

2,2'-Diamino-6,6'-dimethylbiphenyl as an Efficient Ligand in the CuI-Catalyzed Sonogashira Reaction of Aryl Iodides and Bromides with Terminal Alkynes

Bin-Bin Wang, Yue-Mei Ye, Jun-Jun Chen, Xia-Xia Zhou, Jian-Mei Lu, and Li-Xiong Shao*

College of Chemistry and Materials Engineering, Wenzhou University, Chashan University Town, Wenzhou, Zhejiang 325035, P. R. China

Received November 22, 2010; E-mail: Shaolix@wzu.edu.cn

2,2'-Diamino-6,6'-dimethylbiphenyl (**L1**) was found to be a good ligand in the CuI-catalyzed Sonogashira coupling reaction of various aryl iodides and bromides with terminal alkynes. Under suitable conditions, all reactions gave the desired coupling products in moderate to excellent yields.

Acetylenic compounds can be found in a number of natural products, bioactive molecules, and other functional materials.¹ The palladium and copper cocatalyzed reaction of vinyl halides with terminal alkynes, known as the Sonogashira reaction, is a powerful and straightforward method for the construction of arylated internal alkyne compounds.^{2,3} However, the high costs of palladium salts, requirement of copper as cocatalyst, and usually with high oxophilic phosphine compounds as the ligand, limit the applications of the Pd/Cu catalytic system in industrial chemistry. Recently, some new catalytic systems have been developed in order to overcome these drawbacks.⁴ Since it was reported that aryl halides could couple with copper(I) acetylides to give aryl acetylenes,⁵ there has been a resurgence in the copper salt catalyzed coupling of aryl halides with terminal alkynes.⁶ During our investigations using non-phosphine-based ligands in the transition-metal-catalyzed coupling reactions for C–C bond formation,⁷ it was found that 2,2'-diamino-6,6'-dimethylbiphenyl (**L1**) is a good ligand for the CuI-catalyzed Sonogashira coupling of aryl iodides and bromides with terminal alkynes. Herein, we wish to report these results in detail.

Results and Discussion

In preliminary studies, we used 10 mol % **L1** as the ligand with 10 mol % CuI as the catalyst in the presence of NaOH (2.0 equiv) for the coupling of 4-methoxyphenyl iodide (**1a**) with phenylacetylene (**2a**) in DMF (1.0 mL) at 115 °C for 24 h, and the corresponding coupling product **3a** was isolated in 85% yield (Table 1, Entry 1). Using other bases such as KOH, Na₂CO₃, NaHCO₃, KHCO₃, K₂CO₃, and Cs₂CO₃ under identical conditions, **3a** was obtained in somewhat lower yields (Table 1, Entries 2–7). For other copper salts such as Cu₂O, Cu powder, and CuO, all showed inferior results (Table 1, Entries 8–10). When DMSO was used as the solvent in place of DMF, the yield of **3a** can be further increased to 97% (Table 1, Entry 11). Using other analogous diamines **L2**–**L6** as the ligand, all reactions showed inferior results (Table 1, Entries 12–16).

Thus, the optimal reaction conditions are established as CuI (10 mol %) as the catalyst, **L1** (10 mol %) as the ligand, NaOH (2.0 equiv) as the base and DMSO (1.0 mL) as the solvent at the temperature of 115 °C.

