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A Lewis Acid Catalyzed Annulation to 2,1-Benzisoxazoles

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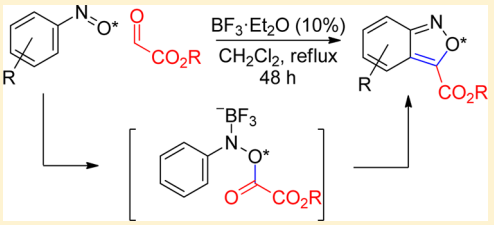
Supporting Information

ABSTRACT: We report here a new, atom economical annulation to 2,1-benzisoxazole scaffolds via the $BF_3{\cdot}Et_2O$-catalyzed reaction of glyoxylate esters and nitrosoarenes. The developed method represents a convergent route to this compound class from previously unexplored inputs and provides a range of 2,1-benzisoxazoles in moderate to high yields under convenient conditions. Along with exploration of substrate scope, initial mechanistic investigation through ^{18}O labeling and the synthesis of a reaction intermediate provides evidence for an unusual umpolung addition of glyoxylates to nitrosobenzenes with high O-selectivity, followed by a new type of Friedel–Crafts cyclization.



INTRODUCTION

In addition to their application as scaffolds in a number of biologically active compounds,[1,2] 2,1-benzisoxazoles serve as useful intermediates in organic synthesis.[2] Of particular note is the reductive cleavage of the benzisoxazole N–O bond to give 2-aminophenyl ketones, which have been widely employed in the synthesis of important pharmaceuticals and materials such as 1,4-benzodiazepines and quinolines.[2,3]

Our lab recently reported the synthesis of indazoles via the reversible Rh(III)-catalyzed addition of azobenzene C–H bonds to aldehydes, followed by intramolecular nucleophilic displacement of the hydroxyl group and aromatization (Figure 1A).[4] We reasoned that 2,1-benzisoxazoles might also be

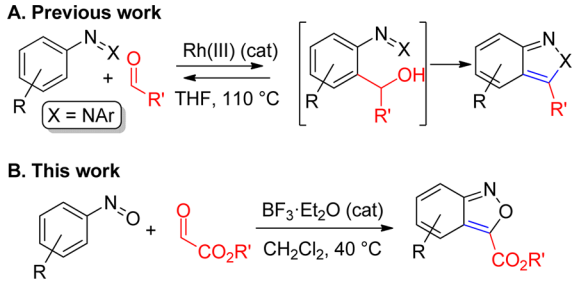


Figure 1. (A) Previous indazole synthesis from azobenzenes. (B) New, Lewis acid catalyzed annulation to give benzisoxazoles from nitrosobenzenes.

prepared by the Rh(III)-catalyzed coupling of isoelectronic nitrosobenzenes and aldehydes, two inputs that had not previously been applied to benzisoxazole synthesis (Figure 1B).[2,5,6] However, in our exploration of this approach, we uncovered an unprecedented Lewis acid catalyzed annulation that generated 2,1-benzisoxazoles from nitrosobenzenes and glyoxylate esters. The reaction can readily be performed on the benchtop under practical conditions with 10 mol % of $BF_3{\cdot}Et_2O$ as the Lewis acid. Subjecting ^{18}O-labeled substrates to the reaction conditions clearly establishes that the nitrosoarene oxygen is incorporated into the isoxazole ring rather than the oxygen from the aldehyde partner. A novel reaction pathway is proposed based upon the observed oxygen incorporation, substrate scope, and product regioselectivity. The proposed mechanism is supported by the independent synthesis and transformation of a putative reaction intermediate.

RESULTS AND DISCUSSION

In our initial efforts to couple nitrosobenzene and ethyl glyoxylate, we employed the catalyst system that we had previously successfully applied to indazole synthesis: $[Cp^*RhCl_2]_2$ as a precatalyst and $AgSbF_6$ as a chloride abstractor (entry 1, Table 1).[4] We were encouraged by the 20% yield of desired product, but before carrying out additional optimization experiments, we first performed control reactions wherein the two constituents of the catalyst system were evaluated separately (entries 2 and 3). To our surprise, $AgSbF_6$ alone was capable of catalyzing the reaction (entry 3). We, therefore, chose to explore the competence of a series of inexpensive Lewis acids in affording the desired 2,1-benzisoxazole products (entries 4–6). Because of its low cost and the promising initial results, we focused our efforts on development of the transformation with $BF_3{\cdot}Et_2O$ as the Lewis acid. Examination of catalyst loading showed 10 mol % of $BF_3{\cdot}Et_2O$ to be ideal, with reduced yields obtained at significantly higher or lower loading (entries 6–9). Extended reaction times resulted in higher conversion (entry 10), as did an increase in the reaction temperature to a gentle reflux (entry 11). A number of aprotic and protic solvents of varying polarity were investigated, but all were inferior to dichloromethane and dichloroethane (data not shown). Inversion of the reaction stoichiometry brought the yield to 70% (entry 12). Conveniently, the reaction proved amenable to scale up (1 mmol) with setup on the benchtop giving a 79% isolated yield (entry 13).

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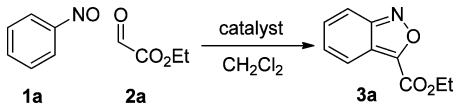
Table 1. Optimization of Reaction Conditions[a]



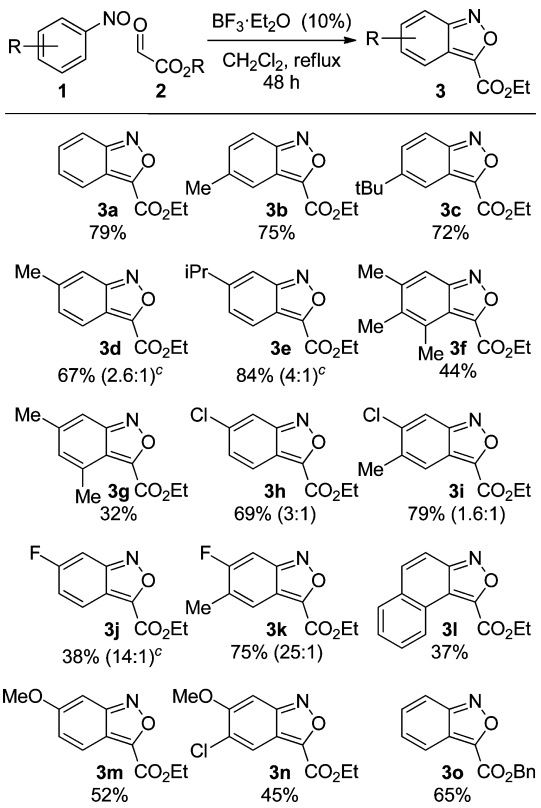
1a 2a 3a

entry	catalyst (mol %)	time (h)	temperature (°C)	1a:2a	yield (%)[c]
1[b]	$[Cp^*RhCl_2]_2$ (5)/$AgSbF_6$ (20)	24	110	1:2	20
2[b]	$[Cp^*RhCl_2]_2$ (5)	24	110	1:2	0
3[b]	$AgSbF_6$ (20)	24	110	1:2	29
4	$FeCl_3$ (20)	24	rt	1:2	31
5	$AlCl_3$ (20)	24	rt	1:2	0
6	$BF_3{\cdot}Et_2O$ (40)	24	rt	1:2	15
7	$BF_3{\cdot}Et_2O$ (20)	24	rt	1:2	22
8	$BF_3{\cdot}Et_2O$ (10)	24	rt	1:2	32
9	$BF_3{\cdot}Et_2O$ (5)	24	rt	1:2	29
10	$BF_3{\cdot}Et_2O$ (10)	48	rt	1:2	40
11	$BF_3{\cdot}Et_2O$ (10)	48	reflux	1:2	63
12	$BF_3{\cdot}Et_2O$ (10)	48	reflux	2:1	70
13[d]	$BF_3{\cdot}Et_2O$ (10)	48	reflux	2:1	79[e]

[a]Conditions: 0.40 mmol limiting reagent in CH_2Cl_2 (0.05 M), in glovebox. [b]DCE as solvent. [c]Determined by GC relative to tetradecane as an internal standard. [d]Conditions: **1a** (2.0 mmol) and **2a** (1.0 mmol) in CH_2Cl_2 (0.05 M), outside glovebox. [e]Isolated yield.

