Copper(I)-Catalyzed Coupling of Terminal Acetylenes with Aryl or Vinyl Halides

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Abstract: Synthetic protocols using copper(I) catalysts for the formation of diaryl acetylenes, 1,3-enynes, benzofurans and indoles are described.

Key words: copper, terminal acetylenes, enynes, benzofurans, indoles

The acetylenic moiety is an important unit found in many compounds that are of pharmaceutical, biological and material interests.[1] Aryl acetylenes are constituent units in important conjugated polymers.[1c] 1,3-Enynes are found in many biologically and pharmaceutically interesting compounds. Compounds containing carbon–acetylene bonds are intermediates for the synthesis of heterocycles. For example, 2-arylethynylphenols are intermediates for the synthesis of 2-arylbenzo[*b*]furans whereas 2-arylethynylanilines are intermediates for the synthesis of 2-arylindoles; benzofurans and indoles are prevalent in many compounds and natural products that have important biological properties.[2]

Due to the importance of the carbon–acetylene bond, many synthetic methods have been developed for its formation. Among these methods, the Sonogashira–Hagihara coupling, which is the palladium(0)-catalyzed cross-coupling of aryl or vinyl halides with terminal acetylenes, is the most widely used method.[3] Various palladium(0) sources have been used for the Sonogashira–Hagihara coupling and the reaction conditions are tolerant to a variety of functional groups.[1c]

In 1963, Stephen and Castro reported in a seminal paper that diaryl acetylenes can be synthesized by the reaction of copper acetylides and aryl iodides, in pyridine.[4] This reaction, Stephen–Castro coupling, was the method of choice for the formation of carbon–acetylene bonds before the advent of palladium(0)-based protocols. The reactions however, need to be done in solvents such as pyridine or DMF, under refluxing conditions. Instead of a terminal acetylene, the reaction requires the addition of pre-formed cuprous acetylide; poorer yields were obtained if the acetylides were generated in situ.[4] Although in 1993, Miura reported a modified copper-based protocol that allowed the coupling of terminal acetylenes,[5] the copper-based methods have been largely supplanted by the palladium-based protocols.

The past five years have witnessed a resurgence in interest in copper(I)-catalyzed cross-coupling reactions.[6] Many synthetic protocols, based on copper(I) catalysts, for the formation of carbon–carbon and carbon–heteroatom bonds have been reported.[6] In addition to being simple and mild, the newer copper-based methods have been shown to accommodate substrates that are difficult to couple by palladium reactions.[7] For example, the cross-coupling reactions of soft nucleophiles such as thiols, selenols, and phosphines have been successfully done using copper catalysts.[6] Furthermore, sterically hindered substrates are easily coupled and β-hydride elimination in nucleophiles bearing alkyl substituents is not observed with copper-based methods. The aforementioned reasons combined with the low cost of the copper catalysts and the avoidance of expensive or air-sensitive ligands make copper-based protocols very attractive for syntheses.

Our group explores the use of well-defined, soluble copper(I) complexes bearing nitrogen-based chelating ligands such as phenanthroline (phen) or neocuproine (2,9-dimethylphenanthroline, neocup) as catalysts for cross-coupling reactions. These complexes can be easily prepared, are stable to ambient air and moisture, and soluble in most common organic solvents.[8] Using these complexes as catalysts, we have developed various copper(I)-catalyzed protocols for the formation of carbon–acetylene, carbon–oxygen, carbon–nitrogen, carbon–sulfur, carbon–selenium, and carbon–phosphorous bonds. In this article, we explore copper-based protocols for the formation of carbon–acetylene bonds.[9]

We examined the efficacy of copper(I) complexes as catalysts for the formation of aryl–acetylene bonds using the coupling of phenyl acetylene and iodobenzene as a test reaction. Through optimization, we found that diphenyl acetylene was obtained in about 80% yield using 10 mol% of [Cu(phen)(PPh_3)Br] and 2 equivalents of K_2CO_3 in toluene at 110 °C for 24 hours.[9c] We did not observe diphenyl acetylene in the reaction when bases such as Et_3N, *t*-BuONa or *t*-BuOK were used instead of K_2CO_3. We also found that copper salts such as CuI or copper salts with ligands as additives were ineffective as catalysts for this reaction. If [Cu(neocup)(PPh_3)Br] was used instead of [Cu(phen)(PPh_3)Br], very low conversions were observed.

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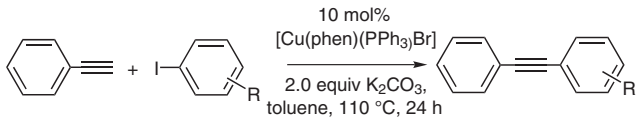
We were able to couple various electron-rich and electron-poor aryl halides with phenylacetylene in high yields using the optimized conditions, i.e., 10 mol% of [Cu(phen)(PPh_3)Br] and 2 equivalents of K_2CO_3 as a base in toluene at 110 °C for 24 hours (Table 1). Our protocol is compatible with substrates bearing *ortho*-functional groups and substrates having base-sensitive groups such as a ketone or methyl esters.

