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Harnessing Polarization Transfer to Indazole and Imidazole Through Signal Amplification By Reversible Exchange to Improve their NMR Detectability

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Abstract

The Signal Amplification by Reversible Exchange (SABRE) approach has been used to hyperpolarize the substrates indazole and imidazole in the presence of the co-ligand acetonitrile through the action of the precataysts [IrCl(COD)(IMes)] and [IrCl(COD)(SIMes)]. ^{2}H-labelled forms of these catalysts were also examined. Our comparison of the two pre-catalysts [IrCl(COD)(IMes)] and [IrCl(COD)(SIMes)], coupled with ^{2}H-labelling of the N-heterocyclic carbene and associated relaxation and polarisation field variation studies demonstrate the critical and collective role these parameters play in controlling the efficiency of SABRE. Ultimately, with imidazole a 700-fold ^{1}H-signal gain per proton is produced at 400 MHz, while for indazole a 90-fold increase per proton is achieved. The co-ligand acetonitrile proved to optimally exhibit a 190-fold signal gain per proton in these measurements, with the associated studies revealing the importance the substrate plays in controlling this value.

Keywords: Hyperpolarization, SABRE, indazole, imidazole, Iridium catalyst

Introduction

Hyperpolarization methods are being used widely to improve the sensitivity of Nuclear Magnetic Resonance (NMR) and Magnetic Resonance Imaging (MRI) to substrate detection.[1],[2] Signal amplification by reversible exchange (SABRE) is one such method where the nuclear spin order from *para*hydrogen (p-H_2) is used to sensitize substrate detection.[3],[4],[5] The process of SABRE relies on breaking the magnetic symmetry of two protons that were originally located within a p-H_2 molecule, whilst retaining a spin-spin coupling between them in addition to introducing new couplings between them and the substrate to be hyperpolarised.[3],[5] This is achieved by creating a SABRE catalyst which acts as a scaffold to bind both p-H_2 and the substrate such that it allows polarization transfer through the resulting scalar coupling network. The process of SABRE is also affected by the magnetic field that is experienced by the catalyst during this process which is often called the polarisation transfer field (PTF).[6] An active SABRE catalyst can break the symmetry of these two protons in one of two ways detailed in Scheme 1 for indazole, where the co-ligand is acetonitrile, and the precatalyst is [IrCl(COD)(IMes)] **1a**.[7] As the original substrate molecule is reformed after ligand dissociation, there is no change in its chemical identity

during this process, but it has now become a hyperpolarized (HP) species. SABRE catalysts based on N-heterocyclic carbene (NHC) iridium complexes which contain 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene (IMes) or 1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene (SIMes) ligands are used in this study,[8], [9] although studies on other templates and a range of substrates have been described in the literature.[6, 9-10] A number of theoretical approaches have been used to model the SABRE effect, of which the level-anti-crossing approach provides a readily understandable solution.[11] Recently the role of relaxation within the SABRE catalyst has also become recognised, and models are being developed that take this into account. [7, 12] These studies have collectively confirmed that the time the substrate spends on the catalyst plays an import role in establishing the level of hyperpolarisation it gains. As consequence the ligating power of the substrate, which is linked to the pK_a of the binding site is important, as too strong an interaction can lead to low success by reducing overall exposure to p-H_2.

One of the drivers for the development of hyperpolarisation methods is the potential to collect *in vivo* data on a hyperpolarised agent which may ultimately prove to be diagnostic of health.[10b] Another is the use of high-sensitivity methods in analytical chemistry.[10a, 13] Other routes to hyperpolarisation include dynamic nuclear polarisation (DNP),[2] parahydrogen induced polarisation (PHIP)[6b, 14] with substrate functionalisation, and spin-exchange optical pumping (SEOP).[10d, 15]

We have selected indazole (ind) and imidazole (im), for this study because this family of nitrogen-containing heterocycles plays a role in a wide variety of biological processes.[16] Additionally, the imidazole motif is also present in the amino-acid histidine and the hormone histamine.[17] Furthermore, antifungal agents such as flutrimazole and antibiotics such as metronidazole[12] also contain this structural element.[17-18] Indazole derivatives therefore take an important place in healthcare as their biological activities include anti-inflammatory, antimicrobial, anti-HIV and anti-cancer roles.[16],[19]

Early reports on SABRE with indazole by Dücker et *al*. using the first generation of phosphine based SABRE catalysts[4] were observed to produce a 2-fold NMR signal enhancement.[6a] A study on imidazole by Moreno et al.[10d] using the second generation of carbene based SABRE catalysts [6b] produced an improved response. Chekmenev has also reported on the ^{15}N hyperpolarisation of imidazole, with the supplementary information suggesting that a 100-fold enhancement is produced in H-2, and 50-fold gain in H-4 and H-5. Here we describe a series of high field studies on polarization transfer to both of these substrates where we detect their ^{1}H and ^{13}C NMR signals. We seek to improve on the degree of SABRE response by exploring the effect of catalyst structure, and the use of a co-ligand, in addition to varying the pH of the methanol solutions that are employed. It has recently been established that pH effects during SABRE can be substantial.[10d, 20] [21]

The role for a co-ligand during SABRE has been highlighted several times. In one manifestation, the use of a ^{2}H-labelled substrate allows the SABRE effect to be successfully focussed into the protons of a second substrate.[22],[23] It has also proven possible to stabilise the active SABRE catalyst in order to successfully hyperpolarised weakly interacting substrates when substoichiometric amounts are available.[7] [24] [25] Specifically, we show here that complex **2a** of Scheme 1 readily forms through the binding of two indazole ligands and one acetonitrile ligand. In SABRE catalysts of this type, the hydride ligands are therefore made chemically and magnetically inequivalent. The second form of catalyst, **3a**, contains three indazole ligands, and now polarization transfer is facilitated by magnetic inequivalence effects. The mechanisms of ligand exchange in these types of complex have been examined previously when the substrate is pyridine and underpin the SARE effect.[7],[22] These studies have enabled the hyperpolarisation of acetonitrile and reveal that it is possible to improve the pyridine response when CD_3CN is used. More recently, the ^{13}C and ^{15}N hyperpolarisation of

acetonitrile by SABRE has been considered. [22] [26] Here we show that, for type **2** complexes, the acetonitrile ligand is more labile than indazole and imidazole. The level of signal enhancement resulting from SABRE relates to the ligand exchange rate constants because polarisation transfer proceeds via the small J-coupling that exists between the hydride ligand and polarisation acceptor.[2] Understanding these effects is critical to optimisation of SABRE.[2] It has also been suggested that because transfer is slow, relaxation by the SABRE catalyst can limit performance[27] and a simple and readily understandable model to assess this has been reported by Koptyug[11d]. We therefore also report on the effects of catalyst deuteration on the level of SABRE by reference to appropriate isotopologues of IMes and SIMes, and by combining these approaches, we achieve high field signal gains in excess of 700-fold. Our co-ligand strategy also enables significant CH_3CN hyperpolarisation to the achieved.