With the optimal reaction conditions in hand, we then investigated the scope of the CuI–**L1**-catalyzed Sonogashira reaction of aryl iodides with terminal alkynes and the results are summarized in Table 2. As can be seen from Table 2, aryl iodides containing electron-donating groups such as methoxy and methyl groups (Entries 2–7) as well as electron-withdrawing groups such as fluorine and chlorine groups (Entries 8 and 9) reacted with terminal acetylenes to provide arylated alkynes in good to excellent yields. The reaction of phenyl iodide (**1b**) with 4-methoxyphenylacetylene (**2b**) also gave the coupling product **3a** in 96% yield (Table 2, Entry 1). Sterically hindered *ortho*-substituted aryl iodides as 2-methoxyphenyl iodide (**1c**) and 2-methylphenyl iodide (**1d**) also provided good yields by reacting with terminal alkynes under the identical reaction conditions (Table 2, Entries 3 and 4). It should be noted that when 1-bromo-2-iodobenzene (**1j**) was used, only the iodine group participated in the reaction to afford **3j** in 82% yield under identical reaction conditions (Table 2, Entry 10). When strongly electron-withdrawing group substituted aryl iodides as 4-acetylphenyl iodide (**1k**), 4-methoxycarbonylphenyl iodide (**1l**), and 4-nitrophenyl iodide (**1m**) were used as the substrates, only trace products were observed (Table 2, Entries 11–13). It should be noted here that almost no expected reaction occurred under the identical conditions with **2b** and 1-cyclohexenyl iodide as the substrates. Maybe alkenyl iodide is more labile to decompose under the identical reaction conditions.

The reaction between **1a** (0.75 mmol) and 1-hexyne (**2c**) (1.5 mmol) was also carried out under identical conditions (Scheme 1). It was found that only moderate yield of the coupling product **3k** was obtained.

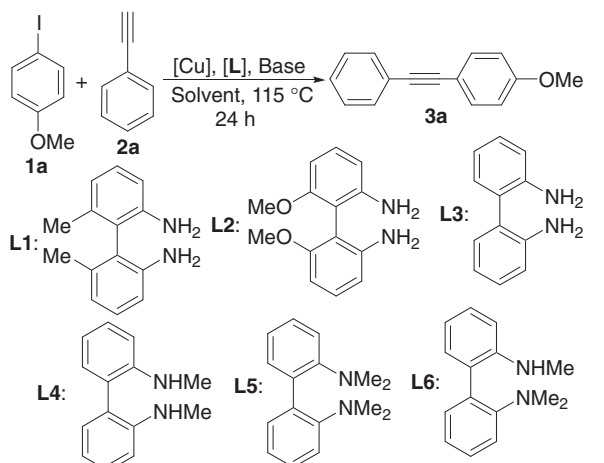
Though under the optimal conditions for the reactions of aryl iodides with terminal alkynes aryl bromides showed almost no reactivity, when the reaction of phenyl bromide (**1n**) with **2b**

was carried out at 160 °C in DMSO for 48 h, the coupling product **3a** could be also obtained in 47% yield (Table 3, Entry 1). Increased amount of both CuI and **L1** to 20 mol %, **3a** was isolated in 85% yield (Table 3, Entry 2). Then we examined a variety of aryl bromides with terminal alkynes in the presence of 20 mol % CuI and 20 mol % **L1** and the results are summarized in Table 3. As can be seen from Table 3, aryl bromides containing electron-donating groups such as methoxy and methyl groups (Entries 4–10) as well as electron-withdrawing group such as chlorine (Entry 3) reacted with

terminal acetylenes to provide the arylated alkynes in moderate to good yields. For sterically hindered *ortho*-substituted 2-methylphenyl bromide (**1r**), the corresponding arylated alkyne **3d** was obtained in 74% yield (Entry 7). When highly sterically hindered 2,6-dimethylphenyl bromide (**1u**) was used as the substrate, product **3n** was obtained only in 44% yield (Entry 10). It should be noted here that when 4-methoxyphenyl bromide (**1p**) was used as the substrate, the corresponding product **3b** was obtained in 86% yield in the presence of 10 mol % CuI and 10 mol % **L1** (Entry 4).

Though the real mechanism for this copper-catalyzed Sonogashira coupling reaction remains unclear at this stage, a proposed one is shown below,⁸ where **L1** means 2,2'-diamino-6,6'-dimethylbiphenyl. First, CuI will coordinate with **L1** to form intermediate **I**, which is believed to be the active species in this catalytic cycle. Then intermediate **II** will be achieved via reaction of alkynes **2** with **I** in the presence of a base. Subsequently, oxidative addition of aryl iodides **1** to intermediate **II** will give intermediate **III**. Finally, products **3** will be formed via reductive elimination of intermediate **III**, releasing active species **I** to complete the catalytic cycle (Scheme 2).

