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Parahydrogen Induced Polarization with Rh-based Monodentate Ligand in Water

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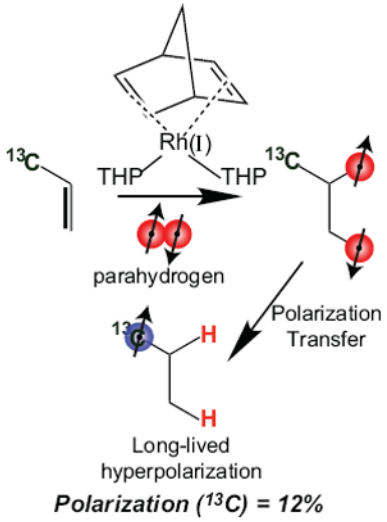
Abstract

Reported here is a water soluble Rh(I)-based catalyst for performing parahydrogen induced polarization (PHIP). The $[Rh(I)(norbornadiene)(THP)_2]^+[BF_4]^-$ catalyst utilizes the monodentate phosphine ligand tris(hydroxymethyl)phosphine (THP). The monodentate PHIP catalyst is less susceptible to oxygenation by air and THP ligand and is significantly less expensive than bidentate water-soluble PHIP ligands. *In situ* PHIP detection with this monodentate Rh(I) based catalyst in water yielded 12% ^{13}C polarization for the parahydrogen addition product, 2-hydroxyethyl 1-^{13}C-propionate-$d_{2,3,3}$ (HEP), with a ^{13}C T_1 relaxation of 108 seconds at 0.0475 T. PHIP polarization yields were high, reflecting efficient hydrogenation even under conditions of high content of the oxidized phosphine form of the THP ligand.



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Detailed experimental methods are provided in Supplementary Information. This material is available free of charge via the Internet at http://pubs.acs.org.

Keywords

Parahydrogen; NMR; PASADENA; hyperpolarization; 13C; PHIP; catalysis; molecular hydrogenation; tris(hydroxymethyl)phosphine; rhodium

Hyperpolarization using spin order of parahydrogen was demonstrated more than 25 years ago by Bowers and Weitekamp.[1] The resulting polarization approaching unity vastly exceeds nuclear spin polarization achievable under equilibrium conditions in any currently available high field magnet by several orders of magnitude. This polarization method requires using a molecular mechanism to chemically add parahydrogen to an unsaturated chemical bond. The technique found practical application in the early 2000s when the Malmö group successfully demonstrated fast molecular quantitative addition of parahydrogen on a time scale of several seconds.[2] The latter allows for inducing Zeeman polarization on nearby ^{13}C spin sites in hydrogenated molecules in a relatively large sample. The resulting ^{13}C polarization[3] of such samples, up to 50%, can be used for bolus injection in living organisms to interrogate metabolic processes with hyperpolarized molecular contrast agents whose *in vivo* lifetime exceeds one minute.[4-6] Preparation of hyperpolarized states using such a process is often termed parahydrogen-induced polarization (PHIP).[7]

If the PHIP requirement for fast molecular addition is not fulfilled, the singlet state of nascent protons obtained during the hydrogenation reaction decays on the time scale of seconds with the net result of poorly polarized ^{13}C sites. Rh(I) based catalyst such as Wilkinson catalyst accelerates the hydrogenation reaction. While water-soluble catalysts are not mandatory in principle, typical solvents such as chloroform severely limit biological applications,[8-11] which is the main driver behind hyperpolarized technologies' recent revival.[12]

The only successful PHIP water-soluble Rh(I) based catalyst utilizes 1, 4-Bis[(phenyl-3-propanesulfonate) phosphine] butane disodium salt (717347, Sigma-Aldrich-Isotec, Miamisburg, OH)[13] and its close variant,[14] where Rh(I) is chelated by norbornadiene (nbd) and two phosphines connected by a four carbon bridge, Scheme 1.[15,16] The latter is critical to the catalyst activity as norbornadiene is replaced by hydrogen molecules during hydrogenation after nbd is hydrogenated and removed. The active catalytic complex features Rh(I) chelated by a bidentate phosphine ligand, 1, 4-Bis[(phenyl-3-propanesulfonate) phosphine]. This bidendate ligand is relatively expensive due to an elaborate chemical structure and it is prone to oxidation by oxygen. The latter cannot be mitigated by balancing the Rh(I) and ligand ratio, because if one chelating phosphine arm is dysfunctional, the other phosphine arm can no longer properly chelate and is disabled. As a result, even a small % of oxidized form leads to undesirable polarization loss.