Table 1 Copper(I)-Catalyzed Cross-Coupling of Phenylacetylene with Various Aryl Iodides



80% 97%

74% 70%

71% 89%

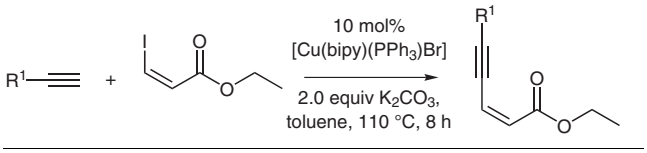
76% 85%

89%

In order to expand the use of our catalysts, we then explored the efficacy of the catalysts in the coupling of vinyl halides with terminal acetylenes.[9g] Upon optimization, we found that [Cu(bipy)(PPh_3)Br], not [Cu(phen)(PPh_3)Br], was the most effective catalyst for the coupling of (*Z*)-ethyl-3-iodoacrylate with phenyl acetylene; the optimum condition being 10 mol% of [Cu(bipy)(PPh_3)Br], 2.0 equivalents of K_2CO_3 in toluene at 110 °C for 8 hours.

We found that a wide range of aryl acetylenes coupled in good to excellent yields with (*Z*)-ethyl-3-iodoacrylate, with complete retention of stereochemistry. The protocol tolerates both electron-rich and electron-poor aryl acetylenes (see Table 2). The successful coupling of *n*-octyne to (*Z*)-ethyl-3-iodoacrylate demonstrated that the protocol is not specific to aryl acetylenes.

Table 2 Copper(I)-Catalyzed Cross-Coupling of Various Acetylenes with (*Z*)-Ethyl-3-iodoacrylate Using the Standard Protocol



99% 85%

91% 88%

95% 87%[a]

85% 92%

77% 89%

62% 65%[c]

98% 90%

96% 88%

51%[a,b]

[a] Reaction time of 12 h.
[b] [Cu(phen)(PPh_3)$_2$]NO_3 (10 mol%) was used as catalyst and Cs_2CO_3 (2.0 equiv) used as base.
[c] Reaction time of 20 h.

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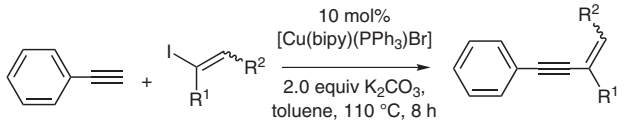
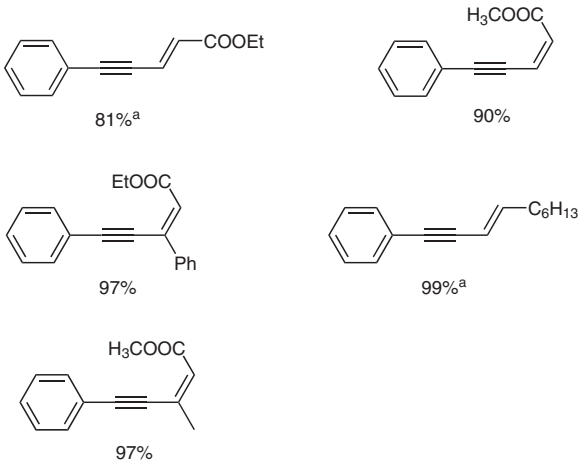
A variety of vinyl iodides can be coupled to phenyl acetylene in excellent yields as shown in Table 3. We found that in general, the *E* isomers coupled much more slowly than *Z* isomers (24 h vs. 8h). In these cases, when [Cu(bipy)(PPh_3)Br] was replaced with [Cu(phen)(PPh_3)$_2$]NO_3 as the catalyst and K_2CO_3 was replaced with Cs_2CO_3 as the base, we were able to successfully couple the *E* isomers in nearly quantitative yields, in 8 hours (Table 4). There was a complete retention in stereochemistry in all of the reactions.

Table 3 Copper(I)-Catalyzed Cross-Coupling of Phenylacetylene with Various Vinyl Iodides Using the Standard Protocol





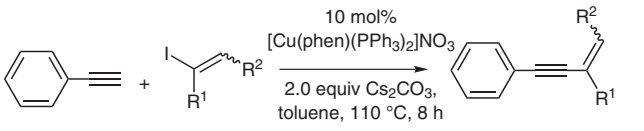
[a] Reaction time of 24 h.

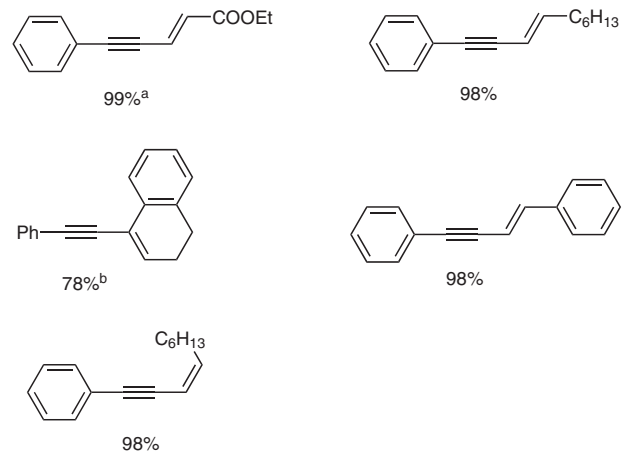
It is evident from the entries in Tables 1– 4 that aryl iodides with functional groups at the *ortho* position couple in excellent yields with copper(I) catalysts. This is in stark contrast to the palladium(0)-based protocols. Therefore, we reasoned that copper(I) complexes may be excellent catalysts for the synthesis of 2-arylethynylphenols and 2-arylethynylanilines; these compounds are intermediates in the synthesis of heterocycles such as benzo[*b*]furans and indoles.

