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Efficient synthesis of substituted biaryl anilines and biaryl phenols via a Suzuki cross-coupling reaction

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Abstract—An efficient synthesis of biaryl building blocks with multiple point diversities via a Suzuki cross-coupling reaction using a commercially available preformed Pd catalyst **1** was reported. Substituted biaryl anilines and phenols were obtained in one step from commercially available aryl halides.

Biaryl moieties, often found in natural products and biologically active compounds, are important fragments in medicinal chemistry.[1] In general, biaryl building blocks have been synthesized by aryl-aryl bond formation via metal-mediated cross coupling reactions.[2] In our computational fragment-based drug discovery program, we needed to access biaryl building blocks with at least three points of diversity (Fig. 1). We were especially interested in developing a general synthetic approach to biaryl compounds where R_1 is either OH or NH_2. Because of the electron donating nature of these functional groups, Suzuki coupling between aniline or phenol halides and aryl boronic or heteroaryl boronic acids is not straightforward. Masking amines or hydroxyl groups have been common solutions.[3a,3b] For example, when we surveyed the literature for methods to synthesize 3-arylanthranilic acid derivatives, to our surprise, only a few examples of practical syntheses of 3-arylanthranilic acid derivatives were reported. A recent example involved formation of 7-iodoisatin from *o*-iodoaniline followed by a Suzuki coupling and hydrolysis of the resulting arylisatins.[4] Moderate yields were obtained for each step resulting in a low yield overall. This led us to investigate a more general and efficient route to approach biaryl aniline and phenol derivatives including 3-phenyl anthranilic derivatives.

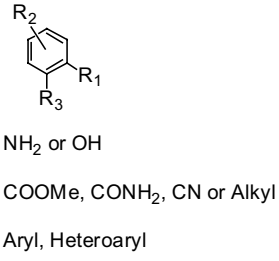

Figure 1. Biaryl aniline or phenol building blocks with three points of diversity.

The advances in palladium-catalyzed coupling reactions have allowed Suzuki couplings to tolerate a broad range of functional groups and different aryl halides. In general, for aryl chloride coupling, the presence of electron-withdrawing groups is thought to be critical for a successful Suzuki coupling reaction.[5] Recently a number of very effective ligands for coupling reactions using aryl chlorides have been reported.[6] In our lab, we have successfully used chloro(di-2-norbornylphosphino)(2′-dimethylamino-1,1′-biphenyl-2-yl)palladium(II) (catalyst **1**, Fig. 2), a newly reported catalyst that is air stable and highly active for C–C and C–N coupling reactions

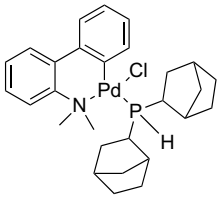

Figure 2. Structure of preformed Pd catalyst **1**.

Keywords: Suzuki coupling; Pd catalyst; Biaryl building blocks.
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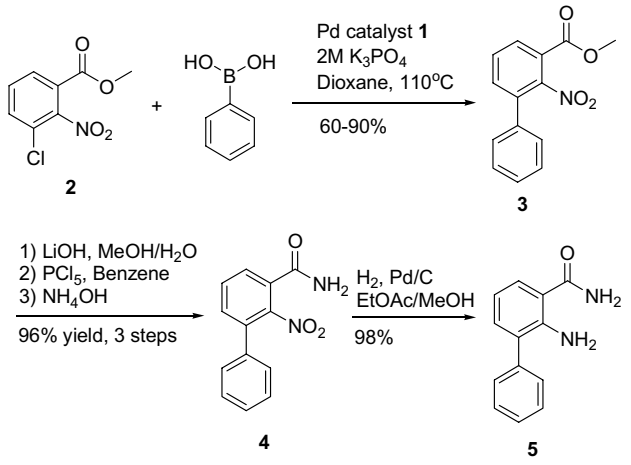
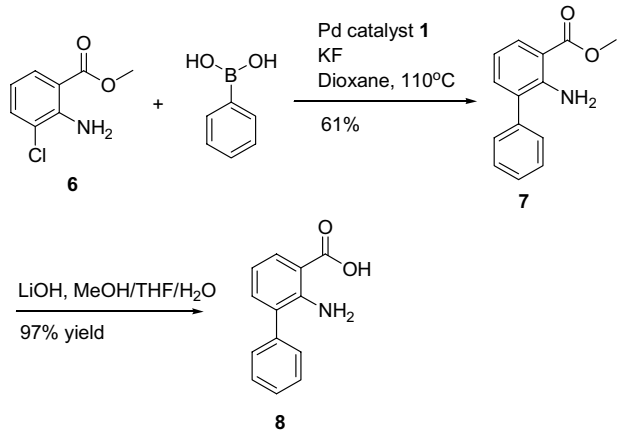


Scheme 1. Synthesis of 3-phenylanthranilic amide.



