

## Palladium(II)-Catalyzed Coupling of *p*-Xylene via Regioselective C–H Activation in TFA

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**Summary:** A homocoupling of *p*-xylene to afford biaryl- or diarylmethane as a major product has been carried out in a catalytic system of Pd(OAc)<sub>2</sub>/CF<sub>3</sub>CO<sub>2</sub>H (TFA)/K<sub>2</sub>S<sub>2</sub>O<sub>8</sub>. In this coupling reaction, the aryl and benzylic C–H bonds of *p*-xylene can be selectively activated just by tuning the concentration of TFA.

Selective C–H bond activation or functionalization is a challenging subject for researchers in organic and organometallic chemistry.<sup>1</sup> More recently, a few studies disclosed the activation of aryl versus benzylic C–H bonds of alkyl-substituted benzenes; for example, the C–H bonds of toluene could be cleaved successfully by platinum(II) or rhodium(III) complexes in an excellent regioselectivity.<sup>2,3</sup> In these selective C–H bond activation processes, steric and electronic factors from both transition-metal complexes and arenes have been emphasized and investigated. Herein, we report that the aryl and benzylic C–H bonds in *p*-xylene could be selectively activated to form biaryl- or diarylmethane as a major product in a catalytic system of Pd(OAc)<sub>2</sub>/CF<sub>3</sub>CO<sub>2</sub>H (TFA)/K<sub>2</sub>S<sub>2</sub>O<sub>8</sub>. It is notable that the regioselectivity of this homocoupling could be readily controlled by tuning the concentration of TFA in this system.

Our current work has been focused on palladium(II)-catalyzed couplings of various arenes via aryl C–H activation under mild conditions. Most recently, we reported that unsymmetrical biaryls could be prepared through a highly selective cross-coupling of two different arenes in a catalytic system of Pd(OAc)<sub>2</sub>/TFA/K<sub>2</sub>S<sub>2</sub>O<sub>8</sub> just by tuning the concentrations of TFA and substrates.<sup>4</sup> In that report, it is concluded that (1) the selectivity of different aryl C–H activations is mainly dependent on the concentrations of various arenes in the mixture when the reactivity of initial Pd(II) complex is high enough; (2) the concentration of TFA may influence enormously the reactivity of Pd(II) complexes especially the arylpalladium intermediate; the more active aryl C–H bonds are preferentially attacked in electron-rich arenes in a lower concentration of TFA. However, in the same system, it was found that not only a biaryl, 2,5,2',5'-tetramethyldiphenyl **3a**, but also a diarylmethane, 4'-methyl-2,5-dimethyldiphenylmethane **2a**, could be observed in a homocoupling of *p*-xylene **1a**, which may suggest that both aryl

and benzylic C–H bonds might be cleaved by the Pd(II) complex under these conditions. More interestingly, the ratio of coupling products (**2a/3a**) was 20/80 in the presence of Pd(OAc)<sub>2</sub> in 1.0 mmol of TFA (Table 1, entry 2); however, the ratio of products (**2a/3a**) was reversed completely to 80/20 just by adding more TFA (20 mmol) in the same reaction (Table 1, entry 4). Moreover, when adding K<sub>2</sub>S<sub>2</sub>O<sub>8</sub> as the oxidant, a catalytic process could be established and the ratio of two different coupling products was not changed too much (Table 1, entries 1–4). On the other hand, increasing the reaction temperature did not strongly affect the ratio of products especially when a larger amount of TFA was employed in the catalytic or stoichiometric reaction (Table 1, entries 5 and 6).

To investigate the effect of TFA on this regioselective homocoupling of *p*-xylene further, we screened the ratio of coupling products (**2a/3a**) and total TON with various amounts of TFA, and the results are shown in Figure 1. They indicate that both the ratio of **2a/3a** and the total TON gradually increased with increasing the amount of TFA added in these reactions, which may imply that the benzylic C–H bond activations are preferred in a higher concentration of TFA.

