

Aqueous Ammonia as a New Activator for Sonogashira Coupling

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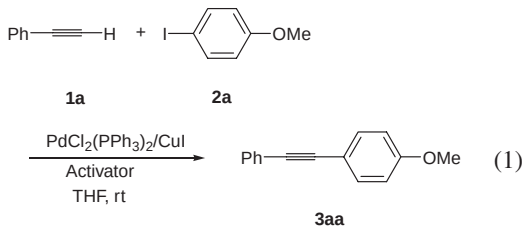
Sonogashira coupling, which is a coupling reaction of terminal alkynes with organic halides, takes place with dilute aqueous ammonia as an activator. The reaction of several terminal alkynes and aryl iodides in the presence of small excess of aqueous ammonia at room temperature furnishes the cross-coupling product in good-to-excellent yields. A water-soluble amine with a high boiling point is alternatively employed for reactions at higher temperatures. A related coupling reaction in the presence of carbon monoxide also proceeded at room temperature and under ambient pressure to afford α,β-alkynyl ketones efficiently.

The coupling of terminal alkynes has attracted considerable attention in organic synthesis because molecules containing a carbon–carbon triple-bond moiety are widely available for various functional organic materials as well as biologically important molecules and their intermediates.[1] Sonogashira–(Hagihara) coupling, which is the palladium/copper-catalyzed coupling reaction of terminal alkynes with organic halides, has been recognized as a highly practical method for introducing an alkyne moiety into organic molecules.[2] However, the use of an amine as a solvent or co-solvent, sometimes causes difficulties in the removal of excess amine of a high boiling point and the formed ammonium salt. Decreasing the amount of amine, however, generally lowers the reactivity.

Continuous efforts to overcome the disadvantages of the Sonogashira coupling reaction have also been made. However, the design of a new ligand of the transition-metal catalyst has indeed improved the reactivity of the metallic species. Using a common palladium and copper catalyst, which are commercially available and obtainable quite easily, the design of an activator as an additive would achieve the amine-free Sonogashira process.[3,4] On the other hand, we envisaged that another solution for the problem of the Sonogashira coupling is to design a new class of activator for the reaction instead of (excess) amine; we found that several activators, such as silver(I) oxide, tetra-*n*-butylammonium fluoride (TBAF), and tetra-*n*-butylammonium hydroxide (TBAOH), remarkably promoted the coupling reaction of terminal alkynes.[5] Herein, we report that a dilute aqueous solution of ammonia is a simple and efficient activator for the Sonogashira coupling. The related carbonylative coupling reaction leading to α,β-alkynyl ketones at room temperature and under an ambient pressure of carbon monoxide is also described.[6]

Results and Discussion

During studies on the development of new activators for the coupling reaction of alkynes, we found that tetra-*n*-butylammonium hydroxide (TBAOH) effected the reaction.[5] It was also noteworthy that the use of aqueous TBAOH (40 w/w % aqueous solution) reacted much faster than that in the presence of TBAF.[5] Encouraged by the result, we studied the effect of several quaternary ammonium hydroxides, such as Et_4NOH, $(n\text{-}C_{16}H_{33})NMe_3OH$ and choline $(HO(CH_2)_2NMe_3OH)$, which are widely used in the field of material science, and/or are recognized as biologically important molecules (Eq. 1). We found that these ammonium hydroxides similarly served as an effective activator for the coupling of terminal alkynes.



(1)

Activator: *n*-Bu_4NOH (99%), Et_4NOH (99%), $(n\text{-}C_{16}H_{33})NMe_3OH$ (36%), $\{HO(CH_2)_2\}NMe_3OH$ (76%).

A further survey of ammonium hydroxides as an activator of the Sonogashira coupling enabled us to find that aqueous ammonia, which is the simplest ammonium hydroxide, NH_4OH, was the best. When phenylethyne (**1a**) was treated with 4-methoxy-1-iodobenzene (**2a**) in the presence of $PdCl_2(PPh_3)_2$ (1 mol%), CuI (2 mol%), and two equivalents of aqueous ammonia (0.5 M), the coupling reaction occurred at room temperature to afford **3aa** in excellent yield. In contrast to the conventional Sonogashira coupling with organic amines, it was not necessary to use a large excess of ammonia. The reaction was found to proceed with only two equivalents of ammonia toward the aryl iodide **2**.

Worthy of note is that the Sonogashira coupling is only effective when a dilute aqueous solution (0.5–2.0 M) is employed as an activator. The reaction with more concentrated ammonia considerably decreased the yield of the coupling product (Fig. 1). The reaction was found to decrease the yield as the concentration of the employed ammonia solution increased. Indeed, the reaction with a 14.9 M solution, which is a commercially available 28%, concentrated aqueous ammonia, resulted in giving 8% of the coupling product. The similar effect toward the concentration of ammonia was also observed in the reaction of trimethylsilylethyne (**1b**).

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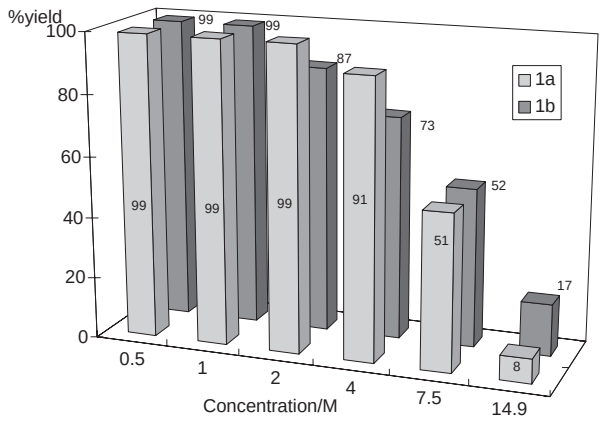
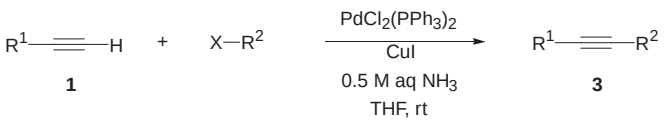


Fig. 1. Relationship of the concentration of aqueous ammonia with the yield of the coupling reaction of phenylethyne (**1a**) and trimethylsilylethyne (**1b**) with 4-methoxy-1-iodobenzene (**2a**) using 1 mol% of $PdCl_2(PPh_3)_2$, 2 mol% of CuI, and 2 equivalents of aqueous ammonia.

