Concept of Improved Rigidity: How to Make Enantioselective Hydrophosphonylation of Cyclic Imines Catalyzed by Chiral Heterobimetallic Lanthanoid Complexes Almost Perfect

Imre Schlemminger,[§] Yoshinobu Saida,[†] Harald Gröger,[†,#] Wolfgang Maison,[§] Nathalie Durot,[§] Hiroaki Sasai,*[,†,‡] Masakatsu Shibasaki,*[,†] and and Jürgen Martens*[,§]

Department of Chemistry, University of Oldenburg, 26111 Oldenburg, Germany, and Graduate School of Pharmaceutical Sciences, University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113, Japan

juergen.martens@uni-oldenburg.de

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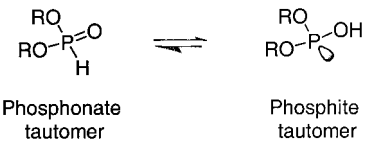
The catalytic and enantioselective hydrophosphonylation of cyclic imines using cyclic phosphites is described for the first time. In contrast to the application of acyclic phosphites, significant improvements are presented arising from the concept of improved rigidity by utilization of cyclic phosphites in the lanthanoid BINOL complex catalyzed hydrophosphonylation of 3-thiazolines. Cyclic phosphites are shown to provide certain improvements within the catalytic cycle. Influence of parameters such as concentration of the catalyst and the phosphite on the catalysis is examined as well as the effects of the substituents on the starting material. The pharmacologically interesting thiazolidinyl phosphonates are synthesized in excellent optical purities of up to 99% ee and high chemical yields of up to 99%. The required amount of catalyst is reduced to 2.5 mol %. The highest efficiency of the reaction involving cyclic phosphites is achieved using the catalytic system "2.5 mol % (*S*)-YbPB/2.5 equiv phosphite/50 °C/48 h/THF−toluene (1:7)". On the basis of the results a refinement of the proposed catalytic cycle has been provided. For comparison cyclic phosphites were used in hydrophosphonylation with a chiral titanium catalyst.

Introduction

α-Amino phosphonic acids, the phosphorus analogues of α-amino acids, and their derivatives play an important role in modern medicinal and pharmaceutical chemistry,[1] since they are actually "long life" transition state analogues of α-amino acids. This structural relationship causes a wide range of applications in the modulation of enzyme activity[2] (including HIV-protease[3]).

The major interest in enantiomerically pure α-amino phosphonic acids faces a lack of powerful stereoselective synthesis of these compounds. Most stereoselective strategies are based on a diastereoselective addition of an appropriate P-nucleophile to chiral imines.[4] In most cases esters of phosphorus acid **1** have been used as P-nucleophiles. These compounds are known to undergo a phosphite−phosphonate tautomerism with the phosphite tautomer as the nucleophilic (active) form and the phosphonate tautomer as the almost exclusively favored but non-nucleophilic (resting) form (Scheme 1). The diastereoselective access to chiral amino phosphonic acids requires cleavage of the chiral auxiliary after carrying out the hydrophosphonylation reaction and therefore is limited to acyclic imines. Catalyzed *enantioselective* approaches to α-functionalized phosphonic acids are still

Scheme 1. Phosphite−Phosphonate Tautomerism[13] of 1



* To whom correspondence should be addressed: Prof. Masakatsu Shibasaki. Fax: ++(81)-3-5684-5206. E-mail: mshibasa@mol.f.u-tokyo.ac.jp. Prof. Jürgen Martens. Fax: ++(49)-441-798-3757.

[§] University of Oldenburg.

[†] University of Tokyo.

[#] Present address: SKW Trostberg AG, Dr.-Albert-Frank-Str. 32, 83308 Trostberg, Germany.

[‡] Present address: Institute of Scientific and Industrial Research, Osaka University, 8-1 Mihogaoka, Ibaraki, Osaka 567, Japan.

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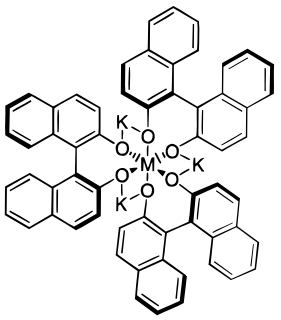
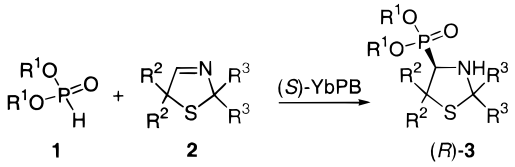


(*S*)-YbPB (M = Yb)

Figure 1. Proposed structure of (*S*)-YbPB.[7]

Scheme 2. Enantioselective Hydrophosphonylation Catalyzed by (*S*)-YbPB

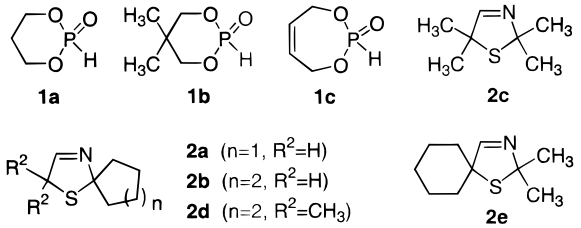


1 **2** (*R*)-**3**

rare.[5] Recently we reported the first highly efficient stereoselective access to enantiomerically pure acyclic[6] and cyclic[7] α-amino phosphonates by enantioselective catalysis. The catalysts were heterobimetallic lanthanoid complexes.[8] Regarding cyclic α-amino phosphonates, the pharmaceutically important[9] 4-thiazolidinylphosphonates **3** have been formed by addition of dimethyl phosphite **1a** (R = Me) to 3-thiazolines **2** in the presence of YbPB (Yb = ytterbium, P = potassium, B = binaphthol, Figure 1) as catalyst (Scheme 2). The reaction proceeds with high enantioselectivity and good yields with 20 mol % of the catalyst. However, while maintaining high enantioselectivity independently from the catalytic amount, the yields drop remarkably from 90% (20 mol %) to 63% (5 mol %) with the decrease of the concentration of YbPB.[7] Finally, almost no product (6%) is obtained using 3 mol % of YbPB catalyst.[7c] Regarding an industrial preparation of enantiomerically pure α-amino phosphonic acids such as the sulfur-containing compounds **3**, YbPB catalysis has to serve both high selectivity and high yield with the lowest possible amounts of catalyst.

This encouraged us to develop strategies to enhance the performance of the catalytic system in order to reduce the required amounts of catalyst. A general route to optimize stereoselectivity of an addition reaction follows the idea that well-preorganized sterically rigid reactants reduce the disfavorable entropic term of the reaction and allow an easier formation of stereospecific transition states. Following this concept of improved steric rigidity, we report herein the use of cyclic esters of phosphoric acid as conformationally rigid agents in enantioselective YbPB-catalyzed hydrophosphonylation of 3-thiazolines. Experimental findings were integrated in a proposed mechanism to refine the picture of the catalytic cycle. In addition we also focused on the use of titanium catalyst of the Sharpless type in the hydrophosphonylation reaction with cyclic phosphites.

Scheme 3



1a **1b** **1c** **2c**

2a (n=1, R^2=H)
2b (n=2, R^2=H)
2d (n=2, R^2=CH_3)

2e

Results and Discussion

I. Scope and Limitations of the Enantioselective Hydrophosphonylation with Cyclic Phosphites via Lanthanoid Heterobimetallic Catalysis. A. Dependence on the Starting Material: The Variation of the Substitution Pattern. All hydrophosphonylation reactions of 3-thiazolines[10] **2** with cyclic phosphites **1b**−**d** (Scheme 3), catalyzed by the YbPB complex, were performed under the previously optimized conditions[7] for the reaction using dimethyl phosphite **1a**. Using 20 mol % of (*S*)-YbPB, we were pleased to find the formation of solely *R*-configured products **3b**−**d** (entries 2−4, Table 1) in excellent yield (87%−99%) and enantioselectivity (92%−97% ee). Surprisingly, this reaction proceeds with high enantioselection and high conversion independently of the type of the involved cyclic phosphite. Regarding the imine counterpart, variation of the substitution pattern of the 3-thiazoline **2** also seems to have only little effect on the enantioselectivity. The presence of sterically demanding substituents such as the cyclohexyl group in spiroderivatives **2d** and **2e** just slightly decreases the chemical yield of the corresponding products **3e**−**h** (entries 5−8, Table 1) without any change in the enantioselectivity. Nevertheless, both of these thiazolines can be hydrophosphonylated with yields above 80% in a highly enantioselective manner choosing the appropriate combination of thiazoline and cyclic phosphite.

