VIP Dehydrogenative Coupling

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Palladium-Catalyzed Oxidative Cross-Coupling between Heterocycles and Terminal Alkynes with Low Catalyst Loading**

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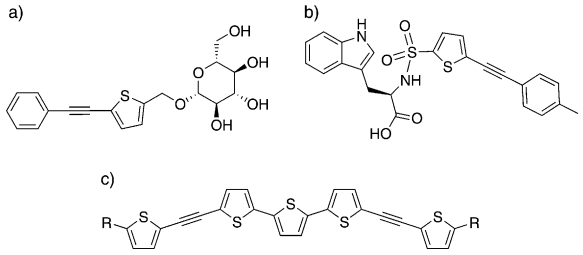
Alkynylated (hetero)arenes represent a recurring structural motif found in bioactive natural products, pharmaceuticals, and organic materials.[1] These compounds are of great importance either as building blocks or synthetic intermediates and have become increasingly attractive for synthetic organic chemists.

The well-known Sonogashira reaction is one of the most commonly used methods for installing alkyne moieties into (hetero)arenes molecules.[2] Recently, the direct alkynylation of (hetero)aromatic compounds has appeared as an alternative to the Sonogashira reaction by using the alkynyl reagents prepared from terminal alkynes, such as alkynyl halides,[3] benziodoxolone-based hypervalent iodine reagents,[4] or arylsulfonylacetylenes.[5] From the viewpoint of step and atom economy, the oxidative cross-coupling[6] between (hetero)arenes and terminal alkynes would be a straightforward and more efficient method for installing alkynyl groups into the (hetero)arene rings, because the need for prefunctionalization of the starting materials would be eliminated. In this context, a few of the seminal examples for such a transformation were recently reported, including the gold-catalyzed alkynylation of electron-rich (hetero)arenes with electron-poor terminal alkynes;[7] the copper-, nickel-, or palladium-catalyzed alkynylation of C–H acidic polyfluoroarenes and azoles;[8] and the palladium-catalyzed alkynylation of C3-blocked 1-methylindoles.[9] However, these established alkynylation methods only worked for specific substrates, and a catalytic method suitable for many important heterocycles such as thiophenes and furans remains elusive. Owing to the importance of alkynylated thiophenes in material science, natural product and medicinal chemistry, as exemplified by the three alkynylated thiophene molecules illustrated in Scheme 1,[10] the general method for cross-coupling thiophenes and other heterocycles with terminal alkynes would be highly desirable. Herein, we report a versatile method that enables the alkynylation of thiophenes bearing various functional groups and other aromatic heterocycles by applying a low loading of a palladium catalyst and using an array of terminal alkynes as alkynylating reagents.



Scheme 1. Three examples of useful alkynylated thiophenes: a) 5-(2-Phenylethynyl)-2-β-glucosylmethyl-thiophene, a natural product;[10a] b) S-3304, a matrix metalloproteinase inhibitor;[10b] c) R = *n*-C_4H_9, a liquid-crystalline semiconductor.[10c]

Several problems hamper the realization of oxidative cross-coupling between aromatic heterocycles and terminal alkynes. The first problem is the undesired terminal alkyne homocoupling under oxidative conditions.[11] The slow addition of terminal alkynes to the reaction system indeed partially overcame the alkyne homocoupling problem but meanwhile brought about the operational inconvenience,[8b,c,9,12] and the use of a large excess of the other coupling partner was capable of suppressing alkyne homocoupling, but sacrificed those reagents.[8a,11b,12] Very recently, the decrease of the palladium catalyst loading proved to be an effective means of overcoming alkyne homocoupling in the Pd-catalyzed cross-coupling of alkynes.[13] Nevertheless, the low palladium catalyst loading is incompatible with the general reaction conditions for the C–H functionalization of aromatic heterocycles, in which relatively high palladium loadings (5–10 mol% Pd catalyst) are usually required to obtain satisfying yields. Hence, we speculated that the establishment of suitable reaction conditions to stabilize the Pd catalyst and enhance its catalytic activity would allow using a low catalyst loading and possibly enable selective cross-coupling reactions of aromatic heterocycles with terminal alkynes.

