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Highly Enantioselective Strecker Reaction of Ketoimines Catalyzed by an Organocatalyst from (*S*)-BINOL and L-Prolinamide

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The catalytic asymmetric Strecker reaction[1] has attracted much attention and a number of successful protocols have been disclosed for its great importance in the synthesis of chiral α-amino acids and their derivatives.[2] However, in contrast to the relatively well-developed cyanation of aldimines,[3] limited reports were related to the cyanation of ketoimines[4] to afford pharmaceutically important disubstituted α-amino nitriles. Especially, it is not easy to promote cyanation of ketoimines with organocatalyst. Since the first successful example reported by Jacobsen's group using chiral urea as catalyst,[4a,c] two types of *N,N′*-dioxides have been developed by our group for the Strecker reaction of ketoimines and moderate to good results were obtained.[4g,i] Herein, we reported a novel kind of *N,N′*-dioxide with an axial chirality for the enantioselective cyanation of *N*-Ts-protected ketoimine, providing excellent results (Figure 1).

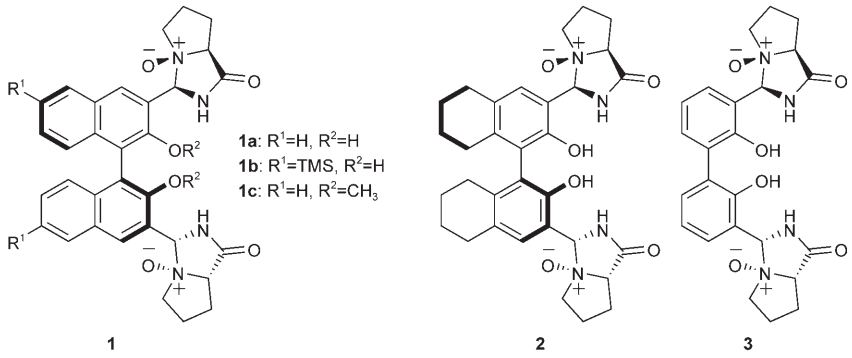

Figure 1. Catalysts used in this research.

Before, the linkers of the previously used *N,N′*-dioxides for the Strecker reaction of ketoimines were achiral moieties. We speculated that the stereocontrol would be enhanced by employing a suitable chiral linker. On the basis of this idea, we designed and synthesized the *N,N′*-dioxide catalyst derived from BINOL and prolinamide. The general route was given in Scheme 1. Firstly, (*S*)-BINOL was formylated via three steps to afford **A1** which was subsequently subjected to the condensation reaction with L-prolinamide. Then the product **B1** was oxidized to achieve the desired novel *N,N′*-dioxide **1a**. Notably, the absolute configuration of the newly formed chiral center in catalyst **1a** was identified as *R* based on the observation of strong NOE signal between H_1 and H_2 (see Supporting Information). However, the attempt to synthesize the similar structure from (*R*)-BINOL and L-prolinamide was failed, which might be attributed to the instability of the corresponding *N,N′*-dioxide. Interestingly, when two hydroxyl groups of **B1** were replaced by two methoxy group, *N,N′*-dioxide **1c** could not be prepared as diastereomerically pure form in the oxidation step. Instead, the mixture of the two epimers with a ratio of 1:1.8 was obtained (see Supporting Information). Other catalysts displayed in Figure 1 were prepared in a similar process (Scheme 1) for the preparation of **1a**.

To examine the initial hypothesis, we evaluated these catalysts in the asymmetric Strecker reaction of *N*-tosyl ketoimines with TMSCN. It was found that a promising result (80% *ee*) was obtained by employing 5 mol% *N,N′*-dioxide **1a** as catalyst, while inferior asymmetric induction was ob-

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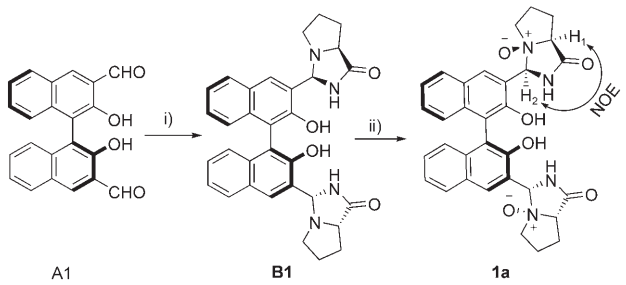
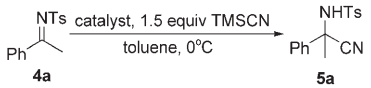


