

## Simultaneous reduction of nitro- to amino-group in the palladium-catalyzed Suzuki cross-coupling reaction

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### Abstract

An efficient method for palladium-catalyzed Suzuki cross-coupling reaction with simultaneous reduction of nitro- to amino-group has been developed. This method allows nitro-substituted aryl halides to readily react with arylboronic acids, to afford aryl substituted aniline in low to excellent yields. The reaction was catalyzed by Pd(OAc)<sub>2</sub> (3 mol %) at 150 °C under atmospheric pressure in the presence of K<sub>2</sub>CO<sub>3</sub> (3 equiv) in DMF/H<sub>2</sub>O (5/1).

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**Keywords:** Palladium; Suzuki cross-coupling; Reduction; Aryl substituted aniline

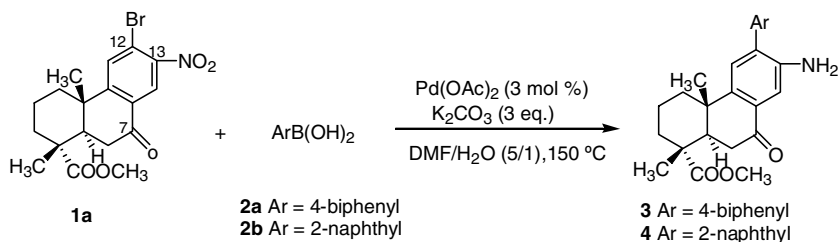
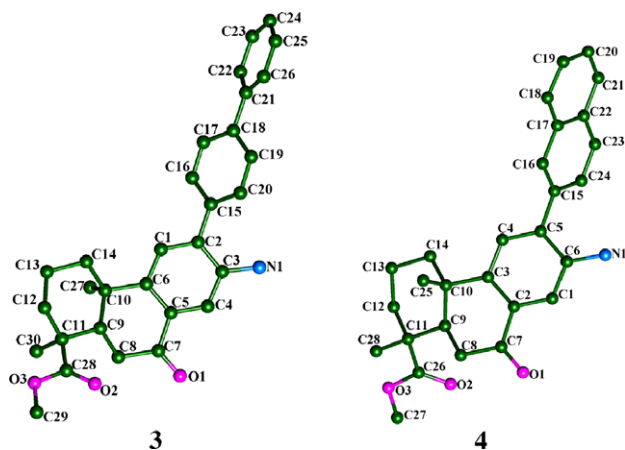
The palladium-catalyzed Suzuki cross-coupling reaction is probably one of the most powerful and well-known chemical tools for the selective construction of carbon–carbon bonds.<sup>1</sup> A variety of improvements have been made for the reaction conditions since the first discovery in 1981 by Suzuki and co-workers to prepare biaryls.<sup>2</sup> However, there are no published data for palladium-catalyzed Suzuki cross-coupling reaction with the simultaneous reduction of nitro- to amino-group to date. On the other hand, many methods have been reported for the reduction of aromatic nitro compounds to the corresponding aromatic amines, including most popular catalytic hydrogenation and metal-mediated reduction. Many valuable sources of hydrogen such as hydrazine,<sup>3</sup> CO/H<sub>2</sub>O,<sup>4</sup> formate,<sup>5</sup> NaBH<sub>4</sub>,<sup>6</sup> and amine boranes<sup>7</sup> have been used. Reported herein is the discovery of a novel Pd(OAc)<sub>2</sub>/DMF/H<sub>2</sub>O catalytic system for Suzuki cross-coupling reaction accompanied by the reduction of a nitro-group to an amine.

As part of our experimental goal to synthesize some chiral fluorescence reagents from methyl 12-bromo-13-nitro-7-oxo-dehydrodeisopropylabietate **1a**, we are interested in developing a general method to prepare methyl 12-aryl substituted-13-amino-7-oxo-dehydrodeisopropylabietates. In the course of our experiments of Pd-catalyzed Suzuki cross-coupling of **1a** with 4-biphenylboronic acid **2a** and 2-naphthylboronic acid **2b**, respectively, we found that Suzuki cross-coupling reaction and nitro reduction reaction synchronously occurred without affecting the other reducible ester and carbonyl groups. Methyl 12-(4-biphenyl)-13-amino-7-oxo-dehydrodeisopropylabietate **3** and methyl 12-(2-naphthyl)-13-amino-7-oxo-dehydrodeisopropylabietate **4** were prepared in a single one-pot reaction in moderate isolated yields (70% and 75%, respectively) after 24 h (Scheme 1). The reaction took place under atmospheric pressure at 150 °C in a mixture of DMF and H<sub>2</sub>O (5/1) in the presence of 3 mol % Pd(OAc)<sub>2</sub>, and 3 equiv of K<sub>2</sub>CO<sub>3</sub>.

