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Catalytic enantioselective Strecker reaction of ketoimines using catalytic amount of TMSCN and stoichiometric amount of HCN

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*

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Abstract—Catalyst loading as low as 0.1 mol% was achieved in the enantioselective Strecker reaction of ketoimines. Excellent enantioselectivity was obtained with a combined use of a catalytic amount of TMSCN and a stoichiometric amount of HCN as a reagent, and a chiral gadolinium complex as a catalyst.
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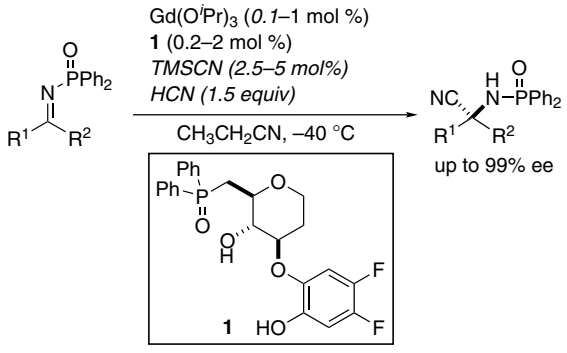
1. Introduction

In the preceding paper, we disclosed a new method for the catalytic enantioselective Strecker reaction of ketoimines. Using 1–2.5 mol% of a chiral gadolinium complex generated from $Gd(O^iPr)_3$ and D-glucose derived ligand **1** in a 1:2 ratio, and 2,6-dimethylphenol (DMP: 1 equiv) as an additive, excellent enantioselectivity was obtained from a wide range of *N*-phosphinoylketoimines including aromatic, heteroaromatic, alkyl, and cyclic ketoimines.[1] This is currently the most general catalytic enantioselective Strecker reaction of ketoimines,[2] which offers an efficient method for the synthesis of very important chiral building blocks, chiral α,α-disubstituted α-amino acids.[3] Here we report the more advanced reaction conditions. The new reaction conditions using a catalytic amount of TMSCN (2.5–5 mol%) and a stoichiometric amount of HCN allowed us to reduce the catalyst amount to as low as 0.1 mol% with maintaining the high enantioselectivity. Reduction of the amount of metals used in chemical reactions (in this case, silicon and gadolinium) should be advantageous for application to an industrial scale synthesis, in terms of cost performance and atom economy.[4]



ESI-MS studies of the active catalyst for the Strecker reaction suggested that the beneficial effect of DMP both on enantioselectivity and catalyst activity appeared to stem from the generation of a proton-containing 2:3 complex **3** through the reaction of initially formed double-silylated complex **2** with DMP (Scheme 1, Eq. 1).[1] We expected that the same active catalyst **3** should be generated through the reaction of HCN with **2** (Scheme 1, Eq. 2). In this protonolysis with HCN, 2 equiv of TMSCN is produced, concomitant with the generation of the active catalyst **3**. Because the Strecker product is produced via a cyanide transfer from the gadolinium cyanide in **3** to the activated substrate,[5] it is expected that only a catalytic amount of TMSCN would be required for this catalysis.

As expected, the reaction of ketoimine **4a** proceeded rapidly using 2.5 mol% catalyst in the presence of

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* Corresponding authors. Tel.: +81-3-5841-4830; fax: +81-3-5684-5206; e-mail: mshibasa@mol.f.u-tokyo.ac.jp

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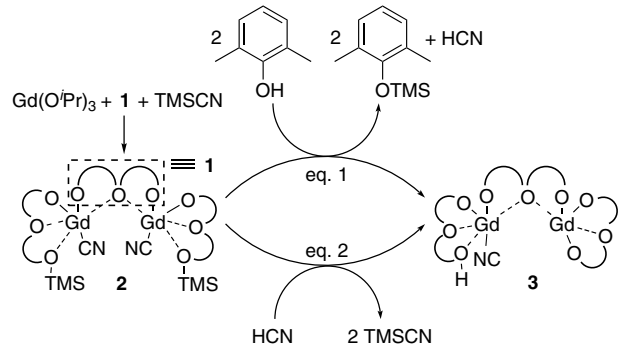


Scheme 1. Active catalyst generation.

