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Synthesis of high purity pyridine-phenolic ligands for metal ion optical sensors

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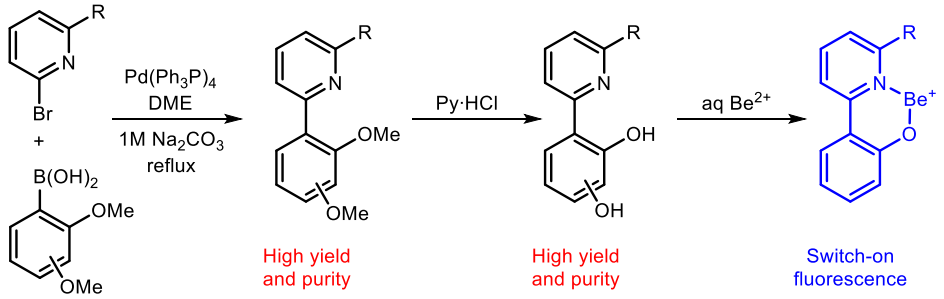
Abstract

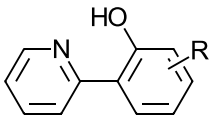
A refined synthesis and facile purification process have been developed to access pyridine-phenolic ligand derivatives in high purity and yield, which are needed for optical detection of low levels of metal ions in biological and environmental sensor applications. The two-step process employs Suzuki coupling and demethylation, and the purification is facilitated by an acid/base extraction protocol that allows for significant impurities to be removed without the need for conventional gradient chromatography. These amphoteric ligands exhibit unique physical, chemical, and spectroscopic properties and are of interest in the complexation of metal ions. The simplest pyridine-phenolic compound, 2-(2'-hydroxyphenyl)pyridine, is shown to have potential as a switch-on fluorescence ligand for beryllium ions under aqueous conditions.



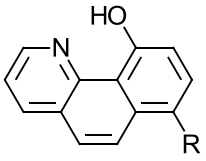
Keywords: Ligand, high yield/purity, phenols, pyridine, beryllium, chemical sensor.

Introduction

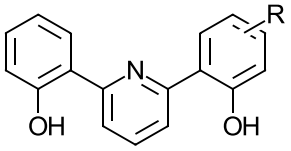
The coordination chemistry of N,O-chelate ligands, such as 2-(2'-hydroxyphenyl)pyridine **1** (Where R = H) and its homologues, have been of primary interest in the synthesis of a variety of metal complexes (B, Zn, Be, Cd, Pd, Co, Cu, Mn, Ni, Ru, Ti and Fe) that exhibit interesting magnetic, chemical, redox and optical properties. These materials have been the subject of detailed studies in electroluminescence,[1-3] magnetic devices,[4,5] chemosensors,[6,7] and catalysis.[8-11] Derivatives of ligand **1** have proved valuable in the synthesis and structure-activity studies of endothelin A receptor anatagonists.[12] Pyridine-phenolic systems are amphoteric, *i.e*., contain both acid and base sites, and therefore have been the basis of ongoing fundamental studies into excited state intramolecular proton transfer (ESIPT), which is important for the understanding and development of laser dyes, photostabilizers, scintillators,[13] and solar collectors.[14]



1



2a R = H
2b R = SO_3H
2c R = OH



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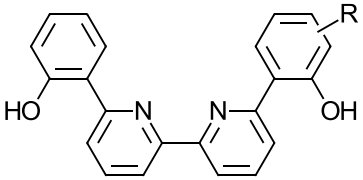


4

Simple chemical modifications to functionalized organic molecules allow them to be easily tuned for their use and development as optical, *i.e*., UV/Vis, IR and fluorescence, primarily for biological applications[15-18] and, to a lesser extent, for environmental applications.[19] To detect metal ions at very low concentrations in biological or environmental applications, at ppm to ppb levels, the molecular structure, stability, and purity of the chemical probes are critical to minimize false positives, cellular toxicity, and to maximize host-guest signal amplification with minimal interference from optically active residues.[15]

Our group previously reported on the development of pyridine-phenol ligand systems, such as 10-hydroxybenzo[*h*]quinolines (10-HBQ) **2**, for coordination studies with aqueous beryllium.[20,21] Although particulate beryllium is extremely toxic, it still has widespread use because of its unique mechanical, thermal, and electronic properties which are extremely difficult to replicate with other materials.[22,23] We have found that the water-soluble derivative 10-HBQS **2b** shows enhanced fluorescence when coordinated to aqueous beryllium under alkaline conditions. Here, the 10-HQBS **2b** requires a very different purification process than the starting material 10-HBQ **2**, but is extremely effective in detection of environmental beryllium at nanogram levels.[24] This has proven to be a practical ligand for sensor applications and is used to detect environmental beryllium at sub-picogram levels.[21] Ligands that exhibit a fluorescence or colorimetric response upon selective complexation with aqueous beryllium are still required for specific applications, such as in the tracking and sequestering of biological and environmental beryllium species, respectively. With limited

examples of design rules for accessing metal-ion selective probes for beryllium,[25,26] we propose that functionalized derivatives of the bidentate ligand **1** (R = H), and tri- and tetradentate ligands, such as **3** and **4** (R = H), could be promising candidates for beryllium chelation.

