醋酸钯催化甲苯中无配体的 Suzuki 反应

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摘要：报道了一种甲苯中醋酸钯催化无配体的 Suzuki 反应体系. 以 $K_3PO_4 \cdot 7H_2O$ 为碱，在该体系中可高效进行芳基溴代物和芳基硼酸的 Suzuki 反应，且具有反应条件温和、无需惰性气体保护等特点. 在 $n(ArBr) = 0.5$ mmol, $n(ArB(OH)_2) = 0.75$ mmol, $x(Pd(OAc)_2) = 1$ mol%, $n(K_3PO_4 \cdot 7H_2O) = 1.0$ mmol, $v(甲苯) = 2$ ml 的优化条件下，4-溴硝基苯和苯硼酸在 75 ℃ 反应 5 min，分离收率即达 99%，TOF 高达 $1\,188\,h^{-1}$.

关键词：Suzuki 反应；芳基硼酸；芳基卤代物；钯；无配体；甲苯

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An Efficient Protocol for a Pd(OAc)₂-Catalyzed Ligand-Free Suzuki Reaction in Toluene

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Abstract: An efficient protocol for a Pd(OAc)₂-catalyzed ligand-free Suzuki reaction of aryl bromides with arylboronic acids in the presence of $K_3PO_4 \cdot 7H_2O$ in toluene under mild and aerobic conditions afforded cross-coupling products in good to excellent yields. Under the optimized reaction conditions (i.e., 0.5 mmol ArBr, 0.75 mmol ArB(OH)₂, 1 mol% Pd(OAc)₂, 1.0 mmol $K_3PO_4 \cdot 7H_2O$, 2 ml toluene), the Suzuki reaction between 4-nitrobromobenzene and phenylboronic acid afforded a 99% isolated yield in 5 min at 75 ℃ and a TOF of up to $1\,188\,h^{-1}$.

Key words: Suzuki reaction; arylboronic acid; aryl halide; palladium; ligand-free; toluene

Pd 催化芳基卤代物和芳基硼酸的交叉偶联反应制备联芳类化合物的 Suzuki 反应，已成为有机合成中构建 C–C 键的主要方法之一[1~7]. 它具有反应条件温和、原料安全、低毒及底物的适用性广等优点，已广泛应用于天然产物、医药、农药、除草剂、高分子传导材料和液晶材料等的合成[8,9]. Pd 催化 Suzuki 反应的效率通常取决于配体的性质和配位能力，迄今，一系列膦配体[10]、环钯络合物[11]和氮杂环卡宾络合物[12]已成功用于 Suzuki 反应. 但是，大多数配体存在合成困难，成本较高，且对水和氧气敏感，反应过程中需要溶剂除水和惰性气体保护等不足. Pd 催化无配体的反应体系因具有操作简单和成本低等优

点而引起化学家的广泛兴趣[13~20]. 甲苯作为一种廉价易得的有机溶剂已被应用于配体促进的 Suzuki 反应[21~23]，但有关甲苯中 Pd 催化无配体的反应体系研究较少[24]. 本文报道一种在甲苯中 Pd(OAc)₂ 催化无配体的 Suzuki 反应体系，该体系可在空气条件下快速、有效地实现芳基溴代物和芳基硼酸的交叉偶联.

芳基溴代物和芳基硼酸由 Alfa Aesar 公司提供. 其它化学试剂使用前未经处理直接使用.

Suzuki 反应操作过程如下. 首先将 2.0 ml 甲苯加入圆底烧瓶中，然后依次加入 0.5 mmol 芳基卤代物、0.75 mmol 芳基硼酸、0.005 mmol Pd(OAc)₂ 和 1.0 mmol 碱，在 75 ℃ 进行反应. 反应结束后，用乙酸乙

酯萃取反应产物 3 次 (15 ml × 3), 合并有机相后, 经真空浓缩有机相得到粗产品, 再经柱层析 (200~300 目硅胶) 分离, 得到分析纯的联芳类化合物, 其氢核磁谱在 Varian Inova 400 核磁仪上获得.

