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Palladium-Catalyzed Primary Amine-Directed Regioselective Mono- and Di-Alkynylation of Biaryl-2-Amines

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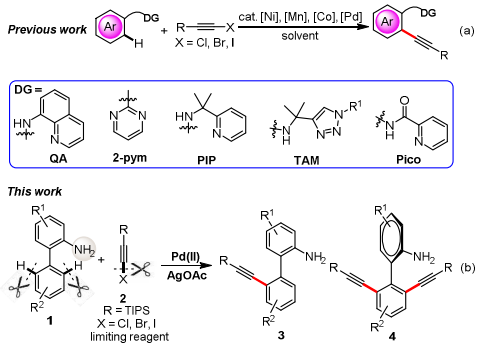
The first example of palladium-catalyzed primary amine-directed C(sp^2)-H alkynylation of biaryl-2-amines has been developed by using (bromoethynyl)triisopropylsilane as an alkynylating reagent. This protocol exhibits broad substrate scope, excellent regioselectivity and gram-scale synthesis. Significantly, the versatility of this straightforward method was further demonstrated by the controlled mono- and di-alkynylation.

Alkynes are significant structural motifs in materials chemistry and bioactive compounds,[1] and they can be utilized as useful and important precursors for further transformations.[2] In this respect, transition metal-catalyzed direct alkynylation of unactivated C-H bonds has emerged as one of the most powerful methods for the construction of C-C bonds over the past decades.[3] In 2014, a palladium-catalyzed alkynylation of *N*-vinylacetamides was elegantly developed by Loh and co-workers.[3f] Very Recently, the groups of Waster,[3a] Sigman,[3h] Fu,[3i] *et.al* used copper, palladium or ruthenium salt as catalyst to achieve the alkynylation of various substrates. Among them, directing groups (DGs) assisted C-H alkynylation reactions are particularly attractive due to their excellent regioselectivity and reactivity.[4] Therefore, a series of nitrogen-containing directing groups, including 8-aminoquinoline,[5] pyrimidine,[6] PIP,[7] TAM,[8] and Pico,[9] have been extensively studied under palladium, cobalt, nickel or manganese catalysis (Scheme 1a). However, these nitrogen-containing DGs suffer from a multi-step operation for the preparation of starting materials. Given the atom economy, practicality and subsequent transformation of the directing groups, the application of primary amine as a simple DG in direct C(sp^2)-H functionalization/C(sp^2)-C(sp)-coupling processes is a highly valuable goal. Previously, using primary amine as a directing group to construct C(sp^2)-C(sp^2) bonds has been studied well.[10] For instance, Daugulis and co-workers reported that primary amine could be used successfully as a chelating group in diarylation reactions. Huang group described a rhodium-catalyzed amidation of 2-aminobiaryls with diazo. In contrast, as for C(sp^x)-C(sp) bond construction, no example has been reported.

During the past decades, haloalkynes have been recognized as versatile and powerful building blocks due to their diversity, easy availability, practicability, and high reactivity.[11] Therefore, to date, transition-metal-catalyzed or transition-metal free reactions involving haloalkynes have already attracted widespread attention.[12] Previously, we have developed a series of palladium-catalyzed alkynylation reactions of alkynes[13] and olefin[14] with haloalkynes as alkynylated reagents. As part of our continuous studies on the transformation of haloalkynes, herein, we disclose a palladium-catalyzed, primary amine-directed regioselective mono- and di-alkynylation of biaryl-2-amines with (bromoethynyl)triisopropylsilane using haloalkynes as the limiting reagents (Scheme 1b).



