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Article

Highly Selective Hydrogenation of C═C Bonds Catalyzed by a Rhodium Hydride

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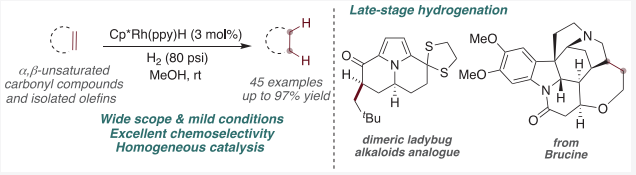
ABSTRACT: Under mild conditions (room temperature, 80 psi of H_2) Cp*Rh(2-(2-pyridyl)phenyl)H catalyzes the selective hydrogenation of the C═C bond in α,β-unsaturated carbonyl compounds, including natural product precursors with bulky substituents in the β position and substrates possessing an array of additional functional groups. It also catalyzes the hydrogenation of many isolated double bonds. Mechanistic studies reveal that no radical intermediates are involved, and the catalyst appears to be homogeneous, thereby affording important complementarity to existing protocols for similar hydrogenation processes.

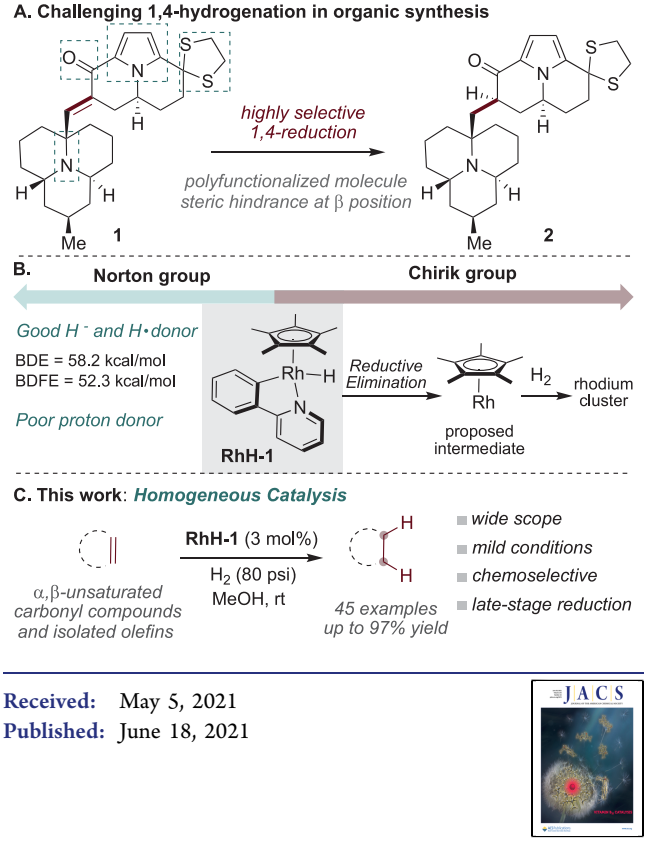


INTRODUCTION

The catalytic hydrogenation of unsaturated organic compounds is a transformation of widespread importance in both academia and industry, particularly as applied for the preparation of pharmaceuticals, fragrances, and other fine chemicals.[1] The 1,4-reduction of α,β-unsaturated carbonyl compounds has attracted particular attention, and much effort has been devoted to its development.[2] Hydrogen sources other than molecular hydrogen,[3] including silicon hydrides,[4] formates,[5] and alcohols,[6] are often efficient and have become widely used.[7,8] To date, the majority of methods possessing both high efficiency and selectivity have used transition metal promoters (Ir,[6] Pd,[9] Co,[10,11] Ni,[12] and others[13]) with a variety of supporting ligands,[14,5] though there have also been recent disclosures of transition-metal-free hydrogenation reagents involving Se powder,[15] borane,[16] and electrons.[17−19]

Nevertheless, most 1,4-reductions still suffer from drawbacks, such as poor tolerance of sensitive functional groups and a lack of effectiveness with highly substituted, sterically encumbered substrates. Indeed, such steric constraints can sometimes lead to an undesired stereochemical outcome and/or prevent hydrogenation entirely. Such issues arose in the Snyder group's recent total syntheses of the coccinellid alkaloids, including targets such as exochomine,[20] arborisidine,[21] and chilocorine C.[22,23] For example, one of the final steps in the exochomine work required the selective 1,4-reduction of the hindered enone **1** to **2** (Scheme 1A). However, the dithiolane group, benzylic ketone, and acyl pyrrole all proved prone to reduction and/or side-product formation; the desired product was best obtained by reducing **1** with silanes in the presence of stoichiometric $Mn(dpm)_3$, a procedure adapted from those reported by Magnus[24] and Shenvi.[25] Given this, and other related, examples, a robust catalytic procedure for the 1,4-reduction of α,β-unsaturated carbonyl compounds using H_2 was viewed as highly desirable.

