Site-Selective Hydrogenation of Electron-Poor Alkenes and Dienes Enabled by a Rh-Catalyzed Hydride Addition/Protonolysis Mechanism

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Abstract: The transition metal catalyzed hydrogenation of alkenes is a well-developed technology used on a lab scale as well as on large scales in the chemical industry. Site- and chemoselective mono-hydrogenations of polarized conjugated dienes remain challenging. Instead, stoichiometric main-group hydrides are used rather than H_2. As part of an effort to develop a scalable route to prepare geranylacetone, we discovered that $Rh(CO)_2$acac/xantphos based catalysts enable the selective monohydrogenation of electron-poor 1,3-dienes, enones, and other polyunsaturated substrates. D-labeling and DFT studies support a mechanism where a nucleophilic Rh(I)-hydride selectively adds to electron-poor alkenes and the resulting Rh-enolate undergoes subsequent inner-sphere protonation by alcohol solvent. The finding that $(L_n)Rh(H)(CO)$ type catalysts can enable selective mono-hydrogenation of electron-poor (poly)enes provides a valuable tool in the design of related chemoselective reduction processes of unsaturated substrates.

Introduction

The chemoselective reduction of α,β-unsaturated carbonyl compounds is a common transformation in synthetic chemistry that is usually achieved by the use of stoichiometric main-group element hydride donors in the presence of transition metal catalysts.[1] Catalytic hydrogenations using H_2, however, are preferred for large-scale industrial production processes.[2] Known homogeneous systems that can promote the chemoselective (and enantioselective) alkene hydrogenation of conjugated enones include Pd-, Ru-, or Rh-bisphosphine based systems,[3] Cp*Rh(ppy)H,[4] and Ir-based catalysts of the Crabtree/Pfaltz-type with P,N-ligands.[5] The site-selective mono-hydrogenation of polarized conjugated dienes is more challenging as compared to alkenes or simple enones and remains largely unaddressed for acyclic substrates. In these cases, the difficulty in controlling the positional selectivity of the initial metal-hydride addition is further complicated by the potential for the target products to undergo further hydrogenation or isomerization in the presence of metal-hydride

catalysts (Fig 1A).[6] Most reported diene reduction processes, including those using Cr-, Ru-, or Rh-catalysts, result in the net C2,C5-hydrogenation of the substrate to generate β,γ-unsaturated carbonyl products.[7] Existing techniques for the C2,C3-reduction of electron-poor conjugated dienes to generate γ,δ-unsaturated products using H_2 are limited to a specific substrate class of C2-disubstituted α,δ-dienamide esters.[8] The C2,C3-reduction of acyclic dienones with H_2 is not established and instead requires the use of stoichiometric silane reductant.[9, 10]

