# Catalytic Asymmetric Hydrogenation of Imines with a Chiral Titanocene Catalyst: Kinetic and Mechanistic Investigations

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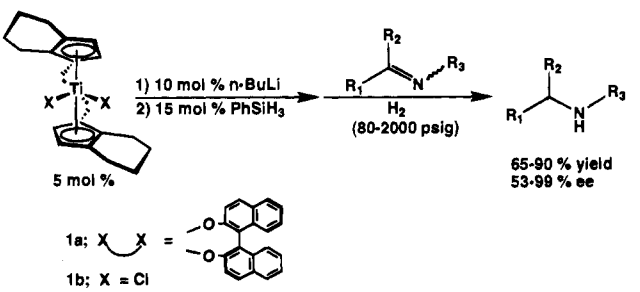
**Abstract:** A kinetic study of the asymmetric titanocene-catalyzed imine hydrogenation has revealed the rate law to be rate = $k_{obs}$[Ti][$H_2$], for cyclic imine **2** and acyclic imine **4**. This rate law is consistent with a mechanism in which the imine reacts with a titanium hydride in a fast 1,2-insertion step, to form a titanium amide intermediate, followed by slow reaction of the amide complex with hydrogen to produce the amine and regenerate the titanium hydride. Labeling studies for the hydrogenation of **2** and studies using enantiomerically enriched aldimine **6** indicate that $\beta$-H elimination is also slow, relative to hydrogenolysis, for both **2** and **4**. The enantiomeric excesses for the hydrogenation of **2** were found to be essentially insensitive to changes in reaction conditions. However, for imine **4**, the ee's were dependent on several variables, most significantly hydrogen pressure. This phenomenon has been explained on the basis of the interconversion of the *syn* and *anti* isomers of **4** during the hydrogenation. It has been shown that *syn*-**4** reacts faster than *anti*-**4**, a necessary condition for the explanation presented to hold true. A stereochemical model based on steric and electronic considerations has been proposed to account for the observed selectivity. This model can aid in predicting the absolute configurations of the amines formed in this process.

The catalytic, asymmetric hydrogenation of unsaturated organic molecules is an efficient method for the synthesis of enantiomerically enriched compounds. Remarkable success has been achieved in the enantioselective reduction of olefins and ketones.[1] More recently, the hydrogenation of imines with chiral metal complexes has received increasing attention.[2] Several homogeneous hydrogenation catalysts have been studied in detail for both asymmetric[3] and nonasymmetric hydrogenations.[4] These studies have provided crucial insight into the mechanism and origin of selectivity for these systems.

We recently reported the first early transition metal catalyst for the asymmetric reduction of imines.[5] The catalyst system affords amines in good isolated yields and with good to excellent enantiomeric excesses (Scheme 1). In this paper, we report the results of a kinetic and mechanistic investigation of this process.

**Scheme 1**




## Results

The chiral titanocene complex employed in our studies was first reported by Brintzinger.[6] It can be readily resolved into enantiomerically pure form by formation of its binaphtholate derivative **1a**.[6] On reaction of **1a** or **1b** with 2 equiv of *n*-butyllithium[7] in THF, followed by 2.5–3 equiv of phenylsilane, an active hydrogenation catalyst is formed, which we propose to be a titanium(III) hydride species.[8–10] The proposed catalytic cycle is shown in Scheme 2. The first step involves 1,2-insertion of the imine into the titanium hydride to form two diastereomeric titanium amide complexes.[11] The second step is hydrogenolysis of these amides, via a $\sigma$-bond metathesis

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(1) (a) Keonig, H. E. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Orlando, FL, 1985; Vol. 5, Chapter 3, p 71. (b) Kitamura, M.; Hsiao, Y.; Ohta, M.; Tsukamoto, M.; Ohta, T.; Takaya, H.; Noyori, R. *J. Org. Chem.* **1994**, *59*, 297. (c) Noyori, R. *Science* **1990**, *248*, 1194. (d) Noyori, R. *J. Am. Chem. Soc.* **1987**, *109*, 1596. (e) Burk, M. J. *J. Am. Chem. Soc.* **1991**, *115*, 8518.

(2) (a) Burk, M. J.; Feaster, J. E. *J. Am. Chem. Soc.* **1992**, *114*, 7266 and references cited therein. (b) Bakos, J.; Orosz, A.; Heil, B.; Laghmari, M.; Lhoste, P.; Sinou, D. *J. Chem. Soc., Chem. Commun.* **1991**, 1684. (c) Spindler, F.; Pugin, B.; Blaser, H. U. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 558. (d) Chan, Y. N. C.; Osborn, J. A. *J. Am. Chem. Soc.* **1990**, *112*, 9400. (e) Becker, R.; Brunner, H.; Mahboobi, S.; Wiegrebe, W. *Angew. Chem.* **1985**, 97.

(3) (a) Halpern, J. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Orlando, FL, 1985; Vol. 5, Chapter 2, p 41. (b) Landis, C. R.; Halpern, J. *J. Am. Chem. Soc.* **1987**, *109*, 1746. (c) Halpern, J. *J. Am. Chem. Soc.* **1991**, *113*, 589. (d) Burk, M. J.; Feaster, J. E.; Nugent, W. M.; Harlow, R. L. *J. Am. Chem. Soc.* **1993**, *115*, 10125. (e) Becalski, A. G.; Cullen, W. R.; Fryzuk, M. D.; James, B. R.; Kand, G.-J.; Rettig, S. J. *Inorg. Chem.* **1991**, *30*, 5002.

(4) (a) Halpern, J.; Riley, D. P.; Chan, A. S. C.; Pluth, J. J. *J. Am. Chem. Soc.* **1977**, *99*, 8055. (b) Chan, A. S. C.; Halpern, J. *J. Am. Chem. Soc.* **1980**, *102*, 838. (c) Rosales, M.; Gonzalez, A.; Alvarado, Y.; Rubio, R.; Andriollo, S.; Sanchez-Delgado, R. A. *J. Mol. Catal.* **1992**, *75*, 1.

(5) (a) Willoughby, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 7562. (b) Willoughby, C. A.; Buchwald, S. L. *J. Org. Chem.* **1993**, *58*, 7627. (c) Willoughby, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 8957.

(6) Wild, F. R. W. P.; Zsolnai, J.; Huttner, G.; Brintzinger, H. H. *J. Organomet. Chem.* **1982**, *232*, 233.

(7) (a) It has been shown by Martin that titanocene dichloride reacts with 2 equiv of an alkyl Grignard reagent, in the presence of a diene to form, first titanocene monochloride and then an allyl titanocene species. This was proposed to occur via a titanium(III) hydride intermediate (Martin, H. A.; Jellinek, F. *J. Organomet. Chem.* **1968**, *12*, 149). (b) Brintzinger has provided EPR evidence that reaction of titanocene dichloride with alkyl Grignard or alkyl lithium reagents forms a titanium(III) hydride, although at temperatures above −20 °C this complex was unstable (cf. Brintzinger, H. H. *J. Am. Chem. Soc.* **1967**, *89*, 6871).

(8) The exact nature of the active species remains unclear. Solutions of this species are extremely air sensitive and exhibit no resonances in the $^1$H NMR spectrum. EPR spectra show several signals, indicating that a complex mixture of paramagnetic Ti(III) species are present, the predominant signal is characteristic of a titanium(III) silyl complex.[31] Treatment of the catalyst solution (using **1a** as a precursor) with lead(II) chloride regenerates **1a**.[29]

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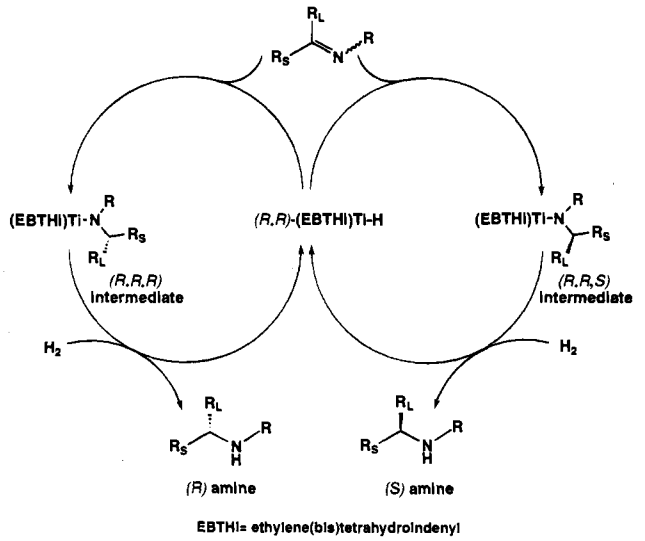
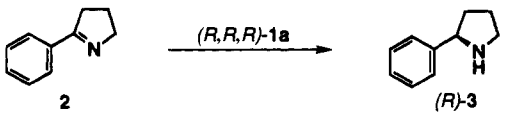
**Scheme 2**




process,[12] to form the enantiomeric amines and regenerate the titanium hydride.

During investigation of the possible utility of this catalyst system for the synthesis of enantiomerically enriched amines, differing patterns of reactivity emerged for cyclic and acyclic imines. Therefore, the behavior of these two classes of imines will be discussed separately.

**Asymmetric Hydrogenation of Cyclic Imines.** We examined the kinetics of the hydrogenation of 2-phenylpyrroline (**2**) with the catalyst system described above (eq 1). The reactions




(1)

were conducted in a Parr model 4565 autoclave at constant catalyst concentration and constant hydrogen pressure. Formation of amine was monitored, versus an internal standard, by capillary GC analysis of aliquots taken from the reaction vessel. During the course of the reaction only **2**, **3**, and phenylsilane were observed by GC.

The effects of varying reaction parameters on the reaction rate are shown by the data in Table 1. When the *(R,R,R)* enantiomer of **1a** was employed as the precatalyst, *(R)*-2-phenylpyrrolidine (**3**), was produced. Of significance is that the observed enantiomeric excess of the isolated amine remained essentially constant under different reaction conditions (Table 1). This behavior distinguishes cyclic imines from acyclic ones as the latter show a dependence of ee on hydrogen pressure (*vide infra*) with this catalyst system.

**Table 1.** Rate Data for the Hydrogenation[a] of 2-Phenylpyrroline (**2**)

| $[Ti]_o$ (mmol/L) | $[imine]_o$ (mmol/L) | $H_2$ pressure (psi) | reaction rate (mmol/(L min)) | ee of amine (%) |
|---|---|---|---|---|
| 3.75 | 150 | 815 | 1.16 (±0.07) | |
| 3.75 | 75 | 815 | 1.20 (±0.07) | 99 |
| 3.75 | 75 | 615 | 0.94 (±0.05) | 99 |
| 3.75 | 75 | 415 | 0.61 (±0.03) | 99 |
| 3.75 | 75 | 215 | 0.32 (±0.02) | 99 |
| 3.75 | 75 | 215[b] | 0.21 (±0.03) | 98 |
| 7.50 | 75 | 415 | 1.33 (±0.05) | 99 |
| 5.63 | 75 | 415 | 0.94 (±0.05) | |
| 1.88 | 75 | 415 | 0.28 (±0.05) | 98 |

[a] All reactions were conducted at 45 ± 1 °C. [b] Run with $D_2$.

