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Chelation-assisted pentafluorophenylation of oximes

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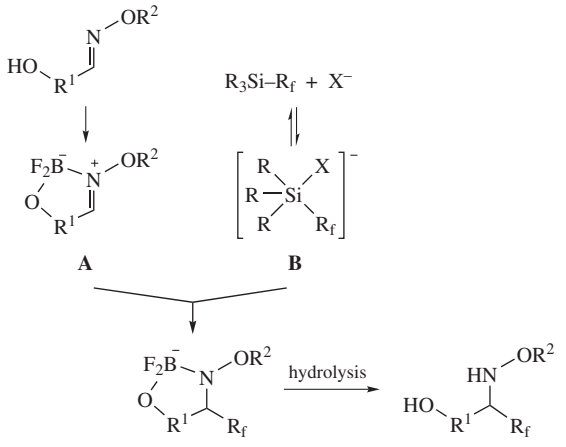
The pentafluorophenylation of salicylic aldehyde *O*-R-oximes is accomplished by their preliminary transformation into difluoroboryl chelate complexes, which react with $(C_6F_5)_3SiF$ in the presence of sodium acetate.

Nucleophilic addition of a fluorinated group at the C=N double bond became topical in recent years[1–4] since thus prepared amines bearing a fluorinated substituent at the α-position find applications in pharmaceutical industry.[5] Several alternative approaches to this family of compounds are also documented.[6]

Organosilicon compounds requiring the application of basic activators are most frequently used as a convenient source of fluorinated carbanion.[7] Whereas addition of perfluorinated fragments to imines,[1(a)–(c),2] hydrazones,[3] and iminium cations[4] proceeded readily, similar reactions of oximes were not performed due to low electrophilicity of oximino C=N bond.† Recently, we developed a method for the activation of C=N bond using intramolecular complexation with the difluoroboryl group possessing Lewis acidity.[2(b),3] Herein we report the application of this methodology for the nucleophilic pentafluorophenylation of oximes that represents the first example of transfer of perfluorinated group from silicon to oximino fragment.

The general mechanistic scenario is shown in Scheme 1. The oxime bearing an adjacent hydroxyl group is converted to chelate complex **A** which is expected to possess a stronger electrophilicity towards pentacoordinated siliconate species **B**. The latter is generated from fluorinated silane and a Lewis base activator.[2–4] As the formation of siliconate **B** is reversible, the Lewis base may also attack at the difluoroboryl group thereby breaking B–N coordination and keeping the desired reaction back. To overcome such an obstacle it was necessary to use a silicon reagent of high Lewis acidity, which should favor the generation of hypervalent siliconate. For this purpose fluorotris(pentafluorophenyl)silane $(C_6F_5)_3SiF$ seemed optimal, since previously[4–6] it proved to be the most efficient silane for C_6F_5 group transfer in the presence of mild Lewis bases.[4(b)]



Scheme 1

In our experiments (Scheme 2), oximes **1a**,**b** were treated with boron trifluoride etherate in the presence of allyltrimethylsilane in dichloroethane[3(a)] to obtain difluoroboron complexes **2a**,**b** in high yields. Complexes **2a**,**b** were isolated and characterized by ^{1}H, ^{13}C, ^{19}F and ^{11}B NMR spectroscopy,‡ and, in case of **2a**, by single crystal X-ray analysis (*vide infra*).§ The reaction of complexes **2a**,**b** with $(C_6F_5)_3SiF$ and sodium acetate as an activator was carried out in refluxing acetonitrile thus providing after aqueous work-up and chromatography hydroxylamines **3a**,**b** in good yields.¶

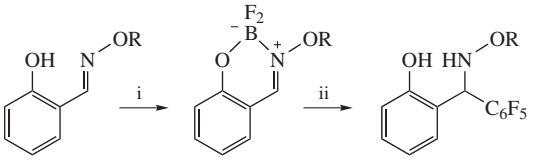
This two-step procedure can be performed without isolation and purification of chelate complexes since the introduction of difluoroboryl group is a very clean process, with volatile

