The First Structure Determination of a Diastereomeric Hydrido−Olefin Putative Intermediate in Catalytic Enantioselective Hydrogenation

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The active catalyst [Ru((*R*)-BINAP)(H)(MeCN)$_n$(THF)$_{3-n}$](BF$_4$) (**2**; $n = 0-2$) is generated by hydrogenation (1 atm of H_2, 25 °C, 5 min) of the catalyst precursor [Ru((*R*)-BINAP)(MeCN)(1−3:5,6-η-C_8H_{11})](BF$_4$) (**3**) in THF. NMR spectra recorded at −40 °C in THF-d_8 show that the active catalyst exists as a mixture of [Ru((*R*)-BINAP)(H)(MeCN)(THF-d_8)$_2$](BF$_4$) (**4**; ≈50%), [Ru((*R*)-BINAP)(H)(MeCN)$_2$(THF-d_8)](BF$_4$) (**5**; ≈25%), and [Ru((*R*)-BINAP)(H)(THF-d_8)$_3$](BF$_4$) (**6**; ≈25%). These complexes rapidly exchange MeCN and THF at room temperature. Reaction of the catalyst system **2** with 1 equiv of the substrate (*Z*)-methyl α-acetamidocinnamate (MAC) in THF-d_8 at −40 °C over 1 h forms the diastereomeric catalyst−olefin adduct [Ru((*R*)-BINAP)(H)(MAC)(MeCN)](BF$_4$) (*si*-**7**) as the major product. The structure and absolute configuration of the hydrido−olefin transient *si*-**7** were unambiguously determined by low-temperature NMR methods. Complex *si*-**7** undergoes first-order olefin−hydride insertion to directly generate [Ru((*R*)-BINAP)((*S*)-MACH)(MeCN)](BF$_4$) (**1**; $t_{1/2} \approx 110$ min at −20 °C, corresponding to $k \approx 1.0 \times 10^{-4}$ s^{-1}). Complexes *si*-**7** and **1** both have the same absolute configuration as the major product enantiomer ((*R*)-*N*-acetylphenylalanine methyl ester ((*R*)-MACH$_2$)) from the catalytic hydrogenation of MAC using **2** as catalyst.

Introduction

The hydrogenation of prochiral olefins is the most studied and developed enantioselective catalytic reaction to date.[1] Despite hundreds of publications describing these reactions, little is known about the true structures of their diastereomeric catalytic intermediates. For example, our recent report[2] of a catalyst−alkyl complex is the first complete structure determination of a diastereomeric putative catalytic intermediate of the same absolute configuration as the hydrogenation product.[3,4] The complex [Ru((*R*)-BINAP)((*S*)-MACH)(MeCN)](BF$_4$) (**1**; BINAP is 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl) forms upon reaction (both during the catalytic hydrogenation and under stoichiometric conditions) between the substrate (*Z*)-methyl α-acetamidocinnamate (MAC) and the catalyst system [Ru((*R*)-BINAP)(H)(MeCN)$_n$(sol)$_{3-n}$](BF$_4$) (**2**; $n = 0-3$, sol = THF, acetone, or MeOH, depending on reaction medium).[5] We designed **2** for this mechanistic study because ruthenium is the most commonly used metal in enantioselective olefin hydrogenations, because BINAP is among the most commonly used ligands, and because MAC is the most commonly used (benchmark) substrate. In previous work on this system we showed

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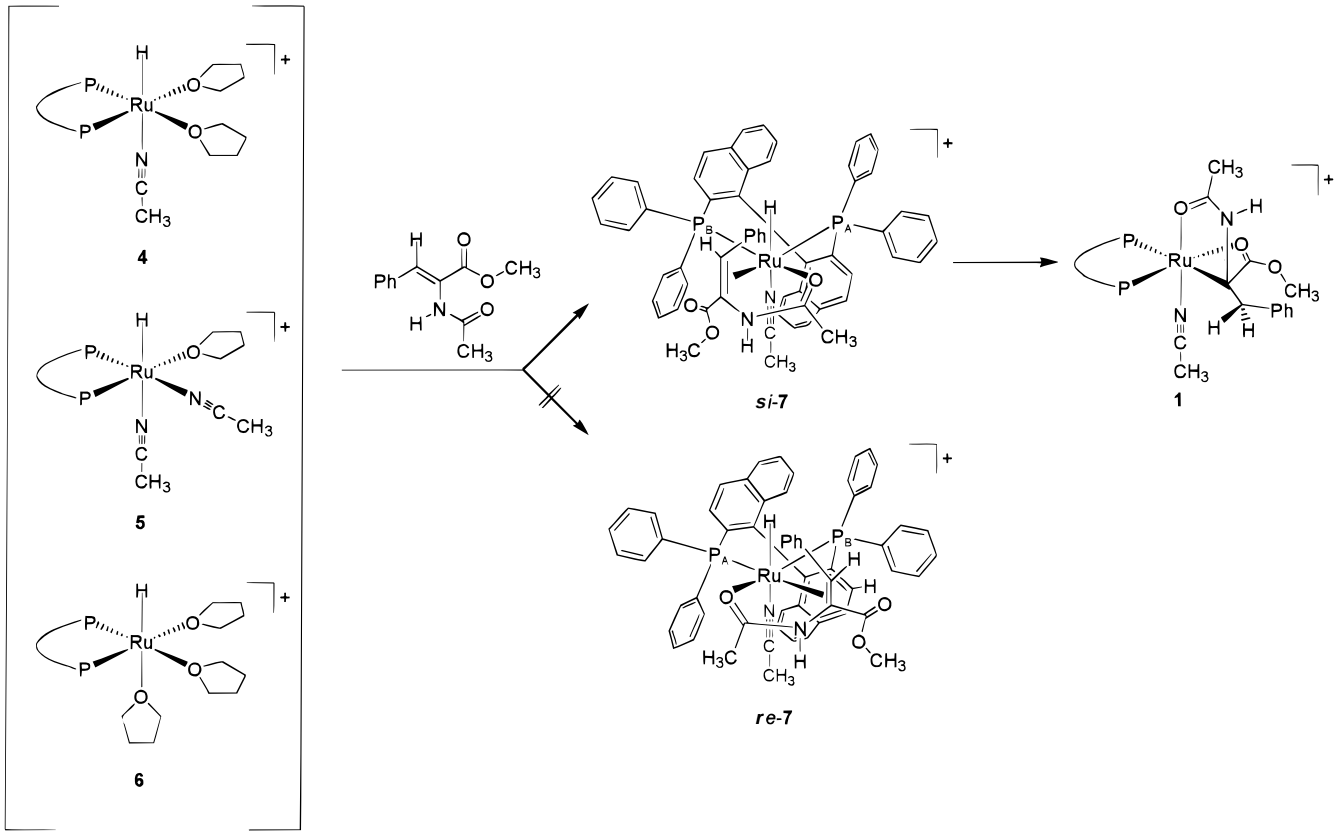
Scheme 1. Formation of the Olefin−Catalyst Adduct *si*-7 at Low Temperature and Its Conversion to 1