Crystals of **3** and **4** were grown from a saturated petroleum ether/ethyl acetate solution by slow evaporation at

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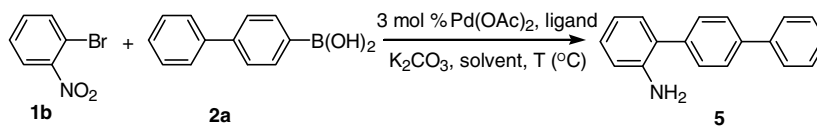
Scheme 1. Synthesis of compounds **3** and **4** from methyl 12-bromo-13-nitro-7-oxo-dehydrodeisopropylabietate **1a**.Fig. 1. Crystal structures of compound **3** and **4**.

room temperature (Fig. 1). All hydrogen atoms are omitted for clarity.

Encouraged by these results, we extended the system to the reaction of 1-bromo-2-nitro-benzene **1b** and 4-biphenylboronic acid **2a**. As shown in Table 1, without

any ligands, 1-bromo-2-nitro-benzene in a mixed solvent of DMF and H<sub>2</sub>O (5/1) reacted with 4-biphenylboronic acid in the presence of 3 mol % Pd(OAc)<sub>2</sub>, and 3 equiv of K<sub>2</sub>CO<sub>3</sub> at 150 °C to give 2-amino-*p*-terphenyl **5** in 78% yield after 16 h (entry 1). Then we turned our attention to optimize reaction conditions using **1b** and **2a** as a model reaction. A number of parameters were evaluated and, all the reactions were carried out under air. Temperature appeared to be crucial to the reaction. Below 80 °C, it afforded only starting materials even after a reaction time of two days (entry 2). The reaction conducted at 120 °C also gave good result but it was necessary to use longer reaction time (24 h) (entry 3). Although the reaction rate was faster at 180 °C, the conversion was not enhanced, and in fact, the yield of 2-amino-*p*-terphenyl was reduced to 70% (entry 4), which may be due to the decomposition of the arylboronic acids. The use of DABCO (triethylenediamine) as a ligand led to higher yield for this reaction (entry 5 vs entry 1), similar to previous reports, in which DABCO was employed as a highly efficient ligand for palladium-catalyzed coupling reaction.<sup>8</sup> But there was no significant improvement when TBAB, CTMAB, and PPh<sub>3</sub> were used

Table 1

Reaction of 1-bromo-2-nitro-benzene **1b** with 4-biphenylboronic acid **2a** in various conditions<sup>a</sup>

| Entry | Solvent                            | Ligand           | Temperature (°C) | Time (h) | Yield <sup>b</sup> (%) |
|-------|------------------------------------|------------------|------------------|----------|------------------------|
| 1     | DMF–H <sub>2</sub> O <sup>c</sup>  | 0                | 150              | 16       | 78                     |
| 2     | DMF–H <sub>2</sub> O <sup>c</sup>  | 0                | 80               | 48       | 0                      |
| 3     | DMF–H <sub>2</sub> O <sup>c</sup>  | 0                | 120              | 24       | 76                     |
| 4     | DMF–H <sub>2</sub> O <sup>c</sup>  | 0                | 180              | 10       | 70                     |
| 5     | DMF–H <sub>2</sub> O <sup>c</sup>  | DABCO            | 150              | 12       | 87                     |
| 6     | DMF–H <sub>2</sub> O <sup>c</sup>  | TBAB             | 150              | 16       | 79                     |
| 7     | DMF–H <sub>2</sub> O <sup>c</sup>  | CTMAB            | 150              | 16       | 76                     |
| 8     | DMF–H <sub>2</sub> O <sup>c</sup>  | PPh <sub>3</sub> | 150              | 24       | 72                     |
| 9     | DMF                                | DABCO            | 150              | 24       | 0                      |
| 10    | Toluene                            | DABCO            | 150              | 24       | 0                      |
| 11    | DME–H <sub>2</sub> O <sup>d</sup>  | DABCO            | 150              | 24       | 0                      |
| 12    | DMSO                               | DABCO            | 150              | 24       | 0                      |
| 13    | DMSO–H <sub>2</sub> O <sup>e</sup> | DABCO            | 150              | 24       | 0                      |