† As a replacement of oximes, nitrones were considered as substrates in reaction with Me_3SiCF_3 providing CF_3-substututed hydroxylamines.[8]

‡ *Complex* **2a**. $BF_3{\cdot}Et_2O$ (570 μl, 4.5 mmol) was added dropwise to a solution of oxime **1a** (453 mg, 3.0 mmol) and allyltrimethylsilane (384 μl, 4.5 mmol) in 1,2-dichloroethane (6.2 ml). The exothermic reaction occurred accompanied by gas evolution. The mixture was stirred for 1 h at room temperature, the stirring was stopped and the reaction flask was kept overnight at 5 °C and 12 h at –25 °C. The solvent was decanted, and the crystals were washed with Et_2O and dried in a vacuum to give 513 mg of **2a** (yield 86%), mp 98–100 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.19 (t, 3H, OMe, *J* 1.3 Hz), 7.00 (td, 1H, CH_{Ar}, *J* 7.5 and 1.0 Hz), 7.06 (d, 1H, CH_{Ar}, *J* 8.5 Hz), 7.40 (dd, 1H, CH_{Ar}, *J* 7.7 and 1.6 Hz), 7.56 (ddd, 1H, CH_{Ar}, *J* 8.5, 7.3 and 1.6 Hz), 8.47 (s, 1H, HC=N). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 64.3 (t, *J* 2.9 Hz), 112.7, 119.0, 120.6, 131.0, 137.6, 155.2, 157.2 (t, *J* 1.8 Hz). ^{11}B NMR (96 MHz, $CDCl_3$) δ: 0.26 (t, *J* 11.0). ^{19}F NMR (282 MHz, $CDCl_3$) δ: –135.7 (m). Complex **2a** was described, but neither spectroscopic no structural data were reported.[9]

Complex **2b**. Allyltrimethylsilane (229 μl, 1.59 mmol) and $BF_3{\cdot}OEt_2$ (202 μl, 1.59 mmol) were successively added to a solution of oxime **1b** (240 mg, 1.06 mmol) in 1,2-dichloroethane (2.2 ml), and the mixture was heated at gentle reflux for 10 min. The solvent was evaporated in a vacuum, and the residue was recristallized from hexane–1,2-dichloroethane to give 256 mg of **2b** (yield 88%), mp 127–129 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 5.43 (s, 2H, CH_2), 6.97 (t, 1H, Ar, *J* 7.3 Hz), 7.10 (d, 1H, Ar, *J* 8.8 Hz), 7.24 (d, 1H, Ar, *J* 8.8 Hz), 7.33–7.65 (m, 6H, Ar), 8.20 (s, 1H, CH=N). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 79.0 (t, *J* 2.8 Hz), 112.7, 119.0, 120.5, 128.7, 129.4, 129.7, 131.1, 133.2, 137.8, 157.5, 157.7. ^{19}F NMR (282 MHz, $CDCl_3$) δ: 135.9 (d, *J* 19.1 Hz). ^{11}B NMR (96 MHz, $CDCl_3$) δ: 0.40 (t, *J* 10.6 Hz).

§ For detailed discussion on boron salicylaldoxime complexes, see ref. 9.



1a R = Me
1b R = Bn

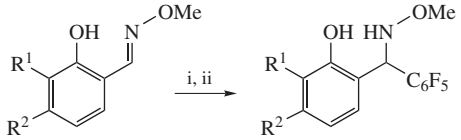
2a 86%
2b 88%

3a 77%
3b 80%

Scheme 2 *Reagents and conditions*: i, 1.5 equiv. $BF_3{\cdot}OEt_2$, 1.5 equiv. $CH_2{=}CHCH_2SiMe_3$, dichloroethane, Δ, 10 min; ii, 1.0 equiv. $(C_6F_5)_3SiF$, 1.2 equiv. AcONa, MeCN, Δ, 3 h.