Having established efficient conditions for the $BF_3{\cdot}Et_2O$-catalyzed transformation, the reaction scope was examined using a variety of substituted nitrosobenzenes (Table 2). Electron-neutral (**3a**), electron-rich (**3b**–**3g**, **3l**–**3n**), and even modestly electron-deficient (**3h**–**3k**) aromatics reacted efficiently. However, the site of substitution of the electronegative chloro group was crucial for reaction success. While 3-nitrosochlorobenzene provided the benzisoxazole **3h** in good yield, the regioisomeric 4-nitrosochlorobenzene gave only trace product. This pronounced sensitivity to the placement of the chloro group is consistent with an electrophilic aromatic substitution reaction pathway where electronegative halogen substituents are known to be deactivating but, due to resonance stabilization, also strongly ortho-/para-directing.

Table 2. Examination of Substrate Scope[a,b,c]

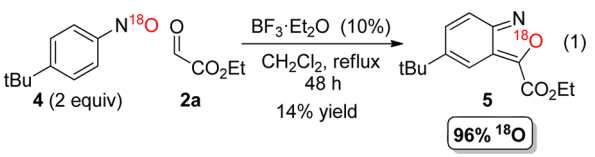


[a]Conditions: nitrosoarene (2.0 mmol), aldehyde (1.0 mmol), $BF_3{\cdot}Et_2O$ (10%) in CH_2Cl_2 (0.05 M). [b]Isolated yield of all regioisomers after silica gel chromatography. Ratio of regioisomers determined by ^1H NMR of crude product. [c]Isolated as an inseparable mixture of regioisomers.

Substitutions at the para and meta positions of the aromatic ring were well-tolerated. In contrast, 2-nitrosotoluene resulted in <10% yield of the desired benzisoxazole (not shown). The regioselectivity of the transformation was examined by employing a number of meta-substituted nitrosoarenes. While only moderate regioselectivity was observed for alkyl and chloro groups (**3d**, **3e**, **3h**, **3i**), a fluoro substituent at the meta position provided significantly higher regioselectivity, with the major site of addition being that most remote from the fluoro group (**3j**, **3k**). Reaction with a meta-methoxy group resulted in a single regioisomer (**3m**, **3n**). Notably, a single benzisoxazole regioisomer was also observed from reaction with 2-nitrosonaphthalene (**3l**). This result parallels the regioselectivity observed in electrophilic aromatic substitution reactions.[7]

While other glyoxylate esters react efficiently under the optimized conditions (**3o**), less electrophilic aldehydes such as benzaldehyde did not give 2,1-benzisoxazole products.

We next aimed to shed light on the reaction mechanism by employing an ^{18}O labeling study to determine the origin of the oxygen in the isoxazole product. First, ^{18}O-enriched 4-*tert*-butyl-nitrosobenzene (**4**) was prepared and subjected to the reaction conditions to give benzisoxazole **5** (eq 1). The ^{18}O-nitrosobenzene was generated by oxidation of the corresponding aniline with $H_2{}^{18}O_2$ in the presence of a diphenyldiselenide



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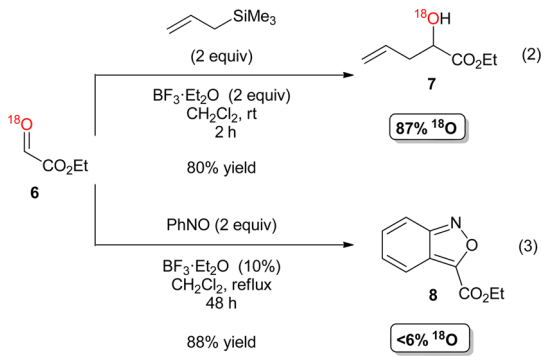
catalyst, and ^{18}O incorporation into the nitroso product was confirmed by GCMS analysis.[8] In order to work with the low concentrations of aqueous $H_2{}^{18}O_2$ that are commercially available,[9] we opted to label 4-*tert*-butyl-nitrosobenzene for this study to alleviate issues with nitrosobenzene sublimation on a small scale. Importantly, reaction of the ^{18}O-labeled nitrosoarene with ethyl glyoxylate resulted in almost complete incorporation of the ^{18}O label in the 2,1-benzisoxazole product **5** as determined by LCMS analysis (eq 1).[10]

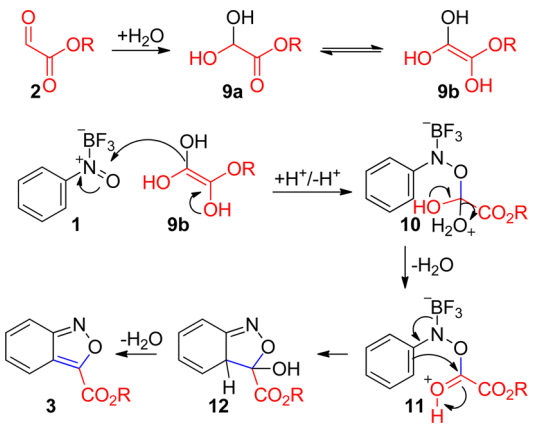
To verify that the isoxazole oxygen originates from nitrosobenzene, a control reaction was conducted with ^{18}O-labeled ethyl glyoxylate. Labeling of the glyoxylate ester was achieved by exchange with $H_2{}^{18}O$. Because ethyl glyoxylate not only readily hydrates and oligomerizes but also poorly ionizes, direct GCMS and LCMS analyses were not effective for accurately quantitating the extent of ^{18}O labeling of the ethyl glyoxylate. Instead, the ^{18}O-labeled glyoxylate was subjected to Sakurai allylation with allyltrimethylsilane to give alcohol **7** for which a high level of ^{18}O incorporation was confirmed by LCMS analysis (eq 2).[11] Notably, when the labeled glyoxylate **6**



was subjected to the reaction conditions, minimal ^{18}O incorporation was observed in benzisoxazole **8** by LCMS (eq 3). Taken together, the results of the described labeling experiments clearly establish that the isoxazole oxygen originates from the nitrosoarene partner rather than from the aldehyde.

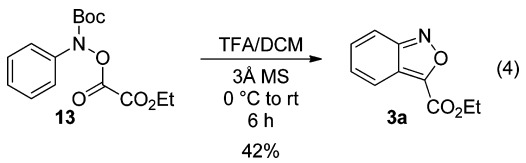
We propose a mechanism shown in Scheme 1 that is based on the ^{18}O incorporation experiments and the clear parallel between this reaction and electrophilic aromatic substitutions in terms of substrate reactivity and regioselectivity. Enol **9b** is proposed to add to the nitroso oxygen upon activation with BF_3

Scheme 1. Proposed Reaction Mechanism



to provide adduct **10**. This step is consistent with previously reported O-selective nucleophilic additions of carbon nucleophiles, including silyl enol ethers, to Lewis acid activated nitrosoarenes.[12] The O-selectivity is postulated to result from coordination of the nitroso nitrogen to the Lewis acid to increase electrophilicity at oxygen.[12−14] Although the proposed umpolung reactivity of the glyoxylate ester upon hydration does not have direct precedent, it is highly analogous to the acid-catalyzed addition of glyoxylate-derived silyl ketene acetals to a variety of electrophiles, including carbonyls and alkyl halides.[15] Following dehydration of addition product **10** to regenerate the carbonyl **11**, an intramolecular Friedel−Crafts cyclization gives bicyclic intermediate **12**, which provides the 2,1-benzisoxazole product **3** upon aromatization.