Scheme. 1. here: Formation of $[Ir(H)_2(ind)_2(NCMe)(IMes)]Cl$ (**2a**) and $[Ir(H)_2(ind)_3(IMes)]Cl$ (**3a**) via reaction of H_2, acetonitrile and indazole (ind) with **1a**; labels as used in the text.

Results and Discussion

IrCl(NHC)(COD) derived SABRE of indazole: formation of $[Ir(H)_2(ind)_2(NCMe)(NHC)]Cl$ (2) and $[Ir(H)_2(ind)_3(NHC)]Cl$ (3). [IrCl(COD)(IMes)] (**1a**) and [IrCl(COD)(SIMes) (**1b**) were found to react with indazole (4-10-fold excess, relative to iridium) and acetonitrile (3-fold excess) to form equilibrium mixtures of $[Ir(H)_2(ind)_2(NCMe)(IMes)]Cl$ (**2**) and $[Ir(H)_2(ind)_3(IMes)]Cl$ (**3**)**.** These four complexes have been characterised by multinuclear NMR spectroscopy, the details of which can be found in the supporting information. In the case of **1a**, when the initial ligand ratio of indazole-acetonitrile is 10 : 3, products **2a** and **3a** exist in a 1 : 34 ratio and hence **3a** dominates. These complexes are diagnostically identified by the chemical shifts of their hydride ligands, which appear at δ_H −20.91 and −21.32 in **2a** and at δ_H −21.26 in **3a** respectively in MeOD at 298 K. The associated product ratio indicates a weaker Ir-NCMe bond, when compared to Ir-$N_{indazole}$**,** and thus **3a** is thermodynamically more stable than **2a**. In contrast, the analogous reaction with **1b** yields **2b** and **3b** in the ratio 1 : 50 under the same initial conditions. This indicates that the relative bond energies of the Ir-NCMe and Ir-$N_{indazole}$ lie further apart when SIMes is the ancillary ligand as there is an even higher preference for **3b**. The corresponding hydride chemical shifts for **2b** are δ_H −20.95 and −21.28, whilst that for **3b** is δ_H −21.23. The hydride chemical shifts in the related complexes **2a** and **3a**, and **2b** and **3b**, are therefore very similar to one another and hence not strongly dependent on the identity of the NHC. Figure 1, panes (a), (b) and (c), show the aromatic and hydride regions of a series of ^{1}H-NMR spectra in methanol-d_4 that were obtained with indazole. The NMR trace in pane (a) corresponds to one that was obtained before the addition of H_2, and signals for H-3 through H-8 of indazole are indicated. The addition of H_2 changes this response as **2a** and **3a** form with the new resonances for the coordinated indazole ligands being indicated with the * and ● labels (equatorial and axial ligands respectively, pane (b)). The hydride region of this NMR spectrum (right) reveals that **3a** dominates.

Fig. 1 here. : Figure 1: Plots (a), (b) and (c) show the aromatic and hydride regions of a series of ^{1}H-NMR spectra that were obtained in methanol-d_4 solution with **1a** and indazole.

When this reaction is completed with *p*-H_2, and observed by ^{1}H NMR spectroscopy, the hydride ligand signals of [Ir(H)$_2$(ind)$_2$(NCMe)(NHC)]Cl (**2**) exhibit antiphase character due to the PHIP effect in the corresponding ^{1}H NMR spectra (Figure 1c, right). The average relative signal intensity gain for the polarized hydride resonances of **2a** is 8 times larger than those of **2b** in comparable experiments (see Figure 1c for a typical result). In addition, the equivalent hydride ligand signals of [Ir(H)$_2$(ind)$_3$(NHC)]Cl (**3**) both exhibit a weak in-phase signal gain when they are first observed after sample transfer from low field, but this gain lies just 1.6-fold in favour of **3a** over **2a**. The difference in **2a** : **2b** signal enhancement level is consistent with the fact that the observed rate of H_2 loss at 298 K, as determined by EXSY methods, from **2a** is 0.65 s^{-1}, and just 0.08 s^{-1} for **3a**. Hence there is more rapid *p*-H_2 introduction into **2a** and a larger signal gain results. These enhancement data therefore indicate that the presence of the acetonitrile facilitates more rapid IrH/H_2 exchange in agreement with observations reported previously for the related products that form with pyridine.[7]

Using an automated polariser. A solution containing such a mixture of **2a** and **3a**, and free indazole was subsequently probed for SABRE. These measurements were made in an automated flow-apparatus that has been described previously.[10a] This device, the Polarizer, is represented in Figure 2. It was designed to enable a solution that contains the catalyst and the hyperpolarisation target to be polarised using *p*-H_2 within a mixing chamber (MC) that is located in low-field. The MC is surrounded by coil that can be used to generate a precise local magnetic field in the range -140 to +140 G and is located within a μ-metal shield to screen the effect of the earth's field. For the flow measurements conducted in this study, a 3 mL volume of methanol-d_4 solution is typically employed that contains the iridium catalyst at a concentration of between 5 and 6 mM. It also contains 2-3 molar equivalents of the co-ligand acetonitrile and 10 molar equivalents of the target substrate. Once a substrate is hyperpolarised, after bubbling *p*-H_2 through the solution for a predefined period, bubbling is stopped and a 3 second N_2 purge activated. The solution then flows under nitrogen pressure into the NMR probe head for measurement in a process that takes 0.6 s, although a further delay of 0.1 s is added to allow the solution to settle before the NMR measurement is started. NMR measurement then proceeds in the usual way, although a receiver gain of one is typically employed to deal with the strongly enhanced signals we expect to detect. It takes therefore a total of 4.8 seconds to make a measurement after the SABRE step has been completed. During this time the sample moves from low to high field and therefore experiences a range of magnetic environments and hence relaxation effects. These effects will act to reduce the level of detected SABRE and must play a larger role in shrinking the measured response of any rapidly relaxing signals. By employing this flow-approach, the solution can ultimately be returned to the MC in order for it to be repolarised and the process started again. In this way signal averaging, signal reproducibility and variable polarisation transfer field plots can be constructed by repeated analysis of the same sample.