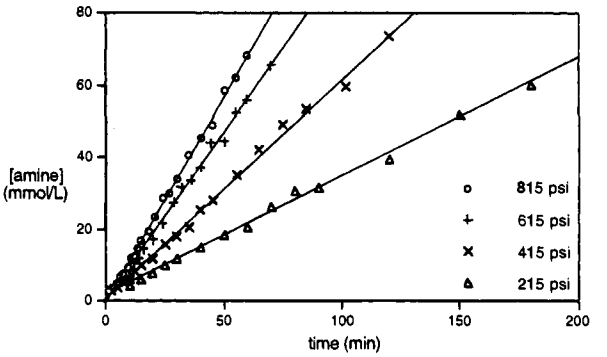



**Figure 1.** Plot of amine concentration vs time for the hydrogenation of **2** at various pressures.

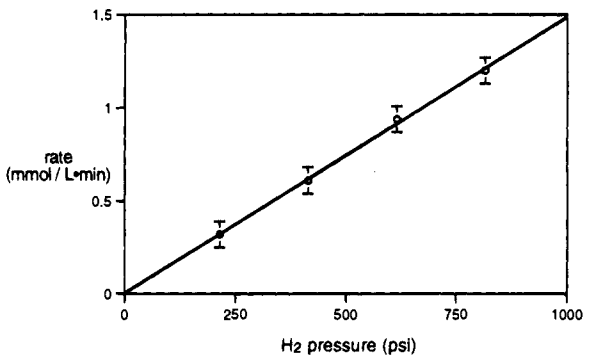



**Figure 2.** Plot of rate vs hydrogen pressure for the hydrogenation of **2**.

Figure 1 shows a plot of amine concentration versus time at various hydrogen pressures. The data fall on a straight lines for at least 3 half-lives, indicating that the reaction rate is independent of imine concentration. (This conclusion was verified by doubling the initial imine concentration and observing no change in rate.) A plot of rate versus hydrogen pressure gave a straight line, as shown in Figure 2. A plot of log rate versus log hydrogen pressure (not shown) yielded a straight line with slope of 1.0, demonstrating that the reaction is first order in hydrogen. Plotting reaction rate versus initial catalyst concentration also yielded a straight line (Figure 3). A plot of log rate versus log titanium concentration (not shown) was also linear with a slope of 1.1, implying first-order dependence in catalyst. Varying the concentration of phenylsilane had a negligible effect on rate (10% over 10-fold excess), suggesting that this parameter is not involved in the rate law.[9] From the above data we obtain the experimental rate expression given in eq 2.

(9) For other examples of titanium(III) hydrides cf.: (a) Pattiasina, J. W.; Bolhius, F.; Teuben, J. H. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 330. (b) Luinstra, G. A.; Teuben, J. H. *J. Am. Chem. Soc.* **1992**, *114*, 3361. (c) Bercaw, J. E.; Brintzinger, H. H. *J. Am. Chem. Soc.* **1969**, *91*, 7301. (d) Bercaw, J. E.; Marvich, R. H.; Bell, L. G.; Brintzinger, H. H. *J. Am. Chem. Soc.* **1972**, *94*, 1219.

(10) Titanium(III) hydrides have been implicated in a variety of reactions of cf. ref 7 and the following: (a) Lehmkuhl, H.; Tsien, Y.-L. *Chem. Ber.* **1983**, *116*, 2437. (b) Colomer, E.; Corriu, R. *J. Organomet. Chem.* **1974**, *82*, 367. (c) Sato, F. *J. Organomet. Chem.* **1985**, *285*, 53. (d) Sato, F.; Jinbo, T.; Sato, M. *Tetrahedron Lett.* **1980**, *21*, 2171. (e) Sato, F.; Jinbo, T.; Sato, M. *Tetrahedron Lett.* **1980**, *21*, 2175. (f) Nakano, T.; Nagai, Y. *Chem. Lett.* **1988**, 481. (g) Sato, F. *Janseen, Chim. Acta*, **1990**, *8*, 3. (h) Burgess, K.; van der Donk, W. A. *Tetrahedron Lett.* **1993**, *34*, 6817.

(11) For examples of titanium(III) amide complexes cf.: (a) Feldman, J.; Calabrese, J. C. *J. Chem. Soc., Chem. Commun.* **1991**, 1042. (b) Pattiasina, J. W.; Heeres, H. J.; Bolhuis, F.; Teuben, J. H.; Spek, A. L. *Organometallics* **1987**, *6*, 1004.

(12) Woo, H. G.; Tilley, T. D. *J. Am. Chem. Soc.* **1989**, *111*, 8043.

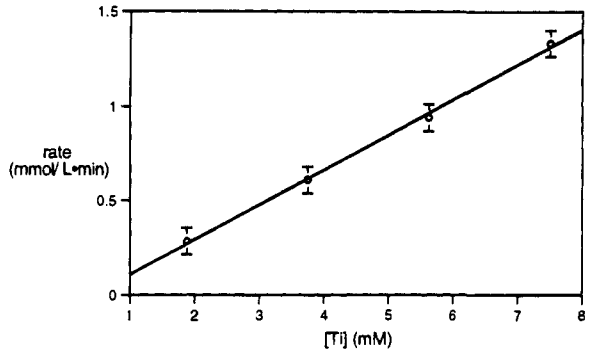



**Figure 3.** Plot of rate vs catalyst concentration for the hydrogenation of **2**.

$$\text{rate} = k_{obs}[\text{Ti}][H_2] \quad (2)$$

Conducting the reaction with deuterium (215 psi) rather than hydrogen resulted in a rate decrease from 0.32 to 0.21 mmol/(L min). From this data, a kinetic isotope effect of 1.5(±0.2) was calculated. As expected when the reduction of **2** was conducted under 80 psig of deuterium at 65 °C complete deuterium incorporation was observed at the stereogenic carbon (Figure 4). Quite unexpectedly, however, about 0.8 mol of deuterium per mole of amine was observed in the ortho position of the phenyl group,[13] as determined by $^1H$ and $^2H$ NMR. Four to five percent deuterium incorporation was observed at the other carbon α to the nitrogen. By $^1H$ and $^2H$ NMR the product was a single diastereomer, the relative stereochemistry of the deuteria was tentatively assigned as *cis* on the basis of the known addition of hydrogen *trans* to the 5-substituent in 2,5-disubstituted pyrrolines.[14] At 50% conversion imine **2** contained ca. 50% deuterium in the ortho position. When the unlabeled amine (*R*)-**3** was subjected to the same reaction conditions (80 psig $D_2$, 65 °C), no deuterium incorporation was observed. This indicates that the process of deuterium incorporation into the phenyl group is independent of the reactions leading to amine since it occurs only with the starting material.

We also examined the use of alternative catalyst precursors for the hydrogenation of **2** (Table 2). Starting with enantiomerically pure **1a** as the precursor, **2** was reduced to **3** with identical an enantiomeric excess and similar isolated yield either in the presence or in the absence of phenylsilane. However, when phenylsilane was not used, activation with *n*-butyllithium had to be conducted under a hydrogen atmosphere.[15] The dimethyl derivative **1c** (used in racemic form), catalyzed the hydrogenation reaction to afford the amine in good yield. In this case no reaction was observed unless hydrogen was added prior to the addition of **2**. Significantly, the titanium(III) complex **1d** when treated with 1 equiv of *n*-butyllithium, catalyzed the conversion of **2** to **3** in good yield. The titanium(III) amide complex **1e** which is an analog of the proposed intermediate in the hydrogenation reaction, catalyzed the reduction of **2** to **3** with no *n*-butyllithium or phenylsilane added.

**Asymmetric Hydrogenation of Acyclic Imines.** As previously mentioned, the behavior of acyclic imines differs dramatically from that of cyclic imines. Typical differences are demonstrated in the behavior of *N*-(1-cyclohexylethylidene)-benzylamine (**4**, eq 3). We note here that an important difference between acyclic imines and cyclic imines is that acyclic imines exist as mixtures of slowly interconverting geometric isomers.[16] The ratio of isomers in **4** is ca. 11/1 ($^1H$ NMR).

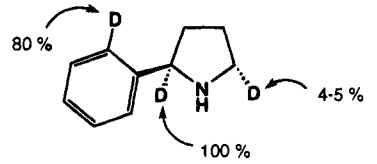



**Figure 4.** Isotope incorporation for the deuteration of **2** at 80 psig and 65 °C.

**Table 2.** Comparison of Catalyst Precursors for the Hydrogenation[a] of **2**

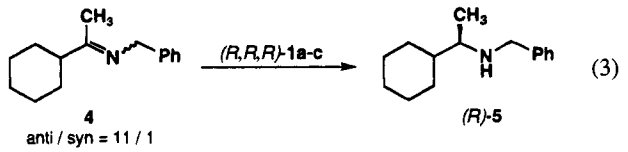
| catalyst precursor | activation | reaction time (h) | yield (%) | ee (%) |
|---|---|---|---|---|
| (*R,R,R*)-**1a** | 2 equiv of *n*-BuLi $PhSiH_3$ | 7 | 84 | 99 |
| (*R,R,R*)-**1a** | 2 equiv of *n*-BuLi $H_2$ | 8 | 80 | 99 |
| *rac* $Cp_2'Ti(CH_3)_2$ (**1c**) | $H_2$ | 12 | 82 | |
| *rac* $Cp_2'TiCl$ (**1d**) | 1 equiv of *n*-BuLi $PhSiH_3$ | 6 | 69 | |
| *rac* $Cp_2'TiN(CH_3)_2$ (**1e**) | $H_2$ | 8 | 70 | |

[a] All reactions were conducted at 80 psig of hydrogen and 65 °C with 5 mol % catalyst precursor. Approximate catalyst concentrations were 0.02 M. $Cp_2'$ = ethylene−bis(tetrahydroindenyl).

**Table 3.** Dependence of Enantiomeric Excess on Reaction Parameters for the Hydrogenation of **4**[a]

| entry | $H_2$ pressure (psi) | solvent | catalyst precursor | *n*-BuLi/ catalyst | ee of amine (%) |
|---|---|---|---|---|---|
| 1 | 2500 | THF | **1a** | 2.0 | 81 |
| 2 | 2000 | THF | **1a** | 2.0 | 76 |
| 3 | 1500 | THF | **1a** | 2.0 | 74 |
| 4 | 1000 | THF | **1a** | 2.0 | 65 |
| 5 | 500 | THF | **1a** | 2.0 | 43 |
| 6 | 150 | THF | **1a** | 2.0 | 12 |
| 7 | 2000 | benzene | **1a** | 2.0 | 81 |
| 8 | 500 | benzene | **1a** | 2.0 | 52 |
| 9 | 2000 | THF | **1b** | 2.0 | 76 |
| 10 | 2000 | THF | **1c** | | 84 |
| 11 | 500 | THF | **1c** | | 61 |
| 12 | 2000 | THF | **1a** | 1.5 | 77 |
| 13 | 2000 | THF | **1a** | 2.5 | 39 |

[a] All reactions were conducted at 65 °C using (*R,R,R*) catalyst precursors.




(3)

Table 3 shows the effects of various reaction parameters on the observed enantiomeric excess of the amine for the hydrogenation of **4**. As in the hydrogenation of **2**, above, when the *(R)* enantiomer of the catalyst precursors are used, the *(R)* enantiomer of the amine is formed. However, in contrast to the cyclic imines, the ee of *(R)*-**5** depends on many factors. First, and most significant, is the effect of hydrogen pressure (Table 3, entries 1−6). At 2500 psig the reaction proceeded to afford **5** with an ee of 81%. As the pressure was decreased, the ee

(13) This type of reactivity has been observed for titanium(III) alkyls. cf. Teuben, J. H. In *Fundamental and Technological aspects of Organo-f-Element Chemistry*; Marks, T. J., Fragala, I. L., Eds.; Reidel, D.: Dordrecht, Holland, 1985; p 195 and references cited therein.

(14) The kinetic resolution of 2,5-disubstituted pyrrolines has recently been investigated with this catalyst system (Viso, A.; Lee, N. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 9373).

(15) Under hydrogen atmosphere no silane is necessary for the formation of an active catalyst. This and the fact that silane is not involved in the rate law suggests that silane serves to stabilize the hydride species under an argon or nitrogen atmosphere.

(16) (a) Harada, K. *Chemistry of the Carbon-Nitrogen Double Bond*; Patai, S., Ed.; Interscience: London, 1970; pp 364−383. (b) Smith, J. K.; Bergbreiter, D. E.; Newcomb, M. *J. Am. Chem. Soc.* **1983**, *105*, 4396.

