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# Suzuki–Miyaura cross-coupling of unprotected *ortho*-bromoanilines with benzyl, alkyl, aryl, alkenyl and heteroaromatic boronic esters†

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A Suzuki–Miyaura cross-coupling reaction was developed on unprotected *ortho*-bromoanilines. This operationally simple reaction was developed for the diversification of glucocorticoid receptor modulators (GRMs), showed compatibility to various boronic esters featuring unique functionalities, and was demonstrated on a gram scale.

The widely used Suzuki–Miyaura cross-coupling reaction employs the use of a palladium catalyst to generate carbon–carbon bonds between an organohalide or triflate and an organoboron nucleophile.<sup>1</sup> Its wide use can be attributed to its mild reaction conditions, low toxicity, and commercial availability of starting materials.<sup>2</sup> Of note, is the application towards natural product synthesis, pharmaceuticals, and fine chemical industries.<sup>3</sup> *Ortho*-substituted anilines are a key structural element in several pharmacologically active compounds. Examples include inhibitors of fatty acid amide hydrolase (FAAH), phosphodiesterase-4 (PDE4), compounds for the prevention of nonalcoholic fatty liver disease (NAFLD), and angiotensin II receptor antagonists (Fig. 1a).<sup>4</sup> Although the Suzuki–Miyaura reaction has been widely utilized, substrates with unprotected *ortho*-anilines are less common. Particularly challenging are  $sp^2$ – $sp^3$  couplings. And thus, the development of a cross-coupling method focusing on unprotected *ortho*-bromoanilines is of wide interest to the broader chemistry community. Reported methods for this type of coupling typically require protection of the free amine.<sup>5</sup> Alternatively, methods exist with direct reactivity on various 2-haloanilines but with limitations on the substrates investigated and functionalities that can be tolerated.<sup>6</sup> Our work focuses on expanding the scope of the reactivity of *ortho*-bromoanilines, with a focus on developing an operationally simple method (Fig. 1b).

As a part of a program to identify glucocorticoid receptor modulators (GRMs),<sup>7</sup> the Suzuki cross-coupling of **1a** was attempted as the diversification step for the preparation of a compound library.<sup>8</sup> Using Pd(dppf)Cl<sub>2</sub> as the catalyst with

K<sub>2</sub>CO<sub>3</sub> as base with boronate **2a** in 10 : 1 dioxane/H<sub>2</sub>O at 90 °C, desired product **3a** was isolated in 11% yield (Fig. 2). The low isolated yield was consistent with conversion by HPLC.

Since this result suggested a lack of catalyst turnover, a high throughput screen was conducted using ChemBeads<sup>9</sup> to identify an optimal catalyst/ligand/base system with the goal of improving the yield. The best conditions identified from the

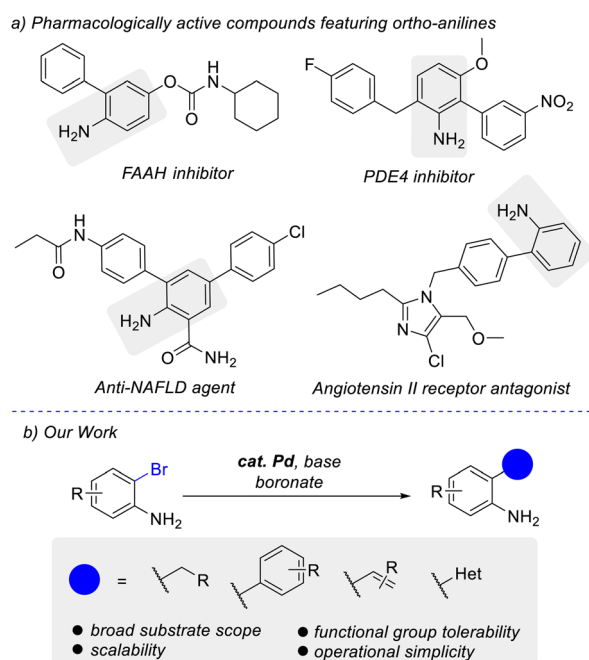


Fig. 1 (a) Examples of pharmacologically active compounds containing *ortho*-substituted anilines. (b) Our work on coupling unprotected *ortho*-bromoanilines with benzyl, alkyl, aryl, alkenyl and heteroaromatic boronic esters.

