as a viable alternative to $Co_2(CO)_8$ for the synthesis of bicyclic cyclopentenones.

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Supplementary Material Available: Listings of ^1H and ^{13}C NMR, IR, MS, and elemental composition data for all new compounds (4 pages). Ordering information is available on any current masthead page.

More than INEPT: Parahydrogen and INEPT+ Give Unprecedented Resonance Enhancement to ^{13}C by Direct ^1H Polarization Transfer

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Enhanced absorptions and emissions in product NMR spectra have been reported to occur when H_2 oxidative addition and homogeneously catalyzed hydrogenation reactions are carried out using H_2 enriched in the para spin state.[1-10] The basis of this phenomenon, described initially by Weitekamp as PASADENA,[1,2] is that the addition of H_2 to substrate or metal complex takes place in a pairwise manner while spin correlation between the added protons is maintained. Termed parahydrogen-induced polarization (PHIP),[3] this phenomenon has been used to examine hydrogenation reaction mechanisms[5-7] and in one study to determine hydrogenation rate constants.[9] PHIP also transfers polarization from ^1H to ^{31}P and ^{13}C by cross-relaxation.[11] We now describe how these effects can be transferred to other nuclei through application of a pulse sequence to give extraordinary signal enhancements, thereby making it possible to rapidly observe naturally abundant ^{13}C resonances from small samples.

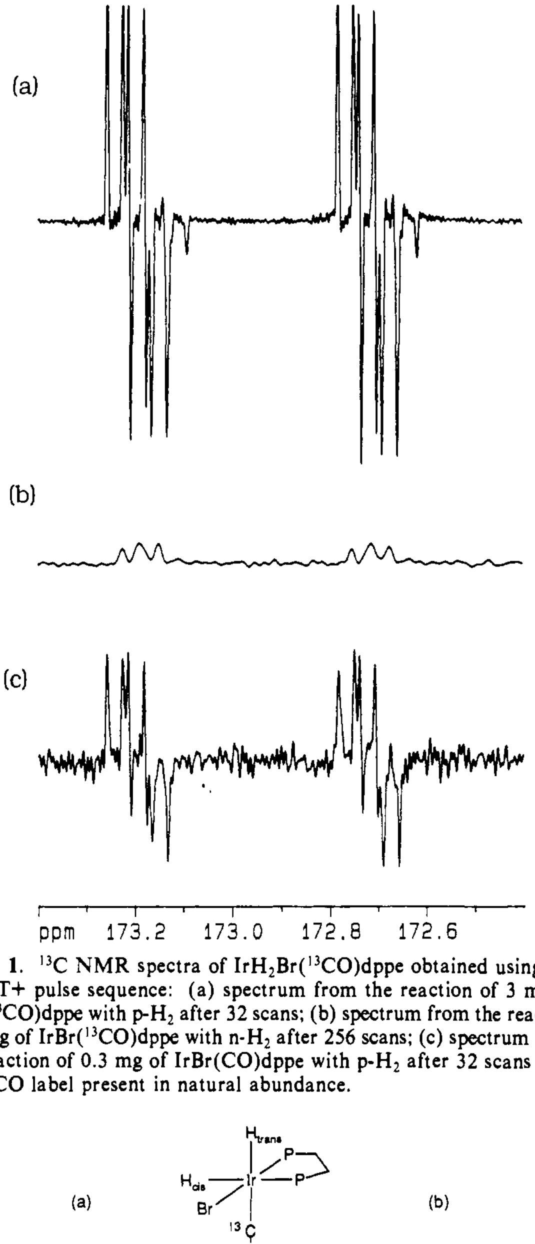

Figure 1. ^{13}C NMR spectra of $IrH_2Br(^{13}CO)dppe$ obtained using the INEPT+ pulse sequence: (a) spectrum from the reaction of 3 mg of $IrBr(^{13}CO)dppe$ with p-H_2 after 32 scans; (b) spectrum from the reaction of 3 mg of $IrBr(^{13}CO)dppe$ with n-H_2 after 256 scans; (c) spectrum from the reaction of 0.3 mg of IrBr(CO)dppe with p-H_2 after 32 scans with the ^{13}CO label present in natural abundance.