Scheme 1. Synthesis of the catalyst: i) L-prolinamide, ethanol, reflux; ii) *m*CPBA, CH_2Cl_2, −78 °C.

served using **1b** with two TMS groups on the 6,6′-position of BINOL (Table 1, entries 1–2). A low *ee* value was obtained by replacing the BINOL framework with H_8-BINOL (Table 1, entry 3), which suggested that a proper dihedral angel in **1a** was of great importance. When catalyst **3** derived from axial flexible 2,2′-biphenol was examined, quite poor enantioselectivity was given, which indicated that the axial chirality of BINOL in **1a** was crucial to achieve the good *ee* value (Table 1, entry 4).

Table 1. Asymmetric cyanation of ketoimine **4a** catalyzed by various catalyst systems.



4a **5a**

Entry[a]	Cat. [mol %]	Solvent	Yield [%][b]	*ee* [%][c]
1	**1a** (5)	toluene	71	80
2	**1b** (5)	toluene	53	55
3	**2** (5)	toluene	40	59
4	**3** (5)	toluene	43	27
5	**1a** (5)	CH_2Cl_2	88	24
6	**1a** (5)	anisole	64	48
7	**1a** (5)	THF	84	18
8	**1a** (5)	CH_3CN	64	23
9[d]	**1a** (5)	toluene	89	81
10[e]	**1a** (5)	toluene	99	60
11	**1a** (10)	toluene	99	75
12	**1a** (2)	toluene	56	84
13	**1a** (1)	toluene	42	86
14[f]	**1a** (2)	toluene	66	90
15[f,g]	**1a** (2)	toluene	93	97

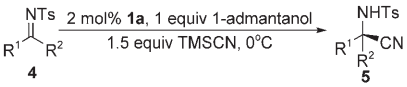
[a] All the reactions were carried out with **4a** (0.1 mmol), TMSCN (1.5 equiv) in toluene (0.5 mL) at 0 °C in a dry flask for 48 h unless otherwise specified. [b] Isolated yield. [c] Determined by chiral HPLC. [d] The reaction was performed at −20 °C for 168 h. [e] The reaction was performed at 30 °C. [f] The reaction was performed in 2.0 mL toluene for 72 h. [g] 1.0 equiv 1-adamantanol was added.

Solvent screening showed that toluene was the best solvent (Table 1, entry 1). Other solvents such as CH_2Cl_2, anisole, THF and CH_3CN gave poor enantioselectivities (Table 1, entries 5–8). When the reaction was performed at −20 °C, slight increase in the enantioselectivity was observed, but the reactivity decreased. High temperature was disadvantageous to asymmetric induction (Table 1, entries 9–10). Although low catalyst loading made the reaction somewhat sluggish, the *ee* value was gradually enhanced (Table 1, entries 11–13). Also, reduced concentration was beneficial to the enantioselectivity (Table 1, entry 14). To further improve the result, some additives were investigated. Fortunately, 1-admantanol was found to be efficient to enhance both reactivity and enantioselectivity, and the best amount was 1.0 equiv (Table 1, entry 15).

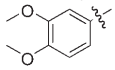
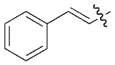
With the optimal conditions (Table 1, entry 15) in hand, the substrate scope was surveyed. As shown in Table 2, various aryl imines bearing no matter electron-withdrawing or electron-donating group were smoothly converted to their corresponding adducts in the range of 93–99 % *ee* with high yields (Table 2, entries 1–11). Heteroaromatic ketoimines showed high reactivities and enantioselectivities as well (Table 2, entries 12–13). Aliphatic substrate **4n** gave 93 % *ee* (Table 2, entry 14). Besides, α,β-unsaturated ketoimine could be transformed to the synthetically important product **5o** with 95 % *ee* (Table 2, entry 15). Cyclic ketoimine could give an excellent result with 98 % *ee* (Table 2, entry 16). Excitingly, current catalyst system could be applied to the aryl ethyl and aryl propyl ketoimines to give excellent results (Table 2, entries 17–18). *ortho*-Chloro diphenylketoimine exhibited good result, too (Table 2, entry 19).

