Palladium-Catalyzed Cross-Coupling Reactions of Paramagnetic Vinyl Bromides and Paramagnetic Boronic Acids

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Received 25 July 2005; revised 18 August 2005

Dedicated to Prof. Ernő Brücher on the occasion of his 70th birthday

Abstract: Suzuki reactions are utilized for the synthesis of hetero-bifunctional cross-linking reagents (thiol- or aminospecific and photoactivatable), polyaromatics (such as phenanthrene) and heterocycles (such as coumarin and quinoline), anellated nitroxides and paramagnetic, biologically active molecules (such as cis-stilbene and nicotinamide). Furthermore, the synthesis of new vinyl and allyl boronic acid esters is also reported.

Key words: boron, cross-coupling, free radicals, heterocycles, palladium

A variety of applications of stable nitroxide free radicals has been described to date. The most important ones are spin-labelling,1 utilization as a co-oxidant,2 as double (fluorescent and spin) sensor reagent,3 as building blocks of organic magnets4 and oxymetry reagents,5 just to mention a few.

Today, most of these applications require properly designed stable nitroxide free radicals; however, the formation of the carbon–carbon bond is often a troublesome reaction in the presence of a nitroxide free radical moiety. Several methods have been reported from our and other laboratories, such as Grignard reaction,6 Wittig reaction,7 aldol condensation,8 Michael addition9 and Diels–Alder reaction.10 Recently, we have found that the palladium-catalyzed cross-coupling reactions11 can be accomplished under mild conditions and tolerate a wide variety of functional groups including the nitroxide moiety. This observation was important because the application of palladium-catalyzed cross-coupling reactions increases exponentially. We were able to underline this tendency12 also in nitroxide chemistry by showing the possibility of synthesizing a variety polysubstituted nitroxides. The only prerequisite of this cross-coupling reaction is the synthesis of paramagnetic vinyl halogenides available from the Favorskii reaction13 or from the oxidation of hydrazones.14 The other challenge in this field was the synthesis of a paramagnetic boronic acid15 in order to couple the paramagnetic boronic acid with any aryl, vinyl, or hetaryl halogenides. In this paper we extend the utilization of cross-coupling reactions to paramagnetic vinyl halogenides to obtain new spin labels, double (spin and fluorescence) sensor molecules with a polyaromatic fluorophore, paramagnetically modified bioactive molecules, and new paramagnetic boronic acid esters.

In the cross-coupling spin-label reagent synthesis β-bromo-α,β-unsaturated ester 1 reacted with 4-benzoylphenylboronic acid under N2 in aqueous dioxane in the presence of Na2CO3 base and Pd(PPh3)4 as catalyst to give compound 2a. The introduction of the benzophenone group makes this reagent photoactivatable at 350 nm. Esters 2a was hydrolyzed to acid 2b, which was converted into succinate 2c with DCC and N-hydroxysuccinimide. This means that 2c is a cross-linking reagent with an amino-specific and with a photoactivatable arm. Reaction of compound 1 with 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol under the above conditions directly gave paramagnetic coumarin 3 as a result of the Suzuki cross-coupling reaction followed by a base-catalyzed transesterification reaction. The Suzuki reaction of alcohol 4 with 4-benzoylphenylboronic acid gave compound 5a in which the alcohol substituent was converted into bromide 5b via its mesylate. This bromide was replaced with SSO2CH3, which is a thiol-specific arm, forming a cleavable S–S bond with a cysteine side-chain,16 meaning that compound 5c can be regarded as a thiol-specific and photoactivatable cross-linking spin-label reagent. It can be utilized in a similar way as the earlier published cross-linking reagent with an aromatic azide (photoactivatable arm) and with a methanethiosulfonate (thiolspecific arm)17 (Scheme 1).

