Cobalt(I)-catalyzed Neutral Diels–Alder Reactions of 1,3-Diynes with Acyclic 1,3-Dienes

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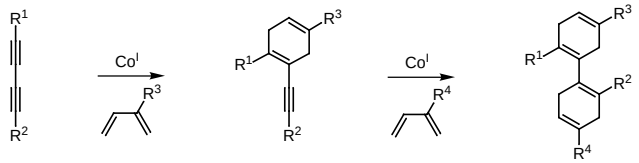
Abstract: The cobalt catalyzed neutral Diels–Alder reaction of various acyclic 1,3-dienes and norbornadiene with 1,3-diynes can be controlled to give the 1:1 adduct, whereas the 1:2 adducts are only formed with sterically less hindered 1,3-dienes. With unsymmetrical 1,3-diynes the regiochemistry is mainly controlled by steric factors for unfunctionalized diynes, whereas the regiodirecting methoxymethyl substituent favors the Diels–Alder reaction at the closest triple bond. The combination of steric effects and the methoxymethyl substituent exclusively generates one of the two possible neutral Diels–Alder products. The mild oxidation of the dihydroaromatic products by stoichiometric amounts of DDQ, or alternatively under electrochemical regeneration of the spent oxidizing agent at the anode, generates phenylacetylene derivatives, from the 1:1 adduct, or biphenyl derivatives, from the 1:2 adduct, respectively.

Key words: cobalt, neutral Diels–Alder reaction, 1,3-diyne, 1,3-diene, dihydroaromatic compounds

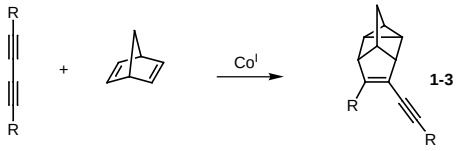
Transition metal catalyzed neutral Diels–Alder reactions and other cycloaddition processes have been extensively studied and among these several Fe, Co, Ti or Ni catalyzed neutral Diels-Alder type reactions are described.[1] Recently, we have investigated cobalt(I)-catalyzed neutral Diels–Alder reactions between terminal as well as internal alkynes and acyclic 1,3-dienes and found that a catalyst system consisting of $Co(dppe)Br_2/ZnI_2/Bu_4NBH_4$ proved to be highly effective in the generation of dihydroaromatic compounds under mild reaction conditions in good to excellent yields.[2]

Herein we describe our investigations into the use of 1,3-diynes as double dienophiles in neutral homo Diels–Alder type reactions with norbornadiene and neutral Diels–Alder type reactions with acyclic 1,3-dienes. While in the presence of a slight excess of the diyne at room temperature the cobalt catalyzed formation of a 1:1 adduct is observed (Scheme 1), the degree of formation of the corresponding 1:2 adducts strongly depends on the substitution pattern of the 1,3-diene, determining its steric hinderance, and to a lesser degree on the reaction temperature.

The cobalt(I)-catalyzed neutral homo Diels–Alder reaction of norbornadiene with symmetrical 1,3-diynes leads selectively to the formation of the 1:1 adducts (see Table 1). Even in the presence of a large excess of norbornadiene, as well as at elevated temperatures, the 1:1 adduct is formed selectively besides norbornadiene dimers as by-product when an excess of norbornadiene is used, while no double addition products could be detected.

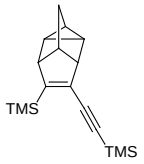
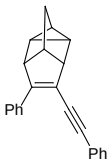
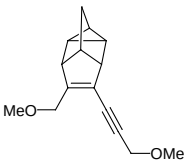


Scheme 1



Scheme 2

Table 1 Cobalt(I)-catalyzed Neutral Homo Diels–Alder Reactions of Symmetrical 1,3-Diynes with Norbornadiene

Entry	R	Product		Time (Temp)	Yield (%)
1	TMS		**1**	16 h 20 °C	76
2	Ph		**2**	16 h 20 °C	82
3	CH_2OMe		**3**	1 h 20 °C	47

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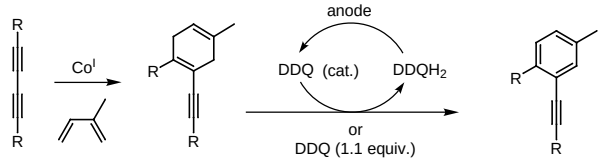
The reactions of simple, sterically less demanding acyclic 1,3-dienes, such as isoprene and 2,3-dimethyl-1,3-butadiene, can be performed at room temperature in a short period of time, while the reaction with 1,3-dienes that are substituted at a terminal position requires longer reaction times for the formation of a 1:1 adduct in good yields. The dihydroaromatic compounds generated by this method can either be isolated under strict exclusion of air and avoiding strong acidic or basic conditions, or the intermediates can immediately be oxidized to the corresponding aromatic derivatives. These oxidations can either be realized using stoichiometric amounts of DDQ or with catalytic amounts of the oxidizing agent under electrochemical reoxidation of the reduced $DDQH_2$ (see Scheme 3) under galvanostatic conditions (100 mA) until 2.2 F/mol are consumed. The aromatic products are then easily isolated by column chromatography.



Scheme 3

Following the reaction sequence outlined in Schemes 2 and 3 we were able to use a variety of different acyclic 1,3-dienes in the neutral Diels–Alder type reaction to generate the 1:1 adducts with symmetrical 1,3-diynes under mild reaction conditions, affording good yields of the corresponding aromatic compounds.

With the methoxy functionalized 1,3-diyne (Table 2, entry 6), a complex mixture of 1:1 adduct regioisomers is formed along with regioisomeric 1:2 adducts, even when an excess of diyne is used. However, with the corresponding THP protected diyne (entry 7), the regioselectivity can be controlled, so that the 1:1 adduct is formed exclusively. However, the regiocontrol for this neutral Diels-Alder reaction is only moderate, with an inseparable 5:2 mixture of regioisomers being formed in favour of the product with the methyl and the CH_2OTHP substituent in a *para* relationship. For the higher homologue (entry 8) the 1:1 adduct is also formed exclusively, while the regiochemistry is comparable to the previous case, with a 4:1 mixture of regioisomers being formed.

