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One-Pot Multi-Component Reaction of Catechols, Ammonium Acetate and Aldehydes for the Synthesis of Benzoxazole Derivatives Using Fe(III)-Salen Complex

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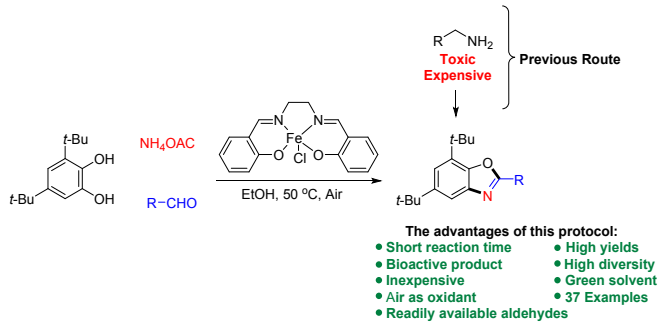


ABSTRACT: The Fe(III)-salen complex has been applied successfully as a catalyst for the novel, simple, efficient, and one-pot multi-component synthesis of benzoxazole derivatives from catechols, ammonium acetate as the nitrogen source and aldehydes (nontoxic and cheap alternatives of amines) for the first time. Using this procedure, a wide range of benzoxazoles was successfully synthesized in the presence of a catalyst in EtOH under mild conditions, and all products were obtained in excellent yields. To the best of our knowledge, this method is the first example of the multi-component synthesis of benzoxazole derivatives using these starting materials. The notable features such as the use of air that is considered the benign oxidant, EtOH as a green solvent, ease of product separation, readily available and inexpensive aldehydes, and mild conditions make our procedure more efficient and practical for organic synthesis. Moreover, the current protocol is successfully applied to synthesize desirable products in large scale.

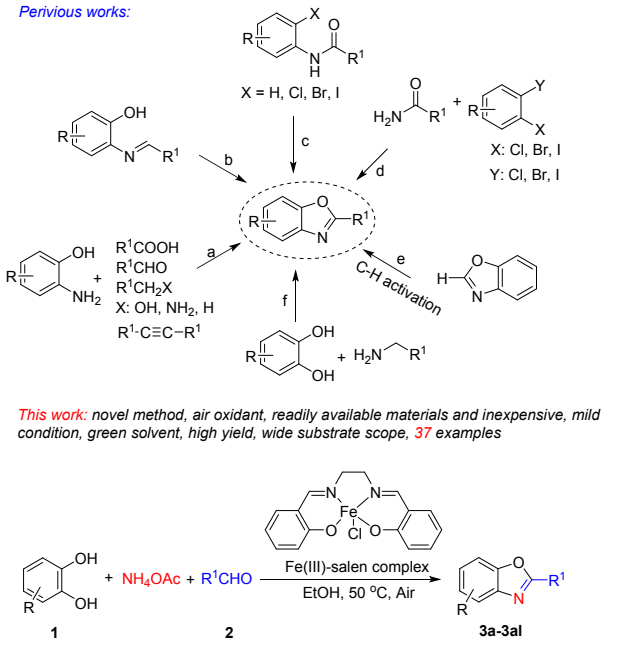
Introduction

Multi-component reactions (MCRs) have emerged as useful synthetic tools in drug discovery, organic synthesis, and material science due to their advantages over conventional multistep synthesis. Being atom economical, efficient, time-saving and straightforward make this approach a powerful method in the synthesis of heterocyclic compounds in the field of industrial chemicals and pharmaceuticals.[1-4]

Between various kinds of heterocyclic compounds,[5] benzoxazoles occupy a significant place since they are the major elements of diverse natural compounds and functionalized products.[6] Benzoxazole derivatives are vital structures in many compounds such as biologically active compounds,[7] therapeutically active molecules,[8] natural products,[9] fluorescent probes,[10] heat-resistant polymers,[11] and functional materials.[12]

There are several pathways for the preparation of benzoxazole derivatives. Often, 2-substituted benzoxazole derivatives are produced through the reaction of *o*-aminophenols with carboxylic acids/aldehydes/alcohols/benzyl amines/toluene or carbon-carbon triple bonds and subsequent oxidative cyclization of the imine intermediate (Scheme 1, a-b).[13-14] Recently, general methods for the synthesis of benzoxazoles *via* intramolecular/intermolecular coupling reaction of *ortho*-substituted acyl anilides or *ortho*-dihaloaromatic compounds were reported (Scheme 1, c-d).[15]

Scheme 1. Different methods for the synthesis of benzoxazoles.



Moreover, transition metal-catalyzed direct C-H bond activation of benzoxazoles has been described (Scheme 1,

e).[16] Recently, Kerr *et al*., 2011; Chen *et al*., 2015; Meng *et al*., 2017; and Sharghi *et al*., 2019; have presented novel protocols for the efficient synthesis of benzoxazoles through the oxidative functionalization of catechol derivatives with amine derivatives in the presence of silver, copper or iron as catalyst (Scheme 1, f).[17] However, drawbacks of these pathways include high temperatures, using strong acids or oxidizing agents, and using expensive and potentially toxic reactants, and reagents, which make them to have a limited substrate scope.

As a fact, metallo-salens have shown broad applicability as catalysts. These complexes are versatile systems and generally applied as effective catalysts in organic reactions.[18] Due to the abundance, availability, inexpensiveness and low toxicity of many iron compounds and their salts they have been used by many organic chemists as a catalyst in the synthesis of different organic compounds.[19]

On the other hand, the development of new and efficient strategies by readily available starting materials under mild reaction conditions is strongly desired for the synthesis of benzoxazoles. In this research, for the first time we report a novel, efficient and multi-component Fe(III)-salen complex-catalyzed method for the synthesis of benzoxazole derivatives *via* catechols, ammonium acetate as the nitrogen source and aldehydes in EtOH as green solvent (Scheme 1).

The notable features of this approach including the use of air that is considered the benign oxidant and EtOH as a green solvent, ease of product separation, using readily available and inexpensive aldehydes, and performing the reaction under mild conditions make the current protocol practical, and eco-friendly for organic synthesis.

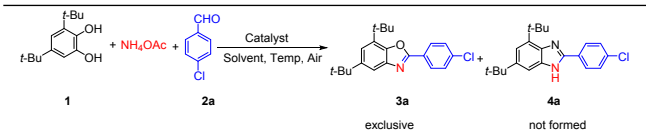
Results and Discussion

In continuation of our previous investigations on the application of metallo-salens as catalysts in organic synthesis,[2, 13e, 20] and as a result of our interest in the preparation of organic compounds,[21] we introduce the synthesis of benzoxazole derivatives in the presence of Fe(III)-salen complex. The metal-salen complexes were produced by previously reported procedures.[2, 13e, 20, 22] To find out the suitable condition for the novel multi-component synthesis of benzoxazole derivatives, a series of experiments were performed with the model reaction of 3,5-di-*tert*-butylbenzene-1,2-diol **1** (1.0 mmol), ammonium acetate as the nitrogen source (1.0 mmol), and 4-chlorobenzaldehyde **2a** (1.0 mmol) shown in Table 1. Under these reaction conditions, we exclusively obtained benzoxazole **3a**, and no benzimidazole **4a** was observed.

At first, a variety of metal-salen complexes were tested to find out the best catalyst for the synthesis of benzoxazole **3a** in EtOH at 25 °C. Among various metal-salen complexes (Cr, V, Cu, Mn, Mo, and Fe) (Table 1, entries 1-6), Fe(III)-salen complex was found to give the best result in terms of yield and reaction time (Table 1, entry 6). No improvement in the yield of the final product was achieved by using other tested salen catalysts, including Cr, V, Cu, Mn, and Mo (Table 1, entries 1-5). Then, the effect of various solvents, such as EtOH, DMF, Toluene, DMSO, CH_3CN, DCM, EtOAc, DCE, $CHCl_3$, MeOH as well as solvent-free condition were explored on the model reaction in the presence of Fe(III)-salen complex at 25 °C (Table 1, entries 6-16). We found that EtOH is the best solvent for the synthesis of benzoxazole **3a** (Table 1, entry 6) not only it showed high reaction rate, and excellent yield of product, but also it is an environment-friendly solvent which makes the method more practical for different industries. Also, no product was obtained under the solvent-free and catalyst-free conditions, indicating that the presence of catalyst and solvent are necessary for this transformation (Table 1, entries 16-17). In continuous, $FeCl_3$ and nano magnetic Fe_3O_4 were applied as catalyst and obtained 65% and 75% yield, respectively (Table 1, entries 18-19). The obtained results showed that the optimum amount of Fe(III)-salen complex loading was 3 mol% in EtOH for the best synthesis of product **3a** (Table 1, entry 20). Increasing the amount of catalyst (10 mol %) did not improve the yield (Table 1, entry 21). The effect of temperature on the preparation of benzoxazole **3a** using Fe(III)-salen complex in EtOH was investigated. This reaction was also accomplished at 50 °C, and 95 % isolated yield of product was obtained after 3 h (Table 1, entry 22). The role of increasing temperature to reflux was screened and as it is shown in Table 1, increasing the temperature did not have any effect on the reaction progress (Table 1, entry 23).

