Electronic Supplementary Material (ESI) for Chemical Science.

Supporting Information

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

Joshua Almond-Thynne,[a] David C. Blakemore,[b] David C. Pryde[b] and Alan C. Spivey[a]*

[a] Department of Chemistry, Imperial College London, South Kensington Campus, London, SW& 2AZ, UK. Fax: (+) 44 (0)1474 813219, E-mail: a.c.spivey@imperial.ac.uk

[b] Pfizer Worldwide Medicinal Chemistry, The Portway Building, Granta Park Great Abington, Cambridge CB21 6GS, UK

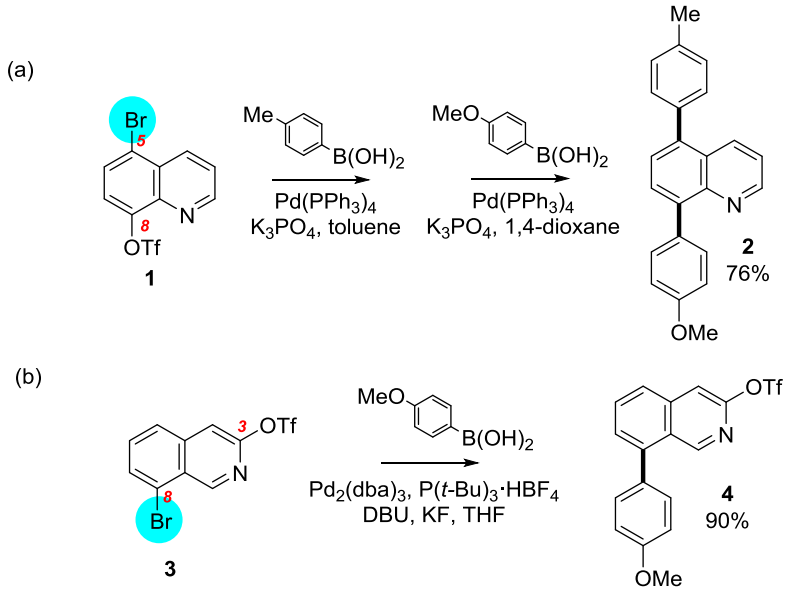
CONTENTS

1) Notes on the use of mixed halide-triflate heterocycles in SMC reactions.

As indicated in Section 3d of the main article, mixed halide containing heteroarenes are often investigated for site selective SMC reactions with the express purpose of overriding the 'intrinsic' site-selectivity of the parent heterocycle. Additionally, triflates can often be relatively easy to introduce into certain positions in heteroarenes *via* pyridone-type precursors. However, predicting the SMC reactivity of triflates *vs*. halides in mixed systems can be challenging, probably due to the strong influence of catalyst ligation state on selectivity. This has been investigated and documented in detail for 4-trifloxychlorobenzene (see Scheme 7, main article and associated text).

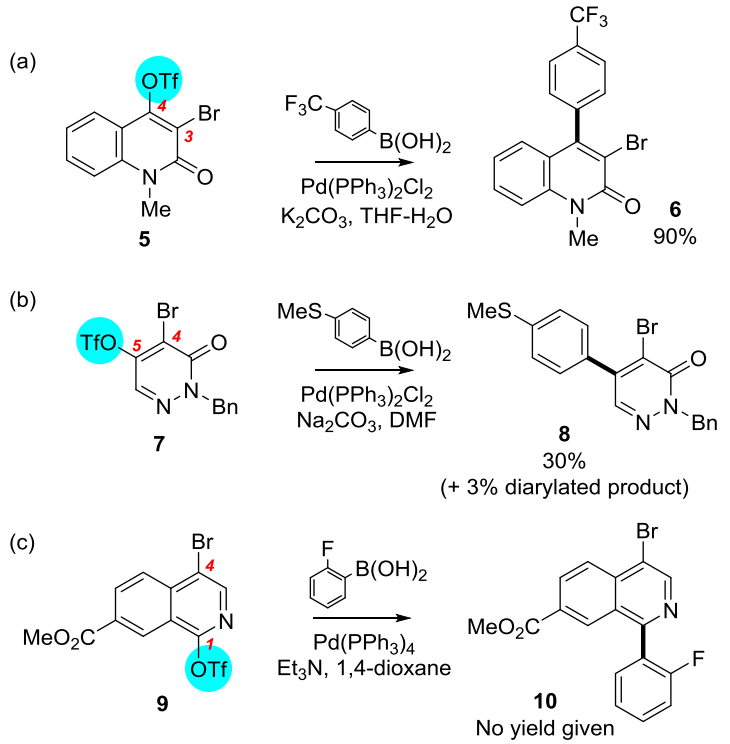
On the basis of average BDEs, triflates would be expected to be less susceptible to OA than chlorides *i.e*. ArBr>ArCl>ArOTf. However, the experimental data indicate that for most Negishi and Kumada reactions the order of reactivity is ArOTf>ArBr>ArCl,[1] and this also holds for Stille coupling in the presence of added salts (*e.g*. KF).[1b, 2] However for Stille reactions in the absence of anionic additives and for SMC reactions, bromides[3] *are* generally more reactive than triflates.[1a] This divergence of behaviour has been attributed to changes in the ligation state of the Pd undergoing OA – anionic complexes *e.g.* $[PdL_2X]^-$ or $[PdLX]^-$ favour reaction at triflate whereas neutral complexes favour reaction at bromide/chloride.[1a, 4] Anionic complexes are favoured in the case of Negishi and Kumada reactions as the organometallic coupling reagents can act as the anionic ligand X irrespective of the solvent (*i.e.* X = ArZnY and ArMgY, respectively). By contrast, for Stille and SMC reactions, it has been argued that neutral complexes are generally the prevalent catalytic species except where polar solvents favour anionic complexes and X is likely a halide or boronate anion (*i.e*. Hal^- and $ArBO_2H^-$, respectively).[4]

