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Reactive Intermediates

Asymmetric Hydrogenation with Iridium C,N and N,P Ligand Complexes: Characterization of Dihydride Intermediates with a Coordinated Alkene**

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Abstract: *Previously elusive iridium dihydride alkene complexes have been identified and characterized by NMR spectroscopy in solution. Reactivity studies demonstrated that these complexes are catalytically competent intermediates. Additional H_2 is required to convert the catalyst-bound alkene into the hydrogenation product, supporting an Ir^{III}/Ir^{V} cycle via an $[Ir^{III}(H)_2(alkene)(H_2)(L)]^+$ intermediate, as originally proposed based on DFT calculations. NMR analyses indicate a reaction pathway proceeding through rapidly equilibrating isomeric dihydride alkene intermediates with a subsequent slow enantioselectivity-determining step. As in the classical example of asymmetric hydrogenation with rhodium diphosphine catalysts, it is a minor, less stable intermediate that is converted into the major product enantiomer.*

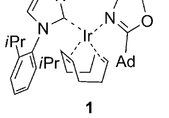
Cationic iridium complexes derived from chiral C,N or N,P ligands have emerged as highly efficient catalysts for the asymmetric hydrogenation of olefins. In contrast to rhodium and ruthenium diphosphine catalysts, they do not require a coordinating functional group in the substrate, and therefore have a very broad scope ranging from purely alkyl-substituted alkenes to a variety of functionalized olefins as well as furans and indoles.[1]

Despite the vast amounts of literature on iridium-catalyzed asymmetric hydrogenation, experimental investigations of the mechanism and the nature of the catalytic intermediates are still scarce. So current mechanistic proposals rely almost entirely on computational studies.[2] Based on DFT calculations Andersson and co-workers and Burgess and co-workers postulated a catalytic cycle starting from an iridium(III) dihydride complex, which as a first step forms a π complex with the substrate. Subsequent coordination of a H_2 molecule then leads to an $[Ir^{III}(H)_2(alkene)(H_2)(L)]^+$ complex (L = C,N or N,P ligand) which rearranges to an $[Ir^{V}(H)_3(alkyl)(L)]^+$ intermediate and undergoes reductive elimination releasing the product and closing the catalytic cycle. An alternative Ir^{I}/Ir^{III} cycle, analogous to the well-established mechanism for rhodium-catalyzed hydrogenation,[3] was found to be energetically less favorable.

Chen and Dietiker, in contrast, found evidence for an Ir^{I}/Ir^{III} cycle occuring in the gas phase, based on a mass spectroscopic study of the hydrogenation of styrene with an Ir/PHOX catalyst (PHOX = phoshinooxazoline).[4] Although their results indicate that an Ir^{I}/Ir^{III} cycle is chemically feasible, they do not rule out an Ir^{III}/Ir^{V} cycle in solution.

In low-temperature NMR experiments in THF we were able to characterize an $[Ir(cod)(PHOX)(dihydride)]^+$ (cod = cyclo-1,5-octadiene) complex as the primary product of the reaction of the corresponding precatalyst $[Ir(cod)(PHOX)]BAr_F$ (BAr_F = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate) with H_2.[5] Upon warming under an H_2 atmosphere, formation of cyclooctane and two diastereoisomeric $[Ir(PHOX)(dihydride)(solvent)]^+$ complexes were observed. Our initial studies were carried out in THF, because the labile hydride species are stabilized by coordination in this solvent. However, as THF inhibits hydrogenation reactions, which require weakly coordinating solvents such as dichloromethane, the crucial part of the catalytic cycle involving the olefinic substrate cannot be studied in THF. NMR studies under hydrogenation conditions in dichloromethane proved to be difficult because of the high reactivity and multifaceted aggregation behavior of iridium hydride complexes. Only recently, we found reliable procedures for the controlled formation of iridium hydride complexes in dichloromethane and succeeded in characterizing several hydride-bridged dinuclear complexes, with C,N and N,P ligands, by NMR spectroscopy and crystal structure analysis.[6] As a next step, we decided to investigate reactions of iridium precatalysts with H_2 in the presence of an alkene, with the aim of identifying catalyst–substrate adducts formed under hydrogenation conditions. Herein we report the results of this study which led to the characterization and elucidation of the three-dimensional (3D) structure of three iridium dihydride alkene complexes by NMR spectroscopy.

