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Catalyst controlled regioselective Suzuki cross-coupling of 2-(4-bromophenyl)-5-chloropyrazine

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ABSTRACT

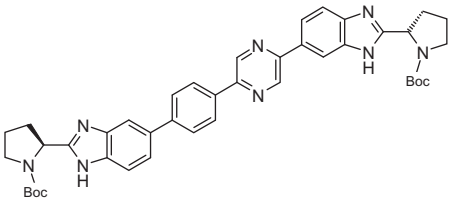
The Suzuki cross-coupling between 2-(4-bromophenyl)-5-chloropyrazine and a range of aryl boronic acids has been investigated. The regioselectivity of the reaction can be switched between the aryl bromide and pyrazinyl chloride positions by changing the ligand associated with the palladium catalyst. Xantphos has shown excellent selectivity for the pyrazinyl chloride, with most other ligands showing preferential selectivity for the aryl bromide.

The palladium-catalysed cross-coupling reaction of organoboron compounds with organic halides and triflates (the Suzuki–Miyaura reaction), is one of the most widely used reactions for the formation of carbon–carbon bonds. First published by Akira Suzuki in 1979, the reaction is firmly established within the pharmaceutical industry as the method of choice for the preparation of biaryl compounds.[1] Whilst chemoselective discrimination between halides and pseudohalides is relatively common in the Suzuki–Miyaura literature,[2,3] examples where the site of reactivity can be efficiently switched by changing the ligand, are much rarer. Herein we report the results of the chemoselective Suzuki–Miyaura cross coupling reaction between 2-(4-bromophenyl)-5-chloropyrazine and a range of boronic esters and acids. The position of reaction can be efficiently discriminated between the bromophenyl and chloropyrazinyl sites by simply changing the ligand.

During the course of alternative route investigations for a series of antiviral targets, the synthesis of a key triaryl intermediate **3** was required. It was hoped that **3** could be accessed via a chemoselective Suzuki–Miyaura cross-coupling between 2-(4-bromophenyl)-5-chloropyrazine (**1**) and the benzimidazole boronic ester **2** (Scheme 1). As an initial starting point, two catalyst systems which had given good results on related substrates were investigated namely Pd(dppf)Cl $_2$·DCM and Pd(t-Bu_3P)$_2$.

The regioselectivity observed for these two systems was intriguing. Using Pd(dppf)Cl_2·DCM, the ratio of products was 9:1 favouring regioisomer **3** over **4**, with an appreciable amount of the over-reaction impurity, **5**. However, with Pd(t-Bu_3P)$_2$, the ratio switched to 1:20, again with appreciable levels of over-reaction impurity **5**. These somewhat surprising results prompted us to further investigate this coupling reaction.

A preliminary investigation of the Suzuki–Miyaura coupling of **1** with **2** was initiated by examining a variety of pre-ligated palladium catalysts supplied by Johnson Matthey. The aim was to afford **3** in high yields whilst minimising **4** and the over-reaction impurity **5**. Several bases and solvents were also studied and the results are summarised in Table 1. Whereas high conversions (>65%) to **4** were generally observed with most electron-rich catalysts, entries 5–10, gratifyingly, high conversion into desired compound **3**, with negligible formation of regioisomer **4** or over reaction product **5**, was obtained using the wide bite angle or *trans*-spanning diphosphine, Pd(Xantphos)Cl_2 with Na_2CO_3 as the base and 1,4-dioxane as the solvent (entry 1). Compared with Pd(d*t*bpf)Cl_2, entry 8, the reaction goes with a complete switch in reactivity from the aryl bromide to the chloropyrazine tail. Interestingly both Pd(dppf)Cl_2 and Pd(PPh_3)$_4$ showed encouraging chemoselectively for the chloropyrazine, but suffered over-reaction to **5**. However, the screening data illustrated that the only catalyst to give high chemoselectivity for the chloropyrazine position was in fact Pd(Xantphos)Cl_2.



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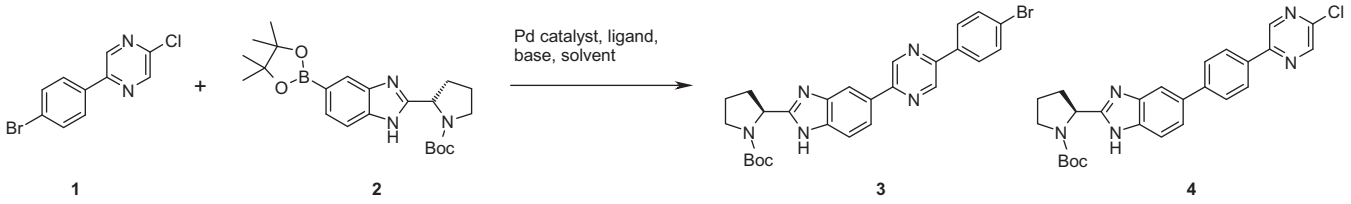


Scheme 1.

