# A New and Highly Efficient Asymmetric Route to Cyclic α-Amino Phosphonates: The First Catalytic Enantioselective Hydrophosphonylation of Cyclic Imines Catalyzed by Chiral Heterobimetallic Lanthanoid Complexes

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**Abstract:** The catalytic and enantioselective hydrophosphonylation of cyclic imines is described for the first time. In addition, we have uncovered a new and highly efficient asymmetric approach to cyclic α-amino phosphonates using thiazolines as the imine model component. The desired pharmaceutically interesting phosphonates **5a**−**e** could be synthesized by a heterobimetallic (*R*)-LnPB-catalyzed (Ln = lanthanoid metal, P = potassium, B = (*R*)=binaphthol) hydrophosphonylation of the C=N double bond with up to 98% enantiomeric excess and up to 98% chemical yield. Using other types of organometallic catalysts (titanium-(IV) complexes), the reaction proceeds with modest enantioselectivity. A detailed investigation concerning the dependence of enantioselectivity and chemical yield, respectively, on a series of reaction parameters (e.g., lanthanoid and alkali metal, solvent, reaction temperature, pressure, and catalytic amount) is reported. An optimized catalytic lanthanoid system "(*R*)-YbPB (5 mol %)/50 °C/48 h/THF−toluene (1:7)" was found. The catalytically active complex was isolated and analyzed by spectroscopic methods. In addition, $^{31}$P and $^{1}$H NMR spectroscopic and LDI-TOF mass spectrometric investigations were carried out to support a postulated mechanistic course for this (*R*)-LnPB-complex-catalyzed hydrophosphonylation reaction.

## Introduction

The synthesis of cyclic and acyclic α-amino phosphonic acids is an important topic in modern pharmaceutical chemistry.[1] Such phosphorus analogues of α-amino acids have been shown to be efficient substitutes for amino carboxylic acids in physiological processes and are used as enzyme inhibitors in a wide range of circumstances.[2] In this application, the stereochemistry at the α-carbon atom plays an important role in the biological activity of the molecule. This is underlined by an increasing number of industrial applications in the field of the synthesis of enantiomerically pure α-amino phosphonic acids.[3]

Unfortunately, despite the high level of interest in the asymmetric synthesis of α-amino phosphonic acids,[4] less is known for the cyclic α-amino phosphonates. In recent years, however, descriptions of promising pharmaceutical applications for the cyclic compounds (and acylated derivatives thereof) have been published.[5] These include functioning as an HIV-protease inhibitor[5d,e] or a dipeptidyl peptidase IV inhibitor.[5c,e] Until now, no efficient general asymmetric route has been available to prepare this class of α-amino phosphonates. This is primarily because the most common and general route for the asymmetric synthesis of acyclic α-amino phosphonates, which involves a diastereoselective addition of phosphites to chiral imines,[4,6] with a subsequent separation of the chiral group, cannot be applied

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(3) Recently Hokko Chemical Industry Co., Ltd. (Tokyo, Japan, Fax: ++(81)-3−3279−3857) has applied our asymmetric hydrophosphonylation method using heterobimetallic potassium lanthanoid catalysts to the preparation of several α-amino phosphonic acids at an industrial scale.

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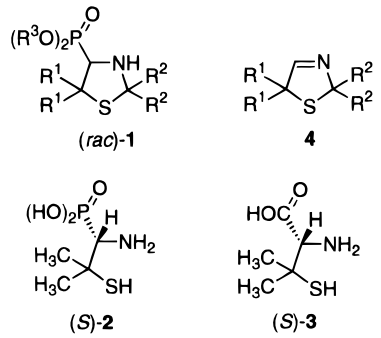
to cyclic imine compounds. Often an insertion of a chiral group in a heterocyclic imine is not possible, or the subsequent separation of the chiral group might result in a ring cleavage. Therefore, until now, an approach to enantiomerically pure cyclic α-amino phosphonic acids has been available primarily by racemic resolution,[7] or a four-step diastereoselective synthesis starting from an acyclic and achiral α-amino phosphonate.[8] However, in recent years, the stereochemical aspects of synthesizing cyclic α-amino phosphonic acids have become increasingly important.[4] Thus, a "stereochemical design" of the hydrophosphonylation process with cyclic imines, which represents a convenient general method for the synthesis of racemic cyclic α-amino phosphonates,[9] has been studied. Several attempts at a diastereoselective synthetic route have been made by the addition of a stoichiometric amount of chiral phosphites (as chirality-inducing hydrophosphonylation agents) to cyclic imines, namely, thiazolines.[10] However, by starting from several types of chiral phosphite components and by using different reaction conditions, the stoichiometric reaction gave only limited diastereoselection ratios of dr = 2:1[10a] or below (dr about 1.5:1[10b]; Scheme 2, pathway b).

An efficient enantioselective synthetic route to cyclic α-amino phosphonates, e.g., the sulfur-containing heterocyclic phosphonates of type **1**, by an addition reaction of dialkyl phosphites to heterocyclic imines, which also avoids the disadvantage of using stoichiometric amounts of chiral auxiliaries, would therefore represent the most convenient synthetic process. Herein, we now report the first enantioselective catalytic approach to cyclic α-amino phosphonates by the hydrophosphonylation of cyclic imines in the presence of heterobimetallic lanthanoid complexes (Scheme 2, pathway a).[11] We chose the thiazolines of type **4** as the model imine substrate in order to better compare the efficiency of our catalytic enantioselective method with the previous results of diastereoselective synthesis[10] and due to the pharmaceutical interest in the desired phosphite adducts thereof (**1**). Thiazolidinylphosphonates (**1**) can be regarded as *N*,*S*-protected phosphonic acid analogues (**2**) of the α-amino carboxylic acid D-penicillamine (**3**), and have been described as biologically active compounds (Scheme 1).[5a,b]

Until now, in contrast to the corresponding carbonyl compounds,[12] the field of catalytic asymmetric hydrophosphonylation of compounds bearing a C=N double bond has been nearly

**Scheme 1**




unknown.[13] Thus, in the following we also present a detailed synthetic investigation of this type of reaction which includes consideration of the influence of a variety of reaction parameters. Continuing our studies of the synthesis of heterobimetallic lanthanoid complexes and their application in enantioselective catalysis,[12d,e,13,14] we mainly focused on the use of this type of complex (*R*)-LnMB[15] as a catalyst. Furthermore, a comparison with the corresponding results which we achieved with other organometallic catalysts, which bore a titanium(IV) ion, is given. In addition, we report our attempts to isolate and identify the catalytically active heterobimetallic lanthanoid complex. Finally a mechanistic course will be discussed on the basis of information obtained from the $^{31}$P and $^{1}$H NMR spectroscopic and LDI-TOF mass spectrometric data.

## Results and Discussion

**I. Enantioselective Hydrophosphonylation Using Different Types of Catalysts: The Role of Heterobimetallic Lanthanoid Complexes and Titanium Complexes. A. Application of Heterobimetallic Lanthanoid Catalysts.** The success of heterobimetallic lanthanoid catalysts in a wide range of enantioselective reactions[12d,e,13,14] encouraged us to apply these catalysts to the field of the asymmetric synthesis of cyclic α-amino phosphonates (Scheme 3). The multifunctionality of the heterobimetallic (*R*)-LnMB[15] catalysts allows for broad variations according to the lanthanoid metal, alkali metal, and binaphthol (derivative) ligand. Up until now, in all investigated LnMB-catalyzed asymmetric syntheses, a "catalyst design" was utilized which led to an (in each case different) optimized LnMB catalyst and which was strongly dependent on the type of reaction. So, LLB (L = La, L = Li, B = binaphthol or derivatives) has been shown to be the most efficient catalyst in the asymmetric nitroaldol reaction (up to 96% ee),[14a,e] whereas the high enantioselectivity in an asymmetric Michael addition reaction was achieved using LSB (L = La, S = Na, B = binaphthol) catalyst (up to 92% ee).[14b,e]

**B. Influence of the Lanthanoid Center Ion Ln(III) in the (*R*)-LnPB Catalyst on Enantioselectivity and Yield.** To

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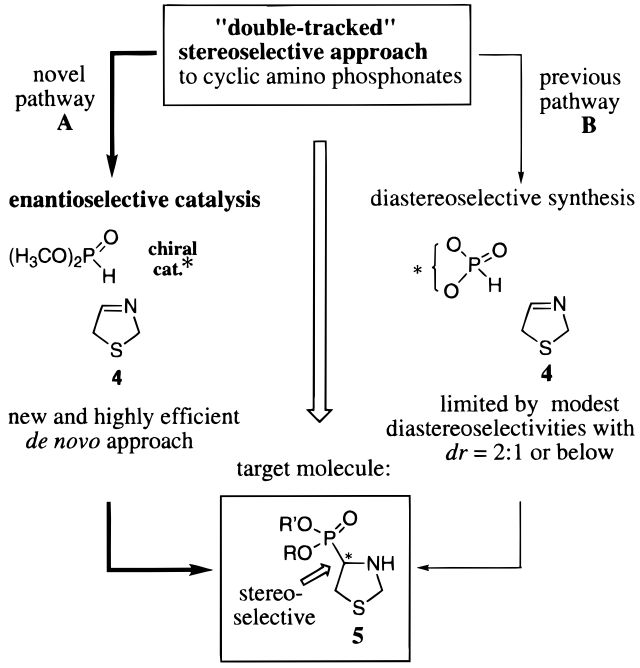
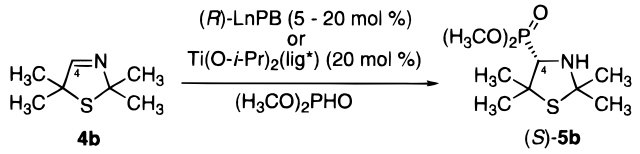
(15) In this paper, the following abbreviations were used in connection with the lanthanoid catalysts of type (*R*)-LnMB, (*R*)-LnLB, (*R*)-LnSB and (*R*)-LnPB: Ln = lanthanoid metal, M = alkali metal, L = lithium, S = sodium, P = potassium, B = (*R*)-binaphthol.

**Scheme 2.** Enantioselective versus Diastereoselective Hydrophosphonylation




**Scheme 3.** Enantioselective Hydrophosphonylation Catalyzed by (*R*)-LnPB or Ti(IV) Complexes




produce the optically active α-amino phosphonate (*S*)-**5b**, the model compound 2,2,5,5-tetramethyl-3-thiazoline (**4b**) was treated with 5 equiv of dimethyl phosphite in the presence of several types of chiral lanthanoid−potassium−binaphthoxide complexes [(*R*)-LnPB] (Scheme 3; for results, see Tables 1 and 3). At first, 20 mol % of $LaK_3$tris(binaphthoxide) ((*R*)-LPB) in THF/toluene (1:7) at room temperature was used, which has been shown to be the most efficient catalytic system in the asymmetric hydrophosphonylation of acyclic imines.[13] However, only a modest enantioselectivity of 61% ee accompanied by a 53% chemical yield was observed in the formation of (*S*)-**5b** after 144 h using this method (Table 1, entry 1). The absolute configuration of the minor enantiomer of the product **5b** (when using (*R*)-LnPB as catalyst) was determined by an X-ray analysis and was shown to be the (*R*)-enantiomer (Figure 1).[16]

The efficiency of the reaction was improved by increasing the reaction temperature to 50 °C. Thus, we obtained (*S*)-**5b** in nearly unchanged chemical yield and enantioselectivity in a reduced 50 h reaction time (Table 1, entry 2). Investigations of the influence of further lanthanoid metal components in the catalyst structure were carried out at 50 °C. Using Sm, Gd, and Dy, the ee values rose to 97% ee accompanied by good

(16) Previously, in our short communication (ref 11) the absolute configuration was determined by hydrolyzation of the product **5b** according to a literature procedure (ref 10a). However, reproducibility of this method has turned out to be low. Thus, the result of the determination of the absolute configuration by X-ray analysis, which we describe herein, seems to be more reliable. By this method, we found the opposite enantiomer (*S*)-**5b** as major enantiomer (when using (*R*)-LnPB as catalyst) compared to that with the other method.

**Table 1.** Asymmetric Synthesis of **5b** via Lanthanoid-Complex-Catalyzed Hydrophosphonylation of **4b** (according to Scheme 3)

| entry | chiral catalyst (mol%)[a] | solvent | temp | time (h) | yield (%) | ee (%)[b] |
|---|---|---|---|---|---|---|
| 1 | (*R*)-LPB (20) | THF/toluene 1:7 | rt | 144 | 53 | 61 (*S*) |
| 2 | (*R*)-LPB (20) | THF/toluene 1:7 | 50 °C | 50 | 55 | 64 (*S*) |
| 3 | (*R*)-PrPB (20) | THF/toluene 1:7 | 50 °C | 50 | 51 | 84 (*S*) |
| 4 | (*R*)-SmPB (20) | THF/toluene 1:7 | 50 °C | 40 | 97 | 93 (*S*) |
| 5 | (*R*)-GdPB (20) | THF/toluene 1:7 | 50 °C | 50 | 77 | 95 (*S*) |
| 6 | (*R*)-DyPB (20) | THF/toluene 1:7 | 50 °C | 50 | 76 | 97 (*S*) |
| 7 | (*R*)-YbPB (20) | THF/toluene 1:7 | rt | 20 | 42 | 97 (*S*) |
| 8 | (*R*)-YbPB (20) | THF/toluene 1:7 | rt | 50 | 86 | 98 (*S*) |
| 9 | (*R*)-YbPB (20) | THF/toluene 1:7 | 50 °C | 20 | 89 | 94 (*S*) |
| 10 | (*R*)-YbPB (20) | THF/toluene 1:7 | 50 °C | 50 | 90 | 96 (*S*) |
| 11 | (*R*)-YbPB (20) | THF | 50 °C | 50 | 52 | 95 (*S*) |
| 12 | (*R*)-YbPB (20) | toluene | 50 °C | 50 | 79 | 85 (*S*) |
| 13 | (*R*)-YbSB (20) | THF/toluene 1:7 | 50 °C | 60 | 56 | 94 (*S*) |
| 14 | (*R*)-YbLB (20) | THF/toluene 1:7 | 50 °C | 60 | 39 | 94 (*S*) |

[a] P = potassium; S = sodium; L = lithium; B = (*R*)-(+)-binaphthol. [b] The enantiomeric excess (ee) was determined by chiral stationary phase HPLC analysis.

