Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters
Tetrahedron Letters 45 (2004) 3147–3151

General and practical catalytic enantioselective Strecker reaction of ketoimines: significant improvement through catalyst tuning by protic additives

Nobuki Kato,[a,b] Masato Suzuki,[a] Motomu Kanai[a,b,*] and Masakatsu Shibasaki[a,*]

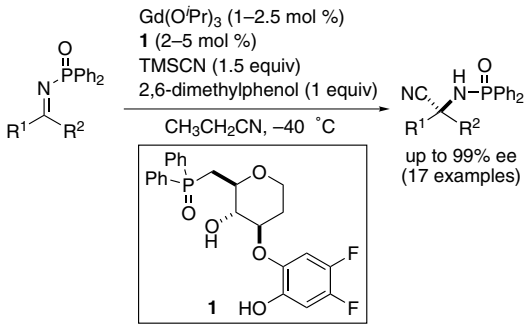
[a]*Graduate School of Pharmaceutical Sciences, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan*
[b]*PRESTO, Japan Science and Technology Corporation, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan*

Received 29 January 2004; revised 12 February 2004; accepted 16 February 2004

Abstract—Significant improvement in enantioselectivity and catalyst activity was achieved for the catalytic enantioselective Strecker reaction. Using a catalyst (1–2.5 mol%) prepared from $Gd(O^iPr)_3$ and D-glucose derived ligand **1**, and in the presence of 2,6-dimethylphenol as an additive, high enantioselectivity was obtained from a wide range of ketoimines, including heteroaromatic and cyclic ketoimines. The new method was applied to an efficient catalytic asymmetric synthesis of sorbinil, a therapeutic agent for diabetic complications.

1. Introduction

Chiral α,α-disubstituted α-amino acids are important building blocks for pharmaceuticals and artificially designed peptides.[1] The catalytic enantioselective Strecker reaction of ketoimines is one of the most direct and practical methods for the synthesis of this class of compounds.[2] There are three examples reported previously on this reaction. Jacobsen and Vachal developed a unique organocatalyst that promotes reactions with aryl methyl and *tert*-butyl methyl ketoimines.[3] Vallée and co-workers reported a reaction with an acetophenone-derived ketoimine, catalyzed by a chiral heterobimetallic complex.[4] We recently reported a reaction with *N*-phosphinoyl ketoimines using a catalyst prepared from $Gd(O^iPr)_3$ and D-glucose-derived ligand **1** in a 1:2 ratio.[5] Despite these contributions, there remains room for improvement in terms of substrate generality and catalyst loading, considering the high importance of chiral disubstituted α-amino acids. For example, there are no reports of an efficient catalysis for heteroaromatic or cyclic ketoimines. Products from these substrates should be useful for the synthesis of biologically active compounds. We report herein the first example in catalytic enantioselective Strecker reaction of ketoimines that can be applied to these unprecedented, yet very important substrates through developing a new proton-containing catalyst. Substrate generality, catalyst loading, and catalyst turnover frequency are significantly improved. Using the new conditions, we developed an efficient catalytic asymmetric synthesis of sorbinil, a pharmaceutical lead for the treatment of diabetic neuropathy.[6]

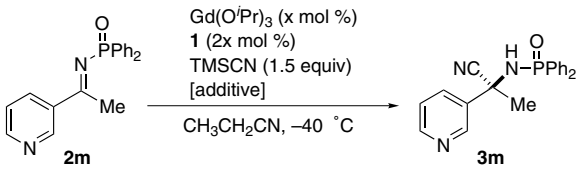


Targeting heteroaromatic ketoimines as substrates, we initially observed an intriguing dependency of enantioselectivity on the catalyst amount. The reaction with 3-pyridylketoimine **2m** proceeded slowly using 10 mol% catalyst, and product **3m** was obtained with only 33% ee

Keywords: Asymmetric catalysis; Strecker reaction; Ketoimines; Disubstituted amino acids; Additive effect.
* Corresponding authors. Tel.: +81-3-5841-4830; fax: +81-3-5684-52-06; e-mail: mshibasa@mol.f.u-tokyo.ac.jp

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.02.082

Table 1. Additive effects on catalytic enantioselective Strecker reaction of heteroaromatic ketoimine **2m**



