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Furoxan incorporation into C–H bonds enabling nitrogen-containing functional group installation into the same

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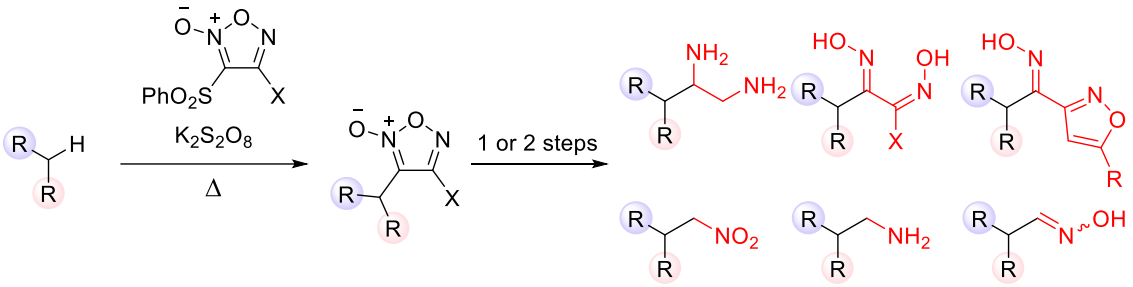
Supporting Information Placeholder



ABSTRACT: A C–C bond forming method was developed, whereby a furoxan ring is incorporated into various types of C–H bonds. The protocol not only offers a concise synthetic route to a variety of alkylated furoxan derivatives, but also provides an efficient strategy for the insertion of various nitrogen-containing functional groups into C–H bonds via transformation of the resultant furoxan ring.

Furoxan is a heterocyclic compound with weak aromaticity.[1] Because furoxan is susceptible to ring-opening under various reaction conditions,[1a] C–C bond-forming reactions on the furoxan ring have been underdeveloped.[2] Recently, however, our group has achieved radical addition to 3-sulfonylfuroxans.[3] In this reaction, carbon-centered radicals generated from the corresponding aliphatic carboxylic acids reacted with 3-sulfonylfuroxans to afford 3-alkylfuroxans via C–C bond formation on the furoxan ring. In addition, the transformation of the resultant furoxans to various nitrogen-containing functional groups was demonstrated. Thus, a furoxan-mediated "build-and-scrap" strategy, which converts carboxylic acids into a range of other functionalities, was established.

C–H bonds are robust covalent bonds with minimal polarization; therefore, in general, they are inert and do not participate in reactions under a range of reaction conditions. However, recent research progress has addressed this limitation, and various C–H activation methods have been reported.[4] One such commonly employed methodology is transition-metal catalysis, whereby metal atoms cleave C–H bonds and the generated carbon-metal species undergo subsequent coupling reactions to form C–C bonds. The hydrogen atom transfer (HAT) process, in which carbon radicals are generated from C(sp^3)–H bonds by reactive radical species, such as oxygen- or nitrogen-centered radicals, is another useful method, and subsequent reactions with radical acceptors result in C–C bond formation (Figure 1A). In the above cases, C–H bonds are directly converted to C–C bonds in one step. On the other hand, initial C–H bond conversion to versatile functional groups followed by their transformation to C–C bonds is another powerful strategy. Although multiple steps are necessary in such indirect methods, the wide choice of C–C bond forming methods applicable after the installation of versatile functional groups is advantageous. Conventional examples include C–H halogenation followed by transformation of the resultant organohalides (Figure 1B–1);

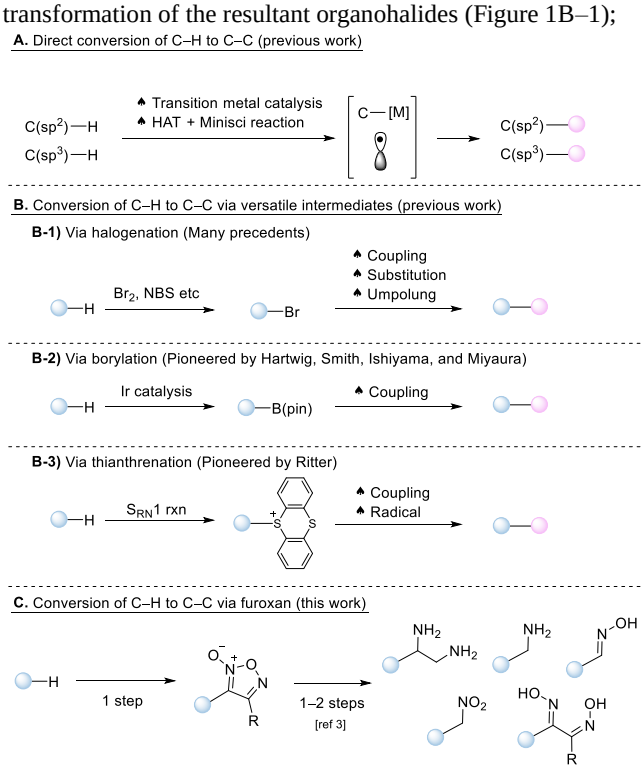


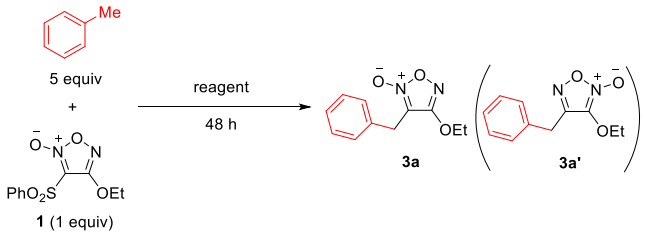
Figure 1. C–H functionalization

transformation of C–H to C–C bonds via iridium-catalyzed C–H borylation (Figure 1B–2);[5] and the recently developed thianthrenation method (Figure 1B–3)[6] are all categorized as indirect approaches.

We envisioned that a method for the direct introduction of a furoxan ring into C–H bonds, or C–H bond "furoxanization", would not only serve as a unique C–C bond forming reaction for accessing a variety of alkylated furoxan derivatives, but also provide a facile route for C–H bond insertion of nitrogen-containing functional groups that are otherwise difficult to prepare in a few steps (Figure 1C). Herein, we report the successful development of this method.

Our investigation into C–H furoxanization commenced using toluene as the substrate (Table 1). The reaction of toluene (5 equiv) and 3-sulfonylfuroxan **1** (1 equiv) in the presence of potassium persulfate, $K_2S_2O_8$ (1.5 equiv)[7] at 70 °C gave adduct **3a** in 70% yield (entry 1). Although furoxan can potentially isomerize to its regioisomer at elevated temperatures, regioisomer **3a'** was not observed. The reaction using a catalytic amount of $K_2S_2O_8$ (0.2 equiv) did not furnish **3a** (entry 2). Reactions at temperatures lower than 70 °C led to a decreased yield (entries 3 and 4), likely as a result of the slow formation of oxygen-centered radicals from persulfate anions. The use of radical generators other than $K_2S_2O_8$ failed to improve the yield under the employed reaction conditions (entries 5–9). Solvent systems other than CH_3CN/H_2O afforded inferior results (entries 10–13). The addition of 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO), a famous radical scavenger, shut down the reaction (entry 14), suggesting the mediation of radical species as a reaction intermediate.

Table 1. Optimization of the reaction conditions.



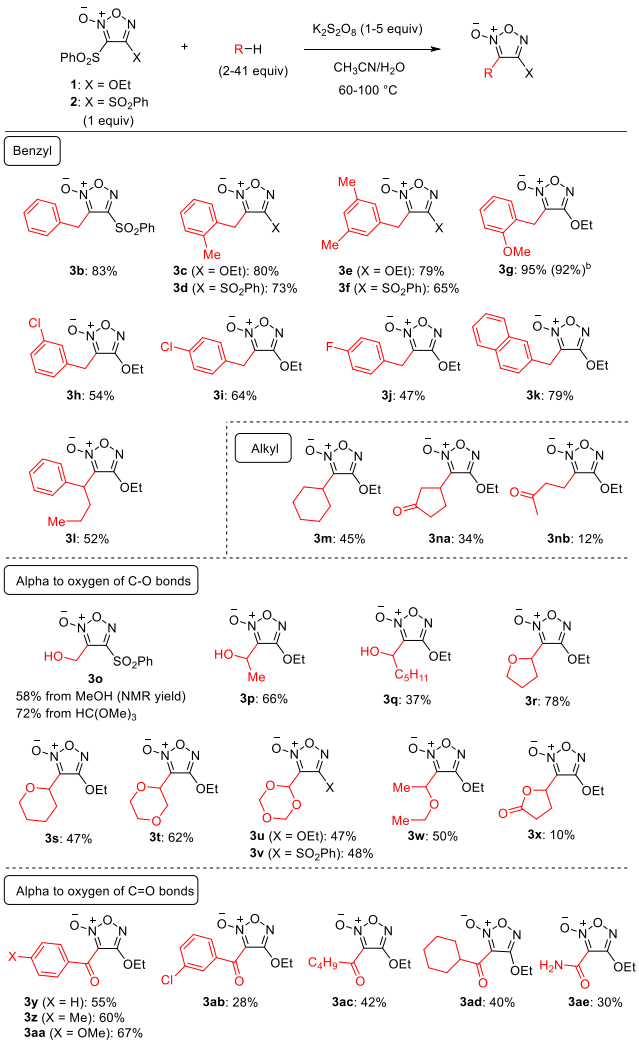
Entry	Solvent	Reagent (equiv)	Temp /°C	Yield of **3a** /%[a]
1	CH_3CN/H_2O (1/1)	$K_2S_2O_8$ (1.5)	70	70 (69)[b]
2	CH_3CN/H_2O (1/1)	$K_2S_2O_8$ (0.2)	70	0
3	CH_3CN/H_2O (1/1)	$K_2S_2O_8$ (1.5)	50	63
4	CH_3CN/H_2O (1/1)	$K_2S_2O_8$ (1.5)	23	0
5	CH_3CN/H_2O (1/1)	TBHP (1.5)	70	0
6	CH_3CN/H_2O (1/1)	DTBP (1.5)	70	0
7	CH_3CN/H_2O (1/1)	BPO (1.5)	70	8
8	CH_3CN/H_2O (1/1)	AIBN (1.5)	70	5
9	CH_3CN/H_2O (1/1)	AIBN (0.2)	70	0
10	CH_3CN	$K_2S_2O_8$ (1.5)	70	0
11	H_2O	$K_2S_2O_8$ (1.5)	70	52
12	DMSO	$K_2S_2O_8$ (1.5)	70	6
13	DMSO/H_2O (1/1)	$K_2S_2O_8$ (1.5)	70	7
14	CH_3CN/H_2O (1/1)	$K_2S_2O_8$ (1.5) TEMPO (3.0)	70	0

[a] Determined by ^{1}H NMR analysis using durene as an internal standard. [b] Isolated yield. TBHP: *t*-butylhydroperoxide, DTBP: di-*tert*-butyl peroxide, BPO: benzoyl peroxide, TEMPO: 2,2,6,6-tetramethylpiperidine 1-oxyl.

With the optimized conditions in hand, we examined the substrate scope (Table 2). To our delight, in addition to **1**, disulfonyl furoxan **2** reacted smoothly with toluene to afford 4-sulfonylfuroxan **3b** in high yield. 4-Alkoxyfuroxan (e.g. **3a**) and 4-sulfonylfuroxan (e.g. **3b**) can be converted to various nitrogen-containing functional groups via subsequent appropriate manipulation and are complementary substrates. As expected based on our previous study,[3] radical addition to **2** was regioselective; only the sulfonyl group at the 3-position was substituted by the alkyl group and the other regioisomer of **3b** was not obtained. Other methylbenzene derivatives were also suitable substrates, providing **3c**–**3k**, although slightly lower yields were obtained for substrates with an electron-deficient benzene ring (**3h**–**3j**). Longer alkyl chain substituents could be introduced via activation at the benzylic position, furnishing furoxan with a branched alkyl substituent (**3l**).

Non-benzylic C–H bonds also participated in the reaction. Thus, the C–H bonds of cyclohexane, cyclopentanone, and betan-2-one were functionalized (**3m, 3na**, and **3nb**, respectively). It is of note that C–H bonds at the β-position of carbonyl groups, not at the α-position, were functionalized (vide infra). Various substrates with a C–O single bond underwent radical formation α to the oxygen atom to deliver the corresponding furoxan products (**3o**–**3x**). Aromatic and aliphatic aldehydes, as well as formamide, underwent hydrogen atom abstraction under the same conditions, providing carbonylated furoxans (**3y**–**3ae**).

