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# Domino Sonogashira Coupling/Cyclization Reaction Catalyzed by Copper and ppb Levels of Palladium: A Concise Route to Indoles and Benzo[*b*]furans

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**Abstract:** Both indoles and benzo[*b*]furans can be obtained in high yield by the reactions of 2-iodoaniline derivatives and 2-iodophenols with terminal alkynes under mild conditions, namely in the presence of cuprous iodide (10 mol%) and a base in ethanol or 1,4-dioxane. Further investigation reveals that palladium contaminants as low as 100 ppb are responsible for these successful couplings. It is worth noting that simple aliphatic substituted terminal alkynes could be tolerated to smoothly produce indole and benzo[*b*]furan derivatives.

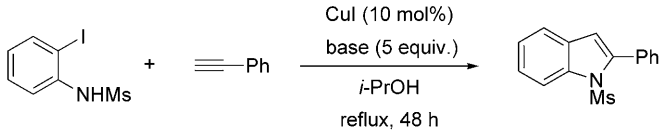
**Keywords:** benzo[*b*]furans; copper catalysis; indoles; palladium contaminant; ppb levels

The palladium-catalyzed Sonogashira reaction has proven to be a powerful approach for preparing arylalkynes and conjugated enynes by coupling of aryl or alkenyl halides or triflates to terminal alkynes in the presence of a copper(I) cocatalyst.[1] The use of 1–10 mol% $Pd(PPh_3)_2Cl_2$ and CuI as the catalytic system in the typical Sonogashira coupling is problematic for large-scale industrial use due to the cost of palladium. In order to overcome this disadvantage, much effort has been directed toward exploring new catalytic systems.[2,3,4,5,6] Owing to the cheap and environmentally friendly aspects of copper catalysis, much attention has been paid to investigating the Cu-catalyzed Sonogashira-type reactions in the absence of palladium species.[6] Some reported successful examples encouraged us to explore the cascade reaction of 2-haloanilines or 2-halophenols with terminal alkynes to produce indoles or benzo[*b*]furans in one pot.

Indole and benzo[*b*]furan are important compounds which display a wide range of biological activities and exist in many natural products as a backbone of their structural frameworks.[9] Classic methods for making indoles and benzo[*b*]furans generally involve multistep reactions, a particular substrate, or display unsatisfactory functional group tolerance.[10] In comparison to the conventional synthetic approaches, domino transition metal-catalyzed coupling/cyclization reactions for the synthesis of indoles and benzo[*b*]furans starting from 2-haloanilines and 2-halophenols with alkynes are particularly attractive.[7,8,10c] Recently, Cacchi et al.[11a] and Ma et al.[11b] independently described the Cu-catalyzed one-pot synthesis of 2-substituted indoles from 2-halotrifluoroacetanilide and terminal alkynes by a Sonogashira-type coupling/cyclization sequence using Venkataraman's catalyst $\{[Cu(phen)(PPh_3)_2]NO_3\}$ or $CuI/PPh_3$ and CuI/L-proline, respectively. The analogous approach to synthesizing benzo[*b*]furans in the presence of catalytic Cu/ligand has also been reported by several groups.[12] In their important pioneering studies, however, the scope of these approaches for synthesizing indoles is generally limited to aryl terminal alkynes and it cannot be extended to simple aliphatic terminal alkynes. Moreover, ligands play a significant role in reaction efficiency and selectivity in these cases. More recently, Novák reported the effect of ppb levels of palladium on the "copper-catalyzed" Sonogashira coupling.[13a] Similar phenomena were also found in other coupling reactions.[3e,13b–f] Herein, we wish to demonstrate the synthesis of indoles and benzo[*b*]furans by the CuI-catalyzed Sonogashira coupling/cyclization reactions of 2-haloaniline derivatives and 2-halophenols with aryl and alkyl terminal alkynes in the absence of a phosphine ligand. Further investigation

