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Substrate effects on the mechanism of enantioselective hydrogenation using ruthenium bis(phosphine) complexes as catalyst: A mechanistic investigation of the hydrogenation of α,β-unsaturated acids and esters based on deuterium labeling studies

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Dedicated to Professor Brian R. James.

Abstract

The mechanism of ruthenium-bis(phosphine) catalyzed enantioselective hydrogenation of olefins was examined using [Ru((*R*)-BINAP)(H)(MeCN)$_n$(sol)$_{3-n}$]BF_4 ($n = 0$–3, sol = solvent used in reaction) as catalyst. Tiglic and angelic acids were used as standard α,β-unsaturated acid substrates; (*Z*)-methyl α-acetamidocinnamate and dimethyl itaconate were used as standard α,β-unsaturated ester substrates. Isotopic labeling studies (deuterium scrambling) indicate that two distinct mechanisms are in operation for α,β-unsaturated acids versus α,β-unsaturated esters. In each case, 5-membered metallocycle intermediates are formed via olefin-hydride insertion. The mechanisms, however, deviate primarily in the activation of dihydrogen, which is strongly affected by the nature of the substrate. Hydrogenation of α,β-unsaturated acids proceed via heterolytic cleavage of dihydrogen, whereas hydrogenation of α,β-unsaturated esters proceed via homolytic cleavage of dihydrogen. A full discussion of the mechanisms is presented.

Keywords: Ruthenium BINAP; Tiglic acid; (*Z*)-Methyl α-acetamidocinnamate; Asymmetric catalysis; Hydrogenation; Mechanism; Isotopic-labeling study

1. Introduction

The controlled hydrogenation of prochiral substrates by chiral catalysts into enantiopure materials is an important process in academia and industry. Over the past decade, many ruthenium(II) bis(phosphine) complexes have been determined to be highly active and selective catalysts for the enantioselective hydrogenation of numerous unsaturated organic substrates. The more successful catalysts often incorporate 2,2′-bis(diphenylphosphino)-1,1′-binaphthalene (BINAP) and related species as the chiral ligand [1–4]. The result is not only systems with exceptional enantioselectivity, but systems that are also capable of extremely high turnover frequencies (TOFs) and turnover numbers (TONs).

Several groups, most notably that of Halpern et al. [5], have reported on the mechanism of enantioselective hydrogenation of α,β-unsaturated acids/esters in alcohol solvents using ruthenium-bis(phosphine)-dicarboxylate species as catalyst [6–10]. The general features of Halpern's proposed mechanism are presented in Scheme 1 with tiglic acid as substrate. The mechanism follows four main steps: first, a rapid equilibrium between the catalyst

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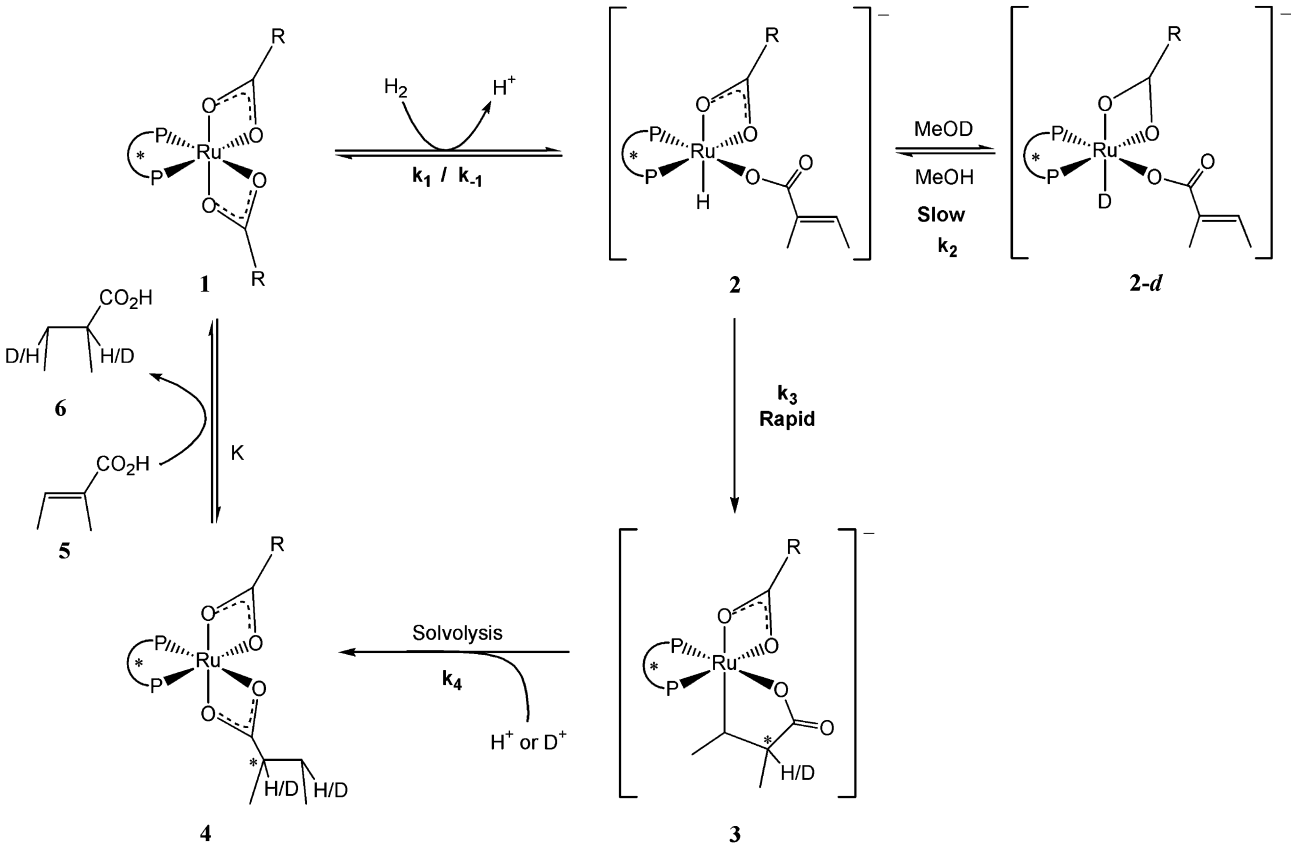
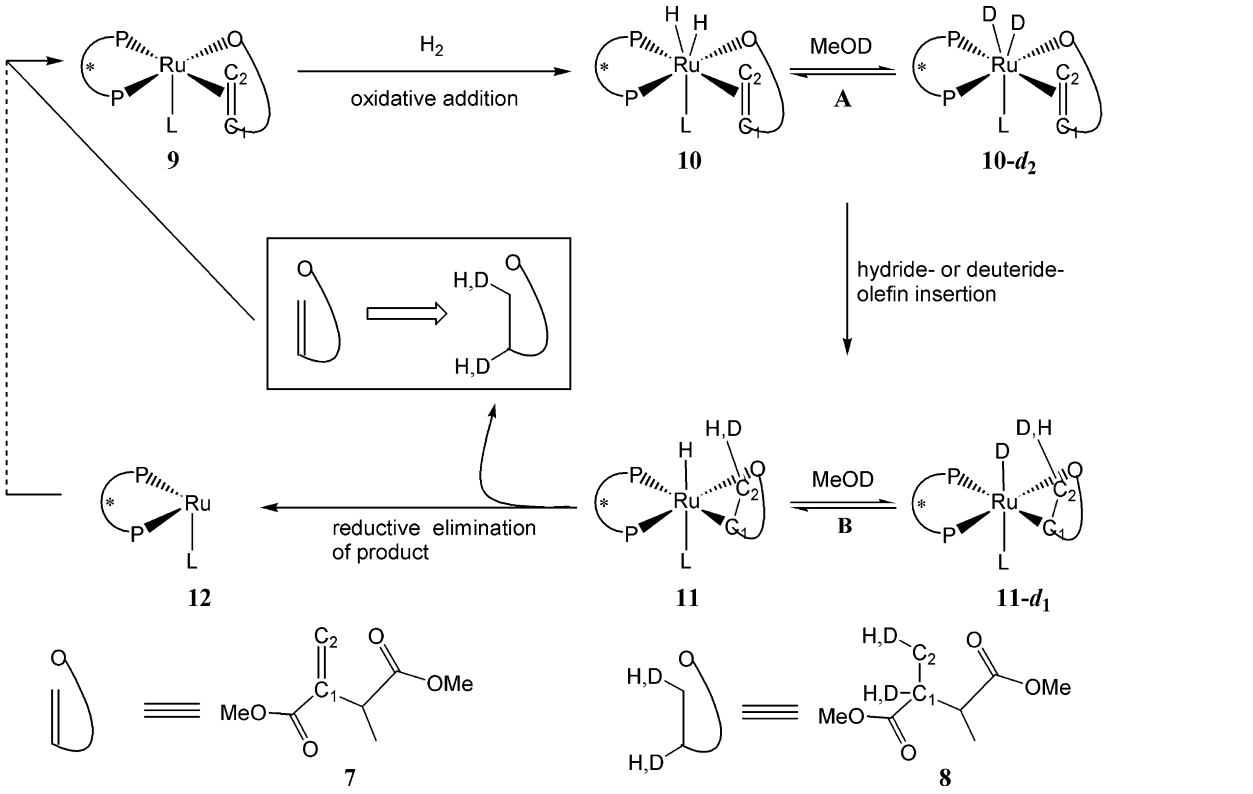


