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# Rhodium-Catalyzed Asymmetric Hydrogenation of Functionalized Olefins Using Monodentate Spiro Phosphoramidite Ligands

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Novel chiral monodentate phosphorus ligands, SIPHOS, were conveniently synthesized from 1,1′-spirobiindane-7,7′-diol. The Rh complexes of SIPHOS can catalyze the hydrogenation of α-dehydroamino esters in mild conditions, providing α-amino acid derivatives in up to 99% ee. Enamides and *β*-dehydroamino esters can also be hydrogenated in good to excellent enantioselectivities (up to 99% and 94% ee, respectively). The SIPHOS ligand with smaller alkyl groups on the N-atom afforded higher enantioselectivity. The X-ray analysis of single crystal showed that the structure of Rh/SIPHOS catalyst is $[Rh(COD)((S)\text{-SIPHOS-Me})_2]^+$, which clarified the configuration of the catalyst with the monodentate chiral phosphorus ligand in Rh-catalyzed asymmetric hydrogenation. A positive nonlinear effect in the relationship of the optical purities of ligand and product was observed in the hydrogenation of dehydroamino acid derivatives. The kinetic study of hydrogenation showed that the reaction is zero order in the concentration of substrate and first order in the concentration of Rh catalyst and the hydrogenation pressure. The rate of hydrogenation decreased when the Rh/L ratio changed from 1:1 to 1:4.

## Introduction

The increasing demand of enantiomerically pure chemicals has expedited the development of asymmetric synthesis. Significant progress has been made in Rh-catalyzed hydrogenation in the past 2 decades.[1] Both the scope of substrate and the class of chiral ligands have been rapidly extended. For example, a great number of chiral phosphorus ligands have been synthesized and applied to the Rh-catalyzed asymmetric hydrogenation of functionalized olefins such as α-dehydroamino acid derivatives, *β*-dehydroamino acid derivatives, and enamides.[2] Among them, most are bidentate phosphine ligands, such as DIOP,[3] BINAP,[4] and DuPhos,[5] though the first utilization of a chiral ligand is monodentate P-chiral phosphines by Knowles[6] and Horner.[7]

Monodentate phosphorus ligands have been neglected for a long period owing to the great success of biphosphine ligands. The main advantage of the application of bidentate ligands is that their catalysts are more rigid, which reduces the number of conformations of catalyst and subsequently provides a higher enantioselectivity.[8] Using monodentate ligands, the catalyst has much more conformational freedom, so that a lower chiral induction was expected. However, easy synthesis and modification of ligands are good features of monophosphorus ligands. Furthermore, monodentate ligands might be good choices for the catalytic asymmetric reactions where bidentate ligands are unfavorable, especially as the catalytic cycle involves one or more steps in which the ligand can only occupy one coordination site. Therefore, monodentate ligands are gaining more attention.[9]

In 1999, Fiaud[10] reported a rhodium complex of monodentate ligand 1,2,5-triphenylphospholane (**1**), achieving 82% ee in the hydrogenation of (*Z*)-2-acetaminocinnamic ester. Only 1 year later, several efficient chiral monophosphorus ligands including phosphonites (**2**), phosphites (**3**), and phosphoramidites (**4**) were applied in asymmetric hydrogenation of functionalized olefins with high enantioselectivities by Pringle,[11] Reetz,[12] and de Vries and Feringa,[13] respectively (Figure 1). It is noteworthy that all of the reported monodentate ligands

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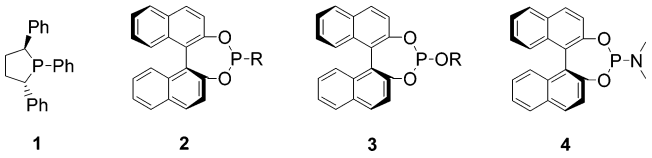



**FIGURE 1.**

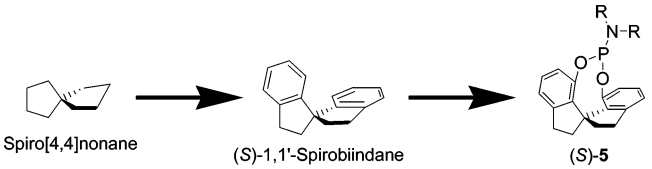
that induced high enantioselectivity are phosphorus derivatives of binaphthol.[14]

In asymmetric catalysis, chiral $C_2$-symmetric biaryls, such as 1,1′-binaphthalene, were widely used as backbones of ligands.[2,15] By contrast, chiral spiranes, another class of $C_2$-symmetric molecules, which also possess an axial chirality, have not been paid much attention.[16] The rigidity of the spiro cyclic framework should decrease the flexibility of ligands and their related complexes and consequently benefit asymmetric induction in catalysis. Spiro[4,4]nonane itself is not a chiral molecule. Substitutions on the spiro cycles introduced more than one chiral center into the molecule and increased the difficulty in the synthesis of optically pure ligands. However, spirobiindane, which can be regarded as a benzo derivative of sprio[4,4]nonane, has only axial chirality and its rigid spiro structure makes it a potential backbone of chiral ligands. By using 1,1′-spirobiindane backbone we have developed novel monodentate chiral phosphoramidite ligands SIPHOS (**5**) (Scheme 1). The ligands **5** were found to be highly efficient in Rh-catalyzed asymmetric hydrogenations of α-dehydroamino acid derivatives[17] and *N*-(α-arylethenyl)acetamides.[18] Here we report the results of our detailed studies on these reactions with emphasis on the kinetics of the reaction, structures of the catalysts, and the new application of SIPHOS ligands in asymmetric hydrogenation of β-dehydroamino acid derivatives.

## Results and Discussion

**Ligand Preparation.** SIPHOS represent a new class of chiral monodentate ligands. It can be conveniently synthesized from enantiomerically pure 1,1′-spirobiindane-7,7′-diol (SPINOL).[19] Ligands SIPHOS-Me (**5a**) and SIPHOS-Et (**5b**), which have small amino groups, were prepared by the reaction of SPINOL with hexamethylphosphorus triamide or hexaethylphosphorus triamide in good yields. The SIPHOS ligands with larger amino groups, such as pyrrolidinyl (SIPHOS-Pyr, **5c**) and diisopropylamino (SIPHOS-Pr$^i$, **5d**), however, were prepared in moderate yields by the reaction of SPINOL with $PCl_3$, followed by treatment with two equivalent corresponding amines (Scheme 2).[20]

**SCHEME 1**




**SCHEME 2. Syntheses of SIPHOS Ligands**

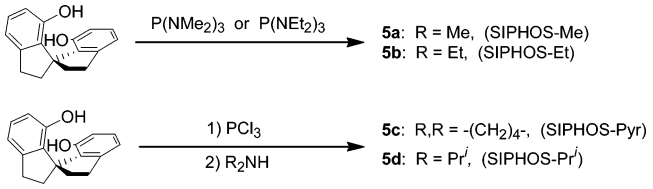
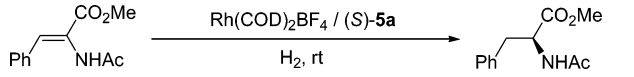



