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Cobalt-Catalyzed Cross-Dehydrogenative Coupling Reactions of (Benz)oxazoles with Ethers

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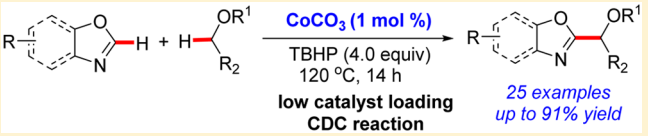
Supporting Information

ABSTRACT: The cobalt-catalyzed cross-dehydrogenative coupling of (benz)oxazoles and ethers is described. Access to some important bioactive heteroaryl ether derivatives was achieved using $CoCO_3$ as an inexpensive catalyst at levels as low as 1.0 mol %. Investigation of the mechanism indicates a catalytic cycle involving a radical process.

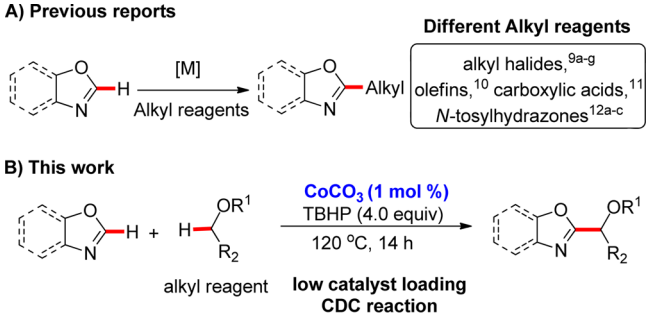


INTRODUCTION

Direct transition-metal-catalyzed C−H functionalization has emerged in synthetic organic and medicinal chemistry[1] as an expedient means of introducing and expanding molecular complexity. Cobalt as a catalyst has recently attracted much attention in the development of applicable transformations due to its economy, low toxicity, and unique reaction modes.[2−4] Cross-dehydrogenative coupling (CDC) reactions are more efficient and direct because they can avoid the introduction of oriented and activated functional groups, shortening synthetic routes and making them more atom economical.[5] Cobalt-catalyzed CDC reactions represent an interesting but challenging research area of C−H functionalization chemistry.[6,7] Although C−C bonds are the most common fundamental units in organic molecules, their formation by cobalt-catalyzed CDC reactions has not been explored fully.[3e,7] In 2006, Li et al. first reported a CDC reaction of 1,3-dicarbonyl compounds with allyl compounds catalyzed by cobalt/copper cocatalysts.[7a] In 2015, Wu et al. reported CDC reactions of tetrahydroisoquinolines and indoles using a cobalt complex as the photosensitizer.[7b] Recently, You et al. reported a CDC reaction between two heteroarenes catalyzed by $Co(OAc)_2$,[7c] and the Du group demonstrated $CoCl_2$-catalyzed cross-coupling reaction of coumarins and ethers under basic conditions.[7d] The catalyst loadings of these catalytic reactions utilized were relatively high, in the range of 5−20 mol %. Development of different CDC reactions with cobalt catalysts, especially those used with low loading, could be of prime synthetic value.

2-Subtituted (benz)oxazoles are present in many medicinally active compounds with a diverse array of biological activities.[8] Earlier methods for the direct synthesis of 2-alkyloxazoles rely primarily on the direct C-2 alkylation of oxazoles, catalyzed by transition metals (Scheme 1A).[9−12] These reactions use alkyl halides,[9] olefins,[10] carboxylic acids,[11] and *N*-tosylhydrazones[12] as the alkylating reagents and are mostly performed under basic conditions. The successful direct catalytic C2-alkylation of

Scheme 1. Metal-Catalyzed C−H Alkylation of (Benz)oxazoles



(benz)oxazoles through CDC reactions has not been reported. Ethers are common structural motifs in natural products, and their construction in complex organic molecules can be demanding, often requiring complicated synthetic routes.[13] Following our recent work on cobalt-catalyzed C−H bond functionalization,[14,15] we report in this paper the first example of a catalytic CDC reaction between oxazoles and ethers (Scheme 1B), forming various oxazoles containing ether motifs, which may have special application in medicines.[16] The reaction uses $CoCO_3$ as an inexpensive catalyst with loadings as low as 0.3−1 mol %.

RESULTS AND DISCUSSION

Initially, we examined the CDC reactions of 5-phenyloxazole (**1a**) and 1,4-dioxane (**2a**) with oxidizing agents, such as di-*tert*-butyl peroxide (DTBP), *tert*-butyl hydroperoxide (TBHP), $K_2S_2O_8$, or dicumyl peroxide (DCP), in which TBHP afforded the highest yield in the absence of any metal catalyst (Table 1, entries 1−4).[17] Subsequently, nine different types of simple

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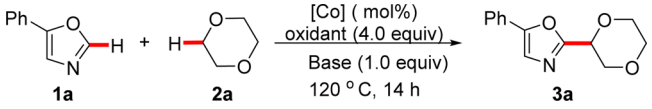
Table 1. Optimization of Reaction Conditions[a]

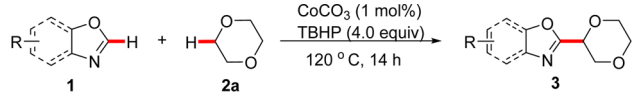


1a 2a 3a

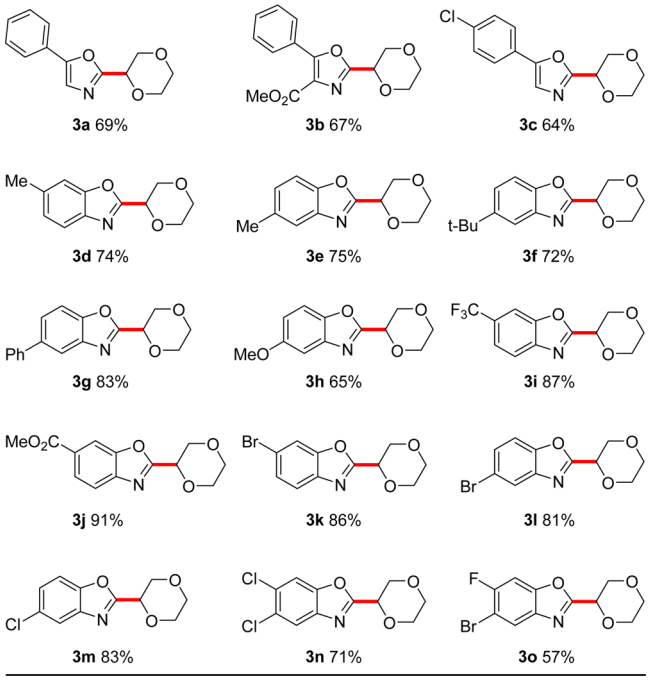
entry	[Co] (mol %)	base	oxidant	3a (%)
1	–	–	DTBP	15
2	–	–	TBHP	19
3	–	–	$K_2S_2O_8$	<5
4	–	–	DCP	none
5	$Co(acac)_2$ (20)	–	TBHP	52
6	$CoCl_2$ (20)	–	TBHP	47
7	$Co(acac)_3$ (20)	–	TBHP	35
8	CoF_2 (20)	–	TBHP	36
9	$CoCO_3$ (20)	–	TBHP	68
10	$Co(NO_3)_2{\cdot}6H_2O$ (20)	–	TBHP	11
11	$CoClO_4{\cdot}6H_2O$ (20)	–	TBHP	46
12	$CoBr_2$ (20)	–	TBHP	34
13	$Co(OAc)_2{\cdot}4H_2O$ (20)	–	TBHP	51
14	$CoCO_3$ (10)	–	TBHP	69
15	$CoCO_3$ (5)	–	TBHP	70
16	**$CoCO_3$ (1)**	–	**TBHP**	**70(69[b])**
17	$CoCO_3$ (0.5)	–	TBHP	65
18	$CoCO_3$ (0.3)	–	TBHP	57
19	$CoCO_3$ (1)	K_2CO_3	TBHP	8
20	–	K_2CO_3	TBHP	trace