Fig. 2 here. : Figure 2: Schematic representation of the automated polariser used here to collect SABRE data.

By using this equipment we are able to precisely vary a number of parameters that control the SABRE effect in order to optimise them. When the initial concentration of **1a** in methanol-d_4 was 6.5 mM, and 49.4 mM of indazole and 17.0 mM of acetonitrile were introduced, strong SABRE enhancements were visible in the NMR signals of both these reagents. The maximum proton signal enhancement for the 5 non-exchangeable protons of indazole proved to total 115-fold which equates to a signal gain of ~20 per proton and resulted when the sample had been exposed to a 70 G magnetic field in conjunction with 20 seconds of exposure to p-H_2 (see supporting information, Fig. S1). The corresponding acetonitrile proton signal was observed to achieve a maximum enhancement of 145-fold after transfer at 80 G which equates to an ~50-fold gain per proton (see supporting information, Fig. S2). Previously, such a high level of polarization transfer into acetonitrile has only been seen when a deuterated ligand scaffold is employed in conjunction with the co-ligand pyridine.[7] This study therefore reveals the importance of the co-ligand is controlling the level of polarisation transfer into a weakly bound ligand, in this case acetonitrile. We note that Tessari et al. further developed the co-ligand approach to enable analyte quantification at low loadings.[28] Additionally, the efficiency of the SABRE effect is polarisation transfer field dependant as a consequence of the matching conditions that must be met between the chemical shift and coupling values within the catalyst.[2, 29] It is therefore usual to quote optimal polarisation transfer field values when reporting data in a similar way to quoting absorption maxima in UV spectroscopy.

When a 6.6 mM solution of **1b** was examined in presence of similar 10 and 3 fold ligand excesses respectively, SABRE was again observed. Now, however, the total indazole proton signal enhancement within the five sites increased to 234-fold (~47 per proton) after transfer at a polarisation transfer field of 70 G and a 20 second p-H_2 exposure time. The corresponding acetonitrile signal gain was 266-fold at 80 G. Hence the catalyst derived from **1b** exhibits superior performance to that derived from **1a**. This observation is in agreement with the fact that the effective rate of build-up of indazole in solution, via dissociation from dominant **3a** and **3b**, at 298 K is 0.26 s^{-1} and 0.64 s^{-1} respectively. Scheme 2 illustrates the SABRE process in a conceptual form. The effective rate of build-up of free substrate in solution used here is defined as the observed rate of magnetisation transfer from the H-3 resonance of **3** into the corresponding signal for free indazole and has units of s^{-1} (see supporting information).

We also undertook a series of control measurements under analogous conditions without acetonitrile. The corresponding H-3 signal of indazole was observed to yield a 330-fold signal again under these conditions where **3a** is the catalyst after transfer at 60 G.

Scheme 2. here: The SABRE process in a conceptual form.

Scheme 2 Conceptual representation of the SABRE process which achieves the catalytic hyperpolarisation of a substrate via polarisation transfer with the iridium catalyst from a pair of protons that were previously located in a molecule of p-H_2.

SABRE hyperpolarisation of residual CHD_2OD and CD_3OH. Mechanistically, the loss of indazole from **3**, and acetonitrile from **2** will lead to a common 16 electron intermediate, $[Ir(H)_2(ind)_2(NHC)]Cl$, alongside hyperpolarised indazole and acetonitrile respectively (Scheme 1). Both H_2, indazole or methanol can then coordinate to this intermediate, with p-H_2 binding providing the route by which the cycling of *para*hydrogen is

achieved that underpins SABRE. As methanol is present in far larger excess than either indazole or acetonitrile, its binding is assured and single-spin hyperpolarization is consequently observed in these experiments in the residual CHD_2OD and CD_3OH solvent signals as detailed in Figure 3. For systems derived from **1a** transfer into the solvent is most readily evident after transfer at 70 G, with both of the residual solvent signals showing a phase change, from absorption to emission, on moving between transfer fields of 50 and 60 G. The maximum signal enhancement seen for these signals, relative to those seen under thermal conditions was 2.6-fold for the CHD_2OD peak and 3.0-fold for the CD_3OH peak. This small level of signal gain results from the low proportion of ^{1}H-labelled species in CD_3OD, which means that most of the methanol binding to the associated 16-electron intermediate $[Ir(H)_2(ind)_2(NHC)]Cl$ forms $[Ir(H)_2(ind)_2(CD_3OD)(NHC)]Cl$ which will be unproductive for methanol-SABRE. Furthermore, the concentration of $[Ir(H)_2(ind)_2(methanol)(NHC)]Cl$ must also be low as this species is not detected in these NMR spectra.

Fig. 3. here: Series of ^{1}H NMR spectra showing the signals for hyperpolarized CD_3OH and CHD_2OD that result from SABRE as a function of the polarisation transfer field. These data were collected using a methanol-d_4 solution that contained a 10-fold excess of indazole and a 3-fold excess of acetonitrile relative to **1a**.

Under SABRE, the level of signal enhancement builds as the exposure time to p-H_2 increases prior to reaching a relaxation controlled maximum.[22] This is commonly referred to as the bubbling time when using the automated system described earlier and it might be expected that a signal builds up in intensity before reaching a plateau.[10a] The low-efficiency of the methanol CHD_2 enhancement allows this effect to be visualised, as detailed in Figure 4 which shows a change in signal phase as the bubbling time is increased; the SABRE effect creates a negative signal which eventually outweighs the thermally polarised state that produces the positive background peak. Bubbling times between 5 and 70 seconds were examined which contrast with the 20 seconds needed to see SABRE with acetonitrile or indazole.

Fig. 4. here: Plot of the p-H_2 bubbling time versus the level of CHD_2OD signal gain. The change in signal phase results from the combination of a positive thermal signal and a negative hyperpolarised signal for the CHD_2OD resonance.

