Silica-Anchored Proline–Copper(I) as an Efficient and Recyclable Catalyst for the Sonogashira Reaction

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Abstract: A novel silica-anchored proline–copper(I) organic–inorganic hybrid material as an efficient catalyst for the Sonogashira reaction was developed. Terminal alkynes were reacted with aryl iodides and bromides smoothly in the presence of a proline-functionalized silica-anchored copper(I) catalyst in DMF to afford the corresponding cross-coupling products in good to excellent yields. Furthermore, silica-anchored proline–copper(I) catalyst was recovered and recycled by a simple filtration of the reaction solution and reused for six times without significant decreases in activity.

Key words: Sonogashira coupling reaction, organic–inorganic hybrid material, silica-anchored proline–copper(I) catalyst, heterogeneous catalysis, terminal alkynes, aryl iodides, aryl bromides

Stephens and Castro first discovered that diarylacetylenes can be prepared by treating aryl iodides with cuprous acetylides in refluxing pyridine under nitrogen in 1963.[1] Later, Cassar observed that acetylene or monosubstituted acetylenes were converted into aryl- and vinyl-substituted acetylene derivatives by reaction with aryl and vinyl halides in the presence of a nickel or palladium-triarylphosphine complex along with a base, in 1975. With the palladium-triphenylphosphine complexes, the conversion could be carried out catalytically under mild conditions.[2] Subsequently, Sonogashira et al. combined these two procedures into a cross-coupling reaction of terminal alkynes with aryl and alkenyl halides catalyzed by the palladium complexes in the presence of a catalytic amount of CuI and an amine (as solvent or in large excess), bearing his name in 1975.[3] Since then, the Sonogashira reaction has become the most important method to prepare arylalkynes and conjugated enynes, which are precursors for natural products, pharmaceuticals, and molecular organic materials.[4] At present, the palladium complex is the most commonly used catalyst for this coupling reaction. In addition, Au, Ag, Ru, Cu, Ni, In, etc. can also be used as catalysts for this transformation.[5] However, the high cost of transition-metal catalysts coupled with the toxic effects has limited its development and application. The development of inexpensive and nontoxic catalyst has gained more and more attention nowdays.[6] To some extent, supported catalyst can facilitate both the isolation and recycling of the catalyst by filtration thus providing environmentally cleaner processes. The development of organic reagents grafted onto silica gel has attracted increasing attention in recent years because industry seeks more environmentally friendly chemical manufacturing processes.[7] However, applications that involve the Sonogashira reaction have been less widely investigated, and usually employ a polystyrene-based support medium rather than a silica-based support.[8]

Most recently, in our preliminary investigation, the preparation of highly active 3-[(2-aminoethyl)amino]propyl-functionalized silica-anchored palladium copper(II) catalyst and subsequently its uses as an efficient and recyclable catalyst for the Sonogashira reaction, Heck reaction, and Ullmann diaryl etherification were reported.[9]

In this paper, we report on a novel silica-anchored proline–copper(I) as an efficient catalyst for the Sonogashira reaction. Terminal alkynes were reacted with aryl iodides and bromides smoothly to afford the corresponding cross-coupling products in good to excellent yields. It is important to note that the silica-anchored proline–copper(I) catalyst could be recovered and recycled by a simple filtration of the reaction solution and could be reused up to six times without significant loss of its activity.

The synthesis of silica-anchored proline–copper(I) catalyst is illustrated in Scheme 1. This was readily prepared through a four-step procedure. The silica gel (100–200 mesh, from Aldrich) was reacted with (4-chloromethyl)phenyltrichlorosilane in anhydrous toluene at 140 °C for 24 hours to afford the 4-chloromethylphenyl functionalized silica gel. The loading of the modified silica was readily quantified via CHN microanalysis and found to be 1.12 mmol/g. The obtained 4-chloromethylphenyl functionalized silica gel then reacted with 1-(*tert*-butoxycarbonyl)-4-hydroxypyrrolidine-2-carboxylic acid in the presence of NaH in anhydrous THF under reflux for 12 hours to afford the organic-inorganic hybrid material. The Boc protective group in the organic-inorganic hybrid material was deprotected through a standard method by shaking with a $CF_3CO_2H–CH_2Cl_2$ solution (1:1) at room temperature for three hours. The modified silica was filtered and subsequently neutralized by washing with Et_3N. The solid was washed with dichloromethane, methanol, and diethyl ether, respectively, and dried under vacuum at

