# Catalytic Concepts for the Enantioselective Synthesis of $\alpha$-Amino and $\alpha$-Hydroxy Phosphonates

**Harald Gröger*[a] and Benedikt Hammer[a]**

**Abstract:** The enantioselective synthesis of $\alpha$-amino- and $\alpha$-hydroxy phosphonates by catalytic processes has attracted considerable interest in the last few years, not least because of the pharmaceutical interest in such compounds. This article contains a compilation of the asymmetric synthesis methods developed to date. The described synthetic routes are based on different catalytic concepts, namely, hydrogenation, reductions, dihydroxylation, aminohydroxylation, and hydrophosphonylation.

**Keywords:** asymmetric catalysis · asymmetric synthesis · hydrogenations · hydrophosphonylations · reductions

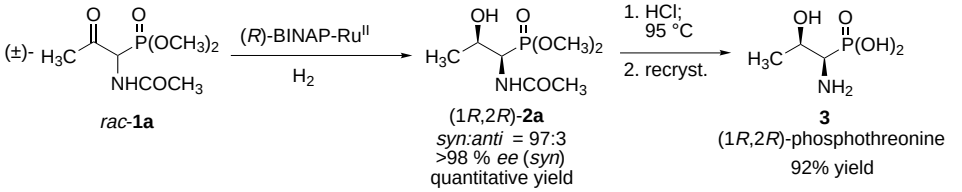
## Introduction

Intense efforts have been made in the stereoselective synthesis of $\alpha$-amino- and $\alpha$-hydroxy-functionalized phosphonates,[1] since these molecules are important biologically active compounds, which are widely used in particular for pharmaceutical applications, for example, as enzyme inhibitors of renin, EPSP synthase, and HIV protease.[2] The growing need for enantiomerically pure $\alpha$-functionalized phosphonates can be seen, not at least, in a remarkably increased number of their industrially manufactured substitutes.[3]

Interestingly, however, until recently most of the asymmetric syntheses were realized by diastereoselective routes that proceeded only with stoichiometric amounts of a chiral auxiliary. For a long time an efficient catalytic asymmetric approach was not available in spite of the obvious advantages of catalytic processes. This limitation has now been overcome, since several protocols of efficient catalytic syntheses for these target molecules have been developed in the last few years. These asymmetric reactions, highlighted in the following, are based on different catalytic concepts, namely hydrogenation, reduction, dihydroxylation, aminohydroxylation, and hydrophosphonylation processes.

## A. Asymmetric hydrogenation

The extension of the BINAP-Ru$^{II}$-catalyzed hydrogenation[4] (BINAP = [1,1′-binaphthalene]-2,2′-diylbis(diphenylphosphane)) to an efficient method for the preparation of $\alpha$-amino phosphonates (with an additional hydroxy-functionality in the $\beta$-position) has been impressively demonstrated by Noyori et al.[5] For example, starting from the racemic $\alpha$-acetamido $\beta$-keto phosphonic ester **1a** the desired product (1*R*,2*R*)-**2a** was prepared with a high diastereoselectivity (*syn*:*anti* ratio 97:3) and an excellent enantioselectivity of $\geq$98% *ee* (Scheme 1). Furthermore, the product (1*R*,2*R*)-**2a** was successfully converted to the enantiomerically pure (1*R*,2*R*)-phosphothreonine **3** in 92% yield.[5a]




Scheme 1. Asymmetric hydrogenation of a racemic keto phosphonate by dynamic kinetic resolution.