In summary, a novel and efficient organocatalyst was developed to promote the Strecker reaction of ketoimines with fairly wide substrate scope and excellent enantioselec-

Table 2. Substrate scope for the Strecker reaction of ketoimines.



4 **5**

Entry[a]	R^1	R^2	Product	*t* [h]	Yield [%][b]	*ee* [%][c]
1	Ph	Me	**5a**	72	93	97 (*R*)
2	2-FC_6H_4	Me	**5b**	72	95	94
3	3-ClC_6H_4	Me	**5c**	72	93	94
4	4-ClC_6H_4	Me	**5d**	72	91	93 (*R*)
5	4-FC_6H_4	Me	**5e**	72	94	95
6	4-MeC_6H_4	Me	**5f**	72	88	98 (*R*)
7	2-$MeOC_6H_4$	Me	**5g**	120	82	97
8	3-$MeOC_6H_4$	Me	**5h**	120	81	96
9	4-$MeOC_6H_4$	Me	**5i**	120	80	99 (*R*)
10		Me	**5j**	120	74	99 (*R*)
11	2-naphthyl	Me	**5k**	72	82	97 (*R*)
12	2-furyl	Me	**5l**	72	88	95
13	2-thienyl	Me	**5m**	72	86	97
14	*t*Bu	Me	**5n**	72	96	93
15		Me	**5o**	72	86	95
16		–	**5p**	120	73	98 (*R*)
17	Ph	Et	**5q**	120	86	98
18	Ph	*n*Pr	**5r**	120	74	95
19	2-ClC_6H_4	Ph	**5s**	120	76	90

[a] All the reactions were carried out in a 0.1 mmol scale of **4** using 1.5 equiv TMSCN in 2.0 mL toluene with 2 mol % catalyst and 1.0 equiv 1-admantanol at 0 °C in a dry tube. [b] Isolated yield. [c] Determined by chiral HPLC.

tivities (up to 99% *ee*). Low catalyst loading (2 mol%), mild reaction conditions, and operational simplicity made this strategy facile to be used in the organic synthesis. Further investigation of the reaction mechanism is underway.

Experimental Section

Typical procedure for the Strecker reaction of ketoimine: To a dry reaction tube charged with *N*-Ts ketoimine (0.1 mmol), catalyst (0.002 mmol), additive (0.1 mmol) and toluene (2.0 mL) was added TMSCN (0.15 mmol) with stirring at 0 °C. After the reaction completed, the reaction mixture was purified by flash chromatography on silica gel to afford the desired product.

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Keywords: asymmetric catalysis · cyanides · ketoimines · organocatalysis · Strecker reaction

[1] A. Strecker, *Ann. Chim. Farm.* **1850**, *75*, 27.

[2] For reviews on the asymmetric Strecker reaction, see: a) L. Yet, *Angew. Chem.* **2001**, *113*, 900; *Angew. Chem. Int. Ed.* **2001**, *40*, 875; b) H. Gröger, *Chem. Rev.* **2003**, *103*, 2795; c) C. Spino, *Angew. Chem.* **2004**, *116*, 1796; *Angew. Chem. Int. Ed.* **2004**, *43*, 1764; d) S. J. Connon, *Angew. Chem.* **2008**, *120*, 1194; *Angew. Chem. Int. Ed.* **2008**, *47*, 1176.