**TABLE 1. Rh/SIPHOS-Catalyzed Asymmetric Hydrogenation of Methyl (*Z*)-2-Acetamidocinnamate**[a]




| entry | solvent | cat. (mol %) | $P_{H_2}$ (atm) | time (h)[b] | ee (%)[c] | config |
|---|---|---|---|---|---|---|
| 1 | MeOH | 1 | 1 | 8 | 94 | *S* |
| 2 | EtOAc | 1 | 1 | 10 | 97 | *S* |
| 3 | toluene | 1 | 1 | 12 | 97 | *S* |
| 4 | acetone | 1 | 1 | 12 | 96 | *S* |
| 5 | THF | 1 | 1 | 10 | 97 | *S* |
| 6 | $CH_2Cl_2$ | 1 | 1 | 10 | 97 | *S* |
| 7 | $CH_2Cl_2$ | 1 | 5 | 4 | 97 | *S* |
| 8 | $CH_2Cl_2$ | 1 | 20 | 1 | 96 | *S* |
| 9 | $CH_2Cl_2$ | 0.5 | 1 | 16 | 96 | *S* |
| 10 | $CH_2Cl_2$ | 0.1 | 50 | 24 | 97 | *S* |
| 11[d] | $CH_2Cl_2$ | 1 | 1 | 20 | 98 | *S* |

[a] The reaction was performed at room temperature with 0.5 mmol of substrate in 5 mL of solvent, $[Rh(COD)_2BF_4]$/(*S*)-**5a** = 1:2.1 unless otherwise mentioned. [b] Time for complete conversion. Yields were quantitative. [c] Determined by chiral HPLC using a CHIRACEL-OJ column. [d] Performed at 0 °C.

**Asymmetric Hydrogenation of α-Dehydroamino Acid Derivatives with Rh/SIPHOS.** Rhodium-catalyzed asymmetric hydrogenation of α-dehydroamino acid derivatives has been extensively studied and afforded a model reaction to test the effectiveness of new chiral ligands.[2] The hydrogenation of methyl (*Z*)-2-acetamidocinnamate was first performed using 1 mol % Rh/SIPHOS catalyst in different solvents. It was found that the reaction, under 1 atm $H_2$ at room temperature, is not very sensitive to the solvent used (Table 1). In aprotic solvents, such as $CH_2Cl_2$, toluene, and EtOAc, the hydrogenation product was obtained in high ee. The hydrogen pressure has no influence on the enantioselectivity, but the reaction rate was accelerated when the hydrogen pressure was increased (entries 6−8). Lowering the catalyst loading from Rh/substrate ratio 1:100 to 1:200 decreased reaction rate but did not change the ee

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**TABLE 2. Asymmetric Hydrogenation of Methyl (*Z*)-2-Acetamidocinnamate with Different Catalysts[a]**

| entry | [Rh] | ligand | ee (%) | config |
|---|---|---|---|---|
| 1 | $[Rh(COD)Cl]_2$ | (*S*)-**5a** | | |
| 2 | $Rh(COD)_2BF_4$ | (*S*)-**5a** | 98 | *S* |
| 3 | $Rh(COD)_2PF_6$ | (*S*)-**5a** | 98 | *S* |
| 4[b] | $Rh(COD)_2SbF_6$ | (*S*)-**5a** | 98 | *S* |
| 5 | $Rh(COD)_2BF_4$ | (*S*)-**5b** | 94 | *S* |
| 6 | $Rh(COD)_2BF_4$ | (*S*)-**5c** | 87 | *S* |
| 7 | $Rh(COD)_2BF_4$ | (*S*)-**5d** | 83 | *S* |

[a] Reaction conditions: 1 mol % catalyst, [Rh]/L = 1:2.1, $P_{H_2}$ = 1 atm, $CH_2Cl_2$, 0 °C, 24 h, unless mentioned otherwise. Conversions are 100%. [b] 70% conversion.

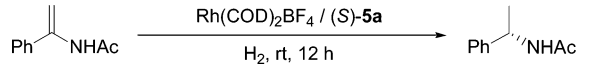
of product. When the Rh/substrate ratio of 1:1000 was employed, the reaction could not complete unless the hydrogen pressure was increased to 50 atm (entry 10). In the optimal conditions, a variety of α-amino acid derivatives were prepared in excellent enantiomerically excesses.[17]

Different catalyst precursors were compared in the asymmetric hydrogenation of methyl (*Z*)-2-acetamidocinnamate catalyzed by Rh/(*S*)-**5a** complex. All ionic rhodium complexes can catalyze the hydrogenation, although $Rh(COD)_2SbF_6$ provided a slow reaction and neutral catalyst precursor $[Rh(COD)Cl]_2$ gave no reaction since $Cl^-$ coordinates to Rh tightly so that the catalyst cannot provide enough coordinate sites to accept ligand or substrate. Using ionic Rh precursors, the reactions had the same level of enantioselectivity (Table 2).

In a previous paper, we reported that small alkyl groups on the nitrogen atom of SIPHOS ligands are necessary for obtaining high enantioselectivity in the asymmetric hydrogenation of α-arylenamides.[18] It was the same in the Rh-catalyzed hydrogenation of methyl (*Z*)-2-acetamidocinnamate. Ligand SIPHOS-Me (**5a**), which has the smallest methyl groups at the nitrogen atom, provided the highest enantioselectivity (98% ee). Replacing the methyl groups of ligand **5a** by other bulkier alkyl groups produced ligands SIPHOS-Et (**5b**), SIPHOS-Pyr (**5c**), and SIPHOS-Pr$^i$ (**5d**) and led to a continuous decrease of ee of hydrogenation product (Table 2, entries 5−7). A similar trend was also observed in the asymmetric hydrogenation of *β*-(acetylamino)acrylates with MonoPhos ligands.[13b] However, the substitutions on the 4,4′-positions of the spirobiindane backbone have almost no impact on the enantioselectivity of reaction.[21]

**Asymmetric Hydrogenation of Enamides with Rh/SIPHOS.** Optically active α-arylalkylamines are an important class of compounds that are widely used in organic and pharmaceutical synthesis, and much effort has been made in developing efficient asymmetric syntheses of these compounds.[22] Asymmetric catalytic hydrogenation of enamides provides a direct and convenient route to chiral amine derivatives. Encouraged by the high enantioselectivities of Rh/SIPHOS catalysts in the asymmetric hydrogenation of α-dehydroamino acid derivatives, we therefore investigated the utility of Rh/SIPHOS in the asymmetric hydrogenation of enamides.