The method for the workup depends on the type of starting material in the hydrophosphonylation reaction. For our model compound **3a** we established a workup via the corresponding hydrochloride (workup A). However, this workup proved to be disadvantageous in the case of **3b**−**h**. While dimethyl (2,2,5,5-tetramethyl-3-thiazolidin-4-yl)phosphonate **3a** could easily be separated from side products by workup A, precipitates and insufficient

(5) The catalytic enantioselective concepts for the preparation of α-hydroxy- and α-amino phosphonates have been summarized in: Groger, H.; Hammer, B. *Chem. Eur. J.* **2000**, *6*, 943−948.

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(10) Independently of the substitution pattern thiazolidinylphosphonates exhibit a remarkably large $^3J_{PC}$ coupling (21−25 Hz) at the acetalic carbon of the heterocycle and an unusual small vicinal $^3J_{PC}$ coupling (2−3 Hz) in α-position on R^2, which is often invisible. See also ref 7a. For a similar system refer to: Buchman, G. W.; Morin, F. G. *Can. J. Chem.* **1977**, *55*, 2885−2892.

Table 1. Enantioselective Hydrophosphonylation Reaction According to Scheme 2 Using (*S*)-YbPB (THF/toluene (1:7), 50 °C, 48 h, 5 equiv phosphite)

entry		R^1/R^1	R^2/R^2	R^3/R^3	YbPB[a] (mol %)	yield[b] (%) workup A	yield[b] (%) workup B	ee[c] (%)
1	**3a**[d]	Me/Me	Me/Me	Me/Me	20	86	90	93 (*R*)
2	**3b**	$-(CH_2)_3-$	Me/Me	Me/Me	20	66	99	97 (*R*)
3	**3c**	$-CH_2C(CH_3)_2CH_2-$	Me/Me	Me/Me	20	95	90	92 (*R*)
4	**3d**	$-CH_2CH=CHCH_2-$	Me/Me	Me/Me	20	27	87	93 (*R*)
5	**3e**	$-(CH_2)_3-$	Me/Me	$-(CH_2)_5-$	20	59	61	97 (*R*)
6	**3f**	$-CH_2C(CH_3)_2CH_2-$	Me/Me	$-(CH_2)_5-$	20	55	82	98 (*R*)
7	**3g**	$-(CH_2)_3-$	$-(CH_2)_5-$	Me/Me	20	61	85	97 (*R*)
8	**3h**	$-CH_2C(CH_3)_2CH_2-$	$-(CH_2)_5-$	Me/Me	20	53	69	96 (*R*)
9	**3c**	$-CH_2C(CH_3)_2CH_2-$	Me/Me	Me/Me	10		88	95 (*R*)
10	**3c**	$-CH_2C(CH_3)_2CH_2-$	Me/Me	Me/Me	5.0		89	96 (*R*)
11	**3c**	$-CH_2C(CH_3)_2CH_2-$	Me/Me	Me/Me	2.5		95	97 (*R*)
12	**3c**	$-CH_2C(CH_3)_2CH_2-$	Me/Me	Me/Me	1.0		72	25 (*R*)
13	**3c**	$-CH_2C(CH_3)_2CH_2-$	Me/Me	Me/Me	0.5		46	13 (*R*)
14	**3c**	$-CH_2C(CH_3)_2CH_2-$	Me/Me	Me/Me	0.1		43	13 (*R*)
15	**3h**	$-CH_2C(CH_3)_2CH_2-$	$-(CH_2)_5-$	Me/Me	2.5		66	96 (*R*)
16[e]	**3c**	$-CH_2C(CH_3)_2CH_2-$	Me/Me	Me/Me	2.5		99	99 (*R*)
17[f]	**3c**	$-CH_2C(CH_3)_2CH_2-$	Me/Me	Me/Me	2.5		53	99 (*R*)

[a] Catalyst with the *S* configuration of BINOL was used. [b] Yields are given for isolation of the product via the corresponding hydrochloride (workup A) and via direct chromatography (workup B). [c] The enantiomeric excess (ee) was determined by chiral stationary phase HPLC analysis. The absolute configuration is given in parentheses. It was determined via crystal structure analysis for **3a** previously[7] and extended to the other products **3** by comparison of the relative eluation from the chiral HPLC. [d] The formation of (*S*)-**3a** via enantioselective hydrophosphonylation using (*R*)-YbPB has already been reported in detail.[7] [e] 2.5 equiv of phosphite used. [f] 1 equiv of phosphite used.

aqueous solubility of the corresponding hydrochlorides lowered the yields of the new products **3b**−**h** significantly in some cases. As a consequence, we preferred the direct isolation of the products via chromatography without converting the thiazolidinyl phosphonates into their corresponding hydrochlorides (workup B).

In this connection it is noteworthy that the unsaturated more bulky cyclic phosphite **1d** undergoes hydrophosphonylation successfully. The resulting allylic bis-ester-protected thiazolidinyl phosphonate **3d** is formed with an enantioselectivity of 93% ee (entry 4, Table 1). However, only the nonacidic workup B leads to the isolation of the product in high yield. Since the saturated cyclic six-membered phosphonate esters **3b** and **3c** formed by phosphites **1b** and **1c** might have an enhanced stability toward an ester cleavage compared to that formed by dimethyl phosphite (like **3a**), the cyclic allyl-ester moiety introduces a more acid labile protecting group.[11] Isolation of **3d** via the corresponding hydrochloride (workup A) diminishes the yield to 27%, indicating partial acidolytic decomposition of **3d**. This dramatic depression of chemical yield was not observed for the acidic workup of any of the other thiazolidinyl phosphonates.

B. Dependence on the Concentrations of the Catalyst and the Phosphite. To investigate a possible improvement of the lanthanoid heterobimetallic catalysis using cyclic phosphites, we investigated the hydrophosphonylation of 2,2,5,5-tetramethyl-3-thiazoline **2c** with the cyclic phosphite **1c** in greater detail. The amount of the (*S*)-YbPB catalyst involved in the reaction was reduced from 20 mol % to 0.1 mol % stepwise. If the utilization of cyclic phosphites **1b**−**d** represents an appropriate method to enhance the performance of the YbPB catalysis compared with dimethyl phosphite, we should be able to reduce the required amount of the catalyst while maintaining yield and enantioselectivity above 90%. The dependence of formation of (*R*)-**3c** on the concentration of the (*S*)-YbPB catalyst is listed in Table 1 (entries 3 and 9−14) and visualized in Figure 2. Figure 2 also shows the dependence of the formation of (*S*)-**3a** on the amounts of (*R*)-YbPB (3.0−20 mol % range) as reported previously.[7] Using the cyclic phosphite **1c** instead of dimethyl phosphite in YbPB-catalyzed hydrophosphonylation of the thiazoline **2c**, the concentration of the catalyst can be reduced significantly to 2.5 mol % without suppression of yields or ee's. Amounts below 2.5 mol % result in both low yields and low selectivity in the formation of **3c**. A different behavior is observed when the acyclic dimethyl phosphite is used in the hydrophosphonylation reaction, as illustrated by the formation of **3a** (Figure 2). While the enantioselectivity remains on a high level, the chemical yield decreases continuously with respect to decreasing catalyst amounts even with a prolonged reaction time (90 h). This difference is most obvious in the range between 2.5 and 5.0 mol % YbPB: while the yield of **3a** drops from 60% at 5.0 mol % down to 6% at 3.0 mol %, the yield of **3c** even improves from 89% at 5.0 mol % to 95% at 2.5 mol %. To extend these results, we carried out the hydrophosphonylation of the

