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Excited-state intramolecular proton transfer in 2-(2′,6′-dihydroxyphenyl) benzoxazole: effect of dual hydrogen bonding on the optical properties

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ABSTRACT

2-(2′,6′-Dihydroxyphenyl)benzoxazole (DHBO) has been synthesized by using palladium-catalyzed oxidative cyclization. The compound utilizes both *O–H···N* and *O–H···O* bonds to ensure a coplanar structure between the benzoxazole and phenol fragments. Optical comparison with the parent compound 2-(2′-hydroxyphenyl)benzoxazole (HBO) reveals that the dual hydrogen bonding in DHBO plays an essential role in raising the desirable *keto* emission for ESIPT and tuning the polarity sensitivity toward the molecular environment. DHBO also exhibits a higher quantum yield ($\phi_{fl} = 0.108$ in methanol) than HBO ($\phi_{fl} = 0.0025$) in the same solvent.

2-(2′-Hydroxyphenyl)benzoxazole (HBO) **1** has emerged to be an interesting material, due to its intrinsic property for the excited state intramolecular proton transfer (ESIPT). A distinctive feature for the HBO derivatives is that their fluorescence is well separated from their absorption maxima, leading to unusually large Stokes' shift.[1] Utilization of this feature has resulted in various applications including chemical sensors for zinc(II)[2,3] and anions,[4] and electronic devices such as organic light-emitting diodes.[5] In recent years, the HBO derivatives have been studied extensively to elucidate the ESIPT process (Scheme 1). In the ground state, the HBO derivative exists in the *enol–imine* form. Upon irradiation with photons, the HBO molecule is driven to the excited state, where a proton is transferred from the hydroxy group to an acceptor to generate the corresponding *keto–amine* tautomer. The entire process occurs in about a picosecond, making the HBO derivative an attractive candidate for optical switching.[6]

The HBO molecule is known to exist in the intramolecular hydrogen-bonded rotamers **1a** and **1b**. X-ray diffraction reveals that the two rotamers **1a** and **1b** exist in about 1:1 ratio in the crystalline state,[7] with the hydroxyl group pointing to either N- or O-atom side of the oxazole ring. It has been demonstrated that only rotamer **1b** undergoes ESIPT process,[8,9] which leads to the *keto* tautomer **2** to give the emission with large Stokes shift. The rotamer **1a** is likely the one responsible for the *enol* emission.

In the solution state, HBO can also exist as the *enol* **3**, especially when the solute molecule has strong interaction with the surrounding solvent molecules. In the extreme cases, the solvent molecules may remove the hydroxy proton to generate the anionic species. The *enol* forms (**1a, 1b**, and **3**) in solution are in equilibrium (Scheme 2), whose actual composition is dependent on the solvent properties. It should be noticed that only tautomer **1b** undergoes the ESIPT to generate the desirable *keto* emission. The effective content of **1b**, therefore, determines the optimum performance of the HBO derivatives. Previous studies have shown that the relative intensity of *keto* emission can be significantly increased by decreasing the temperature (e.g., at 77 K)[10] or solvent polarity.[11] Any environmental changes, which affect the equilibrium among **1a**, **1b**, and **3**, can ultimately influence the population of excited states and photophysical characteristics of HBO. The presence of several ground-states, in addition to their unpredictable composition in equilibrium, dilutes the effective concentration of rotamer **1b**, thereby lowering the intensity of the desirable *keto* emission and hampering a broader application of HBO. For example, the HBO **1** in ethanol[10] and methanol[12] solutions gives both *enol* ($\lambda_{em} \approx 370$ nm) and *keto* ($\lambda_{em} \approx 500$ nm) emission in about equal intensity at room temperature, while the *keto* emission is nearly exclusive in a nonpolar solvent such as 3-methylpentane.[10]

It remains a challenging task to effectively direct the equilibrium toward the useful rotamer **1b**. Decreasing temperature and using nonpolar solvents are either impractical or can only be applied to very limited situations. The known intermolecular hydrogen bond strength[13] for *O–H···N* ($\Delta H = -6.5$ kcal/mol, measured from phenol/pyridine) is only slightly stronger than that for *O–H···O* bond ($\Delta H = -5.0$ kcal/mol, measured from phenol/ether). The small energetic difference between the *O–H···N* and *O–H···O*