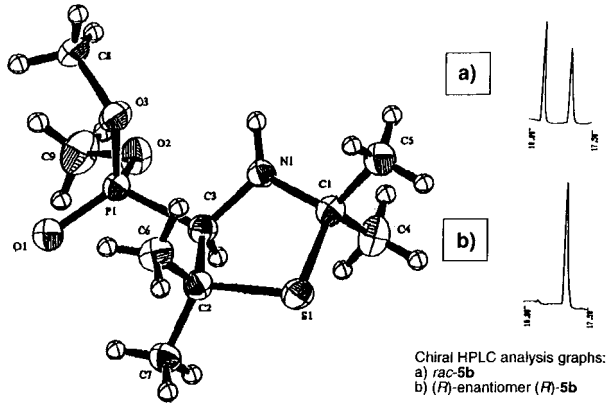



**Figure 1.** X-ray structure of the (*R*)-enantiomer of **5b**.

chemical yields (Table 1, entries 4−6). In addition, we were pleased to receive (*S*)-**5b** in excellent enantioselectivity (96% ee) and high chemical yield using (*R*)-YbPB as a heterobimetallic lanthanoid catalyst (Table 1, entry 10). In the presence of (*R*)-YbPB as catalyst and less than 5 equiv of phosphite as starting material, lower yields were obtained, although enantioselectivity remained high in the range of about ≥90% ee.

In contrast to the asymmetric hydrophosphonylation of acyclic imines, the rare earth metals with lower ionic radii in the range of Yb(III) to Gd(III) were connected with the highest enantioselectivities of approximately 95% ee (whereas high optical purities with acyclic imines were achieved with La(III),[13] a lanthanoid metal with a relatively large ionic radii). The asymmetric hydrophosphonylation of **4b** with (*R*)-LPB was found to be limited, with only 64% ee. To obtain acceptable results, potassium was needed as the alkali metal component in the complex (*R*)-LnPB.[13] This is underlined regarding the results with 20 mol % (*R*)-YbLB and (*R*)-YbSB. In these catalysts, the successful potassium component was replaced by lithium and sodium, respectively. However, even though the maintenance of high ee values was observed using all of these catalysts, the amount of (*S*)-**5b** decreased significantly (compared to the results with (*R*)-YbPB), only achieving chemical yields of 39% and 56% (Table 1, entries 13 and 14).

**C. Application of Other Organometallic Complexes as Catalysts: The Use of Chiral Titanium (IV) Catalysts.** To obtain a comparison with the catalytic abilities of other type of organometallic complexes in this field of the asymmetric

**Table 2.** Asymmetric Synthesis of **5b** via Titanium-Complex-Catalyzed Hydrophosphonylation of **4b** (according to Scheme 3)

| entry | chiral catalyst (20 mol %)[a] | solvent | temp (°C) | time (d) | yield (%)[b] | ee (%)[c] |
|---|---|---|---|---|---|---|
| 1 | Ti(O-*i*-Pr)$_2$(L−dipt) | THF | −2 | 4 | 13 (32) | 0 |
| 2 | Ti(O-*i*-Pr)$_2$(L−dipt) | THF | 5 | 4 | 12 (37) | 6 (*S*) |
| 3 | Ti(O-*i*-Pr)$_2$(L−dipt) | THF | 20 | 6 | 14 (54) | 43 (*S*) |
| 4 | Ti(O-*i*-Pr)$_2$(L−dipt) | THF | 65 | 4 | 42 (67) | 45 (*S*) |
| 5 | Ti(O-*i*-Pr)$_2$(L−dipt) | diethyl ether | 20 | 4 | 43 (66) | 38 (*S*) |
| 6 | Ti(O-*i*-Pr)$_2$(L−dipt) | toluene | 20 | 4 | 29 (51) | 0 |
| 7 | Ti(O-*i*-Pr)$_2$(L−dipt) | THF/toluene[d] | 20 | 4 | 22 (64) | 37 (*S*) |
| 8 | Ti(O-*i*-Pr)$_2$(TAD) | THF | 65 | 4 | 57 (64) | 46 (*R*) |
| 9 | Ti(O-*i*-Pr)$_2$(BIN) | THF | 65 | 5 | 62 (71) | 29 (*S*) |

[a] L-dipt = L-(+)-diisopropyl tartrate; TAD = (−)-*trans*-α,α′-(2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(diphenylmethanol) [(*R*,*R*)-(−)-TADDOL]; BIN = (*R*)−(+)-binaphthol. [b] The yields given in parentheses are for the crude products, which contained the product **5b** in >85−90% yield (according to the proton NMR spectra). [c] The enantiomeric excesses of the thiazolidinylphosphonate **5b** were determined by chiral stationary phase HPLC analysis of the crude products. [d] THF/toluene ratio = 7:1.

hydrophosphonylation of cyclic imines, the model compound 2,2,5,5-tetramethyl-3-thiazoline (**4b**) was treated with the chiral titanium−L-diisopropyl tartrate (dipt) complex (20 mol %),[17] a well-known efficient catalyst in enantioselective syntheses,[17,18] followed by the addition of an equimolar amount of dimethyl phosphite (Scheme 3; for results, see Table 2). The desired products **5b** were isolated in yields up to 62%. The yields of the isolated products strongly depend on the conditions of purification (see the Experimental Section).

Using [Ti(O-*i*-Pr)$_2$(L-dipt)] as a catalyst at 20 °C with THF as a solvent, the desired product (*S*)-**5b** was obtained with 43% ee (Table 2, entry 3). In the following, optimization experiments were carried out in order to examine the influence of reaction parameters such as solvent, temperature, and chiral diol ligand. Concerning the solvent, using pure THF or diethyl ether gave the best results (Table 2, entries 3 and 5), whereas the hydrophosphonylation in toluene led to a racemic product *rac*-**5b** (Table 2, entry 6). Consequently, for a successful enantioselective hydrophosphonylation, the use of solvents containing an ether function seems to be necessary (in the following experiments THF was used as solvent).

With regard to the enantioselectivity of the Ti−(L-dipt)-complex-catalyzed formation of (*S*)-**5b** at different reaction temperatures, a strong dependence between enantioselectivity and the reaction temperature is apparent (Table 2, entries 1−4). At temperatures between −2 and 20 °C, increase of the reaction temperatures is connected with an enhancement of the ee values from 0% ee (at −2 °C) to 43% ee (at 20 °C). A limiting value (43% ee to 45% ee) is reached at temperatures above 20 °C. The best ee value with 45% ee was found under refluxing conditions, accompanied by the highest reaction rate (Table 2, entry 4). The influence of the ligands on enantioselectivity was investigated using several chiral diols as ligands in the titanium complex catalyst. The absolute configuration of the major product enantiomer (optical purities both at close to the maximum 45% ee) changed when (*R*,*R*)-(+)-dipt was replaced by (*R*,*R*)-(−)-TADDOL,[19a] both of which were prepared from (*R*,*R*)-(+)-tartaric acid (Table 2, entry 8). The observed modest enantioselectivities could not be further increased by using (*R*)-(+)-BINOL[19b] (Table 2, entry 9, 29% ee). Thus, regardless of the variations in the reaction conditions such as temperature, solvent, and ligand component, the enantioselectivity of the asymmetric hydrophosphonylation of **4b** in the presence of titanium(IV) catalysts was limited to ee values of about 45% ee.

**II. Enantioselective Hydrophosphonylation Using Heterobimetallic Lanthanoid Complexes (*R*)-LnMB As Catalysts: Optimization of the Reaction Conditions and Investigations into the Influence of Reaction Parameters**

**A. Influence of Reaction Temperature and Reaction Time.** The good values for chemical yield (up to 97%) as well as enantioselectivity (up to 98% ee), which were obtained when using a heterobimetallic lanthanoid catalyst of type (*R*)-LnPB (20 mol %), prompted us to systematically investigate the influence of several reaction parameters. It was thought that reaction conditions could be further improved, resulting in an optimized efficient catalytic system. Variation of temperature and reaction time plays an important role in the reaction rate for the formation of (*S*)-**5b**. A 42−86% yield increase in the asymmetric hydrophosphonylation of **4b** at room temperature by changing reaction times from 20 to 50 h (Table 1, entries 7 and 8) was observed using (*R*)-YbPB as a catalyst (20 mol %). A faster reaction rate was also observed, with an 89% yield after almost 20 h at 50 °C (Table 1, entry 9). After a 50 h reaction time (at 50 °C), (*S*)-**5b** was formed in slightly increased 90% chemical yield (Table 1, entry 10). Furthermore, (*R*)-YbPB showed highly efficient catalytic properties concerning the enantioselectivity of the reaction (Table 1, entries 7−10). By carrying out the phosphite addition with (*R*)-YbPB catalyst at room temperature, (*S*)-**5b** was obtained in 98% ee (Table 1, entry 8). This is the highest enantioselectivity ever to have been observed in a catalytic asymmetric hydrophosphonylation. Encouraged by the high enantioselective efficiency which was reached nearly independent of reaction temperature in the range between room temperature and 50 °C,[20,21] examinations concerning the influence of other parameters were also carried out.

**B. Solvent Effects.** As has been observed in other syntheses, the results of lanthanoid-catalyzed reactions also often depend on the solvent.[13,14e] To check whether the used solvent mixture THF/toluene (1:7) is really the most efficient solvent system, we investigated the influence of other solvents. A solvent effect was evident in the unchanged high 95% ee enantioselectivity but the less than satisfactory 52% yield obtained by using pure THF (Table 1, entry 11). Furthermore, the use of pure toluene as a solvent led to a decreased, but still good, 85% ee (Table 1, entry 12) in 79% yield.

In conclusion, with a catalytic amount of 20 mol % (*R*)-LnPB, the desired chiral product (*S*)-**5b** was synthesized in enantioselectivities of up to 98% ee and chemical yields of up to 97% (using THF/toluene (1:7) as solvent, Table 1).

**C. Limits and Scopes of the Reaction: Catalytic Efficiency with Reduced Amounts of (*R*)-YbPB Complex.** In

(17) (a) Woodard, S. S.; Finn, M. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1991**, *113*, 106−113. (b) Finn, M. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1991**, *113*, 113−126.

(18) For a review, see: Duthaler, R. O.; Hafner, A. *Chem. Rev.* **1992**, *92*, 807−832.

(19) (a) Ti(IV)−(*R*,*R*)-TADDOL complex: Seebach, D.; Plattner, D. A.; Beck, A. K.; Wang, Y. M.; Hunziker, D.; Petter, W. *Helv. Chim. Acta* **1992**, *75*, 2171−2209. (b) Ti(IV)−(*R*)-BINOL complex: Wang, J. T.; Fan, X.; Feng, X.; Qian, Y.-M. *Synthesis* **1989**, 291−292.

(20) At low temperature (−20 °C), a strong decrease in the chemical yield (15%) was observed even after 144 h and with 20 mol % catalytic amount (Table 3, entry 12), whereas the enantioselectivity remained unchanged at high enantiomeric excess (92% ee). However, carrying out the reaction at 60, 70, and 80 °C gave (*S*)-**5b** in decreased chemical yields and (at 70 and 80 °C) in lower enantioselectivities (Table 3, entries 13−15).

(21) In addition, scale-up experiments (50 °C, 40 h, (*R*)-YbPB (20 mol %)) with 3 and 5 times higher concentrations (compared to the standard condition: 0.3 mmol) led to (*S*)-**5b** in nearly unchanged high chemical yield and enantioselectivity (0.9 mmol entry, 85% yield, 91% ee; 1.5 mmol entry, 85% yield, 94% ee).

**Table 3.** Asymmetric Synthesis of **5b** via Lanthanoid-Complex-Catalyzed Hydrophosphonylation of **4b** (according to Scheme 3; solvent THF/toluene 1:7)

| entry | chiral catalyst (mol %)[a] | *P* (atm) | temp | time (h) | yield (%) | ee (%)[b] |
|---|---|---|---|---|---|---|
| 1 | (*R*)-SmPB (20) | 1 | 50 °C | 40 | 94 | 95 (*S*) |
| 2 | (*R*)-SmPB (15) | 1 | 50 °C | 40 | 64 | 91 (*S*) |
| 3 | (*R*)-SmPB (10) | 1 | 50 °C | 40 | 54 | 91 (*S*) |
| 4 | (*R*)-YbPB (20) | 1 | 50 °C | 40 | 90 | 93 (*S*) |
| 5 | (*R*)-YbPB (15) | 1 | 50 °C | 40 | 86 | 94 (*S*) |
| 6 | (*R*)-YbPB (10) | 1 | 50 °C | 40 | 80 | 95 (*S*) |
| 7 | (*R*)-YbPB (5) | 1 | 50 °C | 40 | 63 | 95 (*S*) |
| 8 | (*R*)-YbPB (20) | $1 \times 10^4$ | rt | 24 | 70 | 84 (*S*) |
| 9 | (*R*)-YbPB (10) | $1 \times 10^4$ | rt | 24 | 53 | 83 (*S*) |
| 10 | (*R*)-YbP(B−I)[c] (5) | 1 | 50 °C | 40 | 44 | 95 (*S*) |
| 11 | (*R*)-YbP(B−II)[d] (5) | 1 | 50 °C | 40 | 81 | 96 (*S*) |
| 12 | (*R*)-YbPB (20) | 1 | −20 °C | 144 | 15 | 92 (*S*) |
| 13 | (*R*)-YbPB (5) | 1 | 60 °C | 40 | 49 | 91 (*S*) |
| 14 | (*R*)-YbPB (5) | 1 | 70 °C | 40 | 38 | 64 (*S*) |
| 15 | (*R*)-YbPB (5) | 1 | 80 °C | 40 | 15 | 47 (*S*) |

[a] P = potassium; B = (*R*)-(+)-binaphthol. [b] The enantiomeric excess was determined by chiral stationary phase HPLC analysis. [c] B-I = (*R*)-6,6′-bis((trimethylsilyl)ethynyl)binaphthol. [d] B-II = (*R*)-6,6′-bis(methoxy)binaphthol.

addition to strong enantioselectivity and high chemical yields, the attractiveness of each kind of enantioselective catalysis also depends on the necessary amount of catalyst. A highly efficient catalytic system requires small catalytic amounts in enantioselective reactions. Therefore, in connection with the asymmetric hydrophosphonylation of cyclic imines, our intention was to investigate the influence of reduced catalytic amounts and to identify an efficient catalytic system which could maintain a high ee and yield even in the presence of decreased catalytic amounts (below 20 mol %).