Scheme 1. (A) A Challenging Substrate for 1,4-Hydrogenation, with Alternative Sites of Reaction; (B) Chirik Proposal for Mechanism of Action of (η^5-C_5Me_5)Rh(ppy)H; (C) Homogeneous Hydrogenation of α,β-Unsaturated Carbonyl Compounds and Isolated Olefins Catalyzed by RhH-1



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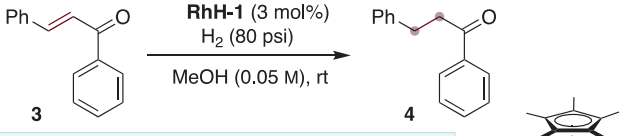
The Norton group initially attempted to employ the Cr $[CpCr(CO)_3H]$ and Co $[Co(dmgBF_2)_2L_2]$ (L = H_2O, THF, etc.) catalysts that they had used[26−30] for H· transfer from H_2 to solve this problem, but neither gave any **2** from **1**. We then considered $(\eta^5\text{-}C_5Me_5)Rh(ppy)H$ (ppy = 2-(2-pyridyl)-phenyl), **RhH-1**, developed in the Norton laboratory and shown to be a fast hydride and hydrogen atom donor, but a relatively poor proton donor (Scheme 1B).[31,32] Related Cp*Rh systems have been shown to effectively catalyze arene and olefin hydrogenation.[33−35] Indeed, in 2019 the Chirik group found that **RhH-1** can catalyze the hydrogenation to ammonia of amides,[36] nitrides,[37] and related ligands.[38] Very recently, the use of the same precatalyst for the hydrogenation of *N*-heteroarenes has been reported by the same group.[39] They have proposed that, upon heating or irradiation, the reductive elimination of 2-phenylpyridine from **RhH-1** can lead to the formation of catalytically active multimetallic clusters (and eventually nanoparticles), under varied H_2 pressures (4−36 atm) at elevated temperatures (80−100 °C).

To our delight, we found that $(\eta^5\text{-}C_5Me_5)Rh(ppy)H$ (**RhH-1**) does indeed show activity for the hydrogenation of the C=C bonds of enones. Herein we describe a highly selective and mild procedure for catalyzing the C=C hydrogenation of α,β-unsaturated carbonyl compounds and isolated olefins (Scheme 1C) which works on an array of substrates with high chemoselectivity and functional group tolerance. We follow-up these studies of scope with mechanistic investigations which reveal that our catalyst appears to be behaving in a homogeneous, rather than heterogeneous, manner.

RESULTS AND DISCUSSION

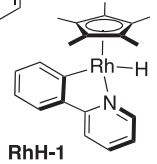
As shown in Table 1, we selected chalcone **3** as a test enone to develop and optimize our rhodium-catalyzed 1,4-hydrogenation method. With 3 mol % **RhH-1** and 80 psi of H_2 gas in MeOH (0.05 M) at 23 °C, the reaction took 24 h to reach completion, affording reduction product **4** in 94% isolated yield (Table 1, entry 1). Lowering the catalyst loading or the pressure of H_2 gas eroded the yield during the same time period (entries 2 and 3). Further, changing the catalyst to the benzo[*h*]quinoline derivative **RhH-2** gave a slightly lower yield (entry 4), while the use of solvents other than MeOH also proved deleterious (entries 5−7). As shown by control experiments, both the H_2 gas and the rhodium promoter are essential (entries 8 and 9).

Table 1. Optimization of the Reaction Conditions[a]

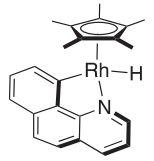


3 4

Entry	Deviation from standard conditions	4 (%)[b]
1	***None***	***99 (94)***[c]
2	Using 1 mol% **RhH-1**	62
3	50 psi instead of 80 psi	58
4	**RhH-2** instead of **RhH-1**	81
5	Hexane as solvent	56
6	MeCN as solvent	23
7	THF as solvent	74
8	Without H_2	trace
9	Without **RhH-1**	0



RhH-1



RhH-2

[a]**3** (0.20 mmol), **RhH-1** catalyst (3 mol %), H_2 (80 psi), MeOH (4 mL) at room temperature, 24 h. [b]NMR yields using CH_2Br_2 as internal standard. [c]Isolated yield.