Upon optimization, we found that 2-iodophenol can couple with phenyl acetylene and cyclize to form 2-phenylbenzo[*b*]furan in the presence of 10 mol% of [Cu(phen)(PPh_3)$_2$]NO_3 as catalyst, 2.0 equivalents of Cs_2CO_3 as base in toluene at 110 °C, in 24 hours.[9d] With our protocol, we were able to couple various terminal aryl acetylenes with 2-iodophenol and various substituted *o*-iodophenols with phenyl acetylene in excellent yields (Tables 5 and 6)

The observed yields are comparable to and in some cases better than the yields reported using palladium-catalyzed reactions.[9d] The protocol tolerates a variety of functional

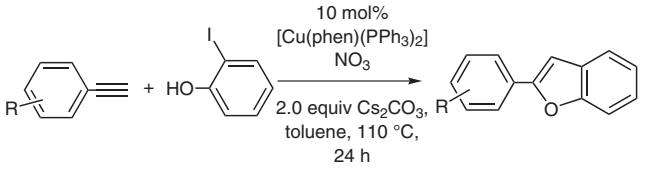
Table 4 Copper(I)-Catalyzed Cross-Coupling of Phenylacetylene with Various Vinyl Iodides Using the 10 mol% of [Cu(phen)(PPh_3)$_2$]NO_3 as the Catalyst and Cs_2CO_3 as the Base

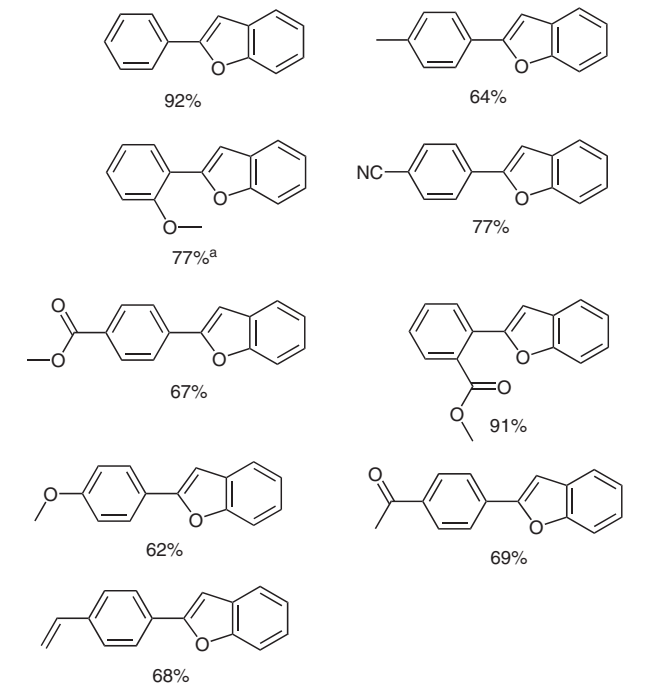




[a] GC yield.
[b] Reaction time of 24 h.

Table 5 Synthesis of 2-Arylbenzo[*b*]furans via Copper(I)-Catalyzed Cross-Coupling of *o*-Iodophenols and Various Aryl Acetylenes





[a] Reaction time of 48 h.

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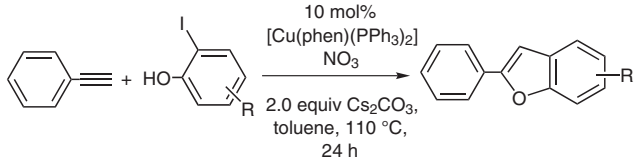
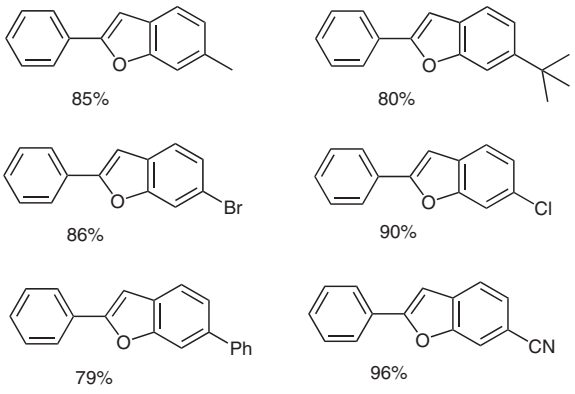
Table 6 Synthesis of 2-Arylbenzo[*b*]furans via Copper(I)-Catalyzed Cross-Coupling of Phenylacetylene and Various 4-Substituted-*o*-Iodophenols[a]





[a] 4-Substituted-*o*-iodophenols were synthesized from readily available phenols following the method reported in literature.[10]

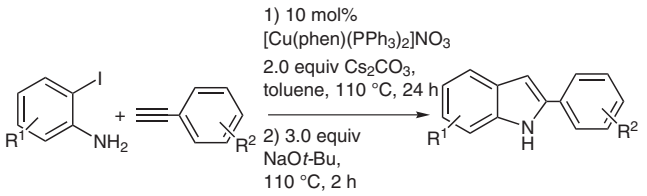
groups and can couple *ortho*-substituted arylacetylenes in good yields. The potential for further functionalization of the benzo[*b*]furan skeleton is made possible by the incorporation of a terminal alkene, bromine, and chlorine groups. With this protocol, no Heck-like coupling was observed for the coupling of phenylacetylene bearing an alkene as substituent, which may occur if a palladium-based system is used.

