

# Spontaneous $^{15}\text{N}$ Nuclear Spin Hyperpolarization in Metal-Free Activation of Parahydrogen by Molecular Tweezers

Kristina Sorochkina,<sup>¶</sup> Vladimir V. Zhivonitko,<sup>\*,||,†,‡,§</sup> Konstantin Chernichenko,<sup>¶</sup> Ville-Veikko Telkki,<sup>||</sup> Timo Repo,<sup>¶</sup> and Igor V. Koptug<sup>†,‡,§</sup>

<sup>¶</sup>Department of Chemistry, University of Helsinki, A. I. Virtasen aukio 1, 00014 Helsinki, Finland

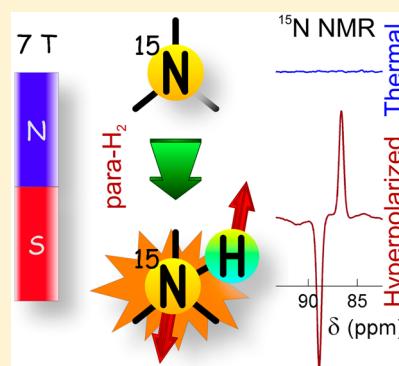
<sup>||</sup>NMR Research Unit, University of Oulu, P.O. Box 3000, 90014 Oulu, Finland

<sup>†</sup>Laboratory of Magnetic Resonance Microimaging, International Tomography Center SB RAS, Institutskaya Street 3A, 630090 Novosibirsk, Russia

<sup>‡</sup>Department of Natural Sciences, Novosibirsk State University, Pirogova Street 2, 630090 Novosibirsk, Russia

## S Supporting Information

**ABSTRACT:** The ability of frustrated Lewis pairs (FLPs) to activate  $\text{H}_2$  is of significant interest for metal-free catalysis. The activation of  $\text{H}_2$  is also the key element of parahydrogen-induced polarization (PHIP), one of the nuclear spin hyperpolarization techniques. It is demonstrated that *o*-phenylene-based *ansa*-aminoboranes (AABs) can produce  $^1\text{H}$  nuclear spin hyperpolarization through a reversible interaction with parahydrogen at ambient temperatures. Heteronuclei are useful in NMR and MRI as well because they have a broad chemical shift range and long relaxation times and may act as background-free labels. We report spontaneous formation of  $^{15}\text{N}$  hyperpolarization of the N–H site for a family of AABs. The process is efficient at the high magnetic field of an NMR magnet (7 T), and it provides up to 350-fold  $^{15}\text{N}$  signal enhancements. Different hyperpolarization effects are observed with various AAB structures and in a broad temperature range. Spontaneous hyperpolarization, albeit an order of magnitude weaker than that for  $^{15}\text{N}$ , was also observed for  $^{11}\text{B}$  nuclei.



Recent findings on the activation of small molecules ( $\text{H}_2$ ,  $\text{CO}_2$ ,  $\text{SO}_2$ , etc.) by metal-free substances have inspired a number of brilliant studies in the field of metal-free catalysis,<sup>1–7</sup> providing perspectives of sustainable, less toxic, and cheaper alternatives to traditional transition-metal catalysts. It includes also multidisciplinary studies at the intersection of chemistry, catalysis, physics, and NMR.<sup>8–11</sup> For instance, metal-free chemical activation of parahydrogen molecules (*para*- $\text{H}_2$ ) has demonstrated a potential to polarize nuclear spins.<sup>8</sup> *para*- $\text{H}_2$  is one of the nuclear spin isomers of molecular hydrogen ( $\text{H}_2$ ), having a total nuclear spin of zero. It is easily accessible via simple cryogenic methods and has a long lifetime. Thus, it constitutes a unique chemical reagent bearing nonequilibrium nuclear spin order for the production of substances with significantly higher polarization of nuclear spins as compared to the thermal equilibrium state. Chemical activation of *para*- $\text{H}_2$  plays a key role in polarizing spins via parahydrogen-induced polarization (PHIP)<sup>12–17</sup> and in the related SABRE<sup>17</sup> method. The product substances hyperpolarized by these methods may boost the sensitivity of NMR spectroscopy and MRI by orders of magnitude. PHIP has been also exploited in mechanistic studies in homogeneous and heterogeneous catalysis.<sup>18–20</sup> Traditionally, metal-containing hydrogenation catalysts, such as metal complexes and metal nanoparticles, have been utilized to activate *para*- $\text{H}_2$ .<sup>16,18–20</sup> Recently, a number of systems based on main group elements have been documented as efficient

metal-free hydrogenation catalysts as well. In particular, pairs of various sterically separated (“frustrated”) Lewis acids and Lewis bases (FLPs) were reported to split  $\text{H}_2$ .<sup>3,21</sup>

