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Carbene-Metal Hydrides Can Be Much Less Acidic Than Phosphine-Metal Hydrides: Significance in Hydrogenations

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Abstract: Acidities of iridium hydride intermediates were shown to be critical in some transformations mediated by the chiral analogues of Crabtree's catalyst, **1**−**3**. To do this, several experiments were undertaken to investigate the acidities of hydrogenation mixtures formed using these iridium-oxazoline complexes. DFT calculations indicated that the acidity difference for Ir−H intermediates in these hydrogenations were astounding; iridium hydride from the N-heterocyclic carbene catalyst **1** was calculated to be around *seven* pK_a units less acidic than those from the *P*-based complexes **2** and **3**. Consistent with this, the carbene complex **1** was shown to be more effective for hydrogenations of acid-sensitive substrates. In deuteration experiments, less "abnormal" deuteration was observed, corresponding to fewer complications from acid-mediated alkene isomerization preceding the D_2-addition step. Finally, simple tests with pH indicators provided visual evidence that phosphine-based catalyst precursors give significantly more acidic reaction mixtures than the corresponding N-heterocyclic carbene ones. These observations indicate carbene-for-phosphine (and similar) ligand substitutions may impact the outcome of catalytic reactions by modifying the acidities of the metal hydrides formed.

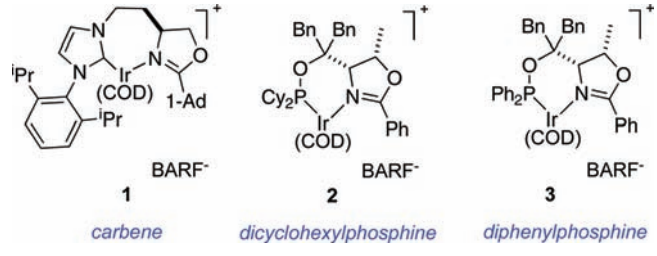
Introduction

Transition-metal hydrides are ubiquitous in catalysis.[1] They are frequently formed as intermediates even in cases where the catalyst precursor does not contain a M−H bond, and they may also be formed en route to catalyst deactivation. The reactivity of transition-metal hydrides is widely variable. Different coordination modes are open to hydride (and dihydrogen) ligands, they may dissociate to donate hydrides or protons, and they can participate in hydrogen bonding.[2,3] In some cases the importance of metal hydrides in catalysis is obvious. In most Heck couplings,[4] for instance, transtion-metal hydrides reductively eliminate acidic molecules, hence it is necessary to add a base to avoid complications that would be caused by accumulation of acid. In other cases, basic additives have equally profound effects, but the underlying reasons may be obscure. For instance, some asymmetric homogeneous hydrogenation reactions give significantly better enantioselectivities in the presence of base for nonevident[5] or undefined[6] reasons. Acidities of transition-metal hydrides,[7] therefore, must also account for some obscure ligand effects;[8] in other words, ligands complexed to metal centers influence the acidities of transition-metal hydrides, and this in turn can impact catalysis.

Despite the considerations outlined above, there is a tendency to regard homogeneous catalytic alkene hydrogenations as pH *neutral* because the starting materials, dihydrogen and alkene, are not acidic. Some hydrogenations may be described as "ionic"[9−12] because heterolytic cleavage of hydrogen occurs; however, to the best of our knowledge, no one has commented on how activation of hydrogen with transition-metal catalysts impacts the pH of the medium in catalytic hydrogenations.

This paper demonstrates that catalytic hydrogenation reactions need not be intrinsically neutral and that this can be significant to the products formed. Specifically, we draw attention to iridium-mediated hydrogenations of alkenes by analogues of Crabtree's catalyst $[(COD)Ir(PCy_3)(py)]^+$ as a situation in which significant concentrations of protons may be generated. Further, the outcome of these hydrogenation reactions can be affected by the acidities of catalytic intermediates.

