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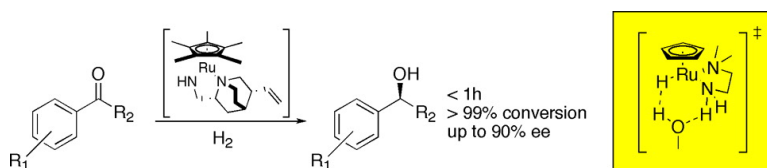
Mechanistic Insights into the Phosphine-Free RuCp*-Diamine-Catalyzed Hydrogenation of Aryl Ketones: Experimental and Theoretical Evidence for an Alcohol-Mediated Dihydrogen Activation

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Mechanistic Insights into the Phosphine-Free RuCp*-Diamine-Catalyzed Hydrogenation of Aryl Ketones: Experimental and Theoretical Evidence for an Alcohol-Mediated Dihydrogen Activation

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Abstract: The commercially available chiral diamine quincorine-amine, originally derived from quinine, was found to be a highly active catalyst for ruthenium-catalyzed hydrogenation of ketones. The complex formed between the quincorine-amine, containing both a primary and a quinuclidine amino function, and RuCp*Cl catalyzes the hydrogenation of aromatic and aliphatic ketones in up to 90% ee approximately 24 times faster than previously reported Ru-diamine complexes. The pseudo-enantiomer of the quincorine-amine, i.e., quincoridine-amine, also showed high activity; however, the enantioselectivities obtained with this catalyst were lower. The reason for the lower, but opposite stereoselectivity seen with the quincoridine-amine, as compared to the quincorine-amine, was rationalized by a kinetic and computational study of the mechanism of the reaction. The theoretical calculations also revealed a significantly lower activation barrier for the alcohol-mediated split of dihydrogen, as compared to the nonalcohol-mediated process, a finding of utmost implication also for the diphosphine/diamine-mediated enantioselective hydrogenation of ketones.

Introduction

Catalytic asymmetric synthesis is, according to a newly published report,[1] the most important synthetic method for the production of chiral products. Definitely, catalytic enantioselective hydrogenation is the reaction most widely used for this purpose, both industrially and in the laboratory.[2] This interest has made homogeneous hydrogenation of functionalized olefins the best-studied enantioselective catalytic reaction.

Of comparable practical interest to the enantioselective reduction of C=C bonds is the hydrogenation of C=O and C=N bonds. Two methods have been developed for homogeneous enantioselective hydrogenation of ketones. These are transfer hydrogenation using organic sources of dihydrogen and the direct use of molecular hydrogen. In the transfer hydrogenation reaction the proton is transferred from 2-propanol or formic acid to the ketone through an iridium, ruthenium, or rhodium catalyst.[3] The most efficient ligands used for this reaction are based on β-amino alcohols or β-diamines together with Ru-

arene or Rh/Ir-cyclopentadiene complexes. The most efficient catalysts for hydrogenation of functionalized ketones with H_2 are based on Rh and Ru diphosphine catalysts.[4] The method of choice for reducing unfunctionalized ketones, on the other hand, is Noyori's newly developed Ru-diphosphine/diamine catalyst system.[5]
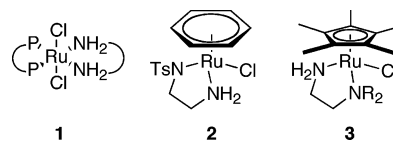

Although both Ru-diphospine/diamine complexes **1** (e.g., *P-P* = (*S*)-BINAP, *N-N* = (*S,S*)-1,2-diphenylethylenediamine) and the widely used Ru-arene/diamine complex RuCl(TsDPEN)-

(1) Rouhi, A. M. *Chem., Eng. News* **2004**, *82*, 47.
(2) For reviews, see: (a) Ohkuma, T.; Noyori, R. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 1, pp 199−246. (b) Blaser, H.-U.; Springer, F. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 1, pp 247−265. (c) Noyori, R. In *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994; pp 16−94. (d) Noyori, R.; Ohkuma, *Angew. Chem., Int. Ed.* **2001**, *40*, 40. (e) T. Blaser, H.-U.; Malan, C.; Pugin, B.; Spindler, F.; Steiner, H.; Studer, M. *Adv. Synth. Catal.* **2003**, *345*, 103.

(3) (a) Zassinovich, G.; Mestroni, G.; Gladiali, S. *Chem. Rev.* **1992**, *92*, 1051. (b) Hashiguchi, S.; Fujii, A.; Noyori, R. *J. Synth. Org. Chem. (Jpn)* **1996**, *54*, 818. (c) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97. (d) Everaere, K.; Mortreux, A.; Carpentier, J.-F. *Adv. Synth. Catal.* **2003**, *345*, 67. (e) Palmer, M. J.; Wills, M. *Tetrahedron: Asymmetry* **1999**, *10*, 2045. (f) Nordin, S. F. M.; Roth, P.; Tarnai, T.; Alonso, D. A.; Brandt, P.; Andersson, P. G. *Chem. Eur. J.* **2001**, *7*, 1431.
(4) For a recent review see: Noyori, R.; Kitamura, M.; Ohkuma, T. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5356.
(5) (a) Ohkuma, T.; Ooka, H.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 2675. (b) Ohkuma, T.; Ooka, H.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 10417. (c) Doucet, H.; Ohkuma, T.; Murata, K.; Yokozawa, T.; Kozawa, M.; Katayama, E.; England, A. F.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed.* **1998**, *37*, 1703. (d) Ohkuma, T.; Ishii, D.; Takeno, H.; Noyori, R. *J. Am. Chem. Soc.* **2000**, *122*, 6510. (e) Ohkuma, T.; Koizumi, M.; Muniz, K.; Hilt, G.; Kabuto, C.; Noyori, R. *J. Am. Chem. Soc.* **2002**, *124*, 6508.