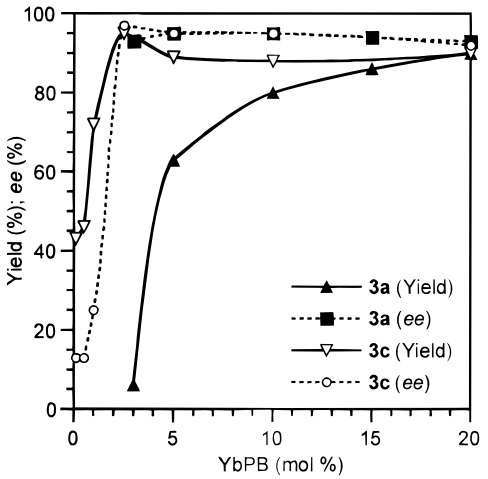


Figure 2. Dependence of formation of (*R*)-**3c** on the amounts of (*S*)-YbPB (0.1−20 mol %, 48 h) and (*S*)-**3a** on the amounts of (*R*)-YbPB (3.0 mol %, 90 h and 5.0−20 mol %, 40 h)

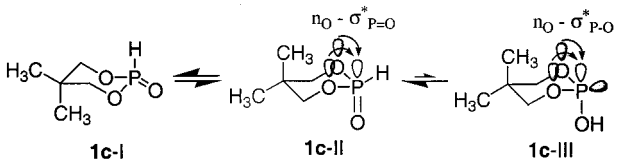
(11) Kocienski, P. J. *Protecting Groups*; Thieme Verlag: Stuttgart, 1994; pp 10−11 and 139−145.

R^3 substituted 3-thiazoline **2e** with the cyclic phosphite **1c** at low catalyst concentration (entry 15, Table 1). We were pleased to find that the results of catalysis with 20 mol % YbPB could be reproduced using just 2.5 mol % catalyst. The next step in the course of our investigation was dedicated to the dependence of enantioselectivity and yield on the concentration of the cyclic phosphite (entries 11, 16−17, Table 1) in the catalysis under the optimized conditions. Therefore 5.0, 2.5, and 1.0 equiv of phosphite **1c** were used for the hydrophosphonylation of the thiazoline **2c**. The results indicate that a surplus of phosphite is needed to maintain high yield, but it can be reduced from 5.0 to 2.5 equiv without any loss in performance. These smaller amounts of phosphite involved in the reaction even improve the catalysis slightly,[12] to 99% yield and 99% ee. So, the best results in enantioselective hydrophosphonylation are obtained with 2.5 mol % (*S*)-YbPB catalyst and 2.5 equiv of phosphite at 50 °C in THF/toluene (1:7) within 48 h. Using these conditions almost quantitative yield and complete enantioselectivity have been obtained for **3c** (entry 16, Table 1).

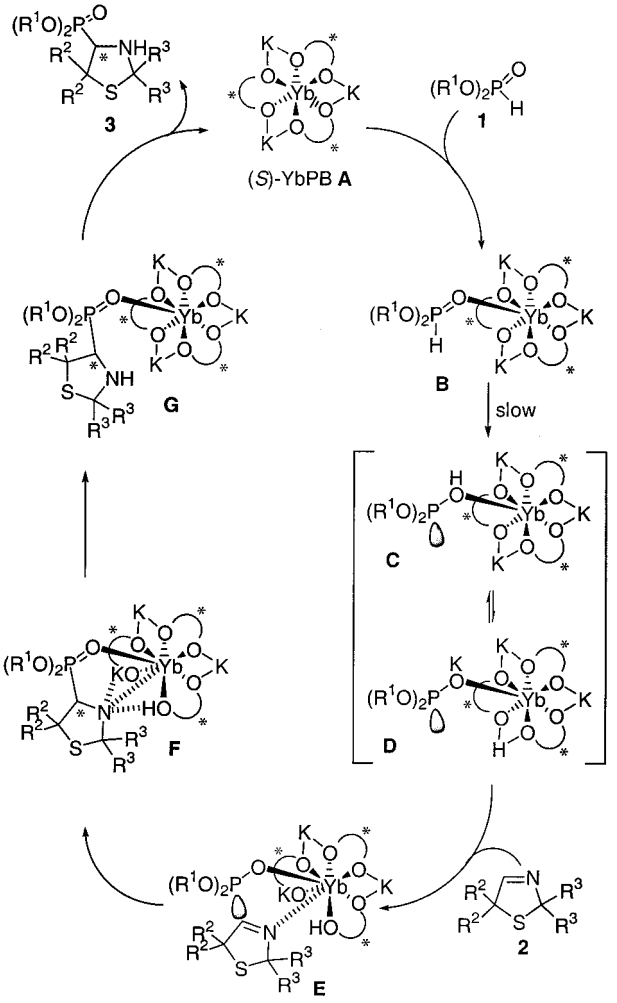
C. What Causes the Different Behavior of Cyclic and Acyclic Phosphites? Mechanistic considerations on YbPB Catalysis. Cyclic phosphites have been shown to be potential substitutes for acyclic phosphites to enhance the performance of the hydrophosphonylation catalyzed by the lanthanoid BINOL bimetal catalyst YbPB. First we will have a look at the hydrophosphonylation involving cyclic phosphites. The dependence of performance of the catalysis on the concentration of the catalyst is visualized in Figure 2 for the formation of the α-amino phosphonate **3c**. The course of the graph exhibits the expected characteristics for a catalytic reaction. There is a certain minimal concentration of the catalyst that is needed to maintain the catalyzed reaction path. If the concentration falls below this critical value, different and less selective reaction pathways become favored. This is probably due to irreversible inactivation (poisoning) or change of constitution (decomposition) of the active catalyst at low concentrations, which causes a breakdown in both chemical yield and selectivity. The observed dependence differs from that using the acyclic dimethyl phosphite **1a** in the case of the formation of α-amino phosphonate **3a**. While the yield decreases with decreasing concentration of YbPB, the enantioselectivity remains high, indicating that the catalyzed reaction path is still favored exclusively. Why should chemical yield suffer from hydrophosphonylation with acyclic phosphites and not enantioselectivity?

The esters of phosphorous acid are known to undergo a phosphite−phosphonate tautomerism, with the phosphonate tautomer as the almost exclusively favored form.[13] The tautomers **1c**-I/**1c**-II (phosphonate) and **1c**-III (phosphite) in Scheme 4 represent such an example. Only the phosphite tautomer, bearing a lone pair (a nucleophilic center) at the phosphorus atom, is able to undergo the nucleophilic addition to the C=N double bond, resulting in a C−P bond formation. Regarding the rich surplus of the (inactive) phosphonate tautomer **1c**-II and the higher nucleophility of the P=O compared with the P−O−H oxygen, the catalyst should be completely coordinated by this tautomer. However, to undergo the hydrophosphonylation reaction successfully, the coordinated phosphonate tautomer has to be converted into the (active) phosphite tautomer **1c**-III. The first combination just represents an inactivated catalyst. Thus referring to Scheme 5 the conversion of structure **B** to **C** and/or **D** is a key step in the catalytic cycle. As dimethyl phosphite actually consists of dimethyl phosphonate and hardly converts into the corresponding dimethyl phosphite species, the catalyst is mainly blocked effectively by the inactive form of the starting material. We believe that *cyclic* phosphites (actually phosphonates) are convertible into the corresponding phosphite tautomers more easily. This difference in the state of tautomerism of cyclic and acyclic phosphites should be caused by two effects. On one hand tautomeric conversion is favored for cyclic

Scheme 4. Anomeric Effect at Cyclic Phosphite 1c



Scheme 5. Refined Catalytic Cycle for the YbPB-Catalyzed Hydrophosphonylation of 3-Thiazolines



(12) The required amount of YbPB cannot be shifted below 2.5 mol % even when 2.5 equiv instead of 5 equiv of phosphite is used.