Continuing our earlier work on heterocycle-anellated nitroxides, aldehyde 6 was treated with 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline in the presence of an aqueous Na2CO3/dioxane solution and Pd(PPh3)4 as catalyst, giving quinoline derivative 7 in a one-pot procedure with an imine formation and Suzuki cross-coupling reaction.18 It is interesting to note that heating aniline with compound 6 in DMF gave isoquinoline 8 which is an isomer of compound 7.19 Reaction of β-bromo-α,β-unsaturated nitrile 9 with 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline in the presence of Cs2CO3, amidoadamantane bases and Pd(OAc)2 as catalyst gave the paramagnetic 2-aminoquinoline20 derivative 10 (Scheme 2).

SYNTHESIS 2006, No. 3, pp 0439–0446
Advanced online publication: 11.01.2006
DOI: 10.1055/s-2006-926279; Art ID: P10305SS
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Reagents and conditions: (a) 2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.1 equiv), Pd(PPh₃)₄ (0.05 equiv), dioxane/aq Na₂CO₃, under N₂, 2 h, 38%; (b) Aniline (1.1 equiv), DMF, 80 °C, 3 h, 56%; (c) 2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.1 equiv), Pd(OAc)₂ (0.05 equiv), 1-adamantane-amine (0.4 equiv), Cs₂CO₃ (2.2 equiv), dioxane, 16 h, 45%

Scheme 2

Reagents and conditions: (a) 4-Benzoylphenylboronic acid (1 equiv), Pd(PPh₃)₄ (0.05 equiv), dioxane/aq Na₂CO₃, under N₂, 4 h, 53–68%; (b) 2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (1.1 equiv), Pd(PPh₃)₄ (0.05 equiv), dioxane/aq Na₂CO₃, under N₂, 2 h, 76%; (c) NaOH/MeOH, reflux, 1 h, then r.t., 12 h, H⁺, 78%; (d) N-Hydroxysuccinimide (1 equiv), DCC (1 equiv), EtOAc, r.t., 3 h, 55%; (e) MsCl (1.1 equiv), Et₃N (1.1 equiv), CH₂Cl₂, 0 °C → r.t., 1 h, then LiBr, acetone, reflux, 30 min, 49%; (f) NaSSO₂CH₃ (2.0 equiv), acetone–H₂O, reflux, 45 min, 62%

Scheme 1

Reagents and conditions: (a) Phenylboronic acid (1 equiv), PdCl₂(PPh₃)₂ (0.05 equiv), Ba(OH)₂·9H₂O (1 equiv), dioxane–H₂O, reflux, 2 h, under N₂, 24% for 12 and 20% for 13; (b) Ascorbic acid (10 equiv), dioxane–H₂O, then extraction, AcCl (1.1 equiv), Et₃N (1.1 equiv), 0 °C → r.t., 1 h, then LiBr, acetone, reflux, 30 min, 49%; (c) NaOH/MeOH, reflux, 1 h, then r.t., 12 h, H⁺, 78%; (d) N-Hydroxysuccinimide (1 equiv), DCC (1 equiv), EtOAc, r.t., 3 h, 55%; (e) MsCl (1.1 equiv), Et₃N (1.1 equiv), CH₂Cl₂, 0 °C → r.t., 1 h, then LiBr, acetone, reflux, 30 min, 49%; (f) NaSSO₂CH₃ (2.0 equiv), acetone–H₂O, reflux, 45 min, 62%