The positive results obtained with both (*R*)-SmPB and (*R*)-YbPB in catalytic amounts of 20 mol % were considered as a starting point for the following studies (results, see Table 3). For the (*R*)-SmPB-catalyzed asymmetric hydrophosphonylation, a steady decrease in chemical yields was observed with smaller catalytic amounts (Table 3, entries 1−3). On the other hand, reducing the concentration of the (*R*)-YbPB catalyst from 20 mol % to 15 mol % and then to 10 mol % resulted in the formation of the product (*S*)-**5b** in high chemical yields of 86% and 80%, respectively (for comparison, 90% yield with 20 mol %; Table 3, entries 4−6). However, even a further decrease in the concentration of the catalyst to 5 mol % (*R*)-YbPB gave the 4-thiazolidinylphosphonate ((*S*)-**5b**) in a still satisfactory 63% yield (Table 3, entry 7). In all cases, the enantioselectivity of the (*R*)-YbPB-catalyzed reaction was approximately 95% ee. The functional dependence of the chemical yield and enantiomeric excess from the catalytic amount is shown schematically in Figure 2.

Considering the superior asymmetric catalysis properties of La−Li-6,6′-disubstituted BINOL complexes in the enantioselective nitroaldol reaction, investigations were carried out with corresponding ytterbium catalysts such as (*R*)-YbP(B-I) and (*R*)-YbP(B-II) to further optimize the catalytic system [(*R*)-YbPB (5 mol %), 40 h, 50 °C, THF/toluene (1:7)]. However, (*R*)-YbP(B-I) [B−I = (*R*)-6,6′-bis((trimethylsilyl)ethynyl)binaphthol] led to limited chemical yields of 44% (Table 3, entry 10). For comparison, entry 11 (Table 3) revealed that the 6,6′-bis-(methoxy) derivative (*R*)-YbP(B−II) [5 mol %; B-II = (*R*)-6,6′-bis(methoxy)binaphthol] resulted in the formation of (*S*)-**5b** (after 40 h) in improved 81% chemical yield [compared to 63% yield with (*R*)-binaphthol (Table 3, entry 7)] while maintaining high enantioselectivity (96% ee).

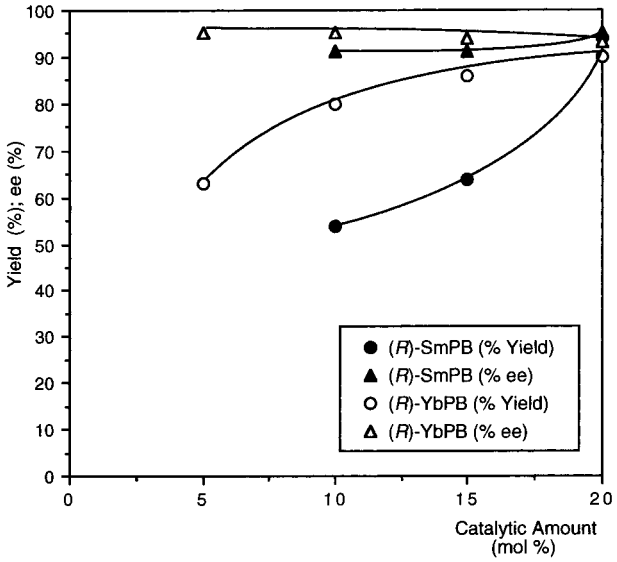



**Figure 2.** Influence of the catalytic amount on asymmetric hydrophosphonylation of imine **4b**.

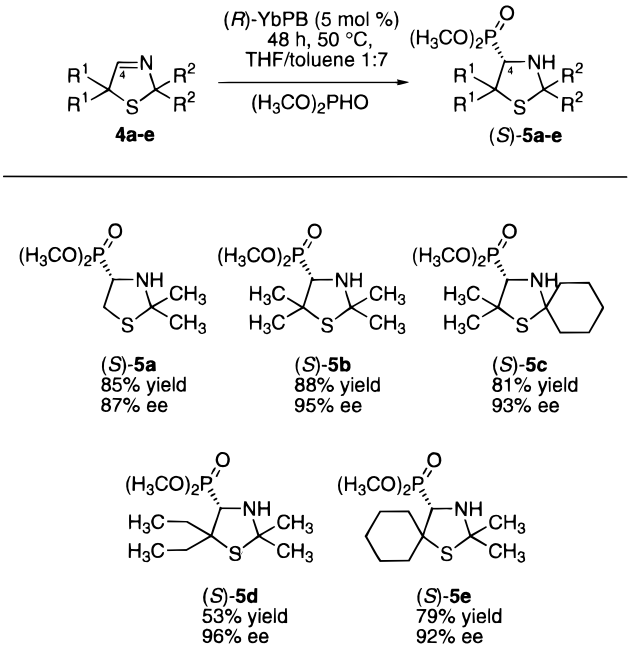
**D. High-Pressure Experiments.** In addition to a broad variety of reaction parameters such as temperature, metal component, solvent, etc., it has been shown that pressure (*P*) can also influence the enantioselectivity and yield of reactions.[22] Therefore, dimethyl phosphite was added to **4b** in the presence of 20 mol % and 10 mol % (*R*)-YbPB at a pressure of $1.00 \times 10^4$ atm to achieve chemical yields of 70% and 53% yield, respectively (reaction time 24 h; Table 3, entries 8 and 9). Regarding the corresponding experiments at atmospheric pressure, these results show that pressure has a considerable influence. A comparison of the results from the high-pressure experiment using the 20 mol % catalyst (Table 3, entry 8) with the 42% yield achieved at room temperature and atmospheric pressure (reaction time 20 h; see Table 1, entry 7) suggests that increasing pressure has a positive influence, with an observed increase in chemical yield of up to 70%. Concerning the enantioselectivity at $1.00 \times 10^4$ atm, (*S*)-**5b** was obtained with 83−84% ee. Compared with the corresponding results at atmospheric pressure, this indicates that there may be a slight decrease in enantioselectivity at high-pressure conditions.

**III. Influence of the Substituents of the Imine Component.** Encouraged by the successful results of the hydrophosphonylation experiments with the model imine component **4b**, we investigated the flexibility of the optimized catalytic conditions with regard to other substituted thiazolines **4a** and **4c**−**e**. We discovered that the use of (*R*)-YbPB as a catalyst (5 mol %) in connection with a reaction temperature of 50 °C and THF/toluene (1:7) as a solvent represents the most efficient catalytic system. After a 48 h reaction time, we were pleased to find that the desired products (*S*)-**5a**−**e**[23] were synthesized in good to high chemical yields of up to 88% with maintenance of high enantioselectivities (up to 96% ee, as can be seen in Scheme 4) nearly independent of the substituents at the thiazoline ring system. Good chemical yields were obtained in almost all cases, with the exception of only the thiazoline **4d**, which led to a decreased yield of only 53% for product **5d**.

(22) Cobianu, M.; Matsumoto, K. *Liebigs Ann./Recl.* **1997**, 623−635.

(23) Regarding the similarity of the structural framework of thiazolidinylphosphonates **5** and the same sign of optical rotation of all products **5** obtained via (*R*)-YbPB catalysis, in analogy to the determined (*S*)-configuration for the major enantiomer in the case of (*S*)-**5b**, we also supposed an (*S*)-configuration for the major enantiomers of **5a**,**c**−**e**.

**Scheme 4.** Effect of Variation of Thiazolines on Enantioselective Hydrophosphonylation




This may be due to the high flexibility of the sterically more demanding ethyl substituents in the C2 position of the thiazoline **4d**.

With these reaction conditions (48 h reaction time), hydrophosphonylation of the model component **4b** gave the product (*S*)-**5b** in further improved 88% chemical yield (compared to 63% after 40 h). In conclusion, the generally good chemical yields and high enantioselectivities of the α-amino phosphonates **5** were achieved with only 5 mol % (*R*)-YbPB catalyst.

**IV. Attempts to Identify the Catalytically Active Complex: Isolation of the Catalyst, Application in Asymmetric Hydrophosphonylation, and Structure Determination by NMR and MS Methods. A. Introduction.** Attempts to clarify the structure of *actual* catalytically active species are some of the most fascinating and challenging topics for chemists working in the field of asymmetric synthesis. Additionally, prior discussions of and investigations into the mechanism of enantioselective reactions, in general available detailed information regarding the structure of the catalysts are of high interest. In this respect, two specific contributions should be mentioned herein: (1) the work of Noyori[24] on chiral dinuclear zinc complexes has led to detailed insight into the mechanism of amino alcohol-promoted enantioselective addition of dialkylzincs to aldehydes and (2) investigations carried out by Sharpless[17] into the structure of titanium(IV) tartrate catalysts represented a breakthrough in understanding the reaction mechanism of asymmetric epoxidation. Concerning the heterobimetallic potassium lanthanoid catalysts (*R*)-LnPB, in contrast to their successful application in different types of organic syntheses,[25] less is known about the structure of *actual* catalytically active complex in solution. Until now, the supposed structural framework (Figure 3) of the catalytically active complex of this type of heterobimetallic alkali metal lanthanoid

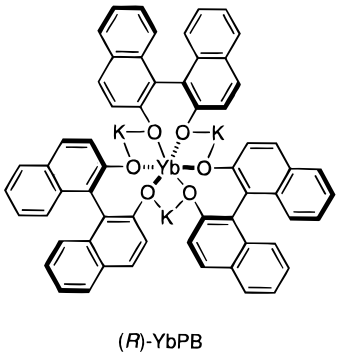



**Figure 3.** Proposed structure for (*R*)-YbPB.

complexes has been proposed according to the X-ray data of sodium-containing lanthanoid complexes, LnSBs, which were isolated and analyzed previously.[14a,b,e]

We, however, were interested in the NMR spectroscopic and mass spectrometric information which could confirm our assumption that the proposed structure of (*R*)-LnPB corresponds with the *actual* catalytically active species in solution. Consequently, in a first step, the isolation of the complex (*R*)-LnPB was planned, followed by the application of these crystals as catalysts in asymmetric hydrophosphonylation, and subsequent determination of the structure by NMR and MS methods. In the following, we present for the first time, in connection with our research on the development and application of heterobimetallic catalysts,[14e] the application of an *isolated* (*R*)-LnPB complex as a catalyst in an asymmetric synthesis (namely, (*R*)-YbPB in asymmetric hydrophosphonylation). In addition, we describe our attempts to characterize the isolated crystals by NMR and mass spectrometric methods, which were carried out to provide detailed insight into the structure of the catalyst in solution.

**B. Are the Isolated Crystals Catalytically Active? Isolation of the Catalyst and Proof of Its Catalytic Ability.** We began our investigations to clarify the structure of the catalyst with crystallization experiments using the (*R*)-YbPB complex, which has been shown to be the most efficient catalyst in the hydrophosphonylation experiments described herein. Evaporation of a (*R*)-YbPB-solution and a subsequent recrystallization of the resulting solid from THF/pentane led to the formation of colorless crystals. To make sure that these crystals actually corresponded with the "real active catalyst structure", the isolated crystals were applied as a catalyst (with a catalytic amount of 15 mol %) in the hydrophosphonylation of **4b** (according to Scheme 3; for a detailed reaction scheme, see the Supporting Information).

We were pleased to find that the desired phosphite adduct (*S*)-**5b** was formed in 78% chemical yield and with 93% ee. Comparing this with the experiment using the nonisolated catalytic complex (*R*)-YbPB with a catalytic amount of 15 mol % (86% yield, 94% ee; see Table 3, entry 5), it can be seen that the results are nearly in the same range. Consequently, this can be interpreted as proof of the isolated crystals' ability to act as an efficient asymmetric catalyst. In the next step, investigations were carried out to analyze the structure of such an isolated complex in detail.

**C. What Does the Catalytically Active Complex Look Like? NMR Spectroscopic and Mass Spectrometric Data for the Crystals.** We next focused on NMR spectroscopic and mass spectrometric methods in order to obtain analytical data about the catalyst structure in solution. If the structure of the isolated catalytically active complex is in correspondence with

(24) (a) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49−69. (b) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley & Sons: New York, 1994; Chapter 5. (c) Kitamura, M.; Suga, S.; Niwa, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 4832−4842.

(25) The potassium lanthanoid complexes (*R*)-LnPB were also successfully applied to an asymmetric nitroaldol reaction, see: Oshida, J.; Okamoto, M.; Azumo, S.; Tanaka, T. *Tetrahedron: Asymmetry* **1997**, *8*, 2579−2584.

the proposed structure for (*R*)-YbPB (see Figure 3), we should get the following information from the NMR and MS analysis:

1. Due to the (proposed) symmetric structure of (*R*)-YbPB, all naphthoxide subunits should show the same NMR spectroscopic behavior. Consequently, only one set of naphthoxide carbon and proton atoms should be found in the corresponding NMR spectra of the crystals.

2. If three binaphthol units coordinate to one Yb(III) center ion (according to the stoichiometry which was used in the reaction, starting from 3 equiv (*R*)-binaphthol and 1 equiv ytterbium(III) triisopropoxide), the proton and carbon NMR of the (*R*)-YbPB solution should be analogous to those of the crystals. This means that the NMR spectra of the (*R*)-YbPB solution should not show an additional set of naphthoxide peaks (caused by nonreacted binaphthol which would be the case if only 1 or 2 equiv of binaphthol are coordinated to Yb(III)).