<sup>a</sup> Unless otherwise indicated, the reaction conditions were as follows: **1b** (1 mmol), **2a** (1.5 mmol), Pd(OAc)<sub>2</sub> (3 mol %), ligand (6 mol %), K<sub>2</sub>CO<sub>3</sub> (3 equiv), and solvent (6 ml).

<sup>b</sup> Isolated yields.

<sup>c</sup> The mixture of DMF (5 ml) and H<sub>2</sub>O (1 ml) was used as a solvent.

<sup>d</sup> The mixture of DME (5 ml) and H<sub>2</sub>O (1 ml) was used as a solvent.

<sup>e</sup> The mixture of DMSO (5 ml) and H<sub>2</sub>O (1 ml) was used as a solvent.

(entries 6–8). In the presence of DABCO, different solvents, including DMF, toluene, DME/H<sub>2</sub>O, DMSO, and DMSO/H<sub>2</sub>O, were tested, but no desired product **5** was obtained in the absence of DMF–water system (entries 9–13). These results suggest that the solvent plays a key role for the success of the reduction of the nitro-group to an amine. Additionally, 1.5 equiv of 4-biphenylboronic acid was required for the completion of 1-bromo-2-nitro-benzene, and an increase in the amount of 4-biphenylboronic acid did not reduce the reaction time or improve the yields.

The scope of the catalytic system was evaluated by the reaction of a series of nitro-substituted aryl halides and

arylboronic acids in a 5:1 mixture of DMF and water using DABCO as the ligand, and the results are summarized in Table 2. As already observed, 1-iodo-4-nitro-benzene **1c** and nitro-substituted aryl bromides, regardless of the nitro group in the *ortho*-, *para*- or *meta*-position, were readily converted to the corresponding aryl-substituted anilines in excellent yields (entries 1–4). It is worth noting that the reaction of 1-chloro-4-nitro-benzene **1f** and **2a** was carried out smoothly to afford 4-amino-*p*-terphenyl **6** in 56% yield (entry 5). However, this catalytic system is less effective for the reaction of phenylboronic acid. Only a 40% yield of 2-aminobiphenyl **8** was obtained after 20 h of

Table 2

Reaction of nitro-substituted aryl halides or **1a** with arylboronic acids catalyzed by the Pd(OAc)<sub>2</sub>/DABCO/DMF/H<sub>2</sub>O catalytic system<sup>a</sup>

| $  \begin{array}{c}  \text{1a or} \\  \text{O}_2\text{N}-\text{C}_6\text{H}_4-\text{X} + \text{ArB(OH)}_2 \xrightarrow[\text{DMF/H}_2\text{O (5/1), 150 }^\circ\text{C}]{\text{Pd(OAc)}_2 \text{ (3 mol \%)} \\  \text{K}_2\text{CO}_3 \text{ (3 eq.)}} \text{H}_2\text{N}-\text{C}_6\text{H}_4-\text{Ar} \\  \text{1b-1f} \qquad \text{2a-2f} \qquad \qquad \qquad \text{5-12}  \end{array}  $ |           |                      |          |                        |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|----------------------|----------|------------------------|
| Entry                                                                                                                                                                                                                                                                                                                                                                                           | Substrate | ArB(OH) <sub>2</sub> | Time (h) | Yield <sup>b</sup> (%) |
| 1                                                                                                                                                                                                                                                                                                                                                                                               | (1b)      | (2a)                 | 12       | 87 ( <b>5</b> )        |
| 2                                                                                                                                                                                                                                                                                                                                                                                               | (1c)      | (2a)                 | 10       | 89 ( <b>6</b> )        |
| 3                                                                                                                                                                                                                                                                                                                                                                                               | (1d)      | (2a)                 | 12       | 85 ( <b>7</b> )        |
| 4                                                                                                                                                                                                                                                                                                                                                                                               | (1e)      | (2a)                 | 12       | 90 ( <b>6</b> )        |
| 5                                                                                                                                                                                                                                                                                                                                                                                               | (1f)      | (2a)                 | 16       | 56 ( <b>6</b> )        |
| 6                                                                                                                                                                                                                                                                                                                                                                                               | (1b)      | (2c)                 | 20       | 40 ( <b>8</b> )        |
| 7                                                                                                                                                                                                                                                                                                                                                                                               | (1b)      | (2d)                 | 20       | 45 ( <b>9</b> )        |
| 8                                                                                                                                                                                                                                                                                                                                                                                               | (1b)      | (2e)                 | 20       | 52 ( <b>10</b> )       |
| 9                                                                                                                                                                                                                                                                                                                                                                                               | <b>1a</b> | (2c)                 | 48       | 28 ( <b>11</b> )       |
| 10                                                                                                                                                                                                                                                                                                                                                                                              | <b>1a</b> | (2f)                 | 24       | 79 ( <b>12</b> )       |

