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Synthesis of functionalized alkynes via palladium-catalyzed Sonogashira reactions

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Abstract

A highly efficient protocol for the copper and phosphine free Sonogashira cross-coupling reactions of aryl iodides with terminal alkynes under aerobic conditions has been developed. Using 1 mol% of the palladium-bis(oxazoline) complex, Pd-BOX A, in the presence of KOH, and a CH₃CN-H₂O solvent system allowed for the cross-coupling reactions to proceed at room temperature or 60 °C. This new catalytic system was found to be highly active for the cross-coupling reaction of aryl diiodo substrates with unactivated alkyl alkynes to produce various symmetrical dialkynes, as well as for the cross-coupling of terminal dialkynes with aryl iodides to generate symmetrical disubstituted internal alkynes.

Keywords: Palladium-bis(oxazoline), Sonogashira coupling, diiodobenzene, alkyl alkynes, dialkynes

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The Sonogashira reaction of aryl halides with aryl and alkyl alkynes provides a powerful tool for the construction of a carbon-carbon bond between acetylenes and alkenes/arenes.¹⁻⁶ The importance of alkynes is directly associated with their occurrence in a wide range of natural products and other biologically active substances,⁷ and with their versatility as intermediates for the production of materials for advanced engineering applications such as conducting polymers, non-linear optical devices and liquid crystals.⁸⁻¹⁰ The development of methods for incorporating carbon-carbon triple bonds into molecules remains an important area of research.¹¹

In general, the Sonogashira reaction, which represents the leading method for the production of internal alkynes, is catalyzed by palladium complexes in combination with copper salts and a large excess of an amine base.¹² However, the presence of copper (I) co-catalysts can result in the *in situ* formation of copper (I) acetylides leading to the oxidative homocoupling of alkynes.¹²⁻¹⁴ To avoid homocoupling reactions, serious efforts have been made, including the employment of new, active palladium complexes as catalysts. Other problems associated with the copper free systems include the frequent requirement for high palladium catalysts loadings, an excess amount of base and rigorously dried organic solvents.^{15,16}

Through a comparison of available literature reports describing the use of phosphorous ligands in copper-free Sonogashira reactions,¹⁷⁻¹⁹ it was found that there were only a relatively limited number of studies on the use of palladium-nitrogen catalyst systems.²⁰⁻²⁴ Moreover, the reported dinitrogen catalyst systems utilize high temperature, a longer reaction time, a relatively high palladium catalyst loading, phosphine ligands, copper as a co-catalyst, or phase transfer agent.²⁵⁻²⁹ Furthermore, many of the reported phosphine and copper free systems were limited to the coupling of aryl iodides with aryl alkynes.^{10,30}

In a continuation of our research efforts on the use of palladium-BOX catalysts in cross-coupling reactions,^{32,33} herein we report an efficient and mild catalytic system for the copper and phosphine free Sonogashira coupling reactions of aryl iodides with aryl alkynes, alkyl alkynes and dialkynes. In comparison with the reported dinitrogen palladium complexes and our previous reports,^{32,33} palladium-BOX complexes are highly effective copper and phosphine free catalysts for cross-coupling reactions of aryl iodides with various terminal alkynes under mild reaction conditions. We also reported, for the first time, the synthesis of 1,3-bis(phenylethynyl)benzene (**4ag**), 6-phenylhex-5-ynenitrile (**6ah**), 6,6'-benzene-1,4-diylbis(hex-5-ynenitrile) (**7gg**), 1,4-bis(5-chloropent-1-yn-1-yl)benzene (**7gh**) and 1,4-bis(3,5-

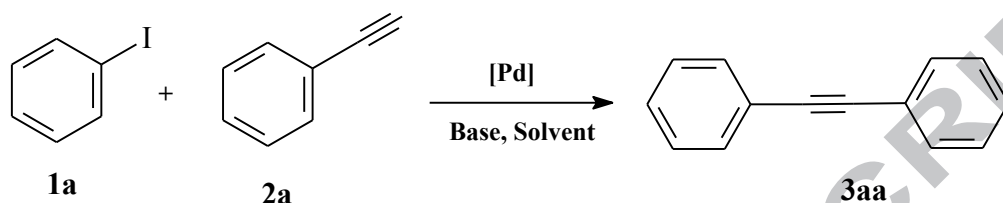
dimethyl-1-hex-1-yn-3-ol)benzene (**7go**) as new materials prepared from the Sonogashira cross-coupling reactions using palladium-BOX catalysts.