Reaction of dibromide 11 with one equivalent of phenylboronic acid gave a mixture of compounds 12 and 13 (2:3 ratio). Vinyl bromide 12 was converted into O-acetyl-protected (to avoid O-butylation) derivative 14. Treatment of compound 14 with n-BuLi afforded the 3-lithiopyrroline whose reaction with trimethylborate gave the corresponding boronic acid. After the oxidation of the nitroxide, the formed boronic acid was not purified, but after isolation it was converted into its pinacolate ester 15 with pinacol alcohol in the presence of MgSO₄ in MeOH. Suzuki reaction of dibromide 11 and 1-naphthylboronic acid in a sealed tube in the presence of DBU as base and Pd₂(dba)₃ as catalyst furnished paramagnetic cyclopent[a]acenaphthylene 16. Our next polyaromatic target was phenanthrene. The Suzuki cross-coupling of bromide 12 and 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline in the presence of Pd(PPh₃)₄ as catalyst provided amine 17. Diazotation of the aromatic amide and heating of an aqueous solution of the diazonium salt in the presence of Cu powder gave phenanthrene-anellated nitroxide 18 in a Pschorr reaction (Scheme 3).
Starting from 4-oxo-TEMPO (19) we synthesized its 4-ido-1,2,3,6-tetrahydro-pyridine derivative. Treatment of the starting ketone with hydrazine hydrate followed by oxidation with iodine in diethyl ether in the presence of tetramethyl guanidine (TMG) yielded compound 20. Unfortunately, our attempt to obtain the six-membered para-tetramethyl guanidine (TMG) yielded compound oxidation with iodine in diethyl ether in the presence of the starting ketone with hydrazine hydrate followed by an addition reaction symmetrical paramagnetic diene 28. This 1,2-addition was proven by 1H NMR spectroscopy studies on the O-acetyl derivative of 28. The assumed arrangement of protons was confirmed by mononuclear decoupling experiments: selective irradiation of the CH triplet (δ = 1.79 ppm) only resulted in the change of the CH₃ multiplet (δ = 1.03 ppm). This proton arrangement is true only for the 1,2-addition product. The addition of bis(pinacolato)diboron to paramagnetic terminal acetylene 29 in DMF catalyzed by Pt(PPh₃)₄ afforded compound 30. A Suzuki reaction of this bis(vinylboronic acid) and 4-bromophenol provided paramagnetic Z-hydroxystilbene compound 31 (Scheme 5). The importance of this type of compound is well supported by the fact that several hydroxylated stilbenes exhibit important biological properties.

In conclusion, Suzuki reactions can be accomplished with paramagnetic vinyl halogenides in synthetic target-oriented syntheses to create heterocycles, carbocycles, anellated nitroxides as well as cross-linking spin-label reagents. Paramagnetic boronic acids can be applied in C–C bond forming reactions in the presence of a great variety of functional groups which are retained to obtain bioactive paramagnetic molecules.

Melting points were determined with a Boetius micro melting point apparatus and are uncorrected. Elemental analyses (C, H, N, S) were performed on Fisons EA 1110 CHNS elemental analyzer. The IR (Specord 85) spectra were in each case consistent with the assigned structure. Mass spectra were recorded on Thermoquest Automass Multi and VG TRIO-2 instruments in EI mode. 1H NMR spectra were recorded on a Varian UNITY/NOVA 400 WB spectrometer. Chemical shifts are referenced to Me₄Si. Measurements were run at 298K-probe temperature in CDCl₃ solution. To obtain high-resolution NMR spectra of the radicals those compounds were reduced by co-dissolved PhNHNHPH additive. ESR spectra were taken on a Miniscope MS 200 in 10⁻⁴ M CHCl₃ solution. All monoradicals gave triplet lines between a_N = 14.7–15.1 G whereas biradical 22 gave a quartet line at a_N = 15.2 G, a_N = 7.4 G. Flash column chromatography was performed on Merck Kieselgel 60 (0.040–0.063 mm). Qualitative TLC was carried out on commercially prepared plates (20 × 20 × 0.2 cm) coated with Merck Kieselgel 60 F₂₅₄. Resolution NMR spectra of the radicals those compounds were recorded on a Varian INOVA 400 WB spectrometer at 400 MHz. 1H NMR spectra were performed on Fisons EA 1110 CHNS elemental analyzer. The IR (Specord 85) spectra were in each case consistent with the assigned structure. Mass spectra were recorded on Thermoquest Automass Multi and VG TRIO-2 instruments in EI mode. 1H NMR spectra were recorded on a Varian UNITY/NOVA 400 WB spectrometer. Chemical shifts are referenced to Me₄Si. Measurements were run at 298K-probe temperature in CDCl₃ solution. To obtain high-resolution NMR spectra of the radicals those compounds were reduced by co-dissolved PhNHNHPH additive. ESR spectra were taken on a Miniscope MS 200 in 10⁻⁴ M CHCl₃ solution. All monoradicals gave triplet lines between a_N = 14.7–15.1 G whereas biradical 22 gave a quartet line at a_N = 15.2 G, a_N = 7.4 G. Flash column chromatography was performed on Merck Kieselgel 60 (0.040–0.063 mm). Qualitative TLC was carried out on commercially prepared plates (20 × 20 × 0.2 cm) coated with Merck Kieselgel G 60 F₂₅₄. 4-Benzoylphenylboronic acid, 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline, 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol, 1-naphthyl boronic acid, compound 19 as well as palladium and platinum catalysts were purchased from Aldrich. Compounds 1, 4, 6, 9, 11, 13, 14, 24, 26, 29 and 27 were prepared according to published procedures.