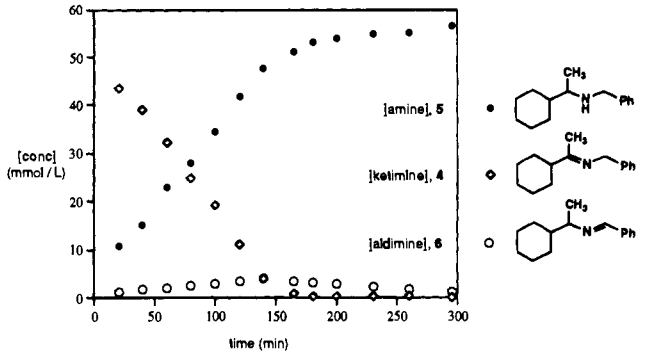



**Figure 5.** Plot of concentration vs time for the hydrogenation of **4** at 2000 psig and 65 °C.

also decreased; at 150 psig the ee of **5** was only 12%. It is important to note that when *(R)*-**5**, with an ee of 93%, was subjected to the activated catalyst at 80 psig and 65 °C no other organic species and no racemization was observed after 30 h.

A second major factor is the amount of *n*-butyllithium used. As indicated in Table 3, using less than 2 equiv (relative to **1a**) resulted in no significant change in ee (77%, entry 12, vs 76%, entry 2). However, when more than 2 equiv were used the ee sharply dropped from 76% with 2.0 equiv (entry 2) to 39% with 2.5 equiv (entry 13). Complex **1c** (entry 10) catalyzed the hydrogenation of **4** to **5** with an ee of 84%. With **1a** (entry 2), the observed ee of **5** is 76%. This difference in ee was also observed at 500 psig (entry 5 vs entry 11). When the dichloride precursor **1b** was used in place of **1a**, the reaction proceed to afford **5** with an identical ee (entry 9).

We also observed a small solvent effect. With **1a**, in benzene, **4** was reduced to **5** with an ee of 81% when the reaction is carried out at 2000 psig (entry 7). In THF under otherwise identical conditions the ee is 76% (entry 2). Similarly, at 500 psig, in benzene, **4** was reduced to **5** with an ee of 52% (entry 8). In THF, under the same conditions **5** was isolated with an ee of 43% (entry 5). It is important to point out that none of these effects were observed for the hydrogenation of cyclic imine **2**.

Another difference between acyclic and cyclic imines is that for acyclic imines formation of another organic compound is observed during the reaction. This compound was identified as the corresponding aldimine. The reduction of **4** typical as illustrated in Figure 5. At 2000 psig of hydrogen and 65 °C the formation of aldimine **6** was observed. The amount of **6** increased to about 7% of the organic products after ca. 2.5 h under these conditions. Only after ketimine **4** had reacted completely did **6** begin to disappear. At lower hydrogen pressure more **6** is observed. At 500 psig of hydrogen, after 64% conversion, 12% (*R*)-**6** (75% ee) and 52% (*R*)-**5** (41% ee) were present when *(R,R,R)*-**1a** was used.

In order to probe the role of **6** in the reaction, we prepared **6**, in both racemic and enantiomerically enriched forms, and subjected it to several sets of reaction conditions. This data is shown in Table 4.

When racemic **6** was hydrogenated with *(R,R,R)*-**1a** a kinetic resolution[14] was observed. After 30% conversion, the ee of isolated **5** was 16%. From this value a $k_{rel}$ of 1.5(±0.2) was calculated. Interestingly *(S)*-**5** is observed as the major enantiomer. This is in contrast to the the hydrogenation of **4** where using (*R,R,R*)-**1a** as the catalyst precursor results in formation of *(R)*-**5**. Thus *(S)*-**6** and *(R,R,R)*-**1a** constitute a matched pair while *(R)*-**6** and *(R,R,R)*-**1a** are a mismatched pair.[17] When

(17) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1.

**Table 4.** Hydrogenation[a] of Aldimine **6** under Various Conditions

| $H_2$ pressure (psig) | catalyst precursor | ee (config) of starting imine | ee (config) of amine |
|---|---|---|---|
| 2000 | *(R,R,R)*-**1a** | 0% (rac) | 16% *(S)*[b] |
| 2000 | *(R,R,R)*-**1a** | 95% *(R)* | 91% *(R)* |
| 2000 | *(S,S,S)*-**1a** | 95% *(R)* | 93% *(R)* |
| 500 | *(R,R,R)*-**1a** | 94% *(R)* | 89% *(R)* |
| 500 | *(S,S,S)*-**1a** | 94% *(R)* | 91% *(R)* |

[a] All reactions were conducted at 65 °C in THF. [b] After 30% conversion.

**Table 5.** Rate Data for the Hydrogenation[a] of Imines **4** and **6**[b]

| $H_2$ pressure (psi) | catalyst precursor | $[Ti]_o$ (mmol/L) | imine | rate (mmol/(L min)) |
|---|---|---|---|---|
| 2015 | *(R,R,R)*-**1a** | 3.75 | **4** | 0.31(±0.02) |
| 2015 | *(R,R,R)*-**1a** | 1.88 | **4** | 0.13(±0.02) |
| 1015 | *(R,R,R)*-**1a** | 3.75 | **4** | 0.14(±0.02) |
| 2015 | *(R,R,R)*-**1a** | 3.75 | *(R)*-**6** | 0.14(±0.03) |
| 1015 | *(R,R,R)*-**1a** | 3.75 | *(R)*-**6** | 0.09(±0.02) |
| 515 | *(R,R,R)*-**1a** | 3.75 | *(R)*-**6** | 0.06(±0.01) |
| 2015 | *(S,S,S)*-**1a** | 3.75 | *(R)*-**6** | 0.12(±0.03) |
| 515 | *(S,S,S)*-**1a** | 3.75 | *(R)*-**6** | 0.06(±0.01) |

[a] All reactions were conducted at 65 ± 1 °C in THF. Initial imine concentrations were 56.3 mmol/L and the hydrogen pressure was held constant. [b] For this imine, initial rates (ca. 25% conversion) were used. In this region, plots of concentration vs time were linear.

**Table 6.** *Anti/Syn* Ratios in the Hydrogenation[a] of **4**

| 2000 psi, 65 °C | | 1500 psi, 75 °C | |
|---|---|---|---|
| | *anti/syn* ratio | | *anti/syn* ratio |
| initial ratio | 11/1 | initial ratio | 11/1 |
| after adding **1a** | 18/1 | after adding **1a** | 15/1[b] |
| after 22% conversion | 30/1 | after 33% conversion | 17/1[b] |
| after 43% conversion | 30/1 | after 60% conversion | 16/1[b] |

[a] Reactions were conducted in THF with 6.7 mol% catalyst. [b] These are the same within experimental error.

enantiomerically enriched *(R)*-**6** was used (94−95% ee), only a small amount of racemization was observed with either *(R,R,R)*-**1a** (mismatched) or *(S,S,S)*-**1a** (matched) when the reaction was run at either 500 or at 2000 psig of hydrogen.

We briefly examined the kinetics for the hydrogenation of **4** and **6** to provide further insight into the reaction mechanism for these substrates. This data is shown in Table 5 and is intended to show qualitative trends only.

For the reduction of imine **6**, the reaction is non-first order in hydrogen. The order of the reaction in hydrogen was about 0.6, for both the matched or mismatched pairs *((R)*-**6** with *(S,S,S)*-**1a** and *(R)*-**6** with *(R,R,R)*-**1a** respectively). We also observed formation of a small amount of **4** for both pairs (matched; ca. 2% at 25% conversion, mismatched; ca. 6% at 25% conversion, both at 500 psig). Interestingly, in view of the kinetic resolution of racemic **6**, the rates for the hydrogenation of *(R)*-**6**, both at 500 psig and at 2000 psig were virtually identical when either *(R,R,R)*-**1a** (mismatched) or *(S,S,S)*-**1a** (matched) was used as the catalyst precursor. This apparent discrepency will be explained below.

The reaction of **4** showed first-order behavior in hydrogen and catalyst, similar to what was observed for the cyclic imine **2**. The ratio of *anti/syn* isomers of **4** did not remain constant over the course of the reaction. We monitored the changes in the *anti/syn* ratio, under two different sets of conditions, by 500 MHz $^1$H NMR analysis of aliquots taken from the reaction vessel. As shown in Table 6, when the reaction was conducted at 2000 psig and at 65 °C, the *anti/syn* ratio changed from an initial ratio of 11/1 to a ratio of 18/1 after mixing **4** with the

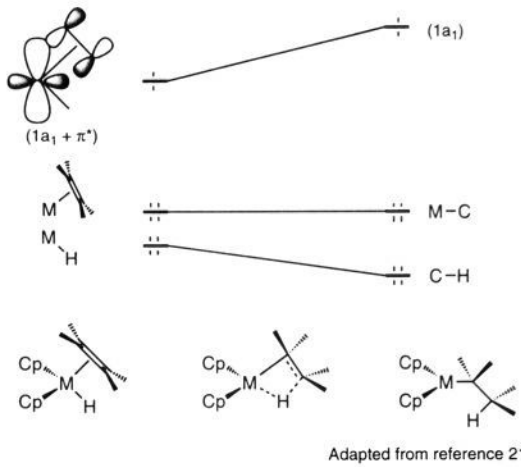
catalyst. The ratio had increased to 30/1 at 22% conversion and leveled off over the rest of the reaction. At 1500 psig and 75 °C, a similar phenomenon was observed. After mixing **4** and the catalyst the ratio had changed from 11/1 to 15/1. As the reaction proceeded, the ratio leveled off at 17/1 after 33% conversion, and at 60% conversion the ratio was 16/1.[18] When ketimine **4** was reacted with 1 equiv of *(R,R,R)*-**1a**, the product, *(R)*-**5** was isolated with an ee of 83%. This corresponds to an *(R)*/*(S)* ratio of 11/1, identical to the ratio of *anti* to *syn* isomers in **4** (11/1).

## Discussion

**Nature of the Active Catalyst.** Since no resonances attributable to any catalytic intermediates were observed in the $^1$H NMR spectra, we are unable to conclusively discern the nature of the active catalyst. However, given the known propensity of titanium to be reduced under the conditions employed[7,10] to generate the active catalyst from **1a** or **1b** it seems most likely that titanium is in the +3 oxidation state. To support the proposal that the catalyst is titanium(III) we have prepared two Ti(III) complexes **1d** and **1e** and studied their activity. Complex **1d**, a titanium(III) chloride reacts with 1 equiv of *n*-butyllithium[19] to form an active catalyst that behaves in an analogous fashion to the catalyst generated from **1a** or **1b** and 2 equiv of *n*-butyllithium. With **1d**, the rate for the hydrogenation of **2** to **3** is approximately the same as when **1a** is used (6 h vs 7 h respectively for 20 turnovers at 65 °C and 80 psig of $H_2$). This suggests that these two systems react to give a common catalytically active species. Most significantly, however, is that complex **1e**, a titanium(III) amide (which is an analog of the proposed intermediate in the catalytic cycle, Scheme 2), catalyzes the hydrogenation of **2** to **3** with no additional reagents necessary. Again the reaction rate with **1e** is similar to that with **1a** (8 h vs 7 h respectively for 20 turnovers at 65 °C and 80 psig of $H_2$). These results, in conjunction with the first-order behavior of the hydrogenation reactions in titanium,[20] support the hypothesis that the active species is titanium(III)

**Origin of Enantioselectivity.** To account for the observed absolute configurations of the products in the asymmetric titanocene-catalyzed hydrogenation of imines, we have previously proposed the stereochemical model shown in Scheme 4, parts a (front view) and b (top view).[5] In order to derive this stereochemical model we have considered the electronic structure of the complex. Hoffmann and Lauher have calculated the valence orbitals for bent metallocene complexes.[21] They discuss the orbital interactions for insertion of an olefin into a metallocene hydride. The molecular orbital diagram for this process is shown in Scheme 3. The diagram illustrates an important feature of the intermediate olefin−hydride complex. One end of the olefin is much closer to the cyclopentadienyl ligands. Therefore the substituents on the carbon that becomes bound to the metal will have a much stronger influence on the selectivity of insertion. This effect has recently been demonstrated for the 1,2-insertion of olefins into cationic zirconium $\eta^2$-pyrid-2-yl complexes containing the ethylenebis(tetrahydroindenyl) ligand.[22] Experimental support for the geometry predicted by calculations is given by the X-ray structure of a

**Scheme 3**




Adapted from reference 21.

