Review

Multifunctional Asymmetric Catalysis

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Two types of general and practical enantioselective catalysts, namely, bimetallic complexes and Lewis acid–Lewis base bifunctional catalysts were developed based on the concept of multifunctional catalysis. In the first part of this review, the first example of a catalytic enatioselective nitro-Mannich reaction as well as a direct catalytic enantioselective aldol reaction of 2-hydroxyacetophenone using bimetallic complexes is discussed. The new complex, composed of ytterbium, potassium, and BINOL in a ratio of 1 : 1 : 3, promoted the nitro-Mannich reaction of nitromethane with up to 91% ee. On the other hand, second generation ALB catalyzed an enantioselective and diastereoselective nitro-Mannich reaction of nitroalkanes in up to 83% ee with a diastereomeric ratio up to 7 : 1. Moreover, the reaction of aldehydes with 2-hydroxyacetophenone in the presence of LLB, KHMDS, and H_2O selectively gave the corresponding *anti*-α,β-dihydroxy ketones in up to 95% ee and, in the presence of the catalyst prepared from linked-BINOL and 2 eq of Et_2Zn, selectively afforded the *syn*-α,β-dihydroxy ketones in up to 86% ee. In the second part, the development of new catalysts displaying a Lewis acidity and a Lewis basicity is described. The Lewis acid of the catalyst activates aldehydes, imines, acyl quinoliniums, and ketones. At the same time, the Lewis base activates the nucleophile (TMSCN). Catalysts of this type produced a highly enantioselective cyanation of these electrophiles. Application of the catalytic enantioselective cyanosilylation of aldehydes to a total synthesis of epothilones is also described.

Key words multifunctional catalysis; enantioselective; bimetallic complex; Lewis acid–Lewis base catalyst; nitro-Mannich reaction; aldol reaction; cyanation

1. Introduction

The development of catalytic asymmetric reactions is a major area of research in the field of organic chemistry. So far, a number of chiral catalysts have been reported, some of which exhibit a much higher catalytic efficiency than do natural catalysts, the enzymes.[1] Most of the synthetic asymmetric catalysts, however, are limited in terms of either enantioselectivity or chemical yield. The major difference between synthetic asymmetric catalysts and enzymes is that the synthetic asymmetric catalysts activate only one side of the substrate in an intermolecular reaction, whereas the enzymes activate both substrates and can also control the orientation of the substrate. One example is the class II, metal-dependent aldolase, which catalyzes an aldol reaction of dihydroxyacetone phosphate (DHAP) and various aldehydes under neutral conditions.[2] In the reaction mechanism of this enzyme, the glutamate-73 residue functions as a Brönsted base to generate the ketone enolate with the assistance of Zn^{2+} (Fig. 1) and at the same time the tyrosine-113′ residue activates the aldehyde as a Brönsted acid. Such dual activation is fundamental to promote the reaction from stable substrates under mild conditions with complete stereoselectivity. If this type of synergistic cooperation can be realized with artificial asymmetric catalysts, the concept will open up a new field in asymmetric synthesis, and a wide range of applications will ensue. Thus, asymmetric catalysts have been developed based on the concept of multifunctional catalysis. The present review discusses two types of asymmetric two-center catalysis promoted by complexes with Lewis acidity and Brönsted basicity and/or Lewis acidity and Lewis basicity.[3]

2. Catalytic Asymmetric Reactions Promoted by Bimetallic Complexes

2-1. Catalytic Asymmetric Nitro-Mannich Reaction Promoted by Heterobimetallic Complexes[4] We developed chiral heterobimetallic complexes (Fig. 1) that promote a variety of catalytic enantioselective transformations, such as nitroaldol,[5] direct aldol,[6] Michael,[7] Michael-aldol,[8] hydrophosphonylation,[9] hydrophosphination,[10] protonation,[11] epoxide opening,[12] Diels–Alder,[13] and epoxidation of enones,[14] with excellent enantioselectivity. The reactions proceed *via* dual activation of both substrates (nucleophiles and electrophiles) by the catalysts. Thus, the Brönsted base moiety of the catalysts (alkali metal naphthoxide) activates the substrates, such as nitroalkanes, ketones, malonates, phosphite, phosphine oxide, thiols, or phenol by deprotonation. At the same time, the Lewis acid moiety (lanthanoid, aluminun, or gallium center metals) activates the other substrates. Because this dual activation occurs at the positions controlled by the asymmetric catalyst, the substrates react with the other substrates from a defined direction, and as a result, high enantioselectivity is obtained (see previous reviews). This section focuses on the Lewis acid–Brönsted base catalysts, a catalytic asymmetric nitro-Mannich reaction, and a direct catalytic asymmetric aldol reaction using 2-hydroxyacetophenone.

The importance of nitrogen-containing compounds for pharmaceuticals has led to intensive progress in the field of catalytic asymmetric nucleophilic addition to imines.[15] There have been several noteworthy reports on the use of organometallic reagents, such as alkyllithiums, ketene silyl acetals, organoboronic acids, or allylstannanes. Moreover, a chiral rhodium-catalyzed highly enantioselective conjugate addition of organoboronic acids to nitroalkenes was recently reported.[16] These reactions, however, inevitably produce stoichiometric amounts of metal hydroxides or their derivatives after quenching. A more atom-economical[17] method involving proton-transfer is needed in order to eliminate these side products. Because the heterobimetallic catalysts have sufficient Brönsted basicity to deprotonate nitroalkanes and Lewis acidity to activate imines, we expected these catalysts to promote the direct catalytic asymmetric nitro-Mannich re-

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action.[18)]

After intensive screening of the heterobimetallic catalysts and substrates, the addition of nitromethane to *N*-phosphinoylimine **7a** was promoted at −20 °C to give the product in 62% yield with 82% ee, using a catalyst (20 mol%) composed of Yb : K : BINOL in a ratio of 1 : 1 : 3. The well-defined catalyst, composed of Yb : K : BINOL = 1 : 3 : 3 (YbPB), gave the product in 64% yield with 52% ee. Studies to elucidate the catalyst structure, using laser desorption/ionization time-of-flight (TOF) mass spectroscopy, indicated that the catalyst contained a partial structure of [YbK(binaphthoxide)$_2$]. The catalyst prepared from Yb : K : BINOL = 1 : 1 : 2, however, did not promote the reaction. Therefore, we assumed that the active catalyst might be a complex of [YbK(binaphthoxide)$_2$] and BINOL, weakly associated by Lewis acid–Lewis base interactions and hydrogen bonding (**10** in Table 1).

The best result using nitromethane was obtained when the reaction was carried out at −40 °C with 20 mol% of catalyst **10** with a slow addition (over 27 h) of nitromethane (5 eq) to

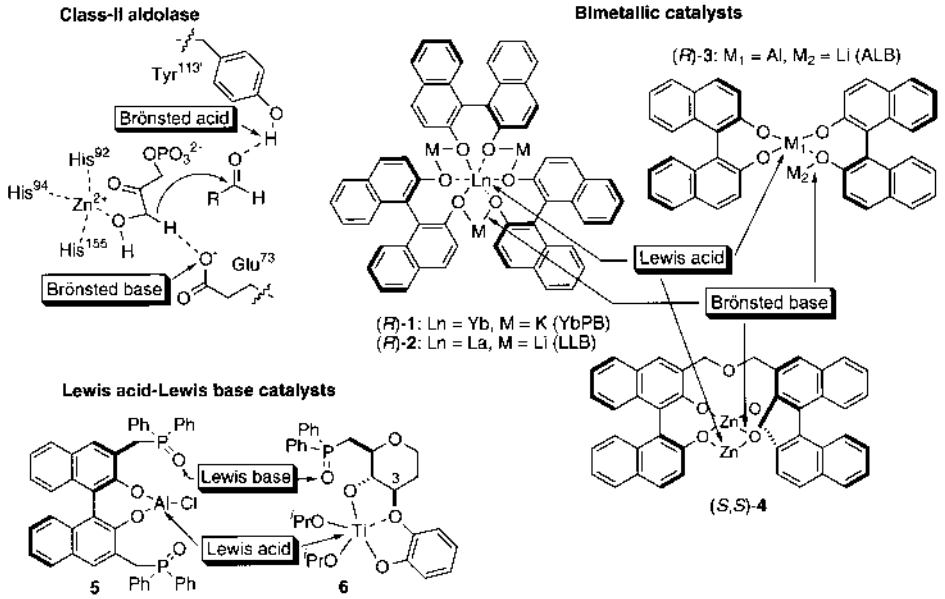
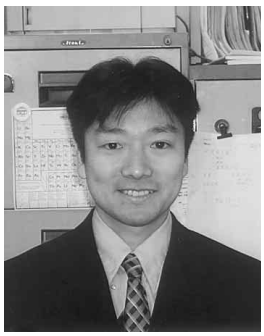


Fig. 1. Natural and Artificial Multifunctional Catalysts

Biographical Information of Masakatsu Shibasaki

Masakatsu Shibasaki was born in 1947 in Saitama, Japan, and received his PhD. from The University of Tokyo in 1974 under the direction of the late Professor Shun-ichi Yamada before doing postdoctoral studies with Professor E. J. Corey at Harvard University. In 1977 he returned to Japan and joined Teikyo University as an associate professor. In 1983 he moved to Sagami Chemical Research Center as a group leader, and in 1986 took up a professorship at the University of Hokkaido, before returning to The University of Tokyo as a professor in 1991. He was a visiting professor at Philipps-Universität Marburg during 1995. He has received the Pharmaceutical Society of Japan Award for Young Scientists (1981), Inoue Prize for Science (1994), Fluka Prize (Reagent of the Year, 1996), the Elsevier Award for Inventiveness in Organic Chemistry (1998), the Pharmaceutical Society of Japan Award (1999) and Molecular Chirality Award (1999). His research interests include asymmetric catalysis, including asymmetric Heck reactions and reactions promoted by multifunctional asymmetric complexes, and also the medicinal chemistry of biologically significant compounds.

