VIP Asymmetric Catalysis

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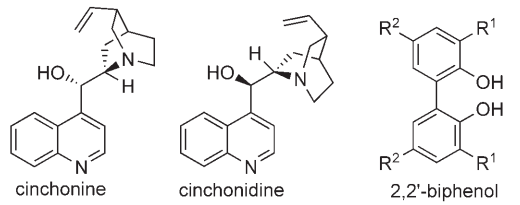
Asymmetric Activation of *tropos* 2,2′-Biphenol with Cinchonine Generates an Effective Catalyst for the Asymmetric Strecker Reaction of *N*-Tosyl-Protected Aldimines and Ketoimines**

*Jun Wang, Xiaolei Hu, Jun Jiang, Shaohua Gou, Xiao Huang, Xiaohua Liu, and Xiaoming Feng**

The catalytic asymmetric Strecker reaction is one of the most powerful strategies for the synthesis of chiral α-amino acids. In the last decade, great endeavors have been devoted to this area and a number of successful protocols have been disclosed.[1–3] However, more efforts are still needed in this area, first, because highly efficient cyanation of ketoimines to afford the precursors of pharmaceutically important α-quaternary amino acids[4] is difficult and little reported, and second, as searching for a catalyst system which could work well not only on aldimines but also on ketoimines is challenging and interesting. Herein, we present a highly enantioselective cyanation of *N*-Ts-protected (Ts = *p*-toluenesulfonyl) aldimines and ketoimines promoted by a novel catalyst generated from the asymmetric activation[5] of axially flexible 2,2′-biphenol (bipol) with a chiral activator **1** through coordinative interaction with a metal (Scheme 1).

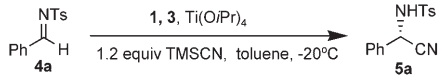
Our initial studies showed that bipol/Ti(O*i*Pr)$_4$ activated by cinchonine **1** was a promising catalyst for the cyanation of *N*-Ts benzaldimine **4a** using trimethylsilyl cyanide (TMSCN) as the cyanide reagent at −20 °C in toluene in the presence of 20 mol % catalyst (Table 1, entry 1). Further improvement of *ee* values was achieved by screening several modified bipol derivatives (Table 1, entries 2–10). Especially, the bipol ligand bearing a sterically demanding aromatic substituent at the 3,3′-position greatly enhanced the enantioselectivity to 94–95 % *ee* (Table 1, entries 7–10). Considering the excellent performance and relatively facile preparation of **3h**, we used this to optimize the other parameters. After adjusting the ratio of **3h**/Ti(O*i*Pr)$_4$/**1** to 1.2:1.2:1, **5a** was obtained in up to 97 % *ee* and greater than 99 % yield (Table 1, entry 11).



3a: $R^1 = R^2 = H$ **3f:** $R^1 = R^2$ = 1-adamantyl
3b: $R^1 = R^2 = Br$ **3g:** $R^1 = Ph$, $R^2 = H$
3c: $R^1 = R^2 = t$Bu **3h:** R^1 = 2-Naphthyl, $R^2 = H$
3d: R^1 = Me, $R^2 = t$Bu **3i:** R^1 = 4-biphenyl, $R^2 = H$
3e: $R^1 = t$Bu, $R^2 = H$ **3j:** R^1 = 2-MeO-3-Ph-C_6H_3, $R^2 = H$

Scheme 1. Ligands used in this study.

Table 1: Identification of the most efficient catalyst system, and optimization of the reaction conditions.[a]



Entry	2,2′-biphenol	**3**/Ti(O*i*Pr)$_4$/**1** [mol %]	*ee* [%][b]
1	**3a**	20:20:20	71
2	**3b**	20:20:20	64
3	**3c**	20:20:20	74
4	**3d**	20:20:20	34
5	**3e**	20:20:20	71
6	**3f**	20:20:20	70
7	**3g**	20:20:20	94
8	**3h**	20:20:20	95
9	**3i**	20:20:20	94
10	**3j**	20:20:20	95
11	**3h**	24:24:20	97
12	**3h**	12:12:10	90
13[c]	**3h**	12:12:10	97
14[c]	**3h**	6:6:5	97

[a] Unless noted otherwise, the reaction was carried out with **4a** (0.1 mmol) and TMSCN (0.12 mmol) in toluene (0.5 mL) at −20 °C for 2.5–18 h, and complete conversion of the imine was observed by TLC detection. [b] Determined by chiral HPLC. [c] *i*PrOH (1.2 equiv) was used as additive.

However, when the catalyst loading was lowered, the presence of 1.2 equivalents of *i*PrOH[6] was essential to maintain the excellent results (Table 1, entries 12–14). Other conditions such as the central metal, solvent, and temperature were also investigated, but no superior results were obtained.