During our optimization studies, the optimal amount of ammonium acetate was examined (Table 1, entries 22, 24-25). By using 1.0 mmol ammonium acetate as the nitrogen source, 95 % product was obtained. According to Table 1, the best results for the one-pot multi-component synthesis of product **3a** from 3,5-di-*tert*-butylbenzene-1,2-diol **1**, ammonium acetate as the nitrogen source, and 4-chlorobenzaldehyde **2a** were obtained in EtOH at 50 ˚C in the presence of Fe(III)-salen complex (3 mol%) as a catalyst (Table 1, entry 22).

Table 1. Optimization of the reaction conditions for synthesis of 4,6-di-*tert*-butyl-2-(4-chlorophenyl)-*1H*-benzo[d]imidazole[a, b]



1 2a 3a exclusive 4a not formed

Entry	Catalyst / mol %	Solvent	Temp.	Time (h)	Yield[a] %
1	Salen-Cr(Cl) / 5	EtOH	25 °C	16	20
2	Salen-V(Cl)$_2$ / 5	EtOH	25 °C	16	30
3	Salen-Cu / 5	EtOH	25 °C	16	35
4	Salen-Mn(OAc) / 5	EtOH	25 °C	7	70
5	Salen-Mo(O) / 5	EtOH	25 °C	16	40
6	Salen-Fe(Cl) / 5	EtOH	25 °C	5	83

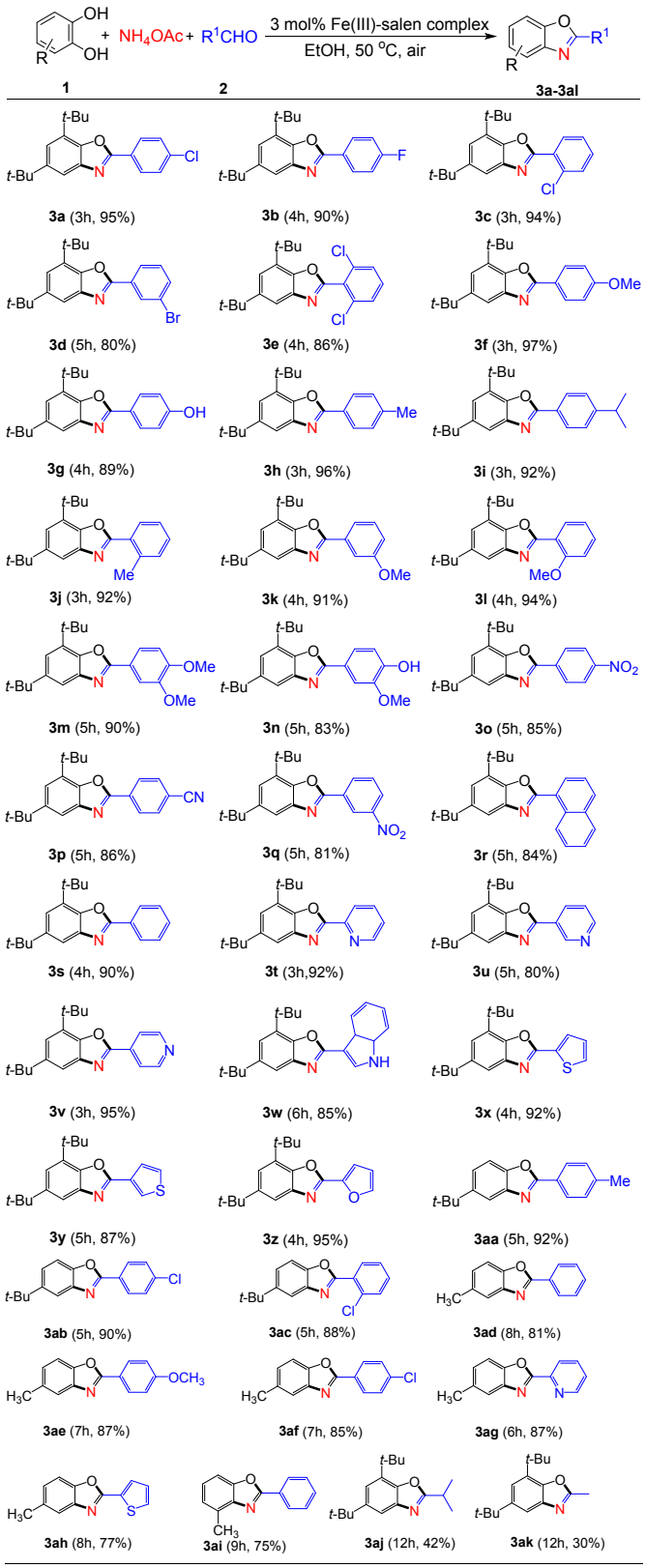
7	Salen-Fe(Cl) / 5	DMF	25 °C	14	60
8	Salen-Fe(Cl) / 5	Toluene	25 °C	10	70
9	Salen-Fe(Cl) / 5	DMSO	25 °C	16	30
10	Salen-Fe(Cl) / 5	CH_3CN	25 °C	8	73
11	Salen-Fe(Cl) / 5	DCM	25 °C	12	55
12	Salen-Fe(Cl) / 5	EtOAc	25 °C	14	52
13	Salen-Fe(Cl) / 5	DCE	25 °C	10	65
14	Salen-Fe(Cl) / 5	$CHCl_3$	25 °C	16	35
15	Salen-Fe(Cl) / 5	MeOH	25 °C	7	75
16	Salen-Fe(Cl) / 5	-	25 °C	24	-
17	-	EtOH	25 °C	24	-
18	$FeCl_3$ / 5	EtOH	25 °C	8	65
19	NM-Fe_3O_4	EtOH	25 °C	6	75
20	Salen-Fe(Cl) / 3	EtOH	25 °C	5	90
21	Salen-Fe(Cl) / 10	EtOH	25 °C	5	75
22	**Salen-Fe(Cl) / 3**	**EtOH**	**50 °C**	**3**	**95**
23	Salen-Fe(Cl) / 3	EtOH	reflux	3	83
24[c]	Salen-Fe(Cl) / 3	EtOH	50 °C	3	89
25[d]	Salen-Fe(Cl) / 3	EtOH	50 °C	3	80

[a]General conditions: 3,5-di-*tert*-butylbenzene-1,2-diol (1.0 mmol), ammonium acetate (1.0 mmol), 4-chlorobenzaldehyde (1.0 mmol), solvent (5.0 mL), air. [b]Isolated yield. [c]Ammonium acetate (2.0 mmol). [d]Ammonium acetate (3.0 mmol).

After optimization of the reaction conditions for the synthesis of benzoxazole **3a**, we screened the scope and generality of this method by varying the aldehydes and catechols under the optimized conditions. The results are shown in **Scheme 2**. All benzoxazole derivatives (**3a-3ak**) were characterized by the melting point, FT-IR, ^{1}H NMR, ^{13}C NMR, and elemental analysis.

As shown in **Scheme 2**, aryl aldehydes containing different electron-donating and electron-withdrawing groups afforded the desired benzoxazole derivatives in good to excellent yields. Halogen groups at the *ortho*, *meta*, and *para* position of benzaldehyde in reaction with 3,5-di-*tert*-butylbenzene-1,2-diol worked well and gave good yields of benzoxazoles regardless of their electronic character (Scheme 2, 3a-e). Moreover, benzaldehyde with electron-donating groups at the *para* position such as methoxy, hydroxyl, methyl, and isopropyl participated well in the reactions to achieve corresponding products in good to high yields under mild reaction conditions (Scheme 2, 3f-i). In addition, benzoxazoles 3j, 3k, and 3l with methyl and methoxy groups in *ortho* and *meta* position of benzaldehyde were obtained in 92%, 91%, and 94% yields, respectively (Scheme 2, 3j-l). Moreover, benzaldehydes with two donor substitutes such as 3,4-dimethoxybenzaldehyde and 4-hydroxy-3-methoxybenzaldehyde were tested (Scheme 2, 3m-n).

Scheme 2. Scope of the reaction[a, b]



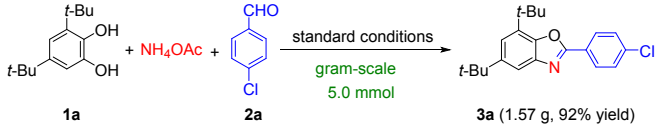
[a]General conditions: **1** (1.0 mmol), NH_4OAc (1.0 mmol) and **2** (1.0 mmol), Fe(III)-salen complex (3 mol%), EtOH (5.0 mL), air, 50 °C. [b]Isolated yield.

For further investigation of the reaction scope, benzaldehyde with electron-withdrawing groups such as cyano and nitro reacted with 3,5-di-*tert*-butylbenzene-1,2-diol to successfully form benzoxazoles in good to excellent yields under mild reaction conditions (Scheme 2, 3o-q).