以 0.5 mmol 4-溴苯甲醚与 0.75 mmol 苯硼酸的偶联为模型反应, 分别考察了 Pd 源、碱种类和反应温度对 Suzuki 反应性能的影响, 结果见表 1. 由表可见, 以二价 Pd 的 Pd(OAc)$_2$ 和 PdCl$_2$ 为催化剂时, Suzuki 反应表现出较高的催化活性 (实验 1 和 2), 尤以 Pd(OAc)$_2$ 催化活性最高, 在 1 mol% Pd(OAc)$_2$ 存在下, 该反应能在 80 min 定量完成, 这与文献结果相符[25]. 零价 Pd 源 Pd/C 和 Pd$_2$(dba)$_3$ (实验 3 和 4) 的催化活性明显低于二价 Pd 源, 这与我们的前期工作[16,17]以及 Venkatraman 等[26]的结果吻合. 因此, 以下实验均以 Pd(OAc)$_2$ 为催化剂.

表 1　Suzuki 反应条件的优化

Table 1　Optimization of reaction conditions for the Suzuki reaction

Entry	Pd source	Base	Temperature (°C)	Time (min)	Isolated yield (%)
1	Pd(OAc)$_2$	K$_2$CO$_3$	100	80	99
2	PdCl$_2$	K$_2$CO$_3$	100	80	65
3	Pd$_2$(dba)$_3$	K$_2$CO$_3$	100	80	25
4	Pd/C	K$_2$CO$_3$	100	80	44
5	Pd(OAc)$_2$	K$_3$PO$_4$·7H$_2$O	100	70	98
6	Pd(OAc)$_2$	CH$_3$ONa	100	210	81
7	Pd(OAc)$_2$	NaOH	100	120	54
8	Pd(OAc)$_2$	Na$_2$CO$_3$	100	180	trace
9*	Pd(OAc)$_2$	K$_3$PO$_4$·7H$_2$O	100	50	95
10*	Pd(OAc)$_2$	K$_3$PO$_4$·7H$_2$O	75	60	99
11*	Pd(OAc)$_2$	K$_3$PO$_4$·7H$_2$O	50	120	97

Reaction conditions: 0.5 mmol 4-bromoanisole, 0.75 mmol arylboronic acid, 1.0 mmol base, 1 mol% catalyst, 4 ml toluene (*2 ml toluene).

碱在 Suzuki 交叉偶联反应中起到极其重要的作用. 由表 1 可见, 在本文所采用的碱中, 以 K$_3$PO$_4$·7H$_2$O 的促进效果最强 (实验 5). 4-溴苯甲醚和苯硼酸的偶联反应在 K$_3$PO$_4$·7H$_2$O 存在下反应 70 min, 产品收率达 98%. 这可能是由于 K$_3$PO$_4$·7H$_2$O 在 Suzuki 反应中不仅起到碱的作用, 而且具有稳定活性中心 Pd 的作用[27,28]. 其次, K$_2$CO$_3$ 也表现出较强的促进作用 (实验 1). 相对于钾盐, CH$_3$ONa 和 NaOH 在反应中的促进作用较弱 (实验 6 和 7). 另外, 弱碱 Na$_2$CO$_3$ 在 Suzuki 反应中几乎没有促进作用, 即使反应延长至 3 h 也难以进行 (实验 8). 由此可见, 就各种碱的促进效果而言, 钾盐好于钠盐, 强碱好于弱碱. Zhang 等[29]认
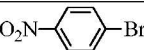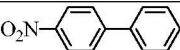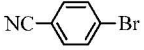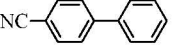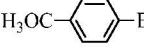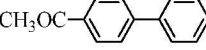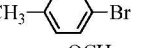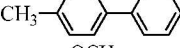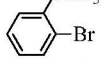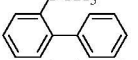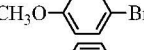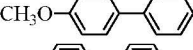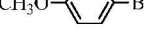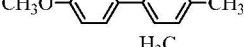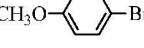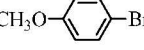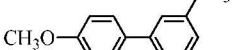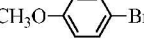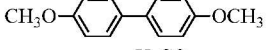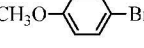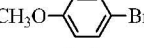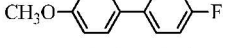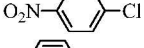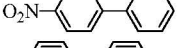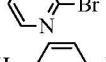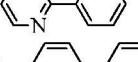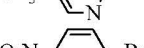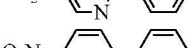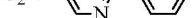
为, 具有较大离子半径的钾离子在金属交换过程中起到模板作用, 因而促进该步骤的进行.