**Table 1.** Effect of base on the domino coupling/cyclization process.[a]




1a 2a 3a

| Entry | Base | Yield[b] [%] |
|---|---|---|
| 1 | *t*-BuOK | N.R. |
| 2 | KOH | N.R. |
| 3 | $K_2CO_3$ | <1 |
| 4 | DABCO | N.R. |
| 5 | $Et_3N$ | N.R. |
| 6 | pyridine | N.R. |
| 7 | quinoline | <1 |
| 8 | isopropylamine | <1 |
| 9 | dimethylamine | 2 |
| 10 | benzylamine | 31 |
| 11[c] | DBU | 78 |
| 12[c,d] | DBU | 90 |

[a] *Reaction conditions:* **1a** (0.07 mmol, 1 equiv.), **2a** (0.19 mmol, 2.7 equiv.), CuI (10 mol%), base (0.35 mmol, 5 equiv.), *i*-PrOH (2 mL), reflux, 48 h.
[b] Yield determined by GC with naphthalene as an internal standard.
[c] Isolated yield.
[d] EtOH as solvent.

indicates that palladium contaminants in the reagents used for these reactions are responsible for these successful couplings.

We started with readily available *N*-mesyl 2-iodoaniline **1a** and phenylacetylene **2a** as model substrates to test the domino CuI-catalyzed Sonogashira coupling/cyclization reaction. A variety of bases, including inorganic and organic bases, were examined. As shown in Table 1, a significant base effect was observed: DBU (1,8-diazabicyclo-[5.4.0]undec-7-ene) was the most effective base for promoting the domino coupling/cyclization, affording indole **3a** in 78% isolated yield (Table 1, entry 11) along with a trace amount of the competing homocoupling product from phenylacetylene. Benzylamine was a less effective base to mediate the formation of indole **3a** (31% yield, Table 1, entry 10). Other bases, such as *t*-BuOK, KOH, $K_2CO_3$, DABCO, $Et_3N$, pyridine, quinoline, isopropylamine and dimethylamine, were ineffective for this cascade reaction (Table 1, entries 1–9). Among the solvents screened, we found that the protic *i*-PrOH and EtOH could efficiently afford *N*-mesyl-2-phenylindole **3a** in 78% yield and 90% yield, respectively (Table 1, entries 11 and 12). At the same time, we observed the formation of the free N–H indole **4a** in a small amount (10%) when using ethanol (Table 2, entry 1). Accordingly, the Cu-catalyzed coupling-cyclization process performed in the presence of CuI (10 mol%) and DBU in EtOH at reflux could provide the desired indole product **3** exclusively.

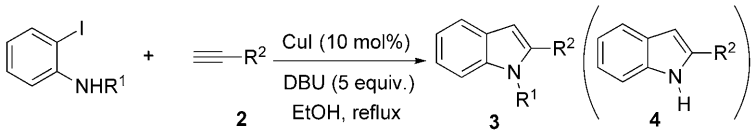
Under these optimal conditions, we examined the scope of this reaction by varying the substituents on the nitrogen atom of 2-iodoaniline and the terminal alkyne component. Gratifyingly, when $R^1$ was an electron-withdrawing group, a wide range of aryl or simple alkyl substituted terminal alkynes could be tolerated (Table 2). *p*-Tolylacetylene **2b** reacted with *N*-mesyl-2-iodoaniline **1a** to afford the corresponding **3b** in 76% yield as well as 14% yield of **4b** with cleavage of the Ms group, likely due to the *in situ* alcoholysis of the N–Ms group in the basic system[14] (Table 2, entry 2). An electron-withdrawing $CF_3$ substituent on the aryl ring seems to facilitate the cleavage of the N–Ms group, giving **3c** and **4c** in 58% and 42% yields, respectively (Table 2, entry 3). It is worth noting that simple aliphatic terminal alkynes were also transformed to indole products with remarkable efficiency, which were not tolerated in previous reports of domino Cu-catalyzed coupling/cyclization.[11] The *n*-propyl, *n*-butyl and *n*-hexyl substituted terminal alkynes smoothly underwent coupling/cyclization with **1a** to produce indoles **3d**–**3f** in good to high yields (70–88%, Table 2, entries 4–6). To our delight, the *tert*-butyl substituted indole **3g** was also successfully isolated in moderate yield (Table 2, entry 7). Upon heating the solution to 120 °C in a sealed tube, the yield of 2-*tert*-butylindole **4g** with a free N–H moeity was increased to 83% (Table 2, entry 8). Furthermore, the reactions of alkyl substituted terminal alkynes bearing free hydroxy and ether functional groups with **1a** favorably led to the formation of indoles **3h** and **3i** in 93% and 90% yields, respectively (Table 2, entries 9 and 10). Therefore this transformation is practical and attractive as it applies also to simple aliphatic terminal alkynes.