Although these pyridine-phenolic ligands appear to be relatively simple molecules, most existing synthetic protocols are relatively complex, have varying yields, or afford product mixtures, suggesting possible issues around the high purity needed for chemical probe applications. Early approaches to compounds similar to ligand **1** (R = H) involved photoarylation[27] and reactions of benzyne with pyridine-N-oxides[28] which gave mixtures and the desired products in low yields. Multidentate ligands **3** and **4** (R = H), have been accessed by employing condensation[29] and a complicated Ziegler 2-methoxyaryllithium addition/oxidation protocol[30] giving desired precursors in 24% and 40% overall yield, respectively. The recent development of metal-catalyzed coupling methodology has seen several reports of organo-copper,[31] organo–magnesium[32,33] and organo-zinc couplings,[34] however, the yields have varied, the characterization properties have differed, and some of these conditions are typically not amenable to the presence of sensitive functional groups.

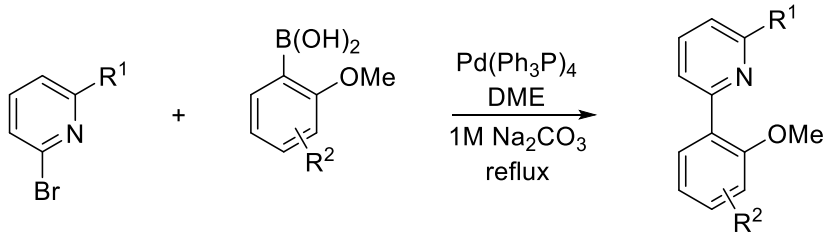
Over the past 50 years, the Suzuki-Miyaura coupling reaction[35] has become a dominant synthetic methodology to access greater functional group diversity in polyaromatic compounds, especially of interest in our studies on these pyridine-phenolic compounds for chemical probe applications. However, as with most of these ligands the authors were surprised to find for the simple molecule 2-(2'-hydroxyphenyl)pyridine **1** (Where R = H), a synthesis search (in 2022) located 36 different papers [see Supplementary Information (SI)], with a range of characterization data and results. A recent report has also indicated that the conditions used for this coupling reaction may impact the product yield and formation of unwanted impurity complicating the purification process.[36] Given the use and interest in these pyridine-phenolic ligands for different end-applications, the authors sought to collate and evaluate the synthetic and characterization data, and use them as a basis to identify and synthesize related key compounds.

Herein, we highlight a simple two-step synthesis and purification protocol to easily access gram quantities of high-purity pyridine-phenolic ligands using a combined Suzuki-Miyaura coupling/demethylation process that greatly improves on previous approaches. We also describe some unique physical and complexation properties of the pyridine-phenolic system. The simple purification employs aqueous-based chemistry, Kugelrhor distillation and recrystallization to afford ultra-pure materials with interesting properties, a scalable synthetic route and key characterization information. By employing this two-step route, the metal-catalyzed coupling can be used first with distillation/recrystallization, followed by efficient demethylation with recrystallization, which dramatically reduces the likelihood of trace contamination in the final products, as reflected by the characterization property data. We also demonstrate the potential value of 2-(2'-hydroxyphenyl)pyridine **8a** as a chemical probe for aqueous beryllium ion, which exhibits switch-on fluorescence.

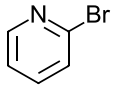
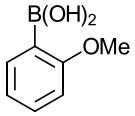
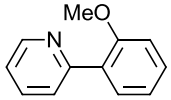
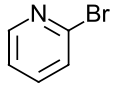
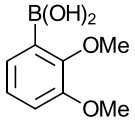
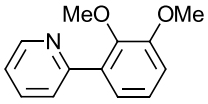
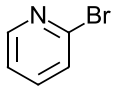
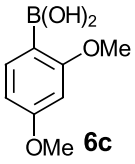
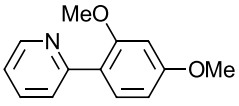
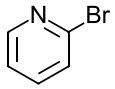
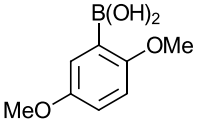
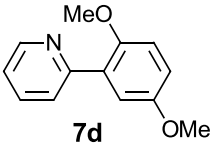
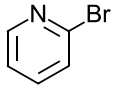
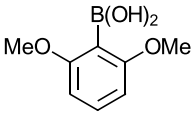
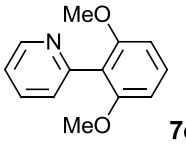
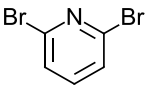
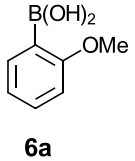
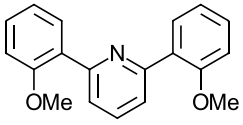
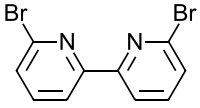
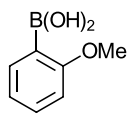
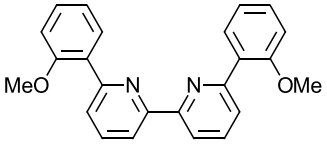
Results and Discussion

Our interest in boron-halide coupling chemistry stems from our previous work on constructing functionalized polyheterocycles[37] and the growing access to a diverse range of commercially available boron building blocks.