3. A mass peak of the molecular mass of (*R*)-YbPB ($M_w$ = 1143) might be found using mass spectrometry with soft ionization methods such as fast atom bombardment mass spectrometry (FAB-MS) and electrospray ionization mass spectrometry (ESI-MS), respectively.

Starting with the NMR spectroscopic investigations of the catalytically active crystals (*R*)-YbPB, the corresponding proton and carbon NMR spectra are shown in Figure 4. Therein, the proton NMR spectra offers a set of six broadly shaped singlets, and the carbon NMR shows a set of 10 different peaks, which corresponds with our assumption, discussed in topic 1 above. Consequently, the isolated complex appears to consist of binaphthol units which are symmetrical to each other (or of only one binaphthol unit).

Proof that the stoichiometric ratio of the binaphthol units to the amount of Yb(III) is 3—according to topic 2—can be provided by comparing the carbon spectra of the (*R*)-YbPB solution with those of the crystals. The similarity of both spectra and the absence of an additional set of carbon NMR peaks[26] strongly supports the supposed structure for (*R*)-YbPB (see Figure 3) as the catalytically active complex. In addition, the mass spectrometric investigations were carried out in order to gather additional information about the molecular mass of the isolated complex. At first, we used fast atom bombardment mass spectrometry (FAB-MS)[27] to find the molecular mass peaks $[M + H]^+$ ($m/z$ = 1144) and $[M + K]^+$ ($m/z$ = 1182) (Figure 5). The relatively low intensity of the mass peaks can be reasonably explained by the low stability of the heterobimetallic lanthanoid complexes at these mass spectrometric conditions.[14a] The mass spectra were recorded in high resolution so that the isotope pattern of the mass peaks $[M + H]^+$ ($m/z$ = 1144) and $[M + K]^+$ ($m/z$ = 1182) could be determined. Therefore, it is worthwhile to point out that the observed isotope distribution is in good agreement with the calculated distribution (Figure 5). This agreement supports our conclusion that the peaks at $m/z$ = 1144 and 1182 are caused by the corresponding proton and potassium adducts of the (*R*)-YbPB complex, respectively.

In recent years, using electrospray ionization mass spectrometry (ESI-MS),[28] a new, highly efficient soft ionization mass spectrometry method was developed. Recently, there have been

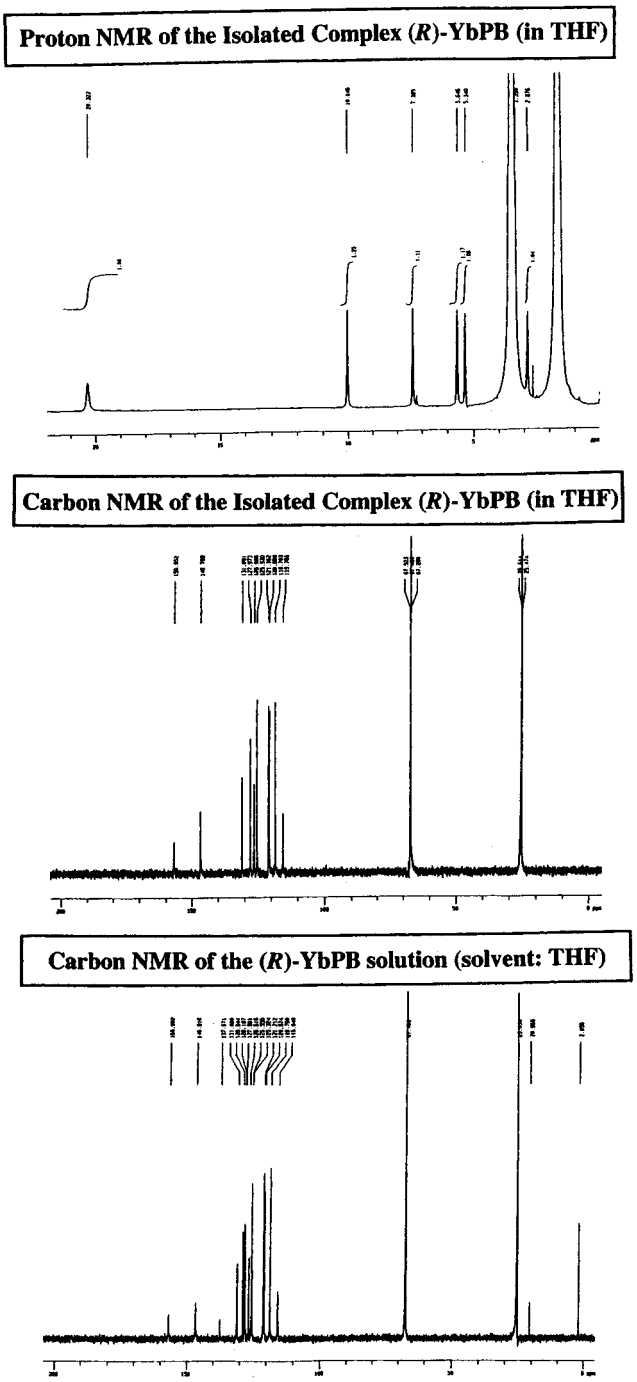



**Figure 4.** NMR spectra of the isolated complex (*R*)-YbPB and the (*R*)-YbPB solution (the peaks at 3.4 and 1.7 ppm in the proton NMR, and 67.4 and 25.6 ppm in the carbon NMR spectra result from the solvent THF).

reports of this method being used for determining the mass of organometallic complexes.[29,30] However, most reports focused on the determination of charged complexes,[29] whereas knowledge about the ESI-MS spectra of neutral complexes is rare.[30]

(26) In the carbon NMR of the (*R*)-YbPB solution, four additional peaks in the aromatic range and one peak at 20.9 ppm occurred, which can be explained by small amounts of (nonremoved) toluene (resulting from the toluene solution of KHMDS).

(27) (a) Barber, M.; Bordoli, R. S.; Sedgwick, R. D.; Tyler, A. N. *J. Chem. Soc., Chem. Commun.* **1981**, 325−327. (b) Caprioli, R. M., Ed.; *Continuous-Flow Fast Atom Bombardment Mass Spectrometry*; Wiley: Chichester, 1990.

(28) (a) Fenn, J. B.; Mann, M.; Meng, C. K.; Wong, S. F.; Whitehouse, C. M. *Science* **1989**, *246*, 64−71. (b) For a recent, excellent review, see: Gaskell, S. J. *J. Mass Spectrom.* **1997**, *32*, 677−688.

(29) For representative publications, see: (a) Katta, V.; Chowdhury, S. K.; Chait, B. T. *J. Am. Chem. Soc.* **1990**, *112*, 5348−5349. (b) Bitch, F.; Dietrich-Buchecker, C. O.; Khemiss, A. K.; Sauvage, J.-P.; Van Dorsselaer, A. *J. Am. Chem. Soc.* **1991**, *113*, 4023−4025.

(30) (a) Kane-Maguire, L. A. P.; Kanitz, R.; Sheil, M. M. *Inorg. Chim. Acta* **1996**, *245*, 209−214. (b) Hori, H.; Ishihara, J.; Koike, K.; Takeuchi, K.; Ibusuki, T.; Ishitani, O. *Chem. Lett.* **1997**, 273−274.

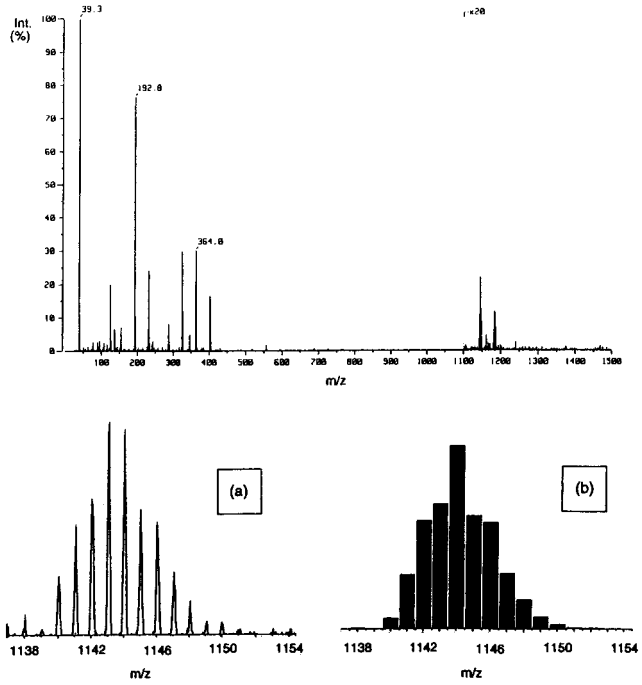



**Figure 5.** Fast-atom bombardment mass spectra (FAB-MS) of the isolated complex (R)-YbPB, with observed (a) and calculated (b) isotope distribution patterns.

In the following, we report the results of the first electrospray ionization mass spectrometric investigation of a neutral heterobimetallic lanthanoid complex. In addition, to our best knowledge, this is the first application of the innovative ESI-MS technique to the broad class of neutral metal−aryloxide complexes (of type $M(-OR)_n$). The resulting ESI-MS spectra of the isolated (*R*)-YbPB complex exhibits a base peak at $m/z = 1142.7$ which (considering the mass accuracy of this method of ± 0.15%) is in reasonable correspondence with the intact $[M + H]^+$ ion ($M_w = 1144.3$) (for the ESI-MS spectra, see the Supporting Information). Thus, electrospray ionization mass spectrometry seems to be an interesting and efficient method for analyzing neutral bimetallic complexes. The extension of this method to other types of heterobimetallic lanthanoid complexes as well as high-resolution experiments in order to obtain the isotopic distribution is now in progress.

In conclusion, the NMR spectroscopic and mass spectrometric investigations provided insight into the assembly of the heterobimetallic complex (*R*)-YbPB and strongly support the previously supposed structure for the catalytically active complex (see Figure 3). In addition, such knowledge of the composition of the heterobimetallic catalysts, namely, the potassium derivative (*R*)-YbPB, in solution represents one of the rare cases in catalytic asymmetric synthesis in which the "real catalytically active species" could be isolated, applied, and analyzed by NMR spectroscopic and mass spectrometric methods.

**V. The Reaction Mechanism: Postulation and Investigations to Clarify the Interactions between Catalyst and Starting Materials. A. Introduction.** In previous reports of the asymmetric hydrophosphonylation of C═X unsaturated compounds (X = O, N) catalyzed by Lewis acids, a variety of mechanisms have been proposed.[12,13] However, additional spectroscopic or X-ray analytic information about the Lewis acid and phosphite or imine interactions which might support a proposed reaction mechanism or several steps thereof are rare.[31−33] Concerning the (*R*)-LnPB-catalyzed addition of phosphite toward imines, the initial feature should be the formation of a phosphite−catalyst complex, which leads to an activation of the phosphite component.[13] However, especially for hydrophosphonylation reactions catalyzed by heterobimetallic lanthanoid complexes, there is more than one possibility for the coordination of the phosphite with the complex, due to the presence of different types of metal ions (lanthanoid and alkali metal ions, respectively). Consequently, the coordination of the phosphite to the (*R*)-LnPB complex could be realized either by an attachment to the potassium or lanthanoid ion (or both of them). Furthermore, in asymmetric hydrophosphonylation using chiral Lewis acids, the role of the coordination of the imine has not yet been made clear. Investigations which might clarify this topic have not been carried out; therefore, additional information regarding whether the imine coordinates to the used Lewis acid would be helpful in postulating the mechanistic course of the reaction.

In connection with our attempts to understand the functionality of heterobimetallic complexes (*R*)-LnPB as highly inducing catalysts in asymmetric synthesis,[14e] even in the case of asymmetric hydrophosphonylation, we have been greatly interested in spectroscopic data which might underline the mechanistic steps. However, although enantioselective hydrophosphonylation, catalyzed by chiral organometallic compounds, has been carried out with aldehydes and imines, to the best of our knowledge no spectroscopic proof has been available for the previously postulated reaction mechanism or for several steps. In the following, we postulate a reaction mechanism for the (*R*)-LnPB-catalyzed, asymmetric hydrophosphonylation of cyclic imines with thiazolines as a model component. In addition, the key steps of the mechanistic course are confirmed by $^{31}P$ and $^{1}H$ NMR spectroscopies and LDI-TOF mass spectrometry.