In our initial studies we showed that metal-free *ansa*-aminoboranes (AABs), considered as molecular tweezers in the literature, can activate *para*- $\text{H}_2$ , leading to significant signal enhancements in  $^1\text{H}$  NMR spectra.<sup>8,10</sup> The mechanism of  $^1\text{H}$  hyperpolarization includes reversible chemical interaction of *para*- $\text{H}_2$  with the metal-free molecules, which was discussed in detail for several *o*-phenylene-based AABs.<sup>10,22</sup> The mechanism has certain similarities to the reversible interaction of *para*- $\text{H}_2$  with a metal complex in SABRE hyperpolarization method,<sup>17</sup> but in this case with no use of metals. The development of nuclear spin hyperpolarization techniques for heteronuclei ( $^{13}\text{C}$ ,  $^{15}\text{N}$ , etc.) is of special interest in NMR because heteronuclei are useful in chemical analysis due to their broad chemical shift range, and they may also be exploited as background-free labels in MRI applications. Furthermore, their long relaxation times allow a prolonged observation window for the hyperpolarization. Typically, *para*- $\text{H}_2$  based hyperpolarization of heteronuclei requires special manipulation to transfer  $^1\text{H}$  hyperpolarization to heteronuclei. It can be done by performing a reaction with

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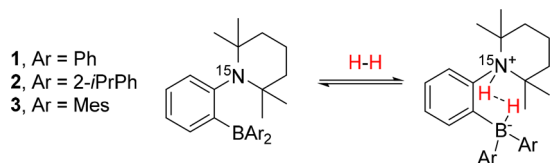
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*para*-H<sub>2</sub> at ultralow magnetic fields matched to maximize the efficiency of the transfer.<sup>23–28</sup> Alternatively, there are methods that use dedicated RF pulse sequences<sup>29–31</sup> or RF field modulations<sup>32</sup> to achieve polarization transfer when the reaction is performed at a high magnetic field. In all of these demonstrations, metal-containing catalysts were utilized, except our work, in which <sup>11</sup>B hyperpolarization for QCAT metal-free molecular tweezers was achieved using the PH-INEPT( $+\pi/4$ ) RF pulse sequence.<sup>8</sup> The additional RF field manipulations may require cumbersome adjustments and equipment. Rare instances of spontaneous high-field polarization transfers to heteronuclei have been reported in PHIP studies.<sup>29,33,34</sup>

In this Letter, we present a family of <sup>15</sup>N-labeled AABs 1–3 that demonstrate spontaneous hyperpolarization of their <sup>15</sup>N nuclei upon reversible addition of *para*-H<sub>2</sub> molecules (Scheme

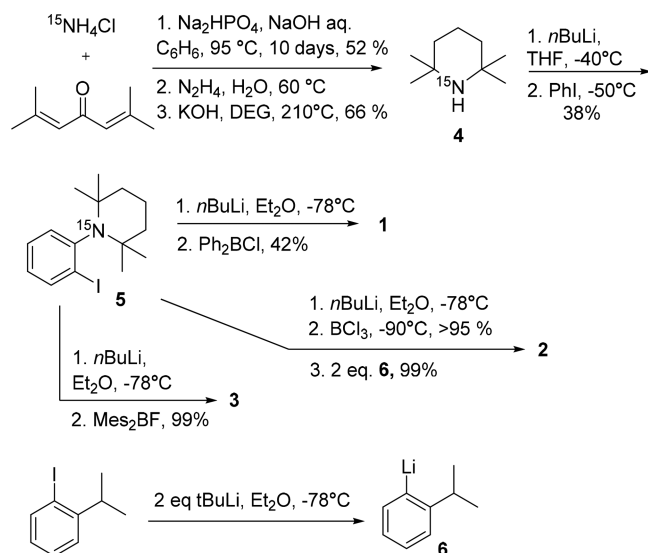
### Scheme 1. Reversible Activation of *para*-H<sub>2</sub> with <sup>15</sup>N-Labeled AABs



1). The hyperpolarization reveals itself as significant <sup>1</sup>H and <sup>15</sup>N NMR signal enhancements. The comparison to thermally polarized signals shows up to 350-fold <sup>15</sup>N signal enhancement depending on the molecular structure. Moreover, we demonstrate that, depending on the system and the reaction temperature, enhanced in-phase or antiphase <sup>15</sup>N doublets are observed. A possible mechanism of the hyperpolarization at high magnetic fields is discussed in terms of cross relaxation.