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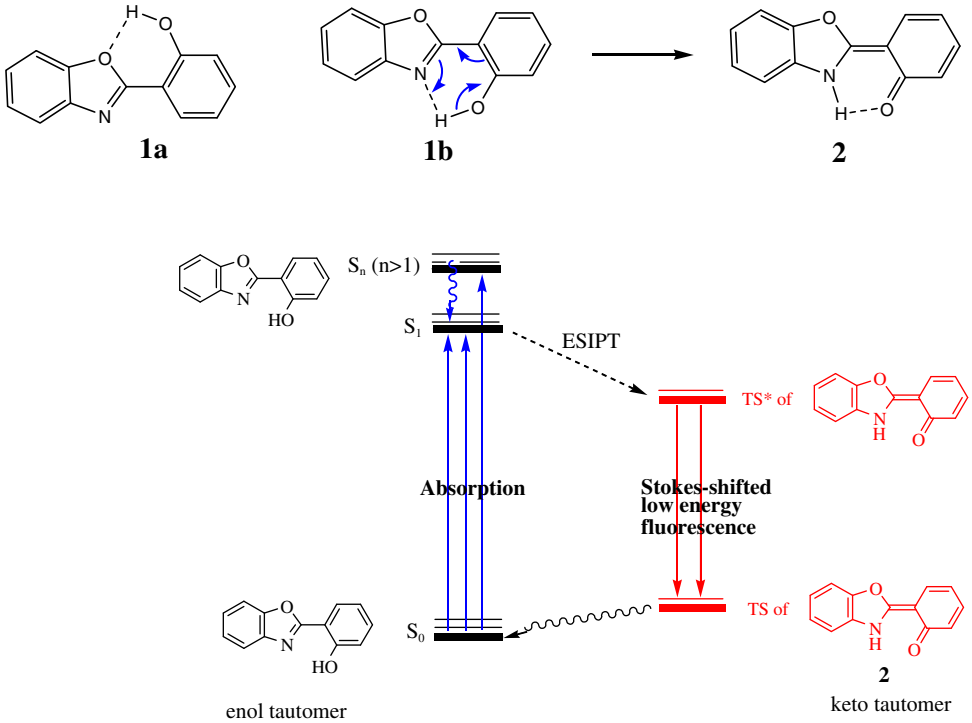
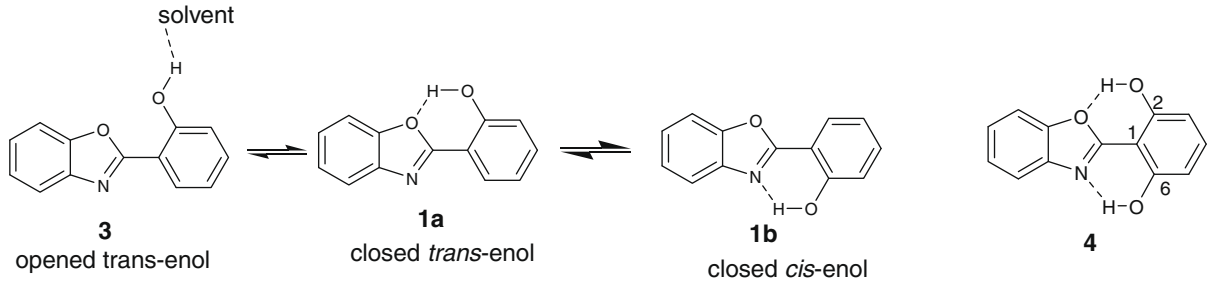
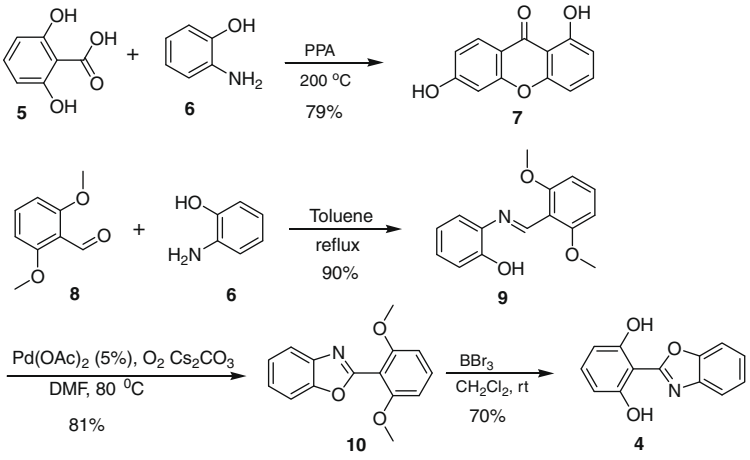