The alternative solution presented here, is to use the monodentate phosphine ligand, Tris(hydroxymethyl)phosphine, $P(CH_2OH)_3$, (THP). While the compound has been known for more than 50 years, its coordination chemistry has only been recently studied.[17] Besides excellent Rh(I) chelation, it is highly soluble and stable in water.[17,18] Moreover, hydroxyl groups of the significantly simpler and less expensive THP ligand offer an intrinsic advantage that can be exploited by preparation of surface tethered Rh(I)-THP complexes paving the road to heterogeneous PHIP (HET-PHIP) catalysis of aqueous contrast agents. HET-PHIP is potentially more biologically compatible, because it avoids the necessity of purifying PHIP hyperpolarized contrast agents' mixtures, as Rh(I) is retained in a solid phase and it does not enter living organisms. Although [Rh(I)-THP] complexes have been recently reported and characterized,[19] the goals of this study were to investigate their

application to PHIP and to simplify their preparation using mildly water soluble [Rh(I)(nbd)$_2$]$^+$[BF$_4$]$^-$ and THP.

[RhCl(cod)]$_2$ is insoluble in water as well as many organic solvents such as acetone and this results in tedious preparation protocols, whereas [Rh(I)(nbd)$_2$]$^+$[BF$_4$]$^-$ as used here is soluble in water and the catalyst preparation procedure is relatively straightforward, Fig. 1.

Proton decoupled ^{31}P spectroscopy was used to validate these complexes by comparison to prior literature,[19] Fig. 2. Free THP in water, THP oxide and [Rh(I)-THP] complexes notably have different ^{31}P chemical shifts. Phosphine resonances of [Rh(I)-THP] are distinctive doublets due to ^{103}Rh-^{31}P spin-spin coupling of 100 Hz or more.[19]

Titration of [Rh(I)(nbd)$_2$]$^+$[BF$_4$]$^-$ with THP and excess NaCl was performed to assign ^{31}P doublets of three different [Rh(I)-THP] complexes: [Rh(I)(nbd)(THP)$_2$]$^+$[BF$_4$]$^-$, [Rh(I)(nbd)(THP)(H$_2$O)]$^+$[BF$_4$]$^-$, and [Rh(I)(nbd)(THP)(Cl)], Figs. 1 and 2. Moreover, because commercial samples of THP have up to 40% oxide form, these titration studies guided our efforts for choosing optimal conditions for preparation of [Rh(I)(nbd)(THP)$_2$]$^+$[BF$_4$]$^-$ and other [Rh(I)-THP] mixtures for the purpose of PHIP studies, Fig. 3.

Briefly, THP (1.0 mmol, 0.124 g) containing 40% of the oxide form was dissolved in 99.8% D$_2$O, Isotec, Miamisburg, OH, (20 mL) resulting in solution containing 0.050 mmol (1 eq) in 1 mL. [Rh(I)(nbd)$_2$]$^+$[BF$_4$]$^-$, Strem Chemicals, Inc., Newburyport, MA, (0.25 mmol, 94 mg) was dissolved in high purity acetone (1 mL) to create a solution containing 0.050 mmol (1 eq) in 0.2 mL. NaCl (0.40 g, 6.8 mmol) was dissolved in D$_2$O (5 mL) resulting in solution containing 1.4 mmol (27 eq) in 1 mL. THP solution was divided between five vials as follows: 2, 3, 4, 5, and 6 mL respectively followed by addition of 0.2 mL (1 eq) of [Rh(I)(nbd)$_2$]$^+$[BF$_4$]$^-$ solution to each vial producing solutions corresponding to Rh(I):non-oxidized THP ratios of 1:1.2, 1:1.8, 1:2.4, 1:3.0, and 1:3.6 respectively. 0.5 mL aliquot was extracted from each vial for ^{31}P spectroscopy, Fig. 2. Following extraction, 1.0 mL of NaCl solution (27 eq) was added to each vial to prepare samples with excess NaCl, Fig. 2.