Results and Discussion



Direct experimental evidence for the mechanism of hydrogenations by Crabtree's catalyst analogues is unavailable and difficult to obtain via kinetic or spectroscopic methods.[13−15] However, calculations first by Andersson[16] on a simplified system with a *N*,*P*-ligand set, then from our laboratories[15,17]

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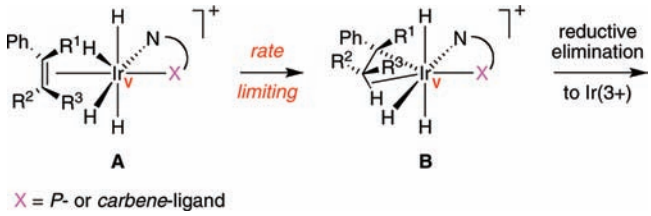

Figure 1. Postulated turnover-limiting step in hydrogenations with Crabtree's catalyst analogues.

on the carbene-oxazoline complex **1** converge on very similar preferred reaction pathways. This involves loss of the COD ligand and complexation with the alkene substrate and two molecules of dihydrogen. The rate-limiting step in the catalytic cycle is transformation of this tetrahydride **A** into the σ-alkyl species **B** (Figure 1).

This mechanism involves alternation between iridium(III) and -(V) oxidation states. It indicates why Crabtree's catalyst analogues are able to hydrogenate "coordinatively unfunctionalized" tri- and tetrasubstituted alkenes, whereas rhodium complexes such as Wilkinson's catalyst do not. Specifically, the positively charged and higher oxidation state Ir complexes are more electrophilic than neutral and lower oxidation state Rh complexes, so they have more affinity to the π-electron density of alkene substrates. Moreover, the small steric demands of a tetrahydride ligand set facilitate coordination of alkenes with three or four substituents that are intrinsically hindered. Finally, hydrogenations with these Ir complexes are *not* particularly sensitive to oxygen, as expected for high oxidation state Ir intermediates. Involvement of intermediates **A** also explains why the catalytic cycle is so hard to follow spectroscopically because these tetrahydrides are in a rapid, dynamic equilibrium with dihydrido-dihydrogen complexes.[15,17]

Figure 2 contrasts the factors driving dissociation of protons from the iridium(V) intermediates **A** (shown in abbreviated form) where the ligating group X is either a phosphine or an N-heterocyclic carbene intermediate. In both cases, an iridium(III) species forms; that is, the metal is reduced as its electron density increases. We postulate that this dissociation is *easier when X is a P-ligand than a carbene* because *P*-ligands are (i) inferior σ-donors, hence are less able to stabilize Ir(V),[18] and (ii) superior π-acceptors, thus better able to stabilize Ir(III). Consequently, Crabtree's catalyst and *P*-ligated derivatives should be *more acidic than the corresponding carbenes*.

Here we used density functional theory (TPSS functional;[19] see Supporting Information) to calculate acidity differences for the key metal hydride complexes involved in hydrogenations

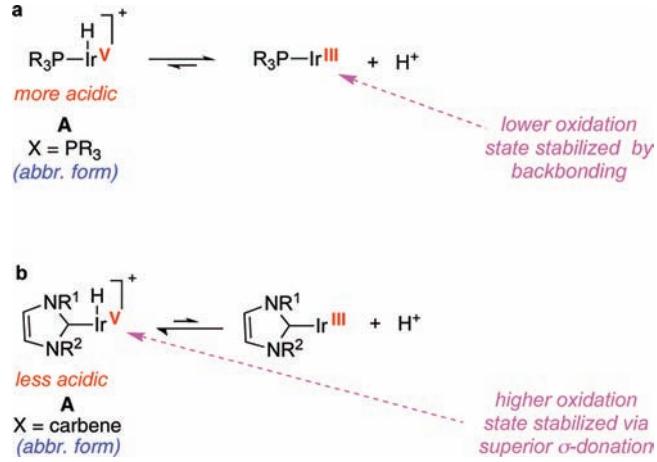

Figure 2. Postulate for acidities of (a) the *P*-Ir-H complexes relative to (b) *carbene*-Ir-H systems.

