Synthesis of New, Paramagnetically Modified Heterocycles

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Dedicated to Prof. Albert Lévai on the occasion of his 65th birthday.

Abstract: Starting from readily available paramagnetic five- and six-membered ketones and pyrroline aldehyde, a range of spin labeled heterocycles such as benzazoles, pyrrole, oxazole, quinoline, benzofuran, thiadiazole have been synthesized in both 'classical' and Pd-catalyzed reactions. These methods were used in the synthesis of paramagnetic ligands such as oxin and porphyrin.

Key words: free radicals, heterocycles, ketones, ligands, palladium

The widespread occurrence of heterocyclic compounds in nature, both as plant and animal cell constituents and as artificial compounds such as dyes, plastics, solvents and pharmaceuticals of economic value, has focused the attention of many organic chemists to this field.[1] Nitroxides are special nitrogen heterocycles as they contain an N–O moiety with an unpaired electron. Such nitroxides have many applications including spin labels,[2] co-oxidants,[3] redox sensors,[4] SOD-mimics,[5] antioxidants,[6] polymerization mediators[7] and many others.

Researchers have been focusing on the synthesis of paramagnetically modified compounds for more than 40 years, but the incompatibility of the nitroxide moiety with many reagents is still a challenge. A properly chosen C–C bond-formation reaction is therefore required for these syntheses, for example Fisher indole synthesis,[8] Diels–Alder reaction,[9] Suzuki reaction[10] and condensation reactions.[11] Our laboratory has previously reported the synthesis of several nitroxide annulated and linked heterocycles such as 2-substituted indole,[10] flavones,[11] pyrrole, furan, pyridine,[12] thiophene,[13] pyrimidine,[14] coumarin[15] and isothiazole.[16] In this paper we have extended this work to include the syntheses of spin labeled heterocycles from paramagnetic aldehydes **1**,[17] **22**[13] and ketones **11**, **17**.[8]

Benzazoles are important heterocycles that possess a variety of biological activities. However, attempts to make the 2-substituted benzothiazole or benzoxazole derivatives using classical methods, e.g. treatment of 2-aminophenol or 2-aminothiophenol with acid chloride followed by heating, were unsuccessful.[18] Treatment of the Schiff base, formed from aldehyde **1** and 4-methyl-2-aminophenol, with iodobenzenediacetate (IBD) in acetonitrile did not gave the expected benzoxazole **3**.[19] However, when the protected *O*-acetyl[20] derivative **2** was employed under the same reaction conditions, followed by saponification with sodium methoxide, the expected 2-substituted paramagnetic benzoxazole derivative **3** was obtained after oxidation of the *N*-hydroxylamine (Scheme 1). The same solution was found for the problematic reaction of 2-aminothiophenol with **1**. Whereas heating these reagents in DMSO did not afford benzothiazole **4**, the reaction of compound **2** with 2-aminothiophenol in DMSO[21] gave, after treatment with base, followed by oxidation with MnO_2, the expected 2-substituted benzothiazole **4**.

Several classical syntheses with unprotected nitroxides such as the Doebner quinoline[22] synthesis or van Leusen synthesis[23] were also conducted. The 5-substituted oxazole **5** was prepared through the reaction of aldehyde **1**, and toluenesulphonylmethyl isocyanide (TosMIC) in the presence of sodium methoxide in refluxing methanol. Heating aldehyde **1**, aniline and pyruvic acid in ethanol yielded the 2-substituted paramagnetic cinchoninic acid **6**. The Horner–Emmons reaction of aldehyde **1** with triethylphosphonoacetate yielded the α,β-unsaturated ester **7**.[24] Reaction of compound **7** with TosMIC and potassium *tert*-butoxide in THF yielded the paramagnetic 3,4-disubstituted pyrrole **8**. Porphyrins occupy a central role in photodynamic therapy of cancer, which relies upon the selective accumulation of a photosensitizer into cancerous tissue, followed by irradiation of the diseased tissue. This idea inspired us to make a paramagnetic porphyrin, as this kind of compound may be a useful tool in the study of cancerous tissue. The method of Lindsey et al. for the synthesis of unsymmetrical porphyrins[25] was thus applied to the condensation of benzaldehyde, pyrrole and aldehyde **1**, to give, after DDQ oxidation, the paramagnetic porphyrine **9**, albeit in low yield due to the formation of tetraphenylporphyrin **10**[26] (Scheme 1).

4-Oxo-TEMPO **11** is a good source of paramagnetic vinyliodide **12**[15] which could be cross-coupled with 2-iodophenol in the presence of CuI, *N*,*N*-dimethylglycine and Cs_2CO_3 in dioxane followed by a Heck reaction in the presence of $Pd(OAc)_2$, Bu_4NHSO_4 and 4 Å molecular sieves[27] to yield the six-membered nitroxide annulated benzo[*b*]furane **13** (Scheme 2). Reaction of ketone **11** and 2-aminobenzaldehyde in the presence of NaOMe in EtOH in a Friedlander reaction gave the quinoline annulated six-

