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FULL PAPER

Photoactivated functionizable tetracarbonyl phenylpyridine manganese(I) complexes as CO-releasing molecules: a direct Suzuki–Miyaura cross-coupling on a thermally-stable CO-RM

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Keywords: Carbon monoxide / CO-RM/irradiation / morpholine / Suzuki-Miyaura

A new class of carbon monoxide-releasing molecules (CO-RMs) are reported based on a previously known tetracarbonyl phenylpyridine manganese(I) motif. A pre-functionalized CO-RM undergoes a direct Pd-catalysed Suzuki–Miyaura cross-coupling with phenylboronic acid to give a π-extended three-ring CO-RM. Cross-coupling conditions were modified to allow coupling of a morpholine-containing boronic acid on to a CO-RM, introducing drug-like functionality. An LED system was used to facilitate controlled CO-release. Irradiation using an LED (400 nm or 365 nm) gives rise to faster CO-release, with lower overall input power compared to traditional use of a TLC lamp (365 nm), as measured by an assay based on the conversion of deoxymyoglobin to carbonmonoxymyoglobin.

Introduction

Despite its deserved reputation as a highly toxic gas, carbon monoxide has been identified as having a wide variety of therapeutic benefits, including increased healing rates, vasodilation and inhibition of bacterial growth.[1],[2] A considerable number of studies have probed the biological effects of CO and clinical trials based on CO inhalation have been performed to investigate the anti-inflammatory effects.[3] An alternative method to harness the beneficial effects of CO is to use a molecular compound which has the ability to carry and subsequently liberate the gas. A wide range of such carbon monoxide-releasing molecules (CO-RMs)[4] have been prepared and in a pivotal series of experiments Motterlini demonstrated that transition metal-based CO-RMs were able to mimic the effects of CO.[5]

CO-RMs may be thought of as a pro-drug, *i.e.* a means of delivering the CO to a biological target. Therefore for a CO-RM to be effective, liberation of CO is required which may be promoted through a number of different stimuli. Thermal stimulus of a molecule that liberates CO when in solution is perhaps the most direct method to initiate release. It may be envisaged that with appropriate design, optimal CO release rates and could be obtained. It should however, be noted that the mechanistic processes which underpin such pathways may be complex.[6]

The liberation of CO from a CO-RM may also be promoted by a chemical trigger such as an enzyme. A number of enzyme-triggered CO-RMs (ET-CORMs) have been developed in which a ligand within the coordination sphere of a metal complex is modified by an appropriate enzyme triggering the CO-release process.[7] It should also be noted that CO-RM3 has been shown to bind to lysozyme[8] and that $[Mn(CO)_4(S_2CNMe\{CH_2CO_2H\})]$, a CO-RM developed by Mann and co-workers, is stable in phosphate buffered saline for several hours[9] however, in the presence of myoglobin CO is rapidly released.

Photochemically stimulated liberation of CO from CO-RMs has received considerable recent attention.[10] So-called PhotoCO-RMs do not degrade significantly over a short period of time, either thermally or in the presence of a CO binder such as myoglobin. The release of CO from photoCO-RMs may be controlled by the light intensity as well as CO-RM concentration. Although topical applications of CO-RMs (*e.g.* skin treatments) would in theory allow lower wavelengths to be used (~400 nm), for use in tissue long wavelengths are needed (> 550 nm).Indeed, the development of photoCORMS which are activated by low-energy light is an area of focus.[10l, 11]

PhotoCO-RMs have also found applications as potential antibiotics. We have recently described a tryptophan-substituted manganese complex (TryptoCORM) which undergoes CO-dissociation when exposed to light with a wavelength of 400 nm.[12] Under these conditions TryptoCORM is highly effective at inhibiting the growth of *Escherichia coli*, whilst being non-toxic to mammalian cells. Poole and Schatzschneider have demonstrated the antibacterial activity of $[Mn(CO)_3(tpa\text{-}\kappa^3N)]^+$ (tpa = *tris*(2-pyridylmethyl)amine) when irradiated at 365 nm.[13]

This paper reports the development of photoactivated CO-RMs, based on a tetracarbonyl phenylpyridine manganese(I) scaffold. Having readily accessible, functionalisable ligand scaffolds will provide a modular approach for the synthesis of a large range of analogues.[10b] Importantly, the installation of synthetic handles onto the ligand allow for late stage functionalisation to be carried out, the thermal sensitivity of the

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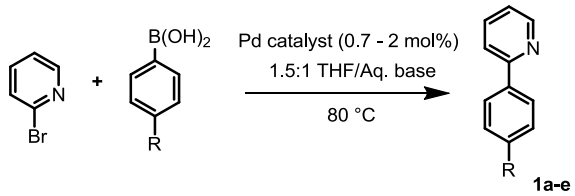
'$Mn(CO)_4$' motif require very mild conditions to prevent degradation.

The parent non-functionalised compound prepared by Bruce and co-workers has been expanded here to include a series of substituents.[14] These were prepared to assess how ligand structural changes affect the ability of the '$Mn(CO)_4$' motif to release CO.

Results and Discussion

Initial experiments were used to establish if the tetracarbonyl phenylpyridine manganese(I) complex would be a strong candidate for further functionalisation, by preparing a series of complexes with varying substituents in the 4-position of the phenyl ring. This position was chosen so that attached groups would not sterically interfere with the manganese(I) centre, or give isomers when reacted with $BnMn(CO)_5$.



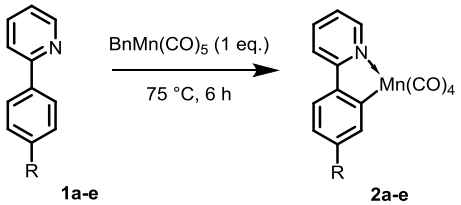
Scheme 1. General reaction scheme for the preparation of substituted phenyl pyridine ligands; R =H (**1a**), F (**1b**), Cl (**1c**), Br (**1d**), Ph (**1e**). Compound **1a** is commercially available.

Table 1. Synthesis details for ligands **1b-e**.