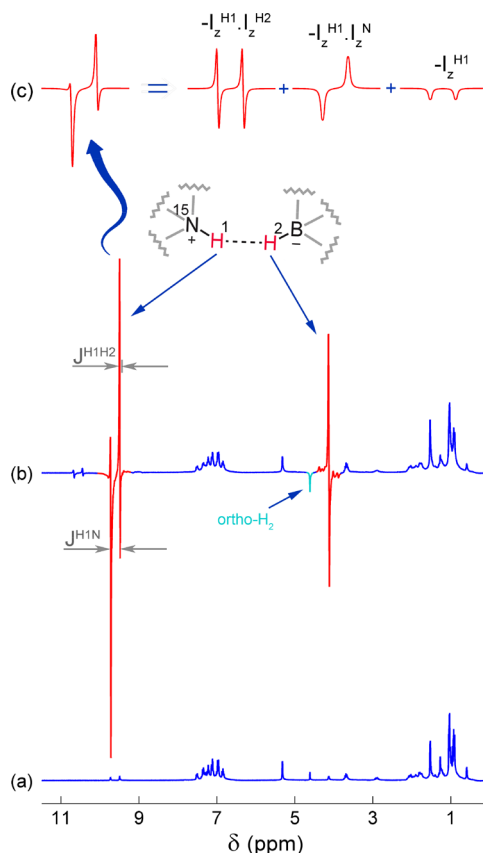
The AABs 1–3, respectively containing phenyl, 2-isopropylphenyl, and 2,4,6-trimethylphenyl substituents at boryl site, were prepared as reported previously for similar compounds that were not isotope-labeled.<sup>10,11</sup> The starting <sup>15</sup>N-labeled 2,2,6,6-tetramethylpiperidine was synthesized according to the known procedure,<sup>35</sup> which was slightly modified (Scheme 2). The NMR experiments were performed in combination with

### Scheme 2. Synthesis of AABs 1–3



bubbling *para*-H<sub>2</sub> (91% *para*-H<sub>2</sub> enriched H<sub>2</sub> gas; see the Supporting Information) through ca. 0.05 M solutions of AABs 1–3 inside of the NMR magnet.

In the first demonstration, we aimed to detect nuclear spin hyperpolarization effects in <sup>1</sup>H NMR spectra. As could be expected from our previous study performed with nonlabeled compounds,<sup>10</sup> hyperpolarization effects for all three AABs were observed for *para*-H<sub>2</sub> originating protons in AAB–H<sub>2</sub> adducts (see Figure 1 and the Supporting Information). For example,

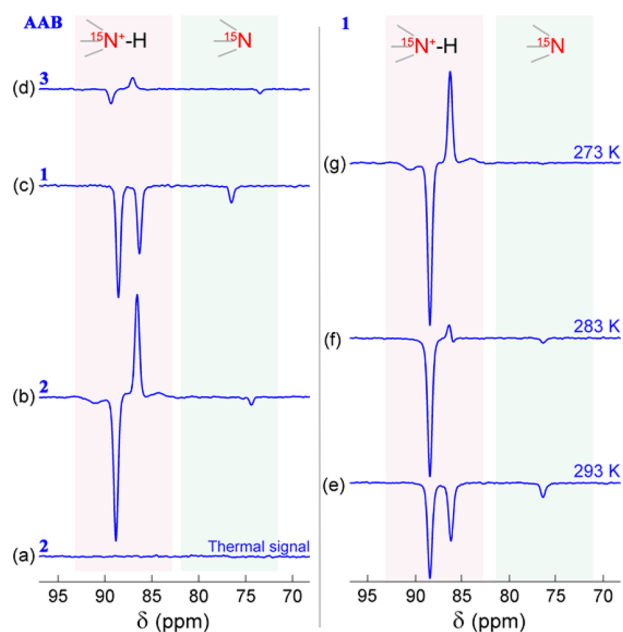


**Figure 1.** <sup>1</sup>H{<sup>15</sup>N} NMR spectra acquired (a) before and (b) after *para*-H<sub>2</sub> bubbling through a 0.05 M solution of **2** in CD<sub>2</sub>Cl<sub>2</sub> in a 7 T magnetic field. (c) Decomposition of the <sup>1</sup>H signal from an –NH group into the contributions from different longitudinal spin orders. The spectra were recorded using  $\pi/4$ -pulses at room temperature.