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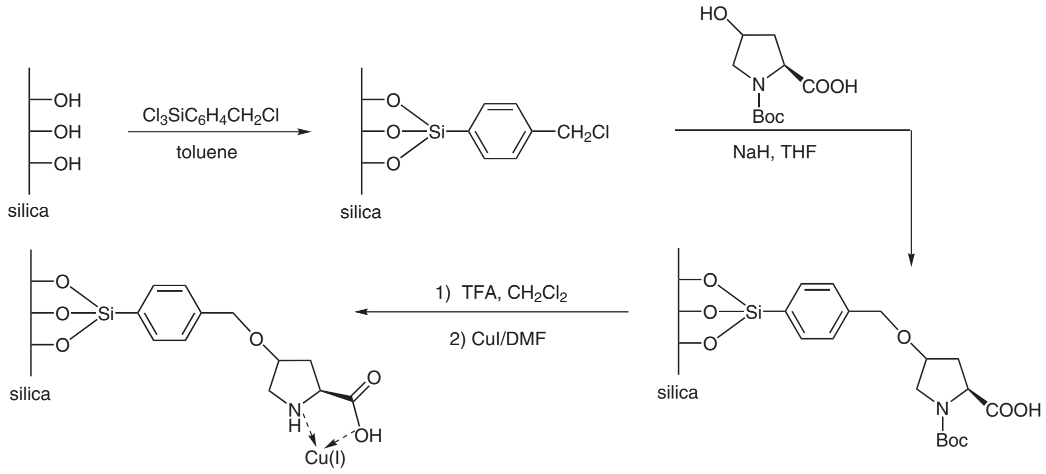
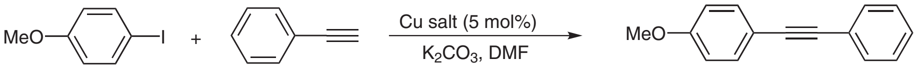


Scheme 1

Table 1 Effect of Copper Source on the Sonogashira Reaction[a]



Entry	Copper source	Yield (%)[b]
1	$CuSO_4$	trace
2	$Cu(OAc)_2$	43
3	CuI	92
4	CuBr	81
5	CuCl	73

[a] Reaction conditions: phenylacetylene (102 mg, 1.0 mmol), 4-iodoanisole (234 mg, 1.0 mmol), silica-anchored proline–copper(I) catalyst (58 mg, contains 0.05 mmol of Cu), and K_2CO_3 (276 mg, 2.0 mmol) in DMF (2 mL) at 110 °C with stirring for 8 h.

[b] Isolated yield.

room temperature to afford a white solid. The obtained white solid was then reacted with copper(I) iodide in *N*,*N*-dimethylformamide at room temperature for four hours to generate the silica-anchored proline–copper(I) catalyst. The copper metal amount of the silica-anchored proline–copper(I) catalyst was found to be 5.48 wt% based on AAS analysis.

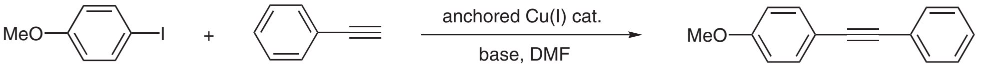
For our optimization of reaction conditions, the Sonogashira coupling reaction of phenylacetylene with 4-iodoanisole was chosen as a model reaction. In our initial screening experiments, the effects of various copper sources, bases, solvents, reaction time, and temperature on the yields of the model cross-coupling reaction were examined.

As shown in Table 1, the effect of copper source on the Sonogashira coupling reaction under the reaction conditions, which involved potassium carbonate as a base in *N*,*N*-dimethylformamide at 110 °C for 8 hours, was surveyed. Among the copper sources tested, a high yield (92%) of the desired cross-coupling product was isolated when copper(I) iodide was used as copper source, whereas good yields (81 and 73%, respectively) of the product were obtained with copper(I) bromide and copper(I) chloride as copper sources. Meanwhile, moderate yield (43% yield) of the product was observed with copper(II) acetate as the copper source and no desired product was generated when copper(II) sulfate was used as the copper source.

