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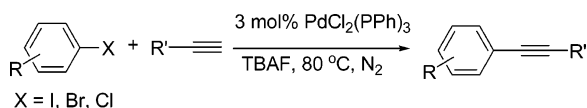
Modified Palladium-Catalyzed Sonogashira Cross-Coupling Reactions under Copper-, Amine-, and Solvent-Free Conditions

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$\text{PdCl}_2(\text{PPh}_3)_2$ combined with TBAF under solvent-free conditions provided general and fast Sonogashira cross-coupling reactions of aryl halides with terminal alkynes. In particular, this protocol could be applied to the reactions of deactivated aryl chlorides. In the presence of 3 mol % of $\text{PdCl}_2(\text{PPh}_3)_2$ and 3 equiv of TBAF, a number of ArX species ($\text{X} = \text{I}, \text{Br}, \text{Cl}$) were coupled with alkynes to afford the corresponding products in moderate to excellent yields under copper-, amine-, and solvent-free conditions.

The Sonogashira cross-coupling reaction is well-known as being one of the most important and utilized reactions for the construction of carbon–carbon bonds, in particular for the formation of alkynes.^{1–9} The most commonly used catalytic systems for this transformation include $\text{PdCl}_2(\text{PPh}_3)_2$, $\text{PdCl}_2/\text{PPh}_3$, and $\text{Pd}(\text{PPh}_3)_4$ together with CuI as the cocatalyst and large amounts of amines as the solvents or cosolvents.^{2–9} However, the presence of CuI can result in the formation of some Cu(I) acetylides in situ that can undergo oxidative

homocoupling reactions of alkynes readily.¹⁰ Buchwald and Gelman have also found that CuI had a deleterious effect on the Sonogashira cross-coupling reaction.^{8c} Amines, another additive, also have a characteristic foul smell and pungent flavor. Furthermore, the scopes of these reactions performed with the combination of $\text{PdCl}_2(\text{PPh}_3)_2$ ($\text{PdCl}_2/\text{PPh}_3$ or $\text{Pd}(\text{PPh}_3)_4$), CuI , and amines as the catalytic system are generally limited to aryl iodides, bromides, and activated chlorides (particularly nitrogen-containing heteroaryl chlorides).^{2,5k,8} For these reasons, a new

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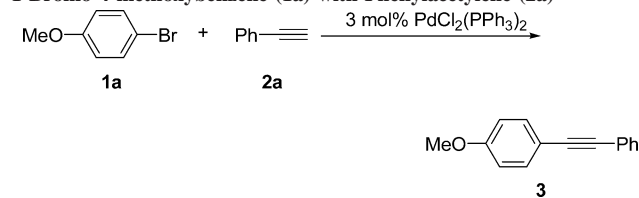
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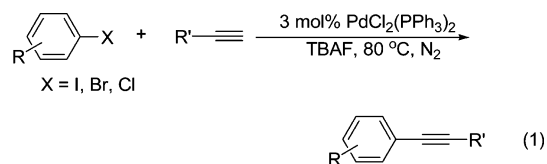
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TABLE 1. Palladium-Catalyzed Sonogashira Cross-Coupling of 1-Bromo-4-methoxybenzene (**1a**) with Phenylacetylene (**2a**)^a

entry	Pd cat. (amt, mol %)	time (h)	yield (%) ^b
1	PdCl ₂ (PPh ₃) ₂ (3)	3	86
2	PdCl ₂ (3)/PPh ₃ (6)	3	65
3	Pd(PPh ₃) ₄ (3)	3	41
4	PdCl ₂ (3)	14	25
5	Pd(OAc) ₂ (3)	14	51
6	Pd(dba) ₂ (3)	14	42
7 ^c	PdCl ₂ (PPh ₃) ₂ (3)	3	88
8 ^{c,d}	PdCl ₂ (PPh ₃) ₂ (3)	24	55
9 ^e	PdCl ₂ (PPh ₃) ₂ (3)	3	16

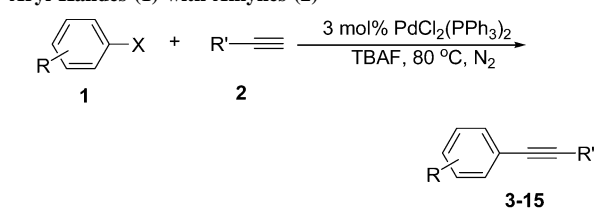
^a Reaction conditions: **1** (0.5 mmol), **2** (0.6 mmol), Pd, TBAF·3H₂O (6 equiv) at 80 °C under N₂. ^b Isolated yield. ^c TBAF·3H₂O (3 equiv). ^d At room temperature. The conversion of **1a** was 61%. ^e KF (3 equiv) instead of TBAF. 80% of **1a** was recovered.

system for the Sonogashira cross-coupling reaction should be developed. Recently, Mori and co-workers have reported that TBAF is a useful promoter for the amine-free palladium-catalyzed Sonogashira cross-coupling reaction; organic solvents such as THF were still required, and only examples of aryl iodides and bromides were described.^{9a} Here we report that PdCl₂(PPh₃)₂ combined with TBAF can afford general and fast Sonogashira cross-coupling reactions of a wide range of ArX species (X = I, Br, Cl) with terminal alkynes under copper-, amine-, and solvent-free conditions (eq 1).