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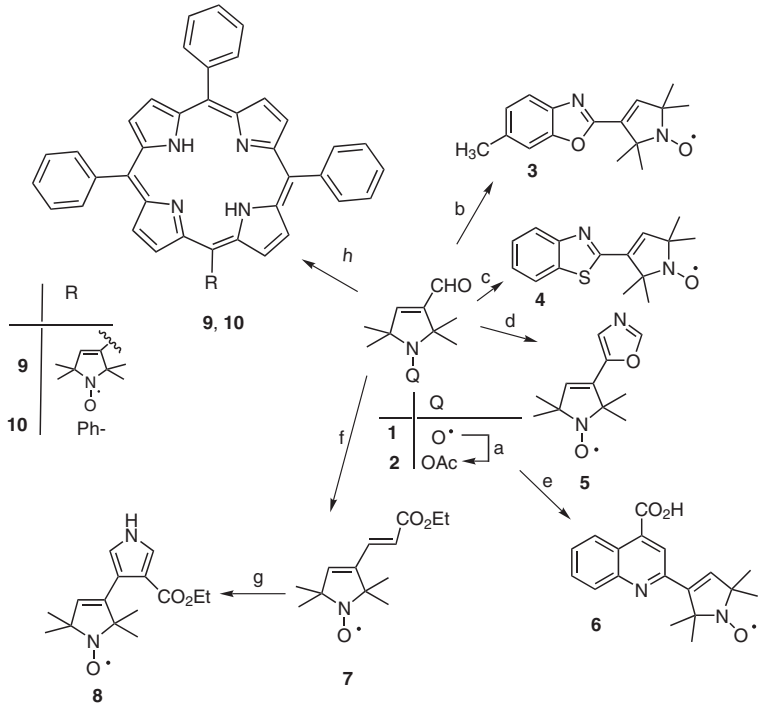
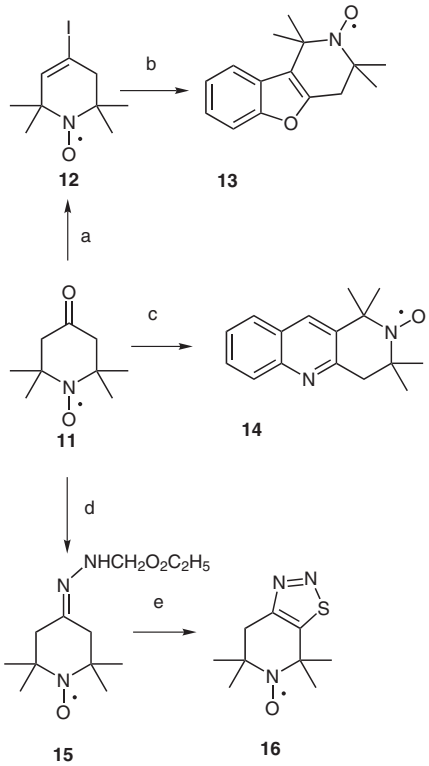


Scheme 1 *Reagents and conditions*: (a) Ascorbic acid (5 equiv), dioxane, H_2O, AcCl (1.1 equiv), Et_3N (1.1 equiv), 0 °C → r.t., 1 h, 61%; (b) **2** (1 equiv), 2-amino-5-methylphenol (1 equiv), TsOH (0.05 equiv), toluene, reflux, 3 h, then $PhI(OAc)_2$, MeCN, r.t., 30 min, then MeOH–NaOMe (0.1 equiv), r.t., 2 h, MnO_2 (0.25 equiv), O_2, r.t., 15 min 36%; (c) **2** (1.0 equiv), 2-aminothiophenol (1.0 equiv), DMSO, 90 °C, 2 h, then MeOH–NaOMe (0.1 equiv), r.t., 2 h, MnO_2 (0.25 equiv), O_2, r.t., 15 min, 33%; (d) **1** (1.0 equiv), NaOMe (5 equiv), TosMIC (1.2 equiv), MeOH, reflux, 4 h, 77%; (e) Aniline (1 equiv), **1** (1 equiv), pyruvic acid (1.5 equiv), EtOH, reflux, 3 h, 25%; (f) Ref. 24; (g), *t*-BuOK (1.1 equiv), TosMIC (1.1 equiv), THF, –78 °C→reflux, 30 min, 59%; (h) pyrrole (4 equiv), benzaldehyde (3 equiv), **1** (1 equiv), CH_2Cl_2, $BF_3{\cdot}Et_2O$ (0.2 equiv), N_2, 1 h, r.t., DDQ, 1 h, r.t., Et_3N, 7% for **9**, 3% for **10**.

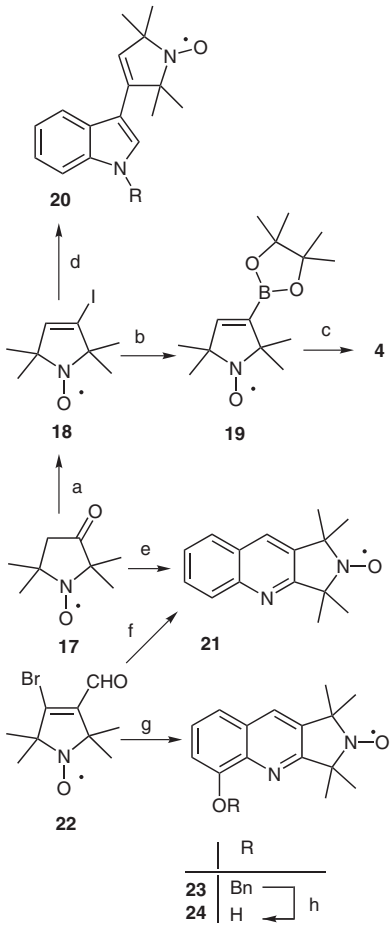
membered nitroxide **14**.[28] Treatment of 4-oxo-TEMPO with ethyl carbazate in the presence of a catalytic amount of acid in ethanol yielded the hydrazone derivative **15**, which was cyclized with a large excess of thionyl chloride in dichloromethane to the thiadiazole anellated nitroxide **16** (Scheme 2).[29] During the syntheses of these heterocycles, the five-membered ketone **17**[8] also proved to be an important starting compound (Scheme 3). Its hydrazone was oxidized with iodine in the presence of tetramethylguanidine in diethylether[15] to give the paramagnetic vinyl iodide **18**, which was converted to the paramagnetic boronic acid ester **19**[14] with bis(pinacolatodiboron) and Pd(dppf) in the presence of KOAc in DMSO.[12] Compound **19** proved to be a key starting material for the synthesis of paramagnetically modified molecules for Suzuki reactions.[14,30] For example, the reaction of 2-iodobenzothiazole[31] and compound **19** in the presence $Pd_2(dba)_3$ and K_2CO_3 in aqueous dioxane[32] yielded benzothiazole **4**, the characterization of which confirmed it to be identical to that synthesized through 'classical' methods. The vinyl iodide **18** is also a valuable substrate for Suzuki reactions. Treatment of **18** with 1-(phenylsulfonyl)-1*H*-indol-3-ylboronic acid[33] in the presence of base and $Pd(PPh_3)_4$ catalyst gave the paramagnetic 3-substituted indole derivative **20** after hydrolysis of the phenylsulfonyl group with ethanolic KOH. Reaction of ketone **17** with 2-aminobenzaldehyde in a base-catalyzed Friedlander reaction, afforded the quinoline anellated pyrroline nitroxide **21**, which has also been prepared very recently in our laboratory by heating aniline and β-bromo-α,β-unsaturated aldehyde **22** in DMF.[15] This latter reaction was successfully extended to the synthesis of paramagnetic 8-hydroxyquinoline. Heating of compound **22** with 2-benzyloxyaniline gave quinoline **23**, which was debenzylated by transfer hydrogenation in MeOH with $HCOONH_4$ in the presence of Pd–C catalyst[34] to yield compound **24** which may serve as a paramagnetic Cu^{2+} ligand (Scheme 3).

