

Exploring the Reactivity of 2-Trichloromethylbenzoxazoles for Access to Substituted Benzoxazoles

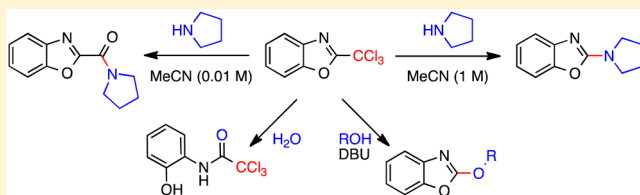
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Supporting Information

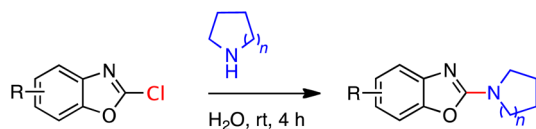
ABSTRACT: The reactivity of 2-trichloromethylbenzoxazoles toward various nucleophiles, under metal-free or iron-catalyzed conditions, for the synthesis of substituted benzoxazoles is described. These methods allow for selective substitution at either the 2- or 2'-position of the benzoxazoles using the same starting materials/reagents. This approach allows for the controlled synthesis of a variety of key derivatives from a single 2-trichloromethylbenzoxazole starting material.



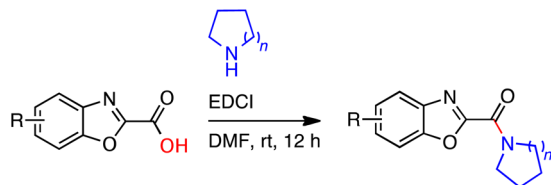
The benzoxazole motif has been incorporated into a number of pharmaceuticals, agrochemicals, and materials that are vital to our everyday lives.¹ Because of the importance of benzoxazoles, widespread research has been conducted on their synthesis² and subsequent functionalization.³ The selective synthesis of 2-amino- or 2-amidobenzoxazoles from both activated substrates^{4,5} and via C–H^{6,7} activation has been extensively developed (Scheme 1a,b).^{4a,5b} Because of the nature

Scheme 1. Methods of Benzoxazole Functionalization

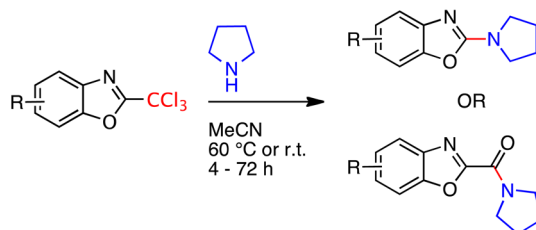
Metal free synthesis of 2-aminobenzoxazoles (a)^{4a}



Metal free synthesis of 2-amidobenzoxazoles (b)^{5b}



This Work - Selective synthesis of 2-amino- or 2-amidobenzoxazoles from 2-trichloromethylbenzoxazoles (c)

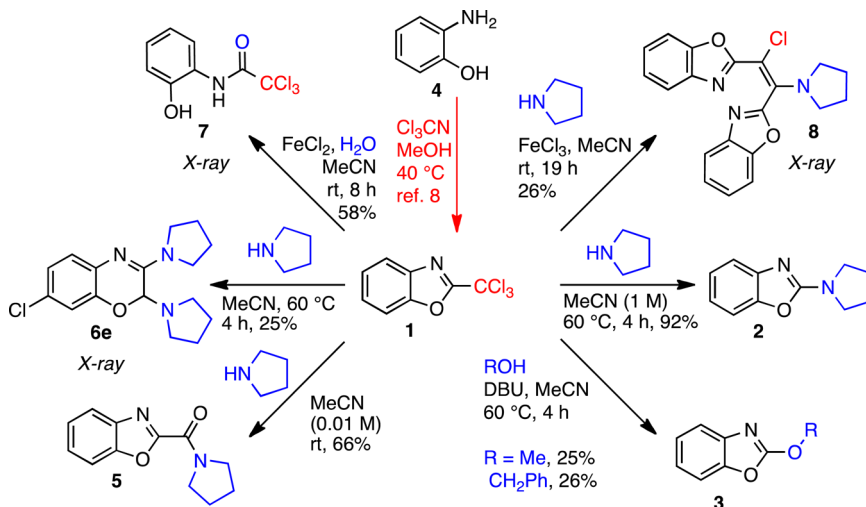


of the methods used for their synthesis, either 2-amino- or 2-amidobenzoxazoles can be accessed, but generally not both, from the same starting materials using the same reagents. Additionally, to mitigate the negative environmental and cost implication of noble metal catalysts, there has been a recent push to develop metal-free or base metal-catalyzed methods.^{8,9} Thus, an opportunity exists to develop selective synthetic methods for the derivatization of this important scaffold. Previously, we showed that 2-trichloromethylbenzoxazoles 1 could be synthesized via a mild metal-free reaction between trichloroacetonitrile¹⁰ and 2-aminophenols 4 in methanol at 40 °C (see Scheme 2).^{11,12} Although the reactivity of some 2-trichloromethylazoles has been investigated,¹³ little work on the reactivity of 2-trichloromethylbenzoxazoles has been reported.¹⁴ Herein, we report our findings into controlling the reactivity of 2-trichloromethylbenzoxazoles for the selective synthesis of 2-amino- or 2-amidobenzoxazoles as well as other derivatives in which the carbon of the trichloromethyl moiety is either extruded or retained (Scheme 1c).