Entry	R	Catalyst	Base	% Yield
1b	F	AB cat (0.7 mol %)	$Na_2CO_{3(aq)}$	79
1c	Cl	$Pd(PPh_3)_4$ (2 mol %)	$K_2CO_{3(aq)}$	83
1d	Br	$Pd(PPh_3)_4$ (2 mol %)	$Na_2CO_{3(aq)}$	59
1e	Ph	$Pd(PPh_3)_4$ (2 mol %)	$Na_2CO_{3(aq)}$	59

A series of Suzuki–Miyaura cross-couplings were used to prepare the desired 2-aryl-pyridine ligands for use in the cyclometallation reactions (Scheme 2), the conditions are outlined in Table 1. For compounds **1c**-**1e**, $Pd(PPh_3)_4$ was used as the catalyst. For fluorinated compound **1b** an alternative di-nuclear pyridyl-bridged palladium catalyst was used.[15] The 2-arylpyridines were then used in a cyclometallation reaction with $BnMn(CO)_5$, an efficient reagent for the addition of a manganese tetracarbonyl group to phenylpyridine.[16] This results in the formation of complexes **2a**-**2e**; the details of preparation and yields are shown in Scheme 3 and Table 2.

The manganese(I) complexes were isolated in moderate to excellent yields, following a simple filtration of the reaction solvent, followed by evaporation to give solid products. Further purification by column chromatography on silica-gel could be performed if required. Due to a slower rate of reaction in the synthesis of **2b** a further 0.2 equivalents of $BnMn(CO)_5$ was needed to ensure that a pure product was obtained.



Scheme 2. General reaction scheme for the preparation of CO-RMs **2a-e**. (R = H, F, Cl, Br, Ph).

Table 2. Yields obtained for complexes **2a-e**.

Entry	R	% Yield
2a	H	88
2b	F	43
2c	Cl	83
2d	Br	72
2e	Ph	72

Crystals of **2c** and **2d** were obtained by layering CH_2Cl_2 solutions with *n*-hexane. Crystals of $BnMn(CO)_5$ have also been obtained by sublimation. The three structures have been confirmed by X-ray crystallography, and all details are presented in the supplementary information. By way of an exemplar, the X-ray structure for complex **2d** is shown in Figure 1. It is interesting to note the C(14)-Mn(1)-C(12) bond angle of 168.51(8) ° is quite distorted from an ideal octahedron. This is due to the size of the phenylpyridine system, which forces the system to change geometry giving a N-Mn-C(11) bond angle of only 79.55(6) °. This geometry could play an important role in determining the properties of the CO-RM. The slight distortion could alter how electron density passes from the ligand to the metal, potentially altering the mode of CO-release.

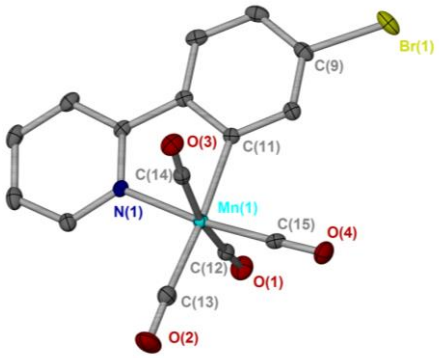


Figure 1. X-ray crystal structure of complex **2d**. Atoms displayed as ellipsoids at 50% probability. Hydrogen atoms have been omitted for clarity. Crystallised from CH_2Cl_2/hexane. Selected bond angles (°) and distances (Å): Mn(1)-C(11) = 2.0477(17) , Mn(1)-N(1) = 2.0638(14), Mn(1)-C(15) = 1.8007(18), Mn(1)-C(12) = 1.8642(19), Mn(1)-C(13) = 1.8401(19), Mn(1)-C(14) = 1.8544(19); C(14)-Mn(1)-C(12) = 168.51(8), C(13)-Mn(1)-C(12) = 95.58(8),C(11)-Mn(1)-C(15) = 93.25(7), C(13)-Mn(1)-N(1) =96.04(7), C(15)-Mn(1)-N(1) = 172.80(7), C(14)-Mn(1)-N(1) =90.03(7) , C(12)-Mn(1)-N(1) =88.03(7), N(1)-Mn(1)-C(11) = 79.55(6).

Myoglobin assay: determination of CO-release rates.

To assess how complexes **2a-e** release carbon monoxide, a myoglobin assay in phosphate buffered saline was carried out. The assay was left in the dark for an initial period of 45 mins in order to ascertain if the compounds are stable in the absence of light and in the presence of sodium dithionite and myoglobin.

Figure *2* shows the CO release profiles for complex **2a-e** using a conventional UV lamp (365 nm) placed above the sample for irradiation.

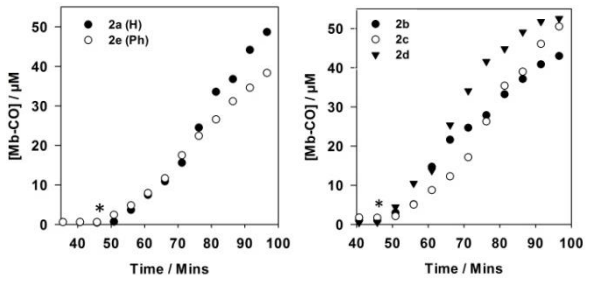


Figure 2. CO release from 40 μM **2a** and **2e** (left) and **2b-d** (right) using 50-60 μM myoglobin in a myoglobin assay. Irradiation with 365 nm TLC lamp. On for 2 min in a 5 min period. * indicates the start of irradiation cycles. 0-35 minutes omitted for clarity as no change is observed throughout this period.

These CO-RMs do not release any significant quantity of CO over a period of 45 minutes in the dark, even on the addition of sodium dithionite. However, following the onset of irradition CO release was observed. Complexes **2a** and **2e** have a similar initial rate of CO release. With irradiation of 40 μM CO-RM, 50 μM myoglobin is saturated with CO. It is evident that the addition of a phenyl group to the parent compound **2a** does not significantly alter the CO-releasing properties of the compound. This is potenially a desirable feature as the structure can be changed and the kinetics of CO release controlled by varying light intensity.

Comparing the halogen-substituted complexes **2b-d**, chloro complex **2c** initially releases slower than the other two complexes. The half life of each complex, defined as the time taken for a 40 μM solution of CO-RM to deliver 20 μM CO to myoglobin, has been calculated from the data in Figure 2 (Table 3). There does not appear to be a direct relationship between half-life and the molar absorption coefficient (Table 3) implying that the efficiency with which the absorbed light results in CO release is different from complex-to-complex.

Table 3. Half-life CO-release values for complexes **2a-e**, with irradiation at 365 nm using a benchtop TLC lamp. Molar absorption coefficients are also given in acetonitrile.

