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A Click Chemistry Approach to 5,5′-Disubstituted-3,3′-Bisisoxazoles from Dichloroglyoxime and Alkynes: Luminescent Organometallic Iridium and Rhenium Bisisoxazole Complexes

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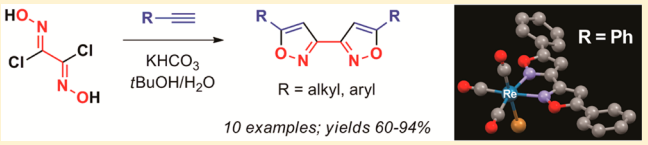
Supporting Information

ABSTRACT: 5,5′-Disubstituted-3,3′-bisisoxazoles are prepared in one step by the dropwise addition of aqueous potassium hydrogen carbonate to a mixture of dichloroglyoxime and terminal alkynes. The reaction exhibits a striking preference for the 5,5′-disubstituted 3,3′-bisisoxazole over the 4,5′-regioisomer. Organometallic iridium and rhenium bisisoxazole complexes are luminescent with emission wavelengths varying depending upon the identity of the 5,5′-substituent (phenyl, butyl).



The presence of two sets of nonaromatic lone pairs endows the isoxazole heterocyclic ring with metal coordinating properties, which have been studied extensively.[1−5] A variety multi-isoxazole arrays have been prepared[6−10] and their potential to act as metal binding ligands highlighted[9,10] but to our knowledge the coordination chemistry of isoxazole arrays has not been explored. The simplest multi-isoxazole arrays are the bisisoxazoles, which can be linked in 6 different ways between the 3, 4, and 5 carbon atoms of each isoxazole ring (Figure 1A). The 3,3′-bisisoxazoles possess a 1,4-dinitrogen system similar to that of 2,2′-bipyridine,[11] phenanthroline,[11] and 4,4′-bis(1,2,3-triazoles)[12] and thus have the potential to act as bidentate ligands to metal atoms (Figure 1B).

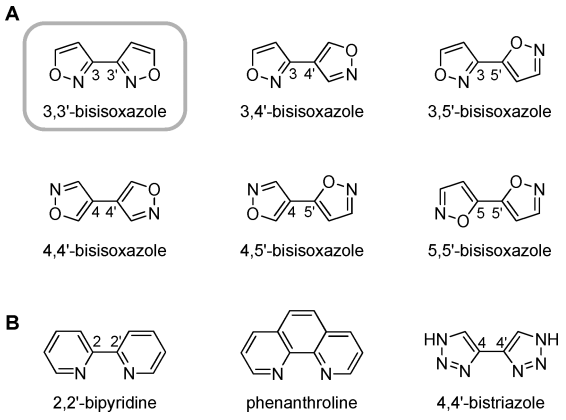


Figure 1. (A) The six possible bisisoxazole isomers. The focus of this study, the 3,3′-bisisoxazole, is highlighted. (B) Common metal-coordinating bidentate ligands with a 1,4-dinitrogen motif.

3,3′-Bisisoxazoles have been assembled in a complex multistep sequence from bis-nitrocyclopropanes,[13] or in two steps by dipolar cycloaddition of the bis-nitrile oxide dicyanide-*N*-oxide and silylenol ethers, followed by aromatization.[14] The most direct route to 3,3′-bisisoxazoles is by 1,3-dipolar cycloaddition of dicyanide-*N*-oxide with 2 molecules of alkyne. Pioneering work by Quilico et al. found that various alkynylmagnesium halides reacted with dichloroglyoxime to afford 5,5′-disubstituted-3,3′-bisisoxazoles in low to moderate yields, presumably via the intermediacy of dicyanide-*N*-oxide.[15] Grundmann and co-workers reported that phenylacetylene reacts with preformed dicyanide-*N*-oxide to afford 5,5′-diphenyl-3,3′-bisisoxazole and a nitrile oxide-derived furoxan dimer in 80% combined yield.[16,17] Subsequently, Cramer and McClellan formed the parent 3,3′-bisisoxazole from the reaction of acetylene with nitric oxide and nitrogen dioxide under pressure.[18] These early reports demonstrated the potential for a direct entry into the interesting 3,3′-bisisoxazole series; however, further studies have not been reported, likely because of the low to moderate yields reported and the difficulty preparing alkynylmagnesium halides and/or dicyanide-*N*-oxide, or high pressures required. As well, when utilizing terminal alkynes, these reactions have the potential to deliver the regioisomeric 4,5′- and 4,4′-disubstituted-3,3′-bisisoxazoles, and the regioselectivity of this reaction has not been studied.

We report here the development of a direct, one-step protocol for the synthesis of 3,3′-bisisoxazoles from dichloroglyoxime. When employing terminal alkynes this procedure has a remarkable intrinsic preference for regioselective dipolar cycloaddition to afford the 5,5′-disubstituted isomers. Further,

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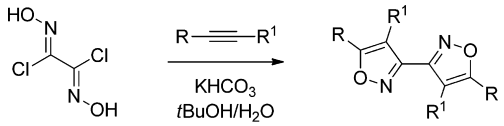
Table 1. Synthesis of 3,3′-bisisoxazoles



entry/compound number	R	R[1]	product	yield (%) by filtration[a]	yield (%) by chromatography[b,c]
1	butyl	H	1	77	68(4)
2	hexyl	H	2	60	76
3	octyl	H	3	64	66(9)
4	cyclohexyl	H	4	66	70(7)
5	phenyl	H	5	93	90
6	4-fluorophenyl	H	6	80	66(2)
7	2-methylphenyl	H	7	76	94(4)
8	4-methylphenyl	H	8	86	61(1)
9	2,3,4,6-tetra-*O*-acetyl-*α*-D-mannopyranosyloxymethyl	H	9	—[d]	64
10	methoxycarbonyl	methoxycarbonyl	10	77	91

[a]See Experimental Section, General procedure A. [b]See Experimental Section, General procedure B. [c]Number in brackets represents yield of the minor 4,5′-disubstituted-3,3′-bisisoxazole. In most cases the 3,3′- and 3,4′-bisisoxazoles could not be resolved by flash chromatography. [d]Isolation by filtration was unsuccessful as the product was contaminated with starting alkyne.

we demonstrate the metal binding properties of 3,3′-bisisoxazoles through the preparation and characterization of luminescent organometallic iridium and rhenium complexes.

