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Efficient Palladium-Catalyzed Homocoupling Reaction and Sonogashira Cross-Coupling Reaction of Terminal Alkynes under Aerobic Conditions

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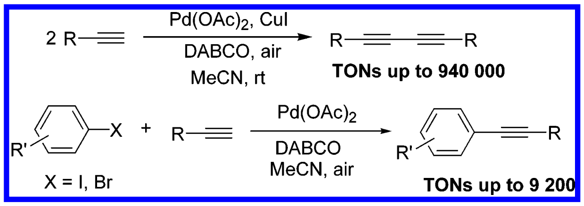

An efficient method for palladium-catalyzed homocoupling reaction of terminal alkynes in the synthesis of symmetric diynes is presented. The results showed that both $Pd(OAc)_2$ and CuI played crucial roles in the reaction. In the presence of 2 mol % $Pd(OAc)_2$, 2 mol % CuI, 3 equiv of Dabco, and air, homocoupling of various terminal alkynes afforded the corresponding symmetrical diynes in moderate to excellent yields, whereas low yields were obtained without either $Pd(OAc)_2$ or CuI. Moreover, high TONs (turnover numbers; up to 940 000 for the reaction of phenylacetylene) for the homocoupling reaction were observed. Under similar reaction conditions, cross-coupling of 1-iodo-4-nitrobenzene with phenylacetylene was also carried out smoothly in quantitative yield. However, the presence of CuI disfavored the palladium-catalyzed Sonogashira cross-coupling reactions of the less active aryl iodides and bromides. In the presence of 0.01−2 mol % $Pd(OAc)_2$, a number of aryl iodides and bromides were coupled with terminal alkynes in good to excellent yields. It is noteworthy that this protocol employs mild, efficient, aerobic, copper-free, and ligand-free conditions.

Introduction

Alkynes are useful building blocks in organic synthesis and a basic functional group in many natural products and bioactive compounds.[1] For these reasons, much attention has been given to the development of efficient and selective methods for the synthesis of alkynes.[2−15] Of these transformations, both the palladium-catalyzed homocoupling reaction of terminal alkynes[2−10] and Sonogashira cross-coupling reaction of aryl halides with terminal alkynes[2,11−15] represent two particularly effective approaches to the synthesis of the functionalized alkynes. For the Pd(II)-catalyzed homocoupling reactions of terminal alkynes,[16] several mild and efficient catalytic systems have been reported, including the use of (1) $Pd(PPh_3)_4$, CuI, Et_3N, and chloroacetone in C_6H_6;[4] (2) $Pd(dba)_2$, n-Bu_4NBr, NaOH, and allyl bromide in CH_2Cl_2;[5] (3) $PdCl_2(PPh_3)_2$, CuI, and I_2 in i-Pr_3N;[6] (4) $PdCl_2(PPh_3)_2$, CuI, amines (Et_3N or Dabco), and bromoacetate in THF;[7] and (5) $PdCl_2(PPh_3)_2$, CuI, PPh_3, and O_2 (or I_2) in Et_3N/MeCN.[8,9] Besides additives such PPh_3 and TBAB, a stoichiometric amount of a reoxidant is necessary for successful homocoupling in all cases,

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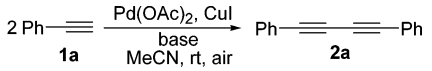
which is consistent with the results of Marder and coworkers.[9,11] Very recently, we also reported a phosphine- and amine-free, $PdCl_2$/CuI-catalyzed method for homocoupling of alkynes in the synthesis of diynes.[10] However, a stoichiometric amount of harmful reoxidant (Me_3NO) was still required. To satisfy environmental concerns, O_2 is an attractive alternative to the reported reoxidants. It is noteworthy that the use of O_2 as the reoxidant by Fairlamb, Marder, [14]and co-workers often results in incomplete reactions to afford moderate to good yields in many cases.[9,11] Therefore, the use of air as an environmentally benign reoxidant for the phosphine-free palladium(II)-catalyzed homocoupling reaction is still significant.

