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A Modular Approach for the Synthesis of Nanometer-Sized Polynitroxide Multi-Spin Systems

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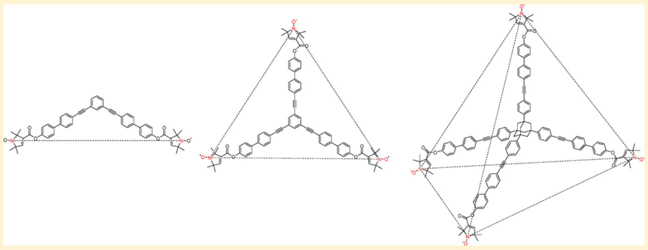
Supporting Information

ABSTRACT: The synthesis of rigid symmetric polyradical model systems with inter-spin distances between 1.4 and 4 nm and their room temperature continuous wave (CW) EPR spectra are reported. Conditions for attachment of the spin-label via esterification have been optimized on the direct synthesis of polyradicals from commercially available polyphenols and the carboxylic acid functionalized nitroxide TPC. A common synthetic protocol utilizing 4-hydroxy-4′-iodobiphenyl as a key building block has been used to synthesize an equilateral biradical and a triradical in only two steps from commercially available starting materials. The first synthesis of a tetraradical based upon an adamantane core bearing six equivalent nitroxide−nitroxide distances is also reported. These systems are very promising candidates for studying multi-spin effects in pulsed EPR distance measurements.



INTRODUCTION

Interest in electron paramagnetic resonance (EPR) spectroscopy has been growing recently as it yields powerful geometric constraints for structure determination in biomacromolecules.[1] Pulsed distance measurements by EPR known as PELDOR (Pulsed Electron−Electron Double Resonance)[2] or DEER (Double Electron−Electron Resonance) give access to distances between paramagnetic centers in the range from 1.8 to 8 nm in biomolecules.[1,3] Distance measurements can be performed between native paramagnetic centers, as either metal centers and cofactor radicals, or chemically introduced spin labels. Spin labels can be introduced into complex biological systems by site-directed spin labeling (SDSL).[1,3,4] Distance measurements in systems containing more than two electron spins are problematic owing to the presence of artifacts in distance distributions derived from distance measurements neglecting multi-spin contributions to the dipolar interaction.[5−7] The latter stem from simultaneous excitation of two or more dipolar couplings, which can be present only in systems with more than two spins. This multiple excitation generates sum and difference frequencies that are not necessarily related to a physical distance. These deviations have been shown to cause "ghost peaks"[8] or reduce the intensity of signals from longer distances[9] in distance distributions generated from multi-spin systems neglecting multi-spin effects. This potentially causes inaccuracies in the structural characterization of biological systems[10,11] and could be a major pitfall in the extraction of reliable constraints for systems of unknown structure, in particular homo-oligomeric membrane transporters and macromolecular complexes. Polyradical synthetic model systems are good candidates for studying these multi-spin effects as the distances and distance distributions between radical moieties can be reasonably well predicted.[12]

Most model systems for EPR distance measurements reported to date consist of a varying number of rigid aromatic units to which different types of spin labels have been attached. The aromatic backbone confers rigidity to the system,[7] while alkyl substitution on the phenyl rings is used to improve the overall solubility.[13] The high accuracy of pulsed EPR distance measurements has led to its successful application for the quantification of the shape-persistence and flexibility of poly(phenyleneethynylenes)[14] and porphyrin-based molecular wires.[15] Furthermore, the spin-exchange mechanism in poly(phenyleneethynylenes) has been characterized by CW EPR and simulations.[16] The combination of shape-persistence and solubility is ideal for assessing the precision of inter-spin distance measurements and for calibrating new EPR experiments.[13] The most commonly used spin labels are nitroxide radicals,[12] while more recently, bulky trityl radicals such as **1** (Scheme 1) have been reported as alternative spin labels[17] that allow distance measurements at ambient temperature.[18] However, nitroxides have found wide applicability because of their stability, restricted mobility, and ease of introduction within different types of systems.[3] Imidazole-based α-iminyl-nitroxide radicals **2** (Scheme 1) have been previously used for the synthesis of biradical model systems.[19] However, they show considerable delocalization of unpaired spin density onto the imine nitrogen atom.[20] This is a drawback when performing EPR distance measurements as it leads to significant deviations

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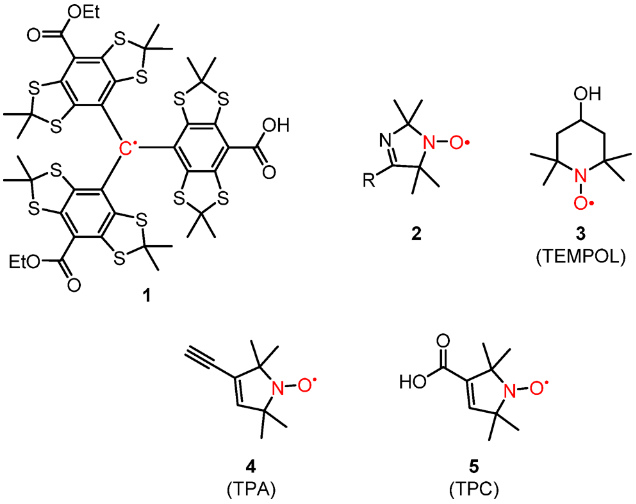
Scheme 1. Commonly Used Spin Labels for Synthetic Model Compounds for Inter-spin Distance Measurements

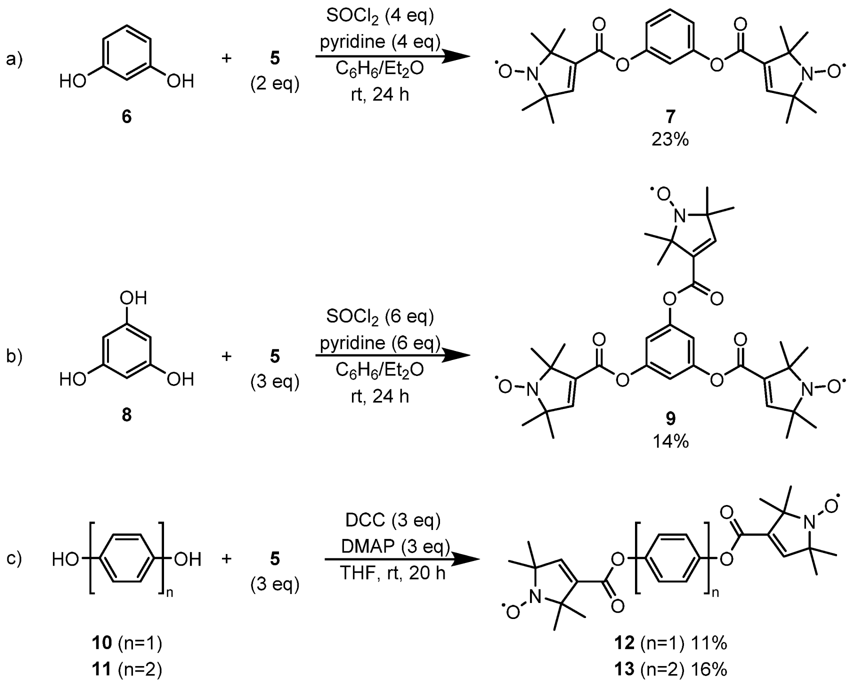


from the point-dipole approximation, as well as giving rise to nonvanishing exchange couplings. 1-Oxyl-2,2,6,6-tetramethylpiperidine (TEMPO) derivatives, for example, 4-hydroxy-1-oxyl-2,2,6,6-tetramethylpiperidine (TEMPOL) **3** (Scheme 1), have also been reported as alternative spin labels.[19] The advantage of pyrroline- or piperidine-based nitroxide radicals over **2** is that the electron spin density is primarily located on the N−O bond, which allows determination of inter-spin distances with greater precision.[21] However, the presence of a six-membered ring in TEMPO and its derivatives causes a lower stability toward both reduction and oxidation and a larger flexibility compared with pyrroline-based nitroxides.[22,23] For this reason, the most commonly used nitroxide spin labels for the synthesis of model systems for EPR distance measurements are 2,2,5,5-tetramethyl-pyrrolin-1-oxyl-3-acetylene (TPA) **4**[24] and commercially available 1-oxyl-2,2,5,5-tetramethylpyrroline-3-carboxylic acid (TPC) **5** (Scheme 1).