Table 1. Suzuki coupling of methoxy-substituted phenylboronic acids with pyridyl bromides



5 **6** **7**

Entry	Bromide	Boronic Acid	Product	Purification	Yield (%)
1	 **5a**	 **6a**	 **7a**	bp 160-2 °C/1 Torr	94
2	 **5a**	 **6b**	 **7b**	bp 143-5 °C/1 Torr and mp 60 °C	92
3	 **5a**	 **6c**	 **7c**	bp 165-7 °C/1 Torr	93
4	 **5a**	 **6d**	 **7d**	bp 198-200 °C/1 Torr	93
5	 **5a**	 **6e**	 **7e**	bp 178-180 °/1 Torr and mp 79-80 °C	58
6	 **5b**	 **6a**	 **7f**	mp 127 °C (lit. mp 117 °C)[29]	79
7	 **5c**	 **6a**	 **7g**	mp 170 °C (lit. mp 175 °C)[30]	54

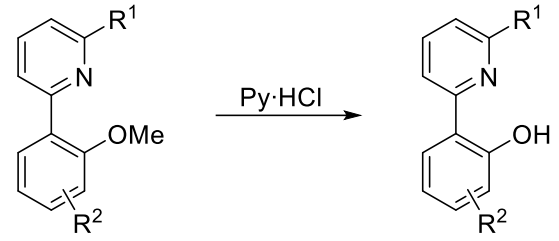
By employing simple coupling conditions using aqueous sodium carbonate, 1,2-dimethoxyethane, and palladium tetrakis(triphenylphosphine) with 2-bromopyridine and the appropriate methoxyphenyl boronic acid derivative, we were able to obtain the coupled precursors (Table 1, Entries 1-5). During the isolation

process, we observed that these simple pyridine-phenolic derivatives **7a-g** were highly water-soluble upon treatment with dilute hydrochloric acid. Therefore, we developed a simple acid wash and base extraction protocol to remove the desired product from other organic impurities and catalyst without the need for gradient chromatography. The products were then easily purified by Kugelrhor bulb-to-bulb distillation, resulting in high yield (> 92%) and purity products (see characterization data here and in SI). In Entry 5, the slightly lower yield of product **7e** likely resulted from the sterically hindered nature of the boronic acid. Tri- and tetradentate ligands **7f** and **7g** (Entries 6 & 7, respectively) were also isolated by employing the acid/base extraction process described earlier. However, due to the larger molecular weight of these compounds, final purification was achieved by conventional recrystallization. These products were obtained in higher yield and purity than other previously reported methods.

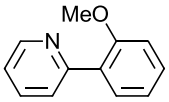
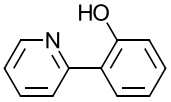
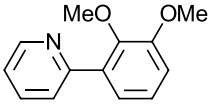
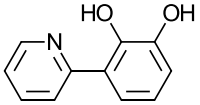
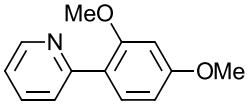
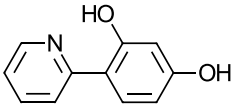
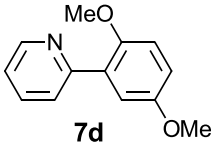
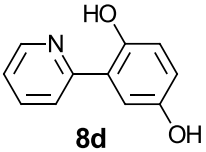
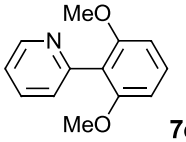
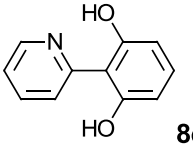
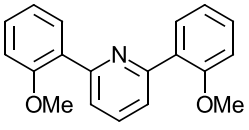
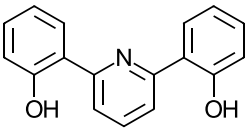
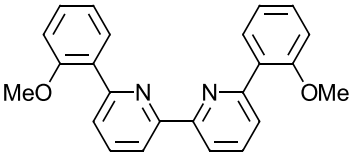
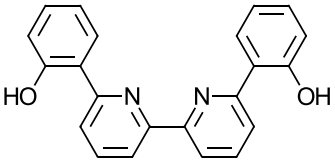
With these pure methyl-ether precursors in hand, we investigated conditions to liberate the phenolic group. Several strategies have been reported, including the use of BBr_3, $NiCl_2$/Zn, pyridine hydrochloride (Py·HCl) and trimethylsilyl iodide (TMSI). We found that demethylation was most efficiently achieved using Py·HCl, which resulted in better conversion efficiencies and crude products that were easier to purify than other typical methods reported for demethylations.[38] By heating a mixture of Py·HCl with the methylether aryl compound at 200 °C for several hours without solvents, we obtained a clean demethylation product. The reaction was quenched with water, neutralized, and extracted with DCM. The crude material was then purified by distillation (Table 2, Entry 1, compound **8a**) or recrystallization (Table 2, Entries 2-7, compounds **8b-g**). The final purified pyridine-phenolic compounds were obtained in yields ranging from ~60-95% with excellent purity. Notably, all compounds were isolated as yellow crystalline materials, which differs from those reported in the literature (see characterization data here and see SI).

