## Monoarylation of Dibromoarenes by Simple Palladium Catalyst Systems: Efficient Synthesis of Bromobiaryls from Dibromoarenes and Arylboronic Acids

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**Abstract:** The Pd/C/Ph<sub>3</sub>P- and Pd(PPh<sub>3</sub>)<sub>4</sub>/Ph<sub>3</sub>P-catalyzed crosscouplings of dibromoarenes with arylboronic acids to form bromobiaryls in good to excellent yields are described. Our study showed that readily available Pd/C/Ph<sub>3</sub>P and Pd(PPh<sub>3</sub>)<sub>4</sub>/Ph<sub>3</sub>P were practically useful catalysts for the synthesis of bromobiaryls from dibromoarenes.

Key words: palladium, cross-coupling, dibromoarenes, monoarylation, arylboronic acids

Bromobiaryls are important synthetic intermediates for the synthesis of unsymmetrically substituted teraryls, highly efficient ligands, and functionalized biaryls.<sup>1-3</sup> As Pd-catalyzed Suzuki cross-coupling reaction of arylboronic acids with aryl halides represents one of the most attractive methods to form biaryls,<sup>4,5</sup> the cross-coupling of arylboronic acids with bromohalobenzenes in principle should also be an efficient method to access bromobiaryls. However, because bromobiaryls could further react with arylboronic acids to form teraryls, such Pd-catalyzed bromobiaryl-forming process is often complicated by the formation of significant amount of teraryls. Separation of bromobiaryls and teraryls often proved to be difficult. Such complication could be overcome by using bromoiodobenzenes, which possess two halo groups with significantly different reactivity, as the substrates (Scheme 1).<sup>6,7</sup> Nevertheless, dibromobenzenes are more attractive substrates than bromoiodobenzenes because they are more readily available and less expensive than bromoiodobenzenes. Over the past years, scattered protocols about the synthesis of bromobiaryls from dibromobenzenes have been reported.<sup>8-11</sup> Most of reported methods required the use of excess of dibromobenzenes to achieve good yields. Recently, Uozumi and Kikuchi reported a very promising protocol with the use of polystyrene-supported palladium-catalyst system.<sup>9</sup> However, the use of less accessible polystyrene-supported palladium catalysts coupled with no reported isolated yields significantly limited the practical use of Uozumi and Kikuchi's method. It is thus still of great synthetic value to develop simple, practically useful catalyst systems to access monobromobiaryls from dibromoarenes.

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**Scheme 1** Palladium(0)-catalyzed cross-coupling reactions of bromoiodobenzenes with arylboronic acids (1 equiv)

We have recently documented the Pd(0)/t-Bu<sub>3</sub>P-catalyzed cross-coupling of dihalobenzenes with arylboronic acids (1 equiv) to form teraryls via 'preferential oxidative addition' process.<sup>12</sup> As shown in Scheme 2, we reasoned that the Pd(0) catalyst regenerated from the first reductive elimination could (a) undergo oxidative addition with 1-aryl-n-halobenzene (AHB, n = 2, 3, or 4, Scheme 2, path A), or diffuse out of the vicinity of the AHB to undergo oxidative addition with more reactive dihalobenzene (Scheme 2, path B). Therefore, factors that can influence the oxidative addition rates or the diffusion process would influence the outcome of the reaction. Increasing the oxidative addition rates of the Pd(0) catalyst, for example, using more electron-rich phosphines as ligands, would thus lead to the formation of diarylbenzenes as the major products. This analysis led to the discovery of  $Pd(0)/t-Bu_3P$ catalyst system, which contains very electron-rich t-Bu<sub>3</sub>P, that can achieve the 'preferential oxidative addition' phenomenon.<sup>12</sup> Our study also demonstrated that the bulky group either in the substrate or ligand destabilized the interaction of the Pd(0) with the phenyl ring, leading to higher diffusion rate. We thus envisioned that by varying



**Scheme 2** Two possible pathways for Pd(0)-catalyzed cross-couplings of dibromobenzenes with arylboronic acids (1 equiv)

factors that could lead to slower oxidative addition, for example, the use of less electron-rich ligand such as  $Ph_3P$  and larger amount of the ligands, and/or faster diffusion rates, for example, bulkier Pd catalysts, higher reaction temperature, etc., it could be possible to develop catalyst systems that would favor the diffusion pathway and the formation of monohalobiarenes as the major products. Herein, we report our effort to substantiate such a possibility.