[a]Reaction conditions: 5-phenyloxazole **1a** (0.5 mmol), 1,4-dioxane (5.0 mL), TBHP (4.0–5.0 equiv), [Co] (0.1–0.0015 mmol), TBHP (5.0–6.0 M in *n*-decane, 0.42 mL, 2.0–2.4 mmol), sealed tube, 120 °C, air, 14 h. Yields are based on **1a**, determined by crude ^{1}HNMR using 1,3,5-trimethoxybenzene as the internal standard. [b]Isolated yield.

Table 2. Scope of (Benz)oxazoles[a]



1 2a 3



[a]Reaction conditions: (benz)oxazole **1** (0.5 mmol), 1,4-dioxane (5.0 mL), TBHP (4.0–5.0 equiv, 5.0–6.0 M in *n*-decane, 0.42 mL, 2.0–2.4 mmol), Co_2CO_3(0.005 mmol), sealed tube, 120 °C, air, 14 h, isolated yield.

cobalt salts were examined (entries 5–13), and we found that the reaction could be improved by addition of different cobalt compounds, including $Co(acac)_2$, $CoCl_2$, $CoCO_3$, $Co(acac)_3$, CoF_2, $Co(ClO_4)_2{\cdot}6H_2O$, $CoBr_2$, and $Co(OAc)_2{\cdot}4H_2O$. Among the cobalt catalysts, $CoCO_3$ provided the desired product (**3a**) in 68% yield and was identified as the most effective catalyst. When the $CoCO_3$ catalyst loading was reduced from 20 to 1 mol %, the yield remained at 70% (entries 9, 14–16), distinguishing this reaction from the majority of cobalt-catalyzed C–H activation reactions, which utilize relatively high catalyst loadings.[15e,18a] When the $CoCO_3$ loading was reduced to 0.3 mol %, the product was still formed in a moderate yield (entry 18). Finally, we showed that the presence of K_2CO_3 blocked the reaction (entries 19 and 20).

Having optimized the reaction conditions, we investigated the scope of the (benz)oxazoles (**1**) in the direct alkylation with 1,4-dioxane (**2a**) and obtained the results shown in Table 2. The reaction of oxazoles with 1,4-dioxane proceeds smoothly to generate the anticipated product (**3a–c**) in moderate yields. Electron-donating groups (Me, *t*-Bu, and MeO) and electron-withdrawing groups (CO_2Me and CF_3) on the phenyl ring are tolerated (**3d–j**), the latter giving generally a higher yield. The benzoxazoles with halogen substituents in the phenyl ring (**3k–o**) were also good coupling partners, and this could provide more options for further potential transformations.

Next, the scope of ethers (**2**) was examined. As shown in Table 3, cyclic aliphatic ethers, such as 1,4-dioxane, tetrahydrofuran, and dioxolane, produce the corresponding cross-dehydrogenative coupling products in moderate to good yield (**3p–t**), and chain aliphatic ethers are also good substrates in the coupling reaction (**3u–x**). With ethers having two different reaction sites, the regioselectivity of the coupling reaction is influenced by bond dissociation energy, steric, and electric effects. For example, the reaction of 1,3-dioxolane shows a tendency to activate C–H bonds with weaker bond dissociation energy, and so the yield of **3t1** is almost three times as high as that of **3t2**. When 1-ethoxybutane is used as the alkylating reagent, the less sterically hindered C–H bond is activated preferentially, and the products **3u1** and **3u2** are produced in a ratio of 1.9:1. When both primary and secondary C–H bonds are present, the secondary C–H bond is functionalized exclusively due to its weaker bond dissociation energy, giving the product **3v**. However, both primary and secondary C–H bonds are activated when 1,2-dimethoxyethane is used as the substrate (**3w1** and **3w2**). This result indicates that the C–H bond with the higher electron-rich property is preferred in the reaction. The contribution of an electronic effect is further evidenced in the reactivity of 1,2-diethoxyethane. In this case, the regioselectivity is quite high (>20/1), and just one product (**3x**) was isolated in good yield. When 2-methyltetrahydrofuran was used as the coupling component, the quaternary carbon center product (**3y1**) is the main product. Unfortunately, no desired product was detected when tetrahydropyran was used as a coupling component.

The intermolecular competition experiment between **1d** and **1j** was performed. In this case, a simple electrophilic-type C–H metalation could be ruled out, as the C–H bond in the benzoxazole whose aromatic ring is substituted with an electron-withdrawing group is preferred in the reaction (Scheme 2).[18]