Scheme 1. *Cinchona* Alkaloid-Derived Diamines **4** and **5** Used as Ligands for Cp*Ru-Mediated Asymmetric Hydrogenation

Quincorine amine
(QCI-amine)
4

Quinine

Quinidine

Quincoridine amine
(QCD-amine)
5
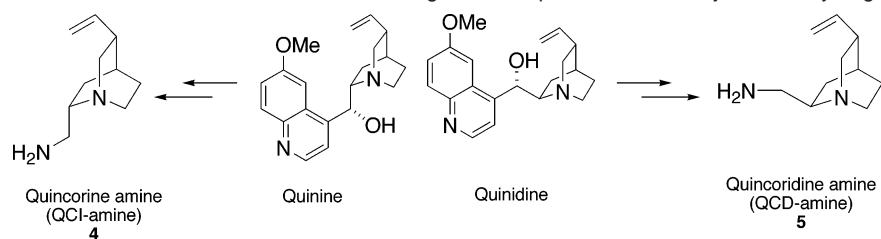
(η^6-arene) (TsDPEN = *N*-(*p*-toluenesulfonyl)-(*S,S*)-1,2-diphenylethylenediamine) **2** contain a characteristic NH functionality, the catalytic activity of these two catalyst systems differs tremendously. The Ru-arene/Tsdiamine complex, typically used for transfer hydrogenation, hardly reacts with H_2,[6] while the Ru-diphospine/diamine complex does so easily.

Recently, Ikariya et al. demonstrated that RuCp*-1,2-diamine complexes of general type **3** (Cp* = pentamethylcyclopentadienyl, η^5-C$_5$-(CH$_3$)$_5$), which are isoelectronic to the transfer hydrogenation catalyst **2**, were active catalysts for the hydrogenation of ketones with H_2 as hydrogen source.[7] This finding is one of the few known example of a homogeneous hydrogenation catalyst that is capable of activating molecular hydrogen without having at least one phosphine ligand around the metal center.[8] This study also concluded that the most active catalyst was obtained with a diamine having one tertiary and one primary amino function.

On the basis of these findings, we figured that an even more potent catalyst could be obtained by increasing the Lewis basicity of the tertiary nitrogen center of the ligand.[9] One possibility to accomplish this would be to incorporate a quinuclidine function in the ligand. Gratifyingly, two pseudo-enantiomeric 1,2-diamines containing a quinuclidine function and a primary amino function are commercially available. The quincorine-amine (QCI-amine) **4** and quincoridine-amine (QCD-amine) **5** are derived from the *Cinchona* alkaloids quinine and quinidine, respectively), Scheme 1.[10]

These *β*-diamines, containing four stereogenic centers each, including a fixed stereogenic (*S*)-configured *N*-bridgehead, have previously been used as ligands in Ir-catalyzed asymmetric transfer hydrogenation of ketones[11] and as chiral acylation catalysts.[12] Other ligands based on the quincorine and quincoridine scaffold, inlcuding *P,N*-ligands, have also been described.[13] However, to the best of our knowledge, no QCI/QCD-based ligands have previously been used in asymmetric hydrogenation reactions.

In this report, we demonstrate how the catalytic activity of the RuCp*-1,2-diamine complex, used for hydrogenation of ketones with H_2, may be substantially enhanced by the quinuclidine-based ligands **4** and **5**. These ligands also furnish fair

to good enantioselectivities for most substrates investigated. A kinetic and computational study was also undertaken. In addition to providing a working selectivity model, this study revealed a significant lowering of the activation energy for the dihydrogen split when a coordinating alcohol molecule mediated this process. Additional calculations showed that the same mechanism is the lowest energy pathway also in the Noyori type of diphosphine/diamine system.

Computational Details

General Procedures. Geometries of all substrates were calculated using the Jaguar program[14] using the B3LYP hybrid density functional,[15] together with the LACVP** and LACV3p+** basis sets. Normal-mode analysis revealed one imaginary frequency for each transition state. LACVP in Jaguar defines a combination of the LANL2DZ basis set[16] for ruthenium and the 6-31G basis set for other atoms. LACVP implies the use of an effective core potential for 28 core electrons of ruthenium and a (5s,6p,4d) primitive basis contracted to [3s,3p,2d]. Final energies were retrieved from single-point calculations at B3LYP/LACV3p+**. LACV3p+** differs from LACVP** by using the 6-311+G** basis set in place of 6-31G**.

Model Systems. Several model systems have been used to cover different aspects of the reaction (Figure 1). To start with, in the
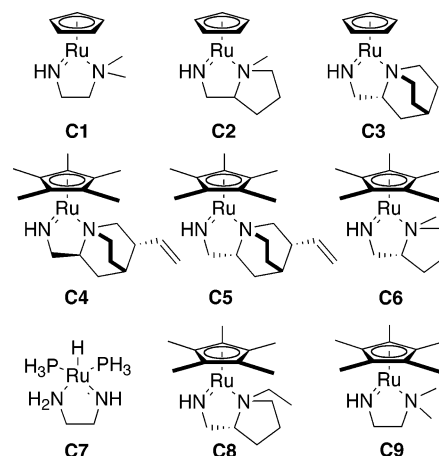

**Figure 1.** Catalytic systems used in the computational study.

investigation of the activation and splitting of H_2, Cp* was replaced by Cp. Also, the vinyl group in the ligands **4** and **5** was replaced by a hydrogen atom. In the study of regioselectivity in the addition of H_2 to Ru and in the study of the enantioselectivity in ketone reduction, the real systems were used.

Results and Discussion

Mechanism. A number of efficient Ru catalysts have been developed for the asymmetric reduction of ketones into optically

(6) Haack, K.; Hashigushi, J. S.; Fujii, A.; Ikaraya, T.; Noyori, R. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 285.
(7) Ito, M.; Hirakawa, M.; Murata, K.; Ikaraya, T. *Organometallics* **2001**, *20*, 379.
(8) (a) Blum, Y.; Czarkie, D.; Rahamim, Y.; Shvo, Y. *Organometallics* **1985**, *4*, 1459. (b) Vicente, C.; Shulpin, G. B.; Moreno, B.; Sabo-Etienne, S.; Chaudret, B. *J. Mol. Catal. A: Chem.* **1995**, *98*, L5.
(9) Ohwada, T.; Hirao, H.; Ogawa, A. *J. Org. Chem.* **2004**, *69*, 7486.
(10) Hoffmann, H. M. R.; Frackenpohl, J. *E. J. Org. Chem.* **2004** (21), 4293.
(11) Hartikka, A.; Modin, S. A.; Andersson, P. G.; Arvidsson, P. I. *Org. Biomol. Chem.* **2003**, *1*, 2522.
(12) Kuendig, E. P.; Lomberget, T.; Bragg, R.; Poulard, C.; Bernardinelli, G. *Chem. Commun.* **2004**, 1548.
(13) Saluzzo, C.; Breuzard, J.; Pellet-Rostaing, S.; Vallet, M.; Le Guyader, F.; Lemaire, M. *J. Organomet. Chem.* **2002**, *643*, 98.