Our study began with the use of palladium on charcoal (10%, Pd/C) as catalyst as we reasoned that this palladium species has relatively large size and slow oxidative addition rate, which both features would favor the diffusion process. Our results are listed in Table 1. We found with no additional ligands, although the conversion was moderate, respectable monocoupling product (2-bromo-4'-biphenyl) to dicoupling product (4,4"-dimethyl-1,1',2',1"-

terphenyl) ratio (89:11) was observed with toluene as solvent and K<sub>2</sub>CO<sub>3</sub> (2 M in H<sub>2</sub>O) as base (Table 1, entries 1– 4). We also examined the catalyst system of Pd/C with additional phosphines. We found Ph<sub>3</sub>P was the most effective ligand for the formation of monocoupling product while more electron-rich PCy<sub>3</sub> and t-Bu<sub>3</sub>P yielded more dicoupling terphenyl products (Table 1, entries 5-9), consistent with our previous observation.<sup>12</sup> Among the solvents and bases we screened, THF and toluene were the best solvents and aqueous K<sub>2</sub>CO<sub>3</sub> was the most effective base (Table 1, entries 5, 8, 10–13). By using 12% Ph<sub>3</sub>P relative to Pd/C and with toluene or THF as solvent, a 97:3 ratio of monocoupling product to dicoupling product was obtained. We have also tested to add more Ph<sub>3</sub>P to catalyst system. We found that the ratio of monocoupling product to dicoupling product did not change much but the conversion slightly increased (Table 1, entries 15–18).



