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Transmetalation of Alkylzirconocenes in Copper-Catalyzed Alkyl–Alkynyl Cross-Coupling Reactions

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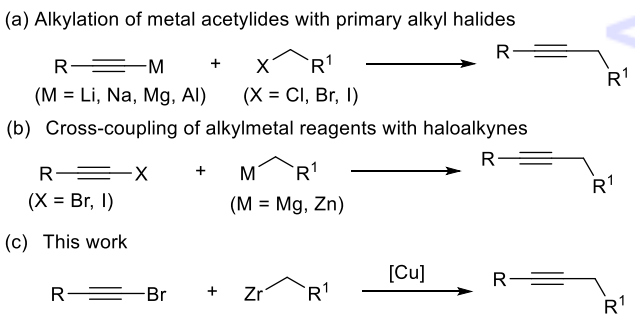
Abstract. A simple copper-catalyzed alkyl-alkynyl cross-coupling strategy has been developed by the reaction between alkynyl bromides and alkylzirconocenes. The alkylzirconocenes were generated in situ via regioselective addition of Schwartz's reagent ($ZrCp_2HCl$) on alkenes. The reaction has a broad scope, a range of functionalized bromoalkynes and alkylzirconium reagents were successfully coupled, resulting moderate to good yields of the desired internal alkynes.

Keywords: Alkylzirconocenes; transmetalation; alkynes; copper catalysis; cross-coupling

Introduction

Internal alkynes are ubiquitous molecules present in a wide range of natural products as well as in biologically important molecules and polymers.[1] These units are often attractive precursors in the total synthesis of complex natural products. For example, several natural products such as epithilone, lactimidomycin, citreofuran, amphidinolide V, etc. have been synthesized via alkyne-alkyne RCM of alkylated alkynes.[2] Recently, they have also been used as essential motifs in OLEDs,[3] liquid crystals[4] and dyes.[5] In addition, a diverse range of products can be obtained by functionalization of the triple bond through electrophilic additions,[6] oxidative cleavage,[7] C–C coupling,[8] reduction,[9] and Diels-Alder reactions.[10] Internal alkynes can also serve as key synthons for the synthesis of highly substituted triazoles via the Huisgen cycloaddition reaction.[11]

Alkyl-alkynyl coupling reactions are an important class of reactions for the synthesis of alkylated alkynes and they are some of the most challenging of cross-coupling processes, due to involvement of undesired β-hydride elimination and other side reactions.[12],[13] There are two major pathways to perform alkyl-alkynyl cross-coupling reactions; (i) alkylation of metal acetylides with primary alkyl halides (Scheme 1a)[12] and (ii) cross-coupling of alkylmetal reagents with haloalkynes (Scheme 1b).[13],[14] Since the development of these methods, numerous efforts have been made to develop efficient catalytic systems. In particular, Pd, Co, Fe, Ni, and Cu catalyzed alkyl-alkynyl cross-coupling reactions involving alkyl or alkynyl organometallic reagents have attracted considerable interest in the past two decades.[12],[13],[14] However, copper catalyzed alkyl-alkynyl cross coupling reactions are very limited, as less than a handful of reports found in the literature. Recently, Cahiez et al. reported the use of Grignard reagents in alkyl-alkynyl cross-coupling reaction using catalytic CuI.[14a] Giri and co-workers documented their findings about copper catalyzed alkyl-alkynyl cross-coupling reactions of alkynylzinc reagents with hetero aryliodides.[14b] Knochel[14c] and Normant[14d] separately published copper mediated cross-coupling reactions between alkylcuprates and alkynyl halides. Despite the progress in this area, poor yields, limited substrate scope, tedious reaction conditions, toxicity, use of expensive metal catalysts and less tolerance towards the reactive functional groups such as esters or nitriles or imides still limit their laboratory applications.



Scheme 1. Different strategies of alkyl-alkynyl cross-coupling reactions.

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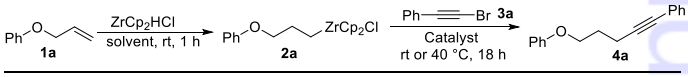
On the other hand, alkylzirconocenes are a unique class of synthetic intermediates and their chemistry has been actively investigated in recent years because of their high functional group tolerance and their simple regioselective generation from alkenes.[15] Moreover, they readily react with various electrophiles to produce functionalized alkanes.[15],[16] Over the years, transmetalation of alkenylzirconocenes to various transition metals has been well studied in cross-coupling reactions because of the high binding capability of zirconium with π-systems, which led to better transmetalation compared to alkylzirconocenes.[15b],[17],[18] Since the first report of Zr-Cu transmetalation reaction by Schwartz in 1977,[19] only a few numbers of innovations have been published to address the utility of alkylzirconium reagents under copper catalysis.[20] These examples include asymmetric allylic alkylation,[20a,b] conjugate addition with enones,[20c,d] acylation using acid chlorides,[20e] bisalkynylation of zirconacycles with bromoalkynes[20f] and carbometalation of nonactivated alkynes by zirconacyclopentanes.[20g] Recently, Giri and coworkers reported first Cu-catalysed cross-coupling of arylzirconocenes with aryl and heteroaryl iodides.[21] Previously, Takahashi and co-workers established a copper-mediated alkenyl-alkynyl cross coupling reaction of alkenylzirconocenes with bromoalkynes.[17a] More recently, Liu et al. demonstrated oxidative cross-coupling between alkenylzirconocenes and alkynylcopper reagents.[17b] The above two methods require stoichiometric amounts of copper, glove box conditions and only few examples of bromoalkynes were explored. To the best of our knowledge, hydrozirconation of alkenes followed by transmetalation to copper and alkyl-alkynyl cross coupling reaction has never been reported in the literature.

Taking cues from the literature and continuing our interest in copper catalyzed cross-coupling reactions,[22] we postulated that similar alkylzirconocenes could be transmetalated under copper catalysis and would participate in alkyl-alkynyl cross coupling reactions with alkynyl halides (Scheme 1c). This method could address some of the limitations of existing methodologies. Furthermore, the wide range of readily available alkenes would allow direct access to a diverse library of alkylated alkynes.