Because of the importance of 2-aminobenzoxazoles, the study began with the direct displacement of the 2-trichloromethyl moiety from 2-(trichloromethyl)benzo[d]oxazole 1 with an amine nucleophile.¹⁵ Initial reactions resulted in a mixture of 2-amino- and 2-amidobenzoxazoles. After screening a variety of Lewis acids, which were hoped to activate the C-2 position toward nucleophilic aromatic substitution, as well as solvents, temperatures, and times, it was found that the key parameters for controlling the product distribution between amine 2 and amide 5 were the molarity of the system and water content.¹⁶ Thus, reaction of 2-trichloromethylbenzoxazole 1 with pyrrolidine (1.1 equiv) in dry acetonitrile (1 M relative to the benzoxazole) at 60 °C for 4 h afforded the desired 2-(pyrrolidin-1-yl)benzo[d]oxazole (2) in excellent yield. The

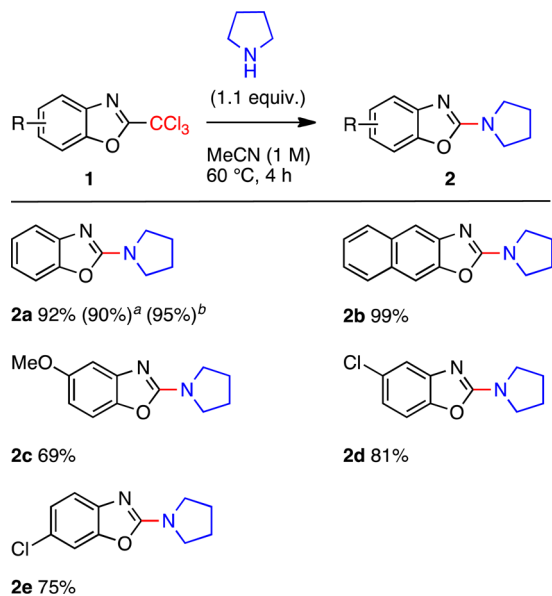
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Scheme 2. DOS Approach to the Functionalization of 2-(Trichloromethyl)benzo[d]oxazole (1)



reaction could also be run at rt, though it required 13 h to go to completion, or in the presence of the nucleophilic catalysts DABCO,¹⁷ which led to slightly improved yields (see Scheme 3). Interestingly, on the basis of the pK_a values, the reaction

Scheme 3. Addition of Pyrrolidine to Substituted 2-Trichloromethylbenzoxazoles



^aAt rt for 13 h. ^bWith DABCO (10 mol %) at 60 °C for 4 h.

should not proceed (see Scheme S1).¹⁸ It is believed that the liberated chloroform decomposes under the reaction conditions to form a reactive carbene intermediate, which then decomposes and thus shifts the reaction equilibrium toward the 2-amino product 2.¹⁹

Building upon the selective C-2 substitution of an amine nucleophile, the addition of an alkoxide,²⁰ generated in situ, to the 2-position of the trichloromethylbenzoxazole was investigated. It was found that methanol and benzyl alcohol could add effectively to 2-(trichloromethyl)benzo[d]oxazole (1) in the presence of DBU in acetonitrile to form either 2-methoxybenzo[d]oxazole (3a) or 2-(benzyloxy)benzo[d]oxazole (3b), albeit in moderate yields. It was previously

reported that strong bases can be used in the addition of alcohols to related trichloromethylazoles.¹³ Unfortunately, these conditions did not lead to an improved yield of the desired addition adducts.

Having established methods for the direct C-2 substitution of 2-trichloromethylbenzoxazoles, the selective C-2' substitution processes were investigated.²¹ After screening a variety of conditions,¹⁶ it was found that reaction of 2-(trichloromethyl)benzo[d]oxazole (1) with pyrrolidine (0.9 equiv) in wet acetonitrile (0.01 M, relative to the benzoxazole) at rt for 76 h afforded the desired benzo[d]oxazol-2-yl(pyrrolidin-1-yl)methanone (5) in 66% yield. Reducing the reaction time to 19 h gave the product in 35% yield. These mild conditions are in contrast to related amide forming processes from heterocyclic trichloromethyl groups that use strong bases, high reaction temperatures, or toxic solvents to achieve similar transformations.²⁰ They therefore should be particularly applicable to substrates that are base or thermally unstable. It was also possible to reduce the reaction time via the addition of FeCl₃ (1.0 equiv), which resulted in the formation of benzo[d]oxazol-2-yl(pyrrolidin-1-yl)methanone (5) after 19 h in 57% yield.