The protocol for synthesis of 5,5′-disubstituted-3,3′-bisisoxazoles is striking for its simplicity. Slow addition of aqueous potassium hydrogencarbonate to a solution of dichloroglyoxime and a range of terminal alkynes with different substituents in *t*-BuOH/H_2O mixtures in most cases resulted in direct precipitation of the bisisoxazoles **1**–**8** with excellent purity solely as the 5,5′-disubstituted-3,3′-bisisoxazole in 60–93% yields (Table 1). The ease of product purification, benign solvents and reagents, and the simple starting materials characterize this process as an example of 'click chemistry'.[19,20] Alternatively, aqueous workup and chromatography afforded the bisisoxazoles **1**–**9** in 61–94% yields, although in these cases the products often contained the 4,5′-disubstituted-3,3′-bisisoxazole as a minor product. The approach has wide scope, and can be applied to terminal alkynes bearing aliphatic (**1**–**4**; entries 1–4) and aromatic (**5**–**8**; entries 5–8) groups, and even a complex acetylated sugar alkyne (**9**; entry 9). On the basis of the order of addition, this reaction most likely proceeds by elimination of HCl from one end of dichloroglyoxime and formation of the nitrile oxide then cycloaddition with the alkyne, followed by the same sequence on the second chloroxime group. The stepwise nature of this process, along with the in situ generation of the nitrile oxide intermediates, limits the potential for yield-limiting dimerization of nitrile oxides, as plagued the early work by Gundmann.[17] The high intrinsic stereoselectivity of this cycloaddition process is at first glance surprising. However, nitrile oxide cycloadditions with terminal alkynes typically favor the 3,5-disubstituted isomers, and in some cases yield the 3,5-disubstituted isoxazole as the sole product (e.g., cycloaddition of 4-chlorophenylcyanide-*N*-oxide and phenylacetylene affords only 3-chlorophenyl-5-phenylisoxazole in 72% yield).[21,22]

Attempts to extend the reaction to internal alkynes met with limited success. Dimethyl acetylenedicarboxylate yielded the 4,5,4′,5′-tetrasubstituted 3,3′-bisisoxazole **10** in 91% yield (Table 1; entry 10). However, with diphenylacetylene and 3-hexyne the corresponding bisisoxazoles could not be detected, a result in concordance with the observations of Grundmann and co-workers using purified dicyanide-*N*-oxide.[17]

In order to understand the structural implications of two 3,3′-linked isoxazole rings, the structure of 5,5′-diphenyl-3,3′-bisisoxazole **5** was determined by single crystal X-ray crystallography (Figure 2). The structure of **5** reveals that the

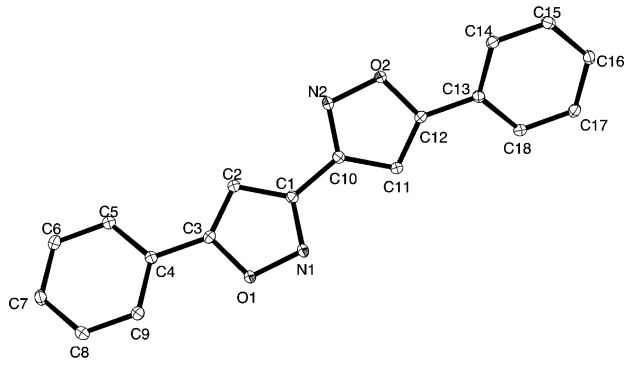


Figure 2. ORTEP representation of the molecular structure of 5,5′-diphenyl-3,3′-bisisoxazole **5**, determined by single-crystal X-ray crystallography. Ellipsoids are at the 20% probability level.

linked isoxazole rings adopt a planar *N*-transoid arrangement, presumably to minimize lone pair–lone pair interactions from the nitrogen atoms. This crystal structure is consistent with that obtained for the parent, 3,3′-bisisoxazole,[23] and reminiscent of that obtained for 2,2′-bipyridine,[24] which are also planar and adopt transoid configurations. While the two isoxazole rings of each molecule of **5** are close to planar the phenyl substituents are twisted out of the plane with an interplanar angle approximated to 13° (approximated by the dihedral angle, C11–12···C13–C18 = 13.5(2)°). Short intermolecular contact (3.341 Å) between C11 of the heterocycle and C16 of the phenyl substituent of an adjacent molecule are indicative of π–π interactions. The aryl substituted bisisoxazoles **5**–**8** absorb in the ultraviolet range; bisisoxazoles **7** and **8** exhibit weak fluorescence (λ_{ex} 275, λ_{em} 327 nm and λ_{ex} 300, λ_{em} 370 nm, respectively) (Figure S1).

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The ability of 5,5′-disubstituted-3,3′-bisisoxazoles to act as ligands to transition metal ions was demonstrated by the preparation of iridium(III) and rhenium(I) d^6 organometallic complexes. Heteroleptic octahedral cyclometalated iridium(III) complexes featuring two 2-phenylpyridine (ppy) bidentate monoanionic ligands and a second neutral bidentate diimine ligand such as bipyridine or phenanthroline are of interest owing to their luminescent properties. The reaction of the chloro-bridged dimer $[\{(ppy)_2Ir\}_2(\mu\text{-}Cl)_2]$, with $AgBF_4$ to assist in the exchange of the chloride ligands, followed by addition of a bisisoxazole ligand **5** or **1** allowed isolation of $[Ir(ppy)_2$(5,5′-diphenyl-3,3′-bisisoxazole)$]BF_4$ (**11**) and $[Ir(ppy)_2$(5,5′-dibutyl-3,3′-bisisoxazole)$]BF_4$ (**12**), respectively, in good yields. The brown−yellow solids were analyzed by electrospray mass spectrometry and signals for the monocations were the major peaks in the observed in the spectrum each with the expected isotope patterns: *m/z* 789.1844 for **11** ($[Ir(C_{40}H_{28}N_4O_2]^+$ requires 789.1838) and *m/z* 749.2451 for **12** ($[IrC_{36}H_{36}N_4O_2]^+$ requires 749.2468). The ^{13}C and ^1H NMR spectra of these diamagnetic low-spin d^6 complexes were as expected. In complex **11** coordination to Ir(III) results in a downfield shift in the resonance attributed to the proton of the isoxazole ring when compared to the "free" ligand **5** (this resonance is at δ 7.09 ppm in **5** and shifts to δ 8.26 ppm in complex **11**). A similar downfield shift is evident in complex **12** when compared to the "free" ligand **1**.