Table 1. Optimization for the Copper-Catalyzed Coupling Reaction of **1a** with **2a**



Entry ^{a)}	[Cu]	[L]	Base	Solvent	Yield/% ^{b)}
1	CuI	L1	NaOH	DMF	85
2	CuI	L1	KOH	DMF	64
3	CuI	L1	Na ₂ CO ₃	DMF	81
4	CuI	L1	NaHCO ₃	DMF	57
5	CuI	L1	KHCO ₃	DMF	79
6	CuI	L1	K ₂ CO ₃	DMF	82
7	CuI	L1	CS ₂ CO ₃	DMF	<10
8	Cu ₂ O	L1	NaOH	DMF	73
9	Cu	L1	NaOH	DMF	48
10	CuO	L1	NaOH	DMF	79
11	CuI	L1	NaOH	DMSO	97
12	CuI	L2	NaOH	DMSO	43
13	CuI	L3	NaOH	DMSO	42
14	CuI	L4	NaOH	DMSO	46
15	CuI	L5	NaOH	DMSO	34
16	CuI	L6	NaOH	DMSO	45

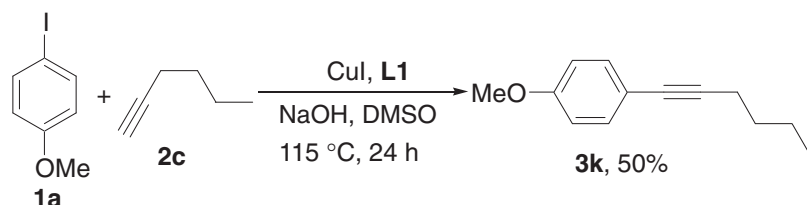
a) All reactions were carried out using **1a** (0.75 mmol) and **2a** (0.90 mmol) in the presence of [Cu] (10 mol %) and [L] (10 mol %) in the listed base (2.0 equiv) and solvent (1.0 mL) at 115 °C for 24 h. b) Isolated yields.

Table 2. CuI-Catalyzed Sonogashira Coupling of Iodides **1** with Terminal Alkynes **2**

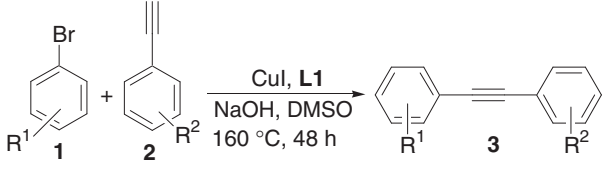


Entry ^{a)}	1 (R ¹)	2 (R ²)	Yield/% ^{b)}
1	1b (H)	2b (4-OMe)	3a (96)
2	1a (4-OMe)	2b	3b (98)
3	1c (2-OMe)	2a (H)	3c (80)
4	1d (2-Me)	2b	3d (88)
5	1e (3,5-Me ₂)	2b	3e (98)
6	1f (3-Me)	2b	3f (99)
7	1g (4-Me)	2b	3g (90)
8	1h (4-Cl)	2b	3h (86)
9	1i (4-F)	2b	3i (74)
10	1j (2-Br)	2b	3j (82)
11	1k (4-Ac)	2b	trace
12	1l (4-CO ₂ Me)	2a	trace
13	1m (4-NO ₂)	2b	<5

a) All reactions were carried out using **1** (0.75 mmol), **2** (0.90 mmol), NaOH (1.5 mmol) in the presence of CuI (10 mol %) and **L1** (10 mol %) in DMSO (1.0 mL) at 115 °C for 24 h. b) Isolated yields.