Table 1 shows the coupling of various terminal alkynes and aryl halides with 0.5 M aqueous ammonia. The reaction with aryl iodides bearing an electron-withdrawing group also proceeded in an excellent yield although it took longer reaction periods. Aryl bromides **4b** and **4j**, which possess an electron-withdrawing group, also reacted smoothly. In contrast, 4-methoxy-1-bromobenzene (**4a**) bearing an electron-donating substituent did not afford the coupling product at room temperature. Several triflates were also found to be available for the reaction. Concerning arylalkynes, the reaction of **1c**, which possessed an electron-donating group, afforded the coupling product in good yield. In contrast, the use of **1d** bearing an electron-withdrawing group resulted in a lower yield. Trimethylsilylethyne (**1b**) was also found to be as reactive as phenylethyne (**1a**) to afford coupling products with both electron-enriched and electron-deficient aryl halides in good-to-excellent yields. The reaction with alkylalkynes was found to be slower than that of arylalkynes. Nevertheless, the coupling products were obtained in good-to-excellent yields after stirring for longer reaction periods.

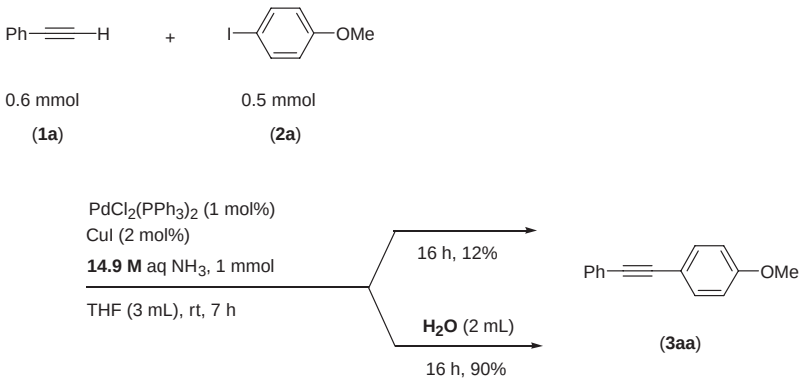
The effect of ammonia to promote the coupling reaction of alkynes would partially be ascribed to the palladium-catalyzed reaction in the presence of water, with which the formation of a cationic palladium species is induced.[7] Indeed, the reaction at a higher concentration of water, which is the use of dilute aqueous ammonia, proceeded smoothly. However, ammonia would also play an additional role for the reaction since use of an aqueous solution of other inorganic bases such as KOH and K_2CO_3 resulted in a lower yield of the coupling product. Although details are not yet clear, ammonia might play a significant role in forming a complex of palladium or copper for the reaction.

Table 1. Coupling of Terminal Alkynes in the Presence of Aqueous Ammonia[a)]



R^1	X–R^2	Time/h	Activator	**3**, % yield
C_6H_5 (**1a**)	4-I–C_6H_4–OCH_3 (**2a**)	2	NH_3	**3aa**, 86
1a	**2a**	6	NH_3	**3aa**, 96
1a	4-I–C_6H_4–$COCH_3$ (**2b**)	18	NH_3	**3ab**, 88
1a	4-Br–C_6H_4–$COCH_3$ (**4b**)	30	NH_3	**3ab**, 92[b)]
1a	4-Br–C_6H_4–$OCOCH_3$ (**4j**)	24	NH_3	**3aj**, 91[b)]
1a	4-NC–C_6H_4–OTf (**5h**)	6	NH_3	**3ah**, 75[b)]
1a	1-naphthyl–OTf (**5i**)	9	NH_3	**3ai**, 78[b)]
4-MeO–C_6H_4 (**1c**)	4-I–C_6H_4–OCH_3 (**2a**)	6	NH_3	**3ca**, 75
4-O_2N–C_6H_4 (**1d**)	4-I–C_6H_4–OCH_3 (**2a**)	8	NH_3	**3da**, 25
$(CH_3)_3Si$ (**1b**)	4-I–C_6H_4–OCH_3 (**2a**)	5	NH_3	**3ba**, 83
1b	**2b**	24	NH_3	**3bb**, 67
1b	I–C_6H_5 (**2c**)	7	NH_3	**3bc**, 59
1b	4-I–C_6H_4–NO_2 (**2d**)	9	NH_3	**3bd**, 72
1b	3-I–C_6H_4–OCH_3 (**2e**)	6	NH_3	**3be**, 75
1b	2-I–C_6H_4–OCH_3 (**2f**)	3	NH_3	**3bf**, 62
1b	4-I–C_6H_4–CH_3 (**2g**)	5	NH_3	**3bg**, 65
1b	**4b**	24	NH_3	**3bb**, 45[b)]
1b	4-Br–C_6H_4–CN (**4h**)	48	NH_3	**3bh**, 47[b)]
1b	**5i**	13	NH_3	**3bi**, 62[b)]
$^nC_6H_{13}$ (**1e**)	**2a**	48	NH_3	**3ea**, 72
$^nC_4H_9$ (**1f**)	**2d**	48	NH_3	**3fd**, 91
1a	**2a**	2	KOH	**3aa**, 21
1a	**2a**	2	K_2CO_3	**3aa**, 36

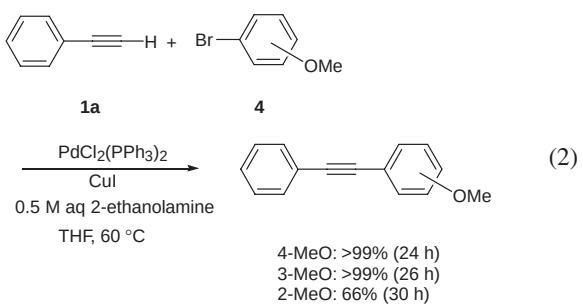
a) Unless noted the reaction was carried out with alkyne **1** (0.6 mmol), aryl halide **2**, **4**, or **5** (0.5 mmol), and 0.5 M of aqueous solution of the activator (1 mmol) in the presence of 1 mol% of $PdCl_2(PPh_3)_2$ and 2 mol% of CuI at room temperature in THF. b) The amount of $PdCl_2(PPh_3)_2$ loaded was 3 mol%.



Scheme 1.

In addition, the metallic complex that might be formed in concentrated ammonia is not irreversibly inactive. The addition of water to the mixture of 14.9 M of aqueous ammonia, in which the coupling product was obtained in 8% yield, initiated the reaction to afford the coupling product in 90% yield after stirring for 16 h whereas further stirring without the addition of water resulted in 12% yield (Scheme 1).

Because ammonia was found to work effectively as an activator for the coupling of alkynes, our interest turned to a similar class of activator that is available to the reaction at a higher reaction temperature. Although aryl bromides bearing an electron-withdrawing group as well as aryl iodides effected the reaction at room temperature, the reaction of aryl bromides bearing an electron-donating group such as 4-methoxy-bromobenzene (**4a**) was unsuccessful at room temperature. However, it is not appropriate to carry out the reaction in the presence of ammonia at an elevated temperature. Accordingly, several water-soluble amines of high boiling points were examined instead of aqueous ammonia. The reaction of **1a** and aryl iodide **2a** was carried out with such amines, among which 0.5 M aqueous solutions of 2-ethanolamine (**6**), 3-propanolamine (**7**), piperazine (**8**), 6-hexanolamine (**9**), and morpholine (**10**) were found to be effective to obtain the coupling product in quantitative yields after stirring at room temperature for 2 h. We then carried out the reaction of 4-methoxy-bromobenzene (**4a**) with phenylethyne (**1a**) at 60 °C with a 0.5 M aqueous solution of **6** to obtain the coupling product in a quantitative yield after stirring for 24 h. Other bromides also reacted similarly (Eq. 2).