In addition, when the $R^1$ on the nitrogen of 2-iodoaniline was a tosyl or a $CF_3CO$ group, the indole products with different substituents at the 2-position could be obtained (Table 2, entries 11–17). Interestingly, we observed that the *N*-trifluoroacetyl group was completely alcoholysed *in situ* under basic conditions, affording only indole **4** with a free N–H moiety (Table 2, entries 15–17). However, when the substituent on the nitrogen atom was an acetyl group, or a hydrogen, or a methyl group, the reactions did not work well, which may be due to the lower acidity of the N–H proton as compared to that of the *N*-sulfonyl or *N*-trifluoroacetyl analogues (Table 2, entries 18–21).

Next, we attempted to apply this method to synthesize benzo[*b*]furans. However, the reaction of 2-iodophenol **5** with phenylacetylene **2a** under the standard conditions optimized for indole synthesis exclusively gave the phenylacetylene homocoupling product without the formation of the desired benzo[*b*]furan **6a**.

**Table 2.** Domino Sonogashira coupling/cyclization for the synthesis of indoles.[a]




$R^1$ = Ms (**1a**), Ts (**1b**), $CF_3CO$ (**1c**), Ac (**1d**), H (**1e**), Me (**1f**)

| Entry | **1** | $R^2$ | Time [days] | Yield [%] of **3**[b] | Yield [%] of **4**[b] |
|---|---|---|---|---|---|
| 1 | **1a** | Ph (**2a**) | 2 | 90 (**3a**) | 10 (**4a**) |
| 2 | **1a** | *p*-tolyl (**2b**) | 2 | 76 (**3b**) | 14 (**4b**) |
| 3 | **1a** | *p*-$CF_3C_6H_4$ (**2c**) | 2 | 58 (**3c**) | 42 (**4c**) |
| 4[c,d] | **1a** | *n*-Pr (**2d**) | 3 | 83 (**3d**) | – |
| 5[c] | **1a** | *n*-Bu (**2e**) | 3 | 88 (**3e**) | – |
| 6 | **1a** | $(CH_2)_5CH_3$ (**2f**) | 3 | 70 (**3f**) | – |
| 7[c,d] | **1a** | *t*-Bu (**2g**) | 3 | 51 (**3g**) | – |
| 8[d,e] | **1a** | *t*-Bu (**2g**) | 3 | – | 83 (**4g**) |
| 9 | **1a** | $CH_2OH$ (**2h**) | 3 | 93 (**3h**) | – |
| 10 | **1a** | $CH_2OPh$ (**2i**) | 1 | 90 (**3i**) | – |
| 11 | **1b** | Ph (**2a**) | 2 | >99 (**3j**) | – |
| 12[c] | **1b** | *n*-Bu (**2e**) | 3 | 67 (**3k**) | – |
| 13 | **1b** | $CH_2OPh$ (**2i**) | 6 | 84 (**3l**) | – |
| 14 | **1b** | $CH_2OH$ (**2h**) | 4 | 54 (**3m**) | – |
| 15 | **1c** | Ph (**2a**) | 1 | – | 68 (**4a**) |
| 16 | **1c** | $(CH_2)_5CH_3$ (**2f**) | 3 | – | 65 (**4n**) |
| 17 | **1c** | *p*-$CF_3C_6H_4$ (**2c**) | 2.5 | – | 50 (**4c**) |
| 18[c,d] | **1d** | *n*-Pr (**2e**) | 6 | – | 38 (**4o**) |
| 19[f] | **1d** | Ph (**2a**) | 6 | 0 | 0 |
| 20[f] | **1e** | Ph (**2a**) | 4 | 0 | 0 |
| 21 | **1f** | Ph (**2a**) | 3 | 0 | 0 |