Scheme 1. Schematic illustration for ESIPT of HBO **1**.



Scheme 2. Enol isomers of HBO in the ground state.

bonds only renders a limited control to minimize the amount of the tautomer **1a**, which is incapable of undergoing ESIPT to give *keto* emission. A rational design to maximize the ESIPT signal demands new strategies to minimize the content of **1a** and **3**, while preserving the valuable optical characteristics of HBO. Herein, we report the synthesis of 2-(2′,6′-dihydroxyphenyl)benzoxazole (DHBO) **4**, in which the second hydroxy group is introduced at the 6-position of the phenol segment. The dual hydrogen bondings



Scheme 3. Synthesis of compound **4**.

in **4**, which are connected to both O- and N-atoms in benzoxazole fragment, not only provides additional structural stability but also eliminates the possibility of rotamer **1a**, thereby increasing the ESIPT output.

Initial attempt to condense 2,6-dihydroxybenzoic acid **5** with 2-aminophenol **6** failed to produce **4**, but gave 1,6-dihydroxyxanthenone **7** in high yield.[14,15] The synthesis of compound **4** is accomplished by using an alternative method (Scheme 3). Thus, condensation of 2,6-dimethoxybenzaldehyde **8** with 2-aminophenol **6** affords the Schiff base **9** in 90% yield upon refluxing in toluene. Conversion of the Schiff base to benzoxazole **8** is accomplished in 81% yield by using the palladium(II)-catalyzed oxidative cyclization under a relatively milder condition.[16] Subsequent deprotection with boron tribromide in dichloromethane[4,17] gave the desirable product.[18]

UV–vis of **4** revealed an absorption band at 306 nm and a shoulder at 322 nm in polar solvents such as methanol, acetonitrile, and DMF (Fig. 1). An additional absorption band was observed in hexanes at about 350 nm, which could be attributed to the aggregate formation as polar molecule **4** is less soluble in the nonpolar solvent. Upon the addition of NaOH, a new absorption band was observed at 365 nm, attributed to the formation of phenoxide anion