According to Scheme 2, benzaldehydes with electron-donating groups showed better reactivity than benzaldehyde bearing electron-withdrawing groups. Furthermore, sterically hindered 1-naphthaldehyde produced naphthyl-substituted benzoxazole in 84% yield (Scheme 2, 3r). Pleasingly, various *N*-heteroaryl aldehydes, such as, pyridine-2-carbaldehyde, pyridine-3-carbaldehyde, pyridine-4-carbaldehyde, and 1*H*-indole-3-carbaldehyde were converted to the corresponding benzoxazole derivatives in the presence of a catalytic amount of Fe(III)-salen complex with good to excellent yields (Scheme 2, 3t-w). *S*-heteroaryl aldehydes and *O*-heteroaryl aldehydes such as thiophene-2-carbaldehyde, thiophene-3-carbaldehyde, and furan-2-carbaldehyde could also give the corresponding benzoxazoles in 92%, 87% and 95% yields, respectively (Scheme 2, 3x-z). In continue, we turned our attention to the variation of catechols. Notably, when 4-*tert*-butylbenzene-1,2-diol and 4-methyl-benzene-1,2-diol, 3-methyl-benzene-1,2-diol were employed as the substrate in the reaction with various functional groups (-Me, -Cl, and -OMe) on the benzaldeyde ring as well as heteroaryl aldehydes (pyridine-2-carbaldehyde, and thiophene-2-carbaldehyde), related benzoxazoles were obtained in reasonable yields (Scheme 2, 3aa-ai). We also applied this synthetic procedure for the preparation of 2-alkylbenzoxazole derivatives using aliphatic aldehydes such as isobutyraldehyde and acetaldehyde under the optimized reaction conditions in the presence of Fe(III)-salen complex (Scheme 2, 3aj-ak). However, ortho-dihydroxybenzenes such as catechol (1,2-dihydroxybenzene), 4-nitrobenzene-1,2-diol, 3,4,5,6-tetrabromobenzene-1,2-diol, 3,4-dihydroxybenzoic acid, 7,8-dihydroxy-4-methyl-2*H*-chromen-2-one, and naphthalene-2,3-diol did not afford the desired products in the presented method.

Importantly, aside from screening different substrates, to demonstrate the practicability of the current methodology, large scale synthesis of the 5,7-di-*tert*-butyl-2-(4-chlorophenyl)benzo[*d*]oxazole (**3a**) was evaluated *via* the reaction between 3,5-di-*tert*-butylbenzene-1,2-diol (5.0 mmol), NH_4OAc (5.0 mmol) and 4-chlorobenzaldehyde (5.0 mmol). Based on the obtained result, the conducted reaction was successfully carried out on a large-scale, and no notable loss of yield was observed (**Scheme 3**).

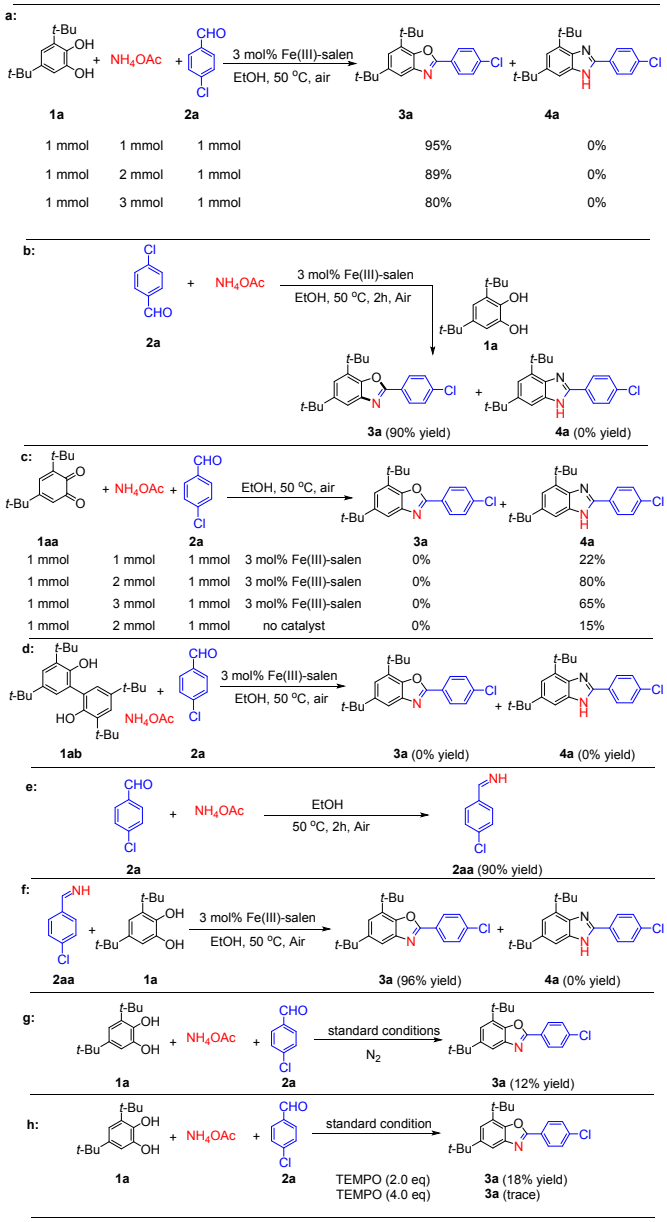
Scheme 3. Gram-Scale Synthesis of Product **3a**.



To obtain deep insight into the reaction mechanism, several different control experiments were performed (**Scheme 4**). As it is shown in Scheme 4, at the beginning of the study, a one-pot three-component reaction using 3,5-di-*tert*-butylbenzene-1,2-diol **1a** (1.0 mmol), ammonium acetate as the nitrogen source (1.0 mmol), and 4-chlorobenzaldehyde **2a** (1.0 mmol) in the presence of 3 mol % Fe(III)-salen complex under the standard reaction conditions, gave 95% yield of **3a** in only 3 h. Also, we applied different amounts of ammonium acetate, and benzoxazole **3a** was exclusively obtained and no benzimidazole **4a** was observed (Scheme 4, **a**). Moreover, 4-chlorobenzaldehyde **2a** was reacted with ammonium acetate using Fe(III)-salen complex as a catalyst in EtOH at 50 ˚C for 2 hours. Next, 3,5-di-*tert*-butylbenzene-1,2-diol **1a** was added to the reaction mixture and benzoxazole **3a** was just obtained with 90% yield (Scheme 4, **b**). According to the obtained results, it is speculated that the reaction pathway was going *via* 3,5-di-*tert*-butyl-*o*-benzoquinone intermediate. Therefore, we used 3,5-di-*tert*-butyl-*o*-benzoquinone **1aa** as starting material to react with ammonium acetate and 4-chlorobenzaldehyde under the standard reaction conditions and benzimidazole product (22%) **4a** was obtained and benzoxazole **3a** was not observed (Scheme 4, **c**). Furthermore, different loadings of ammonium acetate (2.0 mmol and 3.0 mmol) were tested and product **4a** was obtained in 80% and 65% yields, respectively. Additionally, in the absence of the catalyst, 15% product **4a** was just obtained (Scheme 4, **c**). According to the previous reports,[23] homocoupling product (biphenyldiol **1ab**) may be produced as an intermediate in the reaction pathway. For this purpose, the homocoupling product (biphenyldiol **1ab**) was used as the starting material under the same conditions, however **1ab** did not react smoothly with 4-chlorobenzaldehyde **2a** and ammonium acetate to afford products **3a** and **4a** (Scheme 4, **d**). Notably, the phenylmethanimine **2aa** was generated through the reaction between **2a** and ammonium acetate in a significant amount when the reaction was quenched after 2 h (Scheme 4, **e**). Additionally, when the compound **2aa** reacted with **1a** under the standard conditions, 96% yield of the desired product **3a** was obtained (Scheme 4, **f**). Also, when the model reaction was carried out under N_2, only 12% of product **3a** was detected; this result indicated that the atmosphere is necessary for this reaction (Scheme 4, **g**). When, 2.0 equivalents of the TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxyl, well-known radical-capturing agent) was added into the reaction system of **1a**, **2a** and ammonium acetate under the standard conditions, the formation of **3a** was partially observed, then the reaction was quenched by simply increasing the amount of TEMPO to 4.0 equivalents (Scheme 4, **h**). This observation implies that the reaction may happen *via* a radical process. Experiment studies exhibited that the mechanism probably involves a radical intermediate. Based on these experimental studies, we propose the mechanism shown in **Scheme 5**.

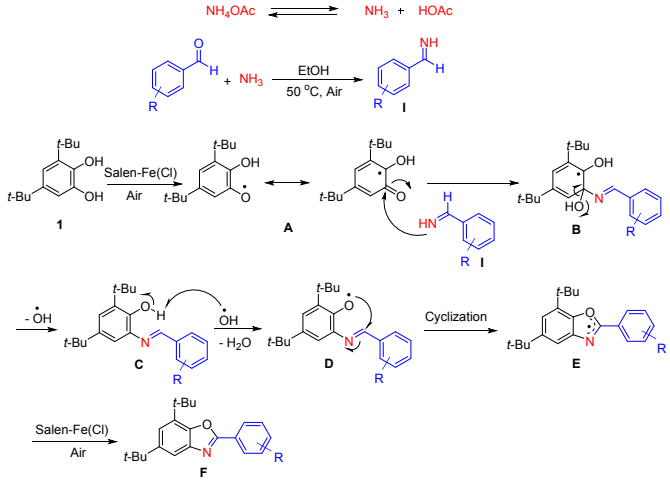
First, ammonium acetate dissociates into ammonia in the reaction, which is needed for the initial condensation with aryl aldehyde. Ammonia reacts with aldehyde to give the phenylmethanimine intermediate **I**.[24]

Scheme 4. Control Experiments (**a-h**).