Entry	Catalyst (x)	Additive (mol%)	Time (h)	Yield (%)[b]	Ee (%)[c]
1	10	—	14	100	33
2	20	—	1	92	78
3	30	—	0.5	89	88
4	5	MeOH(100)	5	81	69
5	5	^{i}PrOH (100)	0.5	80	95
6	5	^{t}BuOH (100)	1	87	95
7	5	Phenol (100)	0.3	88	99
8	5	DMP[a] (100)	0.3	81	99
9	5	DMP[a] (10)	2	84	99

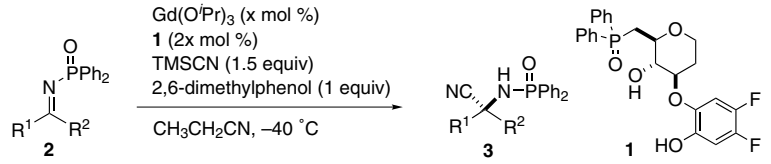
[a] 2,6-Dimethylphenol.
[b] Isolated yield.
[c] Determined by chiral HPLC.

(Table 1, entry 1). When the catalyst amount was increased to 20 and 30 mol%, the reaction was much faster (0.5–1 h), and the enantioselectivity was dramatically improved to 78% and 88% ee, respectively (entries 2 and 3). A similar tendency was observed when 2-furfurylketoimine **2p** was used as a substrate.

Having confirmed the lack of background reaction at −40 °C, we hypothesized that the dramatic enhancement of the enantioselectivity with an increase in the amount of the catalyst might be due to the excess ligand, functioning as a proton source.[7] Although the best enantioselectivity was obtained with the catalyst prepared from Gd(O^{i}Pr)$_3$ and **1** in a 1:2 ratio, the actual catalyst in the absence of additives is a 2:3 complex (**4**) of Gd and **1**, based on the NMR and ESI-MS studies (vide infra and Ref. 9). Thus, the amount of the proton source increased up to 30 mol%, when 30 mol% catalyst was used. Therefore, we investigated the effects of protic additives. As shown in Table 1, entries 4–8, the reaction time was significantly shortened in the presence of any protic additives (100 mol%), even when using only 5 mol% of catalyst. Enantioselectivity was improved up to 99% ee, when phenol or 2,6-dimethylphenol (DMP) was used as an additive. We selected DMP as the best additive, based on the results of a dialkyl-substituted ketoimine **2c**: **3c** was obtained in 96% yield and 89% ee in the presence of phenol, and 96% yield and 93% ee in the presence of DMP (5 mol% catalyst, 2 h).

This new method using DMP as an additive greatly expanded the substrate scope of the catalytic enantioselective Strecker reaction with improved enantioselectivity, catalyst turnover number, and catalyst turnover frequency (Table 2). The catalyst amount could be reduced to 1–2.5 mol%, and the products were obtained with improved enantioselectivity in every case, compared to the previous method. Specifically, excellent

Table 2. Catalytic enantioselective Strecker reaction using DMP as an additive[a]



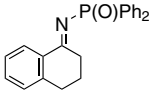
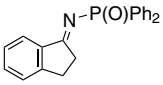
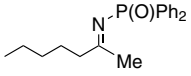
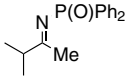
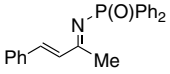
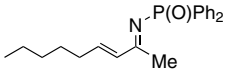
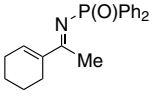
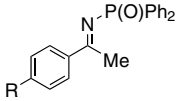
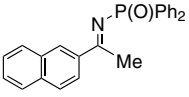
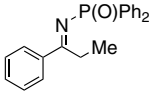
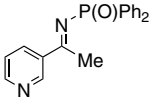
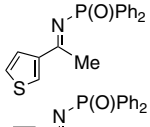
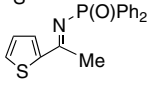
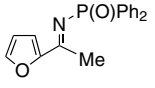
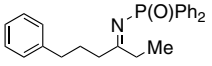
Entry	Substrate		Catalyst (x)	Time (h)	Yield (%)	Ee (%)
1		**2a**	1	22	92	92[b]
2		**2a**	2.5	0.3	94	98[b]
3		**2a**	[2.5	134	70	52[b]][c]
4		**2b**	2.5	48	98	97[b]
5		**2b**	[2.5	158	67	48[b]][c]
6		**2c**	1	43	73	90
7		**2c**	5	2	96	93
8		**2c**	[5	65	73	72][c]