propene and fluorotrimethylsilane being the only secondary products. Simple solvent exchange and subsequent addition of $(C_6F_5)_3SiF$ and sodium acetate allows one to perform the pentafluorophenylation in one experiment. This procedure was applied for the pentafluorophenylation of a variety of oximes **1c–e** (Scheme 3).[††,‡‡]

Molecular structure of complex **2a** is shown in Figure 1.[§§] Its structural characteristics are similar to those of previously reported six-membered oxime boron complexes, which bear aryl groups at boron.[10] Molecule **2a** is virtually planar with slight deviation of BF_2 fragment [torsion angle B(1)O(1)C(3)C(2) equals 10.9(2)°], which is different from the known similar complexes in which such deviation is more pronounced (more than 25° for similar torsion angles).[10]



1c R^1 = OMe, R^2 = H
1d R^1 = $CH_2{=}CHCH_2$, R^2 = H
1e $R^1 + R^2$ = benzo

3c 79%
3d 74%
3e 94%

Scheme 3 *Reagents and conditions*: i, 1.5 equiv. $BF_3{\cdot}OEt_2$, 1.5 equiv. $CH_2{=}CHCH_2SiMe_3$, dichloroethane, Δ, 10 min; ii, 1.0 equiv. $(C_6F_5)_3SiF$, 1.2 equiv. AcONa, MeCN, Δ, 3 h.

¶ *Synthesis of* **3a**,**b**. The difluoroboron complex (0.93 mmol) was successively treated with acetonitrile (1.8 ml), $(C_6F_5)_3SiF$ (510 mg, 0.93 mmol) and AcONa (92 mg, 1.12 mmol), and the mixture was refluxed for 3 h. The mixture was cooled to room temperature, quenched with 0.5 ml of saturated aqueous Na_2CO_3, diluted with excess of water and extracted with diethyl ether (4×5 ml). The combined organic phase was dried with Na_2SO_4, concentrated, and the residue was subjected to flash chromatography on silica gel.

2-[(Methoxyamino)(pentafluorophenyl)methyl]phenol **3a**. R_f 0.21 (hexanes–EtOAc, 5:1), mp 70–71 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.72 (s, 3H, OMe), 6.01 (s, 1H, NCH), 6.22 (br. s, 1H, NH, $\Delta\nu_{1/2}$ 23.4 Hz), 6.67 (d, 1H, CH_{Ar}, *J* 7.7 Hz), 6.82 (t, 1H, CH_{Ar}, *J* 7.5 Hz), 6.96 (d, 1H, CH_{Ar}, *J* 8.4 Hz), 7.19–7.33 (m, 1H, CH_{Ar}). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 57.6 (m), 62.3, 112.2 (tm, *J* 14.3 Hz), 117.5, 119.4, 120.2, 127.3, 130.4, 137.8 (dm, *J* 249.3 Hz), 141.1 (dm, *J* 255.1 Hz), 145.7 (dm, *J* 247.1 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ: –162.0 (m, 2F, *meta*), –154.4 (t, 1F, *para*, *J* 21.1 Hz), –143.3 (dd, 1F, *ortho*, *J* 21.1 and 8.5 Hz). Found (%): C, 52.92; H, 3.27; N, 4.34. Calc. for $C_{12}H_{16}N_2O_3$ (%): C, 52.67; H, 3.16; N, 4.39.