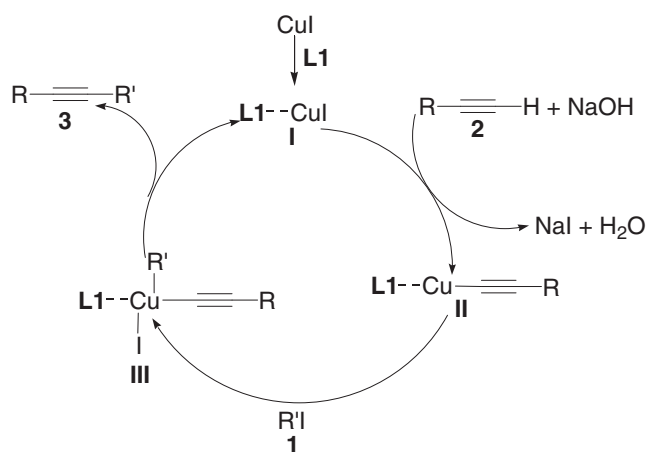


Scheme 1. CuI-catalyzed reaction of 4-iodophenyl iodide (**1a**) with 1-hexyne (**2c**).

Table 3. CuI-Catalyzed Sonogashira Coupling of Bromides **1** with Terminal Alkynes **2**


Entry ^{a)}	1 (R ¹)	2 (R ²)	Yield/% ^{b)}
1 ^{c)}	1n (H)	2b (4-OMe)	3a (47)
2	1n (H)	2b (4-OMe)	3a (85)
3	1o (4-Cl)	2b	3h (74)
4 ^{c)}	1p (4-OMe)	2b	3b (86)
5 ^{c)}	1q (3-OMe)	2b	3l (72)
6	1q	2b	3l (91)
7	1r (2-Me)	2b	3d (74)
8	1s (4-Me)	2b	3g (86)
9	1t (3-OMe)	2a (H)	3m (60)
10	1u (2,6-Me ₂)	2b	3n (44)

a) Otherwise specified, all reactions were carried out using **1** (0.75 mmol), **2** (0.90 mmol), NaOH (1.5 mmol) in the presence of CuI (20 mol %) and **L1** (20 mol %) in DMSO (1.0 mL) at 160 °C for 48 h. b) Isolated yields. c) CuI (10 mol %) and **L1** (10 mol %) were used.

**Scheme 2.** Proposed mechanism.

Conclusion

In conclusion, we have found that 2,2'-diamino-6,6'-dimethylbiphenyl (**L1**), as a non-phosphine, air-stable, and easily available compound, is an efficient ligand in the CuI-catalyzed Sonogashira coupling reaction of various aryl iodides and bromides with terminal alkynes under the appropriate reaction conditions. Both aryl iodides and bromides react with terminal alkynes to provide the corresponding coupling products in high yields. Efforts are underway to disclose other applications of this ligand in this laboratory.

Experimental

General Remarks. ¹H and ¹³C NMR spectra were recorded on a Bruker Avance-300 or 500 MHz spectrometer for solution in CDCl₃ with tetramethylsilane (TMS) as an internal standard;

J-values are in Hertz. DMF and DMSO were distilled from CaH₂ under reduced pressure. Commercially obtained reagents were used without further purification. Flash column chromatography was carried out using Huanghai 300–400 mesh silica gel at increased pressure.

General Procedure for the CuI-L1**-Catalyzed Sonogashira Reaction of Aryl Iodides with Terminal Alkynes.** If Aryl Iodide is a Liquid: Under N₂ atmosphere, CuI (10 mol %), **L1** (10 mol %), NaOH (2.0 equiv), and degassed DMSO (1.0 mL) were added into a Schlenk reaction tube, then aryl iodide **1** (0.75 mmol) and terminal alkyne **2** (0.90 mol) were added. The mixture was stirred at 115 °C for 24 h. Then the solvent was diluted with EtOAc, washed with brine, and dried over anhydrous Na₂SO₄. The product was purified by flash column chromatography (SiO₂) to give pure product **3**.

If Aryl Iodide is a Solid: Under N₂ atmosphere, aryl iodide **1** (0.75 mol), CuI (10 mol %), **L1** (10 mol %), NaOH (2.0 equiv), and degassed DMSO (1.0 mL) were added into a Schlenk reaction tube, then terminal alkyne **2** (0.90 mol) was added. The mixture was stirred at 115 °C for 24 h. Then the solvent was diluted with EtOAc, washed with brine, and dried over anhydrous Na₂SO₄. The product was purified by flash column chromatography (SiO₂) to give pure product **3**.