As part of a substrate scope study (vide infra), it was found that the reaction of 2-(trichloromethyl)benzo[d]oxazole (1) with pyrrolidine (1.1 equiv) in acetonitrile (1 M relative to the pyrrolidine) at 60 °C for 4 h afforded 7-chloro-2,3-di(pyrrolidin-1-yl)-2H-benzo[b][1,4]oxazine (6e), the structure of which was confirmed by X-ray analysis.²² Gauß and Heitzer previously reported a related ring expansion process, though they started from 2-dichloromethylbenzoxazoles rather than 2-trichloromethylbenzoxazole 1.²³ Also, Molinski et al. found that 2-substituted oxazolines could be converted to dihydrooxazinones in the presence of SeO₂.²⁴ Interestingly, compound 6e could only be formed if a reduction was taking place under the reaction conditions, though at which point in the process the reduction is taking place is unclear. In related work, it was also shown that 2-dichloromethylbenzoxazoles can undergo hydrogen/deuterium exchange in the presence of triethylamine.

Furthermore, hydrolysis of 2-trichloromethylbenzoxazole 1 was examined (Scheme 2). It was found that upon treatment of 2-(trichloromethyl)benzo[d]oxazole (1) with FeCl₃ (2 mol %) and H₂O (2.5 equiv)²⁵ that ring-opened 2,2,2-trichloro-N-(2-

hydroxyphenyl) acetamide (7) was formed in good yield. The connectivity of acetamide 7 was confirmed by X-ray analysis.²² Acetamide 7 and related analogues have previously been shown to have germination inhibition activity against lettuce seeds.²⁶ A screen of hydrolysis conditions was undertaken to investigate this process further. It was found that the best nonmetal-containing process for the hydrolysis was to heat 2-trichloromethylbenzoxazole 1 in H₂O at 150 °C for 2 h. This method gave the desired 2,2,2-trichloro-*N*-(2-hydroxyphenyl) acetamide (7) in a moderate 37% yield.²²

In efforts to optimize the addition reactions and control the C-2 vs C-2' selectivity, a variety of Lewis acids were screened.²² During the course of this study, it was found that the reaction of 2-trichloromethylbenzoxazole (1) with pyrrolidine (1.1 equiv) in the presence of FeCl₃ afforded bisbenzoxazole 8 in moderate yield. The structure of this novel compound was confirmed by 2D NMR analysis and X-ray crystallography.²²

With the optimized conditions in hand for the synthesis of 2-aminobenzoxazoles, the effect of substitution on the benzoxazole ring was investigated to assess the effect of electronic factors on the formation of 2-aminobenzoxazoles 2 from 2-trichloromethylbenzoxazoles 1 (Scheme 3). Thus, reaction of 2-(trichloromethyl)benzo[d]oxazole (1a) with pyrrolidine (1.1 equiv) at either 60 °C or rt afforded 2-(pyrrolidin-1-yl)benzo[d]oxazole (2a) in excellent yield. The addition of the nucleophilic catalyst DABCO (10 mol %) led to a slight increase in the yield of 2-aminobenzoxazole 2a.¹⁷ The annulation of an aromatic ring to the starting material led to an increased yield of 2-(pyrrolidin-1-yl)naphtho[2,3-*d*]oxazole (2b). Interestingly, having an electron-rich methoxy moiety in the system resulted in a decrease in yield of 2c relative to that of the electron-deficient 5- and 6-chloro derivatives 2d and 2e. As mentioned previously, the mass balance in the reaction of the chloro-substituted benzoxazoles 1d/1e are the ring-opened species 6d/6e (see Scheme 2).

In conclusion, an investigation into the reactivity of 2-trichloromethylbenzoxazole toward various nucleophiles under metal-free or iron-catalyzed conditions was conducted. The newly developed methods allow for the controlled synthesis of a variety of benzoxazole derivatives starting from the same starting material. Importantly, these methods allow for substitution at either the 2- or 2'- position of the benzoxazoles by simply altering the reactant concentration and water content. Thus, a variety of derivatives can be synthesized from a simple 2-trichloromethylbenzoxazole starting material via this diversity-oriented synthesis (DOS)²⁷ type approach.