related niobocene olefin hydride complex.[23] The situation for 1,2-insertion of an imine into a metallocene hydride should be exactly analogous since imines and olefins are isolobal. For the interaction of an *anti* imine with the titanium hydride **1f** two transition states, **A** and **B**, are possible (Scheme 4). Note that the N−Ti−H plane is perpendicular to the plane containing the nitrogen, $R_S$, and $R_L$. This geometry is required for proper orbital overlap of the C=N $\pi^*$ and the Ti−H $\sigma$ orbitals. In **B**, steric interactions between $R_N$ and the tetrahydroindenyl ligand, as well as between $R_L$ and the ligand are present. In **A**, fewer steric interactions exist (only an interaction between $R_S$ and the ligand), making this transition state more favorable relative to **B**. Thus with an *anti* imine, the *(R,R)* catalyst would be expected to afford the *(R)* enantiomer of the product. For a *syn* imine, two transition states are again possible. Transition state **C** has an unfavorable interaction between $R_N$ and the tetrahydroindenyl ligand, while **D** has an unfavorable interaction between $R_L$ and the ligand. From the front view it is unclear whether transition state **C** or **D** should be favored. However, consideration of the top view (Scheme 4b) clarifies this point. From this perspective it becomes obvious that $R_N$ is much closer to the tetrahydroindenyl ligand than $R_L$ and $R_S$. In **C**, $R_N$ is oriented above of the plane of the paper and interacts unfavorably with the tetrahydroindenyl ligand. In **D**, $R_N$ is projected behind the plane of the paper and points away from the ligand. Note that $R_L$ and $R_S$ are somewhat distant from the ligand and therefore, they are less important than $R_N$ in determining the stereochemical outcome of the insertion step. On this basis transition state **D** is should be more favorable than **C** for the reaction of a *syn* imine. Thus for a *syn* imine the *(R,R)* catalyst would be expected to afford the *(S)* enantiomer of the product. The two important predictions of this model are that $R_N$ should have the greatest influence on the stereochemical outcome of the reaction and the *syn* and the *anti* isomers of an imine should react to give opposite enantiomers of the product.

Evidence to support this model comes from the hydrogenation of the *anti* imine **2**, and the *syn* imine **7** (Table 7). Since **2** and **7** are cyclic, only one geometric isomer is possible. As predicted by this model, with *(R,R,R)*-**1a**, the *anti* imine **2** is hydrogenated to the *(R)* amine, while the *syn* imine **7** reacts to give the *(S)* amine. Furthermore, in both cases the amine is formed with excellent enantiomeric excess. This demonstrates the dominant effect of $R_N$ on stereocontrol. Since no dependence of ee on hydrogen pressure is observed for these cyclic imines, it seems

(18) 15/1, 17/1, and 16/1 are statistically the same number under the conditions of our measurements.

(19) For a study of the reactivity of titanium(III) alkyls cf.: Luinstra, G. A.; ten Cate, L. C.; Heeres, H. J.; Pattiasina, J. W.; Meetsma, A.; Teuben, J. H. *Organometallics* **1991**, *10*, 3227.

(20) Harrod, J. F.; Yun, S. S. *Organometallics* **1987**, *6*, 1381.

(21) Lauher, J. W.; Hoffmann, R. *J. Am. Chem. Soc.* **1976**, *98*, 1729.

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(23) Burger, B. J.; Santarsiero, B. D.; Trimmer, M. S.; Bercaw, J. E. *J. Am. Chem. Soc.* **1988**, *110*, 3134.

**Scheme 4**

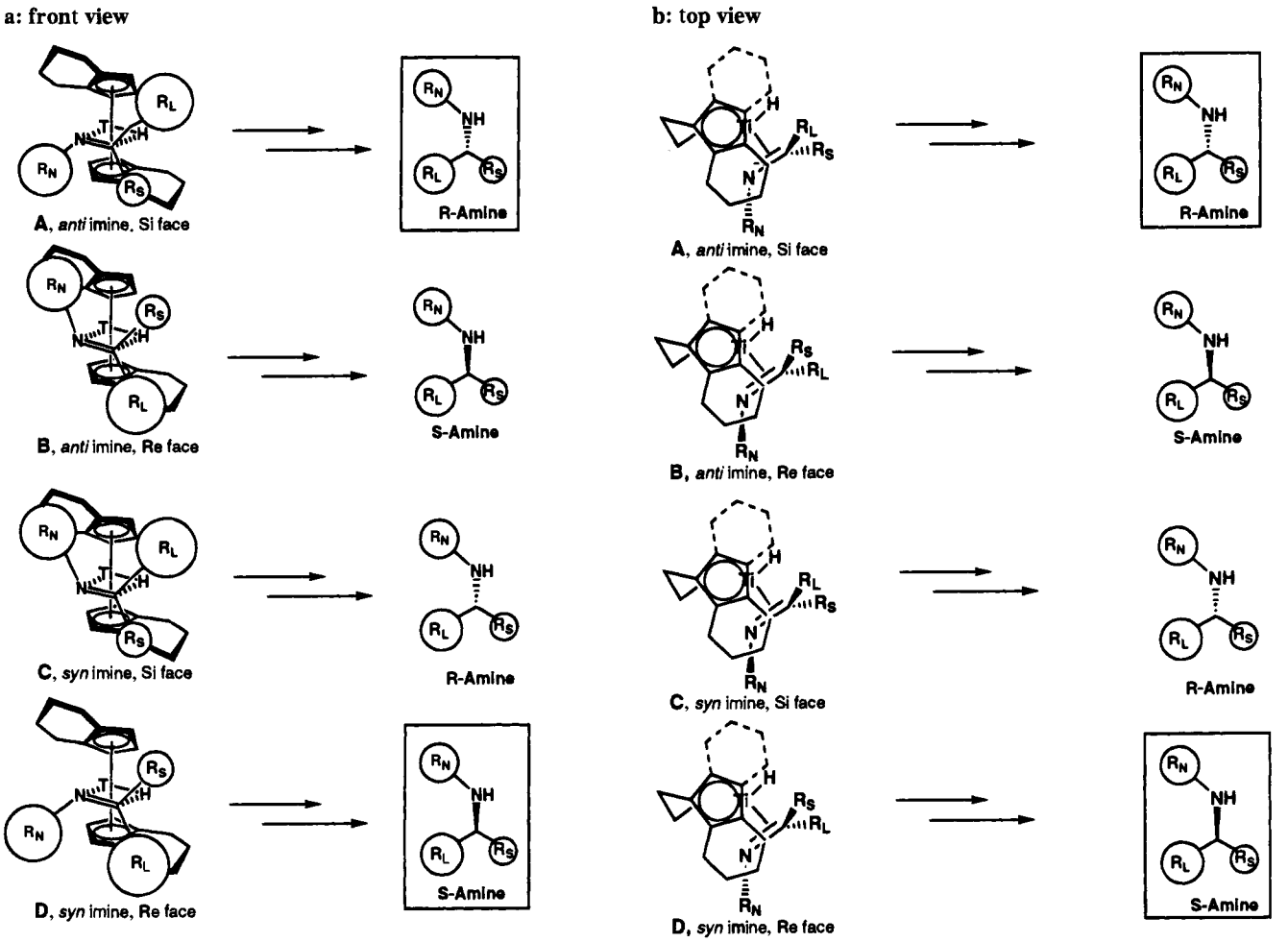
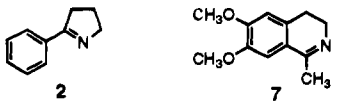



**Table 7.** Hydrogenation of Cyclic Imines at Various Pressures[a]




| $H_2$ pressure (psig) | ee (config)[b] | ee (config)[b] |
|---|---|---|
| 2000 | 98 (*R*) | 98 (*S*) |
| 500 | 99 (*R*) | |
| 80 | 99 (*R*) | 95 (*S*) |

[a] This data is taken from ref 5. [b] Using (*R,R,R*)-**1a**.

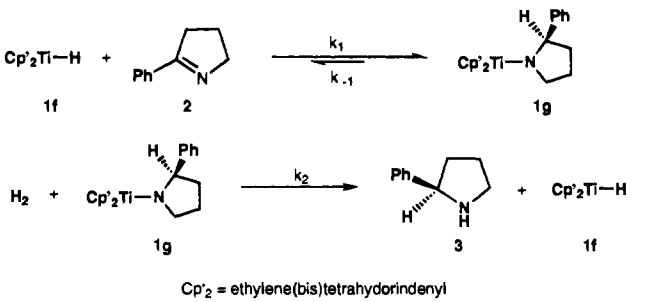
reasonable that the pressure dependence of ee for acylic imines may be related to the interconversion of *anti* and *syn* isomers.

Additional support is gained by the stoichiometric reaction of imine **4** with the catalyst. The observed ee of 83% [*(R)/(S)* ratio = 11/1] is in excellent agreement with the 11/1 ratio of *anti* and *syn* isomers. These results further imply that reaction through transition states **B** and **C** is extremely unfavorable.

**Reaction Mechanism.** The proposed reaction mechanism for the titanocene-catalyzed hydrogenation of **2** is shown in Scheme 5. Because of the high chemo- and enantioselectivity observed for this substrate we can conclude that the pathways leading to the minor enantiomer do not contribute significantly to the mechanism. Therefore, only the major stereochemical manifold of the reaction need be considered. The steady state rate expression for this mechanism is given in eq 4 (the derivation is given in the appendix), where [**2**] is the imine concentration and [Ti] is the total concentration of titanium.

$$\text{rate} = k_2[\text{Ti}][H_2][\mathbf{2}]/[[(k_{-1} + k_2[H_2])/k_1] + [\mathbf{2}]] \quad (4)$$

**Scheme 5**



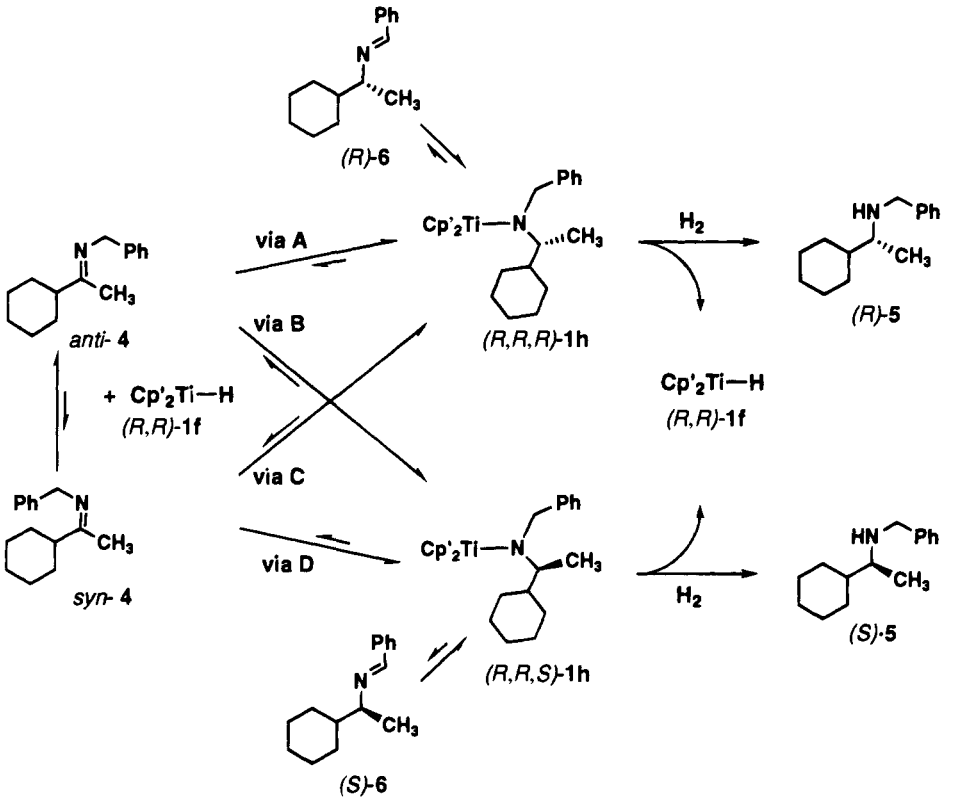

From the kinetic data for the hydrogenation of **2**, we obtained the experimental rate expression given in eq 2. If we assume that insertion is fast relative to hydrogenolysis ($k_1 \gg k_2[H_2]$) and fast relative to $\beta$-H elimination ($k_1 \gg k_{-1}$) then the left-hand term in the denominator of eq 4 goes to zero. Under these constraints eq 4 simplifies to eq 5. Equation 5 is identical to eq

$$\text{rate} = k_2[\text{Ti}][H_2] \quad (5)$$

2, where $k_{obs} = k_2$. Thus, our kinetic data are consistent with a mechanism that involves (1) fast insertion of **2** into the titanium hydride **1f** to form the titanium amide intermediate **1g**, (2) slow $\beta$-H elimination of imine from **1g** to form **2**, and (3) slow hydrogenolysis of **1g** to form amine **3** and regenerate **1f**.