Results and Discussion

To test our hypothesis, we first generated regioselective alkylzirconocene **2a** in situ by the treatment of allyl phenyl ether **1a** with Schwartz's reagent in THF at room temperature and then subjected it to cross-coupling reaction with (bromoethynyl)benzene **3a** using 10 mol% of $Cu(MeCN)_4PF_6$ at 40 °C. The reaction proceeded smoothly and gave the desired alkyne **4a** in 64% ^{1}H NMR yield (Table 1, entry 1). There was no noticeable change in the yield when the reaction temperature was reduced to ambient temperature (Table 1, entry 2). However, we found a little increment in the yield (69%) upon increasing the catalyst loading to 20 mol% (Table 1, entry 3). Other copper salts such as $Cu(OAc)_2$, CuTc and CuI were tested as well and the desired alkyne **4a** was obtained with a yield of 25%, 57%, and 59%, respectively (Table 1, entries 4-6). To our surprise, the yield of the coupling product was enhanced to 76% (entry 7) upon switching the solvent to dichloromethane. The use of 20 mol% of Cu_2O and CuCN in dichloromethane produced the desired product in moderate yields (Table 1, entries 8 and 9). Changes of the loading of $Cu(MeCN)_4PF_6$ did not lead to better results (entries 10 and 11). Then, we further evaluated the effect of ligands such as phenanthroline (Phen), tetramethylethylenediamine (TMEDA), pentamethyldiethyl-enetriamine (PMDTA) and PPh_3 to improve the rate of reaction.

Table 1. Optimization of the reaction.[a]



S.No.	Catalyst/ligand	Mol%	Solvent	Yield [%][b]
1	$Cu(MeCN)_4PF_6$	10	THF	64[c] (62)[d]
2	$Cu(MeCN)_4PF_6$	10	THF	61
3	$Cu(MeCN)_4PF_6$	20	THF	69 (65)[d]
4	$Cu(OAc)_2$	20	THF	25
5	CuTc	20	THF	57
6	CuI	20	THF	59
7	**$Cu(MeCN)_4PF_6$**	**20**	**CH_2Cl_2**	**76 (72)[d]**
8	Cu_2O	20	CH_2Cl_2	60
9	CuCN	20	CH_2Cl_2	69 (64)[d]
10	$Cu(MeCN)_4PF_6$	10	CH_2Cl_2	64
11	$Cu(MeCN)_4PF_6$	100	CH_2Cl_2	31
12	$Cu(MeCN)_4PF_6$/ Phen	20	CH_2Cl_2	12
13	$Cu(MeCN)_4PF_6$/ TMEDA	20	CH_2Cl_2	35
14	$Cu(MeCN)_4PF_6$/ PMDTA	20	CH_2Cl_2	29
15	CuI/Phen	20	CH_2Cl_2	38[e]
16	CuI/TMEDA	20	CH_2Cl_2	18[f]
17	CuI/PMDTA	20	CH_2Cl_2	16[f]
18	$Cu(MeCN)_4PF_6$/ PPh_3	20	CH_2Cl_2	43
19	---	---	CH_2Cl_2	13

[a)]All the reactions were performed at rt with **1a** (0.24 mmol), $ZrCp_2HCl$ (0.24 mmol), solvent (0.6 mL), **3a** (0.2 mmol), and copper catalyst (0.04 mmol) under argon atmosphere; ligand (0.08 mmol) was added. [b)]Yield refers to NMR yield, determined by ^{1}H NMR spectroscopy of the crude reaction mixture using 3,4,5-trimethoxybenzaldehyde as an internal standard. [c)]Reaction was performed at 40 °C. [d)]Yields in the parenthesis refers to isolated yield. [e)]8% of (3-iodopropoxy)benzene was also observed. [f)]Exclusive formation of (3-iodopropoxy)benzene was observed.

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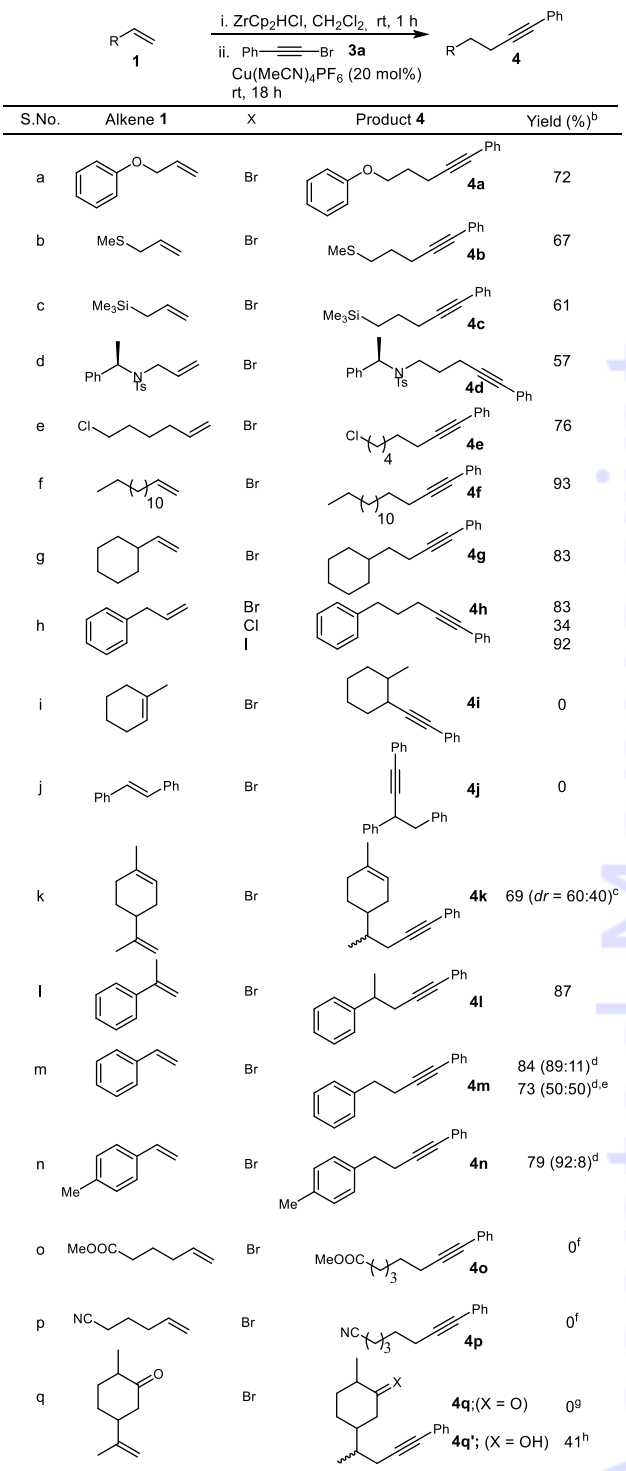
Disappointingly, $Cu(MeCN)_4PF_6$ with these amine ligands afforded the desired alkyne in low yields (entries 12-14). Notably, the use of CuI with these amine ligands furnished either a mixture of alkyne **4a** and iodinated products (Table 1, entry 15), or exclusively iodinated products (Table 1, entries 16-17).[16] On the other hand, $Cu(MeCN)_4PF_6/PPh_3$ system also failed to improve the yield of the reaction (entry 18). Moreover, the absence of catalyst in the reaction led to the desired alkyne in lower yield (13%; Table 1, entry 19).