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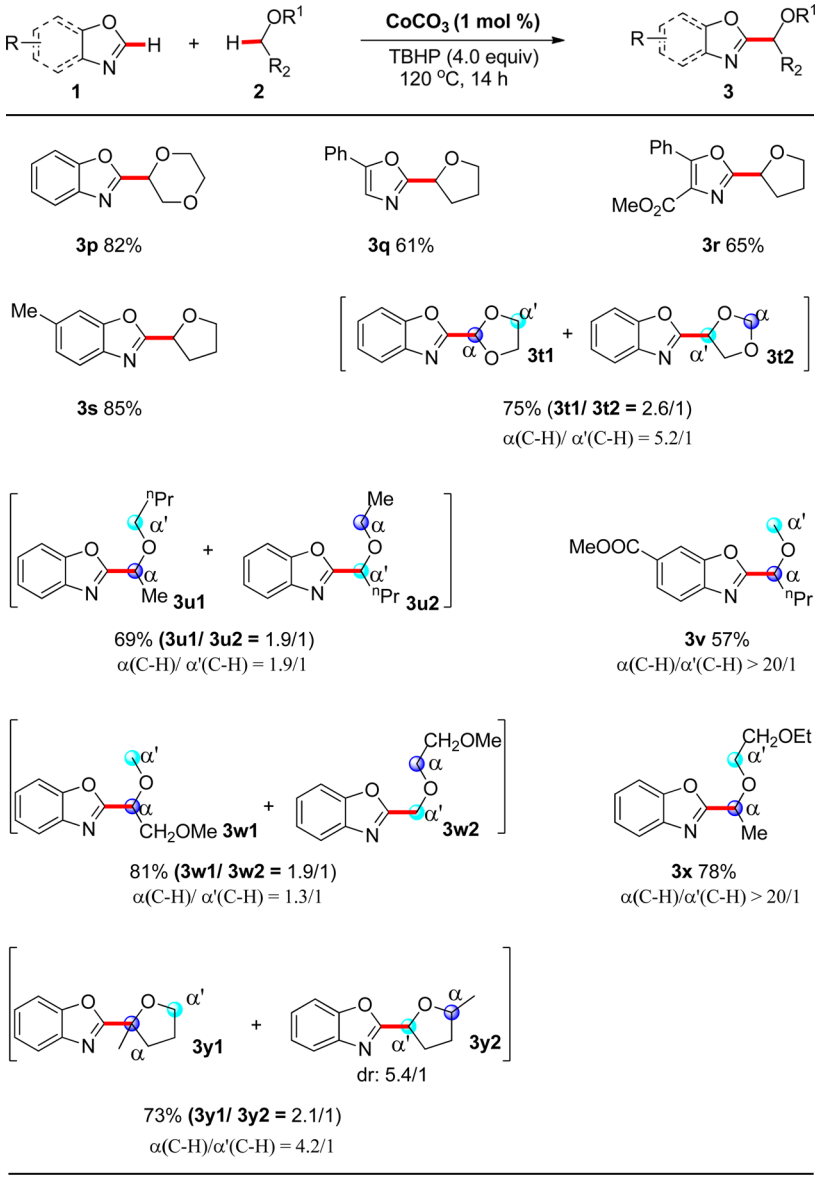
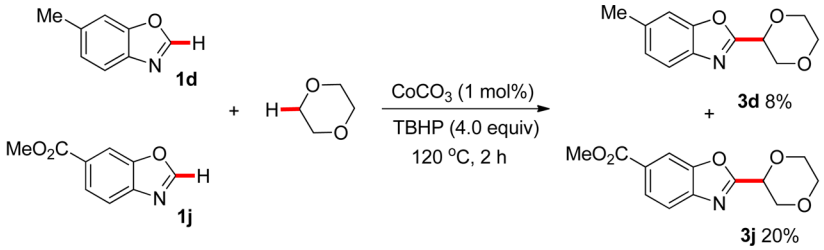
Table 3. Scope of Ethers[a]



[a]Reaction conditions: oxazole **1** (0.5 mmol), ether **2** (5.0 mL), TBHP (4.0–5.0 equiv, 5.0–6.0 M in *n*-decane, 0.42 mL, 2.0–2.4 mmol), Co_2CO_3(0.005 mmol), sealed tube, 120 °C, air, 14 h, isolated yield.

Scheme 2. Intermolecular Competition Experiment



In order to establish the role of the catalyst,[17] reactions with or without catalyst were monitored (Figure 1). The reaction with a cobalt catalyst is obviously faster than that without the catalyst, showing that $CoCO_3$ plays a critical role in the reaction.

To gain further insight into the mechanism of this catalytic CDC reaction, the control experiments depicted in Scheme 3 were performed. The radical trapping experiment outlined in Scheme 3A was conducted, and it was found that the yield of the product (**3p**) decreases when 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) is added, and 1-((1,4-dioxan-2-yl)oxy)-2,2,6,6-tetramethylpiperidine (**4**) is formed in 21% yield when a large amount of TEMPO (6 equiv) is added, suggesting that the reaction may perform through a radical mechanism.

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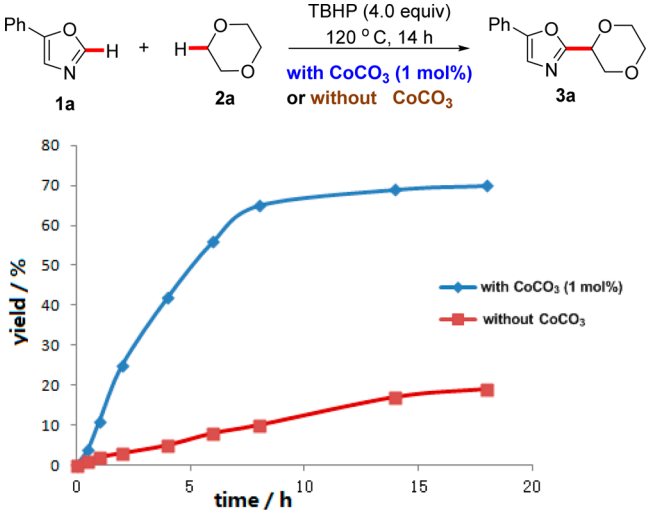
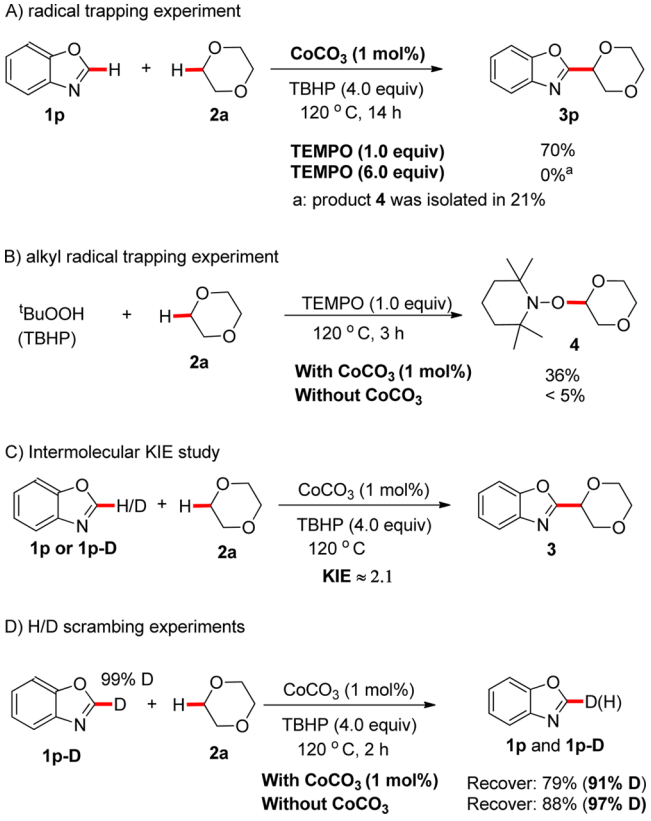


Figure 1. Monitoring the reactions with or without catalyst.