Table 2 (*continued*)

Entry	Substrate		Catalyst (x)	Time (h)	Yield (%)	Ee (%)
9		**2d**	2.5	2.5	91	80
10		**2d**	[5	48	74	51][c]
11		**2e**	1	38	93	96[b]
12		**2e**	5	0.2	95	98[b]
13		**2e**	[5	68	79	83][c]
14		**2f**	2.5	8	94	88[b]
15		**2f**	5	2	94	94[b]
16		**2f**	[5	52	99	88[b]][c]
17		**2g**	1	52	99	97
18		**2g**	2.5	2	95	97
19		**2g**	[5	67	58	90][c]
20		R = H (**2h**)	1	30	94	92[b]
21		**2h**	2.5	2	98	97[b]
22		**2h**	[2.5	24	94	95[b]][c]
23		R = Cl (**2i**)	1	13	93	95
24		**2i**	2.5	0.7	90	97
25		**2i**	[2.5	67	84	89][c]
26		R = Me (**2j**)	1	38	89	87[b]
27		**2j**	2.5	0.7	96	99[b]
28		**2j**	[2.5	52	93	98[b]][c]
29		**2k**	1	67	99	86
30		**2k**	2.5	3.5	93	98
31		**2k**	[2.5	72	67	94][c]
32		**2l**	1	31	97	95[b]
33		**2l**	2.5	2	97	93[b]
34		**2l**	[10	14	72	85[b]][c]
35		**2m**	1	16	90	95
36		**2m**	2.5	0.3	92	99
37		**2n**	1	21	93	93
38		**2n**	2.5	1.3	98	99
39		**2o**	2.5	10	94	96
40		**2p**	2.5	6	98	98
41		**2q**	2.5	16	73	53
42		**2q**	10	6	91	69

[a] For a representative procedure, see Section 2. Yields are isolated yields. Ee's were determined by chiral HPLC.
[b] The absolute configuration was determined to be (*S*).
[c] Results in the absence of the additive (partly reported in Ref. 5).

enantioselectivity was obtained from heteroaromatic ketoimines (entries 35–40) and cyclic ketoimines (entries 1–5). These results are the first examples of a catalytic Strecker reaction that gives high enantioselectivity from heteroaromatic and cyclic ketoimines.

The dramatic improvement in both enantioselectivity and catalyst activity in the presence of DMP suggested that the additive might change the active catalyst structure.[8] Consistent with this expectation, the addition of only 10 mol% of DMP was sufficient for providing excellent enantioselectivity, although the reaction time was longer than when using 100 mol% additive (Table 1, entry 9). To gain preliminary insight into the protic additive effects on the catalyst structure, we investigated the catalyst constitution (molecular weight) using

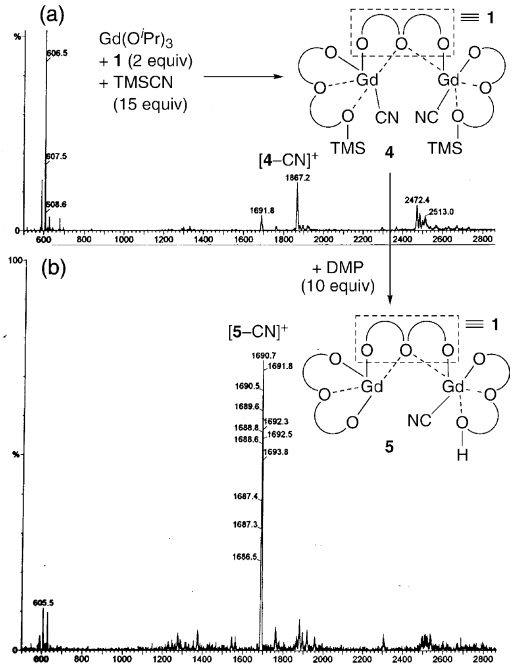
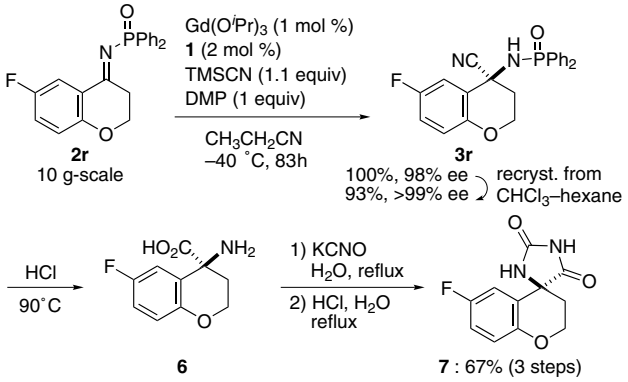