Next, radical intermediate **A** is produced from 3,5-di-*tert*-butylbenzene-1,2-diol **1** *via* an oxidation process.[25] Afterward, the nucleophilic attack of phenylmethanimine **I** to radical intermediate **A** lead to the formation of intermediate **B**.[25] Subsequently, imine intermediate **C** is created by eliminating the hydroxyl radical of intermediate **B**. Phenoxyl radical intermediate **D** is generated through single-electron transfer (SET) from imine intermediate **C** and hydroxyl radical.[16d] Then, an intramolecular cyclization takes place to afford intermediate **E**.[16d] Finally the desired benzoxazole **F** is produced *via* SET and the oxidative dehydrogenation of intermediate **E**.[13d, 16d, 20] Regarding the role of the Fe(III)-salen complex, it may be considered to activate the aldehyde, help radical production and promote the cyclization and the oxidative aromatization.

Scheme 5. The proposed mechanism for the synthesis of benzoxazole derivatives from the reaction of 3,5-di-*tert*-butylbenzene-1,2-diol, ammonium acetate, and aldehyde using Fe(III)-salen complex in EtOH (5.0 mL) at 50 ˚C.



CONCLUSIONS

Fe(III)-salen complex was found as an efficient catalyst for the novel, simple, and one-pot multicomponent synthesis of benzoxazole derivatives from catechols, ammonium acetate as the nitrogen source and aldehydes (nontoxic and cheap alternatives of amines) for the first time under mild and simple conditions. The advantages of this procedure for the synthesis of benzoxazole derivatives, include high product yields, using environmentally safe solvent (EtOH), experimental simplicity, readily available and inexpensive aldehydes, applicability for large scale and short reaction times. The best of our knowledge, this method is the first report for the one-pot multi-component synthesis of benzoxazole derivatives *via* the reaction of catechols, ammonium acetate as the nitrogen source and aldehydes.

EXPERIMENTAL SECTION

General Information. All reagents and solvents were commercially obtained from Merck, Fluka, or Sigma-Aldrich and used without further purification. Melting points were measured in capillary tubes in a Büchi B-545 apparatus. All the reactions were conducted in an oil bath and monitored by thin-layer chromatography on 0.25 mm silica gel (60 F254 in aluminum foil, Merck) visualizing with UV light. All known compounds were identified by comparison of their melting points and proton nuclear magnetic resonance (^{1}H NMR) data with those in the authentic samples. IR spectra were obtained using a Shimadzu FT-IR 8300 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 solvents using Bruker spectrometer (^{1}H NMR: 250, 300, and 400 MHz; ^{13}C NMR (62.5, 75 and 100 MHz). Proton chemical shifts are given as δ values against tetramethylsilane (TMS) as the internal standard and coupling constants (J) are given in hertz (Hz). Chemical shift multiplicities are represented as follows: (s = singlet, d = doublet, t = triple, sep = septet, m = multiplet, dd = double of doublet, td = triple of doublet). The elemental analysis was performed on a Perkin-Elmer 240-B microanalyzer.

General procedure for the synthesis of Schiff-Base (Salen)

To a solution of ethylenediamine (0.6 g, 10.0 mmol) in MeOH (20 mL) was added salicylaldehyde (2.44 g, 20.0

mmol). The reaction mixture was stirred at reflux for 2 h. After completion of the reaction, the precipitate was filtered off and washed by additional MeOH. Then, the residue was recrystallized from MeOH for further purification to give pure product in high yield.

Synthesis of iron salen complex

The salen (268 mg, 1.0 mmol) was dissolved in EtOH (15 mL) and slowly added drop wise to a suspension of $FeCl_3$ anhydrous (162 mg, 1.0 mmol) in the same solvent (10 mL). The homogeneous solution was stirred under nitrogen atmosphere at room temperature for 4 h. The brown Fe(III) salen complex was filtered off, washed with water, ethanol, and diethyl ether. Finally, the solid products dried at room temperature. Fe(III) salen complex was obtained in 85% (274 mg) yields.

General procedure for the Synthesis of Benzoxazoles Derivatives

A solution of catechol (1.0 mmol), aldehyde (1.0 mmol), NH_4OAc (77 mg, 1.0 mmol) and Fe(III)-salen complex (10 mg ≈ 3.0 mol%) in EtOH (5.0 mL) were stirred in an open tube under the air atmosphere at 50 ˚C in an oil bath for the required time. After completion of the reaction (monitoring by TLC), EtOH was removed under reduced pressure. The reaction mixture was diluted with EtOAc (4 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The resulting residue was purified by column chromatography on silica using a mixture of petroleum ether / EtOAc as eluent to achieve the pure product.

2,2'-[1,2-Ethanediylbis (nitrilomethylidyne)]-bis-phenol **(Salen)**.[18d]

Purified by MeOH solvent. Isolated yield: (2.63 g, 98%). Yellow solid; mp: 123-124 °C; FT-IR (KBr cm^{-1}): 3431 (br, OH), 1634 (s, C=N); ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 3.90 (s, 4H), 6.88 (t, *J*= 7.5 Hz, 2H), 6.98 (d, *J*= 9.0 Hz, 2H), 7.25 (dd, J_1= 9.0 Hz, J_2= 3.0 Hz, 2H), 7.29-7.35 (m, 2H), 8.34 (s, 2H), 13.30 (br, 2H); ^{13}C{H} NMR ($CDCl_3$, 75.0 MHz): δ (ppm) 59.7, 116.9, 118.6, 118.7, 131.5, 132.4, 161.0, 166.5.

5,7-Di-*tert*-butyl-2-(4-chlorophenyl)benzo[*d*]oxazole **(3a)**.[17a]

Purified by column chromatography on silica gel and eluted with ethyl acetate/petroleum ether (1:100). Isolated yield: (324 mg, 95%). Colorless liquid (lit. Colorless liquid); ^{1}H NMR (250 MHz, DMSO-d_6): δ (ppm) 1.33 (s, 9H), 1.48 (s, 9H), 7.29 (d, *J*= 2.5 Hz, 1H), 7.60 (d, *J*= 2.5 Hz, 1H), 7.67 (d, *J*= 7.5 Hz, 2H), 8.16 (d, *J*= 7.5 Hz, 2H); ^{13}C{H} NMR (100 MHz, DMSO-d_6): δ (ppm) 29.7, 31.5, 34.0, 34.7, 114.1, 119.5, 125.4, 128.7, 129.5, 133.3, 136.4, 141.8, 146.3, 147.5, 160.8. Anal. Calcd for $C_{21}H_{24}ClNO$: C, 73.78; H, 7.08; N, 4.10; Found: C, 73.72; H, 7.00; N, 4.14.

5,7-Di-*tert*-butyl-2-(4-fluorophenyl)benzo[*d*]oxazole **(3b)**.[17b]

Purified by column chromatography on silica gel and eluted with ethyl acetate/petroleum ether (1:100). Isolated yield: (292 mg, 90%). Colorless liquid (lit. Colorless liquid); ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 1.32 (s, 9H), 1.47 (s, 9H), 7.13 (t, *J*= 7.5 Hz, 2H), 7.24 (t, *J*= 2.5 Hz, 1H), 7.57 (d, *J*= 2.5 Hz, 1H), 8.17 (dd, *J*= 5.0, 7.5 Hz, 2H); ^{13}C{H} NMR (100 MHz, $CDCl_3$): δ (ppm) 30.0, 31.8, 34.5, 35.1, 114.2, 116.0, 116.2, 119.6, 123.8, 123.9, 129.5, 129.6, 133.7, 133.9, 142.2, 146.9, 147.8, 161.6, 163.3, 165.8. Anal. Calcd for $C_{21}H_{24}FNO$: C, 77.51; H, 7.43; N, 4.30; Found: C, 77.40; H, 7.36; N, 4.32.

5,7-Di-*tert*-butyl-2-(2-chlorophenyl)benzo[*d*]oxazole **(3c)**.[17c]

Purified by column chromatography on silica gel and eluted with ethyl acetate/petroleum ether (1:100). Isolated yield: (321 mg, 94%). Colorless liquid (lit. Colorless liquid); ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 1.32 (s, 9H), 1.47 (s, 9H), 7.27 (d, *J*= 2.5 Hz, 1H), 7.32-7.36 (m, 2H), 7.46-7.50 (m, 1H), 7.64 (d, *J*= 2.5 Hz, 1H), 8.08-8.11 (m, 1H); ^{13}C{H} NMR (75 MHz, $CDCl_3$): δ (ppm) 29.9, 31.8, 34.4, 35.1, 114.5, 119.9, 126.6, 126.9, 131.3, 131.6, 131.7, 133.2, 134.0, 141.8, 146.9, 147.8, 160.5. Anal. Calcd for $C_{21}H_{24}ClNO$: C, 73.78; H, 7.08; N, 4.10; Found: C, 73.72; H, 7,06; N, 4.06.

2-(3-Bromophenyl)-5,7-di-*tert*-butylbenzo[*d*]oxazole **(3d)**.

Purified by column chromatography on silica gel and eluted with ethyl acetate/petroleum ether (1:100). Isolated yield: (308 mg, 80%). Pale green solid, mp: 103-104 °C; ^{1}H NMR (250 MHz, DMSO-d_6): δ (ppm) 1.33 (s, 9H), 1.48 (s, 9H), 7.31 (s, 1H), 7.61 (s, 2H), 7.81 (s, 1H), 8.14-8.24 (m, 2H); ^{13}C{H} NMR (100 MHz, DMSO-d_6): δ (ppm) 29.7, 31.4, 34.0, 34.7, 114.1, 119.6, 122.3, 125.9, 128.7, 129.1, 131.5, 133.4, 134.3, 141.6, 146.4, 147.6, 160.1. Anal. Calcd for $C_{21}H_{24}BrNO$: C, 65.29; H, 6.26; N, 3.63; Found: C, 64.66; H, 5.92; N, 3.30.

