DOI: 10.1002/ejoc.200600024

Enantioselective Rhodium-Catalyzed Hydrogenation of Enamides in the Presence of Chiral Monodentate Phosphanes

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Keywords: Asymmetric catalysis / Homogeneous catalysis / Hydrogenation / Monodentate phosphane ligands / Enamides

The rhodium-catalyzed asymmetric hydrogenation of different acyclic and cyclic *N*-acyl enamides to give *N*-acyl-protected optically active amines has been examined for the first time in detail in the presence of chiral monodentate 4,5-dihydro-3*H*-dinaphthophosphepines **5a**–**i**. The enantioselectivity is largely dependent on the nature of the substituent at the phosphorus atom and the enamide substrate. Applying optimized conditions up to 95% *ee* and catalyst activity up to 2000 h^{-1} (TOF) have been achieved.

Introduction

The importance of chiral amines is demonstrated by their broad scope of applications as building blocks and synthons for pharmaceuticals and agrochemicals. In addition, they are of significant use for the synthesis of natural compounds, chiral auxiliaries, and optically active ligands.[1] Hence, the development of new and improved methods for the preparation of enantiomerically pure amines is an important target of industrial and academic research. Several synthetic approaches to optically active amines have been established in the past. Still one of the most practical approaches is the separation of enantiomers through resolution, e.g. in the presence of chiral acids. The main drawback of this concept is the poor atom efficiency and the negative environmental impact. A more attractive access is represented by applying enantiomerically pure starting materials from the "chiral pool". Another powerful strategy is the application of stereoselective syntheses in particular reactions catalyzed by transition-metal complexes.[2] Examples of such transition-metal-catalyzed reactions, which offer a versatile and elegant approach to enantiomerically pure amines, are the alkylation or arylation of imines, hydrocyanation of carbon–carbon double bonds and aziridination.[2c] However, the most popular catalytic reaction with respect to industrial applications is the asymmetric hydrogenation of imines or *N*-protected enamines and enamides.[3]

Pioneering work in the field of enantioselective hydrogenation of enamides has been reported by Kagan and co-workers. Applying diphosphane rhodium catalysts enantioselectivity up to 90% has been obtained.[4] Over a period of nearly 30 years the development of new ligands for asymmetric hydrogenation has focused on the synthesis of bidentate ligands. During this time several effective bidentate phosphanes such as Me-DuPhos, Me-BPE, DIOP, BINAP and others were developed for the hydrogenation of enamides.[4,5] At the end of the 20th century the predominant role of bidentate ligands changed and monodentate ligands received more attention.[6,7] The advantages of monodentate phosphorus ligands are their easier synthesis and tunability compared to bidentate phosphanes. Scheme 1 illustrates some examples of monodentate phosphorus ligands for asymmetric hydrogenation on the basis of the chiral 1,1′-binaphthol skeleton. Important contributions in this area came independently from Feringa and de Vries et al.[8] (phosphoramidites **1**), Reetz et al.[9] (phosphites **2**), and Pringle and Claver et al.[10] (phosphonites **3**). Furthermore, excellent enantioselectivity was shown by Zhou and co-workers applying monodentate spiro phosphoramidites (SIPHOS).[11]

Following the original work of Gladiali[12] and parallel to Zhang,[13] we have established the synthesis of various monodentate phosphanes based on a 4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1′,2′-*e*]phosphepine framework (**4** and **5a**–**i**), which resembles the 1,1′-binaphthol core.[14] Recently, we have shown that asymmetric hydrogenation of amino acid precursors, dimethyl itaconate and β-keto esters proceeds with enantioselectivities up to 95% *ee* in the presence of ligand **5a**.[13] Moreover, other groups demonstrated the usefulness of these ligands in several catalytic asymmetric reactions.[15]

To the best of our knowledge there exists only one publication dealing with the hydrogenation of enamides in the

