Production of Catalyst-Free Hyperpolarised Ethanol Aqueous Solution via Heterogeneous Hydrogenation with Parahydrogen

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An experimental approach for the production of catalyst-free hyperpolarised ethanol solution in water via heterogeneous hydrogenation of vinyl acetate with parahydrogen and the subsequent hydrolysis of ethyl acetate was demonstrated. For an efficient hydrogenation, liquid vinyl acetate was transferred to the gas phase by parahydrogen bubbling and almost completely converted to ethyl acetate with Rh/TiO2 catalyst. Subsequent dissolution of ethyl acetate gas in water containing OH \(^-\) ions led to the formation of catalyst- and organic solvent-free hyperpolarised ethanol and sodium acetate. These results represent the first demonstration of catalyst- and organic solvent-free hyperpolarised ethanol production achieved by heterogeneous hydrogenation of vinyl acetate vapour with parahydrogen and the subsequent ethyl acetate hydrolysis.

Magnetic Resonance Imaging (MRI) is a widely used technique for visualization of various objects, from the routine medical diagnostics of patients to porous media1 and catalytic reactors2,3. However, the capabilities of MRI are largely restricted by its inherently low sensitivity. Therefore, a number of hyperpolarisation techniques4,5 such as Dynamic Nuclear Polarization (DNP)6,7, Spin-Exchange Optical Pumping (SEOP)8 and Parahydrogen-Induced Polarization (PHIP)9,10 are often utilized to overcome this problem. DNP is the most frequently used hyperpolarisation technique, but it has significant drawbacks of long polarization cycles (~20–100 min) and quite expensive equipment4. In contrast, the PHIP technique allows one to produce hyperpolarised (HP) substances in less than 1 min and is relatively inexpensive11. PHIP exploits high spin order of parahydrogen molecule (p-H\(_2\)) which is usually transferred to a substrate of interest via pairwise addition of two H atoms from the same p-H\(_2\) molecule to a double or a triple bond of the substrate molecule. This requirement of the chemical modification of a substrate significantly limits the range of compounds which can be hyperpolarised by PHIP9. This problem can be partially solved by the recently developed version of PHIP technique known as Signal Amplification By Reversible Exchange (SABRE)12. SABRE is based on the interactions of p-H\(_2\) with a suitable ligand upon their reversible binding to a metal complex13. In SABRE, the chemical structure of the substrate remains unchanged; however, the catalyst might be changed irreversibly14,15. Importantly, only a limited range of compounds, mostly nitrogen-containing heterocycles16 (e.g. pyridine) and PPh317 were hyperpolarised by SABRE so far. The second problem is that both the pairwise hydrogen addition in PHIP and the reversible exchange processes in SABRE are usually executed with the use of homogeneous catalysts such as transition metal complexes, that cannot be easily removed from a reaction mixture10,18. However, this problem can be solved by using heterogeneous catalysts19 such as supported metal nanoparticles20–22, immobilized metal complexes23 or bulk metals and metal oxides24 which are able to produce PHIP effects.

The two problems mentioned above, namely the nature of substrate molecules and the difficulty of separating the hyperpolarised molecules from the reaction mixture, make the preparation of HP contrast

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agents for biomedical MRI applications using PHIP technique a strongly challenging task because these contrast agents should be biocompatible and absolutely free from toxic catalysts and organic solvents. There are reports about the production of PHIP-hyperpolarised biomolecules such as succinate25, phospholactate26-28, glucose derivatives29, peptides29 and SABRE-hyperpolarised amino acids, peptides30 and drugs31. Importantly, all of these results were obtained with the use of homogeneous catalysts which were present in the reaction mixture along with HP molecules, making potential biomedical applications questionable.

