scientific reports

OPEN

Zirconium-catalyzed one-pot synthesis of benzoxazoles using reaction of catechols, aldehydes and ammonium acetate

Masoumeh Mohammadi[1,2], Jasem Aboonajmi[1,2], Farhad Panahi[1✉], Maryam Sasanipour[1] & Hashem Sharghi[1]

In this study, an efficient method for the synthesis of benzoxazoles by coupling catechols, aldehydes and ammonium acetate using $ZrCl_4$ as catalyst in ethanol is reported. A wide range of benzoxazoles (59 examples) are smoothly produced in high yields (up to 97%). Other advantages of the method include large-scale synthesis and the use of oxygen as an oxidant. The mild reaction conditions allowed late-stage functionalization, facilitating access to several derivatives with biologically relevant structures such as β-lactam and quinoline heterocycles.

The development of new organic synthesis methods to overcome limitations in access to valuable compounds and also to increase their diversity (to find new potential applications) is highly considered in academic and industrial research[1,2]. Besides the efficiency of these methods, the environmental friendliness of the developed method would be a remarkable advantage[3,4].

Benzoxazoles are a class of heterocyclic compounds that have attracted considerable interest due to their diverse biological activities. These compounds have been reported to have antimicrobial, neuroprotective, anticancer, antiviral, antibacterial, antifungal and anti-inflammatory activitie[5–11]. They are also used in a variety of industrial applications, including pharma, sensors, agrochemistry, ligands (in transition metal catalysis) and materials science[12–17]. Owing to its unique chemical properties and versatility benzoxazole has become an important building block in the synthesis of many complex organic molecules[18–20]. Of interest, some benzoxazoles are important natural products and pharmacologically relevant molecules such as nakijinol[21], boxazomycin A[22], calcimycin[23], tafamidis[24], caboxamycin[25], and neosalvianen (Fig. 1A)[26].

Catechols are used in many different fields, including pharmaceuticals, cosmetics, and materials science[27–31]. Catechols have also been shown to have antioxidant and anti-inflammatory properties. This makes them potential candidates for therapeutic agents[32,33]. This property has led to their use in the development of anti-aging cosmetics and skin care products[34–36]. Furthermore, catechols have proven to be effective precursors for organic synthesis (Fig. 1B)[37,38]. Some of these catechols are abundant in nature. Therefore, their use as raw materials or feedstocks in organic synthesis can fulfil the "use of renewable resources" principle of Green Chemistry. Several different routes to functionalized benzoxazole compounds have been developed[7,39]. Oxidative C(aryl)-OH bond functionalization of catechols is one of the most interesting and recent methods for the synthesis of benzoxazoles. Examples of this approach in benzoxazole synthesis include the reaction of catechols with amines[40–44], with aldehydes[45–47], with alcohols (or ethers)[48], and with ketones, alkenes and alkynes (Fig. 2A)[49]. In this study, multicomponent reactions (MCRs) between catechols, aldehydes, and ammonium acetate were used to synthesize benzoxazoles (Fig. 2B). The reaction was carried out using a catalytic amount of $ZrCl_4$ in ethanol solvent. Note that $ZrCl_4$ can be considered as a green Lewis acid catalyst, being a slightly toxic compound $[LD_{50}\ (ZrCl_4,\ \text{oral rat}) = 1688\ \text{mg.kg}^{-1}]$ and is not considered to be very toxic[50]. Zirconium catalysts are also successfully used as a catalyst in the synthesis of various organic compounds. Their low cost and high stability to water and oxygen make them promising catalysts for use in organic synthesis[51].

Results and discussion

To find the appropriate conditions, we chose a model reaction between 3,5-di-*tert*-butylbenzene-1,2-diol **1a**, 4-methoxybenzaldehyde **2a** and ammonium salts **3** in the presence of different Lewis acids (L.A.), different solvents and temperature to synthesize benzoxazole **4a** (Table 1). In the absence of a catalyst, no product