Under optimal conditions (Table 1, entry 14), a series of imines (**4a**–**4o**) derived from aromatic, heterocyclic, α,β-unsaturated, and aliphatic aldehydes were tested and excellent results (up to 97 % *ee*) were achieved (Table 2, entries 1–

[*] J. Wang, X. Hu, J. Jiang, S. Gou, X. Huang, X. Liu, Prof. X. Feng
Key Laboratory of Green Chemistry & Technology
Ministry of Education, College of Chemistry
Sichuan University
Chengdu 610064 (P.R. China)
Fax: (+86) 28-8541-8249
E-mail: xmfeng@scu.edu.cn
Prof. X. Feng
State Key Laboratory of Biotherapy
Sichuan University
Chengdu 610041 (P.R. China)

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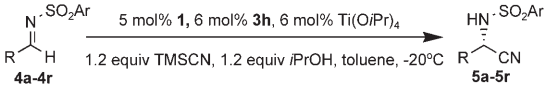
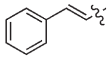
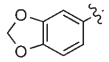
15). Different *N*-sulfonyl-protected imines were also examined, and good results were obtained (Table 2, entries 16–18) which facilitated the preparation of various chiral *N*-sulfonyl-protected amino acids.

Table 2: Substrate scope for the catalytic asymmetric Strecker reaction of *N*-sulfonyl aldimines.[a]



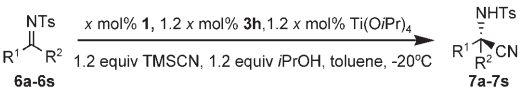
Entry	R	Product	*t* [h]	Yield [%][b]	*ee* [%][c]
1	Ph	**5a**	2.5	>99	97(*S*)
2	4-FC_6H_4	**5b**	3	>99	96
3	4-ClC_6H_4	**5c**	3	97	93
4	4-MeC_6H_4	**5d**	22	>99	97
5	3-MeC_6H_4	**5e**	8	>99	94
6	4-$MeOC_6H_4$	**5f**	8	>99	97
7		**5g**	3	>99	97
8	1-naphthyl	**5h**	4	92	91
9	2-naphthyl	**5i**	22	97	96
10	2-furyl	**5j**	3	93	90
11	2-thienyl	**5k**	5	94	94
12		**5l**	4	96	91
13[d]	*c*-hexyl	**5m**	6	>99	92
14[d]	*i*Pr	**5n**	6	96	84
15[d]	*t*Bu	**5o**	6	98	84
16[e]	Ph	**5p**	4	>99	94
17[f]	Ph	**5q**	4	94	94
18[g]	Ph	**5r**	4	75	90

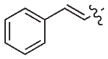
[a] Unless noted otherwise, $ArSO_2$ = Ts and reactions were carried out with imine (0.1 mmol), TMSCN (0.12 mmol), catalyst (5 mol%), *i*PrOH (0.12 mmol), and toluene (0.5 mL) at −20°C. [b] Isolated yield. [c] Determined by HPLC; see Supporting Information for the assignment of the absolute configuration of **5a**. [d] 15 mol% catalyst was used. [e] Ar = 4-ClC_6H_4. [f] Ar = Ph. [g] Ar = 2,4,6-trimethylphenyl.

Given the remarkable performance of the present catalyst system in the cyanation of aldimines, its general applicability in the cyanation of ketoimines **6a–6p** was also examined under the same reaction conditions. The results listed in Table 3 show that a wide spectrum of ketoimines could achieve excellent enantioselectivities (up to 99% *ee*) and high yields employing 5–10 mol% catalyst (Table 3, entries 1–16). Significantly, the current system could be extended to the cyanation of *ortho*-substituted diarylketoimines **6q–6s** (Table 3, entries 17–19)[7] to generate chiral α-diaryl α-amino nitriles, which made it possible to synthesize chiral 5,5-diarylhydantoins[8] and their derivatives. As far as we know, the catalytic asymmetric Strecker reaction of such kind of substrates has not been reported before.