An interesting approach which broadens the range of compounds that can be hyperpolarised by PHIP was suggested by Trantzschel et al.32 They produced HP ethanol, which is not accessible via direct homogeneous hydrogenation, using a two-step procedure consisting of vinyl acetate hydrogenation with p-H2 in D2O and subsequent alkaline hydrolysis with NaOD solution. However, the problem of separation of homogeneous catalyst present in the reaction mixture along with HP ethanol was not solved in that investigation. The described approach was recently extended by Reineri et al.33 First, they carried out similar hydrogenation/hydrolysis experiments with vinyl and propargyl acetates with the addition of field cycling procedure between the two chemical reactions which achieved the hyperpolarisation transfer to 13C nuclei of carboxylic groups. Thus, 13C-hyperpolarised acetate production was implemented. Next, extraction of hyperpolarised molecules from an organic to an aqueous phase was demonstrated for pyruvate. The experimental procedure was similar; however, in this case homogeneous hydrogenation of 2-propynyl-2-oxopropanoate was performed in a mixture of organic solvents (CDCl3/CD3OD). The addition of an aqueous NaOD solution yielded a biphasic system, and the aqueous phase containing HP pyruvate was used for the NMR investigation. Certainly, this phase extraction procedure allowed the authors to separate the HP product from the homogeneous catalyst; however, the obtained aqueous HP pyruvate was used for the NMR investigation. Certainly, this phase extraction procedure allowed the authors to separate the HP product from the homogeneous catalyst; however, the obtained aqueous phase should inevitably contain some amounts of very toxic methanol which is highly undesirable for possible biomedical applications.

The benefit of heterogeneous catalysis is that the catalyst can be easily separated from the reaction mixture even in the case of liquid phase hydrogenation. Moreover, gas phase hydrogenation with parahydrogen allows continuous production of catalyst-free HP substances31. Thus, the use of heterogeneous catalysts for the production of biocompatible HP contrast agents (e.g., ethanol) seems to be a very promising approach. However, recent attempts to produce HP alcohols via heterogeneous hydrogenation of C=O bond with parahydrogen were unsuccessful34. Therefore, in this communication we present for the first time an approach based on the use of heterogeneous hydrogenation with parahydrogen in combination with hydrolysis for HP ethanol production. It will be demonstrated below that heterogeneous hydrogenation of vinyl acetate with p-H2 in the gas phase with subsequent hydrolysis in the liquid phase yields HP ethanol, free from any catalyst and organic solvent. Moreover, our approach enables a continuous production of HP ethanol, which is a significant step toward potential biomedical applications.

Results and Discussion

It was shown recently that heterogeneous catalysts can be used in liquid phase hydrogenation with parahydrogen to produce polarised contrast agents in the liquid phase22. Moreover, utilization of the Rh/TiO2 catalyst allows one to achieve pronounced PHIP effects in water35. Therefore, we first attempted to apply the same procedure to vinyl acetate hydrogenation by bubbling gaseous mixture of reactants (vinyl acetate(gas) + parahydrogen) into the NMR tube containing D2O and the Rh/TiO2 catalyst at the bottom (see Supplementary Fig. S2). Indeed, it was found that pronounced PHIP effects can be observed for the CH3- and CH2-protons of ethyl acetate (see Supplementary Fig. S3). However, because of the very low activity of the catalyst in the heterogeneous liquid phase hydrogenation (confirmed by the absence of any signals of reaction product in the thermal 1H NMR spectrum) along with the presence of the catalyst as a solid powder in the reaction mixture, this approach cannot compete with the gas phase hydrogenation which is significantly more efficient in terms of reactant conversion which can reach 100% upon variation of the catalyst amount or the gas flow rate. Therefore, the combination of a very efficient gas phase heterogeneous hydrogenation with the use of the supported rhodium catalyst which favours pairwise route of hydrogen addition leads to the possibility of an efficient use of the PHIP approaches developed previously.

In our gaseous experiments we used the heterogeneous Rh/TiO2 catalyst which was previously shown to yield the strongest HP signals31. The experimental setup designed for HP ethanol production is presented schematically in Fig. 1b. The main advantages of this setup are: (i) the spatial separation of the hydrogenation process and the hydrolysis process; (ii) gas phase heterogeneous hydrogenation; (iii) dissolution and hydrolysis in water. This was implemented by placing the catalyst in a PTFE capillary located in the middle part of the NMR tube just above the sensitive zone of the rf probe in order to minimize possible losses of hyperpolarisation intensities caused by relaxation processes during gas transport36. The gaseous mixture of reactants obtained by bubbling the parahydrogen through liquid vinyl acetate was supplied through this catalytic reactor (where hydrogenation of vinyl acetate gas to ethyl acetate gas took place) to the bottom of the NMR tube filled with aqueous NaOD solution providing hydrolysis of ethyl acetate to HP ethanol and sodium acetate (see the Methods section for a detailed description of the experiments).