We have also probed the effect of adding CD_3OH and H_2O to these CD_3OD solutions in order to increase the proportion of CD_3OH in solution. These results are detailed in the supporting information and reveal complex behaviour. When H_2O is added, the indazole, acetonitrile, methanol and HOD signal gains all first increase in size before falling as the level of doping is increased. The origin of this fall with added H_2O is likely to result from the reduced solubility of H_2 in water and the associated decrease in ^{1}H-relaxation times.[25, 30] A related series of solutions were then examined in the presence of HCl and NaOH. No significant changes in the level of proton indazole or solvent signal enhancement were evident. This contrasts with the results of Moreno et al. who saw an increased level of polarization transfer into the solvent molecules in acid solution at low field.[10d] We note though that it takes 4.8 s to move the sample from the external mixing chamber into the high field magnet where our measurements are made and hence relaxation could account for this difference.

Effect of changing the ligand scaffold to d_{22}-IMes or d_{22}-SIMes on the level of SABRE shown by indazole. Upon replacing the protio form of these NHC ligands with their deuterated variants d_{22}-IMes[7, 22] and d_{22}-SIMes, the levels of indazole and acetonitrile proton signal enhancements under SABRE changed as detailed in Table 1. For d_{22}-IMes, the maximum indazole proton signal enhancement was now obtained at 90 G rather than 70 G, and after 35 s of contact with *p*-H_2, rather than the 20 s used earlier. Its final value is, however, reduced from 115-fold to just 82-fold and hence it can be concluded that in this case ^{2}H-labelling of the catalyst has a negative effect on the level of indazole polarisation that is achieved when compared with the IMes system. In contrast, the **acetonitrile proton signal enhancement** level increased very dramatically from the original 145-fold value to 572-fold, with transfer now taking place at 90 G rather than the original 80 G field value (190-fold per proton). Hence polarisation transfer into acetonitrile has become more facile and as a consequence it now receives the largest SABRE benefit.

The corresponding change to d_{22}-SIMes, however, resulted in an indazole signal gain that averaged to ~91-fold per proton, and a 372-fold CH_3CN signal gain at the same transfer field values as used earlier, which remained optimal. Deuterating the carbene ligand of **1a** therefore leads to a 41% fall in indazole polarisation but for **1b** it leads to a 60% increase. We note that increases in temperature result in further increases in these signal gains as the ligand exchange rates are slow relative to what might be expected to be their optimum values.[9] In contrast, deuterating the IMes ligand associated with **2a** leads to a 300% gain in acetonitrile polarisation, whilst for **2b** it leads to a 17% fall. This difference will be rationalised later.

Effect of polarisation transfer field (PTF) on the level of SABRE shown by indazole. Figure 5 illustrates how the PTF affects the indazole proton enhancement level as a function of ligand scaffold deuteration. In the case of **3** there is one unique hydride coupling into the bound indazole ligand that will lead to transfer to proton H-3 of Scheme 1; the hydride couplings across the bridge into the second phenyl ring are expected to be too small to receive direct polarisation transfer via the hydride ligand. Protons H-8, H-5, H-7 and H-6 will therefore achieve their hyperpolarised states *via* relayed transfer through H-3. This behaviour accounts for the fact that when the SABRE efficiency of **3** is examined, as a function of PTF, a signal maximum is evident for all of these protons (Figure 5). The breadth of the peak seen in the PTF profile changes, narrowing with deuteration of the NHC, and hence we conclude that the matching transfer condition narrows when the deuterated ligands are employed. This changes means that there is a greater need to place the sample in an appropriate PTF when undertaking studies with deuterated ligands.

Table 1. here: Maximum level of proton signal enhancement seen for indazole and CH_3CN as a function of catalyst at 9.4 T (value for optimum polarisation transfer field in brackets).

Fig. 5. here: Polarisation transfer field plot showing how the indicated ^{1}H NMR signal intensity gains seen for indazole change with catalyst ligand deuteration.

Effect of relaxation within the SABRE catalyst on the level of indazole signal enhancement. An effect that needs to be considered when rationalizing these results is that of relaxation within the catalyst, which is predicted to be reduced by deuteration. The importance of this stems from the fact that the bound and free forms of the ligands are in dynamic exchange and hence any increase in relaxation time of the associated protons in the catalyst should be seen directly in the response of the free substrate. For example, if the

lifetime of the catalyst is too long, the associated signals will suffer from greater relaxation during the polarisation transfer step and hence increasing the catalysts intrinsic proton relaxation times should be beneficial. In contrast, ligand if ligand exchange is rapid then the relaxation times of the free substrate will reflect more closely those of the bound form which will act to limit the period over which hyperpolarised signals for the free substrate can be seen.

The relaxation times of the five protons of indazole and acetonitrile in a methanol-d_4 solution under 3 bar H_2 without the catalyst at 298 K were therefore determined. They are 22.2 s for proton H-3, 12.8 s for H-8, 12.5 s for H-5, 8.5 s for H-7 and 9.3 s for H-6 with the acetonitrile value being 14.4 s at 9.4 T. Upon adding the catalyst and H_2 to this solution, and repeating the associated measurements at 298 K, the apparent relaxation time for proton H-3 of free indazole, and that of the free acetonitrile resonance, were found to decrease to 12.3 s and 8.7 s respectively, while those for the remaining four indazole sites fell by a smaller amount (see Table 2). We confirm therefore that the presence of the catalyst reduces the measured relaxation times of the free substrate in solution and therefore acts to limit the period over which it can be viewed with a high-sensitivity response.

Cooling the sample to reduce the associated ligand exchange rates would be expected to suppress this relaxation based behaviour. We therefore undertook a control measurement on indazole at 263 K in methanol-d_4 at the same 50 mM concentration. The corresponding T_1 values were now 17.4, 7.2, 7.2, 4.0 and 4.5 s respectively. Hence, as expected, lowering of the temperature reduces the T_1 values of indazole.[31] The corresponding T_1 values were then determined for the protons of bound and free indazole in a mixture with **3** at 263 K. Now, as predicted, the corresponding bound proton values proved to be dramatically smaller than those of the free substrate, which in turn were remarkably similar to those determined without **3**. The size of the relaxation effects seen for **3b** proved to be even larger at 298 K in accordance with the higher ligand exchange rates exhibited by this complex and we therefore conclude that relaxation of the hyperpolarisation prior to ligand dissociation is limiting. The corresponding relaxation data for the catalysts containing d_{22}-SIMes or d_{22}-IMes ligands were also determined and found to differ from those of their protio counterparts as shown in Table 2. We note that even though these parameters have been determined at high-field, and the transfer process occurs at low-field where the relaxation times will be different a substantial effect has been seen. Given that the ligand exchange rates would not be predicted to change with remote ^{2}H-labelling, and the hydride-proton couplings should also remain constant this behaviour suggests that the ancillary ligands of the catalyst play a role through relaxation during the SABRE process.