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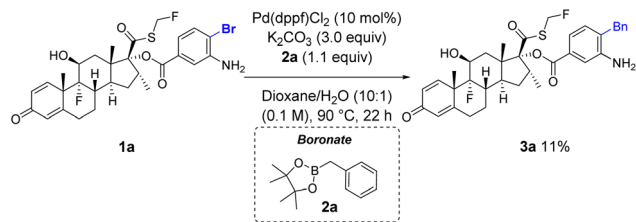
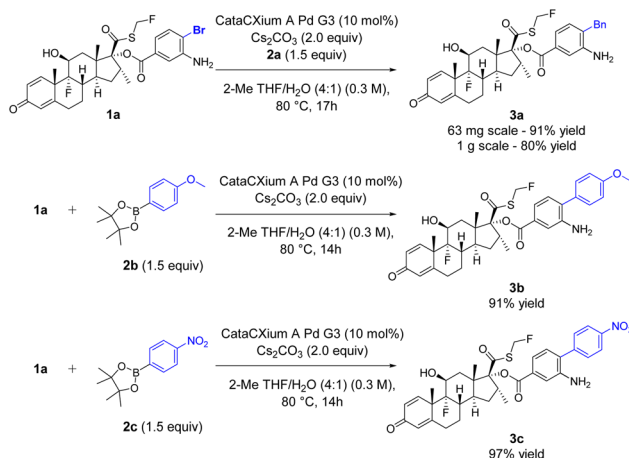



Fig. 2 Initial attempt with GRM substrate.

screen used the preformed CataCXium A palladacycle<sup>10</sup> with Cs<sub>2</sub>CO<sub>3</sub> as the base in dioxane/H<sub>2</sub>O at 80 °C. These results were repeated on a 0.1 mmol scale at a 0.1 M concentration of **1a** with 2 equiv. of boronate to give 51% yield of the desired product by NMR (Table 1, entry 1). Switching the solvent from dioxane to EtOAc or PhMe did not give any appreciable increases in yield (entries 2 and 3). The biggest increase in yield came from switching to 2-MeTHF as the solvent. The product was isolated in 95% yield (entry 4). To confirm the unique reactivity of the CataCXium A palladacycle, these optimized conditions were tested using several additional catalysts, all yielding little to no product (entries 5–10). Decreasing the catalyst loading to 5 mol% also had a detrimental effect on the yield (entry 11). Decreasing the boronate loading to 1.5 equiv. and increasing the reaction concentration to 0.3 M gave 91% yield. We chose to move forward with these conditions since they would be most amenable to scaling up the reaction.

The final optimized conditions were tested on a gram scale on substrate **1a** with the desired product obtained in 80% yield. We also applied these conditions to two analogs, one bearing an electron rich aromatic ring and the other bearing an electron



<sup>1</sup>All reactions were carried out under an atmosphere of N<sub>2</sub> using 0.1 mmol of starting material, unless noted otherwise. Yields reflect isolated yield.

Fig. 3 Scale-up and limited scope of GRM substrate<sup>1</sup>.

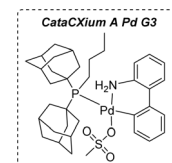
deficient aromatic ring. Our optimized conditions produced both products in excellent isolated yields (Fig. 3).

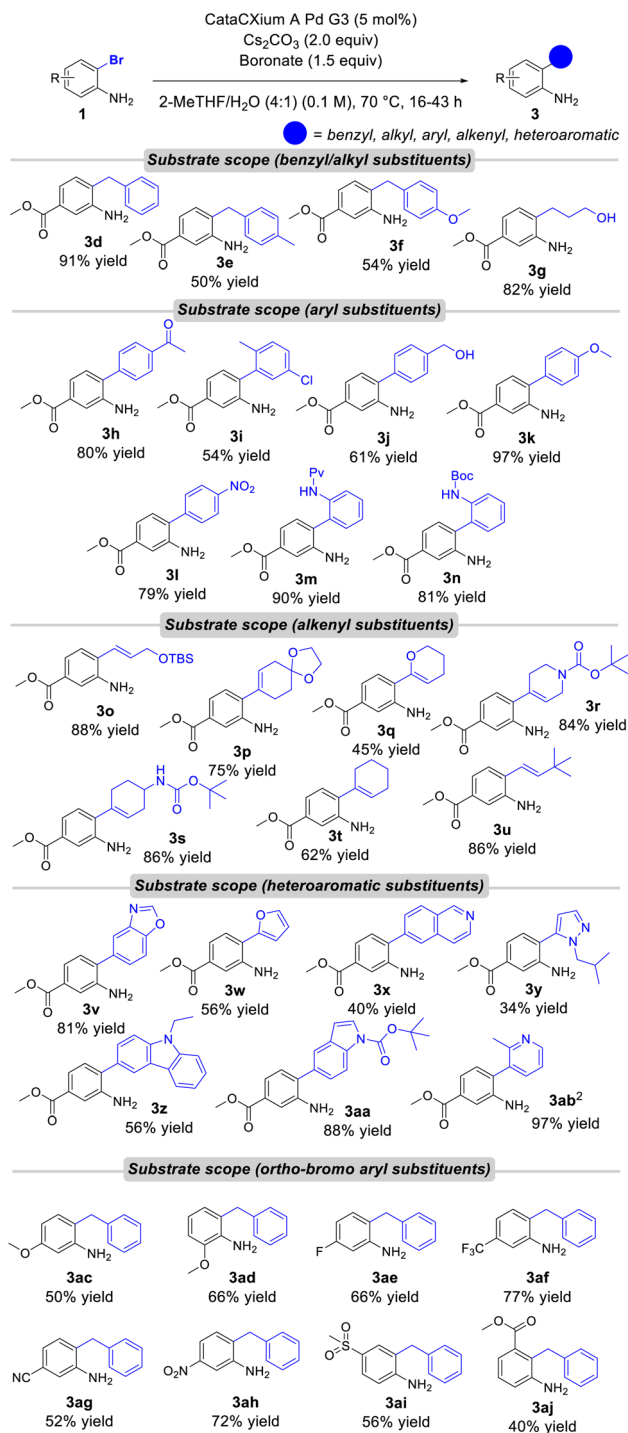
To further explore our reaction, we chose to continue with a more generic substrate (**1**). To accommodate a wide variety of substrates, minor modifications were made to the optimized conditions including decreasing the catalyst loading to 5 mol%, decreasing the temperature to 70 °C and decreasing the concentration to 0.1 M (Fig. 4). With these modified conditions, substrate **3d**, was isolated in 91% yield on a 0.5 mmol scale. Boronates containing electronically neutral and electron-donating substituents were compatible with these conditions and isolated in synthetically useful yields. An alkyl boronate with unprotected alcohol was also amenable in the reaction

