Probing SABRE Polarisation Transfer to Heteronuclei with Earth's Field NMR

Matheus Rossetto,[1] Fraser Hill-Casey,[1] Meghan Halse[1]
[1]Department of Chemistry, University of York, Heslington, York, YO10 5DD, UK

1. Introduction

Hyperpolarisation techniques have been developed to overcome the inherent low sensitivity of Nuclear Magnetic Resonance (NMR). Signal Amplification by Reversible Exchange (SABRE)[1] is one such technique that is typically carried out in the fringe field of the NMR spectrometer for detection at high magnetic fields (> 1 T). Although Earth's field NMR (EFNMR) suffers from significantly lower sensitivity, it provides a route for *in-situ* detection of SABRE hyperpolarised signals enabling the study of the SABRE polarisation transfer process. Of particular interest to this work is the polarisation transfer to ^{19}F in N-heterocyclic substrates. High field and Earth's field NMR simulations are utilised as tools to interpret and analyse complex EFNMR spectra exhibiting strong-coupling and deprived of chemical shift resolution.

2. Earth's Field NMR

- ✓ Instrumentally more compact
- ✓ Instrument cost: ~ £10,000
- ✓ Operates at the Earth's magnetic field (~ 50 µT)
  - • Very homogeneous
- ✓ Good spectral resolution

- – Significantly reduced signal intensities
- – Sample: tens of M in hundreds of mL
- x Zero chemical shift resolution