With the optimized reaction conditions in hand, we then explored the substrate scope of the reaction with various alkylzirconium reagents, generated in situ from alkenes and coupled them directly with (bromoethynyl)benzene **3a**. The results are summarized in Table 2. In all cases, internal alkynes **4a-h** and **4k-n** were observed in moderate to good yields. Alkenes, possessing a hetero atom (O, S, Si and N), furnished the desired alkynes **4a**, **4b, 4c** and **4d** in 72%, 67%, 61% and 57% yields, respectively (Table 2, entries 1-4). The hydrozirconation/cross-coupling of 1-chloro-5-hexene also afforded the desired alkyne **4e** in 76% yield. Simple alkylzirconocenes derived from terminal alkenes such as, 1-tetradecene **1f** and vinylcyclohexane **1g** were also coupled with bromoalkyne **3a**, to give the alkynes **4f** and **4g** in 93% and 83% yields, respectively. Similarly, the allylbenzene gave the corresponding alkyne **4h** in 83% of yield when (bromoethynyl)benzene **3a** was used as coupling partner. To test the reactivity of other haloalkynes in this reaction, we performed the cross-coupling reaction of zirconium reagent generated from allylbenzene with (chloroethynyl)benzene and (iodoethynyl)benzene, observed the formation of pent-1-yne-1,5-diyldibenzene **4h** in 34% and 92% yields, respectively. The improvement of yield from chloroalkyne to iodoalkyne is intriguing as it indicates β- halogen elimination process (**D→4**; if X = I, see mechanism) is more favoured in case of alkynyliodides, because of its good leaving group character. In this protocol, the formation of secondary alkylzirconocenes from internal alkenes **1i-j** took longer time (5h) and the formed secondary zirconium reagents proved difficult to undergo cross-coupling reactions with bromoalkyne **3a**. This might be due to the difficulty of the formation of dialkylcuprate species from sterically hindered secondary alkylzirconocenes. We also observed that the substrate limonene **1k** bearing both internal and terminal alkenes underwent a chemoselective hydrozirconation on the terminal alkene and coupled with (bromoethynyl)benzene **3a** to afford the alkyne **4k** in 68% yield, as an inseparable mixture of diastereomers with a ratio of 60:40. From these observations, it can be concluded that,

Table 2. Scope of the reaction with various alkenes.[a]



S.No.	Alkene **1**	X	Product **4**	Yield (%)[b]
a		Br	**4a**	72
b		Br	**4b**	67
c		Br	**4c**	61
d		Br	**4d**	57
e		Br	**4e**	76
f		Br	**4f**	93
g		Br	**4g**	83
h		Br Cl I	**4h**	83 34 92
i		Br	**4i**	0
j		Br	**4j**	0
k		Br	**4k**	69 (*dr* = 60:40)[c]
l		Br	**4l**	87
m		Br	**4m**	84 (89:11)[d] 73 (50:50)[d,e]
n		Br	**4n**	79 (92:8)[d]
o		Br	**4o**	0[f]
p		Br	**4p**	0[f]
q		Br	**4q**;(X = O) **4q'**; (X = OH)	0[g] 41[h]

[a)]All the reactions were performed with **1a** (0.2 mmol), $ZrCp_2HCl$ (0.2 mmol), solvent (0.6 mL), **3a** (0.2 mmol), and $Cu(MeCN)_4PF_6$ (0.04 mmol) under argon atmosphere [b)]Isolated yield. [c)]Inseparable mixture of diastereomers. [d)]Mixture of regio isomeric alkynes. [e)]Reaction was performed in THF. [f)]Decomposition of alkene was observed. [g)]Dihydrocaveol (**5**; 53%) was isolated. [h)]2 equiv. of $ZrCp_2HCl$ was used in the reaction.

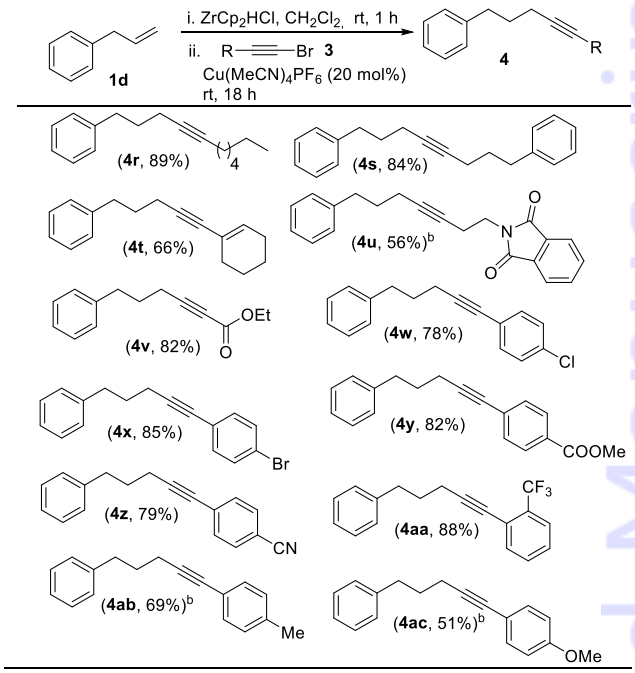
the rate of hydrozirconation on terminal alkenes is much faster, compared to internal alkenes, and the

secondary zirconium reagents could not be coupled with bromoalkynes.