In order to determine the ideal conditions, several different experiments were performed at room temperature under aerobic conditions using iodobenzene and phenylacetylene as model substrates, while utilizing various palladium catalysts including Pd-BOX complexes³² (Table 1). The effect of varying the solvent was investigated using Pd-BOX-A (Figure 1). No reaction was observed using water as the solvent (Table 1, entry 1) and only 10 % of product was obtained in DMF (Table 1, entry 2). It was observed that there were gradual increases in the yield when DMF-water mixtures were used as solvent (Table 1, entries 3 and 4). The yield was severely decreased in acetonitrile (Table 1, entry 5). Remarkably, changing the solvent system to CH₃CN-H₂O led to excellent isolated yields (Table 1, entries 6 and 7). Other solvent systems such as CH₃OH-H₂O gave lower yields (Table 1, entry 8).

The presence of a base is essential for the palladium catalyzed Sonogashira cross-coupling reaction.³²⁻⁴⁰ A control experiment in the absence of any base gave only a trace amount of product (Table 1, entry 9). Various bases such as KOH, NaOH, K₂CO₃, Et₃N (Table 1, entries 1-8, 10-20) were tested. Excellent yields were obtained with KOH and NaOH, (94% and 90% respectively) (Table 1, entries 7 and 10). However, much lower yields were observed with K₂CO₃ and Et₃N (60% and 47% respectively) (Table 1, entries 11 and 12).

During the optimization of the reaction conditions, it was revealed that palladium bis(oxazoline) complexes (Pd-Box A, B, C) (Figure 1, Table 1, entries 7, 13 and 14)^{32,33} all provided excellent yields in comparison with commercially available palladium(II) complexes and salts (Table 1, entries 16-20). Absence of the palladium catalyst gave no coupling product (Table 1, entry 15), showing the crucial role of palladium in the cross-coupling reaction.

It was found that the nature of the palladium complex had a pronounced impact on the reaction. The use of Pd(OAc)₂ (75%, Table 1, entry 17) gave slightly higher yields than PdCl₂ (69%, Table 1, entry 16), PdCl₂-Bipy (40%, Table 1, entry 18) and PdCl₂-Phen (20%, Table 1, entry 19).

Table 1: Optimization of the reaction conditions for the palladium-catalyzed Sonogashira coupling reaction of iodobenzene with phenylacetylene.^a

Entry	Pd Complex	Solvent	Base	Yield (%) ^b
1	Pd-BOX-A	H ₂ O	KOH	Traces
2	Pd-BOX-A	DMF	KOH	10
3	Pd-BOX-A	DMF-H ₂ O (3:1)	KOH	27
4	Pd-BOX-A	DMF-H ₂ O (1:1)	KOH	35
5	Pd-BOX-A	CH ₃ CN	KOH	Traces
6	Pd-BOX-A	CH ₃ CN-H ₂ O (3:1)	KOH	80
7	Pd-BOX-A	CH ₃ CN-H ₂ O (1:1)	KOH	94
8	Pd-BOX-A	CH ₃ OH-H ₂ O (1:1)	KOH	15
9	Pd-BOX-A	CH ₃ CN-H ₂ O (1:1)	-	Traces
10	Pd-BOX-A	CH ₃ CN-H ₂ O (1:1)	NaOH	90
11	Pd-BOX-A	CH ₃ CN-H ₂ O (1:1)	K ₂ CO ₃	60
12	Pd-BOX-A	CH ₃ CN-H ₂ O (1:1)	Et ₃ N	47
13	Pd-BOX-B	CH ₃ CN-H ₂ O (1:1)	KOH	90
14	Pd-BOX-C	CH ₃ CN-H ₂ O (1:1)	KOH	93
15	-	CH ₃ CN-H ₂ O (1:1)	KOH	Traces
16	PdCl ₂	CH ₃ CN-H ₂ O (1:1)	KOH	69
17	Pd(OAc) ₂	CH ₃ CN-H ₂ O (1:1)	KOH	75
18 ^c	PdCl ₂ -Bipy	CH ₃ CN-H ₂ O (1:1)	KOH	40
19 ^d	PdCl ₂ -Phen	CH ₃ CN-H ₂ O (1:1)	KOH	20
20	PdCl ₂ (PPh ₃) ₂	CH ₃ CN-H ₂ O (1:1)	KOH	43

a. Reaction Conditions: Pd-catalyst (1 mol%), iodobenzene (1.0 mmol), phenylacetylene (1.5 mmol), base (2.0 mmol), solvent (4 ml), r.t., 2 h.

b. Isolated yield.

c. PdCl₂-Bipy = (2, 2'-bipyridine)dichloridopalladium(II).

d. PdCl₂-Phen = (1, 10-phenanthroline)dichloridopalladium(II).

