DIRECTARYLATION OF FUROXAN USING POTASSIUM ARYLTRIFLUOROBORATES

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Abstract – Direct arylation of a furoxan ring with potassium aryltrifluoroborates is proposed. A series of aryl-substituted furoxan derivatives have been constructed through the formation of a new C–C bond via a radical pathway. The plausible reaction mechanism is proposed based on the DFT-calculation study.

INTRODUCTION

The history of furoxan (1,2,5-oxadiazole 2-oxide) began in the 1850s. Furoxans exhibit various biological activities and are considered potential pharmaceutical candidates. Furthermore, their ability to release nitric oxide distinguishes them from other heteroaromatic compounds. The structure of furoxan is characterized by an exo-ring oxygen atom that makes the furoxan ring asymmetric leading to the existence of two regioisomers. Moreover, the exo-ring oxygen atom perturbs the aromaticity of the five-membered furoxan ring and makes furoxan prone to ring opening in the presence of a base or nucleophile compared to its parent molecule furazan. Therefore, the formation of C–C bonds on furoxan rings is formidable. We reported the addition of carbon-centered alkyl radicals to 3-sulfonylfuroxans in a previous study. Herein, we have focused on the direct introduction of aryl substituents on the furoxan ring. Conventionally, for the synthesis of aryl group-substituted furoxans, the aryl group must be pre-installed in the precursor before the construction of the furoxan ring (Figure 1A), which often makes the synthetic process tedious. In 2005, Gasco et al. first introduced an aromatic substituent on the furoxan ring using a Grignard reagent (Figure 1B). However, the scope was limited and further studies have not been conducted. Later, we investigated the arylation of dichlorofuroxan using aryl Grignard reagents. Recently, we developed the addition reaction of an aryl radical to sulfonylfuroxans using potassium aryltrifluoroborates as a radical source (Figure 1C), as reported herein.
RESULTS AND DISCUSSION

We screened the reaction conditions and the results are summarized in Table 1 (the rest of the data are shown in the Supporting Information). We observed that sulfonylfuroxan 1a reacted with potassium phenyltrifluoroborate in the presence of K$_2$S$_2$O$_8$ at 80 °C to afford arylfuroxan product 3aa in a 46% yield (entry 1, Table 1). A catalytic amount of AgNO$_3$ was ineffective for the reaction (entry 2). Prolonging the reaction time did not lead to an increase in the yield (entry 3). Different radical generators were also examined (entries 4–6); however, no improvement was observed. Subsequently, the solvent system was tested, revealing that MeCN/H$_2$O (1/1) was the best solvent (entries 1 and 7–11). Based on the observation that, in general, the starting 1a remained unreacted at the end of the reaction and prolonging the reaction was not beneficial (entry 3), the moderate yield can be ascribed to the consumption of 2a and/or K$_2$S$_2$O$_8$. Accordingly, the amount of 2a and K$_2$S$_2$O$_8$ increased (entry 12). Consequently, the isolated yield increased slightly to 44%. Increasing the reaction temperature did not significantly affect the product yield (entry 13).
Table 1. Optimization of the reaction conditions\textsuperscript{a}