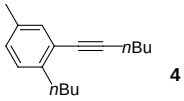
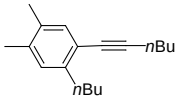
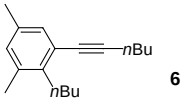
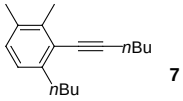
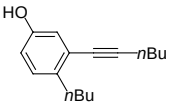
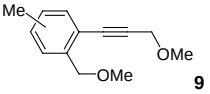
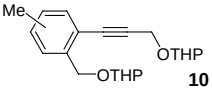
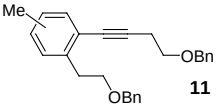
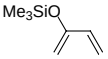
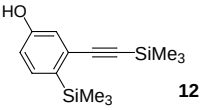
The reactions with sterically less hindered 1,3-dienes result in the formation of the 1:2 adducts with somewhat longer reaction times than the formation of the 1:1 adduct. The primary products are again readily oxidized to the corresponding aromatic biaryl derivatives, which can be easily purified and characterized. The regiochemical outcome of the reactions to form the 1:1 adducts as well as the formation of the 1:2 adducts is mostly influenced by the steric demand of the substituents as outlined in an earlier report.[2b] However, for the formation of the 1:2 adducts the steric bulk is alterned, so that unsymmetrical biaryl type products are formed. For the first neutral Diels–Alder reaction in this sequence, the *n*-butyl group is sterically more demanding (M = medium) than the alkyne substructure (S = small), so that excellent 1,4-selectivity for the reaction with unsymmetrical 1,3-dienes is observed (see Table 2). For the subsequent neutral Diels–Alder reaction, the large steric demand of the dihydroaromatic system (L = large) over the *n*-butyl substituent (M = medium) is again responsible for the excellent 1,4-selective regiochemical outcome of the second addition, forming unsymmetrical biaryl products after mild DDQ oxidation.

Biographical Sketches

Gerhard Hilt (right) was born in Andernach (Germany) in 1968. He studied chemistry in Bonn, where he obtained his diploma in 1992 and his Ph.D. with E. Steckhan on indirect electrochemical regeneration of enzymatic cofactors in asymmetric biosynthesis. From 1996–1998 he worked as a postdoctoral fellow with M. F. Semmelhack (Princeton, U.S.A.) on stoichiometric organometallic chemistry and from 1998–99 in the group of R. Noyori (Nagoya, Japan) on mechanistic investigations in asymmetric catalysis. In late 1999 he started his 'Habilitation' at the Ludwig-Maximilians-University in Munich. His research interests are electron transfer activated (transition-)metal complexes by (electro-)chemical methods and their use in organic synthesis, such as electrochemical regeneration of low valent metals and Co(I)-catalyzed processes.

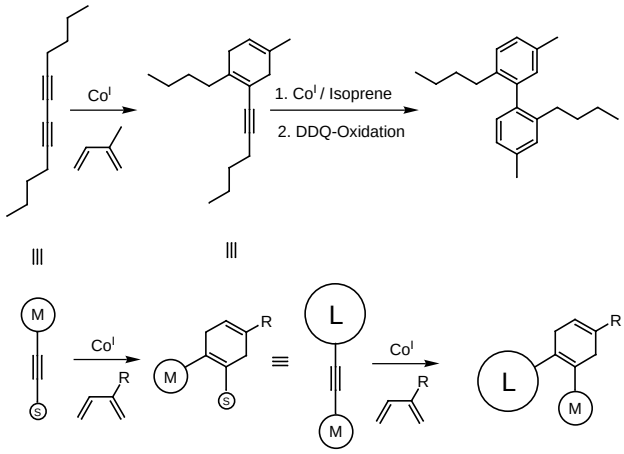
Konstantin Smolko (left) was born in Chelyabinsk (Russia) in 1977. He studied chemistry at the Lomonossov University in Moscow and obtained his diploma in 1999. He joined the Hilt group in 2000 and is working in the fields of electrochemical regeneration of low valent indium reagents and their use in organic synthesis and Co(I)-catalyzed neutral Diels–Alder reactions.

Table 2 Cobalt(I)-catalyzed Neutral Diels–Alder Reactions of Symmetrical 1,3-Diynes with 1,3-Dienes

Entry	R	Diene	Product	Time	Yield (%)
1			 **4**	1 h	91
2			 **5**	1 h	98
3	*n*Bu		 **6**	16 h	84
4			 **7**	16 h	87
5			 **8**	1 h	80
6	$MeOCH_2$		 **9**	0.2 h	-[a]
7	$THPOCH_2$		 **10**	0.5 h	53[b]
8	$BnOCH_2CH_2$		 **11**	1 h	53[c]
9	$SiMe_3$		 **12**	16 h	68

[a] A complex mixture of regioisomeric 1:1 and 1:2 adducts were formed.
[b] A mixture of regioisomers in a 5:2 ratio is formed.
[c] A mixture of regioisomers in a 4:1 ratio is formed.

The situation becomes more complex with higher substituted 1,3-dienes. Thus, with a methyl group in the terminal position, such as in 1,3-pentadiene, the neutral Diels–Alder reactions gave lower regioselectivities compared to reactions with isoprene as the 1,3-diene.[3] This suggests that the substituent in the 2-position is much more directing than the substituent in 1-position. Therefore, the substitution pattern of the products formed with 2-methyl-1,3-pentadiene or 3-methyl-1,3-pentadiene (Table 2, entries 3 and 4) is directed by the isoprene-like methyl group rather than the methyl group in the terminal position.