Encouraged by this result, we continued our research to improve the yield of the product by optimization of the reaction conditions, for example, by studying the effect of base on the reaction. From Table 2, we can see that the Sonogashira coupling reaction can occur in the presence of the bases we tested, except cesium carbonate. The organic bases, such as piperidine and triethylamine can be also used in the reaction, but only low yields (36 and 47%, respectively) of the product were obtained. Potassium carbonate was found to be the most effective one in the reaction. The other bases, such as KF, K_3PO_4, Na_2CO_3, and *t*-BuOK were subsequently less effective (Table 2, entries1–8).

We next turned our attention to investigate the effect of solvent on the coupling reaction. When the reactions were conducted in *N*,*N*-dimethylformamide, dimethyl sulfoxide, and ethanol, good to excellent yields (92, 88 and 80%, respectively) of products were isolated. Use of acetoni-

Table 2 Effect of Base on the Sonogashira Reaction[a]

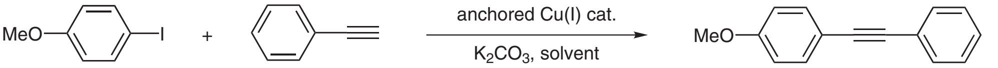


Entry	Base	Yield (%)[b]
1	piperidine	36
2	Et_3N	47
3	K_2CO_3	92
4	KF	57
5	K_3PO_4	82
6	Na_2CO_3	80
7	Cs_2CO_3	trace
8	*t*-BuOK	78

[a] Reaction conditions: phenylacetylene (102 mg, 1.0 mmol), 4-iodoanisole (234 mg, 1.0 mmol), silica-anchored proline–copper(I) catalyst (58 mg, contains 0.05 mmol of Cu), and base (2.0 mmol) in DMF (2 mL) at 110 °C with stirring for 8 h.

[b] Isolated yield.

Table 3 Effect of Solvent on the Sonogashira Reaction[a]



Entry	Solvent	Temp (°C)	Yield (%)[b]
1	DMF	110	92
2	DMSO	110	88
3	EtOH	78	80
4	MeCN	81	58
5	dioxane	100	30
6	toluene	110	24

[a] Reaction conditions: phenylacetylene (102 mg, 1.0 mmol), 4-iodoanisole (234 mg, 1.0 mmol), silica-anchored proline–copper(I) catalyst (58 mg, contains 0.05 mmol of Cu), and K_2CO_3 (276 mg, 2.0 mmol) in solvent (2 mL) at the temperature indicated in Table 3 for 8 h.

[b] Isolated yield.

trile, dioxane, and toluene as solvents led to slower reactions (Table 3, entries1–6).

During the course of our further optimization of the reaction conditions using 5 mol% loading of silica-anchored proline–copper(I) catalyst, the reactions were generally completed in a matter of hours, but the time, as expected, was inversely proportional to the temperature. A reaction temperature of 110 °C was found to be optimal. Thus, the optimized reaction conditions for this reaction are silica-anchored proline–copper(I) catalyst (5% mol) and potassium carbonate (2.0 equiv) in *N*,*N*-dimethylformamide at 110 °C for 8 h.

Under the optimized reaction conditions, the reaction of a wide variety of aryl halides and terminal alkynes underwent Sonogashira coupling smoothly, which generated the corresponding products in good to excellent yields. The electron-deficient aryl iodides and bromides can be nearly completely converted into products (Table 4, entries 4, 9, 10, 14, and 16). But the yield from 3-nitro-substituted iodobenzene was slightly lower than that of its 4-nitro analogue, probably due to the steric hindrance in the 3-nitro-substituted iodobenzene (Table 4, entry 4 vs. entry 5). For electron-neutral aryl iodide, high yield of product was also obtained (Table 4, entry 1), but only moderate yield of the product was isolated for less relatively active bromobenzene as substrate (Table 4, entry 12). This catalytic system was equally efficient for electron-rich aryl iodides. Good yields of products (90 and 93% yield, respectively) were observed for 4-iodoanisole and 4-iodotoluene as organic halide sources (Table 4, entries 2 and 3). The catalytic system was also effective for 2-bromopyridine, which generated the corresponding product in good yield (Table 4, entry 11). To evaluate the

Table 4 Silica-Anchored Proline–Copper(I)-Catalyzed Sonogashira Reaction[a]

$$R^1X + R^2C\equiv CH \xrightarrow[K_2CO_3,\ DMF]{anchored\ Cu(I)\ cat.} R^2C\equiv CR^1$$