Entry	R	$t_{½}$ / mins	ε at 330 nm / mol^{-1} dm^{-3} cm^{-1}	ε at 365 nm / mol^{-1} dm^{-3} cm^{-1}	ε at 400 nm / mol^{-1} dm^{-3} cm^{-1}
2a	H	23	4054	2211	321
2b	F	17	4522	1893	175
2c	Cl	27	4534	2399	243
2d	Br	18	4872	2683	317
2e	Ph	30	13166	4747	885

Complex **2b** has the fastest $t_{½}$ value of 17 mins but is comparable with complex **2d** at 18 minutes. The amount of irradiation recieved in these experiments is 40% of the total time (2 mins on, 3 mins off), so theoretically the amount of irradiation required makes these times much shorter.

The variation in these results may arise from using a TLC lamp to irradiate the samples, leading us to exploit an LED system for all subsequent experiments. The LED irradiation system has been developed so that controlled light emission to CO-RM samples over a narrow wavelength range using high quality LEDs may be achieved.[10f] The system can monitor the current drawn from the LED so that the same light intensity can be used in repeat experiments.

Complexes **2c** and **2d** were taken forward for this study. The CO-RMs were used at concentrations of 10 and 40 μM using either 365 nm or 400 nm narrow-band LEDs drawing a power of 2.4 W. This was attached directly to the UV-vis cuvette so that a high percentage of light passes through the sample, unlike the conventional method of using a TLC lamp in which the bulb is too large to fit close to the cuvette.

Figure 3 shows a comparison of the 40μM CO-RM myoglobin assays for complexes **2c** and **d** when 365 nm, 400 nm LEDs and a TLC lamp are used for irradiation.

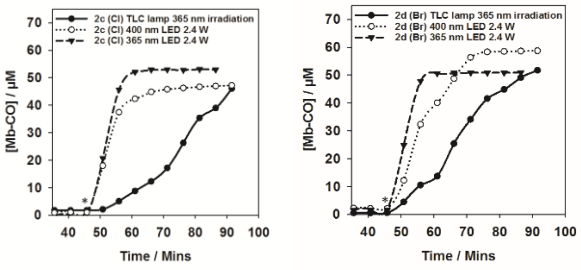


Figure 3. CO release from 40 μM CO-RM **2c** (left) and **2d** (right) using 50-60 μM myoglobin. Irradiation with 365 nm TLC lamp and LEDs (400 nm, 2.4 W and 365 nm, 2.4 W). On for 2m per 5m period. * indicates start of irradiation cycles. 0-35 minutes omitted for clarity as no change is observed throughout this period. Spline curves are added as a guide.

Irradiation from the LEDs is found to be significantly more efficient at the same concentration compared with use of the TLC lamp. The increased efficiency is apparent at both 365 nm and 400 nm using the LED system indicating that this is not simply a wavelength effect. This is especially the case for complex **2c** where the myoglobin is saturated with CO 25 mins before the same experiment with a TLC lamp. With the use of a 400 nm LED, the 20 μM $t_{½}$ value of both **2c** and **2d** is surpassed after just 2 irradiation cycles. Given that the input power of the LED is 2.4 W and that the input power of the TLC used was 6 W, these data demonstrate the efficency of the LED system at promoting CO-release even when irradiation is occuring away from the absorbance maximum.

Figure **4** shows the UV-vis spectrum for complex **2d** in MeCN, in addition to the clean deoxy- to carboxy-myoglobin conversion following irradiation by LED.

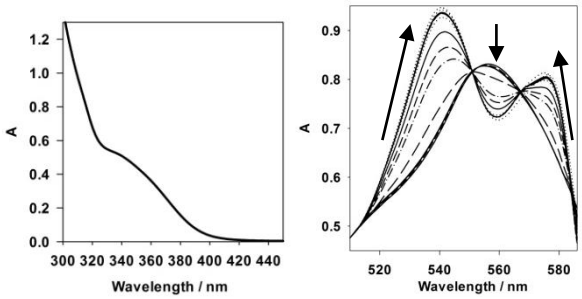


Figure 4. UV spectrum in MeCN at 1.125×10^{-4} mol dm^{-3} for CO-RM **2d** (left) and full spectral conversion from deoxy-Mb to carboxy-Mb (right) using 40 μM **2d** (spectra used to calculate the CO profile curve shown, right).

Another myoglobin assay was also carried out with complexes **2c** and **2d** to assess how many molecules of CO were released per molecule of CO-RM.

Figure *5* shows the 10 µM CO release profile for complexes **2c** and **d** and illustrates that the complexes release almost three molecules of CO per molecule of CO-RM. This is advantageous as a lower concentration of CO-RM is required to get the same amount of CO released.[5a] Complex **2d** releases faster than **2c** at 10 µM which tallies well with the 40 µM TLC lamp irradiation studies.

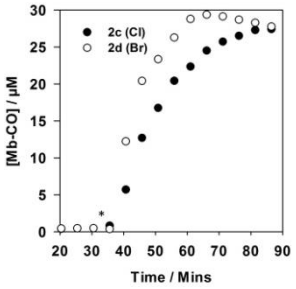
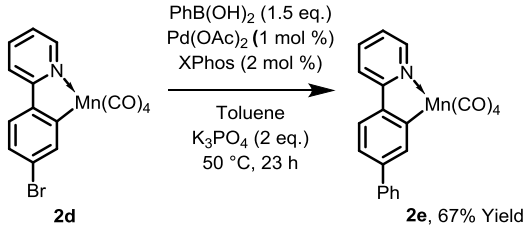


Figure 5. CO release from 10µM **2c** and **2d** using 50-60 µM myoglobin. Irradiation with LED (400 nm, 2.4 W). On for 2m per 5m period. *indicates start of irradiation cycles. 0-20 minutes omitted for clarity as no change is observed throughout this period.