(14) *Jaguar 4.2*; Schrödinger, Inc.: Portland, OR, 1991−2000.
(15) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.
(16) Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 299.
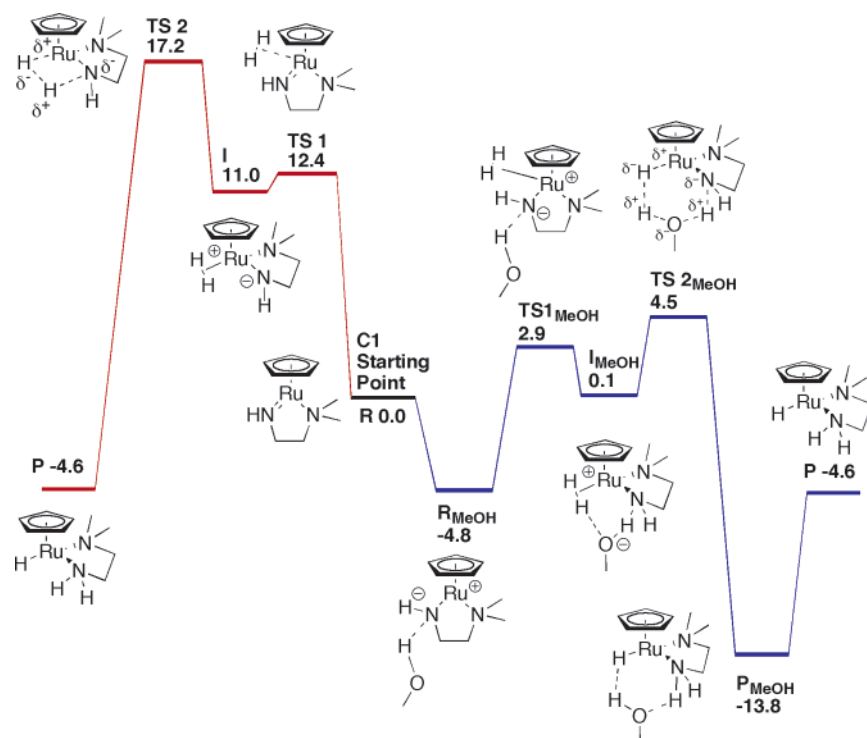
Figure 2. Potential energy surface at the B3LYP/LACV3P+**//B3LYP/LACVP** level including zero-point corrections for addition of H_2 to the 16-electron Ru complex and subsequent heterolytic cleavage in the diamine **C1** model system. Left: Nonalcohol-mediated pathway. Right: alcohol-mediated pathway.

active alcohols, either by hydrogenation or by transfer hydrogenation.[17] It has been postulated that both these reactions, when the ligand contains at least one ruthenium-coordinated sp^3 NH donor atom, proceed via a concerted mechanism where a Ru-hydride and a NH proton are transferred simultaneously from the catalyst to the C=O bond.[18] This mechanism is very likely the mechanism of the hydrogenation of ketones by **3**, and we assume the same mechanism is valid for catalysts **C4** and **C5**. Initially, we looked into the steps where dihydrogen is activated by ruthenium. This part of the reaction is of particular interest considering the low number of phosphine-free catalysts able to use dihydrogen gas as a source of hydrogen atoms. In addition, some reported calculations have shown relatively high activation energies (up to 25.2 kcal/mol) for similar heterolytic splittings of H_2.[18,19] A computed activation energy for a diamine/diphosphine complex has been reported as 13.4 kcal/mol, whereas the experimental activation enthalpy for this reaction in benzene was reported to be only 7.6−8.6 kcal/mol.[18c]

Ikaraya and co-workers have proposed a mechanism of heterolytic splitting of H_2 in which a solvent 2-propanol molecule participates in the transition state.[7] This mechanism has recently received support in the literature.[20] Morris and co-workers reported[18c] that the hydrogenation of acetophenone

catalyzed by a diamine diphosphine complex was independent of the ketone and alcohol concentrations. However, the same group has also reported that the reactions with related bis-(phosphine)[21] and tetradentate[20b] systems are much faster in 2-propanol than in benzene. This effect was presumed to be caused by the higher dielectric constant of 2-propanol compared to benzene and by hydrogen bonds from the solvent to the polarized transition state.

In this part of the study, we have investigated dihydrogen coordination and cleavage both for the diamine system used here and for the Noyori type of diamine/diphosphine system, with and without participation of solvent alcohol. The reaction paths studied are depicted in Figures 2 and 3, and the results are summarized in Tables 1 and 2.

The results in Table 1 indicate similar potential energy surfaces for the systems studied, except for **C7**, which has a higher affinity for dihydrogen. The rate-determining step for the formation of ruthenium hydride complexes is the heterolytic cleavage of η^2-coordinated dihydrogen. The activation energy for this step is around 17 kcal/mol. Experimentally, the ruthenium hydride complexes have been postulated to be formed reversibly for **C1**.[7] This reversible formation of ruthenium hydrides was used to rationalize a H/D scrambling observed in the study. We find formation of ruthenium hydride complexes exothermic by about −5 kcal/mol, and thus, the barrier for the reversible reaction, i.e., the decomposition of the ruthenium hydride to form H_2 from **P/C1**, will be substantial (21.8 kcal/mol).

