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Synthesis of a trisphenol alkyne, towards clickable tripods for graphene functionalization

Mohammad Danish Alhindi[a, b]; Ahmed Mehdi Debela[a], Mayleen Scharre[a], Thomas Alava[b]* and Gad Fuks[a]*

a Centre de recherches Insulaires et Observatoire de l'Environnement, Université de Perpignan Via Domitia. UAR 3278, UPVD-CNRS-EPHE-PSL Labex CORAIL, France.
b Université Grenoble Alpes, CEA, LETI, 38000 Grenoble, France.

Email: gad.fuks@univ-perp.fr ; thomas.alava@cea.fr

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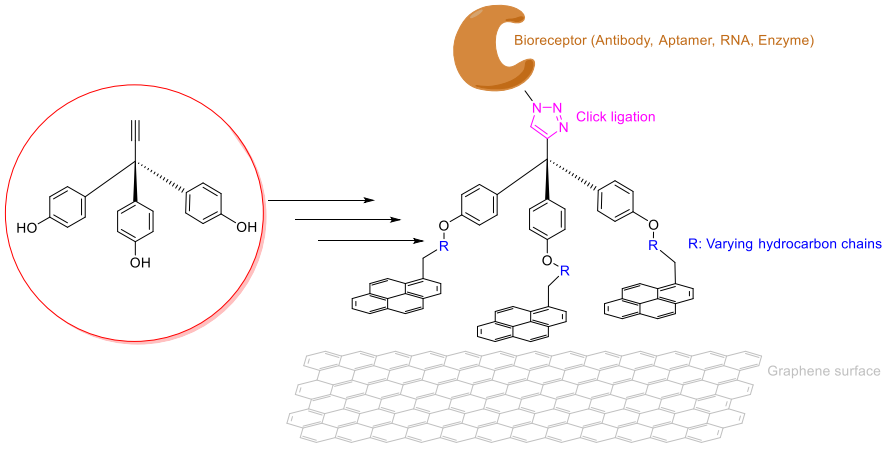
Abstract

In the framework of a project aiming at improving the functionalization of graphene used in Single Graphene Field Effect Transistors (SGFET) biosensors, we have developed a synthetic route to access 4,4',4''-(prop-2-yne-1,1,1-triyl)triphenol which is a key intermediate that can be further functionalized with different pyrene feet leading to clickable tripods. An original method for deprotection of benzyl ethers has been used since the classical hydrogenolysis method led to an undesired compound.



Keywords: TRIPOD, SGFET, surface functionalization, synthon

Introduction

Interfacing graphene with biomolecules is an important challenge if one wants to combine graphene's exceptional properties[1] (transparency, conductivity) with the functions offered by biomolecules such as recognition in order to build biosensors[2] or diagnostic devices[3]. Direct adsorption of biomolecules on graphene has been reported but the extreme hydrophobicity of graphene could lead to denaturation and thus loss of function[4]. Covalent modification strategies have been developed but since Single Layer Graphene (SLG) is atomically thin, it modifies graphene's properties[5]. To overcome this limitation, non-covalent grafting methods have been explored. Taking advantage of strong hydrophobic interactions, the use of pyrene moieties (**PBASE**, **PMAL**, **PBA**) has emerged as a promising strategy to graft biomolecules with free amine residues [6-10] (Figure 1). For example, Myshin et al. have optimized the construction of SGFET biosensors through a systematic comparison of these pyrene anchoring units working on cardiac troponin 1 as a model analyte[11].