**TABLE 3. Asymmetric Hydrogenation of α-Phenylenamide Catalyzed by Rh/SIPHOS Complexes[a]**




| entry | solvent | [Rh] (mol %) | L | $P_{H_2}$ (atm) | ee (%)[b] |
|---|---|---|---|---|---|
| 1 | MeOH | $Rh(COD)_2BF_4$ (1) | **5a** | 10 | 50 |
| 2 | EtOAc | $Rh(COD)_2BF_4$ (1) | **5a** | 10 | 90 |
| 3 | acetone | $Rh(COD)_2BF_4$ (1) | **5a** | 10 | 83 |
| 4 | $CH_2Cl_2$ | $Rh(COD)_2BF_4$ (1) | **5a** | 10 | 83 |
| 5 | THF | $Rh(COD)_2BF_4$ (1) | **5a** | 10 | 81 |
| 6 | toluene | $Rh(COD)_2BF_4$ (1) | **5a** | 10 | 96 |
| 7 | toluene | $Rh(COD)_2BF_4$ (1) | **5a** | 100 | 96 |
| 8 | toluene | $Rh(COD)_2BF_4$ (0.5) | **5a** | 50 | 96 |
| 9 | toluene | $Rh(COD)_2BF_4$ (0.1) | **5a** | 100 | 84 |
| 10[c] | toluene | $Rh(COD)_2BF_4$ (1) | **5a** | 50 | 99 |
| 11 | toluene | $Rh(COD)_2BF_4$ (1) | **5b** | 10 | 57 |
| 12 | toluene | $Rh(COD)_2BF_4$ (1) | **5c** | 10 | 38 |
| 13[d] | toluene | $Rh(COD)_2PF_6$ (1) | **5a** | 10 | 96 |
| 14[d] | toluene | $Rh(COD)_2SbF_6$ (1) | **5a** | 10 | 95 |
| 15 | toluene | $[Rh(COD)Cl]_2$ (1) | **5a** | nr | |

[a] The reaction was performed using 1 mol % catalyst at room temperature with 0.5 mmol of substrate in 5 mL of solvent, $P_{H_2}$ = 10 atm, [Rh]/L = 1:2.2, unless otherwise mentioned. Complete conversions were achieved within 12 h. Yields were quantitative. [b] Determined by chiral capillary GC on a Varian Chirasil-L-Val column (25 m). Configurations were *S*. [c] *T* = 5 °C. [d] Reaction time was 48 h.

The results in Table 3 showed that the enantioselectivity of the reaction was quite sensitive to the solvent used. Toluene appeared to be the best solvent of choice (Table 3, entry 1−6). However, the hydrogen pressure has influence only on the reaction rate and not on the enantioselectivity. For example, in the hydrogenation of α-phenylenamide using SIPHOS-Me in toluene at room temperaturee, the ee values of product at both 10 and 100 atm $H_2$ were 96% (entries 6 and 7). The investigation of catalyst loading showed that 0.5 mol % of catalyst was sufficient to give a high enantioselectivity, while the ee value of the product dropped drastically when 0.1 mol % catalyst was used (entry 9). The effect of ligand structure on the enantioselectivity of the catalysts was also examined. When the alkyl groups on the N-atom of SIPHOS ligands changed from methyl (**5a**) to ethyl (**5b**) and isopropyl (**5c**), the enantioselectivities of the catalysts greatly decreased from 96% to 57% and 38% ee (entries 11 and 12 vs 6). Catalysts prepared in situ from different ionic Rh complexes were active in the asymmetric hydrogenation of enamides and provided a similar level of enantiocontrol, though the catalysts with bulkier counteranions needed a longer time for completion of reaction (entries 13 and 14). However, the catalyst prepared from the neutral complex $[Rh(COD)Cl]_2$ was inert (entry 15). Various α-arylenamides can be hydrogenated under the optimal conditions to produce chiral amines in excellent enantioselectivities.[18]

Chiral 1-aminoindanes are key intermediates for drugs such as rasagiline for Parkinson's disease.[23] Asymmetric hydrogenation of *N*-(1,2-dehydro-1-indanyl)acetamide is a potential method for the production of enantioenriched

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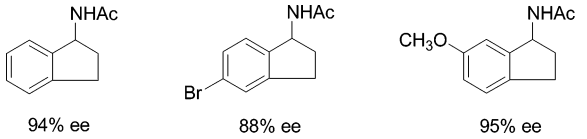
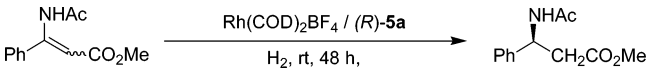



**FIGURE 2.** Chiral 1-aminoindanes.

1-aminoindane. Using the Rh/SIPHOS catalyst, *N*-(1,2-dehydro-1-indanyl)acetamide was hydrogenated in toluene at 0 °C under 100 atm $H_2$, providing 1-aminoindane in 100% yield with 94% ee. Under the same reaction conditions, 5-Br- and 6-MeO-substituted 1-aminoindanes were also prepared in 88% and 95% ee, respectively (Figure 2).

**Asymmetric Hydrogenation of *β*-Dehydroamino Acid Derivatives with Rh/SIPHOS.** Enantiomerically pure *β*-amino acid derivatives are important building blocks in the synthesis of many chiral drugs.[24] Asymmetric hydrogenation of *β*-(acylamino)acrylate derivatives has attracted much attention recently because it provides a convenient method for the synthesis of *β*-amino acid derivatives. Among the ligands used in the Rh-catalyzed hydrogenation of *β*-(acylamino)acrylate derivatives, the diphosphines have been most effective.[25] Recently, monophosphoramidites[13b] were also successfully employed in the Rh-catalyzed asymmetric hydrogenation of *β*-(acylamino)acrylates, providing excellent enantioselectivities. However, for most catalytic systems, high enantioselectivity can only be obtained when pure *Z*- or *E*-isomers of *β*-(acylamino)acrylate substrates are used in the hydrogenation. Very few catalysts have been reported to be efficient for the hydrogenation of *Z*/*E* mixtures of *β*-(acylamino)acrylates. The exceptional examples include Rh/TangPhos[25d] and Ru/*o*-BINAPO[25e] catalysts in the hydrogenations of *Z*/*E* mixtures of *β*-aryl *β*-(acylamino)acrylates, achieving high enantioselectivities.[26] Because the *β*-(acylamino)acrylates are normally formed as a mixture of *Z*- and *E*-isomers, the development of a new efficient catalyst that can hydrogenate the mixture of the two isomers is significantly important. It is our delight that the Rh/SIPHOS complexes can catalyze asymmetric hydrogenations of *Z*/*E* mixtures of *β*-aryl *β*-(acylamino)acrylate derivatives, which cannot be separated by silica gel column chromatography, providing *β*-amino acid derivatives in high enantioselectivities. Methyl (*Z*/*E*)-3-(acylamino)cinnamate (*Z*/*E* = 88:12) was chosen as the substrate for optimizing the reaction condition. Screening of solvents showed that $CH_2Cl_2$ was the best solvent for obtaining high enantioselectivity. Increasing hydrogen pressure led to higher reaction rates, while the enantiomeric excesses remain the same (Table 4).

