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## An efficient one-pot access to *N*-(pyridin-2-ylmethyl) substituent biphenyl-4-sulfonamides through water-promoted, palladium-catalyzed, microwave-assisted reactions<sup>†</sup>

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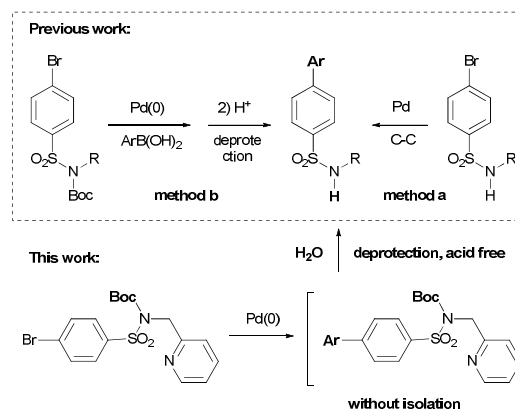
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An efficient one-pot, Pd(PPh<sub>3</sub>)<sub>4</sub> catalyzed, water-promoted method for the synthesis of *N*-(pyridin-2-ylmethyl)biphenyl-4-sulfonamides was developed under microwave irradiation. With acid free, good substrate scope, excellent functional group compatibility, and excellent product yields, this methodology is superior to the existing procedures for the synthesis of biphenyl-4-sulfonamides bearing pyridin-2-ylmethyl group.

The biphenyl-4-sulfonamides has been recognized as the significant biological and pharmacological activities such as anticancer,<sup>1</sup> anti-tumor,<sup>2</sup> antibacterial,<sup>3</sup> anti-allergic,<sup>4</sup> antiviral,<sup>5</sup> and anti-inflammatory.<sup>6</sup> Two derivatives in this family, Valdecoxib and Celecoxib, have been introduced to the market as anti-inflammatory drug.<sup>7</sup>

The biphenyl-4-sulfonamide derivatives, *N*-(pyridin-2-ylmethyl) biphenyl-4-sulfonamides also exhibit crucial biological activity.<sup>8</sup> In particular, agricultural chemists have focused on the core structure to produce abscisic acid (ABA) agonist. For example, pyrabactin(Py)<sup>9</sup> has been successfully designed to simulate the function of ABA which plays a key role in overcoming the abiotic stresses such as drought, cold and soil salinity, as well as in plant development.<sup>10</sup> Being attracted by the biological properties of biphenyl-4-sulfonamides, a variety of strategies to synthesize the core structure have been developed.<sup>1-7, 11</sup> And, the palladium-catalyzed reactions are confirmed to be the most efficient approaches.<sup>11</sup> Recently, Covell *et. al.*<sup>8</sup> reported a Suzuki coupling reaction to construct the *N*-(pyridin-2-ylmethyl)biphenyl-4-sulfonamides

(Scheme 1, method a). But, the yield is near 60%. This could be the result of forming complex between *N*-(pyridin-2-ylmethyl) group and palladium.<sup>12</sup> Recent research also shown that the Boc



**Scheme 1** Selected methods to synthesize biphenyl-4-sulfonamides

protection of sulfonamino group could promote the coupling reaction greatly (method b), while the strong acid was required for deprotection.<sup>13</sup> Otherwise the sulfonylation required very stable reactants.<sup>14</sup> Moreover, a boiling water-catalyzed neutral and selective *N*-Boc deprotection from aromatic heterocycles, aromatic amines, aliphatic amines, and amide has been developed.<sup>15</sup> So, we proposed the Suzuki coupling of *N*-Boc biphenyl-4-sulfonamides followed by deprotection in one pot could produce the *N*-(pyridin-2-ylmethyl)biphenyl-4-sulfonamides conveniently. To the best of our knowledge, there has never been a report on one-pot palladium-catalyzed, water-promoted reaction to afford this scaffold under microwave irradiation before.