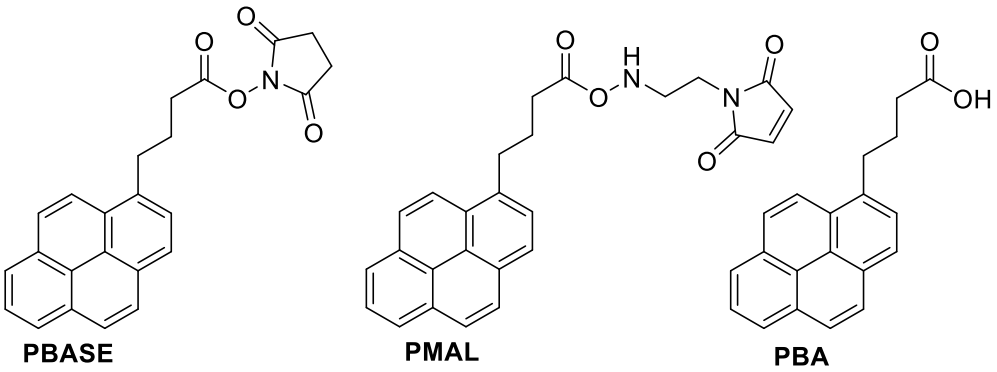
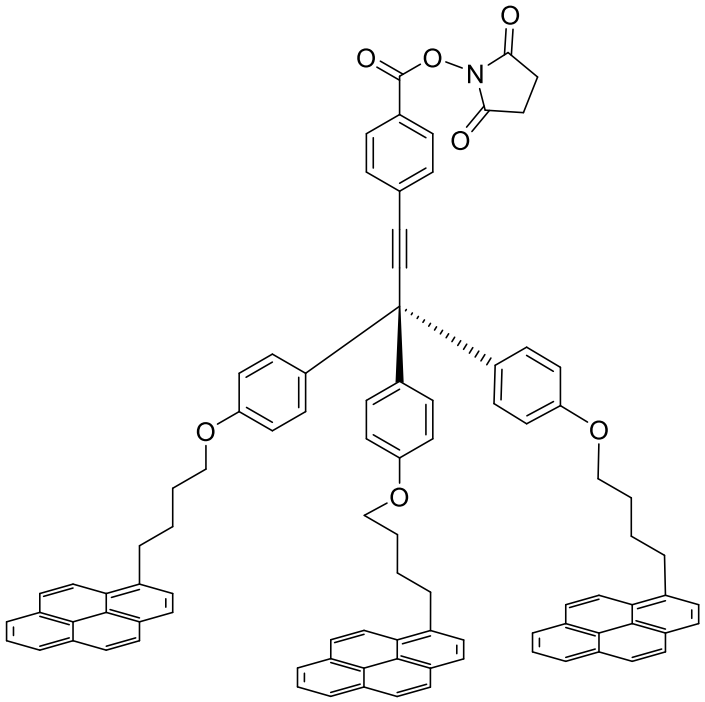
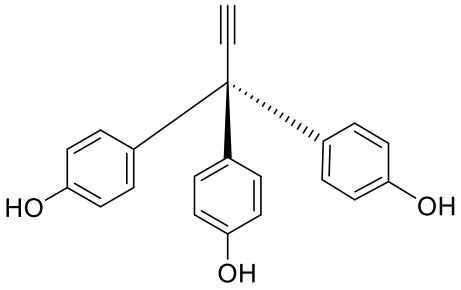


Figure 1: Structures of monodentate pyrene anchoring units

However, the use of these ligands could sometimes lead to disappointing results in terms of grafting density, monolayer viability, loss of functionality. In 2013, Alava et al. reported that a tripodal **T1** (Figure 2) linker could serve as anchoring unit for an anti-*E. Coli* antibody which could retain its activity while adsorbed on graphene (the control experiment using **PBASE** showed poor recognition ability).[12] This tripodal linker anchors on graphene surfaces thanks to the strong hydrophobic interactions of three pyrene feet and at the other end of the molecule, a NHS ester can be linked to any free amine residue present on the biomolecule of interest. Although **T1** has demonstrated superior monolayer stability than monovalent pyrenes,[13] its adoption by the graphene community has been hindered by four intrinsic limitations. First of all, in some applications, biomolecules without free amines can be used (aptamers for instance).[14] Secondly, the presence of the NHS ester renders this tripodal linker susceptible to hydrolysis which complicates the storage of the linker[15].