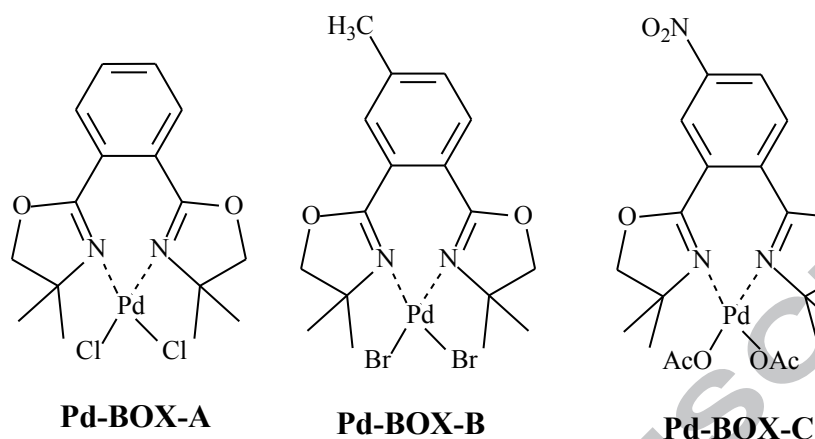
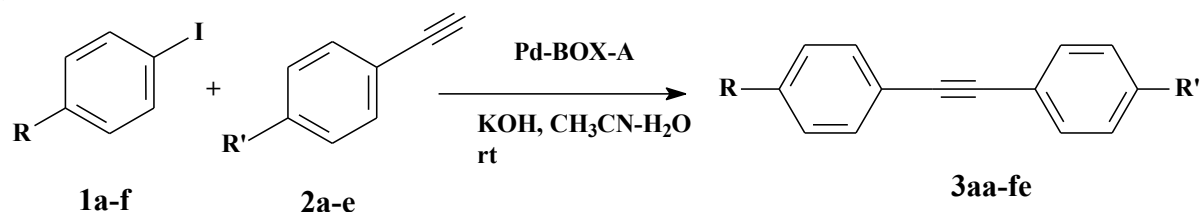


Figure 1. Palladium-BOX complexes used in the Sonogashira coupling reactions

Under the optimized reaction conditions (1 mol% Pd-BOX-A, 2 equiv. KOH, 1:1 CH₃CN-H₂O, R.T.), we then screened a range of aryl iodides with an array of structurally and electronically different aryl alkynes (Table 2). With respect to the aryl iodides, both activated and deactivated aryl iodides reacted smoothly with alkynes bearing electron withdrawing and electron donating substituents and the cross-coupling products were obtained in excellent yields. The coupling of phenylacetylene with deactivated aryl iodides (Table 2, entries 2-5) afforded the internal acetylenes in high yields within 1 h. The coupling reactions of activated aryl iodides such as 4-iodoanisole (Table 2, entry 6) and 4-iodoaniline (Table 2, entry 7) were complete within 3 h. The coupling of iodobenzene with activated aryl alkynes (Table 2, entries 8-10) afforded high yields of internal acetylenes within 3 h. The synthesis of 4,4'-diaminodiphenylacetylene was achieved in high yield from the reaction of 4-iodoaniline with 4-ethynylaniline (Table 2, entry 11).