To test this mechanistic pathway, we prepared Boc derivative **13** that, upon acidic Boc cleavage, should provide intermediate **11**, with the only difference being a proton in place of BF_3. Indeed, upon treatment of **13** with trifluoroacetic acid, 2,1-benzisoxazole **3a** was observed as the major reaction product (eq 4). The acid not only removed the Boc group but



presumably also promoted Friedel−Crafts cyclization. The yield of **3a** from **13** is limited by a competing Bamberger rearrangement to give the 4-aminophenol side product in 20% yield.[16] We also explored cyclization of the less electrophilic benzoate analogue of pyruvate **13**. However, upon acid treatment, benzisoxazole was not detected, and 4-aminophenol and benzoic acid from competing Bamberger rearrangement were instead observed as the sole reaction products.

CONCLUSION

A practical annulation to give 2,1-benzisoxazoles from previously unexplored inputs has been developed. A range of electron-neutral, electron-rich, and modestly electron-deficient nitrosobenzenes serve as efficient inputs for the reaction. On the basis of mechanistic studies that include ^{18}O labeling, substrate scope and regioselectivities, and preparation of a putative reaction intermediate, the reaction likely proceeds by an unusual $BF_3{\cdot}Et_2O$-catalyzed umpolung addition of glyoxylates to nitrosobenzenes with high O-selectivity. A new type of Friedel−Crafts cyclization then occurs, followed by aromatization to give the desired 2,1-benzisoxazole products. Studies are currently underway to capitalize on the uncovered novel reactivity to access other heterocyclic motifs.

EXPERIMENTAL SECTION

General Experimental Methods. Unless otherwise indicated, all reactions were set up under an inert atmosphere (N_2) using flame-dried glassware. Dichloromethane and all other solvents were purified by elution through a column of activated alumina under N_2 before use. Triethylamine was distilled from CaH_2 under nitrogen immediately before use. Dichloromethane-d_2, benzene-d_6, acetone-d_6, and chloroform-d were all used as received. Unless otherwise noted, all reagents were purchased from commercial sources and used without further purification. Products and starting materials were visualized on TLC using UV or by staining with $KMnO_4$. NMR chemical shifts are reported in ppm relative to $CDCl_3$ (7.26 ppm ^1H and 77.16 ppm ^{13}C), C_6D_6 (7.16 ppm ^1H), $(CD_3)CO$ (29.84 ppm ^{13}C), or CD_2Cl_2 (5.32

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ppm ^{1}H and 54.00 ppm ^{13}C). Trifluoroacetic acid (−76.55 pm in $CDCl_3$) was used as an external standard for determining ^{19}F NMR chemical shifts. For IR spectra, only partial data are provided. Melting points are reported uncorrected. High-resolution mass spectra (HRMS) and low-resolution mass spectra (LRMS) data for the benzisoxazole products were obtained using electrospray ionization (ESI) on a time-of-flight (TOF) mass spectrometer. HRMS data for the nitrosoarene starting materials were obtained using an APGC ion source. GC analysis was performed using an Agilent J&W HP-5 column (5%-phenyl)-methylpolysiloxane.

*Ethyl Glyoxylate (**2a**).* Purification of ethyl glyoxylate was adapted from a literature procedure.[17] A 50% technical solution of ethyl glyoxyate in toluene (purchased form Aldrich) was purified by flash chromatography on silica gel (hexanes/ethyl acetate 20:1 to 1:1) and then distilled through a vacuum-jacketed vigereux column under N_2 (90 °C, 60 mmHg) to give a pale yellow oil. The freshly distilled ethyl glyoxylate was stored under N_2 in a Schlenk flask at −20 °C and warmed to ambient temperature before use.

*Benzyl Glyoxylate (**2b**).* Benzyl glyoxyate was prepared according to a literature procedure[18] and purified by distillation using a Kugelrohr apparatus (95 °C, 20 mmHg) to give a yellow oil.

BF_3·Et_2O Catalyst. Boron trifluoride diethyl etherate was purchased from Aldrich and purified according to a literature procedure.[19] The reagent was stored under N_2 in a Schlenk flask at −20 °C and warmed to ambient temperature before use.

*Nitrosoarenes (**1**).* Nitrosobenzene, which was used to prepare **3a** and **3o**, is commercially available. The nitrosoarenes used to prepare 2,1-benzisoxazoles **3b**,[20] **3c**,[21] **3d**,[22] **3e**,[23] **3g**,[24] and **3m**[20] were prepared according to the cited recently published methods.

General Procedure for the Preparation of Nitrosobenzenes.[25] In a round-bottom flask equipped with a stir bar, the indicated aniline (3.7−24 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (0.26 M) and added to a solution of oxone (11−72 mmol, 3.0 equiv) in water (0.60 M). The reaction mixture was stirred at room temperature with vigorous stirring. After 4 h, the reaction mixture was extracted with CH_2Cl_2 (3 × 1 mL/mmol aniline), dried over $MgSO_4$, and concentrated under reduced pressure. Purification by silica gel column chromatography provided the indicated nitrosobenzene.

*1-Isopropyl-3-nitrosobenzene (**1e**).* The general procedure was followed with 3-isopropyl-benzeneamine (2.7 g, 20 mmol, 1.0 equiv) with purification by silica gel chromatography eluting using hexanes/ether (15:1). The product **1h** (1.3 g, 45% yield) was obtained as an amorphous tan paste. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, J = 7.7 Hz, 1H), 7.73 (s, 1H), 7.59 (d, J = 7.4 Hz, 1H), 7.53 (t, J = 7.6 Hz, 1H), 3.18−2.91 (m, 1H), 1.32 (d, J = 6.9 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.7, 150.6, 134.1, 129.3, 119.3, 118.7, 34.1, 23.9. The analytical data for this compound are consistent with previously reported data.[26]

*1-2-3-Trimethyl-5-nitrosobenzene (**1f**).* The general procedure was followed with 3,4,5-trimethyl-benzeneamine (0.50 g, 3.7 mmol, 1.0 equiv) with purification by silica gel chromatography eluting using hexanes/ether (20:1). The product **1f** (0.14 g, 25% yield) was obtained as a pale blue solid. (mp: 36−39 °C). IR (film) 3082, 2915, 1793, 1590, 1511, 1482, 1415, 1343, 1260, 1092, 965, 901, 747, 701 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (s, 2H), 2.42 (s, 6H), 2.25 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.7, 144.9, 137.7, 120.5, 20.8, 16.6; HRMS (APGC/[M + H]$^+$) calcd. for $C_9H_{12}NO^+$: 150.0913. Found: 150.0920.