On the other hand, the effect of temperature on this homocoupling was also studied under a selected reaction condition in which a moderate amount of TFA was employed (Figure 2). It was observed that the total TON was gradually enhanced and the major product was **2a** rather than **3a** at higher temperature, which is consistent with the benzylic C–H activation by Pt(II) complexes being favored thermodynamically in some cases.<sup>2b</sup> Another explanation is possible that the reactivity of Pd(II) complexes can be enhanced to cleave the inactive benzylic C–H bonds at higher temperature. However, when the concentration of TFA was too high or too low, the ratios of homocoupling products could not be controlled efficiently just by changing the reaction temperature. In addition, reaction time cannot greatly influence the distribution of homocoupling products in these reactions (Table S-7 in the Supporting Information). Thus, the concentration of TFA might be the major factor to determine the regioselective C–H activation in the homocoupling of *p*-xylene.

To be compared with **1a**, moreover, other alkylarenes with different steric hindrance such as toluene **1b**, mesitylene **1c**, and *p*-diethylbenzene **1d** were also employed in these catalytic coupling reactions (Table 2). For **1b**, only the biaryl isomers were obtained in the case of using a small amount of TFA (Table 2, entry 1); in contrast, the biaryl products from **1c** or **1d** separately were barely observed by the use of any amounts of TFA in these reactions (Table 2, entries 5–8), which may suggest that the steric hindrance of arenes could block the formation of biaryls through a double aryl C–H activation. On the other hand, on using a larger amount of TFA, the benzylic C–H bonds of any alkylarenes in Table 2 could be activated by Pd(II) complexes to give the corresponding diarylalkanes (Table 2, entries 2, 4, 6, and 8). It is necessary to point out that

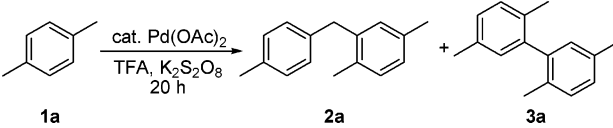
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Table 1. Pd(II)-Catalyzed Coupling of *p*-Xylene in TFA<sup>a</sup>


entry	TFA (mmol)	K <sub>2</sub> S <sub>2</sub> O <sub>8</sub> (mmol)	temp (°C)	ratio (2a:3a)	TON (2a:3a)
1	0.25	0.80	45	28:72	4.1
2 <sup>b</sup>	1.0	none	45	20:80	0.41
3	5.0	0.80	45	89:11	10.6
4 <sup>b</sup>	20.0	none	45	80:20	0.41
5	5.0	0.80	70	86:14	11.8
6 <sup>b</sup>	20.0	none	70	83:17	0.99

<sup>a</sup> Conditions: **1a** (5.0–6.0 mmol), Pd(OAc)<sub>2</sub> (0.025 mmol), 20 h, GC analysis. <sup>b</sup>Pd(OAc)<sub>2</sub> (0.1 mmol).

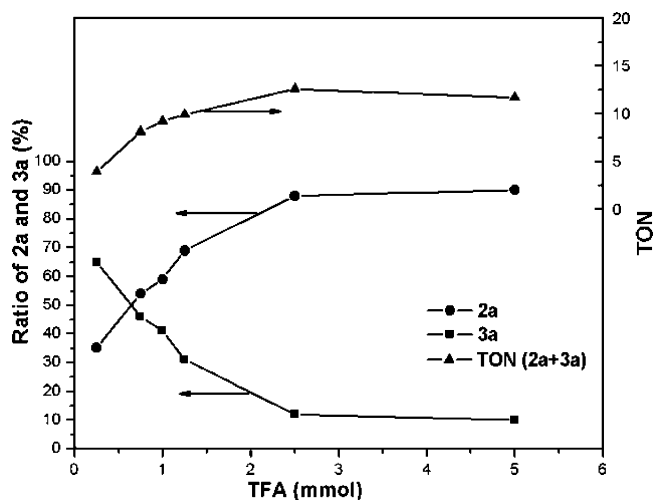


Figure 1. Effect of TFA on Pd(II)-catalyzed coupling of *p*-xylene. Conditions: **1a** (5.0 mmol), Pd(OAc)<sub>2</sub> (0.025 mmol), K<sub>2</sub>S<sub>2</sub>O<sub>8</sub> (0.8 mmol), 45 °C, 16 h, GC analysis.