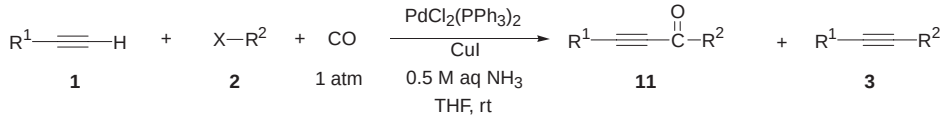


(2)

The coupling reaction of alkynes with aqueous ammonia was then directed for carbonylative coupling in the presence of carbon monoxide. Carbonylative coupling under Sonogashira conditions, which employs a palladium/copper catalyst system in a large excess of amine,[8] has not been reported so far. Although several reports have been shown using a palladium catalyst without copper, the reaction must be carried out at a high reaction temperature and a high pressure of carbon monoxide.[9] Indeed, the conventional Pd/Cu-catalyzed Sonogashira conditions under an ambient pressure of carbon monoxide using Et_3N as a solvent only resulted in slow non-carbonylative coupling. In addition, the similar reaction in the absence of CuI in excess Et_3N hardly proceeded. The treatment of phenylethyne (**1a**) with **2a** in the presence of 1 mol% $PdCl_2(PPh_3)_2$ using triethylamine at room temperature under an ambient pressure of carbon monoxide resulted in giving the carbonylative coupling product **11aa** in 11% yield and non-carbonylative coupling **3aa** in 1% yields, respectively. The addition of 2 mol% CuI to the reaction system of the standard Sonogashira conditions with CO also resulted in non-carbonylative coupling to yield 70% of **3aa** along with only 7% of **11aa** after stirring at room temperature for 4 h. In contrast, the reaction with aqueous ammonia in the presence of carbon monoxide (1 atm) effected the carbonylative coupling to furnish the corresponding α,β-alkynyl ketone in 71% yield after stirring at room temperature for 41 h. Table 2 summarizes the carbonylative coupling of terminal alkynes with aryl halides. Although the reaction in the presence of 2 mol% of CuI proceeded faster, a mixture of carbonylative and non-carbonhylative products **11aa** and **3aa** was obtained in 4% and 28% yields, respectively. The reaction of **1a** with various aryl iodides occurred smoothly and selectively when a substrate bearing an electron-donating substituent was employed. The reaction with electron-deficient aryl iodides resulted in a mixture of **11** and **3**. However, the selectivity was improved by switching the palladium catalyst to $PdCl_2(dppf)$.[9]

On the other hand, the reaction of alkylalkynes was found to proceed with a Pd–Cu catalyst. When the reaction of 1-octyne (**1e**) with **2a** was carried out in the presence of an ambient pressure of CO and 1 mol% of $PdCl_2(PPh_3)_2$, the reaction was rather sluggish, and 15% of the cabonylative-coupling product was obtained after stirring for 86 h. In contrast to the results of phenylethyne, the reaction of 1-octyne was found to be selective to the carbonylative coupling even in the presence of CuI. When the reaction was carried out with 5 mol% of $PdCl_2(PPh_3)_2$ and 2 mol% of CuI, 74% of the carbonylative coupling product was obtained. Several aryl iodides similarly reacted to afford α,β-alkynyl ketones in good-to-excellent

Table 2. Carbonylative Coupling of Terminal Alkynes[a)]



R^1	X–R^2	Pd catalyst (mol%)	CuI /mol%	Time /h	% yield **11**	% yield **3**
Ph (**1a**)	4-I–C_6H_4–OCH_3 (**2a**)	$PdCl_2(PPh_3)_2$ (1)	0	41	72	0
1a	**2a**	$PdCl_2(PPh_3)_2$ (1)	2	5	4	28[b)]
1a	4-I–C_6H_4–$COCH_3$ (**2b**)	$PdCl_2(PPh_3)_2$ (1)	0	61	53	23
1a	**2b**	$PdCl_2$(dppf) (5)	0	25	75	7
1a	I–C_6H_5 (**2c**)	$PdCl_2(PPh_3)_2$ (1)	0	25	76	0
1a	3-I–C_6H_4–OCH_3 (**2e**)	$PdCl_2(PPh_3)_2$ (1)	0	51	81	0
1a	2-I–C_6H_4–OCH_3 (**2f**)	$PdCl_2(PPh_3)_2$ (1)	0	24	76	4
1a	4-I–C_6H_4–CH_3 (**2g**)	$PdCl_2(PPh_3)_2$ (1)	0	47	64	0
1a	1-iodonaphthalene (**2i**)	$PdCl_2(PPh_3)_2$ (1)	0	34	50	1
1a	4-I–C_6H_4–Cl (**2k**)	$PdCl_2(PPh_3)_2$ (1)	0	18	62	29
1a	**2k**	$PdCl_2$(dppf) (5)	0	12	67	0
$^nC_6H_{13}$ (**1e**)	**2a**	$PdCl_2(PPh_3)_2$ (1)	0	86	15	0[b)]
1e	**2a**	$PdCl_2(PPh_3)_2$ (1)	2	48	65	0[b)]
1e	**2a**	$PdCl_2(PPh_3)_2$ (5)	2	24	74	0
1e	**2b**	$PdCl_2(PPh_3)_2$ (5)	2	30	47	5
1e	**2g**	$PdCl_2(PPh_3)_2$ (5)	2	24	78	0
1e	**2i**	$PdCl_2(PPh_3)_2$ (5)	2	25	60	0
1e	**2k**	$PdCl_2(PPh_3)_2$ (5)	2	26	70	4
1e	2-I–C_6H_4–NH_2 (**2l**)	$PdCl_2(PPh_3)_2$ (5)	2	40	71	0
^{t}Bu (**1g**)	**2a**	$PdCl_2(PPh_3)_2$ (5)	2	20	87	0
1g	**2c**	$PdCl_2(PPh_3)_2$ (5)	2	24	77	0
1g	**2i**	$PdCl_2(PPh_3)_2$ (5)	2	19	69	0
$HO(CH_2)_2$ (**1h**)	**2a**	$PdCl_2(PPh_3)_2$ (5)	2	48	56	0

a) The reaction is carried out by using **1** (0.6 mmol), **2** (0.5 mmol), and 0.5 M aq ammonia (1 mmol) under atmospheric pressure of CO at room temperature. b) The yield was estimated by ^{1}H NMR.

yields. Other alkylalkynes effected the carbonylative coupling. Alkynes bearing a hydroxy group **1h** also yielded the product **11** without protection.