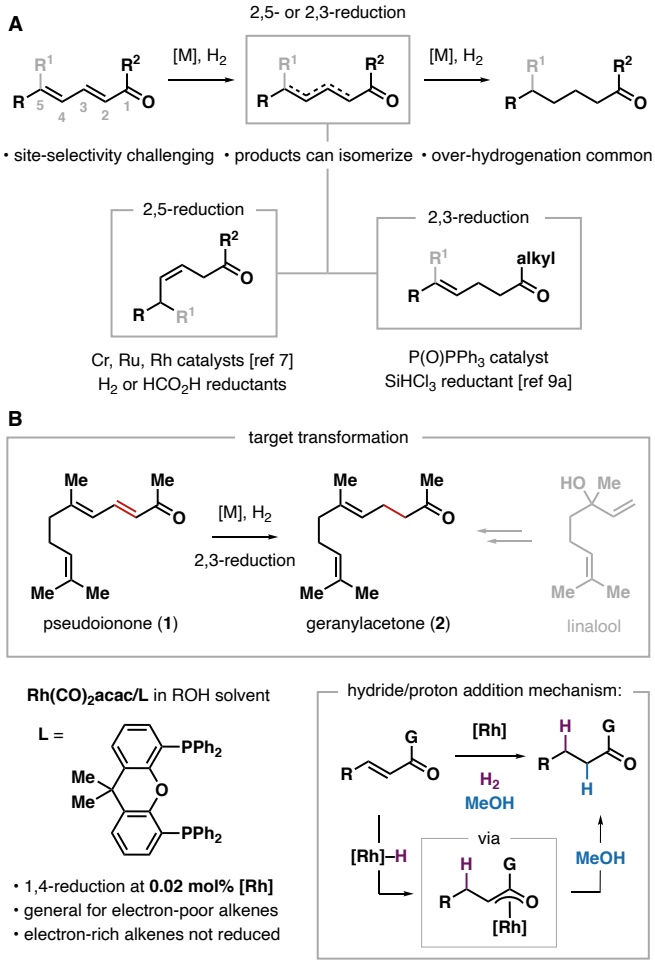

Figure 1. A Challenges in selective diene hydrogenation. **B** Pseudoionone hydrogenation as a route to geranylacetone catalyzed by Rh/xantphos.

We became interested in developing a homogeneous catalyst system for the site-selective C2,C3-hydrogenation of conjugated dienones as an approach to prepare the intermediate geranylacetone (**2**) directly from pseudoionone (**1**) (Fig 1B), a readily available precursor involved in the industrial synthesis of Vitamin A.[11] A hydrogenation route to geranylactone via pseudoionone would be shorter compared to classical synthetic routes that proceed through linalool, with both routes starting from citral.[12] While investigating this challenge, we discovered that a classic hydroformylation catalyst combination of $Rh(CO)_2acac$ and xantphos[13] enables the selective mono-hydrogenation of electron-

poor (poly)enes. The use of H_2 in alcohol solvents results in the formation of a nucleophilic Rh-hydride which adds to the β-position of electron-poor alkenes and undergoes subsequent protonation by solvent. This mechanistic pathway enables chemoselective hydrogenation at the α,β-positions of dienones, like pseudoionone, at low metal loadings (0.02 mol%) without product over-hydrogenation or isomerization that plagues more typical metal dihydride hydrogenation catalysts. The process allows for the hydrogenation of other classes of electron-poor alkenes (α,β-unsaturated esters, amides, nitriles, and nitroalkenes). We interpret more generally that catalysts of the type $(L_n)Rh(H)(CO)$, where L_n is a wide bite angle bisphosphine or two phosphites, enable chemoselective diene mono-hydrogenation dictated by alkene polarization and steric effects akin to nucleophilic metal hydride catalysts generated by using stoichiometric main-group element reductants.[14]

Results and Discussion

The hydrogenation of pseudoionone (**1**) was examined with a wide array of common metal catalysts and reaction conditions. It was found that combinations of 1 mol% $Rh(CO)_2$acac and xantphos in MeOH using 1000 psi H_2 enabled selective mono-hydrogenation to give geranylacetone (**2**) in 95% yield. The use of a Rh-carbonyl catalyst precursor was essential as other Rh-sources or metals gave hydrogenation products with poor selectivity and over-reduction (Fig 2A). Alcohol solvents provided better selectivity for C2,C3-hydrogenation compared to other solvents, where >15% side product formation was observed (Fig 2B, EtOAc, THF, CH_2Cl_2). Using 200 psi of H_2 provided similar results to reaction conducted at higher pressure, however at ~1 atm H_2 reduced conversion and poor yields were observed and Rh precipitated from solution. Use of formic acid as an H_2 surrogate was not productive.[7e]