Under these reaction conditions, α-methylstyrene produced an exclusive coupling product **4l** in 87% yield. Whereas, styrenes **1m-n** under the similar reaction conditions producing a mixture of regio isomeric alkynes, which is due to addition of Schwartz's reagent on styrenes in Markovnikov and anti-Markovnikov fashion. The reason for this unusual formation of isomers is not clear. For example, styrene **1m** afforded a mixture of isomers in 84% yield, with a ratio of 89:11 having linear alkyne **4m** as major one. The same reaction in THF gave a mixture of isomers in 73% yield with 50:50 ratio. Similarly, 4-methylstyrene **1n** in CH_2Cl_2 underwent a smooth coupling to form a mixture of isomers (79%, 92:8) having linear alkyne **4n** as major one. These results proved that dichloromethane plays a vital role in deciding the selectivity of hydrozirconation on styrenes. On the other hand, alkenes bearing ester, nitrile and ketone groups (**4o-q**) were also examined. In contrast to our previous results, decomposition of alkene was observed when starting with methyl-5-hexenoate (**1o**) or 5-hexenenitrile (**1p**). Whereas, dihydrocarvone (**1q**) reduced to dihydrocarveol (**5**) exclusively in 53% yield as a mixture of diastereomers (entry 17; see SI). When we used 2 equivalents of Schwartzs reagent on dihydrocarvone under the reaction conditions, observed an alkyne **4q'** in 41% yield as aninseparable mixture of isomers. The intolerance of these functional groups with zirconium is due to strong coordination of Lewis acidic Zr with the above mentioned functional groups, which further results reduction products via hydride transfer in some cases.[15b,23]

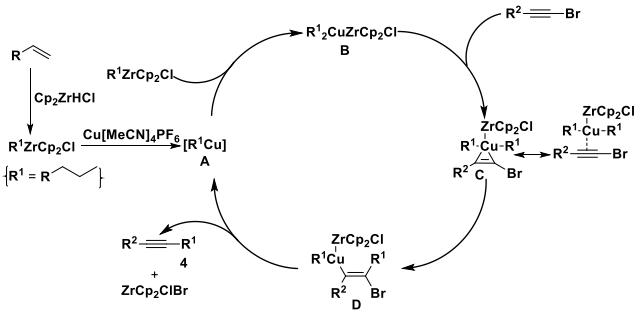
Having demonstrated the utility of the optimized conditions on various alkenes, we turned our attention to the scope of bromoalkynes. As expected, a series of bromoalkynes reacted smoothly with 3-phenylpropylzirconocene as robust model, providing the internal alkynes **4r-4ac** in moderate to good yields. The results are depicted in Scheme 2. Simple aliphatic alkynyl bromides such as 1-bromooct-1-yne and (5- bromopent-4-yn-1-yl)benzene were converted to the corresponding dialkylated alkynes **4r** (89%) and **4s** (84%), respectively. Bromoalkyne derived from 3-ethynylcyclohex-1-ene was also alkylated under these conditions to furnish the enyne **4t** in 66% yield. Moreover, the substrates having imide and ester groups are well tolerated affording the desired alkynes **4u** (56%) and **4v** (82%), respectively. We were also pleased to find that the substitution on the benzene ring of bromophenylacetylenes play a crucial role in the outcome of yield. For example, alkynylbromides bearing electron-withdrawing groups on the benzene ring led to alkynes **4w-4aa** in excellent yields. Here, the formation of **4w-x** suggests that the cross-coupling reaction is highly chemoselective in favor of alkynylbromides over haloarenes. The substrates having electron-donating groups such as, methyl and methoxy were slower to react and gave the corresponding alkynes **4ab-ac** along with small amounts (9-13%) of unreacted bromoalkynes. The higher reactivity of the electron-deficient bromoalkynes indicates the enhancement of the electrophilic nature of the bromoalkyne to facilitate the cross-coupling reaction. It is noteworthy to mention that, electronically diverse functional groups such as chloro, bromo, trifluoromethyl, cyano, ester, imide, silyl, sulfide, methyl, and methoxy substituents were well tolerated under the reaction conditions.

Table 3. Scope of different bromoalkynes in the reaction.[a]



[a]All the reactions were performed with **1d** (0.24 mmol), $ZrCp_2HCl$ (0.24 mmol), CH_2Cl_2 (0.6 mL), **3** (0.2 mmol), and $Cu(MeCN)_4PF_6$ (0.04 mmol) under argon atmosphere; yields refers to isolated yield. [b]Small amounts of unreacted bromoalkyne was also recovered.

Although the mechanism for the copper-catalyzed cross-coupling reaction of alkenyl/alkylzirconocenes is unknown, we here propose a mechanism similar to Cahiez's alkyl-alkynyl cross coupling with Grignard reagents.[14a] The alkylzirconocene generates the



Scheme 2. Plausible reaction mechanism.

corresponding alkylcopper(I) species **A** in situ through transmetalation. These species further react with another molecule of alkylzirconium to give dialkylcuprate complex **B**. This complex undergoes carbocupration with bromoalkynes via a five coordinate, three-membered cyclic organocopper species **C** to generate a β-halo-vinylcopper(I) complex **D**. Finally, the β-halogen elimination of complex **D** gives the cross-coupled product **4** and regenerates the alkylcopper(I) species (Scheme 2).

Conclusion

In summary, we have developed a two-step synthesis of alkylated alkynes from alkenes via sequential hydrozirconation with Schwartz's reagent followed by transmetalation to copper and cross-coupling with bromoalkynes. The 'ligandless' and 'base free' conditions make this methodology more attractive from the standpoints of cost, atom economy and ease of purification. Furthermore, the direct hydrozirconation/transmetalation/cross-coupling sequence from alkenes would be a reliable alternative for the synthesis of dialkylated alkynes, which are quite difficult to afford through known methods.

Experimental Section

Alkene (0.24 mmol; 1.2 equiv.) was added slowly to a solution of Schwartz's reagent (0.24 mmol; 1.2 equiv.) in dichloromethane (0.6 mL) under argon atmosphere at room temperature. After stirring for 1 hr, the resulting clear yellow solution was transferred via cannula to a mixture of haloalkyne (0.2 mmol, 1 equiv.) and $Cu(MeCN)_4PF_6$ (0.04 mmol, 0.2 equiv.) under argon atmosphere. The resulting mixture was stirred at ambient temperature for 18 hours. The solution was diluted with diethyl ether (5 mL), filtrated trough a short pad of silica and eluted with diethyl ether (15 mL). The ethereal solution was evaporated under reduced pressure to afford the crude product. The crude product was purified by flash chromatography using petroleum ether to afford the desired alkyne.