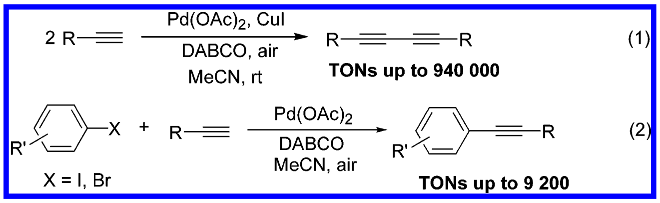
For the Sonogashira cross-coupling reaction, the combination of palladium, phosphines, and CuI is generally employed as the catalytic system under degassed conditions.[2,11,12] However, many phosphine ligands are air-sensitive and expensive, resulting in significant limits on their synthetic applications.[12,13] Furthermore, the presence of CuI can result in the formation of some Cu(I) acetylides in situ that can readily undergo oxidative homocoupling reaction of alkynes.[2−11] To overcome these drawbacks, many phosphine- and copper-free palladium-catalyzed Sonogashira cross-coupling protocols have been developed.[14,15] However, only one report by Yang and coworkers on the palladium-catalyzed Sonogashira cross-coupling reaction employed under aerobic, ligand-free, and copper-free conditions.[15e] In the presence of 1 mol % $PdCl_2$, various aryl iodides were treated with terminal alkynes to afford moderate to good yields of the corresponding cross-coupled products in aqueous media. However, the scope of this method is limited to aromatic iodides, and rather high catalyst loading is required. For these reasons, the development of efficient, ligand-free, and copper-free palladium-catalyzed Sonogashira cross-coupling reaction under aerobic conditions still remains an area of current interest. Here, we report our findings of those reactions in detail (eqs 1 and 2).

TABLE 1. Palladium-Catalyzed Homocoupling Reaction of Phenylacetylene (1a)[a]



entry	base (equiv)	time (h)	isolated yield (%)
1[b]	0	7	8
2	DABCO (0.5)	3.5	74
3	DABCO (1.0)	2.5	83
4	DABCO (2.0)	2	90
5	DABCO (3.0)	2	100
6[c]	DABCO (3.0)	12	88
7	Et_3N (3.0)	7	81
8[d]	NaOAc (3.0)	20	15
9[e]	DABCO (3.0)	2	58
10[f]	DABCO (3.0)	2	65

[a] Unless otherwise indicated, the reaction conditions were as follows: **1a** (1 mmol), $Pd(OAc)_2$ (2.0 mol %), CuI (2.0 mol %), base, and MeCN (5 mL) at room temperature under air. [b] Conversion of **1a** was 10% as determined by GC analysis. [c] Under argon (bubbled). [d] Conversion of **1a** was 25% as determined by GC analysis. [e] Without CuI. Conversion of **1a** was 60% as determined by GC analysis. [f] Without $Pd(OAc)_2$. Conversion of **1a** was 100% as determined by GC analysis.



Results and Discussion

Pd(OAc)$_2$ and CuI-Catalyzed Homocoupling of Terminal Alkynes. As shown in Table 1, our initial goal was to evaluate the effect of bases on the Pd(II)-catalyzed homocoupling of phenylacetylene (**1a**). The results showed that use of DABCO as the base gave the best results, and the amount used also affected both rates and yields of the reaction (entries 1−8). Without base, only 8% yield of the corresponding diyne **2a** was isolated after 7 h in

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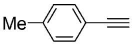
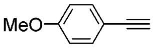
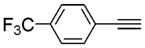
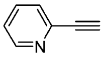
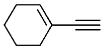
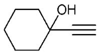
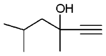
(16) Compared with the copper-mediated homocoupling reactions of terminal alkynes, the palladium-catalyzed homocoupling transformations are arguably more mild, efficient, and chemoselective. Moreover, the palladium-catalyzed homocoupling reactions of aliphatic alkynes as well as aromatic alkynes afford good to excellent yields, whereas low to moderate yields are often obtained when homocoupling of aliphatic alkynes were employed under the Hay reaction conditions. Reference 3a has reviewed the scope and limitations of both the copper-catalyzed homocoupling reactions and palladium-catalyzed homocoupling reactions in detail.