As shown in Scheme 2, the selectivity of the carbonylative vs non-carbonylative coupling would be ascribed to the competition of the insertion of carbon monoxide and the transfer of the alkynyl group onto the Aryl–Pd^{II}–I species (**I**), which is the result of the oxidative addition of Aryl–I to Pd(0). When the Aryl–Pd^{II}–Alkynyl species (**II**) is formed preferencially, following reductive elimination gives the non-carbonylative product **3**. On the other hand, the insertion of CO to **I** leads to the carbonylative product **11** through acylpalladium **III**. In the case of alkylalkynes, **III** is formed preferentially since the transfer of alkynyl copper, which is formed by the terminal alkyne and CuI, is slower than the insertion of CO. By contrast, the reaction of **I** with the alkynyl copper species giving **II** is competitive enough when arylalkynes are employed. In the reaction of arylalkynes without CuI, **III** is predominantly formed and a transfer of the alkyne follows to give **IV**. Alternatively, the addition–elimination of **III** through the formation of **IV′** would also be a possible pathway for the palladium-catalyzed reaction in the absence of CuI.

The variation of several activators for the coupling of alkynes is effective for introducing different alkynyl groups into the aromatic ring. We have previously reported that silver(I) oxide serves as an effective activator for the coupling of terminal alkynes.[5a] The reaction was shown to proceed in a specific manner to an aryl iodide. Indeed, the reaction of 4-iodo-1-bromobenzene (**2m**) with trimethylsilylethyne (**1b**) in the presence of silver(I) oxide underwent substitution at the iodine atom to afford **3bm** in 89% yield. The second coupling with phenylethyne (**1a**) at the bromine atom was carried out with aqueous 2-ethanolamine to give **12** in 84% yield (Scheme 3).

Selective carbonylative/non-carbonylative coupling was also found to be controllable in the reaction of **2m**. The reaction of **1e** with **2m** in the presence of carbon monoxide took place to afford **13**, which reacted at the iodine atom selectively. The treatment of **13** with the same alkyne **1e** in the presence of aqueous 2-ethanolamine at 60 °C led to carbonylative and non-carbonylative coupling product **14** (Scheme 4). In contrast, the reaction of 1,4-diiodobenzene (**4n**) with **1e** in the presence of carbon monoxide afforded a mixture of **14** and **15** in 37% and 53% yields, respectively. The first coupling of **4n** was the selective carbonylative coupling, while the second coupling was less selective since the produced alkynyl ketone served as an electron-withdrawing group, which induced less selective incorporation of carbon monoxide, to result in giving a mixture of **14** and **15**.

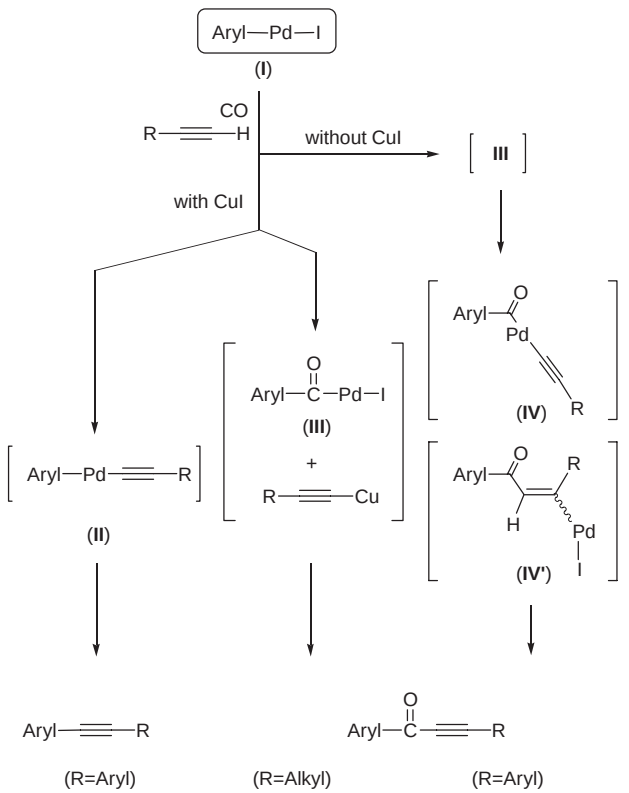
The Sonogashira reaction with aqueous ammonia was found to be applicable for coupling with coumarin derivatives at room temperature. Indeed, the reaction of **1a** with 3-bromocoumarin (**4o**) afforded the coupling product (**16a**) in 88%

yield (Scheme 5). Since coumarins are shown to be available as photoluminescent dyes, the method is a potentially effective synthesis of various coumarin derivatives bearing an alkynyl substituent.[10]

Polyhalogenated arenes were also employed for the coupling reactions of terminal alkynes.[11] The reaction of 1,3,5-tribromobenzene (**4p**) and hexabromobenzene (**4q**) with (4-heptyloxyphenyl)ethyne (**1i**) in the presence of a 0.5 M aqueous solution of 2-ethanolamine at 60 °C afforded the corresponding multi-alkynylated products **17** and **18** in 79% and 40% yields, respectively, as shown in Fig. 2.

Conclusion

In conclusion, a dilute aqueous solution of ammonia with a stoichiometric or a smaller excess amount effected Sonogashira coupling with organic halides. When the reaction was required to be performed at higher temperatures, several water-soluble amines such as 2-ethanolamine were employed instead of ammonia. Carbonylative Sonogashira coupling in the presence or absence of copper(I) iodide as a co-catalyst also took place with aqueous ammonia. The reactions were found to occur at room temperature and under an ambient pressure of carbon monoxide, under which conditions the conventional Sonogashira coupling with amine as a solvent or co-solvent hardly proceeded. The selective introduction of different alkynyl groups into the aromatic ring was found to be available by combining the coupling method using ammonia with that using other activators such as silver(I) oxide. Hence, the method would be a choice for the synthesis of a variety of organic molecules bearing alkynyl moieties leading to a variety of biologically and non-biologically important compounds.



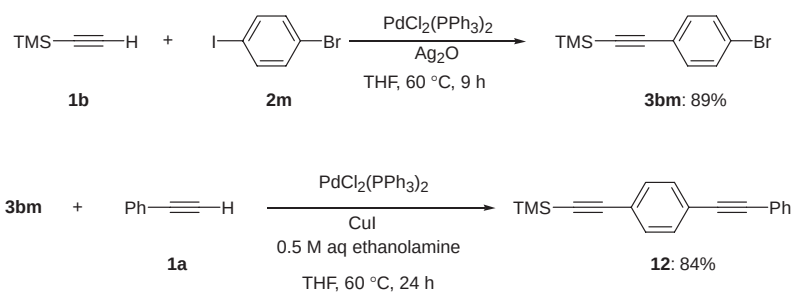
Scheme 2.