Scheme 1. Mechanism proposed by Halpern [5] for ruthenium bis(phosphine) catalyzed hydrogenation. Key steps are heterolytic cleavage of H_2, H–D exchange between **2** and solvent, and solvolysis to complete the catalytic cycle.

and tiglic acid by carboxylate ligand exchange to generate **1**; second, heterolytic cleavage of dihydrogen to generate the ruthenium monohydride species **2**; third, olefin-hydride insertion to generate the 5-membered heterometallacycle **3**; and fourth, protonolysis (solvolysis) of the Ru–C σ bond in **3** to complete the cycle. Use of methanol-d_4 as solvent resulted in significant deuterium incorporation at the β-carbon of the hydrogenation product, but little incorporation at the α-carbon. Halpern et al. thereby concluded that significant H–D exchange did not occur between the methanol-d_4 solvent and free H_2, in the presence of catalyst and also that the rate of H–D exchange between the monohydride species **2** and methanol-d_4 must also be slow relative to the rate of olefin-hydride insertion, i.e., Scheme 1: $k_3 \gg k_{-1}$ and k_2. Reports by Noyori [6], Achiwa [7], and Chan [8] have reaffirmed the overall proposed mechanism.

Brown et al. [9,10] reported that the catalytic hydrogenation of the α,β-unsaturated ester **7**, using a different ruthenium-bis(phosphine) catalyst than that used by Halpern and Noyori but under similar conditions (1 atm H_2, 25 °C, 24 h, methanol-d_4), resulted in essentially no deuterium incorporation into either the α- or β-positions of the hydrogenation product, dimethyl 2,3-dimethylsuccinate (**8**, Scheme 2). Brown thereby showed that solvolysis of a ruthenium–carbon σ bond does not occur during this catalytic hydrogenation, and he proposed a mechanism that involves oxidative addition, not heterolytic cleavage, of dihydrogen gas (Scheme 2). To account for the deuterium distributions observed by both his group and Halpern's, Brown proposed that H–D exchange with solvent can occur at two points in the catalytic cycle: before, or immediately following olefin-hydride insertion, Scheme 2: **A** and **B**, respectively. The rates of H–D exchange with solvent may or may not compete with the rates of olefin-hydride insertion and/or reductive elimination, depending on the nature of the catalyst and substrate used. Brown's mechanism thereby provides a rational for the H–D exchange observed by both groups.

As part of our ongoing efforts to elucidate the mechanism of chirality transfer during enantioselective hydrogenation, we set out to clarify the mechanism of hydrogenation of α,β-unsaturated acids and esters using the same catalyst for a variety of studies. We previously reported on the enantioselective hydrogenation mechanisms of α,β-unsaturated esters [12–15], (i.e., (*Z*)-methyl α-acetamidocinnamate (MAC, **13**) [13–15], and methyl α-acetamidoacrylate (MAA, **14**) [12]) and ketones (i.e., dialkyl 3,3-dimethyloxaloacetate) [11] using [Ru((*R*)-



Scheme 2. Brown [9] mechanism for ruthenium bis(phosphine) catalyzed hydrogenation. Predominant exchange process at step B for ruthenium bis(phosphine) reductions of α,β-unsaturated acids. Predominant exchange process at step A for ruthenium bis(phosphine) reductions of α,β-unsaturated esters.

BINAP)(H)(MeCN)$_n$(sol)$_{3-n}$]BF$_4$ (**15**: $n = 0$–3, sol = solvent used in reaction) [16] as the active catalyst.[1] We now report the mechanistic changes between hydrogenations of the α,β-unsaturated tiglic (**5**), and angelic (**16**) acids, as compared to the α,β-unsaturated esters dimethyl itaconate (**17**), MAC (**13**), and MAA (**14**), all with **15** as the active catalyst. In addition, solvent effects are described. We also disclose the isolation and characterization of the putative catalytic intermediates observed during the hydrogenation of dimethyl itaconate, namely [Ru((*R*)-BINAP)(MeCN)-((*R*)- and (*S*)-C[CH$_3$][CO$_2$CH$_3$]-[CH$_2$CO$_2$CH$_3$])](BF$_4$) (**32a** and **32b**).

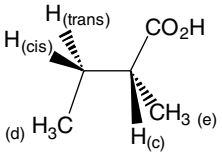
2. Results and discussion

2.1. Ruthenium-BINAP catalyzed enantioselective hydrogenation of α,β-unsaturated carboxylic acids

Table 1 compares the results of the deuterium-labeling studies of Takaya and Noyori where [Ru((*R*)-BINAP)(κ^2-O$_2$CCH$_3$)$_2$] (**19**) [17] was used as catalyst with our results using **15** as catalyst. Use of **15** as catalyst resulted in a greater degree of deuterium scrambling in 2-methylbutyric acid (**6**) than that reported by Halpern, Takaya, and Noyori. Under 3 atm of H$_2$ in methanol-d_4 solution, tiglic acid was hydrogenated to yield **6** in 90% ee (*R*), with an abundance of deuterium located at both the α-(H$_c$) and the β-(H$_{cis}$) positions. The reaction performed under 3 atm of D$_2$ in methanol solution showed the expected reversal of deuterium incorporation.