The reactivity of 5-bromoquinolin-8-yl triflate (SMC at C5 then C8, **1**→**2**)[5] and of 8-bromoisoquinolin-3-yl triflate (SMC at C8, **3**→**4**)[6] are illustrative of the 'normally' observed higher SMC reactivity of bromides relative to triflates (Scheme 1S).



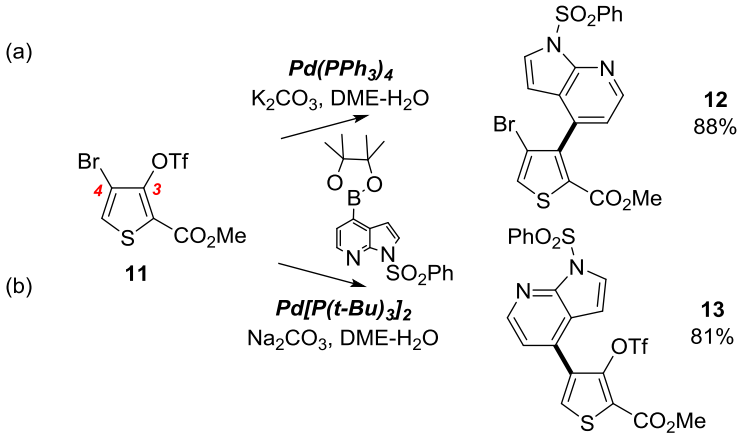
Scheme 1S. *For SMC reactions, triflates are generally less good substrates for OA than bromides: e.g. (a) 5-bromoquinolin-8-yl triflate undergoes SMC at C5 then C8 (**1**→**2**), and (b) 8-bromoisoquinolin-3-yl triflate undergoes SMC at C8 (**3**→**4**).*[5-6]

It is notable that in these two cases neither the triflate groups nor the bromides are located at particularly intrinsically activated ring positions. By contrast, 3-bromo-4-trifloxyquinolin-2(1*H*)-one (**5**)[7] and 2-benzyl-4-bromo-5-trifloxypyridazin-3(2*H*)-one (**7**)[8] undergo SMC at C4 (→**6**) and at C5 (→**8**) respectively. In both cases, the carbonyl is presumably influential in increasing the electrophilicity of the carbons bearing the triflate substituents. Similarly, a triflate at C1 in isoquinoline **9** undergoes SMC reaction more rapidly than a bromide at C4 (→**10**)[9] (Scheme 2S).



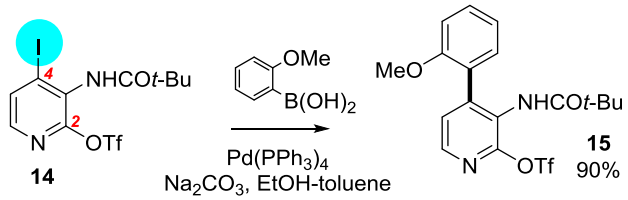
Scheme 2S. *The high intrinsic electrophilicity of certain ring positions (e.g. C4 in quinolin-2(1H)-ones, C5 in pyridazin-3(2H)-ones and C1 in isoquinolines) can perturb the BDE sufficiently to override the usual ArBr>ArOTf order of reactivity: e.g. (a) 3-bromo-4-trifloxyquinolin-2(1H)-one (**5**), and (b) 2-benzyl-4-bromo-5-trifloxypyridazin-3(2H)-one (**7**) undergo SMC at C4 (→**6**) and at C5 (→**8**) respectively,*[7-9] *and (c) methyl 4-bromo-1-trifloxyisoquinoline-7-carboxylate undergoes SMC at C1 (**9**→**10**).*[9]