Scheme 1. Transition metal-catalyzed C(sp^2)-H Alkynylation Using Nitrogen-Containing Group as a Directing Group

Initially, [1,1'-biphenyl]-2-amine (**1a**, 0.2 mmol) and (bromoethynyl)triisopropylsilane (**2a**, 0.2 mmol) were chosen as the model substrate to optimize the monoalkynylation conditions in the presence of $Pd(OAc)_2$ (0.01 mmol) and

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Electronic supplementary information (ESI) available: Experimental section, characterization of all compounds, and copies of ^1H and ^{13}C NMR spectra for selected compounds. For ESI and other electronic format See DOI:10.1039/x0xx00000x

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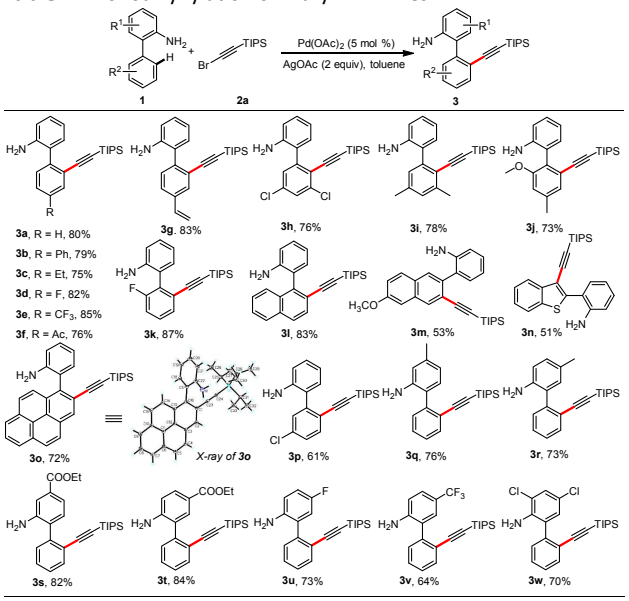
$Cu(OAc)_2$ (0.4 mmol) in toluene (1.5 mL) at 100 °C for 12 h. Unfortunately, no desired alkynylated product **3a** was detected (see entry 1 of Table S1 in the Supporting Information (SI)). To our surprise, **3a** was detected in 76% GC yield by replacing $Cu(OAc)_2$ with AgOAc (Table S1, entry 2). Subsequently, a variety of different palladium catalysts were tested, and the optimal result was obtained in the presence of $Pd(OAc)_2$ (Table S1, entries 3-4). Switching the solvents to DCE and CH_3CN had no satisfactory results on the reaction efficiency (Table S1, entries 5-6). This transformation did not occur in the absence of either $Pd(OAc)_2$ or AgOAc (Table S1, entries 7-8). Moreover, when the chosen substrate ratio was changed, the GC yield of **3a** increased from 76% to 84% (Table S1, entry 2 vs 9). With chloroalkyne **2b** or iodoalkyne **2c** as the substrate, the alkynylated product **3a** was also isolated in reasonable yield (Table S1, entries 10-11). It is noteworthy to mention that the alkynylated products **3a** (monoalkynylation) and **4a** (dialkynylation) could be selectively isolated by adjusting the stoichiometry of **1a**, **2a** and AgOAc. Therefore, when 2.5 equivalents of **2a** and 4 equivalents of AgOAc were used, the dialkynylated product was obtained in 82% isolated yield (see the Supporting Information for details).

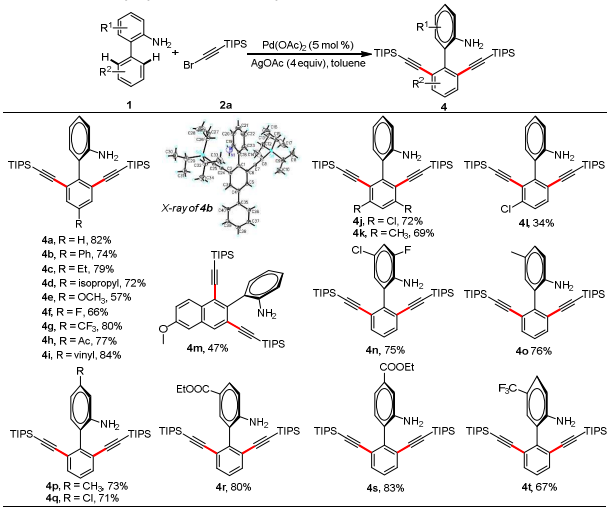
Table 1. Monoalkynylation of Diaryl-2-Amines[a,b]



[a] Reaction conditions: a mixture of **1** (0.2 mmol), **2a** (0.14 mmol), AgOAc (0.28 mmol, 2 equiv), $Pd(OAc)_2$ (0.007 mmol, 5 mol %) and toluene (1.5 mL) were sealed in a 25 mL Schlenk tube at 100 °C for 12 h under N_2. [b] Isolated yields.