*1-Chloro-3-nitrosobenzene (**1h**).* The general procedure was followed with 3-chloro-benzeneamine (3.1 g, 24 mmol, 1.0 equiv) with purification by silica gel chromatography eluting using hexanes/ether (20:1). The product **1h** (2.0 g, 60% yield) was obtained as a white solid (69−73 °C, lit.[27a] 72−73 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, J = 7.8 Hz, 1H), 7.69 (d, J = 8.6 Hz, 1H), 7.66−7.60 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.2, 136.2, 135.1, 130.9, 121.6, 118.9. The analytical data for this compound are consistent with previously reported data.[27b]

*2-Chloro-1-methyl-4-nitrosobenzene (**1i**).* The general procedure was followed with 3-chloro-4-methyl-benzeneamine (3.4 g, 24 mmol, 1.0 equiv) with purification by silica gel chromatography eluting using hexanes/dichloromethane (20:1). The product **1i** (0.74 g, 20% yield) was obtained as a white solid. (mp: 66−68 °C). IR (film) 3089, 2930, 1917, 1580, 1480, 1380, 1249, 1215, 1049, 869, 824, 766, 703, 555 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (dd, J = 8.0, 1.8 Hz, 1H), 7.71 (d, J = 1.8 Hz, 1H), 7.52 (d, J = 8.0 Hz, 1H), 2.47 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.1, 144.8, 136.0, 131.7, 121.1, 120.2, 20.9; HRMS (APGC/[M + H]$^+$) calcd. for $C_7H_7ClNO^+$: 156.0211. Found: 156.0220.

*1-Fluoro-3-nitrosobenzene (**1j**).* The general procedure was followed with 3-fluoro-benzeneamine (2.7 g, 24 mmol, 1.0 equiv) with purification by silica gel chromatography eluting using hexanes/ether (10:1). The product **1j** (2.1 g, 67% yield) was obtained as a white solid. (mp: 52−56 °C) IR (film) 3060, 3039, 1602, 1479, 1446, 1412, 1392, 1234,1144, 1011, 905, 830, 782, 691, 519, 479 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (dt, J = 7.8, 1.0 Hz, 1H), 7.70 (td, J = 8.0, 5.3 Hz, 1H), 7.48−7.40 (m, 1H), 7.16 (dt, J = 8.3, 2.1 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.9 (d, J = 4.7 Hz), 163.3 (d, J = 251.8 Hz), 131.3 (d, J = 7.7 Hz), 122.3 (d, J = 22.4 Hz), 121.2 (d, J = 2.7 Hz), 103.7 (d, J = 22.6 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −106.95 (q, J = 7.6 Hz); HRMS (APGC/[M + H]$^+$) calcd. for $C_6H_5FNO^+$: 126.0350. Found: 126.0356.

*2-Fluoro-1-methyl-4-nitrosobenzene (**1k**).* The general procedure was followed with 3-fluoro-4-methyl-benzeneamine (2.0 g, 16 mmol, 1.0 equiv) with purification by silica gel chromatography eluting using hexanes/ether (20:1). The product **1k** (1.4 g, 63% yield) was obtained as a green oil. IR (neat) 3073, 1593, 1502, 1478, 1400, 1226, 1184, 1065, 879, 821, 784, 745 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (dd, J = 7.9, 1.7 Hz, 1H), 7.52 (t, J = 7.6 Hz, 1H), 7.11 (dd, J = 9.2, 1.7 Hz, 1H), 2.37 (d, J = 2.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.7 (d, J = 4.8 Hz), 161.6 (d, J = 250.6 Hz), 134.1 (d, J = 18.2 Hz), 132.2 (d, J = 4.8 Hz), 121.5, 103.2 (d, J = 23.0 Hz), 15.5 (d, J = 3.5 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −115.82 (ddd, J = 9.6, 7.3, 2.4 Hz); HRMS (APGC/[M + H]$^+$) calcd. for $C_7H_7FNO^+$: 140.0506. Found: 140.0512.

*1-Chloro-2-methoxy-4-nitrosobenzene (**1n**).* The general procedure was followed with 4-chloro-3-methyoxy-benzeneamine (1.0 g, 6.4 mmol, 1.0 equiv) with purification by silica gel chromatography eluting using hexanes/ether (20:1). The product **1n** (0.52 g, 48% yield) was obtained as a pale yellow solid (mp: 115−120 °C). IR (film) 3093, 2935, 1583, 1482, 1281, 1245, 1030, 768, 690 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (dd, J = 8.2, 2.0 Hz, 1H), 7.73 (d, J = 8.2 Hz, 1H), 6.86 (d, J = 1.9 Hz, 1H), 3.97 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.9, 156.0, 131.6, 131.3, 120.7, 98.1, 56.5; HRMS (APGC/[M + H]$^+$) calcd. for $C_7H_7ClNO_2^+$: 172.0160. Found: 172.0163.

*2-Nitrosonaphthalene (**1l**).*[28] In a round-bottom flask positioned in a water bath at ambient temperature, $NOBF_4$ (174 mg, 1.49 mmol, 1.03 equiv) was added in one portion, with vigorous stirring, to a white slurry of potassium naphthalene-2-trifluoroborate (340 mg, 1.45 mmol, 1.00 equiv) in acetonitrile (4.40 mL, 0.330 mL). The reaction mixture immediately turned black and was stirred for 20 s before the addition of H_2O (20 mL) and then CH_2Cl_2 (20 mL). The reaction mixture was extracted with CH_2Cl_2 (3 × 20 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by SiO_2 column chromatography eluting with hexanes/ethyl acetate (4:1) to give **1l** (34.0 mg, 14.9% yield) as a tan solid (mp: 58−63 °C). IR (film) 3089, 3054, 2925, 1596, 1425, 1381, 1347, 868, 814, 751, 566 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.52 (s, 1H), 8.30 (d, J = 8.1 Hz, 1H), 7.90 (d, J = 8.1 Hz, 1H), 7.78 (d, J = 8.9 Hz, 1H), 7.76−7.71 (m, 1H), 7.71−7.66 (m, 1H), 7.01 (dd, J = 8.9, 1.8 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.0, 137.5, 136.7, 133.2, 131.3, 130.7, 129.3, 128.3, 127.9, 108.5; GCMS (EI/[M]$^+$) calcd. for $C_{10}H_6NO^+$: 157.1. Found: 157.1.

General Procedure for the BF_3·Et_2O-Catalyzed 2,1-Benzisoxazole Synthesis. In a flame-dried Schlenk flask equipped with a stir bar, ethyl glyoxylate (90−110 mg, 0.88−1.1 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (0.067 M) under an atmosphere of N_2. To the solution was added BF_3·Et_2O (13−15 mg, 0.088−0.11 mmol, 0.10 equiv), followed by a solution of the indicated nitrosobenzene (1.8−

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2.2 mmol, 2.0 equiv) in CH_2Cl_2 (0.40 M). The Schlenk flask was equipped with a reflux condenser under positive N_2 pressure and placed in a temperature-controlled oil bath set to 45 °C. After 48 h, the flask was removed from the oil bath and cooled to ambient temperature. The mixture was pushed through a plug of SiO_2 with EtOAc and then concentrated under reduced pressure. The crude reaction product was purified via silica gel column chromatography to afford the indicated product.

*Ethyl Benzo[c]isoxazole-3-carboxylate (**3a**).* The general procedure was followed with ethyl glyoxylate (110 mg, 1.08 mmol, 1.00 equiv) and nitrosobenzene (**1a**) (230 mg, 2.16 mmol, 2.00 equiv). Purification via silica gel column chromatography eluting with hexanes:ethyl acetate (4:1) afforded **3a** (165 mg, 79% yield) as a very pale, pink solid (mp: 94−96 °C). IR (film) 3078, 2976, 1731, 1606, 1545, 1476, 1451, 1373, 1310, 1207, 1153, 1105, 1016, 947, 853, 765, 752, 625 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, J = 8.0 Hz, 1H), 7.66 (d, J = 8.2 Hz, 1H), 7.52 (t, J = 7.3 Hz, 1H), 7.45 (t, J = 7.3 Hz, 1H), 4.56 (q, J = 7.1 Hz, 2H), 1.49 (t, J = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.6, 152.9, 151.0, 140.6, 128.2, 125.9, 122.2, 111.8, 63.4, 14.3; HRMS (ESI/$[M + H]^+$) calcd. for $C_{10}H_{10}NO_3^+$: 192.0655. Found: 192.0661.