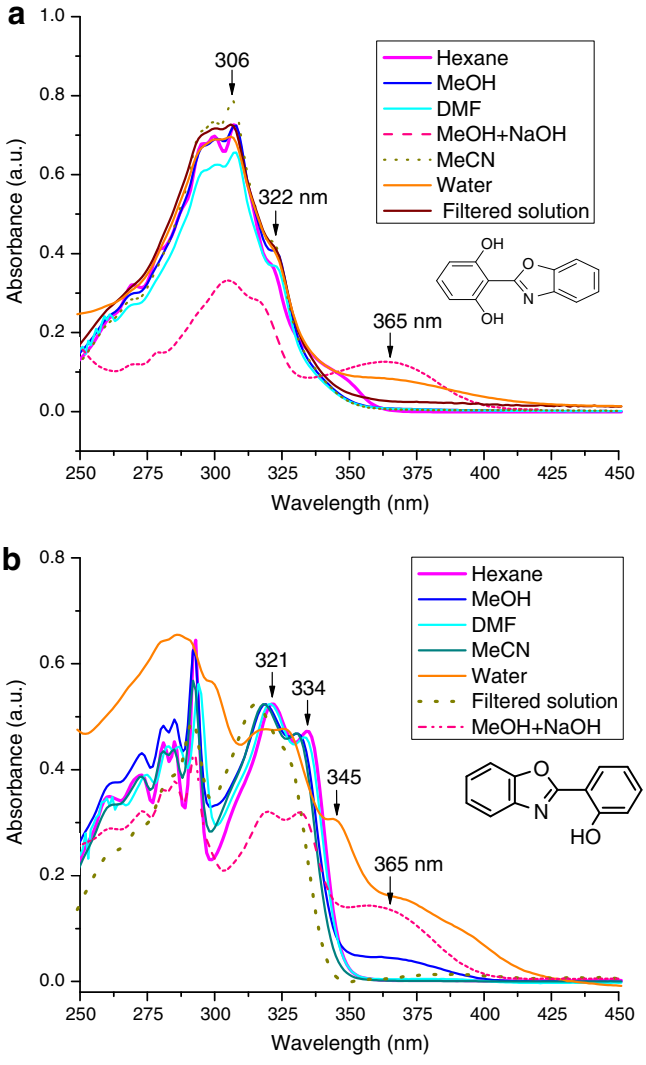


Figure 1. UV–vis of **4** (top) and **1** (bottom) in different solvents. The 'filtered solution' indicates that the aqueous solution is filtered by using a 0.02 μm alumina membrane filter.

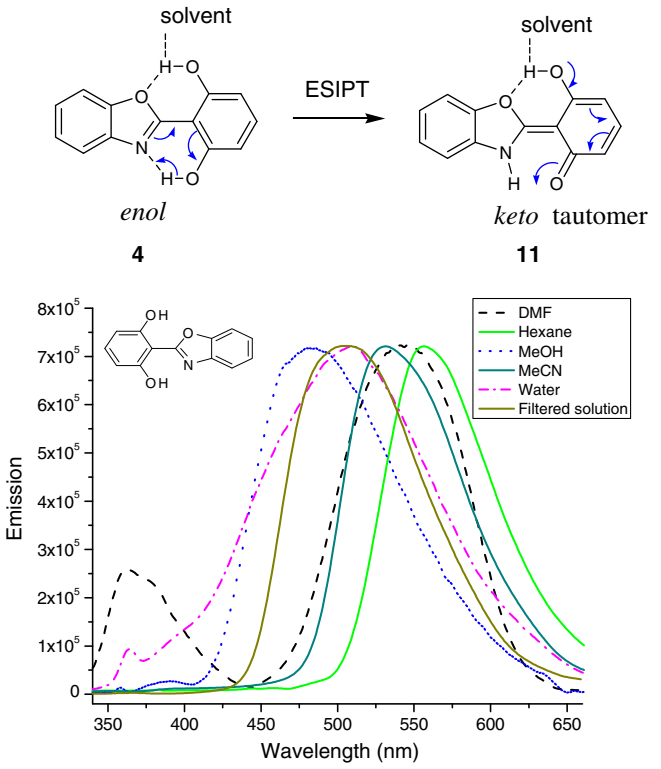


Figure 2. Fluorescence spectra of **4** in various solvents at 25 °C (excitation wavelength λ_{ex} = 322 nm). The 'filtered solution' indicates that the aqueous solution is filtered by using a 0.02 μm alumina membrane filter.

from **4**, Ph–OH→Ph–O⁻. The absorption properties of **4** were compared with that of **1** under the identical conditions. In contrast to **4**, the HBO **1** in hexanes did not show the aggregation band, as the additional hydroxy group in the former makes it less soluble in the nonpolar solvent (aggregation easier to occur). Interestingly, the methanol solution of **1** revealed a broad band at ~365 nm. When water (a more polar solvent) was used, the absorption band became higher in **1**, accompanied with the new band at 345 nm. Both absorption bands at 345 nm and 365 nm are attributed to aggregate formation,[19] as they are absent after the aqueous solu-