With the optimized conditions in hand (Table S1, entry 9), we examined the scope of substituted biaryl-2-amines amenable to this primary amine directed alkynylation reactions (Table 1). Pleasingly, substrates with electron-rich or -poor groups on the 4′-position could undergo this transformation smoothly, delivering the corresponding products with excellent yields (**3a**-**3f**). Notably, a vinyl group which is sensitive to palladium-catalyzed coupling reactions could also remain under the optimal conditions (**3g**). When using the disubstituted biaryl-2-amines as the substrates, the desired products could be obtained in 73-78% yields (**3h**-**3j**). 2′-Fluoro-[1,1′-biphenyl]-2-amine also furnished the products (**3k**) in 87% yield. To our delight, the alkynylation reaction was compatible with 2-(naphthalen-2-yl)aniline and 2-(6-methoxynaphthalen-2-yl)aniline to give the corresponding products in 83% (**3l**) and 53% (**3m**) yields, respectively. Meanwhile, heteroaromatic substrate containing benzothiophene scaffolds could be transformed to the target product **3n** in moderate yield. It is worth noting that 2-(pyren-1-yl)aniline was also tolerated in this reaction, which gave the desired product **3o** in 72% yield. The relative configuration of **3o** was unambiguously confirmed by crystallographic analysis (see the Supporting Information for details). Significantly, 3′-chloro biphenyl-2-amine was successfully alkynylated as well (**3p**), providing a synthetically useful alkynylated synthon. Finally, substrates bearing different R^1 substituents worked well under the standard reaction conditions and the alkynylated products (**3q**-**3w**) were formed in moderate to good yields.

Table 2. Dialkynylation of Biaryl-2-Amines[a,b]



[a] Reaction conditions: a mixture of **1** (0.2 mmol), **2a** (0.5 mmol), AgOAc (0.8 mmol, 4 equiv), $Pd(OAc)_2$ (0.01 mmol, 5 mol %) and toluene (1.5 mL) were sealed in a 25 mL Schlenk tube at 100 °C for 12 h under N_2. [b] Isolated yields.

Next, the scope of this dialkynylation protocol was evaluated to a series of biaryl-2-amines (Table 2). The transformation was well tolerated with substrates containing electron-donating and -withdrawing substituents at the 4′-position, affording the desired dialkynylated products **4a**-**4i** in 57-84% yields. Delightfully, the disubstituted substrates also proceeded well in this catalytic system (**4j**, **4k**). It was noted that 3′-chloro-[1,1′-biphenyl]-2-amine gave comparably lower yield, probably owing to the steric effects (**4l**). Notably, the corresponding product **4m** was also accessed, albeit in 47% yield. Gratifyingly, 5-chloro-3-fluoro-[1,1′-biphenyl]-2-amine was suitable substrate and converted to the desired product **4n** in 75% yield. Moreover, the transformation of 4-methyl-substituted and 5-methyl-substituted substrates also afforded the target products **4o** and **4p** with 73% and 76% yields, respectively. The 5-chloro group could tolerate the catalytic system, making further application on the scaffold possible (**4q**). Finally, electron-

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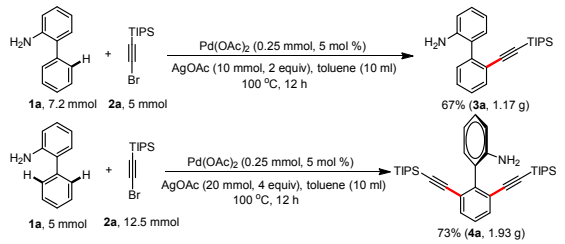
withdrawing substituents such as COOEt and CF_3, were also well tolerated to isolate the desired dialynylated products **4r**, **4s**, and **4t** in 80, 83, and 67% yields, respectively. The structure of the dialkynylated product has been confirmed by single-crystal X-ray analysis of **4b** (for detailed information, see the Supporting Information).

