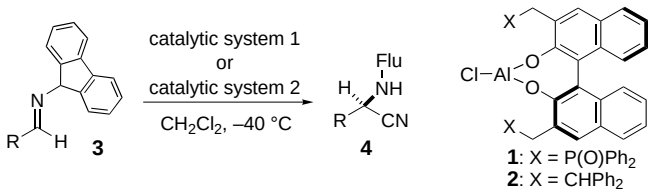
A Catalytic Asymmetric Strecker-Type Reaction: Interesting Reactivity Difference between TMSCN and HCN**

Masahiro Takamura, Yoshitaka Hamashima, Hiroyuki Usuda, Motomu Kanai, and Masakatsu Shibasaki*

The catalytic asymmetric Strecker-type reaction[1] is one of the most direct and efficient methods for the asymmetric synthesis of natural and unnatural α-amino acids. Recently, several excellent reactions of this type were reported, which reflects the importance of this field.[2] However, as far as we know, the reaction is not yet satisfactory in terms of the generality of the imine substrates. Although aromatic aldimines give excellent selectivities and yields, aliphatic aldimines, specifically *n*-aldimines, do not afford satisfactory results.[3] Furthermore, no examples of α,β-unsaturated imines, which should give products that are versatile precursors of functionalized α-amino acids, have been reported so far. Herein we disclose a general asymmetric Strecker-type reaction that is controlled by the bifunctional Lewis acid–Lewis base catalyst **1** (9 mol%; Scheme 1).[4] The reaction



Scheme 1. Catalytic system 1: **1** (9 mol%), TMSCN (2 mol equiv); PhOH (20 mol%, slow addition over 17 h). Catalytic system 2: **1** (9 mol%), TMSCN (20 mol%); HCN (1.2 mol equiv, slow addition over 24 h).

proceeds with good to excellent enantioselectivities toward various imines, including *n*-aldimines and α,β-unsaturated imines, in the presence of a catalytic amount of phenol (20 mol%; catalytic system 1). Furthermore, we have found that TMSCN is more reactive than HCN in the reaction catalyzed by **1**, which led to the idea for developing a novel catalytic system composed of **1** (9 mol%), TMSCN (20 mol%), and HCN (120 mol%; catalytic system 2).

We reported previously that the Lewis acid–Lewis base bifunctional catalyst **1** promotes the addition of TMSCN to a variety of aldehydes with high enantioselectivities.[4] The origin of the highly enantioselective catalysis by **1** is the simultaneous activation of aldehydes and TMSCN by the Lewis acid (Al) and the oxygen atom of the phosphane oxide, respectively. Therefore, it seemed to be a rational extension to apply this catalyst to the development of an asymmetric Strecker-type reaction. We started this project by observing that the nature of the substituent on the nitrogen atom of imines had a dramatic effect on the enantioselectivity of the reaction. Although the reaction of TMSCN (2 mol equivalents) with the *N*-allyl bezaldehydeimine catalyzed by 9 mol% of **1** at $-40\,^{\circ}C$ gave the product with only 4% *ee* in 67% yield (62 h), the reaction of *N*-benzhydrylimine gave the product with 78% *ee* in 84% yield (85 h). The *ee* value was further increased up to 95% (97% yield) by the reaction with *N*-fluorenylimine (**3a**, 111 h). The fluorenyl group is also effective in forming the aminonitrile **4m** in 75% *ee* in 94% yield (192 h) from the corresponding aliphatic pivalaldehydeimine (**3m**).

