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Synthesis of unsymmetrical *N*-(2-*tert*-butylphenyl)-*N*-(4-*tert*-butylphenyl)-nitroxyl radical, the first stable diarylnitroxyl with vacant *para*-position

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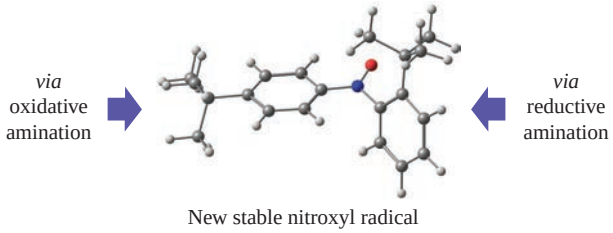
The title compound, first example of a stable diarylnitroxyl with vacant *para*-position, was best synthesized by CuCl-assisted coupling of *o*-*tert*-butylnitrosobenzene and *p*-*tert*-butylphenylboronic acid followed by N-oxidation of the thus obtained unsymmetrical diarylamine. ESR investigation showed that *ortho*-substituted aromatic ring is removed from the conjugation plane providing unusual stability of this radical.



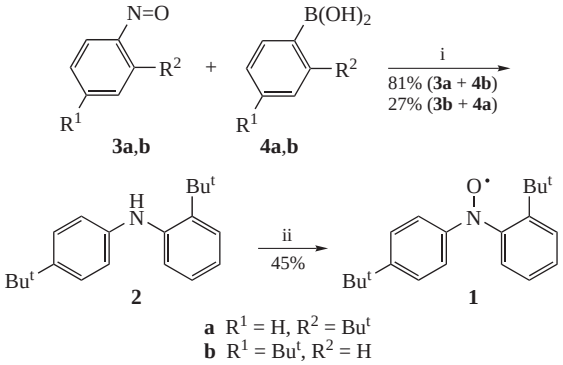
N,N-Disubstituted aminoxyl radicals (so called, nitroxyls), stable organic radicals with spin-density localization on the oxygen atom, are widely used in various areas.[1] The most studied dialkyl-substituted radical is TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl). Diarylnitroxides, contrary to their alkyl counterparts, are much less investigated. The limited number of diarylnitroxides available is attributed, first of all, to a lack of convenient synthetic routes. Commonly, two synthetic approaches to diarylnitroxyls are used, *i.e.*, oxidation of diarylhydroxylamines or diarylamines. Diarylamines are more available starting compounds than hydroxylamines, therefore, the second approach seems preferable. Synthesis of unsymmetrical diarylnitroxyls imposes additional limitations on the scope of the reactions applicable to the preparation of diarylamine precursors.

Metal-catalyzed amination of aromatic substrates is a powerful tool for C(sp^2)–N bond formation.[2–5] Usually, catalysis is most efficient when precious metals are used, commonly as complexes with sophisticated phosphine ligands. Among other compounds, synthesis of *ortho*-substituted aryl derivatives is more difficult due to additional contribution of sterical demands.

Here, we report the synthesis of new stable unsymmetrical *N*-(2-*tert*-butylphenyl)-*N*-(4-*tert*-butylphenyl) nitroxyl radical **1**. In all previously reported stable diarylnitroxyls[6–13] both *para*-positions in the aromatic rings were blocked by appropriate substituents to prevent possible radical coupling onto *para*-position.[14] The herein obtained unsymmetrical radical is the first example of a stable diarylnitroxyl in which one of the phenyl rings has a vacant *para*-position. New compound seems promising as redox active electrode material.

In an effort to develop a practical precious metal-free method for the synthesis of sterically hindered unsymmetrical *N*-(2-*tert*-butylphenyl)-*N*-(4-*tert*-butylphenyl)amine **2** we explored the copper catalyzed oxidative and reductive amination of *o*- and *p*-*tert*-butylphenyl boronic acids. Among them, the most appropriate version is mild reductive amination of arylboronic acids with nitrosoarenes[15] mediated by CuCl which serves as a catalyst and reducing agent. However, it has not been tested for sterically demanding arylboronic acids and arylnitroso compounds. To fill the void, the coupling of *o*-*tert*-butynitrosobenzene **3a** and *p*-*tert*-butylphenylboronic acid **4b** was performed. It turned to be efficient leading to unsymmetrical diarylamine **2** in practical 81% yield (Scheme 1).†

The opposite combination of the reactants **3b** + **4a** gives the same unsymmetrical diarylamine **2** in much lower yield (27%, Scheme 1).



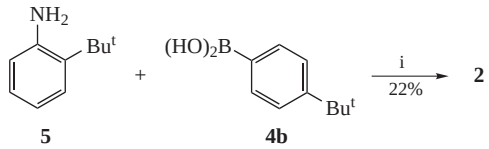
Scheme 1 *Reagents and conditions*: i, CuCl (1 equiv.), DMF, 60 °C; ii, H_2O_2, Na_2WO_4, MeOH, Δ.