Masakatsu Shibasaki



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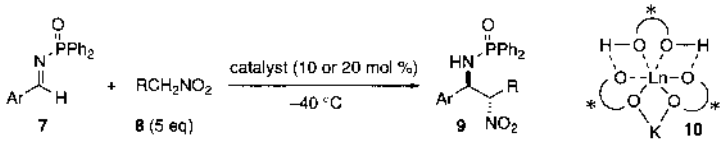
Motomu Kanai was born in 1967 in Tokyo, Japan, and received his PhD. from Osaka University in 1995 under the direction of Professor Kiyoshi Tomioka before doing postdoctoral studies with Professor Laura L. Kiessling at the University of Wisconsin. In 1997 he returned to Japan and joined Professor Shibasaki's group in The University of Tokyo as an assistant professor. He is currently a lecturer in Shibasaki's group. He has received the Pharmaceutical Society of Japan Award for Young Scientists (2001).

Table 1. Catalytic Asymmetric Nitro-Mannich Type Reaction Promoted by Heterobimetallic Catalysts



Entry	Ar	Imine	Nitroalkane (R)	Catalyst (mol%)	Yield (%)	ee (%)	dr (*anti* : *syn*)
1	Ph	**7a**	**8a** (H)	(*R*)-**10** (20)	79	91	—
2	4-Cl–C_6H_4	**7b**	**8a** (H)	(*R*)-**10** (20)	93	87	—
3	*p*-Tolyl	**7c**	**8a** (H)	(*R*)-**10** (20)	85	89	—
4	2-Furyl	**7d**	**8a** (H)	(*R*)-**10** (20)	57	83	—
5	2-Thiophenyl	**7e**	**8a** (H)	(*R*)-**10** (20)	41	69	—
6	Ph	**7a**	**8b** (Me)	(*R*)-**3**-KO^{t}Bu (20)	77	83	6 : 1
7	Ph	**7a**	**8c** (Et)	(*R*)-**3**-KO^{t}Bu (20)	98	74	6 : 1
8	Ph	**7a**	**8d** ($(CH_2)_2OBn$)	(*R*)-**3**-KO^{t}Bu (20)	95	82	7 : 1
9	Ph	**7a**	**8e** ($(CH_2)_3OBn$)	(*R*)-**3**-KO^{t}Bu (20)	75	77	6 : 1
10	*p*-Anisyl	**7f**	**8c** (Et)	(*R*)-**3**-KO^{t}Bu (20)	77	78	6 : 1
11	*p*-Tolyl	**7c**	**8c** (Et)	(*R*)-**3**-KO^{t}Bu (10)	98	81	5 : 1
12	4-Cl–C_6H_4	**7b**	**8c** (Et)	(*R*)-**3**-KO^{t}Bu (10)	97	74	3 : 1

the imines. The results are summarized in Table 1, entries 1 through 5.

Unfortunately, however, catalyst **10** did not promote the reaction with other nitroalkanes such as nitroethane. The binding pocket of catalyst **10** might be too small to hold both the *N*-phosphinoylimine and nitroethane. Therefore, we began to examine the reaction using the AlLi[(*R*)-binaphthoxide]$_2$ complex [(*R*)-ALB, **3**].[8] ALB has two binaphthoxide moieties as a chiral ligand, and might therefore have a larger binding pocket for the substrates compared to catalyst **10**, which has three binaphthoxide units. Although (*R*)-ALB alone did not promote the reaction of **7a** and nitroethane at a low temperature, the complex of ALB (20 mol%) and KO^{t}Bu (18 mol%), the so-called second generation ALB,[19] catalyzed the reaction at −40 °C in dichloromethane giving the product after 48 h in 77% yield, a diastereomeric ratio (dr) of 6 : 1, and of 83% ee for the major diastereomer. (Table 1, entry 6). The system is quite general for aromatic imines and nitroalkanes. In some cases (Table 1, entries 11, 12), the amount of the catalyst could be reduced to 10 mol% without affecting the chemical yield, dr and ee.

The products were readily converted to chiral diamines by reduction with SmI_2 followed by the deprotection of the phosphinoyl group (HCl/MeOH). Therefore, although improvement in terms of enantioselectivity and diastereoselectivity is still needed, this reaction affords an atom-economical route for synthesizing various chiral diamines. Catalytic asymmetric synthesis of lead compounds for drugs, using this reaction as a key step, is currently in progress in our laboratory.

2-2. Direct Catalytic Asymmetric Aldol Reaction of 2-Hydroxyacetophenone Using Bimetallic Complexes[20] The development of a range of catalytic asymmetric aldol reactions is a valuable contribution to asymmetric synthesis.[21] In all of these catalytic asymmetric aldol reactions, however, preconversion of the ketone moiety to a more reactive species such as an enol silyl ether and ketene silyl acetal is an unavoidable necessity. Thus, the development of a direct catalytic asymmetric aldol reaction is highly desirable in terms of atom economy.[17] In 1997, the direct catalytic asymmetric aldol reaction of aldehydes was achieved by us, using unmodified ketones with heterobimetallic asymmetric catalysis.[6] List *et al.*[22] and Trost *et al.*[23] also reported direct asymmetric aldol reactions using L-proline or a chiral semi-crown Zn complex as a catalyst.

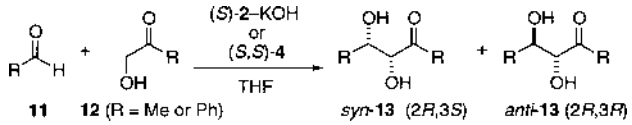


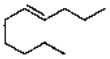
Chart 1. Direct Catalytic Asymmetric Aldol Reaction

Recently List *et al.* reported the first catalytic asymmetric synthesis of *anti*-1,2-diols using hydroxyacetone **12** (R=Me) in the aldol reaction (Chart 1), affording products in a high enantiomeric excess and high diastereomeric ratios.[24,25] Except for 3,3-dimethylbutanal, however, there is no other example for normal primary aldehydes. We developed a general, *anti*-selective, direct catalytic asymmetric aldol reaction using primary aldehydes and 2-hydroxyacetophenone **12** (R=Ph), promoted by the catalyst prepared from $LaLi_3$tris((*S*)-binaphthoxide) ((*S*)-LLB) (10 mol%), KHMDS (9 mol%) and H_2O (20 mol%). The results are summarized in Table 2.

Unfortunately, secondary or tertiary aldehydes produced no satisfactory results, and a new catalyst system had to be developed. The (*S*,*S*)-Zn–Zn-linked-BINOL complex **4** prepared from linked-BINOL and 2 eq of Et_2Zn (see Fig. 1) had interesting results. That is, the *syn*-aldol **13f** (R=Ph) was selectively obtained in a ratio of 5 (*syn*, 86% ee) to 1 (*anti*, 67% ee) in the treatment of 2-methylpropanal (**11f**) with 2-hydroxyacetophenone (**12** (R=Ph), 2 eq) in the presence of **4** (10 mol%) and triphenylphosphine oxide (20 mol%) (Table 3, entry 1). Moreover, as shown in Table 3, the reaction of **12** (R=Ph) with a variety of aldehydes afforded the corresponding *syn*-aldols stereoselectively with good ees.

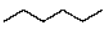
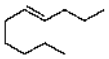
The observed stereoselectivities can be understood with the following mechanism. The formation of a chelate complex between catalyst (*S*)-**2**-KOH or (*S*,*S*)-**4** and the enolate generated from **12** (R=Ph) can result in an efficient shielding of the *Si* face of the enolate from the attack of aldehydes. Thus, the *anti*- and *syn*-products are obtained with an identi-

Table 2. Aldol Reaction Using Heterobimetallic Catalyst (*S*)-**2**-KOH[a)]

Entry	R	Product	Catalyst (mol%)	Time (h)	Yield[b)] (%)	dr (*anti* : *syn*)	ee (*anti*/*syn*)
1	 **11a**	**13a**	10	24	87 (84)	5 : 1	95/74
2[c)]	**11a**	**13a**	5	40	78 (78)	4 : 1	92/70
3	 **11b**	**13b**	10	24	90 (84)	3 : 1	94/84
4	 **11c**	**13c**	10	28	92 (90)	3 : 1	94/83
5	 **11d**	**13d**	10	24	92 (86)	2 : 1	90/83
6	 **11e**	**13e**	10	24	89 (89)	2 : 1	95/87

a) All reactions were performed at −50 °C, unless otherwise noted. *b*) The yield was determined by ^{1}H-NMR of the crude reaction mixture with anisole as an internal standard. The isolated yields after conversion to acetonides are given in parentheses. *c*) The reaction was carried out at −40 °C.