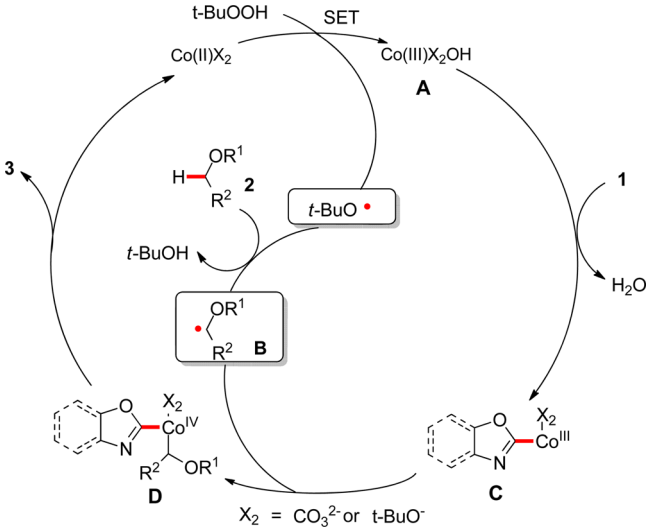
Scheme 3. Mechanistic Studies



We monitored the reactions of TBHP with 1,4-dioxane with or without Co_2CO_3 using TEMPO as a radical trapping reagent (Scheme 3B) and found that in the presence of Co_2CO_3, the alkyl radical trapping product (**4**) was formed. This suggests that Co_2CO_3 plays an important role in the decomposition of *tert*-butylhydroperoxide to generate an alkyl radical.[18] Coordination between cobalt and oxazole is not ruled out by this result.[14b] Primary kinetic isotope effects were observed in parallel deuterium labeling experiments (Scheme 3C). Meanwhile, some intermolecular H/D exchange (91% D retained) was observed when the reaction was performed with an isotopically labeled substrate (Scheme 3D), and the H/D exchange in the absence of the Co catalyst is very little (97% D retained), suggesting a metal-mediated C−H cleavage is involved in the mechanism.

On the basis of these results and previous reports,[3c,14b,18] the Co(III/IV/II) catalytic cycle in Scheme 4 is proposed. First, the

Scheme 4. Proposed Catalytic Cycle



Co^{II} catalyst is oxidized by TBHP giving the Co^{III} species **A**, and alkoxy radical *t*-BuO• which abstracts hydrogen atoms from the ether (**2**) producing the alkyl radical **B**. The Co^{III} species (**A**) reacts with the oxazole (**1**) generating the Co^{III} intermediate **C**. This is followed by oxidative addition of the radical (**B**) formed *in situ*, to give the Co^{IV} species (**D**).[3e,19] Finally, the catalytic cycle is completed by reductive elimination of the Co^{IV} species (**D**), leading to the desired product (**3**) and regeneration of the Co^{II} catalyst.

In summary, an efficient cobalt catalysis for CDC reactions of (benz)oxazoles and ethers has been developed. This transformation is the first example of direct C2-alkylation of (benz)oxazoles through a catalytic CDC strategy and provides an efficient means of construction of bioactive heteroaryl ether derivatives. In particular, the reaction could be performed efficiently with low loading of an inexpensive cobalt catalyst.

EXPERIMENTAL SECTION

General. All solvents and commercially available reagents were purchased from commercial sources and used directly. (Benz)oxazoles were prepared by known methods.[20a−c] Thin layer chromatography (TLC) was performed on EMD precoated plates (silica gel 60). Visualization of TLC plates was achieved with UV light (254 nm). Column chromatography was performed on silica gel (300−400 mesh) using a forced flow of 0.5−1.0 bar.Chemical shifts of ^{1}H NMR are reported in parts per million (ppm) referenced to the appropriate solvent peak or 0.0 ppm for tetramethylsilane. High-resolution mass spectra were obtained with the Q-TOF.

General Procedure for the Synthesis of (Benz)oxazoles. Azoles (**1a**, **1d**, **1e**, **1i**, **1j**) and ethers were purchased from commercial sources and used directly. Azoles (**1f**−**h**, **1k**−**o**) were prepared according to published procedures.[20a] The corresponding 2-aminophenol derivative (1.0 equiv) was dissolved in triethyl orthoformate (12.0 equiv), then the reaction mixture was carefully heated to 140 or 160 °C and stirred for 4−8 h. After cooling to room temperature, the excess orthoformate and EtOH were removed under reduced pressure, and the crude product was then purified by silica gel chromatography to give the desired product. The azole (**1b**) was prepared from methyl

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2-isocyanoacetate and benzoic anhydride in THF according to reported procedures.[20b] Azole (**1c**) was prepared from *p*-toluenesulfonylmethylisocyanide and 4-chlorobenzaldehyde in MeOH according to the reported procedure.[20c] Compounds **1a**,[20e] **1b**,[20b,e] **1c**,[20c,e] **1d**,[20e] **1e**,[20d,e] **1f**,[20d] **1g**,[20d] **1h**,[20d] **1i**,[20e] **1j**,[20e] **1k**,[20e] **1l**,[20e] and **1m**[20d] are known compounds.

*5,6-Dichlorobenzo[d]oxazole (**1n**).* White solid, mp: 104−106 °C, 319 mg, 85%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.69 (d, J = 1.8 Hz, 1H), 7.40 (d, J = 1.7 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.8, 145.6, 141.9, 130.6, 126.2, 119.3, 117.0. IR (neat) ν 3069, 2947, 2856, 1610, 1589, 1453, 1394, 1296, 1246, 1065, 911, 861, 758, 624 cm^{-1}. HRMS (ESI, m/z): calcd for $C_7H_3Cl_2NONa$ $(M + Na)^+$: 209.9490, found: 209.9486. The residue was purified by silica gel chromatography (10% ethyl acetate in hexane, v/v) to give the desired product.

*5-Bromo-6-fluorobenzo[d]oxazole (**1o**).* Light yellow liquid, 350 mg, 81%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.76 (d, J = 1.1 Hz, 1H), 7.34 (dd, J = 9.2, 1.5 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.6, 146.8 (d, J = 257.9 Hz), 144.3 (d, J = 2.2 Hz), 136.7 (d, J = 11.2 Hz), 119.7 (d, J = 4.6 Hz), 116.8 (d, J = 7.2 Hz), 116.2 (d, J = 19.5 Hz). IR (neat) ν 3015, 2969, 2878, 1653, 1576, 1437, 1365, 1228, 1091, 912, 747, 527 cm^{-1}. HRMS (ESI, m/z): calcd for $C_7H_3BrFNONa$ $(M + Na)^+$: 237.9298, found: 237.9291. The residue was purified by silica gel chromatography (10% ethyl acetate in hexane, v/v) to give the desired product.

General Procedure for the Direct Alkylation of (Benz)-oxazole with Ethers. A 35 mL oven-dried pressure tube was charged with 5-phenyloxazole (73 mg, 0.50 mmol), $CoCO_3$ (0.6 mg, 0.005 mmol), *tert*-butyl hydroperoxide (TBHP, 5.0−6.0 M in *n*-decane, 0.4 mL, 2.0−2.4 mmol), and ether (5.0 mL). The tube was then sealed and stirred vigorously at 120 °C. After stirring the mixture at this temperature for 14 h, it was cooled to room temperature, diluted with EtOAc, filtered through a Celite pad, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (10%−20% ethyl acetate in hexane, v/v) to give the desired product. (Note the safety of the reaction for overpressurization associated with heating the *tert*-butyl hydroperoxide solution with a metal catalyst at 120 °C in a sealed vessel.)

