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Rational ligand choice extends the SABRE substrate scope†

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Here we report on chelating ligands for Signal Amplification By Reversible Exchange (SABRE) catalysts that permit hyperpolarisation on otherwise sterically hindered substrates. We demonstrate ^{1}H enhancements of ~100-fold over 8.5 T thermal for 2-substituted pyridines, and smaller, yet significant enhancements for provitamin B_6 and caffeine. We also show ^{15}N-enhancements of ~1000-fold and ^{19}F-enhancements of 30-fold.

Signal Amplification By Reversible Exchange (SABRE) is a relatively recent discovery among hyperpolarisation methods (2009).[1–5] Hyperpolarisation is transferred from *para*-hydrogen (*p*-H_2) to nuclei in a substrate molecule through *J*-coupling interactions mediated by the metal centre of a polarisation transfer catalyst. Both *para*hydrogen and substrate are in reversible exchange on the catalyst and polarisation flows from *para*hydrogen derived hydrides[6] to ligated substrates during the lifetime of the complex.[1,5,7]

SABRE allows for efficient polarisation of ^{1}H and ^{15}N spins within about one minute.[8–10] The technique uses simple hardware and has been expanded to a wide range of other spin-1/2 nuclei including ^{13}C, ^{19}F, ^{31}P, and others[1,4,11–15] Moreover, heterogeneous SABRE and SABRE in aqueous medium have been demonstrated.[16–22] All-in-all, this technique has made large advances for preparation of hyperpolarised substances, and has demonstrated the potential to generate injectable hyperpolarised contrast agents for *in vivo* magnetic resonance spectroscopic imaging.[4,8]

In this paper, we capitalize on the simple insight that steric considerations are of essence and can make a drastic difference in SABRE efficiency. Particularly, substrate size and binding pocket must be well matched. Guided by this insight, we introduce a hyperpolarisation catalyst able to hyperpolarise larger, sterically hindered substrates, primarily 2-substituted pyridines, that are not efficiently hyperpolarised with current widely used catalysts.[10,23] Moreover, we demonstrate hyperpolarisation of provitamin B_6 and caffeine, which bear substituents in the *ortho* position to the N-heteroatom as well.

Historically, SABRE was discovered with Crabtree's catalyst $[Ir(PR_3)(pyr)(COD)]PF_6$ (**1**) (R = cyclohexyl, pyr = pyridine, COD = 1,5-cyclooctadiene) (see Fig. 1).[1] Initially, ^{1}H signal amplifications over thermal signals (enhancements) were found to scale favourably with electron density and steric bulk of the phosphine

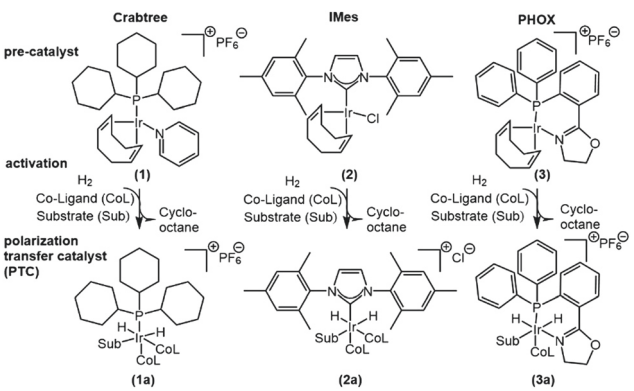

Fig. 1 Three generations of catalysts for SABRE. The canonical Crabtree's catalyst (**1**), the IMes catalyst (**2**) yielding maximal enhancements on pyridine, and the Phox catalyst (**3**) applicable to sterically demanding substrates, as shown here. Coligands (CoL) are constituted by solvent, substrate or an auxiliary compound.

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ligand,[2] but phosphine ligands were quickly replaced by N-heterocyclic carbenes (NHCs), most importantly, IMes[5] (**2**) and (**2a**) (Fig. 1 and 2, IMes = 1,3-bis(2,4,6-trimethylphenyl)-imidazole-2-ylidene), giving rise to a drastic increase of enhancements.[5,24] Most optimization efforts using the NHC motif were geared towards pyridine and structurally similar compounds.[25] Recently, record polarisations on the order of 50% were obtained with perdeuterated[8] or chlorinated[26] variants of the [IrCl(IMes)(COD)] (**2**). However, these improvements do not extend to other substrates with higher steric demands. In efforts to target a broader substrate scope, auxiliary compounds (co-ligands) have been utilized to increase the number of viable polarisation transfer targets and to focus transferred polarisation.[27–31]

Also, chelating ligands have been explored, but polarisation levels remained low.[32,33] While a variety of smaller pyrazole derivatives were studied in ref. 34, polarisation on 2-substituted pyridines was not reported.