由表 1 还可以看出, 当反应温度从 100 °C 降到 75 °C 时, 催化剂活性略有降低, 但继续降至 50 °C 时, 催化剂的催化效率明显降低 (实验 9~11). 因此, 适宜的反应温度为 75 °C.

在催化剂 Pd(OAc)$_2$ 用量 1 mol%、温度 75 °C 和以 K$_3$PO$_4$·7H$_2$O 为碱的反应条件下, 考察了甲苯中无配体的 Suzuki 反应的底物普适性, 结果见表 2. 由表

表2　卤代芳烃和芳基硼酸的 Suzuki 反应

Table 2　Suzuki reaction between aryl halides and arylboronic acids

R^1–Y–X + (HO)$_2$B–R^2 $\longrightarrow$ R^1–Y–（）–R^2

X = Br, Cl; Y = C, N

Entry	Ar-X	Product	Time (min)	Isolated yield (%)
1	O$_2$N–〈〉–Br	O$_2$N–〈〉–〈〉	5	99
2	NC–〈〉–Br	NC–〈〉–〈〉	7	99
3	CH$_3$OC–〈〉–Br	CH$_3$OC–〈〉–〈〉	15	98
4	CH$_3$–〈〉–Br	CH$_3$–〈〉–〈〉	40	98
5	〈OCH$_3$〉–Br	〈OCH$_3$〉–〈〉	60	96
6	CH$_3$O–〈〉–Br	CH$_3$O–〈〉–〈〉	60	99
7	CH$_3$O–〈〉–Br	CH$_3$O–〈〉–〈〉–CH$_3$	150	83
8	CH$_3$O–〈〉–Br	CH$_3$O–〈〉–〈H$_3$C〉	150	91
9	CH$_3$O–〈〉–Br	CH$_3$O–〈〉–〈CH$_3$〉	110	99
10	CH$_3$O–〈〉–Br	CH$_3$O–〈〉–〈〉–OCH$_3$	150	85
11	CH$_3$O–〈〉–Br	CH$_3$O–〈〉–〈H$_3$CO〉	150	24
12	CH$_3$O–〈〉–Br	CH$_3$O–〈〉–〈〉–F	150	35
13	O$_2$N–〈〉–Cl	O$_2$N–〈〉–〈〉	360	7[a]
14	〈N〉–Br	〈N〉–〈〉	480	20/39[b]
15	CH$_3$–〈N〉–Br	CH$_3$–〈N〉–〈〉	480	27/42[b]
16	O$_2$N–〈N〉–Br	O$_2$N–〈N〉–〈〉	480	trace

Reaction conditions: 0.5 mmol 4-bromoanisole, 0.75 mmol arylboronic acid, 1 mmol K$_3$PO$_4$·7H$_2$O, 75 °C ([a]100 °C), 1 mol% Pd(OAc)$_2$ ([b]2 mol% Pd(OAc)$_2$), 2 ml toluene.

可见, 苯硼酸与一系列芳基溴代物的 Suzuki 反应均表现出较高的催化活性. 4-硝基溴苯与苯硼酸反应 5 min, 产品收率即达 99%, TOF 高达 1 188 h^{-1}. 令人惊喜的是, 位阻较大的邻溴苯甲醚与苯硼酸也能顺利发生 Suzuki 偶联反应, 产品收率达 96% (实验 5).

研究表明[16,17,30], 对于水相中的 Suzuki 反应, 含供电子基团的苯硼酸反应活性高于苯硼酸. 但由表 2 可见, 在甲苯中进行 Suzuki 反应, 无论苯硼酸含有供电子基团, 还是吸电子基团, 其反应活性均下降 (实验 7~12). 这与文献结果一致[31]. 在本文反应体系中, 含吸电子基团的苯硼酸反应活性 (实验 12) 比含供电子基团的 (实验 7) 更低, 这与文献结果一致[16,17,25,30]. 令人意外的是, 具有位阻效应的邻甲苯硼酸反应活性 (实验 8) 反而比对甲基苯硼酸 (实验 7) 更高. 并且邻甲基苯硼酸的反应活性也比同样具有位阻效应的邻甲氧基苯硼酸 (实验 11) 更高. 这可能是由于在金属交换步骤中, 邻甲氧基的位阻效应高于邻甲基, 从而导致反应活性降低[32].