The use of phosphorous ligands with wide bite-angles[15] or ligands with relatively weak σ-donating properties generated the most active and selective catalysts. For example, combinations of $Rh(CO)_2$acac and dppm or dppe led to hydrogenation without detectable geranylacetone, while dppp and dppb gave improved results (64% and 78% yield respectively). Along with xantphos, DPEphos, spanphos, and dppf gave >85% selectivity for C2,C3-hydrogenation. Use of $P(OPh)_3$ as the ligand with Rh:L = 1:2 led to a selective hydrogenation and geranylacetone was obtained 91% yield. At lower catalyst loadings (0.02 mol% [Rh]), xantphos was far superior, giving 94% yield at full conversion vs 21% yield at 58% conversion with $P(OPh)_3$ (Fig 2C, inset). Cp*Rh(PhPy)H has been recently reported to be an effective catalyst for the hydrogenation of enones;[4] however its use for the reduction of pseudoionone led to poor conversion with multiple products generated (34% conv., 17% yield). The optimized conditions allow for high yield because undesirable hydrogenation of the remaining alkenes in geranylacetone (**2**) is avoided. When subjecting **2** directly to the standard reaction conditions with $Rh(CO)_2$acac as the catalyst, <10% hydrogenation is observed. This contrasts otherwise identical reactions using $[Rh(COD)Cl]_2$ where complete consumption is observed (Fig 2D).