5,7-Di-*tert*-butyl-2-(2,6-dichlorophenyl)benzo[*d*]oxazole **(3e)**.

Purified by column chromatography on silica gel and eluted with ethyl acetate/petroleum ether (1:100). Isolated yield: (323 mg, 86%). Colorless liquid; ^{1}H NMR (250 MHz, DMSO-d_6): δ (ppm) 1.33 (s, 9H), 1.40 (s, 9H), 7.34 (d, *J*= 2.5 Hz, 1H), 7.67-7.71 (m, 4H); ^{13}C{H} NMR (100 MHz, DMSO-d_6): δ (ppm) 29.5, 31.4, 34.0, 34.7, 114.5, 119.8, 126.9, 128.7, 133.6, 133.7, 134.9, 140.9, 146.4, 147.6, 156.7. Anal. Calcd for $C_{21}H_{23}Cl_2NO$: C, 67.03; H, 6.16; N, 3.72; Found: C, 67.00; H, 6.12; N, 3.74.

5,7-Di-*tert*-butyl-2-(4-methoxyphenyl)benzo[*d*]oxazole **(3f)**.[17c]

Purified by column chromatography on silica gel and eluted with ethyl acetate/petroleum ether (1:100). Isolated yield: (327 mg, 97%). Colorless liquid (lit. Colorless liquid); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.43 (s, 9H),

1.58 (s, 9H), 3.90 (s, 3H), 7.05 (d, *J*= 9.0 Hz, 2H), 7.31 (s, 1H), 7.66 (s, 1H), 8.22 (d, *J*= 9.0 Hz, 2H); $^{13}C\{H\}$ NMR (75 MHz, $CDCl_3$): δ (ppm) 30.0, 31.8, 34.4, 35.0, 55.4, 113.9, 114.3, 119.0, 120.0, 129.1, 133.5, 142.4, 146.8, 147.5, 162.0, 162.6. Anal. Calcd for $C_{22}H_{27}NO_2$: C, 78.30; H, 8.06; N, 4.15; Found: C, 78.24; H, 8.01; N, 4.13.

4-(5,7-Di-*tert*-butylbenzo[*d*]oxazol-2-yl)phenol **(3g)**.[17a]

Purified by column chromatography on silica gel and eluted with ethyl acetate/petroleum ether (1:10). Isolated yield: (288 mg, 89%). Colorless liquid (lit. Colorless liquid); ^1H NMR (250 MHz, DMSO-d_6): δ (ppm) 1.32 (s, 9H), 1.47 (s, 9H), 6.95 (d, *J*= 10.0 Hz, 2H), 7.21 (d, *J*= 2.5 Hz, 1H), 7.52 (d, *J*= 2.5 Hz, 1H), 7.99 (d, *J*= 10.0 Hz, 2H), 10.53 (s, OH); $^{13}C\{H\}$ NMR (100 MHz, DMSO-d_6): δ (ppm) 29.7, 31.5, 34.0, 34.6, 113.5, 116.1, 117.1, 118.3, 128.9, 132.8, 142.1, 146.0, 147.0, 161.1, 162.3. Anal. Calcd for $C_{21}H_{25}NO_2$: C, 77.98; H, 7.79; N, 4.33; Found: C, 77.95; H, 7.77; N, 4.35.

5,7-Di-*tert*-butyl-2-(*p*-tolyl)benzo[*d*]oxazole **(3h)**.

Purified by column chromatography on silica gel and eluted with ethyl acetate/petroleum ether (1:100). Isolated yield: (308 mg, 96%). Cream solid, mp: 94-95 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.33 (s, 9H), 1.48 (s, 9H), 2.37 (s, 3H), 7.23 (d, *J*= 4.0 Hz, 1H), 7.26 (d, *J*= 8.0 Hz, 2H), 7.58 (d, *J*= 4.0 Hz, 1H), 8.07 (d, *J*= 8.0 Hz, 2H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 21.6, 30.0, 31.8, 34.5, 35.0, 114.0, 119.3, 124.8, 127.3, 129.6, 133.6, 141.6, 142.3, 146.8, 147.6, 162.7. Anal. Calcd for $C_{22}H_{27}NO$: C, 82.20; H, 8.47; N, 4.36; Found: C, 82.31; H, 8.54.18; N, 4.45.

5,7-Di-*tert*-butyl-2-(4-isopropylphenyl)benzo[*d*]oxazole **(3i)**.

Purified by column chromatography on silica gel and eluted with ethyl acetate/petroleum ether (1:100). Isolated yield: (321 mg, 92%). Colorless liquid; ^1H NMR (250 MHz, $CDCl_3$): δ (ppm) 1.30 (s, 3H), 1.32 (s, 3H), 1.40 (s, 9H), 1.55 (s, 9H), 2.92-3.08 (m, 1H), 7.30 (d, *J*= 2.5 Hz, 1H), 7.39 (d, *J*= 10.0 Hz, 2H), 7.66 (d, *J*= 2.5 Hz, 1H), 8.19 (d, *J*= 7.5 Hz, 2H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 23.8, 29.0, 30.0, 31.8, 34.2, 34.4, 35.1, 114.1, 119.3, 125.1, 127.0, 127.5, 133.6, 142.3, 146.8, 147.6, 152.5, 162.7. Anal. Calcd for $C_{24}H_{31}NO$: C, 82.47; H, 8.94; N, 4.01; Found: C, 82.20; H, 8.80; N, 3.92.

5,7-Di-*tert*-butyl-2-(*o*-tolyl)benzo[*d*]oxazole **(3j)**.[17c]

Purified by column chromatography on silica gel and eluted with ethyl acetate/petroleum ether (1:100). Isolated yield: (295 mg, 92%). Colorless liquid (lit. Colorless liquid); ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.44 (s, 9H), 1.58 (s, 9H), 2.85 (s, 3H), 7.35 (d, *J*= 3.0 Hz, 1H), 7.39-7.47 (m, 3H), 7.73 (s, 1H), 8.21 (d, *J*= 6.0 Hz, 1H); $^{13}C\{H\}$ NMR (75 MHz, $CDCl_3$): δ (ppm) 22.3, 30.0, 31.8, 34.4, 35.1, 114.3, 119.4, 126.1, 126.6, 129.9, 130.6, 131.7, 133.6, 138.3, 142.2, 146.5, 147.5, 163.0. Anal. Calcd for $C_{22}H_{27}NO$: C, 82.20; H, 8.47; N, 4.36; Found: C, 82.02; H, 8.36; N, 4.31.

5,7-Di-*tert*-butyl-2-(3-methoxyphenyl)benzo[*d*]oxazole **(3k)**.[17a]

Purified by column chromatography on silica gel and eluted with ethyl acetate/petroleum ether (1:100). Isolated yield: (307 mg, 91%). Colorless liquid (lit. Colorless liquid); ^1H NMR (250 MHz, DMSO-d_6): δ (ppm) 1.33 (s, 9H), 1.48(s, 9H), 3.85 (s, 3H), 7.16-7.21 (m, 1H), 7.29 (d, *J*= 2.5 Hz, 1H), 7.52 (t, *J*= 7.5 Hz, 1H), 7.60 (d, *J*= 2.5 Hz, 1H), 7.63-7.65 (m, 1H), 7.72-7.76 (m, 1H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 30.0, 31.8, 34.5, 35.1, 55.5, 112.0, 114.2, 117.6, 119.6, 119.8, 128.7, 129.9, 133.7, 142.2, 146.9, 147.7, 159.9, 162.3. Anal. Calcd for $C_{22}H_{27}NO_2$: C, 78.30; H, 8.06; N, 4.15; Found: C, 78.28; H, 8.05; N, 4.20.

5,7-Di-*tert*-butyl-2-(2-methoxyphenyl)benzo[*d*]oxazole **(3l)**.[17c]

Purified by column chromatography on silica gel and eluted with ethyl acetate/petroleum ether (1:100). Isolated yield: (317 mg, 94%). Colorless liquid (lit. Colorless liquid); ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.45 (s, 9H), 1.52 (s, 9H), 3.91 (s, 3H), 6.99-7.05 (m, 2H), 7.06 (d, *J*= 4.0 Hz, 2H), 7.38-7.43 (m, 1H), 8.11 (d, *J*= 8.0 Hz, 1H); $^{13}C\{H\}$ NMR (100 MHz, DMSO-d_6): δ (ppm) 29.5, 31.5, 33.9, 34.7, 56.0, 112.9, 113.8, 115.6, 118.7, 120.7, 130.6, 133.0, 133.1, 141.5, 146.1, 147.0, 157.9, 160.8. Anal. Calcd for $C_{22}H_{27}NO_2$: C, 78.30; H, 8.06; N, 4.15; Found: C, 78.33; H, 8.11; N, 4.21.

5,7-Di-*tert*-butyl-2-(3,4-dimethoxyphenyl)benzo[*d*]oxazole **(3m)**.