Tripod T1



Key tripodal intermediate 5

Figure 2: Structure of Tripod T1 as well as the tripodal intermediate reported here **5.**

Moreover, the synthetic pathway to access **T1** involves harsh conditions with the use of the strongly acidic boron tribromide as a demethylation reagent. Here we present the first steps towards the facilitated (boron tribromide free) synthesis of a new class of tripods that will display an alkyne termination allowing them to undergo Copper Catalyzed Alkyne Azide Cycloaddition (CuAAC). This ligation method has proven its versatility and usefulness to ligate all kinds of biomolecules with high yields in mild conditions.[16] The key intermediate **5** synthesized in this work can be tailored to access clickable tripods with various anchoring units and feet lengths while preventing storage issues linked to hydrolysis.

Results and Discussion

The retrosynthetic analysis envisioned to obtain compound **5** involved the deprotection of a benzylated tripod **4** to generate the corresponding triphenol (Figure 3). We envisioned that compound **4** could be obtained through the addition of ethynylmagnesium bromide on the chloride **3**[17] which would be generated by chlorination of alcohol **2** resulting from the addition of the Grignard reagent from **1** on dimethylcarbonate.[18] Ultimately, **1** could be obtained by the benzyl protection of *para*-bromophenol. In the reported **T1** synthesis, a methoxy group was used to protect the phenol before the Grignard step but we chose to replace it with a benzyl protection strategy since we wanted to avoid the boron tribromide demethylation step. Indeed, the use of boron tribromide is inconvenient as it is a highly reactive and hazardous reagent. Moreover, in our attempts to reproduce this ether cleavage step we faced numerous reproducibility issues.

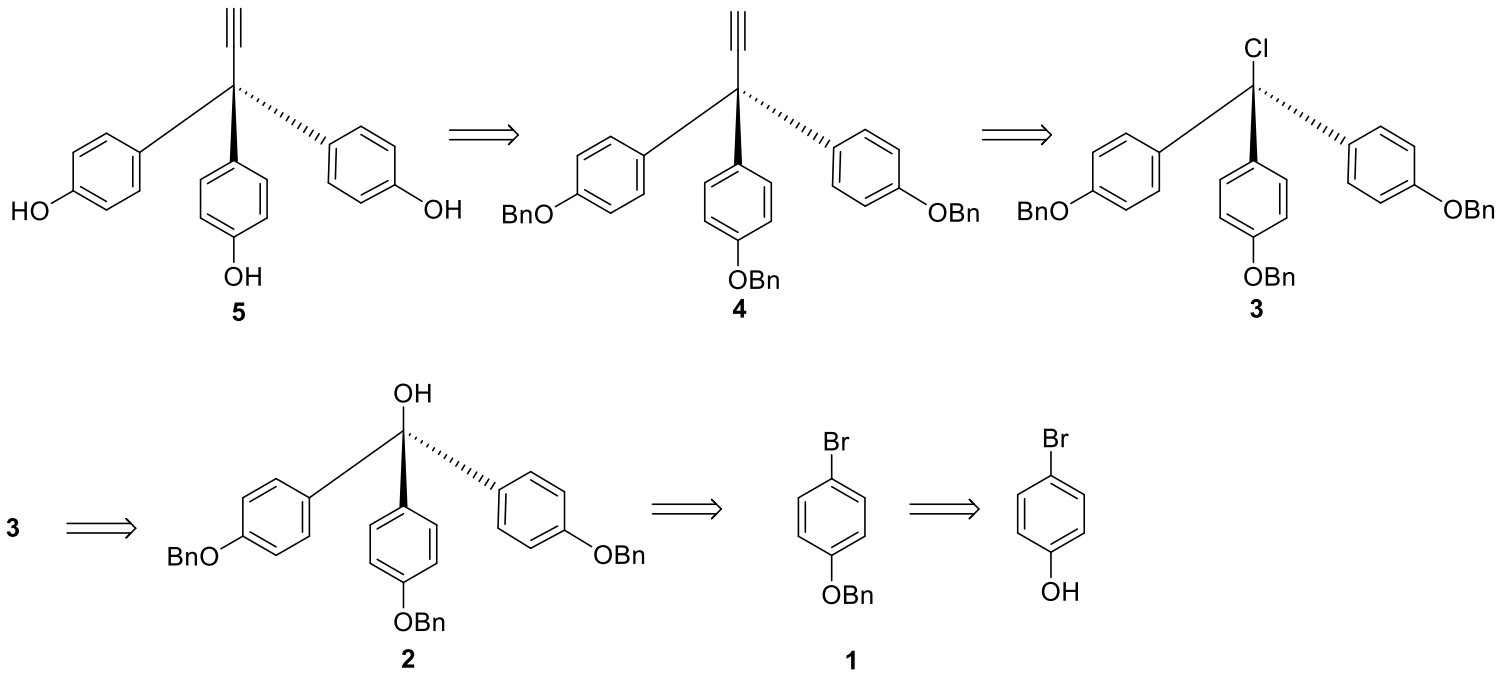
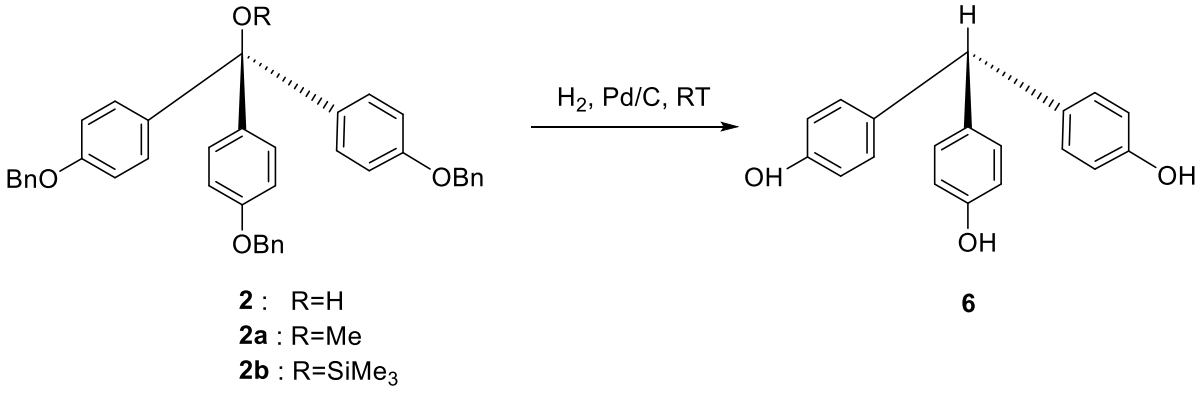