基于溴代底物在该反应体系中表现出良好的活性, 本文继续考察了芳基氯代物和氮杂环芳基溴代物在该反应体系中的活性, 结果见表 2. 可以看出, 芳基氯代物几乎没有反应活性, 即使温度升至 100 ℃, 产品收率也仅为 7% (实验 13). 氮杂环芳基溴代物反应活性也较低 (实验 14~16), 即使催化剂用量增至 2 mol%, 产品收率也仅为 40% 左右.

综上所述, 本文发展了一种以甲苯为溶剂, 醋酸钯为催化剂的 Suzuki 反应体系, 它可高效催化芳基溴代物和芳基硼酸的 Suzuki 反应, 且具有反应条件温和、在空气中进行和无需配体等特点. 但对氮杂环芳基溴代物和芳基氯代物的催化活性有待于提高.

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英 译 文
English Text

Since the first report on the palladium-catalyzed cross-coupling of aryl halides with arylboronic acids in 1979 [1], Suzuki chemistry has attracted attention from many researchers [2–7] and is considered to be an exceedingly important methodology for the construction of carbon-carbon and carbon-heteroatom bonds during the syn-

thesis of biaryls. In particular, structural unit formation in compounds for pharmaceuticals, herbicides, natural products, and advanced materials is of interest [8,9]. Generally, the efficiency of the palladium-mediated catalyst is strongly dependent on the nature of the coordination ligands and a series of ligand-assisted palladium catalysts have been synthesized and screened for various types of reactions and these include phosphines [10], palladacycles [11], and *N*-heterocyclic carbene complexes [12]. However, most of the ligands and complexes are difficult to synthesize and are sensitive to oxygen and/or moisture. Recently, ligand-free catalytic systems for the Suzuki reaction have been developed because they are simpler and cheaper than ligand-promoted systems [13–20]. As a readily accessible and cheap solvent, toluene is widely applied to the ligand-promoted palladium-catalyzed Suzuki reaction [21–23]; however, it is rarely used in ligand-free systems [24]. We thus report a fast and efficient protocol for the $Pd(OAc)_2$-catalyzed ligand-free Suzuki reaction of aryl bromides with arylboronic acids in toluene and under air.

All aryl halides and arylboronic acids were purchased from Alfa Aesar. All other chemicals were obtained commercially and used without any prior purification. ^1H NMR spectra were recorded on a Varian Inova 400 spectrometer. All products were isolated by short chromatography using a silica gel (200–300 mesh) column with petroleum ether unless otherwise noted.

A mixture of aryl halides (0.5 mmol), arylboronic acid (0.75 mmol), $Pd(OAc)_2$ (1 mol%, 1.12 mg), $K_3PO_4 \cdot 7H_2O$ (1.0 mmol, 338 mg), and toluene (2 ml) was stirred at 75 °C for the indicated time and monitored by TLC. The mixture was added to brine (15 ml) and extracted twice with acetic ether (15 ml × 3). The solvent was concentrated under vacuum and the product was isolated.

In general, an efficient palladium-catalyzed cross-coupling reaction is regulated by a number of factors such as palladium source, base, reaction temperature, and time. For our initial studies, the Suzuki reaction was carried out using 0.5 mmol 4-bromoanisole, 0.75 mmol phenylboronic acid in toluene, and 1 mol% palladium salts under specific temperatures and reaction times depending on the reactions executed.

The palladium sources employed in the Suzuki reaction are crucial to the catalytic efficiency. As shown in Table 1, the palladium sources dramatically affect the reaction activity. It is clear that precatalysts with palladium(II) salts such as $Pd(OAc)_2$ and $PdCl_2$ exhibited high catalytic activity (Table 1, entries 1 and 2). $Pd(OAc)_2$ performed more efficiently in the Suzuki reaction than $PdCl_2$ in toluene, which is consistent with the results of Leadbeater and Marco [25]. Using 1 mol% $Pd(OAc)_2$ as the catalyst, the cross-coupling reaction was completed quantitatively within 80 min (Table

1, entry 1). However, the catalytic activity was relatively low using zerovalent palladium sources such as Pd/C or $Pd_2(dba)_3$ (Table 1, entries 3 and 4), which is consistent with our recent results [16,17] and Venkatraman et al. [26]. Among the palladium sources screened, $Pd(OAc)_2$ gave the best results.