We investigated the effect of additives in the reaction and found that protic additives such as alcohols and phenol afforded a beneficial effect on the reaction rate.[5,6] Thus, all the reactions using **3m** were completed in 22 h by slowly (12 h) adding 110 mol% of MeOH, *i*PrOH, *t*BuOH, or PhOH, to give the products **4m** with 66, 68, 72, and 78% *ee*, respectively (>94% yield). Although the *ee* values of the products varied from 66 to 78% depending on the additives, the following results suggested that the additive did not perform a major role in the enantioface selection step. First, when the chiral alcohol 2-phenylethanol was used as an additive, both the *R* and *S* isomer afforded (*R*)-**4m** in almost the same enantioselectivity (64 and 67% *ee*, respectively) and yield (90 and 91%). Second, 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 used, thus suggesting a negligible interaction between the catalyst and the additive.[7] Therefore, the protic additive seems to facilitate the reaction without changing the catalytic species. We next investigated the possibility of promoting the reaction by using a catalytic amount of the best additive (PhOH) without diminishing the synthetic utility of this reaction. Gratifyingly, even when the amount of PhOH was reduced to 20 mol%, the reaction was completed in 44 h to give **4m** in 97% yield with 78% *ee*. Consequently, the effective reaction conditions were found to involve the slow (17 h) addition of PhOH (20 mol%) to a mixture of **1** (9 mol%), the imine, and TMSCN (2 mol equivalents; catalytic system 1).

A variety of *N*-fluorenylaldimines were examined as substrates for this optimized catalytic asymmetric Strecker-type reaction, and the results are shown in Table 1. Aromatic aldimines including heterocyclic aldimines, α,β-unsaturated aldimines, as well as aliphtic aldimines can be converted into Strecker products in excellent yields with good to excellent enantioselectivities. The Strecker products were successfully converted into the corresponding amino acid derivatives in high yields without loss of enantiomeric purity, and the absolute configurations of these products were determined to be *R* (Scheme 2).[8] Furthermore, hydrogenation or dihydroxylation[9] of the products from α,β-unsaturated imines afford-

[*] Prof. Dr. M. Shibasaki, M. Takamura, Y. Hamashima, H. Usuda, Dr. M. Kanai
Graduate School of Pharmaceutical Sciences
The University of Tokyo
Hongo, Bunkyo-ku, Tokyo 113-0033 (Japan)
Fax: (+81) 3-5684-5206
E-mail: mshibasa@mol.f.u-tokyo.ac.jp

[**] This work was supported by CREST and RFTF. We thank Professor Kobayashi and Dr. Ishitani at the University of Tokyo for kindly showing us their recent results and the procedure for the preparation of HCN. We also thank Professor Hoveyda in Boston College for kindly showing us his recent results.

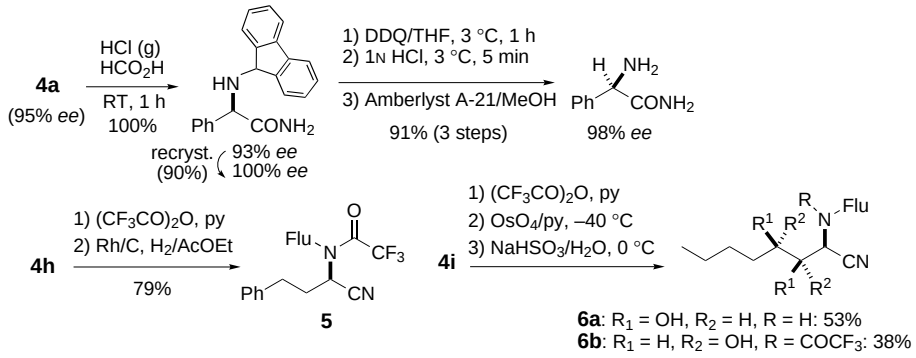
Supporting information for this article is available on the WWW under http://www.wiley-vch.de/home/angewandte/ or from the author.