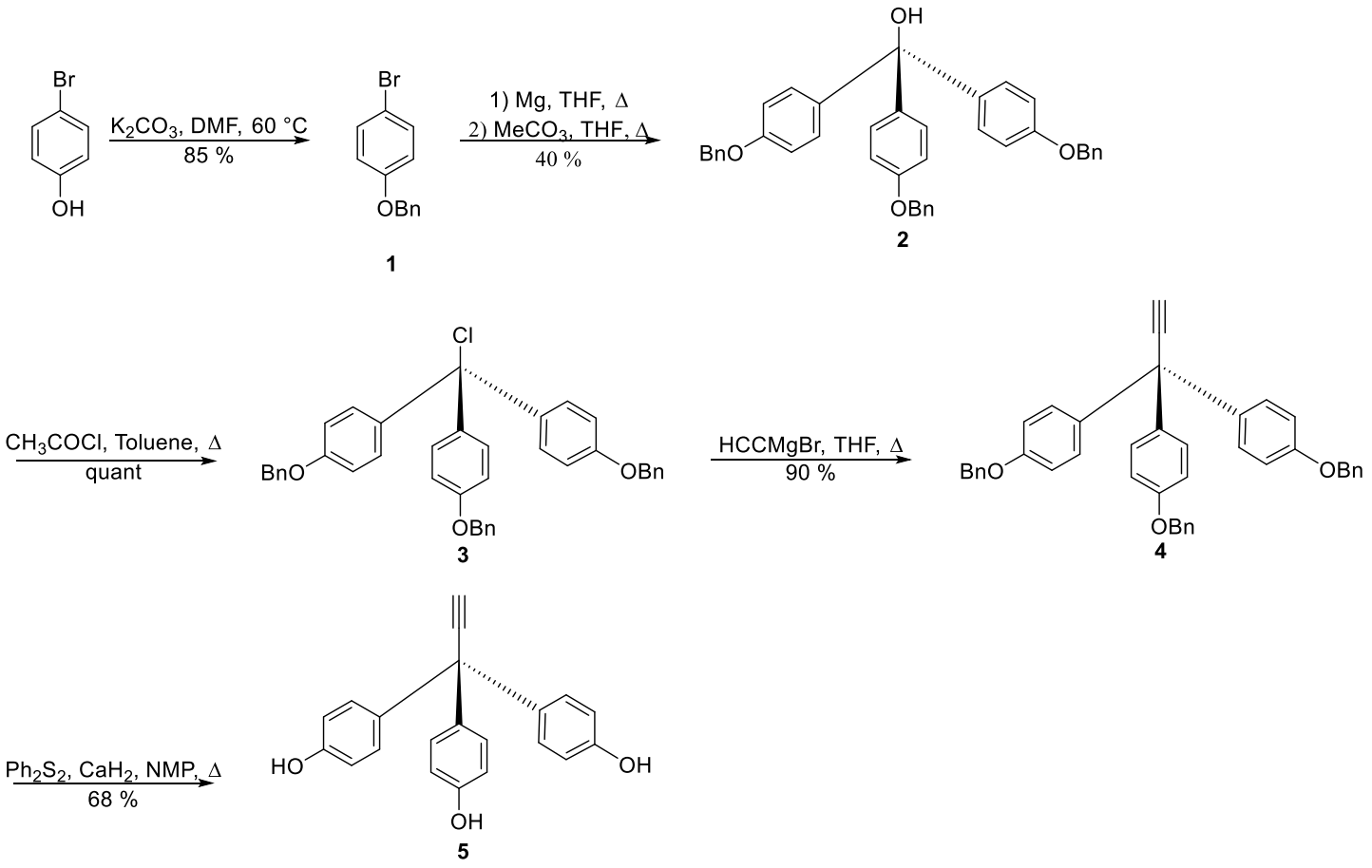
Figure 3: Retrosynthetic analysis to obtain compound **5**