| entry | reagent (equiv) | solvent | time/h | yield/%
<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>K\textsubscript{2}S\textsubscript{2}O\textsubscript{8} (3)</td>
<td>MeCN/H\textsubscript{2}O (1/1)</td>
<td>4</td>
<td>46 (38)\textsuperscript{c}</td>
</tr>
<tr>
<td>2</td>
<td>K\textsubscript{2}S\textsubscript{2}O\textsubscript{8} (3), AgNO\textsubscript{3} (0.2)</td>
<td>MeCN/H\textsubscript{2}O (1/1)</td>
<td>4</td>
<td>45</td>
</tr>
<tr>
<td>3</td>
<td>K\textsubscript{2}S\textsubscript{2}O\textsubscript{8} (3)</td>
<td>MeCN/H\textsubscript{2}O (1/1)</td>
<td>21</td>
<td>45</td>
</tr>
<tr>
<td>4</td>
<td>Mn(OAc\textsubscript{3}) (3)</td>
<td>MeCN</td>
<td>9</td>
<td>25</td>
</tr>
<tr>
<td>5</td>
<td>(NH\textsubscript{4})\textsubscript{2}S\textsubscript{2}O\textsubscript{8} (3)</td>
<td>DMSO</td>
<td>18</td>
<td>trace</td>
</tr>
<tr>
<td>6</td>
<td>(n-Bu\textsubscript{4}N)\textsubscript{2}S\textsubscript{2}O\textsubscript{8} (3)</td>
<td>MeCN</td>
<td>4</td>
<td>trace</td>
</tr>
<tr>
<td>7</td>
<td>K\textsubscript{2}S\textsubscript{2}O\textsubscript{8} (3)</td>
<td>MeCN/H\textsubscript{2}O (2/1)</td>
<td>4</td>
<td>35</td>
</tr>
<tr>
<td>8</td>
<td>K\textsubscript{2}S\textsubscript{2}O\textsubscript{8} (3)</td>
<td>MeCN/H\textsubscript{2}O (1/2)</td>
<td>4</td>
<td>44</td>
</tr>
<tr>
<td>9</td>
<td>K\textsubscript{2}S\textsubscript{2}O\textsubscript{8} (3)</td>
<td>MeCN/H\textsubscript{2}O (1/5)</td>
<td>4</td>
<td>22</td>
</tr>
<tr>
<td>10</td>
<td>K\textsubscript{2}S\textsubscript{2}O\textsubscript{8} (3)</td>
<td>acetone/H\textsubscript{2}O (1/1)</td>
<td>4</td>
<td>22</td>
</tr>
<tr>
<td>11</td>
<td>K\textsubscript{2}S\textsubscript{2}O\textsubscript{8} (3)</td>
<td>NMP</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>12\textsuperscript{d}</td>
<td>K\textsubscript{2}S\textsubscript{2}O\textsubscript{8} (5)</td>
<td>MeCN/H\textsubscript{2}O (1/1)</td>
<td>4</td>
<td>44\textsuperscript{e}</td>
</tr>
<tr>
<td>13\textsuperscript{e}</td>
<td>K\textsubscript{2}S\textsubscript{2}O\textsubscript{8} (3)</td>
<td>MeCN/H\textsubscript{2}O (1/1)</td>
<td>4</td>
<td>40</td>
</tr>
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</table>

\textsuperscript{a} Reaction conditions: 1\textsubscript{a} (1 equiv), 2\textsubscript{a} (3 equiv), solvent (0.1 M), argon atmosphere, and 80 °C; \textsuperscript{b} determined through \textsuperscript{1}H NMR analysis using durene as an internal standard. \textsuperscript{c} Isolated yield. \textsuperscript{d} 5 equiv of 2\textsubscript{a} was used. \textsuperscript{e} Temperature was 100 °C. NMP: N-methylpyrrolidone.

Thereafter, we investigated the substrate scope (Table 2). Although the yield was the highest in entry 12 in Table 1 among the performed experiments, we selected the conditions in entry 1 in Table 1 as the optimal conditions considering the atom economy. The subgram-scale synthesis of 3\textsubscript{aa} could be performed without significant difference in yield compared to a small scale (38% vs. 36%). The reaction tolerated electron-donating (3\textsubscript{ab}–3\textsubscript{ad}) and electron-withdrawing (3\textsubscript{af}–3\textsubscript{ai}) groups, with the former affording a slightly higher yield than the latter. However, substrates with strong electron-withdrawing substituents (−NO\textsubscript{2} and −CN) failed to yield the desired products (3\textsubscript{ak} and 3\textsubscript{al}). Thiophenyl- and indolyl-trifluoroborate performed poorly (3\textsubscript{am} and 3\textsubscript{an}), which can be attributed to the instability of the corresponding heteroaryl radicals under oxidative conditions. Furoxans bearing substituents other than the ethoxy group at the 4-position were also uneventfully synthesized (3\textsubscript{ba}, 3\textsubscript{ca}, and 3\textsubscript{da}).
Table 2. Substrate scope of arylation of furoxan$^a$