When sufficient quantity of THP is present in aqueous solution, [Rh(I)(nbd)(THP)$_2$]$^+$[BF$_4$]$^-$ is formed with excess THP residing in a form of free THP or its protonated form THP•H$^+$, Fig. 2. The excess of THP does not lead to the formation of [Rh(I)(nbd)(THP)$_4$]$^+$[BF$_4$]$^-$ and/or [Rh(I)(nbd)(THP)$_4$(Cl)] as expected from previously reported studies in non-aqueous conditions and with cyclooctadiene (cod) moiety.[19] The addition of excess NaCl to a mixture of [Rh(I)(nbd)(THP)$_2$]$^+$[BF$_4$]$^-$ and [Rh(I)(nbd)(THP)(H$_2$O)]$^+$[BF$_4$]$^-$, obtained using a Rh(I):THP ratio of < 1:2.0 leads to conversion of [Rh(I)(nbd)(THP)(H$_2$O)]$^+$[BF$_4$]$^-$ to [Rh(I)(nbd)(THP)(Cl)], Figs. 1 and 2.

Because [Rh(I)(nbd)(THP)$_2$]$^+$[BF$_4$]$^-$ was a dominant complex based on the above titration study, the PHIP study was primarily focused on this complex. [Rh(I)(nbd)(THP)$_2$]$^+$[BF$_4$]$^-$ was formed using THP and 2.7 mM [Rh(I)(nbd)$_2$]$^+$[BF$_4$]$^-$ with a 1:2 Rh(I):THP molar ratio for starting materials in 99.8% D$_2$O. Approximately 2 equivalents of PHIP substrate HEA (5-6 mM solution) were added to the catalyst solution. The PHIP procedure was performed identically to previously described hardware and protocols,[21] and ^{13}C hyperpolarization was detected *in situ*[22] immediately after ^{13}C hyperpolarization. 97% parahydrogen for PHIP was produced using a semi-automated parahydrogen generator.[23]

The scheme of molecular addition of parahydrogen to HEA leading to ^{13}C hyperpolarized HEP is shown in Fig. 3a. ^{13}C hyperpolarized signal exemplified in Fig. 3c was compared to a reference signal from sodium 1-^{13}C-acetate under conditions of equilibrium Boltzmann polarization at 0.0475 T, Fig. 3b. Maximum achieved ^{13}C polarization was ~12% corresponding to signal enhancement of 3,000,000 fold at this magnetic field

strength. ^{13}C T_1 of hyperpolarized HEP was measured in a separate experiment by monitoring signal decay using a series of NMR single scan acquisitions with 10° excitation RF pulses. The exponential decay was simulated, taking into account polarization loss due to RF pulses, and the ^{13}C T_1 was determined to be 108.7±1.7 seconds, Fig. 3d. This value is somewhat larger than the one previously reported for H_2O[22], which is likely due to the very low concentration of protons in 99.8% D_2O. *In situ* detection also allows for convenient monitoring of percent ^{13}C hyperpolarization as a function of reaction time, Fig. 3e. Reactions are carried out under ^1H RF decoupling, during which (i) the product forms corresponding to the rise shown in Fig. 3e and (ii) nascent proton spin order decays due to unfavorable relaxation processes especially notable after >12 second long hydrogenation. The somewhat slower kinetics of molecular hydrogenation with this catalyst explains why only 12% HEP hyperpolarization was achieved compared to 20%[22] reported by us earlier with bidentate ligand with observed maximum at 4 s of reaction time. The potential reasons for the slower reaction rate besides the different catalyst nature include significant amounts of THP oxide and more importantly small quantities of free THP. The latter was reported to have reducing properties in the absence of Rh(I).[17] If such reduction was indeed the case, THP rather than parahydrogen was a source of reducing material. Any HEA reduced using THP leads to a pool of non-polarized HEP, therefore decreasing the effective percentage of ^{13}C hyperpolarization. The PHIP using $[Rh(I)(nbd)(THP)_2]^+[BF_4]^-$ without NaCl resulted in 2 fold lower ^{13}C hyperpolarization with similar kinetics. Excess of THP leading to a pool of free THP, Fig. 2, also resulted in decreased ^{13}C hyperpolarization. When the THP:Rh(I) ratio was < 2 leading to formation of mono-THP Rh(I) complex, ^{13}C hyperpolarization was also lower indicating that $[Rh(I)(nbd)(THP)_2]^+[BF_4]^-$ is the most efficient among the ones studied here.

