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Research Article

Cobalt-Catalyzed Hyperpolarization of Structurally Intact Olefins

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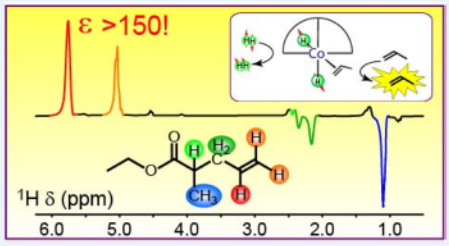
ABSTRACT: Signal amplification by reversible exchange (SABRE) is a tool that generates hyperpolarized species via non-hydrogenative interactions between *para*-hydrogen and selected nitrogen-/oxygen-/sulfur-containing substrates, traditionally with an iridium catalyst. The development of this field has allowed for a broadened substrate range amenable to hyperpolarization for applications including magnetic resonance imaging. Herein, we report the utilization of a cobalt-based catalyst for the hyperpolarization of structurally intact olefins via a SABRE-like mechanism. The hyperpolarization of a variety of olefinic substrates is exhibited using NMR spectroscopy and yields signal enhancement values of up to ∼150-fold for ^{1}H resonances at 14.1 T. Transfer of polarization to ^{13}C (nearly 150-fold) and ^{19}F is demonstrated without the use of isotopic labeling or the application of radio-frequency pulse sequences, both with and without the use of microtesla fields. These results demonstrate and provide further insights into the first first-row transition metal catalyst platform capable of facilitating the dramatic signal enhancement of structurally intact substrates not traditionally observed with iridium SABRE chemistry.



KEYWORDS: *SABRE, hyperpolarization, olefins, p-H$_2$, cobalt*

INTRODUCTION

*Para*hydrogen (p-H_2), one of the two nuclear spin isomers of H_2, has been used as a tool to address the low sensitivity in nuclear magnetic resonance (NMR) spectroscopy and its biomedical analogue, magnetic resonance imaging (MRI).[1,2] The utility of p-H_2 for tackling the sensitivity issue is owed to its pure nuclear spin order, which can perturb the population of energy states of nuclear spins after it is introduced to a molecule or complex.[3] The resulting non-equilibrium spin population distribution, termed hyperpolarization, manifests itself in dramatic NMR signal enhancement under the following conditions:

(i) The H atoms from p-H_2 stay jointly coupled (i.e., they end up on the same substrate).

(ii) The symmetry of p-H_2 is broken (i.e., the H atoms add to magnetically distinct positions).

(iii) The addition of the H atoms occurs faster than the relaxation processes of nuclear spin populations in the reaction intermediates.[2]

If all of these conditions are met, the effect produced is known as *para*hydrogen-induced polarization (PHIP), first demonstrated by Bowers and Weitekamp through the hydrogenation of acrylonitrile with p-H_2 and Wilkinson's catalyst.[4] Since then, the *para*hydrogenation (hydrogenation with p-H_2) of various substrates has been comprehensively explored at both low magnetic fields (known as ALTADENA, adiabatic longitudinal transport after dissociation engenders net alignment) and high magnetic fields (known as PASADENA, *para*hydrogen and synthesis allow dramatically enhanced nuclear alignment).[1,2,5]

Later, Duckett and co-workers proposed and demonstrated the ability to transfer polarization from p-H_2 to a substrate through a non-hydrogenative route termed signal amplification by reversible exchange or SABRE.[6,7] Using Crabtree's catalyst, $[Ir((H)_2(PCy_3)(py)_3][BF_4]$, Duckett and co-workers showed the catalyst's aptitude for the hyperpolarization of ^{1}H, ^{13}C, and ^{15}N nuclei associated with pyridine and other nitrogen-based (N-based) substrates without altering the final structure of the substrate, expanding the collection of substrates amenable to PHIP.[7] Since their initial findings, the phosphine ligand has been replaced with more electron-donating carbene ligands, thereby yielding several iridium catalysts capable of facilitating greater polarization for substrates (e.g., ref 8)—including molecules of biological relevance for potential application as MRI contrast agents (Figure 1).

More recently, SABRE has been extended beyond substrates that bind to the metal center through a nitrogen atom to oxygen-containing substrates such as pyruvate and acetate.[9−11] To date, SABRE has been demonstrated for a variety of nuclei (most commonly ^{1}H, ^{13}C, ^{15}N, and ^{19}F), with polarization enhancements typically varying between ∼10^2 and >10^5—depending on the substrate, catalyst, and conditions.[11−14] Indeed, efficient transfer of polarization to heteronuclei can occur in microtesla fields achieved using mu-metal magnetic shields—a technique

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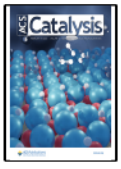