Triflate-containing substrates can also display ligand dependent site-divergent SMC reactions when the effects of ring polarisation *vs*. intrinsic triflate/bromide BDE differential are opposed and of similar magnitude. For example, in methyl 4-bromo-3-trifloxythiophene-2-carboxylate (**11**) the reactivity is finely balanced owing to the 'activation' of the normally less reactive triflate group at C3 by polarisation due to the ester at C2. Experimentally, $Pd(PPh_3)_4$ promotes SMC of the triflate at C3 (→**12**) whereas $Pd(P$*t*-$Bu_3)_2$ promotes SMC of the bromide at C4 (→**13**). The authors suggest a switch in rate-determining step but performed no experiments to probe this further; a change in ligation state could also be responsible for the difference (Scheme 3S).[10]



Scheme 3S. *The site-selectivity for substrates containing an activated triflate vs non-activated bromide can be ligand-dependent: e.g.: methyl 4-bromo-3-trifloxythiophene-2-carboxylate (**11**) undergoes SMC (a) at C3 with $Pd(PPh_3)_4$, (→**12**) and (b) at C4 with $Pd[P(t\text{-}Bu)_3]_2$ (→**13**).*[10]

As with 'conventional' halides, it is possible to invert of the intrinsic SMC selectivity in a given heterocycle by deploying a halide more susceptible to OA than a triflate at the intrinsically less reactive position.[11] This is illustrated for the case of 4-iodo-2-triflylpyridine **14**, which reacts at C4 (→**15**)[12] despite the C2 position being intrinsically the more reactive (see Figure 3, main article and associated text) (Scheme 4S)



Scheme 4S. *4-Iodo-2-triflylpyridine **14** undergoes SMC reactions at C4 (→**15**).*

References

1. a) G. Espino, A. Kurbangalieva and J. M. Brown, *Chem. Commun.*, 2007, 1742-1744; b) T. Kamikawa and T. Hayashi, *Tetrahedron Lett.*, 1997, **38**, 7087-7090; c) A. Jutand and A. Mosleh, *Organometallics*, 1995, **14**, 1810-1817.
2. A. M. Echavarren and J. K. Stille, *J. Am. Chem. Soc.*, 1987, **109**, 5478-5486.
3. Fu has shown that when using the precatalyst system Pd2(dba)3/P(t-Bu)3 in THF, triflates are less reactive even than aryl chlorides, see Scheme 7 and ref 41 (main manuscript).
4. F. Proutiere and F. Schoenebeck, *Angew. Chem. Int. Ed.*, 2011, **50**, 8192-8195.
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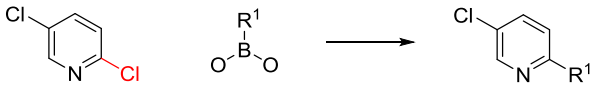
7. a) Z. Wang, B. Wang and J. Wu, *J. Comb. Chem.*, 2007, **9**, 811-817; b) Z. Wang and J. Wu, *Tetrahedron*, 2008, **64**, 1736-1742.
8. J. Y. Gauthier, C. K. Lau, C. S. Li, P. Prasit and M. Therien, WO 1998041511 A1, 1998.
9. W. Hamaguchi, O. Kaneko, K. Kato, Y. Koganemaru and R. Sekioka, WO2012108490 A1, 2012.
10. J. Wang, M. A. Seefeld and J. Luengo, *Tetrahedron Lett.*, 2011, **52**, 6346-6348.
11. R. Rossi, F. Bellina and M. Lessi, *Adv. Synth. Catal.*, 2012, **354**, 1181-1255.
12. A. Godard, J.-C. Rovera, F. Marsais, N. Plé and G. Quéguiner, *Tetrahedron*, 1992, **48**, 4123-4134.

2) Search queries for the Pfizer RKB and CAS Scifinder® databases.

All searches were carried out between July 2014 and September 2014 through the CAS Scifinder® and Pfizer RKB databases. The following example is representative of the procedure of searching and filtering the searches to the number of hits presented from each of the databases to give the data presented within Figures 3-11 (Section 4) of the manuscript:

CAS Scifinder®: Taking the example of the 2,5 dichloropyridine query (Figure 3 in the Manuscript):

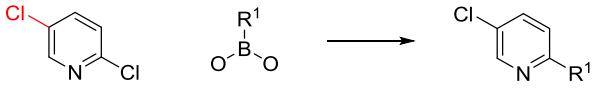


This was searched as a substructure on all atoms. R^1 was limited to heterocycle or carbocycle to remove alkenyl and sp hybridised substituents.