*Ethyl 5-Methylbenzo[c]isoxazole-3-carboxylate (**3b**).* The general procedure was followed with ethyl glyoxylate (102 mg, 1.00 mmol, 1.00 equiv) and 4-methyl-1-nitrosobenzene (**1b**) (242 mg, 2.00 mmol, 2.00 equiv). Purification via silica gel column chromatography eluting with hexanes:ethyl acetate (8:1) afforded **3b** (154 mg, 75% yield) as a pale pink solid (mp: 81−84 °C). IR (film) 2989, 1729, 1599, 1541, 1371, 1313, 1245, 1218, 1163, 1112, 1022, 857, 814, 780, 605 cm^{-1}; ^1H NMR (400 MHz, CD_2Cl_2) δ 7.73 (d, J = 8.3 Hz, 1H), 7.47 (m, 1H), 7.36−7.21 (m, 1H), 4.49 (q, J = 7.1 Hz, 2H), 2.52 (s, 3H), 1.45 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.7, 152.4, 151.3, 139.2, 138.5, 127.4, 121.5, 111.7, 63.3, 22.2, 14.3; HRMS (ESI/$[M + H]^+$) calcd. for $C_{11}H_{12}NO_3^+$: 206.0812. Found 206.0805.

*Ethyl 5-(tert-Butyl)benzo[c]isoxazole-3-carboxylate (**3c**).* The general procedure was followed with ethyl glyoxylate (102 mg, 1.00 mmol, 1.00 equiv) and 4-*tert*-butyl-1-nitrosobenzene (**1c**) (326 mg, 2.00 mmol, 2.00 equiv). Purification via silica gel column chromatography eluting with hexanes:ethyl acetate (4:1) afforded **3c** (178 mg, 72% yield) as a yellow solid (mp: 45−47 °C). IR (film) 2962, 2909, 2875, 1741, 1621, 1547, 1368, 1302, 1192, 1152, 1112, 1016, 954, 930, 859, 829, 779, 659 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, J = 8.6 Hz, 1H), 7.62 (d, J = 1.6 Hz, 1H), 7.49 (dd, J = 8.6, 1.7 Hz, 1H), 4.51 (q, J = 7.1 Hz, 2H), 1.45 (t, J = 7.2 Hz, 3H), 1.35 (s, 9H); ^{13}C NMR (126 MHz, $(CD_3)_2CO$) δ 157.0, 153.8, 153.3, 152.0, 139.3, 124.6, 121.8, 109.0, 63.3, 36.1, 31.8, 14.4; HRMS (ESI/$[M + H]^+$) calcd. for $C_{14}H_{18}NO_3^+$: 248.1281. Found 248.1255.

*Ethyl 6-Methylbenzo[c]isoxazole-3-carboxylate (**3d**).* The general procedure was followed with ethyl glyoxylate (110 mg, 1.08 mmol, 1.00 equiv) and 1-methyl-3-nitrosobenzene (**1d**) (260 mg, 2.16 mmol, 2.00 equiv). Purification via silica gel column chromatography eluting with hexanes:ethyl acetate (4:1) afforded **3d** and **3d′** (150 mg, 67% yield) as an inseparable mixture of two regioisomers in a ratio of 2.6:1 as a pale yellow solid. IR (film) 2994, 2914, 1730, 1606, 1545, 1475, 1375, 1343, 1309, 1298, 1208, 1157, 1113, 1014, 952, 854, 809, 781, 758, 635 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) *major regioisomer* δ 7.65 (s, 1H), 7.53 (d, J = 8.5 Hz, 1H), 7.33 (d, J = 8.5 Hz, 1H), 4.55 (q, J = 7.1 Hz, 2H), 2.50 (s, 3H), 1.49 (t, J = 7.2 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) *major regioisomer* δ 156.7, 152.9, 149.3, 140.8, 136.0, 129.7, 121.8, 111.2, 63.4, 21.7, 14.4; HRMS (ESI/$[M + H]^+$) calcd. for $C_{11}H_{12}NO_3^+$: 206.0812. Found 206.0803.

*Ethyl 6-Isopropylbenzo[c]isoxazole-3-carboxylate (**3e**).* The general procedure was followed with ethyl glyoxylate (110 mg, 1.08 mmol, 1.00 equiv) and 1-isopropyl-3-nitrosobenzene (**1e**) (321 mg, 2.16 mmol, 2.00 equiv). Purification via silica gel column chromatography eluting with hexanes:ethyl acetate (4:1) afforded **3e** and **3e′** (211 mg, 84% yield) as an inseparable mixture of two regioisomers in a ratio of 4:1 as a red solid. IR (film) 2973, 2953, 2869, 1738, 1606, 1553, 1461, 1367, 1294, 1228, 1154, 1108, 1016, 957, 853, 802, 658 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *major regioisomer* δ 7.69 (d, J = 1.3 Hz, 1H), 7.54 (d, J = 8.6 Hz, 1H), 7.41−7.37 (m, 2H), 4.53 (q, J = 7.2 Hz, 2H), 3.04 (p, J = 6.9 Hz, 1H), 1.47 (t, J = 7.1 Hz, 3H), 1.29 (d, J = 6.9 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) *major regioisomer* δ 156.7, 152.9, 149.4, 147.2, 140.8, 127.4, 119.1, 111.3, 63.3, 34.3, 24.4, 14.3; HRMS (ESI/$[M + H]^+$) calcd. for $C_{13}H_{16}NO_3^+$: 234.1125. Found 234.1146.

*Ethyl 4,5,6-Trimethylbenzo[c]isoxazole-3-carboxylate (**3f**).* The general procedure was followed with ethyl glyoxylate (95.0 mg, 0.931 mmol, 1.00 equiv) and 1,2,3-trimethyl-5-nitrosobenzene (**1f**) (278 mg, 1.86 mmol, 2.00 equiv). Purification via silica gel column chromatography eluting with hexanes:ethyl acetate (8:1) afforded **3f** (98 mg, 44% yield) as a white solid (mp: 119−123 °C). IR (film) 2982, 1726, 1537, 1373, 1287, 1231, 1197, 1157, 1027, 881, 857, 781, 652, 627 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.48 (s, 1H), 4.53 (q, J = 7.1 Hz, 2H), 2.51 (s, 3H), 2.39 (s, 3H), 2.30 (s, 3H), 1.48 (t, J = 7.1 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 157.0, 152.1, 149.6, 137.7, 136.3, 135.1, 120.0, 119.2, 63.2, 21.5, 15.9, 14.4, 13.0; HRMS (ESI/$[M + H]^+$) calcd. for $C_{13}H_{16}NO_3^+$: 234.1125. Found 234.1109.