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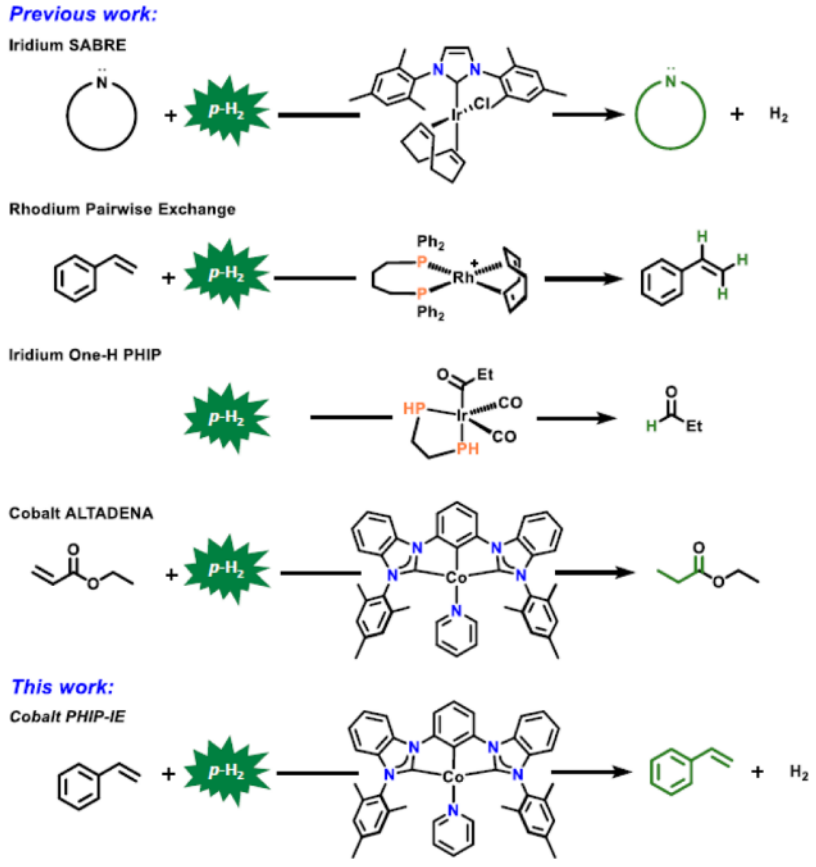
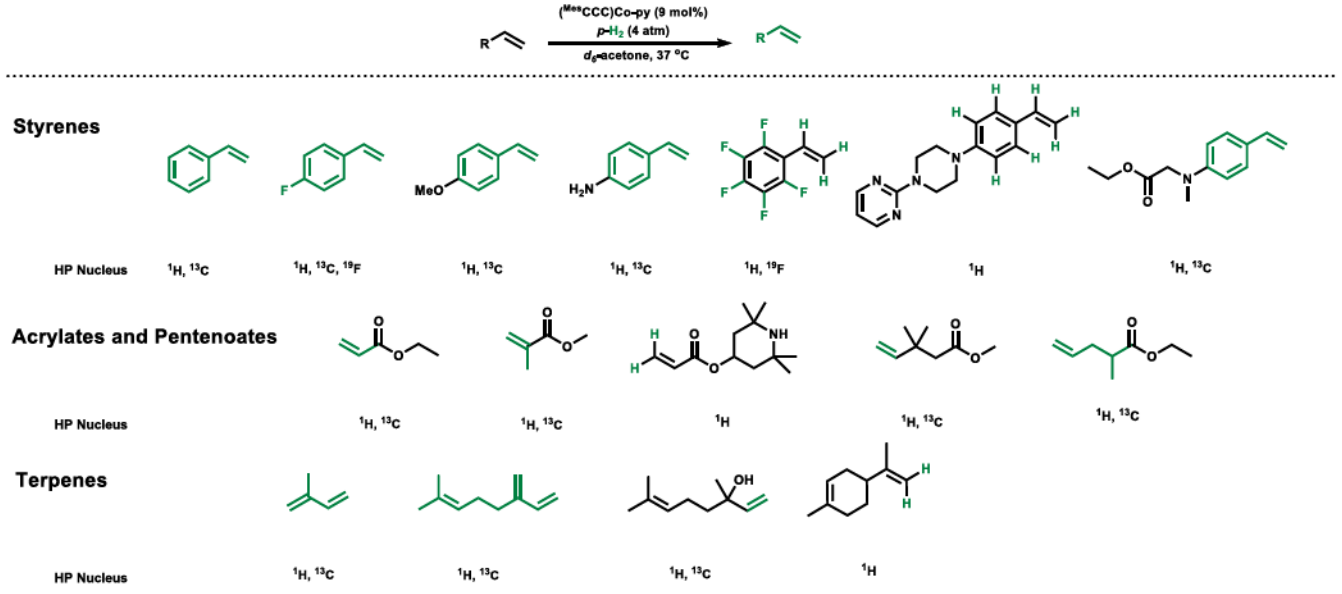


Figure 1. Previously reported classes of PHIP reactivity compared to this work's reactivity.

Table 1. Scope of Olefin Hyperpolarization



dubbed SABRE-SHEATH (for SABRE in SHield Enables Alignment Transfer to Heteronuclei).[9,10,12−15]

Between the discovery of hydrogenative PHIP and SABRE, Eisenberg and Permin confirmed the phenomenon suggested by Natterer, known as one-H PHIP, during the hydroformylation reactions with *para*-enriched H_2 (Figure 1).[16] Despite the presence of only a single *para*hydrogen-derived proton being incorporated into the the product, the hyperpolarization of that aldehydic proton was still observed. Authors attributed this observance to the strong coupling between the two hydrides on the catalyst in the dihydride-acyl species. Additionally, Bargon and co-workers demonstrated, for the first time, the ability to use a rhodium PHIP catalyst to generate the polarization of intact substrates through a process of pairwise exchange of hydrogens on the substrate with those of *p*-H_2 (Figure 1).[17,18]