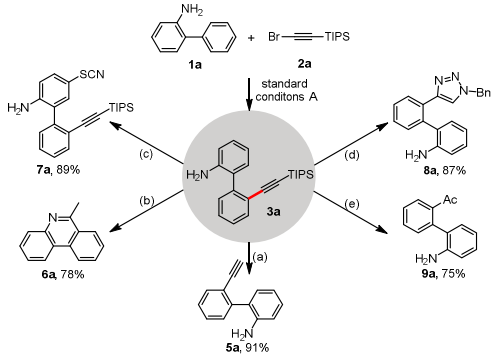
Next, in a gram-scale experiment, the C(sp^2)-H alkynylation of biphenyl-2-amine catalyzed by $Pd(OAc)_2$ could also proceed smoothly to give the mono- or di-alkynylated products in moderate yields (Scheme 2).



Scheme 2. Gram-Scale Experiment

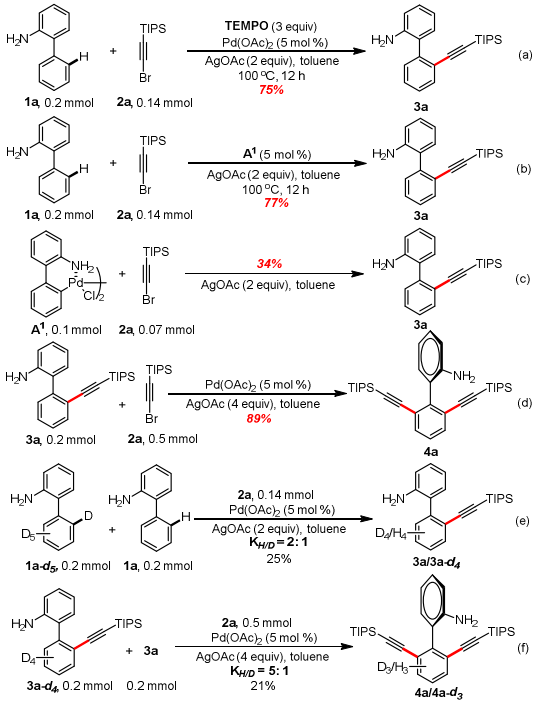
Subsequently, the synthetic utility of this protocol was demonstrated by further transformation of the product **3a** (Table 3).[15] Gratifyingly, the chemoselective removal of the TIPS of **3a** was easily realized under the straightforward reaction conditions. Valuable 6-methylphenanthridine (**6a**) was obtained in 78% yield via a hydrolysis and cyclization process. Under the treatment of KSCN, **3a** was transformed smoothly to the corresponding product **7a** in 89% yield. Finally, 2′-(1-benzyl-1H-1,2,3-triazol-4-yl)-[1,1′-biphenyl]-2-amine (**8a**) and 1-(2′-amino-[1,1′-biphenyl]-2-yl)ethan-1-one (**9a**) were synthesized in excellent yields (see the Supporting Information for details).[16]

Table 3. Further Synthetic Applications



Reaction conditions: a) **3a** (0.2 mmol), TBAF (1 M in THF, 0.4 mL), THF (1 mL), rt, 3 h. b) i) **3a** was hydrolyzed to **5a**. ii) **5a** (0.1 mmol), $PdCl_2$ (5 mol %), CH_3CN 100 °C, 12 h; c) **3a** (0.3 mmol), KSCN (2 equiv); $Cu(OTf)_2$ (20 mol %), TMEDA (20 mol %), $BF_3{\cdot}Et_2O$ (2 equiv), DMSO (1 ml), O_2 balloon, 100 °C, 24 h; d) i) **3a** was hydrolyzed to **5a**. ii) **5a** (0.2 mmol), benzylazide (0.2 mmol), CuI (10 mol %), DMF (2 mL), 80 °C, 12 h; e) **3a** (0.2 mmol), KOH (3 equiv), DMSO (2 mL), 100 °C, 12 h.