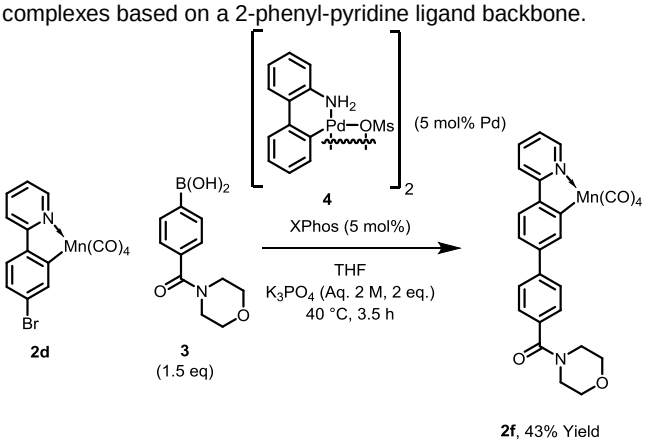
CO-RMs **2c** and **2d** contain an aryl halide motif, providing an opportunity to directly functionalise these CO-RMs and alter their properties. Highly electrophilic η-[5/6] metal (Cr/Mn/Fe) tricarbonyl fragments have previously been used to activate aryl-halides to the oxidative addition of Pd into C-X bonds and to facilitate cross-coupling.[17] So as a proof of concept **2e** was synthesised via a Pd-catalysed Suzuki–Miyaura cross-coupling reaction of **2d** with phenylboronic acid.[18] The optimized conditions are shown in
Scheme *3*.



Scheme 3. Direct Suzuki–Miyaura cross-coupling on **2d** to give arylated product **2e**.

The product **2e** was isolated in 67 % yield following chromatography on silica-gel. The product **2e** has been previously prepared by cyclometallation (Scheme 1) and comparison of ^{1}H and ^{13}C NMR, IR and LIFDI-MS data with the original reported synthesis confirm the presence of cross coupled product **1e** *via* a different route. Crucially the conditions employed here operate at 50 °C lower than those previously reported (100 °C)[18] as above 70 °C, **2e** suffers from considerable degradation.

Application of the previously developed conditions (Scheme 3) to a more challenging boronic acid (**3**) with **2d** however failed to provide any conversion to **2f**. Changing the precatalyst to the 2-aminobiphenylpalladium methanesulfonate dimer (**4**) in the presence of XPhos[19] allowed for **2f** to be isolated in 43% yield after only 3.5 hours at 40 °C (Scheme 4). This further exemplifies the utility of these mild reaction conditions for the late stage functionalisation of tetracarbonyl manganese(I) complexes based on a 2-phenyl-pyridine ligand backbone.



Scheme 4. Implementing a Suzuki-Miyaura cross-coupling with catalyst **4** and boronic acid **3** allows access to **2f** at 40 °C after only 3.5 hours.

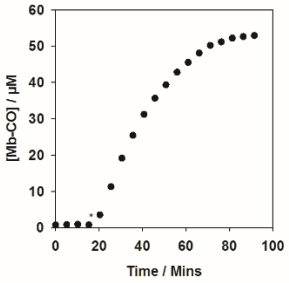


Figure 6. CO release from a 40 µM solution of CO-RM **2f** using 50-60 µM myoglobin. Irradiation with LED (400 nm, 2.4 W). On for 2 min per 5 min period. * indicates start of irradiation cycles.

Figure 6 shows a 40 µM assay of **2f**. This compound also shows stability in the dark in the presence of sodium dithionite and then degrades upon irradiation with the 400 nm LED, albeit at a slightly slower rate than **2c** and **2d**. Whereas **2c** and **2d** reached their half-lives within two irradaiton cycles, **2f** required four such cycles to surpass 20 µM Mb-CO, with a $t_{½}$ value of 14 minutes. This is in spite of ε values of 6872, 2158 and 796 mol^{-1} dm^{-3} cm^{-1} at 330, 365 and 400 nm respectively. This relatively slow release may be attributed to the relatively low water solubility of this compound, though the synthetic flexibility of this work should allow for more water-soluble compounds to be made.

Conclusions

A series of tetracarbonyl manganese(I) complexes based on a 2-phenyl-pyridine system have been prepared in two linear steps in good yield. The manganese(I) complexes release CO efficiently on irradiation at both 365 nm and 400 nm. They are stable in solution until irradiation is initiated, *e.g.* stable to thermal degradation / reaction with sodium dithionite. Other reported photoCO-RMs are stable in water, although susceptible to deleterious interactions with sodium dithionite.[20] PhotoCO-RMs **2a-f** have been found to be thermally stable under the conditions of the myoglobin assay.
Complex **2c** and **2d** were used at 10 µM concentrations in myoglobin assays and release three molecules of CO per CO-RM. The CO-RM can release the required CO at a lower

concentration compared to, for example, CO-RM-3 which only releases one productive CO ligand.

It has been demonstrated that complex **2d** can be functionalised by a direct Pd-catalysed cross-coupling reaction to generate complexes **2e** and **2f**. Late-stage functionalisation of **2d** could be extended to improve water solubility, further conjugation to increase the wavelength of CO release, and fluorescent tagging for cell microscopy studies. All of these aspects are currently being examined within our laboratories.

Experimental Section

General experimental details. All reactions were carried out under a nitrogen atmosphere unless otherwise stated. Chemical reagents were purchased from Sigma Aldrich, Alfa Aesar or Frontier Scientific and used as received. All dry solvents apart from methanol were obtained from a Pure Solv MD-7 solvent machine and were stored in ampules under nitrogen until required. Ether solvents used in reactions came from the same machine but were deoxygenated by sonication with nitrogen bubbling for 30 minutes. All TLC analysis was carried out using Merck 5554 silica plates and spots were visualised using UV light at 254 and 365 nm. Column chromatography was carried out using silica 60 gel purchased from Sigma Aldrich. Solution ^{1}H, and ^{13}C NMR analysis was carried out on Jeol ESC400, ESX400 and ECX500 spectrometers. These were operating at 400 MHz (^{1}H), 100 MHz (^{13}C) frequencies for the appropriate experiments. ^{1}H NMR spectra are reported in ppm(δ) and are referenced to the residual NMR solvent and were processed in MNova v.6 software. ($CHCl_3$: 7.26 ppm DMSO: 2.54 ppm). All chemical shifts in reported ^{13}C NMR spectra are reported in ppm (δ) and are referenced to the NMR solvent. ($CHCl_3$: 77.36 ppm, DMSO: 40.45 ppm). In some instances, the complexes did not prove to be sufficinetly stable to permit observation of the metal carbonyl resonance in the ^{13}C NMR spectrum. Mass Spectrometry was carried out using a Bruker microTOF instrument. All data was acquired in positive ion mode using ESI or LIFDI ionisation. High resolution spectrometry data is reported with less than 5 ppm error unless otherwise stated. All LIFDI data reported is within 120 ppm error. Melting points of all complexes and ligands were obtained on a Perkin Elmer DSC 7 machine. Experiments were all ran using a ramp rate of 10 °C min^{-1} to above the required melting temperature. The melting point was taken as the onset of the observed endothermic peak. IR spectra were taken using a Thermo-Nicolet Avatar-370 FT-IR spectrometer. Spectra were taken in either solid state (KBr Disc or ATR), or in solution using THF or methanol as solvents. UV-Visible spectroscopy for the myoglobin assay and molar absorption co-efficient determination was carried out on a JASCO V-560 spectrometer. A baseline in the required solvent was carried out prior to starting an assay. Photo-initiated carbon monoxide release was carried out using either a 365 nm 6W TLC lamp or a 5W 400 nm LED directly above the solution drawing 2.4 W of power. ABCat was prepared using a literature procedure by Fairlamb and co-workers.[15] $Pd(PPh_3)_4$ was prepared using a literature procedure by Coulson and co-workers.[21] 2-Aminobiphenylpalladium methanesulfonate dimer (**4**) was prepared using a literature procedure by Buchwald and co-workers.[19]