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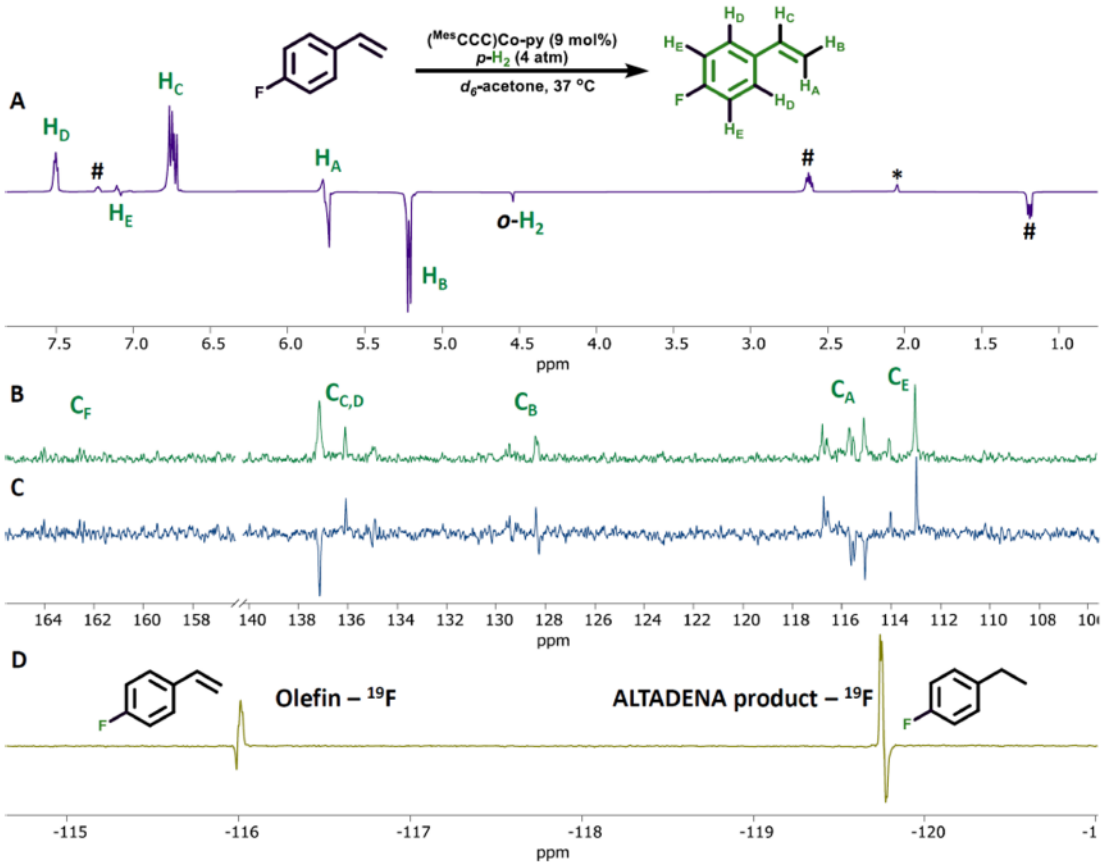

Figure 2. Single-transient NMR spectra of the reaction of a 65 mM solution of 4-fluorostyrene in d_6-acetone (*) with p-H_2 (4 atm). (A) Enhanced ^{1}H NMR spectrum with (#) marking the ^{1}H resonances of the ALTADENA product. (B) Enhanced ^{13}C{^{1}H} NMR spectrum shown in magnitude mode. (C) Same as B, but shown in phased mode. (D) ^{19}F NMR spectrum. Magnetic fields applied during p-H_2 administration were ∼50 G (A) and earth's field (∼1.8 G, B−D), respectively.

While the landscape of both hydrogenative and non-hydrogenative regimes of PHIP has seen advancements, mainly in the physical components of the technique[19−26] and in modifications from a synthetic/chemical standpoint of homogeneous systems—altering the binding of substrates,[8,27−32] offering water solubility,[25,33−38] and allowing for catalyst separation[39−44]—few reports going beyond the use of the seminal iridium and rhodium-based catalysts have been presented (e.g., refs 45 and 46). Research has shown that the use of first-row transition metals in reactivity traditionally dominated by their second- and third-row congeners often allows for access of novel spaces, and the environmental abundance of these elements generally makes them less harmful and more readily accessible.[47−49]

Herein, we report the application of our hydrogenation and ALTADENA[50] catalyst, (^{Mes}CCC)Co-py, [^{Mes}CCC = bis(2,4,6-trimethylphenyl-benzimidazol-2-ylidene)phenyl), py = pyridine], towards the hyperpolarization of structurally unmodified olefins without the need of alkyne precursors (Figure 1, Table 1). While more mechanistic evidence is needed, this electron-rich cobalt center offers reactivity reminiscent of Ir SABRE catalysts and Rh pairwise exchange catalysts.[17,18] These results, taken together with those reported in refs 50 and 51, provide a clearer picture of the reactivity with the first first-row transition metal catalyst of its class.

RESULTS AND DISCUSSION

Styrene and Its Derivatives. Given that the symmetry of p-H_2 must be broken in order to access enhancement and that olefins/alkynes have previously facilitated the activation of H_2 in our (^{Mes}CCC)Co platform,[50−52] we sought to explore the possibility of hyperpolarizing intact olefins through a process akin to SABRE. In our previous reports of olefin hydrogenation with the (^{Mes}CCC)Co platform, we observed some hyperpolarization of non-hydrogenated olefinic substrates, of which the degree of polarization was significantly lower and the source of polarization unclear. In an attempt to further explore these results and improve them, styrene was chosen as the first olefin to determine the suitability of (^{Mes}CCC)Co-py for such a process.[51] Using similar conditions to those previously reported,[50] a solution of styrene (1a) and (^{Mes}CCC)Co-py (9 mol %) in d_6-acetone was subjected to 4 atm of p-H_2 around the 50 G fringe line of a 600 MHz magnet. This procedure resulted in the hyperpolarization of the styrene proton resonances, with enhancement values over 40-fold observed in the intact substrate (Figure S1 and Table S1). Hyperpolarization was observed throughout the entire molecule, with the greatest polarization occurring on the olefin and the *ortho*-protons. In addition to the fact that enhanced, in-phase ^{1}H signal enhancements were observed on multiple sites of the intact substrate, the presence of a SABRE-like mechanism is further supported by observation of the expected qualitative/quantitative field dependence of the polarization transfer (e.g., wherein a significantly more efficient transfer to ^{1}H spins was