(17) For a recent review see: Clapham, S.; Hadzovic, A.; Morris, R. H. *Coord. Chem. Rev.* **2004**, *248*, 2201.
(18) (a) Yamakawa, M.; Ito, H.; Noyori, R. *J. Am. Chem. Soc.* **2000**, *122*, 1466. (b) Noyori, R.; Yamakawa, M.; Hashigushi, S. *J. Org. Chem.* **2001**, *66*, 7931. (c) Abdur-Rashid, K.; Clapham, S. E.; Hadzovic, A.; Harvey, J. N.; Lough, A. J.; Morris, R. H. *J. Am. Chem. Soc.* **2002**, *124*, 15104.
(19) (a) Crabtree, R. H.; Siegbahn, P. E. M.; Eisenstein, O.; Rheingold, A. L.; Koetzle, T. *Acc. Chem. Res.* **1996**, *29*, 348. (b) Shubina, E. S.; Belkova, N. V.; Epstein, L. M. *J. Organomet. Chem.* **1997**, *536*, 17. (c) Crabtree, R. H. *Science* **1998**, *282*, 2000. (d) Guari, Y.; Ayllon, J. A.; Sabo-Etienne, S.; Chaudret, B.; Hessen, B. *Inorg. Chem.* **1998**, *37*, 640. (e) Grundemann, S.; Ulrich, S.; Limbach, H.-H.; Golubev, N. S.; Denisov, G. S.; Epstein, L. M.; Sabo-Etienne, S.; Chaudret, B. *Inorg. Chem.* **1999**, *38*, 2550. (f) Fryzuk, M. D.; MacNeil, P. A.; Rettig, S. J. *J. Am. Chem. Soc.* **1987**, *109*, 2803.

(20) (a) Sandoval, C. A.; Ohkuma, T.; Muñiz, K.; Noyori, R. *J. Am. Chem. Soc.* **2003**, *125*, 13490. (b) Rautenstrauch, V.; Hoang-Cong, X.; Churland, R.; Abdur-Rashid, K.; Morris, R. H. *Chem. Eur. J.* **2003**, *9*, 4954. (c) Casey, C. P.; Johnson, J. B.; Singer, S. W.; Cui, Q. *J. Am. Chem. Soc.* **2005**, *127*, 3100.
(21) Abbel, R.; Abdur-Rashid, K.; Faatz, M.; Hadzovic, A.; Lough, A. J.; Morris, R. H. *J. Am. Chem. Soc.* **2005**, *127*, 1870.
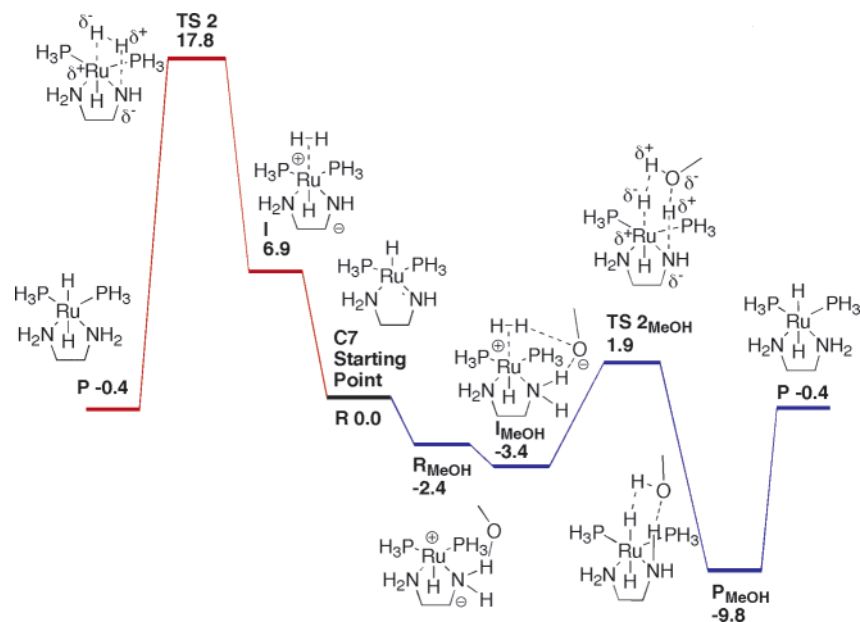
Figure 3. Comparison of reaction pathways for the solvent-nonassisted and -assisted heterolytic dihydrogen cleavage in diamine/diphospine model system **C7** (potential energy surface at the B3LYP/LACV3P+**//B3LYP/LACVP** level including zero-point corrections). Left: Nonalcohol-mediated pathway. Right: alcohol-mediated pathway.

Table 1. Calculated Energies (kcal/mol) for Dihydrogen Coordination and Cleavage *without* Participation of Solvent Alcohol[a]

	model system						
species	**C1**[b]	**C1**	**C1**[c]	**C2**	**C3**	**C3′**	**C7**
R	0	0	0	0	0	0	0
TS1	12.3	12.4	17.5	11.2	11.5	12.0	n.d.
I	12.8	11.0	13.3	10.0	10.9	11.2	6.9
TS2	18.2	17.2	20.3	15.9	18.6	17.6	17.8
P	−5.2	−4.6	−4.3	−6.1	−4.3	−4.2	0.4

[a] Energies at B3LYP/LACV3P+**//B3LYP/LACVP** including zero-point corrections. [b] Energies at B3LYP/LACVP** including zero-point corrections. [c] Free energies at B3LYP/LACV3P+**//B3LYP/LACVP**.

Table 2. Calculated Energies (kcal/mol) for Dihydrogen Coordination and Cleavage *with* Active Participation of Solvent Alcohol[a]

	model system								
species	**C1**[b,d]	**C1**[d]	**C1**[f]	**C2**[d]	**C3**[d]	**C3**[c,d]	**C5**[e]	**C5′**[c,e]	**C7**[d]
R	0	0	0	0	0	0	0	0	0
R$_{R'OH}$	−7.8	−4.8	3.2	−5.2	−5.1	−4.5	−7.8	−12.3	−2.4
TS1$_{R'OH}$	−0.2	2.9	14.4	2.1	3.2	4.3	n.d.	n.d	n.d.
I$_{R'OH}$	−1.8	0.1	10.3	−0.9	0.0	0.4	−6.5	−7.3	−3.4
TS2$_{R'OH}$	0.8	4.6	19.5	3.6	4.5	5.8	−3.2	2.5	1.9
P$_{R'OH}$	−17.6	−13.7	−5.0	−14.0	−13.8	−13.1	−19.2	−16.9	−9.8

[a] Energies at B3LYP/LACV3P+**//B3LYP/LACVP** including zero-point corrections. [b] Energies at B3LYP/LACVP** including zero-point corrections. [c] Addition of H_2 *cis* to the methyleneamine group. [d] R′OH = MeOH. [e] R′OH = *i*-PrOH. [f] Free energies at B3LYP/LACV3P+**//B3LYP/LACVP**.