Scheme 2. An efficient synthesis of 3-phenylanthranilic acid.

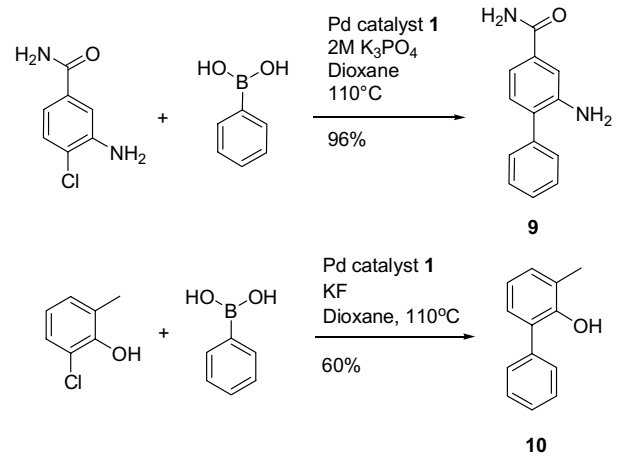
with aryl chlorides.[7,8] As part of our initial strategy towards 3-phenylanthranilic acid derivatives, we first planned to apply a Suzuki coupling between 3-chloro-2-nitro-benzoic acid methyl ester (**2**, obtained from commercially available 3-chloro-2-nitro-benzoic acid) and phenyl boronic acid (Scheme 1). We screened a few catalyst systems that have been reported effective for aryl chloride coupling.[5,9,10] In our hands, catalyst **1** provided the best results. Under optimal reaction conditions (2 mol% catalyst **1**, 2 equiv of 2M K_3PO_4 and dioxane as solvent), Suzuki coupling with the activated aryl chloride **2** afforded biaryl product **3** in 60–90% yield.

With the success of the Suzuki coupling reaction, 3-phenylanthranilic amide **5** was prepared efficiently in multi-gram quantity via this route as shown in Scheme 1. After Suzuki coupling, the ester **3** was converted to the amide **4** by hydrolysis with LiOH in MeOH/H_2O, followed by treatment with PCl_5 in benzene and quenching with aqueous ammonium hydroxide. Although direct conversion of the methyl ester to the amide using aminolysis was also attempted, the three-step sequence outlined here gave a better overall yield, needed less preparation time, and required no column separation. The nitro compound **4** was then reduced to afford the targeted building block **5** (overall 54% yield).[11] The entire sequence starting from **2** required only one column separation after the Suzuki coupling.

Although the above sequence has greatly improved the synthesis of compound **5** compared with the literature procedure,[4] we were curious to learn whether we could approach 3-phenylanthranilic derivatives in a more efficient way, namely starting from an electron-rich substrate like commercially available 2-amino-3-chlorobenzoic acid methyl ester (compound **6**, Scheme 2). In this way, we would be able to obtain anthranilic acid derivatives in one step. To our delight, the Suzuki coupling between **6** and phenyl boronic acid went well with catalyst **1** under similar coupling conditions. In this case, we found that KF is another good choice of base in addition to aqueous K_3PO_4. Biaryl aniline **7** was obtained in 61% yield and 3-phenylanthranilic acid **8** was then obtained by hydrolysis of **7** with LiOH (Scheme 2).