For our studies, we chose the iridium complexes **1** and **2**, which had proven to be efficient catalysts for the hydrogenation of alkenes.[7] When a solution of the Burgess catalyst **1** and (*E*)-1,2-diphenyl-1-propene (**3**; 3 equiv) in CD_2Cl_2 was



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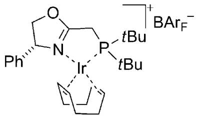

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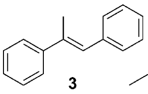

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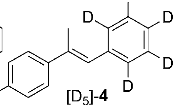
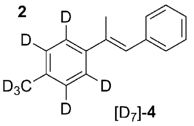


[D5]-4



[D7]-4

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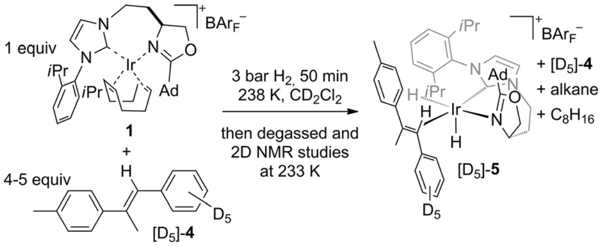
treated with hydrogen gas (1 bar) at 263 K, two-dimensional (2D) NMR analysis indicated partial formation of a dihydride iridium alkene complex. However the structure of this new species could not be firmly established because **1** along with **3** and the hydrogenation product, 1,2-diphenylpropane, were present as major components, and resulted in complex spectra with severe signal overlap. To simplify the spectra and facilitate signal assignments, we synthesized the corresponding deuterated alkenes [D$_5$]-**4** and [D$_7$]-**4**. Under optimized reaction conditions (see Scheme 1) the reaction of **1** with an excess of [D$_5$]-**4** and H$_2$ afforded the new dihydride iridium alkene species [D$_5$]-**5** in greater than 95 % yield[8] and was stable in CD$_2$Cl$_2$ solution at 233 K for several days. In addition, unreacted [D$_5$]-**4** and the hydrogenation product dihydro-[D$_5$]-**4** were present.



Scheme 1. Reaction of **1** and substrate [D$_5$]-**4** in CD$_2$Cl$_2$ at 3 bar hydrogen gas at 238 K.

The ^{1}H NMR spectrum of the reaction mixture showed two hydride signals both as doublets [^2J(H,H) = 7.5 Hz], one at $\delta = -15.56$ ppm and the other at $\delta = -42.64$ ppm. Such a very low frequency shift of a hydride is characteristic for a structure with a hydride ligand positioned *trans* to an empty coordination site which is either vacant or engaged in a C–H agostic interaction.[9] The coordination of the alkene to the iridium metal was verified by a significant low frequency shift of the olefinic proton and the chemical shifts of the olefinic ^{13}C atoms (Figure 1).

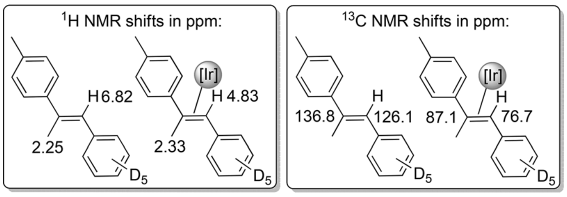


Figure 1. Olefinic ^{1}H and ^{13}C NMR chemical shifts of the free and coordinated alkene, respectively.

On the basis of extensive 2D NMR analyses the 3D structure was assigned. Figure 2 shows two segments through the 2D NOESY spectrum for [D$_5$]-**5**, in which the NOE contacts from the hydrides to various protons of the coordinated alkene and the C,N ligand are visible (for additional spectra, see the Supporting Information). In agreement with DFT calculations by Burgess, Hall, and co-workers[2d,e] the alkene is coordinated *trans* to the N-heterocyclic carbene unit. The C–C double bond axis of the alkene lies approximately in the coordination plane defined by the atoms Ir, N, and C8. The 3D structure of this complex and in particular the coordination mode of the alkene were corroborated by NMR studies of the analogous reaction of [D$_7$]-**4** with **1** and H$_2$, thus leading to complex [D$_7$]-**5** (see the Supporting Information).