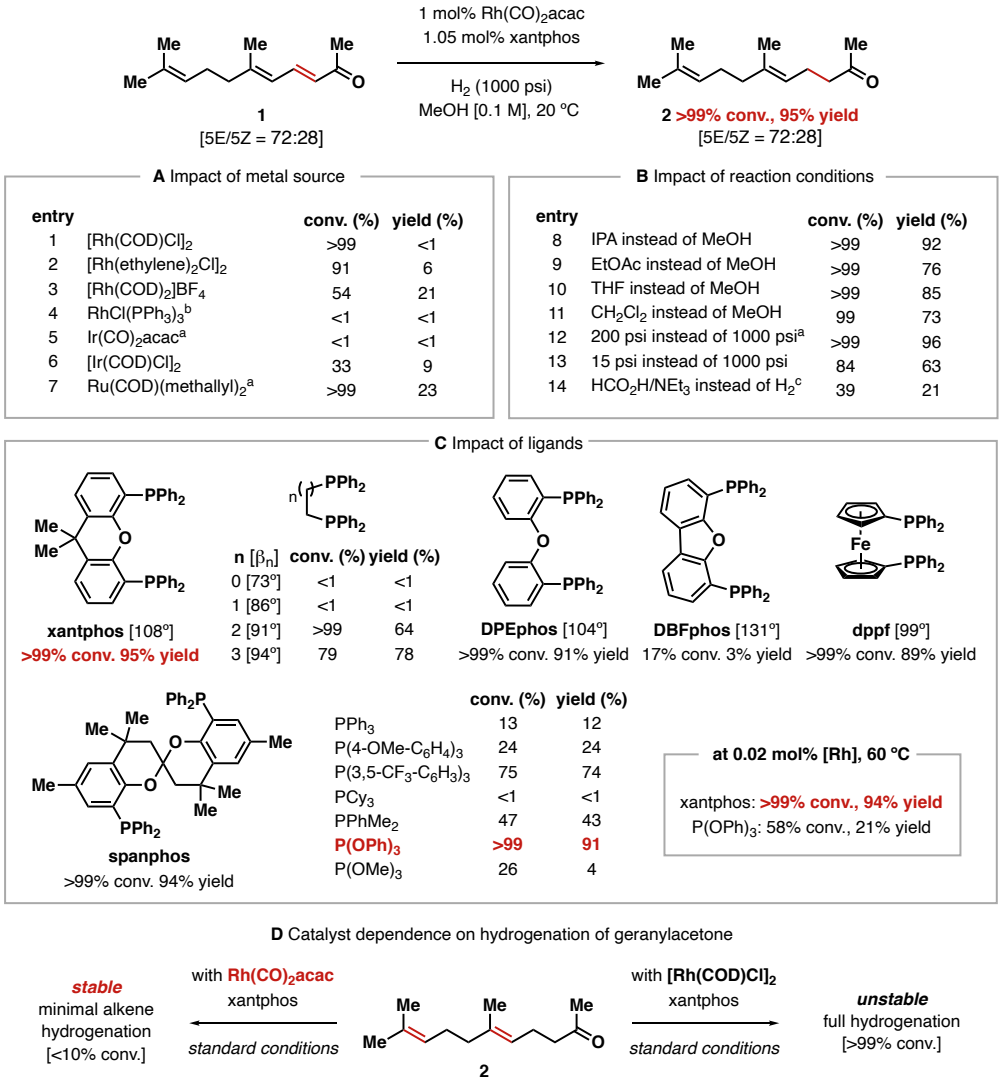

Figure 2. Impact of metal precursor, reaction conditions, and ligand on the hydrogenation of pseudoionone, ligand natural bite angle in brackets. [a] 70 ºC; [b] no additional ligand added; [c] 2 equiv. of HCO_2H/NEt_3 (5:2). For monodentate ligands [Rh]:L = 1:2. In all cases **1** and **2** are a 72:28 5*E*/5*Z* mixture. Conversion and yields determined by calibrated GC.

$Rh(CO)_2acac$/xantphos catalyzed hydrogenation in MeOH enables the reduction of an array of electron-poor alkenes and dienes (Fig 3A). γ-Disubstituted dienones and dienoates undergo selective C2,C3-hydrogenation without *E/Z* isomerization of the unreduced alkene unit (**1**–**6**), as do aryl substituted dienones (**7**, **8**), α- and β-ionone (**9**, **10**), β-damascone (**11**), and the trisubstituted enone **12**. Cyclohexenones (**13**, **14**) are readily hydrogenated without competing ketone reduction. Various electron-poor alkenes, including α,β-unsaturated ketones, esters, amides, nitriles and nitroalkenes are hydrogenated with nearly quantitative yields (**15**–**19**). Enals undergo hydrogenation selectively at the alkene position (**20**, **21**). In these cases, toluene is the optimal solvent. Arylalkenes substituted at the α- or β-position undergo hydrogenation (**22**, **23**), but typically at rates slower than dienones (see substrates **7**, **8**). Electron-rich alkenes are generally unreactive to hydrogenation when using

$Rh(CO)_2$acac/xantphos, with the exception of terminally unsubstituted substrate (**24**). Complex substrates dexamethasone (**25**) and parthenolide (**26**) that bear potentially reducible carbonyl, epoxide, and electron-rich alkenes also undergo selective C2,C3-reduction.

$Rh(CO)_2$acac/xantphos catalyst mixtures under H_2 in MeOH give rise to a highly active catalyst for the hydrogenation of di- or trisubstituted electron-poor alkenes and dienes but do not reduce most 1,2-disubstituted or trisubstituted electron-rich alkenes. For example, geranylacetone (**2**) does not undergo significant hydrogenation at the trisubstituted alkene positions. The less polarized substrates 1,4-diphenylbutadiene, 1,5-cyclooctadiene, or cyclooctene (**27**–**29**) are effectively inert to hydrogenation under the standard conditions and do not impede the reduction of electron-poor dienes in a competition study (Fig 3B). Less successful substrate examples include the tetrasubstituted enone **30** which is unreactive and γ-monosubstituted dienoate **31** which undergoes non-selective hydrogenation. Carvone (**32**) is hydrogenated exclusive at the exocyclic alkene and allyl-substituted enone **33** is reduced at both unsaturated positions. Collectively, with a few exceptions, the reactivity profile of $Rh(CO)_2$acac/xantphos under hydrogen in MeOH resembles that of nucleophilic metal hydrides generated from stoichiometric hydride transfer processes.[1b]