Godt et al.[13] and Weber et al.[25] reported that TPC **5** leads to lower spin density delocalization into the chemical linking group compared with TPA **4** and thus diminishes exchange couplings. Furthermore, TPA **4** is typically introduced through Sonogashira cross-coupling of its terminal alkyne, and purification of the crude product has been reported to be particularly challenging due to highly similar polarities between side-products and target molecules.[7] Sonogashira cross-couplings in the presence of nitroxide radicals often have to be optimized with respect to substrates and catalyst systems to prove efficient.[26] In contrast, TPC **5** can be readily introduced onto polyphenolic aromatic backbones through esterification under mild conditions. It has been shown that the presence of multiple ester groups largely diminishes the through-bond exchange coupling *J*, which would seriously complicate the interpretation of distance measurements.[13,25]

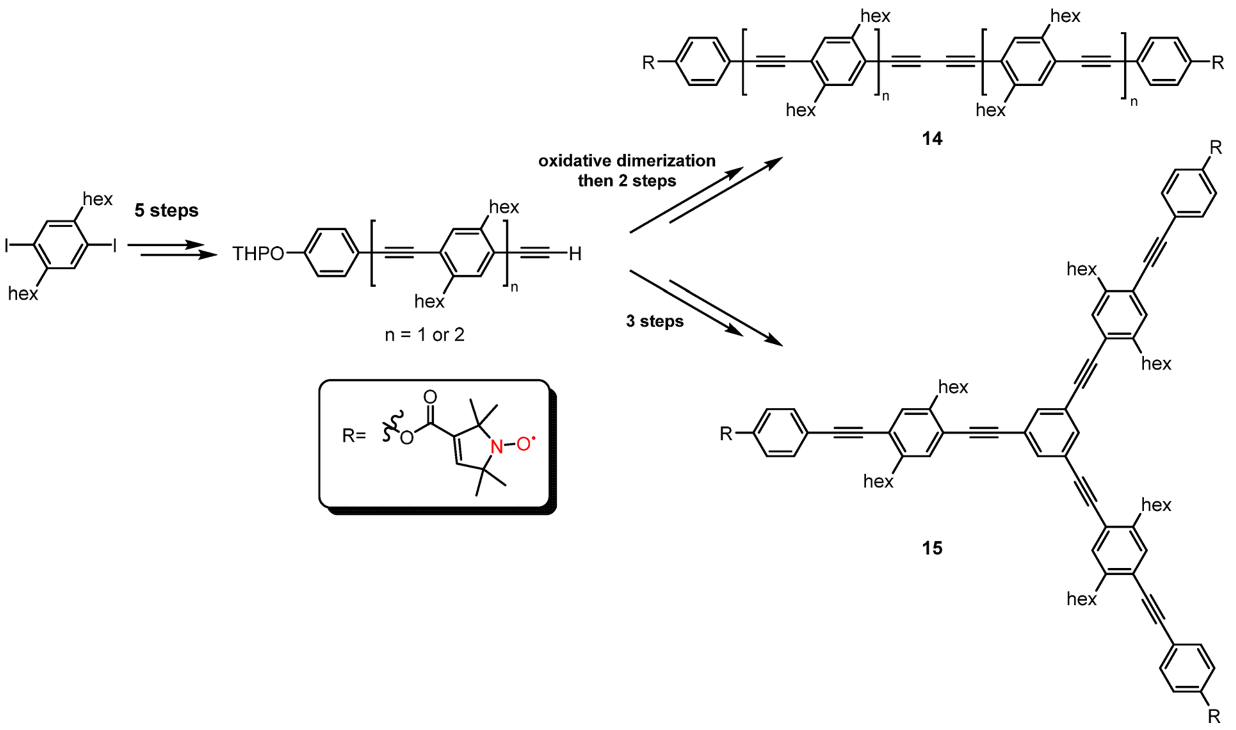
Our aim is to synthesize symmetrical polyradical model systems for use in EPR distance measurements in which multi-spin effects should be prominent. These model systems should consist of rigid ethynyl-substituted aromatic spacers as they provide well-defined incremental spacers for inter-spin distances. Ideally, a modular synthetic approach using a small pool of building blocks could be developed to allow the rapid and efficient synthesis of a series of polyradical model systems with two, three, or four electron spins but only one inter-spin distance per molecule. It was anticipated that this could be achieved using a cross-coupling strategy to create a variety of rigid polyphenolic backbones to which the spin-label TPC **5** could be readily attached. In this regard, Rosantsev has reported the thionyl chloride mediated esterification of TPC **5** with either resorcinol **6** to give biradical **7** or phloroglucinol **8** to yield triradical **9** (Scheme 2a and b).[27] However, **7** and **9** were

Scheme 2. Previous Syntheses of Short Distance Polyradicals[a]



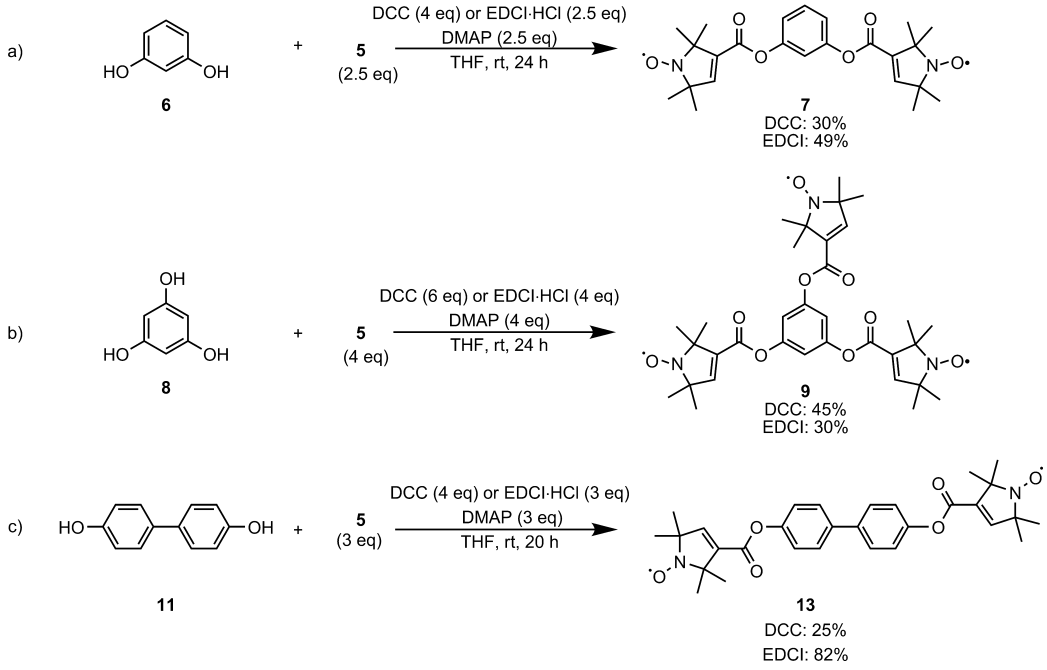
[a] DCC = 1,3′-dicyclohexylcarbodiimide; DMAP = 4-(dimethylamino)pyridine.