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observed with mixing fields of ~50 G versus the earth's field; see Figures S82–S85 and Tables S17–S20). By SABRE-like mechanism, we mean that enhancement is observed in an intact substrate that appears to be transiently and reversibly exchanging with a free substrate reservoir in the bulk solution. Although *para*hydrogenation was also observed via ALTADENA, that reaction appears to be slow enough to allow the hyperpolarization of ^{1}H nuclei in the intact olefin (analysis of the enhancements of styrene and all other tested substrates can be found in the Supporting Information), and polarization of ^{13}C nuclei, with over 50-fold enhancement being observed. While the specific mechanism giving rise to this ^{13}C enhancement will be the subject of future study (see also the subsection "Mechanistic Considerations"), it may be mediated by enhanced singlet order generated within the substrate's ^{1}H spin network at low field.[53]

With this success, derivatives of styrene were also examined to investigate how the substitution of various functional groups may affect the degree of enhancement. The use of 4-fluorostyrene (**1b**) generated an enhanced ^{1}H NMR spectrum similar to that of styrene, containing emissive, absorptive, and anti-phased resonances (consistent with a non-optimal SABRE mixing field, as well as other possible mechanisms), but introduction of that electron-withdrawing group yielded larger enhancement values that exceeded 80-fold (Figure 2A). We also detected polarization transfer to both ^{13}C and ^{19}F nuclei when *p*-H_2 is introduced to the sample at the earth's magnetic field (i.e., without the use of a magnetic shield); the anti-phased peaks in Figure 2C,D are consistent with the creation of pseudo-singlet order.[53,54] Last, we also observed the hyperpolarization of the ^{19}F nuclei associated with both intact substrate and hydrogenated product.

Substitution of styrene with electron-donating groups in **1c** and **1d** led to slower hydrogenation of the substrate and enhancement rates and patterns similar to that of styrene (Figures S13 and S19 and Tables S3 and S4). However, with substrate **1e**, due to the rapid hydrogenation (given its perfluorination), hyperpolarized signals were only observed in its first ^{1}H NMR transient after the initial introduction of *p*-H_2 to the solution (Figure S24). Interestingly, as the reaction progressed with 4-methoxystyrene (**1c**) inside of the magnet, we sometimes observed the enhanced in-phase signals of the entire substrate evolve over time into anti-phased peaks of only the olefinic resonances, exhibiting enhanced spin order with a decay of 53 s (Figure S15). Investigation of the process will be the subject of future studies.

Introduction of steric bulk in the *para* position of the styrene ring did not impede the hyperpolarization of either 2-(4-(4-vinylphenyl)piperazin-1-yl)pyrimidine (**1f**) or ethyl-*N*-methyl-*N*-(4-vinylphenyl)glycinate (**1g**). Hyperpolarization of the ^{1}H nuclei in both substrates was observed (Figures S28 and S30) with enhancement values reaching ~13-fold and ~21-fold for **1f** and **1g**, respectively; however, polarization did not extend past the styrene ring into the substituted *para* position. Hyperpolarization of ^{13}C nuclei was only observed in **1g** and only extended to the styrene ring (Figures S32 and S33).

Interestingly, reactions with **1a**–**c** and **1e** all initially generated a hyperpolarized resonance at 4.54 ppm (which corresponds to the expected resonance shift for H_2 (g) in d_6-acetone) that had enhancement values up to ~30-fold and decayed with a decay constant of ~3 s (Figure S86B), which reflects losses from both T_1 relaxation and RF pulsing. This decay value is in good agreement with T_1 for hyperpolarized orthohydrogen (*o*-H_2) reported in ref 55. The exact mechanism giving rise to this enhancement has not been determined; however, one could imagine this arising from either the recombination of hydrides that have not fully relaxed down to their thermal equilibrium or the polarization of H_2 from a cobalt dihydrogen–dihydride species, (^{Mes}CCC)Co(H)$_2$(H_2) intermediate (Figure S86A), consistent with the previously reported HD scrambling observed with our catalyst (^{Mes}CCC)Co(N_2)-PPh_3.[51]

Acrylates and Pentenoates. After investigating the hyperpolarization of styrenes, we explored the possibility of extending the hyperpolarization lifetimes of our substrates by targeting slow-relaxing nuclei. Acrylates and pentenoates both feature a carbonyl moiety, which typically exhibits a longer relaxation time for its ^{13}C nucleus compared to ^{13}C spins in other moieties.[56] In recent work with (^{Mes}CCC)Co-py and the *para*hydrogenation of ethyl acrylate, minimal hyperpolarization of the ^{1}H and ^{13}C resonances associated with the olefin in ethyl acrylate was observed. Treatment of ethyl acrylate (**2a**) with the conditions reported in this paper similarly led to the hyperpolarization of the olefinic ^{1}H resonances that decayed rapidly (<3-fold enhancement) (Table S8). Although some hyperpolarization of the olefin was observed, the hydrogenative pathway was too competitive to detect lasting olefin polarization (Figures S35 and S36).

Based on these results, we hypothesized that adding more steric bulk around the double bond may favor a net non-hydrogenative pathway over that of the hydrogenative ALTADENA. To this end, we applied methyl methacrylate (**2b**) towards the same hyperpolarizing conditions and observed hyperpolarization of the protons on the olefin moiety and the methyl group, with up to ~40-fold enhancements of the olefinic resonances (Figure S40 and Table S10). While a small amount of hydrogenation is occurring at the same time, we do not see hyperpolarization of the product via ALTADENA or PASADENA. Minimal polarization transfer to ^{13}C nuclei was detected in the NMR spectrum (Figure S42). Introduction of steric bulk to the backside of the molecule (2,2,6,6-tetramethyl-4-piperidyl acrylate, **2c**) yielded a similar ^{1}H NMR spectrum where the terminal protons of the olefin were hyperpolarized and lower levels of signal enhancement extended to portions of the rest of the molecule (Figure S45 and Table S11). Polarization was not extended to ^{13}C nuclei, which was at least partially attributed to the ~20 s delay between the introduction of *p*-H_2 and the collection of the first ^{13}C transient for that experiment.