Table 3. Aldol Reaction Using Zn–Zn-linked-BINOL Complex (*S*,*S*)-**4**[a)]

Entry	R	Product	Catalyst (mol%)	Time (h)	Yield[b)]	dr (*anti* : *syn*)	ee (*anti*/*syn*)
1	 **11f**	**13f**	10	36	92	1 : 5	67/86
2	 **11g**	**13g**	10	48	89	1 : 6	78/85
3	 **11h**	**13h**	10	48	79	1 : 7	72/79
4	 **11b**	**13b**	10	60	80	1 : 2	73/77
5	 **11c**	**13c**	10	60	81	1 : 2	75/79
6	 **11d**	**13d**	10	36	80	1 : 2	79/83
7	 **11e**	**13e**	10	48	89	1 : 3	81/81

a) All reactions were carried out at −40 °C. *b*) Isolated yield after conversion to the corresponding acetonide.

cal configuration at the α-position (2*R*) with good to excellent selectivity. This mechanism differs from that of the direct asymmetric aldol reaction of acetophenone, in which the enantioface of the aldehyde is differentiated. On the other hand, the stereochemistry at the β-position can be affected by the enantioface selection of the aldehyde.

Although the diastereomeric ratios are not very high, these reactions can be regarded as a new tool to synthesize optically active 1,2-diols. Further investigations are ongoing.

3. Bifunctional Asymmetric Catalysis Promoted by Chiral Lewis Acid–Lewis Base Complexes

The success of the bimetallic Lewis acid–Brönsted base catalysts led us to design a new bifunctional asymmetric catalyst consisting of Lewis acid and Lewis base moieties that simultaneously activates both electophiles and nucleophiles at defined positions. This type of asymmetric catalysis is rarely observed.[26,27)] We selected TMSCN as the nucleophile, because TMSCN is activated by the Lewis base, forming hypervalent silicate.[28)] Thus, the studies began with the catalytic enantioselective cyanosilylation of aldehydes.

3-1. Catalytic Enantioselective Cyanosilylation of Aldehydes[29)] The addition of TMSCN to aldehydes is catalyzed by Lewis acids[30)] as well as Lewis bases[31)] to afford trimethylsilylated cyanohydrins. Cyanohydrins are highly versatile synthetic intermediates that can be easily converted to various important building blocks, including α-hydroxy carbonyl derivatives and β-amino alcohols. Because of their importance, there is currently considerable focus on developing methods for the catalytic asymmetric synthesis of

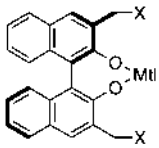
cyanohydrins.[32,33] Although impressive enantiomeric excess was obtained in some cases, the development of a more general asymmetric catalyst that is applicable to a wide variety of aldehydes is desirable.

We selected BINOL as the scaffold for arranging the Lewis acid and Lewis base moieties, as shown in Fig. 2. When the Lewis acid metal is connected to the two naphthols, the Lewis base moieties should be connected to the 3,3′-position of BINOL to promote the reaction efficiently *via* a dual activation pathway. The following two points are important for constructing a successful bifunctional catalyst: (1) The activation ability of the Lewis acid and Lewis base moieties toward an aldehyde and TMSCN should be balanced to promote the reaction *via* a dual activation pathway. (2) The internal coordination of the Lewis base to the metal should be avoided. The design shown in Fig. 2 should be very flexible to optimize these points by altering the metal, the Lewis base, and the linker length connecting the Lewis base and BINOL as needed.

First, the combination of the Lewis acid metal (Al, Ga, Ti, or Zr) and the Lewis base (phosphorus **14**, sulfur **15**, or phosphine oxide oxygen **5**) was optimized by the reaction of TMSCN with benzaldehyde, changing these two moieties independently. The combination of aluminum chloride as a Lewis acid and a phosphine oxide as a Lewis base (**5**) afforded the best catalyst in terms of reactivity as well as enantioselectivity and the product was obtained with 87% ee and 91% yield at −40 °C for 37 h. Catalysts **14** and **15** were partially decomposed by silylation of the ligands during the reaction. Thus, there was a lower reactivity and lower enantioselectivity. On the other hand, there was no silylation of ligand **5-L** in any combination with Lewis acid metals.

To confirm the ability of phosphine oxide to activate TMSCN, we reacted hydrocinnamaldehyde with TMSCN in the presence or absence of $Bu_3P(O)$, without a Lewis acid. Thus, in the presence of 40 mol% of $Bu_3P(O)$, the product was obtained in 81% yield at ambient temperature for 7.5 h. In the absence of the phosphine oxide, the yield was only 12% under the same conditions. At −40 °C for 40 h, however, the reaction did not proceed in the presence of $Bu_3P(O)$. These results suggest that the internal phosphine oxide of **5** activates TMSCN as a Lewis base, even at a low temperature, if the phosphine oxide is at the defined position close to the activated aldehyde, which is important for promoting the reaction *via* a dual activation mechanism.

Next, we investigated the effect of the relative position of the Lewis acid (Al) and the Lewis base (the oxygen atom of the phosphine oxide) by changing the linker length between the phosphine oxide and the scaffolding BINOL (**5** *vs.* **16**). Molecular modeling studies suggest that the coordination of the Lewis base to the internal aluminum is torsionally unfavorable in the case of **5**. The internal coordination of **16**, having an ethylene linker, seemed to be quite stable without strain. Therefore, in the case of catalyst **16**, strong intramolecular coordination of the phosphine oxide should reduce the Lewis acidity of the aluminum, therefore diminishing the catalytic efficiency of **16**. In accordance with this expectation, the reaction of TMSCN with benzaldehyde, catalyzed by **16** (9 mol%), proceeded slowly at −40 °C (37 h) and afforded the cyanohydrin in only 4% yield after hydrolysis. This result stands in contrast to the much higher reactivity of



5: X = $P(O)Ph_2$
14: X = PPh_2
15: X = SEt
16: X = $CH_2P(O)Ph_2$
17: X = $CHPh_2$
18: X = $P(O)(C_6H_4N(CH_3)_2\text{-}p)$

Fig. 2

catalyst **5** (91% yield under the same conditions). Therefore, in the case of **5**, the intramolecular binding of phosphine oxide to the aluminum seems to be labile enough to allow for the coordination of the aldehyde with the aluminum. Consequently, we extensively investigated the best catalyst **5**, in which the aluminum acts as a Lewis acid and the oxygen atom of the phosphine oxide acts as a Lewis base with the methylene linker to connect the Lewis base and the scaffolding BINOL.

Preliminary evidence of the bifunctional catalysis by **5** was obtained in control experiment using catalyst **17**, which contains only a steric bulkiness (diphenylmethyl group), but not a Lewis base, at the 3,3′-position of BINOL. Thus, **17** (9 mol%) gave the cyanohydrin of benzaldehyde in 50% yield and 12% ee (−40 °C, 37 h), of which the absolute configuration was the opposite (*R*) to that obtained by **5**. The reversal of the absolute configuration of the products was generally observed, using either **5** or **17**. In the case of **17**, it would be reasonable to assume that TMSCN attacks the activated aldehyde, coordinating to the aluminum, from the less hindered side (opposite to the diphenylmethyl group). Then, in the case of **5**, TMSCN appears to attack the aldehyde from the side of the phosphine oxide. This can be explained if we assume that TMSCN, which is activated by the phosphine oxide, reacts with the aldehyde.

Encouraged by the result with benzaldehyde using catalyst **5**, the reaction of aliphatic aldehydes was then investigated. Surprisingly, aliphatic aldehydes afforded very low ees. We anticipated that there would be competition between two reaction pathways in the case of the more reactive aliphatic aldehydes. The desired pathway involves a dual interaction between the Lewis acid and the aldehyde and between the Lewis base and TMSCN, whereas the undesired pathway involves mono-activation by the Lewis acid. We assumed that these two pathways could differ more significantly if the Lewis acidity of the catalyst was decreased. Therefore, we investigated the effect of additives that coordinate to the aluminum to reduce its Lewis acidity. Moreover, the additive could change the geometry of the aluminum from tetrahedral to trigonal bipyramidal,[34] which should allow the phosphine oxide to get into a more favorable position relative to the aldehyde (Fig. 3).