Experimental

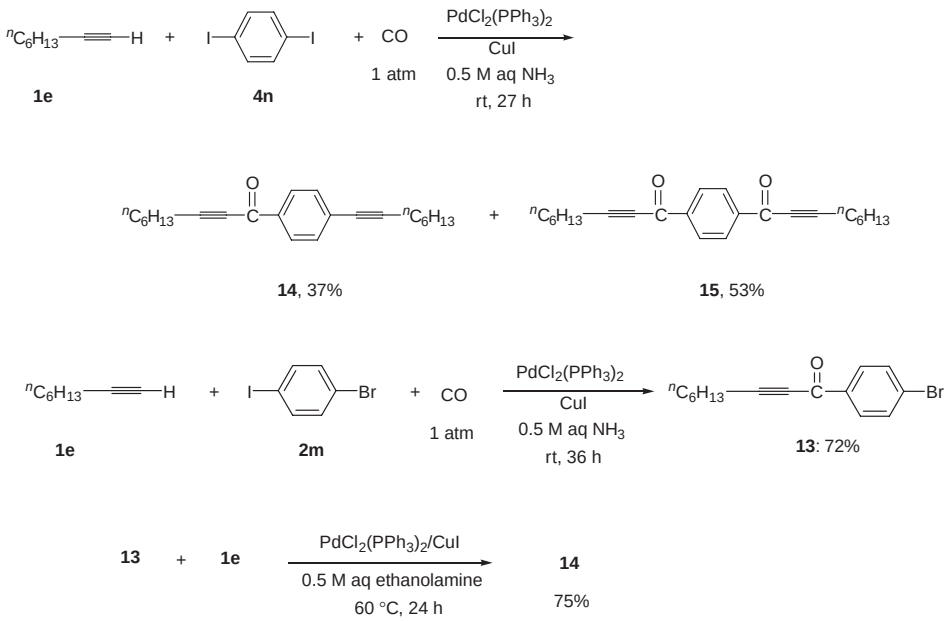
All reactions were performed under either an atmosphere of argon or carbon monoxide in a Schlenk tube. Commercially purchased terminal alkynes and aryl halides were used as received without further purification. Quaternary ammonium hydroxides, TBAOH, TEAOH, Choline, and $C_{16}H_{33}(CH_3)_3NOH$ were purchased as 40, 10, 50% (w/w) aqueous solutions, and a 25% (w/w) methanol solution, respectively.

General Procedure for the Coupling of Terminal Alkyne and Aryl Iodide in the Presence of Aqueous Ammonia at Room Temperature. To $PdCl_2(PPh_3)_2$ (3.5 mg, 0.005 mmol), CuI (1.9 mg, 0.01 mmol), and an aryl halide **2**, **4**, or **5** (0.5 mmol) in 3 mL of THF was added **1** (0.6 mmol) at room temperature under an argon atmosphere. A 0.5 M solution of aqueous ammonia (2 mL, 1 mmol) was then added dropwise and stirring was continued for the period given in Table 1 at room temperature. Two phases of the resulting mixture were separated and the aqueous layer was extracted with diethyl ether. The combined organic layer was concentrated under reduced pressure to leave a crude solid, which was purified by chromatography on silica gel (hexanes–ethyl acetate) to furnish the corresponding coupling product in good-to-excellent yields.

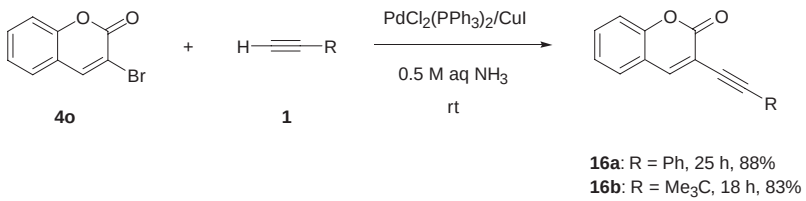
(4-Methoxyphenyl)ethynylbenzene (3aa):[12] According to the general procedure, $PdCl_2(PPh_3)_2$ (70 mg, 0.1 mmol), CuI (38 mg, 0.2 mmol), and 4-methoxyiodobenzene (2.34 g, 10 mmol) in 60 mL of THF was added phenylethyne (1.58 mL, 12 mmol) at room temperature under an argon atmosphere. A 0.5 M solution of aqueous ammonia (40 mL, 20 mmol) was then added dropwise and stirring was continued for 6 h, at room temperature. Two phases of the resulting mixture were separated and the aqueous layer was extracted with diethyl ether (60 mL × 3). The combined organic layer was concentrated under reduced pressure to leave a crude solid, which was purified by chromatography on silica gel (50:1 hexanes–ethyl acetate) to furnish 2.04 g of **3aa** (98%).



Scheme 3.



Scheme 4.



Scheme 5.

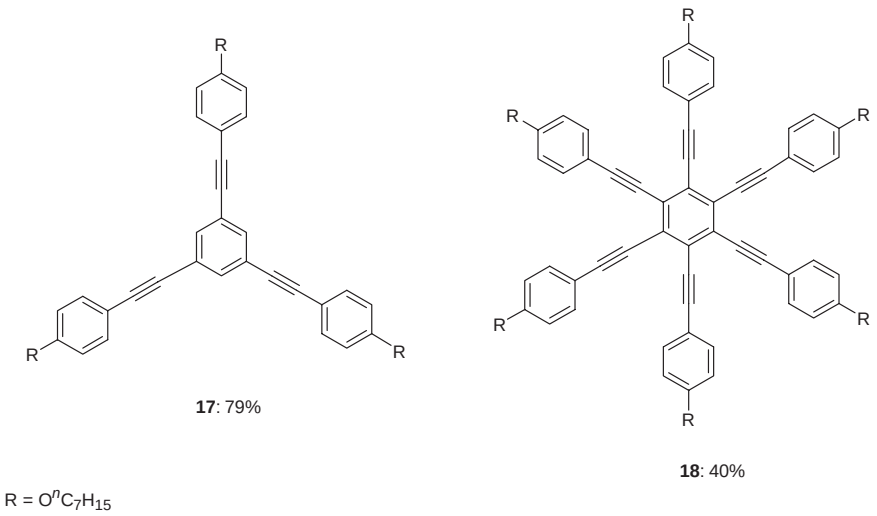


Fig. 2.