(5-Phenoxypent-1-yn-1-yl)benzene (4a): Colorless liquid; yield 34 mg, 72%; R_f (2% EtOAc in petroleum ether) 0.43; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.08 (p, *J* = 6.0 Hz, 2 H), 2.63 (t, *J* = 6.0 Hz, 2 H), 4.12 (t, *J* = 6.0 Hz, 2 H), 6.92−6.97 (m, 3 H), 7.25−7.29 (m, 5 H), 7.37−7.40 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.2, 28.5, 66.3, 81.1, 89.1, 114.5 (2C), 120.7, 123.8, 127.7, 128.2 (2C), 129.5 (2C), 131.6 (2C), 158.9; IR (thin film) 1599, 1587, 1488, 1469, 1301, 1244, 1172, 1080, 1047, 754, 690 cm^{-1}; HRMS (APCI) calcd for $C_{17}H_{16}O$ $(M + H)^+$ 237.1274, found 237.1273.

Methyl(5-phenylpent-4-yn-1-yl)sulfane (4b): Pale yellow liquid; yield 25 mg, 67%; R_f (2% EtOAc in petroleum ether) 0.47; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.92 (p, *J* = 6.0 Hz, 2 H), 2.15 (s, 3 H), 2.57 (t, *J* = 6.0 Hz, 2 H), 2.69 (t, *J* = 6.0 Hz, 2 H), 7.28−7.32 (m, 3 H), 7.40−7.43 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.5, 18.5, 28.1, 33.2, 81.2, 89.1, 123.8, 127.6, 128.2 (2C), 131.5 (2C); IR (thin film) 1596, 1488, 1440, 1429, 756, 692 cm^{-1}; HRMS (APCI) calcd for $C_{12}H_{14}S$ $(M + H)^+$ 191.0889, found 191.0889.

Trimethyl(5-phenylpent-4-yn-1-yl)silane (4c): Pale yellow liquid; yield 27 mg, 61%; R_f (2% EtOAc in petroleum ether) 0.55; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.08 (s, 9 H), 0.70−0.75 (m, 2 H), 1.59−1.73 (m, 2 H), 2.48 (t, *J* = 6.0 Hz, 2 H), 7.32−7.38 (m, 3 H), 7.45−7.49 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -1.7 (3C), 16.5, 23.2, 23.8, 80.1, 90.5, 124.1, 127.5, 128.2 (2C), 131.6 (2C); IR (thin film) 1599, 1488, 1442, 1247, 1164, 1070, 1026, 966, 862, 835, 752, 690 cm^{-1}; HRMS (APCI) calcd for $C_{14}H_{20}Si$ $(M + Na)^+$ 239.1239, found 239.1239.

(*R*)-4-Methyl-*N*-(1-phenylethyl)-*N*-(5-phenylpent-4-yn-1-yl)benzenesulfonamide (4d): Pale yellow liquid; yield 47 mg, 57%; R_f (4% EtOAc in petroleum ether) 0.27; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41 (d, *J* = 6.0, 3 H), 1.45−1.50 (m, 1 H), 1.67−1.79 (m, 1 H), 2.08−2.29 (m, 2 H), 2.42 (s, 3 H), 3.15−3.23 (m, 2 H), 5.22 (q, *J* = 6.0, 1 H), 7.22−7.34 (m, 12 H), 7.76 (d, *J* = 6.0, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.7, 17.0, 21.5, 29.5, 43.3, 55.5, 81.2, 88.9, 123.8, 127.2 (2C), 127.63 (2C), 127.66, 127.70, 128.2 (2C), 128.4 (2C), 129.7 (2C), 131.5 (2C), 138.2, 140.2, 143.1; IR (thin film) 1598, 1490, 1450, 1334, 1159, 1147, 1091, 1028, 958, 859, 742 cm^{-1}; HRMS (ESI) calcd for $C_{26}H_{27}NO_2S$ $(M + Na)^+$ 440.1655, found 440.1654.

(8-Chlorooct-1-yn-1-yl)benzene (4e): Pale yellow liquid; yield 33 mg, 76%; R_f (2% EtOAc in petroleum ether) 0.48; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46−1.59 (m, 4 H), 1.58−1.64 (m, 2 H), 1.76−1.83 (m, 2 H), 2.42 (t, *J* = 6.0 Hz, 2 H), 3.55 (t, *J* = 6.0 Hz, 2 H),7.25−7.30 (m, 3 H), 7.37−7.41 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.3, 26.4, 28.1, 28.5, 32.5, 45.1, 80.8, 90.1, 124.0, 127.5, 128.2 (2C), 131.5 (2C); IR (thin film) 2937, 1599, 1489, 1444, 1388, 1246, 1159, 1070, 1028, 796, 690 cm^{-1}; HRMS (APCI) calcd for $C_{14}H_{17}Cl$ $(M + H)^+$ 221.1092, found 221.1092.

Hexadec-1-yn-1-ylbenzene (4f): Colorless liquid; yield 55 mg, 93%; R_f (2% EtOAc in petroleum ether) 0.50; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (t, *J* = 6.0 Hz, 3 H), 1.21 (s, 20 H), 1.42−1.50 (m, 2 H), 1.63 (p, *J* = 6.0 Hz, 2 H), 2.42 (t, *J* = 6.0 Hz, 2 H), 7.27−7.32 (m, 3 H), 7.40−7.43 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 19.4, 22.7, 28.8, 28.9, 29.2, 29.4, 29.6, 29.7 (5C), 31.9, 80.5, 90.5, 124.1, 127.4, 128.2 (2C), 131.5 (2C); IR (thin film) 2925, 2904, 2851, 1597, 1483, 1437, 1266, 1191, 1059, 1016, 912, 799, 756, 696 cm^{-1}; HRMS (APCI) calcd for $C_{22}H_{34}$ $(M + H)^+$ 299.2733, found 299.2734.

(4-Cyclohexylbut-1-yn-1-yl)benzene (4g): Colorless liquid; yield 35 mg, 83%; R_f (2% EtOAc in petroleum ether) 0.55; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84−0.98 (m, 2 H), 1.13−1.54 (m, 6 H), 1.62−1.68 (m, 5 H), 2.41 (t, *J* =

6.0 Hz, 2 H), 7.24−7.29 (m, 3 H), 7.43−7.46 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.9, 26.3 (2C), 26.6, 33.0 (2C), 36.3, 36.9, 80.4, 90.7, 124.1, 127.4, 128.2 (2C), 131.5 (2C); IR (thin film) 2908, 2848, 1596, 1488, 1442, 1261, 1174, 1068, 1018, 912, 840, 798, 754, 690 cm^{-1}; HRMS (APCI) calcd for $C_{16}H_{20}$ $(M + H)^+$ 213.1638, found 213.1637.