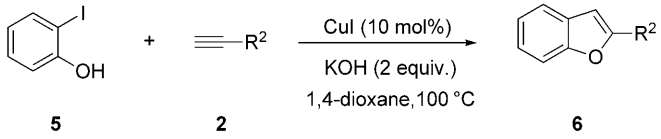
[a] *Reaction conditions:* **1** (0.25 mmol, 1 equiv.), **2** (0.5 mmol, 2 equiv.), CuI (10 mol%), base (5 equiv.), EtOH (1 mL), reflux.
[b] Isolated yield.
[c] Performed in a sealed tube at 80 °C.
[d] **2** (1.25 mmol, 5 equiv.).
[e] Performed in a sealed tube at 120 °C.
[f] *t*-BuOK as a base (0.5 mmol, 2 equiv.).

After screening a series of bases and solvents, we discovered that inexpensive KOH as a base in 1,4-dioxane could facilitate the synthesis of 2-phenylbenzo[*b*]furan **6a** in 91% yield and efficiently suppress the production of the homocoupling product (Table 3, entry 1). Under these mild conditions, other aryl substituted terminal alkynes, such as *p*-tolyl and *p*-$CF_3C_6H_4$, smoothly underwent transformation to produce benzo[*b*]furans **6b** and **6c** in high yields (Table 3, entries 2 and 3). The *n*-butyl, *n*-hexyl and even the sterically bulky *tert*-butyl substituted benzo[*b*]furans **6d–f** could also be afforded in moderate yields (Table 3, entries 4–6). We were pleased that the ether and amine substituted alkyl terminal alkynes **2i–k** could smoothly participate in these reactions to afford the corresponding benzo[*b*]furans **6h** and **6i** in >99% and 76% yields, respectively (Table 3, entries 7 and 8). However, **2h** containing a free hydroxy group gave benzo[*b*]furan **6g** in low yield even after 6 days (Table 3, entry 9).

On the other hand, prompted by recent findings on the Sonogashira coupling catalyzed by ppb-level Pd contaminants from reagents or glassware,[3e,13] we decided to investigate whether the palladium contaminants are responsible for the successful coupling in our reactions. In order to exclude the ppb-level impurities as much as we could, all the equipment, including glassware, new stir bars, etc., were washed well with detergent, and then soaked in *aqua regia* for at least 1 hour followed by washing well with distilled water. The organic reagents employed in the reaction were purified prior to use and the Pd contaminants were determined by AAS (1.7 ng/g Pd in substrate **1b**, <1 ng/g Pd in phenylacetylene and DBU, respectively). To insure the purity of the copper source, we purchased two bottles of CuI (99.999%) from Aldrich with different batch numbers. The remaining Pd impurities were ascertained by ICP-MS, which showed one bottle to contain only 4 ng/g of Pd, while the other one has 627 ng/g of Pd contaminant, and CuI