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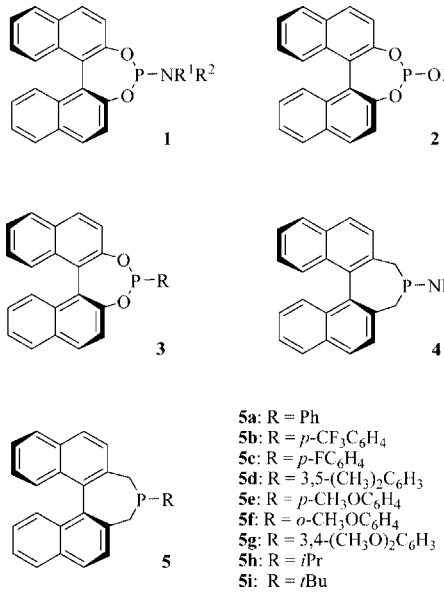


Scheme 1. Chiral monodentate ligands with 2,2′-binaphthyl framework.

presence of monodentate phosphepines. Here, Reetz et al.[16] described the rhodium-catalyzed hydrogenation of *N*-(1-phenylvinyl)acetamide (**6a**) with ligands **5a** [conversion: 50%; enantiomeric excess: 14% (*R*)] and **5i** [conversion: 94%; enantiomeric excess: 24% (*R*)] in dichloromethane. To our surprise the *tert*-butyl-substituted ligand **5i** showed better selectivity and yield than the phenyl-substituted ligand **5a**. In our benchmark tests, for instance, in the asymmetric hydrogenation of amino acid precursors, dimethyl itaconate and β-keto esters, we always observed the opposite behaviour.

Discussion

The interesting results of Reetz and co-workers[15] stimulated us to study the potential of our ligand library **5a**–**i** in the field of asymmetric hydrogenation of enamides in more detail. In general, the ligands are prepared by metallation of 2,2′-dimethylbinaphthyl with two equiv. of *n*-butyllithium, followed by quenching with diethylamino(dichloro)phosphane. Deprotection with gaseous HCl produced 4-chloro-4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1′,2′-*e*]phosphepine in a yield of 80%. This enantiomerically pure chlorophosphane is easily coupled with various Grignard reagents to give a broad selection of ligands of type **5**.

Unsubstituted and substituted *N*-(1-phenylvinyl)acetamides **6a**–**6e** were obtained by reacting the corresponding benzonitrile with a methyl Grignard followed by addition of acetic anhydride.[8e] The cyclic *N*-acyl enamide **6f** was synthesized by a standard protocol implying transformation of the ketone to the corresponding oxime and subsequent reductive acylation with iron in the presence of acetic acid anhydride.[17]

Initial studies on the influence of reaction conditions were carried out with *N*-(1-phenylvinyl)acetamide (**6a**) as substrate and 4-phenyl-4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1′,2′-*e*]phosphepine (**5a**) as our standard ligand. Typically, we used an in situ pre-catalytic mixture of 1 mol-% $[Rh(cod)_2]BF_4$ and 2.1 mol-% of the corresponding ligand. All hydrogenation reactions were carried out in an 8fold parallel reactor array with 3.0 mL reactor volume.[18]

At first, we focused our attention on the influence of different solvents, such as dichloromethane, methanol, ethyl acetate, toluene, and also variation of the initial pressure (1.0 bar, 5.0 bar and 10 bar). Selected results are presented in Figure 1.