*Ethyl 4,6-Dimethylbenzo[c]isoxazole-3-carboxylate (**3g**).* The general procedure was followed with ethyl glyoxylate (95.0 mg, 0.931 mmol, 1.00 equiv) and 1,3-dimethyl-5-nitrosobenzene (**1g**) (251 mg, 1.86 mmol, 2.00 equiv). Purification via silica gel column chromatography eluting with hexanes:ethyl acetate (4:1) afforded **3g** (66 mg, 32% yield) as an off-white solid (mp: 78−80 °C). IR (film) 2925, 1729, 1625, 1547, 1446, 1368, 1307, 1290, 1212, 1155, 1129, 1111, 1024, 958, 848, 637 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (s, 1H), 7.12 (s, 1H), 4.54 (q, J = 7.1 Hz, 2H), 2.54 (s, 3H), 2.44 (s, 3H), 1.48 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.9, 152.8, 148.8, 140.5, 135.9, 130.6, 121.8, 119.0, 63.2, 21.6, 15.3, 14.4; HRMS (ESI/$[M + H]^+$) calcd. for $C_{12}H_{14}NO_3^+$: 220.0968. Found 220.0953.

*Ethyl Chlorobenzo[c]isoxazole-3-carboxylates (**3h** and **3h′**).* The general procedure was followed with ethyl glyoxylate (110 mg, 1.08 mmol, 1.00 equiv) and 1-chloro-3-nitrosobenzene (**1h**) (304 mg, 2.16 mmol, 2.00 equiv). Purification via silica gel column chromatography eluting with hexanes:ethyl acetate (5:1) afforded **3h** (129 mg, 52% yield) as a tan solid and **3h′** (40.3 mg, 16% yield) as an off-white solid. *Characterization for ethyl 6-chlorobenzo[c]isoxazole-3-carboxylate* (**3h**, *major*): (mp: 79−80 °C). IR (film) 3067, 2984, 1734, 1601, 1546, 1472, 1449, 1371, 1305, 1210, 1159, 1113, 1053, 1012, 921, 852, 828, 704, 636 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, J = 2.0 Hz, 1H), 7.60 (d, J = 8.8 Hz, 1H), 7.50 (dd, J = 8.8, 2.1 Hz, 1H), 4.56 (q, J = 7.1 Hz, 2H), 1.49 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.3, 154.0, 149.5, 141.6, 131.6, 128.84, 122.03, 112.74, 63.66, 14.30; HRMS (ESI/$[M + H]^+$) calcd. for $C_{10}H_9ClNO_3^+$: 226.0265. Found 226.0285. *Characterization for ethyl 4-chlorobenzo[c]isoxazole-3-carboxylate* (**3h′**, *minor*): (mp: 84−86 °C). IR (film) 3003, 1742, 1610, 1549, 1471, 1444, 1375, 1310, 1252, 1197, 1140, 1109, 1018, 963, 854, 787, 734, 634 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.79 (d, J = 8.1 Hz, 1H), 7.52 (d, J = 7.9 Hz, 1H), 7.40 (t, J = 8.0 Hz, 1H), 4.57 (q, J = 7.1 Hz, 2H), 1.50 (t, J = 7.1 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 156.1, 153.2, 147.7, 141.7, 128.4, 126.6, 120.7, 117.2, 63.7, 14.3; HRMS (ESI/$[M + H]^+$) calcd. for $C_{10}H_9ClNO_3^+$: 226.0265. Found 226.0294.

*Ethyl Chloro-5-methylbenzo[c]isoxazole-3-carboxylate (**3i** and **3i′**).* The general procedure was followed with ethyl glyoxylate (102 mg, 1.00 mmol, 1.00 equiv) and 2-chloro-1-methyl-4-nitrosobenzene (**1i**) (310 mg, 2.00 mmol, 2.00 equiv). Purification via silica gel column chromatography eluting with hexanes:ethyl acetate (5:1) afforded **3i** (121 mg, 51% yield) as a pale pink solid and **3i′** (68 mg, 28% yield) as a pale orange solid. *Characterization for ethyl 4-chloro-5-methylbenzo[c]isoxazole-3-carboxylate* (**3i**, *major*): (mp: 110−115 °C). IR (film) 3071, 2997, 1737, 1595, 1544, 1448, 1370, 1297, 1247, 1158, 1109, 1007, 950, 851, 781, 691, 650, 626, 509 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.52 (s, 1H), 4.55 (q, J = 7.2 Hz, 2H), 2.52 (s, 3H), 1.48 (t, J = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.4, 153.4, 149.8, 139.7, 137.2, 132.2, 121.9, 113.0, 63.5, 21.4, 14.3; HRMS (ESI/$[M + H]^+$) calcd. for $C_{11}H_{11}ClNO_3^+$: 240.0422. Found 240.0414. *Characterization for ethyl 6-chloro-5-methylbenzo[c]isoxazole-3-carboxylate* (**3i′**, *minor*): (mp: 85−86 °C). IR (film) 3086, 2994, 2943, 1744, 1592, 1551, 1479, 1365, 1330, 1297, 1246, 1202, 1135, 1107, 1030, 943, 854, 809, 633, 599 cm^{-1}; ^1H NMR (600 MHz,

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$CDCl_3$) δ 7.66 (d, J = 8.2 Hz, 1H), 7.33 (d, J = 8.2 Hz, 1H), 4.56 (q, J = 7.1 Hz, 2H), 2.54 (s, 3H), 1.49 (t, J = 7.2 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 156.2, 152.8, 148.2, 139.6, 136.9, 128.5, 119.7, 116.6, 63.5, 19.7, 14.3; HRMS (ESI/[M + H]$^+$) calcd. for $C_{11}H_{11}ClNO_3^+$: 240.0422. Found 240.0395.

*Ethyl 6-Fluorobenzo[c]isoxazole-3-carboxylate (**3j** and **3j′**).* The general procedure was followed with ethyl glyoxylate (102 mg, 1.00 mmol, 1.00 equiv) and 1-fluoro-3-nitrosobenzene (**1j**) (150 mg, 2.00 mmol, 2.00 equiv). Purification via silica gel column chromatography eluting with hexanes:ethyl acetate (4:1) afforded **3j** and **3j′** (80 mg, 38% yield) as an inseparable mixture of two regioisomers in a ratio of 14:1 as a pale yellow solid. IR (film) 3074, 2922, 2852, 1734, 1608, 1553, 1473, 1448, 1437, 1369, 1346, 1302, 1262, 1221, 1148, 1114, 1016, 962, 884, 854, 808, 779, 637, 512 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6) *major regioisomer* δ 7.25 (dd, J = 8.1, 2.6 Hz, 1H), 6.76 (dd, J = 9.0, 4.3 Hz, 1H), 6.62 (td, J = 9.1, 2.6 Hz, 1H), 4.01 (q, J = 7.1 Hz, 2H), 0.93 (t, J = 7.1 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) *major regioisomer* δ 160.7 (d, J = 243.5 Hz), 156.3, 154.4, 147.4 (d, J = 1.0 Hz), 141.4 (d, J = 13.3 Hz), 116.7 (d, J = 26.8 Hz), 112.5 (d, J = 10.0 Hz), 108.2 (d, J = 25.4 Hz), 63.6, 14.30; ^{19}F NMR (376 MHz, $CDCl_3$) δ −116.16 (td, J = 8.5, 4.1 Hz); HRMS (ESI/[M + H]$^+$) calcd. for $C_{10}H_9FNO_3^+$: 210.0561. Found 210.0569.