A key goal in the development of new ligands to coordinate aqueous beryllium is to identify systems that exhibit strong intramolecular hydrogen bonding. For instance, both 10-HBQ **2a** and isomeric 7-HBQ contain the phenolic hydrogen atom and the nitrogen heteroatom.[20] In 10-HBQ **2a**, the phenolic hydrogen atom is in close proximity to the nitrogen atom; the ^{1}H NMR spectrum shows that this hydrogen atom is extremely deshielded and resonates at 14.82 ppm. In contrast, 7-HBQ has the phenolic resonance appearing at 10.29 ppm, indicating the absence of hydrogen bonding. The intramolecular hydrogen bonding observed in solution studies has also been confirmed by solid-state X-ray crystallography for 10-HBQ **2a**.[39] A similar trend is observed with the compounds in Table 2, Entries 1-7. Analysis of the ^{1}H NMR spectra of these compounds **8a-g** shows that phenolic hydrogen nearest to the nitrogen atom undergoes intramolecular hydrogen bonding, with the corresponding signal typically occurring between 12-15 ppm, whilst the other phenolic signals (**8b-d** in Table 2, Entries 2, 3 and 4) appear around 8-10 ppm.

Table 2. Conversion of Suzuki coupled products to pyridine-substituted phenolic compounds



7 **8**

Entry	Precursor	Product	Yield (%)
1	 **7a**	 **8a**	91
2	 **7b**	 **8b**	67
3	 **7c**	 **8c**	63
4	 **7d**	 **8d**	61
5	 **7e**	 **8e**	76
6	 **7f**	 **8f**	92
7	 **7g**	 **8g**	86

As indicated from the purification of these pyridine-phenolic **8a-g**, their acidic and basic sites enable these compounds to be protonated when treated with acid or deprotonated with base under aqueous conditions giving water soluble materials. This feature proved extremely important in undertaking preliminary aqueous beryllium complexation studies with pyridine-phenol **8a**. Previous excited state proton transfer studies on compound **8a** have shown that in organic solvents very strong fluorescence emission exists because of the strong intramolecular hydrogen bonding. However, the introduction of increasing quantities of water in acetonitrile disrupts this feature and results in loss of fluorescence.[14] Qualitative studies of **8a** under alkaline aqueous conditions showed no fluorescence, presumably caused by deprotonation and disruption of the intramolecular hydrogen bonding. However, the addition of small amounts of beryllium sulfate to this solution resulted in the appearance of a new emission peak at ~ 450 nm (Figure 1). The ability of compound **8a** to bind to aqueous beryllium and exhibit switch-on fluorescence makes these systems promising for sensor applications. In building on these studies we reported the use of the tridentate ligand **3** as an intracellular tracking agent for biological beryllium.[40] This is the first example of a ligand **8f** that forms a stable beryllium-ligand complex under physiological pH, eliminating interference from the formation of beryllium-phosphate species, and also exhibits switch–on fluorescence in the presence of beryllium ions.

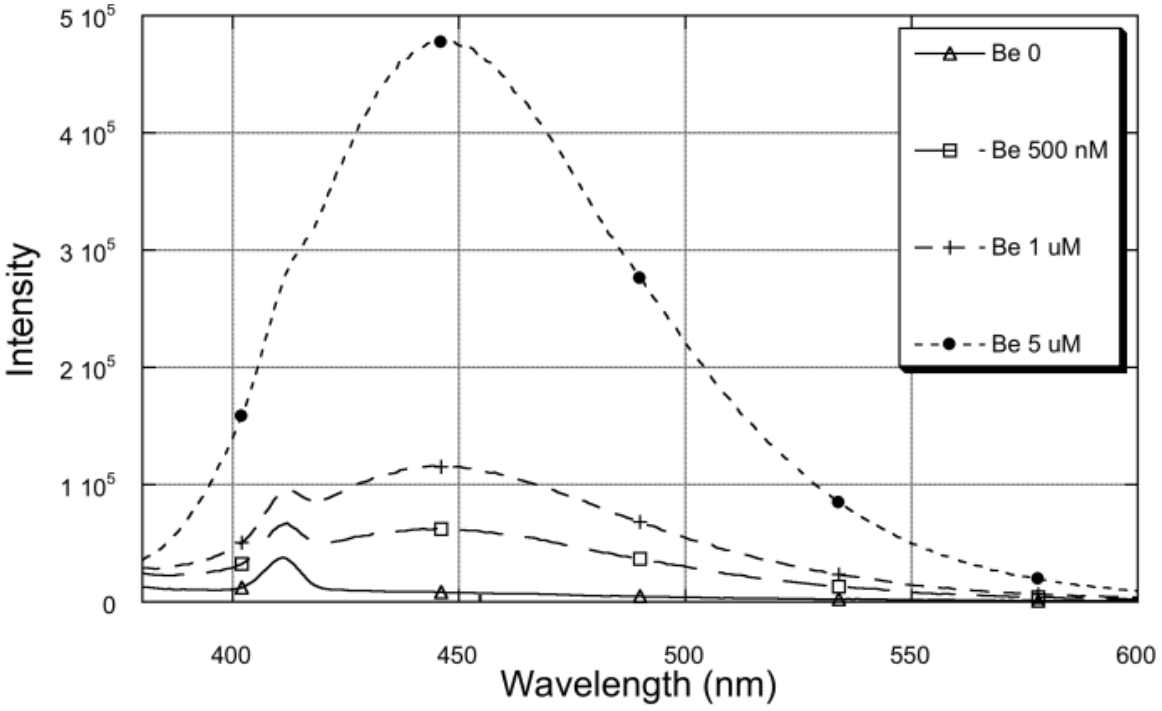


Figure 1. Fluorescence spectrum of 2-(2'-hydroxyphenyl)pyridine ligand **8a** (50 μm) with varying concentrations of beryllium sulfate in alkaline water (pH 10).