The palladium-catalyzed Sonogashira reaction of 1-bromo-4-methoxybenzene (**1a**) with phenylacetylene (**2a**) using TBAF as the base was first examined, and the results are summarized in Table 1. It was found that while PdCl₂(PPh₃)₂, PdCl₂/PPh₃, Pd(PPh₃)₄, PdCl₂, Pd(OAc)₂ and Pd(dba)₂ all catalyzed the Sonogashira reaction without the aid of any solvents as the media, PdCl₂(PPh₃)₂ turned out to be the best catalyst in terms of yields and reaction rates (entries 1–6). In the presence of 3 mol % of PdCl₂(PPh₃)₂, treatment of 1 mmol of **1a** with 1.2 mmol of **2a** and 6 equiv of TBAF afforded an 86% yield of the corresponding coupled product **3** in 3 h,¹¹ whereas the yield of **3** was decreased to 65% when the combination of PdCl₂ and PPh₃ was used as the catalytic system (entries 1 and 2). Low yields of **3** were isolated after 3–14 h using Pd(PPh₃)₄, PdCl₂, Pd(OAc)₂, and Pd(dba)₂ as the catalysts (entries 3–6). Identical results were still observed when the amount of TBAF was reduced to 3 equiv (88% yield; entry 7). It was interesting to find that although the substrate **1a** could not be consumed completely even after 24 h, the isolated yield of the expected

(11) We also attempted to reuse the PdCl₂(MeCN)₂/TBAF system; however, only a 45% yield of **3** was isolated after 12 h from the second run of the reaction of **1a** with **2a**.

TABLE 2. PdCl₂(PPh₃)₂-Catalyzed Sonogashira Cross-Coupling of Aryl Halides (**1**) with Alkynes (**2**)^a

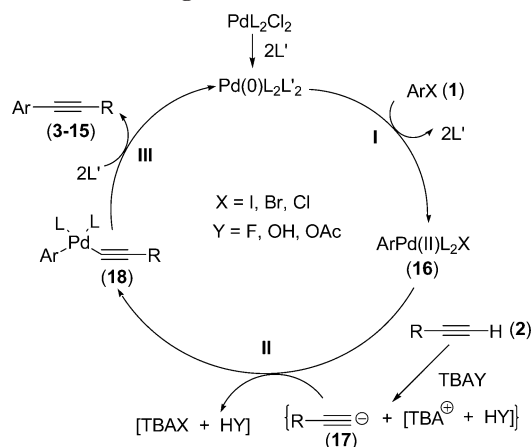
Entry	ArX	Alkyne	Time (h)	Yield (%) ^b
1	(1a)	C ₈ H ₁₇ ≡ (2b)	25	98 (4)
2	(1a)	≡CH ₂ OH (2c)	25	80 (5)
3	(1b)	Ph≡ (2a)	0.5	92 (3)
4	(1c)	(2a)	0.25	>99 (6)
5	(1d)	(2a)	1	96 (6)
6 ^c	(1d)	(2a)	6	98 (6)
7	(1d)	(2b)	1	95 (7)
8	(1d)	(2c)	0.8	85 (8)
9	(1d)	(2d)	1	96 (9)
10	(1d)	(2e)	1	98 (10)
11	(1e)	(2a)	2	>99 (11)
12	(1f)	(2a)	2	98 (12)
13	(1g)	(2a)	3	>99 (13)
14	(1h)	(2a)	2	97 (14)
15	(1i)	(2a)	3	93 (15)
16 ^d	(1j)	(2a)	12	45 (6)
17 ^{ef}	(1j)	(2a)	6	65 (6)
18 ^{eg}	(1j)	(2a)	21	64 (6)
19 ^{eh}	(1j)	(2a)	6	68 (6)
20 ^{ei}	(1j)	(2b)	20	51 (7)
21 ^{ej}	(1k)	(2a)	20	58 (12)
22 ^{ek}	(1l)	(2a)	18	48 (13)
23 ^{el}	(1m)	(2a)	20	40 (3)

^a Reaction conditions: **1** (0.5 mmol), **2** (0.6 mmol), PdCl₂(PPh₃)₂ (3 mol%), and TBAF·3H₂O (3 equiv) at 80 °C under N₂. ^b Isolated yield. ^c At room temperature. ^d 48% of **1j** was recovered. ^e **2** (0.8 mmol). ^f 30% of **1j** was recovered. ^g 28% of **1j** was recovered. ^h At 100 °C, 30% of **1j** was recovered. ⁱ 40% of **1j** was recovered. ^j 30% of **1k** was recovered. ^k 46% of **1l** was recovered. ^l 58% of **1m** was recovered.

product **3** was desirable (entry 8). A relatively low yield was isolated after 3 h when TBAF was replaced by KF (entry 9).