Figure 1a,b shows <sup>11</sup>B-decoupled <sup>1</sup>H NMR spectra for the solution of **2** before and after *para*-H<sub>2</sub> bubbling, respectively. Strong hyperpolarized signal patterns for the protons of N<sup>+</sup>–H and B<sup>–</sup>–H groups are highlighted with red in Figure 1b. The comparison of the signal patterns revealed some noticeable differences between them. The B<sup>–</sup>–H signal has the shape of an antiphase doublet expected for the experiments at the high magnetic field (the PASADENA effect).<sup>13</sup> In other words, the signal multiplet has both negative and positive components, which must have splitting caused by the J-coupling between the protons in N<sup>+</sup>–H (proton 1) and B<sup>–</sup>–H (proton 2) moieties. For **2**, this splitting is ca. 6.5 Hz, in agreement with the B<sup>–</sup>–H hyperpolarized pattern. Such a signal arises from the so-called longitudinal two-spin order, I<sub>z</sub><sup>H1</sup>.I<sub>z</sub><sup>H2</sup>, stemming from *para*-H<sub>2</sub> molecules.<sup>10,15,16</sup> In contrast, the N<sup>+</sup>–H signal has a more complex shape, which reveals correlation within the heteronuclear <sup>1</sup>H–<sup>15</sup>N spin pair of the N<sup>+</sup>–H group. This is evident from the observation of an antiphase doublet contribution with

the splitting between the individual multiplet components equal to  $J^{\text{H}^1\text{N}}$  (70.4 Hz), signifying the presence of the heteronuclear two-spin longitudinal order  $I_z^{\text{H}^1}\cdot I_z^{\text{N}}$ . A mathematical decomposition of this signal to possible contributions from different longitudinal spin orders shown in Figure 1c implies that the reversible interaction of *para*-H<sub>2</sub> with AAB creates at least three different magnetization modes in the N<sup>+</sup>-H group, with the major contributions arising from <sup>1</sup>H-<sup>1</sup>H and <sup>1</sup>H-<sup>15</sup>N correlations. In addition, a clear contribution from single spin magnetization  $-I_z^{\text{H}^1}$  is also observed. It should be noted that for **2** and other AABs, <sup>1</sup>H NMR spectra without <sup>11</sup>B decoupling revealed a contribution from <sup>1</sup>H-<sup>11</sup>B longitudinal two-spin order ( $I_z^{\text{H}^2}\cdot I_z^{\text{B}}$ ) in the B<sup>-</sup>-H group, but this effect was rather weak (see the Supporting Information).

The generated  $I_z^{\text{H}^1}\cdot I_z^{\text{N}}$  nuclear spin order indicates that, in addition to <sup>1</sup>H hyperpolarization, the associated <sup>15</sup>N hyperpolarization should be observable under the same experimental conditions. Indeed, a <sup>15</sup>N NMR spectrum acquired during the reversible interaction of *para*-H<sub>2</sub> with **2** demonstrates the presence of <sup>15</sup>N hyperpolarization (compare Figure 2a,b). The



**Figure 2.** <sup>15</sup>N NMR spectra acquired before (a) and after (b–g) bubbling *para*-H<sub>2</sub> through 0.05 M solutions of AABs. Spectra (a) and (b) correspond to **2**, (c, e–g) to **1**, and (d) to **3**. Polarized signal regions are marked with different background colors for the signals from  $-^{15}\text{N}^+-\text{H}$  (reddish) and  $-^{15}\text{N}$  (greenish) groups of AAB–H<sub>2</sub> and AAB molecules, respectively. Spectra (a–d) were recorded at room temperature (293 K). Spectra (e–g) were measured at 293, 283, and 273 K, respectively. All spectra were acquired using  $\pi/2$ -pulses in a 7 T magnetic field.

signal enhancement was 350-fold, meaning that the <sup>15</sup>N signal can be increased by this factor by just bubbling *para*-H<sub>2</sub> through the solution of **2**, without extra manipulations like the use of ultralow magnetic fields<sup>23–25</sup> or RF irradiation.<sup>29–31</sup> This effect appears spontaneously. Some hyperpolarized signal from free **2** (see greenish background) is also observed.