In conclusion, a range of spin-labeled heterocycles such as paramagnetic quinolines, oxazole, benzazoles, thiadiazoles, pyrrole and benzofuran, porphyrin and indole have been synthesized through both classical and Pd-catalyzed reactions. Most of the synthesis could be carried out without the protection of nitroxide function. We hope that some of the heterocyclic synthesis with nitroxides presented above can be generalized to obtain novel paramagnetic compounds.

Melting points were determined with a Boetius micro melting point apparatus and are uncorrected. Elemental analyses were performed on a 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 a Thermoquest Automass Multi and VG TRIO-2 instruments in the EI mode at 70 eV. ^1H NMR spectra were recorded with a Varian Unity INOVA 400 WB



Scheme 2 *Reagents and conditions*: (a) Ref. 15; (b) 2-iodophenol (1.5 equiv), Cs_2CO_3 (2.1 equiv), CuI (0.1 equiv), *N*,*N*-dimethylglycine–HCl (0.3 equiv), dioxane, 90 °C, N_2, 24 h, 45%, then *n*-Bu_4NHSO_4 (1.0 equiv), $NaHCO_3$ (2.5 equiv), $Pd(OAc)_2$ (0.05 equiv), DMF, 4 Å molecular sieves, Ar, 100 °C, 12 h, 10%; (c) 2-aminobenzaldehyde (1 equiv), NaOMe (1.1 equiv), EtOH, reflux, 3 h, 34%; (d) $H_3N_2CO_2Et$ (1 equiv), AcOH (cat.), reflux, 5 h, 76%; (e) $SOCl_2$ (20 equiv), CH_2Cl_2, r.t., 12 h, aq $NaNO_2$ (1.0 equiv), 10 min, MnO_2 (1 equiv), $CHCl_3$, O_2, 15 min, 36%.



Scheme 3 *Reagents and conditions*: (a) N_2H_4, H_2O (large excess), EtOH, r.t., 1 h, then reflux 1 h, H_2O–$CHCl_3$ extraction, PbO_2 (0.1 equiv), O_2, 30 min then tetramethylguanidine (3.5 equiv), I_2 (2.2 equiv), Et_2O, 1 h, r.t., 45%; (b) Bis(pinacolato)diboron, (1.1 equiv), $PdCl_2$(dppf) (0.05 equiv), KOAc (3 equiv), DMSO, 80 °C, 3 h, N_2, 30%; (c) 4-iodobenzothiazole (1 equiv), $Pd_2(dba)_3$ (0.03 equiv), K_2CO_3 (10% aq), dioxane, reflux, 6 h, 40%; (d) 1-(phenylsulfonyl)-1*H*-indol-3-ylboronic acid (1 equiv), $Pd(PPh_3)_4$ (0.05 equiv), Na_2CO_3 (10% aq), dioxane, N_2, reflux, 3 h, then EtOH, KOH (1 equiv), 1 h, r.t., 36%; (e) 2-aminobenzaldehyde (1 equiv), NaOMe (1.1 equiv), EtOH, reflux, 3 h, 56%; (f) Ref. 15. (g) 2-benzyloxyaniline (1.1 equiv), DMF, 3 h, 120 °C, N_2, 44%; (h) Pd–C, $HCOONH_4$ (10 equiv), MeOH, reflux, 2 h, N_2, then MnO_2, O_2, 10 min, 65%.

spectrometer at 298K probe temperature in $CDCl_3$ solution. Chemical shifts are referenced to TMS. ESR spectra were taken on Miniscope MS 200 in 10^{-4} M $CHCl_3$ solution and all mono-radicals gave triplet lines a_N = 14.7–15.1 G. The UV/VIS spectra were recorded with a Specord 40 (Analytic, Jena) spectrophotometer. 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 × 0.02 cm) coated with Merck Kieselgel GF_{254}. All reagents were purchased from Aldrich with the exception of compounds **1**,[17] **7**,[24] **9**,[26] **11**,[8] **12**,[15] **17**,[8] **19**,[14] **21**,[15] **22**,[35] 4-iodobenzothiazole,[32] 1-(phenylsulfonyl)indol-3-ylboronic acid[33] and 2-aminobenzaldehyde,[36] which were prepared according to published procedures.