Iridium complexes **11** and **12** were structurally characterized by single crystal X-ray crystallography (Figure 3A,B). In both complexes the iridium cations are in a distorted octahedral C_2N_4 environment with three five-membered chelate rings and both enantiomers present in the lattice. The two carbon donor atoms provided by the ppy ligands are in a *cis*-C,C *trans*-N,N disposition about the iridium cation demonstrating that, at the reaction temperatures used for the synthesis, the stereochemistry of the starting material is retained. The Ir−C(ppy) ≈ 2.01 Å, Ir−N(ppy) ≈ 2.05 Å bond distances and similar to those within $[Ir(ppy)_2bipy)]PF_6$.[25] It is also of interest to note that the $Ir-N_{(bisisooxazole)}$ bond distances (≈ 2.14 Å) are similar to the Ir−N(bipy) bond lengths within $[Ir(ppy)_2bipy)]PF_6$.[25]

The reaction of either **5** or **1** with $[Re(CO)_5Br]$ allows isolation of $[Re(CO)_3$(5,5′-diphenyl-3,3′-bisisoxazole)Br] **13** and $[Re(CO)_3$(5,5′-dibutyl-3,3′-bisisoxazole)Br] **14**, respectively. The complexes were characterized by electrospray mass spectrometry and ^1H and ^{13}C NMR spectroscopy. As in the case of the Ir^{III} complexes discussed above, coordination to the metal ion results in a significant downfield shift in the resonance attributed to the proton of the isoxazole ring, but the lower charge of the Re^I means that the shift is less pronounced (δ 6.48 ppm in **1** shifts to δ 6.65 ppm in $[Re(CO)_3$(5,5′-dibutyl-3,3′-bisisoxazole)Br] **14**. Crystals of $[Re(CO)_3$(5,5′-diphenyl-3,3′-bisisoxazole)Br] (**13**) suitable for characterization by X-ray crystallography were isolated by recrystallization from a mixture of dichloromethane and pentane. The structure (Figure 4A) reveals a six coordinate rhenium(I) complex with the metal in a distorted octahedral environment. The three carbon monoxide ligands are in a facial arrangement about the Re^I and remaining apical position is occupied by a coordinated bromide anion. The coordination sphere is completed by the bisisoxazole, which acts as bidentate ligand. The Re−

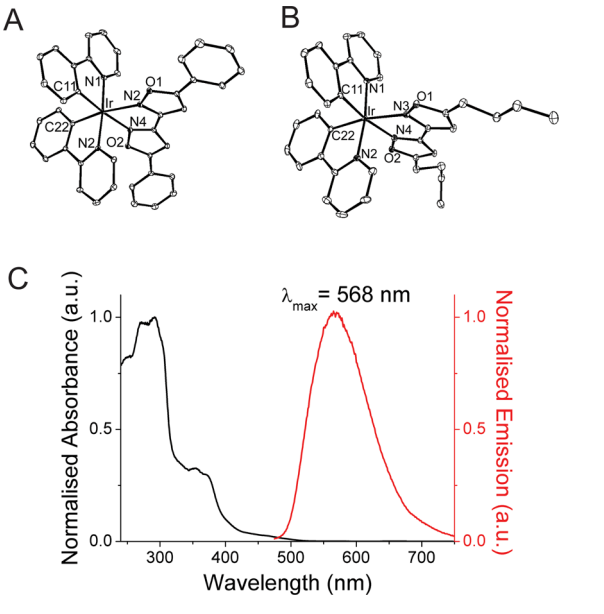

Figure 3. ORTEP representation of one enantiomer of the cations of (A) $[Ir(ppy)_2$(5,5′-diphenyl-3,3′-bisisoxazole)$]BF_4$ **11** and (B) $[Ir(ppy)_2$(5,5′-dibutyl-3,3′-bisisoxazole)$]BF_4$ **12**, determined by single-crystal X-ray crystallography. Ellipsoids are at the 20% probability level. The representation of $[Ir(ppy)_2$(5,5′-dibutyl-3,3′-bisisoxazole)$]BF_4$ is the enantiomer of that in the coordinate list. (C) Normalized absorbance and emission (irradiation at 400 nm) spectra (20 μM solution in CH_2Cl_2) of $[Ir(ppy)_2$(5,5′-diphenyl-3,3′-bisisoxazole)$]BF_4$ **11**.

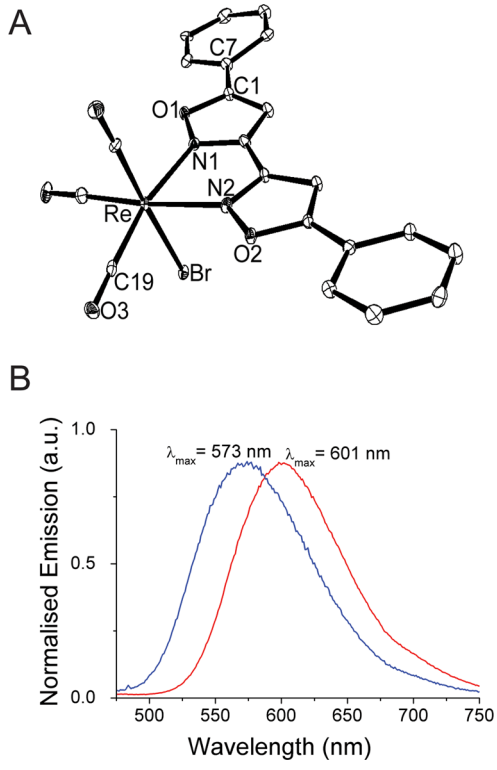

Figure 4. (A) ORTEP representation of a molecule of $[Re(CO)_3$(5,5′-diphenyl-3,3′-bisisoxazole)Br] **13**, determined by single crystal X-ray crystallography. Ellipsoids are at the 20% probability level. Disorder present in the phenyl ring C7−C12 is removed for clarity. (B) Normalized emission spectra (irradiation at 400 nm) of 20 μM dichloromethane solutions of $[Re(CO)_3$(5,5′-diphenyl-3,3′-bisisoxazole)Br] **13** (blue, left) and $[Re(CO)_3$(5,5′-dibutyl-3,3′-bisisoxazole)Br] **14** (red, right).

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$N_{(bisisooxazole)}$ bond distances (≈ 2.169 Å) are similar to the Re−N(bipy) bond lengths found in [Re(bipy)$(CO)_3$Cl] (Re−$N_{(bipy)}$ ≈ 2.17 Å).[26] The local C_s symmetry of the complexes is confirmed by IR spectroscopy with three CO stretches observed.