As shown by the reaction scope in Table 2, the method displays excellent chemoselectivity with various α,β-unsaturated carbonyl compounds, which in all cases underwent 1,4-reduction exclusively to form the indicated products in high yields (with the colored bond marking the site of hydrogenation). As can be discerned, chalcones containing both electron-rich and electron-poor arenes are reduced appropriately, to **4**−**9**, and the reduction of the precursor to **5** can be scaled up without compromising the overall yield. Related substrates containing aromatic heterocycles such as imidazole or thiophene also react smoothly, giving good yields of **10** and **11**. Vinyl phenyl ketones with substituents at the α or β position also undergo 1,4-hydrogenation, making **12** and **13** in good yield. In addition, the vinyl methyl ketones in the substrates leading to **14**−**16** are selectively reduced in excellent yields, while the trisubstituted double bonds in **15** and **16** remain untouched. No 1,6-reduction product was detected along with **16**. Pleasingly, the α,β-unsaturated esters, vinyl amide, and vinyl sulfones within products **17**−**22** all posed no problems even with steric hindrance at the α position (as in the precursor of **17**). The substituted cyclic, α,β-unsaturated ester in **22** was not reduced.

Critically, the scope of the Rh-catalyzed hydrogenation extends to dienes and to cyclic enones. Both of the conjugated double bonds leading to **23** and **24** were hydrogenated with high efficiency, giving these materials in almost quantitative yields. The C=C bonds of cyclic enones are also hydrogenated in 1,4-fashion (leading to **25**−**28**). The cyclic enones found in products **29** and **30**, possessing β ethoxy substituents, are *not* hydrogenated, although the isolated C=C bonds are. The chemoselectivity of the Rh-catalyzed hydrogenation is further illustrated by the fact that acetals (**24** and **26**), esters (**22** and **25**), aryl halides (**21** and **23**), and even unprotected alcohol (**6** and **28**) are well tolerated, leaving ample room for further derivatization, as desired.

Although we did not observe byproducts with 1,2-reduction for any of the substrates used in Table 2, we did find that the 1,4-reduction products (**34**−**36**) from α,β-unsaturated aldehydes (**31**−**33**) undergo slow, further 1,2-reduction to afford **37**−**39** (Table 3). We note that both aliphatic and aromatic substituents seem to be tolerated at the β position. Of particular interest, the hydrogenation of the intermediate aldehyde is considerably slower than the 1,4-hydrogenation of the initial enone, as judged by the reaction times required.

With these initial results in hand, we then returned to the highly substituted substrates that had caused difficulty for the Snyder group in their exochomine synthesis (cf. Scheme 1A).[20] For example, Stryker's reagent $(H_6Cu_6L_6)$ had given a sluggish reaction, with the principal product being the result of 1,6-reduction across the pyrrole ring. A similar 1,6-reduction result was obtained after one-electron reduction by SmI_2; by contrast, catecholborane and DIBAL-H gave the 1,2-reduction product, while DIBAL-H with Cu(I), RedAl, Pd°/*n*-Bu_3SnH, and sulfonylhydrazides (NBSH) gave no reaction. Specifically, we tried to hydrogenate somewhat simpler predecessors of **40** and **41** with our rhodium catalyst **RhH-1** under our optimal conditions, and found that selective 1,4-hydrogenation of the C=C bonds of these two enones could be achieved in the presence of a dithiolane and a pyrrole, providing both **40** and **41** in high yields and diastereoselectivities (Table 3). The