After several attempts, electron donating phosphine oxides were found to have a beneficial effect on the ee. In the case of hydrocinnamaldehyde **19a**, the ee values of **20a** significantly increased from 9 to 41% and 56% by the addition of 36 mol% of $CH_3P(O)Ph_2$ and $Bu_3P(O)$, respectively. Further improvement of the ee (up to 97%) was achieved by the slow addition of TMSCN (10 h) *via* a syringe pump in the presence of $Bu_3P(O)$. In the case of benzaldehyde **19h**, however, addition of $Bu_3P(O)$ resulted in a very slow reaction, affording only a trace amount of the product. The reaction proceeded in 98% yield with 96% ee, however, in the pres-

ence of $CH_3P(O)Ph_2$. Therefore, we used $Bu_3P(O)$ as the additive for aliphatic and α,β-unsaturated aldehydes, and $CH_3P(O)Ph_2$ as the additive for aromatic aldehydes.

To confirm the origin of the beneficial effect of the additive phosphine oxide, the initial kinetics of the reaction of hydrocinnamaldehyde **19a** were measured in the presence or absence of the additive $Bu_3P(O)$. The initial reaction rate in the presence of $Bu_3P(O)$ was 0.6 times slower than in the absence of $Bu_3P(O)$. This result can be explained from the lower Lewis acidity of the pentacoordinated aluminum in the presence of the additive phosphine oxide. Thus, the additive phosphine oxide should finely tune the balance of the Lewis acidity and the Lewis basicity of the bifunctional catalyst, as well as the relative position of the activated aldehyde and TMSCN in the transition state. Because the reaction pathway involving activation by the external phosphine oxide is negligible at −40 °C, only the internal phosphine oxide functions as an activator of TMSCN. The internal phosphine oxide exists at the appropriate position close to TMSCN in the reactive complex.

This catalyst is practical and has a broad generality with respect to a variety of aldehydes that can be used (Table 4). These reactions can be performed on a gram scale.[35] Specifically, aldehyde **19g** was converted to cyanohydrin **20g**, which is a key intermediate for the asymmetric synthesis of the antineoplastic natural product epothilones.[36]

To elucidate the origin of the excellent enantioselectivity with wide generality of the bifunctional catalyst **5**, kinetic studies were performed to compare the initial reaction rate using **5** and **18**, which contained the more electron-rich phosphine oxide. The initial reaction rate using **18** (10 mol%) was 1.2 times faster than using **5** (10 mol%) ($k_{14}/k_3=1.2$), reflecting the higher Lewis basicity of the phosphine oxide in the reaction of hydrocinnamaldehyde **19a** in the presence of $Bu_3P(O)$ (40 mol%). Furthermore, by the one-portion addition of TMSCN, catalyst **18** (10 mol%) gave **20a** in 86% yield and in 68% ee in the presence of $Bu_3P(O)$ (40 mol%) (−40 °C for 36 h), whereas **5** gave **20a** in 60% yield and 56% ee under the same conditions. The increased reaction rate and enantioselectivity by **18** is consistent with the dual activation mechanism of these catalysts. A more electron-rich phosphine oxide should activate TMSCN more efficiently, thus facilitating the desired dual activation pathway.

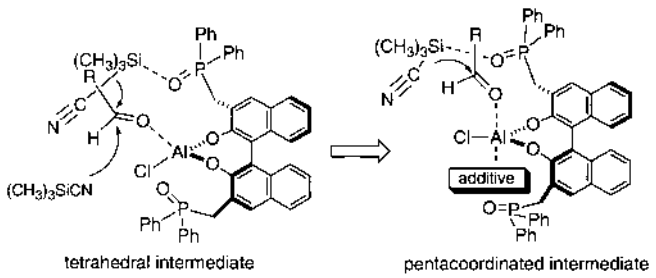
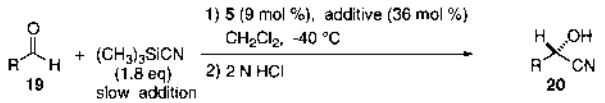


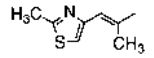
Fig. 3. Assumption for the Improvement of the Enantioselectivity by an Additive

Thus, the enantioselectivity of the reaction catalyzed by **5** may be explained by the working model depicted as **22** in Fig. 4, with the external phosphine oxide coordinating to the pentavalent aluminum. This geometry would allow the aldehyde to position itself at the apical site close to the internal phosphine oxide. TMSCN, interacting with the internal phosphine oxide, could then transfer cyanide to the aldehyde thus giving the observed *S*-product.

3-2. Application to a Catalytic Asymmetric Total Synthesis of Epothilones[36] Epothilones (A: **24**, B: **25**) have potent antitumor activity by binding and stabilizing the microtubules in the same manner as taxol, and they are promising drug candidates. Highly efficient total syntheses of epothilones were recently reported by Danishefsky, Nicolaou, Schinzer, Shibasaki and others.[37] Our retrosynthesis is shown in Fig. 5. The catalytic asymmetric cyanosilylation was utilized for the synthesis of fragment **26** and **27**. Keeping the concentration of TMSCN low was important in the case of the aldehyde **19g**. This situation was special for the aldehyde **19g**, which contained a thiazole moiety. We anticipated that the excess TMSCN would be activated by the coordination of the thiazole to the trimethylsilyl group, causing deactivation of catalyst **5** by exchanging the aluminum chloride for aluminum cyanide. The amount of catalyst **5** could be reduced to 5 mol% using 20 mol% of $Bu_3P(O)$ and slow addition of TMSCN (1.2 eq) for 48 h to give **20g** in 97% yield with 99% ee (50 h including the slow addition time). The

Table 4. Catalytic Asymmetric Cyanosilylation of Various Aldehydes under the Optimized Conditions



Entry	R	Aldehyde	Product	Additive	Time (h)	Yield (%)	ee (%)	*S*/*R*
1	$Ph(CH_2)_2$	**19a**	**20a**	$Bu_3P(O)$	37	97	97	*S*
2	$CH_3(CH_2)_5$	**19b**	**20b**	$Bu_3P(O)$	58	100	98	*S*
3	$(CH_3)_2CH$	**19c**	**20c**	$Bu_3P(O)$	45	96	90	*S*
4	$(CH_3CH_2)_2CH$	**19d**	**20d**	$Bu_3P(O)$	60	98	83	*S*
5	*trans*-$CH_3(CH_2)_3CH=CH_2$	**19e**	**20e**	$Bu_3P(O)$	58	94	97	—
6	$PhCH=CH$	**19f**	**20f**	$Bu_3P(O)$	40	99	98	*S*
7[a]		**19g**	**20g**	$Bu_3P(O)$	50	97	99	*S*
8[b]	Ph	**19h**	**20h**	$CH_3P(O)Ph_2$	96	98	96	*S*
9	*p*-$CH_3C_6H_4$	**19i**	**20i**	$CH_3P(O)Ph_2$	79	87	90	*S*
10[c]		**19j**	**20j**	$CH_3P(O)Ph_2$	70	86	95	*S*

a) 5 mol% of **5** was used. *b*) TMSCN was added over 1 min. *c*) 18 mol% of **5** and 72 mol% of additive were used.

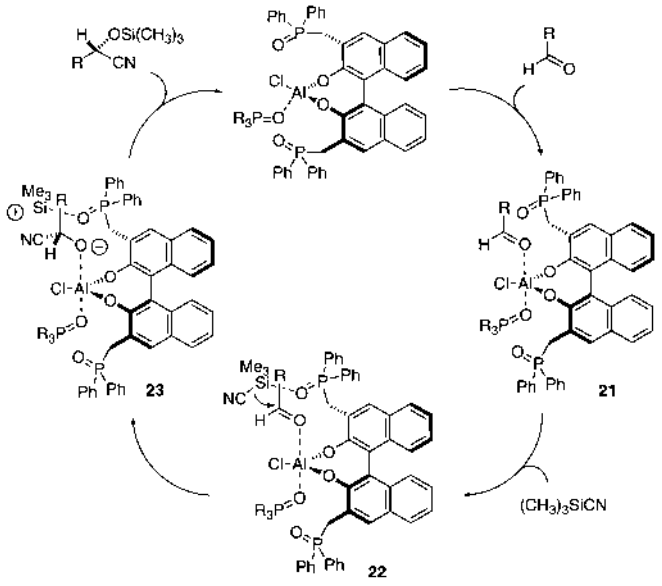


Fig. 4. Proposed Catalytic Cycle

other fragment was synthesized *via* the catalytic asymmetric protonation in the conjugate addition of a thiol to an α,β-unsaturated thioester promoted by the heterobimetallic complex (SmSB)[11] and the direct catalytic asymmetric aldol reaction promoted by a heteropolymetallic complex,[6] as key steps. A unique and efficient catalytic asymmetric total synthesis of epothilones A and B was achieved by combining three original catalytic asymmetric reactions developed in our laboratory, clearly demonstrating the practicality and power of these catalysts for the synthesis of complex molecules.

3-3. Catalytic Enantioselective Strecker-Type Reaction[38] The catalytic asymmetric Strecker-type reaction[39] is one of the most direct and efficient methods for the asymmetric synthesis of natural and unnatural α-amino acids. Several excellent reactions of this type were recently reported.[40] Because the Lewis acid–Lewis base bifunctional complex **5** is an excellent catalyst for the cyanosilylation of aldehydes, we applied this catalyst to an asymmetric Strecker-type reaction (the addition of TMSCN to imines).