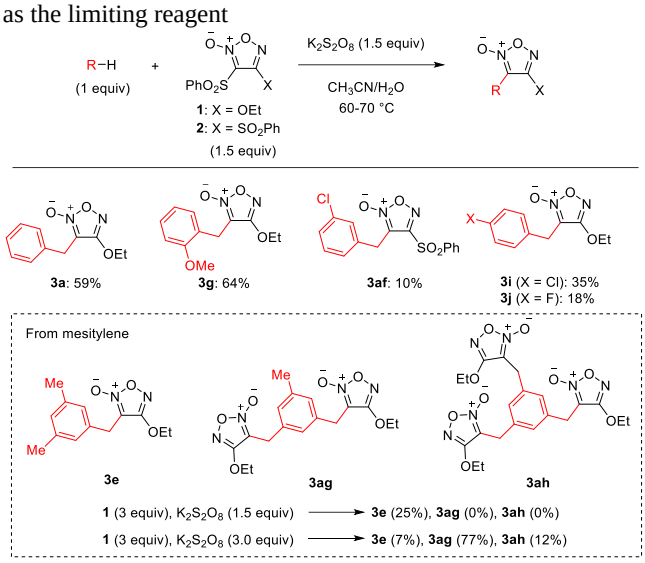
Table 2. Substrate scope for C–H bond furoxanization[a]



[a] Condition: **1** or **2** (1.0 equiv), R–H (2–41 equiv (in most cases 3–5 equiv)), $K_2S_2O_8$ (1–5 equiv), CH_3CN/H_2O, 60–100 °C; see the Experimental Section for the details. [b] On a gram scale.

Although good to high yields were obtained when the radical precursors were used in excess (mainly 3–5 equiv, Table 2), their use as a limiting reagent (1 equiv) is often preferred, especially when the radical precursor is a valuable substrate, as in the case of structurally complex molecules or scarce naturally occurring materials. Thus, we then investigated the furoxanization of C–H bonds using radical precursors as the limiting reagent (Table 3). The use of 1.5 equiv of 3-sulfonylfuroxan and 1.5 equiv of $K_2S_2O_8$ resulted in acceptable product yields. When mesitylene was used as a substrate, mono-, bis-, and tris-furoxanized adducts (**3e**, **3ag**, and **3ah**, respectively) were formed, the ratios of which varied depending on the reaction conditions.

Table 3. Furoxanization of C–H bonds using radical precursors as the limiting reagent



The limitations of the developed methodology are summarized in Figure 2, wherein substrates that provided no or minimal product are listed. The reaction did not progress when the target C–H bonds were electron-deficient (Figure 2a), and the starting material was largely recovered. This is presumably because of the radical polarity mismatch in the transition state of HAT process. It is reasonable to think that, for the same reason, cyclopentanone and butan-2-one selectively reacted at the β-position of carbonyl groups (**3na** and **3nb** in Table 2). In the case of electron-rich heteroaromatics (Figure 2b), the substrates (or the formed products, if any) decomposed under the oxidative conditions used. Secondary alcohols, which are known to serve as good hydrogen atom donors, did not afford the products in this reaction (Figure 2c); this was ascribed to the bulkiness of the formed radical resulting in sluggish radical addition to furoxan. Benzimidazole and *N*-ethylpiperidine were also used as *N*-heterocyclic substrates, but the desired adducts were not obtained (data not shown). The reason for this result is unclear.

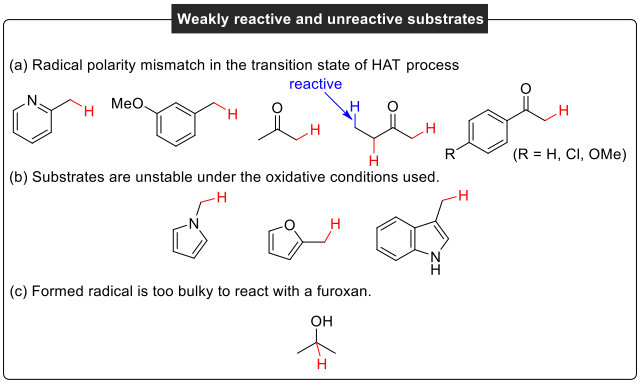


Figure 2. Limitations of the C–H bond furoxanization method.

The proposed reaction mechanism of C–H furoxanization is shown in Figure 3. The reaction is initiated by the heat-induced splitting of a persulfate anion into sulfate radical anions.[8] The sulfate radical anion abstracts a hydrogen atom from the substrate to form a carbon-centered radical, which adds to the 3-position of 3-sulfonylfuroxan affording adduct **A**. Radical adduct **A** is the resonance form of nitroxyl radical **A'**, a well-

known stable radical, as exemplified by TEMPO. Hence, the stability of the formed radical species is the driving force for this radical addition reaction, and additionally, it offers a rationale for the selective addition of the carbon-centered radical to the 3-position of disulfonylfuroxan **2** over the 4-posion. Finally, elimination of the arylsulfonyl radical affords the furoxan product. In our previously reported borylfuroxan synthesis,[9] the arylsulfonyl radical could abstract a hydrogen atom from another substrate molecule, thus, a catalytic amount of the radical initiator was sufficient. A stoichiometric amount of persulfate was required in the present system (entry 2 vs. entry 1, Table 1), implying that the arylsulfonyl radical cannot abstract the hydrogen atom from the C–H function of the substrates.

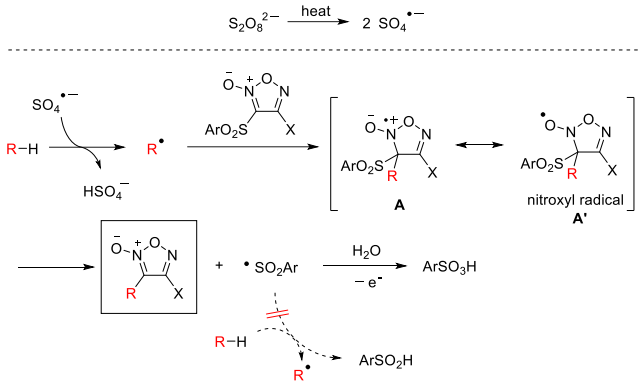


Figure 3. Proposed reaction mechanism

With the successful incorporation of a furoxanyl group into various types of C–H bonds, we turned our attention to transforming the furoxan ring into nitrogen-containing functional groups, implementing the "build-and-scrap" methodology (Figure 4).[3] Using our previously developed reaction conditions, 1,2-diamine-, (*E*,*E*)-dioxime-, amine-, nitro-, oxime-, and isoxazole-containing derivatives were generated from the furoxans; thus, nitrogen-containing functional groups were readily inserted into C–H bonds. It should be noted that some of the functional groups obtained herein cannot be accessed in such few steps using existing C–H activation techniques; therefore, the developed method can be regarded as complementary to the available C–H functionalization strategies.

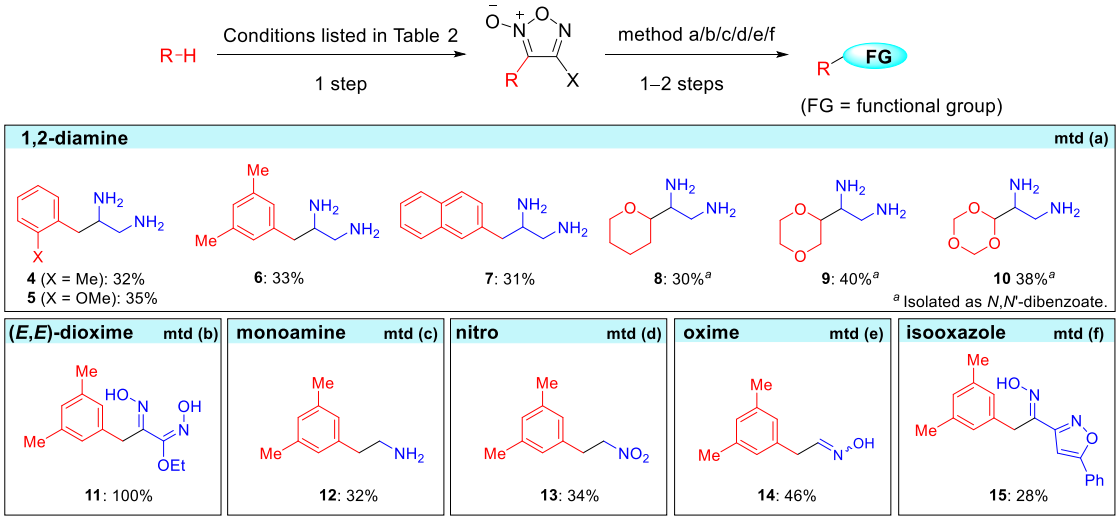


Figure 4. C–H functionalization via furoxan"build-and-scrap" methodology. Method (mtd): (a) Pd/C (2–5 mol%), H_2 (1 atm), MeOH, 23 °C; $LiAlH_4$ (5 equiv), THF, 0 °C; (b) Pd/C (2 mol%), H_2 (1 atm), MeOH, 23 °C; (c) $LiAlH_4$ (5 equiv), THF, 23 °C; (d) Bu_3SnH (2 equiv), benzene, 40 °C; (e) Bu_3SnH (5 equiv), benzene, 40 °C; (f) phenylacetylene (3 equiv), DMF, 130 °C.

In conclusion, we have developed a radical-mediated C–C bond forming method entailing the introduction of a furoxan ring into C–H bonds. This study achieved two notable synthetic advancements. First, an unusual C–C bond forming method was developed for functionalizing the furoxan ring. Second, further manipulation of the resultant furoxan enables the incorporation of various nitrogen-containing functional groups into C–H bond of the original substrate in 2–3 steps. Thus, such a structural diversification protocol, wherein abundant C–H bonds are utilized as a synthetic handle, is anticipated to find wide applicability in pharmaceutical and agrochemical research as it would facilitate target synthesis.

EXPERIMENTAL SECTION

General Unless otherwise noted, all reactions were carried out in well cleaned glasswares 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, m = multiplet and br = broad. 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); a JEOL JMS-T100 GCV 4G (GC-field ionization (FI)) or a JEOL JMS-T100LP (DART method, ambient ionization). Preparative column chromatography was performed using Kanto Chemical silica gel 60 N (spherical, neutral). Thin layer chromatography (TLC) was carried out on Merck 25 TLC silica gel 60 F_{254} aluminium sheets. Preparative TLC was carried out on home-made glass-based TLC plates (20×20 cm) using Wakogel B-5F (FUJIFILM). Starting furoxans, 4-ethoxy-3-(phenylsulfonyl)furoxan (**1**) and 3,4-bis(phenylsulfonyl)furoxan (**2**) were synthesized according to the previous reported methods.[3]

General procedure for C–H bond furoxanization with product 3a as a representative example (Table 1 and 2) 4-Ethoxy-3-(phenylsulfonyl)furoxan (**1**) (54.0 mg, 0.2 mmol, 1.0 equiv), toluene (0.106 mL, 1.0 mmol, 5.0 equiv), potassium peroxodisulfate (162.2 mg, 0.6 mmol, 3.0 equiv) and CH_3CN:H_2O (1:1) (2.0 mL) were added to a flame-dried schlenk flask under argon. The mixture was stirred at 70 °C for 48 h. The reaction was extracted thrice with CH_2Cl_2, the organic layer was dried over Na_2SO_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 **3a** (30.3 mg, 0.14 mmol, 69% yield).

3-Benzyl-4-ethoxyfuroxan (3a) Colorless oil; IR (neat): 2984, 1621, 1549, 1484, 1453, 1420, 1392, 1360, 1296, 1240, 1113, 1022, 886, 841, 735, 695, 631, 567, 521 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.33–7.26 (m, 5H), 4.41 (q, *J* = 7.1 Hz, 2H), 3.80 (s, 2H), 1.44 (t, *J* = 7.1 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ = 163.0, 134.0, 128.9, 128.7, 127.6, 108.7, 66.4, 27.7, 14.3. HRMS *m/z* (ESI) calcd.for $C_{11}H_{12}N_2O_3$ $(M + Na)^+$ 243.0740, found 243.0760.

3-Benzyl-4-(phenylsulfonyl)furoxan (3b) According to the general procedure, **2** (73.3 mg, 0.2 mmol, 1.0 equiv), toluene (0.11 mL, 1.0 mmol, 5.0 equiv), and potassium peroxodisulfate (270 mg, 1.0 mmol, 5.0 equiv) were reacted in CH_3CN:H_2O (1:1) (2.0 mL) at 80 °C for 96 h. The crude material was purified by column chromatography on silica gel (Hexane/EtOAc (3/1)) to afford **3b** (52.4 mg, 0.17 mmol, 83% yield). White solid; Mp. 95.0–95.5 °C. IR (neat): 1605, 1580, 1497, 1461, 1455, 1446, 1426, 1349, 1290, 1199, 1181, 1160, 1088, 1043, 1028, 998, 857, 737, 757, 724, 698, 683, 643, 619, 609, 582, 569 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.89–7.87 (m, 2H), 7.71 (t, *J* = 7.6 Hz, 1H), 7.54 (t, *J* = 8.0 Hz, 2H), 7.29 (m, 5H), 4.14 (s, 2H). $^{13}C\{^{1}H\}$ NMR (100MHz, $CDCl_3$): δ = 158.7, 136.8, 135.5, 133.0, 129.7, 129.0, 129.0, 128.9, 127.9, 112.5, 28.2. HRMS *m/z* (DART); Exact mass calcd for $C_{15}H_{13}N_2O_4S_1$ $[M+H]^+$ 317.0591 Found 317.0596.