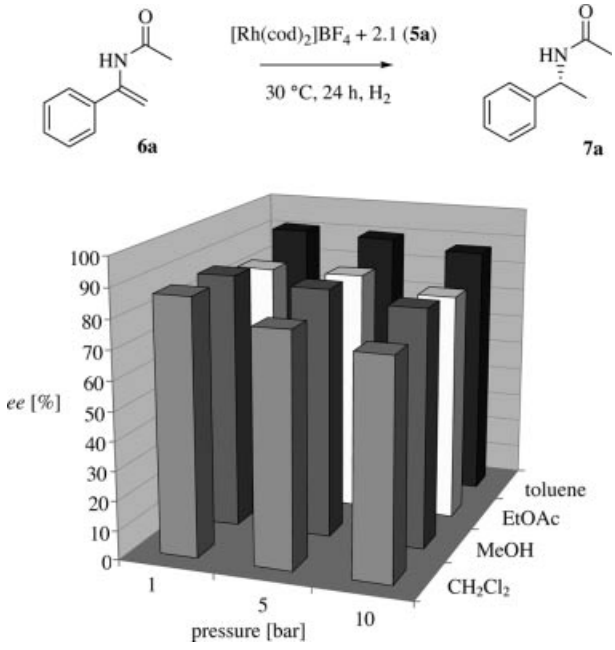


Figure 1. Solvent and pressure variation. Reactions were carried out at 30 °C for 24 h with 0.0024 mmol $[Rh(cod)_2]BF_4$, 0.005 mmol ligand **5a** and 0.24 mmol substrate in 2.0 mL solvent. Conversion and *ee* values were determined by GC [50 m Lipodex E (Macherey–Nagel), 80 °C, (*R*)-**7a** 26.7 min, (*S*)-**7a** 28.3 min]. The absolute configuration was determined by comparing the sign of specific rotation with reported data and the original sample (Aldrich).[5i]

For all solvents best enantioselectivity (80–90% *ee*) is achieved at 1.0 bar, but without complete conversion within reasonable time (24 h). Increasing the pressure of hydrogen to 5.0 bar or 10.0 bar accelerated the reaction and full conversion is reached, but at somewhat lower selectivity. The results also indicated toluene as the solvent of choice for our model reaction (conversion: 96%; enantioselectivity: 91%).

To find the optimum of the enantioselectivity−pressure dependency we performed a fine tuning of the hydrogen pressure in toluene. At 2.5 bar hydrogen pressure both good enantioselectivity (93% *ee*) and acceptable reaction time (6 h) have been achieved.

Next, we investigated the influence of the temperature on the selectivity and yield as described in Figure 2. Applying our model ligand **5a** there is no pronounced effect on the selectivity between 10 and 30 °C.[19] At higher temperatures a decrease of the *ee* is observed (87% *ee* at 50 °C and 83% *ee* at 70 °C).

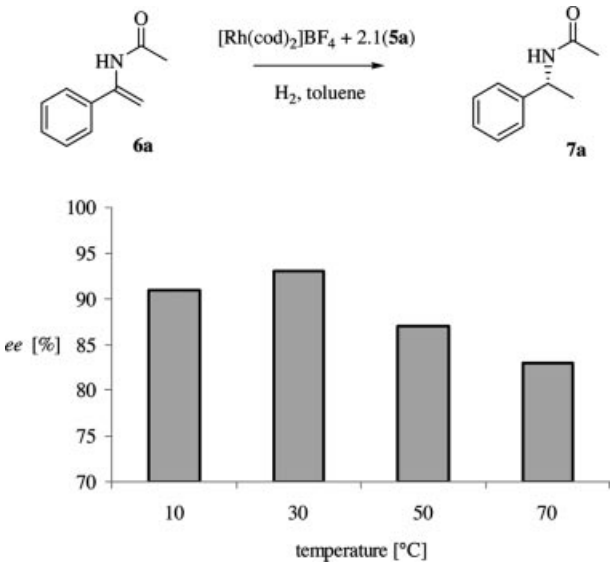
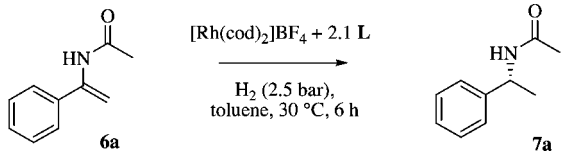


Figure 2. Dependency of enantioselectivity vs. temperature. Reactions were carried out at the corresponding temperature for 1–24 h with 0.0024 mmol $[Rh(cod)_2]BF_4$, 0.005 mmol ligand **5a** and 0.24 mmol substrate in 2.0 mL toluene. Conversion and *ee* values were determined by GC [50 m Lipodex E (Macherey–Nagel), 80 °C, (*R*)-**7a** 26.7 min, (*S*)-**7a** 28.3 min].[5i]

Table 1. Hydrogenation of *N*-(1-phenylvinyl)acetamide (**6a**).[a]