The $[Rh(I)(nbd)(THP)_2]^+[BF_4]^-$ based catalyst solution ejected from the polarizer after performing PHIP hydrogenation was tested for stability when exposed to air. Specifically, $^{31}P\{^1H\}$ NMR spectra of starting THP material, PHIP mixtures for hydrogenation before and after PHIP were recorded, Fig. 4. Briefly, NaCl (0.10 g, 1.7 mmol) and THP (0.050 g, 0.40 mmol) were dissolved in 99.8% D_2O (50 mL) and degassed. The $^{31}P\{^1H\}$ NMR spectrum of THP ligand was recorded using this solution. Rhodium catalyst $[Rh(I)(nbd)_2]^+[BF_4]^-$ (0.050 g, 0.134 mmol) was dissolved in 3 mL of acetone and added to the degassed THP solution. HEA (0.032 g, 0.268 mmol) was added under nitrogen atmosphere. $^{31}P\{^1H\}$ NMR spectra were recorded before and after PHIP, Fig. 4. After ejection of the PHIP polarized sample from the polarizer, it was exposed to air. The $^{31}P\{^1H\}$ spectrum showed only trace amounts of the $[Rh(I)(nbd)(THP)_2]^+[BF_4]^-$ complex and significantly more THP oxide. A likely explanation for this finding is the loss of nbd ligand during PHIP procedure results in rapid oxidation of active Rh(I)-containing species upon exposure to air after PHIP experiments. Therefore, the catalyst solution cannot be re-used. This feature is similar to the single use Rh(I)-based catalyst with bidentate ligand.[14] This is not a limitation as it is not necessary to expose the catalyst to atmosphere with this type of polarizer. This new aqueous catalyst is suitable for PHIP hyperpolarization of biomolecules useful as hyperpolarized metabolic contrast agents for molecular imaging of cancer and other metabolically altering diseases. These molecules include ^{13}C-succinate in ethylsuccinate form,[6] ^{13}C-tetrafluoropropylpropionate,[4] ^{13}C-phospholactate[24] and others that were demonstrated to be amenable to molecular hydrogenation with similar ease as the PHIP polarized HEP presented here.

This work reports on the first use of monodentate Rh(I) based hydrogenation catalyst for PHIP in aqueous medium. Moreover, $[Rh(I)(nbd)(THP)_2]^+[BF_4]^-$ catalyst was prepared in aqueous medium unlike in previously reports, where organic solvents were used. The catalyst is air stable for hours[18] before it enters PHIP hydrogenation and PHIP is efficient even with THP containing high quantities of the oxidized form. The rate of catalytic reaction

appears lower than the reaction rate of the catalyst with the bidentate ligand based on percentage polarization achieved. This can be remedied by the use of higher purity THP or potentially by the use of other THP based Rh(I) complexes such as [Rh(I)$(THP)_4$]. The latter is very attractive as nbd does not enter the PHIP device and consequently living organisms after injection of hyperpolarized contrast agents. More importantly, however, THP is significantly simpler and less expensive compared to the water-soluble bidentate ligand. Moreover, hydroxyl groups offer a moiety that can be exploited to potentially prepare surface tethered Rh(I)-THP complexes paving the road to heterogeneous PHIP catalysis of aqueous contrast agents. This has already been demonstrated in seminal work by Koptyug and Kovtunov for gas phase PHIP.[25,26] Heterogeneous aqueous PHIP catalysis is a 'holy grail' as it would allow for (i) preparation of pure hyperpolarized contrast agents for *in vivo* and human use, (ii) significant size reduction of the reaction chamber and other MR hardware components thereby reducing cost and increasing portability of PHIP polarizers, and (iii) promoting catalyst recycling. This work significantly simplifies the chemistry necessary for such heterogeneous catalysis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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ABBREVIATIONS