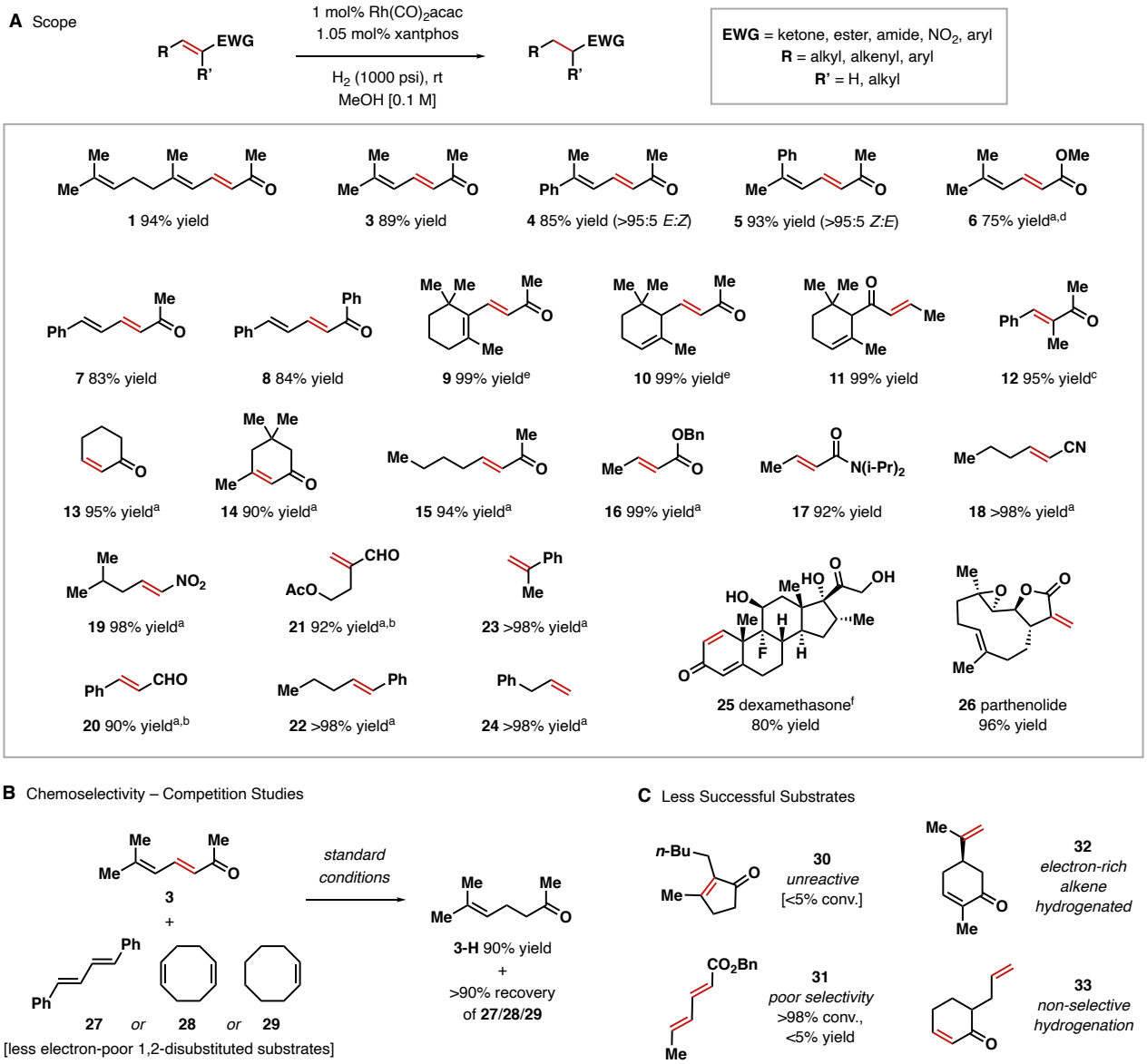

Figure 3. A Reaction scope and limitations for the $Rh(CO)_2acac$/xantphos catalyzed hydrogenation of alkenes and dienes. **B** Competition study between electron poor diene **3** and other dienes and alkenes. **C** Unreactive or poorly selective substrates. [a] Yield determined by calibrated ^1H NMR spectroscopy. [b] Toluene solvent instead of MeOH, 1 atm H_2 instead of 1000 psi H_2. [c] 60 ºC instead of r.t. [d] 50 ºC instead of r.t. [e] 40 ºC instead of r.t. [f] 1:1 MeOH:THF instead of MeOH.