Table 1. pK_a Values for Transition Metal Hydrides

		pK_a			
		MeCN			CH_2Cl_2
	complex	exptl	calc[a]	ΔpK_a[b]	ΔpK_a[b]
1	$[HNi(dmpe)_2]^+$	24.4 ± 0.2	21.7	11.9	13.4
2	$[HPt(dmpe)_2]^+$	31.1	32.3	22.5	24.0
3	$[HNi(dppe)_2]^+$	14.7 ± 0.3	13.8	4.0	5.5
4	$[HPt(dppe)_2]^+$	22.2	24.6	14.8	16.3
5	**C**		11.3	1.5	1.4
6	**D**		9.8	0	0
7	**E**		11.5	1.7	1.8
8	**F**		17.4	7.6	7.4
9	**G**		36.1	26.3	30.0

[a] Experimental pK_a of Ni and Pt complexes as references, and all have a standard deviation of ±2.2. [b] Calculated relative pK_a with the catalyst intermediate **D** as reference.

with Crabtree's catalyst analogues. These data were then compared to reference systems to estimate absolute pK_a values.[20] Almost all reliable experimental pK_a's for metal hydrides in the literature are measured in acetonitrile, so the calculated pK_a's were first obtained by simulating reactions in this medium.

In validation work, calculations were performed for several metal hydrides for which pK_a's have been measured in MeCN (Table 1, entries 1−4). The calculated pK_a differences were then related to absolute pK_a values using the literature experimental data for each of the other three metal hydride controls, then averaged to give the data shown in Table 1, entries 1−4. These numbers are consistent with the experimental data with a maximum deviation of 2.7 for entry l, which concerns a complex of pK_a 21.7. This close agreement for the control complexes indicates a high degree of confidence for application of the same technique to calculate acidities for the key intermediates in hydrogenations by Crabtree's catalyst analogues.

Calculated data for the hydrogenation intermediates are shown in Table 1, entries 5−9. Considering first the data in MeCN, Crabtree's catalyst **C** was calculated to be less acidic than the *P*-oxazoline complex **D**, so the latter was used as a "bottom-line reference". The *N,P*-ligands in **D** and **E** are alike; hence these complexes would be expected to have similar acidities, and the calculations are consistent with this. Moreover, higher acidity for the diphenylphosphinite complex **D** relative to **E** was

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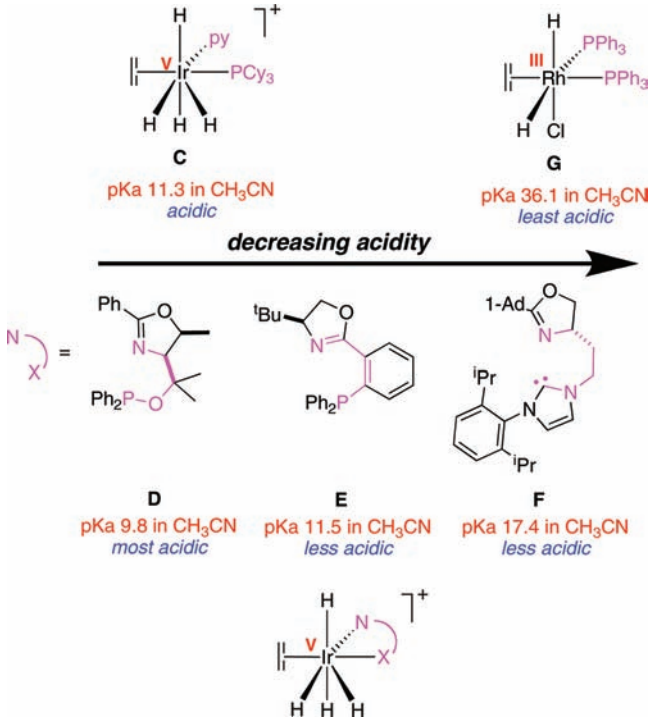

Figure 3. Relative acidities of putative intermediates in hydrogenations.