1-Acetoxy-3-formyl-2,2,5,5-tetramethyl-2,5-dihydo-1*H*-pyrrole (2)

To a solution of radical **1** (1.68 g, 10.0 mmol) in dioxane (30 mL), was added a solution of ascorbic acid (8.8 g, 50.0 mmol) in H_2O (10 mL), and the mixture was stirred at 40 °C for 15 min under N_2. The pale yellow or colorless solution was extracted with $CHCl_3$ (2 × 20 mL) and dried ($MgSO_4$) under N_2. Acetyl chloride (860 mg, 11.0 mmol) was added, followed by the slow addition of Et_3N (1.1 g, 11.0 mmol) keeping the temperature below 10 °C. Stirring was continued for 1 h at r.t. then the mixture was filtered and the filtrate was evaporated in vacuo to dryness. The residue was partitioned between brine (10 mL) and EtOAc (15 mL) and the aqueous phase was washed with EtOAc (2 × 10 mL), the combined organic phase was dried ($MgSO_4$), filtered, evaporated and, after flash chromatography (hexane–Et_2O, 4:1 then 2:1), the *O*-acetyl derivative was obtained.

Yield: 1.28 g (61%); white solid; mp 51–53 °C; R_f = 0.26 (hexane–Et_2O, 2:1).

IR (nujol): 1760, 1680 (C=O), 1620 (C=C) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): d = 1.35 (br s, 12 H, CH_3), 2.12 (s, 3 H, CH_3CO), 6.54 (s, 1 H, vinyl proton), 9.63 (s, 1 H, formyl proton).

MS (EI): *m*/*z* (%) = 211 (4) [M^+], 196 (6), 169 (35), 154 (89), 43 (100).

Anal. Calcd for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.34; H, 8.03; N, 6.54.

2,2,5,5-Tetramethyl-3-(6-methyl-benzoxazol-2-yl)-2,5-dihydro-1*H*-pyrrol-1-yloxyl Radical (3)

A solution of compound **2** (2.11 g, 10.0 mmol), 2-amino-5-methylphenol (1.23 g, 10.0 mmol), $TsOH·H_2O$ (95 mg, 0.05 mmol) in toluene (50 mL) was refluxed for 3 h under Dean–Stark apparatus. After cooling, the toluene was evaporated off and the residue was dissolved in CH_2Cl_2 (25 mL), washed with H_2O (10 mL), immediately separated, dried ($MgSO_4$), filtered and the solvent evaporated. The residue was dissolved in anhyd MeCN (15 mL), $PhI(OAc)_2$ (3.19 g, 11.0 mmol) was added and the mixture was stirred at r.t. for 30 min. After the evaporation of the solvent, the residue was equilibrated between H_2O (15 mL) and $CHCl_3$ (20 mL), the organic phase was separated, dried ($MgSO_4$), filtered and evaporated. The residue was purified by flash column chromatography (hexane–Et_2O, 2:1) to give the *O*-acetyl derivative of **3**.

Yield: 1.41 g (45%); white solid; mp 115–117 °C; R_f = 0.37 (hexane–Et_2O, 2:1).

IR (nujol): 1765 (C=O), 1640 (C=N), 1600, 1520 (C=C) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): d = 1.35 (s, 3 H, CH_3), 1.38 (s, 3 H, CH_3), 1.58 (s, 3 H, CH_3), 1.63 (s, 3 H, CH_3), 2.17 (s, 3 H, CH_3CO), 2.45 (s, 3 H, $ArCH_3$), 6.64 (s, 1 H, vinyl proton), 7.14 (d, *J* = 8.4 Hz, 1 H, ArH), 7.36 (d, *J* = 8.4 Hz, 1 H, ArH), 7.50 (s, 1 H, ArH).

This *O*-acetyl derivative (1.25 g, 4.0 mmol) was dissolved in MeOH (10 mL), and freshly prepared NaOMe (10 mg Na metal in 5 mL MeOH) was added. After standing at r.t. for 2 h the solvents were evaporated off and the residue was partitioned between $CHCl_3$ (20 mL) and sat. aq NH_4Cl (10 mL). The organic phase was separated, dried ($MgSO_4$), MnO_2 (87 mg, 1.0 mmol) was added and O_2 was bubbled through mixture for 15 min. The mixture was filtered, evaporated under reduced pressure and the residue was purified by flash column chromatography (hexane–Et_2O, 2:1).

Yield: 867 mg (80%); yield from **2**, 36%; yellow solid; mp 113–114 °C; R_f = 0.35 (hexane–Et_2O, 2:1).

IR (nujol): 1630 (C=N), 1590, 1520 (C=C) cm^{-1}.

MS (EI): *m*/*z* (%) = 271 (38) [M^+], 256 (34), 241 (88), 226 (100).

Anal. Calcd for $C_{16}H_{19}N_2O_2$: C, 70.83; H, 7.06; N, 10.32. Found: C, 70.97; H, 7.04; N, 10.21.