2-[(Benzyloxyamino)(pentafluorophenyl)methyl]phenol **3b**. R_f 0.20 (hexanes–EtOAc, 6:1). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 4.75–4.92 (m, 2H, CH_2), 5.85 (d, 1H, CHN, *J* 10.3 Hz), 6.13 (d, 1H, NH, *J* 10.3 Hz), 6.61 (d, 1H, Ar, *J* 7.8 Hz), 6.79 (t, 1H, Ar, *J* 7.3 Hz), 6.92 (d, 1H, Ar, *J* 7.8 Hz), 7.24 (t, 1H, Ar, *J* 7.3 Hz), 7.34–7.52 (m, 5H, Ph), 8.61 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 58.2 (m), 76.7, 112.1 (tm, *J* 14.3 Hz), 117.6, 119.2, 120.2, 127.3, 128.78, 128.81, 128.9, 130.5, 136.5, 137.7 (dm, *J* 247.5 Hz), 141.1 (dm, *J* 249.0 Hz), 145.6 (dm, *J* 244.5 Hz), 156.4. ^{19}F NMR (282 MHz, $CDCl_3$) δ: –164.39 (td, *J* 21.2 and 6.4 Hz), –156.75 (t, *J* 21.2 Hz), –145.84 (dd, *J* 21.2 and 6.4 Hz). Found (%): C, 60.77; H, 3.68; N, 3.44. Calc. for $C_{20}H_{14}F_5NO_2$ (%): C, 60.76; H, 3.57; N, 3.54.

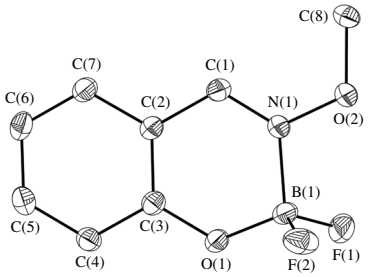


Figure 1 Molecular structure of **2a** presented by thermal ellipsoids with 50% probability. The hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and angles (°): B(1)–N(1) 1.592(2), N(1)–C(1) 1.2874(19), O(2)–N(1) 1.3879(15); N(1)–C(1)–C(2) 119.20(13), O(1)–B(1)–N(1) 108.40(12); N(1)–B(1)–O(1)–C(3) –15.9(2), B(1)–O(1)–C(3)–C(2) 10.9(2), C(8)–O(2)–N(1)–C(1) –6.8(2).

In summary, the method of chelation-assisted C=N bond activation in salicylic aldehyde oximes has been elaborated, which allowed for the first example of Lewis base mediated transfer of fluorinated group from silicon to oximino fragment.

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†† All reactions were performed under argon. Dichloroethane was distilled from CaH_2 before use. Acetonitrile was distilled from CaH_2 and stored over MS 4 Å. Starting compounds were obtained from NH_2OMe[11(*a*)] and NH_2OBn[11(*b*)] and commercially available aldehydes in methanol. Compounds **1a**[9] and **1b**[12] have been described.

2-Hydroxy-3-methoxybenzaldehyde O-*methyloxime* **1c**: mp 81–82 °C (from $MeOBu^t$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.89 (s, 3H, OMe), 3.97 (s, 3H, OMe), 6.74–6.94 (m, 4H, $4CH_{Ar}$), 8.14 (s, 1H, HC=N), 9.82 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 56.1, 62.4, 113.4, 116.4, 119.3, 122.2, 147.1, 148.1, 151.0. Found (%): C, 59.71; H, 6.00; N, 7.84. Calc. for $C_{12}H_{16}N_2O_3$ (%): C, 59.66; H, 6.12; N, 7.73.

3-Allyloxy-2-hydroxybenzaldehyde O-*methyloxime* **1d**: oil, R_f 0.32 (hexanes–EtOAc, 30:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.48 (d, 2H, =CH–CH_2, *J* 6.2 Hz), 4.00 (s, 3H, OMe), 5.06–5.16 (m, 2H, $=CH_2$), 5.98–6.14 (m, 1H, =CH–CH_2), 6.88 (t, 1H, CH_{Ar}, *J* 7.5 Hz), 7.05 (dd, 1H, CH_{Ar}, *J* 7.7 and 1.5 Hz), 7.18 (d, 1H, CH_{Ar}, *J* 7.5 Hz), 8.17 (s, 1H, HC=N), 10.12 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 33.8, 62.4, 115.6, 115.9, 119.4, 127.7, 129.0, 131.7, 136.5, 151.6, 155.2. Found (%): C, 71.71; H, 5.73; N, 7.06. Calc. for $C_{12}H_{16}N_2O_3$ (%): C, 71.63; H, 5.51; N, 6.96.