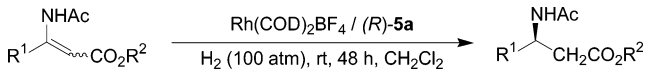
**TABLE 4. Asymmetric Hydrogenation of Methyl 3-Acetylaminocinnamate[a]**




| entry | solvent | $P_{H_2}$ (atm) | conv (%) | ee (%) [b] | config[c] |
|---|---|---|---|---|---|
| 1 | $CH_2Cl_2$ | 20 | 73 | 90 | *S* |
| 2 | $CH_2Cl_2$ | 50 | 90 | 90 | *S* |
| 3 | $CH_2Cl_2$ | 100 | 100 | 90 | *S* |
| 4 | EtOAc | 100 | 92 | 48 | *S* |
| 5 | THF | 100 | 55 | 81 | *S* |
| 6 | toluene | 100 | 63 | 80 | *S* |
| 7 | acetone | 100 | 90 | 76 | *S* |
| 8 | MeOH | 100 | 100 | 85 | *S* |
| 9 | EtOH | 100 | 100 | 65 | *S* |
| 10 | $^i$PrOH | 100 | 100 | 75 | *S* |

[a] Reactions were carried out in 5 mL of solvent using 2 mol % catalyst at room temperature for 48 h. Rh/L = 1:2.1. [b] Determined by chiral capillary GC on a Varian Chirasil-L-Val column (25 m). [c] Determined by comparing the optical rotations with reported values.

**TABLE 5. Hydrogenation of *β*-Dehydroamino Esters[a]**




| substrate | ee (%)[b] | config[c] |
|---|---|---|
| $R^1$ = Ph, $R^2$ = Me | 90 | *S* |
| $R^1$ = 2-BrPh, $R^2$ = Me | 91 | *S* |
| $R^1$ = 3-BrPh, $R^2$ = Me | 92 | *S* |
| $R^1$ = 4-BrPh, $R^2$ = Me | 94 | *S* |
| $R^1$ = 4-ClPh, $R^2$ = Me | 91 | *S* |
| $R^1$ = 4-MePh, $R^2$ = Me | 91 | *S* |
| $R^1$ = 4-$CH_3$OPh, $R^2$ = Me | 93 | *S* |
| $R^1$ = $CH_3$, $R^2$ = Et | 87[d] | *R* |
| $R^1$, $R^2$ = Me | 89[d] | *R* |

[a] Reactions were carried out under 100 atm $H_2$ in 5 mL of $CH_2Cl_2$ using 2 mol % catalyst at room temperature for 48 h. Rh/L = 1:2.1. Conversions are 100%. [b] Determined by chiral capillary GC on a Varian Chirasil-L-Val column (25 m). [c] Determined by comparing the optical rotations with reported values. [d] Determined by chiral capillary GC on a Supelco *β*-dex 120 column (30 m).

Under the optimal conditions, a variety of *β*-(acylamino)acrylate (*Z*/*E* = 98:2 to 50:50) can be hydrogenated in high enantioselectivities, and the results are summarized in Table 5. In the hydrogenations of *β*-aryl *β*-(acylamino)-acrylates, the electronic nature of the aryl group in the substrate had little influence on the ee of product. The hydrogenations of *β*-methyl *β*-(acylamino)acrylates, however, had slightly lower enantioselectivities compared to the hydrogenations of *β*-aryl *β*-(acylamino)acrylates.

**Mechanistic Consideration.** The mechanism of rhodium-catalyzed asymmetric hydrogenation of functionalized olefins using diphosphine ligands has been well-established by Halpern,[27] Brown,[28] Gridnev and Imamoto,[29] and others.[30] However, the investigation into the

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(26) Moderate to good enanstioselectivities were also reported in the hydrogenation of mixtures of *β*-alkyl *β*-(acylamino)acrylates; see ref 25f, 25k, 25l and Jerphagnon, T.; Renaud, J.-L.; Demonchaux, P.; Ferreira, A.; Bruneau, C. *Adv. Synth. Catal.* **2004**, *346*, 33.

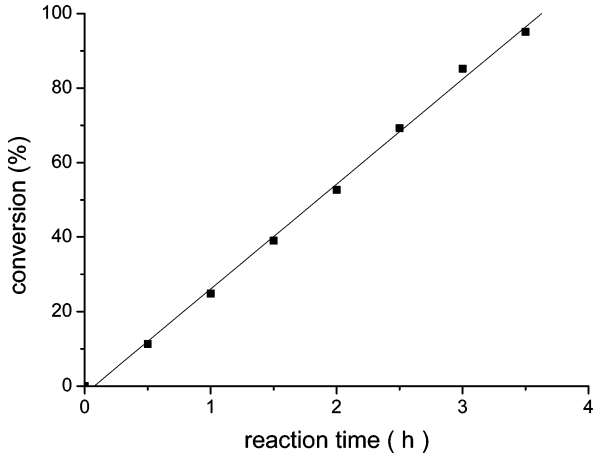


**FIGURE 3.** Dependency of conversion versus reaction time ($T$ = 25 °C, $P_{H_2}$ = 1 atm, $[sub]_0$ = 0.1 M, [Rh] = 1.0 mM).

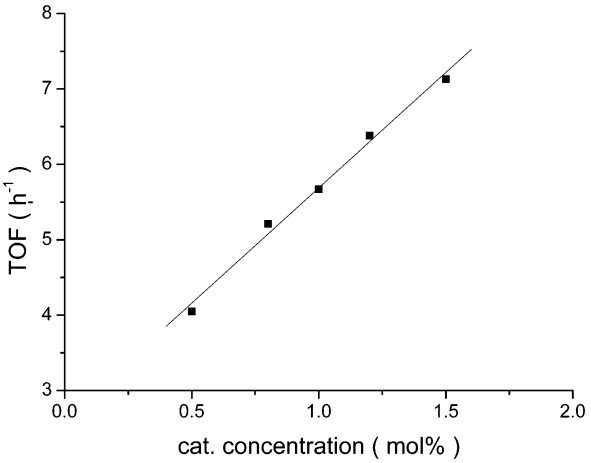


**FIGURE 4.** Dependency of TOF versus catalyst concentration ($T$ = 25 °C, $P_{H_2}$ = 1 atm, $[sub]_0$ = 0.1 M, [Rh] = 0.5−1.5 mM).

mechanism of asymmetric hydrogenation using monophosphorus ligands is still in its infancy. To collect more information about the mechanism of Rh(I)-catalyzed hydrogenation using monophosphorus ligands, we made a kinetic study of the Rh/**5a**-catalyzed hydrogenation of methyl (*Z*)-2-acetamidocinnamate. The kinetic features tested include substrate and catalyst concentration, hydrogen pressure. Using ligand (*S*)-**5a**, all reactions gave the hydrogenation product with the same (*S*)-configuration and the same level of enantioselectivity.

