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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 carboncarbon 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<sup>2</sup>-sp<sup>3</sup> couplings. And thus, the development of a cross-coupling method focusing on unprotected orthobromoanilines 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.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),<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

 $K_2CO_3$  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<sup>9</sup> to identify an optimal catalyst/ligand/base system with the goal of improving the yield. The best conditions identified from the

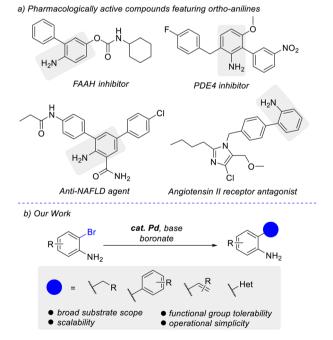


Fig. 1 (a) Examples of pharmacologically active compounds containing *ortho*-substituted anilines. (b) Our work on coupling unprotected *ortho*-bromoanilines with benzyl, alkyl, aryl, alkenyl and heteroaromatic boronic esters.

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Pd(dppf)Cl<sub>2</sub> (10 mol%)

K<sub>2</sub>CO<sub>3</sub> (3.0 equiv)

2a (1.1 equiv)

Dioxane/H<sub>2</sub>O (10:1)

(0.1 M), 90 °C, 22 h

Boronate

3a 11%

Fig. 2 Initial attempt with GRM substrate.

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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

 $^{1}$ 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<sup>1</sup>.

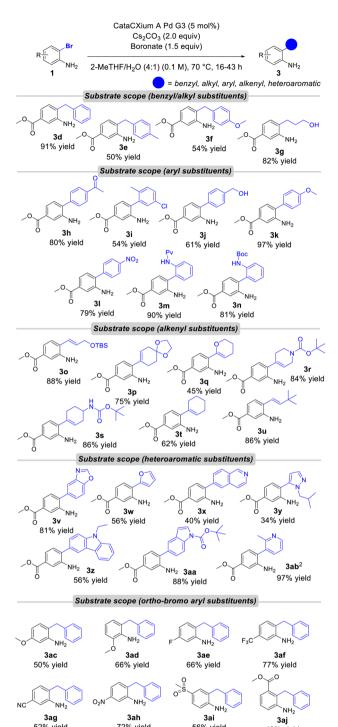
deficient aromatic ring. Our optimized conditions produced both products in excellent isolated yields (Fig. 3).

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%                    | CataCXium A Pd G3  |
| 4      | CataCXium A Pd G3                                  | 2-MeTHF (0.1)   | 2         | $95\%^c$               |                    |
| 5      | Pd(Amphos)Cl <sub>2</sub>                          | 2-MeTHF (0.1)   | 2         | 22%                    |                    |
| 6      | SPhos Pd G4  | 2-MeTHF (0.1)   | 2         | 0%                     | P H <sub>2</sub> N |
| 7      | Pd(OAc) <sub>2</sub>                               | 2-MeTHF (0.1)   | 2         | 0%                     | Do Po              |
| 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%                    |                    |
| $11^d$ | 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>       |                    |

 $<sup>^</sup>a$  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.



 $^1\text{Unless}$  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.  $^2\text{Reaction}$  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-3i). 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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#### References

1 (*a*) K. T. Hylland, S. Øien-Ødegaard and M. Tilset, The Suzuki-Miyaura Cross-Coupling as the Key Step in the Synthesis of 2-Aminobiphenyls and 2,2'-Diaminobiphenyls: Application in the Synthesis of Schiff Base Complexes of

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Zn, Eur. J. Org Chem., 2020, 27, 4208–4226; (b) J. C. H. Lee and D. G. Hall In Metal-Catalyzed Cross-Coupling Reactions and More, ed. A. de Meijere, S. Bräse and M. Oestreich, Wiley, New York, 2013, pp. 65–132; (c) N. Miyaura, T. Yanagi and A. Suzuki, The Palladium-Catalyzed Cross-Coupling of Phenylboronic Acid with Haloarenes in the Presence of Bases, Synth. Commun., 1981, 11, 513–519.