(13) (a) Mastrykukova, T. A.; Aladzheva, I. M.; Leont'eva, I. V.; Petrovski, P. V.; Fedin, E. I.; Kabachnik, M. I. *Pure Appl. Chem.* **1980**, *52*, 945−957, and references therein. (b) Kosolapoff, G. M.; Maier, L. *Organic Phosphorus Compounds*; John Wiley & Sons Inc: New York, 1973; Vol. 5.

phosphonates due to the stabilization[14] of the corresponding cyclic phosphite tautomers compared to the acyclic analogues. On the other hand the conversion of the conformationally flexible[15] cyclic phosphonates (like **1c**-I/**1c**-II) may be favored by a $n_O-\sigma^*_{P=O}$ anomeric effect, preferably established in cyclic phosphites due to fixation of geometry as outlined in Scheme 4. Ab initio exploration of the two HF/6-31G** optimized chair conformations (phosphonate tautomer) of the cyclic phosphite **1c** reveals an electronic stabilization (1.70 kcal/mol) of that conformer with an axial orientation of the oxo ligand (**1c**-II, Scheme 4) versus that with the equatorial one (**1c**-I). Population of the $\sigma^*_{P=O}$ and therefore depletion of $\sigma_{P=O}$ is monitored in conformer **1c**-II as a consequence of the mentioned stereoelectronic effect.[16] Furthermore this anomeric effect increases negative partial charge at the mentioned oxygen atom in the calculated conformer **1c**-II. Therefore a migration of the proton is made easier. This anomeric effect is less distinct in acyclic phosphites, since rotation of P−O ester bonds prevents an efficient interaction of the involved orbitals.

The fixation of geometry in cyclic phosphites such as **1b**−**d** provides a second advantageous effect which causes a slight increase in selectivity for the enantioselective catalysis. The cyclic diester system exhibits fewer degrees of freedom, since the rotation around P−O and O−C bonds is suppressed. Therefore cyclic phosphites contain less entropic energy compared with acyclic analogues. This deficiency of entropic energy stabilizes the aggregation of the cyclic phosphite and the catalyst, whereas rotation of the ester ligands in the acyclic phosphite disturbs their aggregation and "chiral fitting" on the asymmetric space of the catalyst. The improved embedding of the reactants on the catalyst leads to better selectivity in general. Regarding the excellent enantioselectivity with dimethyl phosphite, YbPB is already able to coordinate acyclic phosphites efficiently. However, a further slight gain in enantioselectivity of up to 99% ee was achieved even at low catalyst concentrations (below 5 mol %) by utilization of cyclic phosphites. The enhanced affinity of cyclic phosphites for coordination at the catalyst also diminishes the possibility of the catalyst being inactivated by product molecules bound to it. Thus, in conclusion, this developed catalytic system using YbPB in the presence of cyclic phosphites can exhibit the best performance, leading to a (nearly) perfectly catalyzed reaction with 99% ee and 99% yield.

D. Further Mechanistic Considerations on the Lanthanoid BINOL-Catalyzed Hydrophosphonylation: Refinement of the Proposed Mechanism. The structure of the series of lanthanoid BINOL bimetal complexes has been elucidated via X-ray analysis for certain representatives.[17] Our previously proposed mechanism for the lanthanoid BINOL-catalyzed hydrophosphonylation included an initial interaction of the oxo moiety of a phosphorous acid ester of type **1** (namely, dimethyl phosphite) and the oxophilic lanthanoid center. This thesis was corroborated by hints from NMR analysis and LDI-TOF mass spectroscopy. According to experimental results, the thiazoline **2** subsequently is coordinated (and activated) by an N−Yb interaction[18] to participate in the reaction.[7]

Here we want to extend our considerations of the catalytic cycle according to the results of the hydrophosphonylation using cyclic phosphites. The inhibition of the lanthanoid BINOL catalyst by the phosphonate tautomer, as discussed above, can be interpreted as further confirmation of an initial coordination of the phosphonate tautomer of **1** at the lanthanoid center. The conversion of the phosphonate into the phosphite tautomer seems to be a performance-controlling step within the catalytic cycle. This consideration is supported by the influence of the alkali component of the catalyst on the performance of the catalysis. Thiazoline **2c** has been hydrophosphonylated with dimethyl phosphite (5.0 equiv) using 20 mol % of each of the members of the YbMB catalyst family (for M = Li, Na, and K) at 50 °C in THF/toluene (1:7).[19] It turned out that the type of alkali ion used did not influence the enantioselectivity of the reaction. The product **3a** was obtained in 93−94% ee each time. Chemical yields of **3a**, however, turned out to depend remarkably on the type of catalyst (YbLB 39%, YbSB 56%, and YbPB 90% yield). The major influence of the alkali component on catalyst characteristics possibly is caused by the modulation of Brønsted basicity of the binaphthoxy moiety (ROLi < RONa < ROK). The efficiency for capture of the phosphite proton rises with basicity of the binaphthoxy oxygen atoms. Trapping of this proton helps to convert the phosphonate tautomer of **1** into the reactive phosphite tautomer. In addition, the type of alkali component should also influence the asymmetric space of the catalyst. All these considerations are summarized in a refined model of the catalytic cycle (Scheme 5).

II. Scope and Limitations of Enantioselective Hydrophosphonylation via Titanium Tartaric Ester Catalysis Using Cyclic Phosphites. Despite a variety of work on optimization of the titanium-catalyzed hydrophosphonylation of 2,2,5,5-tetramethyl-3-thiazoline **2c** with dimethyl phosphite as reported in our previous paper,[7] the chemical yield and the achievable selectivity was limited to moderate values. A selectivity of 43% ee for this catalytic reaction was achieved with the Sharpless catalyst (Ti(O*i*-Pr)$_2$L-dipt, L-dipt = L-(+)-diisopropyl tartrate) in THF at 20 °C (entry 1, Table 2). The yield could be increased slightly by heating the reaction mixture to reflux, whereas the enantioselectivity remained in the same range (about 45% ee). Herein we report our results of the application of cyclic phosphites in the titanium-catalyzed hydrophosphonylation of 3-thiazolines **2** (Scheme 6).

Generally, substitution of the acyclic dimethyl phosphite by the cyclic phosphite **1c** provides a slight gain in

(14) Six-membered cyclic phosphites such as 2-methoxy[1,3,2]-dioxaphosphinane are known to favor a single chair conformation. That conformer exhibiting the phosphorus lone pair in a equatorial orientation (as in conformer **1c**-III) is significantly stabilized over the corresponding conformer with a axial phosphorus lone pair. The analogous acyclic phosphites are not fixed in such a convenient conformation and therefore are destabilized. For a review of the stereochemical aspects of phosphorus-containing cyclohexanes see: Maryanoff, B. E.; Hutchins, R. O.; Maryanoff, C. A. *Top. Stereochem.* **1979**, *11*, 187−326, and references therein.

(15) Shakirov, I. K.; Safiullin, A. R.; Shagidullin, R. R.; Polozov, A. M.; Nuretdinova, O. N. *Izv. Akad. Nauk Ser. Khim.* **1992**, 2725−2730.

(16) The HF/6-31G** optimized conformer **1c**-II exhibits a slightly prolonged P=O and shortened P−O bonds as a consequence of the established anomeric effect.

(17) Shibasaki, M.; Sasai, H. *Pure Appl. Chem.* **1996**, *68*, 523−530.

(18) According to the work of Kobayashi et al. on the Yb(OTf)$_3$-activated asymmetric aza Diels−Alder reaction, Yb has been shown to activate imine bonds: (a) Ishitani, H.; Kobayashi, S. *Tetrahedron Lett.* **1996**, *37*, 7357−7360. (b) Kobayashi, S.; Nagayama, S. *J. Org. Chem.* **1997**, *62*, 232−233.

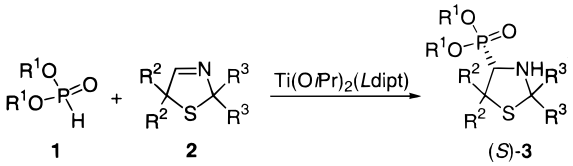
(19) Refer to ref 8a for experimental details.