The synthesis began with the protection of *para*-bromophenol using benzyl chloride and potassium carbonate in DMF affording compound **1** in 85 % yield. This benzyl ether was then reacted with magnesium turnings in THF to obtain a Grignard reagent that was added to dimethylcarbonate to yield compound **2** with 40% yield. We then wanted to cleave the benzyl groups before converting the alcohol to an alkyne. To do so, we subjected **2** to hydrogenolysis conditions using H_2 and Pd/C. Unfortunately, these conditions were efficient in removing the benzyl groups but it also led to the undesired reduction of the alcohol to compound **6** which presented a C-H bond instead of the desired C-OH bond. This kind of reduction of a tertiary benzylic alcohol using hydrogen has already been reported on similar compounds in the literature.[19]To circumvent this, we tried to protect the alcohol function from **2** before the reduction step. We converted the alcohol to a methoxy group (**2a**) or a trimethylsilylether (**2b**) but these two protecting groups never prevented the undesired reduction to compound **6** when subjected to hydrogenolysis conditions (Scheme 1).



Scheme 1: Undesired reductions observed through Pd/C catalyzed hydrogenolysis

We then decided to convert **2** to a terminal alkyne in a two-step one-pot procedure by subjecting it first to acetyl chloride in toluene then ethynylmagnesium bromide leading to the alkyne **4** with a yield of 90% over two steps. Obviously, due to the presence of the Carbon-Carbon triple bond, we could not use the same conditions to cleave the benzyl groups. We found that a thiolate generated by the use diphenyldisulfide in combination with calcium hydride in *N*-methoxypyrrolidone could efficiently cleave the benzyl groups while preserving the terminal alkyne leading to compound **5** in 68% yield (Scheme 2). This deprotection of benzyl groups had already been reported for the cleavage of various alkyl ethers,[20] contrary to the classical hydrogenolysis it is tolerant to alkyne functions which was a key aspect in this synthesis. The use of thiolate to deprotect aryl ethers has been reported in the literature for years,[21] different methods can be used to generate thiolate anions that will cleave ethers (probably through a SN_2 mechanism[22]), this one has the practical advantage that it avoids the use of smelly thiols as well as the use of strong bases or strong reducing agents making it a mild attractive strategy.