Scheme 3. Syntheses of Long Distance Polyradicals[a]



[a]THP = tetrahydropyran; TIPS = triispropylsilyl; hex = hexyl

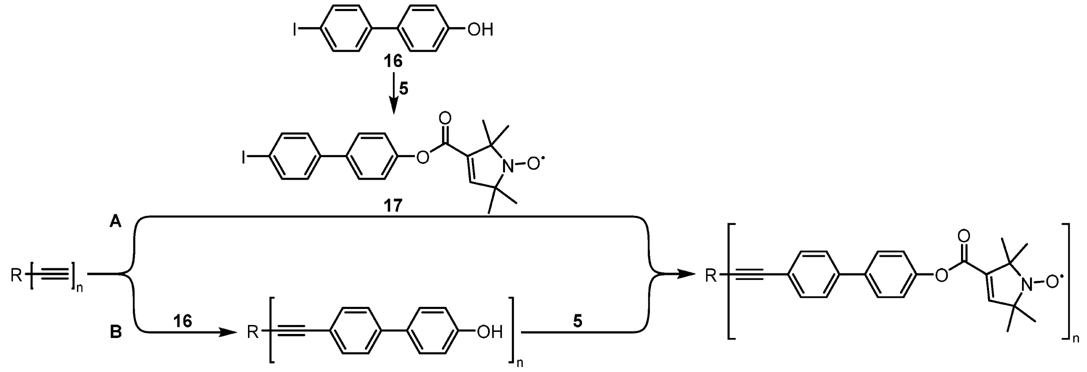
Scheme 4. Syntheses of Short-Distance Model Systems Using TPC 5



obtained only in low yields after sequential purification by column chromatography and recrystallization. Weber et al. utilized standard Steglich esterification conditions to react TPC **5** with either hydroquinone **10** or 4,4′-biphenol **11** to synthesize biradicals **12** and **13**, respectively, although the requisite purification by standard column chromatography followed by preparative HPLC led to low isolated yields (Scheme 2c).[25]

Godt et al. reported the synthesis of longer bi- and triradical model systems **14** and **15** through oxidative ethynyl to butadiynyl dimerization of protected monophenols followed by deprotection and esterification to TPC **5** (Scheme 3).[13] The protected monophenolic precursors were synthesized through a series of palladium-catalyzed Sonogashira cross-coupling reactions. Although each individual reaction proceeded in good yield, the synthesis requires the use of protecting groups leading to a long linear reaction sequence.

Scheme 5. Proposed Synthetic Routes Toward Symmetrical Polyradicals



Herein we report a modular synthetic protocol for the synthesis of rigid and highly symmetric polyradical model systems. The use of a small number of commercially available building blocks allows the synthesis of a number of different polyphenolic backbones to which the spin-label TPC **5** can be esterified. A series of bi- and triradicals together with a tetraradical have been synthesized in an efficient manner under mild reaction conditions without the need for multiple protecting groups. All polyradicals have been characterized via mass spectrometry, elemental analysis, and CW EPR. From CW EPR spectra, parameters such as hyperfine coupling and rotational correlation time can be extracted.

■ RESULTS AND DISCUSSION

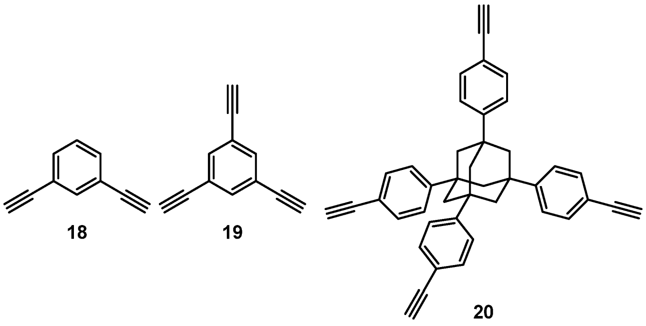
First, the synthesis of small polyradicals with short inter-spin distances from commercially available phenols and TPC **5** was investigated. It was important to establish a reliable esterification protocol as it was hoped that a standard set of conditions could be used for the synthesis of both short and long polyradical model systems. Polyradicals **7** and **9** were first targeted as their previously reported syntheses require harsh reaction conditions and extensive purification and resulted in low yields (see Scheme 2).[27] The synthesis of biradical **13** was also reviewed as it was believed that the yield for a 2-fold esterification reaction of TPC **5** to a polyphenolic backbone using milder conditions could be improved. Treatment of resorcinol **6** with DCC (4 equiv), DMAP (2 equiv), and TPC **5** (2 equiv) in THF at room temperature resulted in the formation of biradical **7** in 30% yield after purification by column chromatography on silica gel (Scheme 4a).[25] The same conditions could also be applied to the esterification of phloroglucinol **8** and 4,4′-biphenol **11** to form triradical **9** and biradical **13** in 45% and 25% yield, respectively (Scheme 4b and c). While these yields are an improvement on those previously reported, the purifications proved to be challenging due the presence of the dicyclohexylurea byproduct.[28] In an attempt to overcome these difficulties with purification, the esterification reactions were repeated using 1-ethyl-3-(3-(dimethylamino)propyl) carbodiimide hydrochloride (EDCI·HCl) as the activating agent. In this case the urea byproduct is completely water-soluble and could be easily removed through an aqueous workup. Pleasingly, this led to an improvement in the isolated yields of biradicals **7** and **13** to 49% and 82%, respectively, after chromatographic purification on activity II aluminum oxide with 4% H_2O (Scheme 4a and c).[29]

Single crystal X-ray crystallographic analysis of biradical **7** revealed a nitroxide−nitroxide distance of 1.33 nm, which is similar to the mean nitroxide−nitroxide distance of 1.32 nm (average of 1.39, 1.26, and 1.30 nm) obtained from analysis of triradical **9**.[30,31] The approximation of triradical **9** being an overlay of three orientations of biradical **7** is therefore reasonably well fulfilled. The X-ray crystal structure of triradical **9** showed the presence of disorder related to multiple occupations, suggesting that at least two rotamers are very similar in energy; this effect was not present in the X-ray crystal structures of biradicals **7** and **13**.[32] It has previously been shown that simulation of EPR data of rod-like biradicals, consisting of a poly(*p*-phenyleneethynylene) backbone to which TPC **5** spin label has been esterified, were satisfactory only when full rotational freedom of the spin label around the phenolic C−O bond is assumed.[12] Biradical **7** and triradical **9** represent systems where the spin−spin distance is considerably shorter than the distance range easily accessible via pulsed EPR (1.8−8 nm). Their use to benchmark PELDOR performance will be scrutinized and reported in due course. Owing to their short inter-spin distance, **7** and **9** might be interesting candidates for cryogenic magic-angle spinning dynamic nuclear polarization (DNP) experiments.[33]

Next, the synthesis of longer polyradical model systems suitable for use in pulsed EPR distance measurements was investigated. The aim was to design a common, modular synthetic route for the synthesis of model systems containing two, three, and four TPC **5**-based nitroxide radicals. Two possible synthetic routes toward such systems were envisaged (Scheme 5). One possibility is that TPC **5** could first be esterified to 4-hydroxy-4′-iodobiphenyl **16** to give nitroxide radical **17**, which would be cross-coupled *n* times to a suitable precursor containing *n* terminal alkynes to form a series of polyradical systems (Scheme 5, route A).[29] Alternatively, 4-hydroxy-4′-iodobiphenyl **16** could be first cross-coupled *n* times to the terminal alkyne precursor to form a polyphenolic backbone that could then undergo global esterification with TPC **5** (Scheme 5, route B). In both cases 4-hydroxy-4′-iodobiphenyl **16** represents a yardstick module that can be used to increase the inter-spin distance by approximately 1 nm without compromising the rigidity of the system.