The concept of this reaction is based on an asymmetric BINAP-Ru$^{II}$-catalyzed hydrogenation of a racemic $\alpha$-acetamido $\beta$-keto phosphonate *rac*-**1** by dynamic kinetic resolution (Scheme 2). In particular, the prerequisite for this highly diastereo- and enantioselective formation of $\alpha$-acetamido $\beta$-keto phosphonates (1*R*,2*R*)-**2** is the combination of the configurational lability of the $\alpha$-substituted $\beta$-keto phosphonate **1**, the electronegative nature of the $\alpha$-amido group, and the chiral discriminating properties of the (*R*)-BINAP-Ru$^{II}$ catalyst in the stereoselective hydrogenation step. This hydrogenation protocol works also efficiently when using the

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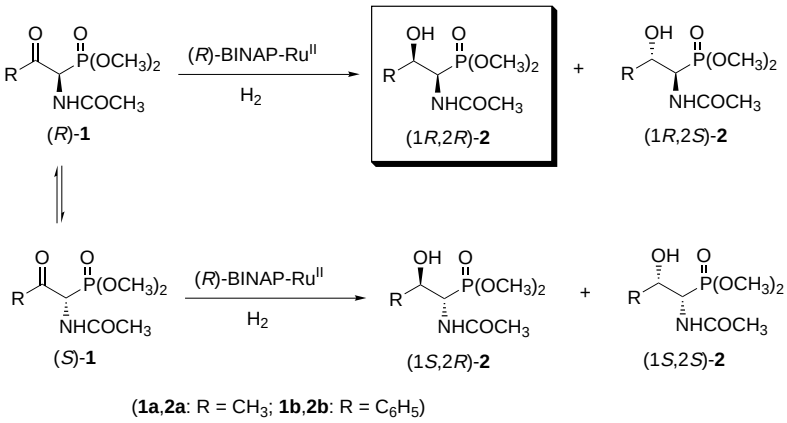



Scheme 2. Concept of the Noyori catalytic asymmetric hydrogenation by dynamic kinetic resolution.

analogous phenyl-substituted keto phosphonate *rac*-**1b** as a substrate (95% *ee*, *syn*:*anti* ratio 98:2).[5a]

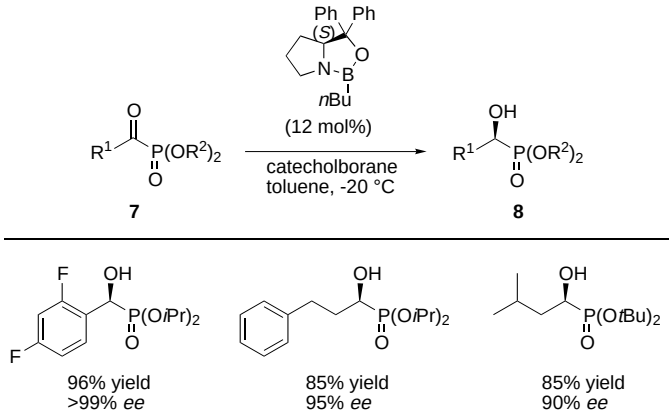
Applying this concept, Noyori et al. also developed a practical catalytic approach to the $\alpha$-hydroxy phosphonate derivative fosfomycin **6**, a clinically used antibiotic. Starting from a racemic $\alpha$-bromo $\beta$-keto phosphonate *rac*-**4**, the desired precursor for fosfomycin, **5**, was obtained in excellent yield (84%) and with an enantioselectivity of 98% *ee* (Scheme 3).[5b] In addition, a *syn:anti* ratio of 90:10 was achieved.

Similar as described for the synthesis of (1*R*,2*R*)-**2a**, the highly stereoselective synthesis of the single stereoisomer **5** was realized by a dynamic kinetic resolution utilizing in situ stereoinversion in combination with an efficient asymmetric hydrogenation process. Furthermore it is noteworthy that this reaction has been carried out on a 20g scale.