Scheme 2: Successful synthesis of **5**

The triphenolic compound **5** represents a key intermediate in the synthesis of various tripods with different functionalization schemes in the legs. Compared to the classical tripod **T1** synthesis, it has the advantage of being easily scalable, boron tribromide free and the obtained tripods are directly linkable to biomolecules thanks to the terminal alkyne function present on top. Moreover, the absence of NHS function on the tripod will simplify the storage of the future tripodal linkers by preventing deleterious hydrolysis issues.

Conclusions

This synthetic project succeeded in the isolation of the key tripodal intermediate **5**. The synthetic strategy displayed good yields and dispensed us from the use of boron tribromide. Following this procedure, we have been able to reach a gram scale synthesis of **5** using mild conditions. Compound **5** will enable the syntheses of different tripodal linkers through click chemistry in the future. We are currently working on the anchoring of various types of pyrene anchors to this compound using Williamson conditions or Mitsunobu couplings. It will allow us to finely tune the structure of tripods depending on the envisioned applications.

Experimental Section

General. All reagents were used as received from commercial suppliers without further purification. For reactions conducted under anhydrous conditions, glassware was oven-dried, and reactions were performed under an argon atmosphere, dry solvents were bought from ACROS with the mention: extra dry over molecular sieve. Reactions were monitored by thin-layer chromatography on precoated aluminum sheets (Merck, Silica Gel 60, F254, and Macherey-Nagel, Aluminum Oxide N/UV254); detection was achieved by UV absorbance (254 nm). Column chromatography was performed on silica gel. ^{1}H and ^{13}C NMR spectra were recorded at room temperature in deuterated solvents on a JEOL 500 instrument. Chemical shifts (δ) are reported relative to TMS as the internal standard or relative to the solvent [^{1}H: δ($CDCl_3$) = 7.26 ppm, δ(acetone-d_6) = 2.05 ppm, δ(CD_3OD) = 3.31 ppm, δ(D_2O) = 4.79 ppm; ^{13}C: δ($CDCl_3$) = 77.2 ppm, δ(acetone-d_6) = 206.7&29.84 ppm, δ(CD_3OD-d_6) = 49.2 ppm, δ(DMSO) = 39.52 ppm].

Synthetic Procedures

1-(Benzyloxy)-4-bromobenzene 1. To a mixture of 4-bromophenol (2 g, 1.1 mmol) and K_2CO_3 (4 g, 2.9 mmol) in DMF (20 mL), benzyl bromide (1.6 mL, 1.39 mmol) was added, and the mixture was heated at 60 °C overnight. After cooling, the reaction mixture was poured into water and extracted with diethyl ether. The organic layer was washed with saturated aqueous NaCl, dried over $MgSO_4$, and concentrated under reduced pressure to yield a white solid. The residue was purified by chromatography (cyclohexane/EtOAc, 90 %:10 %) to afford 1-(benzyloxy)-4-bromobenzene **1**, with 85 % yield as a white solid. *R*f = 0.75 (EtOAc/cyclohexane 10%:90%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42-7.33 (m, 7H), 6.86 (d, J = 9.0 Hz, 2H), 5.03 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.87, 136.56, 132.30, 128.65, 128.12, 127.44, 116.72, 113.14, 70.24.

Tris(4-(benzyloxy)phenyl)methanol 2. In a three-neck round-bottom flask, magnesium (50 mg, 2.08 mmol) was dried under vacuum using a heat gun for 10 minutes, then placed under argon. Dry THF (2 mL) was added by syringe, and 1-(benzyloxy)-4-bromobenzene **1** (550 mg in 5 mL of dry THF, 2.09 mmol) was added dropwise. A pinch of iodine was also added. The mixture was stirred at reflux for two hours, then cooled to room temperature. Dimethyl carbonate (29 µL, 0.34 mmol) was added very slowly by syringe to the solution at room temperature. After the addition, the mixture was refluxed overnight and then cooled to room temperature. 0.1 M HCl (1 mL) and water (3 mL) were added, and the mixture was evaporated to dryness. The residue was