Elegant studies on C−H bond functionalization of (hetero)arenes[14,15] and recent advances in metal-catalyzed oxidative cross-coupling reactions involving terminal alkynes[16] provided useful starting points for our investigation of this direct alkynylation of thiophenes. The reaction of phenylacetylene (**1a**) with 2-acetylthiophene (**2a**) was chosen as a model system for optimization studies (Table 1). Initially, the reaction that was carried out in 1,2-dimethoxyethane (DME) at 90 °C for 4 h in the presence of $Pd(OAc)_2$ (5 mol%) as a catalyst and Ag_2CO_3 (1.5 equiv) as an oxidant did not give the desired product **3a**, but instead formed a large amount of unwanted alkyne homocoupling by-product **4** (Table 1, entry 1). Although the addition of K_2CO_3 or pivalic acid as

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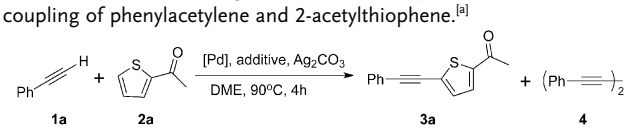
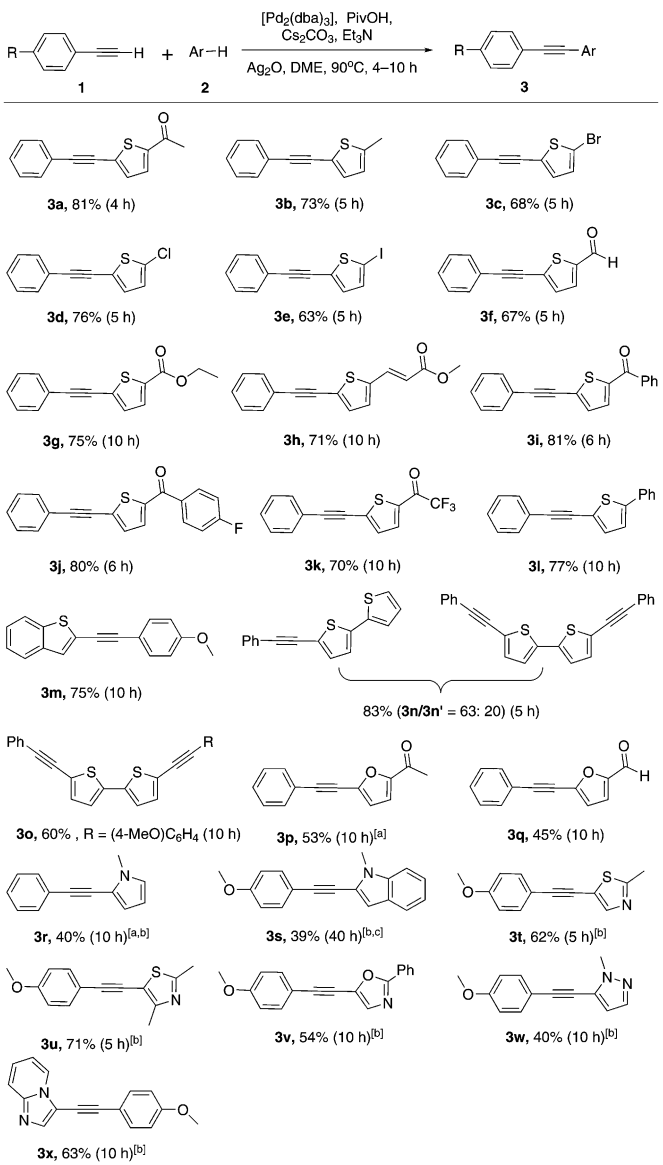
Table 1: Selected screening results for Pd-catalyzed oxidative cross-coupling of phenylacetylene and 2-acetylthiophene.[a]



Entry	[Pd] (mol%)	Additive (equiv)	Yield [%][b] **3a**/**4**
1	$Pd(OAc)_2$ (5)	–	–/48
2	$Pd(OAc)_2$ (5)	K_2CO_3 (1)	–/54
3	$Pd(OAc)_2$ (5)	PivOH (1)	–/34
4	$Pd(OAc)_2$ (5)	K_2CO_3 (1), PivOH (2)	35/20
5	$Pd(OAc)_2$ (5)	Na_2CO_3 (1), PivOH (2)	23/26
6	$Pd(OAc)_2$ (5)	Cs_2CO_3 (1), PivOH (2)	48/20
7	$Pd(OAc)_2$ (5)	Cs_2CO_3 (1), AcOH (2)	–/21
8	$Pd(OAc)_2$ (5)	PivOCs (2)	8/47
9	$Pd(TFA)_2$ (5)	Cs_2CO_3 (1), PivOH (2)	46/24
10	$[PdCl_2(PhCN)_2]$ (5)	Cs_2CO_3 (1), PivOH (2)	36/28
11	$PdCl_2$ (5)	Cs_2CO_3 (1), PivOH (2)	51/28
12	$[Pd_2(dba)_3]$ (2.5)	Cs_2CO_3 (1), PivOH (2)	53/22
13[c]	$[Pd_2(dba)_3]$ (0.2)	Cs_2CO_3 (1), PivOH (2)	56/10
14[c]	–	Cs_2CO_3 (1), PivOH (2)	–/–
15[d]	$[Pd_2(dba)_3]$ (0.2)	Cs_2CO_3 (1), PivOH (2)	69/9
16[d,e]	$[Pd_2(dba)_3]$ (0.2)	Cs_2CO_3 (1), PivOH (2)	80/5
17[d,e]	$[Pd_2(dba)_3]$ (0.2)	Cs_2CO_3 (1), PivOH (2) Et_3N (0.5)	85(81)[f]/4