EXPERIMENTAL SECTION

General Remarks. Unless otherwise indicated, all commercially available reagents and solvents were used directly from the supplier without further purification. Solvents used for column chromatography were of technical grade. Column chromatography was performed on silica gel (60–120) mesh. Visualization was accomplished with UV light and a potassium permanganate solution. ¹H NMR and ¹³C NMR were recorded at ambient temperature using CDCl₃ (7.26 ppm). Chemical shift values are expressed as parts per million (ppm), and *J* values are in hertz. Splitting patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; or combination br.s, broad singlet; or m, multiplet. The melting points reported are uncorrected. Infrared spectra were recorded as diluted solutions in spectroscopic grade chloroform unless otherwise stated. Absorption maxima (λ max) of major peaks are reported in wavenumbers (cm⁻¹) quoted to the nearest integral wavenumber. Reactions were run in a sealed

microwave reaction vessel and heated using an aluminum block on a hot plate.

2-(Pyrrolidin-1-yl)benzo[d]oxazole (2a).²⁸ *Method A.* To a stirred solution of 2-(trichloromethyl)benzo[d]oxazole (1a, 200 mg, 0.8 mmol) in dry acetonitrile (1 M) at rt was added pyrrolidine (79 μL, 0.9 mmol). The resultant solution was stirred at 60 °C for 4 h. The solvent was removed in vacuo, and the residue was purified by flash column chromatography on silica gel (5% ethyl acetate in petroleum ether) to afford 2-(pyrrolidin-1-yl)benzo[d]oxazole (2a, 146 mg, 92% yield) as a yellow solid.

Method B. To a stirred solution of 2-(trichloromethyl)benzo[d]oxazole (1a, 200 mg, 0.8 mmol) in dry acetonitrile (1 M) at rt was added pyrrolidine (79 μL, 0.9 mmol). The resultant solution was stirred at rt for 13 h. The solvent was removed in vacuo, and the residue was purified by flash column chromatography on silica gel (5% ethyl acetate in petroleum ether) to afford 2-(pyrrolidin-1-yl)benzo[d]oxazole (2a, 143 mg, 90% yield) as a yellow solid.

Method C. To a stirred solution of 2-(trichloromethyl)benzo[d]oxazole (1a, 100 mg, 0.42 mmol) in dry acetonitrile (1 M) at rt were added pyrrolidine (40 μL, 0.47 mmol) and DABCO (4.7 mg, 0.042 mmol). The resultant solution was stirred at 60 °C for 4 h. The solvent was removed in vacuo, and the residue was purified by flash column chromatography on silica gel (5% ethyl acetate in petroleum ether) to afford 2-(pyrrolidin-1-yl)benzo[d]oxazole (2a, 75 mg, 95% yield) as a yellow solid. Mp 133–135 °C (lit. mp 136–137 °C); *R*_f = 0.25 (1:9 ethyl acetate/petroleum ether); IR (CHCl₃, cm⁻¹) 3011, 2978, 2880, 1648; ¹H NMR (300 MHz, CDCl₃, 298 K) δ_H 7.36 (1H, d, *J* = 7.8 Hz), 7.26 (1H, d, *J* = 7.8 Hz), 7.15 (1H, apparent td, *J* = 7.7, 1.2 Hz), 6.99 (1H, apparent td, *J* = 7.7, 1.2 Hz), 3.69–3.62 (4H, m), 2.07–2.01 (4H, m); ¹³C{¹H} NMR (75 MHz, CDCl₃, 298 K) δ_C 160.9, 148.9, 143.5, 123.6, 119.9, 115.8, 108.4, 47.2 (2C), 25.4 (2C); HRMS (ESI) *m/z* calcd for [M + H]⁺ C₁₁H₁₃N₂O⁺ 189.1023, found 189.1030.

2-(Pyrrolidin-1-yl)naphtho[2,3-*d*]oxazole (2b). To a stirred solution of 2-(trichloromethyl)naphtho[2,3-*d*]oxazole (1b, 158 mg, 0.55 mmol) in dry acetonitrile (1 M) at rt was added pyrrolidine (51 μL, 0.6 mmol). The resultant solution was stirred at 60 °C for 4 h. The solvent was removed in vacuo, and the residue was purified by flash column chromatography on silica gel (5% ethyl acetate in petroleum ether) to afford 2-(pyrrolidin-1-yl)naphtho[2,3-*d*]oxazole (2b, 130 mg, 99% yield) as a yellow oil. IR (CHCl₃, cm⁻¹) 2969, 2881, 1656; ¹H NMR (300 MHz, CDCl₃, 298 K) δ_H 7.86–7.80 (2H, m), 7.68 (1H, s), 7.58 (1H, s), 7.37 (2H, quint, *J* = 6.9, 1.3 Hz), 3.66 (4H, t, *J* = 6.7 Hz), 2.05–1.97 (4H, m); ¹³C{¹H} NMR (75 MHz, CDCl₃, 298 K) δ_C 161.9, 149.3, 144.1, 131.9, 129.2, 127.6, 127.5, 124.2, 123.5, 111.4, 104.3, 47.5 (2C), 25.5 (2C); HRMS (ESI) *m/z* calcd for [M + H]⁺ C₁₅H₁₅N₂O⁺ 239.1179, found 239.1189.