General procedure 1 - synthesis of 2-(4-bromo-phenyl)pyridine (1d).[15, 21] In a nitrogen atmosphere glove box, to an oven dried Schlenk tube equipped with a magnetic stirrer was added $Pd(PPh_3)_4$ (0.02 eq., 0.033 mmol, 38.3 mg). The Schlenk tube was removed from the glove box and was attached to a Schlenk line. Under a high flow of nitrogen was added 4-bromobenzene boronic acid (1.5 eq., 2.5 mmol, 502 mg), followed by 2-bromopyridine (1 eq., 1.66 mmol, 158 µl/260 mg). 1.9M $Na_2CO_{3\ (aq)}$ (6 ml) and THF (9 ml) was then added via syringe. The reaction was heated to 60 °C for 64 h. The reaction was allowed to cool and deionised water (40 ml) was added. The product was extracted with dichloromethane (3 × 40 ml), dried with $MgSO_4$ and filtered. The solvent was removed under reduced pressure to yield crude product. The crude product was purified using silica gel column chromatography using 90:10 PET ether/ethyl acetate as solvent. The solvent was removed to give a crystalline, slightly off white solid (231 mg, 59% Yield). MP (DSC): 64 °C ; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.69 (dd, *J* = 4.8, 1.0 Hz, 1H), 7.88 (d, *J* = 8.3 Hz, 2H), 7.76 (td, *J* = 8.0, 1.0 Hz, 1H), 7.70 (dd, *J* = 8.0 Hz, 1.0 Hz, 1H), 7.60 (d, *J* = 8.3 Hz, 2H), 7.28–7.23 (m, 1H (under ref. Peak)); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.6, 150.1, 138.5, 137.2, 132.2, 128.8, 123.8, 122.8, 120.7 ; Elemental Analysis (CHN) C : 56.15% H: 3.49% N: 5.77% (Calculated : C: 56.44% H: 3.34 % N: 5.98%); ESI-MS m/z = 233.9917 [M+H]+ (calc. for $C_{11}NH_9Br$ = 233.9913); IR (Pressed KBr disc) : 1581, 1556, 1458, 1426, 1389, 1147, 1095, 1066, 1001, 833, 772, 625, 539, 453 cm^{-1}.

2-(4-Fluoro-phenyl)pyridine (1b).[15, 21] **C**ompound **1e** was synthesised using general procedure 1 using ABcat (0.007 eq., 11.6 µm, 12.2 mg), 4-fluorobenzeneboronic acid (1.5 eq., 2.5 mmol, 502 mg). The product was isolated as a slightly off white solid (226 mg, 79% Yield). Note: ABcat is air stable as a solid and doesn't need to be weighed out in a glove box. ^{1}H NMR (400MHz, $CDCl_3$) δ: 8.67 (ddd, *J* = 4.8, 1.7, 1.0 Hz, 1H), 7.98 (dd, *J* = 9.0, 5.4 Hz 2H), 7.74 (td, *J* = 8.0, 1.7 Hz, 1H) , 7.67 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.22 (ddd, *J* = 8.3, 4.8, 1.0 Hz, 2H), 7.15 (apr. t, *J* = 9.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: δ: 163.6 (d, *J* = 248.2 Hz), 156.7, 150.0, 137.1, 136.6 (d, *J* = 3.0 Hz), 128.8 (d, *J* = 8.5 Hz), 122.3, 121.1, 115.7 (d, *J* = 22.0 Hz); Elemental Analysis (CHN) C: 76.79% H: 4.71% N: 7.95%(Calculated : C: 76.29% H: 4.66% N: 8.09%) ESI-MS *m/z* = 174.0717 $[M+H]^+$ (calc. for $C_{11}NH_9F$ = 174.0713).

2-(4-Chloro-phenyl)pyridine (1c).[15, 21] Compound **1d** was synthesised using general procedure 1 using 4-chlorobenzene boronic acid (1.5 eq., 2.5 mmol, 378 mg) and 2.0 M $K_2CO_{3(aq)}$ (6 ml).The product was isolated as a crystalline, slightly off white solid (261 mg, 83% Yield). MP(DSC): 51°C ; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.69 (dd, *J* = 4.6 Hz, 0.7 Hz, 1H), 7.94 (d, *J* = 8.5 Hz, 2H), 7.76 (td, *J* = 8.0, 1.8 Hz, 1H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.44 (d, *J* = 8.5 Hz, 2H), 7.27-7.22 (m, 1H (under ref. peak)); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.6, 150.1, 138.1, 137.2, 135.4, 129.3, 128.5, 122.8, 120.7; Elemental Analysis (CHN) C: 69.19% H: 4.30% N: 7.18%(Calculated : C: 69.67% H: 4.25% N: 7.39%)ESI-MS *m/z* = 190.0422 $[M+H]^+$ (calc. for $C_{11}NH_9Cl$ = 190.0418); IR (Pressed KBr disc): 1585, 1565, 1491, 1462, 1433, 1397, 1153, 1087, 1009, 985, 847, 829, 773, 734, 702, 676, 633, 613, 541, 491, 452 cm^{-1}.