The mechanism proposed by Halpern et al. can account for these results if H–D exchange with the solvent occurs at

Table 1
Pattern of deuterium incorporation in tiglic acid (**5**) hydrogenation catalyzed by **15** and **19** under various conditions



Catalyst, conditions[a]	Percent deuterium incorporation				
	H_{cis}	H_{trans}	H_c	H_d	H_e
15 (H$_2$, CD$_3$OD)	85		70		
15 (D$_2$, CH$_3$OH)	8		33		
19[b] (H$_2$, CD$_3$OD)	100		30		
19[b] (D$_2$, CH$_3$OH)	5		85		

[a] *Reaction conditions.* Catalyst **15**, 4 atm pressure, ambient temperature, catalyst **19**, 3 atm gas pressure, ambient temperature.
[b] Reported by Takaya and Noyori [6].

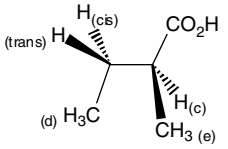
[1] **15** is efficient catalyst precursor for enantioselective hydrogenation of α,β-unsaturated carboxylic acids and ester derivatives, and is comparable in efficiency to other ruthenium-BINAP catalyst systems reported.

either of two stages. The first possibility is if the rate of H–D exchange between the solvent and H_2 gas is comparable to the rate of olefin hydride insertion (i.e., Scheme 1, k_{-1} is comparable to k_3). We note, however, that unlike **19**, **15** does not catalyze the H–D exchange between H_2 and methanol-d_4 in the absence of added substrate [14] (i.e., $k_{-1} = 0$). This possibility is thereby unlikely. The second possibility is if the rate of H–D exchange between solvent and a species such as **2**, Scheme 1 is comparable to the rate of olefin-hydride insertion. Thus to account for the observed exchange pattern, the Halpern mechanism requires that a complex formed from the heterolytic cleavage of H_2 gas (such as **21**, Scheme 3) undergoes H–D exchange with the solvent. Studies on the hydrogenation of the thermodynamically less stable isomer of tiglic acid, angelic acid (**16**) [18], were carried out to provide further evidence for this sequence.

Hydrogenation of **16** (Table 2) under 3 atm of H_2 in methanol-d_4 solution resulted in deuterium incorporation at the β-position ($H_{cis} = 62\%$), the α-position ($H_c = 43\%$), the other β-position ($H_{trans} = 8\%$), and the β-methyl position ($H_d = 43\%$, assuming CH_2D). The hydrogenation performed under 3 atm of D_2 in methanol solution resulted in little-to-moderate deuterium incorporation at either the α-position ($H_c = 30\%$) or the β-position ($H_{cis} = 7\%$). Small amounts of deuterium incorporation also occurred, however, at the other β-position ($H_{trans} = 8\%$) and at the β-methyl position ($H_d = 5\%$, assuming CH_2D).

While deuterium is scrambled more when using **15** than **19** as catalyst, the results of the labeling studies of tiglic (**5**) and angelic (**16**) acids in methanol solution supports a mechanism like Halpern's with both the heterolytic cleavage of H_2 and a 5-membered heterometallocycle intermediate as shown in Scheme 3.

Table 2
Pattern of deuterium incorporation in angelic acid (**16**) hydrogenation catalyzed by **15** as catalyst under various conditions

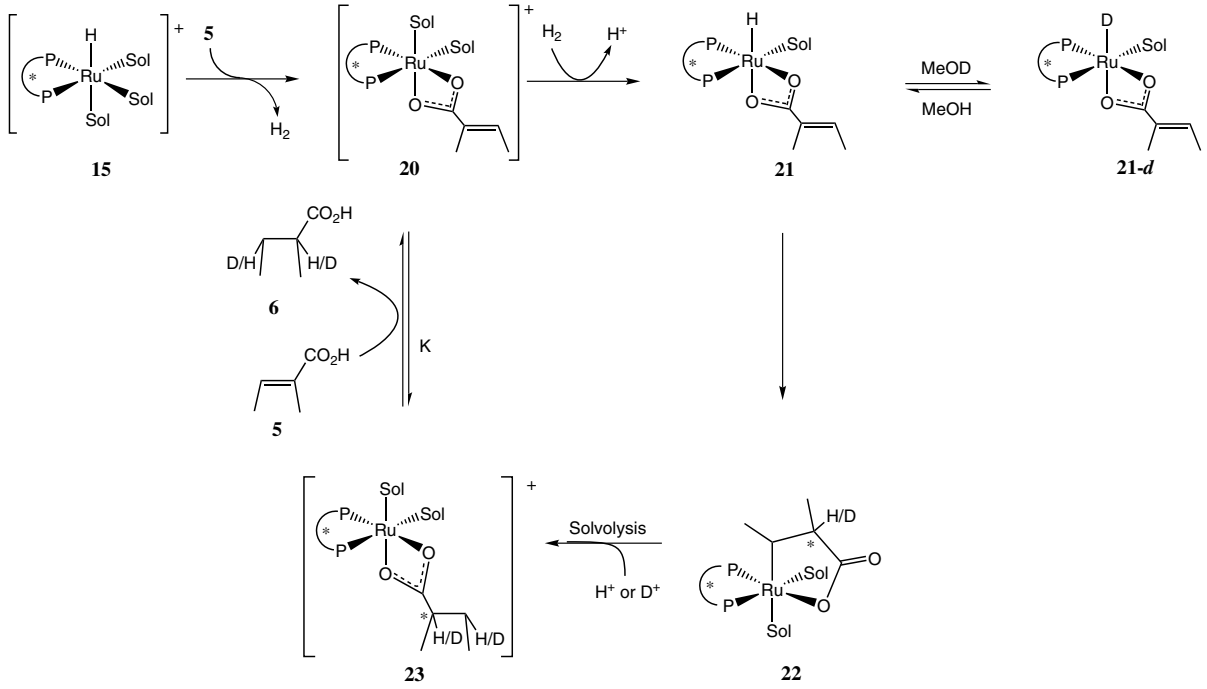


Catalyst, conditions[a]	Percent deuterium incorporation				
	H_{cis}	H_{trans}	H_c	H_d	H_e
15 (H_2, CD_3OD)	8	62	43	43	
15 (D_2, CH_3OH)	5	8	30	5	

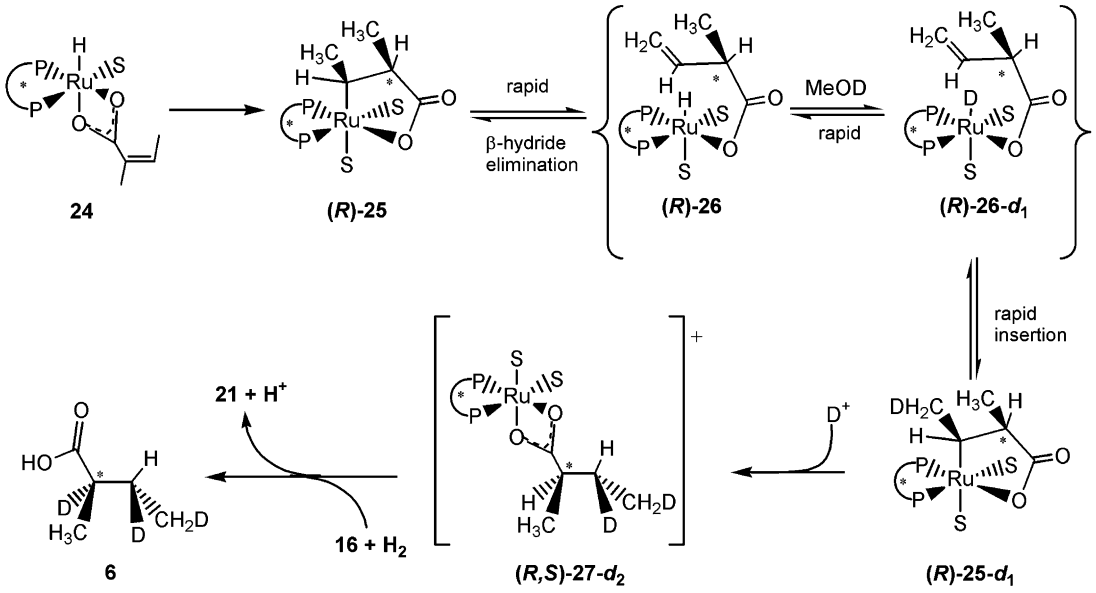
[a] *Reaction conditions.* [Ru] = 2.6 mM, 3 atm gas pressure, ambient temperature.