TABLE 2. Palladium-Catalyzed Homocoupling Reactions of Alkynes[a]

Entry	Alkyne	Time (h)	Isolated yield (%)
1	 (**1b**)	2	98 (**2b**)
2	 (**1c**)	48	70 (**2c**)
3	 (**1d**)	12	75 (**2d**)
4	 (**1e**)	2	91 (**2e**)
5	n-C$_5$H$_{11}$—≡ (**1f**)	2	100 (**2e**)
6[b]	n-C$_5$H$_{11}$—≡ (**1f**)	2	50 (**2f**)
7	n-C$_8$H$_{17}$—≡ (**1g**)	2	100 (**2g**)
8	t-Bu—≡ (**1h**)	2	100 (**2h**)
9	 (**1i**)	3	97 (**2i**)
10	 (**1j**)	30	95 (**2j**)
11	 (**1k**)	40	93 (**2k**)
12	≡—CH$_2$OAc (**1l**)	6	71 (**2l**)
13[c]	≡—CH$_2$OAc (**1l**)	6	26 (**2l**)

[a] Unless otherwise indicated, the reaction conditions were as follows: **1** (1 mmol), Pd(OAc)$_2$ (2.0 mol %), CuI (2.0 mol %), DABCO (3 equiv), and MeCN (5 mL) at room temperature under air. [b] Without Pd(OAc)$_2$. Conversion of **1f** was 55% as determined by GC analysis. [c] Without Pd(OAc)$_2$. Conversion of **1l** was 30% as determined by GC analysis.

the presence of Pd(OAc)$_2$ (2.0 mol %), CuI (2.0 mol %), and air (entry 1), whereas 74% yield of **2a** was obtained after 3.5 h when 0.5 equiv of DABCO was added (entry 2). The yield of **2a** was increased sharply to 100% by further increasing the amount of DABCO to 3 equiv (entry 5). Other bases such as Et$_3$N and NaOAc were less effective than DABCO (entries 5, 7, and 8). The previous results[2,9,11] suggested that the presence of O$_2$ could improve the homocoupling reaction, so we then tested the effect of O$_2$. Indeed, the reaction is slow, and only 90% yield was obtained for 12 h when argon was bubbled to remove air (entry 6). It is noteworthy that both Pd(OAc)$_2$ and CuI play crucial roles in the reaction (entries 5, 9, and 10). Without either Pd(OAc)$_2$ or CuI, low yields of **2a** were isolated after 2 h. The following results in Table 2 also demonstrated that Pd(OAc)$_2$ had a fundamental influence on the reaction. Without Pd(OAc)$_2$, CuI-catalyzed homocoupling of **1f** and **1l**, respectively, afforded the corresponding products **2f** and **2l** in rather low yields in the presence of DABCO and air (50 and 26% yields, respectively; entries 6 and 13 in Table 2).

Under the optimized reaction conditions, the homocoupling reactions of various other terminal alkynes **1b**−**l** were carried out smoothly to afford the corresponding diynes **2b**−**l** in moderate to high yields, and the results are summarized in Table 2. The results show that the palladium-catalyzed homocoupling reaction tolerated a variety of functional groups, and the yields and rates are based upon the substrates. For homocoupling of aromatic alkynes **1b**−**e**, the corresponding diynes **2b**−**e** were obtained in 98, 70, 75, and 91% yields, respectively, in the presence of Pd(OAc)$_2$ (2.0 mol %), CuI (2.0 mol %), and DABCO (3.0 equiv) (entries 1−4). It is noteworthy that aliphatic alkynes **1f**−**h** give the corresponding coupled products **2f**−**h** in quantitative yields (entries 5, 7, and 8). Homocoupling of alkynes bearing different functional groups such as 1-ethynyl cyclohexene (**1i**), 1-ethynyl cyclohexanol (**1j**), 3,3,5-trimethyl hex-1-yn-3-ol (**1k**), and propargyl acetate (**1l**), was also carried out smoothly to afford the corresponding diynes **2i**−**l** in 97, 95, 93, and 71% yields, respectively (entries 9−12).