First of all, the efficiency of pairwise hydrogen addition in heterogeneous hydrogenation of vinyl acetate with p-H2 was studied. For this purpose, the hydrolysis step was omitted and the products of the
hydrogenation reaction were detected in the gas phase using $^1$H NMR spectroscopy. Because hydrogen addition occurred in the strong magnetic field of the 7 T NMR spectrometer, the antiphase PASADENA$^{37}$ patterns should be expected. The acquired $^1$H NMR spectra indeed contained the signals of CH$_3$- and CH$_2$-protons of ethyl acetate which clearly exhibited PASADENA effects with the enhancement factors not less than 15 and 20, respectively (Fig. 2). Importantly, the observed NMR spectra did not contain any signals of the reactant (vinyl acetate) which implies that reactant conversion amounted to at least 95% (according to signal-to-noise ratio measurements).

Next, we aimed to figure out whether the hyperpolarisation of ethyl acetate can be preserved upon its dissolution in D$_2$O. For this purpose, the experimental setup presented in Fig. 1 was used except that NMR tube was filled with pure D$_2$O instead of the NaOD solution. The $^1$H NMR spectra revealed that PASADENA hyperpolarisation was indeed preserved to some extent upon dissolution of ethyl acetate in D$_2$O (see Supplementary Fig. S4). This situation is similar to the previously reported results on the dissolution of hyperpolarised gases with the preservation of significant level of polarization produced by PHIP$^{38}$.

Generally, for the HP ethanol formation the hydrolysis of hyperpolarised ethyl acetate should be performed. Therefore, the final step was to combine the hydrogenation and hydrolysis procedures. This was implemented by filling the NMR tube with 2 mL of 1 M NaOD solution in D$_2$O. The acquired $^1$H NMR spectra clearly show the antiphase PASADENA signals of hyperpolarised ethanol (Fig. 3). Importantly, this is the first presentation of the technique for the HP ethanol production by combing the gas phase heterogeneous hydrogenation and the liquid phase hydrolysis of the product. In addition, it is the first observation of PASADENA type $^1$H NMR spectra of HP ethanol; previously only the ALTADENA$^{39}$ type effects for HP ethanol were reported$^{32}$.
It should be noted that signals of ethyl acetate and vinyl acetate were not observed in the NMR spectra detected after hydrolysis, implying that the hydrolysis step proceeded quantitatively. This was further confirmed by vinyl acetate hydrolysis experiments. The procedure was the same as described earlier except the heterogeneous catalyst was removed from the gas flow path. In the acquired $^1$H NMR spectrum, only the signals of acetate ion and the residual protons of D$_2$O were observed, demonstrating the complete hydrolysis of vinyl acetate (see Supplementary Fig. S5). The absence of acetaldehyde NMR signals may be explained by oligomerisation of acetaldehyde via aldol condensation, which is known...
to occur in alkaline media. This assumption is confirmed by the fact that the solution progressively became yellow, and orange precipitate was formed, which can be easily explained by the formation of oligomers with several conjugated C=C bonds (see Supplementary Fig. S5). We note, however, that the formation of acetaldehyde and aldol condensation products and the associated colour change of the solution are caused by the omission of the hydrogenation step in this control experiment, but are not present when the hydrogenation/hydrolysis combination is used for ethanol production.

In addition to ethanol, ethyl acetate hydrolysis also leads to the formation of sodium acetate from the carboxylic moiety. We note, however, that this is not a problem for \textit{in vivo} applications because acetate is an endogenous substance metabolized, e.g., via the Krebs cycle. In fact, production of ethyl acetate can be advantageous. Indeed, the \(^{13}\)C-hyperpolarised acetate produced by DNP was previously utilized for \textit{in vivo} studies of the TCA cycle.