[1]Department of Chemistry, College of Sciences, Shiraz University, Shiraz, Fars 71454, Iran. [2]Masoumeh Mohammadi and Jasem Aboonajmi contributed equally to this work. ✉email: Panahi@shirazu.ac.ir
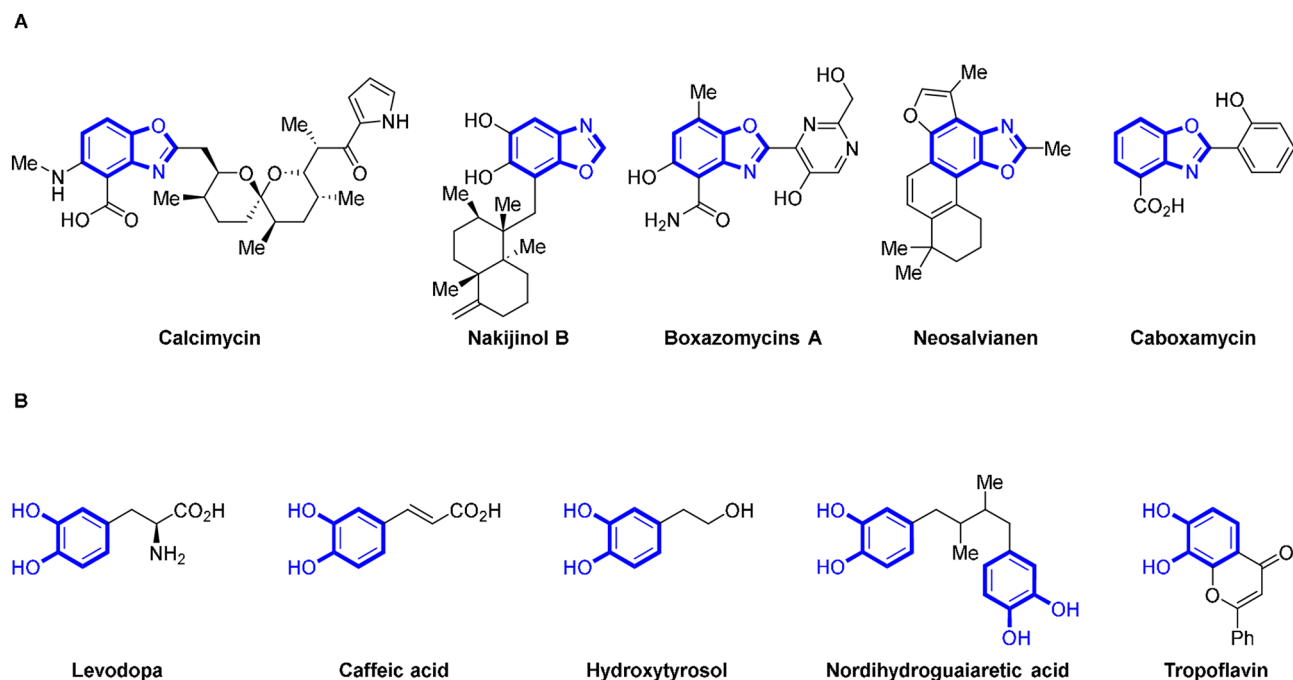
Fig. 1. (**A**) Examples of natural products and benzoxazole-based biological active compounds. (**B**) Some natural sources of catechols.
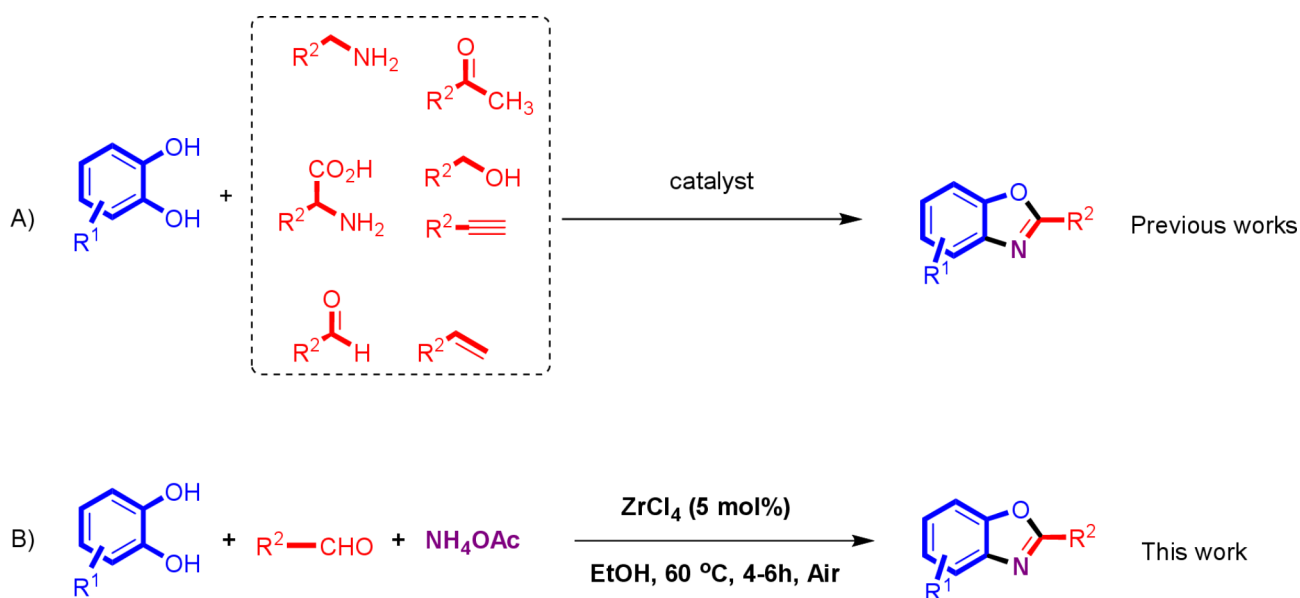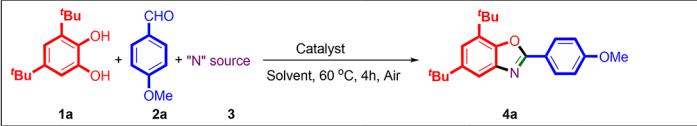

Fig. 2. (**A**) Different methods for the synthesis of benzoxazoles using catechols. (**B**) Our optimized method.

was observed (Table 1, entry 1). Subsequently, 5 mol% of different Lewis acids were tested as catalysts, such as $ZrOCl_2 \cdot 8H_2O$, $Zr(NO_3)_4$, $Zr(SO_4)_2$, $ZrCl_4$, $ZnCl_2$, TiO_2 and MoO_3 in EtOH solvent and $ZrCl_4$ was found to be the best (Table 1, entries 2–8). To improve the efficiency, various solvents were investigated including dioxane, acetonitrile, ethyl acetate, dichloroethane (DCE), tetrahydrofuran (THF), dimethylformamide (DMF), and dimethyl sulfoxide (DMSO). All the solvents tested gave lower yields than ethanol (Table 1, entries 9–15). When ammonium acetate was replaced by other nitrogen sources such as NH_4Cl, NH_4CN and $(NH_4)_2SO_4$, no improvement in reaction yield was observed (Table 1, entries 16–18). Further investigation showed that temperatures lower and higher than 60 °C did not increase the yield of the reaction (Table 1, entries 19 & 20). When the catalyst loading was changed to 2 and 10 mol % respectively, yields of 78 and 92% were obtained, respectively (Table 1, entries 21 & 22). The yield was decreased when the reaction was performed under N_2 gas, indicating that atmospheric oxygen may play a key role in the reaction progress (Table 1, entry 23). Increasing

Table 1. Screening of Lewis acids (L.A) for the synthesis of 5,7-di-*tert*-butyl-2-(4-methoxyphenyl)benzo[*d*]oxazole