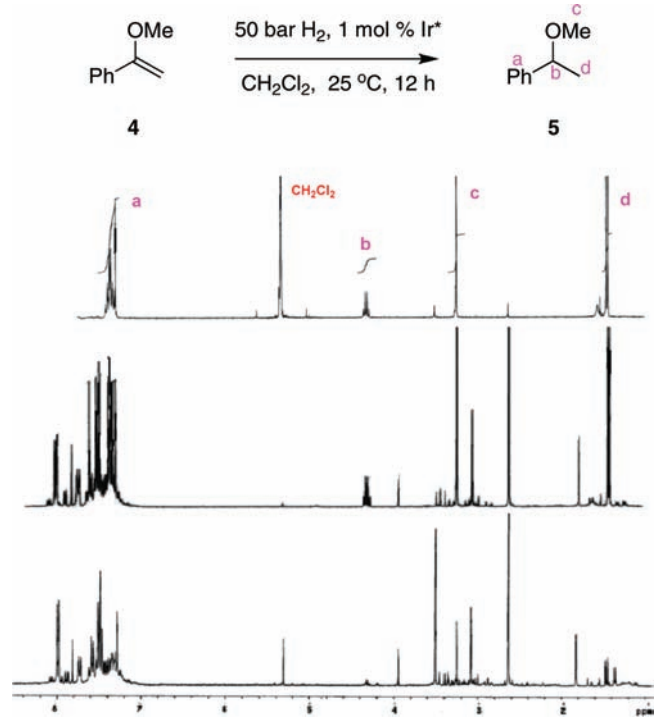

Figure 4. Hydrogenation of the acid-sensitive enol ether **4** with complexes **1**−**3** gives progressively less of the anticipated ether product **5**.

also predicted because the diphenylphosphine in **E** is a superior σ-donor, better able to stabilize Ir(V); again, the calculations support this (Figure 3).

The most important comparison in Table 1 is between the data for the *N*,*P*-complexes **D**/**E** and the corresponding carbene **F**. Hydrides **D** and **E** were calculated to be 7.6 to 5.9 pK_a units *more* acidic than the carbene intermediate **F**, as predicted from the concepts outlined in Figure 2. A 7.6 pK_a difference is similar to the acidity difference between formic acid and ^{t}BuOH.

Finally, it is interesting to compare intermediates from Crabtree's and Wilkinson's catalysts. The hydrogenation intermediate **G** from Wilkinson's catalyst was far less acidic than that from any of the iridium complexes. It was 26.3 pK_a units less acidic than **D** and 24.8 pK_a units less acidic than the tetrahydride **C** from Crabtree's catalyst.

All the calculations discussed so far are for acetonitrile solvent, but hydrogenation reactions with Crabtree's catalyst analogues are generally run in *dichloromethane*. No pK_a data for useful control metal hydrides in dichloromethane have been published; hence calculated pK_a values in that medium cannot be related to absolute values. However, pK_a *differences* between the complexes *are* accessible, and these data are shown in the right-hand column of Table 1, relative to the intermediate that was calculated to be the most acidic, i.e., the diphenylphosphinite oxazoline **D**. The calculated acidity differences for complexes **C**−**G** in dichloromethane (right-hand column) are very similar to those for acetonitrile (first column). This indicates that the differences in pK_a values for the complexes are preserved, no matter how the absolute pK_a values vary between these two solvents.