that formation of **1** is rapid and reversible and that **1** is the only detectable catalyst species in solution during the catalytic hydrogenation of MAC.[5a] Since the formation of **1** (product) is rapid and reversible under catalytic conditions, the Curtin−Hammett principle dictates that the structure and abundance of **1** provides no information about the structure and abundance of the major diastereomeric olefin adduct ([Ru((*R*)-BINAP)(H)(MAC)(MeCN)](BF$_4$), reactant) formed by reaction of MAC with **2**. There are 20 diasteromers of this olefin−catalyst adduct in which the olefin and hydride occupy mutually cis coordination sites and in which MAC is bonded through the olefin and amide groups (there are more diastereomers if ester coordination is considered). It was therefore imperative to determine which of these diastereomers form in order to understand how the stereochemical forces evolve during the catalytic hydrogenation. This paper describes low-temperature NMR experiments that determine the structure of the major olefin−catalyst adduct and that monitor the diastereomeric olefin−hydride insertion reaction to generate **1**.

Results and Discussion

The active catalyst **2** is generated by hydrogenation of the precursor [Ru((*R*)-BINAP)(MeCN)(1−3:5,6-η-C$_8$H$_{11}$)](BF$_4$) (**3**) in THF, acetone, or MeOH.[5] NMR spectra of **2** recorded at −40 °C in THF-d_8 show that it exists as a mixture of [Ru((*R*)-BINAP)(H)(MeCN)(THF-d_8)$_2$](BF$_4$) (**4**; ≈50%), [Ru((*R*)-BINAP)(H)(MeCN)$_2$(THF-d_8)](BF$_4$) (**5**; ≈25%), and [Ru((*R*)-BINAP)(H)(THF-d_8)$_3$](BF$_4$) (**6**; ≈25%).[6,7] These species were labeled with ^{15}N at acetonitrile by ligand exchange between the precursor **3** and MeC^{15}N. The magnitudes of $^2J_{P-H}$ (28−42 Hz) show that the hydride occupies a coordination site cis to both phosphorus centers in **4**−**6**. $^2J_{P-N}$ was not observed in **4**-MeC^{15}N, while $^2J_{N-H}$ was (18.5 Hz), showing that the acetonitrile and hydride ligands occupied the mutually trans coordination sites cis to the phosphorus centers[8] (Scheme 1). The same analysis on [Ru((*R*)-BINAP)(H)(MeC^{15}N)$_2$(THF-d_8)](BF$_4$) (**5**) shows that one MeC^{15}N ligand was trans to the hydride and the other was cis to the hydride.[9] These complexes rapidly exchange MeCN and THF at room temperature. To determine which of **4**, **5**, or **6** is the active catalyst is a somewhat diffuse issue for three reasons: first, exchange of MeCN between these species at room

(4) For studies of ruthenium systems see: (a) Chen, C.-C.; Huang, T.-T.; Lin, C.-W.; Cao, R.; Chan, A. S. C.; Wong, W. T. *Inorg. Chim. Acta* **1998**, *270*, 247−251. (b) Brown, J. M.; Rose, M.; Knight, F. I.; Wienand, A. *Recl. Trav. Chim. Pays-Bas* **1995**, *114*, 242−251. (c) Chan, A. S. C.; Chen, C. C.; Yang, T. K.; Huang, J. H.; Lin, Y. C. *Inorg. Chim. Acta* **1995**, *234*, 95−100. (d) Brown, J. M. *Chem. Soc. Rev.* **1993**, 25−41. (e) Saburi, M.; Takeuchi, H.; Ogasawara, M.; Tsukahara, T.; Ishii, Y.; Ikariya, T.; Takahashi, T. *J. Organomet. Chem.* **1992**, *428*, 155−167. (f) Ashby, M. T.; Khan, M. A.; Halpern, J. *Organometallics* **1991**, *10*, 2011−2015. (g) Ashby, M. T.; Halpern, J. *J. Am. Chem. Soc.* **1991**, *113*, 589−594. (h) Ohta, T.; Takaya, H.; Noyori, R. *Tetrahedron Lett.* **1990**, *31*, 7189−7192.

(5) (a) Wiles, J. A.; Bergens, S. H. *Organometallics* **1998**, *17*, 2228−2240. (b) Daley, C. J. A.; Wiles, J. A.; Bergens, S. H. *Can. J. Chem.* **1998**, *76*, 1447−1456. (c) Wiles, J. A.; Lee, C. E.; McDonald, R.; Bergens, S. H. *Organometallics* **1996**, *15*, 3782−3784.

(6) Complex **6** exists in equal proportions as a mixture of [Ru((*R*)-BINAP)(H)(THF-d_8)$_3$](BF$_4$) and the η^6-arene-bridged dimers [Ru((*R*)-BINAP)(H)]$_2$(BF$_4$)$_2$. The presence of the dimers was deduced from the signals in the range δ 4.2−6.0 ppm in the ^{1}H NMR spectrum, which are from the hydrogen atoms on the bridging phenyl rings. The phenyl-bridged dimers can be prepared in higher relative concentrations by hydrogenation of **3** in CD$_2$Cl$_2$. The signals for the dimers occur between 40 and 60 ppm in the ^{31}P NMR spectrum (Figure 1).

(7) A related chiral hydrido−solvent complex of ruthenium(II) has been crystallographically characterized: Currao, A.; Feiken, N.; Macchioni, A.; Nesper, R.; Pregosin, P. S.; Trabesinger, G. *Helv. Chim. Acta* **1996**, *79*, 1587−1591.