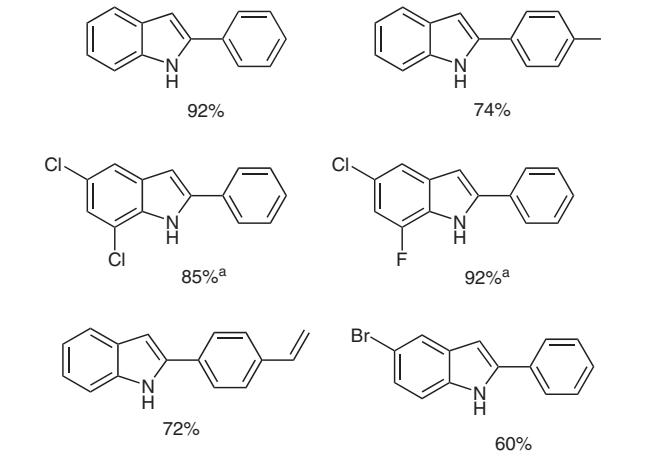
The conditions optimal for the synthesis of benzo[*b*]furans were not optimal for the synthesis of indoles. The coupling of 2-iodoaniline and phenylacetylene under these reactions result in a mixture of 2-phenyindole and the uncyclized 2-phenylethynylaniline. Addition of 3 equivalents of *t*-BuONa to the reaction mixture and heating it to 110 °C for 2 hours resulted in a complete conversion of 2-phenylethynylaniline to 2-phenylindole in 92% yield. Using these modified conditions we were able to synthesize a variety of 2-arylindoles in good yields (Table 7).

Under the aforementioned conditions, when iodobenzene was coupled with 2-ethynylaniline, the coupling occurred with the NH_2 group, instead of the terminal acetylene. Therefore, 2-ethynylacetanilide was used as starting material instead of 2-ethynylanine. A variety of 2-arylindoles with *N*-acetyl protection were synthesized in moderate yields as shown in Table 8.

When our work on the synthesis of indoles was in progress, Cacchi and co-workers reported a protocol for the synthesis of 2-arylindoles by the coupling of terminal acetylenes to 2-iodotrifluoroacetanilides using $[Cu(phen)(PPh_3)_2]NO_3$ as the catalyst and K_3PO_4 as the base in toluene at 110 °C.[11]

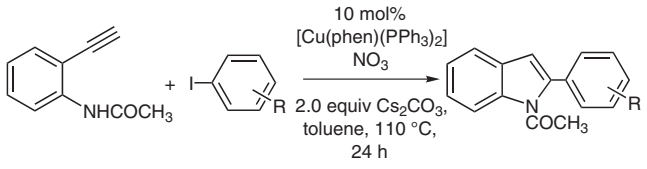
Table 7 Synthesis of 2-Arylindoles via Copper(I)-Catalyzed Cross-Coupling of Arylacetylenes and Various 2-Iodoanilines

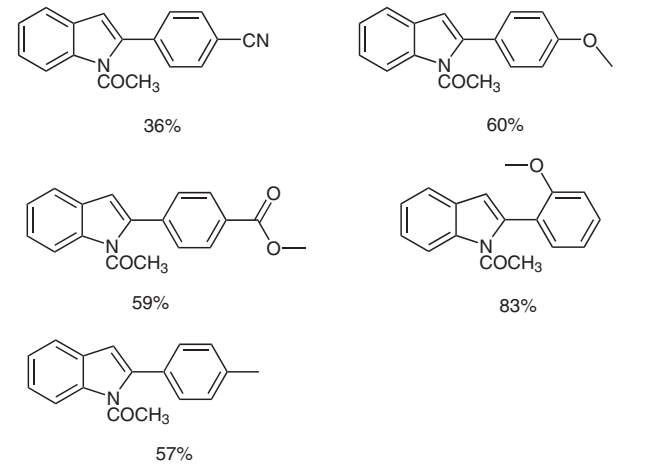




[a] Reaction time of step 2 was 4 h.

Table 8 Synthesis of 2-Arylindoles via Copper(I)-Catalyzed Cross-Coupling of *N*-(2-ethynylphenyl)acetamide and Various Aryliodides





In summary, copper(I)-based protocols are now available as an alternative to palladium(0)-based protocols for the coupling of aryl or vinyl iodides with terminal acetylenes. The copper-based protocols accommodate substrates such as *ortho*-substituted aryl halides, which are difficult to

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couple with the palladium-based protocols. Functional groups such as amines, alkenes, methyl ketones are well-tolerated with the copper-based protocols. At the present time, most copper(I) catalysts allow selective coupling of aryl or vinyl iodides. With the continued interest in copper catalysts for cross-coupling reactions, it is only a matter of time that more active copper catalysts are discovered for the coupling of bromides or chlorides.

All of the reactions reported herein were conducted under an inert atmosphere of Ar in oven-dried glassware. All reagents and solvents were obtained from Acros, Alfa Aesar or Aldrich and were used without further purification. Potassium phosphate (Alfa Aesar, 97%) was stored in an Ar-filled glove box. All vinyl iodides used in this paper have been synthesized using procedures previously reported in the literature.[1–4] Purification was performed by flash chromatography using standard grade silica gel (230–450 mesh) or activated neutral aluminum oxide (50–200 μm). The yields given refer to isolated yields of the characterized compounds, deemed pure by elemental analyses, ^{1}H NMR and ^{13}C NMR. In certain cases GC yields are reported. All GC yields were calculated using *n*-dodecane as an internal standard; the correction factors used to calculate the product yields were determined using an analytically pure sample. The gas chromatograph used was a Hewlett Packard 6850 GC series with a 30-m HP-1 100% dimethylpolysiloxane capillary column. NMR spectra were recorded on a Bruker Avance 400 MHz spectrometer. Chemical shifts are reported for the major isomer in ppm (δ). The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; dd, doublet of doublets; dt, doublet of a triplet; td, triplet of a doublet; sept, septet; m, multiplet; and q, quartet. The coupling constants, *J*, are reported in Hz. TMS was used as the internal reference. IR spectra were recorded using a Midac MD1200-SP3 spectrometer and are reported in cm^{-1} along with the relative intensity (w = weak, m = medium, s = strong absorption). Elemental analyses were performed at the Microanalysis Laboratory, University of Massachusetts Amherst. The reported melting points were uncorrected.