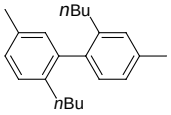
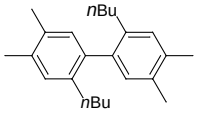
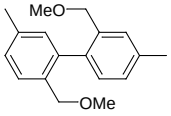
Scheme 4

Besides mono-substituted 1,3-dienes such as isoprene and oxy-substituted dienes, the disubstituted diene 2,3-dimethyl-1,3-butadiene also underwent the reaction to form the 1:2 adducts in good yield.

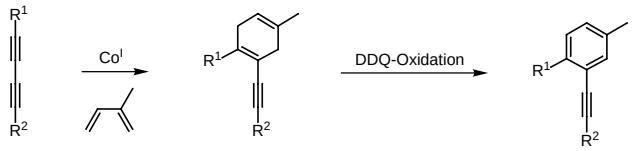
To our dismay, when sterically more hindered dienes, with substituents at the terminal position of the 1,3-butadiene substructure, were used as staring materials, very little or no conversion to the desired bis-dihydroaromatic compounds was observed. Therefore, any possible asymmetric induction by chiral phosphine ligands, to generate chiral atropisomeric biaryl compounds, has so far not been realized.

However, we then turned our attention to the neutral Diels–Alder reaction of unsymmetrical 1,3-diynes (Scheme 5) and we found that the products were mainly directed by the steric bulk of the substituents involved.

Table 3 Cobalt(I)-catalyzed Double Neutral Diels–Alder Reaction of 1,3-Diynes with 1,3-Dienes

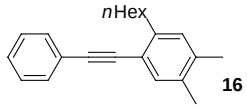
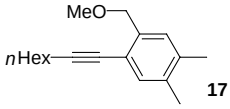
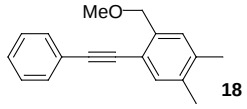
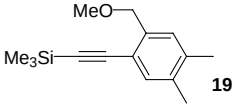
Entry	R	Diene	Product	Time	Yield (%)
1	*n*Bu		 **13**	5 h	76
2	*n*Bu		 **14**	5 h	86
3	CH_2OMe		 **15**	2 h	51[a]

[a] Combined yield of a mixture of regioisomers.



Scheme 5

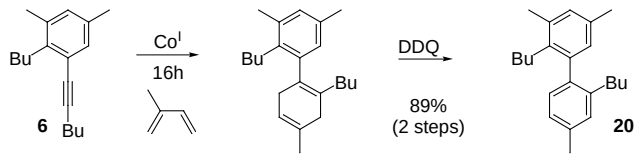
Table 4 Regioselective Neutral Diels–Alder Reaction with Unsymmetrical 1,3-Diynes

Entry	R^1	R^2	Product	Yield (%)
1	*n*-Hex	Ph	 **16**	58
2	CH_2OMe	*n*-Hex	 **17**	67[b]
3	CH_2OMe	Ph	 **18**	53
4	CH_2OMe	$SiMe_3$	 **19**	64

[a] The reaction time was in all cases 1 h.
[b] Combined yield of the regioisomers.

While the formation of **16** starting from the unfunctionalized 1,3-diyne is controlled by steric factors, for the methoxymethyl functionalized diyne (Table 4, entry 2) a regiodirecting effect of the methoxy substituent can be proposed, favoring the formation of **17** over its regioisomer. Although the regioselectivity for the formation of **17** is not excellent, (4:1 ratio of separable regioisomers), combined with sterically demanding substituents (entries 3 and 4) the regioselectivities are complete, with the products (**18** and **19**) being formed in good yield.

Since the formation of 1:2 adducts with higher substituted 1,3-dienes was not successful, the primary product can be isolated and further converted with another 1,3-diene, such as isoprene (Scheme 6), to the unsymmetrical biaryl compound **20** in excellent yield after oxidation with DDQ.



Scheme 6

In summary, we have shown that our cobalt catalyst system is able to generate polysubstituted and polyfunctionalized arene systems in good yields after DDQ oxidation of the dihydroaromatic intermediates. The selective formation of 1:1 adducts can either be controlled by steric factors, for higher substituted 1,3-diene systems, or by the use of a slight excess of the 1,3-diyne, for mono-substituted butadiene derivatives. The regioselectivity for the reaction of unsymmetrical 1,3-dienes is generally good to excellent for symmetrical as well as unsymmetrical 1,3-diynes, with the exception of methoxymethyl substituted diynes, where the reactivity is higher as for other diynes resulting in a lower degree of regioselectivity. However, the regiodirecting effect of the methoxymethyl substituent combined with other sterically bulky substituents resulted in complete regioselectivity when unsymmetrical diynes were used. While the synthesis of atropisomeric biaryl compounds could not be realized, the reaction sequence presented herein provides a method of generating highly substituted biaryl derivatives in an efficient and regioselective fashion.

NMR spectra were recorded on 200, 300 or 500 MHz instruments. IR spectra were recorded on a Nicolet 510 or a Perkin-Elmer 281 spectrometer. Electron impact mass (EI) spectra were recorded on a Varian MAT CH 7A. High resolution mass spectra were recorded on a Finnigan MAT95Q instrument. All reagents were of commercial quality, zinc iodide was dried in vacuo at 150 °C before use. Diynes were synthesized according to literature procedures.[4,5]

Co(I)-catalyzed Neutral Diels–Alder Reaction; Typical Procedure

Under a N_2 atmosphere a 10 mL Schlenk-tube was charged with the $CoBr_2$(dppe) complex (62 mg, 0.1 mmol, 10 mol%) and ZnI_2 (100 mg, 0.31 mmol). The materials were suspended in CH_2Cl_2 (3 mL), 1,3-diyne (1 mmol) and 1,3-diene (1.1 mmol) (for the generation of the 1:1 adduct) or alternately1,3-diene (2.3 mmol)(when the 1:2 adducts was synthesized). After the addition of tetrabutylammomium borohydride, the reaction mixture was stirred at r.t. The progress of the reaction was monitored by GC (1:1 adduct) or TLC (2:1 adduct). After completion of the reaction the solvent was removed in vacuo and the residue was taken up in benzene (20 mL). The mixture was filtered through cotton wool and DDQ (1.1 mmol or 2.3 mmol) was added as a solid in small portions over 5 min. After stirring for an additional 10 min and dilution with Et_2O, the mixture was washed with sat. $Na_2S_2O_3$ (0.5 M), aq NaOH solution (0.5 M, 25 mL) until the aq layer became colourless. The aq phase was extracted with Et_2O (2 × 20 mL), the combined organic layer was then dried over Na_2SO_4 and the solvents were removed in vacuo. The residue was purified by column chromatography to yield the desired product.