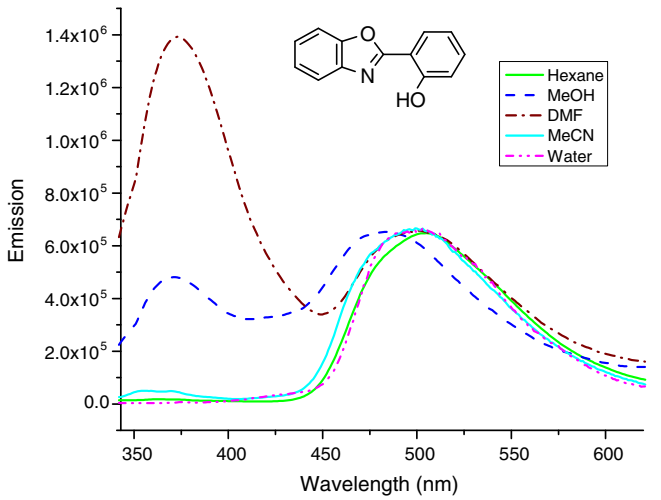


Figure 3. Normalized emission of HBO **1** in different solvents (excitation wavelength λ_{ex} = 331 nm).

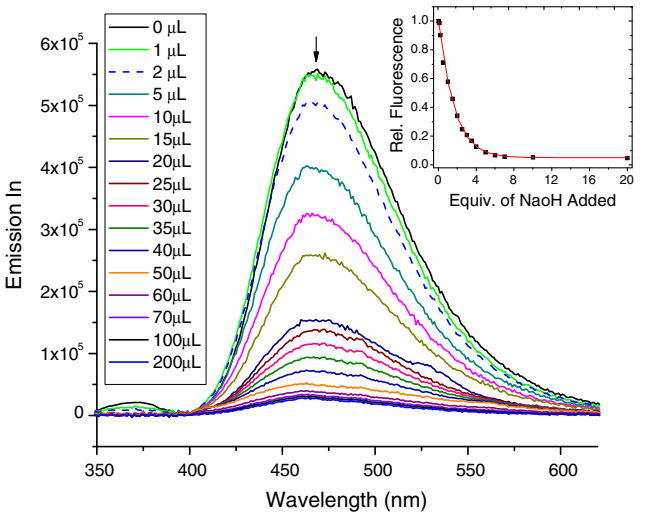


Figure 4. Changes in fluorescence of **4** (2 mL of 5×10^{-6} M in MeOH/H_2O; 10:1) upon successive additions of NaOH (1.0×10^{-3} M aqueous). Excitation wavelength λ_{ex} = 322 nm. The inset shows the dependence of fluorescence on the equivalent base added.

tion is filtered by using a 0.02 μm alumina membrane. Addition of NaOH to the methanol solution induced a new absorption band (λ_{max} = 365 nm), as the consequence of phenoxide anion formation.

The fluorescence of **4** in DMF reveals a major band at 544 nm and a minor band at 366 nm (Fig. 2), attributing to the *keto* and *enol* emissions, respectively. In methanol solution, the *enol* emission from **4** is negligible, in sharp contrast to that from **1** (Fig. 3) where the *enol* emission consists of ~30–40% of total fluorescence signals. In addition, the quantum yield of **4** (ϕ_{fl} = 0.108 in methanol) is significantly higher than that of **1** (ϕ_{fl} = 0.0025 in CH_3OH) under the same conditions,[20] attributing to the increased molecular rigidity and the presence of an additional hydroxy group in the former. While the *keto* emission of **1** varies within 480–505 nm, the *keto* emission of **4** changes between 478 nm and 557 nm in response to solvent polarity. The larger optical response observed in **4** can be rationalized by considering its *keto* tautomer **11**. The hydroxy group in **11**, along with its electronic connection with the carbonyl group, effectively transmits the solvent interaction to the optical response. In summary, the presence of the second hydroxy group in **4** plays several useful functions: suppressing the *enol* emission, increasing the quantum yield, and enhancing the solvent responses.

