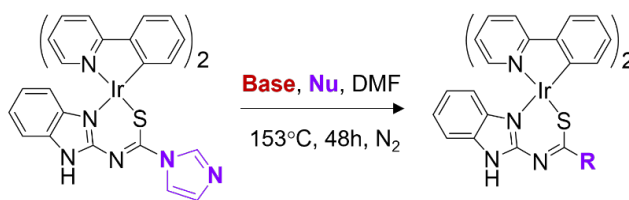


High-Yielding Synthesis of Cyclometallated Iridium Complexes with Hydrogen Bond-Rich Ligands

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Base: Et₃N or KHMDS.

8 Cyclometallated iridium complexes with H-bond rich ligands (85-97% yields).

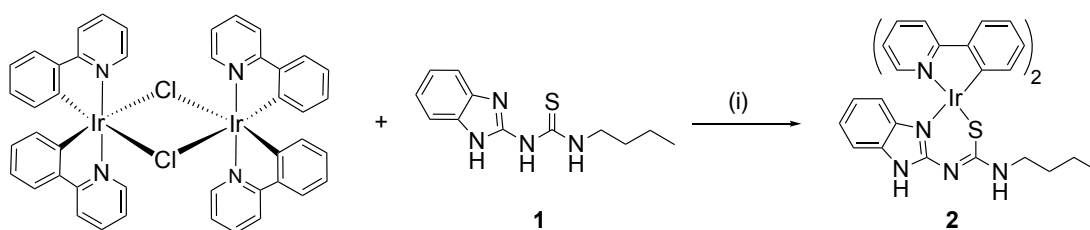
ABSTRACT: A library of cyclometallated iridium (III) complexes with a strong H-bonding motif in their ancillary ligand was synthesized, characterized and their photophysical properties measured. Demonstrated herein is a general synthetic high yield procedure for these compounds. We ascribe these yields to the use of an intermediary primer ligand. This *de novo* strategy circumnavigates the standard synthetic issues of H-bond rich ligand precursors (self-aggregation and poor solubility in organic solvents). Alternative and greener synthetic pathways were also explored to realize the intermediate iridium primer complex.

The last few decades has seen a surge of interest in the use of phosphorescent transition metal complexes in organic light emitting diodes (OLEDs),^{1,2} chemical sensors, and bioimaging labels.³ Pseudooctahedral coordinated t_{2g}^6 metals are often at the forefront of these research developments on account of the prominent phosphorescence behaviour that can be generated.^{4,5} To date, cyclometallated iridium (III) complexes with C[^]N chelating ligands represent a best-in-class category of compounds, which have shown the most exceptional photophysical properties (photoluminescence quantum yield (PLQY), photo- and thermostability, and tunability).⁶ These impressive photoluminescence properties are related to a mixture of metal-to-ligand (MLCT) and ligand centered (LC) states. In particular, the triplet metal-to-ligand charge transfer (³MLCT) which generates strong coupling between the *d*-orbitals of the iridium center and a given ligand's *p*-orbitals that allows for triplet emission (a phosphorescent phenomenon).⁷

Cyclometallated ligands lie at the core of making finely tunable iridium complexes. This is due to their easily modifiable structures and how the electronic contributions

of such ligands can influence the visible light emission of their corresponding complexes by attenuating the HOMO-LUMO (both ¹MLCT and ³MLCT or ³LC) levels.⁸⁻¹⁶ Ancillary ligand modification (primarily enacted before coordination) is also an effective way to impart electronic and functional versatility to the iridium-containing substrates.¹⁷

Recently, our team reported a series of iridium complexes with ancillary ligands based on a benzimidazolyl-thiourea (**1**) and related guanidine molecules, i.e., inherently hydrogen bond (H-bond) rich motifs (Scheme 1).¹⁸ The development of H-bond array-containing iridium complexes akin to **2** have opened new avenues towards transition metal complex-based theranostics.¹⁹ Those with thiourea-like ligands are of very promising interest as they have been previously reported as anticancer agents.²⁰⁻²³ A major hurdle that this burgeoning field faces, however, is the tendency of substrates with available H-bonds to self-recognize and create aggregates in solution.^{24, 25} Consequently, the solubility of such molecules across most typical organic solvents can be markedly low, making further synthetic modifications challenging.