To investigate the reactivity of [D$_7$]-**5** (Figure 3), the solvent was evaporated from the reaction mixture at 213 K and the remaining solid was washed with cold *n*-hexane. The ^{1}H NMR spectrum of the redissolved material in CD$_2$Cl$_2$ showed that all of dihydro-[D$_7$]-**4** and part of alkene [D$_7$]-**4** were removed by this procedure (Figure 3 b). Upon warming to room temperature the alkene complex [D$_7$]-**5** decomposed with concomitant release of free alkene, but no conversion into the corresponding alkane was observed. At the same time new signals belonging to the previously reported dinuclear hydride complex [IrH(C,N)(μ-H)]$_2^{2+}$ (**6**)[6] appeared (Figure 3 c; Figure S1 in the Supporting Information gives an overview of the hydride region). In contrast, when the solution containing [D$_7$]-**5** and [D$_7$]-**4** was warmed to room temperature under hydrogen gas (1 bar, 10 min) almost full conversion of [D$_7$]-**4** into the hydrogenation product was observed, accompanied by the disappearance of [D$_7$]-**5** and the formation of **6**[10] (Figure 3 d).

Obviously, addition of H$_2$ is required to induce turnover of the coordinated alkene in complex [D$_7$]-**5** to the corresponding alkane. These observations support an Ir^{III}/Ir^V cycle via an [Ir^{III}(H)$_2$(alkene)(H$_2$)(L)]$^+$ intermediate, as originally concluded from computational studies.[2] However, no signals of a dihydride complex with an additional coordinated H$_2$ molecule could be detected in reaction mixtures containing [D$_7$]-**5** under 2 bar of hydrogen pressure at 233 K. The presence of [D$_7$]-**5** as the major species in the reaction mixture resulting from treatment of the precatalyst **1** with alkene and H$_2$ indicates that [D$_7$]-**5** is the resting state of the catalyst in the hydrogenation of [D$_7$]-**4**.

A hydrogenation pathway via intermediate [D$_5$]-**5** would lead to the *R*-configured enantiomer if the alkene remains bound to the catalyst with the same enantioface as shown in Figure 2. In contrast, the major enantiomer formed in the hydrogenation of the methylstilbene **3** with the catalyst **1** is known to have an *S* configuration.[7a] Control experiments with the deuterated substrate [D$_7$]-**4** at room temperature and under the low-temperature conditions, used for the characterization of [D$_5$]-**5**, confirmed the *S* configuration of the hydrogenation product with **1** based on optical rotation and chiral-phase HPLC analysis (see Table S1 in the Supporting Information). Consequently, in the course of the hydrogenation reaction, [D$_5$]-**5** has to be converted into an intermediate which coordinates the alkene with the opposite enantioface.

Inspection of the hydride region in the ^{1}H NMR spectrum revealed that a second dihydride iridium alkene complex (doublets at $\delta = -17.10$ and -45.13 ppm) was present in very low concentration.[11] At 233 K the NOESY spectrum showed exchange crosspeaks between this species and [D$_5$]-**5** in the hydride region (see Figure S2 in the Supporting Information). It is tempting to speculate that this minor species is an isomer resulting from enantioface exchange, although a rotational

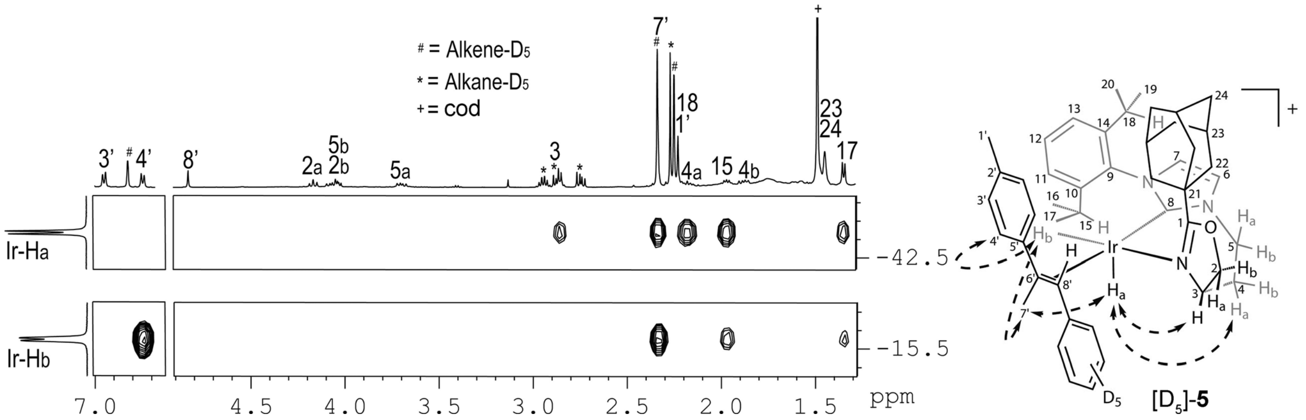


Figure 2. Section of the 2D NOESY spectrum for $[D_5]$-**5** showing the contacts from the hydrides (H_a and H_b) to various protons of the coordinated alkene and the C,N ligand (the contacts to the isopropyl group containing C15 are not shown in the structure; 233 K, 500 MHz, CD_2Cl_2).