In conclusion, the presented approach based on heterogeneous hydrogenation of vinyl acetate and hydrolysis of the hydrogenation product ethyl acetate enables the production of catalyst-free HP ethanol by means of the PHIP technique. The use of heterogeneous Rh/TiO\(_2\) catalyst allows one to perform a very efficient hydrogenation in the gas phase, which has several important advantages compared to liquid phase hydrogenation for the production of HP contrast agents for potential biomedical applications. First of all, the HP reaction product and the catalyst reside in different phases and are separated without any effort. Second, no organic solvent is needed in order to make hydrogenation process efficient. Third, high conversion of the substrate can be achieved even at relatively high gas flow rates. Fourth, HP ethanol can be produced continuously, and no additional steps for catalyst removal are required including decantation of the hyperpolarised solution. Thus, we demonstrated for the first time that HP ethanol which is free from catalyst and organic solvents can be efficiently and continuously produced using heterogeneous hydrogenation in the gas phase with subsequent hydrolysis of the hydrogenation product in aqueous phase. We believe that this approach is very promising for potential applications in medicine, especially when combined with hyperpolarisation transfer to \(^{13}\)C nuclei and/or with the unique properties of long-lived spin states to significantly prolong the hyperpolarisation lifetime. Importantly, utilisation of \(^{13}\)C hyperpolarized ethanol to monitor the oxidation of ethanol to acetate \textit{in vivo} in real time was reported recently. By applying the procedure presented by Reineri \textit{et al.} it should be possible to neutralize the excess of NaOD with aqueous DCl solution and, importantly, to obtain both highly polarised ethanol and sodium acetate which are free from any catalyst and organic solvent.

**Methods**

Commercially available chemicals vinyl acetate (Sigma-Aldrich, > 99%), hydrogen, sodium hydroxide (Fluka, > 98%) and D\(_2\)O were used as received. Rh/TiO\(_2\) catalyst (1 wt. % Rh, 1.7 nm mean particle size) was provided by the group of Prof. V.I. Bukhtiyarov (Boreskov Institute of Catalysis, Novosibirsk, Russia) and was described elsewhere. For PHIP experiments, H\(_2\) gas was enriched with parahydrogen up to 50% by passing it through FeO(OH) powder (Sigma-Aldrich) maintained at liquid nitrogen temperature. The obtained H\(_2\) gas with 1:1 ortho/para ratio was collected in a gas cylinder.

Hydrogenation experiments were performed as follows. Parahydrogen-enriched H\(_2\) gas was bubbled through a two-neck flask containing liquid vinyl acetate. The resulting mixture of H\(_2\) gas and vinyl acetate vapour was preheated to 150\(^\circ\)C by passing it through a 1/8\(”\) outside diameter copper tube (~2.5 m in length) folded several times and placed in the Nabertherm tube furnace. Then the gas mixture was supplied through a 1/16\(”\) PTFE capillary to a 10 mm NMR tube located in the NMR spectrometer and maintained at 90\(^\circ\)C. In vinyl acetate hydrolysis experiments, the gas mixture was supplied directly to the bottom of the NMR tube containing 2 mL of 1 M NaOH solution in D\(_2\)O. In all other experiments, vinyl acetate hydrogenation was performed. For that purpose the Rh/TiO\(_2\) catalyst (16.0 mg) was placed in a 1/8\(”\) PTFE capillary between the two pieces of fibreglass tissue. This reactor was located in the middle part of the NMR tube, so that hydrogenation occurred in the high magnetic field of the NMR spectrometer (the PASADENA experiment). The NMR tube part of the experimental setup is schematically presented in Supplementary Fig. S1. Note that the reactor was located as close as possible to the spectrometer sensitive zone in order to minimize the travel time and the corresponding hyperpolarisation losses. The gas mixture passed through the reactor and then to the bottom of the NMR tube. The tube was empty in the case of gas phase HP ethyl acetate detection, contained 2 mL of pure D\(_2\)O in the case of HP ethyl acetate dissolution experiments, or contained 2 mL of 1 M NaOD solution in the case of HP ethyl acetate hydrolysis experiments. The gas exited through the 1/4\(”\) PTFE tube connected to the NMR tube at the top. All experiments were carried out at atmospheric pressure. The gas flow rate was set to 14.0 mL/s with the use of an Aalborg rotameter.

\(^{1}\)H NMR spectra were acquired using a single \(\pi/4\) rf pulse which provides the maximum PASADENA signal intensities. The spectra were acquired in a single scan on a 300 MHz Bruker AV 300 NMR spectrometer. The NMR spectra of gaseous mixtures were acquired without interrupting gas flow. The NMR spectra of liquid solutions were acquired after a rapid interruption of gas flow in order to avoid magnetic field inhomogeneities caused by bubbles. The NMR spectra of liquids and gases in thermal equilibrium were acquired after the complete relaxation of hyperpolarisation with the stopped gas flow.
References

1. Mantle, M. D. & Sederman, A. J. Dynamic MRI in chemical process and reaction engineering. *Prog. Nucl. Magn. Reson. Spectrosc.* **43**, 3–49 (2003).