2-(Biphenyl)pyridine (1e). [15, 21] Compound **1e** was synthesised using general procedure 1 (1.66 mmol of 2-bromopyridine) using biphenyl boronic acid (1.2 eq., 1.99 mmol, 331 mg). The product was isolated as a white solid (226 mg, 59% Yield). MP(DSC): 144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.72 (dt, *J* = 4.7, 1.1 Hz, 1H), 8.09 (d, *J* = 8.5 Hz, 2H), 7.81–7.75 (m, 2H), 7.72 (d, *J* = 8.5 Hz, 2H), 7.67 (d, *J* = 8.0 Hz, 2H), 7.47 (t, *J* = 8.0 Hz, 2H), 7.37 (t, *J* = 7.3 Hz, 1H), 7.26–7.22 (m, 1H (under ref. peak)); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.4, 150.1, 142.1, 141.0, 138.7, 137.1 129.2, 127.9, 127.8, 127.6, 127.5, 122.5, 120.9; Elemental Analysis (CHN): C: 87.84% H: 5.75% N: 5.92% (Calculated: C: 88.28% H: 5.67% N: 6.06%) ESI-MS *m/z* = 232.1122 $[M+H]^+$ (calc. for $C_{17}NH_{14}$= 232.1120); IR (Pressed KBr disc): 1603, 1595, 1584, 1570, 1556, 1487, 1464, 1448, 1430, 1400, 1296, 1181, 1149, 1058, 1035, 1003, 983, 906, 847, 786, 752, 711, 687, 644, 625, 608, 452 cm^{-1}.

Benzyl pentacarbonyl manganese^{I}. [22] To an oven-dried Schlenk tube equipped with a magnetic stirrer under nitrogen was added mercury (3 cm^3). Sodium metal (4 eq., 1.07 mmol, 246 mg) was added in small pieces with high stirring to allow dissolution. In a separate Schlenk tube under nitrogen was added $Mn_2(CO)_{10}$ (1 eq., 2.68 mmol, 1.04 g), followed by anhydrous, deoxygenated THF (40 ml). The THF solution was then transferred by cannula on to the sodium amalgam and was stirred for 3 hours. In a separate Schlenk tube equipped with a magnetic stirrer under nitrogen was added benzyl chloride (2 eq., 5.36 mmol, 617 µl / 678 mg). The Schlenk tube containing benzyl chloride was placed in an ice bath and put under vacuum with stirring for 60 seconds. At ambient temperature, the THF solution of $NaMn(CO)_5$ was transferred by cannula into the benzyl chloride. The mixture was stirred at ambient temperature (20 °C) for 20 h. The solution was then filtered through a bed of Celite™ and was washed with diethyl ether (5 × 20 ml). The contents were then

loaded on to silica gel and this was added on to a pad of silica (5 cm). The pad was washed with petroleum ether (3 × 40 ml). The solvent was removed to yield product contaminated with benzyl chloride. Benzyl chloride was removed at 35 °C under vacuum. The product must be broken up periodically with a spatula and put back under vacuum. A slightly yellow crystalline product was obtained. (1.18 g, 76% yield). MP (DSC): 40 °C; ^{1}H NMR (400 MHz, $CDCl_3$); δ: 7.18 (m, 4H), 6.97(m, 1H), 2.41 (s, 2H). IR (solution THF): 2107, 2047, 2009, 1987 cm^{-1}; ESI-MS *m/z:* 286.9748 $[M+H]^+$ (Calculated for $MnO_5C_{12}H_8$: 286.9747).

General procedure 2 - Synthesis of Tetracarbonyl (2-phenylpyridine-κ^{2}N,C^8)manganese^I (2a).[23] To an oven dried Schlenk tube equipped with a magnetic stirrer under nitrogen was added 2-phenylpyridine (1 eq., 1 mmol, 143 µl/ 155 mg), $BnMn(CO)_5$ (1 eq., 1 mmol, 286 mg) followed by dry deoxygenated *n*-hexane (16 ml). The mixture was heated with stirring for 6 h. The reaction mixture was allowed to cool to ambient temperature. The hexane solution was filtered through a pipette packed with cotton wool and removal of solvent under reduced pressure yielded a pure yellow crystalline solid (284 mg, 88% Yield). MP(DSC) : 114 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.72 (d, *J* = 5.5 Hz, 1H), 7.97 (d, *J* = 7.5 Hz, 1H), 7.87 (d, *J* = 8.1 Hz, 1H), 7.81–7.74 (m, 2H), 7.28 (td, *J* = 7.5, 1.0 Hz, 1H), 7.17 (td, *J* = 7.5, 1.5 Hz, 1H), 7.11 (ddd, *J* = 7.5, 5.5, 1.5 Hz, 1H): ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.9, 166.4, 153.9, 146.2, 141.7, 137.9, 130.3 124.2, 124.0, 122.4, 119.3. Elemental Analysis (CHN): C: 56.65% H: 2.98% N: 4.06% (Calculated: C: 56.10% H: 2.51% N: 4.36% LIFDI-MS *m/z* = 321.0202 $[M]^+$ (calc. for $MnC_{15}H_8NO_4$ = 320.9834). IR (Solution: THF): 2071, 1986, 1972, 1928, 1600, 1576, 1477 cm^{-1}.

Tetracarbonyl (2-(4-fluoro-phen)κ,C^2-pyridine-κ,N)Manganese^I (2b), Using the details from general procedure **2**, $BnMn(CO)_5$ (1 eq., 0.5 mmol, 143 mg), 2-(4-fluoro-phen-4-yl)pyridine (1 eq., 0.5 mmol, 86.5 mg) and *n*-hexane (8 ml) were used to prepare complex **2b**. After 6 h, the reaction mixture was allowed to cool to ambient temperature. CH_2Cl_2 (10 ml) was added to dissolve the yellow precipitate. The mixture was filtered through cotton wool and solvent was removed under reduced pressure to yield product containing 20% starting material (**1b**). The impure product was reacted with more $BnMn(CO)_5$ (0.2 eq.) at 75 °C in hexane for six hours. Addition of dichloromethane and filtration as previously mentioned yielded a pure yellow solid (74 mg , 43% Yield). MP(DSC): 163 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.69 (dt, *J* = 5.6, 1.2 Hz, 1H), 7.87–7.78 (m, 2H), 7.75 (dd, *J* = 8.5, 5.1 Hz, 1H), 7.68 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.06–7.15(m, 1H), 6.84 (td, *J* = 8.5, 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 179.6, 165.7, 163.6 (d, *J* = 256.0 Hz), 154.2, 142.4, 138.3, 127.0 (d, *J* = 18.0 Hz), 125.22 (d, *J* = 8.5 Hz), 122.5, 119.5, 111.3 (d, J = 23.0 Hz); Elemental Analysis (CHN) C: 52.94% H: 2.21% N: 3.98% (Calculated: C: 53.12% H: 2.08% N: 4.13%) ESI-MS *m/z* = 339.9827 $[M+H]^+$ (calc. for $MnC_{15}H_8FNO_4$= 339.9812). IR (Solution: THF): 2075, 1993, 1977, 1936, 1605, 1587, 1571, 1558, 1480, 1464, 1431, 1315, 1262, 1192 cm^{-1}.