The “make or break” feature was used to highlight the aryl-halide bond of interest (highlighted in red here). In most cases this would lead to a large number of hits that could not easily be sorted manually.

The hits would be reduced to “One Step” – this, in many examples, would reduce the number of hits significantly – due to sequences involving the removal of boronic acid formation followed by Pd cross coupling with an additional aryl halide.

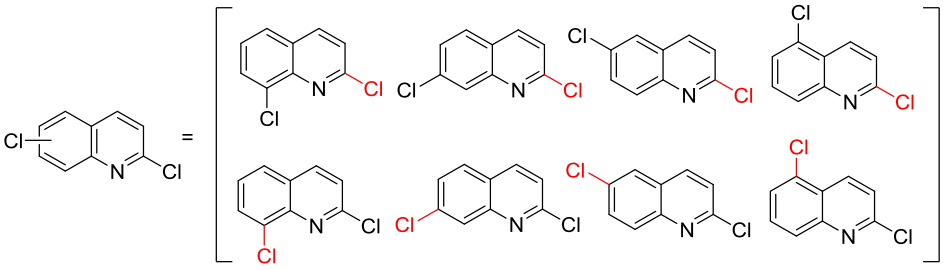
Finally, the hits would be examined individually and any unwanted hits would be removed manually. For instance; any examples including sp^3 hybridised substituents, incorrect submissions to the database or where the desired product was a very minor product.



This would be repeated for the equivalent “reverse selectivity” reaction query where the theoretically less reactive aryl-halide was highlighted with the “make or break” function.

In turn these searches would be repeated for the dibromo and diodo analogues in the same fashion.

In the case of bicyclic systems with the un-activated halide being anywhere on the all carbon ring a separate set of searches was carried out for each position on that carbon ring – for example 2,5 – 2,6 – 2,7 and 2,8 separately and then the numbers collated for both the predicted and non-predicated site-selectively. This would then be repeated for the dibromo and diiodo cases.



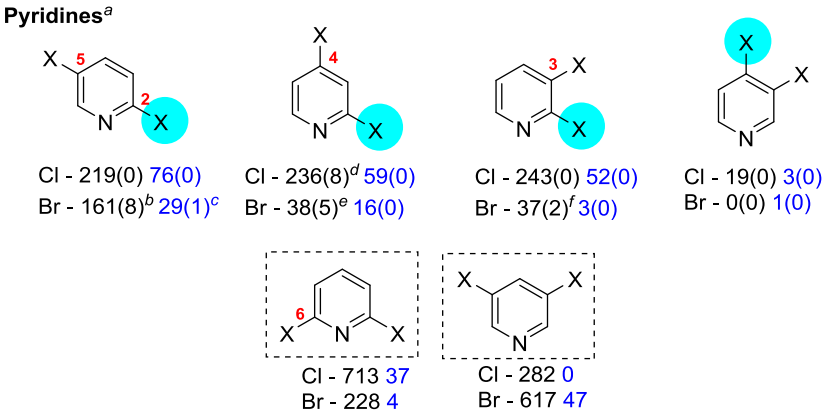
Pfizer RKB: The Pfizer database data mining was carried out in a very similar fashion. The only major differences were the following:

A lack of R group defining meant a more thorough manual filter of alkenyl/sp/sp^3 substituted was carried out but in general number of hits was lower and therefore this process was manageable.

Many ‘failed’ reactions were retrieved from the RKB and therefore rigorous checking of the yields and experimental procedures was undertaken to ensure the results were accurate and relevant.