- 2 (a) A. T. K. Koshvandi, M. M. Heravi and T. Momeni, Current Applications of Suzuki-Miyaura Coupling Re-action in The Total Synthesis of Natural Products: An Update, *Appl. Organomet. Chem.*, 2018, 32(3), e4210; (b) B. C. Barnard, Palladium-Catalysed C-C Coupling: Then and Now, *Platin. Met. Rev.*, 2008, 52(1), 38–45; (c) A. Suzuki, Cross-Coupling Reactions via Organoboranes, *J. Organomet. Chem.*, 2002, 653(1–2), 83–90.
- 3 (*a*) I. Maluenda and O. Navarro, Recent Developments in the Suzuki-Miyaura Reaction: 2010–2014, *Molecules*, 2015, **20**, 7528–7557; (*b*) F. Bellina, A. Carpita and R. Rossi, Palladium Catalysts for the Suzuki Cross-Coupling Reaction: An Overview of Recent Advances, *Synthesis*, 2004, 2419–2440.
- 4 (a) F. Vacondio, C. Silva, A. Lodola, A. Fioni, S. Rivara, A. Duranti, A. Tontini, S. Sanchini, J. R. Clapper, D. Piomelli, M. Mor and G. Tarzia, Structure-Property Relationships of a Class of Carba-mate-Based Fatty Acid Amide Hydrolase (FAAH) In-hibitors: Chemical and Biological Stability, ChemMedChem, 2009, 4(9), 1495–1504; (b) J. Singh, M. E. Gurney, A. Burgin, V. Sandanayaka, A. Kiselyov, A. Motta, G. Schultz, G. Hategan and T. Hagen, Biaryl PDE4 Inhibitors for Treating Inflammation, US pat., US2009067600, 2009; (c) K. Li, B. X. Wang, Y. Li and Q. Li, Amino-Aryl-Benzamide Compounds And Methods Of Use Thereof, US pat., US20210338610, 2021; (d) D. J. Carini, J. J. V. Duncia and P. C. B. Wong, Pharmaceutical Compositions Comprising Angiotensin II Receptor Blocking Imidazoles and Diuretics, EP0733366, 1996.
- 5 (a) R. Emadi, A. B. Nekoo, F. Molaverdi, Z. Khorsandi, R. Sheibani and H. Sadeghi-Aliabadi, Applications of Palladium-Catalyzed C-N Cross-Coupling Reactions in Pharmaceutical Compounds, RSC Adv., 2023, 13(27), 18715-18733; (b) M. O. Tischler, M. B. Tóth and Z. Novák, Mild Palladium Catalyzed Ortho C-H Bond Functionalizations of Aniline Derivatives, Chem. Rec., 2017, 17, 184–199; (c) S. Scherer, A. Meudt, B. Lehnemann, A. Kalinin and V. Snieckus, Preparation of Anilineboronic Acids and Derivatives Thereof, US pat., US7196219, 2007; (d) H. Fang, J. Yan and B. Wang, Biaryl Product Formation from Cross-coupling in Palladium catalyzed Borylation of Boc Protected Aminobromoquinoline Compound, Molecules, 2004, 9, 178-184.
- 6 For examples of cross-coupling strategies and inspiration, see: (a) C. Pinilla, V. Salamanca, A. Lledós and A. C. Albéniz, Palladium-Catalyzed Ortho C-H Arylation of Unprotected Anilines: Chemo- and Regioselectivity Enabled by the Cooperating Ligand [2,2'-Bipyridin]-6(1H)-one, *ACS Catal.*, 2022, **12**, 14527–14532; (b) D. Yousif, S. Tombolato, E. Ould Maina, R. Po, P. Biagini, A. Papagni and L. Vaghi,

Micellar Suzuki Cross-Coupling between Thiophene and Aniline in Water and under Air, Organics, 2021, 2, 415-423; (c) K. T. Hylland, S. Øien-Ødegaard and M. Tilset, The Suzuki-Miyaura Cross-Coupling as the Key Step in the Synthesis of 2-Aminobiphenyls and 2,2'-Diaminobiphenyls: Application in the Synthesis of Schiff Base Complexes of Zn, Eur. J. Org Chem., 2020, 27, 4208-4226; (d) Y. Chen, W. Chen, Y. Qiao and G. Zhou, B2N2-Embedded Polycylic Aromatic Hydrocarbons with Furan and Thiophene Derivatives Functionalized in Crossed Directions, Chem.-Eur. J., 2019, 25, 9326–9338; (e) O. M. Demchuk, K. Kapłon, L. Mazur, D. Strzelecka and K. M. Pietrusiewicz, Readily Available Catalysts for Demanding Suzuki-Miyaura Couplings under Mild Conditions, Tetrahedron, 2016, 72, 6668-6677; (f) P. Ruiz-Castillo and S. L. Buchwald, Applications of Palladium-Catalyzed C-N Cross-Coupling Reactions, Chem. Rev., 2016, 116, 12564-12649; (g) J. Rong, L. Deng, P. Tan, C. Ni, T. Gu and J. Hu, Radical Fluoroalkylation of Isocyanides with Fluorinated Sulfones by Visible-Light Photoredox Catalysis, Angew. Chem., Int. Ed., 2016, 55, 2743-2747; (h) Y. Chen, Y. Chen, Y. Hu, J. Qu and Y. Kang, Transalkylation via C-N Bond Cleavage of Amines Catalyzed by Super Organophotoreductant CBZ6, Org. Lett., 2023, 25(41), 7518-7522; (i) V. Pirovano, E. Brambilla, S. Rizzato, G. Abbiati, M. Bozzi and E. Rossi, Gold-Catalyzed Cascade Reactions of 4H-Furo[3,2-b]indoles with Allenamides: Synthesis of Indolin-3-one Derivatives, J. Org. Chem., 2019, 84(9), 5150-5166; (j) S. Ortgies and Breder, Selenium-Catalyzed Oxidative  $C(sp^2)-H$ Amination of Alkenes Exemplified in the Expedient Synthesis of (Aza-)Indoles, Org. Lett., 2015, 17, 2748–2751; (k) C. L. Vandeusen, A. E. Walts and Y. S. Or, Preparation of tri-substituted thiazole compounds as eIF4 inhibitors and uses thereof, WO2021178488, 2021.