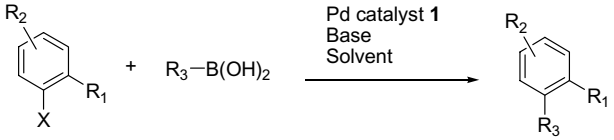
With these Suzuki coupling conditions, we were able to access other functionalized biaryl anilines or phenols such as **9** and **10** efficiently using Pd catalyst **1** (Scheme 3). Compound **9** was obtained in excellent yield directly from commercially available 3-amino-4-chloro-benzamide.[12] Suzuki coupling was also successful with the highly unactivated substrate 2-chloro-6-methyl-phenol (Aldrich) to afford biaryl phenol **10** in one step.[13] Since the examples of Suzuki reactions with aniline halide substrates or phenol halide substrates are still quite limited in the literature[14] and many aniline and phenol halides are readily available at low cost, this method provides an efficient way to assemble biaryl anilines and phenols bearing multiple functional groups.

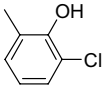
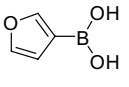
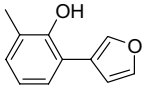
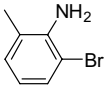
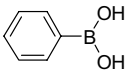
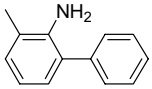
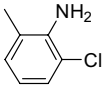
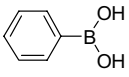
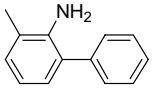
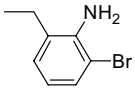
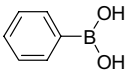
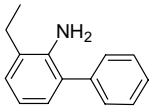
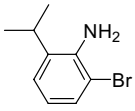
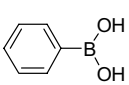
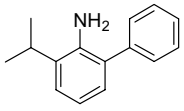
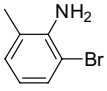
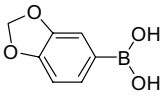
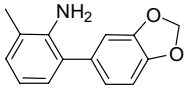
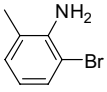
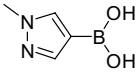
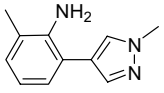
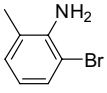
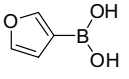
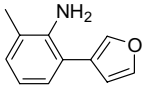
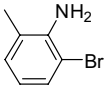
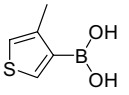
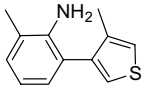
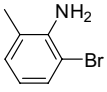
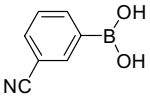
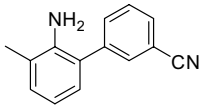
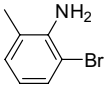
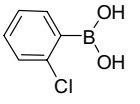
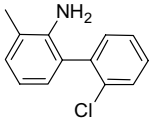
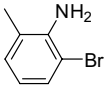
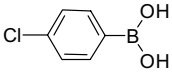
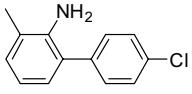
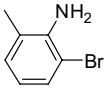
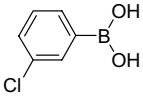
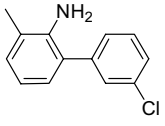
We applied this method to prepare a set of substituted anilines and phenols using similar reaction conditions (Table 1). Based on starting material availability, we either began with an aryl chloride or aryl bromide substrate. In general, these Suzuki coupling conditions worked well between a variety of aniline halides or phenol halides and diversified boronic acids. When aryl bro-



Scheme 3. Suzuki coupling with chloro aniline or chloro phenol derivatives using catalyst **1**.

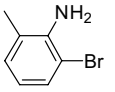
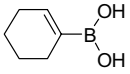
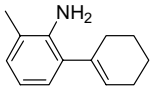
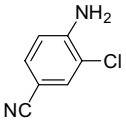
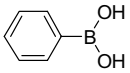
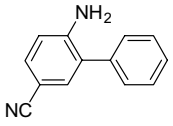
Table 1. Biaryl building blocks with three point diversity via a Suzuki-coupling reaction



Entry	Aryl halide	Boronic acid	Product	Solvent/temp (°C)	Base (equiv)	Yield[a] (%)
1				Dioxane/110	KF (5)	41
2a				THF/60	KF (5)	87
2b				Dioxane/110	KF (5)	76
3				Dioxane/110	KF (5)	64
4				Dioxane/110	KF (5)	50
5				THF/60	KF (5)	87
6				THF/60	KF (5)	69
7				THF/60	KF (5)	67
8				THF/60	KF (5)	92
9				THF/60	KF (5)	92
10				THF/60	KF (5)	78
11				THF/60	KF (5)	59
12				THF/60	KF (5)	51