Tetracarbonyl (2-(4-chloro-phenyl)κ,C^2-pyridine-κ,N)manganese^I (2c). Using the details from general procedure **2**, $BnMn(CO)_5$ (1 eq., 0.25 mmol, 72 mg), 2-(4-chloro-phenyl)pyridine(**1c**)(1 eq., 0.25 mmol, 50 mg) and *n*-hexane (4 ml) were used to prepare complex **2c**. At the end of the reaction, the reaction mixture was allowed to cool to ambient temperature. Dichloromethane (5 ml) was added to the mixture to dissolve the yellow precipitate. The solution was filtered through cotton wool packed in a pipette. Removal of solvent under reduced pressure gave pure product (82 mg, 83% Yield). MP (DSC): 161 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.71 (d, *J* = 4.3 Hz, 1H), 7.93 (s, 1H), 7.85–7.78 (m, 2H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.15(d, *J* = 6.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.2, 165.7, 154.2, 144.7, 140.7, 138.4, 136.8, 125.1, 124.6, 122.9, 119.7. Elemental Analysis (CHN) C: 50.53% H: 2.11% N: 3.72% (Calculated: C: 50.66% H: 1.98% N: 3.94%) LIFDI-MS *m/z* = 354.9831 $[M]^+$ (calc. for $MnC_{15}H_7ClNO_4$= 354.9444). IR (Solution: THF): 2077, 1993, 1978, 1936, 1605, 1567, 1543, 1478, 1424 cm^{-1}.

Tetracarbonyl (2-(4-bromo-phenyl)κ,C^2-pyridine-κ,N)manganese^I (2d). Using the details from general procedure **2**, $BnMn(CO)_5$ (1 eq., 0.75 mmol, 215 mg), 2-(4-bromo-phenyl)pyridine (1 eq., 0.75 mmol, 176 mg) and *n*-hexane (12 ml) were used to prepare complex **2d**. At the end of the reaction, the Schlenk tube was stored in the freezer (−18 °C) overnight. The product had precipitated out of solution and the hexane solution was removed with a pipette. The yellow/brown solid product was then dried under reduced pressure. (217 mg, 72% Yield).

MP (DSC): 208 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.71 (d, *J* = 5.6, 1H), 8.09 (d, *J* = 1.9 Hz, 1H), 7.88–7.78 (m, 2H), 7.61(d, *J* = 8.5 Hz, 1H), 7.31 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.15 (d, *J* = 6.7, 2.1 Hz, 1H); ^{13}C NMR (126 MHz $CDCl_3$) δ: 219.5, 214.0, 213.2, 178.6, 165.6, 154.0, 144.8, 143.3, 138.1, 127.2, 126.1, 125.1, 122.8, 119.5. Elemental Analysis (CHN) C: 44.97% H: 1.75% N: 3.39% (Calculated: C: 45.03% H: 1.76% N: 3.50%) ESI-MS *m/z* = 399.9017 $[M+H]^+$ (calc. for $MnC_{15}H_8BrNO_4$= 399.9012). IR (Solution: THF): 2075, 1992, 1977, 1936, 1259 cm^{-1}.

Tetracarbonyl (2-(biphenyl)κ,C^2-pyridine-κ,N)manganese^I (2e). Using the details from general procedure 2, compound **3**, $BnMn(CO)_5$ (1 eq., 0.5 mmol, 143 mg), 2-(biphenyl)pyridine (1 eq., 0.5 mmol, 116 mg) and *n*-hexane (8 ml) were used to prepare complex **2e**. At the end of the reaction, the reaction mixture was allowed to cool to ambient temperature. Dichloromethane (10 ml) was added to the mixture to dissolve the yellow precipitate. The solution was filtered through cotton wool packed in a pipette. Removal of solvent under reduced pressure gave pure product (144 mg, 72% Yield). MP(DSC): 138 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.74 (ddd, *J* = 6.0, 1.7, 1.0 Hz, 1H), 8.21 (d, *J* = 1.8 Hz, 1H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.83–7.77 (m, 1H), 7.77–7.70 (m, 2H), 7.48 (t, *J* = 7.6 Hz, 2H), 7.42 (dd *J* = 8.0, 1.8 Hz, 1H), 7.38 (t, *J* = 7.5 Hz, 1H), 7.13 (ddd, *J* = 7.5, 6.0, 1.4 Hz, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 175.6, 166.4, 154.2, 154.6, 142.8, 141.7, 140.2, 138.2, 129.1, 127.8, 124.6, 123.6, 122.6, 119.7; Elemental Analysis (CHN) C: 63.61 % H: 3.44 % N: 3.39 % (Calculated: C: 63.49% H: 3.04% N: 3.53%); LIFDI-MS *m/z* = 397.0349 $[M]^+$ (calc. for $MnC_{21}H_{12}NO_4$ = 397.0147). IR (Solution: THF): 2073, 1989, 1974, 1932, 1602, 1582, 1562, 1477, 1475 cm^{-1}.

Alternative synthesis of complex 2e *via* a cross-coupling reaction. This synthesis is based on a modified literature procedure.[18] **Precatalyst solution**: To a dry Schlenk tube was added $Pd(OAc)_2$ (1.0 eq., 22 µmol, 5 mg) and XPhos (2.0 eq., 45µmol, 21.2 mg) under a high flow of nitrogen. Dry, degassed THF (1 ml) was added to make a red stock solution of catalyst/ligand.

To a dry Schlenk tube equipped with a magnetic stirrer bar was added complex **2d** (1 eq., 0.125 mmol, 50 mg), phenyl boronic acid (1.5 eq., 0.188 mmol, 23 mg) and K_3PO_4 (2.0 eq., 0.250 mmol, 34 mg). The Schlenk tube was evacuated and backfilled with N_2 three times. Dry degassed toluene (1 ml) was added to the Schlenk tube and the contents were stirred for 5 minutes at ambient temperature. Catalyst stock solution (60 µl) giving $Pd(OAc)_2$ (1 mol%, 0.3 mg) and Xphos (2 mol%, 1.2 mg) was added *via* syringe to the Schlenk tube. The reaction mixture was then heated to 50 °C with vigorous stirring in the dark for 23 h. The reaction was quenched by cooling to ambient temperature. This was then filtered through a pipette packed with Celite™ and subsequently filtered through a silica plug in a pipette eluting with toluene collecting small fractions. Solvent was then removed under reduced pressure to give crude product. The crude mixture was purified by silica gel column chromatography. It was loaded on to silica using CH_2Cl_2, and then was charged on to a column packed with 5% EtOAc: pet ether. The product was eluted by switching to 10% and finally 15% EtOAc:Pet ether. Removal of column solvent under reduced pressure gave product **2e** as an off white solid (32 mg, 67% yield).

