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A bidentate iridium carbene complex, \(\text{Ir}(\text{C},\text{O}-\text{L})\text{(COD)}\), has been synthesised which contains a strongly electron donating carbene ligand that is functionalised by a \(\text{cis}\)-spanning phenolate group. This complex acts as a precursor to effective magnetisation transfer catalysts which form after reaction with \(\text{H}_2\) and a suitable two electron donor. In solvents such as benzene, containing pyridine, they are exemplified by neutral, chiral \(\text{Ir}(\text{H})_2(\text{k},\text{C},\text{O}-\text{L})\text{(py)}_2\) with inequivalent hydride ligands and \(\text{Ir}-\text{O}\) bond retention, whilst in methanol, \(\text{Ir}-\text{O}\) bond cleavage leads to zwitterionic \(\text{Ir}(\text{H})_2(\text{k},\text{C},\text{O}-\text{L})\text{(py)}_2\) with chemically equivalent hydride ligands. The active catalyst’s form is therefore solvent dependent. Both these complexes break the magnetic symmetry of the hydride ligands and are active in the catalytic transfer of polarisation from para-hydrogen to a loosely bound ligand. Test results on pyridine, nicotinaldehyde and nicotine reveal up to \(\pm 1.2\%\) single spin proton polarisation levels in their \(^1\text{H}\) NMR signals which compare to the normal \(0.003\%\) level at 9.4 Tesla. These results exemplify how rational catalyst design yields a solvent dependent catalyst with good SABRE activity.

The use of hyperpolarisation methods to overcome the inherent insensitivity of NMR spectroscopy reflects an area of research where Parahydrogen Induced Polarisation (PHIP) features heavily.\(^1\) The incorporation of parahydrogen (p-\(\text{H}_2\)), a nuclear singlet, into a molecule was first shown to produce an enhanced NMR signal in 1987.\(^2\) The increase in signal intensity for resonances arising from, or coupled to, p-\(\text{H}_2\) derived protons, has since been the subject of intense investigation. Recently a p-\(\text{H}_2\) technique that does not chemically change a molecule, called Signal Amplification By Reversible Exchange (SABRE), has been developed.\(^3\) Polariisation is transferred through \(\text{J}\)-coupling between the p-\(\text{H}_2\) derived hydride ligands and the substrate ligands.\(^3\) Exchange with free substrate and fresh p-\(\text{H}_2\) enables the build-up of polarisation in the substrate pool through multiple visits to the catalyst. The most commonly used catalysts are cationic species which contain either phosphine or N-heterocyclic carbene (NHC) ligands.\(^4\)\(^-\)\(^6\)\(^-\)\(^7\)

In fact, one of the most effective magnetisation transfer catalysts is \(\text{Ir(COD)(IMes)Cl}\)\(^7\) where IMes = 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene, \(\text{COD} = \text{cyclooctadiene}\) which forms the charged complex, [Ir(H)]\(_3\)IMes\(\text{(substrate)}\)_3Cl once activated with \(\text{H}_2\) and a substrate. This SABRE catalyst contains chemically equivalent but magnetically inequivalent hydride ligands and polarisation transfer has proven particularly efficient in polar protic solvents such as methanol. Furthermore, using this catalyst a wide range of substrates including nicotinamide,\(^8\)\(^-\)\(^10\) isoniazid\(^11\) and pyrazole\(^12\) have been shown to become hyper-polarised. This type of approach has been exemplified for \(\text{H}, \text{C}, \text{N}, \text{P}, \text{F}\) and \(\text{N}\) nuclei.\(^3\),\(^13\)\(^-\)\(^15\) However, due to the charged nature of such a species it has proven less efficient in the range of low polarity solvents commonly used in NMR analysis.