Our recent success in application of microwave irradiation<sup>16</sup> prompted us to try the deprotection of **1a** under the microwave irradiation. As shown in Table 1, enhancing the reaction temperature could accelerate the deprotection and increase the

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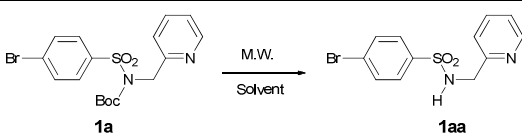
<sup>†</sup> Electronic supplementary information (ESI) available: Experimental procedures, characterization data, and <sup>1</sup>H, <sup>13</sup>C and HRMS

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reaction yields (Table 1, entry 1-5). Subsequently, our study focused on the screening of solvents (Table 1, entry 5-8). We found the water-solubility of the solvent was important for the reaction. The

**Table 1** The water-promoted the SO<sub>2</sub>N-Boc deprotection<sup>a</sup>



Entry	Solvent (4:1)	T(°C)	t(min)	Yield(%) <sup>b</sup>
1	Dioxane : H <sub>2</sub> O	85	6	<5
2	Dioxane : H <sub>2</sub> O	100	6	<5
3	Dioxane : H <sub>2</sub> O	110	6	76
4	Dioxane : H <sub>2</sub> O	120	8	92
5	<b>Dioxane : H<sub>2</sub>O</b>	<b>130</b>	<b>8</b>	<b>96</b>
6	DME : H <sub>2</sub> O	130	8	93
7	DMF : H <sub>2</sub> O	130	8	90
8	Toluene : H <sub>2</sub> O	130	15	<5
9 <sup>c</sup>	Dioxane : H <sub>2</sub> O	Reflux	600	<5

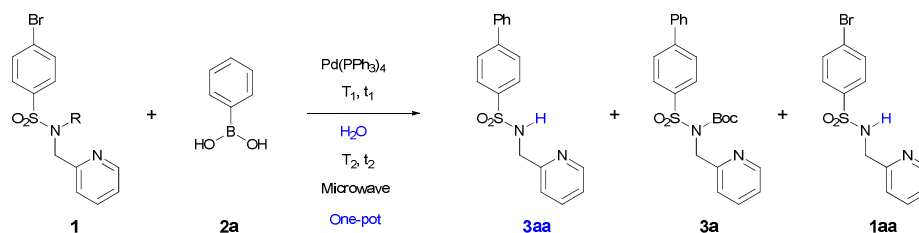
<sup>a</sup> Reactions conditions : **1a** 0.5 mmol, solvent 5 mL. <sup>b</sup> Isolated yield.

<sup>c</sup> Conventional heating method.

**Table 2** Optimization of the Reaction Conditions<sup>a</sup>

better the water solubility the higher the product yield. As a result, dioxane- water was proved to be the suitable solvent.

However, we found the deprotection of **1a** under the conventional heating condition was very difficult. Hence, we chose **1a** and **2a** as a model to optimize the one-pot reaction conditions. As shown in Table 2, 64 % of coupling and deprotection product (**3aa**) was obtained with a temperature of 120 °C (Table 2, entry 1) under microwave irradiation. Process monitoring indicated that **1a** could be removed directly and fast before the Suzuki coupling to produce **1aa** at high temperature (120 °C). Therefore, in order to improve the yield of **3aa**, we should carry out the coupling reaction at low temperature and the subsequent Boc-deprotection reaction at high temperature. Under this assumption, we optimized the temperature for the Suzuki coupling to be 85 °C (Table 2, entry 2-4) and the temperature for the Boc-deprotection reaction to be 130 °C, respectively. Finally, the yield increased to 94% by prolonging the reaction time to 10 min (Table 2, entry 5). We next explored the effect of the bases on this reaction, among the bases we investigated (Na<sub>2</sub>CO<sub>3</sub>, K<sub>2</sub>CO<sub>3</sub>, K<sub>3</sub>PO<sub>4</sub> and Cs<sub>2</sub>CO<sub>3</sub>), Na<sub>2</sub>CO<sub>3</sub> was identified as the best one (Table 2, entry 5-8).