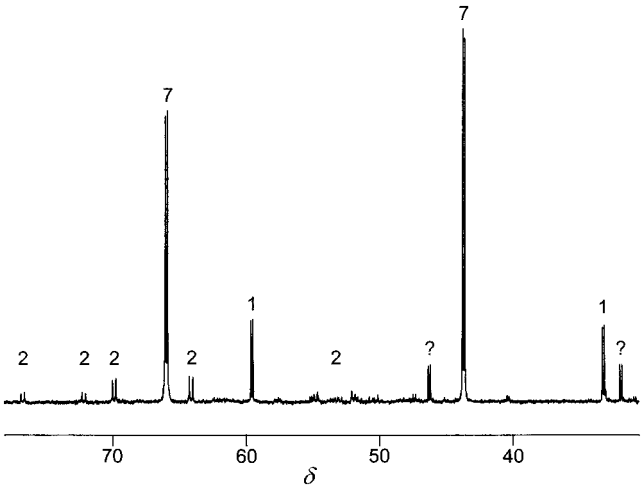


Figure 1. $^{31}P\{^1H\}$ NMR spectrum (161.9 MHz, THF-d_8, −40 °C) of a mixture containing **7** (75%), **1** (13%), and **2** (6%) recorded 1 h after mixing at −40 °C. A small quantity of an unidentified non-hydrido species (**?**; 6%) was also present in the mixture.

temperature is rapid; second, we have shown previously that removal of MeCN from the catalyst system has no effect on the enantiomeric excess of the catalytic hydrogenation; third, all the species in this mixture react quickly with MAC at ambient temperature to form the insertion product **1** in 100% yield.[2,5] Nevertheless, the active catalysts in this hydrogenation are likely **4** and **6**, because **5** must dissociate one MeCN ligand to accommodate the bidentate substrate MAC. We note that stoichiometric reactions between **6** and MAC at room temperature form the η^6-arene adduct [Ru((*R*)-BINAP)(H)(η^6-MAC)](BF_4), suggesting that the active catalyst is **4**. Regardless, we will refer to the active catalyst as **2** to accommodate these possibilities.

Reaction of **2** with 1 equiv of MAC in THF-d_8 at −40 °C over 1 h forms the diastereomeric catalyst−olefin adduct [Ru((*R*)-BINAP)(H)(MAC)(MeCN)](BF_4) (**7**) as the major product (Figure 1). The structure and absolute configuration of this complex was determined as follows. The phosphorus−hydride coupling constants ($^2J_{P_A-H}$ = 34.5 and $^2J_{P_B-H}$ = 21.5 Hz) show that the hydride is cis to both phosphorus centers in this complex. The magnitude of the nitrogen−hydride coupling constant ($^2J_{N-H(trans)}$ = 10.0 Hz) in the MeC^{15}N-labeled isotopomer of **7**, along with the absence of observable phosphorus−nitrogen coupling, shows that the hydride and MeCN ligands are trans to one another and that they occupy coordination sites cis to both phosphorus centers. Labeling MAC with ^{13}C at the olefinic positions shows an upfield shift (versus uncoordinated MAC) and phosphorus−carbon coupling for each olefin carbon signal in the ^{13}C NMR spectrum of **7** (Cβ (terminal): $\Delta\delta$ = −64.9 ppm, $J_{P_A-C(trans)}$ = 17.5 Hz; Cα (internal): $\Delta\delta$ = −46.4 ppm, $J_{P_A-C(trans)}$ = 3.5 Hz), confirming that the olefin group is bonded to ruthenium at a coordination site trans to one of the phosphorus centers (P_A) and cis to the other (P_B). Labeling the carbonyl carbon centers in MAC with ^{13}C shows a downfield shift and phosphorus−carbon coupling of the amide carbonyl signal ($\Delta\delta$ = +9.9 ppm, J_{P_A-C} = J_{P_B-C} = 2.5 Hz), and a downfield shift ($\Delta\delta$ = +8.9 ppm) without observable phosphorus−carbon coupling for the ester carbonyl signal. MAC therefore acts as a bidentate ligand in **7** with the olefin and O-bonded amide groups occupying coordination sites on ruthenium trans to the phosphorus centers (Scheme 1). MAC commonly displays this bonding mode in rhodium and iridium complexes.[3,10]

The insertion product **1** resulted from hydride addition to Cβ (terminal olefin carbon) and ruthenium addition to Cα of MAC with the *S* absolute configuration at the ruthenium-bonded carbon.[2] Apart from those structural features already established, two further conditions must be fulfilled for the olefin−catalyst adduct **7** to be an intermediate between the active catalyst **2** and the insertion product **1**. First, Cβ of MAC and the hydride ligand must be on the same side of the ruthenium−bis(phosphine) plane. If not, the olefin−hydride insertion reaction in **7** would produce the opposite regiochemistry of **1**, with ruthenium at Cβ. This would rule out **7** as an intermediate between **2** and **1**. Second, the olefin group must be bonded to ruthenium through the *si* enantiotopic face (Scheme 1) for olefin−hydride insertion to lead to **1** (the absolute configuration at Cα of MACH in **1** was crystallographically determined[2] as *S*). ^{1}H NOE difference spectra[11,12] at −40 °C showed that irradiation of the hydride signal from **7** resulted in negative nuclear Overhauser enhancement (NOE, −3%) of the olefinic hydrogen (Hβ) signal,[13] confirming that the hydride ligand and Cβ are on the same side of the ruthenium−bis(phosphine) plane. Scheme 1 shows the two possible structures of **7** which are consistent with these structural data. They are diastereomers that differ by which enantiotopic olefin face is coordinated to ruthenium and by which phosphorus center is cis to the coordinated olefin. In *si*-**7**, the substituents on the phosphorus center (P_B) cis to the coordinated olefin are disposed with the naphtha-