3. SABRE

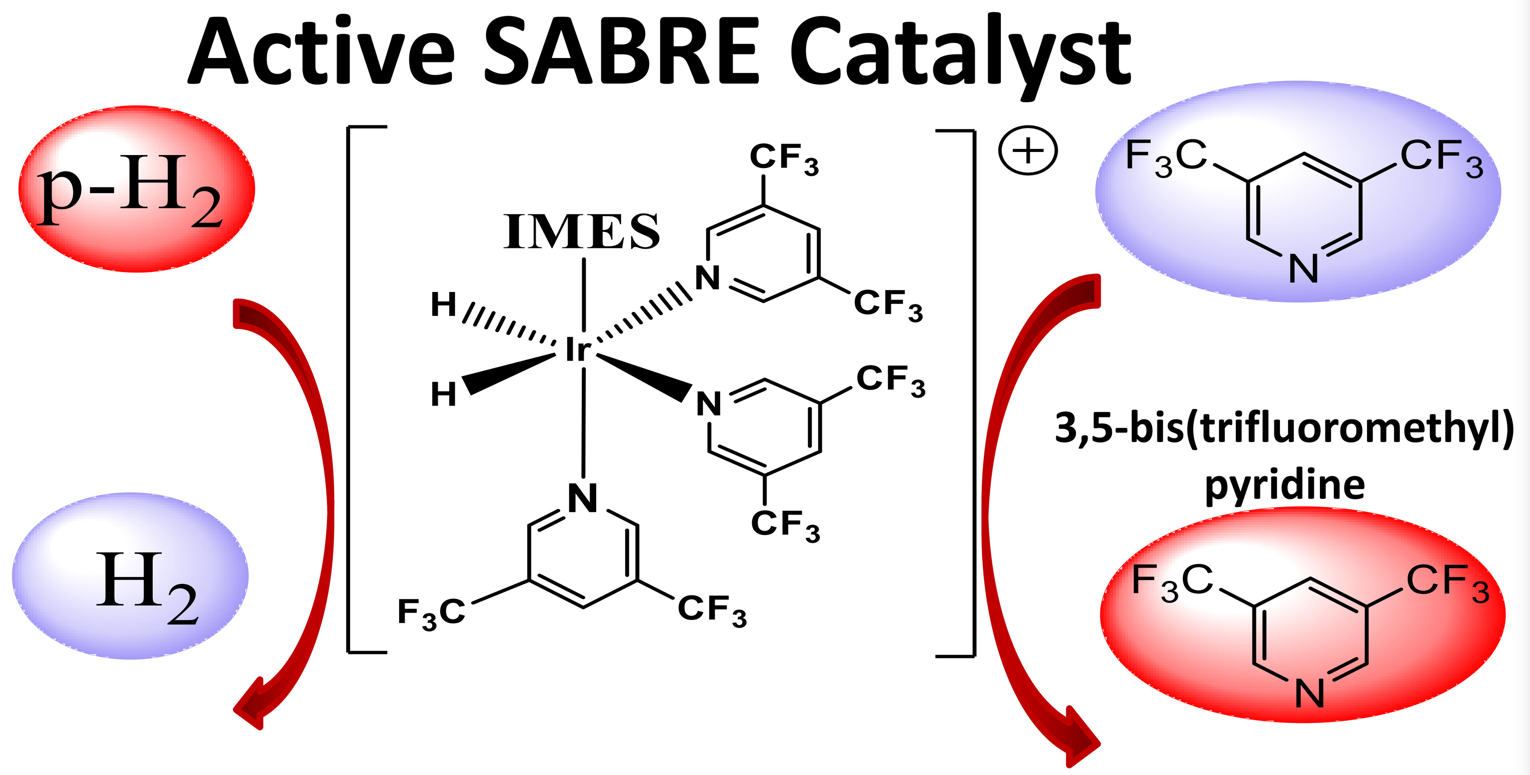


Fig 1 *SABRE polarisation transfer is mediated by a metal catalyst and relies on the reversibility of the p-H_2 and substrate binding.*

Polarisation transfer from p-H_2 occurs once the Polarisation Transfer Condition (PTC) is met. SABRE relies on the reversibility of substrate and p-H_2 binding as this enables build-up of hyperpolarised substrate in solution and displacement of H_2 with p-H_2. Polarisation transfer to fluorine has been demonstrated, using fluoropyridines[2].

Acknowledgments

EPSRC Engineering and Physical Sciences Research Council
University of York

4. *In-situ* SABRE with EFNMR detection

a

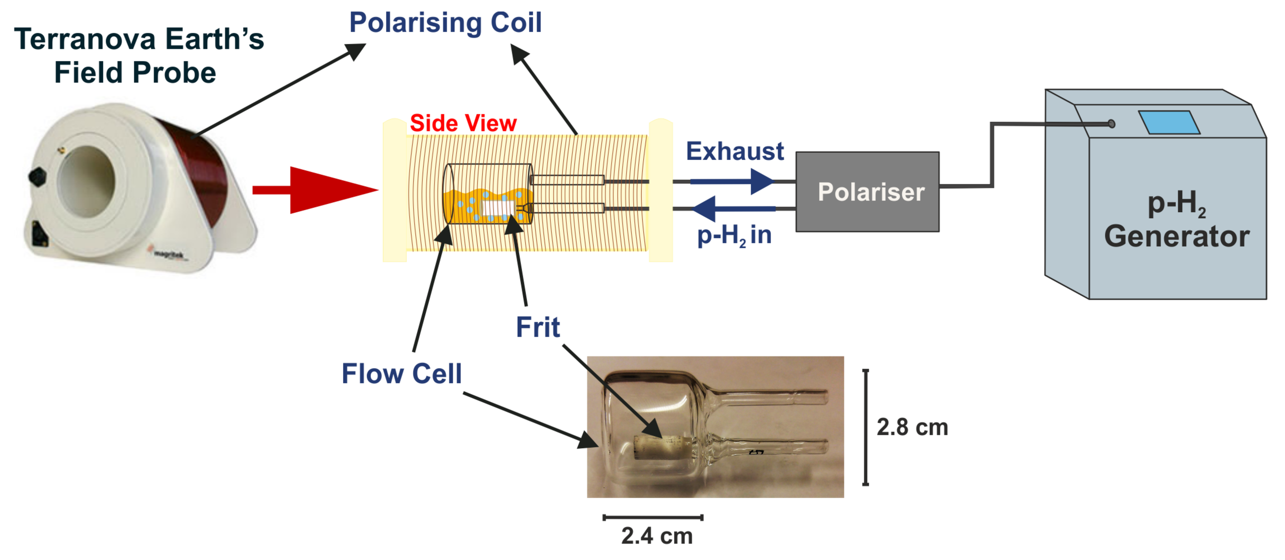


Fig. 2a *Schematic of the EFNMR system, which allows p-H_2 bubbling through the sample within a glass flow-cell, thus enabling in-situ detection of SABRE hyperpolarised signals[3].*