Table 2. Sonogashira coupling reactions of aryl iodides with aryl alkynes catalyzed by Pd-BOX-A.^a



Entry	R 1a-f	R' 2a-e	Time (h)	Yield (%) ^b 3aa-fe
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1	H 1a	H 2a	2	94 3aa
2	NO ₂ 1b	H 2a	1	98 3ba
3	CH ₃ CO 1c	H 2a	1	96 3ca
4	CN 1d	H 2a	1	97 3da
5	CN 1d	CHO 2b	1	98 3db
6	CH ₃ O 1e	H 2a	3	91 3ea
7	NH ₂ 1f	H 2a	3	90 3fa
8	H 1a	CH ₃ 2c	3	93 3ac
9	H 1a	CF ₃ 2d	3	88 3ad
10	H 1a	NH ₂ 2e	3	96 3ae
11	NH ₂ 1f	NH ₂ 2e	4	88 3fe

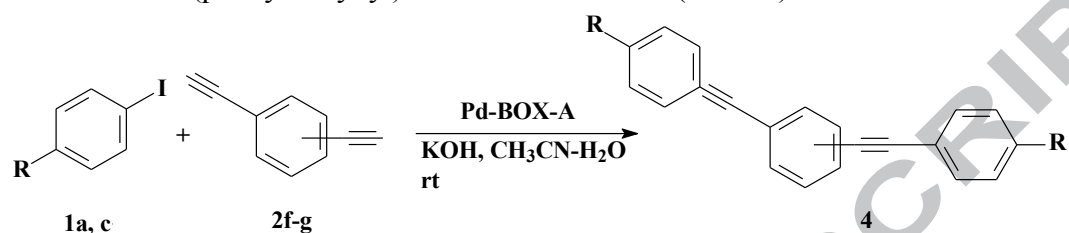
a. Reaction Conditions: Pd-BOX-A (1 mol%), aryl iodide (1.0 mmol), alkyne (1.5 mmol), KOH (2.0 mmol), CH₃CN (2 mL), H₂O (2 mL), rt.

b. Isolated yield.

Bis(phenyl ethynyl)-benzene (BPEB) derivatives have been commonly recognized as important components of liquid crystals for electronic displays⁴²⁻⁴³ and have been applied in the production of note book computer screens, mobile phones, flat screen monitors and LCD televisions. BPEBs are characterized by a high clearing and melting point, as well as large optical anisotropy values.⁴⁴⁻⁴⁶ Our new catalyst system was successfully applied to the synthesis of BPEB's (Table 3). 1,3 and 1,4-Bis(phenylethynyl)-benzenes were obtained from the reactions of aryl iodides with 1,3- and 1,4-diethynyl benzenes, respectively (Table 3). Complete conversions were observed after 1-3 h (Table 3, entries 1-4), depending on the nature of the substituent. The desired cross-coupling products were isolated in excellent yields. It is worth noting that the reactions were conducted at room temperature and the palladium catalysts showed particular air and moisture stability. This phosphine free catalytic

system represents a significant advantage, specifically when the reactions were conducted in air. Moreover, the reactions were conducted in the absence of copper; therefore, no homo-coupling of the alkyne products were detected.

Table 3. Sonogashira coupling reaction of aryl iodides with dialkynes. Synthesis of bis(phenyl ethynyl)-benzene derivatives (BPEBs).



Entry	R 1a,c	Aryl dialkyne 2f-g	Time (h)	Yield (%) ^b 4
1	H 1a		3	90 4af
2	H 1a		3	89 4ag
3	CH ₃ CO 1c		1	97 4cf
4	CH ₃ CO 1c		2	97 4cg

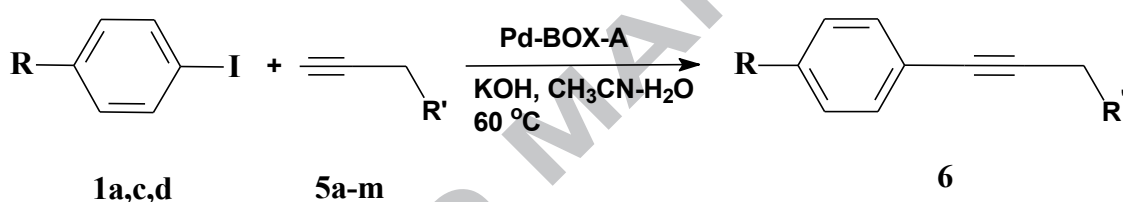
a. Reaction Conditions: Pd-BOX-A (1 mol%), aryl iodide (1.1 mmol), alkyne (0.5 mmol), KOH (2.0 mmol), CH₃CN (2 mL), H₂O (2 mL), rt.

b. Isolated yield.