Purified by column chromatography on silica gel and eluted with ethyl acetate/petroleum ether (1:50). Isolated yield: (330 mg, 90%). Colorless liquid; ^1H NMR (250 MHz, DMSO-d_6): δ (ppm) 1.32 (s, 9H), 1.47 (s, 9H), 3.83 (s, 3H), 3.86 (s, 3H), 7.15 (d, *J*= 10.0 Hz, 1H), 7.23 (d, *J*= 2.5 Hz, 1H), 7.56 (d, *J*= 2.5 Hz, 1H), 7.64 (d, *J*= 2.5 Hz, 1H), 7.73 (dd, *J*= 2.5, 7.5 Hz, 1H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 30.0, 31.8, 34.4, 35.0, 56.0, 56.1, 109.9, 110.9, 113.9, 119.1, 120.2, 120.8, 133.4, 142.3, 146.8, 147.6, 149.2, 151.7, 162.5. Anal. Calcd for $C_{23}H_{29}NO_3$: C, 75.17; H, 7.95; N, 3.81; Found: C, 75.03; H, 7.85; N, 3.68.

4-(5,7-Di-*tert*-butylbenzo[*d*]oxazol-2-yl)-2-methoxyphenol **(3n)**.

Purified by column chromatography on silica gel and eluted with ethyl acetate/petroleum ether (1:10). Isolated yield: (293 mg, 83%). Colorless liquid; ^1H NMR (250 MHz, DMSO-d_6): δ (ppm) 1.33 (s, 9H), 1.47 (s, 9H), 3.87 (s, 3H), 6.98 (d, *J*= 7.5 Hz, 1H), 7.22 (d, *J*= 2.5 Hz, 1H), 7.53 (d, *J*= 2.5 Hz, 1H), 7.60-7.64 (m, 2H), 9.98 (s, OH); $^{13}C\{H\}$ NMR (100 MHz, DMSO-d_6): δ (ppm) 29.7, 31.5, 34.0, 34.6, 55.6, 110.3, 113.5, 115.9, 117.5, 118.5, 120.7, 132.9, 142.0, 146.1, 147.1, 148.0, 150.3, 162.2. Anal. Calcd for $C_{22}H_{27}NO_3$: C, 74.76; H, 7.70; N, 3.96; Found: C, 74.22; H, 7.35; N, 3.47.

5,7-Di-*tert*-butyl-2-(4-nitrophenyl)benzo[*d*]oxazole **(3o)**.[17a]

Purified by column chromatography on silica gel and eluted with ethyl acetate/petroleum ether (1:30). Isolated yield: (299 mg, 85%). Pale yellow solid, mp: 198-200 °C (lit. White solid, mp: 194-196 °C); ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 1.33 (s, 9H), 1.49 (s, 9H), 7.31 (d, *J*= 2.5 Hz, 1H), 7.62 (d, *J*= 2.5 Hz, 1H), 8.32-8.35 (m, 4H); ^{13}C{H} NMR (100 MHz, $CDCl_3$): δ (ppm) 30.0, 31.7, 34.5, 35.1, 114.7, 120.9, 124.2, 128.0, 133.1, 134.1, 142.2, 148.5, 149.1. Anal. Calcd for $C_{21}H_{24}N_2O_3$: C, 71.57; H, 6.86; N, 7.95; Found: C, 71.33; H, 6.51; N, 7.65.

4-(5,7-Di-*tert*-butylbenzo[*d*]oxazol-2-yl)benzonitrile **(3p)**.[17b]

Purified by column chromatography on silica gel and eluted with ethyl acetate/petroleum ether (1:100). Isolated yield: (286 mg, 86%). Colorless liquid (lit. Colorless liquid); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.42 (s, 9H), 1.57 (s, 9H), 7.39 (d, *J*= 3.0 Hz, 1H), 7.70 (d, *J*= 3.0 Hz, 1H), 7.85 (d, *J*= 9.0 Hz, 2H), 8.37 (d, *J*= 6.0 Hz, 2H); ^{13}C{H} NMR (75 MHz, $CDCl_3$): δ (ppm) 30.0, 31.7, 34.5, 35.1, 114.3, 114.6, 118.3, 120.7, 127.7, 131.4, 132.7, 134.0, 142.1, 147.1, 148.4, 160.3. Anal. Calcd for $C_{22}H_{24}N_2O$: C, 79.48; H, 7.28; N, 8.43; Found: C, 79.25; H, 7.04; N, 8.27.

5,7-Di-*tert*-butyl-2-(3-nitrophenyl)benzo[*d*]oxazole **(3q)**.

Purified by column chromatography on silica gel and eluted with ethyl acetate/petroleum ether (1:40). Isolated yield: (285 mg, 81%). White solid, mp: 146-147 °C; ^{1}H NMR (250 MHz, DMSO-d_6): δ (ppm) 1.34 (s, 9H), 1.50 (s, 9H), 7.34 (d, *J*= 2.5 Hz, 1H), 7.65 (d, *J*= 2.5 Hz, 1H), 7.90 (t, *J*= 7.5 Hz, 1H), 8.43 (d, *J*= 10.0 Hz, 1H), 8.56 (d, *J*= 10.0 Hz, 1H), 8.80 (s, 1H); ^{13}C{H} NMR (100 MHz, DMSO-d_6): δ (ppm) 35.0, 36.7, 39.3, 40.0, 119.6, 125.3, 126.5, 131.2, 133.2, 136.5, 138.1, 138.8, 146.8, 151.7, 153.1, 153.5, 165.0. Anal. Calcd for $C_{21}H_{24}N_2O_3$: C, 71.57; H, 6.86; N, 7.95; Found: C, 71.51; H, 6.79; N, 7.92.

5,7-Di-*tert*-butyl-2-(naphthalen-1-yl)benzo[*d*]oxazole **(3r)**.[17a]

Purified by column chromatography on silica gel and eluted with ethyl acetate/petroleum ether (1:100). Isolated yield: (300 mg, 84%). Colorless liquid (lit. Colorless liquid); ^{1}H NMR (250 MHz, DMSO-d_6): δ (ppm) 1.37 (s, 9H), 1.53 (s, 9H), 7.34 (d, *J*= 2.5 Hz, 1H), 7.62-7.77 (m, 4H), 8.08 (d, *J*= 10.0 Hz, 1H), 8.21 (d, *J*= 7.5 Hz, 1H), 8.41 (d, *J*= 7.5 Hz, 1H), 9.43 (d, *J*= 10.0 Hz, 1H); ^{13}C{H} NMR (100 MHz, DMSO-d_6): δ (ppm) 29.7, 31.5, 34.1, 34.8, 114.3, 119.5, 122.7, 125.4, 125.6, 126.6, 127.9, 128.8, 128.9, 129.7, 132.3, 133.2, 133.5, 142.0, 145.5, 147.4, 161.4. Anal. Calcd for $C_{25}H_{27}NO$: C, 83.99; H, 7.61; N, 3.92; Found: C, 83.95; H, 7.60; N, 3.94.

5,7-Di-*tert*-butyl-2-phenylbenzo[*d*]oxazole **(3s)**.[17b]

Purified by column chromatography on silica gel and eluted with ethyl acetate/petroleum ether (1:100). Isolated yield: (276 mg, 90%). Brown liquid (lit. Brown liquid); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.43 (s, 9H), 1.58 (s, 9H), 7.34 (s, 1H), 7.56 (s, 3H), 7.70 (s, 1H), 8.29 (s, 2H); ^{13}C{H} NMR (75 MHz, $CDCl_3$): δ (ppm) 30.0, 31.8, 34.5, 35.1, 114.2, 119.6, 127.3, 127.5, 128.9, 131.2, 133.7, 142.2, 146.9, 147.7, 162.4. Anal. Calcd for $C_{21}H_{25}NO$: C, 82.04; H, 8.20; N, 4.56; Found: C, 81.90; H, 8.05; N, 4.51.

5,7-Di-*tert*-butyl-2-(pyridin-2-yl)benzo[*d*]oxazole **(3t)**.[17b]

Purified by column chromatography on silica gel and eluted with ethyl acetate/petroleum ether (1:100). Isolated yield: (283 mg, 92%). Colorless liquid (lit. Colorless liquid); ^{1}H NMR (250 MHz, DMSO-d_6): δ (ppm) 1.35 (s, 9H), 1.50 (s, 9H), 7.34 (d, *J*= 2.5 Hz, 1H), 7.59-7.64 (m, 1H), 7.67 (d, *J*= 2.5 Hz, 1H), 8.04 (td, *J*= 7.7, 1.7 Hz, 1H), 8.31 (d, *J*= 7.7 Hz, 1H), 8.81 (dd, *J*= 4.7, 1.7 Hz, 1H); ^{13}C{H} NMR (100 MHz, DMSO-d_6): δ (ppm) 29.6, 31.5, 34.1, 34.8, 114.4, 119.9, 123.3, 125.9, 133.7, 137.6, 141.6, 145.4, 146.6, 147.6, 150.2, 160.9. Anal. Calcd for $C_{20}H_{24}N_2O$: C, 77.89; H, 7.84; N, 9.08; Found: C, 77.87; H, 7.80; N, 9.11.

5,7-Di-*tert*-butyl-2-(pyridin-3-yl)benzo[*d*]oxazole **(3u)**.[17a]

Purified by column chromatography on silica gel and eluted with ethyl acetate/petroleum ether (1:100). Isolated yield: (246 mg, 80%). White solid, mp: 99-100 °C (lit. White solid, mp: 99-101 °C); ^{1}H NMR (250 MHz, DMSO-d_6): δ (ppm) 1.34 (s, 9H), 1.49 (s, 9H), 7.32 (d, *J*= 2.5 Hz, 1H), 7.62-7.67 (m, 2H), 8.47-8.52 (m, 1H), 8.78 (d, *J*= 5.0 Hz, 1H), 9.32 (s, 1H); ^{13}C{H} NMR (100 MHz, DMSO-d_6): δ (ppm) 29.7, 31.4, 34.0, 34.7, 114.1, 119.6, 122.9, 124.2, 133.4, 134.4, 141.6, 146.3, 147.6, 147.7, 152.0, 159.7. Anal. Calcd for $C_{20}H_{24}N_2O$: C, 77.89; H, 7.84; N, 9.08; Found: C, 77.84; H, 7.76; N, 9.06.