Entry	R	Solvent (4 : 1)	Base	Pd(PPh <sub>3</sub> ) <sub>4</sub>	T <sub>1</sub> (°C), t <sub>1</sub> (min)	T <sub>2</sub> (°C), t <sub>2</sub> (min)	Yield <sup>b</sup> ( <b>3aa</b> )	Yield <sup>b</sup> ( <b>3a</b> )	Yield <sup>b</sup> ( <b>1aa</b> )
1	Boc	Dioxane : H <sub>2</sub> O	Na <sub>2</sub> CO <sub>3</sub>	2 mol %	120, 10	—, —	64	0	29
2	Boc	Dioxane : H <sub>2</sub> O	Na <sub>2</sub> CO <sub>3</sub>	2 mol %	80, 5	130, 8	35	0	58
3	Boc	Dioxane : H <sub>2</sub> O	Na <sub>2</sub> CO <sub>3</sub>	2 mol %	85, 5	130, 8	53	0	42
4	Boc	Dioxane : H <sub>2</sub> O	Na <sub>2</sub> CO <sub>3</sub>	2 mol %	90, 5	130, 8	48	0	36
5	<b>Boc</b>	<b>Dioxane : H<sub>2</sub>O</b>	<b>Na<sub>2</sub>CO<sub>3</sub></b>	<b>2 mol %</b>	<b>85, 10</b>	<b>130, 8</b>	<b>94</b>	<b>0</b>	<b>0</b>
6	Boc	Dioxane : H <sub>2</sub> O	K <sub>2</sub> CO <sub>3</sub>	2 mol %	85, 10	130, 8	91	0	0
7	Boc	Dioxane : H <sub>2</sub> O	K <sub>3</sub> PO <sub>4</sub>	2 mol %	85, 10	130, 8	89	0	<5
8	Boc	Dioxane : H <sub>2</sub> O	Cs <sub>2</sub> CO <sub>3</sub>	2 mol %	85, 10	130, 8	86	0	<5
9	Boc	Dioxane : H <sub>2</sub> O	—	2 mol %	85, 10	130, 8	0	0	96
10	Boc	Dioxane : H <sub>2</sub> O	Na <sub>2</sub> CO <sub>3</sub>	—	85, 10	130, 8	0	0	95
11	Boc	Toluene : H <sub>2</sub> O	Na <sub>2</sub> CO <sub>3</sub>	2 mol %	85, 10	130, 8	<5	86	<5
12	Boc	DME : H <sub>2</sub> O	Na <sub>2</sub> CO <sub>3</sub>	2 mol %	85, 10	130, 8	92	0	<5
13	Boc	DMF : H <sub>2</sub> O	Na <sub>2</sub> CO <sub>3</sub>	2 mol %	85, 10	130, 8	87	0	<5
14	H	Dioxane : H <sub>2</sub> O	Na <sub>2</sub> CO <sub>3</sub>	2 mol %	85, 10	130, 8	63	0	29
15 <sup>c</sup>	Boc	Dioxane : H <sub>2</sub> O	Na <sub>2</sub> CO <sub>3</sub>	2 mol %	85, 90	reflux, 600	<5	81	<5

<sup>a</sup> Reactions conditions: **1** (0.5 mmol), **2a** (0.5 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (2 mol%), base (1.0 mmol), solvent (5 mL), protected by N<sub>2</sub>. <sup>b</sup> Isolated yield.