*2-(1,4-Dioxan-2-yl)-5-phenyloxazole (**3a**).* White solid, mp: 65−67 °C, 79 mg, yield: 69%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69−7.62 (m, 2H), 7.43 (t, J = 7.5 Hz, 2H), 7.38−7.30 (m, 2H), 4.86 (dd, J = 9.3, 2.9 Hz, 1H), 4.12 (dd, J = 11.7, 2.9 Hz, 1H), 4.02−3.89 (m, 3H), 3.85−3.79 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.3, 152.1, 128.9, 128.8, 127.6, 124.4, 122.0, 70.7, 68.4, 66.5, 66.4. IR (neat) ν 2965, 2914, 2857, 1590, 1487, 1449, 1258, 1120, 1079, 914, 763 cm^{-1}. HRMS (ESI, m/z): calcd for $C_{13}H_{13}NO_3Na$ $(M + Na)^+$: 254.0793, found: 254.0788.

*Methyl-2-(1,4-dioxan-2-yl)-5-phenyloxazole-4-carboxylate (**3b**).* White solid, mp: 83−85 °C, 97 mg, yield: 67%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (dd, J = 6.6, 3.1 Hz, 2H), 7.62−7.39 (m, 3H), 4.90 (dd, J = 9.5, 2.9 Hz, 1H), 4.15 (dd, J = 11.6, 2.9 Hz, 1H), 4.03−3.97 (m, 2H), 3.95 (s, 3H), 3.94−3.88 (m, 1H), 3.86−3.78 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.3, 158.2, 156.1, 130.6, 128.5, 128.4, 126.7, 126.5, 70.6, 68.3, 66.6, 66.3, 52.3. IR (neat) ν 2971, 2925, 2861, 1735, 1586, 1484, 1450, 1259, 1119, 1081, 881, 692 cm^{-1}. HRMS (ESI, m/z): calcd for $C_{15}H_{15}NO_5Na$ $(M + Na)^+$: 312.0848, found: 312.0844.

*5-(4-Chlorophenyl)-2-(1,4-dioxan-2-yl)oxazole (**3c**).* White solid, mp: 75−77 °C, 85 mg, yield: 64%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63−7.58 (m, 2H), 7.45−7.39 (m, 2H), 7.33 (s, 1H), 4.86 (dd, J = 9.3, 2.8 Hz,1H), 4.13 (dd, J = 11.7, 2.8 Hz, 1H), 4.02−3.89 (m, 3H), 3.88−3.78 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.6, 151.1, 134.6, 129.2, 126.1, 125.7, 122.4, 70.7, 68.4, 66.5, 66.4. IR (neat) ν 2969, 2946, 2850, 1587, 1475, 1489, 1255, 1092, 905, 806, 768 cm^{-1}. HRMS (ESI, m/z): calcd For $C_{13}H_{12}ClNO_3Na$ $(M + Na)^+$: 288.0404, found: 288.0401.

*2-(1,4-Dioxan-2-yl)-6-methylbenzo[d]oxazole (**3d**).* White solid, mp: 89−91 °C, 81 mg, yield: 74%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 8.1 Hz, 1H), 7.36 (s, 1H), 7.17 (d, J = 8.0 Hz, 1H), 4.96 (dd, J = 9.1, 2.6 Hz, 1H), 4.20 (dd, J = 11.7, 2.8 Hz, 1H), 3.98 (dtd, J = 15.3, 11.8, 2.8 Hz, 3H), 3.88−3.74 (m, 2H), 2.50 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.1, 150.9, 138.4, 136.0, 125.9, 119.7, 111.0, 71.1, 68.5, 66.6, 66.4, 21.8. IR (neat) ν 3028, 2915, 2866, 1613, 1577, 1487, 1363, 1270, 1130, 820, 602 cm^{-1}. HRMS (ESI, m/z): calcd for $C_{12}H_{13}NO_3Na$ $(M + Na)^+$: 242.0793, found: 242.0791.

*2-(1,4-Dioxan-2-yl)-5-methylbenzo[d]oxazole (**3e**).* White solid, mp: 80−82 °C, 82 mg, yield: 75%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (s, 1H), 7.42 (d, J = 8.3 Hz, 1H), 7.17 (d, J = 8.3 Hz, 1H), 4.95 (dd, J = 9.2, 2.8 Hz, 1H), 4.19 (dd, J = 11.7, 2.8 Hz, 1H), 3.99−3.92 (m, 3H), 3.87−3.77 (m, 2H), 2.47 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.7, 148.8, 140.8, 134.5, 126.7, 120.2, 110.2, 71.2, 68.5, 66.6, 66.4, 21.4. IR (neat) ν 2969, 2921, 2856, 1576, 1365, 1228, 1118, 915, 883, 598 cm^{-1}. HRMS (ESI, m/z): calcd for $C_{12}H_{13}NO_3Na$ $(M + Na)^+$: 242.0793, found: 242.0790.

*5-(tert-Butyl)-2-(1,4-dioxan-2-yl)benzo[d]oxazole (**3f**).* White solid, mp: 83−85 °C, 93 mg, yield: 72%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 1.6 Hz, 1H), 7.44 (dt, J = 8.7, 5.2 Hz, 2H), 4.96 (dd, J = 9.1, 3.0 Hz, 1H), 4.19 (dd, J = 11.7, 3.0 Hz, 1H), 4.04−3.91 (m, 3H), 3.86−3.79 (m, 2H), 1.38 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.8, 148.6, 148.2, 140.5, 123.3, 116.8, 110.0, 71.1, 68.5, 66.5, 66.4, 34.9, 31.7. IR (neat) ν 2961, 2918, 2857, 1573, 1557, 1481, 1395, 1119, 915, 800 cm^{-1}. HRMS (ESI, m/z): calcd for $C_{15}H_{19}NO_3Na$ $(M + Na)^+$: 284.1263, found: 284.1261.

*2-(1,4-Dioxan-2-yl)-5-phenylbenzo[d]oxazole (**3g**).* White solid, mp: 97−99 °C, 117 mg, yield: 83%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.63 (d, J = 6.3 Hz, 4H), 7.49 (t, J = 7.6 Hz, 2H), 7.39 (t, J = 7.3 Hz, 1H), 5.02 (dd, J = 9.1, 2.9 Hz, 1H), 4.24 (dd, J = 11.7, 2.9 Hz, 1H), 4.02 (tdd, J = 11.8, 10.2, 4.2 Hz, 3H), 3.91−3.81 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.4, 150.1, 141.2, 140.8, 138.7, 128.9, 127.5, 127.4, 125.2, 118.9, 110.9, 71.1, 68.5, 66.6, 66.4. IR (neat) ν 3061, 2964, 2913, 2856, 1574, 1469, 1452, 1263, 1118, 915, 762 cm^{-1}. HRMS (ESI, m/z): calcd for $C_{17}H_{15}NO_3Na$ $(M + Na)^+$: 304.0950, found: 304.0952.