TABLE 3. Screening the Catalytic Efficiency of the Palladium-Catalyzed Homocoupling Reaction in Air[a]

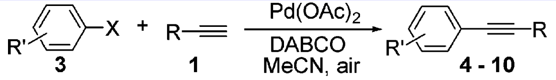
entry	alkyne	Pd(OAc)$_2$ (mol %)	time (h)	yield (%)[b]	TON
1	**1a**	0.001	10	100	100 000
2	**1a**	0.0001	12	94	940 000
3	**1f**	0.001	12	100	100 000
4	**1f**	0.0001	12	90	900 000
5	**1l**	0.001	20	60	60 000
6	**1l**	0.0001	24	41	410 000

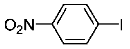
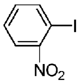
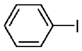
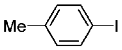
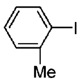
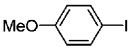
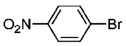
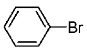
[a] Unless otherwise indicated, the reaction conditions were as follows: **1** (1 mmol), Pd(OAc)$_2$, CuI (2.0 mol %), DABCO (3 equiv), and MeCN (5 mL) at room temperature in air. [b] Isolated yield.

The catalytic efficacy was further evaluated, and the results are summarized in Table 3. For coupling of alkynes **1a**, **1f**, and **1l**, the catalyst loadings could be decreased to 0.0001 mol %, and moderate to good yields could still be obtained after prolonged stirring. For example, phenylacetylene (**1a**) was efficiently coupled in high yield (94%, TON = 940 000) for 12 h when the catalyst loading was decreased to 0.0001 mol %. The results also suggested that Pd(OAc)$_2$ played a criucial role in the reaction. Without Pd(OAc)$_2$, **1a** was consumed completely in 2 h to afford 65% yield of **2a** (entry 10 in Table 1), whereas 94% yield of **2a** was obtained even in the presence of 0.0001 mol % Pd (entry 2 in Table 3).

Pd(OAc)$_2$-Catalyzed Sonogashira Cross-Coupling Reaction of Aryl Halides with Terminal Alkynes. As demonstrated in Table 4, we were gratified to observe that the Sonogashira cross-coupling reactions of aryl halides with terminal alkynes were also carried out smoothly under the above optimized reaction conditions. In the presence of Pd(OAc)$_2$ (2.0 mol %), CuI (2.0 mol %), and air, 1-iodo-4-nitrobenzene (**3a**) was reacted with **1a** to afford the corresponding cross-coupled product **4** in quantitative yield (entry 1). However, our goal was to employ palladium catalysts under ligand-free, copper-free, and aerobic conditions to effect the Sonogashira cross-coupling reaction. As expected, quantitative yield of **4** was still obtained in the absence of CuI (entry 2). Furthermore, the presence of CuI disfavored the cross-coupling reactions of the less active aryl iodides and bromides (entries 7, 8, 11, and 12). For example, in the presence of Pd(OAc)$_2$ (2.0 mol %), CuI (2.0 mol %), and air, only 11% yield of **7** was isolated after 24 h, whereas the yield of **7** was increased to 74% without CuI (entries 7 and 8). The results also indicated that Pd(OAc)$_2$ was highly efficient for the Sonogashira cross-coupling reactions. In the presence of 0.01 mol % Pd(OAc)$_2$, coupling

TABLE 4. $Pd(OAc)_2$-Catalyzed Sonogashira Cross-Coupling Reaction of ArX (X = I, Br) with Terminal Alkynes[a]



Entry	ArX	Alkyne	$Pd(OAc)_2$ (mol%)	Time (h)	Yield[b] (%)
1[c]	 **(3a)**	**(1a)**	2	18	100 (**4**)
2	**(3a)**	**(1a)**	2	18	100 (**4**)
3	**(3a)**	**(1a)**	0.1	20	96 (**4**)
4	**(3a)**	**(1a)**	0.01	26	92 (**4**)
5	**(3a)**	**(1g)**	0.1	20	90 (**5**)
6	 **(3b)**	**(1a)**	0.1	20	95 (**6**)
7[c]	 **(3c)**	**(1a)**	0.1	24	11 (**7**)
8	**(3c)**	**(1a)**	0.1	24	74 (**7**)
9	 **(3d)**	**(1a)**	0.1	24	56 (**8**)
10	 **(3e)**	**(1a)**	0.1	24	55 (**9**)
11[c]	 **(3f)**	**(1a)**	2	24	8 (**10**)
12	**(3f)**	**(1a)**	2	24	98 (**10**)
13	**(3f)**	**(1a)**	0.1	24	85 (**10**)
14	 **(3g)**	**(1a)**	2	40	19 (**4**)
15[d]	**(3g)**	**(1a)**	2	22	42 (**4**)
16[e]	**(3g)**	**(1a)**	2	22	90 (**4**)
17[e]	**(3g)**	**(1g)**	2	24	87 (**5**)
18[e]	 **(3h)**	**(1a)**	2	24	trace (7)