Entry	Ligand	Conversion [%][b]	*ee* [%][b,c]
1	**5a**	>99	**93** (*R*)
2	**5b**	>99	72 (*R*)
3	**5c**	>99	88 (*R*)
4	**5d**	>99	87 (*R*)
5	**5e**	>99	**93** (*R*)
6	**5f**	>99	63 (*R*)
7	**5g**	>99	90 (*R*)
8	**5h**	>99	30 (*R*)
9	**5i**	>99	16 (*S*)
10	**1**	4	19 (*S*)

[a] All reactions were carried out at 30 °C under 2.5 bar pressure of hydrogen for 6 h with 0.0024 mmol $[Rh(cod)_2]BF_4$, 0.005 mmol ligand and 0.24 mmol substrate in toluene (2.0 mL). [b] Conversion and *ee* values were determined by GC [50 m Lipodex E (Macherey–Nagel), 80 °C, (*R*)-**7a** 26.7 min, (*S*)-**7a** 28.3 min]. [c] The absolute configuration was determined by comparing the sign of specific rotation with reported data and the original sample (Aldrich).[5i]

To estimate the activity of the catalyst in more detail the ratio between metal and substrate was varied starting from initially 1:100 to 1:2000. At 50 °C and 2.5 bar of hydrogen complete conversion was observed within one hour, which corresponds to a turnover frequency (TOF) of 2000 h^{-1}.

In order to evaluate the substituent effect at the phosphorus atom of the ligand, we studied the asymmetric hydrogenation of *N*-(1-phenylvinyl)acetamide (**6a**) in the presence of nine different 4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1′,2′-*e*]phosphepines (**5a**–**5i**) using the optimized reaction conditions (2.5 bar hydrogen pressure, toluene, 30 °C, 6 h). These results are presented in Table 1.

In agreement with our previous studies, it appeared that for obtaining good enantioselectivity aryl-substituted phosphepine ligands are necessary, while alkyl-substituted ligands showed significantly lower selectivity. Substitution on the phenyl ring at the phosphorus atom with electron-withdrawing (**5b**, **5c**) as well as electron-donating groups (**5d**–**5g**) resulted in decreased selectivity in comparison to the phenyl ligand **5a**. Here, only ligand **5e** represented an exception (Table 1, Entry 5), which led to 93% *ee*.

Interestingly, the behaviour of the *tert*-butyl ligand **5i** is quite different in the hydrogenation of **6a**. In contrast to the results obtained by Reetz et al., under our reaction conditions compound **5i** induced a change in the absolute configuration of the product to the opposite (*S*)-enantiomer, albeit with significantly lower *ee*.

In addition to the ligands **5**, we also tested the commercially available (*S*)-MonoPhos ligand (**1**, $R^1 = R^2 = Me$), which gives excellent enantioselectivity in various hydrogenations of prochiral double bonds.[8,20] However, in the present test reaction we obtained only poor yield and enantioselectivity (Table 1, Entry 10).

To demonstrate the scope and limitations of our ligand toolbox we performed the asymmetric hydrogenation of four different *N*-(1-phenylvinyl)acetamides (Table 2). Regarding the substrates both electron-donating substituents at the phenyl group, in particularly a methoxy group in *para*- as well as in *meta*-position and electron-withdrawing substituents such as *para*-fluoro or *para*-trifluoromethyl have been tested. Enantioselectivity up to 95% *ee* is obtained with ligands **5a** (Table 2, Entry 1) and **5e** (Table 2, Entry 5) for electron-rich substrates. In general, aryl phosphepines with electron-donating substituents showed better selectivity than phosphepines having electron-withdrawing groups.

The introduction of electron-withdrawing substituents in *N*-(1-phenylvinyl)acetamide **6d** and **6e** decreased the enantioselectivity compared to the non-substituted *N*-(1-phenylvinyl)acetamide (**6a**). Here, the best selectivities of 83–86% *ee* are obtained with ligands **5a**, **5e** and **5g**.

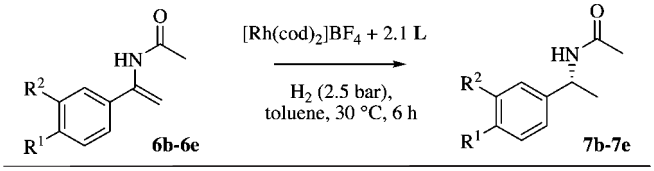
Again for all substrates **6a**–**6e** the alkyl-substituted 4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1′,2′-*e*]phosphepines gave significantly lower selectivity.