**Table 3.** Domino Sonogashira coupling/cyclization for the synthesis of benzo[*b*]furans.[a]

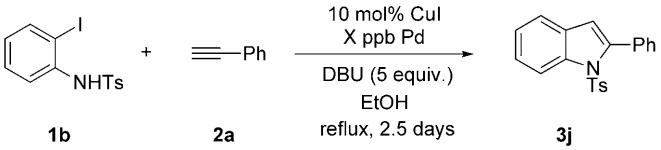



5 2 6

| Entry | $R^2$ | Time [days] | Yield [%] of **6**[b] |
|---|---|---|---|
| 1 | Ph (**2a**) | 2 | 91 (**6a**) |
| 2 | *p*-tolyl (**2b**) | 1 | 82 (**6b**) |
| 3 | *p*-$CF_3C_6H_4$ (**2c**) | 1 | 88 (**6c**) |
| 4[c] | *n*-Bu (**2e**) | 4.5 | 48 (**6d**) |
| 5 | $(CH_2)_5CH_3$ (**2f**) | 4.5 | 40 (**6e**) |
| 6[c] | *t*-Bu (**2g**) | 6 | 46 (**6f**) |
| 7 | $CH_2OPh$ (**2i**) | 1.5 | >99 (**6h**) |
| 8 | $CH_2NHPh$ (**2k**) | 6 | 76 (**6i**) |
| 9 | $CH_2OH$ (**2h**) | 6 | 20 (**6g**) |

[a] *Reaction conditions:* **5** (0.3 mmol, 1 equiv.), **2** (0.6 mmol, 2 equiv.), CuI (10 mol%), base (0.6 mmol, 2 equiv.), 1,4-dioxane (1 mL), performed in a sealed tube at 100 °C.
[b] Isolated yield.
[c] **2** (1.5 mmol, 5 equiv.).

**Table 4.** Effect of ppb levels of palladium.[a]




1b 2a 3j

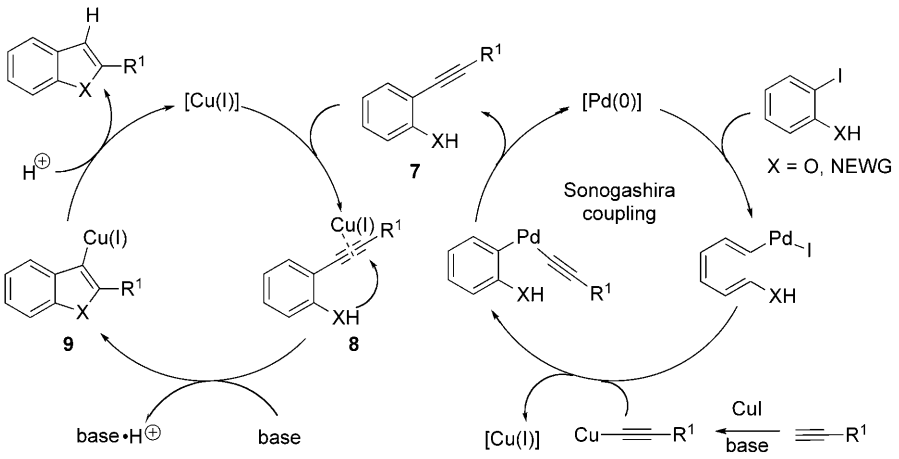
| $CuI/Pd(PPh_3)_2Cl_2$ | Yield[b] |
|---|---|
| >99% (Aladdin, purified, 35 ng/g Pd content) | 32% |
| >99.999% (Aldrich, 4 ng/g Pd content) | 36% |
| >99.999% (Aldrich, 627 ng/g Pd content) | 86% |
| >99.999% (Aldrich, 4 ng/g Pd) + 100 ppb [Pd] | 93% |
| >99.999% (Aldrich, 4 ng/g Pd) + no DBU | N.R. |
| no CuI + 100 ppb $Pd(PPh_3)_2Cl_2$ | N.R. |
| no CuI + no $Pd(PPh_3)_2Cl_2$ | N.R. |

[a] Substrate **1b**, phenylacetylene and DBU were purified by recrystallization or fresh distillation prior to use.
[b] GC yield.

from Aladdin used in the previous reactions contains 35 ng/g of Pd.