Table 2. here: Experimental T_1 values determined at 9.4 T in methanol-d_4 solution for the indicated proton nuclei of free and bound indazole (**3b**), and acetonitrile (**3a**) at 263 K and 298 K respectively, where the associated reagent concentrations were 6.5 mM (iridium), 65 mM (indazole) and 19.5 mM (acetonitrile).

Polarization transfer into the ^{13}C response of indazole, acetonitrile and methanol. SABRE is also evident in the ^{13}C resonances of indazole, acetonitrile and methanol as detailed in Fig. 6 for a 35 second contact time with *p*-H_2 and the **1a** derived catalyst system. Polarization transfer into the quaternary ^{13}C signal for C_A of indazole reaches a maximum at 40 G (132 fold) with transfer into quaternary C_B being observed between 50 (58 fold) and 60 G, and 80 and 90 G, although there is a minimum at 70 G. The effect of the PTF on ^{13}C transfer is therefore complex and reflects the number of different coupling pathways in operation. The size of the SABRE effect is polarisation

transfer field dependant with the ^{13}C quaternary signal of free acetonitrile readily appearing at 116 ppm after transfer a ~0 G in a μ-metal shield (a ^{15}N signal can also be seen, see supporting information). Upon increasing the transfer field beyond this value the acetonitrile signal gain reduces but at points beyond 100 G it is again observed through an enhanced signal. We note that we do not observe polarization transfer into the $^{13}CH_3$ group of acetonitrile nor into the ^{13}C atoms of methanol-d_4 under these conditions. This is consistent with earlier reports that detail how optimal ^{13}C transfer proceeds via small $^3J_{CH}$ couplings rather than the larger $^2J_{CH}$ couplings.[22]

Fig. 6. here: Polarisation transfer field (PTF) effects seen on the intensity of the ^{13}C NMR signals of indazole and $NCCH_3$ that result from SABRE.

The levels of ^{13}C-signal gain achieved with **1b** proved smaller than those with **1a** as detailed in the supporting information, and the replacement of the SIMes or IMes ligands with d_{22}-SIMes and d_{22}-IMes respectively also led to worse SABRE performance with the maximum ^{13}C signal enhancement seen for site A (Scheme 1) being 63 fold in the latter case; adding acid into this system didn`t improved these signal enhancement levels.

Reaction of IrCl(NHC)(COD) with imidazole, H_2 and acetonitrile and the observation of SABRE. [IrCl(COD)(IMes)] (**1a**) and [IrCl(COD)(SIMes)] (**1b**) were then used to hyperpolarize imidazole (im). Similar 5 mM methanol-d_4 solutions of **1** or **2** were employed, with a 10-fold excess of imidazole and a 3-fold excess of acetonitrile. For **1a**, 97% of the products were now in the form $[Ir(H)_2(im)_3(IMes)]Cl$ (**5a**) with the remaining 3% corresponding to $[Ir(H)_2(NCMe)(im)_2(IMes)]Cl$ (**4a**) as detailed in Scheme 2. In the case of **1b** the reaction proceeded cleanly to form **5b** as the sole product. Characterisation data for these products is detailed in the supporting information. When the SABRE effect was explored for imidazole, *p*-H_2 contact times of 60 s were used, rather than the 25-30 s time for indazole, as this resulted in the detection of larger signal enhancements.

Scheme 3. here: Formation of $[Ir(H)_2(im)_2(IMes)(NCMe)]Cl$ (**4a**) and $[Ir(H)_2(im)_3(IMes)]Cl$ (**5a**) via reaction of H_2, acetonitrile and imidazole with **1a**; labels as used in the text.

Effect of polarisation transfer field (PTF) on SABRE with imidazole. Figure 7 illustrates how the PTF affects the imidazole proton signal enhancement level as a function of catalyst. In **5**, there are three unique spin-spin couplings between the hydride ligand (*trans*) and the imidazole protons in the SABRE transfer catalysts of Scheme 3 and 6 routes to relayed transfer between the three protons.[32] These three protons exhibit chemical shifts of δ_H 6.82, 6.86 (H-4 and H-5) and 6.9 (H-2) in **5a**, and will all receive polarisation under SABRE with different efficiencies according to the PTF and couplings they experiences at the point of transfer. Consequently, upon the dissociation of hyperpolarised imidazole from **5** all three of its proton signals should appear enhanced, but only two signals are actually seen, at δ_H 7.70 and 7.07, due to the fact the resonances for H-4 and H-5 have effectively identical chemical shifts. As expected, the SABRE results, with imidazole, therefore show a strong PTF dependence as detailed in Figure 7. For H-2, a signal peak is seen which reaches a maximum at a PTF value of 70 G, while the combination signal for H-4 and H-5 now shows a bimodal result with maxima at 50 and 90 G.

Level of SABRE found for imidazole. In methanol-d_4, the **1a** derived catalyst system proved to deliver signal enhancements of 606- and 830-fold for these two signals respectively per proton, which equates to a total signal enhancement value of 2042-fold within im. It would therefore appear that the NCHN motif, rather than the CHCH arrangement receives the highest level of SABRE transfer. The overall signal gain clearly exceeds the level seen for indazole where the corresponding value was just 115-fold, as detailed in Table 4. Furthermore, upon moving to **1b**, the overall signal enhancement falls to 1028-fold which contrasts with the indazole return of 146-fold and the CHCH arrangement receives the most benefit. We can therefore conclude that imidazole is better suited to SABRE than indazole.

We also undertook a series of control measurements under analogous conditions without acetonitrile. The corresponding H-2 signal of imidazole was now observed to yield a 551-fold signal again under these conditions after transfer at 60 G, while the signals for H-4/5 yielded a 410-fold gain after transfer at 70 G per proton. Hence imidazole polarises better in the presence of acetonitrile.

These results also proved to be pH sensitive, with the overall proton signal enhancement seen for imidazole dropping to 1475-fold (H-2, 571-fold) with **1a** in the presence of $HCl_{(aq)}$ as summarised in Table 3. Additionally, the acetonitrile signal gains, relative to those seen with indazole, proved to be much lower in accordance with the reduced concentrations of the associated catalyst **4**. The level of SABRE exhibited by the solvent CHD_2OD is also worse than that seen with indazole in accordance with **4** play a role in this process, but can be improved 20-fold by ^{2}H-labelling the IMes ligand.