Cod	cyclooctadiene
HEA	2-hydroxyethyl 1-^{13}C-acrylate-$d_{2,3,3}$
HEP	2-hydroxyethyl 1-^{13}C-propionate-$d_{2,3,3}$
nbd	norbornadiene
PASADENA	parahydrogen and synthesis allow dramatically enhanced nuclear alignment
PHIP	parahydrogen induced polarization
THP	tris(hydroxymethyl)phosphine

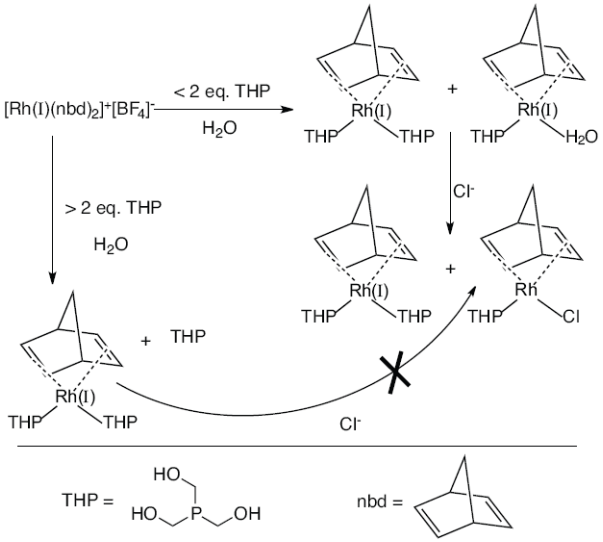


Figure 1.
Molecular diagrams of catalyst preparation in aqueous medium. The presence of THP oxide is not shown.

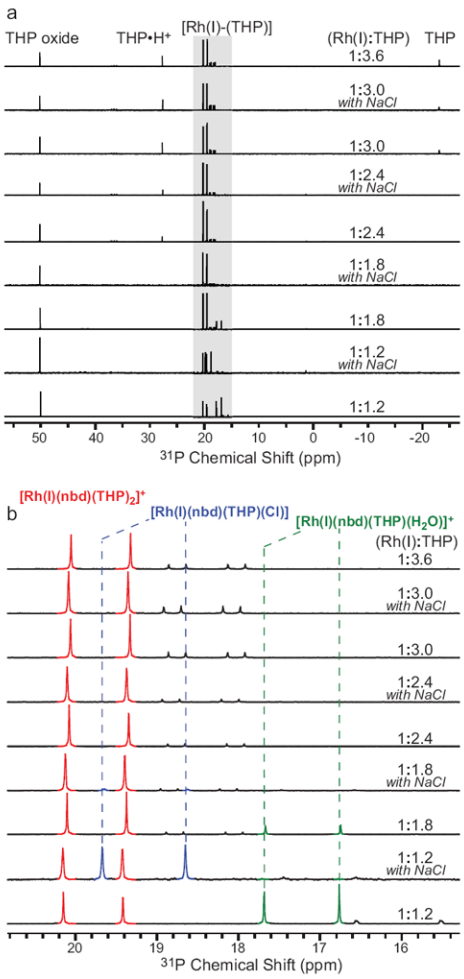


Figure 2.

High resolution $^{31}P\{^{1}H\}$ NMR spectra of Rh(I):THP mixtures in 99.8% D_2O acquired at 11.7 T with proton decoupling: a) entire spectral bandwidth showing all ^{31}P species, and b) zoomed region corresponding to [Rh(I)-THP] complexes (blue trace). The Rh(I):THP ratio and NaCl presence are shown for each spectrum.