In this modification of the Halpern mechanism, the catalyst **15** enters the catalytic cycle by reaction with substrate to generate the carboxylate compound **20** and dihydrogen (vide infra). Heterolytic cleavage of H_2 results in formation of the hydride **21**, and rapid H–D exchange between **21** and methanol-d_4 leads to **21**-*d*. Olefin-hydride or -deuteride insertion leads to the 5-membered metallacycle **22**, and solvolysis of the ruthenium–carbon σ bond leads to **23**.

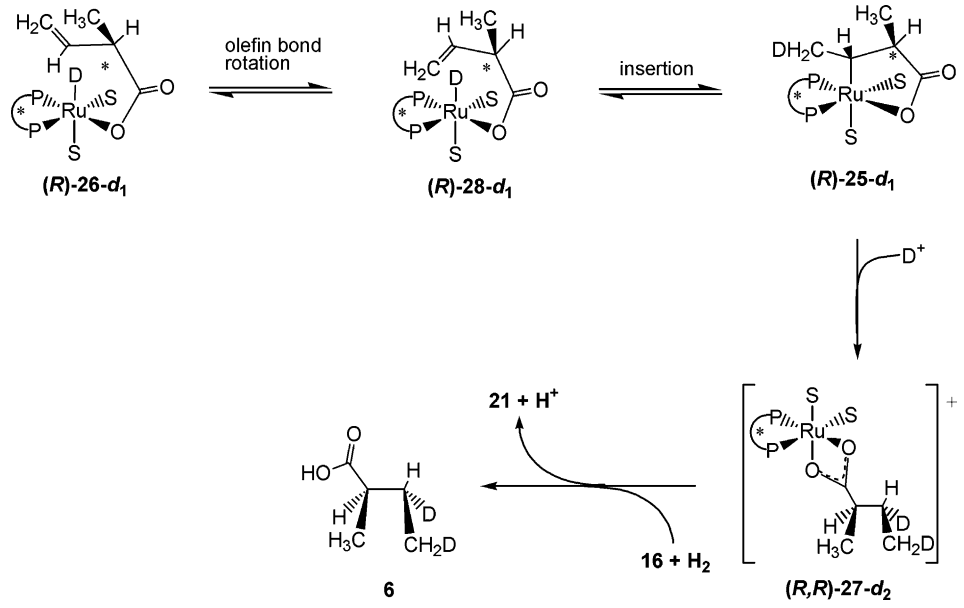
The existence of 5-membered heterometallacycle intermediates is supported by the deuterium-labeling studies with angelic acid (**16**) via the sequence of steps shown in Schemes 4 and 5. Heterolytic cleavage of dihydrogen leads



Scheme 3. Proposed catalytic cycle for the hydrogenation of α,β-unsaturated acids using **15** as catalyst. This cycle is proposed to be generic for ruthenium bis(phosphine) catalysts.



Scheme 4. Proposed mechanism to account for deuterium incorporation at H_a, H_{trans}, and H_d observed in angelic acid (**16**) hydrogenation with **15** as catalyst.



Scheme 5. Proposed mechanism to account for deuterium incorporation at H_a, H_{cis}, and H_d observed in angelic acid (**16**) hydrogenation with **15** as catalyst.

to the species **24** (Scheme 4). From this intermediate, olefin-hydride insertion can occur through the *si*-face to form the 5-membered metallacycle (*R*)-**25**.[2] This species can undergo β-deuteride elimination from either the α-position (H_a) or the β-methyl group (H_d). The removal of the deuteride at the α-position (H_a) is a moot issue as it is the reverse reaction of the olefin-deuteride insertion. Hydride abstraction from the β-methyl group (H_d) will produce (*R*)-**26**. H–D exchange with solvent would yield the deuteride (*R*)-**26**-d_1, that then undergoes insertion to form (*R*)-**25**-d_1, with deuterium now located at the β-methyl position (H_d) as observed (Scheme 4). Solvolysis of the ruthenium–carbon σ bond in (*R*)-**25**-d_1, followed by ligand exchange with **16** completes the catalytic cycle. We propose a net isomerization of the C=C bond during the sequence of steps shown in Scheme 4. Double bond isomerizations during a catalytic transformation has precedent with a number

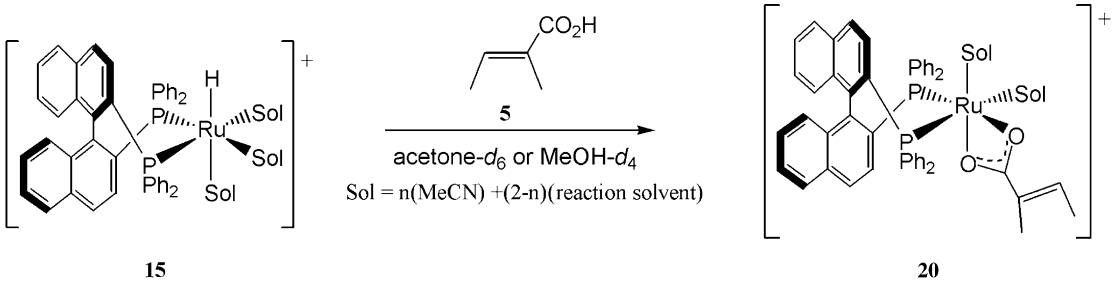
[2] Defined as *R* configuration assuming replacement of ruthenium atom by hydrogen atom as in final hydrogenation product.

of ruthenium bis(phosphine) catalysts [19].[3] Isomerization of the C=C bond of angelic acid (**16**) is not surprising as its geometric isomer, tiglic acid (**5**), is thermodynamically more stable [18]. Rapid, prior isomerization of angelic acid to tiglic acid during this catalytic hydrogenation does not go to completion, however, as the hydrogenation of angelic acid proceeds with 46% ee (*S*), while the hydrogenation of tiglic acid proceeds with 90% ee (*R*).[4] These hydrogenations would both occur with the same ee if they proceeded through a common intermediate formed via olefin isomerization.

Scheme 5 shows how deuterium incorporation into the β-methyl group can occur from (*R*)-**26**-d_1. (*R*)-**26**-d_1 can undergo C_α–C_β bond rotation to form (*R*)-**28**-d_1. Olefin-deuteride insertion would form the 5-membered heterometallacycle (*R*)-**25**-d_1, with deuterium incorporation into the β-methyl group (H_d) (Scheme 5). Solvolysis, followed by exchange between the hydrogenated substrate (**6**) and **16** complete the catalytic cycle.