  0570-0833/00/3909-1650 $ 17.50+.50/0

Table 1. Catalytic asymmetric Strecker-type reaction of various imines.[a]

entry	R	**3a–m**	System 1			System 2		
			time [h]	yield [%][b]	*ee* [%][c]	time [h]	yield [%][b]	*ee* [%][c]
1	Ph	**a**	44	92	95	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	36	92	87
7		**g**	58	90	89			
8	*trans*-PhCH=CH	**h**	41	80	96	36	78	92
9	*trans*-$CH_3(CH_2)_3CH{=}CH_2$	**i**	24	66	86[d]			
10	$CH_3(CH_2)_5$	**j**	24	80	80[e]	36	75	81
11	CH_3CH_2	**k**	44	84	70			
12	*i*Pr	**l**	44	89	72	36	92	71
13	*t*Bu	**m**	44	97	78	36	98	77

[a] See Experimental Section for the preparation of the catalyst and the general reaction procedure. [b] Yield of isolated product. [c] Determined by HPLC analysis. [d] 50 mol% of PhOH was used. The aminonitrile was isolated as the corresponding trifluoroacetamide. [e] Without PhOH.



Scheme 2. Conversion to α-amino acid derivatives and functionalization of α,β-unsaturated Strecker products.

ed saturated or functionalized aminonitriles without loss of enantiomeric purity.

The kinetic profile of this reaction was investigated to gain further insight into the reaction mechanism.[10] After adding PhOH in one portion the reaction was monitored by NMR spectroscopy by observing the disappearance of the imine proton of **3a** ($\delta = 8.58$, Figure 1). The initial reaction rate in the presence of 20 mol% of PhOH was 82 times faster than in the absence of PhOH. After about 20% of the starting imine had been consumed, which corresponds to the complete conversion of PhOH into TMSOPh,[11] the reaction entered a slower phase. However, even in this slower phase, the reaction rate was approximately two times faster than in the absence of PhOH. This result may be a consequence of the regeneration of a very small amount of PhOH from TMSOPh and the product amine. This regeneration of the proton source was also suggested from the fact that the initial reaction rate in the presence of 20 mol% of **4a** and TMSOPh was approximately twice that in the absence of these additives.

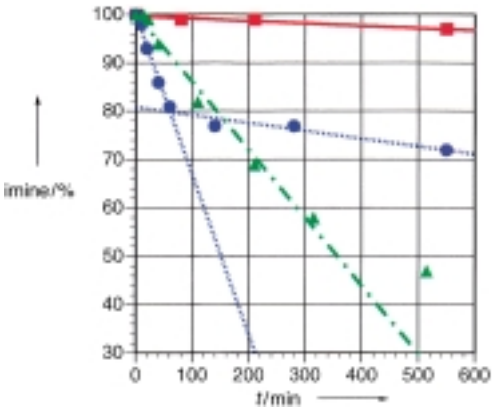
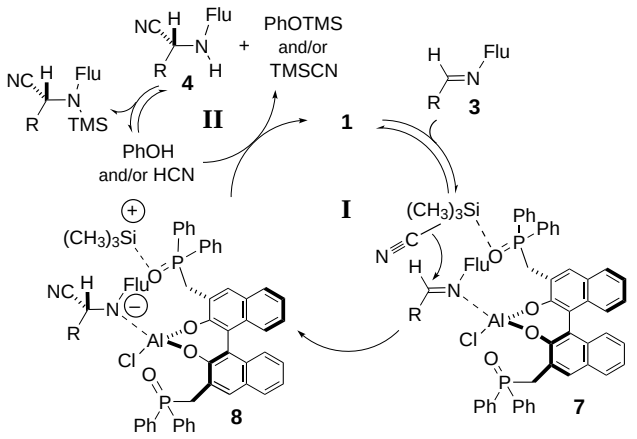


Figure 1. Initial reaction rate of **3a**. The disappearance of **3a** was monitored by ^{1}H NMR spectroscopy. For the experimental details, see the Supporting Information: the reaction of TMSCN in the absence (red ■) and in the presence of 20 mol% (blue ●) of PhOH, and the reaction of HCN (green ▲) are shown.