Entry	R^1X	$R^2C\equiv CH$	Yield (%)[b]
1	PhI	$PhC\equiv CH$	93
2	$4\text{-}MeOC_6H_4I$	$PhC\equiv CH$	92
3	$4\text{-}MeC_6H_4I$	$PhC\equiv CH$	93
4	$4\text{-}O_2NC_6H_4I$	$PhC\equiv CH$	95
5	$3\text{-}O_2NC_6H_4I$	$PhC\equiv CH$	85
6	PhI	$4\text{-}MeC_6H_4C\equiv CH$	94
7	PhI	$n\text{-}C_6H_{13}C\equiv CH$	90
8	PhI	$n\text{-}C_8H_{17}C\equiv CH$	93
9	$4\text{-}CNC_6H_4Br$	$PhC\equiv CH$	91
10	$4\text{-}MeCOC_6H_4Br$	$PhC\equiv CH$	90
11	2-bromopyridine	$PhC\equiv CH$	86
12	PhBr	$PhC\equiv CH$	62
13	$4\text{-}MeOC_6H_4Br$	$PhC\equiv CH$	67
14	$4\text{-}O_2NC_6H_4Br$	$PhC\equiv CH$	92
15	$4\text{-}MeC_6H_4Br$	$PhC\equiv CH$	71
16	$4\text{-}O_2NC_6H_4I$	$4\text{-}MeC_6H_4C\equiv CH$	96

[a] Reaction conditions: terminal alkyne (1.0 mmol), organic halide (1.0 mmol), silica-anchored proline–copper(I) catalyst (58 mg, contains 0.05 mmol of Cu), and K_2CO_3 (276 mg, 2.0 mmol) in DMF (2 mL) at 110 °C for 8 h.

[b] Isolated yield.

scope of this methodology, we also performed the Sonogashira coupling reactions involving aliphatic alkynes. All of them coupled with iodobenzene in high efficiency (Table 4, entries 7 and 8).

The recyclability of the silica-anchored proline–copper(I) catalyst was also investigated. After the reaction was over, the solution was vacuum-filtered using a sintered glass funnel and washed with CH_2Cl_2, Et_2O, EtOH, and hexane, respectively. After drying, it can be reused directly without further purification. The silica-anchored proline–copper(I) catalyst can be recovered, recycled, and reused for six consecutive trials without loss of its activity (Table 5).

In conclusion, a highly efficient silica-anchored proline–copper(I) catalyst has been successfully applied to the cross-coupling of aryl halides, including aryl iodides and bromides with terminal alkynes and the reactions generated the corresponding products in good to excellent yields. The use of silica-supported catalyst permitted the product to be easily separated from the catalyst. Furthermore, the silica-anchored catalyst could be recovered and recycled by a simple filtration of the reaction solution and reused for six consecutive trials without significant loss of activity.

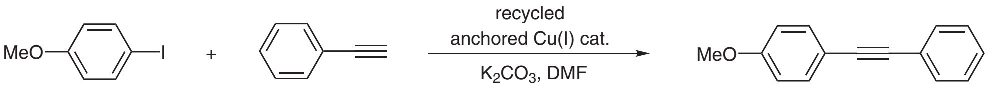
Melting points were recorded on a WRS-2B melting point apparatus and are uncorrected. All ^1H NMR spectra were recorded on a 300 MHz Bruker FT-NMR spectrometer. Chemical shifts are given as δ values with reference to TMS as internal standard. IR spectra were obtained by using a Nicolet NEXUS 470 spectrophotometer. The CHN analysis was performed on a Vario El III elementary analyzer. Products were purified by flash chromatography on 230–400 mesh silica gel.

