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Efficient synthesis of 2-(2′-hydroxyphenyl)benzoxazole by palladium(II)-catalyzed oxidative cyclization

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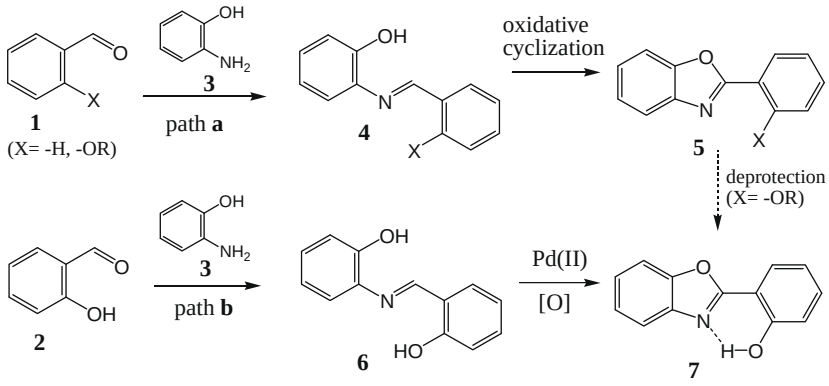
ABSTRACT

An efficient method for the synthesis of 2-(2′-hydroxyphenyl)benzoxazole has been developed by using palladium-mediated oxidative cyclization.

2-(2′-Hydroxyphenyl)benzoxazole (HBO) has emerged to be an interesting material, due to its intrinsic property for the excited state intramolecular proton transfer (ESIPT). A distinctive feature of 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.[5] The benzoxazole group also occurs in many biologically active compounds such as anticancer agents,[6] antibacterial agents,[7] and Alzheimer's disease therapeutics.[8]

Two methods are commonly used for synthesizing 2-substituted benzoxazoles. One method is the condensation of carboxylic acids with 2-aminophenols by dehydration, which is catalyzed by a strong acid such as polyphosphoric acid (PPA).[9–11] Although this method can be used for making large quantities, the strong acidic conditions at high temperature (>180 °C) often cause low yields



Scheme 1. Synthesis of HBO via protected (path **a**) and unprotected (path **b**) phenol aldehydes.

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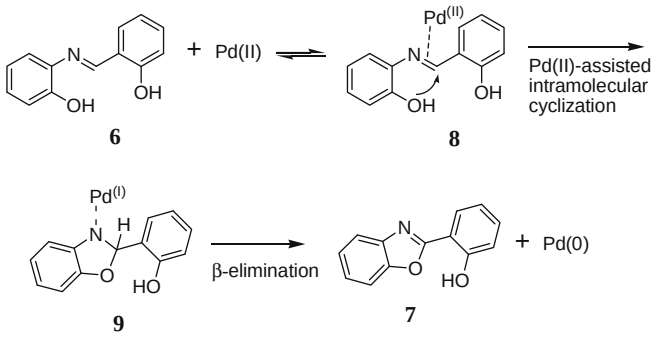
and side reactions. Mechanistic study indicates that the PPA condition could generate benzoyl cation from the corresponding carboxylic acid,[11] which complicates the reaction and increases the by-product formation. In addition, aromatic nitro,[10] *tert*-butyl, and other acid-sensitive functional groups do not survive under the harsh acidic conditions, thereby limiting the scope of the reaction.