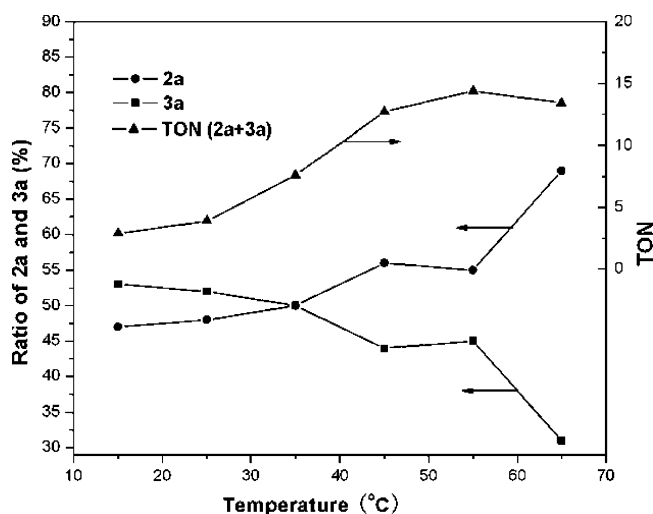


Figure 2. Effect of temperature on Pd(II)-catalyzed coupling of *p*-xylene. Conditions: **1a** (5.0 mmol), Pd(OAc)<sub>2</sub> (0.025 mmol), TFA (1.25 mmol), K<sub>2</sub>S<sub>2</sub>O<sub>8</sub> (0.8 mmol), 16 h, GC analysis.

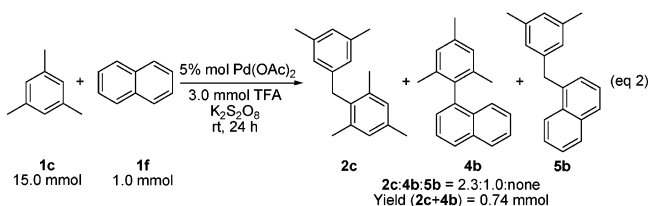
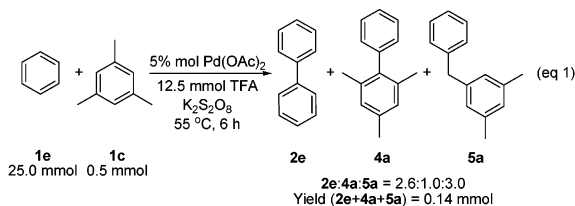
the terminal alkyl C–H bonds in *p*-diethylbenzene could not be cleaved in this system (Table 2, entries 7 and 8). The yields of all coupling products are in the range 2–16%, and the TONs are also limited because these homocoupling products easily undergo further reactions especially when amounts of them are accumulated in the reaction solutions, which is similar to the cross-coupling of arenes reported in our previous work.<sup>4</sup>

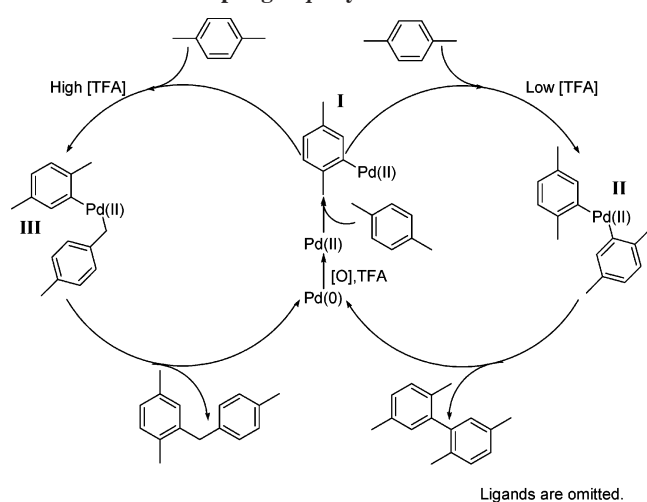
Table 2. Pd(II)-Catalyzed Coupling of Various Alkylarenes<sup>a</sup>