Solutions of [Ir$(ppy)_2$(5,5′-diphenyl-3,3′-bisisoxazole)]BF_4 (**11**) dissolved in dichloromethane are luminescent with excitation at 350 nm resulting in an emission centred at 568 nm presumably arising from metal-to-ligand charge-transfer transitions (^{3}MLCT) that are characteristic of cyclometalled Ir^{III} phenylpyridine complexes (Figure 3C). The corresponding spectrum for [Ir$(ppy)_2$(5,5′-dibutyl-3,3′-bisisoxazole)]BF_4 (**12**) exhibits an emission centered at 551 nm (Figure S2).

Complexes of the type [*fac*-Re(CO_3)N̂ NX] where N̂ N is a bidentate diimine ligand such as bipyridine or phenathroline and X is halide anion have interesting photochemical properties. The absorption spectra of **13** and **14** feature maxima at 250 and 300 nm, respectively, as well as lower energy absorptions at close to 400 nm that are assigned as metal−ligand charge-transfer absorptions (Figures S3,S4). For both rhenium complexes irradiation into the tail of this band (λ_{ex} = 400 nm) results in a broad emission with large Stokes shifts characteristic of ^{3}MLCT (λ_{em} = 573 nm for **13**; λ_{em} = 601 nm for **14**) (Figure 4B).

In this work we have shown that the pioneering work of Quilico et al.[15] and Grundmann et al.[16,17] can be extended to provide a one-pot procedure for the synthesis of 5,5′-disubstituted-3,3′-bisisoxazoles from dichloroglyoxime and terminal alkynes, and a 4,4′,5,5′-tetrasubstituted-3,3′-bisisoxazole from an activated internal alkyne. In most cases the target bisisoxazoles could be directly isolated in crystalline form by filtration in excellent yields and purity. This one-pot approach allows the direct modification of substituents at the 5,5′-positions of the bisisoxazole nucleus. The metal-coordinating properties of these bisisoxazoles was subjected to a preliminary investigation through the synthesis of luminescent rhenium and iridium complexes, with variations in the substituents at the 5,5′-positions allowing tuning of the luminescent properties of the resulting complexes. The simple access to bilaterally symmetrical bis-isoxazoles should facilitate their application in medicinal[27−29] and coordination chemistry.

EXPERIMENTAL SECTION

General. Proton nuclear magnetic resonance spectra (^{1}H NMR, 500 MHz) and proton decoupled carbon nuclear magnetic resonance spectra (^{13}C NMR, 125 MHz) were obtained in deuterochloroform, methanol-d_4, and DMSO-d_6 with residual protonated solvent as internal standard. Chemical shifts are followed by multiplicity, coupling constant(s) (*J*, Hz), integration, and assignments where possible. Flash chromatography was carried out on silica gel 60 according to the procedure of Still et al.[30] Analytical thin layer chromatography (t.l.c.) was conducted on aluminum-backed 2-mm-thick silica gel 60 GF_{254} and chromatograms were visualized with 20% w/w phosphomolybdic acid in ethanol. High resolution mass spectra (HRMS) were obtained by ionizing samples using electron spray ionization (ESI) and a time-of-flight mass analyzer. Dry DMF was obtained by drying over 4 Å molecular sieves. Petrol refers to petroleum ether, boiling range 40−60 °C. *N*-Chlorosuccinimide was recrystallized from water. All other commercially available reagents were used as received. Absorbance and emission spectra were obtained on a fluorescence spectrophotometer in capped quartz cuvettes. IR spectra were obtained as solutions in CH_2Cl_2 in a KBr solution cell.

Preparation of Glyoxime. A solution of NaOH (10 M, 30 mL, 172 mmol) was added slowly to a solution of hydroxylamine hydrochloride (11.9 g, 172 mmol) and glyoxal (12.5 mL, 40% w/v, 86.2 mmol) in H_2O (30 mL) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C. The resultant white solid was collected by vacuum filtration. The white residue was recrystallized from methanol to afford glyoxime as white crystals (5.3 g, 70%); mp 172−174 °C; lit.[31] 176−178 °C; ^{1}H NMR (400 MHz, d_6-DMSO) δ 11.6 (s, 2H), 7.72 (s, 2H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 145.3.

Dichloroglyoxime. N-Chlorosuccinimide (3.0 g, 22.8 mmol) was added portionwise to a stirring solution of glyoxime (1.0 g, 11.4 mmol) in dry DMF (10 mL) at 0 °C. The reaction mixture was stirred at rt for 3 h and then water (50 mL) and Et_2O (50 mL) were added. The aqueous phase was extracted with Et_2O (2 × 50 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated to give a white solid. The solid was recrystallized from toluene to afford dichloroglyoxime as colorless crystals (1.63 g, 91%); mp 202−203 °C; lit.[32] mp 198−199.

^{1}H NMR (500 MHz, d_6-DMSO) δ 13.1 (s, 2H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 130.7.

Cycloaddition Reaction between Dichloroglyoxime and Alkyne. *General Procedure A.* A solution of aq $KHCO_3$ (8.6 equiv, 30% w/v in H_2O) was added dropwise using a syringe pump over 15 min to a stirring mixture of dichloroglyoxime (1.0 equiv) and terminal alkyne (2.3−3.0 equiv) in *t*-BuOH/H_2O (10:1 ratio). Once the addition was complete, the mixture was stirred at rt for 3 h before the addition of water (2 mL) and then stirred at 0 °C for 30 min. The precipitate was collected by filtration using a Hirsch funnel and dried under vacuum.

General Procedure B. A solution of aq $KHCO_3$ (8.6 equiv, 30% w/v in H_2O) was added dropwise using a syringe pump over 15 min to a stirring mixture of dichloroglyoxime (1.0 equiv) and terminal alkyne (2.3−3.0 equiv) in *t*-BuOH/H_2O (10:1 ratio). Once the addition was complete, the mixture was stirred at rt for 3 h before the addition of water and dichloromethane. The aqueous phase was extracted with dichloromethane. The combined organic layer was washed with brine solution, dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by flash chromatography with EtOAc/petroleum spirit mixtures to afford the bisisoxazole.

5,5′-Dibutyl-3,3′-bisisoxazole (1). Method A. Dichloroglyoxime (259 mg, 1.65 mmol, 1.0 equiv), 1-hexyne (407 mg, 4.95 mmol, 3.0 equiv), and 30% $KHCO_3$ (14.3 mmol, 4.76 mL, 8.66 equiv) were used. Filtration afforded **1** (317 mg, 77%) as a yellow solid.