Pent-1-yne-1,5-diyldibenzene (4h): Pale yellow liquid; yield 36 mg, 83%; R_f (2% EtOAc in petroleum ether) 0.52; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.93 (p, *J* = 6.0 Hz, 2 H), 2.42 (t, *J* = 6.0 Hz, 2 H), 2.80 (t, *J* = 6.0 Hz, 2 H), 7.17−7.33 (m, 8 H), 7.39−7.43 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.8, 30.3, 34.8, 81.1, 89.8, 124.0, 125.9, 127.6, 128.2 (2C), 128.4 (2C), 128.6 (2C), 131.6 (2C), 141.6; IR (thin film) 1598, 1488, 1454, 1070, 1027, 756, 692 cm^{-1}; HRMS (APCI) calcd for $C_{17}H_{16}$ $(M + H)^+$ 221.1325, found 221.1325.

(4-(4-Methylcyclohex-3-en-1-yl)pent-1-yn-1-yl)benzene (inseparable mixture of diastereomers with a ratio of 60 :40) (4k): Colorless liquid; yield 33 mg, 69%; R_f (2% EtOAc in petroleum ether) 0.42 ; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06 (d, *J* = 6.0 Hz, 1.8 H), 1.09 (d, *J* = 6.0 Hz, 1.2 H), 1.22−1.39 (m, 1 H), 1.57−1.84 (m, 8 H), 1.97−2.04 (m, 3 H), 2.32−2.53 (m, 2 H), 7.27−7.31 (m, 3 H), 7.40−7.43 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.4, 16.8, 23.5 (2C), 24.4, 24.5, 25.7, 27.0, 28.1, 29.7, 30.6, 30.7, 37.1, 37.3, 37.5, 37.7, 81.5 (2C), 89.5 (2C), 120.6 (2C), 124.1 (2C), 127.4 (2C), 128.2 (4C), 131.5 (4C), 134.0 (2C); IR (thin film) 2929, 1598, 1541, 1491, 1442, 1070, 1027, 912, 800, 756, 690 cm^{-1}; HRMS (APCI) calcd for $C_{18}H_{22}$ $(M + H)^+$ 239.1794, found 239.1793.

Pent-1-yne-1,4-diyldibenzene (4l): Colorless liquid; yield 38 mg, 87%; R_f (2% EtOAc in petroleum ether) 0.52 ; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44 (d, *J* = 5.4 Hz, 3 H), 2.57−2.74 (m, 2 H), 3.01−3.13 (m, 1 H), 7.22−7.37 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.7, 28.7, 39.2, 81.9, 88.8, 123.9, 126.4, 126.9 (2C), 127.6, 128.2 (2C), 128.3 (2C), 131.5 (2C), 145.8; IR (thin film) 1596, 1490, 1452, 1271, 1169, 1070, 1014, 912, 756, 692 cm^{-1}; HRMS (APCI) calcd for $C_{17}H_{16}$ $(M + H)^+$ 221.1325, found 221.1325.

But-1-yne-1,4-diyldibenzene (major isomer, 4m): Colorless liquid; yield 35 mg, 84%; R_f (2% EtOAc in petroleum ether) 0.51; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.73 (t, *J* = 6.0 Hz, 2 H), 2.95 (t, *J* = 6.0 Hz, 2 H), 7.28−7.34 (m, 7 H), 7.38−7.42 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.7, 35.2, 81.3, 89.5, 123.8, 126.3, 127.6, 128.2 (2C), 128.4 (2C), 128.5 (2C), 131.5 (2C), 140.7; IR (thin film) 2212, 1590, 1488, 1454, 1340, 1274, 1068, 756, 692 cm^{-1}; HRMS (APCI) calcd for $C_{16}H_{14}$ $(M + H)^+$ 207.1168, found 207.1169.

1-Methyl-4-(4-phenylbut-3-yn-1-yl)benzene (major isomer, 4n): Colorless liquid; yield 35 mg, 79%; R_f (2% EtOAc in petroleum ether) 0.52; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.36 (s, 3 H), 2.70 (t, *J* = 5.7 Hz, 2 H), 2.92 (t, *J* = 6.0 Hz, 2 H), 7.14−7.21 (m, 4 H), 7.28−7.32 (m, 3 H), 7.38−7.42 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.0, 21.8, 34.8, 81.2, 89.6, 123.9, 127.6, 128.2 (2C), 128.4 (2C), 129.0 (2C), 131.5 (2C), 135.8, 137.7; IR (thin film) 2219, 1596, 1514, 1488, 1442, 1340, 1163, 1070, 916, 806, 754, 690 cm^{-1}; HRMS (APCI) calcd for $C_{17}H_{16}$ $(M + H)^+$ 221.1325, found 221.1325.

2-Methyl-5-(5-phenylpent-4-yn-2-yl)cyclohexan-1-ol (mixture of isomers, 4q'): Pale yellow liquid; yield 21 mg, 41%; R_f (4% EtOAc in petroleum ether) 0.29; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86−1.05 (m, 6 H), 1.25−1.79 (m, 8 H), 2.19−2.48 (m, 3 H), 3.87 (brs, 0.2 H), 4.06−4.10 (m, 0.6 H), 4.68−4.72 (m, 0.2 H), 7.25−7.30 (m, 3 H), 7.37−7.40 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.29, 16.37, 16.63, 16.67, 18.24, 18.31, 24.31, 24.43, 24.55, 27.14, 27.23, 28.13, 29.24, 29.94, 32.79, 34.52, 35.94, 36.02, 36.26, 36.32, 37.23, 37.53, 37.72, 38.51, 38.57, 40.27, 40.47, 70.98, 81.57, 81.84, 85.99, 86.08, 86.15, 86.24, 88.73, 88.80, 89.51, 123.94, 124.11, 127.45, 127.56, 128.20, 131.54; IR (thin film) 2929, 1596, 1498, 1379, 1296, 1058, 1021, 948, 861, 852, 800, 756, 692 cm^{-1}; HRMS (APCI) calcd for $C_{18}H_{24}O$ $(M + H)^+$ 257.1900, found 257.1901.