Another interesting question is whether the reactive nucleophile is TMSCN or HCN.[12] When HCN (2 mol equivalents) was added in one portion, the initial reaction rate was 0.4 times slower than when TMSCN was used in the presence of 20 mol% of PhOH (Figure 1), and the *ee* value of the product **4a** was 53%. Furthermore, under the slow addition (26 h) conditions of HCN, **4a** was obtained in 54% yield with 28% *ee* after 85 h.[13] These results reveal the reactive nucleophile to be TMSCN. Although HCN may be generated under the reaction conditions by the reaction of TMSCN with PhOH,[14] the highly enantioselective pathway with TMSCN as an active nucleophile predominates, since the reaction rate with TMSCN is faster than that with HCN in this catalytic system. Thus, this 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 **1** may be derived from the ability of the Lewis-basic phosphane oxide moiety of the bifunctional catalyst **1** to activate TMSCN.[4] These mechanistic studies suggest that PhOH and/or HCN work as a proton source to protonate the negative charge on the nitrogen atom that is generated by the

  0570-0833/00/3909-1651 $ 17.50+.50/0

addition of CN to the imine, thus accelerating the formation of **4** (Scheme 3).[15] A small amount of the proton source would be re-generated by cycle II, thus significantly accelerating the reaction rate when even a catalytic amount of PhOH is used.



Scheme 3. Working model for the catalytic cycle.

By taking advantage of the intriguing reactivity difference between TMSCN and HCN in this catalytic reaction, we expected that it would be possible to reduce the amount of TMSCN needed if HCN was used instead of PhOH, since TMSCN should be regenerated in catalytic cycle I (Scheme 3). Thus, by using 20 mol% of TMSCN and slowly adding the solution of HCN (120 mol%) in CH_2Cl_2 (system 2) we could obtain the products with comparable results as by the TMSCN–PhOH system (system 1, Table 1).

Although further investigation of the reaction mechanism is needed, the absolute configuration of the products may be explained from the working model **7** (Scheme 3), from analogy with the cyanosilylation of aldehydes. The Lewis acid (Al) and the Lewis base (phosphane oxide) activate the imine and TMSCN, respectively, at defined positions thus affording *R* products. The dual activation mechanism is supported by a control experiment using catalyst **2**, containing a diphenylmethyl group which should work only as a steric hindrance, instead of the diphenylphosphane oxide moiety. Catalyst **2** afforded the opposite enantiomer (*S*)-**4a** with 15% *ee* in 100% yield (42 h), in the presence of 20 mol% of PhOH. Therefore, in the case of **1**, TMSCN seems to attack the activated imine from the side of the phosphane oxide moiety.

In summary, the Lewis acid–Lewis base bifunctional catalyst **1** is shown to be a very general catalyst for the catalytic asymmetric Strecker-type reaction. Specifically, highly enantioselective α,β-unsaturated aminonitriles were obtained for the first time and successfully converted into the *n*- or functionalized aminonitriles. It was found that TMSCN is more reactive than HCN in the presence of 20 mol% of PhOH, which made it possible to use the unique catalytic system with a catalytic amount of TMSCN and a stoichiometric amount of HCN. Further investigations toward the reaction mechanism as well as developing a catalyst with higher activity are currently under investigation.

Experimental Section

The general procedures for the Strecker reaction are described. System 1: Et_2AlCl (17 μL, 16 μmol, 0.96 M in hexane) was added at room temperature to a solution of the chiral ligand (13 mg, 18 μmol) in CH_2Cl_2 (0.5 mL), and the mixture was stirred for 1 h. The resulting solution of **1** was cooled to $-40\,^{\circ}C$ and the solution of the imine (0.17 mmol) in CH_2Cl_2 (0.6 mL) was added . After 30 min, TMSCN (45 μL, 0.34 mmol) was added to this solution. After another 30 min, the solution of PhOH (3 μL, 34 μmol) in CH_2Cl_2 (0.2 mL) was added slowly over 17 h. The reaction was monitored by thin-layer chromatography and after the time shown in Table 1, saturated $NaHCO_3$ solution was added. Extraction, usual workup, and purification by flash column chromatography on SiO_2 gave the pure product.