Table 2 shows the results from the calculations on the alcohol-mediated activation and cleavage of H2. The calculated transition state structures for complexes **C7** and **C5** are shown in Figure 4. The rate-determining step is again found to be the cleavage of the η^2-coordinated dihydrogen, but now, the activation energies are substantially decreased. In particular, the alcohol stabilizes the coordination of H_2 and the subsequent change in coordination geometry around the metal center. As a consequence, the activation energy is decreased by ca. 7−10 kcal/mol using the hydrogen-bonded alcohol complex as a

reference. Hydrogen bonding between the ruthenium complex and alcohol will substantially increase the reversibility of the reaction with an activation barrier for the formation of a hydrogen−hydrogen bond around 18 kcal/mol. However, considering the activation free energy for the formation of I$_{R'OH}$ from P$_{R'OH}$ with **C1** (24.5 kcal/mol), the mechanism proposed by Ikaraya and co-workers for hydrogen/deuterium exchange could not be corroborated.

Morris and co-workers have reported a calculated activation energy for the heterolytic cleavage of H_2 by diamine/diphosphine system **C7** of 13.4 kcal/mol. Our results indicate a considerable decreased activation energy with an active participation of the solvent, from 10.9 to 5.3 kcal/mol for the conversion of **I/C7** to **P/C7**. The importance of an alcoholic solvent for the diamine/diphosphine system was also observed in Noyori's initial report,[5a] and later Casey found a similar role of the alcoholic solvent for the Shvo catalyst.[20c] For the diamine system **C1**, the same activation energy decreased from 6.2 to 4.4 kcal/mol. Here, the accelerating effect could instead be attributed to a stabilization of the dihydrogen complex.

As mentioned above, Ikaraya and co-workers have concluded from a series of experiments using deuterated *i*-PrOH and D2 that the addition of dihydrogen over the Ru−N bond is reversible.[7] Thus, the release of *i*-PrOH and the subsequent coordination/reduction of substrate was concluded to be slower than re-formation of the 16-electron complex. According to our calculations, the activation energy for reduction of acetophenone by **PR′OH/C1** is 14.2 kcal/mol (19.1 kcal/mol in free energy) and the reverse reaction, i.e., formation of a H−H bond, has an activation energy of 18.3 kcal/mol (24.5 kcal/mol in free energy).
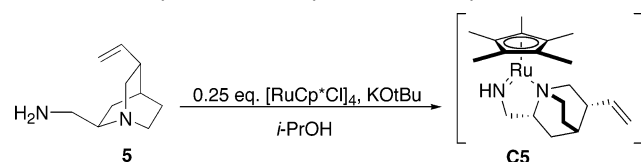
To summarize the calculations, we propose a reaction mechanism starting from R. This species coordinates a solvent alcohol molecule, and this in turn coordinates the dihydrogen, a step greatly facilitated by the hydrogen bond to the ruthenium-coordinated amide nitrogen. The last step is a heterolytic splitting of H_2 mediated by the alcohol hydroxyl group. Thereby, the
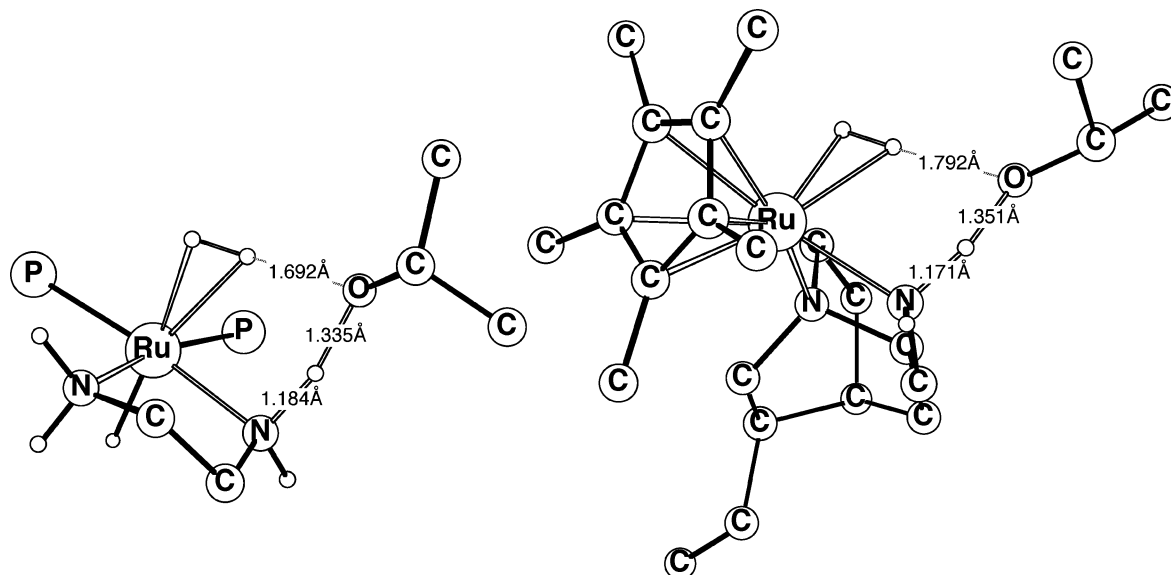
Figure 4. Transition state structures for the alcohol-mediated heterolytic cleavage of coordinated dihydrogen for complexes **C7** and **C5**.

Scheme 2. Preparation of RuCp*-Diamine Complex **C5**

Table 3. Rates of the Reduction of Acetophenone Using Complexes **C5**, **C8**, and **C9** at Different Concentrations[a]

complex	conc (mM)	rate (μmol s^{-1})
C5	4.75	2.10
C5	1.9	0.64
C5	0.95	0.17
C8	4.75	0.086
C9	4.75	0.39

[a] The substrate concentration was 0.475 M in each case. Reactions were performed at 25 °C at 25 bar pressure of H_2.

catalyst is ready to replace the coordinated solvent by a substrate molecule and perform the hydrogenation of the carbonyl. We assume breaking and making of hydrogen bonds to solvent and substrate is a fast and solvent-assisted process in 2-propanol. In absolute numbers, the free energy of activation for the heterolytic cleavage of H_2 by **C1** is slightly lower with an active participation of alcohol. This is largely due to the entropic effect on the free energy caused by solvent coordination. This effect is likely overestimated as the reaction is run in 2-propanol as solvent and not in the gas phase. The reduction of ketones by the ruthenium hydride species was found to be slightly lower in free energy than the heterolytic cleavage of H_2 (19.1 compared to 19.5 kcal/mol); however, the low solubility of hydrogen in 2-propanol will make the heterolytic cleavage of H_2 rate determining. Thus, the overall reaction is expected to be zero-order in substrate, and **R** will be the resting state of the catalyst.