A relatively large kinetic isotope effect (1.5 ± 0.2) was observed for this reaction. This value exceeds the value obtained by Bercaw for the insertion of an olefin into a niobium

**Scheme 6**




hydride bond ($k_H/k_D$ = 1.1).[24] The value for our system is also larger than typical kinetic isotope effects observed for the oxidative addition of hydrogen to late transition metals,[25] which are generally about 1.2. This suggests that there is a significant amount of H—H bond breaking in the rate-limiting step, consistent with hydrogenolysis being the slow step.

Although it is difficult to measure the rate of $\beta$-H elimination from **1g** to form **2**, the incorporation of deuterium in the other carbon $\alpha$ to the nitrogen (4—5%, Figure 4) indicates that $\beta$-H elimination to form the isomeric imine is slow relative to hydrogenolysis. For the $\beta$-H elimination of **1g** to form **2**, the favorable electronic effect of the phenyl group is offset by the unfavorable steric demands required for elimination from a tertiary carbon.[23,24] To a first approximation then, the rates of these two processes are similar. This suggests that indeed $k_2[H_2] > k_{-1}$ and is consistent with the proposed mechanism. If $\beta$-H elimination were fast relative to hydrogenolysis ($k_{-1} \gg k_2[H_2]$), the ee would probably be dependent on hydrogen pressure since it would be determined by the relative concentrations and relative rates of hydrogenolysis of the two diastereomeric amide intermediates **1g** and **1g'**. That this is not observed (Table 7) further supports the proposed mechanism for the hydrogenation of **2**.

**Selectivity and Mechanism for Acyclic Imines.** The reaction scheme for the hydrogenation of **4** is presented in Scheme 6. We note that since the formation of **6** occurs after the selectivity-determining step (the insertion of **4**), that the presence or absence of **6** during the reaction has no effect on the ee of **5**, provided that the reaction is run to completion.

The kinetic data for the hydrogenation of **4** (Table 5) imply that the reaction is first order in titanium and first order in hydrogen. Also, the data in Figure 5 indicate that the rate is independent of imine concentration. Together, these data

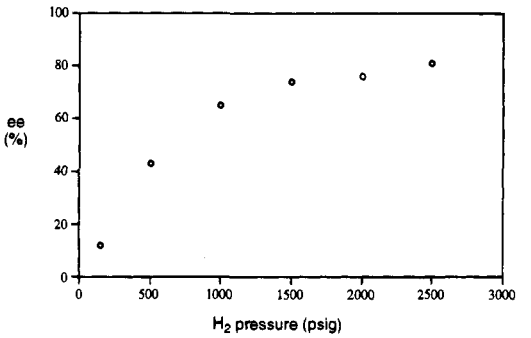



**Figure 6.** Plot of ee vs pressure for the hydrogenation of **4**.

suggest a mechanism for the reaction of **4** that is similar to that for **2**. Namely, fast insertion of the imine to form the intermediate titanium amide, slow hydrogenolysis to form **5**, and slow $\beta$-H elimination to form **4**.

From the stoichiometric reaction of **4** (*anti*/*syn* = 11/1) with *(R,R)*-**1f**, amine **5** was obtained with an ee of 83% as the *(R)* enantiomer [*(R)*/*(S)* = 11/1]. However, when the reduction of **4** is conducted catalytically, the ee is dependent on hydrogen pressure (Table 3), and never reaches or exceeds 83%. In fact the ee appears to approach this value asymptotically (see Figure 6). At 2500 psig (the maximum pressure explored) the observed ee was 81%.

There are three explanations that can account for this pressure dependence of ee: (1) *(R,R,R)*-**1h** and *(R,R,S)*-**1h** are interconverting via $\beta$-H elimination to **4** and the rate of $\beta$-H elimination is faster for *(R,R,R)*-**1h** than for *(R,R,S)*-**1h**;[26] (2) *(R,R,R)*-**1h** and *(R,R,S)*-**1h** are interconverting via $\beta$-H elimination to **4** and hydrogenolysis of *(R,R,S)*-**1h**, to form *(S)*-**5**, is faster than that for *(R,R,R)*-**1h** to form *(R)*-**5**;[3b] (3) *anti*-**4** and *syn*-**4** are interconverting at a rate that is independent of hydrogen pressure

(24) Doherty, N. M.; Bercaw, J. E. *J. Am. Chem. Soc.* **1985**, *107*, 2670.
(25) Zhou, P.; Vitale, A. A.; San Filippo, J.; Sunders, W. H. *J. Am. Chem. Soc.* **1985**, *107*, 8049.
(26) Buschmann, H.; Scharf, H.-D.; Hoffmann, N.; Esser, P. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 477.

and *syn*-**4** reacts to form *(R,R,S)*-**1h** faster than *anti*-**4** reacts to from *(R,R,R)*-**1h**.

We used enantiomerically enriched aldimine **6** as a convenient way to obtain *in situ*, nearly enantiomerically pure *(R,R,R)*-**1h** or *(S,S,R)*-**1h**. By separately studying the behavior of these two species we were able gain some insight into which of the three hypotheses may hold true.

First, when the reduction of *(R)*-**6** was conducted at 500 psig formation of **4** was observed for both the matched and the mismatched pairs [*(S,S,R)*-**1h** and *(R,R,R)*-**1h** respectively]. For the matched pair, after 25% conversion, **4** made up ca. 2% of the mixture. For the mismatched pair, **4** was ca. 6% of the mixture at 25% conversion. This indicates that $\beta$-H elimination for the matched pair is slower than that for the mismatched pair. However the difference is rather small. Secondly, by examining the data in Table 4, we see that very little racemization during the hydrogenation of *(R)*-**6** with either *(R,R,R)*-**1a** or *(S,S,S)*-**1a** at 2000 or at 500 psig, furthermore, the amount of racemization is very similar for both diastereomeric pairs. Although, as expected, it is slightly higher for the mismatched pair. Thus even though a small amount of $\beta$-H elimination is occurring for both the matched and the mismatched pairs, the difference is not enough, in itself, to account for observed pressure dependence.

Although we observed a kinetic resolution of racemic **6** with *(R,R,R)*-**1a**, when we measured the rates of hydrogenation of *(R)*-**6** with both *(R,R,R)*-**1a** and *(S,S,S)*-**1a**, we found that they were almost identical at both 2000 and 500 psig (Table 5). It is important to note that the measured rate is the overall reaction rate and not necessarily the rates of the individual steps of the reaction. The fact that the observed rates are similar for the matched and mismatched pairs means that the kinetic resolution must happen in a fast step that is not reflected in the rate expression. Computer simulation of the kinetics indicate that if $k_1 \sim 5k_2$ the reaction would be 0.6th order in hydrogen. Under these constraints and using a $k_{rel}$ of 1.5 for the insertion step the observed reaction rates for matched and mismatched pairs are predicted to be within experimental error of each other.

If, as in the case of imine **2**, hydrogenolysis were the rate-limiting step we could conclude that the rates of hydrogenolysis of *(S,S,R)*-**1h** and *(R,R,R)*-**1h** were the same. However, we see that the reaction is about 0.6th order in hydrogen, suggesting hydrogenolysis is not entirely rate limiting in this case. Thus the observed reaction rate does not accurately reflect the rate of the hydrogenolysis step and it is difficult to conclude whether *(S,S,R)*-**1h** reacts with hydrogen faster than *(R,R,R)*-**1h**.

We have presented some evidence to support the hypothesis that *syn* and *anti* imines are reduced, with this catalyst, to amines with opposite absolute configurations (Table 7 and the stoichiometric reaction of **4** with the active catalyst). With this in mind the interconversion of the *syn* and *anti* imine isomers appears to be an attractive explanation for the pressure dependence. However, a constraint of this hypothesis is that the *syn* isomer must react faster than the *anti* isomer, either by faster 1,2-insertion or by faster hydrogenolysis of the intermediate. The data in Table 6 indicate that this is true. At 65 °C and 2000 psig the initial 11/1 isomer ratio a **4** changes to 18/1 upon mixing with the active catalyst, suggesting that indeed *syn*-**4** reacts faster than *anti*-**4**. As the reaction proceeds, the ratio levels off at 30/1, implying that *syn*-**4** is being formed as fast as it reacts. When the temperature of the reaction is increased, the rate of interconversion and the rate of reaction to **5** should both increase. When the pressure is decreased the rate of interconversion should not change but the rate of conversion to **5** should decrease. Thus we would expect at steady state that the *anti*/*syn* ratio should be smaller at a higher temperature and a lower pressure. We find that this is the case. When the reaction is conducted at 75 °C and 1500 psig, the isomer ratio (11/1 initially) levels off at ca. 16/1. That the observed steady-state concentrations of *anti*- and *syn*-**4** are different under these two different sets of reaction conditions supports the hypothesis that *syn*-**4** reacts with **1f** faster than *anti*-**4** and that *syn*- and *anti*-**4** are slowly interconverting.

The effect of excess *n*-butyllithium on the ee for the hydrogenation of **4** is also consistent with this explanation. Smith et al.[16b] have shown that the rate of interconversion of *syn* and *anti* imine isomers is greatly enhanced by the presence of a small amount of an azaallyllithium species (the anion formed from the reaction of an imine with lithium diisopropyl amide). In light of this observation, it is reasonable to conclude that the presence of *n*-butyllithium in the reaction mixture could increase the rate of interconversion of *syn*- and *anti*-**4**. Since *syn*-**4** reacts faster than *anti*-**4**, we would expect the ee of **5** to decrease when the rate of interconversion is increased, which is exactly what is observed. That the ee of **3** is not affected by the presence of excess *n*-butyllithium for the hydrogenation of **2** implies that excess *n*-butyllithium does not adversely affect the active catalyst.

## Conclusions

We have studied the asymmetric titanocene-catalyzed hydrogenation of imines **2**, **4**, and **6** in detail. Our kinetic data for imines **2** and **4** are consistent with a mechanism involving fast insertion of the imine into a titanium hydride, slow $\beta$-H elimination of the resulting titanium amide intermediate and slow hydrogenolysis of the titanium amide to form the amine and regenerate the titanium hydride. For imine **6**, the reaction deviates from first-order behavior in hydrogen. This implies that the rate of the insertion step for imine **6** is similar to the rate of the hydrogenolysis step. The observed slower rate of insertion for imine **6** serves to demonstrate the steric sensitivity of this catalyst system.

We have proposed a rational stereochemical model that accounts for the observed selectivity of the system and can be used as a guide to predict the absolute configuration of the products of this reaction. A characteristic of this model is that it predicts that *syn* and *anti* imines react to give opposite enantiomers of the amine, and this has been verified experimentally.

We have also provided evidence that the *syn* isomer of imine **4** reacts faster than the *anti* isomer and that the *syn*- and *anti*-**4** are interconverting under the reaction conditions. This provides a reasonable explanation for the observed pressure dependence of ee that we observed for the hydrogenation of acyclic imine **4**.