Suzuki Coupling Reaction (2a, 3, 5a, 7, 17, 23, 31): General Procedure
A solution of vinylc bromide (1, 4, 6, 12, 5-bromocinomatime, or 4-bromophenol) (2.0 mmol) and Pd(PPh₃)₄ (100 mg, 0.1 mmol) in dioxane (10 mL) was purged with N₂ for 5 min. Then boronic acid or boronic acid ester (2.0 mmol, for 31 only 1.0 mmol diester) was added followed by aq NaOH (10%, 10 mL). The mixture was stirred and heated to reflux under N₂ until the consumption of the starting halogen compound (2–8 h, followed by TLC). After cooling, the dark-yellow or brown solution was evaporated in vacuo, brine (10 mL) was added and the aqueous phase was washed with CHCl₃ (2 × 20 mL). The organic phase was dried (MgSO₄), filtered...
and evaporated. The residue was purified by flash column chromatography (hexane–EtOAc or CHCl₃–Et₂O) to give the compounds in 38–76% yield.

4-(4-Benzoylphenyl)-3-carbethoxy-2,2,5,5-tetramethyl-2,5-dihydro-1H-pyrrol-1-yloxyl Radical (2a)
From compound 1 and 4-benzoylphenylboronic acid with 4 h heating.
Yellow solid; yield: 533 mg (68%); mp 100–101 °C; Rf = 0.44 (hexane–EtOAc, 2:1).
IR (nujol): 1710, 1660 (C=O), 1590 (C=C) cm⁻¹.
MS (EI): m/z (%) = 392 (M⁺, 13), 377 (2), 105 (100), 77 (53).
Anal. Calcd for C₂₄H₂₆NO₄: C, 73.45; H, 6.68; N, 3.57. Found: C, 73.39; H, 6.62; N, 3.41.

1,1,3,3-Tetramethyl-2,3-dihydrochromeno[3,4-c]pyrrol-4(1H)-4-one-2-yloxyl Radical (3)
From compound 1 and 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol with 2 h heating.
Yellow solid; yield: 392 mg (76%); mp 205–206 °C; Rf = 0.4 (hexane–EtOAc, 2:1).
IR (nujol): 1720 (C=O), 1600, 1570 (C=C) cm⁻¹.
MS (EI): m/z (%) = 258 (M⁺, 4), 243 (100), 228 (59), 213 (67), 115 (33).