The substrate concentration dependency of reaction was obtained by following the conversion of substratevs reaction time. The graph in Figure 3 suggests a zero-order dependency of reaction rate on the substrate concentration. The effect of the catalyst concentration on the reaction rate was studied. When the reactions were performed with a catalyst concentration between 0.5 and 1.5 mM, the rate (TOF) of hydrogenation is linear to the catalyst concentration (Figure 4), suggesting a first-order dependency of reaction rate on the catalyst concentration. The hydrogen pressure was varied between 0.25 and 1.0 atm. The graph of TOF vs hydrogen pressure in Figure 5 also shows a first-order dependency of reaction rate on the hydrogen pressure.[31] Temperature is another condition that can affect the reaction result. We also examined the temperature effect of reaction by following conversion

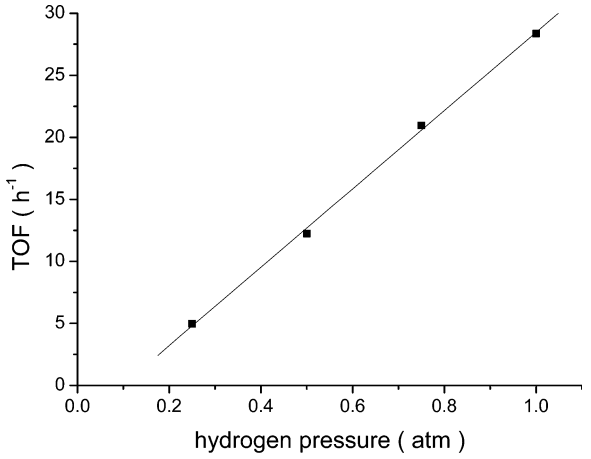


**FIGURE 5.** Dependency of TOF versus hydrogen pressure ($T$ = 25 °C, $P_{H_2}$ = 0.25−1 atm, $[sub]_0$ = 0.1 M, [Rh] = 1.0 mM).

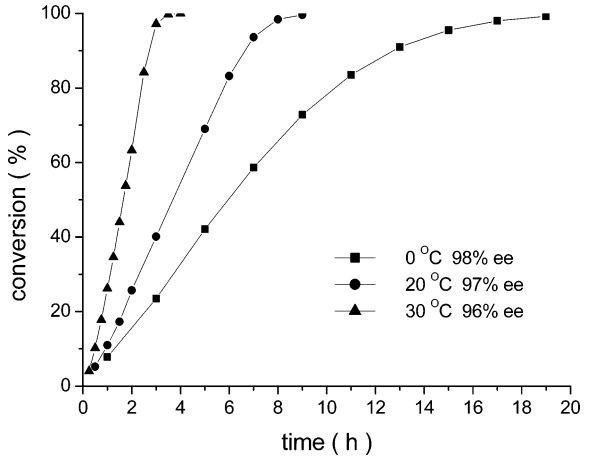


**FIGURE 6.** Dependency of reaction rate versus temperature ($T$ = 0−30 °C, $P_{H_2}$ = 1 atm, $[sub]_0$ = 0.1 M, [Rh] = 1.0 mM).

vs time at 0, 20, and 30 °C. As shown in Figure 6, the reaction became faster at higher temperature, while a higher enantioselectivity was obtained at lower temperature. The kinetic features of Rh/SIPHOS-catalyzed hydrogenation clearly show that the oxidative addition

(27) (a) Halpern, J. *Science* **1982**, *217*, 401. (b) Halpern, J. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: Orlando, FL, 1985. (c) Chan, A. S. C.; Pluth, J. J.; Halpern, J. *Inorg. Chim. Acta* **1979**, *37*, L477. (d) Chan, A. S. C.; Pluth, J. J.; Halpern, J. *J. Am. Chem. Soc.* **1980**, *102*, 5952. (e) Chan, A. S. C.; Halpern, J. *J. Am. Chem. Soc.* **1980**, *102*, 838. (f) Landis, C. R.; Halpern, J. *J. Am. Chem. Soc.* **1987**, *109*, 1746.

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(29) (a) Gridnev, I. D.; Higashi, N.; Asakura, K.; Imamoto, T. *J. Am. Chem. Soc.* **2000**, *122*, 7183. (b) Gridnev, I. D.; Yamanoi, Y.; Higashi, N.; Tsuruta, H.; Yasutake, M.; Imamoto, T. *Adv. Synth. Catal.* **2001**, *343*, 118. (c) Gridnev, I. D.; Yasutake, M.; Higashi, N.; Tsuruta, H.; Imamoto, T. *J. Am. Chem. Soc.* **2001**, *123*, 5268.

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(31) The difference of activities of catalysts shown in Figures 4 and 5 might be attributed to the difference in morphology in the catalysts used from different batches.

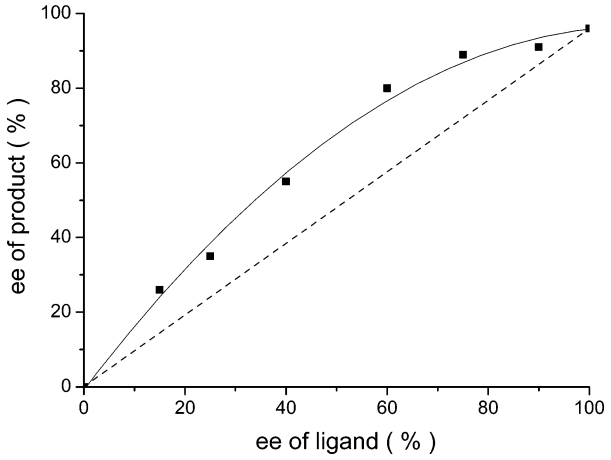



**FIGURE 7.** NLE in Rh/SIPHOS-catalyzed hydrogenation ($T$ = 25 °C, $P_{H_2}$ = 1 atm, [sub] = 0.1 M, [Rh] = 1.0 mM, Rh/**5a** = 1:2.1).

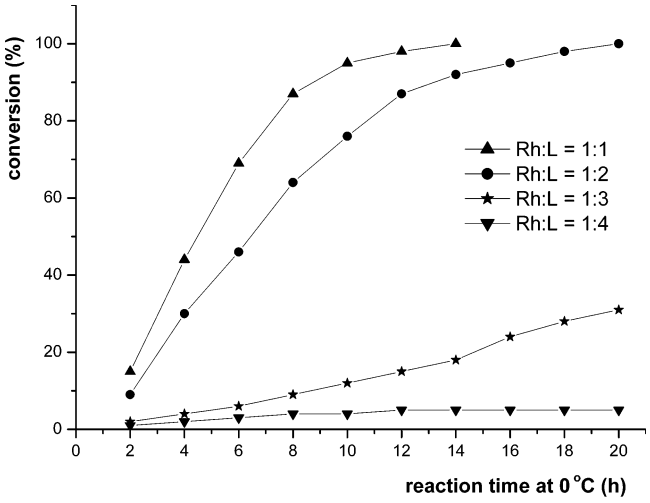



**FIGURE 8.** Dependency of conversion vs time at 0 °C.

of hydrogen to the Rh complex is the rate-determining step, which is similar to that of using diphosphine ligands.