5-Methoxy-2-(pyrrolidin-1-yl)benzo[d]oxazole (2c).²⁹ To a stirred solution of 5-methoxy-2-(trichloromethyl)benzo[d]oxazole (1c, 147 mg, 0.55 mmol) in dry acetonitrile (1 M) at rt was added pyrrolidine (51 μL, 0.6 mmol). The resultant solution was stirred at 60 °C for 4 h. The solvent was removed in vacuo, and the residue was purified by flash column chromatography on silica gel (5% ethyl acetate in petroleum ether) to afford 5-methoxy-2-(pyrrolidin-1-yl)benzo[d]oxazole (2c, 83 mg, 69% yield) as light brown crystals. IR (CHCl₃, cm⁻¹) 2957, 2880, 1650; ¹H NMR (300 MHz, CDCl₃, 298 K) δ_H 7.10 (1H, d, *J* = 8.6 Hz), 6.92 (1H, d, *J* = 2.5 Hz), 6.53 (1H, dd, *J* = 8.6, 2.5 Hz), 3.79 (3H, s), 3.64–3.60 (4H, m), 2.04–1.99 (4H, m); ¹³C{¹H} NMR (75 MHz, CDCl₃, 298 K) δ_C 161.8, 156.9, 144.7, 143.6, 108.3, 106.3, 101.2, 55.8, 47.3 (2C), 25.6 (2C); HRMS (ESI) *m/z* calcd for [M + H]⁺ C₁₂H₁₅N₂O₂⁺ 219.1129, found 219.1134.

5-Chloro-2-(pyrrolidin-1-yl)benzo[d]oxazole (2d).²⁹ To a stirred solution of 5-chloro-2-(trichloromethyl)benzo[d]oxazole (1d, 150 mg, 0.55 mmol) in dry acetonitrile (1 M) at rt was added pyrrolidine (51 μL, 0.6 mmol). The resultant solution was stirred at 60 °C for 4 h. The solvent was removed in vacuo, and the residue was purified by flash column chromatography on silica gel (5% ethyl acetate in petroleum ether) to afford 5-chloro-2-(pyrrolidin-1-yl)benzo[d]oxazole (2d, 100 mg, 81% yield) as a white solid. Mp 121–123 °C; IR (CHCl₃, cm⁻¹) 2979, 2882, 1650; ¹H NMR (300 MHz, CDCl₃, 298 K) δ_H 7.28 (1H, d, *J* = 2.1 Hz), 7.10 (1H, d, *J* = 8.4

Hz), 6.90 (1H, dd, $J = 8.4, 2.1$ Hz), 3.60 (4H, t, $J = 6.7$ Hz), 2.05–1.96 (4H, m); $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3 , 298 K) δ_c 161.6, 147.5, 145.0, 128.9, 119.6, 115.8, 108.9, 47.3 (2C), 25.4 (2C); HRMS (ESI) m/z calcd for $[\text{M} + \text{H}]^+$ $\text{C}_{11}\text{H}_{12}\text{ClN}_2\text{O}^+$ 223.0633, found 223.0637.

6-Chloro-2-(pyrrolidin-1-yl)benzo[d]oxazole (2e). To a stirred solution of 6-chloro-2-(trichloromethyl) benzo[d]oxazole (**1e**, 150 mg, 0.55 mmol) in dry acetonitrile (1 M) at rt was added pyrrolidine (51 μL , 0.6 mmol). The resultant solution was stirred at 60 °C for 4 h. The solvent was removed in vacuo, and the residue was purified by flash column chromatography on silica gel (5% ethyl acetate in petroleum ether) to afford 6-chloro-2-(pyrrolidin-1-yl)benzo[d]oxazole (**2e**, 93 mg, 75% yield) as a white solid. Mp 126–128 °C; IR (CHCl_3 , cm^{-1}) 2979, 2881, 1651; ^1H NMR (300 MHz, CDCl_3 , 298 K) δ_{H} 7.22–7.19 (2H, m), 7.08–7.00 (1H, m), 3.62–3.58 (4H, m), 2.05–1.96 (4H, m); $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3 , 298 K) δ_c 161.2, 149.1, 142.6, 125.0, 124.0, 116.1, 109.3, 47.4 (2C), 25.5 (2C); HRMS (ESI) m/z calcd for $[\text{M} + \text{H}]^+$ $\text{C}_{11}\text{H}_{12}\text{ClN}_2\text{O}^+$ 223.0633, found 223.0639.