Mechanistic studies suggest the $Rh(CO)_2acac$/xantphos catalyzed hydrogenation likely occurs by the formation of a nucleophilic Rh(I)-hydride that adds to the β-position of the electron-poor alkene or diene (Fig 4A). The resultant Rh-enolate[16] intermediate then undergoes protonolysis to give the product. Net hydrogenolysis of the Rh-alkoxide species regenerates the Rh(I)-hydride. This mechanism contrasts typical Rh-catalyzed hydrogenation mechanisms that involve the C–H bond forming reductive elimination from Rh(III)-hydrides[2, 17] and instead resembles the mechanism of Rh-catalyzed reductive couplings that use H_2.[18] A key observation leading to this interpretation was a strict (and initially

surprising) deuterium-labeling pattern consistent with a hydride/protonolysis mechanism. When the hydrogenation of diene **1** is conducted with D_2 in MeOH, exclusive D-incorporation is observed at the β-position (C4) with no detectable D-incorporation at the α-position (C3, Fig 4B, 50% is 1 equivalent, see the SI for details and NMR traces). When reactions are conducted with H_2 and d_4-MeOD, quantitative D-incorporation is found at C3 with no detectable D observed at C4 (Fig 4B). Under the standard conditions, no H/D exchange in **2** at the enolizable α-position in d_4-MeOD is observed, indicating that D-incorporation arises only from the hydrogenation. Conversely, when aprotic solvents like THF, EtOAc or CH_2Cl_2 are used in combination with D_2, approximately one equivalent of D is incorporated at both C3 and C4, suggesting that in the absence of a proton-source a dihydride mechanism with Rh-mediated C–H bond forming reductive elimination is involved (Fig 4B). This change in mechanism explains the lower observed selectivity and tendency for over-hydrogenation when using non-alcohol solvents in the hydrogenation of **1** and related substrates. Norton and co-workers recently suggested a similar mechanism for hydrogenations occurring in MeOH using Cp*Rh(PhPy)H.[4] Here, labeling studies showed only partial D-incorporation when using D_2 or d_4-MeOD (~80%), which indicates multiple mechanistic pathways for reduction and could explain the relatively poor performance in the hydrogenation of **1**.

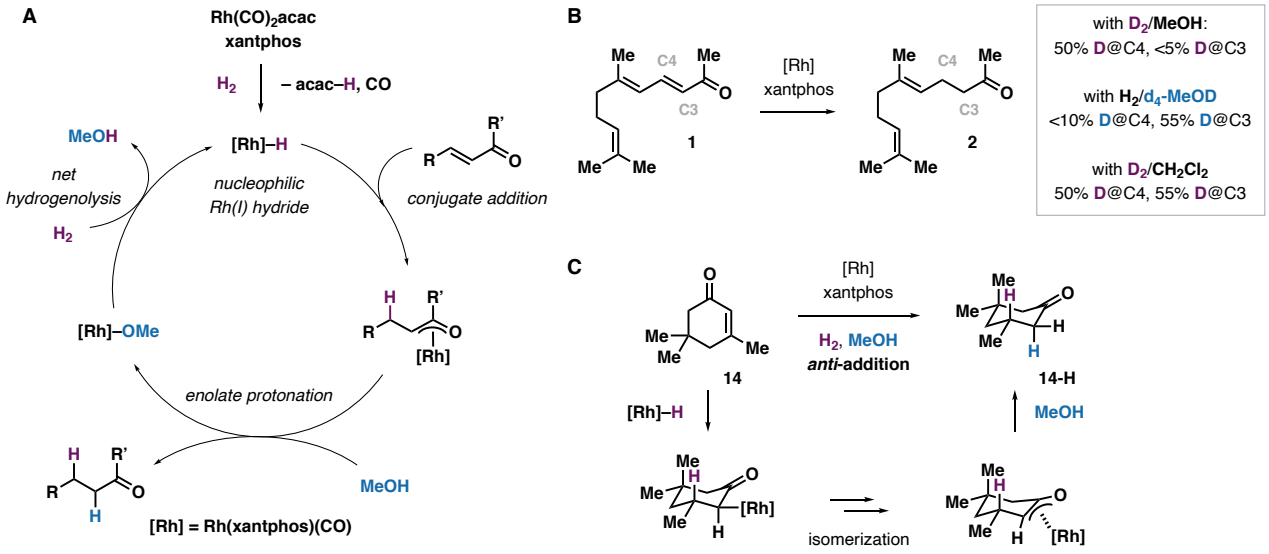

Figure 4. A General mechanistic hypothesis. **B** Labeling studies in the hydrogenation of **1**. **C** Stereoselectivity of labeling using isophorone (**14**).