It has also been shown that species with chemically inequivalent hydride ligands can act as SABRE catalysts. One reported example of this class of catalyst is given by \(\text{Ir(H)}\text{(CH}_2\text{CN)}\text{(IMes)}\)\(_8\)\(_7\), where \(\text{COD} = \text{cyclooctadiene}\) which forms the charged complex, [Ir(H)]\(_3\)IMes\(\text{(substrate)}\)_3Cl once activated with \(\text{H}_2\) and a substrate. This SABRE catalyst contains chemically equivalent but magnetically inequivalent hydride ligands and polarisation transfer has proven particularly efficient in polar protic solvents such as methanol. Furthermore, using this catalyst a wide range of substrates including nicotinamide,\(^8\)\(^-\)\(^10\) isoniazid\(^11\) and pyrazole\(^12\) have been shown to become hyper-polarised. This type of approach has been exemplified for \(\text{H}, \text{C}, \text{N}, \text{P}, \text{F}\) and \(\text{N}\) nuclei.\(^3\),\(^13\)\(^-\)\(^15\) However, due to the charged nature of such a species it has proven less efficient in the range of low polarity solvents commonly used in NMR analysis.

In this study, the related neutral iridium carbene complex, \(\text{Ir}(\text{k},\text{C},\text{O}-\text{L})\text{(COD)}\), \(\text{Ir} = 3\{\text{2-methylene-phenolate}-1\{2,4,6\text{-trimethylphenyl}\text{imidazolylidene}\}, \) has been synthesised starting from salicylaldehyde. It contains a \(\text{cis}\)-spanning phenolate-substituted bidentate NHC (see Scheme 1). Benzyl protection of the phenol\(^18\) allowed conversion of the aldehyde to the bromide\(^19\) via the alcohol.\(^20\) Addition of 1\{2,4,6\text{-trimethylphenyl}\}\text{H-imidazole} then formed the imidazolium bromide salt.\(^21\) Deprotection followed by silver carbene formation and subsequent transmetallation\(^22\)
afforded the product, the phenoxide iridium carbene complex, 1. Key compounds have been characterised by NMR and MS as illustrated in the ESI.†

In solution, complex 1 appears yellow/orange in colour. UV-Vis analysis in DCM showed it exhibits three absorption bands in the visible region of the spectrum (373, 425 and 490 nm) with absorption coefficients in the range of charge transfer bands in the visible region of the spectrum (373, 425 and 490 nm) with absorption coefficients in the range of charge transfer bands (373, 425 and 490 nm) with absorption coefficients in the range of charge transfer bands.‡

At room temperature, the 1H NMR spectrum of complex 1 in CD2Cl2 yields well resolved resonances (see Fig. 1). Two doublets at δ 6.53 and 5.17 are observed for the CH2 linker protons which have a common 3J(HH) coupling of 14.9 Hz. These two protons are diastereotopic due to the seven-membered metallocycle which is indicative of the retention of the Ir–O bond. Complex 1 is air/moisture sensitive but stable as a solid and in solution under N2. It also forms stable complexes once fully reacted with substrate and hydrogen as detailed in the following reactions.

Upon cooling a CD2Cl2 solution of complex 1 to 243 K all of its NMR signals become broad and undefined due to fluxional behaviour and when pyridine is added to this solution no reaction is evident. If, however, H2 gas is added at 255 K, a limited reaction occurs as two pairs of hydride signals are now seen at Δ −12.35 and −18.25 (1.7% conversion) and at Δ −12.39 and −17.64 (0.6%). These minor hydride containing products are conformational isomers of compound 2 (see Scheme 3) which arise due to differing metallocycle orientations; analogous behaviour has been reported.17

When p-H2 is used in this reaction, these hydride ligand signals do not show any significant 1H NMR signal enhancement. However, the free H2 signal in these spectra is substantial which suggests that 1 undergoes rapid and reversible oxidative addition of H2 to form 2 which consumes the p-H2. There is no indication of the hydrogenation of COD at 255 K and upon warming to 298 K, these hydride signals broaden into the baseline of the corresponding NMR spectra and strong signals for 1 are always visible.