## B. Asymmetric borane reduction

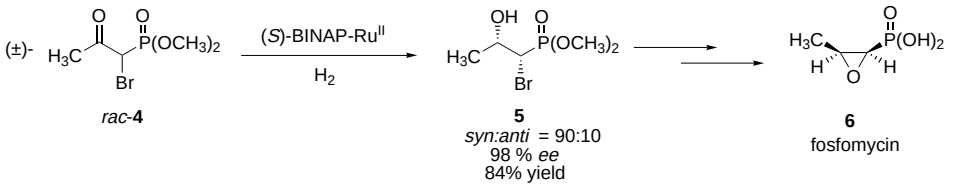
The asymmetric CBS (*C*orey, *B*akshi, *S*hibata) reduction represents a powerful tool for the manufacture of a large variety of chiral alcohol derivatives.[6] Thus, it is not surprising that this method has also been applied to the synthesis of enantiomerically enriched $\alpha$-hydroxy phosphonates **8** by means of an enantioselective catalytic catecholborane reduction of $\alpha$-keto phosphonates **7** (Scheme 4).[7]

In the presence of catalytic amounts of an oxazaborolidine complex (12 mol%) and catecholborane as a reducing agent, Meier et al. obtained




Scheme 4. Enantioselective synthesis of α-hydroxy phosphonates by catecholborane reduction.

the desired products **8** with excellent enantioselectivities of up to >99% *ee*.[7a] In this connection a main feature of the reaction is that hydroxy*aryl*- as well as hydroxy*alkyl* phosphonates have been prepared with a high enantioselection (representative examples are shown in Scheme 4). Furthermore not only good to excellent yields were achieved but also an impressive number of products was synthesized. The use of $BH_3 \cdot Me_2S$ instead of catecholborane as a reducing agent was connected with decreased enantioselectivities ($\leq$80% *ee*).[7b]




Scheme 3. Enantioselective synthesis of fosfomycin (**6**).

**Abstract in German:** *Der enantioselektiven Herstellung von α-Amino- und α-Hydroxyphosphonsäurederivaten mit Hilfe katalytischer Verfahren wurde in den zurückliegenden Jahren verstärkt Aufmerksamkeit entgegengebracht, nicht zuletzt aufgrund des pharmazeutischen Interesses an solchen Verbindungen. Der vorliegende Artikel beinhaltet eine Zusammenstellung der bislang entwickelten asymmetrischen Syntheseverfahren. Die beschriebenen Synthesewege basieren dabei auf verschiedenen Katalysekonzepten aus den Bereichen der Hydrierung, Reduktion, Dihydroxylierung, Aminohydroxylierung und Hydrophosphonylierung.*

## C. Asymmetric dihydroxylation and aminohydroxylation

An alternative catalytic approach applying an asymmetric Sharpless dihydroxylation as a key step was reported by Shibuya and co-workers.[8] Starting from $\alpha,\beta$-unsaturated phosphonates (e.g. **9**) in the presence of a chiral osmium catalyst (AD-mix-$\alpha$), a diastereoselective and enantioselective dihydroxylation process led to the desired products **10** with up to >95% *ee* and in good yields (as representatively shown for **10a** in Scheme 5).[8, 9] Remarkably high enantiose-



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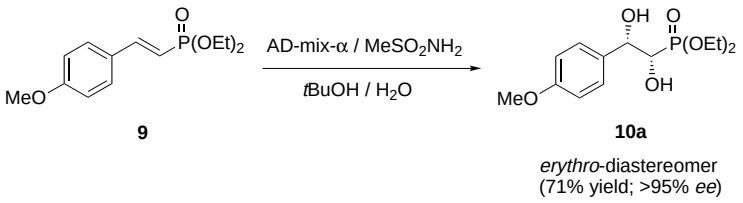



**9** **10a**

*erythro*-diastereomer
(71% yield; >95% *ee*)

Scheme 5. Catalytic asymmetric dihydroxylation (AD) strategy.

lectivities were obtained by using aromatic substituents, whereas the corresponding alkyl-substituted vinyl phosphonates gave lower *ee*.[8a] The steric effects of the ester functionality in the course of the dihydroxylation process were also evaluated. The enantioselectivity and yield were significantly improved when a dimethyl phosphonate was used instead of a corresponding diethyl derivative.[8b]

The resulting chiral glycol phosphonates of type **10**, which are difficult to synthesize by other methods, can be further converted into the modified phosphonates **11** and **12** (Scheme 6).[8a] Thus, the Shibuya protocol represents not only an atttractive route to enantiomerically enriched glycol phosphonates but also an interesting method to produce $\alpha,\beta,\gamma$-trihydroxy structures (of type **11**) as well as $\alpha$-hydroxy phosphonates of type **12**.