Next, the hydrogenation of the sterically more hindered *N*-(3,4-dihydro-1-naphthyl)acetamide (**6f**) was tested (Scheme 2). The use of different pre-catalysts including $[Rh(\mathbf{5a})_2(cod)]BF_4$, $[Rh(\mathbf{5e})_2(cod)]BF_4$ and $[Rh(\mathbf{5i})_2(cod)]BF_4$ gave an excellent yield (>99%) of **7f**.

However, the observed enantioselectivity is significantly lower [**5a**: 15% (*S*); **5e**: 11% (*S*); **5i**: 35% (*R*)] when compared to 1,1-disubstituted enamides. These results indicate a crucial influence of the substitution pattern on the enamide group.

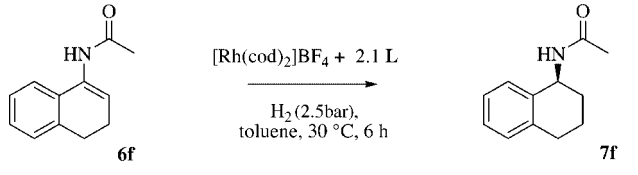
It is important to note that in comparison to bidentate ligands the application of monodentate ligands offers an

Table 2. Asymmetric hydrogenation of substituted *N*-(1-phenylvinyl)acetamides **6b**–**6e**.[a]



Entry	Ligand	**7b** (R^1 = CH_3O; R^2 = H) *ee* [%][b,c]	**7c** (R^1 = H; R^2 = CH_3O) *ee* [%][b,d]
1	**5a**	**91** (*R*)	**95** (*R*)
2	**5b**	63 (*R*)	72 (*R*)
3	**5c**	79 (*R*)	84 (*R*)
4	**5d**	87 (*R*)	87 (*R*)
5	**5e**	**92** (*R*)	89 (*R*)
6	**5f**	33 (*R*)	53 (*R*)
7	**5g**	89 (*R*)	89 (*R*)
8	**5h**	*rac*	26 (*R*)
9	**5i**	21 (*S*)	23 (*S*)
Entry	Ligand	**7d** (R^1 = F) *ee* [%][b,c]	**7e** (R^1 = CF_3) *ee* [%][b,c]
10	**5a**	86 (*R*)	78 (*R*)
11	**5b**	51 (*R*)	62 (*R*)
12	**5c**	71 (*R*)	73 (*R*)
13	**5d**	71 (*R*)	65 (*R*)
14	**5e**	86 (*R*)	78 (*R*)
15	**5f**	34 (*R*)	68 (*R*)
16	**5g**	83 (*R*)	85 (*R*)
17	**5h**	4 (*R*)	44 (*R*)
18	**5i**	*rac*	25 (*S*)

[a] All reactions were carried out at 30 °C under 2.5 bar pressure of hydrogen for 6 h with 0.0024 mmol $[Rh(cod)_2]BF_4$, 0.005 mmol ligand and 0.24 mmol substrate in 2.0 mL toluene. [b] Conversion (>99%) was determined by GC (Agilent Technologies, 30 m, 50–300 °C), *ee* values were determined by GC [50 m Lipodex E (Macherey–Nagel), 100–180 °C, (*R*)-**7b** 36.1 min, (*S*)-**7b** 36.4 min, (*R*)-**7c** 34.8 min, (*S*)-**7c** 35.0 min, (*R*)-**7d** 31.0 min, (*S*)-**7d** 31.2 min, (*R*)-**7e** 32.4 min, (*S*)-**7e** 32.7 min]. [c] The absolute configurations were determined by comparing the sign of specific rotation with reported data.[5i] [d] Absolute configuration of product was assigned by analogy.