*2-(1,4-Dioxan-2-yl)-5-methoxybenzo[d]oxazole (**3h**).* White solid, mp: 99−101 °C, 76 mg, yield: 65%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 8.9 Hz, 1H), 7.21 (d, J = 2.4 Hz, 1H), 6.96 (dd, J = 8.9, 2.4 Hz, 1H), 4.94 (dd, J = 9.1, 2.9 Hz, 1H), 4.18 (dd, J = 11.7, 2.9 Hz, 1H), 4.05−3.91 (m, 3H), 3.84 (s, 3H), 3.83−3.78 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.4, 157.4, 145.2, 141.4, 114.3, 111.0, 103.2, 71.1, 68.5, 66.5, 66.4, 55.9. IR (neat) ν 3010, 2969, 2857, 1575, 1483, 1365, 1279, 1119, 916, 838, 754 cm^{-1}. HRMS (ESI, m/z): calcd for $C_{12}H_{13}NO_4Na$ $(M + Na)^+$: 258.0743, found: 258.0740.

*2-(1,4-Dioxan-2-yl)-6-(trifluoromethyl)benzo[d]oxazole (**3i**).* White solid, mp: 107−108 °C, 118 mg, yield: 87%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.67 (s, 2H), 5.02 (dd, J = 8.9, 2.8 Hz, 1H), 4.23 (dd, J = 11.7, 2.9 Hz, 1H), 4.09−3.95 (m, 3H), 3.85 (dt, J = 10.2, 7.0 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.6, 152.3 (s), 140.8, 127.6 (q, J = 33.1 Hz), 124.0 (q, J = 271 Hz), 122.9 (q, J = 3.6 Hz), 118.2 (q, J = 4.0 Hz), 111.4, 70.9, 68.4, 66.5, 66.4. IR (neat) ν 3041, 2919, 2865, 1629, 1451, 1352, 1339, 1119, 914, 888, 673 cm^{-1}. HRMS (ESI, m/z): calcd for $C_{12}H_{11}F_3NO_3$ $(M + H)^+$: 274.0691, found: 274.0690.

*Methyl-2-(1,4-dioxan-2-yl)benzo[d]oxazole-6-carboxylate (**3j**).* White solid, mp: 117−118 °C, 119 mg, yield: 91%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, J = 1.0 Hz, 1H), 8.10 (dd, J = 8.4, 1.5 Hz, 1H), 7.78 (d, J = 8.4 Hz, 1H), 5.01 (dd, J = 8.9, 3.0 Hz, 1H), 4.22 (dd, J = 11.7, 3.0 Hz, 1H), 4.10−3.99 (m, 2H), 3.97 (s, 3H), 3.96−3.91 (m, 1H), 3.89−3.80 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4, 164.4, 150.2, 144.4, 127.7, 126.4, 120.1, 112.6, 71.0, 68.4, 66.5, 66.4, 52.4. IR (neat) ν 3014, 2969, 2875, 1737, 1607, 1365, 1228, 1118, 882, 772, 605 cm^{-1}. HRMS (ESI, m/z): calcd for $C_{13}H_{14}NO_5$ $(M + H)^+$: 264.0866, found: 264.0868.

*6-Bromo-2-(1,4-dioxan-2-yl)benzo[d]oxazole (**3k**).* White solid, mp: 131−132 °C, 121 mg, yield: 86%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.62 (d, J = 8.5 Hz, 1H), 7.50 (dd, J = 8.5, 1.7 Hz, 1H), 4.97 (dd, J = 9.0, 2.7 Hz, 1H), 4.21 (dd, J = 11.7, 2.9 Hz, 1H), 4.00 (ddd, J = 14.3, 12.1, 7.3 Hz, 3H), 3.90−3.80 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.3, 151.1, 139.8, 128.2, 121.4, 118.6, 114.4, 70.9, 68.4, 66.5, 66.4. IR (neat) ν 3045, 2930, 2869, 1685, 1568, 1482, 1256,

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1125, 917, 841, 689, 590 cm^{-1}. HRMS (ESI, m/z): calcd for $C_{11}H_{10}BrNO_3Na$ $(M + Na)^+$: 305.9742, found: 305.9737.

*5-Bromo-2-(1,4-dioxan-2-yl)benzo[d]oxazole (**3l**).* White solid, mp: 78−79 °C, 114 mg, yield: 81%. ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J = 1.6 Hz, 1H), 7.49 (dd, J = 8.6, 1.8 Hz, 1H), 7.44 (d, J = 8.6 Hz, 1H), 4.97 (dd, J = 9.0, 2.9 Hz, 1H), 4.20 (dd, J = 11.7, 2.9 Hz, 1H), 4.06−3.93 (m, 3H), 3.89−3.76 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.0, 149.6, 142.2, 128.7, 123.4, 117.4, 112.1, 70.9, 68.4, 66.5, 66.4. IR (neat) ν 3051, 2923, 2854, 1685, 1566, 1480, 1258, 1120, 916, 837, 681, 591 cm^{-1}. HRMS (ESI, m/z): calcd for $C_{11}H_{10}BrNO_3Na$ $(M + Na)^+$: 305.9742, found: 305.9739.

*5-Chloro-2-(1,4-dioxan-2-yl)benzo[d]oxazole (**3m**).* White solid, mp: 129−130 °C, 99 mg, yield: 83%. ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, J = 8.5 Hz, 1H), 7.58 (s, 1H), 7.36 (dd, J = 8.4, 1.2 Hz, 1H), 4.97 (dd, J = 9.0, 2.7 Hz, 1H), 4.21 (dd, J = 11.7, 2.7 Hz, 1H), 4.10−3.91 (m, 3H), 3.84 (dt, J = 9.5, 7.1 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.4, 150.8, 139.4, 131.3, 125.5, 121.0, 111.5, 70.9, 68.4, 66.5, 66.4. IR (neat) ν 3015, 2969, 2942, 1563, 1488, 1365, 1228, 1092, 880, 668 cm^{-1}. HRMS (ESI, m/z): calcd for $C_{11}H_{10}ClNO_3Na$ $(M + Na)^+$: 262.0247, found: 262.0244.

*5,6-Dichloro-2-(1,4-dioxan-2-yl)benzo[d]oxazole (**3n**).* White solid, mp: 119−120 °C, 97 mg, yield: 71%. ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, J = 1.6 Hz, 1H), 7.41 (d, J = 1.7 Hz, 1H), 5.00 (dd, J = 8.7, 2.8 Hz, 1H), 4.21 (dd, J = 11.6, 2.5 Hz, 1H), 4.11−3.90 (m, 3H), 3.89−3.80 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.6, 146.1, 142.4, 130.6, 126.1, 119.1, 116.8, 70.8, 68.3, 66.5, 66.4. IR (neat) ν 2989, 2947, 2865, 1610, 1591, 1454, 1387, 1279, 1235, 1120, 881, 769, 628 cm^{-1}. HRMS (ESI, m/z): calcd for $C_{11}H_9$ Cl_2NO_3Na $(M + Na)^+$: 295.9857, found: 295.9853.