Using the proposed routes, bi- and triradical model systems would be accessible in two steps from commercially available 1,3-diethynylbenzene **18** and 1,3,5-triethynylbenzene **19**, respectively (Scheme 6). This follows the design and geometry of previously reported systems using TPA **4**.[7] The route presented here is expected to yield very similar structural and magnetic properties but would significantly shorten the synthetic process. An advantage of using 1,3- and 1,3,5-substituted benzene cores is that they have relatively high

Scheme 6. Proposed Alkyne Precursors for Polyradical Model Systems



symmetry and have the same angular geometry. In terms of multi-spin effects, this means that the distortion induced by the presence of a third spin label could be separated from structural effects. Here, a more efficient synthetic process is reported for the synthesis of similar systems. For further studies of multi-spin effects the logical extension is to target a symmetrical tetraradical with tetrahedral symmetry, which would be accessible using the proposed routes from 1,3,5,7-tetrakis(4-ethynylphenyl)adamantane **20** (Scheme 6).[34]

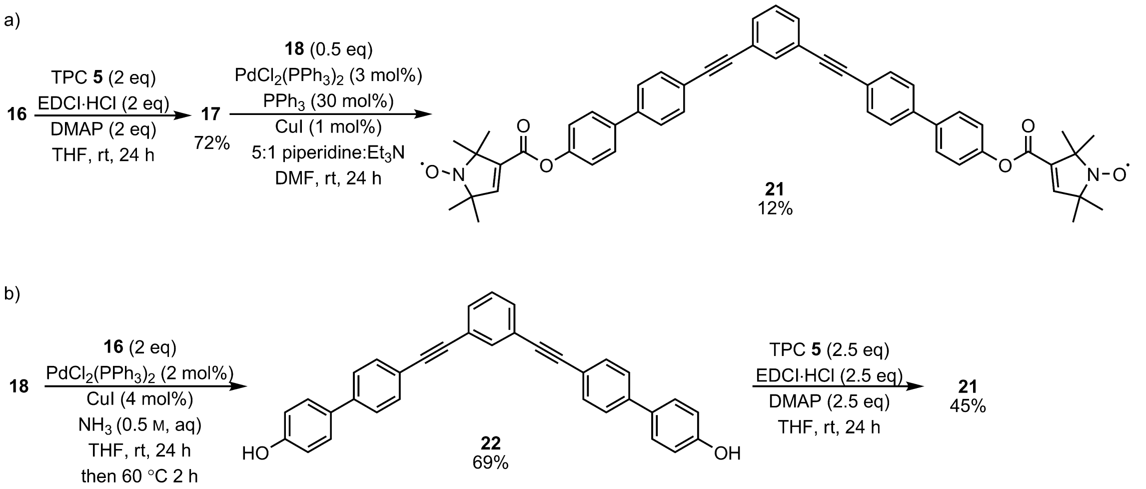
It was initially decided to investigate the synthesis of a biradical starting from 1,3-diethynylbenzene **18** following proposed route A (Scheme 5). First, 4-hydroxy-4′-iodobiphenyl **16** was esterified with TPC **5** using the previously developed EDCI·HCl coupling conditions to form nitroxide radical **17** in 72% yield.[29] The Sonogashira cross-coupling of nitroxide **17** with 1,3-diethynylbenzene **18** was trialled using the previously reported conditions of $PdCl_2(PPh_3)_2$ (3 mol %), PPh_3 (30 mol %), and CuI (1 mol %) in a mixture of piperidine and triethylamine.[7] However, the desired biradical **21** was isolated in a disappointing 12% yield (Scheme 7a). One possible explanation for the low yield is competing Glaser homocoupling of alkyne **18**,[7] although the paramagnetic nature of the crude reaction mixture made identification of unwanted side-products difficult.[35] As this route proved to be low-yielding, it was decided to investigate an alternative synthetic path (Scheme 5, route B). In this case, 4-hydroxy-4′-iodobiphenyl **16** was first reacted with 1,3-diethynylbenzene **18** under aqueous ammonia Sonogashira cross-coupling conditions to afford bis-phenol **22** in 69% yield.[36] The use of these mild Sonogashira conditions was particularly important as it allowed the coupling to proceed in good yield without the use of a protecting group for the phenol. Double esterification of bis-phenol **22** with TPC **5** using EDCI·HCl and DMAP gave desired biradical **21** in an improved 45% yield (Scheme 7b). Route B was therefore chosen to investigate the synthesis of the tri- and tetraradical model systems.

A symmetrical triradical was synthesized in two steps from 1,3,5-triethynylbenzene **19** using the conditions described previously (Scheme 8). The triple cross-coupling process with 4-hydroxy-4′-iodobiphenyl **16** gave tris-phenol **23** in a 60% yield and esterification with TPC **5** proceeded smoothly to give the desired triradical **24** in an excellent 80% yield. The estimated average inter-spin distance for both bi- and triradical **21** and **24** is 3.2 nm, which is well within the distance range that can be accessed via pulsed EPR experiments.[12,37]

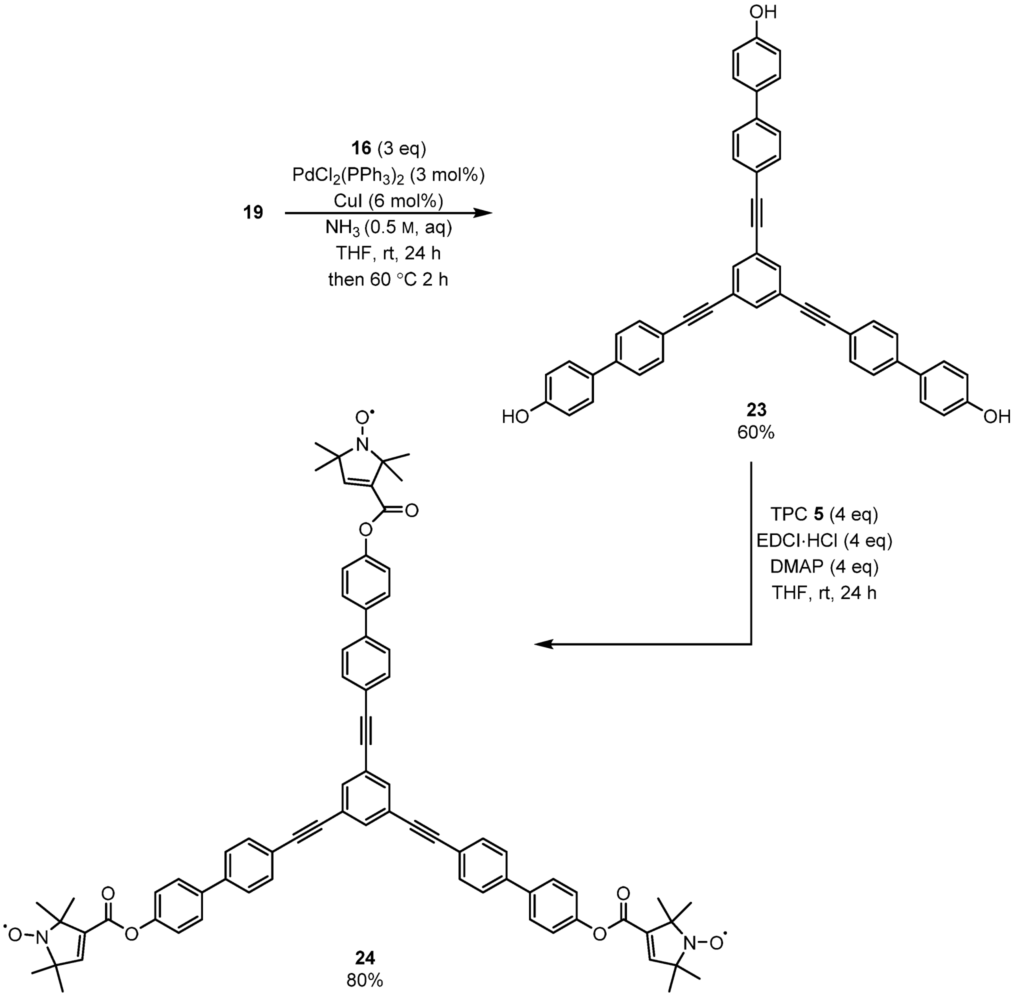
Finally, the synthesis of a rigid tetraradical with single distance symmetry based upon an adamantyl core **20** was investigated. The first aim was to synthesize a tetrahedral core suitable for onward cross-coupling reactions starting from 1-bromo adamantane **25** (Scheme 9). Using the conditions described by Reichert and Mathias, **25** was treated with *tert*-butyl bromide (3 equiv) and a catalytic amount of $AlCl_3$ (10 mol %) and heated under reflux in benzene to give tetraphenyladamantane **26** in 90% yield.[38]

Owing to its low solubility in organic solvents, the purity of **26** was assessed via cross-polarization (CP) magic-angle spinning (MAS) solid-state NMR spectroscopy. The ^{13}C CP MAS NMR spectrum previously reported contained six resonances at 39.4, 45.3, 124.8, 127.3, 129.2, and 149.8 ppm,[38] whereas our measurements presented eight resonances at 39.2, 45.1, 51.3, 124.7, 127.2, 129.1, 130.2, and 149.8 ppm. To evaluate the validity of both measurements, density functional theory (DFT) calculations were carried out using the CASTEP code.[39] Calculations confirmed that the published crystal structure of 1,3,5,7-tetraphenyladamantane (CSD entry BOTWOX)[40] would be expected to give rise to eight ^{13}C resonances for the nine crystallographically distinct C species (two of the calculated shifts differ by only 0.3 ppm, and these species are not resolved in our spectrum). This suggests that the ^{13}C NMR data reported previously are incomplete.[41]