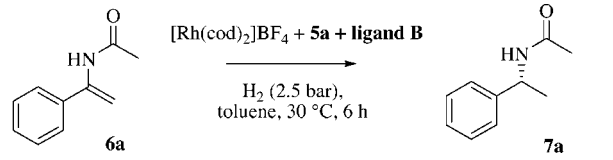


Scheme 2. Asymmetric hydrogenation of *N*-(3,4-dihydro-1-naphthyl)acetamide (**6f**). All reactions were carried out at 30 °C under 2.5 bar pressure of hydrogen for 6 h with 0.0024 mmol $[Rh(cod)_2]BF_4$, 0.005 mmol ligand and 0.24 mmol substrate in 2.0 mL toluene. Conversion was determined by GC (Agilent Technologies, 30 m, 50–300 °C) and *ee* values were determined by HPLC [AD-H Chiralpak (Agilent Technologies), *n*-hexane/ethanol, 95:5, rate 1.0 mL/min, (*S*)-**7f** 6.2 min, (*R*)-**7f** 7.2 min]. The absolute configuration was determined by comparing the sign of specific rotation with reported data.

opportunity to replace one equiv. of the ligand by other chiral or achiral monodentate ligands. This remarkable combinatorial approach was introduced by Reetz et al.,[9d–9f,15,21] and Feringa et al.[22] for different transition-metal-catalyzed reactions.[23]

We followed this concept and used 4-phenyl-4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1′,2′-*e*]phosphepine (**5a**) with different achiral phosphanes in a ratio of 1.05 to 1.05 equiv. in the presence of 1.0 equiv. of $[Rh(cod)_2]BF_4$. The results obtained for the hydrogenation of *N*-(1-phenylvinyl)acetamide (**6a**) under optimized reaction conditions are presented in Table 3.

Table 3. Application of ligand mixtures in the asymmetric hydrogenation of *N*-(1-phenylvinyl)acetamide (**6a**).[a]



Entry	Ligand B	Conversion [%][b]	*ee* [%][b,c]
1	**5a**	>99	93 (*R*)
2	PPh_3	>99	85 (*R*)
3	$P(p\text{-MeO-}C_6H_4)_3$	>99	88 (*R*)
4	$P(p\text{-Me-}C_6H_4)_3$	>99	81 (*R*)
5	PCy_3	>99	74 (*R*)

[a] All reactions were carried out at 30 °C under 2.5 bar pressure of hydrogen for 6 h with 0.0024 mmol $[Rh(cod)_2]BF_4$, 0.0025 mmol ligand **5a**, 0.0025 mmol achiral ligand and 0.24 mmol substrate in 2.0 mL toluene. [b] Conversion and *ee* values determined by GC [50 m Lipodex E (Macherey–Nagel), 80 °C, (*R*)-**7a** 26.7 min, (*S*)-**7a** 28.3 min]. [c] The absolute configuration was determined by comparing the sign of specific rotation with reported data and the original sample (Aldrich).[5i]

In general, we observed a slight decrease in enantioselectivity from that observed when using 2.1 equiv. of ligand **5a**. On the assumption that probably three different metal complexes could be formed, in particular, two homocombination products, the chiral $[Rh(\mathbf{5a})(\mathbf{5a})(cod)]BF_4$ and the achiral $[Rh(L)(L)(cod)]BF_4$, and the hetero-combination product $[Rh(L)(\mathbf{5a})(cod)]BF_4$, we deduce a significantly lower reaction rate or inactivity for the achiral complex $[Rh(L)(L)(cod)]BF_4$ relative to complex $[Rh(\mathbf{5a})(\mathbf{5a})(cod)]BF_4$ or $[Rh(L)(\mathbf{5a})(cod)]BF_4$. Tricyclohexylphosphane (Table 3, Entry 5) was found to be the only exception, as we noticed a more pronounced decrease of the enantiomeric excess.

Conclusions

We demonstrated the application of monodentate 4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1′,2′-*e*]phosphepines **5** in the rhodium-catalyzed asymmetric hydrogenation of various enamides. The influences of different reaction parameters are presented. For the first time high enantioselectivity (up to 95% *ee*) for such reactions is obtained in the presence of

monodentate phosphanes. Best results were observed with aryl-substituted phosphepine ligands for reduction of *N*-(1-phenylvinyl)acetamide, while alkyl-substituted phosphepine ligands yielded only low selectivity.