*5-Bromo-2-(1,4-dioxan-2-yl)-6-fluorobenzo[d]oxazole (**3o**).* Light yellow liquid, 85 mg, yield: 57%. ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J = 1.2 Hz, 1H), 7.32 (dd, J = 9.2, 1.6 Hz, 1H), 4.99 (dd, J = 8.8, 3.0 Hz, 1H), 4.20 (dd, J = 11.7, 3.0 Hz, 1H), 4.09−3.87 (m, 3H), 3.87−3.65 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.5, 146.6 (d, J = 258.0 Hz), 144.8 (d, J = 2.2 Hz), 137.1 (d, J = 11.0 Hz), 119.5 (d, J = 4.5 Hz), 116.8 (d, J = 7.1 Hz), 116.2 (d, J = 19.5 Hz), 70.7, 68.3, 66.5, 66.4. IR (neat) ν 3015, 2999, 2867, 1611, 1450, 1365, 1228, 1121, 921, 750, 529 cm^{-1}. HRMS (ESI, m/z): calcd for $C_{11}H_9BrFNO_3Na$ $(M + Na)^+$: 323.9648, found: 323.9645.

*2-(1,4-Dioxan-2-yl)benzo[d]oxazole (**3p**).* White solid, mp: 61−62 °C, 84 mg, yield: 82% (known compound).[17] ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (dd, J = 5.6, 3.4 Hz, 1H), 7.58 (d, J = 6.1 Hz, 1H), 7.44−7.33 (m, 2H), 5.00 (dd, J = 9.1, 2.6 Hz, 1H), 4.23 (dd, J = 11.7, 2.9 Hz, 1H), 4.08−3.93 (m, 3H), 3.89−3.79 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.7, 150.6, 140.6, 125.5, 124.7, 120.4, 110.9, 71.1, 68.5, 66.6, 66.4. IR (neat) ν 3007, 2981, 1658, 1530, 1472, 1347, 1311, 850, 787, 734 cm^{-1}. HRMS (ESI, m/z): calcd for $C_{11}H_{11}NO_3Na$ $(M + Na)^+$: 228.0637, found: 228.0635.

*5-Phenyl-2-(tetrahydrofuran-2-yl)oxazole (**3q**).* Colorless liquid, 65 mg, yield: 61%. ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J = 7.9 Hz, 2H), 7.42 (t, J = 7.6 Hz, 2H), 7.33 (t, J = 7.4 Hz, 1H), 7.29 (s, 1H), 5.14−5.08 (m, 1H), 4.09 (dd, J = 14.7, 7.3 Hz, 1H), 3.99 (dd, J = 14.1, 7.5 Hz, 1H), 2.44−2.29 (m, 2H), 2.25−2.14 (m, 1H), 2.12−2.01 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.7, 151.8, 128.8, 128.5, 127.9, 124.3, 121.7, 73.5, 69.0, 30.4, 25.9. IR (neat) ν 2979, 2965, 2875, 1656, 1583, 1454, 1273, 1241, 1077, 910, 750 cm^{-1}. HRMS (ESI, m/z): calcd for $C_{13}H_{13}NO_2Na$ $(M + Na)^+$: 238.0844, found: 238.0838.

*Methyl-5-phenyl-2-(tetrahydrofuran-2-yl)oxazole-4-carboxylate (**3r**).* Colorless liquid, 89 mg, yield: 65%. ^1H NMR (400 MHz, $CDCl_3$) δ 8.17−7.94 (m, 2H), 7.48 (ddd, J = 7.2, 4.9, 1.6 Hz, 3H), 5.12 (t, J = 6.8 Hz, 1H), 4.09 (dt, J = 14.0, 7.0 Hz, 1H), 4.03−3.96 (m, 1H), 3.94 (s, 3H), 2.37 (q, J = 7.2 Hz, 2H), 2.22−2.14 (m, 1H), 2.09−2.01 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.5 155.9, 130.4, 128.4, 128.4, 126.8, 126.5, 73.3, 69.3, 52.3, 30.76, 26.0. IR (neat) ν 2954, 2930, 2873, 1725, 1655, 1547, 1451, 1275, 1078, 977, 781 cm^{-1}. HRMS (ESI, m/z): calcd for $C_{15}H_{15}NO_4$ $(M + Na)^+$: 296.0899, found: 296.0892.

*6-Methyl-2-(tetrahydrofuran-2-yl)benzo[d]oxazole (**3s**).* Colorless liquid, 86 mg, yield: 85%. ^1H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, J = 8.1 Hz, 1H), 7.29 (s, 1H), 7.10 (d, J = 8.1 Hz, 1H), 5.15 (t, J = 6.7 Hz, 1H), 4.08 (dd, J = 14.6, 7.3 Hz, 1H), 3.97 (dd, J = 14.2, 7.5 Hz, 1H), 2.44 (s, 3H), 2.36 (dd, J = 14.3, 7.1 Hz, 2H), 2.18−2.10 (m, 1H), 2.07−1.98 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.6, 151.2, 138.6, 135.5, 125.5, 119.4, 110.8, 73.9, 69.2, 30.6, 25.8, 21.7. IR (neat) ν 3015, 2954, 2857, 1645, 1621, 1447, 1363, 1278, 1125, 820, 668 cm^{-1}. HRMS (ESI, m/z): calcd for $C_{12}H_{13}NO_2Na$ $(M + Na)^+$: 226.0844, found: 226.0839.

*2-(1,3-Dioxolan-2-yl)benzo[d]oxazole (**3t1**).* Colorless liquid, 52 mg, yield: 54%. ^1H NMR (400 MHz, $CDCl_3$) δ 7.80−7.73 (m, 1H), 7.63−7.53 (m, 1H), 7.43−7.33 (m, 2H), 6.21 (s, 1H), 4.34−4.27 (m, 2H), 4.20−4.13 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.9, 150.7, 140.4, 125.9, 124.7, 120.8, 111.1, 70.5, 68.7, 65.7. IR (neat) ν 3015, 2969, 2946, 1435, 1366, 1216, 1092, 896, 764 cm^{-1}. HRMS (ESI, m/z): calcd for $C_{10}H_9$ NO_3Na $(M + Na)^+$: 214.0480, found: 214.0477.

*2-(1,3-Dioxolan-4-yl)benzo[d]oxazole (**3t2**).* Colorless liquid, 20 mg, yield: 21%. ^1H NMR (400 MHz, $CDCl_3$) δ 7.80−7.73 (m, 1H), 7.60−7.53 (m, 1H), 7.42−7.34 (m,2H), 5.32 (dd, J = 6.7, 5.5 Hz, 1H), 5.26 (s, 1H), 5.18 (s, 1H), 4.37 (dt, J = 6.8, 3.4 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.4, 150.9, 140.6, 125.6, 124.6, 120.4, 110.9, 70.5, 68.7, 65.7. IR (neat) ν 3015, 2969, 2946, 1435, 1366, 1216, 1092, 896, 764 cm^{-1}. HRMS (ESI, m/z): calcd for $C_{10}H_9NO_3Na$ $(M + Na)^+$: 214.0480, found: 214.0477.