The use of the Sharpless aminohydroxylation method for the synthesis of the related enantiomerically enriched $\beta$-amino $\alpha$-hydroxy phosphonates has been described very recently by Sharpless et al.[10] and Palmisano et al.[11] Sharpless et al. reported that an asymmetric aminohydroxylation reaction with vinyl phosphonates proceeds with high enantioselectivities and in good yields.[10] Independently, Palmisano et al. obtained the desired aminohydroxylation products of type **14** with up to 92% *ee* (Scheme 7).[11]

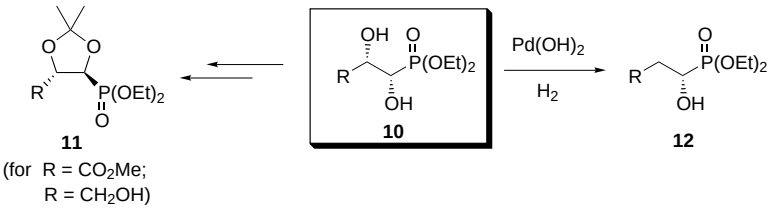
However, a dramatic dependence of the enantioselectivity on the nature of the *p*-aryl substituent has been found. In addition, until now the use of a nonsubstituted vinyl phosphonate was connected with a low *ee* value of 15% *ee*. Nonetheless, this method represents a valuable approach to $\beta$-amino $\alpha$-hydroxy phosphonic acid derivatives, which are well-known precursors for pseudopeptidic chemotherapeutic agents.

In conclusion, a main advantage of these routes developed by Shibuya et al., Sharpless et al., and Palmisano et al. is that starting from achiral compounds molecules with two stereogenic centers are produced in one step.

## D. Asymmetric hydrophosphonylation

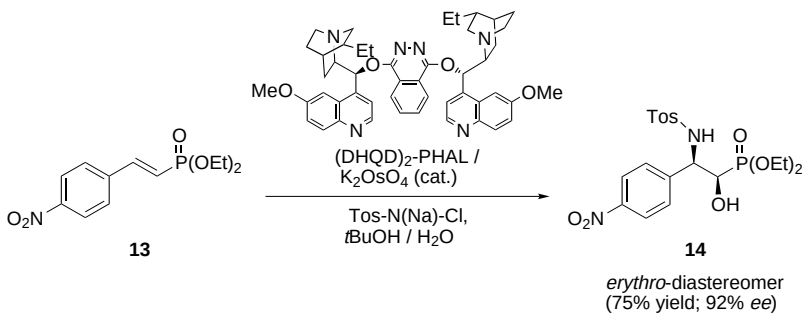
The addition of phosphites to the carbonyl or imine bond is probably the most general and widely applied access to $\alpha$-hydroxy and $\alpha$-amino phosphonates. However, for a long time a catalytic enantioselective version of this type of reaction was not available. For the first time, enantiomerically enriched $\alpha$-hydroxy phosphonates were obtained by Wynberg et al. by using amino alcohols as catalysts.[12] However, the practical usefulness of this method was limited due to the bulky phosphites which were needed for good results (*tert*-butyl phosphite: 80–85% *ee*), whereas the easily available and economically cheap phosphites led to strongly decreased enantioselectivities (e.g. dimethyl phosphite: 28% *ee*). Furthermore, only a few aldehydes could be used efficiently. The first transition metal catalyzed asymmetric hydrophosphonylation was discovered a few years later by Shibuya and coworkers.[13] In the presence of either titanium[13a,c] or lanthanoid[13b,c, 14] catalysts, enantiomerically enriched $\alpha$-hydroxy phosphonates **16** were produced with up to 82% *ee* when starting from aromatic aldehydes **15** (Scheme 8).