#	L.A. (mol %)	N source	Solvent	Time (h)	Yield 4a (%)[a]
1	-	NH$_4$OAc	-	24	-
2	ZrCl$_2$.8H$_2$O (5)	NH$_4$OAc	EtOH	8	70
3	Zr(NO$_3$)$_4$ (5)	NH$_4$OAc	EtOH	6	80
4	Zr(SO$_4$)$_2$(5)	NH$_4$OAc	EtOH	12	15
5	**ZrCl$_4$(5)**	**NH$_4$OAc**	**EtOH**	**4**	**94**
6	ZnCl$_2$ (5)	NH$_4$OAc	EtOH	12	60
7	TiO$_2$ (5)	NH$_4$OAc	EtOH	12	55
8	MoO$_3$ (5)	NH$_4$OAc	EtOH	12	44
9	ZrCl$_4$ (5)	NH$_4$OAc	Dioxane	12	60
10	ZrCl$_4$ (5)	NH$_4$OAc	CH$_3$CN	6	80
11	ZrCl$_4$ (5)	NH$_4$OAc	EtOAc	12	63
12	ZrCl$_4$ (5)	NH$_4$OAc	DCE	7	72
13	ZrCl$_4$ (5)	NH$_4$OAc	THF	12	50
14	ZrCl$_4$ (5)	NH$_4$OAc	DMF	12	55
15	ZrCl$_4$ (5)	NH$_4$OAc	DMSO	12	43
16	ZrCl$_4$ (5)	NH$_4$Cl	EtOH	6	75
17	ZrCl$_4$ (5)	NH$_4$CN	EtOH	6	62
18	ZrCl$_4$ (5)	(NH$_4$)$_2$SO$_4$	EtOH	12	35
19[c]	ZrCl$_4$ (5)	NH$_4$OAc	EtOH	4	83
20[d]	ZrCl$_4$ (5)	NH$_4$OAc	EtOH	6	75
21	ZrCl$_4$ (2)	NH$_4$OAc	EtOH	5	78
22	ZrCl$_4$ (10)	NH$_4$OAc	EtOH	4	92
23[e]	ZrCl$_4$ (5)	NH$_4$OAc	EtOH	8	40
24[f]	ZrCl$_4$ (5)	NH$_4$OAc	EtOH	4	92
25[g]	ZrCl$_4$ (5)	NH$_4$OAc	EtOH	4	88
26[h]	ZrCl$_4$ (5)	NH$_4$OAc	EtOH	4	90

Table 1. Screening of Lewis acids (L.A) for the synthesis of 5,7-di-*tert*-butyl-2-(4-methoxyphenyl)benzo[*d*]oxazole[a, b]. [a]Reaction condition: **1** (1.0 mmol), **2** (1.0 mmol), **3** (1.0 mmol), solvent (3.0 mL), open air. [b]Isolated yield. [c]Reaction was performed at reflux. [d]Reaction was performed at 25 °C. [e]N$_2$. [f]Ammonium acetate (2.0 mmol). [g]Ammonium acetate (3.0 mmol). [h]Catechol (1.5 mmol).

the amount of ammonium acetate did not improve the reaction result, even the yield decreased to some extent (Table 1, entries 24 & 25). Also, no progress in the reaction yield was observed by increasing the amount of catechol (Table 1, entry 26).

Once the optimum reaction conditions were in place, the generality and scope of the reaction was investigated (Fig. 3). Since alkynes and alkenes are valuable functionalities in organic synthesis for further derivatization, some benzoxazole derivatives bearing alkene and alkynes were synthesized (**4b**-**4d**, **4f**-**4 g**). A yield of 90% was obtained when 1-(prop-2-yn-1-yl)-*1 H*-indole-3-carbaldehyde was used as aldehyde substrate (**4e**). Alkyl halide substituted benzoxazoles were also synthesized in high yields, useful for attaching to other molecules and further derivatization (**4h**-**4i**)[52]. 4-((4-Fluorobenzyl)oxy)benzaldehyde and 4-(benzyloxy)benzaldehyde afforded the corresponding benzoxazoles **4j** and **4k**, respectively, in high yields. We have successfully synthesized benzoxazole derivatives with quinolone moiety using our process (**4l** and **4m**)[53–55]. The benzoxazole **4n** with two alkyne groups was obtained in 84% yield from a 2,4-substituted benzaldehyde. The bis-heterocyclic compound **4o**, which contains an indole heterocycle, was successfully synthesized under optimized conditions. Compound **4p** was synthesized using an aldehyde substrate linked to a benzonitrile group, which are useful substrates for the preparation of superamolecules[56]. To highlight the scope of this protocol, the preparation of benzoxazole molecules containing a *β*-lactam moiety was verified by the reaction of aldehyde-functionalized *β*-lactams, catechol and ammonium acetate under optimized conditions (**4q**-**4r**)[57]. These experiments have demonstrated that the new synthetic method developed is capable of late stage functionalization of complex molecules.

To provide further evidence for the generality and functional group tolerance of the method, we investigated a wide range of aromatic aldehydes, including electron-donating and electron-withdrawing groups, heterocycles and polyaromatics (Figs. 4, **4s**-**4aag**). For example, benzaldehyde was converted to the desired product in 92% isolated yield (**4s**). Aromatic aldehydes with electron-donating groups including -Me, iso-propyl, *tert*-butyl, hydroxyl, and -SMe at the *para* position were successfully converted to the corresponding products in excellent yields (**4t**-**4x**). The sterically hindered aldehyde substrates gave rise to benzoxazole products in good to excellent
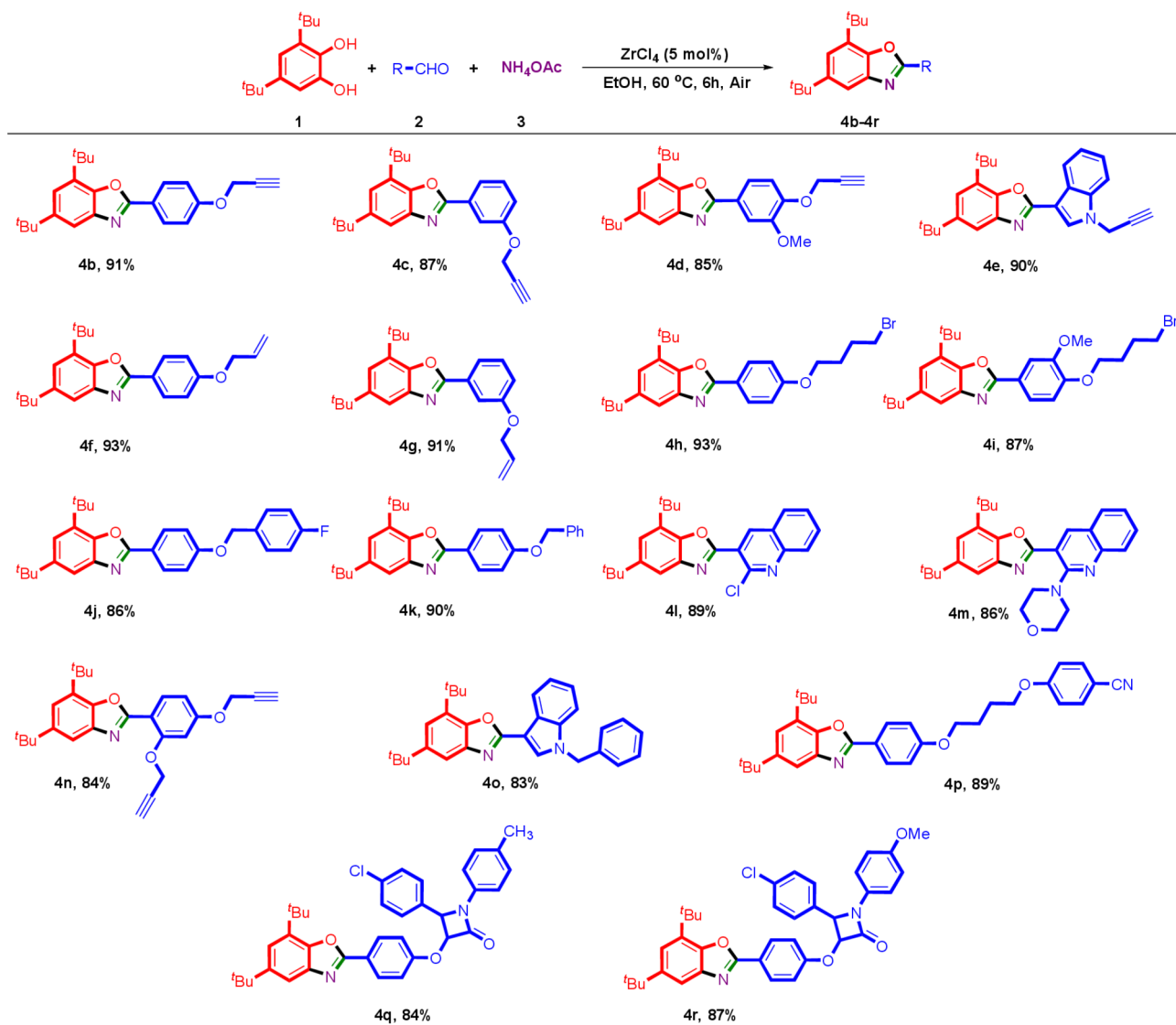
Fig. 3. Scope of the reaction using synthesized aldehydes [a,b]. [a]Reaction conditions: **1** (1.0 mmol), **2** (1.0 mmol), **3** (1.0 mmol), and ZrCl$_4$ (5 mol %) in the EtOH (3 mL) at 60 °C for 6 h. [b]Yields correspond to isolated products.