Early in the project, we observed that a substituent on the nitrogen atom of imines had a dramatic effect on enantioselectivity. Although the reaction of TMSCN (2 mol eq) with the *N*-allyl benzaldehyde imine catalyzed by 9 mol% of **5** at −40 °C gave the product with only 4% ee in 67% yield, the reaction of *N*-benzhydryl imine gave the product with 78% ee in 84% yield. The ee was further increased to 95% (97% yield) by reaction with *N*-fluorenyl imine **34a**. This protecting group was also effective for the aliphatic pivalaldehyde imine **34m** to give the corresponding aminonitrile **35m** in 75% ee in 94% yield (192 h). As will be discussed later, the substituent on the nitrogen atom should be close to the naphthyl moiety of the catalyst in the transition state. The fluorenyl group might be important for stabilizing this desired transition state, possibly by π stacking interaction, thus producing better enantioselectivity.

To increase reaction efficiency by facilitating the reaction rate, we investigated the effect of additives and found that protic additives such as alcohols and phenol had a beneficial effect on the reaction rate. Thus, by slow addition (12 h) of

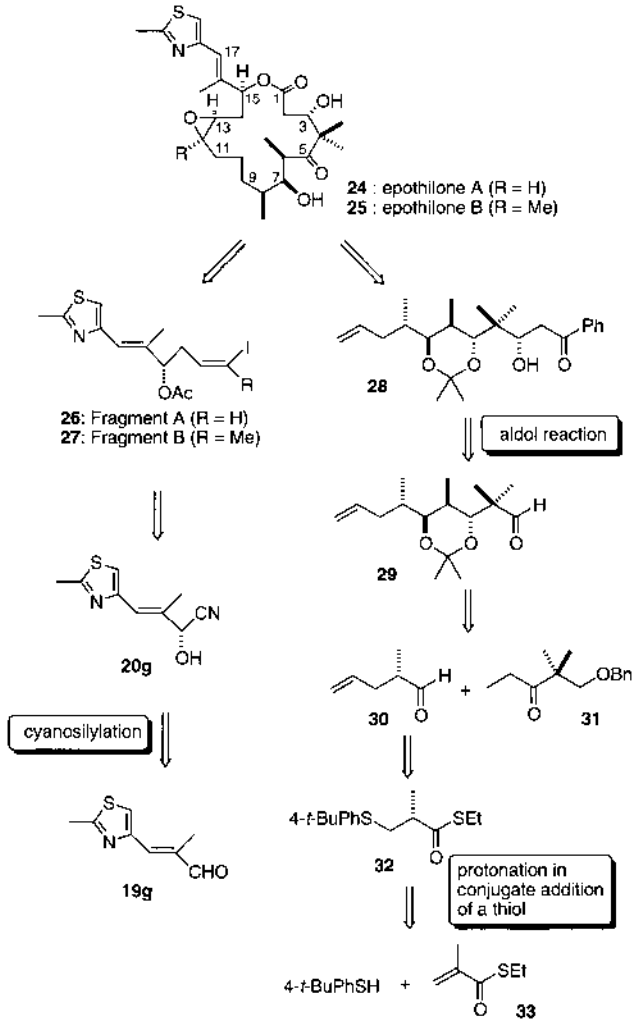


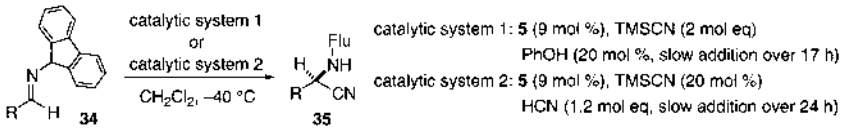
Fig. 5. Retrosynthetic Analysis of Epothilone A and B

110 mol% of MeOH, ^{i}PrOH, ^{t}BuOH, or PhOH, all reactions using **34m** were completed after 22 h, giving the product **35m** in more than 94% yield and with 66, 68, 72, and 78% ee, respectively.

We next investigated the possibility of promoting the reaction using a catalytic amount of the best additive (PhOH) without diminishing the synthetic utility of this reaction. Even when the amount of PhOH was reduced to 20 mol%, the reaction was completed after 44 h to give **35m** in 97% yield with 78% ee. Consequently, the effective reaction conditions involved the slow addition (17 h) of PhOH (20 mol%) to a mixture of **5** (9 mol%), the imine and TMSCN (2 mol eq) (catalytic system 1).

Although the ee of the product varied from 66 to 78% depending on the additive, the following results suggested that the additive did not have a major role in the enantioface selection step. When the chiral alcohol 2-phenylethanol was used as an additive, both the *R* and *S* isomer afforded *R*-**34m** in almost the same enantioselectivity (64 and 67% ee, respectively) and yield (90 and 91%). Moreover, the ^{31}P-NMR spectra of the catalyst in the absence or presence of PhOH (20 mol%) was exactly the same under the reaction conditions (δ=42.2, 51.2 ppm), suggesting a negligible interaction between the catalyst and the additive. Therefore, the protic additive seemed to facilitate the reaction without changing

Table 5. Catalytic Asymmetric Strecker-Type Reaction



Entry	R	34a—m	System 1			Entry	System 2		
			Time (h)	Yield (%)	ee (%)		Time (h)	Yield (%)	ee (%)
1	Ph	**a**	44	92	95	14	36	92	95
2	*p*-ClPh	**b**	44	92	95				
3	*p*-MeOPh	**c**	44	93	93				
4	1-naphthyl	**d**	68	95	89				
5	2-furyl	**e**	44	93	79				
6	3-furyl	**f**	44	92	90	15	36	92	87
7		**g**	58	90	89				
8	*trans*-PhCH=CH	**h**	41	80	96	16	36	78	92
9	*trans*-$CH_3(CH_2)_3CH$=CH	**i**	24	66	86[a]				
10	$CH_3(CH_2)_5$	**j**	24	80	80[b]	17	36	75	81
11	CH_3CH_2	**k**	44	84	70				
12	^{i}Pr	**l**	44	89	72	18	36	92	71
13	^{t}Bu	**m**	44	97	78	19	36	98	77

a) 50 mol% of PhOH was used. The aminonitrile was isolated as the corresponding trifluoroacetamide. *b*) Without PhOH.

the catalytic species.

A variety of *N*-fluorenyl aldimines were examined as substrates for this optimized catalytic asymmetric Strecker-type reaction, and the results are shown in Table 5 (entries 1—13). Aromatic aldimines, including heterocyclic aldimines, α,β-unsaturated aldimines, and aliphatic aldimines can be converted to Strecker products in excellent yields with good to excellent enantioselectivities.

Kinetic studies (Fig. 6) revealed that TMSCN acts as the active nucleophile in this catalytic system. When adding PhOH in one portion, the generation of HCN was observed using ^{1}H-NMR.[41] This HCN could act as a nucleophile. When HCN (2 mol eq) was added in one portion, however, in the absence of TMSCN, the initial reaction rate was 0.4 times slower (Fig. 6, ▲) than when TMSCN was used in the presence of 20 mol% of PhOH (●, initial steep dotted line), and the ee value of the product **35a** was only 53% (95% ee under the best conditions, see Table 5, entry 1). Furthermore, under the slow addition (26 h) conditions of HCN, which should better represent the best reaction conditions using TMSCN and slow addition of PhOH, **35a** was obtained in 54% yield with 28% ee after 85 h. These results revealed that TMSCN is the reactive nucleophile. Although HCN might be generated under these conditions by the reaction of TMSCN with PhOH, the highly enantioselective pathway with TMSCN as an active nucleophile predominates, because the reaction rate with TMSCN is faster than with HCN in this catalytic system. Thus, the described reaction is the first example of a catalytic asymmetric Strecker-type reaction with TMSCN as an active nucleophile. This unique feature of the catalytic system using **5** can be derived from the activation ability of the Lewis basic phosphine oxide moiety of the bifunctional catalyst **5** toward TMSCN.

The role of the additive PhOH was elucidated. The initial reaction rate in the presence of 20 mol% of PhOH (●, initial steep dotted line) was 82 times faster than in the absence of PhOH (■). After approximately 20% consumption of the

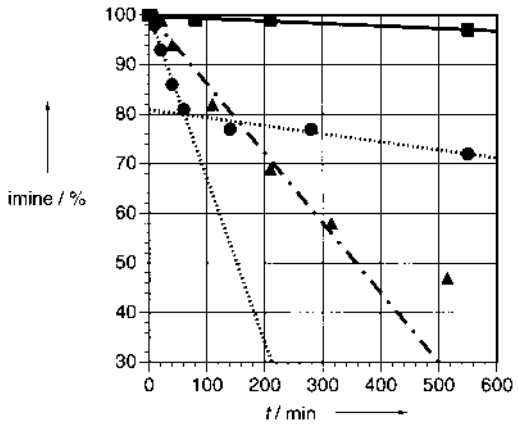


Fig. 6. Initial Reaction Rate of **34a** in the Presence of Various Amounts of PhOH

The disappearance of **34a** was traced by ^{1}H-NMR: the reaction of TMSCN in the absence (■) and in the presence of 20 mol% (●) of PhOH, and the reaction of HCN (▲).

starting imine (*ca.* 80 min), which corresponded to the complete consumption of PhOH to TMSOPh, the reaction entered a slower phase (●, after 80 min). Even in this slower phase, however, the reaction rate was *ca.* 2 times faster than in the absence of PhOH. This might be due to the re-generation of a very small amount of PhOH from TMSOPh and the product amine **35a**. This re-generation of the proton source was also suggested from the fact that the initial reaction rate in the presence of 20 mol% of **35a** and TMSOPh was *ca.* 2 times faster than in the absence of these additives. These kinetic studies, together with the fact that the protic additive did not change the catalytic species, suggest that PhOH should work as a proton source to protonate the negative charge on the nitrogen atom that is generated by the addition of CN to the imine, thus accelerating the formation of **35** (Fig. 7). A small amount of the proton source would be regenerated *via* cycle II, thus significantly accelerating the reaction rate using a catalytic amount of PhOH. A small

amount of HCN, generated from TMSCN and PhOH in the reaction mixture, could also act as a proton source.