Table 2. Enantioselective Hydrophosphonylation Reaction According to Scheme 6 Using 20 mol % Ti(O*i*-Pr)$_2$(L-dipt) Catalyst (THF, 20 °C, 5 days, 1 equiv phosphite)

entry		R^1/R^1	R^2/R^2	R^3/R^3	yield (%)[a]	ee (%)[b]
1	**3a**[8]	Me/Me	Me/Me	Me/Me	54	43 (*S*)
2	3c	$-CH_2C(CH_3)_2CH_2-$	Me/Me	Me/Me	39	50 (*S*)
3	3f	$-CH_2C(CH_3)_2CH_2-$	Me/Me	$-(CH_2)_5-$	41	28 (*S*)
4	3h	$-CH_2C(CH_3)_2CH_2-$	$-(CH_2)_5-$	Me/Me	56	74 (*S*)
5	3i	Me/Me	H/H	$-(CH_2)_4-$	43	58 (*S*)
6	3j	$-CH_2C(CH_3)_2CH_2-$	H/H	$-(CH_2)_4-$	34	66 (*S*)
7	3k	Me/Me	H/H	$-(CH_2)_5-$	63	10 (*S*)
8	3l	$-CH_2C(CH_3)_2CH_2-$	H/H	$-(CH_2)_5-$	38	30 (*S*)

[a] Given yields are of crude products which contained the desired product ≥90% according to proton NMR spectra. [b] See footnote *d* of Table 1.

Scheme 6. Enantioselective Hydrophosphonylation Catalyzed by Ti(O*i*-Pr)$_2$(L-dipt)



1 **2** (*S*)-**3**

selectivity of up to 50% ee for **3c** (entry 2, Table 2). On the other hand the accompanying chemical yield decreases to 39%. This depression of yield is quite opposite of the observations at the YbPB catalysis. Furthermore, in contrast with the latter system the Ti(O*i*-Pr)2(L-dipt) system turned out to be much more dependent on the substitution pattern of the thiazoline **2**. The hydrophosphonylation of the thiazolines **2a**−**e** with the cyclic phosphite **1c** exhibits formation of the desired products from 28% ee for **3f** (entry 3, Table 2) up to 74% ee for **3h** (entry 4, Table 2). Large substituents at the R^3 position seem to lower enantioselectivity, and large substituents at the R^2 position seem to raise enantioselectivity. Comparison with the titanium-catalyzed hydrophosphonylation of the thiazolines **2a**−**c** using the acyclic dimethyl phosphite leads to analogous observations (entries 1, 5, 7, Table 2) with a somewhat lower range of enantioselectivity. It is remarkable that a minor change within the structure of R^3 of the thiazoline (cyclohexyl in **2b** vs cyclopentyl in **2a**, entries 7, 8 vs entries 5, 6) leads to dramatic change in enantioselectivity. From a mechanistic point of view these results can be rationalized as follows. Cyclic phosphites bear a certain facility for the enhancement of the enantioselectivity of titanium catalysis for the steric and electronic reasons discussed above. But titanium catalysis is not able to take advantage of the slightly higher reactivity of cyclic phosphites. This might be due to the more restricted spatial conditions within the coordination sphere of the titanium catalyst. Coordination of the more bulky cyclic phosphites such as **1c** (as well as more bulky acyclic phosphites than dimethyl phosphite) possibly is more difficult due to steric interaction. Further confirmation of this idea arises from hydrophosphonylation reactions with sterically more demanding acyclic phosphites (e.g., diethyl and dibutyl phosphite), which diminish the achievable chemical yield to 16% and 4%, respectively.[20]

(20) Schlemminger, I. Unpublished results.

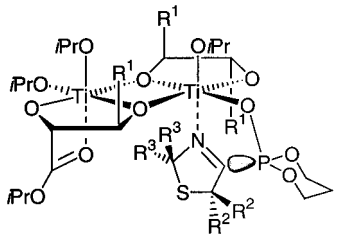


Figure 3. Proposed model of the reactants−catalyst complex during C−P bond formation in the Ti(O*i*-Pr)$_2$L-dipt catalyzed hydrophosphonylation (R^1 = COO*i*-Pr); Compound **1b** is taken as a representative of cyclic phosphites.

According to numerous analytical investigations, the structure of the active Ti(O*i*-Pr)$_2$(L-dipt) complex (Sharpless catalyst) has been assumed as a dimer with each titanium center connected to one neutral carboxylic ester and two alkoxy ligands.[21] In the case of the hydrophosphonylation of thiazolines the coordination of the starting material at the titanium catalyst possibly has to be the following. The phosphite compound substitutes an alkoxy and the thiazoline, the neutral carboxylic ester ligand as depicted in Figure 3.[22] Referring to the described observations the spatial orientation of the coordinated thiazoline within that complex during C−P bond formation should lead to major steric interaction of R^3 with the catalyst residues. The R^2 substituents therefore have to point away from the catalyst. In this way an enhanced steric demand of R^2 can increase enantioselectivity.

Conclusions

In summary, we were able to present a significant improvement in the first efficient enantioselective *de novo* approach to cyclic α-amino phosphonates **3** represented by the lanthanoid BINOL bimetal catalyzed hydrophosphonylation of 3-thiazolines **2**. The performance (enantioselectivity and yield) was increased by utilization of the rigid cyclic phosphites **1b**−**d**. These cyclic phosphites were shown to provide certain amendments within the catalytic cycle for steric and electronic reasons. Various chiral thiazolidinyl phosphonates **3** were synthesized in excellent optical purities of up to 99% ee and high chemical yields of up to 99%. The required amount of catalyst was reduced to 2.5 mol % as well as the required surplus of phosphite. Highest efficiency of the reaction involving cyclic phosphites was achieved using the catalytic system "2.5 mol % (*S*)-YbPB/2.5 equiv phosphite/50 °C/48 h/THF−toluene (1:7)". On the basis of these results the concept of "inactivation of the catalyst" has been introduced. A refinement of the proposed catalytic cycle led to the idea of phosphonate−phosphite conversion as a key step within the catalytic cycle. Further on we presented our experiences using cyclic phosphites in hydrophosphonylation with chiral titanium catalysts. The former modest enantioselectivities using dimethyl phosphite were increased slightly, but efficient application of this system of catalysis is limited to only a few phosphite−thiazoline combinations.

(21) (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.

(22) The analogous transition state has been postulated for the same reaction using dimethyl phosphite; see: Gröger, H. Ph.D. Thesis, University of Oldenburg, 1997.

Experimental Section

General Procedures, Methods, and Materials. NMR spectra were recorded in $CDCl_3$. Chemical shifts are reported relative to TMS ($\delta = 0$) for ^1H NMR and are referred to the $CDCl_3$ resonance ($\delta = 77.00$) for ^{13}C NMR spectra. Mass spectra were measured using chemical ionization with isobutane as reactant gas. Melting points of **3** refer to the racemates. All melting points are uncorrected. In the catalytic asymmetric hydrophosphonylation all reactions were carried out in dry solvents under an argon atmosphere. Tetrahydrofuran (THF) was distilled from $LiAlH_4$. Toluene was distilled from sodium and dichloromethane from anhydrous $CaCl_2$. The enantiomeric excess (ee) was determined by HPLC analysis using DAICEL CHIRALPAK AS with *i*-PrOH/*n*-hexane. The conditions of separation were optimized with the racemic thiazolidinyl phosphonates obtained from BF_3-catalyzed hydrophosphonylation (GP3). The following compounds were synthesized according to known procedures: 2-oxo[1,3,2]-dioxaphosphinane, **1b**,[23] 5,5-dimethyl-2-oxo[1,3,2]-dioxaphosphinane, **1c**,[24] 1-thia-4-aza-spiro[4.5]dec-3-ene, **2b**,[25] 2,2,5,5-tetramethyl-3-thiazoline, **2c**,[26] 2,2-dimethyl-1-thia-4-aza-spiro[4.5]dec-3-ene, **2d**,[26] 2,2-dimethyl-1-thia-3-aza-spiro-[4.5]dec-3-ene, **2e**.[27] The (*S*)-YbPB complex was prepared according to procedures previously described[7] and used as a 0.025 M stock solution in toluene/THF (7:1).