The fluorescence of DHBO **4** is also responsive to the OH^- concentration (Fig. 4). Upon increasing pH from neutral to basic conditions, the fluorescence intensity is gradually decreased, and nearly completely quenched when ~4 equiv NaOH is added (corresponding to hydroxide concentration [OH^-] = 2×10^{-5} M), attributing to the formation of anionic species as a consequence of deprotonation. The result indicates that anionic **12** is weakly fluorescent. And the gradual change in fluorescence intensity shows that the DHBO **4** can be used as a pH sensor.

In summary, we have synthesized 2-(2′,6′-dihydroxyphenyl)benzoxazole (DHBO). In comparison with the parent HBO system, the additional hydrogen bonding in DHBO effectively removes the rotamer formation, thereby increasing the desirable ESIPT signals. As a result, the DHBO exhibits higher fluorescence quantum yield, larger Stokes' shift (due to red-shifted fluorescence) and improved sensitivity to solvent polarity and pH. These improved optical characteristics are expected to find applications in relevant fields, where ESIPT are desirable.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.02.043.

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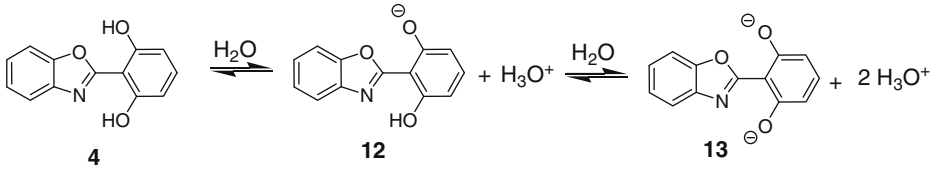
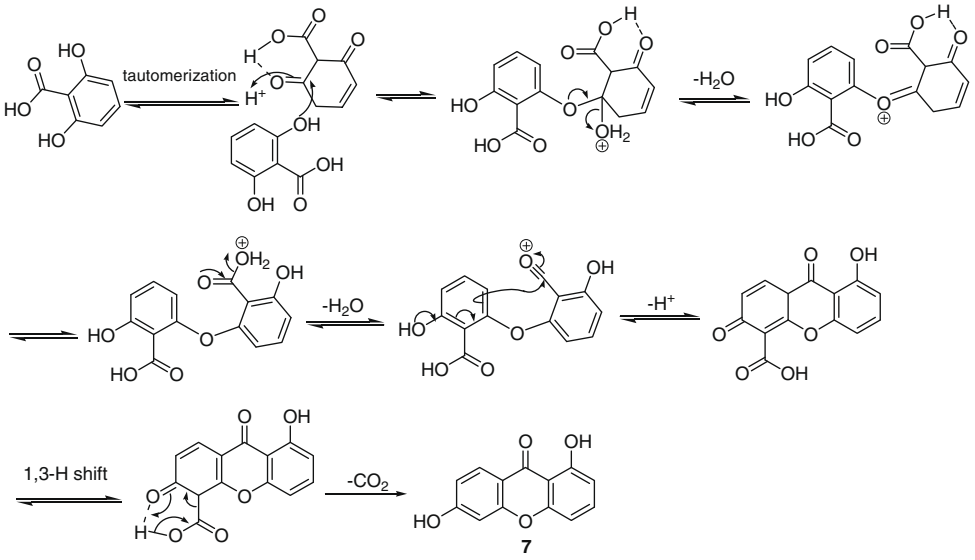
14. *Synthesis of* **7**. 2,6-Dihydroxybenzoic acid (1.5 g, 10 mmol) and 2-aminophenol(1.1 g, 10 mmol) were added into 30 mL preheated polyphosphoric acid to give a stirrable paste. The mixture was then heated slowly to 200 °C, and the resulting solution was stirred at this temperature for 4 h. The reaction mixture was cooled to about 100 °C, and poured in 300 mL of water. The acidic aqueous solution was neutralized with solid K_2CO_3, extracted with EtOAc (100 mL × 4), and dried over Na_2SO_4. After filtration, the solution was concentrated to give a dark crude product which was purified by column chromatography on silica gel using CH_2Cl_2 as an eluent to provide pure product **7** as a white solid (1.8 g, 79%). The NMR spectrum of **7** was identical with the data reported in Refs: (a) Liu, Y.; Zou, L.; Ma, L.; Chen, W.-H.; Wang, B.; Xu, Z.-L. *Bioorg. Med. Chem.* **2006**, *14*, 5683–5690; (b) Fatel, G. F.; Trivedi, K. N. *Synth. Commun.* **1989**, *19*, 1641–1647. This reaction appears to be an improved method to synthesis xanthone derivatives such as **7**, since the current literature examples typically give low yield and by-products.