Here we demonstrate that [Ir(COD)(Phox)]PF_6 (**3**) (Phox = 2-(2-(diphenylphosphanyl)phenyl)-4,5-dihydrooxazole) (Fig. 1), a catalyst for asymmetric hydrogenation of olefins,[35] can serve as a polarisation transfer catalyst for more sterically demanding substrates.[36,37] We target ^{1}H, ^{15}N and ^{19}F hyperpolarisation in *ortho*-substituted pyridine derivatives, including provitamin B_6 and caffeine. It is noteworthy, that although Phox catalyst (**3**) performs *worse* as a polarisation transfer catalyst for pyridine, compared to IMes catalyst (**2**), Phox catalyst (**3**) is superior for sterically congested substrates.

As illustrated in Fig. 1, in SABRE experiments, precatalysts are transformed into their catalytically active species under a H_2 atmosphere in presence of polarisation transfer targets. For pre-catalyst (**2**) and pyridine, one obtains $[Ir(H)_2(IMes)(pyr)_3]^+$ (**2a**). This dihydride derived from *p*-H_2 constitutes the catalytically active complex in polarisation transfer.[5,38] One important consequence of monodentate ligands (*e.g.* an NHC or phosphines) forming octahedral iridium dihydride complexes is that three sites remain for coordination (pyridine in (**2a**)). By using a bidentate ligand, such as [Ir(COD)(Phox)]PF_6 (**3**) the binding pocket size is increased over that of complexes with monodentate ligands.

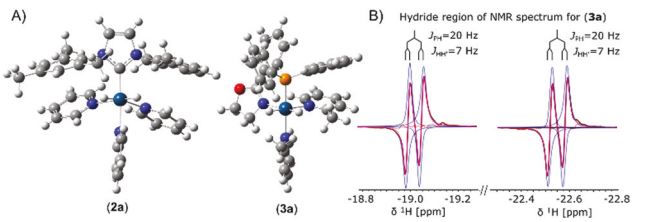


Fig. 2 (A) Comparison of the structure of $[Ir(H)_2(IMes)(pyr)_3]^+$ (**2a**) and the structure predicted for $[Ir(H)_2(Phox)(MP)_2]^+$ (**3a**) (MP = 2-methylpyridine). (B) Experimental spectrum (red) and fit (dashed line, cyan) of the hydride resonances of (**3a**). For the experiment, constant *para*-H_2 flow was supplied at 8.45 T and the excitation pulse is 45°. The fit is the sum of individual resonances (blue curves). The maxima of the blue curves can be used to extract δ = −19.03 and −22.55 ppm, using $J_{HH'} \approx -7$ Hz, $J_{HP} = J_{H'P} \approx 20$ Hz as shown in the small insets directly above the spectra. With a chemical shift difference of approximately 3.5 ppm, a PASADENA-like spectrum is obtained.

When pre-catalyst (**3**) is activated under a hydrogen atmosphere in the presence of substrates, (**3a**) is formed (see Fig. 1 and 2A). Evidence for (**3a**) is provided by NMR data (Fig. 2B) and accompanying density-functional theory (DFT) calculations. The computational approaches (FHI-aims code,[39–41] density functionals including dispersion interactions[42–44] and implicit solvation[45]) have a history of successful use for molecular structure prediction[46,47] and are fully detailed in the ESI.† The DFT calculations find (**3a**) to be the lowest energy dihydride complex. Consistent with this structure, we find different chemical shifts for the two hydride species, as displayed in Fig. 2. Specifically, if *para*-hydrogen is bubbled through the solution at high field (8.45 T) the anti-phase spectrum of Fig. 2B is obtained.[48,49]

We observe chemical shifts of −19.0 and −22.5 ppm for the hydride resonances, pointing to *trans*-to nitrogen coordination for both hydrides, where the chemical shift at −22.5 ppm is identical with the *trans*-to-pyridine hydride in (**2a**).