All chemicals were purchased from commercial suppliers (Aldrich, USA and Shanghai Chemical Company, China) and used without purification prior to use. Activation of silica by using concentrated H_2SO_4 and HNO_3 was done according to the literature.[9]

Silica-Anchored Proline-Copper(I) Catalyst

In a 100 mL round-bottomed flask were introduced successively anhyd toluene (60 mL) and (4-chloromethyl)phenyltrichlorosilane (7.8 g). After stirring the solution for 10 min, activated silica (20.0 g) was added. Then the mixture was refluxed for 24 h at 140 °C. The mixture was filtered and the solid was washed with EtOH (50 mL) in a Soxhlet extractor for 5 h, washed with Et_2O (60 mL), and dried under reduced pressure at 80 °C. The loading of the modified silica was readily quantified via CHN microanalysis and found to be 1.12 mmol/g. Under N_2, an oven-dried round-bottomed flask was charged with anhyd THF (150 mL), 1-(*tert*-butoxycarbonyl)-4-hydroxypyrrolidine-2-carboxylic acid (2.80 g, 12.1 mmol), and NaH (1.02 g, 60%, 25.5 mmol). The mixture was stirred for 1.5 h, then the above functionalized silica (10 g) was added and the mixture was refluxed for 12 h. The solution was filtered and the solid was

Table 5 Successive Trials Using Recovered Silica-Anchored Proline–Copper(I) Catalyst[a]



Entry	Yield (%)[b]	Entry	Yield (%)[b]
1	92	4	88
2	89	5	89
3	91	6	88

[a] Reaction conditions: phenylacetylene (102 mg, 1.0 mmol), 4-iodoanisole (234 mg, 1.0 mmol), recycled silica-anchored proline–copper(I) catalyst (58 mg, contains 0.05 mmol of Cu), and K_2CO_3 (276 mg, 2.0 mmol) in DMF (2 mL) at 110 °C for 8 h.

[b] Isolated yield.

washed with H_2O (30 mL), EtOH (30 mL), and then dried overnight under reduced pressure at 60 °C. In a round-bottom flask were introduced successively CH_2Cl_2 (10 mL), CF_3CO_2H (8 mL), and the *N*-Boc-proline functionalized silica (4 g). The mixture was shaken for 0.5 h, and the silica was filtered, washed with Et_3N (5 mL), CH_2Cl_2 (10 mL), MeOH (10 mL) and Et_2O (10 mL), and then dried overnight under reduced pressure at r.t. A white solid was obtained. The loading of this modified silica was quantified via CHN microanalysis and found to be 0.91 mmol/g. In a small Schlenk tube, the silica-anchored proline (1.0 g, containing 0.91 mmol proline units) was mixed with CuI (0.191 g, 1.0 mmol) in DMF (5 mL). The mixture was stirred for 4 h under N_2 at r.t. The solution was filtered and the solid was washed with acetone (3 mL) and MeOH (3 mL), and the solid was dried under reduced pressure at r.t. for 16 h, affording the silica-anchored proline–copper(I) catalyst as a pale blue powder (1.05 g). The copper metal amount of the silica-anchored proline–copper(I) catalyst was found to be 5.48 wt% based on AAS analysis.

Sonogashira Reaction Using Silica-Anchored Proline–Copper(I) Catalyst; General Procedure

Under N_2, an oven-dried two-necked round-bottomed flask containing a stir bar was charged with organic halide (1.0 mmol), terminal alkyne (1.0 mmol), silica-anchored proline–copper(I) catalyst (58 mg, containing Cu 0.05 mmol), K_2CO_3 (276 mg, 2.00 mmol) and DMF (2 mL). The mixture was heated and stirred at 110 °C for 8 h. After cooling to r.t., the mixture was vacuum-filtered using a sintered glass funnel and washed with CH_2Cl_2 (3 mL). The combined organics were dried (Na_2SO_4), filtered, concentrated, and the residue was purified by flash chromatography on silica gel to give the desired cross-coupling product.

Recyclization of Silica-Anchored Proline–Copper(I) Catalyst

After carrying out the reaction, the mixture was vacuum-filtered using a sintered glass funnel, and washed with CH_2Cl_2 (2 mL), Et_2O (2 mL), EtOH (2 mL), and hexane (3 mL), respectively. After drying in an oven at 60 °C for 4 h, the catalyst can be reused directly without further purification.

Diphenylacetylene

Mp 61–62 °C (Lit.[10] mp 60–62 °C).

IR (KBr): 3056, 2311, 1450, 961, 763, 691 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.52–7.50 (m, 4 H), 7.37–7.10 (m, 6 H).

Phenyl-*p*-tolylacetylene

Mp 71–73 °C (Lit.[11] mp 72–73 °C).