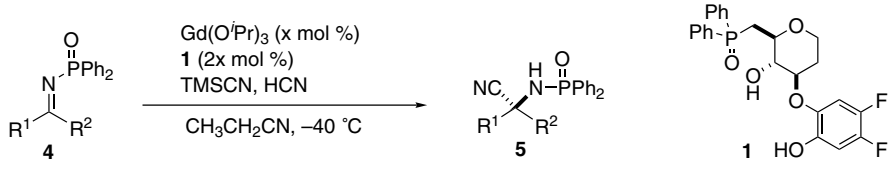
10 mol% TMSCN and 150 mol% HCN, and product **5a** was obtained with 99% ee (Table 1, entry 1). When the catalyst amount was reduced to 1 mol% with maintaining the amount of TMSCN and HCN (entry 2), slight decrease in enantioselectivity was observed (97% ee). The product with 99% ee, however, was again obtained when reducing the amount of TMSCN to 5 mol% (entry 3). These results suggested that there exists an equilibrium between the proton-containing catalyst **3** with high reactivity/enantioselectivity and the silylated catalyst **2** with moderate reactivity/enantioselectivity,[6] and the undesired reaction pathway promoted by **2** might contaminate when the TMSCN/HCN ratio was increased.

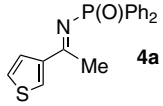
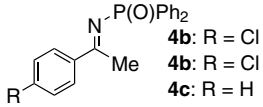
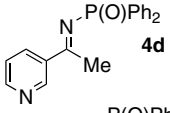
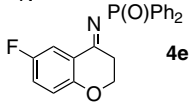
These considerations might explain the dramatic reactivity difference between under the previous reaction conditions using stoichiometric amounts of TMSCN and additive 2,6-dimethylphenol (Table 1, entry 4), and under the current reaction conditions using a catalytic amount of TMSCN and a stoichiometric amount of HCN (entries 2 and 3). Because TMSCN/protic additive ratio is higher in the case of entry 4 compared to entries 2 and 3, the concentration of the desired proton-containing catalyst **3** should be higher under the conditions in entries 2 and 3.[7] This might result in the improvement of the reactivity and enantioselectivity. It is also important to note that the reaction in the absence of TMSCN did not proceed at all at −40 °C, even using high catalyst amount with the prolonged reaction time (entry 5). This feature is crucial for the success of the current reaction.[8]

High reactivity under the combination of a catalytic amount of TMSCN and a stoichiometric amount of HCN allowed us to reduce the catalyst amount as low as 0.1 mol% with maintaining the excellent enantioselectivity (Table 1, entries 7 and 8).[9] Although Jacobsen et al. reported one example using 0.1 mol% catalyst, the product was obtained with only 69% ee from acetophenone-derived ketoimine.[2a] Therefore, this is the first example to achieve excellent enantioselectivity with very high catalyst turnover number. HCN produced from protonolysis of TMSCN[10] could also be used as well (entry 9). Most of the Strecker products are crystalline compounds, and enantiomerically pure amidonitriles were easily obtained by recrystallization.

In conclusion, we developed an efficient method for the catalytic enantioselective Strecker reaction of keto-

Table 1. Catalytic enantioselective Strecker reaction of ketoimines[a]



Entry	Substrate	Cat. (×mol%)	TMSCN (mol%)	HCN (mol%)	Time (h)	Yield (%)	Ee (%)
1		2.5	10	150	0.5	99	99
2	 **4a**	1	10	150	2	99	97
3		1	5	150	3	99	99
4		1	150	0[b]	20	93	93
5		5	0	150	21	0	—
6	 **4b**: R = Cl	1	10	150	0.6	99	95
7	**4b**: R = Cl	0.1	2.5	150	54	99	93
8	**4c**: R = H	0.1	5	150	19	97	90[d]
9	 **4d**	5	20	150[c]	0.25	99	94
10	 **4e**	0.5	5	150	1.3	96	93[d]

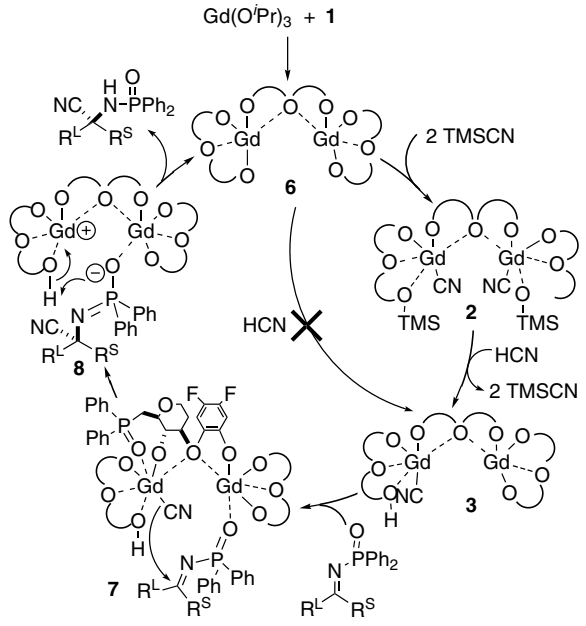
[a] For a representative procedure, see Experimental Section. Yields are isolated yields. Ee's were determined by chiral HPLC.
[b] 2,6-Dimethylphenol (100 mol%) was added instead of HCN (Ref. 1).
[c] HCN was prepared by mixing TMSCN with ^{i}PrOH.
[d] The absolute configuration was determined to be (*S*).

