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First Catalytic Asymmetric Hydrophosphonylation of Cyclic Imines: Highly Efficient Enantioselective Approach to a 4-Thiazolidinylphosphonate via Chiral Titanium and Lanthanoid Catalysts

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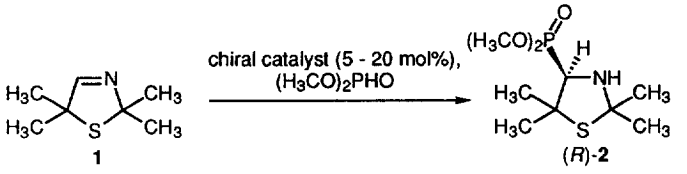
Abstract: The catalytic and enantioselective hydrophosphonylation of a cyclic imine, namely the 3-thiazoline **1**, is described. We have discovered a highly efficient enantioselective *de novo* approach to the pharmaceutically interesting 4-thiazolidinylphosphonate **2** using either titanium or lanthanoid chiral catalysts, which gives excellent enantiomeric purities (up to 98 %*ee*) and high chemical yields.

A general investigation of the asymmetric hydrophosphonylation of a cyclic C=N compound has been carried out for the first time, using a catalytic chiral titanium or lanthanoid complex to give the pharmaceutically interesting 4-thiazolidinylphosphonate[1] (*R*)-**2**, starting from the 2,2,5,5-tetramethyl-3-thiazoline **1**.



To this end **1**[1b] was treated with chiral titanium-diol-complexes (20 mol%)[2] (known to be efficient catalysts in several enantioselective reactions)[3] in THF solution, followed by the addition of an equimolar amount of dimethyl phosphite. The desired products of type (*R*)-**2** were obtained in up to 62 % chemical yield depending on the work-up conditions employed. With regard to the enantioselectivity of the formation of (*R*)-**2**, the use of titanium-(L-dipt)-catalysts led to *ee* values of up to 45 % *ee* (see table 1/entries 1,2).

Table 1. Asymmetric synthesis of **2** via chiral titanium complex catalyzed hydrophosphonylation of **1**

entry	chiral catalyst[a)] (20 mol%)	temperature (°C)	time (d)	yield[b)] (%)	*ee* [c)] (%)
1	Ti(O*i*-Pr)$_2$(L-dipt)	20	6	14 (54)	43 (*R*)
2	Ti(O*i*-Pr)$_2$(L-dipt)	65 (Δ)	4	42 (67)	45 (*R*)
3	Ti(O*i*-Pr)$_2$(TAD)	65 (Δ)	4	57 (64)	46 (*S*)
4	Ti(O*i*-Pr)$_2$(BIN)	65 (Δ)	5	62 (71)	29 (*R*)

[a] L-dipt = L-(+)-diisopropyl tartrate; TAD = (-)-(*R,R*)-TADDOL; BIN = (*R*)-(+)-binaphthol; [b] The yields given in parantheses are for the crude products, which contained the product **2** in >85-90 % yield (according to the proton NMR spectra); [c] The enantiomeric excesses of **2** were determined by chiral stationary phase HPLC analysis of the crude products. The absolute configuration of the major enantiomer was determined as described in reference 6.

The absolute configuration of the major product enantiomer changed when L-(+)-dipt was replaced with (*R,R*)-(-)-TADDOL, both of which were prepared from L-(+)-tartaric acid. However, the asymmetric hydrophosphonylation of **1** was limited to *ee* values of about 45 % *ee*. Consequently, we attempted to further optimize the optical purities of the phosphite adducts (*R*)-**2**. In this connection, the success of heterobimetallic lanthanoid catalysts in a wide range of enantioselective reactions[4,5] encouraged us to apply these catalysts to this field of asymmetric synthesis of 4-thiazolidinylphosphonates. To produce the optically active α-aminophosphonate (*R*)-**2** the 3-thiazoline **1** was treated with 5 equivalents of dimethyl phosphite in the presence of the lanthanoid-potassium-binaphthoxide-complexes [(*R*)-LnPB]. By the use of 20 mol% of LaK$_3$tris(binaphthoxide) [(*R*)-

LPB] in THF/toluene (1:7) at room temperature, which has been shown to be the most efficient catalytic system in asymmetric hydrophosphonylation of acyclic imines,[4] only modest enantioselectivity of 61 % *ee* accompanied by a modest chemical yield of 53 % was observed in the formation of (*R*)-**2** after 144 h (table 2/entry 1).

Table 2. Asymmetric synthesis of **2** via chiral lanthanoid complex catalyzed hydrophosphonylation of **1**

entry	chiral catalyst[a] (mol%)	temperature	time (h)	yield (%)	*ee* [b] (%)
1	(*R*)-LPB (20)	rt	144	53	61 (*R*)
2	(*R*)-LPB (20)	50 °C	50	55	64 (*R*)
3	(*R*)-PrPB (20)	50 °C	50	51	84 (*R*)
4	(*R*)-SmPB (20)	50 °C	40	97	93 (*R*)
5	(*R*)-GdPB (20)	50 °C	50	77	95 (*R*)
6	(*R*)-DyPB (20)	50 °C	50	76	97 (*R*)
7	(*R*)-YbPB (20)	50 °C	50	90	96 (*R*)
8	(*R*)-YbPB (20)	rt	50	86	98 (*R*)
9	(*R*)-YbPB (10)	50 °C	40	80	95 (*R*)
10	(*R*)-YbPB (5)	50 °C	40	63	95 (*R*)

[a] P = potassium; B = (*R*)-(+)-binaphthol; [b] The enantiomeric excess was determined by chiral stationary phase HPLC analysis and the absolute configuration of the major enantiomer was determined as described in reference 6.

The efficiency of the reaction was improved by increasing the reaction temperature to 50 °C, by means of which we obtained (*R*)-**2** in nearly unchanged chemical yield and enantioselectivity but in a significantly reduced 50 h reaction time (entry 2). Our further efforts to increase the efficiency of the reaction by investigating the influence of varying the lanthanoid metal component in the catalyst were therefore carried out at this temperature. A substantial increase in the *ee* values was obtained by using Sm, Gd and Dy, with *ee* values of up to 97 % *ee* and good chemical yields (entries 4-6) being obtained. In addition, we were pleased to obtain the desired phosphite adduct (*R*)-**2** in both excellent enantioselectivity (96 % *ee*) and high chemical yield by using (*R*)-YbPB complex as a heterobimetallic lanthanoid catalyst (entry 7). Furthermore, (*R*)-YbPB showed highly effective catalytic properties in terms of the reaction rate. By carrying out the phosphite addition with (*R*)-YbPB catalyst at room temperature, the product (*R*)-**2** was obtained with in high (86 %) chemical yield and with excellent *ee* (98 % *ee*, entry 8). This is, to our knowledge, the highest enantioselectivity ever to have been observed in a catalytic asymmetric hydrophosphonylation. Reduction of the catalyst loading to first 10 mol% and then 5 mol% gave the α-aminophosphonate (*R*)-**2** after 40 h in still satisfactory 80 % and 63 % yields respectively, with maintenance of the high enantiomeric excesses (entries 9,10).

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