Synthesis of Diaryl Acetylenes; General Procedure

In an Ar-filled glove box, a Pyrex glass tube (2.5 cm in diameter) equipped with a Teflon-coated stir bar was charged with K_2CO_3 (2.0 mmol) and [Cu(phen)(PPh_3)Br] (10 mol% with respect to the phenylacetylene) and was sealed with a rubber septum. The sealed tube was taken out of the glove box and the phenylacetylene (2.50 mmol), the aryl halide (2.00 mmol) and toluene (15.0 mL) were injected into the tube through the septum. The contents were then stirred at 110 °C for 24 h. The reaction mixture was then cooled to r.t. and filtered to remove any insoluble residues. The filtrate was reduced in vacuo and the residue was purified by flash column chromatography on silica gel to obtain the analytically pure product.

Synthesis of 1,3-Enynes; General Procedure

In an Ar-filled glove box, a Pyrex glass tube (2.5 cm in diameter) equipped with a Teflon-coated stir bar was charged with K_2CO_3 (0.553 g, 4.0 mmol) and [Cu(bipy)(PPh_3)Br] (10 mol% with respect to the acetylene). The tube was then sealed with a rubber septum, taken out of the glove box and toluene (4.0 mL), the appropriate acetylene (2.00 mmol) and the appropriate vinyl iodide (2.20 mmol) were injected into the tube through the septum. The contents were then stirred at 110 °C for 8 h. The reaction mixture was then cooled to r.t. and filtered through a pad of celite to remove any insoluble residues. The filtrate was concentrated in vacuo and the residue was purified by flash column chromatography on silica gel to obtain the analytically pure product.

Synthesis of *E* Isomers and Less Reactive Vinyl Halides; Modified Procedure

In an Ar-filled glove box, a Pyrex glass tube (2.5 cm in diameter) equipped with a Teflon-coated stir bar was charged with Cs_2CO_3 (1.303 g, 4.0 mmol) and [Cu(phen)(PPh_3)$_2$]NO_3 (10 mol% with respect to the acetylene). The tube was then sealed with a rubber septum, taken out of the glove box and toluene (4.0 mL), the appropriate acetylene (2.00 mmol) and the appropriate vinyl iodide (2.20 mmol) were injected into the tube through the septum. The contents were then stirred at 110 °C for 8 h. The reaction mixture was then cooled to r.t. and filtered through a pad of celite to remove any insoluble residues. The filtrate was concentrated in vacuo and the residue was purified by flash column chromatography on silica gel to obtain the analytically pure product.

Synthesis of 2-Arylbenzo[*b*]furans; General Procedure

In an Ar-filled glove box, a Pyrex glass tube (2.5 cm in diameter) equipped with a Teflon-coated stir bar was charged with Cs_2CO_3 (1.31 g, 4.0 mmol), [Cu(phen)(PPh_3)$_2$]NO_3 (10 mol% with respect to the iodophenol), and the appropriate 2-iodophenol (2.0 mmol). The tube was then sealed with a rubber septum, taken out of the glove box and toluene (5.0 mL) and the appropriate phenylacetylene (2.00 mmol) were injected into the tube through the septum. The contents were then stirred at 110 °C for 24 h. The reaction mixture was then cooled to r.t. and filtered to remove any insoluble residues. The filtrate was concentrated in vacuo and the residue was purified by flash column chromatography on silica gel to obtain the analytically pure product.

Synthesis of 2-Arylindoles; General Procedure

In an Ar-filled glove box, [Cu(phen)(PPh_3)$_2$]NO_3 (10 mol%), and Cs_2CO_3 (2.0 equiv) were added into a 10 mL Schlenk tube equipped with a Teflon-coated stir bar and a Teflon stopper. After taking the tube out of the box, under flow of N_2 gas, toluene (5.0 mL), 2-iodoaniline (2.0 equiv), phenylacetylene (2.2 equiv) were added. Then, the Schlenk tube was sealed with a glass stopper and the reaction was stirred at 110 °C for 24 h. After reaction was complete, *t*-BuONa (3.0 equiv) was added under N_2 atmosphere, and the reaction mixture was stirred at 110 °C for 2 h. Then, the sat. NH_4Cl solution (25 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic phase was dried over anhyd Na_2SO_4, filtered and the solvent was removed. The solid residue was purified by column chromatography to afford the analytically pure product.

Cu-Catalyzed Synthesis of *N*-Acetyl-2-arylindoles; General Procedure

In glove box under Ar, [Cu(phen)(PPh_3)$_2$]NO_3 (10 mol%), and Cs_2CO_3 (2.0 equiv) were added into a 10 mL Schlenk tube equipped with a Teflon-coated stir bar and a Teflon stopper. After taking the tube out of the box, under flow of N_2 gas, toluene (5.0 mL), *N*-(2-ethynylphenyl)acetamide (2.0 equiv), aryl iodide (2.2 equiv) were added. Then, the Schlenk tube was sealed with a glass stopper and stirred at 110 °C for 24 h. The reaction mixture was then cooled to r.t. and filtered to remove any insoluble residues. The filtrate was concentrated in vacuo and the residue was purified by flash column chromatography on silica gel to obtain the analytically pure product.