(8) This geometry was confirmed by comparison to [Ru((*R*)-BINAP)(H)(MeC^{15}N)$_3$](BF_4) (**8**), in which two signals in the ^{15}N NMR spectrum are coupled to phosphorus but not to the hydride, while the remaining signal is coupled to the hydride but not to the phosphorus centers. NMR data for **8**: ^{1}H (400.1 MHz, THF-d_8/CD_2Cl_2 (6:1 v/v), −40 °C): δ −13.58 (d of apparent t, $^2J_{P-H(cis)}$ = 24.5 Hz, $^2J_{N-H(trans)}$ = 18.5 Hz, 1H, Ru*H*), 1.75 (d, $^3J_{N-H}$ = 2.0 Hz, 3H, C*H*$_3$C^{15}N−Ru), 1.79 (d, $^3J_{N-H}$ = 2.0 Hz, 3H, C*H*$_3$C^{15}N−Ru), 2.16 (d, $^3J_{N-H}$ = 2.0 Hz, 3H, C*H*$_3$C^{15}N−Ru), 6.0−8.4 (aromatic). $^{31}P\{^1H\}$ (161.9 MHz, THF-d_8/CD_2Cl_2 (6:1 v/v), −40 °C): δ 63.6 (apparent t, $^2J_{P-P}$ = $^2J_{P-N(trans)}$ = 39.0 Hz, 1P), 69.6 (apparent t, $^2J_{P-P}$ = $^2J_{P-N(trans)}$ = 39.0 Hz, 1P). ^{15}N INEPT (40.5 MHz, THF-d_8/CD_2Cl_2 (6:1 v/v), −40 °C): δ 196.4 (d, $^2J_{P-N(trans)}$ = 39.0 Hz, $CH_3C^{15}N$−Ru), 196.9 (d, $^2J_{P-N(trans)}$ = 39.0 Hz, $CH_3C^{15}N$-Ru), 208.4 (d, $^2J_{N-H(trans)}$ = 18.5 Hz, $CH_3C^{15}N$-Ru). For a similar analysis see: Chan, A. S. C.; Halpern, J. *J. Am. Chem. Soc.* **1980**, *102*, 838−840.

(9) Only one of the two possible diastereomers of **5** was observed. The absolute configuration of the complex was not determined.

(10) (a) Bender, B. R.; Koller, M.; Nanz, D.; von Philipsborn, W. *J. Am. Chem. Soc.* **1993**, *115*, 5889−5890. (b) McCulloch, B.; Halpern, J.; Thompson, M. R.; Landis, C. R. *Organometallics* **1990**, *9*, 1392−1395. (c) Chan, A. S. C.; Pluth, J. J.; Halpern, J. *J. Am. Chem. Soc.* **1980**, *102*, 5952−5954. (d) Brown, J. M.; Chaloner, P. A.; Glaser, R.; Geresh, S. *Tetrahedron* **1980**, *36*, 815−825. (e) Chan, A. S. C.; Pluth, J. J.; Halpern, J. *Inorg. Chim. Acta* **1979**, *37*, L477−L479.

(11) NOE methods have been used previously in the structure determinations (including absolute configuration) of organometallic complexes containing prochiral substrates. For recent examples see: (a) Pregosin, P. S.; Trabesinger, G. *J. Chem. Soc., Dalton Trans.* **1998**, 727−734. (b) Krafft, M. E.; Yu, X. Y.; Wilson, L. J. *Organometallics* **1998**, *17*, 2076−2088. (c) Motoyama, Y.; Murata, K.; Kurihara, O.; Naitoh, T.; Aoki, K.; Nishiyama, H. *Organometallics* **1998**, *17*, 1251−1253. (d) Steinhagen, H.; Reggelin, M.; Helmchen, G. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2108−2110.

(12) THF-d_8 solutions containing CD_2Cl_2 (THF-d_8/CD_2Cl_2 2:1 v/v) were employed to increase the solubility of **3** in the preparation of **2**.

(13) Typically, solutions of **7** contained traces of excess MAC. The methoxy signal for excess (uncoordinated) MAC in ^{1}H NMR spectra of these mixtures obscured the signal for Hβ of **7**, which required the use of MAC−CO_2CD_3 to obtain unambiguous NOE data.

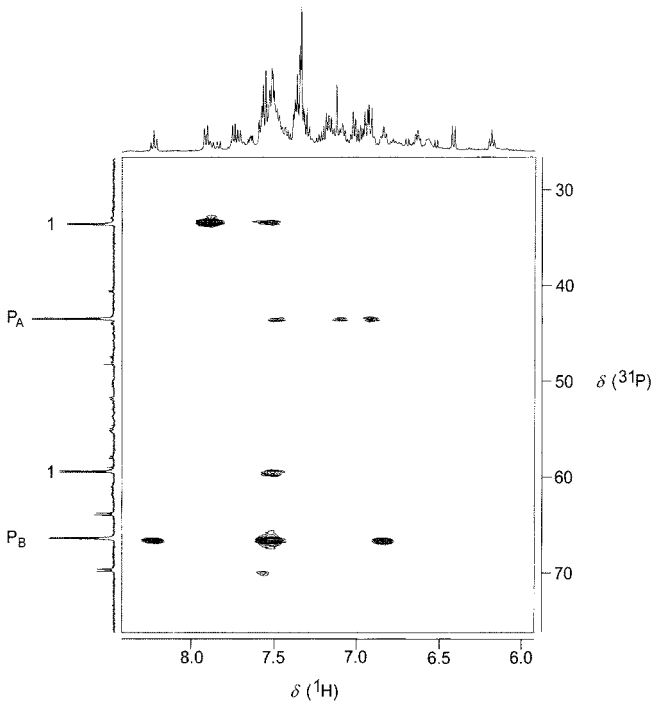


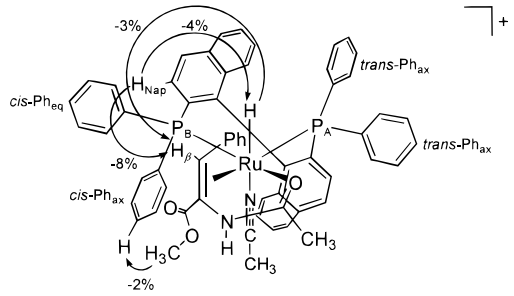
Figure 2. Section of the $^{31}P-^{1}H$ HETCOR NMR spectrum (500 MHz, THF-d_8/CD_2Cl_2 (2:1 v/v), −40 °C) of **7** showing three ortho type protons associated with each ^{31}P resonance. The assignments for P_B are as follows (low field to high field): *o*-Nap, *o*-Ph_{eq}, and *o*-Ph_{ax}.

lene (Nap) ring adjacent (on the same side of the ruthenium−bis(phosphine) plane) to Cβ and with the axial phenyl (Ph_{ax}) group adjacent to the methoxy group of the ester (Scheme 1 and Figure 3). In *re*-**7**, the substituents on the phosphorus center (P_B) cis to the coordinated olefin are disposed with the Ph_{ax} group adjacent to Cβ and with the Nap ring adjacent to the methoxy group of the ester. ^{1}H NMR signals from these groups did not overlap with others[14] and provided an unambiguous assignment of the structure as follows.