IR (KBr): 3058, 2241, 1593, 1510, 1440, 915, 818, 754, 690 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.53–7.50 (m, 2 H), 7.42 (d, *J* = 7.80 Hz, 2 H), 7.33–7.31 (m, 3 H), 7.12 (d, *J* = 7.80 Hz, 2 H), 2.35 (s, 3 H).

(4-Acetylphenyl)phenylacetylene

Mp 95–96 °C (Lit.[12] mp 94–96 °C).

IR (KBr): 3059, 2189, 1679, 1602, 1593, 1484, 1442, 1358, 834, 759 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.91 (d, *J* = 8.41 Hz, 2 H), 7.58 (d, *J* = 8.41 Hz, 2 H), 7.54–7.52 (m, 2 H), 7.36–7.33 (m, 3 H), 2.57 (s, 3 H).

(4-Nitrophenyl)phenylacetylene

Mp 120–122 °C (Lit.[13] mp 120–121 °C).

IR (KBr): 3066, 2175, 1602, 1593, 1442, 1358, 834, 759 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.20 (d, *J* = 9.00 Hz, 2 H), 7.65 (d, *J* = 9.00 Hz, 2 H), 7.57–7.54 (m, 2 H), 7.40–7.38 (m, 3 H).

(3-Nitrophenyl)phenylacetylene

Mp 68–69 °C (Lit.[14] mp 68–70 °C).

IR (KBr): 3082, 2237, 1529, 1514, 1442, 1351, 901, 758, 691 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.36 (s, 1 H), 8.15 (d, *J* = 9.00 Hz, 1 H), 7.81 (d, *J* = 7.50 Hz, 1 H), 7.57–7.52 (m, 3 H), 7.39–7.37 (m, 3 H).

1-Phenyldec-1-yne

Oil.[15]

IR (film): 3059, 2956, 2930, 2857, 2256, 1598, 1490, 1466, 901, 755, 691 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.43–7.38 (m, 2 H), 7.29–7.21 (m, 3 H), 2.39 (t, *J* = 6.96 Hz, 2 H), 1.68–1.56 (m, 2 H), 1.49–1.30 (m, 10 H), 0.89 (t, *J* = 6.54 Hz, 3 H).

1-Phenyloct-1-yne

Oil.[16]

IR (film): 3073, 2946, 2923, 2246, 1590, 1498, 1467, 755, 691 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.42–7.39 (m, 2 H), 7.33–7.25 (m, 3 H), 2.41 (t, *J* = 6.99 Hz, 2 H), 1.69–1.57 (m, 2 H), 1.52–1.32 (m, 6 H), 0.90 (t, *J* = 6.86 Hz, 3 H).

(4-Methoxyphenyl)phenylacetylene

Mp 59–61 °C (Lit.[17] mp 57–61 °C).

IR (KBr): 3059, 2186, 1593, 1511, 1440, 1247, 1028, 834, 754 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.53–7.45 (m, 4 H), 7.33–7.30 (m, 3 H), 6.85 (d, *J* = 7.80 Hz, 2 H), 3.82 (s, 3 H).

(4-Cyanophenyl)phenylacetylene

Mp 109–111 °C (Lit.[18] mp 108.5–109.5 °C).

IR (KBr): 3059, 2227, 2214, 1603, 1502, 1443, 843, 762 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.65–7.59 (m, 4 H), 7.56–7.53 (m, 2 H), 7.39–7.37 (m, 3 H).

2-(2-Phenylethynyl)pyridine

Oil.[19]

IR (film): 2986, 2239, 1598, 1535, 1493, 963, 754, 689 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.60 (dd, *J* = 5.10, 0.90 Hz, 1 H), 7.68–7.59 (m, 3 H), 7.51 (dd, *J* = 8.10, 0.90 Hz, 1 H), 7.37–7.33 (m, 3 H), 7.23–7.19 (m, 1 H).

(4-Nitrophenyl)-*p*-tolylacetylene

Mp 156–157 °C (Lit.[20] mp 157 °C).

IR (KBr): 3059, 2188, 1598, 1501, 1490, 1357, 808 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.23 (d, *J* = 8.61 Hz, 2 H), 7.66 (d, *J* = 7.43 Hz, 2 H), 7.42 (d, *J* = 7.44 Hz, 2 H), 7.21 (d, *J* = 7.82 Hz, 2 H), 2.41 (s, 3 H).

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