As demonstrated in Table 2, coupling of **1a** with the other alkynes **2b,c** was also carried out smoothly to give the corresponding products **4** and **5** in 98% and 80% yields, respectively, in the presence of 3 mol % of PdCl₂(PPh₃)₂ and 3 equiv of TBAF (entries 1 and 2). It is interesting to note that

SCHEME 1. Working Mechanism



the reactions of aryl iodides **1b,c** with **2a**, respectively, were very rapid under the optimal reaction conditions (entries 3 and 4). For example, iodide **1c** could be consumed completely in 0.25 h and a quantitative yield of the desired product **6** was obtained. The results also indicated that the palladium-catalyzed Sonogashira reaction tolerated a variety of functional groups, and couplings of other aryl bromides **1d–i** with alkynes **2a–e** occurred efficiently to produce excellent yields of the corresponding products **6–15** in 1–6 h (entries 5–15). In comparison with the results of entries 7 and 8 in Table 1, the coupling of the activated bromide **1d** with **2a** could be conducted smoothly at room temperature after 6 h to give a yield identical with that at 80 °C (entries 5 and 6). It is noteworthy that moderate yields of the desired products are observed in the reactions of aryl chlorides, including activated and deactivated aryl chlorides (entries 16–23). Treatment of 0.5 mmol of 1-chloro-4-nitrobenzene (**1j**) with 0.6 mmol of phenylacetylene (**2a**), 3 mol % of $\text{PdCl}_2(\text{MeCN})_2$, and 3 equiv of TBAF afforded only a 45% yield of **6** together with 48% of **1j** (entry 16). As indicated in our previous report,^{6d} the amount of alkynes affected the reaction. Thus, we expected to enhance the yield of the present reaction by increasing the amount of alkyne. Indeed, although the substrate **1j** still could not be consumed completely, the yield of **6** was enhanced to 65% when 0.8 mmol of **2a** was added (entry 17). Neither prolonged reaction time nor enhanced reaction temperature affected the yield of **6** (entries 17–19). Under the same reaction conditions, the reactions of chlorides **1k–m** with **2a** were also conducted smoothly in moderate yields (entries 21–23).

Although the effect of TBAF in these reactions was not clear, TBAF acted as a base and phase-transfer catalysis (PTC) to favor the desired reaction is confirmed. To elucidate the effect of TBAF in the palladium-catalyzed Sonogashira cross-coupling reaction, a working mechanism as outlined in Scheme 1 was

formulated on the basis of the mechanism reported earlier.^{2,3,6a,9,12} The Pd(0) species could be generated readily from the reaction of $\text{Pd(PPh}_3)_2\text{Cl}_2$ with solvents, substrates, additives, and/or ligands etc.,² followed by the oxidative addition of Pd(0) with ArX to form intermediate **4**. Then replacement between intermediate **16** and the acetylene anion **17**, which was generated by the reaction of alkyne **2** with TBAF, occurred to afford intermediate **18**. Finally, the reductive elimination of intermediate **5** took place to regenerate the active Pd(0) species and give the desired product **3–15**. Thus, several beneficial roles of TBAF might occur in the reaction on the basis of the previous results^{2,6a,9,12} and the present results: (i) activation of the active Pd(0) species with the formation of anionic Pd species, (ii) stabilization of the low-coordination Pd(0) species (**16** and **18**), (iii) deprotonation of the acidic hydrogen in the alkyne (in pathway II), and (iv) phase-transfer catalysis for the inorganic base/substrate/product phases.^{2,10,12}

In summary, we have developed a general method for the rapid Sonogashira cross-coupling reaction of aryl halides with terminal alkynes using $\text{PdCl}_2(\text{PPh}_3)_2$ combined with TBAF. In comparison with the earlier established palladium-catalyzed Sonogashira cross-coupling reaction, this protocol proceeds under copper-, amine-, and solvent-free conditions and is extended to the deactivated aryl chlorides with moderate to excellent yields.

Experimental Section

Typical Experimental Procedure for the Sonogashira Cross-Coupling Reactions. A mixture of aryl halide **1** (0.5 mmol), alkyne **2** (0.6 mmol), $\text{PdCl}_2(\text{PPh}_3)_2$ (3 mol %), and $\text{TBAF}\cdot 3\text{H}_2\text{O}$ (3 equiv) was stirred under N_2 at 80 °C for the desired time until complete consumption of starting material as monitored by TLC. After the mixture was washed with water, extracted with ether, and evaporated, the residue was purified by flash column chromatography (hexane/ethyl acetate) to afford the corresponding coupled products **3–15**.

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Supporting Information Available: Text and figures giving analytical data and spectra (^1H and ^{13}C NMR) for all the products **3–15** and a typical procedure for the palladium-catalyzed Sonogashira cross-coupling reaction. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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