4-(4-Benzoylphenyl)-3-hydroxymethyl-2,2,5,5-tetramethyl-2,5-dihydro-1H-pyrrol-1-yloxyl Radical (5a)
From compound 4 and 4-benzoylphenylboronic acid with 4 h heating.
Yellow solid; yield: 413 mg (53%); mp 134–136 °C; Rf = 0.23 (CHCl₃–Et₂O, 2:1).
IR (nujol): 3400 (OH), 1660 (C=O), 1560 (C=C) cm⁻¹.
MS (EI): m/z (%) = 350 (M⁺, 4), 335 (3), 128 (15), 105 (100), 77 (79).
Anal. Calcd for C₂₂H₂₄NO₃: C, 75.40; H, 6.90; N, 4.00. Found: C, 75.36; H, 6.88; N, 3.89.

1,1,3,3-Tetramethyl-1,3-dihydro-2H-pyrrolo[3,4-c]quinolin-2-yl Radical (7)
From compound 6 and 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline with 2 h heating.
Yellow solid; yield: 183 mg (38%); mp 157–159 °C; Rf = 0.25 (hexane–EtOAc, 2:1).
IR (nujol): 1650 (C=N), 1570 (C=C) cm⁻¹.
MS (EI): m/z (%) = 241 (M⁺, 91), 226 (95), 211 (100), 196 (62).
Anal. Calcd for C₁₅H₁₇N₂O: C, 74.66; H, 7.10; N, 11.61. Found: C, 74.52; H, 7.06; N, 11.57.

3-(2-Aminophenyl)-2,2,5,5-tetramethyl-4-phenyl-2,5-dihydro-1H-pyrrol-1-yloxyl Radical (17)
From compound 12 and 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline with 2 h heating.
Yellow solid; yield: 374 mg (61%); mp 160–163 °C; Rf = 0.29 (hexane–EtOAc, 2:1).

Scheme 5  Reagents and conditions: (a) Bis(pinacolato)diboron (1 equiv), Pt(PPh₃)₄ (0.05 equiv), toluene, reflux, 5 h, under N₂, 38–63%; (b) 30% H₂O₂, aq NaOH, MeOH, reflux 2 h, 67%; (c) Bis(pinacolato)diboron (1 equiv), Pt(PPh₃)₄ (0.05 equiv), DMF, 80 °C, 24 h, under N₂, 42%; (d) 4-Bromophenol (2.0 equiv), Pd(PPh₃)₄ (0.1 equiv), dioxane/aq Na₂CO₃, under N₂, 8 h, 40%
IR (nujol): 3440, 3300 (NH2), 1610, 1565 (C=C) cm⁻¹.

MS (EI): m/z (%) = 307 (M⁺, 39), 292 (7), 277 (44), 262 (27), 234 (100).

Anal. Calcd for C₁₁H₁₀NO₂: C, 77.58; H, 6.96; N, 7.29. Found: C, 77.55; H, 6.95; N, 7.30.

1′-Oxyl-2′,2′,6′,6′-tetramethyl-1′,2′,3′,6′-tetrahydro-[3,4′]-bipyridyl-5-carboxylic Acid (23)

From 5-bromonicotinamide and compound 21 with 2 h heating.

Yellow solid; yield: 213 mg (39%); mp 145–147 °C; Rf = 0.18 (CHCl₃–MeOH, 9:1).

IR (nujol): 3360, 3160 (NH₂), 1640 (C=O), 1605 (N=C=O) cm⁻¹.

MS (EI): m/z (%) = 274 (M⁺, 50), 244 (15), 229 (100).


3′-[E]-1,2-Bis[4-hydroxyphenyl(vinyl)]-2,2,5,5-tetramethyl-2,5-dihydro-1'H-pyrrrolo-1-yl oxyl Radical (31)

From 4-bromophenol (2 equiv) and diboronic acid ester 30 with 8 h heating.

Yellow solid; yield: 140 mg (40%); mp 228–230 °C; Rf = 0.25 (CHCl₃–MeOH, 9:1).

IR (nujol): 1660, 1560 (C=C) cm⁻¹.