3-[(2-Methylphenyl)methyl]-4-ethoxyfuroxan (3c) According to the general procedure, **1** (54.0 mg, 0.2 mmol, 1.0 equiv), *o*-xylene (0.12 mL, 1.0 mmol, 5.0 equiv), and potassium peroxodisulfate (162 mg, 0.6 mmol, 3.0 equiv) were reacted in CH_3CN:H_2O (1:1) (2.0 mL) at 70 °C for 48 h. The crude material was purified by preparative thin-layer chromatography on silica gel (Hexane/EtOAc (10/1)) to afford **3c** (37.6 mg, 0.16 mmol, 80% yield). Yellow solid; Mp 33.6–34.0 ºC. IR (neat): 2985, 1622, 1551, 1471, 1393, 1361, 1309, 1236, 1135, 1116, 1091, 1020, 888, 848, 828, 743, 713, 702, 633, 597, 539, 517 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.21–7.11 (m, 4H), 4.38 (q, *J* = 7.1 Hz, 2H), 3.80 (s, 2H), 2.36 (s, 3H), 1.40 (t, *J* = 7.1 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ = 163.1, 136.4, 132.0, 130.6, 129.6, 127.7, 126.2, 108.4, 66.3, 25.4, 19.6, 14.3. HRMS *m/z* (ESI) calcd.for $C_{12}H_{14}N_2O_3$ $(M + H)^+$ 235.1077, found 235.1066.

3-[(2-Methylphenyl)methyl]-4-(phenylsulfonyl)furoxan (3d) According to the general procedure, **2** (366 mg, 1.0 mmol, 1.0 equiv), *o*-xylene (0.6 mL, 5.0 mmol, 5.0 equiv), and potassium peroxodisulfate (540 mg, 2.0 mmol, 2.0 equiv) were reacted in CH_3CN:H_2O (1:1) (15.0 mL) at 60 °C for 36 h. The crude material was purified by preparative thin-layer chromatography on silica gel (Hexane/EtOAc (5/1)) to afford **3d** (242 mg, 0.73 mmol, 73% yield). White solid; Mp. 87.5–88.4 °C. IR (neat): 2922, 1608, 1582, 1493, 1448, 1417, 1349, 1312, 1291, 1204, 1181, 1160, 1088, 1053, 1028, 998, 849, 750, 740, 722, 685, 698, 653, 612, 581, 590, 547 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.74–7.71 (m, 2H), 7.67–7.63 (m, 1H), 7.48–7.43 (m, 2H), 7.19–7.17 (m, 2H), 7.03–6.98 (m, 1H), 6.77 (d, *J* = 7.6 Hz, 1H), 4.12 (s, 2H), 2.36 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100MHz, $CDCl_3$) δ = 159.0, 136.8, 136.6, 135.4, 131.1, 130.8, 129.6, 128.8, 128.2, 127.8, 126.4, 112.3, 25.7, 19.7. HRMS *m/z* (ESI) calcd.for $C_{16}H_{14}N_2O_4SNa$ $(M + Na)^+$ 353.0567, found 353.0571.

3-[(3,5-Dimethylphenyl)methyl]-4-ethoxyfuroxan (3e) According to the general procedure, **1** (54.0 mg, 0.2 mmol, 1.0 equiv), mesitylene (0.14 mL, 1.0 mmol, 5.0 equiv), and potassium peroxodisulfate (162 mg, 0.6 mmol, 3.0 equiv) were reacted in CH_3CN:H_2O (1:1) (2.0 mL) at 70 °C for 48 h. The crude material was purified by preparative thin-layer chromatography on silica gel (Hexane/EtOAc (3/1)) to afford **3e** (39.0 mg, 0.16 mmol, 79% yield).White solid; Mp 56.2–56.7 ºC. IR (neat): 2916, 2848, 1616, 1548, 1482, 1418, 1394, 1378, 1361, 1299, 1281, 1243, 1106, 1024, 883, 850, 832, 782, 739, 689, 640, 610, 542, 513, 504 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.90 (s, 1H), 6.88 (s, 2H), 4.42 (q, *J* = 7.0 Hz, 2H), 3.72 (s, 2H), 2.28 (s, 6H), 1.45 (t, *J* = 7.1 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ = 163.1, 138.5, 133.8, 129.2, 126.4, 108.8, 66.3, 27.5, 21.2, 14.3. HRMS *m/z* (ESI) calcd.for $C_{13}H_{16}N_2O_3$ $(M + H)^+$ 249.1234, found 249.1221.

3-[(3,5-Dimethylphenyl)methyl]-4-(phenylsulfonyl)furoxan (3f) According to the general procedure, **2** (800 mg, 2.2 mmol, 1.0 equiv), 1,3,5-trimethylbenzene (1.53 mL, 11.0 mmol, 5.0 equiv), and potassium peroxodisulfate (1.8 g, 6.6 mmol, 3.0 equiv) were reacted in CH_3CN:H_2O (1:1) (40.0 mL) at 80 °C for 18 h. The crude material was purified by column chromatography on silica gel (Hexane/EtOAc (10/1)) to afford **3f** (490.6 mg, 1.42 mmol, 65% yield). Yellow solid; Mp 94.8–96.2 ºC. IR (neat): 2917, 1602, 1459, 1446, 1420, 1346, 1156, 1088, 1043, 1031, 830, 733, 682, 598 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.88–7.85 (m, 2H), 7.70 (tt, *J* = 1.2, 7.5 Hz, 1H), 7.55–7.51 (m, 2H), 6.90 (s, 1H), 6.81 (s, 2H), 4.06 (s, 2H), 2.24

(s, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 158.8, 138.7, 137.2, 135.5, 132.9, 129.7, 129.6, 129.1, 126.7, 112.8, 28.2, 21.3. HRMS *m/z* (ESI) calcd.for $C_{17}H_{16}N_2O_4SNa$ $(M + Na)^+$ 367.0723, found 367.0709.

4-Ethoxy-3-[(2-methoxyphenyl)methyl]furoxan (3g) According to the general procedure, **1** (54.0 mg, 0.2 mmol, 1.0 equiv), 2-methoxyltoluene (0.125 mL, 1.0 mmol, 5.0 equiv), and potassium peroxodisulfate (162 mg, 0.6 mmol, 3.0 equiv) were reacted in CH_3CN:H_2O (1:1) (2.0 mL) at 70 °C for 48 h. The crude material was purified by preparative thin-layer chromatography on silica gel (Hexane/EtOAc (3/1)) to afford **3g** (47.6 mg, 0.19 mmol, 95% yield). Gram-scale synthesis was conducted as follows: According to the general procedure, **1** (1.00 g, 3.7 mmol, 1.0 equiv), 2-methoxyltoluene (2.3 mL, 18.5 mmol, 5.0 equiv), and potassium peroxodisulfate (3.0 g, 11.1 mmol, 3.0 equiv) were reacted in CH_3CN:H_2O (1:1) (37.0 mL) at 70 °C for 48 h. The crude material was purified by column chromatography on silica gel (Hexane/EtOAc (3/1)) to afford **3g** (850 mg, 3.4 mmol, 92% yield). Yellow solid; Mp 51.3–51.9 ºC. IR (neat): 1629, 1550, 1455, 1439, 1424, 1389, 1293, 1248, 1133, 1114, 1098, 1020, 753, 709, 630 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.28–7.24 (m, 1H), 7.18 (d, *J* = 7.5 Hz, 1H), 6.92–6.84 (m, 2H), 4.38 (q, *J* = 7.1 Hz, 2H), 3.81 (s, 3H), 3.80 (s, 2H), 1.40 (t, *J* = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 163.4, 157.3, 130.3, 128.9, 121.7, 120.4, 110.3, 108.4, 66.1, 55.3, 22.9, 14.3. HRMS *m/z* (ESI) calcd.for $C_{12}H_{14}N_2O_4$ $(M + H)^+$ 251.1026, found 251.1013.

3-[(3-Chlorophenyl)methyl]-4-ethoxyfuroxan (3h) According to the general procedure, **1** (81.0 mg, 0.3 mmol, 1.0 equiv), 3-chlorotoluene (0.18 mL, 1.5 mmol, 5.0 equiv), and potassium peroxodisulfate (243.3 mg, 0.9 mmol, 3.0 equiv) were reacted in CH_3CN:H_2O (1:1) (3.0 mL) at 70 °C for 48 h. The crude material was purified by preparative thin-layer chromatography on silica gel (Hexane/EtOAc (3/1)) to afford **3h** (41.4 mg, 0.16 mmol, 54% yield). Yellow oil. IR (neat): 2984, 1621, 1550, 1472, 1432, 1392, 1360, 1301, 1237, 1197, 1113, 1092, 1023, 864, 838, 773, 731, 682, 640 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.27–7.24 (m, 3H), 7.17–7.14 (m, 1H), 4.43 (q, *J* = 7.1 Hz, 2H), 3.78 (s, 2H), 1.45 (t, *J* = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 162.9, 135.8, 134.6, 130.2, 128.8, 127.9, 126.9, 108.1, 66.5, 27.4, 14.3. HRMS *m/z* (ESI) calcd.for $C_{11}H_{15}{}^{37}ClN_3O_3$ $(M + NH_4)^+$ 274.0767, found 274.0753.

3-[(4-Chlorophenyl)methyl]-4-ethoxyfuroxan (3i) According to the general procedure, **1** (45.0 mg, 0.17 mmol, 1.0 equiv), 4-chlorotoluene (0.1 mL, 0.83 mmol, 5.0 equiv), and potassium peroxodisulfate (135 mg, 0.5 mmol, 3.0 equiv) were reacted in CH_3CN:H_2O (1:1) (2.0 mL) at 70 °C for 48 h. The crude material was purified by preparative thin-layer chromatography on silica gel (Hexane/EtOAc (10/1)) to afford **3i** (26.0 mg, 0.1 mmol, 64% yield).Yellow solid; Mp 29.7–30.1 ºC. IR (neat): 2989, 1616, 1550, 1542, 1481, 1466, 1408, 1388, 1358, 1288, 1236, 1122, 1094, 1022, 1013, 882, 835, 802, 782, 734, 712, 645, 622, 507 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.28 (d, *J* = 8.5 Hz, 2H), 7.20 (d, *J* = 8.6 Hz, 2H), 4.42 (q, *J* = 7.1 Hz, 2H), 3.77 (s, 2H), 1.45 (t, *J* = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 162.8, 133.6, 132.4, 130.1, 129.1, 108.3, 66.5, 27.1, 14.3. HRMS *m/z* (ESI) calcd.for $C_{11}H_{15}{}^{37}ClN_3O_3$ $(M + NH_4)^+$ 274.0767, found 274.0752.

4-Ethoxy-3-[(4-fluorophenyl)methyl]furoxan (3j) According to the general procedure, **1** (54.0 mg, 0.2 mmol, 1.0 equiv), 4-fluorotoluene (0.11 mL, 1.0 mmol, 5.0 equiv), and potassium peroxodisulfate (162.0 mg, 0.6 mmol, 3.0 equiv) were reacted in CH_3CN:H_2O (1:1) (2.0 mL) at 70 °C for 48 h. The crude material was purified by preparative thin-layer chromatography on silica gel (Hexane/EtOAc (3/1)) to afford **3j** (22.5 mg, 0.09 mmol, 47% yield). Yellow oil. IR (neat): 2918, 1621, 1550, 1508, 1484, 1419, 1389, 1360, 1221, 1113, 1020, 844, 707, 622, 579, 565, 523, 508 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.25–7.23 (m, 2H), 7.00 (t, *J* = 8.7 Hz, 2H), 4.42 (q, *J* = 7.1 Hz, 2H), 3.78 (s, 2H), 1.45 (t, *J* = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 162.2 (d, *J* = 244.7 Hz), 162.9, 130.3 (d, *J* = 8.1 Hz), 129.6 (d, *J* = 3.2 Hz), 115.8 (d, *J* = 21.4 Hz), 108.6, 66.5, 27.0, 14.4. ^{19}F NMR (376 MHz, $CDCl_3$) δ = –113.0. HRMS *m/z* (ESI) calcd. for $C_{11}H_{11}FN_2O_3$ $(M + H)^+$ 239.0826, found 239.0810.

4-Ethoxy-3-[(naphthalen-2-yl)methyl]furoxan (3k) According to the general procedure, **1** (54.0 mg, 0.2 mmol, 1.0 equiv), 2-methylnaphthalene (142.2 mg, 1.0 mmol, 5.0 equiv), and potassium peroxodisulfate (162.0 mg, 0.6 mmol, 3.0 equiv) were reacted in CH_3CN:H_2O (1:1) (2.0 mL) at 70 °C for 48 h. The crude material was purified by preparative thin-layer chromatography on silica gel (Hexane/EtOAc (3/1)) to afford **3k** (42.8 mg, 0.16 mmol, 79% yield). Yellow oil. IR (neat): 1620, 1549, 1482, 1391, 1358, 1292, 1241, 1107, 1022, 785, 696, 566, 560, 554, 537, 531, 521, 516 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.83–7.79 (m, 3H), 7.73 (s, 1H), 7.51–7.45 (m, 2H), 7.39 (dd, *J* = 8.5, 1.7 Hz, 1H), 4.42 (q, *J* = 7.1 Hz, 2H), 3.97 (s, 2H), 1.45 (t, *J* = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 163.1, 133.4, 132.6, 131.4, 128.7, 127.7, 127.4, 126.6, 126.4, 126.1, 108.7, 66.4, 27.9, 14.4. HRMS *m/z* (ESI) calcd.for $C_{15}H_{14}N_2O_3$ $(M + H)^+$ 271.1077, found 271.1059.