1-Hydroxy-2-naphthaldehyde O-*methyloxime* **1e**: mp 55–59 °C (from MeCN). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.07 (s, 1H, OMe), 7.24 (d, 1H, CH_{Ar}, *J* 9.2 Hz), 7.37 (t, 1H, CH_{Ar}, *J* 7.5 Hz), 7.52 (td, 1H, CH_{Ar}, *J* 7.7 and 1.2 Hz), 7.79 (d, 2H, CH_{Ar}, *J* 8.8 Hz), 7.93 (d, 1H, CH_{Ar}, *J* 8.8 Hz), 9.08 (s, 1H, HC=N), 10.98 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 62.5, 106.7, 118.8, 120.1, 123.4, 127.4, 128.3, 128.9, 131.9, 132.3, 148.1, 157.5. Found (%): C, 71.71; H, 5.73; N, 7.06. Calc. for $C_{12}H_{16}N_2O_3$ (%): C, 71.63; H, 5.51; N, 6.96.

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‡‡ *Synthesis of* **3c**–**e**. $BF_3{\cdot}Et_2O$ (190 μl, 1.5 mmol) was added dropwise to a solution of oxime (1.0 mmol) and allyltrimethylsilane (238 μl, 1.5 μmol) in 1,2-dichloroethane (2 ml), and the mixture was stirred for 1 h at room temperature. The solvent was evaporated in a vacuum, the residue was dissolved in MeCN (2 ml) followed by addition of $(C_6F_5)_3SiF$ (548 mg, 1.0 mmol) and NaOAc (98 mg, 1.2 mmol). The mixture was refluxed for 3 h, cooled to room temperature, and quenched by addition of saturated aqueous Na_2CO_3 (0.25 ml) and water (0.25 ml). After stirring for additional 2 min, the mixture was diluted with Et_2O–hexane (1:1, 10 ml), and the resulting suspension was filtered through anhydrous Na_2SO_4. The filtrate was concentrated and the residue was subjected to flash chromatography on silica gel.

2-Methoxy-6-[(methoxyamino)(pentafluorophenyl)methyl]phenol **3c**. R_f 0.23 (hexanes–EtOAc, 4:1), mp 89–90 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.62 (s, 3H, OMe), 3.88 (s, 3H, OMe), 5.99 (s, 1H, NCH), 6.36 (br. s, 1H, NH, $\Delta\nu_{1/2}$ 12.8 Hz), 6.73–6.89 (m, 4H, $3CH_{Ar}$ + OH). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 55.1 (m), 56.1, 62.0, 111.0, 114.2 (tm, *J* 16.5 Hz), 119.5 (t, *J* 2.0 Hz), 119.8, 122.0, 137.6 (dm, *J* 252.1 Hz), 140.6 (dm, *J* 258.6 Hz), 145.6 (dm, *J* 245.5 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ: –163.2 (m, 2F, *meta*), –156.4 (t, 1F, *para*, *J* 21.2 Hz), –143.0 (dd, 1F, *ortho*, *J* 21.5 and 7.0 Hz). Found (%): C, 51.69; H, 3.55; N, 4.07. Calc. for $C_{12}H_{16}N_2O_3$ (%): C, 51.58; H, 3.46; N, 4.01.