| $ \begin{array}{c} & Br \\ Br \\ Br \end{array} + (HO)_2 B \\ \hline \\ Br \\ base, 100 ^{\circ}C \end{array} + \left( \begin{array}{c} Pd cat. \\ solvent, \\ base, 100 ^{\circ}C \end{array} \right) $ |   |         |                                      |           |                                     |  |  |
|--|---|---------|--------------------------------------|-----------|-------------------------------------|--|--|
| Entry  | Pd Catalyst                                   | Solvent | Base                                 | Conversio | n (%) <sup>b</sup> M/D <sup>c</sup> |  |  |
| 1  | 3% Pd/C                                       | THF     | $K_{3}PO_{4}(S)$                     | 51        | 46:54                               |  |  |
| 2  | 3% Pd/C                                       | toluene | $K_{3}PO_{4}(S)$                     | 45        | 73:27                               |  |  |
| 3  | 3% Pd/C                                       | toluene | K <sub>2</sub> CO <sub>3</sub> (2 M) | 30        | 89:11                               |  |  |
| 4  | 3% Pd/C                                       | toluene | $K_2CO_3(S)$                         | 62        | 70:30                               |  |  |
| 5  | 3% Pd/C + 6% Ph <sub>3</sub> P                | THF     | $K_3PO_4(S)$                         | 14        | 85:15                               |  |  |
| 6  | 3% Pd/C + 6% PCy <sub>3</sub>                 | THF     | $K_{3}PO_{4}(S)$                     | 12        | 27:73                               |  |  |
| 7  | $3\% \text{ Pd/C} + 6\% t - Bu_3 P$           | THF     | K <sub>3</sub> PO <sub>4</sub> (2 M) | 20        | 52:48                               |  |  |
| 8  | $3\% \text{ Pd/C} + 6\% \text{ Ph}_3\text{P}$ | toluene | K <sub>2</sub> CO <sub>3</sub> (2 M) | 74        | 96:4                                |  |  |
| 9  | $3\% \text{ Pd/C} + 6\% t - Bu_3 P$           | toluene | K <sub>2</sub> CO <sub>3</sub> (2 M) | 65        | 15:85                               |  |  |
| 10   | 3% Pd/C + 12% Ph <sub>3</sub> P               | THF     | K <sub>2</sub> CO <sub>3</sub> (2 M) | 62        | 97:3                                |  |  |
| 11   | 2% Pd/C + 8% Ph <sub>3</sub> P                | toluene | K <sub>2</sub> CO <sub>3</sub> (2 M) | 52        | 97:3                                |  |  |
| 12   | 3% Pd/C +12% Ph <sub>3</sub> P                | toluene | K <sub>2</sub> CO <sub>3</sub> (2 M) | 80        | 95:5                                |  |  |
| 13   | 3% Pd/C + 12% Ph <sub>3</sub> P               | _       | K <sub>2</sub> CO <sub>3</sub> (2 M) | 15        | 48:52                               |  |  |
| 14   | 3% Pd/C + 12% Ph <sub>3</sub> P               | DMF     | K <sub>2</sub> CO <sub>3</sub> (2 M) | 30        | 53:47                               |  |  |
| 15   | 3% Pd/C + 15% Ph <sub>3</sub> P               | THF     | K <sub>2</sub> CO <sub>3</sub> (2 M) | 83        | 95:5                                |  |  |
| 16   | 3% Pd/C + 18% Ph <sub>3</sub> P               | THF     | K <sub>2</sub> CO <sub>3</sub> (2 M) | 90        | 94:6                                |  |  |
| 17   | 5% Pd/C + 20% Ph <sub>3</sub> P               | THF     | K <sub>2</sub> CO <sub>3</sub> (2 M) | 90        | 96:4                                |  |  |
| 18   | 5% Pd/C + 25% Ph <sub>3</sub> P               | THF     | K <sub>2</sub> CO <sub>3</sub> (2 M) | 80        | 96:4                                |  |  |

<sup>a</sup> Reaction conditions: 1,2-dibromobenzene (1.0 equiv), *p*-tolylboronic acid (1.0 equiv), base (s: solid, 3 equiv; 2 M: 2 M in H<sub>2</sub>O, 2 mL), solvent (0.5 mL), 100 °C.

<sup>b</sup> Conversion based on 1,2-dibromobenzene by <sup>1</sup>H NMR.

<sup>c</sup> Ratio based on <sup>1</sup>H NMR.

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Our Pd/C/Ph<sub>3</sub>P study suggested that  $Pd(0)/Ph_3P$  complexes might also be good catalysts for the selective monoarylation of dibromobenzenes. We have thus tested the use of readily available Pd(PPh<sub>3</sub>)<sub>4</sub> as catalyst for the reaction (Table 2). With only  $Pd(PPh_3)_4$  as catalyst, we found a ratio of 85:15 (monocoupling product to dicoupling product) was observed with excellent conversion (Table 2, entry 1). As the use of larger amount of ligand would stabilize the Pd(0) catalyst and lead to faster diffusion, we expected that the use of larger amounts of ligands would favor the formation of more monocoupling products. We thus tested to add more Ph<sub>3</sub>P into the catalyst system. We found the addition of 2-4 equivalents of Ph<sub>3</sub>P relative to  $Pd(PPh_3)_4$  gave the best results, with the ratio of monocoupling product to dicoupling product as high as 95:5 (Table 2, entries 2–7). While a similar result was observed for  $Pd_2(dba)_3/Ph_3P$  to that of  $Pd(PPh_3)_4/Ph_3P$ , the combinations of Pd<sub>2</sub>(dba)<sub>3</sub> with other ligands gave inferior results than that of Pd(PPh<sub>3</sub>)<sub>4</sub>/Ph<sub>3</sub>P (Table 2, entries 3-5, 8-11). We have also tested Pd(OAc)<sub>2</sub>/Ph<sub>3</sub>P and PdCl<sub>2</sub>/Ph<sub>3</sub>P as catalysts, we found that Pd(OAc)<sub>2</sub>/Ph<sub>3</sub>P gave similar reaction result as that of  $Pd(PPh_3)_4/Ph_3P$  (Table 2, entry 12), and  $PdCl_2/Ph_3P$  gave a slightly less satisfactory result (Table 2, entry 13).