A $^{31}P-^{1}H$ HETCOR experiment, confirmed by selective $^{1}H\{^{31}P\}$ NMR experiments, showed that each phosphorus center is coupled to three ortho aromatic proton signals, one for each *o*-Ph and one for the *o*-Nap ring (Figure 2). That the signals for the ortho protons on the phenyl rings are not separated shows that rotation around the phosphorus−phenyl bonds is rapid on the NMR time scale at −40 °C.[15] The signals for the phosphorus centers cis and trans to the coordinated olefin were assigned by ^{13}C labeling of MAC at the olefinic positions (vide supra). The cis phosphorus (P_B) was coupled to ortho protons at δ 8.22, 7.52, and 6.84 ppm. The trans phosphorus (P_A) was coupled to ortho

(14) There was significant overlap of the signals for the aromatic protons in the ^{1}H NMR spectrum of **7** (see Figure 2).

(15) This was also shown at room temperature for [Pd((*R*)-BINAP)-(η^3-allyl)](CF_3SO_3), where η^3-allyl = β-pinene allyl and *exo*-methylene cyclopentene allyl: (a) Pregosin, P. S.; Rüegger, H.; Salzmann, R.; Albinati, A.; Lianza, F.; Kunz, R. W. *Organometallics* **1994**, *13*, 5040−5048. (b) Rüegger, H.; Kunz, R. W.; Ammann, C. J.; Pregosin, P. S. *Magn. Reson. Chem.* **1991**, *29*, 197−203. We note that the correlations between P_A and the ortho aromatic protons are weaker than those for P_B. The weaker correlations indicate the signals from the ortho aromatic protons at P_A are broadened (these signals overlap with other aromatic proton signals). This broadening shows that rotation around the P_A−phenyl bond is slower at −40 °C than around the P_B−phenyl bond. These experiments were not optimized to observe correlations within the minor components in solution.



si-**7**

Figure 3. Observed NOE values that were used to determine the structure and absolute configuration of *si*-**7**.

protons at δ 7.51, 7.10, and 6.92 ppm. The signal at δ 8.22 ppm (t, $^{3}J_{P-H} = {}^{3}J_{H-H} = 8.5$ Hz) is from *o*-Nap on P_B (H_{Nap}). It is a one-proton signal (by comparison to the integrated intensity of Hβ), and it is coupled to a one-proton signal from the *m*-Nap proton (δ 7.91 ppm, d, $^{3}J_{H-H} = 8.5$ Hz) which was determined by selective $^{1}H\{^{1}H\}$ and $^{1}H-^{1}H$ COSY NMR experiments. Irradiation of the H_{Nap} signal caused a −8% enhancement of the olefinic Hβ signal and a −4% enhancement of the hydride signal, showing that the hydride, Hβ, and H_{Nap} are on the same side of the ruthenium−bis(phosphine) plane (Figure 3). Consistent with this assignment is that irradiation of the methoxy group caused −2% enhancement for the signal at δ 6.62 (t, $^{3}J_{H-H} = 8.0$ Hz), which we ascribe to the para proton on the *cis*-Ph_{ax} group. The *cis*-Ph_{ax} ring is on the opposite side of the ruthenium−bis(phosphine) plane with regard to the *cis*-Nap ring. Irradiation of the H_{Nap} signal caused enhancement of *cis*-*o*-Ph_{eq} protons but not *cis*-*o*-Ph_{ax} protons.

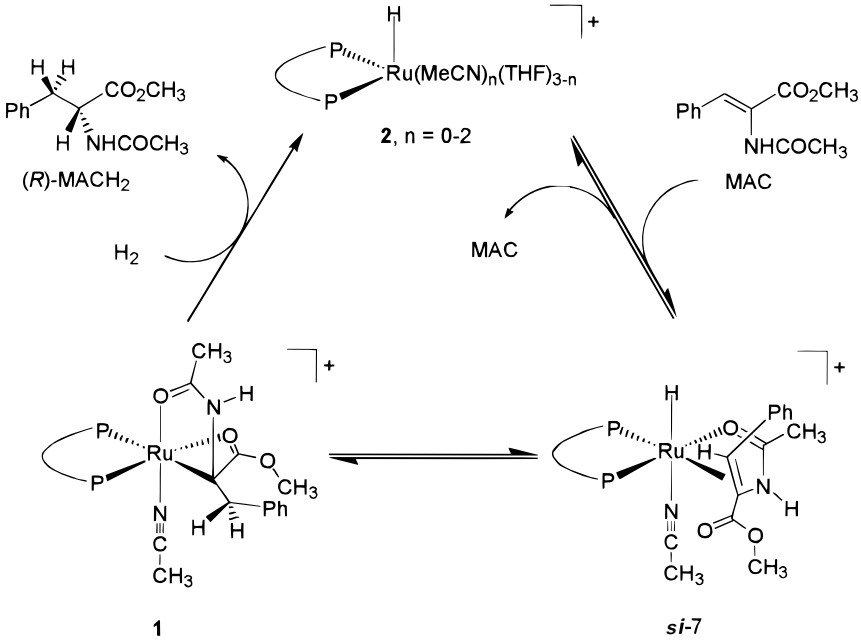
These correlations are not possible in *re*-**7** and therefore unambiguously show that MAC is coordinated by the *si*-olefin face in **7** with the correct regiochemistry for olefin−hydride insertion to form **1**. We therefore conclude that *si*-**7** is a diastereomeric intermediate between the active catalyst **2** and the insertion product **1**. Other correlations could be found which affirm this structure assignment of *si*-**7**, but these we consider to be ambiguous because the proton signals involved were overlapped by other aromatic proton signals.