It was a study on enol ether substrates that originally led us to suspect that more protons were produced when *N*,*P*-Ir-catalyst precursors were used relative to the corresponding carbene catalyst. Specifically, Andersson et al. had noted[21,22] that alkyl enol ethers gave *complex mixtures* when hydrogenated using one of their *N*,*P*-iridium catalysts, but we observed the same reaction gave only the expected hydrogenation products when our *N*,*carbene*-iridium catalyst **1** was used.[23]

In the present work we expanded the scope of our studies to include catalyst precursors **1**−**3** in hydrogenation of the acid-sensitive enol ether **4**. We predicted these catalyst precursors would give progressively more acidic intermediates in hydrogenations. This assertion was based on the assumption that the carbene ligand is a better σ-donor than either of the *P*-ligands and, of those, the PCy_2 system has superior σ-donating properties.[18,24−26] The degree of back-bonding to these ligands is likely to be minor and to follow the opposite trend.[27−29] Figure 4 shows ^{1}H NMR spectra of crude materials isolated from these reactions. The desired product **5**, and almost nothing else, was formed when the carbene complex **1** was used. The dicyclohexylphosphinite complex **2** gave much less of the desired ether product **5** and relatively more byproducts. At the other extreme, the diphenylphosphinite complex **3** gave less than 5% of **5** (i.e., almost none by NMR) and mostly undesired impurities.

The byproducts shown in Figure 4 could not be conveniently isolated and characterized. However, hydrogenation of the enol ether **6** gives mainly two products: **7**, from direct addition of hydrogen, and **8** via acid-mediated rearrangement and hydro-

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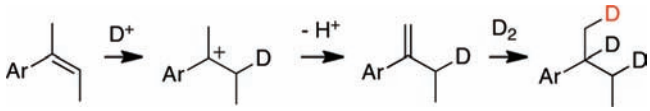
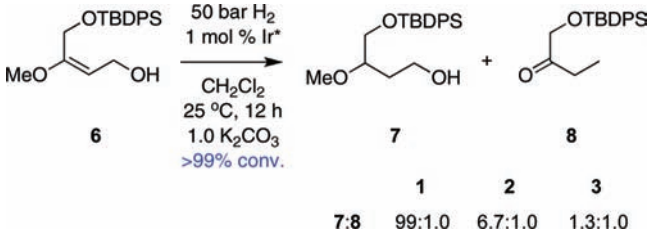
Scheme 1. Rationale for the Deuterium Scrambling



genation.[23] This reaction gave the direct hydrogenation product **7** only if a base, e.g., K_2CO_3, was added.[23] Complete conversion and almost quantitative yields were achieved using all three catalyst precursors **1**−**3** in these reactions. Product ratios obtained (^{1}H NMR) when **6** was hydrogenated using catalysts **1**−**3** are shown below. More of the acid-derived byproduct **8** was formed from the dicyclohexylphosphinite complex **2** than from the carbene, and most accumulated when the diphenylphosphinite complex **3** was used as the catalyst precursor. Thus the amount of direct hydrogenation product follows the order **1** > **2** > **3**; that is, the amount of **7** decreases as the anticipated acidities of the predicted intermediates increase.

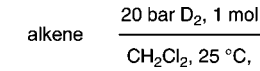


A second set of evidence for the acidity effects comes from deuterium labeling studies. Several years ago we observed deuteration of alkenes catalyzed by chiral analogues of Crabtree's catalyst gave some label incorporation at sites other than those corresponding to direct addition.[30] In the light of the data presented above, we postulated that abnormal D-incorporation arises via addition of D^+ to the alkene, loss of H^+ to give isomerism, and then addition of D_2 (Scheme 1). Table 2 shows experiments designed to test this hypothesis by using complexes **1** and **3**. According to this hypothesis, **3** should generate more protons in the hydrogenation reactions and give more "abnormal" deuteration. Comparing entries 1 with 2, and 4 with 5, for substrate **9** indicates levels of abnormal deuterium incorporation (in red) were *greater* without K_2CO_3 (indicating acidic conditions favor abnormal D-incorporation) and that the *N,carbene*-catalyst **1** (entries 1 and 2) gave significantly *less* abnormal incorporation than the *N,P*-catalyst **3** (entries 4 and 5). This is consistent with less generation of acid from the hydrogenation reactions involving the carbene **1** relative to the *N,P*-complex **3**.