Table 3. here: Change in the level of proton signal enhancement seen before and after adding HCl to the system when using precatalyst **1a** and **1b** where the concentrations are 6.5 mM iridium, 65 mM indazole, 19.5 mM acetonitrile at 298 K and a PTF of 80 G.

Fig. 7. here: Polarisation transfer field (PTF) plot showing how the indicated ^{1}H NMR signal intensity gains seen for imidazole change with catalyst ligand deuteration and the introduction of acid.

Imidazole ligand exchange rates in the active SABRE catalyst. The free imidazole build up rate in solution of **5a**, without HCl, proved to be 3.39 s^{-1} and its H_2 loss rate 3.68 s^{-1}. However, in the presence 0.8 equivalent HCl, the imidazole build up rate in solution fell to 2.52 s^{-1} while the apparent H_2 loss rate became 4.75 s^{-1}. For **5b**, without HCl, the ligand build-up rate was 1.04 s^{-1} and the H_2 loss rate 1.75 s^{-1} but with HCl (0.8-equivalents) they became 1.11 s^{-1} and 1.85 s^{-1} respectively. These ligand build-up rates are therefore faster than those seen for indazole which must account for the improved SABRE performance seen with imidazole. However, it is interesting to see that the IMes system now exchanges more rapidly than the SIMes form which suggests that the buried volume[9, 33] term associated with the NHC plays a greater role here in promoting ligand loss. Promotion of H_2 loss in acid solution suggest that the complex is susceptible to protonation which would be detrimental to SABRE.[10d]

Effect of changing the ligand scaffold to d_{22}-IMes or d_{22}-SIMes on the level of SABRE shown by imidazole. When the catalysts d_{22}-IMes-**1a** and d_{22}-SIMes-**1b** are deployed with imidazole the signal intensities seen under SABRE in indazole and acetonitrile fall dramatically.

Effect of relaxation within the SABRE catalyst on the level of imidazole signal enhancement. The relaxation times of the protons in imidazole were also studied in a similar way to those of indazole and are presented in Table 4. The corresponding values for the free substrates in degassed methanol-d_4 solution are 51.1 s for H-2, and 26.6 s for the H-4 and H-5 response of imidazole while the values for CH_3CN was 16.3 s at 298 K (the corresponding values at 263 K are 33.3, 13.5 and 11.4 s respectively). It is notable that the relaxation times for free imidazole are larger than those of indazole, with the N-isolated proton H-2 having a value of 51 seconds. At 298 K this value falls by 67% to 16.9 s in the presence of **5a** while the corresponding fall in indazole H-2 T_1 value was 39% under analogous conditions and is consistent with the higher ligand exchange rates for imidazole.

For IMes, at 263 K, the relaxation times within **5a** of the three magnetisation receptors are 3.1 s (H-2), 1.6 and 1.0 s (H-4 and H-5), while for **5b** they are 3.5, 1.8, 1.9 s respectively and hence all are larger than the 0.9 s value determined for H-3 in **3a**. This behaviour is therefore consistent with the improvement in SABRE efficiency that is seen on moving to imidazole. In the ^{2}H-labelled form of **5a**, the corresponding T_1 values increase to 4.3, 2.4 and 1.2 s respectively while in **5b** they become 3.7, 1.4 and 1.9 s. Both of these sets of values at 9.4 T are therefore larger than those resulting from the corresponding ^{1}H-labelled catalysts. It is therefore clear that these high field values are not a good indicator of the role relaxation plays during SABRE transfer in low field.

Table 4. here: Experimental T_1 values of imidazole molecule in the presence of **3** and **5**.

Polarization transfer to ^{13}C in imidazole. A series of hyperpolarised imidazole ^{13}C NMR spectra were also recorded using a methanol-d_4 solution that initially contained a 7-fold imidazole and 3-fold acetonitrile excess relative to **1a**, with and without HCl. These NMR spectra are detailed in Figure 8. The ^{13}C signals of free imidazole also proved to exhibit far greater signals gains than those found for indazole. For the signal due to C_A, a strong response was seen while the averaged signal, observed for the two remaining CH sites, was weaker. The intensities exhibited by these signals are again field dependent with both showing maxima after transfer at ca. 40 and 90 G. In contrast, upon adding acid the signals for C_B appear strongly (Fig. 8 right), presumably due to a sharpening of the response due to the increased rate of NH site interchange, although there no effect is seen in the PTF plot. When **1b** is employed, the corresponding signal gains on C_B were around 10-times better than those seen with **1a** in neutral solution. When acid was added, the level of ^{13}C response resulting from **1b** increased by a further 12-fold. We can therefore conclude that while IMes is the better motif for ^{1}H-SABRE, ^{13}C-SABRE benefits from deploying SIMes. When the corresponding d_{22}-IMes and d_{22}-SIMes forms are examined, no real benefits are seen in neutral solution, but in slightly acidic solution d_{22}-SIMes did yield a further doubling in ^{13}C polarisation level. It is therefore clear that the optimal catalyst for SABRE depends on the NMR active nucleus that is targeted. We note that ^{15}N signals can also be seen after transfer in the μ-metal shield as described in the supporting information.

Fig. 8. here: ^{13}C NMR SABRE intensities as a function of PTF before and after adding 0.8 equivalents HCl_{aq} to 3 mL d_4-methanol solution of **1b**, with 7 equivalents of imidazole and 3 equivalents of NCMe at room temperature.

Table 5. here: Maximum level of ^{13}C signal enhancement seen for carbon signals imidazole as a function of catalyst (transfer field maximum in brackets).

Conclusions

In conclusion, we have described a series of studies on the SABRE hyperpolarization of the substrates (sub) indazole and imidazole, in the presence and absence of the co-ligand acetonitrile, using the precatalysts [IrCl(COD)(IMes)] and [IrCl(COD)(SIMes)]. These studies reveal that SABRE delivers a 830-fold signal enhancement for the H-3 resonance of imidazole, and a 178-fold improvement for the H-2 resonance of indazole at 9.4 T in the presence of acetonitrile. These signals gains compare with values of 515 and 334-fold that were observed here in the absence of acetonitrile and therefore indicate that in the case of imidazole the presence of a co-ligand is beneficial. The co-ligand acetonitrile was observed to exhibit a maximum 572-fold signal gain (190-fold per proton) during this study which reveals how this value is controlled by the identity of the substrate. If high acetonitrile polarisation is targeted, working in the presence of ^2H-labelled indazole is therefore likely to reflect a good solution.

