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Catalytic Enantioselective Strecker Reaction of Ketoimines

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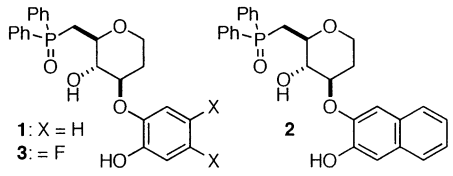
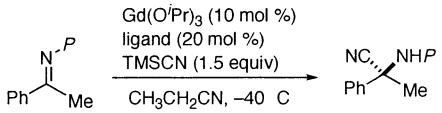
The catalytic enantioselective Strecker reaction (cyanation of imines) is one of the most direct and efficient methods for asymmetric synthesis of natural and unnatural α-amino acids. Recent intensive studies in this field have led to the ability to synthesize chiral monosubstituted α-amino nitriles from a wide range of aldoimines.[1] In the case of the catalytic enantioselective Strecker reaction using ketoimines as substrates, however, only two asymmetric catalyses have been reported: Jacobsen's Shiff base catalysis[2] and Vallée's heterobimetallic catalysis.[3] Of these, Jacobsen's catalysis gave high enantioselectivity from aryl methyl ketoimines and *tert*-butyl methyl ketoimine. Considering the biological importance of disubstituted α-amino acids,[4,5] however, there is room for improvement in terms of substrate generality. We report herein a general catalytic asymmetric Strecker reaction of ketoimines.

We previously reported that the chiral lanthanide complex (Ln-**1**) prepared from Ln(O^iPr)$_3$ (Ln = Gd or Sm) and ligand **1** in a 1:2 ratio is a highly efficient catalyst for enantioselective cyanosilylation of ketones.[6] The active catalyst was a 2:3 complex of the lanthanide cyanide and the ligand. Studies of the reaction mechanism suggested that one of the lanthanide cyanides acts as a Lewis acid to activate the substrate, while the other lanthanide cyanide acts as a nucleophile, and the reaction proceeds through internal transfer of the cyanide to the activated substrate. Moreover, the catalyst activity and enantioselectivity can be improved using ligands **2** and **3** containing electron-withdrawing catechols.[7] These findings prompted us to investigate the applicability of the catalyst to the asymmetric Strecker reaction of ketoimines.



We began with optimization using acetophenone-derived imines as substrates, TMSCN as the nucleophile, and Gd-**1** as the catalyst (10 mol %). When using an *N*-benzyl-protected imine as the substrate, however, the product was obtained with only 35% ee (Table 1, entry 1), even after intensive screening of reaction conditions such as lanthanide metals, metal/ligand ratio, and protic additives.[8] Because of the oxophilic character of lanthanide metals, the use of an *N*-furfuryl-protected imine was examined. As expected, the product was obtained with slightly improved enantioselectivity (entry 2). On the other hand, there was significant improvement when *N*-diphenylphosphinoyl imine[9] **4a** was used as a substrate, and the product was obtained with 72% ee (entry 3). A protic additive was not necessary in this case.[10] Enantioselectivity was further improved to 82% after modifying the addition order of the reagents (entry 4). Finally, a product with 96% ee was obtained when Gd-**3**, containing the difluorocatechol, was used as a catalyst (entry 6).

Table 1. Optimization of the Reaction Conditions



entry	*P*	ligand	time (h)	conversion (%)[a]	ee (%)[b]
1[c,d]	CH_2Ph	**1**	24	95	35
2[c,d]		**1**	88	84	48
3[d]	$P(O)Ph_2$	**1**	16	100	72
4[e]	$P(O)Ph_2$	**1**	14	100	82
5[e]	$P(O)Ph_2$	**2**	8	100	85
6[e]	$P(O)Ph_2$	**3**	6	100	96

[a] Conversions were determined by ^{1}H NMR. [b] Enantiomeric excesses (ee) were determined by HPLC on chiral stationary phases after appropriate conversions. See the Supporting Information for details. [c] 2,6-Dimethylphenol was used as a protic additive. [d] Substrates were added to a solution of the catalyst and TMSCN. [e] The substrate was added to the dried pre-catalyst. The solvent and TMSCN were then added at −40 °C. See ref 11.

Having optimized the reaction conditions, substrate generality was investigated (Table 2).[11] High enantioselectivity was obtained from aryl methyl ketoimines even using 2.5 mol % catalyst (entries 1−4). The reaction was applicable to propiophenone-derived ketoimine **4e** (entry 5) and primary alkyl-substituted ketoimines **4f** and **4g** (entries 6 and 7), although secondary alkyl-substituted **4k** gave moderate enantioselectivity (entry 11).[12] α,β-Unsaturated ketoimines **4h**, **4i**, and **4j** (entries 8−10) gave high enantioselectivity with complete regioselectivity. There are no reports of a catalytic enantioselective Strecker reaction from α,β-unsaturated ketoimines. These products should be very useful for synthesizing a wide variety of chiral disubstituted α-amino acids and their derivatives, due to the high versatility of the olefin function. Thus, this is the most general catalytic enantioselective Strecker reaction of ketoimines reported to date.