**Table 3** Scope of arylboronic acid (**2**) and **1a**<sup>a</sup>

Entry	Boronic acid ( <b>2</b> )	t <sub>1</sub> (min)	<b>3</b>	Yield (%) <sup>b</sup>
1	<b>2a</b> : R <sup>1</sup> =R <sup>2</sup> =R <sup>3</sup> =R <sup>4</sup> =H	10	<b>3aa</b>	94
2	<b>2b</b> : R <sup>1</sup> =R <sup>2</sup> =R <sup>4</sup> =H, R <sup>3</sup> =OCH <sub>3</sub>	10	<b>3ab</b>	94
3	<b>2c</b> : R <sup>1</sup> =R <sup>2</sup> =R <sup>4</sup> =H, R <sup>3</sup> = <sup>t</sup> Bu	10	<b>3ac</b>	95
4	<b>2d</b> : R <sup>1</sup> =R <sup>2</sup> =R <sup>4</sup> =H, R <sup>3</sup> =F	15	<b>3ad</b>	94
5	<b>2e</b> : R <sup>1</sup> =R <sup>3</sup> =R <sup>4</sup> =H, R <sup>2</sup> =F	15	<b>3ae</b>	93
6	<b>2f</b> : R <sup>2</sup> =R <sup>3</sup> =R <sup>4</sup> =H, R <sup>1</sup> =F	15	<b>3af</b>	90
7	<b>2g</b> : R <sup>1</sup> =R <sup>2</sup> =R <sup>4</sup> =H, R <sup>3</sup> =Cl	15	<b>3ag</b>	93
8	<b>2h</b> : R <sup>1</sup> =R <sup>3</sup> =R <sup>4</sup> =H, R <sup>2</sup> =Cl	15	<b>3ah</b>	92
9	<b>2i</b> : R <sup>1</sup> =R <sup>3</sup> =R <sup>4</sup> =H, R <sup>2</sup> =Br	15	<b>3ai</b>	53
10	<b>2j</b> : R <sup>1</sup> =R <sup>2</sup> =R <sup>4</sup> =H, R <sup>3</sup> =Br	15	<b>3aj</b>	51
11	<b>2k</b> : R <sup>1</sup> =R <sup>2</sup> =R <sup>4</sup> =H, R <sup>3</sup> =NO <sub>2</sub>	25	<b>3ak</b>	58
12	<b>2l</b> : R <sup>1</sup> =R <sup>2</sup> =R <sup>4</sup> =H, R <sup>3</sup> =CF <sub>3</sub>	20	<b>3al</b>	91
13	<b>2m</b> : R <sup>1</sup> =R <sup>2</sup> =R <sup>4</sup> =H, R <sup>3</sup> =OCF <sub>3</sub>	15	<b>3am</b>	93
14	<b>2n</b> : R <sup>1</sup> =R <sup>2</sup> =R <sup>4</sup> =H, R <sup>3</sup> =Ac	20	<b>3an</b>	90
15	<b>2o</b> : R <sup>1</sup> =R <sup>3</sup> =R <sup>4</sup> =H, R <sup>2</sup> =CHO	15	<b>3ao</b>	93
16	<b>2p</b> : R <sup>1</sup> =R <sup>3</sup> =R <sup>4</sup> =H, R <sup>2</sup> =OH	15	<b>3ap</b>	87
17	<b>2q</b> : R <sup>2</sup> =R <sup>4</sup> =H, R <sup>1</sup> =F, R <sup>3</sup> =Cl	15	<b>3aq</b>	91
18	<b>2r</b> : R <sup>1</sup> =R <sup>4</sup> =H, R <sup>2</sup> =Cl, R <sup>3</sup> =Cl	25	<b>3ar</b>	92
19	<b>2s</b> : R <sup>1</sup> =R <sup>3</sup> =H, R <sup>2</sup> =Cl, R <sup>4</sup> =Cl	25	<b>3as</b>	92
20	<b>2t</b> : R <sup>1</sup> =R <sup>4</sup> =H, R <sup>2</sup> =CH <sub>3</sub> , R <sup>3</sup> =F	15	<b>3at</b>	91
21	<b>2u</b> : [1,1'-biphenyl]-4-ylboronic acid	15	<b>3au</b>	92
22	<b>2v</b> : furan-2-ylboronic acid	20	<b>3av</b>	93
23	<b>2w</b> : dibenzo[b,d]furan-4-ylboronic acid	25	<b>3aw</b>	85
24	<b>2x</b> : pyridin-3-ylboronic acid	20	<b>3ax</b>	89

<sup>a</sup> Reactions conditions: **1a** (0.5 mmol), **2** (0.5 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (2 mol %), Na<sub>2</sub>CO<sub>3</sub> (1.0 mmol), dioxane:H<sub>2</sub>O = 4 mL : 1 mL, T<sub>2</sub> = 130 °C, t<sub>2</sub> = 8 min, protected by N<sub>2</sub>. <sup>b</sup> Isolated yield.