MS (EI): m/z (%) = 350 (M⁺, 21), 336 (23), 320 (100), 305 (48).

Anal. Calcd for C₁₅H₁₉N_{10}O: C, 75.40; H, 7.52; N, 17.18. Found: C, 75.35; H, 7.29; N, 15.30.

4-(4-Benzoylphenyl)-3-bromomethyl-2,2,5,5-tetramethyl-2,5-dihydro-1'H-pyrrolo-1-yl oxyl Radical (2b)

To a solution of compound 2a (392 mg, 1.00 mmol) in MeOH (10 mL), 10% aq NaOH (5 mL) was added and the mixture was boiled under gentle reflux for 1 h and then allowed to stay at r.t. overnight. After evaporating the alcohol, the mixture was acidified with 5% aq H₂SO₄ and the precipitated solid was filtered off, the filtrate was evaporated and the residue was purified by flash column chromatography (hexane–EtOAc, 2:1).

Yellow solid; yield: 275 mg (62%); mp 156–158 °C; Rf = 0.6 (hexane–EtOAc, 2:1).

IR (nujol): 1780, 1730, 1660 (C=O), 1565 (C=C) cm⁻¹.

MS (EI): m/z (%) = 444 (M⁺, 12), 414 (12), 105 (100), 77 (60).


1,1,3,3-Tetramethyl-1,3-dihydro-2'H-pyrrolo[3,4-b]quinolin-2-yl oxyl Radical (8)

A solution of aniline (511 mg, 5.5 mmol) and aldehyde 6 (1.23 g, 5.0 mmol) in DMF (15 mL) was stirred at 80 °C for the consumption of aldehyde 6 (3 h). DMF was removed under reduced pressure, the residue was dissolved in CH₂Cl₂ (20 mL) and washed with H₂O (10 mL). The organic phase was separated, dried (MgSO₄), filtered and evaporated. The residue was purified by flash column chromatography (hexane–EtOAc, 2:1) to give compound 8.

Yellow solid; yield: 675 mg (56%); mp 156–158 °C; Rf = 0.54 (hexane–EtOAc, 2:1).

IR (nujol): 1640 (C=N), 1570 (C=C) cm⁻¹.

MS (EI): m/z (%) = 241 (M⁺, 49), 226 (26), 211 (100), 196 (80).

Anal. Calcd for C₁₉H₁₇N₃O₂: C, 74.66; H, 7.10; N, 11.61. Found: C, 74.58; H, 7.03; N, 11.55.

4-Amino-1,1,3,3-tetramethyl-1,3-dihydro-2'H-pyrrolo[3,4-c]quinolin-2-yl oxyl Radical (10)

A mixture of compound 9 (244 mg, 1.00 mmol) and Pd(OAc)₂ (12 mg, 0.05 mmol) in dioxane (15 mL) was purged with N₂ for 10 min. Adamantylamine hydrochloride (76 mg, 0.4 mmol), 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (241 mg, 1.1 mmol) and...
C₆H₅CO₂H (715 mg, 2.2 mmol) were added and the mixture was stirred under reflux for 16 h under N₂. After cooling to r.t. the mixture was concentrated in vacuo to a quarter of its initial volume and partitioned between H₂O (10 mL) and CHCl₃ (20 mL). The organic phase was separated, the aqueous phase was washed with CHCl₃ (10 mL) and the combined organic phases were dried (MgSO₄), filtered and evaporated. The residue was purified by flash column chromatography (CHCl₃–MeOH) to give compound 10.

Beige solid; yield: 115 mg (45%); mp 188–190 °C; Rₛ = 0.30 (CHCl₃–MeOH, 9:1).

IR (nujol): 3430, 3300 (NH), 1640 (C=O), 1625 (C=O) cm⁻¹.

MS (EI): m/z (%) = 256 (M⁺, 93), 241 (100), 226 (82), 211 (47).