General Procedure for the CuI-L1**-Catalyzed Sonogashira Reaction of Aryl Bromides with Terminal Alkynes.** Under N₂ atmosphere, CuI (20 mol %), **L1** (20 mol %), NaOH (2.0 equiv), and degassed DMSO (1.0 mL) were added into a Schlenk reaction tube, then aryl bromide **1** (0.75 mmol) and terminal alkyne **2** (0.90 mol) were added. The mixture was stirred at 160 °C for 48 h. Then the solvent was diluted with EtOAc, washed with brine, and dried over anhydrous Na₂SO₄. The product was purified by flash column chromatography (SiO₂) to give pure product **3**.

4-(Phenylethynyl)anisole (3a):⁹ A white solid. ¹H NMR (CDCl₃, 300 MHz, TMS): δ 3.76 (s, 3H, OCH₃), 6.84 (d, *J* = 9.0 Hz, 2H, Ar), 7.29–7.31 (m, 3H, Ar), 7.44–7.52 (m, 4H, Ar). ¹³C NMR (CDCl₃, 125 MHz, TMS): δ 55.3, 88.1, 89.4, 114.0, 115.4, 123.6, 127.9, 128.3, 131.4, 133.0, 159.6.

1,2-Bis(4'-methoxyphenyl)ethyne (3b):⁹ A white solid. ¹H NMR (CDCl₃, 300 MHz, TMS): δ 3.82 (s, 3H, OMe), 6.86 (d, *J* = 8.1 Hz, 2H), 7.45 (d, *J* = 8.1 Hz, 2H, Ar). ¹³C NMR (CDCl₃, 125 MHz, TMS): δ 55.2, 87.9, 113.9, 115.7, 132.8, 159.3.

2-(Phenylethynyl)anisole (3c):¹⁰ A thick-yellow liquid. ¹H NMR (CDCl₃, 500 MHz, TMS): δ 3.89 (s, 3H, OCH₃), 6.88–6.94 (m, 2H, Ar), 7.29–7.33 (m, 4H, Ar), 7.50 (dd, *J* = 7.6, 1.7 Hz, 1H, Ar), 7.56 (dd, *J*₁ = 7.7, 1.5 Hz, 2H, Ar). ¹³C NMR (CDCl₃, 125 MHz, TMS): δ 55.9, 85.7, 93.4, 110.7, 112.4, 120.4, 123.5, 128.1, 128.2, 129.7, 131.6, 133.5, 159.9.

4-(2'-Methylphenylethynyl)anisole (3d):¹¹ A white solid. ¹H NMR (CDCl₃, 300 MHz, TMS): δ 2.50 (s, 3H, CH₃), 3.81 (s, 3H, OCH₃), 6.87 (dd, *J* = 6.8, 3.4 Hz, 2H, Ar), 7.14–7.23 (m, 3H, Ar), 7.44–7.48 (m, 3H, Ar). ¹³C NMR (CDCl₃, 125 MHz, TMS): δ 20.7, 55.2, 87.0, 93.3, 114.0, 115.6, 123.3, 125.5, 127.9, 129.4, 131.6, 132.9, 139.9, 159.5.

4-(3',5'-Dimethylphenylethynyl)anisole (3e): A white solid. Mp: 41–42 °C. ¹H NMR (CDCl₃, 500 MHz, TMS): δ 2.28 (s, 6H, CH₃), 3.77 (s, 3H, OCH₃), 6.84 (d, *J* = 9.0 Hz, 2H,

Ar), 6.92 (s, 1H, Ar), 7.14 (s, 2H, Ar), 7.44 (d, $J = 9.0$ Hz, 2H, Ar). ^{13}C NMR (CDCl_3 , 125 MHz, TMS): δ 21.0, 55.1, 88.4, 88.6, 113.9, 115.5, 123.1, 129.1, 129.8, 132.9, 137.8, 159.4. MS (EI) m/z : 202 (M^+ , 6), 142 (100), 141 (81), 128 (48), 115 (18), 91 (17). HRMS (EI) Calcd for $\text{C}_{17}\text{H}_{16}\text{O}$ requires 236.1201, Found: 202.0990. IR (neat): ν 3037, 2834, 2360 ($\text{C}\equiv\text{C}$), 2342 ($\text{C}=\text{C}$), 1606, 1595, 1508, 1457, 1288, 1266, 1246, 1173, 1106, 1032, 849, 831, 738, 703 cm^{-1} .