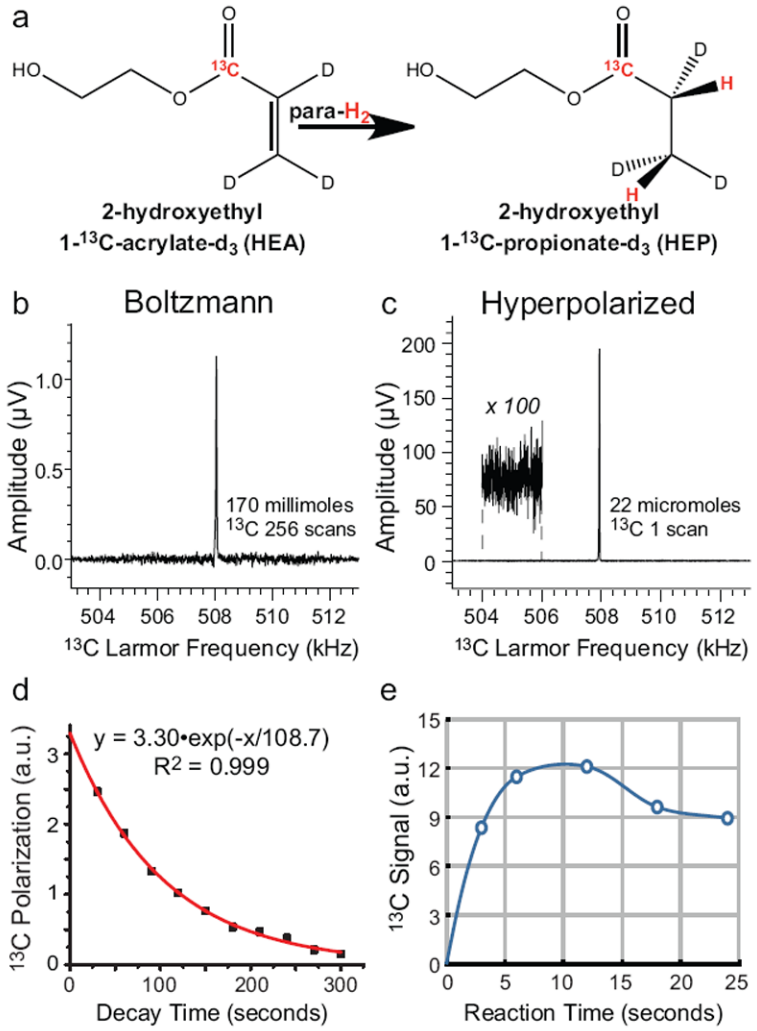


Figure 3.

^{13}C PHIP hyperpolarization of HEP using $[Rh(I)(nbd)(THP)_2]+[BF_4]^-$ catalyst in D_2O with PASADENA[20] (parahydrogen and synthesis allow dramatically enhanced nuclear alignment). a) The diagram of molecular hydrogenation of 2-hydroxyethyl 1-^{13}C-acrylate-$d_{2,3,3}$(HEA) yielding 2-hydroxyethyl 1-^{13}C-propionate-$d_{2,3,3}$(HEP). ^{13}C NMR spectroscopy conducted at 0.0475 T: b) ^{13}C spectrum of 170 millimoles (14 g in 50 mL D_2O) of sodium 1-^{13}C-acetate, Boltzmann polarization at 35 °C, 256 averages, c) ^{13}C spectrum of 22 micromoles (2.6 mg in 4 mL 99.8% D_2O at pH = 4.0) hyperpolarized HEP, polarization P = 12% corresponding to signal enhancement by 3,000,000 fold. d) Decay of ^{13}C hyperpolarized signal was measured with 10° excitation pulses. The T_1 relaxation was modeled (red trace) as an exponential decay taking into account the effect of RF pulses on ^{13}C magnetization, e) *In situ* detected ^{13}C PHIP signal versus reaction time was carried out under conditions of proton decoupling. One reaction was performed for each data point in Fig. 3e with an estimated polarizer reproducibility of approximately 5%. The detected ^{13}C PHIP signal in 3e is proportional to the product of hydrogenated HEP and decay of the proton singlet state during proton decoupling/reaction time. Hyperpolarized ^{13}C decay is negligible, because ^{13}C PHIP signal is induced from nascent parahydrogen protons at the end of the proton decoupling period during approximately 0.1 second polarization transfer step of the pulse sequence and detected immediately.