5,7-Di-*tert*-butyl-2-(pyridin-4-yl)benzo[*d*]oxazole **(3v)**.

Purified by column chromatography on silica gel and eluted with ethyl acetate/petroleum ether (1:100). Isolated yield: (293 mg, 95%). White solid, mp: 102-103 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 1.29 (s, 9H), 1.44 (s, 9H), 7.31 (d, *J*= 4.0 Hz, 1H), 7.61 (d, *J*= 4.0 Hz, 1H), 8.02 (d, *J*= 4.0 Hz, 2H), 8.79 (d, *J*= 8.0 Hz, 2H); ^{13}C{H} NMR (100 MHz, DMSO-d_6): δ (ppm) 34.9, 36.7, 39.3, 40.0, 119.7, 125.6, 125.8, 138.8, 138.9, 146.8, 151.7, 153.2, 156.1, 164.9. Anal. Calcd for $C_{20}H_{24}N_2O$: C, 77.89; H, 7.84; N, 9.08; Found: C, 77.83; H, 7.78; N, 9.10.

5,7-Di-*tert*-butyl-2-(3a,7a-dihydro-1*H*-indol-3-yl)benzo[*d*]oxazole **(3w)**.

Purified by column chromatography on silica gel and eluted with ethyl acetate/petroleum ether (1:60). Isolated yield: (296 mg, 85%). Cream solid, mp: 206-208 °C; ^{1}H NMR (250 MHz, DMSO-d_6): δ (ppm) 1.34 (s, 9H), 1.51 (s, 9H), 7.19 (d, *J*= 2.5 Hz, 1H), 7.23-7.26 (m, 2H), 7.53 (d, *J*= 2.5 Hz, 1H), 7.56 (d, *J*= 2.5 Hz, 1H), 8.27 (t, *J*= 5.0 Hz, 2H), 12.10 (s, NH); ^{13}C{H} NMR (100 MHz, DMSO-d_6): δ (ppm) 29.7, 31.6, 33.9, 34.6, 103.0, 112.5, 113.0, 117.5, 120.1, 121.1, 122.6, 124.6, 128.9, 132.4, 136.6, 142.3,

145.2, 146.7, 160.4. Anal. Calcd for $C_{23}H_{28}N_2O$: C, 79.27; H, 8.10; N, 8.04; Found: C, 79.17; H, 7.95; N, 8.00.

5,7-Di-*tert*-butyl-2-(thiophen-2-yl)benzo[*d*]oxazole **(3x)**.[17a]

Purified by column chromatography on silica gel and eluted with ethyl acetate/petroleum ether (1:100). Isolated yield: (288 mg, 92%). Colorless liquid (lit. Colorless liquid); ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 1.30 (s, 9H), 1.45 (s, 9H), 7.08-7.12 (m, 1H), 7.21 (t, *J*= 2.5 Hz, 1H), 7.45 (dd, *J*= 2.5, 5.0 Hz, 1H), 7.54 (d, *J*= 2.5 Hz, 1H), 7.80-7.82 (m, 1H); ^{13}C{H} NMR (100 MHz, $CDCl_3$): δ (ppm) 30.0, 31.8, 34.4, 35.1, 114.0, 119.5, 128.1, 129.3, 129.7, 130.1, 133.6, 142.1, 146.6, 147.8, 158.5. Anal. Calcd for $C_{19}H_{23}NOS$: C, 72.80; H, 7.40; N, 4.47; Found: C, 72.75; H, 7.37; N, 4.40.

5,7-Di-*tert*-butyl-2-(thiophen-3-yl)benzo[*d*]oxazole **(3y)**.

Purified by column chromatography on silica gel and eluted with ethyl acetate/petroleum ether (1:100). Isolated yield: (272 mg, 87%). Pale yellow liquid; ^{1}H NMR (250 MHz, DMSO-d_6): δ (ppm) 1.33 (s, 9H), 1.48 (s, 9H), 7.27 (d, *J*= 2.5 Hz, 1H), 7.57 (d, *J*= 2.5 Hz, 1H), 7.71 (d, *J*= 5.0 Hz, 1H), 7.78-7.81 (m, 1H), 8.43-8.45 (m, 1H); ^{13}C{H} NMR (100 MHz, $CDCl_3$): δ (ppm) 29.55, 31.36, 34.00, 34.60, 113.66, 118.97, 126.10, 126.39, 126.89, 129.19, 133.12, 141.64, 146.02, 147.23, 158.71. Anal. Calcd for $C_{19}H_{23}NOS$: C, 72.80; H, 7.40; N, 4.47; Found: C, 72.75; H, 7.32; N, 4.39.

5,7-Di-*tert*-butyl-2-(furan-2-yl)benzo[*d*]oxazole **(3z)**.[17b]

Purified by column chromatography on silica gel and eluted with ethyl acetate/petroleum ether (1:100). Isolated yield: (282 mg, 95%). Colorless liquid (lit. Colorless liquid); ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 1.39 (s, 9H), 1.53 (s, 9H), 6.60 (dd, *J*= 1.7, 3.5 Hz, 1H), 7.25 (dd, *J*= 0.8, 3.5 Hz, 1H), 7.31 (d, *J*= 2.0 Hz, 1H), 7.62 (d, *J*= 2.0 Hz, 1H), 7.65-7.66 (m, 1H); ^{13}C{H} NMR (100 MHz, $CDCl_3$): δ (ppm) 29.4, 31.3, 33.9, 34.5, 111.5, 113.0, 113.8, 119.2, 133.2, 141.3, 142.5, 144.8, 145.8, 147.5, 154.3. Anal. Calcd for $C_{19}H_{23}NO_2$: C, 76.74; H, 7.80; N, 4.71; Found: C, 76.68; H, 7.76; N, 4.68.

5-(*tert*-Butyl)-2-(*p*-tolyl)benzo[*d*]oxazole **(3aa)**.[17c]

Purified by column chromatography on silica gel and eluted with ethyl acetate/petroleum ether (1:100). Isolated yield: (244 mg, 92%). Colorless liquid (lit. Colorless liquid); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.33 (s, 9H), 2.37 (s, 3H), 7.26 (d, *J*= 9.0 Hz, 2H), 7.34 (dd, *J*= 3.0 Hz, *J*= 6.0 Hz, 1H), 7.52 (d, *J*= 3.0 Hz, 1H), 7.60 (d, *J*= 9.0 Hz, 1H), 8.06 (d, *J*= 6.0 Hz, 2H); ^{13}C{H} NMR (75 MHz, $CDCl_3$): δ (ppm) 21.6, 31.7, 35.1, 107.2, 118.8, 122.2, 124.5, 127.4, 129.6, 139.6, 141.8, 149.0, 150.8, 163.1. Calcd for $C_{18}H_{19}NO$: C, 81.47; H, 7.22; N, 5.28; Found: C, 81.18; H, 7.01; N, 5.41.

5-(*tert*-Butyl)-2-(4-chlorophenyl)benzo[*d*]oxazole **(3ab)**.[17a]

Purified by column chromatography on silica gel and eluted with ethyl acetate/petroleum ether (1:100). Isolated yield: (256 mg, 90%). Colorless liquid (lit. Colorless liquid); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.33 (s, 9H), 7.36 (dd, *J*= 3.0 Hz, *J*= 9.0 Hz, 1H), 7.42 (d, *J*= 9.0 Hz, 2H), 7.53 (d, *J*= 3.0 Hz, 1H), 7.60 (d, *J*= 9.0 Hz, 1H), 8.10 (d, *J*= 9.0 Hz, 2H); ^{13}C{H} NMR (75 MHz, $CDCl_3$): δ (ppm) 31.6, 35.2, 107.3, 119.1, 122.4, 125.8, 128.6, 129.2, 137.4, 139.5, 149.5, 151.0, 161.9. Calcd for $C_{17}H_{16}ClNO$: C, 71.45; H, 5.64; N, 4.90; Found: C, 71.29; H, 5.47; N, 5.06.

5-(*tert*-Butyl)-2-(2-chlorophenyl)benzo[*d*]oxazole **(3ac)**.[17c]

Purified by column chromatography on silica gel and eluted with ethyl acetate/petroleum ether (1:100). Isolated yield: (251 mg, 88%). Colorless liquid (lit. Colorless liquid); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.43 (s, 9H), 7.41-7.49 (m, 3H), 7.58 (d, *J*= 9.0 Hz, 1H), 7.67 (s, 1H), 7.79 (d, *J*= 9.0 Hz, 1H), 8.15 (d, *J*= 9.0 Hz, 1H); ^{13}C{H} NMR (75 MHz, $CDCl_3$): δ (ppm) 31.7, 35.2, 107.4, 119.5, 122.4, 126.4, 126.9, 131.3, 131.7, 133.3, 139.2, 149.8, 150.8, 160.8. Calcd for $C_{17}H_{16}ClNO$: C, 71.45; H, 5.64; N, 4.90; Found: C, 71.33; H, 5.51; N, 4.98.