General Procedure for the Catalytic Asymmetric Hydrophosphonylation of the 3-Thiazolines 2 Using (*S*)-YbPB Complexes (GP1). To the (*S*)-YbPB catalyst solution (2.4 mL, 0.06 mmol (*S*)-YbPB in THF/toluene (1:7) resulting in 20 mol % catalyst) were added the corresponding 3-thiazoline **2** (0.3 mmol in 0.5 mL of THF) and the corresponding phosphite **1** (corresponding amount from a 1.50 M stock solution) at 50 °C under an argon atmosphere. For lower amounts of (*S*)-YbPB the appropriate volume of the stock solution is used and filled up to 2.4 mL with THF/toluene, 1:7. After being stirred for 48 h, the product was isolated using two different procedures **A** (isolation via hydrochloride) and **B** (direct isolation). **A**: The mixture was quenched by adding 2 N aqueous hydrochloric acid (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 $MgSO_4$. Removal of the solvent and flash column chromatography gave the desired product (*R*)-**3**. The mentioned chromatography was performed on silica gel. Eluent: at first 100 mL of the eluent hexane/EtOAc (1:1) was used for the separation of the remaining binaphthol component, followed by a change of the eluent to acetone/*n*-hexane (1:10) to isolate the product. **B**: The mixture was hydrolyzed by adding a 1 M solution of water in THF (1 mL) and was left overnight. The solution was decanted from the solids, and the reaction tube and the solids were washed with ethyl acetate (2 × 1 mL). Solvents of the combined organics were removed, and the resulting crude products were dried in vacuo. Purification via flash column chromatography gave the desired product (*R*)-**3**. The mentioned chromatography was performed on silica gel. Eluent: at first 110 mL of diethyl ether was used for separation of the binaphthol component, followed by a change of the eluent to diethyl ether/THF (1:1) to isolate the product. Yields and enatiomeric purities of the compounds synthesized according to GP1 are listed in Table 1. Analytical data agree with racemic compounds synthesized according to GP3.

General Procedure for the Catalytic Asymmetric Hydrophosphonylation of 3-Thiazoline 2 Using the Ti-(O-*i*-Pr)$_2$(L-dipt) Complex (GP2). The Ti(O-*i*-Pr)$_2$(*L*-dipt) complex was generated in situ under an argon atmosphere and at 0 °C starting from L-(+)-diisopropyl tartrate [L-(+)-dipt, (*R*,*R*)-(+)-dipt] (0.23 g, 1 mmol) in THF (5 mL), and titanium-(IV) tetraisopropoxide (0.28 g, 1 mmol) in THF (10 mL). After stirring for 0.5 h at 0 °C and 0.5 h at room temperature the corresponding phosphite **1** (5 mmol) in THF (20 mL) was added. The resulting mixture was treated dropwise with the corresponding 3-thiazoline **2** (5 mmol) in THF (20 mL). After stirring for 100 h at room temperature the solution was hydrolyzed with HCl (1 M). The mixture was extracted with MTBE[28] (3 × 15 mL), and the resulting aqueous phase (containing the product as the corresponding hydrochloride) was made slightly alkaline (pH 8) with NaOH (2 M). The solution was extracted with MTBE (3 × 20 mL), and the combined organic layers were dried with $MgSO_4$. After evaporating the solvent in vacuo the crude products (which contain the products **3** in yields about 85−95%) were colorless or light yellow oils, which crystallized at room temperature in some cases. The ee-values were determined from the crude products. As above, flash chromatography may be used for further purification. Yields and enatiomeric purities of the compounds synthesized according GP1 are listed in Table 2. Analytical data agree with racemic compounds synthesized according GP3.

General Procedure for the BF_3 Catalyzed Hydrophosphonylation of 3-Thiazoline 2 (GP3). The 3-thiazoline **2** (5 mmol) was solved in dichloromethane (20 mL) and treated with 1 equiv of BF_3Et_2O at 0 °C for 1 h. The corresponding phosphite **1** (5 mmol) was added at 0 °C, and the resulting mixture was stirred for 5 days without further cooling. After hydrolysis with water (10 mL) the phases were separated and the aqueous layer was extracted with dichloromethane (2 × 20 mL). The combined organic layers were washed with water and dried with $MgSO_4$. After evaporating the solvent in vacuo the crude products were colorless or light yellow oils, which crystallized at room temperature in some cases. Purification via flash column chromatography (silica gel, eluent: *n*-hexane/*i*-PrOH, 95:5) gave the desired racemic compounds **3**.

4,7-Dihydro-2-oxo-2λ^5-[1,3,2]dioxaphosphepine (1d). The title compound was prepared analogous to literature[23] employing *cis*-but-2-en-1,4-diol in 30% yield: n_D^{20} 1.4950; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.42−4.68 (m, 4 H), 5.61 (t, $^3J_{HH} = 3.6$ Hz, 2 H), 6.56 (d, $^1J_{PH} = 702.3$ Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 62.3 (d, $^2J_{CP} = 6.6$ Hz), 126.8; MS *m*/*z* 135 (MH^+, base peak).

1-Thia-4-azaspiro[4.4]non-3-ene (2a). The title compound was prepared using the modified Asinger reaction[26] employing cyclopentanone in 13% yield: bp 41 °C (6.60 mbar); IR (NaCl) ν 1630 cm^{-1} (C═N); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.67−1.85 (m, 6 H), 2.00−2.04 (m, 2 H), 3.86 (d, $^3J_{HH} < 1$ Hz, 2 H), 7.18 (t, $^3J_{HH} < 1$ Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz, 300 K) δ 24.3, 43.3, 44.1, 97.9, 156.3; MS *m*/*z* 142 (MH^+, base peak).

4-(2-Oxo-2λ^5-[1,3,2]dioxaphosphinan-2-yl)-2,2,5,5-tetramethyl-3-thiazolidine (3b). The title compound was prepared according to GP3 in 52% yield: mp 141 °C; IR (NaCl/$CHCl_3$) ν 3280 (NH), 1255 cm^{-1} (P═O); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.48, 1.50, 1.63 (3 s, 12 H), 2.00−2.20 (m, 2 H), 2.79 (s, 1 H), 3.37 (d, $^2J_{PH} = 18.2$ Hz, 1 H), 4.29−4.60 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.3 (d, $^3J_{CP} = 6.5$ Hz), 28.3, 28.6, 31.9, 32.7, 61.5 (d, $^2J_{CP} = 5.1$ Hz), 66.4, 66.7 (2 d, $^2J_{CP} = 6.5$ Hz, $^2J_{CP} = 6.5$ Hz), 66.8 (d, $^1J_{CP} = 143.9$ Hz), 74.3 (d, $^3J_{CP} = 24.0$ Hz); MS *m*/*z* 266 (MH^+, base peak); HPLC (DAICEL CHIRALPAK AS, *n*-hexane/*i*-PrOH, 9:1, flow 0.5 mL × min^{-1}) t_R 15.0 and 26.3 min. Anal. Calcd for $C_{10}H_{20}NO_3PS$ (265.3): C, 45.27; H, 7.60; N, 5.28; S, 12.08. Found: C, 45.19; H, 7.67; N, 4.99; S, 12.19.

4-(5,5-Dimethyl-2-oxo-2λ^5-[1,3,2]dioxaphosphinan-2-yl)-2,2,5,5-tetramethyl-3-thiazolidine (3c). The title compound was prepared according to GP3 in 76% yield: mp 133 °C; IR (NaCl/$CHCl_3$) ν 3280 (NH), 1250 cm^{-1} (P═O); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.95, 1.06 (2 s, 6 H), 1.43, 1.44, 1.57 (3 s, 12 H), 2.76 (s, 1 H), 3.31 (d, $^2J_{PH} = 17.6$ Hz, 1 H), 3.78−3.91,

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(24) McConnell, R. L.; Coover, H. W. *J. Org. Chem.* **1959**, *24*, 630−635.
(25) Thiel, M.; Asinger, F.; Schmiedel, K. *Liebigs Ann. Chem.* **1958**, *611*, 121−138.
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(27) Hatam, M.; Tehranfar, D.; Martens, J. *Synth. Commun.* **1995**, *25*, 1677−1688.

(28) MTBE = methyl *tert*-butyl ether.

4.09−4.20 (2 m, 4 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.4, 21.76, 28.3, 28.6, 32.0, 32.8, 32.6 (d, $^3J_{CP}$ = 6.5 Hz), 61.6 (d, $^2J_{CP}$ = 6.5 Hz), 66.4 (d, $^1J_{CP}$ = 143.9 Hz), 74.5 (d, $^3J_{CP}$ = 24.0 Hz), 75.4, 75.7 (2 d, $^2J_{CP}$ = 6.6 Hz, $^2J_{CP}$ = 6.8 Hz); MS *m*/*z* 294 (MH^+, base peak); HPLC (DAICEL CHIRALPAK AS, *n*-hexane/*i*-PrOH, 95:5, flow 0.5 mL × min^{-1}) t_R 11.6 and 16.2 min. Anal. Calcd for C12H24NO3PS (293.4): C, 49.13; H, 8.25; N, 4.77; S, 10.93. Found: C, 49.04; H, 8.29; N, 4.62; S, 10.62.