While these isotope substitution patterns do not discount Brown's mechanism, we point out that should the reaction proceed with dihydrogen oxidative addition followed by insertion and reductive elimination, as Brown's mechanism would require, one would not expect the use of aprotic solvents to suppress the reaction. Indeed, the hydrogenation of tiglic acid (**5**) was extremely slow in the aprotic solvent acetone, yielding less than 10% conversion to **6** under the same conditions that gave 100% conversion in methanol (4 atm H_2, 25 °C, 20 h). This observation favors a mechanism similar to Halpern's that involves solvolysis of a ruthenium–carbon σ bond, and not a mechanism that involves H_2 oxidative addition followed by reductive elimination. Further, the hydrogenation of **5** in acetone did proceed in good rates to completion in the presence of one equivalent of triethylamine per substrate acid group (4 atm H_2, 25 °C, acetone; NEt_3:**5** = 1:1, 95% ee (*R*)). That this base is required for activity in an aprotic solvent suggests that the role of triethylamine is to act as proton scavenger during the heterolytic cleavage of dihydrogen. The role of the conjugate acid Et_3NH^+ is then likely to act as a proton source for protonolysis of the ruthenium–carbon σ bond.

In a previous report, we showed that the stoichiometric reaction between tiglic acid (**5**) and **15** in acetone proceeds by immediate protonolysis of the Ru–H bond with formation of the Ru–tiglato complex **20** (Eq. (1)) [20]. The stoichiometric reaction between the deuteride **15**-*d*, prepared by reaction between **15** and D_2, and tiglic acid also forms the Ru–tiglato complex (**20**), along with an equivalent of H–D. The reaction between tiglic acid and one equivalent of triethylamine in acetone solution, followed by reaction with one equivalent of **15** also yields **20** as shown by ^1H and ^{31}P NMR.[5] Further, reaction between **15** and tiglic acid yields **20** in the protic solvent methanol. And finally, **20** is the only ruthenium complex detected on NMR analysis of the catalytic reactions (in all cases). These data are strong evidence that the active catalyst is **20** under these conditions.



15 **20** (1)

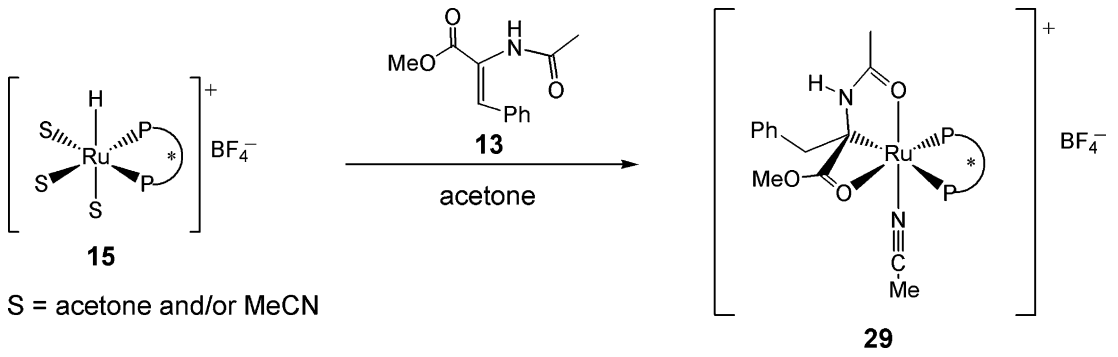
2.2. Ruthenium-BINAP catalyzed enantioselective hydrogenation of α,β-unsaturated carboxylic esters

The above observations strongly support the general Halpern mechanism (Scheme 1) for α,β-carboxylic acids. We now discuss the mechanistic results we have obtained using esters as substrates. In previous reports, we showed that the mechanistic pathway operating with **15** as catalyst for the hydrogenation of the α,β-carboxylic esters MAC (**13**) [13–15] and MAA (**14**) [12] is different from the Halpern mechanism. MAC is hydrogenated by **15** with 92% ee (*R*) in acetone and with 87% ee (*R*) in methanol solvents

[3] Examples of isomerizations of olefinic substrates: Wiles et al. [16]; Saburi et al. [10].

[4] In contrast, the products of hydrogenation of (*Z*)- and (*E*)-MAC (**13**) were formed in similar ee (and formation of the same major enantiomer, *R*), implying that the hydrogenation of the thermodynamically less favored isomer (*E*)-MAC proceeds via a rapid prior isomerization to (*Z*)-MAC. See [13] for details.

[5] It is postulated that the coordination geometry about the ruthenium center is in the Δ configuration on the basis of the X-ray structures and steric arguments previously reported for the related complexes Ru((*R*)-BINAP)$(O_2CCMe{=}CHMe)_2$ and Ru((*S*)-BINAP)$(O_2CC(Me)_3)_2$. It is believed that the relative configuration of the phenyl rings on the phosphines of the BINAP ligand impose a steric environment that preferentially coordinates the tiglato ligands in a Δ configuration for (*R*)-BINAP and a Λ configuration for (*S*)-BINAP complexes.



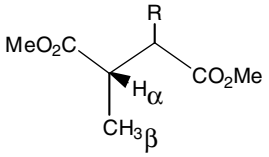
Scheme 6. Structural identification of catalytic intermediate (**29**) in ruthenium-BINAP catalyzed enantioselective hydrogenation of MAC (**13**).

[20,21]. Use of MeOH-d_4 did not result in significant amounts of deuterium labeling of the product, showing the mechanism did not involve solvolysis of a ruthenium–carbon σ bond.

For these hydrogenations, only one ruthenium species was observed in ^{31}P NMR spectroscopic studies of the operating catalytic reaction. The stoichiometric reaction of [Ru((*R*)-BINAP)(H)(Sol)$_n$(MeCN)$_{3-n}$](BF$_4$) ($n = 0$–3; Sol = acetone, **15**) and MAC resulted in a single species with identical NMR characteristics to those of the species observed in the operating catalytic reaction. Isolation and complete identification (NMR spectroscopic and X-ray crystallographic analyses) showed it to be the single diastereomer (RuMAC; **29**) formed via olefin-hydride insertion into the Ru–H bond (Scheme 6) [13–15]. Similar results were observed with MAA [12] as substrate, except that the stoichiometric reaction of **15** with MAA results in two diastereomers in 72:28 ratio. Isolation and complete identification (solution NMR spectroscopic and X-ray crystallographic analyses) of the major diastereomer (RuMAA; **30**) [12] showed the insertion to have occurred from the same face as with RuMAC (**29**) [15]. For both these substrates then, olefin-hydride insertion positions the hydride at the β-position, not at the α-position as observed with tiglic, angelic, and other α,β-unsaturated carboxylic acid substrates. Also the major diastereomer formed upon stoichiometric reaction with **15** and both these substrates corresponded to the major enantiomers formed by the catalytic hydrogenation. These results, with others obtained previously, showed that the hydrogenations of MAC and MAA proceed via reaction of **15** and substrate to make an olefin adduct, olefin-hydride insertion to make the ruthenium-alkyl complexes **29** and **30**, followed by hydrogenolysis of the ruthenium–carbon σ bonds in **29** and **30** to complete the hydrogenations and regenerate **15**. This mechanism more closely resembles that proposed by Brown than Halpern's.

We investigated the mechanism for hydrogenation of the diester dimethyl itaconate (DMI; **17**) with the catalyst **15** because DMI has the same distribution of carbonyl and olefin groups as MAC (**13**), MAA (**14**), and Brown's substrate (**7**). DMI is hydrogenated in 95% ee (*S*) in both methanol or acetone solution using **15** as catalyst [20].