To gain preliminary insight into the catalyst structure, *atropos*[9] (chirally rigid) ligands (*R*)-**8** and (*S*)-**8** were prepared and evaluated in the cyanation of **6a** (Table 4). When (*S*)-**8**/Ti(O*i*Pr)$_4$ was employed, no product was detected (Table 4, entry 2). However, **1**/(*S*)-**8**/Ti(O*i*Pr)$_4$ displayed the same result as that when **1**/**3h**/Ti(O*i*Pr)$_4$ was used (Table 4, entries 1 and 3). When (*R*)-**8** replaced (*S*)-**8**, the reaction proceeded very slowly and led to low *ee* values (Table 4, entry 4). As expected, with cinchonidine **2** as the activator, (*R*)-**8** rather than (*S*)-**8** was demonstrated as the matched ligand (Table 4, entries 5–6). Additionally, asymmetric activation of *tropos* (chirally flexible) **3h** with **2** was also investigated, and a high yield with slightly decreased *ee* value was observed (Table 4, entry 7). With these data in hand, at least three conclusions could be drawn: 1) the absolute configuration of the product was controlled by activator **1** or **2**; 2) on the basis of the large differences

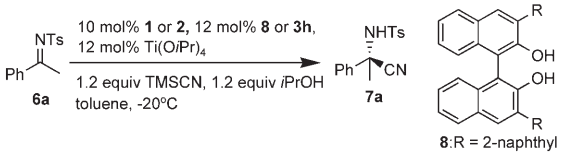
Table 3: Substrate scope for the catalytic asymmetric Strecker reaction of *N*-Ts ketoimines.[a]



Entry	R^1	R^2	Product	*x*	*t* [h]	Yield [%][b]	*ee* [%][c]
1	Ph	Me	**7a**	5	8	>99	>99 (*S*)
2	4-FC_6H_4	Me	**7b**	5	4	90	98
3	4-ClC_6H_4	Me	**7c**	5	4	>99	>99 (*S*)
4	4-BrC_6H_4	Me	**7d**	5	8	>99	>99 (*S*)
5	4-MeC_6H_4	Me	**7e**	10	4	>99	>99 (*S*)
6	4-$MeOC_6H_4$	Me	**7f**	10	4	99	>99 (*S*)
7	3-ClC_6H_4	Me	**7g**	5	4	>99	>99
8	2-FC_6H_4	Me	**7h**	10	4	>99	90
9	2-naphthyl	Me	**7i**	5	22	90	>99 (*S*)
10	2-furyl	Me	**7j**	5	22	97	99
11	2-thienyl	Me	**7k**	5	22	97	>99
12	Ph	Et	**7l**	10	4	>99	>99
13	Ph	*n*Pr	**7m**	10	4	93	>99
14		Me	**7n**	5	17	97	98
15	*c*-hexyl	Me	**7o**	10	4	>99	94
16	*t*Bu	Me	**7p**	10	4	98	69
17	2-FC_6H_4	Ph	**7q**	10	5	96	98
18	2-ClC_6H_4	Ph	**7r**	10	45	95	97
19[d]	2-MeC_6H_4	Ph	**7s**	10	45	90	97

[a] Unless noted otherwise, reactions were carried out with imine (0.1 mmol), TMSCN (0.12 mmol), *i*PrOH (0.12 mmol) and toluene (0.5 mL) at −20°C. [b] Isolated yield. [c] Determined by HPLC and the absolute configurations were determined by comparison with literature data.[3g] [d] 1.5 equiv TMSCN and 1.5 equiv *i*PrOH were used.

Table 4: Identification of the configuration of bipol **3h** in the most active species by taking cyanation of **6a** as the benchmark reaction.[a]



Entry	Activator	Diol	*t* [h]	Yield [%][b]	*ee* [%][c]
1	**1**	**3h**	3.5	>99	>99 (*S*)
2	none	(*S*)-**8**	8	–	–
3	**1**	(*S*)-**8**	3.5	>99	>99 (*S*)
4	**1**	(*R*)-**8**	3.5	25	71 (*S*)
5	**2**	(*R*)-**8**	8	95	98 (*R*)
6	**2**	(*S*)-**8**	8	49	68 (*R*)
7	**2**	**3h**	8	87	94 (*R*)

[a] Unless noted otherwise, reactions were carried out with imine (0.1 mmol), TMSCN (0.12 mmol), *i*PrOH (0.12 mmol), and toluene (0.5 mL) at −20°C. [b] Isolated yield. [c] Determined by HPLC.

observed in activity and enantioselectivity between **1**/(*S*)-**8**/$Ti(OiPr)_4$ and **1**/(*R*)-**8**/$Ti(OiPr)_4$ (Table 4, entry 3 vs 4), if **3h** could adopt either an *R* or *S* configuration in the catalyst complex, these two diastereomers must display large differences in activity and enantioselectivity; and 3) according to the excellent result given by the chirally matched **1**/(*S*)-**8**/$Ti(OiPr)_4$ system, the possible configuration adopted by *tropos* **3h** in the most active species is expected to be similar to that of (*S*)-**8**.

In view of the biological importance[10] of the *N*-sulfonyl amino acids, a representative conversion of **5a** to the corresponding *N*-Ts amino acid was attempted and eventually realized easily without racemization (see Supporting Information).