Kinetics. According to our calculations and proposed reaction mechanism, the reaction catalyzed by **C5** would be first order with respect to catalyst and hydrogen pressure. This mechanism is in conflict with a reversible formation of a ruthenium hydride complex. To investigate this hypothesis, we prepared complex **C5** by reacting quincoridine **5** with [RuCp*Cl]$_4$ in 2-propanol in the presence of potassium *tert*-butoxide for 30 min, Scheme 2, and utilized this complex for the reduction of acetophenone.

As shown in Table 3 and Figure 5a, the reaction showed the expected first-order dependence on both catalyst concentration and hydrogen pressure. We also confirmed the expected zero-order dependence in substrate, Figure 5b.

To compare the reactivity between catalysts, the same reaction was also performed with previously reported[7] complexes **C8** and **C9**. Table 3 shows that catalyst **C5** is approximately 24 times faster than complex **C8**, in agreement with the postulation made at the beginning of this study that the increased basicity

of the quinuclidine nitrogen present in **C5** should yield a more potent catalyst than **C8** and **C9**. The importance of an alcoholic solvent for this reaction was supported by performing the hydrogenation in a nonprotic solvent (THF), where the hydrogenation was found to be substantially slower, as was also observed in Ikariya's initial report.[7] However, it should be noted that the solubility of H_2 varies with solvents. While this quinuclidine-based diamine system is the most reactive phosphine-free ruthenium catalyst reported to date, it is still less efficient than Noyori type of catalysts for the hydrogenation of prochiral ketones.[5]

Selectivity. Encouraged by the high reaction rates obtained for the quincoridine-Ru complex **C5**, we next wanted to examine the enantioselectivity of this catalyst in the reduction of prochiral ketones. The results of these reactions are shown in Table 4.

Interestingly, and *in sharp contrast* with many other asymmetric hydrogenation catalysts, aryl ketones having bulky alkyl groups reacted with higher enantioselectivity than those having smaller substituents. While acetophenone (Table 4, entry 1) was hydrogenated to (*S*)-phenylethanol in 75% ee, the sterically more demanding 2,2-dimethylpropiophenone and valerophenone gave the corresponding alcohols in 90% ee (Table 4, entries 3 and 5).

In an earlier study using Ru(*p*-cymene)(2-azanorbornyl-3-methanols) as catalysts, we found that $\Delta\Delta E^{\ddagger}(R-S)_{\text{Exp}}$ was negatively correlated with the width of the alkyl substituent of the substrate.[22] The parameter used to describe this property was the STERIMOL B1 parameter. In the present study, no

(22) Brandt, P.; Roth, P.; Andersson, P. G. *J. Org. Chem.* **2004**, *69*, 4885.
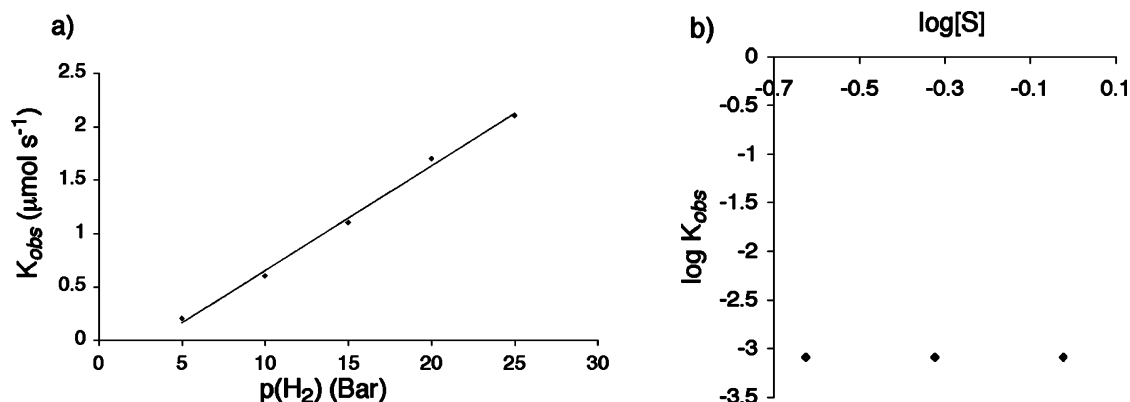
Figure 5. (a) Observed rate of the reaction vs hydrogen pressure (slope = 0.098 μmol bar^{-1} s^{-1}, intercept = -0.3 μmol s^{-1}, R^2 = 0.995) for the **C5**-catalyzed reduction of acetophenone. The hydrogenations were performed at 25 °C as 0.475 M solutions of substrate and 4.75 mM solutions of catalyst. The negative intercept may well be explained by a different rate-determining step at low pressure. (b) Plot of initial rates as a function of substrate concentration; the slope shows reaction order zero with respect to acetophenone.
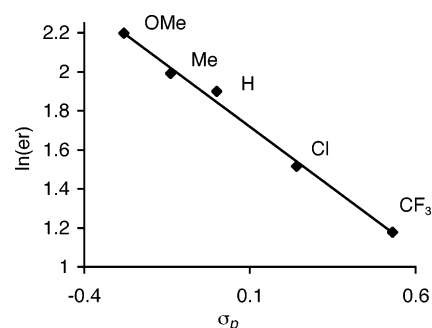
Table 4. Asymmetric Hydrogenation of Aryl Alkyl Ketones Catalyzed by **C5**[a]