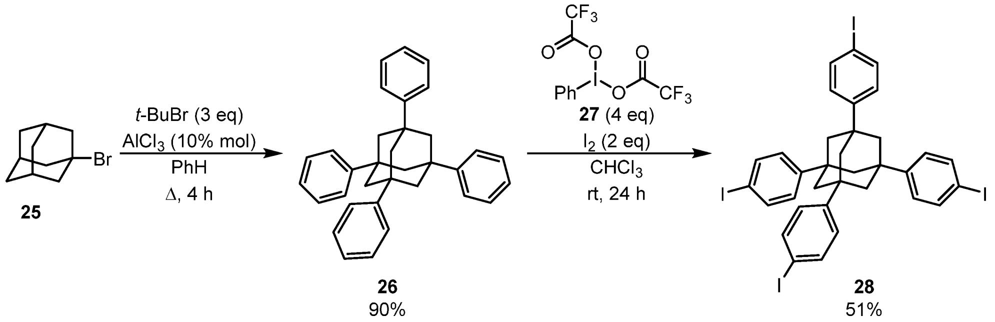
Scheme 7. Synthesis of Symmetrical Biradical 21



Scheme 8. Synthesis of Symmetrical Triradical 24

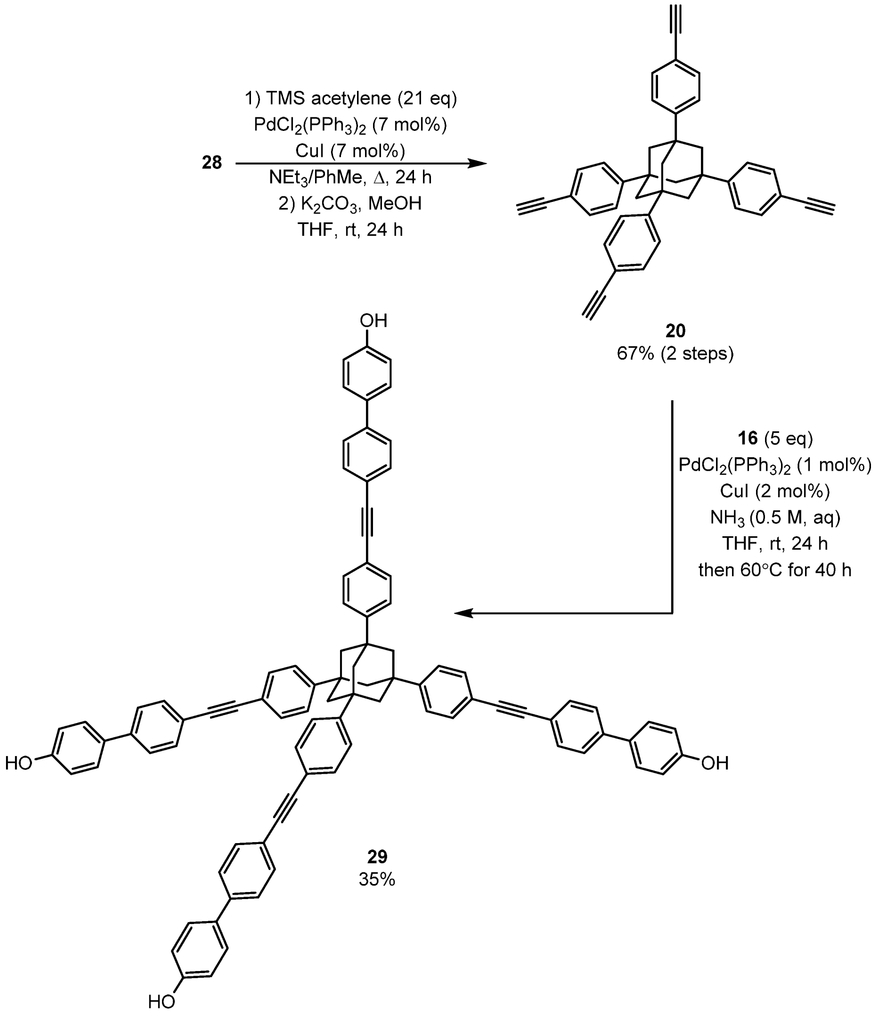


Scheme 9. Synthesis of 1,3,5,7 Tetrakis(4-iodophenyl)-adamantane 28



Tetraphenyladamantane **26** was then iodinated using [bis(trifluoroacetoxy)iodo]benzene **27** (4 equiv) and iodine (2 equiv) to give 1,3,5,7-tetrakis(4-iodophenyl)adamantane **28** in 51% yield (Scheme 9).[42] Next, TMS-acetylene was coupled to **28** followed by TMS deprotection to give the key tetrahedral tetraalkyne **20** in 67% yield over the two steps (Scheme 10). Cross-coupling of **20** with 4-hydroxy-4′-iodobiphenyl **16** using the aqueous ammonia Sonogashira conditions gave the desired tetrakis-phenol **29**, but in a disappointing 35% yield. Therefore, the order of the synthesis was changed in an attempt to provide a higher overall yield (Scheme 11). Coupling of 4-hydroxy-4′-iodobiphenyl **16** with TMS-acetylene followed by silyl deprotection gave alkyne **30** in 80% yield over two steps. Pleasingly, coupling of alkyne **30** with tetrakis-iodoadamantane **28** provided the desired tetrakis-phenol **29** in a much improved 60% yield. The 4-fold esterification of tetrakis-phenol **29** with TPC **5** under the standard EDCI·HCl conditions gave tetraradical **31** in an excellent 72% isolated yield, with the composition confirmed by both MALDI mass spectrometry and elemental analysis. To the best of our knowledge, this is the first example of a nonplanar tetraradical suitable for pulsed EPR distance measurements possessing tetrahedral symmetry, with an estimated average inter-spin distance of 4 nm.[37]