*Ethyl Fluoro-5-methylbenzo[c]isoxazole-3-carboxylate (**3k** and **3k′**).* The general procedure was followed with ethyl glyoxylate (110 mg, 1.08 mmol, 1.00 equiv) and 2-fluoro-1-methyl-4-nitrosobenzene (**1k**) (300 mg, 2.16 mmol, 2.00 equiv). Purification via silica gel column chromatography eluting with hexanes:ethyl acetate (8:1) afforded **3k** (182 mg, 73% yield) as a pale pink solid and **3k′** (5 mg, 2% yield) as an orange solid. *Characterization for ethyl 6-fluoro-5-methylbenzo[c]isoxazole-3-carboxylate* (**3k**, *major*): (mp: 100−104 °C). IR (film) 3036, 2925, 1731, 1601, 1546, 1460, 1375, 1318, 1280, 1215, 1143, 1098, 1026, 1006, 865, 782, 631, 512 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (d, J = 8.8 Hz, 1H), 7.46 (d, J = 6.1 Hz, 1H), 4.55 (q, J = 7.1 Hz, 2H), 2.44 (d, J = 2.3 Hz, 3H), 1.49 (t, J = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.5 (d, J = 242.9 Hz), 156.4, 153.7, 147.4, 139.3 (d, J = 13.5 Hz), 127.4 (d, J = 21.7 Hz), 113.0 (d, J = 5.8 Hz), 107.4 (d, J = 26.7 Hz), 63.4, 15.9 (d, J = 4.5 Hz), 14.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ −118.88 (tt, J = 6.0, 2.6 Hz); HRMS (ESI/[M + H]$^+$) calcd. for $C_{11}H_{11}FNO_3^+$: 224.0717. Found 224.0690. *Characterization for ethyl 4-fluoro-5-methylbenzo[c]isoxazole-3-carboxylate* (**3k′**, *minor*): (mp: 95−98 °C). IR (film) 2926, 1739, 1602, 1561, 1506, 1469, 1369, 1306, 1256, 1232, 1171, 1076, 1012, 954, 819, 777, 693, 607, 540 cm^{-1}; ^{1}H NMR (600 MHz, C_6D_6) δ 7.24 (d, J = 8.2 Hz, 1H), 6.58 (t, J = 7.3 Hz, 1H), 4.00 (q, J = 7.1 Hz, 1H), 1.95 (s, 1H), 0.92 (t, J = 7.2 Hz, 2H); ^{13}C NMR (151 MHz, CD_2Cl_2) δ 156.5 (s), 153.3 (s), 145.9 (d, J = 251.1 Hz), 142.1 (d, J = 1.0 Hz), 139.1 (d, J = 12.0 Hz), 129.0 (d, J = 3.1 Hz), 125.4 (d, J = 12.5 Hz), 117.4 (d, J = 4.8 Hz), 63.8 (s), 14.8 (d, J = 3.2 Hz), 14.5 (s); ^{19}F NMR (376 MHz, C_6D_6) δ −138.26 (dq, J = 6.8, 2.3 Hz); HRMS (ESI/[M + H]$^+$) calcd. for $C_{11}H_{11}FNO_3^+$: 224.0717. Found 224.0746.

*Ethyl Naphtho[2,1-c]isoxazole-1-carboxylate (**3l**).* The general procedure was followed with ethyl glyoxylate (90.0 mg, 0.882 mmol, 1.00 equiv) and 2-nitroso-naphthalene (**1l**) (276 mg, 1.76 mmol, 2.00 equiv). Purification via silica gel column chromatography eluting with hexanes:ethyl acetate (5:1) afforded **3l** (79 mg, 37% yield) as a red solid (mp: 90−92 °C). IR (film) 3055, 2976, 2909, 1729, 1654, 1582, 1537, 1374, 1322, 1247, 1204, 1145, 1023, 815, 754, 636, 561 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 (d, J = 8.2 Hz, 1H), 7.99 (d, J = 8.1 Hz, 1H), 7.87 (d, J = 8.8 Hz, 1H), 7.85 (d, J = 8.8 Hz, 1H), 7.68 (m, 1H), 7.63 (m, 1H), 4.59 (q, J = 7.2 Hz, 2H), 1.52 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.6, 152.3, 147.7, 137.5, 133.2, 128.9, 127.6, 127.4, 127.1, 121.2, 120.5, 119.4, 63.3, 14.4; HRMS (ESI/[M + H]$^+$) calcd. for $C_{14}H_{12}NO_3^+$: 242.0812. Found 242.0787.

*Ethyl 6-Methoxybenzo[c]isoxazole-3-carboxylate (**3m**).* The general procedure was followed with ethyl glyoxylate (102 mg, 1.00 mmol, 1.00 equiv) and 1-methoxy-3-nitrosobenzene (**1m**) (274 mg, 2.00 mmol, 2.00 equiv). Purification via silica gel column chromatography eluting with hexanes:ethyl acetate (2:1) afforded **3m** (115 mg, 52% yield) as a pale pink solid (mp: 80−83 °C). IR (film) 2978, 2944, 2843, 1733, 1608, 1550, 1485, 1434, 1366, 1311, 1257, 12222, 1151, 1105, 1022, 959, 850, 803, 779, 643, 554, 529 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (d, J = 9.0 Hz, 1H), 7.29 (d, J = 2.5 Hz, 1H), 7.12 (dd, J = 9.0, 2.6 Hz, 1H), 4.54 (q, J = 7.2 Hz, 2H), 3.87 (s, 3H), 1.49 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.3, 156.6, 153.5, 145.8, 141.6, 118.2, 112.1, 103.7, 63.3, 56.1, 14.3; HRMS (ESI/[M + H]$^+$) calcd. for $C_{11}H_{12}NO_4^+$: 222.0761. Found 222.0751.

*Ethyl 5-Chloro-6-methoxybenzo[c]isoxazole-3-carboxylate (**3n**).* The general procedure was followed with ethyl glyoxylate (102 mg, 1.00 mmol, 1.00 equiv) and 1-chloro-2-methoxy-4-nitrosobenzene (**1n**) (342 mg, 2.00 mmol, 2.00 equiv). Purification via silica gel column chromatography eluting with hexanes:ethyl acetate (4:1) afforded **3n** (114 mg, 45% yield) as a tan solid (mp: 115−120 °C). IR (film) 3101, 3077, 2970, 2951, 1733, 1603, 1544, 1469, 1437, 1375, 1320, 1278, 1226, 1149, 1042, 1018, 991, 954, 863, 837, 779, 694, 627, 546 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.34 (s, 1H), 4.55 (q, J = 7.1 Hz, 2H), 3.97 (s, 3H), 1.49 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.2, 154.1, 153.6, 144.9, 140.0, 124.7, 113.2, 103.3, 63.4, 56.9, 14.3; HRMS (ESI/[M + H]$^+$) calcd. for $C_{11}H_{11}ClNO_4^+$: 256.0371. Found 256.0378.

^{18}O Labeling Studies. *Synthesis of 1-(tert-Butyl)-4-(nitroso)-benzene (^{18}O) (**4**).*[8] In an oven-dried one dram vial with a Teflon cap, cooled to room temperature in a desiccator, diphenyldiselenide (0.97 mg, 3.1 μmol, 0.10 equiv) and 4-(*tert*-butyl)aniline (5.0 μL, 31 μmol, 1.0 equiv) were dissolved in $CHCl_3$ (100 μL, 0.31 M). Finally, a 2.5% aqueous solution of ^{18}O-labeled hydrogen peroxide[9] (100 mg, 65.8 μmol, 2.10 equiv) was added, and the reaction mixture was stirred vigorously in a water bath at ambient temperature under an atmosphere of air for 5 h. The reaction mixture was extracted with $CHCl_3$ (3 × 0.5 mL) and concentrated under reduced pressure. The crude mixture was purified via SiO_2 column chromatography, eluting with hexanes/dichloromethane (4:1) to give 1-(*tert*-butyl)-4-nitrosobenzene-(^{18}O) (**4**) as a yellow-green oil (0.5 mg, 10% yield). GCMS (EI/[M]$^+$) calcd. for $C_{10}H_{13}N^{18}O^+$: 165.1. Found: 165.1.