b

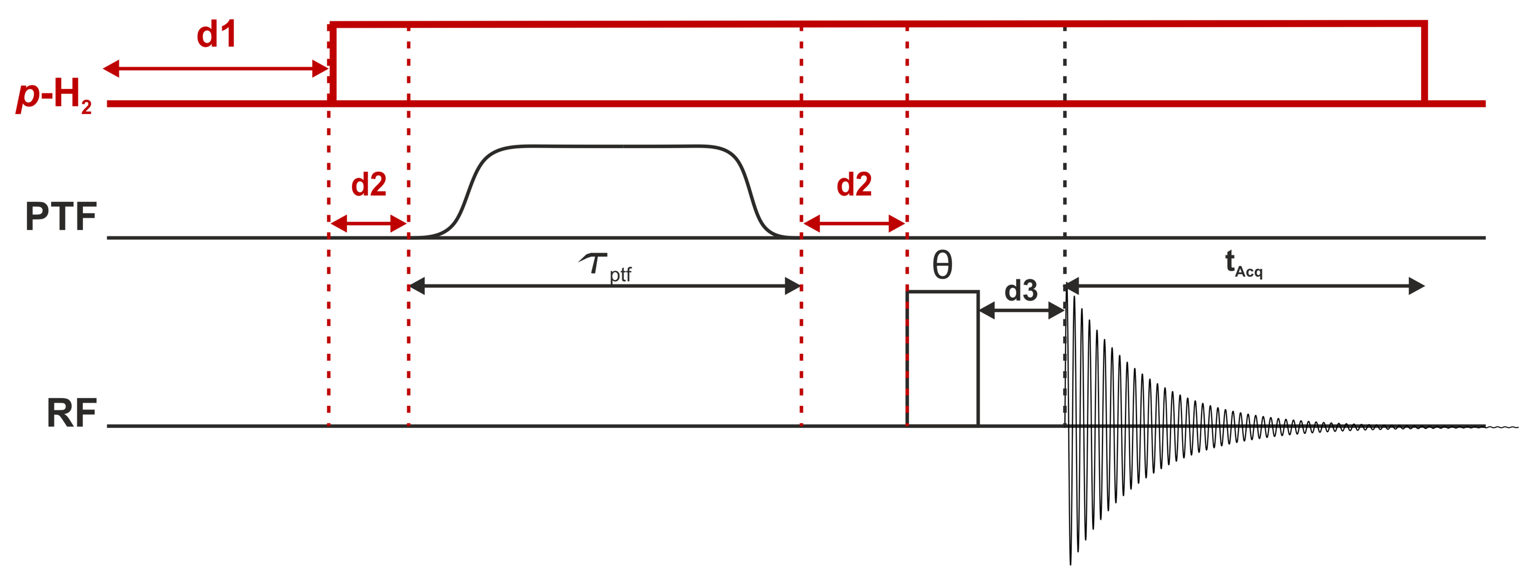


Fig 2b. *In-situ SABRE polarisation pulse sequence demonstrating the use of the switchable PTF coil to induce polarisation transfer before detection in the Earth's magnetic field.*