4-(4,7-Dihydro-2-oxo-2λ^5-[1,3,2]dioxaphosphepin-2-yl)-2,2,5,5-tetramethyl-3-thiazolidine (3d). The title compound was prepared according to GP3 in 47% yield: mp 96 °C; IR (NaCl/$CHCl_3$) ν 3270 (NH), 1260 cm^{-1} (P═O); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.46, 1.48, 1.61, 1.63 (4 s, 12 H), 2.87 (s, 1 H), 3.42 (d, $^2J_{PH}$ = 18.2 Hz, 1 H), 4.52, 4.63 (2 d, $^2J_{HH}$ = 19.0 Hz, 2 H), 4.94, 5.03 (2 d, $^2J_{HH}$ = 15.7 Hz, 2 H), 5.72 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.3, 28.5, 31.9, 32.7, 61.7 (d, $^2J_{CP}$ = 6.5 Hz), 63.8, 64.9 (2 d, $^2J_{CP}$ = 8.7 Hz), 66.0 (d, $^1J_{CP}$ = 143.9 Hz), 74.2 (d, $^3J_{CP}$ = 24.0 Hz), 127.2 (d, $^3J_{CP}$ = 5.5 Hz); MS *m*/*z* 278 (MH^+, base peak); HPLC (DAICEL CHIRALPAK AS, *n*-hexane/*i*-PrOH, 9:1, flow 0.5 mL × min^{-1}) t_R 12.6 and 28.6 min. Anal. Calcd for $C_{11}H_{20}NO_3PS$ (277.3): C, 47.64; H, 7.27; N, 5.05; S, 11.56. Found: C, 47.42; H, 7.26; N, 4.86; S, 11.82.

2,2-Dimethyl-3-(2-oxo-2λ^5-[1,3,2]dioxaphosphinan-2-yl)-1-thia-4-azaspiro[4.5]decane (3e). The title compound was prepared according to GP3 in 50% yield: mp 141 °C; IR (NaCl/$CHCl_3$) ν 3300 (NH), 1250 cm^{-1} (P═O); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.48, 1.62 (2 s, 6 H), 1.17−1.90 (m, 10 H), 2.02−2.22 (m, 2 H), 2.68 (s, 1 H), 3.39 (d, $^2J_{PH}$ = 17.6 Hz, 1 H), 4.31−4.61 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.4, 25.2, 25.6, 40.9, 41.4, 26.4 (d, $^3J_{CP}$ = 7.8 Hz), 28.4, 28.8, 59.0 (d, $^2J_{CP}$ = 4.4 Hz), 65.9 (d, $^1J_{CP}$ = 141.7 Hz), 66.5, 66.9 (2 d, $^2J_{CP}$ = 6.5 Hz), 80.1 (d, $^3J_{CP}$ = 21.8 Hz); MS *m*/*z* 306 (MH^+, base peak); HPLC (DAICEL CHIRALPAK AS, *n*-hexane/*i*-PrOH, 9:1, flow 1.0 mL × min^{-1}) t_R 9.7 and 14.3 min. Anal. Calcd for $C_{13}H_{24}NO_3PS$ (305.4): C, 51.13; H, 7.92; N, 4.59; S, 10.50. Found: C, 50.98; H, 8.07; N, 4.37; S 10.72.

3-(5,5-Dimethyl-2-oxo-2λ^5-[1,3,2]dioxaphosphinan-2-yl)-2,2-dimethyl-1-thia-4-azaspiro[4.5]decane (3f). The title compound was prepared according to GP3 in 52% yield: mp 171 °C; IR (NaCl/$CHCl_3$) ν 3290 (NH), 1250 cm^{-1} (P═O); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.01, 1.12 (2 s, 6 H), 1.47, 1.60 (2 s, 6 H), 1.19−1.86 (m, 10 H), 2.74 (s, 1 H), 3.36 (d, $^2J_{PH}$ = 17.8 Hz, 1 H), 3.86−3.95, 4.13−4.21 (2 m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.4, 21.6, 23.4, 25.1, 25.5, 41.0, 41.4, 28.1, 28.7 (d, $^3J_{CP}$ < 2.4 Hz), 32.6 (d, $^3J_{CP}$ = 6.3 Hz), 59.0 (d, $^2J_{CP}$ = 5.9 Hz), 65.5 (d, $^1J_{CP}$ = 144.4 Hz), 75.3, 75.6 (2 d, $^2J_{CP}$ = 5.9 Hz, $^2J_{CP}$ = 7.0 Hz), 80.0 (d, $^3J_{CP}$ = 23.5 Hz); ^{31}P NMR ($CDCl_3$, 202 MHz) δ 19.5; MS *m*/*z* 334 (MH^+, base peak), 184 (MH^+ − H(O)P($OR)_2$]; HPLC (DAICEL CHIRALPAK AS, *n*-hexane/*i*-PrOH, 95:5, flow 0.5 mL × min^{-1}) t_R 14.3 and 16.0 min. Anal. Calcd for $C_{15}H_{28}NO_3PS$ (333.4): C, 54.03; H, 8.46; N, 4.20; S, 9.62. Found: C, 53.94; H, 8.51; N, 4.40; S, 9.34.

2,2-Dimethyl-4-(2-oxo-2λ^5-[1,3,2]dioxaphosphinan-2-yl)-1-thia-3-azaspiro[4.5]decane (3g). The title compound was prepared according to GP3 in 58% yield: mp 166 °C; IR (NaCl/$CHCl_3$) ν 3300 (NH), 1250 cm^{-1} (P═O); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.53, 1.65 (2 s, 6 H), 1.13−1.93 (m, 10 H), 2.00−2.26 (m, 2 H), 2.99 (s, 1 H), 3.36 (d, $^2J_{PH}$ = 18.1 Hz, 1 H), 4.32−4.63 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.4, 25.1, 27.3, 36.1, 38.4, 26.3 (d, $^3J_{CP}$ = 8.9 Hz), 31.8, 32.5, 66.3, 66.6 (2 d, $^2J_{CP}$ = 6.5 Hz), 66.9 (d, $^1J_{CP}$ = 146.0 Hz), 69.1 (d, $^2J_{CP}$ = 6.5 Hz), 73.2 (d, $^3J_{CP}$ = 24.0 Hz); MS *m*/*z* 306 (MH^+, base peak); HPLC (DAICEL CHIRALPAK AS, *n*-hexane/*i*-PrOH, 9:1, flow 1.0 mL × min^{-1}) t_R 8.6 and 16.5 min. Anal. Calcd for $C_{13}H_{24}NO_3PS$ (305.4): C, 51.13; H, 7.92; N, 4.59; S, 10.50. Found: C, 50.95; H, 8.16; N, 4.54; S, 10.56.

4-(5,5-Dimethyl-2-oxo-2λ^5-[1,3,2]dioxaphosphinan-2-yl)-2,2-dimethyl-1-thia-3-azaspiro[4.5]decane (3h). The title compound was prepared according to GP3 in 50% yield: mp 212 °C; IR (NaCl/$CHCl_3$) ν 3290 (NH), 1255 cm^{-1} (P═O); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.02, 1.14 (2 s, 6 H), 1.51, 1.63 (2 s, 6 H), 1.17−2.16 (m, 10 H), 2.82 (s, 1 H), 3.34 (d, $^2J_{PH}$ = 18.4 Hz, 1 H), 3.86−3.97, 4.19−4.24 (2 m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.4, 21.7, 23.6, 25.3, 27.4, 36.1 (d, $^3J_{CP}$ = 2.4 Hz), 38.5, 32.0, 32.7, 32.7, 66.7 (d, $^1J_{CP}$ = 145.4 Hz), 69.7 (d, $^2J_{CP}$ = 5.6 Hz), 73.6 (d, $^3J_{CP}$ = 24.7 Hz), 75.3, 75.7 (2 d, $^2J_{CP}$ = 7.0 Hz, $^2J_{CP}$ = 7.1 Hz); MS *m*/*z* 334 (MH^+, base peak), 184 (MH^+ − H(O)P($OR)_2$]; HPLC (DAICEL CHIRALPAK AS, *n*-hexane/*i*-PrOH, 99:1, flow 0.5 mL × min^{-1}) t_R 53.9 and 60.9 min. Anal. Calcd for $C_{15}H_{28}NO_3PS$ (333.4): C, 54.03; H, 8.46; N, 4.20; S, 9.62. Found: C, 54.26; H, 8.52; N, 4.07; S, 9.40.