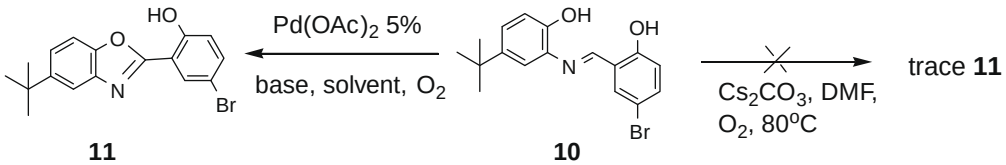
The second method involves the oxidative cyclization of phenolic Schiff bases (e.g., from **4**→**5** in Scheme 1, path **a**), which is derived from the condensation of 2-aminophenols and aldehydes **1** (X = –OR or –H). The reaction is typically carried out in the presence of various oxidants including DDQ,[12,13] MnO_2,[14] pyridinium chlorochromate (PCC),[15] PbO_2, and $Pb(OAc)_4$.[16,17] This oxidative process, however, requires the use of at least 1 equiv mole of oxidant, whose product purification often involves toxic work-up procedures to remove the transition metals. The mild conditions for oxidative cyclization (**4**→**5**) include photon-induced cyclization[18] and use of *N*-iodosuccinimide as an oxidant.[19] In path **a**, the phenol group in the aldehyde **1** (X = –OR) is protected to avoid the potential oxidation in the following steps. Some oxidants such as DDQ[20,21] can be used for the direct cyclization of the unprotected phenolic Schiff base (transformation of **6**→**7**), which often suffers with lower yields. Recently, there has been a significant interest in developing catalytic methods to synthesize benzoxazole derivatives, since the transition metal oxidants will no longer be used in the stoichiometric amount. A catalytic reaction using oxygen as a co-oxidant is of special interest, because its green chemistry aspects offer the additional advantage of developing an environmentally friendly process. The catalytic transformation (**4**→**5**, X = –H) has been demonstrated by using the hydrogen-transfer catalysts,[22] such as $Ru(PPh_3)_3(CO)H_2$, copper(I)-catalyzed oxidation,[23] and aminoxyl radical catalyst.[24] The requirement of acidic additives[22] for the hydrogen-transfer catalyst, however, can limit its application. Competitive formation of two phenoxyl radicals (Ph-OH→Ph-O·) in **6** makes the aminoxyl radical route[24] unsuitable for the transformation of **6**→**7**. Therefore, an efficient methodology that occurs at mild conditions is still needed to overcome these shortcomings.

Organopalladium intermediates are of primary importance in the synthetic reactions.[25] One of the fundamental properties of the palladium(II) is that it interacts with the π-bond electron to



Scheme 2. Reaction sequence showing the Pd(II)-catalyzed cyclization and β-elimination.

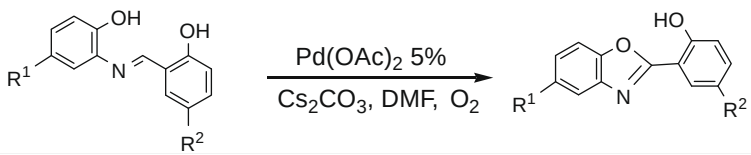
Table 1
Effect of base, solvent, and temperature on the conversion (**10**→**11**)



Entry	Base	Solvent	Time (h)/temp (°C)	Conversion (%)
1	Cs_2CO_3	MeCN	24, rt	5
2	NaOAc	MeCN	24, rt	2
3	K_3PO_4	MeCN	24, rt	0
4	Cs_2CO_3	$CHCl_3$	24, rt	2
5	Cs_2CO_3	PhMe	24, rt	0
6	Cs_2CO_3	THF	24, rt	30
7	Cs_2CO_3	DMSO	24, rt	50
8	Cs_2CO_3	DMF	24, rt	55
9	Cs_2CO_3	DMF	4, 80 °C	97

Note: Compounds **10** and **11** had the same spectral data as reported in the literature.[28]

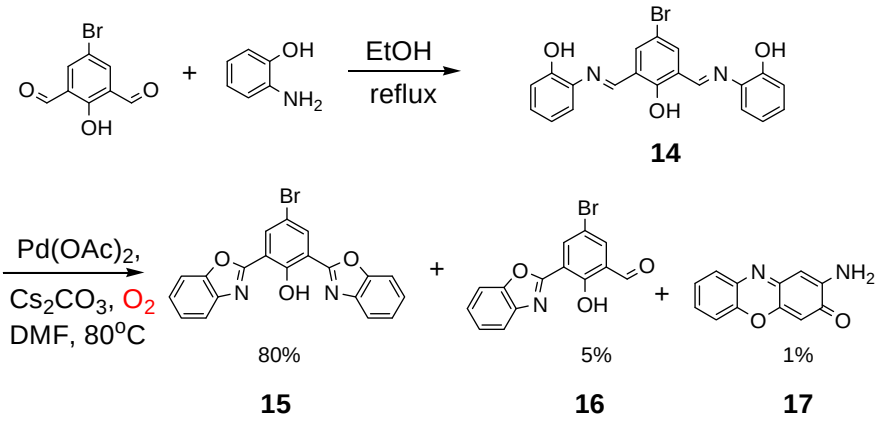
Table 2
Results of Pd(II)-catalyzed synthesis of 2-(2′-hydroxyphenyl)benzoxazole[29]



