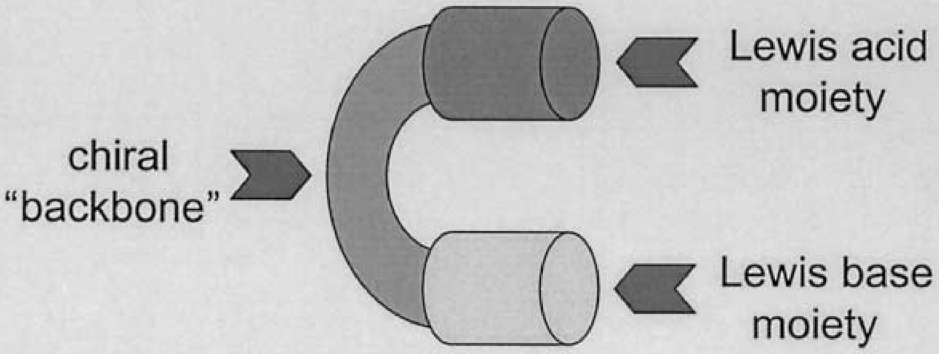
New chiral bifunctional catalysts ...

The concept:



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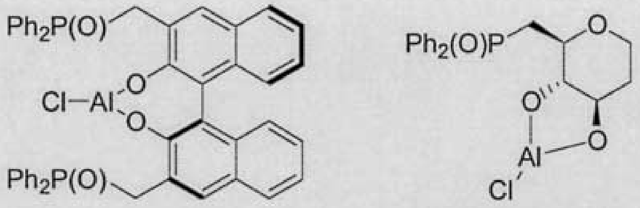
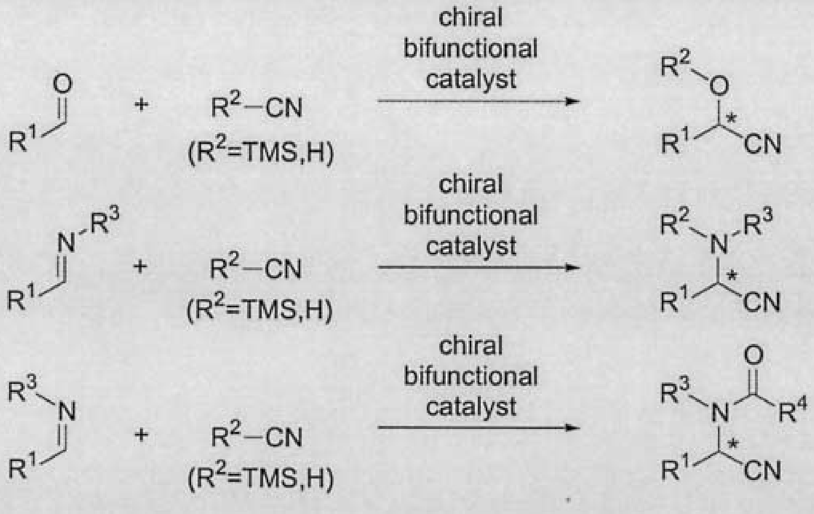


... and more

... and their application in asymmetric cyanation reactions



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The Development of New Monometallic Bifunctional Catalysts with Lewis acid *and* Lewis Base Properties, and their Application in Asymmetric Cyanation Reactions

Harald Gröger*[a, b]

Abstract: Bifunctional catalysts can drastically improve the efficiency of asymmetric processes with respect to enantioselectivity and/or conversion rate. A new type of chiral bifunctional catalyst has been developed recently in the Shibasaki group that contains both Lewis acid and Lewis base moieties. These monometallic and bifunctional phosphinoyl-containing catalysts are able to coordinate both nucleophilic and electrophilic substrates in the transition state. Several successful applications of this new catalytic concept in the field of asymmetric cyanation reactions have already been reported, for example, the asymmetric hydrocyanation of aldehydes and imines as well as the asymmetric Reissert reaction. The development and principle of this catalytic concept as well as main applications thereof are reviewed in this article.