c

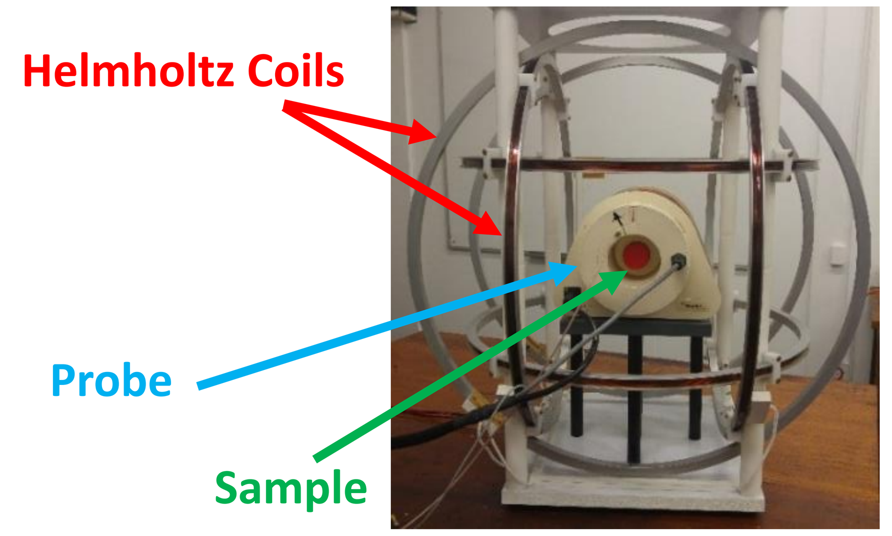


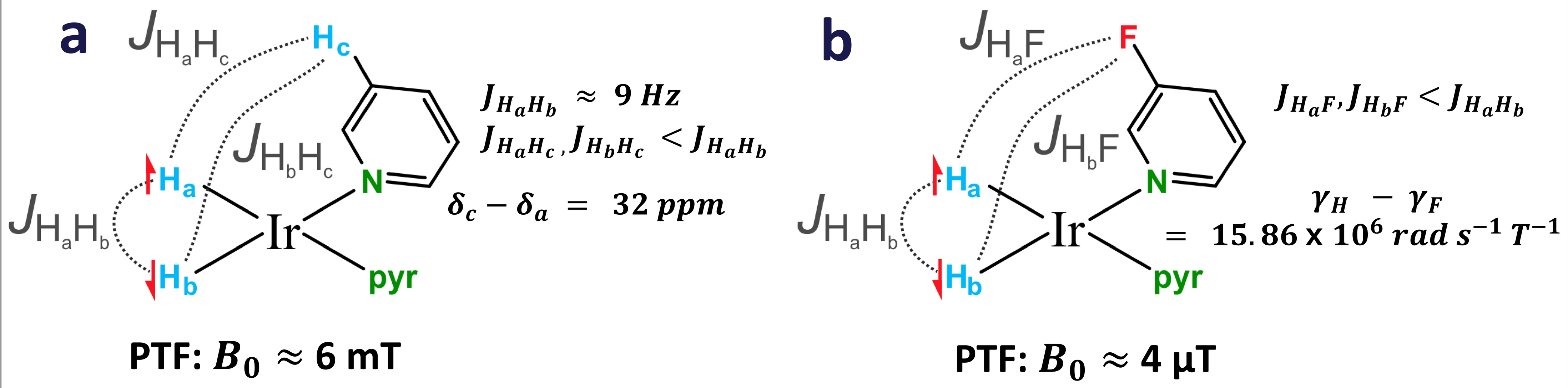
Fig. 2c *Helmholtz coils are used to access polarisation transfer fields below the Earth's magnetic field for heteronuclear polarisation transfer.*

5. Polarisation Transfer Condition

Polarisation transfer occurs spontaneously at low magnetic fields. It is most efficient once the PTC is satisfied.

$$J_{xy} \equiv \Delta\nu_{H_pH_z} = \frac{B_0\gamma_H(\delta_c-\delta_a)}{2\pi} \quad or \quad \frac{B_0(\gamma_H-\gamma_F)}{2\pi}$$

Where J_{xy} is the dominant J-coupling within the active-catalyst coupling network and $\Delta\nu_{H_pH_z}$ is the larmor frequency difference between the p-H_2 derived hydride and proton-z receiving the polarisation.