With Pd/C/Ph<sub>3</sub>P and Pd(PPh<sub>3</sub>)<sub>4</sub>/Ph<sub>3</sub>P as catalyst systems, we have examined several 1,2-dibromoarenes and arylboronic acids (1 equiv) for the cross-coupling reactions, and our results are listed in Table 3. We found in general high ratios of monobromobiaryl to terphenyls were observed, and good to excellent yields of monobromobiaryls were obtained. We also observed that 1,2-dibromobenzenes gave higher ratio of monobromobiphenyls than that of 1,3- and 1,4-dibromobenzenes, likely because more hindered 2-bromobiphenyls underwent oxidative addition slower than 3- and 4-bromobiphenyls. In addition, we observed that unsymmetrical 4-methyl-1,2-dibromobenzene gave the two monoarylated compounds in the ratio of 57:43 (Table 3, entry 8), suggesting the initial oxidative addition rates for the two C-Br bonds with palladium(0) were not much different from each other.

 Table 2
 Pd(0)-Catalyzed Cross-Coupling Reactions of 1,2-Dibromobenzene with p-Tolylboronic Acida



| Entry | Pd Catalyst   | Solvent        | Conversion (%) | <sup>b</sup> M/D <sup>c</sup> |
|-------|---|----------------|----------------|-------------------------------|
| 1     | 3% Pd(PPh <sub>3</sub> ) <sub>4</sub>                                 | toluene        | 96             | 85:15                         |
| 2     | 3% Pd(PPh <sub>3</sub> ) <sub>4</sub> + 3% Ph <sub>3</sub> P          | toluene        | 96             | 88:12                         |
| 3     | $3\% \text{ Pd}(\text{PPh}_3)_4 + 6\% \text{ Ph}_3\text{P}$           | toluene        | 98             | 93:7                          |
| 4     | 3% Pd(PPh <sub>3</sub> ) <sub>4</sub> + 9% Ph <sub>3</sub> P          | toluene        | 93             | 93:7                          |
| 5     | 3% Pd(PPh <sub>3</sub> ) <sub>4</sub> +12% Ph <sub>3</sub> P          | toluene        | 95             | 95:5                          |
| 6     | 3% Pd(PPh <sub>3</sub> ) <sub>4</sub> + 15% Ph <sub>3</sub> P         | toluene        | 96             | 94:6                          |
| 7     | $3\% \text{ Pd}(\text{PPh}_3)_4 + 6\% \text{ Ph}_3\text{P}$           | THF            | 94             | 94:6                          |
| 8     | 1.5% Pd <sub>2</sub> (dba) <sub>3</sub> + 12% P(o-tolyl) <sub>3</sub> | toluene        | 74             | 61:39                         |
| 9     | 1.5% Pd <sub>2</sub> (dba) <sub>3</sub> + 12% P(OPh) <sub>3</sub>     | toluene        | 81             | 75:25                         |
| 10    | 1.5% Pd <sub>2</sub> (dba) <sub>3</sub> + 12%                         | -0 + P toluene | 73             | 69:31                         |
| 11    | 1.5% Pd <sub>2</sub> (dba) <sub>3</sub> +24% Ph <sub>3</sub> P        | toluene        | 90             | 96:4                          |
| 12    | 3% Pd(OAc) <sub>2</sub> +18% Ph <sub>3</sub> P                        | toluene        | 94             | 93:7                          |
| 13    | 3% PdCl <sub>2</sub> +18% Ph <sub>3</sub> P                           | toluene        | 86             | 87:13                         |

<sup>a</sup> Reaction conditions: 1,2-dibromobenzene (1.0 equiv), *p*-tolylboronic acid (1.0 equiv),  $K_2CO_3$  (2 M in  $H_2O$ , 2 mL), toluene or THF (0.5 mL), 80 °C (THF as solvent), 100 °C (toluene as solvent).