Method B. Dichloroglyoxime (259 mg, 1.65 mmol, 1.0 equiv), 1-hexyne (407 mg, 4.95 mmol, 3.0 equiv), and 30% $KHCO_3$ (14.3 mmol, 4.76 mL, 8.66 equiv) were used. Flash chromatography (5% EtOAc/petrol) afforded **1** (281 mg, 68%) as colorless crystals; mp 61−62 °C; lit.[15] 63−65 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.95 (6H, t, *J* = 7.5 Hz), 1.44−1.39 (4H, m), 1.75−1.69 (4H, m), 2.81 (4H, t, *J* = 7.5 Hz), 6.48 (2H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.7, 22.2, 26.5, 25.6, 99.2, 154.6, 174.9; HRMS (ESI) calcd for $C_{14}H_{21}N_2O_2$ $[M+H]^+$ 249.1598. Found 249.1596.

Further elution afforded the regioisomer, 4,5′-dibutyl-3,3′-bisisoxazole (17 mg, 4.1%) as an amorphous solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.95 (6H, q, *J* = 6.5 Hz), 1.39−1.46 (4H, m), 1.70−1.78 (4H, m), 2.83−2.88 (4H, m), 6.64 (1H, s), 6.77 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.7, 22.2, 26.5, 29.5, 100.5, 101.5, 147.5, 148.9, 151.8, 175.5.

5,5′-Dihexyl-3,3′-bisisoxazole (2). Method A. Dichloroglyoxime (324 mg, 2.06 mmol, 1.0 equiv), 1-octyne (682 mg, 6.19 mmol, 3.0 equiv) and 30% $KHCO_3$ (17.8 mmol, 5.96 mL, 8.66 equiv) were used. Filtration afforded **2** (376 mg, 60%) as a yellow solid.

Method B. Dichloroglyoxime (324 mg, 2.06 mmol, 1.0 equiv), 1-octyne (682 mg, 6.19 mmol, 3.0 equiv) and 30% $KHCO_3$ (17.8 mmol, 5.96 mL, 8.66 equiv) were used. Flash chromatography (5% EtOAc/petrol) afforded **2** (481 mg, 76%) as colorless crystals; mp 66−67 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91−0.88 (6H, m), 1.33−1.29 (8H, m), 1.39 (4H, t, *J* = 7.0 Hz), 1.76−1.70 (4H, m), 2.81 (4H, t, *J* = 7.5 Hz), 6.48 (2H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 22.6, 26.8, 27.5, 28.8, 31.5, 99.2, 154.6, 174.9; HRMS (ESI) calcd for $C_{18}H_{28}N_2O_2Na$ $[M+Na]^+$ 327.2043. Found 327.2045.

5,5′-Dioctyl-3,3′-bisisoxazole (3). Method A. Dichloroglyoxime (150 mg, 0.95 mmol, 1.0 equiv), 1-decyne (396 mg, 2.86 mmol, 3.0

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equiv), and 30% $KHCO_3$ (8.27 mmol, 2.76 mL, 8.66 equiv) were used. Filtration afforded **3** (220 mg, 64%) as a white solid.

Method B. Dichloroglyoxime (150 mg, 0.95 mmol, 1.0 equiv), 1-decyne (396 mg, 2.86 mmol, 3.0 equiv), and 30% $KHCO_3$ (8.27 mmol, 2.76 mL, 8.66 equiv) were used. Flash chromatography (5% EtOAc/petrol) afforded **3** (229 mg, 66%) as colorless crystals. Data for **3**: mp 69−70 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87−0.85 (6H, t, J = 5.5 Hz), 1.33−1.23 (16H, m), 1.38−1.32 (4H, m), 1.74−1.69 (4H, m), 2.78 (4H, t, J = 6.5 Hz), 6.46 (2H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 22.6, 26.6, 27.3, 28.9, 29.0, 29.1, 31.7, 99.0, 154.4, 174.8; HRMS (ESI) calcd for $C_{22}H_{36}N_2O_2Na$ $[M+Na]^+$ 383.2669. Found 383.2670.

*5,5′-Dicyclohexyl-3,3′-bisisoxazole (**4**). Method A.* Dichloroglyoxime (75.0 mg, 0.47 mmol, 1.0 equiv), cyclohexylacetylene (119 mg, 1.09 mmol, 2.30 equiv), and 30% $KHCO_3$ (4.13 mmol, 1.38 mL, 8.60 equiv) were used. Filtration afforded **4** (95 mg, 66%) as a yellow−white solid.

Method B. Dichloroglyoxime (75.0 mg, 0.47 mmol, 1.0 equiv), cyclohexylacetylene (119 mg, 1.09 mmol, 2.30 equiv), and 30% $KHCO_3$ (4.13 mmol, 1.38 mL, 8.60 equiv) were used. Flash chromatography (5% EtOAc/petrol) afforded **4** (100 mg, 69%) and the 4,5′-regioisomer (9.85 mg, 6.9%) as colorless crystals. Data for **4**: mp 152−153 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.32−1.26 (2H, m), 1.37 (2H, tt, J = 3.0, 12.5 Hz), 1.57−1.43 (6H, m), 1.75−1.71 (2H, m), 1.82 (4H, dt, J = 3.5, 13.0 Hz), 2.08 (4H, dd, J = 3.5, 13.5 Hz), 2.83 (2H, tt, J = 3.0, 10.5 Hz), 6.44 (2H, d, J = 0.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.7, 25.8, 31.2, 36.4, 97.6, 154.5, 178.9; HRMS (ESI) calcd for $C_{18}H_{25}N_2O_2$ $[M+H]^+$ 301.1910. Found 301.1914.

*5,5′-Diphenyl-3,3′-bisisoxazole (**5**). Method A.* Dichloroglyoxime (358 mg, 2.28 mmol, 1.0 equiv), phenylacetylene (699 mg, 6.85 mmol, 3.0 equiv), and 30% $KHCO_3$ (19.7 mmol, 9.20 mL, 8.66 equiv) were used. Filtration afforded **5** (610 mg, 93%) as a white solid.

Method B. Dichloroglyoxime (358 mg, 2.28 mmol, 1.0 equiv), phenylacetylene (699 mg, 6.85 mmol, 3.0 equiv), and 30% $KHCO_3$ (19.7 mmol, 9.20 mL, 8.66 equiv) were used. Flash chromatography (5% EtOAc/petrol) afforded **5** (592 mg, 90%) as colorless crystals; mp 195−196 °C; lit.[17] 199 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.09 (2H, s), 7.53−7.47 (6H, m), 7.87−7.85 (4H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 97.8, 126.1, 129.2, 130.8, 155.1, 171.2, 155.1; HRMS (ESI) calcd for $C_{18}H_{12}N_2O_2Na$ $[M+Na]^+$ 311.0791. Found 311.0796; UV−vis, 10 μM dichloromethane solution, λ_{max} = 272 nm, ε = 54000 M^{-1} cm^{-1}.