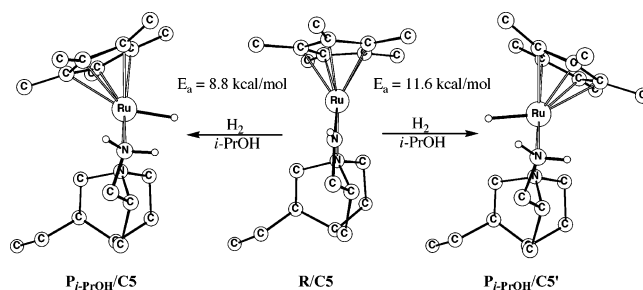| entry	Ar	R	conv (%)	ee (%)[b]	time (min)	abs config[c]
1	C_6H_5	CH_3	+99	75	11	(S)
2	C_6H_5	i-C_3H_7	99	74	30	(S)
3	C_6H_5	t-C_4H_9	99	90	30	(S)
4	C_6H_5	n-C_4H_9	99	81	30	(S)
5	C_6H_5	i-C_4H_9	99	90	30	(S)
6	o-$CH_3C_6H_4$	CH_3	+99	82	15	(S)
7	m-$CH_3C_6H_4$	CH_3	+99	71	15	(S)
8	p-$CH_3C_6H_4$	CH_3	99	76	11	(S)
9	p-$CH_3OC_6H_4$	CH_3	+99	79	11	(S)
10	o-$CH_3OC_6H_4$	CH_3	99	86	14	(S)
11	p-$CF_3C_6H_4$	CH_3	99	62	10	(S)
12	p-Cl-C_6H_4	CH_3	99	54	11	(S)
13	$3,4,5$-FH_2C_6	CH_3	99	44	40	(S)
14	$2,6$-FH_2C_6	CH_3	99	50	42	(S)
15	1-naphthyl	CH_3	+99	81	30	(S)

[a] All reactions were complete within 42 min. Experimental conditions: Substrate-to-catalyst ratio 100:1, 25 bar H_2, 0.475 M in i-PrOH according to the general procedure in the Experimental Section. [b] Enantiomeric excess determined by chiral GC or HPLC. [c] Absolute configuration correlated from previous reported GC or HPLC elution order.

Figure 6. Results of the hydrogenation of aryl ketones. Labels refer to the p-substituent on the aryl ring. ln(er) vs σ_p (er = enantiomeric ratio) (slope = -1.26, intercept = 1.85, R^2 = 0.993).

Figure 7. Coordination and alcohol-assisted cleavage of dihydrogen to 16e Ru complex **R/C5**.

such straightforward trends could be observed. This is indicative of a more complex interaction at the interface between the substrate and the catalyst. Despite the reversed geometrical preference in the favored TS (see also the selectivity model presented below), where the aryl group of the substrate is facing the alkyl part of the ligand, there is an electronic effect of similar size to that for regular Ru−(amino alcohol)(arene) catalysts.[22] That is, the more electron rich the substrate, the better the selectivity. This correlation is depicted in Figure 6. The observed trend implies either of two alternatives, namely, that there is a repulsive electrostatic component between the aryl of the substrate and the formally negatively charged Cp* ligand of the catalyst. Or, there is an attractive electrostatic interaction between the alkyl part of the ligand and the aryl of the substrate. This observation could potentially be used to find substrates electrostatically more suitable for this class of catalysts.

The diastereomeric diamine ligand **4**, derived from quincorine, had reactivity similar to that of **C5** and gave products of opposite configuration but in a markedly less selective manner (99% conversion, ee = 41% (*R*)-phenylethanol).

Selectivity Model. To see how well the postulated mechanism correlates with the experimental results, we compared the selectivities obtained for various ketones with the catalyst structures derived from the DFT calculations. This analysis is greatly facilitated by the presence of the η^5-bonded Cp* ligand, since it occupies three coordination sites on the octahedral Ru and thus reduces the number of possible diastereomeric complexes.

In the initial step, the alcohol-mediated addition of dihydrogen can take place from two sides of the 16e complex **R/C5**, leading to two diastereomeric complexes. Calculations favor formation of complex **P$_{i-PrOH}$/C5**, which has the lowest activation energy for the heterolytic, alcohol-mediated cleavage of the coordinated dihydrogen (8.8 kcal/mol for **P$_{i-PrOH}$/C5** compared to 11.6 kcal/mol for **P$_{i-PrOH}$/C5′**, Figure 7).

The reduction step is found to involve a concerted, but asynchronous, addition of a hydride to the carbonyl carbon followed by the transfer of a proton from nitrogen to oxygen. The calculated and experimentally observed selectivities for the

Table 5. Comparison between Experimental and Calculated Enantioselectivities (energies in kcal/mol) for the Diamine−Ru−Cp*-Catalyzed Hydrogenation of Acetophenone and 2,2-Dimethylpropiophenone

entry	catalyst	substrate	$\Delta\Delta E^{\ddagger}(R{-}S)^{a}_{calcd}{}^{b}$	ee, % (R or S)$_{Exp}$	$\Delta\Delta E^{\ddagger}(R{-}S)_{Exp}{}^{c}$
1	**C5**	PhCOMe	1.9	75 (S)	1.15
2	**C8**	PhCOMe	−2.0	72 (R)	−1.07
3	**C4**	PhCOMe	−1.1	41 (R)	−0.52
4	**C5**	PhCOtBu	5.6	90 (S)	1.74