It was found that the shape of spontaneously enhanced <sup>15</sup>N signals depends on the AAB–H<sub>2</sub> structure. **2**–H<sub>2</sub> and **3**–H<sub>2</sub> provided almost exclusively the antiphase signals (see Figure 2b,d, respectively), meaning that the reversible interaction with corresponding AABs generates mostly longitudinal two-spin

order  $I_z^{\text{H}^1}\cdot I_z^{\text{N}}$ . In contrast, **1**–H<sub>2</sub> provided a much more significant contribution of the in-phase signal corresponding to the net <sup>15</sup>N magnetization  $I_z^{\text{N}}$ , although some two-spin order was also present (Figure 2c) because the amplitudes of the components of the doublet were not equal. Note that the <sup>15</sup>N signal of free AAB is stronger for **1**, which is in accord with the observed in-phase contribution for the corresponding AAB–H<sub>2</sub> adduct (see the discussion below).

It is noteworthy that the strength of the net <sup>15</sup>N magnetization  $I_z^{\text{N}}$  generated in the course of reversible interaction with *para*-H<sub>2</sub> for **1** was strongly temperature dependent (Figure 2e–g). In the temperature range from 273 to 293 K, the in-phase contribution to the signal was strongest at 293 K (Figure 2e), but it vanished almost completely upon the temperature decrease to 273 K (Figure 2g). The antiphase signal contribution resulting from  $I_z^{\text{H}^1}\cdot I_z^{\text{N}}$  nuclear spin order was highest at 273 K. The observed qualitative switch from  $I_z^{\text{N}}$  to  $I_z^{\text{H}^1}\cdot I_z^{\text{N}}$  may be evidence of a significant change in structural parameters or molecular dynamics in **1**–H<sub>2</sub> induced by temperature. If one considers only the reaction rate variations, which naturally take place in variable-temperature experiments, then similar change trends of amplitudes for all nonequilibrium spin orders are expected. However, in the case of **1**, the trends are opposite, with decreasing amplitude for one spin order and increasing for another spin order. This cannot be induced by the exchange rate changes only. More likely, the effect of switching from  $I_z^{\text{N}}$  (in-phase signal) to  $I_z^{\text{H}^1}\cdot I_z^{\text{N}}$  (antiphase signal) is dominated by structural/dynamics changes in **1**–H<sub>2</sub> influencing the spontaneous polarization transfer to <sup>15</sup>N nuclei.

A complete understanding of the observed spontaneous <sup>15</sup>N hyperpolarization is beyond the scope of this Letter. However, a qualitative picture can be drawn in the framework of cross-relaxation.<sup>36</sup> All of our experiments were performed at the high magnetic field (7 T) of the NMR instrument, indicating that polarization transfer is likely incoherent in nature. Indeed, the frequency difference between <sup>1</sup>H and <sup>15</sup>N resonances is huge (ca. 270 MHz) compared to the NMR spin–spin coupling constant (70.4 Hz). The frequency difference between N<sup>+</sup>-H and B<sup>-</sup>-H protons is also large (ca. 1.7 kHz) as compared to the corresponding <sup>1</sup>H-<sup>1</sup>H coupling constant (6.5 Hz), which altogether makes the polarization transfer through the J-coupling network inefficient. As far as the polarization transfer via cross-relaxation is concerned, this incoherent mechanism is operative at high magnetic fields, and is used, for instance, to transfer high thermal polarization of protons to heteronuclei in biological macromolecules.<sup>37</sup>

As the reaction was performed in the high magnetic field and the hydrogens from *para*-H<sub>2</sub> captured by AAB tweezers form a weakly coupled spin system, the initial state can be expressed as the following density operator<sup>10,13,15</sup>

$$\hat{\rho}(0) \propto -K \times I_z^{\text{H}^1}\cdot I_z^{\text{H}^2} \quad (1)$$