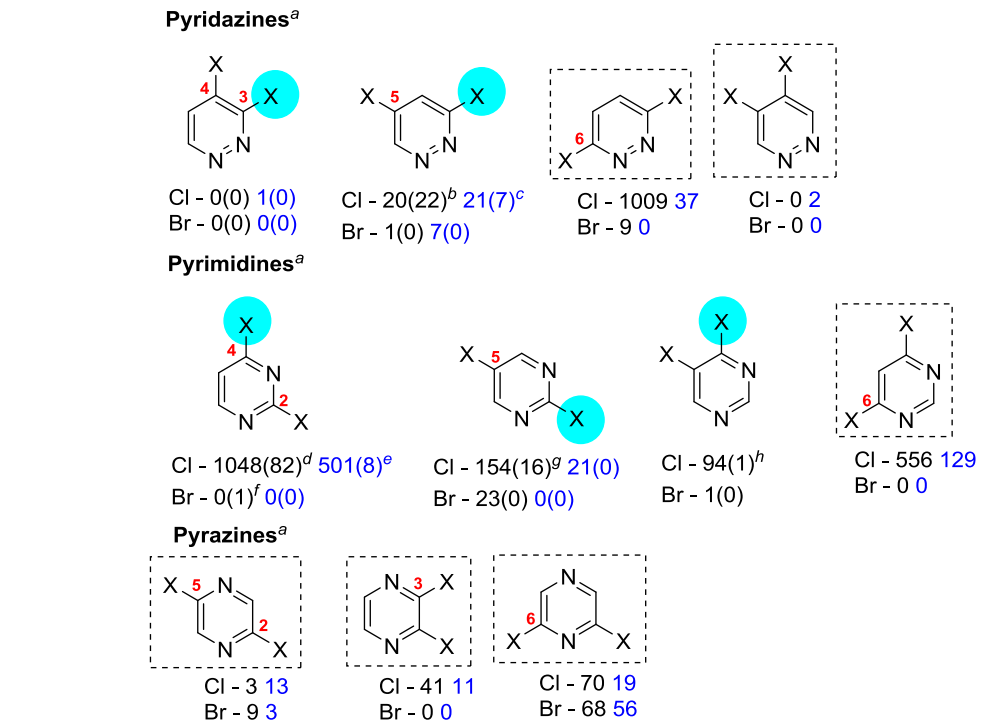
3) Breakdown of Data Mined Results:

The following figures (Figures 3S-11S) correspond to Figures 3-11 in the main manuscript, but additionally have footnotes containing additional details regarding the nature of the hits.



[a]X = Cl/Br/OTf. [b]5 x major products in patents with no details; 2 x minor isomer (<5% yields); 1 x minor isomer in patent with no details. [c]1 x 'major' product (2.3% yield). [d]5 x major products in patents with no details; 1 x major isomer in patent (28% yield); 1 x major isomer in patent (no yield); 1 x major isomer [using $PdCl_2$(dppf)]. [e]5 x minor isomers (<17% yields). [f]2 x minor isomers (<10% yields).

***Figure 3S**. Coupling outcomes for pyridines.*



[a]X = Cl/Br/OTf. [b]14 x single products and 2 x major isomers (using $Pd(OAc)_2$/dppf); 3 x single products in patents with no details; 1 x major isomer (C6 methyl, no yield); 1 x major isomer in patent (2-fluoro boronic acid, no yield); 1 x single product in patent (C4 amino). [c] 7 x single products (using $Pd(OAc)_2$/dppf). [d] 53 x single products in patents with no details; 18 x sngle products in patents (C5/C6-substituted); 6 x minor isomers (<28% yield); 5 x major isomers (<50% yields). [e] 5 x single products (C5-substituted); 3 x minor isomers. [f]1 x single product [using $Pd(PPh_3)_4$]. [g]9 x single products in patents (C4 amino); 6 x single products in patents with no details; 1 x single product in patent (tetrachloropyrimidine, no yield). [h]1 x single product in patent (tetrachloropyrimidine, no yield).