entry	arene	TFA (mmol)	product	ratio (2:3)	TON (2+3)
1		0.5		0:100	3.9
2	<b>1b</b>	7.5		6:94	11.1
3		0.5		30:70 (34:66)	5.1 (7.5)
4	<b>1a</b>	7.5		86:14 (87:13)	18.1 (16.3)
5		0.5		100:0	(14.4)
6	<b>1c</b>	7.5		100:0	33.1
7 <sup>b</sup>		0.5		-	trace
8 <sup>b</sup>	<b>1d</b>	7.5		>99:1	4.4

<sup>a</sup> Conditions: **1a–c** (10.0 mmol), Pd(OAc)<sub>2</sub> (0.025 mmol), 45 °C, 24 h, isolated product (GC analysis in parentheses). <sup>b</sup>**1d** (5.0 mmol).

To gain more insight into the process of benzylic C–H bond activation, mesitylene **1c** was selected to undergo cross-couplings with benzene **1e** and naphthalene **1f**, respectively, in a higher concentration of TFA. On the basis of the previously proposed mechanism of Pd(II)-catalyzed cross-coupling of two different arenes,<sup>4</sup> the use of excess **1e** to react with **1c** could avoid the formation of **2c**, which is the only possible homocoupling product from **1c** (eq 1). Furthermore, since no **2c** was actually observed in eq 1, it is reasonable that the phenyl Pd(II) intermediates were generated by Pd(II) catalysts attacking benzene **1e** and then these intermediates reacted with the aryl and benzylic C–H bonds of **1c** to form the final cross-coupling products **4a** and **5a**, respectively. In addition, in the reaction of **1f** with excess **1c** (eq 2), the absence of the cross-coupling product **5b** indicates that the coupling products **2c** and **4b** resulted from the reactions of the 2,4,6-trimethylphenyl Pd(II) intermediates

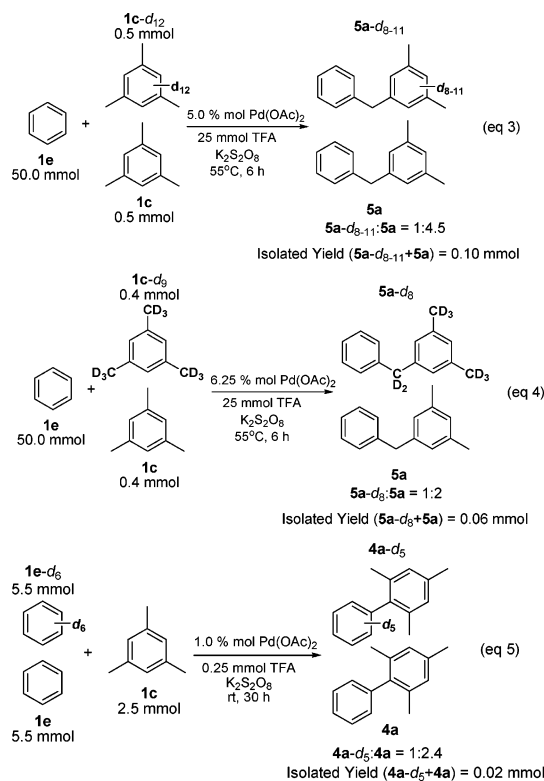


**Scheme 1. Tentative Mechanism of Pd(II)-Catalyzed Coupling of *p*-Xylene in TFA**


with the benzylic C–H bonds of **1c** and the aryl C–H bonds of **1f**, respectively. Therefore, neither benzylic radicals nor benzylic Pd(II) complexes generated by the attack of initial Pd(II) catalysts on the benzylic C–H bonds of alkylarenes are probably involved in these coupling reactions. Moreover, as in our previous report,<sup>4</sup> with a low concentration of TFA, only biaryls could be obtained in these Pd(II)-catalyzed cross-couplings of simple arenes, which is related only to aryl C–H activations.