Treatment of methyl-3,3-dimethylpentenoate (**2d**) with hyperpolarizing conditions and the Co-based catalyst resulted in the enhancement of olefin with a signal lifetime of ~6 s for the 4.96 ppm resonance (with decay resulting from both T_1 relaxation and RF pulsing; Figures S47 and S48). No hyperpolarization was observed in the rest of the molecule within the ^{1}H NMR spectrum. Introduction of *p*-H_2 to the sample of **2d** at earth's magnetic field yielded negligible transfer of polarization to the olefinic ^{13}C nuclei. However, when the same was attempted with the catalyst and ethyl-2-methylpentenoate (**2e**), hyperpolarization of the protons was achieved throughout most of the substrate (with greater than 150-fold ^{1}H enhancement of the 5.76 ppm resonance), except for the ethoxy moiety (Figure S50 and Table S12). While administering *p*-H_2 at earth's field, we observe a difference in the degree of polarization extended to the ^{13}C nuclei when coupling to ^{1}H is on or off, largely owing to cancellation of peaks with opposite phase when superimposed by decoupling. For example, the maximum ^{13}C

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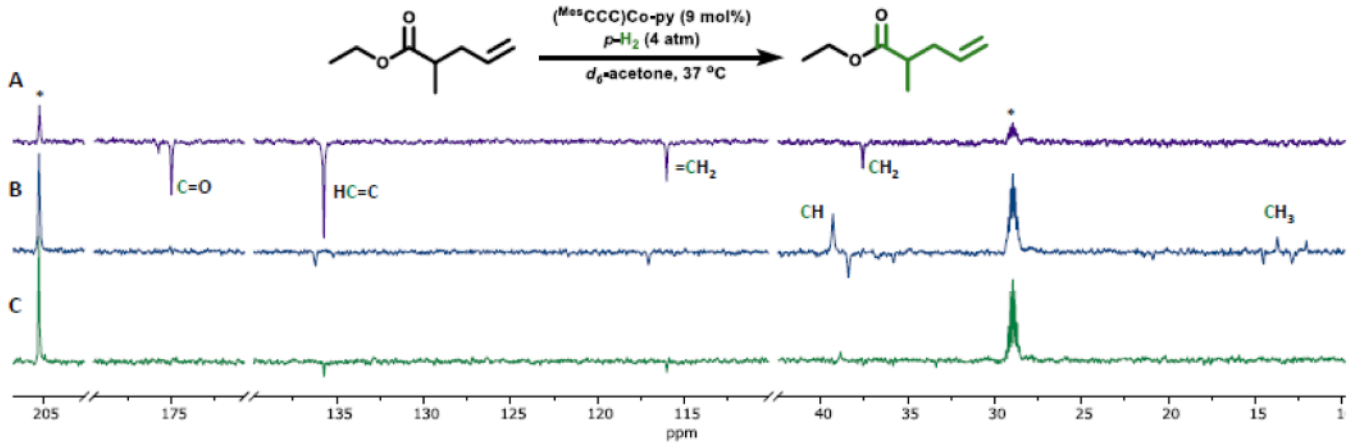

Figure 3. (A) Single-scan ^{13}C NMR spectrum of a 65 mM solution of ethyl-2-methylpentenoate in d_6-acetone (*) immediately after administering p-H_2 by shaking the sample in a μT field provided by a passive mu-metal shield. (B) Corresponding $^{13}C\{^1H\}$ NMR spectrum resulting from shaking at earth's magnetic field. (C) Same as B, but with ^1H decoupling applied, allowing direct comparison with A.