Entry	R^1	R^2	Substrate	Product	Time (h)	Yield[a]
1	–H	–Br	**12a**	**13a**	3.5	88
2	$-C(CH_3)_3$	$-CH_3$	**12b**	**13b**	3.5	88
3	$-NO_2$	–H	**12c**	**13c**	3.5	75
4	$-C(CH_3)_3$	–H	**12d**	**13d**	3	85
5	$-NO_2$	–Br	**12e**	**13e**	3.5	70

[a] The reported yield is based on the isolated product yield.

form π-complexes that are subjected to *nucleophilic attack*. It is assumed that the palladium(II) can react with C=N bond in **6** to form π-complex **8** (Scheme 2), which then undergoes nucleophilic attack to give **9**. The subsequent β-elimination should occur easily in **9**, as the process is driven by aromatization to give **7**. The elimination of β-hydrogen in **9** can be viewed as a reaction similar to the palladium-catalyzed oxidation of primary and secondary alcohols,[26,27] in which H–C–O–PdX→C=O. Reasoning that the mild reaction condition could tolerate the existence of phenol functional group, we decided to explore the palladium(II)-catalyzed intramolecular cyclization, followed by β-elimination, to give HBO. To the best of our knowledge, the palladium(II)-assisted nucleophilic attack on imines (C=N) has not been reported.

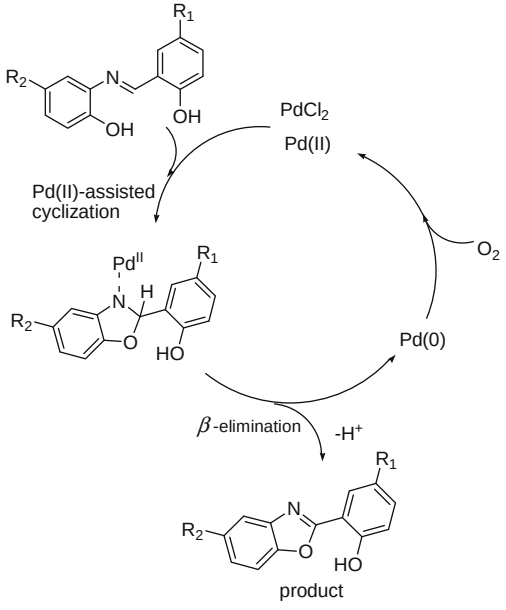


Initial experimental results showed that the transformation of **10**→**11** could be accomplished by using a stoichiometric amount of $Pd(OAc)_2$. When the reaction was monitored by TLC, the rate of the product formation was found to occur at a relatively fast rate, in comparison with other oxidants such as MnO_2. Catalytic amount of $Pd(OAc)_2$ in the presence of oxygen (as a co-oxidant) was also found to be effective in the transformation. In order to optimize the reaction conditions, the reaction was carried out under different conditions and the results are summarized in Table 1. The employment of base was still necessary, since it could deprotonate the phenol in **8** to facilitate the cyclization. Cs_2CO_3 appeared to be a better choice among the bases tested (entries 1–3). The polar aprotic solvent would be preferred, since it facilitates the nucleophilic reaction of phenoxide (entries 4–7). Although the reaction could occur at room temperature, the rate was significantly increased at 80 °C in the polar aprotic solvent. The catalytic effect of Pd(II) was further confirmed by performing the control experiment, as stirring of **10** with Cs_2CO_3, DMF, and O_2 at 80 °C for 24 h afforded only trace amount of product (less than 5% conversion).

Versatility of the reaction was demonstrated by using different substrates of phenolic Schiff bases, and the results are summarized in Table 2. The reaction proceeded smoothly even in the presence of Ar–Br bond, which can be used for further functionalization. The presence of an electron-withdrawing group (–NO_2), which increases the acidity of the phenolic proton, did not appear to influence the rate of the cyclization (entry 3). The result was consistent with the assumption that the palladium(II) played an important role in the cyclization step (**8**→**9**).

The efficiency of the reaction was further examined by synthesizing compound **15**, which requires construction of two benzoxazole groups in a single molecule. The starting material **14** was conveniently prepared by condensation of 5-bromo-2-hydroxyisophthalaldehyde with 2-aminophenol.[30] Reaction of the phenolic Schiff base **14** afforded bis(HBO) **15** in good yield,[31,32] along with partially hydrolyzed product **16**. Trace amount of 2-amino-3H-phenoxazin-3-one (**17**) was also found in the product mixture, which was formed via oxidative dehydrogenation of the hydrolyzed by-product 2-aminophenol.[33]

In summary, we have reported an efficient and versatile method to prepare HBO. The proposed mechanism (Scheme 3) involves the interaction of the imine group with Pd(II) to give π-complexes, which are subjected to *intramolecular nucleophilic attack* by phenol to give a five-membered ring intermediate. The key step is consisting of the β-elimination to generate benzoxazole ring and Pd(0) species, which is subsequently oxidized to regenerate Pd(II) by O_2. The net reaction consumes only the phenolic Schiff base and oxygen.