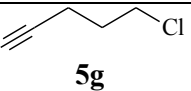
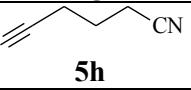
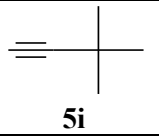
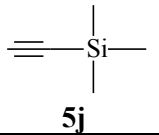
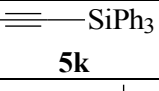
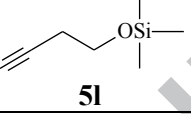
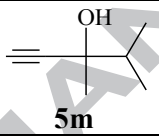
The Sonogashira cross-coupling reactions of aryl iodides with alkyl alkynes using palladium-phosphine catalysts have been widely studied.^{2,5,18} On the other hand, there are only a few reports on the copper and phosphine free Sonogashira cross-coupling of aryl iodides with alkyl alkynes,^{14,31,47} however, in some studies low yields of products were observed at high temperatures.² Interestingly, the Pd-BOX complexes were highly active in the cross-coupling reactions of aryl iodides with alkyl alkynes at 60 °C. For instance, the coupling reactions of 4-iodoacetophenone with various alkyl alkynes was achieved to give the expected internal acetylenes in excellent yield (Table 4, entries 1-6). The reactions were found to be unaffected by the alkyl chain lengths, however, phenyl substituted alkyl alkynes were more reactive

(Table 4, entries 4-5). In fact, 4-iodobenzonitrile reacted with 1-hexyne in a similar manner (Table 4, entry 6). Iodobenzene also reacted efficiently with alkyl alkynes and substituted alkyl alkynes to produce the alkyl alkynes in high yields (Table 4, entries 7-14). Interesting examples were the cross-coupling reactions of trimethylsilyl acetylene (Table 4, entry 11) and triphenyl silyl acetylene (Table 4, entry 12). These reactions led predominantly to the corresponding aryl silyl acetylenes indicating that the new catalytic system containing Pd-BOX were highly effective in the coupling reactions of aryl iodides with silyl acetylenes.^{4,48} Similarly, a silyloxy acetylene was very reactive; however, the silyloxy group was hydrolyzed under the reaction conditions to give the corresponding alkynol (Table 4, entry 13). The cross-coupling reaction of iodobenzene with a terminal alkynol was also successful, giving the desired product in 87 % yield (Table 4, entry 14).

Table 4. Sonogashira coupling reactions of aryl iodide with alkyl alkyne catalyzed by Pd-BOX-A.^a

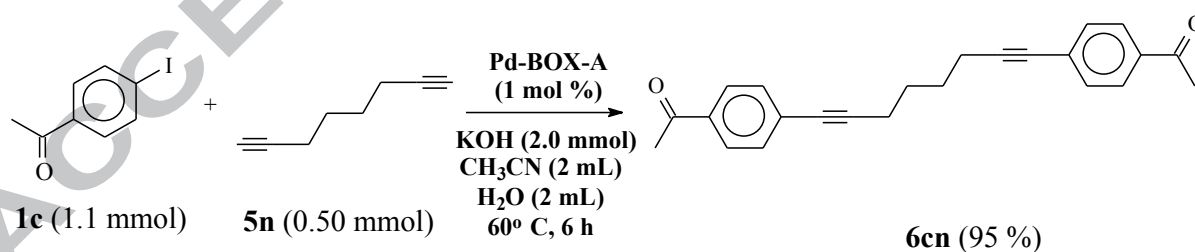


Entry	R 1a,c,d	Alkyl alkyne 5a-n	Time (h)	Yield (%) ^b 6
1	CH ₃ CO 1c	5a	3	95 6ca
2	CH ₃ CO 1c	5b	3	96 6cb
3	CH ₃ CO 1c	5c	3	90 6cc
4	CH ₃ CO 1c	5d	2	98 6cd
5	CH ₃ CO 1c	5e	2	96 6ce
6	CN 1d	5f	3	93 6df
7	H 1a	5f	4	80 6af

8	H 1a		4	95 6ag
9	H 1a		4	90 6ah
10	H 1a		4	92 6ai
11	H 1a		4	93 6aj
12	H 1a		4	95 6ak
13 ^c	H 1a		4	90 6al
14	H 1a		4	87 6am

- a. Reaction Conditions: Pd-BOX-A (1 mol%), aryl iodide (1.0 mmol), alkyl alkyne (1.5 mmol), KOH (2.0 mmol), CH₃CN (2 mL), H₂O (2 mL), 60 °C.
 b. Isolated yield.
 c. The hydrolyzed product was obtained:
 d. aryl iodide (1.1 mmol), alkyl alkyne (0.5 mmol)

Interestingly, the terminal dialkyl alkyne, octa-1,7-diyne, coupled smoothly with 4-iodoacetophenone to afford the corresponding internal dialkynyl ketone in excellent yield (equation 1).