The true structure of the Rh catalyst in the asymmetric hydrogenation with monophosphorus ligand was unknown before we were able to grow a single crystal of the Rh/(*S*)-**5a** complex. The single crystal was obtained by mixing $Rh(COD)_2BF_4$ and 2 equiv of (*S*)-**5a** (Rh/L = 1:2) in a mixed solvent of $CH_2Cl_2$ and $Et_2O$, and its structure was determined by X-ray diffraction to be a $C_2$-symmetric $[Rh(COD)((S)\text{-}\mathbf{5a})_2]^+$.[32] It is surprising that the structure of a single crystal obtained by mixing equal molar $Rh(COD)_2BF_4$ and (*S*)-**5a** (Rh/L = 1:1) was also $[Rh(COD)((S)\text{-}\mathbf{5a})_2]^+$. In the crystal of the catalyst, two (*S*)-**5a** ligands coordinate to Rh through the P-atom and two C=C double bonds of COD occupy the other two coordination sites of Rh. The P−Rh bond lengths (2.286 Å) are close to those reported in Rh-biphosphine complexes. However, the P−Rh−P angle (95.6°) is distinctly larger than those in the Rh complexes of bidentate phosphines.[27c,d]

Although the crystal structure shows that there are two ligands in the solid state of the catalyst, we still do not know the real composition of the active catalyst in the reaction. Nonlinear effect (NLE) of the ee of the product on the ee of ligand provides useful information to determine whether two or more ligands are contained in the active catalyst.[33] In Rh/**5a**-catalyzed hydrogenation of methyl (*Z*)-2-(acetamido)cinnamate, we found a positive NLE (Figure 7), which implies that there are more than one ligand bonded to the Rh in the active catalyst.[34]

Reetz[12a] reported that 1:1 and 1:2 Rh/ligand ratios have no significant difference on the conversion and enantioselectivity in the asymmetric hydrogenation of itaconic ester using chiral monophosphite ligands. Minnaard, Feringa, and de Vries[13c] found that reaction rate increased when the Rh/L ratio was lowered from 1:2 to 1:1 and the ee of product remained the same in the asymmetric hydrogenation of methyl (*Z*)-2-(acetamido)cinnamate using MonoPhos ligands. We compared the rates of reactions with different Rh/L ratios in the Rh/(*S*)-**5a**-catalyzed asymmetric hydrogenation of methyl (*Z*)-2-(acetamido)cinnamate at 0 °C (Figure 8). The reaction with 1:1 Rh/L ratio was found to be faster than the reaction with 1:2 Rh/L ratio, the reaction with 1:3 Rh/L ratio was much slower, and the catalyst with 1:4 Rh/L ratio has almost no activity. This seems to suggest that only one monophosphorus ligand is bonded to rhodium in the active catalyst.

**SCHEME 3**

$$RhL_SL_R \overset{K_1}{\rightleftharpoons} RhL_S + L_R$$

$$Rh(L_S)_2 \overset{K_2}{\rightleftharpoons} RhL_S + L_S$$

On the basis of the results we so far gained from the experiments, it is reasonable to presume that the Rh-catalyst in hydrogenation using SIPHOS ligand contains two ligands and losses one to generate the active catalyst during hydrogenation. The positive NLE of reaction could be attributed to the fact that the heterochiral complex $RhL_SL_R$ is more stable than homochiral complex $Rh(L_S)_2$ or $Rh(L_R)_2$ in the dissociation step, namely, $K_2 > K_1$ in Scheme 3.[33b] Having these analyses, we propose a mechanism for the Rh-catalyzed asymmetric hydrogenation of α-(acylamino)acrylate derivatives using chiral monophosphorus ligands with activation of $H_2$ being the rate-determination step, which is similar to Halpern's mechanism with diphosphine ligand (Scheme 4).[27] However, it is obvious that this mechanism did not give a clear picture about the real catalytic cycle. A complete understanding of the mechanism in this type of asymmetric hydrogenation using monodentate phosphorus ligands needs more detailed information.

## Conclusion

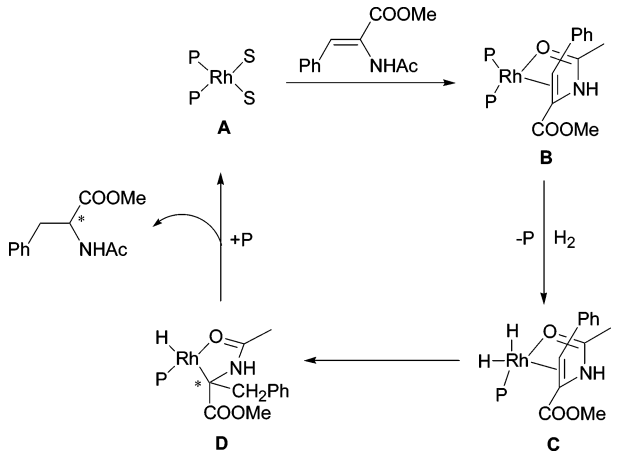
The SIPHOS were demonstrated to be excellent ligands in the Rh-catalyzed hydrogenation of functionalized olefins, such as α-dehydroamino acid derivatives, β-de-

(32) For the structure of the crystal, see ref 18. For the crystal data, structure refinement, and selected bond lengths and angles, see Supporting Information.

(33) (a) Puchot, C.; Samuel, O.; Dunach, E.; Zhao, S.; Agami, C.; Kagan, H. B. *J. Am. Chem. Soc.* **1986**, *108*, 2353. (b) Girard, C.; Kagan, H. B. *Angew. Chem., Int. Ed.* **1998**, *37*, 2922. (c) Kagan, H. B. *Synlett* **2001**, 888.

(34) A positive NLE was reported in the asymmetric hydrogenation using MonoPhos ligand; see ref 13c.

**SCHEME 4. Proposed Mechanism of Rh-Catalyzed Asymmetric Hydrogenation Using Monophosphorus Ligand**




hydroamino acid derivatives, and α-arylenamides. Higher enantioselectivity was achieved as the alkyl groups on the N-atom of the SIPHOS ligand became smaller. The X-ray analysis of the crystal structure of the Rh-SIPHOS catalyst showed that there were two monophosphorus ligands in the catalyst, which was also probed by a positive nonlinear effect in the asymmetric hydrogenation of (*Z*)-2-(acetamido)cinnamate. The rate of hydrogenation with 1:1 Rh/L ratio is faster than that with 1:2 Rh/L ratio, which implied that only one monophosphorus ligand is bonded to Rh in the active catalyst. A possible explanation of the experimental results is that the catalyst preferably contains two ligands but loses one to generate the active catalyst during hydrogenation. Kinetic studies showed that the reaction rate is zero order to the concentration of substrate and first order to the concentration of the Rh catalyst and hydrogen pressure, suggesting that the mechanism of Rh-catalyzed hydrogenation using monodentate phosphorus ligand is similar to the use of diphosphine ligands. Further investigations on the application scope of the SIPHOS ligands and the reaction mechanism are in progress.