<table>
<thead>
<tr>
<th>Reaction conditions:</th>
<th>Isolated yield.</th>
</tr>
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<tbody>
<tr>
<td>$1$ (1.0 equiv), $2$ (3.0 equiv), $K_2S_2O_8$ (3.0 equiv), MeCN/H$_2$O (1/1), and 80 °C.</td>
<td></td>
</tr>
<tr>
<td><strong>3aa, 38% (36%)$^b$</strong></td>
<td></td>
</tr>
<tr>
<td><strong>3ab, 30%</strong></td>
<td></td>
</tr>
<tr>
<td><strong>3ac, 30%</strong></td>
<td></td>
</tr>
<tr>
<td><strong>3ad, 41%</strong></td>
<td></td>
</tr>
<tr>
<td><strong>3ae, 34%</strong></td>
<td></td>
</tr>
<tr>
<td><strong>3af, 26%</strong></td>
<td></td>
</tr>
<tr>
<td><strong>3ag, 21%</strong></td>
<td></td>
</tr>
<tr>
<td><strong>3ah, 18%</strong></td>
<td></td>
</tr>
<tr>
<td><strong>3ai, 10%</strong></td>
<td></td>
</tr>
<tr>
<td><strong>3aj, 11%</strong></td>
<td></td>
</tr>
<tr>
<td><strong>3ak, 0%</strong></td>
<td></td>
</tr>
<tr>
<td><strong>3al, 0%</strong></td>
<td></td>
</tr>
<tr>
<td><strong>3am, &lt;5%</strong></td>
<td></td>
</tr>
<tr>
<td><strong>3an, 0%</strong></td>
<td></td>
</tr>
<tr>
<td><strong>3ba, 31%</strong></td>
<td></td>
</tr>
<tr>
<td><strong>3ca, 31%</strong></td>
<td></td>
</tr>
<tr>
<td><strong>3da, 30%</strong></td>
<td></td>
</tr>
</tbody>
</table>

$^a$ Reaction conditions: $1$ (1.0 equiv), $2$ (3.0 equiv), $K_2S_2O_8$ (3.0 equiv), MeCN/H$_2$O (1/1), and 80 °C. Isolated yield. $^b$ One gram of $1$ was used.
Based on previous studies,\textsuperscript{12,13} the proposed reaction mechanism is illustrated in Figure 2. First, heating induces the generation of sulfate radical anions from the persulfate anions. The aryl radical was generated from aryltrifluoroborate 2a in the presence of a sulfate radical anion. Subsequently, an aryl radical undergoes addition to the 3-sulfonylfuroxan to yield radical intermediate A, which is the resonance form of nitroxy radical A', a well-known stable oxyradical.\textsuperscript{20} Finally, the benzenesulfonyl radical works as a radical-leaving group and the furoxan product is generated.

\[ \text{S}_2\text{O}_8^{2-} \xrightarrow{\Delta} 2 \text{SO}_4^{2-} \]

\[ \begin{array}{c}
\text{PhO}_2\text{S}^+ \text{N} \text{N}^+ \text{O} \text{Et} \\
\text{PhO}_2\text{S}^+ \text{N} \text{N}^+ \text{O} \text{Et} \\
\text{PhO}_2\text{S}^+ \text{N} \text{N}^+ \text{O} \text{Et} \\
\text{PhO}_2\text{S}^+ \text{N} \text{N}^+ \text{O} \text{Et} \\
\text{PhO}_2\text{S}^+ \text{N} \text{N}^+ \text{O} \text{Et} \\
\end{array} \]

\[ \text{PhSO}_2^+ \xrightarrow{\text{H}_2\text{O}} \text{ArSO}_3\text{H} \]

\[ \text{Figure 2. Proposed reaction mechanism} \]

The developed reaction was studied computationally and the results are shown in Figure 3. The reaction of 4-methoxy-3-phenylsulfonylfuroxan with a phenyl radical was investigated. For comparison, the reaction of the same furoxan with a methyl radical was also investigated. In both cases, the first addition step had a higher energy barrier than the second elimination step. There was no significant variance in the energy barriers between the reactions with methyl and phenyl radicals. Therefore, the moderate yields observed in this study compared to the alkyl radical addition reaction\textsuperscript{12,13} can be ascribed to the relatively rapid decomposition of the generated aryl radicals\textsuperscript{21} over the desired addition reaction to sulfonylfuroxan.
Figure 3. Computed potential energy surfaces and relative Gibbs free energies of the methyl (a) and phenyl radicals (b) addition reactions to 3-sulfonylfuroxan at the (U)B3LYP/6-31G(d) level. All energies are indicated in kcal mol$^{-1}$ and interatomic distances are shown in angstroms. *For the reason why the Ph-TS2 is lower in energy than Ph-INT, see the Supporting Information.

With the successful construction of bromo-substituted aryl substituents on furoxan, further derivatization of the furoxan product was considered. Suzuki–Miyaura cross coupling was performed with 3af. The furoxan ring was tolerant to standard coupling reaction conditions, and the corresponding product 3ae was obtained in an 86% yield (Figure 4). This result demonstrates that divergent synthesis of arylfuroxans is feasible.

