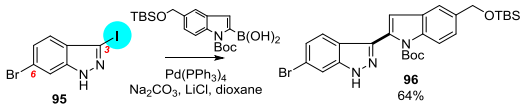
<u>*Benzofurans*</u>: 2,3-Dibromobenzofuran can be reacted sequentially *via* SMC reactions at C2 and then at C3.[189] This preference is confirmed by our data which also reveals that 3,5-dibromobenzofuran undergoes selective SMC reaction at C5[190] (Figure 10, above). By analogy with the selectivity displayed by Pd(0)-catalysed processes other than SMC, it can be anticipated that the order of reactivity in SMC reactions on 2,3,5-tribromobenzofuran will be: at C2 then at C5 then at C3.[191]

<u>*Benzothiophenes*</u>: 2,3-Dibromobenzothiophene can be reacted sequentially *via* SMC reactions at C2 and then at C3,[141c, 189b, 192] and 2,5-dibromobenzothiophene reacts *via* SMC reactions at C2.[193] Our data confirms this (Figure 10, above), and reveals that additionally a substituted 3,7-dichloro- and 3,5,7-trichlorobenzothiophene preferentially undergo SMC reactions at C3 (*e.g.* **93**→**94**)[194]. However, both of the aforementioned 3,7-dichloro-substituted examples also contain a dimethyl amide substituent at C2, so it is possible that the electron-withdrawing influence of this group activates the C3 position towards OA (Scheme 25).



Scheme 25. *A 3,5,7-trichlorobenzothiophene undergoes SMC at C3 (**93**→**94**)*.[194]

<u>*Benzodiazoles (Indazoles & Benzimidazoles)*</u>: Interestingly, our data indicate there to be no examples known of selective SMC reactions of dihaloindazoles or benzimidazoles (Figure 10, above). However, the selective reaction at C3 of 6-bromo-3-iodo-1-*H*-indazole has been reported (**95**→**96**, Scheme 26).[195]



Scheme 26. *6-Bromo-3-iodo-1-H-indazole undergoes SMC at C3 (**95**→**96**)*.[195]

<u>*Benz(is)oxazoles*</u>: Although selective SMC reactions of dihalogenated benzisoxazoles appear to be unknown, reactions of 2,6-dichlorobenzoxazole are known to be selective for C2.[196] These are the only reactions retrieved in our searches (Figure 10, above).

<u>*Benz(iso)thiazoles*</u>: SMC reactions of 2,5-dichloro-,[197] 2,6-dibromo-,[198] 2,6-dichloro-,[197, 199] and 2,7-dichlorobenzothiazoles selectively occur at C2. Our data confirm this and also reveals that 6-methoxy-2,7-dibromobenzothiazole is reactive at C2[200] (Figure 10, above). The dataset is very limited however; no otherwise substituted benzothiazole examples have been reported and no benzisothiazoles at all.

4e. Aza(iso)quinolones (Naphthyridines)

<u>*Aza(iso)quinolines*</u>: remarkably few SMC reactions appear to have been carried out on this type of substrate. When both halides are situated in one ring then the reported cases all react as expected for the corresponding (iso)quinoline, *e.g.* 2,4-dichloro-8-azaquinolines ([1,8]-naphthyridines)[201] and -7-azaquinolines ([1,7]-naphthyridine)[201b, 201c] and -5,8-diazaquinoline (pyrido[2,3-]pyrazine)[202] all react at C2 and 5,7-dichloro-6-azaquinoline ([1,6]-naphthyridine) reacts at C1.[203] When the halides are in different rings then there are even fewer examples (Figure 11).

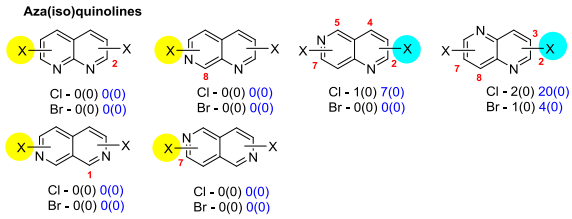
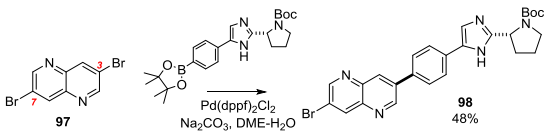


Figure11. Coupling outcomes for azaquinolines and azaisoquinolines.

Our data show that 2,5-dichloro-6-azaquinoline ([1,6]-naphthyridine) undergoes SMC reactions at C2[204] and 4,7-dichloro-6-azaquinoline reacts at C4. 7-Carbethoxy- and 7-carboxamido-2,8-dichloro-5-azaquinolines ([1,5]-naphthyridines) undergo SMC reactions at C2.[205] 3,7-Dibromo-5-azaquinoline ([1,5]-naphthyridine, **97**) is a symmetrical molecule and has been reported to undergo *mono*-SMC reactions with a range of aryl pinnacolato boronates (→**98**, Scheme 27).[69]



Scheme 27. *A SMC reaction of 3,7-dibromo-5-azaquinoline with pinacolatoborane (**97**→**98**)*.[69]

Conclusions

Given the complexity of the catalytic cycle involved in SMC reactions and the myriad of disparate Pd pre-catalysts, ligands, solvents and bases employed in these processes, it is not surprising that no absolutely rigid site-selectivity rules can be provided to predict the outcome of these reactions on heteroaryl polyhalides. As we have seen, experimental parameters can critically impact on the dominant catalytic species in solution and its ability to undergo the site-selectivity-determining OA step. However notwithstanding this, it is clear from the analysis presented in this review that for the majority of SMC reactions on this substrate class, particularly when using 'standard' conditions, the preferred site of reaction *can* be predicted with some confidence by paying attention to the nature of the halides present, the intrinsic relative electrophilicities of different ring-carbons (particularly for strongly polarised systems), and the electronic (and to a lesser extent steric) influence of substituents. We hope that by drawing together published data pertaining to this and summarising additional data mined from the Pfizer global chemistry RKB and the CAS Scifinder® databases, we have contributed to making the design of synthetic strategies for the construction of molecules containing polysubstituted heteroaryl motifs, for whatever purpose but especially in the context of pharmaceutical drug discovery, easier and more reliable.

Acknowledgements

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Notes and references

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15. http://www.cas.org/products/scifinder (>60 million reactions, 1840 onwards).
16. Deploying different boron derivatives and/or controlling the speciation/ligation state of boronic esters and consequent transmetallation reaction rates can be used to effect regioselective sequential SMC reactions but this strategy lies outside the scope of our survey. For details, see *e.g.* the reviews of Lloyd-Jones (refs 17a and 17d) and Watson (ref 17b). Using this approach, Watson achieved an elegant one-pot sequential SMC reaction of 2,4-di-chloropyrimidine at C4 then C2 using MIDA and Pin aryl boronates, see: ref 17c.
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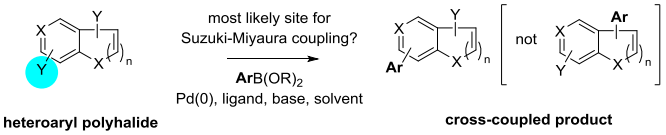
Table of Contents Graphic



Suzuki-Miyaura cross-coupling reactions of heteroaryl polyhalides with aryl boronates are surveyed. Drawing on data from literature sources as well as bespoke searches of Pfizer's global chemistry RKB and CAS Scifinder® databases, the factors that determine the site-selectivity of these reactions are discussed with a view to rationalising the trends observed.