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

Alexandra E. Lubaev,[a] Christopher C. Marvin,[b] Amanda W. Dombrowski[b] and Zafar Qureshi *[b]

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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.[1] Its wide use can be attributed to its mild reaction conditions, low toxicity, and commercial availability of starting materials.[2] Of note, is the application towards natural product synthesis, pharmaceuticals, and fine chemical industries.[3] *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).[4] 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.[5] Alternatively, methods exist with direct reactivity on various 2-haloanilines but with limitations on the substrates investigated and functionalities that can be tolerated.[6] 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),[7] the Suzuki cross-coupling of **1a** was attempted as the diversification step for the preparation of a compound library.[8] Using $Pd(dppf)Cl_2$ as the catalyst with K_2CO_3 as base with boronate **2a** in 10 : 1 dioxane/H_2O 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[9] to identify an optimal catalyst/ligand/base system with the goal of improving the yield. The best conditions identified from the

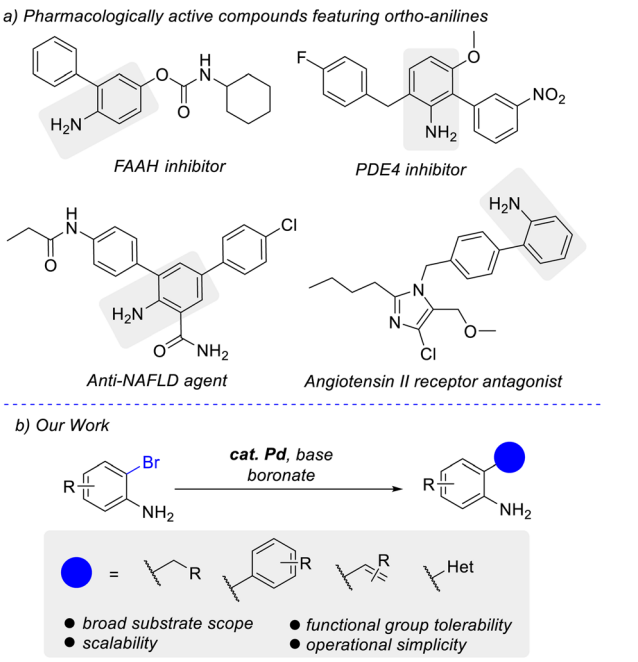

Fig. 1 (a) Examples of pharmacologically active compounds containing *ortho*-substituted anilines. (b) Our work on coupling unprotected *ortho*-bromoanilines with benzyl, alkyl, aryl, alkenyl and heteroaromatic boronic esters.

[a]*Department of Chemistry and Biochemistry, Baylor University, Waco, Texas, 76706, USA*

[b]*AbbVie, Inc., 1 N. Waukegan Road, North Chicago, Illinois, 60064, USA. E-mail: zafar.qureshi@abbvie.com*

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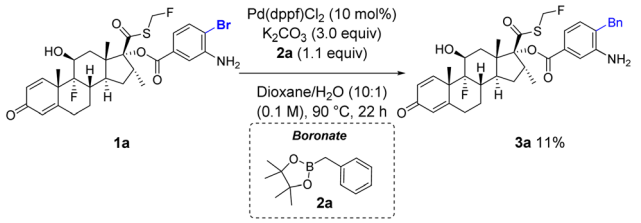
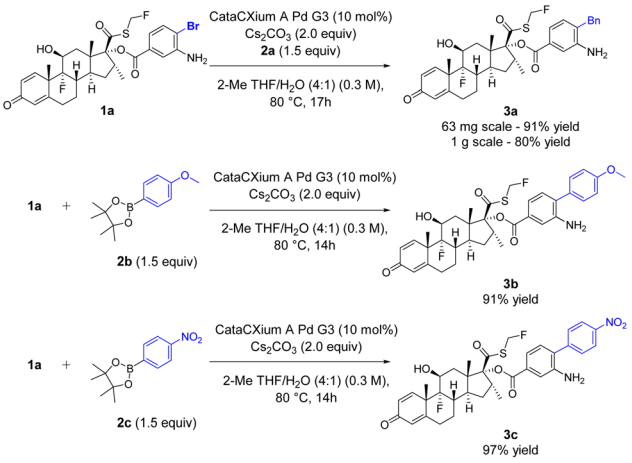


Fig. 2 Initial attempt with GRM substrate.

screen used the preformed CataCXium A palladacycle[10] with Cs_2CO_3 as the base in dioxane/H_2O 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 deficient aromatic ring. Our optimized conditions produced both products in excellent isolated yields (Fig. 3).