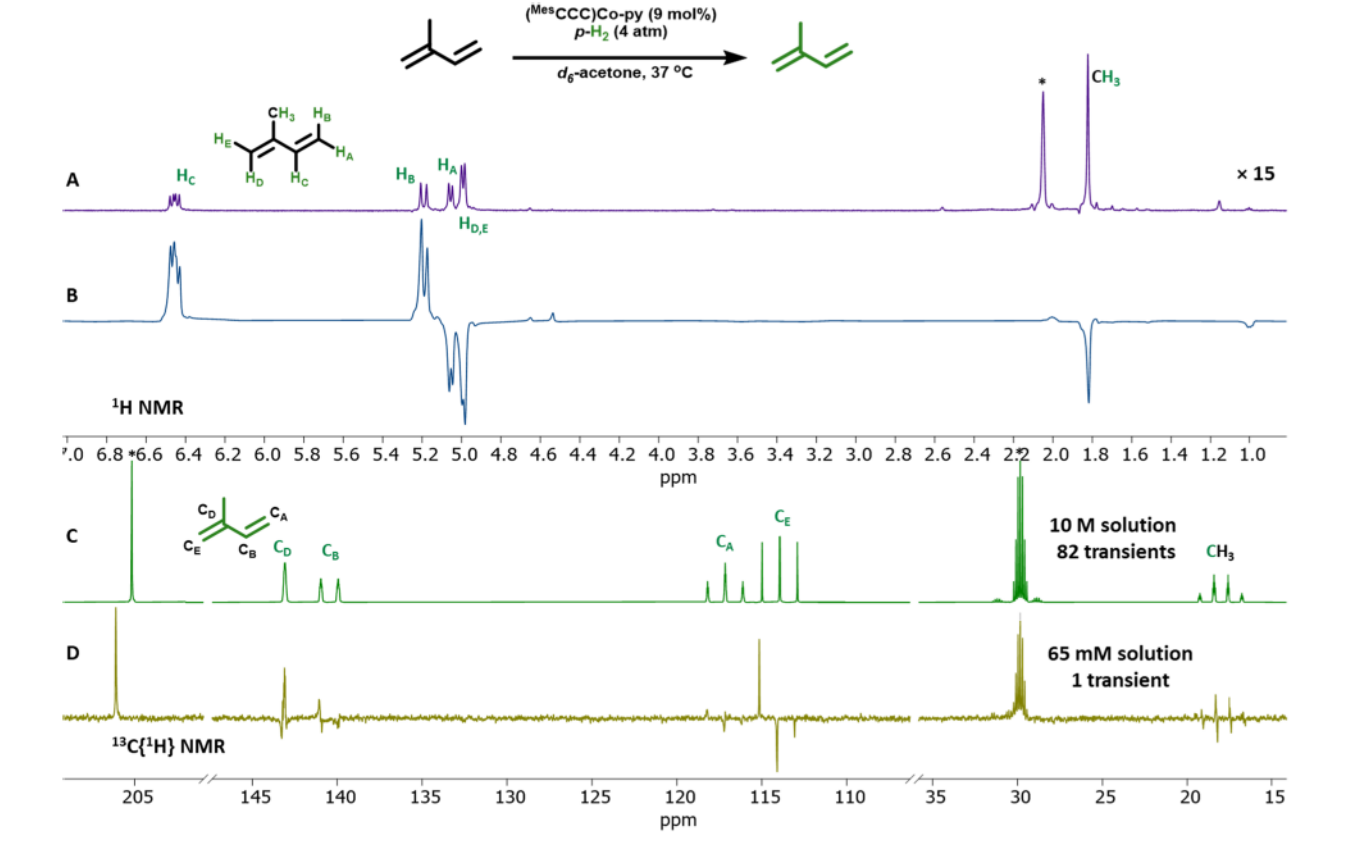

Figure 4. (A) Single-scan ^1H NMR spectrum of a thermally polarized 65 mM solution of isoprene in d_6-acetone (*) with 15-fold vertical expansion relative to the spectrum below it. (B) Single-scan ^1H NMR spectrum taken after hyperpolarization in a 5.0×10^{-3} T field. C: $^{13}C\{^1H\}$ NMR spectrum (82 scans, d_1 = 120 s) of isoprene (10 M) in d_6-acetone (*). (D) Single-scan ^{13}C NMR spectrum (displayed in magnitude mode) of isoprene taken immediately after exposure to p-H_2 and polarization at earth's magnetic field, with the vertical scale increased to 16-fold compared to C.

polarization observed in coupled-enhanced spectra occurs on the CH carbon closest to the carbonyl moiety (enhancement up to 98-fold, Figure 3B), whereas the maximum enhancement observed with the fully decoupled ^{13}C spectrum is found on the resonance of the CH moiety of the olefin, with only a (−)11-fold enhancement achieved (Figure 3C). Interestingly, we note that the use of a passive mu-metal shield (providing a mixing field in the microtesla regime) allowed for a larger increase in polarization transfer to some ^{13}C nuclei in this substrate, as well as a qualitatively different polarization pattern (see Tables S28−S30 in the Supporting Information). Indeed, up to 147-fold enhancement is observed for the olefinic CH resonance (Figure 3A), corresponding roughly to an order-of-magnitude increase compared to those resonances in the spectra in Figure 3B,C.

Isoprene and Terpenes. In addition to providing insights into reaction mechanisms by enhancing the signals of intermediates that otherwise would avoid detection by NMR

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spectroscopy, PHIP has also been employed to produce MRI contrast agents.[1] In particular, SABRE has allowed for the non-hydrogenative polarization of a new set of biologically relevant substrates at low magnetic field, greatly advancing this endeavor.[1,10,28,40] Encouraged to identify biologically relevant olefinic substrates that are compatible with the present Co-based catalytic system, we turned our attention toward terpenes. Composed of recurring isoprene units, terpenes are a class of molecules responsible for the anti-inflammatory/sedative properties found in cannabidiol and tetrahydrocannabinol, in addition to some fragrances, essential oils, and the flavoring of spices.[57,58]

To determine the aptitude of these molecules for non-hydrogenative hyperpolarization, initial studies were conducted with isoprene, 3a. A 65 mM solution of isoprene in d_6-acetone was exposed to 4 atm of p-H_2 in the presence of the cobalt catalyst in the fringe field of the magnet. Polarization transfer from p-H_2 resulted in strong ^{1}H NMR signals corresponding to hyperpolarization of the intact substrate. Very little hydrogenation occurs, allowing for ^{1}H signal enhancement values of up to 130-fold for the intact substrate (Figure 4b). Greatest polarization is observed in the protons of the monosubstituted olefin, consistent with the less sterically olefin binding more frequently to the metal center. However, enhancements up to 47-fold are still observed for the protons on the disubstituted olefin moiety, suggesting that isoprene may also be binding through this moiety as well. Repeating the experiment at earth's magnetic field resulted in the hyperpolarization of all ^{13}C nuclei in isoprene (Figure 4d) with the maximum polarization observed on the terminal carbon of the disubstituted olefin, exhibiting 112-fold enhancement (see also Table 31 of the Supporting Information).