<sup>a</sup> Unless otherwise indicated, the reaction conditions were as follows: nitro-substituted aryl halides or **1a** (1 mmol), arylboronic acids (1.5 mmol), Pd(OAc)<sub>2</sub> (3 mol %), DABCO (6 mol %) and K<sub>2</sub>CO<sub>3</sub> (3 equiv) in DMF (5 ml) and H<sub>2</sub>O (1 ml) at 150 °C.

<sup>b</sup> Isolated yields.

stirring at 150 °C (entry 6), the reaction of activated phenylboronic acid (electron-rich) **2d** with **1b** afforded 45% yield of product **9** (entry 7), and electron-poor phenylboronic acid (entry 8) also gave a low yield (52%). We also explored the reaction of **1a** with phenylboronic acid **2c** and 1-naphthylboronic acid **2f**, the reaction of **1a** with **2f** resulted in a moderate yield after 24 h (entry 10), but only 28% yield of methyl 12-phenyl-13-amino-7-oxo-dehydrode-isopropylabietate **11** was isolated after 48 h (entry 9).

It is known that DMF–water system is widely used as a solvent in the Suzuki–Miyaura cross-coupling reaction.<sup>9</sup> In addition, DMF, when heated with water, can generate hydrogen gas with or without the use of a suitable catalyst.<sup>10</sup> It is reasonable to believe that the DMF–water system probably served as a hydrogen source in this reaction. Although, to the best of our knowledge there is no literature precedent for the Pd-mediated reduction of aromatic nitro compounds to the corresponding aromatic amines employing DMF/H<sub>2</sub>O as a hydrogen source. Thus, we tried to use DMF/H<sub>2</sub>O as the hydrogen source to reduce nitrobenzene in the presence of 3 mol % of Pd(OAc)<sub>2</sub>, 6 mol % of DABCO, and 3 equiv of K<sub>2</sub>CO<sub>3</sub>. Unfortunately, under the present reaction conditions, no hydrogenation was observed after one or two days either under atmospheric pressure or in the Teflon-lined stainless steel Parr bomb. As a result, at the moment we cannot offer a definitive explanation for the process of the reaction and investigations in this reaction are currently underway in our laboratory.

In conclusion, we have developed a novel and efficient Pd(OAc)<sub>2</sub>/DMF/H<sub>2</sub>O catalyzed Suzuki cross-coupling reaction with simultaneous reduction of nitro- to amino-group for synthesizing aryl substituted anilines, especially polycyclic aromatic amines, which can be prepared directly from the corresponding nitro-substituted aryl halides and arylboronic acids in a single step, one-pot reaction in low to excellent yields. We have also found that the additive DABCO has a beneficial effect on the rate and the yield of the reaction. Further efforts to extend the application of the catalytic system are underway in our laboratory.

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## Supplementary data

Supplementary data contains experimental procedure, X-ray crystallographic files (CIF) for **3** and **4**, analytical data, NMR (<sup>1</sup>H and <sup>13</sup>C NMR), and MS spectrum. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.02.082.

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