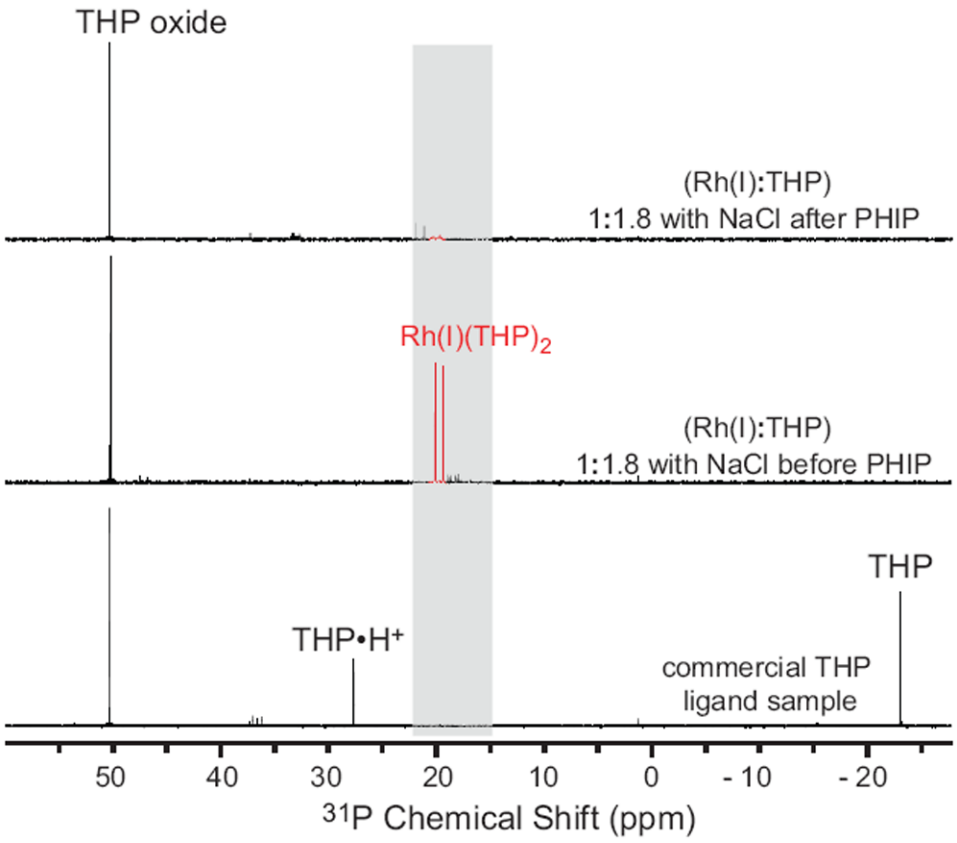
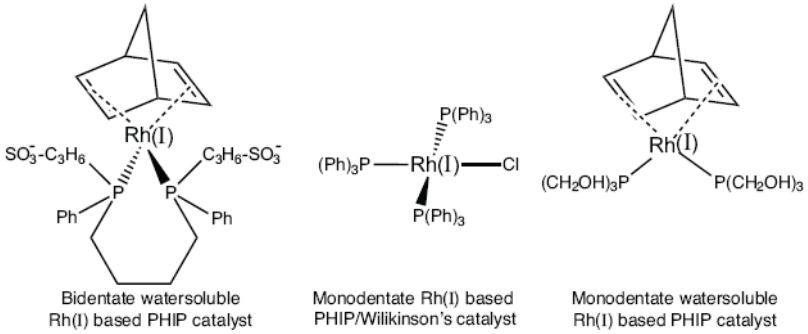


Figure 4.

High-resolution $^{31}P\{^{1}H\}$ NMR spectra of Rh(I):THP mixtures in 99.8% D_2O acquired at 11.7 T with proton decoupling: (bottom) THP without Rh(I) (middle) Rh(I):THP:HEA:NaCl (1:1.8:2:12) before PHIP hydrogenation, (top) Rh(I):THP:HEP:NaCl (1:1.8:2:12) after PHIP hydrogenation.



Scheme 1.
Chemical structures of three PHIP compatible catalysts.