*5,5′-Di-(4-fluorophenyl)-3,3′-bisisoxazole (**6**). Method A.* Dichloroglyoxime (115 mg, 0.73 mmol, 1.0 equiv), 1-ethynyl-4-fluorobenzene (262 mg, 2.18 mmol, 3.0 equiv), and 30% $KHCO_3$ (6.25 mmol, 2.08 mL, 8.60 equiv) were used. Filtration afforded **6** (190 mg, 80%) as a yellow−white solid.

Method B. Dichloroglyoxime (115 mg, 0.73 mmol, 1.0 equiv), 1-ethynyl-4-fluorobenzene (262 mg, 2.18 mmol, 3.0 equiv), and 30% $KHCO_3$ (6.25 mmol, 2.08 mL, 8.60 equiv) were used. Flash chromatography (10% EtOAc/petrol) afforded **6** (158 mg, 69%) and the 4,5′-regioisomer (5 mg, 2.0%) as yellow crystals. Data for **6**: mp 257−259 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.03 (2H, s); 7.21 (4H, t, J = 8.5 Hz), 7.85 (4H, dd, J = 5.5, 8.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 97.6, 116.4, 116.6, 123.4, 128.3, 155.1, 163.2, 165.2, 170.2; HRMS (ESI) calcd for $C_{18}H_{10}F_2N_2NaO_2$ $[M+Na]^+$ 347.0603. Found 347.0611; UV−vis, 10 μM dichloromethane solution, λ_{max} = 271 nm, ε = 46000 M^{-1} cm^{-1}.

*5,5′-Di-(2-methylphenyl)-3,3′-bisisoxazole (**7**). Method A.* Dichloroglyoxime (100 mg, 0.64 mmol, 1.0 equiv), 2-ethynyl toluene (317 mg, 1.91 mmol, 3.0 equiv), and 30% $KHCO_3$ (5.51 mmol, 1.84 mL, 8.60 equiv) were used. Filtration afforded **7** (153 mg, 76%) as a yellow−white solid.

Method B. Dichloroglyoxime (100 mg, 0.64 mmol, 1.0 equiv), 2-ethynyl toluene (317 mg, 1.91 mmol, 3.0 equiv), and 30% $KHCO_3$ (5.51 mmol, 1.84 mL, 8.60 equiv) were used. Flash chromatography (5% EtOAc/petrol) afforded **7** (190 mg, 94%) and the 4,5′-regioisomer (7.4 mg, 4%) as colorless crystals. Data for **7**: mp 121−123 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.58 (6H, s), 7.02 (2H, s), 7.33−7.41 (6H, m), 7.79−7.81 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5, 100.8, 126.40, 126.49, 128.5, 130.4, 131.5, 136.4, 154.7, 171.0; HRMS (ESI) calcd for $C_{20}H_{16}N_2O_2Na$ $[M+Na]^+$ 339.1104. Found 339.1097; UV−vis, 10 μM dichloromethane solution, λ_{max} = 250 nm, ε = 16000 M^{-1} cm^{-1}; Fluorescence, 10 μM dichloromethane solution, λ_{max} = 327 nm (irradiated at 275 nm).

*5,5′-Di-(4-methylphenyl)-3,3′-bisisoxazole (**8**). Method A.* Dichloroglyoxime (75.0 mg, 0.47 mmol, 1.0 equiv), 4-ethynyltoluene (127 mg, 1.09 mmol, 2.30 equiv), and 30% $KHCO_3$ (4.13 mmol, 1.38 mL, 8.60 equiv) were used. Filtration afforded **8** (130 mg, 86%) as a light brown solid.

Method B. Dichloroglyoxime (75.0 mg, 0.47 mmol, 1.0 equiv), 4-ethynyltoluene (127 mg, 1.09 mmol, 2.30 equiv), and 30% $KHCO_3$ (4.13 mmol, 1.38 mL, 8.60 equiv) were used. Flash chromatography (10% EtOAc/petrol) afforded **8** (92 mg, 61%) as a colorless crystals; mp 249−250 °C; lit.[15] 251−253 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.42 (6H, s), 7.02 (2H, s), 7.30 (4H, dd, J = 0.5, 8.0 Hz), 7.74 (4H, dd, J = 1.5, 8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.6, 97.2, 124.4, 126.0, 129.9, 141.1, 155.1, 171.3; HRMS (ESI) calcd for $C_{20}H_{16}N_2O_2Na$ $[M+Na]^+$ 339.1104. Found 339.1129; UV−vis, 10 μM dichloromethane solution, λ_{max} = 277 nm, ε = 50000 M^{-1} cm^{-1}; Fluorescence, 10 μM dichloromethane solution, λ_{max} = 370 nm (irradiated at 300 nm).

*5,5′-Di-(2,3,4,6-tetra-O-acetyl-α-D-mannopyranosyloxymethyl)-3,3′-bisisoxazole (**9**). Method A.* Not successful.

Method B. Dichloroglyoxime (50.0 mg, 0.31 mmol, 1.0 equiv), propargyl 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside[33] (283 mg, 0.73 mmol, 2.30 equiv), and 30% $KHCO_3$ (2.75 mmol, 0.92 mL, 8.60 equiv) were used. Flash chromatography (50−70% EtOAc/petrol) afforded **9** (174 mg, 64%) as an amorphous solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.99 (6H, s), 2.05 (6H, s), 2.11 (6H, s), 2.16 (6H, s), 4.02−4.07 (2H, m), 4.09 (2H, dd, J = 2.5, 12.5 Hz), 4.29 (2H, dd, J = 5.5, 12.5 Hz), 4.81 (4H, q, J = 14.0 Hz), 4.98 (2H, d, J 2.0 Hz), 5.28−5.35 (6H, m), 6.85 (2H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.7, 20.83, 20.88, 20.9, 60.1, 62.4, 68.8, 69.32, 69.36, 97.6, 102.4, 154.3, 168.7, 169.8, 169.9, 170.0, 170.7; HRMS (ESI) calcd for $C_{36}H_{44}N_2O_{22}Na$ $[M+Na]^+$ 879.2278. Found 879.2269.