yields (**4y-4aa,4al**). High yields of benzoxazole products have been obtained with the use of *meta*-substituted benzaldehydes (**4ab,4ai,4am**). Halogen substituted aldehydes such as (-F, -CF$_3$, -Cl and Br) afforded the corresponding benzoxazoles in satisfactory yields (**4af**, **4ag** and **4ai**-**4an**). Aldehydes with electron-withdrawing groups such as -CN, and NO$_2$ also worked well and gave the desired products in high yields (**4ah** and **4ao**).

Polyaromatic aldehydes such as 1-naphthaldehyde, anthracene-9-carbaldehyde and phenanthrene-9-carbaldehyde, which provide the desired products **4ap-4ar** in high yields. A number of heterocyclic aromatic aldehydes, including pyrrole, indole, pyridine, furan and thiophene, tolerated the reaction conditions well to afford the corresponding products in high yields (**4as-4az**). The benzoxazole **4aag** was obtained in a yield of 52% when the corresponding aliphatic aldehyde was used.

To further illustrate the generality and scope of the method, various substituted catechols were also tested. Mono-substituted catechols such as 4-(*tert*-butyl)benzene-1,2-diol and 3-methoxybenzene-1,2-diol reacted well with this protocol to afford benzoxazoles **4aaa-4aac** in 89, 86 and 57% yields, respectively. Some poly-substituted benzoxazoles have also been successfully synthesized using the corresponding poly-substituted catechols (**4aad-4aaf**). No product (**4aah-4aai**) was obtained with electron-poor substituted catechols such as 4-nitrobenzene-1,2-diol and 3,4,5,6-tetrabromobenzene-1,2-diol.

A gram-scale synthesis of benzoxazole was successfully performed under optimized conditions and compound **4f** was synthesized in 85% isolated yield (Fig. 5).