Conclusions

The presented synthetic procedure offers a convenient and easy access to bi-, tri- and tetradentate pyridine-phenolic ligands in high yield and purity through the use of simple and efficient Suzuki-Miyaura chemistry, deprotection, and purification protocols such as acid/base wash, distillation, and recrystallization. It has been demonstrated that the simplest pyridine-phenolic compound, 2-(2'-hydroxyphenyl)pyridine **8a**, has potential

as a switch-on fluorescence ligand for beryllium ions under aqueous conditions at nanomolar concentrations. These pyridine-phenolic ligands have traditionally found use in various applications due to their interesting magnetic, chemical, redox, electronic, and optical properties. Access to a diverse range of analogues of the pyridine-phenolic system is of interest for understanding and developing sensors for tracking aqueous beryllium. The current synthetic and purification process offers researchers a route to design and access key types of high purity pyridine-phenolic ligands for metal complexation, hydrogen bonding studies and provides opportunities in other areas, such as building blocks for metal-organic frameworks and spin-crossover materials.

Experimental Section

General procedure for the Suzuki-Miyaura coupling reactions: A stirred mixture of 2-bromopyridine **5a** (4.99 g, 31.6 mmol), tetrakis(triphenylphosphine)palladium (1.82 g, 1.58 mmol, 5 mol %), phenylboronic acid derivative **6a-d** (1.4-2.0 equiv.), dimethoxyethane (200 mL) and aqueous 1M Na_2CO_3 (150 mL) was heated at reflux under a nitrogen atmosphere for 12-24 h. The reaction mixture was cooled, concentrated under reduced pressure and diluted with water (120 mL). The mixture was extracted with DCM (3 × 50 mL) and the combined organic extract was washed with 1M HCl solution (4 × 100 mL). The combined aqueous phase was made slightly alkaline with NaOH pellets and extracted with DCM (5 × 50 mL). The combined DCM extract was dried (Dry Disk) and concentrated under reduced pressure to give the crude product as a liquid that was purified by Kugelrohr distillation or recrystallization.

2-(2'-Methoxyphenyl)pyridine (7a).[32] Initially isolated as a straw-colored oil.[2,3] This material was subjected to Kugelrohr distillation (bp 160-2 °C/1 Torr) to give the **7a** as a clear colorless liquid (5.49 g, 94%) (lit[41] bp 105 °C, 0.15 mmHg, lit[31] bp 96-99 °C, vacuum, lit[42] bp 92-95 °C /0.01 Torr). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.73-8.67 (m, 1H, H_{Py}), 7.84-7.785 (m, 1H, H_{Py}), 7.76 (dd, 1H, *J* 7.6, 1.8 Hz, H_{Ph}), 7.70 (ddd, 1H, *J* 7.8, 7.8, 1.8 Hz, H_{Py}), 7.39-7.32 (m, 1H, *J* 1.8 Hz, H_{Ph}), 7.20 (ddd, 1H, *J* 7.4, 4.9, 1.2 Hz, H_{Py}), 7.12-7.05 (m, 1H, H_{Ph}), 7.03-6.97 (m, 1H, H_{Ph}), 3.86 (s, 3H, MeO). ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.9, 156.1, 149.3, 135.6, 131.1, 129.9, 129.1, 125.1, 121.6, 121.0, 111.4, 55.6.

2-(2',3'-Dimethoxyphenyl)pyridine (7b).[43] Initially isolated as a dark yellow oil. This material was subjected to Kugelrohr distillation (bp 143-5 °C/1 Torr) to give the **7b** as a colorless clear liquid, which formed a colorless crystalline solid (2.72 g, 92%) on standing (mp 60 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.81-8.68 (m, 1H, H_{Py}), 7.96-7.74 (m, 1H, H_{Py}), 7.77 (ddd, 1H, *J* 7.6, 7.6, 1.8 Hz, H_{Py}), 7.36 (dd, 1H, *J* 8.0, 1.6 Hz, H_{Ph}), 7.23 (m, 1H, H_{Py}), 7.16 (app t, 1H, *J* 8.0, 8.0 Hz, H_{Ph}), 6.98 (dd, 1H, *J* 8.0, 1.5 Hz, H_{Ph}), 3.92 (s, 3H, MeO), 3.69 (s, 3H, MeO). ^{13}C NMR (75 MHz), $CDCl_3$): δ 155.9, 153.0, 149.4, 147.1, 135.9, 134.4, 124.9, 124.2, 121.9, 112.7, 60.9, 56.0. Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.56; H, 6.20; N, 6.41.