*4,4′,5,5′-Tetramethoxycarbonyl-3,3′-bisisoxazole (**10**). Method A.* Dichloroglyoxime (75.0 mg, 0.47 mol, 1.0 equiv), dimethylacetylene dicarboxylate (156 mg, 1.09 mmol, 2.30 equiv), and 30% $KHCO_3$ (4.13 mmol, 1.38 mL, 8.60 equiv) were used. Filtration afforded **10** (119 mg, 77%) as a yellow−white solid.

Method B. Dichloroglyoxime (75.0 mg, 0.47 mol, 1.0 equiv), dimethylacetylene dicarboxylate (156 mg, 1.09 mmol, 2.30 equiv), and 30% $KHCO_3$ (4.13 mmol, 1.38 mL, 8.60 equiv) were used. Flash chromatography (5% EtOAc/petrol) afforded **10** (141 mg, 91%) as colorless crystals; mp 164−166 °C; lit.[17] 167−168; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.84 (6H, s), 4.05 (6H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 53.2, 53.8, 115.9, 152.1, 156.0, 159.6, 160.9; HRMS (ESI) calcd for $C_{14}H_{12}N_2O_{10}Na$ $[M+Na]^+$ 391.0384. Found 391.0386.

*[Ir(ppy)$_2$(5,5′-diphenyl-3,3′-bisisoxazole)]BF$_4$ (**11**).* A solution of silver tetrafluoroborate (18.2 mg, 93 μmol) and $[Ir(ppy)_2Cl]_2$ (50 mg, 47 μmol) in acetonitrile (10 mL) was stirred in the dark for 3 h. The solution was filtered and the filtrate evaporated to dryness under reduced pressure. The yellow solid residue was added to 5,5′-diphenyl-3,3′-bisisoxazole (27 mg, 94 μmol) in 2-ethoxyethanol (3 mL) and the mixture was heated at reflux under an inert atmosphere overnight. The mixture was cooled to room temperature and water (5 mL) was added. The precipitate was collected by filtration and washed with ether (10 mL) then pentane (10 mL) to give **11** as a brown solid (43 mg, 53%). A sample for analysis was prepared by recrystallization from dichloromethane/pentane. Single crystals suitable for X-ray analysis were grown by evaporation of a dichloromethane/pentane solvent solution. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.30 (2H, dd, J = 7.6, 1.0 Hz), 6.92 (2H, td, J = 7.5, 1.3 Hz), 7.06 (2H, td, J = 7.6, 1.2 Hz), 7.13 (2H, ddd, J = 7.3, 5.9, 1.4 Hz), 7.43−7.47 (6H, m), 7.67 (2H, dd, J = 7.9, 1.2 Hz), 7.79 (4H, dd, J = 8.0, 1.7 Hz), 7.82−7.85 (4H, m), 7.94 (2H, dd, J = 8.7, 1.3 Hz), 8.28 (2H, s); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 101.7, 119.7, 123.4, 123.7, 124.5, 125.4, 126.8, 129.4, 130.3, 132.0, 132.2, 138.6, 142.6, 144.2, 150.2, 156.5, 167.9, 174.6; HRMS (ESI) calcd for $C_{40}H_{28}N_4O_2Ir$ $[M]^+$ 789.1842. Found 789.1844. Calcd for

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$C_{22}H_{16}N_2Ir$ [M-(5,5′-diphenyl-3,3′-bisisoxazole)]$^+$ 501.0943 Found 501.0967. Found: C, 54.82; H, 3.43; N, 6.30; Calcd for $C_{40}H_{28}N_4O_2IrBF_4$: C, 54.86; H, 3.22; N, 6.40.

*[Ir(ppy)$_2$(5,5′-dibutyl-3,3′-bisisoxazole)]BF$_4$ (**12**).* 5,5′-Dibutyl-3,3′-bisisoxazole (18.8 mg, 76 μmol) was added to a mixture of $[Ir(ppy)_2(CH_3CN)_2]BF_4$ (47.1 mg, 70 μmol) in 2-ethoxy ethanol (3 mL). The mixture was sparged with N_2 for 30 min then heated at reflux under an atmosphere of N_2 overnight. The yellow solution was cooled to room temperature and hexane (5 mL) was added. The precipitate was collected by filtration and washed with hexane (20 mL) to yield **12** as a dark yellow solid (43.4 mg, 74%). Single crystals suitable for X-ray analysis were grown by diffusion of vapors between a dichloromethane solution of the complex and pentane. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.86 (3H, t, J = 7.4 Hz), 1.26−1.32 (2H, m), 1.63−1.69 (2H, m), 2.79 (2H, sextet, J = 7.8 Hz), 6.24, (1H, dd, J = 7.7, 0.8 Hz), 6.87 (1H, td, J = 7.5, 1.3 Hz), 7.01 (1H, td, J = 7.5, 1.2 Hz), 7.13 (1H, ddd, J = 7.4, 5.9, 1.5 Hz), 7.48 (1H, t, J = 0.8 Hz), 7.63 (1H, dd, J = 7.8, 1.3 Hz), 7.70 (1H, ddd, J = 5.8, 1.5, 0.8 Hz), 7.83 (1H, ddd, J = 8.2, 7.4, 1.5 Hz), 7.91 (1H, dt, J = 7.7, 0.7 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.6, 22.2, 27.0, 29.0, 103.2, 119.5, 123.2, 123.6, 124.4, 130.2, 131.9, 138.4, 142.8, 144.1, 150.1, 156.0, 167.7, 179.6; HRMS (ESI) calcd for $C_{36}H_{36}N_4O_2Ir$ [M]$^+$ 749.2468. Found 749.2451. Calcd for $C_{22}H_{16}N_2Ir$ [M-(5,5′-dibutyl-3,3′-bisisoxazole)]$^+$ 501.0943. Found 501.0963. Found: C, 50.43; H, 4.26; N, 6.45; Calcd for $C_{36}H_{36}N_4O_2IrBF_4.H_2O$: C, 50.65; H, 4.49; N, 6.56.