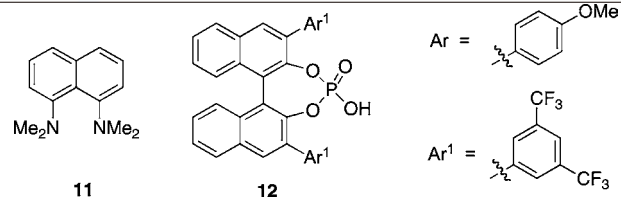
The same trends observed for deuteration of substrate **9** were seen for **10** except that addition of K_2CO_3 did not significantly change the levels of abnormal deuterium incorporation. However, the levels *were* decreased when a stronger base, Proton Sponge **11**, was added to the deuteration mediated by catalyst **3** (compare entries 4−6). Conversely, when the acid **12** was added instead, the levels of abnormal deuteration *increased* (compare entries 1−3).

Perhaps the most dramatic illustration of pH in the hydrogenation reactions came from simple experiments using substrate **13** and the acid−base indicator "methyl red" (orange under basic conditions and red in acid) (Figure 5). Methyl red was added (i) 5 min after the hydrogenation reaction began and, to another

Table 2. Deuteration of Styrene Derivatives[a]



	catalyst/additive	9	10
1	**1**/ none	(0.21) D; D (0.97); D(0.02); D(1.00)	(1.00)D; D (1.00); D (0.09)
2	**1**/ 1.0 eq K_2CO_3	(0.11) D; D (0.91); D (1.00)	(0.99) D; D (1.00); D (0.10)
3	**1**/ 0.015 eq **12**	-	(1.00) D; D (0.92); D (0.34)
4	**3**/ none	(1.00) D; D (0.52); D(0.04); D (0.54)	(0.93)D; D (1.00); D (0.39)
5	**3**/ 1.0 eq K_2CO_3	(0.62) D; D (0.87); D(0.04); D (1.00)	(0.93) D; D (1.00); D (0.41)
6	**3**/ 0.5 eq **11**	-	(1.00) D; D (0.80); D (0.08)



[a] Relative to the maximum, 1.00, with the results of indirect addition shown in red, determined by ^{2}H NMR of the crude deuteration products.

sample, (ii) *after* the reaction was completed (4 h). Control experiments demonstrate methyl red gives a red coloration under acidic conditions in this environment (frame e). Hydrogenations using the carbene catalyst **1** (frames c and d) and the *N,P*-system **3** (frames g and h) show the latter is clearly more acidic. Frames c and d suggest acidic intermediates formed after only 5 min in the reaction.

We suspect that proton concentrations in hydrogenation reactions are particularly important for tetrasubstituted alkene substrates such as **14**.[31] High levels of abnormal deuteration were observed for the catalyst precursors that are most likely to generate acid, i.e., **2** and **3** (Figure 6). Further, carbene **1** did not hydrogenate these same tetrasubstituted alkenes. This could

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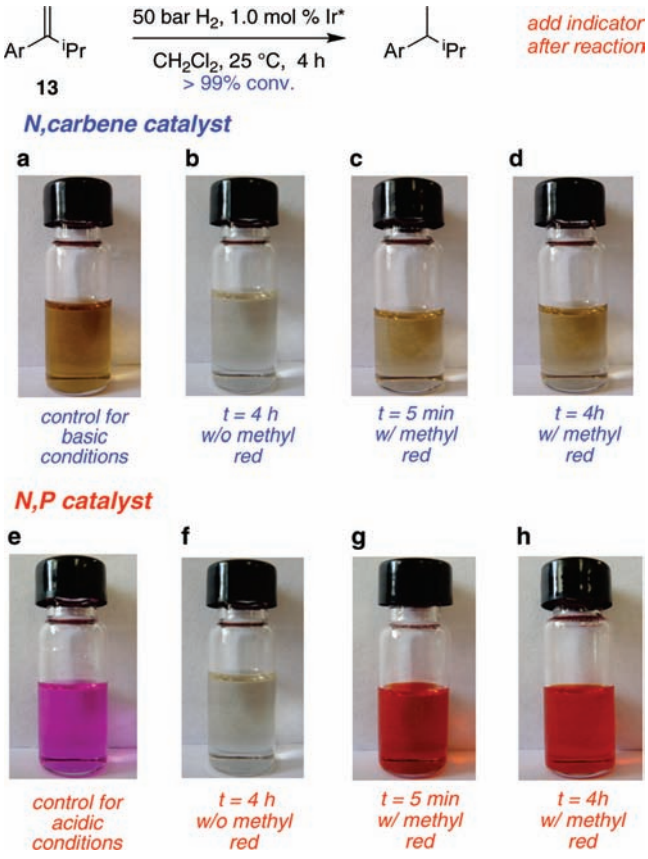