15. The proposed mechanism for **7** is following:



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18. *Synthesis of* **10**. To a 10 mL round-bottomed flask equipped with a sidearm, magnetic stirring bar, and connecting tube were added the Schiff base **9** (100 mg, 0.4 mmol), $Pd(OAc)_2$ (4.6 mg, 0.02 mmol), Cs_2CO_3 (260 mg, 0.8 mmol), and 15 mL DMF. The mixture was stirred at room temperature for 5 min then warmed to 80 °C, while the oxygen gas was bubbled into the flask below the surface of the liquid. The progress of the reaction was monitored by ^1H NMR spectroscopy, which revealed the disappearance of the imine resonance signal at around δ 9.1 ppm when the reaction was complete. Upon completion of the reaction, the mixture was poured into 30 mL of water. The precipitate was collected by vacuum filtration and washed with 20 mL of water. The solid was redissolved in 30 mL of dichloromethane, washed with 1% EDTA aqueous solution (to remove the palladium catalyst), then washed with water. The organic layer was dried over anhydrous Na_2SO_4. Removal of solvent afforded the crude product which was purified by column chromatography on silica gel using a mixed eluent of hexane and EtOAc (10:1) to provide pure product as white solid (84 mg, 81%). ^1H NMR ($CDCl_3$ 300 MHz) δ 7.82 (m, 1H), 7.60 (m, 1H), 7.45 (t, 1H, J = 8.4 Hz), 7.36 (m, 2H), 6.67(d, 2H, J = 8.4 Hz), 3.81(s, 6H).

Synthesis of **4**. Boron tribromide (0.6 mL of 1 M BBr_3 in hexanes, 0.6 mmol) was added to a stirring mixture of **10** (50 mg, 0.2 mmol) in anhydrous CH_2Cl_2 (5 mL), and the reaction was stirred at room temperature under a nitrogen atmosphere. After 48 h, the reaction was quenched with MeOH (2 mL), and the reaction mixture was extracted with EtOAc (20 mL) and washed with H_2O (2×10 mL) and brine (10 mL). The organics were then filtered, dried over Na_2SO_4, and concentrated on a rotatory evaporator. Purification over a silica column with (4:1 hexanes/EtOAc) afforded 2-(2′,6′-dihydroxyphenyl)benzoxazole (**4**) as a white solid (32 mg, 70%). The obtained pure product was recrystallized from hexane/EtOAc to give white needle-like crystals (mp 191–192 °C). ^1H NMR ($CDCl_3$ 300 MHz) δ 9.79 (br, 2H), 7.78 (m, 1H), 7.67 (m, 1H), 7.45 (m, 2H), 7.33 (t, J = 8.4 Hz, 1H), 6.66 (d, 2H, J = 8.4 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.2, 158.2, 147.9, 138.3, 134.5, 126.0, 125.9, 119.5, 110.7, 118.7, 99. IR (KBr) ν_{max} (cm^{-1}): 3485 (s), 1637 (s), 1581 (m), 1533 (w), 1478 (w), 1452 (m), 1412(w), 1250(m), 1157(m), 1041(w), 1017(w), 817(w), 788(w), 744(w), 701(w). HRMS (m/z): $[M+H]^+$ calcd for $C_{13}H_{10}NO_3$, 228.0661, found, 228.0677; $[M+Na]^+$ calcd for $C_{13}H_9NNaO_3$, 250.0480, found 250.0484.
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