Dimethyl (1-Thia-4-azaspiro[4.4]non-3-yl)phosphonate (3i). The title compound was prepared according to GP3 in 6% yield: IR (NaCl/$CHCl_3$) ν 3221 (NH), 1245 cm^{-1} (P═O); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.65−1.95 (m, 7 H), 2.09−2.17 (m, 2 H), 3.05 (ddd, $^3J_{PH}$ = 11.0 Hz, $^3J_{HH}$ = 11.0 Hz, $^2J_{HH}$ = 10.2 Hz, 1 H), 3.17 (ddd, $^2J_{HH}$ = 10.2 Hz, $^3J_{HH}$ = 6.6 Hz, $^3J_{PH}$ = 1.7 Hz, 1 H), 3.32 (ddd, $^2J_{PH}$ = 14.9 Hz, $^3J_{HH}$ = 11.0 Hz, $^3J_{HH}$ = 6.6 Hz, 1 H), 3.77, 3.79 (2 d, $^3J_{PH}$ = 10.4 Hz, $^3J_{PH}$ = 11.0 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.8, 24.3, 39.8, 43.4, 37.0 (d, $^2J_{CP}$ = 1.8 Hz), 52.7, 53.4 (2 d, $^2J_{CP}$ = 6.6 Hz, $^2J_{CP}$ = 5.7 Hz), 58.4 (d, $^1J_{CP}$ = 155.0 Hz), 86.5 (d, $^3J_{CP}$ = 21.8 Hz); MS *m*/*z* 252 (MH^+, base peak); HPLC (DAICEL CHIRALPAK AS *n*-hexane/*i*-PrOH, 90:10, flow 0.5 mL × min^{-1}) t_R 12.5 and 13.5 min. Anal. Calcd for $C_9H_{18}NO_3PS$ (251.3): C, 43.02; H, 7.22; N, 5.57; S, 12.76. Found: C, 43.06; H, 7.20; N, 5.63; S, 12.70.

3-(5,5-Dimethyl-2-oxo-2λ^5-[1,3,2]dioxaphosphinan-2-yl)-1-thia-4-azaspiro[4.4]nonane (3j). The title compound was prepared according to GP3 in 25% yield: mp 119 °C; IR (NaCl/$CHCl_3$) ν 3270 (NH), 1265 cm^{-1} (P═O); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.04, 1.16 (2 s, 6 H), 1.75−2.22 (m, 8 H), 2.73 (s, 1 H), 3.21 (ddd, $^3J_{PH}$ = 11.0 Hz, $^3J_{HH}$ = 11.0 Hz, $^2J_{HH}$ = 10.4 Hz, 1 H), 3.29 (ddd, $^2J_{HH}$ = 10.4 Hz, $^3J_{HH}$ = 6.6 Hz, $^3J_{PH}$ = 2.2 Hz, 1 H), 3.51 (ddd, $^2J_{PH}$ = 13.8 Hz, $^3J_{HH}$ = 11.0 Hz, $^3J_{HH}$ = 6.6 Hz, 1 H), 3.89−3.98, 4.23−4.30 (2 m, 4 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.4, 21.7, 24.1, 24.4, 40.1, 43.5, 32.7 (d, $^3J_{CP}$ = 6.5 Hz), 36.8, 57.7 (d, $^1J_{CP}$ = 152.2 Hz), 75.5, 75.7 (2 d, $^2J_{CP}$ = 6.1 Hz, $^2J_{CP}$ = 6.5 Hz), 87.0 (d, $^3J_{CP}$ = 21.8 Hz); MS *m*/*z* 292 (MH^+, base peak); HPLC (DAICEL CHIRALPAK AS, *n*-hexane/*i*-PrOHmp, 9:1, flow 1.0 mL × min^{-1}) t_R 51.1 and 76.6 min. Anal. Calcd for $C_{12}H_{22}NO_3PS$ (291.4): C, 49.47; H, 7.61; N, 4.81; S, 11.01. Found: C, 49.56; H, 7.59; N, 4.81; S, 11.24.

Dimethyl (1-Thia-4-azaspiro[4.5]dec-3-yl)phosphonate (3k). The title compound was prepared according to GP3 in 33% yield: mp 63 °C; IR (NaCl/$CHCl_3$) ν 3260 (NH), 1247 cm^{-1} (P═O); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.20−1.82 (m, 10 H), 2.08−2.27 (m, 1 H), 2.89, 3.07 (2 m, 2 H), 3.46 (m, 1 H), 3.74, 3.78 (2 d, $^3J_{PH}$ = 9.8 Hz, $^3J_{PH}$ = 9.2 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 75 MHz) d 22.4, 24.1, 24.4, 38.7, 39.3, 34.5, 51.5, 52.2 (2 d, $^3J_{CP}$ = 6.6 Hz, $^3J_{CP}$ = 6.0 Hz), 56.1 (d, $^1J_{CP}$ = 154.1 Hz), 81.7 (d, $^3J_{CP}$ = 21.1 Hz); MS *m*/*z* 266 (MH^+, base peak); HPLC (DAICEL CHIRALPAK AS, *n*-hexane/*i*-PrOH, 90:10, flow 0.5 mL × min^{-1}) t_R 10.0 and 11.4 min. Anal. Calcd for $C_{10}H_{20}NO_3PS$ (265.3): C, 45.27; H, 7.60; N, 5.28; S, 12.09. Found: C, 45.32; H, 7.66; N, 5.19; S, 12.18.

3-(5,5-Dimethyl-2-oxo-2λ^5-[1,3,2]dioxaphosphinan-2-yl)-1-thia-4-azaspiro[4.5]decane (3l). The title compound was prepared according to GP3 in 72% yield: mp 125 °C; IR (NaCl/$CHCl_3$) ν 3290 (NH), 1265 cm^{-1} (P═O); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.03, 1.12 (2 s, 6 H), 1.21−1.90 (m, 10 H), 2.16 (s, 1 H), 3.06 (ddd, $^3J_{PH}$ = 11.0 Hz, $^3J_{HH}$ = 11.0 Hz, $^2J_{HH}$ = 10.4 Hz, 1 H), 3.18 (ddd, $^2J_{HH}$ = 10.4 Hz, $^3J_{HH}$ = 6.1 Hz, $^3J_{PH}$ = 1.7 Hz, 1 H), 3.61 (ddd, $^2J_{PH}$ = 14.3 Hz, $^3J_{HH}$ = 11.0 Hz, $^3J_{HH}$ = 6.1 Hz, 1 H), 3.86−3.99, 4.19−4.27 (2 m, 4 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.3, 21.6, 23.6, 25.2, 25.7, 40.0, 40.5, 32.6 (d, $^3J_{CP}$ = 5.9 Hz), 35.6, 56.4 (d, $^1J_{CP}$ = 151.2 Hz), 75.4, 75.7 (2 d, $^2J_{CP}$ = 6.3 Hz, $^2J_{CP}$ = 6.5 Hz), 83.4 (d, $^3J_{CP}$ = 21.1 Hz); MS *m*/*z* 306 (MH^+, base peak); HPLC (DAICEL CHIRALPAK AS *n*-hexane/*i*-PrOH, 9:1, flow 1.0 mL × min^{-1}) t_R 49.7 and 63.0 min. Anal. Calcd for $C_{13}H_{24}NO_3PS$ (305.4): C, 51.13; H, 7.92; N, 4.59; S, 10.50. Found: C, 50.83; H, 8.08; N, 4.34; S, 10.63.

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