Figure 5. Hydrogenation with catalyst **1**: (a) Methyl red with Et_3N in CH_2Cl_2 (control for base); (b) without indicator (after 4 h); (c) with methyl red added after 5 min; and (d) with methyl red added after 4 h. Hydrogenation with catalyst **3**: (e) Methyl red with acid **12** in CH_2Cl_2 (control for acid); (f) without indicator (after 4 h); (g) with methyl red added after 5 min; and (h) with methyl red added after 4 h.

be because of steric factors. However, if acid was generated and the alkene isomerized to a 1,1-disubstituted form, then complex **1** should reduce this material. Consequently, it is possible that the carbene complex **1** simply generates *less* acid than **2** and **3**; hence the reaction does not proceed in the former case.

Conclusions

The data presented here show that hydrogenations of alkenes using chiral analogues of Crabtree's catalyst can be sensitive to protons generated by the catalytic intermediates. Further, the carbene catalyst precursor **1** is *less* inclined to generate protons than the *N,P*-systems **2** and **3** (in that order). We also have shown that the acidities of catalytic intermediates in hydrogenation reactions may impact the product distributions for acid-sensitive substrates, like enol ethers. For some other alkenes, acid-mediated isomerization might compete with direct addition of hydrogen in ways that is not apparent until deuterium labeling is used. Asymmetric hydrogenations of tetrasubstituted alkenes, for instance, are especially vulnerable to this complication because the direct addition of hydrogen is relatively slow due to steric effects, while protonations are fast because they give carbocations that are both benzylic and trisubstituted. It will be interesting to see how acidities of M−H bonds in hydrogenations can impact other acid-sensitive substrates. Acidities of metal hydride intermediates are important in many transition-metal-catalyzed reactions; in some cases, dramatically altered catalytic behavior on phosphine-to-carbene ligand substitution will be indicative of this.

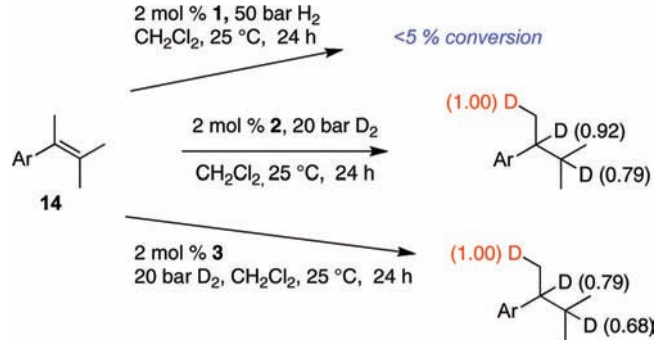

Figure 6. Abnormal deuterium distributions for the tetrasubstituted alkene **14** were *less* for the catalyst precursor **2** than with **3**, whereas minimal conversion was obtained when the carbene **1** was used.

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Supporting Information Available: Details of the calculation information and experimental procedures for the preparation of compounds **1** to **14**, details of the deuterium labeling experiments and ^2H NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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