2-(2',4'-Dimethoxyphenyl)pyridine (7c).[12] Initially isolated as a dark yellow oil. This material was subjected to Kugelrohr distillation (bp 165-7 °C/1 Torr) to give **7c** as a colorless clear liquid (2.78 g, 93%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.65 (ddd, 1H, *J* 4.9, 1.8, 1.0 Hz, H_{Py}), 7.79 (d of t, 1H, *J* 8.0, 1.0 Hz, H_{Py}), 7.78 (d, 1H, *J* 8.5 Hz, H_{Ph}), 7.68-7.58 (ddd, 1H, *J* 7.4, 1.8 Hz, H_{Py}), 7.12 (ddd, 1H, *J* 7.4, 4.9, 1.2 Hz, H_{Py}), 6.61 (dd, 1H, *J* 8.5, 2.4 Hz, H_{Ph}), 6.54 (d, 1H, *J* 2.4 Hz, H_{Ph}), 3.82 (s, 3H, MeO), 3.81 (s, 3H, MeO). ^{13}C NMR (75 MHz), $CDCl_3$): δ 161.2, 158.0, 149.1, 135.4, 131.8, 124.6, 121.0, 104.9, 98.7, 55.4, 55.3. Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.23; H, 6.01; N, 6.59.

2-(2',5'-Dimethoxyphenyl)pyridine (7d). Initially isolated as an olive-colored oil. This material was purified by Kugelrohr distillation (bp 198-200 °C/1 Torr) to give **7d** as a colorless clear liquid (6.41 g, 93%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.72-8.67 (m, 1H, H_{Py}), 7.87-7.81 (m, 1H, *J* 8 Hz, H_{Py}), 7.68 (app d of t, 1H, *J* 7.7, 7.7, 1.9 Hz, H_{Py}), 7.39 (dd, 1H, *J* 2.4, 1.0 Hz, H_{Ph}), 7.19 (ddd, 1H, *J* 7.4, 4.9, 1.1 Hz, H_{Py}), 6.97-6.87 (m, 2H, 2 × H_{Ph}), 3.82 (s, 3H, OMe), 3.79 (s, 3H, OMe). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 155.8, 153.9, 151.2, 149.3, 135.6, 129.8, 125.0, 121.7, 115.7, 115.6, 113.1, 56.3, 55.7. Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 73.00; H, 6.28; N, 6.63.

2-(2',6'-Dimethoxyphenyl)pyridine (7e). Initially isolated as an orange oil. This material was purified by Kugelrohr distillation (bp 178-180 °C/1 Torr) to give **7e** as a colorless clear liquid (2.29 g, 58%), which crystallized upon standing at ambient temperature to give a colorless crystalline solid, mp 79-80 °C (lit[44] mp 81-82 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.75-8.68 (m, 1H, H_{Py}), 7.70 (app d of t, 1H, *J* 7.7, 7.7, 1.9 Hz, H_{Py}), 7.34-7.26 (m, 1H, H_{Py}), 7.30 (app t, 1H, *J* 8.4, 8.4 Hz, H_{Ph}), 7.21 (ddd, 1H, *J* 7.7, 4,9, 1.2 Hz, H_{Py}), 6.64 (d, 2H, *J* 8.4 Hz, 2 × H_{Ph}), 3.71 (s, 6H, 2 × OMe). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.0, 154.5, 149.2, 135.6, 129.6, 126.1, 121.6, 119.0, 104.1, 55.9. ATR IR (ν cm^{-1}) 3017, 2959, 2932, 2838, 1589, 1472, 1458, 1426, 1249, 1106, 1023, 988, 797, 780, 752, 726, 601, 539. Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.54; H, 6.39; N, 6.22.

2,6-Di-(2'-methoxyphenyl)pyridine (7f). Initially isolated as a yellowish solid which was then recrystallized from DCM/ether (charcoal) to **7f** as off-white microcrystalline needles (3.89 g, 79%), mp 127 °C (lit.[45] mp 122-3 °C, lit.[46] mp 120-1 °C, lit.[47] mp 122-4 °C, lit.[48] mp 122-4 °C, lit.[49] mp 112 °C and lit.[50] mp 130 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (dd, 2H, *J* 7.6, 1.7 Hz, 2 × H_{Ph}), 7.70 (m, 3H, 3 × H_{Py}), 7.40-7.30 (m, 2H, *J* 1.8 Hz, 2 × H_{Ph}), 7.08 (app d of t, 2H, *J* 8.3, 7.5, 0.9 Hz, 2 × H_{Ph}), 7.00 (bd, 2H, *J* 8.2 Hz, 2 × H_{Ph}), 3.87 (s, 6H, 2 × OMe). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.1, 155.4, 135.1, 131.5, 129.64, 129.58, 123.1, 121.0, 111.4, 55.6.