A plausible reaction mechanism based on the literature is proposed for the synthesis of benzoxazoles by reaction of catechol, aldehyde and ammonium acetate in the presence of ZrCl$_4$ as catalyst (Fig. 6). Catechol can chelate zirconium by coordinating two hydroxyl groups to form the first core of the catalytic cycle (**I**)[51].
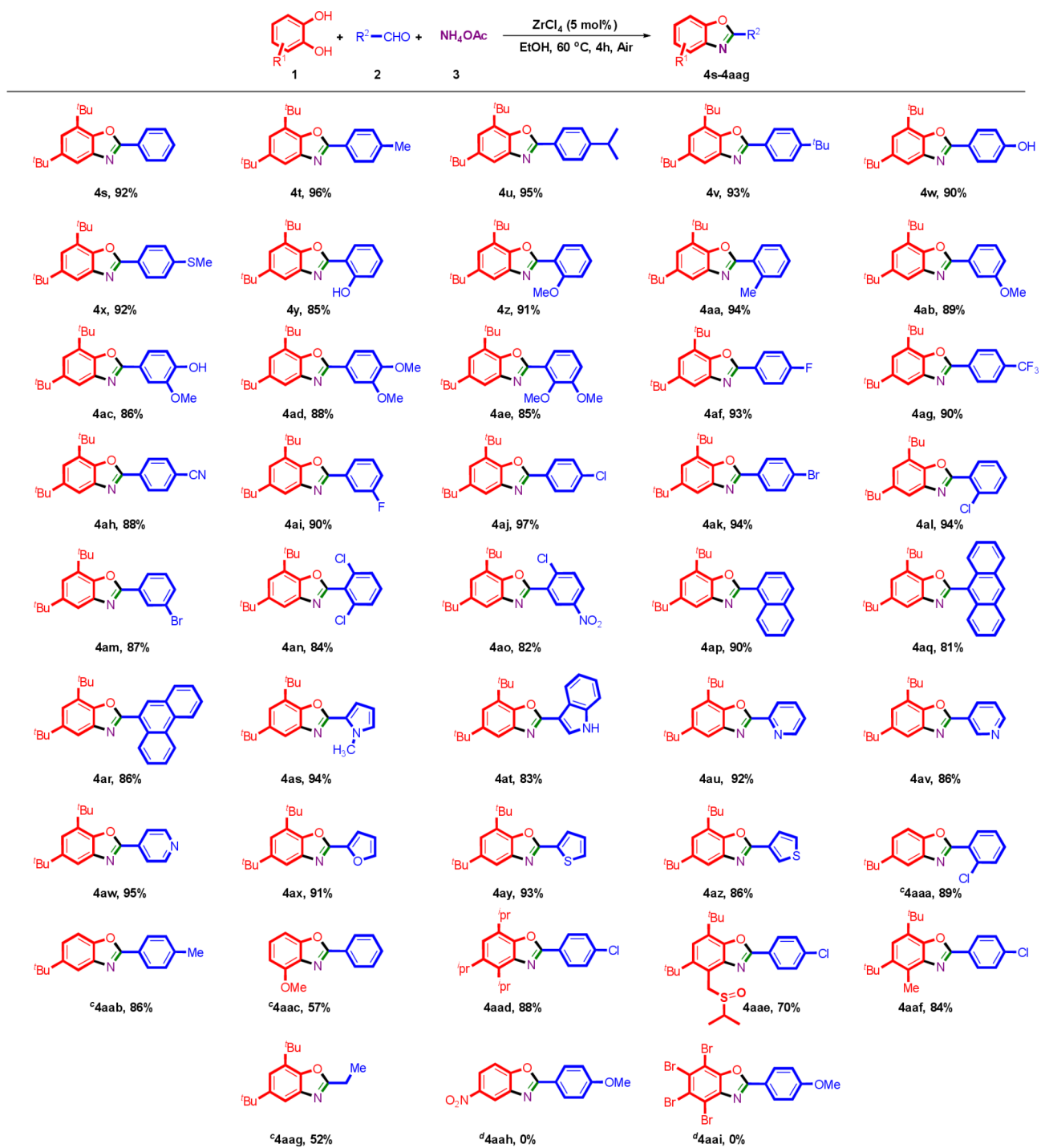
Fig. 4. Scope of the reaction using commercial aldehydes [a,b]. [a]Reaction conditions: **1** (1.0 mmol), **2** (1.0 mmol), **3** (1.0 mmol), and ZrCl$_4$ (5 mol %) in the EtOH (5 mL) at 60 °C for 4 h. [b]Yields correspond to isolated products. [c] Reaction was performed at 80 °C for 6 h; [d] Reaction was performed at 100 °C for 24 h.

In this situation, a semi-quinone moiety (**II**) can be formed by enol-keto tautomerization in complex **I**[58]. It seems that the carbonyl group formed in intermediate (**II**) is reacted with ammonium acetate to form the imine intermediate (**III**)[47]. Another possibility is that the imine formed from the reaction between the aldehyde and ammonium acetate (**III^**) reacts with the carbonyl group to form the imine-phenol intermediate (**IV**)[59,60]. Subsequently, the intermediate (**V**) can be cyclized intramolecularly[40]. Finally, the target product **4** is obtained by the oxidation of the intermediate **V**, probably with the help of oxygen from the air, and a zirconium complex is released to start the next cycle[61,62].
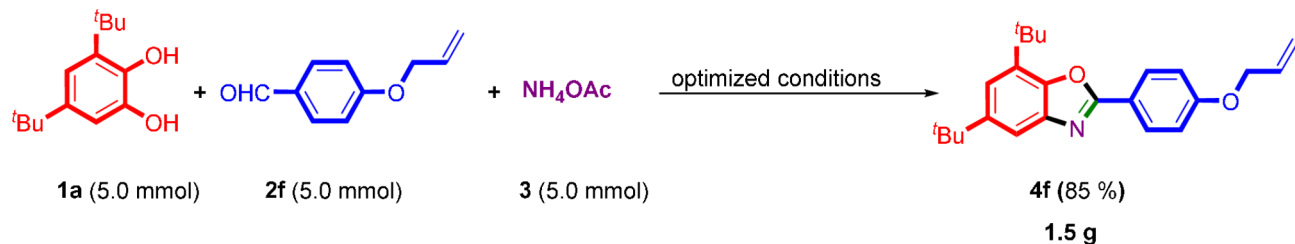
Fig. 5. Gram-scale synthesis of benzoxazole **4f**. Reaction conditions: **1a** (5.0 mmol), **2f** (5.0 mmol), **3** (5.0 mmol), and ZrCl$_4$ (5 mol %) in the EtOH (25 mL) at 60 °C for 4 h.
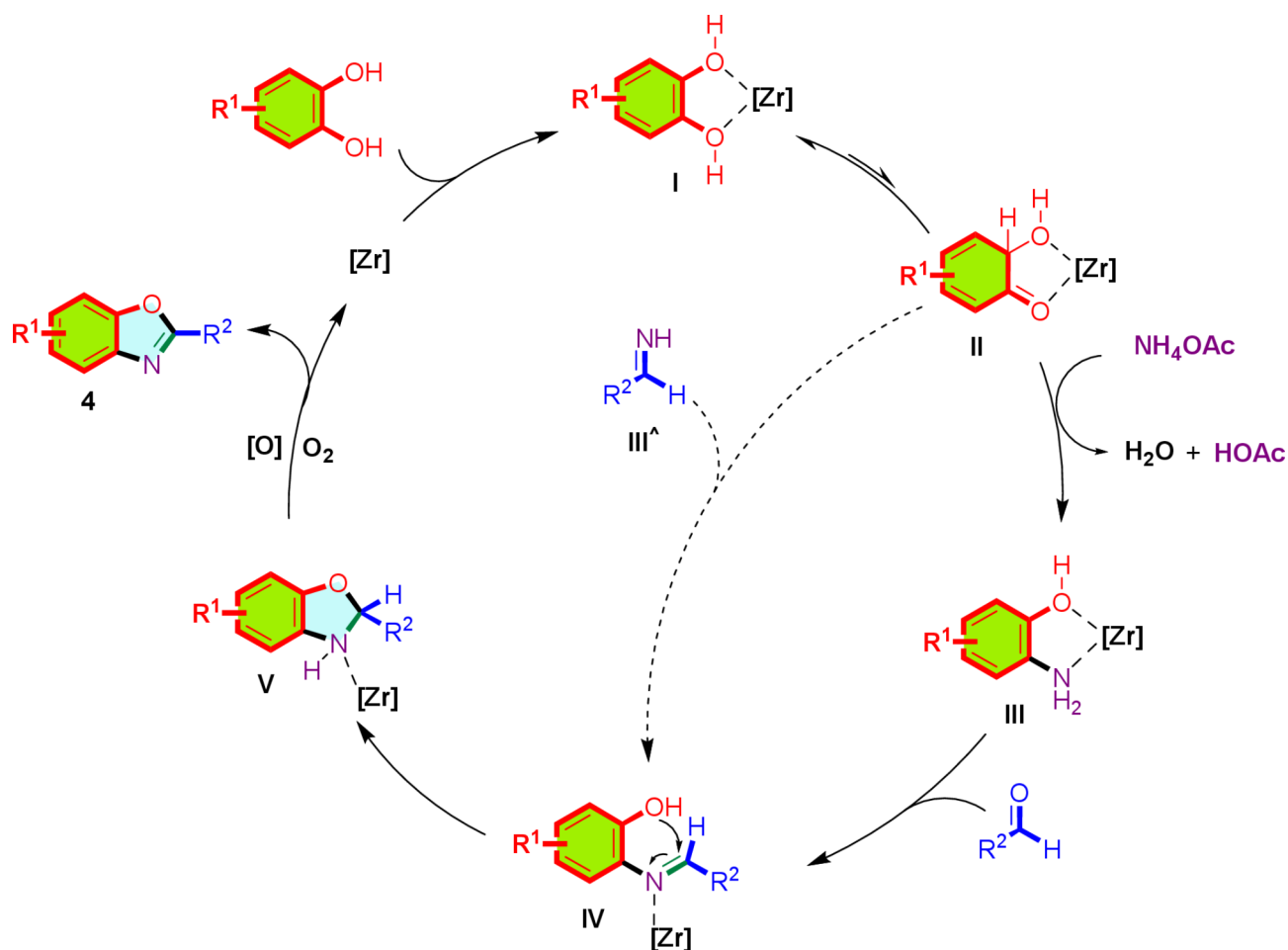