[3] For the asymmetric Strecker reaction of aldimines, see: a) M. S. Iyer, K. M. Gigstad, N. D. Namdev, M. Lipton, *J. Am. Chem. Soc.* **1996**, *118*, 4910; b) M. S. Sigman, E. N. Jacobsen, *J. Am. Chem. Soc.* **1998**, *120*, 4901; c) H. Ishitani, S. Komiyama, S. Kobayashi, *Angew. Chem.* **1998**, *110*, 3369; *Angew. Chem. Int. Ed.* **1998**, *37*, 3186; d) E. J. Corey, M. J. Grogan, *Org. Lett.* **1999**, *1*, 157; 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; f) M. S. Sigman, P. Vachal, E. N. Jacobsen, *Angew. Chem.* **2000**, *112*, 1336; *Angew. Chem. Int. Ed.* **2000**, *39*, 1279; g) M. Takamura, Y. Hamashima, H. Usuda, M. Kanai, M. Shibasaki, *Angew. Chem.* **2000**, *112*, 1716; *Angew. Chem. Int. Ed.* **2000**, *39*, 1650; h) B. Liu, X. M. Feng, F. X. Chen, G. L. Zhang, X. Cui, Y. Z. Jiang, *Synlett* **2001**, 1551; i) Z. G. Jiao, X. M. Feng, B. Liu, F. X. Chen, G. L. Zhang, Y. Z. Jiang, *Eur. J. Org. Chem.* **2003**, 3818; j) W. Mansawat, W. Bhanthumnavin, T. Vilaivan, *Tetrahedron Lett.* **2003**, *44*, 3805; k) S. Nakamura, N. Sato, M. Sugimoto, T. Toru, *Tetrahedron: Asymmetry* **2004**, *15*, 1513; l) V. Banphavichit, W. Mansawat, W. Bhanthumnavin, T. Vilaivan, *Tetrahedron* **2004**, *60*, 10559; m) J. Huang, E. J. Corey, *Org. Lett.* **2004**, *6*, 5027; n) T. Ooi, Y. Uematsu, K. Maruoka, *J. Am. Chem. Soc.* **2006**, *128*, 2548; o) M. Rueping, E. Sugiono, C. Azap, *Angew. Chem.* **2006**, *118*, 2679; *Angew. Chem. Int. Ed.* **2006**, *45*, 2617; p) S. C. Pan, J. Zhou, B. List, *Angew. Chem.* **2007**, *119*, 3028; *Angew. Chem. Int. Ed.* **2007**, *46*, 612; q) S. C. Pan, B. List, *Org. Lett.* **2007**, *9*, 1149; r) Y. H. Wen, Y. Xiong, L. Chang, J. L. Huang, X. H. Liu, X. M. Feng, *J. Org. Chem.* **2007**, *72*, 7715; s) M. Negru, D. Schollmeyer, H. Kunz, *Angew. Chem.* **2007**, *119*, 9500; *Angew. Chem. Int. Ed.* **2007**, *46*, 9339; t) S. C. Pan, B. List, *Chem. Asian J.* **2008**, *3*, 430.

[4] For the asymmetric Strecker reaction of ketimines, see: a) P. Vachal, E. N. Jacobsen, *Org. Lett.* **2000**, *2*, 867; b) J. J. Byrne, M. Chavarot, P.-Y. Chavant, Y. Vallée, *Tetrahedron Lett.* **2000**, *41*, 873; c) P. Vachal, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 10012; d) S. Masumoto, H. Usuda, M. Suzuki, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2003**, *125*, 5634; e) N. Kato, M. Suzuki, M. Kanai, M. Shibasaki, *Tetrahedron Lett.* **2004**, *45*, 3153; f) N. Kato, M. Suzuki, M. Kanai, M. Shibasaki, *Tetrahedron Lett.* **2004**, *45*, 3147; g) X. Huang, J. L. Huang, Y. H. Wen, X. M. Feng, *Adv. Synth. Catal.* **2006**, *348*, 2579; h) N. Kato, T. Mita, M. Kanai, B. Therrien, M. Kawano, K. Yamaguchi, H. Danjo, Y. Sei, A. Sato, S. Furusho, M. Shibasaki, *J. Am. Chem. Soc.* **2006**, *128*, 6768; i) J. L. Huang, X. H. Liu, Y. H. Wen, B. Qin, X. M. Feng, *J. Org. Chem.* **2007**, *72*, 204; j) J. Wang, X. L. Hu, J. Jiang, S. H. Gou, X. Huang, X. H. Liu, X. M. Feng, *Angew. Chem.* **2007**, *119*, 8620; *Angew. Chem. Int. Ed.* **2007**, *46*, 8468.

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