4-Ethoxy-3-(1-phenylbutyl)furoxan (3l) According to the general procedure, **1** (54.0 mg, 0.2 mmol, 1.0 equiv), butylbenzene (0.16 mL, 1.0 mmol, 5.0 equiv), and potassium peroxodisulfate (162.0 mg, 0.6 mmol, 3.0 equiv) were reacted in CH_3CN:H_2O (1:1) (2.0 mL) at 70 °C for 48 h. The crude material was purified by preparative thin-layer chromatography on silica gel (Hexane/EtOAc (10/1)) to afford **3l** (27.2 mg, 0.1 mmol, 52% yield). Colorless oil. IR (neat): 2959, 2932, 2872, 1611, 1547, 1457, 1391, 1358, 1301, 1256, 1153, 1092, 1069, 1025, 880, 847, 754, 716, 696, 617, 606, 546, 507 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.36–7.24 (m, 5H), 4.43 (q, *J* = 7.0 Hz, 2H), 3.96–3.92 (m, 1H), 2.25–2.16 (m, 1H), 2.08–1.98 (m, 1H), 1.47 (t, *J* = 7.1 Hz, 3H), 1.35–1.26 (m, 2H), 0.94 (t, *J* = 7.3 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 162.9, 139.0, 128.8, 127.8, 127.6, 111.0, 66.4, 40.2, 32.6, 20.9, 14.4, 13.7. HRMS *m/z* (ESI) calcd.for $C_{14}H_{18}N_2O_3$ $(M + H)^+$ 263.1390, found 263.1377.

3-Cyclohexyl-4-ethoxyfuroxan (3m) According to the general procedure, **1** (40.0 mg, 0.15 mmol, 1.0 equiv), cyclohexane (0.16 mL, 1.5 mmol, 10.0 equiv), and potassium peroxodisulfate (120 mg, 0.45 mmol, 3.0 equiv) were reacted in CH_3CN:H_2O (1:1) (2.0 mL) at 100 °C for 30 min. The crude material was purified by preparative thin-layer chromatography on silica gel (Hexane/EtOAc (6/1)) to afford **3m** (14 mg, 0.07 mmol, 45% yield). White solid; Mp 79.6–80.3 ºC. IR (neat): 2981, 2935, 2851, 1616, 1544, 1480, 1443, 1395, 1362, 1338, 1271, 1250, 1171, 1122, 1027, 984, 883, 840, 810, 721, 674 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 4.41 (q, *J* = 7.1 Hz, 2H), 2.68 (tt, *J* = 11.8, 4.1 Hz, 1H), 1.86–1.64 (m, 7H), 1.47 (t, *J* = 7.1 Hz, 3H), 1.39–1.22 (m, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 163.1, 112.2, 66.2, 33.3, 27.6, 25.8, 25.4, 14.4. HRMS *m/z* (ESI) calcd.for $C_{10}H_{17}N_2O_3$ $(M + H)^+$ 213.1234, found 213.1229.

4-Ethoxy-3-(3-oxocyclopentyl)furoxan (3na) According to the general procedure, **1** (40.0 mg, 0.15 mmol, 1.0 equiv), cyclopentanone (66 μL, 0.75 mmol, 5.0 equiv), and potassium peroxodisulfate (100 mg, 0.38 mmol, 2.5 equiv) were reacted in

$CH_3CN:H_2O$ (1:1) (2.0 mL) at 80 °C for 17 h. The crude material was purified by preparative thin-layer chromatography on silica gel (Hexane/EtOAc (3/1)) to afford **3n** (10.7 mg, 0.05 mmol, 34% yield). White solid; Mp 29.3–30.5 ºC. IR (neat): 1738, 1622, 1552, 1487, 1471, 1394, 1359, 1269, 1247, 1194, 1162, 1116, 1021, 899, 836, 686 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 4.44 (q, *J* = 7.1 Hz, 2H), 3.49–3.40 (m, 1H), 2.72–2.64 (m, 1H), 2.52–2.42 (m, 2H), 2.36–2.21 (m, 3H), 1.46 (t, *J* = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 215.2, 162.7, 109.7, 66.9, 39.2, 37.9, 30.6, 25.4, 14.5. HRMS *m/z* (ESI) calcd.for $C_9H_{13}N_2O_4$ $(M + H)^+$ 213.0870, found 213.0860.

4-Ethoxy-3-(3-oxobutyl)furoxan (3nb) According to the general procedure, **1** (62 mg, 0.23 mmol, 1.0 equiv), butan-2-one (0.5 mL, 5.59 mmol, 24.3 equiv), and potassium peroxodisulfate (186 mg, 0.69 mmol, 3.0 equiv) were reacted in $CH_3CN:H_2O$ (1:1) (3.0 mL) at 80 °C for 17 h. The crude material was purified by preparative thin-layer chromatographyon silica gel (Hexane/EtOAc (3/1)) to afford **3** (5.7 mg, 0.03 mmol, 12% yield). Yellow oil. IR (neat): 1716, 1622, 1549, 1483, 1472, 1392, 1358, 1304, 1218, 1167, 1133, 1039, 1019, 836 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 4.43 (q, *J* = 7.1 Hz, 2H), 2.88-2.85 (m, 2H), 2.76-2.72 (m, 2H), 2.18 (s, 3H), 1.47 (t, *J* = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 205.6, 163.0, 108.5, 66.4, 37.2, 29.6, 15.9, 14.3. HRMS *m/z* (ESI) calcd.for $C_8H_{12}N_2O_4Na$ $(M + Na)^+$ 223.0689, found 223.0686.

3-(Hydroxymethyl)-4-(phenylsulfonyl)furoxan (3o) According to the general procedure, **2** (73.3 mg, 0.2 mmol, 1.0 equiv), methanol (121 μL, 3.0 mmol, 15.0 equiv), and potassium peroxodisulfate (54.1 mg, 0.2 mmol, 1.0 equiv) were reacted in $CH_3CN:H_2O$ (1:1) (3.0 mL) at 60 °C for 18 h. The yield of **3o** was determined to be 58% by ^1H NMR spectroscopic analysis of the crude material with durene (15.8 mg) as an internal standard. **3o** was also synthesized using trimethyl orthofomate as a reactant instead of methanol. According to the general procedure, **2** (73.3 mg, 0.2 mmol, 1.0 equiv), trimethyl orthoformate (109 μL, 1.0 mmol, 5.0 equiv), and potassium peroxodisulfate (54.1 mg, 0.2 mmol, 1.0 equiv) were reacted in $CH_3CN:H_2O$ (1:1) (3.0 mL) at 60 °C for 6 h. The crude material was purified by column chromatography on silica gel (Hexane/EtOAc (3/1)) to afford **3o** (36.9 mg, 0.144 mmol, 72% yield). Colorless oil; IR (neat): 3342, 2923, 2848, 1716, 1602, 1581, 1447, 1358, 1345, 1310, 1294, 1181, 1162, 1092, 1053, 1041, 1020, 998, 946, 844, 759, 737, 723, 706, 683, 652, 631, 602, 582, 547, 528 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ= 8.11 (d, *J* = 7.9 Hz, 2H), 7.81 (t, *J* = 7.5 Hz, 1H), 7.68 (t, *J* = 7.8 Hz, 2H), 4.83 (d, *J* = 6.0 Hz, 2H), 2.94 (s, 1H). $^{13}C\{^1H\}$ NMR (100MHz, $CDCl_3$) δ= 158.6, 136.5, 136.0, 129.9, 129.1, 111.8, 53.2. HRMS *m/z* (DART) calcd.for $C_9H_9N_2O_5S_1(M+H)^+$ 257.0227, found 257.0243.

4-Ethoxy-3-(1-hydroxyethyl)furoxan (3p) According to the general procedure, **1** (40.0 mg, 0.15 mmol, 1.0 equiv), ethanol (0.2 mL, 3.4 mmol, 23 equiv), and potassium peroxodisulfate (100 mg, 0.38 mmol, 2.5 equiv) were reacted in $CH_3CN:H_2O$ (1:1) (2.0 mL) at 80 °C for 1 h. The crude material was purified by preparative thin-layer chromatography on silica gel (Hexane/EtOAc (3/1)) to afford **3p** (17.0 mg, 0.10 mmol, 66% yield). Colorless oil; IR (neat): 3439, 2987, 1611, 1549, 1471, 1446, 1358, 1278, 1182, 1075, 1019, 990, 902, 881, 838, 727, 609 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 4.92–4.86 (m, 1H), 4.44 (q, *J* = 7.1 Hz, 2H), 2.80 (d, *J* = 6.9 Hz, 1H), 1.59 (d, *J* = 6.8 Hz, 3H), 1.48 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ =162.1, 111.2, 66.9, 60.9, 19.6, 14.5. HRMS *m/z* (ESI) calcd.for $C_6H_{10}N_2O_4Na$ $(M + Na)^+$ 197.0533, found 197.0522.

4-Ethoxy-3-(1-hydroxyhexyl)furoxan (3q) According to the general procedure, **1** (40.0 mg, 0.15 mmol, 1.0 equiv), 1-hexanol (74 μL, 0.6 mmol, 4 equiv), and potassium peroxodisulfate (100 mg, 0.38 mmol, 2.5 equiv) were reacted in $CH_3CN:H_2O$ (1:1) (2.0 mL) at 80 °C for 17 h. The crude material was purified by preparative thin-layer chromatography on silica gel (CH_2Cl_2) to afford **3q** (12.7 mg, 0.06 mmol, 37% yield). Colorless oil; IR (neat): 3449, 2956, 2930, 2860, 1613, 1549, 1469, 1391, 1358, 1159, 1022, 837, 726, 570 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 4.70 (q, *J* = 1.9 Hz, 1H), 4.45 (q, *J* = 7.0 Hz, 2H), 2.65 (d, *J* = 8.2 Hz, 1H), 1.95–1.82(m, 2H), 1.47 (t, *J* = 7.0 Hz, 3H), 1.32–1.31(m, 6H), 0.89 (t, *J* = 6.9 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 162.2, 110.8, 66.9, 65.0, 33.7, 31.4, 24.9, 22.6, 14.5, 14.0. HRMS *m/z* (ESI) calcd.for $C_{10}H_{19}N_2O_4$ $(M + H)^+$ 231.1339, found 231.1326.

4-Ethoxy-3-(oxolan-2-yl)furoxan (3r) According to the general procedure, **1** (40.0 mg, 0.15 mmol, 1.0 equiv), tetrahydrofuran (0.5 mL, 6.2 mmol, 41 equiv), and potassium peroxodisulfate (100 mg, 0.38 mmol, 2.5 equiv) were reacted in $CH_3CN:H_2O$ (1:1) (2.0 mL) at 80 °C for 17 h. The crude material was purified by preparative thin-layer chromatography on silica gel (Hexane/EtOAc (3/1)) to afford **3r** (23.0 mg, 0.11 mmol, 78% yield). Colorless oil; IR (neat): 2983, 1613, 1549, 1471, 1392, 1348, 1195, 1159, 1054, 1018, 921, 832, 618, 567 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 4.95 (t, *J* = 6.9 Hz, 1H), 4.42 (q, *J* = 7.1 Hz, 2H), 4.01–3.87 (m, 2H), 2.30–1.95 (m, 4H), 1.46 (t, *J* = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 162.5, 109.7, 70.1, 69.8, 66.6, 28.6, 26.6, 14.5. HRMS *m/z* (ESI) calcd.for $C_8H_{13}N_2O_4$ $(M + H)^+$ 201.0870, found 201.0862.

4-Ethoxy-3-(oxan-2-yl)furoxan (3s) According to the general procedure, **1** (40.0 mg, 0.15 mmol, 1.0 equiv), tetrahydropyran (143 μL, 1.5 mmol, 10 equiv), and potassium peroxodisulfate (100 mg, 0.38 mmol, 2.5 equiv) were reacted in $CH_3CN:H_2O$ (1:1) (2.0 mL) at 80 °C for 17 h. The crude material was purified by preparative thin-layer chromatography on silica gel (Hexane/EtOAc (10/1)) to afford **3s** (15 mg, 0.07 mmol, 47% yield). Colorless oil; IR (neat): 2987, 2943, 2857, 1617, 1547, 1497, 1472,1375, 1353, 1303, 1206, 1180, 1158, 1102, 1081, 1041, 1019, 987, 912, 850, 814, 667, 560 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 4.47–4.39 (m, 3H), 4.08–4.04 (m, 1H), 3.55 (td, *J* = 11.6, 2.2 Hz, 1H), 2.16–2.06 (m, 1H), 1.98–1.94 (m, 1H), 1.73–1.54 (m, 4H), 1.48 (t, *J* = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 162.7, 109.1, 70.1, 69.4, 66.7, 27.1, 25.3, 23.2, 14.4. HRMS *m/z* (ESI) calcd.for $C_9H_{15}N_2O_4$ $(M + H)^+$ 215.1026, found 215.1018.