A (xantphos)Rh(H)(CO) species is likely the active hydrogenation catalyst that can be transiently generated from more stable (xantphos)Rh(H)(CO)L (L = CO, solvent, or substrate) or carbonyl bridging dimers, as is known for hydroformylation with Rh/xantphos and related bisphosphine systems.[19] Either (xantphos)Rh(H)(CO)PPh_3 or (xantphos)Rh(H)$(CO)_2$ generated in-situ under syngas (as observed by

^{31}P NMR at 21 ppm) could be used to hydrogenate **1**, suggesting that the monocarbonyl (xantphos)Rh(H)(CO) is a plausible and short-lived active catalyst.

The general hydride/proton addition mechanistic picture is further supported by quantum chemical calculations on the level of density functional theory using dienone **3** as the model substrate (see the SI for details). Coordination of the substrate to the catalyst (xantphos)Rh(H)(CO) (**Rh-A**) and subsequent hydride transfer to the β-position leads to the η^3-coordinated enolate complex **Rh-B** (Fig 5). At this stage **Rh-B** can either oxidatively add H_2 to form the Rh(III)-dihydrido complex **Rh-C** with a calculated reaction energy of ΔE = -24.9 kJ/mol, or it can coordinate methanol to form complex **Rh-D** with ΔE = -30.9 kJ/mol. The latter reaction step is slightly more exothermic and given the vast excess of solvent molecules, the coordination of methanol should be strongly preferred over H_2 addition. In **Rh-D**, the enolate has changed to a η^1-coordination, but is stabilized by a hydrogen-bond from the coordinated methanol. The transfer of this proton requires only a small activation energy of 8.8 kJ/mol (**TS-1**), yielding the enol complex **Rh-E**. After liberation of the enol product, which can undergo tautomerization in the methanol solution, the oxidative addition of H_2 and reductive elimination of methanol regenerates the catalyst **Rh-A**. In the absence of protic solvent, the reaction can only proceed via C–H bond forming reductive elimination from dihydrido enolate complex **Rh-C** with a calculated activation energy of 59.9 kJ/mol (**TS-2**). The 3,4-hydrogenated ketone is directly formed in this pathway, regenerating the catalyst **Rh-A**. The high barrier to direct Rh-enolate hydrogenolysis is consistent with observed reactivity of $Rh(PPh_3)_2(CO)$(enolate) intermediates reported by van Leeuwen.[20] Overall, the calculations confirm and explain the experimental observation that, in the presence of d_4-methanol or D_2, the added H/D atom in the 3-position of the reduced product exclusively originates from the methanol OH, whereas without alcohol it comes from H_2 in a less selective, higher barrier pathway.

A hydride/proton addition pathway appears common for other substrates. For example, in labeling experiments using isophorone (**14**) as the substrate similar results were observed, with the net hydrogenation proceeding as *anti*-addition (Fig 4C). We postulate that the stereochemical outcome arises from the protonation of an η^3-Rh-enolate from the less hindered cyclohexanone face which can be generated by transient formation of an η^1-O bound Rh enolate.[14d]