Indirect Electrochemical DDQ-catalyzed Oxidation

The dihydroaromatic compound was dissolved in CH_2Cl_2 (30 mL) containing tetrabutylammonium tetrafluoroborate (0.1 M) in a beaker type cell (50 mL) and a catalytic amount of DDQ (10–20 mol%) was added. The mixture was electrolyzed at constant current (100 mA) using two glassy carbon electrodes (8 cm^2 each) until 2.0 F/mol were consumed. The products were then isolated as described above.

Trimethyl{1,4,5-metheno-3-[(trimethylsilyl)ethynyl]-1,3a,4,5,6,6a-hexahydro-2-pentalenyl}silane (1)
Eluent: pentane; colorless solid; yield: 217 mg (0.76 mmol, 76%).

IR (KBr): 2957 (s), 2136 (w), 1739 (s), 1681 (m), 1415 (m), 1248 (s), 844 (s) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.15 [s, 9 H, $Si(CH_3)_3$], 0.17 [s, 9 H, $Si(CH_3)_3$], 1.14–1.19 (m, 1 H), 1.37–1.42 (m, 1 H), 1.50–1.53 (m, 2 H), 1.63–1.66 (m, 1 H), 1.94 (br s, 1 H), 2.66–2.70 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –1.1, –0.1, 22.1, 22.9, 24.9, 32.6, 53.2, 55.6, 56.6, 99.0, 104.4, 137,9, 157.6.

MS (EI): *m/z* (%) = 286 (M^+,99), 271 (24), 212 (22), 197 (100), 183 (31), 73 (34).

HRMS: (*m/z*) calcd for $C_{17}H_{26}Si_2$, 286.1573; found, 286.1577.

1,2,4-Metheno-5-phenyl-6-(phenylethynyl)-1,2,3,3a,4,6a-hexahydropentalene (2)
Eluent: pentane–Et_2O, 100:1; colorless solid; yield: 241 mg. (0.82 mmol, 82%).

IR (KBr): 3056 (s), 2928 (s), 2859 (s), 2190 (m), 1680 (m), 1598 (m), 1486 (s), 1265 (s), 769 (s), 754 (s), 690 (s) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.52–1.56 (m, 2 H), 1.60–1.65 (m, 2 H), 1.76–1.80 (m, 1 H), 2.21 (m, 1 H), 2.91 (m, 1 H), 3.14 (m, 1 H), 7.20–7.47 (m, 8 H, Ar), 7.82–7.87 (m, 2 H, Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.6, 23.3, 24.7, 51.6, 54.7, 55.3, 88.3, 96.5, 122.4, 124.0, 126.4, 127.3, 128.2, 128.3, 131.3, 136.2, 151.6.

MS (EI): *m/z* (%) = 294 (M^+,100), 278 (20), 265 (13), 252 (13), 215 (49), 202 (22), 138 (7), 91 (6).

HRMS: (*m/z*) calcd for $C_{23}H_{18}$, 294.1409; found, 294.1406.

1,2,4-Metheno-5-(methoxymethyl)-6-(3-methoxy-1-propynyl)-1,2,3,3a,4,6a-hexahydropentalene (3)
Eluent: pentane–Et_2O, 20:1; colorless liquid; yield: 108 mg (0.47 mmol, 47%) unstable.

IR (KBr): 2957 (s), 2930 (s), 2859 (s), 2225 (w), 1665 (w), 1456 (m), 1107 (m) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.33–1.47 (m, 2 H), 1.48–1.53 (m, 2 H), 1.68–1.73 (m, 1 H), 2.00–2.05 (m, 1 H), 2.63–2.67 (m, 1 H), 2.69–2.73 (m, 1 H), 3.28 (s, 3 H), 3.37 (s, 3 H), 4.07 (d, 1 H, *J* = 12.4 Hz), 4.14 (d, 1 H, *J* = 12.4 Hz), 4.25 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.5, 22.7, 25.3, 32.4, 50.1, 53.6, 55.9, 57.5, 57.8, 60.6, 68.9, 85.1, 91.0, 125.8, 152.8.

MS (EI): *m/z* (%) = 230 (M^+,70), 215 (5), 199 (12), 165 (59), 153 (100), 141 (41), 128 (37), 115 (45), 91 (21), 77 (16).

HRMS: (*m/z*) calcd for $C_{15}H_{18}O_2$, 230.1307; found, 230.1310.

1-Butyl-2-(1-hexynyl)-4-methylbenzene (4)
Eluent: pentane; colorless liquid; yield: 207 mg (0.91 mmol, 91%).

IR (KBr): 2957 (s), 2930 (s), 2226 (w), 1610 (w), 1496 (m), 1465 (m), 1387 (w), 883 (w), 816 (m) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.93 (t, 3 H, *J* = 7.3 Hz, CH_3), 0.94 (t, 3 H, *J* = 7.2 Hz, CH_3,), 1.30–1.64 (m, 8 H, CH_2,), 2.26 (s, 3 H, C*H*$_3$Ar), 2.43 (t, 2 H, *J* = 6.3 Hz, $CH_2C{\equiv}C$), 2.71 (t, 2 H, *J* = 7.5 Hz, C*H*$_2$Ar), 6.98 (dd, 1 H, *J* = 7.8, 1.2 Hz, Ar), 7.04 (d, 1 H, *J* = 7.8 Hz, Ar), 7.18 (1 H, br s, Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 14.4, 19.6, 21.1, 22.4, 23.0, 31.4, 33.4, 34.3, 79.8, 93.6, 123.5, 128.7, 128.9, 133.0, 135.2, 142.1.