Keywords: asymmetric catalysis · bifunctional catalysts · cyanohydrins · ligand design · nucleophilic addition

Introduction

In spite of tremendous developments for a broad variety of different type of asymmetric catalytic reactions,[1] the search for new catalysts is still ongoing. It has been found that, in particular, bifunctional catalysts represent promising catalysts owing to the attachment of both electrophilic and nucleophilic substrates to the chiral catalyst in the transition-state complex. Such a coordination of both substrates within an asymmetric space would lead to a stronger stereodiscrimination and should result in a highly enantioselective process. How can we integrate more than one coordination position in synthetic catalytic complexes in order to obtain increased asymmetric selectivity? Several concepts have been developed in the past for catalytic asymmetric reactions.[1, 2] Tremendous contributions have been reported by Corey et al.[3] and Noyori et al.[4] using chiral bimetallic complexes as catalysts for the asymmetric CBS (CBS = Corey–Bakshi–Shibata) borane reduction and diethyl zinc addition, respectively. Recently, Shibasaki et al. developed highly efficient chiral heterobimetallic complexes that have been proved to be efficient catalysts for numerous C–C, C–S, C–P, C–O and C–H bond-forming reactions.[5] These catalytic concepts are based on the presence of two metal moieties with different functionalities in the catalyst. A bifunctional catalyst that is based on gold as a metal component and a phosphine ligand, which contains an additional amine functionality, as a Lewis base was found by Ito, Sawamura, and Hayashi.[6] The application of this metal complex in the asymmetric aldol reaction gave excellent stereoselectivities.

Recently, this concept of bifunctional catalysts[7] has been extended by Shibasaki et al. to another interesting class of chiral catalysts, which were successfully applied in asymmetric cyanation reactions: The concept of monometallic, phosphinoyl-containing catalysts with both Lewis acid and Lewis base properties.[8, 11, 13, 14, 16, 17, 19]

Catalyst Design and Applications

To start with the design of this new type of chiral monometallic Lewis acid/Lewis base catalyst, the first key issue was to find a suitable Lewis acid and Lewis base precursor system. As a lead structure for the ligand system, a BINOL-based diol has been developed which includes a phosphinoyl moiety. This phosphinoyl moiety represents the required neutral base functionality (Lewis base) in the later catalytic complex. Regarding the Lewis acid component, aluminum was choosen as a central metal.[9] It was assumed that in the corresponding complex **1** (Scheme 1), the Al center would work as a Lewis acid activating the carbonyl group. As a counterpart, the role of the oxygen atom of the phosphine

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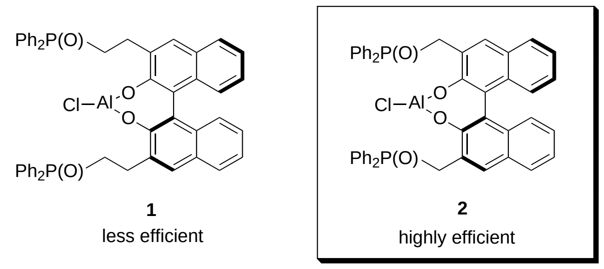
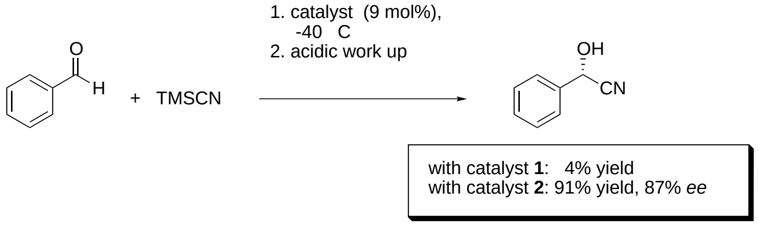


Scheme 1. Structures of bifunctional monometallic complexes.



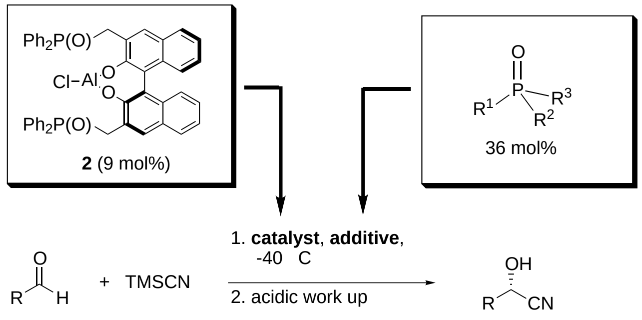
Scheme 2. Application of bifunctional catalysts in asymmetric cyanosilylation.

oxides is to function as a Lewis base by activating (silylated) nucleophiles.