3-(1,4-Dioxan-2-yl)-3-ethoxyfuroxan (3t) According to the general procedure, **1** (40.0 mg, 0.15 mmol, 1.0 equiv), 1,4-dioxane (125 μL, 1.5 mmol, 10.0 equiv), and potassium peroxodisulfate (100 mg, 0.38 mmol, 2.5 equiv) were reacted in $CH_3CN:H_2O$ (1:1) (2.0 mL) at 80 °C for 17 h. The crude material was purified by preparative thin-layer chromatography on silica gel (Hexane/EtOAc (3/1)) to afford **3t** (19.8 mg, 0.09 mmol, 62% yield). White solid; Mp 66.3–68.5 ºC. IR (neat): 2870, 1751, 1609, 1547, 1487, 1471, 1388, 1261, 1169, 1116, 1085, 1016, 911, 856, 834, 728, 702, 582 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 4.70 (dd, *J* = 10.4, 2.8 Hz, 1H), 4.44 (q, *J* = 7.0 Hz 2H), 4.02 (t, *J* = 10.4 Hz, 1H), 3.91–3.69 (m, 5H), 1.48 (t, *J* = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 162.5, 106.4, 68.1, 67.3, 66.9, 66.3, 66.1, 14.4. HRMS *m/z* (ESI) calcd.for $C_8H_{13}N_2O_5$ $(M + H)^+$ 217.0819, found 217.0807.

4-Ethoxy-3-(1,3,5-trioxane-2-yl)furoxan (3u) According to the general procedure, **1** (40.0 mg, 0.15 mmol, 1.0 equiv), 1,3,5-

trioxane (66.6 mg, 0.75 mmol, 5.0 equiv), and potassium peroxodisulfate (120 mg, 0.45 mmol, 3.0 equiv) were reacted in CH_3CN:H_2O (1:1) (2.0 mL) at 80 °C for 17 h. The crude material was purified by preparative thin-layer chromatography on silica gel (Hexane/EtOAc (3/1)) to afford **3u** (15 mg, 0.07 mmol, 47% yield). White solid; Mp 64.9–65.7 ºC. IR (neat): 2996, 2891, 1624, 1567, 1502, 1391, 1183, 1088, 1071, 1025, 958, 940, 887, 841, 732, 690, 566 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 6.02 (s, 1H), 5.33 (d, *J* = 6.8 Hz, 2H), 5.22 (d, *J* = 6.9 Hz, 2H), 4.49 (q, *J* = 7.0 Hz, 2H), 1.51 (t, *J* = 7.0 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 161.7, 106.0, 93.7, 93.7, 67.0, 14.2. HRMS *m/z* (ESI) calcd.for $C_7H_{10}N_2O_6Na$ $(M + Na)^+$ 241.0431, found 241.0429.

4-(Phenylsulfonyl)-3-(1,3,5-trioxane-2-yl)furoxan (3v) According to the general procedure, **2** (73.3 mg, 0.2 mmol, 1.0 equiv), 1,3,5-trioxane (90.1 mg, 1.0 mmol, 5.0 equiv), and potassium peroxodisulfate (54 mg, 1.0 mmol, 5.0 equiv) were reacted in CH_3CN:H_2O (1:1) (3.0 mL) at 60 °C for 24 h. The crude material was purified by column chromatography on silica gel (Hexane/EtOAc (3/1)) to afford **3v** (30.2 mg, 0.096 mmol, 48% yield). Colorless oil: IR (neat): 2923, 2853, 1731, 1620, 1448, 1353, 1261, 1194, 1163, 1112, 1084, 1066, 1051, 1023, 966, 950, 890, 800, 757, 725, 683, 639, 597, 550 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.11–8.09 (m, 2H), 7.81–7.76 (m, 1H), 7.65 (t, *J* = 7.9 Hz, 2H), 6.31 (s, 1H), 5.34 (d, *J* = 6.9 Hz, 2H), 5.25 (d, *J* = 7.0 Hz, 2H). $^{13}C\{^1H\}$ NMR (100MHz, $CDCl_3$): δ = 157.4, 136.8, 135.7, 129.6, 129.1, 108.5, 93.5, 92.9. HRMS *m/z* (DART) calcd for $C_{11}H_{14}N_3O_7S_1$ $(M+NH_4)^+$ 332.0547, found 332.0572.

4-Ethoxy-3-(1-ethoxyethyl)furoxan (3w) According to the general procedure, **1** (40.0 mg, 0.15 mmol, 1.0 equiv), ethyl ether (0.5 mL, 4.8 mmol, 32 equiv), and potassium peroxodisulfate (100 mg, 0.38 mmol, 2.5 equiv) were reacted in CH_3CN:H_2O (1:1) (2.0 mL) at 80 °C for 17 h. The crude material was purified by preparative thin-layer chromatography on silica gel (Hexane/EtOAc (3/1)) to afford **3w** (15 mg, 0.07 mmol, 50%). Colorless oil. IR (neat): 2981, 2939, 2875, 1610, 1548, 1472, 1444, 1392, 1358, 1187, 1101, 1021, 987, 941, 852, 834, 725 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 4.56 (q, *J* = 6.8 Hz, 1H), 4.44 (q, *J* = 7.0 Hz, 2H), 3.53–3.40 (m, 2H), 1.54 (d, *J* = 6.8 Hz, 3H), 1.47 (t, *J* = 7.0 Hz, 3H), 1.19 (t, *J* = 7.0 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 162.8, 109.5, 67.9, 66.6, 65.5, 17.7, 15.2, 14.5. HRMS *m/z* (ESI) calcd.for $C_8H_{15}N_2O_4$ $(M + H)^+$ 203.1026, found 203.1017.

4-Ethoxy-3-(5-oxooxolan-2-yl)furoxan (3x) According to the general procedure, **1** (80.0 mg, 0.3 mmol, 1.0 equiv), γ-Butyrolactone (45.5 μL, 0.6 mmol, 2.0 equiv), and potassium peroxodisulfate (160 mg, 0.6 mmol, 2.0 equiv) were reacted in CH_3CN:H_2O (1:1) (4.0 mL) at 80 °C for 17 h. The crude material was purified by preparative thin-layer chromatography on silica gel (Hexane/EtOAc (3/1)) to afford **3x** (6.1 mg, 0.03 mmol, 10% yield). Colorless oil. IR (neat): 2920, 2850, 1783, 1616, 1553, 1493, 1471, 1350, 1150, 1018, 993, 835, 810, 724, 667 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 5.53–5.49 (m, 1H), 4.50–4.43 (m, 2H), 2.87–2.76 (m, 1H), 2.69–2.54 (m, 3H), 1.48 (t, *J* = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 175.5, 161.9, 107.5, 69.5, 67.3, 27.7, 24.1, 14.4. HRMS *m/z* (ESI) calcd.for $C_8H_{11}N_2O_5$ $(M + H)^+$ 215.0662, found 215.0652.

3-Benzoyl-4-ethoxyfuroxan (3y) According to the general procedure, **1** (40.0 mg, 0.15 mmol, 1.0 equiv), benzaldehyde (45 μL, 0.45 mmol, 3.0 equiv), and potassium peroxodisulfate (60 mg, 0.23 mmol, 1.5 equiv) were reacted in CH_3CN:H_2O (1:1) (2.0 mL) at 80 °C for 17 h. The crude material was purified by preparative thin-layer chromatography on silica gel (Hexane/EtOAc (10/1)) to afford **3y** (19 mg, 0.08 mmol, 55% yield). Colorless oil. IR (neat): 2983, 1656, 1598, 1545, 1474, 1387, 1329, 1228, 1155, 1109, 1023, 1003, 904, 864, 836, 795, 724, 690, 655, 598 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.85–7.82 (m, 2H), 7.67 (tt, *J* = 1.2, 7.4 Hz, 1H), 7.54–7.50 (m, 2H), 4.48 (q, *J* = 7.1 Hz, 2H), 1.43 (t, *J* = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 180.8, 161.3, 135.0, 134.5, 129.7, 128.9, 107.3, 67.3, 14.3. HRMS *m/z* (ESI) calcd.for $C_{11}H_{11}N_2O_4$ $(M + H)^+$ 235.0713, found 235.0704.

4-Ethoxy-3-(4-methylbenzoyl)furoxan (3z) According to the general procedure, **1** (40.0 mg, 0.15 mmol, 1.0 equiv), 4-methylbenzaldehyde (53 μL, 0.45 mmol, 3.0 equiv), and potassium peroxodisulfate (60 mg, 0.23 mmol, 1.5 equiv) were reacted in CH_3CN:H_2O (1:1) (2.0 mL) at 80 °C for 17 h. The crude material was purified by preparative thin-layer chromatography on silica gel (Hexane/EtOAc (10/1)) to afford **3z** (22 mg, 0.09 mmol, 60% yield). Yellow solid; Mp 45.2–46.7 ºC.IR (neat): 2995, 1671, 1598, 1550, 1463, 1395, 1358, 1327, 1231, 1164, 1020, 908, 872, 828, 792, 761, 735, 707, 613, 587 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.76–7.73 (m, 2H), 7.33–7.30 (m, 2H), 4.49 (q, *J* = 7.1 Hz, 2H), 2.46 (s, 3H), 1.44 (t, *J* = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 180.2, 161.4, 146.5, 132.0, 130.0, 129.7, 107.3, 67.2, 22.1, 14.3. HRMS *m/z* (ESI) calcd.for $C_{12}H_{13}N_2O_4$ $(M + H)^+$ 249.0870, found 249.0861.

4-Ethoxy-3-(4-methoxybenzoyl)furoxan(3aa) According to the general procedure, **1** (40.0 mg, 0.15 mmol, 1.0 equiv), 4-methoxybenzaldehyde (45 μL, 0.38 mmol, 2.5 equiv), and potassium peroxodisulfate (100 mg, 0.38 mmol, 2.5 equiv) were reacted in CH_3CN:H_2O (1:1) (2.0 mL) at 80 °C for 18 h. The crude material was purified by preparative thin-layer chromatography on silica gel (Benzene/CH_2Cl_2 (3/1)) to afford **3aa** (26 mg, 0.1 mmol, 67% yield). Yellow solid; Mp 95.2–96.5 ºC. IR (neat): 1654, 1583, 1574, 1548, 1526, 1459, 1386, 1362, 1273, 1224, 1167, 1123, 1010, 928, 844, 769, 704, 614 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ =7.85–7.81 (m, 2H), 7.00–6.96 (m, 2H), 4.49 (q, *J* = 7.1 Hz, 2H), 3.90 (s, 3H), 1.44 (t, *J* = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 178.8, 165.4, 161.4, 132.5, 127.4, 114.3, 107.4, 67.2, 55.8, 14.3. HRMS *m/z* (ESI) calcd.for $C_{12}H_{12}N_2O_5Na$ $(M + Na)^+$ 287.0638, found 287.0634.

3-(3-Chlorobenzoyl)-4-ethoxyfuroxan(3ab) According to the general procedure, **1** (40.0 mg, 0.15 mmol, 1.0 equiv), 3-chlorobenzaldehyde (34 μL, 0.3 mmol, 2.0 equiv), and potassium peroxodisulfate (68 mg, 0.23 mmol, 1.7 equiv) were reacted in CH_3CN:H_2O (1:1) (2.0 mL) at 80 °C for 18 h. The crude material was purified by preparative thin-layer chromatography on silica gel (Hexane/EtOAc (3/1)) to afford **3ab** (11 mg, 0.04 mmol, 28% yield). Yellow oil.IR (neat): 1677, 1594, 1573, 1527, 1486, 1463, 1443, 1419, 1394, 1357, 1326, 1221, 1159, 1025, 919, 874, 841, 804, 756, 729, 710, 689, 653 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.79 (t, *J* = 1.8 Hz, 1H), 7.69 (dt, *J* = 1.0, 7.8 Hz, 1H), 7.65–7.62 (m, 1H), 7.47 (t, *J* = 7.9 Hz, 1H), 4.50 (q, *J* = 7.1 Hz, 2H), 1.44 (t, *J* = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 179.6, 161.0, 136.1, 135.2, 134.8, 130.2, 129.5, 127.8, 107.1, 67.4, 14.3. HRMS *m/z* (ESI) calcd.for $C_{11}H_9N_2O_4ClNa$ $(M + Na)^+$ 291.0143, found 291.0139.