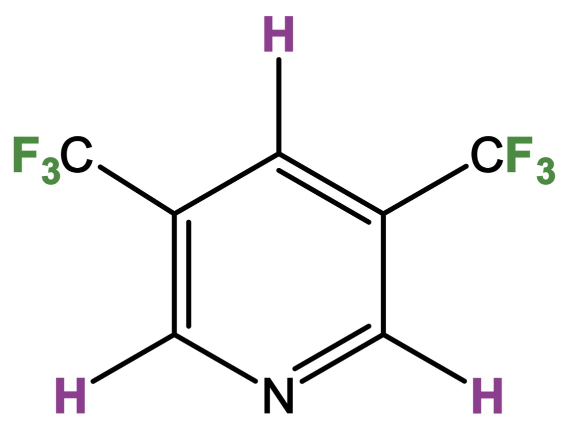
$J_{H_aH_b} \approx 9\ Hz$, $J_{H_aH_c}, J_{H_bH_c} < J_{H_aH_b}$, $\delta_c - \delta_a = 32\ ppm$

$J_{H_aF}, J_{H_bF} < J_{H_aH_b}$, $\gamma_H - \gamma_F = 15.86 \times 10^6\ rad\ s^{-1}\ T^{-1}$

Fig 3 *Schematic illustrating a) homonuclear polarisation transfer to the ortho-hydrogen in pyridine, and b) heteronuclear polarisation transfer to the fluorine in 3-fluoropyridine.*

SABRE polarisation transfer to heteronuclei is typically performed under SABRE in SHield Enables Alignment Transfer to Heteronuclei (SABRE-SHEATH) conditions[2].