MS (EI): *m/z* (%) = 228 (M^+, 57), 185 (49), 157 (28), 143 (100), 128 (39), 115 (17).

HRMS: (*m/z*) calcd for $C_{17}H_{24}$, 228.1878; found, 228.1869.

1-Butyl-2-(1-hexynyl)-4,5-dimethylbenzene (5)
Eluent: pentane; colorless liquid; yield: 237 mg (0.98 mmol, 98%).

IR (KBr): 2958 (s), 2931 (s), 2859 (s), 2229 (w), 1613 (w), 1455 (s), 881 (m), 801 (m) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.93 (t, 3 H, *J* = 7.1 Hz, CH_3), 0.94 (t, 3 H, *J* = 7.1 Hz, CH_3), 1.28–1.64 (m, 8 H, CH_2), 2.16 (s, 3 H, C*H*$_3$Ar), 2.20 (s, 3 H, C*H*$_3$Ar), 2.41 (t, 2 H, *J* = 6.9 Hz, $CH_2C{\equiv}C$), 2.67 (t, 2 H, *J* = 7.7 Hz, C*H*$_2$Ar), 6.92 (s, 1 H, Ar), 7.14 (s, 1 H, Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 14.4, 19.4, 19.6, 20.0, 22.4, 23.0, 31.4, 33.5, 34.3, 79.8, 92.9, 120.9, 130.4, 133.4, 133.9, 136.4, 142.5.

MS (EI): *m/z* (%) = 242 (M^+, 88), 199 (61), 171 (36), 157 (100), 142 (34), 119 (19), 77 (4).

HRMS: (*m/z*) calcd for $C_{18}H_{26}$, 242.2035; found, 242.2044.

2-Butyl-1-(1-hexynyl)-3,5-dimethylbenzene (6)
Eluent: pentane; colorless liquid; yield: 203 mg (0.84 mmol, 84%).

IR (KBr): 2956 (s), 2931 (s), 1606 (w), 1466 (m), 1230 (m), 855 (w) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.93 (t, 3 H, *J* = 7.2 Hz, CH_3), 0.94 (t, 3 H, *J* = 7.3 Hz, CH_3), 1.34–1.63 (m, 8 H, CH_2), 2.21 (s, 3 H, C*H*$_3$Ar), 2.25 (s, 3 H, C*H*$_3$Ar), 2.42 (t, 2 H, *J* = 7.0 Hz, $CH_2C{\equiv}C$), 2.73 (t, 3 H, *J* = 7.8 Hz, C*H*$_2$Ar), 6.85 (s, 1 H, Ar), 7.03 (s, 1 H, Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.3, 16.6, 21.9, 22.2, 23.3, 24.6, 25.8, 33.5, 33.6, 34.6, 82.6, 95.2, 126.2, 133.1, 133.2, 137.2, 138.3, 142.8.

MS (EI): *m/z* (%) = 242 (M^+, 100), 199 (84), 185 (14), 171 (24), 157 (100), 142 (28), 128 (14).

HRMS: (*m/z*) calcd for $C_{18}H_{26}$, 242.2035; found, 242.2022.

1-Butyl-2-(1-hexynyl)-3,4-dimethylbenzene (7)
Eluent: pentane; colorless liquid; yield: 210 mg (0.87 mmol, 87%).

IR (KBr): 2957 (s), 2859 (s), 2872 (s), 2225 (w), 1594 (w), 1456 (s), 814 (m) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.93 (t, 3 H, *J* = 7.2 Hz, CH_3), 0.95 (t, 3 H, *J* = 7.2 Hz, CH_3), 1.31–1.66 (m, 8 H, CH_2), 2.22 (s, 3 H, C*H*$_3$Ar), 2.36 (s, 3 H, C*H*$_3$Ar), 2.49 (t, 2 H, *J* = 6.8 Hz, $CH_2C{\equiv}C$), 2.72 (t, 3 H, *J* = 7.8 Hz, C*H*$_3$Ar), 6.89 (d, 1 H, *J* = 7.7 Hz, Ar), 6.96 (d, 1 H, *J* = 7.7 Hz, Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 14.3, 18.0, 19.7, 20.5, 22.4, 23.1, 31.5, 33.3, 35.1, 78.8, 98.1, 123.7, 125.9, 128.9, 133.9, 138.7, 142.8.

MS (EI): *m/z* (%) = 242 (M^+,59), 199 (54), 185 (10), 171 (22), 157 (100), 141 (31), 128 (16).

HRMS: (*m/z*) calcd for $C_{18}H_{26}$, 242.2035; found, 242.2021.

4-Butyl-3-(1-hexynyl)phenol (8)
Eluent: pentane–Et_2O, 10:1; colorless oil; yield: 184 mg (0.8 mmol, 80%).

IR (KBr): 3369 (s), 2957 (s), 2872 (s), 2228 (w), 1656 (w), 1465 (s), 1290 (s), 1175 (s), 870 (m), 819 (m) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.92 (t, 3 H, *J* = 7.3 Hz, CH_3), 0.94 (t, 3 H, *J* = 7.1 Hz, CH_3), 1.29–1.63 (m, 8 H, CH_2), 2.42 (t, 2 H, *J* = 6.9 Hz, $CH_2C{\equiv}C$), 2.66 (t, 2 H, *J* = 7.7 Hz, CH_2Ar), 4.83 (br s, 1 H, *H*OAr), 6.67 (dd, 1 H, *J* = 8.3, 2.7 Hz, Ar), 6,84 (d, 1 H, *J* = 2.7 Hz, Ar), 6.98 (d, 1 H, *J* = 8.3 Hz, Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.9, 12.9, 18.1, 20.9, 21.5, 29.8, 32.0, 32.4, 78.1, 92.6, 114.0, 117.5, 123.2, 128.6, 136.0, 152.1.