Synthesis of 2-Iodoacetanilide and *N*-Acetyl-2-ethynylaniline

Acetyl chloride (6 mmol) was added dropwise to the mixture of 2-iodoaniline (5 mmol) and NaOH (13 mmol) in THF–H_2O (1:1, 4 mL). The mixture was stirred at 0 °C for 2 h, and then at r.t. for overnight. The mixture was diluted with water (10 mL) and extracted with Et_2O (3 ×). The combined organic layer was washed with water (3 ×) and brine, dried over Na_2SO_4, filtered, and the solvent was removed. The residue was then purified by column chromatography to afford 2-iodoacetanilide as a white solid in 68% yield.

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The *N*-acetyl-2-ethynylaniline was prepared from 2-iodoacetanilide by Sonogashira coupling and was obtained as a light brown solid in 45% yield.

2-Phenyl-1*H*-indole

The general procedure was used to convert phenylacetylene and 2-iodoaniline to the title product. Purification by flash chromatography gave the analytically pure product as a white solid (92% yield); mp 183–184 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.54 (s, 1 H), 7.86–7.84 (d, *J* = 7.15 Hz, 2 H), 7.53–7.50 (d, *J* = 7.72 Hz, 1 H), 7.45–7.40 (t, *J* = 7.72 Hz, 3 H), 7.30–7.25 (t, *J* = 7.34 Hz, 1 H), 7.01–6.96 (t, *J* = 6.97 Hz, 1 H), 6.87 (s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 138.48, 138.01, 133.09, 132.43, 132.30, 129.76, 129.25, 128.24, 125.84, 122.44, 120.93, 120.24, 112.18, 99.55.

Anal. Calcd for $C_{14}H_{11}N$: C, 87.01; H, 5.74; N, 7.25. Found: C, 86.87; H, 5.72; N, 6.99.

2-*p*-Tolyl-1*H*-indole

The general procedure was used to convert 1-ethynyl-4-methylbenzene and 2-iodoaniline to the title product. Purification by flash chromatography gave the analytically pure product as a white solid (74% yield); mp 213–215 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.47 (s, 1 H), 7.74 (d, *J* = 7.72 Hz, 2 H), 7.50 (d, *J* = 7.72 Hz, 2 H), 7.38 (d, *J* = 7.91 Hz, 1 H), 7.25 (d, *J* = 7.72 Hz, 2 H), 7.11–7.06 (t, *J* = 7.91 Hz, 1 H), 7.01–6.96 (t, *J* = 7.35 Hz, 1 H), 6.83 (s, 1 H), 2.34 (s, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 138.63, 137.85, 137.60, 130.31, 129.55, 125.77, 122.17, 120.72, 120.14, 112.04, 98.89, 21.65.

Anal. Calcd for $C_{15}H_{13}N$: C, 86.92; H, 6.32; N, 6.67. Found: C, 86.69; H, 6.24; N, 6.76.

2-(4-Vinylphenyl)-1*H*-indole

The general procedure was used to convert 1-ethynyl-4-vinylbenzene and 2-iodoaniline to the title product. Purification by flash chromatography gave the analytically pure product as a white solid (72% yield); mp 135.5–137.5 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.31 (br s, 1 H), 7.64–7.61 (d, *J* = 8.29 Hz, 3 H), 7.49–7.46 (d, *J* = 8.29 Hz, 2 H), 7.40–7.38 (d, *J* = 8.10 Hz, 1 H), 7.22–7.16 (dt, *J* = 6.97 Hz, 1 H), 7.14–7.09 (dt, *J* = 7.91 Hz, 1 H), 6.84 (s, 1 H), 6.78–6.69 (dd, *J* = 10.73 Hz, 1 H), 5.82–5.76 (dd, *J* = 17.70 Hz, 1 H), 5.30–5.26 (dd, *J* = 10.73 Hz, 1 H).

5,7-Dichloro-2-phenyl-1*H*-indole

The general procedure was used to convert 2,4-dichloro-6-iodophenylamine and phenylacetylene to the title product. Purification by flash chromatography gave the analytically pure product as a white solid (85% yield); mp 143–144 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.82 (s, 1 H), 8.01–7.98 (d, *J* = 8.2 Hz, 2 H), 7.57 (s, 1 H), 7.51–7.46 (t, *J* = 7.15 Hz, 2 H), 7.40–7.36 (t, *J* = 7.15 Hz, 1 H), 7.26 (d, *J* = 1.88 Hz, 1 H), 6.95 (d, *J* = 2.07 Hz, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 141.99, 133.71, 131.98, 131.86, 129.60, 129.10, 126.98, 124.85, 121.56, 119.11, 117.40, 100.90.

Anal. Calcd for $C_{14}H_9Cl_2N$: C, 64.15; H, 3.46; Cl, 27.05; N, 5.34. Found: C, 64.09; H, 3.37; Cl, 27.05; N, 5.28.