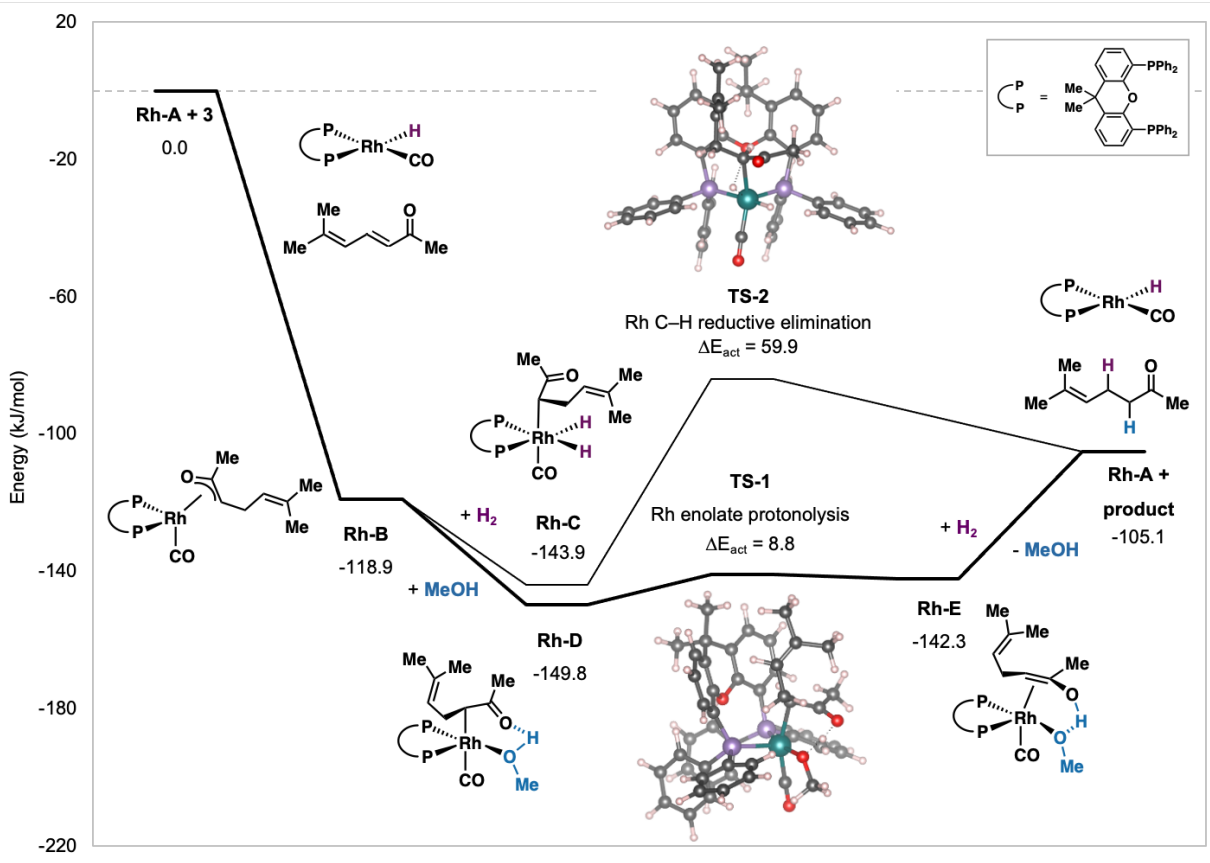

Figure 5. Computed energy profiles of selected key steps in the Rh/xantphos catalyzed hydrogenation of dienone **3**.

Conclusion

In summary, $Rh(CO)_2$acac/xantphos is an efficient catalyst system for the site-selective hydrogenation of electron-poor alkenes and dienes. This allows for an improved synthetic route to geranylacetone directly from pseudoionone at low catalyst loading with minimal undesired over-hydrogenation. The observed selectivity can be rationalized by a mono-hydride addition/protonolysis mechanism where a nucleophilic Rh-hydride enables the positional selectivity of addition to form a Rh-enolate intermediate. Suppression of mechanisms that proceed by Rh-catalyzed C–H reductive elimination prevent over-hydrogenation and isomerization reactions. We interpret more generally that hydrogenation catalysts of the type $(L_n)Rh(H)(CO)$ can enable selective mono-hydrogenation of electron-poor (poly)enes based on predictable electronic and steric factors which will have value in the design of improved catalysts and processes for the selective hydrogenation of related substrates.

Acknowledgements Support was provided by NSERC Canada (ALLRP 556312-20) and Canada Foundation for Innovation (IOF 32691).

Competing Interest: BASF and the University of Alberta have filed a patent application on the reported technology.

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