**B. Postulation of the Reaction Mechanism.** On the basis of the determined structure of (*R*)-YbPB, a general mechanistic scheme for the hydrophosphonylation reaction of dimethyl phosphite with cyclic imines can be proposed. The mechanistic course is shown in Scheme 5. As the first step, an interaction between the oxygen of the P═O bond and the Yb(III) center ion might occur, which results in the formation of a lanthanoid/phosphite complex (**I**). The preferred coordination of phosphite (instead of the theoretically also possible imine bond at the nucleophile N atom) to Yb(III) is due to the high oxophilicity of lanthanide(III) ions. However, in structure **I**, the phosphorus atom does not show any nucleophilic abilities, which are necessary for a nucleophilic attack on the C═N double bond. Consequently, a tautomeric rearrangement[34] of structure **I** should take place, leading to a Ln(III)-coordinated phosphite form **IIb**. Therein, the $\lambda^3$ phosphorus atom shows enhanced nucleophilic character caused by the lone pair, which now allows a nucleophilic attack on the C═N double bond of the thiazolines. The nucleophilicity of the phosphorus atom should be further increased by (partly) deprotonation and an additional coordination of the resulting anion to the potassium in the intermediate

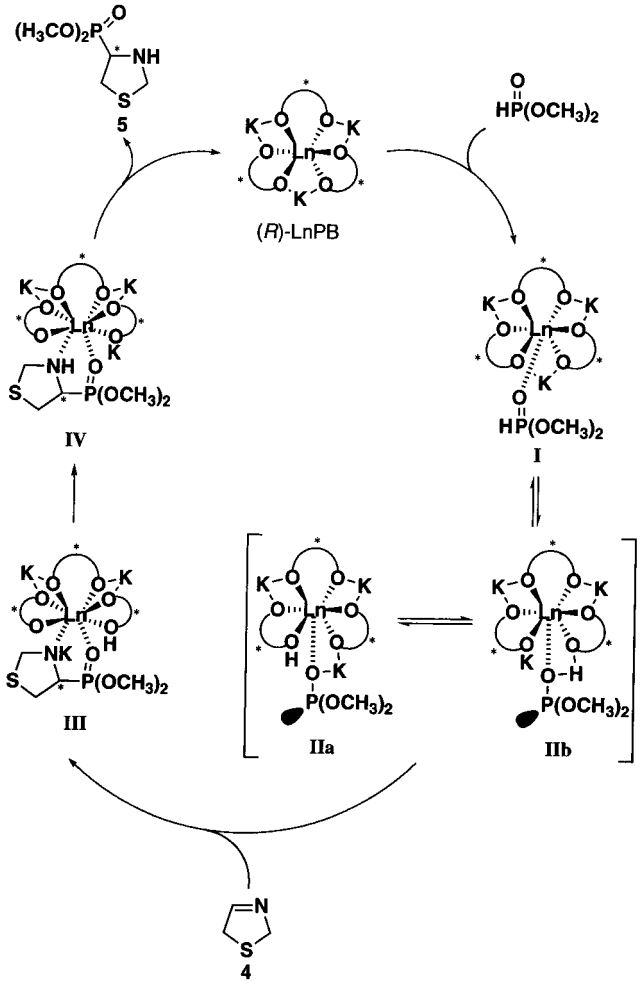
(31) X-ray data of a comparable complex between phosphine oxide and Ln(III) are given in: Aslanov, L. A.; Ionov, V. M.; Rybakov, V. B.; Korythyi, E. F.; Martynenko, L. I. *Koord. Khim.* **1978**, *4*, 1427−1429.

(32) For postulated Lewis acid/imine interactions in comparable stereoselective additions, see: (a) (with titanium complexes) Fujisawa, T.; Ukaji, Z.; Noru, T.; Date, K.; Shimizu, M. *Tetrahedron* **1992**, *48*, 5629−5638. (b) (with lanthanoid complexes) Ishitani, H.; Kobayashi, S. *Tetrahedron Lett.* **1996**, *37*, 7357−7360.

(33) For NMR investigations of $Yb(OTf)_3$/imine complexes, see: Kobayashi, S.; Nagayama, S. *J. Org. Chem.* **1997**, *62*, 232−233.

(34) Moedritzer, K. *J. Inorg. Nucl. Chem.* **1961**, *22*, 19−21.

**Scheme 5.** Proposed Reaction Mechanism (for Graphical Reasons, the Substituents $R^1$ and $R^2$ at the Thiazoline 4 Are Not Shown)




**IIa**. Consequently, the P nucleophile reacts (in a high enantioselective manner) with the C═N double bond of the thiazoline **4** to form the chiral potassium salt of the 4-thiazolidinylphosphonate **III**. A subsequent proton-exchange reaction step produces the α-amino phosphonate (*S*)-**5** and (*R*)-LnPB, which are connected to each other in structure **IV**. The final step of the catalytic cycle is achieved by a dissociation of the α-amino phosphonate (*S*)-**5** from the rare earth complex **IV**, which regenerates the "free" catalyst (*R*)-LnPB.

**C. Initial Coordination Step: NMR Spectroscopic and LDI-TOF Mass Spectrometric Studies on Interactions between Starting Materials and a Heterobimetallic Catalyst.** To gain some insight in the initial mechanistic step, especially if an interaction between dimethyl phosphite and (*R*)-LnPB is reasonable (as postulated in the first step in Scheme 5), $^{31}$P NMR spectroscopic investigations of several (*R*)-LnPB/dimethyl phosphite solutions were carried out. As a heterobimetallic lanthanoid complex, we chose (*R*)-YbPB, because the use of this catalyst led to the best results concerning both enantioselectivity and yields (Tables 1 and 3). Thus, the resulting chemical shifts ($\delta$) have been compared with those observed for the corresponding pure dimethyl phosphite solutions in THF/toluene (1:7). For a better comparison with the reaction conditions, the $^{31}$P NMR experiments were at first carried out under the same conditions as those used for the asymmetric hydrophosphonylation reactions (solvent mixture THF/toluene (1:7), and catalyst concentration $c$[(*R*)-YbPB] = 0.025 M).

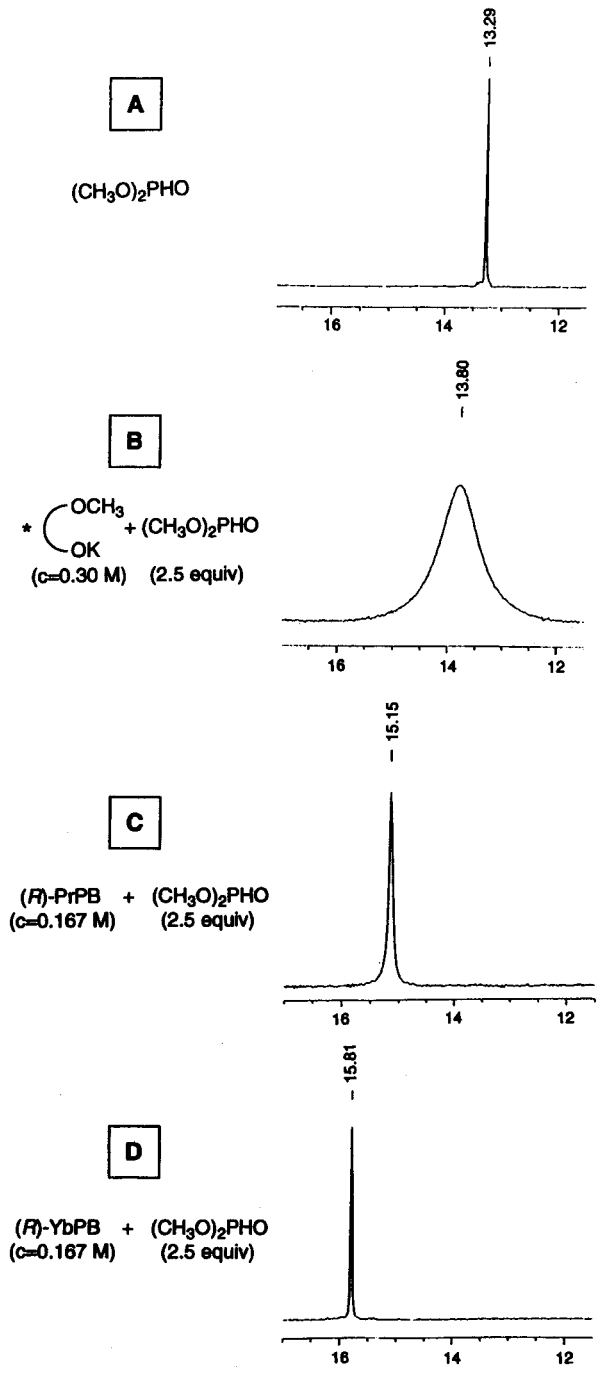



**Figure 6.** $^{31}$P NMR spectra of dimethyl phosphite and (*R*)-LnPB mixtures thereof.

According to the obtained $^{31}$P NMR spectra, we found a downfield shift gradient of $\Delta\delta = -0.68$ when (*R*)-YbPB was added to a dimethyl phosphite (20 equiv) solution in THF (for the corresponding $^{31}$P NMR spectra, see the Supporting Information). This indicates that the heterobimetallic lanthanoid catalyst (*R*)-LnPB interacts with dimethyl phosphite. Thereupon, the concentration of the (*R*)-LnPB/phosphite solutions was increased to $c$[(*R*)-YbPB] = 0.167 M (in THF) (Figure 6). Previous studies[35] on the relationship between the lanthanoid complexes (lanthanoid shift reagents) and substrates showed that increasing the substrate/lanthanoid complex concentration led to larger shift gradients ($\Delta\delta$). As expected, in our experiments, a higher concentration of (*R*)-YbPB/phosphite ((*R*)-YbPB + 2.5 equiv of dimethyl phosphite; $c$[(*R*)-YbPB ] = 0.167 M) was

also connected with a remarkably enhanced downfield shift gradient with $\Delta\delta = -2.52$ (Figure 6, graph D). Consequently, the observed shift gradient can be explained by an (*R*)-YbPB/phosphite interaction. Thus, this supports the hypothesis of an interaction between the (*R*)-YbPB and dimethyl phosphite.[36] In strong contrast, the proton NMR spectra of (*R*)-LnPB/thiazoline solutions show the peak of the imine proton (*H*C═N) with nearly the same chemical shift $\delta$ ($\Delta\delta$ below $-0.02$; see also scheme in the Supporting Information). Even in the corresponding carbon NMR, a shift gradient could not be observed (e.g., $\Delta\delta$ about $-0.2$ for the *C*═N carbon atom).[37] Thus, according to the lack of a significant shift gradient for (*R*)-LnPB/thiazoline mixtures, the formation of a (*R*)-YbPB−phosphite complex **I** appeared to be the most reasonable initial step due to the (*R*)-YbPB/phosphite interaction observed in the phosphorus NMR investigations.

A further hydrophosphonylation experiment led to the same conclusion. Herein, to a dimethyl phosphite/(*R*)-YbPB complex (stoichiometric ratio 1:1), we added a solution of equimolar amounts of thiazoline and an achiral Lewis acid, $Yb(OTf)_3$ (the corresponding reaction scheme is available in the Supporting Information). Supposing a weak phosphite/chiral catalyst interaction and the resulting remarkable amounts of "free" phosphite, the enantioselectivity of the reaction should rapidly decrease. This would be due to the side reaction of "free" phosphite with the imine/achiral Lewis acid complex under formation of racemic product *rac*-**5**.[38] However, although the product (*S*)-**5** was formed in low yield (12%),[39] a high enantioselectivity of 82% ee was observed, which corresponds with a strong (*R*)-YbPB/phosphite interaction.

To obtain additional information which could indicate the existence of lanthanoid complex/phosphite interactions, several mass spectra were recorded using laser desorption/ionization/time-of-flight mass spectrometry (LDI-TOF MS). The LDI-TOF MS method has been shown to be quite a powerful tool in analyzing the structure of rare earth metal complexes of type LnLB and LnSB,[14a,e] whereas the potassium containing complexes (*R*)-LPB and (*R*)-YbPB could not be sufficiently analyzed. Thus, (*R*)-LLB was treated with 2.5 equiv of dimethyl phosphite, and the LDI-TOF mass spectra was measured in the cationic mode. The resulting LDI-TOF mass spectra shows an additional peak at $m/z = 823$, compared to the LDI-TOF mass spectra of pure (*R*)-LLB[14a,e] (Figure 7). This $m/z$ peak of 823 can be explained by a lanthanum/dimethyl phosphite complex, which contains two (*R*)-binaphthoxide units in the presence of 1 equiv of lithium ($m/z = 825$). Because the LDI-TOF mass spectrometric experiments showed a mass accuracy of about ±0.2 %, analogous to our previous report,[14a,e] the proposed frameworks and structures are supported by the similarity of the mass spectra of various heterobimetallic lanthanoid complexes. Accordingly, a LDI-TOF mass spectra of (*R*)-YbLB and 2.5 equiv of dimethyl phosphite was recorded to check whether an additional peak also appears with the ytterbium catalyst. As expected, we found such a peak with $m/z = 857$, corresponding to an ytterbium/phosphite intermediate analogous to the structure described above for the experiment with the (*R*)-LLB catalyst (Figure 7). Consequently, the additional peaks observed in the LDI-TOF mass spectra of phosphite and (*R*)-LLB (or (*R*)-YbLB) can be reasonably explained by the lanthanoid complex/phosphite interactions. In contrast, no remarkable additional peaks occurred in the LDI-TOF mass spectra of a (*R*)-LLB/thiazoline mixture, which was investigated in order to provide information about a lanthanoid metal/imine interaction.

In conclusion, the NMR spectroscopic investigations and the synthetic experiment using two types of Lewis acids (chiral and achiral) as well as the LDI-TOF mass spectrometric data of the lanthanoid catalyst/dimethyl phosphite mixtures confirm the postulated (*R*)-LnPB/phosphite interaction as the initial step of the proposed catalytic cycle. However, these experiments did not provide proof for a lanthanoid(III) ion/phosphite interaction as postulated in Scheme 5 (structure **I**). Alternatively, the shift effects might also occur due to an interaction between the potassium ion and the P═O bond resulting from the structure **Ib** (Figure 8).

To clarify which of the metallic centers in the heterobimetallic lanthanoid complex is responsible for the shift effect, we carried out a $^{31}P$ NMR spectroscopic investigation of a mixture of the phosphite with the potassium salt of (*R*)-binaphthol. In the case of a dominant potassium/phosphite interaction similar to those postulated in structure **Ib**, we should also observe a shift effect in the same range using this mixture. However, due to the insolubility of bis(potassium) binaphthoxide in THF and THF/toluene solution (1:7) at concentrations between 0.0025 and 0.167 M, we used a monomethylated (*R*)-binaphthoxide potassium salt as a suitable substitute for the $^{31}P$ NMR spectroscopic experiments. The resulting $^{31}P$ NMR spectra shows a low (downfield) shift gradient $\Delta\delta$ of ca. $-0.5$ (Figure 6, graph B).[40] Compared to the considerable higher shift change which was observed when (*R*)-YbPB was added (Figure 6, graph D), the spectral data suggests that the coordination of dimethyl phosphite to the catalyst is more than likely caused by a lanthanoid (III)/phosphite interaction according to the proposed intermediate structure **I**.