2. Lysova, A. A. & Koptyug, I. V. Magnetic resonance imaging methods for in situ studies in heterogeneous catalysis. *Chem. Soc. Rev.* **39**, 4585–4601 (2010).

3. Gladden, L. F., Mantle, M. D. & Sederman, A. J. Magnetic resonance imaging of catalysts and catalytic processes. *Adv. Catal.* **50**, 1–75 (2006).

4. Lee, J. H., Okano, Y. & Cavagnero, S. Sensitivity enhancement in solution NMR: Emerging ideas and new frontiers. *J. Magn. Reson.* **241**, 18–31 (2014).

5. Nikolou, P., Goodson, B. M. & Chekmenev, E. Y. NMR hyperpolarization techniques for biomedicine. *Chem. Eur. J.* **21**, 3156–3166 (2015).

6. Griffin, R. G. & Prisner, T. F. High field dynamic nuclear polarization—the renaissance. *Phys. Chem. Chem. Phys.* **12**, 5737–5740 (2010).

7. Ardenkjaer-Larsen, J. H. et al. Increase in signal–to–noise ratio of >10,000 times in liquid-state NMR. *Proc. Natl. Acad. Sci. USA* **100**, 10158–10163 (2003).

8. Goodson, B. M. Nuclear magnetic resonance of laser-polarized noble gases in molecules, materials, and organisms. *J. Magn. Reson.* **155**, 157–216 (2002).

9. Natterer, J. & Bargon, J. Parahydrogen induced polarization. *Prog. Nucl. Magn. Reson. Spectrosc.* **31**, 293–315 (1997).

10. Buljubasich, L., Franzoni, M. B. & Munnemann, K. in *Hyperpolarization Methods in NMR Spectroscopy* (ed. Kuhn, L. T.) 338, 53–74 (Springer-Verlag, 2013).

11. Kovtunov, K. V. et al. High-resolution 3D proton MRI of hyperpolarized gas enabled by parahydrogen and Rh/TiO2 heterogeneous catalyst. *Chem. — A Eur. J.* **20**, 11636–11639 (2014).

12. Atkinson, K. D. et al. Spontaneous transfer of parahydrogen derived spin order to pyridine at low magnetic field. *J. Am. Chem. Soc.* **131**, 13362–13368 (2009).

13. Cowley, M. J. et al. Iridium N-heterocyclic carbene complexes as efficient catalysts for magnetization transfer from parahydrogen. *J. Am. Chem. Soc.* **133**, 6134–6137 (2011).

14. Barskiy, D. A. et al. The feasibility of formation and kinetics of NMR signal amplification by reversible exchange (SABRE) at high magnetic field (9.4 T). *J. Am. Chem. Soc.* **136**, 3322–3325 (2014).

15. Truong, M. L. et al. Irreversible catalyst activation enables hyperpolarization and water solubility for NMR signal amplification by reversible exchange. *J. Phys. Chem. B* **118**, 13882–13889 (2014).

16. Green, R. A. et al. The theory and practice of hyperpolarization in magnetic resonance using parahydrogen. *Prog. Nucl. Magn. Reson. Spectrosc.* **67**, 1–48 (2012).

17. Zhivonitko, V. V., Skovpin, I. V. & Koptyug, I. V. Strong 31P nuclear spin hyperpolarization produced via reversible chemical interaction with parahydrogen. *Chem. Commun.* **51**, 2506–2509 (2015).

18. Blazina, D., Duckett, S. B., Dunne, J. P. & Godard, C. Applications of the parahydrogen phenomenon in inorganic chemistry. *Dalton Trans.* **2601–2609** (2004). doi: 10.1039/B409606A.

19. Kovtunov, K. V., Zhivonitko, V. V., Skovpin, I. V., Barskiy, D. A. & Koptyug, I. V. in *Hyperpolarization Methods in NMR Spectroscopy* (ed. Kuhn, L. T.) 338, 123–180 (Springer-Verlag, 2013).

20. Kovtunov, K. V., Beck, J. E., Bukhtiyarova, V. I. & Koptyug, I. V. Observation of parahydrogen-induced polarization in heterogeneous hydrogenation on supported metal catalysts. *Angew. Chem., Int. Ed.* **47**, 1492–1495 (2008).

21. Zhou, R. et al. Parahydrogen-induced polarization by pairwise replacement catalysis on Pt and Ir nanoparticles. *J. Am. Chem. Soc.* **137**, 1938–1946 (2015).