Scheme 3. Proposed catalytical cycle of the palladium-catalyzed oxidative cyclization.

Acknowledgments

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28. Sridharan, V.; Muthusubramanian, S.; Sivasubramanian, S. *Magn. Reson. Chem.* **2003**, *41*, 291–295.
29. *A typical procedure for the preparation of* **13**: To a 10 mL round-bottomed flask equipped with a side arm, a magnetic stirring bar, and a connecting tube were added the Schiff base **12** (0.2 mmol), $Pd(OAc)_2$ (2.3 mg, 0.01 mmol), Cs_2CO_3 (130 mg, 0.4 mmol), and 10 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 8.8 ppm when the reaction was complete. Upon completion of the reaction, the mixture was poured into 20 mL of water. The precipitate was collected by vacuum filtration and washed with 5 mL of water. The solid was redissolved in 20 mL of dichloromethane, washed with 1% EDTA aqueous solution (to remove the palladium catalyst), and then washed with water. The organic layer was dried over anhydrous Na_2SO_4. Removal of solvent afforded the desirable products.
Compound **13a** (colorless crystals from ethanol solution, mp 177 −178 °C) had the following spectral properties. ^1H NMR ($CDCl_3$, 300 MHz) δ = 11.49 (s, 1H), 8.16 (s, 1H), 7.76 (m, 1H), 7.64 (m, 1H), 7.52 (dd, 1H, *J* = 9.0 Hz, 2.4 Hz), 7.42 (m, 2H), 7.03 (d, 1H, *J* = 9.0 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 161.7, 157.8, 149.2, 140.0, 136.5, 129.5, 126.0, 125.5, 119.6, 119.6, 112.2, 111.4, 111.0. IR (KBr) ν_{max} (cm^{-1}): 3060 (w), 1629 (m), 1584 (m), 1541 (s), 1485 (s), 1451 (s), 1279 (s), 1250 (s), 800 (m), 762 (s).
Compound **13b** (recrystallized from chloroform, mp 165–166 °C) had the following spectral properties. ^1H NMR ($CDCl_3$, 300 MHz) δ = 11.33 (s, 1H), 7.80 (s, 1H), 7.74 (s, 1H), 7.64 (m, 1H), 7.52 (d, *J* = 9.0 Hz, 1H), 7.43 (dd, *J* = 9.0 Hz, 1.8 Hz, 1H), 7.23 (d, *J* = 9.0 Hz, 1H), 7.02 (d, *J* = 9.0 Hz, 1H) 2.36 (s, 3H), 1.40 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 163.3, 156.7, 148.7, 147.3, 140.2, 134.5, 128.9, 127.0, 123.2, 117.3, 115.9, 110.5, 109.9, 35.2, 31.9, 20.7. IR (KBr) ν_{max} (cm^{-1}): 3024 (w), 2951 (m), 2864 (w), 1638 (m), 1596 (m), 1547 (s), 1500 (s), 1282 (s), 1256 (s), 1055 (m), 943 (m), 805 (s).
Compound **13c** (needle-like crystals from methanol/chloroform, mp 190.5–191 °C) had the following spectral properties. ^1H NMR ($CDCl_3$, 300 MHz) δ = 10.99 (s, 1H), 8.63 (d, *J* = 2.1 Hz, 1H), 8.36 (dd, *J* = 9.0 Hz, 2.4 Hz, 1H), 8.04 (dd, *J* = 7.8 Hz, 1.5 Hz, 1H), 7.73 (d, *J* = 9 Hz, 1H), 7.52 (dt, 1H, *J* = 7.8 Hz, 1.5 Hz), 7.16 (d, 1H, *J* = 7.8 Hz) 7.06 (t, 1H, *J* = 7.8 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 166.0, 159.4, 152.8, 145.9, 140.8, 135.1, 127.6, 121.6, 120.2, 118.0, 115.6, 111.0, 109.6. IR (KBr) ν_{max} (cm^{-1}): 3116 (m, Ph-OH), 1628 (s), 1531 (s, $-NO_2$), 1348 (s, $-NO_2$), 1237 (s, Ph–O–C), 1161 (m), 1044 (m), 808 (m), 758 (m), 733 (m). HRMS (*m/z*): $[M+H]^+$ calcd for $C_{13}H_9N_2O_4$, 257.0562; found, 257.0615.