MS (EI): *m/z* (%) = 230 (M^+, 40), 187 (100), 145 (61), 127 (19), 115 (30), 77 (7).

HRMS: (*m/z*) calcd for $C_{16}H_{22}O$, 230.1671; found, 230.1660.

Tetrahydro-2-{[3-(5-methyl-2-{[(tetrahydro-2*H*-pyran-2-yl)-oxy]methyl}phenyl)-2-propynyl]oxy}-2*H*-pyran (10) and Tetrahydro-2-{[3-(4-methyl-2-{[(tetrahydro-2*H*-pyran-2-yl)oxy]methyl}phenyl)-2-propynyl]oxy}-2*H*-pyran (Regioisomer of 10)
The reaction gave an inseperable mixture of regioisomers in a ratio of ~5: 2 in a combined yield: of 183 mg, (0.53 mmol, 53%).

Eluent: pentane–Et_2O 20:1; colorless oil.

IR (KBr): 2942 (s), 2870 (s), 2224 (s), 1610 (w), 1453 (m), 1441 (m), 1348 (m), 1118 (s), 1026 (s), 870 (m), 816 (m) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) major isomer: δ = 1.38–1.97 (m, 12 H, C*H*$_2$THP), 2.29 (s, 3 H, CH_3), 3.37–3.67 (m, 2 H, C*H*$_2$OTHP), 3.75–4.02 (m, 2 H, C*H*$_2$OTHP), 4.50 (s, 2 H, C*H*$_2$Bn), 4.63 (d, 1 H, *J* = 12.7 Hz, $CH_2C{\equiv}C$), 4.72–4.78 (m, 1 H, C*H*O_2THP), 4.84 (d, 1 H, *J* = 12.7 Hz, $CH_2C{\equiv}C$), 4.88–4.94 (m, 1 H, C*H*O_2THP), 7.12 (d, 1 H, *J* = 7.8 Hz, Ar), 7.27 (br s, 1 H, Ar), 7.34 (d, 1 H, *J* = 7.8 Hz, Ar).

Additional signals of minor isomer: δ = 2.34 (s, C*H*$_3$Ar), 4.49 (s, C*H*$_2$Ar), 7.02 (d, *J* = 7.8 Hz, Ar), 7.28 (br s, Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.1, 19.3, 20.8, 21.5, 25.4, 25.5, 30.3, 30.6, 54.7, 62.1, 67.2, 67.4, 83.6, 83.7, 88.8, 89.1 96.7, 96.8, 98.4, 98.5, 118.3, 121.2, 127.6, 127.9, 128.2, 129.4, 132.3, 132.9, 136.8, 137.4, 138.7, 140.2.

MS (EI): *m/z* (%) = Major isomer: 344 (M^+, 0.1), 242 (11), 229 (13), 159 (68), 141 (24), 129 (21), 115 (24), 85 (100). Minor isomer: 344 (M^+, 0.1), 242 (16), 229 (16), 176 (7), 159 (87), 141 (25), 129 (24), 115 (27), 85 (100).

HRMS: (*m/z*) calcd for $C_{21}H_{28}O_4$ (major isomer), 344.1988; found 344.2013. HRMS: (*m/z*) calcd for $C_{21}H_{28}O_4$ (minor isomer), 344.1988; found 344.2018.

2-[4-(Benzyloxy)-1-butynyl]-1-[2-(benzyloxy)ethyl]-4-methylbenzene (11) and 1-[4-(Benzyloxy)-1-butynyl]-2-[2-(benzyloxy)ethyl]-4-methylbenzene (Regioisomer of 11)
The reaction gave an inseparable mixture of two regioisomers in a ratio of ~4:1 in a combined yield: of 271 mg (0.74 mmol, 74%).

Eluent: pentane–Et_2O, 10:1; colorless liquid.

IR (KBr): 3063 (m), 2962 (m), 2858 (m), 1609 (w), 1495 (m), 1261 (s), 1095 (s), 801 (s), 734 (m), 696 (m) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) major isomer: δ = 2.40 (s, 3 H, C*H*$_3$Ar), 2.72 (t, 2 H, *J* = 7.1 Hz, $CH_2C{\equiv}C$), 3.04 (t, 2 H, *J* = 7.3 Hz, C*H*$_2$Ar), 3.67 (t, 2 H, *J* = 7.1 Hz, BnOC*H*$_2$), 3.68 (t, 2 H, *J* = 7.2 Hz, BnOC*H*$_2$), 4.50 (s, 2 H, C*H*$_2$Bn), 4.57 (s, 2 H, C*H*$_2$Bn), 7.01 (d, 1 H, *J* = 8.1 Hz, Ar), 7.11 (d, 1 H, *J* = 8.1 Hz, Ar), 7.20 (br s, 1 H, Ar), 7.27–7.40 (m, 10 H, Ar).

Additional signals of minor isomer: δ = 2.30 (s, C*H*$_3$Ar), 4.51 (s, C*H*$_2$Bn), 6.97 (d, *J* = 8.3 Hz, Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.8, 21.0, 34.5, 68.7, 70.4, 72.8, 73.0, 80.1, 89.9, 126.9, 127.5, 127.6, 127.7, 128.3, 128.4, 128.7, 129.3, 130.2, 132.1, 132.8, 133.7, 135.6, 137.5, 138.2, 138.6.

MS (EI): *m/z* (%) = 384 (M^+, 0.1), 293 (23), 275 (7), 247 (8), 219 (13), 187 (7), 142 (31), 115 (10), 91 (100).

HRMS: (*m/z*) calcd for $C_{27}H_{28}O_2$, 384.2089; found, 384.2089.

4-(Trimethylsilyl)-3-[(trimethylsilyl)ethynyl]phenol (12)
Eluent: pentane–Et_2O, 10:1; colorless oil; yield: 178 mg (0.68 mmol, 68%).