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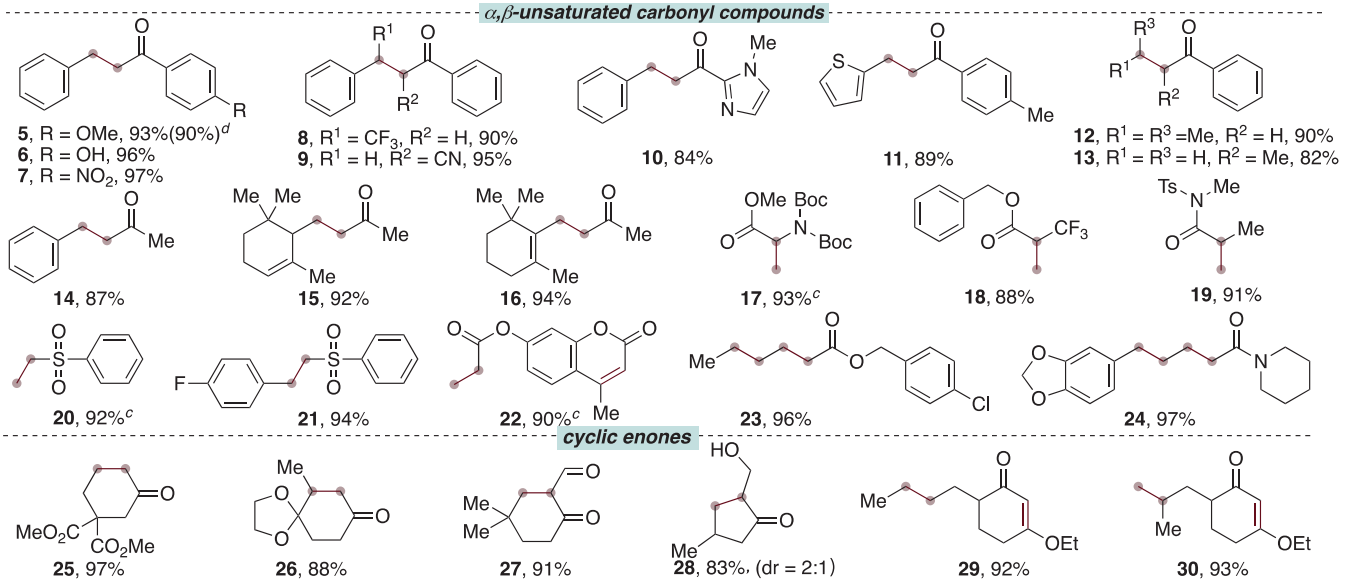
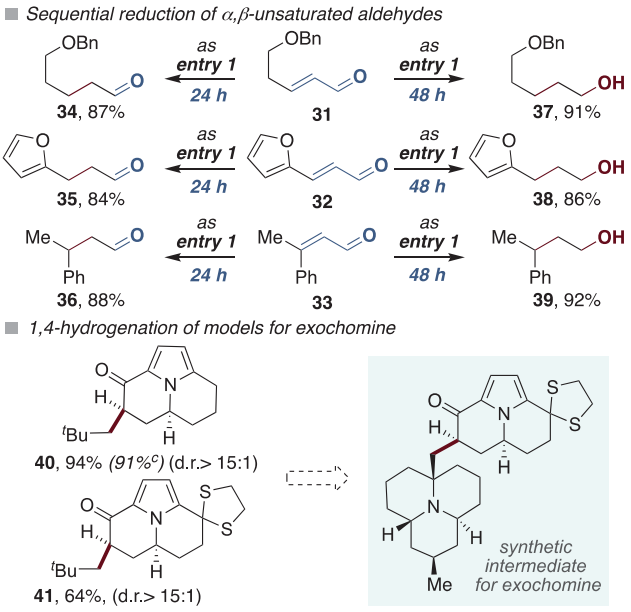
Table 2. Scope of the Rhodium-Catalyzed Hydrogenation of α,β-Unsaturated Carbonyl Compounds[a,b]



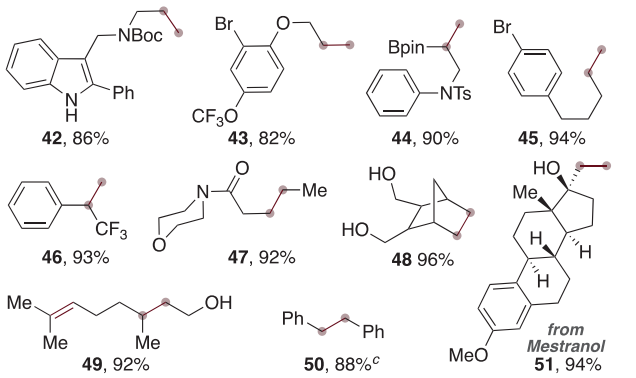
[a]Under the conditions of entry 1 in Table 1. [b]Isolated yields, average of two independent runs. [c]Using ^{i}PrOH as solvent instead of MeOH. [d]Gram scale (10 mmol reaction).