The developed complex was examined in the asymmetric addition of trimethylsilylcyanide to aldehydes, which offers an interesting access to enantiomerically enriched cyanohydrins.[10] However, the use of this catalyst exhibits a low conversion resulting in only 4 % yield (Scheme 2). This low activity of the catalyst clearly indicates a further key issue for designing such a Lewis acid/Lewis base catalyst: The prevention of internal coordination of aluminum and a phosphinoyl moiety. In the ligand of **1** the internal coordination seemed to be quite stable due to the ethylene linker. As a consequence, an ethylene linker was replaced by a methylene functionality in the ligand of **2**, in order to cleave the strong internal coordination between the phosphinoyl group and the Lewis acid aluminum. In the presence of this improved monometallic and bifunctional catalyst **2** (9 mol %), the cyanosilylation reaction proceeds very efficiently. The yield rose up from 4 % to 91 % and the enantioselectivity reached 87 % *ee*.[8]

Abstract in German: *Bifunktionelle Katalysatoren können die Effizienz asymmetrischer Reaktionen, sowohl hinsichtlich Enantioselektivität als auch Umsatz, beträchtlich erhöhen. Ein neuartiger Typ eines chiralen bifunktionellen Katalysators, der eine Lewis-Säure als auch Lewis-Base enthält, wurde nun kürzlich in von Shibasaki et al. entwickelt. Diese monometallischen, aber zugleich bifunktionellen phosphinoylhaltigen Katalysatoren sind in der Lage, sowohl das nukleophile und elektrophile Substrat im Übergangszustand zu binden. Verschiedene erfolgreiche Anwendungen dieses neuen katalytischen Konzepts wurden auf dem Gebiet der asymmetrischen Cyanierungsreaktionen berichtet, so die asymmetrische Hydrocyanierung von Aldehyden und Iminen wie auch die asymmetrische Reisert-Reaktion. Die Zusammenfassung der Entwicklung und des zugrundeliegenden Prinzips dieses katalytischen Konzepts sowie die bisherigen Hauptanwendungsgebiete sind Gegenstand dieses Artikels.*

It is noteworthy, that there is a remarkable potential to modify selectively the Lewis acid and/or Lewis base properties of the catalyst simply by adding a cheap and achiral additive. This can be of help to fine tune the catalyst. This concept was efficient in the above-mentioned reaction when aliphatic aldehydes were used as a starting material. The hydrocyanation of aliphatic aldehydes is known to be very difficult and, for a long time, no synthetic methods have been available. In addition, even the bifunctional complex **2** catalyzes this reaction with low *ee* (e.g., the cyanosilylation of hydrocinnamaldehyde gave 9 % *ee*). Use of tributylphosphine oxide as an additive, however, led to a remarkable increased enantioselectivity of up to 97 % *ee* (Scheme 3, Table 1). It was found that tributylphosphine oxide works efficiently for aliphatic and α,β-unsaturated aldehydes, whereas diphenylmethylphosphine oxide is a suitable additive for aromatic aldehydes (Scheme 3).[8]



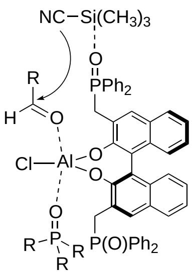
Scheme 3. Fine-tuning of bifunctional catalysts by using additives.

Table 1. Effect of additives.

Entry	R	Yield [%]	*ee* [%]
1[a]	$Ph(CH_2)_2$	97	97
2[a]	$CH_3(CH_2)_5$	100	98
3[a]	*trans*-$CH_3(CH_2)CH{=}CH_2$	94	97
4[b]	C_6H_5	98	96
5[b]	*p*-$CH_3C_6H_4$	87	90

[a] $Bu_3P(O)$ was used as an additive. [b] $CH_3P(O)Ph_2$ was used as an additive.

The surprising additive effect, the high enantioselectivity, and the absolute configuration of products are explained by the working model depicted in Scheme 4. Accordingly, the external phosphine oxide should be coordinated to the aluminum, thus converting the tetragonal Al^{III} into a pentavalent center metal. This geometry would allow the aldehyde to position itself at the apical side and close to the phosphine oxide of the ligand. Additionally, the trimethylsilylcyanide



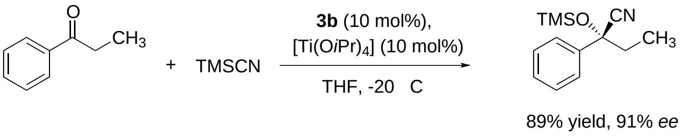
Scheme 4. Mechanism of Lewis acid/Lewis base catalysis.