Independently, Spilling et al. found that chiral lanthanoid complexes are also suitable catalysts for the hydrophosphonylation of $\alpha,\beta$-unsaturated aldehydes.[15] However, the resulting *ee* values of the products did not exceed 31% *ee*. The final breakthrough in the asymmetric hydrophosphonylation of aldehydes **17** was realized recently by Shibasaki et al.[16] A reinvestigation of the protocol using heterobimetallic lithium- and lanthanoid-containing catalysts[17] (e.g. LLB: $LaLi_3$tris-(binaphthoxide)[14]) led to remarkably increased enantioselectivities of up to 95% *ee* with an impressive number of aldehydes (Scheme 9).[16a] This effect was due to an improved method for the preparation of the chiral lanthanoid catalysts and optimized reaction conditions. In addition, the enantio-




**11** (for R = $CO_2Me$; R = $CH_2OH$) **10** **12**

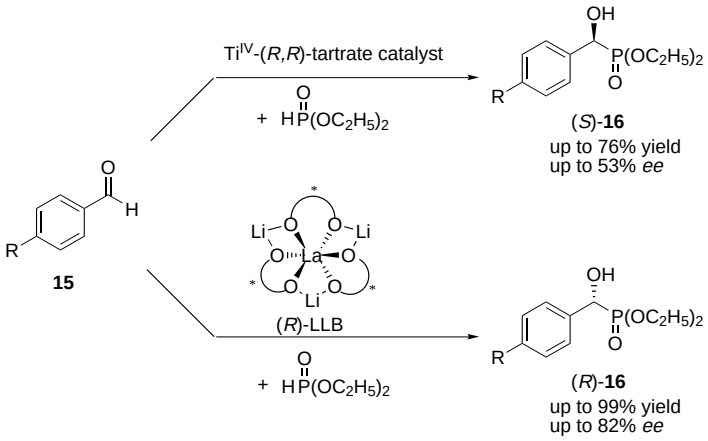
Scheme 6. Access to other phosphonate structures by conversion of **10**.




**13** **14**

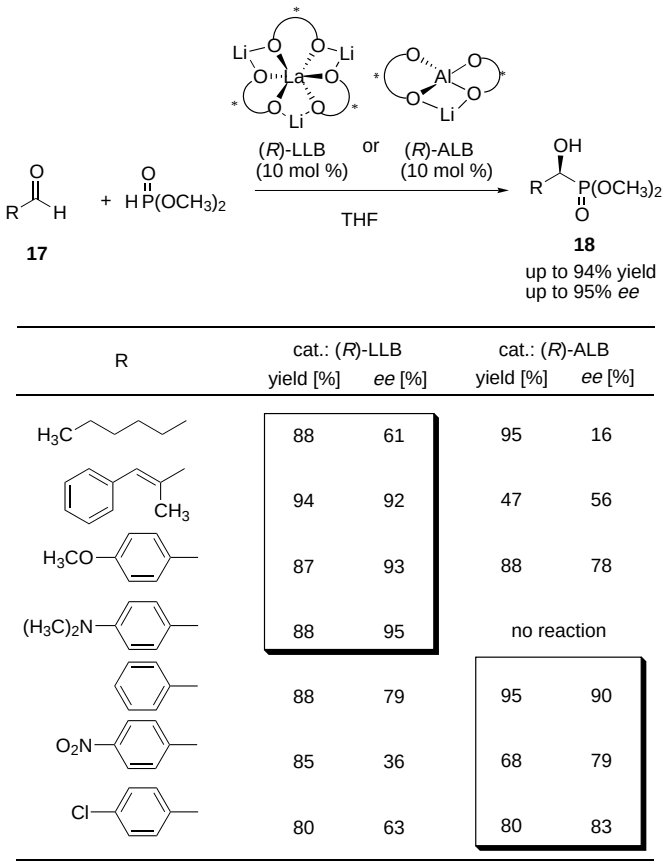
*erythro*-diastereomer
(75% yield; 92% *ee*)

Scheme 7. Catalytic asymmetric aminohydroxylation strategy.




Scheme 8. Enantioselective hydrophosphonylation of aldehydes using La or Ti catalysts ((*R*)-LLB = $LaLi_3$tris((*R*)-binaphthoxide)[14]).