2-Methoxybenzo[d]oxazole (3a).³⁰ To a stirred solution of 2-(trichloromethyl)benzo[d]oxazole (**1a**, 150 mg, 0.6 mmol, 1 equiv) in acetonitrile (0.6 mL, 1 M) at ambient temperature were added methanol (28 μL , 0.7 mmol, 1.1 equiv) and DBU (104 μL , 0.7 mmol, 1.1 equiv). The resultant solution was stirred at 60 °C for 16 h. The mixture was allowed to cool to rt and filtered through silica (dichloromethane). The solvent was removed in vacuo, and the residue was purified by flash column chromatography on base-washed silica gel (3% ethyl acetate in petroleum ether) to afford 2-methoxybenzo[d]oxazole (**3a**, 24 mg, 25%) as a clear oil. $R_f = 0.50$ (1:2 ethyl acetate/petroleum); IR (CHCl_3 , cm^{-1}) 3156, 2927, 2254, 1792, 1747, 1552; ^1H NMR (300 MHz, CDCl_3 , 298 K) δ_{H} 7.90 (1H, d, $J = 7.9$ Hz) 7.67 (1H, d, $J = 8.1$ Hz), 7.56–7.44 (2H, m), 4.10 (3H, s); $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3 , 298 K) δ_c 156.9, 150.9, 140.5, 128.3, 125.9, 122.2, 111.8, 53.7; HRMS (ESI) m/z calcd for $[\text{M} + \text{H}]^+$ $\text{C}_8\text{H}_8\text{NO}_2^+$ 150.0550, found 150.0540.

2-(Benzyloxy)benzo[d]oxazole (3b).³¹ To a stirred solution of 2-(trichloromethyl)benzo[d]oxazole (**1a**, 150 mg, 0.6 mmol, 1 equiv) in acetonitrile (0.6 mL, 1 M) were added benzyl alcohol (73 μL , 0.7 mmol, 1.1 equiv) and DBU (104 μL , 0.7 mmol, 1.1 equiv). The resultant solution was stirred at 60 °C for 16 h. The mixture was allowed to cool to rt and filtered through silica (dichloromethane). The solvent was removed in vacuo, and the residue was purified by flash column chromatography on base-washed silica gel (1% ethyl acetate in petroleum ether) to afford 2-(benzyloxy)benzo[d]oxazole (**3b**, 37 mg, 26%) as a clear oil. IR (CHCl_3 , cm^{-1}) 3009, 2928, 2855, 1741, 1613, 1568; ^1H NMR (300 MHz, CDCl_3 , 298 K) δ_{H} 7.81–7.79 (2H, m) 7.64–7.62 (2H, m), 7.47 (2H, apparent td, $J = 7.7, 1.4$ Hz), 7.42–7.35 (3H, m), 6.87 (2H, s); $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3 , 298 K) δ_c 159.6, 151.0, 140.1, 128.6, 128.3, 126.9 (2C), 125.3 (2C), 121.2 (2C), 119.4, 111.3, 61.0; HRMS (ESI) m/z calcd for $[\text{M} + \text{H}]^+$ $\text{C}_{14}\text{H}_{12}\text{NO}_2^+$ 226.0863, found 226.0873.

Benzo[d]oxazol-2-yl(pyrrolidin-1-yl)methanone (5). *Method A.* To a stirred solution of 2-(trichloromethyl)benzo[d]oxazole (**1a**, 100 mg, 0.42 mmol) in acetonitrile (0.01 M) at ambient temperature was added pyrrolidine (40 μL , 0.47 mmol). The resultant solution was stirred at ambient temperature for 76 h. The solvent was removed in vacuo, and the residue was purified by flash column chromatography on silica gel (5% ethyl acetate in diethyl ether) to afford benzo[d]oxazol-2-yl(pyrrolidin-1-yl)methanone (**5**, 60 mg, 66%) as a yellow solid.

Method B. To a stirred solution of 2-(trichloromethyl)benzo[d]oxazole (**1a**, 100 mg, 0.42 mmol) in acetonitrile (0.01 M) at ambient temperature was added pyrrolidine (40 μL , 0.47 mmol). The resultant solution was stirred at ambient temperature for 19 h. The solvent was removed in vacuo, and the residue was purified by flash column chromatography on silica gel (5% ethyl acetate in diethyl ether) to afford benzo[d]oxazol-2-yl(pyrrolidin-1-yl)methanone (**5**, 32 mg, 35%) as a yellow solid.