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

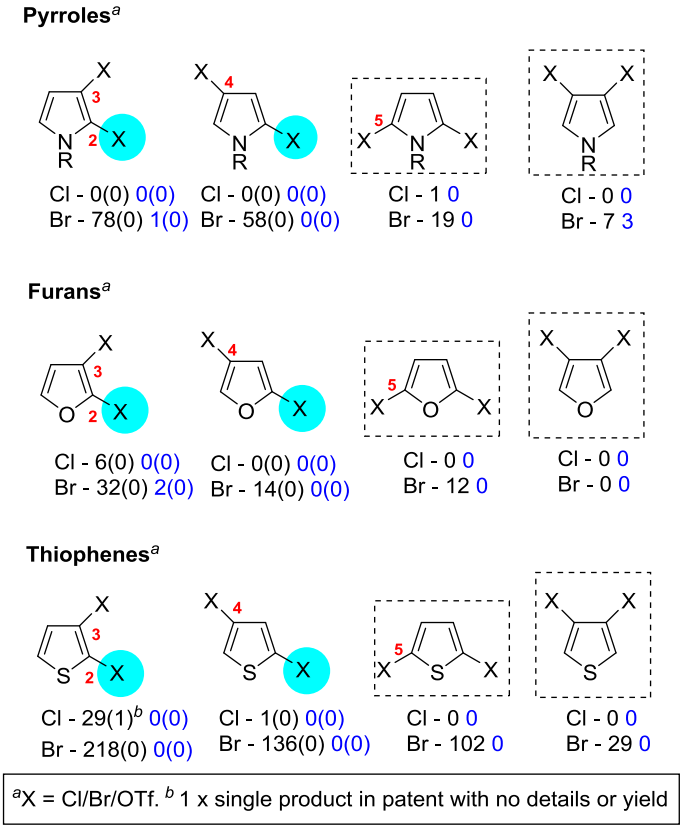


***Figure 5S**. Coupling outcomes for pyrroles, furans and thiophenes.*

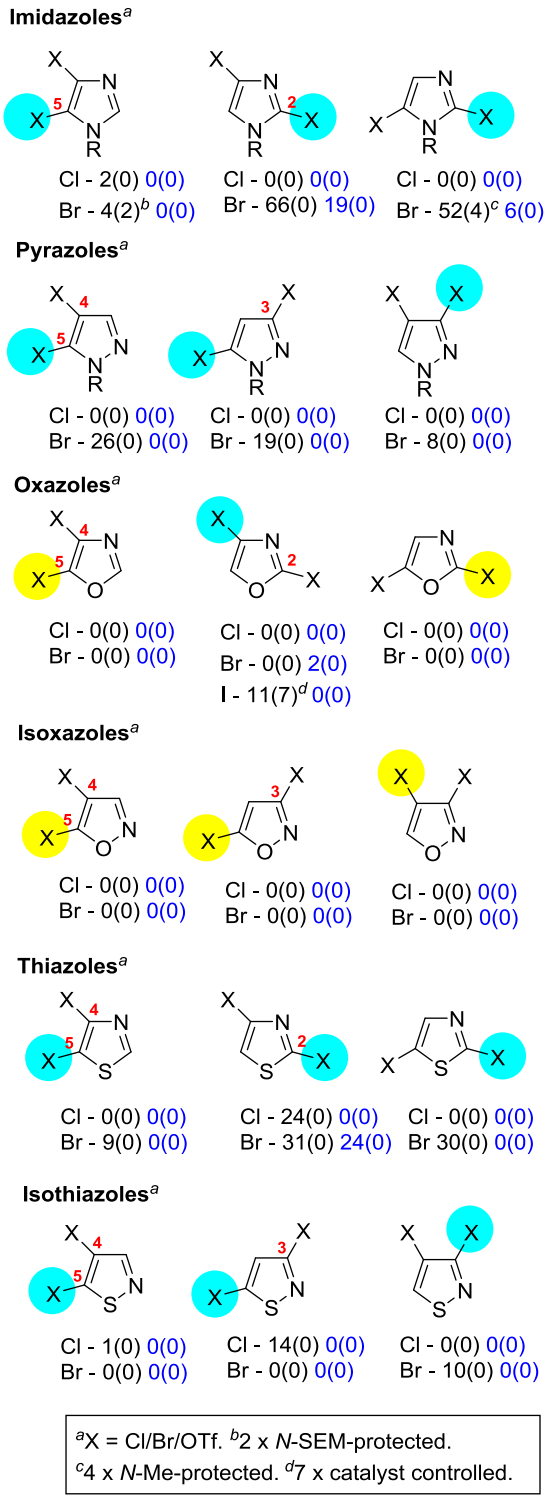
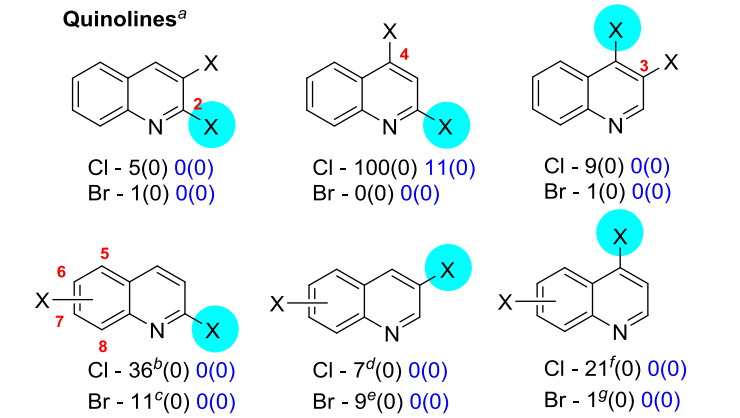
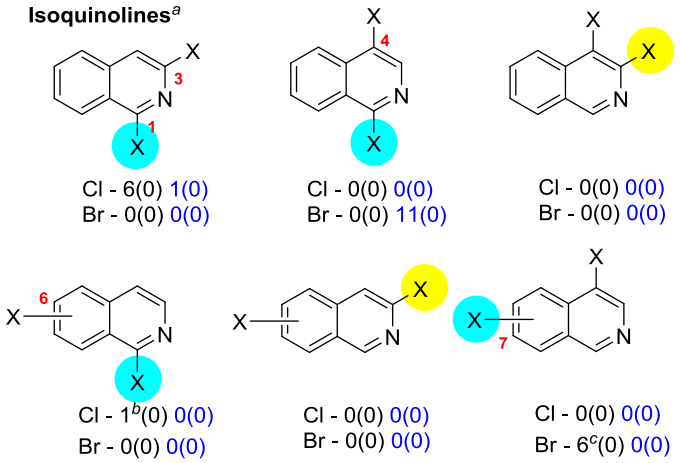