IR (KBr): 3391 (m), 2958 (m), 2154 (m), 1589 (m), 1249 (s), 842 (s), 760 (m) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.24 [s, 9 H, $Si(CH_3)_3$], 0.33 [s, 9 H, $Si(CH_3)_3$), 5.05 (s, 1 H, O*H*Ar], 6.77 (dd, 1 H, *J* = 8.1, 2.5 Hz, Ar), 6.96 (d, 1 H, *J* = 2.5 Hz, Ar), 7.32 (d, 1 H, *J* = 8.1 Hz, Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –1.0, –0.3, 97.1, 106.2, 115.2, 119.6, 129.7, 134.1, 135.6, 155.7.

MS (EI): *m/z* (%) = 262 (M^+,20), 247 (100), 231 (10), 161 (7), 116 (18), 73 (31).

HRMS: (*m/z*) calcd for $C_{14}H_{22}OSi_2$, 262.1209; found, 262.1191.

2,2'-Dibutyl-4,5′-dimethyl-1,1′-biphenyl (13)
Eluent: pentane–Et_2O, 50:1; colorless liquid, yield: 223 mg (0.76 mmol, 76%).

IR (KBr): 2927 (s), 2871 (s), 2859 (s), 1612 (w), 1488 (m), 1456 (m), 887 (w), 820 (m) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.77 (t, 3 H, *J* = 7.2 Hz, C*H*$_3$), 1.11–1.24 (m, 4 H, C*H*$_2$Me), 1.34–1.46 (m, 4 H, CH_2), 2.22–2.40 (m, 4 H, 2 C*H*$_2$Ar), 2.31 (s, 3 H, C*H*$_3$Ar), 2.37 (s, 3 H, C*H*$_3$Ar), 6.89–7.16 (m, 6 H, Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2, 14.3, 21.3, 21.6, 22.9, 22.9, 32.7, 33.0, 33.4, 33.5, 126.2, 128.0, 128.9, 129.7, 130.1, 131.2, 134.7, 136.8, 138.6, 140.8, 141.3.

MS (EI): *m/z* (%) = 294 (M^+, 82), 251 (23), 237 (25), 209 (15), 195 (100), 180 (19), 165 (15).

HRMS: (*m/z*) calcd for $C_{22}H_{30}$, 294.2348; found, 294.2363.

2,2'-Dibutyl-4,4′,5,5′-tetramethyl-1,1′-biphenyl (14)
Eluent: pentane–Et_2O, 50:1; colorless liquid; yield: 276 mg (0.86 mmol, 86%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.77 (t, 6 H, *J* = 7.2 Hz, CH_3), 1.12–1.24 (m, 4 H, C*H*$_2$Me), 1.33–1.45 (m, 4 H, CH_2), 2.17–2.37 (m, 4 H, C*H*$_2$Ar), 2.21 (s, 6 H, C*H*$_3$Ar), 2.28 (s, 6 H, C*H*$_3$Ar), 6.84 (s, 2 H, Ar), 7.02 (s, 2 H, Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.3, 19.6, 19.9, 22.9, 32.6, 33.6, 130.2, 131.7, 133.3, 135.2, 138.3, 138.9.

IR (KBr): 2956 (s), 2871 (s), 2860 (s), 1691 (w), 1490 (m), 1454 (s), 1105 (s), 886 (w) cm^{-1}.

MS (EI): *m/z* (%) = 322 (M^+, 72), 279 (11), 265 (17), 223 (100), 208 (26), 193 (19).

HRMS: (*m/z*) calcd for $C_{24}H_{34}$, 322.2661; found, 322.2660.

1-Hexyl-4,5-dimethyl-2-(phenylethynyl)benzene (16)
Eluent: pentane; colorless liquid; yield: 89 mg (0.30 mmol, 58%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.87 (t, 3 H, *J* = 7.1 Hz, CH_3), 1.26–1.42 (m, 6 H, CH_2), 1.62–1.72 (m, 2 H, CH_2), 2.22 (s, 3 H, C*H*$_3$Ar), 2.25 (s, 3 H, C*H*$_3$Ar), 2.78 (t, 2 H, *J* = 7.5 Hz, C*H*$_2$Ar), 6.98 (s, 1 H, Ar), 7.28 (s, 1 H, Ar), 7.30–7.53 (m, 5 H, Ph).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 19.1, 19.8, 22.6, 29.3, 31.0, 31.8, 24.3, 88.7, 91.8, 119.7, 123.9, 127.8, 128.3, 130.2, 131.4, 133.1, 133.8, 137.15, 142.5.

IR (KBr): 2954 (s), 2925 (s), 2856 (s), 2210 (w), 1597 (w), 1497 (m), 1453 (m), 880 (m), 754 (s), 689 (s).

MS (EI): *m/z* (%) = 290 (M^+, 100), 233 (34), 219 (66), 203 (35), 189 (18).

HRMS: (*m/z*) calcd for $C_{22}H_{26}$, 290.2034; found, 290.2036.

1-(Methoxymethyl)-4,5-dimethyl-2-(1-octynyl)-benzene (17)
The reaction gave a mixture of **17** and its regioisomer in a combined yield: of 67% (172 mg), from which pure **17** (41%) and its regioisomer (12%) could be separated by extended chromatography.

Eluent: pentane–Et_2O, 50:1; colorless liquid; yield: 105 mg (0.41 mmol, 41%).

IR (KBr): 2927 (s), 2226 (w), 1596 (w), 1453 (s), 1118 (s), 1091 (s), 881 (m) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.89 (t, 3 H, *J* = 7.2 Hz, CH_3), 1.28–1.64 (m, 8 H, CH_2), 2.19 (s, 3 H, C*H*$_3$Ar), 2.22 (s, 3 H, C*H*$_3$Ar), 2.41 (t, 2 H, *J* = 7.0 Hz, C*H*$_2$C≡C), 3.40 (s, 3 H, CH_3O), 4.54 (s, 2 H, OC*H*$_2$Ar), 7.15 (s, 2 H, Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 19.2, 19.5, 19.6, 22.5, 28.6, 28.8, 31.3, 58.3, 72.5, 78.3, 93.7, 120.0, 128.8, 133.0, 135.5, 136.4, 136.9.