4-(3'-Methylphenylethynyl)anisole (3f):⁹ A yellow liquid. ^1H NMR (CDCl_3 , 500 MHz, TMS): δ 2.33 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 6.86 (d, $J = 8.5$ Hz, 2H, Ar), 7.11 (d, $J = 8.0$ Hz, 1H, Ar), 7.21 (t, $J = 8.0$ Hz, 1H, Ar), 7.31–7.34 (m, 2H, Ar), 7.46 (d, $J = 8.5$ Hz, 2H, Ar). ^{13}C NMR (CDCl_3 , 125 MHz, TMS): δ 21.2, 55.2, 88.2, 89.0, 113.9, 115.4, 123.3, 128.2, 128.5, 128.8, 132.0, 133.0, 137.9, 159.5.

4-(4'-Methylphenylethynyl)anisole (3g):¹² A white solid. ^1H NMR (CDCl_3 , 500 MHz, TMS): δ 2.36 (s, 3H, CH_3), 3.82 (s, 3H, OCH_3), 6.87 (d, $J = 8.5$ Hz, 2H, Ar), 7.14 (d, $J = 8.0$ Hz, 2H, Ar), 7.40 (d, $J = 8.0$ Hz, 2H, Ar), 7.46 (d, $J = 8.5$ Hz, 2H, Ar). ^{13}C NMR (CDCl_3 , 125 MHz, TMS): δ 21.5, 55.3, 88.2, 88.7, 114.0, 115.6, 120.5, 129.1, 131.3, 133.0, 138.0, 159.5.

4-(4'-Chlorophenylethynyl)anisole (3h):¹² A white solid. ^1H NMR (CDCl_3 , 300 MHz, TMS): δ 3.81 (s, 3H, OCH_3), 6.87 (d, $J = 8.9$ Hz, 2H, Ar), 7.30 (d, $J = 8.6$ Hz, 2H, Ar), 7.42 (d, $J = 8.6$ Hz, 2H, Ar), 7.47 (d, $J = 8.9$ Hz, 2H, Ar). ^{13}C NMR (CDCl_3 , 125 MHz, TMS): δ 55.3, 87.0, 90.4, 114.1, 115.0, 122.2, 128.6, 132.6, 133.1, 133.9, 159.8.

4-(4'-Fluorophenylethynyl)anisole (3i):¹³ A white solid. ^1H NMR (CDCl_3 , 500 MHz, TMS): δ 3.83 (s, 3H, OCH_3), 6.88 (d, $J = 8.5$ Hz, 2H, Ar), 7.03 (t, $J = 8.5$ Hz, 2H, Ar), 7.45–7.50 (m, 4H, Ar). ^{13}C NMR (CDCl_3 , 125 MHz, TMS): δ 55.3, 87.0, 89.0, 114.0, 115.2, 115.6 (d, $J_{\text{C-F}} = 22$ Hz), 119.7 (d, $J_{\text{C-F}} = 3.5$ Hz), 133.0, 133.3 (d, $J_{\text{C-F}} = 8.1$ Hz), 159.7, 162.3 (d, $J_{\text{C-F}} = 247.5$ Hz).