Undec-4-yn-1-ylbenzene (4r): Pale yellow liquid; yield 41 mg, 89%; R_f (2% EtOAc in petroleum ether) 0.47 ; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (t, *J* = 6.0 Hz, 3 H), 1.29−1.57 (m, 8 H), 1.83 (p, *J* = 6.0 Hz, 2 H), 2.17−2.22 (m, 4 H), 2.75 (t, *J* = 6.0 Hz, 2 H), 7.18−7.34 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 18.2, 18.8, 22.6, 28.6, 29.1, 30.8, 31.4, 34.8, 79.7, 80.9, 125.8, 128.3 (2C), 128.5 (2C), 141.9; IR (thin film) 2927, 2916, 2856, 2063, 1602, 1496, 1454, 1377, 1330, 1078, 1029, 744, 691 cm^{-1}; HRMS (APCI) calcd for $C_{17}H_{24}$ $(M + H)^+$ 229.1951, found 229.1951.

1,8-Diphenyloct-4-yne (4s): Pale yellow liquid; yield 44 mg, 84%; R_f (2% EtOAc in petroleum ether) 0.53 ; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.83 (p, *J* = 6.0 Hz, 4 H), 2.21 (t, *J* = 6.0 Hz, 4 H), 2.71 (t, *J* = 6.0 Hz, 4 H), 7.16−7.31 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.3 (2C), 30.8 (2C), 34.9 (2C), 80.3 (2C), 125.9 (2C), 128.4 (4C), 128.6 (4C), 141.9 (2C); IR (thin film) 3022, 2921, 2896, 1947, 1602, 1494, 1452, 1332, 1080, 1029, 908, 744, 696 cm^{-1}; HRMS (APCI) calcd for $C_{20}H_{22}$ $(M + H)^+$ 263.1794, found 263.1793.

(5-(Cyclohex-1-en-1-yl)pent-4-yn-1-yl)benzene (4t): Pale yellow liquid; yield 29 mg, 66%; R_f (2% EtOAc in petroleum ether) 0.57 ; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.53−1.67 (m, 4 H), 1.84 (p, *J* = 6.0 Hz, 2 H), 2.07−2.12 (m, 4 H), 2.31 (t, *J* = 6.0 Hz, 2 H), 2.73 (t, *J* = 5.7 Hz, 2 H), 6.02−6.04 (m, 1 H), 7.16−7.31 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.7, 21.6, 22.4, 25.6, 29.6, 30.5, 34.8, 82.9, 86.8, 121.0, 125.8, 128.3 (2C), 128.5 (2C), 133.3, 141.8; IR (thin film) 2937, 2931, 2860, 2212, 1730, 1716, 1670, 1600, 1452, 1348, 1259, 1172, 1078, 748, 700 cm^{-1}; HRMS (APCI) calcd for $C_{17}H_{20}$ $(M + H)^+$ 225.1638, found 225.1637.

2-(7-Phenylhept-3-yn-1-yl)isoindoline-1,3-dione (4u): Colorless semi solid; yield 36 mg, 56%; R_f (10% EtOAc in petroleum ether) 0.38 ; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.70

(p, *J* = 6.0 Hz, 2 H), 2.07−2.13 (m, 2 H), 2.57−2.65 (m, 4 H), 3.86 (t, *J* = 6.0 Hz, 2 H), 7.11−7.28 (m, 5 H), 7.69 (dd, *J* = 3.0 and 4.5 Hz, 2 H), 7.83 (dd, *J* = 3.0 and 4.5 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.1, 18.7, 30.3, 34.7, 37.1, 76.4, 81.9, 123.3 (2C), 125.8, 128.2 (2C), 128.5 (2C), 132.0 (2C), 133.9 (2C), 141.7, 168.1 (2C); IR (thin film) 1772, 1710, 1614, 1467, 1433, 1394, 1361, 1298, 1188, 1114, 1000, 869, 717 cm^{-1}; HRMS (APCI) calcd for $C_{21}H_{19}NO_2$ $(M + H)^+$ 318.1489, found 318.1489.

Ethyl 6-phenylhex-2-ynoate (4v): Pale yellow gum; yield 35 mg, 82%; R_f (5% EtOAc in petroleum ether) 0.53 ; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31 (t, *J* = 6.0 Hz, 3 H), 1.90 (p, *J* = 6.0 Hz, 2 H), 2.33 (t, *J* = 6.0 Hz, 2 H), 2.73 (t, *J* = 6.0 Hz, 2 H), 4.22 (q, *J* = 6.0 Hz, 2 H), 7.17−7.32 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 18.0, 29.1, 34.7, 61.8, 73.6, 88.8, 126.1, 128.47 (2C), 128.51 (2C), 140.8, 153.8; IR (thin film) 2233, 1704, 1496, 1454, 1365, 1247, 1070, 750, 700 cm^{-1}; HRMS (APCI) calcd for $C_{14}H_{16}O_2$ $(M + H)^+$ 217.1223, found 217.1223.

1-Chloro-4-(5-phenylpent-1-yn-1-yl)benzene (4w): Colorless gum; yield 40 mg, 78%; R_f (2% EtOAc in petroleum ether) 0.43 ; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.92 (p, *J* = 6.0 Hz, 2 H), 2.41 (t, *J* = 6.0 Hz, 2 H), 2.78 (t, *J* = 6.0 Hz, 2 H), 7.20−7.34 (m, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.8, 30.2, 34.9, 80.1, 90.9, 122.5, 126.0, 128.4 (2C), 128.5 (2C), 128.6 (2C), 132.8 (2C), 133.5, 141.5; IR (thin film) 1602, 1488, 1454, 1244, 1091, 1014, 827, 746, 698 cm^{-1}; HRMS (APCI) calcd for $C_{17}H_{15}Cl$ $(M + H)^+$ 255.0935, found 255.0934.

1-Bromo-4-(5-phenylpent-1-yn-1-yl)benzene (4x): Pale yellow gum; yield 51 mg, 85%; R_f (2% EtOAc in petroleum ether) 0.48 ; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.92 (p, *J* = 5.7 Hz, 2 H), 2.40 (t, *J* = 6.0 Hz, 2 H), 2.77 (t, *J* = 6.0 Hz, 2 H), 7.17−7.33 (m, 7 H), 7.41 (d, *J* = 6.0 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.9, 30.2, 34.9, 80.2, 91.2, 121.7, 122.9, 126.0, 128.4 (2C), 128.6 (2C), 131.4 (2C), 133.0 (2C), 141.5; IR (thin film) 1601, 1491, 1449, 1384, 1251, 1139, 1071, 1008, 826, 749, 696 cm^{-1}; HRMS (APCI) calcd for $C_{17}H_{15}Br$ $(M + H)^+$ 299.0430, found 299.0431.