5-Chloro-7-fluoro-2-phenyl-1*H*-indole

The general procedure was used to convert 4-chloro-2-fluoro-6-iodo-phenylamine and phenylacetylene to the title product. Purification by flash chromatography gave the analytically pure product as a white solid (92% yield); mp 153–155 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 12.13 (s, 1 H), 7.98–7.95 (d, *J* = 7.72 Hz, 2 H), 7.51–7.46 (t, *J* = 7.53 Hz, 2 H), 7.44 (s, 1 H), 7.40–7.35 (t, *J* = 7.72 Hz, 1 H), 7.11–7.07 (d, *J* = 10.92 Hz, 1 H), 6.96 (s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 150.98, 147.70, 141.53, 133.51, 132.04, 129.73, 129.04, 126.54, 124.59, 124.10, 116.44, 108.27, 100.39.

Anal. Calcd for $C_{14}H_9ClFN$: C, 68.44; H, 3.69; Cl, 14.43; F, 7.73; N, 5.70. Found: C, 68.26; H, 3.76; Cl, 14.70; F, 7.5; N, 5.72.

5-Bromo-2-phenyl-1*H*-indole

The general procedure was used to convert 4-bromo-2-iodobenzenamine and phenylacetylene to the title product. Purification by flash chromatography gave the analytically pure product as a white solid (60% yield); mp 181–183 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.77 (s, 1 H), 7.88–7.85 (d, *J* = 7.4 Hz, 2 H), 7.72 (s, 1 H), 7.50–7.45 (t, *J* = 7.5 Hz, 2 H), 7.39–7.35 (m, 2 H), 7.23–7.20 (dd, *J* = 8.5, 1.8 Hz, 1 H), 6.89 (s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 139.06, 135.69, 131.54, 130.41, 128.88, 127.78, 125.09, 123.89, 122.04, 113.15, 111.78, 98.16.

Anal. Calcd for $C_{14}H_{10}BrN$: C, 61.79; H, 3.70; Br, 29.36; N, 5.15. Found: C, 61.60; H, 3.74; N, 5.02.

4-(1-Acetyl-1*H*-indol-2-yl)benzonitrile

The general procedure was used to convert 4-iodobenzonitrile and *N*-(2-ethynylphenyl)acetamide to the title product. Purification by flash chromatography gave the analytically pure product as a white solid (36% yield); mp 158–160 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.16–8.13 (d, *J* = 8.4 Hz, 1 H), 7.95–7.92 (d, *J* = 8.6 Hz, 2 H), 7.76–7.73 (d, *J* = 8.4 Hz, 2 H), 7.67–7.65 (d, *J* = 7.7 Hz, 1 H), 7.42–7.36 (dt, *J* = 7.3, 1.5 Hz, 1 H), 7.33–7.28 (dt, *J* = 7.7, 1.1 Hz, 1 H), 6.94 (s, 1 H), 2.28 (s, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 171.42, 139.15, 139.09, 137.98, 133.23, 130.31, 129.57, 126.25, 124.40, 121.99, 119.54, 116.08, 113.63, 111.49, 28.56.

Anal. Calcd for $C_{17}H_{12}N_2O$: C, 78.44; H, 4.65; N, 10.76. Found: C, 78.19; H, 4.63; N, 10.68.

1-[2-(4-Methoxyphenyl)-1*H*-indol-1-yl]ethanone

The general procedure was used to convert 1-iodo-4-methoxybenzene and *N*-(2-ethynylphenyl)acetamide to the title product. Purification by flash chromatography gave the analytically pure product as a slightly yellow solid (60% yield); mp 68–71 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.23–8.21 (d, *J* = 8.1 Hz, 1 H), 7.56–7.54 (d, *J* = 7.5 Hz, 1 H), 7.43–7.40 (d, *J* = 8.8 Hz, 2 H), 7.31–7.21 (m, 2 H), 7.02–7.00 (d, *J* = 8.8 Hz, 2 H), 6.64 (s, 1 H), 3.78 (s, 3 H), 2.03 (s, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 171.96, 160.37, 140.53, 137.75, 131.13, 129.71, 126.58, 125.29, 124.24, 121.18, 116.30, 114.97, 111.10, 56.06, 28.33.

Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.90; H, 5.74; N, 5.08.

1-(2-*p*-Tolyl-1*H*-indol-1-yl)ethanone

The general procedure was used to convert 1-iodo-4-methylbenzene and *N*-(2-ethynylphenyl)acetamide to the title product. Purification

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by flash chromatography gave the analytically pure product as a white solid (57% yield); mp 67–69 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.24–8.22 (d, *J* = 8.2 Hz, 1 H), 7.61–7.59 (d, *J* = 6.3 Hz, 1 H), 7.43–7.40 (d, *J* = 8.0, 2 H), 7.36–7.24 (m, 4 H), 6.71 (s, 1 H), 2.37 (s, 3 H), 2.07 (s, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 171.94, 140.70, 138.95, 137.81, 131.53, 130.12, 129.67, 129.64, 125.44, 124.26, 121.31, 116.24, 111.41, 28.41, 21.70.

Anal. Calcd for $C_{17}H_{15}NO$: C, 81.90; H, 6.06; N, 5.62. Found: C, 81.66; H, 6.02; N, 5.62.