MS (EI): *m/z* (%) = 258 (M^+,60), 243 (22), 229 (9), 197 (54), 187 (100), 173 (24), 157 (65), 141 (28), 128 (23), 115 (15).

HRMS: (*m/z*) calcd for $C_{18}H_{26}O$, 258.1984; found, 258.1962.

1-Hexyl-2-(3-methoxy-1-propynyl)-4,5-dimethyl-benzene (Regioisomer of 17)
Eluent: pentane– Et_2O, 50:1; colorless liquid; yield: 32 mg (0.12 mmol, 12%).

IR (KBr): 2926 (s), 2857 (s), 2223 (w), 2182 (w), 1609 (w), 1453 (s), 1110 (s), 882 (m) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.87 (t, 3 H, *J* = 7.1 Hz, CH_3), 1.22–1.65 (m, 8 H, CH_2), 2.17 (s, 3 H, C*H*$_3$Ar), 2.22 (s, 3 H, C*H*$_3$Ar), 2.68 (t, 3 H, *J* = 7.6 Hz, C*H*$_2$Ar), 3.44 (s, 3 H, CH_3O), 4.34 (s, 3 H, MeOC*H*$_2$), 6.94 (s, 1 H, Ar), 7.18 (s, 1 H, Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 19.0, 19.7, 22.6, 29.2, 30.9, 31.7, 34.1, 57.4, 60.5, 85.5, 87.1, 119.1, 130.1, 133.4, 133.7, 137.2, 142.5.

MS (EI): *m/z* (%) = 258 (M^+,36), 169 (21), 157 (100), 141 (29), 128 (19), 115 (14).

HRMS: (*m/z*) calcd for $C_{18}H_{26}O$, 258.1984; found, 258.1961.

1-(Methoxymethyl)-4,5-dimethyl-2-(phenylethynyl)benzene (18)
Eluent: pentane–Et_2O, 15:1; colorless liquid; yield: 132 mg, (0.53 mmol, 53%, unstable).

IR (KBr): 2974 (s), 2921 (s), 2212 (w), 1776 (s), 1691 (s), 1598 (s), 1497 (s), 1450 (s), 882 (m), 756 (s), 691 (s) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.23 (s, 3 H, C*H*$_3$Ar), 2.27 (s, 3 H, C*H*$_3$Ar), 3.45 (s, 3 H, CH_3O), 4.64 (s, 2 H, MeOC*H*$_2$), 7.22–7.54 (m, 7 H, Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.2, 19.8, 58.4, 72.5, 87.9, 119.2, 123.5, 128.1, 128.3, 128.5, 129.1, 131.4, 131.6, 133.0, 135.8, 137.2, 137.5.

MS (EI): *m/z* (%) = 250 (M^+, 35), 235 (100), 219 (12), 202 (17), 192 (21), 178 (6), 165 (6), 115 (5).

{[2-(Methoxymethyl)-4,5-dimethylphenyl]ethynyl}(trimethyl)silane (19)
Eluent: pentane–Et_2O, 50:1; colorless liquid; yield: 157 mg (0.64 mmol, 64%).

IR (KBr): 2959 (s), 2862 (s), 2156 (s), 1609 (w), 1489 (s), 1452 (s), 1247 (s), 1117 (s), 842 (s) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.24 [s, 9 H, $Si(CH_3)_3$], 2.19 [s, 3 H, C*H*$_3$Ar], 2.24 (s, 3 H, C*H*$_3$Ar), 3.41 (s, 3 H, CH_3O), 4.56 (s, 2 H, MeOC*H*$_2$), 7.17 (s, 1 H, Ar), 7.23 (s, 1 H, Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.1, 19.7, 58.4, 72.4, 97.5, 103.1, 119.2, 129.0, 133.2, 135.6, 137.6, 137.6.

MS (EI): *m/z* (%) = 246 (M^+, 36), 231 (55), 201 (100), 173 (34), 157 (21), 73 (51).

HRMS: (*m/z*) calcd for $C_{15}H_{22}OSi$ 246.1440; found 246.1455.

2,2'-Dibutyl-3,4′,5-trimethyl-1,1′-biphenyl (20)
Eluent: pentane–Et_2O, 50:1; colorless liquid; yield: 274 mg (0.89 mmol, 89%).

IR (KBr): 2956 (s), 2871 (s), 2859 (s), 1611 (w), 1465 (s), 857 (m), 822 (m) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.75 (t, 3 H, *J* = 7.1 Hz, CH_3), 0.81 (t, 3 H, *J* = 7.1 Hz, CH_3), 1.10–1.50 (m, 8 H, CH_2), 2.17–2.47 (m, 4 H, C*H*$_2$Ar), 2.30 (s, 3 H, C*H*$_3$Ar), 2.37 (s, 3 H, C*H*$_3$Ar), 2.40 (s, 3 H, C*H*$_3$Ar), 6.77 (br s, 1 H, Ar), 6.98 (br s, 1 H, Ar), 7.01 (s, 1 H, Ar), 7.02 (s, 1 H, Ar), 7.10 (s, 1 H, Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7, 13.9, 19.8, 20.8, 21.3, 22.6, 23.0, 29.7, 32.0, 32.7, 33.0, 125.7, 128.7, 129.2, 129.7, 129.9, 134.0, 135.9, 136.2, 136.4, 138.8, 140.2, 141.2.

MS (EI): *m/z* (%) = 308 (M^+,74), 293 (5), 265 (40), 251 (23), 223 (8), 209 (100), 194 (23), 179 (16), 165 (4).

HRMS: (*m/z*) calcd for $C_{23}H_{32}$ 308.2504; found 308.2518.

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