Preliminary kinetic investigations show that *si*-**7** undergoes first-order olefin−hydride insertion to directly form **1** ($k \approx 1.0 \times 10^{-4}$ s^{-1} at −20 °C) without detection of further intermediates by ^{31}P NMR spectroscopy.

Conclusions

Despite that all enantioselective catalytic hydrogenations of olefins must involve diastereomeric hydrido−olefin intermediates, *si*-**7** is the first example of such a putative intermediate to be observed and structurally characterized. We note that because the alkyl complex **1** (product) forms under Curtin−Hammett conditions during the catalytic hydrogenation, it was impossible before this study to predict the stereochemistries and the distribution of the hydrido−olefin diastereomers (reactant(s)) formed by reaction of the active catalyst **2** with MAC. That *si*-**7** is the only olefin−catalyst adduct formed in detectable amounts, and that it *is* the immediate predecessor to **1** (of correct regio- and stereo-

Scheme 2



chemistry), allowed this direct structural and kinetic study of an olefin−hydride insertion reaction as part of a diastereomeric pathway for an enantioselective olefin hydrogenation. The most direct pathway for the observed first-order transformation of *si*-**7** into **1** is olefin−hydride insertion (via hydride migration) followed by rotation around the ruthenium−Cα bond to result in coordination of the amide carbonyl trans to MeCN and the ester carbonyl trans to P_B. We also note that *si*-**7** and **1** are of the same absolute configuration as the major product enantiomer of the catalytic hydrogenation and that the sequence of reactions involving **2**, *si*-**7**, and **1** is the most detailed structural observation to date of a diastereomeric pathway in enantioselective catalytic hydrogenation (Scheme 2).

Experimental Section

General Comments. Reactions requiring oxygen- and/or moisture-free conditions were conducted under an atmosphere of dry argon gas using standard Schlenk and glovebox techniques. One-dimensional NMR spectra were recorded using a Bruker AM-400 (^{1}H at 400.1 MHz, ^{2}H at 61.4 MHz, ^{13}C at 100.6 MHz, ^{19}F at 376.5 MHz, ^{15}N at 40.5 MHz, and ^{31}P at 161.9 MHz) spectrometer. Two-dimensional NMR spectra were recorded using a Varian Unity 500 (^{1}H at 499.8 MHz and ^{31}P at 202.4 MHz) spectrometer. The chemical shifts for ^{1}H, ^{2}H, and ^{13}C are reported in parts per million (δ) relative to external tetramethylsilane and were referenced to residual solvent signals. The chemical shifts for ^{19}F, ^{15}N, and ^{31}P are reported in parts per million (δ) relative to external trichlorofluoromethane, external liquid ammonia, and external 85% phosphoric acid, respectively. Electron-impact high-resolution mass spectra (HRMS (EI)) were recorded using a Kratos MS50 spectrometer.

Materials. Argon gas (Praxair, 99.998%) was purified by passage through a column of 3 Å molecular sieves and phosphorus pentoxide. Dihydrogen gas (Praxair, 99.99%) was used as received. Protiated solvents (Caledon) and deuterated solvents (99.5−99.9% D, Cambridge Isotope Laboratories) were distilled from appropriate drying agents and were thoroughly degassed prior to use.[16] All reagents were used as received from Aldrich unless stated otherwise. Isotope-labeled derivatives of MAC were prepared via methanolysis[5a,17] of the corresponding oxazolones[18] using appropriately labeled glycine, benzaldehyde, and methanol as reagents. The exception was MAC-*1′*-^{13}*C*, which was prepared via methanolysis of the oxazolone derived from *N*-acetyl-*1′*-^{13}*C*-glycine (obtained via hydrolysis of ethyl *N*-acetyl-1′-^{13}*C*-glycinate) as outlined below.

Synthesis of Ethyl *N*-Acetyl-1′-^{13}*C*-glycinate. To a stirred suspension of glycine ethyl ester hydrochloride (3.55 g, 0.025 mol) in CH_2Cl_2 (150 mL) at −10 °C under argon gas was added NEt_3 (7.1 mL, 0.051 mol) dropwise. The reaction mixture was stirred at −10 °C for 1 h, and then $CH_3{}^{13}COCl$ (1.8 mL, 0.025 mol) was added dropwise. The resulting mixture was stirred at −10 °C for 1 h and then warmed to room temperature and stirred for an additional 1 h. The suspension was evaporated to dryness, and the product was extracted from the solid with benzene (200 mL). Yield after recystallization (benzene/*n*-pentane): 3.30 g (90%). ^{1}H NMR (400.1 MHz, $CDCl_3$, 25 °C): δ 1.28 (t, $^3J_{H-H}$ = 7.0 Hz, 3H, $CO_2CH_2CH_3$), 2.04 (d, $^2J_{C-H}$ = 6.0 Hz, 3H, CH_3CONH), 4.02 (dd, $^3J_{H-H}$ = 5.5 Hz, $^3J_{C-H}$ = 3.0 Hz, 2H, $NHCH_2CO_2$), 4.21 (q, $^3J_{H-H}$ = 7.0 Hz, 2H, $CO_2CH_2CH_3$), 6.09 (br, 1H, NH). ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 14.1 (s, $CO_2CH_2CH_3$), 22.9 (d, $^1J_{C-C}$ = 51.5 Hz, CH_3CONH), 41.4 (s, $NHCH_2CO_2$), 61.5 (s, $CO_2CH_2CH_3$), 170.2 (s, CH_3CONH), 170.5 (s, $CO_2CH_2CH_3$). HRMS (EI): *m*/*z* 146.0772 (M^+, exact mass calcd for $C_5{}^{13}CH_{11}NO_3$ 146.0773).