Methyl 4-(1-Acetyl-1*H*-indol-2-yl)benzoate

The general procedure was used to convert methyl 4-iodobenzoate and *N*-(2-ethynylphenyl)acetamide to the title product. Purification by flash chromatography gave the analytically pure product as a white solid (59% yield); mp 103–104 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.20–8.17 (d, *J* = 8.2 Hz, 1 H), 8.06–8.04 (d, *J* = 8.2 Hz, 2 H), 7.70–7.67 (d, *J* = 8.3 Hz, 2 H), 7.66–7.64 (d, *J* = 7.7 Hz, 1 H), 7.41–7.28 (m, 2 H), 6.91 (s, 1 H), 3.89 (s, 3 H), 2.20 (s, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 171.63, 166.71, 139.56, 139.00, 138.06, 130.21, 129.96, 129.78, 129.56, 126.06, 124.37, 124.33, 121.81, 116.10, 113.06, 53.12, 28.53.

Anal. Calcd for $C_{18}H_{15}NO_3$: C, 73.71; H, 5.15; N, 4.78. Found: C, 73.50; H, 5.21; N, 4.54.

1-[2-(2-Methoxyphenyl)-1*H*-indol-1-yl]ethanone

The general procedure was used to convert 1-iodo-2-methoxybenzene and *N*-(2-ethynylphenyl)acetamide to the title product. Purification by flash chromatography gave the analytically pure product as a slightly yellow oil (83% yield).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.40–8.36 (m, 1 H), 7.57–7.53 (m, 1 H), 7.45–7.41 (m, 2 H), 7.36–7.22 (m, 2 H), 7.09–7.04 (m, 1 H), 6.95–6.92 (m, 1 H), 6.54 (s, 1 H), 3.76 (s, 3 H), 2.10 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.26, 156.93, 137.29, 136.39, 130.66, 130.55, 129.06, 124.76, 123.43, 123.16, 121.04, 120.21, 116.07, 111.30, 110.65, 55.38, 25.80.

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References

(1) (a) *The Chemistry of Triple-Bonded Functional Groups*; Patai, S.; Rappoport, Z., Eds.; Wiley: New York, **1983**. (b) Brandsma, L. *Preparative Acetylenic Chemistry*, 2 ed.; Elsevier: New York, **1988**. (c) Stang, P. J.; Diederich, F. *Modern Acetylene Chemistry*; VCH: New York, **1995**. (d) Rutledge, T. F. *Acetylenic Compounds: Preparation and Substitution Reactions*; Reinhold Book Corp: New York, **1968**.

(2) (a) Donnelly, D. M. X.; Meegan, M. J. *Comprehensive Heterocyclic Chemistry*, Vol. 4; Pergamon Press: New York, **1984**. (b) Erber, S.; Ringshandl, R.; von Angerer, E. *Anti-Cancer Drug Des.* **1991**, *6*, 417. (c) Malamas, M. S.; Sredy, J.; Moxham, C.; Katz, A.; Xu, W.; McDevitt, R.; Adebayo, F. O.; Sawicki, D. R.; Seestaller, L.; Sullivan, D.; Taylor, J. R. *J. Med. Chem.* **2000**, *43*, 1293. (d) Watanabe, Y.; Yoshiwara, H.; Kanao, M. *J. Heterocycl. Chem.* **1993**, *30*, 445.

(3) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467.

(4) Stephens, R. D.; Castro, C. E. *J. Org. Chem.* **1963**, *28*, 3313.

(5) Okuro, K.; Furuune, M.; Enna, M.; Miura, M.; Nomura, M. *J. Org. Chem.* **1993**, *58*, 4716.

(6) For reviews on copper-catalyzed cross-coupling reactions, see: (a) Kunz, K.; Scholz, U.; Ganzer, D. *Synlett* **2003**, 2428. (b) Ley, S. V.; Thomas, A. W. *Angew. Chem. Int. Ed.* **2003**, *42*, 5400. (c) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337. (d) Deng, W.; Liu, L.; Guo, Q. X. *Chin. J. Org. Chem.* **2004**, *24*, 150.

(7) (a) Hennessy, E. J.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 269. (b) Job, G. E.; Buchwald, L. *Org. Lett.* **2002**, *4*, 3703. (c) Kwong, F. Y.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 581. (d) Wolter, M.; Nordmann, G.; Job, G. E.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 973.

(8) For the preparation of these complexes, see ref. 9; [Cu(phen)(PPh_3)Br] and [Cu(phen)(PPh_3)$_2$]NO_3 are commercially available from Strem Chemicals.

(9) (a) Gujadhur, R.; Venkataraman, D. *Synth. Commun.* **2001**, *31*, 2865. (b) Gujadhur, R.; Venkataraman, D.; Kintigh, J. T. *Tetrahedron Lett.* **2001**, *42*, 4791. (c) Bates, C. G.; Gujadhur, R. K.; Venkataraman, D. *Org. Lett.* **2002**, *4*, 2803. (d) Bates, C. G.; Saejueng, P.; Murphy, J. M.; Venkataraman, D. *Org. Lett.* **2002**, *4*, 4727. (e) Gujadhur, R. K.; Venkataraman, D. *Tetrahedron Lett.* **2003**, *44*, 81. (f) Van Allen, D.; Venkataraman, D. *J. Org. Chem.* **2003**, *68*, 4590. (g) Bates, C. G.; Saejueng, P.; Venkataraman, D. *Org. Lett.* **2004**, *6*, 1441. (h) Bates, C. G.; Saejueng, P.; Doherty, M. Q.; Venkataraman, D. *Org. Lett.* **2004**, *6*, 5005.

(10) Edgar, K. J.; Falling, S. N. *J. Org. Chem.* **1990**, *55*, 5287.

(11) Cacchi, S.; Fabrizi, G.; Parisi, L. M. *Org. Lett.* **2003**, *5*, 3843.

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