Anal. Calcd for C₄H₅N₂O₂C: 70.21; H, 7.00; N, 16.28.

3-Bromo-2,2,5,5-tetramethyl-4-phenyl-2,5-dihydro-1H-pyrrol-1-ylperoxyl Radical (12)

A solution of compound 11 (2.98 g, 10.0 mmol), phenylboronic acid (1.21 g, 10.0 mmol), PdCl₂(PPh₃)₂ (350 mg, 0.5 mmol) and Na₂CO₃ (3.15 g, 10.0 mmol) in dioxane (32 mL) and H₂O (8 mL) was stirred and heated to reflux for 2 h under N₂. After cooling, the brownish-black mixture was filtered through celite and the celite pad was washed with MeOH (20 mL). The filtrate was evaporated in vacuo. The residue was partitioned between brine (10 mL) and EtOAc (20 mL). The aqueous phase was washed with EtOAc (20 mL) and dried (MgSO₄) under N₂. First acetyl chloride (430 mg, 5.5 mmol) was added followed by Et₃N (555 mg, 5.5 mmol), 1-(Acetyloxy)-3-bromo-2,2,5,5-tetramethyl-4-phenyl-2,5-dihydro-1H-pyrrole (12) was added and the mixture was purged with N₂ for 10 min. The tube was closed, immersed in an oil bath and the solution was stirred at 150 °C for 10 min. Then the tube was cooled, immersed in an oil bath and the solution was stirred at 150 °C for 2 h. Stirring was continued for 1 h at r.t., the mixture was filtered, evaporated and the residue was suspended in toluene (50 mL) and heated under reflux for 1 h in a Dean–Stark apparatus to remove water. The toluene was evaporated and the residue was dissolved in anhyd MeOH (20 mL). MgSO₄ (4.8 g, 40 mmol) and anhyd pinacol (472 mg, 4.0 mmol) were added and the mixture was stirred overnight at r.t. Then the MgSO₄ was filtered off, the filtrate was evaporated and the residue was partitioned between H₂O (10 mL) and EtOAc (20 mL). The organic phase was dried (MgSO₄), filtered and evaporated and the residue was purified by flash column chromatography (hexane–EtOAc, 2:1) to yield compound 15.

Yellow solid; yield: 452 mg (33%); mp 148–150 °C; Rₛ = 0.71 (hexane–EtOAc, 2:1).

IR (nujol): 1600, 1560 (C=C) cm⁻¹.

MS (EI): m/z (%) = 342 (M⁺, 28), 327 (52), 312 (100).

Anal. Calcd for C₂₀H₂₉BNO₃: C, 70.19; H, 8.54; N, 4.09.

1,1,3,3-Tetramethyl-1,3-dihydro-2H-dibenzo[e]isoindol-2-ylperoxyl Radical (18)

To a stirred solution of compound 17 (307 mg, 1.0 mmol) in aq 1 M HCl (10 mL), Na₂O₂ (76 mg, 1.1 mmol) dissolved in H₂O (5 mL) was added dropwise under reflux and the mixture was stirred at this temperature for 30 min. The solution of the diazonium salt was poured onto a vigorously stirred suspension of Cu powder (5 g, 78.0 mmol)
in H2O (10 mL) and the mixture was heated to 60 °C and stirred at this temperature for 40 min. After cooling, the aqueous phase was extracted with EtOAc (2 x 10 mL), the combined organic phase was dried (MgSO4), filtered and evaporated. Chromatographic purification (hexane–EtOAc, 2:1) of the residue afforded the paramagnetic phenanthrene derivative 18.

Yield: 78 mg (27%); mp 174–176 °C; Rf = 0.42 (hexane–EtOAc, 2:1).

IR (nujol): 1600, 1560 cm⁻¹.

MS (EI): m/z (%) = 290 (M⁺, 33), 275 (100), 260 (41).