When a CD2Cl2 solution of 1 reacts with both pyridine and H2 at 298 K a new neutral iridium species, Ir(H2)(κC2O-L1)(py)2, 3 is observed to slowly form containing two bound pyridine environments in a ratio of 1:1 (see ESI† for details). This species is also formed in C6D6. The mutually coupled inequivalent hydride signals appear in CD2Cl2 at Δ −22.55 and −25.49 (3J(HH) = 8.1 Hz) and in C6D6 at Δ −21.94 and −24.52 (3J(HH) = 7.7 Hz). Their inequivalence suggests Ir–O bond retention, a fact which is further supported by the diastereotopic nature of the CH2 linker protons which appear as doublets in both CD2Cl2 and C6D6. Both complexes undergo pyridine and H2 exchange as highlighted in Scheme 2, although only the pyridine ligand trans to hydride dissociates. The use of ESY NMR31 experiments enabled determination of experimental rate constants for pyridine loss in 3 at 294 K of 3.74 ± 0.06 s−1 in CD2Cl2 and 13.5 ± 0.6 s−1 in C6D6. The corresponding H2 loss rates were 0.80 ± 0.01 s−1 and 3.02 ± 0.07 s−1 respectively and are therefore much slower than those of pyridine loss.

This behaviour changes significantly upon moving to protic methanol. Now, the addition of H2 to a CD3OD solution of complex 1 at 250 K, results in a very limited reaction to form a dihydride (<1%, with resonances at Δ −12.65 and −18.27 and the low concentration presumably prevents observation of its conformational isomer) but upon warming further, rapid and total decomposition of 1 follows. In contrast, the addition of pyridine to a CD3OD solution of complex 1 at 243 K forms the

![Scheme 2](image)

Scheme 2 Transfer of hydride polarisation into the indicated pyridine ligand is followed by ligand exchange to build-up hyperpolarised pyridine in solution.

Fig. 1 1H NMR spectrum of 1 showing evidence for the diastereotopic CH2 linker protons with key CH resonances labelled.
phenolate dissociation product, square planar 4 quantitatively (see Scheme 3 and ESI†) where the COD ligand yields four inequivalent alkene proton resonances.

Upon the addition of p-H₂ and pyridine to 4 at 243 K, two PHP enhanced hydride signals become immediately visible at δ−12.34 and −17.50 that are shown to couple via COSY. They arise from H₂ addition to 4 which initially forms the alkene dihydride complex, 5. The CH₃ linker protons of 5 remain diastereotopic on phenolate rotation due to the absence of a mirror plane. Upon warming to 265 K, this system evolves further and a single hydride signal becomes visible at δ−22.18 due to the formation of [Ir(H)₃(CO₂−L₁)(py)]⁺, 6; the COD is converted to cyclooctene. Further NMR analysis confirms that 6 contains two bound pyridine ligand environments, in a 2:1 ratio, two hydride ligands and an iridium–carbene bond. Its CH₂ linker protons are now equivalent, appearing as a singlet at δ 4.83 due to the existence of a mirror plane as detailed in Scheme 3.

Complex 6 is zwitterionic, and its cationic Ir[n] centre is balanced by phenoxide ion formation. Hence the final reaction product formed from 1 with pyridine and H₂ is solvent dependent. The two pyridine ligands of 6 that lie trans to hydride are shown to dissociate with an experimental rate constant of 1.35 ± 0.03 s⁻¹ at 294 K, although no exchange of the pyridine trans to the carbene is observed. In CD₂OD, rapid H/D exchange, accompanied by HD formation, is observed which prevents the quantification of the H₂ loss rate in this solvent. At 294 K, the ligand exchange rates of species 3 in C₆D₆ are therefore much faster than those in CD₂Cl₂, but both are faster than those of 6 in CD₂OD as shown in the ESL†.