Fig. 6. Proposed reaction mechanism.

Experimental section
General information
All reagents and solvents were obtained from commercial sources. All known products were identified by comparison of their spectral data and melting points with those of the valid samples ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz), spectra were recorded on Brucker Avance DRX. Melting points were checked by a Büchi B-545 apparatus in open capillary tubes. All reactions were monitored by thin-layer chromatography (TLC) using silica gel plates (silica gel 60 F254 Merck Chemical Company). The elemental analysis was performed using a PerkinElmer240-B microanalyzer.

General experimental procedure for the preparation of benzoxazoles derivatives
Sequentially, a solution of catechol (1.0 mmol), aldehyde (1.0 mmol), ammonium acetate (1.0 mmol), and ZrCl$_4$ (5 mol %) in ethanol (3.0 mL) was stirred in an open tube under the air atmosphere at 60 °C in an oil bath for the required time. The progress of the reaction was monitored by thin layer chromatography (TLC). After completion

of the reaction, the resulting mixture was cooled to room temperature and ethanol was removed under reduced pressure. The reaction mixture was diluted with EtOAc (3×5 mL). Afterward, the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum. Eventually, the crude mixtures were purified by column chromatography using an eluent (petroleum ether/EtOAc) to obtain the pure benzoxazoles **4**.

Conclusions

In conclusion, we have developed a novel, mild, and green protocol for the synthesis of benzoxazoles *via* sequential C-N, and C-O bond formation in the presence of a zirconium catalyst. Under optimized reaction conditions, 59 examples of different benzoxazoles were synthesized. The reaction conditions tolerated many functional groups and it was successful in the synthesis of some biologically active nuclei, suggesting its high potential in late stage functionalization. Therefore, an efficient, simple and practical strategy has been developed that uses a low-cost catalyst to produce various benzoxazole derivatives from natural source catechol on a large scale under environmentally friendly conditions.

Data availability

All data generated or analysed during this study are included in this published article and its supplementary information files.