**D. The Addition Step of Imines: Hydrophosphonylation Experiments in the Presence/Absence of a Lewis Acid.** Concerning the addition step of cyclic imines to the intermediate **IIa** (or **IIb**) (Scheme 5),[41] two different types of addition to the C═N double bonds are conceivable. As shown in Figure 9, a transition state in which the thiazoline is integrated into the catalyst complex due to an Yb(III)/imine interaction can be

(35) (a) Armitage, I.; Dunsmore, G.; Hall, L. D.; Marshall, A. G. *J. Chem. Soc., Chem. Commun.* **1971**, 1281−1282. (b) Sanders, J. K. M.; Hanson, S. W.; Williams, D. H. *J. Am. Chem. Soc.* **1972**, *94*, 5325−5335. (c) For a review, see: Cockerill, A. F.; Davies, G. L. O.; Harden, R. C.; Rackham, D. M. *Chem. Rev.* **1973**, *73*, 533−588.

(36) The $^{31}P$ NMR spectra of a solution of (*R*)-PrPB (*c*[(*R*)-PrPB ] = 0.167 M) and dimethyl phosphite (2.5 equiv) also led to a downfield shift gradient ($\Delta\delta = -1.82$; Figure 6C). This might be explained by previous $^{31}P$ NMR data, in which a reversal in the direction of the $^{31}P$ shift of the phosphoryl group to downfield shifts was observed when changing the ligand L from "dpm" to the stronger acidic "fod" in the Pr(III) shift reagent Pr(L)$_3$, see: (a) Mandel, F. S.; Cox, R. H.; Taylor, R. C. *J. Magn. Reson.* **1974**, *14*, 235−240. (b) Gerken, T. A.; Ritchey, W. M. *J. Magn. Reson.* **1976**, *24*, 155−164.

(37) This observation corresponds with previous investigations into the interactions between imines and lanthanoid shift reagents. So, Yb(dpm)$_3$, a versatile lanthanoid NMR shift reagent, shows no shift gradient when being added to certain mono− and diimines, see: (a) Beaute, C.; Wolkowski, Z. W.; Thoai, N. *J. Chem. Soc., Chem. Commun*. **1971**, 700−701. (b) Wenzel, T. J. *NMR shift reagents*; CRC Press: Boca Raton, FL 1987; p 54.

(38) $Yb(OTf)_3$ has been shown to be a suitable Lewis acid for the activation of imines (see ref 33). The reaction of dimethyl phosphite with $Yb(OTf)_3$-activated thiazoline proceeds well in the formation of *rac*-**5b** (according to the TLC check after 40 h reaction time at room temperature).

(39) The low yield might be explained by the sterical repulsion of the two ytterbium(III) complexes (*R*)-YbPB/phosphite and $Yb(OTf)_3$/thiazoline in the addition step.

(40) In this spectra, an additional peak at 143.6 ppm appeared with a low intensity (below 5%), which might result from a deprotonated dimethyl phosphite.

(41) Regarding the basic moiety of binaphthoxide and the acidic character of the phosphite, a protonation of the binaphthoxide unit leading to **IIa** seems to be more reasonable than the structure **IIb**. Nevertheless, we cannot exclude the possibility that the structure **IIb** could also play a role during the mechanistic process. However, in the following, structure **IIa** is assumed to be the dominant intermediate.

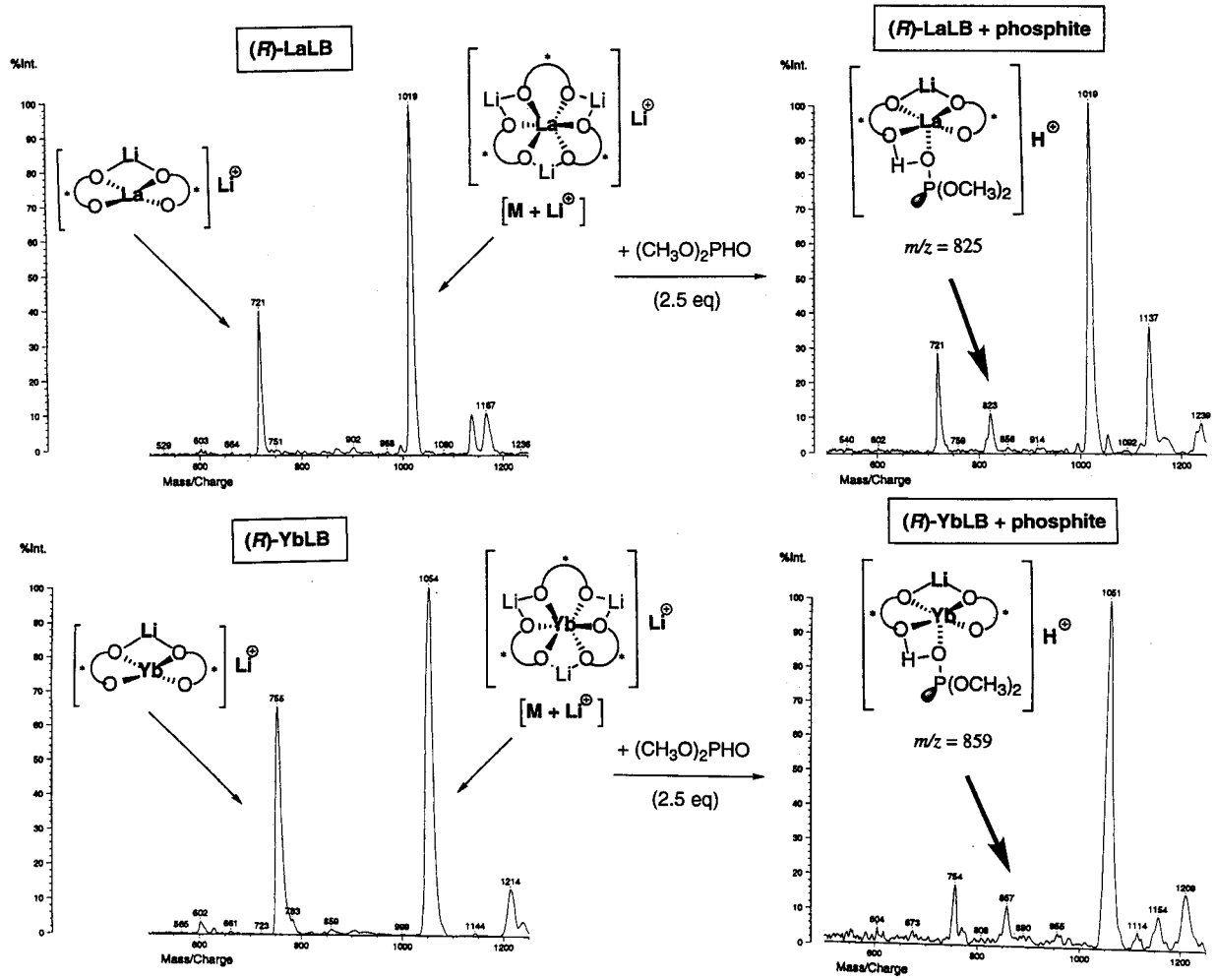
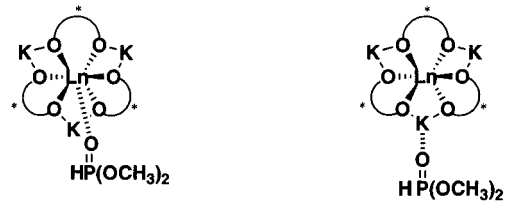
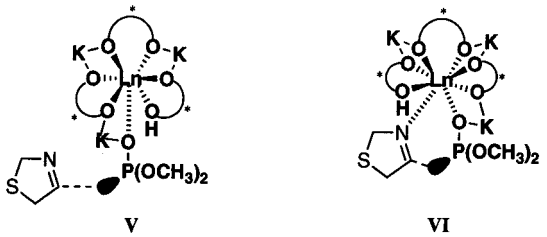



**Figure 7.** LDI-TOF mass spectra of (*R*)-LnLB and (*R*)-LnLB/phosphite (with Ln = La, Yb).




**I** **Ib**

**Figure 8.** Two possibilities for coordination of phosphite to (*R*)-LnPB.




**V** **VI**

**Figure 9.** Two possibilities for coordination of imine in the addition step.

postulated as well as an external attack of the imine bond without further coordination to the lanthanoid(III) center ion. Due to the (probably) stronger Lewis acidity of the Yb(III) center ion of intermediate **IIa** (compared to the pure (*R*)-YbPB complex), in principle, an imine coordination might take place at this stage. The increase in the Lewis acidity of **IIa** can be understood in terms of the protonation of a binaphthoxide unit (resulting in a weak Yb−O bond) and the lower donor tendency of the phosphite oxygen (which is coordinated to Yb) in the $\lambda^3$ phosphite structure in **IIa** compared to the oxygen anion of the binaphthol moiety in (*R*)-YbPB. Recently, in an asymmetric hetero Diels−Alder reaction using a comparable lanthanoid-containing catalyst system, Kobayashi[32b] proposed a Yb(III)/imine interaction in the transition state.

To determine whether structure **V** or **VI** seems to be the more reasonable in the addition reaction of a dimethyl phosphite with the C═N double bond of cyclic imines, we carried out several experiments in the presence or absence of Lewis acids using different types of phosphite structures. In this system, the following preliminary reflections were made prior to carrying out these experiments:

1. It is known that the reaction of a phosphite with imines is caused by the addition of a nucleophilic $\lambda^3$ phosphorus compound which is in equilibria with the $\lambda^4$ compound. Concerning transition state **V**, this structure shows noncoordination (and consequently nonactivation!) of the imine but a conversion of the phosphite into a tricoordinated, nucleophilic $\lambda^3$ phosphorus structure. If transition state **V** does exist, an analogous reaction between a tricoordinated phosphite derivative (namely $\lambda^3$ structures such as sodium dimethyl phosphite and dimethyl trimethylsilyl phosphite, which possess an even stronger nucleophilicity than the $\lambda^3$ phosphorus system in **V** and **VI**) and the imine **4b** should also proceed well (even in the absence of a Lewis acid activation of the imine component).[42,43]

2. If, however, a transition state of type **VI** exists as the dominant transition state structure, a high level of Lewis acid activation of the imine is required. Consequently, independent from the nucleophilicity at the phosphorus atom in the phosphite and in $\lambda^3$ derivatives thereof, the additional presence of a Lewis acid, which led to the formation of an imine/Lewis acid complex (bearing a polarized and higher reactive C═N double bond), is necessary for the reaction process.

On the basis of these observations, we at first carried out the hydrophosphonylation of the model imine compound **4b** with a dimethyl phosphite and the corresponding derivatives sodium phosphite and trimethylsilyl phosphite,[42a] respectively, at room temperature and in the absence of a Lewis acid (reaction time, 40 h). The resulting conversion rates of the product *rac*-**5b** (40% or below; the conversion rates were determined from the proton NMR spectra of the crude products) suggested that none of these entries could explain the good yield which was received with (*R*)-YbPB (20 mol %) under similar conditions (room temperature, reaction time 50 h; see Table 1, entry 8). Consequently, the (*R*)-YbPB-catalyzed hydrophosphonylation of cyclic imines **4**, which proceeded well even at room temperature, can only be reasonably explained by postulating a transition state of type **VI**, in which the thiazoline is integrated into the catalyst complex (with coordination of the nitrogen of the C═N double bond to the Yb(III) center ion).

The importance of imine activation for the success of the reaction is underlined when carrying out the addition of dimethyl phosphite or the corresponding $\lambda^3$-tricoordinated derivatives sodium phosphite and trimethylsilyl phosphite, respectively, to imine **4b** in the presence of a Lewis acid, herein boron trifluoride. Compared to the corresponding results without Lewis acids, a much more rapid increase in the formation rate of the product **5b** was now observed (conversion rate up to ≥90%). A graphical summary of the hydrophosphonylation experiments in the absence or presence of an achiral Lewis acid is given in the Supporting Information. In conclusion, it appears that the postulation of a nucleophilic attack of the phosphorus nucleophiles to the cyclic imine **4b**, which is coordinated to the lanthanide(III) center, is more reasonable. Consequently, in asymmetric hydrophosphonylation of cyclic imines a transition state structure like **VI** should be formed.

## Conclusion

In summary, we have succeeded in developing an efficient enantioselective *de novo* approach to cyclic α-amino phosphonates, namely, the biologically active thiazolidinylphosphonates of type **5** by catalytic asymmetric hydrophosphonylation of cyclic imines (thiazolines **4**). Compared to the modest enantioselectivities which we observed with chiral titanium catalysts, a highly efficient route was found by the use of heterobimetallic lanthanoid catalysts (*R*)-LnPB. In this way, the desired chiral products of type (*S*)-**5b** were synthesized in excellent optical purities of up to 98% ee and high chemical yields of up to 97%. Further investigations included the variation of the lanthanoid and alkali metal component, (*R*)-binaphthol derivative ligands as well as the substituent effects of the cyclic imines **4**. Enhancement of the efficiency of the reaction was achieved using the catalytic system "5 mol % (*R*)-YbPB/50 °C/48 h/toluene−THF (7:1)". Furthermore, the "catalytically active complex" was isolated and analyzed by NMR spectroscopic and mass spectrometric methods which provided insight into the catalyst structure in solution. Thereupon, a mechanistic cycle was proposed in which the main steps could be supported by spectroscopic and experimental investigations.

## Outlook

The uncovered route of enantioselective C−P bond formation by the addition of dimethyl phosphite to cyclic imines in the presence of heterobimetallic lanthanoid catalysts offers a perspective on an innovative, alternative enantioselective synthesis of many classes bearing an amino−phosphorus functionality, e.g., α-amino phosphine oxides, α-amino phosphine sulfides, etc. Investigations concerning the scope and limitations of this reaction regarding the use of further P nucleophiles, such as dialkyl- and diarylphosphine oxide and sulfide derivatives, as starting materials are therefore currently in progress. In addition, we also plan to extend the heterobimetallic lanthanoid-complex-catalyzed hydrophosphonylation to more complicated cyclic imine systems with and without further heteroatoms (than nitrogen) included therein. Moreover, we are highly interested in an extension of our heterobimetallic catalysis with (*R*)-LnPB complexes to the enantioselective hydrophosphonylation of related imine systems, e.g., oxime ethers and nitrones. In connection with the determination of the catalysts structure, the first ESI-MS investigation of a heterobimetallic lanthanoid complex can be regarded as a starting point for attempts to use the method of electrospray ionization mass spectrometry as a standard tool for the analysis of heterobimetallic lanthanoid catalysts (and comparable organometallic complexes in general).