Figure 4. Derivatization of furoxan product 3af
In conclusion, we developed a novel method for the introduction of an aryl group on the furoxan ring. This method is expected to be applicable in the synthesis of biologically active furoxans.

**EXPERIMENTAL**

Unless otherwise noted, all reactions were carried out in a well-cleaned glassware with magnetic stirring. Operations were performed under an atmosphere of dry argon using Schlenk and vacuum techniques, unless otherwise noted. Heated reactions were conducted in an oil bath and the indicated temperatures are ones of oil bath, unless otherwise noted. All starting materials were obtained from commercial sources or were synthesized using standard procedures. Melting points were measured on a Yanaco MP-500D and are not corrected. \(^1\)H and \(^{13}\)C\({}^1\)H\)NMR (400 and 100 MHz, respectively) were recorded on a Bruker Avance III HD 400 using TMS (0 ppm) and CDCl\(_3\) (77.0 ppm) as an internal standard, respectively. The following abbreviations are used in connection with NMR; s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet and m = multiplet. IR spectra were obtained using a Nicolet\textsuperscript{TM} iS5 IR spectrometer with an iD5 attenuated total reflectance (ATR) accessory (Thermo Scientific\textsuperscript{TM}) operating at room temperature. Mass spectra were measured using a LTQ Orbitrap Elite or XL (Thermo Fisher Scientific, Brehmen, Germany) with an electrospray ionization (ESI) ion source and an atmospheric pressure chemical ionization (APCI). Thin layer chromatography (TLC) was carried out on Merck 25 TLC silica gel 60 F\(_{254}\) aluminum sheets. Preparative TLC was carried out on homemade glass-based TLC plates (20 × 20 cm) using Wakogel B-5F (FUJIFILM). 3-(Phenylsulfonyl)furoxans \(^1\)1\(_2\)-\(^1\)3\(_{22}\)-\(^1\)3\(_{24}\) and potassium aryl trifluoroborates \(^2\)\(_{22}\)-\(^2\)\(_{24}\) were synthesized according to the previous reported methods.

**General procedure for the arylation of sulfonylfuroxan with the synthesis of 3aa as the representative example.** 4-Ethoxy-3-(phenylsulfonyl)furoxan 1a (40 mg, 0.15 mmol, 1.0 equiv), potassium phenyltrifluoroborate 2a (81.7 mg, 0.44 mmol, 3.0 equiv), potassium peroxodisulfate (120 mg, 0.44 mmol, 3.0 equiv), and MeCN–H\(_2\)O (1:1) (1.5 mL) were added to a Schlenk flask under argon. The mixture was stirred at 80 °C for 4 h. The reaction was extracted three times with EtOAc, the organic layer was dried over Na\(_2\)SO\(_4\), filtrated, and concentrated in vacuo. The crude residue was purified by preparative thin-layer chromatography on silica gel (hexane/EtOAc (3/1)) to afford 3aa (11.6 mg, 38% yield).

**4-Ethoxy-3-phenylfuroxan (3aa)** Yield: 38%. Colorless prisms; Mp 75.4–76.3 °C. IR (neat): 2914, 1590, 1550, 1497, 1436, 1391, 1358, 1320, 1161, 1114, 1069, 1022, 967, 877, 850, 766, 735, 690, 653, 571 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 8.16–8.13\) (m, 2H), 7.53–7.45 (m, 3H), 4.57 (q, \(J = 7.1\) Hz, 2H), 1.56 (t, \(J = 7.1\) Hz, 3H). \(^{13}\)C\({}^1\)H\)NMR (100 MHz, CDCl\(_3\)) \(\delta = 162.3, 130.4, 128.8, 126.2, 122.6, 107.6, 66.9, 14.5\). HRMS \textit{m/z} (APCI) calcd for C\(_{10}\)H\(_{11}\)O\(_3\)N\(_2\) (M + H\)\(^+\) 207.0764, found 207.0763.
4-Ethoxy-3-(4-methylphenyl)furoxan (3ab) Yield: 30%. Colorless prisms; Mp 74.6–75.5 °C. IR (neat): 2985, 1598, 1550, 1517, 1466, 1437, 1387, 1335, 1317, 1185, 1115, 1018, 968, 879, 844, 807, 733, 589 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ = 8.06–8.02 (m, 2H), 7.33–7.29 (m, 2H), 4.56 (q, J = 7.1 Hz, 2H), 2.41 (s, 3H), 1.56 (t, J = 7.1 Hz, 3H). ¹³C{¹H} NMR (100 MHz, CDCl₃) δ = 162.3, 140.9, 129.6, 126.1, 119.6, 107.8, 66.9, 21.6, 14.5. HRMS m/z (ESI) calcd for C₁₁H₁₂O₃N₂Na (M + Na)+ 243.0740, found 243.0741.