***Figure 6S**. Coupling outcomes for imidazoles, pyrazoles, (is)oxazoles and (iso)thiazoles.*



[a]X = Cl/Br/I/OTf. [b]5 x 2,5-diCl; 11 x 2,6-di-Cl; 1 x 2,7-di-Cl; 19 x 2,8-di-Cl. [c]11 x 2,8-di-Br. [d]7 x 3,7-di-Cl. [e]1 x 3,6-di-Br; 8 x 3,8-di-Br. [f]4 x 4,6-di-Cl; 9 x 4,7-di-Cl; 8 x 4,8-di-Cl. [g]1 x 4,8-di-Br.

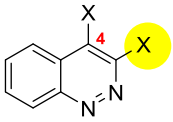
Figure 7S. *Coupling outcomes for quinolines.*



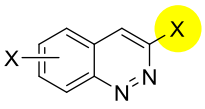
[a]X = Cl/Br/OTf. [b]1 x 1,6-di-Cl. [c]6 x 4,7-di-Br.

Figure 8S*. Coupling outcomes for isoquinolines.*

Benzopyridazines (Cinnolines & Phthalazines)[a]



Cl - 0(0) 0(0)
Br - 0(0) 0(0)



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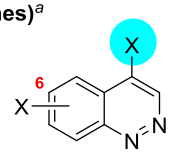

Cl - 1[b](0) 0(0)
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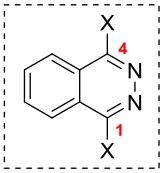
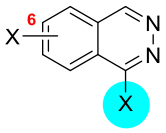
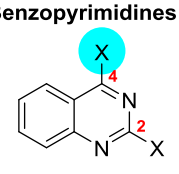


Cl - 11 11
Br - 0 0

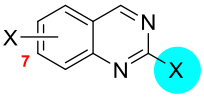


Cl - 6[c](0) 0(0)
Br - 0(0) 0(0)

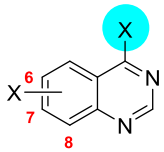
Benzopyrimidines (Quinazolines)[a]



Cl - 45(0) 45(0)
Br - 0(0) 0(0)

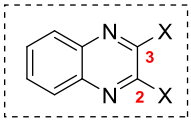


Cl - 10[d](0) 0(0)
Br - 0(0) 0(0)

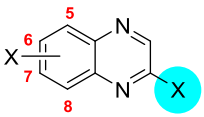


Cl - 50[e](0)
Br - 0(0) 0(0)

Benzopyrazines (Quinoxalines)[a]