With isoprene proving to be a viable substrate, myrcene (3b) was the first terpene attempted. Myrcene has been shown to block inflammation and act as a painkiller, sedative, and muscle relaxant.[57] Our catalyst did indeed yield SABRE-like hyperpolarization of structurally intact myrcene, with ^{1}H signal enhancement levels of up to 46-fold (Figure S65 and Table S14). Myrcene has three potential binding sites, each with increasing substitution, and the enhancement patterns tracked with the number of substituents, with the greatest enhancement being observed on the least substituted olefin. Addition of p-H_2 at earth's magnetic field led to the hyperpolarization of some of the ^{13}C nuclei. This hyperpolarization approach was extended to two other terpenes, linalool (3c) (yielding ^{1}H enhancements near 80-fold, Figure S70), and limonene (3d) (yielding ^{1}H enhancements <3-fold, Figure S75); linalool also gave rise to superior polarization transfer to the ^{13}C nuclei over limonene, which exhibited no observable ^{13}C polarization transfer under our conditions (Figure S74).

N-Based Substrates. Lastly, efforts were taken to observe the hyperpolarization of pyridine, its fluorine derivatives, and imidazole, with our cobalt catalyst; however, no polarization was observed from any member of this substrate class (Figures S78–S81). We propose that this lack of effect could be due to the competitive binding of N-based substrates and p-H_2 for the same equatorial position in the cobalt complex. In addition, it is necessary to activate p-H_2 in order to produce hyperpolarization; however, pyridine and other nitrogen-based substrates do not seem to have the capability to induce such activation under these conditions as evidenced by the fact that introduction of H_2 and D_2 gas to the (^{Mes}CCC)Co-py complex does not result in the formation of HD gas as demonstrated with our (^{Mes}CCC)-Co(N_2)PPh_3 complex.

Mechanistic Considerations. Considering the hyperpolarization results presented above, we propose three potential mechanisms in Figure 5, which may explain the origin of hyperpolarized intact olefin. In a traditional SABRE mechanism, the olefin binds to the cobalt center bearing two *para*hydrogen-derived hydrides. Through scalar coupling, spin order is passed from the hydrides to the olefin that is rapidly and reversibly exchanging with other olefins in the bulk solution, resulting in the bulk polarization of the intact olefin. Such polarization has been shown to be magnetic field-dependent (with optimal ^{1}H results obtained in the millitesla regime to roughly match the frequency difference of the resonances to the magnitude of the ^{1}H scalar coupling network),[8] with the spectral pattern of polarization also varying with that field. In the present work, we hyperpolarize structurally intact olefins, with polarization enhancements often observed throughout the extended molecule (instead of merely at the double bond); moreover, although the present experimental setup prevented the mixing field from being varied with precision, the polarization enhancement was observed to depend on field strength (comparing results at earth's field with those at the fringe field).

Another potential route is reminiscent of that reported by Bowers and co-workers where they proposed that their heterogeneous catalytic system dehydrogenates an olefin to an alkyne, followed by the pairwise addition of p-H_2 to generate hyperpolarized structurally intact olefin, in a process termed PR-PHIP for pairwise replacement PHIP.[59] Imagining a scenario akin to this with our homogeneous system, the olefin would coordinate to the metal center, followed by the extraction of two hydrides from the substrate to form a transient dihydride–alkyne complex. A molecule of p-H_2 would have to displace the thermal H_2 and add to the terminal alkyne to observe the polarization that is reported here. While this mechanism would break down for a substrate like methyl methacrylate, and potentially isoprene and myrcene (if binding through disubstituted olefin where the reaction would have to go through a carbene-like intermediate), we still sought to investigate this possibility. Theoretically, if this mechanism were important and if terminal alkynes were added to the catalyst in the presence of p-H_2, we should observe the same hyperpolarization profile achieved above. However, when attempting to use ethynylbenzene (Figure S87) as the substrate to achieve the polarization observed with styrene, we instead observe minimal polarization of the olefin, with no polarization extending beyond this to the rest of the substrate. This result is attributed to the non-productive interaction of the Co-py catalyst with terminal C–H bonds, indicating that this mechanism is probably not operative in this system. Additionally, the introduction of deuterium gas (D_2) to styrene in the presence of Co-py catalyst did not reveal the presence of (ethynyl-*d*)benzene on the time course of the hyperpolarization reactivity.

The final proposed mechanism comprises a series of insertion/elimination reactions. Previous hydrogenation studies with our (^{Mes}CCC)Co system revealed the ability of the catalyst to readily undergo this type of reactivity with the incorporation of deuterium in the olefin of styrene over the course of 2 h.[51] With respect to this present polarization mechanism, one could imagine the incorporation of a single hydride similar to the one-H PHIP reactivity,[16] followed by β-hydride elimination to afford the structurally unmodified olefin. While this route would