System 2: A solution of the imine (0.352 mmol) in CH_2Cl_2 (1 mL) and TMSCN (70 μmol) were added to the solution of the catalyst (33 μmol) in CH_2Cl_2 (1 mL) prepared as above at $-40\,^{\circ}C$. The solution of HCN (0.422 mmol) in CH_2Cl_2 (0.26 mL) was slowly added over 24 h to this mixture. The reaction was worked up as described above after 12 h (total 36 h).

Received: January 25, 2000 [Z 14595]

[1] A. Strecker, *Ann. Chem. Pharm.* **1850**, *75*, 27–45.

[2] a) M. S. Iyer, K. M. Gigstad, N. D. Namdev, M. Lipton, *J. Am. Chem. Soc.* **1996**, *118*, 4910–4911; b) M. S. Sigman, E. N. Jacobsen, *J. Am. Chem. Soc.* **1998**, *120*, 4901–4902; c) M. S. Sigman, E. N. Jacobsen, *J. Am. Chem. Soc.* **1998**, *120*, 5315–5316; d) H. Ishitani, S. Komiyama, S. Kobayashi, *Angew. Chem.* **1998**, *110*, 3369–3372; *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 3186–3188; e) C. A. Krueger, K. W. Kuntz, C. D. Dzierba, W. G. Wirschun, J. D. Gleason, M. L. Snapper, A. H. Hoveyda, *J. Am. Chem. Soc.* **1999**, *121*, 4284–4285; f) E. J. Corey, M. J. Grogan, *Org. Lett.* **1999**, *1*, 157–160.

[3] The imines prepared from hydrocinnamaldehyde and *n*-nonanal reported in ref. [2d] had 83% *ee* (55% yield) and 74% *ee* (72% yield), respectively. The imine from *n*-heptanal in ref. [2f] was obtained with 63% *ee*. Recently, Kobayashi succeeded in greatly improving the catalytic asymmetric Strecker-type reaction using aliphatic imines (personal communication).

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

[5] A similar effect of *i*PrOH on the reaction rate has been reported by Hoveyda et al. in ref. [2e].

[6] The addition of an external phosphane oxide ($CH_3P(O)Ph_2$ or $Bu_3P(O)$), which was essential for high enantioselectivity in the cyanosilylation of aldehydes,[4] gave less satisfactory results.

[7] Two ^{31}P NMR signals were observed at $\delta = 42.2$ and 51.2 in the presence of TMSCN and **3a** in CD_2Cl_2.

[8] For the conversion of products from aliphatic imines into α-amino acid derivatives, see the Supporting Information.

[9] The relative configuration of **6a** was determined by X-ray crystallographic analysis of the cyclic carbonate derived from **6a**. See Supporting Information.

[10] When PhOH was added in one portion, the reaction pathway seemed to be nearly the same as under the best reaction conditions. Thus, the *ee* values of the product **4a** in these kinetic studies were 95% (in the absence of PhOH) and 88% (20 mol% of PhOH).

[11] When PhOH was added in one portion, the generation of TMSOPh and HCN was confirmed by ^1H NMR spectroscopic studies.

[12] In all the precedent examples,[2] except ref. [2d] (using Bu_3SnCN), HCN works as the reactive nucleophile.

[13] Hoveyda has found that the reaction is highly enantioselective only when HCN (or *i*PrOH) is added slowly.[2e]

[14] K. Mai, G. Patil, *J. Org. Chem.* **1986**, *51*, 3545–3548.

[15] For the discussion about the role of the proton source in the catalytic asymmetric Strecker-type reaction, see ref. [2e].

  0570-0833/00/3909-1652 $ 17.50+.50/0