The following coupling products were obtained in a similar manner to the above procedure: 4-(1-oxoethyl)-1-phenylethynylbenzene (**3ab**),[13] (4-cyanophenyl)ethynylbenzene (**3ah**),[14] 1-(phenylethynyl)naphthalene (**3ai**),[15] methyl-4-(1-phenyethynyl)-benzoate (**3aj**),[3b] 4-methoxy-1-trimethylsilylethynylbenzene (**3ba**),[16] 4-(1-oxoethyl)-1-trimethylsilylethynylbenzene (**3bb**),[17] trimethylsilylethynylbenzene (**3bc**),[18] 4-nitro-1-trimethylsilylethynylbenzene (**3bd**),[3b] 3-methoxy-1-trimethylsilylethynylbenzene (**3be**),[19] 2-methoxy-1-trimethylsilylethynylbenzene (**3bf**),[20] 4-methyl-1-trimethylsilylethynylbenzene (**3bg**),[21] 4-trimethylsilylethynylbenzenonitrile (**3bh**),[14] 1-trimethylsilylethynylnaphthalene (**3bi**),[22] bis-(4-methoxyphenyl)ethyne (**3ca**),[23] 4-methoxyphenylethynyl-4-nitrobenzene (**3da**),[24] 1-(4-methoxyophenyl)-1-octyne (**3ea**),[3b] 1-(4-nitrophenyl)-1-hexyne (**3fd**).[25]

General Procedure for the Carbonylative Coupling of Phenylethyne (1a) with an Aryl Iodide (2). To a Schlenk tube equip-

ped with a magnetic stirring bar under argon were added $PdCl_2(PPh_3)_2$ (1 mol%), THF, phenylethyne (**1a**) (1.2 equiv), and **2** successively to the mixture to form a pale-yellow solution. Then, aqueous ammonia (0.5 M, 2 equiv) was added dropwise via a syringe. The atmosphere was replaced with carbon monoxide with a balloon and stirring was continued at room temperature. After the period shown in Table 2, the mixture was passed through a Celite pad and the filtrate was washed with brine. The aqueous layer was extracted with diethyl ether and the combined organic layers were dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography using hexanes–ethyl acetate to afford the corresponding α,β-alkynyl ketones **11**. [**CAUTION**: The reaction using carbon monoxide should be carried out in a well ventilated hood.]

1-(4-Methoxyphenyl)-3-phenyl-2-propyn-1-one (11aa):[26] According to the general procedure, $PdCl_2(PPh_3)_2$ (3.5 mg, 0.005 mmol) and THF (3 mL). Phenylethyne (**1a**) (0.066 mL, 0.6 mmol) and **2a** (0.117 g, 0.5 mmol) were added successively to the mixture to form a pale-yellow solution. Then, aqueous ammonia (0.5 M, 2 mL, 1.0 mmol) was added dropwise via a syringe. The atmosphere was replaced with carbon monoxide with a balloon and stirring was continued at room temperature for 41 h; the mixture was passed through a Celite pad and the filtrate was washed with brine. The aqueous layer was extracted with diethyl ether (3×15 mL) and the combined organic layers were dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (30:1 hexanes–ethyl acetate) to afford 85 mg of **11aa** (72%).

Carbonylative coupling reaction with other aryl halides was carried out in a similar manner to the above procedure to afford the following α,β-alkynyl ketones: 1-(2-methoxyphenyl)-3-phenyl-2-propyn-1-one (**11af**),[27] 3-phenyl-1-(4-methylphenyl)-2-propyn-1-one (**11ag**),[28] 1,3-diphenyl-2-propyn-1-one (**11ac**),[29] 1-(1-nahpthyl)-3-phenyl-2-propyn-1-one (**11ai**),[8] 1-(4-chlorophenyl)-3-phenyl-2-propyn-1-one (**11ak**).[9c]

1-(3-Methoxyphenyl)-3-phenyl-2-propyn-1-one (11ae): Purified by flash chromatography (50:1 hexanes–ethyl acetate) afforded 95 mg of **11ae** (81%) as a colorless oil. IR (neat) 2205, 1642, 1597, 1582 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.90 (s, 3H), 7.18 (ddd, $J = 8.1$, 1.7, 1.2 Hz, 1H), 7.40–7.53 (m, 4H), 7.67–7.72 (m, 3H), 7.87 (ddd, $J = 7.8$, 1.5, 1.2 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 55.44, 86.90, 92.97, 112.72, 120.03, 120.94, 122.85, 128.65, 129.61, 130.79, 133.05, 138.17, 159.74, 177.75. HRMS (EI) m/z calcd for $C_{16}H_{16}O_2$ 236.0837, found 236.0845.

1-{4-(1-Oxoethyl)phenyl}-3-phenyl-2-propyn-1-one (11ab): Purified by flash chromatography (50:1 hexanes–ethyl acetate) afforded 93 mg of **11ab** (75%) as a colorless solid. Mp 103–104 °C. IR (KBr) 2199, 1686, 1632 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.67 (s, 3H), 7.42–7.54 (m, 3H), 7.69–7.73 (m, 2H), 8.09 (d, $J = 8.7$ Hz, 2H), 8.31 (d, $J = 8.7$ Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 26.95, 86.75, 94.28, 119.70, 128.42, 128.74, 129.67, 131.10, 133.15, 139.77, 140.75, 177.11, 197.42. HRMS (EI) m/z calcd for $C_{17}H_{12}O_2$ 248.0837, found 248.0831.

General Procedure for the Carbonylative Coupling of Alkylalkynes (1) with Aryl Halides (2). To a solution of an alkylalkyne (**1**, 1.2 equiv), **2**, $PdCl_2(PPh_3)_2$ (5 mol%), and CuI (2 mol%) in THF was added aqueous ammonia (0.5 M, 2 equiv). The atmosphere was replaced with carbon monoxide with a balloon and stirring was continued at room temperature for the period shown in Table 2. The resulting mixture was passed through a Celite pad and the filtrate was washed with brine. The aqueous layer was extracted with diethyl ether and the combined organic layers were dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel using hexanes–ethyl acetate to afford the corresponding α,β-alkynyl ketones **11**.

The following carbonylative coupling products were obtained in the manner described above: 4,4-dimethyl-1-phenyl-2-pentyn-1-one (**11gc**),[30] 1-(4-bromophenyl)-2-nonyn-1-one (**13**).[31]

1-(4-Methoxyphenyl)-2-nonyn-1-one (11ea): According to the general procedure, 1-octyne (1.246 mL, 8.4 mmol), 4-methoxyiodobenzene (1.638 g, 7.0 mmol), $PdCl_2(PPh_3)_2$ (245 mg, 0.35 mmol), and CuI (26.6 mg, 0.14 mmol) in 42 mL THF was added aqueous ammonia (0.5 M, 28 mL, 14 mmol). The atmosphere was replaced with carbon monoxide with a balloon and stirring was continued at room temperature for 24 h. The resulting mixture was passed through a Celite pad and the filtrate was washed with brine. The aqueous layer was extracted with diethyl ether (3×60 mL) and the combined organic layers were dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (30:1 hexanes–ethyl acetate) to afford 1.22 g of **11ea** (71%) as a colorless oil. IR (neat) 2932, 2858, 2199, 1638, 1597 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.93 (t, $J = 6.6$ Hz, 3H), 1.31–1.68 (m, 8H), 2.48 (t, $J = 6.9$ Hz, 2H), 3.88 (s, 3H), 6.94 (d, $J = 8.4$ Hz, 2H), 8.11 (d, $J = 6.6$ Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 13.98, 19.15, 22.45, 27.78, 28.60, 31.19, 55.51, 79.59, 95.97, 113.65, 130.29, 131.86, 164.21, 176.95. HRMS (EI) m/z calcd for $C_{16}H_{20}O_2$ 244.1463, found 244.1461.