4-Ethoxy-3-pentanoylfuroxan (3ac) According to the general procedure, **1** (40.0 mg, 0.15 mmol, 1.0 equiv), pentanal (32 μL, 0.3 mmol, 2.0 equiv), and potassium peroxodisulfate (68 mg, 0.23 mmol, 1.7 equiv) were reacted in CH_3CN:H_2O (1:1) (2.0 mL) at 80 °C for 17 h. The crude material was purified by preparative thin-layer chromatography on silica gel (Hexane/EtOAc (7/1)) to afford **3ac** (13.4 mg, 0.06 mmol, 42%

yield). Colorless oil. IR (neat): 2960, 2935, 2874, 1705, 1595, 1531, 1464, 1389, 1356, 1331, 1174, 1017, 945, 878, 840, 675 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 4.51 (q, *J* = 7.1 Hz, 2H), 2.87 (t, *J* = 7.2 Hz, 2H), 1.81–1.68 (m, 2H), 1.52 (t, *J* = 7.1 Hz, 3H), 1.43–1.33 (m, 2H), 0.93 (t, *J* = 7.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 187.8, 161.3, 107.6, 67.3, 41.5, 25.2, 22.2, 14.4, 13.9. HRMS *m/z* (ESI) calcd.for $C_9H_{14}N_2O_4Na$ $(M + Na)^+$ 237.0846, found 237.0835

3-(Cyclohexanecarbonyl)-4--ethoxyfuroxan (3ad) According to the general procedure, **1** (40.0 mg, 0.15 mmol, 1.0 equiv), cyclohexanecarboxaldehyde (54 μL, 0.45 mmol, 3.0 equiv), and potassium peroxodisulfate (100 mg, 0.38 mmol, 2.5 equiv) were reacted in $CH_3CN:H_2O$ (1:1) (2.0 mL) at 80 °C for 1 h. The crude material was purified by preparative thin-layer chromatography on silica gel (Hexane/EtOAc (6/1)) to afford **3ad** (14.1 mg, 0.06 mmol, 40% yield). Colorless oil. IR (neat): 2935, 2857, 1694, 1591, 1534, 1472, 1460, 1445, 1384, 1352, 1172, 1019, 963, 885, 830, 798, 678 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 4.52 (q, *J* = 7.0 Hz, 2H), 3.10–3.04 (m, 1H), 1.89–1.81 (m, 4H), 1.74–1.69 (m, 1H), 1.53 (t, *J* = 7.1 Hz, 3H), 1.45–1.18 (m, 5H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 189.6, 160.2, 105.9, 66.1, 47.1, 26.6, 24.6, 24.4, 13.3. HRMS *m/z* (ESI) calcd.for $C_{11}H_{16}N_2O_4Na$ $(M + Na)^+$ 263.1002, found 263.1008.

3-(Carbamoyl)-4-ethoxyfuroxan (3ae) According to the general procedure, **1** (60.0 mg, 0.22 mmol, 1.0 equiv), formamide (27 μL, 0.66 mmol, 3.0 equiv), and potassium peroxodisulfate (150 mg, 0.55 mmol, 2.5 equiv) were reacted in $CH_3CN:H_2O$ (1:1) (2.4 mL) at 80 °C for 17 h. The crude material was purified by preparative thin-layer chromatography on silica gel (Hexane/EtOAc (1/1)) to afford **3ae** (11.4 mg, 0.07 mmol, 30% yield). White solid; Mp 86.3–87.9 ºC. IR (neat): 3435, 1705, 1685, 1558, 1542, 1485, 1391, 1352, 1169, 1112, 1017, 874, 848, 769, 644 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.38 (br,1H), 6.09 (br, 1H), 4.55 (q, *J* = 7.1 Hz, 2H), 1.54 (t, *J* = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 161.9, 155.6, 104.6, 67.8, 14.3. HRMS *m/z* (ESI) calcd.for $C_5H_8N_3O_4$ $(M + H)^+$ 174.0509, found 174.0503.

Experimental procedures for furoxanization of C–H bonds using radical precursors as a limiting reagent (Table 3)

3-Benzyl-4-ethoxyfuroxan (3a) 4-Ethoxy-3-(phenylsulfonyl)furoxan (**1**) (81.0 mg, 0.30 mmol, 1.5 equiv), toluene (22 μL, 0.20 mmol, 1.0 equiv), potassium peroxodisulfate (81.0 mg, 0.30 mmol, 1.5 equiv) and $CH_3CN:H_2O$ (1:1) (2.0 mL) were added to a flame-dried schlenk flask under argon. The mixture was stirred at 70 °C for 48 h. The reaction was extracted thrice with CH_2Cl_2, the organic layer was dried over Na_2SO_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 **3a** (26.0 mg, 0.12 mmol, 59% yield). The spectral data of this compound were already described above.

4-Ethoxy-3-[(2-methoxyphenyl)methyl]furoxan (3g) 4-Ethoxy-3-(phenylsulfonyl)furoxan (**1**) (83.0 mg, 0.31 mmol, 1.5 equiv), 2-methoxytoluene (24.8 μL, 0.20 mmol, 1.0 equiv), potassium peroxodisulfate (81.0 mg, 0.30 mmol, 1.5 equiv) and $CH_3CN:H_2O$ (1:1) (2.0 mL) were added to a flame-dried schlenk flask under argon. The mixture was stirred at 70 °C for 48 h. The reaction was extracted thrice with CH_2Cl_2, the organic layer was dried over Na_2SO_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 **3g** (32.2 mg, 0.13 mmol, 64% yield). The spectral data of this compound were already described above.

3-[(3-Chlorophenyl)methyl]-4-(phenylsulfonyl)furoxan (3af) 3,4-Bis(phenylsulfonyl)furoxan (**2**) (110.0 mg, 0.30 mmol, 1.5 equiv), 3-chlorotoluene (23.6 μL, 0.20 mmol, 1.0 equiv), potassium peroxodisulfate (81.2 mg, 0.30 mmol, 1.5 equiv) and $CH_3CN:H_2O$ (1:1) (2.0 mL) were added to a flame-dried schlenk flask under argon. The mixture was stirred at 70 °C for 48 h. The reaction was extracted thrice with CH_2Cl_2, the organic layer was dried over Na_2SO_4, filtrated, and concentrated in vacuo. The crude residue was purified by preparative thin-layer chromatography on silica gel (Hexane/EtOAc (2/1)) to afford **3af** (6.7 mg, 0.02 mmol, 10% yield). Yellow oil. IR (neat): 2923, 2851, 1603, 1582, 1456, 1447, 1351, 1159, 1080, 1023, 722, 681, 598, 586 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.95–7.92 (m, 2H), 7.76–7.72 (m, 1H), 7.60–7.56 (m, 2H), 7.30–7.17 (m, 4H), 4.11 (s, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 158.6, 136.8, 135.7, 134.8, 134.8, 130.2, 129.7, 129.0, 129.0, 128.2, 127.2, 111.9, 27.9. HRMS *m/z* (ESI) calcd.for $C_{15}H_{11}ClN_2O_4SNa$ $(M + Na)^+$ 373.0020, found 373.0011.

3-[(4-Chlorophenyl)methyl]-4-ethoxyfuroxan (3i) 4-Ethoxy-3-(phenylsulfonyl)furoxan (**1**) (81.0 mg, 0.30 mmol, 1.5 equiv), 4-chlorotoluene (23.6 μL, 0.20 mmol, 1.0 equiv), potassium peroxodisulfate (81.0 mg, 0.30 mmol, 1.5 equiv) and $CH_3CN:H_2O$ (1:1) (2.0 mL) were added to a flame-dried schlenk flask under argon. The mixture was stirred at 70 °C for 48 h. The reaction was extracted thrice with CH_2Cl_2, the organic layer was dried over Na_2SO_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 **3i** (17.7 mg, 0.07 mmol, 35% yield). The spectral data of this compound were already described above.

4-Ethoxy-3-[(4-fluorophenyl)methyl]furoxan (3j) 4-Ethoxy-3-(phenylsulfonyl)furoxan (**1**) (81.0 mg, 0.30 mmol, 1.5 equiv), 4-fluorotoluene (22.0 μL, 0.20 mmol, 1.0 equiv), potassium peroxodisulfate (81.0 mg, 0.30 mmol, 1.5 equiv) and $CH_3CN:H_2O$ (1:1) (2.0 mL) were added to a flame-dried schlenk flask under argon. The mixture was stirred at 70 °C for 48 h. The reaction was extracted thrice with CH_2Cl_2, the organic layer was dried over Na_2SO_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 **3j** (8.7 mg, 0.04 mmol, 18% yield). The spectral data of this compound were already described above.

3-[(3,5-Dimethylphenyl)methyl]-4-ethoxyfuroxan (3e) 4-Ethoxy-3-(phenylsulfonyl)furoxan (**1**) (162.0 mg, 0.60 mmol, 3.0 equiv), mesitylene (28.0 μL, 0.20 mmol, 1.0 equiv), potassium peroxodisulfate (81.0 mg, 0.30 mmol, 1.5 equiv) and $CH_3CN:H_2O$ (1:1) (2.0 mL) were added to a flame-dried schlenk flask under argon. The mixture was stirred at 70 °C for 48 h. The reaction was extracted thrice with CH_2Cl_2, the organic layer was dried over Na_2SO_4, filtrated, and concentrated in vacuo. The crude residue was purified by preparative thin-layer chromatography on silica gel (Hexane/EtOAc (10/1)) to afford **3e** (12.6 mg, 0.05 mmol, 25% yield). The spectral data of this compound were already described above.

1,3-Bis[(4-ethoxyfuroxan-3-yl)methyl]-5-methylbenzene (3ag) and 1,3,5-Tris[(4-ethoxyfuroxan-3-yl)methyl]benzene (3ah) 4-Ethoxy-3-(phenylsulfonyl)furoxan (**1**) (54.0 mg, 0.20 mmol, 3.0 equiv), mesitylene (9.2 μL, 0.07 mmol, 1.0 equiv), potassium peroxodisulfate (54.0 mg, 0.20 mmol, 3.0 equiv) and $CH_3CN:H_2O$ (1:1) (3.0 mL) were added to a flame-dried schlenk flask under argon. The mixture was stirred at 60 °C for 96 h. The reaction was extracted thrice with CH_2Cl_2, the organic layer was dried over Na_2SO_4, filtrated, and concentrated in

vacuo. The crude residue was purified by preparative thin-layer chromatography on silica gel (benzene/CH_2Cl_2 (40/1)) to afford **3e** (1.2 mg, 0.005 mmol, 7% yield), **3ag** (20.4 mg, 0.05 mmol, 77% yield), and **3ah** (4.1 mg, 0.008 mmol, 12% yield).

3ag Yellow oil. IR (neat): 2984, 1620, 1548, 1483, 1471, 1421, 1391, 1359, 1304, 1247, 1109, 1023, 837, 730, 690, 629 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 6.98 (s, 3H), 4.42 (q, *J* = 7.1 Hz, 4H), 3.73 (s, 4H), 2.30 (s, 3H), 1.45 (t, *J* = 7.1 Hz, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 163.0, 139.4, 134.6, 128.7, 126.0, 108.5, 66.4, 27.5, 21.3, 14.3. HRMS *m/z* (ESI) calcd.for $C_{17}H_{21}N_4O_6$ $(M + H)^+$ 377.1456, found 377.1463.

3ah Yellow oil. IR (neat): 2984, 2917, 1620, 1549, 1483, 1471, 1390, 1359, 1306, 1246, 1153, 1110, 1022, 837, 731, 688, 616 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.10 (s, 3H), 4.43 (q, *J* = 7.1 Hz, 6H), 3.75 (s, 6H), 1.46 (t, *J* = 7.1 Hz, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 162.9, 135.5, 128.2, 108.1, 66.6, 27.4, 14.3. HRMS *m/z*(ESI) calcd.for $C_{21}H_{25}N_6O_9$ $(M + H)^+$ 505.1678, found 505.1668.

Experimental procedures for functionalization of R–H substrates via furoxan (Figure 4)

3-(2-Methylphenyl)propane-1,2-diamine (4) Furoxan **3c** (50 mg, 0.21 mmol, 1 equiv), 10% Pd/C (11.5 mg, 0.01 mmol, 0.05 equiv), and MeOH (2 mL) were added to a reaction vessel under argon. The atmosphere was exchanged to H_2 and kept using a balloon. The mixture was stirred at 23 °C for 2 h. The mixture was filtered through celite and concentrated in vacuo. To a suspension of $LiAlH_4$ (40.2 mg, 5 equiv) in anhydrous THF (4 mL) was added the crude material thus obtained at 0 °C. The mixture was stirred for 6 h at 0 °C and the reaction was quenched by the subsequent addition of water (0.04 mL), 15% NaOH (0.04 mL), and water (0.12 mL). The mixture was filtered through celite, washed with hot THF and concentrated in vacuo. The crude residue was purified by preparative thin-layer chromatography on silica gel (CH_2Cl_2/MeOH (10/1) with 15% triethylamine) to afford **4** (11 mg, 0.07 mmol, 32% yield). Yellow oil; IR (neat): 3291, 2919, 1575, 1489, 1470, 1382, 1365, 1312, 1163, 1071, 820, 741, 728 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.17–7.11 (m, 4H), 3.00–2.94 (m, 1H), 2.84–2.76 (m, 2H), 2.60–2.48 (m, 2H), 2.33 (s, 3H), 1.56 (br, 4H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 137.6, 136.5, 130.6, 130.1, 126.5, 126.1, 54.0, 48.5, 39.8, 19.7. HRMS *m/z* (ESI) calcd.for $C_{10}H_{17}N_2$ $(M + H)^+$ 165.1386, found 165.1392.