The ligand exchange rates of 6 in CD₂OD were examined as a function of temperature and activation parameters for these processes were calculated (see ESI†). The activation enthalpy values for both pyridine and hydride loss are very similar to each other (90.7 ± 1.6 kJ mol⁻¹ and 88.3 ± 9.1 kJ mol⁻¹ respectively). The entropy of activation values of 71.3 ± 5.3 J K⁻¹ and 56.1 ± 30.6 J K⁻¹ for pyridine and hydride loss respectively are also similar and positive thereby confirming the dissociative character of these steps.7 Similar ligand exchange processes, in a series of related complexes, yield values of similar size.7,32 A ligand exchange mechanism featuring reversible pyridine dissociation with H₂ loss via [Ir(xC₄O₂−L₁)(H₂)(H₂)(py)]⁺ is therefore indicated.33

Both catalysts 3 and 6 therefore exhibit the substrate and H₂ exchange characteristics required for them to act as SABRE catalysts. To test their substrate signal enhancing performance, samples were prepared containing catalyst 1 and a chosen substrate in the desired NMR solvent. These were rigorously degassed before the addition of 3 bars of H₂. Samples were tested by reintroducing p-H₂ into the headspace of the NMR tube, shaking the sample in the low field outside of the spectrometer and then rapidly transferring the sample into the spectrometer for examination. This resulted in the observation of enhanced signals in the corresponding single scan ¹H NMR spectra for the hydride ligands, bound substrate and free substrate in solution as exemplified by Fig. 2. The total enhancement value seen for the five protons of pyridine in C₆D₆ proved to be 1850-fold under the conditions detailed. For CD₂Cl₂, this enhancement level was reduced to ca. 1660-fold whilst for CD₂OD solution it became 710-fold. Given the corresponding gain in signal-to-noise levels that these enhancements

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provide, the resulting time savings are substantial in all solvents. For comparison purposes, the site specific enhancement values for the substrates pyridine, nicotinaldehyde and nicotine are summarised in Table 1. The performance of 1 as a SABRE catalyst for pyridine like substrates has therefore been established.

It is known that the amount of signal enhancement observed in the $^1$H NMR spectrum of a substrate under SABRE is significantly affected by the ligand exchange rates, as previously explained by Green et al.\textsuperscript{14} For comparison, $[\text{Ir(H)}_3(\text{IMes})(\text{py})]_3\text{Cl}$ is commonly used as the catalyst benchmark for SABRE and its pyridine dissociation rate\textsuperscript{32} was found to be 23 s\textsuperscript{-1}. While the ligand dissociation rates for 3 and 6 are much lower, they still achieve good hyperpolarisation levels. In fact, these data show that one pyridine substrate trans to hydride in CD$_2$Cl$_2$ or CD$_6$ is more efficient at receiving SABRE than the two equivalent pyridine ligands of 6 in CD$_3$OD. Furthermore, the concept of an active solvent responsive catalyst is illustrated.

In summary, the iridium precatalyst Ir([xCO-\text{L}]_3)(COD), 1 containing a phenol substituted NHC has been synthesised and shown to act as an efficient SABRE catalyst precursor. The active catalytic species is solvent dependent. Complex 1 contains an Ir-O bond which is affected by solvent polarity and proton availability; in non-polar Cd$_6$, and polar aprotic CD$_2$Cl$_2$, this bond is strong and substitution resistant with 1 forming Ir[\text{CD$_2$Cl$_2$}], (3) on reaction with H$_2$ and pyridine. In contrast, on changing to polar protic methanol, the Ir-O bond becomes labile and the phenolate easily dissociates from the iridium centre, such that tautomeric $[\text{Ir(}\text{xCO-\text{L}}_3\text{H})(\text{py})]_3$(6) forms. 6 is directly analogous to the efficient SABRE catalyst $[\text{Ir(H)}_3(\text{IMes})(\text{py})]_3\text{Cl}$ which performs well in CD$_3$OD but has lower activity in non-polar CD$_2$Cl$_2$ and Cd$_6$. Both 3 and 6 undergo pyridine and H$_2$ exchange thereby enabling them to act as SABRE catalysts. Whilst 6 works well in CD$_3$OD, catalyst neutrality in the non-polar solvents CD$_2$Cl$_2$ and Cd$_6$ results in the formation of 3 which is highly active for SABRE catalysis. This study therefore shows that catalyst design and control can lead to improved magnetisation transfer in a range of solvents, a requirement for future studies that seek to identify low concentration analytes\textsuperscript{35-37} and to produce hyperpolarised MRI contrast agents.

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References