Scheme 10. Initial Synthesis of Tetraphenol 29



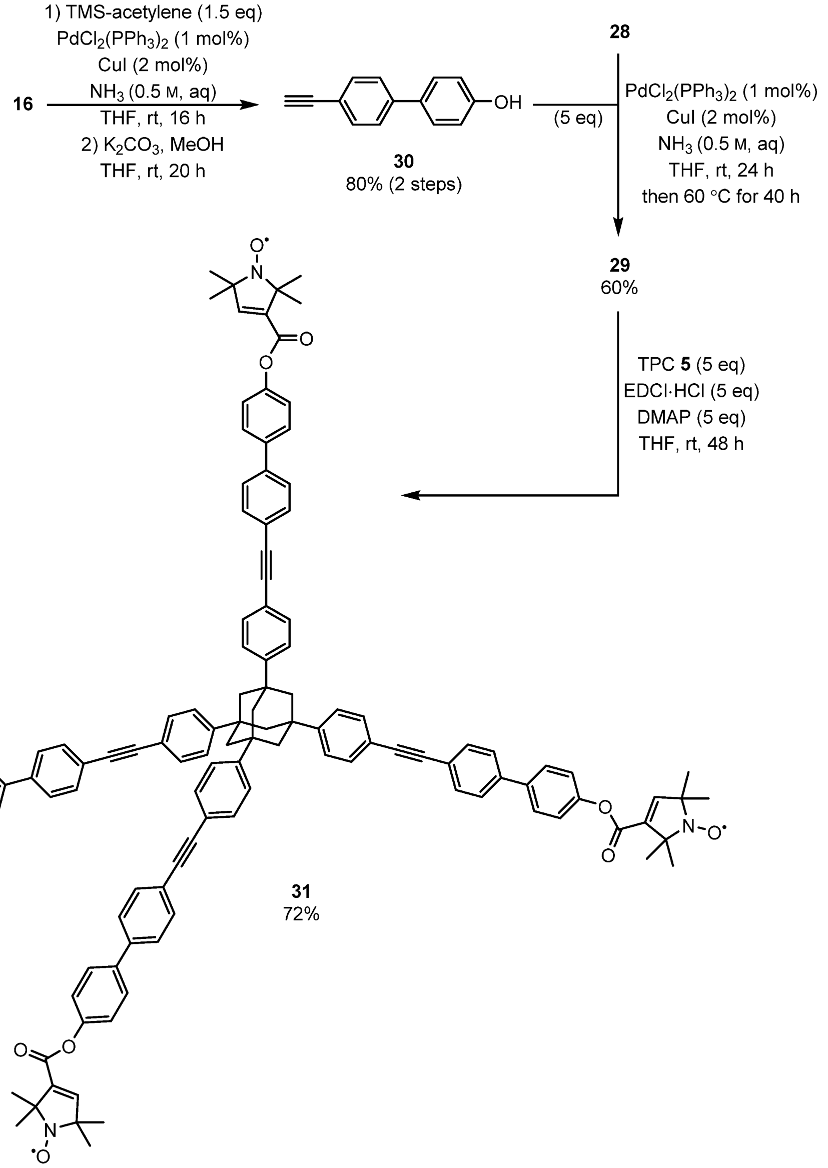
CONCLUSION

In conclusion, an efficient modular approach to a series of polyradical model systems for studying multi-spin effects in EPR distance measurements has been developed. Sonogashira cross-coupling of 4-hydroxy-4′-iodobiphenyl **16** to suitable symmetric polyalkynes under aqueous ammonia conditions provides a range of polyphenols without the need for a phenolic protecting group. EDCI·HCl mediated esterification of the polyphenols with the spin-label TPC **5** gives the corresponding polyradical systems in good yield with a simplified workup and purification procedure compared with those previously reported for related systems. This common protocol has been successfully applied to the synthesis of bi-, tri-, and tetraradical systems in a short number of synthetic steps. Importantly, the synthesis of tetraradical **31** represents the first example of a nonplanar polyradical with fixed inter-spin distances exhibiting tetrahedral symmetry. Ongoing studies within our laboratory are focused on the synthesis and applications of polyradical model systems for application in EPR spectroscopy. The short distance biradicals and triradicals will be used for investigation of short-distance measurements and as potential polarizing agents for Dynamic Nuclear Polarization (DNP) nuclear magnetic resonance.

EXPERIMENTAL SECTION

General Methods. Moisture- and air-sensitive reactions were carried out under a nitrogen atmosphere using standard Schlenk techniques and freshly distilled solvents. All glassware was flame-dried and cooled under vacuum before use. Solvents (THF, CH_2Cl_2, and toluene) were obtained anhydrous and purified by a SPS alumina column. All other solvents and commercial reagents were used without further purification. Solvents used for cross-coupling reactions were degassed using freeze−pump−thaw cycles (×3). ^1H and $^{13}C\{H^1\}$ nuclear magnetic resonance (NMR) spectra were acquired on either a 400 MHz ^1H, 100 MHz ^{13}C, or a 500 MHz ^1H, 125 MHz ^{13}C NMR spectrometer at ambient temperature, if not otherwise stated, in the deuterated solvents reported. All chemical shifts are reported in parts per million (ppm) relative to TMS with the solvent used as an internal standard. All coupling constants *J* are reported in Hz. Multiplicities are reported as s (singlet), d (doublet), m (multiplet). Solid-state NMR spectra were acquired at 14.1 T (^{13}C Larmor frequency of 151 MHz) with magic-angle spinning (MAS) rates between 11 and 12.5 kHz. Cross-polarization from ^1H was employed to enhance sensitivity, and high-power ^1H decoupling was applied during acquisition to enhance resolution. Chemical shifts are reported relative to TMS using the CH_3 resonance of L-alanine (δ = 20.5 ppm) as an external reference. FT Infrared spectra were recorded using an ATR probe, and only characteristic peaks are reported. Melting points recorded are uncorrected. Mass spectrometry (m/z) data were acquired using electron spray (ES), atmospheric solids analysis probe (ASAP), and matrix-assisted laser desorption/ionization MALDI. CW EPR spectra were obtained with an X-band spectrometer operating at ~9.7 GHz

Scheme 11. Synthesis of Tetrahedral Tetraradical 31



with 100 kHz modulation. Samples were dissolved in deuterated toluene and deoxygenated by saturation with nitrogen. Samples were contained in 4 mm OD quartz tubes sealed with rubber septa.

Spectra of **7**, **9**, **13**, **21**, **24**, and **31** were recorded at room temperature using a 60 mT field sweep centered at 348 mT with 1024 points resolution, a time constant and conversion time of 40.96 ms each, and a modulation amplitude of 0.05 mT.

General Procedure A: Esterification of TPC 5. The appropriate phenol, TPC **5**, and DMAP were dissolved in anhydrous THF. The flask was covered in aluminum foil before addition of EDCI·HCl. The reaction mixture was stirred under a nitrogen atmosphere at rt for the time stated. The reaction mixture was filtered to remove the urea precipitate and washed with CH_2Cl_2. The organic filtrate was washed with water (×3) before being dried over $MgSO_4$ and filtered. Solvents were removed under reduced pressure to give the crude product, which was purified via 4% H_2O aluminum oxide column chromatography.

General Procedure B: Aqueous Ammonia Sonogashira Coupling. The appropriate aryl iodide was dissolved in anhydrous THF before $PdCl_2(PPh_3)_2$ and CuI were added. The obtained solution was degassed via freeze−pump−thaw cycles (×3). The appropriate alkyne was then added portionwise as a solid or dropwise as a degassed solution in THF. The reaction mixture was degassed once more before dropwise addition of a 0.5 M aqueous ammonia solution (2 equiv), which had been purged with nitrogen for 3 min. The reaction mixture was stirred at rt and/or heated for the time stated. The two phases were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with 10% HCl and water before being dried over $MgSO_4$ and filtered. Solvents were removed under reduced pressure to give the crude product that was purified via silica column chromatography or trituration.

Biradical (7). Resorcinol **6** (0.08 g, 0.73 mmol), TPC **5** (0.33 g, 1.82 mmol), EDCI·HCl (0.28 g, 1.82 mmol), and DMAP (0.22 g, 1.82 mmol) in THF (10 mL) were reacted according to general procedure A. The reaction mixture was stirred for 24 h. The crude product (0.25 g) was purified (4% H_2O aluminum oxide, CH_2Cl_2, R_f 0.3) to give **7** as a pale yellow solid (0.16 g, 49%): mp 169−171 °C {lit.[27] mp 183−185 °C (benzene/heptane)}; FT-IR (ATR) 2980 (m), 2929 (m), 1730 (s), 1597 (s), 1344 (m), 1286 (m), 1244 (s), 1154 (s), 1130(s), 1026 (s), 805(s), 754 (s); HRMS [ASAP, ion trap] (SOLID) $[M + H]^+$ calcd for $C_{24}H_{31}N_2O_6$ 443.2177, found 443.2176. Anal. Calcd for $C_{24}H_{30}N_2O_6$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.18; H, 6.94; N, 6.38. Room temperature CW EPR displays a characteristic three line nitroxide spectrum: $a_{iso}(^{14}N)$ =1.42(1) mT.

Triradical (9). Phloroglucinol **8** (0.04 g, 0.32 mmol), TPC **5** (0.23 g, 1.27 mmol), EDCI·HCl (0.19 g, 1.27 mmol) and DMAP (0.15 g, 1.27

mmol) in THF (10 mL) were reacted according to general procedure A. The reaction mixture was stirred 48 h. The crude product (0.13 g) was purified (4% H_2O aluminum oxide, CH_2Cl_2, R_f 0.1) to give **9** as a bright yellow solid (0.06 g, 30%): mp 214−216 °C {lit.[27] mp 225−226 °C (benzene-heptane)}; FT-IR (ATR) 2978 (w), 2931 (m), 1732 (s), 1604 (m), 1456 (m), 1348 (m), 1286 (s), 1168 (s), 1128 (s), 1030 (s), 752 (m); HRMS [ASAP, ion trap] (SOLID) $[M + H]^+$ for $C_{33}H_{43}N_3O_9$: calcd. 625.2994, found 625.2989. Anal. Calcd for $C_{33}H_{42}N_3O_9$: C, 63.45; H, 6.78; N, 6.73. Found: C, 63.31; H, 6.85; N, 6.81. Room temperature CW EPR displays a characteristic three line nitroxide spectrum: $a_{iso}(^{14}N)$ =1.41(1) mT.