Tetracarbonyl (2-(4-morpholinocarbonyl) biphenyl)κ,C^2-pyridine-κ,N)manganese^I (2f). This synthesis is based on a modified literature procedure.[24] **Precatalyst solution**: A dried schlenk tube equipped with a magnetic stirrer bar was charged with 2-Aminobiphenylpalladium methanesulfonate dimer (**4**) (1.0 eq., 0.01 mmol, 7.4 mg) and ligand (2.0 eq., 0.02 mmol, 9.5 mg). This tube was evacuated and refilled with N_2

three times. THF (1 ml) was then added and the colourless solution was allowed to age for thirty minutes with stirring at room temperature before use in the coupling reaction. No colour change was observed.

Suzuki-Miyaura Coupling of Tetracarbonyl (2-(4-bromo-phenyl)κ,C^2-pyridine-κ,N)manganese^I (2d) with 4-morphoninocarbonylphenyl boronic acid (3): The 0.5 M K_3PO_4 solution was prepared by dissolving K_3PO_4 (10.6 g, 50 mmol) in deionized water (100 ml) and degassed by performing several evacuation/N_2 refill cycles (until bubbling stops) under sonication prior to use. A dry Schlenk tube equipped with a magnetic stirrer bar and Teflon septum was charged with 3 (1.5 eq., 0.188 mmol, 44 mg) and **2d** (1.0 eq., 0.126 mmol, 50 mg). It was then evacuated and refilled with N_2 three times and the aged precatalyst solution in THF (314 µl, 5 mol % Pd) and aqueous K_3PO_4 (2.0 eq., 1.0 mmol, 0.5 M, 2.00 ml) were added by syringe. The reaction was stirred at 40 °C for 3.5 hours, after which it was opened to air and passed through a small plug of celite. The solvent was removed under reduced pressure and the crude mixture purified by silica gel column chromatography. It was loaded onto silica using CH_2Cl_2, and then was charged onto a column packed with 80% EtOAc: pet ether. The product was eluted with 80% EtOAc: pet ether. Removal of the solvent under reduced pressure provided the product as a white solid (28 mg, 43% yield). MP: 146–148°C (dec); ^{1}H NMR (400 MHz, CD_2Cl_2) δ: 8.73 (d, *J* = 5.7 Hz, 1H), 8.18 (d, *J* = 1.8 Hz, 1H), 7.93 (d, *J* = 8.1 Hz, 1H), 7.88 (d, *J* = 8.1 Hz, 1H), 7.86–7.80 (m, 1H), 7.76 (d, *J* = 7.6 Hz, 2H), 7.48 (d, *J* = 7.6 Hz, 2H), 7.43 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.41 – 7.33 (m, 2H), 7.15 (ddd, *J* = 7.2, 5.7, 1.3 Hz, 1H), 3.39-3.30 (m, 8H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ: 175.4, 165.7, 154.1, 146.1, 142.8, 141.3, 139.6, 138.1, 129.7, 128.5, 127.7, 127.3, 127.1, 124.3, 123.2, 122.8, 119.6, 66.9, 66.8; Elemental Analysis (CHN) C: 61.30% H: 3.70 % N: 5.72% (Calculated: C: 61.19% H: 3.75% N: 5.59%); LIFDI-MS *m/z* = 510.06 $[M]^+$ (calc. for $MnC_{26}H_{19}N_2O_6$= 510.0624); ESI-MS *m/z* = 511.0705 $[M+H]^+$ (calc. for $MnC_{26}H_{20}N_2O_6$= 511.0696), 533.0509 $[M+Na]^+$ (calc for $MnC_{26}H_{19}N_2NaO_6^=$ 533.0516). IR (ATR): 2855, 2072, 1965, 1922, 1629, 1603, 1580, 1561, 1474, 1456, 1427, 1277, 1257, 1114, 1010, 954, 784, 763, 675, 6454, 550, 438 cm^{-1}.

Myoglobin assay for determining CO-release rates. The procedure was carried out as previously described,[10f] taking into consideration the precautions noted by McLean *et al.*.[20]

CCDC-1488805 (**2c**)contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via <url>www.ccdc.cam.ac.uk/data_request/cif</url>

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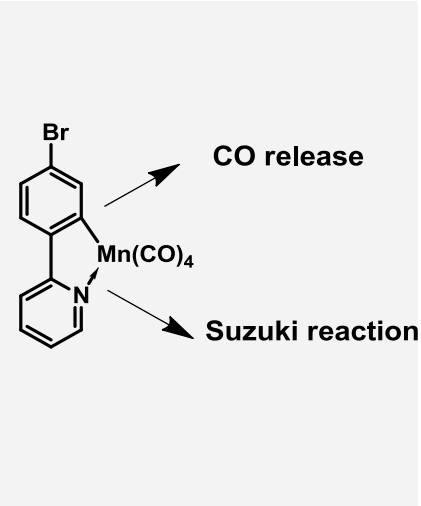
Entry for the Table of Contents (Please choose one layout)

Layout 1:

Key Topic

Photoactivated CO-releasing molecules have been traditionally irradiated using a TLC lamp. In this paper the use of LEDs close to the sample is reported. This gives efficient CO release compared to a TLC lamp. The complex shown releases CO efficiently and can be functionalised further with a Suzuki reaction.



Jonathan S. Ward, Joshua T. W. Bray, Benjamin J. Aucott, Conrad Wagner, Natalie E. Pridmore, Adrian C. Whitwood, James W. B. Moir, Jason M. Lynam*, and Ian J. S. Fairlamb*…….. Page No. – Page No.

Photoactivated functionizable tetracarbonyl phenylpyridine manganese(I) complexes as CO-releasing molecules: a direct Suzuki–Miyaura cross-coupling on a thermally-stable CO-RM

Keywords: Carbon monoxide/ CO-releasing molecules/CO-RM /morpholine/Suzuki–Miyaura