22. Balu, A. M., Duckett, S. B. & Luque, R. Parahydrogen induced polarization effects in liquid phase hydrogenations catalysed by supported metal nanoparticles. *Dalton Trans.* **5074–5076** (2009). doi: 10.1039/b906449d.

23. Koptyug, I. V. et al. Para-hydrogen-induced polarization in heterogeneous hydrogenation reactions. *J. Am. Chem. Soc.* **129**, 5580–5586 (2007).

24. Kovtunov, K. V. et al. Parahydrogen-induced polarization (PHP) in heterogeneous hydrogenation over bulk metals and metal oxides. *Chem. Commun.* **50**, 875–878 (2014).

25. Chekmenev, E. Y. et al. PASADENA hyperpolarization of succinic acid for MRI and NMR spectroscopy. *J. Am. Chem. Soc.* **130**, 4212–4213 (2008).

26. Schepin, R. V., Coffey, A. M., Waddell, K. W. & Chekmenev, E. Y. PASADENA hyperpolarized 13C phospholactate. *J. Am. Chem. Soc.* **134**, 3957–3960 (2012).

27. Schepin, R. V., Coffey, A. M., Waddell, K. W. & Chekmenev, E. Y. Parahydrogen induced polarization of 1-13C-phospholactate-d2 for biomedical imaging with >30,000,000-fold NMR signal enhancement in water. *Anal. Chem.* **86**, 5601–5605 (2014).

28. Reineri, F. et al. Para-hydrogenated glucose derivatives as potential 13C hyperpolarized probes for magnetic resonance imaging. *J. Am. Chem. Soc.* **132**, 7186–7193 (2010).

29. Sauer, G. et al. Effective PHP labeling of bioactive peptides boosts the intensity of the NMR signal. *Angew. Chem., Int. Ed.* **53**, 12941–12945 (2014).

30. Glogler, S. et al. Para-hydrogen induced polarization of amino acids, peptides and deuterium-hydrogen gas. *Phys. Chem. Chem. Phys.* **13**, 13759–13764 (2011).

31. Zeng, H. et al. Optimization of SABRE for polarization of the tuberculosis drugs pyrazinamide and isoniazid. *J. Magn. Reson.* **237**, 73–78 (2013).

32. Trantzaschel, T. et al. Parahydrogen induced polarization in face of keto–enol tautomerism: proof of concept with hyperpolarized ethanol. *Phys. Chem. Chem. Phys.* **14**, 5601–5604 (2012).

33. Reineri, F., Boi, T. & Atme, S. Parahydrogen induced polarization of 14CO2 carbonate resonance in acetate and pyruvate. *Nat. Commun.* **6**, 5858 (2015).

34. Salnikov, O. G. et al. Evaluation of the mechanism of heterogeneous hydrogenation of α,β-unsaturated carbonyl compounds via pairwise hydrogen addition. *ACS CATAL.* **4**, 2022–2028 (2014).

35. Koptyug, I. V., Zhivonitko, V. V. & Kovtunov, K. V. New perspectives for parahydrogen-induced polarization in liquid phase heterogeneous hydrogenation: an aqueous phase and ALTADENA study. *ChemPhysChem* **11**, 3086–3088 (2010).

36. Barskiy, D. A., Salnikov, O. G., Kovtunov, K. V. & Koptyug, I. V. NMR signal enhancement for hyperpolarized fluids continuously generated in hydrogenation reactions with parahydrogen. *J. Phys. Chem. A* **119**, 996–1006 (2015).

37. Bowers, C. R. & Weitekamp, D. P. Parahydrogen and synthesis allow dramatically enhanced nuclear alignment. *J. Am. Chem. Soc.* **109**, 5541–5542 (1987).

38. Kovtunov, K. V. et al. Toward continuous production of catalyst-free hyperpolarized fluids based on biphasic and heterogeneous hydrogenations with parahydrogen. *J. Phys. Chem. C* **117**, 22887–22893 (2013).

39. Pravica, M. G. & Weitekamp, D. P. Net NMR alignment by adiabatic transport of parahydrogen addition products to high magnetic field. *Chem. Phys. Lett.* **145**, 255–258 (1988).
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Author Contributions
K.V.K. suggested the idea. O.G.S. and K.V.K. performed the experiments. O.G.S., K.V.K. and I.V.K. discussed the results and wrote the paper.

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