Scheme 1. Established synthetic route towards Ir(C[^]N)₂(N[^]S) **2**.

Conditions and reagents: (i) K₂CO₃, toluene, 110°C, 24h, N₂, 44%.

Typically, cyclometallated iridium (III) complexes with an ancillary ligand (LX) have been synthesized by applying the following synthetic route (Scheme 1):²⁶⁻³⁰ (i) separate synthesis of each cyclometallating (C[^]N) and ancillary (LX) ligands; (ii) complexation reaction or the iridium chloride salt (IrCl₃·xH₂O) with the bidentate (C[^]N) ligands to generate the corresponding [Ir(C[^]N)₂(μ-Cl)]₂ dimer; (iii) ligand exchange reaction of the bridging chloride ligands with the ancillary ligand (LX) to form two equivalents of Ir(C[^]N)₂(LX).¹⁸

In this letter, we demonstrate an alternative synthetic strategy towards a diverse range of cyclometallated iridium complexes with H-bond motifs in their ancillary ligands. This *de novo* approach circumvents the practical issue of self-aggregation caused by H-bonding in the preparation of the ancillary ligand itself. Notably, the system becomes more soluble in non-polar solvents upon coordination to the iridium(III) centre. Our approach employs carbothioamide **3** (Figure 1) as a 'primer ligand' due to the presence of an imidazole leaving group, while otherwise being chemically similar (i.e., in H-bond array structure) to our previously explored thiourea-based ancillary ligands.³⁰ Post-coordination modifications to the ancillary primer ligand of complex **4** were performed with a variety of primary amines in a high-yielding coupling reaction.

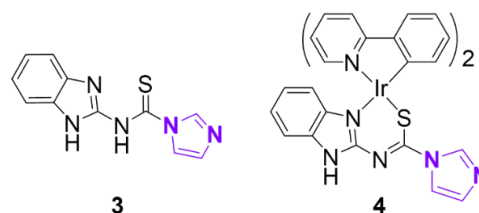
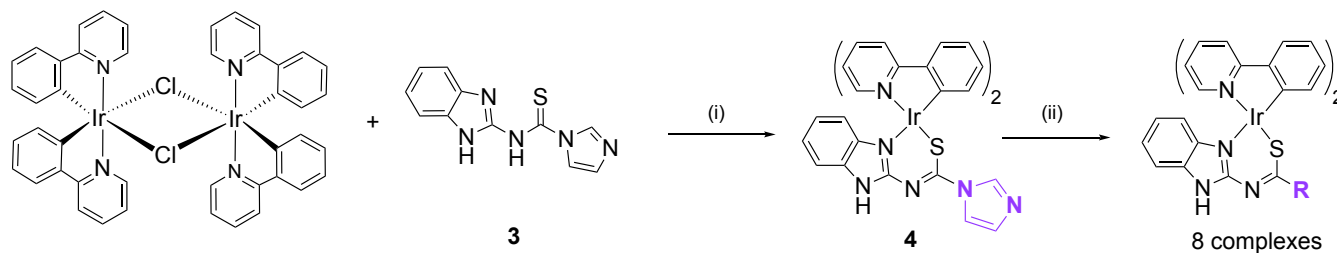


Figure 1. Proposed primer - ligand (**3**) and cyclometallated (C[^]N) iridium (III) complex (**4**, iridium primer).

Iridium primer **4** was assembled *via* a ligand-exchange reaction of the dichloro-bridged iridium dimers with primer ligand **3** (Scheme 2). Encouragingly, this step could be achieved to a yield of 75% and afforded us a metal complex equipped with a synthetic handle to exploit in subsequent steps. As there is limited potential for H-bonding at this stage, synthetic modifications through nucleophilic attack on the ancillary ligand of the primer complex **4** can be easily performed to synthesize a wide variety of H-bond rich metal complexes.