Table 1 Reaction optimization<sup>a</sup>

Entry	Catalyst	Solvent (conc.)	2a equiv.	NMR yield <sup>b</sup>
1	CataCXium A Pd G3	Dioxanes (0.1)	2	51%
2	CataCXium A Pd G3	EtOAc (0.1)	2	56%
3	CataCXium A Pd G3	PhMe (0.1)	2	56%
4	CataCXium A Pd G3	2-MeTHF (0.1)	2	95% <sup>c</sup>
5	Pd(Amphos)Cl <sub>2</sub>	2-MeTHF (0.1)	2	22%
6	SPhos Pd G4	2-MeTHF (0.1)	2	0%
7	Pd(OAc) <sub>2</sub>	2-MeTHF (0.1)	2	0%
8	Pd(dbe) <sub>3</sub>	2-MeTHF (0.1)	2	0%
9	XPhos Pd G3	2-MeTHF (0.1)	2	0%
10	(PPh <sub>3</sub> ) <sub>2</sub> PdCl <sub>2</sub>	2-MeTHF (0.1)	2	46%
11 <sup>d</sup>	CataCXium A Pd G3	2-MeTHF (0.1)	2	42%
12	CataCXium A Pd G3	2-MeTHF (0.1)	1.5	91% <sup>c</sup>

<sup>a</sup> All reactions were carried out under an atmosphere of N<sub>2</sub> using 0.1 mmol of starting material. <sup>b</sup> NMR yields were calculated on the crude reaction mixtures, using 0.05 mmol of mesitylene as an internal standard. <sup>c</sup> Isolated yield. <sup>d</sup> 5 mol% catalyst used.





<sup>1</sup>Unless specified otherwise, reactions were carried out under an atmosphere of N<sub>2</sub> using 0.5 mmol of the *o*-bromoaniline for a duration of 16-43h. Yields reflect isolated yield. <sup>2</sup>Reaction was run using 0.3 mmol of *o*-bromoaniline with 10 mol% catalyst, 2.0 equiv. of boronate at 80 °C.

Fig. 4 Substrate scope<sup>1</sup>.

giving **3g** in 82% yield, however sterically hindered alkyl boronates isopropylboronic acid pinacol ester and cyclohexylboronic acid pinacol ester did not give the desired product. Arylated substrates (**3h–3n**) were compatible with these conditions with the products isolated in up to 97% yield. Ketone containing

compound **3h** reacted smoothly in 80% yield. Aryl chloride and free alcohol substrates reacted in moderate yields (**3i–3j**). Both electron-rich and electron-poor aryl boronates afforded the coupled products in high yield (**3k–3l**). The nitrated substrate **3l** precipitated out of solution after completion of the reaction and simple filtration led to the isolation of pure product without the need for chromatographic purification. Substrates **3m** and **3n** provide differentially protected anilines to aid in downstream synthesis. Alkenyl substrates also reacted smoothly giving good yields for the coupled products **3o–3u**. The reaction was tolerant of benzoxazole, furan, isoquinoline, pyrazole, carbazole, indole and pyridine motifs (**3v–3ab**). *Ortho*-bromoanilines with different substituents were also tested. Methoxy and fluorinated analogs **3ac–3af** were produced in good yields. Alternative electron withdrawing groups such as nitrile, nitro and sulfone were also tolerated in the reaction (**3ag–3ai**). Finally, the reaction was also successful in coupling an *ortho/ortho'* substituted analog giving product **3aj** in 40% yield.

In conclusion, we identified CataXCium A Pd G3 as a uniquely effective catalyst system for Suzuki–Miyaura cross-couplings on GRM substrate **1a**. This method facilitates coupling of benzyl, alkyl, aryl, alkenyl, and heteroaromatic substituents on model substrate **1**. Diverse functional group tolerability has been exemplified with support of electron-rich and electron-poor groups, halogenated aryls, protected and unprotected amines, and various heterocycles.

## Data availability

The data supporting this article have been included as part of the ESI.†

## Conflicts of interest

There are no conflicts to declare.

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