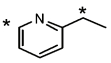
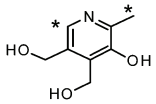
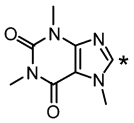
The observed hydride to hydride *J*-coupling in (**3a**) is $J_{HH'} \approx -7$ Hz and the hydride to ^{31}P *J*-couplings are $J_{HP} = J_{H'P} \approx 20$ Hz. The *J*-couplings, chemical shifts, and magnetic field dependence of hyperpolarisation (see ESI†) are similar to those of Crabtree's catalyst, serving as further evidence for structure (**3a**). While a full conformational study is beyond the scope of this work, the gathered insights explain the ability to hyperpolarise larger substrates *vs.* common SABRE substrates.

Table 1 contrasts ^{1}H enhancements obtained with the first-generation Crabtree's catalyst (**1**), the IMes catalyst (**2**) optimized for pyridine, and the bidentate Phox catalyst (**3**). As in studies using (**1**), maximum enhancements on substrate ^{1}H nuclei with (**3**) are obtained at 140 G irrespective of substrate identity (see ESI†). This is consistent with the study of Pravdivtsev *et al.*, where presence of ^{31}P in the first coordination sphere of Ir changes the matching conditions to a higher magnetic field when compared to (**2**).[50] It is noteworthy that catalyst (**3**) yields enhancements of aromatic protons in α-picoline and 2-fluoropyridine (Table 1, entries 2 and 3), comparable to those originally reported for SABRE with Crabtree's catalyst (**1**) and pyridine (Table 1, entry 1).[1,2] Interestingly, Crabtree's catalyst yields a small but non-negligible hyperpolarisation effect on 2-fluoropyridine.

This shows that the activity of Crabtree's catalysts is not strictly zero for this substrate but still drastically lower than that of (**3**). Similar small but non-zero activity is possible for the other cases labeled "—" in Table 1, however, remained below the detection limits of our experiments.

The enhancements for aliphatic proton are relatively poor for all entries (~10-fold). Comparing entries 2 and 4, increasing the chain length of the aliphatic substituent reduces aromatic proton enhancements by 80%. Potentially the most interesting structure, from an application viewpoint, is provitamin B_6 (entry 5). Enhancements of aromatic and aliphatic protons of 7 and 2 respectively were achieved. The enhancements were limited since the provitamin B_6 was commercially available only as a hydrochloride salt, which necessitated addition of a base (triethylamine or NaOD) for neutralization.

Table 1 Comparison of average ^{1}H enhancements ε at RT (over thermal signals at 8.5 T). Asterisks in the molecular sketches denote the enhanced ^{1}H moieties. No enhancements are observed for substrate 6

#	Substrate name	Structure	^{1}H ε with (1)	^{1}H ε with (2)	^{1}H ε with (3) aromatic/aliphatic
1	Pyridine		100	1300	2
2	α-Picoline		—	—	132/11
3	2-Fluoro-pyridine		1[a]	—[b]	140
4	2-Ethyl-pyridine		—	—	25/5
5	Provitamin B_6		—[c]	—[c]	7/2[c]
6	2,6-Lutidine		—	—	—
7	Caffeine		—	—	4[d]

[a] Non-thermal signal (negative sign relative to thermal reference) but identical integral observed. [b] HD exchange of 2-fluoropyridine with solvent observed, see Fig. S16 in ESI. [c] From pyridoxine*HCl (neutralized with NaOD 40 wt% in D_2O). [d] Saturated in MeOH-d_4 (23 mM); only aromatic H enhanced.

This procedure also resulted in addition of a small amount of water, which reduces SABRE efficiency. Regarding the limitations by sterical congestion, we note that hyperpolarisation of 2,6-dimethylpyridine (entry 6) remained unsuccessful. To rationalize this finding, we show in the supplement by DFT (Fig. S5 and Table S9, as well as an analysis of strain effects in Section S2d and Tables S10–S13, ESI†) that substitution of 2-methylpyridine (entry 2) by 2,6-dimethylpyridine results in an energy increase of $\sim$+0.5 eV (48 kJ mol^{-1}), much larger than $N_a k_B T$. Adding additional co-ligands (CH_3CN, H_2O, pyridine), an approach that was successful in prior instances with sterically hindered substrates,[10,27,28,30,51] also failed to effect hyperpolarisation of 2,6-dimethylpyridine in the present work. Entry 7 (caffeine) also shows small but non-zero enhancements which may be expected as caffeine is the largest substrate we examined.