These results have been rationalised by studies on the catalyst, which in this case revealed two complexes result, $[Ir(H)_2(sub)_2(NCMe)(NHC)]Cl$ and $[Ir(H)_2(sub)_3(NHC)]Cl$. When the NHC is IMes or SIMes, the *tris*-substituted complex is favoured over the *bis*-substituted complex. Furthermore, both of these complexes undergo the necessary substrate and H_2 loss processes that allow them to drive the hyperpolarisation of these agents. The H_2 loss rates for the complexes with indazole were 0.65 s^{-1} for IMes and 0.08 s^{-1} for SIMes, while for imidazole they were 3.68 s^{-1} and 1.75 s^{-1}. Given that p-H_2 is the source of hyperpolarisation, these values suggest that indazole should show weaker polarisation than imidazole, and that the IMes form of the catalyst is superior. However, substrate loss rates also play a role in controlling the level of SABRE. In the case of **2a**, this is reflected in the bound acetonitrile and indazole ligands, while in **3a** it is just indazole ligand loss that is important. The effective ligand build up rates in solution for indazole were 0.24 s^{-1} in **3a** and compare to that for imidazole of 3.39 s^{-1} in **5a**. Hence the higher substrate loss rate matches with the observation of better SABRE performance in the hyperpolarization of imidazole through **5a**. However, as all three of these free ligand build-up rates are substantially smaller than that exhibited for pyridine by $[Ir(H)_2(IMes)(pyridine)_3]Cl$, which is 22 s^{-1}. The hyperpolarisation of indazole and imidazole reported here is therefore less efficient than that achieved for pyridine.[6b]

One further impact of these ligand exchange values is reflected in the optimum p-H_2 contact time, which is referred to here as the bubbling time when the automated polariser is used. While polarisation transfer proceeds under J-coupling, the catalyst gains its polarisation for transfer through the addition of fresh p-H_2. Hence if the complex lifetime is short, p-H_2 addition and transfer must proceed on a relatively rapid timescale and a short bubbling time can be employed. If the catalyst lifetime is longer, p-H_2 addition and transfer will proceed on a slower timescale and a longer bubbling time can be employed to reach the point where relaxation acts to limit the ultimate level of polarisation that is exhibited by the free substrate.

The recent paper by Barskiy et al. develops these points.[11d] It is for this reason that we used a 20 second bubbling time when detecting a ^{1}H response for indazole, extending to 35 seconds when looking at the corresponding ^{13}C signals, and 60 seconds for imidazole. Furthermore, upon changing the NHC to SIMes, the corresponding indazole build-up rates increase to 0.64 s^{-1} for **3b**, but fall to 1.04 s^{-1} for **5b**. This suggests that for indazole, SIMes works better due to higher exchange, but for imidazole the reverse is found experimentally and hence the H_2 exchange rate must be more critical.

We also utilised a series of ^{2}H labelled forms of these catalysts with a view to improve on the level of SABRE by harnessing potentially longer catalyst relaxation times. An earlier report by Fekete et al.[7] demonstrated how ^{2}H labelling of the catalyst led to a dramatic increase in the level of SABRE. Barskiy et al. have built on these, and other results, to produce a simple analytical model to describe this behaviour which suggests that relaxation and not ligand dissociation is critical to achieving optimal enhancement.[11d] The dominant mechanisms for relaxation within these small-molecule system are predicted to be dipole-dipole based, with scalar relaxation through coupling to a second quadrupolar nucleus playing a role.[31, 34] The SIMes system proved optimal for indazole, and the 90-fold signal gain per proton with d_{22}-SIMes exceeded the performance of the ^{1}H-labelled form by 150%. In contrast, the better performing ^{1}H-form of IMes yielded a 680-fold signal gain per proton in imidazole but upon changing to its d_{22}-IMes counterpart SABRE efficiency fell by 60%. Hence ^{2}H-labelling does not automatically lead to improved SABRE.

SABRE derived signals gains were also revealed in the ^{13}C and ^{15}N responses of these agents, which in the case of imidazole were improved by the addition of trace amounts of HCl to promote proton transfer, resulting in a sharp coalesced response for its two nominally inequivalent CH-CH centres (see supporting information).

Results were presented here that detail the relaxation effects of the active form of the catalyst. All of these catalysts proved to contain bound substrate molecules whose protons had relaxation times that were between 25 and 5 times smaller than those of the free material. For imidazole, the longer proton relaxation times that are exhibited by the free material were found to translate into longer relaxation times in the corresponding protons on the catalyst at field. If this situation is mimicked at low-field where SABRE transfer takes place, this will act to minimise the loss of p-H_2 derived hyperpolarisation during polarisation transfer. The use of ^{2}H-labelled NHCs in the form of d_{22}-IMes-**1a** and d_{22}-SIMes-**1b,** however, resulted in a slight reduction in these relaxation times. It is noteworthy, however, that the level of acetonitrile hyperpolarisation was dramatically improved by using d_{22}-IMes rather than its ^{1}H-containing version by over 390%. These results serve therefore to illustrate the complexity of this process and suggest that a series of rigorous experimental studies are needed to produce a truly optimised catalyst for a specific substrate.

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Table 1. : Overall proton signal enhancement values returned for indazole and CH_3CN as a function of catalyst at 9.4 T using the polarisation transfer field detailed in brackets; the associated reagent concentrations were 6.5 mM (iridium), 65 mM (indazole) and 19.5 mM (acetonitrile).

	Enhancement (PTF)	
Catalyst	**Indazole**	**Acetonitrile**
IMes	116 (70 G)	146 (80 G)
d_{22}-IMes	82 (90 G)	572 (90 G)
SIMes	294 (70 G)	437 (80 G)
d_{22}-SIMes	457 (70 G)	372 (80 G)

Table 2.: Experimental T_1 values determined at 9.4 T in methanol-d_4 solution for the indicated proton nuclei of free and bound indazole at 263 K and 298 K respectively; the associated reagent concentrations were 6.5 mM (iridium), 65 mM (indazole) and 19.5 mM (acetonitrile) and the labelling follows that in Scheme 1.