## Experimental Section

**General Considerations.** All reactions were conducted under an atmosphere of argon, nitrogen, or hydrogen using standard Schlenk and/or glove box techniques. Hydrogenation reactions at pressures above 100 psig were conducted in a Parr Model 4751 or Model 4565 high-pressure autoclave. Hydrogenation reactions run at below 100 psig were conducted in a Fisher-Porter bottle (purchased from Aerosol Lab Equipment, Walton, NY). Nuclear magnetic resonance (NMR) spectra were recorded with a Varian Unity-300, Varian XL-300, Varian VXR-500, or Bruker AC-250 Fourier transform spectrometer. Electron paramagnetic resonance (EPR) spectra were recorded with a Bruker ESP 300 spectrometer. Infrared (IR) spectra were recorded with a Perkin-Elmer 1600 series Fourier transform spectrometer. Gas chromatography (GC) analyses were performed on a Hewlett-Packard model 5890 gas chromatograph with a flame ionization detector and a model 3392A integrator using a 25 m capillary column with cross-linked HP-1 as a stationary phase. High-pressure liquid chromatography (HPLC) was conducted using a Hewlett-Packard model 1050 pumping system

with a Hewlett-Packard model 1040A ultraviolet detector and a Chiralcel OD chiral stationary phase (Daicel Chemical Industries, Ltd.). Elemental analyses were performed by Onieda Research Services (Whitesboro, NY) or by Desert Analytics (Tucson, AZ).

Tetrahydrofuran (THF), ether, benzene, and pentane were dried and deoxygenated by refluxing and distilling from sodium/benzophenone ketyl under an argon atmosphere. Phenylsilane and pentadecane used in kinetics experiments were dried by refluxing and distilling from $CaH_2$ under a nitrogen atmosphere. Preparative flash chromatography was performed on silica (E. M. Science Kieselgel 60, 230−400 mesh) or neutral alumina (ICN Alumina N, Akt. I).

Unless otherwise stated, yields refer to isolated yields of products of greater than 95% purity as determined by capillary GC and/or $^1$H NMR spectrometry.

**Preparation of Materials. 2-Phenylpyrroline (2)** was prepared by the method of Sorgi et al.[27] and was further purified, for use in kinetics experiments, by recrystallization from hexanes.

***N*-(1-Cyclohexylethylidene)benzylamine (4).** This was prepared as previously described[5] as an 11/1 ratio of isomers.

**Benzylidene(1-cyclohexylethyl)amine (6).** A solution of benzaldehyde (3.76 mL, 37 mmol) and 1-cyclohexylethylamine (5.0 g, 37 mmol) in 120 mL of ether was stirred over magnesium sulfate (6.0 g) for 12 h. The resulting mixture was filtered and concentrated. Vacuum distillation (99 °C, 0.01 mmHg), afforded 6.27 g (79% yield) of desired **6** as a colorless liquid. $^1$H NMR (300 MHz, $CDCl_3$, TMS): 8.21 (s, 1H), 7.8−7.71 (m, 2H), 7.47−7.40 (m, 3H), 3.00 (pentet, 1H), 1.86−1.5 (m, 5H), 1.52−1.40 (m, 1H), 1.3−1.15 (m, 3H), 1.22 (d, 3H), 1.0−0.8 (m, 2H). $^{13}$C NMR (75 MHz, $CDCl_3$): 158.5, 136.6, 128.4, 128.0, 71.9, 43.8, 29.9, 29.8, 26.6, 26.4, 26.2, 19.9. IR (neat): 3082, 3061, 3025, 2965, 2928, 2851, 2662, 1953, 1881, 1705, 1645, 1601, 1580, 1491, 1449, 1380, 1330, 1307, 1289, 1263, 1217, 1189, 1169, 1155, 1127, 1100, 1090, 1071, 1041, 1024, 1000, 987, 938, 903, 891, 873, 850, 789. Enantiomerically enriched *(R)*-**6** (94−95% ee) was prepared in an analogous manner from *(R)*-1-cyclohexylethylamine (Aldrich). The enantiomeric excess of this material was determined by HPLC analysis.

**[Ethylene-1,2-bis($\eta^5$-4,5,6,7-tetrahydro-1-indenyl)]titanium 1,1′-binaphth-2,2′-diolate** [*(R,R,R)*-**1a** and *(S,S,S)*-**1a**] were prepared as previously described.[5,6,28] **[Ethylene-1,2-bis($\eta^5$-4,5,6,7-tetrahydro-1-indenyl)]titanium dichloride** [*(R,R)*-**1b**] and **[ethylene-1,2-bis($\eta^5$-4,5,6,7-tetrahydro-1-indenyl)]dimethyltitanium (1c)** were prepared by method of Brintzinger et al.[6]

**Racemic [Ethylene-1,2-bis($\eta^5$-4,5,6,7-tetrahydro-1-indenyl)]titanium Chloride (1d).** In a glove box, a mixture of racemic ethylene-1,2-bis($\eta^5$-4,5,6,7-tetrahydro-1-indenyl)titanium dichloride (**1b**, 1.50 g, 3.9 mmol) and 3 g Na/Hg (22 mol% Na, 4.2 mmol) was stirred for 4 h in 50 mL of THF. The purple solution was filtered through celite and concentrated *in vacuo*. The residue was recrystallized from a saturated diethyl ether solution, at −40 °C, to afford 0.91 g (70% yield) green-brown crystals. IR (KBr): 2928, 2852, 1489, 1440, 1377, 1320, 1241, 1116, 1029, 905, 768. EPR (THF, room temperature): $g$ = 1.9687. Anal. Calcd for $C_{20}H_{24}TiCl$: C, 69.08; H, 6.96. Found C, 68.90; H, 7.11. Treatment of a small amount of this material with $PbCl_2$[29] afforded **1b**.

**Racemic [Ethylene-1,2-bis($\eta^5$-4,5,6,7-tetrahydro-1-indenyl)](dimethylamido)titanium (1e).** In a glove box, a mixture of **1d** (0.694 g, 2.0 mmol) and $LiN(CH_3)_2$ (0.102 g, 2.0 mmol) was stirred in 20 mL of ether for 12 h, affording an orange-brown solution. The solvent was removed *in vacuo* and the residue was extracted with pentane. The pentane solution was concentrated to ca. 10 mL and cooled to −40 °C to afford 0.11 g (15% yield) of desired **1e** as brown needles. IR (KBr): 3077, 2922, 2843, 2788, 2749, 1437, 1223, 1036, 946, 765, 723, 645. EPR (THF, room temperature; $g$ = 1.9787. Anal. Calcd for $C_{22}H_{30}NTi$: C, 74.14; H, 8.48; N, 3.93. Found C, 74.38; H, 8.43; N, 3.57. Treatment of a small amount of this material with $PbCl_2$[29] gave a product with an $^1$H NMR spectrum consistent with the chloro amide.

**Kinetics Experiments.** All kinetics reactions were conducted in a Parr model 4565 autoclave complete with a magnetically driven stirrer, a thermocouple, and a sampling tube. The reactions were maintained at constant temperature (±1 °C) with a Parr model 4842 temperature controller and stirred at constant speed (300 rpm). Samples were withdrawn from the reaction and analyzed by capillary GC. Formation of amine was monitored versus *n*-pentadecane as an internal standard. Plots of amine concentration versus time were constructed and reaction rates were calculated from the slope of the linear portion of the data (85% conversion for **2** and **4**, 25% conversion for **6**). Errors were derived from the standard deviation of the data. *Anti/syn* isomer ratios of **4** during the reaction were determined by integration of the benzylic resonances in the 500 MHz $^1$H NMR spectra of withdrawn aliquots.

**Typical Procedure for the Hydrogenation of 2.** To a dry Schlenk flask under argon were added *(R,R,R)*-**1a** (0.090 g, 0.15 mmol) and 36 mL THF. A solution of *n*-butyllithium (176 μL, 0.30 mmol, 1.7 M in hexanes) was added and after 2−3 min the color of the solution was green-brown. Phenylsilane (55 μL, 0.45 mmol) was added and the color turned dark brown. Imine **2** (4 mL of a 0.75 M stock solution in THF containing 10 mol % *n*-pentadecane) was added via syringe. The mixture was moved to a glove box and transferred to a Parr model 4565 reactor. The vessel was sealed and moved to a bench. A hydrogen tank was connected and the line was evacuated. The temperature was set to 45 °C. When the temperature had reached equilibrium, hydrogen was added (815 psi) initiating the reaction. Liquid samples were withdrawn at 2−5 min intervals and analyzed by capillary GC. The pressure was kept constant by adding hydrogen after each aliquot was taken. The ee of the amine was determined to be >99% by HPLC analysis of the 1-naphthamide.

**Typical Procedure for the Hydrogenation of *(R)*-6.** To a dry Schlenk flask under argon were added *(R,R,R)*-**1a** (0.090 g, 0.15 mmol) and 34 mL THF. A solution of *n*-butyllithium (176 μL, 0.30 mmol, 1.7 M in hexanes) was added and after 2−3 min the color of the solution was green-brown. Phenylsilane (55 μL, 0.45 mmol), was added and the color turned dark brown. Imine **6** (6 mL of a 0.375 M stock solution in THF containing 20 mol % *n*-pentadecane) was added via syringe. The mixture was moved to a glove box and transferred to a Parr model 4565 reactor. The vessel was sealed and moved to a bench. A hydrogen tank was connected and the line was evacuated. The temperature was set at 65 °C. When the temperature had reached equilibrium, hydrogen was added (2000 psig) initiating the reaction. Liquid samples were withdrawn at 15−20 min intervals and analyzed by capillary GC. The pressure was kept constant by adding hydrogen after each aliquot was taken.

**Typical Procedure for the Hydrogenation of 4.** To a dry Schlenk flask under argon were added *(R,R,R)*-**1a** (0.090 g, 0.15 mmol) and 40 mL THF. A solution of *n*-butyllithium (173 μL, 0.30 mmol, 1.73 M in hexanes) was added and after 2−3 min the color of the solution was green-brown. Phenylsilane (55 μL, 0.45 mmol) was added and the color turned dark brown. The mixture was moved to a glove box and transferred to a Parr model 4565 reactor. Imine **4** (0.484 g, 2.25 mmol) and *n*-pentadecane (88 mg, 0.41 mmol) were added. The vessel was sealed and moved to a bench. A hydrogen tank was connected and the line was evacuated. The temperature was set to 65 °C. When the temperature had reached equilibrium, hydrogen was added (2000 psig) initiating the reaction. Liquid samples were withdrawn at 15−20 min intervals and analyzed by capillary GC. The pressure was kept constant by adding hydrogen after each aliquot was taken.

**Synthetic Experiments. Hydrogenation of 2 with *(R,R,R)*-1a.** A dry Fisher-Porter bottle properly fitted with a pressure coupling closure complete with a gas inlet, pressure gauge, inlet valve, and a pressure release valve was charged with *(R,R,R)*-**1a** (59 mg, 0.10 mmol) and a magnetic stir bar. The vessel was evacuated and filled with hydrogen (5−10 psig). THF (10 mL) was added via high-pressure syringe. After the complex had dissolved, a solution of *n*-butyllithium (117 μL, 1.70 M in hexanes, 0.20 mmol) was added and the mixture was stirred for 2−3 min at which point it was a green color. Phenylsilane (37 μL, 0.30 mmol) was added and no color change was observed. A solution

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(29) Teuben has introduced lead((I) chloride as mild reagent for the oxidation of Ti(III) species to the corresponding titanium(IV) chlorides. cf.: Luinstra, G. A.; Teuben, J. H. *J. Chem. Soc., Chem. Commun.* **1990**, 1470.

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of **2** (290 mg, 2.0 mmol, in 2 mL THF) was added *via* syringe and the vessel was placed in an oil bath at 65 °C. The pressure was then adjusted to 80 psig (caution: an appropriate safety shield should be used) and the mixture was allowed to stir for 7 h. The vessel was cooled and carefully vented. The crude mixture was diluted with ether (10 mL) and extracted with 1 M HCl (3 × 10 mL). The aqueous portion was made basic with NaOH and extracted with methylene chloride (3 × 20 mL). The combined organic portions were dried over $Na_2SO_4$ and concentrated *in vacuo* to afford 247 mg (84% yield) of the desired *(R)*-(+)-**2**-phenylpyrrolidine [*(R)*-**3**].[30] HPLC analysis of the 1-naphthamide (85/15 hexane−2-propanol) indicated 99% ee.