† Mass spectra were measured with a high-resolution time-of-flight Bruker maXis instrument using electrospray ionization (ESI-MS).[20] Measurements were performed in positive ion mode, interface capillary voltage at 4.5 kV, effective scan range at *m*/*z* 100–1200, external calibration (0.016 M sodium formate in MeCN–water 1 : 1 mixture or ESI-L Low Concentration Tuning Mix, Agilent Technologies), direct syringe injection at flow rate of 3 μl min^{-1}, nitrogen as dry gas at 4 dm^3 min^{-1}, interface temperature 180 °C. The spectra were processed using Bruker Data Analysis 4.0 software package.

ESR spectra were recorded on a Bruker EMX-plus instrument for solutions in toluene deaerated using standard freeze-pump-thaw technique containing approximately 5×10^{15} radical molecules.

^{1}H (400.0 MHz) and ^{13}C (100.6 MHz) NMR spectra were recorded using an Agilent 400-MR spectrometer in $CDCl_3$. Chemical shifts were referenced to residual protons.

N-*(2*-tert-*butylphenyl)*-N-*(4*-tert-*butylphenyl)amine* **2**. Into an argon filled two-neck flask fitted with reflux condenser and pressure-equalizing dropping funnel and containing CuCl (79 mg, 0.80 mmol), a solution of *o*-*tert*-butylnitrosobenzene **3a (**130 mg, 0.80 mmol) in dry deaerated DMF (20 ml) was added. The mixture was stirred at 60 °C (water bath)



Scheme 2 *Reagents and conditions*: i, $Cu(OAc)_2$, Et_3N, CH_2Cl_2, ~20 °C, 48 h.

As an alternative route, the oxidative amination[16–19] of arylboronic acid with anilines was also considered (Scheme 2). In our case, *o*-*tert*-butylaniline **5** was reacted with *p*-*tert*-butylphenylboronic acid **4b** in the presence of equimolar amount of $Cu(OAc)_2$ in CH_2Cl_2 and Et_3N, which afforded the unsymmetrical amine **2** in 22% yield.‡ This result indicates that oxidative amination is more sensitive to the presence of bulky substituents in the reactants than reductive amination. Taking into account that the location of a bulky group in arylboronic acid is less beneficial than in the N-containing reactant, one can expect that alternative combination (*o*-*tert*-butylphenylboronic acid **4a** and *p*-*tert*-butylaniline) should be unsuccessful.

For oxidation of *N*-(2-*tert*-butylphenyl)-*N*-(4-*tert*-butylphenyl)-amine **2**, several oxidants were tested. The best results were achieved using H_2O_2 in boiling methanol in the presence of H_2O_2/Na_2WO_4 (45% yield of **1**, see Scheme 1). The oxidation with mCPBA in diethyl ether provided the targeted nitroxyl in essentially lower yield (19%).§ This result is in line with the previously reported data for symmetrical bis(*p*-*tert*-butylphenyl)-nitroxyl.[12]

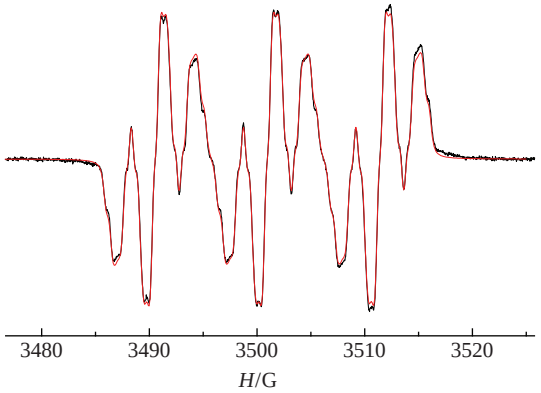


Figure 1 Experimental (black) and simulated (red) ESR spectra of *N*-(2-*tert*-butylphenyl)-*N*-(4-*tert*-butylphenyl)nitroxyl in toluene. g = 2.0060, a_N = = 10.43 G, $a_{H,ortho}$ = 2.65 G (2H), $a_{H,meta}$ = 0.88 G (2H); spin-coupling constants for the second aromatic moiety: a_H = 0.66 G (1H), a_H = 0.50 G (1H), a_H = 0.43 G (1H); H_{pp}(Gauss) = 0.325 G, H_{pp}(Lorentz) = 0.198 G.

The new unsymmetrical *N*-(2-*tert*-bytylphenyl)-*N*-(4-*tert*-butylphenyl)nitroxyl radical **1** obtained was characterized by ESI-HRMS.§

ESR investigation of nitroxyl radical **1** gave an explanation for unusual stability of the compound, in spite of the presence of the vacant *para*-position in one of the aromatic rings. It turned out that the *ortho*-substituted aromatic ring is removed from the conjugation plane, which becomes evident from the characteristic spin splitting (Figure 1) pattern. Splitting on two equivalent *ortho*-protons and two equivalent *meta*-protons of only one aromatic system is observed for asymmetrical radical. Almost undetectable deviation of the shape of the observed signal from the perfect triple of triplets of triplets indicates the presence of negligible spin density on the second aromatic ring. Hence, the conjugation of this aromatic system (containing *o*-*tert*-butyl group) with the nitroxyl radical is almost absent thus preventing possible follow-up radical transformations *via* vacant *para*-position.