interacts with the Lewis base part of the chiral ligand. Thus, in the transition state both substrates are coordinated to the monometallic, bifunctional catalytic complex. The subsequent transfer of the cyanide to the aldehyde takes place in a highly enantioselective manner. This dual Lewis acid/Lewis base activation pathway has also been supported by kinetic studies.[8]

The power of Shibasaki's asymmetric bifunctional catalytic system has also been shown in a recent application of his elegant methodology in a total synthesis of epothilone A.[11, 12] On gram-scale a thiazole-based aldehyde was cyanosilylated with high enantioselectivity of 99% *ee* and excellent yield of 97% when using the Lewis acid/Lewis base catalyst **2** (Scheme 5).

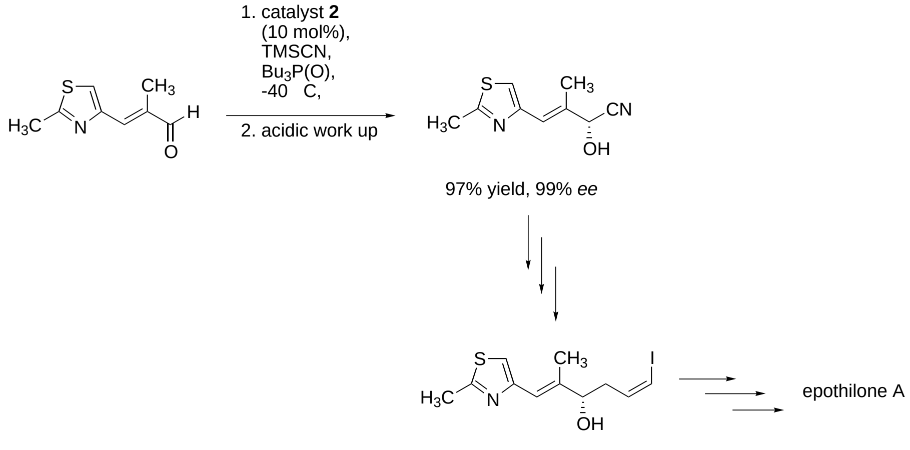
The concept of monometallic and bifunctional catalysts, however, is not restricted to the use of Al as a metal or binaphthol derivatives as ligands. Recently, Shibasaki et al. reported bifunctional catalysts that are based on chiral carbohydrate ligands (Scheme 6).[13] Among a variety of such catalysts, an Al complex based on **3a** has been proven to be a very active catalyst for the cyanosilylation of aldehydes with nearly quantitative yields and *ee*s in the range of 70 to 80%.

Most interestingly, it was found that replacing the metal (Ti instead of Al) led to an excellent catalyst for the cyanosilylation of ketones (when **3b** was used as a ligand).[14a] In the presence of 10 mol% of the titanium catalyst, the products were obtained in yields in the range of 72 to 92% and with enantioselectivities of up to 95% *ee* (see, for example, Scheme 7). Thus, this catalytic reaction not only provided a new strategy for the construction of quarternary carbon centers, but also represents the first general highly enantioselective cyanosilylation of ketones. In addition, kinetic studies showed a first-order dependence of the initial reaction rate on the catalyst concentration. Thus, it can be concluded that *one* monometallic, bifunctional catalytic complex functions both as a Lewis acid and Lewis base. Very recently, an improvement of the enantioselectivity as well as the turn-over number by ligand tuning was reported.[14b] Use of the modified ligand **3d**, which bears a benzoyl substituent at the catechol moiety, led to >80% *ee* even with "difficult" substrates, for example, 1-indanone and 2-heptanone. Furthermore, in the reaction with acetophenone 92% yield and 94% *ee* were obtained with a catalytic amount of 1 mol%.

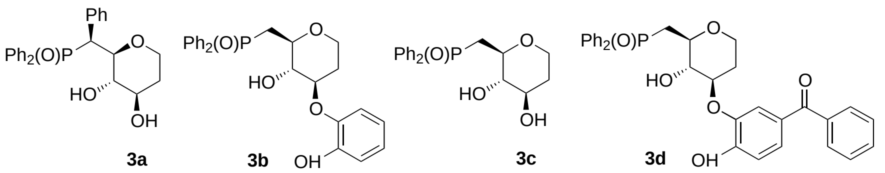


Scheme 7. Asymmetric cyanosilylation of ketones with a sugar-based bifunctional catalyst.