Method C. To a stirred solution of 2-(trichloromethyl)benzo[d]oxazole (**1a**, 100 mg, 0.42 mmol) in acetonitrile (0.01 M) at ambient temperature were added iron(III) chloride (68 mg, 0.42 mmol) and pyrrolidine (40 μL , 0.47 mmol). The resultant solution was stirred at

ambient temperature for 19 h. The solvent was removed in vacuo, and the residue was purified by flash column chromatography on silica gel (5% ethyl acetate in diethyl ether) to afford benzo[d]oxazol-2-yl(pyrrolidin-1-yl)methanone (**5**, 52 mg, 57%) as a yellow solid. Mp 126–128 °C; $R_f = 0.20$ (1:9 ethyl acetate/petroleum ether); IR (CHCl_3 , cm^{-1}) 3006, 2886, 1640; ^1H NMR (300 MHz, CDCl_3 , 298 K) δ_{H} 7.83 (1H, d, $J = 7.5$ Hz) 7.66 (1H, d, $J = 7.6$ Hz) 7.48–7.42 (2H, m), 4.14 (2H, t, $J = 6.8$ Hz), 3.76 (2H, t, $J = 6.8$ Hz), 2.11–1.93 (4H, m); $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3 , 298 K) δ_c 155.8, 155.3, 150.1, 140.6, 127.2, 125.2, 121.4, 111.7, 49.3, 47.5, 26.5, 23.9; HRMS (ESI) m/z calcd for $[\text{M} + \text{H}]^+$ $\text{C}_{12}\text{H}_{13}\text{N}_2\text{O}_2^+$ 217.0972, found 217.0970.

6-Chloro-2,3-di(pyrrolidin-1-yl)-2H-benzo[b][1,4]oxazine (6d). To a stirred solution of 5-chloro-2-(trichloromethyl) benzo[d]oxazole (**1d**, 150 mg, 0.55 mmol) in dry acetonitrile (1 M) at rt was added pyrrolidine (51 μL , 0.6 mmol). The resultant solution was stirred at 60 °C for 4 h. The solvent was removed in vacuo, and the residue was purified by flash column chromatography on silica gel (5% ethyl acetate in petroleum ether) to afford 6-chloro-2,3-di(pyrrolidin-1-yl)-2H-benzo[b][1,4]oxazine (**6d**, 24 mg, 14% yield) as a yellow gummy solid. IR (CHCl_3 , cm^{-1}) 3690, 2929, 2876, 1610; ^1H NMR (300 MHz, CDCl_3 , 298 K) δ_{H} 7.08 (1H, d, $J = 2.1$ Hz), 6.80–6.72 (2H, m), 5.45 (1H, s), 3.65 (3H, br.s), 3.36 (1H, br.s) 2.96–2.89 (2H, m) 2.68–2.61 (2H, m) 1.97 (4H, br.s) 1.72–1.60 (4H, m); $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3 , 298 K) δ_c 152.3, 144.7, 136.0, 125.8, 123.3, 121.9, 115.0, 80.2, 46.7 (4C), 24.4 (4C); HRMS (ESI) m/z calcd for $[\text{M} + \text{H}]^+$ $\text{C}_{16}\text{H}_{21}\text{ClN}_3\text{O}^+$ 306.1368, found 306.1373.

7-Chloro-2,3-di(pyrrolidin-1-yl)-2H-benzo[b][1,4]oxazine (6e). To a stirred solution of 6-chloro-2-(trichloromethyl) benzo[d]oxazole (**1e**, 150 mg, 0.55 mmol) in dry acetonitrile (1 M) at rt was added pyrrolidine (51 μL , 0.6 mmol). The resultant solution was stirred at 60 °C for 4 h. The solvent was removed in vacuo, and the residue was purified by flash column chromatography on silica gel (5% ethyl acetate in petroleum ether) to afford 7-chloro-2,3-di(pyrrolidin-1-yl)-2H-benzo[b][1,4]oxazine (**6e**, 42 mg, 25% yield) as a yellow gummy solid. IR (CHCl_3 , cm^{-1}) 3667, 2974, 2876, 1607; ^1H NMR (300 MHz, CDCl_3 , 298 K) δ_{H} 7.01 (1H, dd, $J = 7.9, 0.7$ Hz), 6.84–6.80 (2H, m), 5.46 (1H, s), 3.63 (3H, br.s), 3.37 (1H, br.s) 2.96–2.88 (2H, m) 2.68–2.61 (2H, m) 2.01–1.94 (4H, m) 1.69–1.60 (4H, m); $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3 , 298 K) δ_c 151.8, 146.5, 133.5, 126.6, 124.1, 121.3, 114.6, 80.2, 46.6 (4C), 24.4 (4C); HRMS (ESI) m/z calcd for $[\text{M} + \text{H}]^+$ $\text{C}_{16}\text{H}_{21}\text{ClN}_3\text{O}^+$ 306.1368, found 306.1360.