## Experimental Section

**General Procedures, Methods, and Materials.** Infrared (IR) spectra were recorded on a Perkin-Elmer 1600 diffraction grating infrared spectrophotometer. NMR spectra of the compounds **5** were measured on a JEOL JNM-EX-270 spectrometer, operating at 270 MHz for $^1$H NMR and at 67.8 MHz for $^{13}$C NMR. Chemical shifts, in $CDCl_3$ solution, are reported downfield from TMS ($\delta = 0$) for $^1$H NMR. For $^{13}$C NMR spectra, chemical shifts in $CDCl_3$ are reported relative to the central $CDCl_3$ resonance ($\delta = 77.00$). The $^1$H, $^{13}$C, and $^{31}$P NMR spectroscopic investigations of the (*R*)-LnPB complexes and mixtures thereof with phosphite and thiazoline, respectively, were carried out using a JEOL JNM-LA500 spectrometer, operating at 500 MHz for $^1$H NMR, at 125.65 Hz for $^{13}$C NMR, and at 500 MHz for $^{31}$P NMR. Phosphoric acid (85%) was used as an external standard, and THF or THF/toluene (1:7) were used as the solvents for these NMR investigations. Optical rotations were measured on a JASCO DIP-140 polarimeter. Mass spectra of compounds **5** were measured on JEOL JMS-DX303 and Shimadzu MALDI IV for EIMS and LDI-TOF mass, respectively. All reactions were carried out in dry solvents under an argon atmosphere, unless noted otherwise. Tetrahydrofuran (THF) and diethyl ether were distilled from sodium benzophenone ketyl. Toluene was distilled from sodium. The enantiomeric excess (ee) was determined by HPLC analysis using DAICEL CHIRALPAK AS with 2-PrOH/*n*-hexane. The lanthanoid isopropoxides Ln(O-*i*-Pr)$_3$ were purchased from Kojundo Chemical Laboratory Co., Ltd., 5-1-28, Chiyoda, Sakado-shi, Saitama 350-02, Japan (fax, ++(81)-492-84-1351). The thiazolines **4** were synthesized according to the literature.[9c] The racemic samples *rac*-**5** for the standardization of the chiral HPLC measurement were prepared by a method analogous to the procedure described in ref 10a. Sodium phosphite was prepared from dimethyl phosphite and sodium hydride. Dimethyl trimethylsilyl phosphite was prepared according to the literature.[42a]

**General Procedure for the Preparation of the (*R*)-LnPB Complex (GP1).** To a stirred solution of (*R*)-binaphthol (258 mg, 0.90 mmol) in THF (8.40 mL) was added a solution of Ln(O-*i*-Pr)$_3$ (1.50 mL, 0.30 mmol, 0.2 M in THF for all lanthanoids with exception of Yb(O-*i*-

(42) (a) Afarinkia, K.; Cadogan, J. I. G.; Rees, C. W. *Tetrahedron* **1990**, *46*, 7175−7196. (b) Afarinkia, K.; Cadogan, J. I. G.; Rees, C. W. *Synlett* **1990**, 124−125.

(43) Tricoordinated $\lambda^3$ forms of phosphite (e.g., trimethylsilylated derivatives of type **7**) possess a high nucleophilic potential in the reaction with imines even in the absence of Lewis acids (see ref 42).

$Pr)_3$; for Yb(O-*i*-$Pr)_3$, a 0.1 M solution in THF was used), KHMDS (1.80 mL, 0.90 mmol, 0.5 M in toluene), and $H_2O$ (0.30 mL, 0.30 mmol, 1.0 M in THF) at room temperature under argon atmosphere. After 1 h of stirring at room temperature, the solvent was removed under vacuum, and toluene/THF (7:1) (12 mL) was added to give a 0.025 M (*R*)-LnPB−catalyst solution, which was used in the asymmetric hydrophosphonylation reactions with a 20 mol % catalytic amount. For the hydrophosphonylation experiments using a catalytic amount of 5 mol % of (*R*)-LnPB, a 0.00625 M (*R*)-LnPB−catalyst solution was prepared in an analogous manner.

**General Procedure for the Catalytic Asymmetric Hydrophosphonylation of the 3-Thiazolines 4 Using (*R*)-LnPB Complexes at Atmosphere Pressure (GP2).** (Acting for all entries using (*R*)-LnPB catalysts (see Tables 1 and 3)). In the following, the synthesis of thiazolidinylphosphonate (*S*)-**5b** starting from 3-thiazoline **4b** and 5 mol % (*R*)-YbPB catalyst is described. To the corresponding (*R*)-LnPB catalyst solution (2.4 mL, 0.00625 M in THF/toluene 1:7) were slowly added the 3-thiazoline **4b** (43 mg, 0.3 mmol) in THF (0.5 mL) and dimethyl phosphite (138 μL, 1.5 mmol) at 50 °C under Ar atmosphere. After 40 h of stirring, the mixture was quenched by adding aqueous saturated ammonium chloride solution (2 mL) and extracted with ethyl acetate (3 × 2 mL). Subsequently, the aqueous layer was neutralized with saturated sodium bicarbonate solution (2 mL), followed by extraction with ethyl acetate (3 × 5 mL). The combined organic layers were washed with saturated brine and dried over anhydrous sodium sulfate. Removal of the solvent and flash column chromatography (silica gel; eluent, at first 100 mL of eluent *n*-hexane/EtOAc (1:1) were used for the separation of the binaphthol component, followed by a change of the eluent to acetone/*n*-hexane (1:10) to isolate the product) gave the desired product (*S*)-**5b** as an oil, which crystallized after several hours at room temperature.

**General Procedure for the Catalytic Asymmetric Hydrophosphonylation of 3-Thiazoline 4b Using Chiral Ti(IV) Complexes (GP3).** (Synthesis of thiazolidinylphosphonate (*S*)-**5b** from 3-thiazoline (**4b**) using 20 mol % Ti(O-*i*-$Pr)_2$(L-dipt) catalyst.) In the first step, the chiral titanium complex was furnished in situ under Ar atmosphere and at 0 °C starting from L-(+)-diisopropyl tartrate [L-(+)-dipt, (*R*,*R*)-(+)-dipt] (0.24 g, 1 mmol) in THF (5 mL) and titanium(IV) tetraisopropoxide (0.29 g, 1 mmol) in THF (10 mL). After 0.5 h of stirring at 0 °C and 0.5 h at room temperature, dimethyl phosphite (0.62 g, 5 mmol) in THF (20 mL) was added, and the resulting mixture was then treated dropwise with 2,2,5,5-tetramethyl-3-thiazoline (0.72 g, 5 mmol) in THF (20 mL). After 4−6 d of stirring (see Table 2, as well as the reaction temperature), the solution was hydrolyzed with HCl (1 M). An extractive workup with methyl *tert*-butyl ether was carried out (3 × 15 mL), and the resulting aqueous phase (which contained the product (*S*)-**5b** in the form of the corresponding hydrochloride) was neutralized with an equivalent amount of NaOH (2 M). The solution was extracted with methyl *tert*-butyl ether (4 × 20 mL), and the combined organic layers were dried with magnesium sulfate. After the solvent was evaporated in vacuo, the crude products (which contained the products **5b** in yields of about >85−90%) were obtained as colorless or light yellow oils, which crystallized at room temperature. Treatment with light petroleum (workup A; for entries 1−3 and 7 in Table 2), treatment with light petroleum/diethyl ether, and storage at −28 °C (workup B; for entries 4−6 in Table 2), followed by subsequent filtration, and chromatographic purification (workup C; for entries 8 and 9 in Table 2), respectively, furnished the products (*S*)-**5b** as colorless solids. In the asymmetric hydrophosphonylation experiments with the catalysts Ti(O-*i*-$Pr)_2$(TAD)[19a] and Ti(O-*i*-$Pr)_2$(BIN),[19b] the same procedure was used, but the catalysts were isolated prior to use according to the literature.

**General Procedure for the Catalytic Asymmetric Hydrophosphonylation of the 3-Thiazolines Using (*R*)-LnPB Complexes at High Pressure (1.00 × $10^4$ atm) (GP4).** (Synthesis of thiazolidinylphosphonate (*S*)-**5b** from 3-thiazoline **4b** using 20 mol % (*R*)-LnPB catalyst.) To the corresponding (*R*)-YbPB catalyst solution (1.6 mL, 0.025 M in THF/toluene 1:7) were added 3-thiazoline **4b** (28.7 mg, 0.2 mmol) in THF (0.4 mL) and dimethyl phosphite (91 μL, 1.0 mmol) at room temperature in a high-pressure reaction tube. After being stored for 24 h at 1.00 × $10^4$ atm, the mixture was quenched by addition of an aqueous saturated ammonium chloride solution (2 mL) and extracted with ethyl acetate (3 × 2 mL). Subsequently, the further workup was carried out as described in the procedure GP2.

**Dimethyl (2,2-dimethyl-4-thiazolidinyl)phosphonate (5a):** IR (neat) $\nu$ 3470, 1459, 1248, 1032, 821 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 270 MHz) $\delta$ 3.86 (d, 3H, $J$ = 10.6 Hz, $CH_3OP$), 3.84 (d, 3H, $J$ = 10.5 Hz, $CH_3OP$), 3.60−3.50 (m, 1H, C4−H), 3.33−3.10 (m, 2H, $CH_2$), 2.17 (br s, 1H, NH), 1.70 (s, 3H, C2−$CH_3$), 1.52 (s, 3H, C2−$CH_3$); $^{13}C$ NMR ($CDCl_3$, 270 MHz) $\delta$ 77.2 (C2), 58.3 (d, $J$ = 155 Hz, C4), 53.5 (d, $J$ = 6.2 Hz, $CH_3OP$), 53.1 (d, $J$ = 7.3 Hz, $CH_3OP$), 38.0 ($CH_2$), 32.4 (C2−$CH_3$), 30.6 (C2−$CH_3$); MS *m*/*z* 225 ($M^+$), 210 ($M^+ - CH_3$), 116 ($M^+ - PO(OCH_3)_2$, base peak); $[\alpha]^{25}_D$ = +71.9 (*c* 1.0, $CHCl_3$); (88% ee); HPLC (DAICEL CHIRALCEL AS, 2-PrOH/*n*-hexane, 5:95, flow 1.0) $t_R$ 15.1 and 16.5 min. Anal. Calcd for $C_7H_{15}O_3NPS$ (225.2): C, 37.33; H, 7.16; N, 6.22. Found: C, 37.47; H, 7.26; N, 6.34.

**Dimethyl (2,2,5,5-tetramethyl-4-thiazolidinyl)phosphonate (5b):** IR (KBr) $\nu$ 3258, 1463, 1247, 1036, 824 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 270 MHz) $\delta$ 3.81 (d, 3H, $J$ = 10.6 Hz, $CH_3OP$), 3.80 (d, 3H, $J$ = 10.9 Hz, $CH_3OP$), 3.28−3.38 (m, 1H, C4−H), 2.89 (brs, 1H, NH), 1.65 (s, 3H, C2−$CH_3$), 1.62 (s, 3H, C2−$CH_3$), 1.51 (s, 3H, C5−$CH_3$), 1.46 (s, 3H, C5−$CH_3$); $^{13}C$ NMR ($CDCl_3$, 270 MHz) $\delta$ 74.5 (d, $J$ = 23.2 Hz, C2), 66.5 (d, $J$ = 146.4 Hz, C4), 61.7 (d, $J$ = 4.9 Hz, C5), 53.3 (d, $J$ = 7.1 Hz, $CH_3OP$), 52.7 (d, $J$ = 7.3 Hz, $CH_3OP$), 32.8 (C2−$CH_3$), 32.0 (C2−$CH_3$), 28.5 (C5−$CH_3$), 28.5 (C5−$CH_3$); MS *m*/*z* 253 ($M^+$), 238 ($M^+ - CH_3$), 144 ($M^+ - PO(OCH_3)_2$); $[\alpha]^{25}_D$ = +50.6 (c 1.0, $CHCl_3$) (94% ee); HPLC (DAICEL CHIRALCEL AS, 2-PrOH/*n*-hexane, 5:95, flow 1.0) $t_R$ 5.2 and 6.4 min. Anal. Calcd for $C_9H_{20}O_3NPS$ (253.2): C, 42.68; H, 7.96; N, 5.53; Found C, 42.68; H, 8.25; N, 5.26.

**Dimethyl (2,2-dimethyl-1-thia-4-azaspiro[4.5]dec-3-yl)phosphonate (5c):** IR (neat) $\nu$ 3462, 1446, 1248, 1031, 824 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 270 MHz) $\delta$ 3.82 (d, 3H, $J$ = 10.9 Hz, $CH_3OP$), 3.80 (d, 3H, $J$ = 10.9 Hz, $CH_3OP$), 3.31 (d, 1H, $J$ = 18.4 Hz, C3−H), 2.70 (brs, 1H, NH), 1.93−1.17 (m, 10H, $-(CH_2)_5-$), 1.59 (s, 3H, C2−$CH_3$), 1.44 (s, 3H, C2−$CH_3$); $^{13}C$ NMR ($CDCl_3$, 270 MHz) $\delta$ 80.0 (d, $J$ = 22.0 Hz, C5), 65.5 (d, $J$ = 147.7 Hz, C3−H), 59.1 (d, $J$ = 4.9 Hz, C2), 53.4 (d, $J$ = 6.1 Hz, $CH_3OP$), 52.6 (d, $J$ = 7.3 Hz, $CH_3OP$), 41.4, 41.0, 25.5, 25.2, 23.5 (5× $CH_2$), 28.7 ($CH_3$), 28.3 ($CH_3$); MS *m*/*z* 293 ($M^+$), 184 ($M^+ - PO(OCH_3)_2$, base peak); $[\alpha]^{25}_D$ = +35.1 (c 0.78, $CHCl_3$) (90% ee); HPLC (DAICEL CHIRALCEL AS, 2-PrOH/*n*-hexane, 5:95, flow 1.0) $t_R$ 5.1 and 7.0 min. Anal. Calcd for $C_{12}H_{24}O_3NPS$ (293.3): C, 49.12; H, 8.24; N, 4.78. Found: C, 49.09; H, 8.32; N, 4.52.