Here,  $K$  is a factor ( $0 \leq K \leq 1$ ) arising from the influence of nuclear spin relaxation taking place during the reversible chemical exchange of *para*-H<sub>2</sub> and the AAB in the solution. The origin of the  $K$  factor is discussed in detail elsewhere,<sup>10</sup> but importantly, the two-spin longitudinal nuclear spin order is created. The corresponding magnetization mode,  $\langle I_z^{\text{H}^1}\cdot I_z^{\text{H}^2} \rangle = \text{Tr}[\hat{\rho}(t)\cdot I_z^{\text{H}^1}\cdot I_z^{\text{H}^2}]$ , can be transformed to a heteronuclear two-spin magnetization mode, e.g.,  $\langle I_z^{\text{H}^1}\cdot I_z^{\text{N}} \rangle$ , via a dipolar cross-relaxation mechanism.<sup>38</sup>  $\langle I_z^{\text{H}^1}\cdot I_z^{\text{N}} \rangle$ , in turn, can be transformed to the single spin magnetization mode  $\langle I_z^{\text{N}} \rangle$  via cross-

correlation between dipolar and chemical shift anisotropy mechanisms<sup>12</sup>

$$\langle I_z^{H1} \cdot I_z^{H2} \rangle \xrightarrow{DD} \langle I_z^{H1} \cdot I_z^N \rangle \xrightarrow{DD+CSA} \langle I_z^N \rangle \quad (2)$$

In the experiments, we observed both transformations with varying weights depending on the AAB structure (Figure 2b–d) and reaction temperature (Figure 2e–g). The formation of the  $\langle I_z^{H1} \cdot I_z^N \rangle$  magnetization mode dominated for **2** and **3**. For **1**, this mode was clearly observed at lower temperatures (Figure 2g), whereas at ambient temperature the single-spin  $\langle I_z^N \rangle$  mode was stronger (Figure 2e). Because the nuclear spin relaxation is strongly dependent on structure and dynamics parameters, the latter observation nicely demonstrates that a significant structure/dynamics alteration may take place under variable-temperature conditions for **1**.

In conclusion, we have shown that, in addition to <sup>1</sup>H hyperpolarization produced in metal-free activation of *para*-H<sub>2</sub> by AABs **1**–**3** based on a 2-aminophenylborane core, a significant <sup>15</sup>N hyperpolarization is spontaneously produced. This finding is interesting as the studied AABs provide good and easy to explore models for further investigations of “metal-free” nuclear spin hyperpolarization. The simplicity of *para*-H<sub>2</sub> activation in this case makes reliable determination of kinetic parameters a relatively easy task.<sup>10</sup> The observed spontaneous heteronuclear hyperpolarization supported by the knowledge of the kinetic parameters may lead to the establishment of an efficient tool for detailed experimental research on H<sub>2</sub> activation with AABs because it characterizes structure/dynamics features influencing cross-relaxation in AAB–H<sub>2</sub> adducts. On the other hand, in order to observe the <sup>15</sup>N hyperpolarization, there is no need to have special equipment like magnetic field shields or to use sophisticated pulse sequences, and it does not even require taking the sample out of the magnet because the hyperpolarization is formed during *para*-H<sub>2</sub> bubbling inside of the high-field magnet. We believe that this feature is general for AABs based on an *ortho*-phenylene moiety as already three members of this class have demonstrated their efficiency. A targeted molecular design can lead to even higher <sup>15</sup>N hyperpolarization levels. Moreover, depending on the structure, it is possible to generate different magnetization modes and observe net or multiplet effects. We envision that the hyperpolarization of the N<sup>+</sup>–H group in metal-free AABs might serve as a model for hyperpolarizing those groups in macromolecules, if there were Lewis acid sites attached nearby. While the current versions of AAB molecules cannot be used in aqueous solutions and thus are not biocompatible, we believe that further research in the field may provide oxygen- and moisture-insensitive metal-free probes for *para*-H<sub>2</sub> molecules. Parahydrogen activation with AABs has certain similarities with both traditional PHIP and SABRE because we observed <sup>15</sup>N hyperpolarization of both hydrogenated (AAB–H<sub>2</sub>) and nonhydrogenated (AAB) species. With AABs, however, we avoid the use of toxic metal complexes as catalysts, and hence, we avoid otherwise necessary separation of the hyperpolarized product from the catalyst. The requirement of metal catalyst separation is one of the major obstacles for extending parahydrogen hyperpolarization methods to living systems, which we believe can be solved with the use of metal-free catalysts.

## ■ ASSOCIATED CONTENT

### 📄 Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jpcllett.7b03433.

Description of the experimental procedure and additional NMR spectra illustrating results of the work (PDF)

## ■ AUTHOR INFORMATION

### Corresponding Author

\*E-mail: vladimir.zhivonitko@oulu.fi.

### ORCID

Vladimir V. Zhivonitko: 0000-0003-2919-8690

Ville-Veikko Telkki: 0000-0003-0846-6852

Igor V. Koptuyug: 0000-0003-3480-7649

### Notes

The authors declare no competing financial interest.

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