Table 1
Palladium catalysed Suzuki–Miyaura screen performed in a range of solvents at 80 °C for 16 h

Entry	Catalyst	Base	Solvent	% **3**[a]	% **4**[a]	% **5**[a]
1	Pd(Xantphos)Cl_2	Na_2CO_3	1,4-Dioxane	83	1	3
2	Pd(dppf)Cl_2	Cs_2CO_3	MeCN	48	6	23
3	Pd(PPh_3)$_4$	Cs_2CO_3	1,4-Dioxane	32	21	23
4	Pd(XPhos)Cl[b]	Na_2CO_3	MeCN	3	6	1
5	Pd(amphos)Cl_2	K_3PO_4	1,4-Dioxane	0	69	5
6	Pd(*t*-Bu_3P)$_2$	Na_2CO_3	1,4-,1,4-Dioxane	0	74	10
7	$PdCl_2$[P(*o*-Tol)$_3$]$_2$	K_3PO_4	1,4-Dioxane	0	77	9
8	Pd(dtbpf)Cl_2	Na_2CO_3	MeCN	0	82	6
9	Pd(QPhos)$_2$	Na_2CO_3	1,4-Dioxane	0	87	6
10	cataCXium® C	Cs_2CO_3	1,4-Dioxane	0	88	5

[a] Conversion by HPLC.
[b] High levels of protodeboration observed.

Table 2
Palladium-catalysed Suzuki–Miyaura screen performed in 1,4-dioxane/water, with Na_2CO_3 as the base and Pd(OAc)$_2$ as the precatalyst, 80 °C, for 24 h

Ligand	Bite angle (°)	% **3**[a]	% **4**[a]	% **5**[a]
6[b]	108	83	1	3
7[c]	130	5	2	1
8	111	45	14	19
9	107	18	22	17
10	108	25	20	18

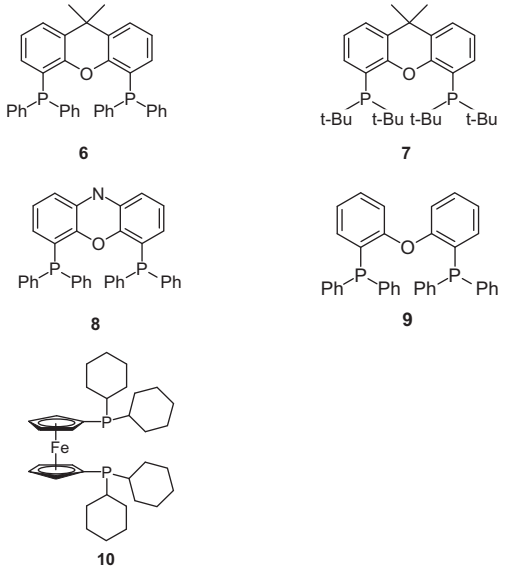
[a] Conversion by HPLC.
[b] Preformed Johnson Matthey catalyst used.
[c] High levels of chloropyrazine remained.

Reports in the literature of chemoselective cross-couplings using a Xantphos (**6**) complex are infrequent. In the palladium catalysed carbonylative Sonogashira reaction a Xantphos ligand was used to selectively couple an aryl triflate with phenyl acetylene in the presence of an aryl chloride.[4] Furthermore, in the amination of 5-bromo-2-chloropyridine a palladium-Xantphos complex is reported to give 5-amino-2-chloropyridine as the major product.[5] More recently a chemoselective alkyl–alkyl Suzuki–Miyaura coupling utilising an iron–Xantphos complex has been illustrated.[6] Strotman et al. also reported the unique properties of a palladium-Xantphos catalyst in Suzuki coupling of 2,4-diiodooxazole.[7] As in our example, the Xantphos ligand was shown to mediate highly selective coupling where alternative ligands tested, PPh_3, X-Phos and dppf, gave large amounts of the unwanted bis-arylated product from over-reaction. This literature report, coupled with the success of the Pd(Xantphos)Cl_2 catalyst in our system, encouraged us to further probe into the effect of ligands on the regioselectivity of this Suzuki reaction.

A range of ligands was chosen based on the ligand type with a bite angle similar to that of Xantphos. To investigate the influence of the electronic properties and bite angle, Nixantphos **8** was chosen as a good comparison. DPEPhos **9** was selected to assess the donating properties of the oxygen, and dicyclohexylphosphino ferrocene **10** to investigate a different structural moiety with a similar bite angle. *t*-Bu-Xantphos **7** was also chosen to investigate the effect of increased steric bulk around the chelating phosphines.

The results in Table 2 seemingly indicate no obvious correlation between regioselectivity and bite angle, when comparing ligand **6** to either **9** or **10**. Alternative Xantphos type ligands **7**–**9** resulted in reactions with a reduction in regioselective control, giving higher levels of both **4** and **5**. Nixantphos **8** intriguingly gave increased levels of the desired product **3** compared with DPEPhos **9**, suggesting that a rigid catalyst structure is preferred. However, Xantphos **6** was the only catalyst system to afford **3** with high conversions illustrating the unique properties of this catalyst system.

The most chemoselective catalyst systems for both the chloropyrazine (Xantphos) and bromophenyl positions (dtbpf) were selected for scale up (see Supplementary data for detailed procedures). Gratifyingly, these reactions performed very similarly to the screen leads. The Xantphos reaction gave 1.7% of the regioisomer **4**, which was reduced to none detected after crystallisation, with an isolated yield of **3** at 76%. The d*t*bpf reaction resulted in a 75% yield with no regioisomer detected after crystallisation.



To study the general applicability of the catalytic control for the regioselective coupling we investigated a range of alternative arylboronic acids and esters with 2-(4-bromophenyl)-5-chloropyrazine (1). As illustrated in Table 3, Pd(Xantphos)Cl_2 was able to catalyse the coupling of a range of arylboronic acids at the chloropyrazine position, to give substituted biaryl products in excellent yields. Conversely, Pd(d*t*bpf)Cl_2 switched the selectivity to the