3-(2-Methoxyphenyl)propane-1,2-diamine (5) Furoxan **3g** (80 mg, 0.32 mmol, 1 equiv), 10% Pd/C (17 mg, 0.02 mmol, 0.05 equiv), and MeOH (2 mL) were added to a reaction vessel under argon. The atmosphere was exchanged to H_2 and kept using a balloon. The mixture was stirred at 23 °C for 2 h. The mixture was filtered through celite and concentrated in vacuo. To a suspension of $LiAlH_4$ (60.3 mg, 5 equiv) in anhydrous THF (5 mL) was added the crude material thus obtained at 0 °C. The mixture was stirred for 6 h at 0 °C and the reaction was quenched by the subsequent addition of water (0.06 mL), 15% NaOH (0.06 mL), and water (0.18 mL). The mixture was filtered through celite, washed with hot THF and concentrated in vacuo. The crude residue was purified by preparative thin-layer chromatography on silica gel (CH_2Cl_2/MeOH (10/1) with 15% triethylamine) to afford **5** (20 mg, 0.11 mmol, 35% yield). Yellow oil; IR (neat): 3356, 3277, 2917, 1598, 1584, 1492, 1463, 1438, 1240, 1049, 1026, 817, 750 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.20 (td, *J* = 7.6, 1.7 Hz, 1H), 7.12 (dd, *J* = 7.4, 1.6 Hz, 1H), 6.90–6.84 (m, 2H), 3.80 (s, 3H), 3.01–2.94 (m, 1H), 2.81–2.72 (m, 2H), 2.53 (d, *J* = 7.7 Hz, 1H), 2.49 (d, *J* = 7.6 Hz, 1H), 1.56 (br, 4H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ =157.8, 131.2, 127.7, 127.7, 120.5, 110.5, 55.3, 54.0, 48.3, 36.8. HRMS *m/z* (ESI) calcd.for $C_{10}H_{17}N_2O$ $(M + H)^+$ 181.1335, found 181.1330.

3-(3,5-Dimethylphenyl)propane-1,2-diamine (6) Furoxan **3e** (50 mg, 0.2 mmol, 1.0 equiv), 5% Pd/C (8.6 mg, 0.004 mmol, 0.02 equiv), and MeOH (2 mL) were added to a reaction vessel under argon. The atmosphere was exchanged to H_2 and kept using a balloon. The mixture was stirred at 23 °C for 2 h. The mixture was filtered through celite and concentrated in vacuo. To a suspension of $LiAlH_4$ (38 mg, 5 equiv) in anhydrous THF (4 mL) was added the crude material thus obtained at 0 °C. The mixture was stirred for 6 h at 0 °C and the reaction was quenched by the subsequent addition of water (0.04 mL), 15% NaOH (0.04 mL), and water (0.12 mL). The mixture was filtered through celite, washed with hot THF and concentrated in vacuo. The crude residue was purified by preparative thin-layer chromatography on silica gel (CH_2Cl_2/MeOH (10/1) with 15% triethylamine) to afford **6** (11.6 mg, 0.07 mmol, 33%yield). Colorless oil; IR (neat): 3276, 3011, 2195, 2851, 1604, 1462, 1375, 1036, 846, 706 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 6.86 (s, 1H), 6.81 (s, 2H), 2.99–2.92 (m, 1H), 2.80 (dd, *J* = 12.7, 4.1 Hz, 1H), 2.71 (dd, *J* = 13.3, 5.0 Hz, 1H), 2.58–2.51 (m, 1H), 2.43–2.38 (m, 1H), 2.29 (s, 6H), 1.72 (br, 4H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 139.1, 138.0, 127.9, 127.1, 55.1, 48.3, 42.2, 21.3. HRMS *m/z* (ESI) calcd.for $C_{11}H_{18}N_2$ $(M + H)^+$ 179.1543, found 179.1540.

3-(Naphthalen-2-yl)propane-1,2-diamine (7) Furoxan **3k** (60 mg, 0.22 mmol, 1.0 equiv), 5% Pd/C (9.45 mg, 0.004 mmol, 0.02 equiv), and MeOH (2 mL) were added to a reaction vessel under argon. The atmosphere was exchanged to H_2 and kept using a balloon. The mixture was stirred at 23 °C for 2 h. The mixture was filtered through celite and concentrated in vacuo. To a suspension of $LiAlH_4$ (42.2 mg, 5 equiv) in anhydrous THF (4 mL) was added the crude material thus obtained at 0 °C. The mixture was stirred for 6 h at 0 °C and the reaction was quenched by the subsequent addition of water (0.04 mL), 15% NaOH (0.04 mL), and water (0.12 mL). The mixture was filtered through celite, washed with hot THF and concentrated in vacuo. The crude residue was purified by preparative thin-layer chromatography on silica gel (CH_2Cl_2/MeOH (10/1) with 15% triethylamine) to afford **7** (13.6 mg, 0.07 mmol, 31% yield). Yellow oil. IR (neat): 3357, 3272, 3049, 2915, 2848, 1598, 1506, 1442, 1364, 1270, 1124, 1017, 893, 856, 810, 747, 621 cm^{-1}. ^1H NMR (400 MHz,$CDCl_3$) δ = 7.83–7.78 (m, 3H), 7.64 (s, 1H), 7.49–7.42 (m, 2H), 7.33 (dd, *J* = 8.4, 1.7 Hz, 1H), 3.10–3.04 (m, 1H), 2.95 (dd, *J* = 13.3, 4.9 Hz, 1H), 2.85 (dd, *J* = 12.6, 4.1 Hz, 1H), 2.68–2.57 (m, 2H), 1.55 (br, 4H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 136.7, 133.5, 132.2, 128.2, 127.6, 127.6, 127.5, 126.1, 125.4, 55.0, 48.3, 42.5. HRMS *m/z* (ESI) calcd.for $C_{13}H_{16}N_2$ $(M + H)^+$ 201.1386, found 201.1387.

N,N'-Dibenzoyl 3-(oxan-2-yl)propane-1,2-diamine (8') Furoxan **3s** (50 mg, 0.23 mmol, 1 equiv), 10% Pd/C (12.4 mg, 0.01 mmol, 0.05 equiv), and MeOH (2 mL) were added to a reaction vessel under argon. The atmosphere was exchanged to H_2 and kept using a balloon. The mixture was stirred at 23 °C for 2 h. The mixture was filtered through celite and concentrated in vacuo. To a suspension of $LiAlH_4$ (44 mg, 5 equiv) in anhydrous THF (4 mL) was added the crude material thus obtained at 0 °C. The mixture was stirred for 6 h at 0 °C and the reaction was quenched by the subsequent addition of water (0.04 mL), 15% NaOH (0.04 mL), and water (0.12 mL). The mixture was filtered through celite, washed with hot THF and concentrated in vacuo. The obtained crude material containing diamine **8** was dissolved in 4 mL CH_2Cl_2, then benzoyl chloride (53 μL, 0.46

mmol, 2 equiv) and Et_3N (64 μL, 0.46 mmol, 2 equiv) were added into the solution. The mixture was stirred under argon at 23 °C for 2 h, after which the volatiles were removed under vacuum. The residue was purified by preparative thin-layer chromatography on silica gel (CH_2Cl_2/MeOH (20/1)) to afford **8'** (24.7 mg, 0.07 mmol, 30% yield). White solid; Mp 150–151.7 ºC. IR (neat): 3322, 2937, 2848, 1633, 1578, 1538, 1491, 1295, 1206, 1089, 1047, 930, 895, 800, 692, 649 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.81–7.78 (m, 4H), 7.51–7.36 (m, 7H), 7.28 (s, 1H), 4.36–4.27 (m, 1H), 4.04 (d, *J* = 10.4 Hz, 1H), 3.89–3.38 (m, 4H), 1.90–1.43 (m, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ =168.6, 168.3, 134.3, 134.2, 131.7, 131.5, 128.7, 128.6, 127.2, 127.1, 79.2, 69.1, 53.5, 41.7, 28.6, 26.1, 23.3. HRMS *m/z* (ESI) calcd.for $C_{21}H_{24}N_2O_3Na$ $(M + Na)^+$ 375.1679, found 375.1674.

N,N'-Dibenzoyl 3-(1,4-dioxan-2-yl)propane-1,2-diamine (9') Furoxan **3t** (50 mg, 0.23 mmol, 1 equiv), 10% Pd/C (12.3 mg, 0.01 mmol, 0.05 equiv), and MeOH (2 mL) were added to a reaction vessel under argon. The atmosphere was exchanged to H_2 and kept using a balloon. The mixture was stirred at 23 °C for 2 h. The mixture was filtered through celite and concentrated in vacuo. To a suspension of $LiAlH_4$ (43.5 mg, 5 equiv) in anhydrous THF (4 mL) was added the crude material thus obtained at 0 °C. The mixture was stirred for 6 h at 0 °C and the reaction was quenched by the subsequent addition of water (0.04 mL), 15% NaOH (0.04 mL), and water (0.12 mL). The mixture was filtered through celite, washed with hot THF and concentrated in vacuo. The obtained crude material containing diamine **9** was dissolved in 4 mL CH_2Cl_2, then benzoyl chloride (53 μL, 0.46 mmol, 2 equiv) and Et_3N (64 μL, 0.46 mmol, 2 equiv) were added into the solution. The mixture was stirred under argon at 23 °C for 2 h, after which the volatiles were removed under vacuum. The residue was purified by preparative thin-layer chromatography on silica gel (CH_2Cl_2/MeOH (20/1)) to afford **9'** (32.5 mg, 0.09 mmol, 40% yield). White solid; Mp 181.5–183.2 ºC. IR (neat): 3876, 3315, 2850, 1633, 1539, 1490, 1354, 1296, 1125, 1092, 970, 899, 885, 691, 662 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.85–7.81 (m, 2H), 7.77–7.74 (m, 2H), 7.62 (d, *J* = 8.2 Hz, 1H), 7.51–7.46 (m, 2H), 7.43–7.37 (m, 4H), 7.04 (t, *J* = 5.7 Hz, 1H), 4.38–4.31 (m, 1H), 3.89–3.81 (m, 3H), 3.74–3.67 (m, 4H), 3.65–3.55 (m, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 169.5, 168.1, 133.9, 133.8, 131.9, 131.8, 128.7, 128.7, 127.3, 127.1, 76.6, 69.3, 67.2, 66.6, 51.3, 41.9. HRMS *m/z* (ESI) calcd.for $C_{20}H_{22}N_2O_4Na$ $(M + Na)^+$ 377.1472, found 377.1469.

N,N'-Dibenzoyl 3-(1,3,5-trioxan-2-yl)propane-1,2-diamine (10') Furoxan **3u** (50 mg, 0.23 mmol, 1 equiv), 10% Pd/C (12.2 mg, 0.01 mmol, 0.05 equiv), and MeOH (2 mL) were added to a reaction vessel under argon. The atmosphere was exchanged to H_2 and kept using a balloon. The mixture was stirred at 23 °C for 2 h. The mixture was filtered through celite and concentrated in vacuo. To a suspension of $LiAlH_4$ (43.2 mg, 5 equiv) in anhydrous THF (4 mL) was added the crude material thus obtained at 0 °C. The mixture was stirred for 6 h at 0 °C and the reaction was quenched by the subsequent addition of water (0.04 mL), 15% NaOH (0.04 mL), and water (0.12 mL). The mixture was filtered through celite, washed with hot THF and concentrated in vacuo. The obtained crude material containing diamine **10** was dissolved in 4 mL CH_2Cl_2, then benzoyl chloride (53 μL, 0.46 mmol, 2 equiv) and Et_3N (64 μL, 0.46 mmol, 2 equiv) were added into the solution. The mixture was stirred under argon at 23 °C for 2 h, after which the volatiles were removed under vacuum. The residue was purified by preparative thin-layer chromatography on silica gel (CH_2Cl_2/MeOH (20/1)) to afford **10'** (31 mg, 0.09 mmol, 38% yield).,White solid; Mp 172.1-173.4 ºC. IR (neat): 3372, 3333, 2858, 1637, 1579, 1539, 1494, 1390, 1318, 1168, 1113, 1055, 1037, 989, 956, 691 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.84–7.78 (m, 4H), 7.51–7.31 (m, 8H), 5.27 (d, *J* = 2.6 Hz, 1H), 5.22 (t, *J* = 5.4 Hz, 2H), 5.09–5.05 (m, 2H), 4.47–4.41 (m, 1H), 4.02–3.94 (m, 1H), 3.82–3.76 (m, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ =169.0, 168.5, 134.1, 133.7, 131.9, 131.7, 128.7, 128.6, 127.3, 127.2, 99.7, 93.3, 93.3, 53.4, 39.7. HRMS *m/z* (ESI) calcd.for $C_{19}H_{20}N_2O_5Na$ $(M + Na)^+$ 379.1264, found 379.1261.

Ethyl 3-(3,5-dimethylphenyl)-N-hydroxy-2-(hydroxyimino)propanimidate (11) Furoxan **3e** (250 mg, 1.0 mmol, 1 equiv), 5% Pd/C (42.6 mg, 0.02 mmol,0.02 equiv), and MeOH (16 mL) were added to a reaction vessel under argon. The atmosphere was exchanged to H_2 and kept using a balloon. The mixture was stirred at 23 °C for 2 h. The mixture was filtered through celite and concentrated in vacuo to afford **11** (252 mg, 1.0 mmol, 100% yield). Brownish solid; Mp 102.2–102.7 ºC. IR (neat): 3163, 3016, 2978, 2868, 1601, 1546, 1489, 1470, 1441, 1427, 1369, 1317, 1221, 1115, 1048, 992, 797, 686 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 9.86 (br, 1H), 7.64 (br, 1H), 6.89 (s, 2H), 6.86 (s, 1H), 4.03 (q, *J* = 7.0 Hz, 2H), 3.91 (s, 2H), 2.28 (s, 6H), 1.28 (t, *J* = 7.0 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 154.6, 152.4, 137.9, 135.1, 128.3, 126.9, 63.3, 30.8, 21.3, 14.2. HRMS *m/z* (ESI) calcd.for $C_{13}H_{18}N_2O_3$ $(M + H)^+$ 251.1390, found 251.1390.