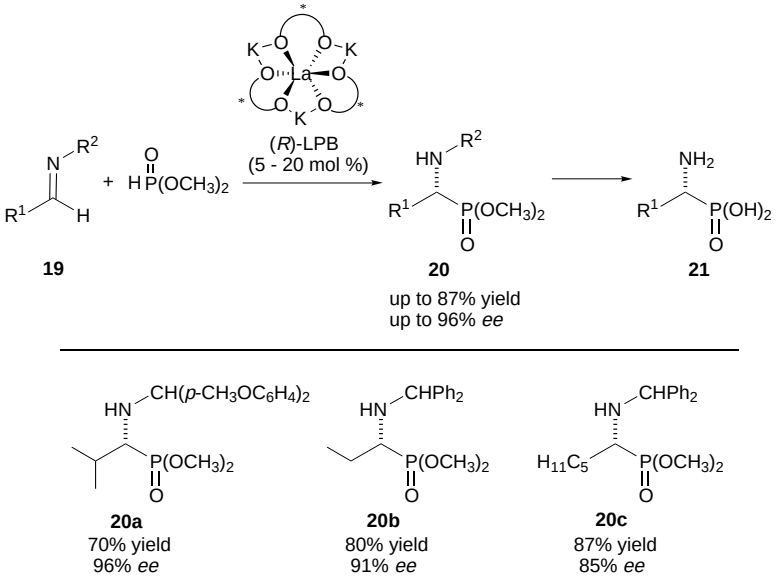
selectivities of some hydrophosphonylation products with a low *ee* (in the case of LLB) were improved dramatically by changing the type of the catalyst from LLB to the analogous chiral bimetallic aluminum catalyst ALB.[14] For example, benzaldehyde was converted into the desired phosphonate with 90% *ee* when using ALB as a catalyst (instead of 79% *ee* with the LLB catalyst).[16b] Similar effects were observed for several benzaldehyde derivatives with electron-withdrawing substituents (e.g. chloro, and nitro groups). This phenomena that LLB and ALB are tailor-made catalysts, each one useful for special types of aldehydes, can be regarded as an interesting example for a complementary effect in asymmetric catalysis and thereupon shows the efficiency of the Shibasaki heterobimetallic catalysis concept (Scheme 9).




| R | cat.: (*R*)-LLB yield [%] | cat.: (*R*)-LLB *ee* [%] | cat.: (*R*)-ALB yield [%] | cat.: (*R*)-ALB *ee* [%] |
|---|---|---|---|---|
| $H_3C$ | 88 | 61 | 95 | 16 |
| $CH_3$ | 94 | 92 | 47 | 56 |
| $H_3CO$ | 87 | 93 | 88 | 78 |
| $(H_3C)_2N$ | 88 | 95 | no reaction | |
| | 88 | 79 | 95 | 90 |
| $O_2N$ | 85 | 36 | 68 | 79 |
| Cl | 80 | 63 | 80 | 83 |

Scheme 9. LLB- and ALB-catalyzed asymmetric hydrophosphonylation of aldehydes (ALB[14] in which A = aluminum, L = lithium, and B = BINOL (BINOL = 2,2′-dihydroxy-1,1′-biphenyl).

That not only aldehydes but also imines are able to undergo a highly efficient hydrophosphonylation process, leading to the pharmaceutically important $\alpha$-amino phosphonates **20** (which are biologically active isosters of $\alpha$-amino carboxylic acids), has been demonstrated by Shibasaki and co-workers (for representative examples, see Scheme 10).[18] In the presence of 5–20 mol% of potassium-containing heterobimetallic lanthanoid catalysts, the first catalytic enantioselective synthesis of $\alpha$-amino phosphonates **20** was realized with excellent enantioselectivities of up to 96% *ee* and yields of up to 87%. Interestingly, the potassium-containing catalyst (*R*)-LPB[14] was shown to be the most efficient catalyst and superior to the analogous lithium catalysts which have been used in the hydrophosphonylation of aldehydes. The obtained phosphonates **20a** and **20b** were further converted into the corresponding $\alpha$-amino phosphonic acids **21** in up to quantitative yields (**21a**: 100% yield; **21b**: 90% yield). Very recently this impressive enantioselective preparation strategy for the manufacture of $\alpha$-amino phosphonic acids has found an industrial application.[19]