Site	**IMes T_1/ s**		**d_{22}-IMes T_1/ s**		**SIMes T_1/ s**		**d_{22}-SIMes T_1/ s**	
263 K	**Free**	Coord	**Free**	Coord	**Free**	Coord	**Free**	Coord
H-3	**15 ± 4[x]**	0.9	**4.8**	0.8	**16.1**	1.3	**10.7**	0.9
H-8	**7.0**	xx	**3.5**	1.4	**8.4**	2.7	**5.8**	2.2
H-5	**7.0**	1.9	**3.3**	1.6	**7.3**	-	**5.5**	-
H-7	**4.1**	2.2	**2.6**	-	**4.6**	1.7	**3.6**	1.1
H-6	**xx**	1.7	**2.7**	0.9	**4.8**	1.9	**3.6**	1.7
NCMe	**8.2**	-	**4.8**	-	**11.5**	1.3	**8.2**	-
Site 298 K								
H-3	**13.6**	2.1	**9.8**	1.9	**11.8**	0.6	**11.7**	5.6
H-8	**10.3**	5.8	**7.4**	3.7	**10.8**	-	**8.9**	4.2
H-5	**10.5**	2.7	**7.5**	-	**10.9**	2.9	**9.0**	-
H-7	**6.7**	4.0	**5.5**	2.3	**7.0**	1.7	**6.2**	3.75
H-6	**7.2**	-	**5.6**	-	**7.6**	-	**6.6**	1.56
NCMe	**8.7**	-	**8.9**	-	**12.4**	-	**10.2**	-

[x] Peak behaviour anomalous due to ^{2}H label incorporation

[xx] peak overlap prevents accurate assessment

Table 3.: Indicated proton signal enhancement levels achieved at 298 K, with a PTF of 80 G, when measured at 9.4 T, by the action of the precatalysts **1a** and **1b** on imidazole, with and without HCl, where the concentrations are 6.5 mM iridium, 65 mM indazole and 19.5 mM acetonitrile.

Resonance (without HCl)	^{1}H-Signal Enhancement (fold)			
	IMes	***d*$_{22}$-IMes**	**SIMes**	***d*$_{22}$-SIMes**
H-2	-830	-198	-517	-280
H-4 & H-5	-606	-300	-197	-206
CD_3OH	1.5	10	1.4	1.2
CHD_2OD	2.5	45	7.5	0.5
NCMe	-35	-30	-4	0
Resonance (with 5 mM HCl)	**IMes**	***d*$_{22}$-IMes**	**SIMes**	***d*$_{22}$-SIMes**
H-2	-571	-210	-647	-225
H-4 & H-5	-456	-153	-562	-251
CD_3OH	-22	-13	-7	-31
CHD_2OD	2	0.2	1.5	-0.5
NCMe	-16	-168	-12	11

Table 4.: Experimental T_1 values, determined at 9.4 T in methanol-d_4 solution for the indicated proton nuclei of free and bound imidazole (**5b**) at 263 K and 298 K respectively; the associated reagent concentrations were 6.5 mM (iridium), 65 mM (imidazole) and 19.5 mM (acetonitrile) and the labelling follows that in Scheme 2.

Temperature		263 K		298 K		298 K (with HCl)	
Catalyst	Proton / T_1(s)	**IMes**	***d*$_{22}$-IMes**	**IMes**	***d*$_{22}$-IMes**	**IMes**	***d*$_{22}$-IMes**
Free substrates	**H-2**	**33.7**	**25.5**	**16.9**	**22.9**	**15.8**	**21.8**
	H-4 & H-5	**14.1**	**12.0**	**12.2**	**15.1**	**11.9**	**14.8**
	NCMe	**8.2**	**9.6**	**8.3**	**9.5**	**7.9**	**10.3**
Bound imidazole	*H-2$_{eq}$*	*3.1*	*4.3*	*13.7*	*14.1*	*8.7*	*13.4*
	H-4$_{eq}$	*1.6*	*2.4*	*13.6*	*17.4*	*11.2*	*17.8*
	H-5$_{eq}$	*1.0*	*1.2*	*9.3*	*9.4*	*3.2*	*6.6*
	H-2$_{ax}$	4.1	3.1	4.0	3.0	4.4	7.6
	H-4$_{ax}$	2.7	3.6	7.9	3.5	9.5	7.1
	H-5$_{ax}$	2.8	1.7	4.6	2.5	5.5	4.9

Temperature		263 K		298 K		298 K (with HCl)	
Catalyst	Proton / T_1(s)	**SIMes**	***d*$_{22}$-SIMes**	**SIMes**	***d*$_{22}$-SIMes**	**SIMes**	***d*$_{22}$-SIMes**
Free substrates	**H-2**	**34.4**	**25.9**	**17.0**	**14.8**	**13.2**	**12.8**
	H-4 & H-5	**14.7**	**13.0**	**12.8**	**14.0**	**10.5**	**12.1**
	NCMe	**11.5**	**10.8**	**9.8**	**14.7**	**8.2**	**14.3**
Bound imidazole	*H-2$_{eq}$*	3.5	*3.7*	*13.0*	*11.0*	*13.1*	*9.9*
	H-4$_{eq}$	1.8	*1.4*	*11.1*	*10.0*	*11.0*	*10.2*
	H-5$_{eq}$	1.9	*1.9*	*9.7*	*8.8*	*10.6*	*10.5*
	H-2$_{ax}$	-	3.0	-	8.2	-	-
	H-4$_{ax}$	2.8	3.6	7.9	6.0	17.9	7.5
	H-5$_{ax}$	-	2.6	4.2	3.8	13.8	4.8

Table 5.: ^{13}C NMR signal enhancement levels seen for the indicated carbon signals of imidazole as a function of catalyst (optimum polarisation transfer field in brackets) at 9.4 T, with and without 5 mM HCl; the associated reagent concentrations were 6.5 mM (iridium), 65 mM (imidazole) and 19.5 mM (acetonitrile).

Catalyst ^{13}C signal	C_A	C_B	C_A	C_B
	without HCl		with HCl	
IMes	61 (90 G)	9 (120 G)	59 (90 G)	40 (30 G)
***d*$_{22}$-IMes**	243 (90 G)	-	144 (80 G)	149 (40 G)
SIMes	446 (100 G)	89 (100 G)	365 (90 G)	489 (110 G)
***d*$_{22}$-SIMes**	274 (110 G)	-	221 (30 G)	322 (30 G)