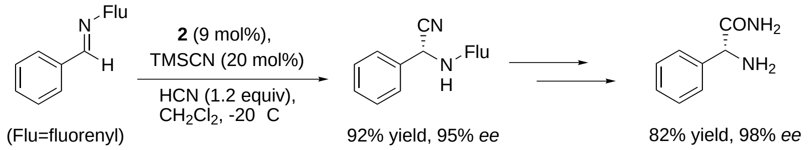
In addition to the asymmetric cyanosilylation of carbonyl compounds, the corresponding reaction with imines is of interest, since it allows an access to chiral α-amino acids.[15] This type of reaction, the so-called Strecker reaction, can be also carried out efficiently with a broad substrate range by using the Shibasaki catalysts.[16] Furthermore, this catalytic reaction proceeds well with aliphatic *N*-aldimines and α,β-unsaturated imines (which gave unsatisfactory enantioselectivities from other methods). Thus, application of the bifunctional catalyst **2** leads to a highly asymmetric Strecker-type reaction in good yields of up to 97% and with *ee*s up to 96%.[16a,b] It is noteworthy that trimethylsilylcyanide (TMSCN) as well as HCN (in presence of 20 mol% TMSCN) can act as a cyanide donor. The products can be successfully converted into the pure amino acid amides by subsequent cleavage of the protecting group. A representative example is shown in Scheme 8.



Scheme 5. Use of **2** in an asymmetric key step in the synthesis of epothilones.

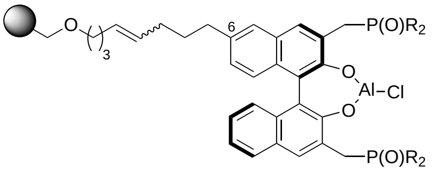


Scheme 6. Sugar-based ligands **3** for the preparation of bifunctional catalysts.



Scheme 8. Chiral amino acid amides from an asymmetric Strecker reaction using a bifunctional catalyst.

An interesting extension of this concept towards an asymmetric Strecker reaction with an immobilized Lewis acid/Lewis base catalyst of type **4a** (Scheme 9) was also reported by Shibasaki and co-workers.[16c] Although the enantioselectivities are slightly lower, the solid-supported bifunctional catalyst **4a** can be recycled several times and its reactivity is comparable to that of the "homogenous analogue" **2**.



4a: R=Ph
4b: R=*o*-Tol

Scheme 9. Immobilized solid-supported bifunctional catalysts **4**.

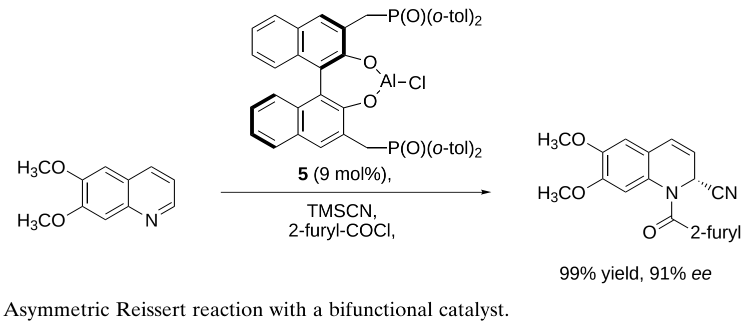
Furthermore, for the first time an asymmetric Reissert-type reaction has been revealed by using the new bifunctional and monometallic catalyst **5**.[17] Starting from quinolines or isoquinolines, the desired *N*-acylated Reissert products have been obtained with good *ee* (up to 91%) and in up to nearly quantitative yields (see, for example, Scheme 10).[17a] In addition, the Reissert product can be converted into the tetrahydroquinoline-2-carboxylate without any loss of enantiomeric purity. The asymmetric catalytic Reissert reaction has been also successfully applied as a key step in a ten step synthesis of Merck's potent NMDA receptor antagonist (−)-L-689,560, which represents a promising drug candidate for Alzheimer's disease.[16b] It is noteworthy that the reaction can also be carried out in the presence of an immobilized aluminum catalyst **4b**.