**Deuteration of 2 with *(R,R,R)*-1a.** A dry Fisher-Porter bottle properly fitted with a pressure coupling closure complete with a gas inlet, pressure gauge, inlet valve, and a pressure release valve was charged with *(R,R,R)*-**1a** (30 mg, 0.05 mmol) and a magnetic stir bar. The vessel was evacuated and filled with deuterium (5−10 psig). THF (5 mL) was added via high-pressure syringe. After the complex had dissolved, a solution of *n*-butyllithium (59 μL, 1.70 M in hexanes, 0.10 mmol) was added and the mixture was stirred for 2−3 min at which point it was a green color. Phenylsilane (19 μL, 0.15 mmol) was added, and no color change was observed. A solution of **2** (145 mg, 1.0 mmol, in 1 mL of THF) was added via syringe, and the vessel was placed in an oil bath at 65 °C. The pressure was then adjusted to 80 psig (*caution*: an appropriate safety shield should be used) and the mixture was allowed to stir for 23 h. The solvent was removed *in vacuo* and Kugelrohr distillation afforded 120 mg (81% yield) of the desired *(R)*-(+)-2-phenylpyrrolidine [*(R)*-**3**]. $^1H$ NMR analysis (300 MHz, $CDCl_3$, TMS) showed absence of the triplet resonance at 4.1 ppm for the benzylic hydrogen. $^2H$ NMR analysis (46 MHz, $CDCl_3$, TMS) showed a resonance for the benzylic deuterium ($\delta$ = 4.08, 1 D), resonances for the ortho phenyl deuterium ($\delta$ = 7.4, 0.8 D), and a resonance for the deuterium α to the nitrogen (nonbenzylic, $\delta$ = 3.18, 0.04 D). The stereochemistry of this deuterium, relative to the phenyl group, was assigned on the basis of the known addition of hydrogen *trans* to substituents in the 5 position for the hydrogenation of 5-substituted pyrrolines with this catalyst system.[14]

**Reaction of *(R)*-3 with *(R,R,R)*-1a under Deuterium.** A dry Fisher-Porter bottle properly fitted with a pressure coupling closure complete with a gas inlet, pressure gauge, inlet valve and a pressure release valve was charged with *(R,R,R)*-**1a** (30 mg, 0.05 mmol) and a magnetic stir bar. The vessel was evacuated and filled with deuterium (5−10 psig). THF (5 mL) was added via high-pressure syringe. After the complex had dissolved, a solution of *n*-butyllithium (59 μL, 1.70 M in hexanes, 0.10 mmol) was added and the mixture was stirred for 2−3 min at which point it was a green color. Phenylsilane (19 μL, 0.15 mmol) was added, and no color change was observed. A solution of *(R)*-**3** (147 mg, 1.0 mmol, in 1 mL of THF) was added via syringe, and the vessel was placed in an oil bath at 65 °C. The pressure was then adjusted to 80 psig (*caution*: an appropriate safety shield should be used), and the mixture was allowed to stir for 8 h. The solvent was removed *in vacuo* and Kugelrohr distillation afforded 101 mg (69% yield) of the desired *(R)*-(+)-2-phenylpyrrolidine, *(R)*-**3**. $^2H$ NMR analysis (46 MHz, $CDCl_3$, TMS) showed no resonances. GC/MS showed no peaks for deuterated **3**.

**Hydrogenation of 2 with *(R,R,R)*-1a (without phenylsilane).** A dry Fisher-Porter bottle properly fitted with a pressure coupling closure complete with a gas inlet, pressure gauge, inlet valve, and a pressure release valve was charged with *(R,R,R)*-**1a** (59 mg, 0.10 mmol) and a magnetic stir bar. The vessel was evacuated and filled with hydrogen (5−10 psig). THF (10 mL) was added via high-pressure syringe. After the complex had dissolved, a solution of *n*-butyllithium (117 μL, 1.70 M in hexanes, 0.20 mmol) was added and the mixture was stirred for 2−3 min at which point it was a green color. A solution of **2** (290 mg, 2.0 mmol, in 1 mL of THF) was added via syringe, and the vessel was placed in an oil bath at 65 °C. The pressure was then adjusted to 80 psig (*caution*: an appropriate safety shield should be used), and the mixture was allowed to stir for 8 h. The vessel was cooled and carefully vented. The solvent was removed *in vacuo*, and Kugelrohr distillation afforded 235 mg (80% yield) of the desired *(R)*-(+)-2-phenylpyrrolidine [*(R)*-**3**]. HPLC analysis of the 1-naphthamide (85/15 hexane−2-propanol) indicated >99% ee.

**Hydrogenation of 2 with 1c.** A dry Fisher-Porter bottle properly fitted with a pressure coupling closure complete with a gas inlet, pressure gauge, inlet valve, and a pressure release valve was charged with *(rac)*-**1c** (26 mg, 0.075 mmol) and a magnetic stir bar. The vessel was evacuated and filled with hydrogen (5−10 psig) resulting in an immediate color change to green. Benzene (4 mL) was added via high-pressure syringe. A solution of **2** (218 mg, 1.5 mmol, in 1 mL benzene) was added via syringe and the vessel was placed in an oil bath at 65 °C. The pressure was then adjusted to 80 psig (*caution*: an appropriate safety shield should be used), and the mixture was allowed to stir for 12 h. The vessel was cooled and carefully vented. The crude mixture was diluted with ether (10 mL) and extracted with 1 M HCl (3 × 10 mL). The aqueous portion was made basic with NaOH and extracted with methylene chloride (3 × 20 mL). The combined organic portions were dried over $Na_2SO_4$ and concentrated *in vacuo* to afford 182 mg (82% yield) of the desired 2-phenylpyrrolidine (**3**).

**Hydrogenation of 2 with 1d.** In a glove box, a dry Fisher-Porter bottle properly fitted with a pressure coupling closure complete with a gas inlet, pressure gauge, inlet valve, and a pressure release valve was charged with *(rac)*-**1d** (26 mg, 0.075 mmol) and a magnetic stir bar. The vessel was moved to a vacuum line, evacuated, and filled with hydrogen (5−10 psig). THF (6 mL) was added via syringe. After the complex had dissolved, a solution of *n*-butyllithium (42 μL, 1.78 M in hexanes, 0.075 mmol) was added and the mixture was stirred for 2−3 min at which point it was a green color. Phenylsilane (28 μL, 0.23 mmol) was added and no color change was observed. A solution of **2** (218 mg, 1.5 mmol, in 1.5 mL of THF) was added via syringe, and the vessel was placed in an oil bath at 65 °C. The pressure was then adjusted to 80 psig (*caution*: an appropriate safety shield should be used), and the mixture was allowed to stir for 6 h. The vessel was cooled and carefully vented. The crude mixture was diluted with ether (10 mL) and extracted with 1 M HCl (3 × 10 mL). The aqueous portion was made basic with NaOH and extracted with methylene chloride (3 × 20 mL). The combined organic portions were dried over $Na_2SO_4$ and concentrated *in vacuo* to afford 151 mg (69% yield) of the desired 2-phenylpyrrolidine (**3**).

**Hydrogenation of 2 with 1e.** In a glove box, a dry Fisher-Porter bottle properly fitted with a pressure coupling closure complete with a gas inlet, pressure gauge, inlet valve, and a pressure release valve was charged with *(rac)*-**1e** (27 mg, 0.075 mmol), **2** (218 mg, 1.5 mmol), and a magnetic stir bar. The vessel was moved to a vacuum line, evacuated, and filled with hydrogen (5−10 psig). THF (10 mL) was added via high-pressure syringe, and the vessel was placed in an oil bath at 65 °C. The pressure was then adjusted to 80 psig (*caution*: an appropriate safety shield should be used), and the mixture was allowed to stir for 8 h. The vessel was cooled and carefully vented. The crude mixture was diluted with ether (10 mL) and extracted with 1 M HCl (3 × 10 mL). The aqueous portion was made basic with NaOH and extracted with methylene chloride (3 × 20 mL). The combined organic portions were dried over $Na_2SO_4$ and concentrated *in vacuo* to afford 153 mg (70% yield) of the desired 2-phenylpyrrolidine (**3**).

**General Procedure for the Hydrogenation of Imines 4 and 6 at High Pressure.** In a dry Schlenk flask under an argon atmosphere, *(R,R,R)*-**1a** was dissolved in THF (10 mL). A solution of *n*-butyllithium (1.6 M in hexanes, 2 equiv) was added and the mixture was allowed to stir for 5 min, at which point it was a brown-green color. Phenylsilane (2.5−3.0 equiv) was added and mixture immediately turned dark brown. The resulting solution was moved into a dry box and transferred to a Parr high-pressure autoclave containing a magnetic stir bar. The imine (20 equiv based on Ti) was added. The vessel was sealed and moved to a fume hood where it was charged with hydrogen (specified below) and placed in an oil bath at 65 °C. The reaction mixture was allowed to stir (time specified below) under hydrogen pressure. The vessel was cooled to room temperature, carefully vented, and opened to air. The solvent was removed *in vacuo*. The amine extracted with 1 M HCl (3 × 10 mL). The aqueous layers were combined and made basic with solid NaOH (0 °C) and then extracted with ether (3 × 20 mL). The combined organic fractions were dried over $Na_2SO_4$ and concentrated to afford **5**.

**Hydrogenation of 4 at 2500 psig.** *N*-(1-Cyclohexylethylidene)-benzylamine (430 mg, 2.0 mmol) was reduced according to the general procedure with 5 mol % catalyst [*(R,R,R)*-**1a**, 59 mg (0.10 mmol); *n*-butyllithium, 129 μL (1.55 M in hexanes, 0.20 mmol); phenylsilane, 37 μL (0.30 mmol)]. The reaction vessel was charged to 2500 psig

and the reaction mixture was stirred for 10 h. The pure amine[5] (404 mg, 94% yield) was obtained after extraction. HPLC analysis indicated 81% ee [*(R)* enantiomer]. The absolute configuration was determined by independent synthesis.

**Hydrogenation of 4 at 2000 psig.** *N*-(1-Cyclohexylethylidene)-benzylamine (430 mg, 2.0 mmol) was reduced according to the general procedure with 5 mol % catalyst [*(R,R,R)*-**1a** 59 mg, (0.10 mmol); *n*-butyllithium, 120 μL (1.66 M in hexanes, 0.20 mmol); phenylsilane, 37 μL (0.30 mmol)]. The reaction vessel was charged to 2000 psig and the reaction mixture was stirred for 9 h. The pure amine (400 mg, 93% yield) was obtained after extraction. HPLC analysis indicated 76% ee [*(R)* enantiomer].

**Hydrogenation of 4 at 1500 psig.** *N*-(1-Cyclohexylethylidene)-benzylamine (430 mg, 2.0 mmol) was reduced according to the general procedure with 5 mol % catalyst [*(R,R,R)*-**1a**, 59 mg (0.10 mmol); *n*-butyllithium, 114 μL (1.75 M in hexanes, 0.20 mmol); phenylsilane; 37 μL (0.30 mmol)]. The reaction vessel was charged to 1500 psig, and the reaction mixture was stirred for 24 h. The pure amine (386 mg, 89% yield) was obtained after extraction. HPLC analysis indicated 74% ee [*(R)* enantiomer].

**Hydrogenation of 4 at 1000 psig.** *N*-(1-Cyclohexylethylidene)-benzylamine (430 mg, 2.0 mmol) was reduced according to the general procedure with 5 mol % catalyst [*(R,R,R)*-**1a**, 59 mg (0.10 mmol); *n*-butyllithium, 114 μL (1.75 M in hexanes, 0.20 mmol); phenylsilane, 37 μL (0.30 mmol)]. The reaction vessel was charged to 1000 psig and the reaction mixture was stirred for 48 h. The pure amine (341 mg, 79% yield was obtained after extraction. HPLC analysis indicated 65% ee [*(R)* enantiomer].

**Hydrogenation of 4 at 500 psig.** *N*-(1-Cyclohexylethylidene)-benzylamine (430 mg, 2.0 mmol) was reduced according to the general procedure with 5 mol % catalyst [*(R,R,R)*-**1a**, 59 mg (0.10 mmol); *n*-butyllithium, 114 μL (1.75 M in hexanes, 0.20 mmol); phenylsilane, 37 μL (0.30 mmol)]. The reaction vessel was charged to 500 psig, and the reaction mixture was stirred for 72 h. The pure amine (367 mg, 85% yield) was obtained after extraction. HPLC analysis indicated 43% ee [*(R)* enantiomer].