References

1. Nicolaou, K. C. Organic synthesis: the art and science of replicating the molecules of living nature and creating others like them in the laboratory. *Proc. R Soc. A*. **470**, 2013069 (2014).
2. Ananikov, V. P. et al. Development of new methods in modern selective organic synthesis: preparation of functionalized molecules with atomic precision. *Russ Chem. Rev.* **83**, 885 (2014).
3. Ganesh, K. N. et al. Green chemistry: a framework for a sustainable future. *Org. Process. Res. Dev.* **25**, 1455–1459 (2021).
4. Yue, K. et al. Trends and opportunities in Organic synthesis: global state of research metrics and advances in precision, efficiency, and green chemistry. *J. Org. Chem.* **88**, 4031–4035 (2023).
5. Li, C. J. & Trost, B. M. Green chemistry for chemical synthesis. *PNAS*. **105**, 13197–13202 (2008).
6. Ertan-Bolelli, T., Yildiz, I. & Ozgen-Ozgacar, S. Synthesis, molecular docking and antimicrobial evaluation of novel benzoxazole derivatives. *Med. Chem. Res.* **25**, 553–567 (2016).
7. Sattar, R., Mukhtar, R., Atif, M., Hasnain, M. & Irfan, A. Synthetic transformations and biological screening of benzoxazole derivatives: a review. *J. Heterocycl. Chem.* **57**, 2079–2107 (2020).
8. Yildiz-Oren, I., Yalcin, I., Aki-Sener, E. & Ucarturk, N. Synthesis and structure-activity relationships of new antimicrobial active multisubstituted benzazole derivatives. *Eur. J. Med. Chem.* **39**, 291–298 (2004).
9. Akbay, A., Ören, I., Temiz-Arpaci, Ö., Aki-Sener, E. & Yalçin, I. Synthesis and HIV-1 reverse transcriptase inhibitor activity of some 2,5,6-substituted benzoxazole, benzimidazole, benzothiazole and oxazolo (4,5-*b*)pyridine derivatives. *Arzneimittel-Forschung/Drug Res.* **53**, 266–271 (2003).
10. Osmaniye, D. et al. Synthesis of some new benzoxazole derivatives and investigation of their anticancer activities. *Eur. J. Med. Chem.* **210**, 112979 (2021).
11. Rida, S. M. et al. Synthesis of some novel benzoxazole derivatives as anticancer, anti-HIV-1 and antimicrobial agents. *Eur. J. Med. Chem.* **40**, 949–959 (2005).
12. Demmer, C. S. & Bunch, L. Benzoxazoles and oxazolopyridines in medicinal chemistry studies. *Eur. J. Med. Chem.* **97**, 778–785 (2015).
13. Paderni, D. et al. A new benzoxazole-based fluorescent macrocyclic chemosensor for optical detection of Zn^{2+} and Cd^{2+}. *Chemosensors*. **10**, 188 (2022).
14. Zou, Y. et al. Research progress of benzothiazole and benzoxazole derivatives in the discovery of agricultural chemicals. *Int. J. Mol. Sci.* **24**, 10807 (2023).
15. Wu, Y. et al. Two Cu(I) complexes constructed by different *N*-heterocyclic benzoxazole ligands: syntheses, structures and fluorescent properties. *J. Mol. Struct.* **1191**, 95–100 (2019).
16. Walker, K. L., Dornan, L. M., Zare, R. N., Waymouth, R. M. & Muldoon, M. J. Mechanism of catalytic oxidation of styrenes with hydrogen peroxide in the presence of cationic palladium(II) complexes. *J. Am. Chem. Soc.* **139**, 12495–12503 (2017).
17. Agag, T., Liu, J., Graf, R., Spiess, H. W. & Ishida, H. Benzoxazole resin: a novel class of thermoset polymer via smart benzoxazine resin. *Macromolecules*. **45**, 8991–8997 (2012).
18. Basak, S., Dutta, S. & Maiti, D. Accessing C₂-functionalized 1,3-(benz)azoles through transition metal-catalyzed C–H activation. *Chem. - Eur. J.* **27**, 10533–10557 (2021).
19. Singh, S. et al. Recent advances in the development of pharmacologically active compounds that contain a benzoxazole scaffold. *Asian J. Org. Chem.* **4**, 1338–1361 (2015).
20. Wong, X. K. & Yeong, KY. A patent review on the current developments of benzoxazoles in drug discovery. *ChemMedChem*. **16**, 3237–3262 (2021).
21. Ovenden, S. P. B. et al. Sesquiterpene benzoxazoles and sesquiterpene quinones from the marine sponge Dactylospongia elegans. *J. Nat. Prod.* **74**, 65–68 (2011).
22. Kusumi, T., Ooi, T., Wülchli, M. R. & Kakisawa, H. Structure of the novel antibiotics boxazomycins a, B, and C. *J. Am. Chem. Soc.* **110**, 2954–2958 (1988).
23. Chaney, M. O., Demarco, P. V., Jones, N. D. & Occolowitz, J. L. The structure of A23187, a divalent cation ionophore. *J. Am. Chem. Soc.* **96**, 1932–1933 (1974).
24. Park, J. et al. Tafamidis: a first-in-class transthyretin stabilizer for transthyretin amyloid cardiomyopathy. *Ann. Pharmacother.* **54**, 470–477 (2020).
25. Sivalingam, P., Hong, K., Pote, J. & Prabakar, K. Extreme environment streptomyces: potential sources for new antibacterial and anticancer drug leads? *Int. J. Microbiol.* **2019**, 5283948 (2019).
26. Pal, S., Manjunath, B., Ghorai, S. & Sasmal, S. Benzoxazole alkaloids: occurrence, chemistry, and biology. *Alkaloids Chem. Biol.* **79**, 71–137 (2018).
27. Shafiq, Z. et al. Bioinspired underwater bonding and debonding on demand. *Angew Chemie*. **124**, 4408–4411 (2012).
28. Lee, H., Dellatore, S. M. Miller, W. M. & Messersmith PB. Mussel-inspired surface chemistry for multifunctional coatings. *Science*. **318**, 420–426 (2007).

29. Nasibipour, M., Safaei, E., Wrzeszcz, G. & Wojtczak, A. Tuning of the redox potential and catalytic activity of a new Cu(II) complex by: *O*-iminobenzosemiquinone as an electron-reservoir ligand. *New. J. Chem.* **44**, 4426–4439 (2020).

30. D'Aquila, P. S., Collu, M., Gessa, G. L. & Serra, G. The role of dopamine in the mechanism of action of antidepressant drugs. *Eur. J. Pharmacol.* **405**, 365–373 (2000).

31. Ghaedi, M., Mehranbod, N. & Khorram, M. Facile fabrication of robust superhydrophobic polyurethane sponge modified with polydopamine- silica nanoparticle for effective oil/water separation. *React. Funct. Polym.* **191**, 105657 (2023).

32. Bruno, F. et al. Design and synthesis of functionalized 4-aryl-catechol derivatives as new antinflammatory agents with in vivo efficacy. *Eur. J. Med. Chem.* **243**, 114788 (2022).

33. Kiss, L. E. & Soares-Da-Silva, P. Medicinal chemistry of catechol *O*-methyltransferase (COMT) inhibitors and their therapeutic utility. *J. Med. Chem.* **57**, 8692–8717 (2014).

34. Kim, J., Lee, C. & Ryu, J. H. Adhesive catechol-conjugated hyaluronic acid for biomedical applications: a mini review. *Appl. Sci.* **11**, 1–14 (2021).

35. Wang, J., Park, J. N., Wei, X. Y. & Lee, C. W. Room-temperature heterogeneous hydroxylation of phenol with hydrogen peroxide over Fe^{2+}, Co^{2+} ion-exchanged Naβ Zeolite. *Chem. Commun.* **3**, 628–629 (2003).

36. Fukuhara, K. et al. DTPA-Bound planar catechin with potent antioxidant activity triggered by Fe^{3+} coordination. *Antioxidants.* **12**, 225 (2023).

37. Abdel-Mohsen, H. T., Conrad, J. & Beifuss, U. Laccase-catalyzed domino reaction between catechols and 6-substituted 1,2,3,4-tetrahydro-4-oxo-2-thioxo-5-pyrimidinecarbonitriles for the synthesis of pyrimidobenzothiazole derivatives. *J. Org. Chem.* **78**, 7986–8003 (2013).

38. Meadows, M. K., Roesner, E. K., Lynch, V. M., James, T. D. & Anslyn, E. V. Boronic acid mediated coupling of catechols and *N*-hydroxylamines: a bioorthogonal reaction to label peptides. *Org. Lett.* **19**, 3179–3182 (2017).