In addition, we noted that the coupling reaction will not take place in the absence of catalyst or base, but the deprotection reaction can go smoothly (Table 2, entry 9, 10). Subsequently, we screened the reaction solvents, such as the water mixed with dioxane, toluene, DMF, and DME (Table 2, entry 5, 11-13). The

mixture of dioxane and water (v/v = 4:1) was proved to be the best results. On the contrary, the coupling reaction between **1aa** and **2a** under the same condition produced much lower yield of **3aa** (Table 2, entry 14). Compared with conventional heating (Table 2, entry 15), microwave irradiation can significantly accelerate the reaction and notably improve the yield of product.

With the optimized reaction conditions in hand, we screened the substrate scope of the one-pot reaction of Suzuki coupling and deprotection. Various aryl and heteroarylboronic acids were tested, the results were summarized in Table 3. The reactions between **1a** and arylboronic acids always went smoothly. Both electron-donating and electron-withdrawing groups, such as methoxy, *t*-butyl, halogen(F, Cl), and trifluoromethyl groups, afforded the corresponding products in excellent yields (Table 3, entry 2-8, 12, 13). The reaction yields of brominated or nitrated phenylboronic acids were moderate due to the self-coupling or other unexpected side reactions (Table 3, entry 9-11). More importantly, the reaction was proved to be well tolerant of valuable but unstable groups, such as hydroxyl, acetyl and formyl (Table 3, entry 14-16). In addition, disubstituted and heteroarylboronic acid were also investigated and afforded the desired products in good to excellent yields (Table 3, entry 17-24). To further examine the efficiency of this one-pot reaction and rapidly expand our unique compound collection, we also carried out the reaction between 4-bromo-*N*-Boc-*N*-(pyridin-2-ylmethyl)-naphthalene-1-sulfonamide (**1b**) and phenylboronic acids (**2**), which produced the desired products in good to excellent yield (Table 4, entry 1-9).

Through a further high-throughput computational screening, compounds **3aa** and **3ai** have been found to be active on the ABA receptor PYL1. Very interestingly, both compounds are predicted

**Table 4** Scope of phenylboronic acid (**2**) and **1b**<sup>a</sup>

Entry	Boronic acid ( <b>2</b> )	t <sub>1</sub> (min)	<b>3</b>	Yield (%) <sup>b</sup>
1	<b>2b</b> : R <sup>1</sup> =R <sup>2</sup> =R <sup>4</sup> =H, R <sup>3</sup> =OCH <sub>3</sub>	10	<b>3bb</b>	93
2	<b>2c</b> : R <sup>1</sup> =R <sup>2</sup> =R <sup>4</sup> =H, R <sup>3</sup> = <sup>t</sup> Bu	10	<b>3bc</b>	95
3	<b>2d</b> : R <sup>1</sup> =R <sup>2</sup> =R <sup>4</sup> =H, R <sup>3</sup> =F	10	<b>3bd</b>	91
4	<b>2e</b> : R <sup>1</sup> =R <sup>3</sup> =R <sup>4</sup> =H, R <sup>2</sup> =F	15	<b>3be</b>	92
5	<b>2h</b> : R <sup>1</sup> =R <sup>3</sup> =R <sup>4</sup> =H, R <sup>2</sup> =Cl	15	<b>3bh</b>	93
6	<b>2j</b> : R <sup>1</sup> =R <sup>3</sup> =R <sup>4</sup> =H, R <sup>2</sup> =Br	15	<b>3bj</b>	52
7	<b>2m</b> : R <sup>1</sup> =R <sup>2</sup> =R <sup>4</sup> =H, R <sup>3</sup> =OCF <sub>3</sub>	15	<b>3bm</b>	91
8	<b>2q</b> : R <sup>2</sup> =R <sup>4</sup> =H, R <sup>1</sup> =F, R <sup>3</sup> =Cl	15	<b>3bq</b>	90