2,2,2-Trichloro-N-(2-hydroxyphenyl) acetamide (7).³² *Method A.* To a stirred solution of 2-(trichloromethyl)benzo[d]oxazole (**1a**, 237 mg, 1 mmol, 1 equiv) and iron(III) chloride (3.0 mg, 0.02 mmol, 2 mol %) in acetonitrile (0.2 mL, 5 M) at rt was added water (18 μL , 1 mmol, 1.0 equiv). The resultant mixture was stirred at rt for 5 h. Water (27 μL , 1.5 mmol, 1.5 equiv) was added. The mixture was stirred at rt for 3 h. The solvent was removed in vacuo, and the residue was purified by flash column chromatography on silica gel (5% ethyl acetate in petroleum ether) to afford 2,2,2-trichloro-N-(2-hydroxyphenyl) acetamide (**7**, 148 mg, 58%) as a yellow solid.

Method B. 2-(Trichloromethyl)benzo[d]oxazole (**1a**, 61 mg, 0.26 mmol) in H_2O (1.0 mL) was stirred at 150 °C for 2 h. The solution was allowed to cool to rt, and dichloromethane (10 mL) was added. The resultant solution was washed with water (3 \times 5 mL). The organic layer was dried over magnesium sulfate, and the solvent was removed in vacuo to afford 2,2,2-trichloro-N-(2-hydroxyphenyl) acetamide (**7**, 24 mg, 37%) as a yellow solid. Mp 160–161 °C (lit. mp 160 °C); IR (CHCl_3 , cm^{-1}) 3594, 3397, 1720, 1615; ^1H NMR (300 MHz, CDCl_3 , 298 K) δ_{H} 8.98 (1H, br.s) 7.95 (1H, d, $J = 8.0$ Hz), 7.13–7.09 (1H, m), 7.02–6.93 (2H, m) 5.99 (1H, br.s); $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3 , 298 K) δ_c 159.7, 146.1, 126.6, 124.5, 121.7, 121.2, 116.5, 92.5; HRMS (ESI) m/z calcd for $[\text{M} + \text{H}]^+$ $\text{C}_8\text{H}_7\text{Cl}_3\text{NO}_2^+$ 253.9537, found 253.9534.

(Z)-2,2'-(1-Chloro-2-(pyrrolidin-1-yl)ethene-1,2-diyl)bis(benzo[d]oxazole) (8). To a stirred suspension of 2-(trichloromethyl)benzo[d]oxazole (**1a**, 150 mg, 0.6 mmol, 1.0 equiv) and iron(III) chloride (97 mg, 0.6 mmol, 1.0 equiv) in acetonitrile (6 mL, 0.1 M) at rt was added pyrrolidine (260 μL , 3.17

mmol, 5.0 equiv). The resultant mixture was stirred at rt for 19 h and then filtered through base-washed silica. The solvent was removed in vacuo, and the residue was purified by flash column chromatography on silica gel (5% diethyl ether in petroleum ether) to afford (Z)-2,2'-(1-chloro-2-(pyrrolidin-1-yl)ethene-1,2-diyl)bis(benzo[d]oxazole) (**8**, 58 mg, 26%) as a yellow solid. R_f = 0.40 (1:9 ethyl acetate/petroleum); IR (CHCl₃, cm⁻¹) 2982, 2882, 1607, 1578, 1549; ¹H NMR (300 MHz, CDCl₃, 298 K) δ_H 7.80–7.77 (1H, m), 7.56–7.54 (1H, m), 7.44–7.39 (3H, m), 7.13 (1H, apparent td, J = 7.7, 1.1 Hz), 7.05 (1H, apparent td, J = 7.8, 1.3 Hz), 6.87 (1H, d, J = 7.8 Hz), 3.66–3.62 (4H, m), 2.00–1.97 (4H, m); ¹³C{¹H} NMR (75 MHz, CDCl₃, 298 K) δ_C 161.8, 158.1, 150.5, 150.4, 141.9, 141.2, 138.6, 126.1, 124.8, 124.1, 124.0, 120.9, 119.3, 111.1, 109.5, 94.7, 51.3 (2C), 25.6 (2C); HRMS (ESI) m/z calcd for [M + H]⁺ C₂₀H₁₇ClN₃O₂⁺ 366.1004, found 366.1000.

■ ASSOCIATED CONTENT

● Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02315.

Tables of reaction parameters examined and copies of ¹H and ¹³C NMR spectra of all newly synthesized products (PDF)

X-ray details of compound **6e** (CIF)

X-ray details of compound **7** (CIF)

X-ray details of compound **8** (CIF)

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The authors declare no competing financial interest.

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