*[Re(CO)$_3$(5,5′-diphenyl-3,3′-bisisoxazole)Br] (**13**).* 5,5′-Diphenyl-3,3′-bisisoxazole (70.8 mg, 245 μmol) was added to a mixture of $[Re(CO)_5Br]$ (100 mg, 247 μmol) in toluene (3 mL) and the mixture was heated at reflux for 4 h under an atmosphere of N_2. Upon reaching temperature the solution turned yellow/orange within minutes. The solution was cooled to room temperature and pentane (10 mL) was added. The yellow precipitate was collected by filtration and washed with pentane (20 mL), then dried *in vacuo* to yield **13** as a yellow powder (142 mg, 90%). Single crystals suitable for X-ray analysis were grown by diffusion of vapors between a dichloromethane solution of the complex and pentane. The poor solubility of this complex in noncoordinating solvents (e.g., $CDCl_3$, benzene, acetone) prevented the acquisition of NMR spectra. HRMS (ESI) calcd for $C_{21}H_{12}N_2O_5Re$ [M-Br]$^+$ 559.0304. Found 559.0316. IR (CH_2Cl_2 solution) υ (CO) 2037, 1946, 1913 cm^{-1}.

*[Re(CO)$_3$(5,5′-dibutyl-3,3′-bisisoxazole)Br] (**14**).* 5,5′-Dibutyl-3,3′-bisisoxazole (62 mg, 250 μmol) was added to a mixture of $[Re(CO)_5Br]$ (102 mg, 250 μmol) in toluene (3 mL) and the mixture was heated at reflux for 3 h under an inert atmosphere. Upon reaching temperature the solution turned yellow/orange within minutes. The solution was cooled to room temperature and pentane (20 mL) added. The precipitate was collected by filtration and washed with pentane, then dried *in vacuo* to yield **14** as a bright yellow powder (123 mg, 82%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.99 (6H, t, J = 7.4 Hz), 1.47 (4H, sextet, J = 7.4 Hz), 1.79 (4H, quintet, J = 7.7, 2.9 Hz), 2.96 (4H, triplet, J = 7.8 Hz), 6.65 (2H, s); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 13.7, 22.3, 27.0, 29.3, 100.8, 155.1, 179.3, 185.3, 194.1; HRMS (ESI) calcd for $C_{19}H_{23}N_3O_5Re$ [M-Br+CH_3CN]$^+$ 560.1195. Found 560.1187. Calcd for $C_{17}H_{20}N_2O_5Re$ [M-Br]$^+$ 519.0930. Found 519.0927. Found: C, 34.16; H, 3.37; N, 4.70; Calcd for $C_{17}H_{20}N_2O_5ReBr$: C, 34.12; H, 3.37; N, 4.68; IR (CH_2Cl_2 solution) υ (CO) 2036, 1944, 1910 cm^{-1}.

X-ray Crystallography. Crystals of compounds **4**, **11**, **12**, and **14** were mounted in low temperature oil then flash cooled. Intensity data were collected at 130 K (unless otherwise stated) on an X-ray diffractometer with CCD detector using Cu−Kα (λ = 1.54184 Å) or Mo−Kα (λ = 0.71073 Å) radiation. Data were reduced and corrected for absorption.[34] The structures were solved by direct methods and difference Fourier synthesis using the SHELX suite of programs[35] as implemented within the WINGX[36] software. Thermal ellipsoid plots were generated using the program ORTEP-3.

Crystal Data for Compound 5. $C_{18}H_{12}N_2O_2$ M = 288.30, T = 130.0(1) K, λ = 1.54184, triclinic, space group P-1 a = 5.8521(2), b = 8.9267(3), c = 13.1255(5) Å, α = 98.920(3), β = 91.029(3), γ = 96.137(3), V = 673.08(4) Å^3, Z = 2, D_c = 1.422 Mg M^{-3} μ(Cu−Kα) 0.767 mm^{-1}, F(000) = 300, crystal size 0.58 × 0.23 × 0.08 mm. 9255 reflections measured, 2418 independent reflections (R_{int} = 0.0156), the final R was 0.0324 [I > 2σ(I)] and $wR(F^2)$ (all data) was 0.0878. CCDC 935274.

Crystal Data for Compound 11. $C_{40}H_{28}BF_4N_4O_2Ir.(CH_2Cl_2)$ M = 960.60, T = 130.0(1) K, λ = 0.71073, monoclinic, space group $P2_1/c$ a = 13.5470(2), b = 14.1554(2), c = 19.7922(3) Å, β = 96.101(2), V = 3773.9(1) Å^3, Z = 4, D_c = 1.691 Mg M^{-3} μ(Mo−Kα) 3.742 mm^{-1}, F(000) = 1888, crystal size 0.49 × 0.24 × 0.12 mm. 39752 reflections measured, 14989 independent reflections (R_{int} = 0.0326), the final R was 0.0295 [I > 2σ(I)] and $wR(F^2)$ (all data) was 0.0664. CCDC 935275.

Crystal Data for Compound 12. $C_{36}H_{36}BF_4N_4O_2Ir$ M = 835.70, T = 115.0(1) K, λ = 0.71073, triclinic, space group P-1 a = 10.3409(3), b = 10.4801(4), c = 15.8279(5) Å, α = 85.762(3), β = 88.992(3), γ = 73.461(3)°, V = 1639.85(9) Å^3, Z = 2, D_c = 1.692 Mg M^{-3} μ(Mo−Kα) 4.134 mm^{-1}, F(000) = 828, crystal size 0.60 × 0.32 × 0.13 mm. 12621 reflections measured, 5775 independent reflections (R_{int} = 0.0405), the final R was 0.0337 [I > 2σ(I)] and $wR(F^2)$ (all data) was 0.0831. CCDC 935273.

Crystal Data for Compound 14. $C_{21}H_{12}BrN_2O_5Re$ M = 638.44, T = 130.0(1) K, λ = 1.54184, monoclinic, space group $P2_1/c$ a = 21.8354(7) b = 12.8132(4), c = 7.0674(2) Å, β = 92.155(3), V = 1975.9(1) Å^3, Z = 4, D_c = 2.146 Mg M^{-3} μ(Cu−Kα) 14.730 mm^{-1}, F(000) = 1208, crystal size 0.23 × 0.07 × 0.03 mm. 7192 reflections measured, 3882 independent reflections (R_{int} = 0.0367), the final R was 0.0431 [I > 2σ(I)] and $wR(F^2)$ (all data) was 0.1193. CCDC 935276.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Emission spectra of bisisoxazoles **5**−**8** (Figure S1); absorbance and emission spectra of organometallic complexes **11**−**14** (Figures S2−4); final atomic coordinates of **5** and **11**−**13** (Tables S1−4); copies of ^{1}H and ^{13}C NMR spectra of all compounds except complex **13**. Crystallographic data can be obtained from the Cambridge Crystallographic Data Centre via the Internet at http://www.ccdc.cam.ac.uk. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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