According to the above results, a tentative mechanism of Pd(II)-catalyzed coupling of *p*-xylene via regioselective C–H activation in TFA has been proposed (Scheme 1). The first step is still the Pd(II) catalyst attacking an aryl C–H bond electrophilically to form an aryl Pd(II) intermediate, I.<sup>4</sup> Subsequently, if complex I is not very reactive in a small amount of TFA, it prefers to attack another aryl C–H bond selectively to generate a diaryl Pd(II) intermediate, II, which is similar to the case of cross-coupling of arenes;<sup>4</sup> on the contrary, if the reactivity of complex I is greatly enhanced in a large amount of TFA, the difference of activity between the aryl C–H bond and the relatively inactive benzylic C–H bond cannot affect the following process as before, and the benzylic C–H bond, which is sterically less-hindered, is preferentially activated by complex I to give an aryl benzyl Pd(II) intermediate, III. After reductive eliminations of complexes II and III, biaryl- and diarylmethane are obtained, respectively. Although we favor the formation of aryl benzyl Pd(II) complex III by an electrophilic attack of the aryl Pd(II) complex II on a benzylic C–H bond in this coupling, partly supported by eq 1 and eq 2, the generation of benzylic radicals under these reaction conditions, especially at higher temperature as mentioned in other reports,<sup>5</sup> could not be ruled out completely. The actual effects of TFA on the reactivity of Pd(II) catalysts are still unclear even though a few investigations and explanations were reported.<sup>6</sup> Furthermore, since stoichiometric couplings could occur in the presence of a Pd(II) complex in TFA without any oxidants and bases (Table 1, entries 2, 4, and 6), the involvement of Pd(IV) and proton abstraction of arene should be excluded in our processes.<sup>7</sup>

To investigate the aryl versus benzylic C–H activations further, a series of cross-coupling reactions involving deuterated arenes were tested. It was found that the results either from the



reaction of **1e** with **1c/1c-d<sub>12</sub>** in eq 3 (**5a-d<sub>8-11</sub>/5a** = 1/4.5) or from the reaction of **1e** with **1c/1c-d<sub>9</sub>** in eq 4 (**5a-d<sub>8</sub>/5a** = 1/2) indicate that the activation of benzylic C–H bonds in the second step affects the reaction rate of the formation of diarylmethane mostly, although a few D/H exchanges may happen between the aryl-D atoms of **1c-d<sub>12</sub>** and the TFA protons when the concentration of TFA is higher.<sup>8</sup> On the other hand, the ratio of biaryls **4a-d<sub>5</sub>/4a** is 1/2.4 in the cross-couplings of **1e/1e-d<sub>6</sub>** with **1c** in eq 5;<sup>8</sup> thus, the activation of aryl C–H bonds of **1e/1e-d<sub>6</sub>** in the first step with a lower concentration of TFA may determine the entire reaction rate of the formation of biaryl, which is analogous to the Pd(II)-catalyzed cross-coupling of benzene with naphthalene.<sup>4</sup>

In summary, we report the first regioselective coupling of *p*-xylene in the presence of Pd(II) catalyst to generate biaryl- or diarylmethane as a major product just by tuning the concentration of TFA used in the reaction. Although this method is not a practical one because of its low yields, it is expected to be helpful to further realize the relationships among transition-metal complexes, reaction conditions, and alkylarenes in aryl versus benzylic C–H activations. The actual mechanism and the application of this regioselective coupling reaction will be explored.

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**Supporting Information Available:** Experimental details and characterization of coupling products. The material is available free of charge via the Internet at <http://pubs.acs.org>.

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