The influence of the base on the reaction was examined and the results are listed in Table 1. The cross-coupling of 4-bromoanisole with phenylboronic acid was complete within 70 min in the presence of 1.0 mmol $K_3PO_4 \cdot 7H_2O$ (Table 1, entry 5). The reason for this might be that $K_3PO_4 \cdot 7H_2O$ acts as a base and a stabilizer for the active palladium species [27,28]. K_2CO_3 also exhibited high activity in the model reaction (Table 1, entry 1). However, CH_3ONa and $NaOH$ were not noticeably effective in the cross-coupling reaction (Table 1, entries 6 and 7). To our surprise, only a trace amount of cross-coupling product was obtained when using Na_2CO_3 as a base, even over a prolonged reaction time of 3 h (Table 1, entry 8). An explanation has been proposed by Zhang et al. [29] who found that the large potassium cation has a templating effect during the nucleophilic attack of phenylboronic acid on the Pd(II) intermediate formed by oxidative addition. However, the smaller sodium cation is less reactive because of more steric crowding in the transmetalation step.

To optimize the reaction temperature, we carried out experiments at different temperatures (50, 75, and 100 °C) for the Suzuki reaction between 4-bromoanisole and phenylboronic acid and the results are shown in Table 1 (Entry 9–11). We found that better results were obtained in terms of reaction time and yield at 75 °C in toluene and in the presence of $Pd(OAc)_2$ as well as $K_3PO_4 \cdot 7H_2O$ (Table 1, entry 10).

To evaluate the scope and limitations of this procedure, the reactions of a series of aryl halides with arylboronic acids were examined using 1 mol% $Pd(OAc)_2$ at 75 °C in toluene and with $K_3PO_4 \cdot 7H_2O$ as a base. As shown in Table 2, the cross-coupling reactions of the phenylboronic acids with various aryl bromides resulted in high isolated yields of the products. The Suzuki reaction of 4-nitrobromobenzene with phenylboronic acid afforded a 99% isolated yield in 5 min and a TOF of up to 1 188 h^{-1}. In addition, the sterically demanding aryl bromides were coupled with phenylboronic acid to give high yields of the product. For example, 2-bromoanisole was as reactive as 4-bromoanisole and resulted in a high product yield (Table 2, entry 5).

The effect of substituents in different positions for the arylboronic acids on the Suzuki coupling reaction was studied further (Table 2, entries 7–12). Generally, the coupling reactions of the arylboronic acids containing electron-rich groups such as methyl and methoxy proceeded more efficiently than those of phenylboronic acid in aqueous media [16,17,30]. However, our results show that the presence of substituent groups (Table 2, entries 7–12) on the aromatic

ring of the arylboronic acid reduced its reactivity in toluene, which was consistent with the report of Klingensmith et al. [31]. In agreement with previous literature [16,17,25,30], the arylboronic acid with an electron-withdrawing group (Table 2, entry 12) was found to be less catalytically active than that with an electron-donating group (Table 2, entry 7). Interestingly, the arylboronic acid bearing an electron-donating group at the *para*-position (Table 2, entry 7) showed lower reactivity compared to that with an electron-donating group at the *ortho*-position (Table 2, entry 8). The sterically hindered arylboronic acid with a 2-CH$_3$ substituent (Table 2, entry 8) was more reactive than that with a 2-OCH$_3$ substituent (Table 2, entry 11). Presumably, the 2-CH$_3$ group results in weak steric crowding in the transmetalation step, however, the 2-OCH$_3$ group gave a lower yield because of increased steric crowding in the transmetalation step [32].

We subsequently investigated the application of this catalytic system to the coupling reaction between aryl chloride or heteroaryl bromides with arylboronic acids, respectively. Under our reaction conditions, the cross-coupling between the aryl chloride and the arylboronic acid gave incomplete conversion even with an increase in the reaction temperature (100 °C). We then screened representative heteroaryl bromides for the Pd(OAc)$_2$-mediated Suzuki reaction. The heteroaryl bromides can be coupled using this protocol but only in low yields even with the use of 2 mol% Pd(OAc)$_2$.

In conclusion, we developed a fast and efficient protocol for the Suzuki reaction between aryl bromides and arylboronic acids catalyzed by Pd(OAc)$_2$ in toluene under air and ligand-free conditions. The advantages of this procedure are a rapid reaction time, low catalyst loading, absence of ligands, aerobic reaction conditions and relatively mild reaction temperatures.

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