The synthesis of Ir(PPy)₂(N[^]S) **4** (Scheme 2) was also explored using two other methodologies. Table 1 outlines microwave (Anton Paar-monowave 400) and mechanochemistry-based (RETSCH MM 400 Mixer Mill) approaches towards **4**.

Scheme 2. Improved synthetic route towards Ir(C[^]N)₂(N[^]S) **4** and iridium complexes Ir(C[^]N)₂(N[^]S)-R.

Conditions and reagents: (i) K₂CO₃, DMF, reflux, 24h, N₂, 75%, (ii) NEt₃ or KHMDS, primary amine (*vide infra*, Table 2), DMF, reflux, 48h, N₂, 85-97%.

Table 1. Outcomes of different synthetic methods to realize Ir(PPy)₂(N[^]S) **4**.

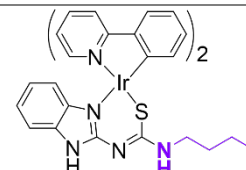
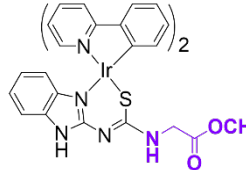
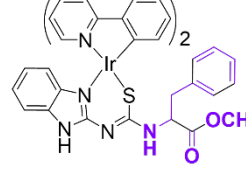
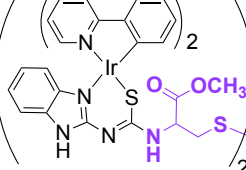
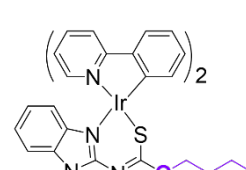
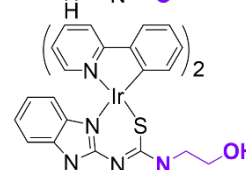
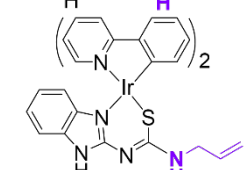
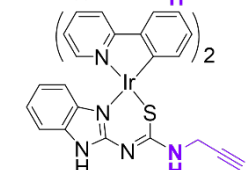
Method	T (°C)	Time	Solvent	Yield (%)
Hotplate stirrer	153	24h	DMF (20 mL)	75
Microwave	200	40 min	DMF (10 mL)	43
Ball Shaker Mill	23	1h	EtOH (1-2 drops)	83

Both methodologies represent more time-efficient and greener means of **4** when compared to the classical stirrer hotplate methods. These results are recapitulated, alongside further exploration of reaction conditions, in the supporting information (Table I, S1). Among this data for the microwave approach are varying reaction times (20-90 min) and bases (K₂CO₃, Na₂CO₃, Cs₂O₃ and NaHCO₃), however our best yield with this method was limited to 43%. Similarly, for the mechanochemistry approach, several reaction times (15-90 min) and bases (K₂CO₃, Na₂CO₃, Cs₂O₃ and NaHCO₃) were trialed (Table II, S1). This ultimately led to a very wide range of yields, with the optimized conditions delivering a pleasing 83% yield of **4**. This improvement to the yield with respect to conventional wet-chemical synthesis was achieved by applying a 30 Hz vibrational frequency for an hour at room temperature.

With iridium primer **4** in hand, a broad range of nucleophiles were incorporated into the ancillary ligand (N[^]S) *via* transamidation reaction (Figure 2). These late-stage functionalization reactions were all gratifyingly high-yielding (yields ranging from 85-97%), which marks a general overall improvement on previous synthetic approaches while establishing a wide and varied scope of complexes that can be realized through this approach (Table 2).

Balónová's iridium complex **2** was synthesized with this novel methodology (Table 2) with a yield improvement from 44%¹⁸ to 75%. Several protected amino acids, e.g., glycine methyl ester hydrochloride, L-phenylalanine methyl ester hydrochloride, and L-cystine dimethyl ester hydrochloride (Table 2, complexes **5-7**, respectively) were used in order to make their corresponding novel cyclometallated (C[^]N) iridium (III) complexes with yields ranging from 85-94%. We consider it prudent to work towards such complexes on account of the opportunity for further synthetic modifications, such as transesterification reactions, ester hydrolyses, etc., or to use as building blocks for larger supramolecular structures constructed by peptide synthesis. Also noteworthy, is the unique dimeric complex **7**, which could undergo a reduction of the disulfide bond, thereby affording two equivalents of monomeric iridium complex with a terminal thiol group.