6,6'-Di-(2''-methoxyphenol)-2,2'-bipyridine (7g). Initially isolated as a dark solid that was recrystallized from dichloromethane/petroleum ether (charcoal) to give **7g** as a faint yellow powder (1.26 g, 54%), mp 170 °C (lit. [30] mp 175 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.51 (bd, 2H, *J* 7.6 Hz, 2 × H_{Py}), 8.04 (dd, 2H, *J* 7.6, 1.8 Hz, 2 × H_{Ph}), 7.92 (bd, 2H, *J* 7.1 Hz, 2 × H_{Py}), 7.88-7.78 (m, 2H, 2 × H_{Py}), 7.45-7.35 (m, 2H, *J* 1.8 Hz, 2 × H_{Ph}), 7.14 (app d of t, 2H, *J* 7.5, 7.5, 0.9 Hz, 2 × H_{Ph}), 7.04 (bd, 2H, *J* 8.2 Hz, 2 × H_{Ph}), 3.90 (s, 6H, 2 × MeO). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.3, 155.9, 154.8, 136.4, 131.5, 129.9, 129.2, 125.0, 121.1, 119.1, 111.6, 55.7.

General procedure for demethylation conditions and isolation of phenolic compounds: A stirred mixture of methoxyphenyl derivative **7a-g** (3.43 mmol) and pyridine hydrochloride (Py·HCl) (3.0-12.0 equiv.) under an atmosphere of nitrogen was heated to 200 °C for 4-8 h. The cooled reaction mixture was treated with water (200 mL) and adjusted to pH 7 with a combination of initially solid NaOH pellets and then $NaHCO_3$. The mixture was extracted with DCM (3 × 35 mL), the organic extract was dried (Dry Disk) and concentrated under vacuum.

2-(2'-Hydroxyphenyl)pyridine (8a).[32] Initially isolated as a brown liquid. This material was subjected to Kugelrohr distillation (bp 178-180 °C/1 Torr) to give a bright fluorescent colored liquid (1.65 g, 91%) which slowly crystallized upon standing to give **8a** as a faint lime colored solid, mp 53-4 °C (lit.[51] mp 56–8 °C, lit.[52] mp 55-6 °C, lit.[53] mp 56 °C and lit.[42] mp 56-7 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 14.35 (s, 1H, OH), 8.54-8.48 (m, 1H, H_{Py}), 7.92 (bd, 1H, *J* 8.3 Hz, H_{Py}), 7.88-7.82 (m, 1H, H_{Py}), 7.82-7.76 (m, 1H, *J* 1.6 Hz, H_{Ph}), 7.30 (ddd, 1H, *J* 8.4, 7.2, 1.6 Hz, H_{Ph}), 7.27-7.20 (m, 1H, H_{Py}), 7.03 (dd, 1H, *J* 8.3, 1.2 Hz, H_{Ph}), 6.95-6.86 (m, 1H, *J* 1.2 Hz, H_{Ph}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.0, 157.9, 145.9, 137.8, 131.5, 126.1, 121.5, 119.1, 118.81, 118.76, 118.6.

2-(2',3'-Dihydroxyphenyl)pyridine (8b).[43] The crude yellow solid was dissolved in a small amount of DCM/acetone and passed through a plug of silica gel to remove baseline impurities. The solvent was removed and the solid was recrystallized (DCM/petroleum ether) to afford **8b** as yellow needles (1.55 g, 67%), mp 126-7

°C. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 14.33 (s, 1H, OH_{C-2}), 8.85 (s, 1H, OH_{C-3}), 8.65-8.59 (m, 1H, H_{Py}), 8.16 (d, 1H, *J* 8.3 Hz, H_{Py}), 7.99 (app d of t, 1H, *J* 7.8, 1.8 Hz, H_{Py}), 7.48-7.37 (m, 2H, H_{Ph} and H_{Py}), 6.85 (dd, 1H, *J* 7.8, 1.2 Hz, H_{Ph}), 6.72 (app t, 1H, *J* 7.8 Hz, H_{Ph}). ^{13}C NMR (75 MHz, DMSO-d_6) δ 157.3, 148.0, 146.5, 146.0, 138.6, 122.1, 119.9, 118.7, 118.3, 116.9, 116.7. Anal. Calcd for $C_{11}H_9NO_2$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.33; H, 5.05; N, 7.41.

2-(2',4'-Dihydroxyphenyl)pyridine (8c). The crude yellow solid was dissolved in a small amount of EtOAc/petroleum ether and passed through a plug of silica gel to remove baseline impurities. The solvent was removed and the product was obtained **8c** as bright yellow crystals (1.44 g, 63%), mp 171-2 °C (lit.[12] mp 170-2 °C). ^{1}H NMR (300 MHz, DMSO-d_6) δ 14.39 (s, 1H, OH_{C-2}), 9.80 (s, 1H, OH_{C-4}), 8.54-8.47 (m, 1H, H_{Py}), 8.01 (d, 1H, *J* 8.5 Hz, H_{Py}), 7.91 (ddd, 1H, *J* 7.4, 7.4, 1.8 Hz, H_{Py}), 7.81 (d, 1H, *J* 8.8 Hz, H_{Ph}), 7.33-7.25 (m, 1H, *J* 1.8 Hz, H_{Py}), 6.36 (dd, 1H, *J* 8.8, 2.5 Hz, H_{Ph}), 6.29 (d, 1H, *J* 2.4 Hz, H_{Ph}). ^{13}C NMR (75 MHz, DMSO-d_6) δ 161.1, 160.4, 157.4, 145.7, 138.3, 128.0, 120.8, 118.5, 110.7, 107.3, 103.5.