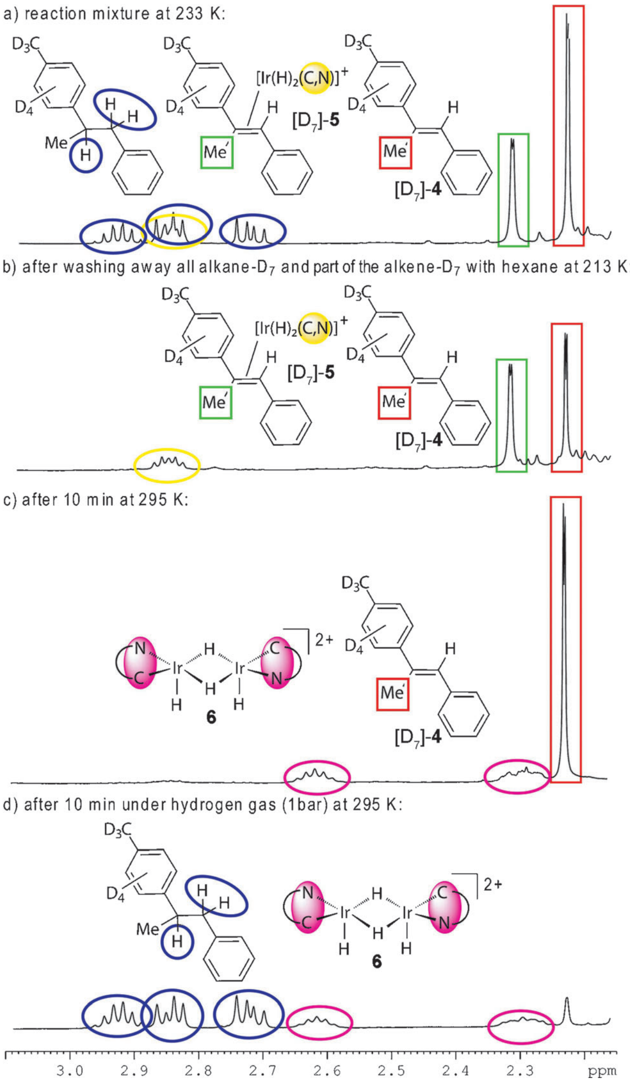


Figure 3. Reactivity studies of $[D_7]$-**5** in the absence and presence of hydrogen gas (233 K, 500 MHz, CD_2Cl_2).

isomer with the alkene C–C axis aligned with the axial Ir–H bond cannot be excluded.

In view of these results, demonstrating that substrate catalyst adducts are indeed observable by NMR spectroscopy, we decided to extend our studies to N,P ligand complexes. After initial experiments with various iridium catalysts, the phosphinooxazoline complex **2**, which is a very reactive hydrogenation catalyst as shown in entries 3 and 4 in Table S1 of the Supporting Information, was chosen as the most promising candidate for further investigations.

When a CD_2Cl_2 solution of the iridium complex **2** and 4.5 equivalents of $[D_5]$-**4** was treated with 3 bar of hydrogen gas at 233 K for 35 minutes and then degassed, 2D NMR analysis revealed the formation of two isomeric dihydride alkene iridium complexes in a ratio of about 11:1. Coordination of the alkene to the iridium metal was verified for both species by a significant low-frequency shift of the olefinic proton and the ^{13}C chemical shifts (see Figure S3 in the Supporting Information). The ^1H NMR spectra of both isomers showed a coupling between the olefinic proton and the phosphorus atom, which was identified by ^{31}P decoupling.

In the ^1H NMR spectrum two hydride resonances appear as doublets of doublets at $\delta = -20.41$ and -32.32 ppm for the major species $[^2J(H,H) = 5.8\,Hz]$ and at $\delta = -20.75$ and -31.61 ppm for the minor species $[^2J(H,H) = 6.1\,Hz$; Figure 4]. The $^2J(H,P)$ values of 15–20 Hz observed for both isomers confirm that both hydrides are located *cis* to the phosphorus atom.[12] On the basis of additional 2D NMR studies the 3D structures for $[D_5]$-**7a** (major) and $[D_5]$-**7b** (minor) were assigned as shown in Figure 4.