7 (a) C. C. Marvin, A. D. Hobson, M. J. McPherson, M. Hayes, J. Randolph, M. V. Patel, Z. Wang, D. Schmidt, T. Li, M. M. Fettis, A. Bischoff, J. Fitzgibbons, L. Wang, L. Wang, A. Hernandez, Jr, Y. Jia, C. Goess, S. Bryant, S. Mathieu and J. Xu, Anti-TNF Thioester Glucocorticoid Antibody-Drug Conjugate Fully Inhibits Inflammation with Minimal Effect on Systemic Corticosterone Levels In Mouse Arthritis Model, J. Med. Chem., 2024, 67, 9495-9515; (b) A. D. Hobson, J. Xu, D. S. Welch, C. C. Marvin, M. J. McPherson, B. Gates, X. Liao, M. Hollmann, M. J. Gattner, K. Dzeyk, H. Sarvaiya, V. M. Shenoy, M. M. Fettis, A. K. Bischoff, L. Wang, L. C. Santora, L. Wang, J. Fitzgibbbons, P. Salomon, A. Hernandez Jr, Y. Jia, C. A. Goess, S. L. Mathieu, S. H. Bryant, M. E. Larsen, B. Cui and Y. Tian, Discovery of ABBV-154, Glucocorticoid anti-TNF Receptor Immunology Antibody-Drug Conjugate (iADC), J. Med. Chem., 2023, 66, 12544-12558; (c) A. D. Hobson, J. Xu, C. C. Marvin, M. J. McPherson, M. Hollmann, M. Gattner, K. Dzeyk, M. M. Fettis, A. K. Bischoff, L. Wang, J. Fitzgibbons, L. Wang, P. Salomon, Jr., A. Hernandez, Y. Jia, H. Sarvaiya, C. A. Goess, S. L. Mathieu and L. C. Santora, Optimization of Drug-Linker to Enable Long-

term Storage of Antibody-Drug Conjugate for Subcutaneous Dosing, J. Med. Chem., 2023, 66, 9161-9173; (d) A. D. Hobson, M. J. McPherson, M. E. Hayes, C. Goess, X. Li, J. Zhou, Z. Wang, Y. Yu, J. Yang, L. Sun, Q. Zhang, P. Qu, S. Yang, A. Hernandez Jr, S. H. Bryant, S. L. Mathieu, A. K. Bichoff, J. Fitzgibbons, L. C. Santora, L. Wang, L. Wang, M. M. Fettis, X. Li, C. C. Marvin, Z. Wang, M. V. Patel, D. L. Schmidt, T. Li, J. T. Randolph, R. F. Henry, C. Graff, Y. Tian, A. L. Aguirre and A. Shrestha, Discovery of ABBV-3363, an Anti-TNF Glucocorticoid Modulator **Immunology** Antibody Receptor Conjugate, J. Med. Chem., 2022, 65, 15893-15934; (e) A. D. Hobson, M. J. McPherson, W. Waegell, C. A. Goess, R. J. Stoffel, X. Li, J. Zhou, Z. Wang, Y. Yu, A. Hernandez Jr, S. H. Bryant, S. L. Mathieu, A. K. Bischoff, J. Fitzgibbons, M. Pawlikowsha, S. Puthenveetil, L. C. Santora, L. Wang, L. Wang, C. C. Marvin, M. E. Hayes, A. Shrestha,

- K. A. Sarris and B. Li, Design and Development of Glucocorticoid Receptor Modulators as Immunology Antibody-Drug Conjugate Payloads, *J. Med. Chem.*, 2022, **65**, 4500–4533.
- 8 Prepared according to literature procedure: A. D. Hobson, M. E. Hayes, A. Hernandez Jr, C. L. Ihle, C. C. Marvin, M. J. McPherson and W. Waegell, Glucocorticoid Receptor Agonist and Immunoconjugates Thereof, *US pat.*, US2021161263, 2021.
- 9 N. P. Tu, A. W. Dombrowski, G. M. Goshu, A. Vasudevan, S. W. Djuric and Y. Wang, High-Throughput Reaction Screening with Nano-moles of Solid Reagents Coated on Glass Beads, *Angew. Chem., Int. Ed.*, 2019, 58, 7987.
- 10 F. Rataboul, A. Zapf, R. Jackstell, S. Harkal, T. Riermeier, A. Monsees, U. Dingerdissen and M. Beller, New Ligands for a General Palladium-Catalyzed Amination of Aryl and Heteroaryl Chlorides, *Chem. Eur J.*, 2004, 10, 2983–2990.