(*continued on next page*)

Table 1 (*continued*)

Entry	Aryl halide	Boronic acid	Product	Solvent/temp (°C)	Base (equiv)	Yield[a] (%)
13				THF/80	KF (5)	51
14				Dioxane/110	K_3PO_4 (2)	91

Reaction conditions: 1 equiv of aryl halide, 1.0–1.5 equiv of aryl boronic acid, 5 mol% of Pd catalyst **1**. Reaction time: 4–16 h.
[a] All the yields were isolated yields and all the products gave satisfactory ^{1}H NMR and MS.

mides were used as substrate, milder reaction conditions could be used (entries 2a, and 5–13). For example, both 2-chloro-6-methyl-aniline and 2-bromo-6-methyl-aniline provided 3-methyl-biphenyl-2-ylamine in good yields (entries 2a and 2b). Not surprisingly, even at a lower reaction temperature (60 °C in THF) the bromide substrate gave a better yield compared with the chloride substrate at a higher reaction temperature (110 °C in dioxane). Heteroaryl substituted anilines and phenols were also obtained in good yield (entries 1, 6, 7, 8). In addition, at a lower reaction temperature, Suzuki coupling was successful between 2-bromo-6-methyl-phenylamine and phenyl boronic acids with chloro substitutions (entries 10–12). The R_3 group was not just limited to aryl or heteroaryl moieties. For example, when cyclohexen-1-ylboronic acid was used, the corresponding substituted aniline was obtained in moderate yield (entry 13). This coupling reaction can be easily scaled up. We have carried out reaction 2a at 5 g scale and obtained 88% isolated yield.

Suzuki coupling with Pd catalyst **1** was easily carried out according to the following representative experimental procedure for synthesizing compound **10**: To a mixture of 2-chloro-6-methyl-phenol (1.00 g, 7.0 mmol), phenyl boronic acid (0.85 g, 7.0 mmol) and KF (2.0 g, 35.0 mmol) in a flask was added catalyst **1** (150 mg, 5% mol). The flask was then flushed with nitrogen and 10.0 mL of degassed dioxane was added. The flask was then sealed and heated at 120 °C overnight. The reaction mixture was cooled to room temperature, filtered through Celite®, and concentrated under vacuum. The residue was then purified by flash chromatography (hexanes to 30% ethyl acetate) to afford the desired product as pale yellow oil (0.70 g, 54%).

In conclusion, we have reported Suzuki coupling reaction conditions amenable to prepare substituted biaryl anilines or phenols without protection of amino or hydroxyl groups. Using preformed catalyst **1**, these biaryl building blocks with multiple diversity points were efficiently obtained from commercially available aryl chlorides or aryl bromides.

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11. Analytical data for compound **5**: ^{1}H NMR (400 MHz, CD_3OD): δ 7.52 (d, J = 8.0 Hz, 1H), 7.46–7.42 (m, 2H), 7.38–7.34 (m, 3H), 7.11 (d, J = 7.2 Hz, 1H), 6.69 (t, J = 8 Hz, 1H); ^{13}C (100 MHz, CD_3OD): δ 172.6, 146.2, 139.2, 133.4, 129.4, 129.1, 128.8, 128.1, 127.4, 115.9, 115.4; MS (APCI+): 214.5 ($M+H^+$).
12. Analytical data for compound **9**: ^{1}H NMR (400 MHz, C_2D_6CO): δ 7.50–7.28 (m, 7H), 7.25 (d, J = 8.0 Hz, 1H), 7.09 (d, J = 7.8 Hz, 1H), 6.59 (s, 1H), 4.58 (s, 2H); ^{13}C NMR (100 MHz, C_2D_6CO): δ 168.7, 145.1, 139.6, 134.8, 130.2, 129.6, 129.0, 128.9, 127.5, 116.4, 114.9; MS (APCI+): 213.2 ($M+H^+$).
13. Analytical data for compound **10**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50–7.37 (m, 5H), 7.13 (d, J = 8 Hz, 1H), 7.07 (d, J = 8.0 Hz, 1H), 6.88 (t, J = 7.2 Hz, 1H), 2.24 (s, 3H).
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