Table 3. Sequential Reductions & Synthetic Applications[a,b]



[a]Under the conditions of entry 1 in Table 1. [b]Isolated yields, average of two independent runs. [c]Triethylamine (1.0 equiv) was added.

Table 4. Hydrogenation of Isolated Olefins[a,b]



[a]Under the conditions of entry 1 in Table 1. [b]Isolated yields, average of two independent runs. [c]Reaction time is 6 h.

presence of the *tert*-butyl substituents caused no issues in these transformations, and the addition of Et_3N did not suppress the formation of **40** (suggesting that the tertiary amine found in exochomine itself would not be problematic if executed on even more advanced intermediates).

In view of the hydrogenation of the isolated double bonds leading to **29** and **30**, we have further explored the utility of **RhH-1** as a catalyst for the hydrogenation of other such olefins (cf. Table 4). As shown, carbon−carbon double bonds with a variety of electronic and steric properties gave high yields of the hydrogenated products **42**−**49**. Functional groups that are not affected under these conditions include a boronic ester, a brominated arene, an unprotected indole, and free alcohols (both primary and tertiary). The trisubstituted C=C bond that belongs to the allylic alcohol precursor of **49** was reduced, but the remote, trisubstituted double bond remained untouched; in this case, the hydroxyl group might be serving as a directing group. Complete reduction of diphenylacetylene to **50** was observed in 6 h, while the terminal alkyne in mestranol is hydrogenated to afford **51** in high yield (94%).

The observed chemoselectivity of our Rh-catalyzed hydrogenation reactions suggested to us that they may also be useful in late-stage reductions during the synthesis of fine chemicals and/or pharmaceutical agents. Indeed, we can carry out such reactions (Scheme 2): for example, cyproheptadine is exclusively hydrogenated at the less substituted double bond, producing a good yield of the reduced pharmaceutical **52**; reduction of the trisubstituted olefin in brucine delivers **53** in 94% yield. The late-stage hydrogenation of levofloxacin was similarly achieved with ease to give **54** in high yield, along with decarboxylation of the β-keto acid that occurs with standard hydrogenation protocols.[40]

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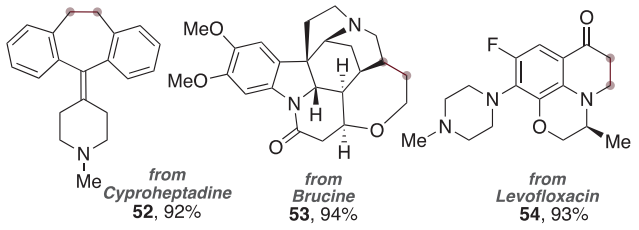
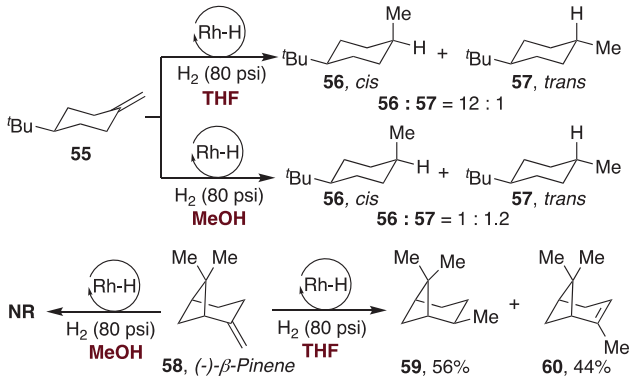
Scheme 2. Late-stage Hydrogenation of Pharmaceuticals



In view of the effectiveness of **RhH-1** in catalyzing the hydrogenation of unactivated alkenes, we have attempted its use on the exomethylene of **55**, a substrate whose stereochemical outcomes in catalytic hydrogenation have been investigated in detail by Shenvi.[25] As shown in Scheme 3, we

Scheme 3. Effect of Solvent on Exomethylene Reduction



obtained in THF mostly the *cis*-disposed reduction product **56** (which is also the predominant product with traditional catalysts).[41−43] We obtained a near-equimolar mixture of the epimers **56** and **57** when the reaction was conducted in MeOH. Under no conditions did our catalyst prefer to form the more stable product **57**, one which Shenvi has found to be the kinetic product with $Mn(dpm)_3$ or $Co(dpm)_2$ as the catalyst.[44]

The outcome of such hydrogenation reactions is determined by both substituent effects and by solvent. With *β*-pinene (**58**), for example, there is no hydrogenation in MeOH, but in THF the equatorial methyl product **59** is obtained in 56% yield along with 44% of the isomerization product **60**. The isomerization surely arises from the reversibility of the olefin insertion.