In addition to enantioselective synthesis, the bifunctional, sugar-based catalyst Al-**3c** was applied to a diastereoselective synthesis. A three-step synthesis of 4-phenyl-β-amino-α-hydroxybutyric acid, an intermediate in the production of bestatine,[18] has been jointly reported by researchers from the Shibasaki group and former SKW Trostberg AG (now: Degussa AG).[19] Starting from a chiral BOC-protected amino aldehyde, the hydrocyanation proceeds on a multi-gram scale with a high diastereoselectivity of $dr = 94{:}6$ (Scheme 11).[19] A total yield of 75% for the enantiomerically pure β-amino α-hydroxy carboxylic acid as well as a low catalytic amount of only 1 mol% indicates the suitability of this methodology for an application on a commercial scale.

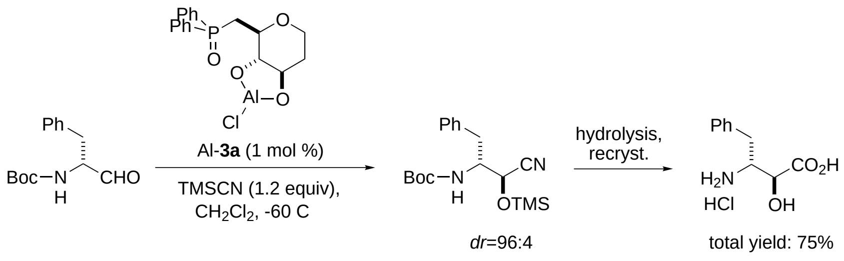
Conclusion

In conclusion, new asymmetric bifunctional catalysts have been developed by Shibasaki et al. that contain both Lewis acid and Lewis base moieties. This new catalytic system based on monometallic *and* bifunctional phosphinoyl-containing catalysts is able to coordinate both nucleophilic and electrophilic substrates in the transition state, thus leading to highly enantioselective reactions. These new catalysts have already been proven to be efficient in several type of asymmetric catalytic cyanation reactions. In the future, applications of this type of catalysts on a large-scale as well as the extension to other asymmetric reactions can be expected.

Note added in proof: Very recently, the Shibasaki group and the Curran group jointly reported that replacing titanium by samarium or gadolinium in the sugar-ligand-based catalyst for the asymmetric cyanosilylation of ketones gives the opposite enantiomer as a product in up to 97% *ee* (K. Yabu, S. Masumoto, S. Yamasaki, Y. Hamashima, M. Kanai, W. Du, D. P. Curran, M. Shibasaki, *J. Am. Chem. Soc.* **2001**, *123*, 9908–9909; see also *Chem. Eng. News* **2001**, issue October 8, p. 27). In addition, very recently Shibasaki et al. reported an extension of the asymmetric Reissert-type reaction towards the enantioselective construction of quaternary stereo-



Scheme 10. Asymmetric Reissert reaction with a bifunctional catalyst.



Scheme 11. Diastereoselective synthesis of a bestatine building block.

genic carbon centers with enantioselectivities of up to 98% *ee* (K. Funabashi, H. Ratni, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2001**, *123*, 10784–10785).

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[1] a) G. Helmchen, R. W. Hoffmann, J. Mulzer, E. Schaumann, *Houben-Weyl*, *Methods of Organic Chemistry*, *Stereoselective Synthesis*, *Vol. E21*, Thieme, Stuttgart/New York, **1995**; b) *Catalytic Asymmetric Synthesis*, 2nd ed. (Ed.: I. Ojima), Wiley-VCH, Weinheim, **2000**; c) *Comprehensive Asymmetric Catalysis I–III* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**.

[2] *Lewis Acids in Organic Synthesis* (Ed.: H. Yamamoto), Wiley-VCH, Weinheim, **2000**.

[3] For a review, see: E. J. Corey, C. J. Helal, *Angew. Chem.* **1998**, *110*, 2092–2118; *Angew. Chem. Int. Ed.* **1998**, *37*, 1986–2012.

[4] For a review, see: R. Noyori, M. Kitamura, *Angew. Chem.* **1991**, *103*, 34–55; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 34–48.

[5] For reviews, see: a) M. Shibasaki, H. Sasai, T. Arai, *Angew. Chem.* **1997**, *109*, 1290–1310; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1236–1256; b) M. Shibasaki, H. Gröger in *Topics in Organometallic Chemistry Vol. 2*: *Lanthanides*: *Chemistry and Use in Organic Synthesis* (Ed.: S. Kobayashi), Springer, Berlin, **1999**, pp. 199–233.