2,2,5,5-Tetramethyl-3-(benzothiazol-2-yl)-2,5-dihydro-1*H*-pyrrol-1-yloxyl Radical (4)

Method A: A solution of **2** (2.11 g, 10.0 mmol) and 2-aminothiophenol (1.25 g, 10.0 mmol) in dry DMSO (10 mL) was heated to 90 °C for 2 h. After cooling, the solvent was evaporated off and the residue was partitioned between H_2O (10 mL) and Et_2O (20 mL) and the organic phase was separated, dried ($MgSO_4$), filtered and evaporated. The residue was dissolved in MeOH (10 mL) and freshly prepared NaOMe (23 mg Na in 5 mL MeOH) was added. The solution was allowed to stay at r.t. for 2 h then the methanol was evaporated off, sat. aq NH_4Cl (15 mL) was added and the aqueous phase was extracted with $CHCl_3$ (2 × 15 mL). The organic phase was dried ($MgSO_4$), MnO_2 (217 mg, 2.5 mmol) was added and O_2 was bubbled through the solution for 15 min. The mixture was filtered and evaporated and the residue was purified by flash column chromatography (hexane–Et_2O, 2:1) to give the title compound.

Yield: 900 mg (33%); yellow solid; mp 66–68 °C; R_f = 0.40 (hexane–Et_2O, 2:1).

IR (nujol): 1630 (C=N), 1610, 1580 (C=C) cm^{-1}.

MS (EI): *m*/*z* (%) = 273 (21) [M^+], 258 (16), 243 (17), 228 (100).

Anal. Calcd for $C_{15}H_{17}N_2OS$: C, 65.90; H, 6.27; N, 10.25; S, 11.73. Found: C, 66.05; H, 6.13; N, 10.24; S, 11.78.

Method B: A stirred solution of 2-iodobenzothiazole (261 mg, 1.0 mmol) and $Pd_2(dba)_3$ (27 mg, 0.03 mmol) in dioxane (15 mL), was deaerated with N_2 for 10 min then boronic acid **19** (266 mg, 1.0 mmol) was added followed by aq Na_2CO_3 (10%, 5 mL). The mixture was stirred and heated to reflux for 6 h under N_2. After cooling, the solvent was evaporated off and the residue was partitioned between brine (10 mL) and EtOAc (15 mL). The organic phase was separated, dried ($MgSO_4$), filtered and evaporated to give a residue that was purified by flash column chromatography (hexane–Et_2O, 2:1) to give compound **4**.

Yield: 109 mg, (40%); mp 66–68 °C; R_f = 0.40 (hexane–Et_2O, 2:1).

All the spectroscopic data of paramagnetic benzothiazole obtained by the two different methods were identical.

2,2,5,5-Tetramethyl-3-(oxazol-5-yl)-2,5-dihydro-1*H*-pyrrol-1-yloxyl Radical (5)

To a solution of aldehyde **1** (168 mg, 1.0 mmol) in MeOH (10 mL) was added NaOMe solution (115 mg Na metal dissolved in 7 mL MeOH), followed by tosylmethyl isocyanide (234 mg, 1.2 mmol) as a solid, in portions. The resulting solution was heated to reflux for 4 h, cooled, the solvents were evaporated off, and the residue was partitioned between H_2O (10 mL) and $CHCl_3$ (15 mL). The organic phase was separated, dried ($MgSO_4$), filtered and evaporated and the residue was purified by column chromatography (hexane–EtOAc, 4:1) to give the title compound.

Yield: 159 mg (77%); yellow solid; mp 90–92 °C; R_f = 0.23 (hexane–EtOAc, 2:1).

IR (nujol): 1650 (C=N), 1620, 1545 (C=C) cm^{-1}.

MS (EI): *m*/*z* (%) = 207 (32) [M^+], 192 (84), 177 (50), 41 (100).

Anal. Calcd for $C_{11}H_{15}N_2O_2$: C, 63.75; H, 7.30; N, 13.52. Found: C, 63.87; H, 7.13; N, 13.48.

2-(1-Oxyl-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-3-yl)-quinoline-4-carboxylic Acid Radical (6)

A solution of aniline (465 mg, 5.0 mmol), aldehyde **1** (840 mg, 5.0 mmol) and pyruvic acid (660 mg, 7.5 mmol) in EtOH (10 mL) was heated to reflux for 3 h and allowed to cool overnight. The resulting solid was collected by filtration, washed with cold EtOH (5 mL) and air-dried to yield the title compound.

Yield: 388 mg (25%); pale-yellow solid; mp 258–260 °C; R_f = 0.58 (MeOH).

IR (nujol): 1705 (C=O), 1630 (C=C) cm^{-1}.

MS (EI) *m*/*z* (%) = 311 (3) [M^+], 297 (18), 281 (100), 266 (21).

Anal. Calcd for $C_{18}H_{19}N_2O_3$: C, 69.44; H, 6.15; N, 9.00. Found: C, 69.25; H, 6.17; N, 8.90.

1′-Oxyl-2′,2′,5′,5′-tetramethyl-2′,5′-dihydro-1*H*,1*H*′-[3,3′]bipyrrolyl-4-carboxylic Acid Ethyl Ester Radical (8)

To a stirred solution of ester **7** (476 mg, 2.0 mmol) and TosMIC (429 mg, 2.2 mmol) in THF (20 mL) was added *t*-BuOK solution (1 M in THF, 2.2 mL, 2.2 mmol)) at –78 °C. The mixture was allowed to warm to r.t. and then refluxed for 30 min. After cooling, the mixture was quenched with sat. aq NH_4Cl (10 mL), Et_2O (10 mL) was added and the organic phase was separated, dried ($MgSO_4$), filtered and evaporated to give a residue that was purified by flash column chromatography (hexane–EtOAc, 2:1) to give compound **8**.

Yield: 327 mg (59%); yellow solid; mp 155–157 °C; R_f = 0.25 (hexane–EtOAc, 2:1).

IR (nujol): 3195 (NH), 1700 (C=O), 1510 (C=C) cm^{-1}.

MS (EI): *m*/*z* (%) = 277 (29) [M^+], 262 (29), 247 (35), 174 (100).