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (3 equiv), Pd catalyst, additive, Ag_2CO_3 (1.5 equiv), DME (1.5 mL). [b] Yield determined with GC by using dodecane as an internal standard. [c] Phenylacetylene (0.6 mmol) and DME (3 mL) were used. [d] Phenylacetylene (0.6 mmol) and DME (1.5 mL) were used. [e] Ag_2O (1.5 equiv) was used instead of Ag_2CO_3. [f] Yield of isolated product.



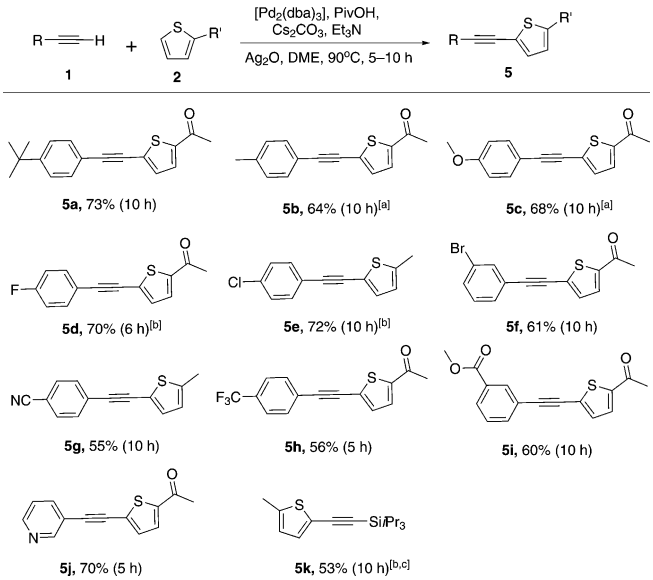
Scheme 2. The scope of heterocycles. Reaction conditions: **1** (0.6 mmol), **2** (3 equiv), $[Pd_2(dba)_3]$ (0.2 mol%), Cs_2CO_3 (1 equiv), PivOH (2 equiv), Ag_2O (1.5 equiv), Et_3N (0.5 equiv), DME (1.5 mL), 90°C, 4–10 h. Yields of isolated products are reported. [a] 2.5 equiv Ag_2O were used. [b] Without Et_3N. [c] $Pd(TFA)_2$ (0.5 mol%) and DMF (1.5 mL) were used. See the Supporting Information for details.

additives to the reaction system also failed to afford **3a**, the presence of pivalic acid was observed to diminish the alkyne dimerization (entries 2–3). When simultaneously adding K_2CO_3 (1 equiv) and PivOH (2 equiv) as additives, we were pleased to find that **3a** was obtained in 35% yield (entry 4). Next, we tested the effect of the metal ions of the base, which revealed that Cs_2CO_3 was the base of choice (entries 5–6). In contrast, the use of acetic acid in place of pivalic acid was ineffective for this reaction (entry 7). Notably, the combination of Cs_2CO_3 (1 equiv) and PivOH (2 equiv) was not merely the equivalent of cesium pivalate (PivOCs), because the use of PivOCs (2 equiv) as base dramatically lowered the yield and increased the alkyne dimerization (entry 8). The attempts to use cheaper copper oxidants or a catalytic amount of silver with nonmetallic stoichiometric oxidants were unsuccessful.[17] Further screening of the palladium sources showed that $[Pd_2(dba)_3]$ (dba = dibenzylidenacetone) gave better result (entries 9–12). Interestingly, 0.2 mol% of $[Pd_2(dba)_3]$ could be used without comprising the yield of **3a** (entry 13). And a control experiment revealed that palladium was indispensable in this reaction (entry 14). Further experiments showed that both doubling the reaction concentration and replacing Ag_2CO_3 with Ag_2O enhanced the yield of **3a** (entries 15–16). Finally, when Et_3N (0.5 equiv) was added to the reaction system, the product was isolated in 81% yield (entry 17).