We started examining the role of trace amounts of Pd contaminants for the reaction with **1b** as a model substrate since this substrate did not afford the free N–H indole **4j**. As shown in Table 4, when >99% CuI (35 ng/g Pd) and >99.999% CuI (4 ng/g Pd) were empoyed low yields were obtained, however, when the reation was run using 10 mol% CuI (627 ng/g Pd content), in fact, 112 ppb of palladium from CuI was introduced into the reaction, affording the desired product **3j** in 86% yield. These findings led us to believe that, although the reaction occurs without the direct addition of a Pd catalyst, it is catalyzed by ppb levels of palladium contaminants originating from the commercially available CuI. In order to further investigate the cause of these findings, small amounts of Pd were added to the reaction with >99.999% CuI (4 ng/g Pd content). Using only a 100 ppb level of $Pd(PPh_3)_2Cl_2$, a significant increase in yield was observed. In contrast, in the absence of CuI, the added $Pd(PPh_3)_2Cl_2$ could not catalyze this transfomation. Not surprisingly, no reaction was observed when neither CuI nor Pd were added. These experiments demonstrated the essential role of the copper catalyst for this reaction and reveal that our reaction is catalyzed by both CuI and Pd contaminants down to a level of 100 ppb from reagents. At the same time, we were pleased that the reaction can be reproducible in the presence of trace amounts of Pd.

Based on previous mechanistic studies,[13a,15] a plausible reaction mechanism is outlined in Scheme 1. First, Pd/Cu-catalyzed Sonogashira coupling of 2-iodoaniline or 2-iodophenol with the terminal alkyne affords intermediate **7**. Then, with the assistance of a base, the nitrogen atom or oxygen acts as a nucleo-




**Scheme 1.** Plausible mechanism for Pd/Cu-catalyzed coupling/cyclization reaction.

phile and attacks the copper coordinated alkyne **8** to give the indole-containing copper intermediate **9**. Protonolysis of **9** can provide the corresponding indole (or benzo[*b*]furan) product.

In conclusion, we have demonstrated a concise and practical method for the synthesis of indoles and benzo[*b*]furans. Both heterocycles could be obtained in high yield by the reactions of *N*-substituted 2-iodoanilines or 2-iodophenol with terminal alkynes under mild conditions, namely in the presence of CuI (10 mol%), traces of palladium, and a base in EtOH or 1,4-dioxane without using a phosphine ligand. It is worth noting that simple aliphatic substituted terminal alkynes could be tolerated to smoothly produce indole and benzo[*b*]furan derivatives. Therefore, these methods are complementary to those of the previously reported Cu-catalyzed coupling/cyclizations. In addition, this study serves to further highlight the importance of testing for trace metal impurities in reagents.

## Experimental Section

### General Remarks

All experiments were carried out under anhydrous conditions and an atmosphere of dry nitrogen. EtOH and dioxane were freshly distilled and stored with 4 Å molecular sieves under a nitrogen atmosphere. Reactions were monitored using thin-layer chromatography (TLC). All copper catalysts were purified prior to use according to literature methods. $^{1}H$ and $^{13}C$ NMR spectra were obtained on a Bruker DMX-400 at 400 and 100 MHz, respectively. Mass spectra were recorded on an AMD 402/3 or an HP 5989 A mass selective detector. Infrared spectra were recorded on an AVATAR 370 spectrometer.

### Synthesis of 1-(Methanesulfonyl)-2-phenyl-*1H*-indole (3a) as an Example

Under nitrogen, a mixture of *N*-mesyl-2-iodoaniline (74 mg, 0.25 mmol), CuI (4.8 mg, 10 mol%), and DBU (177 μL, 1.25 mmol) was dissolved in EtOH (1 mL), and ethynylbenzene (65 μL, 0.5 mmol) was added dropwise with stirring into the reaction. The reaction system was stirred at reflux and monitored by TLC. Upon completion, the mixture was diluted with $H_2O$ and extracted with EtOAc (3×15 mL). The extract was washed with brine (2×15 mL) and dried over $Na_2SO_4$. After evaporation, the residue was purified *via* flash column chromatography on silica gel with petroleum ether/ethyl acetate [50/1–15/1 (v/v)] as the eluent to afford the white solid **3a** in 90% yield and **4a** in 10% yield resulting from the cleavage of the Ms group.

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