To gain more insight into this palladium-catalyzed alkynylation reaction, a range of mechanistic experiments were conducted (Scheme 3). First, when 3 equivalents of radical scavenger TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) was employed in the reaction condition A, the corresponding monoalkynylated product **3a** was obtained in 75% yield (Scheme 3a). This result indicated that the mechanism of present method should not be a radical process. To better understand the mechanism of this transformation, we conducted the reaction using the bimetallic complex $\mathbf{A}^1$, which was prepared according to the literature.[10f] Surprisingly, the corresponding product **3a** was obtained in 77% yield (Scheme 3b). The stoichiometric conversion from $\mathbf{A}^1$ under the same conditions also delivered the corresponding products **3a**, albeit in 34% yield (Scheme 3c). In addition, when **3a** and (bromoethynyl)triisopropylsilane (**2a**) were treated in toluene using AgOAc as additive, the dialkynylated product **4a** was isolated in 89% yield (Scheme 3d). This observation suggested that **3a** might be a possible intermediate in this dialkynylation reaction. Moreover, the protocol exhibited intermolecular kinetic isotope effect both in monoalkynylation (k_H/k_D = 2) and in dialkynylation reaction (k_H/k_D = 5) (Scheme 3e, f), implying that the cleavage of C(sp^2)-H bond of biphenyl-2-amine is likely to be the rate-determining step in the catalytic process.



Scheme 3. Control Experiments

Based on our experimental results and related literature reports,[8,17] we proposed that the transformation may proceed through a Pd(II)/Pd(IV) catalytic process (Scheme 4). Initially, $Pd(OAc)_2$ was coordinated by the biphenyl-2-amine to form the active palladium(II) species. Subsequently, directed C(sp^2)-H activation leads to the formation of bimetallic Pd(II)-Pd(II) intermediate **A**. Next, the oxidative addition of (bromoethynyl)triisopropylsilane (**2a**) to intermediate **A** gives the corresponding Pd(IV) species **B**, which underwent reductive elimination to afford the alkynylation product **3a** along with regeneration of palladium(II) catalyst.

In summary, we have successfully developed a primary amine directed alkynylation reaction of biaryl-2-amines with

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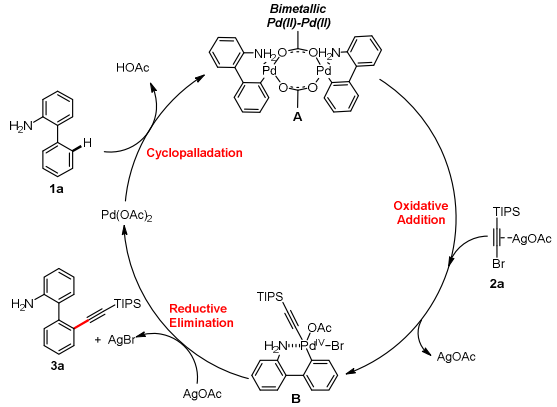
palladium(II) catalysis. This novel protocol provides a practical and robust method for the formation of mono- and dialkynylated biaryl-2-amines in excellent yields. The transformation has remarkable features, including excellent regioselectivity, good functional group compatibility, and gram-scale synthesis. Further studies regarding the synthetic applications are currently underway in our laboratory.



Scheme 4. Proposed Mechanism

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Conflicts of interest

There are no conflicts to declare.

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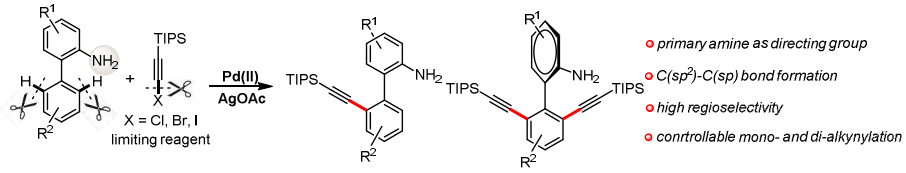

Palladium-catalyzed primary amine-directed controlled alkynylation of biaryl-2-amines has been developed by using haloalkynes as an alkynylating reagent.