The absolute configuration of the products can be explained from the working model shown as **36** in Fig. 7. The Lewis acid (Al) and the Lewis base (phosphine oxide) activate the imine and TMSCN, respectively, at defined positions, thus affording the *R*-products. The dual activation mechanism of **5** is supported by the following results. Control catalyst **17**, containing the diphenylmethyl group that normally functions to produce steric hindrance, afforded the opposite enantiomer *S*-**35a** with 15% ee in 100% yield (42 h), using 20 mol% of PhOH. Therefore, in the case of **5**, TMSCN attacked the activated imine from the side of the phosphine oxide moiety.

Taking advantage of the intriguing reactivity difference between TMSCN and HCN in this catalytic reaction, we attempted to reduce the amount of TMSCN using HCN instead of PhOH. After the attack of TMSCN and protonation of the resulting intermediate **37** in Fig. 7 by HCN, TMSCN should be re-generated, and should again work as the nucleophile. Because the reaction of HCN with the imine might compete with the desired reaction of TMSCN as the nucleophile, we expected that it would be important to keep the concentration of HCN low by the slow addition of HCN. Thus, using 20 mol% of TMSCN and slowly adding the HCN (120 mol%) in CH_2Cl_2 (system 2), we obtained the products with results (Table 5, entries 14—19) comparable to that of the TMSCN-PhOH system (system 1). Optimization of the amount of TMSCN and the slow addition of HCN increases the potential for the application of this catalytic asymmetric reaction to a large-scale Strecker-type synthesis using HCN as a stoichiometric cyanide source.

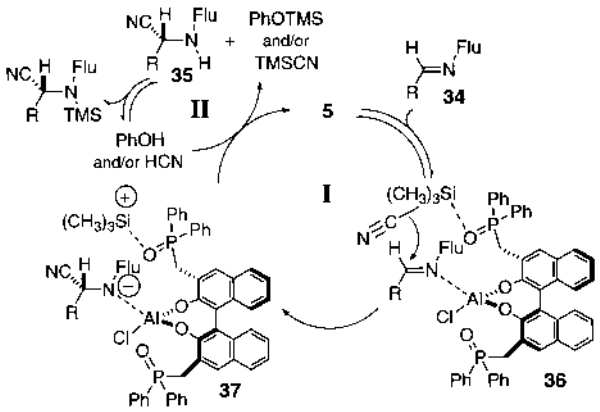


Fig. 7. Proposed Catalytic Cycle for Strecker-Type Reaction

Because a fluorenyl group is not often used as a protecting group for a nitrogen atom, we developed a procedure to deprotect this group without racemization. We first oxidized the amine to a fluorenone-derived imine, followed by hydrolysis to the amino acid (Chart 2). When the aromatic aminonitrile **35a** was directly treated under oxidation conditions (MnO_2, DDQ, CAN, or NBS), however, the target imine was not obtained. So, first **35a** (95% ee) was hydrolyzed to the amide **38** ($HCl(g)/HCO_2H$, room temperature, 1 h). Recrystallization from THF/ether gave the enantiomerically pure **38** in 90% yield. Oxidation of **38** by DDQ gave the corresponding fluorenone-derived imine **39**, which was converted to the amide **40** in 91% yield by acid hydrolysis. Enantiomeric purity of **40** was determined to be 98% ee after conversion to the corresponding urethane by *p*-nitrobenzyloxycarbonyl chloride. In the case of the aliphatic aminonitrile **35m** (78% ee), direct oxidation by activated MnO_2 gave the imine **41** in 95% yield with 77% ee. After acid hydrolysis to the corresponding aminonitrile **42**, the nitrile group was hydrolyzed to the amino acid **43**. The enantiomeric purity of **43** (78% ee) was determined after conversion to the protected form (*N*-Fmoc, methyl ester). Therefore, we established efficient routes for the conversion of the Strecker products. Similarly, **35k** was converted to the α-amino acid derivative. The absolute configurations were determined by comparing the optical rotations with the reported values.

Other important conversions, like the hydrogenation and the dihydroxylation of unsaturated aminonitriles **35h** and **35i**, were also performed. Direct hydrogenation of **35h** (96% ee) catalyzed by Pd/C afforded the corresponding saturated aminonitrile with complete racemization. This result was due to the migration of the olefin to the thermodynamically more

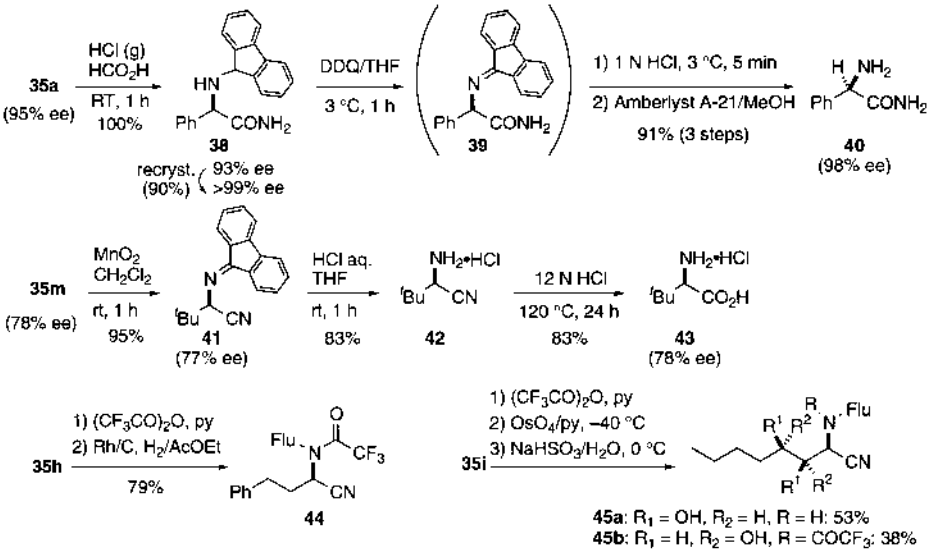


Chart 2. Conversion to α-Amino Acid Derivatives and Functionalization of Unsaturated Strecker-Products

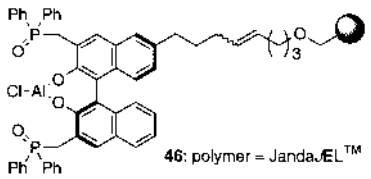
stable enamine, followed by reduction. When **35h** was treated with other transition metals, *e.g.*, $(Ph_3P)_3RhCl$ or Raney Ni, under a hydrogen atmosphere, elimination of HCN and hydrogenation of the resulting imine occurred to give the secondary amine. Therefore, we tried hydrogenation after protection of the amine as the trifluoroacetamide. Fortunately, hydrogenation of the protected amidonitrile by Rh/C afforded saturated **44** in 79% yield (2 steps) without any loss of enantiomeric purity. In addition, dihydroxylation of the trifluoroacetamide, derived from **35i**, afforded the amidonitriles **45a** and **45b** with functionalized side chains. These results clearly demonstrate the utility of this catalytic asymmetric Strecker-type reaction to synthesize a wide variety of natural and unnatural α-amino acid derivatives.

Furthermore, the catalyst was successfully immobilized on a solid-support (Janda*J*EL^{TM}) without significantly losing the enantioselectivity (Table 6).[42] The development of immobilized asymmetric catalysts is very important for easy separation of the product and the ability to reuse the catalyst. Solid-supported catalysts have considerable advantages over homogeneous ones, especially in high throughput organic chemistry.[43] The catalyst supported by the broken resin, which was prepared under stirring, was more reactive and enantioselective than the catalyst supported by the spherical resin, which was prepared under gentle shaking. The increased surface area of the broken resin should be advantageous for the access of TMSCN and aldehydes to the catalyst to promote the reaction in a dual activation manner. Although the resin was broken, the solid-supported catalyst **46** could be recovered and recycled at least five times (Table 7). The utility of the bifunctional asymmetric catalyst is enormously enhanced by immobilization. Further application to other reactions reported in this review is currently under investigation.