4-Ethoxy-3-(4-methoxyphenyl)furoxan (3ac) Yield: 30%. Colorless prisms; Mp 78.2–79.6 °C. IR (neat): 2934, 1593, 1554, 1518, 1454, 1385, 1335, 1303, 1255, 1186, 1166, 1116, 1025, 964, 839, 811, 737, 594 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ = 8.14–8.11 (m, 2H), 7.04–7.00 (m, 2H), 4.56 (q, J = 7.1 Hz, 2H), 3.87 (s, 3H), 1.56 (t, J = 7.1 Hz, 3H). ¹³C{¹H} NMR (100 MHz, CDCl₃) δ = 162.3, 161.0, 127.9, 114.7, 114.3, 107.6, 66.9, 55.4, 14.5. HRMS m/z (ESI) calcd for C₁₁H₁₂O₄N₂Na (M + Na)+ 259.0689, found 259.0691.

4-Ethoxy-3-(4-t-butylphenyl)furoxan (3ad) Yield: 41%. Colorless prisms; Mp 32.4–33.6 °C. IR (neat): 2963, 1602, 1549, 1464, 1385, 1337, 1321, 1171, 1126, 1111, 1018, 970, 879, 842, 833, 704, 567, 556 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ = 8.09–8.05 (m, 2H), 7.54–7.51 (m, 2H), 4.56 (q, J = 7.1 Hz, 2H), 1.55 (t, J = 7.1 Hz, 3H), 1.34 (s, 9H). ¹³C{¹H} NMR (100 MHz, CDCl₃) δ = 162.3, 153.9, 126.0, 125.8, 119.6, 107.6, 66.8, 35.0, 31.1, 14.5. HRMS m/z (ESI) calcd for C₁₄H₁₈O₃N₂Na (M + Na)+ 285.1210, found 285.1212.

4-Ethoxy-3-(4-biphenyl)furoxan (3ae) Yield: 34%. Colorless prisms; Mp 104.5–105.3 °C. IR (neat): 1598, 1545, 1466, 1387, 1355, 1333, 1319, 1169, 1118, 1020, 975, 876, 844, 763, 725, 695 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ = 8.25–8.22 (m, 2H), 7.75–7.72 (m, 2H), 7.65–7.62 (m, 2H), 7.50–7.45 (m, 2H), 7.42–7.38 (m, 1H), 4.59 (q, J = 7.1 Hz, 2H), 1.59 (t, J = 7.1 Hz, 3H). ¹³C{¹H} NMR (100 MHz, CDCl₃) δ = 162.3, 143.0, 139.9, 129.0, 128.1, 127.4, 127.1, 126.6, 121.4, 107.6, 67.0, 14.5. HRMS m/z (ESI) calcd for C₁₆H₁₄O₃N₂Na (M + Na)+ 305.0897, found 305.0898.

4-Ethoxy-3-(4-bromophenyl)furoxan (3af) Yield: 26%. Colorless prisms; Mp 78.6–79.4 °C. IR (neat): 2980, 1599, 1563, 1551, 1499, 1467, 1387, 1335, 1305, 1166, 1114, 1072, 1018, 1008, 970, 878, 824, 761, 689 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ = 8.06–8.03 (m, 2H), 7.66–7.62 (m, 2H), 4.58 (q, J = 7.1 Hz, 2H), 1.57 (t, J = 7.1 Hz, 3H). ¹³C{¹H} NMR (100 MHz, CDCl₃) δ = 162.0, 132.1, 127.5, 124.8, 121.5, 107.2, 67.1, 14.5. HRMS m/z (APCI) calcd for C₁₀H₁₀O₃N₂Br (M + H)+ 284.9869, found 284.9871.