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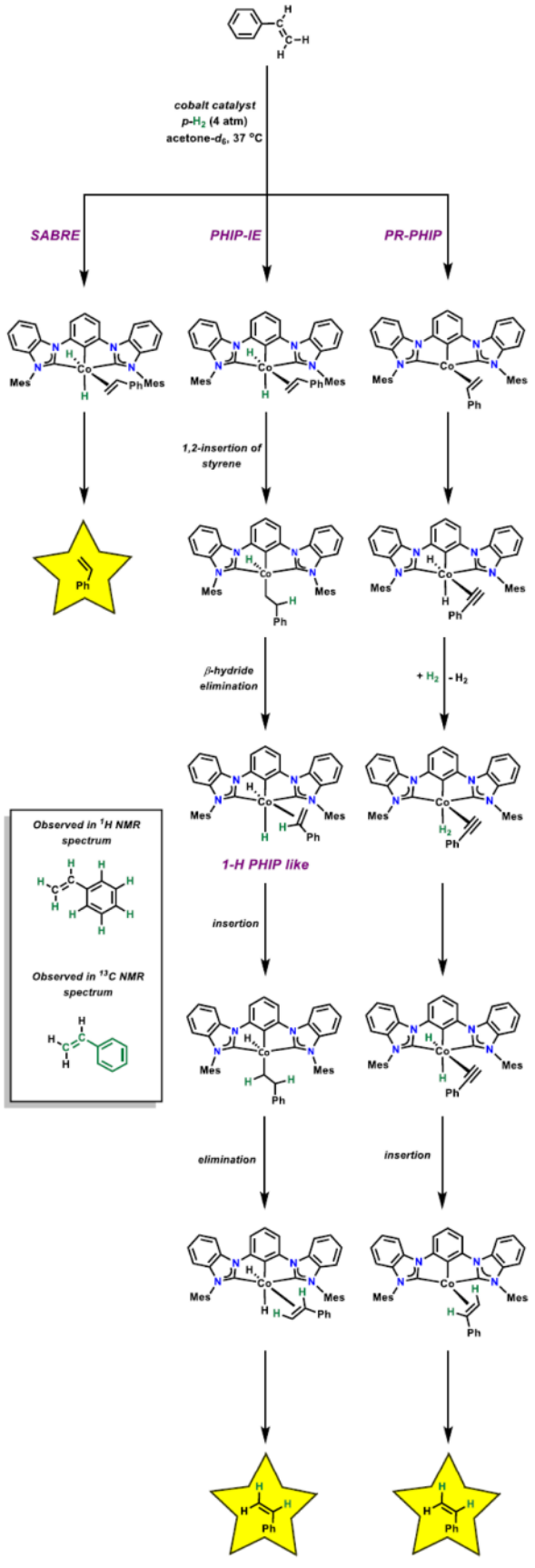

Figure 5. Proposed mechanisms for the generation of hyperpolarized intact olefins.

explain the observance of dissolved hyperpolarized *o*-H_2, the likelihood of strong coupling to a transiently bound olefin species in an η^2 fashion is small, in addition to the relatively large polarization observed throughout the larger substrate when compared to that observed in Eisenberg's report. Instead, we propose a potential mechanism composed of consecutive insertion−elimination steps, likely involving reversible exchange with a free substrate in the solution (along with consequent polarization transfer to other spins in the substrate via the scalar coupling network in low field), in a process we have termed PHIP-IE, for PHIP-insertion and elimination, akin to that reported by Bargon and co-workers with their rhodium and palladium systems.[17,18] In order to investigate this mechanism, D_2 was introduced to select model substrates under the same hyperpolarization conditions described above to determine the rate of exchange and the sites of exchange. To our surprise, we observed rapid incorporation of deuterium into both methyl methacrylate (up to the carbonyl moiety) and isoprene, with the monosubstituted site of isoprene becoming exchanged more rapidly than the disubstituted olefin (Figures S88−S91, Graphs S1−S2). The results support the rapid exchange of hydrogens on the substrate, leading to eventual pairwise transfer of *para*-hydrogen-derived hydrides to the substrates and exchange of this substrate with a free intact substrate in the solution. Altogether, this results in enhancements observed, not just on the olefinic site, but in adjacent sites as well and in some cases, throughout the entire molecule.

While our experimental results suggest one or more of the above mechanisms (SABRE and/or PHIP-IE) contributing to the bulk hyperpolarization of the intact substrate in solution, further studies are necessary to elucidate the dominant mechanism—which in turn may depend on the nature of the substrate involved.

CONCLUSIONS

In conclusion, we have shown that a cobalt-based catalyst can be used to hyperpolarize olefins via a SABRE-like mechanism, an expansion and improvement on what was initially hypothesized when using the (^{Mes}CCC)Co(N_2)PPh_3 catalyst.[51] Reactivity with (^{Mes}CCC)Co-py, previously demonstrated for hydrogenative PHIP,[50] results in the net non-hydrogenative hyperpolarization of ^{1}H nuclei in olefinic substrates, with observed transfer of hyperpolarization to ^{13}C and ^{19}F nuclei. Enhancement values of up to ∼150-fold were observed for both protons and ^{13}C nuclei at 14.1 T. Notably, these results were achieved without the use of isotopic labeling or rf pulse sequences, and enhancements of ^{13}C spins were shown both with and without the use of a magnetic shield. Moreover, this type of chemistry with a first-row transition metal catalyst further demonstrates that precious metal catalysts—which are expensive, rare, and potentially toxic—are not required for these types of "transformations". A wide variety of olefinic substrates were amenable to this SABRE-like hyperpolarization with our catalyst, including biologically relevant terpenes.

Although a definitive mechanism is not presented, we propose a combination of SABRE and PHIP-IE chemistry—that is, PHIP produced via consecutive insertion and elimination reactions—that results in the hyperpolarization reported here. While irreversible hydrogenation via ALTADENA is observed in varying degrees, substrates such as isoprene and methyl methacrylate demonstrate the potential for this catalytic system to operate in a fashion that is practically similar to SABRE, wherein a given dissolved, structurally intact substrate can be

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hyperpolarized continuously in bulk—but here, involving an entirely new class of substrates not previously amenable to SABRE and otherwise could only be hyperpolarized via irreversible PHIP on alkyne precursors which may not be accessible.

Future work will be directed toward mechanistic and kinetic studies to determine the pathways involved in the transfer of spin order to substrates. In addition, efforts will be put toward achieving higher polarization and longer polarization lifetimes, likely required, for example, for the generation of viable MRI contrast agents. We note that our hyperpolarization setup is rudimentary, and resulting polarization can be significantly improved by the optimization of magnetic fields, p-H_2 distribution (e.g., using a "bubbler"), and catalytic conditions (i.e., temperature, hydrogen pressure, substrate concentrations, catalyst loading, catalyst design, etc.). Taken together, these results open a door to new types of catalyst structures and compositions—opportunities that we hope will inspire scientists across NMR/MRI, chemistry, physics, and biomedicine.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.0c03727.

Experimental spectra (PDF)

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Notes

The authors declare no competing financial interest.

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