Methyl 4-(5-phenylpent-1-yn-1-yl)benzoate (4y): White solid, mp 89-91 °C; yield 46 mg, 82%; R_f (5% EtOAc in petroleum ether) 0.44 ; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.94 (p, *J* = 6.0 Hz, 2 H), 2.45 (t, *J* = 6.0 Hz, 2 H), 2.79 (t, *J* = 6.0 Hz, 2 H), 3.91 (s, 3 H), 7.18−7.33 (m, 5 H), 7.46 (d, *J* = 9.0 Hz, 2 H), 7.96 (d, *J* = 9.0 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.9, 30.1, 34.8, 52.2, 80.6, 93.4, 126.0, 128.4 (2C), 128.5 (2C), 128.8, 128.9, 129.4 (2C), 131.5 (2C), 141.4, 166.7; IR (thin film) 2229, 1720, 1604, 1434, 1307, 1293, 1107, 1018, 964, 858, 769, 744, 698 cm^{-1}; HRMS (APCI) calcd for $C_{19}H_{18}O_2$ $(M + H)^+$ 279.1380, found 279.1380.

4-(5-Phenylpent-1-yn-1-yl)benzonitrile (4z): Pale yellow solid, mp 73-75 °C; yield 39 mg, 79%; R_f (5% EtOAc in petroleum ether) 0.54 ; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.97 (p, *J* = 6.0 Hz, 2 H), 2.47 (t, *J* = 6.0 Hz, 2 H), 2.81 (t, *J* = 6.0 Hz, 2 H), 7.23−7.36 (m, 5 H), 7.49 (d, *J* = 9.0 Hz, 2 H), 7.60 (d, *J* = 9.0 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.9, 30.0, 34.8, 79.9, 95.0, 110.9, 118.6, 126.0, 128.4 (2C), 128.5 (2C), 129.0, 131.9 (2C), 132.1 (2C), 141.3; IR (thin film) 2230, 1602, 1499, 831, 748 , 700 cm^{-1}; HRMS (APCI) calcd for $C_{18}H_{15}N$ $(M + H)^+$ 246.1277, found 246.1276.

1-(5-Phenylpent-1-yn-1-yl)-2-(trifluoromethyl)-benzene (4aa): Pale yellow gum; yield 51 mg, 88%; R_f (2% EtOAc in petroleum ether) 0.34 ; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.98 (p, *J* = 6.0 Hz, 2 H), 2.51 (t, *J* = 6.0 Hz, 2 H), 2.86 (t, *J* = 6.0 Hz, 2 H), 7.22−7.42 (m, 6 H), 7.50 (dt, *J* = 1.8 and 9.0 Hz, 1 H), 7.59 (d, *J* = 6.0 Hz, 1 H), 7.68 (d, *J* = 9.0 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.0, 30.1, 34.7, 77.3, 96.1, 122.3, 123.7 (q, $^1J_{CF}$ = 272 Hz), 125.7 (q, $^3J_{CF}$ = 5.2 Hz), 125.9, 127.3, 128.4 (2C), 128.6 (2C), 131.3, 131.5 (q, $^2J_{CF}$ = 30 Hz), 134.0, 141.7; ^{19}F NMR (282 MHz, $CDCl_3$) δ -62.4; IR (thin film) 1611, 1415, 1325, 1249, 1167, 1070, 837, 751, 694 cm^{-1}; HRMS (APCI) calcd for $C_{18}H_{15}F_3$ $(M + H)^+$ 289.1199, found 289.1198.

1-Methyl-4-(5-phenylpent-1-yn-1-yl)benzene (4ab): Pale yellow liquid; yield 32 mg, 69%; R_f (2% EtOAc in petroleum ether) 0.42 ; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.92 (p, *J* = 6.0 Hz, 2 H), 2.33 (s, 3 H), 2.41 (t, *J* = 6.0 Hz, 2 H), 2.79 (t, *J* = 6.0 Hz, 2 H), 7.09 (d, *J* = 9.0 Hz, 2 H), 7.18−7.32 (m, 7 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.9, 21.4, 30.4, 34.9, 81.2, 89.0, 120.9, 125.9, 128.4 (2C), 128.6 (2C), 129.0 (2C), 131.4 (2C), 137.5, 141.7; IR (thin film) 2215, 1710, 1604, 1541, 1508, 1454, 1251, 1182, 1048, 815, 746, 698 cm^{-1}; HRMS (APCI) calcd for $C_{18}H_{18}$ $(M + H)^+$ 235.1481, found 235.1480.

1-Methoxy-4-(5-phenylpent-1-yn-1-yl)benzene (4ac): Pale yellow liquid; yield 25 mg, 51%; R_f (2% EtOAc in petroleum ether) 0.38 ; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.95 (p, *J* = 6.0 Hz, 2 H), 2.44 (t, *J* = 6.0 Hz, 2 H), 2.82 (t, *J* = 6.0 Hz, 2 H), 2.83 (s, 3 H), 6.85 (d, *J* = 9.0 Hz, 2 H), 7.22−7.40 (m, 7 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.9, 30.4, 34.9, 55.3, 80.8, 88.2, 113.8 (2C), 116.1, 125.9, 128.4 (2C), 128.6 (2C), 132.9 (2C), 141.7, 159.0; IR (thin film) 2933, 1604, 1508, 1454, 1288, 1245, 1172, 1105, 1031, 831, 744, 700 cm^{-1}; HRMS (APCI) calcd for $C_{18}H_{18}O$ $(M + H)^+$ 251.1430, found 251.1429.

Dihydrocaveol (5, mixture of isomers): Pale yellow liquid; yield 17 mg, 53%; R_f (5% EtOAc in petroleum ether) 0.31 ; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97 (d, *J* = 6.0 Hz, 1.5 H), 1.03 (d, *J* = 6.0 Hz, 1.5 H), 1.11-1.28 (m, 2 H), 1.37-1.51 (m, 2 H), 1.67-1.80 (m, 5 H), 1.88-2.05 (m, 1.5 H), 2.22-2.32 (m, 0.5 H), 3.15-3.23 (m, 0.5 H), 3.87-3.91 (m, 0.5 H), 4.69 (brs, 2 H),; ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.3, 20.9, 21.0, 28.1, 31.1, 31.4, 33.2, 36.0, 37.8, 38.6, 40.0, 40.5, 44.1, 71.0, 76.4, 108.4, 108.6, 149.4, 150.3; HRMS (APCI) calcd for $C_{18}H_{18}O$ $(M + H)^+$ 155.1430, found 155.1430.

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FULL PAPER

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