## Experimental Section

The ligands were synthesized according to the literature: **5a**,[20a] **5b**,[20a] **5c**,[20b] **5d**.[20a] For general procedures for asymmetric hydrogenations, see Supporting Information.

**Determination of Conversion and Enantioselectivity. α-Amino Esters. Methyl 2-acetamido-3-phenylpropionate:** GC (Varian Chirasil-L-Val column 25 m × 0.25 mm × 0.25 μm; $N_2$ 1.8 mL/min; 90 °C then 4 °C/min to 160 °C) $t_R$ = 17.54 min, $t_S$ = 18.40 min, $t_{sub}$ = 23.40 min. Or HPLC (Chiralcel OJ, $^i$PrOH/Hex (10/90), 1.0 mL/min) $t_R$ = 12.76 min, $t_S$ = 19.45 min. **Methyl 2-acetamido-3-(2-chlorophenyl)-propionate:** HPLC (Chiralcel OJ column, 25 cm, $^i$PrOH/Hex (10/90), 1.0 mL/min) $t_R$ = 11.17 min, $t_S$ = 13.89 min. **Methyl 2-acetamido-3-(4-chlorophenyl)propionate:** HPLC (Chiralcel OJ column, $^i$PrOH/Hex (10/90), 1.0 mL/min) $t_R$ = 12.86 min, $t_S$ = 17.21 min. **Methyl 2-acetamido-3-(4-methylphenyl)-propionate:** HPLC (Chiralcel OJ column, $^i$PrOH/Hex (10/90), 1.0 mL/min) $t_R$ = 9.33 min, $t_S$ = 15.34 min. **Methyl 2-acetamido-3-(4-methoxyphenyl)propionate:** HPLC (Chiralcel OJ column, $^i$PrOH/Hex (10/90), 1.0 mL/min) $t_R$ = 6.42 min, $t_S$ = 11.43 min. **Methyl 2-acetamido-3-(3-nitrophenyl)propionate:** HPLC (Chiralcel OD column, 25 cm, $^i$PrOH/Hex (15/85), 1.0 mL/min) $t_R$ = 13.76 min, $t_S$ = 17.20 min. **Methyl 2-acetamido-3-(4-nitrophenyl)propionate:** HPLC (Chiralcel OD column, $^i$PrOH/Hex (15/85), 1.0 mL/min) $t_R$ = 17.13 min, $t_S$ = 19.74 min. **Methyl 2-acetamido-butyrate:** GC (Supelco γ-dex 225 column 30 m × 0.25 mm × 0.25 μm; $N_2$ 1.4 mL/min; 100 °C then 2 °C/min to 160 °C) $t_R$ = 20.88 min, $t_S$ = 21.27 min. **Methyl 2-acetamidopropionate:** GC (Supelco γ-dex 225 column; $N_2$ 1.0 mL/min; 100 °C then 2 °C/min to 160 °C) $t_R$ = 19.60 min, $t_S$ = 20.33 min.

**Arylamines. *N*-Acetyl-1-phenylethylamine:** GC (Varian Chirasil-L-Val column; $N_2$ 1.0 mL/min; 130 °C) $t_R$ = 10.36 min, $t_S$ = 10.93 min. ***N*-Acetyl-1-(3-methylphenyl)ethylamine:** GC (Varian Chirasil-L-Val column; $N_2$ 1.0 mL/min; 140 °C) $t_R$ = 15.37 min, $t_S$ = 16.73 min. ***N*-Acetyl-1-(4-methylphenyl)-ethylamine:** GC (Varian Chirasil-L-Val column; $N_2$ 1.0 mL/min; 130 °C) $t_R$ = 15.81 min, $t_S$ = 16.78 min. ***N*-Acetyl-1-(4-trifluoromethylphenyl)ethylamine:** GC (Varian Chirasil-L-Val column; $N_2$ 1.0 mL/min; 140 °C) $t_R$ = 9.35 min, $t_S$ = 9.94 min. ***N*-Acetyl-1-(2-fluorophenyl)ethylamine:** GC (Varian Chirasil-L-Val column; $N_2$ 1.0 mL/min; 130 °C) $t_R$ = 8.34 min, $t_S$ = 8.67 min. ***N*-Acetyl-1-(4-fluorophenyl)ethylamine:** GC (Varian Chirasil-L-Val column; $N_2$ 1.0 mL/min; 140 °C) $t_R$ = 8.00 min, $t_S$ = 8.37 min. ***N*-Acetyl-1-(4-chlorophenyl)-ethylamine:** GC (Varian Chirasil-L-Val column; $N_2$ 1.0 mL/min; 150 °C) $t_R$ = 11.27 min, $t_S$ = 11.87 min. ***N*-Acetyl-1-(4-bromophenyl)ethylamine:** GC (Varian Chirasil-L-Val column; $N_2$ 1.0 mL/min; 150 °C) $t_R$ = 17.19 min, $t_S$ = 18.22 min. **1-Acetylaminoindane:** GC (Supelco γ-dex-225 column; $N_2$ 1.8 mL/min, 150 °C then 2 °C/min to 180 °C, constant 5 min) $t_R$ = 15.8 min, $t_S$ = 16.1 min. **1-Acetylamino-7-methoxyindane:** GC (Supelco γ-dex-225 column; $N_2$ 1.8 mL/min, 150 °C then 2 °C/min to 180 °C, constant 20 min) $t_R$ = 30.46 min, $t_S$ = 31.56 min. **1-Acetylamino-6-bromoindane:** GC (Varian Chirasil-L-Val column; $N_2$ 1.8 mL/min, 100 °C then 1 °C/min to 160 °C) $t_R$ = 58.01 min, $t_S$ = 58.88 min.