**Dimethyl (2,2-dimethyl-5,5-diethyl-4-thiazolidinyl)phosphonate (5d):** IR (KBr) $\nu$ 1459, 1036, 824 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 270 MHz) $\delta$ 3.83 (d, 3H, $J$ = 10.6 Hz, $CH_3OP$), 3.80 (d, 3H, $J$ = 10.9 Hz, $CH_3OP$), 3.43 (d, 1H, $J$ = 20.0 Hz, C4−H), 2.80 (brs, 1H, NH), 2.00−1.65 (m, 4H, C5($CH_2CH_3$)$_2$), 1.64 (s, 3H, C2−$CH_3$), 1.51 (s, 3H, C2−$CH_3$), 1.05 (t, 3H, $J$ = 7.3 Hz, C5−$CH_2CH_3$), 1.01 (t, 3H, $J$ = 7.3 Hz, C5−$CH_2CH_3$); $^{13}C$ NMR ($CDCl_3$, 270 MHz) $\delta$ 73.6 (d, $J$ = 24.4 Hz, C2), 71.9 (C5), 62.0 (d, $J$ = 147.7 Hz, C4), 53.4 (d, $J$ = 6.1 Hz, $CH_3OP$), 52.6 (d, $J$ = 7.4 Hz, $CH_3OP$), 32.5 (C2−$CH_3$), 32.2 (d, $J$ = 4.0 Hz, $CH_2CH_3$), 31.8 (C2−$CH_3$), 27.5 ($CH_2CH_3$), 9.8 ($CH_2CH_3$), 9.8 ($CH_2CH_3$); MS *m*/*z* 281 ($M^+$), 172 ($M^+ - PO(OCH_3)_2$); $[\alpha]^{25}_D$ = +62.2 (*c* 0.95, $CHCl_3$) (92% ee); HPLC (DAICEL CHIRALCEL AS, 2-PrOH/*n*-hexane, 5:95, flow 1.0) $t_R$ 4.5 and 6.5 min. Anal. Calcd for $C_{11}H_{24}O_3NPS$ (281.3): C, 46.95; H, 8.60; N, 4.98. Found: C, 46.97; H, 8.80; N, 4.68.

**Dimethyl (2,2-dimethyl-1-thia-3-azaspiro[4.5]dec-4-yl)phosphonate (5e):** IR (neat) $\nu$ 3462, 1448, 1250, 1059, 1031, 818 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 270 MHz) $\delta$ 3.82 (d, 6H, $J$ = 10.9 Hz, $(CH_3O)_2P$), 3.27 (d, 1H, $J$ = 19.1 Hz, C4−H), 2.80 (brs, 1H, NH), 2.20−1.10 (m, 10H, $-(CH_2)_5-$), 1.64 (s, 3H, C2−$CH_3$), 1.51 (s, 3H, C2−$CH_3$); $^{13}C$ NMR ($CDCl_3$, 270 MHz) $\delta$ 73.5 (d, $J$ = 23.2 Hz, C2), 69.7 (d, $J$ = 4.9 Hz, C5), 65.8 (d, $J$ = 147.7 Hz, C4), 53.2 (d, $J$ = 7.3 Hz, $CH_3OP$), 52.8 (d, $J$ = 7.3 Hz, $CH_3OP$), 38.6, 27.5, 25.5, 23.6 (4× $CH_2$), 36.1 (d, $J$ = 3.6 Hz, $CH_2$), 32.7 ($CH_3$), 32.0 ($CH_3$); MS *m*/*z* 293 ($M^+$), 278 ($M^+ - CH_3$), 184 ($M^+ - PO(OCH_3)_2$); $[\alpha]^{25}_D$ = +37.6 (*c* 0.75, $CHCl_3$) (94% ee); HPLC (DAICEL CHIRALCEL AS, 2-PrOH/*n*-hexane, 5:95, flow 1.0) $t_R$ 5.2 and 7.1 min. Anal. Calcd for $C_{12}H_{24}O_3NPS$ (293.3): C, 49.12; H, 8.24; N, 4.78. Found: C, 48.95; H, 8.52; N, 4.63.

**Isolation of the Catalyst Complex (*R*)-YbPB by Crystallization (GP5).** To a stirred solution of (*R*)-binaphthol (258 mg, 0.90 mmol) in THF (6.90 mL) was added a solution of $Yb(O\text{-}i\text{-}Pr)_3$ (3.0 mL, 0.30 mmol, 0.1 M in THF), KHMDS (1.80 mL, 0.90 mmol, 0.5 M in toluene), and $H_2O$ (0.30 mL, 0.30 mmol, 1.0 M in THF) at room temperature under argon atmosphere. After 1 h of stirring at room temperature, the volatile components were removed under vacuum, and THF (1.8 mL) was added to give a 0.167 M (*R*)-YbPB−catalyst solution. To 0.6 mL of this solution, *n*-pentane (0.3 mL) was added dropwise. Subsequently, the catalyst complex (*R*)-YbPB slowly crystallized as colorless crystals. Removal of the supernatant with a syringe, followed by washing the solid with *n*-pentane (3 × 0.5 mL) and drying in a vacuum, gave (*R*)-YbPB as a powder (during this workup the cystalline character of (*R*)-YbPB changed to amorphous) which was used for the asymmetric hydrophosphonylation reactions and the NMR spectroscopic and mass spectrometric investigations. $^1$H NMR ($CDCl_3$, 500 MHz): $\delta$ 2.88 (br s, 6H, binaphthol-H), 5.34 (br s, 6H, (*R*)-binaphthol-H), 5.65 (br s, 6H, binaphthol-H), 7.39 (br s, 6H, binaphthol-H), 10.05 (br s, 6H, binaphthol-H), 20.32 (br s, 6H, binaphthol-H). $^{13}$C NMR ($CDCl_3$, 125.65 MHz): $\delta$ 115.77 (6C, binaphthol-C), 118.70 (6C, binaphthol-CH), 120.86 (6C, binaphthol-CH), 121.16 (6C, binaphthol-CH), 125.53 (6C, binaphthol-CH), 126.61 (6C, binaphthol-C), 127.97 (6C, binaphthol-CH), 131.09 (6C, binaphthol-CH), 146.77 (6C, binaphthol-C), 156.95 (6C, binaphthol-COH).

**Mass Spectrometric Investigation of the Isolated Catalyst Complex (*R*)-YbPB by Fast-Atom Bombardment Mass Spectrometry (FAB-MS).** The FAB mass spectra of the (*R*)-YbPB crystals was recorded using an EB sector high-resolution mass spectrometer (JMS-HX110). Therefore we used (*R*)-YbPB crystals (which were obtained after removing the supernatant from the crystal-containing mixture; the crystallization procedure is described in detail in GP5), which were dissolved in a *p*-nitrobenzyl alcohol (NBA) matrix according to the general method and then introduced to the EB sector high-resolution mass spectrometer (JMS-HX110). This mass spectrometer can be used for exact mass analysis at a resolution of 10 000. In this connection, Xe was used as the fast atom and the acceleration volt was 10 000 V.

**Mass Spectrometric Investigation of the Isolated Catalyst Complex (*R*)-YbPB by Electrospray Ionization Mass Spectrometry (ESI-MS).** The ESI-MS mass spectra of the (*R*)-YbPB crystals were recorded using a JMS-700t tandem mass spectrometer equipped with both an ESI and APCI ion source. Therefore, 50 mg of (*R*)-YbPB crystals (which were obtained after removal of the supernatant from the crystal-containing mixture; the crystallization procedure is described in detail in GP5) were dissolved in THF (30 mL). The flow was 7 mL/h, and the desolvation plate temperature was 170 °C. The resolution was about 2000, and the acceleration volt was 5000 V.

**Catalytic Asymmetric Hydrophosphonylation of Imine 4b Using the Isolated Catalyst Complex (*R*)-YbPB.** The (*R*)-YbPB complex was isolated according to GP5. Subsequently, 52.2 mg of the resulting powder was dissolved in 0.36 mL of THF and 2.55 mL of toluene to give the (*R*)-YbPB−catalyst solution (corresponding to a catalytic amount of ca. 15 mol %; solvent THF /toluene 1:7). This catalyst solution was added to the 3-thiazoline **4b** (43 mg, 0.3 mmol), followed by the addition of dimethyl phosphite (138 $\mu$L, 1.5 mmol) at 50 °C under Ar atmosphere. After 40 h of stirring, the reaction was quenched by adding an aqueous saturated ammonium chloride solution (2 mL) and extracted with ethyl acetate (3 × 2 mL). Subsequently, further workup was carried out as described in the procedure GP2.

**Catalytic Asymmetric Hydrophosphonylation of Imine 4b in the Presence of the Isolated Catalyst Complex (*R*)-YbPB and an Achiral Lewis Acid.** The (*R*)-YbPB complex was isolated according to GP5, and the 352 mg of the resulting powder (0.3 mmol), dissolved in THF (2.4 mL), was treated with dimethyl phosphite (27.5 $\mu$L, 0.3 mmol) at room temperature. Subsequently, the mixture was stirred for 1 h at room temperature and 1 h at 0 °C. In parallel, a thiazoline−$Yb(OTf)_3$ complex was generated by stirring a mixture of thiazoline **4b** (43 mg, 0.3 mmol) and ytterbium(III) triflate (186 mg, 0.3 mmol) in THF (0.74 mL) for 1.5 h at room temperature and 1 h at 0 °C. The resulting thiazoline−$Yb(OTf)_3$ solution was added dropwise (over 30 min) to the (*R*)-YbPB/dimethyl phosphite solution at 0 °C. After 5 h of stirring at 0 °C and 37 h of stirring at room temperature, the reaction was quenched by adding an aqueous saturated ammonium chloride solution (2 mL) and extracted with ethyl acetate (3 × 2 mL). Subsequently, further workup was carried out as described in the procedure GP2 to give the desired product (*S*)-**5b** (9.0 mg, 12%).

**General Procedure for the Hydrophosphonylation of Imine 4b with Phosphite and Derivatives Thereof in the Absence/Presence of an Achiral Lewis Acid (GP6).** Concerning the investigations of the reaction in the absence of a Lewis acid, the phosphite component (1.5 mmol, neat, for dimethyl phosphite, and dissolved in THF for sodium dimethyl phosphite and dimethyl trimethylsilyl phosphite) was added to a thiazoline **4b** solution (0.43 mmol, 0.3 mmol) in THF at room temperature, and the reaction mixture was stirred for 40 h at this temperature. Subsequently, the reaction was quenched by addition of aqueous saturated ammonium chloride solution (3 mL). After the addition of ethyl acetate (3 mL), the organic phase was separated and washed with saturated brine (4 mL). The combined aqueous layer was neutralized with saturated sodium bicarbonate solution, followed by an extraction of the aqueous phases with ethyl acetate (3 × 5 mL). The combined organic layers were washed with saturated brine (2 × 3 mL) and dried over anhydrous sodium sulfate. Removal of the solvent gave the oily crude product. The conversion rate was determined from the content of *rac*-**5b** in the crude product according to the integration in the proton NMR spectra. For the investigations of the reaction in the presence of a Lewis acid, a thiazoline **4b**/boron trifluoride solution in THF, which was prepared starting from imine **4b** (43 mg, 0.3 mmol) and boron trifluoride diethyl etherate (38 $\mu$L, 0.3 mmol), was used instead of the pure thiazoline solution.

**Crystallographic Structure Determination.** Crystallographic data of (*R*)-**5** and details associated with data collection, data reduction, and structure solution and refinement are given in the Supporting Information. Recrystallization of a product (*R*)-**5b** (94% ee), which was obtained by asymmetric hydrophosphonylation using the (*S*)-YbPB catalyst (reaction scale, 1.2 mmol; 86% yield; 94% ee), from small amounts of diethyl ether gave crystals (*R*)-**5b** suitable for an X-ray analysis (for HPLC data of the crystal, see Figure 1; DAICEL CHIRALCEL AS, 2-PrOH/*n*-hexane, 5:95, flow 0.5, $t_R$ 11.6 and 14.8 min). A clear prism crystal of (*R*)-**5b** having approximate dimensions of 0.35 × 0.20 × 0.40 mm was mounted on a glass fiber. All measurements were made on a Rigaku RAXIS-II imaging plate area detector with graphite-monochromated Mo K$\alpha$ radiation. The structure was solved by direct methods[44] and expanded using Fourier techniques.[45] The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. Compound (*R*)-**5** crystallized in a primitive orthorhombic crystal system with systematic absences indicating the space group $P2_12_12_1$ (No. 19) with the following cell parameters: $a = 11.236(3)$ Å, $b = 13.69(1)$ Å, $c = 8.344(7)$ Å, $V = 1283.2600$ Å$^3$, $Z = 4$.

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**Supporting Information Available:** Crystallographic data of (*R*)-**5b** and details associated with data collection, data

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reduction, structure solution and refinement, phosphorus NMR spectra of the NMR experiments with a dimethyl phosphite/(*R*)-YbPB solution at a catalyst concentration c[(*R*)-YbPB] = 0.025 M, information about the proton and carbon NMR spectra of a (*R*)-LnPB/thiazoline solution, a graph illustrating the effect of lanthanoid ionic radii on enantioselectivity, several schemes in connection with the sections IV and V, and ESI-MS spectra of (*R*)-YbPB (22 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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