**Hydrogenation of 4 at 150 psig.** *N*-(1-Cyclohexylethylidene)-benzylamine (430 mg, 2.0 mmol) was reduced according to the general procedure with 5 mol % catalyst [*(R,R,R)*-**1a**, 59 mg (0.10 mmol); *n*-butyllithium,, 114 μL (1.75 M in hexanes, 0.20 mmol); phenylsilane, 37 μL (0.30 mmol)]. The reaction vessel was charged to 150 psig, and the reaction mixture was stirred for 102 h. The pure amine (372 mg, 86% yield) was obtained after extraction. HPLC analysis indicated 12% ee [*(R)* enantiomer].

**Hydrogenation of 4 at 2000 psig in benzene.** *N*-(1-Cyclohexylethylidene)benzylamine (430 mg, 2.0 mmol) was reduced according to the general procedure, using benzene in place of THF, with 5 mol % catalyst [*(R,R,R)*-**1a**, 59 mg (0.10 mmol); *n*-butyllithium, 129 μL (1.55 M in hexanes, 0.20 mmol); phenylsilane, 37 μL (0.30 mmol)]. The reaction vessel was charged to 2000 psig, and the reaction mixture was stirred for 14 h. The pure amine (390 mg, 89% yield) was obtained after extraction. HPLC analysis indicated 81% ee [*(R)* enantiomer].

**Hydrogenation of 4 at 500 psig in Benzene.** *N*-(1-Cyclohexylethylidene)benzylamine (430 mg, 2.0 mmol) was reduced according to the general procedure, using benzene in place of THF, with 5 mol % catalyst [*(R,R,R)*-**1a**, 59 mg (0.10 mmol); *n*-butyllithium, 122 μL, (1.63 M in hexanes, 0.20 mmol); phenylsilane, 37 μL (0.30 mmol)]. The reaction vessel was charged to 500 psig, and the reaction mixture was stirred for 72 h. The pure amine (390 mg, 89% yield) was obtained after extraction. HPLC analysis indicated 52% ee [*(R)* enantiomer].

**Hydrogenation of 4 at 2000 psig with *(R,R)*-1b.** *N*-(1-Cyclohexylethylidene)benzylamine (101 mg, 0.47 mmol) was reduced according to the general procedure, using *(R,R)*-**1b** in place of *(R,R,R)*-**1a**, with 10 mol% catalyst [*(R,R)*-**1b**, 18 mg (0.047 mmol); *n*-butyllithium, 68 μL (1.39 M in hexanes, 0.094 mmol); phenylsilane, 15 μL (0.12 mmol)]. The reaction vessel was charged to 1950 psig, and the reaction mixture was stirred for 3 h. The amine (83 mg, 94% pure by GC, 82% yield) was obtained after extraction. HPLC analysis indicated 76% ee [*(R)* enantiomer].

**Hydrogenation of 4 at 2000 psig with *(R,R)*-1c.** In a glove box, a Parr Model 4751 high-pressure autoclave containing a magnetic stir bar was charged with *(R,R)*-**1c** (35 mg, 0.10 mmol) and 10 mL THF. Phenylsilane (31 mL, 0.25 mmol) was added, and the mixture was stirred for 10 min. Imine **4** (215 mg, 1.0 mmol) was added and the vessel sealed, moved to a fume hood, and charged with hydrogen (1950 psig). The mixture was heated in an oil bath at 65 °C for 22 h. The solvent was removed *in vacuo*, and the amine (150 mg, 69% yield) was isolated by extraction. HPLC analysis indicated 84% ee [*(R)* enantiomer].

**Hydrogenation of 4 at 500 psig with *(R,R)*-1c.** In a glove box, a Parr Model 4751 high-pressure autoclave containing a magnetic stir bar was charged with *(R,R)*-**1c** (35 mg, 0.10 mmol) and 10 mL THF. Phenylsilane (37 mL, 0.30 mmol) was added. Imine **4** (430 mg, 2.0 mmol) was added and the vessel sealed, moved to a fume hood, and charged with hydrogen (500 psig). The mixture was heated in an oil bath at 65 °C for 72 h. The solvent was removed *in vacuo*, and the amine (337 mg, 78% yield) was isolated by extraction. HPLC analysis indicated 61% ee [*(R)* enantiomer].

**Hydrogenation of 4 at 2000 psig with Excess *n*-Butyllithium.** *N*-(1-Cyclohexylethylidene)benzylamine (430 mg, 2.0 mmol) was reduced according to the general procedure with 5 mol % catalyst [*(R,R,R,)*-**1a**, 59 mg (0.10 mmol); *n*-butyllithium, 149 μL (1.68 M in hexanes, 0.25 mmol); phenylsilane, 37 μL (0.30 mmol)]. The reaction vessel was charged to 2000 psig, and the reaction mixture was stirred for 12 h. The pure amine (332 mg, 76% yield) was obtained after extraction. HPLC analysis indicated 39% ee [*(R)* enantiomer].

**Hydrogenation of 4 at 2000 psig with a Deficiency of *n*-Butyllithium.** *N*-(1-Cyclohexylethylidene)benzylamine (430 mg, 2.0 mmol) was reduced according to the general procedure with 5 mol % catalyst [*(R,R,R)*-**1a**, 59 mg (0.10 mmol); *n*-butyllithium, 89 μL (1.68 M in hexanes, 0.15 mmol); phenylsilane, 37 μL (0.30 mmol)]. The reaction vessel was charged to 2000 psig, and the reaction mixture was stirred for 12 h. The pure amine (400 mg, 92% yield) was obtained after extraction. HPLC analysis indicated 77% ee [*(R)* enantiomer].

**Kinetic Resolution of Racemic 6 at 2000 psig.** Benzylidene(1-cyclohexylethyl)amine (430 mg, 2.0 mmol) was reduced according to the general procedure with 5 mol % catalyst [*(R,R,R)*-**1a**, 59 mg (0.10 mmol); *n*-butyllithium, 114 μL (1.75 M in hexanes, 0.20 mmol); phenylsilane, 37 μL, 0.30 mmol)]. The reaction vessel was charged to 2000 psig, and the reaction mixture was stirred for 4 h. At this point GC showed 71% remaining **6** and 29% **5** (only a trace of **4** was observed). The mixture was transferred to a flask containing 5 mL of 1 M HCl and stirred overnight. The layers were separated, and the aqueous layer was made basic with NaOH and extracted with ether (3 × 20 mL). The organic portions were dried with $N_2SO_4$ and concentrated. Column chromatography (silica, 2% triethylamine–hexane) afforded 88 mg (20% yield) of amine **5**. HPLC analysis indicated 16% ee [*(S)* enantiomer].

**Hydrogenation of *(R)*-6 at 2000 psig with *(R,R,R)*-1a.** Benzylidene(1-cyclohexylethyl)amine (6 mL of a 0.375 M stock solution in THF, 2.25 mmol, 95% ee) was reduced according to the general procedure with 6.7 mol % catalyst [*(R,R,R)*-**1a**, 90 mg (0.30 mmol); *n*-butyllithium, 176 μL (1.70 M in hexanes, 0.10 mmol); phenylsilane, 55 μL, 0.45 mmol)]. The reaction vessel was charged to 2000 psig, and the reaction mixture was stirred for 10 h. HPLC analysis of amine *(R)*-**5** (not purified) indicated 91% ee.

**Hydrogenation of *(R)*-6 at 2000 psig with *(S,S,S)*-1a.** Benzylidene-(1-cyclohexylethyl)amine (6 mL of a 0.375 M stock solution in THF, 2.25 mmol, 95% ee) was reduced according to the general procedure, using *(S,S,S)*-**1a** in place of *(R,R,R)*-**1a**, with 6.7 mol % catalyst [titanium complex, 90 mg (0.15 mmol); *n*-butyllithium, 176 μL (0.30 mmol, 1.70 M in hexanes); phenylsilane, 55 μL (0.45 mmol)]. The reaction vessel was charged to 2000 psig and the reaction mixture was stirred for 10 h. HPLC analysis of amine *(R)*-**5** (not purified) indicated 93% ee.

**Hydrogenation of *(R)*-6 at 500 psig with *(R,R,R)*-1a.** Benzylidene-(1-cyclohexylethyl)amine (215 mg, 1.0 mmol, 94% ee) was reduced according to the general procedure with 5 mol % catalyst [titanium complex, 30 mg (0.05 mmol); *n*-butyllithium, 59 μL (1.70 M in hexanes, 0.10 mmol); phenylsilane, 19 μL (0.15 mmol)]. The reaction vessel was charged to 500 psig, and the reaction mixture was stirred for 40 h. The pure amine *(R)*-**5** (199 mg, 92% yield) was obtained after Kugelrohr distillation. HPLC analysis indicated 89% ee.

**Hydrogenation of *(R)*-6 at 500 psig with *(S,S,S)*-1a.** Benzylidene-

(1-cyclohexylethyl)amine (215 mg, 1.0 mmol, 94% ee) was reduced according to the general procedure, using *(S,S,S)*-**1a** in place of *(R,R,R)*-**1a**, with 5 mol % catalyst [titanium complex, 30 mg (0.05 mmol); *n*-butyllithium, 59 μL (1.70 M in hexanes, 0.10 mmol); phenylsilane, 19 μL (0.15 mmol)]. The reaction vessel was charged to 500 psig, and the reaction mixture was stirred for 40 h. Pure amine *(R)*-**5** (201 mg, 93% yield) was obtained after Kugelrohr distillation. HPLC analysis indicated 91% ee.

**Stoichiometric Reaction of 4 with *(R,R,R)*-1a.** A dry Schlenk flask, under an argon atmosphere, was charged with *(R,R,R)*-**1a** (120 mg, 0.2 mmol) and 10 mL THF. A solution of *n*-butyllithium (235 μL, 0.4 mmol, 1.70 M in hexanes) was added via syringe. After 2−3 min the solution was brown in color. Phenylsilane (65 μL, 0.6 mmol) was added and the solution turned dark brown. Imine **4** was added and the color lightened slightly. The mixture was stirred for 30 min and quenched with 1 M NaOH (2 mL). The solvent was removed *in vacuo*, and the residue passed down a column of silica using 2% triethylamine−hexane (to remove the metal complex). HPLC analysis of the crude residue indicated 83% ee for amine **5** [*(R)* enantiomer].

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## Appendix

**Derivation of the Rate Expression (eq 4).**

$$\text{rate} = k_2[\mathbf{1g}][H_2] \tag{A1}$$

Applying the steady state approximation to **1g** gives

$$d[\mathbf{1g}]/dt = 0$$

therefore

$$k_1[\mathbf{1f}][\mathbf{2}] = k_{-1}[\mathbf{1g}] + k_2[\mathbf{1g}][H_2]$$

$$k_1[\mathbf{1f}][\mathbf{2}] = (k_{-1} + k_2[H_2])[\mathbf{1g}]$$

$$[\mathbf{1g}] = [k_1/(k_{-1} + k_2[H_2])][\mathbf{1f}][\mathbf{2}] \tag{A2}$$

The total titanium concentration, [Ti] is

$$[\text{Ti}] = [\mathbf{1f}] + [\mathbf{1g}]$$

$$[\mathbf{1f}] = [\text{Ti}] - [\mathbf{1g}] \tag{A3}$$

Substituting eq A3 into eq A2 gives

$$[\mathbf{1g}] = [k_1/(k_{-1} + k_2[H_2])]\,([\text{Ti}] - [\mathbf{1g}])[\mathbf{2}]$$

Which simplifies to

$$[\mathbf{1g}] = [\text{Ti}][\mathbf{2}]/[[(k_{-1} + k_2[H_2])/k_1] + [\mathbf{2}]]$$

Substituting this expression into eq A1 gives the rate law

$$\text{rate} = k_2[\text{Ti}][H_2][\mathbf{2}]/[[(k_{-1} + k_2[H_2])/k_1] + [\mathbf{2}]] \tag{A4}$$