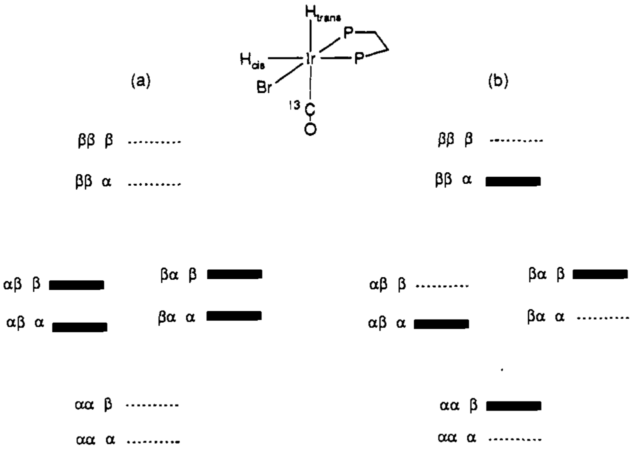

Figure 2. (a) Idealized representation of the initial populations of the energy levels for an AMX spin system produced from reaction with p-H_2, in which the spin function labels ααα etc. refer to H_{trans}, H_{cis}, and ^{13}C nuclei, respectively. (b) After execution of the INEPT+ pulse sequence, the energy level populations have been rearranged to yield non-Boltzmann distributions across the ^{13}C transitions.

The reaction chemistry employed in the present study is the well-known oxidative addition of H_2 to $IrCl(CO)(PPh_3)_2$[12] and IrBr(CO)(dppe)[13] (dppe = bis(diphenylphosphino)ethane), which proceeds in a concerted way.[14-16] Utilization of *para-enriched* hydrogen (p-H_2)[17] yields polarized hydride resonances upon placement of the sample into the NMR probe immediately after thawing from 77 K and shaking to dissolve p-H_2.[2,4,11] In addition to normal J_{PH} couplings, the hydride resonances in these systems all show antiphase doublets corresponding to transitions that differ by J_{HH}. The antiphase character of these product resonances indicates overpopulation of the αβ and βα proton spin states

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(17) Hydrogen was enriched to ca. 50 mol % parahydrogen by immersion of a 1-L flask containing iron(III) oxide on silica in liquid N_2 up to its neck. H_2 was added while 730-mm ambient hydrogen pressure was maintained. In this manner ~3-4 atm of p-H_2 at ambient temperature was produced.

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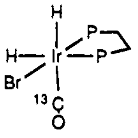
produced by coherent transfer of the reactant parahydrogen spin state, $\alpha\beta-\beta\alpha$.[18] A striking feature of the present study is the observation that larger enhancements result from less sample. Thus, a 4.6-mg sample of IrBr(CO)(dppe) in C_6D_6 under 3 atm of p-H_2 at a probe temperature of 342 K gives hydride resonances that are 40-fold greater in relative total signal area than unpolarized $IrH_2Br(CO)(dppe)$, but 95-fold enhancements are produced with 0.3 mg of complex.[2,19] With $IrCl(CO)(PPh_3)_2$ (Vaska's complex), the oxidative addition process is less facile than for the dppe analog; nevertheless, 40-fold enhancements were observed with 1 mg under the same conditions.

The non-Boltzmann spin populations of the hydride resonances were transferred to ^{13}C and ^{31}P nuclei in the product complexes via polarization-transfer pulse sequences with striking results. When a 3-mg sample of labeled IrBr(^{13}CO)(dppe) in C_6D_6 under p-H_2 was examined at 342 K using the INEPT+[20] sequence, the spectrum shown in Figure 1a was obtained after 32 scans. The ^{13}C carbonyl resonance of $IrH_2Br(^{13}CO)dppe)$, A, exhibits a large trans proton coupling (47.8 Hz), normal cis couplings to the nearly equivalent phosphine donors (4.3 and 3.3 Hz), and an extraordinary antiphase coupling to the cis hydride nucleus of 5 Hz. For comparison, Figure 1b shows a 256-transient ^{13}C\{INEPT+\} NMR spectrum of the same sample with n-H_2. On the basis of the observed 158-fold enhancement in signal strength, a single scan collected in the presence of p-H_2 is equivalent to 25 000 scans acquired under *normal* hydrogen (n-H_2).[21,22] In a different experiment, using the same INEPT+ pulse sequence, IrCl(^{13}CO)$(PPh_3)_2$ (6 mg) and p-H_2 produced a ^{13}C carbonyl resonance that was 25-fold stronger in S/N than that produced with n-H_2.