In agreement with computational studies[2a–c] the alkene is coordinated *trans* to the phosphorus atom in both $[D_5]$-**7a** and $[D_5]$-**7b**. In the major isomer the C–C double bond axis of the alkene is positioned approximately in the coordination plane defined by the Ir, N, and P atoms, whereas in the minor isomer it is rotated out of plane by 90°.[13] A clear distinction between $[D_5]$-**7a** and $[D_5]$-**7b** can be made based on the absence or presence of ^1H NOE contacts between the proton at the stereogenic center of the ligand and the protons of the *p*-tolyl residue of the alkene (for full characterization, see the Supporting Information). Notably, the major and the minor

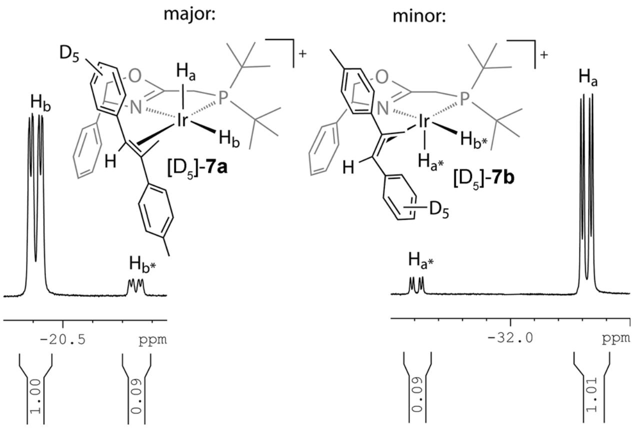


Figure 4. Section of the ^1H NMR spectrum showing the hydride signals for [D$_5$]-**7a** and [D$_5$]-**7b** and their 3D structures (233 K, 500 MHz, CD_2Cl_2).

isomer coordinate the alkene with the opposite enantioface. These assignments and the 3D structures were fully confirmed by analogous NOE studies of reaction mixtures of alkene [D$_7$]-**4** and iridium complex **2**.

The NOESY spectrum of the reaction mixture at 253 K showed an exchange process between the alkene ligands in [D$_5$]-**7a** and [D$_5$]-**7b** (Figure 5). In addition, an exchange between the bound alkene in [D$_5$]-**7a** and [D$_5$]-**7b** and the free alkene [D$_5$]-**4** was observed, thus indicating fast equilibration of the major and minor isomer by alkene dissociation/association. The configuration of the product obtained from hydrogenation under the conditions used for the NMR analyses is *S* (72% *ee*, see Table S1), which requires coordination of the alkene as determined for minor isomer [D$_5$]-**7b**. Thus the major pathway leading to the *S*-configured product seems to proceed via a minor intermediate, similar to the mechanism of the asymmetric hydrogenation of acetamidoacrylates with rhodium diphosphine catalysts.[3]

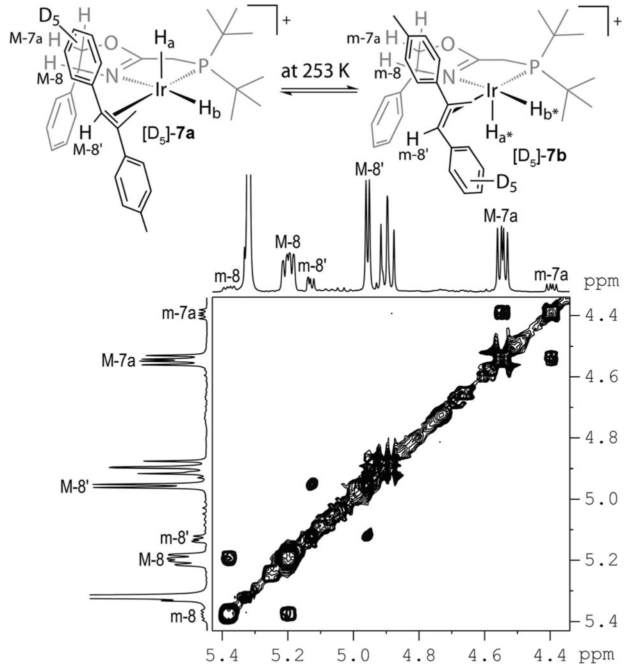


Figure 5. Section of the phase-sensitive 2D NOESY spectrum for the reaction mixture containing [D$_5$]-**7a** and [D$_5$]-**7b** showing only the exchange crosspeaks between the protons M-8 and *m*-8, M-8′ and *m*-8′ as well as between M-7a and *m*-7a (253 K, 500 MHz, CD_2Cl_2).