Experimental Section

All manipulations were performed under argon using standard Schlenk techniques. Diethyl ether and toluene were distilled from sodium benzophenone ketyl under argon. Methanol was distilled from Mg under argon. Dichloromethane was distilled from CaH_2 under argon. The ligands **5** were synthesized according to our previously published protocols.[13] $[Rh(cod)_2]BF_4$ (purchased from Fluka) was used without further purification.

General Procedure for the Synthesis of Substituted *N*-(1-Phenylvinyl)-acetamides 6a–6e: To a stirred solution of methylmagnesium bromide (17.0 mmol, 3.0 mol/L diethyl ether, 6.0 mL) in diethyl ether (50 mL) at 0 °C a solution of the corresponding benzonitrile (17.0 mmol) in diethyl ether (20 mL) was added dropwise during a period of 30 minutes. After complete addition the solution was refluxed for eight hours. Within a few hours a yellow precipitate was formed. After refluxing the reaction mixture was cooled to 0 °C, and a solution of acetic anhydride (17.0 mmol) in diethyl ether (20 mL) was added carefully over 30 minutes. The reaction mixture was refluxed for eight hours. To the resulting suspension methanol was added at room temperature whilst stirring until all precipitates were dissolved (approximately 50 mL). The homogeneous solution was mixed with water/ethyl acetate (1:1, 100 mL). After phase separation the aqueous layer was extracted three times with ethyl acetate (50 mL). The combined organic layers were dried with $MgSO_4$. After removing of the solvents the semi crystalline crude oil was purified by column chromatography (*n*-hexane/ethyl acetate, 1:1). Removal of the solvent yielded the crystalline products. [yields: (**6a**) 1.51 g (55%), (**6b**) 1.66 g (51%), (**6c**) 1.50 g (46%), (**6d**) 1.52 g (50%), (**6e**) 1.91 g (49%)]

General Procedure for the Synthesis of the Cyclic *N*-Acyl Enamide 6f: A stirred solution of the corresponding ketone (30.3 mmol), hydroxylamine–hydrochloride (73 mmol) and pyridine (62.2 mmol) in ethanol (40 mL) was heated to 85 °C for a period of 16 hours. The solvent was removed, and the residue was dissolved in ethyl acetate/water. The organic phase was washed two times with water (20 mL) and dried with $MgSO_4$. After removal of the solvents the product was recrystallized from toluene. The corresponding ketoximine (18.6 mmol) was solved in toluene (30 mL) under argon. To the stirred solution acetic acid anhydride (55.9 mmol), acetic acid (55.9 mmol), and Fe powder (37.3 mmol, Aldrich 325 mesh) were added and then heated to 70 °C for 4 hours. The mixture was filtered through a plug of celite after cooling to room temperature. Dichloromethane was added to the filtrate, followed by washing with 2.0 M NaOH (2×25 mL) at 0 °C. The separated organic phase was concentrated to half volume. The crystalline product was obtained after 12 hours at 0 °C. The crystals were filtered and dried in vacuo. [overall yield: 2.05 g (59%)]

General Procedure for the Catalytic Hydrogenation of Enamides: A solution of enamide (0.24 mmol) and 1.0 mL solvent was transferred via syringe into the secured autoclave. Because of the poor solubility in toluene at room temperature the solution was heated to 50 °C before it was transferred. The catalyst was generated in situ by mixing $[Rh(cod)_2]BF_4$ (0.0024 mmol) and the corresponding 4,5-dihydro-3*H*-dinaphthophosphepine ligands (0.005 mmol) in 1.0 mL solvent for a period of 10 min, and afterwards, it was transferred via syringe into the autoclave. Then, the autoclave was charged with hydrogen and the mixture was stirred at the required temperature. After the predetermined time the hydrogen was released and the reaction mixture passed through a short plug of silica gel. The enantioselectivity and conversion were measured by GC or HPLC without further modifications.

Acknowledgments

We thank M. Heyken, S. Buchholz and Dr. C. Fischer (all Leibniz-Institut für Katalyse e. V. an der Universität Rostock) for excellent technical assistance and Prof. Dr. S. Gladiali for general discussions. Generous financial support from the state of Mecklenburg-Western Pomerania and the BMBF is gratefully acknowledged.

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Received: January 13, 2006
Published Online: April 26, 2006