4-Ethoxy-3-(3-bromophenyl)furoxan (3ag) Yield: 21%. Colorless prisms; Mp 75.2–76.4 °C. IR (neat): 2920, 1596, 1556, 1543, 1489, 1381, 1358, 1336, 1165, 1114, 1075, 1022, 978, 896, 870, 856, 785, 692, 680, 646 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ = 8.32 (t, J = 1.8 Hz, 1H), 8.12–8.09 (m, 1H), 7.62–7.59 (m, 1H), 7.38 (t, J = 8.0 Hz, 1H), 4.58 (q, J = 7.1 Hz, 2H), 1.58 (t, J = 7.1 Hz, 3H). ¹³C{¹H} NMR (100 MHz,
CDCl$_3$ $\delta$ = 161.9, 133.5, 130.3, 128.8, 124.6, 124.5, 123.0, 106.7, 67.2, 14.4. HRMS m/z (APCI) calcd for C$_{10}$H$_{10}$O$_3$N$_2$Br (M + H)$^+$ 284.9869, found 284.9871.

4-Ethoxy-3-(3-acylphenyl)furoxan (3ah) Yield: 18%. Colorless prisms; Mp 74.3–75.6 °C. IR (neat): 1691, 1597, 1554, 1502, 1421, 1390, 1358, 1331, 1254, 1168, 1119, 1016, 985, 860, 813, 721, 685, 649, 597, 553 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 8.76–8.75 (m, 1H), 8.38–8.35 (m, 1H), 8.07–8.05 (m, 1H), 7.65–7.61 (m, 1H), 4.60 (q, $J$ = 7.1 Hz, 2H), 2.66 (s, 3H), 1.59 (t, $J$ = 7.1 Hz, 3H). $^{13}$C{[1H]} NMR (100 MHz, CDCl$_3$) $\delta$ = 197.2, 162.1, 137.5, 130.2, 129.8, 129.3, 126.2, 123.3, 107.1, 67.2, 26.6, 14.4. HRMS m/z (ESI) calcd for C$_{12}$H$_{12}$O$_4$N$_2$Na (M + Na)$^+$ 271.0689, found 271.0691.

4-Ethoxy-3-(4-acylphenyl)furoxan (3ai) Yield: 10%. Colorless prisms; Mp 109.2–110.1 °C. IR (neat): 2914, 1687, 1594, 1550, 1466, 1407, 1355, 1316, 1257, 1171, 1117, 1021, 958, 840, 716, 604, 591 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 8.29–8.26 (m, 2H), 8.09–8.06 (m, 2H), 4.60 (q, $J$ = 7.1 Hz, 2H), 2.64 (s, 3H), 1.58 (t, $J$ = 7.1 Hz, 3H). $^{13}$C{[1H]} NMR (100 MHz, CDCl$_3$) $\delta$ = 271.0689, found 271.0691. 

4-Ethoxy-3-(2-naphthyl)furoxan (3aj) Yield: 11%. Colorless prisms; Mp 69.8–70.7 °C. IR (neat): 2920, 1604, 1590, 1549, 1487, 1476, 1394, 1342, 1147, 1117, 1027, 899, 856, 813, 752, 736, 709, 581 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 8.73 (d, $J$ = 0.8 Hz, 1H), 8.18 (dd, $J$ = 8.7, 1.8 Hz, 1H), 7.95–7.93 (m, 2H), 7.88–7.86 (m, 1H), 7.60–7.53 (m, 2H), 4.62 (q, $J$ = 7.1 Hz, 2H), 1.61 (t, $J$ = 7.1 Hz, 3H). $^{13}$C{[1H]} NMR (100 MHz, CDCl$_3$) $\delta$ = 162.4, 133.8, 132.8, 128.9, 128.6, 127.7, 127.7, 126.9, 126.8, 122.4, 119.9, 107.9, 67.0, 14.5. HRMS m/z (ESI) calcd for C$_{12}$H$_{12}$O$_3$N$_2$Na (M + Na)$^+$ 279.0740, found 279.0742.

4-Phenoxy-3-phenylfuroxan (3ba) Yield: 31%. Colorless prisms; Mp 107.5–108.6 °C. IR (neat): 2917, 1604, 1542, 1483, 1467, 1429, 1335, 1318, 1191, 1066, 970, 842, 765, 723, 685, 648 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 8.22–8.19 (m, 2H), 7.57–7.51 (m, 3H), 7.50–7.45 (m, 2H), 7.40–7.36 (m, 2H), 7.34–7.30 (m, 1H). $^{13}$C{[1H]} NMR (100 MHz, CDCl$_3$) $\delta$ = 162.0, 152.7, 130.7, 130.1, 129.0, 126.6, 126.4, 122.1, 120.1, 107.9. HRMS m/z (APCI) calcd for C$_{14}$H$_{12}$O$_3$N$_2$ (M + H)$^+$ 255.0764, found 255.0765.