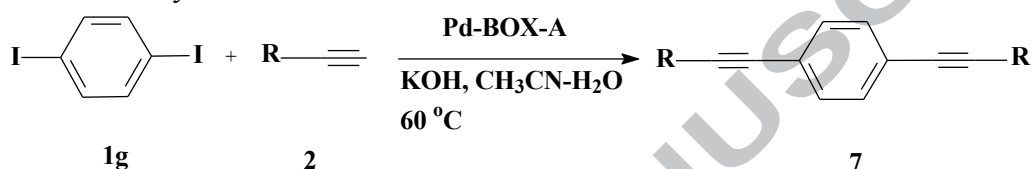


Eq. 1

We further studied the Sonogashira cross-coupling reaction of diiodobenzene with aryl and alkyl alkynes. Remarkably, the reaction proceeded successfully to give new internal alkynes in excellent yields (Table 5). The reactions of 1,4-diiodobenzene with phenylacetylene or 4-ethynyl aniline (Table 5, entries 1 and 2) successfully yielded the corresponding bis(phenylethynyl)-benzene derivatives. Similarly, the reaction of 1,4-diiodobenzene with

various alkyl alkynes gave the corresponding symmetrically disubstituted alkynyl benzenes in excellent yields (Table 5, entries 3-7). Alkynols and alkyndiols represent important building blocks for the synthesis of a wide variety of industrially and pharmaceutically important heterocycles.⁴⁹ Representative dialkyndiols, 4,4'-benzene-1,4-diylbisbut-3-yn-1-ol (Table 5, entry 6)⁵⁰ and 1,1'-benzene-1,4-diylbis-(3,4-dimethylpent-1-yn-3-ol) (Table 5, entry 7)⁵⁰, were successfully synthesized from the coupling of 1,4-diiodobenzene with 1-trimethylsiloxy-3-butyne and 3,5-dimethylhex-1-yn-3-ol, respectively.

Table 5. Sonogashira coupling reaction of 1,4-diiodobenzene with aryl and alkyl alkynes.^a



Entry	Alkyne 2	Yield (%) ^b 7
1		95 7ga
2		96 7ge
3		96 7gf
4		95 7gh
5		96 7gg
6		90 7gl
7		93 7go

a. Reaction Conditions: Pd-BOX-A (1 mol%), 1,4-diiodobenzene (0.5 mmol), alkyne (1.5 mmol), KOH (2.0 mmol), CH₃CN (2 mL), H₂O (2 mL), 60 °C, 12 h.

b. Isolated yield.

In conclusion, we have developed a highly efficient protocol for the synthesis of various internal alkynes from the Sonogashira cross-coupling reaction of aryl halides with a wide range of aryl and alkyl alkynes based on palladium-bis(oxazoline) complexes. This new copper and phosphine free catalytic system provides a significant advantage in terms of activity, selectivity, and tolerance to various functional groups on both the aryl halide and the alkyne.