3-4. Catalytic Enantioselective Reissert-Type Reaction[44] The addition of cyanide to quinoline or isoquinoline derivatives in the presence of acid halides (the Reissert-type reaction[45]) is widely used as a key step for the synthesis of various heterocyclic compounds, especially for the synthesis of biologically important alkaloids.[46] Mechanistically, the reaction proceeds *via* an acyl quinolinium or isoquinolinium intermediate. Despite the importance of Reissert compounds as a versatile chiral building block, no asymmetric Reissert-type reaction of cyanide has yet been reported, even by using a stoichiometric amount of a chiral promoter. Developing a catalytic asymmetric Reissert-type reaction is a great challenge, for the following reasons. First, strong electrophiles such as an acid halide or TMSCl (generated during the reaction) could decompose the catalyst by acylating and/or silylating the ligand. Second, the conformation (the *s*-trans/*s*-cis isomers of the amide bond, see **52** and **51**) of the reactive acyl quinolinium or isoquinolinium ion is rather flexible. The two conformers produce opposing enantiomers even if TMSCN attacks the reactive intermediate from a defined side. Therefore, these two conformers should be strictly differentiated by the catalyst.

Optimization of the reaction conditions such as the acylating reagent, solvent, and chiral ligand using quinoline as the substrate, led to the conditions that involve 2-furoyl chloride, CH_2Cl_2-toluene mixed solvent, and the new catalyst **47**. Catalyst **47** contained di-*o*-tolylphosphine oxide, and therefore, had a higher Lewis basicity than the original catalyst **5**.

Table 6. Catalytic Enantioselective Strecker-Type Reaction Promoted by Solid-Supported Catalyst **46**[a]



Entry	Imine (R)	Time (h)	Yield (%)	ee (%)
1	**34a** (Ph)	60	98	87
2	**34b** (*p*-ClPh)	59	98	85
3	**34c** (*p*-MeOPh)	41	98	83
4	**34f** (3-furyl)	66	97	86
5	**34n** (*p*-MePh)	64	100	83
6	**34h** ((*E*)-PhCH=CH)	66	96	83

a) The reaction was performed at −50 °C.

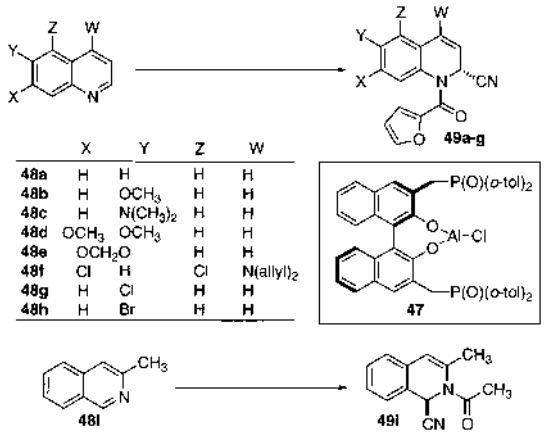
Table 7. Recycle of **46** Using **34a** as Substrate

Cycle	Time (h)	Yield (%)	ee (%)
1	60	98	87
2	44	95	81
3	44	78	83
4	110	97	80
5	204	83	77

Using **47**, the Reissert products were obtained in 57—99% yield with 67—96% ee (Table 8). Specifically, the reaction was successfully applied to the quinoline derivative **48f** even with 1 mol% of **47** (entry 7). The Reissert product **49f** could be converted to a potent NMDA-receptor antagonist L-689,560.[47,48] It is noteworthy that this reaction can be applied to the isoquinoline derivative **48i** (entry 10), giving the product **49i** with 71% ee in 99% yield by using **5** as the catalyst and acetyl chloride as the acylating reagent.

Although the detailed reaction mechanism is still not clear, the reaction should be promoted by the dual activation of the acyl quinolinium or isoquinolinium ion and TMSCN by the Lewis acid (Al) and the Lewis base (oxygen atom of the phosphine oxide) moieties of the catalyst, respectively. The results using the control catalyst **17** suggest the dual activation mechanism by **5** and **47**. Catalyst **17** contained diphenylmethyl groups that function only to produce steric bulkiness without any Lewis basicity. Thus, catalyst **17** afforded **49a** (R=Ph, 24% ee in 73% yield) and **49d** (R=2-furyl, 46% ee in 95% yield) with the opposite configuration (*S*). These results suggested that, in the case of **5** and **47**, TMSCN appeared to attack the acyl quinolinium intermediate from the side of phosphine oxide. Therefore, we postulated a working model for the catalytic cycle depicted in Fig. 8. The first step is the formation of the reactive acyl quinolinium intermediate **50** by the reaction of quinoline with the acid chloride. The acyl quinolinium ion is activated by complexation of the amide oxygen to the Lewis acid (Al). The two conformers of the amide bond **51** and **52** would exist in equilibrium. When TMSCN is activated by the Lewis-base moiety of the catalyst, reaction *via* **52** would be more favorable than *via* **51**. In the case of **51**, the distance between the activated TMSCN and the electrophilic carbon would be too far for catalysis.

Table 8. Catalytic Enantioselective Reissert-Type Reaction



Entry	Substrate	Catalyst (mol%)	Solvent	Time (h)	Yield (%)	ee (%)
1	**48a**	**47** (9)	CH_2Cl_2/toluene	64	91	85
2	**48b**	**47** (9)	CH_2Cl_2/toluene	40	74	89
3	**48c**	**47** (9)	CH_2Cl_2/toluene	40	72	89
4	**48d**	**47** (9)	CH_2Cl_2/toluene	40	99	91
5	**48e**	**47** (9)	CH_2Cl_2/toluene	60	77	83
6	**48f**	**47** (9)	CH_2Cl_2/toluene	40	80	96
7	**48f**	**47** (1)	CH_2Cl_2/toluene	40	83	93
8	**48g**	**47** (9)	CH_2Cl_2	64	57	67
9	**48h**	**47** (9)	CH_2Cl_2	112	63	67
10	**48i**	**5** (9)	CH_2Cl_2	15	99	71

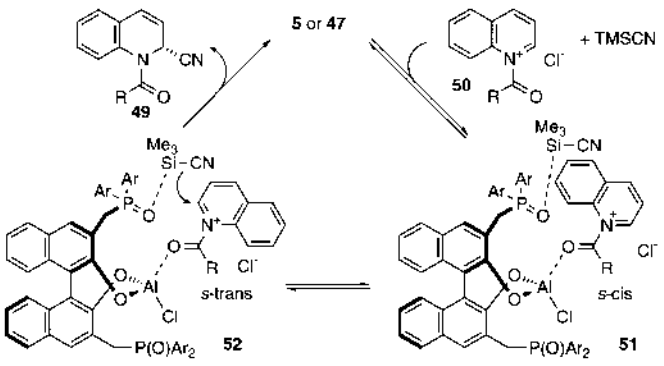


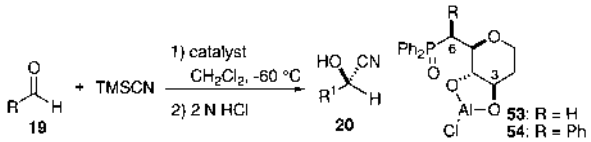
Fig. 8. Proposed Catalytic Cycle of Reissert-Type Reaction

The hypothetical transition state **52** could explain the absolute configuration of the product as *R*. Further investigations to clarify the reaction mechanism and a catalytic enantioselective total synthesis of biologically active alkaloids using this reaction is in progress.

3-5. Development of a Lewis Acid–Lewis Base Bifunctional Catalyst from a Carbohydrate Core[49] No perfect catalyst has yet been developed. Therefore, although catalyst **5** was satisfactory for the cyanosilylation of aldehydes, we began to develop a new bifunctional catalyst for this reaction. We hypothesized that carbohydrates would provide an ideal matrix for a bifunctional catalyst by arranging multifunctionalities at defined positions. The relative arrangement of the Lewis acid and the Lewis base could be tuned, selecting the optimum arrangement from various combinations of these functionalities as well as carbohydrate isomers. Although carbohydrates are among the most easily available chiral compounds in nature, they are rarely used as chiral scaffolds of Lewis acid catalysts. Extensive investigation indicated catalyst **53** to be a good catalyst (Table 9). In order to improve enantioselectivity by facilitating the dual activation pathway, we introduced a conformationally constraining group at position 6, to which the phosphine oxide is connected. If the substituent restricted the conformation to arrange the Lewis base moiety at the optimum position for cooperation with the Lewis acid, the transition state of the dual activation pathway would be more stable, thus being more favored. Catalyst **54**, containing a β-phenyl group, afforded an improved enantioselectivity compared to the original catalyst **53**. Although the enantioselectivity using **54** was still not satisfactory, these results clearly indicate that the orientation of the Lewis base moiety constrained by the substituent at the 6-position is very important for a high asymmetric induction. There was higher activity of catalysts **53** and **54**, compared to **5**. Thus, cyanosilylation of the much less reactive acetophenone proceeded with **53** with 20% ee. This reaction did not proceed at all with catalyst **5**.