We used the reaction conditions of entry 17 in Table 1 to first examine the substrate scope of this reaction with respect to thiophenes. As shown in Scheme 2, this reaction was compatible with keto, bromo, chloro, iodo, aldehyde, ester, alkenyl, and trifluoroacetyl substituents, and furnished the desired product in good yields (**3a**–**3l**). Notably, the iodo group is extremely reactive in the Sonogashira reaction, and its tolerance is seldom reported in Pd-catalyzed C–H/C–H cross-coupling reactions. Benzothiophene also smoothly underwent this reaction to generate the corresponding products in good yields (**3m**). In the reaction with 2,2′-bithiophene, which has two nucleophilic positions available, monoalkynylation took place in good yield with a small amount of dialkynylated product formed (**3n** and **3n′**). Thus, the unsymmetrical bisalkynylated product **3o** could be obtained by starting from **3n**. Gratifyingly, in addition to thiophenes, our reaction conditions were also applicable to

various other heterocycles. Among them, furans were alkynylated in synthetically useful yields (**3p** and **3q**). In the cases of *N*-methyl pyrrole and indole, dimerizations of both alkyne and heterocycle led to a decrease in the yield of the cross-coupling product (**3r** and **3s**). Notably, thiazoles and an oxazole afforded the corresponding alkynylated product at the C5-position in good yields (**3t**–**3v**). Finally, *N*-methylpyrazole and N-fused imidazo[1,2-a]pyridine were also alkynylated in reasonable yields (**3w** and **3x**).

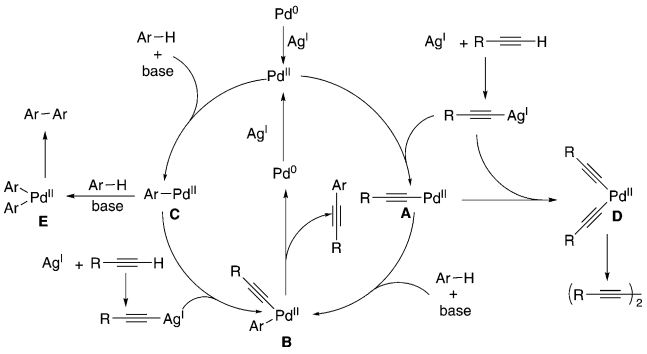
Subsequently, we evaluated the substrate scope with respect to terminal alkynes (Scheme 3). Both electron-donating (**5a**–**5c**) and electron-withdrawing (**5d**–**5i**) groups were compatible on the aryl alkynes, generating highly



Scheme 3. The scope of terminal alkynes. Reaction conditions: See Scheme 2 for details of the reaction conditions. [a] Ag_2CO_3 (1.5 equiv) was used instead of Ag_2O. [b] Carried out at 100 °C. [c] Without Cs_2CO_3 and Et_3N. See the Supporting Information for details.

functionalized products in generally good yields. The heterocyclic alkynes also served as suitable coupling partners as exemplified by (pyridin-3-yl)acetylene (for **5j**). Notably, the silyl-protected (triisopropylsilyl)acetylene afforded alkynylated thiophene in synthetically useful yield (**5k**), which could be easily converted into free acetylene products or used as a precursor for further functionalization.[4a] Unfortunately, only a trace of product was observed for aliphatic alkynes.[18]

A possible reaction pathway is proposed to rationalize the direct alkynylation reaction (Scheme 4). First, the alkynylsilver derivative generated in situ undergoes transmetalation with a Pd^{II} species to form the alkynyl–palladium intermediate **A**. Then, the intermediate **A** attacks the heterocycles through concerted metalation–deprotonation to generate the intermediate **B**, which delivers the desired alkynylated product through reductive elimination. The oxidation of Pd^0 to Pd^{II} by a Ag^I species finishes the catalytic cycle. Alternatively, the reaction may proceed through the initial palladation of the heterocycle to form the intermediate **C** and subsequent transmetalation from Ag to Pd to give



Scheme 4. A possible reaction pathway for the Pd-catalyzed oxidative cross-coupling between heterocycles and terminal alkynes.

intermediate **B** and final reductive elimination of the cross-coupling product from **B**. The low catalyst loading (0.2 mol%) in this reaction may be associated with the in situ generated insoluble alkynylsilver derivative, which is a coordinating polymer $(RC{\equiv}CAg)_n$[19] and serves as a solid support to prevent the Pd catalyst from agglomeration of Pd^0 to inactive Pd black. Additionally, because of its insolubility, the alkynylsilver derivative slowly liberates the alkynyl group into the reaction system and therefore suppresses the undesired homocoupling of terminal alkynes.[17]

In summary, we have developed a Pd-catalyzed method for the direct alkynylation of heterocycles with terminal alkynes. Most of the aromatic heterocycles described herein, such as thiophenes and furans, were for the first time observed to undergo direct alkynylation with terminal alkynes. Because of the low catalyst loading (0.2 mol%), the simple operational process, and excellent functional group tolerance, we believe this protocol will find applications in synthetic chemistry.

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[17] See the Supporting Information for details.

[18] Cyclohexylacetylene and 1-octyne were tested.

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