Anal. Calcd for $C_{15}H_{21}N_2O_3$: C, 64.96; H, 7.63; N, 10.10. Found: C, 64.90; H, 7.64; N, 9.96.

5,10,15,20-Tetraphenylporphyrin (9), 5-(1-Oxyl-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-3-yl)-10,15,20-triphenylporphyrin Radical (10)

Benzaldehyde (636 mg, 6.0 mmol), aldehyde **1** (336 mg, 2.0 mmol) and pyrrole (536 mg, 8.0 mmol) were dissolved in CH_2Cl_2 (400 mL) and the reaction flask was protected from light. N_2 was bubbled through this solution for 10 min then $BF_3{\cdot}Et_2O$ (0.2 mL, 1.6 mmol) was added and the reaction mixture was stirred under N_2 for 1 h. DDQ (1.36g, 6.0 mmol) was added and the mixture was stirred for a further 1 h exposed to air before Et_3N (4.04 g, 40 mmol) was added and the reaction mixture was evaporated to give a black tarry solid. This crude product was adsorbed onto silica gel and purified by flash column chromatography (hexane–CH_2Cl_2, 3:1 to 1:1). The earlier-eluting, brown band was collected as the tetraphenylporphyrin **10**.

Yield: 86 mg (7%); mp >360 °C, R_f = 0.72 (hexane–CH_2Cl_2, 1:1).

The second brown band [R_f = 0.14 (hexane–CH_2Cl_2, 1:1)] was collected and purified further by column chromatography (hexane–EtOAc, 2:1) to yield compound **9**.

Yield: 40 mg (3%); brown solid; mp 80–82 °C.

UV/Vis (MeOH): λ_{max} = 224, 413, 511, 544, 588, 644 nm.

IR (nujol): 1690 (C=N), 1660, 1635, 1610 (C=C) cm^{-1}.

MS (ESI): 676 $[M + H]^+$.

Anal. Calcd for $C_{46}H_{38}N_5O$: C, 81.63; H, 5.66; N, 10.35. Found: C, 81.59; H, 5.57; N, 10.30.

1,1,3,3-Tetramethyl-1,2,3,4-tetrahydro-2*H*-benzo[4,5]furo[3,2-*c*]pyridin-2-yloxyl Radical (13)

A mixture of vinyl iodide **12** (280 mg, 1.0 mmol), 2-iodophenol (330 mg, 1.5 mmol), Cs_2CO_3 (684 mg, 2.1 mmol), CuI (19 mg, 0.1 mmol) and *N*,*N*-dimethylglycine hydrochloride (42 mg, 0.3 mmol) in dioxane (4 mL) was heated at 90 °C under N_2 for 24 h. After cooling, the dioxane was evaporated off and the residue was dissolved in EtOAc (10 mL). The organic phase was washed with H_2O (10 mL), dried, filtered and evaporated to give a residue that was subjected to chromatography on a silica gel column (hexane–Et_2O, 4:1) to remove most of the phenol and vinyl iodide starting materials. The crude aryl vinyl ether (167 mg, 45% mass balance) was transferred to a dry, 25-mL, Schlenk flask module vessel equipped with a magnetic stirrer and charged with $NaHCO_3$ (105 mg), crushed 4Å molecular sieves (200 mg), Bu_4NHSO_4 (152 mg, 0.45 mmol), $Pd(OAc)_2$ (6 mg, 0.025 mmol) and anhyd DMF (2 mL). The reaction vessel was flushed with Ar for 10 min and, after closing the vessel, the reaction mixture was stirred and heated at 100 °C for 12 h. After cooling, the mixture was diluted with Et_2O (10 mL), sat. aq NH_4Cl (10 mL) was added, and the organic phase was separated, the aqueous phase was extracted again with Et_2O (10 mL), dried ($MgSO_4$), filtered and evaporated. The residue was purified by flash column chromatography (hexane–Et_2O, 2:1) to give the paramagnetic benzofuran **13**.

Yield: 56 mg (51%, 23% from **12**); red crystals; mp 61–62 °C; R_f = 0.57 (hexane–Et_2O, 2:1).

IR (nujol): 1680, 1640, 1585 (C=C) cm^{-1}.

MS (EI): *m*/*z* (%) = 244 (13) $[M^+]$, 214 (13), 199 (50), 171 (100).

Anal. Calcd for $C_{15}H_{18}NO_2$: C, 73.74; H, 7.43; N, 5.73. Found: C, 73.59; H, 7.56; N, 5.80.

Friedlander Paramagnetic Quinoline Synthesis (14, 21); General Procedure

To a solution of freshly prepared 2-aminobenzaldehyde (363 mg, 3.0 mmol) and either ketone **11** (510 mg, 3.0 mmol) or **17** (468 mg, 3.0 mmol) in dry EtOH (15 mL) was added freshly prepared NaOMe (76 mg Na metal dissolved in 5 mL MeOH) and the mixture was refluxed for 3 h. After cooling, the reaction mixture was evaporated in vacuo to give a residue which was partitioned between H_2O (10 mL) and $CHCl_3$ (15 mL). The organic phase was separated, dried ($MgSO_4$), filtered and evaporated to give a residue that was purified by flash column chromatography (hexane–EtOAc, 4:1 to 2:1) to give the quinolines **14** and **21**.

1,1,3,3-Tetramethyl-1,2,3,4-tetrahydro-2*H*-benzo[*b*]-[1,6]naphthyridin-2-yloxyl Radical (14)

Yield: 260 mg (34%); red crystals; mp 53–55 °C; R_f = 0.43 (hexane–EtOAc, 2:1).

IR (nujol): 1640 (C=N), 1610, 1590 (C=C) cm^{-1}.