extracted with diethyl ether and water. The aqueous phase was separated and extracted with Et_2O (twice). The combined organic layers were dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography using 90 %:10 % cyclohexane/EtOAc to **2**, with 40 % yield as a dark brown solid. *R*f = 0.275 in 90 %:10 % cyclohexane/EtOAc. ^{1}H NMR (500 MHz, $CDCl_3$) : δ = 7.44-7.31 (m, 15H), 7.18 (d, *J* = 9 Hz, 6H), 6.92 (d, *J* = 9 Hz, 6H), 5.05 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) : δ = 158.04, 140.11, 137.18, 129.35, 128.83, 128.23, 127.86, 114.25, 81.35, 70.21. HRMS: m/z calculated for $C_{40}H_{34}O_4$ 578,2457, Found 579,1662.

4,4',4''-Methanetriyltriphenol 6. To a stirred solution of tris(4-(benzyloxy)phenyl)methanol **2** (100 mg, 0.173 mmol) or trimethyl(tris(4-(benzyloxy)phenyl)methoxy)silane **2a** or 4,4',4''-(methoxymethanetriyl)-tris((benzyloxy)benzene **2b** in EtOAc (3 mL) was added Pd/C 10 % (56 mg) at room temperature. After stirring for 16 hours under H_2, the reaction mixture was filtered through a pad of Celite and washed with EtOAc. The filtrate was concentrated to afford the phenol **6**, with 99 % yield as a colorless oil. *R*f 0.5 (cyclohexane/EtOAc 50 %:50 %). ^{1}H NMR (500 MHz, DMSO-d_6) : δ = 7.00 (d, *J* = 8.5 Hz, 6H), 6.74 (d, *J* = 8.5 Hz, 6H), 5.33 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 155.84, 135.82, 130.29, 115.44, 54.14. HRMS: m/z calculated for $C_{19}H_{16}O_3$ 292,109, Found 292,108.

Trimethyl(tris(4-(benzyloxy) phenyl) methoxy) silane 2a. In a three neck round bottom flask, tris(4-(benzyloxy)phenyl)methanol **2** (50 mg, 0.0865 mmol) was dried under vaccum for 2 hours and placed under argon for one hour. The tertiary alcohol dissolved in acetonitrile (3 mL) then DMAP (105.6 mg, 0.865 mmol) and triethyl amine (180 µL, 1.2 8mmol) were added. The mixture was stirred at room temperature for 10 minutes under argon. Finally, trimethylsilyl chloride was added dropwise to the mixture by syringe and the solution mixture was stirred overnight at room temperature. Et_2O (3 mL) and H_2O (2 mL) were added, and the layers were separated. The aqueous layer was further extracted with Et_2O (2 x 3 mL). The combined organic layers were washed with brine (2 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The crude product was purified by column chromatography (cyclohexane/EtOAc = 90:10) to afford silyl ether **2a** (50 mg, 88.9 % yield) as a light orangish solid, *R*f = 0.55 (cyclohexane/EtOAc = 90:10). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.43-7.29 (m, 21H), 6.88 (d, *J* = 9 Hz, 6H), 5.03 (s, 6H), -0.15 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$: δ= 157.63, 140.27, 137.13, 129.60, 128.63, 127.98, 127.59, 113.80, 83.83, 70.03, 1.91.

4,4',4''-(Methoxymethanetriyl) tris((benzyloxy) benzene) 2b. In a three neck round bottom flask, tris(4-(benzyloxy)phenyl)methanol **2** (100 mg, 0.173 mmol) was dried under vaccum for 5 hours and placed under argon overnight. Then, it was dissolved in THF (7 mL) at room temperature, NaH (60 % dispersion in mineral oil, 123 mg, 3.08 mmol) was added. After stirring for 2 min at 0 °C, MeI was added (250 µL, 4.01 mmol). The resulting mixture was stirred overnight, from 0 °C to room temperature, and quenched with saturated aq. NH_4Cl (4 mL). Et_2O (10 mL) and H_2O (5 mL) were added. The aqueous layer was further extracted with Et_2O (2 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The crude product was purified by column chromatography (cyclohexane/EtOAc =90:10) to afford methyl ether **2b** (102 mg, 100% yield) as a light orange oil. *R*f = 0.55 (90 %:10 % cyclohexane:EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$) : δ = 7.43-7.31 (m, 21H), 6.91 (d, *J* = 9 Hz, 6H), 5.03 (s, 6H), 3.03 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) : δ= 157.75, 137.20, 137.00, 130.01, 128.70, 128.07, 127.65, 114.12, 86.29, 70.05, 51.92.