Scheme 10. Asymmetric hydrophosphonylation of acyclic imines catalyzed by (*R*)-LPB ((*R*)-LPB[14] in which L = lanthanum, P = potassium, B = BINOL).



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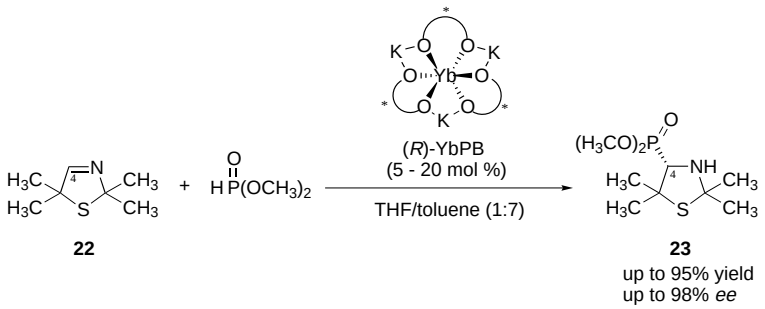
Furthermore, by using the Shibasaki hydrophosphonylation the first catalytic asymmetric synthesis of cyclic $\alpha$-amino phosphonates has been realized (Scheme 11).[20] The pharmaceutically interesting 4-thiazolidinyl phosphonates of type **23** were synthesized with enantioselectivities of up to 98% *ee* and in yields of up to 95% when using (*R*)-YbPB[14]




Scheme 11. Enantioselective hydrophosphonylation catalyzed by a (*R*)-YbPB complex. ((*R*)-YbPB[14] in which Yb = ytterbium, P = potassium, B = BINOL).

(20 mol%) as a catalyst. It is noteworthy that—in contrast to the reaction with acyclic imines **19**—the use of (*R*)-LnPB catalysts, which include a (relatively) small lanthanoid(III) center ion (e.g. ytterbium), was connected with the best results. Additionally, the catalytic amount for this reaction, which proceeds at a convenient reaction temperature (temperature range between room temperature and 50 °C), could be reduced to 5 mol% without loss of enantioselectivity.

Very recently, Shibasaki et al. showed that it is also possible to use diphenylphosphane oxide ($Ph_2P(:O)H$) instead of the analogous dimethyl phosphite ($(MeO)_2P(:O)H$) as a nucleophilic phosphorus component in the asymmetric addition reaction with several cyclic imines.[21] In the presence of (*R*)-PrPB (PrPB: Pr = praseodymium, P = potassium, B = BINOL), which has been proved to be the most efficient catalyst, the corresponding cyclic $\alpha$-amino diphenylphosphane oxides have been obtained in good yields and with enantioselectivities of up to 93% *ee*.

In summary, the first catalytic enantioselective approaches to $\alpha$-hydroxy and $\alpha$-amino phosphonates (based on different catalytic concepts) have been realized with excellent enantioselectivities and high yields. The developed catalytic asymmetric concepts represent competitive (and probably superior) synthetic routes to these important target molecules compared to the "classical routes" such as racemic resolution and diastereoselective reactions.

## Acknowledgment

We are very grateful to Dr. Stefan Weiss for his kind support and for his encouragement to write this manuscript.

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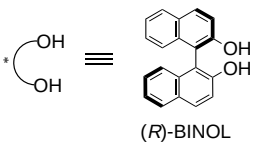
[14] The simplified depicted chiral ligand in the structures of the catalysts LLB, ALB, LPB, and YbPB (see Schemes 8–11) should represent the (deprotonated) enantiomerically pure (*R*)-binaphthol ((*R*)-BINOL).

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