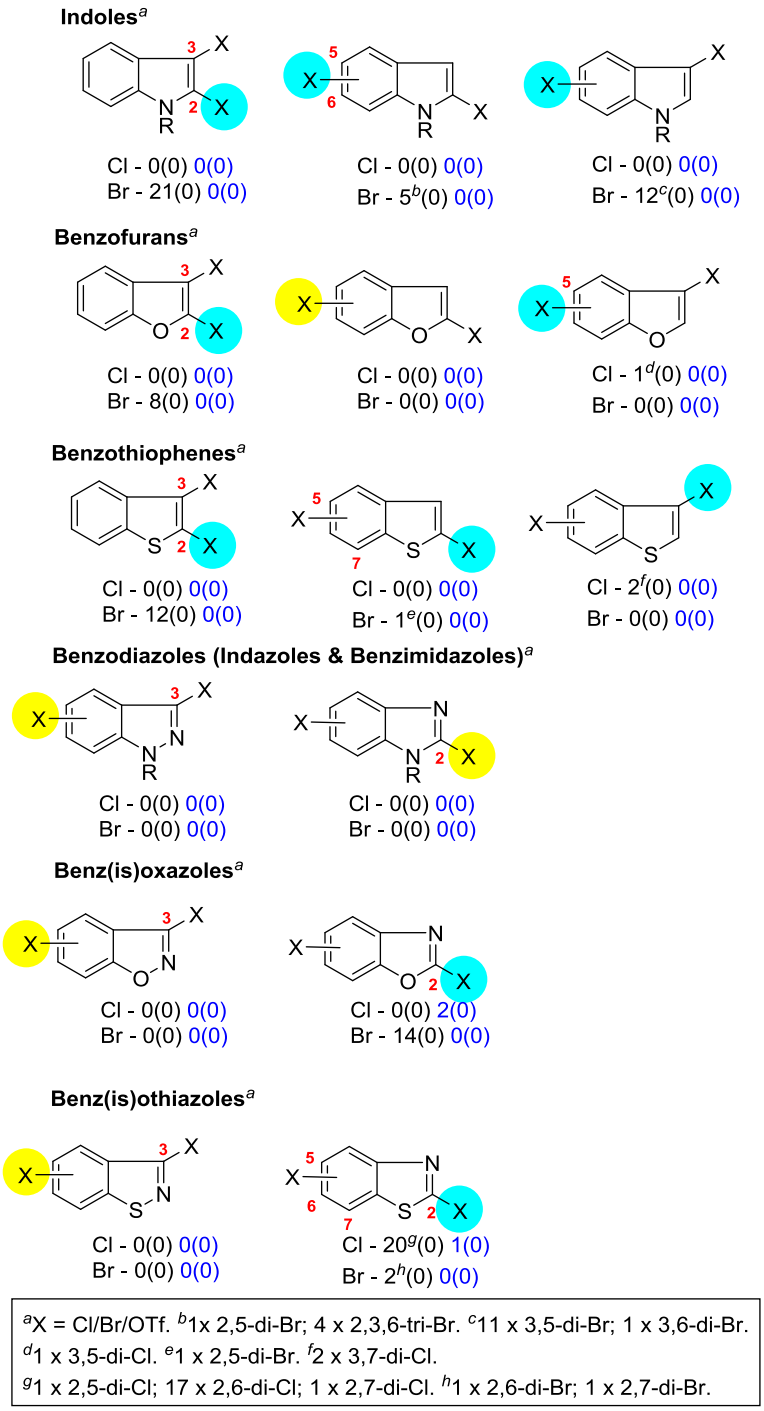
Cl - 10 0
Br - 0 0



Cl - 27[f](0) 0(0)
Br - 0(0) 0(0)

[a]X = Cl/Br/OTf. [b]1 x 4,6-di-Cl-cinnoline.
[c]6 x 1,6-di-Cl-phthalazines. [d]10 x 2,7-di-Cl
[e]3 x 4,6-di-Cl; 34 x 2,4,6-tri-Cl; 9 x 4,7-di-Cl; 4 x 4,8-di-Cl.
[f]2 x 2,5-di-Cl; 20 x 2,6-di-Cl; 1 x 2,6,7-tri-Cl; 4 x 2,8-di-Cl.

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



[a]X = Cl/Br/OTf. [b]1x 2,5-di-Br; 4 x 2,3,6-tri-Br. [c]11 x 3,5-di-Br; 1 x 3,6-di-Br.
[d]1 x 3,5-di-Cl. [e]1 x 2,5-di-Br. [f]2 x 3,7-di-Cl.
[g]1 x 2,5-di-Cl; 17 x 2,6-di-Cl; 1 x 2,7-di-Cl. [h]1 x 2,6-di-Br; 1 x 2,7-di-Br.

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

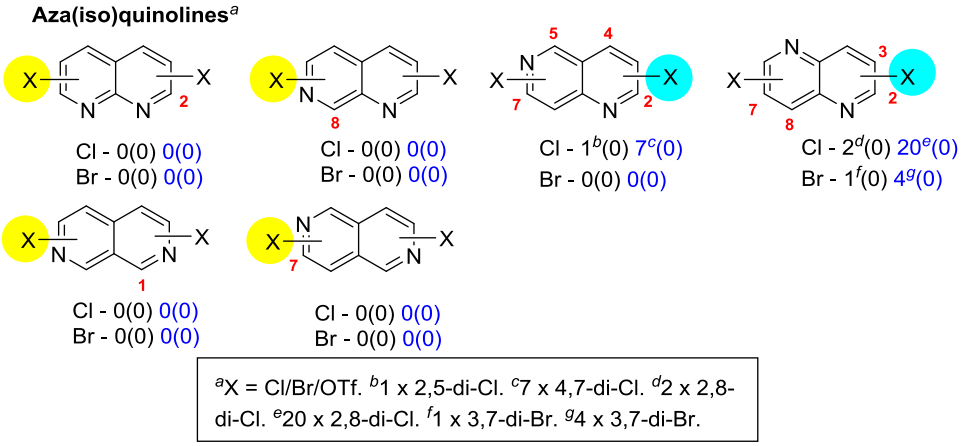


***Figure11S**. Coupling outcomes for azaquinolines and azaisoquinolines.*