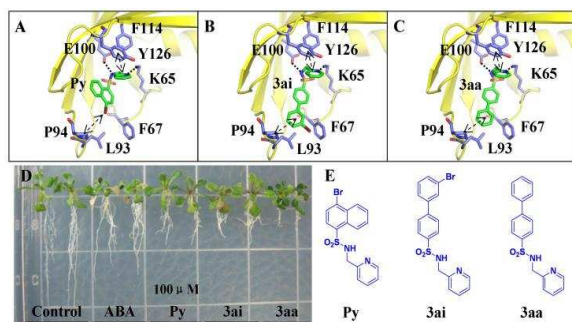
<sup>a</sup> Reactions conditions: **1b** (0.5 mmol), **2** (0.5 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (2 mol %), Na<sub>2</sub>CO<sub>3</sub> (1.0 mmol), dioxane:H<sub>2</sub>O = 4 mL : 1 mL, T<sub>2</sub> = 130 °C, t<sub>2</sub> = 8 min, protected by N<sub>2</sub>. <sup>b</sup> Isolated yield.

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9 **2r**: R<sup>1</sup>=R<sup>4</sup>=H, R<sup>2</sup>=Cl, R<sup>3</sup>=Cl 15 **3br** 91

<sup>a</sup> Reactions conditions: **1a** (0.5 mmol), **2** (0.5 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (2 mol %), Na<sub>2</sub>CO<sub>3</sub> (1.0 mmol), dioxane : H<sub>2</sub>O = 4 mL : 1 mL, T<sub>2</sub> = 130 °C, t<sub>2</sub> = 8 min, protected by N<sub>2</sub>. <sup>b</sup> Isolated yield.



**Fig 1.** Computational modeling and chemical mediated root growth inhibition. (A). Computational modeling of pyrabactin(Py) in PYL1 (PDB code: 3NEG). (B). Computational modeling of **3ai** in PYL1. (C). Computational modeling of **3aa** in PYL1. (D). Arabidopsis plant wild type lines show sensitivity in root growth with 100 μM treated chemicals. The root growth in **Py**, **3ai**, and **3aa**-containing medium is more inhibited than ABA. (E). The chemical structures of Pyrabactin, **3aa**, and **3ai**.

to bind PYL1 in a similar fashion to a known ABA agonist pyrabactin (Fig. 1). The sulfonamide functional group of **3ai** and **3aa** can form hydrogen bond with residue E100. The pyridine ring can form another hydrogen bond with residue K65 and  $\pi$ - $\pi$  stacking interaction with residue Y126 (Fig. 1B and 1C). The binding differences can be found in the other side of the pocket. There is a hydrophobic interaction between bromine atom and residue P94. However, the biphenyl group makes **3ai** and **3aa** bind with P94 more closely. The estimated binding free energies are respectively -8.89 kcal/mol and -8.20 kcal/mol for **3ai** and **3aa**, which are a little lower than that of pyrabactin (-7.98 kcal/mol). The root growth inhibition experiment showed that *Arabidopsis thaliana* plant is a little more sensitive to the treatment of **3ai**, **3aa**, and pyrabactin than ABA (Fig. 1D). As shown in Fig. S1 (supporting information), the root growth inhibition rates of **3ai**, **3aa**, and pyrabactin were 82±12 %, 98±5 %, and 94±7 %, respectively, while that of ABA was only 68±13 %.

In summary, we have reported an efficient method to prepare *N*-(pyridin-2-ylmethyl)biphenyl-4-sulfonamides via a palladium-catalyzed, water-promoted and microwave-assisted one-pot reaction. In addition, the excellent reactivity and broad substrate scopes make the developed methodology operationally concise and facilitate rapid library construction. Further efforts to examine the bioactivity of these compounds are underway and will be reported in due course.

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