Compound **13d** (pale yellow crystals from chloroform, mp 158.5–159.5 °C) had the following spectral properties. ^1H NMR ($CDCl_3$, 300 MHz) δ = 11.56 (s, 1H), 8.02 (dd, 1H, *J* = 7.8 Hz, 1.5 Hz), 7.76 (d, 1H, *J* = 1.5 Hz,) 7.53 (d, *J* = 9.0 Hz, 1H), 7.44 (m, 2H), 7.13 (d, 1H, *J* = 7.8 Hz), 7.01 (t, 1H, *J* = 7.8 Hz), 1.42 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 163.1, 158.8, 148.8, 147.3, 140.1, 133.5, 127.2, 123.3, 119.7, 117.5, 115.9, 110.9, 109.9, 35.2, 31.9. IR (KBr) ν_{max} (cm^{-1}): 2959 (m), 1630 (m), 1591 (m), 1543 (m), 1487 (s), 1257 (s), 1157 (m), 1054 (m), 751 (m).
Compound **13e** had the following spectral properties. ^1H NMR ($CDCl_3$, 300 MHz) δ = 11.08 (s, 1H), 8.55 (d, *J* = 2.1 Hz, 1H), 8.40 (dd, 1H, *J* = 9.0 Hz, 2.1 Hz,), 8.19 (d, 1H, *J* = 2.4 Hz) 7.86 (d, *J* = 9.0 Hz, 1H), 7.60 (dd, 1H, J = 9.0 Hz, 2.4 Hz), 7.06 (d, 1H, *J* = 9.0 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 163.3, 158.3, 152.7, 142.7, 140.7, 137.7, 129.8, 128.3, 122.0, 120.0, 115.8, 111.9, 111.2. IR (KBr) ν_{max} (cm^{-1}): 3108 (m), 1630 (m), 1547 (m), 1532 (s), 1482 (m), 1345 (s), 1248 (m), 1047 (m), 811 (m). HMRS (*m/z*): $[M+H]^+$ calcd for $C_{13}H_8BrN_2O_4$, 334.9667; found, 334.9787.
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31. Synthesis of **14**: 4-Bromo-2,6-diformylphenol (100 mg, 0.44 mmol), prepared from *p*-bromophenol by following the literature procedure (*Synthesis* **1998**, *7*, 1029–1032), and 2-aminophenol (96 mg, 0.88 mmol) were refluxed in absolute ethanol (15 mL) for 5 h. The reaction mixture was cooled to room temperature, and the precipitate was filtered and crystallized from absolute ethanol to give the compound **14** as reddish needle-like crystals (mp 292–293 °C). ^1H NMR ($CDCl_3$, 300 MHz) δ = 8.78 (s, 2H), 7.79 (s, 2H), 7.04 (d, 2H, *J* = 7.8 Hz), 6.90 (t, 2H, *J* = 7.8 Hz), 6.76 (d, 2H, *J* = 7.8 Hz), 6.65 (t, 2H, *J* = 7.8 Hz).
32. Compound **15** was prepared by using the same procedure as for **13**, and purified on a silica gel column with dichloromethane as an eluent. The compound **15** had the following spectral properties. ^1H NMR ($CDCl_3$, 300 MHz) δ = 12.95 (s, 1H), 8.42 (s, 2H), 7.83 (m, 2H), 7.67 (m, 2H), 7.43 (m, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 160.4, 156.7, 149.9, 140.8, 134.6, 126.2, 125.3, 120.3, 115.9, 111.4, 111.0. HRMS (*m/z*) calcd for $[C_{20}H_{11}BrN_2O_3 + Na]^+$, 428.9851. Found: 428.9885. IR (KBr) ν_{max} (cm^{-1}): 3061 (w), 3027 (w), 1628 (w), 1536 (m), 1441 (s), 1248 (s), 1158 (m), 842 (m), 772 (m), 740 (m). The by-product **16** had the following spectral properties. ^1H NMR ($CDCl_3$, 300 MHz) δ = 12.22 (s, 1H), 10.5 (s, 1H, CHO), 8.38 (s, 1H), 8.03 (s, 1H), 7.78 (m, 1H), 7.64 (m, 1H), 7.44 (m, 2H).
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