In conclusion, the obtained results demonstrate that the rational design of the structure of stable diarylnitroxyls can be based not only on introducing substituents with appropriate electronic effects in the aromatic rings but on changing the degree of conjugation between nitroxyl group and aromatic moiety as well. The latter sterical factor can be considered as an additional important instrument for fine structural tuning.

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for 30 min. Then the solution of *p*-*tert*-butylphenylboronic **4b** (155 mg, 0.87 mmol) acid in dry deaerated DMF (7 ml) was added and the mixture was stirred at 60 °C for 16 h. The colour of the solution changed from light green to black *via* light yellow, green and greenish blue. Afterwards the mixture was diluted with water (100 ml) and saturated aqueous ammonia (50 ml) and extracted with diethyl ether. The extracts were dried with anhydrous sodium sulfate, evaporated and purified by column chromatography on silica gel (eluent, toluene–hexane, 1 : 20). Three fractions were collected (in order of elution): 4,4′-di-*tert*-butylbiphenyl (34 mg), *o*-*tert*-butylnitrosobenzene (10 mg) and product **2** (183 mg, 81% yield).

For **2**: white crystals, mp 86–88 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.40 (dd, 1H, *o*-H, *J* 7.9 and 1.5 Hz), 7.28 (dd, 1H, *o*-H, *J* 7.9 and 1.5 Hz), 7.25–7.21 (m, 2H, *p*-H), 7.14 (ddd, 1H, *o*-H, *J* 7.9, 7.3 and 1.6 Hz), 7.01 (ddd, 1H, *o*-H, *J* 7.9, 7.3 and 1.5 Hz), 6.83–6.79 (m, 2H, *p*-H), 5.37 (s, 1H, 7-NH), 1.45 (s, 9H, Bu^t), 1.31 (s, 9H, Bu^t). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 142.99 (*p*-C), 142.59 (*o*-C), 142.09 (*o*-C), 142.05 (*p*-C), 127.04 (*o*-C), 126.93 (*o*-C), 126.18 (*p*-C), 124.47 (*o*-C), 123.07 (*o*-C), 116.65 (*p*-C), 34.90 (CMe_3), 34.19 (CMe_3), 31.68 (CMe_3), 30.70 (CMe_3). ESI-HRMS, *m*/*z*: 228.2216 $[M + H]^+$ (calc. for $C_{20}H_{28}N$, *m*/*z*: 282.2217).

‡ To a stirred solution of 560 mg of *o*-*tert*-butylaniline **5**, 1.0 g of *p*-*tert*-butylphenylboronic acid **4b** and 1.6 ml of triethylamine in 12 ml of CH_2Cl_2, 1.36 g of anhydrous copper(II) acetate was added. The slurry was stirred under ambient conditions for 48 h and filtered; the filtrate was evaporated and the residue was purified by column chromatography on silica gel (toluene–hexane, 1 : 20). The unsymmetrical amine **2** was obtained as white crystals in 22% yield (220 mg).

§ N-*(2*-tert-*bytylphenyl)*-N-*(4*-tert-*butylphenyl)nitroxyl* **1**.

Method 1. A solution of diarylamine **2** (281 mg, 1.0 mmol) in 5 ml of methanol was heated to the boiling point, then 30% hydrogen peroxide (340 μl, 3.0 mmol) and a solution of $Na_2WO_4 \cdot 2H_2O$ (33 mg, 0.1 mmol) in water (70 μl) were successively added and the mixture was refluxed for 12 h. New portions of hydrogen peroxide (340 μl) were added every 3 h. The consumption of diarylamine was monitored by TLC (eluent, toluene–hexane, 1 : 10). After all the starting material was consumed, the mixture was cooled, diluted with water and extracted with diethyl ether. The organic fractions were washed with water, dried over sodium sulfate and purified by column chromatography on silica gel (eluent, toluene; R_f 0.44). Nitroxyl was obtained as an orange-red oil (133 mg, 45% yield). ESI-HRMS, *m*/*z*: 296.2012 $[M]^+$ (calc. for $C_{20}H_{26}NO$, *m*/*z*: 296.2009), 297.2078 $[M + H]^+$ (calc. for $C_{20}H_{27}NO$, *m*/*z*: 297.2087).

Method 2. A solution of mCPBA (46 mg, 0.29 mmol) in diethyl ether (1 ml) was added to a solution of diarylamine **2** (50 mg, 0.18 mmol) in diethyl ether (1.5 ml) cooled to –15 °C. The mixture was kept at –15 °C for 10 min and, afterwards, at room temperature for 2 h. The colour of the solution gradually changed to dark red. The mixture was quenched with water, washed with saturated aqueous $NaHCO_3$, dried over Na_2SO_4, evaporated and purified by column chromatography on silica gel (eluent, toluene); 10 mg (19%) of the nitroxyl was obtained.

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