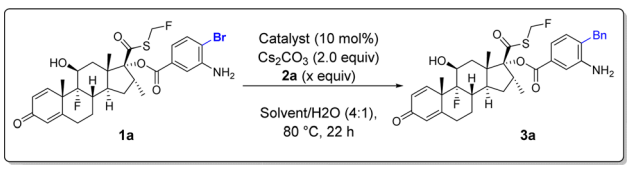


[1]All reactions were carried out under an atmosphere of N_2 using 0.1 mmol of starting material, unless noted otherwise. Yields reflect isolated yield.

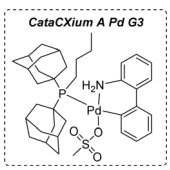
Fig. 3 Scale-up and limited scope of GRM substrate[1].

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

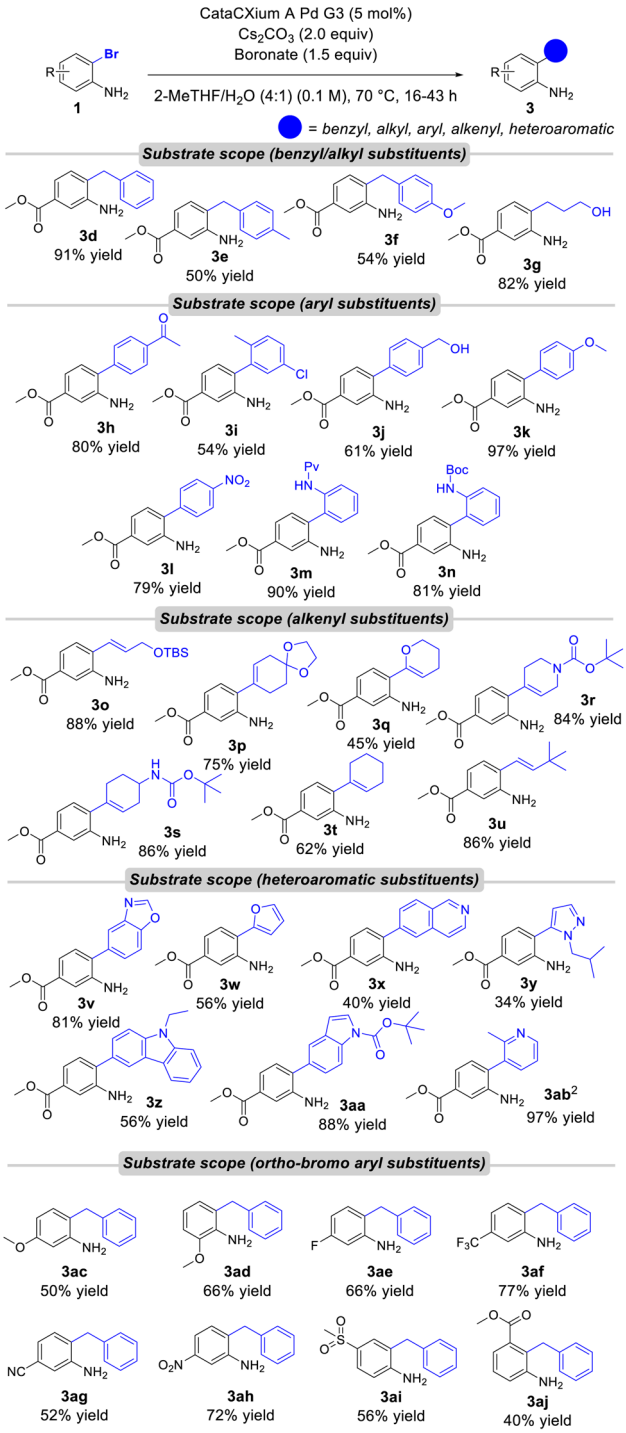
Table 1 Reaction optimization[a]



Entry	Catalyst	Solvent (conc.)	**2a** equiv.	NMR yield[b]
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%[c]
5	$Pd(Amphos)Cl_2$	2-MeTHF (0.1)	2	22%
6	SPhos Pd G4	2-MeTHF (0.1)	2	0%
7	$Pd(OAc)_2$	2-MeTHF (0.1)	2	0%
8	$Pd(dbe)_3$	2-MeTHF (0.1)	2	0%
9	XPhos Pd G3	2-MeTHF (0.1)	2	0%
10	$(PPh_3)_2PdCl_2$	2-MeTHF (0.1)	2	46%
11[d]	CataCXium A Pd G3	2-MeTHF (0.1)	2	42%
12	**CataCXium A Pd G3**	**2-MeTHF (0.1)**	**1.5**	**91%[c]**



[a] All reactions were carried out under an atmosphere of N2 using 0.1 mmol of starting material. [b] NMR yields were calculated on the crude reaction mixtures, using 0.05 mmol of mesitylene as an internal standard. [c] Isolated yield. [d] 5 mol% catalyst used.



[1]Unless specified otherwise, reactions were carried out under an atmosphere of N_2 using 0.5 mmol of the *o*-bromoaniline for a duration of 16-43h. Yields reflect isolated yield. [2]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[1].

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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