Figure 1. ESI-MS observation in the absence (a) and in the presence (b) of DMP.

ESI-MS. The catalyst prepared from Gd(O^{i}Pr)$_3$ and **1** in a 1:2 ratio, in the presence of TMSCN (15 equiv to the catalyst) in acetonitrile as a solvent, afforded the peak at 1862 (calcd observed: 1867), which corresponds to the previously proposed O-silylated 2:3 complex **4** (Fig. 1(a)).[9] When DMP (10 equiv) was added to the catalyst solution, the peak corresponding to **4** disappeared and a new peak appeared at 1691, which corresponds to an O-protonated 2:3 complex **5** (Fig. 1(b)). Therefore, the protic additive changes the active catalyst structure from the O-silylated form **4** to the O-protonated form **5**.[10] This proton containing complex should be the highly active and enantioselective catalyst in this asymmetric Strecker reaction of ketoimines.

As far as we know, this is one of the rare cases that protic additives optimize the asymmetric environment of the catalyst, as well as improve its activity.[11] Thus, the role of protic additives is to generate a new complex **5**, and is distinct from that reported in the catalytic enantioselective Strecker reaction of aldoimines.[7]

Success in the high enantio-induction from cyclic ketoimines prompted us to apply this new method to a catalytic asymmetric synthesis of sorbinil (**7**), a therapeutic agent for chronic complications of diabetes mellitus, developed by the Pfizer group. Sorbinil contains a chiral spirohydantoin structure, and its biological activity resides in the (*S*)-enantiomer. A straightforward synthesis of **7** was achieved using the catalytic asymmetric Strecker reactions, as shown in Scheme 1. The reaction with **2r** proceeded using 1 mol % catalyst in the presence of 1 equiv of DMP, and **3r** was isolated as an enantiomerically pure form by direct recrystallization of the crude product. The reaction was performed on a 10 g-scale without any difficulty. Acid hydrolysis followed by hydantoin formation gave **7** in high overall yield. No silica gel chromatography was necessary from **2r** to **7**.



Scheme 1. Catalytic enantioselective synthesis of sorbinil.

In conclusion, we developed a highly general and practical catalytic enantioselective Strecker reaction of ketoimines, using DMP as a catalyst modulator. The improvement appeared to stem from the generation of new proton-containing catalyst, demonstrated by ESI-MS studies. This new method made it possible to use heteroaromatic and cyclic ketoimines as substrates for the first time. The reported reaction is the most general and practical catalytic enantioselective Strecker reaction of ketoimines. The practicality was clearly demonstrated by application to an efficient synthesis of an important pharmaceutical lead, sorbinil.

2. Experimental

2.1. General procedure for catalytic enantioselective Strecker reaction

A solution of Gd(O^{i}Pr)$_3$ (0.2 M in THF, 1.37 mL, 0.274 mmol, purchased from Kojundo Chemical Laboratory Co., Ltd. Fax: +81-492-84-1351) was added to a solution of ligand **1** (256 mg, 0.556 mmol, commercially available from Junsei Chemical Co., Ltd. Fax: +81-3-3270-5461) in THF (5.5 mL) in an ice bath. The mixture was stirred for 40 min at 45 °C, and then the solvent was evaporated. After drying the resulting pre-catalyst under vacuum (~5 mmHg) for 2 h, substrate **2r** (10 g, 27.4 mmol) was added as a solid in one portion. Propionitrile (12.3 mL) was added at −40 °C, and after 20 min, TMSCN (4.15 mL, 30.1 mmol) was added. After 20 min, 2,6-dimethylphenol (3.35 g, 27.4 mmol) in propionitrile (12.3 mL) was added to start the reaction. After 83 h, silica gel (10 g) was added to the reaction mixture at −40 °C (caution! HCN is generated). The mixture was carefully evaporated until no HCN gas remained with monitoring by HCN sensor. The silica gel was filtrated, and the filtrate was washed with MeOH/CHCl$_3$ (1:9). The combined liquid was evaporated, and the resulting residue was recrystallized from CHCl$_3$/