Table 3
Deuterium incorporation in hydrogenation of **7** and DMI (**17**) with **31** (Brown's catalyst) and **15** as catalyst, respectively



8 R = CH$_3$ **18** R = H

Catalyst, conditions, substrate[a]	H_α	H_β
15, (H_2, MeOD), **17**	30	–
15, (D_2, MeOH), **17**	65	80
31, (H_2, MeOD), **7**	10	10
31, (D_2, MeOH), **7**	70	60

[a] *Reaction conditions*. Catalyst **15**, [Ru] = 2.6 mM, 3 atm gas pressure, ambient temperature. Catalyst **31** (Brown; Ru(BINAP)(η^2-MeC(O)CH-C(O)Me)$_2$(η^2-allyl)), 1 atm gas pressure, ambient temperature.

Deuterium-labeling studies were performed and the results are listed in Table 3 along with the proton assignments. Under 3 atm of dihydrogen gas at 25 °C in methanol-d_4, deuterium incorporation occurred solely and to 30% extend at H_α of the product **18**. Under 3 atm of dideuterium gas at 25 °C in methanol, the deuterium incorporation was largely reversed, with deuterium at H_α (~65%) and at H_β (~80%, assuming formation of CH_2D) [22]. These results are in agreement with those observed by Brown, where significant deuterium incorporation from dideuterium gas is found at both the α-position (H_α) (Brown: 70% D; here: 65% D) and β-methyl position (H_β) (Brown: 60%; here: 80%) [22].

^{31}P NMR analysis of the operating catalytic hydrogenation of DMI (**17**) showed the presence of only two species in detectable quantities. Further, the stoichiometric reaction of DMI with **15** yielded the same two species, with ^{31}P NMR spectra consistent with those observed with the catalytic hydrogenation. Analysis of these NMR data along with comparison to those of RuMAC (**29**) and RuMAA (**30**) allows identification of these species as the olefin-hydride inserted diastereomers **32a** and **32b**. Fig. 1 depicts the major isomer; **32a** with is structurally analogous to RuMAC (**29**) and RuMAA (**30**).

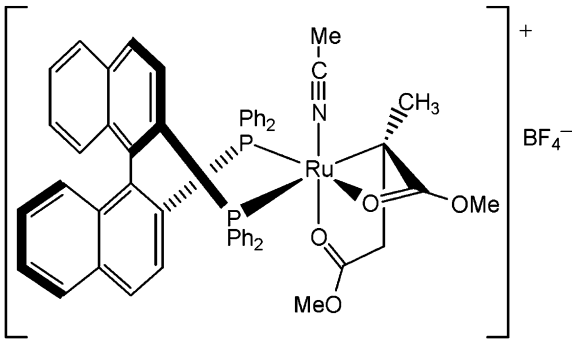


Fig. 1. Isolation and structural identification of putative catalytic intermediate (major species **32a**) in ruthenium bis(phosphine) catalyzed enantioselective hydrogenation of **17**.

The stoichiometric hydrogenolysis of the ruthenium–carbon σ bonds in the mixture of diastereomers **32a** and **32b** produced the hydrogenation product, **18**, in 92% ee (*S*). This stoichiometric ee is nearly identical to the catalytic ee obtained with the hydrogenation of DMI, 95% ee (*S*). We observed the same similarities between the stoichiometric and catalytic ee's for the analogous ruthenium-alkyl intermediates RuMAC (**29**) and RuMAA (**30**). These investigations have thus yielded results that largely parallel those we obtained previously with the hydrogenations of MAC and MAA. These results are thereby strong evidence that **32a** and **32b** are intermediates in the catalytic hydrogenation of DMI, and that the hydrogenation of DMI proceeds by the same mechanism as MAC and MAA. Not by the mechanism proposed by Halpern.[6]

3. Conclusion

The mechanism of the ruthenium bis(phosphine) catalyzed enantioselective hydrogenation of olefins has been complicated by discrepancies in deuterium-labeling studies reported in the literature for various substrates. Here, we have shown that two mechanisms can account for the observed differences. In each case, 5-membered metallocycle intermediates are formed via olefin-hydride insertions. However, the nature of the substrate affects the choice of mechanistic pathway utilized primarily in the activation of dihydrogen. α,β-Unsaturated acids, are prone to proceed with heterolytic cleavage of dihydrogen gas while the α,β-unsaturated esters are prone to proceed with homolytic cleavage of dihydrogen gas. The favored pathway may result from electronic factors, from the disposition of the functional group in the substrate, or from a combination of both. A complete investigation using a wide variety of olefins must be performed in order to determine which factors prejudice which mechanistic pathway.

[6] The 5-membered metalloheterocycle is formed from the substrate C_1 through to the β-carbonyl (amido carbonyl of MAC and MAA) of dimethyl itaconate. The 4-membered metalloheterocycle is formed from the C_1 through to the α-ketone carbonyl.

4. Experimental

4.1. Methods and materials

The solvents tetrahydrofuran (K, Ph_2CO), diethyl ether (K, Ph_2CO), triethylamine (CaH_2), acetone (3 Å sieves), and methanol (Mg) were distilled from drying agents under argon gas. The argon and dinitrogen gases were passed through a bed of Drierite drying agent. Unless stated otherwise, commercial reagents were used without further purification, except dimethyl itaconate (distilled under argon atmosphere), and all operations were performed under an inert atmosphere of argon or dinitrogen gas. The compounds [Ru((*R*)-BINAP)(1-3;5,6-η-C_8H_{11})(MeCN)][BF_4] (**33**)[7] and angelic acid (**16**) [23] were synthesized via the literature procedures.

All ^1H, ^{13}C, and ^{31}P NMR spectra were measured with a Bruker AM-400 NMR spectrometer operating at 400.13, 100.61, and 161.97 MHz, respectively. ^1H and ^{13}C NMR chemical shifts are reported in parts per million (δ) relative to tetramethylsilane using the solvent as an internal reference. ^{31}P NMR chemical shifts are reported in parts per million (δ) relative to an 85% H_3PO_4 external reference. All ^{13}C and ^{31}P NMR spectra are ^1H decoupled unless stated otherwise. Mass spectra were measured using Kratos MS50. Microanalyses were performed at the University of Alberta Microanalysis Laboratory. Optical rotations were measured with a Perkin–Elmer 241 polarimeter at 589 nm (sodium D line) using 1.0 dm cells. Specific rotations, $[\alpha]_D$, are reported in degrees per decimeter at 25 °C, and the concentration (c) is given in grams per 100 mL.

4.2. Hydrogenations of tiglic acid (*5*) with D_2 in methanol or H_2 in methanol-d_4 using *33* as catalyst precursor

The catalyst precursor **33** (10.0 mg, 1.04×10^{-5} mol) was transferred to a glass bomb along with 100 equiv of tiglic acid (**5**) (104.1 mg, 1.04×10^{-3} mol) in the glove box. The dry, deoxygenated methanol, or methanol-d_4, was then added (4.0 mL) and the solution was stirred for 5 min. The atmosphere was then flushed with dihydrogen gas, or dideuterium gas, and once flushed the bomb was sealed under 3 atm of dihydrogen or dideuterium. The solution was stirred for 20 h at 25 °C to complete hydrogenation. Once completed, the solvent was removed under reduced pressure, and the product was dissolved in CH_2Cl_2 and passed through a Florisil plug to remove the catalyst. The solvent was then removed under reduced pressure and the product analyzed by NMR.