2-(2',5'-Dihydroxyphenyl)pyridine (8d). The crude product was recrystallized (DCM/petroleum ether) to give **8d** as a yellow solid (1.39, 61%), mp 169 °C (lit.[54] mp 169-172 °C). ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.22 (s, 1H, $OH_{C-2'}$), 8.92 (s, 1H, $OH_{C-5'}$), 8.63-8.57 (m, 1H, H_{Py}), 8.07-8.01 (m, 1H, H_{Py}), 8.01-7.93 (m, 1H, *J* 1.7 Hz, H_{Py}), 7.44-7.36 (m, 1H, *J* 1.3 Hz, H_{Py}), 7.34-7.30 (m, 1H, H_{Ph}), 6.81-6.71 (m, 2H, 2 × H_{Ph}). ^{13}C NMR (75 MHz, DMSO-d_6) δ 156.8, 151.7, 149.5, 146.4, 138.5, 122.1, 119.8, 119.0, 118.9, 118.3, 112.2. Anal. Calcd for $C_{11}H_9NO_2$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.51; H, 5.06; N, 7.35.

2-(2',6'-Dihydroxyphenyl)pyridine (8e). The crude yellow solid was dissolved in a small amount of DCM/acetone and passed through a plug of silica gel to remove baseline impurities. The solvent was removed and the solid was recrystallized (DCM/petroleum ether) to give **8e** as a yellow microcrystalline solid (1.32 g, 76%), mp 180-1 °C (lit.[44] mp 182 °C). ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.38 (s, 2H, $OH_{C-2' \text{ and } C-6'}$), 8.63-8.53 (m, 2H, H_{Py}), 8.01-7.92 (m, 1H, H_{Py}), 7.41-7.33 (m, 1H, H_{Py}), 7.05 (app t, 1H, *J* 8.1, 8.1 Hz, H_{Ph}), 6.42 (d, 2H, *J* 8.1 Hz, H_{Ph}). ^{13}C NMR (75 MHz, DMSO-d_6) δ 158.9, 156.0, 145.4, 137.9, 130.7, 125.0, 121.5, 107.8, 107.5. Anal. Calcd for $C_{11}H_9NO_2$: C, 70.58; H, 4.85; N, 7.48. Found: C, 71.02; H, 4.73; N, 7.30.

2,6-Di-(2'-hydroxyphenyl)pyridine (8f). The crude yellow solid was dissolved in a small amount of DCM/acetone and passed through a plug of silica gel to remove baseline impurities. The solvent was removed and **8f** was obtained as very pale yellow flakes (1.66 g, 92%), mp 143 °C (lit.[29] mp 138 °C, lit.[46] mp 120-121 °C, lit.[47] mp 122-124 °C, lit.[48] mp 122-124 °C, lit.[50] mp 139 °C and lit.[29] mp 117 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.30 (s, 2H, 2 × $OH_{C-2'}$), 8.10-7.94 (m, 3H, 3 × H_{Py}), 7.82 (dd, 2H, *J* 7.7, 1.5 Hz, 2 × H_{Ph}), 7.31 (m, 2H, *J* 1.5 Hz, 2 × H_{Ph}), 7.00-6.90 (m, 4H, 4 × H_{Ph}). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.2. 154.7, 138.6, 130.9, 128.3, 121.9, 120.0, 119.2, 117.3.

6,6'-Di-(2''-hydroxyphenyl)-2,2'-bipyridine (8g).[55, 56] The crude yellow solid was dissolved in a small amount of DCM/petroleum ether and passed through a plug of silica gel to remove baseline impurities. The solvent was removed and the product recrystallized (DCM/petroleum ether) to give **8g** as fluffy yellow crystals (1.03 g, 86%), mp 236-7 °C (lit. mp 238 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.36 (s, 2H, 2 × $OH_{C-2'}$), 8.34 (d, 2H, *J* 7.9 Hz, 2 × H_{Py}), 8.23 (app t, 2H, *J* 7.9 Hz, 2 × H_{Py}), 8.19-8.08 (m, 4H, 2 × H_{Py} and 2 × H_{Ph}), 7.41-7.31 (m, 2H, 2 × H_{Ph}), 7.03-6.94 (m, 4H, 4 × H_{Ph}). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.4. 156.8, 152.0, 139.6, 131.5, 128.0, 121.5, 119.9, 119.3, 119.2, 117.7.

Acknowledgements

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Supplementary Material

The Supplementary Information (SI) contains a Table SI9 summarizing the large number of reports for the synthesis and characterization data for 2-(2'-hydroxyphenyl)pyridine **8a**[32] that has been synthesized by different methods, in different yields, levels of purity and characterization data.

A summary of relevant literature papers has been included Table SI1-8 and 9-15 for the characterization data of the methoxyphenyl-pyridine **7a-g** and hydroxyphenyl-pyridine **8a-g** derivatives, respectively. These tables highlight the different end application use of the ligands, purification, characterization, and slight differences reported for these compounds. ^{1}H and ^{13}C NMR spectroscopic data for compounds **7g** and **8g** is shown as representation of the purity of the materials obtained after the described purification process.

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