2-Allyl-6-[(methoxyamino)(pentafluorophenyl)methyl]phenol **3d**. R_f 0.10 (hexanes–EtOAc, 40:1), mp 65–66 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.47 (d, 2H, =CH–CH_2, *J* 6.2 Hz), 3.74 (s, 3H, OMe), 5.02–5.23 (m, 2H, $=CH_2$), 5.97–6.15 (m, 2H, =C*H*–CH_2 + NCH), 6.18–6.30 (m, 1H, NH), 6.53 (d, 1H, CH_{Ar}, *J* 7.7 Hz), 6.77 (t, 1H, CH_{Ar}, *J* 7.5 Hz), 7.17 (d, 1H, CH_{Ar}, *J* 7.7 Hz), 9.18 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 34.2, 57.6, 62.3, 112.2 (tm, *J* 15.5 Hz), 115.7, 119.0, 119.9, 125.3, 128.4, 130.9, 136.6, 137.7 (dm, *J* 254.5 Hz), 141.1 (dm, *J* 248.7 Hz), 145.5 (dm, *J* 249.7 Hz), 154.2. ^{19}F NMR (282 MHz, $CDCl_3$) δ: –162.0 (m, 2F, *meta*), –154.3 (t, 1F, *para*, *J* 21.2 Hz), –143.4 (dm, 1F, *ortho*, *J* 21.7 Hz). Found (%): C, 56.77; H, 3.85; N, 3.91. Calc. for $C_{12}H_{16}N_2O_3$ (%): C, 56.83; H, 3.93; N, 3.90.

2-[(Methoxyamino)(pentafluorophenyl)methyl]-1-naphthol **3e**. Glassy oil, R_f 0.15 (hexanes–EtOAc, 8:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.67 (s, 3H, OMe), 6.05 (br. s, 1H, NH, $\Delta\nu_{1/2}$ 28.3 Hz), 7.16 (d, 1H, CH_{Ar}, *J* 8.6 Hz), 7.32 (d, 1H, CH_{Ar}, *J* 7.3 Hz), 7.47 (td, 1H, CH_{Ar}, *J* 7.6 and 1.1 Hz), 7.66 (d, 1H, CH_{Ar}, *J* 8.6 Hz), 7.72–7.82 (m, 2H, $2CH_{Ar}$), 10.4 (br. s, 1H, OH, $\Delta\nu_{1/2}$ 43.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 56.3, 62.4, 108.9, 112.3 (tm, *J* 16.1 Hz), 120.0, 120.2 (t, *J* 2.0 Hz), 123.0, 127.3, 128.8, 129.1, 130.9, 132.1, 137.6 (dm, *J* 252.8 Hz), 141.2 (dm, *J* 255.6 Hz), 145.7 (dm, *J* 250.5 Hz), 156.2 (t, *J* 1.4 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ: –161.6 (br. s, 2F, *meta*, $\Delta\nu_{1/2}$ 55.9 Hz), –153.7 (br. s, 1F, *para*, $\Delta\nu_{1/2}$ 57.5 Hz), –140.8 (dm, 1F, *ortho*, *J* 22.7 and 7.0 Hz). Found (%): C, 60.87; H, 6.77; N, 11.74. Calc. for $C_{12}H_{16}N_2O_3$ (%): C, 61.00; H, 6.83; N, 11.86.

§§ *Crystallographic data for* **2a**: crystals of $C_8H_8BF_2NO_2$ are monoclinic, space group $P2_1/n$, a = 7.3072(8), b = 11.8254(13) and c = 9.7344(11) Å, β = 97.608(2)°, V = 833.75(16) Å^3, Z = 4, M = 198.96, d_{calc} = 1.585 g cm^{-3}, μ(MoKα) = 0.14 mm^{-1}, F(000) = 408. Intensities of 9342 reflections were measured with a Bruker Smart 1000 diffractometer at 120 K [λ(MoKα) = 0.71073 Å] and 2406 independent reflections (R_{int} = 0.0210) were used in further refinement. The structure was solved by direct method and refined by the full-matrix least-squares technique against F^2 in the anisotropic-isotropic approximation. All hydrogen atoms were calculated from geometrical point of view. Hydrogen atoms were refined in the rigid body approximation with the U_{iso}(H) parameters equal to $1.2U_{eq}$(C) and $1.5U_{eq}(C_{Me})$, where U_{eq}(C) are the equivalent thermal parameters of the carbon atoms to which corresponding H atoms are bonded. The refinement converged to wR_2 = 0.0895 and GOF = 1.000 for all independent reflections [R_1 = 0.0417 was calculated against F for 1352 observed reflections with $I > 2\sigma(I)$].

CCDC 766904 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2010.

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