In summary, a highly efficient catalytic asymmetric Strecker reaction with an extremely broad substrate scope was accomplished by a strategy of asymmetric activation of *tropos* bipol derivative **3h** with cinchonine under mild conditions. In the presence of 5–10 mol% catalyst, excellent enantioselectivities up to 99% *ee* and high yields were achieved for most of the substrates. Preliminary studies of the catalyst structure were performed, and application of this catalyst to other reactions is underway.

Experimental Section

General procedure for the Strecker reaction of *N*-Ts imine: The freshly prepared catalyst (5–10 mol%) (see Supporting Information) was introduced to a dry reaction tube charged with *N*-Ts imine (0.1 mmol) and toluene under Ar atmosphere at −20 °C. The cyanide reagent (0.12 mmol) and *i*PrOH (0.12 mmol) were sequentially added with stirring. After the imine was consumed, the residue was purified by silica gel column chromatography to afford the desired product.

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[1] For reviews, 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.

[2] For the 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.

[3] For the Strecker reaction of ketoimines, 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.

[4] a) W. S. Saari, W. Halczenko, D. W. Cochran, M. R. Dobrinska, W. C. Vincek, D. C. Titus, S. L. Gaul, C. S. Sweet, *J. Med. Chem.* **1984**, *27*, 713; b) G. Fenteany, R. F. Standeart, W. S. Lane, S. Choi, E. J. Corey, S. L. Schreiber, *Science* **1995**, *268*, 726.

[5] For the asymmetric activation of racemic ligands, see: a) N. W. Alcock, J. M. Brown, P. J. Maddox, *J. Chem. Soc. Chem. Commun.* **1986**, 1532; b) K. Maruoka, H. Yamamoto, *J. Am. Chem. Soc.* **1989**, *111*, 789; c) K. Mikami, M. Terada, T. Korenaga, Y. Matsumoto, M. Ueki, R. Angelaud, *Angew. Chem.* **2000**, *112*, 3676; *Angew. Chem. Int. Ed.* **2000**, *39*, 3532; d) K. Mikami, K. Aikawa, Y. Yusa, J. J. Jodry, M. Yamanaka, *Synlett* **2002**, 1561; e) K. Mikami, M. Yamanaka, *Chem. Rev.* **2003**, *103*, 3369; f) J. W. Faller, A. R. Lavoie, J. Parr, *Chem. Rev.* **2003**, *103*, 3345, and references therein; g) K. Ding, H. Du, Y. Yuan, J. Long, *Chem. Eur. J.* **2004**, *10*, 2872, and references therein.

[6] Slow addition of *i*PrOH was unnecessary in this system to ensure high enantioselectivity. For a detailed discussion of the role of protic additives, see Ref. [2e,g]. For examples in this area of adding a protic additive to achieve good results, see: Ref. [2e–g,l,3f–h] and X. H. Liu, B. Qin, X. Zhou, B. He, X. M. Feng, *J. Am. Chem. Soc.* **2005**, *127*, 12224.

[7] However, *meta*- and *para*-substituted benzophenone imines gave poor *ee* values (see Supporting Information).

[8] For the biological studies of achiral 5,5-diarylhydantoins, see: a) M. Kanyonyo, S. J. Govaerts, E. Hennans, J. H. Poupaert, D. M. Lambert, *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2233; b) F. Ooms, J. Wouters, O. Oscari, T. Happaerts, G. Bouchard, P. Carrupt, B. Testa, D. M. Lambert, *J. Med. Chem.* **2002**, *45*, 1748; c) G. G. Muccioli, J. Wouters, G. K. E. Scriba, W. Poppitz, J. H. Poupaert, D. M. Lambert, *J. Med. Chem.* **2005**, *48*, 7486; d) G. G. Muccioli, N. Fazio, G. K. E. Scriba, W. Poppitz, F. Cannata, J. H. Poupaert, J. Wouters, D. M. Lambert, *J. Med. Chem.* **2006**, *49*, 417.

[9] In Greek, "*a*" means "not" and "*tropos*" means "turn"; see Ref. [5d].

[10] For examples, see: a) P. M. O'Brien, D. F. Ortwine, A. G. Pavlovsky, J. A. Picard, D. R. Sliskovic, B. D. Roth, R. D. Dyer, L. L. Johnson, C. F. Man, H. Hallak, *J. Med. Chem.* **2000**, *43*, 156; b) S. Pikul, N. E. Ohler, G. Ciszewski, M. C. Laufersweiler, N. G. Almstead, B. De, M. G. Natchus, L. C. Hsieh, M. J. Janusz, S. X. Peng, T. M. Branch, S. L. King, Y. O. Taiwo, G. E. Mieling, *J. Med. Chem.* **2001**, *44*, 2499.