The alkene complexes [D$_5$]-**7a** and [D$_5$]-**7b** proved to be less stable than the analogous C,N ligand complex [D$_5$]-**5**. At 233 K slow formation of additional dihydride species could be detected and likely arose from complexation of the isomerized *cis*-alkene [D$_5$]-**4**, which could be identified after reaction workup (see Figure S4 in the Supporting Information). The instability of [D$_5$]-**7a** and [D$_5$]-**7b** precluded reactivity studies as described for complex [D$_7$]-**5**. Nevertheless, we could show that under 2 bar of hydrogen gas at 233 K complexes [D$_5$]-**7a** and [D$_5$]-**7b** did not form any hydride species with an additional coordinated H_2 molecule. These findings are consistent with DFT calculations of Hopmann and Bayer, according to which coordination of a H_2 molecule to an $[Ir(PHOX)(dihydride)(alkene)]^+$ complex is energetically unfavorable, mainly as a result of entropic destabilization.

In conclusion, we were able to identify and characterize previously elusive iridium dihydride alkene complexes which were generated under hydrogenation conditions. Reactivity studies indicated that these complexes are catalytically competent intermediates which represent the resting state of the catalyst. The observation that H_2 is required to convert the catalyst-bound alkene into the hydrogenation product supports an Ir^{III}/Ir^{V} cycle via an $[Ir^{III}(H)_2(alkene)(H_2)(L)]^+$ intermediate, as originally proposed by Andersson and coworkers. The 3D structures of the two major alkene complexes derived from the Burgess catalyst and an Ir/PHOX precursor revealed that the C=C bond enantioface which coordinates to the catalyst does not correlate with the absolute configuration of the major product enantiomer formed in the corresponding preparative hydrogenation. In case of the Ir/PHOX complex we observed a second minor hydride complex, which is bound to the opposite enantioface of the alkene and is in rapid equilibrium with the major isomer. These findings imply a reaction pathway proceeding through rapidly equilibrating isomeric dihydride alkene intermediates with a subsequent slow enantioselectivity-determining step. As in the classical example of asymmetric hydrogenation with rhodium diphosphine catalysts, it is a minor, less stable intermediate which is converted into the major product enantiomer.

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[8] Estimated yield based on ^{1}H NMR analysis. The hydride region showed that only trace amounts of other iridium hydride species were present.

[9] We have recently reported two structures with the formula $[IrH(C,N)(\mu\text{-}H)]_2(BAr_F)_2$ with a hydride shift *trans* to an empty cooridnation site appearing at $\delta = -36.85$ and -34.45 ppm, respectively; See Ref. [6]. See also: a) H. E. Selnau, J. S. Merola, *Organometallics* **1993**, *12*, 3800 – 3801; b) N. M. Scott, V. Pons, E. D. Stevens, D. M. Heinekey, S. P. Nolan, *Angew. Chem.* **2005**, *117*, 2568 – 2571; *Angew. Chem. Int. Ed.* **2005**, *44*, 2512 – 2515; c) M. R. Castillo, M. Martín, J. M. Fraile, J. A. Mayoral, E. Sola, *Angew. Chem.* **2011**, *123*, 3298 – 3301; *Angew. Chem. Int. Ed.* **2011**, *50*, 3240 – 3243.

[10] We have shown that the dinuclear hydride complex **6** is not an active catylst at 1 bar hydrogen pressure; see Ref. [6].

[11] Four additional hydride signals at $\delta = -22.24$, -24.17, -28.19, and -36.55 ppm were present. However, COSY data indicate that they are correlated with each other and they were also present in hydrogenations of complex **1** in the absence of alkene $[D_5]$-**4**.

[12] For an orientation *trans* to a phosphorus atom a coupling constant of 100 – 200 MHz would be expected: see P. S. Pregosin, *NMR in Organometallic Chemistry*, Wiley-VCH, Weinheim, **2012**.

[13] The effective rotation of the complexed alkenes were drawn on the basis of preliminary calculations.