<sup>b</sup> Conversion based on 1,2-dibromobenzene by <sup>1</sup>H NMR.

<sup>c</sup> Ratio based on <sup>1</sup>H NMR.

Table 3Pd/C/Ph3P- and Pd(PPh3)4/Ph3P-Catalyzed Cross-Coupling Reactions of Dibromobenzenes with Arylboronic Acidsa



<sup>a</sup> Reaction conditions: dibromobenzene (1.0 equiv), arylboronic acid (1.0 equiv),  $K_2CO_3$  (2 M, 1.5 mL), THF or toluene (0.5 mL). Method A: 3% Pd(PPh<sub>3</sub>)<sub>4</sub> + 6% Ph<sub>3</sub>P, THF, 80 °C; method B: 3% Pd/C + 12% Ph<sub>3</sub>P, toulene, 100 °C.

<sup>b</sup> Ratio based on <sup>1</sup>H NMR.

<sup>c</sup> Isolated yields of bromobiphenyls.

<sup>d</sup> Two isomers (57:43) were obtained.

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As aryl-substituted pyridines have attracted great interest in organic synthesis,<sup>13</sup> we have further expanded the dibromoarene scope to dibromopyridines. Our results are listed in Table 4. We found both Pd/C/Ph<sub>3</sub>P and Pd(PPh<sub>3</sub>)<sub>4</sub>/Ph<sub>3</sub>P were highly efficient catalyst systems. High yields of 2-aryl-3-bromopyridines were obtained. The observed excellent ratio of monobromobiaryls and diarylpyridines might likely be due to the different reactivity of the two C–Br bonds in 2,3-dibromopyridine.<sup>14</sup> Our study provides a highly efficient method to access 2-aryl-3-bromopyridines, which could further be converted to other aryl-substituted pyridines.

 Table 4
 Pd/C/Ph<sub>3</sub>P- and Pd(PPh<sub>3</sub>)<sub>4</sub>/Ph<sub>3</sub>P-Catalyzed Cross-Coupling Reactions of 2,3-Dibromopyridine with Arylboronic Acids<sup>a</sup>



<sup>a</sup> Reaction conditions: dibromobenzene (1.0 equiv), arylboronic acid (1.0 equiv),  $K_2CO_3$  (2 M, 1.5 mL), THF or toluene (0.5 mL). Method A: 3% Pd(PPh<sub>3</sub>)<sub>4</sub> + 6% Ph<sub>3</sub>P, THF, 80 °C; method B: 3% Pd/C + 12% Ph<sub>3</sub>P, toluene, 100 °C.

- <sup>b</sup> Ratio based on <sup>1</sup>H NMR.
- <sup>c</sup> Isolated yields of 2-bromobiaryls.
- <sup>d</sup> A ratio of M/D = 87:13 was observed with 3% Pd(PPh<sub>3</sub>)<sub>4</sub> as catalyst.

In summary, based on our understanding of the mechanism of Pd-catalyzed cross-coupling reactions and our previous study on 'preferential oxidative addition', we identified, by varying factors that could influence the oxidative addition rates and/or diffusion rates of the Pd(0) intermediates, readily available Pd/C/Ph<sub>3</sub>P and Pd(PPh<sub>3</sub>)<sub>4</sub>/ Ph<sub>3</sub>P complexes as highly efficient catalysts for the monocross-coupling reaction of dibromoarenes with arylboronic acids. The easy availability of the catalyst systems, and the high yields of monobromobiaryl products make our protocols potentially very useful in the preparation of monobromobiaryls including 2-aryl-3-bromopyridines.<sup>15</sup>

**Supporting Information** for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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