Table 2. Preparation of a series of iridium (III) complexes accessing a diverse range of thiourea ancillary ligands.

Complex	Ir(C [^] N) ₂ (N [^] S)-R	Yield (%) ^a
2		94 ^b
5		94 ^c
6		91 ^d
7		85 ^e
8		87 ^f
9		97 ^g
10		90 ^h
11		92 ⁱ

^aYields are an average of three or more repetitions. ^bNEt₃, butylamine; ^cNEt₃, glycine methyl ester hydrochloride; ^dNEt₃, L-phenylalanine methyl ester hydrochloride; ^eNEt₃, L-cystine; ^fKHMDS, 1-butanol; ^gNEt₃, ethanolamine; ^hKHMDS, allylamine; ⁱKHMDS, propargylamine.

1-Butanol and ethanolamine (Table 2, yielding complexes **8** and **9**, respectively) were also used to expand the library of known complexes with ancillary ligands of the type R-N-(C=S)-O-R'/ R-N-(C=S)-NH-R'. Iridium complex **8** was synthesized using KHMDS (pK_a ~ 26)³¹ instead of NEt₃ (pK_a ~ 10.75)³² as the base to ensure the full deprotonation of the alcohol (pK_a ~ 16.1),³³ thereby encouraging the desired esterification chemistry. With ethanolamine (pK_a ~ 9.5)³⁴ as the nucleophile of choice, wherein a terminal alcohol and amine are both present, different products can be afforded depending on the choice of base. That is, if the reaction is carried out with triethylamine, iridium complex **9** is obtained selectively with 97% yield, however, if the reaction is performed with KHMDS, a mixture of the terminal alcohol- and amine-substituted iridium complexes are obtained.

Lastly, two primary amines with a terminal alkene and alkyne (Table 2, complexes **10** and **11**, respectively) were used to introduce two new handles for further post-synthetic modifications. We envisage the possibility of performing cross-coupling,³⁵ metathesis,^{36,37} and hydrosilylation reactions³⁸ with **10**, and both oxidative and copper catalyzed azide-alkyne coupling reactions³⁹⁻⁴¹ with **11**. We anticipate that both will provide the groundwork for the building of iridium-based higher-order supramolecular structures. Its noteworthy here, that employment of triethylamine as the base for these reactions resulted in poorer yields (~60%) as compared to when KHMDS was used (~90% yield).

In conclusion, we have described a novel synthetic approach towards a diverse range of H-bond rich thiourea-based ligands and their chelation into cyclometallated iridium complexes. Crucially, this approach circumvents any potential issues of H-bond driven self-aggregation. At the core of this strategy is the synthesis of an iridium primer (**4**) which features a good leaving group, thus permitting late-stage modifications around the thiourea-based ancillary ligand through facile transamidation chemistry. We have also presented three different methodologies towards iridium primer **4**, highlighting alternative, green chemistries. Among these was a mechanochemical approach which led to an optimized yield of **4** of 83%. Finally, we have demonstrated the versatility and

effectiveness of the last synthetic step - the transamidation/transesterification chemistry - using a broad range of alcohol- and amine-bearing nucleophiles, resulting in yields ranging from 85-97%, which we will employ in more complex supramolecular assemblies.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

General experimental and characterization information, synthetic and characterization details, synthetic optimization of iridium primer and cyclometallated iridium (III) complexes, as well as their photophysical characterization.

Data Availability Statement

The datasets that underpin this work can be found in the University of New Brunswick Dataverse:

<https://doi.org/10.25545/KG4ERJ>

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Author Contributions

MTP: conceptualization, methodology, investigation, formal analysis, data curation, writing – original draft. HJH:

investigation, validation. RW: investigation, validation. BAB:

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