Synthesis of *N*-Acetyl-*1′*-^{13}*C*-glycine. To a stirred aqueous solution (50 mL) of ethyl *N*-acetyl-*1′*-^{13}*C*-glycinate (3.10 g, 0.021 mol) was added concentrated HCl (1 mL). The solution was heated (75 °C) with stirring for 16.5 h and then evaporated to give a white solid. The solid was washed with dry THF (100 mL), yielding 2.40 g of a mixture containing 67% *N*-acetyl-*1′*-^{13}*C*-glycine and 33% glycine hydrochloride (by ^{1}H NMR and HRMS analyses). This mixture was used without further purification for the preparation of enriched (*Z*)-methyl-4-benzaloxazolone-*2*-^{13}*C*. ^{1}H NMR (400.1 MHz, CD_3OD, 25 °C): δ 1.99 (d, $^2J_{C-H}$ = 6.0 Hz, 3H, CH_3CONH), 3.88 (d, $^3J_{C-H}$ = 4.0 Hz, 2H, $NHCH_2CO_2H$). ^{13}C{^{1}H} NMR (100.6 MHz, CD_3OD, 25 °C): δ 22.3 (d, $^1J_{C-C}$ = 50.0 Hz, CH_3CONH), 41.8 (s, $NHCH_2$-

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CO_2), 173.1 (s, $NHCH_2CO_2$), 173.7 (s, CH_3CONH). HRMS (EI): *m*/*z* 118.0459 (M^+, exact mass calcd for $C_3{}^{13}CH_7NO_3$ 118.0459).

Synthesis of Enriched (*Z*)-Methyl-4-benzaloxazolone-*2*-^{13}*C*. This compound was prepared according to established procedures[18] using the above mixture of 67% *N*-acetyl-*1′*-^{13}*C*-glycine and 33% glycine hydrochloride as starting material. Yield: 25%. ^{1}H NMR (400.1 MHz, $CDCl_3$, 25 °C): δ 2.41 (d, $^2J_{C-H}$ = 8.0 Hz, 3H, C*H*$_3$), 7.15 (s, 1H, olefinic C*H*), 7.44 (m, 3H, C_6H_5), 8.08 (m, 2H, C_6H_5). ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 15.7 (*C*H$_3$), 128.9 (C_6H_5), 131.1 (C_6H_5), 131.4 (Cβ, olefinic *C*H), 132.1 (C_6H_5), 132.6 (C4, quaternary olefin), 133.1 (*i*-C_6H_5), 166.1 (C2), 167.8 (C5, carbonyl). HRMS (EI): *m*/*z* 188.0665 (M^+, exact mass calcd for $C_{10}{}^{13}CH_9NO_2$ 188.0667).

Synthesis of Enriched MAC-*1′*-^{13}*C*. This compound was prepared according to established procedures[5a,17] using the above enriched (*Z*)-methyl-4-benzaloxazolone-*2*-^{13}*C* as starting material. Yield after flash column chromatography (neutral alumina with CH_2Cl_2 as eluent) followed by recrystallization (CH_2Cl_2/*n*-pentane): 35%. ^{1}H NMR (400.1 MHz, THF-d_8/CD_2Cl_2 (2:1 v/v), −40 °C): δ 2.02 (d, $^2J_{C-H}$ = 6.0 Hz, 3H, NHCOC*H*$_3$), 3.74 (s, 3H, CO_2CH_3), 7.14 (s, 1H, olefinic C*H*), 7.36 (m, 3H, *m*- and *p*-C_6H_5), 7.57 (d, $^3J_{H-H}$ = 7.0 Hz, 2H, *o*-C_6H_5), 9.15 (s, 1H, N*H*COCH$_3$). ^{13}C{^{1}H} NMR (100.6 MHz, THF-d_8/CD_2Cl_2 (2:1 v/v), −40 °C): δ 22.9 (d, $^1J_{C-C}$ = 49.0 Hz, NHCO*C*H$_3$), 52.8 (CO_2CH_3), 127.7 (Cα, quaternary olefin), 129.3 (C_6H_5), 129.9 (C_6H_5), 130.5 (C_6H_5), 130.8 (Cβ, olefin), 134.7 (*i*-C_6H_5), 166.6 (C1, *C*O$_2$CH$_3$), 170.3 (C1′, NH*C*OCH$_3$). HRMS (EI): *m*/*z* 220.0929 (M^+, exact mass calcd for $C_{11}{}^{13}CH_{13}NO_3$ 220.0929).

Synthesis of 3-MeC^{15}N. To a stirred solution of **3**[5c] (138.0 mg, 0.144 mmol) in CH_2Cl_2 (3.0 mL) at room temperature under argon gas was added MeC^{15}N (300 μL, 5.709 mmol). The reaction mixture was stirred at room temperature for 2 h and then Et_2O (200 mL) was slowly added to give a yellow solid. The product was collected by filtration and washed with Et_2O (5 × 10 mL) to give 120.0 mg (87%) of **3**-MeC^{15}N (>95% ^{15}N-enriched). ^{31}P{^{1}H} NMR (161.9 MHz, CD_2Cl_2, −20 °C): δ 33.0 (dd, $^2J_{P-P}$ = 33.5 Hz, $^2J_{P-N}$ = 2.5 Hz, 1P), 35.5 (dd, $^2J_{P-P}$ = 39.0 Hz, $^2J_{P-N}$ = 3.0 Hz, 1P*), 45.6 (dd, $^2J_{P-P}$ = 39.0 Hz, $^2J_{P-N}$ = 3.0 Hz, 1P*), 46.8 (dd, $^2J_{P-P}$ = 33.5 Hz, $^2J_{P-N}$ = 4.0 Hz, 1P). ^{15}N INEPT NMR (40.5 MHz, CD_2Cl_2, −20 °C): δ 189.1 (dd, $^2J_{P-N}$ = 4.0 Hz, $^2J_{P-N}$ = 2.5 Hz), 195.7 (apparent t, $^2J_{P-N}$ = 3.0 Hz*). Asterisks denote signals attributed to the labile diastereomer of **3**-MeC^{15}N.