Next, we used the Phox catalyst (3) for polarising ^{15}N at μT magnetic fields with SABRE-SHEATH.[7,10,16,52] The simple substrate CH_3CN previously gave 190-fold ^{1}H enhancements when used as a coligand with IMes catalyst.[53] We investigated ^{15}N polarisation with $CH_3C^{15}N$ (50 mM) and 2.6 mM (3) as a function of temperature at microTesla fields as displayed in Fig. 3A. We found that ^{15}N polarisation levels of 1.5% are readily obtained, identical to polarisation levels achieved with (2) at these moderately high concentrations.[10] As indicated in Fig. 3, the optimal temperature is elevated when using the Phox catalyst (3). Here the maximum is found between 60 °C and 70 °C, whereas IMes works best at room temperature for ^{15}N-acetonitrile (2).[52] Shown in Fig. 3B, the Phox catalyst (3) hyperpolarises ^{15}N at natural

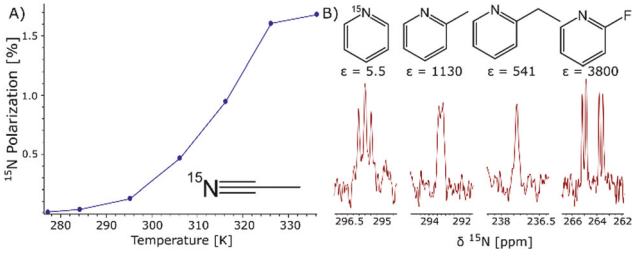


Fig. 3 (A) ^{15}N polarisation with PHOX (3) as a function of the sample temperature during polarisation build-up on ^{15}N labelled CH_3CN in the magnetic shield. Evolution field is 0.66 μT, build-up time 60 s. (B) ^{15}N spectra of naturally abundant 2-substituted pyridine derivatives and ^{15}N labelled pyridine hyperpolarised by SABRE-SHEATH at room temperature. 2.6 mM catalyst (3) and 50 mM substrate were used in all samples.

abundance in substrates 1–4 using 2.6 mM catalyst and 50 mM substrate. Nitrogen enhancements are larger for ^{15}N than for ^{1}H. However, the absolute polarisation levels are similar because the enhancement refers to thermal polarisation of ^{15}N, which is ten times lower than for ^{1}H.

Finally, we also tested the previously challenging[12] ^{19}F polarisation of 2-fluoropyridine (*i.e.*, ^{19}F in the *ortho* position) with (3) and achieved a 30-fold enhancement over thermal polarisation at 9.4 T, at an optimised polarisation transfer field of 5.4 mT (Fig. S15 in the ESI†).

In conclusion, the introduced PHOX multidentate ligand for SABRE catalysts allows for polarisation of bulkier substrates, including biologically relevant molecules such as provitamin B_6 or caffeine. Interestingly, hyperpolarisation is worse for pyridine than for 2-substituted pyridine derivatives. This shows that testing potential SABRE catalysts on a small set of substrates is insufficient and opportunities for expanding the SABRE substrate scope may be missed. Indeed, the Phox catalyst performs better than the highly optimised IMes catalyst when considering bulkier substrates. Moreover, attractive features of chelating ligands, such as reliable immobilization and simplification of kinetics to suppress non-hyperpolarising exchange pathways, give a promising handle towards the rational design of SABRE catalysts. Altogether, these finding provide a path towards a broader scope of SABRE hyperpolarisation with numerous applications in biomedicine and beyond.[29,54]

J. F. P. C. and A. W. J. L. contributed equally, conducted most experimental work, wrote and edited the paper. Z. Z. and J. R. L. helped with experimental work and edited the paper. R. L. conducted all ab-initio calculations. R. V. S. and E. Y. C. conducted the fluorine hyperpolarisation experiments and edited the paper. V. B. advised the ab-initio calculations and edited/revised the paper, W. S. W. advised the team. S. J. M. advised on chemical design and edited the paper. T. T. advised on data acquisition, wrote, edited and revised the paper.

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Conflicts of interest

There are no conflicts of interests to declare.

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