6. 3,5-bis(trifluoromethyl)pyridine EF Spectra & Simulations



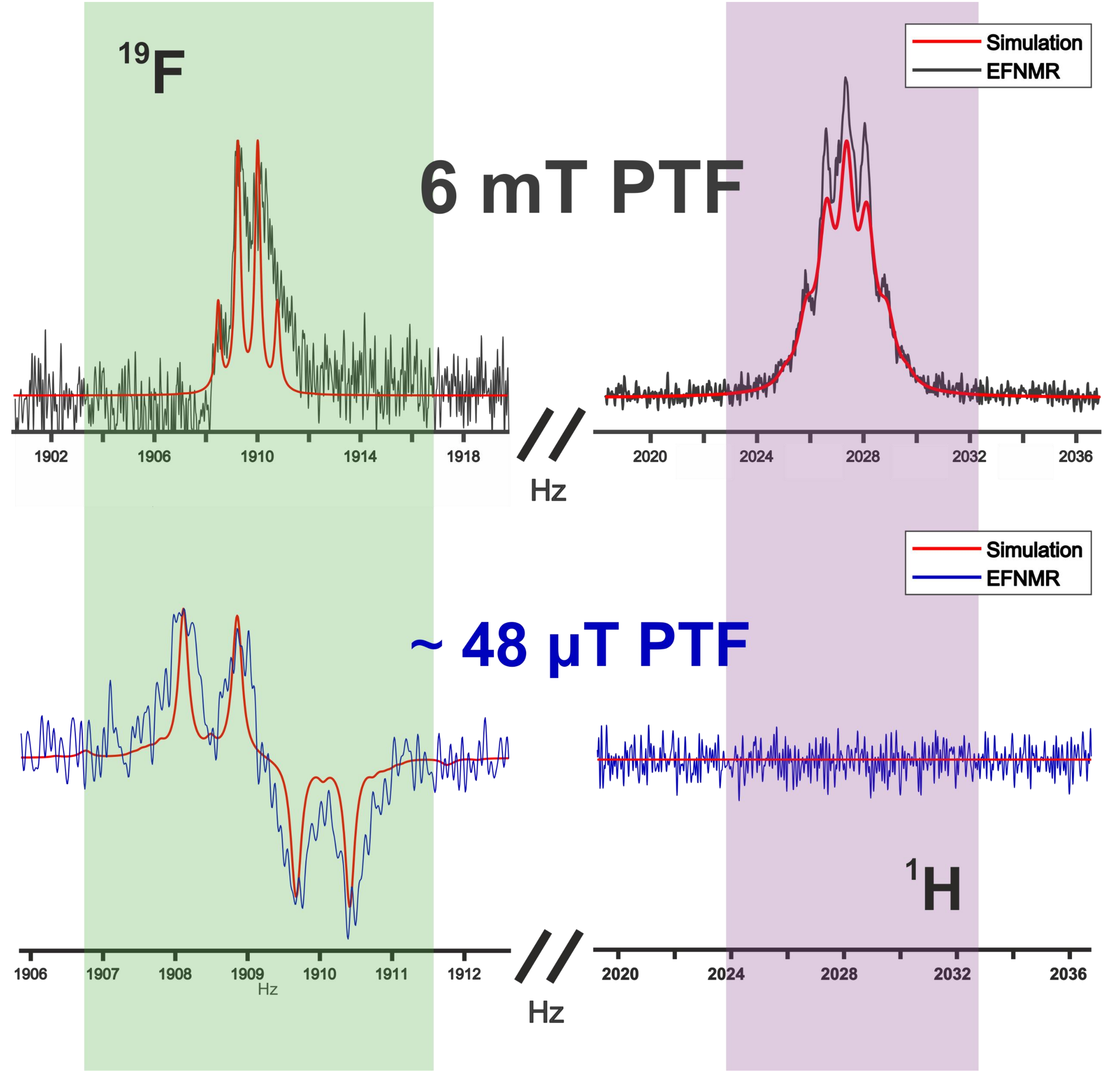


Fig 4 *Comparison of experimental SABRE hyperpolarised ^{19}F and ^1H EFNMR signals with EFNMR simulations acquired using Spinach[4]. The form of the SABRE-enhanced ^1H and ^{19}F EFNMR spectra are diagnostic of the the identity of the specific magnetic states that have been hyperpolarised and so can be used to explore the SABRE hyperpolarisation transfer process.*

References

1 R. W. Adams, J. A. Aguilar, K. D. Atkinson, M. J. Cowley, P. I. P. Elliott, S. B. Duckett, G. G. R. Green, I. G. Khazal, J. Lopez-Serrano and D. C. Williamson, *Science (80-.).*, 2009, 323, 1708–1711.

2 A. M. Olaru, T. B. R. Robertson, J. S. Lewis, A. Antony, W. Iali, R. E. Mewis and S. B. Duckett, *ChemistryOpen*, 2018, 7, 97–105.

3 Hill-Casey, F.; Sakho, A.; Mohammed, A.; Rossetto, M.; Ahwal, F.; Duckett, S.B.; John, R.O.; Richardson, P.M.; Virgo, R.; Halse, M.E. In Situ SABRE Hyperpolarization with Earth's Field NMR Detection. *Molecules* 2019, *24*, 4126.

4 H.J. Hogben, M. Krzystyniak, G.T.P. Charnock, P.J. Hore, I. Kuprov, "*Spinach - a software library for simulation of spin dynamics in large spin systems*", Journal of Magnetic Resonance, 208 (2011) 179-194.

7. Conclusion

With the use of a commercial EF Terranova MRI system, consisting of a built-in polarising coil, *in-situ* SABRE experiments can be carried out with detection in the Earth's magnetic field. Control over the magnetic field during SABRE *via* the polarising coil enables direction of polarisation from *p*-H_2 to a desired nucleus on the target substrate through the *J*-coupling network.

In-situ SABRE hyperpolarisation experiments were successful in acquiring hyperpolarised proton and fluorine signals of 3,5-bis(trifluoromethyl)pyridine, demonstrating the difference magnetic states that are observed under different PTF conditions. This will be interrogated further with simulations and experiments with a range of PTF's in order to build a better understanding of the polarisation transfer process.