A

The observation that smaller amounts of sample yielded larger ^1H resonance amplification suggested the possibility of observing the ^{13}C carbonyl resonance using *unlabeled* complex under p-H_2. This was indeed the case. Specifically, the spectrum in Figure 1c corresponds to that of a 0.3-mg sample of $IrH_2Br(CO)(dppe)$ under p-H_2 after only 32 transients at 342 K. Thus, less than 1 mg or 1.5 μmol of complex with naturally abundant ^{13}C in the carbonyl ligand yields a spectrum in less than 2 min of spectrometer time, a truly amazing degree of signal amplification. The magnitude of ^{13}C enhancement in these two experiments (Figure 1b,d) can be compared through their S/N ratios after normalization for ^{13}C label content. Calculation thus shows that the ^{13}C resonance amplification observed with the unlabeled sample was really 18 times larger than that produced with the more concentrated labeled counterpart.

From a vector analysis, we can follow the effect of the INEPT+ pulse sequence on the non-Boltzmann spin population of the hydride ligands formed using p-H_2.[23] For the purposes of this analysis, we can ignore coupling to ^{31}P, thereby simplifying the nuclear spins of $IrH_2Br(^{13}CO)(dppe)$ to an AMX system. Without ^{31}P coupling, the spectrum in Figure 1a would consist of a doublet of antiphase doublets with the larger splitting due to $J_{CH_{(trans)}}$ (47.8 Hz) and the smaller to $J_{CH_{cis}}$ (5 Hz). Figure 2a shows the spin function energy levels for the AMX system of A with spin labels corresponding, respectively, to H_{trans}, H_{cis}, and ^{13}C. The overpopulation of $\alpha\beta$ and $\beta\alpha$ ^1H spin states arises from the oxidative addition of p-H_2; at this point, there is no enhancement of ^{13}C resonances, as the inverted populations are between levels relating to ^1H transitions. Application of the pulse sequence

^1H	$(90°)_x$ - τ - $(180°)_x$ - τ -	$(90°)_y$ - τ -	180° - τ -	90°
^{13}C	180°	90°	180°	Acquire

where τ is $(4J_{CH_{(trans)}})^{-1}$ leads to the relative spin populations shown in Figure 2b when acquisition commences. Inverted populations now exist between levels corresponding to ^{13}C transitions, thus explaining why the ^{13}C carbonyl resonance is enhanced.

Transfer of polarization from ^1H to ^{31}P using p-H_2 and INEPT+ has also been accomplished with $IrH_2Br(CO)(dppe)$. The ortho phenyl and methylene bridge protons were decoupled during data acquisition. For a system composed of 1 mg of IrBr(CO)(dppe) under 3 atm of p-H_2 at 342 K, the ^{31}P resonance, corresponding to the position trans to hydride, is 61 times more intense than that produced under n-H_2.[24]

The amazing *p*arahydrogen-*a*ided *r*esonance *t*ransfer (PART)[25] reported here opens the possibility of detecting species never seen before in catalytic hydrogenation and H_2 oxidative addition reactions. Our efforts are now progressing in that vein.

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[18] Parahydrogen with its nondegenerate spin state has no magnetic moment and is NMR silent.

[19] The 95-fold signal enhancement is lower than the theoretical maximum value.

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[21] The degree of signal enhancement was calculated using the signal-to-noise ratios obtained from the spectra with and without p-H_2 according to the equation $[(S/N_1)/(S/N_2)]^2 = N_1/N_2$ where N_1 and N_2 are the respective numbers of scans.

[22] The ratios of S/N values obtained after 4, 16, and 32 scans, respectively, were 1:1.7:1.7 rather than the 1:2:2.8 ratio theory predicts because during the period of observation there is relaxation of the spin distribution of p-H_2. These enhancements correspond to single scan equivalents of 25 000, 21 000, and 10 000, respectively.

[23] A more rigorous analysis of the spin physics associated with p-H_2 during polarization transfer is beyond the scope of this communication.

[24] The 61-fold enhancement in S/N was obtained by comparison with a partially decoupled spectrum. If a fully decoupled $^{31}P\{^1H\}$ spectrum is used in the comparison, the enhancement drops by a factor of 4 because the signal intensity of the ^{31}P resonance increases 4-fold on removal of the hydride couplings.

[25] Chemical Abstracts Service advises us that parahydrogen is one word, any acronymic difficulties thus being avoided.

Determination of the Equilibrium Constant for Coordination of an Amide Carbonyl to a Metal Complex in Water

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Over the years, there has been considerable interest in developing artificial metallopeptidases that hydrolyze unactivated amides under mild conditions.[1] Sequence specific hydrolytic cleavage of protein molecules has recently been achieved under oxidative conditions.[2] The mechanism of this remarkable hy-

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