1-(4-Methylphenyl)-2-nonyn-1-one (11eg): Purified by flash chromatography (30:1 hexanes–ethyl acetate) afforded 89 mg of **11eg** (78%) as a colorless oil. IR (neat) 2955, 2936, 2859, 2199, 1646, 1605 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.91 (t, $J = 7.2$ Hz, 3H), 1.20–1.75 (m, 8H), 2.49 (t, $J = 7.2$ Hz, 2H), 7.27 (d, $J = 8.7$ Hz, 2H), 8.03 (d, $J = 7.2$ Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 13.94, 19.13, 21.69, 22.42, 27.73, 28.56, 31.16, 79.67, 96.27, 129.12, 129.60, 134.60, 144.81, 177.90. HRMS (EI) m/z calcd for $C_{16}H_{20}O$ 228.1514, found 228.1511.

1-(1-Naphthyl)-2-nonyn-1-one (11ei): Purified by flash chromatography (30:1 hexanes–ethyl acetate) afforded 79 mg of **11ei** (60%) as a colorless oil. IR (neat) 3050, 2955, 2936, 2859, 2209, 1638 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.91 (t, $J = 6.9$ Hz, 3H), 1.32–1.69 (m, 8H), 2.51 (t, $J = 7.2$ Hz, 2H), 7.54–7.66 (m, 3H), 7.89 (d, $J = 7.2$ Hz, 1H), 8.06 (d, $J = 8.1$ Hz, 1H), 8.54 (dd, $J = 7.5$, 1.5 Hz, 1H), 9.18 (d, $J = 8.7$ Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 13.99, 19.18, 22.46, 27.74, 28.63, 31.19, 81.25, 95.37, 124.34, 125.95, 126.58, 128.44, 128.73, 130.63, 132.94, 133.75, 134.41, 134.76, 180.00. HRMS (EI) m/z calcd for $C_{19}H_{20}O$ 264.1514, found 264.1518.

1-{4-(1-Oxoethyl)phenyl}-2-nonyn-1-one (11eb): Purified by flash chromatography (30:1 hexanes–ethyl acetate) afforded 60 mg of **11eb** (47%) as a colorless oil. IR (neat) 2967, 2930, 2859, 2238, 2203, 1691, 1649 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.91 (t, $J = 6.9$ Hz, 3H), 1.20–1.75 (m, 8H), 2.53 (t, $J = 7.8$ Hz, 2H), 2.66 (s, 3H), 8.04 (d, $J = 6.6$ Hz, 2H), 8.22 (d, $J = 6.6$ Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 13.99, 19.23, 22.44, 26.95, 27.65, 28.60, 31.16, 79.57, 98.27, 128.29, 129.64, 139.82, 140.56, 177.33, 197.51. HRMS (EI) m/z calcd for $C_{17}H_{20}O_2$ 256.1463, found 256.1474.

1-(2-Aminophenyl)-2-nonyn-1-one (11el): Purified by flash chromatography (30:1 hexanes–ethyl acetate) afforded 81 mg of **11el** (71%) as a pale yellow oil. IR (neat) 3449, 3341, 2955, 2930, 2859, 2226, 1622, 1586 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.90 (t, $J = 6.9$ Hz, 3H), 1.25–1.72 (m, 8H), 2.48 (t, $J = 7.8$ Hz, 2H), 6.29 (brs, 2H), 6.61–6.71 (m, 2H), 7.29–7.31 (m, 1H),

8.06–8.09 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 13.93, 19.08, 22.40, 27.73, 28.53, 31.13, 79.75, 95.77, 115.80, 116.58, 118.68, 134.53, 134.92, 150.89, 179.83. HRMS (EI) m/z calcd for $C_{15}H_{19}NO$ 229.1467, found 229.1474. Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11%. Found C, 78.76; H, 8.28; N, 5.99%.

1-(4-Chlorophenyl)-2-nonyn-1-one (11ek): Purified by flash chromatography (30:1 hexanes–ethyl acetate) afforded 87 mg of **11ek** (70%) as a colorless oil. IR (neat) 2930, 2859, 2238, 2201, 1637, 1597, 1576 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 0.91 (s, 3H), 1.20–1.75 (m, 8H), 2.50 (t, $J = 7.2$ Hz, 2H), 7.44 (d, $J = 8.1$ Hz, 2H), 8.05 (d, $J = 8.1$ Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 13.95, 19.16, 22.42, 27.66, 28.58, 31.14, 79.33, 97.45, 128.77, 130.78, 135.27, 140.37, 176.81. HRMS (EI) m/z calcd for $C_{15}H_{17}ClO$ 248.0968, found 248.0967.

4-Bromo-1-(trimethylsilylethynyl)benzene (3bm):[32] To $PdCl_2(PPh_3)_2$ (7.0 mg, 0.01 mmol), Ag_2O (0.232 g, 1 mmol), and 4-bromo-1-iodobenzene (**2m**, 0.283 g, 1.0 mmol) in 5 mL of THF was added trimethylsilylethyne (**1b**) (0.17 mL, 1.2 mmol) under an argon atmosphere. Stirring was continued at 60 °C for 9 h. After cooling to ambient temperature, the mixture was diluted with 20 mL of diethyl ether and then passed through a Celite pad to remove the silver residue, which was washed with 20 mL of diethyl ether. The combined filtrate was concentrated under reduced pressure to leave a crude solid, which was subjected to column chromatography on silica gel (hexane–ethyl acetate as an eluent) to furnish 0.225 g of **3bm** (89%).

4-(Phenylethynyl)-1-(trimethylsilylethynyl)benzene (12).[33] To $PdCl_2(PPh_3)_2$ (3.5 mg, 0.005 mmol), CuI (1.9 mg, 0.01 mmol), and 4-bromo-(1-trimethylsilylethynyl)benzene (0.127 g, 0.5 mmol) in 3 mL of THF was added phenylethyne **1a** (0.066 mL, 0.6 mmol) under an argon atmosphere. A 0.5 M aqueous solution of 2-ethanolamine (2.0 mL, 1.0 mmol) was then added dropwise and stirring was continued for 24 h at 60 °C. Two phases of the resulting mixture were separated and the aqueous layer was extracted with diethyl ether. The combined organic layer was concentrated under reduced pressure to leave a crude solid, which was purified by chromatography on silica gel (hexanes–ethyl acetate) to furnish 115.3 mg of **12** (84%).