***β*-Amino Esters. Methyl 3-acetylamino-3-phenylpropionate:** GC (Varian Chirasil-L-Val column; $N_2$ 1.8 mL/min, 120 °C then 1 °C/min to 150 °C) $t_R$ = 27.57 min, $t_S$ = 28.24 min. **Methyl 3-acetamido-3-(2-bromophenyl)-propionate**: GC (Varian Chirasil-L-Val column; $N_2$ 1.8 mL/min, 120 °C then 1 °C/min to 150 °C) $t_R$ = 27.26 min, $t_S$ = 27.96 min. **Methyl 3-acetamido-3-(3-bromophenyl)-propionate**: GC (Varian Chirasil-L-Val column; $N_2$ 2.0 mL/min, 120 °C then 1 °C/min to 160 °C) $t_R$ = 26.28 min, $t_S$ = 26.93 min. **Methyl 3-acetamido-3-(4-bromophenyl)-propionate:** GC (Varian Chirasil-L-Val column; $N_2$ 2.0 mL/min, 120 °C then 1 °C/min to 160 °C) $t_R$ = 32.08 min, $t_S$ = 32.67 min. **Methyl 3-acetamido-3-(4-chlorophenyl)-propionate:** GC (Varian Chirasil-L-Val column; $N_2$ 1.8 mL/min, 120 °C then 1 °C/min to 170 °C) $t_R$ = 44.35 min, $t_S$ = 45.28 min. **Methyl 3-acetamido-3-(4-methylphenyl)-propionate:** GC (Varian Chirasil-L-Val column; $N_2$ 2.0 mL/min, 120 °C then 1 °C/min to 160 °C) $t_R$ = 33.07 min, $t_S$ = 33.97 min. **Methyl 3-acetamido-3-(4-methoxylphenyl)-propionate:** GC (Varian Chirasil-L-Val column; $N_2$ 1.8 mL/min, 100 °C then 1 °C/min to 170 °C) $t_R$ = 67.03 min, $t_S$ = 67.82 min. **Methyl 3-acetamido-butyrate:** GC (Supelco *β*-dex 120 column; $N_2$ 1.0 mL/min, 70 °C then 1 °C/min to 140 °C) $t_S$ = 63.10 min, $t_R$ = 64.54 min. **Ethyl 3-acetamido-butyrate**: GC (Supelco *β*-dex 120 column; $N_2$ 1.0 mL/min, 70 °C then 1 °C/min to 140 °C) $t_S$ = 63.13 min, $t_R$ = 64.73 min.

**Mechanistic Study. Kinetic Study on the Substrate Concentration Dependency.** To a Schlenk tube equipped with a septum and a stirring bar were added 2.0 mg (5 μmol) of $Rh(COD)_2BF_4$ and 3.4 mg (10.5 μmol) of **5a**. Another Schlenk tube was added with 110 mg (0.5 mmol) of methyl (*Z*)-2-acetamidocinnamate. After three vacuum/hydrogen cycles, 5.0 mL of $CH_2Cl_2$ was added by a syringe to the catalyst Schlenk tube and stirred for 0.5 h at 0 °C. The resulting catalyst solution was transferred into the substrate Schlenk tube. The reaction was left stirring under ambient hydrogen pressure at 0 °C. A sample of reaction mixture (0.2 mL) was taken at regular time intervals, filtered through a short silica column, and then submitted to analysis for conversion and ee values.

**Kinetic Study on the Catalyst Concentration Dependency.** To a Schlenk tube equipped with a septum and a stirring bar were added 12.0 mg (30 $\mu$mol) of $Rh(COD)_2BF_4$ and 21.0 mg (61 $\mu$mol) of **5a**. Another Schlenk tube was charged with 660 mg (3 mmol) of methyl (*Z*)-2-acetamidocinnamate. After three vacuum/hydrogen cycles, 12 mL of $CH_2Cl_2$ was charged by a syringe to the catalyst tube. The two Schlenk tubes were stirred for 0.5 h at 0 °C under ambient hydrogen pressure. The reactions with different catalyst concentration were performed by mixing the proper amount of the above catalyst solution, substrate solution, and $CH_2Cl_2$ (saturated with $H_2$) and allowing the mixture to stir at 0 °C under ambient hydrogen pressure. A sample of reaction mixture (0.2 mL) was taken at regular time intervals, filtered through a short silica column, and then submitted to analysis for conversion and ee values. **0.5 mM [Rh]:** 2.0 mL of $CH_2Cl_2$, 2.0 mL of substrate solution and 1.0 mL of catalyst solution. **0.8 mM [Rh]:** 1.4 mL of $CH_2Cl_2$, 2.0 mL of substrate solution and 1.6 mL of catalyst solution. **1.0 mM [Rh]:** 1.0 mL of $CH_2Cl_2$, 2.0 mL of substrate solution and 2.0 mL of catalyst solution. **1.2 mM [Rh]:** 0.6 mL of $CH_2Cl_2$, 2.0 mL of substrate solution and 2.4 mL of catalyst solution. **1.5 mM [Rh]:** 2.0 mL of substrate solution and 3.0 mL of catalyst solution.

**Kinetic Study on the Hydrogen Pressure Dependency.** Under 0.25 atm $H_2$ ($P_{H_2}$ = 0.25 atm, $P_{N_2}$ = 0.75 atm), to a Schlenk tube equipped with a septum and a stirring bar were added 2.0 mg (5 $\mu$mol) of $Rh(COD)_2BF_4$, 3.4 mg (10.5 $\mu$mol) of **5a**, and 2 mL of $CH_2Cl_2$. Another Schlenk tube was charged with 110 mg (0.5 mmol) of methyl (*Z*)-2-acetamidocinnamate and 3 mL of $CH_2Cl_2$. The two Schlenk tubes were stirred for 0.5 h at 0 °C under 0.25 atm $H_2$ pressure. Then the substrate solution was transferred to the catalyst solution, and the reaction was left stirring at 0 °C. A sample of reaction mixture (0.2 mL) was taken at regular time intervals, filtered through a short silica column, and then submitted to analysis for conversion and ee values. Other reactions under different hydrogen pressure were performed similarly by using different hydrogen pressure. **0.50 atm $H_2$:** ($P_{H_2}$ = 0.5 atm, $P_{N_2}$ = 0.5 atm). **0.75 atm $H_2$**: ($P_{H_2}$ = 0.75 atm, $P_{N_2}$ = 0.25 atm). **1.00 atm $H_2$**: ($P_{H_2}$ = 1.00 atm, $P_{N_2}$ = 0 atm).

**Kinetic Study on the Temperature Dependency.** To a Schlenk tube equipped with a septum and a stirring bar were added 2.0 mg (5 $\mu$mol) of $Rh(COD)_2BF_4$ and 3.4 mg (10.5 $\mu$mol) of **5a**. After three vacuum/hydrogen cycles, 5.0 mL of $CH_2Cl_2$ was added by a syringe to the catalyst Schlenk tube and stirred under ambient hydrogen for 0.5 h at request temperature. Another Schlenk tube was charged with 110 mg (0.5 mmol) of methyl (*Z*)-2-acetamidocinnamate and filled with ambient hydrogen at corresponding temperature. The catalyst solution was transferred into the substrate Schlenk tube and left stirring under ambient hydrogen pressure at the same temperature. A sample of reaction mixture (0.2 mL) was taken at regular time intervals, filtered through a short silica column, and then submitted to analysis for conversion and ee values.

**Preparation and Crystal Structure of [Rh(COD)((*S*)-SIPHOS-Me)$_2$] Catalyst.** To a Schlenk tube were added 10 mg (25 $\mu$mol) of $Rh(COD)_2BF_4$, 16.5 mg (51 $\mu$mol) of ligand, and 1.0 mL of $CH_2Cl_2$ to form a solution; 2.0 mL of $Et_2O$ was then added slowly while keeping the two-phase interface clear. The single crystal was collected after the mixture stood overnight and was subjected to X-ray analysis. The X-ray structure was described in a previous communication,[18] and the crystal data in CIF format are in the Supporting Information.

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**Supporting Information Available:** General remarks and general procedures for asymmetric hydrogenations; crystal data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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