*Biradical (**13**).* 4,4′-Biphenol **11** (0.10 g, 0.54 mmol), TPC **5** (0.30 g, 1.63 mmol), DMAP (0.20 g, 1.64 mmol) and EDCI·HCl (0.16 g, 1.03 mmol) in THF (10 mL) were reacted according to general procedure A. The reaction mixture was stirred 24 h. The crude product (0.31 g) was purified (4% H_2O aluminum oxide, CH_2Cl_2, R_f 0.2) to give **13** as yellow crystals (0.23 g, 82%). Data are in accordance with the literature:[25] mp 211−213 °C; FT-IR (ATR) 2976 (w), 2931 (w), 1732 (s), 1490 (m), 1346 (m), 1286 (m), 1244 (m), 1194 (s), 1147 (s), 1024 (s), 1001 (s), 792 (s), 759 (s); HRMS [NSI, ion trap] $[M + H]^+$ calcd for $C_{30}H_{35}N_2O_6$ 519.2490, found 519.2476. Anal. Calcd for $C_{30}H_{34}N_2O_6$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.30; H, 6.75; N, 5.54. Room temperature CW EPR displays a characteristic three line nitroxide spectrum: $a_{iso}(^{14}N)$ =1.42(1) mT.

*Monoradical (**17**).* 4-Hydroxy-4′-iodobiphenyl **16** (0.10 g, 0.34 mmol), TPC **5** (0.12 g, 0.67 mmol), EDCI·HCl (0.10 g, 0.67 mmol), DMAP (0.08 g, 0.67 mmol) in THF (15 mL) were reacted according to general procedure A. The reaction mixture was stirred 24 h. The crude product (0.20 g) was purified (4% H_2O aluminum oxide, 3:2 CH_2Cl_2, ethyl acetate, R_f 0.8) to give **17** as a yellow solid (0.08 g, 72%). Data in accordance with literature:[29] mp 157−158 °C; FT-IR (ATR) 2978 (w), 1730 (s), 1624 (m), 1477 (s), 1458 (m), 1442 (m), 1344 (m), 1282 (m), 1197 (s), 1182 (s), 1165 (s), 1149 (s), 1014 (m), 999 (s), 760(s); MS [ESI, ion trap] $[M + H]^+$ calcd for $C_{21}H_{22}INO_3$ 463.31, found 463.32.

*1,3,5,7-Tetrakis(4-ethynlphenyl)adamantane (**20**).* Following the procedure described by Lu et al.,[34] **28** (1.20 g, 1.27 mmol), trimethylsilylacetylene (2.7 g, 27.49 mmol), $PdCl_2(PPh_3)_2$ (0.062 g, 0.09 mmol) and CuI (0.37 g, 1.92 mmol) in toluene (25 mL) and triethylamine (11 mL). The crude product (2.30 g) was suspended in anhydrous MeOH (38 mL) together with K_2CO_3 (4.20 g, 30.39 mmol). The reaction was sirred for 24 h. The crude product (0.50 g) was purified via silica column chromatography (10% CH_2Cl_2 in hexane, R_f 0.28) to give **20** as a white solid (0.7 g, 67%). Data are in accordance with the literature:[34] mp 178−180 °C; FT-IR (ATR) 3284 (s), 2924 (m), 2899 (m), 2850 (m), 2106 (w), 1606 (w), 1504 (s), 1446 (w), 1402 (w), 1357 (m), 1259 (w), 1112 (w), 1016 (m), 893 (w), 830 (s), 790 (s); ^1H NMR (400 MHz, Chloroform-*d*) δ 7.52−7.46 (m, 8H), 7.45−7.38 (m, 8H), 3.06 (s, 4H), 2.12 (s, 12H); HRMS [ASAP, ion trap] (SOLID) $[M + H]^+$ calcd for $C_{42}H_{33}$ 537.2577, found 537.2572.

*Biradical (**21**).* Bis-phenol **22** (0.09 g, 0.19 mmol), TPC **5** (0.09 g, 0.5 mmol), DMAP (0.06 g, 0.49 mmol), and EDCI·HCl (0.08 g, 0.52 mmol) in THF (15 mL) were reacted according to general procedure A. The mixture was left stirring for 40 h. The crude product (0.25 g) was purified (4% H_2O aluminum oxide; CH_2Cl_2, R_f 0.4) to give **21** as a pale yellow solid (0.07 g, 45%): mp 212−214 °C; FT-IR (ATR) 2933 (w), 2868 (w), 1730 (s), 1490 (m), 1346 (m), 1286 (m), 1185−1149 (s), 999 (s), 800 (s); HRMS [ESI, ion trap] $[M + NH_4]^+$ calcd for $C_{52}H_{50}N_3O_6$ 812.3694, found 812.3697. Anal. Calcd for $C_{52}H_{46}N_2O_6$: C, 78.57; H, 5.83; N, 3.52. Found: C, 78.47; H, 5.84; N, 3.42. Room temperature CW EPR displays a characteristic three line nitroxide spectrum: $a_{iso}(^{14}N)$ = 1.42(1) mT.

*Bis-phenol (**22**).* 4-Hydroxy-4′-iodobiphenyl **16** (0.30 g, 1.01 mmol), $PdCl_2(PPh_3)_2$ (0.01 g, 0.02 mmol), CuI (0.005 g, 0.02 mmol), and 1,3-diethynylbenzene **18** (0.09 mL, 0.61 mmol), 0.5 M aqueous ammonia solution (5 mL) in THF (5 mL) were reacted according to general procedure B. The mixture was stirred for 24 h before being heated to 60 °C for 2 h. The crude product (0.48 g) was purified (silica gel, 10% EtOAc in CH_2Cl_2, R_f 0.5) to give **22** as a pale brown solid (0.32 g, 69%): mp 272−274 °C; ^1H NMR (300 MHz, DMSO-d_6) δ_H 9.67 (s, 2H), 7.81−7.46 (m, 16H), 6.87 (4H, d, *J* 8.6); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ_C 157.7, 140.6, 133.9, 132.0, 131.4, 129.7, 129.4, 127.9, 126.1, 123.1, 119.7, 115.9, 90.3, 88.7; HRMS [NSI, ion trap] $[M - H]^-$ calcd for $C_{34}H_{21}O_2$ 461.1547, found 461.1544.

*Tris-phenol (**23**).* 4-Hydroxy-4′-iodobiphenyl **16** (0.27 g, 0.91 mmol), $PdCl_2(PPh_3)_2$ (0.02 g, 0.03 mmol), CuI (0.003 g, 0.02 mmol), and 1,3,5-triethynylbenzene **19** (0.05 g, 0.3 mmol), 0.5 M aqueous ammonia solution (15 mL) in THF (15 mL) were reacted according to general procedure B. The reaction mixture was stirred at room temperature for 24 h and heated to 60 °C for 2 h. The crude product (0.26 g) was purified (silica gel, dry-load, 2% MeOH in CH_2Cl_2, R_f 0.5) to give **23** as a colorless oil, which turned into pale brown flakes when washed with CH_2Cl_2 (0.09 g, 60%): mp 134−136 °C; ^1H NMR (300 MHz, DMSO-d_6) δ_H 9.68 (s, 3H), 7.76−7.55 (m, 21H), 6.88 (6H, d, *J* 8.6); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ_C 157.7, 140.7, 133.6, 132.1, 129.7, 127.9, 126.1, 123.9, 119.5, 115.9, 91.1, 87.9; HRMS [NSI, ion trap] $[M - H]^-$ calcd for $C_{48}H_{29}O_3$ 654.2122, found 654.2122.