MECHANISM

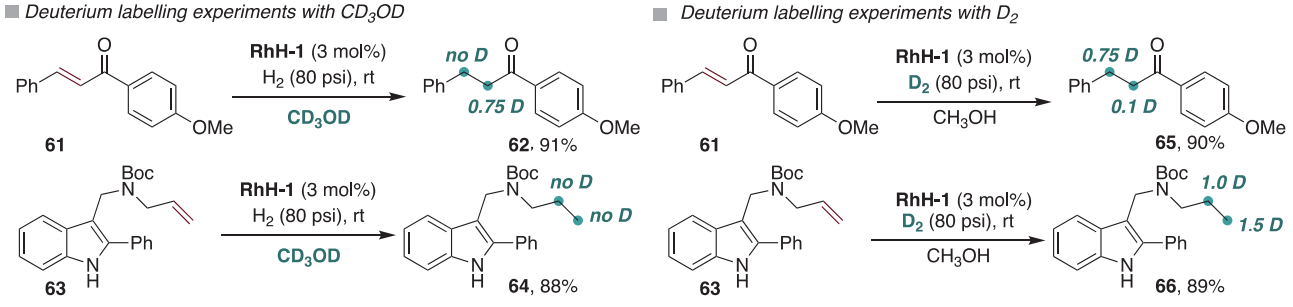
In order to probe the difference between the mechanism of enones and that of isolated olefins, we have compared the results of deuterium labeling experiments with the *α,β*-unsaturated ketone in **61** with the results of such experiments with the isolated terminal olefin in **63**. The extent of label incorporation is shown in Scheme 4. When CD_3OD was used as solvent, 0.75 D was transferred to the *α* position of **62**, while no deuterium was detected in **64**. The protonation of a Rh-enolate intermediate with methanol is faster than reductive elimination of the enolate ligand with the H on rhodium.[45] The H_2 gas supplies the H atom added to the *β* carbon of **61**, and both of the H atoms added to **63**; the solvent supplies only the H atom found at the other *α* carbon of enone substrate **61**! Reaction of the same substrate **61** with D_2 instead of H_2 gas resulted in 90% deuteration of **65** with only 0.25 hydrogen at the *β* position. Given that both the H_2 gas and the MeOH are present in large excess relative to the substrate and the catalyst, there is little scrambling between the H_2/D_2 and the solvent during these experiments.[46,47]

Mechanisms that explain the results in Scheme 4 are shown in Scheme 5, with substrates bearing enones on the left and those with isolated olefins on the right. The generation of the active catalyst probably begins with the reductive elimination of phenylpyridine from **RhH-1** (as suggested by Chirik),[39] followed by the addition of H_2 to the Cp*Rh(I). The resulting Cp^*RhH_2 has been drawn by the Maitlis,[33] Finke,[34] and Chirik[39] groups in catalytic cycles, but to our knowledge has never been isolated or identified.

To determine if the generation of carbon-centered radicals by MHAT (metal hydrogen atom transfer) was involved in this **RhH-1** catalyzed hydrogenation, we treated **71** and **74** with H_2 in the presence of **RhH-1**. Although **RhH-1** has a low bond dissociation free energy (BDFE = 52.3 kcal/mol)[32] no trace of the radical cyclization products **73** or **76** was observed (the predominant products are shown in Scheme 6, i.e. **72** and **75**).

Heterogeneous and homogeneous catalysis have been established by Finke and Chirik in related Cp*Rh systems,[33−35,39,48−51] but it appears that our catalyst is homogeneous. All materials dissolved with our reactions being clear and red within 20 min. We observed no precipitates even after 24 h of reaction time, and the kinetic plot in Scheme 7 suggests a clean first-order transformation of the tested substrate (**S15**, it is the precursor to compound **15**) to product with a rate constant of about 2.3×10^{-5} M^{-1} s^{-1}. A sigmoidal curve is typical of metal-particle formation. Furthermore, we found the addition of excess mercury after 200 min did not change the observed rate constant, a result typical of a homogeneous catalyst. Finally, TEM analysis (see the