2-(3,5-Dimethylphenyl)ethan-1-amine (12) To a suspension of $LiAlH_4$ (44.1 mg, 1.16 mmol, 5.0 equiv) in anhydrous THF (4 mL) was added portionwise **3f** (80 mg, 0.23 mmol, 1.0 equiv) at 0 °C. The mixture was stirred for 7 h at 23 °C and the reaction was quenched by subsequent addition of water (0.04 mL), 15% NaOH (0.04 mL), and water (0.12 mL). The mixture was filtered through celite, washed with hot THF and concentrated in vacuo. The crude residue was purified by preparative thin-layer chromatography on silica gel (CH_2Cl_2/MeOH (10/1) with 15 % triethylamine) to afford **12** (11 mg, 0.07 mmol, 32% yield). Yellow oil; IR (neat): 3309, 2917, 1606, 1575, 1476, 1447, 1380, 1321, 1306, 1034, 842, 822, 702, 668 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 6.86 (s, 1H), 6.82 (s, 2H), 2.95 (t, *J* = 6.9 Hz, 2H), 2.68 (t, *J* = 6.9 Hz, 2H), 2.30 (d, *J* = 0.7 Hz, 6H), 1.26 (br, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 139.8, 138.0, 127.9, 126.8, 43.7, 40.1, 21.4. HRMS *m/z* (ESI) calcd.for $C_{10}H_{16}N$ $(M + H)^+$ 150.1277, found 150.1283.

1,3-Dimethyl-5-(2-nitroethyl)benzene (13) Furoxan **3f** (80 mg, 0.23 mmol,1 equiv), tributyltin hydride (125 μL, 0.46 mmol, 2 equiv) and benzene (1.2 mL) were added to a reaction vessel. The mixture was stirred at 40 °C for 5 d. The solvents were removed with a rotary evaporator. The crude residue was purified by preparative thin-layer chromatography on silica gel (Hexane/EtOAc (3/1)) to afford **13** (14 mg, 0.08 mmol, 34% yield). Yellow oil; IR (neat): 2919, 1607, 1548, 1431, 1377, 846, 695, 553 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 6.91 (s, 1H), 6.82 (s, 2H), 4.58 (t, *J* = 7.5 Hz, 2H), 3.24 (t, *J* = 7.5 Hz, 2H), 2.29 (s, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ =138.6, 135.5, 129.1, 126.4, 76.4, 33.4, 21.3. HRMS *m/z* (FI) calcd.for $C_{10}H_{13}NO_2$ $(M)^+$ 179.0946, found 179.0943.

N-[2-(3,5-Dimethylphenyl)ethylidene]hydroxylamine (14) Furoxan **3f** (80 mg, 0.23 mmol, 1 equiv), tributyltin hydride (312 μL, 1.16 mmol, 5 equiv) and benzene (1.2 mL) were added to a reaction vessel. The mixture was stirred at 40 °C for 5 d. The solvents were removed with a rotary evaporator. The crude residue was purified by preparative thin-layer chromatography on silica gel (Hexane/EtOAc (3/1)) to afford **14** (17.6 mg, 0.11

mmol, 46% yield). White solid; Mp 82.1–83.5ºC. IR (neat): 3150, 2916, 1605, 1454, 1407, 1329, 1260, 1056, 932, 844, 815, 695 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 8.32 (br, 1H), 6.82–6.76 (m, 4H), 3.60 (d, *J* = 5.3 Hz, 2H), 2.23 (s, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 151.2, 138.4, 136.5, 128.3, 126.6, 31.5, 21.2. HRMS *m/z* (ESI) calcd.for $C_{10}H_{14}NO$ $(M + H)^+$ 164.1070, found 164.1065.

N-[2-(3,5-Dimethylphenyl)-1-(5-phenyl-1,2-oxazol-3-yl)-ethylidene]hydroxylamine (15) Furoxan **3f** (80 mg, 0.23 mmol, 1 equiv), phenylacetylene (77 μL, 0.70 mmol, 3 equiv) and DMF (4.0 mL) were added to a reaction vessel. The mixture was stirred under Ar at 130 °C for 36 h. Extracted thrice with EtOAc, washed five times with water, the organic layer was dried over Na_2SO_4, filtrated, and concentrated in vacuo. The crude residue was purified by preparative thin-layer chromatography on silica gel ($CHCl_3$) to afford **15** (20 mg, 0.07 mmol, 28% yield). Yellow solid; Mp 149.2–151.7 °C. IR (neat): 3174, 2917, 1602, 1574, 1434, 1247, 1101, 1009, 829, 898, 759, 682 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 8.48 (br, 1H), 7.78–7.74 (m, 2H), 7.47–7.42 (m, 3H), 7.03 (s, 2H), 6.83 (s, 1H), 6.79 (s, 1H), 4.20 (s, 2H), 2.26 (s, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ =170.2, 160.6, 151.7, 138.0, 135.9, 130.4, 129.0, 128.3, 127.2, 126.9, 125.9, 97.1, 31.0, 21.3. HRMS *m/z* (ESI) calcd.for $C_{19}H_{18}N_2O_2Na$ $(M + Na)^+$ 329.1260, found 329.1253.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

NMR spectra of compounds (PDF).

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Author Contributions

The manuscript was written through contributions of all authors.

Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Gasco, A.; Boulton, A. J., Furoxans and Benzofuroxans. In *Adv. Heterocycl. Chem.*, Katritzky, A. R.; Boulton, A. J., Eds. Academic Press: **1981**; Vol. 29, pp 251-340; (b) Sheremetev, A. B.; Makhova, N. N.; Friedrichsen, W., Monocyclic furazans and furoxans. In *Adv. Heterocycl. Chem.*, Academic Press: **2001**; Vol. 78, pp 65-188; (c) Cerecetto, H.; Porcal, W., Pharmacological properties of furoxans and benzofuroxans: recent developments. *Mini Rev. Med. Chem.* **2005,** *5*, 57-71; (d) Mancini, R. S.; Barden, C. J.; Weaver, D. F.; Reed, M. A., Furazans in Medicinal Chemistry. *J. Med. Chem.* **2021**, *64*, 1786−1815.

(2) (a) Del Grosso, E.; Boschi, D.; Lazzarato, L.; Cena, C.; Di Stilo, A.; Fruttero, R.; Moro, S.; Gasco, A., The Furoxan System: Design of Selective Nitric Oxide (NO) Donor Inhibitors of COX-2 Endowed with Anti-Aggregatory and Vasodilating Activities. *Chem. Biodivers.* **2005,** *2*, 886-900; (b) Matsubara, R.; Ando, A.; Hayashi, M., Synthesis of cyanofuroxans from 4-nitrofuroxans via CC bond forming reactions. *Tetrahedron Lett.* **2017,** *58*, 3337-3340; (c) Matsubara, R.; Eguchi, S.; Ando, A.; Hayashi, M., Synthesis of alkynyl furoxans. Rare carbon−carbon bond-forming reaction on a furoxan ring. *Org. Biomol. Chem.* **2017,** *15*, 1965-1969.

(3) Matsubara, R.; Kim, H.; Sakaguchi, T.; Xie, W.; Zhao, X.; Nagoshi, Y.; Wang, C.; Tateiwa, M.; Ando, A.; Hayashi, M.; Yamanaka, M.; Tsuneda, T., Modular Synthesis of Carbon-Substituted Furoxans via Radical Addition Pathway. Useful Tool for Transformation of Aliphatic Carboxylic Acids Based on "Build-and-Scrap" Strategy. *Org. Lett.* **2020,** *22*, 1182-1187.

(4) (a) Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N., Efficient catalytic addition of aromatic carbon-hydrogen bonds to olefins. *Nature* **1993,** *366*, 529-531; (b) Chen, D. Y.-K.; Youn, S. W., C–H Activation: A Complementary Tool in the Total Synthesis of Complex Natural Products. *Chem. Eur. J.* **2012,** *18*, 9452-9474; (c) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K., C–H Bond Functionalization: Emerging Synthetic Tools for Natural Products and Pharmaceuticals. *Angew. Chem. Int. Ed.* **2012,** *51*, 8960-9009; (d) Wencel-Delord, J.; Glorius, F., C–H bond activation enables the rapid construction and late-stage diversification of functional molecules. *Nat. Chem.* **2013,** *5*, 369-375; (e) Cernak, T.; Dykstra, K. D.; Tyagarajan, S.; Vachal, P.; Krska, S. W., The medicinal chemist's toolbox for late stage functionalization of drug-like molecules. *Chem. Soc. Rev.* **2016,** *45*, 546-576; (f) He, J.; Wasa, M.; Chan, K. S. L.; Shao, Q.; Yu, J.-Q., Palladium-Catalyzed Transformations of Alkyl C–H Bonds. *Chem. Rev.* **2017,** *117*, 8754-8786; (g) Wei, Y.; Hu, P.; Zhang, M.; Su, W., Metal-Catalyzed Decarboxylative C–H Functionalization. *Chem. Rev.* **2017,** *117*, 8864-8907; (h) Gandeepan, P.; Müller, T.; Zell, D.; Cera, G.; Warratz, S.; Ackermann, L., 3d Transition Metals for C–H Activation. *Chem. Rev.* **2019,** *119*, 2192-2452; (i) Dalton, T.; Faber, T.; Glorius, F., C–H Activation: Toward Sustainability and Applications. *ACS Central Science* **2021,** *7*, 245-261.

(5) (a) Chen, H.; Hartwig, J. F., Catalytic, Regiospecific End-Functionalization of Alkanes: Rhenium-Catalyzed Borylation under Photochemical Conditions. *Angew. Chem. Int. Ed.* **1999,** *38*, 3391-3393; (b) Iverson, C. N.; Smith, M. R., Stoichiometric and Catalytic B−C Bond Formation from Unactivated Hydrocarbons and Boranes. *J. Am. Chem. Soc.* **1999,** *121*, 7696-7697; (c) Ishiyama, T.; Takagi, J.; Ishida, K.; Miyaura, N.; Anastasi, N. R.; Hartwig, J. F., Mild Iridium-Catalyzed Borylation of Arenes. High Turnover Numbers, Room Temperature Reactions, and Isolation of a Potential Intermediate. *J. Am. Chem. Soc.* **2002,** *124*, 390-391; (d) Ishiyama, T.; Miyaura, N., Metal-catalyzed reactions of diborons for synthesis of organoboron compounds. *The Chemical Record* **2004,** *3*, 271-280; (e) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F., C−H Activation for the Construction of C−B Bonds. *Chem. Rev.* **2010,** *110*, 890-931; (f) Hartwig, J. F., Borylation and Silylation of C–H Bonds: A Platform for Diverse C–H Bond Functionalizations. *Acc. Chem. Res.* **2012,** *45*, 864-873.

(6) (a) Engl, P. S.; Häring, A. P.; Berger, F.; Berger, G.; Pérez-Bitrián, A.; Ritter, T., C–N Cross-Couplings for Site-Selective Late-Stage Diversification via Aryl Sulfonium Salts. *J. Am. Chem. Soc.* **2019,** *141*, 13346-13351; (b) Berger, F.; Plutschack, M. B.; Riegger, J.; Yu, W.; Speicher, S.; Ho, M.; Frank, N.; Ritter, T., Site-selective and versatile aromatic C−H functionalization by thianthrenation. *Nature* **2019,** *567*, 223-228; (c) Li, J.; Chen, J.; Sang, R.; Ham, W.-S.; Plutschack, M. B.; Berger, F.; Chabbra, S.; Schnegg, A.; Genicot, C.; Ritter, T., Photoredox catalysis with aryl sulfonium salts enables site-selective late-stage fluorination. *Nat. Chem.* **2020,** *12*, 56-62.

(7) (a) Caronna, T.; Citterio, A.; Grossi, L.; Minisci, F.; Ogawa, K., Nucleophilic character of alkyl radicals−XII: Mechanism and new syntheses in the oxidation of alcohols by peroxydisulphate. *Tetrahedron* **1976,** *32*, 2741-2745; (b) Huie, R. E.; Clifton, C. L.; Kafafi, S. A., Rate constants for hydrogen abstraction reactions of the sulfate radical, $SO4^-$: experimental and theoretical results for cyclic ethers. *J. Phys. Chem.* **1991,** *95*, 9336-9340; (c) Jin, J.; MacMillan, D. W. C., Direct α-Arylation of Ethers through the Combination of

Photoredox-Mediated C–H Functionalization and the Minisci Reaction. *Angew. Chem. Int. Ed.* **2015,** *54*, 1565-1569.

(8) (a) Mora, V. C.; Rosso, J. A.; Mártire, D. O.; Gonzalez, M. C., Phenol depletion by thermally activated peroxydisulfate at 70°C. *Chemosphere* **2011,** *84*, 1270-1275; (b) Ahmadi, S.; Igwegbe, C. A.; Rahdar, S., The application of thermally activated persulfate for degradation of Acid Blue 92 in aqueous solution. *International Journal of Industrial Chemistry* **2019,** *10*, 249-260.

(9) Xie, W.; Hayashi, M.; Matsubara, R., Borylfuroxans: Synthesis and Applications. *Org. Lett.* **2021,** *23*, 4317-4321.