MS (EI): *m*/*z* (%) = 255 (27) $[M^+]$, 225 (18), 210 (100).

Anal. Calcd for $C_{16}H_{19}N_2O$: C, 75.26; H, 7.50; N, 10.97. Found: C, 75.13; H, 7.64; N, 11.00.

1,1,3,3-Tetramethyl-1,3-dihydro-2*H*-pyrrolo[3,4-*b*]quinolin-2-yloxyl Radical (21)

Yield: 405 mg (56%); yellow crystals; mp 156–158 °C; R_f = 0.54 (hexane–EtOAc, 2:1).

All spectroscopic data were identical to those previously reported.[15]

***N*′-(1-Oxyl-2,2,6,6-tetramethylpiperidin-4-ylidene)hydrazinecarboxylic Acid Ethyl Ester Radical (15)**

A solution of ketone **11** (850 mg, 5.0 mmol), ethyl carbazate (520 mg, 5.0 mmol) and AcOH (0.1 mL) in EtOH (15 mL) was heated to reflux until complete consumption of ketone was observed through TLC monitoring (~5 h). After cooling, EtOH was evaporated and the residue was partitioned between $CHCl_3$ (20 mL) and H_2O (10 mL). The organic phase was separated, dried ($MgSO_4$), filtered and evaporated to give a residue that was purified by flash column chromatography ($CHCl_3$–Et_2O, 1:4) to yield the title compound **15**.

Yield: 973 mg (76%); orange-pink solid; mp 115–117 °C; R_f = 0.25 ($CHCl_3$–Et_2O, 2:1).

IR (nujol): 3205 (NH), 1695 (C=O), 1530 (C=N) cm^{-1}.

MS (EI): *m*/*z* (%) = 256 (18) $[M^+]$, 226 (8), 211 (82), 41 (100).

Anal. Calcd for $C_{12}H_{22}N_3O_3$: C, 56.23; H, 8.65; N, 16.39. Found: C, 56.39; H, 8.81; N, 16.50.

4,4,6,6-Tetramethyl-4,5,6,7-tetrahydro-5*H*-1,2,3-thiadiazolo[4,5-*c*]pyridin-5-yloxyl Radical (16)

A stirred suspension of **15** (512 mg, 2.0 mmol) in dry CH_2Cl_2 (20 mL) was treated with $SOCl_2$ (4.76 g, 40.0 mmol) at 0 °C. The mixture was allowed to come to r.t. and stirred for 6 h. Solvents were evaporated in vacuo and the residue was dissolved in $CHCl_3$ (15 mL). To this brown solution was added $NaNO_2$ (138 mg, 2.0 mmol) dissolved in H_2O (5.0 mL), with vigorous stirring, in an efficient fume cupboard (**Caution: NO_2 evolved!**). The mixture was stirred for 10 min, then the organic phase was separated, dried ($MgSO_4$) and MnO_2 (174 mg, 2.0 mmol) was added. O_2 was bubbled through the solution for 15 min then the mixture was filtered, and the filtrate was evaporated under reduced pressure. The oily residue was purified by flash column chromatography (hexane–EtOAc, 2:1) to give the title compound **16**.

Yield: 152 mg (36%); deep-yellow solid; mp 80–82 °C; R_f = 0.70 (hexane–EtOAc, 2:1).

IR (nujol): 1570 (C=C) cm^{-1}.

MS (EI): *m*/*z* (%) = 212 (14) $[M^+]$, 182 (10), 139 (40).

Anal. Calcd for $C_9H_{14}N_3OS$: C, 50.92; H, 6.65; N, 19.79; S, 15.10. Found: C, 51.03; H, 6.80; N, 19.90; S, 14.99.

3-Iodo-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-1-yloxyl Radical (18)

A solution of compound **17** (1.56 g, 10.0 mmol) dissolved in EtOH (10 mL) was added dropwise to hydrazine hydrate (5 mL, 0.08 mol) over 1 h and the mixture was then boiled at gentle reflux for 1 h. After cooling, the colorless solution was evaporated to dryness and the residue was taken up in a mixture of $CHCl_3$–MeOH (9:1, 30 mL). The organic phase was washed with brine (10 mL), separated, dried ($MgSO_4$), PbO_2 (239 mg, 1.0 mmol) was added and O_2 was bubbled through the mixture for 30 min. The yellow solution was filtered, evaporated and the remaining yellow oil (hydrazone) was stored in a refrigerator or used immediately. This hydrazone was dissolved in anhyd. Et_2O (15 mL) and added dropwise to the stirred solution of I_2 (5.6 g, 22.0 mmol) and tetramethylguanidine (4.02 g, 35 mmol) in Et_2O (20 mL). After addition of hydrazone was complete, the mixture was stirred at r.t. for 60 min, then diluted with Et_2O (20 mL), washed with H_2O (10 mL) and aq H_2SO_4 (5%, 20 mL). The organic phase was separated, dried ($MgSO_4$), filtered and evaporated to give a dark-brown residue that was purified by flash column chromatography (hexane–Et_2O, 2:1) to afford vinyliodide **18**.

Yield: 1.19 g (45%); yellow solid; mp 109–111 °C; R_f = 0.51 (hexane–Et_2O, 2:1).

IR (nujol): 1590 (C=C) cm^{-1}.

MS (EI): *m*/*z* (%) = 266 (4) [M^+], 251(1), 236 (6), 109 (80), 41 (100).

Anal. Calcd for $C_8H_{13}INO$: C, 36.11; H, 4.92; N, 5.26. Found: C, 36.19; H, 4.97; N, 5.30.