39. Sunny, S., John, S. E. & Shankaraiah, N. Exploration of C-H activation strategies in construction of functionalized 2-aryl benzoazoles: a decisive review. *Asian J. Org. Chem.* **10**, 1986–2009 (2021).

40. Chen, X. et al. Copper-catalyzed aerobic oxidative C(aryl)-OH bond functionalization of catechols with amines affording benzoxazoles. *Adv. Synth. Catal.* **357**, 2924–2930 (2015).

41. Sharghi, H., Aboonajmi, J., Aberi, M. & Shekouhy, M. Amino acids: nontoxic and cheap alternatives for amines for the synthesis of benzoxazoles through the oxidative functionalization of catechols. *Adv. Synth. Catal.* **362**, 1064–1083 (2020).

42. Meng, X. et al. OMS-2-Supported Cu hydroxide-catalyzed benzoxazoles synthesis from catechols and amines via domino oxidation process at room temperature. *J. Org. Chem.* **82**, 6922–6931 (2017).

43. Sharghi, H., Aali Hosseini, M., Aboonajmi, J. & Aberi, M. Use of vitamin B_{12} as a nontoxic and natural catalyst for the synthesis of benzoxazoles via catechols and primary amines in water under aerobic oxidation. *ACS Sustain. Chem. Eng.* **9**, 11163–11170 (2021).

44. Aboonajmi, J., Sharghi, H., Aberi, M. & Shiri, P. Consecutive oxidation/condensation/cyclization/aromatization sequences catalyzed by nanostructured iron(III)-porphyrin complex towards benzoxazole derivatives. *Eur. J. Org. Chem.* **2020**, 5978–5984 (2020).

45. Sharghi, H., Aboonajmi, J. & Aberi, M. One-pot multicomponent reaction of catechols, ammonium acetate, and aldehydes for the synthesis of benzoxazole derivatives using the Fe(III)-salen complex. *J. Org. Chem.* **85**, 6567–6577 (2020).

46. Li, F. et al. Novel dual-enzyme system for synthesis of 2-alkyl and 2-arylbenzoxazoles via aerobic oxidation. *Org. Chem. Front.* **10**, 3509–3514 (2023).

47. Wu, S. et al. Metal-free oxidative condensation of catechols, aldehydes and NH_4OAc towards benzoxazoles. *Adv. Synth. Catal.* **363**, 3607–3614 (2021).

48. Aboonajmi, J., Panahi, F. & Sharghi, H. One-pot multicomponent coupling reaction of catechols, benzyl alcohols/benzyl methyl ethers, and ammonium acetate toward synthesis of benzoxazoles. *ACS Omega.* **6**, 22395–22399 (2021).

49. Aboonajmi, J., Panahi, F., Hosseini, M. A., Aberi, M. & Sharghi, H. Iodine-catalyzed synthesis of benzoxazoles using catechols, ammonium acetate, and alkenes/alkynes/ketones via C-C and C-O bond cleavage. *RSC Adv.* **12**, 20968–20972 (2022).

50. Smitha, G., Chandrasekhar, S. & Reddy, C. S. Applications of zirconium(IV) chloride in organic synthesis. *Synthesis (Stuttg)* 829–855 (2008).

51. Peng, L. et al. Zirconium-based catalysts in Organic synthesis. *Top. Curr. Chem. (Z).* **380**, 41 (2022).

52. Li, Z. et al. Discovery of a novel class of benzoxazole derivatives as histamine H3 receptor ligands for the treatment of neuropathic pain. *Bioorg. Chem.* **127**, 106039 (2022).

53. Zuo, S. J. et al. Discovery of novel 3-benzylquinazolin-4(3H)-ones as potent vasodilative agents. *Bioorg. Med. Chem. Lett.* **24**, 5597–5601 (2014).

54. Chioua, M. et al. Novel quinolylnitrones combining neuroprotective and antioxidant properties. *ACS Chem. Neurosci.* **10**, 2703–2706 (2019).

55. Chioua, M. et al. New quinolylnitrones for stroke therapy: antioxidant and neuroprotective (*Z*)- *N*- *tert*-butyl-1-(2-chloro-6-methoxyquinolin-3-yl)methanimine oxide as a new lead-compound for ischemic stroke treatment. *J. Med. Chem.* **62**, 2184–2201 (2019).

56. Jiang, W. et al. Chelate cooperativity and spacer length effects on the assembly thermodynamics and kinetics of divalent pseudorotaxanes. *J. Am. Chem. Soc.* **134**, 1860–1868 (2012).

57. Borazjani, N. et al. Three-component synthesis of chromeno β-lactam hybrids for inflammation and cancer screening. *Eur. J. Med. Chem.* **179**, 389–403 (2019).

58. Yuan, H., Yoo, W. J., Miyamura, H. & Kobayashi, S. Discovery of a metalloenzyme-like cooperative catalytic system of metal nanoclusters and catechol derivatives for the aerobic oxidation of amines. *J. Am. Chem. Soc.* **134**, 13970–13973 (2012).

59. Zhou, M. et al. Enantioselective reductive coupling of imines templated by chiral diboron. *J. Am. Chem. Soc.* **142**, 10337–10342 (2020).

60. Chen, Y. et al. Four-component synthesis of 9H-pyrimido[4,5-b]indoles using ammonium iodide as the nitrogen source. *Catalysts.* **13**, 623 (2023).

61. Niknam, E., Panahi, F., Daneshgar, F., Bahrami, F. & Khalafi-Nezhad, A. Metal-organic framework MIL-101(cr) as an efficient heterogeneous catalyst for clean synthesis of benzoazoles. *ACS Omega.* **3**, 17135–17144 (2018).

62. Khalafi-Nezhad, A. & Panahi, F. Ruthenium-catalyzed synthesis of benzoxazoles using acceptorless dehydrogenative coupling reaction of primary alcohols with 2-aminophenol under heterogeneous conditions. *ACS Catal.* **4**, 1686–1692 (2014).

Acknowledgements

Author contributions

The work was conceived by FP and HS. MM and JA performed the experiments. MS synthesized some starting materials. The first draft of the manuscript was prepared by JA and FP. All authors reviewed the manuscript.

Declarations

Competing interests
The authors declare no competing interests.

Additional information
Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-024-76839-3.

Correspondence and requests for materials should be addressed to F.P.

Reprints and permissions information is available at www.nature.com/reprints.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.