4,4',4''-(Prop-2-yne-1,1,1-triyl)tris((benzyloxy)benzene) 4. In a three-neck round-bottom flask, tris(4-(benzyloxy)phenyl)methanol **2** (100 mg, 0.173 mmol) was dried under vacuum for 5 hours and then placed under argon overnight. Acetyl chloride (185 µL, 2.59 mmol) was added to the tertiary alcohol dissolved in dry toluene (3 mL), resulting in an orange color. The mixture was stirred under reflux for two hours in an argon atmosphere. After two hours, the volatiles were removed under reduced pressure, the solid was dissolved in dry toluene (5 mL) and evaporated to dryness three times. Then, the solid was dispersed in dry toluene (1.5 mL) and cooled to 0 °C. Ethynyl magnesium bromide (692 µL, 0.5 M in THF) was added to the stirred solution, resulting in an orange solution. After 15 minutes, the mixture was refluxed for two hours, then allowed to cool to 25 °C. The reaction was quenched with saturated aqueous NH_4Cl and extracted with diethyl ether (3 mL) three times. The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure to obtain the crude product. The crude product was purified by column chromatography (cyclohexane/ethyl acetate = 90:10) to yield tertiary alkyne **4** (92 mg, 0.156 mmol) as an orange solid, with a yield of 90 % and *R*f = 0.55 (cyclohexane/EtOAc = 90:10). ^{1}H NMR (500 MHz, $CDCl_3$) : δ = 7.41-7.30 (m, 15H), 7.18 (d, *J* = 8.5 Hz, 6H), 6.88 (d, *J* = 8.5 Hz, 6H), 5.01 (s, 6H), 2.64(s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 157.55, 137.50, 136.75, 130.19, 128.70, 128.09, 127.64, 114.25, 90.08, 73.01, 70.12, 53.79.

4,4',4''-(Prop-2-yne-1,1,1-triyl)triphenol 5. In a 100 mL round bottom flask, (5.36 mmol) in NMP (20 mL) was added to a magnetically stirred mixture of Ph_2S_2 (1200 mg, 5.5 mmol) and CaH_2 (700 mg, 16.6 mmol) in NMP (20 mL) and the mixture was heated under reflux (around 200 °C) overnight. The cooled reaction mixture was diluted with water (150 mL) and extracted with Et_2O (3 times 150 mL) to separate any neutral component. The combined ethereal extracts were washed with 5 % aqueous NaOH (100 mL) and the alkaline washing was added to the aqueous portion. The aqueous part was acidified in an ice bath with 6 M HCl (25 mL) and extracted with Et_2O (3 times 75 mL). The combined ethereal extracts were washed with brine (75 mL), dried ($MgSO_4$) and concentrated under vacuum to afford the crude product which was purified by column chromatography (cyclohexane/EtOAc = 50:50) to afford tri-phenol **5**, as a brownish solid (1.15 g, 3.64 mmol, 68 % yield), *R*f = 0.525 (cyclohexane/EtOAc = 90:10). ^{1}H NMR (500 MHz, MeOD): δ 7.03 (d, *J* = 9 Hz, 2H), 6.69 (d, *J* = 9 Hz, 2H), 2.95 (s). ^{13}C NMR (125 MHz, MeOD): δ = 156.86, 137.97, 131.05, 115.32, 91.78, 73.65, 54.53. GC-HRMS: m/z calculated for $C_{21}H_{16}O_3$ 316,110, Found 316,109.

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Supplementary Material

All data generated or analyzed during this study are included in this published article and its supplementary

information files.

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