The stability of product **5** is another advantage of this reaction. Most of the products could be directly subjected to acid hydrolysis to produce the corresponding amino acids.[13] Representative conversion sequences to enantiomerically pure amino acid derivatives are shown in Scheme 1. After the reaction and aqueous workup, recrystallization of the crude mixture[14] from CH_2Cl_2/hexane gave **5a** with >99% ee (84% yield). The major side product in the hydrolysis step, diphenylphosphinic acid, was eliminated from the amino acid by extraction. Esterification and Boc protection gave the protected **6a** isolated in 78% yield from the ketoimine **4a** (five operations). **5i** obtained in high enantioselectivity from **4i** could

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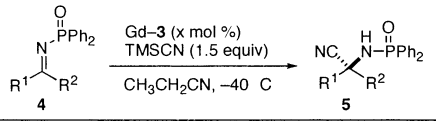
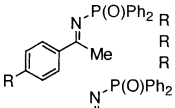
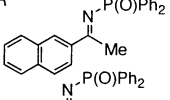
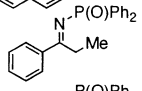
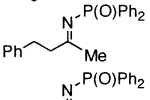
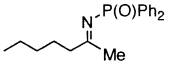
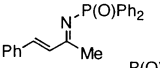
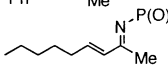
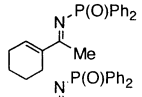
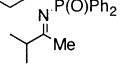
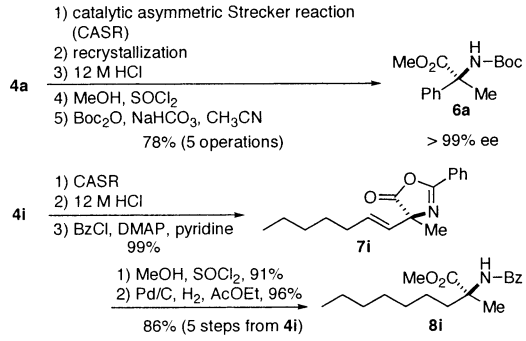
Table 2. Catalytic Enantioselective Strecker Reaction of Ketoimines[a]



entry	substrate		cat. (x)	time (h)	yield (%)[b]	ee (%)[d]
1		R = H (**4a**)	2.5	24	94	95[e]
2		R = Cl (**4b**)	2.5	67	84	89
3		R = Me (**4c**)	2.5	52	93	98
4[f]		**4d**	2.5	72	67	94
5		**4e**	10	14	72	85
6		**4f**	10	5	87	89
7		**4g**	8	65	73	72[g]
8		**4h**	5	68	79[c]	83
9		**4i**	5	52	99	88[e]
10		**4j**	5	67	58	90[g]
11		**4k**	5	48	74	51[g]

[a] For a representative procedure, see ref 11. [b] Isolated yield is after conversion to the corresponding oxazolidone, unless otherwise noted. [c] Isolated yield was determined after purification of **5** by column chromatography. [d] Determined by chiral HPLC after appropriate conversions. See the Supporting Information for details. [e] The absolute configuration was determined to be (*S*). [f] $CH_3CH_2CN/CH_2Cl_2 = 4/1$ was used as the solvent. [g] Ee decreased using 10 mol % of catalyst.

Scheme 1. Conversion of the Products



also be converted to the saturated derivative **8i** (Scheme 1). This procedure might supplement the moderate enantioselectivity from primary alkyl-substituted ketoimines.

In conclusion, we achieved a catalytic enantioselective Strecker reaction with broad substrate generality using *N*-diphenylphosphinoyl ketoimines as substrates. The products could easily be converted to disubstituted α-amino acids and their derivatives. Detailed mechanistic studies and further applications of this methodology to the synthesis of biologically active compounds are ongoing.

Acknowledgment. Financial support was provided by RFTF of the Japan Society for the Promotion of Science and PRESTO of the Japan Science and Technology Corporation.

Supporting Information Available: Experimental procedures and characterization of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) Catalytic asymmetric alkylation is another powerful methodology for disubstituted α-amino acid synthesis. For recent examples, see: (a) Ooi, T.; Takeuchi, M.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2000**, *122*, 5228. (b) Trost, B. M.; Dogra, K. *J. Am. Chem. Soc.* **2002**, *124*, 7256.

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(7) (a) Masumoto, S.; Yabu, K.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2002**, *43*, 2919. (b) Yabu, K.; Masumoto, S.; Kanai, M.; Curran, D. P.; Shibasaki, M. *Tetrahedron Lett.* **2002**, *43*, 2923. Chiral ligands **1** and **3** can be synthesized through 12 steps from triacetyl-D-glucose (ca. 20% overall yield, not optimized), and are commercially available from Junsei Chemical Co., Ltd. (Fax: +81-3-3270-5461).

(8) For the beneficial effects of protic additives on catalytic enantioselective Strecker reaction of aldoimines, see refs 1h, 1j, 1l, and 1m.

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(10) The product appeared to be silylated **5** in the reaction mixture. The silyl ether was hydrolyzed during the aqueous workup.

(11) **Representative procedure:** A solution of $Gd(O^iPr)_3$ (0.2 M in THF, 37.5 μL, 0.0075 mmol, purchased from Kojundo Chemical Laboratory Co., Ltd. Fax: +81-492-84-1351) was added to a solution of ligand **3** (7.5 mg, 0.015 mmol) in 0.15 mL of THF in an ice bath. The mixture was stirred for 30 min at 45 °C, and then the solvent was evaporated. After drying the resulting pre-catalyst under vacuum (~5 mmHg) for 1 h, substrate **4a** (96 mg, 0.3 mmol) was added as a solid in one portion. Propionitrile (0.1 mL) and TMSCN (60 μL, 0.45 mmol) were added to the mixture at −40 °C to start the reaction.

(12) On the basis of the NMR studies, imines **4** appear to exist in a very fast equilibrium between *E* and *Z* isomers. See the Supporting Information for details.

(13) Formylation was necessary for further conversion of the *N*-benzyl-protected aminonitriles to the deprotected amino acid derivatives, due to their lability. See ref 2.

(14) The crude mixture after workup contains product **5**, ligand **3**, and the silylated ligand. The ligand was recoverable after acid hydrolysis in 83% yield.

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