[6] a) Y. Ito, M. Sawamura, T. Hayashi, *J. Am. Chem. Soc.* **1986**, *108*, 6405–6406; b) T. Hayashi, M. Sawamura, Y. Ito, *Tetrahedron* **1992**, *48*, 1999–2012.

[7] For reviews on the application of bifunctional catalysts in asymmetric synthesis, see: a) H. Steinhagen, G. Helmchen, *Angew. Chem.* **1996**, *108*, 2489–2492; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2337–2340; b) G. J. Rowland, *Tetrahedron* **2001**, *57*, 1865–1882; c) E. K. van der Beuken, B. L. Feringa, *Tetrahedron* **1998**, *54*, 12985–13011.

[8] Y. Hamashima, D. Sawada, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **1999**, *121*, 2641–2642.

[9] In previous work on bimetallic asymmetric catalysis it was found that aluminum complexes bearing binaphthoxide moieties have been very efficient in several asymmetric reactions, see: a) T. Arai, H. Sasai, K. Aoe, K. Okamura, T. Date, M. Shibasaki, *Angew. Chem.* **1996**, *108*, 103–105; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 104–106; b) see ref. [7a]; c) K. Ishihara, J. Kobayashi, K. Inanaga, H. Yamamoto, *Synlett* **2001**, 394–396.

[10] Cyanohydrins are of industrial importance, since these molecules are key building blocks for a broad range of compounds, for example, β-amino alcohols and α-hydroxy acids. Furthermore, cyanohydrins are applied as intermediates in the production of pyrethroids. For reviews about the synthesis and applications of chiral cyanohydrins, see: a) M. North, *Synlett* **1993**, 807–820; b) F. Effenberger, *Angew. Chem.* **1994**, *106*, 1609–1619; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1555–1564; c) R. J. H. Gregory, *Chem. Rev.* **1999**, *99*, 3649–3682.

[11] D. Sawada, M. Shibasaki, *Angew. Chem.* **2000**, *112*, 215–218; *Angew. Chem. Int. Ed.* **2000**, *39*, 209–213.

[12] Epothilones show potent antitumor activity, thus representing promising drug candidates; for a review on the total synthesis and biology of epothilones, see: K. C. Nicolaou, F. Roschangar, D. Vourloumis, *Angew. Chem.* **1998**, *110*, 2120–2153; *Angew. Chem. Int. Ed.* **1998**, *37*, 2014–2045.

[13] M. Kanai, Y. Hamashima, M. Shibasaki, *Tetrahedron Lett.* **2000**, *41*, 2405–2409.

[14] a) Y. Hamashima, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2000**, *122*, 7412–7413; b) Y. Hamashima, M. Kanai, M. Shibasaki, *Tetrahedron Lett.* **2001**, *42*, 691–694.

[15] L. Yet, *Angew. Chem.* **2001**, *113*, 900–902; *Angew. Chem. Int. Ed.* **2001**, *40*, 875–877.

[16] a) M. Takamura, Y. Hamashima, H. Usuda, M. Kanai, M. Shibasaki, *Angew. Chem.* **2000**, *112*, 1716–1718; *Angew. Chem. Int. Ed.* **2000**, *39*, 1650–1652; b) M. Takamura, Y. Hamashima, H. Usuda, M. Kanai, M. Shibasaki, *Chem. Pharm. Bull.* **2000**, *48*, 1586–1592; c) H. Nogami, S. Matsunaga, M. Kanai, M. Shibasaki, *Tetrahedron Lett.* **2001**, *42*, 279–283.

[17] a) M. Takamura, K. Funabashi, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2000**, *122*, 6327–6328; b) M. Takamura, K. Funabashi, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2001**, *123*, 6801–6808.

[18] Bestatin is used clinically as an anticancer agent; for selected examples of the synthesis of bestatin or its components, see: a) H. Nemoto, R. Ma, I. Suzuki, M. Shibuya, *Org. Lett.* **2000**, *2*, 4245–4247, and references therein; b) S. C. Bergmeier, D. M. Stanchina, *J. Org. Chem.* **1999**, *64*, 2852–2859, and references therein; c) F. Matsuda, T. Matsumoto, M. Ohsaki, Y. Ito, S. Terashima, *Bull. Chem. Soc. Jpn.* **1992**, *65*, 360–365, and references therein.

[19] G. Manickam, H. Nogami, M. Kanai, H. Gröger, M. Shibasaki, *Synlett* **2001**, 617–620.

0947-6539/01/0724-5251 $ 17.50+.50/0