hexane (1:1) to give colorless needles in 93% yield (10.0 g).

2.2. Sorbinil synthesis from Strecker product 3r

Enantiomerically pure **3r** (10.0 g, 25.5 mmol) was treated with concd HCl (500 mL) under reflux for 16 h. Volatiles were evaporated, and the residue was purified through ion exchange chromatography [Dowex 50Wx8-100 (acidic) (300 g)], loading and eluting with MeOH (1.5 L) to get rid of $Ph_2P(O)OH$, and then eluting with 1.4 M NH_4 OH aq (1.5 L)] to give quaternary amino acid **6** as a white solid in 86% yield (4.63 g). A mixture of **6** (4.63 g, 21.9 mmol) and KCNO (6.09 g, 75 mmol) in H_2O (130 mL) was heated at 80 °C for 14 h. After cooling to room temperature, 6 M HCl was added to acidify the solution. The resulting white solid was filtrated and washed with EtOH (100 mL). The filtrate white solid was treated with 3 M HCl (100 mL) under reflux for 8 h. Evaporation of volatiles and recrystallization from ^{i}PrOH gave sorbinil **7** in 67% yield (three steps: 3.98 g, $[\alpha]_D^{23}$ +53.5 ($c = 1.0$, MeOH): lit.[6] $[\alpha]_D^{25}$ +53.1 ($c = 1.0$, MeOH)).

Acknowledgements

Financial support was provided by RFTF of the Japan Society for the Promotion of Science (JSPS) and PRESTO of the Japan Science and Technology Corporation (JST). We thank Mr. Usuda and Mr. Takita for helpful discussions.

References and notes

1. For reviews, see: (a) Cativiela, C.; Diaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **1998**, *9*, 3517; (b) Ohfune, Y.; Shinada, T. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 1115.
2. Gröger, H. *Chem. Rev.* **2003**, *103*, 2795.
3. (a) Vachal, P.; Jacobsen, E. N. *Org. Lett.* **2000**, *2*, 867; (b) Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 10012.
4. Chavarot, M.; Byrne, J. J.; Chavant, P. Y.; Vallée, Y. *Tetrahedron: Asymmetry* **2001**, *12*, 1147.
5. Masumoto, S.; Usuda, H.; Suzuki, M.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 5634.
6. Sarges, R.; Howard, H. R.; Kelbaugh, P. R. *J. Org. Chem.* **1982**, *47*, 4081, and references cited therein.
7. For beneficial additive effects of the proton source on catalytic enantioselective Strecker reaction of aldoimines, see: (a) Krueger, C. A.; Kuntz, K. W.; Dzierba, C. D.; Wirschun, W. G.; Gleason, J. D.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 4284; (b) Josephsohn, N. S.; Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 11594; (c) Takamura, M.; Hamashima, Y.; Usuda, H.; Kanai, M.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 1650. In these cases, protic additives do not change the active catalyst structure. The enantioselectivity was not affected by the protic additives.
8. The possibility that HCN generated from TMSCN and the additive acts as the catalyst modulator can not be denied.
9. Yabu, K.; Masumoto, S.; Yamasaki, S.; Hamashima, Y.; Kanai, M.; Du, W.; Curran, D. P.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 9908.
10. Addition of ^{t}BuOH (10 equiv) also gave the same peak corresponding to **5**, however with lower intensity than when DMP was added.
11. For examples of beneficial effects of protic additives on catalyst structures, see: Yamashita, Y.; Ishitani, H.; Shimizu, H.; Kobayashi, S. *J. Am. Chem. Soc.* **2002**, *124*, 3292, and references cited therein.