Residue from hydrogenation with H_2 in methanol-d_4: ^1H (400.1 MHz, acetone-d_6): δ 0.9('d', H_d, 0% D incorp.), 1.10 ('s', H_e, 0% D incorp.), 1.43 (m, H_{trans}, 0% D incorp.), 1.62 (m, H_{cis}, 85% D incorp.), 2.34 (m, H_c, 70.5% D incorp.), 10.45 (br s, H_{acid}).

[7] Examples of isomerizations of olefinic substrates: Wiles et al. [16].

Residue from hydrogenation with D_2 in methanol: ^1H (400.1 MHz, acetone-d_6): δ 0.9 ('t', H_d, 0% D incorp.), 1.10 ('d', H_e, 0% D incorp.), 1.43 (m, H_{trans}, 0% D incorp.), 1.62 (m, H_{cis}, 7.5% D incorp.), 2.34 (m, H_c, 33% D incorp.), 10.45 (br s, H_{acid}).

4.3. Hydrogenations of angelic acid (16) with D_2 in methanol or H_2 in methanol-d_4 using 33 as catalyst precursor

The catalyst precursor **33** (12.0 mg, 1.25×10^{-5} mol) was transferred to a glass bomb along with 100 equiv of angelic acid (**16**) (125.5 mg, 1.25×10^{-3} mol). The dry, deoxygenated methanol, or methanol-d_4, was then added (4.8 mL) and the solution was stirred for 5 min. The atmosphere was then flushed with dihydrogen gas, or dideuterium gas, and once flushed the bomb was sealed under 3 atm of dihydrogen or dideuterium. The solution was stirred for 20 h at 25 °C to complete hydrogenation. Once completed, the solvent was removed under reduced pressure, and the product was dissolved in CH_2Cl_2 and passed through a Florisil plug to remove the catalyst. The solvent was then removed under reduced pressure and the product analyzed by NMR.

Residue from hydrogenation with H_2 in methanol-d_4: ^1H (400.1 MHz, acetone-d_6): δ 0.9 ('d', H_d, 43% D incorp.), 1.10 ('s', H_e, 0% D incorp.), 1.43 (m, H_{trans}, 62% D incorp.), 1.62 (m, H_{cis}, 8% D incorp.), 2.34 (m, H_c, 43% D incorp.), 10.45 (br s, H_{acid}).

Residue from hydrogenation with D_2 in methanol: ^1H (400.1 MHz, acetone-d_6): δ 0.9 ('d', H_d, 5% D incorp.), 1.10 ('s', H_e, 0% D incorp.), 1.43 (m, H_{trans}, 7.5% D incorp.), 1.62 (m, H_{cis}, 5% D incorp.), 2.34 (m, H_c, 30% D incorp.), 10.45 (br s, H_{acid}).

4.4. Stoichiometric reaction of [Ru((R)-BINAP)(H)$(MeCN)_n(Sol)_{3-n}$](BF4) (n = 0–3) with tiglic acid and 1 equivalent of NEt_3 in acetone-d_6

Compound **33** (20.0 mg, 2.09×10^{-5} mol) was partially dissolved in acetone-d_6 (~0.6 mL) in an NMR tube under an argon atmosphere. At room temperature, the tube was flushed with H_2, pressurized (1-2 atm), and shaken until a deep orange-yellow solution was generated (~5 min). The H_2 atmosphere was replaced by argon gas and the solution was then transferred to an NMR tube containing tiglic acid (2.1 mg, 2.09×10^{-5} mol) and NEt_3 (2.9 μL, 2.1 mg, 2.09×10^{-5} mol) in acetone-d_6 (0.2 mL) under an argon atmosphere. To this solution was added excess CD_3CN (2.0 μL, 3.83×10^{-5} mol) via a gas-tight syringe. The solution was immediately analyzed by ^1H NMR. The product was found to be identical to that formed upon stoichiometric reaction of tiglic acid with **15** in the absence of added NEt_3 in acetone solution. The product readily loses MeCN in vacuo. NMR spectroscopic data of the complex: ^1H (400.1 MHz, acetone-d_6): δ 1.45 (apparent t, $CH_3CHC(CH_3)CO_2Ru$, $^4J_{H-H} = 1.5$ Hz, $^5J_{H-H} = 1.2$ Hz), 1.56 (dd, $CH_3CHC(CH_3)CO_2Ru$, $^3J_{H-H} = 7.2$ Hz, $^5J_{H-H} = 1.2$ Hz), 2.01 (s, CH_3CN), 2.03 (s, CH_3CN), 6.45 (dq, $CH_3CHC(CH_3)CO_2Ru$, $^3J_{H-H} = 7.2$ Hz, $^4J_{H-H} = 1.5$ Hz), 6.58–7.89 (m, 32 H, BINAP). ^{31}P (161.9 MHz, acetone-d_6): δ 52.6 (dd, $^2J_{P-P} = 37.5$ Hz), 56.9 (d, $^2J_{P-P} = 37.5$ Hz). ^{13}C (100.6 MHz, acetone-d_6): δ 2.4 (CH_3CN), 4.65 (CH_3CN), 10.72 and 13.90 ($CH_3CHC(CH_3)CO_2Ru$), 123.99 (CH_3CN), 124.14 (CH_3CN), 124.42–141.45 (BINAP and $CH_3CHC(CH_3)CO_2Ru$), 185.46 ($CH_3CHC(CH_3)CO_2Ru$).

4.5. Stoichiometric reaction of [Ru((R)-BINAP)(H)$(MeCN)_n(Sol)_{3-n}$](BF4) (n = 0–3) with tiglic acid in methanol-d_4

Compound **33** (20.0 mg, 2.09×10^{-5} mol) was partially dissolved in methanol-d_4 (~0.8 mL) in an NMR tube under an argon atmosphere. At room temperature, the tube was flushed with H_2, pressurized (1–2 atm), and shaken until a deep orange-yellow solution was generated (~5 min). The H_2 atmosphere was replaced by argon gas and the solution was then transferred to an NMR tube containing tiglic acid (2.10 mg, 2.09×10^{-5} mol) under an argon atmosphere. To this solution was added excess CD_3CN (2.0 μL, 3.83×10^{-5} mol) via a gas-tight syringe. The solution was immediately analyzed by ^1H NMR. The product was found to be identical to that formed upon stoichiometric reaction of tiglic acid with **15** in acetone solution.

4.6. Hydrogenations of dimethyl itaconate (17) with D_2 in methanol or H_2 in methanol-d_4 using 15 as catalyst

The catalyst precursor **33** (11.5 mg, 1.20×10^{-5} mol) was transferred to a glass bomb along with 75 equiv of dimethyl itaconate **17** (126 μL, 9.00×10^{-4} mol) via gas-tight syringe. The methanol, or methanol-d_4, was then added (4.6 mL) and the solution was stirred for 5 min. The atmosphere was then flushed with dihydrogen gas, or dideuterium gas, and once flushed the bomb was sealed under 3 atm of dihydrogen or dideuterium. The solution was stirred for 20 h at 25 °C to complete hydrogenation. Once completed, the solvent was removed under reduced pressure, and the product was dissolved in CH_2Cl_2 and passed through a Florisil plug to remove the catalyst. The solvent was then removed under reduced pressure and the product analyzed by NMR.