Acknowledgements

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- 31. General procedure for Sonogashira coupling reaction**
- In a 10 mL round bottom flask, the palladium complex (0.010 mmol) was dissolved in acetonitrile (2 mL). Aryl halide (1.0 mmol), alkyne (1.2 mmol), KOH (2.00 mmol) and distilled water (2 mL) were added. The mixture was stirred at room temperature (or 60 °C) for the required time. After reaction completion, the product was extracted with ethyl acetate (3 x 5 mL). The combined organic layers were dried with anhydrous sodium sulfate. The product was analyzed with GC and GC-MS. The product was purified using column chromatography with hexane-ethyl acetate as eluent. The characterization data were in entire agreement with the previously reported literature.³²⁻³⁹
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50. Analytical and Spectroscopic Data of New Compounds: **1,3-Bis(phenylethynyl)benzene (4ag)**: Brown solid; Yield 89 %; ^1H NMR (500 MHz, CDCl_3) δ (ppm): 7.70-7.64 (m, 1H), 7.52-7.42 (m, 6H), 7.34-7.32 (m, 7H), ^{13}C NMR (125 MHz, CDCl_3) δ (ppm):134.6, 131.6, 131.2, 128.4, 128.3, 88.5, GC-MS m/z 278 (M^+) Anal. Calc. for $\text{C}_{22}\text{H}_{14}$, (278.35): C, 94.93; H, 5.07. Found: C, 95.01.61; H, 5.01; **6-phenylhex-5-ynenitrile (6ah)**: Yellow oil; Yield 90 %; ^1H NMR (500 MHz, CDCl_3) δ (ppm): 7.34-7.32 (m, 2H), 7.24 – 7.22 (m, 3H), 2.53 (t, $J = 6.7$ Hz, 2H), 2.49 (t, $J = 7.3$ Hz, 2H), 1.89 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ (ppm):131.5, 128.2, 127.9, 123.1, 119.1, 86.8, 82.3, 24.6, 18.5, 16.1, GC-MS m/z 169 (M^+) Anal. Calc. for $\text{C}_{12}\text{H}_{11}\text{N}$ (169.08): C, 85.17; H, 6.55; N, 8.28. Found: C, 85.21; H, 6.62; N, 8.73; **6, 6'-Benzene-1,4-diylbis-hex-5-ynenitrile (7gg)**: Yellow oil, Yield 95 %; ^1H NMR (500 MHz, CDCl_3) δ (ppm): 7.29 (s, 4H), 2.59 (t, $J = 6.7$ Hz, 4H), 2.53 (t, $J = 7.3$ Hz, 4H), 1.94 (m, 4H); ^{13}C NMR (125 MHz, CDCl_3) δ (ppm):132.2, 123.5, 119.8, 89.4, 82.8, 25.2, 19.3, 16.9; IR (KBr, vcm^{-1}) 2953, 2246, 1919, 1672, 1505, 1446, 1296, 1215, 1056, 838; GC-MS m/z 260 (M^+). Anal. Calc. for $\text{C}_{18}\text{H}_{16}\text{N}_2$ (260.13): C, 83.04; H, 6.19; N, 10.76. Found: C, 83.24; H, 6.23; N, 10.92; **1,4-Bis(5-chloropent-1-yn-1-yl)benzene (7gh)**: Yellow oil, Yield 96 %; ^1H NMR (500 MHz, CDCl_3) δ (ppm): 7.24 (s, 4H), 4.0 (t, $J = 6.4$ Hz, 4H), 2.54 (t, $J = 6.7$ Hz, 4H), 1.98 (m, 4H); ^{13}C NMR (125 MHz, CDCl_3) δ (ppm):131.3, 122.9, 89.7, 81.2, 43.7, 31.3, 16.9; IR (CH_2Cl_2 , vcm^{-1}) 2947, 2230, 1915, 1706, 1501, 1437, 1283, 1064; GC-MS m/z 279 (M^+) Anal. Calc. for $\text{C}_{16}\text{H}_{16}\text{Cl}_2$ (279.21): C, 68.83; H, 5.78. Found: C, 68.51; H, 5.43; **1,4-Bis(3,5-dimethyl-1-hex-1-yn-3-ol)benzene (7go)**: Yellow viscous oil, Yield 93 %; ^1H NMR (500 MHz, CDCl_3) δ (ppm): 7.31 (s, 4H), 1.98 (m, 2H), 1.67 (d, $J = 6.2$ Hz, 4H), 1.55 (s, 6H); 1.03 (d, $J = 4.6$ Hz, 12H), ^{13}C NMR (125 MHz, CDCl_3) δ (ppm):131.4, 122.6, 95.0, 83.1, 68.5, 51.9, 30.9, 25.2, 24.2; IR (CH_2Cl_2 , vcm^{-1}) 3373, 2953, 2225, 1910, 1658, 1457, 1367, 1153, 926, 834; GC-MS m/z 326 (M^+) Anal. Calc. for $\text{C}_{22}\text{H}_{30}\text{O}_2$, (326.22): C, 80.94; H, 9.26. Found: C, 80.61; H, 9.33.

Synthesis of functionalized alkynes via palladium-catalyzed Sonogashira reactions

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Graphical Abstract