5-Methyl-2-phenylbenzo[*d*]oxazole **(3ad)**.[14d]

Purified by column chromatography on silica gel and eluted with ethyl acetate/petroleum ether (1:100). Isolated yield: (169 mg, 81%). Colorless liquid (lit. Colorless oil); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.50 (s, 3H), 7.16 (d, *J*= 9.0 Hz, 1H), 7.46 (d, *J*= 9.0 Hz, 1H), 7.51-7.55 (m, 3H), 7.59 (s, 1H), 8.26-8.29 (m, 2H); ^{13}C{H} NMR (75 MHz, $CDCl_3$): δ (ppm) 21.5, 109.9, 119.9, 126.2, 127.3, 127.5, 128.8, 131.3, 134.3, 142.3, 149.0, 163.0. Calcd for $C_{14}H_{11}NO$: C, 80.36; H, 5.30; N, 6.69; Found: C, 80.19; H, 5.14; N, 6.52.

2-(4-Methoxyphenyl)-5-methylbenzo[*d*]oxazole **(3ae)**.[14b]

Purified by column chromatography on silica gel and eluted with ethyl acetate/petroleum ether (1:100). Isolated yield: (208 mg, 87%). White solid, mp: 106-108 ^{o}C (lit. White solid, mp: 107-109 ^{o}C); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.48 (s, 3H), 3.84 (s, 3H), 7.00 (d, *J*= 9.0 Hz, 2H), 7.11 (d, *J*= 9.0 Hz, 1H), 7.40 (d, *J*= 9.0 Hz, 1H), 7.53 (s, 1H), 8.18 (d, *J*= 9.0 Hz, 2H); ^{13}C{H} NMR (75 MHz, $CDCl_3$): δ (ppm) 21.5, 55.3, 109.7, 114.2, 119.5, 119.8, 125.6, 129.2, 134.1, 142.4, 148.8, 162.1, 163.2. Calcd for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85; Found: C, 75.18; H, 5.41; N, 7.87.

2-(4-Chlorophenyl)-5-methylbenzo[*d*]oxazole **(3af)**.[14f]

Purified by column chromatography on silica gel and eluted with ethyl acetate/petroleum ether (1:100). Isolated yield: (206 mg, 85%). White solid, mp: 151-153 ^{o}C (lit. White solid, mp: 149-151 ^{o}C); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.48 (s, 3H), 7.14 (d, *J*= 6.0 Hz, 1H), 7.41 (d, *J*= 9.0 Hz, 1H), 7.45 (d, *J*= 6.0 Hz, 2H), 7.53 (s, 1H), 8.12 (d, *J*= 6.0 Hz, 2H); ^{13}C{H} NMR (75 MHz, $CDCl_3$): δ (ppm) 21.5, 109.9, 119.9, 125.7, 126.4, 128.6, 129.1, 134.4, 137.4, 142.1, 148.9, 162.0. Calcd for $C_{14}H_{10}ClNO$:

C, 69.00; H, 4.14; N, 5.75; Found: C, 68.71; H, 4.02; N, 5.68.

5-Methyl-2-(pyridin-2-yl)benzo[*d*]oxazole **(3ag)**.[16h]

Purified by column chromatography on silica gel and eluted with ethyl acetate/petroleum ether (1:100). Isolated yield: (183 mg, 87%). Yellow solid, mp: 87-88 °C (lit. Yellow solid, mp: 89.5-89.7 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.40 (s, 3H), 7.11 (d, *J*= 9.0 Hz, 1H), 7.32 (t, *J*= 6.0 Hz, 1H), 7.44 (d, *J*= 9.0 Hz, 1H), 7.52 (s, 1H), 7.76 (t, *J*= 7.5 Hz, 1H), 8.23 (d, *J*= 9.0 Hz, 1H), 8.72 (d, *J*= 6.0 Hz, 1H); ^{13}C{H} NMR (75 MHz, $CDCl_3$): δ (ppm) 21.4, 110.4, 120.3, 123.2, 125.3, 127.1, 134.6, 136.9, 141.9, 146.0, 149.2, 150.1, 161.4. Calcd for $C_{13}H_{10}N_2O$: C, 74.27; H, 4.79; N, 13.33; Found: C, 74.35; H, 4.82; N, 13.47.

5-Methyl-2-(thiophen-2-yl)benzo[*d*]oxazole **(3ah)**.[13f]

Purified by column chromatography on silica gel and eluted with ethyl acetate/petroleum ether (1:100). Isolated yield: (165 mg, 77%). Yellow solid, mp: 90-92 °C (lit. Yellow solid, mp: 89-91 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.47 (s, 3H), 7.11-7.17 (m, 2H), 7.39 (d, *J*= 8.1 Hz, 1H), 7.51-7.53 (m, 2H), 7.88 (dd, *J*= 1.2, 3.9 Hz, 1H); ^{13}C{H} NMR (75 MHz, $CDCl_3$): δ (ppm) 21.5, 109.7, 119.7, 126.1, 128.1, 129.7, 129.8, 130.0, 134.5, 142.1, 148.6, 159.0. Calcd for $C_{12}H_9NOS$: C, 66.95; H, 4.21; N, 6.51; Found: C, 6.90; H, 4.09; N, 6.42.

4-methyl-2-phenylbenzo[*d*]oxazole **(3ai)**.[17b]
Purified by column chromatography on silica gel and eluted with ethyl acetate/petroleum ether (1:100). Isolated yield: (156 mg, 75%). White solid, mp: 81-83 °C; ^{1}H NMR (250 MHz, DMSO-d_6): δ (ppm) 2.52 (s, 3H), 6.95 (d, *J*= 5.0 Hz, 1H), 7.07 (t, *J*= 7.5 Hz, 1H), 7.39-7.52 (m, 4H), 8.15 (d, *J*= 7.5 Hz, 2H); ^{13}C{H} NMR (75 MHz, DMSO-d_6): δ (ppm) 16.8, 112.4, 122.4, 122.8, 124.9, 126.5, 128.9, 129.6, 129.9, 138.4, 144.7, 150.9. Calcd for $C_{14}H_{11}NO$: C, 80.36; H, 5.30; N, 6.69; Found: C, 80.21; H, 5.08; N, 6.58.

5,7-Di-*tert*-butyl-2-isopropylbenzo[*d*]oxazole **(3aj)**.[17a]

Purified by column chromatography on silica gel and eluted with ethyl acetate/petroleum ether (1:100). Isolated yield: (115 mg, 42%). Brown liquid (lit. Brownness liquid); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.39 (s, 9H), 1.47 (s, 3H), 1.49 (s, 3H), 1.50 (s, 9H), 3.27 (sep, 1H), 7.26 (d, *J*= 3.0 Hz, 1H), 7.60 (d, *J*= 3.0 Hz, 1H); ^{13}C{H} NMR (75 MHz, $CDCl_3$): δ (ppm) 20.4, 28.8, 29.9, 31.8, 34.3, 35.0, 113.8, 118.6, 133.4, 141.3, 146.9, 147.1, 170.7. Anal. Calcd for $C_{18}H_{27}NO$: C, 79.07; H, 9.95; N, 5.12; Found: C, 79.18; H, 10.15; N, 4.91.

5,7-Di-*tert*-butyl-2-methylbenzo[*d*]oxazole **(3ak)**.[17b]

Purified by column chromatography on silica gel and eluted with ethyl acetate/petroleum ether (1:100). Isolated yield: (73 mg, 30%). Brown liquid (lit. Brown liquid); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.39 (s, 9H), 1.49 (s, 9H), 2.65 (s, 3H), 7.25 (d, *J*= 3.0 Hz, 1H), 7.53 (d, *J*= 3.0 Hz, 1H); ^{13}C{H} NMR (75 MHz, $CDCl_3$): δ (ppm) 14.6, 29.9, 31.8, 34.4, 35.0, 113.6, 118.6, 133.3, 141.7, 147.1, 147.2, 163.1. Anal. Calcd for $C_{16}H_{23}NO$: C, 78.32; H, 9.45; N, 5.71; Found: C, 78.15; H, 9.60; N, 5.84.

4,6-Di-*tert*-butyl-2-(4-chlorophenyl)-1*H*-benzo[*d*]imidazole **(4a)**.

Purified by column chromatography on silica gel and eluted with ethyl acetate/petroleum ether (5:100). Isolated yield: (316 mg, 93%). Colorless liquid; ^{1}H NMR (250 MHz, DMSO-*d6*): δ (ppm) 1.33 (s, 9H), 1.55 (s, 9H), 7.09 (d, *J*= 2.5 Hz, 1H), 7.28 (s, 1H), 7.60 (d, *J*= 10.0 Hz, 2H), 8.15 (d, *J*= 7.5 Hz, 2H), 12.78 (s, NH); ^{13}C{H} NMR (100 MHz, DMSO-d_6): δ (ppm) 30.2, 31.6, 34.6, 35.2, 105.2, 115.2, 127.8, 128.9, 129.4, 133.9, 135.4, 139.8, 140.2, 145.0, 147.7. Anal. Calcd for $C_{21}H_{25}ClN_2$: C, 73.99; H, 7.39; N, 8.22; Found: C, 73.81; H, 7.30; N, 8.18.

ASSOCIATED CONTENT

Supporting Information

Copy of ^{1}H and ^{13}C NMR of synthesized compounds. All of these data are available in supporting information.

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