BF_3·Et_2O-Catalyzed Reaction with 1-(tert-Butyl)-4-(nitroso)-benzene (^{18}O) (eq 1). In a N_2-filled glovebox, a solution of ethyl glyoxylate (**2a**) in CH_2Cl_2 (0.025 M, 59 μL, 1.5 μmol, 1.0 equiv) was added to 1-(*tert*-butyl)-3-(nitroso)benzene-^{18}O (**4**) (0.50 mg, 2.9 μmol, 2.0 equiv) in an oven-dried one dram vial with a Teflon cap. To the reaction mixure was added BF_3·Et_2O (0.02 μL, 0.2 μmol, 0.1 equiv). The vial was capped tighly, removed from the glovebox, and placed into a temperature-controlled oil bath set to 40 °C with stirring for 48 h. The reaction solution was cooled to ambient temperature, pushed through a SiO_2 plug with ethyl acetate, and concentrated under reduced pressure. A reaction yield was determined by GC using tetradecane as an external standard (14%). The crude reaction mixture was purified by prep-TLC with hexanes/ethyl acetate (3:1), and product was collected as a fluorescent band at R_f 0.68. LCMS (ESI/[M + H]$^+$) calcd. for $C_{14}H_{18}NO_2{}^{18}O^+$: 250.1324. Found: 250.1253.

*Ethyl 2-(Oxo-^{18}O)acetate (**6**).* In a flame-dried 5 mL Schlenk flask under positive N_2 pressure, ethyl glyoxylate (**2a**) (52.5 mg, 0.514 mmol, 1.00 equiv) was dissolved in $H_2{}^{18}O$ (262 mg, 13.1 mmol, 25.5 equiv).[29] The solution was stirred in an ambient temperature water bath under N_2 for 12 h. After 12 h, the mixture was frozen with liquid N_2 and then placed onto the lyophilizer to remove water. Ethyl 1-(oxo-^{18}O)acetate (**6**) was recovered after lyophilization for 4 h (20 mg, 38% yield).

*Trapping of **6** To Give Ethyl 2-(Hydroxyl)pent-4-enoate-2-^{18}O (**7**) (eq 2).*[11] In the same flame-dried 5 mL Schlenk flask used for the preparation of **6**, under positive N_2 pressure, ^{18}O-ethyl glyoxyate (**6**) (18 mg, 0.17 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (0.86 mL, 0.20 M). Allyltrimethylsilane (60 μL, 0.35 mmol, 2.0 equiv) was added to the solution, which was then cooled to 0 °C. BF_3·Et_2O (40 μL, 0.35 mmol, 2.0 equiv) was added dropwise over 15 min. The reaction mixture was stirred at 0 °C for 15 min before warming slowly to ambient temperature and stirring for an additional 2 h in an ambient temperature water bath. The reaction was quenched with a saturated solution of NH_4Cl (1.2 mL), extracted with CH_2Cl_2 (3× 1.5 mL), washed with brine (3× 1.5 mL), dried over Na_2SO_4, filtered, and

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concentrated under reduced pressure to give **7** as a pale yellow oil (20.2 mg, 80%). LCMS (ESI/$[M + H]^+$) calcd. for $C_7H_{13}O_2{}^{18}O^+$: 147.0902. Found: 147.0956.

*$BF_3{\cdot}Et_2O$-Catalyzed Reaction with Ethyl 2-(Oxo-^{18}O)acetate (**3a**) (eq 3).* In a flame-dried 10 mL Schlenk flask under positive N_2 pressure, ^{18}O-ethyl glyoxylate (**6**) (20 mg, 0.20 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (3 mL). A solution of nitrosobenzene (**1a**) (43 mg, 0.40 mmol, 1.0 equiv) in CH_2Cl_2 (1 mL) was added to the reaction mixture, followed by $BF_3{\cdot}Et_2O$ (2.8 μL, 0.020 mmol, 0.10 equiv). The Schlenk flask was fitted with a reflux condenser under positive N_2 pressure and placed in a temperature-controlled oil bath set to 45 °C. After stirring at a gentle reflux for 48 h, the reaction mixture was cooled to ambient temperature, pushed through a SiO_2 plug with ethyl acetate, and concentrated under reduced pressure. The crude mixture was purified via SiO_2 column chromatography eluting with hexanes/ethyl acetate (4:1) to give a pale pink solid (34 mg, 88% yield). LCMS (ESI/$[M + H]^+$) cacld. for $C_{10}H_{10}NO_3{}^+$: 192.0655. Found: 192.0873.

Preparation of *N*-Boc-*O*-acylphenylhydroxylamine and Conversion to 2,1-Benzisoxazole. *Ethyl 2-(((tert-Butoxycarbonyl)-(phenyl)amino)oxy)-2-oxoacetate (**13**).* In a flame-dried round-bottom flask, *N*-Boc-phenylhydroxylamine[30] (1.0 g, 4.8 mmol, 1.0 equiv) was dissolved in THF (50 mL, 0.10 M) under a N_2 atmosphere and cooled to 0 °C. Triethylamine (1.3 mL, 9.6 mmol, 2.0 equiv) was added dropwise, and the reaction mixture was stirred at 0 °C for 15 min before dropwise addition of ethyl oxalyl chloride (1.2 mL, 5.7 mmol, 1.2 equiv). A white gas evolved, and the reaction mixture warmed slowly to rt over 1.5 h. After stirring for an additional 6 h in a rt water bath, the reaction mixture was diluted with ether (20 mL) and washed with saturated $NaHCO_3$ (2 × 25 mL), water (2 × 25 mL), and brine (2 × 25 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give a yellow oil (1.43 g, 97%). IR (neat) 2981, 2939, 1803, 1750, 1730, 1596, 1492, 1346, 1300, 1157, 1094, 1004, 852, 747, 692 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, J = 7.7 Hz, 2H), 7.38 (t, J = 7.9 Hz, 2H), 7.29 (t, J = 7.3 Hz, 1H), 4.40 (q, J = 7.1 Hz, 2H), 1.50 (s, 9H), 1.39 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.3, 152.1, 139.8, 129.1, 128.0, 124.8, 121.1, 84.3, 63.9, 28.1, 14.0; LRMS (ESI/$[M + H]^+$) calcd. for $C_{16}H_{19}NO_6{}^+$: 310.1. Found: 310.1.

*Deprotection of N-Boc-O-acylphenylhydroxylamine To Give **3a** (eq 4).* In a flame-dried round-bottom flask, **13** (124 mg, 0.400 mmol, 1.00 equiv) was dissolved in CH_2Cl_2 (12 mL, 0.030 M) with 3 Å MS and cooled to 0 °C under N_2. TFA (0.80 mL, 10 mmol, 26 equiv) was added dropwise with stirring at 0 °C, and the reaction mixture slowly warmed to rt over 1.5 h. After stirring for an additional 6.5 h in a rt water bath, the crude reaction mixture was washed with water (2 × 20 mL) and brine (2 × 20 mL), dried over Na_2SO_4, and concentrated. The crude mixture was purified by SiO_2 column chromatography eluting with hexanes/ethyl acetate (4:1) to give **3a** as a white solid (32 mg, 42%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, J = 8.0 Hz, 1H), 7.67 (d, J = 8.3 Hz, 1H), 7.53 (t, J = 7.8 Hz, 1H), 7.46 (t, J = 7.7 Hz, 1H), 4.56 (q, J = 7.1 Hz, 2H), 1.50 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.6, 152.9, 151.0, 140.7, 128.3, 125.9, 122.3, 111.9, 63.4, 14.3.

■ ASSOCIATED CONTENT

Supporting Information

Spectral data for all compounds shown in Table 2 and LCMS traces for the labeling studies described in eqs 1−3. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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