*2-(1-Butoxyethyl)benzo[d]oxazole (**3u1**) and 2-(1-Ethoxybutyl)-benzo[d]oxazole (**3u2**) Mixture.* Colorless liquid, 75 mg, yield: 69%.^1H NMR (400 MHz, $CDCl_3$) δ 7.80−7.69 (m, 1H), 7.60−7.53 (m, 1H), 7.40−7.34 (m, 2H), 4.76 (q, J = 6.6 Hz, 0.66H), 4.62 (t, J = 6.9 Hz, 0.34H), 3.66−3.48 (m, 2H), 1.68 (d, J = 6.7 Hz, 1.97H), 1.61−1.22 (m, 5.03H), 0.91 (t, J = 7.4 Hz, 1.98H), 0.97 (t, J = 7.4 Hz, 1.02H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4, 166.1, 150.8, 150.9, 140.8, 140.7, 125.2, 125.1, 124.4, 124.3, 120.2, 120.1, 110.8, 75.4, 71.5, 69.7, 65.6, 36.1, 31.7, 29.7, 19.6, 19.2, 18.6, 15.1, 13.8. IR (neat) ν 2963, 2934, 2869, 1616, 1430, 1293, 1261, 1112, 906, 773 cm^{-1}. HRMS (ESI, m/z): calcd for $C_{13}H_{17}NO_2$ $(M + Na)^+$: 242.1157, found: 242.1153.

*Methyl-2-(1-methoxybutyl)benzo[d]oxazole-6-carboxylate (**3v**).* Colorless liquid, 75 mg, yield: 57%. ^1H NMR (400 MHz, $CDCl_3$) δ 8.25 (s, 1H), 8.09 (dd, J = 8.4, 1.1 Hz, 1H), 7.77 (d, J = 8.4 Hz, 1H), 4.56−4.51 (m, 1H), 3.97 (s, 3H), 3.44 (s, 3H), 2.07−1.93 (m, 2H), 1.55−1.39 (m, 2H), 0.97 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.5, 166.5, 150.5, 144.6, 127.4, 126.2, 119.8, 112.6, 77.1, 57.9, 52.4, 35.8, 18.4, 13.7. IR (neat) ν 3073, 2961, 2926, 2867, 1724, 1606, 1432, 1297, 1263, 1071, 977, 742 cm^{-1}. HRMS (ESI, m/z): calcd for $C_{14}H_{17}NO_4Na$ $(M + Na)^+$: 286.1056, found: 286.1051.

*2-(1,2-Dimethoxyethyl)benzo[d]oxazole (**3w1**).* Colorless liquid, 55 mg, yield: 53%. ^1H NMR (400 MHz, $CDCl_3$) δ 7.74 (dd, J = 5.3, 3.7 Hz, 1H), 7.56 (dd, J = 5.8, 3.3 Hz, 1H), 7.39−7.30 (m, 2H), 4.74 (dd, J = 6.8, 4.9 Hz, 1H), 3.88 (ddd, J = 15.2, 10.3, 5.9 Hz, 2H), 3.49 (s, 3H), 3.42 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.3, 150.8, 140.7, 125.4, 124.5, 120.3, 110.9, 76.5, 73.3, 59.5, 58.3. IR (neat) ν 2999, 2969, 2939, 1611, 1454, 1365, 1228, 1112, 765, 539 cm^{-1}. HRMS (ESI, m/z): calcd for $C_{11}H_{13}NO_3Na$ $(M + Na)^+$: 230.0793, found: 230.0789.

*2-((2-Methoxyethoxy)methyl)benzo[d]oxazole (**3w2**).* Colorless liquid, 30 mg, yield: 28%. ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 (dd, J = 5.6, 3.2 Hz, 1H), 7.57 (dd, J = 5.7, 2.9 Hz, 1H), 7.37 (dd, J = 6.4, 2.7 Hz, 2H), 4.86 (s, 2H), 3.83 (dd, J = 5.4, 3.6 Hz, 2H), 3.64 (dd, J = 5.4, 3.6 Hz, 2H), 3.41 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.6, 151.1, 140.8, 125.4, 124.5, 120.3, 110.8, 71.8, 70.7, 65.8, 59.1. IR (neat) ν 3015, 2969, 2945, 1536, 1435, 1358, 1205, 1092, 899, 754, 539 cm^{-1}. HRMS (ESI, m/z): calcd for $C_{11}H_{13}$ NO_3Na $(M + Na)^+$: 230.0793, found: 230.0790.

*2-(1-(2-Ethoxyethoxy)ethyl)benzo[d]oxazole (**3x**).* Colorless liquid, 92 mg, yield: 78%. ^1H NMR (400 MHz, $CDCl_3$) δ 7.78−7.66 (m, 1H), 7.61−7.46 (m, 1H), 7.41−7.30 (m, 2H), 4.84 (q, J = 6.7 Hz, 1H), 3.72 (t, J = 4.8 Hz, 2H), 3.63−3.58 (m, 2H), 3.50 (q, J = 7.0 Hz, 2H), 1.70 (d, J = 6.7 Hz, 3H), 1.17 (t, J = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.0, 150.8, 140.7, 125.2, 124.4, 120.2, 110.8, 71.9, 69.7, 69.2, 66.6, 19.5, 15.1. IR (neat) ν 2969, 2932, 2869, 1646,

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1621, 1488, 1455, 1365, 1228, 1112, 765, 688 cm^{-1}. HRMS (ESI, *m*/*z*): calcd for $C_{13}H_{17}NO_3Na$ $(M + Na)^+$: 258.1106, found: 258.1105.

*2-(2-Methyltetrahydrofuran-2-yl)benzo[d]oxazole (**3y1**) and 2-(5-Methyltetrahydrofuran-2-yl)benzo[d]oxazole (**3y2**) Mixture.* Light yellow liquid, 74 mg, yield: 73%. ^1H NMR (400 MHz, $CDCl_3$) δ 7.66−7.60 (m, 1H), 7.45−7.40 (m, 1H), 7.24−7.18 (m, 2H), 5.20 (t, J = 7.0 Hz, 0.26H), 5.07 (dd, J = 7.9, 5.5 Hz, 0.04H), 4.32−4.22 (m, 0.27H), 4.18−4.08 (m, 0.06H), 4.02−3.88 (m, 1.36H), 2.68−2.55 (m, 0.63H), 2.41−2.28 (m, 0.59H), 2.20−2.09 (m, 0.32 H), 2.09−1.86 (m, 2.11H), 1.68 (s, 2.03H), 1.52 (ddd, J = 17.0, 12.2, 8.6 Hz, 0.44H), 1.29 (d, J = 6.1 Hz, 0.13H), 1.24 (d, J = 6.1 Hz, 0.79H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.9, 166.5, 150.9, 150.8, 140.8, 125.0, 124.9, 124.2, 124.2, 120.0, 110.6, 80.3, 77.5, 77.4, 76.5, 74.0, 73.6, 68.9, 37.3, 33.3, 32.9, 30.9, 30.8, 26.0, 25.6, 20.9, 20.6. IR (neat) ν 3011, 2959, 2866, 1621, 1451, 1366, 1275, 1128, 925, 670 cm^{-1}. HRMS (ESI, *m*/*z*): calcd for $C_{12}H_{13}NO_2Na$ $(M + Na)^+$: 226.0844, found: 226.0841.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02211.

Experimental details and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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