1-(1-Octyn-1-yl)-4-(1-oxo-2-nonyn-1-yl)benzene (14): Purified by flash chromatography (30:1 hexanes–ethyl acetate) afforded 60 mg of **14** (37%) as a colorless oil. IR (neat) 2957, 2932, 2859, 2234, 2201, 1647, 1601 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 0.90 (t, $J = 6.9$ Hz, 6H), 1.25–1.70 (m, 16H), 2.40–2.55 (m, 4H), 7.46 (d, $J = 8.7$ Hz, 2H), 8.04 (d, $J = 8.7$ Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 14.00, 14.03, 19.21, 19.55, 22.47, 22.52. 27.72, 28.46, 28.59, 28.62, 31.19, 31.30, 79.59, 80.18, 95.15, 97.13, 129.34, 129.96, 131.52, 135.51, 177.43. HRMS (EI) m/z calcd for $C_{23}H_{30}O$ 322.2297, found 322.2288.

1,4-Di-(1-oxo-2-nonyn-1-yl)benzene (15): Purified by flash chromatography (30:1 hexanes–ethyl acetate) afforded 93 mg of **15** (53%) as a colorless oil. IR (neat) 2957, 2930, 2859, 2236, 2199, 1657 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 0.91 (t, $J = 7.2$ Hz, 6H), 1.30–1.76 (m, 16H), 2.53 (t, $J = 6.9$ Hz, 4H), 8.22 (s, 4H). ^{13}C NMR ($CDCl_3$) δ 13.99, 19.25, 22.45, 27.66, 28.62, 31.17, 79.63, 98.40, 129.47, 140.33, 177.33. HRMS (EI) m/z calcd for $C_{24}H_{30}O_2$ 350.2246, found 350.2237.

4,4-Dimethyl-1-(4-methoxyphenyl)-2-pentyn-1-one (11ga): Purified by flash chromatography (30:1 hexanes–ethyl acetate) afforded 94 mg of **11ga** (87%) as a colorless oil. IR (neat) 2993, 2932, 2903, 2842, 2211, 1647, 1597, 1576 cm^{-1}. ^{1}H NMR ($CDCl_3$) 1.37 (s, 9H), 3.88 (s, 3H), 6.95 (d, $J = 8.4$ Hz, 2H), 8.10 (d, $J = 8.4$ Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 27.95, 30.18, 55.50, 78.02, 103.05, 113.66, 130.41, 131.83, 164.17, 177.06. HRMS (EI) m/z calcd for $C_{14}H_{16}O_2$ 216.1150, found 216.1158.

4,4-Dimethyl-1-(1-naphthyl)-2-pentyn-1-one (11gi): Purified by flash chromatography (30:1 hexanes–ethyl acetate) afforded 82 mg of **11gi** (69%) as a colorless oil. IR (neat) 2973, 2930, 2869, 2207, 1637, 1619, 1591, 1574 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 9H), 7.53–7.65 (m, 3H), 7.88 (d, $J = 7.2$ Hz, 1H), 8.06 (d, $J = 8.1$ Hz, 1H), 8.50 (d, $J = 7.2$ Hz, 1H), 9.15 (d, $J = 8.7$ Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 27.96, 30.14, 79.79, 102.31, 124.35, 125.96, 126.57, 128.43, 128.67, 130.64, 133.19, 133.76, 134.13, 134.66, 180.13. HRMS (EI) m/z calcd for $C_{17}H_{16}O$ 236.1201, found 236.1208.

5-Hydroxy-1-(4-methoxyphenyl)-2-pentyn-1-one (11ha): Purified by flash chromatography (3:1 hexanes–ethyl acetate) afforded 57 mg of **11ha** (56%) as a colorless solid. Mp 104 °C. IR (KBr) 3420, 2204, 1635 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.44 (brs, 1H), 2.76 (t, $J = 6.3$ Hz, 2H), 3.88 (s, 3H), 3.89 (t, $J = 6.3$ Hz, 2H), 6.95 (d, $J = 9.0$ Hz, 2H), 8.11 (d, $J = 9.0$ Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 23.52, 55.54, 60.27, 80.65, 92.62, 113.78, 129.93, 132.03, 164.48, 176.90. HRMS (EI) m/z calcd for $C_{12}H_{12}O_3$ 204.0786, found 204.0794.

3-(Phenylethynyl)coumarin (16a):[10] To $PdCl_2(PPh_3)_2$ (10.5 mg, 0.015 mmol), CuI (1.9 mg, 0.01 mmol) in 3 mL of THF and 0.5 M solution of aqueous ammonia (2 mL, 1 mmol) were added **1a** (0.066 mL, 0.6 mmol) and **4o** (0.113 g, 0.5 mmol) at room temperature under an argon atmosphere. Stirring was continued for 25 h at room temperature. Two phases of the resulting mixture were separated and the aqueous layer was extracted with diethyl ether (15 mL × 2). The combined organic layer was concentrated under reduced pressure to leave a crude solid, which was purified by chromatography on silica gel (hexanes–ethyl acetate 10:1) to furnish 0.108 g of **16** (88%).

The reaction of **4o** with 3,3-dimethyl-1-butyne was carried out in the above manner to afford 3-(3,3-dimethylbutynyl)coumarin (**16b**).[10]

Tris-1,3,5-[(4-heptyloxyphenyl)-1-ethynyl]benzene (17): To $PdCl_2(PPh_3)_2$ (6.3 mg, 0.009 mmol), CuI (1.1 mg, 0.006 mmol) in 3 mL of THF and 0.5 M aqueous solution of 2-ethanolamine (1.2 mL, 0.6 mmol) were added (4-heptyloxyphenyl)ethyne (**1i**) (78 mg, 0.36 mmol) and 1,3,5-tribromobenzene (**4p**) (32 mg, 0.1 mmol) at room temperature under an argon atmosphere. Stirring was continued for 24 h at 60 °C. Two phases of the resulting mixture were separated and the aqueous layer was extracted with diethyl ether (15 mL × 2). The combined organic layer was concentrated under reduced pressure to leave a crude solid, which was purified by chromatography on silica gel (hexanes–ethyl acetate 30:1) to furnish 57 mg of **17** (79%) as a pale-yellow oil. IR (neat) 3044, 2945, 2211, 1607, 1565 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 0.90 (t, $J = 6.9$ Hz, 9H), 1.31–1.47 (m, 24H), 1.74–1.84 (m, 6H), 3.87 (t, $J = 6.6$ Hz, 6H), 6.87 (d, $J = 9.0$ Hz, 6H), 7.45 (d, $J = 9.0$ Hz, 6H), 7.58 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 14.04, 22.57, 25.92, 29.04, 29.14, 31.72, 67.88, 86.62, 90.55, 114.39, 114.52, 124.21, 133.02, 133.17, 159.33. HRMS (EI) m/z calcd for $C_{51}H_{60}O_3$ 720.4542, found 720.4555.

Hexakis-1,2,3,4,5,6-{(4-heptyloxyphenyl)-1-ethynyl}benzene (**18**)[34] was obtained in 40% yield in a similar manner as above (60 °C, 24 h).

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