Residue from hydrogenation with H_2 in methanol-d_4: ^1H (400.1 MHz, CD_2Cl_2): δ 1.18 (d, H_β, 0% D incorp.), 2.46 (dd, 0% D incorp.), 2.68 (dd, 0% D incorp.), 2.88 (m, H_α, 30% D incorp.), 3.62 (s, OCH_3, 0% D incorp.), 3.63 (s, OCH_3, 0% D incorp.).

Residue from hydrogenation with D_2 in methanol: ^1H (400.1 MHz, CD_2Cl_2): δ 1.18 (d, H_β, 80% D incorp. assuming CH_2D), 2.46 (dd, 0% D incorp.), 2.68 (dd, 0% D incorp.), 2.88 (m, H_α, 65% D incorp.), 3.62 (s, OCH_3, 0% D incorp.), 3.63 (s, OCH_3, 0% D incorp.). Actual amounts

of product were determined by ^{13}C NMR chemical shifts based on reported assignments: **18** (5%), **18**-α-d_1 (15%), **18**-β-d_1 (30%), **18**-α,β-d_2 (50%).[15]

4.7. Synthesis of [Ru((R)-BINAP)(MeCN)-(C[CH$_3$][CO$_2$CH$_3$] [CH$_2$CO$_2$CH$_3$])](BF$_4$) (RuDMI; 32a/32b)

To a 50 mL solvent Schlenk flask was added **33** (102.2 mg, 1.07×10^{-4} mol). The Schlenk flask was placed under reduced pressure and purged with argon gas several times to remove traces of oxygen. To the Schlenk flask was added acetone (7.5 mL) via gas-tight syringe. The solution was stirred for 5 min then dihydrogen gas was bubbled through the solution until complete hydrogenation of **33** was achieved (2 min). The solution was then bubbled with argon gas to remove all traces of excess dihydrogen gas (5 min). Once all traces of dihydrogen gas were removed, dimethyl itaconate (**17**) was added (17.4 μL, 1.23×10^{-4} mol) via gas-tight syringe. The golden orange solution turned bright orange-yellow immediately. The flask was shaken for 5 min, then it was placed under reduced pressure to remove the solvent. The residue was dissolved in a minimal amount of acetone (~1.0 mL) and then precipitated out of solution with Et_2O (40 mL). The solution was filtered to dryness, the solid washed with Et_2O (3 × 10 mL), dried under a stream of argon gas (20 min), and finally dried under high vacuum overnight. The sample was then transferred to a vial and stored at −30 °C in the glove box: yield = 75.6 mg (70.2%). Attempts to obtain X-ray quality crystals by slow diffusion of a variety of solvents (CH_2Cl_2/Et_2O, CH_2Cl_2/pentane, CH_2Cl_2/*n*-Bu_2O, acetone/Et_2O, acetone/*n*-Bu_2O, MeOH/Et_2O, MeCN/Et_2O, benzene/Et_2O) were unsuccessful. ^1H NMR of major product (85%) (*R*)-**32a** (400 MHz, 25 °C, acetone-d_6): δ 0.56 (d, 1H, Ru-C(CH$_3$)(CO$_2$CH$_3$)(C*H*$_2$CO$_2$CH$_3$), $^2J_{H-H}$ = 19.5 Hz), 1.49 (d, 3H, RuC(C*H*$_3$)(CO$_2$CH$_3$)(CH$_2$CO$_2$CH$_3$), $^4J_{H-Pa}$ = 5.8 Hz), 1.95 (s, 3H, C*H*$_3$CN), 2.28 (dd, 1H, RuC(CH$_3$)(CO$_2$CH$_3$)(C*H*$_2$CO$_2$CH$_3$), $^2J_{H-H}$ = 19.5 Hz, $^4J_{H-Pa}$ = 6.0 Hz), 3.83 (s, 3H, OC*H*$_3$), 4.00 (s, 3H, OC*H*$_3$), 6.45–8.15 (m, 32H, BINAP, overlap with minor). ^{13}C (400 MHz, 25 °C, CD_2Cl_2): δ 4.6 (s, *C*H$_3$CN), 20.7 (s, RuC(*C*H$_3$)(CO$_2$CH$_3$)(CH$_2$CO$_2$CH$_3$)), 38.4 (dd, Ru*C*(CH$_3$)(CO$_2$CH$_3$)(CH$_2$CO$_2$CH$_3$), $^2J_{C-P}$ = 42.0 Hz, $^2J_{C-P}$ = 3.0 Hz), 40.8 (d, RuC(CH$_3$)(CO$_2$CH$_3$)(*C*H$_2$-CO$_2$CH$_3$), $^3J_{C-P}$ = 4.0 Hz), 52.8 (s, OCH$_3$), 55.8 (s, OCH$_3$), 126.4–142.8 (m, BINAP and CH$_3$*C*N), 167.2 (s, *C*O$_2$CH$_3$, $^3J_{C-P}$ = 3 Hz), 190.0 (d, *C*O$_2$CH$_3$, $^3J_{C-P}$ = 6.5 Hz). ^{31}P (MHz, 25 °C, acetone-d_6): δ 34.64 (d, 1P$_a$, $^2J_{P-P}$ = 21.5 Hz)*, 56.65 (d, 1P$_b$, $^2J_{P-P}$ = 21.5 Hz). Note, P$_a$ is *trans* to the Ru–C and P$_b$ is *cis* to the Ru–C. Complete identification of ^1H and ^{13}C of minor complex (15%, (*S*)-**32b**) could not be performed due to lack of concentration and overlap with major product signals. ^{31}P (MHz, 25 °C, acetone-d_6): δ 40.8 (d, $^2J_{P-P}$ = 36.5 Hz), 63.6 (d, $^2J_{P-P}$ = 36.5 Hz). ESIMS. Calc. for $C_{53}H_{46}O_4NP_2Ru$ $(M - BF_4)^+$: 924.194. Found: 924.1. *Anal.* Calc. for $C_{53}H_{46}O_4NP_2Ru$: C, 62.98; H, 4.59; N, 1.39. Found: C, 62.47; H, 4.67; N, 1.31%.

4.8. Stoichiometric hydrogenation of [Ru((R)-BINAP)-(MeCN)(C[CH$_2$(D)]-[CO$_2$CH$_3$][CH$_2$CO$_2$CH$_3$])]-(BF$_4$) (32a-d_1/32b-d_1)

To a glass bomb was added **32a**-d_1/**32b**-d_1 (100.8 mg, 9.96×10^{-5} mol), made exactly like **32a/32b** only with dideuterium gas replacing dihydrogen gas. The bomb was flushed with argon gas for 20 min to ensure no oxygen gas was present. To the bomb was added acetone (7.5 mL) via gas-tight syringe. The bomb was then flushed with dihydrogen gas for 2 min, then it was sealed under 4 atm of dihydrogen gas. The reaction was stirred at room temperature for 10 min and then the bomb was depressurized. The solution was transferred to a flask and the solvent was removed under reduced pressure. The residue was then dissolved in CH_2Cl_2 (0.2 ml) and passed through a Florisil plug with Et_2O (~5 mL) to remove the catalyst. NMR analysis showed complete conversion to dimethyl methylsuccinate in 93% ee (*S*), with D–H exchange (~35%) occurring at the β-methyl position corresponding to reversibility of formation of **32a/32b** on time-scale of irreversible hydrogenolysis of Ru–C$_\alpha$ bond. Similar reversibility was observed in the studies with **14** as substrate and **15** as catalyst.

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