Synthesis of 2-MeC^{15}N. This compound was prepared as described previously[5] using **3**-MeC^{15}N (>95% ^{15}N-enriched) as starting material. Complex **2**-MeC^{15}N exists at −40 °C as a mixture of **4**, **5**, and **6** (see the Results and Discussion for relative proportions in THF-d_8). **4**: ^{1}H NMR (400.1 MHz, THF-d_8/CD_2Cl_2 (6:1 v/v), −40 °C): δ −13.10 (m, overlapping with **5**, 1H, Ru*H*), 2.68 (br s, 3H, C*H*$_3$C^{15}N−Ru), 6.0−8.5 (aromatic, overlapping with **5** and **6**). ^{31}P{^{1}H} NMR (161.9 MHz, THF-d_8/CD_2Cl_2 (6:1 v/v), −40 °C): δ 71.8 (d, overlapping with **5**, $^2J_{P-P}$ = 49 Hz, 1P), 81.1 (d, $^2J_{P-P}$ = 49 Hz, 1P). ^{15}N INEPT NMR (40.5 MHz, THF-d_8/CD_2Cl_2 (6:1 v/v), −40 °C): δ 211.3 (d, overlapping with **5**, $^2J_{N-H(trans)}$ = 18.5 Hz, $CH_3C^{15}N$-Ru). **5**: ^{1}H NMR (400.1 MHz, THF-d_8/CD_2Cl_2 (6:1 v/v), −40 °C): δ −13.10 (m, overlapping with **4**, 1H, Ru*H*), 1.84 (s, 3H, C*H*$_3$C^{15}N−Ru), 2.12 (s, 3H, C*H*$_3$C^{15}N−Ru), 6.0−8.5 (aromatic, overlapping with **4** and **6**). ^{31}P{^{1}H} NMR (161.9 MHz, THF-d_8/CD_2Cl_2 (6:1 v/v), −40 °C): δ 71.9 (apparent t, overlapping with **4**, $^2J_{P-P}$ = $^2J_{P-N}$ = 42 Hz, 1P), 76.4 (d, $^2J_{P-P}$ = 42 Hz, 1P). ^{15}N INEPT NMR (40.5 MHz, THF-d_8/CD_2Cl_2 (6:1 v/v), −40 °C): δ 199.5 (d, $^2J_{P-N(trans)}$ = 39.0 Hz, $CH_3C^{15}N$-Ru), 211.3 (d, overlapping with **4**, $^2J_{N-H(trans)}$ = 18.5 Hz, $CH_3C^{15}N$-Ru). **6** ([Ru((*R*)-BINAP)(H)(THF-d_8)$_3$](BF$_4$)): ^{1}H NMR (400.1 MHz, THF-d_8, −40 °C): δ −19.45 (br, Ru*H*), 6.0−8.5 (aromatic, overlapping with **4** and **5**). ^{31}P{^{1}H} NMR (161.9 MHz, THF-d_8, −40 °C): δ 74.1 (br d, $^2J_{P-P}$ = 50.0 Hz, 1P), 82.0 (br, 1P). ([Ru((*R*)-BINAP)(H)]$_2$(BF$_4$)$_2$, major): ^{1}H NMR (400.1 MHz, THF-d_8/CD_2Cl_2 (6:1 v/v), −40 °C): δ −9.53 (dd, $^2J_{P-H}$ = 42.0 Hz, 30.0 Hz, 2H, Ru*H*), 4.2−6.0 (br m, 10H, bridging aromatic), 6.0−8.5 (aromatic, overlapping with **4**, **5**, and **6**). ^{31}P{^{1}H} NMR (161.9 MHz, THF-d_8/CD_2Cl_2 (6:1 v/v), −40 °C): δ 51.5 (d, $^2J_{P-P}$ = 42.0 Hz, 1P), 54.9 (d, $^2J_{P-P}$ = 42.0 Hz, 1P).

Synthesis of *si*-7. In a 5 mm NMR tube, appropriately labeled **3** (1 equiv, typically ca. 25 mg) was partially dissolved in a mixture of THF-d_8 (0.50 mL) and CD_2Cl_2 (0.15 mL) under an atmosphere of argon gas. The tube was flushed with dihydrogen gas and shaken at room temperature for 5 min, causing the original yellow solution to change to orange. The solution was sparged with argon gas, then cooled to −78 °C, and transferred via cannula to another NMR tube containing an argon-saturated solution of appropriately labeled MAC (1 equiv) in CD_2Cl_2 (0.1 mL) at −78 °C. The tube was briefly removed from the cooling bath, quickly shaken, and immediately placed in a −40 °C bath for 1 h before NMR analysis. ^{1}H NMR (400.1 MHz, THF-d_8/CD_2Cl_2 (2:1 v/v), −40 °C): δ −7.48 (dd, $^2J_{P_A-H}$ = 34.5, $^2J_{P_B-H}$ = 21.5 Hz, 1H, Ru*H*), 1.34 (s, 3H, NHCOC*H*$_3$), 1.92 (s, 3H, C*H*$_3$CN), 2.96 (br s, 3H, CO_2CH_3), 3.74 (apparent t, $^3J_{P_A-H}$ = $^3J_{P_B-H}$ = 4.0 Hz, 1H, Hβ), 6.2−8.2 (aromatic, see the Results and Discussion for signals that could be assigned with certainty), 9.83 (s, 1H, N*H*COCH$_3$). ^{13}C{^{1}H} NMR (100.6 MHz, THF-d_8/CD_2Cl_2 (2:1 v/v), −40 °C): δ 65.9 (d, $^2J_{P_A-C}$ = 17.5 Hz, Cβ), 81.3 (d, $^2J_{P_A-C}$ = 3.5 Hz, Cα), 175.5 (s, *C*O$_2$CH$_3$), 180.2 (br apparent t, $^3J_{P_A-C}$ = $^3J_{P_B-C}$ = 2.5 Hz, NH*C*OCH$_3$). ^{31}P{^{1}H} NMR (161.9 MHz, THF-d_8/CD_2Cl_2 (2:1 v/v), −40 °C): δ 43.1 (d, $^2J_{P-P}$ = 24.0 Hz, 1P, P_A), 66.3 (d, $^2J_{P-P}$ = 24.0 Hz, 1P, P_B). ^{15}N INEPT NMR (40.5 MHz, THF-d_8/CD_2Cl_2 (2:1 v/v), −80 °C): δ 202.5 (d, $^2J_{N-H(trans)}$ = 10.0 Hz, CH_3CN-Ru). ^{19}F NMR (376.5 MHz, THF-d_8/CD_2Cl_2 (2:1 v/v), −40 °C): δ −152.1 (s, 20%, $^{10}BF_4$), −152.2 (s, 80%, $^{11}BF_4$).

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