2,2,5,5-Tetramethyl-3-(4,4,5,5-tetramethyl[1,3,2]dioxaborolan-2-yl)-2,5-dihydro-1*H*-pyrrol-1-yloxyl Radical (19)

A solution of bis(pinacolato)diboron (279 mg, 1.1 mmol), $PdCl_2$(dppf) (40 mg, 0.05 mmol), KOAc (294 mg, 3.0 mmol) in DMSO (6 mL) was flushed with N_2 for 10 min, then compound **18** (266 mg, 1.0 mmol) was added and the mixture was stirred at 80 °C for 3 h. After cooling, the mixture was poured onto H_2O (20 mL) and extracted with Et_2O (2 × 15 mL). The organic phase was dried ($MgSO_4$), filtered and evaporated to give a residue that was purified by flash column chromatography (hexane–Et_2O, 2:1) to give the compound **19** along with a small amount of earlier-eluting starting material **18**.

Yield: 79 mg (30%); yellow solid; mp 142–144 °C; R_f = 0.40 (hexane–Et_2O, 2:1).

All spectroscopic data were identical with those previously reported.[14]

3-(1*H*-Indol-3-yl)-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-1-yloxyl Radical (20)

A solution of vinyl iodide **18** (266 mg, 1.0 mmol) and $Pd(PPh_3)_4$ (50 mg, 0.05 mmol) in dioxane (10 mL) was purged with nitrogen for 5 min, then 1-(phenylsulfonyl)-1*H*-indol-3-ylboronic acid (301 mg, 1.0 mmol) was added, followed by aq Na_2CO_3 (10%, 10 mL) and the mixture was stirred at reflux under N_2 for 3 h. After cooling, the dark yellow solution was evaporated in vacuo and the residue was equilibrated between brine (10 mL) and $CHCl_3$ (20 mL). The organic phase was separated and the aqueous phase was washed with $CHCl_3$ (2 × 10 mL). The combined organic phase was dried ($MgSO_4$), filtered and evaporated to give a residue that was dissolved in EtOH (10 mL) containing KOH (56 mg, 1.0 mmol). The mixture was allowed to stay at r.t. for 1 h, then concentrated in vacuo. The residue was equilibrated between $CHCl_3$ (20 mL) and sat. aq NH_4Cl (10 mL). The organic phase was separated, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a light-brown residue that was purified by flash column chromatography (hexane–Et_2O, 2:1) to yield the paramagnetic indole **20**.

Yield: 97 mg (36%); light-brown solid; mp 203–205 °C; R_f = 0.36 (hexane–EtOAc, 2:1).

IR (nujol): 1645, 1600 (C=C) cm^{-1}.

MS (EI): *m*/*z* (%) = 255 (29) [M^+], 240 (14), 225(49), 182 (100).

Anal. Calcd for $C_{16}H_{19}N_2O$: C, 75.26; H, 7.50; N, 10.97. Found: C, 75.31; H, 7.57; N, 10.98.

5-Benzyloxy-1,1,3,3-tetramethyl-1,3-dihydropyrrolo[3,4-*b*]quinolin-2-yloxyl Radical (23)

A solution of aldehyde **22** (1.23 g, 5.0 mmol) and 2-benzyloxyaniline (1.09 g, 5.5 mmol) in DMF (10 mL) was heated at 120 °C for 3 h. After cooling, the solvent was evaporated in vacuo and the residue was equilibrated between aq K_2CO_3 (10%, 10 mL) and $CHCl_3$ (15 mL). The organic phase was separated, dried ($MgSO_4$), filtered and evaporated to give a residue that was purified by flash column chromatography (hexane–EtOAc, 2:1) to give the O-protected 8-oxyquinoline **23.**

Yield: 763 mg (44%); beige solid; mp 130–132 °C; R_f = 0.49 (hexane–EtOAc, 2:1).

IR (nujol): 1680 (C=N), 1600, 1560 (C=C) cm^{-1}.

MS (EI): *m*/*z* (%) = 347 (1) [M^+], 317 (2), 226 (12), 91 (100).

Anal. Calcd for $C_{22}H_{23}N_2O_2$: C, 76.05; H, 6.67; N, 8.06. Found: C, 76.04; H, 6.70; N, 8.09.

5-Hydroxy-1,1,3,3-tetramethyl-1,3-dihydropyrrolo[3,4-*b*]quinolin-2-yloxyl Radical (24)

To a solution of paramagnetic quinoline **23** (347 mg, 1.0 mmol) and HCO_2NH_4 (630 mg, 10.0 mmol) in dry MeOH (15 mL) was added Pd/C (10%, 100 mg) under N_2 and the mixture was stirred under reflux for 2 h. If TLC monitoring indicated the presence of starting material, further Pd/C (30 mg) and HCO_2NH_4 (189 mg) were added. After cooling, the mixture was filtered through Celite and the solids were washed with MeOH (10 mL). The solvents were evaporated and the residue was dissolved in $CHCl_3$ (20 mL), washed with brine (10 mL) and the organic phase was separated, dried ($MgSO_4$), MnO_2 (87 mg, 1.0 mmol) was added to the solution and O_2 was bubbled through for 10 min. Filtration, followed by evaporation gave a residue that was purified by flash column chromatography (hexane–EtOAc, 2:1) to afford compound **24**.

Yield: 168 mg (65%); brownish-yellow solid; mp 206–208 °C; R_f = 0.58 (hexane–EtOAc, 2:1).

IR (nujol): 3160 (OH), 1610 (C=C) cm^{-1}.

MS (EI): *m*/*z* (%) = 257 (49) [M^+], 243 (100), 227 (55), 212 (52).

Anal. Calcd for $C_{15}H_{17}N_2O_2$: C, 70.02; H, 6.66; N, 10.89. Found: C, 70.11; H, 6.55; N, 10.69.

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