4-Methoxy-3-phenylfuroxan (3ca) Yield: 31%. Colorless prisms; Mp 65.8–66.6 °C. IR (neat): 2917, 1598, 1557, 1471, 1443, 1414, 1320, 1199, 1161, 1073, 999, 842, 766, 740, 690, 643 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 8.14–8.11 (m, 2H), 7.53–7.45 (m, 3H), 4.22 (s, 3H). $^{13}$C{[1H]} NMR (100 MHz, CDCl$_3$) $\delta$ = 162.9, 130.5, 128.8, 126.2, 122.4, 107.7, 57.5. HRMS m/z (APCI) calcd for C$_{9}$H$_{8}$O$_3$N$_2$ (M + H)$^+$ 193.0608, found 193.0608.

4-Ethylsulfanyl-3-phenylfuroxan (3da) Yield: 30%. Colorless prisms; Mp 32.4–33.3 °C. IR (neat): 1573, 1503, 1437, 1393, 1247, 1121, 1100, 1024, 953, 823, 766, 726, 688, 666 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 7.91–7.87 (m, 2H), 7.55–7.47 (m, 3H), 3.28 (q, $J$ = 7.4 Hz, 2H), 1.49 (t, $J$ = 7.4 Hz, 3H). $^{13}$C{[1H]} NMR
(100 MHz, CDCl$_3$) $\delta = 154.4, 130.7, 129.0, 127.4, 122.5, 114.3, 25.6, 14.1$. HRMS $m/z$ (APCI) calcd for C$_{10}$H$_{11}$O$_2$N$_2$S (M + H)$^+$ 223.0536, found 223.0536.

**DFT calculations** All calculations were performed with the Gaussian 09 packages. Gas-phase geometry optimization and analytical vibrational frequency analysis for the ground state were performed by the (U)B3LYP/6-31G(d) DFT method. The transition states were optimized with Beryn algorithm. Frequency analyses were also carried out to identify the stationary points (RT, INT, PD: no imaginary frequency, TS: one imaginary frequency) and to estimate thermodynamic properties at 298.15 K and 1 atm and Gibbs free energies. The molecular structures were depicted by using the CYLview v1.0.561.$^\beta$

**Larger scale synthesis of 3aa.** 4-Ethoxy-3-(phenylsulfonyl)furoxan 1a (1.0 g, 3.7 mmol, 1.0 equiv), potassium phenyltrifluoroborate 2a (2.0 g, 11.1 mmol, 3.0 equiv), potassium peroxydisulfate (3.0 g, 11.1 mmol, 3.0 equiv), and MeCN–H$_2$O (1:1) (37 mL) were added to a Schlenk flask under argon. The mixture was stirred at 80 °C for 4 h. The reaction was extracted three times with EtOAc, the organic layer was dried over Na$_2$SO$_4$, filtrated, and concentrated in vacuo. The crude residue was purified by column chromatography on silica gel (hexane/EtOAc (3/1)) to afford 3aa (274.7 mg, 36% yield).

**Procedure for the Suzuki-Miyaura coupling reaction**$^{28}$

The reaction was performed in a Schlenk flask. To a degassed solution of 4-ethoxy-3-(4-bromophenyl)furoxan 3af (30 mg, 0.11 mmol, 1.0 equiv) in 1,2-dimethoxyethane (0.8 mL), Pd(PPh$_3$)$_4$ (3.6 mg, 3 mol%) was added, and the mixture was stirred under argon for 40 min. Phenylboronic acid (16.7 mg, 0.14 mmol, 1.3 equiv) was added, and the mixture was degassed by pumping followed by argon filling. Then a freshly prepared degassed solution of sodium carbonate (22.3 mg, 0.21 mmol, 2.0 equiv) in water (0.1 mL) was added, and the mixture was refluxed for 6 h, cooled, diluted with water, and extracted with EtOAc for three times. The combined extracts were dried with Na$_2$SO$_4$ and concentrated in vacuo. The residue was purified by preparative thin-layer chromatography on silica gel (hexane/EtOAc (3/1)) to afford 3ae (25.5 mg, 86%).

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