3-6. Catalytic Enantioselective Cyanosilylation of Ketones[50] The catalytic promotion and stereocontrol of the cyanosilylation of ketones is much more difficult than of aldehydes, because ketones are much less reactive and the differentiation of two lone pairs of carbonyl oxygens is more difficult. Therefore, no practical asymmetric cyanosilylation of ketones had been reported before our contribution. For example, the best result using a chemical catalyst was 72% ee in the case of aryl methyl ketones.[51] This catalyst could not be applied, however, to aryl ethyl ketones (*ca.* 30% ee) or aliphatic substrates. Enzymatic reactions give cyanohydrins from methyl alkyl ketones with high enantioselectivity. Synthesis of cyanohydrins from ketones containing an aromatic or ethyl substituent, however, is not efficient using en-

Table 9. Catalytic Asymmetric Cyanosilylation of Aldehydes by a Sugar-Based Bifunctional Catalyst



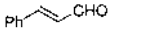
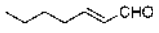
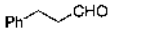
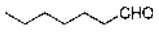
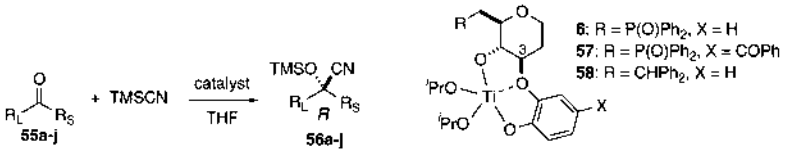
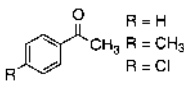
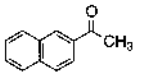
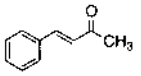
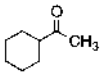
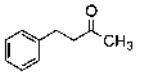
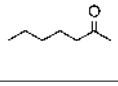
Entry	Aldehydes		Catalyst (mol%)	h	Yield (%)	ee (%)
1	PhCHO	**19h**	**53** (9)	24	95	66
			54 (9)	50	96	80
2		**19f**	**54** (5)	76	82	76
3		**19e**	**54** (5)	63	97	76
4		**19a**	**54** (5)	50	96	70
5		**19b**	**54** (5)	38	98	80

Table 10. Catalytic Asymmetric Cyanosilylation of Ketones



Entry	Ketone		Catalyst **6** (10 mol%)				Catalyst **57** (x mol%)					
			°C	h	Yield/%	ee/%	Entry	x	°C	h	Yield/%	ee/%
1	 R = H	**55a**	−30	36	85	92	11	1	−20	88	92	94
2	R = CH_3	**55b**	−30	84	80	90						
3	R = Cl	**55c**	−40	80	82	92	12	1	−25	92	72	90
4		**55d**	−40	80	82	95						
5		**55e**	−40	96	72	69	13	10	−40	96	90	84
6		**55f**	−20	64	89	91	14	1	−10	92	90	92
7		**55g**	−50	88	72	91						
8		**55h**	−50	36	86	90	15	2.5	−30	70	91	93
9		**55i**	−50	36	92	85						
10		**55j**	−50	24	79	84	16	10	−50	44	71	86
							17	2.5	−45	92	80	82

zymes.[52] Because ketone cyanohydrins are precursors of important chiral building blocks (chiral quaternary α-hydroxy carbonyl derivatives), and the reaction proceeds by the new bifunctional catalyst **53**, we began to develop a general enantioselective catalyst of cyanosilylation of ketones.

To improve the enantioselectivity of **53**, we planned to sterically hinder the undesired coordination site on the Lewis acid, introducing a catechol moiety at the C3 hydroxyl group. The coordination of the ether oxygen at C3 should make it possible to form a complex such as **6**. As a result, the phenyl group of the catechol should be fixed at the position shielding the α-side (*anti* to the phosphine oxide, concave side) of the catalyst, thus defining the position of the coordinating ketone at the β-side, *syn* to the Lewis basic phosphine oxide. This type of consideration would not be necessary if the reaction was promoted only *via* a dual activation by the bifunctional catalyst. However, there seemed to be a competitive pathway *via* a mono-activation by the Lewis acid. Therefore, we designed catalyst **6**.

After optimization of the reaction conditions such as choosing the best combination of Lewis acid metal and solvent, **6** promoted cyanosilylation of acetophenone with 92%

ee. As shown in Table 10, the newly developed catalyst **6** has a broad applicability for reactions of various ketones with high enantioselectivity, including both aromatic and aliphatic ketones. Specifically, less reactive ketones such as propiophenone **55f** and indanone **55e** gave the product in 89% and 72% yield with 91% and 69% ees. The enone **55g** gave the 1,2-adduct with complete regioselectivity. Even the simple *n*-alkanone **55j** gave the product in 84% ee. Thus, this is the first example of a general cyanosilylation reported to date. Product **56** was successfully converted to the quaternary hydroxy ester (HCl–EtOH, 90 °C for 3 h) or aldehyde (DIBAL-H) in a single step without a decrease in enantiomeric excess.

The catalyst was prepared as follows. Ligand **6-L** was reacted with 1 eq of $Ti(O^iPr)_4$ at 70 °C for 1 h in toluene. ^{1}H-NMR at this stage indicated that 2 eq of ^{i}PrOH were liberated. After evaporation of the solvent, 1 eq of ^{i}PrOH remained coordinating to the titanium metal. As a result, 1 eq of HCN was generated adding 1 eq of TMSCN. This solution was normally used as catalyst.

Because the catalyst solution contains 1 eq of HCN to the catalyst, HCN could act as a nucleophile. This possibility was eliminated, however, from the following labeling experiments. We prepared the active titanium catalyst containing $H^{12}CN$ from $Ti(O^iPr)_4$, **6-L** (1 eq) and $TMS^{12}CN$ (1 eq) (room temperature for 10 h). After complete conversion of $TMS^{12}CN$ to $H^{12}CN$ was confirmed by ^{1}H-NMR, **55a** (1 eq) and $TMS^{13}CN$ (1 eq) were added. Incorporation (77%) of ^{13}CN into the product **56a** was confirmed using ^{13}C-NMR. These results suggest that TMSCN, not HCN, is the cyanide source.

To gain further insight into the nature of this reaction, kinetic studies were performed and the reaction rate showed a first-order dependency on the catalyst. Meanwhile, preliminary studies to elucidate the role of the phosphine oxide revealed the importance of this moiety on enantioselectivity and catalytic activity. Thus, using the control ligand **58** containing a diphenylmethyl group, instead of the phosphine oxide, neither reaction of **55a** nor the more reactive **55i** proceeded at low temperature. These reactions proceeded very slowly at ambient temperature to give **56a** and **56i** in only 31% and 33% yields (80 h), respectively, and both with 2% ee. From these observations and previous results from our laboratory, we propose a dual activation transition state using the catalyst **6**, in which the titanium and the oxygen atom of the phosphine oxide activate the ketone and TMSCN as a Lewis acid and a Lewis base, respectively (Fig. 9).

Although this first example of cyanosilylation of ketones can be applied to a wide range of ketones, we planned to improve the enantioselectivity, particularly in the case of linear aliphatic ketones **55j** and cyclic ketones **55e**, and catalyst loading, by tuning the ligand structure. For the highly enantioselective dual activation pathway to occur, it is essential that the ketone coordinates to titanium at the position *syn* to the phosphine oxide (site A, Fig. 9). The catechol moiety at C-3 should differentiate the coordination sites A and B, sterically shielding site B. We expected that introducing a bulky group to this catechol moiety would hinder site B more effectively, further favoring the desired coordination of the ketone at site A. Furthermore, if substituent X is an electron-withdrawing group, the Ti-phenoxide bond should become stronger, thus giving rise to the more stable catalyst complex,

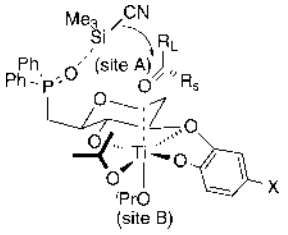


Fig. 9. Working Transition State Model

which should be advantageous for a minimized catalyst loading. For these steric and electronic reasons, we introduced a benzoyl group at the *para*-position of the phenoxide (**57-L**). Catalyst **57** is actually an improved catalyst in terms of enantioselectivity as well as catalyst loading. As shown in Table 10, chiral quaternary α-hydroxynitriles were obtained with excellent ees using 1 mol% of **57** in the case of aryl ketones and 2.5 mol% of **57** in the case of aliphatic substrates.

To further understand the mechanism of this reaction, determination of the catalyst structure by X-ray analysis is currently under investigation. A catalytic asymmetric total synthesis of a natural product using this reaction as a key step is also underway.

4. Conclusion

We believe that the successful development of the multifunctional concept has opened up a new field in asymmetric catalysis. We hope that the findings discussed herein will prove to be a significant landmark in the development of the field of catalytic asymmetric synthesis.

Acknowledgments The research reviewed in this paper was possible only through the dedication, enthusiasm, and creativity of scores of co-workers, whose names are acknowledged on the publications from our laboratory cited here.

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