[a] Unless otherwise indicated, the reaction conditions were as follows: **3** (1 mmol), **1** (1.2 mmol), $Pd(OAc)_2$, DABCO (3 equiv), and MeCN (5 mL) at room temperature under air. [b] Isolated yield. [c] CuI (2 mol %), and ca. 90% yield of **2a** was isolated (yield based on **1a**). [d] At 70 °C. [e] **1** (1.8 mmol) at 50 °C.

of **3a** with **1a** still afforded good yield of **4** after prolonged stirring (92%, TON: 9200; entry 4). It is noteworthy that coupling of a number of aryl iodides, including the deactivated 1-iodo-4-methoxybenzene (**3f**), with alkynes are carried out smoothly to afford moderate to excellent yields in the presence of 0.1 mol % $Pd(OAc)_2$ (entries 5–13). For the coupling reactions of aryl bromides; however, the catalytic efficiency was decreased to some extent (entries 14–18). For example, treatment of 1-bromo-4-nitrobenzene (**3g**) with **1a**, $Pd(OAc)_2$ (2 mol %), and DBCO (3 equiv) afforded a rather low yield even at 70 °C due to the competition between the homocoupling reaction and the cross-coupling reaction (entries 14 and 15). As earlier reports,[2,11,13,14] we expected to shift the selectivity toward the cross-coupling reaction by increasing the amount of alkynes. Indeed, good yields of the desired products were obtained at 50 °C when the amount of alkynes was increased to 1.8 equiv (entries 16 and 17). An attempt to couple bromobenzene (**3h**) was not successful (entry 18).

Conclusion

In summary, both ligand-free palladium-catalyzed homocoupling reaction and Sonogashira cross-coupling reaction under aerobic conditions have been developed. In the presence 2 mol % of $Pd(OAc)_2$, 2 mol % CuI, 3 equiv of DABCO, and air, homocoupling of various terminal alkynes was carried out efficiently, providing moderate to excellent yields and high TONs (maximal TONs up to 940 000). This protocol not only tolerates a range of functional groups but also does not require any additives such as phosphine ligands and TBAB. We also found that the presence of CuI disfavored the palladium-catalyzed Sonogashira cross-coupling reactions of the less active aryl iodides and bromides. Without CuI, the cross-coupling reactions of a number of aryl iodides and bromides with terminal alkynes afforded good to excellent yields of the desired products in the presence of 0.01–2 mol % $Pd(OAc)_2$. It is noteworthy that our protocol employs a relatively low palladium catalyst loading under mild, aerobic, copper-free, and ligand-free conditions. Currently, further efforts to apply these methods in other transformations are underway in our laboratory.

Experimental Section

(1) Typical Experimental Procedure for the Palladium-Catalyzed Homocoupling Reactions of Alkynes. A mixture of alkyne **1** (1 mmol), $Pd(OAc)_2$ (2.0 mol %), CuI (2.0 mol %), DABCO (3 equiv), and MeCN (5 mL) was stirred under air at room temperature for the desired time until complete consumption of starting material as judged by TLC and GC analysis. After the usual workup, the residue was purified by flash column chromatography to give **2** (hexane or hexane/ethyl acetate).

(2) Typical Experimental Procedure for the $Pd(OAc)_2$-Catalyzed Sonogashira Cross-Coupling Reactions. First, $Pd(OAc)_2$ (4.5 mg, 2.0 mol %) was dissolved in MeCN (200 mL). Then, the indicated amount of $Pd(OAc)_2$ acetonitrile solution was added to a mixture of alkyne **1** (the indicated amount in Table 4), aryl halide **3** (1 mmol), DABCO (3 equiv), and MeCN (5 mL). Then, the mixture was stirred under air at the indicated reaction temperature for the desired time until complete consumption of starting material as judged by TLC and GC analysis. After the mixture was filtered and evaporated, the residue was purified by flash column chromatography (hexane or hexane/ethyl acetate) to afford the desired coupled products **4**–**10**.

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Supporting Information Available: Analytical data and spectra (^1H and ^{13}C NMR) for all products **2** and **4**–**10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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