Anal. Calcd for C15H27BNO3: C, 64.30; H, 9.71; N, 5.00. Found: C, 64.27; H, 9.62; N, 4.87.

Addition of Bis[pinacolato]diboron to Dienes and Acetylene (25, 28, 30): General Procedure
A solution of bis[pinacolato]diboron (508 mg, 2.0 mmol) and Pt(PPh3)4 (124 mg, 0.1 mmol) in toluene (10 mL, for 25 and 28) or in DMF (10 mL, for 30) was purged with N2. Then diene 24 or 27, or acetylene 29 was added and the mixture was heated to reflux in toluene for 5 h (25 and 28) or heated at 80 °C for 24 h (30) under N2. After cooling, the solvents were evaporated under reduced pressure, the residue was taken up in EtOAc (20 mL), and washed with H2O (10 mL). The organic phase was separated, dried (MgSO4), filtered and evaporated and the residue was purified by flash column chromatography (hexane–EtOAc, 2:1) to give the diboronic esters in 38–63%.

2,2,5,5-Tetramethyl-3,4-bis[(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl]-2,5-dihydro-1H-1-pyrrol-1-yl oxide Radical (25)

Yield: 529 mg (63%); mp 78–80 °C; Rf = 0.51 (hexane–EtOAc, 2:1).

IR (nujol): 1650 (C=C) cm⁻¹.

1H NMR of 25: Ac derivative (400 MHz, CDCl3): δ = 1.25 (s, 24 H, CH3), 1.41 (s, 12 H, CH2), 1.66 (s, 4 H, CH). MS (EI): m/z (%) = 420 (M⁺, 11), 405 (10), 390 (100).


3-[1,2-Bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl]-2,2,5,5-tetramethyl-2,5-dihydro-1H-1-pyrrol-1-yl oxide Radical (28)

Yield: 319 mg (38%); mp 71–73 °C; Rf = 0.51 (hexane–EtOAc, 2:1).

IR (nujol): 1650 (C=C) cm⁻¹.

1H NMR of 28: OAc derivative (400 MHz, CDCl3): δ = 1.05 (m, J = 3.2 Hz, 2 H, CH2), 1.21 (s, 36 H, CH3), 1.79 (t, J = 1.6 Hz, 1 H, CH), 2.13 (s, 3 H, CH2CO), 5.25 (d, J = 1.6 Hz, 1 H, =CH). MS (EI): m/z (%) = 420 (M⁺, 7), 406 (16), 390 (100).


3-[1,2-Bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl]-2,2,5,5-tetramethyl-2,5-dihydro-1H-1-pyrrol-1-yl oxide Radical (30)

Yield: 351 mg (42%); mp 69–71 °C; Rf = 0.51 (hexane–EtOAc, 2:1).

IR (nujol): 1650 (C=C) cm⁻¹.

MS (EI): m/z (%) = 418 (M⁺, 8), 403 (25), 388 (100).


3,4-Bis(hydroxymethyl)-2,2,5,5-tetramethyl-2,5-dihydro-1H-1-pyrrol-1-yl oxide Radical (26)

To a stirred solution of compound 25 (420 mg, 1.0 mmol) in MeOH (10 mL), 10% aq NaOH solution (1 mL) and 30% H2O2 (1 mL) were added and the mixture was heated to reflux for 2 h. After cooling,
the mixture was extracted with CHCl₃ (2 × 10 mL), the organic phase was dried (MgSO₄), filtered and evaporated. Compound 26 was obtained after flash column chromatography purification (CHCl₃–MeOH, 9:1).

Yellow solid; yield: 134 mg (67%); mp 155–156 °C; \( R_f = 0.55 \) (CHCl₃–MeOH, 9:1).

Acknowledgment
This work was supported by a grant from Hungarian National Research Foundations (OTKA T042951, T48334 and M045190). The authors thank Noémi Lazsányi for elemental analyses and Mária Szabó for mass spectral measurements (ICN, Hungary).

References