Scheme 4. Deuterium Labelling Experiments



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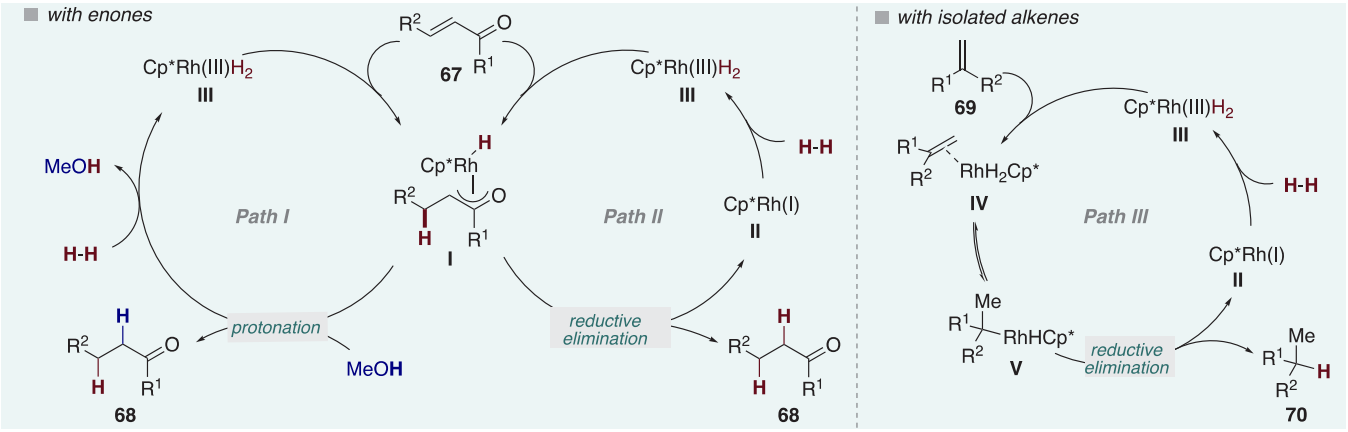
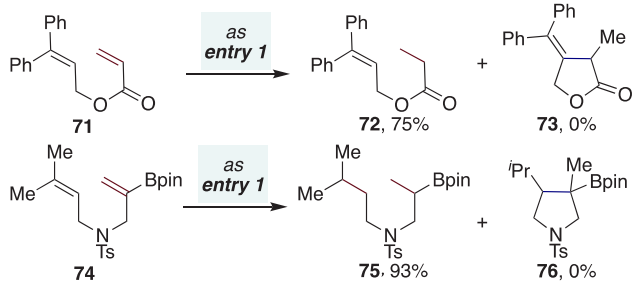
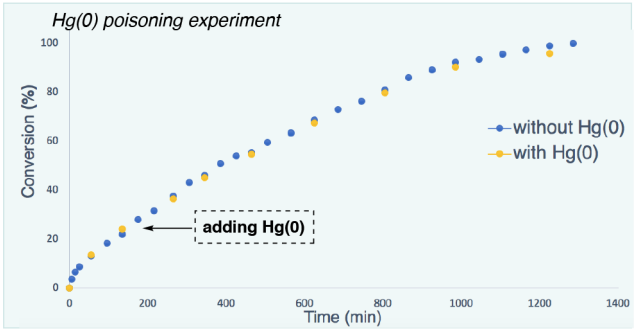
Scheme 5. Mechanistic Proposal



Scheme 6. Evidence against MHAT and Radical Formation



Scheme 7. Mercury Poisoning Study



Supporting Information section for full details) of the residue when solvent was removed after the reaction showed neither heterogeneous metal particles nor rhodium clusters.[52]

CONCLUSION

In summary, (η^5-C_5Me_5)Rh(2-(2-pyridyl)phenyl)H (**RhH-1**) catalyzes the selective 1,4-reduction of α,β-unsaturated carbonyl compounds—even ones with bulky substituents—under H_2. It also catalyzes the hydrogenation of many isolated alkenes under mild reaction conditions. The system shows excellent selectivity and functional group compatibility, and appears to operate mechanistically under conditions that are homogeneous. The rhodium catalyst is a significant complement to the existing toolbox for metal-catalyzed selective hydrogenations and offers an opportunity to overcome longstanding challenges in the hydrogenation of polyfunctionalized molecules.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c04683.

Experimental procedures, spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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