*Triradical (**24**).* Tris-phenol **23** (0.05 g, 0.08 mmol), TPC **5** (0.06 g, 0.33 mmol), DMAP (0.03 g, 0.25 mmol), and EDCI·HCl (0.05 g, 0.32 mmol) in THF (10 mL) were reacted according to general procedure A. The reaction mixture was stirred 48 h. The crude product (0.08 g) was purified (4% H_2O aluminum oxide; 10% EtOAc in CH_2Cl_2, R_f 0.7) to give **24** as a yellow solid (0.1 g, 80%): mp 159−160 °C; FT-IR (ATR) 2974 (w), 2927 (w), 1730 (m), 1490 (m), 1286 (m), 1203(s), 1180(s), 1002 (s), 798 (s); HRMS [NSI, ion trap] $[M + NH_4]^+$ calcd for $C_{75}H_{70}N_4O_9$ 1170.5137, found 1170.5142. Anal. Calcd for $C_{75}H_{66}N_3O_9$: C, 78.10; H, 5.77; N 3.64. Found: C, 77.86; H, 5.85; N, 3.54. Room temperature CW EPR displays a characteristic three line nitroxide spectrum: $a_{iso}(^{14}N)$ = 1.42(1) mT.

*1,3,5,7-Tetraphenyladamantane (**26**).* 1-Bromo adamantane **25** (6.00 g, 27.89 mmol) was reacted following the procedure described by Reichert et al.[38] in the presence of *tert*-butyl bromide (9.5 mL, 84.59 mmol) and $AlCl_3$ (0.37 g, 2.77 mmol) to give **26** as a white solid after chloroform Soxhlet extraction (11.50 g, 90%): mp > 300 °C; FT-IR (ATR) 3020 (m), 1597 (m), 1494 (m), 1442 (m), 1355 (m), 1078 (m), 1031 (m), 750 (s); ^{13}C CP/MAS NMR (14.1 T) δ_C (ppm) 39.2, 45.1, 51.3, 124.7, 127.2, 129.1, 130.2, 149.8.

*1,3,5,7-Tetrakis(4-iodophenyl)adamantane (**28**).* Following the procedure described by Drew et al.,[42] **26** (2.00 g, 4.54 mmol) was reacted with iodine (4.60 g, 9.06 mmol) and [bis(trifluoroaceteoxy)-iodo]benzene **27** (4.00 g, 9.30 mmol). The crude product (4.80 g) was purified via silica column chromatography (5:1 hexane in CH_2Cl_2, R_f 0.13) to give **28** as a white solid (2.20 g, 51%) with data in accordance with the literature:[31] mp 236−238 °C {lit.[42] 250 °C ($CHCl_3$, MeOH)}; FT-IR (ATR) 2920 (w), 2897 (w), 2850 (w), 1483 (s), 1446 (w), 1388 (m), 1355 (m), 1211 (w), 1176 (w), 1064 (m), 1002 (s), 887 (w), 821 (s), 775 (s); ^1H NMR (400 MHz, methylene chloroform-*d*) δ 7.72−7.61 (m, 8H), 7.23−7.14 (m, 8H), 2.06 (s, 12H); HRMS [ASAP, ion trap] (SOLID) $[M]^+$ calcd for $C_{34}H_{28}I_4$ 943.8364, found 943.8366.

*Tetrakis-phenol (**29**).* Compound **28** (0.5 g, 0.53 mmol), $PdCl_2(PPh_3)_2$ (0.02 g, 0.03 mmol), and CuI (0.002 g, 0.01 mmol) were dissolved THF (10 mL). 4′-Ethynyl-[1,1′-biphenyl]-4-ol **30** (0.53 g, 2.72 mmol) was dissolved THF (5 mL) in a separate flask. The two flasks were degassed using freeze−pump−thaw cycles (×3). The alkyne solution was added dropwise to the first flask. The obtained mixture was degassed once more before dropwise addition of 10 mL of a 0.5 M aqueous ammonia solution. The reaction mixture was heated to 60 °C under nitrogen atmosphere for 40 h before being heated under reflux for 30 min. The two phases were separated, and the aqueous layer was extracted with EtOAc. The organic layer was dried over $MgSO_4$, and solvents were removed. The obtained solids (3.5 g) were triturated with toluene and filtered to give **29** as a brown solid (0.65 g, 60%): mp > 300 °C; FT-IR (ATR) 2927 (w), 1734 (m), 1718 (m), 1604 (w), 1506 (m), 1490 (m), 1438 (w), 1348 (m), 1286 (m), 1238 (m), 1990 (s), 1002 (s), 810 (s), 800 (s); ^1H NMR (400 MHz, DMSO-d_6) δ_H 9.66 (s, 4H), 7.64−7.54 (m, 40H), 6.86 (d, *J* 8.2, 8H), 2.12 (s, 12H); $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6, 80 °C) δ_C 157.2, 149.6, 140.0, 131.4, 130.9, 129.7, 127.3, 125.6, 125.2, 120.0, 119.8, 115.6, 89.5, 88.8, 45.6; HRMS [MALDI, TOF] [M]+ calcd for $C_{90}H_{64}O_4$ 1208.4805, found 1208.4633.

4′-Ethynyl-[1,1′-biphenyl]-4-ol (**30**). 4-Hydroxy-4′-iodobiphenyl **16** (2.00 g, 6.75 mmol), $PdCl_2(PPh_3)_2$ (0.05 g, 0.07 mmol), CuI (0.04 g, 0.21 mmol), trimethylsilylacetylene (1.5 mL, 10.54 mmol), and 0.5 M aqueous ammonia solution (35 mL) in THF (120 mL) were reacted according to general procedure B. The reaction was stirred at room temperature for 16 h. The crude product (2.16 g) was purified (silica gel, 10% MeOH in CH_2Cl_2, R_f 0.16). The obtained product (1.62 g, 6.08 mmol) and K_2CO_3 (1.00 g, 7.24 mmol) were dissolved in dry methanol (20 mL). The solution was left stirring under nitrogen atmosphere for 20 h. The reaction mixture was taken up in EtOAc and washed with water (×3). The organic phase was dried over $MgSO_4$, and solvents were removed under reduced pressure. No further purification was carried out, giving **30** as a pale brown solid (1.18 g, 80%). Data in accordance with literature:[43] mp 152−154 °C; FT-IR (ATR) 3373 (w), 3356 (w), 1595 (m), 1522 (m), 1477 (m), 1259 (m), 1246 (m), 997 (m), 800 (s); ^1H NMR (400 MHz, chloroform-*d*) δ_H 7.59−7.43 (m, 6H), 6.91 (d, 2H), 4.86 (s, 1H); HRMS [ASAP, ion trap] $[M + H]^+$ calcd for $C_{14}H_{11}O$ 195.0804, found 195.0805.

Tetraradical (**31**). Tetraphenol **29** (0.15 g, 0.12 mmol), TPC **5** (0.12 g, 0.65 mmol), DMAP (0.08 g, 0.65 mmol), and EDCI·HCl (0.10 g, 0.64 mmol) in THF (20 mL) were reacted according to general procedure A. The reaction mixture was stirred 48 h. The crude product (0.30 g) was purified (4% H_2O aluminum oxide; 20% ethyl acetate in CH_2Cl_2, R_f 0.03) to give **31** as a dark orange solid (0.23 g, 72%): mp > 300 °C; FT-IR (ATR) 3034 (w), 2974 (w), 2927 (w), 1732 (m), 1504 (m), 1490 (m), 1288 (m), 1200 (s), 1002 (s), 831 (m), 800 (m); MS [MALDI, TOF] $[M + H]^+$ calcd for $C_{126}H_{113}N_4O_{12}$ 1872.8, found 1872. Anal. Calcd for $C_{126}H_{113}N_4O_{12}$: C, 80.74; H, 6.02; N, 2.99. Found: C, 80.65; H, 6.15; N, 3.12. Room temperature CW EPR displays a characteristic three line nitroxide spectrum: $a_{iso}(^{14}N)$ = 1.43(1) mT.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^1H and ^{13}C $\{^1H\}$ NMR spectra for newly synthesized diamagnetic compounds, analysis of the ^{13}C CP MAS NMR spectrum of 1,3,5,7-tetraphenyladamantane, continuous wave EPR spectra of target molecules **7**, **9**, **13**, **21**, **24**, and **31**, and X-ray crystal structures in CIF format of bi- and triradicals **7** and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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