4-(2'-Bromophenylethynyl)anisole (3j):¹⁴ A pale-yellow solid. ^1H NMR (CDCl_3 , 300 MHz, TMS): δ 3.82 (s, 3H, OCH_3), 6.87 (d, $J = 9.0$ Hz, 2H, Ar), 7.14 (td, $J = 7.8, 1.8$ Hz, 1H, Ar), 7.27 (td, $J = 7.8, 1.2$ Hz, 1H, Ar), 7.50–7.54 (m, 3H, Ar), 7.59 (dd, $J = 13.0, 1.5$ Hz, 1H, Ar). ^{13}C NMR (CDCl_3 , 125 MHz, TMS): δ 55.3, 86.8, 94.0, 114.0, 114.9, 125.4, 125.7, 127.0, 129.0, 132.3, 133.0, 133.1, 159.9.

1-Hex-1-ynyl-4-methoxybenzene (3k):¹⁵ A colorless liquid. ^1H NMR (500 MHz, CDCl_3): δ 7.29 (d, $J = 8.5$ Hz, 2H), 6.80 (d, $J = 8.5$ Hz, 2H), 3.79 (s, 3H), 2.38 (t, $J = 7.0$ Hz, 2H), 1.26–1.6 (m, 7H).

4-(3'-Methoxyphenylethynyl)anisole (3l):¹⁶ A yellow liquid. ^1H NMR (CDCl_3 , 500 MHz, TMS): δ 3.785 (s, 3H, OCH_3), 3.787 (s, 3H, OCH_3), 6.86 (d, $J = 8.5$ Hz, 3H, Ar), 7.04 (dd, $J = 2.0, 1.5$ Hz, 1H, Ar), 7.10–7.11 (t, $J = 1.5$ Hz, 1H, Ar), 7.22 (t, $J = 8.0$ Hz, 1H, Ar), 7.46 (d, $J = 8.5$ Hz, 2H, Ar). ^{13}C NMR (CDCl_3 , 125 MHz, TMS): δ 55.18, 55.19, 88.0, 89.2, 114.0, 114.6, 115.2, 116.2, 124.0, 124.6, 129.3, 133.0, 159.3, 159.6.

3-(Phenylethynyl)anisole (3m):¹⁷ A pale-yellow solid. ^1H NMR (CDCl_3 , 500 MHz, TMS): δ 3.81 (s, 3H, OCH_3), 6.89 (dd, $J = 8.5, 2.5$ Hz, 1H, Ar), 7.06 (s, 1H, Ar), 7.13 (d, $J = 7.5$ Hz, 1H, Ar), 7.23–7.26 (m, 1H, Ar), 7.32–7.34 (m, 3H, Ar), 7.53–7.54 (m, 2H, Ar). ^{13}C NMR (CDCl_3 , 125 MHz,

TMS): δ 55.3, 89.2, 89.3, 114.9, 116.3, 123.2, 124.2, 124.3, 128.27, 128.32, 129.4, 131.6, 159.4.

4-(2',6'-Dimethylphenylethynyl)anisole (3n): A white solid. Mp: 69–70 °C. ^1H NMR (CDCl_3 , 500 MHz, TMS): δ 2.50 (s, 6H, CH_3), 3.83 (s, 3H, OCH_3), 6.88 (d, $J = 9.0$ Hz, 2H, Ar), 7.05–7.12 (m, 3H, Ar), 7.47 (d, $J = 9.0$ Hz, 2H, Ar). ^{13}C NMR (CDCl_3 , 125 MHz, TMS): δ 21.1, 55.3, 85.8, 97.8, 114.0, 116.0, 123.3, 126.6, 127.4, 132.8, 140.0, 159.5. MS (EI) m/z : 202 (M^+ , 6), 142 (100), 141 (81), 128 (48), 115 (18), 91 (17). HRMS (EI) Calcd for $\text{C}_{17}\text{H}_{16}\text{O}$ requires 236.1201, Found: 202.0990. IR (neat): ν 3003, 2956, 2921, 2852, 1603, 1511, 1465, 1441, 1377, 1287, 1246, 1182, 1169, 1106, 1025, 832, 809, 790, 768, 732 cm^{-1} .

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Supporting Information

^1H NMR and ^{13}C NMR spectra of selected compounds. This material is available free of charge on the web at <http://www.csj.jp/journals/bcsj/>.

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