imines, using the combination of a catalytic amount of TMSCN and a stoichiometric amount of HCN. The catalyst amount was reduced as low as 0.1 mol%. This new procedure should be advantageous for a large-scale synthesis of chiral α,α-disubstituted α-amino acids.

2. Experimental

2.1. General procedure for catalytic enantioselective Strecker reaction using a catalytic amount of TMSCN and a stoichiometric amount of HCN

A solution of $Gd(O^iPr)_3$ (0.2 M in THF, 18.8 μL, 3.8 μmol, purchased from Kojundo Chemical Laboratory Co., Ltd. Fax: +81-492-84-1351) was added to a solution of ligand **1** (3.5 mg, 7.6 μmol, commercially available from Junsei Chemical Co., Ltd. Fax: +81-3-3270-5461) in THF (75 μL) 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 1 h, substrate **4b** (1.33 g, 3.8 mmol) was added as a solid in one portion. Propionitrile (1 mL) was added at −40 °C, and after 30 min, TMSCN (12.5 μL, 0.094 mmol) was added. After 5 min, HCN[11] (4 M in propionitrile stock solution, 1.4 mL, 5.6 mmol) was added to start the reaction. After completion of the reaction, silica gel 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 purified by silica gel column chromatography.



Scheme 2. Proposed catalytic cycle.

Acknowledgements

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References and notes

1. See the preceding paper. *Tetrahedron Lett.* **2004**, *45*, 3147–3151.
2. For previous examples for catalytic enantioselective Strecker reaction of ketoimines, see: (a) Vachal, P.; Jacobsen, E. N. *Org. Lett.* **2000**, *2*, 867; (b) Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 10012; (c) Chavarot, M.; Byrne, J. J.; Chavant, P. Y.; Vallée, Y. *Tetrahedron: Asymmetry* **2001**, *12*, 1147; (d) Masumoto, S.; Usuda, H.; Suzuki, M.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 5634; For an excellent review, see: (e) Gröger, H. *Chem. Rev.* **2003**, *103*, 2795.
3. 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.
4. Trost, B. M. *Science* **1991**, *254*, 1471.
5. The gadolinium cyanide, not TMSCN itself, is the actual nucleophile in the catalytic cyanosilylation of ketones, confirmed by labeling studies: Yabu, K.; Masumoto, S.; Yamasaki, S.; Hamashima, Y.; Kanai, M.; Du, W.; Curran, D. P.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 9908, See also the proposed catalytic cycle in Ref. 8 (Scheme 2).
6. For the reactivity and enantioselectivity differences between in the absence and presence of protic additive, see *Tetrahedron Lett.* **2004**, *45*, 3147–3151.
7. Other factors such as the fact that the substrates are more readily soluble to the reaction media under the TMSCN (cat.)-HCN conditions than under TMSCN-DMP conditions, and/or the retardation effect of the trimethylsilylated DMP, cannot be excluded as origins of the reactivity difference.
8. Lack of reactivity using only HCN is also important from the mechanistic point of view, that is, the pre-catalyst **6** cannot be directly converted to the active catalyst **3** (Scheme 2). Working hypothesis for the catalytic cycle is postulated in Scheme 2, based on these new experimental results and previous mechanistic studies (Ref. 5). The catalytic cycle should always proceed through the intermediary of silylated **2**. Thus, TMSCN produced in the active catalyst (**3**) formation step functions as a catalyst re-generator (from **6** to **3** through **2**).
9. High purity of the substrate *N*-phosphinoylketoimines is very important especially when catalyst loading was reduced. Substrate purification through flash column chromatography followed by recrystallization using anhydrous solvents under argon atmosphere was effective to obtain the substrates with high purity.
10. Mai, K.; Patil, G. *J. Org. Chem.* **1986**, *51*, 3545. For in situ preparation of HCN, we treated TMSCN with ^{i}PrOH (1:1) in propionitrile (1.1 M) under ice bath for 2 h.
11. Slatta, K. H. *Ber.* **1934**, *67*, 1028.