[a] Refers to the absolute configuration of the alcohol product. [b] All calculations were performed on the full structures. Energies reported are from the B3LYP/LACV3P+**//B3LYP/LACVP** including zero-point correction. [c] Calculated from the observed ee.
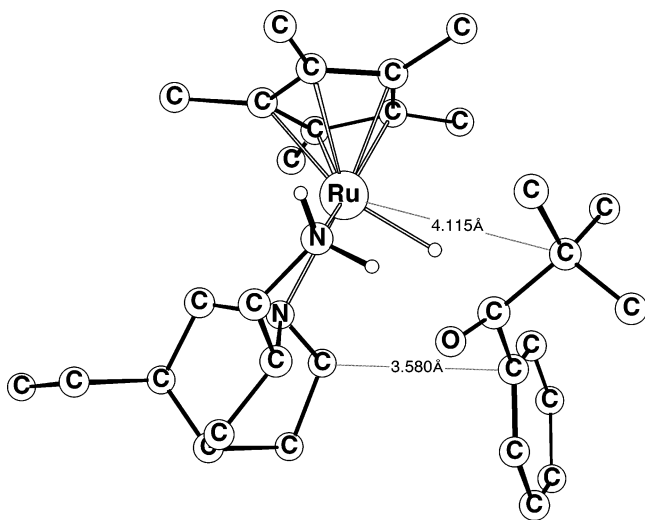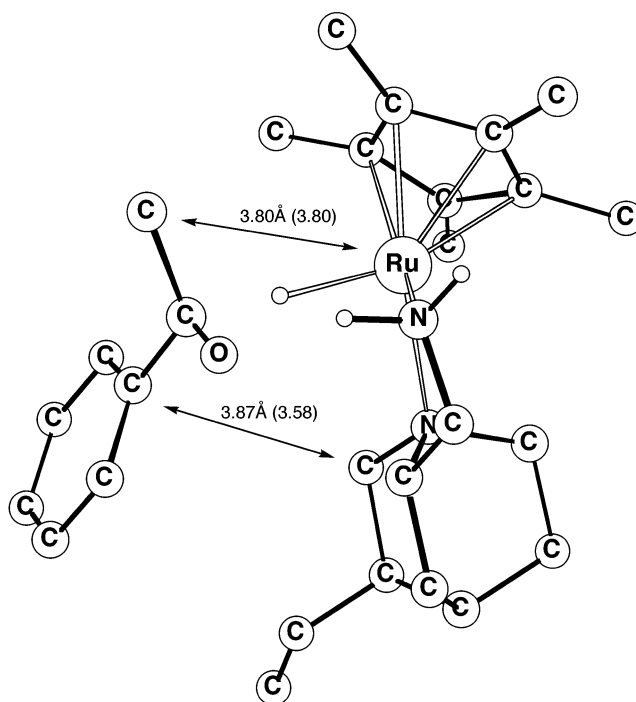

Figure 8. Interactions between the substrate, ligand, and the Cp* ring in the **C5**-catalyzed addition of hydride to the *re*-face of the ketone.
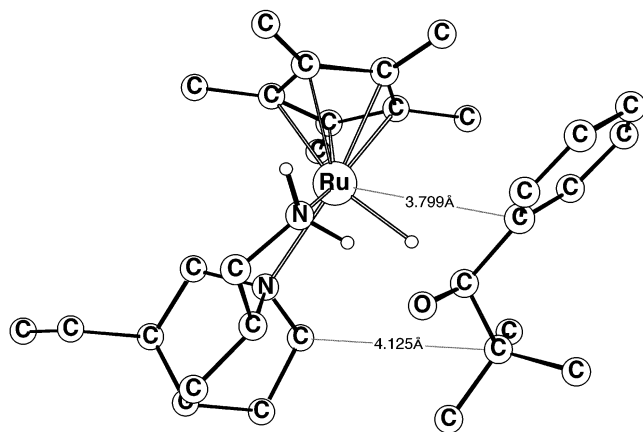
Figure 9. Interactions between the substrate, ligand, and the Cp* ring in the **C5**-catalyzed addition of hydride to the *si*-face of the ketone.

enantioselective reduction step for different catalysts and substrates are summarized in Table 5.

The experimental and theoretically predicted selectivities agree well for **C5**, showing that the model may be used to provide both quantitative and qualitative information concerning the stereochemical outcome of the reaction. The addition to the *re*-face of the ketone (Figure 8) is favored by 2.2 kcal/mol, probably as this will avoid a steric clash between the phenyl group and the Cp* ligand, being present in the corresponding addition to the *si*-face, Figure 9.

As seen in Table 5, the model also correctly predicts the *si*-face addition by **C8** to be favored over *re*-face addition, which is in agreement with the results published earlier by Ikariya.[7]

The lower selectivities obtained for complex **C4** originate from a collision between the vinyl group of the ligand and the

Figure 10. Interactions between acetophenone, the quincorine-derived ligand **4**, and the Cp* ring in the addition to the *si*-face of the ketone. Values given in parentheses refer to the reduction of acetophenone using **C5**.

phenyl ring of the substrate (Figure 10). This interaction leads to destabilization of the TS giving *si*-face addition, and the calculated energy difference between the two diastereomeric TSs is now only 1.2 kcal/mol (compared to 2.0 kcal/mol for the quincoridine complex).

Finally, the increased enantioselectivity observed for the bulky 2,2-dimethylpropiophenone is also in agreement with the DFT model, which predicts the *si*-addition to be favored by 5.5 kcal/mol. This can be attributed to (i) a reasonable fit of the *t*-Bu group into the pocket formed between the H−Ru−N−H moiety and the Cp* ligand (Figure 8) and (ii) the collision between the *t*-Bu group and the quinuclidine in the TS, giving *si*-face addition (Figure 9).

Conclusions

In conclusion, we have shown that the complex formed between [RuCp*Cl]₄ and the commercially available chiral diamine quincorine-amine, originally derived from quinine, is a highly reactive catalyst for the phosphine-free enantioselective hydrogenation of aryl ketones. A detailed mechanistic investigation revealed that the quinuclidine-based ligand is approximately 24 times more reactive than previously described catalysts, and the enantioselectivities obtained are modest to good (up to 90% ee). The straightforward methodology and the availability of

all reagents imply that this method will find broad practical use. Interestingly, the diastereomer of quincorine-amine, i.e., quincoridine-amine, also showed high activity; however, the enantioselectivities obtained with this catalyst were lower. This finding represents a rare exception where these diastereoisomers do not function as pseudo-enantiomeric reagents for an asymmetric reaction. The reason for the lower, but opposite stereoselectivity seen with the quincoridine-amine, as compared to the quincorine-amine, could be rationalized through a computational study of the mechanism of the reaction. In addition to providing a working selectivity model, these calculations also revealed that the activation energy for the dihydrogen split involved is significantly lowered when a solvent alcohol molecule mediates the process. This finding is of utmost importance, as it allows a rational design of a second-generation phosphine-free catalysts; moreover, it provides an explanation for the reported discrepancy between experimental and theoretical activation energies reported for Noyori's diphosphine/diamine-mediated enantioselective hydrogenation system, which was computationally shown to involve the same alcohol-mediated activation.

Supporting Information Available: General experimental methods, details for the chiral separation methods, and coordinates for all calculated structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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